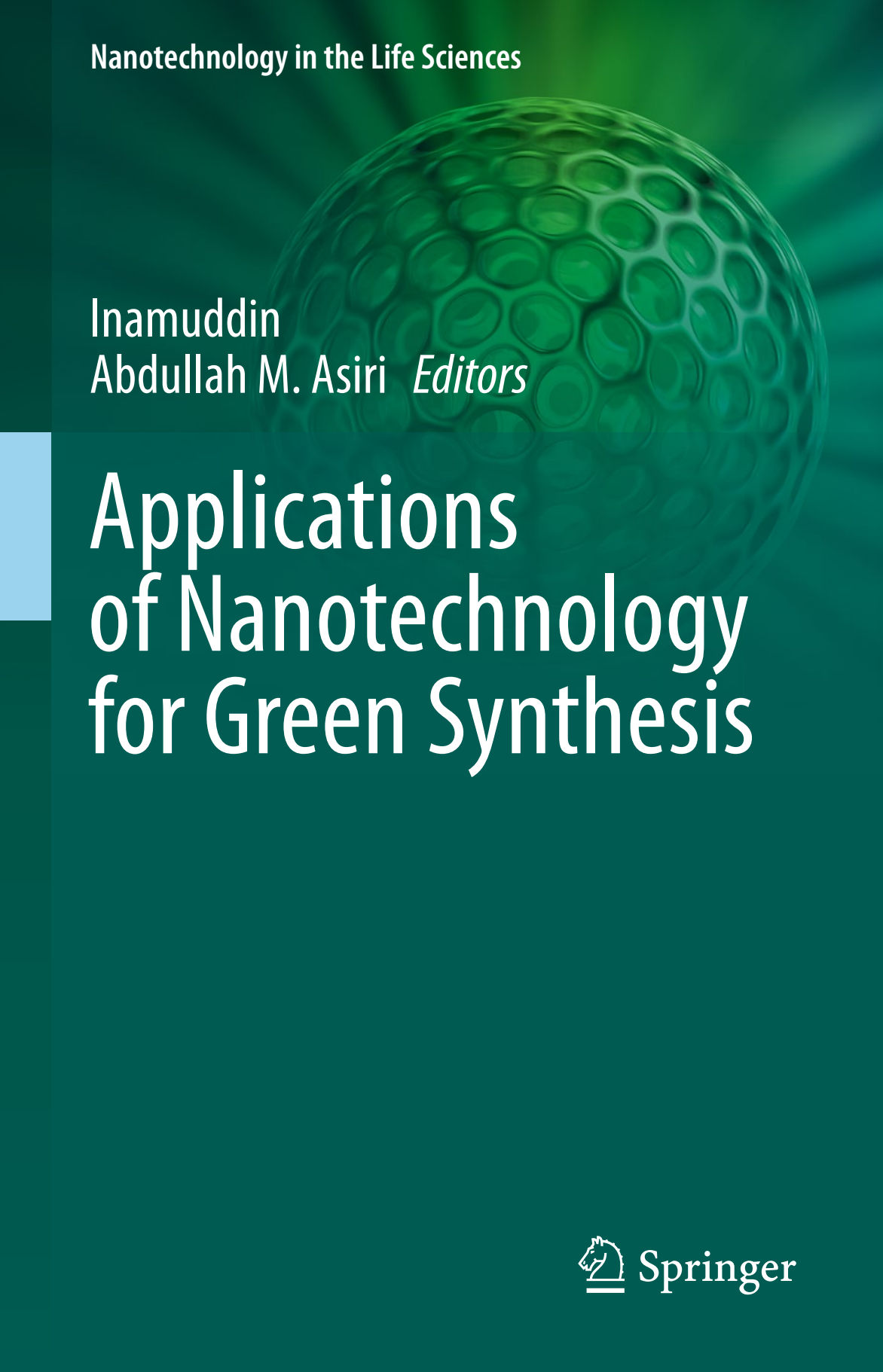
Nanotechnology in the Life Sciences



Inamuddin
Abdullah M. Asiri *Editors*

# Applications of Nanotechnology for Green Synthesis

Springer

# Nanotechnology in the Life Sciences

**Series Editor**

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Nano and biotechnology are two of the 21st century's most promising technologies. Nanotechnology is demarcated as the design, development, and application of materials and devices whose least functional make up is on a nanometer scale (1 to 100 nm). Meanwhile, biotechnology deals with metabolic and other physiological developments of biological subjects including microorganisms. These microbial processes have opened up new opportunities to explore novel applications, for example, the biosynthesis of metal nanomaterials, with the implication that these two technologies (i.e., thus nanobiotechnology) can play a vital role in developing and executing many valuable tools in the study of life. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale, to investigating whether we can directly control matters on/in the atomic scale level. This idea entails its application to diverse fields of science such as plant biology, organic chemistry, agriculture, the food industry, and more.

Nanobiotechnology offers a wide range of uses in medicine, agriculture, and the environment. Many diseases that do not have cures today may be cured by nanotechnology in the future. Use of nanotechnology in medical therapeutics needs adequate evaluation of its risk and safety factors. Scientists who are against the use of nanotechnology also agree that advancement in nanotechnology should continue because this field promises great benefits, but testing should be carried out to ensure its safety in people. It is possible that nanomedicine in the future will play a crucial role in the treatment of human and plant diseases, and also in the enhancement of normal human physiology and plant systems, respectively. If everything proceeds as expected, nanobiotechnology will, one day, become an inevitable part of our everyday life and will help save many lives.

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Editors

# Applications of Nanotechnology for Green Synthesis

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ISSN 2523-8027 ISSN 2523-8035 (electronic)
Nanotechnology in the Life Sciences
ISBN 978-3-030-44175-3 ISBN 978-3-030-44176-0 (eBook)
https://doi.org/10.1007/978-3-030-44176-0



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# Preface

Individuals are at the focal point of worries for feasible advancement. They are entitled to a healthy and productive life in concordance with nature. Green chemistry has found its foundations in effectively accessible contemplations and research endeavors, which prompted more prominent consideration toward issues relating to harmful chemical waste and resource depletion. The demand for global environmentally friendly chemical processes, efficient methods of syntheses, atom-economical syntheses, multicomponent reactions, and usage of environmentally benign solvents requires the development of novel and cost-effective approaches to pollution control, prevention, and environmental degradation. Hence, knowledge and understanding concerning green synthetic tools and its concepts are essential for an advanced sustainable community.

This book titled *Applications of Nanotechnology for Green Synthesis* presents the latest advances on the green chemistry avenues toward sustainable technologies. Chapters highlighted eco-friendly methods; green solvents; selective transformations; biosynthesis; eco-friendly catalysis; production of valuable chemicals, drugs, and technologies; and so on. A layout of different studies for the development of green chemical processes and applications is highlighted. This book is an extremely well-structured and essential resource for undergraduate and postgraduate students, faculty, R&D professionals, scientists, environmental chemists, and industrial experts. This book will bring together panels of highly accomplished experts in the field of green chemistry technologies. Based on thematic topics, the book edition contains the following 17 chapters:

Chapter 1 reviews ionic liquids as potential alternatives to organic solvents. Reactions that have been carried out successfully in ionic liquids and their advantages over reactions in conventional solvents are discussed. Some examples of how industries replacing their media with ionic liquids are also discussed in this chapter.

Chapter 2 discusses the use of greener solvent, i.e., water in industrial and synthetic applications. Several environmentally sustainable processes in the multicomponent reactions (MCRs), synthesis of pharmaceutical intermediates, and products are discussed in detail. The applications of synthesis, MCRs, and surfactant-mediated chemistry in water to a selected number of reaction types are also presented.

Chapter 3 discusses the applications of ionic liquids (ILs) in organic synthesis. ILs have developed itself as a sustainable alternative to organic solvents, catalysts, and reagents. The five name reactions, namely, Biginelli reaction, Knoevenagel reaction, Michael reaction, Heck reaction, and Friedel–Crafts reaction, have been discussed in detail to show the utility of ILs in organic synthesis.

Chapter 4 summarizes the recent developments on various aqueous-mediated catalyst-free organic transformations under conventional stirring at room temperature or reflux conditions. From this chapter, it is also well established that, on many occasions, we can avoid the use of catalysts by employing ultrasound or microwave-irradiated techniques in water.

Chapter 5 details various modification methods on polymeric membranes to enhance the isopropanol dehydration. The role of modification during solution preparation is also discussed. The major focus is given to enlighten the advantages and weaknesses of modifications of pervaporation membranes and give a future trend in modification techniques.

Chapter 6 outlines the basic concepts and importance of green chemistry. The major issues of conventional organic synthesis are discussed with special emphasis on atom economy, hazards of solvents and reagents, handling of reactions and process economy.

Chapter 7 discusses various greener aspects involved in the scale-up synthesis of different active pharmaceutical ingredients and other such molecules reported in recently published literature, to familiarize the young process scientists with the intricacies of eco-friendly process development.

Chapter 8 discusses green chemistry approaches applied in organic synthesis utilized by chemical as well as pharmaceutical industries. Greener synthetic approaches have tremendous potential for growth, and medical scientists can gain knowledge about eco-friendly protocols for synthesizing a wide range of organic compounds.

Chapter 9 details the fundamental understanding and technical requirements of multicomponent catalysts for selective glycerol conversion to lactic acid through various combinations of non-precious metals, bases, and porous supports. Their catalytic behaviors are critically reviewed with the highlights on the influencing parameters as well as the sustainable way forward.

Chapter 10 mainly focuses on the synthesis of metal nanoparticles using different green biological approaches based on the prokaryotic systems, for example, bacteria, and eukaryotic systems such as plants, algae, yeast, fungi, and virus. Further, it also discusses the different biological applications of biologically synthesized nanoparticles.

Chapter 11 details on silver nanostructures in various dimensions, their various chemical reduction-based synthesis methods, and antimicrobial activities with special emphasis on their mechanism of antimicrobial actions. The role of various synthesis parameters on the morphologies of silver nanostructures along with their further antimicrobial properties is discussed in detail.

Chapter 12 discusses important aspects regarding the characterization of the biomass composition, the main pretreatments for separating the cellulose, hemicellulose, and lignin fractions, as well as important advances in using heterogeneous catalysis, highlighting that acid-catalyzed hydrolysis of biomass is fundamental for glucose and platform chemical production.

Chapter 13 details the synthesis of reduced graphene oxide (rGO) from the reuse of discarded batteries. Several characterization techniques are mentioned in detail. Produced rGO was compared to commercial graphene. This synthesis can be considered as cheap, sustainable, and eco-friendly to produce high-quality graphene.

Chapter 14 stresses majorly on the exploitation of enzymes (biocatalyst) concerning the treatment of numerous industrial wastes. The major focus is to communicate how biocatalysis as a green approach helps to treat the wastes coming out of industries. All types of classification of enzymes are discussed along with their application in industrial waste treatment such as effluents from food industries, effluents from chemical industries, wastes from pharmaceutical industries, etc.

Chapter 15 discusses the synthesis of biodiesel using immobilized lipases and non-conventional feedstocks. The latest trends of immobilization of lipases, different methods of biodiesel production, and variables affecting the production of biodiesel are also discussed. The main focus is to use microbial lipases as catalysts to produce "greener" biodiesel.

Chapter 16 describes the advantages of different types of green solvent, e.g., water, ionic liquid, in technologies of organic synthesis. In this chapter, the background, perspective, and future trend of application of green solvents are investigated. Also, based on the 12 principles of green chemistry, the procedure for the future green solvent selection is presented.

Chapter 17 discusses the utility of boric acid as a green catalyst in the synthesis of numerous biologically important heterocycles. The advantages of boric acid include easy availability and eco-friendly physicochemical properties. The use of boric acid in catalyzing various organic conversions like addition, esterification, substitution, and condensation has been discussed in detail.

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# Contents

# Sustainable Organic Synthesis in Ionic Liquids

**Afifa Ahmed**

## Contents



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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_1

# 1 Introduction

The demand of naturally occurring chemicals is so multiplying that synthesis of these materials is the only left option. Despite the tremendous achievements made by chemical scientists, the burden of chemical wastes onto the environment is also increasing. At this point in the history of science and technology, the demand for greener processes is increasing everyday (Li and Trost 2008). In order to achieve best results from any chemical processes, organic chemists are spending significant time and energy on designing synthesis that are in compliance with the standards of green chemistry (Anastas and Eghbali 2010). The main considerations when designing an organic synthesis following the principles of green chemistry are discussed here.

## *1.1 Chemical Feedstock*

The chemical process should be designed to minimize dependence on chemical feedstock from petroleum and divert it to other renewable natural resources (Li and Trost 2008).

## *1.2 Reactions*

Green chemistry requires every reaction to be energy efficient, selective toward the desired product, simple to operate, and safe for health and environment (Li and Trost 2008).

## *1.3 Atom Economy*

Atom economy means the maximum incorporation of the reactants into the product (Trost 1991).

$$\text{Atom economy} = \left(\text{Molecular wt. of desired product} / \text{Molecular wt. of all products}\right) \times 100$$

For example, isomerization, polymerization, and addition reactions (Li and Trost 2008).

### *1.4 Coupling Reactions*

Direct conversion of C-H bond to C-C bonds so that unnecessary steps may be avoided (Ritleng et al. 2002).

### *1.5 Synthesis Without Protection*

Synthesis needs to be designed in a way that resources are not wasted on steps for protecting and deprotecting of functional groups (Li and Trost 2008). Click Chemistry serves as a good example of tolerating functionalities (Kolb et al. 2001).

### *1.6 Biocatalysis*

No one is as friendly to nature as nature itself. Biocatalysis is the utilization of nature's ideas and processes in labs. Biological catalysts like enzymes are employed in synthetic organic chemistry and are giving good results (Wong 1989).

### *1.7 Solvents*

Since, the main topic of this book revolves around green Solvents, the solvents will be discussed extensively.

## 2 Role of Solvents in Organic Synthesis

Solvents do not take part in the reactions themselves, yet they are an integral part of a reaction. The amount of solvent used in any reaction is more than any other auxiliary material. This makes solvents the largest auxiliary waste in any reaction (Sheldon 2005). The efforts to eliminate or minimize the harmful effects solvents on human health and safety as well as environment have been multiplied on different scales.

These efforts have made evident that desired results can only be achieved if sustainable strategies are made at the earliest point in designing a chemical process. There have been several efforts to set guidelines for sustainable solvent selection. Some of the factors considered in solvent selection are (Curzons et al. 1999):

- Emissions on incineration
- Ease of recovery and recycling

- Mineralization through wastewater treatment
- Volatile organic carbon
- Environmental impact in water
- Environmental impact in air
- Health hazard: Acute or chronic toxic effects on humans
- Exposure potential
- Inherent safety

## *2.1 Sustainable Organic Synthesis in Natural Solvents*

### 2.1.1 Water

Water has long been Nature's solvent of choice for organic reactions, and it suits best to the requirements of sustainable organic reactions. Water as a solvent is noticed to facilitate a number of organic reactions like Diels–Alder (Rideout and Breslow 1980), dipolar Cycloadditions (Ros et al. 1996), Claisen rearrangements (Grieco et al. 1989), Nucleophillic additions (Khatik et al. 2006), Transition metal complex catalyzed reactions (Casalnuovo and Calabrese 1990), Organometallic Reaction (Breno et al. 2006), Oxidation Reductions (Li and Chen 2006), and others.

In addition to reactions that take place in water for reactants that are not soluble in water, "on-water" techniques have also been introduced where aqueous suspensions of reactants in water are used (Klijn and Engberts 2005).

Despite many advantages of water, there are a few limitations in using it as solvent. Recovery of water-soluble products from the reaction mixture and regeneration of pure water with minimum soluble impurities are some of the challenges (Li and Trost 2008).

### 2.1.2 Supercritical $CO_2$

Supercritical $CO_2$ has been extensively studied as a green solvent, because it is nonflammable, relatively non-toxic, relatively inert, and naturally abundant. Other than these, $CO_2$ has some chemical advantages as well, for example $CO_2$ cannot be oxidized. Supercritical $CO_2$ is an aprotic solvent; it is generally immune to free radical reactions; $CO_2$ acts as a solvent that can be immiscible with both organic and fluorous materials and low viscosity (Beckman 2004). One more advantage of using supercritical fluid is the ease of tuning solvent properties by controlling temperature and pressure. $CO_2$ has a critical pressure of 72.8 bar and critical temperature of 31.1 °C, which can be achieved easily (Peach and Beilstein 2014).

CO2 is used as the solvent in synthetic organic chemistry, which includes reaction with gaseous phase reactants like hydrogenation, hydroformylation and oxidation, polymerization and polymer processing, enzymatic reactions, Diels–Alder chemistry, and Friedel–Crafts Reaction (Beckman 2004).

## 2.2 Sustainable Organic Synthesis in Non-natural Solvents

**Ionic Liquids**

The discovery of ionic liquids goes back to 1914 when Paul Walden in his search for molten salts at room temperature discovered $[EtNH_3][NO_3]$ has a melting point of 12 °C. This was followed by several other discoveries of room temperature ionic liquids, but $[EtNH_3]$ $[NO_3]$ again came into focus in 1981when it was considered as an alternative non-aqueous solvent. Thus, this new class of liquids came into spot light in the field of solvents (Welton 2018). In recent years, there has been a tremendous increase in the research on ionic liquids. This can very well be explained by the fact that many ionic liquids that were earlier known only for their electrochemical applications were now considered as green alternatives to conventional solvents (Wasserscheid and Welton 2002). The initial definitions of ionic liquids, as liquids with ions only, confused them with molten salts, but it has now been established that only ionic liquids that have a melting point below melting point of water are ionic liquids and their physicochemical properties are much different from molten salts, which have high viscosity, high melting points, and are highly corrosive (Zhao and Malhotra 2002) (Fig. 1.1).

There is a huge number of cations and anions that can, in different combinations, form ionic salts. Generally, an organic cation and a polyatomic inorganic anion form ionic liquids, but not all combinations result in ionic liquids with desirable solvent properties. It requires a lot of computational work before actually synthesizing an ionic liquid that fits the definition of a sustainable solvent (Peach and Beilstein 2014) (Fig. 1.2).

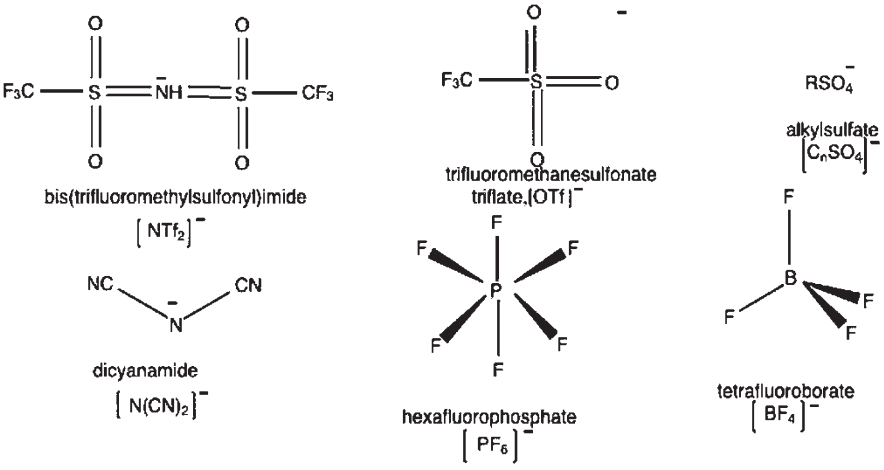


**Fig. 1.1** Some commonly used anions in ionic liquids

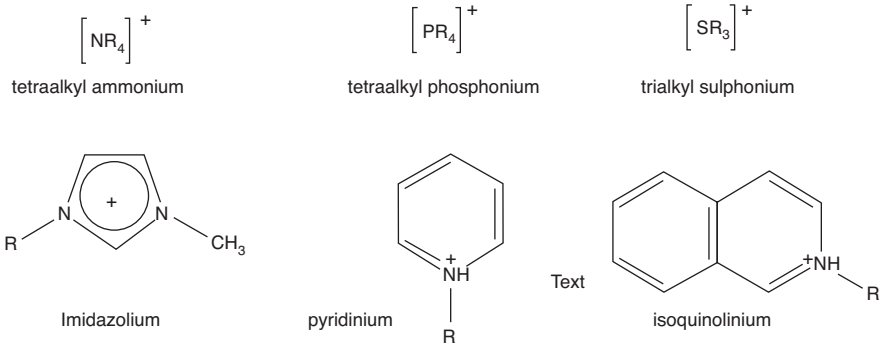


**Fig. 1.2** Some commonly used cations in ionic liquids

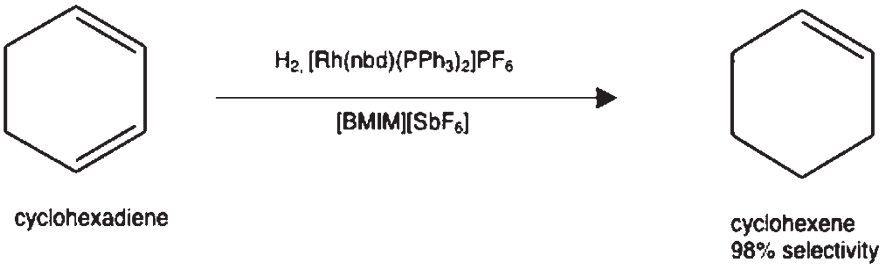


**Fig. 1.3** Catalytic hydrogenation of cyclohexadiene to cyclohexene

## 3 Ionic Liquids as Green Solvents in Catalysis

Ionic liquids exhibit all those properties that make them potential candidates for a solvent in a sustainable homogeneous catalytic reaction (Fig. 1.3).

- They have no vapor pressure so can be easily contained,
- They can dissolve many organic, inorganic, and organometallic compounds along with some gases including $H_2$ and $O_2$, which makes catalytic hydrogenation and aerobic oxidation easy in ionic liquids.
- They generally have thermal stability of around 300 °C which is remarkable.
- By carefully choosing cations and anions, we can alter the polarity of ionic liquids as solvents.
- They can be immiscible in organic solvents or water and hence can be used is biphasic reactions.
- The cation in the solvent can also act as intermediate in certain reactions.
- Some protic ionic liquids are super acidic yet handled easily as compared to other acids (Sheldon 2001).

## 3.1 Hydrogenation

The first-time catalytic hydrogenation in ionic liquids as a solvent was carried out by Chauvin et al. in 1995. They took [Rh nbd($Ph_3P)_{2]}PF_6$] complex as the catalyst in 1-n-butyl-3-methylimidazolium

as ionic liquid for catalytic hydrogenation of 1-pentene. The rate of reaction was five times higher than in acetone (Chauvin et al. 1996).

The group further subjected compounds like cyclohexadiene to cyclohexene and achieved remarkable selectivity (Chauvin et al. 1996). Other than alkenes and cycloalkenes, they also hydrogenated sorbic acid to S9(cis-3-hexenoic acid) in Ruthenium complex catalyzed reaction (Steines et al. 2000). Ever since, considerable amount of research has been done on hydrogenation in ionic liquids through transition metal catalysis (Wasserscheid and Welton 2002) (Fig. 1.4).

## 3.2 Oxidation Reactions

The study of oxidation reactions in ionic liquids is a relatively new field in organic synthesis. One of the earliest catalytic oxidations was reported in 2000 by Song and Roh. The reaction was carried out in [BMIM][PF6] with Mn complex as catalyst. It is an epoxidation reaction with NaOCl that gives 86% yield (Song and Roh 2000). Since then, it is an ongoing field of research in an attempt to adopt greener alternatives to reactions that take place on industrial scale. A very recent attempt was made to convert glucose into 5-hydroxymethylfurfural through Lewis acid catalyzed oxidation in 1-ethyl-3-methylimidazolium bromide (EMIMBr) as ionic liquid solvent (Hou et al. 2019) (Figs. 1.5 and 1.6).

## 3.3 Hydroformylation

Hydroformylation of olefins through homogenous catalysis in ionic liquids has been an area of interest since as early as 1972 when along with successful hydrogenation, isomerization and carboalkoxylation of different olefins, hydroformylation of 1-octene was carried out, and the results were absolutely selective (Parshall 1972). One of the recent examples of hydroformylation in ionic liquids is the one-pot

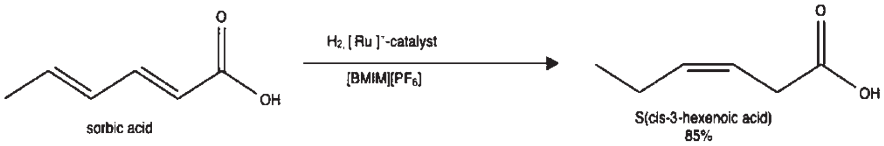


**Fig. 1.4** Stereoselective hydrogenation of sorbic acid to S(cis-3-hexenoic acid)

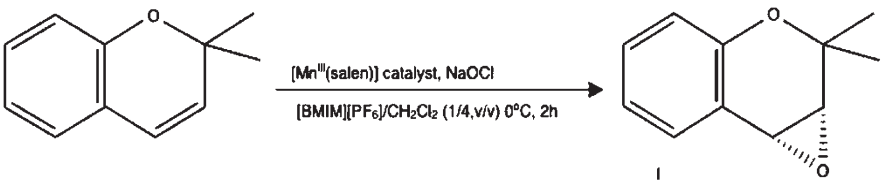


**Fig. 1.5** Catalytic epoxidation

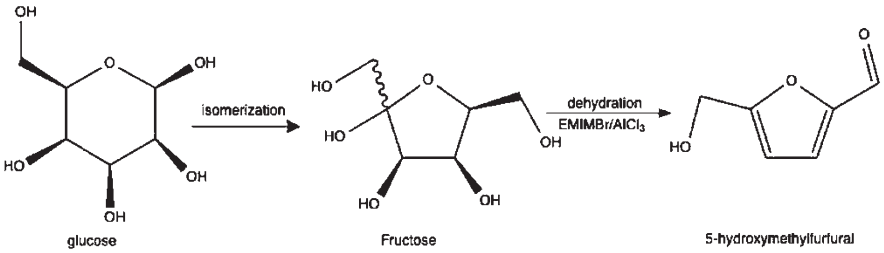


**Fig. 1.6** Conversion of glucose to 5-hydroxymethylfurfural in an ionic liquid

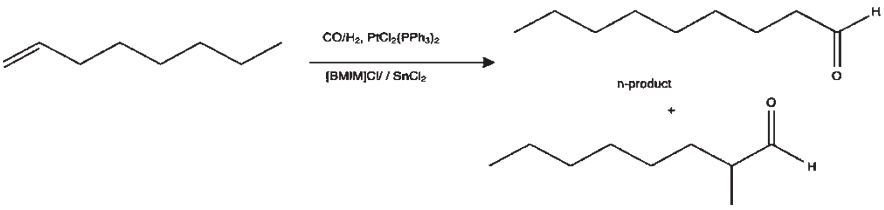


**Fig. 1.7** Hydroformylation of 1-octene in ionic liquid

hydroformylation-acetalization of olefins that was carried out in diphenyl phosphonium-based ionic liquids with recyclable Rh-catalytic systems. The reactions gave an yield of between 90 and 99% (Wang et al. 2017) (Figs. 1.7 and 1.8).

## *3.4 Coupling Reactions*

### 3.4.1 Hecks Coupling Reaction

Along with being a green alternative to the conventional organic solvents in Hecks reactions, ionic liquids also solve the issue of catalyst instability (Bellina and Chiappe 2010). The first reported Hecks reaction was in 1996. Aryl halide was treated with butyl acrylate in tetraalkylammonium and phosphonium salts as

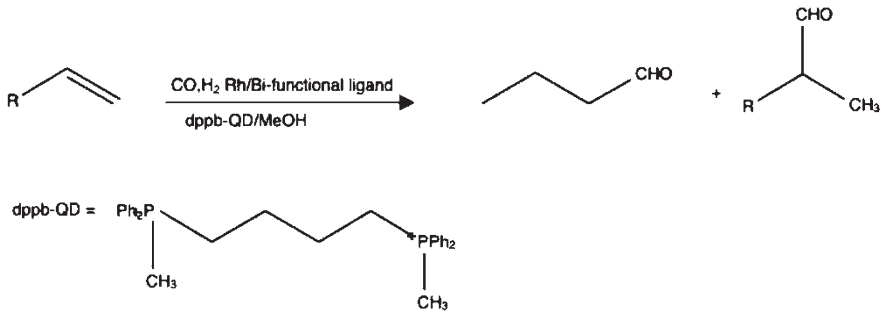


**Fig. 1.8** Hydroformylation of alkenes

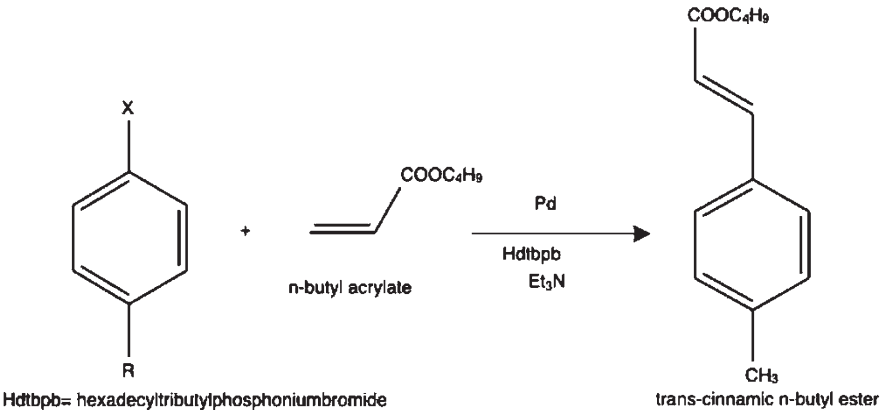


**Fig. 1.9** Heck's coupling reaction between an aryl halide and n-butyl acrylate

solvent and gave good yields of trans cinnamic n-butyl esters. The catalyst system was stable enough to run multiple reactions (Kaufmann et al. 1996).

Moving one step forward in a number of reactions in ionic liquids, Pd complexes catalyst were replaced by Pd metal nanoparticles (Prechtl et al. 2010) (Fig. 1.9).

### 3.4.2 Suzuki Coupling Reaction

Suzuki coupling reactions have also been carried out in ionic liquids. The reaction of an aryl halide with aryl boronic acid using Pd(PPh3)4 as catalyst in ionic liquid[BMIM][BF4] gave improved yields; the formation of homo-coupling products were suppressed. The catalyst in the ionic layer will be easily recycled after removal of the product. The catalytic mixture is so stable that it can catalyze three to four further reactions without any change in stability (Mathews et al. 2000).

### 3.4.3 Stille Coupling Reactions

Another example of Pd catalyzed coupling reaction in [BMIM][BF4]. The reaction between alpha-iodenones and vinyl and aryl stannanes was reported to give improved yield and catalyst recovery of the product, although the reaction rate was slower (Handy and Zhang 2001) (Fig. 1.10).

### 3.4.4 Negishi Coupling Reaction

Negishi coupling reaction was carried out in [BMIM][BF4] /toluene biphasic solvent system in presence of a Pd catalyst between an organozinc compound and 3-Iodo-2-cyclohexene-1-one to give

3-substituted-cyclohexeneone in 90% yield. The catalyst could be recycled following the reaction, but after third cycle, only 20% yield was obtained, and reaction was slower (Sirieix et al. 2000) (Fig. 1.11).

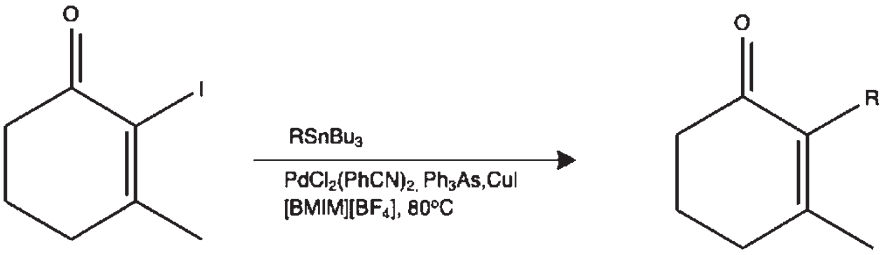


**Fig. 1.10** Stille coupling of iodinones an alkyl stannanes

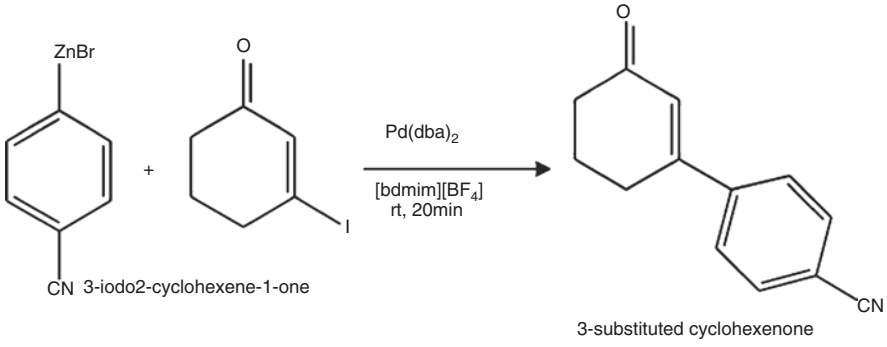


**Fig. 1.11** Negishi coupling reaction

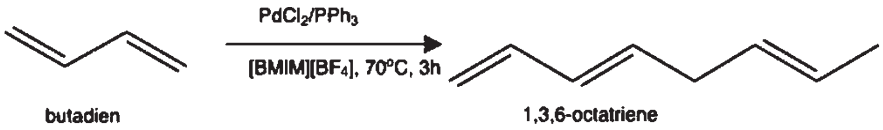


**Fig. 1.12** Dimerization of butadiene

## *3.5 Dimerization in Ionic Liquids*

In dimerization reactions, chloroaluminate-free ionic liquids are preferred because of the moisture-sensitive nature of chloroaluminate ionic liquids. One example of dimerization reaction in [BMIM][BF4] in a biphasic system using Pd catalyst is dimerization of 1,3-butadiene into 1,3,6-octatriene with 100% selectivity. The catalyst system is easily recovered and recycled several times (Silva et al. 1998) (Fig. 1.12).

## *3.6 Diels–Alder Reaction*

Diels–Alder reactions are one of the most important reactions in Carbon–Carbon bond formation. Being addition reactions, these are highly atom efficient. One concern about Diels–Alder reaction products is that they are a mixture of isomers. Therefore, research has been going on to develop new methodologies to give selectively one product of a Diels–Alder reaction (Aggarwal et al. 2002).

Ionic liquids were used as a solvent in Diels–Alder reactions for the first time in 1989. Cyclopentadiene was treated with methyl acrylate and methyl vinyl ketone in ethylammonium nitrate as the solvent. The endo product was favored in this reaction (Jaeger and Tucker 1989).

In another attempt, the rate and selectivity of Diels–Alder reaction between cyclopentadiene and ethyl acrylate was recorded in three different solvents. Water, lithium perchlorate in diethyl ether, and an ionic liquid [BMIM][PF6] were used as solvents. The rate of reaction in ionic liquids was similar to that of water but lower than in lithium perchlorate in diethyl ether while the selectivity was higher than water but similar to that in lithium perchlorate in diethyl ether. The main benefit of the ionic liquid was its ease of recycling, minimal vapor pressure, and thermal stability which makes this reaction applicable on industrial scale (Earle et al. 1999) (Fig. 1.13).

## *3.7 Nucleophilic Substitution Reactions*

Nucleophilic substitution reactions generally take place in polar aprotic organic solvents which are soluble in water and have high boiling points, so separation of organic product is very difficult in such reaction. To solve this problem, the solvent

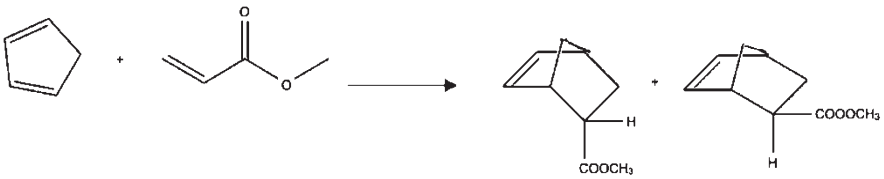


**Fig. 1.13** Cycloaddition of cyclopentadiene and methyl acrylate

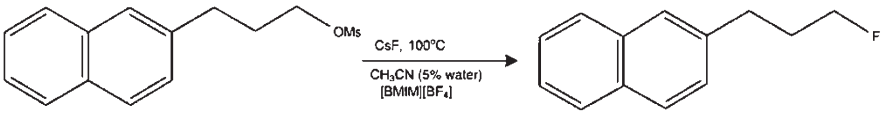


**Fig. 1.14** Nucleophilic fluorination of mesyl alkane

was replaced with an ionic liquid [BMIM][BF6]. In a reaction, nucleophilic fluorination of a mesyl alkane by a series of alkali metals was carried out to optimize the best possible yield of the product fluoro alkane. The best yield was obtained with CsF which was 95%. The ionic liquid along with the increase in reaction efficiency also reduces the chance of other byproducts (Kim et al. 2003) (Fig. 1.14).

## *3.8 Friedel–Crafts Reaction*

### 3.8.1 Alkylations

Friedel–Craft alkylation reactions are of significance in both academia and industries for making C–C bonds. The reaction takes place in the presence of a Lewis or Bronsted Acid. Despite its wide range of applications, the results are not so easy to achieve as there are challenges of isomerization, rearrangements, and other reactions between the reactants and products. In order to minimize these side reactions and improve the yield of the product, ionic liquids have been considered in many experiments (Wasserscheid and Welton 2002) (She et al. 2004).

A sulfonyl containing Bronsted acid ionic liquid was optimized as the catalyst in a solvent-free reaction between indoles and cyclic ketones to result in a series of C3-cyclicindoles. The reaction is of importance in many aspects. It is green as it is solvent free, recyclable catalyst, gives about 92% yield, and the product indoles are a class of medicinally important compounds (Taheri et al. 2015) (Fig. 1.15).

### 3.8.2 Acylations

Just the way alkylation reactions are very useful but have certain challenges in getting to the product, Friedel–Craft acylations are also very useful specially in the synthesis of some aromatic ketones, but the product is quite unstable and can form

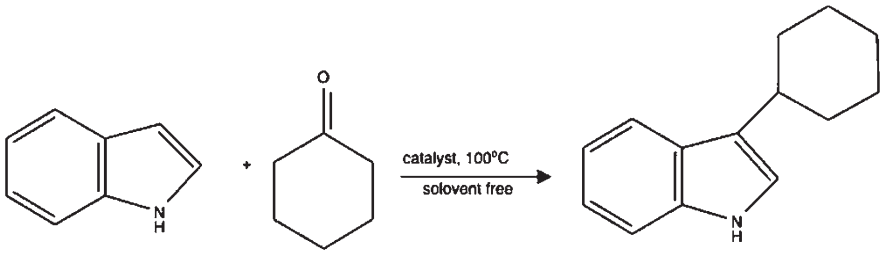


**Fig. 1.15** Friedel–Craft alkylation of indole with cyclohexanone

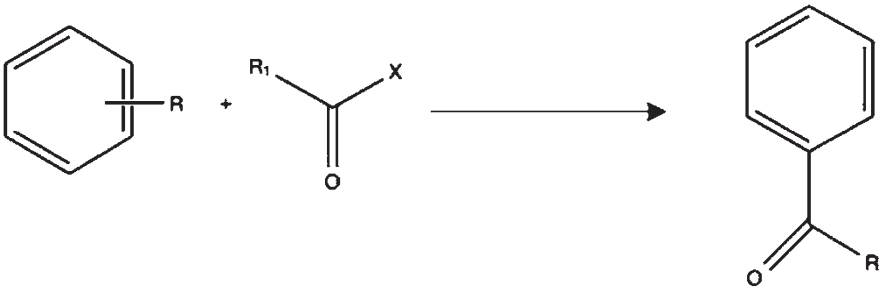


**Fig. 1.16** Friedel–Craft acylation of aromatic compound with benzoyl halide

complexes with the Lewis/Bronsted acid catalyst a lot of unwanted products form. To combat these issues with a greener approach, an ionic liquid [BMI][BF6] as solvent and Bismuth triflate as the catalyst is dissolved in the ionic liquids. Upon acylation of aromatic compounds with Benzoyl chloride that gave best results with acylation, study was carried out under microwave irradiation. The results were in good yield and the catalytic system was recycled and stayed stable for up to five cycles (Tran et al. 2012) (Fig. 1.16).

### 3.8.3 Sulfonylation

Another attempt of an ecofriendly Friedel–Craft sulfonylation reaction was made using the ionic liquid [BMIM][AlCl4] both as a solvent and a Lewis Acid catalyst. Benzene and its derivatives were treated with 4-methyl benzenesulfonyl Chloride to give diaryl sulfones in very good yield (Nara et al. 2001) (Fig. 1.17).

## *3.9 Biocatalysis*

Like all other reactions, applications of ionic liquids are also being investigated in bio catalysis. Ionic liquids can be used in different ways. They can be the main solvent, a co-solvent in aqueous systems or in a biphasic system. The biocatalyst that

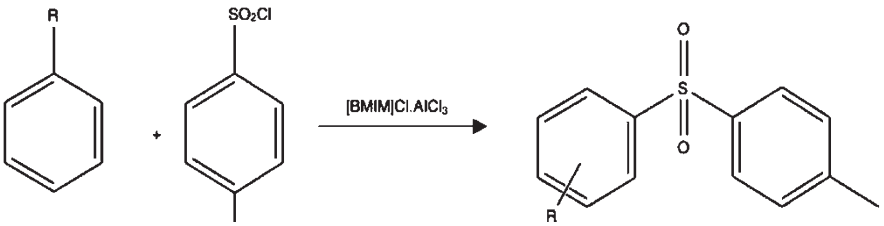


**Fig. 1.17** Friedel–Craft sulfonylation

is most studied is lipase. Lipase is used for the resolution of different enantiomers. Its activity has been compared in ionic liquids and organic solvents, and in some cases, lipase has been proven more active in ionic liquids, for example, trans esterification of alcohols in [BMIM][$BF_4$] and [BMIM][$PF_6$] (Lozano et al. 2001).

## 4 Ionic Liquids in Chemical Industries

A number of industries in an attempt to adopt greener alternatives have limited their use of organic solvents and moved to ionic liquids.

BASF has replaced phosgene with Hydrogen Chloride dissolved in an ionic liquid in reaction where 1,4-butanediol reacts with $COCl_2$ to give 1,4-dichlorobutane. When phosgene was replaced with hydrogen chloride, it gave a mixture of four products, where the desired product was a minor one while the hydrogen chloride dissolved in ionic liquid obtained 98% selective yield of 1,4-dichloro butane (Plechkovaa and Seddon 2008).

Eastman Chemical Company has also patents for different isomerization reactions in ionic liquids (Monnier and Muehlbauer 1990).

ExxonMobil has also a number of patents for carbonylation catalysis in Lewis acid ionic liquids (Saleh 2000).

## 5 Ionic Liquids in Pharmaceutical Industries

Industrial synthesis of pharmaceutical products involves organic solvents. At the end of the reactions, there are traces of the solvents present in the final products. These traces are called the 'residual solvent', which should be below a specific concentration in order to register the product for human use.

These solvents even in traces are a serious threat to human health. Considering the importance of an alternative to these solvents, ionic liquids are of serious importance. The attempts made by pharmaceutical industries are mostly laboratory scale, which can potentially be successful drugs to be upscaled to reach the market (Siódmiak et al. 2012).

### *5.1 Synthesis of Nucleoside-Based Antiviral Drugs*

Three of the nucleoside-based antiviral drugs already in the market, Stavudine, Brivudine, and Trifluridine, have been synthesized in ionic liquids. They are industrially synthesized in organic solvents and it requires tedious procedures to remove the traces of these solvents from the final product. Therefore, the ionic liquids have been tried as alternate solvents, and the results were far improved.

Three different ionic liquids 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]), 1-methoxyethyl-3-methylimidazolium trifluoroacetate ([MoeMIm][TFA]), and 1-butyl-3-3methylimidazolium trifluoroacetate ([BMIm][TFA]) are used as solvents of the main steps in the drug synthesis. The reaction rates were far higher, and the solvent consumption much less in all three cases (Kumar and Malhotra 2008).

**Synthesis of Non-steroidal Anti-inflammatory Drugs**
Synthesis of Pravadoline has been carried out in an ionic liquid in a two-step procedure, that is Friedel–Craft reaction and nucleophilic substitution reaction. The reaction does not require any anhydrous condition and is catalyst free. After using a set of ionic liquids as solvents, the reaction was optimized at 99% yield of the alkylated product in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ([BMIM][$PF_6$]) (Earle et al. 2000).

**Resolution of (*R*,S) Ibuprofen**
Ionic liquids play a very important role in the resolution of (*R,S*) Ibuprofen. A two-phase solvent system of [BMIM][$PF_6$] and isooctane were used to resolve the racemic mixture to an enantiopure product with the help of a lipase enzyme (Contesini and Carvalho 2006).

**Synthesis of Potential Anticancer Drugs**
Ionic liquids have also been used as a solvent in the synthesis of a class of compounds that possess anti-tumor activity. 1-buty-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIM][$NTf_2$]) was used as the ionic liquid solvent, and a series of caffeic acid phenethyl esters (CAPE) derivatives were synthesized using Candida Antarctica lipase B (Novozyme 435). The yield using ionic liquid was 91%, as compared to 65% in organic solvent isooctane (Kurata et al. 2010a).

## 6 Conclusion

In the context of developing sustainable chemical processes, the study of solvents and their role is of central importance. To make the whole process greener, alternate solvents need to be developed. In this quest, ionic liquids have come up as potential candidates due to their minimal vapor pressure, immiscibility in organic solvents, ease of recycling, and recovery of product. In this chapter, we went through how

ionic liquids can replace conventional toxic media for chemical process. The examples studied in this chapter are just a few of the numerous reactions that are being studied daily and are in process of reaching industries; their benefits can make an impact on a higher scale. Different chemical and pharmaceutical industries have already started using ionic liquids in their procedures to acquire sustainability. One main hurdle in adopting ionic liquids is its cost. More research needs to be done to come up with evidences that prove ionic liquids economical over organic solvents.

## References

Aggarwal A, Lancaster NL, Sethi AR, Welton T. The role of hydrogen bonding in controlling the selectivity of Diels–Alder reactions in room-temperature ionic liquids. Green Chem. 2002;4:517–20. https://doi.org/10.1039/B206472C.

Anastas P, Eghbali N. Green chemistry:principle and practice. Chem Soc Rev. 2010;39:301–12. https://doi.org/10.1039/B918763B.

Beckman EJ. Supercritical and near-critical CO2 in green chemical synthesis and processing. J Supercrit Fluids. 2004;28(2–3):121–91. https://doi.org/10.1016/S0896-8446(03)00029-9.

Bellina F, Chiappe C. The Heck reaction in ionic liquids: progress and challenges. Molecules. 2010;15(4):2211–45. https://doi.org/10.3390/molecules15042211.

Breno KL, Ahmed TJ, Pluth MD, Balzarek C, Tyler DR. Organometallic chemistry in aqueous solution: reactions catalyzed by water-soluble molybdocenes. Coord Chem Rev. 2006;250(9–10):1141–51. https://doi.org/10.1016/j.ccr.2005.12.001.

Casalnuovo AL, Calabrese JC. Palladium-catalyzed alkylations in aqueous media. J Am Chem Soc. 1990;112(11):4324–30. https://doi.org/10.1021/ja00167a032.

Chauvin Y, Mussmann L, Olivier H. A novel class of versatile solvents for two-phase catalysis: hydrogenation, isomerization, and hydroformylation of alkenes catalyzed by rhodium complexes in liquid 1,3-dialkylimidazolium salts. Angew Chem Int Ed Engl. 1996;34(23–24):2698–700. https://doi.org/10.1002/anie.199526981.

Contesini FJ, Carvalho PDO. Esterification of (RS)-ibuprofen by native and commercial lipases in a two-phase system containing ionic liquids. Tetrahedron Asymmetry. 2006;17(14):2069–73. https://doi.org/10.1016/j.tetasy.2006.07.020.

Curzons AD, Constable DC, Cunningham VL. Solvent selection guide: a guide to the integration of environmental, health and safety criteria into the selection of solvents. Clean Prod Process. 1999;1:82–90.

Earle MJ, McCormac PB, Seddon KR. Diels–Alder reactions in ionic liquids. A safe recyclable alternative to lithium perchlorate–diethyl ether mixtures. Green Chem. 1999;1:23–5. https://doi.org/10.1039/A808052F.

Earle MJ, McCormac PB, Seddon KR. The first high yield green route to a pharmaceutical in a room temperature ionic liquid. Green Chem. 2000;2(6):261–2. https://doi.org/10.1039/B006612P.

Grieco PA, Brandes EB, McCann S, Clark JD. Water as a solvent for the Claisen rearrangement: practical implications for synthetic organic chemistry. Org Chem. 1989;54(25):5849–51. https://doi.org/10.1021/jo00286a010.

Handy ST, Zhang X. Organic synthesis in ionic liquids: the Stille coupling. Org Lett. 2001;3(2):233–6. https://doi.org/10.1021/ol0068849.

Hou Q, Zhen M, Li W, Liu L, Liu J, Zhang S, et al. Efficient catalytic conversion of glucose into 5-hydroxymethylfurfural by aluminum oxide in ionic liquid. Appl Catal B Environ. 2019;353:1–10. https://doi.org/10.1016/j.apcatb.2019.04.003.

Jaeger DA, Tucker CE. Diels-Alder reactions in ethylammonium nitrate, a low-melting fused salt. Tetrahedron Lett. 1989;30(14):1785–8. https://doi.org/10.1016/S0040-4039(00)99579-0.
Kaufmann DE, Nouroozian M, Henze H. Molten salts as an efficient medium for palladium catalyzed C-C coupling reactions. Synlett. 1996;11:1091–2. https://doi.org/10.1055/s-1996-5658.
Khatik GL, Kumar R, Chakraborti AK. Catalyst-free conjugated addition of thiols to α,β-unsaturated carbonyl compounds in water. Org Lett. 2006;8(11):2433–6. https://doi.org/10.1021/ol060846t.
Kim DW, Song CE, Chi CY. Significantly enhanced reactivities of the nucleophilic substitution reactions in ionic liquid. J Organomet Chem. 2003;68(11):4281–5. https://doi.org/10.1021/jo034109b.
Klijn JE, Engberts JBFN. Fast reactions "on water". Nature. 2005;435:46–7. https://doi.org/10.1038/435746a.
Kolb HC, Finn MG, Sharpless KB. Click chemistry: diverse chemical function from a few good reactions. Angew Chem. 2001;40(11):2001–21.
Kumar V, Malhotra SV. Synthesis of nucleoside-based antiviral drugs in ionic liquids. Bioorg Med Chem Lett. 2008;18(20):640–2. https://doi.org/10.1016/j.bmcl.2008.08.090.
Kurata A, Kitamura Y, Irie S, Takemoto S, Akai Y, Hirota Y, et al. Enzymatic synthesis of caffeic acid phenethyl ester analogues in ionic liquid. J Biotechnol. 2010a;148(2–3):133–8. https://doi.org/10.1016/j.jbiotec.2010.05.007.
Li CJ, Trost BM. Green chemistry for chemical synthesis. PNAS. 2008;105(36):13197–202. https://doi.org/10.1073/pnas.0804348105.
Trost BM. The atom economy—a search for synthetic efficiency. Science. 1991;254(5037):1471–7. https://doi.org/10.1126/science.1962206.
Ritleng V, Sirlin C, Pfeffer M. Ru-, Rh-, and Pd-catalyzed C−C bond formation involving C−H activation and addition on unsaturated substrates: reactions and mechanistic aspects. Chem Rev. 2002;102:1731–69. https://doi.org/10.1021/cr0104330.
Wong CH. Enzymatic catalysts in organic synthesis. Science. 1989;244(4909):1145–52. https://doi.org/10.1126/science.265805.
Sheldon RA. Green solvents for sustainable organic synthesis: state of the art. Green Chem. 2005;7:267–78. https://doi.org/10.1039/B418069K.
Rideout DC, Breslow R. Hydrophobic acceleration of Diels-Alder reactions. J Am Chem Soc. 1980;102:7816–7. https://doi.org/10.1021/ja00546a0.
Ros TD, Prato M, Novello F, Maggini M, Banf E. Easy access to water-soluble fullerene derivatives via 1,3-dipolar cycloadditions of Azomethine Ylides to C60. J Org Chem. 1996;61(25):9070–2. https://doi.org/10.1021/jo961522t.
Li CJ, Chen L. Organic chemistry in water. Chem Soc Rev. 2006;35:68–82. https://doi.org/10.1039/B507207G.
Peach J, Beilstein EJ. Supercritical carbon dioxide: a solvent like no other. J Organomet Chem. 2014;10:1878–95. https://doi.org/10.3762/bjoc.10.196.
Welton T. Ionic liquids: a brief history. Biophys Rev. 2018;10(3):691–706.
Wasserscheid P, Welton T. Ionic liquids in synthesis. Weinheim: Wiley-VCH; 2002.
Zhao H, Malhotra SV. Applications of ionic liquids in organic synthesis. Adrichimica Acta. 2002;35(3):75–83.
Sheldon R. Catalytic reactions in ionic liquids. Chem Commun. 2001:2399–407. https://doi.org/10.1039/B107270F.
Steines S, Wasserscheid P, Drießen-Hölscher B. An ionic liquid as catalyst medium for stereoselective hydrogenations of sorbic acid with ruthenium complexes. Angew Chem. 2000;342(4):348–54. https://doi.org/10.1002/(SICI)1521-3897(200004)342:4%3C348::AID-PRAC348%3E3.0.CO;2-6.
Song CE, Roh EJ. Practical method to recycle a chiral (salen)Mn epoxidation catalyst by using an ionic liquid. Chem Commun. 2000;10:837–8. https://doi.org/10.1039/B001403F.
Parshall GW. Catalysis in molten salt media. J Am Chem Soc. 1972;94(25):8716–9. https://doi.org/10.1021/ja00780a013.

Wang P, Chen X, Wang DL, Li YQ, Liu Y. Efficient and recyclable Rh-catalytic system with involvement of phosphine-functionalized phosphonium-based ionic liquids for tandem hydroformylation-acetalization. Green Energy Environ. 2017;2:419–27. https://doi.org/10.1016/j.gee.2017.01.003.

Prechtl MHG, Scholten JD, Dupont J. Carbon-carbon cross coupling reactions in ionic liquids catalysed by palladium metal nanoparticles. Molecules. 2010;15(5):3441–61. https://doi.org/10.3390/molecules15053441.

Mathews CJ, Smith PJ, Welton T. Palladium catalysed Suzuki cross-coupling reactions in ambient temperature ionic liquids. Chem Commun. 2000:249–1250. https://doi.org/10.1039/B002755N.

Sirieix J, Oßberger M, Betzemeier B, Knochel P. Palladium catalyzed cross-couplings of organozincs in ionic liquids. Synlett. 2000;11:1613–5.

Silva MS, Suarez PAZ, de Souza RF, Dupont J. Selective linear dimerization of 1,3-butadiene by palladium compounds immobilized into 1-n-butyl-3-methyl imidazolium ionic liquids. Polym Bull. 1998;40(4–5):401–5. https://doi.org/10.1007/s002890050.

She HY, Judeh ZMA, Ching CB, Xia QH. Comparative studies on alkylation of phenol with tert-butyl alcohol in the presence of liquid or solid acid catalysts in ionic liquids. J Mol Catal A Chem. 2004;212(1–2):301–8. https://doi.org/10.1016/j.molcata.2003.11.007.

Taheri A, Lai B, Cheng C, Gu Y. Brønsted acid ionic liquid-catalyzed reductive Friedel-Crafts alkylation of indoles and cyclic ketones without using external reductant. Green Chem. 2015;17(2):812–6. https://doi.org/10.1039/C4GC01299B.

Tran PH, Duus F, Le TN. Friedel–crafts acylation using bismuth triflate in [BMI][PF6]. Tetrahedron Lett. 2012;53(2):222–4. https://doi.org/10.1016/j.tetlet.2011.11.022.

Nara SJ, Harjani JR, Salunkhe MM. Friedel-crafts sulfonylation in 1-butyl-3-methylimidazolium chloroaluminate ionic liquids. J Organomet Chem. 2001;66(25):8616–20. https://doi.org/10.1021/jo016126b.

Lozano P, Diego T, Guegan PJ, Vaultier M, Iborra JL. Stabilization of α-chymotrypsin by ionic liquids in transesterification reactions. Biotechnol Bioeng. 2001;75(5):563–9. https://doi.org/10.1002/bit.10089.

Plechkovaa NV, Seddon KR. Applications of ionic liquids in the chemical industry. Chem Soc Rev. 2008;37:123–50. https://doi.org/10.1039/B006677J.

Monnier JR, Muehlbauer PJ Selective monoepoxidation of olefins. US Pat 4,897,498. 1990

Saleh YR Preparation of aromatic aldehydes from alkylaromatics and carbon monoxide in the presence of acidic ionic liquids. World Pat 15594. 2000

Siódmiak T, Marsza MP, Proszowska A. Ionic liquids: a new strategy in pharmaceutical synthesis. Mini-Rev Org Chem. 2012;9(2):203–8. https://doi.org/10.2174/157019312800604698.

Kurata A, Kitamura Y, Irie S, Takemoto S, Akai Y, Hirota Y, et al. Enzymatic synthesis of caffeic acid phenethyl ester analogues in ionic liquid. J Biotechnol. 2010b;148(2–3):133–8. https://doi.org/10.1016/j.jbiotec.2010.05.007.

# Industrial Applications of Green Solvents in Organic and Drug Synthesis for Sustainable Development of Chemical Process and Technologies

**Clement Osei Akoto**

## Contents



## Abbreviations

| | |
|---|---|
| $AgNO_3$ | Silver nitrate |
| API | Active pharmaceutical ingredient |
| C18-OPC | 1-Octadecyl-5-oxopyrrolidine-3-carboxylic acid |
| COMU | 1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCC | N,N′-Dicyclohexylcarbodiimide |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DMTMM | (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride |
| EDCl | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_2

| | |
|---|---|
| ee | Enantiomeric excess |
| Fe | Iron |
| GSK | GlaxoSmithKline |
| $H_2O_2$ | Hydrogen peroxide |
| HATU | Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium |
| HCl | Hydrochloric acid |
| HOBt | Hydroxybenzotriazole |
| HPA | Heteropolyacid |
| Kg | Kilogram |
| MCR | Multicomponent reaction |
| MIC | Minimum inhibitory concentration |
| MPEG | Methoxy poly (ethylene glycol) |
| MT | Metric tons |
| MWI | Microwave irradiation |
| NaCl | Sodium chloride |
| NMM | N-methylmorpholine |
| NMP | N-Methyl-2-pyrrolidone |
| NPs | Nanoparticles |
| Pd | Palladium |
| $Pd(dtbpf)Cl_2$ | 1,1′-Bis(di-tert-butylphosphino)ferrocene palladium |
| PDE | Phosphodiesterase |
| $S_NAr$ | Nucleophilic aromatic substitution |
| TBAB | Tetrabutylammonium bromide |
| THF | Tetrahydrofuran |
| TPGS | Tocopheryl Polyethylene Glycol Succinate |
| US | Ultrasound |

## 1 Introduction

Human beings are at the centre of concerns for sustainable development. They are entitled to a healthy and productive life in harmony with nature (United Nations Conference 1992). The above quotation is the first of the 27 principles of the Rio Declaration on Environment and Development by the United Nations. This first principle highlight the challenge for mankind to define the objectives of sustainable development, as well as to provide scientific, technological, and social tools to achieve those objectives. The demand for environmentally friendly chemical processes, efficient methods of synthesis, atom-economical syntheses, multicomponent reactions, and usage of environmentally benign solvents requires the development of novel and cost-effective approaches globally to control and prevent pollution and environmental degradation. Green chemistry is one of the most attractive concepts in chemistry for sustainability, which involves the use of a set of principles that prevents or reduces the use and or generation of hazardous chemicals and solvents

in the design, synthesis, and applications of chemical products (Anastas and Warner 1998). The green chemistry approach strives to achieve sustainability at the molecular level, hence its application to all industry sectors ranging from cosmetic, aerospace, automobile, electronics, energy, healthcare, household products, medical devices, chelating agents, pharmaceutical, to agriculture (Anastas and Eghbali 2010). Green chemistry is a multidisciplinary field and covers areas such as greener synthetic pathways, which include natural processes including fermentation and biomimetic syntheses; usage of innocuous and renewable feedstocks; atom-economical syntheses; multicomponent reactions (MCRs); and convergent syntheses (Trost 1991; Sheldon 2017). Green chemistry also involves elimination or replacement of hazardous solvents with greener solvents like water, novel processing methods, elimination or improved usage of energy, and cost-effective separations and purifications (Sheldon 2017; Noce 2018; Blakemore et al. 2018). Green chemistry also encompass designing greener chemicals that are environmentally benign, less pollutant or toxic than current alternatives; chemicals recyclable or biodegradable after use; chemicals that are safer and less prone to accident; and chemicals safer for the atmosphere that do not cause ozone depletion or formation of smog (Sheldon 2017; Sherwood et al. 2019).

The excessive use of organic solvents in the organic synthesis of drug candidates by the industrial and manufacturing processes has resulted in an uncontrolled rise in toxicity, hazard, pollution, and waste treatment issues (Lipshutz et al. 2016). Large usage of solvents by the manufacturing processes and chemical synthesis accounts for the major source of wasted mass (Constable et al. 2002). The manufacturing and pharmaceutical industries are identified as major sources of chemical waste (Abou-Shehada et al. 2016). The annual industrial-scale production of organic solvents has been estimated at almost 20 million MT (metric tons) (Clark et al. 2015). A life cycle study of waste produced from GlaxoSmithKline (GSK) Active Pharmaceutical Ingredient (API) manufacturing facilities, reported that 80% of their waste is solvent-related (Jiménez-González et al. 2004; Curzons et al. 2007). This high proportion of solvent waste, assuming similar situation pertains at other pharmaceutical companies is environmentally detrimental, too costly, untenable, and an outstanding example of unsustainable practices. Green chemistry could address this problem, from the environmental perspective, by switching to alternative greener reaction media (such as selection, use, recovery, and disposal of solvents), and in particular water, for following nature's lead.

This review has a couple of objectives: showcasing representative examples such as reactions that can be conducted in water, multicomponent reactions (MCRs) in (atom-economical syntheses, mild conditions, efficiency, and high convergence rate) water, and green chemistry and synthetic pathways in the synthesis of drug candidates and compounds in micellar water. Such a greener practice of using water as a solvent can lead to enormous sustainability benefits which will enhance the overall environmental impact of green chemistry. This review has focused on greener chemistry in water without tackling other solvents, like "neoteric" solvents such as ionic liquids, supercritical-fluid, and fluorous phase solvent systems.

Sheldon (2017) and Ashcroft et al. (2015) have current reviews on the application of "neoteric" solvents.

## 2 Water as Greener Solvent in Organic and Drug Synthesis

Organic solvents constitute the bulk of chemicals used in chemical reactions and pharmaceutical industries. This is a global environmental challenge as a result of pollution impact, rising toxicity, hazard, and waste treatment issues. The use of water as a solvent in organic synthesis for achieving enhanced sustainability, non-toxicity, and safety reasons have been in the ascendency over the last decades (Sheldon 2017). The use of water as solvent due to its innocuous nature offers a wide range of benefits, such as improving reaction efficiency and selectivity, enabling the recycling of the catalyst, simplifying reaction workup procedures, and allowing mild reaction conditions, renewability, protecting group-free synthesis and wide availability compared with other solvents (Simon and Li 2012).

The pharmaceutical industries and the manufacturing companies are in growing demand for chemical transformations that are novel and environmentally friendly. As a result, researchers from Hunan University have reported the synthesis of quinolin-2-yl substituted urea, using highly atom-economical aqueous organic reaction conditions (Xie et al. 2019). They reported, a one-pot, sequential oxidation of quinolone (**2**) followed by copper-catalyzed ureation reaction in water to produce quinolin-2-yl substituted urea (**1**) in 81% yield (Fig. 2.1). The researchers outline a couple of advantages resulting from their novel synthetic scheme such as (1) the reactions resulted in higher yields with excellent regioselectivity and 100% atom economy; (2) the starting materials being easily accessible; (3) compatibility of functional group was high; (4) the reaction medium was recycled by five consecutive cycles; and (5) the synthesis involves one-pot sequential transformations, being practical with gram-scale synthesis. The synthesis involves simple work up via filtration and washing of the product with alcohol, thus eliminating the extraction of organic solvent which is expensive and tedious.

Prof. Xie and co-workers in 2018 developed an efficient synthesis of allylic sulfones selectively from sulfonic acid moieties in aqueous media without any metal

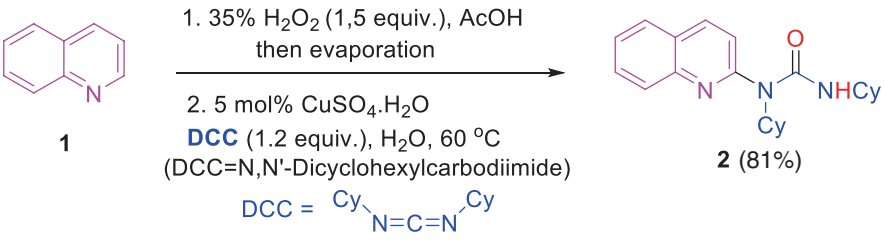



**Fig. 2.1** Novel one-pot large-scale synthesis in water

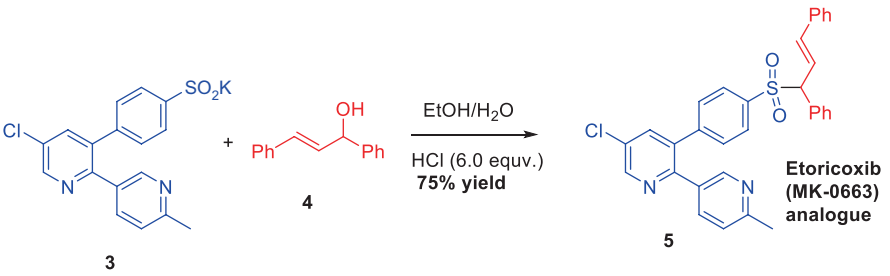


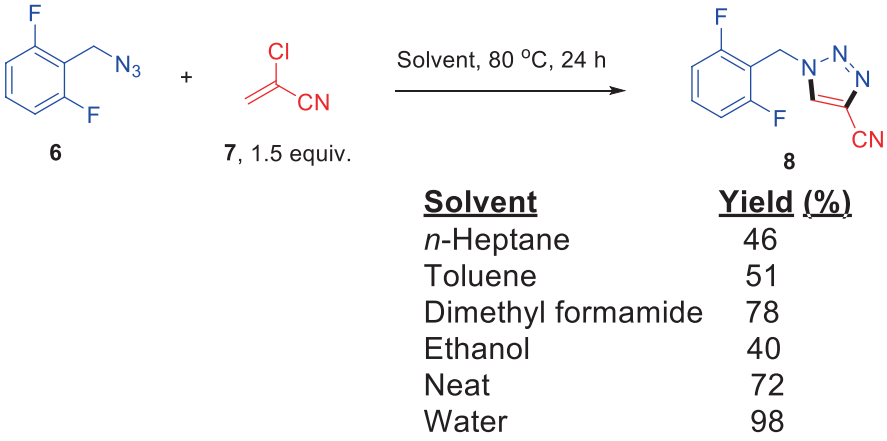

**Fig. 2.2** Preparation of Etoricoxib (MK-0663) analogue **5**

under physiological pH at room temperature (Xie et al. 2018). Theoretically, this protocol offers a greener synthesis of allylic sulfones and also shed light on protein sulfinylation detection, including matrilysin, nitrile hydratase, and Parkinson's disease protein DJ-1 (Lo Conte and Carrol 2012; Lo Conte et al. 2015). They reported that under acidic conditions, the sulfonate (**3**) reacts with allylic alcohol (**4**) to generate Etoricoxib (MK-0663) analogue **5** (Fig. 2.2). The researchers reported that in addition to their methodology for the water-promoted C–S bond synthesis, could serve as the rational drug design concerning cysteine metabolism for pharmacology and biochemistry studies.

The use of water as a greener solvent could potentially eliminate or reduce side reactions as well as improve the reaction yield and acceleration. Researchers at Novartis have applied this concept at industrial level for the synthesis of substituted cyano triazoles (**8**) from 2-chloroacrylonitrile (**7**) and organic azides (**6**), (Fig. 2.3) (Portmann 1998). This synthesis involves a 1,3-dipolar cycloaddition reaction, followed by an aromatization which generates the by-product hydrogen chloride (HCl). The major problem of this reaction is that 2-chloroacrylonitrile polymerizes under both basic and acidic conditions. The HCl released raises the acidity of the reaction mixture, thus favoring the polymerization of the olefin in organic solvents (Fig. 2.3), and this leads to a decrease in the yield of the product. Using water as a solvent has a couple of advantages in this reaction such as (1) water serves as a sustainable alternative and very convenient solvent since it enables the reaction to take place in the organic phase and (2) the HCl generated is solubilized in the aqueous phase, thus resulting in the polymerization of the alkene being minimized.

The use of greener solvent water and the enzyme lipase had been applied in the enzymatic process for the synthesis of the key chiral intermediate in the manufacture of the antihypertensive drug, diltiazem (**12**), developed and commercialized by DSM-Andeno in the 1980s. The reaction was catalyzed by Thermomyces lanuginosus lipase (E.C. 3.1.1.3), also known as lipolase, which involved highly enantioselective hydrolysis of a chiral glycidate ester (**10**) (Fig. 2.4) (Hulshof and Roskam 1989; Sheldon 1996).

Pharmaceutically active compounds and a large number of natural products contain aryl sulfides. Most of the reliable conventional methods available for the synthesis of these biologically important compounds usually required harsh reaction




| Solvent | Yield (%) |
|---|---|
| *n*-Heptane | 46 |
| Toluene | 51 |
| Dimethyl formamide | 78 |
| Ethanol | 40 |
| Neat | 72 |
| Water | 98 |

**Fig. 2.3** The synthesis of triazole in water, the greener solvent

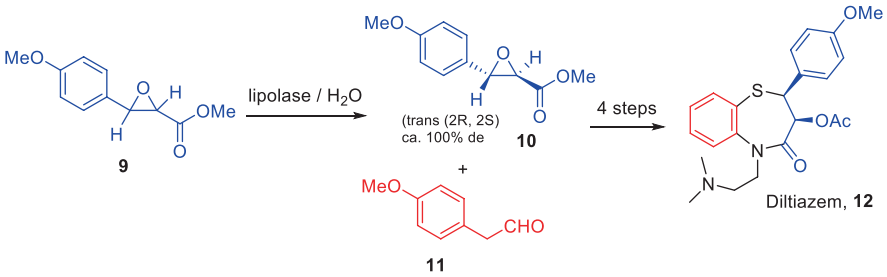



**Fig. 2.4** Enzymatic and aqueous processes for diltiazem **12**, using lipolase

conditions (Ahmad and Iqbal 1986; Meshram et al. 1998; Katritzky et al. 2004; Magens and Plietker 2011). A perfect synergy for eco-compatible synthesis of aryl thio ethers, using metal catalyzed (bulk and/or nano) S-arylation reactions of thiols with aryl halides in water has been described by Prof. G. He and co-workers (He et al. 2013). They synthesized an array of biologically active 2-(arylthio)benzothiazole derivatives **15**, reacting 2-mercaptobenzothiazoles **13** with aryl iodides **14** using a catalytic amount of CuI and refluxing in water (Fig. 2.5). Their synthesis resulted in a good to high yields of coupling product **15**, which tolerated a variety of functional groups. The researchers further applied their green and ligand-free synthetic strategy to synthesize Cathepsin-D inhibitor **16** in high yield.

Gambogin (**21**), a natural product isolated from the gamboge resin of *Garcina hamburyi*, has an unusual molecular architecture and exhibits cytotoxic properties against the Hela and HEL cell lines (MIC: 6.25 and 3.13 μg/mL, respectively) (Asano et al. 1996). The research group of Prof. Nicolaou at the Scripps Research Institute, La Jolla, reported the synthesis of Gambogin (**21**) in two key steps using considerable rate improvement of pericyclic reactions in aqueous media (Fig. 2.6)

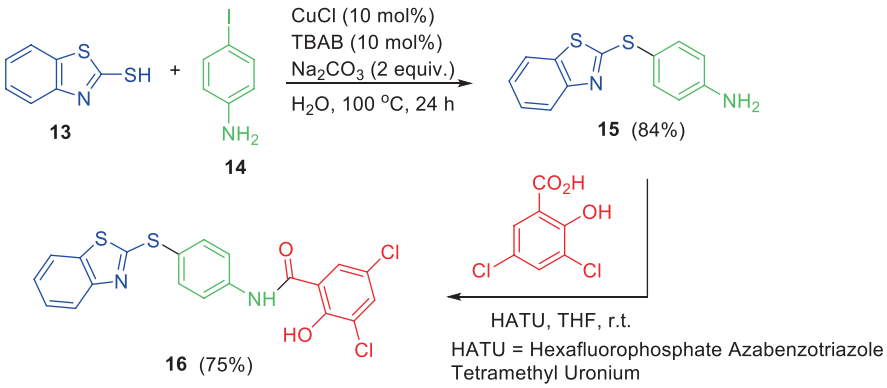



**Fig. 2.5** Green chemistry in water for the synthesis of Cathepsin-D inhibitor **16**

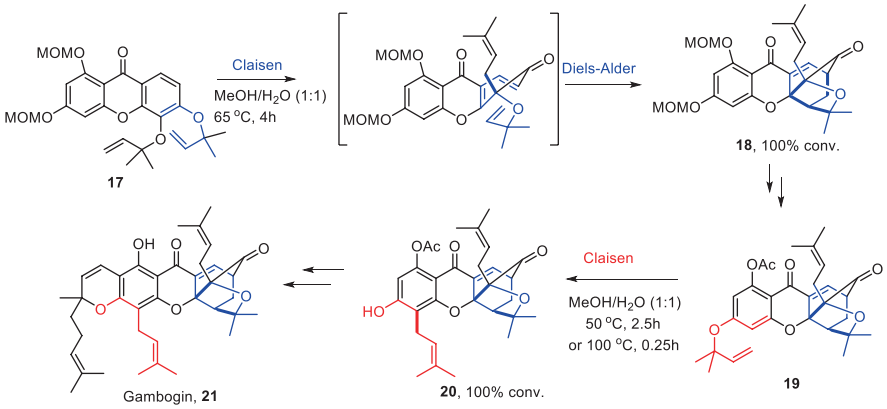



**Fig. 2.6** Synthesis of gambogin (**21**) using Claisen rearrangement and Diels–Alder cycloaddition reactions in aqueous media

(Nicolaou et al. 2005). Through a cascade sequence involving a Claisen rearrangement and a Diels–Alder cycloaddition, the first intermediate **18** was obtained from precursor **17**. The reaction was highly solvent dependent favoring a 1:1 mixture of water/methanol at 65 °C. This reaction condition led to the formation of the expected product in 4 h. The same reaction conditions did not work in the presence of the various organic solvents such as ethanol, methanol, trifluoroethanol, benzene, or DMF. The Claisen rearrangement for the formation of **20** from **19** was successfully carried out afterward in a mixture of water/methanol at 50 or 100 °C within 2.5 h or 0.25 h, respectively. This unique synthetic strategy has proven that greener solvent water is critical to obtain decent conversions for the synthesis.

Researchers from Codexis, Incorporated, and Merck Research Laboratories have reported an elegant enzymatic synthesis of sitagliptin, an antidiabetic drug, involving an overall enantioselective reductive amination of a ketone using an

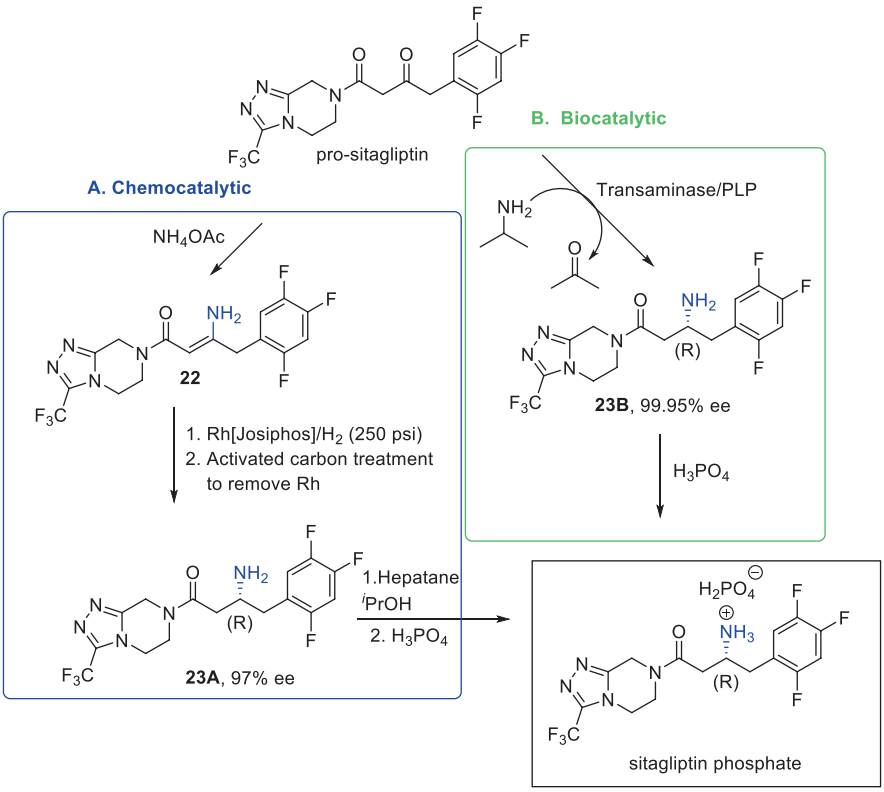



**Fig. 2.7** (**a**) A chemocatalytic synthesis of sitagliptin phosphate. (**b**) A biocatalytic synthesis of sitagliptin phosphate

(R)-transaminase catalyzed reaction with $H_2O$/DMSO (1:1) (Fig. 2.7) (Savile et al. 2010). Initial studies of the ketone substrate with an (R)-selective transaminase showed no activity. The researchers using in-silico studies identified the binding pocket of the enzyme needed to fit the ketone. Under the optimized conditions in $H_2O$/DMSO (1:1), using 6 g/L of the best variant, converted 200 g/L of the ketone substrate into sitagliptin, in 24 h in 92% yield and > 99.95% ee. The biocatalytic process was efficient, atom-economical, and cost effective which afforded sitagliptin with a better 10–13% yield, a 53% increase in productivity (kg/L per day) compared to the chemical process. In addition, they reported no usage of all heavy metals, total waste reduction of 19% and total manufacturing cost reduction compared with the chemical process (a rhodium catalyzed asymmetric hydrogenation of an enamine). Furthermore, the enzymatic reaction was run in multipurpose vessels, avoiding the need for specialized high-pressure hydrogenation equipment.

Kumar and co-workers studied the synthesis of benzothiazole ring **27** in water (Kumar et al. 2012). Their synthesis involves the formation of the intermediate, thiourea derivative **26** (not isolated) from the reaction of iodo-benzo-isothiocy-

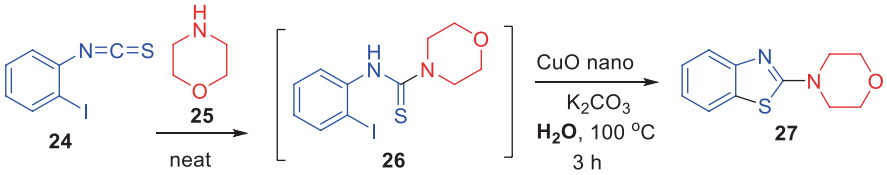
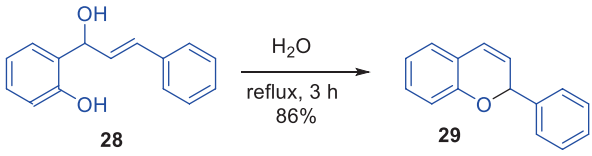
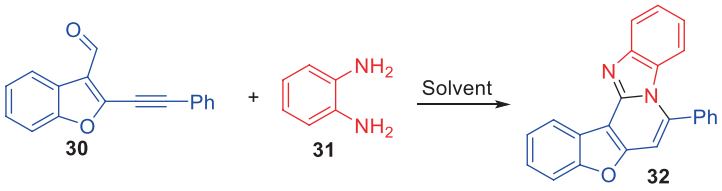



**Fig. 2.8** On water reaction synthesis of benzothiazole (**27**)

**Fig. 2.9** Synthesis of chromene derivatives (**29**) in water




| Solvent | Yield |
|---|---|
| DMSO | 45 |
| DMF | 50 |
| $H_2O$ | 88 |
| Dioxane | 40 |

**Fig. 2.10** Synthesis of tetracyclic rings (**32**) in water

anate (**24**) and morpholine (**25**). The thiourea intermediate **(26)** was cyclized using CuO-nanocatalyst on water to produce **27** in 92% yield (Fig. 2.8). They reported some benefits of using their synthetic protocol such as stereoselectivity, reusability of the catalyst, and no chromatographic purification resulting in higher yields. They also reported the effects of different solvents such as dioxane, DMF, and toluene on their reaction conditions which gave lower yields of 63, 70, and 55%, respectively than the greener solvent water.

Zhang and co-workers reported the chromene derivative **29** formation from **28** in water (Zhang et al. 2015). They reported that their reaction was highly green and eco-friendly because toxic solvents, additives, catalysts, and bases were not used. They reported varied yields between 74 and 95% (Fig. 2.9).

Mishra and Verma studied the synthesis of tetracyclic rings in water. Tetracyclic motifs (**32**) were synthesized from benzofuran derivatives (**30**) and orthophenylendiamine (**31**) in water at appreciable yield of 88% (Fig. 2.10) (Mishra and Verma 2016). Solvents were tested for yields of the reaction, and they reported that the most suitable solvent was water, and the others (such as DMSO, DMF, and

Dioxane) resulted in decreasing of the product yields down to 40–50%. They reported unsatisfactory reaction using $AgNO_3$ as a catalyst. They concluded after optimization of the reaction that catalysts, additives, and toxic solvents are not needed, hence greener synthesis.

## 3 Multicomponent Reactions (MCRs) in Water, a Greener Solvent in Organic and Drug Synthesis

Multicomponent reactions (MCRs) combine at least three readily available reactants (Brauch et al. 2013) in the same pot to generate a target product containing most (preferably all) atoms of the starting material (Zhu and Bienaymé 2005). Multicomponent reactions (MCRs) generally proceed under milder conditions, high convergence rate, atom economical rate, and high efficiency in greener solvents for sustainable synthetic methodologies (Cioc et al. 2014). One of the fundamental questions needed for sustainable synthetic methodology is "how much of what you put into the reaction system ends up in your product." The answer to this question has been defined clearly by Professor Barry M. Trost in outlining what constitutes synthetic efficiency, thus selectivity and atom economy (Trost 1991). Atom economy requires employment of reactions that produce minimal byproducts. This could be achieved either through the intrinsic stoichiometry of a reaction or as a result of minimizing competing undesirable reactions (such as making reactions more selective). Although there is an increasing number of applications of MCRs reported in medicinal chemistry and drug discovery programs (Ruijter and Orru 2013; Magedov and Kornienko 2012), combinatorial chemistry (Moos et al. 2009), natural product synthesis (Touré and Hall 2009), agrochemistry (Lamberth et al. 2008), and polymer chemistry (Kakuchi 2014), there is still not a general awareness among synthetic and medicinal chemist community that MCRs are able to address some of the delicate chemical problems in a greener, sustainable, and an eco-friendly manner. This review points out the opportunities and challenges the utilization of MCRs brings for green synthesis and process design, especially for reactions in water.

Researchers at Shahid Beheshti University have developed a novel synthesis of pseudopeptides (**39**) containing rhodanine scaffolds in a diversity-oriented catalyst-free system via a one-pot sequential isocyanide-based six-component reactions in water using ultrasound (US) irradiation (Shaabani and Hooshmand 2018). The synthesis involves the assembly of MCRs strategy through tandem Michael–domino cycloaddition–Ugi reactions sequence. The synthesis involves the combination of readily available starting materials such as primary amines (**33**), carbon disulfide (**34**), maleic anhydride (**35**) or itaconic anhydride (**35**), aniline derivatives (**36**), aromatic aldehydes (**37**), and isocyanides (**38**) in water without the use of catalysts or other additives (Fig. 2.11). Their remarkable synthetic protocol resulted in the target products through tandem formation of one new heterocyclic ring and seven new

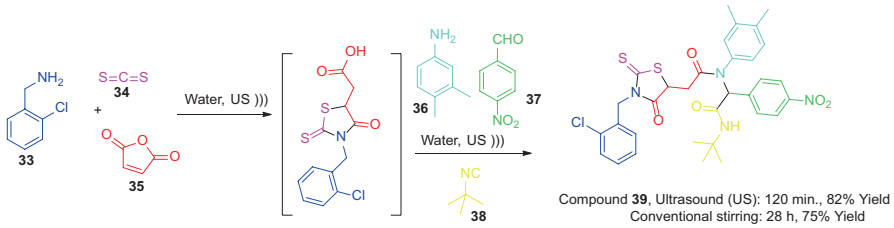



**Fig. 2.11** MCR synthesis of pseudopeptide **39** in water

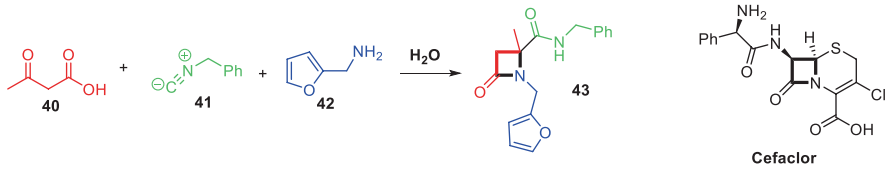



**Fig. 2.12** Synthesis of β-lactam motif (**43**) in water

bonds consisting of carbon-carbon, carbon-nitrogen, carbon-oxygen and carbon-sulfur. The synthesis was cleaner and eco-friendly as it involves greener solvent water, with no catalysts, additives under ultrasonic-irradiation. It also involves the use of readily available and inexpensive starting materials, easy work-up conditions and no column chromatography. They reported that their synthetic strategy falls within the goals of sustainable and green chemistry and would lead to the synthesis of biologically active and pharmacologically useful drugs.

Beta-Lactam motifs are an important ring system as it forms part of antibiotic medicines such as Cefaclor. Researchers Pirrung and Sarma (2004) have reported the MCR synthesis of β-lactam compound (**43**) from readily available acetoacetic acid (**40**), izonitrile (**41**), and amine (**42**) in water in 2 hours with 93% yield (Fig. 2.12). The researchers stated that changing the solvent from water to $CH_2Cl_2$ gave the same result albeit low yield, 45%. This synthetic protocol is biologically significant since it gives β-lactam ring in a water medium, mimicking nature.

Javanshir and co-workers (2014) have reported a one-port, three-component condensation of an appropriate aldehydes (**44**), 2-naphthol (**45**), and 2-aminobenzothiazole (**46**) catalyzed by heteropolyacid (HPA) in an aqueous medium to produce the *Mannich* adduct 2-aminobenzothiazolomethylnaphthols (**47**) at 45 °C under ultrasound irradiation (Fig. 2.13). The synthetic protocol meets the goals for sustainable and green chemistry such as short reaction time, simple work-up procedure, available starting materials, high efficiency, and yields for a moiety with broad spectrum of biological activities including anti-inflammatory and anti-carcinogenic.

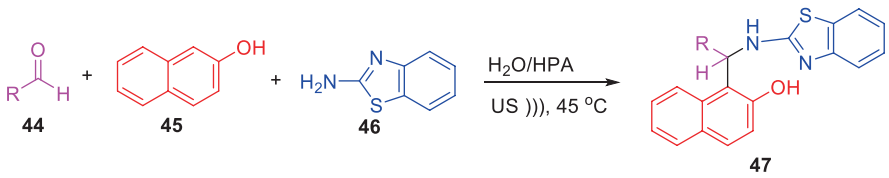



**Fig. 2.13** Synthesis of 2-aminobenzothiazolomethylnaphthols (**47**) in water

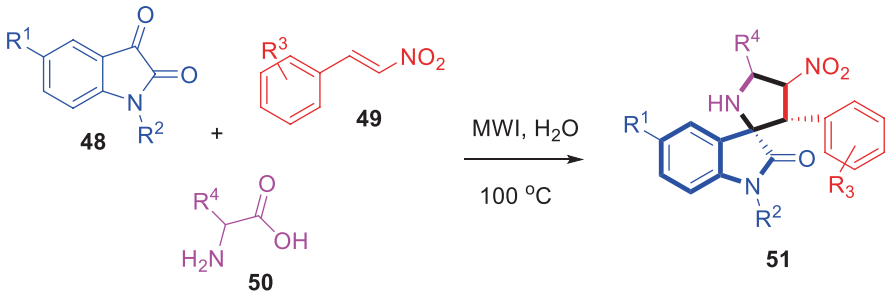



**Fig. 2.14** Synthesis of pyrrolidine spirooxindoles **51** in water

Mali et al. (2016) have synthesized pyrrolidine spirooxindoles (**51**) using MCR system in a one-pot three-component aqueous media in an eco-friendly, high regioselective, and efficient manner under microwave irradiation (Fig. 2.14). Spirooxindole derivatives (**51**) were synthesized with good diastereoselectivity from a mixture of isatins (**48**), β-nitrostyrene (**49**), and α-amino acids (**50**). The synthesized spirooxindole derivatives (**51**) showed significant antimicrobial activity against different microbes such as *Escherichia coli*, *Candida tropicalis*, *Staphylococcus aureus,* and *Pseudomonas aeruginosa*.

Zong and co-workers (2019) developed the synthesis of β-sulfonyl Amides (**56**) through a MCR of styrenes (**52**), aryldiazonium tetrafluoroborates (**53**), sulfur dioxide (**54**), nitriles (**55**), and water in the presence of a photo catalyst at room temperature (Fig. 2.15). This synthesis led to the formation of β-sulfonyl amides with good efficiency and excellent chemoselectivity in appreciable yields. Mechanistically, they reported initial formation of the aryl radical, which then underwent intramolecular 5-exo-cyclization with subsequent insertion of sulfur dioxide (from DABCO·$(SO_2)_2$).

Researchers at the National Institute of Technology, Patna, have designed the synthesis of aminouracil-tethered tri-substituted methanes (**60**) in water, catalyzed by iodine in MCR (Kumari et al. 2018). The synthesis of aminouracil-tethered tri-substituted methane derivatives (**60**) involves readily available 2-hydroxy-1,4-naphthaquinone (**57**), 6-amino-1,3-dimethyluracil (**58**), and aldehydes (**59**) under reflux in water (Fig. 2.16). They reported that their synthetic strategy falls within the goals of sustainable and green chemistry since it involves greener solvent water, no

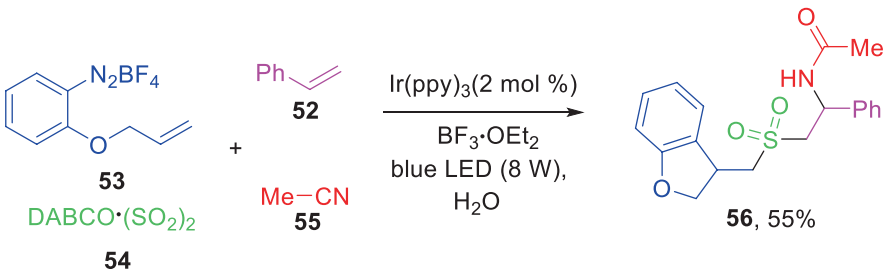



**Fig. 2.15** Synthesis of β-sulfonyl Amides (**56**) in water

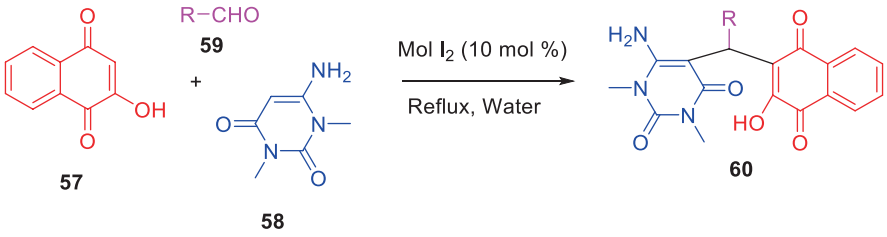



**Fig. 2.16** Synthesis of aminouracil-tethered tri-substituted methanes (**60**) in water

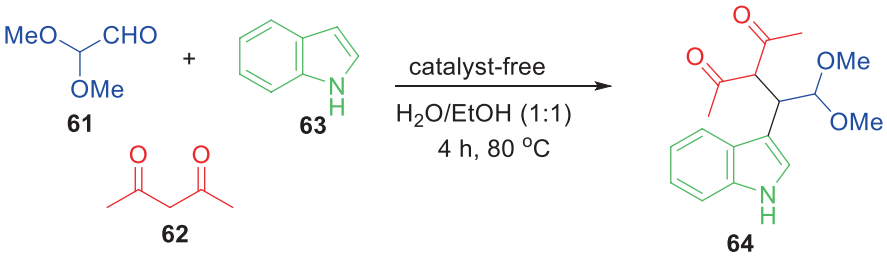



**Fig. 2.17** Three-component reactions for the synthesis of 1,4-diketones (**64**)

column chromatographic separation, use of cheaper catalyst, easy work-up conditions, and appreciable yields of products.

Yang and co-workers (2018) reported a facile catalyst-free synthesis of 1,4-diketones (**64**) via three-component reactions of glyoxal dimethyl acetal (**61**), 1,3-dicarbonyl compound (**62**), and a nucleophile (**63**) in an aqueous media (Fig. 2.17). They reported that their synthesized product 1,4-diketones (**64**) could serve as a reactive precursor tethered for the preparation of substituted pyrroles, furans, and other bioactive compounds.

Researchers at the Malaviya National Institute of Technology have reported a novel synthesis of highly fluorogenic heterobioconjugates (**67**) from nonfluorescent 3-azidocoumarins (**66**) and terminal alkynes (**65**) using aqueous NaCl as a salting-out

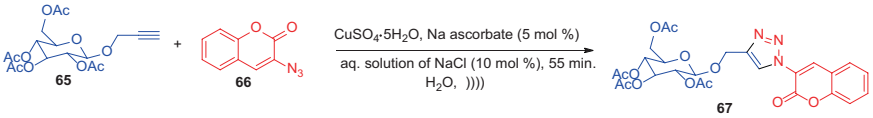


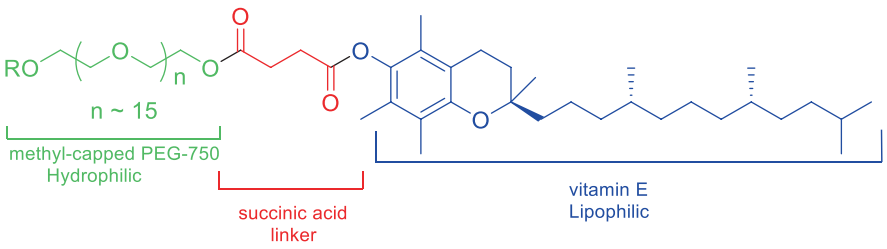

**Fig. 2.18** A regioselective synthesis of fluorogenic 1,4-disubsituted triazoles (**67**) in water

agent under ultrasonication at ambient temperature in water (Fig. 2.18) (Jain et al. 2019). They reported that the aqueous NaCl enhances the reactivity and augments the hydrophobic interaction of water insoluble reactants. They reported high efficiency, cost effectiveness, recyclable process, excellent turn-over number (4850), low copper loading (100 ppm), and turnover frequency (88.18 $min^{-1}$). They reported a gram-scale synthesis at 92% yield and potential application in live cell imaging for bioligation and bioimaging (Jain et al. 2019).

## 4 Surfactant in Water, as a Greener Solvent in Organic and Drug Synthesis

Most industrial, pharmaceutical, and chemical processes use mostly organic solvents for their reactions, which tend to be wasted, volatile, toxic, expensive, and flammable. The annual industrial scale production of organic solvents has been estimated at almost 20 million MT (metric tons) (Clark et al. 2015). Water the most reliable and easily accessible greener solvent could curtail this shortfall, but many chemicals do not react and dissolve in water. In order to overcome the solubility issues of water, Prof. Lipshutz and his research group at the University of California, Santa Barbara, designed safe surfactants, TPGS and TPGS-750-M, that form tiny droplets (micelles) in water (Lipshutz et al. 2008; Lipshutz and Ghorai 2008; Lipshutz and Ghorai 2012). This surfactant is composed of tocopherol (vitamin E), succinic acid (an intermediate in cellular respiration), and methoxy poly (ethylene glycol) (a common, degradable hydrophilic group also called MPEG-750) (Scheme 2.1) (Lipshutz et al. 2016; Lipshutz 2017). This review outlines few applications of this technology in academic laboratories and industries to a variety of transformations.

Researchers at Novartis process group have studied the formation of peptide bonds, in which the use of co-solvent (THF) has proven critical to the success of the reaction in water (Fig. 2.19) (Gallou et al. 2016). From their findings, the peptide couplings in water were successful at large scale of more than 200 g. Compared to the use of dipolar aprotic solvents such as DMF and NMP, the synthesis was safe, cost-effective, and environmentally benign. After optimization of their synthetic protocol using (N-methylmorpholine, NMM) as base, a triazine derivative as the acid-activating moiety, and co-solvent (THF), the coupling proceeded to produce (**70**) in 88% yield on a 228 g scale.




**Scheme 2.1** Structure of the surfactants TPGS-750-M (R = Me, n ~ 15) and TPGS (R = H, n ~ 20)

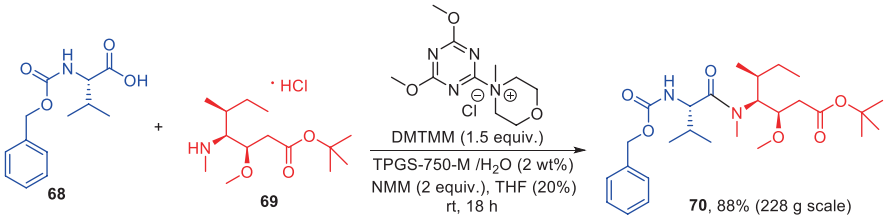



**Fig. 2.19** Amide bond (**70**) formation between acid (**68**) and amine (**69**) in 2 wt % TPGS-750-M/$H_2O$ in the presence of THF as co-solvent

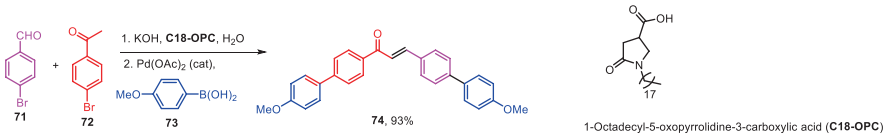



**Fig. 2.20** Synthesis of (bis)biarylated chalcone **74** in water and C18-OPC

Armenise and co-workers (2016) have studied a MCR cascade synthesis of biaryl-based chalcones in an aqueous micellar environment. Chalcones show a wide range of biological activities such as anti-inflammatory, antimicrobial, antimalarial, antimitotic, antioxidant, and anticancer properties. The synthesis involves a Pd-catalyzed, aerobic Suzuki–Miyaura coupling of aryl and heteroaryl bromides (**71, 72**) with different arylboronic acids (**73**) in aqueous medium. In-situ aldol condensation reaction of the resulting intermediates gave biaryl(hetero)chalcones (**74**) in appreciable yields (Fig. 2.20). The researchers disclosed that the biaryl(hetero) chalcones (**74**) products were obtained by simple recrystallization from methanol, without any column chromatographic separation. In addition, the $Pd(OAc)_2$/C18-OPC/$H_2O$ catalytic system was recycled at least five times without significant loss in activity, showcasing greener synthesis.

A medicinal chemistry group at AbbVie (in Ludwigshafen, Germany) has reported an efficient one-pot synthesis of dihydroquinolinones (**78**) in water at room temperature via 1,4-addition of ortho-aminoboronic acids (**75**) to α,β-unsaturated ethyl esters (**76**) catalyzed using $[RhOH(COD)]_2$ in aqueous TPGS-750-M

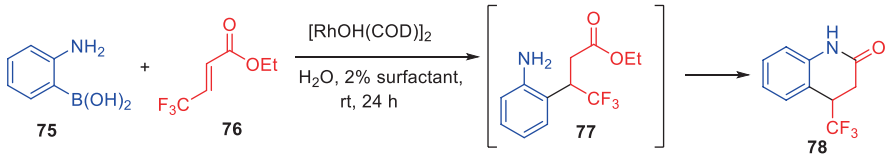



**Fig. 2.21** Synthesis of dihydroquinolinones (**78**) using TPGS-750-M in water as medium

(Fig. 2.21) (Linsenmeier and Braje 2015). The dihydroquinolinone structural motif is found in some significant drug candidates such as aripiprazole and cilostazol, an antipsychotic used for the treatment of schizophrenia and a PDE3 phosphodiesterase inhibitor for the treatment of peripheral vascular disease, respectively. They enumerated a couple of advantages in using their greener solvent strategy compared to the organic solvents in conventional reactions, such as (1) simplified purification process and improved impurity formation; (2) minimization of protodeboronation as a result of no heating leading to higher reaction yields; and (3) simplified isolation process, coupled with reduced use of organic solvents resulted in saving cost, atom economy, sustainable, and greener chemistry.

Feng et al. (2016) have designed nitro group reductions synthesis in a safe and selective manner, catalyzed by Fe/ppm Pd nanoparticles, which are sustainable and recyclable in water at room temperature. They showcased a three-step subsequent reduction, amidation, and coupling steps. In their synthetic sequence, 1-bromo-4-nitrobenzene **79** was reduced to an amine which amidated with carboxylic acid **80** to generate an amide which then coupled with **81** leading to the formation of complex biaryl **82** in an appreciable yield, with relatively little organic waste (Fig. 2.22). In their concluding remarks, a highly chemoselective and efficient nitro group reductions technology in water at ambient temperature has been developed. They reported that their synthetic strategy addresses some of the goals of sustainable and green chemistry with the newly developed Fe/ppm Pd NPs which offers MCRs in a single-pot, recycle catalyst, easy work-up, and mild reaction in aqueous medium.

The group of Kumar and Bishnoi (2015) has shown that copper iodide nanoparticles can be used for C–N bond formation involving cyclic secondary amines, primary anilines (**83**), and azoles (**84**), when using vitamin E analogues TPGS (6) as the surfactant in water (Fig. 2.23). The method has been successfully leveraged against the synthesis of pharmaceutical compounds including the antitubercular natural product tryptanthrin (**85**).

Researchers at the University of California, Santa Barbara, and Novartis have reported a safe and selective amidation reaction using COMU in a TPGS-750-M (3) medium exploited for the liquid phase assembly of polypeptide fragments (Fig. 2.24) (Cortes-Clerget et al. 2017). These conditions have been used to synthesize a streptocidin C precursor **88**, the precursor of a tripeptide (Lys-Pro-Val) with anti-inflammatory properties, and a linear 10 residue precursor of the antibiotic gramicidin S.

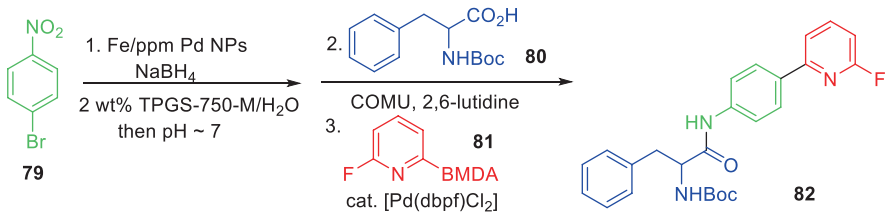



**Fig. 2.22** Sequential one-pot reactions of nitro (**79**), acid (**80**), and coupling agent (**81**) to form complex biaryl **82**

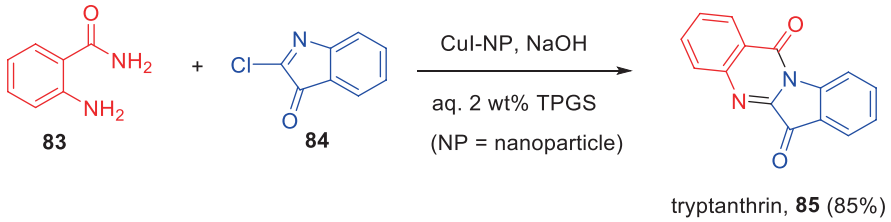



**Fig. 2.23** Copper-catalyzed amine arylation for the synthesis of tryptanthrin (85) using TPGS in water as medium

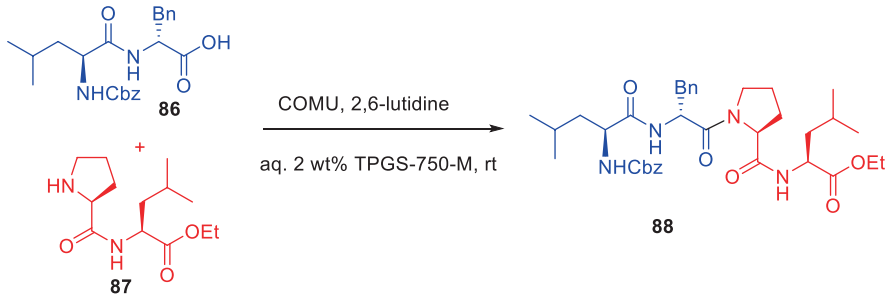



**Fig. 2.24** Synthesis of streptocidin C precursor (**88**) from acid (**86**) and amine (**87**) using TPGS-750-M in water as medium

Suzuki–Miyaura (SM) couplings that forge $sp^3$–$sp^2$ bonds have been successfully performed under micellar conditions by scientists at the University of California, Santa Barbara, and Novartis (Lee et al. 2018). Even with coupling partners rich in Lewis basic nitrogen functionality, the couplings work with low levels (0.5 mol%) of the catalyst, and the $sp^3$-coupling partner can include amines (**89**), α,β-unsaturated ketones, as well as heterocycles while aryl halides (**90**) for the $sp^3$-partner (Fig. 2.25). An example can be found in Fig. 2.25 where the product **91** is structurally related to compound **92**, which itself features in the synthesis of inhibitors of ACK1/TNK2 tyrosine kinase (Mahajan et al. 2017).

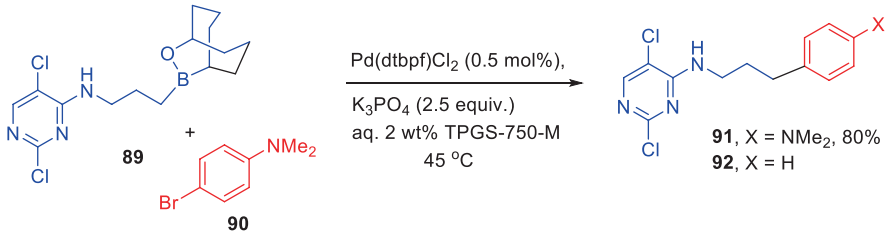



**Fig. 2.25** Suzuki–Miyaura (SM) $sp^3$–$sp^2$ coupling for the formation of **91**

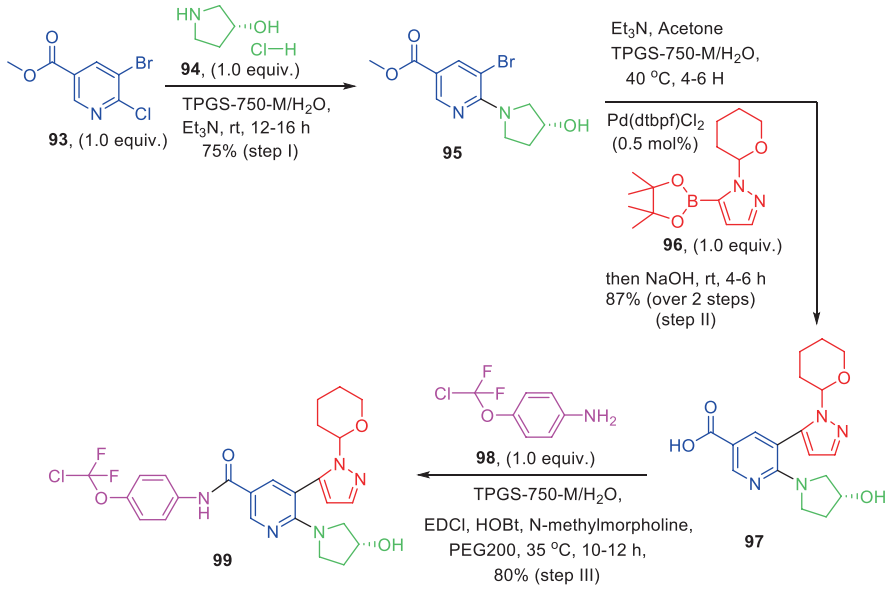



**Fig. 2.26** Multistep synthesis of product **99** using TPGS-750-M in water as medium

Researchers from Novartis and the Scripps Research Institute have reported an outstanding synthesis highlighting the virtues of a single reaction medium consisting of water and nanoreactors in the form of nanomicelles to accommodate many reactions of interest in organic synthesis. They reported a 4-step, 1-pot sequence shown in (Fig. 2.26), featuring a selective Nucleophilic Aromatic Substitution $S_NAr$ reaction between methyl 5-bromo-6-chloronicotinate (**93**) and nucleophile (**94**) to get (**95**), followed by a Suzuki–Miyaura (SM) cross-coupling with boronic ester (**96**) and hydrolysis to intermediate (**97**) (Parmentier et al. 2017). Without isolation (although yields for individual steps are shown), the carboxylic acid group is smoothly aminated 4-(chlorodifluoromethoxy) aniline (**98**) resulting in the amide derivative, final product **99**.

## 5 Conclusion

This review has summarized applications of synthesis, MCRs, and surfactant-mediated chemistry in water to a select number of reaction types that underpin the discovery, development, and manufacture of pharmaceuticals. The structures used for method exemplification show that the reactions exhibit high selectivity (such as chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity), atom economy and high-yielding for a cross section of pharmaceutically relevant structures. The transformations discussed are workhorses for synthetic chemists in the pharmaceutical industry and academics, are also have highlighted opportunities for the application of synthesis, MCRs and micellar methods in water to the assembly of other specialty and fine chemicals. The ability to dramatically reduce, and in many cases avoid, the need for organic solvents in reaction medium when making complex molecules means greener synthesis, MCRs, and surfactant-mediated chemistry in water are key to achieving the sustainable development of chemical process and technologies. In addition, the development of organic chemistry and surfactant-mediated chemistry in water can unravel complex reactivities and reverse selectivities compared to organic solvents, thus mimicking the biosynthesis of natural products as well as complementing the medicinal, organic, and biochemists' synthetic toolbox.

**Acknowledgements** The author is highly indebted to his mentor Prof. Jon D. Rainier in the Department of Chemistry, University of Utah, Salt Lake City, Utah, USA. The author wishes to acknowledge Prof. Christian Agyare in the Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, KNUST, for introducing this chapter. The author acknowledge Prof. Evans Adei in the Department of Chemistry, Dr. (Mrs.) Cynthia Amaning Danquah in the Department of Pharmacology, and Dr. Yaw Duah Boakye in the Department of Pharmaceutics, KNUST, for their immense contributions.

## References

Abou-Shehada S, Clark JH, Paggiola G, Sherwood J. Tunable solvents: shades of green. Chem Eng Process. 2016;99:88–96.

Ahmad S, Iqbal J. Cobalt (II) chloride catalysed coupling of thiols and anhydrides: a new and efficient synthesis of thiol esters. Tetrahedron Lett. 1986;27:3791–4.

Anastas PT, Eghbali N. Green chemistry: principles and practice. Chem Soc Rev. 2010;39(1):301–12. https://doi.org/10.1039/b918763b.

Anastas PT, Warner JC. Green chemistry: theory and practice. Oxford: Oxford University Press; 1998.

Armenise N, Malferrari D, Ricciardulli S, Galletti P, Tagliavini E. Multicomponent cascade synthesis of biaryl-based chalcones in pure water and in an aqueous micellar environment. Eur J Org Chem. 2016;81:3177–85.

Asano J, Chiba K, Tada M, Yoshii T. Cytotoxic xanthones from Garcinia hanburyi. Phytochemistry. 1996;41(3):815–20. https://doi.org/10.1016/0031-9422(95)00682-6.

Ashcroft CP, Dunn PJ, Hayler JD, Wells AS. Survey of solvent usage in papers published in organic process research & development 1997–2012. Org Process Res Dev. 2015;19:740–7.

Blakemore DC, Castro L, Churcher I, Rees DC, Thomas AW, Wilson DM, Wood A. Organic synthesis provides opportunities to transform drug discovery. Nat Chem. 2018;10(4):383–94. https://doi.org/10.1038/s41557-018-0021-z.

Brauch S, van Berkel SS, Westermann B. Higher-order multicomponent reactions: beyond four reactants. Chem Soc Rev. 2013;42(12):4948. https://doi.org/10.1039/c3cs35505e.

Cioc RC, Ruijter E, Orru RVA. Multicomponent reactions: advanced tools for sustainable organic synthesis. Green Chem. 2014;16(6):2958–75. https://doi.org/10.1039/c4gc00013g.

Clark JH, Farmer TJ, Hunt AJ, Sherwood J. Opportunities for bio-based solvents created as petrochemical and fuel products transition towards renewable resources. Int J Mol Sci. 2015;16:17101–59.

Constable DJC, Curzons AD, Cunningham VL. Metrics to "green" chemistry—which are the best? Green Chem. 2002;4(6):521–7. https://doi.org/10.1039/b206169b.

Cortes-Clerget M, Berthon J-Y, Krolikiewicz-Renimel I, Chaisemartin L, Lipshutz BH. Tandem deprotection/coupling for peptide synthesis in water at room temperature. Green Chem. 2017;19:4263.

Curzons AD, Jiménez-González C, Duncan AL, Constable DJC, Cunningham VL. Fast life cycle assessment of synthetic chemistry (FLASC™) tool. Int J Life Cycle Assess. 2007;12(4):272–80. https://doi.org/10.1065/lca2007.03.315.

Feng J, Handa S, Gallou F, Lipshutz BH. Safe and selective nitro group reductions catalyzed by sustainable and recyclable Fe/ppm Pd nanoparticles in water at room temperature. Angew Chem Int Ed. 2016;55:8979–83.

Gallou F, Guo P, Parmentier M, Zhou J. A general and practical alternative to polar aprotic solvents exemplified on an amide bond formation org. Process Res Dev. 2016;20:1388–91.

He G, Huang Y, Tong Y, et al. Substrate-promoted ligand-free CuI catalyzed S-arylation of 2-mercaptobenzothiazoles with aryl iodides in water. Tetrahedron Lett. 2013;54:5318–21.

Hulshof LA, Roskam JH Eur. Pat. Appl. EP343714A119891129. 1989

Jain Y, Gupta R, Yadav P, Kumari M. Chemical waltz of organic molecules "on water": saline-assisted sustainable regioselective synthesis of fluorogenic heterobioconjugates via click reaction. ACS Omega. 2019;4(2):3582–92. https://doi.org/10.1021/acsomega.8b03167.

Javanshir S, Ohanian A, Heravi MM, Naimi-Jamal MR, Bamoharram FF. Ultrasound-promoted, rapid, green, one-pot synthesis of 2′-aminobenzothiazolo methylnaphthols via a multicomponent reaction, catalyzed by heteropolyacid in aqueous media. J Saudi Chem Soc. 2014;18(5):502–6. https://doi.org/10.1016/j.jscs.2011.10.013.

Jiménez-González C, Curzons AD, Constable DJC, Cunningham VL. Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds. Int J Life Cycle Assess. 2004;9(2):114–21. https://doi.org/10.1007/bf02978570.

Kakuchi R. Multicomponent reactions in polymer synthesis. Angew Chem Int Ed. 2014;53:46–8.

Katritzky AR, Shestopalov AA, Suzuki K. A new convenient preparation of thiol esters utilizing N-acylbenzotriazoles. Synthesis (Mass). 2004;11:1806–13.

Kumar A, Bishnoi AK. Application of nanoparticle mediated N-arylation of amines for the synthesis of pharmaceutical entities using vitamin-E analogues as amphiphiles in water. RSC Adv. 2015;5(26):20516–20. https://doi.org/10.1039/c4ra15267k.

Kumar S, Guin S, Nath J, Patel BK. An "on-water" exploration of CuO nanoparticle catalysed synthesis of 2-aminobenzothiazoles. Green Chem. 2012;14:2491.

Kumari P, Bharti R, Parvin T. Synthesis of aminouracil-tethered tri-substituted methanes in water by iodine-catalyzed multicomponent reactions. Mol Divers. 2018;23:205. https://doi.org/10.1007/s11030-018-9862-z.

Lamberth C, Jeanguenat A, Cederbaum F, De Mesmaeker A, Zeller M, Kempf H-J, Zeun R. Multicomponent reactions in fungicide research: the discovery of mandipropamid. Bioorg Med Chem. 2008;16(3):1531–45. https://doi.org/10.1016/j.bmc.2007.10.019.

Lee NR, Linstadt RTH, Gloisten DJ, Gallou F, Lipshutz BH. B-Alkyl $sp^3$–$sp^2$ Suzuki–Miyaura couplings under mild aqueous micellar conditions. Org Lett. 2018;20:2902.

Linsenmeier AM, Braje M. Efficient one-pot synthesis of dihydroquinolinones in water at room temperature. Tetrahedron. 2015;71:6913–9.
Lipshutz BH. When does organic chemistry follow nature's lead and "make the switch"? J Organomet Chem. 2017;82:2806–16.
Lipshutz BH, Ghorai S. Transition-metal-catalyzed crosscouplings going green: in water at room temperature. Aldrichim Acta. 2008;41:59–72.
Lipshutz BH, Ghorai S. "Designer"surfactant-enabled cross couplings in water at room temperature. Aldrichim Acta. 2012;45:3–16.
Lipshutz BH, Aguinaldo GT, Ghorai S, Voigtritter K. Olefin crossmetathesis reactions at room temperature using the nonionic amphiphile "PTS": just add water. Org Lett. 2008;10:1325–8.
Lipshutz BH, Gallou F, Handa S. Evolution of solvents in organic chemistry. ACS Sustain Chem Eng. 2016;4(11):5838–49. https://doi.org/10.1021/acssuschemeng.6b01810.
Lo Conte M, Carrol KS. Chemoselective ligation of sulfinic acids with aryl-nitroso compounds. Angew Chem Int Ed. 2012;51:6502–5.
Lo Conte M, Lin J, Wilson MA, Carrol KS. A chemical approach for the detection of protein sulfinylation. ACS Chem Biol. 2015;10:1825–30.
Magedov IV, Kornienko A. Multicomponent reactions in alkaloid-based drug discovery. Chem Heterocycl Compd. 2012;48(1):33–8. https://doi.org/10.1007/s10593-012-0965-7.
Magens S, Plietker B. Fe-catalyzed thioesterifcation of carboxylic esters. Chem Eur J. 2011;17:8807–9.
Mahajan NP, Mahajan KN, Lawrence NJ, Lawrence HR Inhibitors of ACKl /TNK2 tyrosine kinase. WO2017023899A1. 2017
Mali PR, Chandrasekhara Rao L, Bangade VM, Shirsat PK, George SA, Jagadeesh Babu N, Meshram HM. A convenient and rapid microwave-assisted synthesis of spirooxindoles in aqueous medium and their antimicrobial activities. New J Chem. 2016;40(3):2225–32. https://doi.org/10.1039/c5nj02126j.
Meshram H, Reddy GS, Bindu KH, et al. Zinc promoted convenient and general synthesis of thiol esters. Synlett. 1998;1998(8):877.
Mishra PK, Verma AK. Metal-free regioselective tandem synthesis of diversely substituted benzimidazo-fused polyheterocycles in aqueous medium. Green Chem. 2016;18:6367–72.
Moos WH, Hurt CR, Morales GA. Combinatorial chemistry: oh what a decade or two can do. Mol Divers. 2009;13(2):241–5. https://doi.org/10.1007/s11030-009-9127-y.
Nicolaou KC, Xu H, Wartmann M. Biomimetic total synthesis of gambogin and rate acceleration of pericyclic reactions in aqueous media. Angew Chem Int Ed. 2005;44(5):756–61. https://doi.org/10.1002/anie.200462211.
Noce AM. Green chemistry and the grand challenges of sustainability. Phys Sci Rev. 2018;72:1–8. https://doi.org/10.1515/psr-2018-0072.
Parmentier M, Gabriel CM, Guo P, Isley NA, Zhou J, Gallou F. Switching from organic solvents to water at an industrial scale. Curr Opin Green Sustainable Chem. 2017;7:13–7. https://doi.org/10.1016/j.cogsc.2017.06.004.
Pirrung MC, Sarma KD. Multicomponent reactions are accelerated in water. J Am Chem Soc. 2004;126:444–5.
Portmann R Process for preparing 1-substituted 4-cyano-1,2,3-triazoles. World Patent WO 9802423. 1998
Rio Declaration on Environment and Development Rio de Janeiro, Brazil, June 3–14. 1992. http://www.unesco.org/education/information/nfsunesco/pdf/RIO_E.PDF.
Ruijter E, Orru RVA. Multicomponent reactions – opportunities for the pharmaceutical industry. Drug Discov Today Technol. 2013;10(1):e15–20. https://doi.org/10.1016/j.ddtec.2012.10.012.
Savile CK, Janey JM, Mundorff EC, Moore JC, Tam S, Jarvis WR, Hughes GJ. Biocatalytic asymmetric synthesis of chiral amines from ketones applied to Sitagliptin manufacture. Science. 2010;329(5989):305–9. https://doi.org/10.1126/science.1188934.
Shaabani A, Hooshmand SE. Diversity-oriented catalyst-free synthesis of pseudopeptides containing rhodanine scaffolds *via* a one-pot sequential isocyanide-based six-component reac-

tions in water using ultrasound irradiation. Ultrason Sonochem. 2018;40:84–90. https://doi.org/10.1016/j.ultsonch.2017.06.030.

Sheldon RA. Review chirotechnology: designing economic chiral syntheses. J Chem Technol Biotechnol. 1996;67(1):1–14. https://doi.org/10.1002/(SICI)1097-4660(199609)67:1<1:AID-JCTB531>3.0.CO;2-L.

Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19:18–43.

Sherwood J, Clark JH, Fairlamb IJS, Slattery JM. Solvent effects in palladium catalysed cross-coupling reactions. Green Chem. 2019;21:2164. https://doi.org/10.1039/c9gc00617f.

Simon MO, Li CJ. Green chemistry oriented organic synthesis in water. Chem Soc Rev. 2012;41(4):1415–27. https://doi.org/10.1039/c1cs15222j.

Touré BB, Hall DG. Natural product synthesis using multicomponent reaction strategies. Chem Rev. 2009;109(9):4439–86. https://doi.org/10.1021/cr800296p.

Trost B. The atom economy: a search for synthetic efficiency. Science. 1991;254(5037):1471–7. https://doi.org/10.1126/science.1962206.

Xie P, Wang J, Liu Y, Fan J, Wo X, Fu W, Loh TP. Water-promoted C-S bond formation reactions. Nat Commun. 2018;9(1):1321. https://doi.org/10.1038/s41467-018-03698-8.

Xie LY, Peng S, Liu F, Liu YF, Sun M, Tang Z, He WM. Clean preparation of quinolin-2-yl substituted Ureas in water. ACS Sustain Chem Eng. 2019;7:7193. https://doi.org/10.1021/acssuschemeng.9b00200.

Yang J, Mei F, Fu S, Gu Y. Facile synthesis of 1,4-diketones via three-component reactions of α-ketoaldehyde, 1,3-dicarbonyl compound, and a nucleophile in water. Green Chem. 2018;20(6):1367–74. https://doi.org/10.1039/c7gc03644b.

Zhang F-Z, Tian Y, Li G-X, Qu J. Intramolecular etherification and polyene cyclization of π-activated alcohols promoted by hot water. J Organomet Chem. 2015;80:1107–15.

Zhu J, Bienaymé H. Multicomponent reactions. Weinheim: Wiley-VCH; 2005.

Zong Y, Lang Y, Yang M, Li X, Fan X, Wu J. Synthesis of β-sulfonyl amides through a multicomponent reaction with the insertion of sulfur dioxide under visible light irradiation. Org Lett. 2019;216:1935–8. https://doi.org/10.1021/acs.orglett.9b00620.

# Applications of Ionic Liquids in Organic Synthesis

**Poonam, Geetanjali, and Ram Singh**

## Contents



## Abbreviations

| | |
|---|---|
| ([bmim]OH) | 1-Butyl-3-methylimidazolium hydroxide |
| $[(CH_2)_2COOHmim][HSO_4]$ | N-carboxyethyl- N-methylimidazolium hydrosulphate |
| $[C_2O_2BBTA][TFA]$ | 1-Butyl-3-carboxymethyl-triazoliumtrifluoroacetate |
| $[HexPy][PF_6]$ | N-hexylpyridinium hexafluorophosphate |
| {[Cbmim]Cl} | 3-(2-Carboxybenzoyl)-1-methyl-1-H-imidazol-3-ium chloride |
| DHPs | Dihydropyrimidinones |
| ILs | Ionic Liquids |
| MW | Microwave |

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_3

| | |
|---|---|
| PSBIL | Poly-(4-(1-(4-vinylbenzyl)-1H-benzimidazol-3-ium-3-yl)-butane-1-sulfonate |
| RTILs | Room Temperature Ionic Liquids |
| TBAB | Tetrabutylammonium bromide |
| TBHPB | Tributylhexadecylphosphonium bromide |

## 1 Introduction

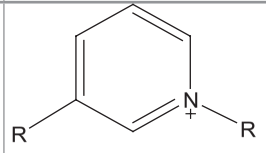
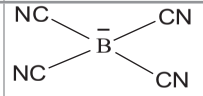
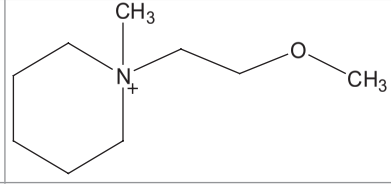
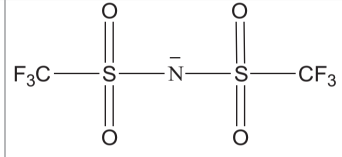
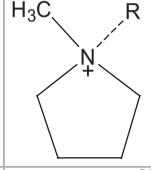
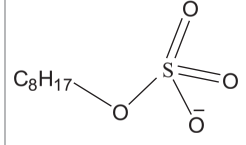
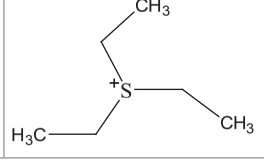
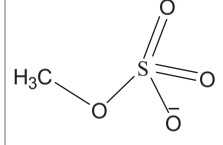
Organic synthesis is the construction of organic compounds using chemical reactions (Cornforth 1993). This is one of the important branches of organic chemistry. The study of organic synthesis exposes a chemist to a wide range of interrelated organic reactions along with the use of varied reagents, reactants, and reaction conditions. New compounds are generated either by breaking and formation of C–C bond or incorporating different functional group. The design and process of organic synthesis has shifted from traditional reaction condition to more environmental benign methods. The use of ionic liquids (ILs) in organic synthesis is a step towards this shifting (Qureshi et al. 2014; Jindal and Surya 2015).

The popularity of ILs in recent years has increased in organic synthesis (Ghandi 2014; Fumino and Ludwig 2014; Eyckens and Henderson 2019; Wasserscheid and Welton 2007). The history and concepts of ILs have been well documented in the form of books (Wasserscheid and Welton 2007), reviews (Ghandi 2014; Davis 2004; Kaur 2019), and research papers (Hardacre and Parvulescu 2014; Hallett and Welton 2011; Patel and Lee 2012; Rodríguez 2016). In this chapter, an attempt has been made to cover various chemical transformations taking place using ILs as solvents and reagents.

## 2 Ionic Liquids (ILs)

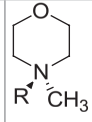
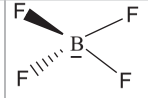
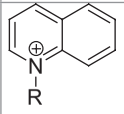
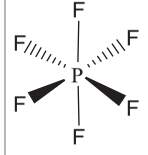
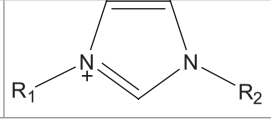
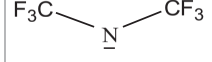
Ionic liquids (ILs) consist of ions and remain in liquid physical state at or below 100 °C (Ghandi 2014; Welton 2018). When ILs are present in liquid state at room temperature, they are known as room temperature ionic liquids (RTILs). These ILs consists of two ions that interact with each other from a combination of Coulombic forces, π–π interactions, hydrogen bonds, and dispersion forces (Fumino and Ludwig 2014). One of the ions consists of organic cations like imidazolium, pyridinium, piperidinium, quinolinium, etc., and other ions include organic or inorganic anions. Examples of some frequently utilised cations and anions are given in Table 3.1. The ILs have developed over generations, starting from the first generation in the 1980s as tetrachloroaluminates (Fig. 3.1) (Wilkes et al. 1982). The 1990s gave the second-generation ILs, which were more air and water stable (Wilkes and

**Table 3.1** Examples of cations and anions frequently used for ILs

| Name of cations | Chemical structure of cations | Name of anions | Chemical structure of anions |
|---|---|---|---|
| Pyridinium |  | Tetracyanoborate TCB: $[B(CN)_4]$ |  |
| Piperidinium |  | Bis(trifluoromethylsulfonyl)imide NTF: $[N(SO_2CF_3)_2]^-$ |  |
| Pyrrolidinium |  | Octyl sulfate |  |
| Sulfones |  | Methyl sulfate |  |

(continued)

**Table 3.1** (continued)

| Name of cations | Chemical structure of cations | Name of anions | Chemical structure of anions |
|---|---|---|---|
| Morpholinium |  | Tetrafluoroborate |  |
| Quinolinium |  | Hexafluoroborate |  |
| Imidazolium |  | Bis(trifluoromethyl)amide |  |

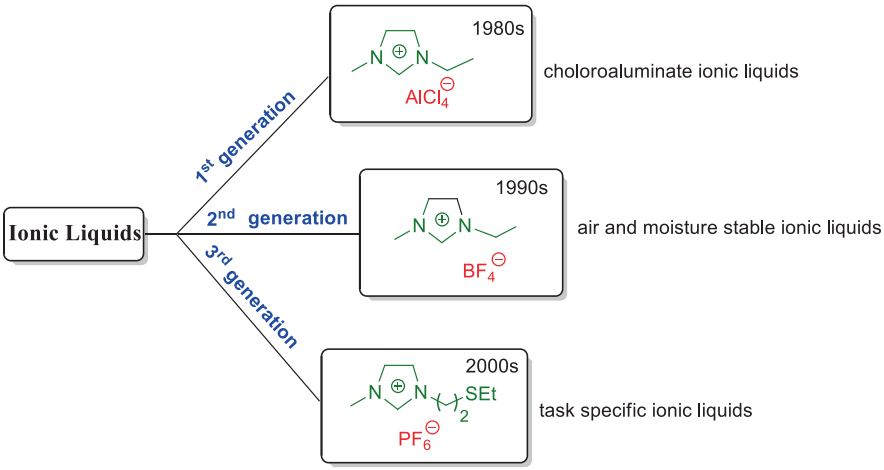
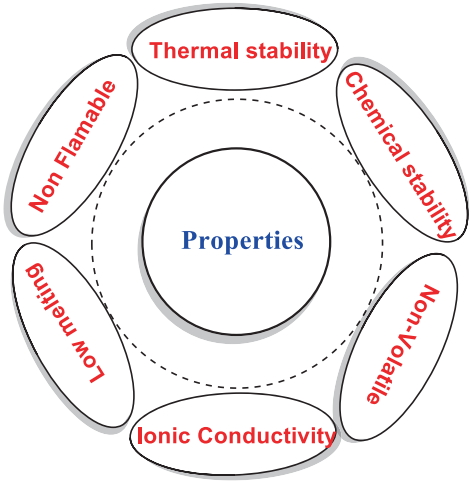



**Fig. 3.1** Development of ILs in different generations

**Fig. 3.2** Properties of ILs




Zaworotko 1992). The third-generation ILs were more task s`pecific (Fig. 3.1) (Davis 2004). With time, the ILs developed various properties such as thermal stability (Vekariya 2017; Fox et al. 2008; Villanueva et al. 2013), ionic conductivity (Zech et al. 2010), non-flammability (Fox et al. 2008), and so on (Fig. 3.2).

Due to their unique and extraordinary properties, ILs find applicability in varied fields like organic synthesis (Hallett and Welton 2011; Zhang et al. 2011; Headley and Headley 2010; Sawant et al. 2011), catalysis (Hardacre and Parvulescu 2014; Dupont and Kollár 2015; Dupont et al. 2015; Mohammad 2012), separations (Patel and Lee 2012; Lei et al. 2014; Rodríguez 2016; Vidal et al. 2012; Cowan et al. 2016), biotransformation (Wasserscheid and Welton 2007), nano-organization and

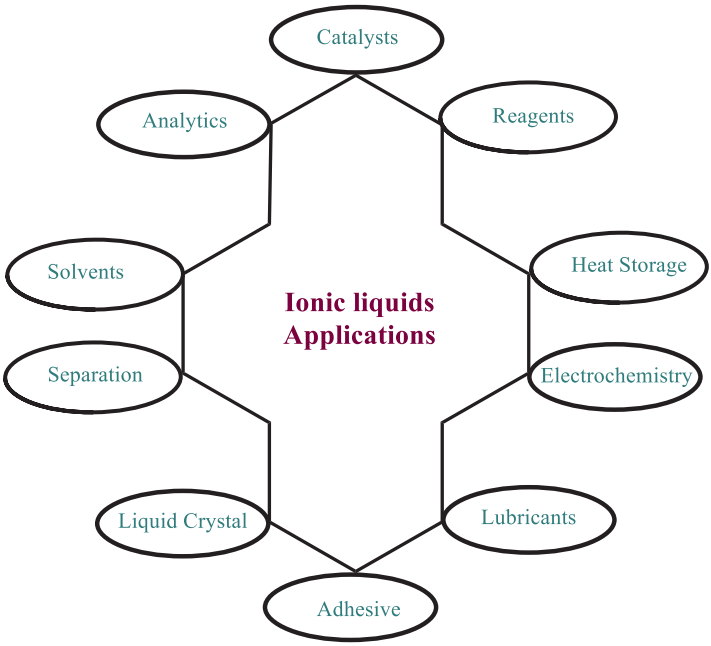



**Fig. 3.3** Some applications of ILs

self-assembly (Hayes et al. 2015; Dong and Zhang 2012), and many other fields (Fig. 3.3) (Zhang and Shreeve 2014; Ho et al. 2011; Freire et al. 2012; Smiglak et al. 2014; Naushad et al. 2012; Weingärtner et al. 2012; Patel et al. 2014; Plechkova and Seddon 2014; Plechkova and Seddon 2016; Jordan and Gathergood 2015; Egorova et al. 2017).

## 3 Applications of Ionic Liquids (ILs) in Organic Synthesis

The use of ILs in organic synthesis has been a step forward towards green and sustainable chemical synthesis and green chemistry movements. The suitable physiochemical properties helped the utilization of ILs in the inorganic, organic, and biocatalytic reactions (Wasserscheid and Welton 2007). The ILs provided alternative reaction media for the reactions mainly associated with transition metal catalysis, acids and bases leading to better organic transformations. A large number of review articles have been compiled on this topic like reaction chemistry in ILs by Welton (Welton 1999), catalysis in ILs by Dupont (Dupont et al. 2000) and Sheldon (Sheldon 2001), applications of ILs in organic synthesis and catalysis by Qureshi (Qureshi et al. 2014), solvate ILs by Eyckens (Eyckens and Henderson 2019), chloroaluminate(III) ionic liquids and industrial applications by Seddon (Seddon et al. 2002), and many others (Elgharbawy et al. 2018; Kaur

2019). This section deals with the applications of ILs in selected named reactions like Biginelli reaction, Knoevenagel reaction, Michael reaction, Heck reaction, and Friedel–Crafts alkylation and acylation.

## *3.1 Biginelli Reaction*

The Biginelli reaction is a classic multicomponent one-pot process for the preparation of dihydropyrimidinones (DHPs) using 1,3-dicarbonyl compounds, aldehydes, and thiourea/urea in presence of an acid catalyst. The ILs have been utilised for the synthesis of Biginelli reactions (Gui et al. 2009; Jawale et al. 2011; Zarnegar and Safari 2014; Khiratkar et al. 2016). The IL $[(CH_2)_2COOHmim][HSO_4]$ has been reported to catalyse the synthesis of various DHPs using urea, various aromatic aldehydes, and methyl acetoacetate. The yield of the products was up to 97%. The ionic liquid was found to catalyse benzaldehydes with both electron donating and withdrawing groups (Fig. 3.4) (Gui et al. 2009).

Jawale et al. have utilised the catalytic properties of IL 3-methyl-1-[3-(methyl-1H-imidazolium-1-yl)propyl]-1H-imidazolium dibromide (C3[min]$_2$2[Br$^-$]) for the synthesis of DHPs (Jawale et al. 2011). The dicationic ionic liquid possessed two imidazole cations and two bromide ions. This IL was advantageous over the traditional mono cationic ILs because they established stronger hydrogen bonds with the substrate. The dual nature of the IL has reported to perform the following roles: formation of intermolecular H-bonding between carbonyl oxygen of the aldehydes and H-atoms of imidazole cations thereby increasing the electrophilic character of the aldehydic carbonyl carbon, increased nucleophilicity of N atom of urea due to formation of hydrogen bonds between bromide ions of ionic liquid and H-atom of urea that lead to the increased rate of nucleophilic attack of urea on electrophilic carbonyl carbon giving rise to intermediate *N*-acyliminium (Jawale et al. 2011). The intermediate undergoes nucleophilic addition by enolic ethyl acetoacetate forming new intermediate which upon dehydration gave DHPs (Fig. 3.5) (Jawale et al. 2011).

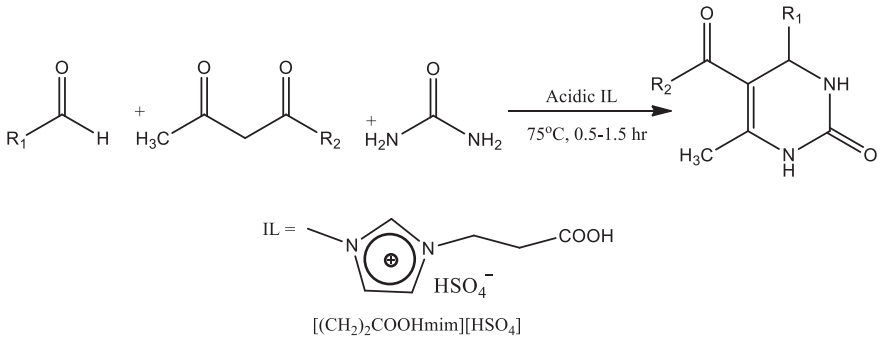



**Fig. 3.4** Synthesis of dihydropyrimidinones using acidic ILs

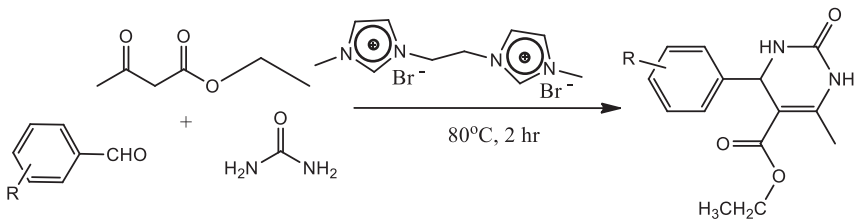



**Fig. 3.5** Synthesis of dihydropyrimidinones using dicationic ILs

Zarnegar et al. used magnetic nano-catalysts, $Fe_3O_4$ nanoparticles supported on imidazolium-based ILs for the synthesis of DHPs (Zarnegar and Safari 2014). The reaction was performed under microwave irradiations in solvent-free conditions media. The MNP–IL–$HSO_4$ acts as a Lewis acid and helps activating the aldehyde to which urea attacks as nucleophilic agent to form N-acylimine intermediate. This intermediate reacts with ethyl acetoacetate enolate leading to formation of ureide intermediate which undergoes cyclization and dehydration forming DHPs (Fig. 3.6) (Zarnegar and Safari 2014).

The poly-(4-(1-(4-vinylbenzyl)-1H-benzimidazol-3-ium-3-yl)-butane-1-sulfonate (PSBIL) reported to catalyse the synthesis of DHPs from aliphatic/aromatic aldehydes, ethyl acetoacetate, and urea or thiourea in ethanol media (Khiratkar et al. 2016). The reaction was heated for 18 h at 110 °C. Aldehydes having electron withdrawing groups were found to give lower yields of DHPs as compared to electron donating groups. PSBIL helps facilitating the reaction between β-keto-ester and aldehyde following Knoevenagel condensation route forming the intermediate. The intermediate undergoes dehydration producing olefin, which reacts with $NH_2$ group of urea/thiourea. The compound formed tautomerizes into a more stable keto form and then cyclizes through nucleophilic attack of $NH_2$ on electrophilic carbonyl carbon. The elimination of water molecule leads to DHPs (Fig. 3.7) (Khiratkar et al. 2016).

The 1-butyl-3-carboxymethyl-triazoliumtrifluoroacetate $[C_2O_2BBTA][TFA]$ ionic liquid with Bronsted acid properties is reported to catalyse Biginelli reaction in solvent-free media to form DHPs. The ionic liquid was found to be equally effective for both electron-withdrawing and electron-donating substituents on aldehyde (Fig. 3.8) (Liu et al. 2016).

An acidic IL, 3-(2-carboxybenzoyl)-1-methyl-1-H-imidazol-3-ium chloride {[Cbmim]Cl}, was reported to perform dual function as catalyst and solvent, both for the synthesis of DHPs (Heidarizadeh et al. 2013). Aldehydes having electron-withdrawing substituents are reported to react slowly hence longer reaction time as compared to aldehydes with electron-donating species. Rate determining step is the formation of acyl imine intermediate which is stabilized by the ionic liquid (Heidarizadeh et al. 2013).

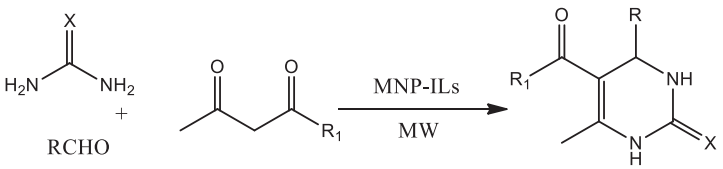



**Fig. 3.6** Synthesis of dihydropyrimidinones using ILs under MW

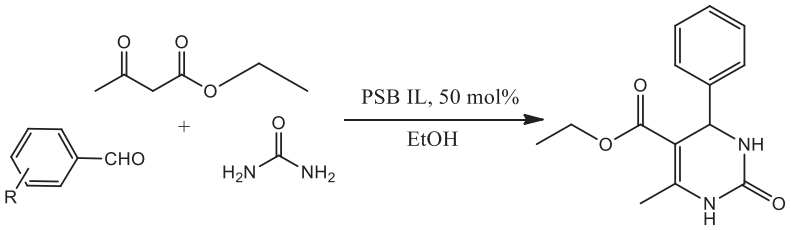
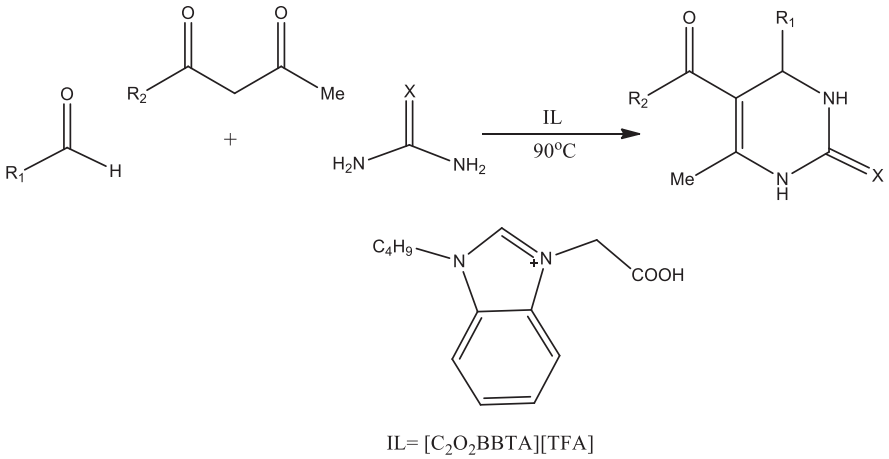



**Fig. 3.7** Synthesis of dihydropyrimidinones using polymeric ILs




IL= [$C_2O_2$BBTA][TFA]

**Fig. 3.8** Synthesis of dihydropyrimidinones using ILs

## *3.2 Knoevenagel Reaction*

Knoevenagel reaction is a reaction of aldehydes with active methylene compounds to form C=C bond and proceed through nucleophilic addition reaction on carbonyl functionality followed by dehydration (Rupainwar et al. 2019). These types of reactions have also been performed in ILs. Burate et al. reported the Knoevenagel con-

densation of aromatic aldehydes, cyclic ketones, heteroaromatic aldehydes, and aliphatic ketones with various active methylene compounds at room temperature and in a solvent-free media catalysed by an acidic Bronsted IL amino acid amide (1-((4-chlorophenyl) amino)-1-oxopropan-2-aminium perchlorate) (Burate et al. 2018). Being protic in nature, the IL protonated the aldehyde forming the intermediate. The nucleophilic attack on the active methylene group is facilitated forming another intermediate. The IL was regenerated by the loss of water molecule forming intermediate-(II) and forming the Knoevenagel product (Fig. 3.9) (Burate et al. 2018).

The tetrabutylammonium salts (cation) of 8 natural amino acids (anion) have also been used as co-solvent with water and catalyst for Knoevenagel condensation (Ossowicz et al. 2013; Ossowicz et al. 2016). These ILs are biodegradable and prepared from renewable material. Out of the synthesised ILs, tetrabutylammonium salts with L-valinate and L-leucinate were found to produce the highest yields, that is 89%. Amino acid anion makes the catalyst a proton acceptor. The reaction proceeds by deprotonation of methylene group by catalyst. Tetrabutylammonium cation favours nucleophilic attack by making the carbonyl carbon more electron deficient. Water plays an important role by preventing the formation of Schiff's base which gets formed by reaction of AAILs with aldehyde in anhydrous medium (Ossowicz et al. 2013; Ossowicz et al. 2016) (Fig. 3.10).

Another basic IL, [bnmim]OH, was reported to act as solvent as well as catalyse Knoevenagel condensation by simple grinding. Hence, provides a simple and time efficient process yielding 96% product. Ionic liquids were reported to absorb the water produced during the condensation (Shelkea and Khadse 2015).

Ionic liquid–supported proline IV ([Promim]$CF_3COO$) has been used to catalyse Knoevenagel condensation between aryl/conjugated or aliphatic aldehydes and malononitrile; $CH_3CN$ is used as solvent. The product was obtained in 96% yield. Aromatic and conjugated aldehydes produced better yields of product. The reaction proceeded due to stability of imine electrophile provided by the electron-donating groups of aromatic aldehyde and ionic liquid (Zhuo et al. 2011).

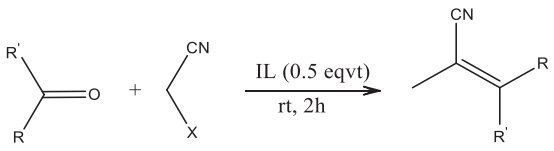



**Fig. 3.9** Formation of C–C bond using ILs in Knoevenagel reaction

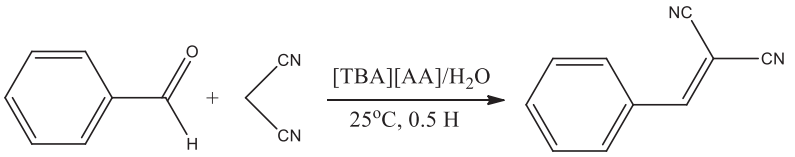



**Fig. 3.10** Synthesis of 2-benzylidenemalononitrile

## 3.3 Heck Reaction

The Heck reaction is an efficient and powerful synthetic method for the C–C bond formation between haloarenes or haloalkenes and alkenes in the presence of a palladium(0) catalyst and a base. These are a class of stereo- and regioselective reactions (Adams 1992). The ILs have shown their utility in the Heck reaction (Singh et al. 2008; Kaufmann et al. 1996). The reaction of bromobenzene with butyl acrylate reported first time in IL catalysed by palladium salts (Fig. 3.11) (Vallin et al. 2002). The IL utilized was 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF6) under microwave irradiation.

The α,β-unsaturated acetals cross couple with aryl derivatives using different ionic liquids as a solvent in the presence of a Pd catalyst (Beccaria et al. 2006). The reaction showed regio- and stereoselectivity. The reaction in molten tetraalkylammonium bromide (Bouquillion et al. 2001), 1-butyl-3-methyl imidazolium hexafluorophosphate [bmim][$PF_6$], and *N*-hexylpyridinium hexafluorophosphate [HexPy][$PF_6$] had also been reported (Carmichael et al. 1999; Howarth and Dallas 2000). The ionic liquids solubilise the catalysts which made the extraction of product easy in non-polar solvent (Singh et al. 2008).

The Heck coupling using palladium chloride ($PdCl_2$) in molten tetraalkylammonium bromide (n-$Bu_4NBr$) between haloarene and allylic alcohols using sodium bicarbonate ($NaHCO_3$) gave arylated carbonyl compounds (Bouquillion et al. 2001) (Fig. 3.12). The reaction was further extended for the synthesis of a non-steroidal anti-inflammatory drug nabumetone (Fig. 3.13). The reaction was done with allyl alcohol and 2-bromo-6-methoxynaphthalene through Heck coupling in IL (Bouquillion et al. 2001).

The application of $Pd_2(allyl)_2Cl_2$ has been reported for the Heck reaction as surface active agent for the synthesis of ethyl cinnamate using ethyl acrylate and iodobenzene in the IL-aqueous micellar solution (Fig. 3.14) (Taskin et al. 2017). A number of dodecylimidazolium-based ILs were utilized and studied for this reac-

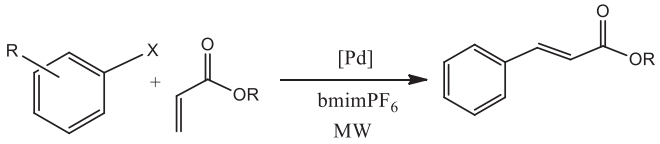



**Fig. 3.11** Heck Arylations in IL, bmim$PF_6$

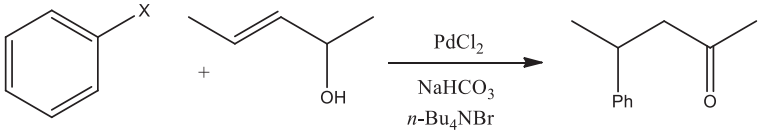
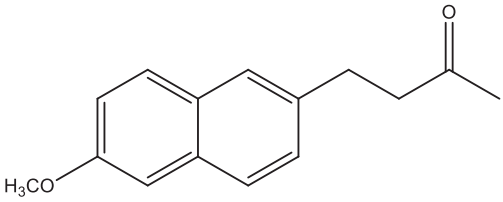



**Fig. 3.12** Heck arylation with allyl alcohol

**Fig. 3.13** Nabumetone



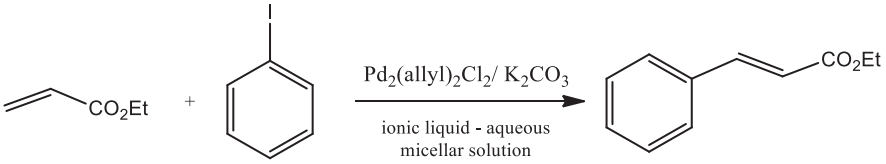




**Fig. 3.14** Heck reaction of ethyl acrylate and iodobenzene in IL-aq micellar solutions

tion. The authors studied the role of concentration of ILs in water and observed its importance in the formation of the catalytically active species (Taskin et al. 2017).

A comparison between imidazolium and pyridinium ionic liquids has been reported stating that imidazolium ionic liquids provide better media for Heck reaction. The former carries acidic protons and deprotonates to form a carbene in the presence of a basic species (Herrmann and Kocher 1997). These imidazolylidine carbenes work as ligands for several metals like palladium(II) which lead to the formation of an imidazolylidine–palladium carbenoid complex (McGuinness et al. 1999). This complex has been reported to re-dissolve palladium black at lower temperature (Carmichael et al. 1999). Mo et al. performed Heck arylation using the IL, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][$BF_4$]) as solvent (Fig. 3.15) (Mo et al. 2005). The electron-rich olefins with aryl bromides and iodides gave excellent regioselectivity.

Mo et al. further prepared γ-arylated γ,δ-unsaturated ketones using the Heck arylation with electron-rich olefin (Mo et al. 2007). The regioselectivity was observed with the change in ligand (Fig. 3.16). The reaction of 5-hexen-2-one with aryl bromides in the IL [bmim][$BF_4$] showed regioselectivity, leading predominantly to branched γ-arylated products with Pd-DPPP [DPPP = 1,3-bis(diphenylph osphino)propane] catalysis. However, the use of ligand 1,1′-bis(diphenylphosphino) ferrocene (DPPF) afforded predominantly the (E)-type of the product (Mo et al. 2007).

Ionic liquids with functionalized networks such as [bmim][OAc] and [bmim] [TPPMS] in the presence of $PdCl_2(CH_3CN)_2$ helped the Heck reaction of bromobenzene and ethyl cinnamate efficiently (Liu et al. 2006). The catalytic activity was retained after 11 cycles as well. This advantageous effect of the ionic liquid is due to the synergic ligand effects [bmim][TPPMS] and [bmim] [OAc]. [Bmim][OAc] acts as base and prevents sodium or potassium ammo-

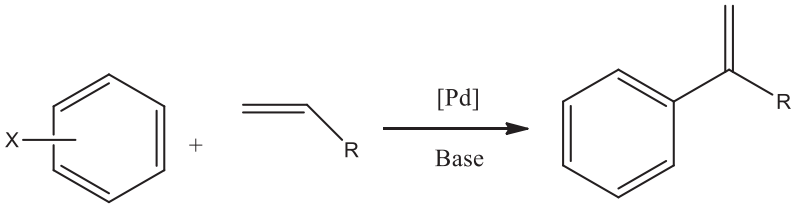



**Fig. 3.15** Arylation of electron-rich olefins

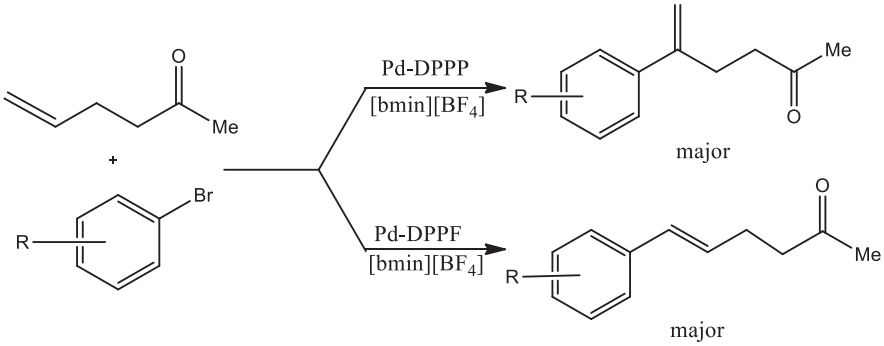



**Fig. 3.16** Regioselective Heck arylation

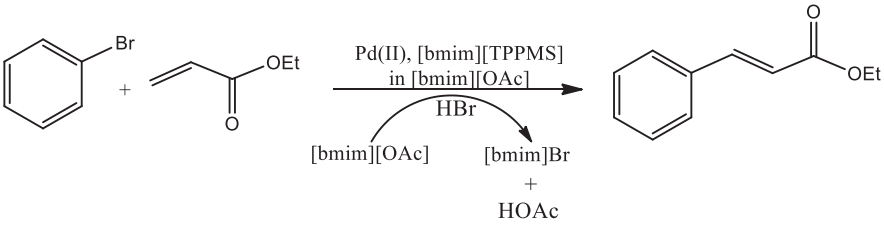



**Fig. 3.17** Heck arylation of ethyl acrylate

nium bromide from accumulation, whereas [bmim][Br] quench the formation of Pd black (Fig. 3.17) (Liu et al. 2006; Singh et al. 2008).

The coupling between alkenes or alkynes and iodoarenes with Pd(II) catalyst at room temperature has been reported to be facilitated by ultrasonic irradiation in the presence of imidazolium ionic liquids (Deshmukh et al. 2001; Singh et al. 2008). Palladium acetate [$Pd(OAc)_2$] or palladium chloride [$PdCl_2$] serves as Pd source for the reaction between ethyl acrylate and iodobenzene in the presence of [bmim][$BF_4$] needed to heat at 90 °C for 24 hours to produce 43% ethyl cinnamate (Xu et al. 2000; Singh et al. 2008).

## 3.4 Michael Reaction

The Michael reaction or Michael addition is a useful method for the C–C bond formation. This reaction uses the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound. This reaction has also been extended for the formation of C–X type of bonds (Fig. 3.18) (Yadav et al. 2003). Yadav et al. used a hydrophobic ionic liquid [bmim]$PF_6$/$H_2O$ solvent system (2:1) without catalyst to obtain Michael adducts with excellent 1,4-selectivity under mild and neutral conditions (Yadav et al. 2003). The used ILs (Fig. 3.19) recycled for four to five times with consistent activity.

Meciarova et al. synthesized the Michael product using thiophenols and chalcones in different ILs and organocatalysts with excellent chemical yields and very low enantioselectivity (Figs. 3.20 and 3.21) (Meciarova et al. 2006). The structure of ionic liquid played an important role in the rate of the reaction when used without any catalyst. The aza-Michael addition reaction was performed in ILs using 2′-aminochalcones. The IL used for the intramolecular cyclization was 1-N-butyl-3-methylimidazolium tetrafluoroborate as the solvent and catalyst, which was also regenerated and reused (Fig. 3.22) (Chelghoum et al. 2012).

The chiral ionic liquids have also been used for Michael reaction. The enantioselective Michael reaction was performed using imidazolium-based chiral ILs and

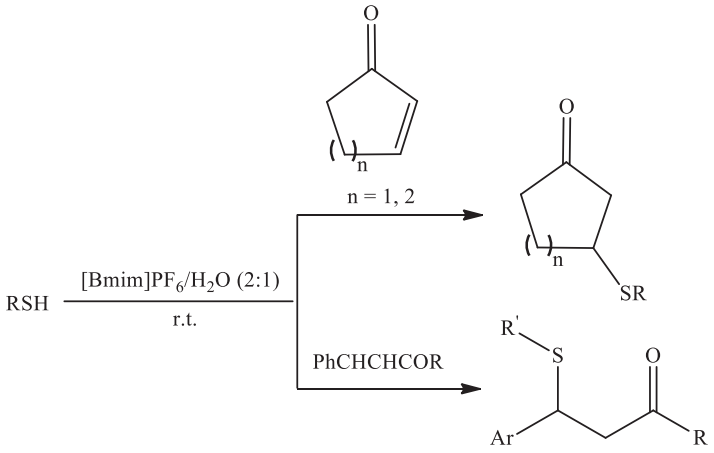



**Fig. 3.18** Formation of C–S bond in ILs

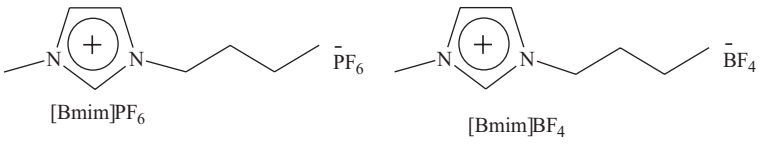



**Fig. 3.19** Chemical structures of Bmim ILs

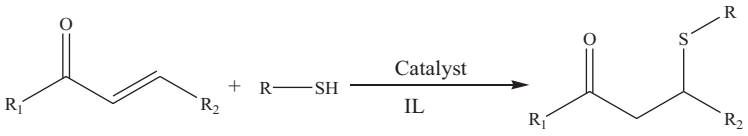



**Fig. 3.20** Formation of Michael products with thiophenols and chalcones

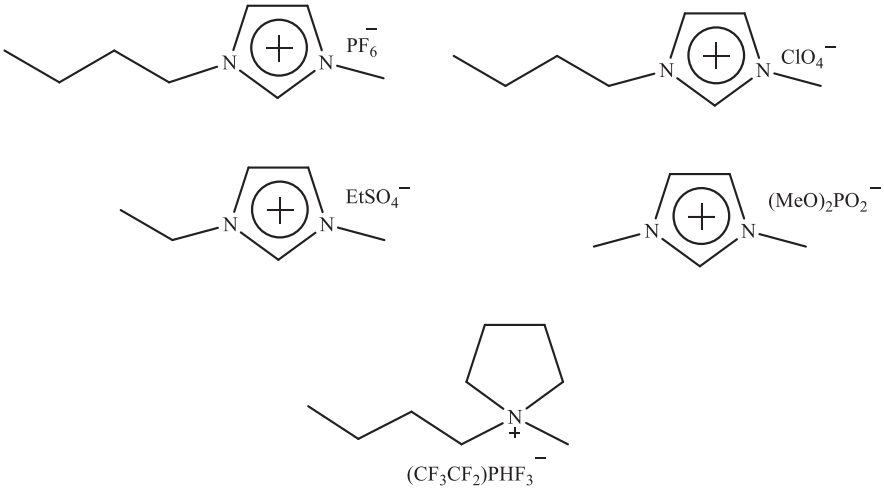



**Fig. 3.21** Chemical structures of ILs

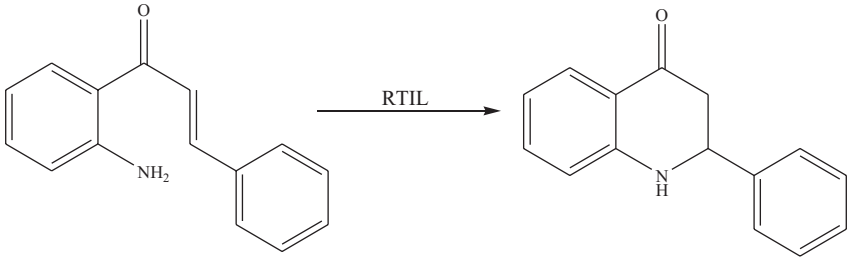



**Fig. 3.22** Formation of C–N bond in ILs

acetonitrile as the co-solvent for the reaction between diethyl malonate to chalcone (Suzuki 2018; Ou and Huang 2006). The chiral ILs were prepared from 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride and L-amino alcohols exhibiting enantioselectivity up to 15% enantiomeric excess (ee) (Fig. 3.23) (Ou and Huang 2006). In 2013, Suzuki et al. synthesized chiral ILs and used them for Michael reactions (Fig. 3.24) (Suzuki et al. 2013).

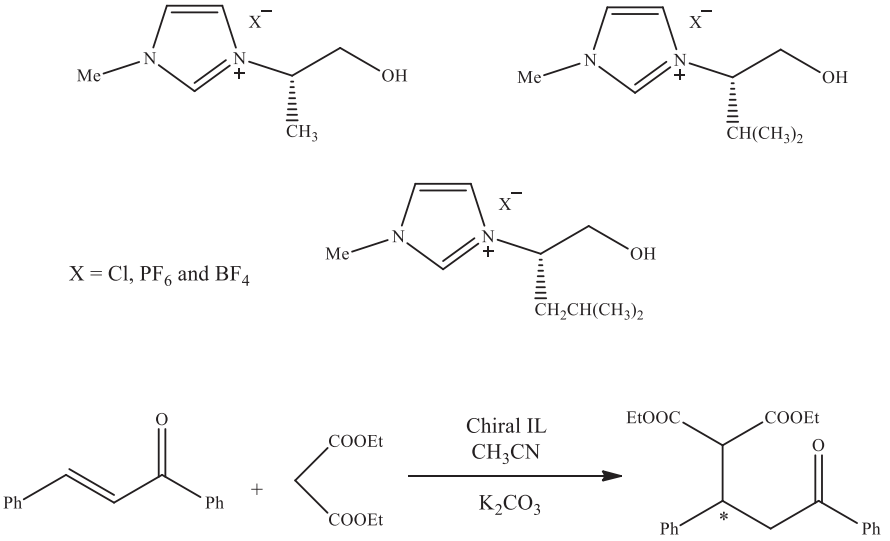



**Fig. 3.23** Michael reaction with chiral ILs

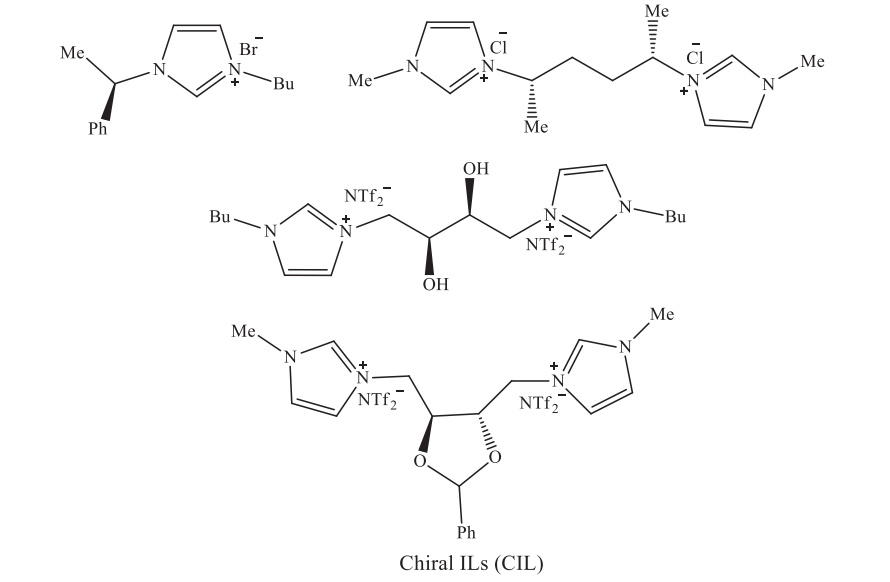



**Fig. 3.24** Chiral ILs and their application in Michael reaction

## 3.5 *Friedel–Crafts Alkylation and Acylation*

The alkylation and acylation of an aromatic ring using the electrophilic substitution reaction takes place through the Friedel–Crafts reaction. The alkyl halide is used for alkylation and acyl halide for acylation in the presence of strong Lewis acid catalyst. The Friedel–Crafts reaction was first performed in the IL, 3-ethyl-1-methylimidazolium [emim]–aluminium chloride where methyl chloride and acetyl chloride utilized as the alkylating and acylating agents (Fig. 3.25) (Boon et al. 1986). The authors discussed the Lewis acidic character of IL with cation, [emim]. Many works have been carried out since then. The ILs have been found to be good for regiochemical reactions where control of the reaction was excellent (Earle et al. 1998). The reversibility of the reaction was also observed for the electron-rich polyaromatics like anthracene (Earle et al. 1998). Supported ILs have also been useful in the Friedel–Crafts reactions (Joni et al. 2009). The silica supported ILs have been successfully used for slurry-phase alkylation of cumene (Joni et al. 2009). An acidic and non-chloroaluminate IL system has been successfully used for the reaction of benzene with 1-decene to give the Friedel–Crafts alkylation products (Fig. 3.26) (Wasserscheid et al. 2002). Hydrogensulfate and tetrakis(hydrogensulfato)borate ILs are being used to study the regioselectivities of the reaction.

The two ionic liquids, 1-ethylpyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) and 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF4]^-$), have been successfully used for the acylation of benzene and their derivatives (Liu et al. 2009; Xiao and Malhotra 2005). The Friedel–Crafts alkylation and acylation in ILs are facile, show high selectivity and conversion rate but also face a lot of limitations, mainly in product separation.

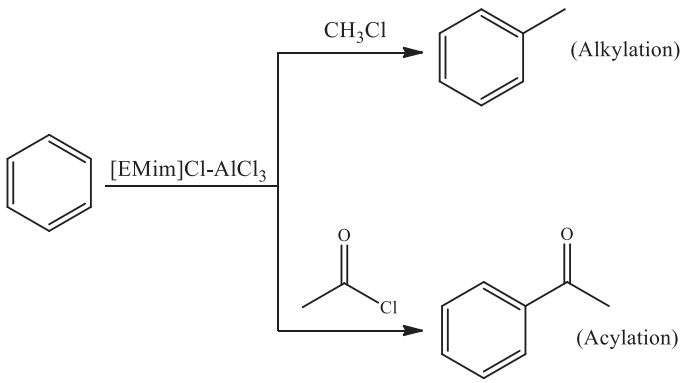



**Fig. 3.25** Friedel–Crafts alkylation and acylation in IL

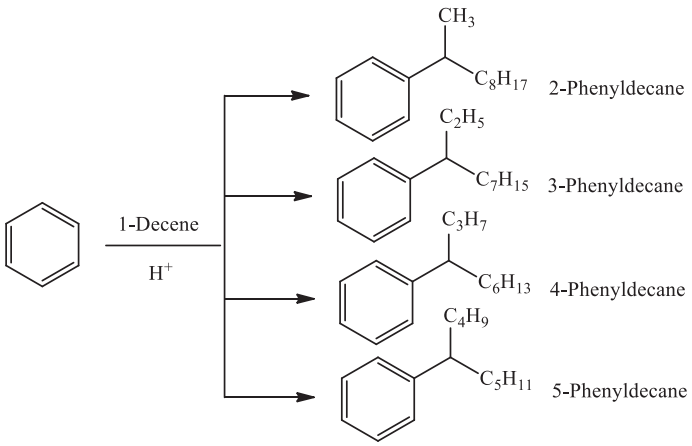



**Fig. 3.26** Regioselectivities in Friedel–Crafts alkylation

## 4 Conclusion

Ionic liquids (ILs) are sustainable alternatives to many reagents, catalysts, and most of the volatile organic solvents. ILs consist of cationic and ionic part; together they exist as salts and possess melting points less than 100 °C. As the research on ILs progress, the organic heterocyclic moieties as cationic part become more prevalent and useful. ILs possess unique set of properties with respect to their cationic and anionic components due to which ILs are used in varied fields.

The application of ILs in organic synthesis have been widely exploited and used in almost all types of reactions. This chapter gave a brief introduction on the ILs and their applications in organic synthesis by giving examples of five named reactions, Biginelli reaction, Knoevenagel reaction, Michael reaction, Heck reaction, and Friedel–Crafts alkylation and acylation.

**Acknowledgements** The authors are grateful to Delhi Technological University for providing necessary facilities to carry out this work. The author Poonam is thankful for financial support.

## References

Adams DL. Toward the consistent use of regiochemical and stereochemical terms in introductory organic chemistry. J Chem Educ. 1992;69:451. https://doi.org/10.1021/ed069p451.

Beccaria L, Deagostino A, Prandi C, Zavattaro C, Venturello P. Heck reaction on 1-alkoxy-1,3-dienes in ionic liquids: a superior medium for the regioselective arylation of the conjugated dienic system. Synlett. 2006;2006:2989–92. https://doi.org/10.1055/s-2006-948183.

Boon JA, Levisky JA, Pflug JL, Wilkes JS. Friedel–crafts reactions in ambient-temperature molten salts. J Organomet Chem. 1986;51:480–3. https://doi.org/10.1021/jo00354a013.

Bouquillion S, Ganchegui B, Estrine B, Henin F, Muzart J. Heck arylation of allylic alcohols in molten salts. J Organomet Chem. 2001;634:153–6. https://doi.org/10.1016/S0022-328X(01)01149-4.

Burate PA, Javle BR, Desale PH, Kinage AK. Solvent-free Knoevenagel condensation over amino acid amide based ionic liquid as an efficient and eco-friendly catalyst. Synth Catal. 2018;3:6. https://doi.org/10.4172/2574-0431.100024.

Carmichael AJ, Earle MJ, Holbrey JD, McCormac PB, Seddon KR. The Heck reaction in ionic liquids: a multiphasic catalyst system. Org Lett. 1999;1:997–1000. https://doi.org/10.1021/ol9907771.

Chelghoum M, Bahnous M, Bouraiou A, Bouacida S, Belfaitah A. An efficient and rapid intramolecular aza-Michael addition of 2′-aminochalcones using ionic liquids as recyclable reaction media. Tetrahedron Lett. 2012;53:4059–61. https://doi.org/10.1016/j.tetlet.2012.05.097.

Cornforth JW. The trouble with synthesis. Aust J Chem. 1993;46(2):157–70. https://doi.org/10.1071/CH9930157.

Cowan MG, Gin DL, Noble RD. Poly(ionic liquid)/ionic liquid ion-gels with high “free” ionic liquid content: platform membrane materials for CO2/light gas separations. Acc Chem Res. 2016;49:724–32. https://doi.org/10.1021/acs.accounts.5b00547.

Davis JH. Task-specific ionic liquids. Chem Lett. 2004;33:1072–7. https://doi.org/10.1246/cl.2004.1072.

Deshmukh RR, Rajagopal R, Srinivasan KV. Ultrasound promoted C–C bond formation: Heck reaction at ambient conditions in room temperature. Chem Commun. 2001;2001:1544–5. https://doi.org/10.1039/B104532F.

Dong K, Zhang SJ. Hydrogen bonds: a structural insight into ionic liquids. Chem Eur J. 2012;18:2748–61. https://doi.org/10.1002/chem.201101645.

Dupont J, Consorti CS, Spencer J. Room temperature molten salts: neoteric "green" solvents for chemical reactions and processes. J Braz Chem Soc. 2000;11:337–44. https://doi.org/10.1590/S0103-50532000000400002.

Dupont J, Itoh T, Lozano P, Malhotra SV. Environmentally friendly syntheses using ionic liquids. Boca Raton/London/New York: CRC Press; 2015. https://doi.org/10.1201/b17508.

Dupont J, Kollár L. Ionic liquids (ILs) in organometallic catalysis. Berlin/Heidelberg: Springer-Verlag; 2015.

Earle MJ, Seddon KR, Adams CJ, Robert G. Friedel–crafts reactions in room temperature ionic liquids. Chem Commun. 1998:2097–8. https://doi.org/10.1039/A805599H.

Egorova KS, Gordeev EG, Ananikov VP. Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev. 2017;117:7132–89. https://doi.org/10.1021/acs.chemrev.6b00562.

Elgharbawy AA, Riyadi FA, Alam MZ, Moniruzzaman M. Ionic liquids as a potential solvent for lipase-catalysed reactions: a review. J Mol Liq. 2018;251:150–66. https://doi.org/10.1016/j.molliq.2017.12.050.

Eyckens DJ, Henderson LC. A review of solvate ionic liquids: physical parameters and synthetic applications. Front Chem. 2019;7 https://doi.org/10.3389/fchem.2019.00263.. Article 263

Fox DM, Gilman JW, Morgan AB, Shields JR, Maupin PH, Lyon RE, Long HCD, Trulove PC. Flammability and thermal analysis characterization of imidazolium-based ionic liquids. Ind Eng Chem Res. 2008;47(16):6327–32. https://doi.org/10.1021/ie800665u.

Freire MG, Claudio AF, Araujo JM, Coutinho JA, Marrucho IM, Canongia Lopes JN, Rebelo LP. Aqueous biphasic systems: a boost brought about by using ionic liquids. Chem Soc Rev. 2012;41:4966–95. https://doi.org/10.1039/C2CS35151J.

Fumino K, Ludwig R. Analyzing the interaction energies between cation and anion in ionic liquids: the subtle balance between coulomb forces and hydrogen bonding. J Mol Liq. 2014;192:94–102. https://doi.org/10.1016/j.molliq.2013.07.009.

Ghandi K. A review of ionic liquids, their limits and applications. Green Sustainable Chem. 2014;4:44–53. https://doi.org/10.4236/gsc.2014.41008.

Gui J, Liu D, Wang C, Lu F, Lian J, Jiang H, Sun Z. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by acidic ionic liquids under solvent-free conditions. Synth Commun. 2009;39:3436–43. https://doi.org/10.1080/00397910902774042.

Hallett JP, Welton T. Room-temperature ionic liquids: solvents for synthesis and catalysis. 2. Chem Rev. 2011;111:3508–76. https://doi.org/10.1021/cr1003248.
Hardacre C, Parvulescu V. Catalysis in ionic liquids: from catalyst synthesis to application. Cambridge: The Royal Society of Chemistry; 2014. https://doi.org/10.1039/9781849737210.
Hayes R, Warr GG, Atkin R. Structure and nanostructure in ionic liquids. Chem Rev. 2015;115:6357–426. https://doi.org/10.1021/cr500411q.
Headley N, Headley AD. Ionic liquid supported (ILS) catalysts for asymmetric organic synthesis. Chem Eur J. 2010;16:4426–36. https://doi.org/10.1002/chem.200902747.
Heidarizadeh T, Nezhad ER, Sajjadifar S. Novel acidic ionic liquid as a catalyst and solvent for green synthesis of dihydropyrimidine derivatives. Sci Iran. 2013;20:561–5. https://doi.org/10.1016/j.scient.2012.12.039.
Herrmann WA, Kocher C. N-Heterocyclic carbenes. Angew Chem Int Ed Eng. 1997;36:2163–87. https://doi.org/10.1002/anie.199721621.
Ho TD, Canestraro AJ, Anderson JL. Ionic liquids in solid-phase microextraction: a review. Anal Chim Acta. 2011;695:18–43. https://doi.org/10.1016/j.aca.2011.03.034.
Howarth J, Dallas A. Moisture stable ambient temperature ionic liquids: solvents for the new millennium. 1. The Heck reaction. Molecules. 2000;5:851–5. https://doi.org/10.3390/50600851.
Jawale DV, Pratap UR, Mulay AA, Mali JR, Mane RA. Synthesis of new dihydropyrimidinones catalysed by dicationic ionic liquid. J Chem Sci. 2011;123:645–55. https://doi.org/10.1007/s12039-011-0127-y.
Jindal R, Surya AS. Preparation and applications of room temperature ionic liquids in organic synthesis: a review on recent efforts. Curr Green Chem. 2015;2(2):135–55. https://doi.org/10.2174/2213346101666140915212515.
Joni J, Haumann M, Wasserscheid P. Development of a supported ionic liquid phase (SILP) catalyst for slurry-phase Friedel–crafts alkylations of cumene. Adv Synth Catal. 2009;351:423–31. https://doi.org/10.1002/adsc.200800672.
Jordan A, Gathergood N. Biodegradation of ionic liquids – a critical review. Chem Soc Rev. 2015;44:8200–37. https://doi.org/10.1039/C5CS00444F.
Kaufmann DE, Nouroozian M, Henze H. Molten salts as an efficient medium for palladium catalyzed C-C coupling reactions. Synlett. 1996;1996(11):1091–2. https://doi.org/10.1055/s-1996-5658.
Kaur N. Ionic liquids: a versatile medium for the synthesis of six-membered two nitrogen-containing heterocycles. Curr Org Chem. 2019;23:76–96. https://doi.org/10.2174/1385272823666190111152917.
Khiratkar AG, Muskawarb PN, Bhagat PR. Polymer-supported benzimidazolium based ionic liquid: an efficient and reusable Brønsted acid catalyst for Biginelli reaction. RSC Adv. 2016;6:105087–93. https://doi.org/10.1039/C6RA23781A.
Lei Z, Dai C, Zhu J, Chen B. Extractive distillation with ionic liquids: a review. AICHE J. 2014;60:3312–29. https://doi.org/10.1002/aic.14537.
Liu Y, Li M, Lu Y, Gao GH, Yang Q, He MY. Simple, efficient and recyclable palladium catalytic system for heck reaction in functionalized ionic liquid network. Catal Commun. 2006;7:985–9. https://doi.org/10.1016/j.catcom.2006.05.002.
Liu Z, Ma R, Cao D, Liu C. New efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by benzotriazolium-based ionic liquids under solvent-free conditions. Molecules. 2016;21:462. https://doi.org/10.3390/molecules21040462.
Liu ZC, Meng XH, Zhang R, Xu CM. Friedel-crafts acylation of aromatic compounds in ionic liquids. Pet Sci Technol. 2009;27:226–37. https://doi.org/10.1080/10916460701700898.
McGuinness DS, Cavell KJ, Skelton BW, White AH. Zerovalent palladium and nickel complexes of heterocyclic carbenes: oxidative addition of organic halides, carbon−carbon coupling processes, and the Heck reaction. Organometalics. 1999;18:1596–605. https://doi.org/10.1021/om9809771.
Meciarova M, Toma S, Kotrusz P. Michael addition of thiols to α-enones in ionic liquids with and without organocatalysts. Org Biomol Chem. 2006;4:1420–4. https://doi.org/10.1039/B516289K.

Mo J, Ruan J, Xu L, Hyder Z, Saidi O, Liu S, Pei W, Xiao J. Palladium-catalyzed Heck arylation of 5-hexen-2-one in ionic liquid: a novel approach to arylated $\gamma,\delta$-unsaturated ketones. J Mol Catal A Chem. 2007;261:267–75. https://doi.org/10.1016/j.molcata.2006.08.024.

Mo J, Xu L, Xiao J. Ionic liquid-promoted, highly regioselective Heck arylation of electron-rich olefins by aryl halides. J Am Chem Soc. 2005;127:751–60. https://doi.org/10.1021/ja0450861.

Mohammad AI. Green solvents II: properties and applications of ionic liquids. Berlin/Heidelberg: Springer-Verlag; 2012.

Naushad M, Alothman ZA, Khan AB, Ali M. Effect of ionic liquid on activity, stability, and structure of enzymes: a review. Int J Biol Macromol. 2012;2012(51):555–60. https://doi.org/10.1016/j.ijbiomac.2012.06.020.

Ossowicz P, Janus E, Schroeder G, Rozwadowski Z. Spectroscopic studies of amino acid ionic liquid supported Schiff bases. Molecules. 2013;18(5):4986–5004. https://doi.org/10.3390/molecules18054986.

Ossowicz P, Rozwadowski Z, Gan M, Janus E. Efficient method for Knoevenagel condensation in aqueous solution of amino acid ionic liquids (AAILs). Pol J Chem Technol. 2016;18:90–5. https://doi.org/10.1515/pjct-2016-0076.

Ou WH, Huang ZZ. An efficient and practical synthesis of chiral imidazolium ionic liquids and their application in an enantioselective Michael reaction. Green Chem. 2006;8:731–4. https://doi.org/10.1039/B604801C.

Patel DD, Lee JM. Applications of ionic liquids. Chem Rec. 2012;12:329–55. https://doi.org/10.1002/tcr.201100036.

Patel R, Kumari M, Khan AB. Recent advances in the applications of ionic liquids in protein stability and activity: a review. Appl Biochem Biotechnol. 2014;172:3701–20. https://doi.org/10.1007/s12010-014-0813-6.

Plechkova NV, Seddon KR. Ionic liquids completely uncoiled: critical expert overviews. Hoboken: Wiley; 2016.

Plechkova NV, Seddon KR. Ionic liquids further uncoiled: critical expert overviews. Hoboken: Wiley; 2014.

Qureshi ZS, Deshmukh KM, Bhanag BM. Applications of ionic liquids in organic synthesis and catalysis. Clean Techn Environ Policy. 2014;16:1487–513. https://doi.org/10.1007/s10098-013-0660-0.

Rodríguez H. Ionic liquids for better separation processes. Berlin/Heidelberg: Springer-Verlag; 2016.

Rupainwar R, Pandey J, Smrirti R. The importance and applications of knoevenagel reaction (brief review). Orient J Chem. 2019;35(1):423–9. https://doi.org/10.13005/ojc/350154.

Sawant AD, Raut DG, Darvatkar NB, Salunkhe MM. Recent developments of task-specific ionic liquids in organic synthesis. Green Chem Lett Rev. 2011;4:41–54. https://doi.org/10.1080/17518253.2010.500622.

Seddon RA, Lau RM, Sorgedrager MJ. Biocatalysis in ionic liquids. Green Chem. 2002;4:147–51. https://doi.org/10.1039/B110008B.

Sheldon R. Catalytic reactions in ionic liquids. Chem Commun. 2001;23:2399–407. https://doi.org/10.1039/B107270F.

Shelkea KF, Khadse RE. Ionic liquid is an efficient catalyst for Knoevenagel condensation under grinding method. Der Pharma Chemica. 2015;7(1):191–6.

Singh R, Sharma M, Mamgain R, Rawat DS. Ionic liquids: a versatile medium for palladium-catalyzed reactions. J Braz Chem Soc. 2008;19:357–79. https://doi.org/10.1590/S0103-50532008000300002.

Smiglak M, Pringle JM, Lu X, Han L, Zhang S, Gao H, MacFarlane DR, Rogers RD. Ionic liquids for energy, materials, and medicine. Chem Commun. 2014;50:9228–50. https://doi.org/10.1039/C4CC02021A.

Suzuki Y. Asymmetric Michael addition mediated by chiral ionic liquids. Mini-Rev Org Chem. 2018;15:236–45. https://doi.org/10.2174/1570193X15666171211165344.

Suzuki Y, Wakatusuki J, Tsubaki M, Sato M. Imidazolium based chiral ionic liquids: synthesis and application. Tetrahedron. 2013;69(46):9690–700. https://doi.org/10.1016/j.tet.2013.09.017.
Taskin M, Cognigni A, Zirbs R, Reimhult E, Bica K. Surface-active ionic liquids for palladium-catalysed cross coupling in water: effect of ionic liquid concentration on the catalytically active species. RSC Adv. 2017;7:41144–51. https://doi.org/10.1039/C7RA07757B.
Vallin KSA, Emilsson P, Larhed M, Hallberg A. High-speed Heck reactions in ionic liquid with controlled microwave heating. J Organomet Chem. 2002;67:6243–6. https://doi.org/10.1021/jo025942w.
Vekariya RL. A review of ionic liquids: applications towards catalytic organic transformations. J Mol Liq. 2017;227:44–60. https://doi.org/10.1016/j.molliq.2016.11.123.
Vidal L, Riekkola ML, Canals A. Ionic liquid-modified materials for solid-phase extraction and separation: a review. Anal Chim Acta. 2012;715:19–41. https://doi.org/10.1016/j.aca.2011.11.050.
Villanueva M, Coronas A, Garcí J, Salgado J. Thermal stability of ionic liquids for their application as new absorbents. Ind Eng Chem Res. 2013;52(45):15718–27. https://doi.org/10.1021/ie401656e.
Wasserscheid P, Sesing M, Korth W. Hydrogensulfate and tetrakis(hydrogensulfato)borate ionic liquids: synthesis and catalytic application in highly Brønsted-acidic systems for Friedel–crafts alkylation. Green Chem. 2002;4:134–8. https://doi.org/10.1039/B109845B.
Wasserscheid P, Welton T. Ionic liquids in synthesis. 2nd ed. Weinheim: Wiley-VCH Verlag GmbH & Co.; 2007.
Weingärtner H, Cabrele C, Herrmann C. How ionic liquids can help to stabilize native proteins. Phys Chem Chem Phys. 2012;14:415–26. https://doi.org/10.1039/C1CP21947B.
Welton T. Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev. 1999;99:2071–83. https://doi.org/10.1021/cr980032t.
Welton T. Ionic liquids: a brief history. Biophys Rev. 2018;10:691–706. https://doi.org/10.1007/s12551-018-0419-2.
Wilkes JS, Levisky JA, Wilson RA, Hussey CL. Dialkylimidazolium chloroaluminate melts: a new class of room-temperature ionic liquids for electrochemistry, spectroscopy and synthesis. Inorg Chem. 1982;21:1263–4. https://doi.org/10.1021/ic00133a078.
Wilkes JS, Zaworotko MJ. Air and water stable 1-ethyl-3-methylimidazolium based ionic liquids. Chem Commun. 1992;13:965–7. https://doi.org/10.1039/C39920000965.
Xiao Y, Malhotra SV. Friedel-crafts acylation reactions inpyridinium based ionic liquids. J Organomet Chem. 2005;690:3609–13. https://doi.org/10.1016/j.jorganchem.2005.04.047.
Xu L, Chen W, Xiao J. Heck reaction in ionic liquids and the in-situ identification of *n*-heterocyclic carbene complexes of palladium. Organometallics. 2000;19:1123–7. https://doi.org/10.1021/om990956m.
Yadav JS, Reddy BVS, Gakul B. Green protocol for conjugate addition of thiols to α,β-unsaturated ketones using a [Bmim]$PF_6$/$H_2O$ system. J Organomet Chem. 2003;68:7098–100. https://doi.org/10.1021/jo0343351.
Zarnegar Z, Safari J. Magnetic nanoparticles supported imidazolium-based ionic liquids as nanocatalyst in microwave-mediated solvent-free Biginelli reaction. J Nanopart Res. 2014;16:2509. https://doi.org/10.1007/s11051-014-2509-9.
Zech O, Stoppa A, Buchner R, Kunz W. The conductivity of imidazolium-based ionic liquids from (248 to 468) K. B variation of the anion. J Chem Eng Data. 2010;55(5):1774–8. https://doi.org/10.1021/je900793r.
Zhang Q, Shreeve JM. Energetic ionic liquids as explosives and propellant fuels: a new journey of ionic liquid chemistry. Chem Rev. 2014;114:10527–74. https://doi.org/10.1021/cr500364t.
Zhang Q, Zhang S, Deng Y. Recent advances in ionic liquid catalysis. Green Chem. 2011;13:2619–37. https://doi.org/10.1039/C1GC15334J.
Zhuo C, Xian D, Jian-wei W, Hui X. An efficient and recyclable ionic liquid-supported proline catalyzed Knoevenagel condensation. Int Sch Res Not. 2011; https://doi.org/10.5402/2011/676789.

# Water-Mediated Catalyst-Free Organic Transformations

**Bubun Banerjee**

**Contents**



## 1 Introduction

To protect our *Mother Nature* from the ever-increasing chemical hazards, scientists are constantly trying to develop green and sustainable protocols by avoiding harsh reaction conditions, extensive use of toxic reagents, solvents, and catalysts (Kaneda and Mizugaki 2009); (Trost 2002); (Sankar et al. 2012). It is not required to mention that catalyst has played a crucial role in organic transformations. To reduce the toxicity level of catalysts, scientists are constantly trying to modify them. But above all, catalyst-free condition is the most sustainable way to carry out organic transformations.

On the other hand, water is the safest solvent to carry out organic transformations. It is environment friendly, non-flammable, abundantly available, and cheap. In many occasions, water molecules activate the reactive sites by forming hydrogen bonds (Banerjee 2017a, b). In order to minimize the exposed surface area, hydrophobic organic reactants prefer to form aggregates in water, which helps to increase the rate of the reaction (Gawande et al. 2013); (Breslow 1991); (Butler and Coyne 2010). Thus, a fruitful collaboration between 'catalyst-free reaction condition' and 'water as solvent' can develop the most suitable environmentally benign protocol. Such beneficial features related to

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_4

sustainable developments have motivated organic methodologists to explore water-mediated catalyst-free organic transformations in more depth. As a result, a huge number of protocols have been developed for the preparation of various heterocyclic as well as non-heterocyclic scaffolds under catalyst-free conditions in water.

The main aim of this chapter is to highlight the recent developments on catalyst-free organic transformations occurring in aqueous media. However, no spectroscopic or analytical data are documented herein as it's out of the scope of this chapter.

## 2 Catalyst-Free Organic Transformations in Water

### *2.1 Catalyst-Free Organic Synthesis in Water at Room Temperature*

#### 2.1.1 Chemoselective N-Tert-Butyloxycarbonylation of Amines

*N*-Boc protection of amine was achieved by employing a number of catalysts under various reaction conditions (Grehn and Ragnarsson 1984); (Handy et al. 2004); (Guibé-Jampel and Wakselman 1977); (Basel and Hassner 2000). These reported methods suffered from many demerits such as generation of unwanted by-products, long reaction times, harsh reaction conditions, use of only selective amines, etc. In 2006, a simple, clean, and straightforward aqueous-mediated, catalyst-free chemoselective protocol was developed for the *N*-tert-butyloxycarbonylation of amines (**1**) using di-*tert*-butyl dicarbonate [$(Boc)_2O$] at ambient temperature (Fig. 1) (Chankeshwara and Chakraborti 2006). A variety of amines that include aromatic amines, both primary and secondary aliphatic amines, amino acid ester, amino alcohols were undergone smoothly and produced excellent yields of compound 2 under this catalyst-free reaction conditions. Amine groups selectively protected even in the presence of hydroxyl functionality.

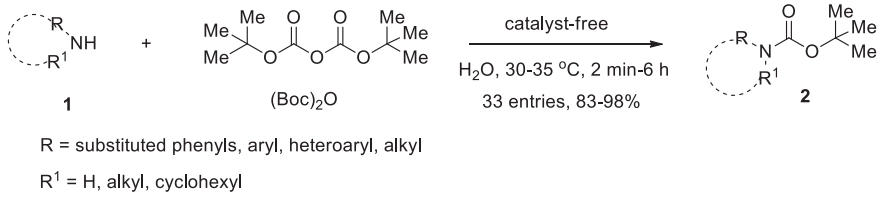



**Fig. 1** Aqueous-mediated Boc-protection of amines at room temperature

### 2.1.2 Aldol Addition Reaction

A catalyst-free aldol addition reaction was accomplished between various aromatic aldehydes (**3**) and *N*-substituted thiazolidinediones (**4**) as aldol donors in aqueous medium which afforded the corresponding β-hydroxy carbonyl adducts (**5**) at room temperature (Fig. 2) (Paladhi et al. 2012). Another type of β-hydroxy carbonyl compounds (**5a**) were synthesized via the addition reactions between Rawal's diene (**6**) and various aldehydes (**3**) in water under catalyst-free conditions at ambient temperature (Fig. 3) (De Rosa and Soriente 2011). Use of water as a solvent, catalyst-free clean reaction conditions, simple work-up procedure, and excellent yields are some of the notable advantages of this protocol.

### 2.1.3 Synthesis of Various Thioethers via Anti-Markovnikov Addition

Addition of thiols to various styrene derivatives was achieved by employing various protic as well as Lewis acidic catalysts (Screttas and Micha-Screttas 1979); (Ipatieff et al. 1938); (Belly and Zamboni 1989); (Kumar et al. 1999); (Braga et al. 1995); (Kanagasabapathy et al. 2001). In maximum cases, these reactions proceeded through Markovnikov addition pathway. In 2008, a series of structurally diverse thioethers (**9**) was synthesized under catalyst-free conditions via anti-Markovnikov addition of thiophenols (**8**) to various styrene derivatives (**7**) in water at room temperature (Fig. 4) (Movassagh and Navidi 2008).

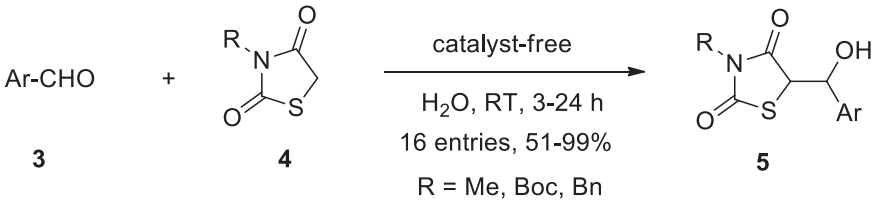



**Fig. 2** Aqueous-mediated catalyst-free aldol addition reaction at room temperature

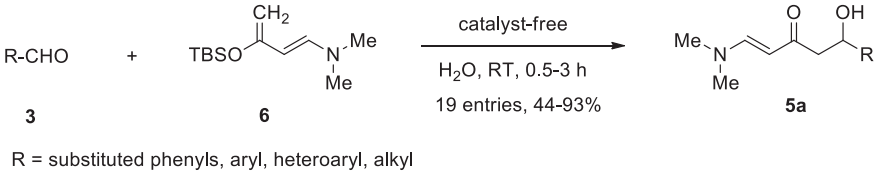



**Fig. 3** Aqueous-mediated Mukaiyama aldol addition reaction at room temperature

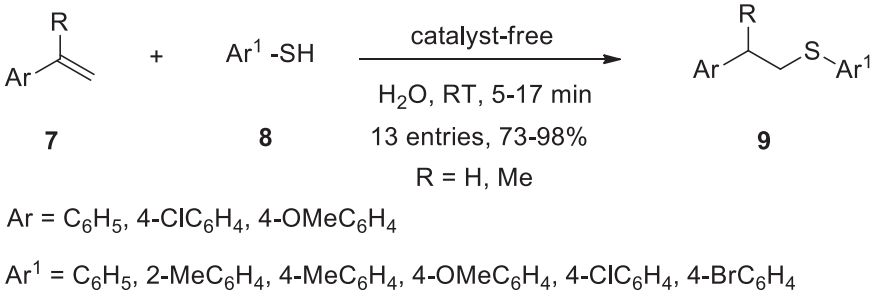



**Fig. 4** Aqueous-mediated anti-Markovnikov addition reaction at room temperature

### 2.1.4 Synthesis of α-Aminonitriles

During last decade, a number of methods were reported for the synthesis of α-aminonitriles via one-pot three-component Strecker reactions of various carbonyl compounds, amines, and trimethyl silyl cyanide (TMSCN) as cyanide source under the influence of various catalytic systems (Bhanu Prasad et al. 2004); (Shen et al. 2009); (Ramesh et al. 2010); (Brahmachari and Banerjee 2012). In 2011, a simple, facile, and environmentally benign catalyst-free protocol was developed for the efficient synthesis of α-aminonitriles (**12**) starting from various aldehydes (**3**) or ketones (**10**), primary or secondary amines (**1**), and acetone cyanohydrins (**11**) as the cyanide source in water at room temperature (Fig. 5) (Galletti et al. 2011).

### 2.1.5 Synthesis of Substituted Bis(Hydroxyethyl)Thioethers

Synthesis of structurally diverse *bis*(hydroxyethyl)thioethers (**14**) was achieved via the ring opening reactions of various epoxides (**13**) with sodium sulphide ($Na_2S$) in aqueous medium without using any catalyst at room temperature (Fig. 6) (Azizi et al. 2010).

### 2.1.6 Synthesis of β-Hydroxyl Thioesters

Catalyst-free ring opening of epoxides (**13**) was also achieved using thio-acetic or benzoic acid (**15**) which afforded corresponding β-hydroxyl thioesters (**16**) in aqueous medium at room temperature (Fig. 7) (Ziyaei-Halimehjani et al. 2011).

### 2.1.7 Conjugate Addition of Thioacids to Activated Olefins

Addition of alkyl or aryl thioacids (**15**) to activated olefins (**17**) was also achieved without employing any catalyst in water at room temperature (Fig. 8) (Marjani et al. 2011). A variety of olefins with electron withdrawing substituent afforded the desired products with excellent yields.

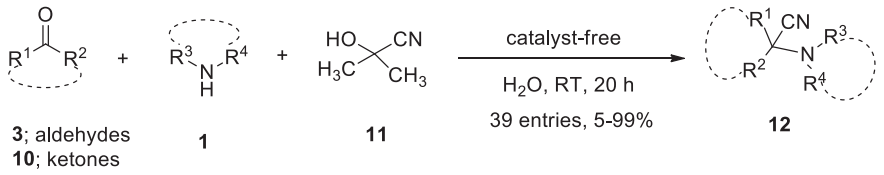
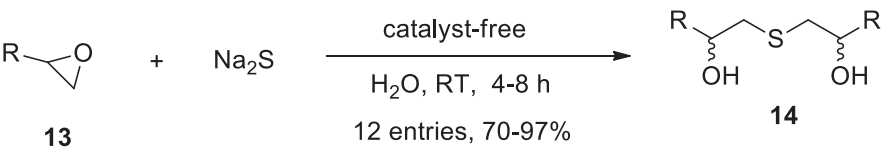
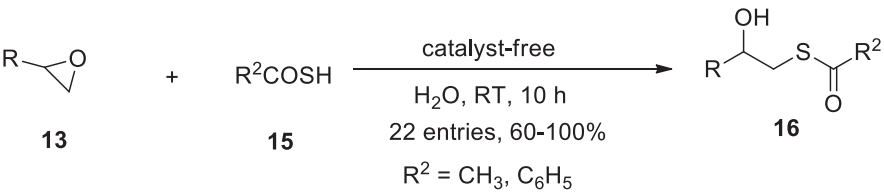



**Fig. 5** Catalyst-free synthesis of α-aminonitriles in water at room temperature




R = $C_6H_5$, $C_2H_5$, $CH_3$, $CH(CH_3)_2$, $CH_2OC_3H_7$, $CH_2OCH(CH_3)_2$, $CH_2OCH_2CH{=}CH$, $CH_2OC_4H_9$, $CH_2OC_6H_5$

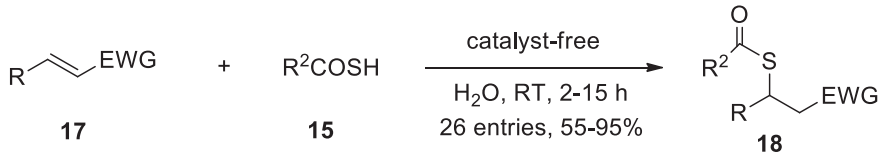
**Fig. 6** Aqueous-mediated catalyst-free synthesis of substituted *bis*(hydroxyethyl)thioethers at room temperature




$R^2$ = $CH_3$, $C_6H_5$

R = $CH_2OC_6H_5$, $CH_2OCH(CH_3)_2$, $CH_2CH_3$, $CH_2OCH_2CH{=}CH_2$, $CH_3$, $CH_2Br$, $CH_2Cl$, $(CH_2)_{11}CH_3$, $C_6H_5$, $CH_2O(CH_2)_3CH_3$, $CH_2OCOC(CH_3){=}CH_2$

**Fig. 7** Synthesis of β-hydroxyl thioesters in water under catalyst-free conditions at room temperature




R = substituted phenyl, heteroaryl, cyclohexene

EWG = aldehyde, ketone, ester, amide; $R^2$ = $CH_3$, $C_6H_5$

**Fig. 8** Aqueous-mediated catalyst-free conjugate addition of thioacids to activated olefins at room temperature

### 2.1.8 Synthesis of β-Sulfido Carbonyl Compounds

A facile, mild, and convenient catalyst-free practical method was reported for the synthesis of a series of β-sulfido carbonyl compounds (**19**) via conjugate addition of various thiols (**8a**) to α,β-unsaturated carbonyl compounds (**17**) in aqueous medium at ambient temperature (Fig. 9) (Khatik et al. 2006). No undesired products were formed. Short reaction times, excellent yields, high chemoselectivity, energy efficiency, use of water as solvent, and catalyst-free reaction conditions made this protocol attractive for the synthesis of β-sulfido carbonyl compounds (**19**). It was proposed that carbonyl compounds and thiols were activated simultaneously by water molecules (Fig. 10).

### 2.1.9 Synthesis of N-Aryl-α-Naphthylglycine Derivatives

Synthesis of novel *N*-aryl-α-naphthylglycine derivatives (**23**) was achieved via the one-pot three-component condensation between naphthols (**20**), glyoxalic acid (**21**), and heteroaryl primary amines (**22**) under catalyst-free conditions in aqueous medium at room temperature (Fig. 11) (Olyaei et al. 2010). All the products were obtained pure with high yields.

### 2.1.10 Synthesis of Bis(1,3-Diones-2-yl)Alkyl/Aryl Methanes

In 2009, synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives (**25**) was achieved from the reactions substituted benzaldehydes (**3**) and dimedone (**24**) under catalyst-free conditions in water at room temperature (Fig. 12) (Bayat et al. 2009). Next year, in 2010, synthesis of diverse *bis*(1,3-diones-2-yl)alkyl/aryl methane derivatives (**25**,**27**) were also reported without using any catalyst via tandem Knoevenagel condensation reactions between one equivalent of aromatic or aliphatic aldehydes (**3**) and two equivalents of various cyclic-1,3-diketones (**24**,**24a**,**26a**,**26b**,**26c**,**26d**,**26e**) in water at room temperature (Fig. 13) (Yu et al. 2010).

### 2.1.11 Synthesis of Substituted Bis(6-Amino-1,3-Dimethyluracil-5-yl) Methanes

Inspired by the above outcomes, a simple, convenient, and environmentally benign catalyst-free practical method was demonstrated for the efficient synthesis of aryl/alkyl/heteroaryl substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methane derivatives (**29**). Synthesis of this biologically promising scaffold was achieved via the condensation between various aldehydes (**3**) and 6-amino-1,3-dimethyluracil (**28**) in water at ambient temperature (Fig. 14) (Das and Thakur 2011).

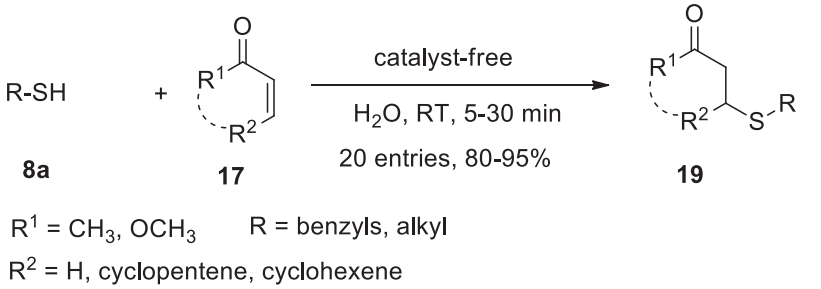



**Fig. 9** Synthesis of β-sulfido carbonyl compounds in water under catalyst-free conditions at room temperature

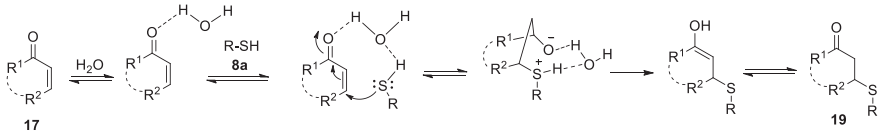



**Fig. 10** Plausible mechanistic approach for the dual activation of carbonyls and thiols by water

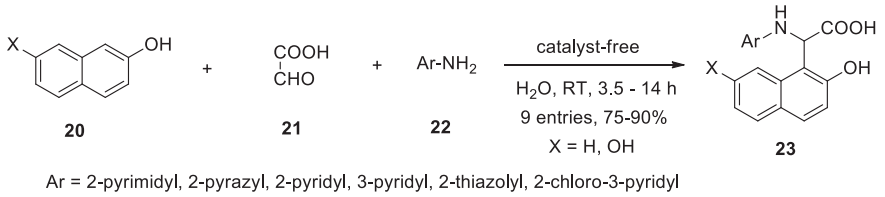



**Fig. 11** Synthesis of novel *N*-heteroaryl α-naphthylglycines under catalyst-free conditions in water at room temperature

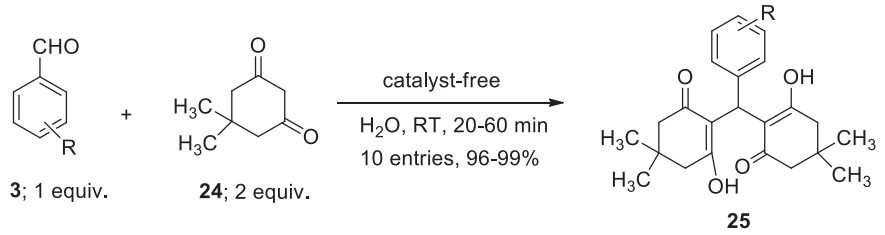



**Fig. 12** Synthesis of 2,2′-arylmethylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives in water under catalyst-free conditions at room temperature

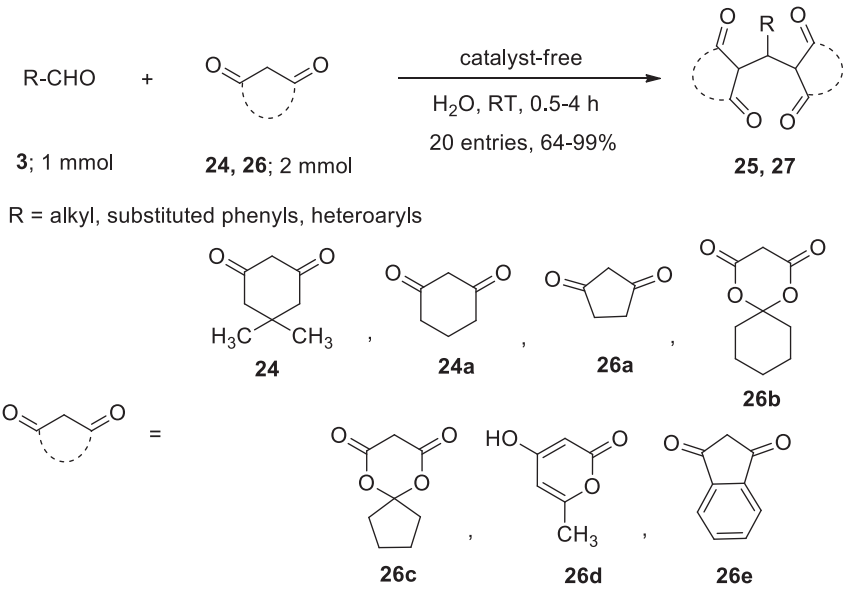



**Fig. 13** Synthesis of *bis*(1,3-diones-2-yl)alkyl/aryl methane derivatives in water under catalyst-free conditions at room temperature

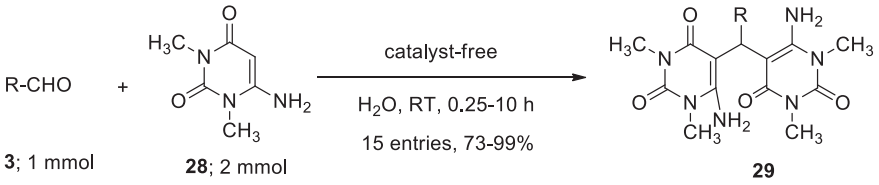



**Fig. 14** Catalyst-free synthesis of substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes in water at room temperature

### 2.1.12 Synthesis of 2-Amino-3-Cyano-4-(1H-Pyrazol-4-yl)-4H-Chromenes

A number of novel 2-amino-3-cyano-4-(1*H*-pyrazol-4-yl)-4*H*-chromene derivatives (**34**) were prepared from the reactions of ethyl acetoacetate (**30**), hydrazine hydrate (**31**), malononitrile (**32**), and salicaldehydes (**33**) under catalyst-free conditions in water at room temperature (Fig. 15) (Kumaravel and Vasuki 2009). High atom economy, excellent yields, short reaction times, use of green solvent, catalyst-free reaction conditions are some of the notable advantages of this protocol.

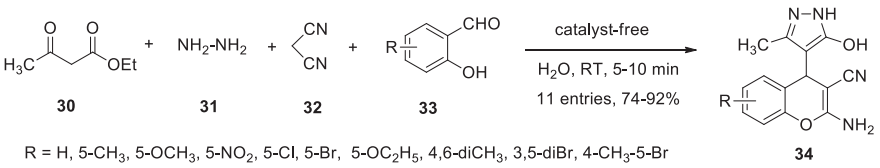



**Fig. 15** Aqueous-mediated catalyst-free synthesis of 2-amino-3-cyano-4-(1*H*-pyrazol-4-yl)-4*H*-chromenes at room temperature

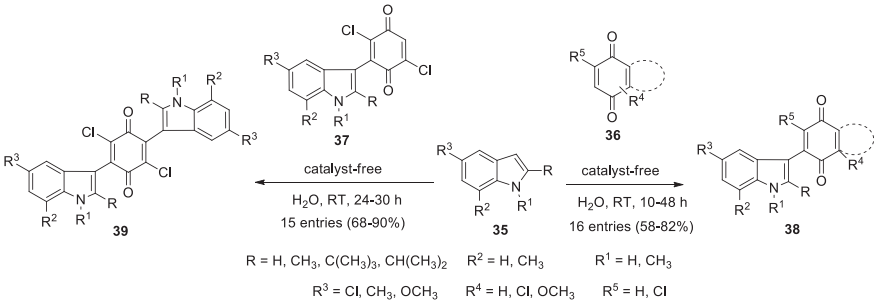



**Fig. 16** Aqueous-mediated catalyst-free coupling reactions of indoles with 1,4-benzoquinones at room temperature

### 2.1.13 Coupling of Indoles with 1,4-Benzoquinones

Coupling of indoles with 1,4-benzoquinones was achieved by using various protic as well as Lewis acidic catalysts such as acetic acid (Pirrung et al. 2002), indium(III) bromide (Yadav et al. 2004), bismuth(III) triflate (Yadav et al. 2003), zinc(II) triflate (Pirrung et al. 2005a, b), and Pd(II)/$Cu(OAc)_2$ (Pirrung et al. 2005a, b) under various solvents. In 2006, a catalyst-free approach for the coupling of indoles (**35**) with 1,4-benzoquinones (**36**) was designed which afforded the corresponding indolyl-1,4-benzoquinone derivatives (**38**) with high yields in water at room temperature (Fig. 16) (Zhang et al. 2006). Under the same optimized reaction conditions, synthesis of *bis*(indolyl)-1,4-benzoquinones was achieved by the reactions between **37** and **35**.

### 2.1.14 Synthesis of Diverse 3-Hydroxy-2-Oxindole Scaffolds

A facile and convenient catalyst-free protocol was developed for the efficient synthesis of novel 3-pyrazolone substituted 3-hydroxy-2-oxindoles (**43**) from the reactions of substituted isatins (**40**) and 3-pyrazolones (**41**) in water at room temperature (Fig. 17) (Thakur and Meshram 2014a, b). Products were isolated with excellent yields. In another report, under the same optimized reaction conditions, 3-thiazolidinedione substituted 3-hydroxy-2-oxindoles (**44**) or 3-oxindole substituted 3-hydroxy-2-oxindoles (**45**) were also synthesized involving

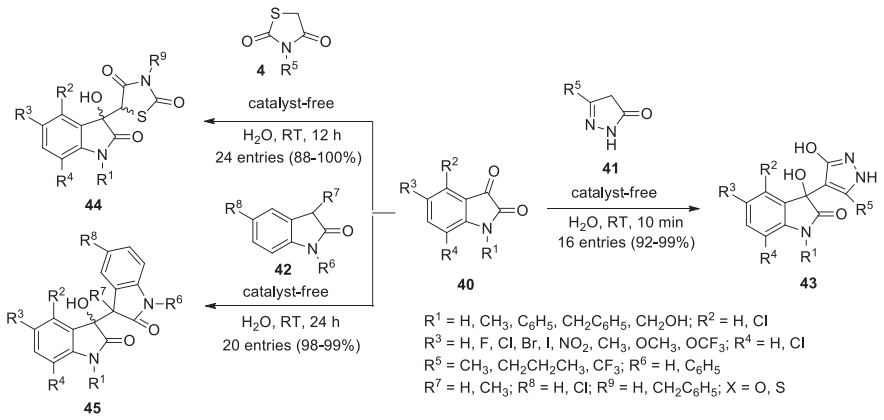



**Fig. 17** Aqueous-mediated catalyst-free synthesis of 3-substituted, 3-hydroxy-2-oxindoles at room temperature

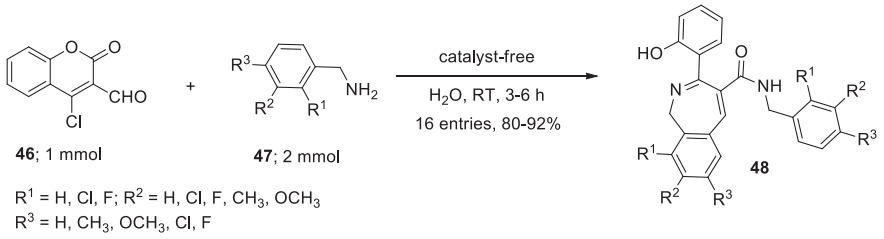



**Fig. 18** Aqueous-mediated catalyst-free synthesis of novel 5-(2′-hydroxyaryl)-4-amido-2-benzazepines at room temperature

2,4-thiazolidinedione (**4**) or oxindole derivative (**42**), respectively instead of 3-pyrazolones (**41**) (Fig. 17) (Thakur and Meshram 2014a, b).

### 2.1.15 Synthesis of Novel 2-Benzazepines

A facile catalyst-free approach was reported for the efficient synthesis of highly substituted 5-(2′-hydroxyaryl)-4-amido-2-benzazepines (**48**) with excellent yields (Fig. 18) (Prasad et al. 2010). The above synthesis was achieved by the reactions of 4-chloro-3-formyl coumarin (**46**) and various benzyl amines (**47**) under catalyst-free conditions in aqueous medium at ambient temperature.

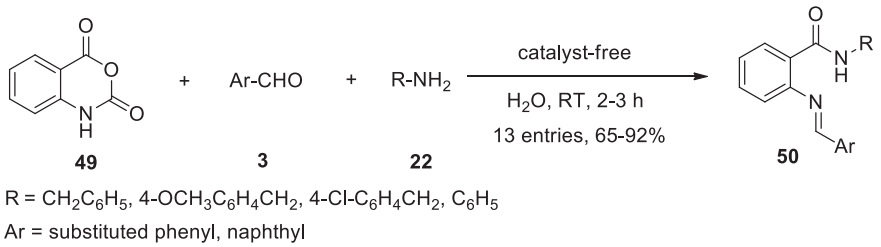



**Fig. 19** Synthesis of anthranilamide Schiff bases in water under catalyst-free conditions at room temperature

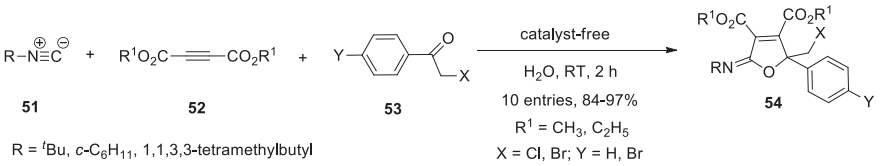



**Fig. 20** Catalyst-free synthesis of γ-iminolactone derivatives in water at room temperature

### 2.1.16 Synthesis of Anthranilamide Schiff Bases

A simple, aqueous mediated and catalyst-free one-pot three-component approach was designed for the synthesis of novel anthranilamide Schiff bases (**50**) starting from isatoic anhydride (**49**), aromatic aldehydes (**3**) and amines (**22**) at room temperature (Fig. 19) (Ebrahimi et al. 2014).

### 2.1.17 Synthesis of γ-Iminolactone Derivatives

Reactions between alkyl isocyanides (**51**), dialkyl acetylenedicarboxylates (**52**), and phenacyl halides (**53**) were accomplished under catalyst-free conditions which yielded the corresponding γ-iminolactone derivatives (**54**) in aqueous medium at room temperature (Fig. 20) (Ramazani et al. 2010).

### 2.1.18 Synthesis of 1,6-Dihydro-6,6-Dimethylpyrazine-2,3-Dicarbonitriles

A facile and convenient one-pot three-component catalyst-free practical method was reported for the efficient synthesis of 1,6-dihydropyrazine-2,3-dicarbonitriles (**57**) starting from alkyl or aryl isocyanides (**51**), 2,3-diaminomaleonitrile (**55**), and 3-oxopentanedioic acid (**56**) in aqueous medium at room temperature (Fig. 21) (Shaabani et al. 2012).

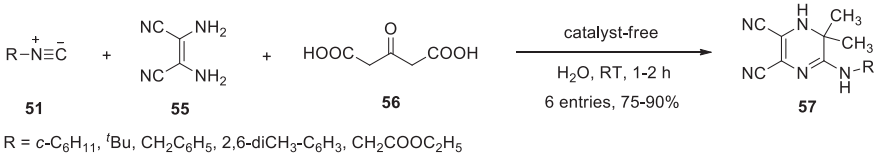



**Fig. 21** Aqueous-mediated catalyst-free synthesis of 1,6-dihydro-6,6-dimethylpyrazine-2,3-dicarbonitrile at room temperature

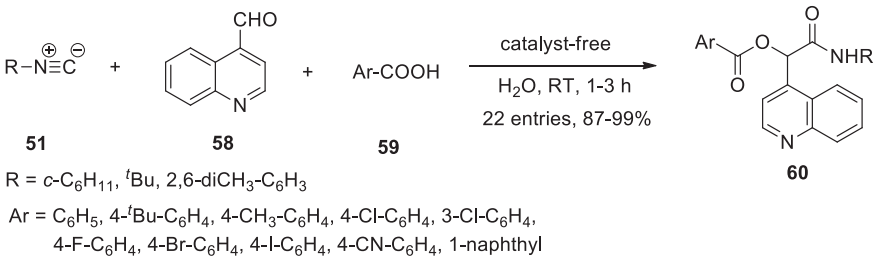



**Fig. 22** Aqueous-mediated catalyst-free synthesis of novel α-(acyloxy)-α-(quinolin-4-yl)acetamides at room temperature

### 2.1.19 Synthesis of Novel α-(Acyloxy)-α-(Quinolin-4-yl)Acetamides

Another isocyanide-based aqueous-mediated one-pot three-component reaction protocol was developed without using any catalyst. The reactions of isocyanides (**51**), quinoline-4-carbaldehyde (**58**), and arenecarboxylic acids (**59**) under catalyst-free conditions afforded the corresponding novel α-(acyloxy)-α-(quinolin-4-yl) acetamides (**60**) with good to excellent yields in aqueous medium at room temperature (Fig. 22) (Tarana et al. 2014).

## *2.2 Catalyst-Free Organic Synthesis in Water Under Reflux Conditions*

### 2.2.1 Synthesis of 2-Substituted Benzothiazoles

Benzothiazoles are found to possess a broad range of biological activities (Yoshida et al. 2005). They are also used as plant growth regulator (Loos et al. 1999), enzyme inhibitors (Choi et al. 2006), fluorescence material (Ji and Shi 2006), and dyes (Razus et al. 2007). A large number of protocols have been reported for the efficient synthesis of this significant bioactive scaffold utilizing diverse catalytic system under various reaction conditions (Itoh and Mase 2007); (Evindar and Batey 2006); (Heo et al. 2006); (Mu et al. 2005); (Rostamizadeh and Housaini 2005); (Rudrawar et al. 2005);

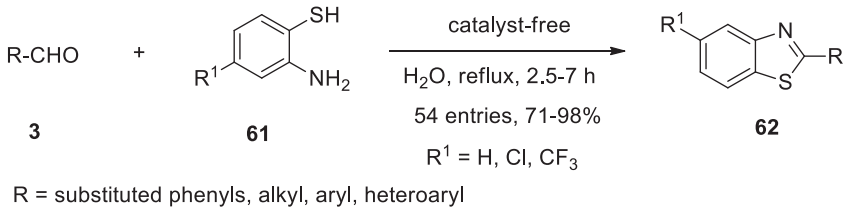



**Fig. 23** Catalyst-free synthesis of 2-substituted benzothiazoles in water at 110 °C

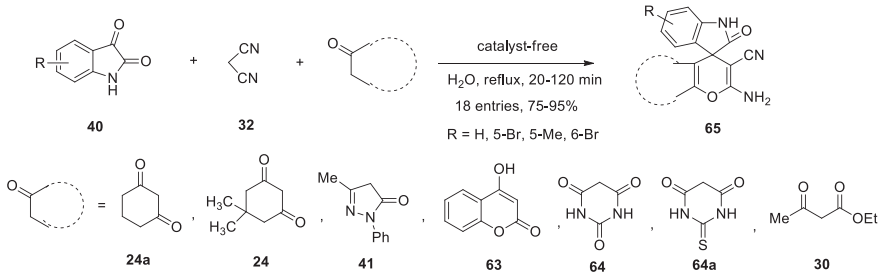



**Fig. 24** Catalyst-free synthesis of functionalized spiropyrans in water under reflux conditions

(Chakraborti et al. 2004). In 2007, a facile, mild, and convenient catalyst-free approach was reported for the aqueous-mediated synthesis of 2-substituted benzothiazoles (**62**) from the reactions of various aromatic or heteroaromatic aldehydes (**3**) and 2-amino-thiophenol (**61**) under reflux conditions at 110 °C (Fig. 23) (Chakraborti et al. 2007).

### 2.2.2 Synthesis of Functionalized Indoline-2-One Fused Spiropyrans

Spiro-oxindole and its derivatives are widely distributed among the naturally occurring bioactive compounds (Brahmachari and Banerjee 2016). A series of structurally diverse spirooxindole derivatives (**65**) were prepared via simple one-pot three-component catalyst-free reactions between isatins (**40**), malononitrile (**32**) and various C-H activated acids in aqueous medium under reflux conditions (Fig. 24) (Zhao et al. 2011). A number of activated carbonyl compounds such as 1,3-cyclohexanone (**24a**), dimedone (**24**), pyrazole-3-ones (**41**), 4-hydroxycoumarin (**63**), barbituric acid (**64**), thiobarbituric acid (**64a**), and ethyl acetoacetate (**30**) were produced the desired products with excellent yields.

### 2.2.3 Synthesis of 3-(2-Hydroxynaphthalen-1-yl)Isoindolin-1-Ones

Recently, in 2018, a simple and straightforward catalyst-free method was documented for the facile synthesis of 3-(2-hydroxynaphthalen-1-yl)isoindolin-1-ones (**67**) via one-pot three-component Mannich type cyclization reactions of 2-formylbenzoic acids (**66**), various primary amines (**22**) and 2-naphthols (**20**) in

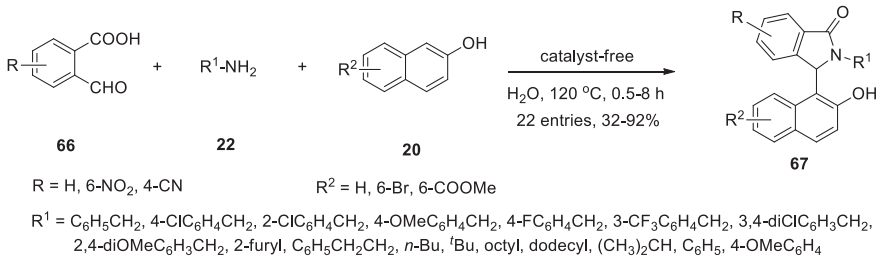



**Fig. 25** Catalyst-free synthesis of 3-(2-hydroxynaphthalen-1-yl)isoindolin-1-ones in water under reflux conditions

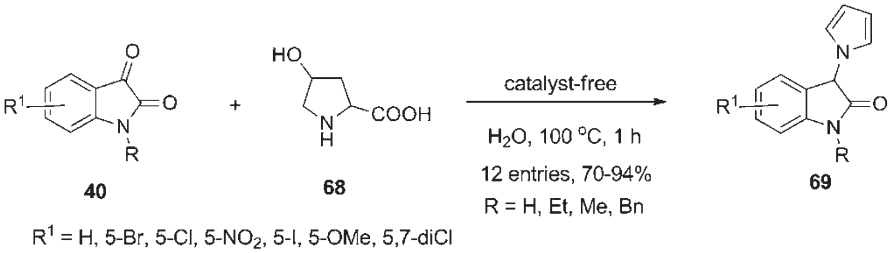



**Fig. 26** Catalyst-free synthesis of 3-(1*H*-pyrrol-1-yl) indolin-2-ones in water under reflux conditions

aqueous medium under reflux conditions (Fig. 25) (Tian et al. 2018). Simple reaction procedure, operational simplicity, a wide range of substrate tolerance, use of water as solvent, easy purification process, catalyst-free reaction conditions are some of the major benefits of this reported method.

### 2.2.4 Synthesis of 3-(1H-Pyrrol-1-yl)Indolin-2-Ones

An aqueous-mediated catalyst-free reaction protocol was developed for the synthesis of 3-(1*H*-pyrrol-1-yl)indolin-2-ones (**69**) with good yields from the reactions of substituted isatins (**40**) and 4-hydroxyproline (**68**) under reflux conditions (Fig. 26) (Ahmad et al. 2014). It was proposed that the reaction proceeded through the formation of Schiff base (**70**) followed by decarboxylation as well as dehydration (Fig. 27).

### 2.2.5 Synthesis of Knoevenagel Adducts

Water-mediated Knoevenagel condensation reaction between Meldrum's acid (**71**) and various aromatic as well as aliphatic aldehydes (**3**) was studied at 75 °C under catalyst-free conditions which afforded the corresponding Knoevenagel adducts (**72**) with excellent yields (Fig. 28) (Bigi et al. 2001).

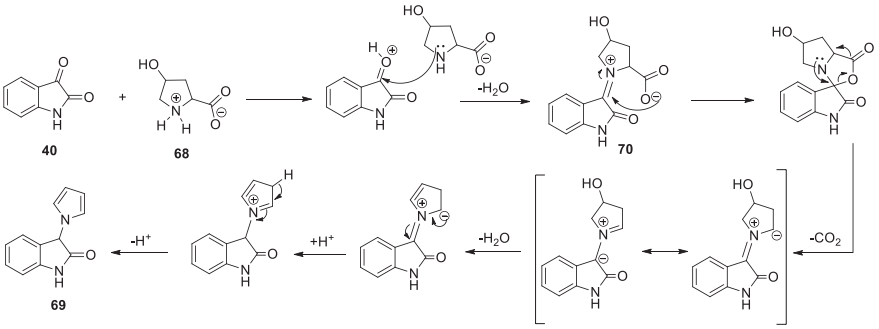



**Fig. 27** Plausible mechanism for the catalyst-free synthesis of 3-(1*H*-pyrrol-1-yl) indolin-2-ones

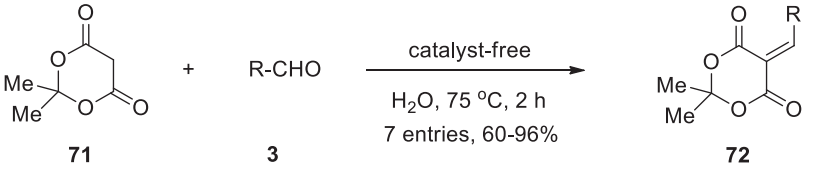



**Fig. 28** Synthesis of Knoevenagel adducts in water under catalyst-free conditions at 75 °C

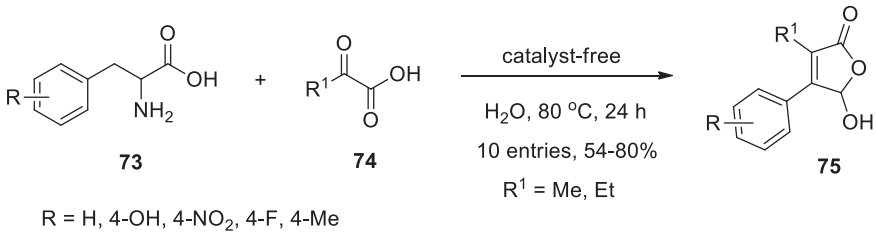



**Fig. 29** Synthesis of γ-hydroxybutenolides in water under catalyst-free conditions at 80 °C

### 2.2.6 Synthesis of γ-Hydroxybutenolides

A number of γ-hydroxybutenolide derivatives (**75**) were synthesized from the catalyst-free annulation reactions of α-amino-β-aryl-acids (**73**) and α-keto acids (**74**) in aqueous medium at 80 °C (Fig. 29) (Hea et al. 2017). Using this strategy, gram-scale synthesis of these products was also achieved.

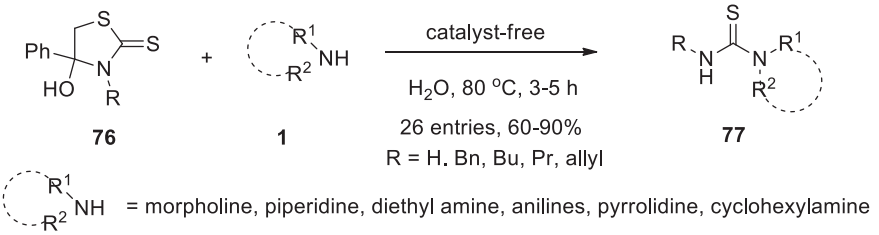



**Fig. 30** Synthesis of substituted thioureas without employing any catalyst in water at 80 °C

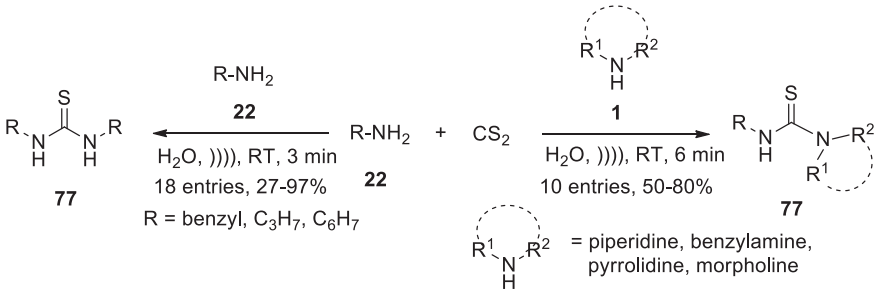



**Fig. 31** Ultrasound-irradiated catalyst-free synthesis of substituted thiourea in water

### 2.2.7 Synthesis of Substituted Thioureas

A number of substituted thiourea derivatives (**77**) were synthesized via the reactions between various amines (**1**) and thiazolidine-2-thiones (**76**) as the sulphur source under catalyst-free conditions in aqueous medium at 80 °C (Fig. 30) (Gan et al. 2011). Under sonication, another series of thiourea derivatives (**77**) was synthesized using carbon disulphide as the sulphur source without using any catalyst at room temperature (Fig. 31) (Azizi et al. 2014). Primary amines along with secondary amines such as morpholine, piperidine, pyrrolidine, benzyl amines, etc. also produced the desired thiourea derivatives with excellent yields within just 6 min.

### 2.2.8 Synthesis of Unsymmetrical Thioethers via $S_NAr$ Reaction

A catalyst-free $S_NAr$ reaction between various pyridyl halides (**78**) and thiophenols (**8**) was carried out in aqueous medium under reflux conditions. The reaction afforded the corresponding unsymmetrical biaryl thioethers (**79**) with good yields (Fig. 32) (Sreedhar et al. 2009). Simple reaction procedure, catalyst-free reaction conditions, use of water as solvent, excellent yields of the products are some of the major benefits of this developed protocol.

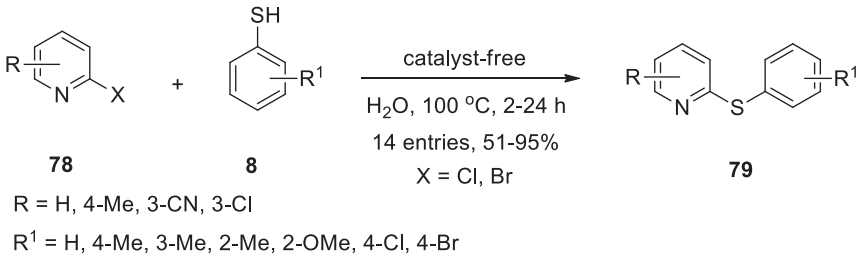



**Fig. 32** Catalyst-free synthesis of unsymmetrical thioethers via $S_NAr$ reaction

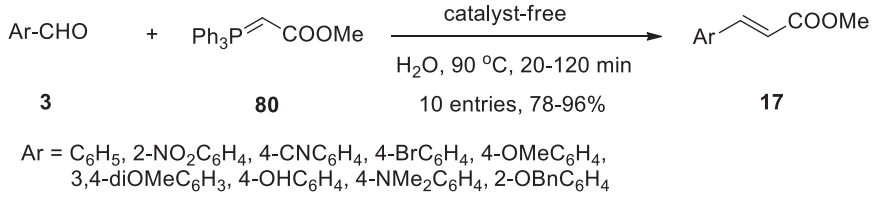



**Fig. 33** Catalyst-free Wittig reactions in aqueous medium at 90 °C

### 2.2.9 Wittig Reactions

In 2005, Wittig reaction between various aldehydes (**3**) and methyl 2-(triphenylphosphoranylidene) acetate (**80**) as a stable yields was investigated under catalyst-free conditions in various solvents such benzene, water, methanol, [bmim]$BF_4$, and chloroform (Fig. 33) (Dambacher et al. 2005). Water, at 90 °C, produced the highest yields of the corresponding substituted methyl cinnamate derivatives (**17**).

### 2.2.10 *N*-Boc Deprotection

*N*-Boc deprotection of various protected amines (**2**) was also achieved in aqueous medium under catalyst-free conditions at high temperature (Fig. 34) (Wang et al. 2009). Deprotection was successful on both aromatic as well as aliphatic *N*-Boc-amines. It was proposed that at high temperature water may behave as subcritical liquid, and as the ion product of subcritical water is higher than the ordinary water, it may boost higher concentration of $H^+$ and $OH^-$ than normal water (Krammer and Vogel 2000). Under catalyst-free conditions, deprotection was not accomplished under neat conditions even at high temperature.

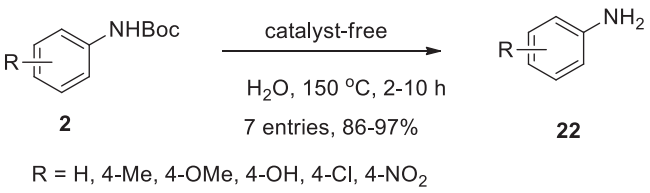



**Fig. 34** Catalyst-free *N*-Boc deprotection of various protected amines in water at 150 °C

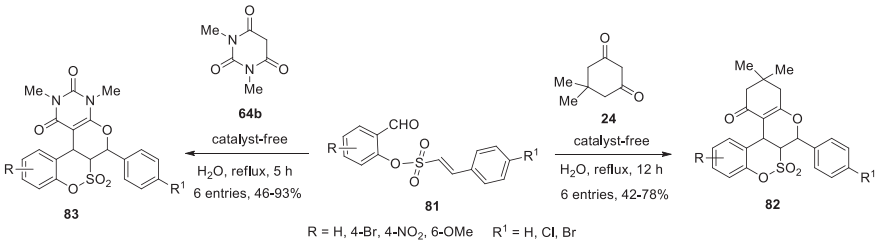



**Fig. 35** Synthesis of fused benzo-δ-sultones without using any catalyst in water under reflux conditions

### 2.2.11 Synthesis of Fused Benzo-δ-Sultones

A simple and efficient water-mediated eco-friendly catalyst-free novel approach was developed for the synthesis of hexahydro-chromene annulated benzo-δ-sultones (**82**) from the reactions of (*E*)-2-formylphenyl 2-phenylethenesulfonates (**81**) and dimedone (**24**) under reflux conditions (Fig. 35) (Ghandi et al. 2011). The reaction proceeded through the domino Knoevenagel followed by hetero-Diels–Alder reaction. All the reactions required 12 h to complete. Under the same optimized condition, when *N*,*N*-dimethylbarbituric acid (**64b**) was employed instead of dimedone (**24**), the rate of the reaction accelerated and it yielded the corresponding tetrahydro-pyrano[2,3-*d*]pyrimidine-annulated benzo-δ-sultone derivatives (**83**) with good to excellent yields.

### 2.2.12 Synthesis of Bis(2-Acylvinyl) Selenides

Under catalyst-free conditions, diphenethylphosphine selenide (**85**) reacted efficiently with acylacetylenes (**84**) to afford the corresponding *bis*(2-acylvinyl) selenides (**86**) with moderate yields in aqueous medium at 70–71 °C (Fig. 36) (Volkov et al. 2018).

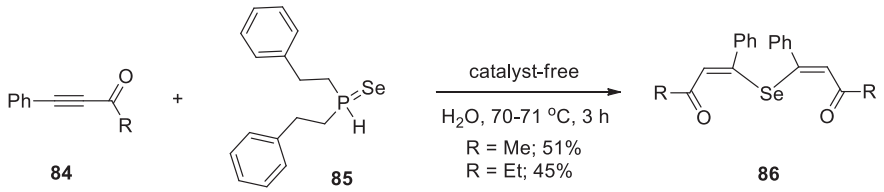



**Fig. 36** Catalyst-free synthesis of *bis*(2-acylvinyl) selenides in water at 70–71 °C

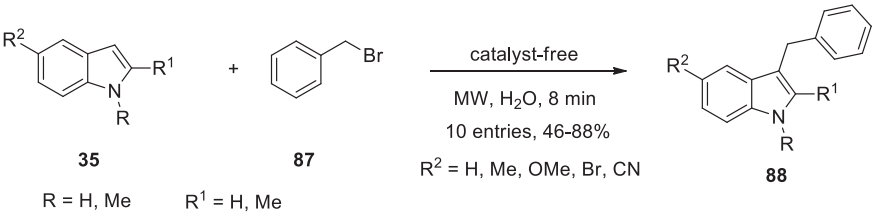



**Fig. 37** Microwave-assisted catalyst-free Friedel–Crafts alkylation of indoles in aqueous medium

## *2.3 Catalyst-Free Organic Synthesis in Water under Microwave Irradiation*

### 2.3.1 Friedel–Crafts Alkylation of Indoles

Microwave irradiation is one of the helpful techniques to carry out organic transformations under catalyst-free conditions. A series of 3-benzylated indole derivatives (**88**) was synthesized via microwave-assisted Friedel–Crafts alkylation reactions between of indoles (**35**) and benzylbromide (**87**) without using any catalyst in aqueous medium (Fig. 37) (De Rosa and Soriente 2010a, b). All the reactions were completed within 8 min.

### 2.3.2 Synthesis of 2,4,5-Trisubstituted 1,3-Thiazoles

In absence of any catalyst, only microwave irradiation was sufficient for the synthesis of 2,4,5-trisubstituted 1,3-thiazoles (**90**) via one-pot three-component domino cyclization reactions of arylglyoxals (**74**), 4-hydroxycoumarin (**63**), and thioamides (**89**) in aqueous medium. All the reactions were completed within just 15 min (Fig. 38) (Karamthulla et al. 2014).

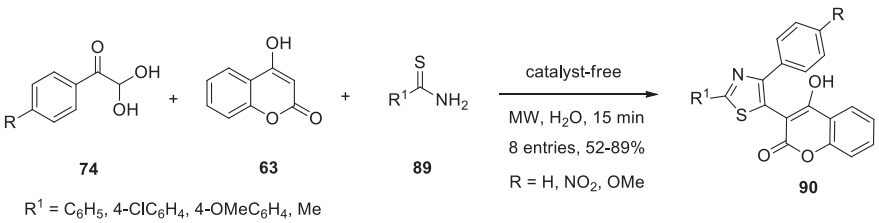



**Fig. 38** Microwave-assisted catalyst-free synthesis of 2,4,5-trisubstituted 1,3-thiazoles in water

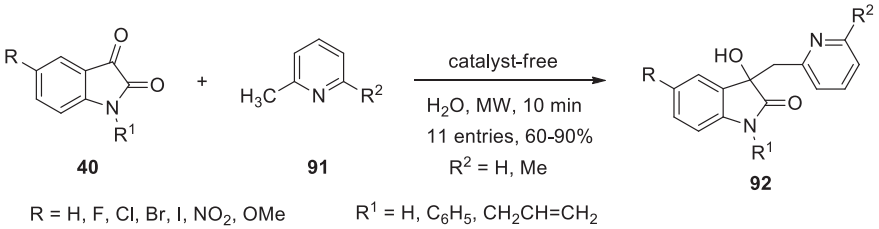



**Fig. 39** Microwave-irradiated synthesis of 3-hydroxy-2-oxindoles starting from isatins and methyl pyridine in water under catalyst-free conditions

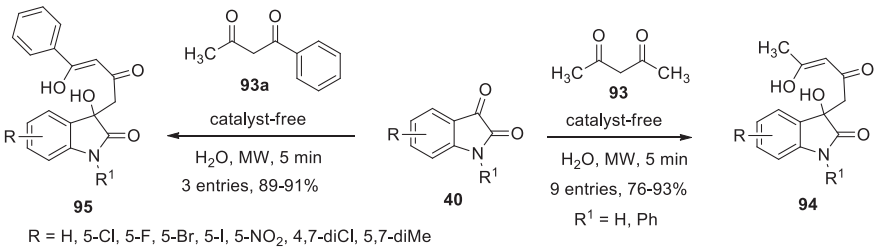



**Fig. 40** Microwave-irradiated synthesis of 3-hydroxy-2-oxindoles starting from 1,3-diketone and isatins in water under catalyst-free conditions

### 2.3.3 Synthesis of 3-Hydroxy-2-Oxindoles Under Microwave Irradiation

A variety of 3-hydroxy-2-oxindole derivatives (**92**,**94**,**95**,**97**) were synthesized under microwave-irradiated catalyst-free conditions in water. These syntheses were accomplished by the reactions of substituted isatins (**40**) and various activated C–H compounds such as 2-methylpyridines (**91**) (Fig. 39) (Meshram et al. 2012a, b), 1,3-diketones (**93**,**93a**) (Fig. 40) (Thakur et al. 2014), and arylmethyl ketones (**96**) (Fig. 41) (Meshram et al. 2012a, b).

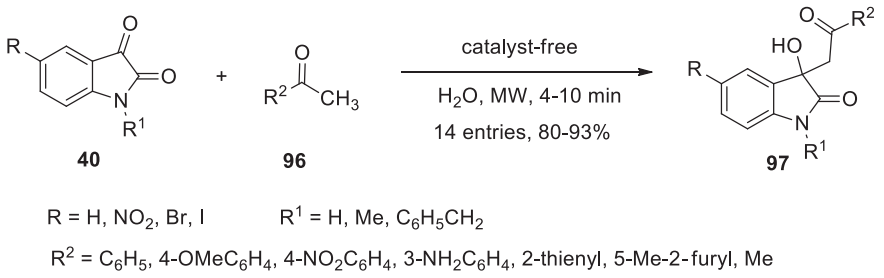



**Fig. 41** Microwave-irradiated synthesis of 3-hydroxy-2-oxindoles starting from isatins and ketones in water under catalyst-free conditions

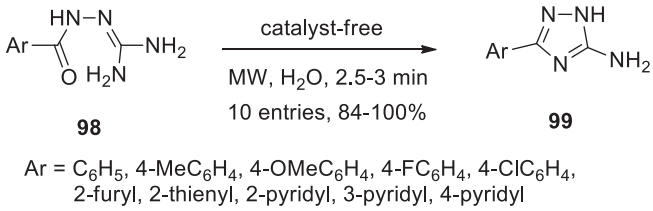



**Fig. 42** Microwave-assisted catalyst-free synthesis of 5-amino-3-aryl-1,2,4-triazoles in water

### 2.3.4 Synthesis of 5-Amino-3-Aryl-1,2,4-Triazoles

Synthesis of 5-amino-3-aryl-1,2,4-triazoles (**99**) was achieved via the intramolecular Schiff base formation of arylamidoguanidines (**98**) under microwave-irradiated conditions in water (Fig. 42) (Dolzhenko et al. 2009). No additional catalyst was required to use for this transformation. Along with aromatic aldehydes, a number of heteroaromatic aldehydes were also reacted smoothly and produced the desired products with high yields.

### 2.3.5 Synthesis of Pyrano[2,3-d]Pyrimidine-6-Carboxylates

An aqueous-mediated environmentally benign catalyst-free protocol was developed for the efficient synthesis of pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives (**100**) via one-pot three-component reactions of substituted benzaldehydes (**3**), methylcyanoacetate (**32a**), and thio-barbituric acid (**64a**) under the influence of microwave irradiation (Fig. 43) (Bhat et al. 2015). Under the microwave-assisted condition, all the reactions were completed within just 6 min. Long reaction times were recorded when the same reactions were carried out under convention heating conditions. In vitro screening revealed that the compounds synthesized possess antimicrobial and antifungal activities.

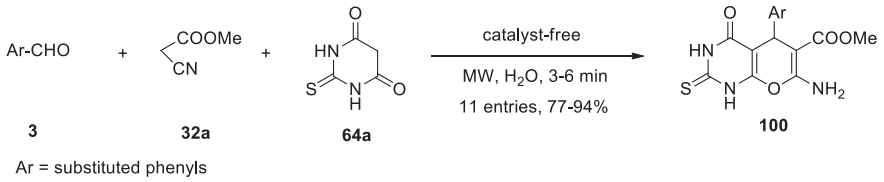



**Fig. 43** Microwave-assisted synthesis of pyrano[2,3-*d*]pyrimidine-6-carboxylates in water under catalyst-free conditions

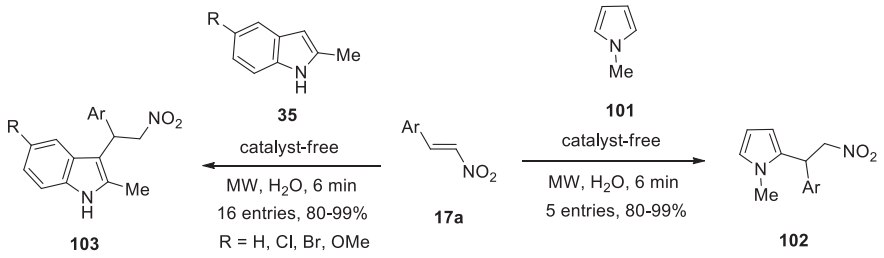



**Fig. 44** Catalyst-free nitro-Michael addition reaction under microwave irradiation in water

### 2.3.6 Nitro-Michael Addition Reaction

Microwave-assisted water-mediated catalyst-free protocol was designed to carry out nitro-Michael addition reactions between β-nitrostyrenes (**17a**) and pyrroles (**101**) or indoles (**35**) which afforded the corresponding adducts (**102**,**103**) with excellent yields (Fig. 44) (De Rosa and Soriente 2010a, b). All the reactions were completed within just 6 min. Reactions of indoles (**35**) and β-nitrostyrenes (**17a**) took longer times under conventional reflux conditions at 100 °C (Habib et al. 2008).

## *2.4 Catalyst-Free Organic Synthesis in Water Under Ultrasonic Irradiation*

### 2.4.1 Synthesis of Pyrroles and Pyridazines

In many occasions, organic transformations were successfully carried out without using any catalyst under ultrasound-irradiated conditions (Banerjee 2017a, b). A simple, mild, and eco-friendly water-mediated ultrasound-irradiated practical method was reported for the efficient synthesis of highly substituted pyrrole-3-car-

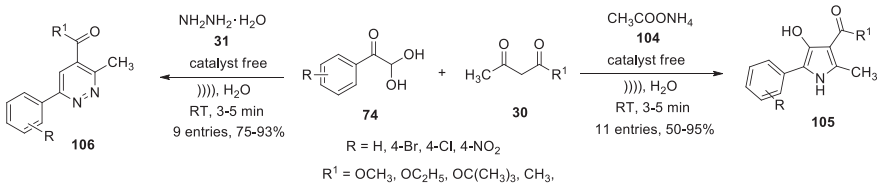



**Fig. 45** Catalyst-free synthesis of pyrroles and pyridazines under ultrasonic irradiation in water

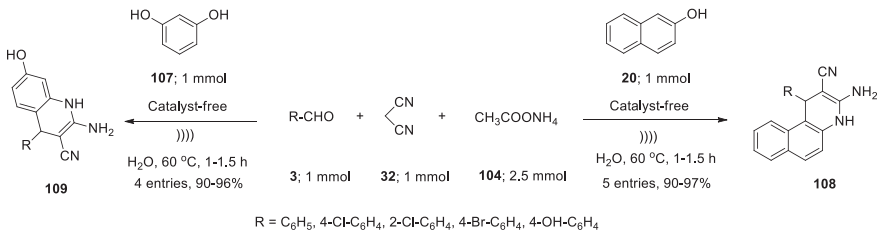



**Fig. 46** Synthesis of dihydroquinolines in absence of any catalyst under sonication in water

boxylate derivatives (**105**) starting from arylglyoxals (**74**), β-keto esters (**30**), and ammonium acetate (**104**) in absence of any catalyst at room temperature (Fig. 45) (Eftekhari-Sis and Vahdati-Khajeh 2013). Under the same optimized reaction conditions, a series of pyridazine-4-carboxylate derivatives (**106**) was also synthesized by using hydrazine hydrate (**31**) instead of ammonium acetate (**104**). All the reactions accomplished within just 5 min.

### 2.4.2 Synthesis of Dihydroquinolines

A variety of dihydroquinoline derivatives (**108**,**109**) were prepared with excellent yields via one-pot four-component reactions of substitute benzaldehydes (**3**), malononitrile (**32**), ammonium acetate (**104**), and β-naphthol (**20**) or resorcinol (**107**) in absence of any further catalyst using ultrasonic irradiation in water at 60 °C (Fig. 46) (Pagadala et al. 2014). Absence of ultrasound irradiation didn't afford the desired product.

### 2.4.3 Synthesis of Bis-coumarins

Under the influence of ultrasonic irradiation, a number of bis-coumarin derivatives (**110**) were synthesized under catalyst-free conditions via the condensation of various aromatic aldehydes (**3**) and 4-hydroxycoumarin (**63**) in aqueous medium at room temperature (Fig. 47) (Al-Kadasi and Nazeruddin 2012). Excellent yields of the desired products were obtained within just 15 min. In absence of catalyst, the

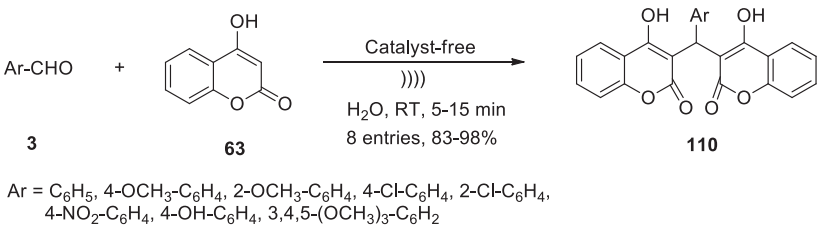



**Fig. 47** Synthesis of biscoumarins without using any catalyst in water under sonication

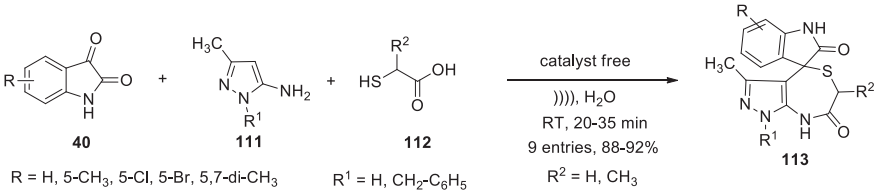



**Fig. 48** Synthesis of spiro[indole-3,4′-pyrazolo[3,4-*e*][1,4] thiazepines] under ultrasound-irradiated catalyst-free conditions in water

same reaction was also carried out under microwave irradiated conditions (Gong et al. 2009).

### 2.4.4 Synthesis of Spiro[Indole-3,4′-Pyrazolo[3,4-e][1,4]Thiazepines]

Ultrasound-assisted catalyst-free novel approach was designed for the aqueous-mediated synthesis of biologically promising spiro[indole-3,4′-pyrazolo[3,4-*e*][1,4] thiazepines] (**113**) starting from isatins (**40**), 5-amino-3-methylpyrazoles (**111**), and α-mercaptoacetic acid derivatives (**112**) at room temperature (Fig. 48) (Dandia et al. 2013). The compounds synthesized were found to possess inhibitory activities against α-amylase enzyme.

### 2.4.5 Synthesis of Rhodanines

Simple and efficient three-component reactions between primary amines (**22**), dimethyl acetylenedicarboxylate (**52**), and carbon disulphide ($CS_2$) were accomplished without employing any catalyst under ultrasound-assisted conditions in water at ambient temperature (Fig. 49) (Rostamnia and Lamei 2011). The reactions afforded a number of rhodanine derivatives (**114**) with excellent yields within just 5 min.

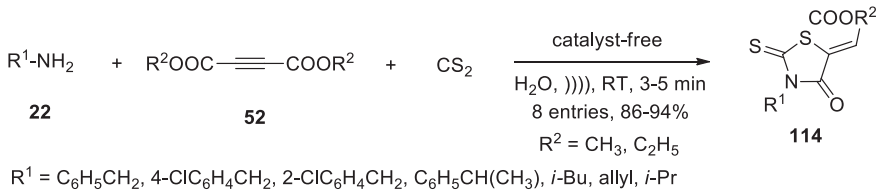



**Fig. 49** Catalyst-free synthesis of rhodanines under sonication in aqueous medium

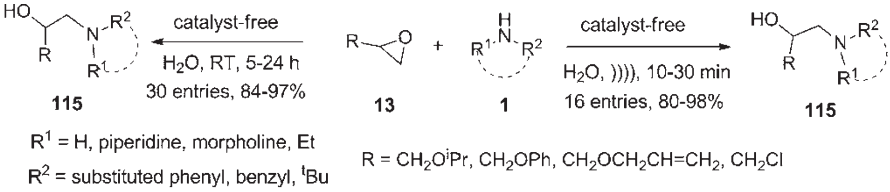



**Fig. 50** Ultrasound-assisted synthesis of β-aminoalcohols without using any catalyst in water

### 2.4.6 Synthesis of β-Aminoalcohols

Without using any catalyst, both aromatic as well as aliphatic amines (**1**) reacted efficiently with epoxides (**13**) to afford corresponding β-aminoalcohols (**115**) in water under conventional stirring at room temperature (Fig. 50) (Abaee et al. 2008). The rate of the reaction increased dramatically and all the reactions were completed within just 30 min when those were carried out under sonication in aqueous medium.

### 2.4.7 Synthesis of Substituted Propanamides

A number of structurally diverse propanamide derivatives (**117**) were synthesized without using any catalyst via one-pot three-component reactions of 2-oxopropyl benzoate (**116**), isocyanides (**51**), and aromatic carboxylic acids (**59**) under ultrasound-irradiated conditions in water at room temperature (Fig. 51) (Ramazani et al. 2016).

### 2.4.8 Synthesis of Dithiocarbamates

Reaction between 2-cyano-1-arylallyl acetate (**118**), various amines (**1**) and carbon disulphide was achieved under catalyst-free conditions which afforded the corresponding [*E*]-allyl dithiocarbamate derivatives (**119**) in water at room temperature (Fig. 52) (Yadav et al. 2009). Reactions required 10 h to complete under conventional stirring conditions. Later on, in 2012, a number of other dithiocar-

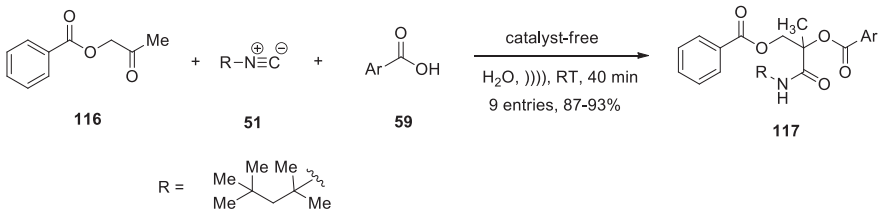



**Fig. 51** Ultrasound-irradiated catalyst-free synthesis of propanamides in aqueous medium

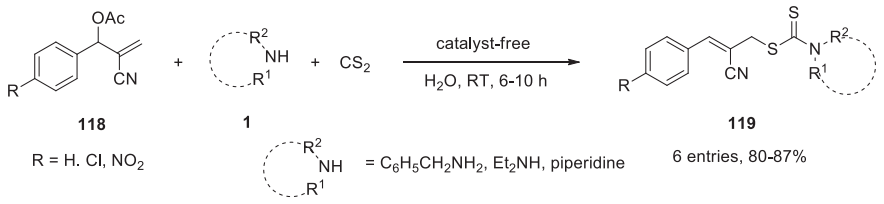



**Fig. 52** Synthesis of dithiocarbamates in absence of any catalyst under sonication in water

bamate derivatives (**119a**,**119b**) were also prepared with excellent yields starting from various amines (**1**), carbon disulphide and activated olefins (**17**) or benzyl halides (**87**) without using any catalyst under ultrasonic-assisted reaction conditions in water at room temperature (Fig. 53) (Azizi et al. 2012). Involvement of sonication accelerated the reaction rate, and thus all the reactions were completed within just 10 min.

### 2.4.9 Synthesis of Aza-Michael Addition Reaction Adduct

Without using any catalyst, aza-Michael addition reaction between various amines (**1**) and activated olefins (**17**) was achieved in water which afforded the corresponding adducts (**120**) with 85–92% yields (Fig. 54) (Ranu and Banerjee 2007). All the reactions were completed within 50 min. The same reactions were completed within just 10 min under ultrasonic-assisted catalyst-free conditions in water at room temperature (Fig. 54) (Bandyopadhyay et al. 2012).

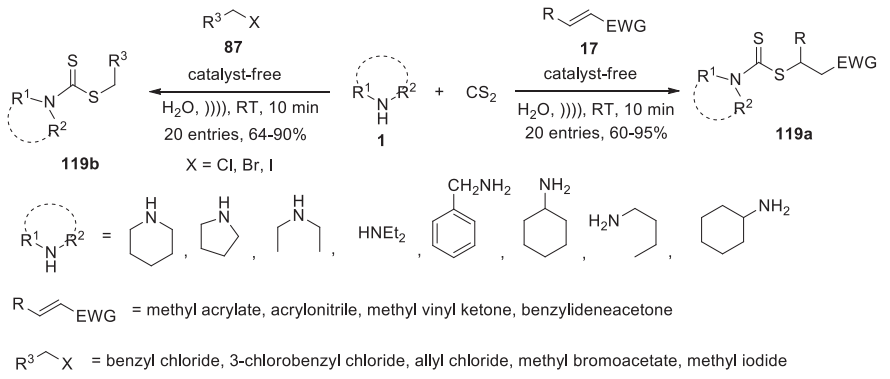



**Fig. 53** Synthesis of dithiocarbamates under ultrasound-irradiated catalyst-free conditions

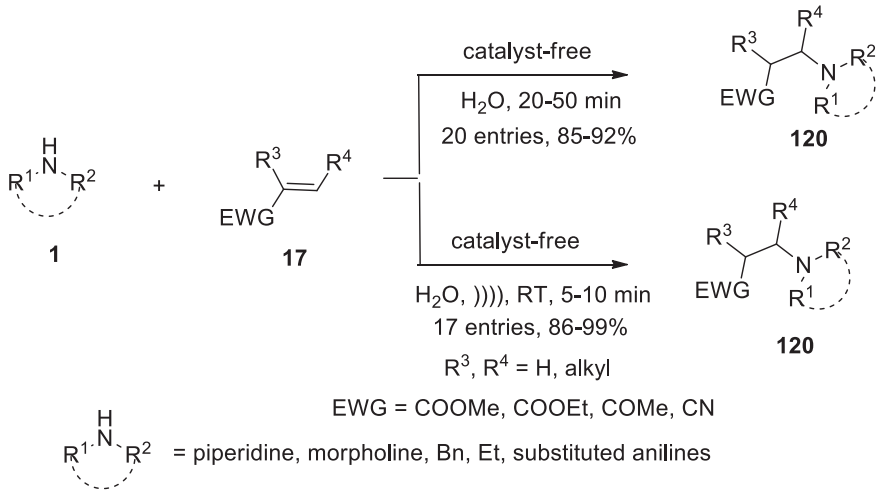



**Fig. 54** Catalyst-free aza-Michael addition reaction under the influence of ultrasound in water

## 3 Conclusions

Ongoing researches are directed towards the developments of greener and more efficient pathways for the syntheses of biologically promising organic compounds. Among various achievements in this direction, catalyst-free organic syntheses have attracted most to the researchers. This chapter summarizes a broad range of examples, such as various organic named reactions, protection-deprotections of amines, ring opening of epoxides, one-pot multi-component synthesis of bioactive heterocycles, condensations, etc., to illustrate the significance of catalyst-free organic reactions occurring in aqueous media.

**Acknowledgements** BB is thankful to Indus International University as well as Kartha Education Society, Mumbai, India, for their kind support.

## References

Abaee MS, Hamidi V, Mojtahedi MM. Ultrasound promoted aminolysis of epoxides in aqueous media: a rapid procedure with no pH adjustment for additive-free synthesis of β-aminoalcohols. Ultrason Sonochem. 2008;15:823–7. https://doi.org/10.1016/j.ultsonch.2007.12.006.

Ahmad NAA, Rokade SM, Garande AM, Bhate PM. Catalyst- and chromatography-free synthesis of pyrrole-substituted indolinone derivatives in water. Tetrahedron Lett. 2014;55:5458–61. https://doi.org/10.1016/j.tetlet.2014.08.001.

Al-Kadasi AMA, Nazeruddin GM. Ultrasound assisted catalyst-free one-pot synthesis of bis-coumarins in neat water. Int J Chem Sci. 2012;10:324–30.

Azizi N, Akbari E, Ebrahimi F, Saidi MR. Simple and highly efficient catalyst- and waste-free ring opening of epoxides with $Na_2S$ in water. Monatsh Chem. 2010;141:323–6. https://doi.org/10.1007/s00706-010-0261-0.

Azizi N, Gholibeglo E, Nayeri SD. An efficient synthesis of dithiocarbamates under ultrasound irradiation in water. Monatsh Chem. 2012;143:1171–4. https://doi.org/10.1007/s00706-011-0687-z.

Azizi N, Rahimzadeh-Oskooee A, Yadollahy Z, Ourimi AG. Ultrasound-assisted rapid sustainable synthesis of substituted thiourea. Monatsh Chem. 2014;145:1675–80. https://doi.org/10.1007/s00706-014-1238-1.

Bandyopadhyay D, Mukherjee S, Turrubiartes LC, Banik BK. Ultrasound-assisted aza-Michael reaction in water: a green procedure. Ultrason Sonochem. 2012;19:969–73. https://doi.org/10.1016/j.ultsonch.2011.11.009.

Banerjee B. Recent developments on ultrasound assisted catalyst-free organic synthesis. Ultrason Sonochem. 2017a;35:1–14. https://doi.org/10.1016/j.ultsonch.2016.09.023.

Banerjee B. Recent developments on ultrasound-assisted organic synthesis in aqueous medium. J Serb Chem Soc. 2017b;82:755–90. https://doi.org/10.2298/JSC1702170578.

Basel Y, Hassner A. Di-tert-butyl dicarbonate and 4-(dimethylamino)pyridine revisited. Their reactions with amines and alcohols. J Organomet Chem. 2000;65:6368–80. https://doi.org/10.1021/jo000257f.

Bayat M, Imanieh H, Hossieni SH. Synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) in aqueous medium at room temperature. Chin Chem Lett. 2009;20:656–9. https://doi.org/10.1016/j.cclet.2008.12.050.

Belly M, Zamboni RJ. Addition of Thiols to Styrenes: formation of Benzylic Thioethers. Org Chem. 1989;54:1230–2. https://doi.org/10.1021/jo00266a053.

Bhat AR, Shalla AH, Dongre RS. Microwave-assisted one-pot catalyst-free green synthesis of new methyl-7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylates as potent in vitro antibacterial and antifungal activity. J Adv Res. 2015;6:941–8. https://doi.org/10.1016/j.jare.2014.10.007.

Bigi F, Carloni S, Ferrari L, Maggi R, Mazzacani A, Sartori G. Clean synthesis in water. Part 2: Uncatalysed condensation reaction of Meldrum's acid and aldehydes. Tetrahedron Lett. 2001;42:5203–5. https://doi.org/10.1016/S0040-4039(01)00978-9.

Braga AL, Silveira CC, Dornelles L, Zeni G, Galarza FAD, Wessjohann LA. Catalyst-dependent selective synthesis of O/S- and S/S acetals from enol ethers. Synth Commun. 1995;25:3155–62. https://doi.org/10.1080/00397919508015466.

Brahmachari G, Banerjee B. A comparison between catalyst-free and $ZrOCl_2{\cdot}8H_2O$-catalyzed Strecker reactions for the rapid and solvent-free one-pot synthesis of racemic α-aminonitrile derivatives. Asian J Org Chem. 2012;1:251–8. https://doi.org/10.1002/ajoc.201200055.

Brahmachari G, Banerjee B. Facile and chemically sustainable one-pot synthesis of a wide array of fused *O*- and *N*-heterocycles catalyzed by trisodium citrate dihydrate under ambient conditions. Asian J Org Chem. 2016;5:271–86. https://doi.org/10.1002/ajoc.201500465.

Breslow R. Hydrophobic effects on simple organic reactions in water. Acc Chem Res. 1991;24:159–64. https://doi.org/10.1021/ar00006a001.

Butler RN, Coyne AG. Water: nature's reaction enforcers comparative effects for organic synthesis "in-water" and "on-water". Chem Rev. 2010;110:6302–37. https://doi.org/10.1021/cr100162c.

Chakraborti AK, Selvam C, Kaur G, Bhagat S. An efficient synthesis of benzothiazoles by direct condensation of carboxylic acids with 2-aminothiophenol under microwave irradiation. Synlett. 2004;2004:0851–5. https://doi.org/10.1055/s-2004-820012.

Chakraborti AK, Rudrawar S, Jadhav KB, Kaur G, Chankeshwara SV. "On water" organic synthesis: a highly efficient and clean synthesis of 2-aryl/heteroaryl/styryl benzothiazoles and 2-alkyl/aryl alkyl benzothiazolines. Green Chem. 2007;9:1335–40. https://doi.org/10.1039/B710414F.

Chankeshwara SV, Chakraborti AK. Catalyst-free chemoselective *N*-tert-butyloxycarbonylation of amines in water. Org Lett. 2006;15:3259–62. https://doi.org/10.1021/ol06111.

Choi S-J, Park HJ, Lee SK, Kim SW, Han G, Choo H-YP. Solid phase combinatorial synthesis of benzothiazoles and evaluation of topoisomerase II inhibitory activity. Bioorg Med Chem. 2006;14:1229–35. https://doi.org/10.1016/j.bmc.2005.09.051.

Dambacher J, Zhao W, El-Batta A, Anness R, Jiang C, Bergdahl M. Water is an efficient medium for Wittig reactions employing stabilized ylides and aldehydes. Tetrahedron Lett. 2005;46:4473–7. https://doi.org/10.1016/j.tetlet.2005.04.105.

Dandia A, Singh R, Joshi J, Maheshwari S, Soni P. Ultrasound promoted catalyst-free and selective synthesis of spiro[indole-3,4′-pyrazolo[3,4-*e*][1,4]thiazepines] in aqueous media and evaluation of their anti-hyperglycemic activity. RSC Adv. 2013;3:18992–9001. https://doi.org/10.1039/C3RA43745K.

Das S, Thakur AJ. A clean, highly efficient and one-pot green synthesis of aryl/alkyl/ heteroaryl-substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes in water. Eur J Org Chem. 2011;2011:2301–8. https://doi.org/10.1002/ejoc.201001581.

De Rosa M, Soriente A. A combination of water and microwave irradiation promotes the catalyst-free addition of pyrroles and indoles to nitroalkenes. Tetrahedron. 2010a;66:2981–6. https://doi.org/10.1016/j.tet.2010.02.055.

De Rosa M, Soriente A. Rapid and general protocol towards catalyst-free Friedel-crafts C-alkylation of indoles in water assisted by microwave irradiation. Eur J Org Chem. 2010b;2010:1029–32. https://doi.org/10.1002/ejoc.200901333.

De Rosa M, Soriente A. Water opportunities: catalyst and solvent in Mukaiyama aldol addition of Rawal's diene to carbonyl derivatives. Tetrahedron. 2011;67:5949–55. https://doi.org/10.1016/j.tet.2011.06.035.

Dolzhenko AV, Pastorin G, Dolzhenko AV, Chui WK. An aqueous medium synthesis and tautomerism study of 3(5)-amino-1,2,4-triazoles. Tetrahedron Lett. 2009;50:2124–8. https://doi.org/10.1016/j.tetlet.2009.02.172.

Ebrahimi SM, Mahdavi M, Emami S, Saeedi M, Asadi M, Firoozpour L, Khoobi M, Divsalar K, Shafiee A, Foroumadi A. Green and catalyst-free one-pot synthesis of anthranilamide schiff bases: An approach toward sirtinol. Synth Commun. 2014;44:665–73. https://doi.org/10.1080/00397911.2013.833627.

Eftekhari-Sis B, Vahdati-Khajeh S. Ultrasound-assisted green synthesis of pyrroles and pyridazines in water via three-component condensation reactions of arylglyoxals. Curr Chem Lett. 2013;2:85–92. https://doi.org/10.5267/j.ccl.2013.02.002.

Evindar G, Batey RA. parallel synthesis of a library of benzoxazoles and benzothiazoles using ligand-accelerated copper-catalyzed cyclizations of ortho-halobenzanilides. J Organomet Chem. 2006;71:1802–8. https://doi.org/10.1021/jo051927q.

Galletti P, Pori M, Giacomini D. Catalyst-free strecker reaction in water: a simple and efficient protocol using acetone cyanohydrin as cyanide source. Eur J Org Chem. 2011;2011:3896–903. https://doi.org/10.1002/ejoc.201100089.

Gan S-F, Wan J-P, Pan Y-J, Sun C-R. Highly efficient and catalyst-free synthesis of substituted thioureas in water. Mol Divers. 2011;15:809–15. https://doi.org/10.1007/s11030-010-9298-6.

Gawande MB, Bonifácio VD, Luque R, Branco PS, Varma RS. Benign by design: catalyst-free in-water, on-water green chemical methodologies in organic synthesis. Chem Soc Rev. 2013;42:5522–51. https://doi.org/10.1039/C3CS60025D.

Ghandi M, Mohammadimehr E, Sadeghzadeh M, Bozcheloei AH. Efficient access to novel hexahydro-chromene and tetrahydro-pyrano[2,3-d]pyrimidine-annulated benzo-d-sultones via a domino Knoevenagel-hetero-Diels-Alder reaction in water. Tetrahedron. 2011;67:8484–91. https://doi.org/10.1016/j.tet.2011.09.010.

Gong G-X, Zhou J-F, An L-T, Duan X-L, Ji S-J. Catalyst-free synthesis of *bis*(4-hydroxycoumarin-3-yl)toluene in aqueous media under microwave irradiation. Synth Commun. 2009;39:497–505. https://doi.org/10.1080/00397910802398272.

Grehn L, Ragnarsson U. A convenient method for the preparation of 1-(tert-butyloxycarbonyl) pyrroles. Angew Chem Int Ed Eng. 1984;23:296–301. https://doi.org/10.1002/anie.198402961.

Guibé-Jampel E, Wakselman M. An easy preparation of the water-solublet-butoxycarbonylating agent 1-Boc-4-dimethylaminopyridinium tetrafluoroborate. Synthesis. 1977;1977:772. https://doi.org/10.1055/s-1977-24570.

Habib PM, Kavala V, Kuo C-W, Yao C-F. Catalyst-free aqueous-mediated conjugative addition of indoles to β-nitrostyrenes. Tetrahedron Lett. 2008;49:7005–7. https://doi.org/10.1016/j.tetlet.2008.09.109.

Halimehjani AZ, Jalali A, Khalesi M, Ashouri A, Marjani K. Catalyst-free efficient regioselective ring opening of oxiranes with thioacids in water. Synth Commun. 2011;41:1638–43. https://doi.org/10.1080/00397911.2010.491172.

Handy ST, Sabatini JJ, Zhang Y, Vulfova I. Protection of poorly nucleophilic pyrroles. Tetrahedron Lett. 2004;45:5057–60. https://doi.org/10.1016/j.tetlet.2004.04.178.

Hea Z, Fanga F, Lva J, Zhang J. One-pot gram-scale synthesis of γ-hydroxybutenolides through catalyst-free annulation of α-amino acids with α-keto acids in water. Tetrahedron Lett. 2017;58:1034–6. https://doi.org/10.1016/j.tetlet.2017.01.080.

Heo Y, Song YS, Kim BT, Heo J-N. A highly regioselective synthesis of 2-aryl-6-chlorobenzothiazoles employing microwave-promoted Suzuki-Miyaura coupling reaction. Tetrahedron Lett. 2006;47:3091–4. https://doi.org/10.1016/j.tetlet.2006.02.152.

Ipatieff VN, Pines H, Friedman BS. Reaction of aliphatic olefins with Thiophenol. J Am Chem Soc. 1938;60:2731–4. https://doi.org/10.1021/ja01278a055.

Itoh T, Mase T. A novel practical synthesis of benzothiazoles via Pd-catalyzed thiol cross-coupling. Org Lett. 2007;9:3687–9. https://doi.org/10.1021/ol7015737.

Ji S-J, Shi H-B. Synthesis and fluorescent property of some novel benzothiazoyl pyrazoline derivatives containing aromatic heterocycle. Dyes Pigments. 2006;70:246–50. https://doi.org/10.1016/j.dyepig.2005.03.007.

Kanagasabapathy S, Sudalai A, Benicewicz BC. Montmorillonite K 10-catalyzed regioselective addition of thiols and thiobenzoic acids onto olefins: an efficient synthesis of dithiocarboxylic esters. Tetrahedron Lett. 2001;42:3791–4. https://doi.org/10.1016/S0040-4039(01)00570-6.

Kaneda K, Mizugaki T. Development of concerto metal catalysts using apatite compounds for green organic syntheses. Energy Environ Sci. 2009;2:655–73. https://doi.org/10.1039/B901997A.

Karamthulla S, Pal S, Khan MN, Choudhury LH. "On-water" synthesis of novel trisubstituted 1, 3-thiazoles *via* microwave-assisted catalyst-free domino reactions. RSC Adv. 2014;4:37889–99. https://doi.org/10.1039/C4RA06239F.

Khatik GL, Kumar R, Chakraborti AK. Catalyst-free conjugated addition of thiols to α,β-unsaturated carbonyl compounds in water. Org Lett. 2006;8:2433–6. https://doi.org/10.1021/ol060846t.

Krammer P, Vogel H. Hydrolysis of esters in subcritical and supercritical water. J Supercrit Fluids. 2000;16:189–206. https://doi.org/10.1016/S0896-8446(99)00032-7.

Kumar P, Pandy RK, Hegde VR. Anti-Markovnikov addition of thiols across double bonds catalyzed by h-rho-zeolite. Synlett. 1999;1999:1921–2. https://doi.org/10.1055/s-1999-2976.

Kumaravel K, Vasuki G. Four-component catalyst-free reaction in water: combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*chromene- 3-carbonitrile derivatives. Green Chem. 2009;11:1945–7. https://doi.org/10.1039/B913838B.

Loos D, Sidoova E, Sutoris V. Benzothiazole derivatives. 48. Synthesis of 3-alkoxycarbonylmethyl-6-bromo-2-benzothiazolones and 3-alkoxycarbonylmethyl-6-nitro-2-benzothiazolones as potential plant growth regulators. Molecules. 1999;4:81–93. https://doi.org/10.3390/40400081.

Marjani K, Khalesi M, Ashouri A, Jalali A, Ziyaei-Halimehjani A. Catalyst-free conjugate addition of thioacids to activated olefins accelerated in water. Synth Commun. 2011;41:451–8. https://doi.org/10.1080/00397911003587515.

Meshram HM, Rao NN, Kumar NS, Rao LC. Microwave assisted catalyst free synthesis of 3-hydroxy-2-oxidoles by aldol condensation of acetophenones with isatins. Der Pharma Chemica. 2012a;4:1355–60.

Meshram HM, Rao NN, Rao LC, Kumar NS. Microwave assisted catalyst-free synthesis of azaarene-substituted 3-hydroxy-2-oxindoles by the functionalization of $sp^3$ C-H bond in methyl pyridine. Tetrahedron Lett. 2012b;53:3963–6. https://doi.org/10.1016/j.tetlet.2012.05.077.

Movassagh B, Navidi M. Water promoted catalyst-free anti-Markovnikov addition of thiols to styrenes. ARKIVOC. 2008;xv:47–53.

Mu X-J, Zou J-P, Zeng R-S, Wu J-C. Mn(III)-promoted cyclization of substituted thioformanilides under microwave irradiation: a new reagent for 2-substituted benzothiazoles. Tetrahedron Lett. 2005;46:4345–7. https://doi.org/10.1016/j.tetlet.2005.04.090.

Olyaei A, Parashkuhi EC, Raoufmoghaddam S, Sadeghpour M. One-pot, three-component coupling reaction: catalyst-free green synthesis of novel *N*-heteroaryl α-naphthylglycines. Synth Commun. 2010;40:3609–17. https://doi.org/10.1080/00397910903457407.

Pagadala R, Maddila S, Jonnalagadda SB. Ultrasonic-mediated catalyst-free rapid protocol for the multicomponent synthesis of dihydroquinoline derivatives in aqueous media. Green Chem Lett Rev. 2014;7:131–6. https://doi.org/10.1080/17518253.2014.902505.

Paladhi S, Chauhan A, Dhara K, Tiwari AK, Dash J. An uncatalyzed aldol reaction of thiazolidinediones. Green Chem. 2012;14:2990–5. https://doi.org/10.1039/C2GC35819K.

Pirrung MC, Li Z, Park K, Zhu J. Total syntheses of demethylasterriquinone B1, an orally active insulin mimetic, and demethylasterriquinone A1. J Organomet Chem. 2002;67:7919–26. https://doi.org/10.1021/jo020182a.

Pirrung MC, Fujita K, Park K. Organometallic routes to 2,5-dihydroxy-3-(indol-3-yl)benzoquinones. synthesis of demethylasterriquinone B4. J Organomet Chem. 2005a;70:2537–42. https://doi.org/10.1021/jo048126s.

Pirrung MC, Liu Y, Deng L, Halstead DK, Li Z, May JF, Wedel M, Austin DA, Webster NJG. Methyl scanning: total synthesis of demethylasterriquinone B1 and derivatives for identification of sites of interaction with and isolation of its receptor(s). J Am Chem Soc. 2005b;127:4609–24. https://doi.org/10.1021/ja044325h.

Prasad BAB, Bisai A, Singh VK. Trimethylsilyl cyanide addition to aldimines and its application in the synthesis of (S)-phenylglycine methyl ester. Tetrahedron Lett. 2004;45:9565–7. https://doi.org/10.1016/j.tetlet.2004.11.015.

Prasad JV, Prabhakar M, Manjulatha K, Rambabu D, Solomon KA, Krishna GG, Kumar KA. Efficient catalyst-free domino approach for the synthesis of novel 2-benzazepine derivatives in water. Tetrahedron Lett. 2010;51:3109–11. https://doi.org/10.1016/j.tetlet.2010.04.020.

Ramazani A, Rezaei A, Mahyari AT, Rouhani M, Khoobi M. Three-component reaction of an isocyanide and a dialkyl acetylenedicarboxylate with a phenacyl halide in the presence of water: An efficient method for the one-pot synthesis of γ-iminolactone derivatives. Helv Chim Acta. 2010;93:2033–6. https://doi.org/10.1002/hlca.201000057.

Ramazani A, Rouhani M, Joo SW. Catalyst-free sonosynthesis of highly substituted propanamide derivatives in water. Ultrason Sonochem. 2016;28:393–9. https://doi.org/10.1016/j.ultsonch.2015.08.019.

Ramesh S, Sivakumar K, Panja C, Arunachalam PN, Lalitha A. Water-mediated strecker reaction: An efficient and environmentally friendly approach for the synthesis of α-aminonitriles

via a three-component condensation. Synth Commun. 2010;40:3544–51. https://doi.org/10.1080/00397910903457381.
Ranu BC, Banerjee S. Significant rate acceleration of the aza-Michael reaction in water. Tetrahedron Lett. 2007;48:141–3. https://doi.org/10.1016/j.tetlet.2006.10.142.
Razus AC, Birzan L, Surugiu NM, Corbu AC, Chiraleu F. Syntheses of azulen-1-yl-benzothiazol-2-yl diazenes. Dyes Pigments. 2007;74:26–33. https://doi.org/10.1016/j.dyepig.2006.01.041.
Rostamizadeh S, Housaini SAG. Microwave-assisted preparation of 2-substituted benzothiazoles. Phosphorus Sulfur Silicon Relat Elem. 2005;180:1321–6. https://doi.org/10.1080/10426500590912268.
Rostamnia S, Lamei K. A rapid, catalyst-free, three-component synthesis of rhodanines in water using ultrasound. Synthesis. 2011;2011:3080–2. https://doi.org/10.1055/s-0030-1260158.
Rudrawar S, Kondaskar A, Chakraborti AK. An efficient acid- and metal-free one-pot synthesis of benzothiazoles from carboxylic acids. Synthesis. 2005;2005:2521–6. https://doi.org/10.1055/s-2005-872092.
Sankar M, Dimitratos N, Miedziak PJ, Wells PP, Kiely CJ, Hutchings GJ. Designing bimetallic catalysts for a green and sustainable future. Chem Soc Rev. 2012;41:8099–139. https://doi.org/10.1039/C2CS35296F.
Screttas CG, Micha-Screttas M. Markownikoff two-step hydrolithiation of α-olefins. Transformation of secondary and tertiary alkyl phenyl sulfides to the relevant alkyllithium reagents. J Organomet Chem. 1979;44:713–9. https://doi.org/10.1021/jo01319a011.
Shaabani A, Hajishaabanha F, Mofakham H, Mahyari M, Lali B. Isocyanide-based three-component synthesis of highly substituted 1,6-dihydro-6,6-dimethylpyrazine-2,3- dicarbonitrile, 3,4-dihydrobenzo[*g*]quinoxalin-2-amine, and 3,4-dihydro-3,3-dimethylquinoxalin-2-amine derivatives. Helv Chim Acta. 2012;95:246–54. https://doi.org/10.1002/hlca.201100270.
Shen K, Liu XH, Cai YF, Lin LL, Feng XM. Facile and efficient enantioselective strecker reaction of ketimines by chiral sodium phosphate. Chem Eur J. 2009;15:6008–14. https://doi.org/10.1002/chem.200900210.
Sreedhar B, Reddy PS, Reddy MA. Catalyst-free and base-free water-promoted $S_NAr$ reaction of heteroaryl halides with thiols. Synthesis. 2009;2009:1732–8. https://doi.org/10.1055/s-0029-1216644.
Tarana J, Ramazani A, Joo SW, Ślepokura K, Lis T. Synthesis of novel α-(acyloxy)-α-(quinolin-4-yl)acetamides by a three-component reaction between an isocyanide, quinoline-4-carbaldehyde, and arenecarboxylic acids. Helv Chim Acta. 2014;97:1088–96. https://doi.org/10.1002/hlca.201300378.
Thakur PB, Meshram HM. "On water" catalyst-free, column chromatography-free and atom economical protocol for highly diastereoselective synthesis of novel class of 3-substituted, 3-hydroxy-2-oxindole scaffolds at room temperature. RSC Adv. 2014a;4:5343–50. https://doi.org/10.1039/C3RA46271D.
Thakur PB, Meshram HM. "On water" highly atom economical and rapid synthesis of a novel class of 3-hydroxy-2-oxindole scaffolds under a catalyst-free and column chromatography-free protocol at room temperature. RSC Adv. 2014b;4:6019–26. https://doi.org/10.1039/C3RA46613B.
Thakur PB, Sirisha K, Sarma AVS, Meshram HM. Microwave assisted rapid, catalyst-free, and efficient synthesis of a new class of diversely functionalized 3-hydroxy-2-oxindole scaffolds under aqueous reaction media. Tetrahedron Lett. 2014;55:2459–62. https://doi.org/10.1016/j.tetlet.2014.03.008.
Tian Y, Liu Q, Liu Y, Zhao R, Li G, Xu F. Catalyst-free Mannich-type reactions in water: expedient synthesis of naphthol-substituted isoindolinones. Tetrahedron Lett. 2018;59:1454–7. https://doi.org/10.1016/j.tetlet.2018.02.083.
Trost BM. On inventing reactions for atom economy. Acc Chem Res. 2002;35:695–705. https://doi.org/10.1021/ar010068z.
Volkov PA, Gusarova NK, Khrapova KO, Telezhkin AA, Ivanova NI, Albanov AI, Trofimov BA. Catalyst-free selenylation of acylacetylenes with secondary phosphine selenides and

water: a short-cut to *bis*(2-acylvinyl) selenides. J Organomet Chem. 2018;867:79–85. https://doi.org/10.1016/j.jorganchem.2017.09.031.

Wang G, Li C, Li J, Jia X. Catalyst-free water-mediated N-Boc deprotection. Tetrahedron Lett. 2009;50:1438–40. https://doi.org/10.1016/j.tetlet.2009.01.056.

Yadav JS, Reddy BVS, Swamy T. $Bi(OTf)_3$-catalyzed conjugate addition of indoles to *p*-quinones: a facile synthesis of 3-indolyl quinines. Tetrahedron Lett. 2003;44:9121–4. https://doi.org/10.1016/j.tetlet.2003.10.041.

Yadav JS, Reddy BVS, Swamy T. $InBr_3$-catalyzed conjugate addition of indoles to *p*-quinones: an efficient synthesis of 3-indolylquinones. Synthesis. 2004;2004:106–10. https://doi.org/10.1055/s-2003-44364.

Yadav LDS, Patel R, Srivastava VP. An easy access to functionalized allyl dithiocarbamates from Baylis-Hillman adducts in water. Tetrahedron Lett. 2009;50:1335–9. https://doi.org/10.1016/j.tetlet.2009.01.023.

Yoshida M, Hayakawa I, Hayashi N, Agatsuma T, Oda Y, Tanzawa F, Iwasaki S, Koyama K, Furukawa H, Kurakata S, Sugano Y. Synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents. Bioorg Med Chem Lett. 2005;15:3328–32. https://doi.org/10.1016/j.bmcl.2005.05.077.

Yu JJ, Wang LM, Liu JQ, Guo FL, Liu Y, Jiao N. Synthesis of tetraketones in water and under catalyst-free conditions. Green Chem. 2010;12:216–9. https://doi.org/10.1039/B913816A.

Zhang H-B, Liu L, Chen Y-J, Wang D, Li C-J. "On water"-promoted direct coupling of indoles with 1,4-benzoquinones without catalyst. Eur J Org Chem. 2006;2006:869–73. https://doi.org/10.1002/ejoc.200500863.

Zhao L, Zhou B, Li Y. An efficient one-pot three-component reaction for synthesis of spirooxindole derivatives in water media under catalyst-free condition. Heteroat Chem. 2011;22:673–7. https://doi.org/10.1002/hc.20723.

# Modifications on Polymeric Membranes for Isopropanol Dehydration Using Pervaporation: A Review

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_5

## Abbreviation

| | |
|---|---|
| A | The effective surface area of the membrane ($m^2$) |
| CB | Carbon black |
| EDA | Ethylenediamine |
| F | Mass fraction of the species at the feed |
| GA | Glutaraldehyde |
| GFT | Gesellschaft für trenntechnik |
| GOTMS | 3-Glycidyloxypropyltrimethoxysilane |
| GTMAC | Glycidyl trimethyl ammonium chloride |
| HDA | 1,6-Hexanediamine |
| HEC-g-AAm | Hydroxyethyl cellulose grafting with acrylamide |
| HPEI | Hyperbranched polyethyleneimine |
| HTPB | Hydroxyl-terminated polybutadiene |
| IP | Interfacial polymerization |
| IPA | Isopropanol |
| IPAC | Isopropyl acetone |
| J | The flux of the mass transfer |
| mPAN | Polyacrylonitrile |
| MPD | M-Phenylenediamine |
| MPDA | M-Phenylenediamine |
| MPDASA | 1,3-Phenylenediamine-4-sulfonic acid |
| NaAlg | Sodium alginate |
| NaSS | Sodium 4-styrenesulfonate |
| P | Mass fraction of the species at the permeate |
| P84 | Co-polyimide |
| PAI | Polyamide-imide |
| PAN | Polyacrylonitrile |
| PDA | 1,3-Propanediamine |
| PDMS | Polydimethylsiloxane |
| PE | Polyethylene |
| PEBA | Polyether-block-polyamide |
| PEI | Polyetherimide |
| PIP | Piperazine |
| PP | Polypropylene |
| PS | Polysulfone |
| PTFE | Polytetrafluoroethylene |

| | |
|---|---|
| PU | Polyurethane urea |
| PV | Pervaporation |
| PVA | Poly(vinyl alcohol) |
| PVDF | Poly(vinylidene fluoride) |
| PVME | Poly(vinyl methyl ether) |
| SA | Sodium alginate |
| SPVA | Sulfonated-poly(vinyl alcohol) |
| t | The experiment time (h) |
| TETA | Triethylenetetramine |
| TFC | Thin-film composite |
| TMC | Trimesoyl chloride |
| W | Mass of the permeate (kg) |
| α | Selectivity |

## 1 Introduction

Commercially, isopropanol (IPA) was produced in two ways. This solvent is either produced by indirect hydration method or direct hydration of chemical grade. The indirect method involved the production of isopropyl sulphate at the first stage before IPA is generated along with sulphuric acid using refinery-grade propylene. Meanwhile, the direct production of IPA is by using chemical-grade propylene. The propylene-water mixture is heated until the liquid-vapour phase mixture is formed before separating by a reactor comprised with the sulphonated polystyrene cation ion exchange resins. The IPA is acquired from the aqueous solution by distillation. There is also small production by the hydrogenation of acetone. However, this method is not practicable due to the acetone present as a side product.

IPA is commonly used as a cleaning and drying agent in the manufacture of electronic parts and metals, extraction and purification of natural products, a coupling agent, a polymerization modifier, a de-icing agent and a preservative and as an aerosol solvent in medical and veterinary products. Nevertheless, IPA is most known as the main organic ingredient in the wastewater of the semiconductor manufacturing industry which is a prime focus to be treated. The demand for IPA is getting high yearly. Like any other sources, the IPA tends to decrease. This contributes to the higher price of pure IPA. Thus, recycling of IPA is also well received by the industry as the recovery IPA can be purchased with lower prices compared with pure IPA. In this regard, the demands for the pure solvents are able to be reduced, which also leads to decreasing the production costs and the impact that this has on the environment. This condition is eventually able to control the IPA market prices.

High concentrated IPA content in the wastewater as well as volatile properties, this waste cannot be disposed to the landfill as this solvent contributes harmful impact on soil and water resources, agriculture, animals, plants and the climate (Cheng et al. 2010). IPA waste is commonly contaminated with water, grease and oil. Recycling IPA waste helps in a significant reduction in the quantity of this

solvent waste, which in turn minimizes the impact on the environment and costs associated with the disposal of the waste. On top of these, IPA recovery is necessary for our country to comply with the standard quality of industrial and sewage 1979. IPA waste falls under alcohols with less or equal to four carbon atoms, which, according to the Material Safety Data Sheet, is higher than 1% concentration; disposal of the waste to the sewer is intolerable. An industry is only allowed to incinerate, fuel blend or recycle the waste due to the much higher concentration used in industries (Seyler et al. 2005). Recycling is always the green option and able to turn the waste to wealth with an efficient technique. However, the industry has a dilemma for waste management cost. Waste management needs to consider the budget that covers the storage, transport or handling of the waste.

Thus, in an effort to conserve the environment with the low overall cost treatment, many studies have been pulled off and purposed throughout the years. The isopropanol waste is mainly treated by distillation and extraction methods (Dahl et al. 2010). Extracting solvent method was also applied for recycling the phenol by Yang et al. (2006) but no report on IPA waste. Despite distillation provides more favourable for IPA and water separation, the focus should be that industrial waste may produce azeotropic which suggests that pervaporation (PV) is more appropriate (Andre et al. 2018). Moreover, these two techniques are still considered expensive. To this recent, purifying IPA using membranes is getting more attention, namely, vapour permeation membranes and pervaporation. Both separation technologies comprised high performance; however, for energy conservation, PV reflects much more green alternatives due to a very low temperature required for separation to take place.

The main issue in separating IPA from wastewater is when the mixture reaches the azeotropic phase. Azeotropic would occur when the mixture consists of 87.4% and 12.6% of IPA and water, respectively. The purification of IPA is considered as economically impractical using the traditional distillation method or solvent extraction (Rodriguez and Kroon 2015). Separating IPA from water mixture can be complicated however achievable using PV technique. Several researchers have reported the principle process of PV and have revealed the experimental results using IPA. The dehydration technique for purifying IPA has getting acknowledged attention from industries due to the reasons. Alternatively, a potential separation system using PV that is energy efficient, environmentally friendly and a simple operation has been developed (Ong and Tan 2016).

The term ‘pervaporation’ was introduced based on the permeation process of permeates through the collodion and parchment membrane and evaporation when it was first found this process in the 1910s. Since then, numerous PV studies have been developed. The first commercialized PV membrane was known as the Gesellschaft für Trenntechnik (GFT). GFT is a composite porous polyacrylonitrile (PAN) membrane, where the membrane is coated with crosslinked poly(vinyl alcohol) (PVA) as a thin film on top of the membrane (Tusel and Brüschke 1985).

Application of dense, symmetric structure and hydrophilic polymeric membranes in the PV system in the laboratory is very common. However, the limitations of these membranes such as relatively low transmembrane flux and low mechanical

strength make the membranes unfavourable to be applied in PV processes. To counter these limitations, various modification techniques have been introduced throughout the years. This chapter reviews the properties of PV membranes, as well as the types and techniques of modifications available for enhancing the performance. In membrane alteration, there are several procedures, namely, blending, crosslinking, grafting a specific chemical onto the membrane and copolymerization, presented. Modifications proposed by researchers were by controlling the membrane structure by manipulating the casting parameter during fabrication. There is also modification during dope solution by introducing other components or polymer and adding fillers. The surface modification by solvent coating and thin-film layer is mainly the recent trend in the PV membrane followed by post-modification for much stable membrane for IPA dehydration application (Huang and Chang 2010).

## 2 Pervaporation Procedure and Isopropanol Dehydration Process

The pervaporation experimental set-up is shown in Fig. 1 for hollow fibre membranes. The feed solution with a composition of IPA and water is prepared and the mixture circulated through the shell side of the hollow fibre by a pump. The mixture is then heated until it reaches the desired temperature. The lumen side of the hollow fibre is connected to a vacuum, which is also called the permeate side. The permeate side pressure is maintained at a very low pressure. In the PV system, the vacuum pump at the downstream of the membrane is set at a very low absolute pressure that ranges between 133.3 and 400.0 Pa (1–3 mmHg) to ensure constant mass transport. The system is also used for removing the molecules transferring to the surface and, eventually, to provide a concentration difference for the driving force across the

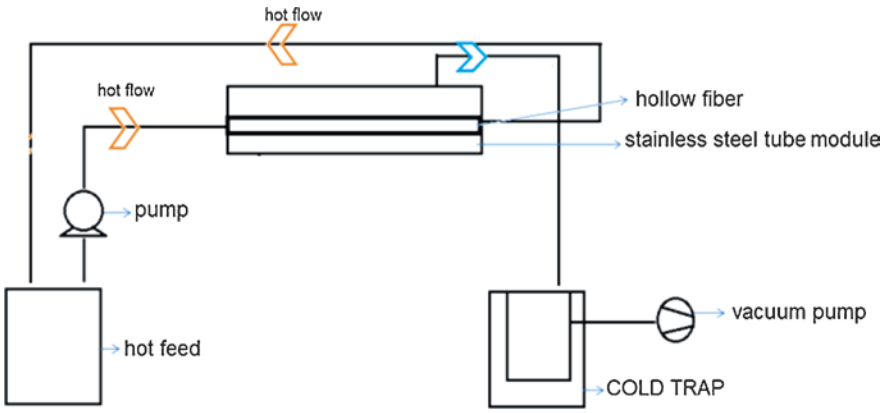


**Fig. 1** The pervaporation set-up

membrane. The system is conditioned for 1 h to ensure that the membrane stabilized before the collection of the permeate samples. During the PV process, the selected components in the mixture will transform the phase from liquid to vapour while the components pass through the membrane. The sample from permeate side is condensed in a cold trap and collected at a time interval of 1 h. The mass of the collected sample is weighted by a Mettler Toledo balance for flux and selectivity calculations.

PV is operated with a mild setting, environmentally friendly and does not require additional chemicals in the feed stream. These advantages make PV more favourable compared to the traditional method of distillation (Chapman et al. 2008). PV is known for a low operating temperature where the aqueous solutions do not require to heat up to the boiling points. At higher temperature than ambient temperature, the vaporized liquid exists in binary phase, both liquid and vapours. The kinetic diameter parameters are more likely to influence permeation flux.

## 3 Membranes for Pervaporation

Ceramic, composite and polymeric membranes are the materials mainly applied for PV. The structure in ceramic mainly comprises of similar pore structure and less dense packing compared to the polymeric membrane based. Ceramic is composed of a superior mechanical strength, heat resistance and performances; however, the expenses are much higher compared with the polymeric. Meanwhile, polymeric is a flexible and versatile material which can provide a wider scope to be explored. Meanwhile, the composite membrane typically enclosed the thin-film composite is considered as one of the modified technique which discovers further in this chapter.

### *3.1 Ceramic*

Ceramic membranes are also known as inorganic membranes. These membranes are mainly made from silica, alumina or zeolite. The membrane poses high solvent-resistant properties, high-temperature stability and free of swelling which provide better performance compared with the polymeric membrane. Silica consists of a highly porous material and provides a high flux inorganic membrane but very weak when in contact with water (Asaeda and Yamasaki 2001). Zeolite membranes present pore structure, adsorption properties and the mechanical, chemical and biological stability, which is relevant to be applied in PV (Huang et al. 2007).

The common zeolite structures, namely, ZSM-5, zeolite A, mordenite and zeolite Y, are used for PV studied. Zhou et al. use ZSM- 5 membranes to separate water-alcohol mixtures (Zhou et al. 2005). There is a study reported that high PV selectivity of water in methanol, ethanol, and IPA-water mixtures were able to obtain. Another study using the synthesized silicalite-1 poses high performance for PV study were operated membranes for methanol-water, ethanol-water,

2-propanol–water and 1-propanol–water mixtures respectively were accomplished by Chen et al. (2017).

Some types of zeolite had been used for low pH mixtures such as the separation of acetic acid mixtures by PV, namely, silicalite-1, mordenite and ZSM-5. However, there is also a zeolite membrane that is not suitable for very acidic mixture such as NaA-type zeolite membrane (Hasegawa et al. 2010). NaA-type zeolites are very hydrophilic and hence only allow for water molecules to pass through. Due to these applicable properties, NaA-type zeolite membranes are widely studied as pervaporation membranes for the dehydration of alcohol (Zhang and Liu 2011).

A comparison study was executed on the dehydration performance of a commercial NaA-type zeolite membrane with the polymeric membranes for IPA-water, acetonitrile-water and methyl ethyl ketone-water by Van Hoof et al. (2004). Results revealed all the solvents performed very best by polymeric membranes when properties at the azeotrope, meanwhile NaA membrane exhibited the highest separation especially, at low water concentration. Another comparison of commercial polymeric and microporous silica membrane performance for separating IPA was studied (Gallego-Lizon et al. 2002). IPA fluxes of silica membrane are observed to be higher than through polymeric membrane, resulting in a significant drop in separation performance.

## *3.2 Composite Membrane*

Studies on thin-film composite (TFC) membranes are primary about the application in reverse osmosis or nanofiltration. Recently, the composite membrane also known as hybrid membranes received well attention in the alcohol dehydration field (Kao et al. 2010). The composite membrane consists of a very TFC which is deposited on a porous structure membrane referred to as substance. These membranes improve selectivity and productivity, low energy consumption and higher mechanical strength as compared to typical asymmetric membranes (Kao et al. 2010; Zhang et al. 2007a, b). The thickness of the thin film is ~0.2 μm with the interstitial void size of ~0.5 nm (Ismail et al. 2015).

For water-perm selective composite membrane, in order to increase the swelling resistance, the support layer should be high hydrophobic; conversely, to increase the permeability and selectivity, the active layer should be very hydrophilic. A typical issue is that active layer is challenging to be strongly coated on the support layer due to the great surface tension and weak interfacial interaction between these two layers (Guo et al. 2008).

The most main effective technique to prepare a composite membrane with a selective thin layer is interfacial polymerization (IP). For alcohol dehydration, a hydrophilic selective layer is recommended as the membrane offers a thin and dense layer as well as provides good performance. Studies on interfacially polymerized TFC membranes mainly involve a reaction between amines and monomers to form a thin

layer. The common amines used are m-phenylenediamine (MPD), 1,6-hexanediamine (HDA), triethylenetetramine (TETA), piperazine (PIP), ethylenediamine (EDA), hyperbranched polyethyleneimine (HPEI), 1,3-phenylenediamine-4-sulfonic acid (MPDASA) and m-phenylenediamine (MPDA); meanwhile typically monomer is trimesoyl chloride (TMC) (Kao et al. 2010; Zuo et al. 2012, 2013).

### *3.3 Polymeric Membrane*

For the dehydration purpose, good membrane material should have high flux, high separation efficiency and long-term stability to maintain the original permselectivity under operating condition. The well-known polymeric membranes such as polytetrafluoroethylene (PTFE), polyethylene (PE), polypropylene (PP) and poly(vinylidene fluoride) (PVDF) show the optimum fluxes were successfully obtained for both commercially available and a lab fabricated membrane (Ahmad and Lone 2012; Feng et al. 2013). Selection of suitable material will significantly assist in overcoming a few limitations for the PV process. Not only is polymeric membrane suitable for PV process but also relatively economical to fabricate (Namboodiri and Vane 2007).

Out of these materials, PTFE has the highest hydrophobicity (largest contact angle with water), good chemical and thermal stability and oxidation resistance, but also has the highest conductivity which will cause greater heat transfer through PTFE membranes. PVDF has good hydrophobicity, thermal resistance and mechanical strength and can be easily prepared into membranes with versatile pore structures by different methods. Some of the previous works choose PVDF, polydimethylsiloxane (PDMS), polyether-block-polyamide (PEBA), poly(octyl methyl siloxane), sulfonated poly(vinyl alcohol) (SPVA), incorporating sulfophthalic acid, polyamide-imide (PAI), PAN, poly(vinyl alcohol) and polyetherimide (PEI) membranes as the membrane material. The membranes need to be making sure to get non-wetted by feed aqueous solution.

Dense membranes in the PV system in the laboratory are widely used to understand the intrinsic behaviour of the materials. The common polymeric membranes for PV application, namely, PVDF, PEI, SPVA and polyimide (PI), are listed in Table 1**.** Wang et al. (2009a) stress that polymer concentration is found very important during membrane casting for solvent dehydration. Meanwhile, Liu et al. (2005a, b) in the study manipulated the co-polyimide (P84) membrane morphology effect on the IPA dehydration and found higher performance (both flux and separation factor) with the higher microporous structure. However, still, consider lower compared with the PV membrane studied elsewhere. Few researchers agreed that isopropanol dehydration is much higher when used PAI due to the high hydrophilicity properties (Jiang et al. 2009; Zuo et al. 2012). However, when a hydrophilic membrane is in contact with aqueous feed solutions, extreme swelling of the membrane would occur that could decrease the mechanical strength as well as its selective behaviour and low transmembrane flux. These made this type of membrane

**Table 1** Types of membranes applied in the pervaporation system

| Polymer | IPA in the feed mixture | Feed temp (°C) | Flux (kg or $m^2$.h) | Separation factor | References |
|---|---|---|---|---|---|
| P84 | 85 wt% | 60 | 0.50 | 3800 | Liu et al. (2005a, b) |
| PVDF | 4 wt% | 45 | 7.00 | 1.4 | Shi et al. (2006) |
| Matrimid PI | 84 wt% | 80 | 6.2 | 7.9 | Jiang et al. (2008) |
| PAI with PEI | 85 wt% | 60 | 0.765 | 1944 | Jiang et al. (2009) |
| Matrimid | 85 wt% | 80 | 3.80 | 8.2 | |
| SPVA | 90 wt % | 40 | $3.51 \times 10^{-2}$ | 3452 | Rachipudi et al. (2011) |
| PAI | 85 wt % | 50 | 2.53 | 8 | Zuo et al. (2012) |
| PAN | 90 wt% | 25 | 0.186 | 1100 | Tsai et al. (2012) |
| PVA with PAN | 95 wt% | 70 | 0.27 | 1903 | Chen et al. (2013) |
| SWC5 | 90 wt% | 30 | $20.77 \times 10^8$ in unit pascal | 18 | Albo et al. (2014) |
| ESPA2 | | | $28.99 \times 10^8$ in unit pascal | 13 | |
| CPA5 | | | $9.2 \times 10^8$ in unit pascal | 40 | |

structure unfavourable especially for applications in industrial separation processes (Wang et al. 2009a; Zuo et al. 2012). Meanwhile, hydrophobic membranes may offer high durability due to membrane plasticization characterization, which, however, influences towards poor selectivity data. The membranes with high flux while generating a low selectivity or vice versa are very common in the pervaporation application. Albo et al. (2014) applied the commercial polyamide membranes, namely, seawater membrane (SWC5), energy-saving RO membrane (ESPA2) and high rejection RO membrane (CPA5), and found satisfaction results using commercial membrane comparing with the self-fabricated membranes.

PV membrane demands for a highly mechanically resistant characteristic. The microporous substrate is coated with a thin layer composite that is significantly effective to reduce the substructure opposition towards the permeant passage, which would consequently boost the transmembrane flux, as well as increases the mechanical strength (Ong and Tan 2016). Due to the technological advancement, several types of novel membranes such as composite membrane with ceramic and tri-layer porous membrane were proposed compared to the conventional single-layer porous hydrophobic membrane (Li et al. 2010). However, the material is expensive to make the membranes undesirable. Thus, for cheaper options, polymeric materials are mainly focused in this report. Somehow, some researchers combined the hydrophobic and hydrophilic characteristic into a dual layer in the polymeric membrane.

Chapman et al., agree that higher composition of hydrophobic inside the hydrophobic-hydrophilic blends in a membrane, the swelling resistant also can be

improved, thus enhance the separation factor and lower the selectivity (Chapman et al. 2008). To balance the performance of the membrane in terms of flux and selectivity, the hydrophilic-hydrophobic properties contained in a membrane must also be well-adjusted. To mitigate this problem, an asymmetric membrane is familiarized. Introduction of the hydrophobic or hydrophilic membrane is applied by numerous membrane preparation procedures. Modifying the surface of the membrane is one of the simple methods to introduce the hydrophilic membrane into hydrophobic membrane support. Different approaches such as applying a thin layer of hydrophilic polymer on a substrate, crosslinking via interfacial polymerization and surface coating techniques can be used (Chapman et al. 2008; Ong et al. 2016). This is crucial for the membrane to maintain a proper hydrophilic-hydrophobic balance as hydrophilic membranes do swell when introducing to aqueous solvents. Ideally, the hydrophilic thin layer should offer outstanding flux and selectivity, while the substrate, as a support layer, should offer mechanical stability and does not interfere with the mass transport.

## 4 Preparation of Polymeric Membranes

The PV membranes available nowadays are fabricated widely from polymeric and inorganic materials. Even so, polymers are still considered as the best materials in terms of flexibility and practicality compared with the other materials. Polymeric material is also easy to be produced with relatively low production costs (Jiang et al. 2009). Phase inversion is the main method to produce polymeric membrane.

The common membrane structure for PV is either dense or asymmetric. Dense membranes are fabricated by slow and thorough evaporation of the solvent from the membrane surfaces, leaving the pores. On the other hand, asymmetric membranes which comprise of interconnected cell structures are established by the phase inversion process. The process got the name from the solvent removal process via immersion in a non-solvent bath. Introduce very volatile liquid into the casting solution with an evaporation step before the phase inversion develops the formation of a top dense layer (Ong and Tan 2016).

Phase inversion is a crucial process to control the pore formation during the phase transformation of the polymer. There are four basic techniques employed on polymeric membrane fabrication: precipitation from the vapour phase, precipitation by controlled evaporation, thermally induced phase separation and immersion precipitation. The immersion precipitation is the most preferably employed procedure for preparing polymeric membranes among the listed.

## 5 Structured Polymer Membranes in Pervaporation

A membrane is defined as a thin film of semipermeable material that is used for solute separation when transmembrane pressure is applied across the membrane. Membranes with symmetric pore structures are more uniform, while asymmetric pore structures have inconsistent pore diameters. Besides, porous membranes are regularly used for microfiltration and ultrafiltration, as separation is based on particle size, while non-porous membranes are used for nanofiltration and reverse osmosis processes.

### *5.1 Dense Structure*

Dense membranes show no detectable pore structure, as analysed using the electron microscope. For the molecules to permeate into a dense film, the driving force, known as diffusion, is necessary. Dense membranes can be found either as an asymmetric or symmetric structure. The first type is known as homogeneous membranes, which have a similar configuration and structure throughout the cross- section. The thickness of the membrane defines the flux. The second type is the ununiformed membrane, where both thin and dense selective layers (skin) are deposited on a thicker microporous substrate. The top thin layer is created in a separate step, for example, by coating. In both cases, high flux is contributed by the thinner permselective layer. In a comparison between these two structures, asymmetric membranes could accomplish higher fluxes while preserving the selectivity of the preferred permeate compared to dense homogeneous membranes (Chapman et al. 2008).

## 6 Mechanism for Pervaporation in Polymeric Membrane

The most widely accepted model to describe permeation mechanism in polymeric membranes for the PV process is sorption-diffusion. Separation via PV can be determined by the dimension, adsorption capability and flexibility of the molecules involved in the separation process (Tuan et al. 2002). The compatibility of a polymer composite is most likely influenced by the relationship between the penetrant and the membrane. Meanwhile, a compound's ability to penetrate the membrane could be influenced by the fractional free volume (Ong et al. 2012). To obtain a high PV selectivity, both sorption and diffusion must be in favour of the particular component.

Even though the solution-diffusion model has been well received for explaining the PV process, the actual process of how the liquid turns into the vapour is still not fully understood. Nonetheless, not all PV processes can be explained by the solution-diffusion model too. The pore-flow model was recommended by Sukitpaneenit

and Chung (2011) to describe the mass transport that takes place during PV. According to this model, there are three consequent steps: first, the compounds must dissolve at the feed at one side of the membrane; the second stage is when the selected compounds diffuse through the membrane; and the third step is the desorption of the components on the other side of the membrane into vapour phase, known as permeate. The PV membrane is assumed as non-porous (dense); therefore, diffusion is the only possible transport mechanism. Solution-diffusion models most often reported are by defect-free dense, flat membranes and asymmetric membranes that consist of a thin defect-free dense-selective layer. The solubility of the component into the membrane material is considered to occur thermodynamically, while the diffusion of the penetrant across the membrane occurs kinetically.

## 7 Characteristics of Pervaporation Parameter

For the porous membrane, the pore-flow mechanism is applied. In contrast to the solution-diffusion model, this distinctive process includes three steps. First, the permeant passes across the pore; second, the liquid phase is transformed into a vapour-stage that occurs inside the pores; and, finally, the permeant in the vapour phase crosses through the pores (Sukitpaneenit and Chung 2011). The pore-flow mechanism is capable of expressing the PV process only if the membrane comprises of micropores. This is considering the mass transport mechanism of liquid and vapour in sequence.

The two main parameters that need to be considered when choosing a membrane for a particular mixture are the mass flux through the membrane, presented as J (kg $m^{-2}$ $h^{-1}$), as expressed by Eq. (1), and the membrane separation factor or selectivity, α, which can be written as Eq. (2) (Ong et al. 2012):

$$J = W / At \tag{1}$$

$$\alpha_{IPA} = \left(P_{IPA} / P_{H2O}\right) / \left(F_{IPA} / F_{H2O}\right) \tag{2}$$

$$PSI = J\left(\alpha - 1\right) \tag{3}$$

where W is the mass of the permeate (kg), A is the effective surface area of the membrane ($m^2$), t is the experiment time (h) and P and F denote the mass fraction of the species at the feed and permeate, respectively. A higher degree of separation is exhibited by a greater value of α. Super-selectiveness can be achieved as α is infinity (∞). As aforementioned, a membrane's performance relies on the flux and separation parameter. The trade-off between separation and flux can be predicted by researchers based on experimental results.

To describe a membrane's separation capability, PV separation index (PSI, kg $m^{-2}$ $h^{-1}$) is applied, which can also be described as J × α. This equation is useful for comparing similar types of membranes. On the other hand, the equation is not the

best fit to describe separation achievements in general since a membrane with a low separation factor and high flux can have a similar PSI as one with a high separation factor and low flux. Thus, specific separation requirements must be met for a distinct process as opposed to using the highest PSI for determining the best membrane choice for a process.

## 8 Modification Techniques

Polymeric membranes can be chemically modified and can be crosslinked to enhance the performance. The modification of PVDF can be achieved using various hydrophilic treatments. These approaches can be attained by surface modification and blending modification or a combination of both. The main purpose is to refine the fouling resistance of the PVDF membranes as well as better performance. The most common modification techniques are crosslinking, grafting, blending and copolymerization, as listed in Table 2. Grafting techniques by far show the most promising to enhance as well as balance the flux and selectivity of IPA separation. Sajjan et al. (2015) believed that the grafting method was able to enhance both responses due to increasing the hydrophobicity membrane which also attributed to better interaction towards water transport.

### *8.1 Crosslinking*

Crosslinking is accomplished via three methods. The first method uses the chemical reaction of a mixture to chemically couple polymers together, and the second method introduces irradiation, while the final method is known as physical crosslinking (Ong et al. 2016). The common reactive polymer chains for crosslinking are –OH, –NH2 and –COOH. The crosslink can be built by the covalent or ionic bond. The earliest and most promising results were accomplished by chemical crosslinking between GFT composite membranes with PVA as the top layer. Since then, the chemical crosslinking of numerous materials was studied, especially hydrophilic materials, such as chitosan, nylon 6 and cellulose sulphate (Shao and Huang 2007). However, polymers can be fragile because the structural strength would decrease if the crosslinking was overdone, which would be incompatible for PV application. There are two advantages from crosslinking the polymers; first, the crosslinked polymers become resistant in the aqueous feed and, second, the decent yield on one particular molecule can be obtained due to the stronger polymer chain developed by this technique (Guo et al. 2008; Ong and Tan 2016).

**Table 2** Type of modification applied by previous studies for isopropanol dehydration

| Polymer | Modifications | IPA wt% | T(°C) | IPA permeate (kg/m$^2$.h) | | Selectivity | | References |
|---|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before | After | |
| CS | Crosslinking with TDI | 60 | 30 | – | 11.11 | – | 1.24 | Devi et al. (2005) |
| | | 87.5 (azeotropic) | | | 2.27 | | 0.39 | |
| PTFE | Grafting polymerization AAm | 90 | 65 | 0.26 | 0.31 | – | – | Tu et al. (2006) |
| | Grafting polymerization NaSS | | | 0.26 | 0.31 | – | – | |
| NaAlg | Blending with 40 wt% HEC-g-AAm | 90 (azeotropic) | 30 | $2.8 \times 10^{-3}$ | 0.01 | 500 | 2000 | Rao et al. (2008) |
| | | | 30 | 0.02 | $4.36 \times 10^{-3}$ | $2.83 \times 10^{-3}$ | $5.59 \times 10^{-4}$ | |
| Matrimid | Thermal and chemical crosslinking | 84 | 80 | 6.2 | 1.8 | 7.9 | 132 | Jiang et al. (2008) |
| | Chemical crosslinking with PDA | | | 6.2 | 2.3 | 7.9 | 70 | |
| P84 with 20%13X- | Thermal crosslinking at 240 °C | 85 | 100 | 0.10 | 0.20 | 500 | 600 | Mosleh et al. (2012) |
| PVA | Blending with 25% CS | 90 | 60.18 | 0.01 | 0.02 | 0.05 | 0.07 | Liu et al. (2012) |
| CS | Grafting using 40 wt% GTMAC | 90 | | 350 | 700 | 200 | 2200 | Sajjan et al. (2015) |
| PVA | Blending with 23 wt% PVAm | 85 | 30 | 0.025 | 0.01 | 2900 | 3500 | Chaudhari et al. (2017) |

*TDI*, toluene-2,4-diisocyanate; *NaAlg*, sodium alginate; *HEC-g-AAm*, hydroxyethyl cellulose grafting with acrylamide; *PDA*, 1,3-propanediamine; *PS*, polysulfone; *NaSS*, sodium 4-styrenesulfonate; *GTMAC*, glycidyl trimethyl ammonium chloride

Zhang et al. studied several crosslinking approaches on the selective layer of PVA composites as well as produced PVA membranes that were crosslinked with glutaraldehyde for dehydration of caprolactam, where high flux and selectivity were achieved (Zhang et al. 2007a, b). Teli et al. studied PVA membranes that were crosslinked with glutaraldehyde (GA) for PV dehydration of IPA (Teli et al. 2007). The crosslinking solution typically comprises of sulphuric acid as the catalyst, sodium sulphate and various compositions of GA. The results showed that the membrane's selectivity was enhanced with increasing GA composition.

### 8.1.1 Thermal Crosslinking

Thermal crosslinking is employed for polymer bonds that consist of carboxylic substances. This technique provides detachment of the carboxylic groups from the main chain at elevated heat for the crosslinking reaction to take place using free radicals. On the other hand, the crosslinking reaction through esterification between carboxylic groups and diol substances often occurs at higher temperatures.

Several researchers have used the thermal crosslink technique on PVDF membranes. The crosslinked membranes are found to improve the permeate flux for the PV experiments. On the other hand, Hyder et al. found that thermally crosslinked membranes showed better results compared with chemically crosslinked membranes (Hyder et al. 2009).

### 8.1.2 Chemical Crosslinking

Contrary to the findings by Hyder et al., Devi et al. found that crosslinked chitosan utilized in the dehydration of isopropanol revealed higher selectivity when the membrane was thermally crosslinked compared to the membrane that was chemically crosslinked (Devi et al. 2005; Hyder et al. 2006).

## *8.2 Grafting*

Grafting is a modification technique that is used when dealing with polymer membranes, prepared by either chemical reaction or by irradiation. Oligomeric chains are the side chains that branch out of the main polymer chain. Grafting by chemical reaction happens when the molecules comprise a functional group that can react with a functional group of the polymer. Meanwhile, grafting by irradiation is a flexible technique for modifying insoluble polymer films. The grafting process is executed after chemically resistant polymer films are produced via melt extrusion. Numerous researchers have grafted films via irradiation on PVDF, PVF, PAN and PTFE as the base polymers and N-vinyl pyrrolidone, 4-vinylpyridine, vinyl acetate, acrylic acid and N-vinyl imidazole as the grafting monomers.

A non-selective silica membrane was grafted with covalently bonded polyvinyl acetate chains using the graft polymerization method (Jou et al. 1999). The results revealed that the PV of trichloroethylene and chloroform from dilute aqueous solutions was achievable even with a large substrate pore size (~500 Å), and the active separation phase was a macromolecular layer. The thin polymer layer provided the desired chemical selectivity and allowed a controlled reduction of pore size near the membrane surface, as well as being chemically and physically stable.

## *8.3 Blending*

Blending technique is used mainly for maximizing both the physical strength and stability of the membrane when facing feed solutions (Shao and Huang 2007; Wang et al. 2009b). This modification method involves a combination of two polymer solutions that are not defined by the covalent bond. Researchers often use this technique to obtain maximum hydrophilicity in the hydrophobic membranes for PV application (Ahmad and Hägg 2013). There are two types of blends, namely, the homogeneous blend, in which the two polymers are miscible on a molecular scale for all compositions, and the heterogeneous blend, where the two polymers are not perfectly miscible. One polymer territory can be observed within the matrix of another polymer. However, homogeneous blends only are considered as potential membrane materials for PV. It is greater in mechanical strength to the thin membranes compared to heterogeneous blends. In terms of stability and resistance to water, the blended membranes were better than those of pure membranes (Svang-Ariyaskul et al. 2006).

Blended chitosan and PVA membranes were fabricated to be used for PV dehydration of isopropanol in an aqueous solution. The membrane was found that the ratio of the blended membrane, with chitosan, to PVA at 3:1 performed the best, with high flux and excellent selectivity (Xu et al. 2003). Via blending, the properties of both materials can be gathered into one polymer.

## *8.4 Copolymerization*

Copolymerization is similar to the blending technique, with one significant difference. This method enhances the mechanical stability of the membrane by bonding the two polymers covalently. Grafted copolymers and block and random copolymers are commonly formed using this technique. An important characteristic in copolymerization is the degree of crystallinity. A membrane prepared from random copolymers cannot be applied in a PV system as a certain degree of crystallinity is essential for the membrane to show preferable sorption towards one of the two organic components.

## 9 Modifications Within the Membranes

As the effort to enhance the performance of the membrane, previous researchers have studied various modification techniques during membrane preparation because membrane materials are the key element in a PV process. However, a pure polymer membrane's trade-off relationship between permeability and selectivity is one of the challenges that limit the commercialization of this process, especially for chemical applications (Gu et al. 2013).

Nonetheless, mixed matrix membranes have emerged as a suitable material for use in the PV system. Inorganic fillers are fused into a polymer solution, which was found to have successfully improved the mixed matrix membrane's performance by enhancing mass transfer. Other advantages offered by these membranes include better selectivity and enhanced mechanical properties and thermal endurance. Table 3 shows the various fillers which had been incorporated into the polymer to separate organic matters such as aqueous mixture and hydrophobic inorganic fillers. The common fillers added into the polymer solution can be carbon black (CB) zeolite, carbon molecular sieve and $SiO_2$ (Hashim et al. 2011; Peng et al. 2006; Sardarabadi et al. 2016). Zeolite comprises of high Si/Al ratio (ZSM-5) and that silicate (Al-free zeolite) is intensely studied for the removal of different types of organic compounds from water (Caro and Noack 2008; Van Hoof et al. 2006). The advantages offered by this material include higher hydrophobicity, greater surface area and void volume as well as identical pore size distribution. Recently, a report from a study presents very high results with a strong mechanical structure when the blending and filler techniques were combined (Caudhari et al. 2018). Blending membrane of PVA and PVAm with the melamine-modified silicotungstic acid filler was able to stand a long period, which is suitable for the industry without compromising the separation effectiveness. Comparing with carbon black and zeolite filler, zeolite shows a better result; however, it is much more expensive, which has made these materials as the last choice, especially considering the large volume of IPA waste which needs to be recovered by the industry.

### *9.1 Carbon Black*

The incorporation of carbonaceous materials into the polymeric PV membranes has been studied for the preparation of modified PV membranes by several investigators (Panek and Konieczny 2007; Shi et al. 2006). CB was added to a PDMS membrane to investigate PV characteristics for the separation of alcohol from water mixtures (Shi and Chung 2013). The obtained data showed that the flux was significantly improved, without compromising the selectivity of the membrane in the definite scope of the composition.

Panek and Konieczny proved that adding carbon black to PDMS and PEBA membranes had influenced the total permeate flux for the PV removal of toluene

**Table 3** Different fillers incorporated into polymers for preparing pervaporation membrane

| Polymer + filler | PV operation | IPA permeate (kg or $m^2$.h) | | Selectivity | | References |
|---|---|---|---|---|---|---|
| | | Before | After | Before | After | |
| P84 + 20 wt% ZSM-5A | Temp. = 100 °C | 0.10 | 0.15 | 500 | 500 | Qiao and Chung (2005) |
| CS+ 40 wt% ZSM-5 | Conc. =90 wt% IPA | | | | | Kittur et al. (2005) |
| | Temp. = 30 °C | 478 | 1230 | 171 | 603.2 | |
| | Temp. = 40 °C | 863 | 2460 | 104.8 | 323.1 | |
| | Temp. = 50 °C | 141 | 5460 | 72.9 | 271.4 | |
| P84+ 20 wt% ZSM-13x | | 0.10 | 0.20 | 500 | 600 | |
| PDMS +4.5 wt% CB | Conc. = 13.73 wt% Ethanol Temp. = 30 °C | – | 0.18 | – | 8.9 | Shi et al. (2006) |
| PDMS+ 15 wt% CB | | 0.60 | 0.60 | 80 | 210 | |
| PEBA +15 wt% CB | Conc. =0.02 wt% Toluene Temp. = 25 °C | 0.46 | 0.75 | 2450 | 1800 | Panek and Konieczny (2007) |
| HTPB-PU + 20 wt% ZSM-5 | Conc. = 0.37 wt% IPAC Temp. =30 °C | 0.24 | 0.27 | 28 | 75 | Zhang et al. (2012) |
| P84MMMs + ZIF-90 | Conc. = 85 wt% IPA Temp. = 60 °C | 0.05 | 0.11 | 5000 | 400 | Hua et al. (2014) |
| PVDF +2 wt% CB | Conc. = 4 wt% IPA Temp. = 45 °C | 0.40 | 0.85 | 1.5 | 6.34 | Sardarabadi et al. (2016) |
| PVA+ 5 wt % NaA | Conc. = 90 wt% Temp. = 30 °C | 0.18 | 0.40 | 800 | 1900 | Malekpour et al. (2017) |
| PVA with PVAm + 8 wt% M-STA | Conc. = 80% IPA Temp. = 60 °C | 0.28 | 0.36 | 300 | 490 | Caudhari et al. (2018) |

*IPAC*, isopropyl acetone; *HTPB*, hydroxyl-terminated polybutadiene; *PU*, polyurethane urea

from toluene solutions (Panek and Konieczny 2007, 2008). Meanwhile, for the filled PEBA membranes with CB, contradicting results of permeate flux and separation factor can be observed. The flux was increased, while the separation factor was decreased. On the other hand, in the case of the filled PDMS membranes with CB, water permeation was decreased and the competence indexes of the process were enhanced (Panek and Konieczny 2008). Adding CB to the PVDF membrane had also successfully improved the flux compared with typical PV membranes (Sardarabadi et al. 2016).

### *9.2 Zeolite*

Zeolite membranes are often used for separating liquid-phase mixtures using PV, especially for dehydrating organic compounds because the membrane surfaces are uniform, do not swell and have molecular-sized pores as well as are chemically and thermally stable. These membranes are capable to separate molecules based on the differences in the molecules' adsorption and diffusion behaviours (Bowen et al. 2004). Zeolites have come in different size, shape and dispersion which have distinguished effects on the strength and stiffness of the membrane fabricated.

Kittur et al. (2005) reported the separation of water-IPA mixtures by incorporating NaY zeolite into chitosan membrane. Meanwhile, Kariduraganavar et al. (2004) studied NaY zeolite-incorporated sodium alginate subjected to PV separation of water-isopropanol mixtures. These studies were in agreement that both the permeation flux and selectivity of the membranes were increased, which corresponded to the increasing zeolite content in the membrane matrix. There were also improvements in hydrophobicity and selective adsorption. The creation of molecular sieving action was also discovered. Zeolites were added as fillers to PAN that acted as the base polymer for the dehydration of azeotropic ethanol-water mixture (Okumuş et al. 2003). Membranes with zeolite showed that flux was increased, but lower selectivity was relative to native PAN membranes. Overall, Zeolite eventually performance much better than CB in the small batch for purifies the IPA waste.

## 10 Modification of the Membrane Surface

Several techniques can be used to alter the surface of the membrane for numerous purposes, especially to enhance the performance. Solution coating, IP and post-modification technique are among the methods introduced by various researchers to modify the membrane surface (Svang-Ariyaskul et al. 2006). Table 4 shows the types of modifications performed on membrane surfaces for PV application used by previous researchers. Researchers have mentioned the surface coating by using polymers resulting in higher separation factors compared with the TFC membrane but yielding much lower flux (Liu et al. 2005a, b; Shi and Chung 2013). Depositing

**Table 4** Interfacial polymerization on membrane surfaces for isopropanol and water mixture separation

| Membrane | Coating method | PV operating condition | Flux (kg or $m^2$.h) | Selectivity | References |
|---|---|---|---|---|---|
| P84 | Silicon rubber coating | 85 wt%, 60 °C | 0.46 | 179 | Liu et al. (2005a, b) |
| mPAN | TETA-TMC | 70 wt%, 70 °C | 3.40 | 1150 | Li et al. (2008) |
| PTFE | EDA + TMC | 70 wt%, 70 °C | 1.70 | 200 | Liu et al. (2008) |
| mPAN | EDA-TMC | 90 wt%, 25 °C | 0.25 | 0.0331 | Huang et al. (2008) |
| | MPDA-TMC | | 0.18 | 0.045 | |
| | PIP-TMC | | 0.31 | – | |
| | had-TMC | | 0.36 | – | |
| mPAN | MPDA-TMC | 70 wt%, 25 °C | 1.52 | $1.29x10^{-3}$ | Kao et al. (2010) |
| | MPDASA-TMC | | 1.67 | $1.29x10^{-3}$ | |
| Torlon® polyamide-imide | MPD-TMC | 85 wt%, 50 °C | 1.37 | 53 | Zuo et al. (2012) |
| | HPEI-TMC | | 1.90 | 39 | |
| TFC α-alumina | PDMS coating | 85 wt%, 80 °C | 6.05 | 1396 | Shi and Chung (2013) |
| PEI (Ultem® 1010) | HPEI + GOTMS | 85 wt%, 50 °C | 3.10 | 467 | Zuo et al. (2013) |
| Ceramic tube | PEI coating | 85 wt%, 50 °C | 97.50 | 220 | Shi and Chung (2013) |
| | PDA coating | | 95.40 | 110 | |
| | MPD-TMC | | 3.40 | 27.8 | |
| PVDF | MPD and TMC | 85 wt%, 50 °C (EtOH) | 0.69 | 30 | Zhang et al. (2014) |
| PES | HPEI and aldehydes | 85 wt%, 50 °C | 5.01 | 38 | Hua and Chung (2015) |
| Ultem | HPEI and aldehydes | 85 wt%, 50 °C | 2.192 | 202 | |
| PEI (Ultem) | MPD-TMC | 86.7 wt%, 80 °C | 6.51 | 98 | Zuo et al. (2017) |

TFC on top of substrate is not offers simple and effective steps to modify the PV membrane but relevant at room temperature. There were also few efforts to deposit the TFC membrane on top of the hydrophobic support membrane considered the mechanical strength, however, the possibility of producing a loose TFC membrane is high as the different characteristic between these two layers (Jimenez-Solomon et al. 2013a, b). Solomon et al. (2016a, b) were utilized the hydrophobic membrane as the support membrane for thin-film composite coated by announces the post-modification techniques but necessity for extra effort as well as the cost.

## *10.1 Solution Coating*

Coating a porous membrane with a thin film is known as a solution coating technique. This method is utilized to produce composite membranes for most membrane modules. The main objective of the solution coating is to reduce the substructure resistance. Therefore, the substrate is required to be fully porous so that membrane resistance is mainly controlled by the coated selective layer. The support membrane is preferable for the pore size distribution on the top of the substrate membrane to be sharp and there should be no main defects. Pre-wetting the substrate with a low boiling point solvent or immiscible with the coating solvent must be done prior to the coating process to minimize the intrusion of the coating solution. After the solvent from the pre-wetting step has evaporated, a coated membrane is then obtained. Coating hollow fibres can be more challenging compared with coating flat sheets. The outer surface of the membrane would normally be coated with sodium hydroxide to enhance the membrane surface hydrophilicity before proceeding to interfacial polymerization (Zhang et al. 2014).

## *10.2 Interfacial Polymerization*

IP is a simple, rapid reaction and easy process for depositing an ultra-thin layer of composite, mainly polyamide, on a microporous membrane to be used for dehydration. A rapid reaction between amine (aqueous monomer) and acyl chloride (organic monomer) to coat the porous membrane would occur and form a thin active layer, known as TFC. The common amines consist of MPD, ethylene diamine (EDA), HAD, PIP and TETA; meanwhile for acyl chloride, mainly TMC was utilized. TMC is considered superior as organic solvents and applied in the most TFC membrane (Khorshidi et al. 2017; Shi and Chung 2013; Zuo et al. 2012). The monomer selection is very important to determine a good TFC membrane. The molecular structures affect the interaction between the atoms inside the molecule which contribute to the rigidness of the final TFC membrane.

The acyl chloride-based monomer is compatible in the organic phase, while the amine-based monomer is soluble in the aqueous phase. However, many studies speculated that the growth of the thin polyamide layer at the bi-solution interface begins from the water phase towards the organic phase. This technique offers the formation of a very thin, selective layer on top of the substrate, which would enhance the membrane's flux. Thus, the first important step is to have an accurate selection of monomers and parameters for the IP process. This technique can optimize the permeability, the opening size of the pore and the thickness of the membrane. When appropriate monomers are used to produce polyamide thin layers, the thermal and chemical resistance of the membrane also developed as well as extend the durability when utilized in PV applications. Zuo et al. (2013) applied the interfacial polymerization technique on TFC membranes, with MPD and HPEI (aqueous monomers), as well as TMC (organic monomer), and found that this modification had contributed to the major increase in the separation factor.

## 11 Post-Modification

Post-modification processes are sometimes necessary to increase the selectivity and stability of membranes that would be applied in PV after some modifications. Sometimes, the process is known as annealing process. Post-modification is a versatile technique that would be able to coat the imperfections on the active layer of the membranes (Zuo et al. 2013). This modification can be in the form of heat treatment or chemical treatment to ensure the enhancement of the crosslinking (Tai-Shung et al. 2003). The treatment is mainly to change the properties of the hydrophobic membrane prior introduced with the hydrophilic coating layer. Due to the different properties between the support membranes, which are mainly hydrophobic with the hydrophilic thin layers, the repulsive forces exist. This step of modification is crucial to ensure the membrane produced is not loose and the post-modification is functioned for sealing the coating layer on the top of support membrane surfaces and also for maintaining the pores for a long period especially in the storage.

A new approach has been introduced of producing, for example, a hydrophilic PVDF membrane was successfully casting by Zhang et al. (2009). The hydrophilic membranes can be generated by polymerization of a hydrophilic monomer but Mullette et al. performed the post-treatment to produce the same type of membrane by soaking PVDF hollow fibre membranes in a solution of poly(vinyl methyl ether) (Mullette et al. 2010).

Table 5 shows the post-modification methods used by previous researchers after performing membrane treatments. This step is found able to moderate the active TFC membrane, to decline the pore size as well as to eliminate the defects on the membrane surface (Jiang et al. 2009; Zuo et al. 2012). Kim et al.(2002) introduced the PAN membranes in 70–96 °C heating water subsequently immersed into room

**Table 5** Post-treatment on the polymeric membranes for isopropanol dehydration

| Type | Modifications | Conc. (wt%) | Temp. (°C) | IPA permeate (kg or $m^2$.h) | | Selectivity | | References |
|---|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before | After | |
| P84 | Post-heat treatment at 300 °C | 85 | 60 | 1.6 | 0.9 | 78.0 | 10.6 | Liu et al. (2005a, b) |
| P84 | Post-heat treatment at 100 °C | | | 21.0 | 3.4 | 65.0 | 335.0 | Qiao and Chung (2005) |
| | Post-heat treatment at 200 °C | 85 | 60 | | 0.6 | | 592.0 | |
| PAN | Heat treatment at 90 °C for 12 h | | | 0.1 | 0.2 | | | Tsai et al. (2008) |
| | Water bath post-treatment for 4 h and heat treatment at 120 °C for 12 h | 90 | 25 | | 0.2 | | | |
| PAI | Post methanol treatment | 85 | 50 | 1.3 | 2.,0 | 624.0 | 349.0 | Zuo et al. (2012) |

temperature water and then hydrolysed with sodium hydroxide and sodium methoxide. Meanwhile, Solomon et al. (2013a, b) applied the post-treatment by introducing hydrophobic membranes in the organic compound dimethylformamide after IP surface modification. This kind of treatment is to activate solvent flux which yields both flux and selectivity successfully as able to form a stable hydrophobic TFC. Post-modification also required attaching functional groups onto the surfaces to enhance the hydrophilicity in a hydrophobic porous. Post-polymerization, acrylic acid was used to increase hydrophilicity in the poly(high internal phase emulsion), which is possible to apply in the PV membrane (Luo et al. 2015).

## 12 Conclusion

Increasing research on the pervaporation membrane field to enhance isopropanol dehydration performance is becoming important for the country in terms of economic and future generation. PV system offers a great alternative for electric and electronic industries to manage the disposal cost as well as to sustain the source. As PV processes involve organic solvents at the feed, introducing modifications on the surface of the membranes is crucial, to improve the strength and to limit swelling effects. The different types of membrane modifications discussed in this chapter can improve the ability of the membrane performances as well as development in PV membranes for IPA dehydration.

**Acknowledgements** The authors would like to thank the sponsor for the financial support for this research through grants, RDU1803113 (UMP Grant).

## References


Ahmad J, Hägg MB. Development of matrimid/zeolite 4A mixed matrix membranes using low boiling point solvent. Sep Purif Technol. 2013;115:190–7. https://doi.org/10.1016/j.seppur.2013.04.049.

Ahmad SA, Lone SR. Hybrid process (pervaporation-distillation): a review. Int J Sci Eng Res. 2012;3:549–53.

Albo J, Wang J, Tsuru T. Application of interfacially polymerized polyamide composite membranes to isopropanol dehydration: effect of membrane pre-treatment and temperature. J Memb Sci. 2014;453:384–93. https://doi.org/10.1016/j.memsci.2013.11.030.

Andre A, Nagy T, Toth AJ, Haaz E, Fozer D, Tarjani JA, Mizsey P. Distillation contra pervaporation: comprehensive investigation of isobutanol-water separation. J Clean Prod. 2018;187:804–18. https://doi.org/10.1016/j.jclepro.2018.02.157.

Asaeda M, Yamasaki S. Separation of inorganic/organic gas mixtures by porous silica membranes. Sep Purif Technol. 2001;25:151–9. https://doi.org/10.1016/S1383-5866(01)00099-5.

Bowen TC, Wyss JC, Noble RD, Falconer JL. Inhibition during multicomponent diffusion through ZSM-5 zeolite. Ind Eng Chem Res. 2004;43:2598–601. https://doi.org/10.1021/ie0343216.

Caro J, Noack M. Zeolite membranes - Recent developments and progress. Microporous Mesoporous Mater. 2008;115:215–33. https://doi.org/10.1016/j.micromeso.2008.03.008.

Caudhari HS, Kwon YS, Moon MY, Shon MY, Park YI, Nam SE. Melamine-modified silicotungstic acid incorporated into the polyvinyl alcohol/polyvinyl amine blend membrane for pervaporation dehydration of water/isopropanol mixtures. Vacuum. 2018;147:115–25. https://doi.org/10.1016/j.vacuum.2017.10.024.

Chapman PD, Oliveira T, Livingston AG, Li K. Membranes for the dehydration of solvents by pervaporation. J Memb Sci. 2008;318:5–37. https://doi.org/10.1016/j.memsci.2008.02.061.

Chaudhari S, Kwon Y, Moon M, Shon M, Nam S, Park Y. Poly(vinyl alcohol) and poly(vinyl amine) blend membranes for isopropanol dehydration. J Appl Polym Sci. 2017;134:45572–80. https://doi.org/10.1002/app.45572.

Chen T, Chen T, Wu R, Huang Y. The novel of high efficiency recovery technology for dehydration of alcohol solutions by a pervaporation process. Sustain Environ Res. 2013;23:171–7.

Chen D, Werber JR, Zhao X, Elimelech M. A facile method to quantify the carboxyl group areal density in the active layer of polyamide thin-film composite membranes. J Memb Sci. 2017;534:100–8. https://doi.org/10.1016/j.memsci.2017.04.001.

Cheng K, Hsieh L, Yao K, Lin C, Chang E, Chang C. Decomposition of wastewater containing isopropyl alcohol using the gamma-ray/hydrogen peroxide process. Environ Eng Manag J. 2010;20:151–6.

Dahl I, Kjølseth C, Fjeld H, Prytz Ø, Inge P, Estournès C, Haugsrud R, Norby T. Open Archive Toulouse Archive Ouverte (OATAO). Solid State Ionics. 2010;181:268–75. https://doi.org/10.1016/j.ssi.2010.01.014.

Devi DA, Smitha B, Sridhar S, Aminabhavi TM. Pervaporation separation of isopropanol/water mixtures through crosslinked chitosan membranes. J Memb Sci. 2005;262:91. https://doi.org/10.1016/j.memsci.2005.03.051.

Feng CY, Khulbe KC, Matsuura T, Ismail AF. Recent progresses in polymeric hollow fiber membrane preparation, characterization and applications. Sep Purif Technol. 2013;111:43–71. https://doi.org/10.1016/j.seppur.2013.03.017.

Gallego-Lizon T, Edwards E, Lobiundo G, Freitas Dos Santos L. Dehydration of water/t-butanol mixtures by pervaporation: comparative study of commercially available polymeric, microporous silica and zeolite membranes. J Memb Sci. 2002;197:309–19. https://doi.org/10.1016/S0376-7388(01)00650-0.

Gu J, Zhang X, Bai Y, Yang L, Zhang C, Sun Y. ZSM-5 filled polyether block amide membranes for separating EA from aqueous solution by pervaporation. Int J Polym Sci. 2013;1–3:1. https://doi.org/10.1155/2013/760156.

Guo R, Fang X, Wu H, Jiang Z. Preparation and pervaporation performance of surface crosslinked PVA/PES composite membrane. J Memb Sci. 2008;322:32. https://doi.org/10.1016/j.memsci.2008.05.015.

Hasegawa Y, Nagase T, Kiyozumi Y, Hanaoka T, Mizukami F. Influence of acid on the permeation properties of NaA-type zeolite membranes. J Memb Sci. 2010;349:189–94. https://doi.org/10.1016/j.memsci.2009.11.052.

Hashim NA, Liu Y, Li K. Preparation of PVDF hollow fiber membranes using SiO 2 particles : the effect of acid and alkali treatment on the membrane performances. Ind Eng Chem Res. 2011;50:3035–40. https://doi.org/10.1021/ie102012v.

Hua D, Chung T-SS. Universal surface modification by aldehydes on polymeric membranes for isopropanol dehydration via pervaporation. J Memb Sci. 2015;492:197–208. https://doi.org/10.1016/j.memsci.2015.05.056.

Hua D, Ong YK, Wang Y, Yang T, Chung TS. ZIF-90/P84 mixed matrix membranes for pervaporation dehydration of isopropanol. J Memb Sci. 2014;453:155–67. https://doi.org/10.1016/j.memsci.2013.10.059.

Huang Y-P, Chang J. Biodiesel production from residual oils recovered from spent bleaching earth. Renew Energy. 2010;35:269–74.

Huang A, Yang W, Liu J. Synthesis and pervaporation properties of NaA zeolite membranes prepared with vacuum-assisted method. Sep Purif Technol. 2007;56:158–67. https://doi.org/10.1016/j.seppur.2007.01.020.

Huang SH, Hsu CJ, Liaw DJ, Hu CC, Lee KR, Lai JY. Effect of chemical structures of amines on physicochemical properties of active layers and dehydration of isopropanol through interfacially polymerized thin-film composite membranes. J Memb Sci. 2008;307:73–81. https://doi.org/10.1016/j.memsci.2007.09.014.

Hyder MN, Huang RYM, Chen P. Correlation of physicochemical characteristics with pervaporation performance of poly(vinyl alcohol) membranes. J Memb Sci. 2006;283:281. https://doi.org/10.1016/j.memsci.2006.06.045.

Hyder MN, Huang RYM, Chen P. Pervaporation dehydration of alcohol-water mixtures: optimization for permeate flux and selectivity by central composite rotatable design. J Memb Sci. 2009;326:343–53. https://doi.org/10.1016/j.memsci.2008.10.014.

Ismail AF, Padaki M, Hilal N, Matsuura T, Lau WJ. Thin film composite membrane – recent development and future potential. Desalination. 2015;356:140–8. https://doi.org/10.1016/j.desal.2014.10.042.

Jiang LY, Chung TS, Rajagopalan R. Dehydration of alcohols by pervaporation through polyimide Matrimid?? Asymmetric hollow fibers with various modifications. Chem Eng Sci. 2008;63:204. https://doi.org/10.1016/j.ces.2007.09.026.

Jiang LY, Wang Y, Chung TS, Qiao XY, Lai JY. Polyimides membranes for pervaporation and biofuels separation. Prog Polym Sci. 2009;34:1135–60. https://doi.org/10.1016/j.progpolymsci.2009.06.001.

Jimenez-Solomon MF, Gorgojo P, Munoz-Ibanez M, Livingston AG. Beneath the surface: influence of supports on thin film composite membranes by interfacial polymerization for organic solvent nanofiltration. J Memb Sci. 2013a;448:102–13. https://doi.org/10.1016/j.memsci.2013.06.030.

Jimenez-Solomon MF, Bhole Y, Livingston AG. High flux hydrophobic membranes for organic solvent nanofiltration (OSN)-interfacial polymerization, surface modification and solvent activation. J Memb Sci. 2013b;434:193–203. https://doi.org/10.1016/j.memsci.2013.01.055.

Jimenez-Solomon MF, Song Q, Jelfs KE, Munoz-Ibanez M, Livingston AG. Polymer nanofilms with enhanced microporosity by interfacial polymerization. Nat Mater. 2016a;15:1–26. https://doi.org/10.1038/nmat4638.

Jimenez-Solomon MF, Song Q, Jelfs KE, Munoz-Ibanez M, Livingston AG. Polymer nanofilms with enhanced microporosity by interfacial polymerization. Nat Mater. 2016b;15:760–7. https://doi.org/10.1038/nmat4638.

Jou JD, Yoshida W, Cohen Y. A novel ceramic-supported polymer membrane for pervaporation of dilute volatile organic compounds. J Memb Sci. 1999;162:269–84. https://doi.org/10.1016/S0376-7388(99)00154-4.

Kao S-T, Huang S-H, Liaw D-J, Chao W-C, Hu C-C, Li C-L, Wang D-M, Lee K-R, Lai J-Y. Interfacially polymerized thin-film composite polyamide membrane: positron annihilation spectroscopic study, characterization and pervaporation performance. Polym J. 2010;42:242–8. https://doi.org/10.1038/pj.2009.334.

Kariduraganavar MY, Kittur AA, Kulkarni SS, Ramesh K. Development of novel pervaporation membranes for the separation of water-isopropanol mixtures using sodium alginate and NaY zeolite. J Memb Sci. 2004;238:165–75. https://doi.org/10.1016/j.memsci.2004.03.033.

Khorshidi B, Soltannia B, Thundat T, Sadrzadeh M. Synthesis of thin film composite polyamide membranes: effect of monohydric and polyhydric alcohol additives in aqueous solution. J Memb Sci. 2017;523:336–45. https://doi.org/10.1016/j.memsci.2016.09.062.

Kim IC, Yun HG, Lee KH. Preparation of asymmetric polyacrylonitrile membrane with small pore size by phase inversion and post-treatment process. J Memb Sci. 2002;199:75–84. https://doi.org/10.1016/S0376-7388(01)00680-9.

Kittur AA, Kulkarni SS, Aralaguppi MI, Kariduraganavar MY. Preparation and characterization of novel pervaporation membranes for the separation of water-isopropanol mixtures using chitosan and NaY zeolite. J Memb Sci. 2005;247:75–86. https://doi.org/10.1016/j.memsci.2004.09.010.

Li CL, Huang SH, Liaw DJ, Lee KR, Lai JY. Interfacial polymerized thin-film composite membranes for pervaporation separation of aqueous isopropanol solution. Sep Purif Technol. 2008;62:694–701. https://doi.org/10.1016/j.seppur.2008.03.031.

Li S, Srivastava R, Parnas RS. Separation of 1-butanol by pervaporation using a novel tri-layer PDMS composite membrane. J Memb Sci. 2010;363:287–94. https://doi.org/10.1016/j.memsci.2010.07.042.

Liu R, Qiao X, Chung TS. The development of high performance P84 co-polyimide hollow fibers for pervaporation dehydration of isopropanol. Chem Eng Sci. 2005a;60:6674–86. https://doi.org/10.1016/j.ces.2005.05.066.

Liu YL, Su YH, Lee KR, Lai JY. Crosslinked organic-inorganic hybrid chitosan membranes for pervaporation dehydration of isopropanol-water mixtures with a long-term stability. J Memb Sci. 2005b;251:233–8. https://doi.org/10.1016/j.memsci.2004.12.003.

Liu YL, Yu CH, Lai JY. Poly(tetrafluoroethylene)/polyamide thin-film composite membranes via interfacial polymerization for pervaporation dehydration on an isopropanol aqueous solution. J Memb Sci. 2008;315:106–15. https://doi.org/10.1016/j.memsci.2008.02.019.

Liu G, Wei W, Jin W, Xu N, Gongping LIU, Wang WEI, Wanqin JIN, Nanping XU. Polymer/ceramic composite membranes and their application in pervaporation process. Chinese J Chem Eng. 2012;20:62–70. https://doi.org/10.1016/S1004-9541(12)60364-4.

Luo Y, Wang AN, Gao X. One-pot interfacial polymerization to prepare PolyHIPEs with functional surface. Colloid Polym Sci. 2015;293:1767–79. https://doi.org/10.1007/s00396-015-3567-y.

Malekpour A, Mostajeran B, Koohmareh GA. Pervaporation dehydration of binary and ternary mixtures of acetone, isopropanol and water using polyvinyl alcohol/zeolite membranes. Chem Eng Process Process Intensif. 2017;118:47–53. https://doi.org/10.1016/j.cep.2017.04.019.

Mosleh S, Khosravi T, Bakhtiari O, Mohammadi T. Zeolite filled polyimide membranes for dehydration of isopropanol through pervaporation process. Chem Eng Res Des. 2012;90:433–41. https://doi.org/10.1016/j.cherd.2011.07.021.

Daniel Mullette, N.S.W., (AU); Joachim Muller, New South Wales (AU); Neeta Patel, N.S.W., 2010. (12) United States Patent (10) Patent No.: Total Naof Hisofsoaking 2.

Namboodiri VV, Vane LM. High permeability membranes for the dehydration of low water content ethanol by pervaporation. J Memb Sci. 2007;306:209–15. https://doi.org/10.1016/j.memsci.2007.08.050.

Okumuş E, Gürkan T, Yilmaz L. Effect of fabrication and process parameters on the morphology and performance of a PAN-based zeolite-filled pervaporation membrane. J Memb Sci. 2003;223:23–38. https://doi.org/10.1016/S0376-7388(03)00287-4.

Ong YT, Tan SH. Pervaporation separation of a ternary azeotrope containing ethyl acetate, ethanol and water using a buckypaper supported ionic liquid membrane. Chem Eng Res Des. 2016;109:116–26. https://doi.org/10.1016/j.cherd.2015.10.051.

Ong YT, Yee KF, Cheng YK, Tan SH. A review on the use and stability of supported liquid membranes in the pervaporation process. Sep Purif Rev. 2012;43:62–88. https://doi.org/10.1080/15422119.2012.716134.

Ong YK, Shi GM, Le NL, Tang YP, Zuo J, Nunes SP, Chung T-S. Recent membrane development for pervaporation processes. Prog Polym Sci. 2016;57:1–31. https://doi.org/10.1016/j.progpolymsci.2016.02.003.

Panek D, Konieczny K. Preparation and applying the membranes with carbon black to pervaporation of toluene from the diluted aqueous solutions. Sep Purif Technol. 2007;3:507–12. https://doi.org/10.1016/j.seppur.2006.10.011.

Panek D, Konieczny K. Applying filled and unfilled polyether-block-amide membranes to separation of toluene from wastewaters by pervaporation. Desalination. 2008;222:280–5. https://doi.org/10.1016/j.desal.2007.01.172.

Peng F, Jiang Z, Hu C, Wang Y, Xu H, Liu J. Removing benzene from aqueous solution using CMS-filled PDMS pervaporation membranes. Sep Purif Technol. 2006;48:229–34. https://doi.org/10.1016/j.seppur.2005.07.029.

Qiao X, Chung TS. Fundamental characteristics of sorption, swelling, and permeation of P84 Co-polyimide membranes for pervaporation dehydration of alcohols. Ind Eng Chem Res. 2005;44:8938–43. https://doi.org/10.1021/ie050836g.

Rachipudi PS, Kariduraganavar MY, Kittur AA, Sajjan AM. Synthesis and characterization of sulfonated-poly(vinyl alcohol) membranes for the pervaporation dehydration of isopropanol. J Memb Sci. 2011;383:224–34. https://doi.org/10.1016/j.memsci.2011.08.040.

Rao KSVK, Lokesh BG, Rao PS, Rao KC. Synthesis and characterization of biopolymeric blend membranes based on sodium alginate for the pervaporation dehydration of isopropanol/water mixtures. Sep Sci Technol. 2008;43:1065–82. https://doi.org/10.1080/01496390801888045.

Rodriguez NR, Kroon MC. Isopropanol dehydration via extractive distillation using low transition temperature mixtures as entrainers. J Chem Thermodyn. 2015;85:216–21. https://doi.org/10.1016/j.jct.2015.02.003.

Sajjan AM, Premakshi HG, Kariduraganavar MY. Synthesis and characterization of GTMAC grafted chitosan membranes for the dehydration of low water content isopropanol by pervaporation. J Ind Eng Chem. 2015;25:151–61. https://doi.org/10.1016/j.jiec.2014.10.027.

Sardarabadi H, Mousavi SM, Saljoughi E. Removal of 2-propanol from water by pervaporation using poly(vinylidene fluoride) membrane filled with carbon black. Appl Surf Sci. 2016;368:277–87. https://doi.org/10.1016/j.apsusc.2016.01.227.

Seyler C, Hofstetter TB, Hungerbühler K. Life cycle inventory for thermal treatment of waste solvent from chemical industry: a multi-input allocation model. J Clean Prod. 2005;13:1211–24. https://doi.org/10.1016/j.jclepro.2005.05.009.

Shao P, Huang RYM. Polymeric membrane pervaporation. J Memb Sci. 2007;287:162–79. https://doi.org/10.1016/j.memsci.2006.10.043.

Shi GM, Chung TS. Thin film composite membranes on ceramic for pervaporation dehydration of isopropanol. J Memb Sci. 2013;448:34–43. https://doi.org/10.1016/j.memsci.2013.07.049.

Shi S, Du Z, Ye H, Zhang C, Li H. A novel carbon black/polydimethylsiloxane composite membrane with high flux for the separation of ethanol from water by pervaporation. Polym J. 2006;38:949–55. https://doi.org/10.1295/polymj.PJ2005238.

Sukitpaneenit P, Chung TS. Molecular design of the morphology and pore size of PVDF hollow fiber membranes for ethanol-water separation employing the modified pore-flow concept. J Memb Sci. 2011;374:67–82. https://doi.org/10.1016/j.memsci.2011.03.016.

Svang-Ariyaskul A, Huang RYM, Douglas PL, Pal R, Feng X, Chen P, Liu L. Blended chitosan and polyvinyl alcohol membranes for the pervaporation dehydration of isopropanol. J Memb Sci. 2006;280:815–23. https://doi.org/10.1016/j.memsci.2006.03.001.

Tai-Shung XQ, Chung, Torkkeli A. Droplet microfluidics on a planar surface. VTT Publ. 2003;52:3–194. https://doi.org/10.1002/aic.

Teli SB, Gokavi GS, Sairam M, Aminabhavi TM. Mixed matrix membranes of poly(vinyl alcohol) loaded with phosphomolybdic heteropolyacid for the pervaporation separation of water-isopropanol mixtures. Colloids Surfaces A Physicochem Eng Asp. 2007;301:55–62. https://doi.org/10.1016/j.colsurfa.2006.12.030.

Tsai HA, Ma LC, Yuan F, Lee KR, Lai JY. Investigation of post-treatment effect on morphology and pervaporation performance of PEG added PAN hollow fiber membranes. Desalination. 2008;234:232–43. https://doi.org/10.1016/j.desal.2007.09.090.

Tsai HA, Chen YL, Lee KR, Lai JY. Preparation of heat-treated PAN hollow fiber membranes for pervaporation of NMP/H 2O mixtures. Sep Purif Technol. 2012;100:97–105. https://doi.org/10.1016/j.seppur.2012.09.005.

Tu CY, Liu YL, Lee KR, Lai JY. Hydrophilic surface-grafted poly(tetrafluoroethylene) membranes using in pervaporation dehydration processes. J Memb Sci. 2006;274:47–55. https://doi.org/10.1016/j.memsci.2005.08.001.

Tuan VA, Li S, Falconer JL, Noble RD. Separating organics from water by pervaporation with isomorphously-substituted MFI zeolite membranes. J Memb Sci. 2002;196:111–23. https://doi.org/10.1016/S0376-7388(01)00590-7.

Tusel GF, Brüschke HEA. Use of pervaporation systems in the chemical industry. Desalination. 1985;53:327–38. https://doi.org/10.1016/0011-9164(85)85070-0.

Van Hoof V, Van den Abeele L, Buekenhoudt A, Dotremont C, Leysen R. Economic comparison between azeotropic distillation and different hybrid systems combining distillation with pervaporation for the dehydration of isopropanol. Sep Purif Technol. 2004;37:33–49. https://doi.org/10.1016/j.seppur.2003.08.003.

Van Hoof V, Dotremont C, Buekenhoudt A. Performance of Mitsui NaA type zeolite membranes for the dehydration of organic solvents in comparison with commercial polymeric pervaporation membranes. Sep Purif Technol. 2006;48:304–9. https://doi.org/10.1016/j.seppur.2005.06.019.

Wang Y, Goh SH, Chung TS, Na P. Polyamide-imide/polyetherimide dual-layer hollow fiber membranes for pervaporation dehydration of C1-C4 alcohols. J Memb Sci. 2009a;326:222–33. https://doi.org/10.1016/j.memsci.2008.10.005.

Wang Y, Hong Goh S, Chung T-S, Na P. Polyamide-imide/polyetherimide dual-layer hollow fiber membranes for pervaporation dehydration of C1-C4 alcohols. J Membr Sci. 2009b;326:222. https://doi.org/10.1016/j.memsci.2008.10.005.

Xu Z-K, Dai Q-W, Liu Z, Kou R-Q, Xu Y. Microporous polypropylene hollow fiber membranes Part II. Pervaporation separation of water/ethanol mixtures by the poly (acrylic acid) grafted membranes. J Memb Sci. 2003;214:71–81.

Yang C, Qian Y, Zhang L, Feng J. Solvent extraction process development and on-site trial-plant for phenol removal from industrial coal-gasification wastewater. Chem Eng J. 2006;117:179–85. https://doi.org/10.1016/j.cej.2005.12.011.

Zhang J, Liu W. Thin porous metal sheet-supported NaA zeolite membrane for water/ethanol separation. J Memb Sci. 2011;371:197–210. https://doi.org/10.1016/j.memsci.2011.01.032.

Zhang QG, Liu QL, Chen Y, Chen JH. Dehydration of isopropanol by novel poly(vinyl alcohol)-silicone hybrid membranes. Ind Eng Chem Res. 2007a;46:913–20. https://doi.org/10.1021/ie0609719.

Zhang L, Yu P, Luo Y. Dehydration of caprolactam-water mixtures through cross-linked PVA composite pervaporation membranes. J Memb Sci. 2007b;306:93–102. https://doi.org/10.1016/j.memsci.2007.08.036.

Zhang M, Nguyen QT, Ping Z. Hydrophilic modification of poly (vinylidene fluoride) microporous membrane. J Memb Sci. 2009;327:78–86. https://doi.org/10.1016/j.memsci.2008.11.020.

Zhang C, Yang L, Bai Y, Gu J, Sun Y. ZSM-5 filled polyurethaneurea membranes for pervaporation separation isopropyl acetate from aqueous solution. Sep Purif Technol. 2012;85:8–16. https://doi.org/10.1016/j.seppur.2011.07.008.

Zhang Y, Le NL, Chung TS, Wang Y. Thin-film composite membranes with modified polyvinylidene fluoride substrate for ethanol dehydration via pervaporation. Chem Eng Sci. 2014;118:173–83. https://doi.org/10.1016/j.ces.2014.07.040.

Zhou L, Wang T, Nguyen QT, Li J, Long Y, Ping Z. Cordierite-supported ZSM-5 membrane: preparation and pervaporation properties in the dehydration of water-alcohol mixture. Sep Purif Technol. 2005;44:266–70. https://doi.org/10.1016/j.seppur.2004.12.016.

Zuo J, Wang Y, Sun SP, Chung TS. Molecular design of thin film composite (TFC) hollow fiber membranes for isopropanol dehydration via pervaporation. J Memb Sci. 2012;405–406:123–33. https://doi.org/10.1016/j.memsci.2012.02.058.

Zuo J, Wang Y, Chung TS. Novel organic-inorganic thin film composite membranes with separation performance surpassing ceramic membranes for isopropanol dehydration. J Memb Sci. 2013;433:60–71. https://doi.org/10.1016/j.memsci.2013.01.002.

Zuo J, Hua D, Maricar V, Ong YK, Chung TS. Dehydration of industrial isopropanol (IPA) waste by pervaporation and vapor permeation membranes. J Appl Polym Sci. 2017;135:1–7. https://doi.org/10.1002/app.45086.

# Environmentally Benign Organic Synthesis

**Altaf Hussain and Bashir Ahmad Dar**

**Contents**



## 1 General Introduction

"Green chemistry is not just a mere catch phrase: it is the key to the survival of mankind" (Professor Ryoji Noyori, Nobel Laureate). Green chemistry has found its roots in already available thoughts and research efforts like catalysis and atom economy which led to greater attention toward problems pertaining to harmful chemical waste

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_6

and resource depletion. In Europe and the USA, a movement started to protect the environment and human health from huge chemical wastes generated from industries and toward vigorous anticipation of pollution by means of the pioneering design of production strategies themselves. This led to the development of environmentally benign chemistry called green chemistry (Woodhouse and Breyman 2005; Linthorst 2009). Green chemical methods aim to decrease the off-putting impact of the chemical industry on human health and the surroundings. Chemists do this by developing alternative ways which are environmentally friendly. The word green chemistry was first used by Anastas in 1991 (Anastas and Warner 1988). According to the International Union of Pure and Applied Chemistry, green chemistry refers to invention, design, and use of products and chemical processes to decrease or completely avoid the exercise of harmful substances as well as generation of hazardous substances (Tundo et al. 2000). The US Environmental Protection Agency (USEPA) devises a few easy rules for green/sustainable chemistry called as the green chemical principles (Dar 2019) which are as follows:

- Prevention of waste instead of remediation
- Atom economy
- Utilization of less hazardous chemicals
- Designing of safer products
- Use of inoffensive solvents
- Designing of energy-efficient processes
- Utilization of renewable raw materials
- Designing of shorter synthetic routes
- Use of catalytic reagents
- Designing of degradable products
- Analytical methodologies for pollution prevention
- Use of inherently safer processes

The US Environmental Protection Agency (USEPA) and the Organisation for Economic Co-operation and Development (OECD) identified seven research areas in green/sustainable chemistry which include:

(i) Alternative feedstock: Use of renewable and less toxic feedstock in chemical transformations.
(ii) Innocuous reagents: Use of inherently less toxic and catalytic reagents instead of stoichiometric reagents.
(iii) Employing natural processes: For efficiency and selectivity, make use of chemical transformations which are based on biosynthesis, biocatalysis, and biotechnology.
(iv) Alternative solvents: Replace the frequently used hazardous solvents (organic solvents, chlorinated solvents, etc.,) with alternative solvents that are less harmful for the.
(v) Safer chemicals: Use of molecular structure design to reduce the intrinsic toxicity of the product without affecting its efficiency.

(vi) Alternative reaction conditions: Increase the selectivity of the product by designing alternative reaction conditions, therefore dematerializing the process of separation of product.
(vii) Reducing the energy consumption**:** Design such processes which decrease the energy consumption (mechanical or thermal energy).

Organic reactions are the most widely used reactions in industry (pharmaceutical, polymer, R&D, etc.), and the usage as well as generation of materials toxic to human health and environment is a common practice. It is only after the 1990s that scientists realized that enough is enough and chemists must focus on the alternative ways of reactions which are environmentally benign and least hazardous to human health. Therefore, a new version of chemical transformations emerged—*environmentally benign organic synthesis or green organic chemistry or green synthesis.*

Any ordinary organic synthesis can be made environmentally benign synthesis by following any one or more of the USEPA's 12 principles. In this endeavor, many organic chemists made several breakthroughs and replaced the environment enemy organic reactions with environmentally friendly organic reactions. The 2005 Nobel Prize for Chemistry was given to Y. Chauvin, R. H. Grubbs, and R. R. Schrock, for developing the metathesis technique in synthetic organic chemistry, with special contribution to green chemistry. A review in the same year identified three important developments in environmentally benign organic synthesis: (i) employment of supercritical $CO_2$ as a green solvent, (ii) aq. $H_2O_2$ for green oxidation reactions, and (iii) utilization of $H_2$ in chiral synthetic routes (Noyori 2005). Other green endeavors include supercritical $H_2O$ oxidation and dry media reactions. Green chemistry goals could also be possibly achieved via bioengineering technique. For example, important chemical transformations could be achieved by engineered organisms (shikimate, a precursor of Tamiflu fermented by Roche in bacteria). Click chemistry is also one the environmentally benign organic synthetic strategies which sits in compliance with the targets of green chemistry.

One of the most common environmentally benign syntheses/green organic syntheses is to stop using harmful or volatile solvents. In pharmaceutical industry, synthesis of drugs involves large volumes of harmful volatile solvents. So replacing greener solvents is one of the major centers of attention of many environmentally benign organic synthesis strategies. Continuous efforts are being made to identify green solvents which are required in lesser amounts and are not toxic to the environment or humans (Prat et al. 2013; Sherman et al. 1998). It's not only the solvents that must be removed from ordinary organic synthesis, but also there are several other chemical species used in organic synthesis that can be detrimental to the environment. Thus, the replacement of harmful catalysts with nature's catalysts is just another way of making the ordinary organic synthesis an environmentally benign process, for example, pregabalin, a drug for pain due to damaged nerve and epileptic seizures. Environmentally benign synthesis of this drug used a natural catalyst lipase and water as a green solvent, thereby removing the environmentally harmful solvents and metal catalysts (Shenghui et al. 2009). Additionally, this process reduced the production of $CO_2$ as by-product by three million tons.

Another environmentally benign synthetic strategy involves getting rid of dangerous heavy metals. For example, synthesis of drug sildenafil citrate (Viagra™ and Revatio™) used tin chloride catalyst and a volatile chlorinated solvent (both harmful to the environment). Chemists made its synthesis environmentally benign by using catalytic hydrogenation instead of tin catalysis with water as a by-product. After many efforts, chemists went even further and designed a totally new green synthetic process, for the manufacture of sildenafil citrate, which is estimated to have reduced several thousand tons of waste until 2013 (Dunn et al. 2004).

Likewise, chemists around the world are now in search of environmentally benign organic synthetic processes which could possibly replace the already reported strategies which are harmful to the environment as well as humans. This chapter shall focus on the important aspects of environmentally benign organic synthesis. Five main aspects of organic synthesis which could be focused to make the organic synthesis environmentally benign are the solvent or the medium under which the reaction is being carried out, the reagent system which brings about the chemical change, type of reaction (multicomponent reactions), solid-phase synthesis, and the catalytic system which plays a significant part in an organic reaction in several ways. On this basis, the present chapter shall be studied under the following sections:

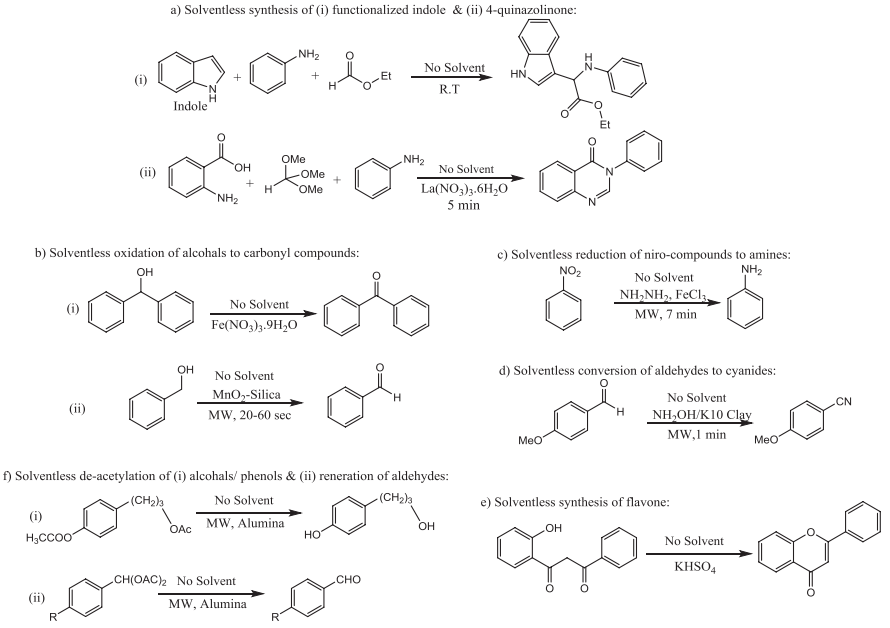
## 2 Environmentally Benign Organic Synthesis Through Greener Solvents

The solvents which do not pollute the environment or are not hazardous to humans should be chosen for chemical transformations. As the chlorinated solvents are volatile and toxic and are responsible for the depletion of ozone layer, hence they should be avoided. Therefore, organic chemists are working on organic transformations that make use of alternative solvents or green solvents, which are generally obtained from renewable resources, are harmless, biodegradable, and occur in nature (Prat et al. 2013; Sherman et al. 1998).

Four principal approaches to avoid traditional hazardous organic solvents have been identified over a period of time: (i) solventless reactions, (ii) water as green solvent, (iii) supercritical fluids, and (iv) ionic liquids (Seddon 1996, 1997).

### *2.1 Solventless Reactions*

Petrochemical industry has found the best way of avoiding volatile organic solvents, i.e., solventless reactions (Ertl et al. 1997), and is now considered as the greenest chemical sector (Sheldon 1994). Solventless organic synthesis has led to "grinding chemistry" which involves the mixing or grinding of reagents and substrates without

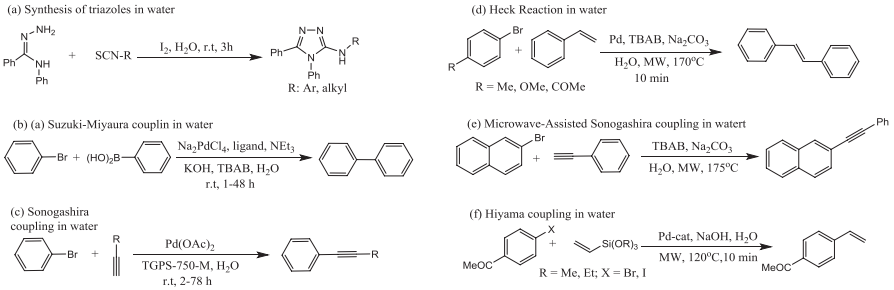



**Scheme 1** Environmentally benign organic synthesis under solventless conditions (first approach)

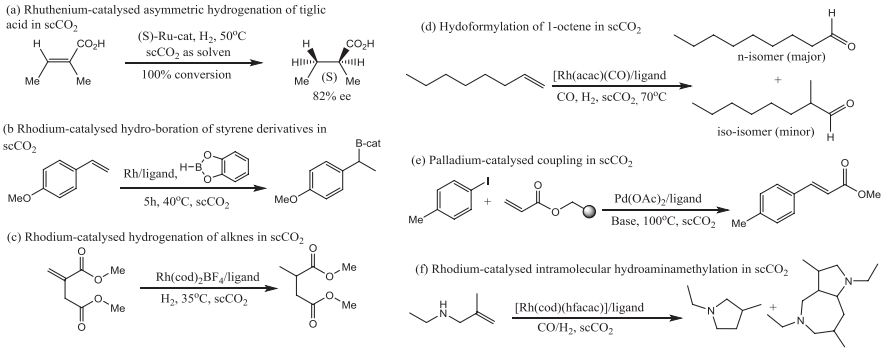
any solvent. For example, a three-component Friedel–Crafts reaction of indoles produced the functionalized indoles (Zhao et al. 2006). Furthermore, synthesis of 4-quinazolinone has also been achieved by a solventless approach (Narashimulu et al. 2006). A review has appeared in recent literature on grinding chemistry (Geng et al. 2005). The expanding area of solventless green approach involves the use of microwaves to irradiate reaction mixture containing neat reagents such as synthesis of 4,4′-diaminotriphenylmethanes using microwave irradiation (Guzman-Lucero et al. 2005). Some of the reported organic syntheses or conversions using the first approach, i.e., under solventless conditions, are outlined in Scheme 1 (Varma et al. 1993a, b, 1997; Namboodiri et al. 2007; Varma and Dahiya 1998; Vass et al. 2001; Varma and Naicker 1998).

## *2.2 Water as Solvent*

The second approach involves water as the green solvent as it is nonhazardous. In spite of its compatibility issues, many important synthetic routes have been designed by using water as solvent (Kolb et al. 2001). One such reaction is the Diels–Alder reaction which has been carried out in water, and it has been found that the reaction occurs even faster in water as compared to conventional solvents. Thus, the need of the hour is that organic chemists should focus on developing new synthetic strategies




**Scheme 2** Environmentally benign organic synthesis in water (second approach)




**Scheme 3** Environmentally benign organic synthesis in $scCO_2$ (third approach)

which can employ water or other aqueous media as solvent. Some of the examples of environmentally benign synthesis using water as solvent are depicted in Scheme 2 (Jatangi et al. 2018; Chen et al. 2018; Handa et al. 2018; Arvela et al. 2007; Appukkuttan et al. 2003; Alcida and Najera 2006).

## *2.3 Supercritical $CO_2$ ($scCO_2$) as Solvent*

The third approach for greener solvents includes the use of supercritical fluids (SCFs) like supercritical $CO_2$ ($scCO_2$) in organic syntheses (Poliakoff et al. 2002). These can be employed for avoiding the use of harmful organic solvents in a lot of synthetic methods. SCFs have numerous extraordinary qualities like excellent salvation power, excellent diffusivity, and zero surface tension. $ScCO_2$ is nonflammable, nontoxic, and cheap and possesses easily obtainable critical point. Efficient use of $scCO_2$ as greener solvent has gained a great deal attraction from last few years (Poliakoff and Licence 2007; Eckert et al. 1996). Several important organic syntheses using $scCO_2$ as green solvent are outlined in Scheme 3 (Wittmann et al. 2001; Estorach et al. 2008; Lyubimov et al. 2007; Xiao et al. 1996).

### *2.4 Ionic Liquids as Solvent*

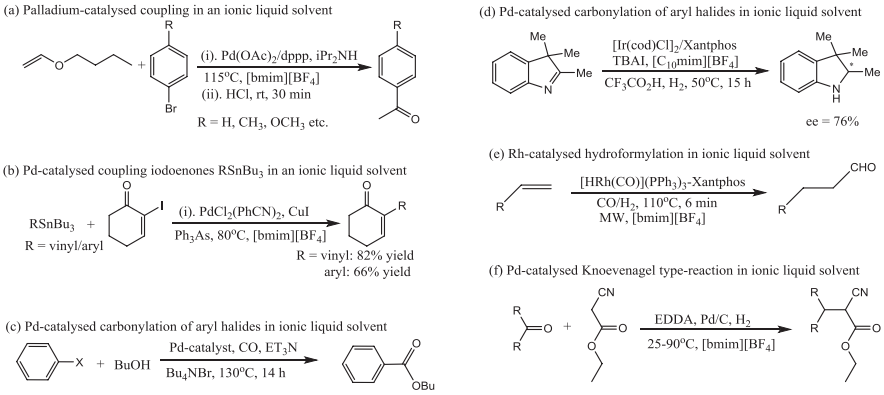
The fourth approach involves the use of ionic liquids also designated as "designer solvents" (Freemantle 1998) are neoteric solvents like SCFs), non-volatile and establish a nonaqueous media of a wide range of polarity inside the reaction system. It is also possible to develop techniques in which the catalyst remains in ionic liquids and reaction products are recovered by distillation or extraction; therefore, catalyst and solvent could be reused. Many organic and other substances are soluble in ionic liquids; therefore, it is feasible to tune the solubility of the substances in organic and aqueous solvents by varying the side chain length or the nature of the cation or anion of ionic liquid. These solvents appear as very interesting and newer reaction media toward environmentally benign organic synthesis. Ionic liquids as green solvents have been successfully applied to many organic reactions such as hydrogenation (Anderson et al. 2002), polymerization (Hardacre et al. 2002), Heck catalysis (Carmichael et al. 1999), Friedel–Crafts (Seddon et al. 2003), Diels–Alder (Earle et al. 1999), cracking (Adams et al. 2000), oxidation (Seddon and Stark 2002), and enzyme catalysis (Van Rantwijk et al. 2003; Cull et al. 2000), and it has been observed that the use of ionic liquids in organic synthesis is the cleanest recyclable protocol for Heck coupling (Beletskaya and Cheprakov 2000).

Detailed discussions on ionic liquids are available elsewhere (Wasserscheid and Welton 2003); the following features of ionic liquids make them useful as green solvents (highlighted by Tundo et al. 2007): (i) liquid range of −96 to 200 °C, (ii) good solvents for organic as well as inorganic substances, (iii) super-acidic, (iv) air stable and hydro-phobic in nature, (v) thermally stable (up to 200 °C), (vi) no measurable vapor pressure at room temperature, (vii) mostly nonflammable, (viii) high salvation properties and hence low volumes used, (ix) sometimes act as catalysts as well as solvents, and (x) highly selective reactions.

The nonflammability of these solvents is an added advantage as the solvents which do not burn are safer in industrial processes than conventional solvents. Some important examples of environmentally benign synthesis in ionic liquid media are shown in Scheme 4 (Mo and Xiao 2006; Handy and Zhang 2001; Calo et al. 2002; Giernoth and Krumm 2004; Petricci et al. 2006; Baidossi et al. 2005).

## 3 Environmentally Benign Organic Synthesis Using Greener Reagents

One of the most basic aspects of environmentally benign organic syntheses that a green reaction must accomplish is to eliminate the use of toxic and dangerous chemicals by replacing the conventional reagents or substrates with greener reagents or substrates. The main focus of this section shall be to highlight the plethora of greener reagents or substrates which have replaced the use of harmful and undesirable compounds (common in conventional organic synthesis). Over the last several decades,



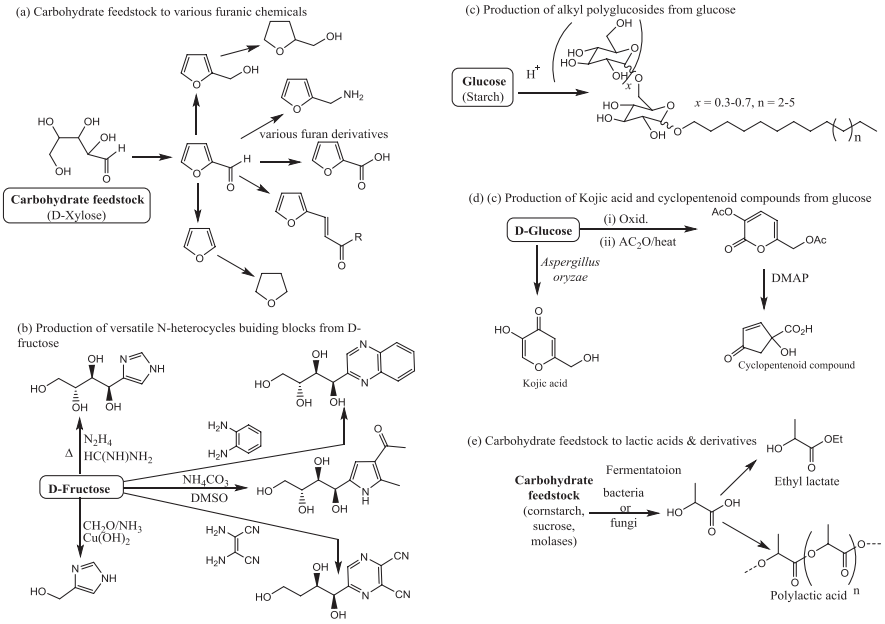

**Scheme 4** Environmentally benign organic synthesis in $scCO_2$ (third approach)

many new approaches have been developed that are based on conventional organic transformations. The use of greener reagents or substrates is often coupled with other green features such as the use of more environmentally friendly solvents (already discussed in previous section).

## *3.1 Carbohydrates as Renewable Chemical Feedstock: A Green Alternative*

Currently, the major chemical feedstock/reagents/substrates for organic syntheses come from nonrenewable fossil fuel (petroleum) which is being depleted rapidly for energy needs and for chemical industry. But the Mother Nature bestowed us with a huge amount of renewable feedstock in the form of carbohydrates which could be exploited as green reagents.

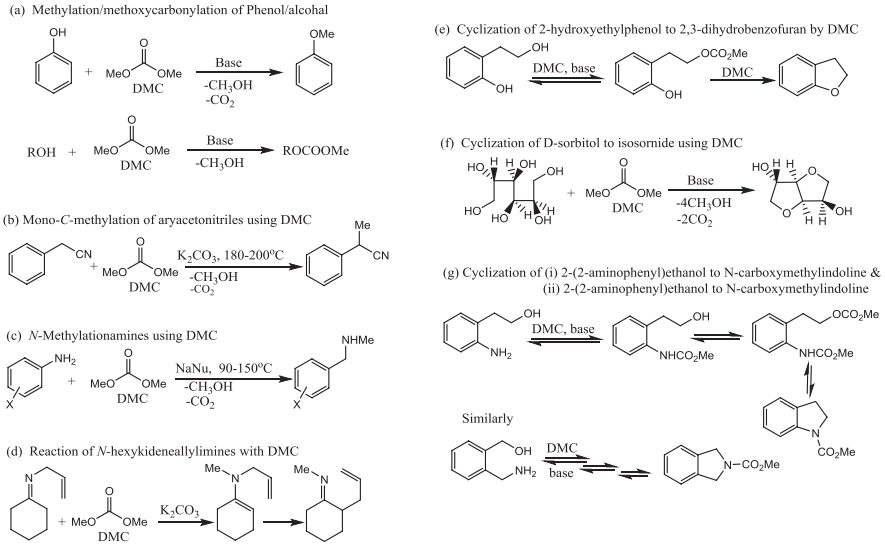
The use of carbohydrates as chemical feedstock has added advantage of being a prospective spring of carbon and a sink for $CO_2$ in the course of photosynthesis so that consequence of their use on climate change can be regarded as neutral. The constituent repeating units of carbohydrates (e.g., glucose, fructose, xylose, or their disaccharides like sucrose) are less expensive and easily available in large amounts and are thus more suitable raw materials than polysaccharides for organic synthesis or industrial applications. Presently, the use of carbohydrates as intermediate scaffolds, bulk chemicals, or fine chemicals for chemical industry is very low in spite of ready availability at low cost and enormous potential. Brief outlines of some of their important illustrations presently recognized on an industrial level are depicted in Scheme 5 (McKillip et al. 2007; Gandini and Belgacem 1997; Klingler 2007; Tajima 1987; Ritter 2002).




**Scheme 5** Carbohydrates as renewable feedstock for environmentally benign organic synthesis

## *3.2 Dimethyl Carbonate as Green Reagent*

Due to its wide use as reagent and as solvent and its nontoxicity for human health and the environment, dimethyl carbonates (DMCs) have achieved increasing significance as green reagents or solvents with diverse uses in laboratory-scale reactions as well as in chemical industry (Wang et al. 2007). To concentrate on the area of replacement of hazardous and unwanted reagents with greener reagents, an interesting example is given by dimethyl carbonate (DMC) which is a potential nontoxic green alternative reagent (Tundo and Selva 2002). It has replaced conventional methylating agents like dimethyl sulfate (DMS) or methyl halide ($CH_3X$) as well as methoxy-carbonylating agent like phosgene ($COCl_2$), and many other green methods have also been reported for DMC-mediated transformations (Barcelo et al. 1990; Shieh et al. 2001). Thus, organic chemists found a green alternative in DMC in place of toxic- and waste-producing reagents (DMS, $CH_3X$, & $COCl_2$). The properties of DMC that make it a green reagent are as follows: (i) Nontoxic compound (ii) can be handled safely with no extra care that is required for $CH_3X$, DMS, and $COCl_2$ and (iii) possesses tunable reactivity depending on the conditions, e.g., under different temperature conditions, DMC can react with a nucleophile as a methylating agent or methoxy-carbonylating agent (Ouk et al. 2002). Some of the important organic transformations using DMC as green reagents are summarized in Scheme 6 (Mikolajczyk et al. 1975; Selva et al. 2003; Tundo et al. 2005; Arico et al. 2012).

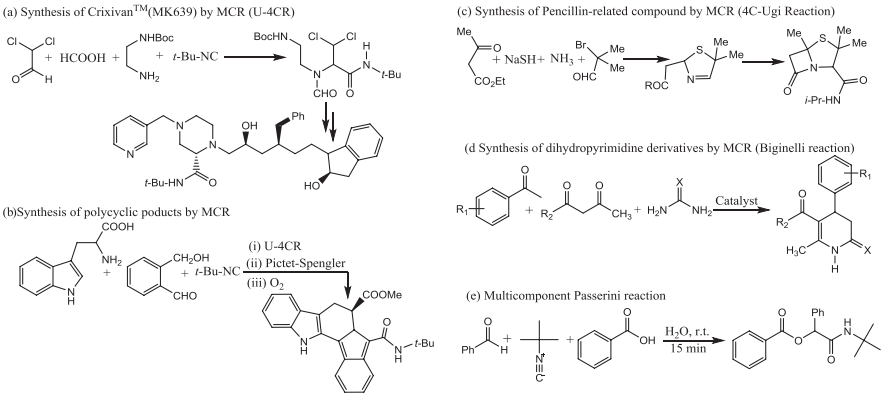



**Scheme 6** Environmentally benign organic syntheses using DMC as green reagent

## 4 Environmentally Benign Synthesis Through Multicomponent Reactions (MCRs)

Conventional organic syntheses of molecules from three or more components would be achieved by a number of preparative steps, and its intermediate products have to be isolated and purified subsequent to every reaction step. Consequently, the number of reaction steps increases, quantity of solvents employed is larger, preparative steps increase, product quantities reduce, and the solvents as well as the by-products of each step must be removed. Therefore, rarely the aspects of green chemistry can be achieved, and hence MCRs provide an alternative strategy to make synthesis of such products (which require a large number of steps) greener and environmentally benign. Multicomponent reactions (MCRs) involve three or more components that react directly to produce important chemicals. The importance of MCRs for green organic synthesis stems from the following features: good atom economy (Zhu and Bienaymé 2005; Pandey et al. 2005; Ugi et al. 2003; Kappe 2000), more sustainability, an easy purification method, minimum number of steps, saves solvents/time, and additional resources. These features are in accordance with several of principles of green chemistry (Anastas and Warner 1998):

(i) Prevention: The formation of side products is minimum.
(ii) Atom economic process: The method is designed to incorporate maximum of the atoms of reactants into the desired product.
(iii) Safer solvents or minimization of solvent use: No need for purification of intermediate products and avoid the production of wastes; therefore, a bulk amount of solvents required for purifications in multistep synthesis could be avoided.




**Scheme 7** Environmentally benign organic syntheses using DMC as green reagent

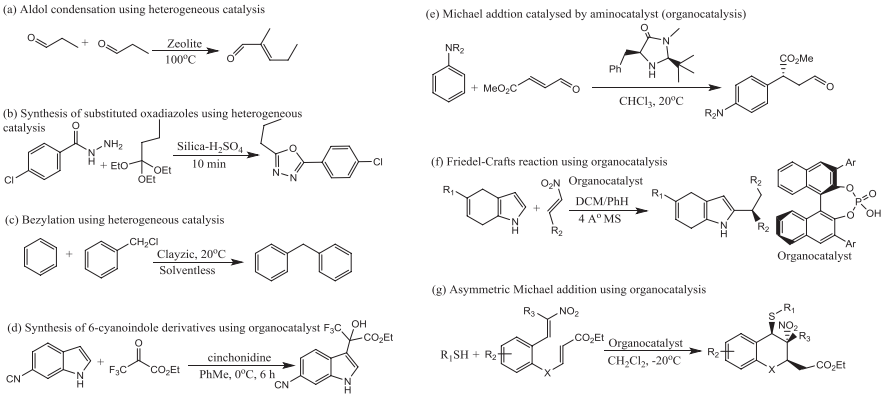
(iv) Reduce derivatization: No need of protection-deprotection, blocking groups, and temporary modification of processes.

MCRs are useful for producing functionalized small molecules from easily accessible substrates in one step with potential for generating molecular diversity and complexity along with minimization of cost, labor, time, and waste products. MCRs such as Ugi, Passerini, and Biginelli reactions are well exploited for the synthesis of medicinally and pharmaceutically important molecules that has been achieved through MCRs (Scheme 7), (Rossen et al. 1998; Do¨mling et al. 1999; Ugi et al. 1962; Dar et al. 2013; Sharma et al. 2007).

## 5 Environmentally Benign Organic Synthesis by Using Green Catalysts

A catalyst must fulfill the following criteria to be designated as a green catalyst: (i) must have better activity than the existing catalysts, (ii) minimization of waste produced during catalytic cycle, (iii) reduced waste production even during the preparation of catalyst itself, (iv) recyclability of the catalyst, (v) ease of isolation of final products, and (vi) nontoxic or least toxic.

One of the most useful aspects to achieve greener methods is to replace ordinary catalysts with heterogeneous catalysts as the latter are more active, less toxic, safer, recyclable, selective, easy to handle, and less reactive to the environment. The substances like zeolites, silica, alumina, clays, etc., may either directly act as heterogeneous catalysts or act as a solid support for actual catalytic species. A fine example of application of zeolites as heterogeneous catalyst is solventless aldol reaction (Scheme 8a) (Dabiri et al. 2010), while that of supported heterogeneous catalysts is silica-supported sulfonic acids which produce oxadiazoles from acyl hydrazides and ortho esters (Scheme 8b) (Clark and Macquarrie 2002). Envirocats™ are clay- and



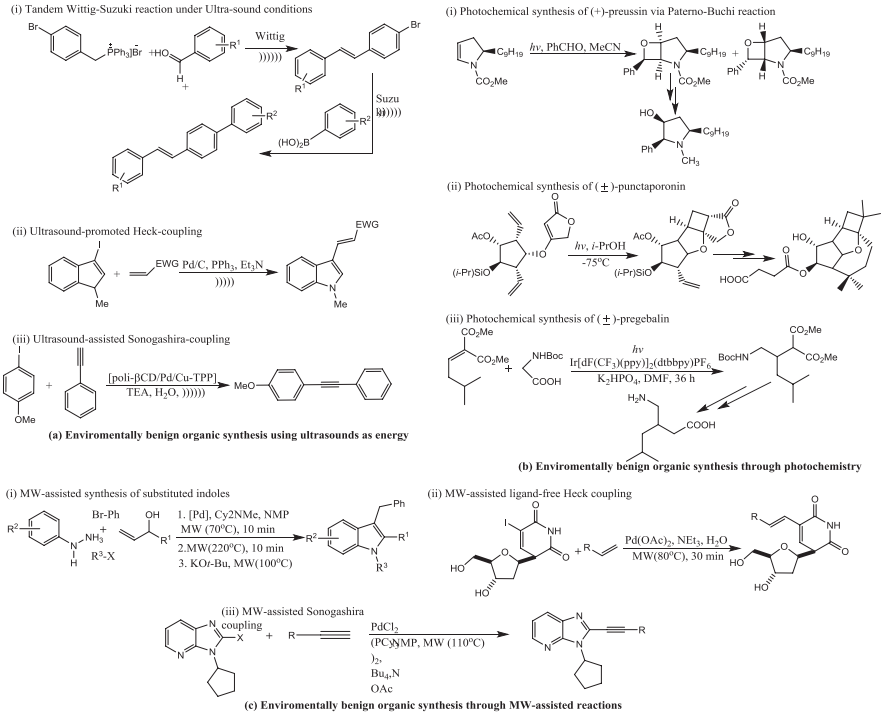

**Scheme 8** Environmentally benign organic syntheses using heterogeneous catalysis and organocatalysis

alumina-based heterogeneous catalysts which have wide applications in the synthesis of useful organic moieties, e.g., benzylation of benzene and benzyl chloride with clayzic produces diphenylmethane, a precursor to many pharmaceuticals (Scheme 8c) (List 2007).

Another important aspect of green catalysis is organocatalysis which is catalysis with small organic molecules. These catalysts are advantageous over the conventional metal catalysts because of their insensitivity to oxygen and moisture and availability as single enantiomers; metal-free catalysis, derived from natural sources, hence, is nontoxic and environmentally friendly. Organocatalysis is being well exploited for the preparation of pharmaceutically active compounds and total synthesis of natural products. Amino acids like L-proline and derivatives, diaminocyclohexane-derived thioureas, and cinchona alkaloid derivatives are some of the examples of organocatalysts. Organocatalysts are extremely helpful and eliminate the steps such as isolation and purification of intermediates; therefore, this approach may represent a key advancement toward sustainable synthesis of medicinally important molecules, drugs, and other biologically significant compounds (Sumiyoshi et al. 2011). Exploitation of organocatalysis for organic synthesis is well documented in the literature, and a few examples are depicted in Scheme 8 (Zhu et al. 2008; Enders et al. 2010; Loh et al. 2014; Suslick 1990).

## 6 Environmentally Benign Organic Synthesis by Using Alternative Energy Source

The chemical strategies which use alternative source of energy in agreement with the green chemistry principles are divided into three main categories: (i) sonochemistry (reactions using ultrasound as energy of source), (ii) photochemistry (reactions




**Scheme 9** Environmentally benign organic synthesis by using alternative energy source

using UV, VIS, and IR radiations as source of energy), and (iii) microwave (MW)-assisted reactions (reactions using MW radiations as energy source).

The reactions in which the ultrasound is used as a source of energy are termed as sonochemical reactions, and the science of using ultrasonic irradiation to uphold chemical transformations is termed as sonochemistry. The ultrasonic irradiation generates the energy required in an organic reaction through cavitations which provokes exceptionally elevated local temperatures and pressures. Ultrasound-promoted organic transformations are environmentally benign methods which can facilitate the minimization of quantities of unwanted harmful chemicals and solvents, decrease energy utilization, and augment the selectivity of the desired product. Ultrasonic irradiation has proved its potential to hasten the speed of an array of organic chemical transformations (Cravotto and Cintas 2006; Fillion and Luche 1998; Chaudhary and Bedekar 2012). Some of the important applications of sonochemistry for green organic synthesis such as tandem Wittig–Suzuki (Tzschucke et al. 2002) are shown in Scheme 9a.

Those chemical transformations which occur in the presence of UV or visible or IR radiations are studied under photochemistry and are regarded as one among the key approaches to green organic chemical transformations (Ugi et al. 1994) and complex strategies (Bach et al. 2000; Fleck and Bach 2008). Photochemical

reactions correspond to the principles of green chemistry due to very mild reaction conditions under which such reactions are carried and photon is either captured in the reaction or escapes out, thereby leaving no residue behind (no waste). However, these reactions are least exploited in laboratory scale as well as in industrial level. Photochemical reactions are well exploited for the synthesis of medicinally important scaffolds such as (±)-Preussin (Fleck and Bach 2008), (±)-punctaporonin (Chu et al. 2014), and (±)-pregabalin (Lidstrom et al. 2001; Roberts and Strauss 2005), as depicted in Scheme 9b.

The microwave energy (MW) has been well exploited in many fields of chemistry as alternative green source of energy in organic synthesis (Kappe 2004). The salient features of MW-assisted reactions are reduced time, high yield, and high product purities when compared to conventional synthesis. Microwave radiations transfer energy by dielectric heating which depends on the capacity of the reaction mixture to absorb microwaves (Lew et al. 2002). The direct interaction between microwaves and ionic molecules leads to very fast energy transfer (less than a nanosecond), thereby increasing the temperature of reaction mixture rapidly (Dallinger and Kappe 2007). It has been reported that MW heating leads to the development of uncontaminated products in very less time. Owing to the aforementioned rationale, the utilization of microwave energy for the preparation of small organic moieties plus assembly of complex molecules has engrossed a huge interest in past few years. The MW-assisted organic synthesis is very crucial from the economic point of view, environment friendliness, and sustainability (Zhang 2006). Some of the applications of MW-assisted environmentally benign organic synthesis of substituted indoles (Hope et al. 2004), Heck coupling, and Sonogashira coupling (Wang et al. 2010) are shown in Scheme 9c.

## 7 Conclusion

In contrast to the conventional organic synthesis, environmentally benign organic synthesis plays an important role in saving our globe from a big threat. Being an important tool of green chemistry, these synthetic routs have a foundation in ethics which serves environmental, economic, and social goals. This tool of green chemistry addresses the challenge like environmental sustainability by offering a broad and comprehensive research choice, thus permitting the discovery of synthetic methodologies that can minimize the by-products and waste and maximize the desired products. Environmentally benign organic synthesis plays a pivotal role in green chemistry and makes maximum use of the green chemistry principles. This application of these principles led to the discovery of many unconventional methods of organic synthesis which are more time saving, economic, and more efficient, wherewith established cost and performance standards will be the continual endeavor for economies for the chemical industry.

## References


Adams CJ, Earle MJ, Seddon KR. Catalytic cracking reactions of polyethylene to light alkanes. Green Chem. 2000;2(1):21–4. https://doi.org/10.1039/A908167D.

Alcida E, Najera C. The first fluoride-free Hiyama reaction of vinylsiloxanes promoted by sodium hydroxide in water. Adv Synth Catal. 2006;348:2085–91. https://doi.org/10.1002/adsc.200600262.

Anastas PT, Warner J. Green chemistry: theory and practice. Oxford: Oxford University Press; 1988.

Anastas PT, Warner JC. Green chemistry: theory and practice. New York: Oxford University Press; 1998.

Anderson K, Goodrich P, Hardacre C, McCath SEJ. Hydrogenation processes performed in ionic liquids, World Patent, WO 02, 094740. 2002.

Appukkuttan P, Dehaen W, der Eycken EV. Transition-metal-free Sonogashira-type coupling reactions in water. Eur J Org Chem. 2003;2003:4713–6. https://doi.org/10.1002/ejoc.200300587.

Arico F, Toniolo U, Tundo P. 5-membered *N*-heterocyclic compounds by dimethyl carbonate chemistry. Green Chem. 2012;14:58–61. https://doi.org/10.1039/C1GC15698E.

Arvela RK, Pasquini S, Larhed M. Highly regioselective internal Heck arylation of hydroxyalkyl vinyl ethers by aryl halides in neat water. J Organomet Chem. 2007;72:6390–6. https://doi.org/10.1021/jo0705768.

Bach T, Brummerhop H, Harms K. The synthesis of (+)-preussin and related pyrrolidinols by diastereoselective patern'o-B¨uchi reactions of chiral 2-substituted 2,3-dihydropyrroles. Chem Eur J. 2000;6:3838–48. https://doi.org/10.1002/1521-3765(20001016)6:20.

Baidossi M, Joshi AV, Mukhopadhyay S, Sasson Y. Tandem catalytic condensation and hydrogenation processes in ionic liquids. Tetrahedron Lett. 2005;46:1885–7. https://doi.org/10.1016/j.tetlet.2005.01.092.

Barcelo G, Grenouillat D, Senet JP, Sennyey G. Pentaalkylguanidines as etherification and esterification catalysts. Tetrahedron. 1990;46:1839–48. https://doi.org/10.1016/S0040-4020(01)89753-2.

Beletskaya IP, Cheprakov AV. The Heck reaction as a sharpening stone of palladium catalysis. Chem Rev. 2000;100:3009–66. https://doi.org/10.1021/cr9903048.

Calo V, Giannoccaro P, Nacci A, Monopoli AJ. Pd–benzothiazole carbene catalysed carbonylation of aryl halides in ionic liquids. Organomet Chem. 2002;645:152–7. https://doi.org/10.1016/S0022-328X(01)01401-2.

Carmichael AJ, Earle MJ, Holbrey JD, McCormac PB, Seddon KR. The Heck reaction in ionic liquids: a multiphasic catalyst system. Org Lett. 1999;1:997–1000. https://doi.org/10.1021/ol9907771.

Chaudhary AR, Bedekar AV. 1-(α-Aminobenzyl)-2-naphthol as phosphine-free ligand for Pd-catalyzed Suzuki and one-pot Wittig-Suzuki reaction. Appl Organomet Chem. 2012;26:430–7. https://doi.org/10.1002/aoc.2877.

Chen W, Lu XY, Hua B, Yu WG, Zhou ZN, Hu Y. The rational design and synthesis of water-soluble thiourea ligands for recoverable Pd-catalyzed aerobic aqueous Suzuki–Miyaura reactions at room temperature. Synthesis. 2018;50:1499–510. https://doi.org/10.1055/s-0036-1589150.

Chu L, Ohta C, Zuo Z, MacMillan DWC. Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of (±)-pregabalin. J Am Chem Soc. 2014;136:10886–9. https://doi.org/10.1021/ja505964r.

Clark JH, Macquarrie DJ. Chapter 13: green catalysts for industry. In: Handbook of green chemistry and technology. Oxford: Blackwell Science Ltd; 2002.

Cravotto G, Cintas P. Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications. Chem Soc Rev. 2006;35:180–96. https://doi.org/10.1039/B503848K.

Cull SG, Holbrey JD, Vargas-Mora V, Seddon KR, Lye GJ. Room-temperature ionic liquids as replacements for organic solvents in multiphase bioprocess operations. Biotechnol Bioeng. 2000;69(2):227–33. https://doi.org/10.1002/(SICI)1097-0290(20000720)69:2.

Dabiri M, Salehi P, Baghbanzadeh M, Zolfigol MA, Bahramnejad M. Silica sulfuric acid: an efficient and versatile acidic catalyst for the rapid and ecofriendly synthesis of 1,3,4-oxadiazoles at ambient temperature. Synth Commun. 2010;37:1201–9. https://doi.org/10.1080/00397910701199151.

Dallinger D, Kappe CO. Microwave-assisted synthesis in water as solvent. Chem Rev. 2007;107:2563–91. https://doi.org/10.1021/cr0509410.

Dar BA. Fundamentals of green chemistry. Denmark: Bookboon; 2019.

Dar BA, Patidar P, Kumar S, Wagay MA, Sahoo AK, Sharma PR, Pandey S, Sharma M, Singh B. Fe–Al/clay as an efficient heterogeneous catalyst for solvent-free synthesis of 3, 4-dihydropyrimidones. J Chem Sci. 2013;125:545–53.

Do¨mling A, Chi K, Berrere M. A novel method to highly versatile monomeric PNA building blocks by multi component reactions. Bioorg Med Chem Lett. 1999;9:2871–4. https://doi.org/10.1016/S0960-894X(99)00491-6.

Dunn PJ, Galvin S, Hettenbach K. The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by green chemistry metrics. Green Chem. 2004;6:43–8. https://doi.org/10.1039/B312329D.

Earle MJ, McCormac PB, Seddon KR. Diels-Alder reactions in ionic liquids: a safe recyclable green alternative to lithium perchlorate-diethyl ether mixtures. Green Chem. 1999;1(1):23–5. https://doi.org/10.1039/A808052F.

Eckert CA, Knutson BL, Debenedetti PG. Supercritical fluids as solvents for chemical and materials processing. Nature. 1996;383:313–8. https://doi.org/10.1038/450810a.

Enders D, Seppelt M, Beck T. Enantioselective organocatalytic synthesis of arylglycines via Friedel-Crafts alkylation of arenes with a glyoxylate imine. Adv Synth Catal. 2010;352:1413–8. https://doi.org/10.1002/adsc.201000143.

Ertl G, Kno¨zinger H, Weitkamp J. Handbook of heterogeneous catalysis, vol. 5. Weinheim: Set VCH; 1997.

Estorach CT, Orejo´n A, Masdeu-Bulto´ AM. Hydroformylation of 1-octene in supercritical carbon dioxide with alkyl P-donor ligands on rhodium using a peracetylated β-cyclodextrin as a solubiliser. Eur J Inorg Chem. 2008;17:2659–63. https://doi.org/10.1002/ejic.200800153.

Fillion H, Luche JL. Synthetic organic sonochemistry. New York: Plenum Press; 1998.

Fleck M, Bach T. Total synthesis of the tetracyclic sesquiterpene (±)-punctaporonin C. Angew Chem Int Ed. 2008;47:6189–91. https://doi.org/10.1002/anie.200801534.

Freemantle M. Designer solvents—ionic liquids may boost clean technology development. Chem Eng News. 1998;76(13):32–7. https://doi.org/10.1021/cen-v076n013.p032.

Gandini A, Belgacem MN. Furans in polymer chemistry. Prog Polym Sci. 1997;22:1203–379. https://doi.org/10.1016/S0079-6700(97)00004-X.

Geng LJ, Li JT, Wang SX. Application of grinding method to solid state organic synthesis. Chin J Org Chem. 2005;25(5):608–13.

Giernoth R, Krumm MS. Enantioselective hydrogenation of trimethylindolenine in ionic liquids. Adv Synth Catal. 2004;346:989–92. https://doi.org/10.1002/adsc.200404050.

Guzman-Lucero D, Guzman J, Likhatchev D, Martinez-Palou R. Microwave- assisted synthesis of 4,4-diaminotriphenylmethanes. Tetrahedron Lett. 2005;46(7):1119–22. https://doi.org/10.1016/j.tetlet.2004.12.091.

Handa S, Smith JD, Zhang Y, Takale BS, Gallou F, Lipshutz BH. Sustainable HandaPhos-*ppm* palladium technology for copper-free Sonogashira couplings in water under mild conditions. Org Lett. 2018;20:542–5. https://doi.org/10.1021/acs.orglett.7b03621.

Handy ST, Zhang X. Organic synthesis in ionic liquids: the stille coupling. Org Lett. 2001;3:233–6. https://doi.org/10.1021/ol0068849.

Hardacre C, Holbrey JD, Katdare SP, Seddon KR. Alternating copolymerization of styrene and carbon monoxide in ionic liquids. Green Chem. 2002;4(2):143–6. https://doi.org/10.1039/b111157b.

Hope EG, Stuart AM, West AJ. Recovery and recycle of fluoroalkyl-derivatised BINAP ligands using FRP silica gel. Green Chem. 2004;5:345–50. https://doi.org/10.1039/b404824e.

Jatangi N, Tumula N, Palakodety RK, Nakka M. $I_2$-mediated oxidative C-N and N-S bond formation in water: a metal-free synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles. J Organomet Chem. 2018;83:5715–23. https://doi.org/10.1021/acs.joc.8b00753.

Kappe C. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. Acc Chem Res. 2000;33:879–88. https://doi.org/10.1021/ar000048h.

Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed. 2004;43:6250–84. https://doi.org/10.1002/anie.200400655.

Klingler FD. Levulinic acid. In: Ullmann's encyclopedia industrial chemistry. 7th ed. Weinheim: Wiley-VCH; 2007. (Electronic Release).

Kolb HC, Finn MG, Sharpless KB. Click chemistry: diverse chemical function from a few good reactions. Angew Chem Int Ed. 2001;40:2004–21. https://doi.org/10.1002/1521-3773(20010601)40:11.

Lew A, Krutzik PO, Hart ME, Chamberlin AR. Increasing rates of reaction: microwave-assisted organic synthesis for combinatorial chemistry. J Comb Chem. 2002;4:95–105. https://doi.org/10.1021/cc010048o.

Lidstrom P, Tierney J, Wathey B, Westman J. Microwave assisted organic synthesis—a review. Tetrahedron. 2001;57:9225–83. https://doi.org/10.1016/S0040-4020(01)00906-1.

Linthorst JA. An overview: origins and development of green chemistry. Found Chem. 2009;12:55–68. https://doi.org/10.1007/s10698-009-9079-4.

List B. Introduction: organocatalysis. Chem Rev. 2007;107:5413–5. https://doi.org/10.1021/cr078412e.

Loh CCJ, Chauhan P, Hack D, Lehmann C, Enders D. Rapid asymmetric synthesis of highly functionalized indanols via a Michael/Henry organocascade with submol% squaramide catalyst loadings. Adv Synth Catal. 2014;356:3181–6. https://doi.org/10.1002/adsc.201400499.

Lyubimov SE, Tyutyunov AA, Kalinin VN, Said-Galiev EE, Khokhlov AR, Petrovskii PV, Davankov VA. Carboranylphosphites—new effective ligands for rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate. Tetrahedron Lett. 2007;48:8217–9. https://doi.org/10.1016/j.tetlet.2007.09.079.

McKillip WJ, Collin G, Ho¨ke H, Zeitsch KJ. Furan and derivatives. In: Ullmann's encyclopedia industrial chemistry. 7th ed. Weinheim: Wiley-VCH; 2007.. (Electronic Release).

Mikolajczyk M, Grzejszczak S, Zatorski A, Montanari F, Cinquini M. α-Phosphoryl sulphoxides and sulphones: new catalysts in two-phase alkylation of ketones. Tetrahedron Lett. 1975;16(43):3757–60. https://doi.org/10.1016/S0040-4039(00)91329-7.

Mo J, Xiao JL. The Heck reaction of electron-rich olefins with regiocontrol by hydrogen-bond donors. Angew Chem Int Ed. 2006;45:4152–7. https://doi.org/10.1002/anie.200600799.

Namboodiri VV, Polshettiwar V, Varma RS. Expeditious oxidation of alcohols to carbonyl compounds using iron (III) nitrate. Tetrahedron Lett. 2007;48:8839–42. https://doi.org/10.1016/j.tetlet.2007.10.068.

Narashimulu M, Mahesh KC, Reddy TS, Rajesh K, Venkateswarlu Y. Lanthanum(III) nitrate hexahydrate or *p*-toluenesulfonic acid catalyzed one-pot synthesis of 4(3*H*)-quinazolinones under solvent-free conditions. Tetrahedron Lett. 2006;47:4381–3. https://doi.org/10.1016/j.tetlet.2006.04.096.

Noyori R. Pursuing practical elegance in chemical synthesis. Chem Commun. 2005;14:1807–11. https://doi.org/10.1039/B502713F.PMID15795753.

Ouk S, Thiebaud S, Borredon E, Le Gars P. Dimethyl carbonate and phenols to alkyl aryl ethers *via* clean synthesis. Green Chem. 2002;4:431–5. https://doi.org/10.1039/B203353B.

Pandey G, Singh R, Gary A, Singh V. Synthesis of Mannich type products via a three-component coupling reaction. Tetrahedron Lett. 2005;46:2137–40. https://doi.org/10.1016/j.tetlet.2005.01.118.

Petricci E, Mann A, Schoenfelder A, Rota A, Taddei M. Microwaves make hydroformylation a rapid and easy process. Org Lett. 2006;8:3725–7. https://doi.org/10.1021/ol061312v.

Poliakoff M, Licence P. Sustainable technology: green chemistry. Nature. 2007;450:810–2.

Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. Green chemistry: science and politics of change. Science. 2002;297:807–10. https://doi.org/10.1126/science.297.5582.807.

Prat D, Pardigon O, Flemming HW, Letestu S, Ducandas V, Isnard P, Guntrum E, Senac T, Ruisseau S, Cruciani P, Hosek P. Sanofi's solvent selection guide: a step toward more sustainable processes. Org Proc Res Devel. 2013;17:1517–25. https://doi.org/10.1021/op4002565.

Ritter SK. Green chemistry progress report. Chem Eng News. 2002;80(47):19–23. https://doi.org/10.1021/cen-v080n047.p019.

Roberts BA, Strauss CR. Towards rapid, "green", predictable microwave assisted synthesis. Acc Chem Res. 2005;38:653–61. https://doi.org/10.1021/ar040278m.

Rossen K, Pye PJ, DiMichele LM, Volante RP, Reider PJ. An efficient asymmetric hydrogenation approach to the synthesis of the Crixivan® piperazine intermediate. Tetrahedron Lett. 1998;39(38):6823–6. https://doi.org/10.1016/S0040-4039(98)01484-1.

Seddon KR. Room-temperature ionic liquids—neoteric solvents for clean catalysis. Kinet Catal. 1996;37(5):693–7.

Seddon KR. Ionic liquids for clean technology. J Chem Technol Biotechnol. 1997;68(4):351–6. https://doi.org/10.1002/(SICI)1097-4660(199704)68:4.

Seddon KR, Stark A. Selective catalytic oxidation of benzyl alcohol and alkylbenzenes in ionic liquids. Green Chem. 2002;4(2):119–23. https://doi.org/10.1039/B111160B.

Seddon KR, Hardacre C, McCauley BJ. Catalyst comprising indium salt and organic ionic liquid and process for Friedel-Crafts reactions, World Patent WO 03,028883. 2003.

Selva M, Tundo P, Perosa A. Reaction of functionalized anilines with dimethyl carbonate over NaY faujasite. 3. Chemoselectivity toward mono-*N*-methylation. J Organomet Chem. 2003;68:7374–8. https://doi.org/10.1021/jo034548a.

Sharma SK, Parikh PA, Jasra RV. Solvent free aldol condensation of propanal to 2-methylpentenal using solid base catalysts. J Mol Catal A Chem. 2007;278(1):135–44. https://doi.org/10.1016/j.molcata.2007.09.002.

Sheldon RA. Consider the environmental quotient. ChemTech. 1994;24(3):38–47.

Shenghui H, Carlos AM, Junhua T, William ET, Patrich GTK, Yves RD. Preparation of Pregabalin and related compounds. Canadian Patent application no: CA2571040C (Warner Lambert Co LLC). 2009.

Sherman J, Chin B, Huibers PDT, Garcia-Valls R, Hatton TA. Solvent replacement for green processing. Environ Health Perspect. 1998;106:253–71. https://doi.org/10.2307/3433925.

Shieh WC, Dell S, Repic O. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and microwave-accelerated green chemistry in methylation of phenols, indoles, and benzimidazoles with dimethyl carbonate. Org Lett. 2001;32(6):4279–81. https://doi.org/10.1021/ol016949n.

Sumiyoshi T, Tojo K, Urabe DM, Tobe M. Asymmetric synthesis of the 6-cyanoindole derivatives as non-steroidal glucocorticoid receptor modulators using (+)- and (−)-tert-butyl 6-cyano-3-[3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl]-1H-indole-1-carboxylate. Tetrahedron Asymmetry. 2011;22:153–60. https://doi.org/10.1016/j.tetasy.2011.01.020.

Suslick KS. Sonochemistry. Science. 1990;247:1439–45. https://doi.org/10.1126/science.247.4949.1439.

Tajima K. Conversion of 3-Acetoxy-6-acetoxymethyl-2*H*-pyran-2-one to cyclopentenone derivatives and 1,3-cyclopentanedione. Chem Lett. 1987;16:1319–22. https://doi.org/10.1246/cl.1987.1319.

Tundo P, Selva M. The chemistry of dimethyl carbonate. Acc Chem Res. 2002;35:706–16. https://doi.org/10.1021/ar010076f.

Tundo P, Anastas P, Black DSC, Breen J, Collins T, Memoli S, Miyamoto J, Polyakoff M, Tumas W. Synthetic pathways and processes in green chemistry. Introductory overview. Pure Appl Chem. 2000;72(7):1207–28.

Tundo P, Rossi L, Loris A. Dimethyl carbonate as an ambident electrophile. J Organomet Chem. 2005;70:2219–24. https://doi.org/10.1021/jo048532b.

Tundo P, Perosa A, Zucchini F. Methods and reagents for green chemistry: an introduction. Hoboken: Wiley; 2007.

Tzschucke CC, Markert C, Glatz H, Bannwarth W. Fluorous biphasic catalysis without perfluorinated solvents: application to Pd-mediated Suzuki and Sonogashira couplings. Angew Chem Int Ed. 2002;41:4500–3. https://doi.org/10.1002/1521-3773(20021202)41:23.

Ugi I, Wischho¨fer E. Isonitrile, XI Synthese einfacher Penicillansäure-Derivate. Chem Ber. 1962;95:136–40. https://doi.org/10.1002/cber.19620950123.

Ugi I, D¨omling A, H¨orl W. Multicomponent reactions in organic chemistry. Endeavour. 1994;18:115–22. https://doi.org/10.1016/S0160-9327(05)80086-9.

Ugi I, Werner B, Domling A. The chemistry of isocyanides, their multicomponent reactions and their libraries. Molecules. 2003;8:53–66. https://doi.org/10.3390/80100053.

Van Rantwijk F, Lau RM, Sheldon RA. Biocatalytic transformations in ionic liquids. Trends Biotechnol. 2003;21(3):131–8. https://doi.org/10.1016/S0167-7799(03)00008-8.

Varma RS, Dahiya R. Sodium borohydride on wet clay: solvent-free reductive amination of carbonyl compounds using microwaves. Tetrahedron. 1998;54:6293–8. https://doi.org/10.1016/S0040-4020(98)00326-3.

Varma RS, Naicker KP. Hydroxylamine on clay: a direct synthesis of nitriles from aromatic aldehydes using microwaves under solvent-free conditions. Mol Online. 1998;2:94–6. https://doi.org/10.1007/s007830050.

Varma RS, Varma M, Chatterjee AK. Microwave-assisted deacetylation on alumina: a simple deprotection method. J Chem Soc Perkin Trans. 1993a;1:999–1000. https://doi.org/10.1039/P19930000999.

Varma RS, Chatterjee AK, Varma M. Alumina-mediated deacetylation of benzaldehyde diacetates. A simple deprotection method. Tetrahedron Lett. 1993b;34:3207–10. https://doi.org/10.1016/S0040-4039(00)73662-8.

Varma RS, Saini RK, Dahiya R. Active manganese dioxide on silica: oxidation of alcohols under solvent-free conditions using microwaves. Tetrahedron Lett. 1997;38:7823–4. https://doi.org/10.1016/S0040-4039(97)10093-4.

Vass A, Dudas J, Toth J, Varma RS. Solvent-free reduction of aromatic nitro compounds with alumina-supported hydrazine under microwave irradiation. Tetrahedron Lett. 2001;42:5347–9. https://doi.org/10.1016/S0040-4039(01)01002-4.

Wang M, Wang H, Zhao N, Wei W, Sun Y. High-yield synthesis of dimethyl carbonate from urea and methanol using a catalytic distillation process. Ind Eng Chem Res. 2007;46:2683–7. https://doi.org/10.1021/ie061101u.

Wang L, Cai C, Curran DP, Zhang W. Enantioselective a-chlorination of aldehydes with recyclable fluorous (S)-pyrrolidine-thiourea bifunctional organocatalyst. Synlett. 2010;3(2010):433–6. https://doi.org/10.1055/s-0029-1219198.

Wasserscheid P, Welton T. Ionic liquids in synthesis. Weinheim: Wiley-VCH; 2003.

Wittmann K, Wisniewski W, Mynott R, Leitner W, Kranemann CL, Rische T, Eilbracht P, Kluwer S, Ernsting JM, Elsevier CL. Supercritical carbon dioxide as solvent and temporary protecting group for rhodium-catalyzed hydroaminomethylation. Chem Eur J. 2001;7:4584–9. https://doi.org/10.1002/1521-3765(20011105)7:21.

Woodhouse EJ, Breyman S. Green chemistry as social movement. Sci Technol Hum Values. 2005;30(2):199–222. https://doi.org/10.1177/0162243904271726.

Xiao JL, Nefkens SCA, Jessop PG, Ikariya T, Noyori R. Asymmetric hydrogenation of α,β-unsaturated carboxylic acids in supercritical carbon dioxide. Tetrahedron Lett. 1996;37:2813–6. https://doi.org/10.1016/0040-4039(96)00436-4.

Zhang W. Microwave-enhanced high-speed fluorous synthesis. Top Curr Chem. 2006;266:145–66. https://doi.org/10.1007/128-045.

Zhao JL, Liu L, Zhang HB, Wu YC, Wang D, Chen YF. Three component Friedel-Crafts reaction of indoles, glyoxylate, and amine under solvent-free and catalyst-free conditions—synthesis of (3-indolyl)glycine derivatives. Synlett. 2006;1:96–100. https://doi.org/10.1055/s-2005-922764.

Zhu J, Bienaymé H. Multicomponent reactions. Weinheim: Wiley-VCH; 2005.

Zhu S, Yu S, Ma D. Highly efficient catalytic system for enantioselective Michael addition of aldehydes to nitroalkenes in water. Angew Chem Int Ed. 2008;47:545–8. https://doi.org/10.1002/anie.200704161.

# Green Aspects of Scale-Up Synthesis of Some APIs, Drug Candidates Under Development or Their Critical Intermediates

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_7

## Abbreviations

| | |
|---|---|
| $[Ir(COD)OMe]_2$ | bis(1,5-Cyclooctadiene)di-μ-methoxydiiridium |
| 2,2′-bpy | 2,2′-Bipyridyl |
| $B_2Pin_2$ | bis(Pinacolato)diborane |
| $Boc_2O$ | di-tert-Butyl dicarbonate |
| CDI | N,N′-Carbonyldiimidazole |
| CyH | Cyclohexane |
| DBH | 1,3-Dibromo-5,5-dimethylhydantoin |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCM | Dichloromethane |
| DIPEA | Diisopropylethylamine |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DTTA | di-p-Toluoyl-L-tartaric acid |
| IPA | Isopropyl alcohol |
| $IPy_2BF_4$ | bis(Pyridine)iodonium tetrafluoroborate |
| LDA | Lithium diisopropylamide |
| MsOH | Methane sulfonic acid |
| NBS | N-Bromosuccinimide |
| NMM | N-Methylmorpholine |
| NMP | N-Methylpyrrolidone |
| *$Pd(dppf)Cl_2$* | *[1,1'-bis(Diphenylphosphino)ferrocene]dichloropalladium(II)* |
| RT | Room temperature |
| TBAB | Tetrabutylammonium bromide |
| TBz-Cl | tert-Butyldimethylsilyl chloride |
| TEA | Trimethylamine |
| TFA | Trifluoroacetic acid |
| TsCl | Tosyl chloride |
| TsOH | p-Toluenesulfonic acid |

## 1 Introduction

Drug synthesis passes through various phases from conception to market. It is the medicinal chemist who conceives the target therapeutic areas such as cardiovascular drug candidates, anti-inflammatories, antibacterials, candidates for neurological disorders like Parkinson's disease and Alzheimer's disease and the pain targets to name a few. During initial stages of evaluation of a therapeutic area, the medicinal chemist synthesizes several molecules having desired chromophores that can bind with the target receptors and elicit the desired response. Once it is established, the candidate molecule under research goes through various preclinical studies that

include toxicological evaluation and animal studies before regulatory evaluation of the lead molecules.

All these studies need various quantities of prospective candidates during their evolution cycle. Preliminary studies may need amounts ranging from a few milligrams to a gram scale for chemical characterization and therapeutic evaluation. Further preclinical studies need a few hundreds of grams to a kilogram scale, and regulatory studies need quantities ranging from a few kilograms to hundreds of kilograms and finally on a ton's scale, depending on the safe dosage needed to elicit a therapeutic response. It is the chemists' responsibility to look into the material supply needs uninterruptedly for the various studies lined up during its evaluation.

During initial synthesis and characterization on a milligram scale, the goal is to achieve the synthesis of the target molecule without much emphasis on the cost-effectiveness; bulk availability of the fine chemicals, reagents or solvents; the mass balance in a particular step; control of pollution levels; and the green chemistry aspects. All these factors gain importance once the study progresses, needing scaled-up materials in higher quantities. Then, the concentration of the medicinal/organic/process chemist shifts to sustained material supplies in a cost-effective manner involving greener chemistry principles. The route of synthesis involving the least number of steps, solvent usage as per the International Conference on Harmonization (ICH) guidelines, achieving higher yields, minimal impurity formation at each step and impurity profiling, avoidance of carcinogenic materials and degradation products, synthesis of active metabolites and characterization, study of greener aspects of synthesis and finally the temperature conditions and the types of reactors needed giving importance to safety principles of production acquire paramount importance.

For a thorough understanding on the green chemistry aspects on usage of solvents and other aspects of scale-up synthesis and good manufacturing practices of active pharmaceutical ingredients, the International Conference on Harmonization (ICH) guidelines are of immense use (ICH, Q3C (R5), February 2011; ICH, Q11, Current *Step 4* version 2012; ICH, Q7, Current *Step 4* version 2000). The guidelines recommend acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The guidelines also recommend the use of less toxic solvents and describe levels considered to be toxicologically acceptable for some residual solvents. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance may enhance the yield or determine characteristics such as crystal form, purity and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices and other quality-based requirements. Drug products should not contain higher levels of residual solvents than the levels that can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (*Class 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly

justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (*Class 2*) should be limited to protect patients from potential adverse effects. Ideally, less toxic solvents (*Class 3*) should be used where practical. Testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. The residual solvents are evaluated for their possible risk to human health and placed into one of the three classes as follows:

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens and environmental hazards. The solvents listed here are benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethane and 1,1,1-trichloroethane.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity and solvents suspected of other significant but reversible toxicities. The solvents listed here include acetonitrile, chlorobenzene, chloroform, cyclohexane, 1,1-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane and 2-ethoxy ethanol.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have permitted daily exposures (PDEs) of 50 mg or more per day. The solvents listed here include acetic acid, acetone, 1-butanol, 2-butanol, butyl acetate, tert-butyl methyl ether, cumene, dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methyl ethyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol and isopropyl acetate.

However, it is not in the scope of this review to give elaborate details on residual solvents. For a thorough understanding of the subject, the reader is requested to refer to the ICH guidelines on the relevant topic.

During the scale-up synthesis of the lead molecules selected as drug candidates, the process chemists take over the material supplies for preclinical and regulatory phases. The initial medicinal chemistry route involving first time synthesis is subjected to thorough process research to evolve a robust manufacturing method, wherein the priority goes for the selection of proper route of synthesis involving lesser number of high-yielding steps that can be implemented on larger volumes, cutting down on the pollutants, and can be operated preferably at lower temperatures and atmospheric pressures using cost-effective reagents. Ideally, pressure reactors need to be avoided to the extent possible. The unit operations should be such that they can be handled with ease, giving high priority to safety principles. Once the individual steps involved in the selected route for scale-up synthesis are high yielding, the impurity formations will be minimal and avoid elaborate purification procedures, cutting down on the pollution levels. In the case of chiral molecules

selected as drug candidates, the regulatory requirement involves synthesis, chemical characterization, configurational studies, therapeutic evaluation and toxicological profile of all the possible enantiomers and/or diastereomers, regional isomers, etc. This is of paramount importance especially in light of the thalidomide episode. In short, all greener aspects gain importance during the production of drug substances.

Some of these aspects will be highlighted, wherever possible, during this review of green aspects of scale-up synthesis, considering some examples of APIs, drug candidates under various phases of development or their critical intermediates from recently published literature so that the young scientists in the relevant field derive the maximum benefit in sharpening their innovative skills. We thankfully acknowledge the original contributors of the papers and the publishers cited, on the scale-up processes chosen here, for the overall benefit of mankind in general and the scale-up scientists in particular.

The green chemistry elements a process chemist looks into during process development for a robust and viable scaled-up synthetic process, to meet the demands of preclinical and clinical studies initially, ultimately leading to the development of manufacturing process on a commercial scale are as follows.

The process scientist keeps an eye on the number of steps involved in achieving the target molecule. Any reduction in the number of steps in the synthetic route saves cost and reduces the environmental burden. In doing so, there is no compromise on the quality of the drug substance. The chemists concentrate on a short viable route, out of a variety of possible schemes to achieve the target molecule with appropriate purity checks and impurity controls. In an ideal situation, the synthetic route chosen should not involve any mutagenic fine chemicals and intermediates or degradation products. Otherwise, the chemist needs to develop elaborate procedures to get rid of those impurities and analytical procedures to have checks on them contributing to a shoot up in the economics.

The process chemist always needs to concentrate on the economic viability of the process, to lessen the cost burden on the end-user throughout the world, including underdeveloped Third World countries.

Each step in a chosen scheme should lead to a pure intermediate, with controls on the impurities generated with simple chemical purification methodologies. Purification procedures should not be long and cumbersome and should be easily adaptable on a larger scale. To the extent possible, a scale-up scientist prefers to avoid chromatographic purification techniques, as these are not viable on a larger scale and shoot up the cost of the drug substance enormously and contribute to environmental burden.

Choice of solvents at each step is very important. The solvents chosen should preferably be green, easily available on a large scale, environment friendly and reusable after short purification processes. The process scientist prefers solvents suggested in the ICH guidelines, briefly discussed above. The most preferred solvent is water if it works in any of the steps in a scheme.

Identification of impurities formed at individual steps is another important feature during scale-ups. The accrued impurities from each step, unless they are controlled, have the potential of contaminating the drug substance (DS). Hence, process

scientist identifies the impurities formed beyond acceptable levels at each step and synthesizes and characterizes them wherever necessary to ensure that these impurities or their further degradation products do not contaminate the final DS. The regulatory submissions also insist on profiling of impurities formed beyond the acceptable levels in the DS. Documentation of process controls at each stage in the manufacturing process of a drug substance is a requirement for regulatory submissions as per ICH guidelines.

The scale-up chemist looks into the thermal conditions required in a particular step. It is always preferred that the temperatures at which the reactions are carried out should be moderate. Too high temperatures or too low temperatures pose a stumbling block in scale-ups on commercial levels. To an extent possible, the scheme should be chosen in such a way that the reactions work well under mild conditions.

The scale-up chemist always looks at the adaptability of the scheme chosen on a plant scale and the requirement of the reactors. Stainless steel (SS) reactors are preferred. Glass-lined reactors (GLRs) are occasionally used for the particular types of reactions that cannot be conducted in SS reactors. Pressure vessels are the least preferred as they are to be handled with caution.

A scheme that does not involve pyrophoric or mutagenic fine chemicals, intermediates and inflammatory solvents with a low flash point like diethyl ether is the preferred scheme for the scale-up scientist.

All the steps, in the chosen scheme, should be high yielding. High yields of the desired product restrict the levels of formation of impurities. This will avoid elaborate and cumbersome purification procedures, reducing the environmental burden.

At every step in the scheme, a process chemist keeps an eye on rational input and output balance to reduce the environmental burden. Otherwise, it will lead to unviable pollution levels needing elaborate and costly pollution control measures.

The process that does involve a minimum number of material isolations at different intermediate steps is the best one. It is always preferred to proceed to the next steps without isolation, of course with appropriate quality checks/controls in place. This will avoid lengthy time-consuming procedures associated with material isolations like drying and powdering.

Another important factor a process scientist looks into, during scale-up synthesis, is the time consumed at every step. The higher the time of occupation of the reactors, the lower will be the monthly/annual output. This will escalate the cost burden. Hence, it is always preferred that the scheme chosen involves reactions with shorter periods and maximum output, reducing the reactor occupancy time.

The stability studies of the drug substance under accelerated, intermediate, long-term and refrigerator conditions occupy an important place during these scale-up studies to ensure that the API so produced is stable and does not pose any issues in the long run.

The last but not the least important element in the scale-up synthesis is having a thorough understanding of the various safety and environmental hazards associated with the unit operations during such scale-ups to the men and material. For example, the stirring (revolutions per minute) and reaction efficiency, the filtrations, the

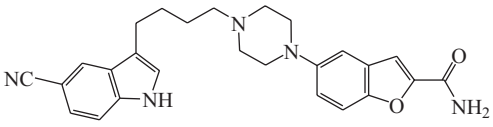
high vacuum distillations and the drying processes on plant scale differ from those carried out on laboratory scale, with manifold increase in the chances of confronting the hazards. One should have an understanding of the compatibility issues associated with the choice of solvents, reagents, catalysts, fine chemicals and intermediates. It is another subject matter of paramount importance to have a thorough understanding of the unit operations, the online automation for monitoring the reaction progress using chromatographic techniques, the equipment needs and the associated hazard analysis during the manufacture of the drug substance.

Finally, a cost-effective improvement at any step in the synthetic scheme chosen, avoiding pollutants' burden, will go a long way in the economic viability of the process undertaken by the scale-up scientist. The final process should be commercially viable, both technologically and economically, wherein all the raw materials and fine chemicals involved are locally available and/or can be procured with ease at required levels.

This is to emphasize further that the articles/publications chosen for review here may or may not have the final say on the subject. It is only indicative of methodologies used for scale-up synthesis in this review. There is every possibility that the latest literature might be available on greener aspects of scale-up synthesis of the active pharmaceutical ingredients, drug candidates or their intermediates chosen for review here. Hence, the readers are advised to go through more recent literature in addition to the references cited here, for further update on the subject. The authors of the current article have no commercial interest and do not undertake any liability due to any shortfall in expectation. The review was authored purely out of academic interest to familiarize the young process scientists with the intricacies of process development and guide them in understanding green chemistry aspects of scale-up synthesis.

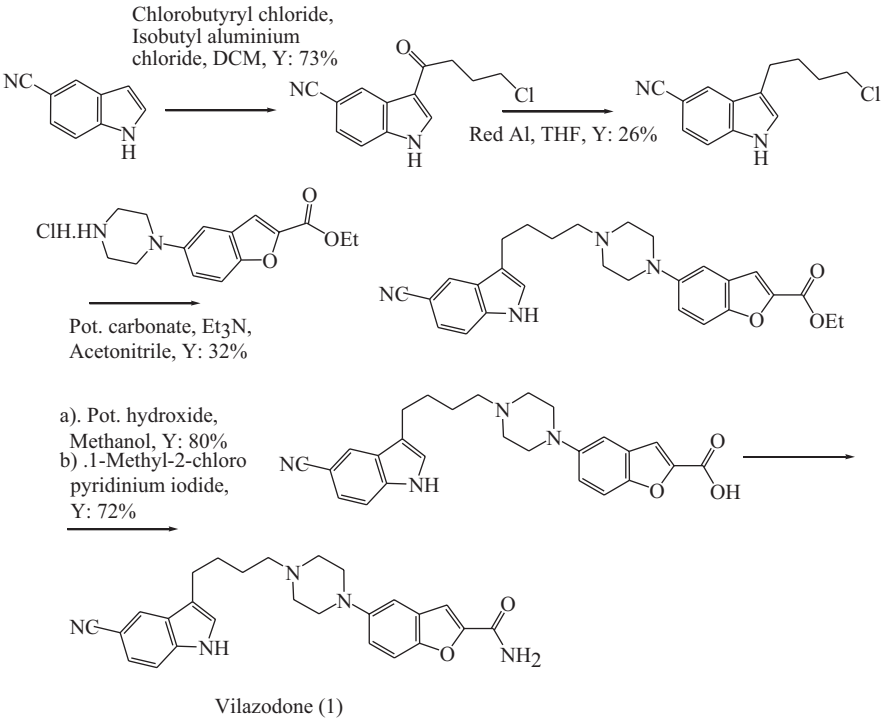
## 2 Examples of Scale-Up Synthesis from Literature

### *2.1 Vilazodone*




Vilazodone (1)

A novel antidepressant drug, vilazodone (1), is a dual selective serotonin reuptake inhibitor (SSRI) and serotonin 5-$HT_{1A}$ receptor partial agonist, useful in the treatment of major depressive disorder (MDD). The earlier reported methodologies suffer from several disadvantages such as the use of expensive and non-user friendly reagents or catalysts, the formation of unwanted side products, low overall yields

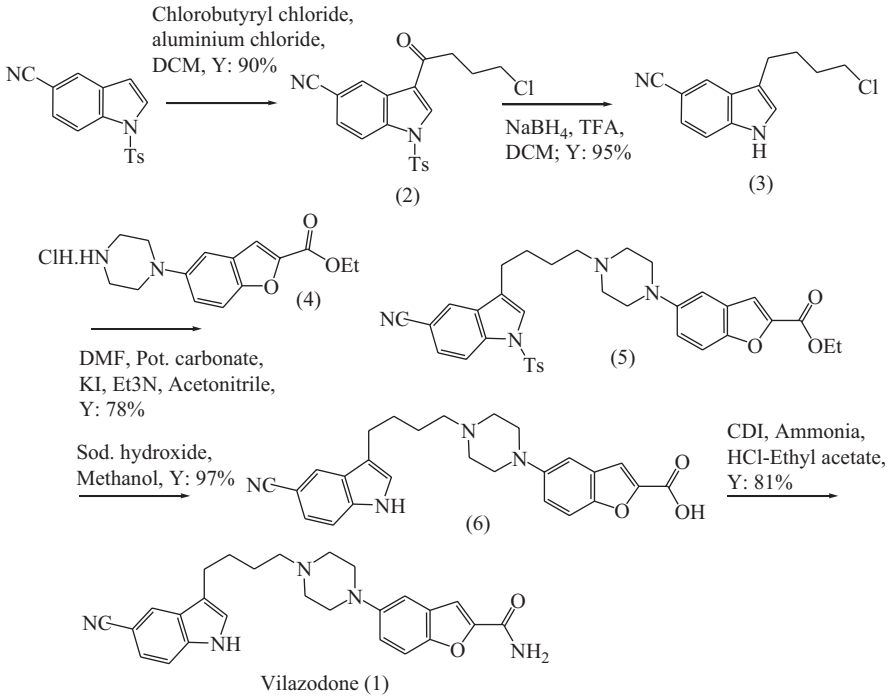



**Scheme 1** Initial synthesis of vilazodone (1) (Modified after Bin, Hu et al., oprd, 2012, 16, 1552–1557)
*DCM* dichloromethane, *THF* tetrahydrofuran, *$Et_3N$* triethylamine

and complicated purification procedures (Scheme 1) (Heinrich et al. 2004; Heinrich et al. 2010; Li et al., 2011a, b; Xu et al., 2011, Chen 2011; Andreas 2006).

In their interesting research, publication by Bin Hu et al. (2012) from China Pharmaceutical University, Nanjing, China, disclosed a convenient, economical, five-step scale-up process for the drug vilazodone (1) in 52.4% overall yield and 99.7% purity (Scheme 2), using readily available, environment friendly, cost-effective reagents and solvents.

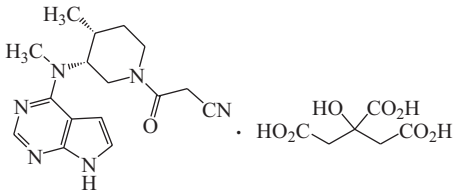
1-Tosyl-1H-indole-5-carbonitrile was treated with chlorobutyryl chloride in presence of aluminium chloride in dichloromethane solvent to afford 3-(4-chlorobutanoyl)-1-tosyl-1H-indole-5-carbonitrile in 90% yield, and the latter was further reduced to 3-(4-chlorobutyl)-1-tosyl-1H-indole-5-carbonitrile (3), using sodium borohydride and trifluoroacetic acid in 95% yield. Formation of competitive substitution products as well as over-reduction products (indole to indoline) was avoided by starting the process from N-protected compound. Intermediate ester (5) was prepared by the reaction of (3) and (4) in presence of triethylamine, KI and $K_2CO_3$ in dimethylformamide (DMF) in 78% yield. Conversion of compound (5) to (6) was completed in a single step in NaOH in methanol by esterolysis and deprotection in 97% yield. Compound (6) was subjected to ammonolysis with ammonia




**Scheme 2** Scale-up synthesis of vilazodone (1) (Modified after Bin, Hu et al. oprd, 2012, 16, 1552–1557)
*DCM* dichloromethane, *TFA* trifluoroacetic acid, *DMF* dimethylformamide, *CDI* N,N′-carbonyldiimidazole

and DMF in the presence of *N,N′-carbonyldiimidazole* (CDI) to obtain vilazodone base, which was converted to its hydrochloride salt, the overall yield being 81% in this step. The process sequence was carried out at 2.4 Kg scale (vilazodone hydrochloride).

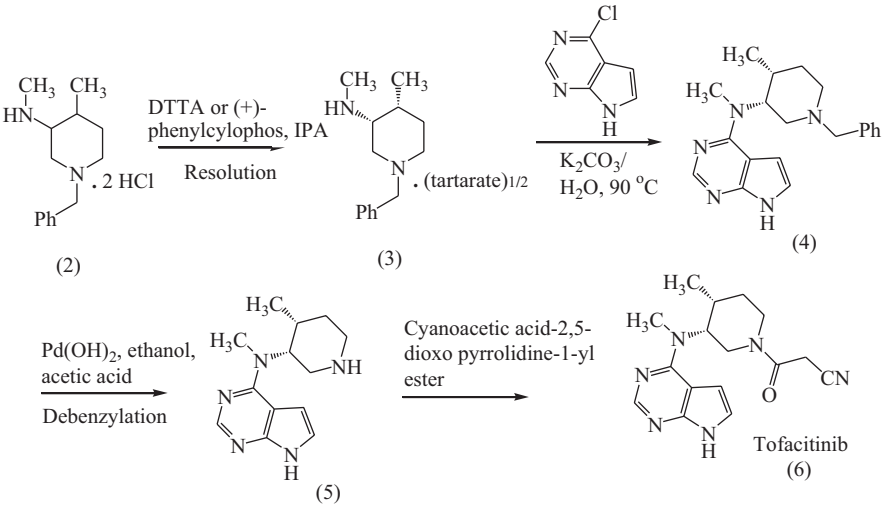
## 2.2 *Tofacitinib Citrate*



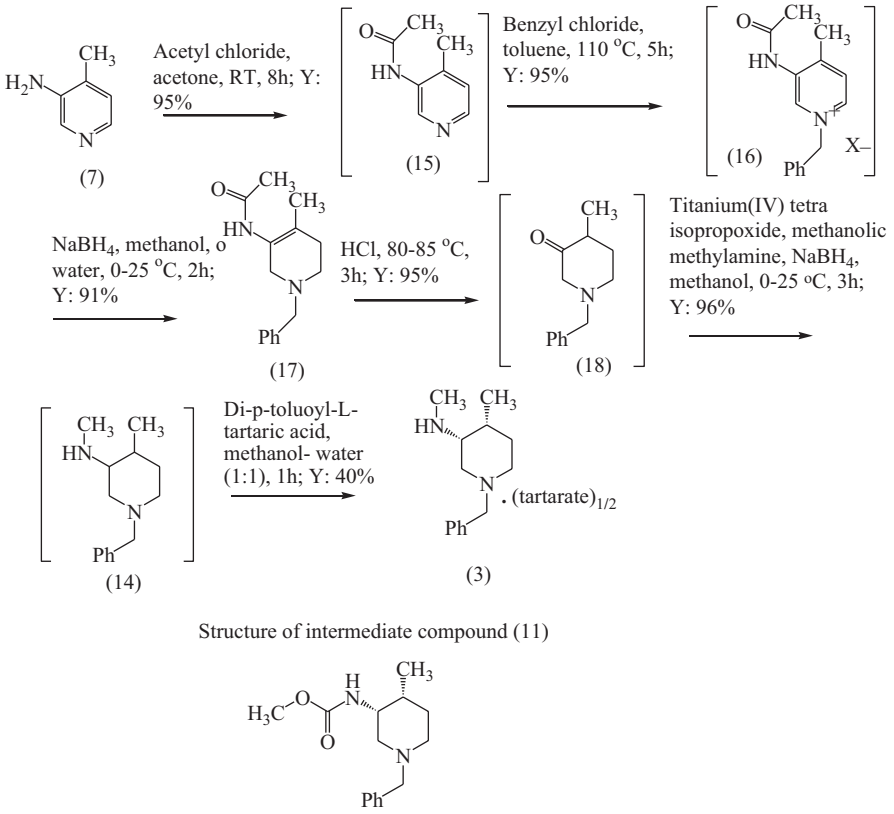
Tofacitinib Citrate (1)

Tofacitinib citrate (1), an approved drug of 2012, was useful in the treatment of rheumatoid arthritis. Apart from the original route (Blumenkopf et al. 2010; Flanagan and Munchhof 2007; Ernest et al. 2002) (Scheme 3), many other complex approaches were available for this drug molecule (Adolfo et al. 2013; Stavber and Cluzean 2014; Kristin et al. 2009). The synthesis of key intermediate (3) (3R,4R)-(1-benzyl-4-methylpiperidin-3-yl)-methylamine salt was the most crucial aspect, as it requires expensive reagents and involves tedious processes, escalating the costs of manufacturing.

Considering the complex methodologies and other drawbacks of the existing synthetic routes of both intermediate (3) and tofacitinib, Yogesh S. Patil et al. (2014) from Unichem Laboratories Ltd., India, attempted to develop an efficient and improved scale-up process. Their investigations and studies centred around two




**Scheme 3** Reported synthetic route for the preparation of tofacitinib (Modified after Yogesh S. Patil et al. oprd, 2014, 18, 1714–1720)
*DTTA* Di-p-toluoyl-L-tartaric acid, *IPA* isopropyl alcohol




Structure of intermediate compound (11)

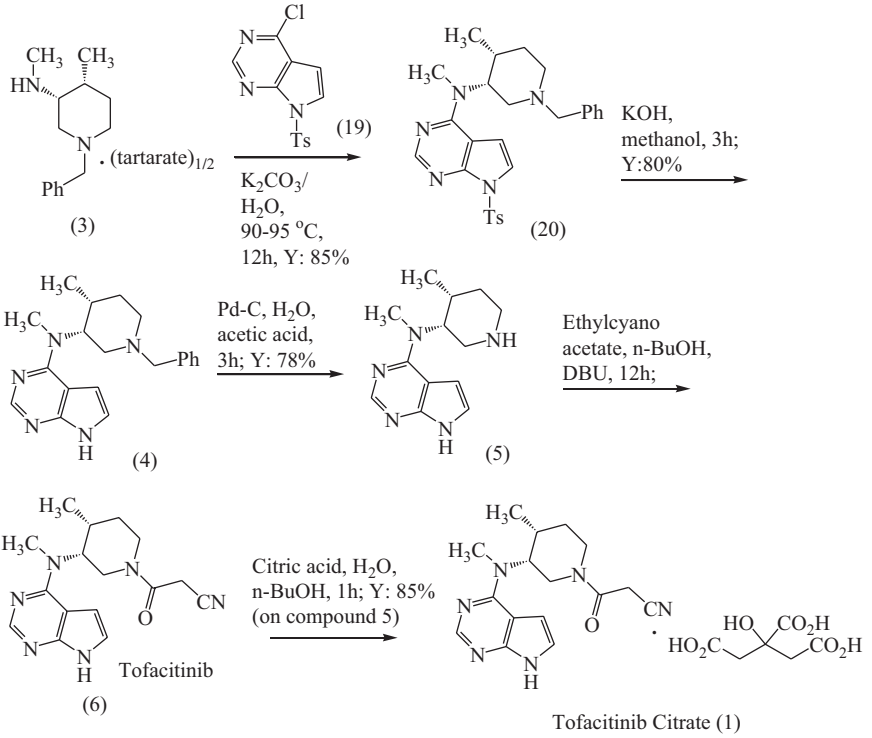


**Scheme 4** Synthesis of critical intermediate (3) of tofacitinib (Modified after Yogesh S. Patil et al. oprd, 2014, 18, 1714–1720)

aspects: (i) to develop a cost-effective approach to intermediate (3) (Scheme 4) and (ii) to find a facile route to tofacitinib citrate (Scheme 5):

(i) Synthesis of intermediate (3) was achieved starting from a very economical and commercially available 3-amino-4-methylpyridine (7), in a two-step process without the use of any expensive reagent such as platinum oxide, iridium or rhodium catalyst and lithium aluminium hydride. Intermediate stages of (14), (15), (16) and (18) were not isolated. The intermediate (3) was produced in an overall yield of 26% as compared to 15% of reported yields. The enantiomeric excess (ee) was more than 97% as compared to 67% ee of critical intermediate (11), reported in literature. It was reported that compound (3) produced has shown 98.6% of the required (R, R) isomer.

(ii) Synthesis of tofacitinib citrate starts from the condensation reaction of intermediates (3) and (19). It was carried out successfully to obtain higher yields

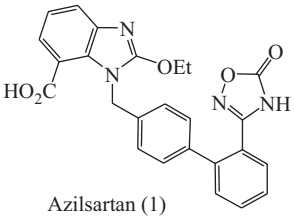



**Scheme 5** Improved and efficient process for the preparation of tofacitinib citrate (Modified after Yogesh S. Patil et al. oprd, 2014, 18, 1714–1720)
*DBU* 1,8-diazabicyclo[5.4.0]undec-7-ene

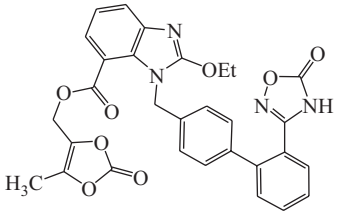
and purity by conducting the reaction in presence of 12 equivalents of potassium carbonate in water at 90–100 °C. Compound (20) was detosylated with KOH and methanol, followed by debenzylation with Pd/C; further, the base (5) was reacted with ethyl cyanoacetate in n-butanol in presence of *1,8-diazabicyclo[5.4.0]undec-7-ene* (DBU). Finally, tofacitinib base (6) was converted to citrate salt in aqueous citric acid. The process sequence was carried out at 35 gm scale (tofacitinib citrate). The yield in the last step, involving preparation of tofacitinib base and citrate salt is 85% with chiral purity of 99.9%.

The scale-up studies of this facile, cost-effective and efficient protocol involve appropriate screening studies for the identification of reagents, solvents and conditions at each step to arrive at higher yields and purities of the products.

## 2.3 Azilsartan




Azilsartan (1)

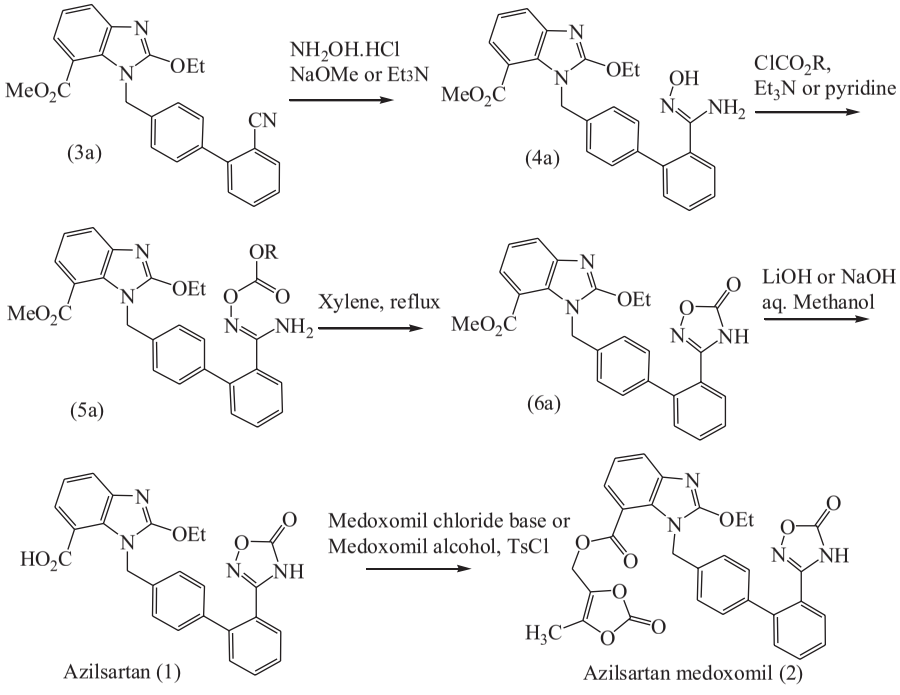



Azilsartan medoxomil (2)

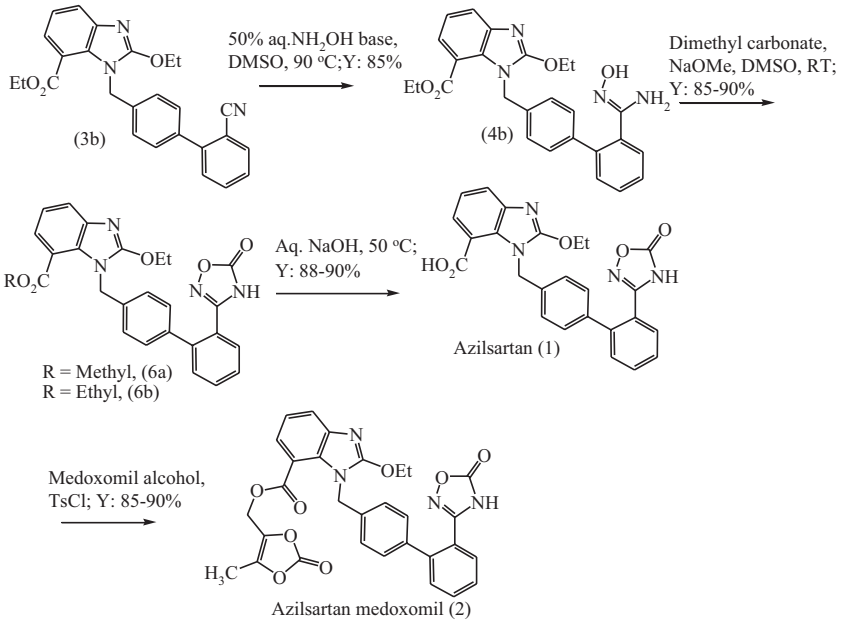
Sartans are drugs that interact with renin-angiotensin-aldosterone system. Azilsartan (1) used in the treatment of hypertension and cardiovascular diseases is a new angiotensin receptor blocker, approved in 2011.

Stanislav Radl et al. (2013), scientists from Zentiva, a Sanofi company, Czech Republic, in their interesting report described an improvement in the manufacturing process of azilsartan medoxomil (2) over the existing synthetic route and other limited variations (Naka and Inada 1992, 1996; Kohara et al. 1995, 1996; Kuroita et.al. 2005, 2007). In the existing approach (Scheme 6), the methyl ester (3a) was treated with hydroxylamine affording 55% of amidoxime (4a) which was further reacted with alkyl chloroformates in presence of trimethylamine or pyridine resulting in intermediate (5a). The crude (5a) without purification was thermally cyclized to give esters with much lower yields (6a, yield: 23%). Side products or impurities in these steps were not described. The compound (6a) was further saponified to azilsartan (1). It was converted to azilsartan medoxomil (2) by treating sodium salt of (1) with medoxomil chloride to provide compound (2) in 14% to 22%, or azilsartan was reacted with medoxomil alcohol in presence of tert-butyldimethylsilyl chloride (TBz-Cl) or tosyl chloride (Ts-Cl). Impurities were not indicated in earlier literature.

To overcome the related issues as well as the associated impurities with various reported processes, exhaustive and critical studies were taken up at Zentiva to develop a robust and more simplified approach to azilsartan (1) and azilsartan medoxomil (2) (Scheme 7) and to identify impurities and degradation products. The nitrile compound (3b) was successfully converted to amidoxime (4b) in 85% yield by treating with 50% aqueous hydroxylamine base at 90 °C in dimethyl sulfoxide, followed by transforming (4b) to azilsartan ester (6a/6b) in a single step in 85–90% yield using dimethyl carbonate, an economical and green reagent, as well as commercially available sodium methoxide in dimethyl sulfoxide (DMSO) at room temperature. The ester (6a or 6b) was hydrolyzed in aqueous sodium hydroxide at 50 °C to obtain azilsartan (1) in 88–90% yield, which on further reaction with medoxomil alcohol in presence of tosyl chloride provided azilsartan medoxomil (2) in 85–90% yield. According to the authors, all the minor impurities were properly assessed in this improved scaled-up process.

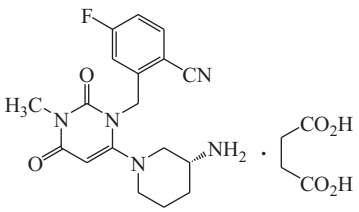



**Scheme 6** Reported synthetic scheme for azilsartan medoxomil (Modified after Stanislav Radl et al., oprd, 2013, 17, 77–86)




**Scheme 7** Improved process for the synthesis of azilsartan medoxomil (Modified after Stanislav Radl et al., oprd, 2013, 17, 77–86)
DMSO, dimethyl sulfoxide; TsCl, tosyl chloride

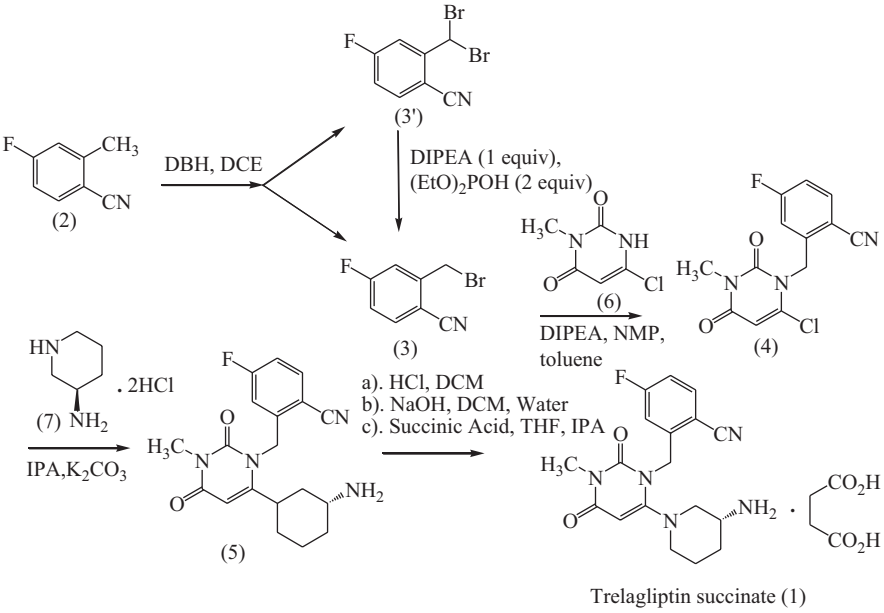
## *2.4 Trelagliptin Succinate*



Trelagliptin succinate (1)

Trelagliptin succinate (1), an antidiabetic drug approved in 2015, is a novel once a week oral dipeptidyl peptidase-4 (DPP-4) inhibitor. It exhibited excellent selectivity as well as slow binding properties and proved to be more potent than sitagliptin and alogliptin (Grimshaw et al. 2016). Its synthesis has attracted the attention of researchers due to the promising market and significant therapeutic efficiency.

The original synthetic approach (Feng et al. 2007) starts from 4-fluoro-2-methylbenzonitrile (2) (Scheme 8). Compound (2) on bromination with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in dichloroethane (DCE) afforded 2-bromomethyl-4-fluorobenzonitrile (3) and a dibromo compound (3′) as the main product, which could be converted back to compound (3) on treatment with diethyl

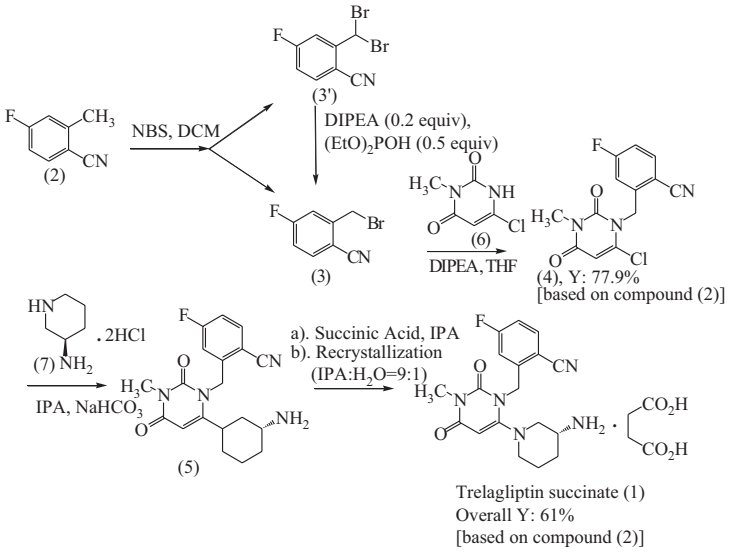



**Scheme 8** Reported synthesis of trelagliptin succinate (Modified after Shenghui Xu et al., oprd, 2017, 21, 585–589)
*DBH* **1,3-dibromo-5,5-dimethylhydantoin,** *DCE* **dichloroethane,** *DIPEA* **diisopropylethylamine,** *NMP* **N-methylpyrrolidone,** *DCM* **dichloromethane**

phosphite and diisopropylethylamine (DIPEA) in 2:1 ratio. The key intermediate (4), obtained by the condensation of (3) with 3-methyl-6-chloro uracil (6), was further reacted with (R)-3-aminopiperidine to provide trelagliptin. High regioselectivity is required in the last step of the above synthesis. An improvement for the last step was introduced by way of reacting the intermediate compound (4) with (R)-3-N-protected aminopiperidine (Zhang et al. 2013, 2016).

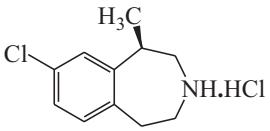
An improved and concise synthetic route was explored by Shenghui Xu et al., from State Key Lab of New Drug and Pharmaceutical Process, State Institute of Pharmaceutical Industry, Shanghai, China (Scheme 9) (Shenghui Xu et al. 2017).

While working on it, several nucleophilic substitution conditions were assessed, and impurity profiles were worked out. In this process, compound (2) was brominated with N-bromosuccinimide in dichloromethane as solvent in place of dichloroethane, a Class 1 solvent. Dibromo compound was formed in a lesser amount than in the original route. Compound (3) was directly reacted with 3-methyl uracil (6), without purification to afford intermediate (4) in 77.9% yield based on compound (2) charged. Key substitution reaction was investigated, experimenting with different solvents, with several bases. Best results of 99.1% yield of compound (5) were obtained when compound (4) was reacted with (R)-3-aminopiperidine dihydrochloride in isopropanol solvent in the presence of sodium bicarbonate. Crude product (5) was directly treated with succinic acid in isopropanol at 60 °C to provide monosuccinate salt in 90.6% yield. According to the authors, the impurity profiles were well established.




**Scheme 9** Improved process for the synthesis of trelagliptin succinate (Modified after Shenghui Xu et al., oprd, 2017, 21, 585–589)
*NBS* **N-bromosuccinimide,** *DIPEA* **diisopropylethylamine,** *DCM* **dichloromethane,** *THF* **tetrahydrofuran,** *IPA* **isopropyl alcohol**

## *2.5 Lorcaserin Hydrochloride*

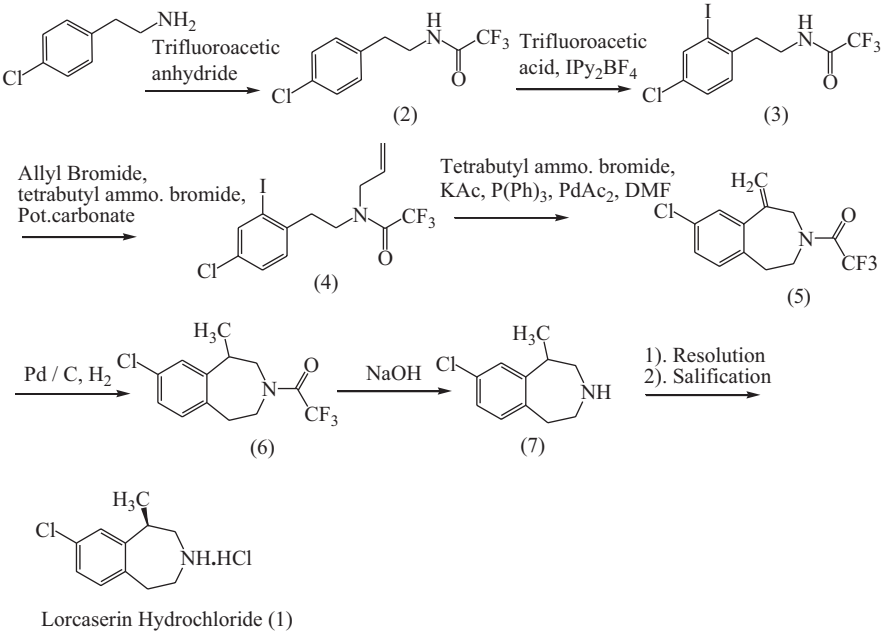



LorcaserinHydrochloride(1)

Lorcaserin hydrochloride (1), a novel antiobesity drug, is a selective serotonin 5-$HT_{2C}$ receptor agonist, approved by FDA in 2012. Initially, Smith and Smith (2003, 2005) described the synthetic process for lorcaserin hydrochloride in eight steps involving expensive, environmentally unfriendly and unstable catalysts and reagents as well as complicated workups and tedious purification procedures, leading to an overall yield of 3.7% (Scheme 10). Some of the later patented procedures also suffered from such drawbacks of low yields and use of hazardous reagents and chemicals (Weigl et al. 2009; Gharbaoui et al. 2008; Smith et al. 2005; Liu 2009; Burbaum et al. 2005).

Patent reported (Gharbaoui et al. 2008) synthetic approaches (methods 1–4) also employed toxic reagents with overall lower yields of the products.

The disadvantages of the method 1 are the following:




**Scheme 10** Initial synthesis of lorcaserin hydrochloride (Modified after Qihua Zhu et al., oprd, 2015, 19, 1263–1267)
*$IPy_2BF_4$* bis(pyridine)iodonium tetrafluoroborate, *DMF dimethylformamide*

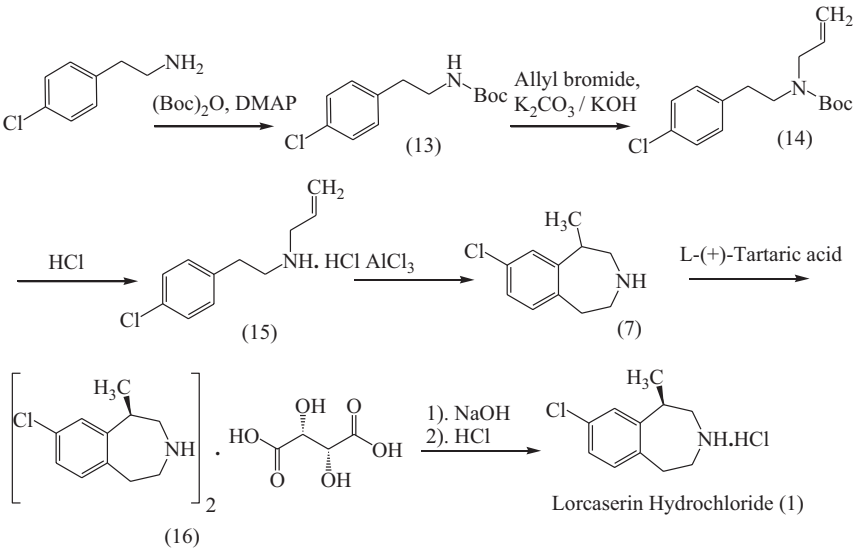
(i) The use of expensive condensation agent 3,4,5-trimethoxybenzene boronic acid and reducing agent borane
(ii) Large amounts of acid waste generated from thionyl chloride
(iii) Hazardous procedures
(iv) Lower yields of 11.6%

Even though method 2 (Smith et al. 2005) was comparatively shorter, high-temperature reactions using large amounts of aluminium chloride, employing toxic and expensive borane and overall lower yield of 7.2%, were the disadvantages.

In the other two asymmetric synthesis approaches (method 3 and method 4) (Stavber et al. 2014a, b), millimole-scale synthesis involving chiral ligands and flash chromatographic purifications are the disadvantages. Methods 1–4 are not given here for brevity.

Given the above-mentioned issues related to the earlier reported protocols, rendering them unsuitable for scale-up, Qihua Zhu et al. (2015) from China Pharmaceutical University, Nanjing, China, explored a novel, convenient, economically feasible and scalable synthetic route for the preparation of lorcaserin hydrochloride (Scheme 11).

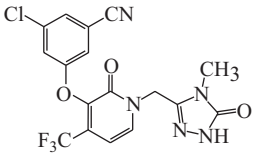
This procedure consisting of six steps starts from readily available and inexpensive 2-(4-chlorophenyl)ethanamine. The N-protected 2-(4-chlorophenyl)ethana-




**Scheme 11** Novel synthesis of lorcaserin hydrochloride (Modified after Qihua Zhu et al., oprd, 2015, 19, 1263–1267)
*$Boc_2O$* di-tert-butyl dicarbonate, *DMAP* 4-dimethylaminopyridine

mine (13) is alkylated with allyl bromide, and the deprotected intermediate is subjected to intramolecular Friedel-Crafts reaction with aluminium chloride to obtain 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (7), in 92.3% yield. It is further subjected to resolution with L(+)-tartaric acid, without purification to provide lorcaserin tartrate salt (16). The final product, lorcaserin hydrochloride (1), was obtained in an overall yield of 23.1% with 99.9% purity and > 99.8% enantiomeric excess.

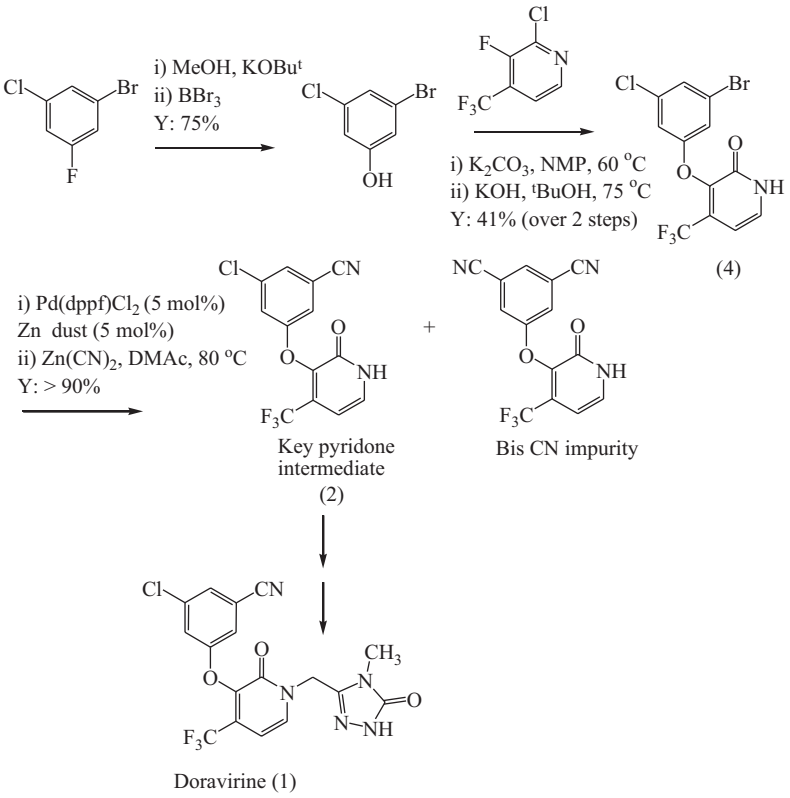
## *2.6 Doravirine*




Doravirine (1)

Doravirine (1), which is in phase III clinical trials, is a potential second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), useful for the treatment of HIV infection (Côté et al. 2014).

Louis-Charles Campeau et al. (2016) described a robust kilo-scale synthesis for the manufacture of doravirine. All the major impurities of the original process were

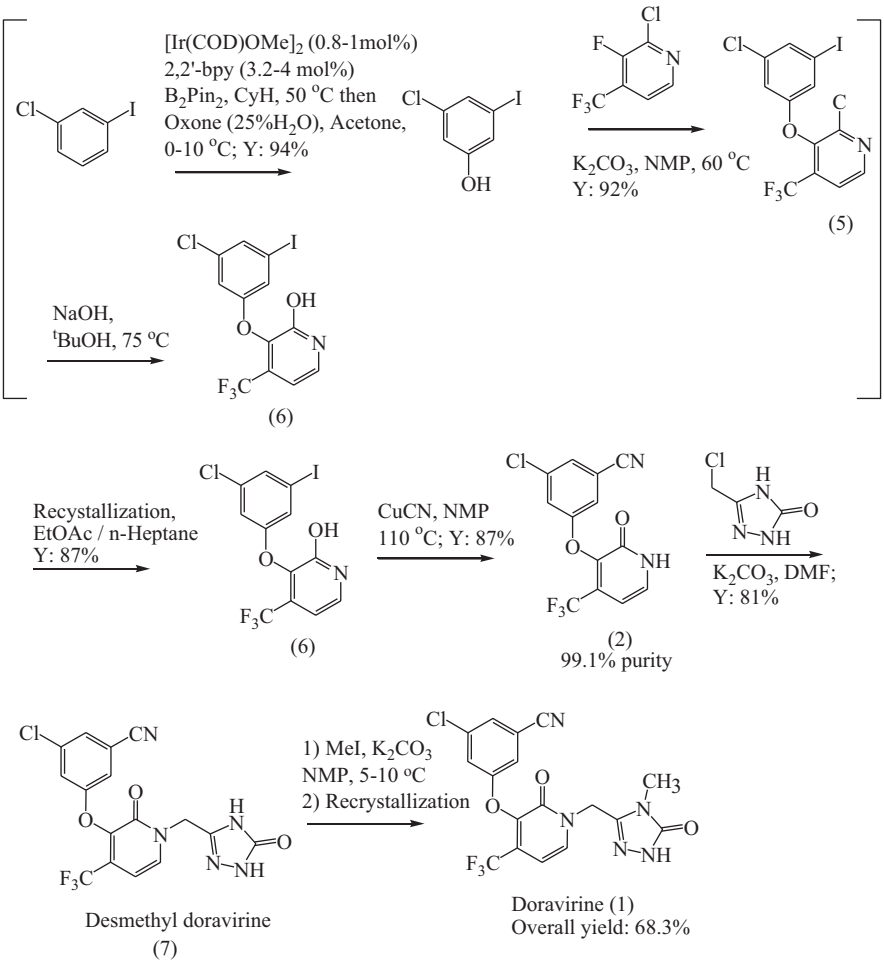



**Scheme 12** Original route for the preparation of doravirine (1) (Modified after Louis-Charles Campeau et al., oprd, 2016, 20, 1476–1481)
*NMP* N-methylpyrrolidone, *MeOH* methanol, *DMAc* dimethylacetamide, *Pd(dppf)Cl$_2$* [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

determined and controlled to an acceptable range by redesigning the approach by introducing key nitrile functionality via copper-mediated cyanation.

The major impurity, an obstacle for upscaling the first developed route, was identified as a bis-CN doravirine and was tracked to the upstream pyridone (2) synthesis. To critically limit the bis-cyano compound in the process, researchers are determined to develop an alternative approach to address the issue.

In the original synthesis (Scheme 12) to pyridone intermediate (2), the synthetic sequence started with 1-bromo-3-chloro-5-fluorobenzene to achieve differentiated substitution. 1-Bromo-3-chloro-5-fluorobenzene underwent selective aromatic nucleophilic substitution (SNAr) reaction with methoxide, affording an intermediate which was converted to phenol by $BBr_3$. Cyanation precursor (4) was obtained by two successive substitution reactions on 2-chloro-3-fluoro-4-trifluoromethyl pyridine. Key pyridine intermediate (2) was obtained by cyanation of (4) in the presence of palladium catalyst and zinc dust and $Zn(CN)_2$.

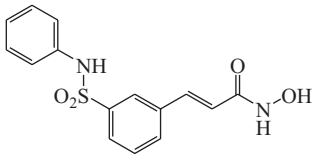



**Scheme 13** Improved synthesis of doravirine (1) (Modified after Louis-Charles Campeau et al., oprd, 2016, 20, 1476–1481)
*[Ir(COD)OMe]₂* bis(1,5-cyclooctadiene)di-μ-methoxydiiridium, *2,2′-bpy* 2,2'-bipyridyl, *NMP* N-methylpyrrolidone, *$B_2Pin_2$* bis(pinacolato)diborane, *CyH* cyclohexane, *NMP* N-methylpyrrolidone, *DMF* dimethylformamide, *MeI* methyl iodide

In the alternate approach (Scheme 13), as disclosed by Louis-Charles Campeau et al., pyridone (2) synthesis was achieved by starting from 3-chloro-5-iodophenol, which was coupled with 2-chloro-3-fluoro-4-trifluoromethylpyridine by carbonate-mediated aromatic nucleophilic substitution affording the product (5), in 91% yield. Intermediate (6) was prepared by the hydrolysis of (5) with NaOH in tert-butanol. Compound (6) underwent cyanation with CuCN in N-methylpyrrolidone (NMP) providing full conversion to (2) in 87% yield with 99.1% purity. This alternate, facile and efficient route was successful in that the

bis-cyano pyridine (2-CN) impurity was not detected. Pyridone (2) was alkylated with triazolinone chloride in presence of potassium carbonate in dimethylformamide to afford des-methyl doravirine (7) in 81% yield, which was methylated to provide doravirine (1) by treating with methyl iodide/potassium carbonate in N-methylpyrrolidone. Recrystallization from N-methylpyrrolidone-ethanol resulted in 99.1% pure doravirine in 68.3% yield, limiting other minor impurities. The scale-up has provided material on >90 Kg batches of final API. This scalable, economically viable and robust process, reported by authors, was very much useful for the manufacturing of doravirine.

## *2.7 Belinostat*

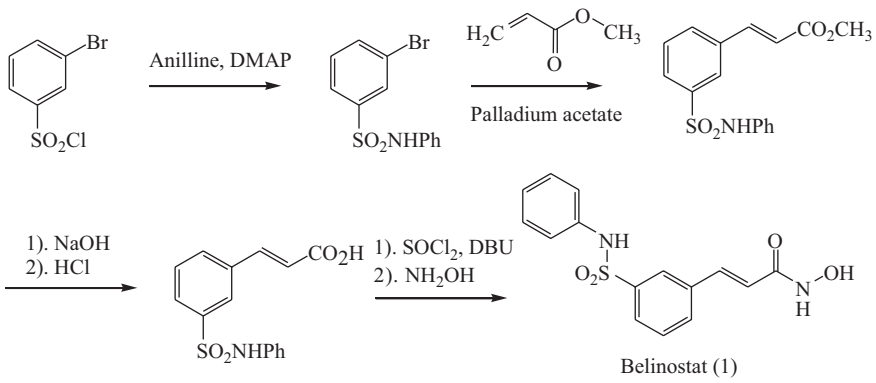



Belinostat (1)

Belinostat (1), a small-molecule histone deacetylase (HDAC) inhibitor, approved in the United States in 2014 for the treatment of relapsed or refractory peripheral T-cell lymphoma, was developed by CuraGen/TopoTarget (Lee et al. 2015). It was also in clinical trials and development stage for cutaneous T-cell treatment, other T-cell non-Hodgkin's lymphomas (NHL) and thymic epithelial tumours (Foss et al., 2015; O'Connor et al. 2015; Thomas et al. 2014).

Several research-scale synthetic methods were reported for obtaining belinostat (1). In the initial method reported by Finn et al. (2005) and Watkins et al. (2005), the starting material benzaldehyde was sulfonylated with oleum followed by a six-step reaction sequence affording the title compound (1) in an overall yield of 12%. In another method disclosed by Qian et al. (2012), the product (1) was obtained in an overall yield of 13% in a six-step process starting from sodium 3-sulfobenzoic acid. Both the routes suffered from tedious workup procedures, low yields and long reaction sequences. Another approach described by Yang et al. (2010) started from 3-nitrobenzaldehyde and involved diazotization and sulfonylation to obtain compound (1) in an overall yield of 33%. The process evolved by Wang et al. (2016) utilized conventionally unavailable 3-formyl-N-phenyl-benzenesulfonamide. Even though the scale-up synthesis of compound (1) by Reisch et al. (2009) was high yielding, the protocol also involved commercially non-available starting material and expensive palladium acetate.

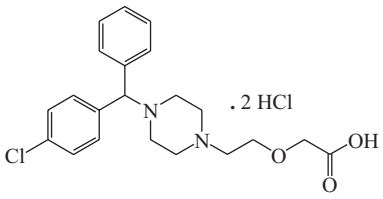
The manufacturing process developed based on Qian's method also suffered from drawbacks such as low yields (21.6%), tedious procedures, long reaction sequence and use of expensive oxidant (Scheme 14) (Luo et al. 2015).




**Scheme 14** Reported large-scale synthetic route of belinostat (Modified after Xuefei Bao et al., oprd, 2016, 20, 1482–1488)
*DMAP* 4-dimethylaminopyridine, *DBU* 1,8-diazabicyclo[5.4.0]undec-7-ene

After several investigative studies, Xuefei Bao et al. (2016) from Shenyang Pharmaceutical University, China, developed a facile and effective scale-up process for belinostat (1) starting from easily available starting materials, benzaldehyde and aniline in five linear steps reaction sequence (Scheme 15). Sodium bisulfite adduct of benzaldehyde was reacted with chlorosulfonic acid in presence of $K_2SO_4$ to yield 3-formyl-benzenesulfonyl chloride (4), which was further reacted with aniline in presence of pyridine to provide 3-formyl-N-phenyl-benzenesulfonamide (5) in 93% yield. Compound (5) was subjected to Knoevenagel condensation with malonic acid, followed by conversion to an acid chloride, and the reaction of it with hydroxylamine provided belinostat in 66% yield (overall yield being ~ 33%).

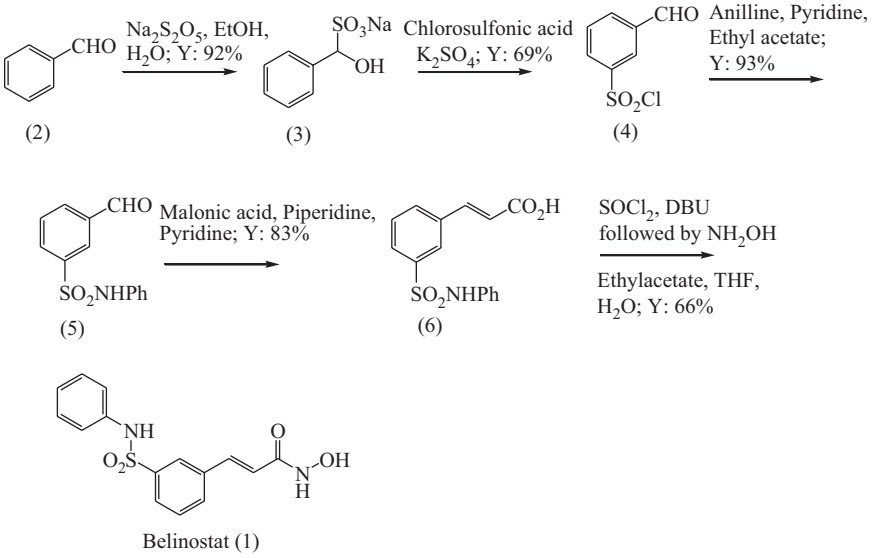
## 2.8 *Cetirizine Dihydrochloride*




Cetirizine dihydrochloride (1)

Cetirizine dihydrochloride (1), a non-sedating antihistamine, is extensively used in the treatment of allergic syndromes. Various methodologies were reported in the literature for the synthesis of compound (1).

In the original synthesis (Baltes et al. 1983), compound (1) was obtained by the alkaline hydrolysis of (2a/2b), which were prepared by the N-alkylation of




**Scheme 15** Novel and effective synthetic route of belinostat (Modified after Xuefei Bao et al., oprd, 2016, 20, 1482–1488)
*DBU* 1,8-diazabicyclo[5.4.0]undec-7-ene, *THF* tetrahydrofuran

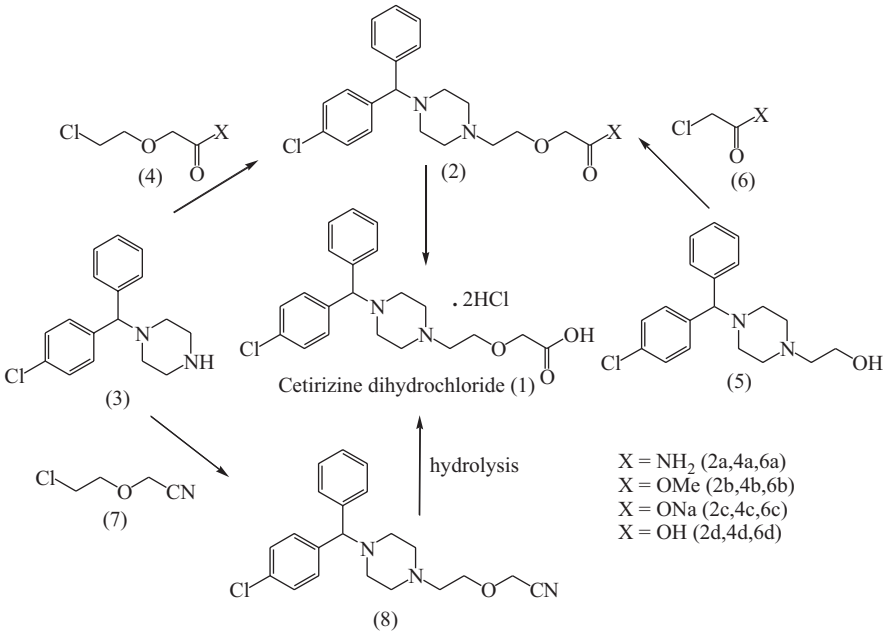
1-[(4-chlorophenyl(phenyl)methyl]piperazine (3) with 2-(2-chloroethoxy)acetamide (4a) or methyl 2-(2-chloroethoxy)acetate (4b). Compounds (2a/2b) can also be synthesized by the O-alkylation route as shown in Scheme 16. The overall yields are low.

In another approach (Cossement et al. 1990a), 2-(2-chloroethoxy)acetonitrile (7) was reacted with compound (3) to yield intermediate (8) which on hydrolysis provided compound (1). Isolation and purification of the intermediate (8) were possible only by column chromatography (Scheme 16).

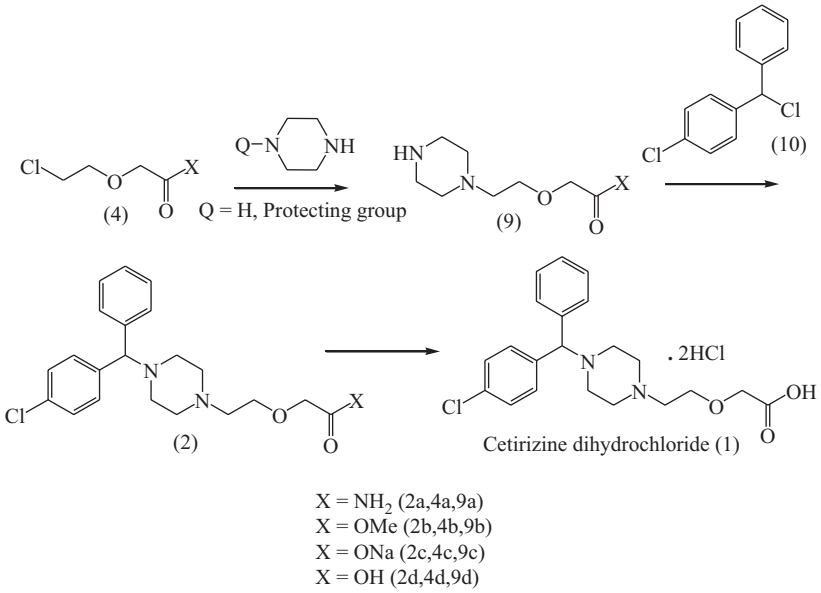
Cetirizine (2d) was also produced (Cossement et al. 1990b) by the reaction of alcohol (5) with sodium chloroacetate (6c) in the presence of potassium tert-butoxide and further acidification of (2c) (Scheme 16).

Further improvement (Bobrowska et al. 1995) for the above process was done by reacting alcohol (5) with chloroacetic acid (6d) in presence of alkali metal oxide and phase transfer catalyst (PTC) in a biphasic system. In another report (Fairfax et al. 2001), O-alkylation of compound (5) with base and phase transfer catalyst, followed by hydrolysis of ester, was reported, involving more steps without isolating the intermediate. In an alternate strategy for compound 1, aliphatic side chain was introduced into piperazine ring before the benzhydryl group (Scheme 17).

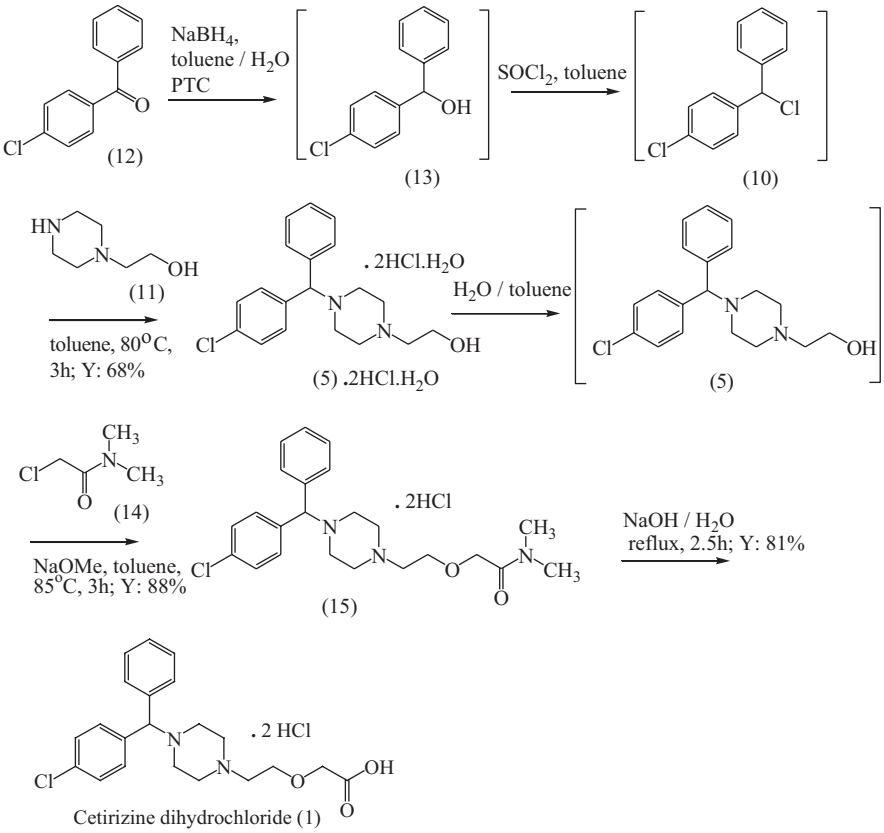
A new, efficient and improved manufacturing process (Scheme 18) for cetirizine dihydrochloride (1) was developed and described by Josef Reiter et al. (2012) via a new intermediate 2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazine-1-yl} ethoxy)-N,N-dimethylacetamide dihydrochloride (15) prepared by O-alkylation of




**Scheme 16** Reported synthetic schemes of cetirizine dihydrochloride (Modified after Jozsef Reiter et al., oprd, 2012, 16, 1279–1282)



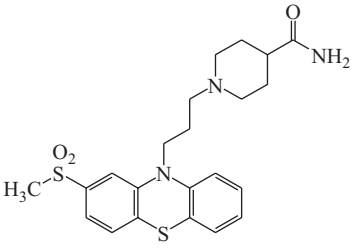

**Scheme 17** Alternate strategy for the preparation of cetirizine dihydrochloride (Modified after Jozsef Reiter et al., oprd, 2012, 16, 1279–1282)




**Scheme 18** Improved manufacturing process for the synthesis of cetirizine dihydrochloride (Modified after Jozsef Reiter et al., oprd, 2012, 16, 1279–1282)

2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazine-1-yl}ethanol (5) with 2-chloro-N,N-dimethylacetamide (14). Compound (5) was prepared in an improved technology from 4-chlorobenzophenone, which is reduced with sodium borohydride in a system containing toluene, water and phase transfer catalyst (methyltrioctylammonium chloride), and without isolation of the product, it was chlorinated with thionyl chloride. The resulting 4-chlorobenzhydryl chloride (10) without isolation was reacted with N-(2-hydroxyethyl)piperazine (11) to obtain (5) 2HCl**.**$H_2O$ in 68% yield with 99.7% purity. Finally, alkaline hydrolysis of amide (15) and further salification provided compound (1), in this scale-up synthesis in higher yields and purity.

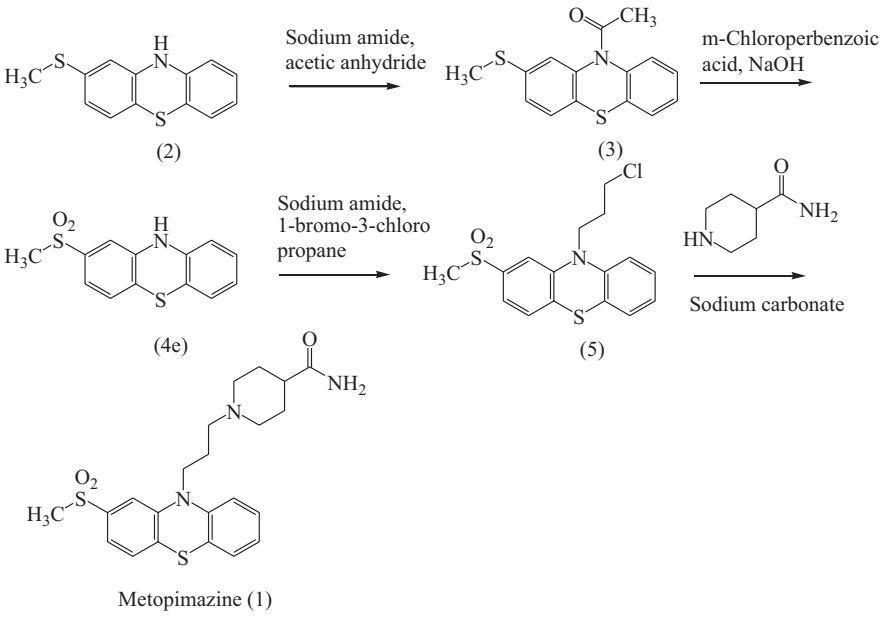
## 2.9 *Metopimazine*



Metopimazine (1)

Metopimazine (1) is a dopamine $D_2$ receptor antagonist with potent antiemetic properties, used to prevent emesis during chemotherapy and also plays a key role as an alternative to ondansetron.

After the initial synthesis by Bernthsen (1883), various approaches for the preparation of compound (1) were reported (Knoevenagel 1914; Massie 1954). Jacob and Robert (1959) disclosed the first manufacturing process (Scheme 19) starting from the protection of 2-(methylsulfonyl)-10H-phenothiazine. The method suffers from complications due to formation of by-products.

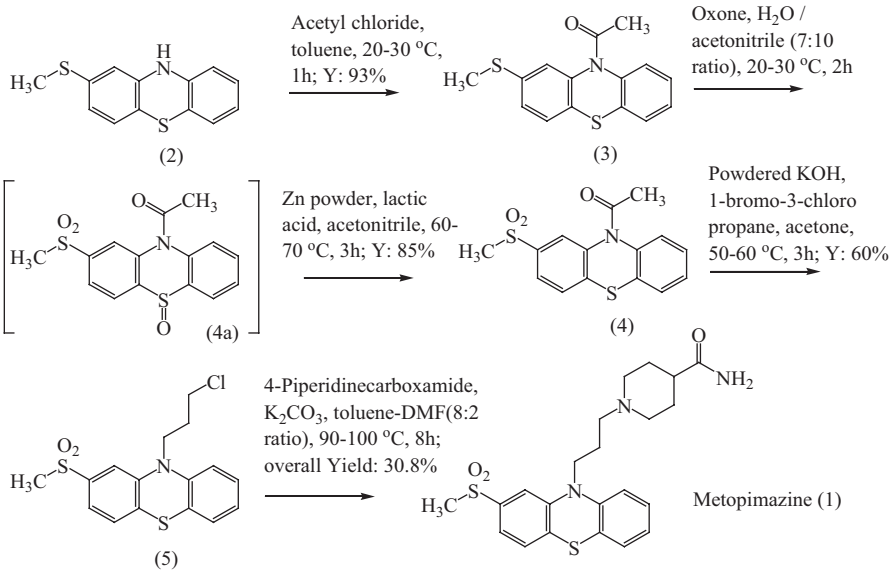



**Scheme 19** First synthesis of metopimazine (1) (Modified after Venumanikanta Karicherla et al., oprd, 2017, 21, 720–731)

Sindelar's process starts from 2-fluorothiophenol and 4-chloro-3-nitrophenyl methyl sulfone. The disadvantages of this route are harsh reaction conditions, lower yields and non-viability for scale-up (Sindelar 1990). Satyanarayana Reddy et al. (2011) reported a modified approach, which starts from N-acetyl phenothiazine derivative. The process suffers from the disadvantage of using ammonium molybdate, a hazardous chemical, chloroform (Class 2 solvent), etc. and lower yields. Significantly, these reported methodologies have the disadvantages of a) use of toxic catalysts and reagents, b) overall lower yields, c) non-satisfactory evaluation of impurity profiles, d) inadequate study of intermediates as well as by-products and e) inadequate optimization studies.

Venumanikanta Karicherla et al. (2017) described a practical, commercially viable and efficient manufacturing process for metopimazine with 99.7% purity and 31% overall yield, compared to the earlier yields of lower than 15%. According to the authors, for the first time, the entire characterization data of metopimazine (1), its intermediates and all the impurities were disclosed, and all the related issues were addressed, after conducting exhaustive studies for each step. The process involves two in situ one-pot methodologies (Scheme 20).

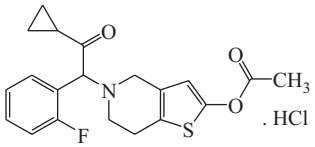
This route starts from compound (2), which is acetylated with acetyl chloride in toluene at 20–30 °C, to obtain compound (3) in 93% yield. The N-acetylated compound (3) is oxidized with non-toxic, stable, economical and green oxidizing agent, Oxone, in water and acetonitrile at 20–30 °C. The successive in situ selective reduction using zinc-lactic acid, an eco-friendly, biodegradable green reagent, resulted in compound (4) in 85% yield. The deprotection and in situ alkylation of




**Scheme 20** Improved process for the synthesis of metopimazine (1) (Modified after Venumanikanta Karicherla et al., oprd, 2017, 21, 720–731)

compound (4) with 1-bromo-3-chloropropane in the presence of powdered potassium hydroxide gave compound (5). In the final step, compound (5) is condensed with 4-piperidinecarboxamide in presence of potassium carbonate to obtain compound (1) in an overall yield of 30.8%. During the process, one-pot method is developed by the authors for the oxidation and selective reduction, for which exhaustive studies were conducted for screening and finding suitable oxidizing agent; reducing agent, solvents and reaction conditions; and minimizing the formation of by-products. An improved yield of 85% of compound (4) was observed over existing methodologies, with the modified zinc-lactic acid-acetonitrile system.

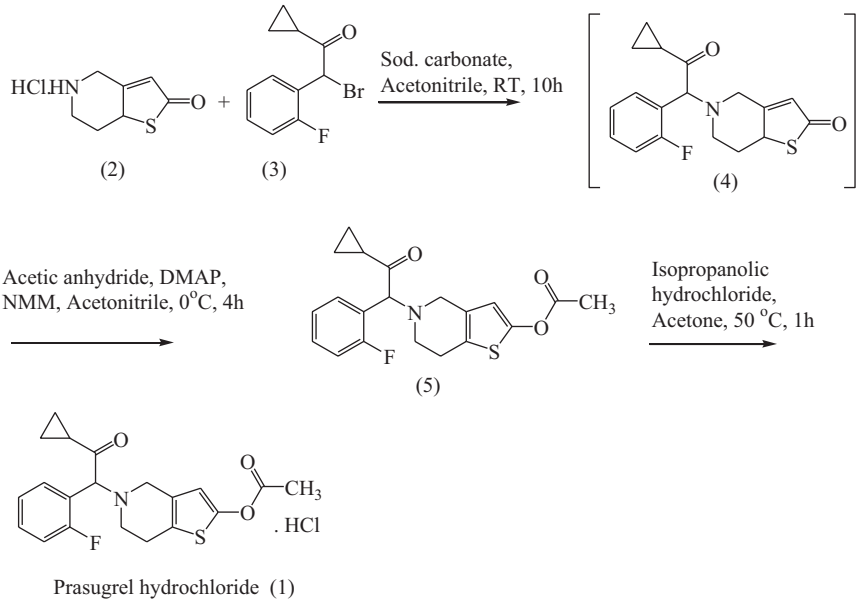
## *2.10 Prasugrel Hydrochloride*




Prasugrel hydrochloride (1)

Prasugrel hydrochloride (1), a new platelet inhibitor, was developed by Daiichi Sankyo and co. for acute coronary syndrome. Like ticlopidine and clopidogrel, prasugrel belongs to thienopyridine class of adenosine diphosphate receptor inhibitor. In literature, various strategies were reported for the synthesis of (1) (Koike et al. 1994; Ataka et al. 1999; Srinivas et al. 2009; Reddy et al. 2010; Mubeen et al. 2010; Zhu 2009). However, many processes follow the N-alkylation of thienopyridine derivative (2) with cyclopropyl ketone derivative (3) followed by acetylation and salt formation, wherein they involve tedious isolation, extraction and other workup procedures, resulting in overall lower yields and purities. In a communication, Sampath Aalla et al. (2012a) described an improved, redesigned and commercially viable process for (1), with an overall yield of 58% and purity of 99.9%, starting from N-alkylation of thienopyridine derivative, using commercially available materials (Scheme 21).

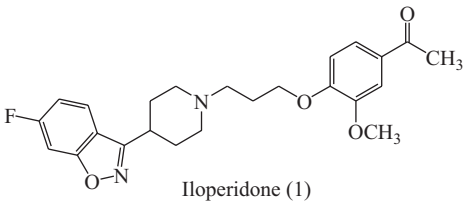
After exhaustive screening studies, the authors reported that the yield of N-alkylated derivative (4) seems to be encouraging when performed in acetonitrile in the presence of sodium carbonate. Next step of acetylation was carried out without isolating the compound (4), by adding acetic anhydride in presence of 4-dimethylaminopyridine and N-methylmorpholine. The product, prasugrel base, was simply achieved by the addition of water, recrystallization and converting to hydrochloride salt (1), with isopropanolic hydrochloride in place of aqueous HCl, by which formation of impurity, desacetyl prasugrel, was significantly reduced. The authors also observed that the concentration of isopropanolic hydrochloride, as well



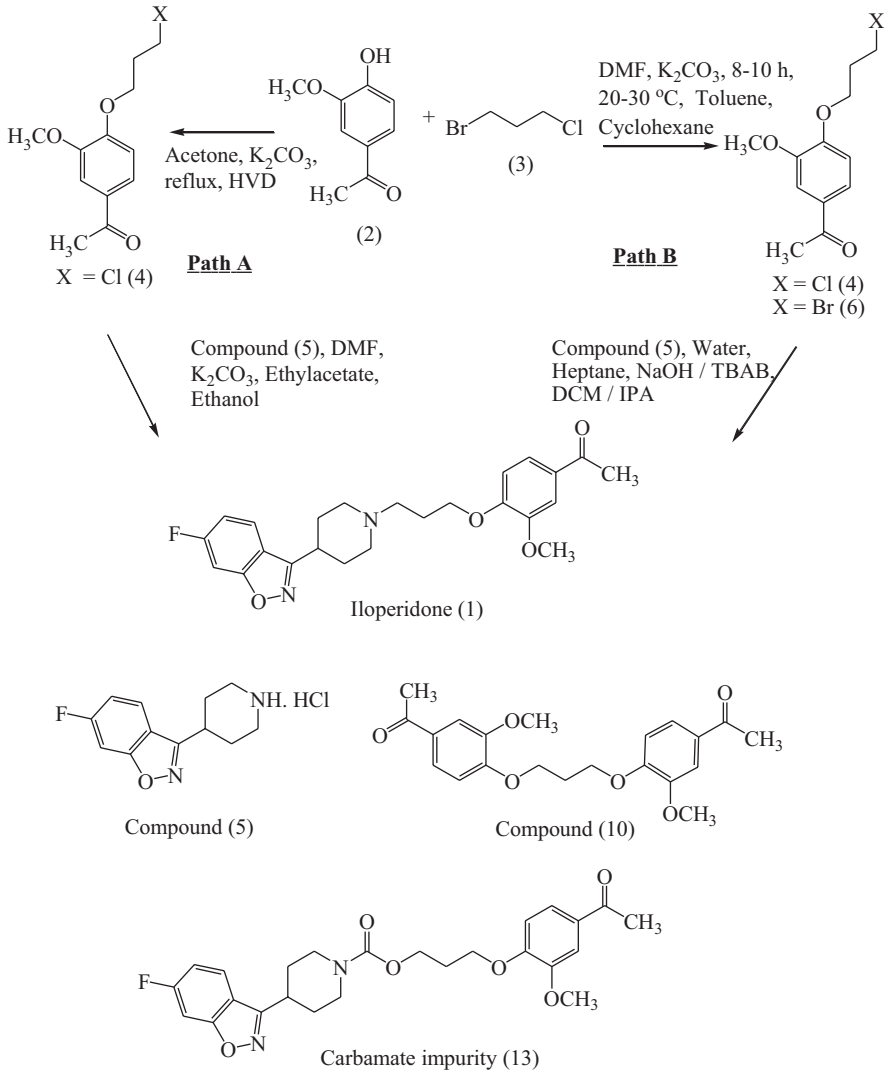

**Scheme 21** Synthetic scheme for prasugrel hydrochloride (Modified after Sampath Aalla et al. oprd, 2012a, 16, 240–243)
*DMAP* 4-dimethylaminopyridine, *NMM* N-methylmorpholine

as reaction temperature, influences the purity of the product. Hence, the parameters were well studied to achieve the target, meeting all the quality requirements.

## *2.11 Iloperidone*




Iloperidone (1), a second-generation atypical antipsychotic agent approved by FDA in 2009, is useful in the acute treatment of schizophrenia and acts as an antagonist at all tested receptors. The literature methods (Bjork et al. 1982; Strupczewski et al. 1990) (Scheme 22 – Path A) for the preparation of (1) mainly involve (a) O-alkylation of acetovanillone (2) with 1-bromo-3-chloropropane (3) in acetone in the presence of potassium carbonate affording compound (4) and (b) N-alkylation of piperidine

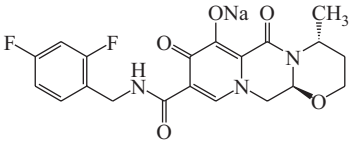



**Scheme 22** Reported synthetic scheme (Path A) and improved process (Path B) for iloperidone (Modified after Pavankumar V. Solanki et al., oprd, 2014, 18, 342–348)
*DCM* dichloromethane, *DMF* dimethylformamide, *IPA* isopropyl alcohol, *TBAB* tetrabutylammonium bromide, *HVD* high vacuum distillation

intermediate (5) with (4) in DMF in the presence of potassium carbonate. The disadvantages associated with the above are (a) longer reaction times and the formation of dimer impurity (6–7%) (10) in the first step and (b) lower yields, formation of carbamate impurity (13) (15–20%), coloured product formation and imperfect purification.

Even though some improvements were reported later to the above process, impurity formations could not be controlled and addressed (Ansari et al. 2012; Azad et al. 2012; Dwivedi et al. 2012; Athalye et al. 2012; Raman et al. 2011; Reguri et al. 2011; Shiwei and Feng 2012; Bettoni et al. 2013). In a recent communication, Pavan Kumar V. Solanki et al. (2014) described an improved, efficient, commercially viable and high-yielding approach for the preparation of (1) in an overall yield of 82% and purity of 99.8% (Scheme 22 – Path B). The product is substantially free from impurities, as claimed by the authors, by performing phase transfer catalyzed N-alkylation of (5) with (4) in water/heptane in the presence of sodium hydroxide. As per the communication, the formation of the impurities was eliminated or controlled to acceptable levels. To control all the process-related impurities, the processes were checked by extensive optimization studies, involving solvents, bases, mole ratios and proper selection of other conditions.

## *2.12 Dolutegravir Sodium*



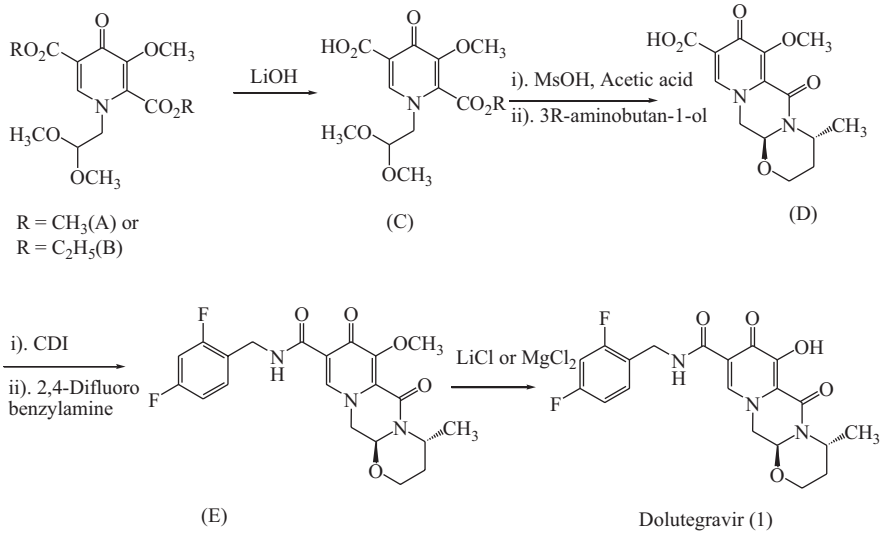

Dolutegravir (1) Sodium

Integrase strand transfer inhibitors (INSTIs) are attractive drug targets for controlling the HIV infection, and dolutegravir (1) is an approved drug of choice for antiretroviral therapy. Though many synthetic routes were invented and applied for the synthesis of (1), including scale-up studies, they did not work on detailed impurity profiling as well as control strategies for them (Kawasuji et al., 2012, 2013; Johns et al. n.d.; Wang et al. 2015; Yoshida et al. n.d.; Sumino et al. n.d.).

The scalable approach (Scheme 23) starts from pyridine heterocyclic derivative and involves selective hydrolysis of diester (B) to half ester (C) which will be easier to isolate and purify as a salt (Goodman et al. n.d.). The phenolic group is protected in the form of ether.

An alternate, improved, high-yielding, four-stage and scalable strategy was reported by Srimurugan Sankareswaran et al. (2016) (Scheme 24) starting from benzyl-protected pyranone and dimethyl 3-(benzyloxy)-4-oxo-4H-pyran-2,5-dicarboxylate (2). The authors identified, synthesized and established the unknown process impurities and optimized the scale-up conditions while demonstrating the control procedures.

Pyran compound (2) was ring-opened with aminoacetaldehyde dimethyl acetal and converted to pyridinone (3), which reacted selectively with



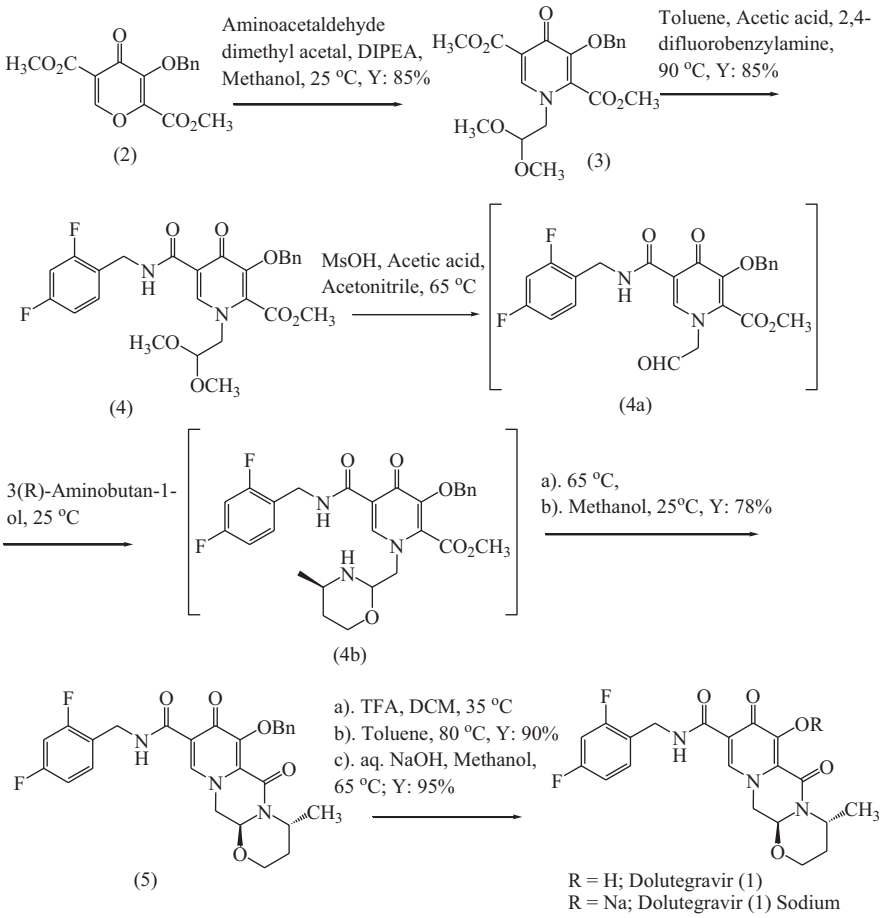

**Scheme 23** Reported route for the synthesis of dolutegravir. (Modified after Srimurugan Sankareswaran et al., oprd, 2016, 20, 1461–1468)
*MsOH* methanesulfonic acid, *CDI* N,N′-carbonyldiimidazole

2,4-difluorobenzylamine affording amidoester (4). Chiral hemiaminal (4b) was formed by acetal hydrolysis and reaction with 3R-aminobutan-1-ol. Critical substrate-controlled diastereoselective cyclization of (4b) resulted in benzyl-protected dolutegravir (5), which on debenzylation followed by salification provided sodium salt of dolutegravir (1). During step 1, two possible impurities were controlled by optimized process and by opting for diisopropylethylamine (DIPEA) instead of inorganic bases, to form compound (3) in good yield.

Attempts at in situ conversion of compound (3) to compound (4) and portion-wise addition of 2,4-difluorobenzylamine and effective crystallization of (4) with isopropyl alcohol afforded pure compound (4), in good yields devoid of impurities.

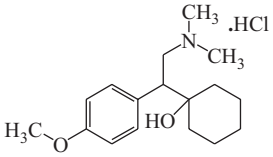
Fine-tuning of reaction temperatures, mole equivalents of methane sulfonic acid and its portion-wise addition lead to (4a), controlling impurities. The authors further proceeded to the next step of the reaction with 3R-aminobutan-1-ol to yield hemiaminal (4b) without isolation of (4a).

Benzyl-protected dolutegravir (5) was obtained by careful optimization process, in which compound (4b) underwent cyclization with ester functionality. Select solvent system and proper identification of de-benzylating agent, trifluoroacetic acid, afforded impurity-free compound (6), which on treatment with aqueous sodium hydroxide at reflux provided highly pure sodium salt of dolutegravir (1), with an overall yield of 57%.

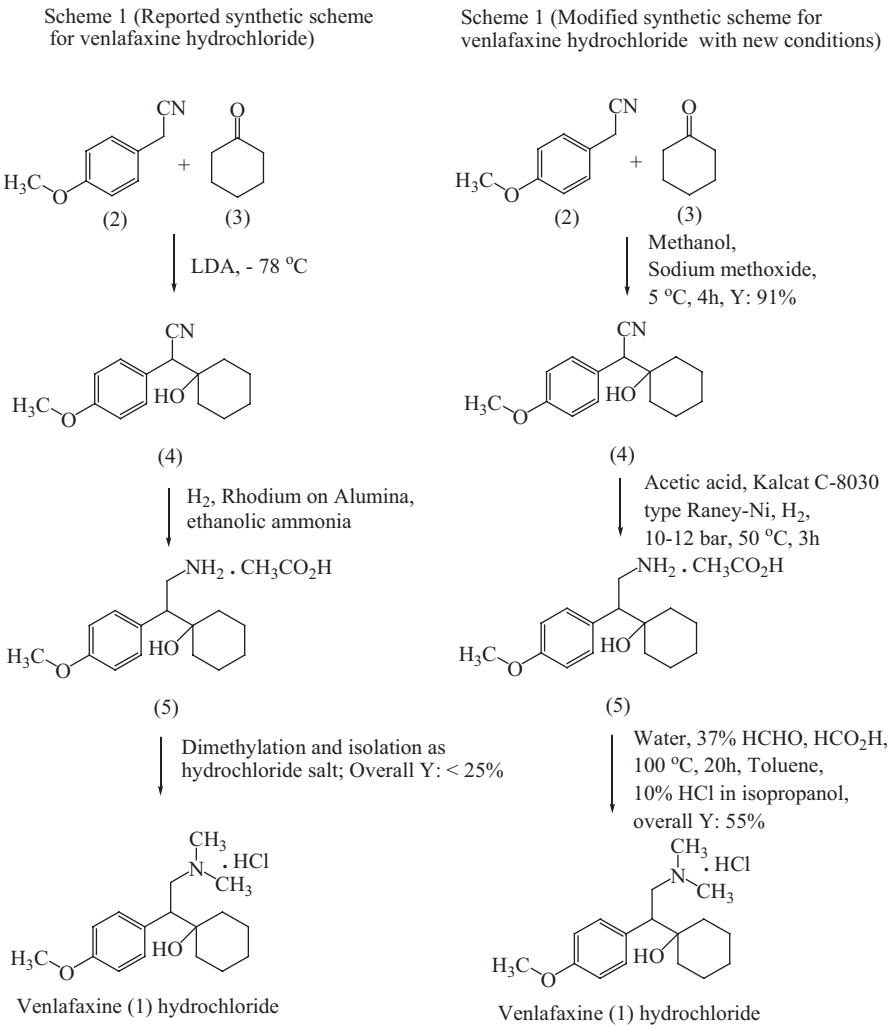



**Scheme 24** Optimized route for the synthesis of dolutegravir sodium. (Modified after Srimurugan Sankareswaran et al., oprd, 2016, 20, 1461–1468)
*MsOH* methanesulfonic acid, *DIPEA* diisopropylethylamine, *TFA* trifluoroacetic acid, *DCM* dichloromethane

## *2.13 Venlafaxine Hydrochloride*



Venlafaxine (1) hydrochloride




**Scheme 25** Reported synthetic scheme for venlafaxine hydrochloride and modified synthetic scheme for venlafaxine hydrochloride with new conditions. (Modified after Mohanarangam Saravanan et al., oprd, 2011, 15, 1392–1395)
*LDA* lithium diisopropylamide

Venlafaxine (1), developed by Wyeth Laboratories, with a cycloalkanol ethylamine scaffold, is a dual-acting serotonin and norepinephrine reuptake inhibitor (SNRI) useful in the treatment of depression and anxiety disorders.

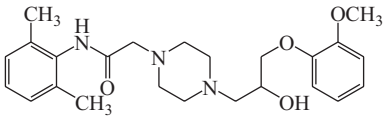
The first-described scalable approach is displayed in Scheme 25 (Morris Husbands et al. 1985; Yardley et al. 1990). In this strategy, 4-methoxy phenyl acetonitrile (2) undergoes nucleophilic addition with cyclohexanone (3) in presence of lithium diisopropylamide (LDA) at −78 °C providing compound (4), which on

hydrogenation with rhodium on alumina in ethanolic ammonia yielded compound (5). Venlafaxine is obtained in an overall yield of <25% after the last step of methylation. The disadvantages of the process are (a) reaction at very low temperatures, such as −78 °C; (b) use of expensive reagent rhodium on alumina in excess quantity; (c) use of industrially unfavourable and pyrophoric materials such as lithium diisopropylamide and n-BuLi; (d) end product that is associated with several impurities, requiring a lot of purifications; and (e) lesser overall yield. Few more routes are reported, involving tedious processes and expensive reagents (Chavan et al. 2004, 2007; Basappa et al. 2004; Burgos et al. 2008; Dhiraj et al. 2004).

Mohanarangam Saravanan et al. (2011) developed an improved, impurity-free, cost-effective and large-scale strategy for the synthesis of venlafaxine hydrochloride with an overall yield of 55% and purity of 99.9% (Scheme 25, a modified synthetic scheme under new conditions).

Even though this route also starts from compound (2) and compound (3), the initial step is performed with sodium methoxide in methanol at 5 °C instead of lithium diisopropylamide at −78 °C, providing compound (4) in 91% yield with 99% purity. Avoiding cryogenic conditions, the authors also simplified the work-up procedure in this step. It is reported that replacing rhodium on alumina with economical and reusable Kalcat C 8030-type Raney nickel/acetic acid for hydrogenation and simplified work-up procedures led to the minimization of impurities in this methodology. Besides, the authors also adopted low catalyst loadings in this step, along with other optimization studies, isolating compound (5) as an acetate salt. The latter compound on treatment with $HCO_2H$, HCHO and $H_2O$ at 100 °C provided venlafaxine (1) as hydrochloride salt in 82% yield and 99.9% purity after the possible impurities are removed by washing with dichloromethane, basified and converted to hydrochloride salt with 10% HCl in isopropyl alcohol.

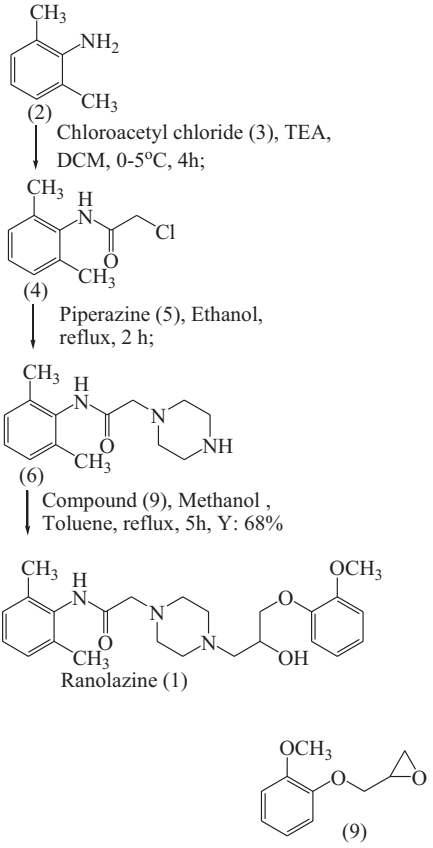
## 2.14 Ranolazine




Ranolazine (1)

Ranolazine (1), developed by Syntex, a new cardioselective and metabolism-regulating antianginal drug, is useful in the treatment of myocardial infarction, angina, arrhythmia and congestive heart diseases (Allely and Alps 1988; Hale and Kloner 2006; Fraser et al. 2006; Jerling 2006).

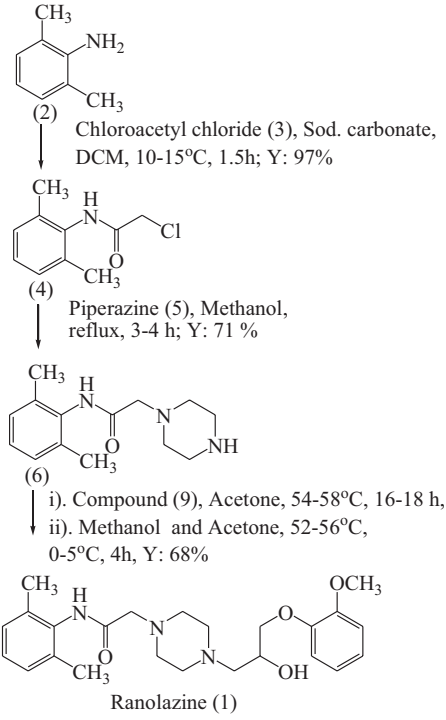
Among different approaches available for its synthesis, the methodology that starts with piperazine derivative (6) and epoxy derivative (9) is the popular one (Scheme 26) (Kluge et al. 1986, 1987a, b, Eva et al. 1992; Lisheng et al. 2003; Shuchun et al. 2003; Xiao-lin and Yong-zhou 2004; Rahul et al. 2008). However, root




**Scheme 26** Reported synthetic scheme for ranolazine (Modified after Sampath Aalla et al., oprd, 2012b, 16, 748–754)

causes and control measures, as well as profiling of process impurities, were not thoroughly discussed and established satisfactorily.

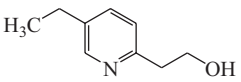
In an interesting article, Sampath Aalla et al. (2012b) described an improved and scalable process for (1) with 47% overall yield and purity of 99.9% starting from chloroacetylation of 2,6-dimethylaniline with chloroacetyl chloride in dichloromethane solvent in presence of sodium carbonate (Scheme 27). Chloroacetylated product (4) was obtained in 97% yield and purity of 99.8%. Compound (6) was prepared in 71% yield, with 99.6% purity, by adopting new process conditions for the N-alkylation of piperazine (5) with compound (4) using methanol as medium and three mole ratio for compound (5). Piperazine content was reduced to 0.01% level by appropriate purification procedures of compound (6) by salt formations and conversion to the free base. Finally, the reaction between compound (6) and epoxy derivative (9) was performed in refluxing acetone to afford good yields with 99.92% purity. The authors also determined proper crystallization parameters for compound (1).



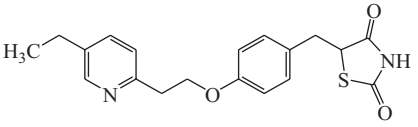

**Scheme 27** Synthetic scheme for ranolazine with new conditions (Modified after Sampath Aalla et al., oprd, 2012b, 16, 748–754) *TEA* trimethylamine, *DCM* dichloromethane

Origin and identification of impurities were established for each step. Moreover, appropriate solvent selection, molar ratio modifications, altering reaction conditions and changes in work-up procedures resulted in high-yielding redesigned process with minimized impurity profiles.

## *2.15 Improved and Scalable Process for 2-(5-Ethylpyridin-2-yl)Ethan-1-ol (Pioglitazone Intermediate)*



2-(5-Ethylpyridin-2-yl) ethane-1-ol (1)



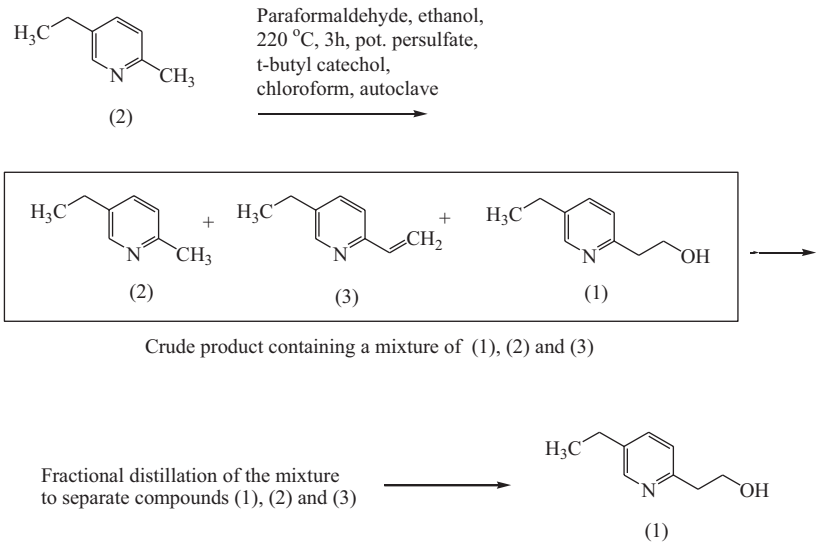
Pioglitazone

2-(5-Ethylpyridin-2-yl)ethan-1-ol (1) is one of the critical intermediates of the drug, pioglitazone, used in the chronic management of diabetes mellitus type 2.

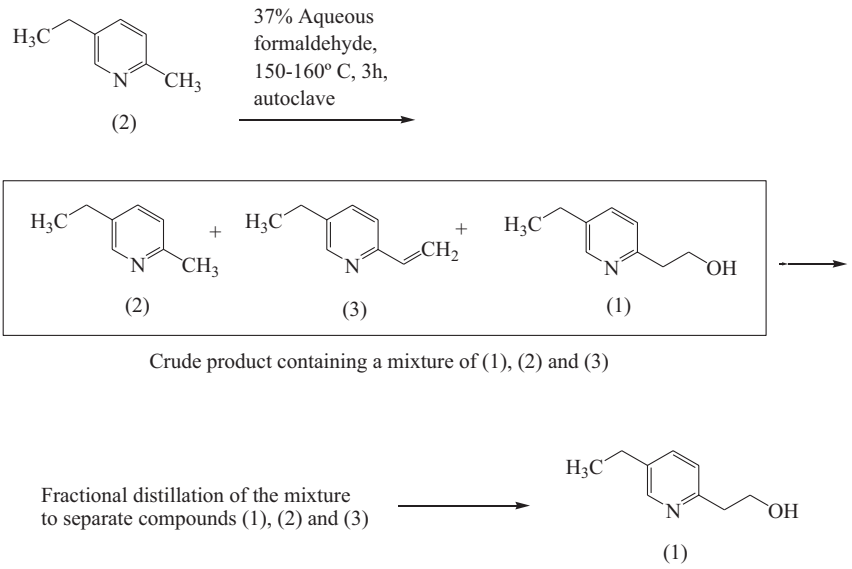
In one of the synthesis, for the preparation of 2-(5-ethylpyridin-2-yl)ethan-1-ol (1), a key intermediate in the synthesis of pioglitazone, 5-ethyl-2-picoline (2), was reacted with paraformaldehyde in presence of potassium persulfate and tert-butyl catechol in ethanol at 220 °C to obtain compound (1) in 21% yield, along with 42% recovery of the starting material and 10% formation of the by-product, 5-ethyl-2-vinylpyridine (3) (Scheme 28). High reaction temperatures, use of chlorinated solvent and potassium persulfate reagent with tert-butyl catechol as catalyst are the disadvantages in this process on a larger scale (Robert et al. 1946).

In an interesting research article, Sandeep Mohanty et al. (2014) revealed a newly developed, improved and scalable process for 2-(5-ethylpyridin-2-yl) ethan-1-ol (1) in a solvent-free reaction, by recycling starting material 5-ethyl-2-picoline (2).

In the present efficient and cost-effective approach, the authors claim a green process with improved yields by conducting the reaction at lower temperatures, with an additional advantage of recovery and recyclability of the starting material (2) and low generation of waste on a larger scale. The process was improved, by replacing paraformaldehyde/ethanol with commercially available 37% aq. formaldehyde, devoid of any other organic co-solvent, and by totally avoiding potassium persulfate reagent and tert-butyl catechol catalyst. Several parameters, like formaldehyde equivalents, temperature, reaction time and recovery and recycling of starting material, were optimized to obtain the desired product, increasing the overall productivity by 27% (Scheme 29). The authors also claim that the total effluent load generated by their process is 75% lower than the other route, proving the eco-friendly advantage of the approach.

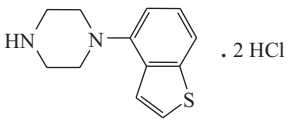



**Scheme 28** Reported synthetic route for 2-(5-ethylpyridin-2-yl)ethan-1-ol (1). (Modified after Sandeep Mohanty et al., oprd, 2014, 18, 168–173)

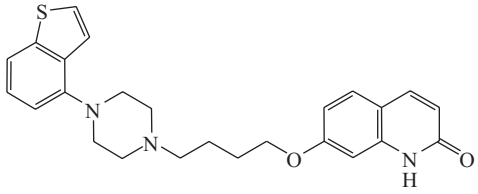



**Scheme 29** Improved and scalable process for 2-(5-ethylpyridin-2-yl)ethan-1-ol (1) (Modified after Sandeep Mohanty et al., oprd, 2014, 18, 168–173)

## *2.16 Synthesis of 4-(1-Piperazinyl)Benzo[b]thiophene Dihydrochloride (Brexpiprazole Intermediate)*



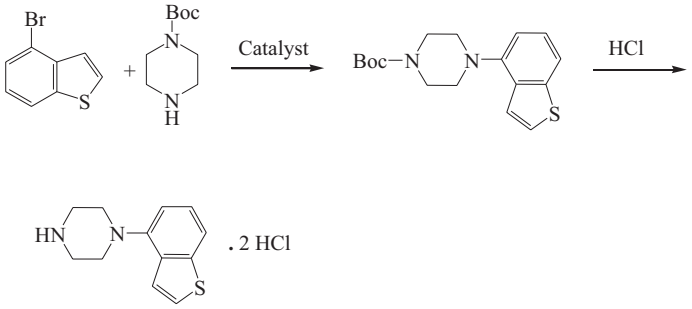

4-(1-Piperazinyl)benzo[b]thiophene dihydrochloride (1)




Brexpiprazole

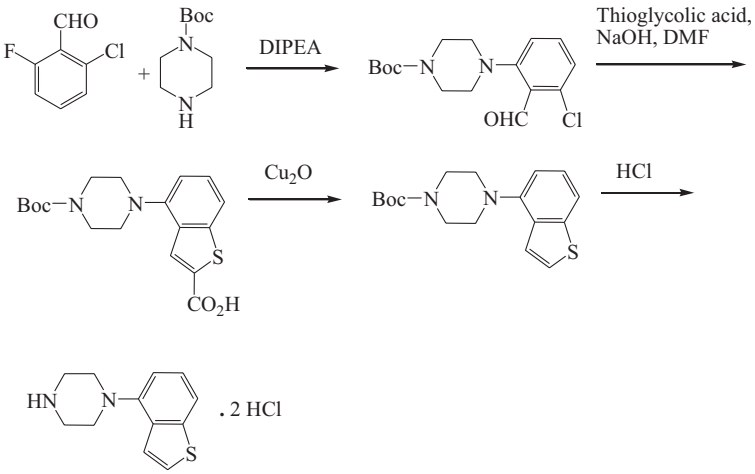
4-(1-Piperazinyl)benzo[b]thiophene dihydrochloride (1) is an intermediate for brexpiprazole, an investigational new drug currently in phase III clinical trials for the treatment of depression, schizophrenia and attention deficit hyperactivity disorder. Compound (1) was originally synthesized by Yamashita et al. (2006) starting from 4-bromobenzo[b]thiophene and unprotected piperazine using tris(dibenzylideneacetone)dipalladium as catalyst, with the formation of some impurities. Later, Shinhama et al. (2013) proposed alternate method (Scheme 30) using protected piperazine and expensive catalyst, to minimize impurities.

Chunhui Wu et al. (2015) developed an improved, scalable and cost-effective synthetic route to compound (1) with an overall yield of 54% and 99.8% purity. The




4-(1-Piperazinyl)benzo[b]thiophene dihydrochloride (1)

**Scheme 30** Reported synthetic route for 4-(1-piperazinyl)benzo[b]thiophene dihydrochloride (1) (Modified after Chunhui Wu et al., oprd, 2015, 19, 555–558)




4-(1-Piperazinyl)benzo[b]thiophene dihydrochloride (1)

**Scheme 31** Improved synthetic route for 4-(1-piperazinyl)benzo[b]thiophene dihydrochloride (1) (Modified after Chunhui Wu et al., oprd, 2015, 19, 555–558)
*DIPEA* diisopropylethylamine, *DMF* dimethylformamide

route does not involve expensive catalysts or the formation of side products (Scheme 31). The present method starts with the reaction of 2-chloro-6-fluorobenzaldehyde with 1-tert-butoxy carbonyl piperazine in the presence of diisopropylethylamine. The product is cyclized with thioglycolic acid using sodium hydroxide in dimethylformamide to obtain 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)benzo[b]thiophene-2-carboxylic acid, which is treated with cuprous oxide in dimethylformamide to provide decarboxylated product in 85% yield, with excellent

purity of 98.7%. The latter compound, on treatment with excess hydrochloric acid, provided the desired compound (1) in 85% yield and 99.8% purity.

## 3 Conclusion

In conclusion, effort has been made to review greener aspects of scale-up synthesis from recently published literature to highlight various aspects of scale-up activity to familiarize the young process scientists with the intricacies of process development and guide them in understanding greener chemistry aspects. The examples highlighting these elements of greener aspects of scale-up synthesis are innumerable in literature, and the scope of this review is to introduce a few of those examples. The readers are advised to go through the original papers for more information. As a scale-up scientist, with an ambitious wish list, one needs to develop the best manufacturing process emphasizing the following features:

(i) The process for the target API should be economically viable with a shorter number of industrially feasible steps, following green chemistry aspects.
(ii) The reagents, fine chemicals, solvents and intermediates are so chosen that they are industrially acceptable, economical, environmental friendly, non-pyrophoric, non-mutagenic and readily available.
(iii) Each step in the process so chosen should be high yielding to contain environmental burden of the pollutants.
(iv) The various stages in the final manufacturing chemical scheme should have shorter periods avoiding larger occupation times for the reactors.
(v) Proper identification of the impurities and degradation products at each stage, their synthesis and thorough characterization must be carried out to guide the API manufacture.
(vi) Avoid extreme thermal conditions like too low or too high temperatures and high-pressure reactions, thus eliminating the use of highly specialized equipment and reactors for process viability during manufacture.
(vii) The purification processes of the intermediates and the final API should be simple, avoiding sophisticated procedures and chromatographic methods on a larger scale.
(viii) If the manufacturing process involves chiral API molecules, separation procedures for enantiomers and diastereomers should be simple, avoiding chiral chromatographic methods as it negates the feasibility of the process on a larger scale.
(ix) Extreme care and appropriate remedial measures should be taken concerning effluents from the manufacturing process, as they can pose environmental, fire and explosion hazards if let out untreated.

Thus, the wish list goes on for the process chemist, with an eye on developing the best viable manufacturing process, which is greener and environmental friendly, providing medicines economically for humanity at large.

**Acknowledgements** The review was authored purely out of academic interest to familiarize the young process scientists with the intricacies of process development and guide them in understanding green chemistry aspects of scale-up synthesis. The examples covered are chosen from *Organic Process Research and Development* journal in this review. The authors of this review are highly appreciative of the scale-up research articles published in *Organic Process Research and Development* for their in-depth analysis and discussion. The authors of this review further acknowledge the original contributors and publishers of the articles cited here for their contributions, with a larger interest for the well-being of humanity the world over.

## References

Aalla S, Gilla G, Metil DS, Anumula RR, Vummenthala PR, Padi PR. Org Process Res Dev. 2012a;16:240–3. https://doi.org/10.1021/op200325u.

Aalla S, Gilla G, Anumula RR, Kurella S, Padi PR, Vummenthala PR. Org Process Res Dev. 2012b;16:748–54. https://doi.org/10.1021/op300026r.

Adolfo M, Mario JS, Leonardo SS. Tetrahedron Lett. 2013;54:5096–8.

Allely MC, Alps BJ. Br J Pharmacol. 1988;93:375–82.

Andreas B. WO Patent 2006114202, 2006.

Ansari SA, Hirpara HM, Yadav AK, Gianchandani JP. WO2012164516, 2012.

Ataka K, Miyata H, Kohno M, Yokota N, Yamamoto Y. U.S. 5,874,581, 1999.

Athalye SS, Parghi KD, Ranbhan KJ, Sarjekar PB. WO2012/153341, 2012.

Azad MAK, Pandey G, Singh K, Prasad M, Arora SK. WO2012/090138 A1, 2012.

Baltes E, de Lannoy J, Rodrigez L. EP 0058146, 1982, Chemical Abstract. 1983; 98:34599r.

Xuefei Bao, Dake Song, Xuejun Qiao, Xuan Zhao, Guoliang Chen. Org Process Res Dev. 2016; 20:1482–1488. https://doi.org/10.1021/acs.oprd.6b00170.

Basappa, Kavitha CV, Rangappa KS. Bioorg Med Chem Lett. 2004;14:3279–81.

Bernthsen A. Ber Dtsch Chem Ges. 1883;16:2896.

Bettoni P, Roletto J, Paissoni P. EP 2644608A1, 2013.

Bjork AKK, Abramo AL, Kjellberg BES US 4366162, 1982.

Blumenkopf TA, Flanagan ME, Munchhof MJ. U.S. patent USRE41783E, 2010.

Bobrowska E, Stelmach P, Kalbarczyk E, Witkowska T. PL 163415, 1990, Chemical Abstract. 1995; 123:55923s.

Burbaum BW, Gilson CA, Aytes S, Estrada SA, Sengupta D, Smith B, Rey M, Weigl U. WO Patent 2005019179, 2005.

Burgos A, Tonnel J, Dambrin V, Lucet D, Poirier P. U.S. Patent 7,462,742 B2, 2008.

Louis-Charles Campeau, Qinghao Chen, Danny Gauvreau, Melina Girardin, Kevin Belyk, Peter Maligres, Guoyue Zhou, Chaozhan Gu, Wei Zhang, Lushi Tan, Paul D. O'Shea. Org Process Res Dev. 2016; 20:1476–1481. https://doi.org/10.1021/acs.oprd.6b00163.

Chavan SP, Kamat SK, Sivadasan L, Balakrishnan K, Khobragade DA, Ravindranathan T, Gurjar MK, Kalkote UR. Tetrahedron Lett. 2004;45:7291–5.

Chavan SP, Khobragade DA, Thakkar MT, Kalkote UR. Synth Commun. 2007;37:3901–6.

Chen M. China patent CN102180868, 2011.

Cossement E, Motte G, Bodson G, Gobert J. GB 2225321, 1990, Chemical Abstract. 1990a; 113:191396t.

Cossement E, Gobert J, Bodson G. GB 2225320, 1990, Chemical Abstract. 1990b; 113:191395s.

Côté B, Burch JD, Asante-Appiah E, Bayly C, Bédard L, Blouin M, Campeau L-C, Cauchon E, Chan M, Chefson A, Coulombe N, Cromlish W, Debnath S, Deschênes D, Dupont-Gaudet K, Falgueyret J-P, Forget R, Gagné S, Gauvreau D, Girardin M, Guiral S, Langlois E, Li CS, Nguyen N, Papp R, Plamondon S, Roy A, Roy S, Seliniotakis R, St-Onge M, Ouellet S, Tawa P, Truchon J-F, Vacca J, Wrona M, Yan Y, Ducharme Y. Bioorg Med Chem Lett. 2014; 24:917.

Dhiraj MR, Srinivasan R, Milind MG, Nishant MP, Mandar MD. U.S. Patent 6,756,502 B2, 2004.

Dwivedi SD, Patel DJ, Shah AP. WO2012/063269, 2012.
Ernest WG, Christian K, Ton V, Edward FM, Munchhof MJ. PCT WO 02096909, 2002.
Eva A–C, Tibor G, Kalman H, Ferenc T, Aniku D–S, Attila C, Eva V, Gyorgyi S–K. EP 0,483,932 A1, 1992.
Fairfax DJ, Hemandez PE, Michalson ET. US 6265579, 1999, Chemical Abstract. 2001; 134:340523.
Feng J, Gwaltney SL, et al. Dipeptidyl Peptidase Inhibitors. PCT International Application WO 2007035629, March 29, 2007.
Finn PW, Bandara M, Butcher C, Finn A, Hollinshead R, Khan N, Law N, Murthy S, Romero R, Watkins C, Andrianov V, Bokaldere RM, Dikovska K, Gailite V, Loza E, Piskunova I, Starchenkov I, Vorona M, Kalvinsh I. Helv Chim Acta. 2005; 88:1630.
Flanagan ME, Munchhof MJ. U.S. patent US7301023B2, 2007.
Foss F, Advani R, Duvic M, Hymes KB, Intragumtornchai T, Lekhakula A, Shpilberg O, Lerner A, Belt RJ, Jacobsen ED, Laurent G, Ben-Yehuda D, Beylot-Barry M, Hillen U, Knoblauch P, Bhat G, Chawla S, Allen LF, Pohlman B. Br J Haematol. 2015; 168:811.
Fraser H, Belardinelli L, Wang L, Light PE, McVeigh JJ, Clanachan AS. J. Mol Cell Cardiol. 2006;41:1031–8.
Gharbaoui T, Tandel SK, Ma Y, Carlos M, Fritch JR. WO Patent 2008070111, 2008.
Goodman SN, Wang H, Mans D, Kowalski M. US9120817B2. n.d.
Grimshaw CE, Jennings A, Kamran R, Ueno H, Nishigaki N, Kosaka T, Tani A, Sano H, Kinugawa Y, Koumura E, Shi L, Takeuchi K. PLoS One. 2016;11:e0157509.
Hale SL, Kloner RA. J Cardiovasc Pharmacol Ther. 2006;11:249–55.
Heinrich T, Bottcher H, Gericke R, Bartoszyk GD, Anzali S, Seyfried CA, Greiner HE, Amsterdam CV. J Med Chem. 2004; 47:4684. https://doi.org/10.1021/jm040793q
Heinrich T, Gradler U, Bottcher H, Blaukat A, Shutes A. ACS Med Chem Lett. 2010; 1:199. https://doi.org/10.1021/ml100044h
Hu B, Song Q, Xu Y. Org Process Res Dev. 2012;16:1552–7. https://doi.org/10.1021/op300171m.
International Conference on Harmonisation (ICH). Q7, Current Step 4 version, dated 10 November 2000.
International Conference on Harmonisation (ICH). Q3C (R5), February 2011.
International Conference on Harmonisation (ICH). Q11, Current Step 4 version, dated 1 May 2012.
Jacob RM, Robert JG. German Patent No. DE1092476, 1959.
Jerling M. Clin Pharmacokinet. 2006;45:469–91.
Johns BA, Kawasuji T, Taishi T, Taoda Y. WO 2006116764A1. n.d.
Karicherla V, Phani K, Bodireddy MR, Prashanth KB, Gajula MR, Pramod K. Org Process Res Dev. 2017;21:720–31. https://doi.org/10.1021/acs.oprd.7b00052.
Kawasuji T, Johns BA, Yoshida H, Taishi T, Taoda Y, Murai H, Kiyama R, Fuji M, Yoshinaga T, Seki T, Kobayashi M, Sato A, Fujiwara T. J Med Chem. 2012;55:8735. https://doi.org/10.1021/jm3010459.
Kawasuji T, Johns BA, Yoshida H, Weatherhead JG, Akiyama T, Taishi T, Taoda Y, Mikamiyama-Iwata M, Murai H, Kiyama R, Fuji M, Yoshinaga T, Seki T, Kobayashi M, Sato A, Garvey EP, Fujiwara T. J Med Chem. *2013*;56:1124. https://doi.org/10.1021/jm301550c.
Kluge AF, Clark RD, Strosberg AM, Pascal JG, Whiting R. U.S. 4,567,264, 1986.
Kluge AF, Clark RD, Strosberg AM, Pascal JC, Whiting RL. EP 0,126,449, 1987a.
Kluge AF, Clark RD, Strosberg AM, Pascal JC, Whiting R. CA 1,256,874, 1987b.
Knoevenagel EJ. J Prakt Chem. 1914;89:1–50.
Kohara Y, Imamiya E, Kubo K, Wada T, Inada Y, Naka T. Bioorg Med Chem Lett. 1995;5:1903–8.
Kohara Y, Kubo K, Imamiya E, Wada T, Inada Y, Naka T. J Med Chem. 1996;39:5228–35.
Koike H, Asai F, Sugidachi A, Kimura T, Inoue T, Nishino S, Tsuzaki Y. U.S. 5,288,726, 1994.
Kristin EP, Claude L-A, Brett ML, Robert WM, Jason M, Kevin WH, Jeol MH, Rajappa V. Org Lett. 2009;11:2003–6.
Kuroita T, Sakamoto H, Ojima M. (Takeda Chemical Industries). U.S. Patent Application 0,187,269, 2005.

Kuroita T, Sakamoto H, Ojima M. (Takeda Chemical Industries). U.S. Patent Application 7,157,584, 2007.
Lee, H. Z., Witkowski VE, Del Valle POL, Ricci MS, Saber H, Habtemariam BA, Bullock J, Bloomquist E, Li Shen Y, Chen XH, Brown J, Mehrotra N, Dorff S, Charlab R, Kane RC, Kaminskas E, Justice R, Farrell AT, Pazdur R. Clin Cancer Res. 2015; 21:2666.
Li JQ, Wang G, Wang C, Wang JJ. China patent CN102267932, 2011a.
Li JQ, Wang G, Wang C, Huang L. China patent CN102267985, 2011b.
Lisheng W, Xiaoyu, F., Hong-yuan, Z. J. Guangxi University (Natural Science Education). 2003; 28:301–303.
Liu JF. WO Patent 2009051747, 2009.
Luo J, Li R, Li C, Lei G, Su Y, Chen Q. China Patent 104478769 A, Apr 1, 2015.
Massie SP. Chem Rev. 1954;54:797.
Mohanty S, Talasila S, Roy AK, Karmakar AC. Org Process Res Dev. 2014;18:168–73. https://doi.org/10.1021/op400196y.
Morris Husbands GE, Yardley JP, Mills G, Muth EA. U.S. Patent 4,535,186, 1985.
Mubeen AK, Reddy SS, Rao AB, Shankar S. WO 2010/ 070677 A2, 2010.
Naka T, Inada Y. (Takeda Chemical Industries). European Patent Application EP 0,520,423, 1992.
Naka T, Inada Y. (Takeda Chemical Industries). U.S. Patent 5,583,141, 1996.
O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, Bhat G, Choi MR, Walewski J, Savage K, Foss F, Allen LF, Shustov A. J Clin Oncol. 2015; 33:2492.
Patil YS, Bonde NL, Kekan AS, Sathe DG, Das A. Org Process Res Dev. 2014;18:1714–20. https://doi.org/10.1021/op500274j.
Qian J, Zhang G, Qin H., Zhu Y, Xiao Y. China Patent 102786448 A, Nov 21, 2012.
Radl S, Cerny J, Stach J, Gablikova Z. Org Process Res Dev. 2013;17:77–86., dx.doi.org. https://doi.org/10.1021/op3002867.
Rahul S, Venkateswaran SC, Lalit W WO 2008/047388 A2, 2008.
Raman JV, Rane D, Kevat J, Patil D. WO2011/154860, 2011.
Reddy PP, Sarma PSR, Reddy GM, Srinivas P, Praveen C, Babu I, Shailaja P, Krishna J, Krishna V, Kavitha N. U.S. 2010/0261908 A1, 2010.
Reguri BR, Arunagiri M, Yarroju PC, Kasiyappan GS, Ponnapall K. WO2011/055188, 2011.
Reisch H, Leeming P, Raje PS. WO Patent 2009040517 A2, Apr 2, 2009.
Reiter J, Trinka P, Bartha FL, Pongo L, Volk B, Simig G. Org Process Res Dev. 2012;16:1279–82. https://doi.org/10.1021/op300009y.
Robert LF, James RB, Robert JD, Robert LM, Fared EW. J Am Chem Soc. 1946;68:1368.
Sankareswaran S, Mannam M, Chakka V, Mandapati SR, Kumar P. Org Process Res Dev. 2016;20:1461–8. https://doi.org/10.1021/acs.oprd.6b00156.
Saravanan M, Satyanarayana B, Reddy PP. Org Process Res Dev. 2011;15:1392–5. https://doi.org/10.1021/op200221y.
Satyanarayana Reddy M, Eswaraiah S, Satyanarayana K. Indian Patent No. 360/CHE/2010 A, Aug 19, 2011.
Shinhama K, Utsumi N, et al. Method for producing benzo[b]thiophene compound. PCT International Application WO 2013015456, Jan 31, 2013.
Shiwei Z, Feng J. US 2012/0172699A1, 2012.
Shu-chun L, He-qing H, Zhong-jun L. Chin J Med Chem. 2003;13:283–5.
Sindelar K, Holubek J, Koruna I, Hrubantova M, Protiva M. Collect Czechoslov Chem Commun. 1990;55:1586–601.
Smith J, Smith B. U.S. Patent 2003225057, 2003.
Smith B, Smith J. U.S. Patent 6953787, 2005.
Smith B, Gilson C, Schultz J, Smith J. WO Patent 2005003096, 2005.
Solanki PV, Uppelli SB, Pandit BS, Mathad VT. Org Process Res Dev. 2014;18:342–8. https://doi.org/10.1021/op400335p.
Srinivas RAVV, Jalindar J, Srinivas G, Pillai BG, Sadanand NS. WO 2009/122440 A1, 2009.
Stavber G, Cluzean J. PCT WO 2014016338A1, 2014.
Stavber G, Jerome C, Frank R, Gerhard L, Ivana GS. WO Patent 2014173928, 2014a.

Stavber G, Ivana GS, Jerome C, Frank R. WO Patent 2014202765, 2014b.
Strupczewski JT, Helsley GC, Chiang Y, Bordeau KJ. EP 0402644A1, 1990.
Sumino Y, Masui M, Yamada D, Ikarashi F, Okamoto K. US20140011995. n.d.
Thomas A, Rajan A, Szabo E, Tomita Y, Carter CA, Scepura B, Lopez-Chavez A, Lee MJ, Redon CE, Frosch A, Peer CJ, Chen Y, Piekarz R, Steinberg SM, Trepel JB, Figg WD, Schrump DS, Giaccone G. Clin Cancer Res. 2014; 20:5392.
Wang H, Kowalski MD, Lakdawala AS, Vogt FG, Wu L. Org Lett. 2015;17:564. https://doi.org/10.1021/ol503580t.
Wang Q, Luo J, Cao Y, Zhang L, Li C, Yuan Q. China Patent 105367455 A, Mar 2, 2016.
Watkins CJ, Romero-Martin MR, Moore KG, Ritchie J, Finn PW, Kalvinsh I, Loza E, Dikovska K, Gailite V, Vorona M, Piskunova I, Starchenkov I, Adrianov V, Harris CJ, Duffy JES. U.S. Patent 6,888,027 B2, May 3, 2005.
Weigl U, Porstmann F, Straessler C, Ulmer L, Koetz U. U.S. Patent 20090143576, 2009.
Chunhui Wu, Weiming Chen, Dehui Jiang, Xiangrui Jiang, Jingshan Shen. Org Process Res Dev. 2015; 19:555–558. https://doi.org/10.1021/acs.oprd.5b00027.
Xiao-lin C, Yong-zhou H. West China J Pharm Sci. 2004;19:191–2.
Xu W, Zhang RJ, Zhu B. China patent CN102249979, 2011.
Shenghui Xu, Qun Hao, Hongyan Li, Zhenren Liu, Weicheng Zhou. Org Process Res Dev. 2017; 21:585–589. https://doi.org/10.1021/acs.oprd.7b00013.
Yamashita H, Matsubara J, et al. Piperazine-Substituted benzothiophenes for treatment of mental disorders. PCT International Application WO 2006112464, Oct 26, 2006.
Yang L., Xue X, Zhang Y. Synth Commun. 2010, 40, 2520.
Yardley JP, MorrisHusbands GE, Stack G, Butch J, Bicksler J, Moyer JA, Muth EA, Andree T, Fletcher H III, James MNG, Sielecki AR. J Med Chem. 1990;33:2899–905. https://doi.org/10.1021/jm00172a035.
Yoshida H, Taoda Y, Johns BA, Kawasuji T, Nagamatsu D. US8754214B2. n.d.
Zhang X, Zhang K, et al. Compound for Preparing Pyrimidinedione DPP-IV Inhibitors. China Patent. CN 103030631, April 10, 2013.
Zhang H, Sun L, Zou L, Hui W, Liu L, Zou Q, Ouyang PJ. J Pharm Biomed Anal. 2016;128:18–27.
Zhu G. CN 101531667 A, 2009.
Qihua Zhu, Junwei Wang, Xueguo Bian, Lingzhi Zhang, Ping Wei, Yungen Xu. Org Process Res Dev. 2015; 19:1263–1267. https://doi.org/10.1021/acs.oprd.5b00144.

# Green Approaches to Synthesize Organic Compounds and Drugs

**Yogesh Murti, Devender Pathak, and Kamla Pathak**

**Contents**



## 1 Introduction

The classical synthetic methods, in general, generate substantial amounts of waste products, and both chemical and pharmaceutical industries are under continual pressure to minimize or, preferably, eliminate the waste generation. The term "green chemistry" was introduced in the year 1991 by the US Environmental Protection Agency (EPA) in view of initiating sustainable development in chemical and pharmaceutical technology (Wardencki et al. 2005). EPA's emphasis to hasten the adoption of this revolutionary and diverse discipline has led to significant innovations, environmental benefits, and strengthened economy (www.epa.gov/greenchemistry). An annual recognition by the US EPA, namely, Presidential Green Chemistry Challenge Awards, is a strengthening approach in green chemistry that recognizes its applications in pharmaceutical industry. Merck Research Laboratories in the year 2019 was recognized by EPA for redesigning the manufacturing of the antibiotic

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_8

Zerbaxa™. Key to the redesign is a crystallization oriented purification process that reduces the process mass index by 75%, reduces raw material expense by 50%, and improves the yield by more than 50%. Merck claims that the novel process will save approximately 3.7 million gallons of water annually and reduce the carbon footprint and energy usage by 50% and 38%, respectively. This patented process was successfully implemented, demonstrated, filed, and approved in the USA and the EU in 2018 and is currently being used on commercial scale to manufacture ceftolozane sulfate for Zerbaxa™. (www.epa.gov/greenchemistry/green-chemistry-challenge-2019). Sustainable green chemistry development has now become a deliberate chemical and pharmaceutical industrial focus. The need of hour is to assess the requirements of present generation without compromising the future generation's needs. The chapter covers the methodologies of green chemistry that find application both in organic chemistry and pharmaceutical industry.

## 2 Considerations of Green Chemistry

### *2.1 Principles*

Anastas and Warner (1988) presented 12 principles of green chemistry that are globally accepted set of principles for assessing the acceptability of the given manufacturing process. Later in 2005, Tang et al. reported a mnemonic PRODUCTIVELY that essentially embraces the essence of the key principles of green chemistry (Fig. 1). Furthermore, in 2008, Tang and his coworkers presented a condensed volume of 24 principles of green chemistry and green engineering, in the form of the mnemonic "IMPROVEMENTS PRODUCTIVELY." A companion set of the green engineering principles, with the mnemonic IMPROVEMENTS, is presented in Fig. 2. They clearly emphasized the manageability of the two sets of principles in their condensed forms for evaluating a given manufacturing process. These can be used in combination to tackle most of the key issues related to green and sustainable chemistry.

### *2.2 Atom Economy*

Atom economy aims to maximize the incorporation of the reactants into the final product of any given reaction. It takes into consideration the reagents used, the desired product, and the undesirable side products. The atom economy yield is calculated by using Eq. 1:

$$\text{Atom economy} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weight of all products}} \times 100\% \qquad (1)$$

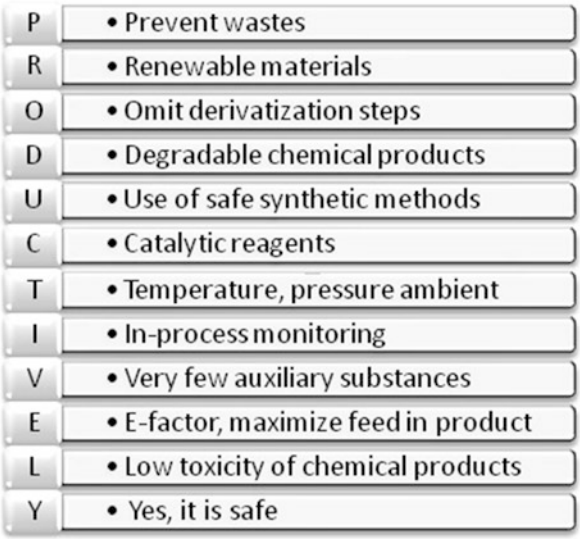


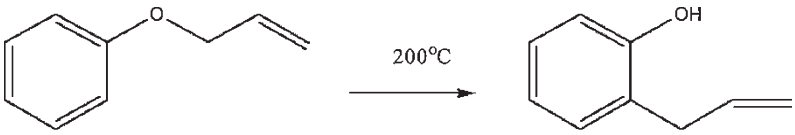

**Fig. 1** The condensed twelve principles of green chemistry


**Fig. 2** The condensed twelve principles of green engineering, based on those in full in Fig. 1

A reaction is considered to be "perfect" when the yield is 90% or more. The allylic rearrangement reaction is an example of 100% atom economy as all the reactants in the reaction are incorporated in the final product (Scheme 1) (Trost 2002).

## *2.3 E Factor*

The E factor is the actual amount of waste produced in the reaction/process and includes all except the final product. It takes into account the chemical yield, reagents, solvent losses, process aids, and the fuel. GlaxoSmithKline estimated that




**Scheme 1** Allylic rearrangement with 100% atom economy

approximately 85% of the overall quantity of reagents/chemicals utilized for pharmaceutical manufacturing comprises solvents, thereby suggesting that solvents are the major contributor to the E factor (Jiminez-Gonzales et al. 2004). Consequently, pharmaceutical manufacturing industries are directing their efforts in minimizing organic solvent usage and replacing them with eco-friendly substitutes.

## 3 Green Chemistry Approach

Green chemistry has garnered considerable interest in researchers as it uses both green solvents and reagents, instead of toxic and hazardous materials (Kazemi et al. 2015). Many pharmaceutical units across the globe have initiated their sincere efforts on utilizing green chemistry processes for drug discovery, its development, and manufacturing. These include Abbott, the Merck Group, Roche, Johnson and Johnson, Amgen, and Eli Lilly (John et al. 2016). The conduct of chemical reactions in green medium or in conditions without solvent, by the use of ultrasonic and microwave technologies, is one of a few significant green synthetic strategies. Furthermore, the use of green catalysts such as enzymes, catalytic antibodies, and whole cells for organic synthesis has gained recognition. Frequently, the biocatalysis leads to very high reaction rates and selectivity like enantioselectivity that are beyond the prerogative of chemical catalysis. These can be considered as powerful alternative tools in the toolbox of synthetic chemist.

The solvents used in conventional chemical reactions play a significant role in waste generation. In green chemistry, an ideal solvent means the one that primarily functions to facilitate the mass transfer only without dissolving. However, 80% of the waste produced from the API manufacturing units is correlatable to the solvents used. This clearly indicates judiciously selecting the solvent, and its disposal will play a key role in alleviating the solvent-related waste generation issue. A desirable green solvent should be natural (e.g., water, supercritical $CO_2$) or nonnatural (e.g., ionic liquids having low volatility), nontoxic, cheap, and readily available (Webb et al. 2005; Wasserscheid and Welton 2002). Solvents and stoichiometric reagents are the important considerations for green strategies and are currently under investigation by many pharmaceutical units such as Sanofi-Aventis and GlaxoSmithKline. These companies emphasize the replacement of halogenated and petroleum-based solvents with greener solvents such as glycerol, ethyl lactate (Kua et al. 2016), and water (Simon and Li 2012). Furthermore, tools for designing green syntheses are available from sources like the EPA guidelines, Practical Process Research and

Development (Gadamasetti 1999), and the write-up on pharmaceutical waste minimization by Zhang (2002). In this chapter, one can find interesting examples of the application of the green chemistry principles for synthesis of organic compounds and for products of pharmaceutical interest.

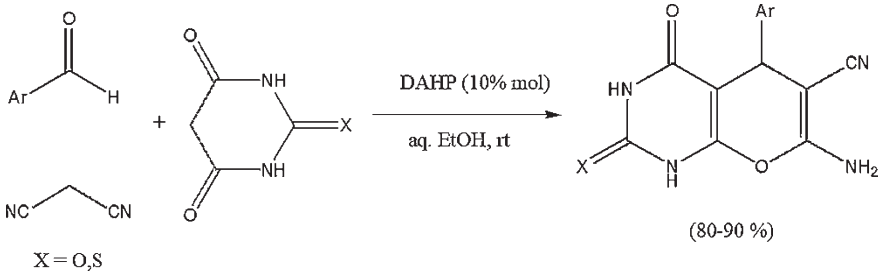
## 4 Applications in the Organic Industry

A significant number of green methods are reported for synthesis of pyrano[2,3-*d*] pyrimidine derivatives. Balalaie et al. (2008) reported green preparation of various pyrimidine derivatives using diammonium hydrogen phosphate (DAHP) in water/ethanol at room temperature (Scheme 2) that was completed in 2 h.

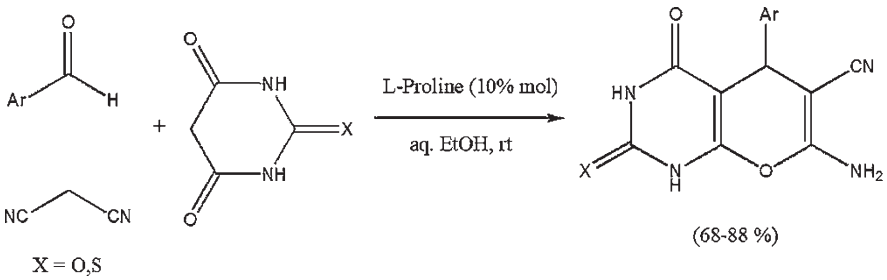
Later, Bararjanian et al. (2009) used L-proline, a neutral biocatalyst for the condensation of barbituric/thiobarbituric acid, malononitrile, and aromatic aldehydes in hydroethanolic medium (Scheme 3). Mobinikhaledi and Bodaghi-Fard (2010) used tetrabutylammonium bromide (TBAB) for green catalytic condensation of aromatic aldehydes, barbituric acid, and malononitrile (Scheme 4). Potash alum ($KAl(SO_4)_2.12\ H_2O$) in water was also reported by Mobinikhaledi et al. (2010) for efficient green synthesis of pyrano[2,3-*d*]pyrimidinone derivatives (Scheme 5). Another green and convenient protocol was developed by Jain et al. (2011), for the synthesis of pyrano[2, 3, d]pyrimidine derivatives using 1,4-diazabicyclo[2.2.2]octane (5% mol; DABCO) as efficient catalyst in a hydroethanolic mixture (Scheme 6).

Ionic liquids (ILs) are versatile solvents for improvising the condensation reactions. However, problems like cost, high viscosity, sensitivity to oxygen and water (e.g., chloroaluminates), and leaching into the product still need to be addressed before their use becomes widespread.

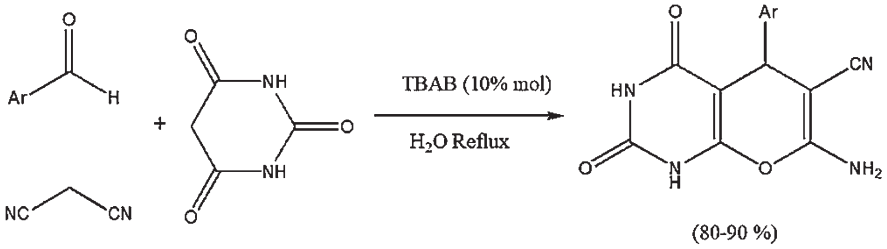
Earle et al. (1998) used acidic chloroaluminate (IL) in Friedel-Crafts acylation reaction, in contrast to the conventional Friedel-Crafts acylation wherein the acylium ion is generated in situ by reaction between $FeCl_3/AlCl_3$ and acyl chloride. However, acylation of mono-substituted aromatic compounds in the presence of IL caused exclusive substitution at the 4-position on the ring (Scheme 7). Yu and Wang (2005) reported condensation of arylmethylidene malononitrile with barbituric acid



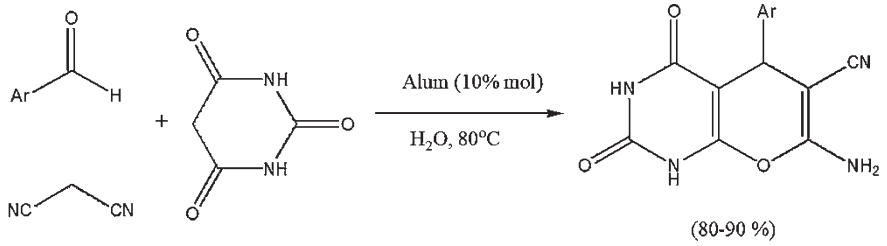

**Scheme 2** Green synthesis of pyrano[2,3-d] pyrimidine derivatives in an aqueous media catalyzed by DAHP



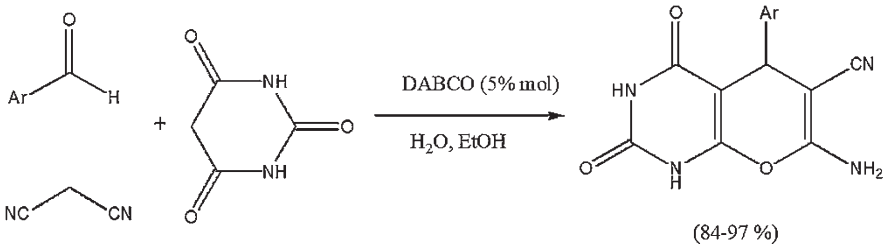

**Scheme 3** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in an aqueous media catalyzed by L-proline



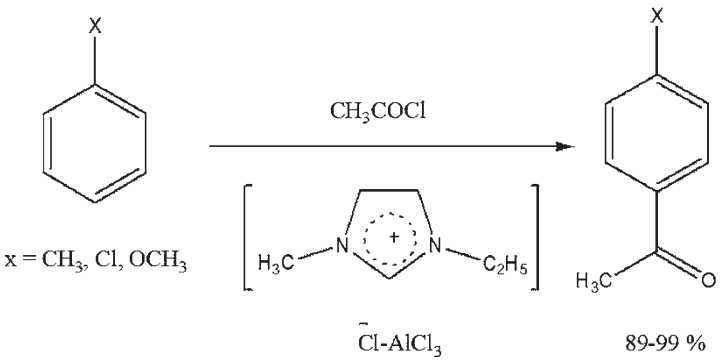

**Scheme 4** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in an aqueous media catalyzed by TBAB



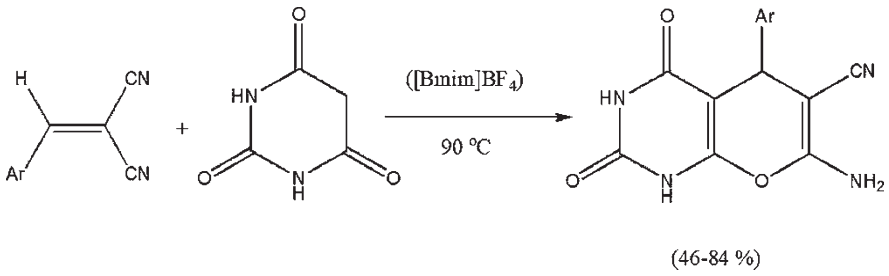

**Scheme 5** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in an aqueous media catalyzed by alum




**Scheme 6** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in an aqueous media catalyzed by DABCO




**Scheme 7** Acylation of aromatic compounds in acidic chloroaluminate ionic liquid



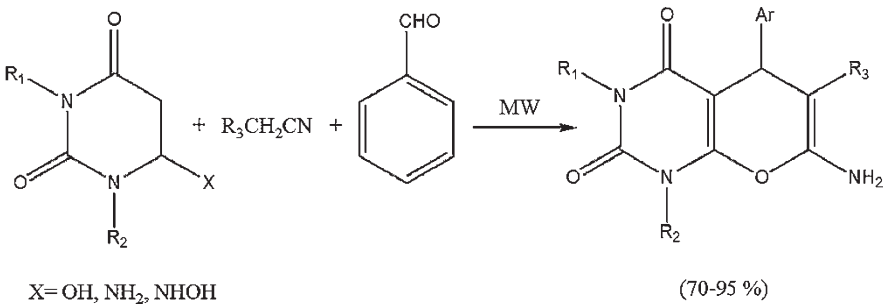

(46-84 %)

**Scheme 8** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in an anionic liquid [Bmim] BF4

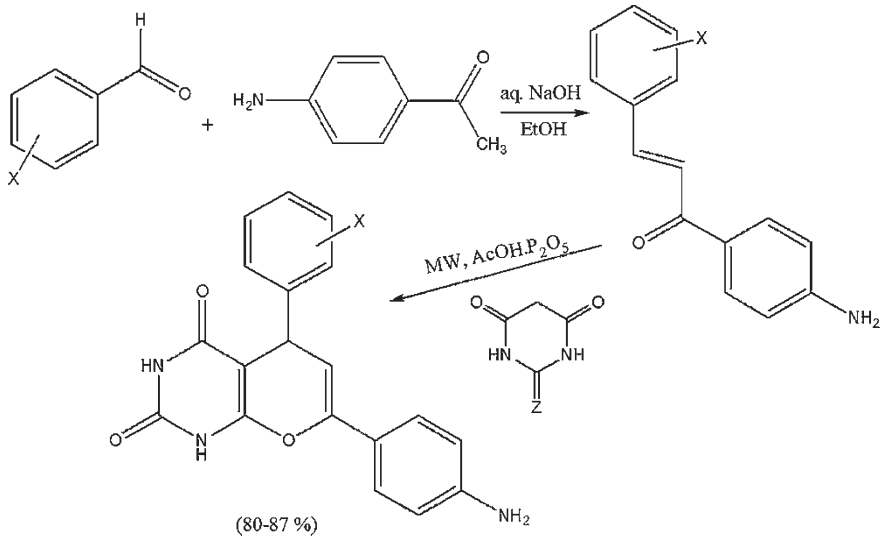
using recyclable IL, 1-*n*butyl-3-methyl-imidazolium tetrafluoroborate ([Bmim] $BF_4$) which acted both as reaction medium and promoter for the synthesis of pyrimidine derivatives in neutral medium (Scheme 8).

Green chemistry also utilizes the principles of microwave-assisted chemistry, which suggests reduction in unwanted side reactions, efficiency, high yield, easy scale-up, reproducibility, purity of the compounds, and reduced environmental heat loss for the synthesis of a plethora of compounds (Chemat-Djenni et al. 2007; Kappe et al. 2013; Gupta et al. 2016). Furthermore, solvent-free microwave-assisted synthesis provides an opportunity to work in open vessels that reduces the risks associated with development of high pressure in the microwave reactor and provides scale-up possibilities for such reactions (Kidwai 2001). Devi et al. (2003) described a novel and convenient multicomponent synthetic protocol in the solid state for the synthesis of pyrimidines using microwave irradiation in a polar medium for the cyclocondensation of benzaldehyde, barbituric acids, and alkyl nitriles (Scheme 9). A series of pyrano[2,3]pyrimidine derivatives was also prepared by Mazaahir et al. (2007) in aqueous medium under microwave conditions (yield = 81–87%) in less than 8 min (Scheme 10).

Solvent-free microwave-assisted preparation of substituted imidazoles of biological interest was reported by Sharma and Pathak (2010). Firstly, the condensation



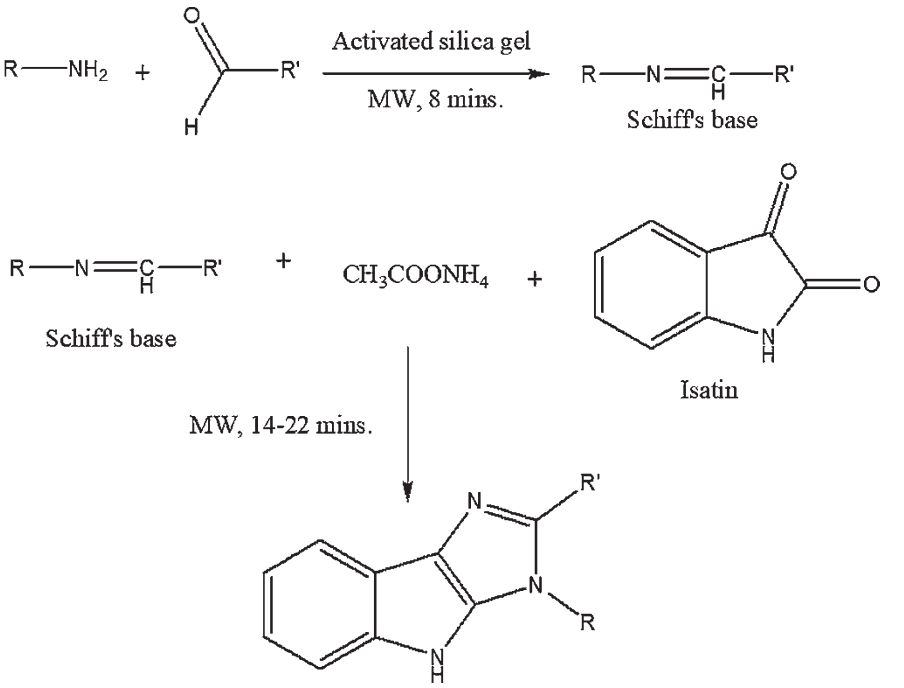

**Scheme 9** Green synthesis of pyrano[2,3-d]pyrimidine derivatives under microwave conditions




**Scheme 10** Green synthesis of pyrano[2,3-d]pyrimidine derivatives in aqueous medium under microwave conditions

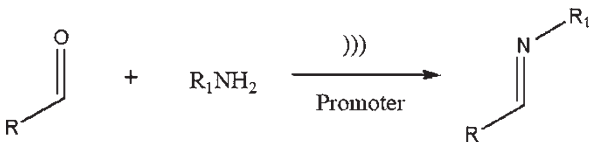
of primary aromatic or heteroarylamine was affected with aryl or heteryl aldehydes to obtain Schiff's base. Schiff's base is then treated with isatin and ammonium acetate in the presence of the solvent, glacial acetic acid (Scheme 11).

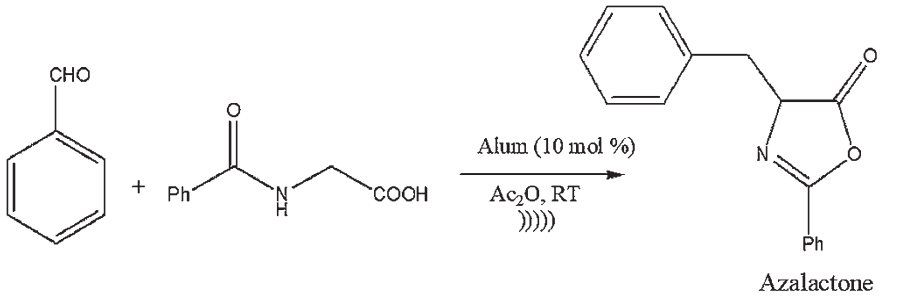
Ultrasound also finds application in affecting chemical reactions and was first reported by Khurana in 1990. Since then, it has been extensively investigated for enhancing reaction rates of a plethora of classical chemical reactions. Guzen et al. (2007) carried out ultrasound-assisted reaction of aldehydes and primary amines for the synthesis of a series of imines in the presence of silica as the reaction promoter (Scheme 12). Likewise, Madje et al. (2010) carried out synthesis of azlactone using benzaldehyde, hippuric acid, acetic anhydride, and potash alum under ultrasound irradiation for 8 min at ambient temperature (Scheme 13). The technique was rapid and did not utilize thermal energy.



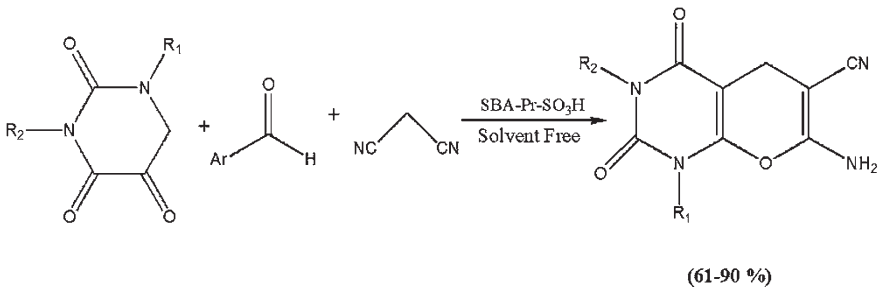

**Scheme 11** Green synthesis of substituted imidazaoles under microwave conditions

**Scheme 12** Green synthesis of imines using alternative energy source




**Scheme 13** Green synthesis of azlactone using alternative energy source



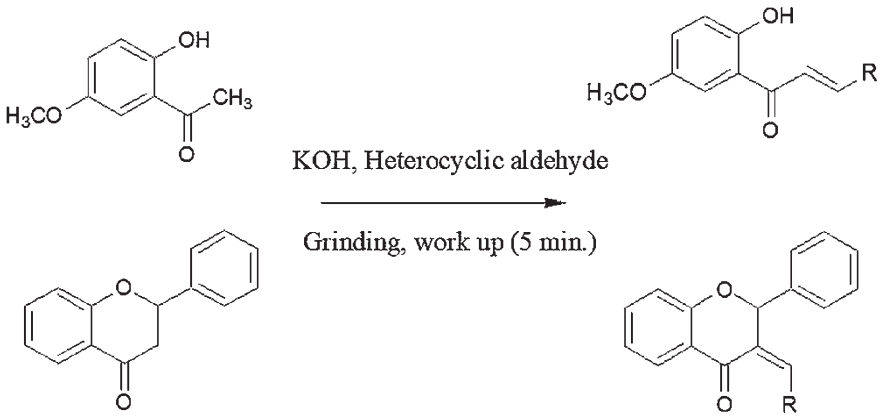

**Scheme 14** Green synthesis of pyrano[2,3-d]pyrimidine derivatives by using SBA-Pr-$SO_3H$ under solvent-free condition

Efforts are being dedicated to reinvestigate established reactions to achieve rapid, safe, and solvent-free organic synthesis (Modarresi-Alam et al. 2007; Epps et al. 2014). Solvent-free synthesis is gaining momentum for reasons to improve selectivity, yield, and simplicity of the reaction strategies (Dong et al. 2008; Baron et al. 2010) and also minimize environmental damage. In the past decades, a large number of synthetic protocols via microwave irradiation without using solvent have been documented in the literature. Sulfonic acid nanoporous silica (SBA-Pr-$SO_3H$), a recyclable nano-reactor, was used as a catalytic system for the synthesis of pyrano[2,3*d*]pyrimidines by Mohammadi-Ziarani et al. (2013) in solvent-free environment (Scheme 14).

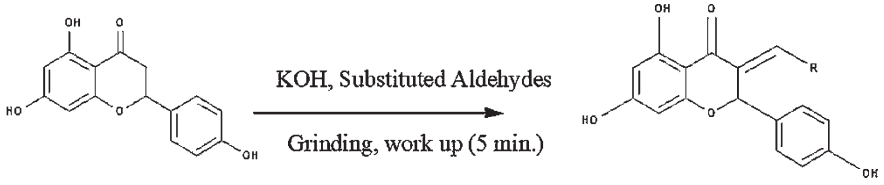
Solid-state reactions are economical, do not require much purification, possess high reaction rate, and are environmentally friendly. Pioneering work by Tanaka (2003) and Tanaka and Toda (2008) introduced the technique of "grindstone chemistry" (Bose et al. 2004) that has been adapted by the pharmaceutical industry for the industrial-scale production of pharmaceuticals. The requisite activation energy for the reaction is generated by close contact of the reactive molecules in the absence of the solvent. Solvent-free reactions require simple workup and purification procedures and are often completed within minutes. Murti and Mishra (2016) reported a series of chalcones and flavanones, with anticancer potential and discriminated by the presence of a heterocyclic moiety (R) in their structures synthesized by the Claisen-Schmidt condensation method using grinding technique (Scheme 15). Furthermore, Murti and Mishra (2019) synthesized a series of substituted naringenin derivatives by the Claisen-Schmidt reaction using grinding technique. The high-yield derivatives showed anticancer potential (Scheme 16).

In order to purify and characterize, the carbonyl functionalities are often converted into oximes by classical reactions. To overcome the drawbacks of classical synthesis of oximes, a mixture of aldehyde/ketone, hydroxylamine hydrochloride, and bismuth oxide ($Bi_2O_3$) was grounded in pestle mortar (Scheme 17), and the oxime was yielded in high percentage (60–98%) by Saikia et al. (2011).

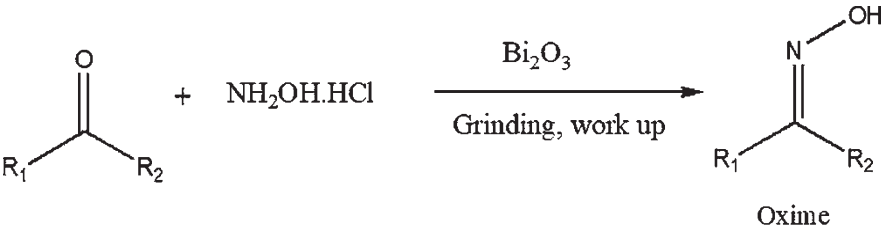
Mechanoheterocyclic chemistry is an emerging technique for the synthesis of heterocycles and has garnered interest among the heterocyclic chemists. This strategy is able to cater three of the green chemistry objectives, namely, high atom econ-




**Scheme 15** Green synthesis of chalcones and flavanones using grinding technique

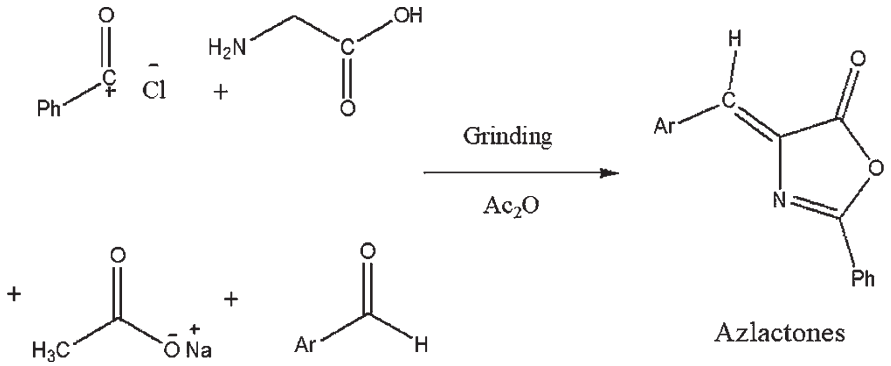



**Scheme 16** Green synthesis of naringenin derivatives using grinding technique

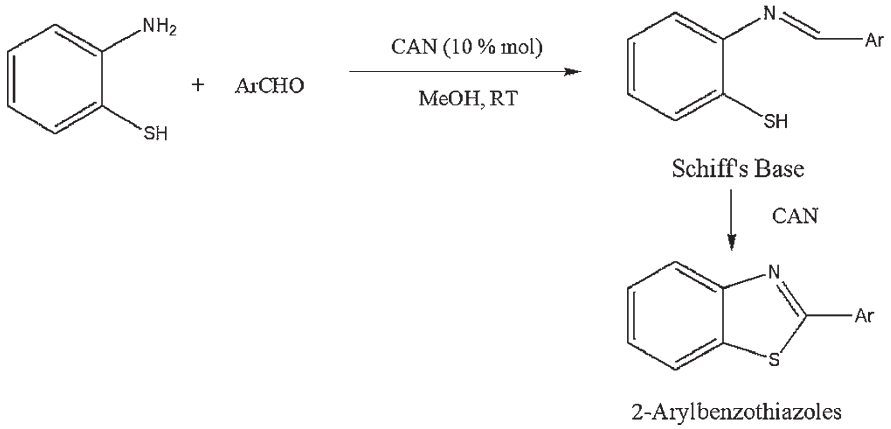



**Scheme 17** Green synthesis of oximes using grinding technique

omy, solvent-free operation, and step efficient. In mechanochemical synthesis (grindstone technique), cogrinding of the crystals of two different compounds generates local heat for mediation of reaction between the two. The cogrinding is accomplished by mixing of the components, either neat or with minimal solvent (liquid-assisted grinding; Trask and Jones 2015). The mechanochemical reactions are more selective and efficient than solution phase reactions, owing to tight and regular arrangement of the molecules in crystal lattice than those in the liquid state (Rothenberg et al. 2001). However, the technique cannot be used for reacting shock-sensitive materials. Cogrinding of glycine, an aromatic aldehyde, benzoyl chloride, and fused sodium acetate in the presence of acetic anhydride resulted in the synthe-




**Scheme 18** Green synthesis of azlactones using mechanochemical grinding technique

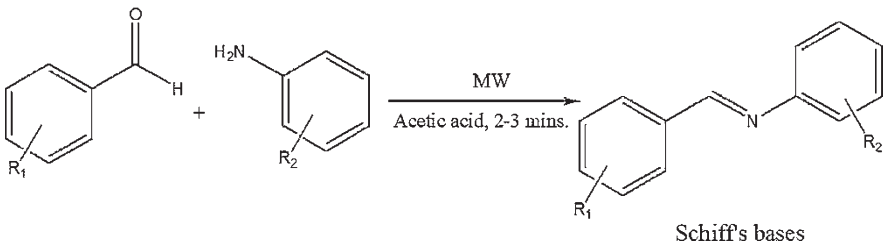



**Scheme 19** Green synthesis of Schiff's base

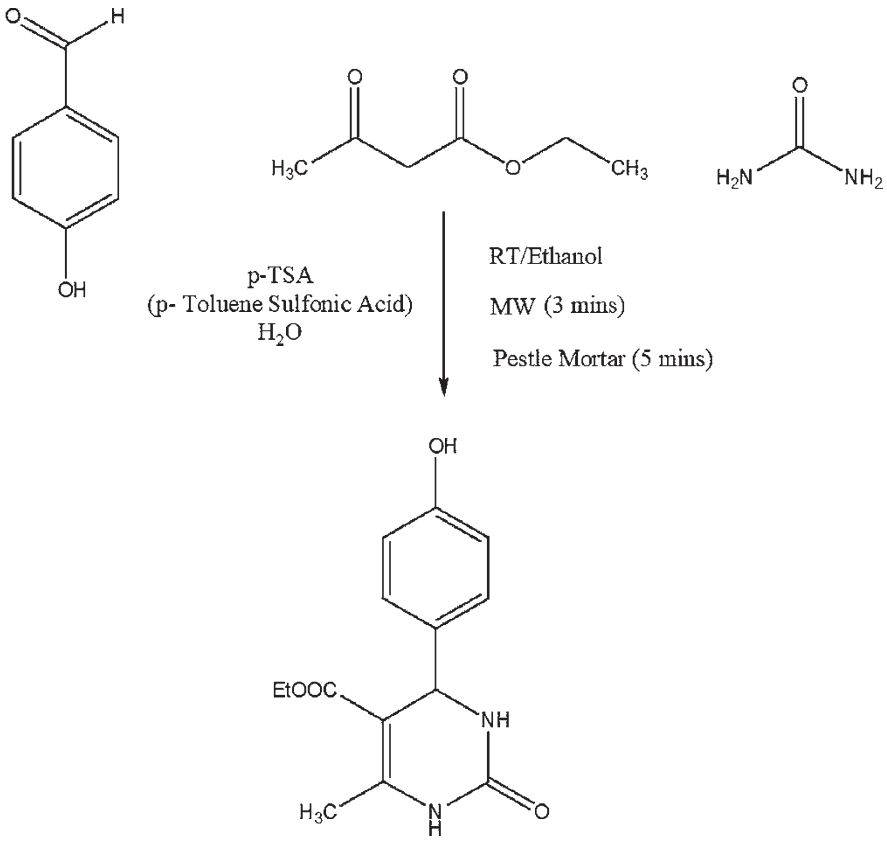
sis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) (Scheme 18). This single-step green synthesis was reported by Fahmy et al. (2016). Azlactones exhibit a wide range of pharmacological activities including anticancer (Jat et al. 2012), antitumor (Dayakar et al. 2018), antimicrobial, antiviral (Perron-Sierra et al. 2002), anti-inflammatory (Salgin-Goksen et al. 2007), and anti-HIV (Witvrouw et al. 1999).

Schiff's base is an important class of compound which can be used for the determination of metals such as iron in pharmaceutical samples spectrophotometrically (Mandhare and Barhate 2016), as well as may show diverse pharmacological activities (Mohan and Rao 2014). The conventional method of preparation of Schiff's bases involves either refluxing of aldehyde and amine in solvents like benzene or mixing at room temperature in chlorinated solvents, but Al-Qalaf et al. (2008) documented a one-pot synthesis of 2-arylbenzothiazoles by reacting 2-aminothiophenol and aromatic aldehydes catalyzed by cerium (IV) ammonium nitrate (CAN) (Scheme 19).

Schiff's bases can also be synthesized by the reacting aromatic aldehydes and various aromatic amines along with the catalytic amount of glacial acetic acid under




**Scheme 20** Green synthesis of Schiff's base under microwave radiations




**Scheme 21** Green synthesis of pyrimidine derivatives

microwave irradiation (Scheme 20) to save time. The conventional method requires about 1–2 h, while microwave irradiation method requires 2–3 min only (Miglani et al. 2012). Pyrimidine derivatives showed diverse pharmacological activities (Patil 2018) can be synthesized by using microwave, mortar-pestle method, and the use of green solvents for the synthesis. Jagwani and Joshi (2015) synthesized 4(4-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl ester using Scheme 21.

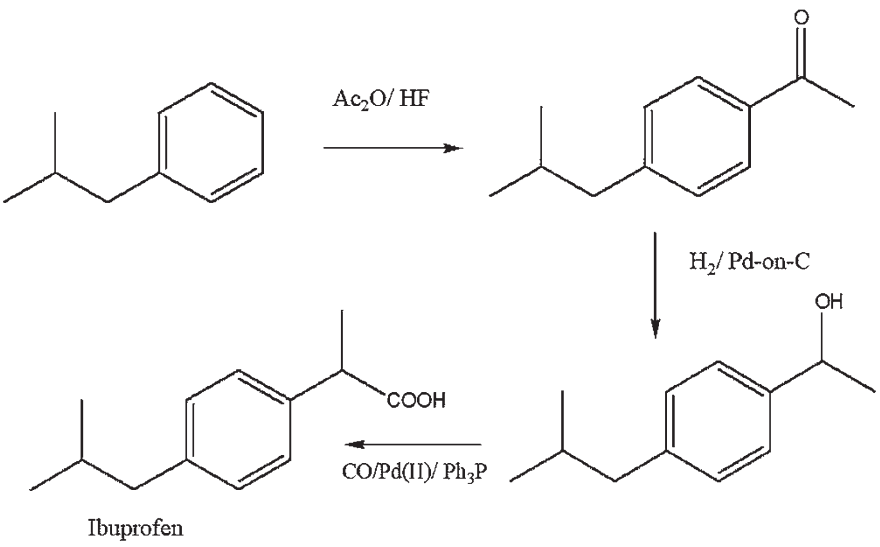
## 5 Applications in Pharmaceutical Industry

The pharmaceutical industries are aggressively embracing the principles of green chemistry to improve their environmental credentials and manufacturing process efficiency. As a well-known fact, the pharmaceutical manufacturing units generate more waste than other allied industries. Routinely, a pharmaceutical industry generates around 25–100 kilograms of waste per kilogram of the product made by synthetic protocols involving six to eight steps (Dunn et al. 2010). There is an urgent need to embrace "greener" methods, to minimize solid waste and industrial effluents. Synthetic routes of certain bestselling drugs that utilize the principles of green chemistry for their synthetic protocols are discussed below.

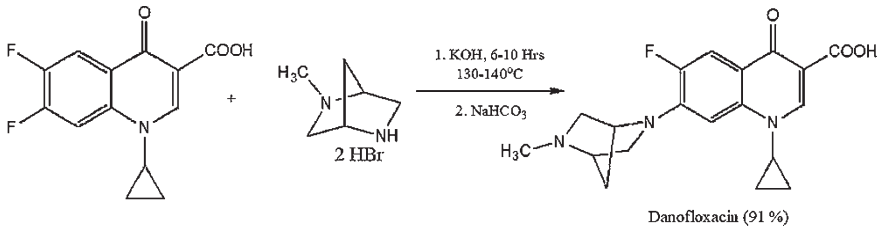
The Boots-Hoechst-Celanese company developed an elegant process for ibuprofen, a nonsteroidal anti-inflammatory agent which involves only three catalytic steps, as shown in Scheme 22, in contrast to classical six-step route (Elango et al. 1991). The primary step is the Friedel-Crafts acylation that uses recyclable anhydrous hydrogen fluoride both as catalyst and solvent, thus eliminating waste generation. The subsequent catalytic steps are apparently 100% atom efficient.

Danofloxacin, a quinolone-based drug, is indicated for the treatment of bacterial infections in livestock. The improvisation was affected by conducting product forming amination step in pressurized water at higher temperature than classical reaction resulting in high reaction rate (Scheme 23). The high quality yield (91%) was obtained by filtration at the isoelectric pH.

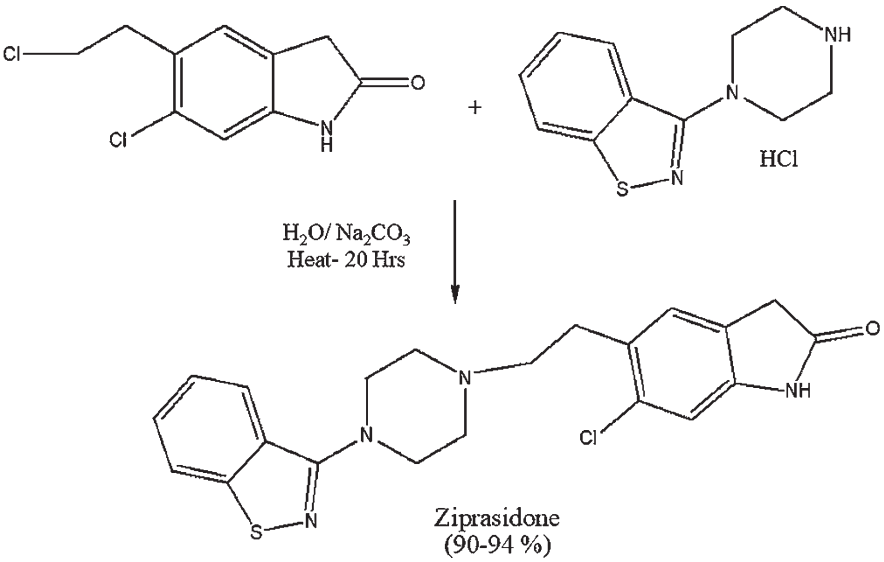
Ziprasidone (Geodon), an antipsychotic agent, was synthesized by joining two fragments through alkylation reaction in the presence of sodium carbonate and sodium iodide (Scheme 24). Water as a solvent to enhance the solubility of the reagents resulted in high yield of 90–94% (Bowles 1993).




**Scheme 22** Green synthesis of ibuprofen using Boots-Hoechst-Celanese process

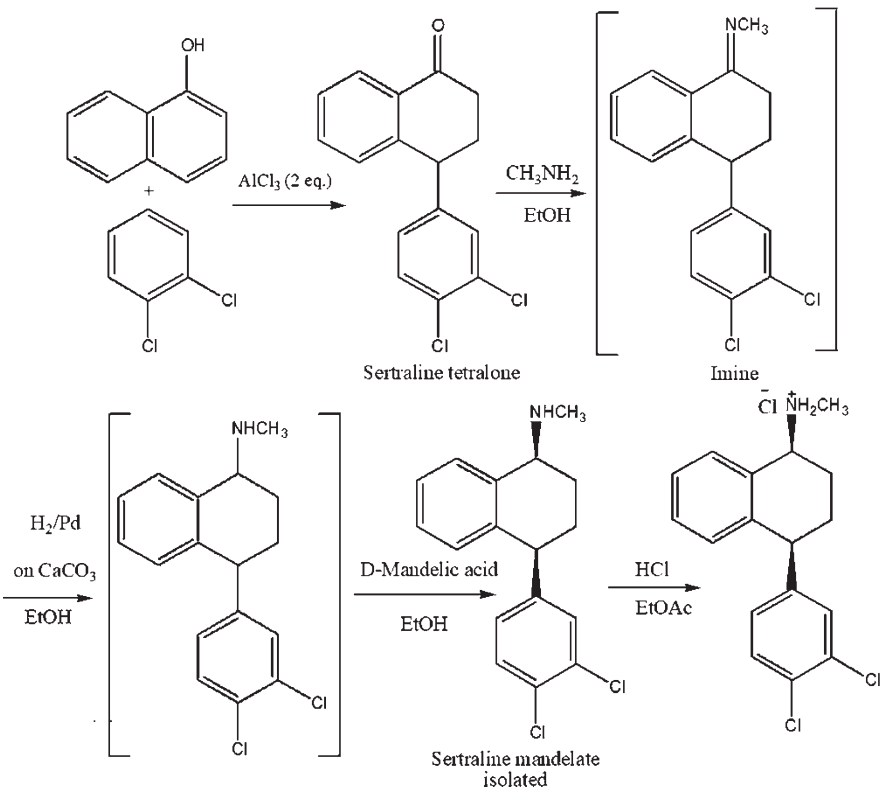



**Scheme 23** Green synthesis of danofloxacin using water as solvent under pressure to permit higher reaction temperature




**Scheme 24** Green synthesis of ziprasidone using water as solvent

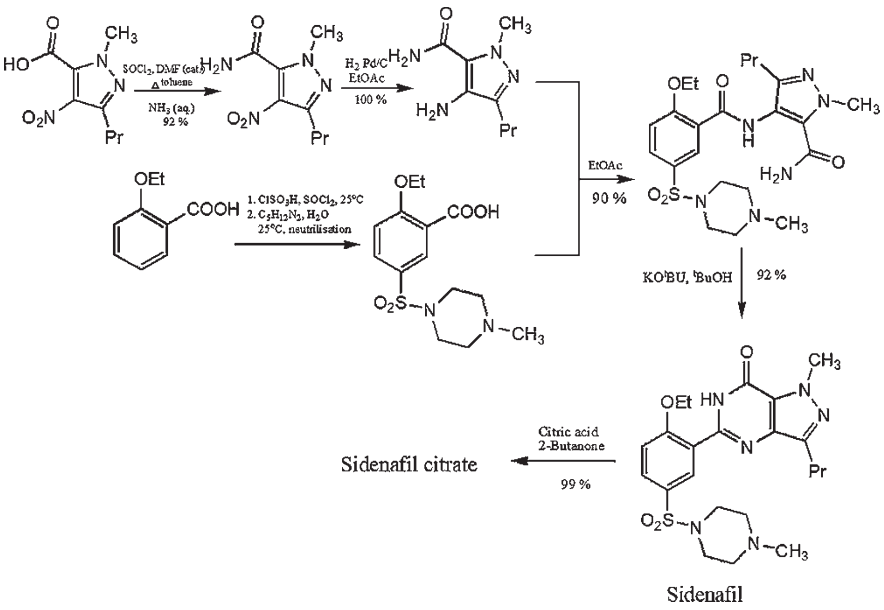
The prestigious Presidential Green Chemistry Challenge Award was received by Pfizer in 2002 for redesigning the manufacturing of sertraline, a three-step process (Scheme 25). Sertraline hydrochloride is used to treat clinical depression and other anxiety-related disorders. Taber et al. (2004) documented a green synthesis of sertraline that offered numerous benefits inclusive of improved material handling and safety, reduced water consumption and energy, and increased the product yield by twice. Essentially, a sequential three-step manufacturing process was minimized to a single-step synthesis. The condensation reaction between 4(3, 4-dichlorophenyl)-3,4-dih ydro-1(2*H*)-naphthalenone and monomethylamine was carried out in ethanol. Poor solubility of the imine in ethanol was exploited so as to tilt the reaction equilibrium toward imine formation. Subsequently, highly selective catalytic reduction of imine in ethanol and effective resolution of the cis-isomer yielded a successful process for sertraline mandelate production. The requirement to distill and recover the solvents was eliminated that decreased the solvent usage by tenfold.




**Scheme 25** Green synthesis of sertraline

Pfizer is recipient of the UK Award for Green Chemical Technology (2003) for the synthesis of sildenafil citrate. Dunn et al. (2004) reported a synthetic procedure that could impressively reduce the solvent usage in the manufacturing of sildenafil. The solvent usage dropped to 7 L/kg from 1700 L/kg of product in the current commercial process. The target is to bring it down to 4 L/kg in the future. The sildenafil synthesis was restructured to incorporate convergency and clean cyclization in the final step to achieve a very clean product (Scheme 26). 2-Ethoxybenzoic acid was subjected to chlorosulfonation followed by aqueous quenching to get water-wet sulfonyl chloride that was reacted with *N*-methylpiperazine to yield sulfonamide. The sulfonamide with amine was subsequently reacted with *N,N′*-carbonyldiimidazole (CDI) to get the coupled product. Though the product was expensive, the methodology yielded good-quality product. The benefits include combining all three reactions, enabling usage of single solvent, allowing solvent recovery, and avoiding volatile organic compound emission and high chemical yield (90%) that was subsequently optimized to 96%. The overall yield of sildenafil citrate rose to 75%, and the high yield affirmatively minimized the environmental impact of the previous steps.

Celecoxib is a COX-2 inhibitor, and its green synthesis was established using two benign solvents isopropanol and methanol (Scheme 27; Letendre et al. 2005).

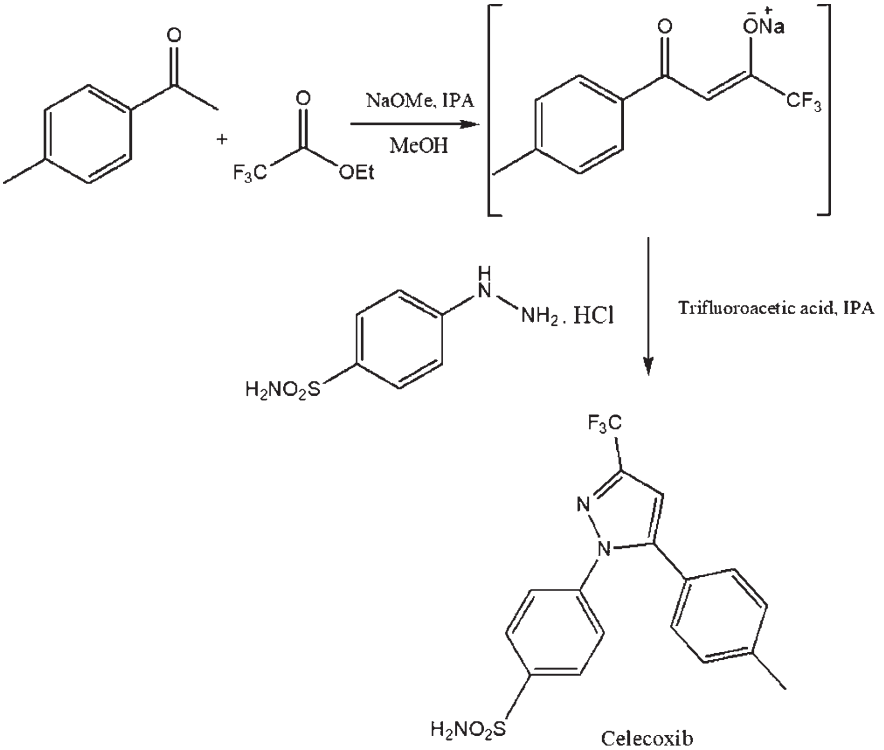



**Scheme 26** Green synthesis of sidenafil

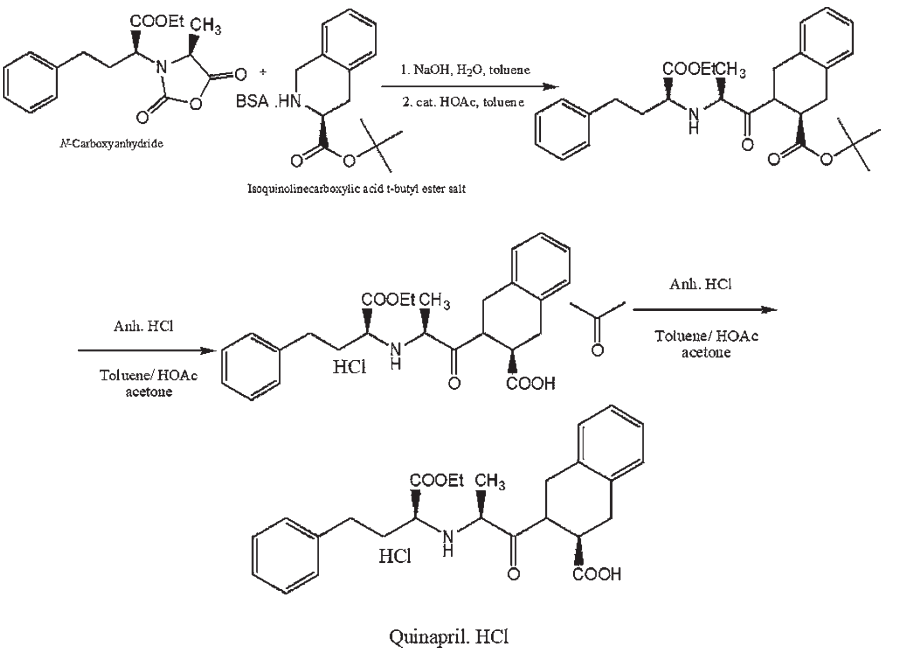
The green benefits include increase in yield from 63 to 84, considerable reduction in waste (35%), and decrease in the use of hydrazine (hazardous material). The modification in reaction conditions permitted product isolation at 20 °C instead of 5 °C (lesser energy requirement). Moreover, the cleaner product permitted the use of 50% aqueous isopropanol as the cake wash solvent instead of 100% isopropanol, thereby reducing solvent usage. This process was thus devoid of using undesirable solvents hexane and methylene chloride. Combined with the other changes, the green process eliminated the requirement of 5200 metric tons of the solvent annually.

Quinapril hydrochloride is used to treat hypertension and congestive heart failure. The redesigned synthesis of quinapril hydrochloride was primarily aimed at the elimination of acetic acid, thereby minimizing the generation of diketopiperazine, a side product formed via intramolecular cyclization in the presence of acetic acid. The synthesis involved reacting *N*-carboxyanhydride (starting material) with the isoquinoline carboxylic acid t-butyl ester. The use of self-activated anhydride paved way for direct amide coupling and elimination of the solvent NN'-dicyclohexylcarbodiimide, its waste product (dicyclohexylurea), and a chlorinated solvent (Scheme 28; Jennings 2005). Consequently, the total yield increased from 58% to 90%, waste generation was reduced, throughput got quadrupled, and green solvents in lesser quantities were used.

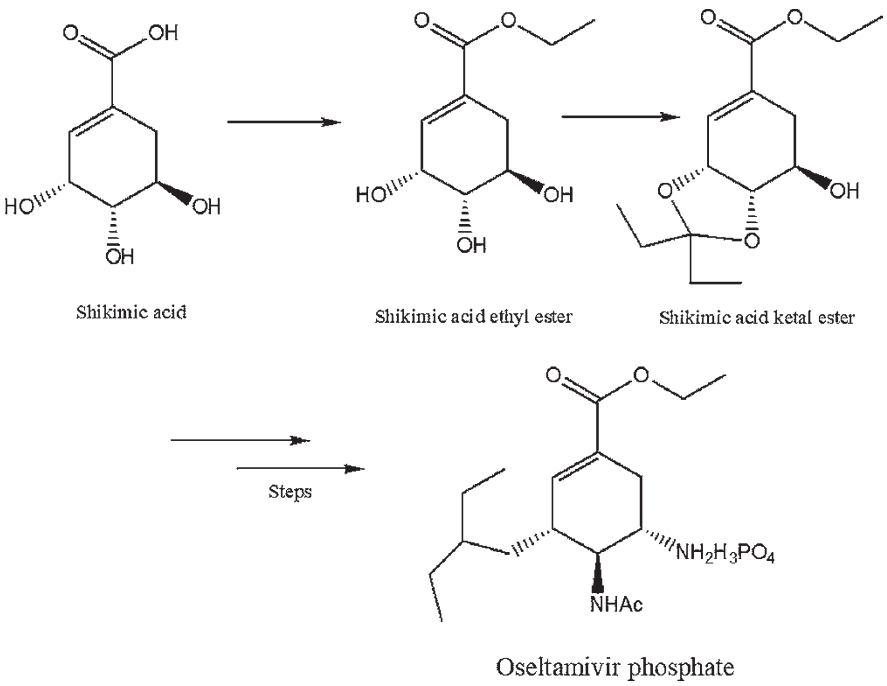
Oseltamivir phosphate is used clinically for the treatment and prevention of influenza. Shikimic acid isolated from Chinese star anise seeds (*Illicium verum*) is the starting material for its production. For the generation of catalyst for an initial esterification step (anhydrous hydrochloric acid), corrosive and toxic thionyl chloride is used. In order to omit the use of thionyl chloride, Ressmann et al. described




**Scheme 27** Green synthesis of celecoxib




**Scheme 28** Green synthesis of quinapril

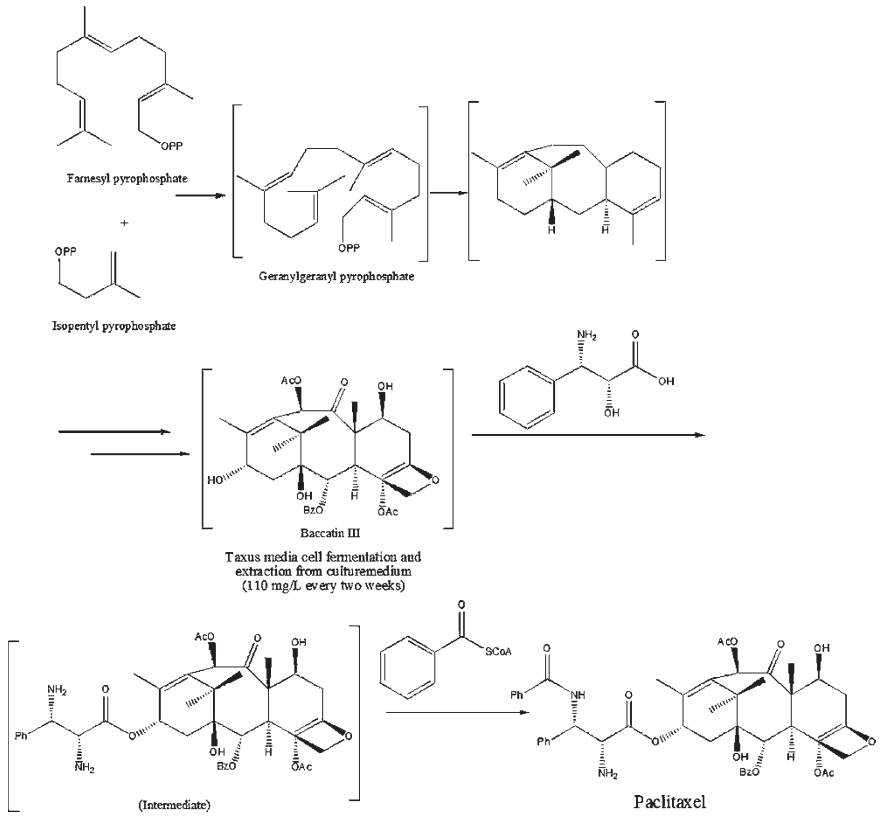



**Scheme 29** Green synthesis of oseltamivir

an ionic liquid-based strategy for reactive dissolution of seeds of star anise. The process used Bronsted-acidic ionic liquid both as catalyst and solvent for the production of shikimic acid ethyl ester and subsequently for in situ generation of ketal ester in order to improvise the synthesis of oseltamivir phosphate (Scheme 29; Gabel et al. 2007). This novel single-step strategy provided high yielding environmentally benign manufacturing process of oseltamivir phosphate.

Paclitaxel is clinically used as the therapeutics of aggressive forms of lung, breast, and ovarian cancer and is indicated for AIDS-related Kaposi's sarcoma (Bhattacharyya et al. 2000; Sung et al. 2005). The Taxus cell fermentation process which is a semisynthetic route was developed to downsize 11 chemical reactions, large quantities of hazardous solvent usage, and waste generation in the production of paclitaxel (Zhong 2002). The procedure makes use of two precursors, namely, farnesyl diphosphate and isoprenyl diphosphate. The coupling of the precursors is catalyzed by a series of enzymatic reactions to yield baccatin III (Scheme 30; Singh et al. 2003). The intermediate is then converted to paclitaxel.

The use of atom-efficient catalytic methodologies has become imperative for the manufacturing of drugs. Consequently, biocatalyzed reactions are accomplished under mild conditions of pressure and temperature preferably in water. Saxagliptin is an orally active hypoglycemic (Augeri et al. 2005), which inhibits dipeptidyl peptidase-IV (DPP-IV). For its synthesis, an intermediate (S)-N-BOC-3-hydroxyadamantyl glycine is required that was originally prepared using phenylalanine dehydrogenase.

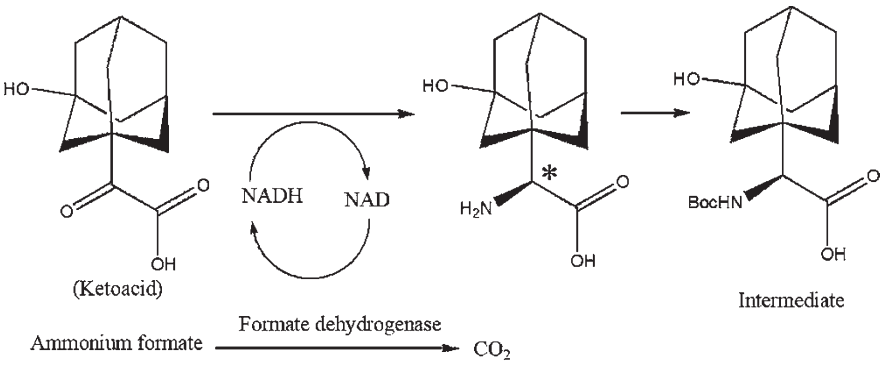



**Scheme 30** Green synthesis of paclitaxel by cell fermentation

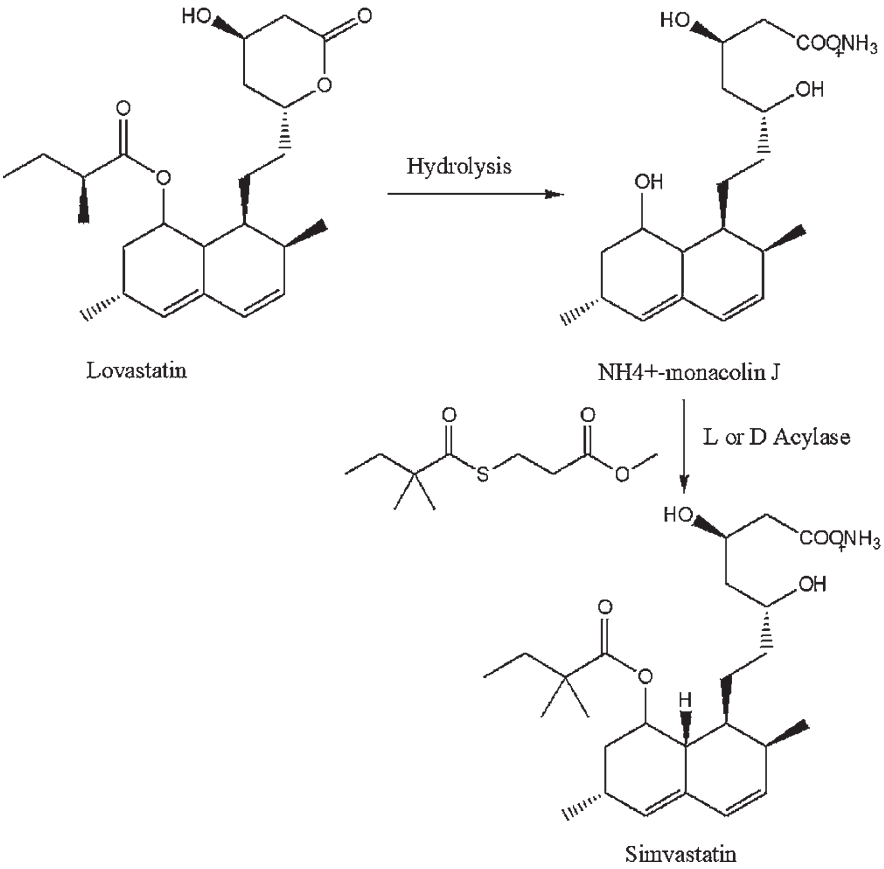
The chiral center was successfully positioned via enzyme-based reductive amination of keto acid (Scheme 31; Hanson et al. 2007), thereby decreasing the five-step process to a single-step process and eliminating the reactants cyanide and chiral reagent, (*R*)-(-)-2-phenylglycinol, and hence reducing the cost. Other green benefits include surpassing weak oxidation in the final step and accomplishing reaction in water as solvent.

Simvastatin, marketed by Merck as Zocor®, is a hypocholestermic drug indicated for the prevention of cardiovascular diseases and treatment of dyslipidemia. Xie and Tang (2007) reported an efficient whole-cell biocatalytic process for the conversion of monacolin J to simvastatin (Scheme 32). The acyl donor (L/D) that could precisely induct 2-methylbutyryl side chain at the C8 alcohol of sodium/ammonium salt of monacolin J resulted in more than 99% conversion in single step.

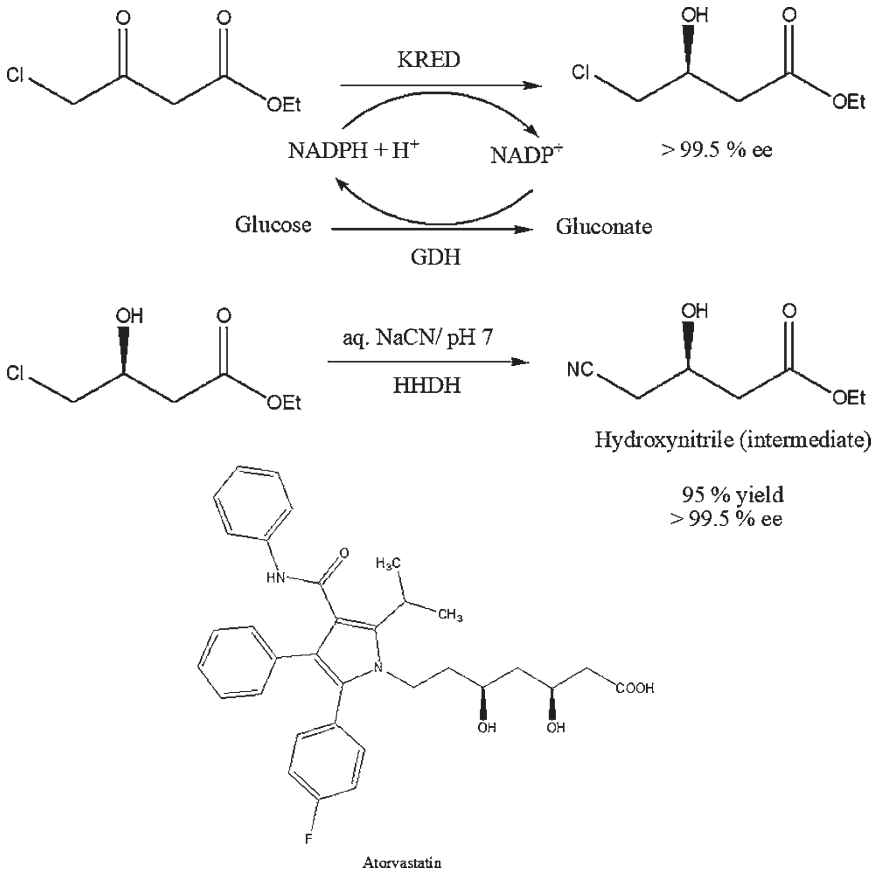
The green synthesis of atorvastatin received the distinguished Presidential Green Chemistry Challenge Award in 2006. Atorvastatin characteristically reduces low-density lipoproteins and triglycerides in the blood while increasing the levels of




**Scheme 31** Green synthesis of intermediate of saxagliptin



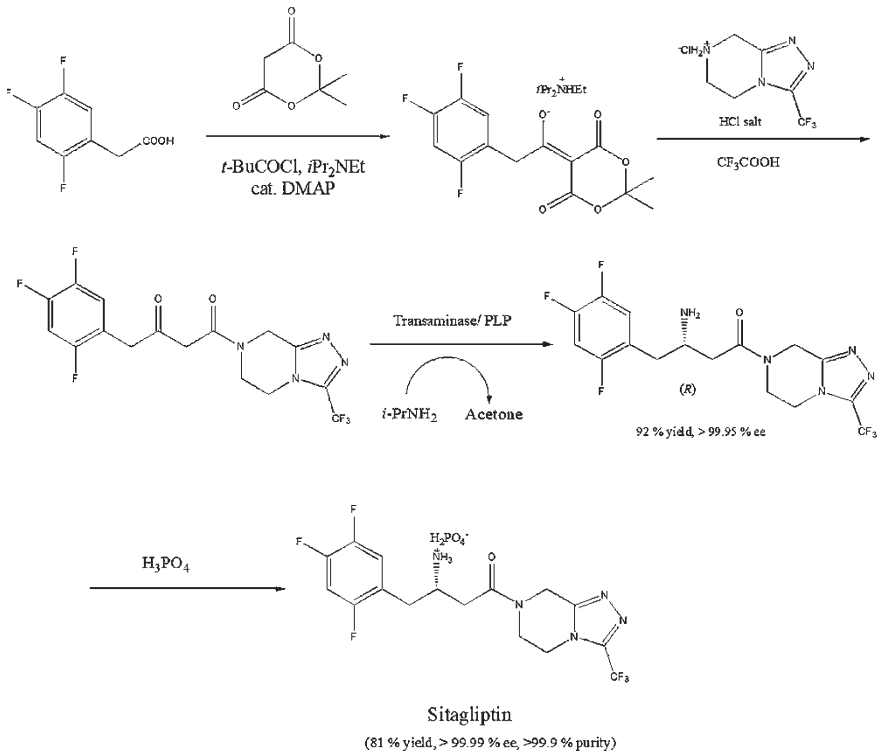

**Scheme 32** Green synthesis of simvastatin




**Scheme 33** Green synthesis of hydroxynitrile, an intermediate atorvastatin (Codexis process)

high-density lipoproteins. Its synthesis is a two-step process as shown in Scheme 33 that involves three enzymes (one for cofactor regeneration; Fox et al. 2007). A 96% yield of (S) ethyl-4-chloro-3-hydroxybutyrate was achieved. Subsequently, halohydrin dehalogenase (HHDH) catalysis for the replacement of the chloro substituent with cyano at neutral pH afforded environmentally benign and economical production of the intermediate, hydroxynitrile. The highly selective biocatalysis accomplished by the use of three highly active enzymes at low loadings afforded a considerable reduction in waste generation. The E factor (kg waste/kg product) for the overall process was 5.8, when process water was not included. The cofactor and enzymes accounted for < 1% of the waste. Furthermore, the solvent butyl acetate was recyclable with an efficiency of 85% (Ma et al. 2010).

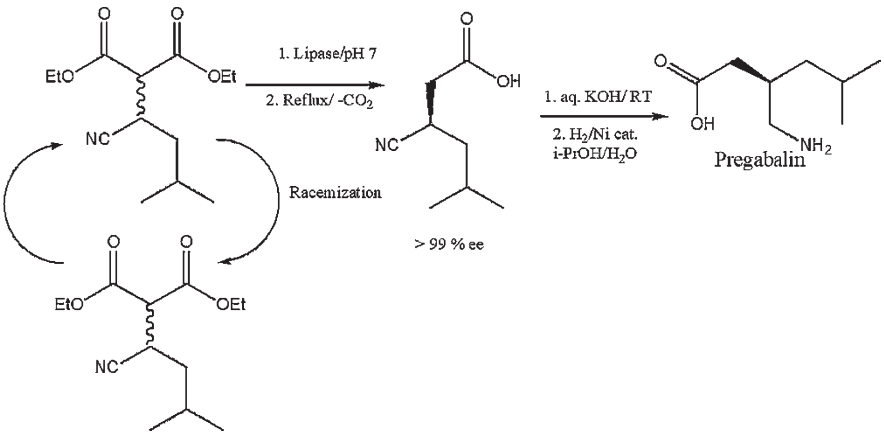
Sitagliptin, a selective, potent dipeptidyl peptidase-IV inhibitor, is used clinically for the treatment of type 2 diabetes (Herman et al. 2007). The synthesis of sitagliptin gradually evolved to a greener one that fulfilled eight principles of sustainable chemistry. Savile et al. (2010) reported the bioacatalyzed synthesis of sitagliptin using transaminase instead of a rhodium metal resulting in purer product with higher yield in fewer steps (Scheme 34).



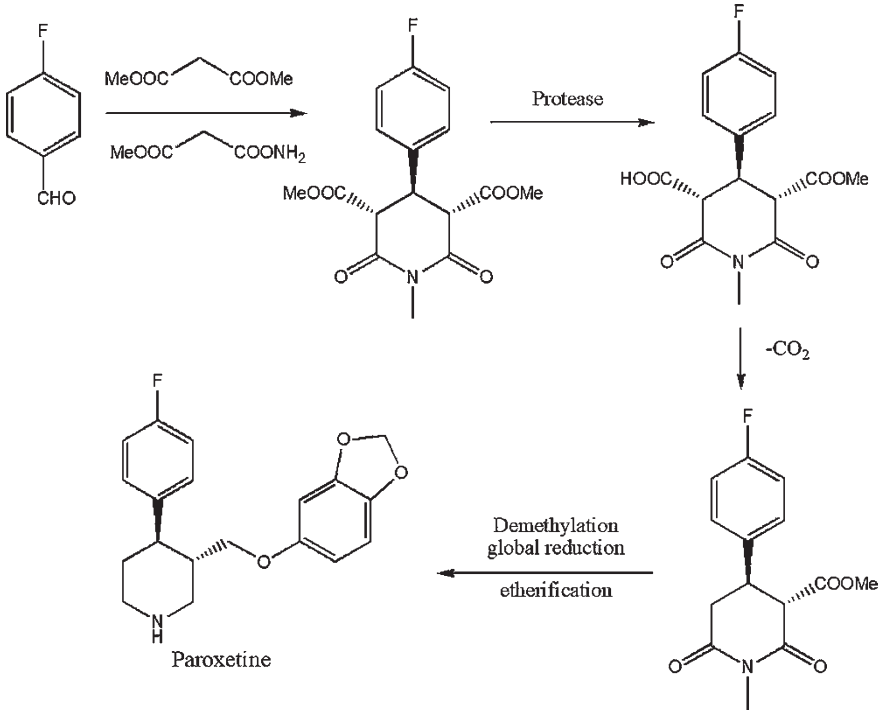

**Scheme 34** Green synthesis of sitagliptin

Pfizer has reported an environmentally friendly and economical chemoenzymatic method for the synthesis of pregabalin, marketed as Lyrica, for the management of epilepsy, anxiety, neuropathic pain, and social phobia (Lauria-Horner and Pohl 2003). Biocatalytic green synthesis of pregabalin is lipolase (lipase enzyme from *Thermomyces lanuginosus*) catalyzed resolution of a cyano diester to generate (*S*)-enantiomer with high enantioselectivity of 98% ee and resolution yield of 45%. The enantiomer was subsequently decarboxylated, hydrolyzed, and hydrogenated to pregabalin ion (Scheme 35; Koenig 2013). The enzymatic step demonstrated a volumetric activity of more than 500 g/L. As the undesirable (R)-enantiomer was susceptible to racemization to CNDE, the process yield was improved to 40% after single recycling consequently doubling the yield of the product. The E factor dropped from 86 to 17 as approximately 2000 metric tons of raw materials and over 10 million gallons of organic solvents were eliminated on yearly basis (Martinez et al. 2008).

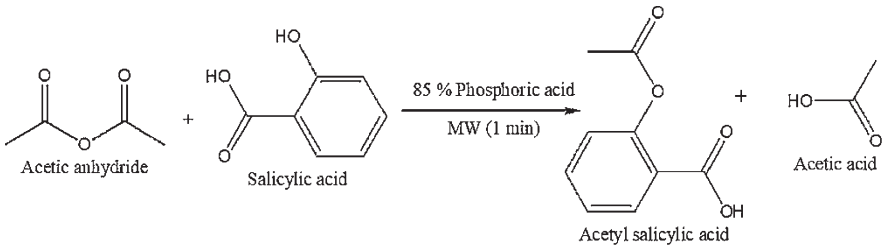
GlaxoSmithKline described a green synthesis for paroxetine (antianxiety agent) that almost doubled the yield obtained by conventional route, resulting in cost-efficient and shorter process. The significant green step was regioselectively hydrolysis of an ester group utilizing protease enzyme (Scheme 36; Koenig 2013). Mitra et al. (2010) carried out microwave-induced synthesis of aspirin, an NSAID class of drug, as shown in Scheme 37. The microwave method of synthesis of aspirin was not only energy efficient but also gave higher yield.




**Scheme 35** Green synthesis of pregabalin




**Scheme 36** Green synthesis of paroxetine

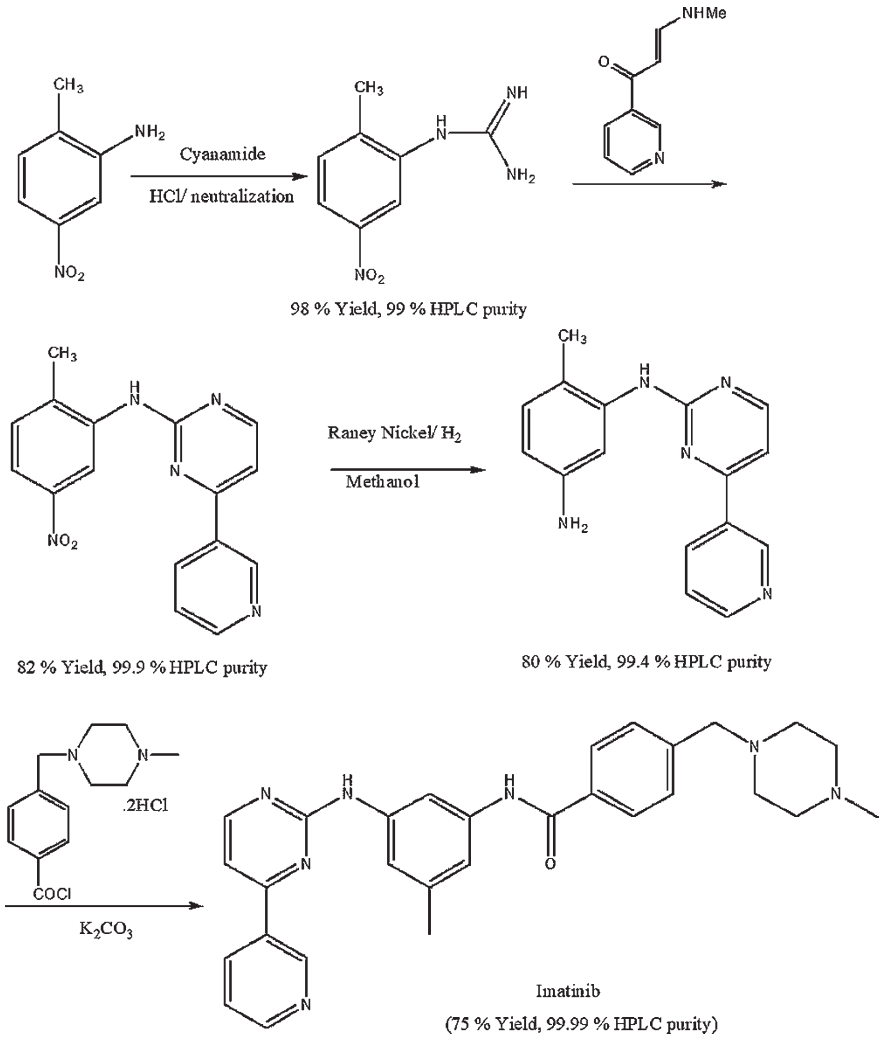



**Scheme 37** Green synthesis of aspirin

Imatinib is a potent selective inhibitor of c-kit oncogenic tyrosine kinase and BCR-ABL and is indicated for the chemotherapy of gastrointestinal stromal tumor and chronic myeloid leukemia (Arora and Scholar 2005). Kompella et al. (2012) reported an efficient microwave synthesis for imatinib that resulted in a product with 99.99% purity, and the overall yield was 50% (Scheme 38). (S)-(+)-Clopidogrel bisulfate is an orally active antithrombotic agent clinically used for managing ischemic stroke and myocardial infarction (Ressmann et al. 2011). A four-step green synthesis in one pot has been reported for clopidogrel by Wang et al. (2007). The starting material 2(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)yl) acetonitrile is reacted with L-camphor sulfonic acid (L-CSA) in toluene. Furthermore, an efficient and selective resolution of racemic mixture of clopidogrel resulted in an overall yield of 88% and more than 98.3% ee (Scheme 39). Valsartan angiotensin II receptor antagonist is indicated for cardiovascular therapeutics, namely, hypertension and heart failure (Farsang 2011). In an attempt to develop green synthesis of valsartan, Pandarus et al. (2013) reported a heterogeneous Suzuki-Miyaura coupling reaction between 2-chlorobenzonitrile and 4-tolylboronic acid in ethanol, to generate 4-methyl-2-biphenylcarbo-nitrile catalyzed by SiliaCat DPP-Pd (organosilica matrix functionalized with diphenylphosphine ligands bound to Pd(II)) (Scheme 40).

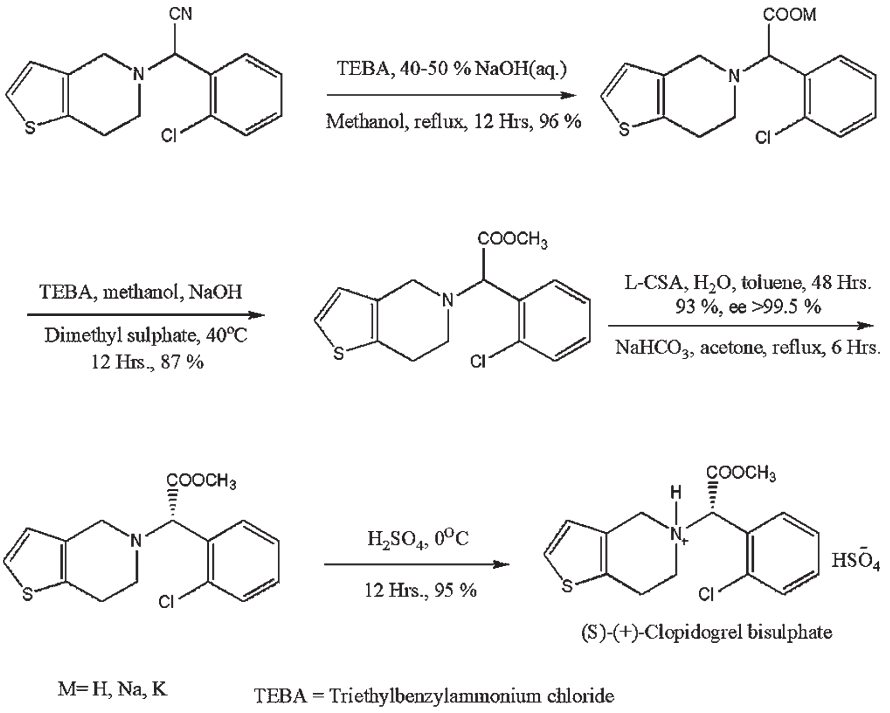
To resolve poor aqueous solubility issue of drug candidates, a supercritical technology RESOLV has been utilized that affects particle size reduction (Pathak et al. 2004). This technology has been used for reducing the particle size of the drugs naproxen and ibuprofen. RESOLV produced nanoscale particles of less than 100 nm suspended in aqueous medium. The nanosuspensions were stabilized by polymeric and oligomeric stabilizing agents in order to protect from particle agglomeration and precipitation. The technology offers a green solution for nanosizing drugs aimed at developing modulated drug delivery systems (Subramaniam et al. 2001).

The design of the final chemical products should be such that, after fulfilling its functions, these products should easily degrade to harmless substances that do not cause environmental pollution. This approach is exemplified by the creation of biodegradable (green) polymers, which can be disposed of in bioactive environments to




**Scheme 38** Green synthesis of imatinib

be degraded by the enzymatic action of microbes. For example, poly(capro-lactone) and poly(alkylene succinate) are biodegradable polymers. For continuous environmental monitoring, a real-time field measurement evaluation is desirable (Wang 2002). In view of radical changes in the pharmaceutical industry in the last decade, research alliances with academia (Fig. 3) are now imperative for extensive use of the green principles.




**Scheme 39** Green synthesis of plavix


**Scheme 40** Green synthesis of valsartan using Suzuki-Miyaura coupling reaction

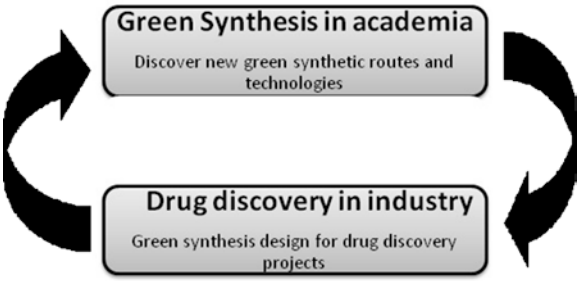



**Fig. 3** Molecule-value relationship in drug discovery and organic synthesis

## 6 Conclusion

Increased awareness on environmental protection favors applications of green chemistry both in chemical industries and pharmaceutical companies. The green synthetic strategies facilitate organic transformations by being simple and selective, amenability to manipulation, increased reaction rates, minimizing waste generation, and being economical. The fundamental innovations in chemical sciences have impacted the chemical and pharmaceutical industries and will lead us to many more economical and efficient chemical syntheses. Conclusively, the more the green chemistry rules are put into practice, the better will be the world as a place to live.

## References

Al-Qalaf F, Mekheimer RA, Sadek KU. Cerium (IV) ammonium nitrate (CAN) catalyzed the one-pot synthesis of 2arylbenzothiazoles. Molecules. 2008;13:2908–14.

Anastas PT, Warner J. Green chemistry: theory and practice. Oxford: Oxford University Press; 1988.

Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther. 2005;315:971–9.

Augeri J, Robl A, Betebenner DA, Magnin DR, Khanna A, Robertson JG, Wang A, Simpkins LM, Taunk P, Huang Q, Han S-P, Abboa-Offei B, Cap M, Xin L, Tao L, Tozzo E, Welzel GE, Egan DM, Marcinkeviciene J, Chang SY, Biller SA, Kirby MS, Parker RA, Hamann LG. Discovery and preclinical profile of saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase iv inhibitor for the treatment of type 2 diabetes. J Med Chem. 2005;48:5025–37.

Balalaie SCC, Abdolmohammadi SC, Bijanzadeh HRC, Amani AMC. Diammonium hydrogen phosphate as a versatile and efficient catalyst for the one-pot synthesis of pyrano[2,3-*d*]pyrimidinone derivatives in aqueous media. Mol Divers. 2008;12:85–91. https://doi.org/10.1007/s11030-008-9079-7.

Bararjanian MC, Balalaie S, Movassagh BC, Amani AMC. One-pot synthesis of pyrano[2,3-*d*]pyrimidinone derivatives catalyzed by *L*-proline in aqueous media. J Iran Chem Soc. 2009;6:436–42.

Baron AC, Martinez JC, Lamaty FC. Solvent-free synthesis of unsaturated amino esters in a ball-mill. Tetrahedron Lett. 2010;5:6246–62.

Bhattacharyya S, Fan L, Vo L, Labadie J. Titanium (IV) isopropoxide mediated solution phase reductive amination on an automated platform: application in the generation of urea and amide libraries. Comb Chem High Throughput Screen. 2000;3:117–24.

Bose AK, Pednekar S, Ganguly SN, Chakraborty G, Manhas MS. A simplified green chemistry approach to the Biginelli reaction using 'grindstone chemistry'. Tetrahedron Lett. 2004;45:8351–3.

Bowles P (Pfizer Inc., USA). Process for preparing aryl piperazinyl-heterocyclic compounds. US Patent 5206366, April 27. 1993.

Chemat-Djenni ZC, Hamada BC, Chemat FC. Atmospheric pressure microwave assisted heterogeneous catalytic reactions. Molecules. 2007;12:1399–409.

Dayakar C, Mounika L, Rajkumar K, Zehra A, Murthy TR, Kalivendi SV, Tiwari AK, Raju BC. Synthesis of biological activities of nicotinaldehyde based azlactones. Indian J Chem. 2018;57B:98–107.

Devi I, Kumar BSDC, Bhuyan PJC. A novel three-component one-pot synthesis of pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines using microwave heating in the solid state. Tetrahedron Lett. 2003;44:8307–10.

Dong YWC, Wang GWC, Wang LC. Solvent-free synthesis of naphthopyrans under ball-milling conditions. Tetrahedron. 2008;64:10148–53.

Dunn PJ, Galvin S, Hettenbach K. The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by green chemistry metrics. Green Chem. 2004;6:43–8.

Dunn P, Wells A, Williams MT. Green chemistry in the pharmaceutical industry. Weinheim/New York/Chichester/West Sussex: Wiley-VCH Verlag; 2010.

Earle MJ, Seddon KR, Adams CJ, Roberts G. Friedel–Crafts reactions in room temperature ionic liquids. Chem Commun. 1998;19:2097–9.

Elango V, Murhpy MA, Smith, BL, Davenport KG, Mott GN, Zey EG, Moss GL. Method for producing ibuprofen. US Patent 4981995 granted, January 1. 1991.

Epps A, Barbas J, Mandouma G. Synthesis of substituted 2, 2′-dinitrobiphenyls by a novel solvent-free high yielding Ullmann coupling biarylation. Int J Innov Educ Res. 2014;2:133–49.

Fahmy AF, El-Sayed AA, Hemdan MH. Multicomponent synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) using a mechanochemical approach. Chem Cent J. 2016;10:59. https://doi.org/10.1186/s13065-016-0205-9.

Farsang C. Indications for and utilization of angiotensin receptor II blockers in patients at high cardiovascular risk. Vasc Health Risk Manag. 2011;7:605–22.

Fox RJ, Davis CS, Mundorff EC, Newman LM, Gavrilovic V, Ma SK, Chung LM, Ching C, Tam S, Muley S, Grate J, Gruber J, Whitman JC, Sheldon RA, Huisman GW. Improving catalytic function by ProSAR-driven enzyme evolution. Nat Biotechnol. 2007;25:338–44.

Gabel MD, Groaning F, Johnston DA. WIPO patent WO 2007/074091, July 5. 2007.

Gadamasetti KG. Process chemistry in the pharmaceutical industry. New York: Marcel Dekker; 1999. p. 3–17. https://doi.org/10.1021/jm990629g.

Gupta AD, Sepay N, Mallik AK. An efficient microwave-assisted synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones by a three component reaction under catalyst-and solvent-free conditions. Eur Chem Bull. 2016;5:185–8.

Guzen KP, Guarezemini AS, Orfao ATG, Cella R, Pereira CMP, Stefani HA. Eco-friendly synthesis of imines by ultrasound irradiation. Tetrahedron Lett. 2007;48:1845–8.

Hanson RL, Goldberg SL, Brzozowski DB, Tully TP, Cazzulino D, Parker WL, Lyngberg OK, Vu TC, Wong MK, Patel RN. Preparation of an amino acid intermediate for the dipeptidyl peptidase iv inhibitor, saxagliptin, using a modified phenylalanine dehydrogenase. Adv Synth Catal. 2007;349:1369–78.

Herman GA, Stein PP, Thornberry NA, Wagner JA. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: focus on sitagliptin. Clin Pharmacol Ther. 2007;81:761–7.

Jagwani D, Joshi P. A greener chemistry approach for the synthesis of 4(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester. Int J Pharm Sci Res. 2015;6:783–90.

Jain S, Pradeep KC, Paliwal GC, Babu NC, Bhatewara AC. DABCO promoted one-pot synthesis of dihydropyrano(*c*)chromene and pyrano[2,3-*d*]pyrimidine derivatives and their biological activities. J Saudi Chem Soc. 2011;1:535–40.

Jat LR, Mishra R, Pathak D. Synthesis and anticancer activity of 4-benzylidene- 2-phenyl oxazol-5 (4*H*)-one derivatives. J Pharm Pharm Sci. 2012;4:378–80.

Jennings S (Pfizer). A green process for the synthesis of quinapril hydrochloride: summary for the presidential green chemistry challenge awards program. 2005. Available online at: https://www.epa.gov/sites/production/files/documents/award_entries_and_recipients2005.pdf. Accessed on 01 July 2019.

Jiminez-Gonzales C, Curzons AD, Constable DJC, Cunningham VL. Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds: a case-study. Int J Life Cycle Assess. 2004;9:114–21.

John L, Tucker M, Faul MM. Industrial research: drug companies must adopt green chemistry. Nature. 2016;534:27–9. https://doi.org/10.1038/534027a.
Kappe CO, Peiber B, Dallinger DC. Mikrowelleneffekte in der organischen Synthese – Mythos oder Wirklichkeit? Angew Chem. 2013;52:1124–30. https://doi.org/10.1002/ange.201204103.
Kazemi M, Kohzadi H, Abdi M. Alkylation of thiols in green mediums. J Mater Environ Sci. 2015;6:1451–4.
Khurana JM. Sonochemistry. Chem Educ. 1990; 70:24–29.
Kidwai M. Dry media reactions. Pure Appl Chem. 2001;73:147–51.
Koenig SG. Scalable green chemistry, case studies from the pharmaceutical industry. Boca Raton: Taylor & Francis Group, CRC Press; 2013.
Kompella A, Adibhatla BRK, Muddasani PR, Rachakonda S, Gampa VK, Dubey PK. A facile total synthesis for large-scale production of imatinib base. Org Process Res Dev. 2012;16:1794–804.
Kua YL, Gan S, Morris A, Kiat H. Ethyl lactate as a potential green solvent to extract hydrophilic (polar) and lipophilic (non-polar) phytonutrients simultaneously from fruit and vegetable by-products. Sustain Chem Pharm. 2016;4:21–31.
Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs. 2003;12:663–72.
Letendre LJ, Snoddy C, Klemm GH, McGhee W (Pfizer). Green chemistry in the redesign of the celecoxib process. Summary for the presidential green chemistry challenge awards program. 2005. Available online at: https://aiche.confex.com/aiche/2008/techprogram/P134118.HTM. Accessed on 01 July 2019.
Ma SK, Gruber J, Davis C, Newmann L, Gray D, Wang A, Grate J, Huisman GW, Sheldon RA. A green-by-design biocatalytic process for atorvastatin intermediate. Green Chem. 2010;12:81–6.
Madje BR, Ubale MB, Bharad JV, Shingare MS. Alum an efficient catalyst for Erlenmeyer synthesis. S Afr J Chem. 2010;63:158–61.
Mandhare DB, Barhate VD. Development of extractive spectrophotometric method for the determination of iron (III) with schiff base 2-[(2-hydroxyphenylimino) methyl]-4-nitrophenol. Int J Curr Pharm Res. 2016;8:89–91.
Martinez CA, Hu S, Dumond Y, Tao J, Kelleher P, Tully L. Development of a chemoenzymatic manufacturing process for pregabalin. Org Process Res Dev. 2008;12:392–8.
Mazaahir KC, Ritu GC, Kavita SC. A selective synthesis for novel pyranodipyrimidines. Indian J Chem. 2007;46B:1159–63.
Miglani S, Mishra M, Chawla P. The rapid synthesis of schiff bases without solvent under microwave irradiation and their antimicrobial activity. Der Pharm Chem. 2012;4:2265–9.
Mitra S, Ragunath S, Mitra A, Sae KO. Green chemistry in teaching laboratory: microwave-induced reactions. New Jersey's Science and Technology University, pp 18–19. 2010. Available online at https://web.njit.edu/~mitra/green_chemistry/Content/Manual-april-2010.pdf. Accessed on 03 July 2019.
Mobinikhaledi AC, Bodaghi-Fard MAC. Tetrabutylammonium bromide in water as a green media for the synthesis of pyrano[2,3-*d*]pyrimidinone and tetrahydrobenzo[*b*]pyran derivatives. Acta Chim Slov. 2010;57:931–5.
Mobinikhaledi AC, Foroughifar NC, Bodaghi-Fard MAC. Eco-friendly and efficient synthesis of pyrano[2,3-*d*] pyrimidinone and tetrahydrobenzo[*b*]pyran derivatives in water. Synth React Inorg Met-Org Metal Org Nano-Met Chem. 2010;40:179–85.
Modarresi-Alam AR, Nasrollahzadeh M, Khamooshi F. Solvent free preparation of primary carbamates using silica sulfuric acid as an efficient reagent. ARKIVOC: Arch Org Chem. 2007;16:238–45. https://doi.org/10.3998/ark.5550190.0008.g23.
Mohammadi-Ziarani G, Faramarzi S, Asadi S, Badiei A, Bazl R, Amanlou M. Three-component synthesis of pyrano [2, 3-*d*]-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO 3 H) and their docking and urease inhibitory. DARU J Pharm Sci. 2013;21:1–3.
Mohan PC, Rao JV. Biological evaluation of schiff bases of new isatin derivatives for anti Alzheimer's activity. Asian J Pharm Clin Res. 2014;7:114–7.

Murti Y, Mishra P. Expeditious synthesis and evaluation of heterocyclic chalcones and flavanones as anticancer agents. Indian J Heterocycl Chem. 2016;26:113–20.
Murti Y, Mishra P. Synthesis, characterization, and biological evaluation of novel naringenin derivatives as anticancer agents. Curr Bioact Compd. 2019;15:1–6. https://doi.org/10.2174/1573407215666181214114927.
Pandarus V, Desplantier-Giscard D, Gingras G, Béland F, Ciriminna R, Pagliaro M. Silia*Cat*: a versatile catalyst series for synthetic organic chemistry. Org Process Res Dev. 2013;17:1492–7.
Pathak P, Meziani MJ, Desai T, Sun YPJ. Nanosizing drug particles in supercritical fluid processing. Am Chem Soc. 2004;126:10842–3.
Patil SB. Biological and medicinal significance of pyrimidines: a review. Int J Pharm Sci Res. 2018;9:44–52.
Perron-Sierra FM, Pierre A, Burbridge M, Guilband N. Novel bicyclic oxazolone derivatives as anti-angiogenic agents. Bioorg Med Chem Lett. 2002;12:1463–6.
Ressmann AK, Gaertner P, Bica K. From plant to drug: ionic liquids for the reactive dissolution of biomass. Green Chem. 2011;13:1442–7.
Rothenberg G, Downie AP, Raston CL, Scott JT. Understanding solid/solid organic reactions. J Am Chem Soc. 2001;123(36):8701–8.
Saikia L, Baruah JM, Thakur AJ. A rapid, convenient, solvent less green approach for the synthesis of oximes using grindstone chemistry. Org Med Chem Lett. 2011;1:12. https://doi.org/10.1186/2191-2858-1-12.
Salgin-Goksen U, Gokhan-Kelekci N, Goktas O, Koysal Y, Kilic E, Isik S, Aktay G, Ozalp M. 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4*H*)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: synthesis analgesic-anti-inflammatory and antimicrobial activities. Bioorg Med Chem. 2007;15(17):5738–51.
Savile CK, Janey JM, Mundorff EC, Moore JC, Tam S, Jarvis WR, Colbeck JC, Krebber A, Fleitz FJ, Brands J, Devine PN, Huisman GW, Hughes GJ. Biocatalytic asymmetric synthesis of chiral amines from ketones applied to sitagliptin manufacture. Science. 2010;329:305–9. https://doi.org/10.1126/science.1188934.
Sharma GK, Pathak D. Microwave-assisted, solvent-free and parallel synthesis of some novel substituted imidazoles of biological interest. Chem Pharm Bull. 2010;58(3):375–80.
Simon M-O, Li C-J. Green chemistry oriented organic synthesis in water. Green Chem. 2012;12:1415–27.
Singh AK, Weaver RE, Powers GL, Rosso VW, Wei C, Lust DA, Kotnis AS, Comoezoglu ET, Liu M, Bembenek KS, Phan BD, Vanyo DJ, Davies ML, Mathew RJ, Palaniswamy VA, Li W-S, Gadamasetti K, Spagnuolo CJ, Winter WJ. Trifluoroacetic acid-mediated cleavage of a triethylsilyl protecting group: application in the final step of the semisynthetic route to paclitaxel (Taxol). Org Process Res Dev. 2003;7:25–7.
Subramaniam B, Saim S, Rajewski R, Stella VJ. ACS symposium series 2001. Green engineering, pp 96–110. 2001.
Sung FL, Poon TCW, Hui EP, Ma BBY, Liong E, To KF, Huang DPWS, Chan AT. Antitumor effect and enhancement of cytotoxic drug activity by cetuximab in nasopharyngeal carcinoma cells. In Vivo. 2005;19:237–45.
Taber GP, Pfisterer DM, Colbeg JC. A new and simplified process for preparing *N*-[4(3,4dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenylidene]methanamine and a telescoped process for the synthesis of (1*S*-cis)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro-*N*-methyl1-naphthalenamine mandelate: key intermediates in the synthesis of sertraline hydrochloride. Org Process Res Dev. 2004;8:385–8.
Tanaka K. Solvent-free organic synthesis. Weinheim: Wiley-VCH; 2003. https://doi.org/10.1021/op034052v.
Tanaka K, Toda F. Solvent-free organic synthesis. Chem Rev. 2008;100:1025–74.
Tang SLY, Smith RL, Poliakoff M. Principles of green chemistry: productively. Green Chem. 2005;7:761–2.

Tang S, Bourne R, Smith R, Poliakoff M. The 24 principles of green engineering and green chemistry: “improvements productively”. Green Chem. 2008;10:268–9.
Trask AV, Jones W. Crystal engineering of organic cocrystals by the solid-state grinding approach. In: Toda F. (eds) Organic solid state reactions. Topics in Current Chemistry. 2015; 254:41–70, Springer, Berlin, Heidelberg.
Trost BM. On inventing reactions for atom economy. Acc Chem Res. 2002;35:695–705.
Wang J. Real-time electrochemical monitoring: toward green analytical chemistry. Acc Chem Res. 2002;35:811–6.
Wang L, Shen J, Tang Y, Chen Y, Wang W, Cai Z, Du Z. Synthetic improvements in the preparation of clopidogrel. Org Process Res Dev. 2007;11:487–9.
Wardencki W, Curylo J, Namiesnic J. Green chemistry – current and future. Pol J Environ Stud. 2005;14:389–95.
Wasserscheid P, Welton T. Ionic liquids in synthesis. Weinheim: Wiley-VCH; 2002. https://doi.org/10.1002/9783527621194.
Webb PB, Kunene TE, Cole-Hamilton DJ. Continuous flow homogeneous hydroformylation of alkenes using supercritical fluids. Green Chem. 2005;7:373–9.
Witvrouw M, Pannecouque C, Clercq E, Fernandez-Alvarez E, Marco JL. Inhibition of human immunodeficiency virus type (HIV-1) replication by some diversely functionalized spirocyclopropyl derivatives. Arch Pharm Pharm Med Chem. 1999;332:163–6.
www.epa.gov/greenchemistry. Accessed on 10 July 2019.
www.epa.gov/greenchemistry/green-chemistry-challenge-2019-greener-synthetic-pathways-award. Accessed on 10 July 2019.
Xie X, Tang Y. Efficient synthesis of simvastatin by use of whole-cell biocatalysis. Appl Environ Microbiol. 2007;73:2054–60. https://doi.org/10.1128/AEM.02820-06.
Yu JC, Wang HC. Green synthesis of pyrano[2,3-*d*]-pyrimidine derivatives in ionic liquids. Synth Commun. 2005;35:3133–40.
Zhang TY. In: Clark J, Macquarrie D, editors. Waste minimization in pharmaceutical process development: principles, practice and challenges in handbook of green chemistry and technology. Oxford: Blackwell Science; 2002. p. 306–20.
Zhong J-J. Plant cell culture for production of paclitaxel and other taxanes. J Biosci Bioeng. 2002;94:591–9.

# Selective Transformation of Glycerol to Lactic Acid by Porous Multifunctional Mixed Oxide Catalysts Under Alkaline Environment

**Mohamed Hussein Abdurahman, Muhammad Hazim Yaacob, Nor Irwin Basir, and Ahmad Zuhairi Abdullah**

**Contents**



## 1 Introduction to Glycerol

Glycerol is known as a biodegradable, renewable, and environmentally friendly product. With such properties, glycerol grabs the attention as alternative green chemical feedstock for various organic reactions and is applicable in many areas. Glycerol is mainly produced as a side product from the biodiesel production process when triglycerides of plant or animal origins that consist of long-chain fatty acids

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_9

are attached to three hydroxyl groups upon reaction with alcohol (particularly methanol) with the assistance of alkaline catalysts (Pagliaro et al. 2008). Generally, biodiesel production process through the transesterification of triglyceride will produce 10 wt. % of crude glycerol, or in other words, 10 kg of crude glycerol will be obtained from every 100 kg of methyl ester (biodiesel) (Yang et al. 2012).

The global glycerol market nowadays is facing an oversupply problem because of the remarkable increase in biodiesel production. More recently, biodiesel industry became the highest contributor to the glycerol market at around 67% in comparison to other contributing industries such as fatty acid (21%), fatty alcohol (8%), soap, and others (4%) (ABG Inc 2010). Besides, it was reported that the residual glycerol produced from biodiesel industry has the potential to be the source of energy by using incineration method. Although this method seems to be plausible in order to solve the problem regarding the oversupply of glycerol, its incineration at high temperature will also generate highly toxic materials such as acrolein (Guerrero-Pérez et al. 2009).

From 2000 to 2005, glycerol production was dominated by fatty acid industry where the annual production of glycerol remained relatively stable with the price per ton of refined glycerol during that period ranged between USD 1600 and 1800 (Quispe et al. 2013). However, by 2006, biodiesel industry started to dominate the glycerol production causing a significant increase in its production rate. This massive increase caused its price to decline each year. This trend was expected to continue since there was a high demand on biodiesel in the market as it is the most promising energy source to replace fossil fuel, especially when fossil fuel is estimated to be depleted by 2050 (Goyal et al. 2013).

To address the surplus of glycerol in the market, a lot of researches are focusing their research on the use of glycerol to produce other downstream useful chemicals that could help stabilize glycerol market price and biodiesel industry as a whole. The unique properties of glycerol offer a variety of versatile products to be produced in downstream industries. At present, a large number of value-added products (e.g., propionic acid, 1,3-propanediol, acrolein, alcohols (methanol and ethanol), monoglyceride, and many more) can be obtained from glycerol. Table 1 shows the possible products that can be derived from glycerol via different approaches and their respective usages.

Among several value-added chemicals possible to be produced from glycerol, lactic acid has been receiving a particular research attention. The exploration of lactic acid generation by catalytic conversion of glycerol has been rarely attempted until recently despite the high demand in various industries. Thus, the present paper critically reviews related studies on selective glycerol to lactic acid conversions catalyzed by homogeneous and heterogeneous base catalysts.

**Table 1** The summary of products derived from glycerol

| Product | Process | Uses | References |
|---|---|---|---|
| Mono-,di-, and tri-tertiary butyl ethers | Etherification | As alternative fuel additives | Bozkurt et al. (2015) |
| 1,3-Propanediol | Hydrogenolysis | Used in cosmetics, foods, and medicine industry | Tan et al. (2013) |
| Acrolein | Dehydration | Intermediate in the synthesis of acrylic acid | Haider et al. (2012) |
| Propionic acid | Fermentation | Used as antifungal agent in food industries | Dishisha et al. (2015) |
| Hydrogen | Steam reforming | Raw material for ammonia and fertilizers, energy carrier for PEM fuel cells | Davda et al. (2005) |
| Dihydroxyacetone (DHA) | Direct and indirect oxidation | Used in skin care products | Zheng et al. (2015) |
| Cyclic acetals | Transacetalization, acetalization | Used as fuel additives | Trifoi et al. (2016) |
| Monoglyceride | Esterification | Used in food and pharmaceutical industries | Hermida et al. (2011) |
| Lactic acid | Hydrothermal | Used in cosmetic, food, cosmetics, and packaging industries | Razali and Abdullah (2017) |

## 2 Lactic Acid

Chemically known as 2-hydroxypropanoic, lactic acid is a 3-C molecule consisting of a hydroxyl group located adjacent to a carboxyl group as shown in Fig. 1. These hydroxyl and carboxyl groups are responsible for the modification of lactic acid into other valuable chemicals such as lactide, lactic amide, pyruvic acid, and acrylic acid that have various applications in industry (Andres et al. 2013). Moreover, lactic acid is also incorporated into cosmetic and personal care products for its humectant properties. Due to its ability to form other value-added chemicals, this unsaturated carboxylic acid is also commonly used in other industries such as packaging, textile, and pharmaceutical. The common applications of lactic acid are summarized in Table 2. As can be seen, this substance has high demand in industry and sustainable production from widely available substances at low price such as glycerol will provide a new prosperous future, especially for biodiesel-producing countries.

There are two alternative routes for producing lactic acid either by fermentation or catalytic process. Presently, the commercial production of lactic acid is achieved mostly through fermentation of carbohydrates (glucose or sucrose). Microbes like *L. delbrueckii, L. amylophilus*, *and L. bulgaricus* are commonly used in the fermentation process these conversions (Andres et al. 2013). The selection of a suitable microorganism for the fermentation processes is a topic of great research interest as each microorganism has its own characteristics that can influence its behavior in the lactic acid production process.

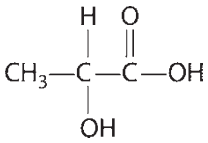


**Fig. 1** Chemical structure of lactic acid

**Table 2** Applications of lactic acid in different industries

| Application | Uses | Purposes | References |
|---|---|---|---|
| Food industry | Food additives, preservative agent, and pH regulator | Production of yogurt and cheese | Razali and Abdullah (2017) |
| Textile industry | Polymer additives, adhesives, coatings, printing toners, and surfactants | For use in tents, patio umbrellas, and awnings | Kwan et al. (2018) |
| Cosmetic industry | Moisturizing, pH adjuster, exfoliant, antimicrobial and rejuvenating effects on the skin | Manufacture of hygiene such as toothpaste, mouthwashes, and many others | Andres et al. (2013) |
| Pharmaceutical industry | Prostheses, surgical sutures, dialysis solution mineral, and drug delivery systems | Production of dermatologic drugs and prevention for osteoporosis | Pagliaro et al. (2008) |
| Packaging industry | Production of biodegradable plastic | Food packaging | Hu et al. (2017) |

Alternatively, commercial lactic acid production can also be achieved through a chemical synthesis route involving the hydrolysis of lactonitrile by strong acids such as sulfuric acid. Lactonitrile could be obtained as a by-product from the manufacture of acrylonitrile (Chen et al. 2014). It is formed when acetaldehyde is reacted with hydrogen cyanide with the assistance of a base at high pressure. The advantage of using lactonitrile route to manufacture lactic acid is that the procedure is simple in comparison to the fermentation route as described earlier. However, because of the limitations for the raw materials and expensive operational costs, this process is not very feasible for industrial application.

In many respects, catalytic production of lactic acid provides an interesting alternative to the biochemical routes. The catalyst, or sometimes a suitable combination of catalysts, can be used to drive the reaction toward the desired route. As the process involves a multistep reaction with different requirements, the right combination of catalytic components is the key to success in meeting this objective. The reaction conditions that are likely to post significant influence on the reactivity of the reactant as well as the products' selectivity should also be properly understood and optimized.

## 3 Reaction Mechanism

Based on observations and intermediates detected in various studies, the mechanism to obtain lactic acid from glycerol catalyzed by a base can be proposed to follow the mechanism as depicted in Fig. 2. The scheme is initiated by the dehydrogenation step of glycerol to give glyceraldehyde with the release of one hydrogen atom by the glycerol molecule. As glycerol is a stable compound, this step might be the rate-controlling step in the reaction, and the reaction temperature should be sufficiently high to allow appreciable chemisorption of the reacting species. In this step, it was reported that the presence of dehydrogenation catalyst such as noble metals and transition metals (usually Cu and Ni) could promote the transformation of glycerol to glyceraldehyde (Arcanjo et al. 2017; Ftouni et al. 2015; Maris et al. 2007; Yin et al. 2018). These elements have half-filled *d*-orbitals to effectively participate in this reaction.

The dehydrogenation reaction is then followed by the dehydration of glyceraldehyde to form 2-hydroxypropenal, and it can readily convert to pyruvaldehyde via keto-enol tautomerization. The equilibrium of this tautomerization reaction is very thermodynamically driven, and therefore the reaction temperature is very influential in dictating the favorable products to be formed. Lastly, lactate is formed from pyruvaldehyde by benzylic rearrangement and hydration in the presence of alkaline medium. In short, an ideal catalyst for this conversion should be of different components serving different needs to be effective in producing lactic acid. The reaction conditions especially temperature will need accurate control to allow favorable formation of intermediates leading to the desired product.

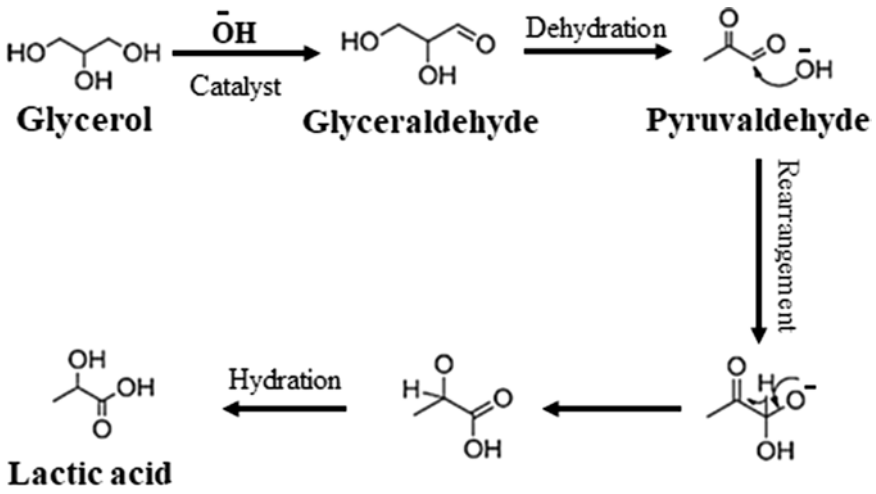


**Fig. 2** Proposed reaction pathway for conversion of glycerol to lactic acid

# 4 Catalysts for Glycerol to Lactic Acid Conversions

## *4.1 Homogeneous Catalysts*

Investigation on glycolaldehyde to lactic acid conversion via chemical catalysis was first reported by Kishida et al. (2005). Glycolaldehyde is a substance with high similarity with glyceraldehydes that is produced from glycerol. They found that sodium hydroxide was an effective basic catalyst to enhance the hydrothermal reaction to lactic acid. It was observed that almost all glycolaldehyde could be converted to the desired product when NaOH was used as the basic catalyst in the reaction at shorter reaction time. The lactic acid yield recorded in 1.5 h for the reaction performed at 300 °C was around 28.0% from aqueous solution of glycerol (0.33 M). This study confirmed the formation of an aldehyde through dehydration of glycerol prior to the formation of a carboxylic acid from glycerol.

The performances of a series of alkaline catalysts (alkali metal hydroxides and alkaline earth metal hydroxides) have been further demonstrated by Shen et al. (2009). They suggested that all the alkaline catalysts could promote lactic acid formation from glycerol. The alkali metal hydroxides showed improved catalytic activity with respect to lactic acid yield compared to alkaline earth metal hydroxides. This observation concluded that alkali metal hydroxides could also result in the lactic acid formation, but the yield was rather low. This indicated that a certain rate-controlling step during the process needed significant acceleration to increase the lactic acid yield. The results also showed that KOH had the highest activity among the tested catalysts which was consistent with basicity level of the catalyst. The high activity was attributed to the formation of lactate from pyruvaldehyde by benzylic rearrangement at higher hydroxide ion concentration (Kishida et al. 2006). Moreover, the benzylic rearrangement can only take place significantly in a basic solution. Thus, variation in the basicity condition of the reaction medium would affect the product selectivity. From this finding, it is suggested that the selectivity to lactic acid was strongly dictated by the strength of base catalysts but fast reaction rate could not be achieved without the use of a catalytic component to induce dehydrogenation step of glycerol molecule to form glyceraldehyde.

Although high yield of lactic acid could be obtained using strong basic homogeneous catalyst, there are also important drawbacks for industrial development. The biggest problem is due to the fact that these catalysts could dissolve in glycerol and cannot be recovered for recycle. The leached metal could also affect the purity of product, and further purification process is needed. Besides, this reaction requires high concentration hydroxide ion to achieve good yield of lactic acid. According to Ramirez-López et al. (2010), high concentration of $OH^-$ (> 1 M) can result in serious corrosion to the commonly used stainless-steel reactors. Moreover, the reaction usually requires high temperature and pressure which cause the reactor to corrode faster. Therefore, the process is not economically feasible for production of lactic acid. In addition, shape selectivity effect that could influence the product selectivity does not exist in homogeneous catalytic system so that the product selectivity is

completely influenced by the physicochemical properties of the catalyst and the conditions of the catalytic process.

## *4.2 Heterogeneous Catalysts*

Heterogeneous catalysts have received a considerable attention due to their advantages over homogeneous catalysts, such as (i) being easily separated from the products, (ii) reusable, and (iii) thermally stable, which could be used at high reaction temperature (Hattori 2015). In addition, the physical and geometrical dimensions of the pores could allow certain degree of shape selectivity effect to come into play during the reaction. Therefore, it is clear that heterogeneous catalyst offers an added advantage to be used in place of homogeneous catalysts in this conversion. Furthermore, multiple reaction steps with different requirements could mean that a multicomponent catalyst could be the key solution to the problem of poor lactic acid selectivity in the process.

The performance of heterogeneous basic catalyst has been studied using potassium feldspar (Xue et al. 2014). In this study, potassium feldspar was immersed into sodium hydroxide solution through isometric impregnation treatment. The reaction was then performed in a batch reactor at a reaction temperature of 280 °C. The treated potassium feldspar gave high lactic acid yield compared to the untreated potassium feldspar. This observation was attributed to the fact that the amount of basicity of potassium feldspar increased after being treated with sodium hydroxide with the highest lactic acid yield of 12.4%. However, it was also noted that the catalytic activity of the catalyst kept changing even at the same reaction conditions, suggesting that lactic acid distribution was highly sensitive to the changes in the basicity in this reaction.

Later, Gao et al. (2016) were encouraged to investigate the performance of bentonite in this hydrothermal conversion of glycerol. Bentonite was selected due to its being inexpensive and abundant in nature. In this study, they observed that bentonite could perform as a solid base since it could promote the desired lactic acid formation. The formation of lactic acid was mainly attributed to the role of Brönsted-base sites located on the surface. Moreover, it was observed that almost all glycerol could be converted to products. Unfortunately, the yield of lactic acid obtained in this reaction was only around 11% to suggest the undesired course of reaction. Low amount of lactic acid produced in this reaction was associated with the high reaction temperature and long reaction time to reach significantly high conversion which favored the formation of products including formic acid and acetic acid which were undesirable. In this study, the reaction was performed at 275 °C for 12 h to compensate for the poor activity of the catalyst.

The production of lactic acid by hydrotalcites as the solid base catalysts has been reported by Onda et al. (2008). They reported that the production of lactic acid improved with the increasing number of Brönsted-base sites on the catalyst's surface. In addition, the number of Brönsted-base sites could be varied, depending on

the calcination temperature of the hydrotalcite acid. Furthermore, this catalyst showed high stability for repeated uses in several runs without demonstrating significant activity loss. However, the results showed that glycerol conversion and lactic acid yield were still low to indicate that a certain rate-limiting step in the lactic acid formation was yet to be addressed. The conversion of glycerol to lactic acid achieved only 57% with a corresponding lactic acid yield of 10.7% even when the reaction temperature was set at 323 K for 8 h. Despite giving higher glycerol conversion, higher temperature was however detrimental to the lactic acid yield to indicate the promotion of side reactions.

Oxides of alkaline earth metals (i.e., MgO, CaO, SrO, and BaO) are promising catalysts in fine chemical industries. Among them, CaO catalyst has drawn the attention of researchers working on lactic acid synthesis considering its advantages such as inexpensive, strong basicity, noncorrosive, and environmentally friendly. Chen et al. (2014) investigated the reaction of glycerol to yield lactic acid using CaO catalyst. A glycerol conversion of 97% was recorded with a lactic acid yield of around 40.8% after 150 min of reaction at 290 °C. However, the dissolution of CaO catalyst in the reactant (glycerol) during the reaction was the main problem. This created the need for further purification process to obtain a high-purity product.

Later, Yin et al. (2016) further investigated a series of heterogeneous catalysts for production of lactic acid from glycerol. The study was carried out using Cu/MgO and Cu/hydroxyapatite as catalysts. A stainless-steel batch reactor was used for this purpose. Based on the results, they claimed that the simultaneous presence of metallic and basic sites in Cu/hydroxyapatite and Cu/MgO catalysts allowed them to act synergistically in the hydrothermal reaction. Both Cu/MgO and Cu/hydroxyapatite showed high conversions of glycerol of above 90.0% at 230 °C for 2 h. Due to high basicity and more porous surface, Cu/hydroxyapatite catalyst demonstrated relatively higher activity compared to Cu/MgO. However, it was also noted in this study that they used low concentration of glycerol (1 M), probably to stimulate the base catalytic effect at high temperature. Unfortunately, it would also affect the concentration of the desired product at the completion of the run (Kishida et al. 2006).

Besides, other researchers have also reported the use of Pt and Pd as examples of noble metal-based catalysts (Rosiene et al. 2017), Ru (Maris and Davis 2007), Ir (Auneau et al. 2011), and Au (Maris et al. 2007; Kumar et al. 2014) for this particular process. Rosiene et al. (2017) observed up to 74% lactic acid yield when the reaction was conducted at 230 °C for 3 h. This indicated a significant improvement in the lactic acid selectivity with the use of catalytic element with vacancy in its *f*-orbitals. Based on their studies, it could be concluded that high catalytic activities could also be generally seen by using noble metal-based catalysts in the lactic acid production. However, the prices for preparing this catalyst are too high to justify their use in industrial scale despite the high conversion of glycerol demonstrated. As such, the use of other similar catalytic elements, especially those with multiple oxidation state capability, should be an economically justifiable endeavor.

### 4.3 Multifunctional Mixed Metal Oxide Catalysts

Heterogeneous catalyst is commonly used in various reactions such as individual metal oxides, mixed metal oxides, supported alkali metal components, zeolites, and more. These catalysts generally show good results in the reaction (Chang et al. 2014). Among them, mixed metal oxides have received a significant attention due to their ability to utilize their acid-base properties to accelerate similar processes (Gawande et al. 2012).

Combinations of two or more metal oxides, generally noble metals and transition metals, form mixed metal oxides that can be used as catalysts for many reactions. Besides, mixed metal catalysts have been used in various reactions such as dehydrogenation, dehydration, and oxidation (Kaur and Ali 2014; Taufiq-Yap et al. 2011; Yu et al. 2011). Some of mixed metal oxides have been reported to show relatively higher catalytic activity compared to single metal oxides in many reactions. This was due to the fact that mixed metal oxides can be designed to increase the basic and acidic sites of the catalyst, as well as to improve their stability to prevent leaching problem in the reaction. Different components in the catalysts could also address different requirements or steps in the overall reaction mechanism. The performances of mixed metal oxide catalyst that have been reported are as presented in Table 3. It is clear that the catalytic components could act synergistically in the intended reaction.

**Table 3** Summary of the performances of mixed metal oxide catalysts in various reactions

| Catalyst | Product | Remark | References |
|---|---|---|---|
| $MgO/Al_2O_3$ | α,β-Unsaturated esters and nitriles | The reaction gave high yields of the product of about 80% in short reaction time. In addition, this catalyst could be recycled once with high activity | Di Cosimo et al. (1996) |
| $MoO_3/SiO_2$ | Tinidazole | The $MoO_3/SiO_2$ catalyst showed high stability and could be recycled up to five times without significant losses in conversion and selectivity | Chandorkar et al. (2007) |
| $(MoVW)_5O_{14}$ | Acrylic acid | Tungsten played an important role as a structural promoter for the formation and stabilization of this catalyst. Besides, vanadium was also responsible for high catalytic activity for this reaction | Mestl (2006) |
| CaO/NiO | Biodiesel | The basicity of mixed metal oxide catalyst was higher compared to CaO catalyst. In addition, this catalyst showed remarkable stability with six successful runs without losing active sites in the reactant | Teo et al. (2014) |
| CuO/MgO | Lactic acid | The synthesized CuO/MgO catalyst exhibited high basicity which was helpful in this reaction. In addition, CuO also effectively catalyzed the hydrothermal conversion of glycerol through dehydrogenation reaction | Yin et al. (2016) |

### *4.4 Alkaline Earth Metal Oxide Catalysts*

Oxides of alkaline earth metals (particularly CaO and MgO) are widely studied due to their benefits such as high basic strength, inexpensiveness, and environmentally friendly. CaO has already found its use in biodiesel production because of its properties as a heterogeneous base catalyst. The transesterification reaction and glycerol to lactic acid reaction share some similarities as they are base-catalyzed reactions. Many researchers have subsequently dedicated their works to increase the activity of CaO catalyst. Huaping et al. (2006) showed excellent catalytic activity in the transesterification process by using CaO treated with ammonium carbonate solution. It was found that the high basic sites located on the surface of modified CaO resulted in a good conversion of *Jatropha curcas* oil of about 93%.

Zabeti et al. (2010) developed basic heterogeneous catalyst of $CaO/Al_2O_3$ to produce biodiesel from palm oil. It was found that the catalyst had a large surface area and strong basic sites. Notably, $Al_2O_3$ acted as the catalyst support which allowed calcium to be well distributed on its surface, thereby improving the stability of the catalyst. At optimum conditions, a biodiesel yield that could be achieved was around 98.64%. Besides, this catalyst could also be reused at least twice while maintaining high activity in the reaction. This result indicated that increased porosity and surface area allowed better interaction between the catalyst and the reacting species leading to higher rate of reaction while at the same time allowing a certain degree of shape selectivity effect.

Yan et al. (2009) investigated the correlations between different preparation methods with the performance of $CaO/La_2O_3$ catalyst. They used four different methods to synthesize $CaO/La_2O_3$ catalyst including ammonia-ethanol-$CO_2$ treatment, physical mixing, coprecipitation, and impregnation. It was found that the catalyst prepared via ammonia-ethanol-$CO_2$ treatment method exhibited high activity owing to its high specific surface area, base strength, and basic site concentration compared to other preparation methods. In addition, this catalyst showed remarkable stability with three successful runs in a batch reactor.

It has been proven by Wen et al. (2010) that the combination of other metals with alkaline earth metal oxide could improve the stability of the catalyst, plus it could enhance the catalytic performance in the production of methyl esters (biodiesel). The FAME yield could reach over 85% by using a mixed metal oxide, i.e., a $TiO_2$/MgO catalyst prepared via sol-gel method. Furthermore, this catalyst also demonstrated high stability with four successful runs while maintaining high product yields. They suggested that the presence of Ti ions helped improve the stability of the catalyst because of the defects created by the substitution of Ti ions for Mg ions in the magnesium oxide lattice. Besides, it has been recorded in many studies that oxides of alkaline earth metals (e.g., CaO, MgO) could be effectively improved in terms of their stability and catalytic performance by the incorporation with other metal oxides including $Ce_2O$, $ZrO_2$, ZnO, SrO, and many others. Table 4 summarizes the performance of basic mixed metal oxides in the transesterification reaction of triglycerides.

**Table 4** Summary of the performances of mixed metal oxide catalysts in biodiesel production

| Catalyst | Catalyst preparation | Remark | References |
|---|---|---|---|
| CaO/$Al_2O_3$ | Sol-gel | The CaO/$Al_2O_3$ catalyst showed high catalytic activity with 98.64% biodiesel yield. This catalyst possessed high surface area together with strong basic sites. Besides, this catalyst could also be reused at least twice | Zabeti et al. (2010) |
| CaO/$La_2O_3$ | Ammonia-ethanol-$CO_2$, physical mixing, impregnation, coprecipitation | The catalysts were prepared by using four different methods. The catalyst prepared by ammonia-ethanol-$CO_2$ exhibited the highest specific area, and base strength resulted in high FAME yield of 94.3% within 60-min reaction time. This catalyst could be recycled three times in the batch reactor | Yan et al. (2009) |
| CaO/ZnO | Ball milling, coprecipitation | The catalyst prepared by ball milling method showed high catalytic activity than that by coprecipitation method. Besides, they observed that the presence of basic sites on the surface of CaO/ZnO was attributed to $Ca^{2+}$-$O_2$ pairs | Rubio-Caballero et al. (2013) |
| CaO/NiO | Coprecipitation | The basicity of mixed metal oxide catalyst was higher compared to CaO catalyst. Also, the catalytic activity of mixed metal oxide was higher in comparison to CaO only. This catalyst showed remarkable stability with six successful runs without significant loss of active sites in the reactant | Teo et al. (2014) |
| CaO/MgO | Coprecipitation | The reactivity of catalyst could be changed with the alteration of the MgO amount. This catalyst also demonstrated high reusability (four times) while maintaining its product yield | Taufiq-Yap et al. (2011) |
| MgO/ZnO | Coprecipitation | The synthesized catalyst demonstrated higher activity in comparison with the single metal oxides of MgO and ZnO | Lee et al. (2013) |
| SrO/MgO | Coprecipitation | They compared the performance of MgO, SrO, and SrO/MgO catalysts for biodiesel production. SrO/MgO exhibited the highest catalytic activity | Paula et al. (2012) |

## *4.5 Noble and Transition Metals as the Dehydrogenation Catalysts*

As mentioned earlier, the first step for producing lactic acid is through the dehydrogenation reaction of glycerol molecule to give glyceraldehydes. In this reaction, one hydrogen atom is released from the glycerol molecule. In this case, the inclusion of a dehydrogenation catalyst could efficiently transform glycerol to glyceraldehyde leading to high activity for glycerol conversion to lactic acid. Generally, noble metals particularly platinum, palladium, and rhodium are most commonly used for lactic acid production. Table 5 summarizes the performance of noble metal catalysts in

**Table 5** Summary of the performance of noble metal catalysts in the production of lactic acid

| Catalyst | Operating condition | Glycerol conversion (%) | Lactic acid yield (%) | Remark | References |
|---|---|---|---|---|---|
| Pt/C, Pd/C | $T$ = 230 °C, $t$ = 4 h | 99 | 74, 68 | Noble metals of Pt and Pd had significant effects on the catalytic performance. The catalysts also showed high stability with five successful runs while maintaining high lactic acid yields | Arcanjo et al. (2017) |
| $Pt/ZrO_2$ | $T$ = 180 °C, $t$ = 8 h | > 90 | 80 | The presence of Pt-based catalysts decreased the reaction temperature. However, it took longer time to complete the reaction | Ftouni et al. (2015) |
| Au-Pt/$CeO_2$ | $T$ = 200 °C, $t$ = 20 min | 99 | 80 | Au-Pt/$CeO_2$ was an efficient catalyst for one-pot conversion of glycerol to lactic acid. Lactic acid could be obtained at a yield of 80% in 20 min | Kumar et al. (2014) |
| Pt/C, Ru/C | $T$ = 200 °C, $t$ = 4.5 h | 92, 99 | 62, 47 | With the addition of NaOH, the yield of lactic acid could be significantly increased | Maris and Davis (2007) |
| Pd/C, Ru/C, Rh/C | $T$ = 220 °C, $t$ = 6 h | 91.1, 97.7, 87.0 | 40.1, 39.6, 37.9 | Pd/C catalyst exhibited good catalytic activity in this reaction compared to Ru/C and Rh/C. These catalysts assisted the dehydrogenation step of glycerol in the process | Iqbal et al. (2015) |

lactic acid production. It has been postulated that the partially filled *f*-orbital of those elements allowed their interaction with the reacting species leading to an extraction of one hydrogen atom from the glycerol molecule. This reaction is deemed a rate-limiting step bearing in mind the relative stability of glycerol molecule. Although several studies showed promising results with respect to glycerol conversion and yield of lactic acid, expensive cost and low availability limit noble metal uses in large-scale processes.

Recently, a few studies have been turned toward transition metals such as Ni, Co, and Cu due to the fact that these metals are low-cost alternatives and have similar properties as noble metals as dehydrogenation catalysts. Younas et al. (2016) used NiO nanoplate as catalyst in the synthesis of lactic acid from rice straw in the presence of NaOH. It was observed that the yield of lactic acid could obtain nearly 58.8% in 2 h for a reaction at 260 °C. They observed that with the presence of NiO within the system, the yield of lactic acid could be improved compared to that without NiO catalyst. This suggested that NiO catalyst had a promotional effect toward lactic acid yield in this process, especially in the dehydrogenation of glycerol molecules to initiate the subsequent steps. Similar observation was also made by Yin

et al. (2018) when they used NiO supported on graphite. It was reported that the use of nickel catalyst resulted in high catalytic activity in this process. They reported that at 230 °C for 3 h, the glycerol conversion could reach 97.6% with a lactic acid selectivity of almost 92.2%. Furthermore, they also managed to propose the reaction pathways for the selective conversion of glycerol to lactic acid assisted by nickel catalyst. Table 6 summarizes few recent reported works using supported transition metal-based catalysts for lactic acid production. In general, the use of relatively cheap transition metals could reduce the severity of the reaction conditions to achieve sufficiently high glycerol conversion. Lower reaction temperature will limit the occurrence of side reactions, while shorter reaction time also limits the chance for the further reaction of lactic acid to its undesired derivatives.

## 5 Effect of Catalyst Preparation Steps on the Physicochemical Properties

Generally, the amount of nickel loaded on the alkaline earth metal could affect the surface and physicochemical properties of the catalyst. Alca and Cruz-Herna (2016) investigated the morphological structure of NiO/CaO catalyst prepared using incipient impregnation method. They observed that relatively small polyhedral particles of roughly 200–300 nm were dispersed on the surface of CaO. This observation resembled that reported by Hwa et al. (2014) where a coprecipitation method was used for the preparation of the NiO/CaO catalyst.

Nevertheless, the presence of nickel particles on the surface of CaO could have significant effect on the catalyst's specific surface area. The result from $N_2$ adsorption-desorption analysis proved that the specific surface area decreased from 9.2 to 7.2 $m^2/g$ after the incorporation of nickel particles (Teo et al. 2014). This phenomenon was attributed to the formation of larger crystallite sizes of the catalyst after the coupling of NiO with CaO. Furthermore, it was learned that total surface area of NiO/CaO catalyst could further decrease with increasing nickel loading (Chanburanasiri et al. 2011; Choudhary and Rajput 1996). These decreases might be related to the large amount of nickel particle agglomerates on the surface of CaO (Taufiq-Yap et al. 2012).

Interestingly, it was also found that the incorporation of NiO with CaO could affect the basicity of the catalyst. Hwa et al. (2014) compared the total basicity between pure CaO and NiO/CaO catalyst using $CO_2$–TPD analysis. They reported that NiO/CaO possessed high basicity in comparison with the pure CaO catalyst. This observation suggested that the improvement basicity of NiO/CaO catalyst might be due to the synergism effect between NiO and CaO (Taufiq-Yap et al. 2011). However, it was also reported that as the amount of nickel was increased, the basicity of NiO/CaO catalyst could reduce (Chanburanasiri et al. 2011). This phenomenon might be due to the damage on the binary oxide structure which was ascribed to the high amount of nickel content deposited on the surface of CaO (Teo et al. 2014).

**Table 6** Summary of the performance of transition metal catalysts in the production of lactic acid

| Catalyst | Operating condition | Glycerol conversion (%) | Lactic acid yield (%) | Remark | References |
|---|---|---|---|---|---|
| $Co_3O_4/CeO_2$ | $T$ = 250 °C, $t$ = 4 h | 86 | 68 | Highly dispersed crystalline $Co_3O_4$ particles in close interaction with the $CeO_2$ support surface created a synergetic effect to selectively form lactic acid | Palacio et al. (2018) |
| 0.5%Cu–1.0%Pt/AC | $T$ = 90 °C, $t$ = 4 h | 80 | 55 | Cu could improve the Pt dispersion, and some Pt-Cu interfaces would facilitate the glycerol transformation. $Cu^+$ and $Cu^0$ species favored lactic acid production, and large CuO led to glyceric acid | Zhang et al. (2016) |
| $CuO/ZrO_2$ | $T$ = 160 °C, $t$ = 6 h | 100 | 95 | The catalyst preparation method and reaction conditions significantly affected on reaction. Glyceric acid was the main by-product, and subsequent C–C splitting produced glycolic acid, oxalic acid, and formic acid | Yang et al. (2016) |
| Cu-Zn-Al | $T$ = 175 °C, $t$ = 4 h | 95 | 94 | LA selectivity was constant until 95% conversion. The rate of glycerol disappearance exhibited first-order dependence on glycerol concentration. The glycerol dehydrogenation on copper surface was the rate-limiting step | Li et al. (2017) |
| Cu/hydroxyapatite and Cu/MgO | $T$ = 230 °C, $t$ = 2 h | 90 | 81 | Cu/HAP was more active and could be recycled. Metallic $Cu^0$ nanoparticles effectively catalyzed the glycerol dehydrogenation reaction. Basic sites affectively promoted the formation of lactic acid | Yin et al. (2016) |

Changes in the basicity characteristics of the catalytic elements will likely to cause significant improvement in the lactic acid formation reaction from glycerol. As such, the composition of the active catalytic species should be varied for the desired effect, while a suitable porous catalytic support could play a physical role in suppressing the undesired reaction leading to the desired product.

## 6 Effect of Process Conditions

Reaction conditions also play important roles in the catalytic activity for lactic acid production. Generally, reaction temperature, catalyst loading, and reaction time can strongly affect the reactant's conversion as well as the yield and selectivity of lactic acid. Therefore, it is necessary to locate the optimum conditions so that high conversion of glycerol and at the same time high yield of lactic acid can be obtained.

### *6.1 Effect of Reaction Temperature*

Temperature is known to be an important parameter for many chemical reactions. Finding the most suitable reaction temperature is the key parameter for any reaction to be successful. Based on the previous studies, usually the range of reaction temperature for glycerol to transform to lactic acid is between 200 and 300 °C (Chen et al. 2014; Kishida et al. 2006; Ramirez-López et al. 2010). Attempts to lower the reaction temperature often subject to low glycerol conversion, while the use of low-activity catalyst would require high reaction temperature to achieve sufficiently high conversion. Unfortunately, it often leads to poor lactic acid yield owing to the tendency of lactic acid to undergo further reaction under the extreme conditions.

Ramirez-López et al. (2010) investigated the influence of reaction temperature on the conversion of glycerol to lactic acid by using 1.33 M of NaOH. The reaction run was performed using aqueous glycerol (3 M) for 90 min with the reaction temperatures varied between 250 and 290 °C. It was found that by increasing the reaction temperature from 250 to 280 °C, the conversion of glycerol significantly increased from 72% to 98%. Similar trend was also observed in the lactic acid yield, in which it increased from 59% to 90%. It was also noted that when the temperature was raised above 280 °C, the yield of lactic acid rapidly decreased. The reduction in the lactic acid yield was probably caused by the decomposition of the desired product to form by-products such as acetate and formate in the solution. Based on this observation, they also proposed two reaction pathways for the decomposition of lactic acid which are (a) lactate oxidative cleavage and (b) lactate dehydration as shown in Fig. 3.

Recently, Yin et al. (2018) studied the effect of reaction temperature on the selectivity of lactic acid in the presence of Ni nanoparticles supported on graphite and further assisted by NaOH. Increasing the temperature of the reaction from 200 to

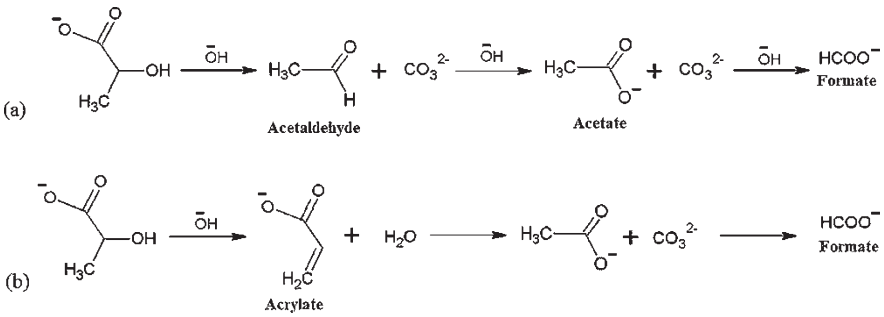


**Fig. 3** Reaction pathways of oxidative cleavage of lactic acid under alkaline medium (**a**) and dehydration of lactate (**b**). (Modified after Ramirez-López et al. 2010)

250 °C increased the conversion of glycerol from 33.8% to 100%. However, the corresponding lactic acid selectivity decreased from 94.2% to 80.4% when the reaction temperature was further increased especially from 230 to 250 °C. This could be attributed to the formation of by-products (1,2-propanediol, oxalic acid, acetic acid, and formic acid) at higher temperature which adversely influenced lactic acid selectivity. In the presence of the nickel catalyst, both glycerol and pyruvaldehyde could undergo hydrogenation to 1,2-propanediol (Ftouni et al. 2015; Yin et al. 2018). Meanwhile, other by-products such as acetate and formate could also be formed during lactic acid decomposition (Ramirez-López et al. 2010; Ftouni et al. 2015; Yin et al. 2018).

On the other hand, Chen et al. (2014) varied the reaction temperature between 280 and 300 °C using refined glycerol in the presence of CaO catalyst. They found that sufficiently high temperature was necessary to convert glycerol to lactic acid. This was due to the fact that the reaction is an endothermic one and therefore high temperature is usually required to remove the hydroxyl group of glycerol to glyceraldehyde in the first step (Rosiene et al. 2017). Thus, this finding was consistent with the general expectation that the conversion of glycerol increases with increasing reaction temperature. However, when the reaction temperatures exceeded 290 °C coupled with longer reaction period, coke formation occurred in the reaction indicating the formation of undesired by-products, which could negatively influence the lactic acid yield. Nevertheless, 40.8% was obtained at the highest lactic acid yield at 290 °C after 150 min of reaction time. Therefore, it can be concluded that at certain range of temperature, lactic acid can be the intermediate for further formation of other by-products.

## 6.2 *Effect of Reaction Time*

Reaction time can strongly influence the glycerol conversion and yield of lactic acid in the reaction process. Generally, most researchers agreed that glycerol conversion will increase with reaction time until equilibrium is reached at a certain point (Kishida et al. 2005; Chen et al. 2014; Liu and Ye 2015; Yin et al. 2016). The effect of reaction time on the selectivity of lactic acid using CuO/MgO in the presence of base catalyst was studied by Yin et al. (2016). They varied the reaction time within the range of 2–8 h and observed an increasing trend of the glycerol conversion from 76% to 88%. The increase in the conversion of glycerol was more significant at the beginning of the reaction. With further extension of reaction time beyond 7 h, no significant change was observed on the glycerol conversion. This was because the reaction started to reach its equilibrium. Similar observation was found by Ftouni et al. (2015) when they used $Pt/ZrO_2$ catalyst for 24 h of reaction.

Although studies generally show that the conversion of glycerol increases with time, further prolonging the reaction time to a certain point would result in the formation of undesired products in the reaction (Chen et al. 2014). They observed a sudden drop in the lactic acid yield to less than 30% when the reaction time was extended beyond 3 h at a temperature of 290 °C. It is therefore quite likely that the desired product had decomposed to undesired by-products (acetate and formate) at such a high reaction temperature. The problem was made worse with the long reaction time. Similar observation was also reported (Ramirez-López et al. 2010; Ftouni et al. 2015; Liu and Ye 2015). Chen et al. (2014) also mentioned that there were bubbles detected in the product after sulfuric acid was added because of the formation of carbonate ion in the reaction. This was due to the fact that carbonate ion could be formed through acetaldehyde, acetate, and formate as intermediates under alkaline conditions (Ramirez-López et al. 2010). Therefore, it could be concluded that prolonging the reaction time beyond the optimum level could result in the decomposition of the lactic acid to undesired by-products.

## 6.3 *Effect of Catalyst Loading*

Catalyst loading is another important parameter that gives significant effect on the reaction process. It is essential to determine the suitable catalyst amount required in order to maximize the yield of lactic acid. Excessive amount of catalyst used in the reaction could change the reactant-catalyst mixture to become viscous which impairs the stirring effect during the run of the reaction. On the other hand, if an insufficient amount of catalyst is used during the reaction, the optimum conversion of glycerol could not be achieved. The reaction is deemed to undergo kinetic controlling regime to the detriment of the glycerol conversion.

In order to determine the effect of catalyst loading on the conversion of glycerol and lactic acid yield, Chen et al. (2014) varied the amount of CaO catalyst to

glycerol molar ratios from 0.2 to 0.3. They observed an improvement in the glycerol conversion from 81% to 97.7%, while lactic acid yield markedly increased from 28.0% to 40.8%. An increase in lactic acid productivity was due to the higher number of basic sites on the catalyst which could provide an effective interaction with glycerol molecules. As a result, more conversion of glycerol was made possible. However, no obvious change in the glycerol conversion and lactic acid yield was observed when the amount of CaO catalyst loading was further increased to molar ratios higher than 0.3. This result suggested that there were more active sites still available in the reaction system than that actually required to catalyze the reaction to give high yield of the desired product (Liu and Ye 2015). This finding was consistent with the one reported by Liu and Ye (2015) who studied the influence of amount of alkaline earth metal oxide catalysts for the same reaction.

## 7 Reaction Kinetics

Kinetic modeling study is useful especially to demonstrate the effect of reaction parameters as well as to enable the system to be scaled up for future uses. Chen et al. (2014) developed a kinetic model for this conversion with NaOH as the catalyst in a batch mode. In this study, they found that the kinetic model of glycerol conversion to lactic acid satisfactorily fitted a pseudo-first-order kinetic model with respect to glycerol concentration as expressed in Eq. 1:

$$C_G = C_0 \exp\left(-A \exp\left(-\frac{E_a}{RT}\right) t\right) \tag{1}$$

where $C_G$ is concentration of glycerol, $C_0$ is the initial concentration of glycerol, $E_a$ is the activation energy, $R$ is the gas constant, $A$ is the pre-exponential factor, $t$ is the reaction time, and $T$ is the temperature. As such, this simple kinetic model can be used to represent the overall glycerol to lactic acid reaction that allows the calculation of an apparent activation energy.

It was also found that no significant difference could be observed between the experiment data and predicted glycerol concentration to indicate that this model could well describe (supported with high coefficient of determination, $R^2 = 0.946$) the actual reaction occurring in the batch reactor. The activation energy obtained from their study was 114 kJ/mol which was lower compared to the activation energy reported by Kishida et al. (2006) which was 174 kJ/mol. Although both research works used the same concentration of NaOH as homogeneous catalyst in this reaction, a study by Chen et al. (2014) showed that lower activation energy was obtained due to the fact that they used different types of reactor that had different temperature ramping rates during heating.

## 8 Conclusions and Recommendations

The generation of lactic acid from glycerol is an economically justified process, but it is a rather challenging task as multiple active components should involve. The basicity of the catalyst plays a significant role in determining the selective conversion of glycerol to lactic acid. Many homogeneous basic catalysts could show promising results, but heterogeneous catalysts could offer a greener process. There are some problems that remain unsolved with regard to the dissolution of active metals in the glycerol which could influence their stability during the reaction. Mixed metal oxide catalysts with *d*- and *f*-block elements are deemed a potential catalyst system for this reaction. The catalyst should address the needs in the dehydrogenation to glyceraldehydes with the help of suitable metals to be subsequently dehydrated to pyruvaldehyde and finally to lactic acid upon benzylic rearrangement reaction in alkaline medium. The quest for an efficient catalyst relies on the combinations of non-precious metals with the presence of basic sites to be further assisted by porous support materials. Optimization of the composition and the preparation method is essential. The reported catalysts perform optimally at 250–300 °C with lactic acid yields exceeding 90% in about 8 h of reaction. It needs to be shortened with the use of a more active catalyst to avoid undesired reaction leading to better lactic acid yields. The roles of influencing parameters affecting the catalytic behaviors of the catalysts should also be properly understood for an optimal process.

**Acknowledgment** FRGS grant (6071366) from the Ministry of Education Malaysia and an RUI grant (8014059) from Universiti Sains Malaysia are acknowledged.

## References

ABG Inc. Glycerin market analysis. 2010. Retrieved December 22, 2017, from https://www.scribd.com/document/93745860/Glycerin-Market-Analysis-Final

Alca B, Cruz-Herna A. Structural and microstructural analysis of different CaO–NiO composites and their application as $CO_2$. React Kinet Mech Catal. 2016;119(2):445–55. https://doi.org/10.1007/s11144-016-1066-x.

Andres F, Martinez C, Marcos E, Dom M, De Souza RP. Lactic acid properties, applications and production : a review. Trends Food Sci Technol. 2013;30(1):70–83. https://doi.org/10.1016/j.tifs.2012.11.007.

Arcanjo MRA, Silva IJ, Rodríguez-Castellón E, Infantes-Molina A, Vieira RS. Conversion of glycerol into lactic acid using Pd or Pt supported on carbon as catalyst. Catal Today. 2017;279:317–26. https://doi.org/10.1016/J.CATTOD.2016.02.015.

Auneau F, Noël S, Aubert G, Besson M, Djakovitch L, Pinel C. On the role of the atmosphere in the catalytic glycerol transformation over iridium-based catalysts. Catal Commun. 2011;16(1):144–9. https://doi.org/10.1016/j.catcom.2011.09.011.

Bozkurt ÖD, Tunç FM, Ba N, Çelebi S, Do İ, Uzun A. Alternative fuel additives from glycerol by etherification with isobutene : structure-performance relationships in solid catalysts. Fuel Process Technol. 2015;138:780–804. https://doi.org/10.1016/j.fuproc.2015.06.047.

Chanburanasiri N, Ribeiro AM, Rodrigues AE, Arpornwichanop A, Laosiripojana N, Praserthdam P, Assabumrungrat S. Hydrogen production via sorption enhanced steam methane reforming process using Ni/CaO multifunctional catalyst. Ind Eng Chem Res. 2011;50(24):13662–71. https://doi.org/10.1021/ie201226j.

Chandorkar JG, Umbarkar SB, Rode CV, Kotwal VB, Dongare MK. Synthesis of tinidazole by condensation-oxidation sequence using $MoO_3/SiO_2$ bifunctional catalyst. Catal Commun. 2007;8(10):1550–5. https://doi.org/10.1016/j.catcom.2007.01.001.

Chang F, Zhou Q, Pan H, Liu X, Zhang H, Xue W. Solid mixed-metal-oxide catalysts for biodiesel production : a review. Energ Technol. 2014;2:865–73. https://doi.org/10.1002/ente.201402089.

Chen L, Ren S, Ye XP. Lactic acid production from glycerol using CaO as solid base catalyst. Fuel Process Technol. 2014;120:40–7. https://doi.org/10.1016/j.fuproc.2013.11.019.

Choudhary VR, Rajput AM. Simultaneous carbon dioxide and steam reforming of methane to syngas over NiO-CaO catalyst. Ind Eng Chem Res. 1996;35(11):3934–9. https://doi.org/10.1021/ie960002l.

Davda RR, Shabaker JW, Huber GW, Cortright RD, Dumesic JA. A review of catalytic issues and process conditions for renewable hydrogen and alkanes by aqueous-phase reforming of oxygenated hydrocarbons over supported metal catalysts. Appl Catal B. 2005;56:171–86. https://doi.org/10.1016/j.apcatb.2004.04.027.

Di Cosimo JI, Diez VK, Apesteguía CR. Base catalysis for the synthesis of α,β,-unsaturated ketones from the vapor-phase aldol condensation of acetone. Appl Catal A. 1996;137(1):149–66. https://doi.org/10.1016/0926-860X(95)00289-8.

Dishisha T, Ibrahim MHA, Cavero VH, Alvarez MT, Hatti-kaul R. Improved propionic acid production from glycerol: combining cyclic batch and sequential batch fermentations with optimal nutrient composition. Bioresour Technol. 2015;176:80–7. https://doi.org/10.1016/j.biortech.2014.11.013.

Ftouni J, Villandier N, Auneau F, Besson M, Djakovitch L, Pinel C. From glycerol to lactic acid under inert conditions in the presence of platinum-based catalysts: the influence of support. Catal Today. 2015;257:267–73. https://doi.org/10.1016/j.cattod.2014.09.034.

Gao X, Zhong H, Yao G, Guo W, Jin F. Hydrothermal conversion of glucose into organic acids with bentonite as a solid-base catalyst. Catal Today. 2016;274:49–54. https://doi.org/10.1016/j.cattod.2016.02.008.

Gawande MB, Pandey K, Jayaram RV. Role of mixed metal oxides in catalysis science-versatile applications in organic synthesis. Cat Sci Technol. 2012;2:1113–25. https://doi.org/10.1039/c2cy00490a.

Goyal P, Sharma MP, Jain S. Optimization of transesterification of Jatropha curcas oil to biodiesel using response surface methodology and its adulteration with kerosene. J Mater Environ Sci. 2013;4(2):277–84.

Guerrero-Pérez MO, Rosas JM, Bedia J, Rodríguez-Mirasol J, Cordero T. Recent inventions in glycerol transformations and processing. Recent Pat Chem Eng. 2009;2(1):11–21. https://doi.org/10.2174/1874478810902010011.

Haider MH, Dummer NF, Zhang D, Miedziak P, Davies TE, Taylor SH, Hutchings GJ. Rubidium- and caesium-doped silicotungstic acid catalysts supported on alumina for the catalytic dehydration of glycerol to acrolein. J Catal. 2012;286:206–13. https://doi.org/10.1016/J.JCAT.2011.11.004.

Hattori H. Solid base catalysts: fundamentals and their applications in organic reactions. Appl Catal A. 2015;504:103–9. https://doi.org/10.1016/J.APCATA.2014.10.060.

Hermida L, Abdullah AZ, Mohamed AR. Synthesis of monoglyceride through glycerol esterification with lauric acid over propyl sulfonic acid post-synthesis functionalized SBA-15 mesoporous catalyst. Chem Eng J. 2011;174(2–3):668–76. https://doi.org/10.1016/J.CEJ.2011.09.072.

Hu Y, Daoud WA, Fei B, Chen L, Him T, Sze C, Lin K. Efficient ZnO aqueous nanoparticle catalysed lactide synthesis for poly (lactic acid) fibre production from food waste. J Clean Prod. 2017;165:157–67. https://doi.org/10.1016/j.jclepro.2017.07.067.

Huaping ZHU, Zongbin WU, Yuanxiong C, Ping Z, Shijie D, Xiaohua LIU. Preparation of biodiesel catalyzed by solid super base of calcium oxide and its refining process. Chin J Catal. 2006;27:391–6. https://doi.org/10.1016/S1872-2067(06)60024-7.

Hwa S, Rashid U, Taufiq-Yap YH. Biodiesel production from crude jatropha curcas oil using calcium based mixed oxide catalysts. Fuel. 2014;136:244–52. https://doi.org/10.1016/j.fuel.2014.07.062.

Iqbal S, Kondrat SA, Jones DR, Schoenmakers DC, Edwards JK, Lu L, Hutchings GJ. Ruthenium nanoparticles supported on carbon: an active catalyst for the hydrogenation of lactic acid to 1, 2-propanediol. ACS Catal. 2015;5(9):5047–59. https://doi.org/10.1021/acscatal.5b00625.

Kaur M, Ali A. Potassium fluoride impregnated CaO/NiO: an efficient heterogeneous catalyst for transesterification of waste cottonseed oil. Eur J Lipid Sci Technol. 2014;116(1):80–8. https://doi.org/10.1002/ejlt.201300213.

Kishida H, Jin F, Zhou Z, Moriya, Enomoto H. Conversion of glycerin into lactic acid by alkaline hydrothermal reaction. Chem Lett. 2005;34(11):1560–1. https://doi.org/10.1246/cl.2005.1560.

Kishida H, Jin F, Yan X, Moriya T, Enomoto H. Formation of lactic acid from glycolaldehyde by alkaline hydrothermal reaction. Carbohydr Res. 2006;341(15):2619–23. https://doi.org/10.1016/J.CARRES.2006.06.013.

Kumar R, Purushothaman P, van Haveren J, van Es DS, Melián-Cabrera I, Meeldijk JD, Heeres HJ. An efficient one pot conversion of glycerol to lactic acid using bimetallic gold-platinum catalysts on a nanocrystalline $CeO_2$ support. Appl Catal B. 2014;147:92–100. https://doi.org/10.1016/j.apcatb.2013.07.068.

Kwan TH, Hu Y, Sze C, Lin K. Techno-economic analysis of a food waste valorisation process for lactic acid, lactide and poly(lactic acid) production. J Clean Prod. 2018;181:72–87. https://doi.org/10.1016/j.jclepro.2018.01.179.

Lee HV, Taufiq-Yap YH, Hussein MZ, Yunus R. Transesterification of jatropha oil with methanol over Mg-Zn mixed metal oxide catalysts. Energy. 2013;49(1):12–8. https://doi.org/10.1016/j.energy.2012.09.053.

Li KT, Li JY, Li HH. Conversion of glycerol to lactic acid over Cu-Zn-Al and Cu-Cr catalysts in alkaline solution. J Taiwan Inst Chem Eng. 2017;79:74–9. https://doi.org/10.1016/j.jtice.2017.03.029.

Liu L, Ye XP. Simultaneous production of lactic acid and propylene glycol from glycerol using solid catalysts without external hydrogen. Fuel Process Technol. 2015;137:55–65. https://doi.org/10.1016/J.FUPROC.2015.04.007.

Maris EP, Davis RJ. Hydrogenolysis of glycerol over carbon-supported Ru and Pt catalysts. J Catal. 2007;249(2):328–37. https://doi.org/10.1016/J.JCAT.2007.05.008.

Maris EP, Ketchie WC, Murayama M, Davis RJ. Glycerol hydrogenolysis on carbon-supported PtRu and AuRu bimetallic catalysts. J Catal. 2007;251:281–94. https://doi.org/10.1016/j.jcat.2007.08.007.

Mestl G. MoVW mixed metal oxides catalysts for acrylic acid production: from industrial catalysts to model studies. Top Catal. 2006;38(1–3):69–82. https://doi.org/10.1007/s11244-006-0072-z.

Onda A, Ochi T, Kajiyoshi K, Yanagisawa K. Lactic acid production from glucose over activated hydrotalcites as solid base catalysts in water. Catal Commun. 2008;9(6):1050–3. https://doi.org/10.1016/j.catcom.2007.10.005.

Pagliaro BM, Rossi M, Pagliaro M. Glycerol : properties and production. In: Rossi M, editor. Future of glycerol: new usages for a versatile raw materials. Cambridge: Springer; 2008. p. 1–17.

Palacio R, Torres S, Lopez D, Hernandez D. Selective glycerol conversion to lactic acid on $Co_3O_4$/$CeO_2$ catalysts. Catal Today. 2018;32:196–202. https://doi.org/10.1016/j.cattod.2017.05.053.

Paula A, Dias S, Bernardo J, Felizardo P, Joana M, Correia N. Biodiesel production by soybean oil methanolysis over SrO/MgO catalysts: the relevance of the catalyst granulometry. Fuel Process Technol. 2012;102:146–55. https://doi.org/10.1016/j.fuproc.2012.04.039.

Quispe CAG, Coronado CJR, Carvalho JA. Glycerol : production, consumption, prices, characterization and new trends in combustion. Renew Sust Energ Rev. 2013;27:475–93. https://doi.org/10.1016/j.rser.2013.06.017.

Ramírez-López CA, Ochoa-Gómez JR, Fernández-Santos M, Gómez-Jiménez-Aberasturi O, Alonso-Vicario A, Torrecilla-Soria J. Synthesis of lactic acid by alkaline hydrothermal conversion of glycerol at high glycerol concentration. Ind Eng Chem Res. 2010;49(14):6270–8. https://doi.org/10.1021/ie1001586.

Razali N, Abdullah A. Production of lactic acid from glycerol via chemical conversion using solid catalyst: a review. Appl Catal A. 2017;543:234–46. https://doi.org/10.1016/j.apcata.2017.07.002.

Rosiene M, Arcanjo A, Silva IJ, Rodríguez-Castellón E, Infantes-Molina A, Vieira RS. Conversion of glycerol into lactic acid using Pd or Pt supported on carbon as catalyst. Catal Today. 2017;279(2):317–26. https://doi.org/10.1016/j.cattod.2016.02.015.

Rubio-Caballero JM, Santamaría-González J, Mérida-Robles J, Moreno-Tost R, Alonso-Castillo ML, Vereda-Alonso E, Maireles-Torres P. Calcium zincate derived heterogeneous catalyst for biodiesel production by ethanolysis. Fuel. 2013;105:518–22. https://doi.org/10.1016/j.fuel.2012.09.054.

Shen Z, Jin F, Zhang Y, Wu B, Kishita A, Tohji K, Kishida H. Effect of alkaline catalysts on hydrothermal conversion of glycerin into lactic acid. Ind Eng Chem Res. 2009;48(19):8920–5. https://doi.org/10.1021/ie900937d.

Tan HW, Aziz ARA, Aroua MK. Glycerol production and its applications as a raw material: a review. Renew Sust Energ Rev. 2013;27:118–27. https://doi.org/10.1016/J.RSER.2013.06.035.

Taufiq-Yap YH, Lee HV, Yunus R, Juan JC. Transesterification of non-edible Jatropha curcas oil to biodiesel using binary Ca–Mg mixed oxide catalyst: effect of stoichiometric composition. Chem Eng J. 2011;178:342–7. https://doi.org/10.1016/J.CEJ.2011.10.019.

Taufiq-Yap YH, Sivasangar S, Salmiaton A. Enhancement of hydrogen production by secondary metal oxide dopants on NiO/CaO material for catalytic gasification of empty palm fruit bunches. Energy. 2012;47(1):158–65. https://doi.org/10.1016/J.ENERGY.2012.09.026.

Teo SH, Rashid U, Taufiq-Yap YH. Biodiesel production from crude Jatropha curcas oil using calcium based mixed oxide catalysts. Fuel. 2014;136:244–52. https://doi.org/10.1016/J.FUEL.2014.07.062.

Trifoi AR, Agachi PS, Pap T. Glycerol acetals and ketals as possible diesel additives: a review of their synthesis protocols. Renew Sust Energ Rev. 2016;62:804–14. https://doi.org/10.1016/j.rser.2016.05.013.

Wen Z, Yu X, Tu ST, Yan J, Dahlquist E. Biodiesel production from waste cooking oil catalyzed by $TiO_2$-MgO mixed oxides. Bioresour Technol. 2010;101(24):9570–6. https://doi.org/10.1016/j.biortech.2010.07.066.

Xue Y, Jin F, Yoshikawa K. Hydrothermal lactic acid production from glucose over feldspars as solid base catalysts in water. Energy Procedia. 2014;61:2474–7. https://doi.org/10.1016/J.EGYPRO.2014.12.026.

Yan S, Kim M, Salley SO, Ng KYS. Oil transesterification over calcium oxides modified with lanthanum. Appl Catal A. 2009;360(2):163–70. https://doi.org/10.1016/J.APCATA.2009.03.015.

Yang F, Hanna MA, Sun R. Value-added uses for crude glycerol-a byproduct of biodiesel production. Biotechnol Biofuels. 2012;5(13):1–10. https://doi.org/10.1186/1754-6834-5-13.

Yang GY, Ke YH, Ren HF, Liu CL, Dong WS. The conversion of glycerol to lactic acid catalyzed by $ZrO_2$-supported CuO catalyst. Chem Eng J. 2016;283:759–67. https://doi.org/10.1016/j.cej.2015.08.027.

Yin H, Zhang C, Yin H, Gao D, Shen L, Wang A. Hydrothermal conversion of glycerol to lactic acid catalyzed by Cu/hydroxyapatite, Cu/MgO, and Cu/$ZrO_2$ and reaction kinetics. Chem Eng J. 2016;288:332–43. https://doi.org/10.1016/J.CEJ.2015.12.010.

Yin H, Yin H, Wang A, Shen L. Catalytic conversion of glycerol to lactic acid over graphite-supported nickel nanoparticles and reaction kinetics. J Ind Eng Chem. 2018;57:226–35. https://doi.org/10.1016/J.JIEC.2017.08.028.

Younas R, Zhang S, Zhang L, Luo G, Chen K, Cao L, Hao S. Lactic acid production from rice straw in alkaline hydrothermal conditions in presence of NiO nanoplates. Catal Today. 2016;274:40–8. https://doi.org/10.1016/J.CATTOD.2016.03.052.

Yu X, Wen Z, Li H, Tu S, Yan J. Transesterification of Pistacia chinensis oil for biodiesel catalyzed by CaO-$CeO_2$ mixed oxides. Fuel. 2011;90:1868–74. https://doi.org/10.1016/j.fuel.2010.11.009.

Zabeti M, Daud WMAW, Aroua MK. Biodiesel production using alumina-supported calcium oxide: an optimization study. Fuel Process Technol. 2010;91(2):243–8. https://doi.org/10.1016/J.FUPROC.2009.10.004.

Zhang C, Wang T, Liu X, Ding Y. Cu-promoted Pt/activated carbon catalyst for glycerol oxidation to lactic acid. J Mol Catal A. 2016;424:91–7. https://doi.org/10.1016/j.molcata.2016.08.018.

Zheng X, Jin K, Zhang L, Wang G, Liu Y. Effects of oxygen transfer coefficient on dihydroxyacetone production from crude glycerol. Braz J Microbiol. 2015;47(1):129–35. https://doi.org/10.1016/j.bjm.2015.11.020.

# Green Biological Synthesis of Nanoparticles and Their Biomedical Applications

**Shakeel Ahmad Khan and Chun-Sing Lee**

**Contents**



## 1 Introduction

Nanotechnology has been transformed from a multi-disciplinary research concept to an important scientific area during the last decade (Nasrollahzadeh et al. 2019). Research and development in nanotechnology is growing expeditiously globally (Marchiol 2012; Khan et al. 2019). Importance of the nanotechnology is evident from the huge investments in different countries like the United States, the European Union, and Japan that have invested $3.7, 1.2, and 0.75 billion, respectively, in 2012

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_10

for research in this area (World Intellectual Property Report 2019). According to the National Nanotechnology Initiative, "nanotechnology is the manipulation of matter with at least one dimension sized from 1 to 100 nanometers." With the nanoscaled dimensions, properties of matter changes due to both the quantum size effect and the much larger surface-to-volume ratio (Celebioglu et al. 2019). These can lead to modifications in physical, chemical, as well as biological properties of the original bulk materials (Devi et al. 2019). These modifications lead to many novel properties, which can be exploited for applications in advanced sensors and nanoscaled devices (Daniel and Astruc 2004). At present, nanomedicine, nanobiotechnology, and bionanotechnology are the most domineering fields attracting most attention. In particular, applications in bioelectronics, biosensor, nanorobotics, drug delivery systems, antimicrobial, anticancer are considered to have excellent potentials (Ramanavičius et al. 2005).

Nanomaterials can be fabricated either with bottom-up or top-down approaches. In the bottom-up approach, nanomaterials are synthesized by assembling molecular components, while the top-down approach involves reducing the sizes of bulk materials to nanoscale via division or material removal (Fig. 1a) (Kralj and Makovec 2015). By adopting these approaches, nanomaterials with various sizes and morphologies like wire, rods, tubes, particles, spheres, flowers, and cubes have been successfully fabricated (Fig. 1b). The bottom-up approach comprises of physical process such as nanoprecipitation and vapor condensation; chemical approach, for example, sol-gel, solvothermal, co-precipitation, chemical reduction and oxidation, and pyrolysis as well as biological techniques, such as bacteria, fungi, viruses, plants, and algae. On the other hand, the top-down approach use various physiochemical techniques, such as photolithography and ball milling to subdivide bulk materials into many nanoscaled objects or to reduce the bulk size into nanoscale via removing surface atoms by chemical or plasma etching (Fig. 2).

While chemical, physical, and physiochemical approaches have been widely exploited for the synthesis of nanoparticles, they often involve the use of toxic chemicals and are costly (Narayanan and Sakthivel 2011). Actually, presence of noxious chemical entities on the surface of synthesized nanomaterials might not be removed easily and could prohibit their biological and clinical applications. Moreover, chemicals and physiochemical techniques often have high-energy demand and many are not easily scalable (Alijani et al. 2019). Therefore, it is highly important to develop low-cost and environmental friendly manufacturing processes for synthesizing nanomaterials for future commercial applications (Khan et al. 2018).

Recent advancements in green chemistry has led to the development of eco-friendly and low-cost methods for the fabrication of nanomaterials (Narayanan and Sakthivel 2011; Hutchison 2008). On the other hand, synthesis of nanomaterials via biological processes has been developing rapidly in the past couple of decades. Either these processes based on eukaryotic such as plants, algae, and fungi or prokaryotic systems, for example, bacteria and archaea which do not require any external toxic chemicals as a stabilizer, capping and reducer (Khan et al. 2018). While they are also cost-effective, energy-efficient, and easily scalable, some of these processes do require careful handling of microbial organisms for safety reason (Nath

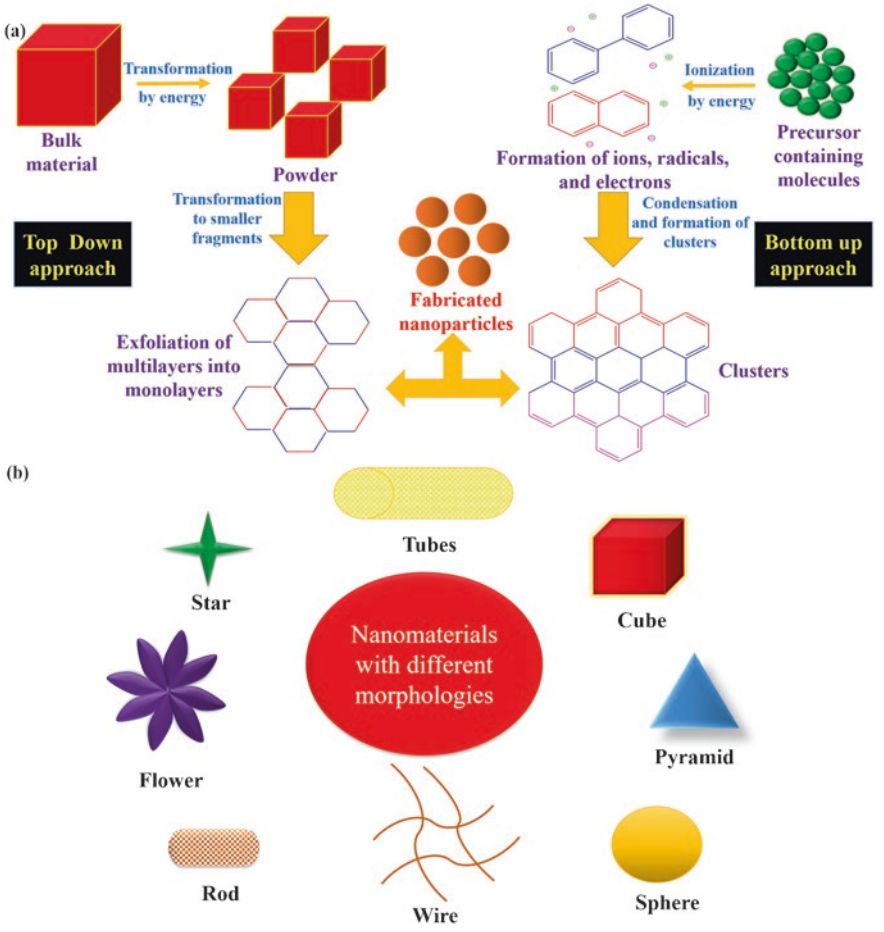


**Fig. 1** The top-down and bottom-up approaches for the fabrication of nanomaterials (**a**). The nanomaterials have been fabricated with different morphologies such as tube, star, flower, cube, pyramid, rod, wire, and sphere (**b**) (Modified after Zielonka and Klimek-Ochab 2017)

and Banerjee 2013). In this chapter, we give a summary on different biological processes and compare their performance and safety implications.

## 2 Biological-Inspired Green Synthesis of Nanomaterials

Green chemistry is also referred to as sustainable chemistry involving synthesis processes designing to reduce or eliminate use and generation of toxic substances while minimizing energy consumption (Clark et al. 2012; Dahl et al. 2007). In fact, many recently reports described that biological approaches for nanomaterial

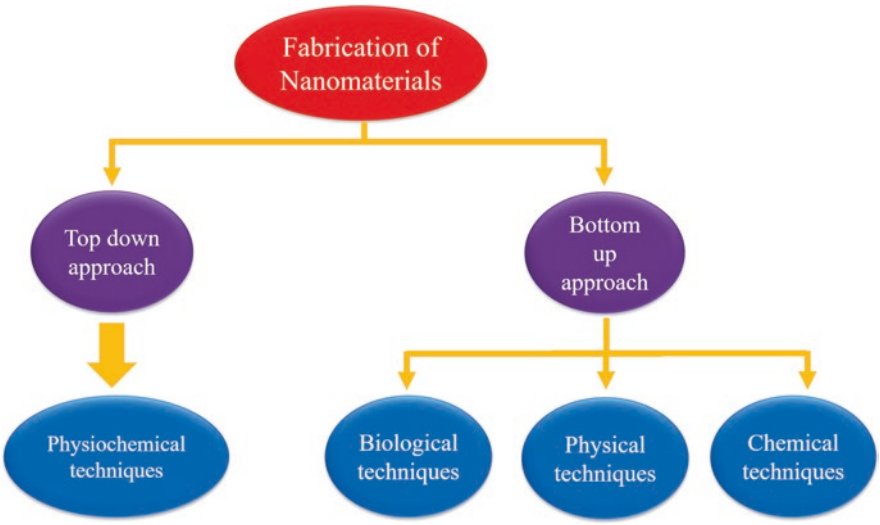


**Fig. 2** Classification of top-down and bottom-up approaches into different techniques for the synthesis of nanomaterials based on the involvement of different methods (Modified after Nabi et al. 2018)

synthesis fitted well with the essence of green chemistry, as they do not require usage of nontoxic substances such as reducer, stabilizer, and capping agents. This typically led to more biocompatible products with little contamination from toxic substance (Wang et al. 2019).

It is well established that biological processes such as metabolism, catabolism, and anabolism in all organisms proceed at optimum conditions of temperatures. Without needing the high-temperature synthesis step, these processes are typically highly energy efficient (Mann 1993). An example of this is the bio-mineralization process through which several micro and macro-organisms such as algae, invertebrates, vertebrates, virus, and bacteria produce different kinds of inorganic materials, for example silicates, carbonates, calcium phosphate, and gold with well-controlled structures at both macro and nano scales (Gadd 2007).

Nature has blessed us with various kinds of progressions including eukaryotic and prokaryotic systems for the development of micro- and nano-scaled inorganic materials (Fig. 3) (Saratale et al. 2018). As mentioned in Fig. 2, the biological synthesis is a bottom-up approach, in which redox reactions are involved for synthesizing the nanoparticles. Several natural occurring biological active substances, such as alkaloids, flavonoids, polyphenols, saponins, terpenoids, co-enzymes, proteins, sugars, and vitamins are present in plants, algae, fungi, yeast, bacteria, archaea, and virus which can act as reducing, capping, and stabilizing agents in the fabrication of nanoparticles (Fig. 4) (Pal et al. 2019).

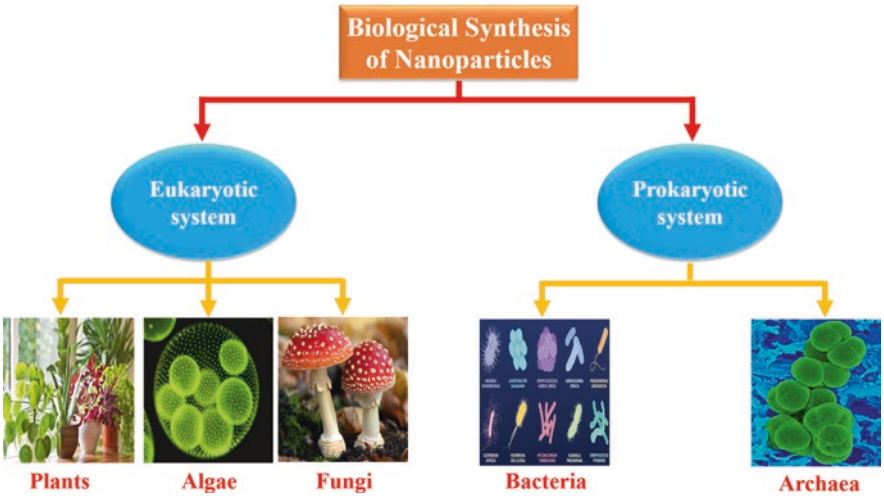


**Fig. 3** Schematic illustration of the green synthesis of nanomaterials through different biological systems such as eukaryotic and prokaryotic systems (Modified after Singh et al. 2018)

## *2.1 Microbial (Prokaryotic and Eukaryotic)-Inspired Green Synthesis of Nanoparticles*

Nanoparticles fabrication by employing different microorganisms is considered as green chemistry approach, which links microbial technology and nanoscience (Razavi et al. 2015). Microorganisms serve as nanofactories, which hold an enormous potential to act as cost-effective, environment friendly tools for replacing some chemical and physiochemical processes, which require the usage of noxious chemical entities and have high-energy demand. Therefore, during the past couple of decades, tremendous research has been accomplished in the direction of green nanotechnology for fabricating the nanoparticles of several morphologies and sizes (Fig. 1) by using different microorganisms including bacteria, fungi, viruses, and yeast. These microbial-synthesized nanoparticles of various morphologies and dimensions have demonstrated extraordinary applications as anticancer, antioxidants, antibacterial, and antimycotic agents.

### 2.1.1 Bacterial-Mediated Green Synthesis of Nanoparticles

Bacteria make a large dominion of prokaryotic microorganisms that have been extensively exploited for several kinds of commercially viable biotechnological applications, which include bioleaching, for example ores extraction, genetic engineering such as insulin production, and bio-remediation, for example oil spills (Dudek et al. 2017). Moreover, both intrinsic and genetically modified bacterial species can be used for the metallic ions bio-mineralization (Faramarzi and Sadighi

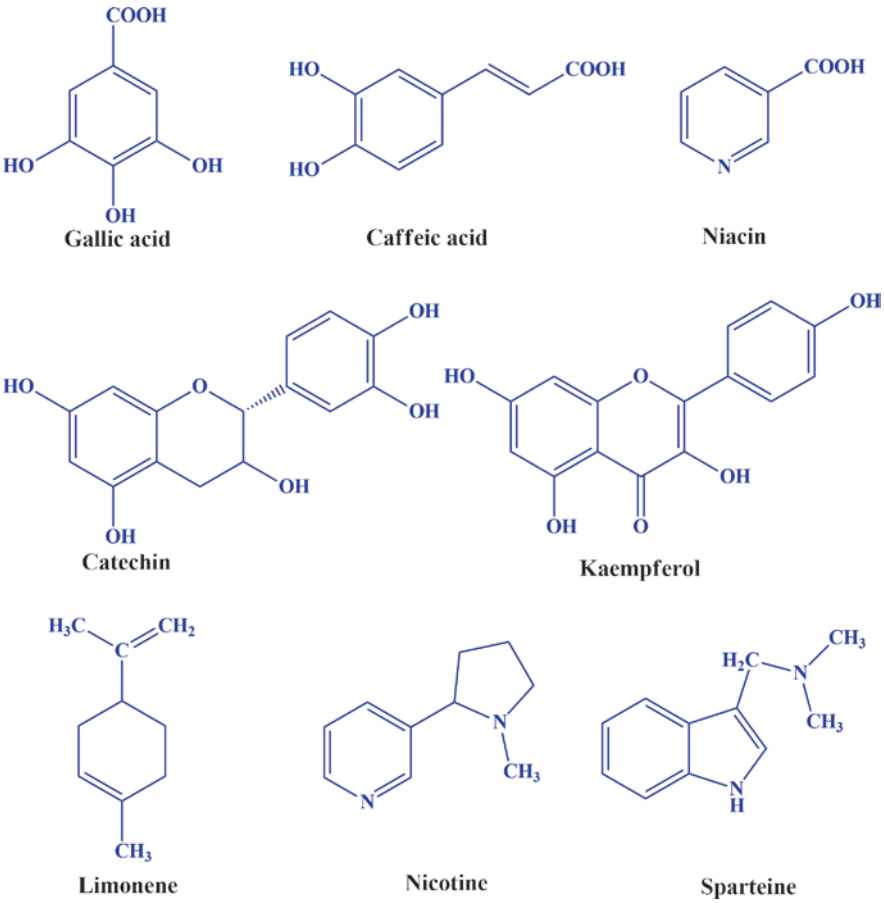


**Fig. 4** Examples of natural compounds present in eukaryotic and prokaryotic systems involved in biological synthesis of nanoparticles. Gallic acid and caffeic acid, catechin and kaempferol, nicotine and sparteine, limonene, and niacin are the examples of polyphenols, flavonoids, alkaloids, terpenoids, and vitamins, respectively (Modified after Nasrollahzadeh et al. 2019)

2013). As bacteriological microorganisms are continuously exposed to noxious and harsh environmental conditions because of the accumulation of higher quantities of the heavy metal ions in their surrounding ecospheres, they have developed distinguish self-defense mechanisms including extracellular-precipitation, modify metallic ion concentration in the environment, efflux-pumping, bioaccumulation, bio-sorption, and intracellular-sequestrations to confront various ecological circumstances (Iravani 2014). For example, owing to these self-defense mechanisms, literature demonstrated that magnetotactic bacteria *Magnetospirillium magneticum* are responsible for the formation of magnetite ($Fe_3O_4$) and greigite ($Fe_3S_4$). While sulfate-reducing bacteria *Desulfovibrio desulfuricans* NCIMB 8307 are involved in the formation of pyrite such as $FeS_2$ of cubic crystal structure and marcasite, such as

$FeS_2$ of orthorhombic crystal structure deposits in sedimentary rocks (Dudek et al. 2017). Therefore, these bacterial self-defense systems could be used for synthesizing metal or metallic oxide nanoparticles for various biological applications.

Human beings have also taken the benefits of microbial self-defense systems against noxious environs to harvest nanomaterials and to clean wastes from the ecological-unit via bio-mineralization and bio-remediation process (Razavi et al. 2015). Thus, bacterial species have significant and distinctive aptitude to reduce metal ions into their respective elements. They are considered as one of the top contenders for synthesizing metal nanoparticles because of their handling easiness and high propagation rate. Haefeli first reported a bacterial-mediated biological synthesis process in 1984. This process utilizes the *Pseudomonas stutzeri* AG259 for fabricating silver nanoparticles (Haefeli et al. 1984; Thostenson et al. 2005). Later on, several types of bacteria including gram-positive, such as *Bacillus cereus, Bacillus subtilis, Rhodococcus, Bacillus methylotrophicus, Streptomyces anulatus,* and *Bacillus amyloliquefaciens*, gram-negative, such as *Alcaligenes faecalis, Escherichia coli, Klebsiella pneumonia,* and *Pseudomonas aeruginosa*, and cyanobacteria, such as *Spirulina platensis, Oscillatoria willei,* and *Phormidium tenue* have been widely explored for synthesizing different nanoparticles including Au, Ag, Cu, Zn, Pd, Pt, and CdS (Table 1).

These bacteria synthesize the nanoparticles through two distinctive mechanistic pathways. One is known as extracellular synthesis and other is termed as intracellular synthesis (Patil and Kim 2018). In extracellular synthesis, nanoparticles fabricate outside the cell, either on the cell's surfaces or between the cells inside bacterial colonies. Extracellular synthesis of nanoparticles occurs via bio-mineralization, bio-sorption, complexation, or precipitation processes of the metal salts outside the cell. With the change in solution of pH, nanoparticles with several morphologies and different sizes are achievable through extracellular synthesis. While, intracellular synthesis is an approach to fabricate nanoparticles inside the cell, in cytoplasm or in cytosol by the action of reductases enzymes (Sengani et al. 2017).

### 2.1.2 Fungi-Inspired Green Synthesis of Nanoparticles

Fungi are eukaryotic organisms, which include microorganisms such as yeasts, molds, and mushrooms. They are widely distributed all over the world. Literature demonstrates that taxonomists have identified almost 120,000 fugal species. Including those which have not been identified, there could be 2.2 to 3.8 million mycological species on earth (Hawksworth and Lücking 2017). This mycological population possesses enormous variations in molecular, physiological, and biological applications. They have abilities to grow in harsh ecological conditions and in wide-range of different habitats including deep-sea sedimentation, ionizing, UV or cosmic radiation, deserts, as well as area with high salt concentration (Raghukumar and Raghukumar 1998). Fungal species traditionally known as heterotrophs are based on their mode of nutrition.

**Table 1** A representative list of different bacteriological strains utilized for nanoparticles fabrication

| Bacteriological species | Nanoparticles with size (nm) | Morphology | Synthesis location | Method | References |
|---|---|---|---|---|---|
| *Bacillus amyloliquefaciens* | CdS (3–4) | Cubic, hexagonal | Extracellular | Reduction | Singh et al. (2011) |
| *Bacillus licheniformis* | Ag (77–92) | Triangular, hexagonal and spherical | Extracellular | Reduction | Elbeshehy et al. (2015) |
| *Bacillus methylotrophicus* | Ag (10–30) | Spherical | Extracellular | Reduction | Wang et al. (2016) |
| *Bhargavaea indica* | Ag (30–100) | Nanobar, pentagon, spherical | Extracellular | Reduction | Singh et al. (2015) |
| *Bacillus subtilis* | Ag (76.38–143.60) | Spherical and hexagonal | Extracellular | Reduction | Soni and Prakash (2015) |
| *Weissella oryzae* | Ag (10–30) | Spherical | Intracellular | Reduction | Singh et al. (2016a, b, c) |
| *Escherichia coli* | Pd (15–20) | Spherical | Extracellular | Reduction | Deplanche et al. (2010) |
| *Bhargavaea indica* | Au (30–100) | Flower | Extracellular | Reduction | Singh et al. (2016a, b, c) |
| *Escherichia coli* | CuO (10–40) | Quasi-spherical | Extracellular | Reduction | Singh et al. (2010) |
| *Aeromonas hydrophila* | ZnO (57.72) | Spherical, oval | Extracellular | Reduction | Jayaseelan et al. (2012) |
| *Pseudomonas aeruginosa* | Ag (13) | Spherical | Extracellular | Reduction | Kumar and Mamidyala (2011) |
| *Rhodococcus sp.* | Au (5–15) | Spherical | Intracellular | Enzyme reduction | Ahmad et al. (2003) |
| *Stenotrophomonas maltophilia* | Au (40) | Spherical | Extracellular | Enzyme reduction | Nangia et al. (2009) |
| *Plectonema boryanum* | Pd (1–20 nm) | Spherical and elongate | Intracellular and extracellular | Reduction | Lengke et al. (2007) |
| *Shewanella loihica PV-4* | Pd (2–7), Pt (2–7), au (2–7) | Spherical | Extracellular | Reduction | Ahmed et al. (2018) |
| *Kocuria flava* | Cu (5–30) | Spherical | Extracellular | Reduction | Kaur et al. (2015) |
| *Ochrobactrum sp.* | Te | Spherical and rod | Extracellular | Enzyme reduction | Zonaro et al. (2017) |

Fungi are well acknowledged, being widely exploited for biosynthesis of nanoparticles. They have ability to grow in the form of thin layer material and develop sufficient concentrations of different extracellular enzymes, which enable them to be used for metabolite and enzyme production as an important industrial

agent (Longoria et al. 2012). Moreover, some salient features of mycological species that enable their capability for large-scale synthesis of nanoparticles include their fast propagation rate, intracellular metal-absorption, sufficient cell-wall binding, biomass application simplicity, and large available resources as initial raw material (Longoria et al. 2011). In contrast to bacteria, mycological species have higher production rate of nanoparticles and better ability to bind metal ions on their cell wall. Higher bioaccumulation of metals in fungal species leads to an efficient and economical nanoparticles fabrication. In addition, biomass treatments and down-stream processing easily take place in fungi rather than bacteriological and viruses species (Alghuthaymi et al. 2015). Moreover, because of the mycelia existence (demonstrate more surface area), more secretion of proteins and enzymes by fungi are also an important advantage over the bacteria which would enhance the productivity of nanoparticles.

Like the case of bacteria, fungi also synthesize metal nanoparticles via reduction of metal ions via intracellular or extracellular enzymes and biomolecules such as proteins, sugars, and quinones. Now-a-days, several mycological species, for example *Aspergillus clavatus*, *Rhizopus oryzae, Bipolaris nodulosa, Penicillium fellutanum, Penicillium brevicompactum, Phoma glomerata, Coriolus versicolor, Aspergillus niger, Aspergillus flavus, Fusarium semitectum, Trichoderma viride, Phyllanthus amarus,* and *Fusarium solani,* had been utilized widely for fabricating the nanoparticles of different metals and metal oxides (Table 2). Among different metals, silver has been extensively studied for its biological synthesis through different fungal species. In addition to Ag, other metals nanoparticles, e.g. Au, Zn, Ti, Cu, Al, Pt, and Cd, have also been synthesized by mycological species (Razavi et al. 2015). Morphology, size, and production rate of nanoparticles can be controlled by the adjustment of different environmental parameters such as pH, temperature, concentration of precursor solutions, and incubation time.

It has been demonstrated that most mycological species utilized for synthesizing the nanoparticles are pathogenic for both plants and humans. This is the main hindrance for nanoparticles production at large scale (Vahabi and Karim Dorcheh 2014). On the other hand, reports show that *Trichoderma* species, for example *Trichoderma reesei*, is an industrially adapted species with no toxic effect for both plant and human beings, can be utilized for commercial scale production of nanoparticles (Vahabi et al. 2011). Nanoparticles synthesized by mycological strains have been exploited for different biological applications, such as antibacterial, antimycotic, anticancer, antiviral, biosensor, and bio-imaging.

### 2.1.3 Yeast-Inspired Green Synthesis of Nanoparticles

Apart from exploiting the mycological species, some researchers have explored yeast for biosynthesis of nanoparticles. Yeast is a member of the fungus kingdom and is a eukaryotic microorganism. Literature reports demonstrate that taxonomist have recognized almost 1500 species of yeast (Hoffman et al. 2015). It is a unicellular microorganism that has grown from multicellular dynasties. However, some

**Table 2** A representative list of different mycological species employed for fabricating nanoparticles

| Mycological species | Nanoparticles with size (nm) | Morphology | Synthesis point | Method | References |
|---|---|---|---|---|---|
| *Verticillium* | Ag (25 ± 12), | Spherical | Intracellular | Reduction | Mukherjee et al. (2001) |
| *Trichoderma viride* | Au (20) | Spherical | Extracellular | Reduction | Mishra et al. (2014) |
| *Phoma sp.3.2883* | Ag (71.06) | Spherical | Extracellular | Adsorption | Chen et al. (2003) |
| *Fusarium oxysporum* | $Fe_3O_4$ (20–50) | Quasi-spherical | Extracellular | Reduction | Bharde et al. (2006) |
| *Verticillium sp.* | $Fe_3O_4$ (100–400) | Cubo-octahedrally | Extracellular | Reduction | Bharde et al. (2006) |
| *Fusarium oxysporum* | Pt (10–100) | Hexagons, pentagons, circles, squares, rectangles | Intracellular | Reduction | Riddin et al. (2006) |
| *Fusarium oxysporum* | Pt (10–100) | Hexagons, pentagons, circles, squares, rectangles | Extracellular | Reduction | Riddin et al. (2006) |
| *Cladosporium cladosporioides* | Ag (10–100) | Spherical | Extracellular | Reduction | Balaji et al. (2009) |
| *Aspergillus fumigatus* | Ag (5–25) | Spherical | Extracellular | Reduction | Bhainsa and D'souza (2006) |
| *Neurospora crassa* | Ag (11), Au (32), Ag/Au (70/30) (3–90) | Spherical | Extracellular and intracellular | Reduction | Longoria et al. (2011) |
| *Aspergillus terreus* | ZnO (28–63) | Spherical | Intracellular | Reduction | Baskar et al. (2015) |
| *Aspergillus fumigatus* | Au (85–210) | Spherical | Intracellular | Reduction | Bathrinarayanan et al. (2013) |
| *Verticillium luteoalbum* | Au (1–100) | Spherical | Intracellular | Reduction | Gericke and Pinches (2006) |
| *Alternaria alternata* | Ag (32.5) | Spherical | Extracellular | Reduction | Gajbhiye et al. (2009) |
| *Trichoderma harzianum* | CdS (3–8) | Spherical | Extracellular | Reduction | Bhadwal et al. (2014) |
| *Trichoderma longibrachiatum* | Ag (17.75) | Spherical, triangular, cuboid and hexagonal | Extracellular | Reduction | Omran et al. (2019) |
| *Trichoderma harzianum* | Se (50) | Spherical | Extracellular | Reduction | Hu et al. (2019) |

(continued)

**Table 2** (continued)

| Mycological species | Nanoparticles with size (nm) | Morphology | Synthesis point | Method | References |
|---|---|---|---|---|---|
| *Trichoderma reesei* | Ag (15–25) | Cubic | Extracellular | Reduction | Gemishev et al. (2019) |
| *Trichoderma asperellum* | CuO (110) | Spherical | Extracellular | Reduction | Saravanakumar et al. (2019) |
| *Cochliobolus geniculatus* | ZnO (2–6) | Quasi-spherical | Extracellular | Reduction | Kadam et al. (2019) |
| *Aspergillus flavus* | $TiO_2$ (62–74) | Spherical, oval | Extracellular | Reduction | Rajakumar et al. (2012) |

species of yeast have capability to develop multicellular features, that is, pseudohyphae. Yeast constitutes 1% of all mycological species on earth (Kurtzman and Fell 2006).

Yeast has special physiological properties such as absorption, adsorption, and accumulation, and fermenting characteristics, which enable them to be widely exploited in various fields including biotechnology, genetics, cell biology, bioremediation, and bio-mineralization. The species has inherent ability to absorb, adsorb, and accumulate large amount of toxic chemical entities from their surroundings. They also have capacity to adopt various toxicological conditions of different chemical entities, such as metals and metal ions via different self-defense detoxification mechanisms (Shah et al. 2015). Yeast's self-defense detoxification mechanisms comprise of intracellular-sequestration, enzymatic oxidation or reduction, biosorption of yeast cell wall, chelation with polysaccharides or extracellular peptides, and bioprecipitation (Apte et al. 2013). By employing different detoxification mechanisms, some yeast species such as *Yarrowia lipolytica* are well known to degrade palm oil, explosive materials such as trinitrotoluene, and some hydrocarbons; *Saccharomyces cerevisiae* bioremediates toxic contaminants (arsenic from industries) (Zinjarde et al. 2014; Bankar et al. 2009). Moreover, *Yarrowia lipolytica* has been extensively explored for its potential application as a heavy metal absorbent. These properties of yeast species attract human beings to exploit them as a green tool for the fabrication of nanoparticles for different biological applications.

Many researchers have investigated yeast species such as *Saccharomyces cerevisiae, Rhodosporidium diobovatum, Yarrowia lipolytica, Candida utilis, Cryptococcus laurentii, Extremophilic yeast, Candida albicans, Pichia pastoris,* and *Pichia jadinii* for synthesizing the different nanoparticles such as metal, metallic oxide, and metal sulfides (Table 3). Alike, bacteria and mycological species, yeast species also use extracellular or intracellular synthesis approach via cytosolic as well as membrane-bound oxido-reductases and quinones (Boroumand et al. 2015). Same as fungi, yeast species also have advantages over the bacteria for better, safer and more scalable processes (Fig. 5).

**Table 3** A representative list of different yeast species employed for fabricating the nanoparticles

| Yeast species | Nanoparticles with size (nm) | Morphology | Synthesis location | Method | References |
|---|---|---|---|---|---|
| *Rhodosporidium diobovatum* | PbS (2–5) | Spherical | Extracellular | Reduction | Seshadri et al. (2011) |
| *Yarrowia lipolytica* | Ag (15) | Various shapes | Extracellular | Reduction | Apte et al. (2013) |
| *Candida albicans* | CdS (50–60) | Spherical | Extracellular | Reduction | Kumar et al. (2019) |
| *Candida utilis* | Ag (20–80) | Spherical | Extracellular | Reduction | Waghmare et al. (2015) |
| *Cryptococcus laurentii* | Ag (25–45) | Spherical | Extracellular | Reduction | Ortega et al. (2015) |
| *Pichia pastoris* | Ag, se (70–180) | Spherical | Extracellular | Reduction and biosorption | Elahian et al. (2017) |
| *Pichia jadinii* | Au (100) | Spherical | Intracellular | Enzymatic reduction | Gericke and Pinches (2006) |
| *Rhizopus stolonifer* | Ag (2.56–3.06 nm) | Cubic | Extracellular | Reduction | AbdelRahim et al. (2017) |
| *Saccharomyces cerevisiae* | ZnS (30–40) | Spherical | Intracellular | Reduction | Mala and Facile (2014) |
| *Saccharomyces cerevisiae* | $Sb_2O_3$ (2–10) | Spherical | Extracellular | Reduction | Jha et al. (2009) |
| *Saccharomyces cerevisiae* | SeS (5–7) | Spherical | Intracellular | Enzymatic reduction | Asghari et al. (2019) |

### 2.1.4 Virus-Mediated Green Synthesis of Nanoparticles

Viruses are contagious microorganisms that live only inside the cells of living organisms (Koonin et al. 2006). The body of virus is known as virion that comprises of nucleic acid shielded by thick proteinaceous coat termed as capsid (Selvakumar et al. 2014). Virus species have generally four morphological forms including helical, icosahedral, prolate, and envelope. Viruses act as nonliving agent outside the host body but living agent inside the host body, which implies that they lack their innate metabolic activities outside the host organism. This special feature of virus can be exploited as a safe contender for the synthesis of composite materials and nanoparticles (Fischlechner and Donath 2007).

Moreover, similar to other microorganisms, such as bacteria, fungi, and yeast, virus can also tolerate severe and toxicological environments due to the presence of different amino acid functionalities, such as proline, cysteine, arginine, lysine, glutamic acid, aspartic acid, and histidine, on their cell wall surface by which they accomplish bio-mineralization process. As amino acids have carboxylate (-COOH), thiol (-SH), and amine ($-NH_2$) functional groups, which enable viral cell wall to become more attractive for the adsorption of metal and metal ions. The affinity of

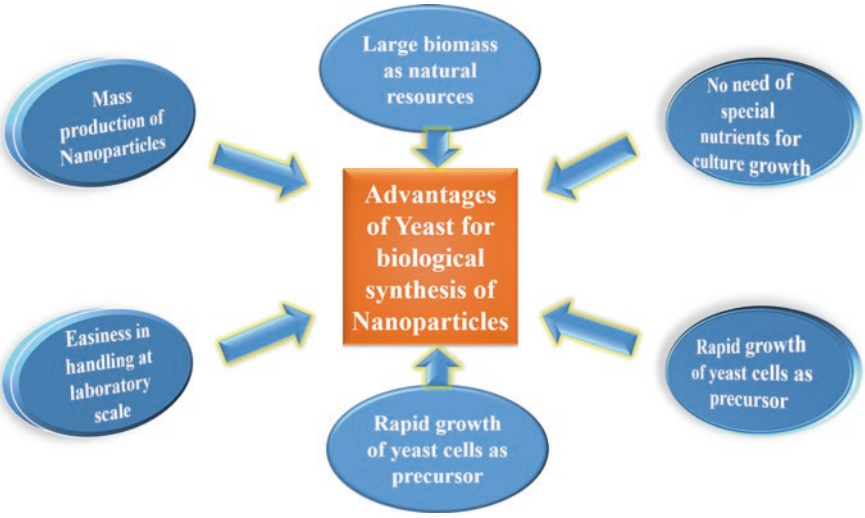


**Fig. 5** Advantages of yeast for biological synthesis of nanoparticles over bacteria

virus species for metal and metal ions has found wide applications as a template for synthesizing nanostructured materials and nanodevices of various shapes and sizes (Fischlechner and Donath 2007). Moreover, virus species can be manipulated by chemical engineering and molecular biology techniques to obtain desirable physical features of nanoconjugates and nanocomposites, such as two- or three-dimensional vessels for various biological applications in drug delivery and cancer therapy (Gahlawat and Choudhury 2019).

So far, most viruses explored for biosynthesis are plant viruses that are nonvirulent to either human beings or animals (Selvakumar et al. 2014). Species such as Tobacco mosaic, fd, M13, fd phage, Chilo iridescent, Z1 peptide, Cucumber mosaic, Potato virus X, Red clover necrotic mosaic, and Hepatitis E viruses are extensively investigated for synthesizing nanoconjugates, nanoparticles, and nanocarriers (Table 4). For example, the tobacco mosaic virus was exploited for synthesizing the $Fe_2O_3$ through hydrolysis, CdS and PbS via co-crystallization, and silica by sol gel employing amino acids such as glutamate and aspartate that exist on the outer layer of virus cell (Shenton et al. 1999). Although, virus-mediated synthesized nanomaterials, nanoconjugates, and nanoparticles have demonstrated interesting applications in nanomedicine, the processes do have important disadvantages (Selvakumar et al. 2014). The disadvantages include the involvement of host body for protein expression, not fully explored for synthetic methodology, limited research on large-scale application, not sufficient resources as an initial precursor, difficulty in handling at laboratory scale, and limitation of large-scale production.

**Table 4** A representative list of different virus species employed for synthesizing nanoparticles

| Virus species | Nanoparticles with size (nm) | Morphology | Synthesis location | Method | References |
|---|---|---|---|---|---|
| Tobacco mosaic virus | $SiO_2$ (3–5), $Fe_2O_3$ (2.0), CdS (5.0), PbS (30) | Disordered, prismatic, and film | On surface | Reduction | Shenton et al. (1999) |
| Cowpea mosaic virus | Co, Ni, Fe, Pd, Co-Pt, Ni-Fe (35) | Various shapes | On surface | Reduction | Aljabali et al. (2010) |
| Tobacco mosaic virus | Ni (3.0), co (3.0) | Nanowires | Central channel | Reduction | Knez et al. (2003) |
| M13 bacteriophage | $TiO_2$ (2–40) | Wire film | On surface | Reduction | Chen et al. (2015) |
| Tobacco mosaic virus | ZnO (100) | Rods | On surface | Reduction | Balci et al. (2009) |
| Tobacco mosaic virus | Ni (100) | Rods | On surface | Reduction | Gerasopoulos et al. (2008) |
| Tobacco mosaic virus | CoPt (50–100), $FePt_3$ (4.0) | Nanowires | Central channel | Reduction | Tsukamoto et al. (2007) |
| M13 virus | $Co_3O_4$ (2–3) | Nanowires | On surface | Reduction | Nam et al. (2006) |
| Chilo iridescent virus | Au (2–5) | Nanoshell | On surface | Reduction | Radloff et al. (2005) |
| Z1 peptide | ZnO (5–25) | Nanorods and platelets | On surface | Reduction | Tomczak et al. (2009) |

## *2.2 Generalized Protocol for the Green Synthesis of Nanoparticles by Different Microorganisms*

It is well established that microorganisms adopt two-synthesis pathways such as extracellular synthesis and intracellular synthesis for the fabrication of nanoparticles (Fig. 6).

In case of extracellular synthesis approach, the first step involves culturing the microorganisms of interest, for example bacteria, fungi, yeast, and virus under optimum conditions such as temperature, pH, and medium components. The cultured microorganisms are then centrifuged to confiscate biomass. The resulted supernatant is utilized to fabricate nanoparticles upon addition of sterilized metal salts solutions and incubation. Nanoparticles synthesis will be accompanied by color change in the cultured media. For example, literature demonstrates that upon completion of Ag nanoparticles reaction, the color of the media is deep brown, while in case of Au nanoparticles, it is ruby red. After centrifugation, proceed at different speed with the reaction mixture to eliminate any impure substance or large-sized particles. The centrifugation proceeding speed depends on the nature of the nanoparticles. Furthermore, nanoparticles can be centrifuged with density gradient or at high-speed and washing with the water or organic solvents, such as ethanol or methanol, and finally collect nanoparticles as pellet (Fig. 6) (Singh et al. 2016a, b, c).


**Fig. 6** Schematic presentation of a generalized protocol for green synthesis of nanoparticles by different microorganisms

In intracellular synthesis, same as extracellular synthesis, micro-organisms are first cultured in laboratory at optimum conditions of temperature, pH, and medium components. Biomass is then collected upon centrifugation. The collected biomass is then purified by using sterilized water. Purified biomass is dissolved in sterilized water treated with the filtered and sterilized metal salts solution and further incubated until completion of reaction. The synthesis process is again monitored by visual inspection as in the case of extracellular synthesis. The sample is then treated with ultra-sonication to destroy the microorganisms' cell wall so that the nanoparticles can be released out from cytosol. All remaining steps are identical with the extracellular synthesis approach. The differences between intracellular and extracellular synthesis are the exploitation of biomass and supernatant, respectively, and the additional step of ultra-sonication (Fig. 6) (Singh et al. 2016a, b, c).

## *2.3 Anticipated Mechanistic Pathway for Biosynthesizing the Nanoparticles by Microorganisms*

### 2.3.1 Extracellular Synthesis Mechanism

Extensive studies have been carried out to study the mode of action behind the nanoparticles synthesis utilizing microorganisms. In extracellular synthesis, metal salts solutions bearing a positive charge enable the microorganism's cells to excrete reducing proteins to stabilize the pH disturbance due to the accumulation and adsorption of metal ions. Moreover, the microorganism's cells also secrete

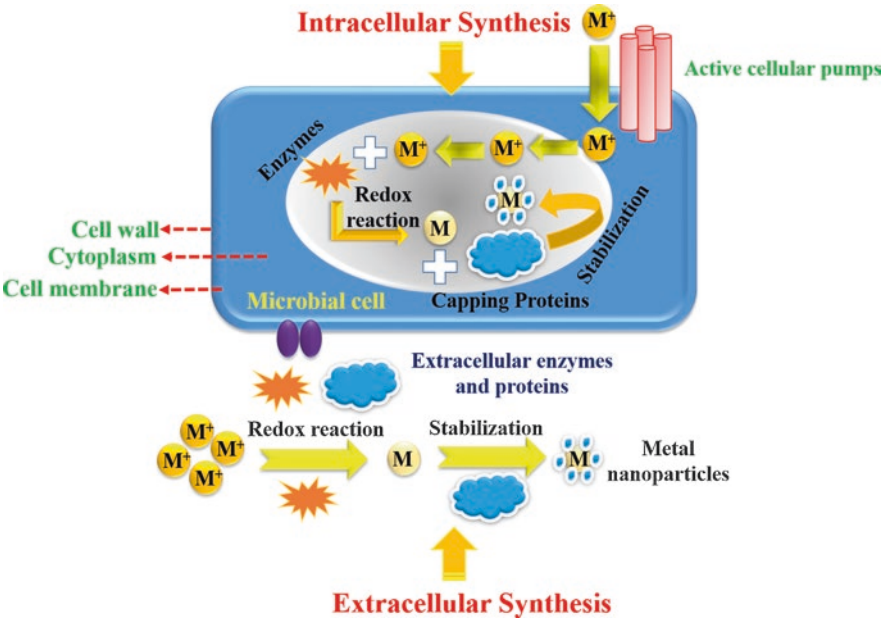


**Fig. 7** Schematic illustration showing the extracellular and intracellular mechanistic pathways for biosynthesizing the nanoparticles by microorganisms (Modified after Sengani et al. 2017)

oxidoreductases enzymes such as nitrate reductases and hydrogenases simultaneously to cope with the toxicity of metal ions by reducing them into their respective metal nanoparticles. After the nucleation of metal nanoparticles on the cell's surfaces, already secreted proteins cap them and stabilize the nanoparticles (Fig. 7). Literature demonstrates that extracellular synthesis pathway of microorganisms for the fabrication of nanoparticles merely depends upon the nature of enzymes secretions, proteins, and other biomolecules present on their cell wall surfaces (Patil and Kim 2018). For example, earlier reports have described the inclusion of nicotinamide adenine dinucleotide (NADH) dependent nitrate reductases, DNA, and proteins in metal ions bio-reduction. The role of DNA and proteins as a biological template while enzyme nitrate reductases for biosynthesizing the nanoparticles are well established (Mirkin et al. 1996).

Extracellular synthesis of Ag nanoparticles by using different bacterial strains, such as *Streptomyces sp*., *Alcaligenes faecalis*, and mycological specie like *Fusarium oxysporum* had been documented by Karthik et al. (2014), Divya et al. (2019), and Hamedi et al. (2017), respectively. Their studies corroborated that bioreduction of $Ag^+$ to Ag nanoparticles accomplished by the redox reaction of enzyme nitrate reductases in the presence of cofactor NADH act as a reducing agent (Fig. 7). Their investigations showed that the fabricated Ag nanoparticles are extremely stable showing not at all aggregation. Overall, it can be established that extracellular green synthesis of nanoparticles employing yeast, bacteria, fungi, and virus is the result of the bioreduction of metal salts by enzymes, proteins, and other

biomolecules, such as quinones and hydroxyquinoline, which are also known as electron shuttles.

### 2.3.2 Intracellular Synthesis Mechanism

In case of intracellular synthesis by microbial species, the metal ions in solution come into the vicinity of microorganism's cells. There they are attracted by the negatively charged functionalities such as peptidoglycan and polysaccharides of the microbial cell wall. These metallic ions are further moved into the cell's cytoplasm through the cell wall under the influential action of active cellular pumps (Romero et al. 2018). The metallic ions in the cytosol or cytoplasm disturb the pH of the surroundings. This will trigger the microbial cells to secrete some oxidoreductases enzymes such as nitrate reductases and hydrogenases and proteins. These secreted enzymes reduce the metal ions into their respective metal nanoparticles by redox reactions. After nucleation at cytoplasm or cytosol, the secreted capped proteins bind with the nanoparticles to stabilize them by capping. The capped proteins play an important role for preventing the nanoparticles from aggregation. Moreover, these capped proteins also provide site on nanoparticles for bio-conjugation to other biomolecules. As these capped proteins stabilize the nanoparticles naturally, no extrinsic surfactants will be needed. This is one important reason for the environment friendliness and biocompatibility of the biosynthesis processes.

Figure 7 illustrated the generalized intracellular synthesis mechanism by different microorganisms. Literature reports demonstrate that bacterial species such as *Rhodococcus Sp.* have synthesized Au nanoparticles on the cytoplasmic membrane due to the involvement of enzymes present on the cell membrane (Ahmad et al. 2003). Same as bacteria, mycological species such as *Verticillium Sp.* and yeast species such as *Pichia jadinii* are observed to synthesize Ag and Au nanoparticles on the vicinity of cell membrane by the action of enzymes and proteins (Mukherjee et al. 2001; Gericke and Pinches 2006). It can be concluded that the intracellular synthesis of nanoparticles by fungi, bacteria, yeast, and virus occur due to the oxidoreductases enzymes and proteins present in the cytoplasm, cytosol, and cell membrane.

## *2.4 Eukaryotic Macroorganisms-Mediated Green Synthesis of Nanoparticles*

### 2.4.1 Algae-Inspired Green Synthesis of Nanoparticles

Algae are photosynthetic eukaryotic organisms that produce their food themselves via photosynthesis. They are not truly photosynthetic eukaryotic, which is why they are also known as polyphyletic (Keeling 2004). This is because of the fact that their photosynthetic system has gradually evolved from cyanobacteria through

endosymbiosis process (Palmer et al. 2004). Algae comprises of different groups of organisms ranging from unicellular to multicellular organisms. Most algae are autotrophs and have their habitat in aqueous environment (Xiao et al. 2004). Like other microorganisms, bioremediation has been observed in alga species such as *Stichococcus bacillaris*, which can biodegrade synthetic polymers such as silicone resins (Cappitelli and Sorlini 2008). Moreover, it has been shown that algae also have potential to synthesize nanoparticles by exploiting them as they have several secondary metabolites and biological active compounds as well, which can be used as reducing, capping, and stabilizing agent (Fawcett et al. 2017). Based on these secondary metabolites and biological active compounds, they have several potential applications in biological medicines as antibacterial, anticancer, antimycotic, antioxidants, and antidiabetic agents (da Silva Ferreira et al. 2017).

Recently, researchers have focused to exploit algae for synthesizing biocompatible and eco-friendly nanoparticles for various biological applications especially in nanomedicine. Among several algal species, *Chlorella sp.* have been found to produce nanoparticles of different heavy metals including Ni, Cu, U, and Cd (Wilde and Benemann 1993). The dried powder and aqueous extracts of *Chlorella vulgaris* have been utilized for synthesizing the monodisperse Ag and Pd nanospheres of 4–14 and 5–20 nm diameters, respectively (da Silva Ferreira et al. 2017; Arsiya et al. 2017). Furthermore, Pd nanoparticles synthesis has also been reported using *Sargassum bovinum* (Momeni and Nabipour 2015). Using algal species such as *Sargassum plagiophyllum* and *Caulerpa racemose*, efficient and economical synthesis of Ag nanoparticles has been described by Dhas et al. (2014) and Edison et al. (2016). By exploiting aqueous extract of brown algal species such as *Turbinaria conoides* and *Sargassum tenerrimum*, Au nanoparticles were synthesized which had demonstrated the outstanding photocatalytic propensity against organic dye and 4-nitro-phenol (Ramakrishna et al. 2016). All these reports have shown that algae have enormous potential for the green synthesis of biocompatible nanoparticles. However, very less attention has been paid by the researchers to synthesize nanoparticles by using them.

### 2.4.2 Plant-Mediated Green Synthesis of Nanoparticles

Plants are multicellular eukaryotic photosynthetic species classified in the kingdom of plantae. They are well known being have capacity to adsorb, hyperaccumulate, and disintegrate metal and metal oxide ions from their surrounding biosphere alike other bioorganisms (Kulkarni and Muddapur 2014). It has been demonstrated that plants have several molecular functionalities, natural occurring substances and secondary metabolites, that is, phytochemicals that could be used as effective biological factories to cope with the environmental toxicities results from industrial wastes (Huang et al. 2019). Moreover, because of the existence of biological active compounds, such as alkaloids, flavonoids, polyphenols, saponins, terpenoids, coenzymes, proteins, sugars, and vitamins, plants have several potential applications in biomedicine (Khan et al. 2013). Plants have been widely used for the treatments

of various kinds of diseases such as rheumatism, skin disease, veneral infections, and beri-beri in Ayurvedic, Chinese, and Thai traditional medicines (Ashraf et al. 2018; Khalid et al. 2018). It has been reported that plants have several biological effects including antibacterial, antimycotic, antiviral, anticancer, free radical scavenging, and anti-inflammatory (Khan et al. 2013).

Recently, researchers have started paying attention towards plants for biosynthesizing the biocompatible nanoparticles from them. It has been reported that secondary metabolites of plants can play an important and crucial role as reducers, stabilizers, and capping agents for biosynthesizing nanoparticles (Ijaz et al. 2017). Moreover, phytochemicals being adsorbed on the surface lead to synthesis of biocompatible nanoparticles. They can also enhance the biological properties of nanoparticles rather than utilizing conventionally synthesized nanoparticles. By using plants, the synthesis of nanoparticles have several advantages, as this approach is simple, reliable, economical, easy to scale up, and eco-friendly in contrast to chemical and physiochemical approaches. Plants also have advantages such as less time, no lab culturing, harmless, one-step process, and no sophisticated laboratory facilities required over the microbial synthesis approaches for the green synthesis of nanoparticles (Nasrollahzadeh et al. 2019).

Several plants such as *Cymbopogon flexuosus* (lemon grass), *Brassica juncea* (Mustard), *Coriandrum sativum* (Coriander), *Azadirachta indica* (Neem), *Citrus limon* (Limon), *Osimum sanctum* (Tulsi), *Medicago sativa* (alfalfa), *Avena sativa* (Oat), and *Aloe barbadensis Miller* (aloe vera) have been widely explored for the synthesis of various biocompatible and eco-friendly nanoparticles. Ijaz et al. (2017) have described the CuO nanoparticles synthesis by employing leaves aqueous extract of *Abutilon indicum*. In another study, Khan et al. reported the one-port synthesis of ZnO and Cu-doped ZnO nanoparticles by utilizing the aqueous leaves extracts of *Clerodendrum inerme*, *Abutilon indicum,* and *Clerodendrum infortunatum* (Khan et al. 2018). It has been stated that several parts of plants such as leaves, fruits, fruits peel, seeds, and roots have been utilized for the synthesis of nanoparticles including Ag, Au, Pd, Pd/CuO, and Pd/$Fe_3O_4$, respectively.

In the synthesis of nanoparticles by plants, collection of plants parts such as leaves, roots, and fruits of interest, washing, and drying is the first step. Next, dried material is pulverized and dissolved in water and heat for a while at optimum temperature. Plant extract is used to filter the solid debris of plants. Aqueous plant extract and metal salts solution mix are heated at optimum temperature conditions. The nanoparticles synthesis formation can be identified through visual inspection, as discussed in Sect. 2.2. As a next step, reaction media containing nanoparticles and plant extracts centrifuge for repeated cycles to confiscate loosely bound phytochemicals and other impurities and finally nanoparticles are arrived in pellet form (Fig. 8).

During the synthesis of nanoparticles by plants, electron-rich phytochemical molecular functionalities such as polyphenols, sugars, and flavonoids of plant extract reduce the metal ions into nanoparticles via redox reaction such as enol- to keto-transformation. Other phytochemicals in plant extracts such as alkaloids,

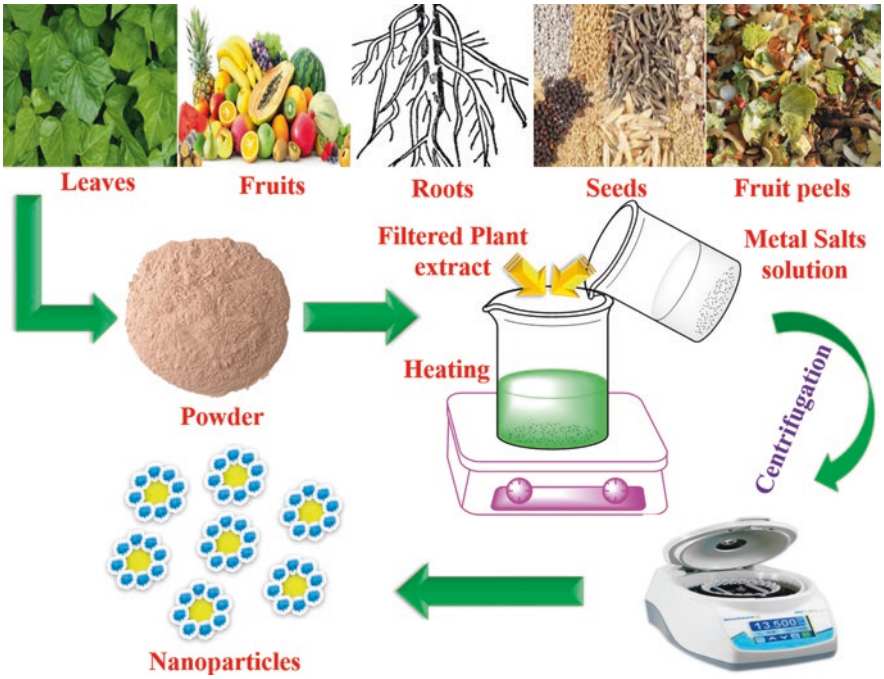


**Fig. 8** Schematic presentation of a generalized protocol for the green synthesis of nanoparticles by different parts of plants including leaves, fruits, fruits peel, seeds, and roots.

saponins, terpenoids, co-enzymes, and proteins capped and stabilized the nanoparticles (Fig. 9)

## *2.5 Critical Parameters for the Green Synthesis of Nanoparticles Using Biological Species*

Although green synthesis of nanoparticles using biological species such as fungi, bacteria, yeast, plants, algae, and virus have many advantages over chemical and physiochemical techniques, the polydispersity of the biologically synthesized nanoparticles is a serious challenge (Singh et al. 2016a, b, c). Therefore, recently many researchers have attempted to design and develop systems, which can produce biologically synthesized nanoparticles with homogenized morphology and size. Reports demonstrate that morphology and size of the biologically synthesized nanoparticles can be tuned either by controlling their growth environments or through changing the molecules functionalities (Kathiresan et al. 2009). For example, by using *Ganoderma spp*. biocompatible and monodispersed Au, nanoparticles of size 20 nm have been successfully synthesized by tuning the reaction parameters,

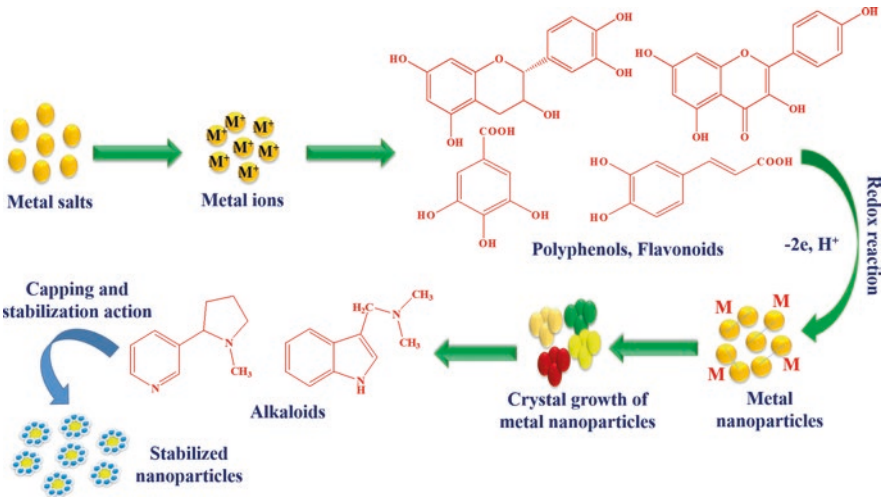


**Fig. 9** Schematic illustration showing the phytochemicals mediated synthesis pathway for biosynthesizing the nanoparticles by plants

such as irradiation time, mixing ratio, redox conditions, aeration, temperature, pH, and salt concentrations (Gurunathan et al. 2014).

It has also been shown that biosynthesis at temperatures higher than the room temperature is preferred. This is because of the fact that at elevated temperature, the enzymes liable for nanoparticles fabrication are more energetic and robust (Gurunathan et al. 2009). For example, Song et al. (2009) showed that synthesis rate of Ag nanoparticles using Magnolia leaf extracts increases with temperature. In addition, they also showed that the average Ag nanoparticle size decreases from 50 nm at 25 °C to 16 nm at 95 °C (Song et al. 2009). The size reduction at higher temperature is attributed to increase of nucleation rate (Gurunathan et al. 2009).

The pH of reaction media is also the most important and influential parameter. Literature shows that the reaction media at different pH levels produce different nanoparticles. Gurunathan et al. (2009) described that the Ag nanoparticle of spherical morphology with size of 50 nm were synthesized at highly basic pH level of 10 by using *E. coli*. Furthermore, different pH levels are required for different microbial species. For instance, acidic, slightly acidic, and alkaline pH levels have demonstrated the optimum growth of nanoparticles by using different mycological species such as *Fusarium acuminatum, Penicillium fellutanum,* and *Isaria fumosorosea,* respectively (Kathiresan et al. 2009; Banu and Balasubramanian 2014).

While synthesizing the nanoparticles using plants extracts, the pH changes disturb the charge distribution of natural products, which ultimately affects the metal ions reduction process and phytochemicals binding ability (Singh et al. 2016a, b, c). All these factors would affect the nanoparticle's monodispersity and yield. For example, Au nanoparticles of various sizes have been synthesized by using *Avena sativa* extract at pH level of 3.0 and 4.0. On the other hand, at pH 2.0, agglomeration

and aggregation in Au nanoparticles were observed (Singh et al. 2016a, b, c). Other reports demonstrate alkaline pH is most favorable in plant-mediated synthesized nanoparticles as plant extracts may possess more functionalities groups bearing negative charges at alkaline pH level that can efficiently bind and reduce metal ions leading to more nanoparticles yield (Sathishkumar et al. 2010). For instance, size- and morphology-controlled Au, Ag nanoparticles have been synthesized by using peers and *Curcuma longa* extracts at alkaline pH, respectively (Ghodake et al. 2010; Sathishkumar et al. 2010).

Thus, it can be concluded that acidic pH values favor aggregation of nanoparticles over the reduction process in comparison to alkaline pH. Other factors such as salt concentrations, mixing ratio and duration of time depend on the microbial species and nature of plant extracts (Singh et al. 2016a, b, c).

## 3 Applications of Biologically Synthesized Nanoparticles in Medical Biology

The nanoparticles synthesized by exploiting different biological approaches have several applications in biological and medicine field. Reports demonstrate that numerous metal and metal oxide nanoparticles have been exploited for their antimycotic, antibacterial, anticancer, antiviral properties in therapeutic and diagnostic applications. Moreover, applications of different biological synthesized nanoparticles has ascribed in following sections.

### *3.1 Antibacterial Agents*

The exploitation of metal or metal oxide nanoparticles in biomedical field is a new scope. Antibacterial potential of nanoparticles are being investigated because pathogenic microbes have started resistance against commercially available antibiotic drugs. As a result, antibiotics are not showing their efficacy against multi-drug-resistant bacteria. Therefore, there is a huge demand to develop new antibacterial drugs with better efficacy. In this instance, researchers have developed synergistic strategy such as nanosize with biological active compounds to tackle multi-drug-resistant bacteria. Because of the nanosize, nanoparticles can easily penetrate into the cells of pathogenic bacterial strains. The existence of biologically active compounds on the surface of nanoparticles can further enhance their antibacterial action.

It has been reported that biosynthesized metal and metal oxide nanoparticles including Ag, Au, ZnO, Cu, CuO, Ni, and NiO nanoparticles have demonstrated the signification inhibitory action against bacterial strains. Fayaz et al. (2010) reported

that fungus-mediated synthesized Ag nanoparticles (5–40 nm) have shown the enhanced bactericidal propensity against both the gram-positive and gram-negative bacterial strains. In other studies by Khan et al. (2018) and Ijaz et al. (2017), plant-mediated synthesized ZnO, Cu-doped ZnO, and CuO nanoparticles have demonstrated the significant bactericidal propensity against both gram-positive (*S. aureus* and *B. subtilis*) and gram-negative (*E. coli* and *Klebsiella*) bacteriological species. Their studies show that the nanoparticles antibacterial action is size and dose dependent. Furthermore, nanoparticles show different antibacterial action towards gram-positive and gram-negative bacterial strains due to differences in their cell wall composition. Nanoparticles demonstrates their mode of action against bacterial strains by arresting their cell wall synthesis, destroying cell wall and cell membrane, producing oxidative stress by reactive oxygen species in cell, denaturation of proteins and DNA (Khan et al. 2018) (Fig. 10).

## *3.2 Antimycotic Agents*

Biological synthesized nanoparticles have also been widely explored for their antimycotic potential against different pathogenic mycological species. Gajbhiye et al. (2009) have reported the enhanced antimycotic activity against different mycological species presented by Ag nanoparticles synthesized using fungal strain such as *Alternaria alternate*. Khan et al. (2018) has reported the improved antimycotic propensity of ZnO and Cu-doped ZnO synthesized by using leaves extracts of plants such as *A. indicum, C. infortunatum,* and *C. inerme* against three fungal strains such as *A. flavus*, *A. niger, and T. harzianum*. Moreover, CdS nanoparticles synthesized by using microbes have been reported for their enhanced fungicidal activity against two mycological species such as *A. flavus* and *A. niger* (Rajeshkumar et al. 2014). Several other biologically synthesized nanoparticles including CuO, Au, Ni, NiO, Pt, and Pd have been reported for their antifungal potential.

The antifungal mechanism of nanoparticles against mycological species is not cleared and well explained. However, Reidy et al. (2013) described that Ag nanoparticles present their antifungal action by attaching on the cell's surface. From where they penetrate into the cell and interact with phosphorous containing molecular functionalities such as DNA or arrest the respiratory process of the fungal cells, which ultimately led the death of fungal cell. It also has been suggested that Ag nanoparticles can also interact with thiol (-SH) groups of enzymes and make them inactive. As a result, death of fungi cell occur (Reidy et al. 2013). All these factors contribute towards nanoparticles inhibitory action against mycological species. It can be concluded that nanoparticles antifungal mode of action is somehow similar to their antibacterial mode of action.

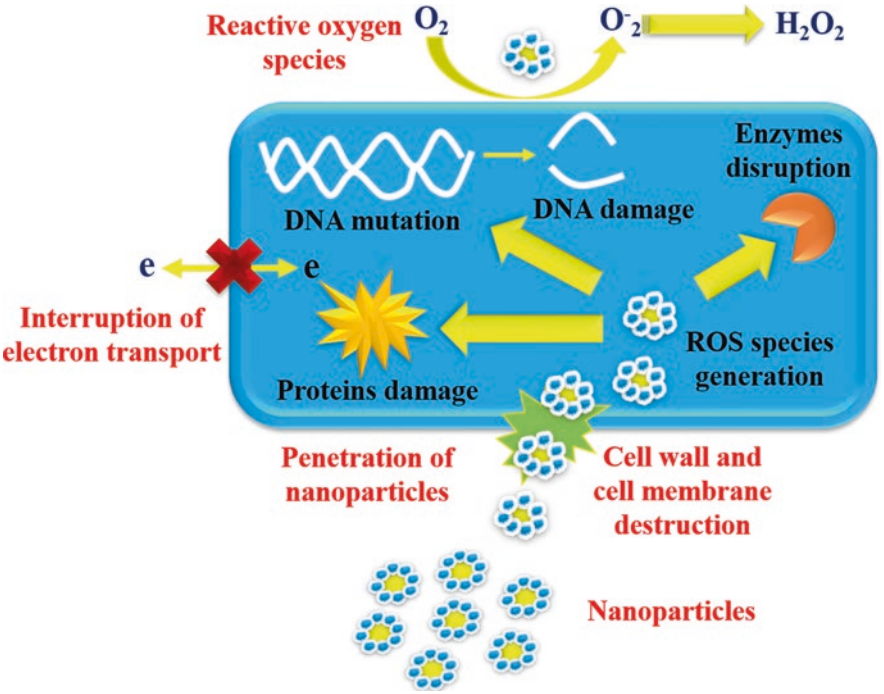


**Fig. 10** Schematic illustration of the antibacterial mode of action of nanoparticles against bacterial strains (Modified after Patil and Kim 2017). *ROS* reactive oxygen species

## *3.3 Anticancer Agents*

In anticancer diagnosis and therapy applications, biosynthesized metal and metal oxide nanoparticles have also been widely investigated and explored. Several biosynthesized nanoparticles such as Ag, Au, Zn, Cu-doped ZnO, CuO, MgO, Ni, NiO, and Co-doped SnO have demonstrated their potential application as anticancer agents. Khan et al. (2018) reported the enhanced anticancer activity of plant-mediated synthesized ZnO and Cu-doped ZnO nanoparticles against breast-cancer cell-line. In another study, Manivasagan et al. (2015) reported the anticancer propensity of Au nanoparticles synthesized by *Nocardiopsis sp*. against human cervical cancer cells. Moreover, they also reported that HeLa cells and breast cancer cells death resulted due to apoptosis. Pugazhendhi et al. (2019) reported the synthesis of MgO by using aqueous extract of *Sargassum wightii*, which further evaluated for anticancer activity against lung cancer cells. The biosynthesized MgO nanoparticles exhibited enhanced anticancer activity by inducing cytotoxicity to lung cancer cells. They also described that lung cancer cells dies because of the apoptosis resulted from the generation of reactive oxygen species. Reactive oxygen species play significant role in several cellular events such as inflammation, senescence mutation, DNA damage, and apoptosis. As a result of apoptosis in breast, HeLa, and lungs

cancer cells, they have observed morphological changes and condensation in DNA, loss of membrane integrality, and cell shrinkage. Their investigations also demonstrate that nanoparticles exhibit dose-dependent cytotoxicity activity against cancer cells.

### *3.4 Sensors*

Biological synthesized metal and metal oxide nanoparticles could be employed in sensing application as sensors. In analytic chemistry, optical and electronic properties sensing of biomaterial's surfaces is a general practice. Thus, immobilization of conjugate of biomolecules-nanoparticles on the surface will lead to the development of electronic and optical biosensors. Among various nanoparticles, metal nanoparticles, i.e. Au and Ag nanoparticles, exhibit Plasmon resonance in visible spectrum. Plasmon resonance can be controlled by size variations of metal nanoparticles. Therefore, metal nanoparticles optical properties can be modified by binding with molecules. As a result it will allow quantification of analytes and ion detection. It has been reported that upon agglomeration, Au nanoparticles properties are changed significantly. Spectral shift arises in agglomerated metal nanoparticles which have a key role in the development of biosensors. Many researchers adopting this approach have reported tissue staining and bioassay labeling (Razavi et al. 2015; Huo 2007). For example, Han et al. (2006) have reported the DNA functionalized Au nanoparticles system and they have exploited that system for the colorimetric identification of triplex DNA binding molecules. Furthermore, based on melting temperature, they have also utilized it for the determination of their relative binding affinities.

### *3.5 Drug Delivery*

An effective dosage of drug molecules can be reached to a specific target site. However, the delivering of drug molecules within scheduled period with better efficacy could be succeeded by the development of drug-delivery systems. Nanoparticles have abilities to be exploited as drug-delivery systems in conjunction with other biomolecules (Ghosh et al. 2008). In this instance, among metals, Au nanoparticles are considered as nontoxic and nonimmunogenic and have the ability to be functionalized. Such properties make Au nanoparticles appropriate contender for the development of platforms and vehicles for drug-delivery systems.

Therefore, Aubin-Tam and Hamad-Schifferli (2008) have developed a drug-delivery system based on infrared light and Au nanoparticles. Thus developed drug-delivery system has successfully delivered various dosages of drug molecules in a very meticulous, proficient manner as different morphologies of Au nanoparticles have given the response on different wavelength of infrared radiations, e.g. nanocubes and nanocapsules are melted at the wavelength of 1100 and 800, nm

respectively. Hence, at specific wavelength of infrared radiation excitation, respective Au nanocubes can melt and release specific kind of DNA.

## 4 Conclusion

Nanomaterials, especially metal and metal oxide nanoparticles, have attracted much consideration in several arenas including materials science, chemistry, biology, biotechnology, medicine, and environment. Large-scale applications of these nanoparticles require large-scale synthesis processes, which are eco-friendly, biocompatible, and energy efficient. These requirements are mostly met with biosynthesis using different bio-organisms such as plants, algae, virus, bacteria, fungi, and yeast. In this chapter, advantages, disadvantages, and mechanisms of biosynthesis using different bio-organisms are summarized. These processes offer good potential for large-scale industry production of biocompatible, size, and morphology-controlled metal nanoparticles at low cost. Nanoparticles biosynthesis employing genetic engineering, molecular cloning, and photobiological techniques are expected to have fabulous developments in the field of nanobiotechnology.

**Acknowledgement** This work was supported by City University of Hong Kong (CityU Applied Research Grant: Project no. 9667160).

## References

AbdelRahim K, Mahmoud SY, Ali AM, Almaary KS, Mustafa AE-ZMA, Husseiny SM. Extracellular biosynthesis of silver nanoparticles using Rhizopus Stolonifer. Saudi J Biol Sci. 2017;24(1):208–16. https://doi.org/10.1016/j.sjbs.2016.02.025.

Ahmad A, Senapati S, Khan MI, Kumar R, Ramani R, Srinivas V, Sastry M. Intracellular synthesis of gold nanoparticles by a novel alkalotolerant actinomycete, Rhodococcus species. Nanotechnology. 2003;14(7):824. https://iopscience.iop.org/article/10.1088/0957-4484/14/7/323/meta

Ahmed E, Kalathil S, Shi L, Alharbi O, Wang P. Synthesis of ultra-small platinum, palladium and gold nanoparticles by Shewanella loihica PV-4 electrochemically active biofilms and their enhanced catalytic activities. J Saudi Chem Soc. 2018;22(8):919–29. https://doi.org/10.1016/j.jscs.2018.02.002.

Alghuthaymi MA, Almoammar H, Rai M, Said-Galiev E, Abd-Elsalam KA. Myconanoparticles: synthesis and their role in phytopathogens management. Biotechnol Biotechnol Equip. 2015;29:221–36. https://doi.org/10.1080/13102818.2015.1008194.

Alijani HQ, Pourseyedi S, Mahani MT, Khatami M. Green synthesis of zinc sulfide (ZnS) nanoparticles using Stevia rebaudiana Bertoni and evaluation of its cytotoxic properties. J Mol Struct. 2019;1175:214–8. https://doi.org/10.1016/j.molstruc.2018.07.103.

Aljabali AA, Barclay JE, Lomonossoff GP, Evans DJ. Virus templated metallic nanoparticles. Nanoscale. 2010;2(12):2596–600. https://doi.org/10.1039/C0NR00525H.

Apte M, Sambre D, Gaikawad S, Joshi S, Bankar A, Kumar AR, Zinjarde S. Psychrotrophic yeast yarrowia lipolytica NCYC 789 mediates the synthesis of antimicrobial silver nanoparticles

via cell-associated melanin. AMB Express. 2013;3(1):32. https://link.springer.com/article/10.1186/2191-0855-3-32

Arsiya F, Sayadi MH, Sobhani S. Green synthesis of palladium nanoparticles using chlorella vulgaris. Mater Lett. 2017;186:113–5. https://doi.org/10.1016/j.matlet.2016.09.101.

Asghari-Paskiabi F, Imani M, Rafii-Tabar H, Razzaghi-Abyaneh M. Physicochemical properties, antifungal activity and cytotoxicity of selenium sulfide nanoparticles green synthesized by Saccharomyces cerevisiae. Biochem Biophys Res Commun. 2019;516(4):1078–84. https://doi.org/10.1016/j.bbrc.2019.07.007.

Ashraf I, Zubair M, Rizwan K, Rasool N, Jamil M, Khan SA, Tareen RB, Ahmad VU, Mahmood A, Riaz M, Zia-Ul-Haq M. Chemical composition, antioxidant and antimicrobial potential of essential oils from different parts of Daphne mucronata Royle. Chem Cent J. 2018;12(1):135. https://doi.org/10.1186/s13065-018-0495-1.

Aubin-Tam M-E, Hamad-Schifferli K. Structure and function of nanoparticle–protein conjugates. Biomed Mater. 2008;3:034001. https://iopscience.iop.org/article/10.1088/1748-6041/3/3/034001/meta

Balaji DS, Basavaraja S, Deshpande R, Mahesh DB, Prabhakar BK, Venkataraman A. Extracellular biosynthesis of functionalized silver nanoparticles by strains of Cladosporium cladosporioides fungus. Colloids Surf B Biointerfaces. 2009;68(1):88–92. https://doi.org/10.1016/j.colsurfb.2008.09.022.

Balci S, Bittner AM, Schirra M, Thonke K, Sauer R, Hahn K, Kadri A, Wege C, Jeske H, Kern K. Catalytic coating of virus particles with zinc oxide. Electrochim Acta. 2009;54(22):5149–54. https://doi.org/10.1016/j.electacta.2009.03.036.

Bankar AV, Kumar AR, Zinjarde SS. Removal of chromium (VI) ions from aqueous solution by adsorption onto two marine isolates of Yarrowia lipolytica. J Hazard Mater. 2009;170(1):487–94. https://doi.org/10.1016/j.jhazmat.2009.04.070.

Banu AN, Balasubramanian C. Optimization and synthesis of silver nano- particles using Isaria fumosorosea against human vector mosquitoes. Parasitol Res. 2014;113:3843–51. https://link.springer.com/article/10.1007/s00436-014-4052-0

Baskar G, Chandhuru J, Fahad KS, Praveen AS, Chamundeeswari M, Muthukumar T. Anticancer activity of fungal L-asparaginase conjugated with zinc oxide nanoparticles. J Mater Sci Mater Med. 2015;26(1):43. https://link.springer.com/article/10.1007/s10856-015-5380-z

Bathrinarayanan PV, Thangavelu D, Muthukumarasamy VK, Munusamy C, Gurunathan B. Biological synthesis and characterization of intracellular gold nanoparticles using biomass of Aspergillus fumigatus. Bull Mater Sci. 2013;36(7):1201–5. https://link.springer.com/article/10.1007/s12034-013-0599-0

Bhadwal AS, Tripathi RM, Gupta RK, Kumar N, Singh RP, Shrivastav A. Biogenic synthesis and photocatalytic activity of CdS nanoparticles. RSC Adv. 2014;4(19):9484–90. https://pubs.rsc.org/en/content/articlelanding/2014/ra/c3ra46221h/unauth#!divAbstract

Bhainsa KC, D'souza SF. Extracellular biosynthesis of silver nanoparticles using the fungus Aspergillus fumigatus. Colloids Surf B Biointerfaces. 2006;47(2):160–4. https://doi.org/10.1016/j.colsurfb.2005.11.026.

Bharde A, Rautaray D, Bansal V, Ahmad A, Sarkar I, Yusuf SM, Sanyal M, Sastry M. Extracellular biosynthesis of magnetite using fungi. Small. 2006;2(1):135–41. https://doi.org/10.1002/smll.200500180.

Boroumand Moghaddam A, Namvar F, Moniri M, Azizi S, Mohamad R. Nanoparticles biosynthesized by fungi and yeast: a review of their preparation, properties, and medical applications. Molecules. 2015;20(9):16540–65. https://doi.org/10.3390/molecules200916540.

Cappitelli F, Sorlini C. Microorganisms attack synthetic polymers in items representing our cultural heritage. Appl Environ Microbiol. 2008;74(3):564–9. https://aem.asm.org/content/74/3/564

Celebioglu A, Topuz F, Yildiz ZI, Uyar T. One-step green synthesis of antibacterial silver nanoparticles embedded in electrospun cyclodextrin nanofibers. Carbohydr Polym. 2019;207:471–9. https://doi.org/10.1016/j.carbpol.2018.12.008.

Chen JC, Lin ZH, Ma XX. Evidence of the production of silver nanoparticles via pretreatment of Phoma sp.3.2883 with silver nitrate. Lett Appl Microbiol. 2003;37:105–8. https://doi.org/10.1046/j.1472-765X.2003.01348.x.

Chen P-Y, Dang X, Klug MT, Courchesne N-MD, Qi J, Hyder MN, Belcher AM, Hammond PT. M13 virus-enabled synthesis of titanium dioxide nanowires for tunable mesoporous semiconducting networks. Chem Mater. 2015;27(5):1531–40. https://doi.org/10.1021/cm503803u.

Clark JH, Luque R, Matharu AS. Green chemistry, biofuels, and biorefinery. Annu Rev Chem Biomol. 2012;3:183–207. https://doi.org/10.1146/annurev-chembioeng-062011-081014.

da Silva Ferreira V, ConzFerreira ME, Lima LM, Frasés S, de Souza W, Sant'Anna C. Green production of microalgae-based silver chloride nanoparticles with antimicrobial activity against pathogenic bacteria. Enzyme Microb Technol. 2017;97:114–21. https://doi.org/10.1016/j.enzmictec.2016.10.018.

Dahl JA, Maddux BL, Hutchison JE. Toward greener nanosynthesis. Chem Rev. 2007;107:2228–69. https://doi.org/10.1021/cr050943k.

Daniel MC, Astruc D. Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem Rev. 2004;104(1):293–346. https://pubs.acs.org/doi/abs/10.1021/cr030698+

Deplanche K, Caldelari I, Mikheenko IP, Sargent F, Macaskie LE. Involvement of hydrogenases in the formation of highly catalytic Pd (0) nanoparticles by bioreduction of Pd (II) using Escherichia coli mutant strains. Microbiology. 2010;156(9):2630–40. https://doi.org/10.1099/mic.0.036681-0.

Devi HS, Boda MA, Shah MA, Parveen S, Wani AH. Green synthesis of iron oxide nanoparticles using Platanus orientalis leaf extract for antifungal activity. Green Process Synth. 2019;8(1):38–45. https://doi.org/10.1515/gps-2017-0145.

Dhas TS, Kumar VG, Karthick V, Angel KJ, Govindaraju K. Facile synthesis of silver chloride nanoparticles using marine alga and its antibacterial efficacy. Spectrochim Acta A Mol Biomol Spectrosc. 2014;120:416–20. https://doi.org/10.1016/j.saa.2013.10.044.

Divya M, Kiran GS, Hassan S, Selvin J. Biogenic synthesis and effect of silver nanoparticles (AgNPs) to combat catheter-related urinary tract infections. Biocatal Agric Biotechnol. 2019;18:101037. https://doi.org/10.1016/j.colsurfb.2018.09.007.

Dudek NK, Sun CL, Burstein D. Novel microbial diversity and functional potential in the marine mammal oral microbiome. Curr Biol. 2017;27(24):3752–62. https://doi.org/10.1016/j.cub.2017.10.040.

Edison TN, Atchudan R, Kamal C, Lee YR. Caulerpa racemosa: a marine green alga for eco-friendly synthesis of silver nanoparticles and its catalytic degradation of methylene blue. Bioprocess Biosyst Eng. 2016;39(9):1401–8. https://link.springer.com/article/10.1007/s00449-016-1616-7

Elahian F, Reiisi S, Shahidi A, Mirzaei SA. High-throughput bioaccumulation, biotransformation, and production of silver and selenium nanoparticles using genetically engineered pichia pastoris. Nanomedicine NBM. 2017;13(3):853–61. https://doi.org/10.1016/j.nano.2016.10.009.

Elbeshehy EK, Elazzazy AM, Aggelis G. Silver nanoparti- cles synthesis mediated by new isolates of Bacillus spp., nano- particle characterization and their activity against Bean yellow mosaic virus and human pathogens. Front Microbiol. 2015;6:453. https://doi.org/10.3389/fmicb.2015.00453.

Faramarzi MA, Sadighi A. Insights into biogenic and chemical production of inorganic nanomaterials and nanostructures. Adv Colloid. 2013;189:1–20. https://doi.org/10.1016/j.cis.2012.12.001.

Fawcett D, Verduin JJ, Shah M, Sharma SB, Poinern GEJ. A review of current research into the biogenic synthesis of metal and metal oxide nanoparticles via marine algae and seagrasses. J Nanosci. 2017;2017:1–15. https://doi.org/10.1155/2017/8013850.

Fayaz AM, Balaji K, Girilal M, Yadav R, Kalaichelvan PT, Venketesan R. Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. Nanomedicine NBM. 2010;6(1):103–9. https://doi.org/10.1016/j.nano.2009.04.006.

Fischlechner M, Donath E. Viruses as building blocks for materials and devices. Angew Chem Int Ed Engl. 2007;46(18):3184–93. https://doi.org/10.1002/anie.200603445.

Gadd GM. Geomycology: biogeochemical transformations of rocks, minerals, metals and radionuclides by fungi, bioweathering and bioremediation. Mycol Res. 2007;111(1):3–49. https://doi.org/10.1016/j.mycres.2006.12.001.

Gahlawat G, Choudhury AR. A review on the biosynthesis of metal and metal salt nanoparticles by microbes. RSC Adv. 2019;9(23):12944–67.

Gajbhiye M, Kesharwani J, Ingle A, Gade A, Rai M. Fungus-mediated synthesis of silver nanoparticles and their activity against pathogenic fungi in combination with fluconazole. Nanomedicine NBM. 2009;5(4):382–6. https://doi.org/10.1016/j.nano.2009.06.005.

Gemishev O, Panayotova MI, Mintcheva N, Djerahov L, Tyuliev G, Gicheva G. A green approach for silver nanoparticles preparation by cell-free extract from Trichoderma reesei fungi and their characterization. Mater Res Express. 2019;6(9):095040. https://iopscience.iop.org/article/10.1088/2053-1591/ab2e6a/meta

Gerasopoulos K, McCarthy M, Royston E, Culver JN, Ghodssi R. Nanostructured nickel electrodes using the Tobacco mosaic virus for microbattery applications. J Micromech Microeng. 2008;18:104003. https://iopscience.iop.org/article/10.1088/0960-1317/18/10/104003/meta

Gericke M, Pinches A. Biological synthesis of metal nanoparticles. Hydrometallurgy. 2006;83(1):132–40. https://doi.org/10.1016/j.hydromet.2006.03.019.

Ghodake GS, Deshpande NG, Lee YP, Jin E. Pear fruit extract-assisted room-temperature biosynthesis of gold nanoplates. Colloids Surf B Biointerfaces. 2010;75:584–9. https://doi.org/10.1016/j.colsurfb.2009.09.040.

Ghosh P, Han G, De M, Kim CK, Rotello VM. Gold nanoparticles in delivery applications. Adv Drug Deliv Rev. 2008;60:1307–15. https://doi.org/10.1016/j.addr.2008.03.016.

Gurunathan S, Kalishwaralal K, Vaidyanathan R, Venkataraman D, Pandian SR, Muniyandi J, Hariharan N, Eom SH. Biosynthesis, purification and characterization of silver nanoparticles using Escherichia coli. Colloids Surf B Biointerfaces. 2009;74:328–35. https://doi.org/10.1016/j.colsurfb.2009.07.048.

Gurunathan S, Han J, Park JH, Kim JH. A green chemistry approach for synthesizing biocompatible gold nanoparticles. Nanoscale Res Lett. 2014;9:248. https://doi.org/10.1186/1556-276X-9-248.

Haefeli C, Franklin C, Hardy K. Plasmid-determined silver resistance in Pseudomonas stutzeri isolated from a silver mine. J Bacteriol. 1984;158:389–92. https://jb.asm.org/content/158/1/389.short

Hamedi S, Ghaseminezhad M, Shokrollahzadeh S, Shojaosadati SA. Controlled biosynthesis of silver nanoparticles using nitrate reductase enzyme induction of filamentous fungus and their antibacterial evaluation. Artif Cells Nanomed Biotechnol. 2017;45(8):1588–96. https://doi.org/10.1080/21691401.2016.1267011.

Han MS, Lytton-Jean AK, Mirkin CA. A gold nanoparticle based approach for screening triplex DNA binders. J Am Chem Soc. 2006;128(15):4954–5. https://doi.org/10.1021/ja0606475.

Hawksworth DL, Lücking R. Fungal diversity revisited: 2.2 to 3.8 million species. Microbiol Spectr. 2017;5:79–95. https://doi.org/10.1128/microbiolspec.FUNK-0052-2016.

Hoffman CS, Wood V, Fantes PA. An ancient yeast for young geneticists: a primer on the Schizosaccharomyces pombe model system. Genetics. 2015;201(2):403–23. https://doi.org/10.1534/genetics.115.181503.

Hu D, Yu S, Yu D, Liu N, Tang Y, Fan Y, Wang C, Wu A. Biogenic Trichoderma harzianum-derived selenium nanoparticles with control functionalities originating from diverse recognition metabolites against phytopathogens and mycotoxins. Food Control. 2019;106:106748. https://doi.org/10.1016/j.foodcont.2019.106748.

Huang Y, Song Y, Johnson D, Huang J, Dong R, Liu H. Selenium enhanced phytoremediation of diesel contaminated soil by Alternanthera philoxeroides. Ecotoxicol Environ Saf. 2019;173:347–52. https://doi.org/10.1016/j.ecoenv.2019.02.040.

Huo Q. A perspective on bioconjugated nanoparticles and quantum dots. Colloids Surf B: Biointerfaces. 2007;59:1–10. https://doi.org/10.1016/j.colsurfb.2007.04.019.

Hutchison JE. Greener nanoscience: a proactive approach to advancing applications and reducing implications of nanotechnology. ACS Nano. 2008;2:395–402. https://pubs.acs.org/doi/abs/10.1021/nn800131j

Ijaz F, Shahid S, Khan SA, Ahmad W, Zaman S. Green synthesis of copper oxide nanoparticles using Abutilon indicum leaf extract: antimicrobial, antioxidant and photocatalytic dye degradation activities. Trop J Pharm Res. 2017;16(4):743–53. https://doi.org/10.4314/tjpr.v16i4.2.

Iravani S. Bacteria in nanoparticle synthesis: current status and future prospects. Int Scholarly Res Notices. 2014;2014:1–18. https://doi.org/10.1155/2014/359316.

Jayaseelan C, Rahuman AA, Kirthi AV, Marimuthu S, Santhoshkumar T, Bagavan A, Gaurav K, Karthik L, Rao KB. Novel microbial route to synthesize ZnO nanoparticles using Aeromonas hydrophila and their activity against pathogenic bacteria and fungi. Spectrochim Acta A Mol Biomol Spectrosc. 2012;90:78–84. https://doi.org/10.1016/j.saa.2012.01.006.

Jha AK, Prasad K, Prasad K. A green low-cost biosynthesis of $Sb_2O_3$ nanoparticles. Biochem Eng J. 2009;43(3):303–6. https://doi.org/10.1016/j.bej.2008.10.016.

Kadam VV, Ettiyappan JP, Balakrishnan RM. Mechanistic insight into the endophytic fungus mediated synthesis of protein capped ZnO nanoparticles. Mater Sci Eng B. 2019;243:214–21. https://doi.org/10.1016/j.mseb.2019.04.017.

Karthik L, Kumar G, Kirthi AV, Rahuman AA, Rao KB. Streptomyces sp. LK3 mediated synthesis of silver nanoparticles and its biomedical application. Bioprocess Biosyst Eng. 2014;37(2):261–7. https://link.springer.com/article/10.1007%2Fs00449-013-0994-3

Kathiresan K, Manivannan S, Nabeel MA, Dhivya B. Studies on silver nanoparticles synthesised by a marine fungus, Penicillium fellutanum isolated from coastal mangrove sediment. Colloids Surf B Biointerfaces. 2009;71:133–7. https://doi.org/10.1016/j.colsurfb.2009.01.016.

Kaur H, Dolma K, Kaur N, Malhotra A, Kumar N, Dixit P, Sharma D, Mayilraj S, Choudhury AR. Marine microbe as nano-factories for copper biomineralization. Biotechnol Bioprocess Eng. 2015;20(1):51–7. https://link.springer.com/article/10.1007/s12257-014-0432-7

Keeling PJ. Diversity and evolutionary history of plastids and their hosts. Am J Bot. 2004;91(10):1481–93. https://doi.org/10.3732/ajb.91.10.1481.

Khalid A, Shahid S, Khan SA, Kanwal S, Yaqoob A, Rasool ZG, Rizwan K. Antioxidant activity and hepatoprotective effect of Cichorium intybus (Kasni) seed extract against carbon tetrachloride-induced liver toxicity in rats. Trop J Pharm Res. 2018;17(8):1531–8. https://doi.org/10.4314/tjpr.v17i8.10.

Khan SA, Rasool N, Riaz M, Nadeem R, Rashid U, Rizwan K, Zubair M, Bukhari IH, Gulzar T. Evaluation of antioxidant and cytotoxicity studies of Clerodendrum inerme. Asian J Chem. 2013;25(13):7457–62. https://doi.org/10.14233/ajchem.2013.14831.

Khan SA, Noreen F, Kanwal S, Iqbal A, Hussain G. Green synthesis of ZnO and Cu-doped ZnO nanoparticles from leaf extracts of Abutilon indicum, Clerodendrum infortunatum, Clerodendrum inerme and investigation of their biological and photocatalytic activities. Mater Sci Eng C. 2018;82:46–59. https://doi.org/10.1016/j.msec.2017.08.071.

Khan SA, Arshad Z, Shahid S, Arshad I, Rizwan K, Sher M, Fatima U. Synthesis of $TiO_2$/Graphene oxide nanocomposites for their enhanced photocatalytic activity against methylene blue dye and ciprofloxacin. Compos Part B Eng. 2019;175(C):107120. https://doi.org/10.1016/j.compositesb.2019.107120.

Knez M, Bittner AM, Boes F, Wege C, Jeske H, Maib E, Kern K. Biotemplate synthesis of 3-nm nickel and cobalt nanowires. Nano Lett. 2003;3(8):1079–82. https://doi.org/10.1021/nl0342545.

Koonin EV, Senkevich TG, Dolja VV. The ancient Virus World and evolution of cells. Biol Direct. 2006;1:29. https://doi.org/10.1186/1745-6150-1-29.

Kralj S, Makovec D. Magnetic assembly of superparamagnetic iron oxide nanoparticle clusters into nanochains and nanobundles. ACS Nano. 2015;9(10):9700–7. https://pubs.acs.org/doi/10.1021/acsnano.5b02328.

Kulkarni N, Muddapur U. Biosynthesis of metal nanoparticles: a review. J Nanotechnol. 2014;2014:1–8. https://doi.org/10.1155/2014/510246.

Kumar CG, Mamidyala SK. Extracellular synthesis of silver nanoparticles using culture supernatant of Pseudomonas aeruginosa. Colloids Surf B Biointerfaces. 2011;84(2):462–6. https://doi.org/10.1016/j.colsurfb.2011.01.042.

Kumar V, Sowmya B, Geetha R, Karpagambigai S, Rajeshkumar S, Lakshmi T. Preparation of yeast mediated semiconductor nanoparticles by candida albicans and its bactericidal potential against Salmonella typhi and Staphylococcus aureus. Int J Pharm Sci Res. 2019;10(2):861–4. https://doi.org/10.26452/ijrps.v10i2.262.

Kurtzman CP, Fell JW. Biodiversity and ecophysiology of yeasts. In: Gábor P, de la Rosa CL, editors. The yeast handbook. Berlin: Springer; 2006. p. 11–30. https://link.springer.com/content/pdf/10.1007/3-540-30985-3.pdf.

Lengke MF, Fleet ME, Southam G. Synthesis of palladium nanoparticles by reaction of filamentous cyanobacterial biomass with a palladium (II) chloride complex. Langmuir. 2007;23(17):8982–7. https://doi.org/10.1021/la7012446.

Longoria EC, Vilchis-Nestor AR, Avalos-Borja M. Biosynthesis of silver, gold and bimetallic nanoparticles using the filamentous fungus Neurospora crassa. Colloids Surf B Biointerfaces. 2011;83:42–8. https://doi.org/10.1016/j.colsurfb.2010.10.035.

Longoria EC, Velasquez SM, Nestor AV, Berumen EA, Borja MA. Production of platinum nanoparticles and nanoaggregates using Neurospora crassa. J Microbiol Biotechnol. 2012;22:1000–4. https://doi.org/10.4014/jmb.1110.10085.

Mala JG, Facile RC. Production of ZnS quantum dot nanoparticles by Saccharomyces cerevisiae MTCC 2918. J Biotechnol. 2014;170:73–8. https://doi.org/10.1016/j.jbiotec.2013.11.017.

Mann S. Molecular tectonics in biomineralization and biomimetic materials chemistry. Nature. 1993;365:499–505. https://www.nature.com/articles/365499a0.

Manivasagan P, Alam MS, Kang KH, Kwak M, Kim SK. Extracellular synthesis of gold bionanoparticles by Nocardiopsis sp. and evaluation of its antimicrobial, antioxidant and cytotoxic activities. Bioproc Biosyst Eng. 2015;38(6):1167–77. https://doi.org/10.1007/s00449-015-1358-y.

Marchiol L. Synthesis of metal nanoparticles in living plants. Ital J Agron. 2012;7:274–82. https://doi.org/10.4081/ija.2012.e37.

Mirkin CA, Letsinger RL, Mucic RC, Storhoff JJ. A DNA-based method for rationally assembling nanoparticles into macroscopic materials. Nature. 1996;382(6592):607. https://www.nature.com/articles/382607a0

Mishra A, Kumari M, Pandey S, Chaudhry V, Gupta KC, Nautiyal CS. Biocatalytic and antimicrobial activities of gold nanoparticles synthesized by Trichoderma sp. Bioresour Technol. 2014;166:235–42. https://doi.org/10.1016/j.biortech.2014.04.085.

Momeni S, Nabipour I. A simple green synthesis of palladium nanoparticles with sargassum alga and their electrocatalytic activities towards hydrogen peroxide. Appl Biochem Biotechnol. 2015;176(7):1937–49. https://link.springer.com/article/10.1007%2Fs12010-015-1690-3

Mukherjee P, Ahmad A, Mandal D, Senapati S, Sainkar SR, Khan MI, Parishcha R, Ajaykumar PV, Alam M, Kumar R, Sastry M. Fungus-mediated synthesis of silver nanoparticles and their immobilization in the mycelial matrix: a novel biological approach to nanoparticle synthesis. Nano Lett. 2001;1(10):515–9. https://doi.org/10.1021/nl0155274.

Nabi G, Khalid NR, Tahir MB, Rafique M, Rizwan M, Hussain S, Iqbal T, Majid A. A review on novel eco-friendly green approach to synthesis $TiO_2$ nanoparticles using different extracts. J Inorg Organomet Polym Mater. 2018;28(4):1552–64. https://doi.org/10.1007/s10904-018-0812-0.

Nam KT, Kim DW, Yoo PJ, Chiang CY, Meethong N, Hammond PT, Chiang YM, Belcher AM. Virus-enabled synthesis and assembly of nanowires for lithium ion battery electrodes. Science. 2006;312(5775):885–8. https://science.sciencemag.org/content/312/5775/885

Nangia Y, Wangoo N, Goyal N, Shekhawat G, Suri CR. A novel bacterial isolate Stenotrophomonas maltophilia as living factory for synthesis of gold nanoparticles. Microb Cell Factories. 2009;8(1):39. https://microbialcellfactories.biomedcentral.com/articles/10.1186/1475-2859-8-39

Narayanan KB, Sakthivel N. Green synthesis of biogenic metal nanoparticles by terrestrial and aquatic phototrophic and heterotrophic eukaryotes and biocompatible agents. Adv Colloid Interf Sci. 2011;169:59–79. https://doi.org/10.1016/j.cis.2011.08.004.

Nasrollahzadeh M, Atarod M, Sajjadi M, Sajadi SM, Issaabadi Z. Plant-mediated green synthesis of nanostructures: mechanisms, characterization, and applications. Interface Science and Technology. 2019;28:199–322. Elsevier. https://doi.org/10.1016/B978-0-12-813586-0.00006-7.

Nath D, Banerjee P. Green nanotechnology–a new hope for medical biology. Environ Toxicol Pharmacol. 2013;36:997–1014. https://doi.org/10.1016/j.etap.2013.09.002.

Omran BA, Nassar HN, Younis SA, Fatthallah NA, Hamdy A, El-Shatoury EH, El-Gendy NS. Physiochemical properties of Trichoderma longibrachiatum DSMZ 16517-synthesized silver nanoparticles for the mitigation of halotolerant sulphate-reducing bacteria. J Appl Microbiol. 2019;126(1):138–54. https://doi.org/10.1111/jam.14102.

Ortega FG, Fernández-Baldo MA, Fernández JG, Serrano MJ, Sanz MI, Diaz-Mochón JJ, Lorente JA, Raba J. Study of antitumor activity in breast cell lines using silver nanoparticles produced by yeast. Int J Nanomed. 2015;10:2021. https://doi.org/10.2147/IJN.S75835.

Pal G, Rai P, Pandey A. Green synthesis of nanoparticles: a greener approach for a cleaner future. In: Green synthesis, characterization and applications of nanoparticles. Amsterdam: Elsevier; 2019. p. 1–26. https://doi.org/10.1016/B978-0-08-102579-6.00001-0.

Palmer JD, Soltis DE, Chase MW. The plant tree of life: an overview and some points of view. Am J Bot. 2004;91(10):1437–45. https://doi.org/10.3732/ajb.91.10.1437.

Patil MP, Kim GD. Eco-friendly approach for nanoparticles synthesis and mechanism behind antibacterial activity of silver and anticancer activity of gold nanoparticles. Appl Microbiol Biotechnol. 2017;101(1):79–92. https://doi.org/10.1007/s00253-016-8012-8.

Patil MP, Kim GD. Marine microorganisms for synthesis of metallic nanoparticles and their biomedical applications. Colloids Surf B Biointerfaces. 2018;172:487–95. https://doi.org/10.1016/j.colsurfb.2018.09.007.

Pugazhendhi A, Prabhu R, Muruganantham K, Shanmuganathan R, Natarajan S. Anticancer, antimicrobial and photocatalytic activities of green synthesized magnesium oxide nanoparticles (MgONPs) using aqueous extract of Sargassum wightii. J Photochem Photobiol. 2019;190:86–97. https://doi.org/10.1016/j.jphotobiol.2018.11.014.

Radloff C, Vaia RA, Brunton J, Bouwer GT, Ward VK. Metal nanoshell assembly on a virus bioscaffold. Nano Lett. 2005;5(6):1187–91. https://doi.org/10.1021/nl050658g.

Raghukumar C, Raghukumar S. Barotolerance of fungi isolated from deep-sea sediments of the Indian Ocean. Aquat Microb Ecol. 1998;15(2):153–63. https://www.int-res.com/abstracts/ame/v15/n2/p153-163/

Rajakumar G, Rahuman AA, Roopan SM, Khanna VG, Elango G, Kamaraj C, Zahir AA, Velayutham K. Fungus-mediated biosynthesis and characterization of $TiO_2$ nanoparticles and their activity against pathogenic bacteria. Spectrochim Acta A Mol Biomol Spectrosc. 2012;91:23–9. https://doi.org/10.1016/j.saa.2012.01.011.

Rajeshkumar S, Ponnanikajamideen M, Malarkodi C, Malini M, Annadurai G. Microbe-mediated synthesis of antimicrobial semiconductor nanoparticles by marine bacteria. J Nanostruct Chem. 2014;4(2):96. https://link.springer.com/article/10.1007/s40097-014-0096-z

Ramakrishna M, Babu DR, Gengan RM, Chandra S, Rao GN. Green synthesis of gold nanoparticles using marine algae and evaluation of their catalytic activity. J Nanostruct Chem. 2016;6(1):1–3. https://link.springer.com/article/10.1007%2Fs40097-015-0173-y

Ramanavičius A, Kaušaitė A, Ramanavičienė A. Polypyrrole-coated glucose oxidase nanoparticles for biosensor design. Sens Actuators B-Chem. 2005;111:532–9. https://doi.org/10.1016/j.snb.2005.03.038.

Razavi M, Salahinejad E, Fahmy M, Yazdimamaghani M, Vashaee D, Tayebi L. Green chemical and biological synthesis of nanoparticles and their biomedical applications. In: Green processes for nanotechnology. Cham: Springer; 2015. p. 207–35. https://link.springer.com/chapter/10.1007/978-3-319-15461-9_7.

Reidy B, Haase A, Luch A, Dawson K, Lynch I. Mechanisms of silver nanoparticle release, transformation and toxicity: a critical review of current knowledge and recommendations for future studies and applications. Materials. 2013;6:2295–350. https://doi.org/10.3390/ma6062295.

Riddin TL, Gericke M, Whiteley CG. Analysis of the inter-and extracellular formation of platinum nanoparticles by Fusarium oxysporum f. sp. lycopersici using response surface methodology. Nanotechnology. 2006;17(14):3482. https://iopscience.iop.org/article/10.1088/0957-4484/17/14/021/meta

Romero CM, Alvarez A, Martínez MA, Chaves S. Fungal nanotechnology: a new approach toward efficient biotechnology application. In: Fungal nanobionics: principles and applications. Singapore: Springer; 2018. p. 117–43. https://link.springer.com/chapter/10.1007/978-981-10-8666-3_5.

Saratale RG, Saratale GD, Shin HS, Jacob JM, Pugazhendhi A, Bhaisare M, Kumar G. New insights on the green synthesis of metallic nanoparticles using plant and waste biomaterials: current knowledge, their agricultural and environmental applications. Environ Sci Pollut R. 2018;25(11):10164–83. https://link.springer.com/article/10.1007/s11356-017-9912-6

Saravanakumar K, Shanmugam S, Varukattu NB, MubarakAli D, Kathiresan K, Wang MH. Biosynthesis and characterization of copper oxide nanoparticles from indigenous fungi and its effect of photothermolysis on human lung carcinoma. J Photochem Photobiol B. 2019;190:103–9. https://doi.org/10.1016/j.jphotobiol.2018.11.017.

Sathishkumar M, Sneha K, Yun YS. Immobilization of silver nanoparticles synthesised using curcuma longa tuber powder and extract on cotton cloth for bactericidal activity. Bioresour Technol. 2010;101:7958–65. https://doi.org/10.1016/j.biortech.2010.05.051.

Selvakumar R, Seethalakshmi N, Thavamani P, Naidu R, Megharaj M. Recent advances in the synthesis of inorganic nano/microstructures using microbial biotemplates and their applications. RSC Adv. 2014;4(94):52156–69. https://doi.org/10.1039/C4RA07903E.

Sengani M, Grumezescu AM, Rajeswari VD. Recent trends and methodologies in gold nanoparticle synthesis–a prospective review on drug delivery aspect. OpenNano. 2017;2:37–46. https://doi.org/10.1016/j.onano.2017.07.001.

Seshadri S, Saranya K, Kowshik M. Green synthesis of lead sulfide nanoparticles by the lead resistant marine yeast, Rhodosporidium diobovatum. Biotechnol Prog. 2011;27(5):1464–9. https://doi.org/10.1002/btpr.651.

Shah M, Fawcett D, Sharma S, Tripathy S, Poinern G. Green synthesis of metallic nanoparticles via biological entities. Materials. 2015;11:7278–308. https://doi.org/10.3390/ma8115377.

Shenton W, Douglas T, Young M, Stubbs G, Mann S. Inorganic–organic nanotube composites from template mineralization of tobacco mosaic virus. Adv Mater. 1999;11(3):253–6. https://doi.org/10.1002/(SICI)1521-4095(199903)11:3%3C253::AID-ADMA253%3E3.0.CO;2-7.

Singh AV, Patil R, Anand A, Milani P, Gade WN. Biological synthesis of copper oxide nano particles using Escherichia coli. Curr Nanosci. 2010;6(4):365–9. https://doi.org/10.2174/157341310791659062.

Singh BR, Dwivedi S, Al-Khedhairy AA, Musarrat J. Synthesis of stable cadmium sulfide nanoparticles using surfactin produced by Bacillus amyloliquifaciens strain KSU-109. Colloids Surf B Biointerfaces. 2011;85(2):207–13. https://doi.org/10.1016/j.colsurfb.2011.02.030.

Singh P, Kim YJ, Singh H, Mathiyalagan R, Wang C, Yang DC. Biosynthesis of anisotropic silver nanoparticles by Bhargavaea indica and their synergistic effect with antibiotics against pathogenic microorganisms. J Nanomater. 2015;2015(4):1–10. https://doi.org/10.1155/2015/234741.

Singh P, Kim YJ, Wang C, Mathiyalagan R, Yang DC. Microbial synthesis of flower-shaped gold nanoparticles. Artif Cells Nanomed Biotechnol. 2016a;44(6):1469–74. https://doi.org/10.3109/21691401.2015.1041640.

Singh P, Kim YJ, Wang C, Mathiyalagan R, Yang DC. Weissella oryzae DC6-facilitated green synthesis of silver nano- particles and their antimicrobial potential. Artif Cells Nanomed Biotechnol. 2016b;44(6):1569–75. https://doi.org/10.3109/21691401.2015.1064937.

Singh P, Kim YJ, Zhang D, Yang DC. Biological synthesis of nanoparticles from plants and microorganisms. Trends Biotechnol. 2016c;34(7):588–99. https://doi.org/10.1016/j.tibtech.2016.02.006.

Singh J, Dutta T, Kim KH, Rawat M, Samddar P, Kumar P. 'Green' synthesis of metals and their oxide nanoparticles: applications for environmental remediation. J Nanobiotechnol. 2018;16(1):84. https://doi.org/10.1186/s12951-018-0408-4.

Song JY, Jang HK, Kim BS. Biological synthesis of gold nanoparticles using magnolia kobus and Diopyros kaki leaf extracts. Process Biochem. 2009;44(10):1133–8. https://doi.org/10.1016/j.procbio.2009.06.005.

Soni N, Prakash S. Antimicrobial and mosquitocidal activity of microbial synthesized silver nanoparticles. J Parasitol Res. 2015;114(3):1023–30. https://link.springer.com/article/10.1007/s00436-014-4268-z

Thostenson ET, Li C, Chou TW. Nanocomposites in context. Compos Sci Technol. 2005;65(3–4):491–516. https://doi.org/10.1016/j.compscitech.2004.11.003.

Tomczak MM, Gupta MK, Drummy LF, Rozenzhak SM, Naik RR. Morphological control and assembly of zinc oxide using a biotemplate. Acta Biomater. 2009;5(3):876–82. https://doi.org/10.1016/j.actbio.2008.11.011.

Tsukamoto R, Muraoka M, Seki M, Tabata H, Yamashita I. Synthesis of CoPt and $FePt_3$ nanowires using the central channel of tobacco mosaic virus as a biotemplate. Chem Mater. 2007;19(10):2389–91. https://doi.org/10.1021/cm062187k.

Vahabi K, Karimi Dorcheh S. Biosynthesis of silver nano-particles by Trichoderma and its medical applications. In: Biotechnology and biology of Trichoderma. Amsterdam: Elsevier; 2014. p. 393–404. https://doi.org/10.1016/B978-0-444-59576-8.00029-1.

Vahabi K, Mansoori GA, Karimi S. Biosynthesis of silver nanoparticles by fungus Trichoderma reesei (A route for large-scale production of AgNPs). Insci J. 2011;1(1):65–79. https://doi.org/10.5640/insc.010165.

Waghmare SR, Mulla MN, Marathe SR, Sonawane KD. Ecofriendly production of silver nanoparticles using Candida utilis and its mechanistic action against pathogenic microorganisms. 3 Biotech. 2015;5(1):33–8. https://link.springer.com/article/10.1007/s13205-014-0196-y

Wang C, Kim YJ, Singh P, Mathiyalagan R, Jin Y, Yang DC. Green synthesis of silver nanoparticles by Bacillus methylotrophicus, and their antimicrobial activity. Artif Cells Nanomed Biotechnol. 2016;44(4):1127–32. https://doi.org/10.3109/21691401.2015.1011805.

Wang Y, O'Connor D, Shen Z, Lo IM, Tsang DC, Pehkonen S, Pu S, Hou D. Green synthesis of nanoparticles for the remediation of contaminated waters and soils: constituents, synthesizing methods, and influencing factors. J Clean Prod. 2019;226:540–9. https://doi.org/10.1016/j.jclepro.2019.04.128.

Wilde EW, Benemann JR. Bioremoval of heavy metals by the use of microalgae. Biotechnol Adv. 1993;11:781–812. https://doi.org/10.1016/0734-9750(93)90003-6.

World Intellectual Property Report: Breakthrough Innovation and Economic Growth (PDF). World Intellectual Property Organization 2015 12–4. 2019. Retrieved July 9, 2019, https://www.wipo.int/edocs/pubdocs/en/wipo_pub_944_2015.pdf.

Xiao S, Knoll AH, Yuan X, Pueschel CM. Phosphatized multicellular algae in the Neoproterozoic Doushantuo formation, China, and the early evolution of florideophyte red algae. Am J Bot. 2004;91(2):214–27. https://doi.org/10.3732/ajb.91.2.214.

Zielonka A, Klimek-Ochab M. Fungal synthesis of size-defined nanoparticles. Adv Nat Sci Nanosci Nanotechnol. 2017;8(4):043001. https://doi.org/10.1088/2043-6254/aa84d4.

Zinjarde S, Apte M, Mohite P, Kumar AR. Yarrowia lipolytica and pollutants: interactions and applications. Biotechnol Adv. 2014;32(5):920–33. https://doi.org/10.1016/j.biotechadv.2014.04.008.

Zonaro E, Piacenza E, Presentato A, Monti F, Dell'Anna R, Lampis S, Vallini G. Ochrobactrum sp. MPV1 from a dump of roasted pyrites can be exploited as bacterial catalyst for the biogenesis of selenium and tellurium nanoparticles. Microb Cell Fact. 2017;16(1):215. https://microbialcellfactories.biomedcentral.com/articles/10.1186/s12934-017-0826-2

# Silver Nanostructures, Chemical Synthesis Methods, and Biomedical Applications


**Pragatisheel and Jai Prakash**

## Contents



## Abbreviations

| | |
|---|---|
| $AgNO_3$ | Silver nitrate |
| BSPP | Bis(p-sulfonatophenyl)phenylphosphine dihydrate dipotassium |
| CTAB | Cetyl trimethyl ammonium bromide |
| DMF | Dimethylformamide |
| LSPR | Localized surface plasmon resonance |
| $Na_2S$ | Sodium sulfide |
| $NaBH_4$ | Sodium borohydride |
| NaHS | Sodium hydrosulfide |
| PVA | Polyvinyl alcohol |
| PVP | Polyvinylpyrrolidone |

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_11

## 1 Introduction

Nanomaterials are the backbone of modern technology which is growing very fast covering almost all fields of life ranging from energy, environment, to human health (Marambio-Jones and Hoek 2010). In the last decades, there is a huge development in the field of nanotechnology by developing new synthesis methods, new strategies, and their multifunctional applications (Prakash et al. 2016, 2018). Particularly, a great deal of research has been directed toward the biomedical applications of nanomaterials due to their excellent physical, chemical, and biological properties (Burdușel et al. 2018; Kumar et al. 2017).

Silver-based nanomaterials are one of the most investigated nanomaterials in the field of biomedical applications especially in antimicrobial activities for curing the health of the society (Liao et al. 2019; Roy et al. 2019). Figure 1 shows the various biomedical applications of Ag nanomaterials (Bélteky et al. 2019). Moreover, silver nanostructures are being used in many fields such as food industries, cosmetics, textiles, and antibacterial coatings, removing environmental hazards (Burdușel et al. 2018). They have been reported to exist in different geometries such as nanoparticles (Zielińska et al. 2009; Wuithschick et al. 2013), nanorods (Bachenheimer et al. 2017; Tian et al. 2017), nanotriangles (Wu et al. 2015; Wang et al. 2016; Dai et al. 2019), nanowires, and nanoprism (de Guzman and Balela 2017; Jin et al. 2001; Dai et al. 2019). A recent review article (Zhang et al. 2018)

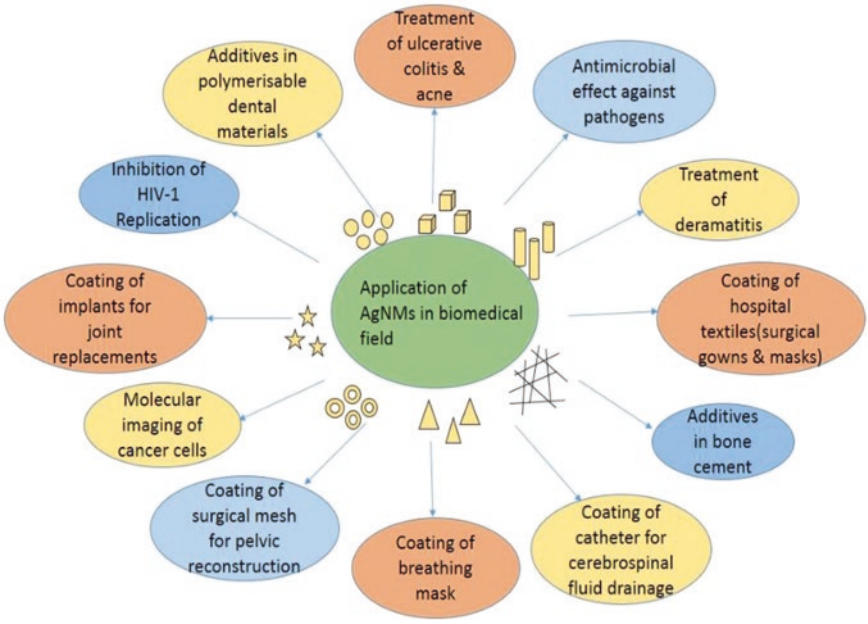


**Fig. 1** Schematic representation of the application of silver nanostructured materials in the biomedical field

describes the synthesis of several silver nanostructures and its various applications. Silver nanomaterials possess significant broad-spectrum antibacterial and cytotoxic properties due to their unusual, specific, and genuine intrinsic physical, chemical, and biological properties. Therefore, due to the improved and unconventional antimicrobial activity of silver nanomaterials, a huge interest and research efforts are directed toward their applications in the biomedical engineering field contributing widely to the health industry in developing infection-resistant medical devices.

Furthermore, these nanomaterials have been used in developing novel and advanced drug delivery systems as a suitable carrier of various therapeutic molecules including anti-inflammatory, antimicrobial, antioxidant, and anticancer biomolecules and as additives in dental materials (Abou El-Nour et al. 2010). It is also important to note that silver nanomaterial-based treatment of human cell culture may induce cytotoxicity, inflammatory response, and genotoxicity through specific modifications of optical properties and chemical environment (Burdușel et al. 2018).

These nano-dimensional silver structures with several morphologies exhibit excellent toxicity toward bacteria where the nanosize plays an important role in improving the antibacterial activity which is attributed to their specific effects such as adsorption at bacterial surfaces (Le Ouay and Stellacci 2015; Kim et al. 2007). Therefore, the proper selection of the synthesis method to achieve high monodispersity and shape specificity is necessary (Tang and Zheng 2018). These nano-dimensional silver systems provide many advantages, making them very promising nanomaterials as antibacterial. They are firstly not very costly and easy to prepare and exhibit great antibacterial activity against a broad range of bacteria at very low concentrations (Le Ouay and Stellacci 2015; Tang and Zheng 2018).

As discussed above, silver nanostructures have been produced in several geometries using several methods (Zielińska et al. 2009; Wuithschick et al. 2013; Bachenheimer et al. 2017; Wu et al. 2015; Tian et al. 2017). Nevertheless, the most common approach is the chemical reduction method as it is easy to control and effective in achieving monodispersity and shaping specificity. In this chapter, we report on chemical reduction synthesis methods for the preparation of silver nanostructures in different geometries and their promising antibacterial applications in recent years.

## 2 Chemical Reduction Synthesis of Silver Nanostructures

There are numerous synthesis methods for silver nanostructures like physical, chemical, and biological methods; however, only chemical synthesis methods have been reported here. The chemical techniques for the preparation of nanomaterials are simple and inexpensive and take lesser time without the use of sophisticated instruments. For the past few years, various rapid chemical methods have been developed for the synthesis of various silver nanostructures (Shankar et al. 2004; Cakić et al. 2018; Panáček et al. 2006). Reduction of silver nitrate ($AgNO_3$) using various reducing agents such as citrate, ascorbic acid, or borohydride (Turkevich

et al. 1951; Lee and Meisel 1982; Abou El-Nour et al. 2010; Chekin and Ghasemi 2014) is one of the most promising and extensively used methods for the synthesis of silver nanostructures. Here, we provide in brief various chemical reduction methods.

Using trisodium citrate, silver nanoparticles are prepared by adding dropwise trisodium citrate to the heated aqueous solution of silver precursors (Fig. 2). The solution is mixed vigorously until the color of the solution turns to pale brown (Ur Rashid et al. 2013) following the mechanism:

$$4Ag^{+} + C_6H_5O_7Na_3 + 2H_2O \rightarrow 4Ag^{0} + C_6H_5O_7H_3 + 3Na^{+} + H^{+} + O_2 \uparrow$$

For example, Fang et al. (2005) demonstrated that when 50 ml of $1 \times 10^{-3}$ M $AgNO_3$ was heated to boiling followed by addition of 5 ml of 1% trisodium citrate dropwise, the solution becomes pale brown eventually exhibiting the formation of

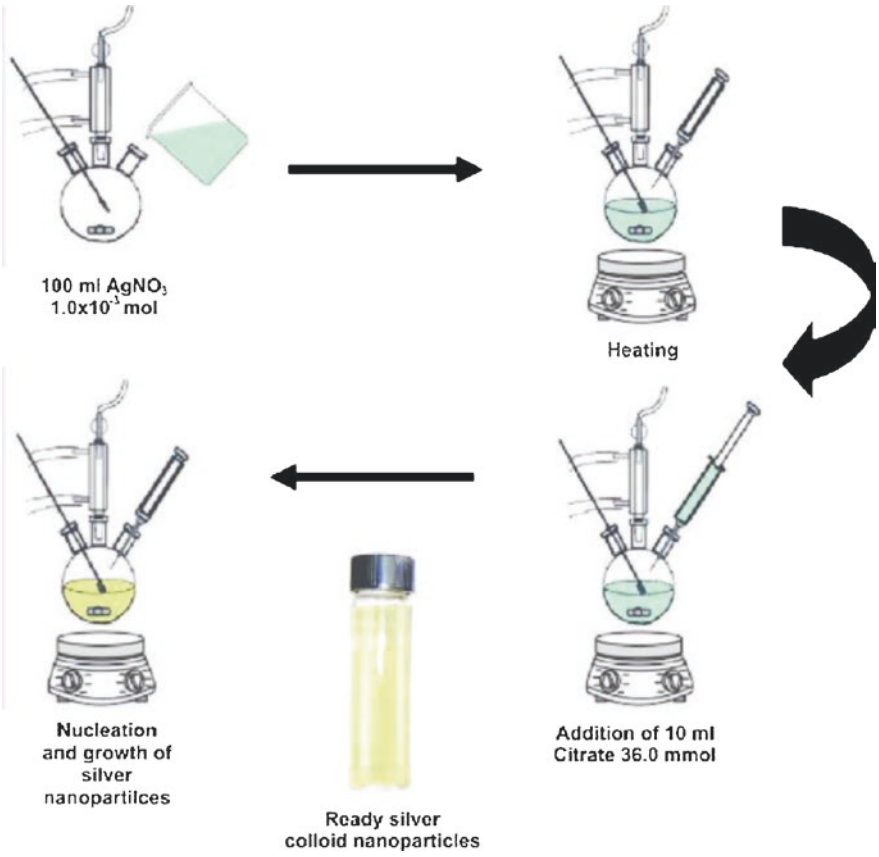


**Fig. 2** The schematic diagram for the representation of the synthesis of silver nanoparticles using sodium citrate. (Reprinted with permission from Monteiro et al. 2009)

silver nanoparticles. During this process, silver ions ($Ag^{+}$) formed in the solution are reduced to atomic silver ($Ag^{0}$) which then agglomerates forming clusters. These clusters are combined to form silver particles (Kapoor and Gopinathan 1998; Chadha et al. 2014). Janata et al. (Janata 2012) studied the growth of silver nanoparticles in aqueous solution and explained with the help of a theoretical model.

These silver nanoparticles thus formed are generally characterized by their ultraviolet–visible absorption spectra where they intensely absorb ranging from 300 nm to 500 nm due to the localized surface plasmon resonance (LSPR) (Panda et al. 2018; Bhui et al. 2009). Varying the strength of the reducing agent, the size of the nanoparticles formed in aqueous solution can be tuned. For example, if the stronger reducing agents with a fast reduction rate provide the small size of nanoparticles, the weaker reducing agents with slower reduction process provide the bigger size of nanoparticles (Schneider et al. 1994). Panda et al. (2018) demonstrated that photo-mediated citrate reduction can be used to tailor the shape and size of the silver nanoparticles under the effect of light source varying from ultraviolet to visible light.

Using sodium borohydride ($NaBH_4$) as reducing agents for the fabrication of silver nanoparticles, generally aqueous solution of chilled sodium borohydride is dropwise added to the aqueous solution of silver precursors. This process results in the formation of silver nanoparticles with pale yellow color as per the following mechanism (Mulfinger et al. 2007):

$$AgNO_3 + NaBH_4 \rightarrow Ag + \tfrac{1}{2} H_2 + \tfrac{1}{2} B_2H_6 + NaNO_3$$

A lot of research has been carried out following this process. For example, Zielinska et al. (Zielińska et al. 2009) studied the formation of silver nanoparticles using different silver precursors such as silver citrate, silver acetate, or silver nitrate and their reduction with sodium borohydride producing spherical particles. It was found that when silver citrate was used as a precursor, the obtained colloids were transparent and stable for at least 3 months, whereas when silver nitrate or silver acetate was used as a precursor, it was unstable and silver gets precipitated after 1 day. Ajitha et al. (Abou El-Nour et al. 2010) demonstrated that the size of silver nanoparticles could be varied by varying the pH while using sodium borohydride reductant and polyvinyl alcohol (PVA) as a stabilizer as shown schematically in Fig. 3.

The reduction of silver precursors using ascorbic acid as a reducing agent in the presence of PVP has also been reported extensively (Qin et al. 2010; Malassis et al. 2016; Chekin and Ghasemi 2014). Similarly, the reduction of silver nitrate with dimethylformamide (DMF) in the presence of PVP provides silver nanostructures of different geometries (García-Barrasa et al. 2011; Pastoriza-Santos and Liz-Marzán 1999, 2002) (Fig. 4).

Various other co-reduction methods have been used to prepare silver nanostructures with different morphologies. Interestingly, Jin et al. (2001) reported the observation of yellow-colored spherical silver particles by addition of sodium borohydride solution to an aqueous silver nitrate in the presence of trisodium citrate followed by

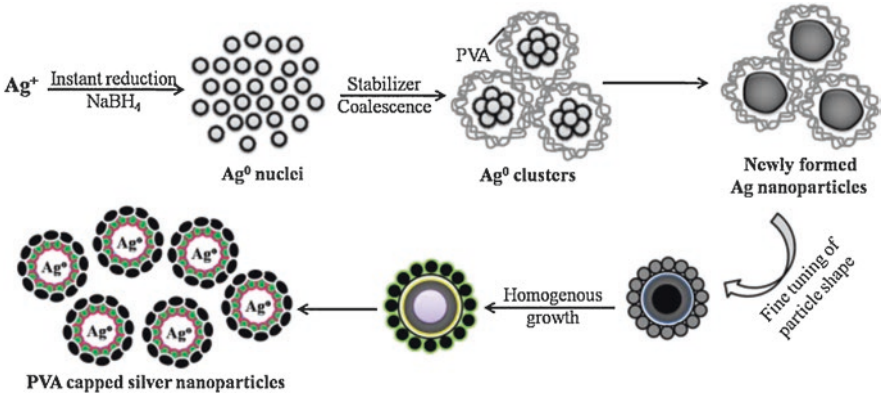


**Fig. 3** Schematic diagram for the representation of the synthesis of silver nanoparticles using sodium borohydride. (Reprinted with permission from Ajitha et al. 2015)

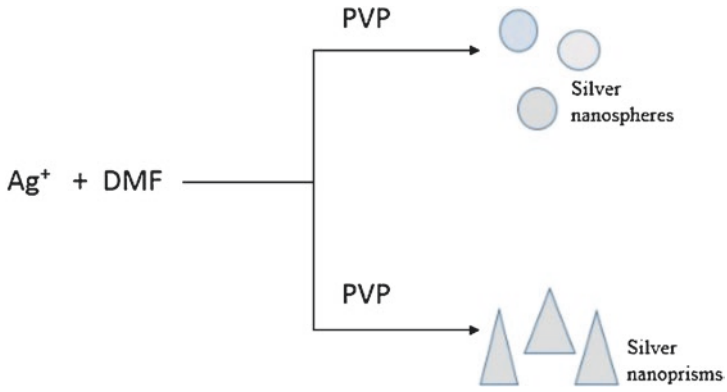


**Fig. 4** Diagrammatic representation of the synthesis of silver nanospheres and silver nanoprisms using DMF as a reducing agent and PVP as a stabilizing agent. (García-Barrasa et al. 2011)

bis(p-sulfonatophenyl)phenylphosphine dihydrate dipotassium (BSPP), a stabilizing agent. After 70 h of irradiation, obtained spherical silver nanoparticles were converted to silver nanoprisms. Silver nanoprisms could also be fabricated by adding sodium borohydride in sodium citrate, polyvinylpyrrolidone (PVP), and hydrogen peroxide-containing silver precursor solution (Van Dong et al. 2012). Dong et al. (2012) demonstrated that triangular-shaped silver nanoprisms could be synthesized reducing silver nitrate which is highly effective for antibacterial applications as shown in Fig. 5.

Murphy et al. (Murphy and Jana 2002) developed a two-step method for the fabrication of unidirectional silver nanowires and nanorods with controlled aspect ratios. In this method, firstly, silver spherical nanoparticles are formed by the reduction of silver nitrate as reported above. The synthesized silver nanoparticles are

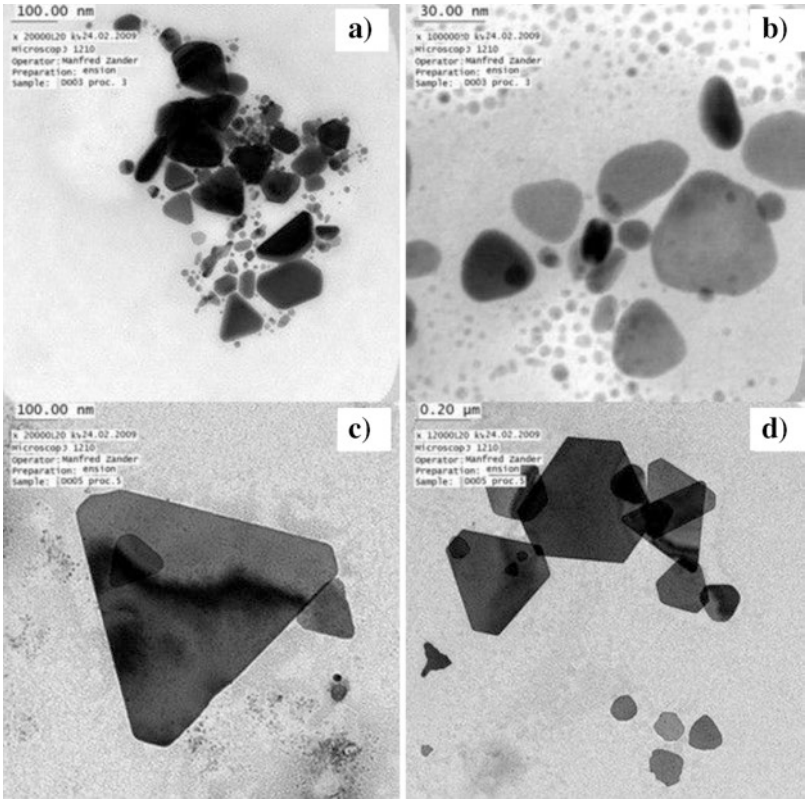


**Fig. 5** TEM micrographs showing triangular Ag nanoparticles. Different size distributions range from (**b**) 30 nm to 400 nm (**a**, **c**, **d**). (Van Dong et al. 2012)

further reduced in the presence of ascorbic acid, sodium hydroxide by adding $AgNO_3$, and surfactant cetyl trimethyl ammonium bromide (CTAB) as a micellar template to fabricate silver nanowires and nanorods (Fig. 6). Similarly, Ojha et al. (2013) synthesized well-dispersed silver nanorods varying aspect ratios and studied their antibacterial applications.

Sun et al. (Sun and Xia 2003; Sun et al. 2002) prepared silver nanocubes and nanowires using ethylene glycol ($HOCH_2CH_2OH$) as a reducing agent in the presence of PVP, which played an important role in producing different shapes and sizes of silver nanostructures. The following mechanism has generally taken place (Siekkinen et al. 2006; Khodashenas and Ghorbani 2015):

$$2HOCH_2CH_2OH \rightarrow 2CH_3CHO + 2H_2O$$

$$2Ag^+ + 2CH_3CHO \rightarrow CH_3CHO - OCCH_3 + 2Ag + 2H^+$$

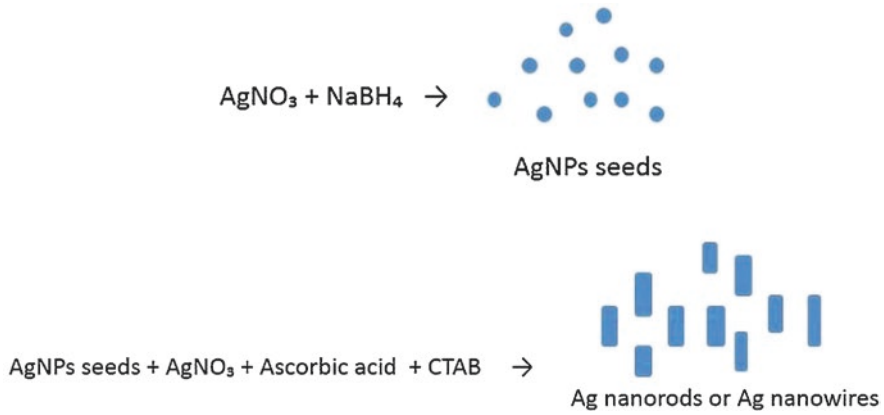


**Fig. 6** Schematic representation of the synthesis of silver nanostructures using CTAB micelle. (Jana et al. 2001, García-Barrasa et al. 2011)

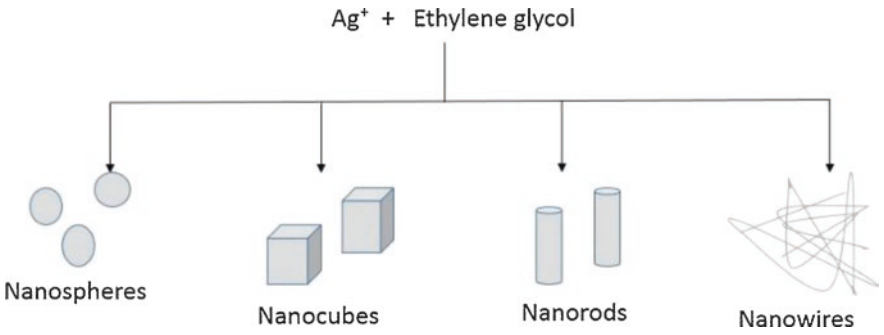


**Fig. 7** Synthesis of silver nanostructures using ethylene glycol as a reducing agent in the presence of PVP. (García-Barrasa et al. 2011)

It was found that there are various parameters such as temperature, the concentration of silver nitrate, and PVP which influenced the morphology of the silver nanostructures. In this method, silver nitrate can be reduced in the presence of ethylene glycol using PVP as a stabilizer that results in the synthesis of several geometrical nanostructures such as nanowires, nanospheres, nanocubes, or nanorods as shown in Fig. 7.

In the similar process using ethylene glycol as reducing agent, Siekkinen et al. (2006) showed that addition of small traces of sodium sulfide ($Na_2S$) or sodium hydrosulfide (NaHS) resulted in a fast synthesis of silver nanocubes attributed to the slower reaction time as shown in Fig. 8. These silver nanocubes were found to be applicable in various biomedical fields.

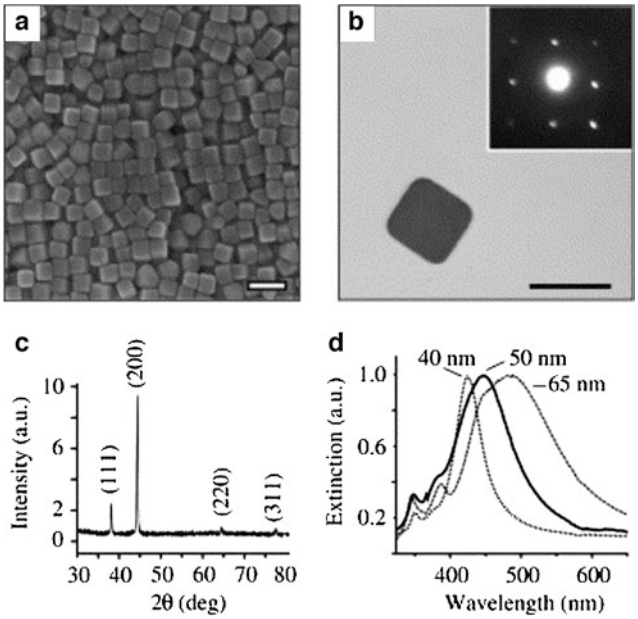


**Fig. 8** (**a**) SEM image of silver nanocubes synthesized under the mediation of sodium sulfide (scale bar is 100 nm). (**b**) TEM image and electron diffraction pattern (inset) taken from a single nanocube, indicating that it is single crystal and enclosed by (1 0 0) facet (scale bar is 50 nm). (**c**) XRD pattern is taken from the same batch of silver nanocubes. (**d**) UV–Vis spectra taken from silver nanocubes of different sizes that were all synthesized under the mediation of sodium sulfide. The main peak blue-shifted as the size was reduced. (Reprinted with permission from Siekkinen et al. 2006)

The reduction of silver nitrate using ethylene glycol in the presence of PVP could be accelerated followed by microwave-assisted synthesis methods to stimulate the chemical reduction process. Using this process, typically silver nanostructures of different morphologies such as nanocubes, nanospheres, and nanowires have been synthesized (Hong et al. 2016; Gou et al. 2007; Chen et al. 2009).

For example, Hong et al. (2016) reported the fabrication of variously shaped silver nanostructures by reducing silver nitrate followed by microwave-assisted synthesis and studied the effect of shape on antibacterial property. Interestingly, nanostructures with higher effective surface area and facets were found to be more efficient for antibacterial activity. They also used a small amount of NaCl responsible for geometrical changes from nanocube to nanowire nanostructures (Fig. 9). The low or higher concentration of released $Cl^-$ controlled the free silver ions in the solutions leading to the different reaction rates. Schuette et al. (Schuette and Buhro 2013) also demonstrated the synthesis of silver nanowires using NaCl. Similarly, Zhang et al. (2010) and Chen et al. (2009) reported the synthesis of silver nanocubes adding a trace amount of NaSH/HCl and $Na_2S$, respectively.

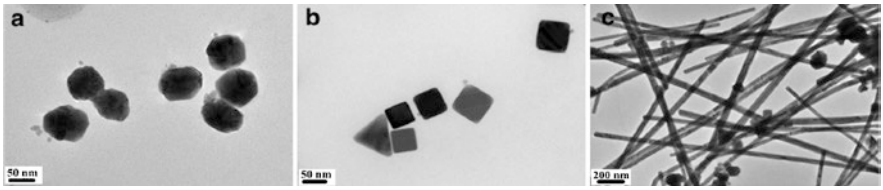


**Fig. 9** TEM image of silver nanostructures formed by the reduction of silver nitrate using ethylene glycol as a reducing agent in the presence of PVP followed by microwave-assisted synthesis. Different amounts of NaCl (**a**) 0 mg, silver nanospheres; (**b**) 1 mg, silver nanocubes; and (**c**) 5 mg, silver nanowires. (Reprinted with permission from Hong et al. 2016)

Apart from the reduction of silver nitrate using the reducing agent, there are other green synthesis methods which are environmentally friendly approaches where plants and microorganisms are used to fabricate silver nanostructures (Ahmed et al. 2016; Roy et al. 2019, Ana-Alexandra et al. 2016). This eco-friendly synthesis method includes the use of biological agents, plants, or microbial agents as reducing as well as capping agents (Ahmed et al. 2016, Okafor et al. 2013). Various bacterial strains have been reported for the effective synthesis of silver nanoparticles. The plants possess biomolecules such as tannins, saponins, phenolics, terpenoids, flavones, alkaloids, protein, enzymes, amino acids, alcoholic components, and polysaccharides that can promote the reduction of silver ions. Generally, a related part of the plant is collected and washed to remove the impurities and dried. The dried powder is used to prepare the plant broth followed by extraction using the filtration process. This plant extract is then added to the silver nitrate solution which reduces $Ag^{+}$ to $Ag^{0}$ and is confirmed by the color change of the reactant solution (Fig. 10).

As mentioned above, there are several chemical reductions/green synthesis methods where silver precursors are reduced in the presence of some stabilizing agents or protective agents which can prevent the agglomeration of those silver nanostructures and facilitate their dispersion as well as tailor shape and size. Besides, various parameters, for example, the concentration of precursors, the strength of the chemical interaction of and different crystallographic planes of silver, rate of driving force for crystallization, the surfactant used, temperature, and pH, play important role in determining the final geometry of the synthesized nanostructures. These silver nanostructures are very important for various biomedical applications as mentioned in Fig. 1. The next section describes the antibacterial activities of such silver nanostructures.

## 3 Silver Nanostructures: Mechanisms and Antibacterial Applications

Silver nanostructures of variable shapes and sizes are known as the promising materials applicable in many fields including energy, environment, and biomedical because of their unique LSPR properties. As discussed in Sect. 1, these nanostruc-

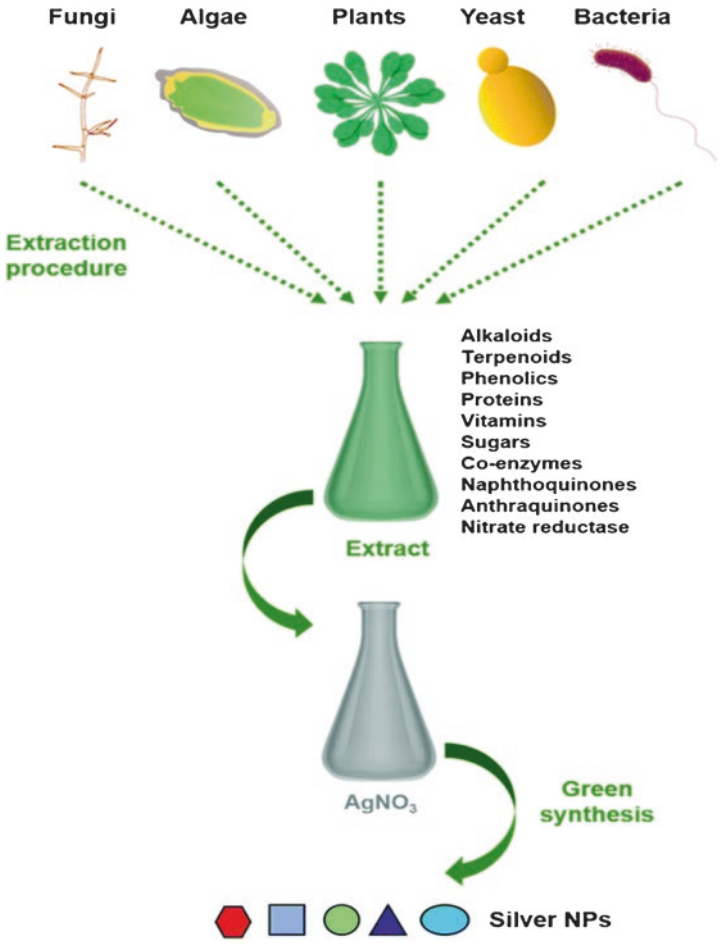


**Fig. 10** Schematic representation of the procedure for the green synthesis of silver nanoparticles using various biological entities. (Roy et al. 2019)

tures are being used in several biomedical applications including as antibacterial agents for several kinds of bacteria, fungi, and microorganisms. The antibacterial activity of silver nanostructures is due to their large surface-to-volume ratio and excellent physical and chemical properties along with their highly toxic nature. As reported in the literature, the silver nanostructures exhibit antibacterial action mechanisms as direct contact killing mechanisms or ion-mediated killing (Fig. 11). Generally, the silver nanostructures first attach to the surface of the microbes on the cell wall. Due to the penetration and induced structural changes in the bacterial membrane, there is a cellular leakage leading to the death of the cell. Silver nanostructure has shown excellent antibacterial response toward both kinds of bacteria, that is gram-positive and gram-negative bacteria. This behavior of the silver nanostructures is due to the difference in the cell wall composition and thickness of these

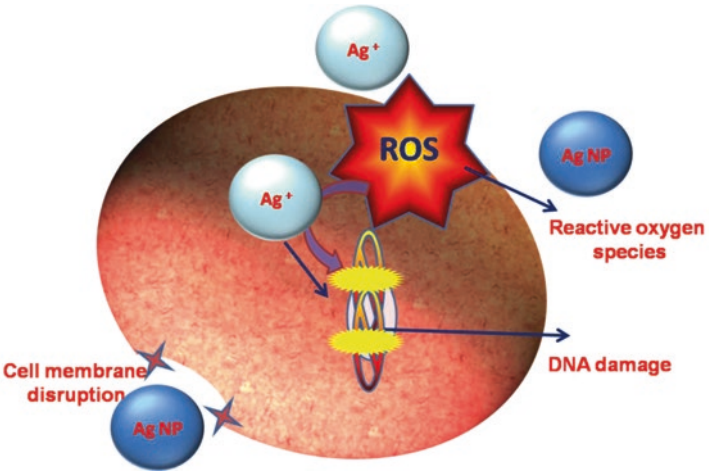


**Fig. 11** Schematic representation of silver nanoparticles on the bacterial cell. (Reprinted with permission from Prakash et al. 2018)

bacteria (Chatterjee et al. 2015; Mandal et al. 2016; Prakash et al. 2018). In the latter mechanism, the effective cell wall damage is due to the release of silver ions and also due to the creation of reactive oxygen species (ROS) free radicals which directly inactivate membrane /DAN damage and interrupt their respiratory system that lead to the cell death (Kumar et al. 2017; Prakash et al. 2016, 2018; Gokulan et al. 2017; Carlson et al. 2008).

It has been reported that silver nanostructures having equal surface area but different morphologies/structures exhibit variable antibacterial efficiency (Pal et al. 2007). Though it is known that several capping and stabilizing agents are used in different methods to prevent agglomeration of silver nanostructures, they also have an influence on the antibacterial activity of nanostructures. It is also to be mentioned that the antibacterial mechanisms of silver nanoparticles are influenced by surface charges attained by them due to stabilizers since there is an electrostatic interaction between positively charged $Ag^+$ ion and the negatively charged cell wall of bacteria which results in disruption of bacterial cell membrane to initiate antibacterial action (Liao et al. 2019).

Nanoparticles having the larger effective surface area and facet reactivity exhibit stronger antibacterial activity (Hong et al. 2016). Silver nanoparticles of variable sizes have been synthesized by various methods, and their antibacterial activities have been extensively studied (Lok et al. 2007; Basavegowda et al. 2014; Wei et al. 2007; Bindhu and Umadevi 2014; Ajitha et al. 2015; Biao et al. 2018; Agnihotri et al. 2014). In this chapter, we mainly focused on silver nanoparticles synthesized by using the chemical reduction method in recent years and their antibacterial applications. For example, Agnihotri et al. (2014) reported on the detailed size-dependent antibacterial study for silver nanoparticles of variable sizes. The size of the silver nanoparticles was controlled and found to be between 5 and 100 nm. It

was found that silver nanoparticles with a size of less than 10 nm showed better antibacterial efficiency with the best antibacterial effect of silver nanoparticles of size 5 nm. Ajitha et al. (2015) demonstrated the effect of solution pH and antibacterial effect on the size variation of silver nanoparticles (Fig. 12). It was found that the SPR peak shifted to a blue end indicating the reduction in size with increasing pH. The antibacterial effect also followed the similar trend of increasing the pH of the solution, i.e., decreasing the size of silver nanoparticles (Fig. 13).

Recently, it was studied by Helminger et al. (2016) that the different silver nanostructures that possessed the same cytotoxicity exhibit different antibacterial properties. They synthesized silver nanostructures of different shapes and sizes using different chemical reduction methods (Fig. 14). The synthesized silver nanostructures were investigated for studying their antibacterial effect against *S. aureus* by determining the minimal bactericidal concentration (MBC). Shape-dependent antibacterial activity was demonstrated and is shown in Fig. 15; it was found that silver nanoplatelets exhibited good antibacterial activity followed by spherical silver nanoparticles, then silver nanorods, and nanocubes. It was demonstrated that nanostructures with a high specific surface area showed a higher dissolution rate as com-

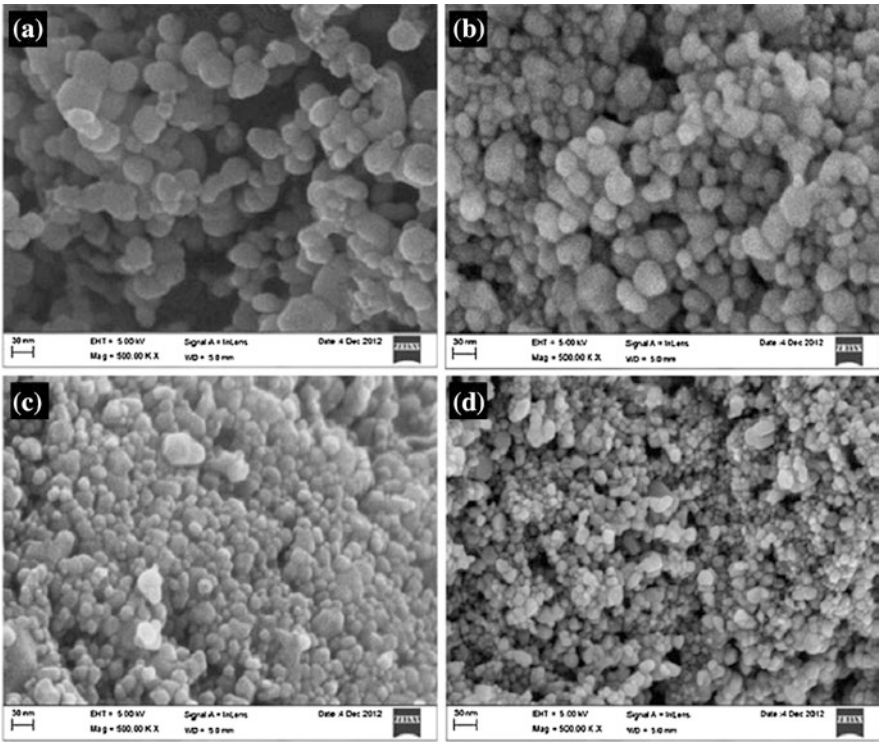


**Fig. 12** FESEM images of AgNPs at (**a**) pH 6, (**b**) pH 8, (**c**) pH 10, and (**d**) pH 12. (Reprinted with permission from Ajitha et al. 2015)

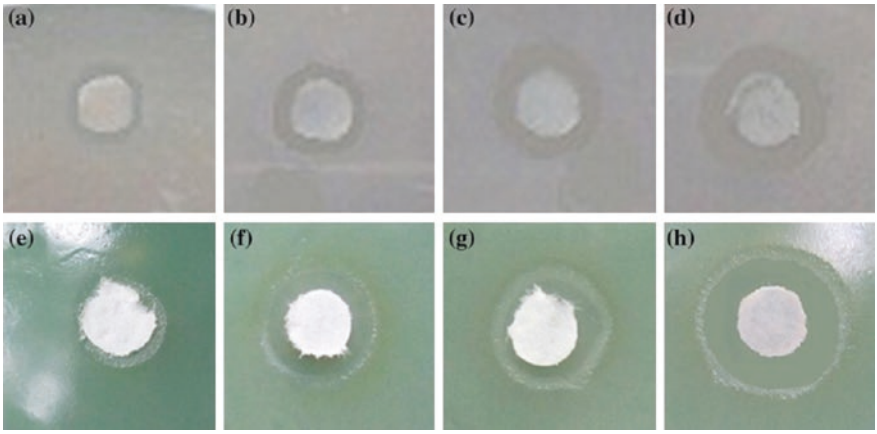


**Fig. 13** Antibacterial activity of silver nanoparticles against *Escherichia coli* (**a**–**d**) and *Pseudomonas sp.* (**e**–**h**) at different pH values of (**a**, **e**) pH 6, (**b**, **f**) pH 8, (**c**, **g**) pH 10, and (**d**, **h**) pH 12. Corresponding morphology of the silver nanoparticles is shown in Fig. 12. (Reprinted with permission from Ajitha et al. 2015)

pared to those with a smaller specific surface area. That resulted in a greater release of silver ions exhibiting higher antibacterial activity.

In the case of various dimensional/geometrical silver nanostructures, the reactivity of facets depends on the shape and atom density of silver nanostructures (Ren et al. 2011; Suresh et al. 2013). The more reactive facets had a high silver ion dissolution rate and affinity with the bacterial membrane, which led to the increased antimicrobial activity of silver nanostructures (Bansal et al. 2010; Rojas-Andrade et al. 2015; Vukoje et al. 2014). Similarly, Hong et al. (2016) studied the shape effect of silver nanostructures (nanospheres, nanocubes, and nanowires as shown in Fig. 9) as synthesized by chemical reduction of silver nitrate with ethylene glycol via the microwave-assisted method, toward the antibacterial activity. In an antibacterial test against *E. coli*, the antibacterial mechanism was studied with the help of transmission electron microscopy.

As shown in Fig. 16, the antibacterial study demonstrated that as a result of poor contact between bacteria and silver nanowires, nanowires showed the poorest response toward the antibacterial activity, whereas the silver nanocubes and nanospheres showed better antibacterial response attributed to the (100) and (111) facets, respectively, with stronger antibacterial activity in the case of nanocubes. These results indicated the importance of the shape of the nanostructures that belonged to the specific surface area and facet reactivity (Hong et al. 2016).

Similarly, Dong et al. (2012) studied the antibacterial effect of silver spherical as well as triangular nanoparticles (as shown in Fig. 5) and found that the latter showed excellent antibacterial activity compared with former nanoparticles, which were attributed to their geometric and specific (111) crystal planes. Besides, small size and sharp edges, as well as vertexes of the triangular silver nanoparticles, provide

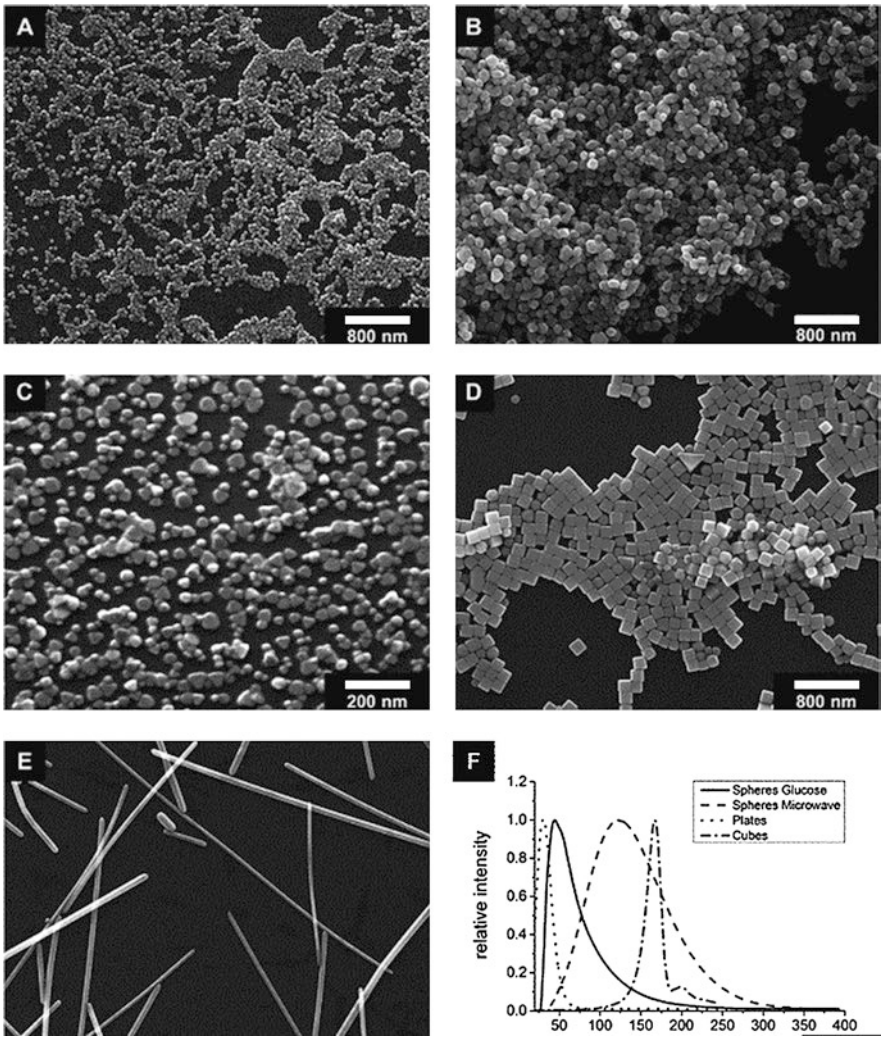


**Fig. 14** SEM images of (**a**) silver nanospheres, (**b**) silver nanospheres, (**c**) silver nanoplatelets, (**d**) silver nanocubes, and (**e**) silver nanorods. (**f**) The size distribution of all particles except silver nanorods. (Helmlinger et al. 2016)

great antibacterial functionality as compared to the spherical nanoparticles as shown in Fig. 17 (Van Dong et al. 2012).

Ojha et al. (2013) reported the fabrication of silver nanorods with different aspect ratios as shown in Fig. 18. UV–visible spectra also showed the shift in the absorption band, indicating the different aspect ratios of the silver nanostructures. These nanorods were used for studying their antibacterial properties against *B. subtilis (gram-positive)* and *E. coli (gram-negative)* microbes. It was found that the nanorods

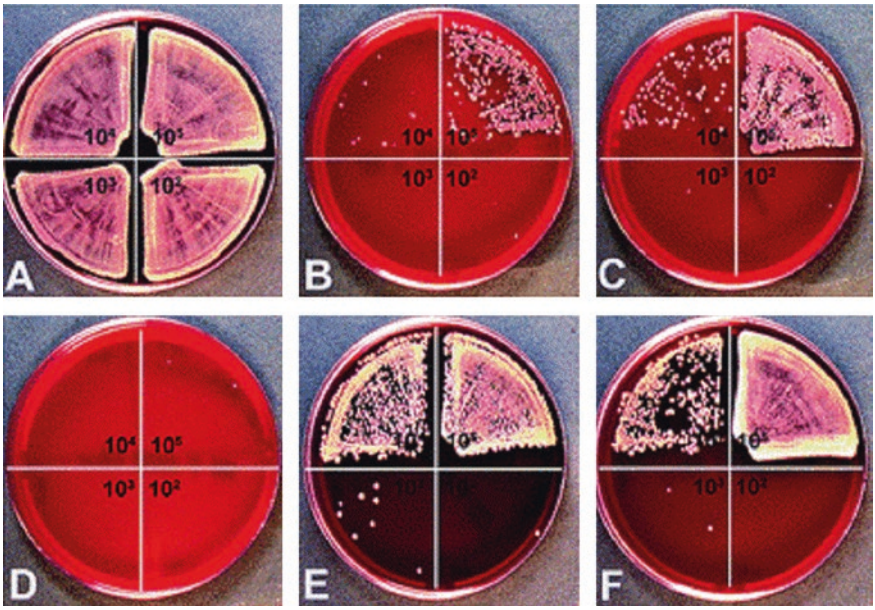


**Fig. 15** Effects of silver nanoparticles with a different shape on the viability of *S. aureus*. Representative images of *S. aureus* colonies on blood agar platelets. *S. aureus* with different bacteria concentrations (top right quadrant $1 \times 10^5$; lower right quadrant $1 \times 10^2$; top left quadrant $1 \times 10^4$; lower left quadrant $1 \times 10^3$) were treated without (**a**) or with 25 μg $mL^{-1}$ silver nanoparticles with different particle shapes ((**b**) sphere from glucose synthesis, (**c**) spheres from microwave synthesis, (**d**) platelets, (**e**) cubes, and (**f**) rods) under cell culture conditions. After 24 h, the bacteria were plated (100 μL) on blood agar platelets and incubated for another 24 h at 37 °C to determine the MBC. (Helmlinger et al. 2016)

with an intermediate aspect ratio (R = 1.8) exhibited greater antibacterial effect against both the microbes, whereas nanorods with aspect ratio R = 3.0 showed better antibacterial response against gram-positive as compared to the gram-negative (Fig. 19).

Moreover, Shaheen et al. (2019) studied the antibacterial effect of nano-hexagonal, nanorod, and nanoprism silver nanoparticles against a wide range of microorganisms and carcinoma cells. The study demonstrated strong antibacterial and anticancer effects. The overall discussion shows that the antibacterial activity of silver nanoparticles is shape, size, and surface area dependent and interesting results have been reported which show the unique antibacterial behavior of the silver nanostructures along with their multifunctional applications in other fields.

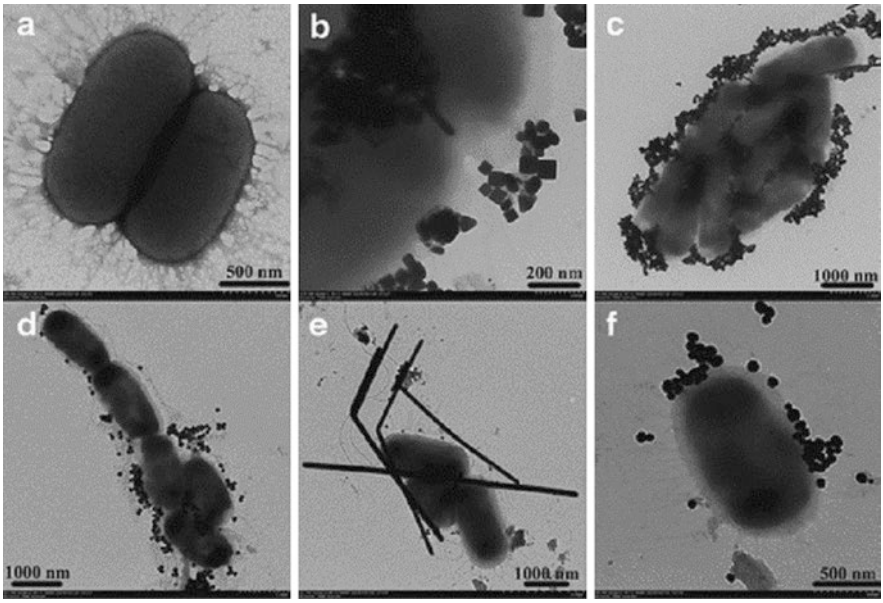


**Fig. 16** TEM images of *E. coli* cells treated without AgNPs (**a**), with silver nanocubes (**b**) and (**c**), silver nanospheres (**d**) and (**e**), and silver nanowires (**f**). (Reprinted with permission from Hong et al. 2016)

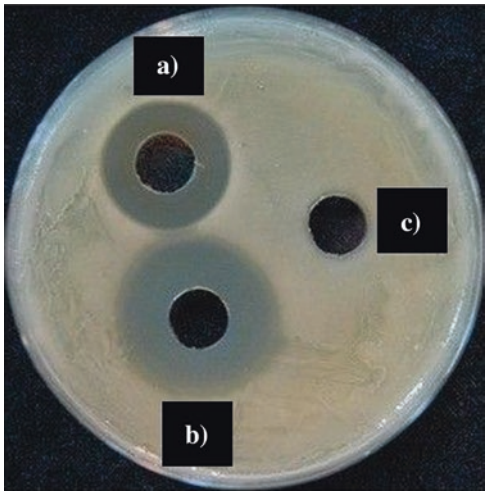


**Fig. 17** Extended inhibition zones. (**a**) Spherical silver nanoparticles and (**b**) triangular silver nanoprisms and (**c**) $H_2O$. (Van Dong et al. 2012)

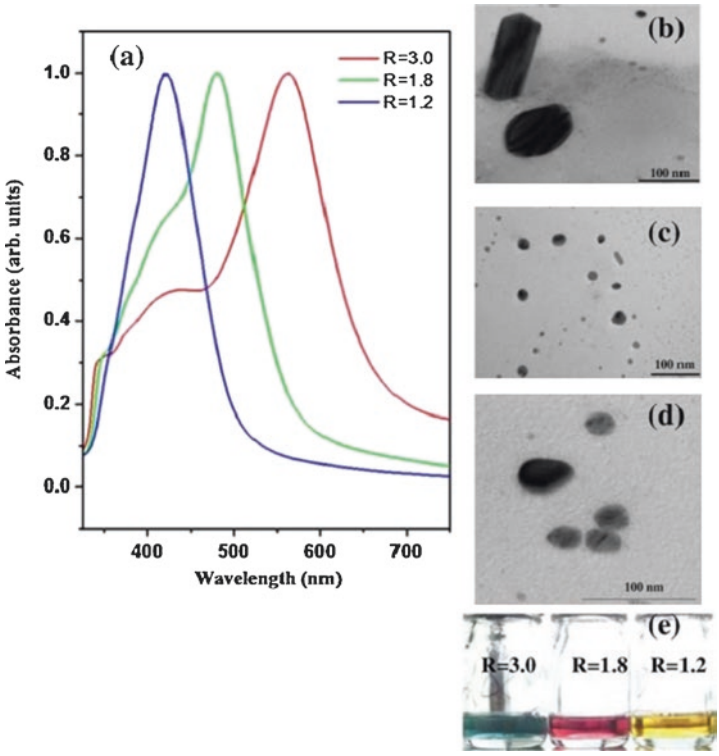


**Fig. 18** UV–visible spectrum of synthesized silver nanorods of different aspect ratios (**a**), TEM micrograph of nanorods with aspect ratios 3.0 (**b**), 1.8 (**c**), and 1.2 (**d**), and a picture of synthesized nanorod solutions (**e**). (Ojha et al. 2013)

## 4 Outlook and Summary

Silver nanostructures are promising nanomaterials for antibacterial applications along with various biomedical applications. Silver nanostructures of variable shapes and sizes have attracted researchers from all disciplines due to their fascinating and tunable, optical physiochemical, and antibacterial properties. Also, the synthesis of these silver nanostructures using chemical reduction is one of the simple and straightforward methods.

The present chapter focuses on the recent progress in the synthesis of various silver nanostructures and their promising antibacterial applications with emphasis on the various mechanisms and dependence of antibacterial applications on their shape and size. We hope that the present chapter will be a useful guide for researchers who wish to work on antibacterial applications of silver nanostructures.

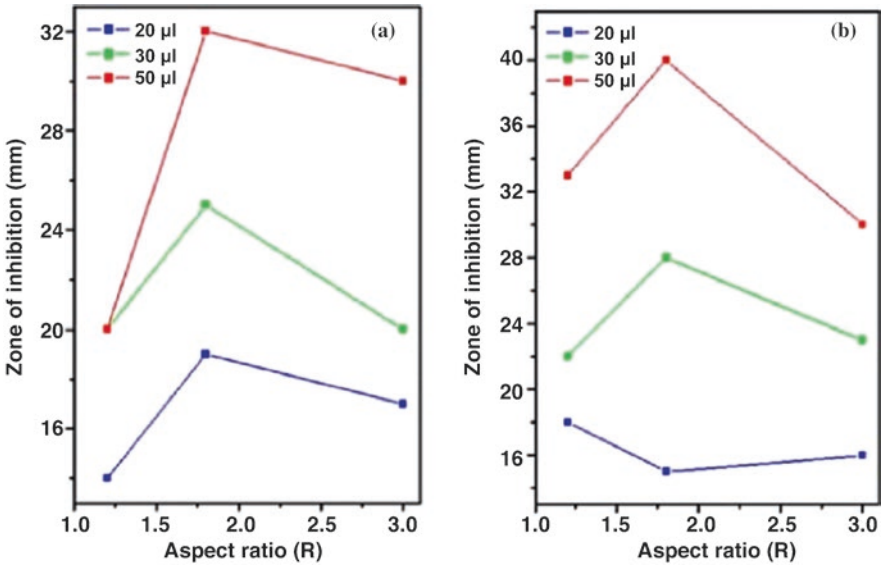


**Fig. 19** Variation of inhibition zones as the function of aspect ratios of nanorods (**a**) *E. coli* (gram-negative) and (**b**) *B. subtilis* (gram-positive) microbes. (Ojha et al. 2013)

**Acknowledgments** The authors (JP) acknowledge the financial supports from the Department of Science and Technology (DST), India, for the prestigious INSPIRE faculty award (IFA/2015/MS-57) and research grant.

## References

Abou El-Nour, Kholoud MM, Eftaiha A'a, Al-Warthan A, Ammar RAA. Synthesis and applications of silver nanoparticles. Arab J Chem. 2010;3(3):135–40. https://doi.org/10.1016/j.arabjc.2010.04.008.

Agnihotri S, Mukherji S, Mukherji S. Size-controlled silver nanoparticles synthesized over the range 5–100 nm using the same protocol and their antibacterial efficacy. RSC Adv. 2014;4(8):3974–83. https://doi.org/10.1039/C3RA44507K.

Ahmed S, Saifullah MA, Swami BL, Ikram S. Green synthesis of silver nanoparticles using Azadirachta indica aqueous leaf extract. J Radiat Res Appl Sci. 2016;9(1):1–7. https://doi.org/10.1016/j.jrras.2015.06.006.

Ajitha B, Ashok Kumar Reddy Y, Sreedhara Reddy P. Enhanced antimicrobial activity of silver nanoparticles with controlled particle size by pH variation. Powder Technol. 2015;269:110–7. https://doi.org/10.1016/j.powtec.2014.08.049.

Ana-Alexandra S, Nuta A, Ion R-M, Bunghez R. Green synthesis of silver nanoparticles using plant extracts. Chemical Sciences. 2016;188 (2016). 0.18638/scieconf.2016.4.1.386

Bachenheimer L, Scherzer R, Elliott P, Stagon S, Gasparov L, Huang H. Degradation mechanism of Ag Nanorods for surface enhanced Raman Spectroscopy. Sci Rep. 2017;7(1):16282. https://doi.org/10.1038/s41598-017-16580-2.

Bansal V, Li V, O'Mullane AP, Bhargava SK. Shape dependent electrocatalytic behaviour of silver nanoparticles. CrystEngComm. 2010;12(12):4280–6. https://doi.org/10.1039/C0CE00215A.

Basavegowda N, Idhayadhulla A, Lee YR. Preparation of Au and Ag nanoparticles using Artemisia annua and their in vitro antibacterial and tyrosinase inhibitory activities. Mater Sci Eng C. 2014;43:58–64. https://doi.org/10.1016/j.msec.2014.06.043.

Bélteky P, Rónavári A, Igaz N, Szerencsés B, Toth I, Pfeiffer I, Kiricsi M, Kónya Z. Silver nanoparticles: aggregation behavior in biorelevant conditions and its impact on biological activity. Int J Nanomedicine. 2019;14:667–87.

Bhui DK, Bar H, Sarkar P, Sahoo GP, De SP, Misra A. Synthesis and UV–vis spectroscopic study of silver nanoparticles in aqueous SDS solution. J Mol Liq. 2009;145(1):33–7. https://doi.org/10.1016/j.molliq.2008.11.014.

Biao L, Tan S, Zhang X, Gao J, Liu Z, Yujie F. Synthesis and characterization of proanthocyanidins-functionalized Ag nanoparticles. Colloids Surf B Biointerfaces. 2018;169:438–43. https://doi.org/10.1016/j.colsurfb.2018.05.050.

Bindhu MR, Umadevi M. Surface plasmon resonance optical sensor and antibacterial activities of biosynthesized silver nanoparticles. Spectrochim Acta A Mol Biomol Spectrosc. 2014;121:596–604. https://doi.org/10.1016/j.saa.2013.11.019.

Burdușel A-C, Gherasim O, Grumezescu AM, Mogoantă L, Ficai A, Andronescu E. Biomedical applications of silver nanoparticles: an up-to-date overview. Nanomaterials. 2018;8(9):681.

Cakić M, Glišić S, Cvetković D, Cvetinov M, Stanojević L, Danilović B, Cakić K. Green synthesis, characterization and antimicrobial activity of silver nanoparticles produced from Fumaria officinalis L. plant extract. Colloid J. 2018;80(6):803–13. https://doi.org/10.1134/s1061933x18070013.

Carlson C, Hussain SM, Schrand AM, Braydich-Stolle LK, Hess KL, Jones RL, Schlager JJ. Unique cellular interaction of silver nanoparticles: size-dependent generation of reactive oxygen species. J Phys Chem B. 2008;112(43):13608–19. https://doi.org/10.1021/jp712087m.

Chadha R, Maiti N, Kapoor S. Reduction and aggregation of silver ions in aqueous citrate solutions. Mater Sci Eng C. 2014;38:192–6. https://doi.org/10.1016/j.msec.2014.01.041.

Chatterjee T, Chatterjee BK, Majumdar D, Chakrabarti P. Antibacterial effect of silver nanoparticles and the modeling of bacterial growth kinetics using a modified Gompertz model. Biochim Biophys Acta Gen Subj. 2015;1850(2):299–306. https://doi.org/10.1016/j.bbagen.2014.10.022.

Chekin F, Ghasemi S. Silver nanoparticles prepared in presence of ascorbic acid and gelatin, and their electrocatalytic application. Bull Mater Sci. 2014;37(6):1433–7. https://doi.org/10.1007/s12034-014-0093-3.

Chen D, Qiao X, Qiu X, Chen J, Jiang R. Convenient, rapid synthesis of silver nanocubes and nanowires via a microwave-assisted polyol method. Nanotechnology. 2009;21(2):025607. https://doi.org/10.1088/0957-4484/21/2/025607.

Dai H, Li H, Li Z, Zhao J, Yu X, Sun J, An Q. Sonication induced amorphisation in Ag nanowires. Sci Rep. 2019;9(1):2114. https://doi.org/10.1038/s41598-019-38863-6.

de Guzman N, Balela MDL. Growth of ultralong Ag nanowires by electroless deposition in hot ethylene glycol for flexible transparent conducting electrodes. J Nanomater. 2017;2017:14. https://doi.org/10.1155/2017/7896094.

Fang J, Zhong C, Renwang M. The study of deposited silver particulate films by simple method for efficient SERS. Chem Phys Lett. 2005;401(1):271–5. https://doi.org/10.1016/j.cplett.2004.11.055.

García-Barrasa J, López-de-Luzuriaga JM, Monge M. Silver nanoparticles: synthesis through chemical methods in solution and biomedical applications. Cent Eur J Chem. 2011;9(1):7–19. https://doi.org/10.2478/s11532-010-0124-x.

Gokulan K, Williams K, Khare S. Silver ion-mediated killing of a food pathogen: melting curve analysis data of silver resistance genes and growth curve data. Data Brief. 2017;11:49–53. https://doi.org/10.1016/j.dib.2017.01.002.

Gou L, Chipara M, Zaleski JM. Convenient, rapid synthesis of Ag nanowires. Chem Mater. 2007;19(7):1755–60. https://doi.org/10.1021/cm070160a.

Helmlinger J, Sengstock C, Groß-Heitfeld C, Mayer C, Schildhauer TA, Köller M, Epple M. Silver nanoparticles with different size and shape: equal cytotoxicity, but different antibacterial effects. RSC Adv. 2016;6(22):18490–501. https://doi.org/10.1039/C5RA27836H.

Hong X, Wen J, Xiong X, Yongyou H. Shape effect on the antibacterial activity of silver nanoparticles synthesized via a microwave-assisted method. Environ Sci Pollut Res. 2016;23(5):4489–97. https://doi.org/10.1007/s11356-015-5668-z.

Jana NR, Gearheart L, Murphy CJ. Wet chemical synthesis of silver nanorods and nanowires of controllable aspect ratio. Chem Commun. 2001;7:617–8. https://doi.org/10.1039/B100521I.

Janata E. Early stages in the growth of small silver clusters in aqueous solution. Radiat Phys Chem. 2012;81(9):1404–6. https://doi.org/10.1016/j.radphyschem.2011.11.039.

Jin R, Cao YW, Mirkin CA, Kelly KL, Schatz GC, Zheng JG. Photoinduced conversion of silver nanospheres to nanoprisms. Science. 2001;294(5548):1901–3. https://doi.org/10.1126/science.1066541.

Kapoor S, Gopinathan C. Reduction and aggregation of silver, copper and cadmium ions in aqueous solutions of gelatin and carboxymethyl cellulose. Radiat Phys Chem. 1998;53(2):165–70. https://doi.org/10.1016/S0969-806X(98)00012-7.

Khodashenas B, Ghorbani HR. Synthesis of silver nanoparticles with different shapes. Arab J Chem. 2015; https://doi.org/10.1016/j.arabjc.2014.12.014.

Kim JS, Kuk E, Yu KN, Kim J-H, Park SJ, Lee HJ, Kim SH, Park YK, Park YH, Hwang C-Y, Kim Y-K, Lee Y-S, Jeong DH, Cho M-H. Antimicrobial effects of silver nanoparticles. Nanomedicine. 2007;3(1):95–101. https://doi.org/10.1016/j.nano.2006.12.001.

Kumar V, Prakash J, Singh JP, Chae KH, Swart C, Ntwaeaborwa OM, Swart HC, Dutta V. Role of silver doping on the defects related photoluminescence and antibacterial behaviour of zinc oxide nanoparticles. Colloids Surf B Biointerfaces. 2017;159:191–9. https://doi.org/10.1016/j.colsurfb.2017.07.071.

Le Ouay B, Stellacci F. Antibacterial activity of silver nanoparticles: a surface science insight. Nano Today. 2015;10(3):339–54. https://doi.org/10.1016/j.nantod.2015.04.002.

Lee PC, Meisel D. Adsorption and surface-enhanced Raman of dyes on silver and gold sols. J Phys Chem. 1982;86(17):3391–5. https://doi.org/10.1021/j100214a025.

Liao C, Li Y, Tjong SC. Bactericidal and cytotoxic properties of silver nanoparticles. Int J Mol Sci. 2019;20(2):449.

Lok C-N, Ho C-M, Chen R, He Q-Y, Yu W-Y, Sun H, Tam PK-H, Chiu J-F, Che C-M. Silver nanoparticles: partial oxidation and antibacterial activities. J Biol Inorganic Chem. 2007;12(4):527–34. https://doi.org/10.1007/s00775-007-0208-z.

Malassis L, Dreyfus R, Murphy RJ, Hough LA, Donnio B, Murray CB. One-step green synthesis of gold and silver nanoparticles with ascorbic acid and their versatile surface post-functionalization. RSC Adv. 2016;6(39):33092–100. https://doi.org/10.1039/C6RA00194G.

Mandal D, Dash SK, Das B, Chattopadhyay S, Ghosh T, Das D, Roy S. Bio-fabricated silver nanoparticles preferentially targets gram positive depending on cell surface charge. Biomed Pharmacother. 2016;83:548–58. https://doi.org/10.1016/j.biopha.2016.07.011.

Marambio-Jones C, Hoek EMV. A review of the antibacterial effects of silver nanomaterials and potential implications for human health and the environment. J Nanopart Res. 2010;12(5):1531–51. https://doi.org/10.1007/s11051-010-9900-y.

Monteiro DR, Gorup LF, Takamiya AS, Ruvollo-Filho AC, de Camargo ER, Barbosa DB. The growing importance of materials that prevent microbial adhesion: antimicrobial effect of medical devices containing silver. Int J Antimicrob Agents. 2009;34(2):103–10. https://doi.org/10.1016/j.ijantimicag.2009.01.017.

Mulfinger L, Solomon SD, Bahadory M, Jeyarajasingam AV, Rutkowsky SA, Boritz C. Synthesis and study of silver nanoparticles. J Chem Educ. 2007;84(2):322. https://doi.org/10.1021/ed084p322.

Murphy CJ, Jana NR. Controlling the aspect ratio of inorganic nanorods and nanowires. Adv Mater. 2002;14(1):80–2. https://doi.org/10.1002/1521-4095(20020104)14:1<80::aid-adma80>3.0.co;2-#.

Ojha AK, Forster S, Kumar S, Vats S, Negi S, Fischer I. Synthesis of well-dispersed silver nanorods of different aspect ratios and their antimicrobial properties against Gram positive and negative bacterial strains. J Nanobiotechnol. 2013;11:42. https://doi.org/10.1186/1477-3155-11-42.

Okafor F, Janen A, Kukhtareva T, Edwards V, Curley M. Green synthesis of silver nanoparticles, their characterization, application and antibacterial activity. Int J Environ Res Public Health. 2013;10(10):5221–38. https://doi.org/10.3390/ijerph10105221.

Pal S, Tak YK, Song JM. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the gram-negative bacterium Escherichia coli. Appl Environ Microbiol. 2007;73(6):1712–20. https://doi.org/10.1128/aem.02218-06.

Panáček A, Kvítek L, Prucek R, Kolář M, Večeřová R, Pizúrová N, Sharma VK, Nevěčná T'j, Zbořil R. Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity. J Phys Chem B. 2006;110(33):16248–53. https://doi.org/10.1021/jp063826h.

Panda SK, Chakraborti S, Basu RN. Size and shape dependences of the colloidal silver nanoparticles on the light sources in photo-mediated citrate reduction technique. Bull Mater Sci. 2018;41(4):90. https://doi.org/10.1007/s12034-018-1609-z.

Pastoriza-Santos I, Liz-Marzán LM. Formation and stabilization of silver nanoparticles through reduction by N,N-dimethylformamide. Langmuir. 1999;15(4):948–51. https://doi.org/10.1021/la980984u.

Pastoriza-Santos I, Liz-Marzán LM. Formation of PVP-protected metal nanoparticles in DMF. Langmuir. 2002;18(7):2888–94. https://doi.org/10.1021/la015578g.

Prakash J, Promod K, Harris RA, Chantel S, Neethling JH, Janse van Vuuren A, Swart HC. Synthesis, characterization and multifunctional properties of plasmonic Ag–$TiO_2$ nanocomposites. Nanotechnology. 2016;27(35):355707. https://doi.org/10.1088/0957-4484/27/35/355707.

Prakash J, Sun S, Swart HC, Gupta RK. Noble metals-$TiO_2$ nanocomposites: from fundamental mechanisms to photocatalysis, surface enhanced Raman scattering and antibacterial applications. Appl Mater Today. 2018;11:82–135. https://doi.org/10.1016/j.apmt.2018.02.002.

Qin Y, Ji X, Jing J, Liu H, Wu H, Yang W. Size control over spherical silver nanoparticles by ascorbic acid reduction. Colloids Surf A Physicochem Eng Asp. 2010;372(1):172–6. https://doi.org/10.1016/j.colsurfa.2010.10.013.

Ren J, Wang W, Sun S, Zhang L, Lu W, Chang J. Crystallography facet-dependent antibacterial activity: the case of $Cu_2O$. Ind Eng Chem Res. 2011;50(17):10366–9. https://doi.org/10.1021/ie2005466.

Rojas-Andrade M, Cho AT, Hu P, Lee SJ, Deming CP, Sweeney SW, Saltikov C, Chen S. Enhanced antimicrobial activity with faceted silver nanostructures. J Mater Sci. 2015;50(7):2849–58. https://doi.org/10.1007/s10853-015-8847-x.

Roy A, Bulut O, Some S, Mandal AK, Deniz Yilmaz M. Green synthesis of silver nanoparticles: biomolecule-nanoparticle organizations targeting antimicrobial activity. RSC Adv. 2019;9(5):2673–702. https://doi.org/10.1039/C8RA08982E.

Schneider S, Halbig P, Grau H, Nickel U. Reproducible preparation of silver sols with uniform particle size for application in surface-enhanced Raman spectroscopy. Photochem Photobiol. 1994;60(6):605–10. https://doi.org/10.1111/j.1751-1097.1994.tb05156.x.

Schuette WM, Buhro WE. Silver chloride as a heterogeneous nucleant for the growth of silver nanowires. ACS Nano. 2013;7(5):3844–53. https://doi.org/10.1021/nn400414h.

Shaheen MNF, El-hadedy DE, Ali ZI. Medical and microbial applications of controlled shape of silver nanoparticles prepared by ionizing radiation. BioNanoScience. 2019;9(2):414–22. https://doi.org/10.1007/s12668-019-00622-2.

Shankar SS, Rai A, Ahmad A, Sastry M. Rapid synthesis of Au, Ag, and bimetallic Au core–Ag shell nanoparticles using Neem (Azadirachta indica) leaf broth. J Colloid Interface Sci. 2004;275(2):496–502. https://doi.org/10.1016/j.jcis.2004.03.003.

Siekkinen AR, McLellan JM, Chen J, Xia Y. Rapid synthesis of small silver nanocubes by mediating polyol reduction with a trace amount of sodium sulfide or sodium hydrosulfide. Chem Phys Lett. 2006;432(4):491–6. https://doi.org/10.1016/j.cplett.2006.10.095.

Sun Y, Xia Y. Shape-controlled synthesis of gold and silver nanoparticles. Science (New York, NY). 2003;298:2176–9. https://doi.org/10.1126/science.1077229.

Sun Y, Yin Y, Mayers BT, Herricks T, Xia Y. Uniform silver nanowires synthesis by reducing $AgNO_3$ with ethylene glycol in the presence of seeds and poly(vinyl Pyrrolidone). Chem Mater. 2002;14(11):4736–45. https://doi.org/10.1021/cm020587b.

Suresh AK, Pelletier DA, Doktycz MJ. Relating nanomaterial properties and microbial toxicity. Nanoscale. 2013;5(2):463–74. https://doi.org/10.1039/C2NR32447D.

Tang S, Zheng J. Antibacterial activity of silver nanoparticles: structural effects. Adv Healthcare Mater. 2018;7(13):1701503. https://doi.org/10.1002/adhm.201701503.

Tian X-D, Lin Y, Dong J-C, Zhang Y-J, Wu S-R, Liu S-Y, Zhang Y, Li J-F, Tian Z-Q. Synthesis of Ag nanorods with highly tunable plasmonics toward optimal surface-enhanced Raman scattering substrates self-assembled at interfaces. Adv Optical Mater. 2017;5(21):1700581. https://doi.org/10.1002/adom.201700581.

Turkevich J, Stevenson PC, Hillier J. A study of the nucleation and growth processes in the synthesis of colloidal gold. Discuss Faraday Soc. 1951;11(0):55–75. https://doi.org/10.1039/DF9511100055.

Ur Rashid M, Bhuiyan MK, Emran QM. Synthesis of silver nano particles (Ag-NPs) and their uses for quantitative analysis of vitamin C tablets. Dhaka Univ J Pharm Sci. 2013;12:29–33.

Van Dong P, Ha CH, Binh LT, Kasbohm J. Chemical synthesis and antibacterial activity of novel-shaped silver nanoparticles. Int Nano Lett. 2012;2(1):9. https://doi.org/10.1186/2228-5326-2-9.

Vukoje I, Lazić V, Vodnik V, Mitrić M, Jokic B, Ahrenkiel SP, Nedeljković J, Radetić M. The influence of triangular silver nanoplates on antimicrobial activity and color of cotton fabrics pretreated with chitosan. J Mater Sci. 2014;49:4453–60. https://doi.org/10.1007/s10853-014-8142-2.

Wang C, Liu B, Dou X. Silver nanotriangles-loaded filter paper for ultrasensitive SERS detection application benefited by interspacing of sharp edges. Sensors Actuators B Chem. 2016;231:357–64. https://doi.org/10.1016/j.snb.2016.03.030.

Wei QS, Ji J, JinHong F, Shen JC. Norvancomycin-capped silver nanoparticles: synthesis and antibacterial activities against E. coli. Sci Chn Ser B Chem. 2007;50(3):418–24. https://doi.org/10.1007/s11426-007-0028-6.

Wu C, Xue Z, Wei J. Localized surface plasmon resonance of silver nanotriangles synthesized by a versatile solution reaction. Nanoscale Res Lett. 2015;10(1):354. https://doi.org/10.1186/s11671-015-1058-1.

Wuithschick M, Paul B, Bienert R, Sarfraz A, Vainio U, Sztucki M, Kraehnert R, Strasser P, Rademann K, Emmerling F, Polte J. Size-controlled synthesis of colloidal silver nanoparticles based on mechanistic understanding. Chem Mater. 2013;25(23):4679–89. https://doi.org/10.1021/cm401851g.

Zhang Q, Li W, Wen L-P, Chen J, Xia Y. Facile synthesis of Ag nanocubes of 30 to 70 nm in edge length with $CF_3COOAg$ as a precursor. Chem Eur J. 2010;16(33):10234–9. https://doi.org/10.1002/chem.201000341.

Zhang Z, Shen W, Xue J, Liu Y, Liu Y, Yan P, Liu J, Tang J. Recent advances in synthetic methods and applications of silver nanostructures. Nanoscale Res Lett. 2018;13(1):54. https://doi.org/10.1186/s11671-018-2450-4.

Zielińska A, Skwarek E, Zaleska A, Gazda M, Hupka J. Preparation of silver nanoparticles with controlled particle size. Proc Chem. 2009;1(2):1560–6. https://doi.org/10.1016/j.proche.2009.11.004.

# The Role of Heterogeneous Catalysts in Converting Cellulose to Platform Chemicals


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**Contents**



## 1 Introduction

Biomass is a renewable carbon source, plentiful worldwide, which can be used to generate biofuels and value-added chemicals as a feasible alternative to nonrenewable fossil raw materials. Accordingly, two crucial concepts arise in this scenario: biorefinery and bio-based platform chemicals. Biorefinery refers to a network of

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_12

integrated and correlated conversion processes whose shared aim is to target the utilization of all carbon atoms from the biomass resource to the production of fuels, power, heat, and high-value chemicals (Mika et al. 2018). When these chemicals comprised entirely of biomass-derived carbon atoms undergo other routes to synthesize other valuable products, they fall into the concept of bio-based platform chemicals (Farmer and Mascal 2015). Many studies have been carried out over the last decades concerning the use of a vast range of lignocellulosic materials to generate such products on a large industrial scale. However, the recalcitrance of the lignocellulosic matrix still represents a significant bottleneck for the consolidation of biorefinery productive chains.

Agro-industrial residues represent a broad and cheap source of lignocellulose throughout the world. Sugarcane bagasse and straw, rice husk, corn stover, and spent coffee grounds are examples of widely produced lignocellulosic agro-industrial residues whose produced and whose exploitation for industrial purposes has been studied in recent years (Philippini et al. 2019; Canettieri et al. 2018; Yang et al. 2016; Shahabazuddin et al. 2018; Ballesteros et al. 2014). Cellulose, hemicellulose, and lignin are the three leading constituents of lignocellulose, which is an inherent feature to all lignocellulosic materials. Moreover, the proportion of such components can vary depending on the type and source of biomass (Kucharska et al. 2018; Baig et al. 2019). The close association between these polymers results in the recalcitrance of biomass to hydrolysis, thus leading the pretreatment of these materials to become an inevitable step (Mosier et al. 2005; Sun et al. 2016). Different types of pretreatment are applied to various kinds of biomass, considering their singularities, costs, and economic balances, as well as approaches that do not harm the environment. In this context, ionic liquids and supercritical fluids, such as supercritical carbon dioxide, have shown to be potential green solvents for efficient pretreatment of biomass (Brodeur et al. 2011; Gu et al. 2013).

Concerning hydrolysis of cellulose, the main fraction of lignocellulose, most of the studies reported in the literature evaluate homogeneous chemical catalysis, especially with mineral acids. Although high yields of glucose can be obtained using these treatments, many drawbacks occur during the process, such as reactor corrosion, the formation of inhibitor products, less recyclability of the solvents, and environment hazards, among others. Studies have addressed heterogeneous catalysts to convert cellulose into sugar and other value-added chemicals such as hydroxymethylfurfural and levulinic acid, aiming to overcome problems related to homogeneous catalysis. Among the advantages of these catalysts are the high yield of glucose, good recyclability, uncomplicated separation steps, and no reactor corrosion.

Having said that, this work aims to discuss the role heterogeneous catalysts play in cellulose conversion into glucose and value-added products, elucidating some critical points within the process chain such as understanding the recalcitrant nature of lignocellulose and the pretreatment approach to be taken.

## 2 Structure of Lignocellulosic Materials

Lignocellulosic biomass refers to the organic materials constituted by cellulose, hemicellulose, lignin, and extractives (Cantero et al. 2019). This type of biomass can be used for producing valuable products, such as biofuels, bio-based materials, and chemicals (Kim et al. 2019). Its structure consists of a hetero-matrix formed by the close association between the cellulose, hemicellulose, and lignin polymers (Fig. 1), and the chemical composition can vary depending on the type, species, and even the source of the biomass (Table 1) (Kucharska et al. 2018). Therefore, different lignocellulosic materials have different physicochemical characteristics (Bychkov et al. 2019), and understanding those singularities can lead to better exploitation of their structural carbohydrates for industrial purposes. Based on this assumption, this section will address the components and structural features of lignocellulose.

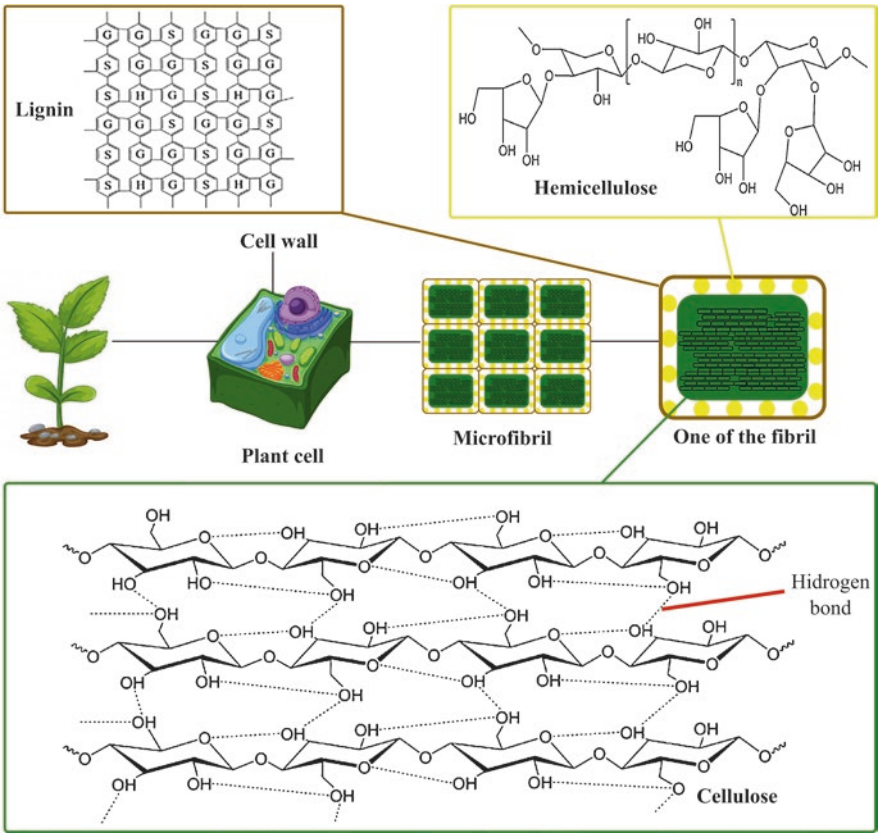


**Fig. 1** Lignocellulose matrix (Adapted from Shrotri et al. 2015 and Chio et al. 2019)

**Table 1** Chemical composition of different types of biomass

| Biomass | Cellulose (% w/w) | Hemicellulose (% w/w) | Lignin (% w/w) | References |
|---|---|---|---|---|
| Sugarcane bagasse | 40.84 | 24.07 | 33.71 | Philippini et al. (2019) |
| Sugarcane straw | 31.46 | 27.03 | 31.14 | Canettieri et al. (2018) |
| Corn stover | 36.50 | 22.10 | 18.80 | Yang et al. (2016) |
| Rice husk | 32.65 | 18.08 | 26.68 | Shahabazuddin et al. (2018) |
| Coffee silverskin | 23.77 | 16.68 | 28.58 | Ballesteros et al. (2014) |
| Spent coffee grounds | 12.40 | 39.10 | 23.90 | Ballesteros et al. (2014) |

This table summarizes the chemical composition of some agro-industrial residues

## *2.1 Cellulose*

Cellulose is a linear unbranched polymer of cellobiose, its repetitive disaccharide, which consists of β-D-glucose residues connected with β-(1 → 4)-glycosidic bonds and rotated 180° toward each other (Henriksson and Lennholm 2009). Its degree of polymerization is around 10,000, but it can be even higher, reaching values of 15,000 residues (Henriksson and Lennholm 2009; Motaung and Linganiso 2018). It has an average molecular weight of 100,000, and despite the resistance to strong alkali, cellulose is readily hydrolyzed by acid to water-soluble sugars (Motaung and Linganiso 2018). This biopolymer probably has no common origin since several, not closely related, organisms can produce it, for instance, plants, Oomycetes and some other protists, sea squirt, some algae, and also procaryotic bacteria, such as *Acetobacter* (Henriksson and Lennholm 2009). Land plants, however, are the main source of cellulose (Ioelovich 2016). Hence, cellulose represents the most abundant biological polymer on Earth, and although it occurs as the primary component in plant cell walls, its biosynthesis is not limited to higher plants (McNamara et al. 2015).

Each cellulose unit contains three hydroxyl functional groups (Ioelovich 2016). Hydrogen bonds between the C-6 hydroxyl and the C-2 hydroxyl and between the C-5 oxygen and C-3 hydroxyl stabilize the glycosidic bond conferring stiffness to the structure, whereas the C-6 and C-3 hydroxyls form one hydrogen bond between parallel chains for each glucose residue, creating a cellulose sheet (Henriksson and Lennholm 2009). Henriksson and Lennholm (2009) state that these cellulose sheets lay on each other via van der Waals bonds and hydrophobic interactions, and because their glucose residues do not accumulate directly over each other, there is a shift in the position of the chains in the cellulose sheets that results in the two different crystalline forms of cellulose, Iα and Iβ. Finally, these long, relatively narrow sheets form the fibrils, highly organized three-dimensional crystals (Henriksson and Lennholm 2009).

This linear, stereoregular, and semicrystalline polysaccharide is an inexhaustible raw material source for producing diverse and essential materials and compounds (Ioelovich 2016). Among these products is bioethanol, whose production, especially from sugarcane bagasse, has been studied extensively in recent years. Besides

bioethanol, the cellulose fraction in lignocellulose can also be exploited to produce a wide range of bio-based platform chemicals, adding more value to the agro-industrial productive chains (see more details in section "Pretreatment for cellulose fraction"). However, its recalcitrant structure, which occurs as a result of its 3D network of inter- and intramolecular hydrogen bonds, still makes the efficient and economical conversion of cellulose to platform chemicals a challenge, as the recalcitrant crystalline phase restricts the access of catalyst to the β (1 → 4) glycoside bonds (Shrotri et al. 2015).

## *2.2 Hemicellulose*

Hemicellulose is the next most abundant polysaccharide after cellulose (Deutschmann and Dekker 2012). Teleman (2009) and Scheller and Ulvskov (2010) report that hemicelluloses have been traditionally described as cell wall noncellulosic and non-pectic polysaccharides of land plants. According to Teleman (2009), hemicelluloses typically occur as heteropolysaccharides, and they are present in the matrix between cellulose fibrils in the cell walls of hardwood, softwood, switchgrass, cereals, and some other plants. Farhat et al. (2017) state that hexoses such as D-glucose, D-mannose, and D-galactose and pentoses such as D-xylose and L-arabinose are the main building units of these polymers, along with little amounts of deoxyhexoses L-rhamnose and L-fucose and certain uronic acids, including 4-O-methyl-D-glucuronic acid, D-galacturonic acid, and D-glucuronic acid. The chemical structures of these units are mostly pyranose rings either in the α- or β-anomeric forms (Teleman 2009; Farhat et al., 2017).

Although these carbohydrates are extracted with alkaline solutions, some hemicelluloses are partially or even easily extractable without alkaline treatments, which means that definitions based only on extractability are not useful for grouping them (Teleman 2009; Scheller and Ulvskov 2010). In this study, the explanation for hemicellulose is given by Scheller and Ulvskov (2010), who suggest that only wall polysaccharides that share a β-(1 → 4)-linked backbone with an equatorial configuration at C1 and C4 are hemicelluloses, given the fact that their backbones have significant structural similarity. As a result, some polysaccharides, such as galactans, arabinans, and arabinogalactans, will not be considered. Hence, this heterogeneous group of polysaccharides will comprise of xylans, xyloglucan, mannans, glucomannans, and β-(1 → 3,1 → 4)-glucans (Scheller and Ulvskov 2010).

Xylans are chains of β-D-xylopyranosyl (β-D-xylose) units linked via β-(1 → 4)-glycosidic bonds, and they are the most abundant form of hemicellulose in nature (Naidu et al. 2018). The types of branching from the β-D-xylopyranosyl backbone, which varies depending on species and tissue, result in different types of xylans, arabinoxylans, and arabinoglucuronoxylans, with many arabinose residues attached to the backbone, and glucuronoxylan, with several substitutions with α-(1 → 2)-linked glucuronosyl and 4-O-methyl glucuronosyl residues (Scheller and Ulvskov 2010; Deutschmann and Dekker 2012; Naidu et al. 2018). These differences

in relation to substituents (arabinose, glucuronic acids, acetyl groups) and the substitution pattern will lead to xylans isolated from different sources to have various applications in the industry. From xylans, for example, it is currently possible to obtain xylitol, bioethanol, xylooligosaccharides, and many other derivatives with the potential for different applications in the future (Deutschmann and Dekker 2012).

Xyloglucan is a nonionic, neutral, branched polysaccharide consisting of a cellulose-like main chain of (1 → 4)-β-D-glucan backbone chain which is partially substituted with side chains of α-D-xylose at O-6 position and (1 → 2)-β-D-galactosyl units at O-2 position (Kulkarni et al. 2017; Pique et al. 2018). This xylosylated glucan is considered a ubiquitous plant polysaccharide since it occurs and has been structurally characterized in the walls of all land plants studied up to the present date, which includes even the phylogenetically ancient nonvascular plants (Pauly and Keegstra 2016). Despite the diverse array of glycosyl and non-glycosyl residues that can be xyloglucan substituents and the order that they appear, resulting in the unique 24 unique structures identified to date, Pauly and Keegstra (2016) state that the extension of the xylosyl substituent at O-2 by a galactosyl residue, leading to the side chain L, is a ubiquitous structural feature to xyloglucans of all plants.

Xyloglucans have properties that make them alternative polymers for biomedical applications such as drug delivery and reconstruction of tissues. Some xyloglucans derived from tamarind seeds can help to treat a range of diseases related to mucosal disruption and tight junction alterations since, due to their mucoadhesive properties, they can act as a reducing invasion and bacterial adherence barrier, also preserving tight junctions and paracellular flux (Pique et al. 2018). In addition to having distinctive mucoadhesive properties, tamarind seeds' xyloglucans have in situ gelling properties that make them suitable for drug delivery applications (Kulkarni et al. 2017). When the effects of degalactosylated xyloglucans of *Tamarindus indica* on murine peritoneal macrophages in vitro were evaluated, they showed that they stimulated the release of pro-inflammatory mediators such as NO, TNF-α, IL-1β, and IL-6, which means that they can help to potentialize the immune system against infections or toxicity to tumor cells (do Rosario et al. 2017).

Softwoods, plant seed endosperms, and fruits are abundant in mannans (Malgas et al. 2015; Singh et al. 2018). Taking into consideration the backbone structure and the presence of galactose side chains, mannans fall into four categories, namely, glucomannans, galactomannans, galactoglucomannans, and pure mannans (Schröder et al. 2009). Pure mannan and galactomannan backbones consist entirely of mannose, whereas glucomannan and galactoglucomannan backbones consist of mannose and glucose in a nonrepeating pattern, and they are both often acetylated (Scheller and Ulvskov 2010). Mannans have several health benefits in the gut, including the increase of defecation frequency; lactobacilli and bifidobacteria growth promotion; immune-enhancing effects; the capability of working as a lectin-binding substrate preventing pathogens from adhering to the gut, bladder, or urinary tract linings; and reduction of Crohn's disease and ulcerative colitis (Tester and Al-Ghazzewi 2013).

Another polysaccharide formed by D-glucose monomers linked by β-glycosidic bonds is β-glucans, often found as the main components of cell walls in cereals,

yeast, mushrooms, some bacteria, and seaweeds (Du et al. 2014; Bai et al. 2019). The different β-glucan sources will provide β-glucans with distinct types of linkage, branching manners, and molecular weight (Du et al. 2014). β-Glucan from baker's yeast consists of β-(1 → 3) and (1 → 6) linkages, whereas cereal-derived β-glucans are polysaccharides of glucose residues with β-(1 → 3) and β-(1 → 4) linkages (Zhu et al. 2016). β-(1 → 4)-linked glucans with interspersed single β-(1 → 3) linkages also occur in grasses (Scheller and Ulvskov 2010). According to Tohamy et al. (2003), these naturally occurring polysaccharides are biological response modifiers, which means they can stimulate the defense mechanisms of the organism. Among their immunopharmacological activities are the increased host resistance to parasitic, fungal, bacterial, and viral infections; antitumor effect and prevention of carcinogenesis; radioprotective activity and adjuvant effects; and increased phagocytic and proliferative activity of the reticuloendothelial system (Tohamy et al. 2003). β-Glucan fiber intake can also help to control diabetes by slowing down the gastric emptying and decreasing the absorption of glucose by enterocytes (Bozbulut and Sanlier 2019).

## *2.3 Lignin*

Lignin represents the most abundant natural phenolic polymers in the world, and along with hemicellulose and cellulose, it forms the matrix of lignocellulose (Chio et al. 2019). It has the most complex structure among naturally occurring polymers with a mixture of aliphatic hydroxyl, phenolic hydroxyl, and methoxyl group moieties (Henriksson 2009; Chio et al. 2019). The reactivity and chemical properties of lignin are affected by these functional groups, especially the hydroxyl groups and aromatic structure, which are crucial to determining the characteristics of the polymers (Chio et al. 2019).

Three precursor monomers (monolignols), p-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol, are polymerized by various percentages, forming the lignin from different plants (Henriksson 2009; Chio et al. 2019). These monolignols lead to 4-hydroxyphenyl, guaiacyl (4-hydroxy-3-methoxyphenyl), and syringyl (4-hydroxy-3,5-dimethoxyphenyl) units in lignin (Dorrestijn et al. 2000), whose content will classify lignin in softwood lignin or guaiacyl lignin, hardwood lignin or syringyl-guaiacyl lignin, and grass lignin or HGS-lignin (hydroxy phenol, guaiacyl, syringyl) (Henriksson 2009). Lignins from the first group have coniferyl alcohol exclusively, while syringyl-guaiacyl lignin contains both coniferyl and sinapyl alcohols with proportions varying from approximately equal amounts to three times higher levels of sinapyl, and the grass lignin typically has all three monolignols with a higher content of p-coumaryl alcohol than other types of lignin (Henriksson 2009).

Chio et al. (2019) state that lignin cannot be obtained precisely, as it naturally occurs, since it only exists as part of the lignocellulose, and during extraction processes its structure is modified, obtaining what is called technical or modified lignin. The technical lignin composition and molecular weight differ according to the

sources and extraction methods, which also designate their names, for example, to kraft lignin, hydrolysis lignin, organosolv lignin, and pyrolytic lignin (Chio et al. 2019). It is common to burn the lignin to generate the energy necessary to transform biomass in large-scale industrial processes that employ plant polysaccharides (Lauwaert et al. 2019). Many studies, however, suggest better industrial applications of these phenolic polymers. The applications for technical lignins are diverse, including using them as a copolymer in biocomposites with olefins; as a reinforcement in the rubber industry; as flocculants and adhesives; as a precursor for carbon fibers; as electrodes in lithium-ion batteries; and, even for controlled drug delivery, as a copolymer in hydrogels (Ten and Vermerris 2015).

## 3 Pretreatment for Cellulose Fraction

As said previously, cellulose, lignin, and hemicellulose are the main constituents of lignocellulosic materials (Baig et al. 2019). The heterogeneous character of biomass particles, high crystallinity of cellulose, the protection of it by lignin, and cellulose sheathing by hemicellulose (Fig. 1) all contribute to forming strong native recalcitrance to hydrolysis, which requires appropriate pretreatment methods to make the polysaccharides available (Mosier et al. 2005; Sun et al. 2016). These pretreatment methods can be either physical or chemical or even present both features (Mosier et al. 2005). In addition to these, there are also biological pretreatments (Hu et al. 2008).

The pretreatment processes can reduce the recalcitrance of lignocellulose by removing the content of lignin and hemicellulose to a certain extent and by increasing accessible surface area, porosity, and concentration of amorphous cellulose (Ravindran and Jaiswal 2016; Sun et al. 2016). Many pretreatments such as high pressure or temperature or a combination of both, corrosive chemicals (acids and alkalis), or the use of molecular disruption techniques (ultrasound and plasma) are used trying to circumvent the lignocellulose recalcitrance problem (Ravindran and Jaiswal 2016). Comminution, such as milling, which aims to reduce the substrate particle size and affects the degree of polymerization of cellulose, is sometimes needed to make material handling easier through subsequent processing steps (Mosier et al. 2005; Baig et al. 2019). Table 2 shows the effects that some pretreatment processes used in recent years have on lignocellulosic biomass, along with the advantages and disadvantages of applying these technologies.

Some of the lignocellulosic biomass pretreatments most reported in the literature are alkaline, acid, steam explosion, liquid hot water, and ammonia fiber/freeze explosion (AFEX) pretreatments. Pretreatment of lignocellulosic biomass to break the recalcitrant of its structure can be done using bases such as sodium, potassium, calcium, and ammonium hydroxide (alkaline pretreatment) or concentrated or diluted acids (acid pretreatment) (Brodeur et al. 2011). Steam explosion, liquid hot water, and ammonia fiber explosion (AFEX) are physicochemical pretreatments. According to Maurya et al. (2015), the steam explosion pretreatment is a method in

**Table 2** Effects of different pretreatment processes on lignocellulosic materials

| [1,2,3,4]Pretreatment | [1,2,3,4]Source | [1,2,3,4]Means | [4]Effect[a] | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Physical pretreatment | Comminution | Milling | Increasing accessible area (H); decrystallizing cellulose (H); generating inhibitors (L) | [4]Increases the accessible specific surface area and reduces crystallinity | [3]High power and energy consumption |
| Physicochemical pretreatment | Hydrothermolysis | Liquid hot water | Removing lignin (M) and hemicellulose (H); increasing accessible area (M) and porosity (M); generating inhibitors (H) | [3]Size reduction of the biomass is not needed; no chemicals are generally required; no requirement of corrosion-resistant materials | [3]High-energy and high-water requirement; formation of toxic compounds |
| | Steam explosion | High-pressure steam | Removing lignin (L) and hemicellulose (H); decrystallizing cellulose (L); increasing accessible area (H) and porosity (H); generating inhibitors (H) | [3]Causes lignin transformation and hemicellulose solubilization | [3]Generation of toxic compounds; partial hemicellulose degradation |
| | Ammonia fiber explosion (AFEX) | Anhydrous ammonia, high pressures, and moderate temperatures | Removing lignin (M) and hemicellulose (L); decrystallizing cellulose (H); increasing accessible area (H) and porosity (H); generating inhibitors (L) | [3]Increases accessible surface area; less inhibitor formation; does not require small particle size of biomass | [3]Not very effective for the biomass with high lignin content; high cost of large amount of ammonia |
| | Supercritical fluid (SCF) | E.g., supercritical carbon dioxide ($SC\text{-}CO_2$) | Removing lignin (L) and hemicellulose (L); increasing accessible area (H) and porosity (H); generating inhibitors (L) | [4]Increases accessible specific surface area | [4]High equipment cost |
| Chemical pretreatment | Alkaline | E.g., sodium hydroxide | Removing lignin (H) and hemicellulose (H); increasing accessible area (H) and porosity (H); generating inhibitors (L) | [3]Decrease in the degree of polymerization and crystallinity of cellulose | [3]High cost; not used for a large-scale plant |

(continued)

**Table 2** (continued)

| [1,2,3,4]Pretreatment | [1,2,3,4]Source | [1,2,3,4]Means | [4]Effect[a] | Advantages | Disadvantages |
|---|---|---|---|---|---|
| | Acid | E.g., sulfuric acid | Removing lignin (M) and hemicellulose (H); increasing accessible area (H) and porosity (M); generating inhibitors (H) | [3]High glucose yield; ambient temperatures | [3]High cost of acid and need to be recovered; corrosion-resistant equipment are required; concentrated acids are toxic and hazardous |
| | Oxidative | E.g., wet oxidation ($O_2$); $H_2O_2$; $O_3$. | Removing lignin (H); increasing porosity (H); generating inhibitors (L) | [4]Efficient removal of lignin | [4]High cost of bleaching agents |
| | Organosolv | Organic solvents | Removing lignin (H) and hemicellulose (L); increasing accessible area (H) and porosity (M); generating inhibitors (L) | [3]Causes lignin and hemicellulose hydrolysis | [3]Solvents need to be drained and recycled; high cost |
| | Green solvents | Ionic liquids | Removing lignin (M) and hemicellulose (L); decrystallizing cellulose (H); increasing accessible area (H) and porosity (H); generating inhibitors (L) | [4]Reduces the crystallinity of lignocellulose efficiently | [4]High costs of ionic liquids |
| Biological pretreatment | Microorganisms | Fungi Actinomycetes | Removing lignin (H) and hemicellulose (M); increasing accessible area (H) and porosity (H); generating inhibitors (L) | [3]Low-energy requirements and mild environmental conditions; [4] degrades lignin and hemicelluloses | [3]Slow process rate; very low treatment rate; not very effective for commercial application |

[a]*H* high effect, *M* medium effect, *L* low effect

**References: 1-**Hu et al. (2008); **2-** Brodeur et al. (2011); **3-**Maurya et al. (2015);**4-** Sun et al. (2016)

which biomass cut in small pieces is treated under pressure saturated steam for a short time, which can range from seconds to several minutes, and then the pressure is suddenly released. Liquid hot water, on the other hand, is a hydrothermal pretreatment that does not require rapid decompression, where high pressure is mainly needed only to maintain the water in the liquid state at high temperatures, so that the hemicellulose removal from the lignocellulosic materials takes place, making the access to cellulose easier for further steps (Maurya et al. 2015). Ammonia fiber explosion or AFEX, in turn, entails using anhydrous liquid ammonia to treat cellulosic materials in a process quite similar to steam explosion. They differ by the fact that the mixture of ammonia and biomass in the pressure vessel, usually in the weight ratio of about 1:1, is under room temperature, instead of high temperatures, and is under the vapor pressure of liquid ammonia at the determined ambient temperature, which allows the ammonia to boil when the pressure is released, facilitating the separation and recovery steps of ammonia (Hu et al. 2008).

It should be pointed out that few pretreatments cope with converting cellulose into glucose quantitatively. Moreover, using expensive and toxic reagents, production of toxic by-products and high energy requirement are some of the notable limitations pretreatments still face (Baig et al. 2019). It is mandatory that there is a balance among the pretreatment results and the operating costs, the downstream processing step costs, the capital costs, and the biomass costs (Mosier et al. 2005). However, not only the economic aspects of the process should be considered when it comes to choosing an appropriate pretreatment for lignocellulosic agro-industrial residues; a sustainable and environmentally friendly approach must also be taken into consideration. Green solvents such as ionic liquids and supercritical carbon dioxide satisfy such requirements.

Ionic liquids are thermally stable organic salts, typically composed of a small anion and a large organic cation, that usually melt below 100 °C and that can readily dissolve polar and nonpolar organic, inorganic, and polymeric compounds when used as solvents in chemical processes (Lee and Lee 2005; Brodeur et al. 2011; Lee et al. 2009). Their characteristic physicochemical properties, such as extremely low vapor pressure, high thermal stability, high conductivity, and wide range of electrochemical and polarity properties, not only distinguish them from conventional organic solvents but also make them better alternatives in many chemical processes (Choi and Verpoorte 2019). Among the advantages of using ionic liquids rather than other pretreatment methods is the possibility of decreasing the cellulose crystallinity with partial removal of hemicellulose and lignin without degradation product formation and with lower energy demand, besides being more environmentally safe and easier to handle (Qiu et al. 2012), although the exposure hazard to the environment due to their non-volatility is unclear (Singh 2019).

The requirements for an ionic liquid to be used in the pretreatment of biomass, in addition to having high dissolution capacity, are a low melting point, low viscosity, no or low toxicity, and high stability (Brodeur et al. 2011). Based on that, there are several works in the literature regarding ionic liquids for the pretreatment of lignocellulosic biomass. Lignin was effectively extracted from sugarcane bagasse using the ionic liquid [$C_2$mim][ABS] at ambient pressure and high temperatures, with

over 93% yield, and recovered masses of ionic liquid ranging from 96.1% to 99.4% (Tan et al. 2009). Ammonium-based ionic liquids [DIPEA][Ac], [DIPEA][P], [DIPEA][O], and [DIPEA][B] showed to be efficient for dissolving coffee husk and also for extracting and degrading its lignin content under mild conditions, with the highest lignin extraction yield of 71.2% observed for coffee husk treated with [DIPEA][Ac] at 120 °C, for 4 h (Tolesa et al. 2018). Qiu et al. (2012) pretreated energy cane bagasse with 1-ethyl-3-methylimidazolium acetate [EMIM][OAc] 5% (w/w) at 120 °C, for 30 min, which resulted in 32% of lignin removal with few losses of glucan and xylan.

A combination with other pretreatments and adjuvants can also improve the biomass fractioning by ionic liquids. Sharma et al. (2019) carried out a combinatorial application of ultrasound with 1-butyl-3-methylimidazolium chloride ([Bmim]Cl) and surfactant PEG-8000 to pretreat sugarcane bagasse. These authors also state that ionic liquids are able to dissolve the lignin and cellulose fractions in the lignocellulosic biomass, whereas surfactants decrease the surface tension between the two liquid phases enhancing the lignin removal. The physicochemical characterization of the pretreated biomass showed that the combined action of ionic liquid, surfactant, and ultrasound had different and severe ultrastructural alteration effects on sugarcane bagasse. The combined ionic liquid [Bmim]Cl and surfactant PEG-8000 pretreatment led to more significant ultrastructural alterations in the sugarcane bagasse biomass than ionic liquid pretreatments alone, leading to enhanced access to biomass by cellulases and xylanases from an ionic liquid-tolerant *Aspergillus assiutensis* strain and hence enhanced sugar yield (Sharma et al. 2019).

One of the drawbacks faced by implementing ionic liquids on an industrial level for the pretreatment of lignocellulosic materials is the economic aspect since ionic liquids are expensive and still need to be synthesized at a lower cost and on a larger scale (Brodeur et al. 2011). Moreover, quite often the need for ample washing of the biomass after the ionic liquid pretreatment, to avoid latter saccharifying enzyme inhibition later, leads to enormous water wastage, effluent generation, and sugar loss (Vaid and Bajaj 2017). Therefore, when the saccharification step is performed biologically/enzymatically, testing is required to evaluate the ability of microorganisms to ferment sugars in the presence of these solvents and also to produce ionic liquid-resistant enzymes (Brodeur et al. 2011; Sharma et al. 2019). The pretreatment of lignocellulosic biomass with ionic liquids, however, still represents a feasible approach to reduce costs and help to develop consolidated biorefinery processes (Brodeur et al. 2011).

The first generation of green solvents was supercritical fluids, which has properties somewhere in between gas and liquid (Choi and Verpoorte 2019). The supercritical phase occurs above the critical temperature and critical pressure where gases and liquids coexist (Brodeur et al. 2011). These fluids display liquid-like density and solvating power besides exhibiting gas-like transport properties of diffusivity and viscosity (Brodeur et al. 2011; Maurya et al. 2015). Supercritical carbon dioxide (SC-$CO_2$), which has a critical temperature (Tc) of 31 °C and critical pressure (Pc) of 7.4 MPa, is an excellent supercritical fluid for biomass pretreatment (Brodeur et al. 2011). It is a modified steam explosion involving $CO_2$ instead of atmospheric

air, in which wetted biomass is loaded in a reactor and then the pressure within the reactor is built up using supercritical $CO_2$ (Ravindran and Jaiswal 2016). The watering step is essential since this pretreatment is efficient concerning wet biomass only, which is probably linked to the formation of carbonic acid as a result of $CO_2$ dissolution in water (Kucharska et al. 2018).

The use of higher pressure during supercritical $CO_2$ explosion is important to achieve a better $CO_2$ penetration through biomass micropores and a more powerful explosion (Gu et al. 2013). Gao et al. (2010) reported the active play of the pretreatment pressure in supercritical $CO_2$ pretreatment of rice straw. After enzymatic hydrolysis, the authors had a final glucose yield of 32.4% for rice straw pretreated with supercritical $CO_2$ at 30 MPa and 110 °C for half an hour, compared with 27.7% for unpretreated straw. The glucose yield for corn stover with 75% moisture content pretreated with supercritical $CO_2$ increased considerably when the pressure and temperature increased, with a maximum glucose yield of 30%, at 24,13 MPa and 150 °C for 1 h, compared with 12% from untreated corn stover (Narayanaswamy et al. 2011). Supercritical $CO_2$ pretreatment of bagasse alone was responsible for the efficiency of 74.2% for fermentable sugar obtained by enzymatic hydrolysis, an increase of about 280% compared to the non-treated bagasse, and when combined with ultrasound led to an increase of about 16% in the amount of fermentable sugar in comparison with the treatment using only ultrasound (Benazzi et al. 2013).

Both the supercritical carbon dioxide and ionic liquids are green solvents (Gu et al. 2013), and they present advantages and disadvantages that must be taken into consideration when applied as pretreatments of biomass. Although the supercritical $CO_2$ is an inexpensive solvent, due to the high operating pressure, high-cost equipment is necessary (Gu et al. 2013; Sun et al. 2016). Ionic liquids, on the other hand, are high-cost solvents (Sun et al. 2016) whose residual amounts in the treated biomass could interfere with enzyme hydrolysis and downstream fermentation steps (Gu et al. 2013; Maurya et al. 2015). However, because they do not require high pressure for biomass pretreatment, they demand much more effortless types of processing equipment than supercritical $CO_2$ (Gu et al. 2013). Therefore, more studies are necessary to make the application of these solvents more economically sustainable.

## 4 Heterogeneous Catalysts for Cellulose Conversion

### *4.1 Platform Chemicals*

In recent years, the production of bioenergy and biomass-derived chemicals has attracted notable attention, mainly due to the crucial need for fossil fuel replacement and concern about climate change (Kang et al. 2018). Biomass is a renewable and natural carbon source, available worldwide, that can be used as an alternative raw material to produce carbon-based chemicals (Mika et al. 2018). In this context, acid-catalyzed hydrolysis of biomass under relatively mild temperatures has been considered a crucial step for the production of bioenergy and value-added interme-

diary chemicals such as glucose, furfural, 5-hydroxymethylfurfural, and levulinic acid, which are regarded as crucial platform chemicals (Kang et al. 2018).

Bio-based platform molecules, also known as biomass-derived building block chemicals, or just platform chemicals, are simple and small molecules whose constituent elements originate entirely from biomass and that can act as synthetic precursors in the production of several chemical compounds and value-added materials (Farmer and Mascal 2015). Consequently, the concept of platform chemicals is closely associated with the concept of biorefinery, which relates to the integration of conversion processes to produce fuels, energy, heat, and the most variable types of value-added chemicals, managing to use all the carbon atoms of the biomass (Mika et al. 2018). Based on that, it should be stated that the hydrolysis of cellulose into glucose is the central point of biorefinery and its whole selective transformation chain (Hu et al. 2015a).

Bozell and Petersen (2010) provide an updated list of target structures that could be produced from biorefinery carbohydrates. Following Bozell and Petersen's list, these platform chemicals are ethanol, furans, glycerol and derivatives, biohydrocarbons, lactic acid, succinic acid, hydroxy propionic acid/aldehyde, levulinic acid, sorbitol, and xylitol. From the selective transformation of cellulose, 5-hydroxymethylfurfural, levulinic acid, alkyl glucoside, lactic acid, ethylene glycol, sorbitol, and propylene glycol can be obtained (Hu et al. 2015a). Among these chemicals, levulinic acid and 5-hydroxymethylfurfural stand out since they are intermediate for a variety of other high-value chemicals (Fig. 2).

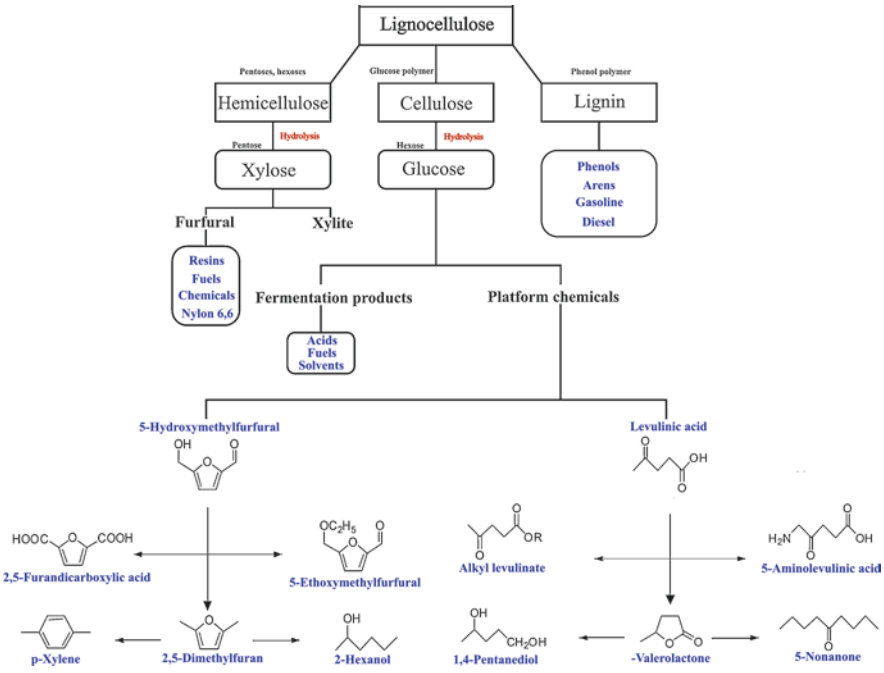


**Fig. 2** Utilization of lignocelluloses to produce chemicals (Adapted from Huang and Fu 2013 and Hu et al. 2015a)

Levulinic acid, also known as 3-acetylpropionic acid, 4-oxovaleric acid, or 4-oxopentanoic acid, is a promising platform chemical due to the presence of functional carboxyl and carbonyl groups and an α-H in its structure, which allows this acid to act as a crucial synthetic precursor in different segments of the industry, such as pharmaceutical, food, fragrances, polymers, agrochemicals/pesticides, fuel additives, textile industries, solvents, and organic synthesis, among others (Antonetti et al. 2016; Badgujar et al. 2019). Bozell and Petersen (2010) stated that levulinic acid is a chemical platform of great interest because of its simple production and the high yield from the acid treatment of six-carbon sugars although the presence of difficult-to-treat materials can complicate their isolation and purification.

The six-carbon sugar dehydration in the presence of an acid catalyst produces levulinic acid in a single step through hydroxymethylfurfural as an intermediate. More precisely, depolymerization of the polysaccharide by hydrolysis occurs first, providing glucose monomers that will isomerize into fructose molecules, which are then dehydrated by removing three water molecules, into 5-hydroxymethylfurfural; finally, 5-hydroxymethylfurfural suffers rehydration and rearrangement to levulinic acid and formic acid. High yields are obtained with homogeneous mineral acids; however, the high costs of the neutralization, separation, and purification steps limit the commercialization of 5-hydroxymethylfurfural, levulinic acid, and its derivatives when this route is followed (Alonso et al. 2013; Badgujar et al. 2019).

## *4.2 Heterogeneous Acid Catalysts*

Heterogeneous catalysts are a suitable alternative to increase the yield of biomass hydrolysis to chemical compounds. There are many advantages of heterogeneous catalysts over homogeneous catalysis, including easy separation of the product, recyclability, minor damage to the reactor, economic efficiency, and respect for the environment. Due to these advantages, much has been investigated in recent years regarding the use of heterogeneous catalysts to generate glucose from cellulose (Huang and Fu 2013; Qiu et al. 2018). Solid acid catalysts for hydrolysis of cellulose into glucose and its subsequent dehydration into platform chemicals include acidic resins, metal oxides, H-form zeolites, functionalized silica, supported metals, and sulfonated carbonaceous-based acids, also known as carbonaceous solid acids (Huang and Fu 2013; Hu et al. 2015a).

Lanzafame et al. (2012) studied the direct catalytic conversion of cellulose to glucose and 5-hydroxymethylfurfural in water under moderate reaction conditions using solid microporous and mesoporous acid catalysts, and they reiterate the pros of heterogeneous catalysis rather than other routes. According to the authors, solid acid catalysts are not only efficient in the selective hydrolysis of cellulose to glucose in aqueous solution but overcome the many problems inherent to the other routes. Among these problems are the large volume of salts produced when homogeneous acids, such as sulfuric acid, are used in the reaction; the high energy consumption due to intense biomass pretreatment, for example, by steam explosion or ball mill,

necessary when opting for enzymatic conversion; and costs incurred by separating organic solvents or ionic liquids, as well as the environmental impact caused by them (Lanzafame et al. 2012).

Nevertheless, it is worth mentioning that although the conversion of cellulose to glucose using heterogeneous catalysts shows a promising pathway, cellulose recalcitrance is still a bottleneck. The low solubility of cellulose in water and the resistance to mass transfer between solid cellulose and solid catalysts are still a remarkable challenge to achieve the highly selective production of glucose in aqueous media (Qiu et al. 2018). Moreover, experiments reported in the literature have often been made using conditions far removed from those necessary for the possible industrial exploitation of the results, in particular high catalyst/cellulose ratios and the use of expensive physical pretreatments in energy or non-environmentally friendly chemical pretreatments, as well as high reaction temperatures (Lanzafame et al. 2012).

According to Huang and Fu (2013), regarding polymer-based acids or acidic resins, styrene-divinylbenzene resins with sulfonic groups (-$SO_3H$), known as Amberlyst, are well known for their availability in the market at affordable prices and for being stable in most solvents. Moreover, their macroporous structures allow small molecules to enter the pores and interact with the most active acid sites. According to the authors, besides the Amberlyst-type resins, sulfonated tetrafluoroethylene-based fluoropolymer-copolymer, known as Nafion, is another type of solid acid useful for the hydrolysis of cellulose, as well as the so-called porous coordination polymers (PCPs) with sulfonic acid groups, which are a class of porous solids with a wide variety of pore surfaces and pore structures. The authors also cite the use of chloromethyl polystyrene resin (CP) as a support for -$SO_3H$ groups introduced by partial replacement of -Cl groups with sulfanilic acid. The obtained catalyst mimics cellulose, where the -Cl groups play the cellulose-binding role, forming hydrogen bonds, and the sulfonic acid groups (-SO3H) act as the hydrolytic domains (Huang and Fu 2013).

Hegner et al. (2010) carried out the chemical conversion of cellulose into glucose and levulinic acid via hydrolysis under relatively mild reaction conditions, using Nafion and $FeCl_3$ supported on amorphous silica. The authors used a Parr stainless steel reactor charged with 0.94 g of Nafion SAC 13 (amorphous silica-supported Nafion polymer), 2.0 g (6 mmol) of cellulose, and 30 ml of water. The reactor underwent heating cycles (1 day and two sequential periods of 3 days), and at the end of each cycle, the insoluble solid residues (catalyst and unreacted cellulose) were separated by filtration and combined with additional cellulose (1.0 g) and water (30 mL) in order to return to the reaction conditions for the next cycle. This process, also applied to $FeCl_3$, was repeated to determine the recyclability of the catalyst. At the end of the experiment, the authors found that the hydrolysis of cellulose by Nafion SAC 13 is highly temperature dependent, with the increase of temperature from 130 °C to 190 °C leading to the improvement of conversion rates in glucose – which they attributed to the increased solubilization of cellulose with temperature. Significant concentrations of levulinic acid were observed when the temperature and retention time raised, and the catalyst had good recyclability. The

hydrolysis of cellulose by $FeCl_3$ supported in silica gave similar results, except for the less efficient recyclability of the catalyst due to the leaching of $Fe^{3+}$ (Hegner et al. 2010).

To produce levulinic acid, Alonso et al. (2013) used Amberlyst 70 as a catalyst and gamma-valerolactone (GVL), which is a levulinic acid-derived product, as a solvent for solubilization of cellulose at 159 °C. The goal was to obtain more gamma-valerolactone from levulinic acid with a second reaction using a RuSn catalyst. According to the authors, due to the better solubility of cellulose in GVL, the interactions between the cellulose and solid acid catalyst are facilitated, which means that the accessibility of the sugar oligomers to the acid sites, where the dehydration reactions occur, increases. This phenomenon may allow the production of levulinic acid under mild conditions without the need for a pretreatment step or the use of salts that can exchange with the protons of the solid catalysts leading to homogeneous catalysis. The authors achieved promising results with a solution of 90% (w/w) GVL and 10% (w/w) water, with levulinic acid yields of 69% for cellulose hydrolysis and 54% for direct hydrolysis of corn stover, both after 16 h.

Metal oxides, porous solid catalysts with many Lewis acid sites and having a large specific surface area, can be applied for hydrolysis of sucrose, cellobiose, and even cellulose (Huang and Fu 2013). Aiming to overcome the low catalytic efficiency of metal oxides for raw cellulose conversion, partially due to the small surface contact area between the metallic oxides and the raw cellulose in water, and also to avoid heavy pretreatments, Jing et al. (2018) combined in situ carbonic acid, which acted as Brønsted acid in the reaction, and the metal oxides $ZrO_2$ and $TiO_2$ to obtain hydroxymethylfurfural. According to the authors, the in situ carbonic acid condition obtained by light acidification of the medium with $CO_2$ improved the conversion of cellulose catalyzed by $TiO_2$ and $ZrO_2$, achieving a hydroxymethylfurfural yield of 48.4%.

Yang et al. (2013) carried out studies involving the direct degradation of cotton cellulose into hydroxymethylfurfural, glucose, and oligosaccharides, using mixed metal oxide catalysts based on zirconia ($ZrO_2$ – zirconium oxide). Degradation of cotton cellulose was carried out under the hydrothermal conditions of 189.85 °C and 1.4 MPa by testing the following mixed metal oxide catalysts: $Na_2O$-$ZrO_2$, $K_2O$-$ZrO_2$, CaO-$ZrO_2$, MgO-$ZrO_2$e, and ZnO-$ZrO_2$. According to the authors, the introduction of $ZrO_2$ promoted the conversion of cellulose and resulted in the production of fructose by isomerization of glucose, except for MgO-$ZrO_2$, which presented a meager glucose yield of only 0.16%. ZnO-$ZrO_2$ showed the best catalytic performance, which the authors attributed to their higher density of acidic sites. The conversion rate of cotton cellulose with ZnO-$ZrO_2$ was 60.64%, an increase of 40.76% over the reaction without a catalyst under hydrothermal conditions only. The hydroxymethylfurfural yield increased by 41.46% compared to the reaction conducted without a catalyst; however, it represented a yield of only 5.8%. Further experiments were then performed, and a better hydroxymethylfurfural yield of 10.05% was obtained for a hydrothermal temperature of 199.85 °C, a reaction time of 6 h, and ZnO-$ZrO_2$ catalyst loading of 0.2 g (Yang et al. 2013).

Zeolites are three-dimensional crystalline aluminosilicates, whose main characteristic is that their primary tetrahedral blocks are connected through oxygen atoms, producing a three-dimensional network containing channels and cavities of molecular dimensions (Corma 1995). The tetrahedral atoms that constitute the structural unit of construction of the zeolites are silicon (Si) and/or aluminum (Al). In the case of the H-form zeolites, the oxygen atom connecting the Si and Al tetrahedra is linked to hydrogen, thus forming the Brønsted acid sites, which are responsible for the acidity of the H-form zeolites (Gomes 2016).

H-form zeolites have catalytic activity for cellulose hydrolysis. Onda et al. (2008) reported a chemically green process for selective hydrolysis of cellulose into glucose using H-form zeolites varying their structures and Si/Al ratio, under the temperature of 150 °C in water, using filtration to separate the products and catalysts. The zeolites used were H-beta (12) (Si/Al = 12), H-beta (75) (Si/Al = 75), H-mordenite (10) (Si/Al = 10), and H-ZSM5 (45) (Si/Al = 45). The authors also investigated sulfated zirconia, ion exchange resin, and sulfonated activated carbon for the hydrolysis of cellulose under the same hydrothermal conditions. According to the authors, zeolite catalysts with high Si/Al ratio showed a higher activity for glucose formation than those with lower Si/Al ratio. The sulfonated activated carbon catalyst, however, showed higher catalytic activity and glucose selectivity than the catalysts made with zeolites, which, according to the authors, may be due to the higher hydrophobic character of this catalyst and the strongly acidic functional -$SO_3H$ groups present on its surface (Onda et al. 2008).

Among the various types of acidic solids for cellulose hydrolysis, carbon-based solid (or carbonaceous) acids stand out because they have better catalytic activities (Huang and Fu 2013). These solids have been prepared by the incomplete carbonization of natural organic matter and the subsequent addition of sulfonic radicals to the resulting amorphous carbons in the presence of concentrated sulfuric acid, fuming sulfuric acid, or chlorosulfonic acid for hydrolysis of cellulose (Hu et al. 2015a).

Hara et al. (2004) were the first to report the synthesis of a strong and stable carbonaceous solid acid with a high density of sulfonic acid groups (-$SO_3H$). Through incomplete carbonization of sulfoaromatic hydrocarbons, the authors obtained an amorphous carbon material consisting of polycyclic aromatic carbon sheets with attached -$SO_3H$ groups, functioning as a strong solid acid with a high density of acid sites. One year later, based on the work of Hara et al. (2004), Toda et al. (2005) carbonized D-glucose and sucrose incompletely under a low temperature (> 300 °C) to induce pyrolysis and formation of small polycyclic aromatic carbon rings. The result was a rigid carbon material comprising small polycyclic aromatic carbon sheets in a three-dimensional structure of sp3 bonds. Subsequently, sulfonic groups (-$SO_3H$) were introduced by sulfuric acid, under 150 ° C, and the catalyst obtained was then tested for the catalysis of the esterification reaction of oleic acid and stearic acid to produce biodiesel. The authors report an efficiency of more than half of a liquid sulfuric acid catalyst and much higher than the efficiency achieved by conventional solid acid catalysts.

Another interesting approach to obtain carbonaceous catalysts consists of solvent-free carbonization, that is, mechanochemical synthesis of these acidic sol-

ids. Shrotri et al. (2016) worked on a mechanochemical approach to oxidase carbon to prepare carbonaceous catalysts with a high density of carboxyl groups and use them for the hydrolysis of cellulose. According to the authors, oxygenated carbon catalysts can use their weak acidic functional groups to hydrolyze the glycosidic bonds, and unlike the sulfonated carbonaceous catalysts, they last much longer under the hydrothermal conditions required for the polysaccharide hydrolysis reaction. For the mechanochemical oxidation to preferentially oxidize the carbon to introduce carboxylic groups without incorporation of sulfonated groups, the authors ground persulfate salts (potassium peroxymonosulfate, $KHSO_5$, and ammonium persulfate, $(NH_4)_2S_2O_8$; oxidizing agents) in a ball mill with activated carbon, without any solvent. The catalysts obtained were active for cellulose hydrolysis and subsequent glucose production, where the oxidized $KHSO_5$ carbon showed the highest activity and a glucose yield of 85% (reaction time of 20 min, 180 °C, presence of HCl at 0.012% (m/m), high-pressure reactor, and cellulose and catalyst ground together by ball milling prior to the reaction) (Shrotri et al. 2016).

Qiu et al. (2018) also synthesized a carbonaceous solid acid catalyst through solvent-free carbonization. Initially, two types of catalysts containing -$SO_3H$ groups were prepared with p-toluenesulfonic acid. The first was made from sucralose, which provides -Cl groups, and the other one was made from sucrose, which does not offer -Cl groups, aiming to promote cellulose hydrolysis in the water at 200 °C for 1 h with a ratio mass cellulose to the catalyst of 1:2, without any pretreatment. After observing the higher activity of the catalyst obtained from sucralose, due to the presence of -Cl groups, which provide better contact between the cellulose molecules and the active sites of the catalyst via hydrogen bonding, new tests were carried out to verify the effects of a pretreatment with ball milling and the use of sulfuric acid. The best glucose yield found by the authors was 71%, obtained when cellulose was mixed with the catalyst in a ball mill and hydrolyzed in an aqueous solution of sulfuric acid diluted to 0.02% (w/w).

Lignin, a significant but underused fraction of the biomass, was used by Hu et al. (2015b) to make one-dimensional (1D) solid acid catalysts for direct hydrolysis of crystalline cellulose and simultaneous production of sugars and nanocellulose (nanostructured cellulose). To obtain these catalysts, precursor fibers of nanoscale diameters obtained from lignin electrospinning were simultaneously carbonized and activated at 900 °C to generate activated carbon fibers of submicron size with a large specific surface area (1400 $m^2/g$) and large pore volumes (0.7 $cm^3/g$). The 1D solid acid catalysts were then obtained from the sulfonation of these activated carbon fibers using concentrated sulfuric acid at a temperature of 150 °C, with subsequent heating in the water at 150 °C, under 5 atm pressure, for 24 h, to obtain a hydrothermally treated sulfonated activated carbon fiber catalyst. This catalyst was then used in the direct hydrolysis of highly crystalline rice straw cellulose under the hydrothermal conditions of 150 °C and 5 atm, hydrolyzing 77.9% of cellulose in three consecutive runs, producing 64% glucose (selectivity of 91.7%) and 8.1% of cellulose nanofibrils (Hu et al. 2015b).

## 5 Conclusions

The structural complexity of lignocellulosic biomass was discussed, formed by a tight interaction among cellulose, hemicellulose, and lignin. We also addressed how each of these fractions can be used as raw material to obtain several bioproducts by different processes, encouraging their industrial application.

The need for biomass pretreatments was also considered to reduce its recalcitrance and remove the hemicellulose and lignin fractions, making the cellulose more accessible. Different pretreatment processes – physical, chemical, physicochemical, and biological – were presented. Their main advantages and disadvantages were addressed, noting that among the most used processes are acids, alkalis, steam explosion, AFEX, ionic liquids, and supercritical fluids.

After the pretreatment stage, soluble oligosaccharides were converted to monosaccharides by hydrolysis processes, and then monosaccharides (mainly glucose) were converted to bioenergy and high-value-added intermediary chemicals. These include ethanol, furfural, hydroxymethylfurfural, and levulinic acid. Homogeneous or heterogeneous catalysts can be used at this stage, but homogeneous catalysts have been associated with high toxicity, corrosion, and inefficient reutilization. On the other hand, heterogeneous catalysts, principally solid acid catalysts (acidic resins, metal oxides, H-form zeolites, functionalized silica, supported metals, and sulfonated carbonaceous-based acids) were chosen because they do not present the disadvantages of homogeneous catalysts and they offer advantages such as high hydrolysis yield and easy catalyst separation from the reaction mixture with a reduction of process stages and wastes.

Despite the advances already accomplished, indicating that the use of acidic solid catalysts is a good alternative for the hydrolysis of cellulose in aqueous medium under mild or moderate reaction conditions to obtain platform chemicals of industrial interest, most of them were made on a laboratory scale. Therefore, as a future perspective, there is a great need to have studies for biomass conversion using heterogeneous catalysts in full scale, aiming at implementing these green processes in the biorefinery industry.

New research must focus on design and use of heterogeneous catalysts to improve the biomass conversion in biofuels and platform chemicals with higher yield, reusability, versatility, and stability associated with the reduction of production cost.

**Acknowledgements** The authors are grateful to the São Paulo Research Foundation - FAPESP (Process BIOEN #2016/23209-0) and Coordenacão de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for financial support.

## References

Alonso DM, Gallo JMR, Mellmer MA, Wettstein SG, Dumesic JA. Direct conversion of cellulose to levulinic acid and gamma-valerolactone using solid acid catalysts. Cat Sci Technol. 2013;3(4):927–31. https://doi.org/10.1039/c2cy20689g.

Antonetti C, Licursi D, Fulignati S, Valentini G, Galletti AMR. New frontiers in the catalytic synthesis of levulinic acid: from sugars to raw and waste biomass as starting feedstock. Catalysts. 2016;6(196):1–29. https://doi.org/10.3390/catal6120196.

Badgujar KC, Wilson LD, Bhanage BM. Recent advances for sustainable production of levulinic acid in ionic liquids from biomass: current scenario, opportunities and challenges. Renew Sust Energ Rev. 2019;102:266–84. https://doi.org/10.1016/j.rser.2018.12.007.

Bai J, Ren Y, Li Y, Fan M, Qian H, Wang L, Wu G, Zhang H, Qi X, Xu M, Rao Z. Physiological functionalities and mechanisms of β-glucans. Trends Food Sci Technol. 2019;88:57–66. https://doi.org/10.1016/j.tifs.2019.03.023.

Baig KS, Wu J, Turcotte G. Future prospects of delignification pre-treatments for the lignocellulosic materials to produce second generation bioethanol. Int J Energy Res. 2019;43(4):1411–27. https://doi.org/10.1002/er.4292.

Ballesteros LF, Teixeira JA, Mussatto SI. Chemical, functional, and structural properties of spent coffee grounds and coffee silverskin. Food Bioprocess Technol. 2014;7(12):3493–503. https://doi.org/10.1007/s11947-014-1349-z.

Benazzi T, Calgaroto S, Astolfi V, Dalla Rosa C, Oliveira JV, Mazutti MA. Pre-treatment of sugarcane bagasse using supercritical carbon dioxide combined with ultrasound to improve the enzymatic hydrolysis. Enzym Microb Technol. 2013;52(4):247–50. https://doi.org/10.1016/j.enzmictec.2013.02.001.

Bozbulut R, Sanlier N. Promising effects of β-glucans on glyceamic control in diabetes. Trends Food Sci Technol. 2019;83:159–66. https://doi.org/10.1016/j.tifs.2018.11.018.

Bozell JJ, Petersen GR. Technology development for the production of biobased products from biorefinery carbohydrates – the US Department of Energy's "Top 10" revisited. Green Chem. 2010;12(4):539–54. https://doi.org/10.1039/b922014c.

Brodeur G, Yau E, Badal K, Collier J, Ramachandran KB, Ramakrishnan S. Chemical and physicochemical pre-treatment of lignocellulosic biomass: a review. Enzym Res. 2011;2011:17. https://doi.org/10.4061/2011/787532.

Bychkov A, Podgorbunskikh E, Bychkova E, Lomovsky O. Current achievements in the mechanically pretreated conversion of plant biomass. Biotechnol Bioeng. 2019;116(5):1231–44. https://doi.org/10.1002/bit.26925.

Canettieri EV, da Silva VP, Neto TGS, Hernández-Pérez AF, da Silva DDV, Dussán KJ, das Graças Almeida Felipe M, de Carvalho JA. Physicochemical and thermal characteristics of sugarcane straw and its cellulignin. J Braz Soc Mech Sci Eng. 2018;40(9):416. https://doi.org/10.1007/s40430-018-1331-1.

Cantero D, Jara R, Navarrete A, Pelaz L, Queiroz J, Rodríguez-Rojo S, Cocero MJ. Pre-treatment processes of biomass for biorefineries: current status and prospects. Annu Rev Chem Biomol Eng. 2019;10(1):289–310. https://doi.org/10.1146/annurev-chembioeng-060718-030354.

Chio C, Sain M, Qin W. Lignin utilization: a review of lignin depolymerization from various aspects. Renew Sust Energ Rev. 2019;107:232–49. https://doi.org/10.1016/j.rser.2019.03.008.

Choi YH, Verpoorte R. Green solvents for the extraction of bioactive compounds from natural products using ionic liquids and deep eutectic solvents. Curr Opin Food Sci. 2019;26:87–93. https://doi.org/10.1016/j.cofs.2019.04.003.

Corma A. Inorganic solid acids and their use in acid-catalyzed hydrocarbon reactions. Chem Rev. 1995;95(3):559–614. https://doi.org/10.1021/cr00035a006.

Deutschmann R, Dekker RFH. From plant biomass to bio-based chemicals: latest developments in xylan research. Biotechnol Adv. 2012;30(6):1627–40. https://doi.org/10.1016/j.biotechadv.2012.07.001.

do Rosario MMT, Noleto GR, Petkowicz CLD. Degalactosylation of xyloglucans modify their pro-inflammatory properties on murine peritoneal macrophages. Int J Biol Macromol. 2017;105:533–40. https://doi.org/10.1016/j.ijbiomac.2017.07.068.

Dorrestijn E, Laarhoven LJJ, Arends IWCE, Mulder P. The occurrence and reactivity of phenoxyl linkages in lignin and low rank coal. J Anal Appl Pyrolysis. 2000;54(1):153–92. https://doi.org/10.1016/S0165-2370(99)00082-0.

Du B, Bian Z, Xu B. Skin health promotion effects of natural beta-glucan derived from cereals and microorganisms: a review. Phytother Res. 2014;28(2):159–66. https://doi.org/10.1002/ptr.4963.

Farhat W, Venditti RA, Hubbe M, Taha M, Becquart F, Ayoub A. A review of water-resistant hemicellulose-based materials: processing and applications. ChemSusChem. 2017;10:305–23. https://doi.org/10.1002/cssc.201601047.

Farmer TJ, Mascal M. Platform molecules. In: Clark J, Deswarte F, editors. Introduction to chemicals from biomass. 2nd ed. New York: Wiley; 2015. p. 89–155. https://doi.org/10.1002/9781118714478.ch4.

Gao M, Xua F, Li S, Ji X, Chen S, Zhan D. Effect of SC-$CO_2$ pretreatment in increasing rice straw biomass conversion. Biosyst Eng. 2010;106(4):470–5. https://doi.org/10.1016/j.biosystemseng.2010.05.011.

Gomes GJ. Estudo experimental e teórico de zeólitas H-BETA e H-ZSM-5 na produção de ésteres alquílicos. Universidade Estadual do Paraná-Cascavel; 2016.

Gu T, Held MA, Faik A. Supercritical $CO_2$ and ionic liquids for the pre-treatment of lignocellulosic biomass in bioethanol production. Environ Technol. 2013;34(13–14):1735–49. https://doi.org/10.1080/09593330.2013.809777.

Hara M, Yoshida T, Takagaki A, Takata T, Kondo JN, Hayashi S, Domen K. A carbon material as a strong protonic acid. Angew Chem Int Ed. 2004;43:2955–8. https://doi.org/10.1002/anie.200453947.

Hegner J, Pereira KC, DeBoef B, Lucht BL. Conversion of cellulose to glucose and levulinic acid via solid-supported acid catalysis. Tetrahedron Lett. 2010;51(17):2356–8. https://doi.org/10.1016/j.tetlet.2010.02.148.

Henriksson G. Lignin. In: Ek M, Gellerstedt G, Henriksson G, editors. Volume 1: Wood chemistry and wood biotechnology, vol. 1. Berlin/Boston: De Gruyter; 2009. p. 320. https://doi.org/10.1515/9783110213409.

Henriksson G, Lennholm H. Cellulose and carbohydrate chemistry. In: Ek M, Gellerstedt G, Henriksson G, editors. Volume 1: Wood chemistry and wood biotechnology, vol. 1. Berlin/Boston: De Gruyter; 2009. p. 320. https://doi.org/10.1515/9783110213409.

Hu G, Heitmann JA, Rojas OJ. Feedstock pre-treatment strategies for producing ethanol from wood, bark, and forest residues. Bioresources. 2008;3(1):25.

Hu L, Lin L, Wu Z, Zhou S, Liu S. Chemocatalytic hydrolysis of cellulose into glucose over solid acid catalysts. Appl Catal B. 2015a;174–175:225–43. https://doi.org/10.1016/j.apcatb.2015.03.003.

Hu S, Jiang F, Hsieh Y-l. 1D lignin based solid acid catalysts for cellulose hydrolysis into glucose and nanocellulose. ACS Sustain Chem Eng. 2015b;3(10):2566–74. https://doi.org/10.1021/acssuschemeng.5b00780.

Huang YB, Fu Y. Hydrolysis of cellulose to glucose by solid acid catalysts. Green Chem. 2013;15(5):1095–111. https://doi.org/10.1039/c3gc40136g.

Ioelovich MY. Models of supramolecular structure and properties of cellulose. Polym Sci Ser A. 2016;58(6):925–43. https://doi.org/10.1134/S0965545X16060109.

Jing S, Cao X, Zhong L, Peng X, Sun R, Liu J. Effectively enhancing conversion of cellulose to HMF by combining in-situ carbonic acid from $CO_2$ and metal oxides. Ind Crop Prod. 2018;126:151–7. https://doi.org/10.1016/j.indcrop.2018.10.028.

Kang S, Fu J, Zhang G. From lignocellulosic biomass to levulinic acid: a review on acid-catalyzed hydrolysis. Renew Sust Energ Rev. 2018;94:340–62. https://doi.org/10.1016/j.rser.2018.06.016.

Kim J-Y, Lee HW, Lee SM, Jae J, Park Y-K. Overview of the recent advances in lignocellulose liquefaction for producing biofuels, bio-based materials and chemicals. Bioresour Technol. 2019;279:373–84. https://doi.org/10.1016/j.biortech.2019.01.055.

Kucharska K, Rybarczyk P, Holowacz I, Lukajtis R, Glinka M, Kaminski M. Pre-treatment of lignocellulosic materials as substrates for fermentation processes. Molecules. 2018;23(11):E2937. https://doi.org/10.3390/molecules23112937.

Kulkarni AD, Joshi AA, Patil CL, Amale PD, Patel HM, Surana SJ, Belgamwar VS, Chaudhari KS, Pardeshi CV. Xyloglucan: a functional biomacromolecule for drug delivery applications. Int J Biol Macromol. 2017;104:799–812. https://doi.org/10.1016/j.ijbiomac.2017.06.088.

Lanzafame P, Temi DM, Perathoner S, Spadaro AN, Centi G. Direct conversion of cellulose to glucose and valuable intermediates in mild reaction conditions over solid acid catalysts. Catal Today. 2012;179(1):178–84. https://doi.org/10.1016/j.cattod.2011.07.018.

Lauwaert J, Stals I, Lancefield CS, Deschaumes W, Depuydt D, Vanlerberghe B, Devlamynck T, Bruijnincx PCA, Verberckmoes A. Pilot scale recovery of lignin from black liquor and advanced characterization of the final product. Sep Purif Technol. 2019;221:226–35. https://doi.org/10.1016/j.seppur.2019.03.081.

Lee SH, Lee SB. The Hildebrand solubility parameters, cohesive energy densities and internal energies of 1-alkyl-3-methylimidazolium-based room temperature ionic liquids. Chem Commun. 2005;27:3469–71. https://doi.org/10.1039/B503740A.

Lee SH, Doherty TV, Linhardt RJ, Dordick JS. Ionic liquid-mediated selective extraction of lignin from wood leading to enhanced enzymatic cellulose hydrolysis. Biotechnol Bioeng. 2009;102(5):1368–76. https://doi.org/10.1002/bit.22179.

Malgas S, van Dyk JS, Pletschke BI. A review of the enzymatic hydrolysis of mannans and synergistic interactions between β-mannanase, β-mannosidase and α-galactosidase. World J Microbiol Biotechnol. 2015;31(8):1167–75. https://doi.org/10.1007/s11274-015-1878-2.

Maurya DP, Singla A, Negi S. An overview of key pre-treatment processes for biological conversion of lignocellulosic biomass to bioethanol. 3 Biotech. 2015;5(5):597–609. https://doi.org/10.1007/s13205-015-0279-4.

McNamara JT, Morgan JLW, Zimmer J. A molecular description of cellulose biosynthesis. Annu Rev Biochem. 2015;84(1):895–921. https://doi.org/10.1146/annurev-biochem-060614-033930.

Mika LT, Cséfalvay E, Németh A. Catalytic conversion of carbohydrates to initial platform chemicals: chemistry and sustainability. Chem Rev. 2018;118:505–613. https://doi.org/10.1021/acs.chemrev.7b00395.

Mosier N, Wyman C, Dale B, Elander R, Lee YY, Holtzapple M, Ladisch M. Features of promising technologies for pre-treatment of lignocellulosic biomass. Bioresour Technol. 2005;96(6):673–86. https://doi.org/10.1016/j.biortech.2004.06.025.

Motaung TE, Linganiso LZ. Critical review on agrowaste cellulose applications for biopolymers. Int J Plast Technol. 2018;22(2):185–216. https://doi.org/10.1007/s12588-018-9219-6.

Naidu DS, Hlangothi SP, John MJ. Bio-based products from xylan: a review. Carbohydr Polym. 2018;179:28–41. https://doi.org/10.1016/j.carbpol.2017.09.064.

Narayanaswamy N, Faik A, Goetz DJ, Gu T. Supercritical carbon dioxide pre-treatment of corn stover and switchgrass for lignocellulosic ethanol production. Bioresour Technol. 2011;102(13):6995–7000. https://doi.org/10.1016/j.biortech.2011.04.052.

Onda A, Ochi T, Yanagisawa K. Selective hydrolysis of cellulose into glucose over solid acid catalysts. Green Chem. 2008;10(10):1033–7. https://doi.org/10.1039/b808471h.

Pauly M, Keegstra K. Biosynthesis of the plant cell wall matrix polysaccharide xyloglucan. Annu Rev Plant Biol. 2016;67(1):235–59. https://doi.org/10.1146/annurev-arplant-043015-112222.

Philippini RR, Martiniano SE, Chandel AK, de Carvalho W, da Silva SS. Pre-treatment of sugarcane bagasse from cane hybrids: effects on chemical composition and 2G sugars recovery. Waste Biomass Valoriz. 2019;10(6):1561–70. https://doi.org/10.1007/s12649-017-0162-0.

Pique N, Gomez-Guillen MD, Montero MP. Xyloglucan, a plant polymer with barrier protective properties over the mucous membranes: an overview. Int J Mol Sci. 2018;19(3):19. https://doi.org/10.3390/ijms19030673.

Qiu Z, Aita GM, Walker MS. Effect of ionic liquid pre-treatment on the chemical composition, structure and enzymatic hydrolysis of energy cane bagasse. Bioresour Technol. 2012;117:251–6. https://doi.org/10.1016/j.biortech.2012.04.070.

Qiu M, Bai C, Yan L, Shen F, Qi X. Efficient mechanochemical-assisted production of glucose from cellulose in aqueous solutions by carbonaceous solid acid catalysts. ACS Sustain Chem Eng. 2018;6(11):13826–33. https://doi.org/10.1021/acssuschemeng.8b01910.

Ravindran R, Jaiswal AK. A comprehensive review on pre-treatment strategy for lignocellulosic food industry waste: challenges and opportunities. Bioresour Technol. 2016;199:92–102. https://doi.org/10.1016/j.biortech.2015.07.106.

Scheller HV, Ulvskov P. Hemicelluloses. Annu Rev Plant Biol. 2010;61(1):263–89. https://doi.org/10.1146/annurev-arplant-042809-112315.

Schröder R, Atkinson RG, Redgwell RJ. Re-interpreting the role of endo-β-mannanases as mannan endotransglycosylase/hydrolases in the plant cell wall. Ann Bot. 2009;104(2):197–204. https://doi.org/10.1093/aob/mcp120%.

Shahabazuddin M, Sarat Chandra T, Meena S, Sukumaran RK, Shetty NP, Mudliar SN. Thermal assisted alkaline pre-treatment of rice husk for enhanced biomass deconstruction and enzymatic saccharification: Physico-chemical and structural characterization. Bioresour Technol. 2018;263:199–206. https://doi.org/10.1016/j.biortech.2018.04.027.

Sharma V, Nargotra P, Bajaj BK. Ultrasound and surfactant assisted ionic liquid pre-treatment of sugarcane bagasse for enhancing saccharification using enzymes from an ionic liquid tolerant Aspergillus assiutensis VS34. Bioresour Technol. 2019;285:121319. https://doi.org/10.1016/j.biortech.2019.121319.

Shrotri A, Kobayashi H, Fukuoka A. Efficient catalytic conversion of cellulose to platform chemicals using mechanical treatment. J Jpn Pet Inst. 2015;58(1):1–8. https://doi.org/10.1627/jpi.58.1.

Shrotri A, Kobayashi H, Fukuoka A. Mechanochemical synthesis of a carboxylated carbon catalyst and its application in cellulose hydrolysis. ChemCatChem. 2016;8(6):1059–64. https://doi.org/10.1002/cctc.201501422.

Singh SK. Solubility of lignin and chitin in ionic liquids and their biomedical applications. Int J Biol Macromol. 2019;132:265–77. https://doi.org/10.1016/j.ijbiomac.2019.03.182.

Singh S, Singh G, Arya SK. Mannans: an overview of properties and application in food products. Int J Biol Macromol. 2018;119:79–95. https://doi.org/10.1016/j.ijbiomac.2018.07.130.

Sun SN, Sun SL, Cao XF, Sun RC. The role of pre-treatment in improving the enzymatic hydrolysis of lignocellulosic materials. Bioresour Technol. 2016;199:49–58. https://doi.org/10.1016/j.biortech.2015.08.061.

Tan SSY, MacFarlane DR, Upfal J, Edye LA, Doherty WOS, Patti AF, Pringle JM, Scott JL. Extraction of lignin from lignocellulose at atmospheric pressure using alkylbenzenesulfonate ionic liquid. Green Chem. 2009;11(3):339–45. https://doi.org/10.1039/B815310H.

Teleman A. Hemicelluloses and pectins. In: Ek M, Gellerstedt G, Henriksson G, editors. Volume 1: Wood chemistry and wood biotechnology, vol. 1. Berlin/Boston: De Gruyter; 2009. p. 320. https://doi.org/10.1515/9783110213409.

Ten E, Vermerris W. Recent developments in polymers derived from industrial lignin. J Appl Polym Sci. 2015;132(24). https://doi.org/10.1002/app.42069.

Tester RF, Al-Ghazzewi FH. Mannans and health, with a special focus on glucomannans. Food Res Int. 2013;50(1):384–91. https://doi.org/10.1016/j.foodres.2012.10.037.

Toda M, Takagaki A, Okamura M, Kondo JN, Hayashi S, Domen K, Hara M. Biodiesel made with sugar catalyst. Nature. 2005;438:178. https://doi.org/10.1038/438177a.

Tohamy AA, El-Ghor AA, El-Nahas SM, Noshy MM. β-Glucan inhibits the genotoxicity of cyclophosphamide, adriamycin and cisplatin. Mutat Res/Genet Toxicol Environ Mutagen. 2003;541(1):45–53. https://doi.org/10.1016/S1383-5718(03)00184-0.

Tolesa LD, Gupta BS, Lee M-J. Treatment of coffee husk with ammonium-based ionic liquids: lignin extraction, degradation, and characterization. ACS Omega. 2018;3(9):10866–76. https://doi.org/10.1021/acsomega.8b01447.

Vaid S, Bajaj BK. Production of ionic liquid tolerant cellulase from Bacillus subtilis G2 using agroindustrial residues with application potential for Saccharification of biomass under one pot consolidated bioprocess. Waste Biomass Valoriz. 2017;8(3):949–64. https://doi.org/10.1007/s12649-016-9626-x.

Yang F, Li G, Gao P, Lv XN, Sun X, Liu ZH, Fan H. Mild hydrothermal degradation of cotton cellulose by using a mixed-metal-oxide ZnO–$ZrO_2$ catalyst. Energ Technol. 2013;1(10):581–6. https://doi.org/10.1002/ente.201300068.

Yang S, Zhang Y, Yue W, Wang W, Wang YY, Yuan TQ, Sun RC. Valorization of lignin and cellulose in acid-steam-exploded corn stover by a moderate alkaline ethanol post-treatment based on an integrated biorefinery concept. Biotechnol Biofuels. 2016;9:14. https://doi.org/10.1186/s13068-016-0656-1.

Zhu F, Du B, Xu B. A critical review on production and industrial applications of beta-glucans. Food Hydrocoll. 2016;52:275–88. https://doi.org/10.1016/j.foodhyd.2015.07.003.

# Production of Reduced Graphene Oxide (rGO) from Battery Waste: Green and Sustainable Synthesis and Reduction


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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_13

# 1 Introduction

## *1.1 Battery and Its Recycling*

Improvements in quality of life and technological advance have resulted in increased consumption of electric and electronic portable equipment around the world. As a consequence, household batteries are highly demanded to powering electric and electronic daily life devices as portable radios, telephones, clocks, flashlights, remote controls, toys, GPS, and so on (Dolci et al. 2016; Charef et al. 2017; Kalmykova et al. 2017; Bandi et al. 2019). In order to meet the requirements of electric and electronic equipment, there are a variety of household batteries available in the market. It is available in sizes AAA, AA, C, D, and 9 V (Krekeler et al. 2012) as can be seen in Fig. 1.

The household batteries can be classified as primary cells (single use and non-rechargeable) and secondary cells (rechargeable). The most common household batteries used are the primary zinc-carbon (dry cell), zinc-manganese dioxide (alkaline), and lithium-manganese dioxide, and the secondary are nickel-cadmium, nickel-metal hybrid, and lithium-ion (Terazono et al. 2015; Sun et al. 2015). The zinc-carbon dry cell is the widely used of all primary battery, especially in developing countries, due to its good performance, wide availability, and low cost, which is its major attractiveness (Khan et al. 2013).

The zinc-carbon battery (Fig. 2) consists basically of a positive electrode (cathode), negative electrode (anode), and an immobilized electrolyte separating both, which is why it is called dry cell. The cathode is a graphite rod, generally cylindrical, positioned at the center of the cell, surrounded by a mixture of manganese dioxide and carbon powder. As a second layer, the cell has the immobilized electrolyte, a paste formed by the mixture of ammonium chloride and zinc chloride, which are wrapped by the zinc case that is the anode (Bandi et al. 2019). The zinc electrode usually contains lead and cadmium in its alloy to improve its mechanical properties and can have a mercury coat to reduce its corrosion and enhance the cell performance (Bernardes et al. 2004).

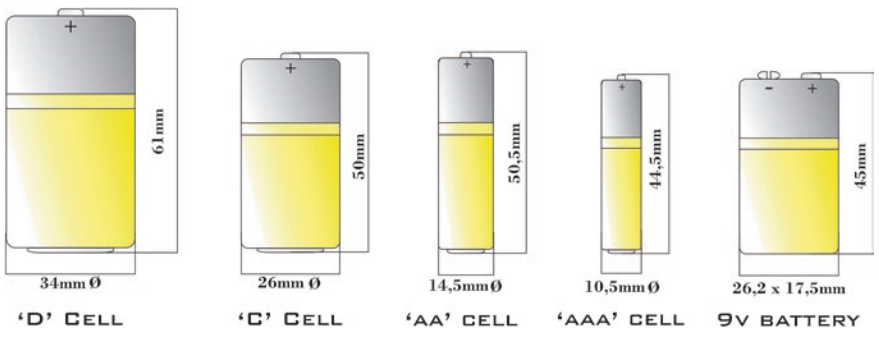


**Fig. 1** The most common standard battery sizes

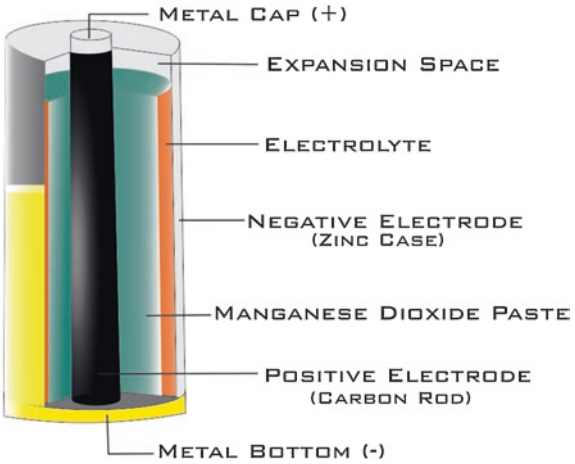


**Fig. 2** Zinc-carbon battery internal structure

The used batteries at the end of their useful lives, if they are not correctly discarded they may affect the health and the environment. They probably will be incinerated or disposed into municipal landfill (Dolci et al. 2016; Patricio et al. 2015; Gallegos et al. 2018). This practice increases the concentrations of heavy metals in landfill leachate (Guevara-García and Montiel-Corona 2012; Fikri et al. 2015), contaminating soil and water and increasing the concentration of metals in flue gas and solid residues (ashes) when incinerated (Bigum et al. 2017; Astrup et al. 2011).

Although it is very important to correctly collect and recycle spent batteries both in terms of resource recovery and hazardous substance control, their collection rate is still small (Sun et al. 2015; Ebin et al. 2016). The companies and researches of battery recycling process are only focusing on metal recovery like zinc, cadmium, manganese, and others (Biswas et al. 2016; Ebin et al. 2019; Ippolito et al. 2016; Petranikova et al. 2018; Sobianowska-Turek et al. 2016; Singh et al. 2017). Thus, the graphite rod is usually being burnt, incinerated, or disposed as residue (Bandi et al. 2019).

## *1.2 Graphene and Its Derivatives*

Carbon was one of the first elements known to humans and is one of the most remarkable of all chemical elements (Zhen and Zhu 2018). Worldwide, the use of carbon-based materials as graphite (Gurzęda and Krawczyk 2019; Yang and Zuo 2019), carbon nanotubes (Noé et al. 2018; Rahman et al. 2019), and graphene (Ali 2019; Pogacean et al. 2019) for an infinity of applications has been increasing daily year by year (Collins et al. 2019; Zaytseva and Neumann 2016; Meng et al. 2017; Metzelder et al. 2018).

Graphene was discovered in 2004 by Nobel laureates Geim and Novoselov (Geim and Novoselov 2007). And since then, various industry sectors and researchers

have shown interest in the area, mainly in physics (Dresselhaus and Araujo 2010), materials science (Papageorgiou et al. 2019), energy storage (Wei et al. 2019), supercapacitors (Le Fevre et al. 2019), sensors (Zhang and Fahrenthold 2019), biomedicine (Ma et al. 2018), and environmental technologies (Yap et al. 2019).

This huge interest throughout the world is due to graphene exhibiting superior chemical, magnetic, optical, electrical, and mechanical properties (Fadeel et al. 2018; Hashimoto et al. 2019) over other materials already developed, and the industry projects a demand above 4000 tons year$^{-1}$ by 2026 (Achee et al. 2018).

The term graphene has been incorrectly used to represent graphene derivatives, namely, graphene oxide (GO) and reduced graphene oxide (rGO), leading to a large confusion of names in the literature (Kumar and Pattammattel 2017) (Fig. 3). Pristine graphene is a two-dimensional molecule and consists of a perfectly flat sheet of sp$^2$-hybridized carbon atoms. This sheet is extremely compact and has a single carbon layer thickness arranged in a honeycomb hexagonal structure through σ- and π-bonds (Ali et al. 2019).

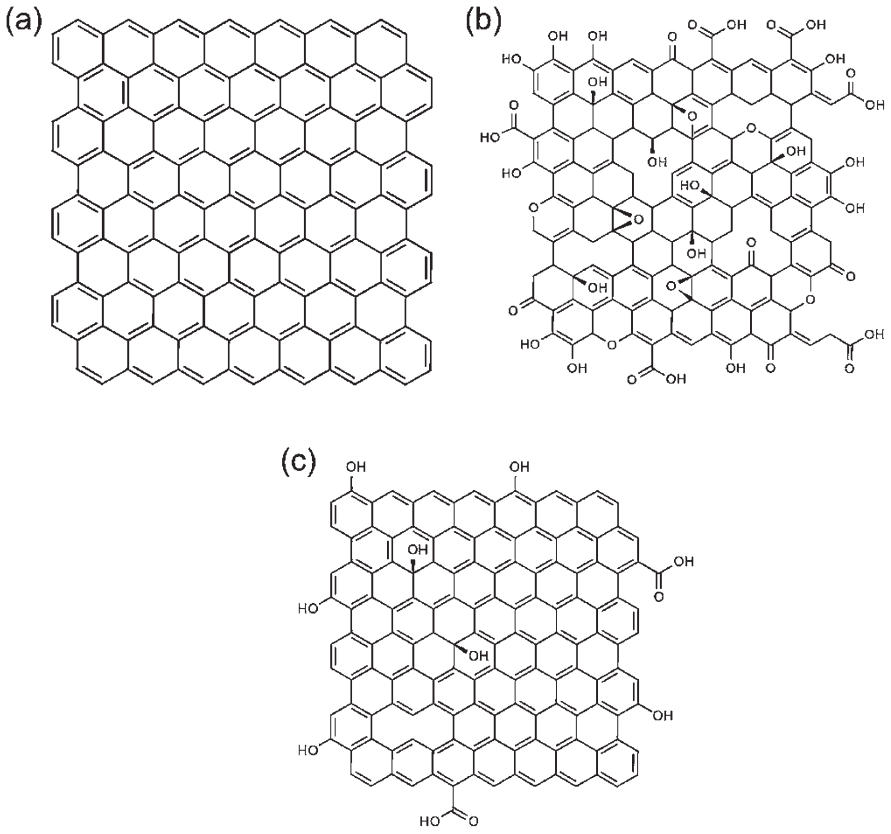


**Fig. 3** The representative structure of graphene (**a**), graphene oxide (**b**), and reduced graphene oxide (**c**)

GO is the oxidized form of graphene obtained through the oxidation of graphite that has in its structure several functional groups that contain reactive oxygen, such as hydroxyl, carboxylic acid, carbonyl, and alkoxy, among others. The GO sheets mainly consist of $sp^2$-hybridized carbon atoms, but when the carbon atoms are bonded to the oxygen-containing groups, they have $sp^3$ hybridized and can be displaced below or above the graphene plane (Pei and Cheng 2012; Smith et al. 2019; Tahriri et al. 2019).

GO sheets may contain defects, wrinkles, structural disorder, latches, vacancies, impurities, fragmentation, and other structural problems due to the oxidation process. These structural problems can affect the properties of the GO produced. In order to correct or diminish these imperfections, the GO can be reduced to rGO. The reduction process not only consists in the elimination of oxygenated functional groups but also in the production of a graphene-like material that can have its properties improved (de Silva et al. 2018; Lee et al. 2019; Smith et al. 2019).

## *1.3 Synthesis of GO*

Graphene was obtained by Novoselov and coworkers through graphite stripping exfoliation (Novoselov et al. 2004). Since then, two synthetic routes have been performed to produce graphene from graphite. Since then, two synthetic routes have been made to produce graphene from graphite. The first one is bottom-up methods that are based on the chemical deposition of graphene onto a substrate, and top-down methods are based on mechanical or electrochemical exfoliation of graphite (Ali et al. 2019; Smith et al. 2019). Thus, GO can be prepared by thermal synthesis (Huang et al. 2018; Bleu et al. 2019), micromechanical exfoliation (Yi and Shen 2015; Sinclair et al. 2019), microwave synthesis (Fei et al. 2018; Xie et al. 2019), chemical vapor deposition (Sultanov et al. 2019; Moreno-Bárcenas et al. 2018), and electrochemical exfoliation (Ali et al. 2019; Assis Filho et al. 2019).

In relation to GO synthesis, some important parameters, such as reproducibility, processability, production cost, scalability, quality of the obtained material, and affordability, should be considered (Coros et al. 2016; Ejigu et al. 2018; Pogacean et al. 2019). Among these, electrochemical exfoliation of graphite is promising method for the production of GO. It has been reported as a safe, very simple, controllable, green, and rapid GO synthesis process (Fang et al. 2019; Htwe et al. 2019; Muhsan and Lafdi 2019).

Electrochemical exfoliation has several advantages over non-electrochemical exfoliation process like the following:

1. It is one of a few of possibly cost-effective, scalable, and feasible methods for large-scale and rapid production (Hashimoto et al. 2019; Lowe et al. 2019).
2. The quality (e.g., defect density, oxidation degree, chemical and structural features) and quantity of produced GO can be regulated by controlling the electrolyte solutions and oxidation conditions (Fang et al. 2019; Teran-Salgado et al. 2019).

3. It is free of strong chemical oxidants and elevated temperatures, since current serves as a green oxidant and can be carried out under ambient temperature (Chen et al. 2019; Fang et al. 2019).
4. It can be performed within a few minutes to hours (Abdelkader et al. 2015).
5. It preserves the highly conductive $sp^2$ structure of graphene (Pogacean et al. 2019).

Electrochemical exfoliation consists of applying an electric potential or current to an electrolytic solution. This potential is needed to insert the ions into the interstitial spaces of the graphite rods, weakening the van der Waals forces and resulting in the gradual expansion of interlayer graphite leading to exfoliation of the material. In some cases, the intercalant or co-intercalant species locally form gas bubbles (such as $SO_2$, $O_2$, $CO_2$), which force adjacent sheets apart and assist the exfoliation (Abdelkader et al. 2015; Ambrosi et al. 2016; Achee et al. 2018; Kairi et al. 2018).

Based on the polarity of applied potential or current, electrochemical exfoliation can be carried out using cathodic reduction (reductive) or anodic oxidation (oxidative) to intercalate positive or negative ionic species, respectively (Ambrosi and Pumera 2018; Ejigu et al. 2018). The cathodic exfoliation is performed in a quaternary ammonium cation or an organic alkaline solution. In contrast, anodic exfoliation is usually carried out in aqueous solution which makes it very attractive from a practical and environmental point of view (Munuera et al. 2017; Yang et al. 2019).

Although there is a possibility of applying two types of potential in electrochemical exfoliation, anodic exfoliation is the most widely used method in relation to cathodic exfoliation because of its high exfoliation efficiency and higher yield. However, there is the disadvantage of increasing the number of defects and the insertion of functional oxygen groups in the produced GO. However, the number of defects produced by this method is lower when compared to traditional chemical methods. Thus, GO produced via anodic exfoliation must be reduced to form the rGO and obtain a material similar to pristine graphene (Yu et al. 2015; Ejigu et al. 2018; Mooste et al. 2018).

## *1.4 Reduction of GO*

The GO reduction process consists in the regeneration or repair of the conjugated graphitic structure and also in the removal of functional oxygen groups and other structure defects (de Silva et al. 2018). Various methods to obtain rGO have been applied and include chemical (Hou et al. 2018; Vázquez-Sánchez et al. 2019), thermal (Saleem et al. 2018; Gnanaseelan et al. 2019), electrochemical (García-Argumánez et al. 2019; Marrani et al. 2019), microwave (Voiry et al. 2016), and photochemical (Yin et al. 2019). Of the many methods mentioned, chemical and thermal reductions are the most common and used in recent years (Vázquez-Sánchez et al. 2019).

High temperature and/or pressure is necessary for preparing high-quality graphene by thermal reduction (Zhang et al. 2018), which makes it energy-intensive

(Yin et al. 2019) and too expensive to produce. Furthermore, the temperature selection is determined by time of process, which can make the cost of production even more expensive if the time is long. Therefore, it is not easy to use this method for GO films on inorganic and organic substrates or in liquid mean (Dideikin and Vul 2019). An excellent alternative to chemical or thermal reduction methods is the photoreduction method. But the disadvantage of this process involves the need to add chemical or photocatalysts to increasing efficiency, consequently enhancing the cost, as only UV irradiation is not sufficient to GO reduction (Yin et al. 2019).

Chemical reduction can be considered a very versatile process as it is applicable in both acid and alkaline media. It also has the advantage of being an effective, attainable, scalable, cost-effective, relatively rapid, and simple route which also enables high yield levels of material with controllable properties (Wang et al. 2017; de Silva et al. 2018). But this method can be considered disadvantageous or dangerous because it requires long reaction times and rigorous reaction conditions and uses very toxic and environmentally unfriendly reducing agents such as hydrazine, dimethylhydrazine, hydroquinone, and sodium borohydride. These reducing agents may insert nitrogen groups in the GO structure that changed their features, and it can be an irreversible aggregation of the produced GO. In addition, some undesired intermediates to rGO are hazardous, and contaminant can be formed and prejudice its properties (Hou et al. 2018; Ghosh et al. 2019; Vázquez-Sánchez et al. 2019; Yin et al. 2019).

To solve this problem, many environmentally friendly reductants known as "green" reducing agents have been studied in the preparation of the rGO like plant extracts (Roy et al. 2017; Khojasteh et al. 2019), alanine (Wang et al. 2017), *Lycium barbarum* (Hou et al. 2017), artemisinin (Hou et al. 2018), onion (Khanam and Hasan 2019), sugar (Gan et al. 2019), and L-ascorbic acid (Cabral et al. 2019). Among all these, the first reducing agent for GO that was considered environmentally friendly was L-ascorbic acid (Zhang et al. 2010).

L-ascorbic acid, which is one of forms of vitamin C, is a natural antioxidant essential for maintenance of metabolic and body functions of living beings and widely used as a food additive (Khosroshahi et al. 2018). It is an abundant and cheap substance and a sustainable option to substitute conventional reducing agents of GO (Abdolhosseinzadeh et al. 2015; Ucar et al. 2018). Fernandez-Merino et al. (2010) studied the GO reduction by different reducing agents (pyrogallol, ascorbic acid, sodium borohydride, and hydrazine) and showed that just ascorbic acid is comparable with that of hydrazine (considered to be the best reducing agent).

## 2 Methodology

### *2.1 Preparation of Graphite Rods from Waste Batteries*

The waste batteries were collected at a discard point and then sent to the laboratory for removal of graphite rods (Fig. 4). The batteries were opened, with the aid of a sharp object and a pair of pliers, and all the components were separated. Paper,

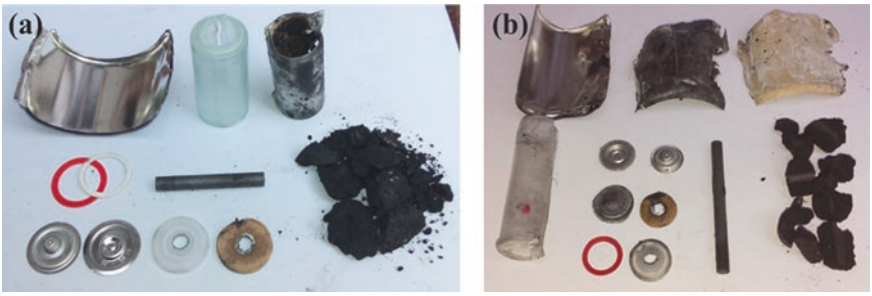


**Fig. 4** Components of zinc-carbon battery standard C size (**a**) and standard AA size (**b**)

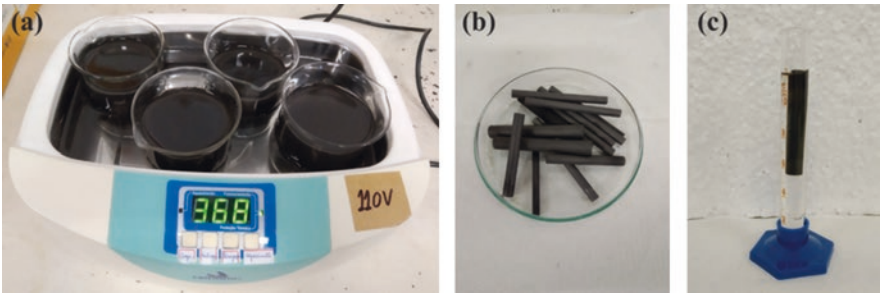


**Fig. 5** Cleaning the graphite rods by ultrasonic (**a**), clean graphite rods after agitation (**b**), and pretreatment of the graphite rods with acid (**c**)

plastics, and metals were recycled, and the wet paste ($NH_4Cl$, $MnO_2$, carbon) was stored for the correct destination.

The preparation of the graphite for the synthesis of electrochemical exfoliation started with the cleaning of the rods by ultrasonic agitation for 30 min using distilled water. After cleaning, the rods underwent a pretreatment, being submerged in acid ($H_2SO_4$) in a 10 mL beaker for 48 h (Fig. 5). This pretreatment eliminates possible residues that were not eliminated by ultrasonic cleaning and prepares the graphite structure for the next exfoliation step.

## *2.2 Synthesis of Electrochemically Exfoliated Graphene Oxide*

The electrochemically exfoliated GO was easily synthesized by the electrochemical exfoliation process using a graphite rod as anode and a Pt wire as cathode (Fig. 6). Pretreatment with $H_2SO_4$ was performed by immersing the graphite electrode in 250.0 mL of the concentrated acid at room temperature for 48 h. Subsequently, the material was washed with distilled water to remove the excess acid and dried under ambient conditions (Munuera et al. 2017).

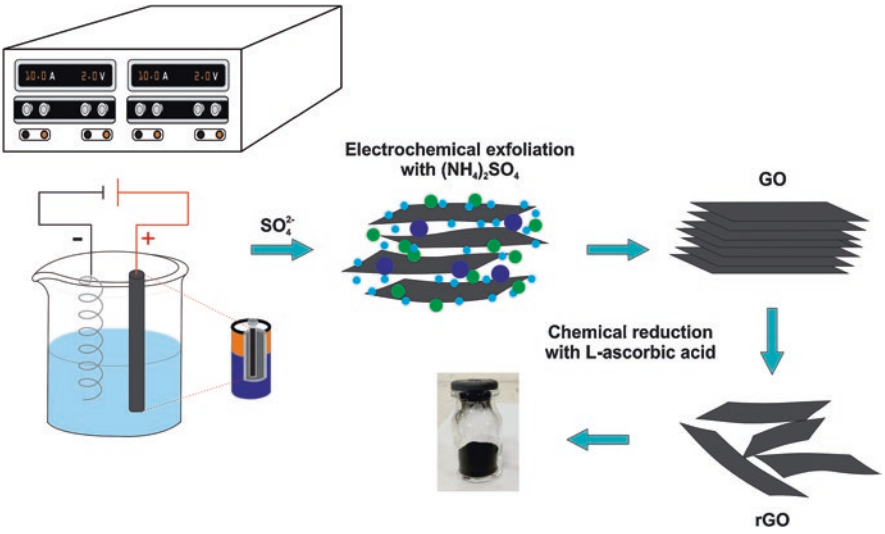


**Fig. 6** The schematic representation of the synthesis by electrochemical exfoliation using graphite of waste battery for production of graphene

The experiments were conducted according to Kim et al. (2017), Bandi et al. (2019), and Parvez et al. (2014). The electrodes were introduced in a 200.0 mL beaker, with a distance of 2.5 cm between them. The support electrolyte was $(NH_4)_2SO_4$ dissolved in ultrapure water (Milli-Q system, Millipore, USA) at 0.1 mol $L^{-1}$ and neutral pH (NaOH, 1.0 mol $L^{-1}$).

For exfoliation to be proportional to the full length of the graphite rod, giving regular characteristics to the exfoliated graphite, it is necessary to have the complete wetting of electrodes in the electrolyte. This provides a regular flow of electrons and therefore a regular voltage gradient along the graphite rod surface. Once the direct current (DC) voltage supply is started, the electrons that flow between anode and cathode must be continuous and smooth. For this purpose, in the first two minutes, a voltage of 2.0 V was supplied using a DC power supply (Instruthern FA-1030); then it was increased to three different voltages (5.0, 7.5, and 10.0 V). During exfoliation process, the simultaneous effect of hydrogen bubble release was observed. The end of the process occurred when the graphite rod became thin enough.

After electrolysis, the exfoliated powder was collected by vacuum filtration using polytetrafluoroethylene (PTFE) membrane (0.45 μm pore and 47 mm diameter, Whatman, USA) and washed repeatedly with distilled water. Then it underwent dialysis with membrane (Inlab 33 mm) for 72 h until pH is neutral. In this procedure, the support electrolyte and small size graphite flakes were washed away. Then, the material was dispersed in a DMF/$H_2O$ solution (75:25 $vv^{-1}$) and sonicated for 60 min. The aqueous dispersion of electrochemically exfoliated graphene oxide was then allowed to stand for 24 h, for the sedimentation of unexfoliated flakes and large particles. In the next step, the sedimented material was

discarded and the solution centrifuged at 5.000 rpm for 30 min. Finally, the material was heat-treated at 200 °C to remove the solvent.

## 2.3 Synthesis of rGO

The reduction process was performed in 300.0 mL of a solution of electrochemically exfoliated GO (0.1 mg $mL^{-1}$) diluted in ultrapure water. Another solution was prepared by adding 300.0 mg of L-ascorbic acid in 100.0 mL of ultrapure water. These two solutions were mixed, and then $NH_3$ (28%) was added to adjust the pH between 9.0 and 10.0, thus ensuring greater stability to the electrochemically exfoliated graphene oxide sheets that exhibit electrostatic repulsion under alkaline conditions (Fernandez-Merino et al. 2010).

After these procedures, the solution was sonicated during 30 min and then kept under stirring for 2 h at 95 °C. The precipitates were vacuum filtered and repeatedly washed with distilled water until pH 7.0. Then, they were centrifuged during 30 min at 5.000 rpm and finally dried (Xu et al. 2015). The percentage of yield of the rGO was 80% (Fig. 7).

## 2.4 Characterization of Samples

For the analysis of the textural properties of the samples, nitrogen adsorption-desorption isotherms were performed at 77 K in QuantaChrome® Nova 1200e equipment. The surface area was estimated using the Brunauer, Emmett, and Teller (BET) equation with range of relative pressure from 0.05 to 0.30. The mesopore volume and pore size distribution were estimated using the Barrett, Joyner, and Halenda (BJH) method using nitrogen adsorption data.

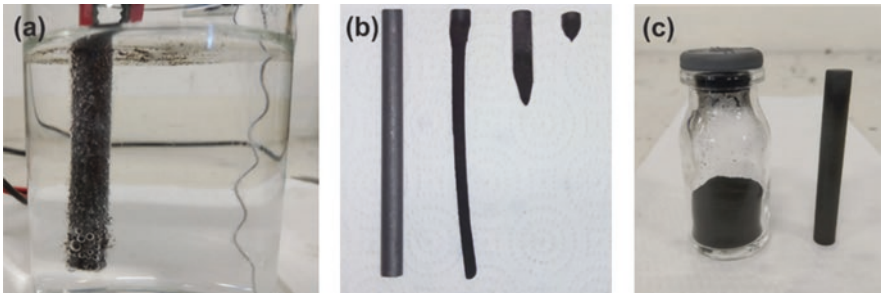


**Fig. 7** Details of the gases on the surface of the graphite electrode during the exfoliation process (**a**), reduction the graphite electrode during the synthesis (**b**), bottle containing rGO (approximate yield of 80%) (**c**)

The X-ray diffraction (XRD) patterns were realized in an X-ray diffractometer (Shimadzu model XRD-7000, Kyoto, Japan) at 20 kV and 30 mA with $CuK\alpha_1$ radiation ($\lambda = 1.5406$ Å) with a 2θ angle of 10 to 60°. To increase resolution, K $\alpha_2$ radiation was filtered by a Ge monochromator placed in the incident beam. Prior to plotting results, the background correction of spectra was made.

Raman spectroscopy was held using a Senterra Bruker spectrometer (Bruker, Billerica, MA), with laser excitation at 532 nm with 5 up to 50 mV, 1200 grooves/mm grating, a 20 x objective, acquisition time of 60 s, and a slit of 50 x $10^3$ μm. All of the spectra were an average of 128 scans with a 4 $cm^{-1}$ resolution. The transmission electron microscopy (TEM) analysis were carried out by using a transmission electron microscope (JEM-1400, Jeol, USA), equipped with a cold field emission gun, working at an acceleration voltage of 120 kV. For the TEM sample preparation, the graphene samples were dispersed in ethanol solution (1:1 $vv^{-1}$). For each suspension sample, two drops were deposited on a copper grid coated by carbon-formvar film, which were dried at ambient conditions prior to TEM analysis.

Scanning electron microscopy (SEM) and dispersive X-ray spectrometry (EDS) analysis were performed using a Quanta 650 scanning electron microscope assembled with an energy dispersive X-ray spectrometer. Graphene samples were attached to aluminum stubs using carbon tape and subsequently coated by a 20 nm layer of gold. EDS spectra as well as chemical maps for the elements were obtained using a Dual EDX System (X-Max N100TLE Silicon Drift Detector).

## 3 Results and Discussion

### *3.1 Pretreatment of Graphite Rods*

In general, electrochemical exfoliation methods have graphite rod as electrode. However, a barrier to this method is the production of large quantities due to low yields. An easy way to increase the yield of graphene produced by anodic exfoliation of the graphite rods is by soaking it in concentrated sulfuric acid as a pretreatment method. Thus, this simple idea pushes up large-scale production to be more significant (Munuera et al. 2017).

The immersion process makes the empty spaces and interstices of the graphite layers to be filled with the $H_2SO_4$ molecules, promoting a greater intercalation. When the electrochemical exfoliation is carried out, the ions present in the electrolyte solution can enter the interlayers more easily. In addition to producing graphene with fewer layers, this intercalation also promoves a faster and more effective exfoliation (Munuera et al. 2017).

Elementary analyses were performed by EDS and XRF in order to identify the composition of the graphite rod after chemical treatment with acid (Fig. 8 and Table 1, respectively). Figure 8 also shows the morphological characteristics obtained by SEM image.

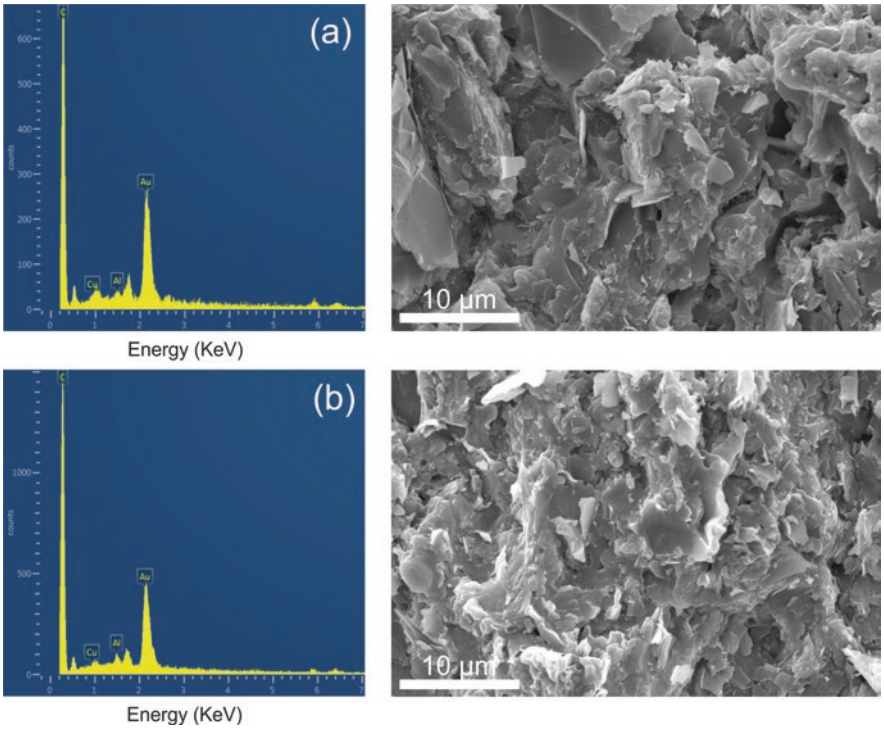


**Fig. 8** EDS of graphite rods and their respective SEM images. Without treatment with acid (**a**) and treatment with $H_2SO_4$ (**b**)

Battery waste graphite rod without treatment and after treatment with acid does not show morphological changes as can be observed in SEM image. The EDS spectra have identified the presence of C, Au, Al, and Cu. Au comes from the treatment the sample receives before it is analyzed. Both samples presented a high percentage of carbon and inexpressive amounts of Al and Cu, which is essential for the synthesis of rGOs.

Eighteen chemical elements were identified in the battery waste graphite rod and eight elements in the commercial graphite (Table 1). Although commercial graphite had smaller number of elements, all mass concentrations were higher compared to battery waste graphite rod. From XRF data, $Al_2O_3$, $SiO_2$, $SO_3$, CaO, and $Fe_2O_3$ can be considered the main contaminants in battery waste graphite. The graphite is basically composed of carbon and clay minerals (kaolinite and montmorillonite) (Wang et al. 2016). The chemical compositions of kaolinite and montmorillonite are $Al_2Si_2O_5(OH)_4$ and $(Na,Ca)_{0.33}(Al_{1.67}Mg_{0.33})(Si_4O_{10})(OH)_2.nH_2O$, respectively (Clay Minerals Society, 2019). Espinosa and Tenório (2009) studied several types of batteries and found Fe, Ni, Mn, Zn, Cd, Co, Hg, and Pb in the Zn-C cells, while Vieira et al. (2013) found Mn, Zn, Fe, Cd, Hg, Pb, Ni, Cu, Na, K, and Cl.

**Table 1** XRF results of waste battery and commercial graphite rod before and after pretreatment with $H_2SO_4$

| | Waste battery graphite rod | | Commercial graphite rod | |
|---|---|---|---|---|
| Component (wt%) | without treatment | $H_2SO_4$-treatment | without treatment | $H_2SO_4$-treatment |
| $Na_2O$ | 0.52 | 0.31 | | |
| MgO | 0.79 | 0.68 | | |
| $Al_2O_3$ | 14.70 | 9.65 | 26.01 | 1.22 |
| $SiO_2$ | 30.60 | 27.10 | 41.60 | 2.65 |
| $P_2O_5$ | 0.45 | 0.11 | 1.98 | 0.06 |
| $SO_3$ | 22.50 | 38.50 | 3.93 | 93.71 |
| Cl | 0.18 | 0.27 | | |
| $K_2O$ | 3.60 | 2.31 | 2.02 | 0.51 |
| CaO | 10.10 | 2.83 | | 0.27 |
| $TiO_2$ | 2.36 | 0.85 | | |
| $V_2O_5$ | 0.12 | 0.13 | | |
| $Cr_2O_3$ | 0.13 | 0.12 | | |
| MnO | 0.41 | 0.15 | | |
| $Fe_2O_3$ | 16.60 | 12.80 | 17.20 | 0.52 |
| NiO | 0.40 | 0.11 | | |
| CuO | 0.05 | 0.03 | 4.71 | 0.49 |
| ZnO | 0.19 | 0.16 | 2.53 | 0.54 |
| $As_2O_3$ | 0.13 | 0.05 | | |

Abbreviations: *wt%* mass concentration in percentage

Except for $SO_3$, pretreatment significantly decreased concentration of inorganic substances, especially metals. The increase in concentration of $SO_3$ comes from $H_2SO_4$ residues. Zn-C batteries have been composed of high purity natural graphite rods. Natural graphite most often needs purification and grading to be used commercially (Baio et al. 2014). Thus, the pretreatment for both graphites is as important in the graphene synthesis by the electrochemical exfoliation process as in the elimination of possible contaminants.

## *3.2 Textural Analysis*

According to the IUPAC, adsorption-desorption isotherms can be divided into six characteristic types (I, II, III, IV, V, and VI), and types II and IV are subdivided into (a) and (b). In addition, it is also possible to identify five main types of hysteresis, which correspond to different pore structures (Thommes et al. 2015). Before obtaining the textural information of the material, it is important to understand the shape of the adsorption isotherm, since this profile is associated to the surface structure and the pore geometry (Cychosz and Thommes 2018). Figure 9 shows the $N_2$ adsorption-desorption isotherms of waste battery graphite and rGOs. Table 2 shows the numerical values obtained from textural analysis for the same samples.

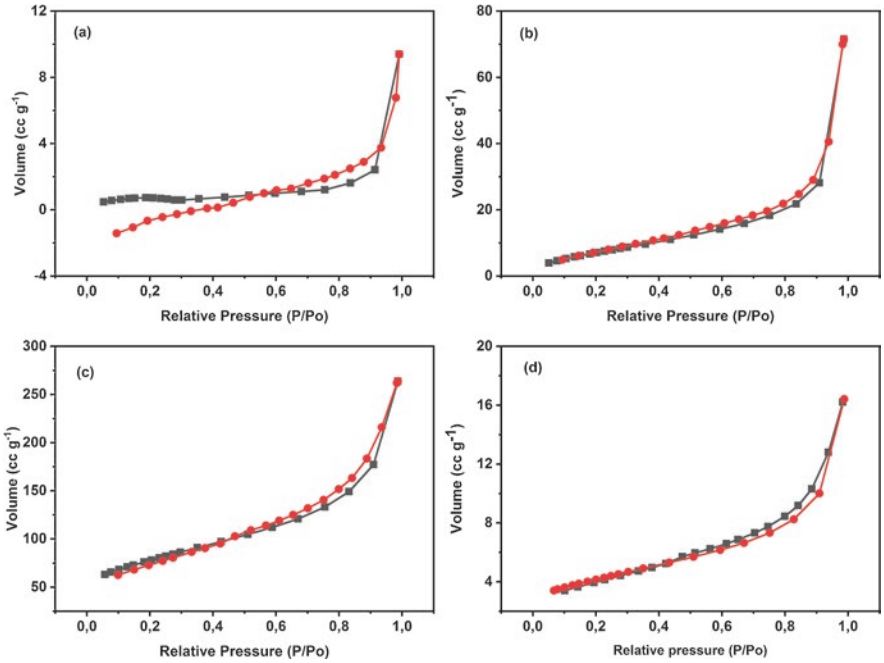


**Fig. 9** Nitrogen adsorption/desorption isotherms at 77 K of battery graphite (**a**), rGO 5.0 V (**b**), rGO 7.5 V (**c**), and rGO 10.0 V (**d**)

**Table 2** Structural characterization of graphite and rGO

| Samples | Surface area ($m^2\ g^{-1}$) | Pore volume ($cm^3\ g^{-1}$) | Pore size (nm) |
|---|---|---|---|
| Battery graphite | 1.355 | 0.017 | 3.846 |
| rGO 5.0 V | 29.38 | 0.107 | 3.954 |
| rGO 7.5 V | 261.8 | 0.332 | 3.579 |
| rGO 10.0 V | 267.7 | 0.408 | 3.598 |

Abbreviations: *rGO* reduced graphene oxide

From physisorption data, all samples presented type IV isotherm with type 3 hysteresis (H3) demonstrating that the adsorption-desorption process is irreversible. This is due to the phenomenon of capillary condensation characterized by hysteresis, where the amount adsorbed is always higher at any relative pressure along the desorption curve when compared to adsorption. The type IV isotherms are typical for mesoporous materials, where again the difference between the two is related to the mesopore size and the H3 is associated with nonrigid aggregates of plate-like particles, resulting in cracked pores (Thommes et al. 2015).

Textural analysis was placed in terms of BET surface area and pore size. For rGOs, an increase in applied voltage leads to increasing the surface area, 29.1, 261.8, and 267.7 $m^2\ g^{-1}$, for the samples exfoliated at 5.0, 7.5, and 10.0 V, respec-

tively. As can be seen, the difference between 7.5 and 10.0 V is quite small. The surface area of graphite (1.355 $m^2 g^{-1}$) is considerably lower than the three produced rGOs. When we compare with values obtained by other researchers, we observe different values of surface areas. Nawaz et al. (2017) obtained rGO by one-step hydrothermal method, and their surface area was 209.0 $m^2 g^{-1}$. Bandi et al. (2019) also synthesized rGO from waste battery graphite through electrochemical exfoliation (applying 10.0 V), but their reduction was thermal. The surface area reported by them was much smaller (27.0 $m^2 g^{-1}$) in relation to that found in this work at the same voltage (267.7 $m^2 g^{-1}$), but the value is very close to the 5.0 V voltage (29.1 $m^2 g^{-1}$). They did not use acid pretreatment, and the electrolyte solution was prepared in acid medium. Confirming that acid pretreatment assists in the intercalation of the graphite layers. The surface area (292.6 $m^2 g^{-1}$) reported by Yu et al. (2018) is greater than any presented in this paper. They produced rGO using modified Hummer's method and chemical reduction - hydrazinium hydroxide as a reductant.

Since the synthesis of rGO depends on several factors, for example, type of reduction treatment, level of oxygenated groups, method of synthesis of GO, time, reaction medium, etc., the surface area is very variable (Bandi et al. 2019), which explains the differences in the area values found. In the case of rGOs produced from electrochemical exfoliation, a large surface area value relative to graphite indicates a great graphene exfoliation rate. However, a big difference between the theoretical value (2600 $m^2 g^{-1}$) and the one found in this work can be attributed to the process of agglomeration of single graphene layers during the reduction process or partial exfoliation of GO (Xu et al. 2012; Wang et al. 2014; Yu et al. 2018).

The pore size of both waste battery graphite and rGOs is very close, with values ranging from 3.579 to 3.954 nm. Thus, all samples are classified as mesoporous material according to the 1985 IUPAC recommendations, i.e., pore size varies between 2 and 50 nm (Sing et al. 1985), confirming the suggestion given by the type of isotherm. It was observed that the increase in voltage applied in the synthesis process causes a slight decrease in pore size. The pore size between 7.5 and 10.0 V showed no significant difference.

### *3.3 Raman Spectroscopy*

Raman spectroscopy is the best technique to check the quality and structure of carbonaceous materials. This nondestructive technique is a strong, fast, and sensitive analytical approach that provides structural and electronic particulars and high resolution. These parameters are, however, capable of supplying both qualitative and quantitative information of material. This method is capable of identifying the structural defects, structural organization, chemical alterations entered on the preparation, and undesirable by-products and hence also evaluating the quality of exfoliated samples and functionality through the positions, shape, and intensity of Raman bands making very useful for graphene characterization (Ferrari and Basko 2013;

Hu et al. 2017; Kumar and Pattammattel 2017). Raman spectra of graphite, commercial graphene, and rGOs produced by electrochemical exfoliation are shown in Fig. 10.

Carbon materials, including graphite and graphene, contain three important bands in the Raman spectra, denoted 2D, D, and G bands. All samples showed these bands but with different intensities. An intense G band, wide 2D band, and moderate D band appeared in the region of 1570, 2680, and 1345 $cm^{-1}$, respectively. The presence of disorder and defects, primarily produced by vacancies or malformations in the network connection and defects related to the edges or "walls" of the sheet, and some graphene oxide impurity is reported by the appearance of the D-band located between 1200 and 1400 $cm^{-1}$. It arises from breathing vibrations of C-atoms ($sp^2$) in aromatic rings. The 2D band (2640–2680 cm − 1), sometimes also denominated as G', has been assigned to graphite restructuring caused by reduction process and the number of layers a graphene can have (maximum of 10 layers). The last band, called G and located around 1500 to 1600 $cm^{-1}$, in terms of their vibrational character,

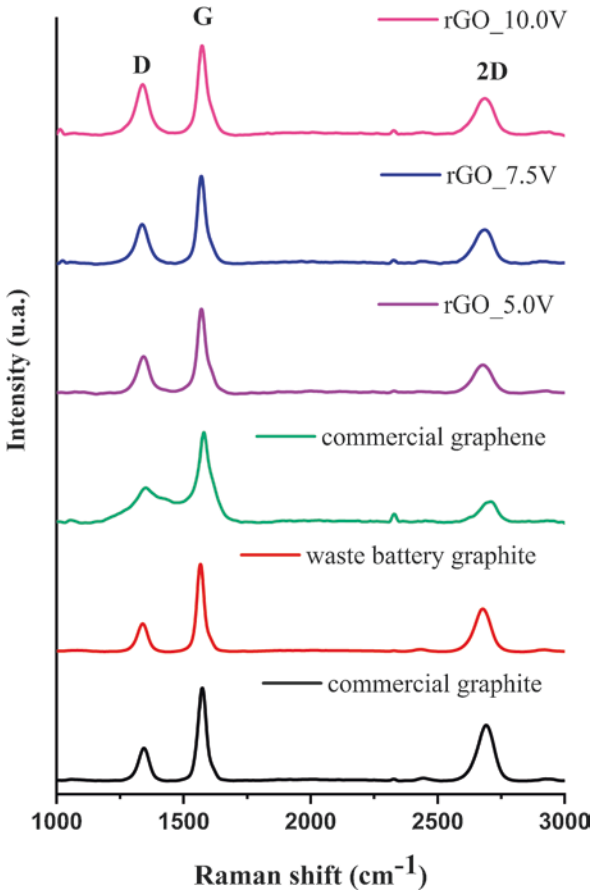


**Fig. 10** Raman spectra of commercial graphite (black), waste battery graphite (red), commercial graphene (green), rGO 5.0 V (purple), rGO 7.5 V (blue), and rGO 10.0 V (pink)

corresponds both in rings and chains to $sp^2$-hybridized carbon atoms (García-Argumánez et al. 2019; Dimiev and Eigler 2017; Muzyka et al. 2018; Jorio et al. 2011; Malard et al. 2009).

Comparing commercial and waste battery graphite, the D band is lower than G, indicating a structural arrangement with few crystalline defects. In this case, these samples can be considered as monocrystalline, i.e., the carbon sheets are orderly stacked. The profile of both spectra is very similar, indicating that the graphite obtained from the battery waste has the same quality as a commercial one and can be used for rGO synthesis.

The quality of produced graphene is very important and necessary to study both D and 2D peak. Data of D peak can be used to verify the defective order. By dividing the intensity of peak D by the intensity of peak G ($I_D/I_G$), it is possible to quantify the structural defects in the material produced. And from this value it is also possible to estimate the size of the crystallite by the Tuinstra-Koenig relation. However, the full width at half the maximum peak (FWHM) of 2D, the ratio of the 2D and G peak intensities ($I_{2D}/I_G$), and the 2D peak position are used to determine with high degree of precision the number of graphene layers. The number of layers is assumed to increase when there is an increase in G peak intensity and 2D peak decrease simultaneously (Bleu et al. 2019; Muzyka et al. 2018). The position and intensity of peak, intensity ratios, and FWHM 2D for commercial graphene and rGOs produced from waste battery graphite were shown in Table 3.

$I_D/I_G$ ratio for rGOs has enhanced from 0.40 to 0.52 when applied potential has grown from 5.0 V to 10.0 V. These $I_D/I_G$ values increase in the order rGO 5.0 V > rGO 7.5 V > rGO 10.0 V and are associated with decreasing of crystallite size, which exhibits the opposite trend rGO 10.0 V < rGO 7.5 V < rGO 5.0 V. The crystallite size declined from 48 to 37 nm. The measure of crystallites size may be considered as the average distance of the inter-defects. Smaller values correspond to more defects. Thus, perfect graphene structure shows high crystallite size value (Hu et al. 2017).

Since rGOs are composed of graphene oxide layers after undergoing the reduction process, even though this process is highly effective, there may be remnant oxygen groups bonded to the edges and planes. These groups may cause defects and/or damage that is confirmed by intense G and D bands (Muzyka et al. 2018). Kumar and Pattammattel (2017) suggest that the highly defective graphene oxide has the $I_D/I_G$ ratio above 1.0, while the exfoliated graphene ranges from 0.1 to 0.6 as observed in the produced rGOs. The intensity of D band increases as more edges and vacancies are formed during exfoliation of graphite or when there are remnant oxygenated functional groups. An increase in applied potential led to increasing the defects, representing by $I_D/I_G$ values, but the difference between 5.0 and 7.5 V is very small (0.1) compared to 10.0 V. The $I_D/I_G$ value of commercial graphene is 0.35. Defect density is higher for rGOs produced by electrochemical exfoliation compared to commercial graphene.

rGO spectra presented the same profile as the graphite, that is, the G band is more intense than the D band. When applied voltage has grown from 5.0 V to 10.0 V, the $I_{2D}/I_G$ and FWHM values have raised from 0.30 to 0.37 and from 81 to 86 $cm^{-1}$,

**Table 3** Intensity and position of the peaks in the Raman spectra, intensity ratios, and full width at half the maximum 2D peak for commercial graphene and rGOs produced from waste battery graphite

| | Position peak ($cm^{-1}$) | | | Intensity peak | | | Intensity ratio | | FWHM 2D ($cm^{-1}$) | Crystallite size (nm) |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | D | G | 2D | D | G | 2D | $I_D/I_G$ | $I_{2D}/I_G$ | 2D | |
| Commercial graphene | 1353 | 1579 | 2706 | 441 | 1259 | 256 | 0,35 | 0,20 | 76 | 55 |
| rGO 5.0 V | 1344 | 1570 | 2678 | 1805 | 4556 | 1351 | 0,40 | 0,30 | 81 | 48 |
| rGO 7.5 V | 1336 | 1569 | 2686 | 919 | 2261 | 770 | 0,41 | 0,34 | 84 | 47 |
| rGO 10.0 V | 1339 | 1573 | 2683 | 1214 | 2313 | 844 | 0,52 | 0,37 | 86 | 37 |

Abbreviations: *FWHM 2D* full width at half the maximum 2D peak, $I_D/I_G$ intensity ratio of the D to G peaks, $I_{2D}/I_G$ intensity of the 2D peak in relation to the intensity of the G peak, *rGO* reduced graphene oxide

respectively. The $I_{2D}/I_G$ values indicate that the produced rGOs are from 5 to 10 layers. But this behavior cannot be confirmed by the value of FWHM because when there are more than four or five layers, the 2D band shape is quite close to graphite. For this reason, FWHM is not able to measure the number of layers (Bleu et al. 2019). Commercial graphene presented a smaller $I_{2D}/I_G$ ratio than the rGOs produced by the electrochemical exfoliation, indicating a larger agglomeration.

## *3.4 X-Ray Diffraction (XRD)*

X-ray diffractograms of graphite (commercial or battery waste), commercial graphene, and rGOs were shown in Fig. 11. Commercial and waste battery graphite exhibited a narrow and intense peak at 26.5° (2θ) equivalent to the plane (002). This plane is characteristic of graphite of high purity and crystallinity. The smaller peaks at 43.2° and 45° (2θ) correspond to reflections (100) and (101), respectively. The last peak located at 54.7°(2θ) corresponds to plane (004) and is also characteristic of graphite. A high purity graphite is essential for graphene production; the presence of contaminants can interfere in the quality as well as the synthesis of graphene.

The XRD analyses for electrochemically exfoliated graphene and commercial graphene sample presented that after oxidation, a new diffraction peak appears at 26.8°(2θ) that is broader and less intense. This may have been due to the highly defective stacking of graphene coverslips, indicating that there are still aggregate reduced graphene oxide particles, i.e., low-layer graphene or nanoplate graphene. The emergence of the peak near 26°(2θ) indicates the partial restoration of the electronic structure of the graphite, with a majority removal of oxygenated functional groups. Reduction process promotes the reconstitution of the graphite structure resulting in a high conductivity material. The purpose of the reduction process is to

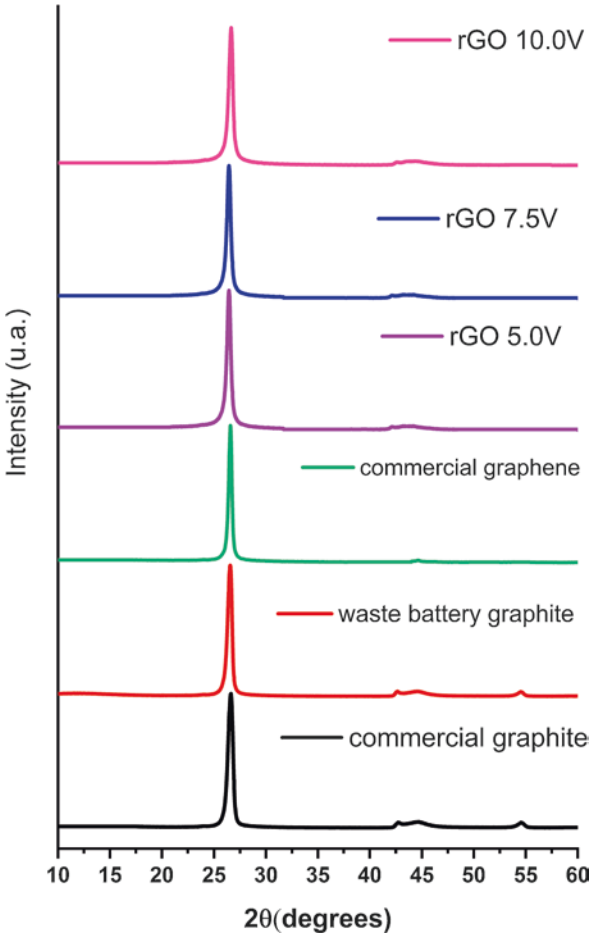


**Fig. 11** XRD patterns of commercial graphite (black), waste battery graphite (red), commercial graphene (green), rGO 5.0 V (purple), rGO 7.5 V (blue), and rGO 10.0 V (pink) samples

get as close as possible to the graphene structure (pristine), since rGO is very similar to graphene in terms of surface morphology, as well as thermal, electrical, and mechanical properties. However, rGO has a little structural defect and remaining oxygenated functional groups (Acik et al. 2011; Dreyer et al. 2010; Paci et al. 2007).

The absence of peak close to 11°(2θ) for band (001), which only occurs in GO, i.e., in non-reduced form, confirms that the preparation method for obtaining graphene nanosheets is correct because there was no partial oxidation of the graphite rod (Amaro-Gahete et al. 2019), indicating that the reduction synthesis using natural reducing agent was effective for the three rGO samples. In the region near 45°, a small characteristic band of rGO can be observed. They are most evident in the rGO 7.50 V and rGO 10.0 V and weaker in commercial graphene and the rGO 5.0 V.

### 3.5 *Transmission Electron Microscopy (TEM)*

The surface morphology of the rGO from waste battery graphite was examined by TEM images (Fig. 12). The structure of rGO depends strongly on the synthesis chosen for the production of GO and also on the method used in the reduction; variations may occur in its structure as size and thickness of leaves, number of leaves, number of defects, specific surface area, C/O ratio, and electrical conductiv-

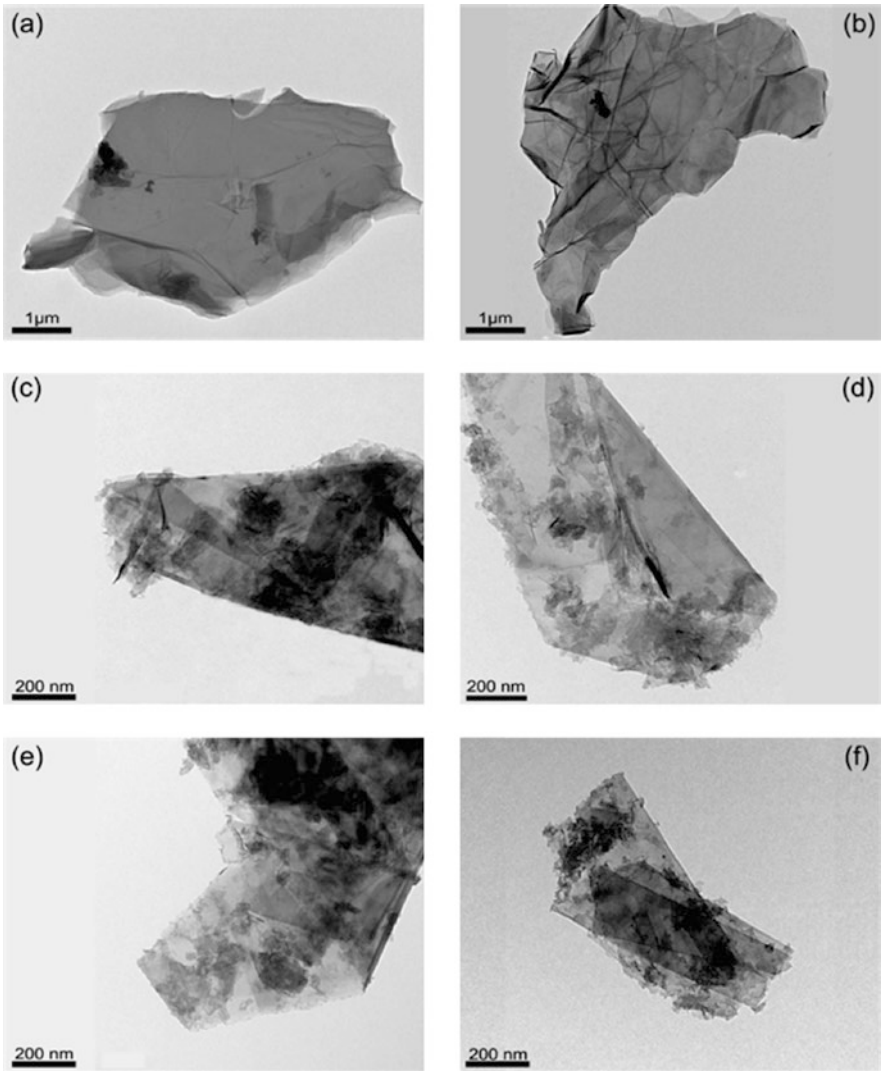


**Fig. 12** The micrographs of rGO analyzed by electron transmission electron microscopy (TEM). Exfoliated at 5.0 V (**a**–**b**), exfoliated at 7.50 V (**c**–**d**), and exfoliated at 10.0 V (**e**–**f**)

ity. Another factor that may interfere with the characteristics of the material is the type of graphite, for example, the graphite powder used in chemical and mechanical syntheses (i.e., Hummer's, grinding, adhesive tape) and rod or sheet graphite, which are used as electrodes in electrochemical synthesis. In addition, the electrochemical synthesis presents many variations, which can also change the characteristics of graphene, such as type of electrolyte support, work potential, and pH.

The electrochemical synthesis with graphite rods from waste batteries produced graphene with different characteristics in relation to the applied potential. Figure 12 a–b shows that when performing the synthesis with potential of 5.0 V, rGO sheets presented a size ranging from 3 to 7 μm and a mean of 5 μm. At higher potentials (7.5 and 10.0 V), rGO presented smaller particles, ranging from 0.5 to 2 μm, and a mean size of 1 μm (Fig. 12 c–f). The main difference observed in the images of TEM is that the rGO synthesized at 5.0 V presented agglomerates of microleaves and the samples of 7.5 and 10.0 V presented nanosheets with the presence of aggregates of nanoparticles, having its characteristic similar to graphene nanoplatelets.

### *3.6 Scanning Electron Microscopy (SEM) and Dispersive X-Ray Spectrometry (EDS)*

rGOs exfoliated at 5.0, 7.5, and 10.0 V were analyzed by SEM and EDS (Fig. 12). In comparison, commercial graphene was also evaluated. SEM images clearly showed the sheet-like nature of all samples like suggested by the XRD results. The rGO and commercial graphene sheets seem as wrinkled and bent papers. This crumpled appearance of thin sheets is very characteristic of rGOs, and the presence of wrinkles on the surface validates that the sheets were very thin.

Regarding the EDS analyses performed on rGO samples, it was observed that all samples have carbon as the main element. Commercial graphene (Fig. 13a) presented only carbon and a small fraction of oxygen in its composition. In rGO 5.0 V besides C and O, the elements Al and Si were also observed. These contaminants are derived from graphite (see Table 1, graphite FRX) which were not completely eliminated by pretreatment with $H_2SO_4$ and electrochemical synthesis. However, pretreatment, electrochemical synthesis, and reduction were efficient for the rGO 7.5 and 10.0 V samples. It can be confirmed by the absence of the oxygen element and the metals present in the graphite rod. Thus, rGO 7.5 and 10.0 V presented the best efficiency in relation to the proposed rGO synthesis route using waste battery graphite as anodic electrode, electrochemical exfoliation, and GO reduction with natural reducers.

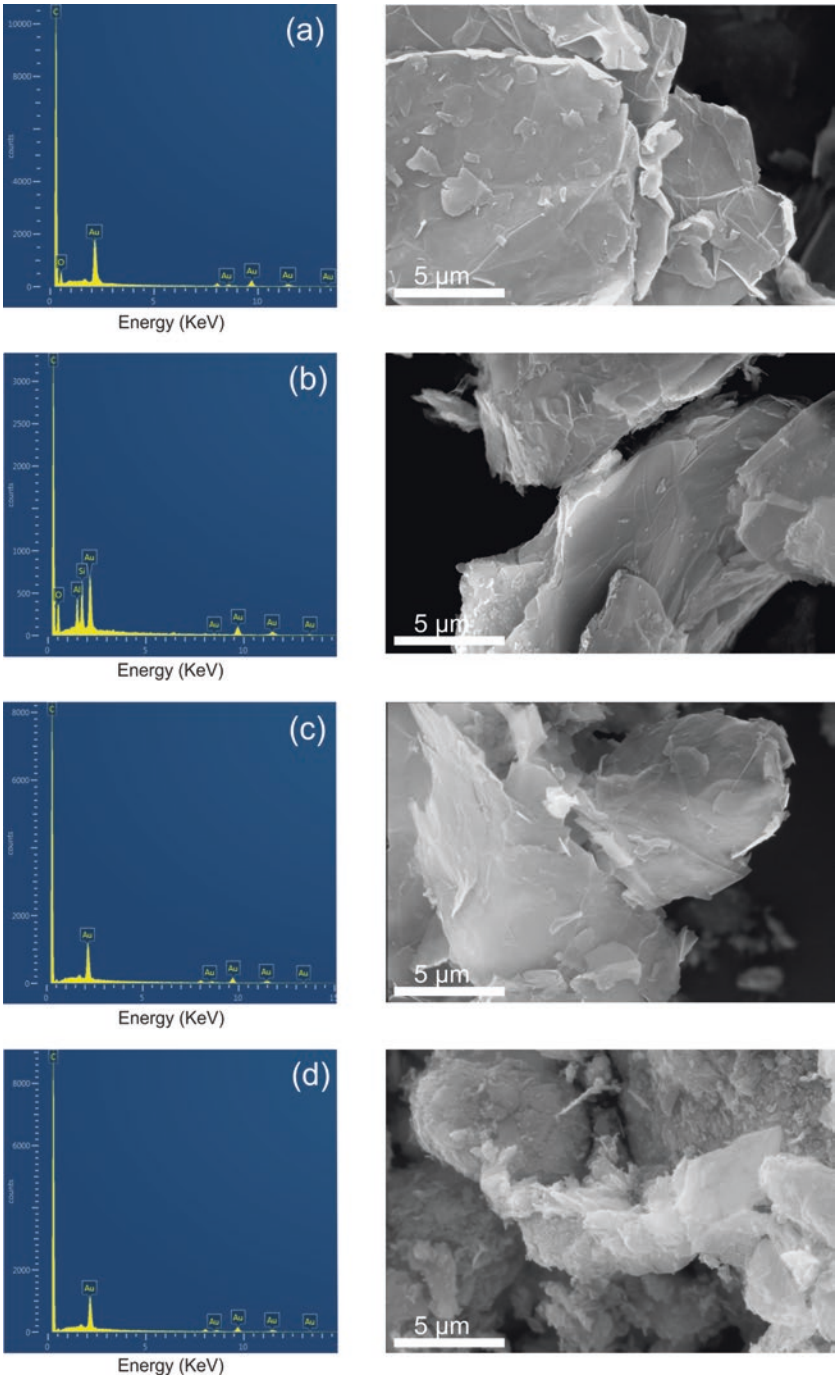


**Fig. 13** SEM and EDS images of commercial graphene (**a**), rGO 5.0 V (**b**), rGO 7.5 V (**c**), e rGO 10.0 V (**d**)

## 4 Conclusions

A green and sustainable route for rGO synthesis has been successfully developed from waste battery graphite as anode electrode. The yield of the rGO using waste battery graphite was 80%. The pretreatment of graphite rod is as important in the graphene synthesis by electrochemical exfoliation as to eliminate inorganic substances. Raman analysis showed that both commercial graphene and produced rGO were within 5–10 layers in structure. Defect density increased with increasing applied potential, but the difference between 5.0 and 7.5 V is very small (0.1). An increase in applied potential also leads to increasing the BET area, but difference between 7.5 and 10.0 V is quite small. Graphite and synthetized rGOs were classified as mesoporous. XRD showed that GO reduction using natural reducing agent was effective for the three rGO samples. SEM images clearly showed the sheet-like nature of all rGO samples. rGO synthesized at 5.0 V presented agglomerates of microleaves, and the samples of 7.5 and 10.0 V presented nanosheets with the presence of aggregates of nanoparticles. EDS showed that pretreatment and reduction process was effective for 7.5 and 10.0 samples only. From the data, 7.5 V is the optimum voltage to produce high-quality graphene.

**Acknowledgments** The authors thank the State University of Maringá (Paraná, Brazil), Chemical Engineering and Chemistry Department, for laboratorial support. We also thank the FINEP, CAPES, COMCAP-UEM, and CNPq for research funding and equipment availability.

## References

Abdelkader AM, Cooper AJ, Dryfe RAW, Kinloch IA. How to get between the sheets: a review of recent works on the electrochemical exfoliation of graphene materials from bulk graphite. Nanoscale. 2015;7:6944–56. https://doi.org/10.1039/C4NR06942K.

Abdolhosseinzadeh S, Asgharzadeh H, Kim HS. Fast and fully-scalable synthesis of reduced graphene oxide. Sci Rep. 2015;5:10160. https://doi.org/10.1038/srep10160.

Achee TC, Sun W, Hope JT, Quitzau SG, Sweeney CB, Shah SA, Habib T, Green MJ. High-yield scalable graphene nanosheet production from compressed graphite using electrochemical exfoliation. Sci Rep. 2018;8:14525. https://doi.org/10.1038/s41598-018-32741-3.

Acik M, Lee G, Mattevi C, Prikle A, Wallace RM, Chhowalla M, Cho K, Chabal Y. The role of oxygen during thermal reduction of graphene oxide studied by infrared absorption spectroscopy. J Phys Chem C. 2011;115:19761–81. https://doi.org/10.1021/jp2052618.

Ali MEA. Preparation of graphene nanosheets by electrochemical exfoliation of a graphite-nanoclay composite electrode: application for the adsorption of organic dyes. Colloids Surf A Physicochem Eng Asp. 2019;570:107–16. https://doi.org/10.1016/j.colsurfa.2019.02.063.

Ali I, Basheer AA, Mbianda XY, Burakov A, Galunin E, Burakova I, Mkrtchyan E, Tkachev A, Grachev V. Graphene based adsorbents for remediation of noxious pollutants from wastewater. Environ Int. 2019;127:160–80. https://doi.org/10.1016/j.envint.2019.03.029.

Amaro-Gahete J, Benítez A, Obter R, Esquivel D, Jiménez-Sanchidrián C, Morales J, Caballero A, Romero-Salguero FJ. A comparative study of particle size distribution of graphene nanosheets synthesized by an ultrasound-assisted method. Nano. 2019;9(152):1–17. https://doi.org/10.3390/nano9020152.

Ambrosi A, Pumera M. Exfoliation of layered materials using electrochemistry. Chem Soc Rev. 2018;47(19):7213–24. https://doi.org/10.1039/c7cs00811b.

Ambrosi A, Chua CK, Latiff NM, Loo AH, Wong CHA, Eng AYS, Bonanni A, Pumera M. Graphene and its electrochemistry – an update. Chem Soc Rev. 2016;45:2458–93. https://doi.org/10.1039/c6cs00136j.

Assis Filho RB, Araújo CMB, Baptisttella MAS, Batista EB, Barata RA, Ghislandi MG, Motta Sobrinho MA. Environmentally friendly route for graphene oxide production via electrochemical synthesis focused on the adsorptive removal of dyes from water. Environ Technol. 2019;2019:1–43. https://doi.org/10.1080/09593330.2019.1581842.

Astrup T, Riber C, Pedersen AJ. Incinerator performance: effects of changes in waste input and furnace operation on air emissions and residues. Waste Manag Res. 2011;29(10 Suppl):57–68. https://doi.org/10.1177/0734242X11419893.

Baio JAF, Ramos LA, Cavalheiro ETG. Construção de eletrodo de grafite retirado de pilha comum: Aplicações didáticas. Quim Nova. 2014;37(6):1078–84. https://doi.org/10.5935/0100-4042.20140151.

Bandi S, Ravuri S, Peshwe DR, Srivastav AK. Graphene from discharged dry cell battery electrodes. J Hazard Mater. 2019;366:358–69. https://doi.org/10.1016/j.jhazmat.2018.12.005.

Bernardes AM, Espinosa DCR, Tenório JAS. Recycling of batteries: a review of current processes and technologies. J Power Sources. 2004;130:291–8. https://doi.org/10.1016/j.jpowsour.2003.12.026.

Bigum M, Damgaard A, Scheutz C, Christensen TH. Environmental impacts and resource losses of incinerating misplaced household special wastes (WEEE, batteries, ink cartridges and cables). Resour Conserv Recycl. 2017;122:251–60. https://doi.org/10.1016/j.resconrec.2017.02.013.

Biswas RK, Karmakar AK, Kumar SL. Recovery of manganese and zinc from spent Zn–C cell powder: experimental design of leaching by sulfuric acid solution containing glucose. Waste Manag. 2016;51:174–81. https://doi.org/10.1016/j.wasman.2015.11.002.

Bleu Y, Bourquard F, Loir A, Barnier V, Garrelie F, Donnet C. Raman study of the substrate influence on graphene synthesis using a solid carbon source via rapid thermal annealing. J Raman Spectrosc. 2019;2019:1–12. https://doi.org/10.1002/jrs.5683.

Cabral CSD, Miguel SP, Melo-Diogo D, Louro RO, Correia IJ. Green reduced graphene oxide functionalized 3D printed scaffolds for bone tissue regeneration. Carbon. 2019;146:513–23. https://doi.org/10.1016/j.carbon.2019.01.100.

Charef SA, Affoune AM, Caballero A, Cruz-Yusta M, Morales J. Simultaneous recovery of Zn and Mn from used batteries in acidic and alkaline mediums: a comparative study. Waste Manag. 2017;68:518–26. https://doi.org/10.1016/j.wasman.2017.06.048.

Chen D, Wang F, Li Y, Wang W-W, Huang T-X, Li J-F, Novoselov S, Tian Z-Q, Zhan D. Programmed electrochemical exfoliation of graphite to high quality graphene. Chem Commun. 2019;55:3379. https://doi.org/10.1039/C9CC00393B.

Clay Minerals Society. The Clay Minerals Society glossary of clay science. Chantilly: The Clay Minerals Society; 2019. Available online at http://www.clays.org/CMS_Nomenclature_Glossary_April_2019_Part_2.htm. Accessed Aug 2019.

Collins SP, Perim E, Daff TD, Skaf MS, Galvão DS, Woo TK. Idealized carbon-based materials exhibiting record deliverable capacities for vehicular methane storage. J Phys Chem C. 2019;132(2):1050–8. https://doi.org/10.1021/acs.jpcc.8b09447.

Coros M, Pogacean F, Rosu M-C, Socaci C, Borodi G, Magerusan L, Biris AR, Pruneanu S. Simple and cost-effective synthesis of graphene by electrochemical exfoliation of graphite rods. RSC Adv. 2016;6:2651–61. https://doi.org/10.1039/C5RA19277C.

Cychosz KA, Thommes M. Progress in the physisorption characterization of nanoporous gas storage materials. English. 2018;4:559–66. https://doi.org/10.1016/j.eng.2018.06.001.

de Silva KKH, Huang H-H, Yoshimura M. Progress of reduction of graphene oxide by ascorbic acid. Appl Surf Sci. 2018;447:338–46. https://doi.org/10.1016/j.apsusc.2018.03.243.

Dideikin AT, Vul AY. Graphene oxide and derivatives: the place in graphene family. Front Phys. 2019;6:149. https://doi.org/10.3389/fphy.2018.00149.

Dimiev AM, Eigler S. Graphene oxide: fundamentals and applications. Chichester. ISBN 978-1-11-906944-7: Wiley; 2017. https://doi.org/10.1002/9781119069447.

Dolci G, Tua C, Grosso M, Rigamonti L. Life cycle assessment of consumption choices: a comparison between disposable and rechargeable household batteries. Int J Life Cycle Assess. 2016;21:1691–705. https://doi.org/10.1007/s11367-016-1134-5.

Dresselhaus MS, Araujo PT. Perspectives on the 2010 Nobel prize in physics for graphene. ACS Nano. 2010;4(11):6297–302. https://doi.org/10.1021/nn1029789.

Dreyer DR, Park S, Bielawski CW, Ruoff RS. The chemistry of graphene oxide. Chem Soc Rev. 2010;39:228–40. https://doi.org/10.1039/B917103G.

Ebin B, Petranikova M, Steenari BM, Ekberg C. Production of zinc and manganese oxide particles by pyrolysis of alkaline and Zn–C battery waste. Waste Manag. 2016;51:157–67. https://doi.org/10.1016/j.wasman.2015.10.029.

Ebin B, Petranikova M, Steenari BM, Ekberg C. Recovery of industrial valuable metals from household battery waste. Waste Manag Res. 2019;37(2):168–75. https://doi.org/10.1177/0734242X18815966.

Ejigu A, Miller B, Kinloch IA, Dryfe RAW. Optimisation of electrolytic solvents for simultaneous electrochemical exfoliation and functionalization of graphene with metal nanostructures. Carbon. 2018;128:257–66. https://doi.org/10.1016/j.carbon.2017.11.081.

Espinosa DCR, Tenório JAS. Caracterização de pilhas e baterias proveniente de programa de devolução voluntária. Rev Bras Ciênc Ambient. 2009;14:33–9.. ISSN 2176-9478

Fadeel B, Bussy C, Merino S, Vazquez E, Flahaut E, Mouchet F, Evariste L, Gauthier L, Koivisto AJ, Vogel U, Martín C, Delogu LG, Buerki-Thurnherr T, Wick P, Beloin-Saint-Pierre D, Hischier R, Pelin M, Carniel FC, Tretiach M, Cesca F, Benfenati F, Scaini D, Ballerini L, Kostarelos K, Prato M, Bianco A. Safety assessment of graphene-based materials: focus on human health and the environment. ACS Nano. 2018;12:10582–620. https://doi.org/10.1021/acsnano.8b04758.

Fang S, Lin Y, Hu YH. Recent advances in green, safe and fast production of graphene oxide via electrochemical approaches. ACS Sustain Chem Eng. 2019;7(15):12671–81. https://doi.org/10.1021/acssuschemeng.9b02794.

Fei H, Dong J, Wan C, Zhai Z, Xu X, Lin Z, Wang Y, Liu H, Zang K, Luo J, Zhao S, Hu W, Yan W, Shakir I, Huang Y, Duan X. Microwave-assisted rapid synthesis of graphene-supported single atomic metals. Adv Mater. 2018;30:1802146. https://doi.org/10.1002/adma.201802146.

Fernandez-Merino MJ, Guardia L, Paredes JI, Villar-Rodil S, Solís-Fernández P, Martínez-Alonso A, Tascón JMD. Vitamin C is an ideal substitute for hydrazine in the reduction of graphene oxide suspensions. J Phys Chem C. 2010;114:6426–32. https://doi.org/10.1021/jp100603h.

Ferrari AC, Basko DM. Raman spectroscopy as a versatile tool for studying the properties of graphene. Nat Nanotechnol. 2013;8:235–46. https://doi.org/10.1038/nnano.2013.46.

Fikri E, Purwanto P, Sunoko HR. Modelling of household hazardous waste (HHW) management in Semarang City (Indonesia) by using life cycle assessment (LCA) approach to reduce greenhouse gas (GHG) emissions. Procedia Environ Sci. 2015;23:123–9. https://doi.org/10.1016/j.proenv.2015.01.019.

Gallegos MV, Peluso MA, Sambeth JE. Preparation and characterization of manganese and zinc oxides recovered from spent alkaline and Zn/C batteries using biogenerated sulfuric acid as leaching agent. JOM. 2018;70(10):2351–8. https://doi.org/10.1007/s11837-018-3043-5.

Gan L, Li B, Chen Y, Yu B, Chen Z. Green synthesis of reduced graphene oxide using bagasse and its application in dye removal: a waste-to-resource supply chain. Chemosphere. 2019;219:148–54. https://doi.org/10.1016/j.chemosphere.2018.11.181.

García-Argumánez A, Llorente I, Caballero-Calero O, González Z, Menéndez R, Escudero ML, García-Alonso MC. Electrochemical reduction of graphene oxide on biomedical grade CoCr alloy. Appl Surf Sci. 2019;465:1028–36. https://doi.org/10.1016/j.apsusc.2018.09.188.

Geim AK, Novoselov KS. The rise of graphene. Nat Mater. 2007;6:183–91. https://doi.org/10.1038/nmat1849.

Ghosh TK, Sadhukhan S, Rana D, Bhattacharyya A, Chattopadhyay D, Chakraborty M. Green approaches to synthesize reduced graphene oxide and assessment of its electrical properties. Nano-Struct Nano-Objects. 2019;19:100362. https://doi.org/10.1016/j.nanoso.2019.100362.

Gnanaseelan M, Samanta S, Pionteck J, Jehnichen D, Simon F, Pötschke P, Voit B. Vanadium salt assisted solvothermal reduction of graphene oxide and the thermoelectric characterisation of the reduced graphene oxide in bulk and as composite. Mater Chem Phys. 2019;229:319–29. https://doi.org/10.1016/j.matchemphys.2019.03.002.

Guevara-García JA, Montiel-Corona V. Used battery collection in Central Mexico: metal content, legislative/management situation and statistical analysis. J Environ Manag. 2012;95:S154–7. https://doi.org/10.1016/j.jenvman.2010.09.019.

Gurzęda B, Krawczyk P. Electrochemical formation of graphite oxide from the mixture composed of sulfuric and nitric acids. Electrochim Acta. 2019;310:96–103. https://doi.org/10.1016/j.electacta.2019.04.088.

Hashimoto H, Muramatsu Y, Nishina Y, Hidetaka A. Bipolar anodic electrochemical exfoliation of graphite powders. Electrochem Commun In Press. 2019; https://doi.org/10.1016/j.elecom.2019.06.001.

Hou D, Liu Q, Cheng H, Zhang H, Wang S. Green reduction of graphene oxide via *Lycium barbarum* extract. J Solid State Chem. 2017;246:351–6. https://doi.org/10.1016/j.jssc.2016.12.008.

Hou D, Liu Q, Wang X, Quan Y, Qiao Z, Yu L, Ding S. Facile synthesis of graphene via reduction of graphene oxide by artemisinin in ethanol. J Mater. 2018;4:256–65. https://doi.org/10.1016/j.jmat.2018.01.002.

Htwe YZN, Chow WS, Suda Y, Thant AA, Mariatti M. Effect of electrolytes and sonication times on the formation of graphene using an electrochemical exfoliation process. Appl Surf Sci. 2019;469:951–61. https://doi.org/10.1016/j.apsusc.2018.11.029.

Hu M, Yai Z, Wang X. Characterization techniques for graphene-based materials in catalysis. AIMS Mater Sci. 2017;4(3):755–88. https://doi.org/10.3934/matersci.2017.3.755.

Huang G, Kang W, Geng Q, Xing B, Liu Q, Jia J, Zhang C. One-step green hydrothermal synthesis of few-layer graphene oxide from humic acid. Nano. 2018;8(4):215. https://doi.org/10.3390/nano8040215.

Ippolito NM, Belardi G, Medici F, Piga L. Utilization of automotive shredder residues in a thermal process for recovery of manganese and zinc from zinc–carbon and alkaline spent batteries. Waste Manag. 2016;51:182–9. https://doi.org/10.1016/j.wasman.2015.12.033.

Jorio A, Dresselhaus MS, Saito R, Dresselhaus G. Raman spectroscopy in graphene related systems. Weinheim. ISBN 978-3-527-63269-5: Wiley-VCH Verlag GmbH & Co. KGaA; 2011. https://doi.org/10.1002/9783527632695.

Kairi MI, Dayou S, Kairi NI, Bakar SA, Vigolo B, Mohamed AR. Toward high production of graphene flakes - a review on recent developments in their synthesis methods and scalability. J Mater Chem A. 2018;6:15010–26. https://doi.org/10.1039/c8ta04255a.

Kalmykova Y, Berg PEO, Patrício J, Lisovskaja V. Portable battery lifespans and new estimation method for battery collection rate based on a lifespan modeling approach. Resour Conserv Recycl. 2017;120:65–74. https://doi.org/10.1016/j.resconrec.2017.01.006.

Khan MH, Gulshan F, Kurny ASW. Recovery of metal values from spent zinc–carbon dry cell batteries. J Inst Eng India Ser D. 2013;94(1):51–6. https://doi.org/10.1007/s40033-013-0017-1.

Khanam PN, Hasan A. Biosynthesis and characterization of graphene by using non-toxic reducing agent from *Allium Cepa* extract: anti-bacterial properties. Int J Biol Macromol. 2019;126:151–8. https://doi.org/10.1016/j.ijbiomac.2018.12.213.

Khojasteh H, Safajou H, Mortazavi-Derazkola S, Salavati-Niasari M, Heydaryan K, Yazdani M. Economic procedure for facile and eco-friendly reduction of graphene oxide by plant extracts; a comparison and property investigation. J Clean Prod. 2019;229:1139–47. https://doi.org/10.1016/j.jclepro.2019.04.350.

Khosroshahi Z, Kharaziha M, Karimzadeh F, Allafchian A. Green reduction of graphene oxide by ascorbic acid. AIP Conf Proc. 2018;1920:020009. https://doi.org/10.1063/1.5018941.

Kim JM, Ko D, Oh J, Lee J, Hwang T, Jeon Y, Antink WH, Piao Y. Electrochemically exfoliated graphene as a novel microwave susceptor: the ultrafast microwave-assisted synthesis of carbon-coated silicon-graphene film as a lithium-ion battery anode. Nanoscale. 2017;9:15582–90. https://doi.org/10.1039/C7NR04657J.

Krekeler MPS, Barrett HA, Davis R, Burnette C, Doran T, Ferraro A, Meyer A. An investigation of mass and brand diversity in a spent battery recycling collection with an emphasis on spent alkaline batteries: implications for waste management and future policy concerns. J Power Sources. 2012;203:222–6. https://doi.org/10.1016/j.jpowsour.2011.11.040.

Kumar CV, Pattammattel A. Discovery of graphene and beyond. In: Kumar CV, Pattammattel A (Eds.,) Introduction to Graphene: chemical and biochemical applications, chapter 1. New York: Academic; 2017. p. 1–15. ISBN 978-0-12-813182-4. https://doi.org/10.1016/B978-0-12-813182-4.00001-5.

Le Fevre LW, Cao J, Kinloch IA, Forsyth AJ, Dryfe RAW. Systematic comparison of graphene materials for supercapacitor electrodes. Chem Open. 2019;8(4):419–28. https://doi.org/10.1002/open.201900004.

Lee XJ, Hiew BYZ, Lai KC, Lee LY, Gan S, Thangalazhy-Gopakumar S, Rigby S. Review on graphene and its derivatives: synthesis methods and potential industrial implementation. J Taiwan Inst Chem Eng. 2019;98:163–80. https://doi.org/10.1016/j.jtice.2018.10.028.

Lowe SE, Shi G, Zhang Y, Qin J, Jiang L, Jiang S, Al-Mamun M, Liu P, Zhong YL, Zhao H. The role of electrolyte acid concentration in the electrochemical exfoliation of graphite: mechanism and synthesis of electrochemical graphene oxide. Nano Mater Sci, In Press. 2019; https://doi.org/10.1016/j.nanoms.2019.07.001.

Ma Y, Bai D, Hu X, Ren N, Gao W, Chen S, Chen H, Lu Y, Li J, Bai Y. Robust and antibacterial polymer/mechanically exfoliated graphene nanocomposite fibers for biomedical applications. ACS Appl Mater Interfaces. 2018;10(3):3002–10. https://doi.org/10.1021/acsami.7b17835.

Malard LM, Pimenta MA, Dresselhaus G, Dresselhaus MS. Raman spectroscopy in graphene. Phys Rep. 2009;473:51–87. https://doi.org/10.1016/j.physrep.2009.02.003.

Marrani AG, Motta A, Schrebler R, Zanoni R, Dalchiele EA. Insights from experiment and theory into the electrochemical reduction mechanism of graphene oxide. Electrochim Acta. 2019;304:231–8. https://doi.org/10.1016/j.electacta.2019.02.108.

Meng X, Prawang P, Li Z, Wang H, Zhang S. Carbon-based materials enhanced emulsification to improve product distribution in isobutene/butane alkylation catalyzed by sulfuric acid. Ind Eng Chem Res. 2017;56(27):7700–7. https://doi.org/10.1021/acs.iecr.7b01878.

Metzelder F, Funck M, Hüffer T, Schmidt TC. Comparison of sorption to carbon-based materials and nanomaterials using inverse liquid chromatography. Environ Sci Technol. 2018;52(17):9731–40. https://doi.org/10.1021/acs.est.8b01653.

Mooste M, Kibena-Põldsepp E, Ossonon BD, Bélanger D, Tammeveski K. Oxygen reduction on graphene sheets functionalised by anthraquinone diazonium compound during electrochemical exfoliation of graphite. Electrochim Acta. 2018;267:246–54. https://doi.org/10.1016/j.electacta.2018.02.064.

Moreno-Bárcenas A, Perez-Robles JF, Vorobiev YV, Ornelas-Soto N, Mexicano A, García AGB. Graphene synthesis using a CVD reactor and a discontinuous feed of gas precursor at atmospheric pressure. J Nanomater. 2018;2018:1–11. https://doi.org/10.1155/2018/3457263.

Muhsan AA, Lafdi K. Numerical study of the electrochemical exfoliation of graphite. SN Appl Sci. 2019;1:276. https://doi.org/10.1007/s42452-019-0296-8.

Munuera JM, Paredes JI, Villar-Rodil S, Martínez-Alonso A, Tascón JMD. A simple strategy to improve the yield of graphene nanosheets in the anodic exfoliation of graphite foil. Carbon. 2017;115:625–8. https://doi.org/10.1016/j.carbon.2017.01.038.

Muzyka R, Drewniak S, Pustelny T, Chrubasik M, Gryglewics G. Characterization of graphite oxide and reduced graphene oxide obtained from different graphite precursors and oxidized by different methods using Raman spectroscopy. Materials. 2018;11:1050. https://doi.org/10.3390/ma11071050.

Nawaz M, Miran W, Jang J, Lee DS. One-step hydrothermal synthesis of porous 3D reduced graphene oxide/$TiO_2$ aerogel for carbamazepine photodegradation in aqueous solution. Appl Catal B. 2017;203:85–95. https://doi.org/10.1016/j.apcatb.2016.10.007.

Noé JC, Nutz M, Reschauer J, Morell N, Tsioutsios I, Reserbat-Plantey A, Watanabe K, Taniguchi T, Bachtold A, Högele A. Environmental electrometry with luminescent carbon nanotubes. Nano Lett. 2018;18(7):4136–40. https://doi.org/10.1021/acs.nanolett.8b00871.

Novoselov KS, Geim AK, Morozov SV, Jiang D, Zhang Y, Dubonos SV, Grigorieva IV, Firsov AA. Electric field effect in atomically thin carbon films. Science. 2004;306(5696):666–9. https://doi.org/10.1126/science.1102896.

Paci JT, Belytschko T, Schatz GC. Computational studies of the structure, behavior upon heating, and mechanical properties of graphite oxide. J Phys Chem C. 2007;111:18099–111. https://doi.org/10.1021/jp075799g.

Papageorgiou DG, Liu M, Li Z, Vallés C, Young RJ, Kinloch IA. Hybrid poly(ether ether ketone) composites reinforced with a combination of carbon fibres and graphene nanoplatelets. Compos Sci Technol. 2019;175:60–8. https://doi.org/10.1016/j.compscitech.2019.03.006.

Parvez K, Wu Z, Li R, Liu X, Graf R, Feng X, Müllen K. Exfoliation of graphite into graphene in aqueous solutions of inorganic salts. J Am Chem Soc. 2014;136:6083–91. https://doi.org/10.1021/ja5017156.

Patrício J, Kalmykova Y, Berg PEO, Rosado L, Åberg H. Primary and secondary battery consumption trends in Sweden 1996–2013: method development and detailed accounting by battery type. Waste Manag. 2015;39:236–45. https://doi.org/10.1016/j.wasman.2015.02.008.

Pei S, Cheng HM. The reduction of graphene oxide. Carbon. 2012;50(9):3210–28. https://doi.org/10.1016/j.carbon.2011.11.010.

Petranikova M, Ebin B, Mikhailova S, Steenari BM, Ekberg C. Investigation of the effects of thermal treatment on the leachability of Zn and Mn from discarded alkaline and ZneC batteries. J Clean Prod. 2018;170:1195–205. https://doi.org/10.1016/j.jclepro.2017.09.238.

Pogacean F, Coros M, Mirel V, Magerusan L, Barbu-Tudoran L, Vulpoi A, Staden R-I S-V, Pruneanu S. Graphene-based materials produced by graphite electrochemical exfoliation in acidic solutions: application to sunset yellow voltammetric detection. Microchem J. 2019;147:112–20. https://doi.org/10.1016/j.microc.2019.03.007.

Rahman G, Najaf Z, Mehmood A, Bilal S, Shah AHA, Mian SA, Ali G. An overview of the recent progress in the synthesis and application of carbon nanotubes. J Carbon Res. 2019;5:3. https://doi.org/10.3390/c5010003.

Roy B, Jing Y, Basu B. Reduced graphene oxides (rGOs) using nature-based reducing sources: detailed studies on properties, morphologies and catalytic activity. Curr Graphene Sci. 2017;1:71–9. https://doi.org/10.2174/2452273201666170519155915.

Saleem H, Haneef M, Abbasi HY. Synthesis route of reduced graphene oxide via thermal reduction of chemically exfoliated graphene oxide. Mater Chem Phys. 2018;204:1–7. https://doi.org/10.1016/j.matchemphys.2017.10.020.

Sinclair RC, Suter JL, Coveney PV. Microchemical exfoliation of graphene on the atomistic scale. Phys Chem Chem Phys. 2019;21:5716–22. https://doi.org/10.1039/C8CP07796G.

Sing KSW, Everett DH, Haul RAW, Moscou L, Pierotti RA, Rouquérol J, Siemienieewska T. Reporting physisorption data for gas/solid systems – with special reference to the determination of surface area and porosity. Pure Appl Chem. 1985;57(4):603–19. https://doi.org/10.1515/iupac.57.0007.

Singh R, Mahandra H, Gupta B. Recovery of zinc and cadmium from spent batteries using Cyphos IL 102 via solvent extraction route and synthesis of Zn and Cd oxide nanoparticles. Waste Manag. 2017;67:240–52. https://doi.org/10.1016/j.wasman.2017.05.027.

Smith AT, LaChance AM, Zeng S, Liu B, Sun L. Synthesis, properties and applications of graphene oxide/reduced graphene oxide and their nanocomposites. Nano Mater Sci. 2019;1(1):31–47. https://doi.org/10.1016/j.nanoms.2019.02.004.

Sobianowska-Turek A, Szczepaniak W, Maciejewski P, Gawlik-Kobylinska M. Recovery of zinc and manganese, and other metals (Fe, Cu, Ni, Co, Cd, Cr, Na, K) from Zn-$MnO_2$ and Zn-C

waste batteries: hydroxyl and carbonate co-precipitation from solution after reducing acidic leaching with use of oxalic acid. J Power Sources. 2016;325:220–8. https://doi.org/10.1016/j.jpowsour.2016.06.042.

Sultanov FR, Daulbayev C, Bakbolat B, Mansurov ZA, Urazgaliyeva AA, Ebrahim R, Pei SS, Huang K-P. Microwave-enhanced chemical vapor deposition graphene nanoplatelets-derived 3D porous materials for oil/water separation. Carbon Lett. 2019:1–12. https://doi.org/10.1007/s42823-019-00073-5.

Sun M, Yang X, Huisingh D, Wang R, Wang Y. Consumer behavior and perspectives concerning spent household battery collection and recycling in China: a case study. J Clean Prod. 2015;107:775–85. https://doi.org/10.1016/j.jclepro.2015.05.081.

Tahriri M, Monico MD, Moghanian A, Yaraki MT, Torres R, Tadegari A, Tayebi L. Graphene and its derivatives: opportunities and challenges in dentistry. Mater Sci Eng C. 2019;102:171–85. https://doi.org/10.1016/j.msec.2019.04.051.

Teran-Salgado E, Bahena-Uribe D, Márquez-Aguilar PA, Reyes-Rodriguez JL, Cruz-Silva R, Solorza-Feria O. Platinum nanoparticles supported on electrochemically oxidized and exfoliated graphite for the oxygen reduction reaction. Electrochim Acta. 2019;298:172–85. https://doi.org/10.1016/j.electacta.2018.12.057.

Terazono A, Oguchi M, Iino S, Mogi S. Battery collection in municipal waste management in Japan: challenges for hazardous substance control and safety. Waste Manag. 2015;39:246–57. https://doi.org/10.1016/j.wasman.2015.01.038.

Thommes M, Kaneko K, Neimark AV, Olivier JP, Rodriguez-Reinoso F, Rouquerol J, Sing KSW. Physisorption of gases, with special reference to the evaluation of surface area and pore size distribution (IUPAC technical report). Pure Appl Chem. 2015;87(9–10):1051–69. https://doi.org/10.1515/pac-2014-1117.

Ucar N, Gokceli G, Yuksek IO, Onen A, Yavuz NK. Graphene oxide and graphene fiber produced by different nozzle size, feed rate and reduction time with vitamin C. J Ind Text. 2018;48(1):292–303. https://doi.org/10.1177/1528083716685903.

Vázquez-Sánchez P, Rodríguez-Escudero MA, Burgos FJ, Llorente I, Caballero-Calero O, Gonzáles MM, Fernández R, García-Alonso MC. Synthesis of cu/rGO composites by chemical and thermal reduction of graphene oxide. J Alloys Compd. 2019;800:379–91. https://doi.org/10.1016/j.jallcom.2019.06.008.

Vieira LHC, Silva RG, Silva BO, Souza Júnior S, Câmara CS, Afonso JC. Avaliação da qualidade de pilhas alcalinas e zinco-carbono de diferentes procedências. Ecletica Quim. 2013;38:9–24. https://doi.org/10.26850/1678-4618eqj.v38.1.2013.p09-24.

Voiry D, Yang J, Kupferberg J, Fullon R, Lee C, Jeong HY, Shin HS, Chhowalla M. High-quality graphene via microwave reduction of solution-exfoliated graphene oxide. Science. 2016;353(6306):1413–6. https://doi.org/10.1126/science.aah339.

Wang J, Chen Z, Chen B. Adsorption of polycyclic aromatic hydrocarbons by graphene and graphene oxide nanosheets. Environ Sci Technol. 2014;48(9):4817–25. https://doi.org/10.1021/es405227u.

Wang H, Feng Q, Tang X, Liu K. Preparation of high-purity graphite from a fine microcrystalline graphite concentrate: effect of alkali roasting pre-treatment and acid leaching process. Sep Sci Technol. 2016;51(14):2465–71. https://doi.org/10.1080/01496395.2016.1206933.

Wang J, Salihi EC, Šiller L. Green reduction of graphene oxide using alanine. Mater Sci Eng C. 2017;72:1–6. https://doi.org/10.1016/j.msec.2016.11.017.

Wei N, Yu L, Sun Z, Song Y, Wang M, Tian Z, Xia Y, Cai J, Li YY, Zhao L, Li Q, Rümmeli MH, Sun J, Liu Z. Scalable salt-templated synthesis of nitrogen-doped graphene nanosheets toward printable energy storage. ACS Nano. 2019;13:7517–26. https://doi.org/10.1021/acsnano.9b03157.

Xie X, Zhou Y, Huang K. Advances in microwave-assisted production of reduced graphene oxide. From Chem. 2019;7:1–11. https://doi.org/10.3389/fchem.2019.00355.

Xu J, Wang L, Zhu Y. Decontamination of bisphenol A from aqueous solution by graphene adsorption. Langmuir. 2012;28:8418–25. https://doi.org/10.1021/la301476p.

Xu C, Shi X, Ji A, Shi L, Zhou C, Cui Y. Fabrication and characteristics of reduced graphene oxide produced with different green reductants. PLoS One. 2015;10(12):1–15. https://doi.org/10.1371/journal.pone.0144842.

Yang J, Zuo S. Facile synthesis of graphitic mesoporous carbon materials from sucrose. Diam Relat Mater. 2019;95:1–4. https://doi.org/10.1016/j.diamond.2019.03.018.

Yang Y, Hou H, Zou G, Shi W, Shuai H, Li J, Ji X. Electrochemical exfoliation of graphene-like two-dimensional nanomaterials. Nanoscale. 2019;11:16–33. https://doi.org/10.1039/C8NR08227H.

Yap PL, Kabiri S, Tran DNH, Losic D. Multifunctional binding chemistry on modified graphene composite for selective and highly efficient adsorption of mercury. ACS Appl Mater Interfaces. 2019;11(6):6350–62. https://doi.org/10.1021/acsami.8b17131.

Yi M, Shen Z. A review on mechanical exfoliation for the scalable production of graphene. J Mater Chem A. 2015;3:11700–15. https://doi.org/10.1039/C5TA00252D.

Yin R, Shen P, Lu Z. A green approach for the reduction of graphene oxide by the ultraviolet/sulfite process. J Colloid Interface Sci. 2019;550:110–6. https://doi.org/10.1016/j.jcis.2019.04.073.

Yu P, Lowe SE, Simon GP, Zhong YL. Electrochemical exfoliation of graphite rod and production of functional graphene. Curr Opin Colloid Interface Sci. 2015;20:329–38. https://doi.org/10.1016/j.cocis.2015.10.007.

Yu L, Wang L, Xu W, Chen L, Fu M, Wu J, Ye D. Adsorption of VOCs on reduced graphene oxide. J Environ Sci. 2018;67:171–8. https://doi.org/10.1016/j.jes.2017.08.022.

Zaytseva O, Neumann G. Carbon nanomaterials: production, impact on plant development, agricultural and environmental applications. Chem Biol Technol Agric. 2016;3:17. https://doi.org/10.1186/s40538-016-0070-8.

Zhang J, Fahrenthold EP. Graphene-based sensing of gas-phase explosives. ACS Appl Nano Mater. 2019;2(3):1445–56. https://doi.org/10.1021/acsanm.8b02330.

Zhang J, Yang H, Shen G, Cheng P, Zhang J, Guo S. Reduction of graphene oxide via L-ascorbic acid. Chem Commun. 2010;46(7):1112–4. https://doi.org/10.1039/b917705a.

Zhang P, Li Z, Zhang S, Shao G. Recent advances in effective reduction of graphene oxide for highly improved performance toward electrochemical energy storage. Energy Environ Mater. 2018;1:5–12. https://doi.org/10.1002/eem2.12001.

Zhen Z, Zhu H. Structure and properties of graphene. In: Zhu H, Xu Z, Xie D, Frang Y, editors. Graphene: fabrication, characterizations, properties and application, chapter 1. New York: Academic; 2018. p. 1–12. ISBN 978-0-12-812651-6. https://doi.org/10.1016/B978-0-12-812651-6.00001-X.

# Bio-catalysis as a Green Approach for Industrial Waste Treatment

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## Contents



## Abbreviations

| | |
|---|---|
| AOPs | Advanced oxidation processes |
| CLEA | Cross-linked enzyme aggregates |
| CaLB | *Candida antarctica* lipase B |
| COD | Chemical oxygen demand |

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_14

| | |
|---|---|
| DMF | Dimethylformamide |
| DEP | Deep eutectic solvents |
| DCW | Dry cell weight |
| FAE | Fatty acid esters |
| FT-IR | Fourier transform infrared spectroscopy |
| HiC | *Humicola insolens* cutinase |
| HSP | 6-Hydroxy-3-succinoyl-pyridine |
| HPLC | High-pressure liquid chromatography |
| ISM | Iterative saturation mutagenesis |
| IPR | Intellectual property rights |
| PCR | Polymerase chain reaction |
| MDH | Mannitol 1-dehydrogenase |
| MNCs | Multinational companies |
| NAD | Nicotinamide adenine dinucleotide |
| PET | Poly(ethylene terephthalate) |
| $scCO_2$ | Supercritical carbon dioxide |
| SF | Submerged fermentation |
| SEN | Single enzyme nanoparticle |
| $SO_3H$ | Sulfonic acid |
| SP | 3-Succinoyl-pyridine |
| TAGs | Triacylglycerols |
| WRF | White rot fungi |

## 1 Introduction

In recent time, bio-catalysts have been researched significantly with extensive applications in industries for the generation of size pharmaceuticals and chemical products (de Carvalho 2011; Du et al. 2011; Patel 2011; Zhao 2011). Bio-catalysis has some significant advantages over chemical catalysis like better efficiency, an elevated degree of selectivity (enantio- and regio-, chemo-), and factors for the response to proceed (Hudlicky and Reed 2009; Reetz and Wu 2009). For example, (1) the nitrile hydratase which is catalyzed with the conversion of acrylonitrile to acrylamide to have their apply in plastics, with production level of ten thousand tons per year, (2) catalytic conversion of cephalosporin C to -keto-adipyl-7-aminocephalosporinic acid with the aid of D-amino acid oxidase for its utilization in the generation of antibiotics (Wandrey et al. 2000).

With blessing of contemporary advancements in the field of functional genomics, various novel enzymes have been studied and bring to light from numerous roots. But, in almost all instances, there is no optimization of the natural origin enzymes for applications on a practical basis because of the disparity in the cellular environment and in their industrial background. To sort this problem, various approaches like maneuver the manufacturing process of the target chemical accord-

ing to the bio-catalyst with an exploration of the homolog's of the enzymes suiting best to the appropriate industrial process (Fernandez-Arrojo et al. 2010). Bio-catalysis can be optimized efficiently for certain industrial applications considering factors like cycles of mutation, selection, amplification, thermostability, and organic solvents (Wang et al. 2012).

For the pharmaceutical industry, the application of enzymes for synthesizing industrially important compounds is becoming significantly important. Nowadays, various MNCs are now using bio-catalysis keenly as an approach to develop technology for programs like the production of drugs. Using enzymes for chemical processes is considered as one such possible route in lowering down the consumption of the energy along with the reduction in the generation of the wastes. Enzyme selectivity processes also help in the reduction of the costs of the raw materials with the safety issues that surround the production of by-products of the wastes. These little steps have to lead to an economically, sustainable, and cost-effective production of compounds (Littlechild 2015).

Bio-catalysis is the process of transformation of the chemical or biological substances using enzymes which were generated by diverse living organisms. Apart from the field of bio-catalysis, the chemical synthesis process in the feed, food, pharmaceutical, and industrial sector, it has also participated into the bioremediation sector, which is an additional field in which enzymes play a noteworthy role. The reason for the huge success of bio-catalysis being applied to synthetic chemistry is mainly because of (i) the high enantioselectivities and regioselectivities which enzymes show to their respective substrates. Since enzymes engage in recreation a role in speeding up of the chemical processes that otherwise would lope slowly or run without selectivity, (ii) enzymes reaction underneath mild conditions to precede any reaction, (iii) enzymes are easy to control and (iv) enzymes are biodegradable in nature. Hence, as compared to the traditional chemical synthesis pathways, bio-catalysis is a superior pathway (i) in the simplicity or the way the reactions are accomplished and (ii) economical option and (iii) takes into consideration the prospects of the environment (Regil and Sandoval 2013).

Using organic solvents as reaction media is a significant landmark of bio-catalysis reaction, as enzymes work only in the aqueous medium, under natural conditions. Organic solvents help in dissolving hydrophobic and organic molecules, which accounts for the major portion of organic chemicals that have been used in synthetic chemistry. These organic chemicals precisely increase the reaction rates in a possible manner to carry out reactions due to better solubility of reactants. This also aids in shortening the steps of the purification with an easy method as (i) it avoids the surfactants which are being used in the aqueous media and (ii) usage of solvents of low boiling point which evaporates easily. With the usage of these low boiling point solvents, issues like low product yields from the reactions that make use of hydrolytic enzymes and, secondary, water-dependent reactions and microbial growth when stored, used, or grown in containers and pipes can be averted due to the lack of water and the hard side effects of solvents to the living cells (Regil and Sandoval 2013).

Yet, there are certain limitations that still require attention with respect to biocatalysis like (i) the cost of production of the enzymes and (ii) restricted stability bracket of various enzymes under diverse reaction environment. This narrow bracket restricts the applications of the enzymes over a large scale like in industrial processes (iii) majority of the chemicals that have been used in industries have an artificial origin. Also, enzymes do not evolve much against the novel man-made chemicals and hence they are not applicable to work in the synthetic industry (Regil and Sandoval 2013).

Considering the end-use market, industrial enzymes have an extremely broad market with various commercial applications in numerous industries (Adrio and Demain 2005). Nowadays, enzymes are being used in manufacturing over 500 products for use in numerous industries (Johannes and Zhao 2006; Kumar and Singh 2013). Their demand has a continuous surge in order to satiate the growing needs for sustainable solutions. Also in future researchers are now selecting genetically and chemically modified enzymes in order to intensify some important characteristics like the stability of the enzymes, specificity of the enzymes, and specific activity of the enzymes. The usage of these modified enzymes also carries drawbacks like the need of cofactors for some enzymes. However, researchers are working on numerous approaches to solving this issue like recycling of the cofactors and using whole cells. There are approximately about 150 processes in the industries that make use of the enzymes or the whole microbial cell catalysts. The market for industrial enzymes worldwide is extremely tough and cutthroat. In this industry, the company Novozymes is the largest player, followed by DSM and DuPont (after acquiring a major stake in Danisco and its Genencor division), among others. These particular MNCs primarily compete on the factor like (i) quality of the product, (ii) performance of the products, and (iii) using intellectual property rights (IPR), for novel innovation. Globally, Europe and North America are the biggest patrons of enzymes being used in industries with quick increase in the demand of the industrial enzymes in the Asia Pacific, that is, China, Japan, and India, which in turn reflects the size and strength of the economies of the aforementioned countries (Adrio and Demain 2014).

## 2 Enzymes and Their Industrial Applications

### *2.1 Oxidoreductases*

#### 2.1.1 Oxidases

Oxidases with nonspecific nature like peroxidases and laccases have enhanced the strength in various processes of industries, for example, bleaching process of paper pulp and bioremediation process (Demarche et al. 2012). Numerous properties of enzymes belonging to this class have been enhanced with the directed evolution

approach and thus render them more compatible with recent processes of industries (Gupta and Farinas 2010; Liu et al. 2011; Ribitsch et al. 2010).

The former one is obtained from basidiomycete PM1 and the latter one is acquired from *Pleurotus eryngii* via mutagenic staggered extension method (Zhao et al. 1998) following DNA shuffling (in vivo) assembly of mutant (IvAM) with the difference in their mutation. The thermostability of both the enzymes was enhanced by a factor of threefold along with tenfold (Garcia-Ruiz et al. 2010), whereas while considering another example of the same enzyme, that is, laccase obtained from the strain *Pleurotus ostreatus*, it was observed that there was an improvement of half-life by a factor of fourfold pH acidic (Miele et al. 2010), which has favored numerous application of the industries.

$P_{450}$ monooxygenases have the property of high selectivity and ability to perform catalytic reactions at a wide range. These properties have gained a lot of attention of the researchers nowadays. But, the problems with the application of $P_{450}$ monooxygenases (i) low efficiency in catalyzing the reactions, (ii) low stability of the enzyme, (ii) the requirement of a complex system to transfer electrons. With fresh research, it has been recommended that various properties of $P_{450}$ monooxygenase enzyme like the enzymatic activity (Fujii et al. 2009; Kabumoto et al. 2009; Koch et al. 2009).

With this regard, a mixture of site-specific mutagenesis and error-prone PCR was used for the production of 7800 alternatives of the enzyme $P_{450}$ CYP116B3 by strain of *Rhodococcus ruber*. The dealkylation activity of $P_{450}$ CYP116B3, after going through four rounds of direct evolution method, was significantly increased by a factor of 240-fold (Liu et al. 2010a). Another approach to enhance the characteristics of this enzyme can be altering the selectivity. In the recent past, a group of researchers has developed an effective high-throughput enantiomeric excess screening approach. There have been reports regarding the inversion of enantioselectivity of the enzyme P450pyr monooxygenase through directed evolution. The results obtained were the production of favorable enantiomers that are significant intermediates from pharmaceutical industries' point of view (Tang et al. 2010).

### 2.1.2 Dehydrogenases

Pure alcohols of enantiomers are important structure blocks with respect to agriculture, pharmaceuticals, and chemicals. The technique to synthesize them biologically consists of reduction (asymmetrically) of racemic substances. Practically, high activity of the enzyme and selective nature of the bio-catalysts are needed. This particular variant amino alcohol dehydrogenase has a double mutation and resulted in increased activity in the presence of product d-pseudoephedrine with a 100 mg/mL volume (Urano et al. 2011).

Researchers produced a variant from DL-propargylglycine, phenylalanine dehydrogenase, through heading for development (Chen and Engel 2009). Substantial application of directed evolution of NAD-dependent mannitol 1-dehydrogenase (MDH), from the strain *Apium graveolens* practice has novel in the synthesis of L-sugar because of its region selectivity, was done by a group of researchers in order

to increase the activity and thermostability of mannitol-1-dehydrogenase (MDH) (Christ et al. 2010; Woodyer et al. 2010). Dehydrogenases have gained the interest of researches because of the applications to produce renewable energy whereas problems like low activity of dehydrogenases, high sensitive nature inactivates oxygen and thus not suitable for using them practically.

### 2.1.3 Reductases

By using the approach of directed evolution to increase the thermostability and activity of the enzymes of this class (Imamura and Shigemori 2010; Suzuki et al. 2010). For example, there was an evolution of copper which consists of nitrite reductase from the strain *Alcaligenes faecalis* S-6 with enhanced activity (MacPherson et al. 2010). A double mutant was recognized when twenty thousand colonies were screened. This double mutant showed improvement in the activity by a factor of 5.5-fold when di-oxygen is used as an electron acceptor.

## *2.2 Transferases*

Carbohydrates like glycans (glucoconjugate form) show significant importance in various biological methods. This significance and complex nature of carbohydrates are drawing the attention of researchers. The traditional approach to synthesize chemicals either can't render fine regioselectivity and stereoselectivity. On the other side, glycosylation approach using enzymes gives high regioselectivity and stereoselectivity without any requirement of protection and deprotection steps (Wang et al. 2012).

Intense research has been done by the researchers to synthesize carbohydrates from both glycosyltransferases and glycosidases (Wang and Huang 2009). Additionally, using directed evolution helps to tame the issues of low enzymatic activity and the hydrolysis of the product (De Groeve et al. 2009, 2010; Kittl and Withers 2010). Researchers have engineered β-glycosidase from strain *Thermus thermophilus* via high throughput screening method based on digital imaging and resulted in the increase in the ratio of transglycosidase-hydrolysis activity by a factor of 70-fold. Another example includes engineering of glycosyltransferases and glycosidase for the synthesis of glycol conjugates. This broadens the scope of the substrate with improvement in their catalytic efficiency (Hancock et al. 2009).

There exists another class of transferases that have been evolved to enhance their characteristics practically. For example, engineering of acyl transferase LovD from the biosynthetic pathway of lovastatin through directed evolution enhances the enzymatic activity by a factor of 11-fold (Gao et al. 2009). Enzyme transaminase with an edge in the activity for inactive substrates for synthesizing chiral amine was designed via directed evolution. After eleven rounds of direct evolution, there has

been an improvement in the properties of the enzyme which is important processes in numerous industries (Savile et al. 2010).

## *2.3 Hydrolases*

Hydrolytic bio-catalysis is significantly applied in organic fusion and in the claim of various industries. These hydrolytic enzymes perform a broad range of bioconversion like hydrolysis, transesterification reaction, esterification reaction, hydrolysis of alcohol, hydrolysis of acids, and hydrolysis of amines. Hence, researchers have engaged in this even more to boost the features of hydro-lyases (Wang and Wan 2009).

### 2.3.1 Lipases

This class of enzymes consists of the main enzymes that are used in the industries. Novel efforts are being made to maximize the mutant libraries' quality with respect to frequency. Iterative saturation mutagenesis (ISM) has come to the rescue and improves stereoselectivity and thermostability, respectively (Prasad et al. 2011). In this approach, libraries were made with proper protein sites which consist of more than one amino acid position. This particular method is frequent until the quality of favorable catalyst quality is accomplished and there is no possibility to further improve the product (Wang et al. 2009).

Lipase from the strain *Bacillus subtilis* was isolated and later then subjected to directed evolution via B-FIT method and hydrolysis was done using *para*-nitrophenyl caprylate. This resulted in a variant with an increase in the temperature in T-50, that is, from 45°C to 93°C. These thermostable variants have enhanced robustness for organic solvents of hostile nature (Reetz et al. 2010).

### 2.3.2 Esterases

These enzymes represent 8% of enzymes applied in bio-catalysis, approximately (Schmidt et al. 2009). Much effort is now being applied by the scientists to enhance the enantioselectivity of esterase enzymes for kinetic resolution of tertiary alcohols that are optically active (Kourist and Bornscheuer 2011). Esterase from *Bacillus subtilis* strain results in total inversion in the enantioselectivity for tertiary alcohols (Bartsch et al. 2008). For thermostable variants, two strategies are followed: first, an increase in the thermostability on the basis of highly active parents. For instance, the strategy of using directed evolution with the B – FIT to produce a variant of the esterase from the strain *Pseudomonas fluorescens* with an increase in the melting point (9°C) with no compromise in the catalytic properties of the enzymes (Jochens et al. 2010). Second, an increase in the activity of those enzymes that originates

from thermophilic areas. Example, acylaminoacyl peptidase from the hyperthermophilic Aeropyrum archaeon pernix K1 (apAAP) showed the low activity of the enzyme esterase (Wang et al. 2006).

### *2.4 Lyases*

Screening on the basis of enzymatic activity is performed when properties like product concentrations, pH, thermostability, and solubility are monitored spectrometrically easily (Khersonsky et al. 2011; Asano et al. 2011). The resultant deviations are identified to have enhanced thermostability and enzymatic activity.

If information about the structure of the high quality of the protein is known, iterative saturation mutagenesis can be applied to hasten the production procedure and strengthen the results of direct evolution. For example, on the basis of the developed inhibitor-bound arrangement of enzyme arylmalonate decarboxylase from the strain *Bordetella bronchiseptica*, residues of five major dynamic sites were recognized and then categorized into two groups, which by using iterative saturation mutagenesis approach mutations can be done separately (Okrasa et al. 2009).

### *2.5 Isomerases/Ligases*

In the case of enzymes isomerases, researchers have made use of error-prone PCR on a metallic L-arabinose isomerase enzyme obtained by *E. coli* and nonmetallic tagatose-6-phosphate isomerase enzyme obtained by *Staphylococcus aureus* (SATI), respectively (Kim et al. 2010). This SATI option has shown bigger isomerization activity (190%) for the aberrant substrate, namely, galactose.

Systems of transport cells like efflux pumps and sugar transporters play a significant function in biological procedure but used as a target for directed evolution, rarely since membranes are proteins with less or not applicable for biotransformation (single step). This has one advantage of increasing the competence of a cell factory.

Export systems of the cells like efflux pumps endow a straight device for diminishing the toxicity of the biofuels (Dunlop et al. 2011). Hence, efflux pumps engineered with the high- level performance are favored for improving the production of the biofuels (Bokma et al. 2006).

## 3 Bio-catalysis in Green Chemistry

Green approaches are just not considered as an environmental option, but now it has become a strategic approach in the urbanized economy (Chemistry & Industry. Building a Greener Future 2009). Recent chemical methodologies which are not

fully optimized and are not even eco-friendly must be redesigned using 12th ideology of green chemistry (Anastas and Eghbali 2010; Chemical Business. Green Chemical Principles 2013). Green chemistry with extensive potential has applications in various fields of the chemical industry with many significant advantages like safer methodologies, safe products, less use of solvents, less production of toxic substances, minimal disposal of wastes, and few emissions, and it saves energy and water. Thus, redesigning the traditional chemical approaches with green chemistry is an optimized investment and comparatively cheaper.

The ideology of green chemistry are (a) proper prevention of waste rather than remediation, (b) economic and efficient, (c) using less hazardous/toxic chemicals, (d) designing safe products, (e) using harmless solvent, (f) energy-efficient design, (g) using renewable resources as raw materials, (h) short synthesis with no derivatives, (i) use of stoichiometric reagents instead of catalytic reagents, (j) biodegradable products with respect to environmental concern, (k) analytical move toward for the prevention of pollution in the environment, (l) and a safer approach, inherently (Ferreira-Leitão et al. 2017).

In recent past, metabolite production and its utilization using microbial or plant source is gaining attention from various industrial fields like fuels, pharmaceuticals, food, and chemicals. This is because of their potential to replace traditionally products produced majorly from nonrenewable raw materials like petrochemicals. Development of certain technologies that help in reusing wastes and some by-products of the industries results in the reduction of costs of the process and thus adding value to the waste materials (Straathof 2014; Bozell and Petersen 2010). Residues of agro-industries and forest area are valuable renewable raw materials for manufacturing renewable products like energy, fuels, and chemicals. Waste (bagasse, barks, and cereals and straw) utilization is valuable as it protects the environment by avoiding their accumulation and their accessibility where there is no hard competition between food and fuel (Ferreira-Leitão et al. 2010; Nigam et al. 2009). The promotion of bio-catalysis and their benefits to the environment are supported by the fact that enzymes and microorganisms have the capability to catalyze the hydrolysis and degradation of every macromolecule which is present in the materials of agro-industries with good conversion and more specificity (Sheldon and Woodley 2018).

## *3.1 Reaction Media*

In every production methodologies, usage of solvent is a significant factor in transformation processes using bio-catalysts. There will be a serious failure with a general preconceived notion that enzymes work with proper optimization only in water. Also, there are certain reactions like transesterification reaction and amidation reaction which are not possible to conduct these reactions in water with limitations to equilibrium and hydrolysis of product. Considering this, the interests of the researchers are shifting toward nonaqueous bio-catalysis (Gutarra et al. 2009). But the cau-

tion lays the same for both organic solvents (volatile) in bio-catalytic method and organic synthesis. Also, high polar substances like nucleosides, carbohydrates, and peptides are soluble partially usual organic solvents. Accumulation to this, enzymes get denatured generally in polar aprotic solvents like dimethylformamide (DMF) (Sheldon and Woodley 2018).

### 3.1.1 Water as a Solvent for Bio-catalysis Processes

For biological reactions water is considered as a universal solvent which means with the ongoing reaction there is a requirement to separate water and product individually. But, removal of the water, which is present in a huge amount, is comparatively expensive with respect to its extreme boiling point. From the economic analysis of various bio-catalytic methodologies, in order to lessen the burden of removing water from downstream, it is important to accomplish enough concentration of the product after it leaves the reactor. If using water as a solvent, it is advised to remove all the traces of organic content before discharging (Dominguez de Maria and Hollman 2015). Thus, it is suggested to use high substrate or suspension concentrations (approximately >10 wt %) in order to limit the quantity of water to be used. There exists a dilemmatic statement till date that, in spite of certain obstacles about the replacement of water with some organic solvents, most of the reactions using bio-catalysis take place in water. Comparing aqueous-based approaches with traditional chemical approaches where the purity of the product leaving the reactor reflects the downstream processing cost, the concentration of products predominates since the costs associated with removal of water are much more significant, where the product concentration after leaving the reactor is associated with the downstream process cost. The reported value of high-priced products is 50 g/L and that of low-priced products is 300 g/L for economical products (Lima-Ramos et al. 2014). This strategy keeps the size during the separation process manageable (Hermann and Patel 2007).

Initially, using aqueous solutions for certain reactions is extremely luring, but this hides the issues regarding downstream processing. The product present within the aqueous material at concentration <300 g/L requires removal of water by a simple method like evaporation before isolation of product following purification. Water has a high boiling point; thus it is expensive and more luring for product extraction into a solvent with low boiling even at higher concentration, which can later be evaporated quite cheaply and thus called solvent swap (Elgue et al. 2006; Hsieh et al. 2009; Papadakis et al. 2016). From recent past, research like methods dealing with the improvement in the concentration of the product with significant effectiveness and enhanced downstream processing have become significant priorities for the researchers.

### 3.1.2 Organic Solvents for Enzymes

Enzymes are comparatively more dynamic in organic solvents (Zaks and Klibanov 1984), indicating the emergence of the nonaqueous enzymology (Carrea and Riva 2008). There are enormous merits of bio-catalysis in organic media like easy recovery of the product, significant solubility as compared to water, elimination of the contamination of the microbes, enhancement in the enantioselectivity, and optimization in the utility of transformations using enzymes (Carrea et al. 1995; Klibanov 1990).

On the other side, there are certainly serious problems of bio-catalysis in the organic media with respect to problems pertaining to the environment, for example, low reaction rates as compared to the reaction rates when water is used. The catalytic efficiency of the enzymes is significantly higher when organic solvents are used as compared to the catalytic efficiency of the enzymes when water is used as a solvent (Klibanov 1997).

### 3.1.3 Supercritical Carbon Dioxide ($scCO_2$)

Supercritical carbon dioxide ($scCO_2$) is an appealing alternative of organic solvents (volatile). It is under supercritical conditions, that is, 31°C and 7.4 MPa, from where the name arises, which makes it beneficial to bio-catalysis (Budisa and Schulze-Makuch 2014; Matsuda 2013), and it uses a renewable medium in a natural solvent.

Also, $scCO_2$ has a high capability of solubilizing a liquid in combination with the less viscosity of a gas. It also takes care of high mass transfer rates and recovery of the product recovery. Generally, enzymes show good activity and stability in supercritical $CO_2$, but apart from this, there are two potential properties with drawbacks; firstly, there is the production of carbamates when the reaction takes place with the free amine groups in residues of the lysine with carbon dioxide and, secondly, the formation of carbonic acid when water is used in reaction media and thus results in low pH (Sheldon and Woodley 2018).

Immobilizing enzymes covalently onto free amine groups present on the surface of the enzyme results in suppressing the inactivation which is caused by the reaction of the enzymes with carbon dioxide. For example, cross-linked enzyme aggregates (CLEA) of 1-phenylethanol by *Candida antarctica* lipase B (CaLB) help in catalyzing transesterification reactions. It has been observed that the reaction rates were higher in supercritical $CO_2$ compared to n-hexane (Hobbs et al. 2006).

The advantage of using liquid instead of $scCO_2$ is that there is the requirement of low pressure and temperature conditions, that is, 4.5 MPa and 10°C, and results in increasing the enantioselectivity (Matsuda et al. 2005). A recent development with respect to supercritical carbon dioxide is the transesterification of triglycerides which is catalyzed by enzyme lipases (Gumba et al. 2016).

### 3.1.4 Ionic Liquids for Enhancing the Activity of the Enzymes

Bulk amount of salts like potassium chloride is gaining interest to increase the enzymatic activity in organic solvents by lyophilization (Khmelnitsky et al. 1994). There might be an increase in the reaction rates significantly when compared to the organic solvents by suspending enzymes in ionic liquids present at room temperature. Nonvolatile in nature is more useful in reaction media of catalytic methods (Steinrück and Wasserscheid 2015).

It has been observed that ionic liquids have biocompatible property with numerous enzymes and are effectively suitable enough as a substitute to reaction media for biotransformations (van Rantwijk and Sheldon 2007). Ionic liquids have reported increased enzymatic stability with better enantioselectivities (Park and Kazlauskas 2001). This might be the result of some changes in the conformation of the enzymes in ionic liquid media. As ionic liquids easily dissolve in polar substrates, they might be considered a as a best option for bio-transformation of carbohydrates (Liu et al. 2005), nucleosides (Li et al. 2008) because of their low solubility's in the organic solvents.

Ionic liquids has the biggest advantage over the volatile organic solvents is the reduction of the risk of air pollution because of their nonvolatile. However there are exceptions like tetraalkyl ammonium and dialkyl imidazolium ionic liquids that show better solubility in are non-biodegradable in nature (Coleman and Gathergood 2010) and shows toxicity to the aquatic microorganisms (Bruzzone et al. 2011) and the anions, namely, $BF_4$ and $PF_6$, are not easily hydrolyzable, results in forming hydrogen fluoride. Synthesis of these quaternary ionic liquids has relatively high costs (Deetlefs and Seddon 2010).

These aforementioned problems gave birth to the second-generation ionic liquids that are way more biocompatible and not very expensive and have eco-friendly products like carbohydrates (Chiappe et al. 2010) and amino acids (Fukumoto et al. 2005). The example consists of cholinium carboxylates, which is a derivative of choline hydroxide, carboxylic acids (Petkovic et al. 2010), and amino acids (Hou et al. 2013) which are not expensive, nontoxic, and biodegradable.

### 3.1.5 Deep Eutectic Solvents (DESs) for Biotransformation

The generation of DESs is when ammonium/phosphonium salts are mixed with a hydrogen bond donor (HBD) or alcohol, the carboxylic acid (XH) with gentle heating XH. Example includes when choline chloride (an inexpensive, easily available additive) with 302°C a melting point is mixed with urea with a melting point of 132°C in a molar ratio of 1:2 results formation of the deep eutectic solvent having a melting point of 12°C. Deep eutectic solvents were not considered as ionic solvents since they consist of uncharged substances, which show the same features as that of ionic solvents like low volatile nature and better thermal stability. The most important feature is that (i) comparatively synthesize just by mixing the two substances together (ii) formed from natural, biocompatible materials (urea-fertilizer, glycerol-

bio-diesel production), thus do not show much toxicity and are biodegradable in nature (Alonso et al. 2016).

Example consists of mixing choline chloride with urea (Hammond et al. 2016) and glycerol (Abbott et al. 2011) in a ratio of 1:2 molar have certain properties like easy availability, non-expensive, biocompatible, and biodegradable. One can prepare deep eutectic solvents by simply mixing choline chloride and carbohydrates (Maugeri and Dominguez de Maria 2012). Eutectic solvents (NADESs) (Choi et al. 2011) are a derivative of certain metabolites like sugars, amino acids (AAs), choline, and organic acids. They basically perform their function as reaction media for synthesizing compounds that are partially soluble in water like steroids and flavonoids in living cells. The very first example of bio-catalysis in deep eutectic solvents was immobilization of *Candida antarctica* lipase B (Novozym 435) (Gorke et al. 2008).

This happened because of easy diffusion of urea to the core of the protein in the absence of choline chloride. Also, urea has the potential to denature the protein. Urea denatures the enzyme when intramolecular hydrogen bonds are disrupted. Contrastingly, in choline chloride with urea the hydrogen bonds formed between urea, choline, and chloride ions inhibit the diffusion of urea to the core of the protein (Monhemi et al. 2014). Choline-based eutectic solvents are significant reaction media either alone or as cosolvents with water, to perform bio-catalytic reactions which will be catalyzed by numerous bio-catalysis (Guajardo et al. 2016) such as lipases (Durand et al. 2012), proteases (Zhao et al. 2011), and peroxidases (Wu et al. 2014).

# 4 Applications of Bio-catalysis

## *4.1 Bio-catalysis in the Residues*

### 4.1.1 Using Solid Wastes to Obtain Bio-catalysts

Enzymes being the central player in the bioprocesses and in various recent industrial processes, numerous researches are going on in order to accomplish high yields and low costs of the bio-catalysts (Ramachandran et al. 2007). This process grabs the attention since it holds a promising alternative for the generation of enzymes in different industries (Selwal et al. 2011) among other products like aromas (Fadel et al. 2015), pigments (Velmurugan et al. 2011), biopesticides (Ballardo et al. 2016), organic acids (Dhillon et al. 2011), and some other biochemicals.

Producing enzymes with the help of solid state fermentation has offered numerous advantages while comparison with the traditional submerged fermentation, which includes (i) enhancing the productivity of the fermentation, (ii) higher concentration of the final products, (iii) reduction in the catabolic repression (Holker et al. 2004). The high productivity obtained from the solid-state fermentation is due to the similarity between the cultivation conditions and conditions of the natural

**Table 1** Examples of industrial bio-catalysts produced from solid state fermentation

| Substrate (solid) | Microorganisms | References |
|---|---|---|
| *Lipases* | | |
| Babassu cake | *Penicillium restricitum* | Gutarra et al. (2007) |
| Wheat bran | *Aspergillus niger* | López et al. (2010) |
| Barley bran | *Rhizopus oryzae* | Mahadik et al. (2002) |
| *Proteases* | | |
| Soy cake | *Bacillus subtilis* | Soares et al. (2005) |
| Wheat bran | *Aspergillus oryzae* MTCC 5341 | Vishwanatha et al. (2010) |
| *Cellulases* | | |
| Corncob residue | *Trichoderma reesei* ZU-02 | Xia and Cen (1999) |
| Steam-exploded wheat straw | *Neurospora sitophila* | Li et al. (2008) |
| *Xylanases* | | |
| Rice straw | *Aspergillus niger* KK2 mutant | Park et al. (2002) |
| *Pectinases* | | |
| Dried de-seeded sunflower head | *Aspergillus niger* | Patil and Dayanand (2006) |
| *Amylase* | | |
| Coconut oil cake | *Aspergillus oryzae* | Ramachandran et al. (2004) |
| *Tannases* | | |
| Citrus residue | *Paecilomyces variotii* | Madeira et al. (2015) |
| *Inulinases* | | |
| Soybean bran | *Kluyveromyces marxianus* | Mazutti et al. (2010) |

media of filamentous fungi and the low protease activity as compared to the process of the submerged fermentation (Diaz et al. 2006). Because of these advantages, researchers are showing interest to obtain numerous bio-catalysts for industrial purposes like lipases (López et al. 2010), proteases (Vishwanatha et al. 2010), cellulases (Li et al. 2010), xylanases (Park et al. 2002), pectinases (Patil and Dayanand 2006), amylases (Castro et al. 2010), phytases (Gaind and Singh 2015), inulinases (Mazutti et al. 2010), and tannases (Novelli et al. 2016) (Table 1). The metabolic expression of fungi differs is dependent upon the residue type being used as a substrate and which helps in the enzyme production with varied properties which later can be implemented in the industry for some biotechnological purposes (Novelli et al. 2016). Also, certain characteristics of biomass like carbohydrates, inorganic matter, protein content, lipid content, elemental analysis, and bulk density which includes carbon (C), nitrogen (N), hydrogen (H), sulfur (S), and porous nature can change the performance of the processes where they are utilized and evaluated in accordance with the aim of the research (Castro et al. 2016). An example where it is reported by the researchers that higher carbon to nitrogen ratio, that is, C/N greater than 10, are profitable for the generation of enzymes such as celluloses, proteases, xylanases, amylasesin solid state fermentation methods (Castro et al. 2011). The solid-state fermentation methods make use of the residues of agro-industries because they are budget friendly and easily available in various nations like India, Brazil, the United States (Gutarra et al. 2009). A team of researchers has executed

the equilibrium of economy associated with the lipase production from the strain *Penicillium restrictum* on the basis of submerged and solid state fermentation. The submerged fermentation process was 78% more expensive with respect to total capital investments as compared to the solid state fermentation process which utilizes babassu cake (Table 1) as their substrate. This later resulted in the less catabolic repression. Overcoming the catabolic repression using solid state fermentation process is because of the difficulty in transferring a mass of gases and the nutrients that have been employed for producing various enzymes of microbial nature (Gutarra et al. 2007). Therefore, producing enzymes of industrial importance by using solid wastes has a big contribution toward the reduction in the costs and adding value to solid wastes. Apart from all the aforementioned advantages, there are major relevant drawbacks of solid state fermentation process like transfer of heat, limitations in monitoring the process online, a proper control on the parameters of the solid state fermentation process, estimation of the biomass yield, scale-up process, and end product purification (Pandey 2003). However, various researches are still ongoing by the researchers to find solutions for these particular issues and challenges.

### 4.1.2 Bio-catalysis for the Production of Generic Fermentation Feedstock's Medium

During solid state fermentation, there is a production of various hydrolytic enzymes by the microorganisms like endoglucanases, exoglucanases, proteases, xylanases, cellulases, and amylases for the hydrolysis of most of the bio-macromolecules. Monomers will produce a nutrient-rich solution which consists of sugars (assimilation) like fructose, glucose, and xylose along with various other nutrients like phosphorus, amino acids, and mineral salts. These sugars and nutrients are later used as a growth medium for submerged fermentation (SF), which resulted in their easy metabolism (López et al. 2013).

Researchers have studied the conversion process of starch granule from babassu flour with the help of multienzyme complex (Cinelli et al. 2014), which is produced by solid state fermentation in babassu cake (Table 2). Wheat bran is used by the researchers for the synthesis of enzymes protease and glucoamylase through solid state fermentation, which later results in the hydrolysis of flour and gluten (Du et al. 2008). Solid state fermentation of rapeseed meal results in a generic media which is

**Table 2** Products obtained from generic fermentation feedstock medium

| Substrate (solid) | Microorganisms | Feedstock | References |
|---|---|---|---|
| *Ethanol* | | | |
| Babassu cake | *A. awamori* | Babassu flour | Cinelli et al. (2014) |
| *Succinic acid* | | | |
| Wheat bran | *A. awamori* | Gluten | Du et al. (2011) |
| *1,3-Propanediol* | | | |
| Rapeseed meal | *A. oryzae* | Rapeseed meal | Chatzifragkou et al. (2014) |

supplemented with crude glycerol and results in the formation of product 1,3-propanediol (65.5 g/L), with double productivity (Chatzifragkou et al. 2014).

## *4.2 Bio-catalysts for the Treatment of Effluents*

Traditional technologies for treating effluents are not able to remove all contaminants from the water completely. These treatments result in depletion of various organic substances, partially or completely. In sort to reduce the cost of the treatment, toxic substances are specifically degraded with treating the residual organic material, biologically. For this, bio-catalysts are employed to remove selective substances for treating effluents (Demarche et al. 2012).

Treatment using enzymes are more suitable for certain applications like removing specific substances from the mixtures of complex and diluted substances where traditional biological treatment is not helping much like removing toxic substances from groundwater; waste treatment produced in remote locations which includes disposal areas of uncontrolled wastes. These treatments are helpful for treated wastewater with the retrieval of the products of soluble nature and elimination of toxic substances that create issues while combining with certain other residues from different industries (Ruggaber and Talley 2006). Apart from the advantages, the issues when treating toxic substances with the enzymes are a huge amount of enzyme for effective elimination because of the inactivation of enzymes. The usage of the enzymes is not appropriate regarding the treatment of the effluents that have a high concentration of toxic substances which will interfere with the activity of the enzymes. Certain researchers are now doing extensive study on how to increase the use of enzymes for treatment. The approaches are (i) using additives to suppress the inactivation of the enzymes, (ii) reduction in the number of enzymes needed, and (iii) enzyme immobilization. The approach of the immobilization of the enzymes helps in improving the stability of the operations of the bio-catalysts by preventing the contamination of the substances or with the combination of this approach with nanotechnology, which is known as single enzyme nanoparticle (SEN) (Mugdha and Usha 2012).

However, there are various technical issues that must be solved when using enzymatic treatment in order to have a technical and economical approach (Aitken 1993). The final products should be of biodegradable nature, low toxicity, and susceptibility for further treatment. The bio-catalysts must act in a selective manner by considering both, that is, the removal of the toxic compounds from the solution and toxicity of the products being generated. The design of the reactors for enzymatic approach must be simple or have membrane reactors along with for recycling enzymes after or during every cycle in continuous reactors. After doing the economic analysis, the configuration of a best-fit reactor should be done. Also, enzymes have natural origin; thus, there is no negative or harsh impact on the environment; thus, enzymes result in the conversion of the wastewater with an environmentally sustainable approach (Mugdha and Usha 2012).

Apart from the stability, enzyme immobilization helps in the reduction of the associated costs. For example, enzymes laccases which are immobilized over silica nanoparticles, and results in the removal of bisphenol from secondary effluents from the treatment plant of municipal wastewaters (Arca-Ramos et al. 2016) and removal of phenol from coking wastewater (Villegas et al. 2016; Mugdha and Usha 2012). Applications of single enzyme nanoparticles for the treatment of wastewaters are in the rational design phase, till date (Ahmad and Sardar 2015). Another approach for reducing associated costs is to collect enzymes from the wastes. An example includes the residue of the starch industries, that is, potato pulp which consists of a high level of activity of peroxidase enzyme (Kurnik et al. 2015), and the by-product of soybean processing industries, namely, soybean seed hulls which are a good source of peroxidase enzyme (Chagas et al. 2015; Neoh et al. 2015).

Bio-catalysts are now being used to treat various effluents, like wastewater which consists of contaminants or toxic substances such as pesticides, phenols, surfactants, heavy metals, residues of paper industries, and residues of food industries (Karam and Nicell 1997).

### 4.2.1 Bio-catalysts for the Treatment of Food Industry Effluents

Food industries have led to an increase in productivity globally and this results in the increase in solid and liquid processed effluents from the food industries. Certain factors like large effluent volumes, more restrictions to the environment, high treatment costs, and more consumer awareness have led researchers to dig into this particular matter with all seriousness with respect to the food industry (Ferreira-Leitão et al. 2017).

The huge effluent volume per ton of product which is generated from these industries are different and vary in every sector of the food industries, for example, 2 $m^3$/t from cheese production sector, 1.7 $m^3$/t from milk processing sector, 15 $m^3$/t from meat sector, 7 $m^3$/t from the production of several types of beers, and 8 $m^3$/t from the processing of the fishes (Henze et al. 2001). The effluent concentration also varies from low effluents of, for example, sugar and dairy sectors to high effluents from, for example, cheese, wine, and oil processing sector, but focuses majorly on proteins, acids, organic content, aromatic compounds, and nutrients (Rajagopal et al. 2013).

It has been reported by the scientists that effluents, like salts with 10%, proteins with 0.5%, fats with 3.8%, and carbohydrates with 1.2%, are extensive components of the food industry effluents (Efremenko et al. 2008). Hydrolysis of fats, which is the component of dairy and canning industry effluents, is slower compared to other organic components, thus resulting in major inconvenience when treatment is done biologically. If there is no complete removal of fat during preliminary steps of treatment, various problems might occur in the biological treatment system which includes scum formation, poor-quality effluents, clogging, low activity floating sludge development, washout of the biomass, and accumulation of long-chain fatty acids which inhibits acetogenic and methanogenic microorganisms. Treatment

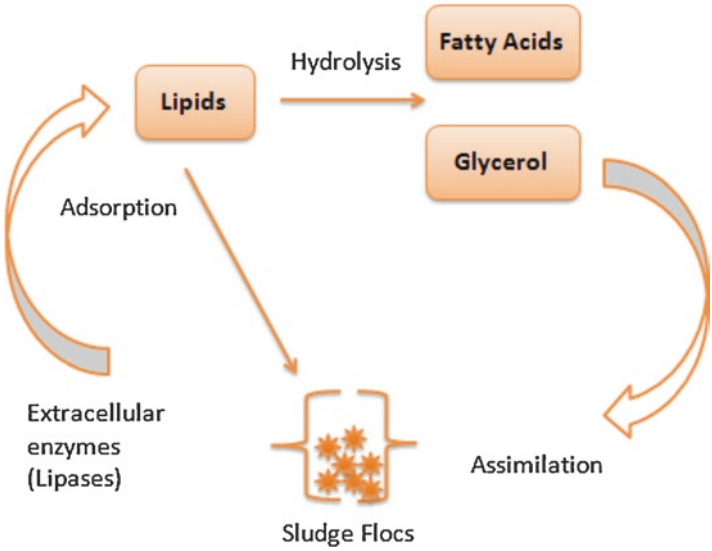


**Fig. 1** Accumulation of lipids in sludge flocs (Ferreira-Leitão et al. 2017)

using bio-catalysts is considered as an alternative for effluents which consists of high levels of fats. Enzymes lipases can be used for treating wastewaters by the hydrolysis of fats. In pretreatment processes with enzymes, conversion of triglycerides (fatty acids and glycerol) decreases the diameter of particles, thus more surface area (Fig. 1). This approach results in improving the activity of the microbes in the next treatment stages (Valladão et al. 2011). Pretreatment process with pancreatic lipase has resulted in reduction in the mean particle size of the fat and generation of long-chain fatty acids (Masse et al. 2001, 2003). It has been reported that researchers have isolated *Pseudomonas* sp. strain which produces lipase, that is, 38.5 U/g DCW, while using optimal medium after 9 h. It has been found out the biodegradation potential of lipase at 30°C with pH 8 with an efficiency of 62–94% to remove various fats (Shon et al. 2002). Scientists have researched the hydrolysis of oils and greases from wastewaters of animal feed industry with the use of *Candida rugosa* lipase enzyme immobilized onto calcium alginate, that is, 890 U/mg at 35°C for 3 days. The results were 65% and 69% elimination of chemical oxygen demand (COD). When compared in the bioreactor where these are used as a control, this efficiency was 49% of chemical oxygen demand (COD) and 45% oil and grease, respectively (Jeganathan et al. 2006). Effluents from certain industries like the dairy industry which is rich in lipids were hydrolyzed partially with porcine pancreatic lipase enzyme available commercially (Nuclear, São Paulo, Brazil, 1.77 U/mg). The researches have got enhanced results when they carried out hydrolysis and degradation simultaneously when an enzyme is used in lower concentrations, that is, 0.05% w/v (Ferreira-Leitão et al. 2017).

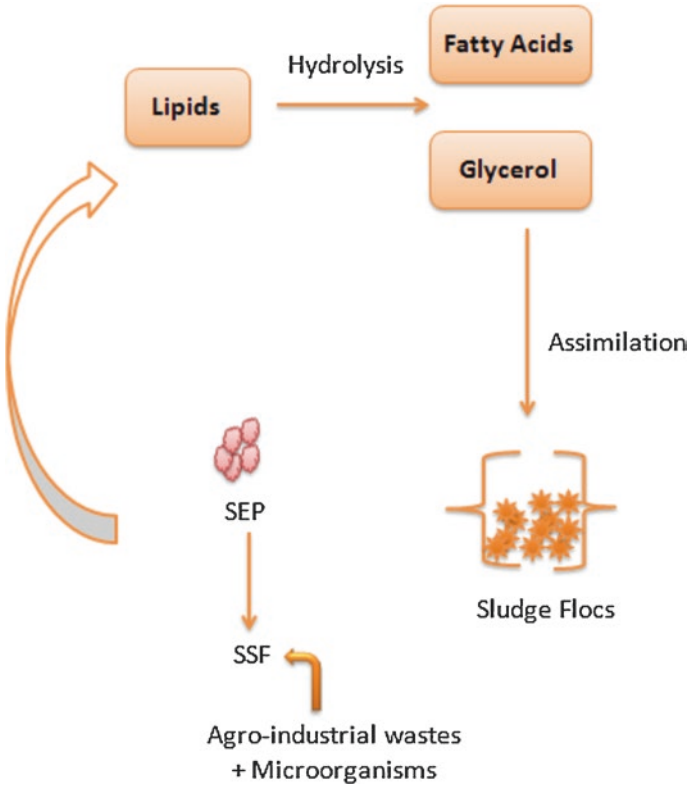


**Fig. 2** Quick assimilation of the hydrolysis products (oil and grease industry) (Valladão et al. 2011)

For producing hydrolytic enzymes through solid state fermentation using filamentous fungi like *Penicillium* sp, *P. brevicompactum*, and *P. simplicissimum* which is isolated from the wastes of agro-industries (Ferreira-Leitão et al. 2017).

Traditionally, oil and grease are adsorbed over flocs of the sludge, and microorganisms produced in the production of lipases and other enzymes for the hydrolysis of the contaminants. There is an accumulation of lipids (Fig. 1) in effluents and sludge flocs due to high feed rates of lipids when compared to the speed of hydrolysis and consumption of the lipids (Ferreira-Leitão et al. 2017).

This issue can be solved with the aid of pre-hydrolysis of agro-industrial wastes with the enzymes via solid state fermentation. There is rapid consumption by the microorganisms (Fig. 2) when introduced in the bioreactors as substrate, and thus there is no accumulation of triacylglycerols (TAGs) and, hence, no issues in the operation because of this accumulation (Valladão et al. 2011).

### 4.2.2 Bio-catalysts for the Elimination of Colors from the Effluents

Generation of wastewaters from the textile industries is a laborious treatment as it consists of complex aromatic and stable heterocyclic colorants which are not easily accessible for treating wastewaters biologically. Colored water results in the less availability of light, an essential aspect for proper enlargement of the aquatic organisms. In recent researches, wastewater treatment approaches to mineralize dyes are studied for removing color (Holkar et al. 2016).

Secondhand tints in the textile industries are azo composite, that is, one or more azo links which are connecting with aromatic (–N=N–). The unique feature of this class is because of (i) the ease which helps in synthesizing azo compounds and (ii) they show good fixing and affordable properties (Solís et al. 2012). But these dyes are difficult compounds with xenobiotic origin owed to the occurrence of N=N bond and due to the presence of certain other groups which are not easily biodegradable in nature, such as groups of sulfonic acid ($SO_3H$). Apart from toxicity, they are carcinogenic and mutagenic in nature because of the breakage of azo bond and thus the formation of aromatic amines (Gad 2014).

Apart from the traditional physicochemical approaches used to remove the color from wastewaters, the following methods can also be taken into consideration, namely, (i) cavitations, (ii) coagulation or flocculation, (iii) adsorption, (iv) oxidation, (v) membrane separations used as membrane bioreactors, (vi) ion exchange, (vii) photochemical method, (viii) ultrasonic method, and (ix) electrochemical method. The reward and weakness of chemical treatment, physical treatment, and microbial treatment are economic restrains, low efficiency, production of toxic substances, and formation of toxic sludge. To overcome the aforementioned limitations and to achieve the task of complete removal of color from the wastewaters, recently studies have been evaluated by combining two or more methodologies such as (i) electrocoagulation, (ii) electrocoagulation-electrooxidation, and (ii) electrocoagulation-photooxidation which are gaining a lot of attention for processing fabric wastewaters (Li et al. 2008).

Scientists are now making use of microorganisms such as yeasts, algae, bacteria, and filamentous fungi for decolorizing and mineralizing dyes with an azo group (Arslan et al. 2016). Considering this, an extract of the enzymes can be used which hold significant advantages like easy standardization, easy implementation, and easy alteration with respect to the specific removal of dye while comparing with the direct use of these microorganisms (Imran et al. 2014).

Enzymes polyphenol oxidases and peroxidases (oxidoreductases) have been researched the elimination of color from wastewater without any interference and presence of inhibitors which are present normally in the effluent coming from the industries (Solís et al. 2012). But it is advised to do all the evaluations of decolorization of actual effluents from the industries which are an intricate system with strong coloration, changes in the pH, high-degree temperatures, more suspended solids, and chemical oxygen demand (Forgacs et al. 2004). With less availability of research on actual industrial effluents and their applications in different domains, Table 3 signifies the elimination of colors from actual effluents by using bio-catalysts

**Table 3** Elimination of colors from effluents of industries using bio-catalysts

| Source | Treatment conditions | Decolorization | References |
|---|---|---|---|
| Bitter gourd (*Momordica charantia*) peroxidases (BGP—99 U/mg protein) immobilized on concanavalin A layered calcium alginate-starch beads | Textile effluent continuous two-reactor system; first column with immobilized BGP (1162 U) and second column with activated silica, 1.0 mmol/L hydroxybenzotriazole, 0.72 mmol/L $H_2O_2$, 16 mL/h, pH 5.0, 37°C, 2 months | 90% decolorization was observed during initial 10 days of operation with gradual decrease, that is, 40% decolorization after 60 days | Matto and Husain (2009) |
| Laccase from *Trametes trogii* | Textile factory effluent (20%), laccase with or without a mediator 1-hdroxybenzotriazole (HBT), pH 5, 30°C | 10% decolorization after 9 h using 9 U/mL laccase. 81%, 70%, 65%, and 58% after 6 h with laccase-HBT system (5 U/mL; 3 mmol/L) and 5%, 10%, 20%, and 30% effluent | Khlifi et al. (2010) |
| Potato polyphenol oxidase (PPO) soluble and immobilized on Celite 545 | Dyeing effluent 1.5 U/mL, pH 3, 37°C, stirring/hour | 82% decolorization with soluble potato polyphenol oxidase. 95% decolorization with immobilized potato polyphenol oxidase | Ma et al. (2014) |
| Lignin peroxidase from *Phanerochaete chrysosporium* | Methylene blue (MB) 50 mg/L, 30°C, pH 4, 30 min, ratio MB:$H_2O_2$ of 1:5 | Efficient elimination of 90% color in reactions with methylene blue (MB) | Khan and Husain (2007) |

obtained from various biological sources. From Table 3, it can be inferred that immobilized bio-catalysts are effective for processing stubborn wastewater which consists of various colorants from different sources like textile industries, dye industries, and stamp industries.

## 5 Bio-catalysis for Treating Industrial Wastes: Examples

### *5.1 Hydrolysis of Poly(ethylene terephthalate) (PET) from Textile Waste*

Because of rise in the awareness to protect the environment globally, recycling strategies to recycle the waste with the principles of the economy are required on an urgent basis. Polyesters are the materials being used in the textile industries, majorly. To accomplish the task of complete hydrolysis of textile industry waste, that is,

poly(ethylene terephthalate) (PET), in an eco-friendly way is currently a big challenge. Nearly about 75% of the fabrics that have been recovered were recycled or reused primarily for their use in the industries (Jorgensen et al. 2008). But recycling options have a positive impact on the environment like savings in the energy convention since recycling requires much less energy when compared to the energy practice for production of material from initial raw materials (Clark et al. 2016).

An alternative has been suggested by researchers, like giving the treatment of chemo-enzymes in order to recycle the poly(ethylene terephthalate) waste material into products. The hydrolysis of poly(ethylene terephthalate) was done using esterase enzyme. The poly(ethylene terephthalate) was pretreated chemically because of the high crystalline structure of the poly(ethylene terephthalate) fibers. The poly(ethylene terephthalate) fibers were later incubated with *Humicola insolens* cutinase (HiC) for the hydrolysis of leftover oligomers. Various characterization practices like Fourier transform infrared spectroscopy (FT-IR), $^{1}$HNMR, and Raman spectroscopy have been done and samples were characterized and later concluded. Terephthalic acid (97% purity) was obtained from the enzymatic treatment. This chemo-enzymatic treatment for recycling poly(ethylene terephthalate) is eco-friendly under neutral reaction conditions, thus no use of harsh chemicals during the treatment (Quartinello et al. 2017).

## *5.2 Generation of 6-Hydroxy-3-Succinoyl-Pyridine (HSP) from Tobacco Waste*

There has been an increased interest for producing worthy chemicals using microbes from the raw materials of renewable nature. For instance, production of tobacco to manufacture cigarettes and cigars results in the generation of 75% residue, that is, tobacco waste. This residue is considered as a raw material of renewable nature which has the capability to use biorefineries for generating energy and numerous products (Wang et al. 2013). Additionally, this waste from tobacco industries is an environmental pollutant due to high nicotine concentration, the major alkaloid present in tobacco, and constitutes 0.6–3% (w/w) of dry tobacco leaves (Forster-Carneiro et al. 2013). Degrading nicotine using microbes results in the production of numerous metabolite intermediates majorly pyridine derivatives which are present significantly in the natural products and pharmaceuticals products. But the production of derivatives of pyridine is majorly done through organic synthesis along with the production of by-products and thus leads to an increase in the costs (Hill 2010).

Bio-catalysis is nowadays a supportive technology for chemical industries for those reactions that are quite impossible to conduct in an easy way using the methods of organic chemistry (Schmid et al. 2001). For instance, the reactions involving the production of 2-substituted pyridines and their derivatives from N-oxides of pyridines are helpful methods, synthetically. But these particular methods need strict reaction conditions for increased yield of the product (Liu et al. 2013; Tang

et al. 2013). In order to catalyze the pyridine 2-hydroxylation step, a protein is required which consists of molybdenum. This particular hydroxylation step can put back the reaction of 2-substituted pyridine during organic synthesis (Hao et al.).

The metabolic intermediate of nicotine, that is, 6-Hydroxy-3-succinoyl-pyridine (HSP), is considered as a building block for synthesis of drugs, insecticides, compounds with bio- activity like molecules of analgesics, epibatidine (Schmid et al. 2001). 6-Hydroxy-3-succinoyl-pyridine (HSP) has a hydroxyl group at position 6 and a side chain is a favorable precursor for synthesizing derivatives of 2,5-disubstituted and 2,3,5-trisubstituted pyridine, respectively (Balzarini et al. 2005). These derivatives are present in numerous drugs marketed recently like pioglitazone (Actos, diabetes), eszopiclone (Lunesta, insomnia), and crizotinib (Xalkori, cancer) which has been approved recently (Goetz and Garg 2013). In addition, this metabolic intermediate is present in numerous pathways that degrade nicotine (Ma et al. 2014). Till date there is no protocol to mediate the synthesis of this intermediate using method of organic chemistry but biotransformation of 6-hydroxy-3-succinoyl-pyridine using nicotine is one such practical approach, commercially (Schmid et al. 2001).

For this, researchers have engineered a bio-catalyst, namely, *Pseudomonas putida* P-HSP. This bio-catalyst results in the efficient production of 6-hydroxy-3-succinoyl-pyridine from the wastes of tobacco industries which consist of high nicotine (Roduit et al. 1997).

To determine the capacity of *Pseudomonas putida* P-HSP for the production of 6-hydroxy-3-succinoyl-pyridine, biotransformation was done with the help of 3.4 g dry cell weight (DCW) of whole cells of *Pseudomonas putida* P-HSP as a bio-catalyst, 3 g nicotine as substrate, and double distilled water, with final pH of 10, as the reaction buffer at temperature 30°C with centrifugation at 120 RPM (Roduit et al. 1997). After 5 h of the reaction, the sample was later centrifuged, and the supernatant was collected and later analyzed by high-pressure liquid chromatography (HPLC). One peak was observed having a retention time of 12.93 min, corresponding to the peak and spectrum of 6-hydroxy-3-succinoyl-pyridine. The results of the characterization techniques confirm that 6-hydroxy-3-succinoyl-pyridine was generated from nicotine as a single product by whole cells of *Pseudomonas putida* P-HSP (Yu et al. 2014).

Biotransformation was done at a large scale with optimal reaction conditions like pH = 9, temperature at 30°C, 6 g as initial concentration of nicotine (Roduit et al. 1997), and 3.4 g of dry cell weight (DCW) (Roduit et al. 1997) of whole cells of *Pseudomonas putida* P-HSP. Reactions for the production of 6-hydroxy-3-succinoyl-pyridine in (1) cell-free system, (ii) with resting cells of wild strain S16, (iii) engineered strain of *Pseudomonas putida* P-HSP, and (iv) heat-killed strain of *Pseudomonas putida* P-HSP were analyzed. The results were the yield of 6-Hydroxy-3-succinoyl-pyridine with an engineered strain of *Pseudomonas putida* P-HSP was 99.4% which is higher when compared with the strain that is not modified, that is, 38.9% after 5 h of bio-transformation. Thus, engineered strain is 3.7-fold more effective for the production of 6-hydroxy-3-succinoyl-pyridine, comparatively (Yu et al. 2014).

## 5.3 Production of 3-Succinoyl-pyridine (SP) from Tobacco Wastes

Tobacco (*Nicotiana*) belongs to the family of Solanaceae, which is cultivated extensively in a lot of countries such as the USA, China, Brazil, India, and Cuba (Davis et al. 2007). But certain portions of tobacco leaves inappropriate to use for the production of cigarette are later discarded due to the high content of nicotine, that is, within a range of 3–6% (w/w) (Zhang et al. 2003).

Nicotine (*N*-heterocyclic alkaloid) is the major toxic compound of organic nature in solid and liquid wastes of tobacco leaves (Mayer 2014). Nicotine has increased solubility in aqueous solutions, thus easy leaching of the nicotine from the wastes of the tobacco leaves to the groundwater. It is reported in the previous investigations that the presence of nicotine is detected more in the seepage areas and in the leaking water coming from the wastes of the landfills (Slack et al. 2005; Schwarzbauer et al. 2002).

Researchers are functioning to develop a method for easy cleanup and easy removal of nicotine when present in substantial amounts from the tobacco wastes. Using microorganisms that work under methanogenic and aerobic reaction conditions, an efficient bioremediation method has been developed that focuses on the reduction of the nicotine from the wastes of the tobacco leaves (Piotrowska-Cyplik et al. 2009). Considering the biological methods, bacteria which belong to the genera of *Pseudomonas* and *Arthrobacter* depict two main species of bacteria amidst such nicotinophilic microorganisms (Gurusamy and Natarajan 2013; Kaiser et al. 1995).

3-Succinoyl-pyridine (SP), also known as $\gamma$-oxo-3-pyridine butanoic acid, is a copy of nicotine (McEvoy et al. 1981). A green approach with a potential to reuse and reduce the toxicity of wastes of the tobacco leaves will be developed for efficient synthesis of 3-succinoyl-pyridine by using *Pseudomonas putida*, which is engineered genetically. Also, the initiation of the production of 3-succinoyl-pyridine can be done via an aqueous solution of nicotine (scheme A), which is extracted from the tobacco leaves of low grade. Apart from the aqueous solution, SP production can be done directly via crude suspension of powder of tobacco leaves (scheme B). Thus, these two green schemes (Fig. 3) are helpful for converting nicotine from the tobacco wastes (having a high content of nicotine) into commercial valuable substances.

High-performance liquid chromatography was done in category to find out actual content of the nicotine of the tobacco wastes by drawing linear standard curves of nicotine and 3-succinoyl-pyridine, in accordance with the data. The content of the nicotine in tobacco wastes is calculated in the form of a percentage (%) from the standard curve. The results obtained were 3.09% ± 0.02% (w/w) which is calculating the total amount of nicotine nearby in leaves of tobacco (Wang et al. 2015).

The first step (Fig. 3) was using water as solvent (pure) in order to obtain the crude suspension of the leaves of the tobacco. The nicotine recovered showed a yield of 74.3% with 500 ml of leach liquor and 50 g powder of tobacco leaves. In

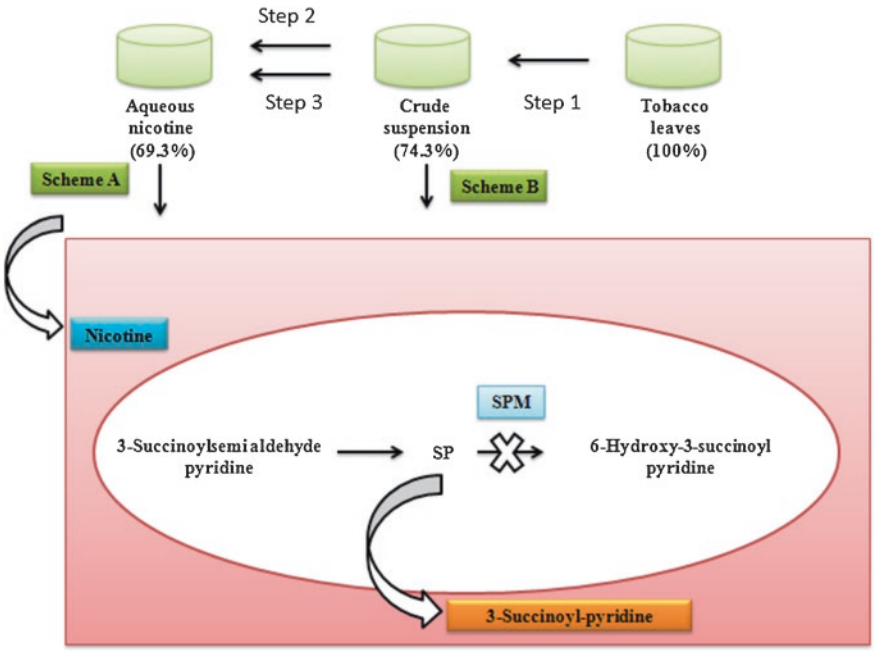


**Fig. 3** Schemes for the production of 3-succinoyl-pyridine (SP) from the leaves of the tobacco using strain *Pseudomonas putida* S16dspm (*SSF* solid state fermentation) (Wang et al. 2015)

the second step (Fig. 3), chloroform extraction and thin-layer chromatography were done. The results obtained have shown that very little amount of residue of nicotine was present in the aqueous phase after extraction was done. The final step (Fig. 3) of nicotine separation from the sulfuric acid (aqueous). The recovery yield observed was 64.3% with an aqueous solution of 20 ml and the content of the nicotine was 49 g/L (Fig 3). The integrity of the cell is very important for biotransformation of nicotine to 3-succinyl pyridine due to no synthesis of 3-succinyl pyridine in cell-free conditions. Also, after 10 h the content of the nicotine was still the same in the cell-free conditions. Thus, the bio-catalytic reactions should be performed in the whole-cell system (Wang et al. 2015).

The biotransformation reactions were conducted at various temperatures and values of pH in deionized water. The activity of 3-succinyl pyridine synthesis was optimal at a temperature of 24°C. Thus high temperature (42°C) degrades the efficiency of 3-succinyl pyridine formation. It was observed that the acidic pH hinders the formation of 3-succinyl pyridine. Hence, the optimum pH value for 3-succinyl pyridine synthesis was 9.0. The initial concentration of nicotine was 3 g/L is an appropriate initial nicotine concentration, but with an increase in the concentration of the substrate the final yield of the 3-succinyl pyridine was improved instead of the rate of 3-succinyl pyridine formation (Wang et al. 2015).

Under the optimal process of biotransformation, the observed yield of the isolated crystal compound 3-succinyl pyridine on nicotine was 54.2%. In addition, this

process to produce 3-succinyl pyridine showed that gene *spmA* is important in 3-succinyl pyridine deterioration of strain S16 instead of gene *pps_3984* which is a *sirA*-like gene. To recover a resource from tobacco wastes is still a long-term challenge. Hence, this approach can be considered as a helpful scheme to achieve the revival of tobacco wastes (Wang et al. 2015).

## 5.4 *Fungal Oxidoreductase for Removing Pharmaceutical Compounds (PhACs)*

Pharmaceutically lively compounds are pollutants in water noticed regularly in treatment plants of wastewater effluents (Marco-Urrea et al. 2009). They are broadly used as prescription or nonprescription medicines (Naghdi et al. 2017). This has become a matter of grave concern since wastewater treatment plants are not much effective for efficient removal of pharmaceutically active compounds because of their recalcitrant nature and their discharge water (Lienert et al. 2007; Burkhardt-Holm 2011). Some shreds of evidences regarding mobilization of pharmaceutically active compounds into the food chains have also been reported and hence result in the increase in the concentration of pharmaceutically active compounds (Lagesson et al. 2016). The pharmaceutically active compounds into the aquatic system have led to many environmental issues like feminization of male fish because of the exposure to steroidal hormones and antibiotic-resistant genes because of the release of the non-metabolized antibiotics into water (Nazaret and Aminov 2014).

This has triggered the researchers to work and evaluate the biodegradation of pharmaceutically active compounds in wastewater treatment plants (Stackelberg et al. 2007). Developments have been made to treat wastewater when compared to conventional treatment methods (activated sludge). The methods developed recently are (i) membrane separation, (ii) advanced oxidation processes (AOPs), and (iii) adsorption onto activated carbon. They have the capacity to accomplish the task of efficient removal of pharmaceutically active compounds (Tadkaew et al. 2011). But these recent technologies do have some issues or challenges, for example, the formation of toxic by-products during advanced oxidation process (Kosjek et al. 2009), the discarding concentrated stream in membrane separation (Westerhoff et al. 2009), and the generation of absorbents again (Bathen 2003). Thus, nowadays the removal of these compounds efficiently is a need of an hour.

Conversion of pharmaceutically active compounds through bio-catalysis can be considered as an alternative approach with respect to the environment. There is no or less production of toxic by-products when evaluated to conventional methods (Asif et al. 2017). The enzyme specificity for the substrate results in the minimum formation of unfavorable side reactions, where ever possible (Senthivelan et al. 2016). Also, enzymes can perform biochemical reactions rapidly and thus play an important role to prevent pollution of these compounds via clean methods (Arora and Sharma 2010).

Recently, various researchers have investigated the wastewater treatment with the use of enzymes, especially oxidoreductases because they have the capability to oxidize persistent pollutants in the wastewater. They even have the potential to degrade various aromatic pollutants of recalcitrant nature (Christian et al. 2005). The molecular mass and the reaction conditions of lignin peroxidase are 37–50 kDa, 35–55°C, and ph within a range of 2–5 (Table 4), respectively (Christian et al. 2005).

It has been reported that treatment via whole-cell fungal species makes use of extracellular enzymes, intracellular enzymes, and mycelium-bound enzymes for the degradation of recalcitrant compounds and thus certain differences are there when treatment is done by whole-cell WRF (white rot fungi) and by using extracted enzymes (Nguyen et al. 2016) (Fig. 4). From all the species of fungi, white rot fungi have the ability to remove the broad spectrum of organic compounds which show resistance toward degradation from species of bacteria in an efficient (Hata et al. 2010b). This aforementioned ability is because of the exploit of intracellular enzymes, namely, CYP450, and extracellular enzymes, that is, lignin peroxidase, manganese peroxidase, and laccase (Hata et al. 2010b; Nguyen et al. 2013). Due to the effect of intracellular and extracellular enzymes in combination along with sorption of pharmaceutical compounds onto biomass, the treatment using whole-cell fungi is helpful in removing a broad range of pharmaceutical compounds like antibiotics, anti-inflammatory compounds, and antiepileptics (Table 5) as compared to the single enzyme use (Hata et al. 2010a; Marco-Urrea et al. 2009).

White rot fungi have numerous properties that make them a promising candidate for removing pharmaceutical compounds like (i) nonspecific nature of the enzyme produced which makes them suitable to degrade a broad range of micro-pollutants, (ii) rapid colonization via hyphal growth thus easy access to the pollutants, (iii) degradation of compounds with low solubility of them in water, and (4) compounds

**Table 4** Properties of enzymes with applications (Asgher et al. 2008; Duran and Esposito 2000; Husain and Husain 2007)

| Enzymes | Source | Molecular weight (kDa) | Reaction conditions | Co-substrate | Applications |
|---|---|---|---|---|---|
| Laccase | *T. versicolor*, *T. hispida* | 58–90 | 40–65°C, pH 2–10 | Oxygen | Decoloration and degradation of dyes |
| Tyrosinase | *Agaricus bisporus* | 119.5–133 | 20–40°C, pH 5–8 | Oxygen | Degradation of phenols and amines |
| Lignin peroxidase (LiP) | *Phanerochaete chrysosporium* | 37–50 | 35–55°C, pH 2–5 | Hydrogen peroxide | Degradation of phenolic and aromatic substances |
| Manganese peroxidase (MnP) | *Phlebia radiata* | 32–62.5 | 40–60°C, pH 4–7 | Hydrogen peroxide | Degradation of phenolics, dyes, lignins |

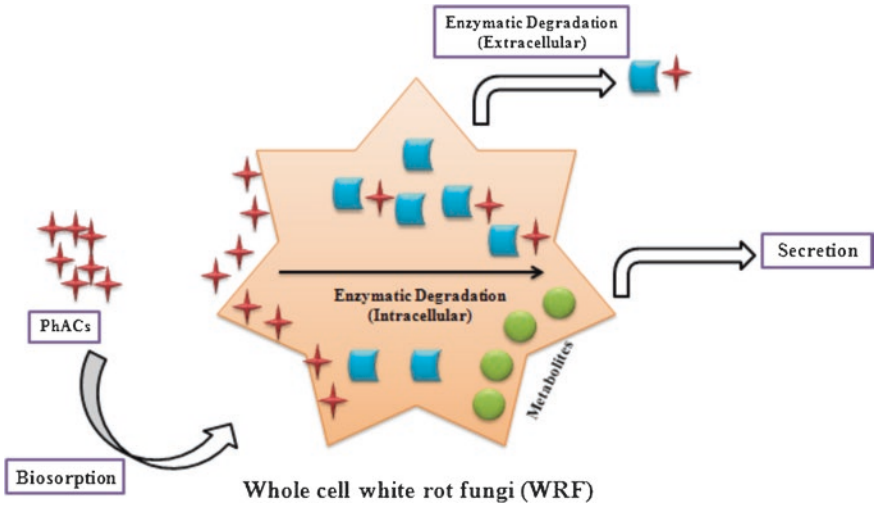


**Fig. 4** Removal of pollutant by white rot fungi (WRF) (Naghdi et al. 2018) (*PhACs* pharmaceutically active compounds)

which can be diminished in the media where nutrients are deficient media with a broad range of pH, that is, pH 3–9. Figure 4 represents the removal of pharmaceutical compounds from whole-cell fungi (white rot fungi). From the figure, pollutants (pharmaceutically active compounds) can be adsorbed (biosorption) onto the surface of white rot fungi which later gets degraded by the action of intracellular and extracellular enzymes, respectively (Naghdi et al. 2018).

## *5.5 Lipases for Bioremediation of Cooking Oil Wastes*

Wastes generated from the food industries mainly consist of lipids and carbohydrates which damage the environment because of the oil film formation on aquatic surfaces disrupting the diffusion of oxygen. This may result in clogging because of the emulsification of organic matter (Brown et al. 2016; Kumar et al. 2012). It is reported earlier that one liter of waste containing lipids makes use of one million liters of natural water approximately at high temperatures. These oils are toxic when heated at high temperatures (Nwobi et al. 2006; Hocevar et al. 2012). Applications of bioremediation aim at neutralizing target molecules and thus benefit the living systems. Bioremediation can be done by using microbes in the process of fermentation or by directly using enzymes to catalyze toxic element (Sivaperumal et al. 2017).

Wastes of the cooking oil have renowned impacts on the environment. Bioremediation of cooking oil wastes can be done through the enzymatic activity of lipase, which can help in minimizing the cytotoxic effect. Additionally, they are

**Table 5** Removal (in percentage) of pharmaceutical compounds by various species of white rot fungi under different reaction conditions (Naghdi et al. 2018)

| Compound | Type of wastewater | Species | Reaction conditions | % removal | References |
|---|---|---|---|---|---|
| Acetaminophen | Hospital wastewater | *T. versicolor* | Continuous fluidized bed (10 L)<br>8 days, 25°C, pH 4.5 | 100 | Cruz-Morat_o et al. (2014) |
| Amitriptyline | Synthetic water | *T. versicolor* | Continuous membrane bioreactor (5.5 L)<br>110 days, 27°C, pH 4.5 | 85 | Nguyen et al. (2013) |
| Carbamazepine | Spiked water | *P. chrysosporium* | Continuous stirred tank (1.5 L)<br>50 days, 30°C, pH 4.5 | 25–60 | Rodarte-Morales et al. (2012) |
| Ciprofloxacin | Non-sterile urban wastewater | *T. versicolor* | Batch fed fluidized bed (10 L)<br>8 days, 25°C, 135 rpm, pH 4.5 | 35 | Cruz-Morat_o et al. (2013) |
| Ibuprofen | Hospital wastewater | *T. versicolor* | Continuous fluidized bed (1.5 L)<br>5 days, 25°C, pH 4.5 | 90 | Mir-Tutusaus et al. (2016) |
| Tetracycline | Hospital wastewater | *T. versicolor* | Continuous fluidized bed (10 L)<br>8 days, 25°C, pH 4.5 | 0 | Cruz-Morat_o et al. (2014) |

used commercially all over the globe because of the versatile nature of reactions and substrates. Though lipases have the potential in processing of wastes of cooking oil, the products generated after the process are not less toxic in nature (Okino-Delgado et al. 2017).

Lipase helps in the modification of oils via hydrolysis approach. The bond of triglyceride ester breaks down when water is present in the hydrolysis reaction and results in the production of glycerol and fatty acids (Paques and Macedo 2006). When alcohol is used instead of water, there is a change in the transesterification reaction. Firstly, there is a conversion of triglycerides into diglyceride. Secondly, the diglyceride is converted into monoglyceride. The final step will be the conversion of monoglyceride to glycerol, which results in the formation of methyl/ethyl ester of each glyceride in every stage of transformation (Murugesan et al. 2009).

Enzyme lipases were extracted from the waste of processing of concentrated orange juice manufacture. Three fractions of wastes were used: (i) frit, the fragment of a peel, (ii) peel, and (iii) core. The processing of the samples was done via mechanical milling, freezing, and lyophilization (Okino-Delgado and Fleuri 2014, 2017). The crude extracts were concentrated in accordance with various approaches. Enzyme extracts were concentrated via precipitation reaction with the help of ammonium sulfate (60% saturation), following centrifugation, dialysis, and lyophilization along with acetone (acetone/sample, 1:4 (v/v)). Later microfiltration was done via centrifugation using the membrane of 10 kDa centrifugal filter (Millipore1). The activities of the enzyme lipase were calculated before and after every stage in accordance with titration methods which uses (i) olive oil (emulsified) as a substrate in order to measure hydrolysis activity (Macedo et al. 1997) and (ii) ethanol and oleic acid as a substrate (acid/alcohol, 1:5) in order to determine the esterification activity (Talukder et al. 2007). Biuret method was used for the quantification of the total proteins (Gornall et al. 1949).

It was found out that the extract of concentration via ammonium sulfate precipitation reaction following dialysis and lyophilization has the highest activity of lipase (U/g). The frit extract has a lipase activity of 50.86 U/g. The concentration of acetone and microfiltration has diminished the lipase activity of peel to 0 U/g (Okino-Delgado et al. 2017).

The waste of the cooking oil (soyabean oil) was collected in controlled reaction conditions to assure the experiment reproducibility. This was later heated at 200°C (35 heating cycles) (Stacke et al. 2009). The untreated waste of oil was evaluated for more comparison with waste which is treated enzymatically. The unheated oil, that is, crude oil, was later also accessed with and without treatment with enzymes, to avoid false positives due to the normal reaction of enzyme-oil. The orange-waste lipases were further tested in two modified reactions by using two substrates: (i) the waste of soybean oil and (ii) the waste of crude soybean oil which is not heated without heating. Porcine pancreatic lipase (Sigma Aldrich) and lipase from the strain *Candida antarctica* (Novozymes) which is available commercially were used during the analysis of the performance for comparative studies (Okino-Delgado et al. 2017).

Porcine pancreatic lipase and orange-waste lipases have a high release of FAE (fatty acid esters) as compared to controls, that is, crude soybean and soybean oil wastes. During commercial treatments of lipase, it was observed that wastes of crude soybean oil and soybean oil have a different release of fatty acid esters which indicates that lipolytic extracts modify the soybean oil when it was raw and when it was heated for a prolonged duration. Thus, one can assume that lipase from orange juice has the capacity to modify the oil for bioremediation method. Also, the compounds obtained by heating the oil have no influence on the catalytic power of the extracted lipase. The researchers analyzed the profile of FAE via gas chromatography. The results were all the extracts of lipase have the potential to catalyze the transesterification reaction of crude soybean oil and respective residues when ethanol was solvent (Okino-Delgado et al. 2017).

The low activities of enzyme lipase from microfiltration concentration are because of the porosity of the membrane, which is not appropriate for the lipases.

While comparing, frit fraction extracts and peel fraction extracts both have the same profiles, but the core extract has a distinct one. Explaining on the basis of anatomy, frit, and the peel corresponds to the fruit epicarp and the core belongs to the mesocarp (Okino-Delgado and Fleuri 2015). Thus, core lipases and frit lipases were efficient in the bioremediation of wastes of soybean oil via transesterification reactions (Okino-Delgado et al. 2017).

## *5.6 Immobilized Laccase for Synthetic Dyes*

Special attention has been given to the efficiency and the positive effect of technologies on the environment. The properties specific to the bio-catalysts have become the subject of interest to many in various fields of science and industry (Chapman et al. 2018). There has been an increase in the research interest for using bio-catalysts in various technological fields which are quite visible through the increase in the value of the enzymes in the market (Market and Market 2020). Enzyme laccases have certain catalytic and physicochemical characteristics and hence are used as bio-catalysts in industries like the food industry, textile industry, pharmaceutical industry, medical industry, and paper and pulp industry and also used in the bioremediation methods (Jaiswal et al. 2016). But laccase enzyme has certain issues like less stability of the proteins of free enzyme and sensitive to changing reaction conditions and thus new developments are being made in order to enhance the properties of the enzyme laccase.

Recent trends dealing with the research of the enzymes are the modifications of enzymes along with the development of advanced functions and performance optimization of the enzymes in order to use the bio-catalysts commercially (Chapman et al. 2018). The improved stability can be accomplished by using immobilization methods. An immobilization method has a significant advantage like the reuse of the enzymes being immobilized over solid support when compared to the free enzymes (Fernández-Fernández et al. 2013). The complex structure and the shelf-life of the synthetic dyes in wastewaters in a major problem, thus, requires the development of desirable techniques with certain features like cost-effective, eco-friendly removal of these synthetic dyes from the residues of the industries. Technologies like immobilization of enzyme laccase over a solid matrix can be considered as a potential approach (Deska and Konczak 2019).

Dyes are basically compounds that consist of many chemical structures. They are used mainly in textile industries, clothing industries, paper industries, cosmetics industries, dye industries, and plastic industries. The toxicity of dyes is because of the complex chemical structure which renders more stability and increased resistance toward degradation methods like chemical degradation, photolytic degradation, and biological degradation. Latest, efficient, and eco-friendly approaches are the need of an hour to remove these dyes from the wastewater. Hence, the approach where the enzyme laccase is immobilized is grabbing the attention of many researchers because of their ability to degrade numerous types of synthetic dyes. Enzymes with modified characteristics like high stability, more resistant toward the

environment of the reaction, reusability and thus, results in high catalytic efficiency and low costs of the process (Deska and Konczak 2019).

Examples includes, a group of researchers immobilized enzyme laccase from the fungal strain *Trametes pubescens* by using entrapment approach on chitosan and cross-linking was done using glutaraldehyde and later analyzed the capacity of the bio-catalyst to decolorize the sample (Zheng et al. 2016). Both free enzyme and immobilized enzyme results in somewhat same amount of degradation of Acid Black 172, that is, 69%. After 30 days, it was observed that free enzymes are left with only 15% of their initial activity whereas the enzyme immobilized has 40% of its initial activity. Furthermore, laccase immobilized onto the chitosan shows high pH in the range of 3.5–12.0 along with high thermal stabilities when compared to the free enzyme. In addition, there has been a major loss in the activity of the free enzyme while storing. Also, after doing incubation at temperatures 60°C and 70°C for 2 h, the activity of the entrapped enzyme was less than 50%, whereas it was only 22.3% in case of free enzyme. Hence, the entrapped enzyme has better stability and, thus, can be reused possibly (Zheng et al. 2016). In another reported work where researchers immobilized enzyme laccase from the strain *Coriolopsis gallica* via entrapment method into the calcium-alginate beads (Daassi et al. 2014). The ratio of calcium to alginate used was 1:4 in order to have a high catalytic activity of immobilized enzymes, that is, approximately 85%, and high yield of the immobilization process, that is, 96%. The particular preparation was used to remove dyes from wastewaters coming from the textile industries. The biopolymer shell of the enzyme maintains the catalytic activity over a longer duration. The 50% of the Bismarck Brown R dye was removed when dissolved in the solution which is to be evaluated (Daassi et al. 2014). Other examples that show immobilization of enzyme laccase from fungal strain for decolorization studies of synthetic dyes are mentioned in Table 6.

## 6 Conclusion and Future Prospects

In the recent years, bio-catalysis for industrial processes has gained a lot of attention of researchers. Microbes engender a huge amount of catalysts and thus have a wide spectrum of benefits in numerous industries like chemical industries, pharmaceutical industries, food industries, dye industries, and many more. Green chemistry is flourishing rapidly and is chosen by many researchers nowadays by taking into consideration the cost factor apart from their applications in industrial processes. With the possibility to gain access of a broad range of enzymes of wild-type nature, their potential tunable properties can be used seamlessly to curb the havoc of industrial wastes into the environment and for sustainable chemical manufacture by adopting green synthetic pathways, a green condition in which the reaction will operate. This results in an improvement in the yield and reduction in the generation

**Table 6** Immobilized laccase enzyme and their decolorization studies of synthetic dyes (Deska and Konczak 2019)

| Fungal strains | Matrix for immobilization | Technique | Dyes | % of decolorization | Time of reaction | References |
|---|---|---|---|---|---|---|
| *Trametes pubescens* | Beads of copper-alginate | Encapsulation | RBBR | 75.8 | 4 h | Le et al. (2016) |
| *Coriolopsis gallica* | Beads of calcium-alginate | Entrapment | BB5 | 58.2 | 24 h | Deska and Konczak (2019) |
| *P. florida* NCIM 1243 | Nanofibers of cellulose | – | SDE | 70 | 12 h | Sathishkumar et al. 2014 |
| *G. lucidum* | Sol-gel (hydrophobic) | Entrapment | MTE | 97.3 | 24 h | Irshad et al. (2012) |
| *Aspergillus* | Nano-sheets of grapheme oxide | Covalent attachment | AB92 | 48.7 | 60 min | Kashefi et al. (2019) |
| *Trametes versicolor* IBL-04 | Beads of chitosan | Cross-linking | SF Black BR | 89.36 | 4 h | Asgher et al. (2017) |
| *Cyathus bulleri* | Beads of PVA | Cross-linking | AR 27 | 95 | – | Chhabra et al. (2015) |

of the industrial wastes. Hence, bio-catalysis has a significant role in sustainable chemistry as reactions are operating under mild optimum conditions which are employing a biodegradable and biocompatible catalyst. Thus, no issues of scarcity and contamination of catalysts of metals. This chapter has summarized some of the applications of the enzymes for the treatment of wastes generated by industries. The cost associated with the enzyme bio-catalyst is sometimes an expensive component in the biotransformation reaction of industrial processes. Apart from the cost, stability is also a significant challenge as an enzyme can be reused ideally after every repeated cycle of bio-catalysis. To sort out this particular issue, researchers started using immobilized enzymes that will help in increasing the stability of the enzyme along with easy recovery in order to reuse it after every cycle. Every concerned authority, researchers, and industrialists must step forward and take necessary significant steps with a concern to intensify the implementation of the enzymes for the sake of an environment. The study of bio-catalysts is one such superior approach for minimizing wastes generated from various industrial processes. Apart from this, these bio-catalytic studies help in preparing the basement that will grab more attention and novel thoughts to minimize the industrial wastes enzymatically. The products and by-products generated after enzymatic treatment can be later utilized effectively and endow economic benefits and eco-friendly benefits along with the competition with chemical and various other chemical processes. Thus, the process of bio-catalysis is a green, cost-effective, environmentally sound, and sustainable approach.

## References

Abbott AP, Harris RC, Ryder KS, D'Agostino C, Gladden LF, Mantle MD. Glycerol eutectics as sustainable solvent systems. Green Chem. 2011;13:82–90. https://doi.org/10.1039/C0GC00395F.

Adrio JL, Demain AL. Microbial cells and enzymes – a century of progress. In: Barredo JL, editor. Methods in biotechnology. Microbial enzymes and biotransformations, vol. 17. Totowa: Humana Press; 2005. p. 1–27.

Adrio JL, Demain AL. Microbial enzymes: tools for biotechnological processes. Biomolecules. 2014;4:117–39. https://doi.org/10.3390/biom4010117.

Ahmad R, Sardar M. Enzyme immobilization: an overview on nanoparticles as immobilization matrix. Biochem Anal Biochem. 2015;4:178. https://doi.org/10.4172/2161-1009.1000178.

Aitken MD. Waste treatment applications of enzymes: opportunities and obstacles. Chem Eng J. 1993;52:49–58. https://doi.org/10.1016/0300-9467(93)80057-U.

Alonso D, Baeza A, Chinchilla R, Guillena G, Pastor IM, Ramon DJ. Deep eutectic solvents: the organic reaction medium of the century. Eur J Org Chem. 2016:612–32. https://doi.org/10.1002/ejoc.201501197.

Anastas P, Eghbali N. Green chemistry: principles and practice. Chem Soc Rev. 2010;39:301–12. https://doi.org/10.1039/b918763b.

Arca-Ramos A, Ammann EM, Gasser CA, Nastold P, Eibes G, Feijoo G, Lema JM, Moreira MT, Corvini PFX. Assessing the use of nanoimmobilized laccases to remove micropollutants from wastewater. Environ Sci Pollut Res. 2016;23:3217–28. https://doi.org/10.1007/s11356-015-5564-6.

Arora DS, Sharma RK. Ligninolytic fungal laccases and their biotechnological applications. Appl Biochem Biotechnol. 2010;160:1760–88.

Arslan S, Eyvaz M, Gürbulak E, Yüksel E. A review of state-of-the-art technologies in dye-containing wastewater treatment-The textile industry case. Textile Wastewater Treatment; Emriye Akcakoca Kumbasar, InTech; 2016. Available online: http://www.intechopen.com/books/textile-wastewater-treatment/a-reviewof-state-of-the-art-technologies-in-dye-containing-wastewater-treatment-the-textile-industr. Accessed 10 Nov 2016.

Asano Y, Dadashipour M, Yamazaki M, Doi N, Komeda H. Functional expression of a plant hydroxynitrile lyase in Escherichia coli by directed evolution: creation and characterization of highly in vivo soluble mutants. Protein Eng Des Sel. 2011;24:607–16. https://doi.org/10.1093/protein/gzr030.

Asgher M, Bhatti HN, Ashraf M, Legge RL. Recent developments in biodegradation of industrial pollutants by white rot fungi and their enzyme system. Biodegradation. 2008;19:771–83. https://doi.org/10.1007/s10532-008-9185-3.

Asgher M, Noreen S, Bilal M. Enhancing catalytic functionality of *Trametes versicolor* IBL-04 laccase by immobilization on chitosan microspheres. Chem Eng Res Des. 2017;119:1–11. https://doi.org/10.1016/j.cherd.2016.12.011.

Asif MB, Hai FI, Singh L, Price WE, Nghiem LD. Degradation of pharmaceuticals and personal care products by white-rot fungi – a critical review. Curr Pollut Rep. 2017:1–16.

Ballardo C, Abraham J, Barrena R, Artola A, Gea T, Sanchez A. Valorization of soy waste through SSF for the production of compost enriched with *Bacillus thuringiensis* with biopesticide properties. J Environ Manag. 2016;169:126–31. https://doi.org/10.1016/j.jenvman.2015.12.029.

Balzarini J, Stevens M, De Clercq E, Schols D, Pannecouque C. Pyridine N-oxide derivatives: unusual anti-HIV compounds with multiple mechanisms of antiviral action. J Antimicrob Chemother. 2005;55:135–8. https://doi.org/10.1093/jac/dkh530.

Bartsch S, Kourist R, Bornscheuer UT. Complete inversion of enantioselectivity towards acetylated tertiary alcohols by a double mutant of a *Bacillus subtilis* esterase. Angew Chem Int Ed Engl. 2008;47:1508–11. https://doi.org/10.1002/anie.200704606.

Bathen D. Physical waves in adsorption technology – an overview. Sep Purif Technol. 2003;33:163–77. https://doi.org/10.1016/S1383-5866(03)00004-2.

Bokma E, Koronakis E, Lobedanz S, Hughes C, Koronakis V. Directed evolution of a bacterial efflux pump: adaptation of the E-coli TolC exit duct to the *Pseudomonas* MexAB translocase. FEBS Lett. 2006;580:5339–43. https://doi.org/10.1016/j.febslet.2006.09.005.

Bozell JJ, Petersen GR. Technology development for the production of biobased products from biorefinery carbohydrates-The US Department of Energy's "Top 10" revisited. Green Chem. 2010;12:539–54. https://doi.org/10.1039/B922014C.

Brown LD, Cologgi KF, Ulrich AC. Chapter 12: Bioremediation of oil spills on land. In: Oil spill science and technology. Boston: Elsevier; 2016. p. 699–729. Available in: https://books.google.com.br/books?hl=pt-BR&lr=&id=err2CwAAQBAJ&oi=fnd&pg=PP1&dq=Chapter+12:+Bioremediation+of+oil+spills+on+land.+&ots=raQk3UhWq9&sig=6EOjtQ8twFWYiSIP-WfxArXkagHw#v=onepage&q=Chapter%2012%3A%20Bioremediation%20of%20oil%20spills%20on%20land.&f=false.

Bruzzone S, Chiappe C, Focardi SE, Pretti C, Renzi M. Theoretical descriptor for the correlation of aquatic toxicity of ionic liquids by quantitative structure−toxicity relationships. Chem Eng J. 2011;175:17–23. https://doi.org/10.1021/ci010011r.

Budisa N, Schulze-Makuch D. Supercritical carbon dioxide and its potential as a life-sustaining solvent in a planetary environment. Life. 2014;4:331–40. https://doi.org/10.3390/life4030331.

Burkhardt-Holm P. Linking water quality to human health and environment: the fate of micropollutants. Inst Water Policy Nat Univ Singap. 2011:1–62.

Carrea G, Riva S. Organic synthesis with enzymes in non-aqueous media. Weinheim: Wiley-VCH; 2008. ISBN:978-3-527-31846-9

Carrea G, Ottolina G, Riva S. Role of solvents in the control of enzyme selectivity in organic media. Trends Biotechnol. 1995;13:63–70. https://doi.org/10.1016/S0167-7799(00)88907-6.

Castro AM, de Andréa TV, Castilho LR, Freire DMG. Use of mesophilic fungal amylases produced by solid-state fermentation in the cold hydrolysis of raw babassu cake starch. Appl Biochem Biotechnol. 2010;162:1612–25. https://doi.org/10.1007/s12010-010-8942-z.

Castro AM, Andréa TV, Carvalho DF, Teixeira MMP, Castilho LR, Freire DMG. Valorization of residual agroindustrial cakes by fungal production of multienzyme complexes and their use in cold hydrolysis of raw starch. Waste Biomass Valoriz. 2011;2:291–302. https://doi.org/10.1007/s12649-011-9075-5.

Castro AM, Castilho LR, Freire DMG. Characterization of babassu, canola, castor seed and sunflower residual cakes for use as raw materials for fermentation processes. Ind Crops Prod. 2016;83:140–8. https://doi.org/10.1016/j.indcrop.2015.12.050.

Chagas PMB, Torresa JA, Silva MC, Corrêa AD. Immobilized soybean hull peroxidase for the oxidation of phenolic compounds in coffee processing wastewater. Int J Biol Macromol. 2015;81:568–75. https://doi.org/10.1016/j.ijbiomac.2015.08.061.

Chapman J, Ismail AE, Dinou CZ. Industrial of enzymes: recent advances, techniques, and outlooks. Catal. 2018;8:1–26. https://doi.org/10.3390/catal8060238.

Chatzifragkou A, Papanikolaou S, Kopsahelis N, Kachrimanidou V, Dorado MP, Koutinas AA. Biorefinery development through utilization of biodiesel industry by-products as sole fermentation feedstock for 1,3-propanediol production. Bioresour Technol. 2014;159:167–75. https://doi.org/10.1016/j.biortech.2014.02.021.

Chemical Business. Green chemical principles; 2013. Available online: http://search.ebscohost.com/login.aspx?authtype=uid&user=ns240517main&,password=main&profile=ehost&defaultdb=bth. Accessed 20 July 2014.

Chemistry & Industry. Building a greener future; 2009. Available online: http://search.ebscohost.com/login.aspx?authtype=uid&user=ns240517main&password=main&profile=ehost&defaultdb=bth. Accessed 20 July 2014.

Chen S, Engel PC. Efficient screening for new amino acid dehydrogenase activity: directed evolution of *Bacillus sphaericus* phenylalanine dehydrogenase towards activity with an unsaturated non-natural amino acid. J Biotechnol. 2009;142:127–34. https://doi.org/10.1016/j.jbiotec.2009.03.005.

Chhabra M, Mishra S, Sreekrishnan TR. Immobilized laccasemediated dye decolorization and transformation pathway of azo dye acid red 27. J Environ Health Sci Eng. 2015;13:1–9. https://doi.org/10.1186/s40201-015-0192-0.

Chiappe C, Marra A, Mele A. Synthesis and applications of ionic liquids derived from natural sugars. Top Curr Chem. 2010;295:177–95.

Choi YH, Van Spronsen J, Dai Y, Verberne M, Hollmann F, Arends IWCE, Witkamp GJ, Verpoorte R. Are natural deep eutectic solvents the missing link in understanding cellular metabolism and physiology? Plant Physiol. 2011;156:1701–5. https://doi.org/10.1104/pp.111.178426.

Christ TN, Deweese KA, Woodyer RD. Directed evolution toward improved production of L-ribose from ribitol. Comb Chem High Throughput Screen. 2010;13:302–8. https://doi.org/10.2174/138620710791054277.

Christian V, Shrivastava R, Shukla D, Modi H, Vyas BRM. Mediator role of veratryl alcohol in the lignin peroxidase-catalyzed oxidative decolorization of Remazol Brilliant Blue R. Enzyme Microb Technol. 2005;36:327–32. https://doi.org/10.1016/j.enzmictec.2004.09.006.

Cinelli BA, López JA, Castilho LR, Freire DMG, Castro AM. Granular starch hydrolysis of babassu agroindustrial residue: a bioprocess within the context of biorefinery. Fuel. 2014;124:41–8. https://doi.org/10.1016/j.fuel.2014.01.076.

Clark JH, Farmer TJ, Herrero-Davila L, Sherwood J. Circular economy design considerations for research and process development in the chemical sciences. Green Chem. 2016;14:3914–34. https://doi.org/10.1039/C6GC00501B.

Coleman D, Gathergood N. Biodegradation studies of ionic liquids. Chem Soc Rev. 2010;39:600–37. https://doi.org/10.1039/B817717C.

Cruz-Morato C, Ferrando-Climent L, Rodriguez-Mozaz S, Barcelo D, Marco-Urrea E, Vicent T, Sarra M. Degradation of pharmaceuticals in non-sterile urban wastewater by *Trametes versicolor* in a fluidized bed bioreactor. Water Res. 2013;47:5200–10. https://doi.org/10.1016/j.watres.2013.06.007.

Cruz-Morato C, Lucas D, Llorca M, Rodriguez-Mozaz S, Gorga M, Petrovic M, Barcelo D, Vicent T, Sarra M, Marco-Urrea E. Hospital wastewater treatment by fungal bioreactor: removal efficiency for pharmaceuticals and endocrine disruptor compounds. Sci Total Environ. 2014;493:365–76. https://doi.org/10.1016/j.scitotenv.2014.05.117.

Daassi D, Rodriguez-Couto S, Nasri M, Mechichi T. Biodegradation of textile dyes by immobilized laccase from *Coriolopsis gallica* into Ca-alginate beads. Int Biodeterior Biodegrad. 2014;90:71–8. https://doi.org/10.1016/j.ibiod.2014.02.006.

Davis RM, Wakefield M, Amos A, Gupta PC. The hitchhiker's guide to tobacco control: a global assessment of harms, remedies, and controversies. Annu Rev Public Health. 2007;28:171–94. https://doi.org/10.1146/annurev.publhealth.28.021406.144033.

de Carvalho CC. Enzymatic and whole cell catalysis: finding new strategies for old processes. Biotechnol Adv. 2011;29:75–83. https://doi.org/10.1016/j.biotechadv.2010.09.001.

De Groeve MR, De Baere M, Hoflack L, Desmet T, Vandamme EJ, Soetaert W. Creating lactose phosphorylase enzymes by directed evolution of cellobiose phosphorylase. Protein Eng Des Sel. 2009;22:393–9. https://doi.org/10.1093/protein/gzp017.

De Groeve MR, Tran GH, Van Hoorebeke A, Stout J, Desmet T, Savvides SN, Soetaert W. Development and application of a screening assay for glycoside phosphorylases. Anal Biochem. 2010;401:162–7. https://doi.org/10.1016/j.ab.2010.02.028.

de Regil R, Sandoval G. Biocatalysis for biobased chemicals. Biomolecules. 2013;3:812–47. https://doi.org/10.3390/biom3040812.

Deetlefs M, Seddon KR. Assessing the greenness of some typical laboratory ionic liquid preparations. Green Chem. 2010;12:17–30. https://doi.org/10.1039/B915049H.

Demarche P, Junghanns C, Nair RR, Agathos SN. Harnessing the power of enzymes for environmental stewardship. Research review paper. Biotechnol Adv. 2012;30:933–53. https://doi.org/10.1016/j.biotechadv.2011.05.013.

Deska M, Konczak B. Immobilized fungal laccase as "green catalyst"for the decolourization process–state of the art. Process Biochem. 2019; https://doi.org/10.1016/j.procbio.2019.05.024.

Dhillon GS, Brar SK, Vera M, Tyagi RD. Utilization of different agro-industrial wastes for sustainable bioproduction of citric acid by *Aspergillus niger*. Biochem Eng J. 2011;54:83–92. https://doi.org/10.1016/j.bej.2011.02.002.

Diaz JCM, Rodríguez JA, Roussos S, Cordova J, Abousalham A, Carriere F, Baratti J. Lipase from the thermotolerant fungus *Rhizopus homothallicus* is more thermostable when produced using solid state fermentation than liquid fermentation procedures. Enzyme Microb Technol. 2006;39:1042–105. https://doi.org/10.1016/j.enzmictec.2006.02.005.

Dominguez de Maria P, Hollmann F. On the (Un) greenness of biocatalysis: some challenging figures and some promising options. Front Microbiol. 2015;6:01257. https://doi.org/10.3389/fmicb.2015.01257.

Du C, Lin SKC, Koutinas A, Wang R, Dorado P, Webb C. A wheat biorefining strategy based on solid-state fermentation for fermentative production of succinic acid. Bioresour Technol. 2008;99:8310–5. https://doi.org/10.1016/j.biortech.2008.03.019.

Du J, Shao Z, Zhao HM. Engineering microbial factories for synthesis of value-added products. J Ind Microbiol Biotechnol. 2011;38:873–90. https://doi.org/10.1007/s10295-011-0970-3.

Dunlop MJ, Dossani ZY, Szmidt HL, Chu HC, Lee TS, Keasling JD, Hadi MZ, Mukhopadhyay A. Engineering microbial biofuel tolerance and export using efflux pumps. Mol Syst Biol. 2011;7:487. https://doi.org/10.1038/msb.2011.21.

Duran N, Esposito E. Potential applications of oxidative enzymes and phenoloxidase-like compounds in wastewater and soil treatment: a review. Appl Catal B Environ. 2000;28:83–99. https://doi.org/10.1016/S0926-3373(00)00168-5.

Durand E, Lecomte J, Barea B, Piombo G, Dubreucq E, Villeneuve P. Evaluation of deep eutectic solvents as new media for *Candida Antarctica* lipase B catalyzed reactions. Process Biochem. 2012;47:2081–9. https://doi.org/10.1039/C3GC40899J.

Efremenko E, Senko O, Zubaerova D, Podorozhko E, Lozinsky V. New biocatalyst with multiple enzymatic activities for treatment of complex food wastewaters. Food Technol Biotechnol. 2008;46:208–12.

Elgue S, Prat L, Cabassud M, Cezerac J. Optimisation of solvent replacement procedures according to economic and environmental criteria. Chem Eng J. 2006;117:169–77. https://doi.org/10.1016/j.cej.2005.11.017.

Fadel HHM, Mahmoud MG, Asker MMS, Lotfy SN. Characterization and evaluation of coconut aroma produced by *Trichoderma viride* EMCC-107 in solid state fermentation on sugarcane bagasse. Electron J Biotechnol. 2015;18:5–9. https://doi.org/10.1016/j.ejbt.2014.10.006.

Fernandez-Arrojo L, Guazzaroni ME, Lopez-Cortes N, Beloqui A, Ferrer M. Metagenomic era for biocatalyst identification. Curr Opin Biotechnol. 2010;21:725–33. https://doi.org/10.1016/j.copbio.2010.09.006.

Fernández-Fernández M, Sanromán MÁ, Moldes D. Recent developments and applications of immobilized laccase. Biotechnol Adv. 2013;31:1808–25. https://doi.org/10.1016/j.biotechadv.2012.02.013.

Ferreira-Leitão VS, Gottschalk LMF, Ferrara MA, Nepomuceno AL, Molinari HBC, Bon EPS. Biomass residues in Brazil: availability and potential uses. Waste Biomass Valoriz. 2010;1:65–76. https://doi.org/10.1007/s12649-010-9008-8.

Ferreira-Leitão VS, Cammarota MC, Aguieiras ECG, de Sá LRV, Lafuente R, Freire DMG. The protagonism of biocatalysis in green chemistry and its environmental benefits. Catalysts. 2017;7:9. https://doi.org/10.3390/catal7010009.

Forgacs E, Cserháti T, Oros G. Removal of synthetic dyes from wastewaters: a review. Environ Int. 2004;30:953–71. https://doi.org/10.1016/j.envint.2004.02.001.

Forster-Carneiro T, Berni M, Dorileo I, Rostagno M. Biorefinery study of availability of agriculture residues and wastes for integrated biorefineries in Brazil. Resour Conserv Recycl. 2013;77:78–88. https://doi.org/10.1016/j.resconrec.2013.05.007.

Fujii Y, Kabumoto H, Nishimura K, Fujii T, Yanai S, Takeda K, Tamura N, Arisawa A, Tamura T. Purification, characterization, and directed evolution study of a vitamin D3 hydroxylase

from *Pseudonocardia autotrophica*. Biochem Biophys Res Commun. 2009;385:170–5. https://doi.org/10.1016/j.bbrc.2009.05.033.

Fukumoto K, Yoshizawa M, Ohno H. Room temperature ionic liquids from 20 natural amino acids. J Am Chem Soc. 2005;127:2398–9. https://doi.org/10.1021/ja043451i.

Gad SS. Polyciclic aromatic amines. Encyclopedia of toxicology. 3rd ed. Cambridge, MA: Academic Press; 2014. p. 1038–9.

Gaind S, Singh S. Production, purification and characterization of neutral phytase from thermotolerant *Aspergillus flavus* ITCC 6720. Int Biodeterior Biodegrad. 2015;99:15–22. https://doi.org/10.1016/j.ibiod.2014.12.013.

Gao X, Xie X, Pashkov I, Sawaya MR, Laidman J, Zhang W, Cacho R, Yeates TO, Tang Y. Directed evolution and structural characterization of a simvastatin synthase. Chem Biol. 2009;16:1064–74. https://doi.org/10.1016/j.chembiol.2009.09.017.

Garcia-Ruiz E, Mate D, Ballesteros A, Martinez AT, Alcalde M. Evolving thermostability in mutant libraries of ligninolytic oxidoreductases expressed in yeast. Microb Cell Factories. 2010;9:17. https://doi.org/10.1186/1475-2859-9-17.

Goetz AE, Garg NK. Regioselective reactions of 3,4-pyridynes enabled by the aryne distortion model. Nat Chem. 2013;5:54–60.

Gorke JT, Srienc F, Kazlauskas RJ. Hydrolase-catalyzed biotransformations in deep eutectic solvents. Chem Commun. 2008:1235–7. https://doi.org/10.1039/B716317G.

Gornall AG, Bardawill CJ, David MM. Determination of serum proteins by means of biuret reaction. J Biol Chem. 1949;177:51–66. Available in: https://s3.amazonaws.com/academia.edu.documents/7522360/gornall_etal.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1504211294&Signature=G%2BsPS%2FmddQ9n7jd1FjsEHydjTMw%3D&response-content-disposition=inline%3B%20filename%3DDetermination_of_serum_proteins_by_means.pdf.

Guajardo N, Müller CR, Schrebler R, Carlesi C, Dominguez de Maria P. Deep Eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations. ChemCatChem. 2016;8:1020–7. https://doi.org/10.3390/catal8050217.

Gumba RE, Saallah S, Misson M, Ongkudon CM, Anton A. Green biodiesel production: a review on feedstock, catalyst, monolithic reactor and supercritical fluid technology. Biofuel Res J. 2016;3:431–47. https://doi.org/10.18331/BRJ2016.3.3.3.

Gupta N, Farinas ET. Directed evolution of CotA laccase for increased substrate specificity using *Bacillus subtilis* spores. Protein Eng Des Sel. 2010;23:679–82. https://doi.org/10.1093/protein/gzq036.

Gurusamy R, Natarajan S. Current status on biochemistry and molecular biology of microbial degradation of nicotine. Sci World J. 2013:e125385. https://doi.org/10.1155/2013/125385.

Gutarra MLE, Godoy MG, Castilho LR, Freire DMG. Ioculum strategies for *Penicillium simplicissimum* lipase production by solid-state fermentation using a residue from the babassu oil industry. J Chem Technol Biotechnol. 2007;82:313–8. https://doi.org/10.1002/jctb.1674.

Gutarra MLE, Godoy MG, Maugeri F, Rodrigues MI, Freire DMG, Castilho LR. Production of an acidic and thermostable lipase of the mesophilic fungus *Penicillium simplicissimum* by solid-state fermentation. Bioresour Technol. 2009;100:5249–54. https://doi.org/10.1016/j.biortech.2008.08.050.

Hammond OS, Bowron DT, Edler KJ. Liquid structure of the choline chloride-urea deep eutectic solvent (reline) from neutron diffraction and atomistic modelling. Green Chem. 2016;18:2736–44. https://doi.org/10.1039/C5GC02914G.

Hancock SM, Rich JR, Caines ME, Strynadka NC, Withers SG. Designer enzymes for glycosphingolipid synthesis by directed evolution. Nat Chem Biol. 2009;5:508–14. https://doi.org/10.1038/nchembio.191.

Hao Yu, Hongzhi Tang & Ping Xu. Green strategy from waste to value-added-chemical production: efficient biosynthesis of 6-hydroxy-3-succinoyl-pyridine by an engineered biocatalyst, SCIENTIFIC REPORTS. 2014;4:5397, https://doi.org/10.1038/srep05397

Hata T, Kawai S, Okamura H, Nishida T. Removal of diclofenac and mefenamic acid by the white rot fungus *Phanerochaete sordida* YK-624 and identification of their metabolites after fungal transformation. Biodegradation. 2010a;21:681–9. https://doi.org/10.1007/s10532-010-9334-3.

Hata T, Shintate H, Kawai S, Okamura H, Nishida T. Elimination of carbamazepine by repeated treatment with laccase in the presence of 1-hydroxybenzotriazole. J Hazard Mater. 2010b;181:1175–8. https://doi.org/10.1016/j.jhazmat.2010.05.103.

Henze M, Harremoës P, La Cour JJ, Arvin E. Wastewater treatment: biological and chemical processes. Berlin/Heidelberg: Springer; 2001. p. 36–7.

Hermann BG, Patel M. Today's and tomorrow's bio-based bulk chemicals from white biotechnology. Appl Biochem Biotechnol. 2007;136:361–88. https://doi.org/10.1007/s12010-007-9031-9.

Hill MD. Recent strategies for the synthesis of pyridine derivatives. Chemistry (Weinheim Bergstr Ger). 2010;16:12052–62. https://doi.org/10.1002/chem.201001100.

Hobbs HR, Kondor B, Stephenson P, Sheldon RA, Thomas NR, Poliakoff M. Continuous kinetic resolution catalysed by cross-linked enzyme aggregates, 'CLEAs', in supercritical CO2. Green Chem. 2006;8:816–21. https://doi.org/10.1039/B604738F.

Hocevar L, Soares VRB, Oliveira FS, Korn MGA, Teixeira LSG. Application of multivariate analysis in mid-infrared spectroscopy as a tool for the evaluation of waste frying oil blends. J Am Oil Chem Soc. 2012;89:781–6. https://doi.org/10.1007/s11746-011-1968-8.

Holkar CR, Jadhav AJ, Pinjari DV, Mahamuni NM, Pandit AB. A critical review on textile wastewater treatments: possible approaches. J Envriron Manag. 2016;182:351–66. https://doi.org/10.1016/j.jenvman.2016.07.090.

Holker U, Hofer M, Lenz J. Biotechnological advantages of laboratory-scale solid state fermentation with fungi. Appl Microbiol Biotechnol. 2004;64:175–86. https://doi.org/10.1007/s00253-003-1504-3.

Hou XD, Liu QP, Smith TJ, Li N, Zong MH. Evaluation of toxicity and biodegradability of cholinium amino acids ionic liquids. PLoS One. 2013;8:e59145. https://doi.org/10.1371/journal.pone.0059145.

Hsieh D, Marchut AJ, Wei C, Zheng B, Wang SSY, Kiang S. Model-based solvent selection during conceptual process design of a new drug manufacturing process. Org Process Res Dev. 2009;13:690–7. https://doi.org/10.1021/op900058e.

Hudlicky T, Reed JW. Applications of biotransformations and biocatalysis to complexity generation in organic synthesis. Chem Soc Rev. 2009;38:3117–32. https://doi.org/10.1039/b901172m.

Husain M, Husain Q. Applications of redox mediators in the treatment of organic pollutants by using oxidoreductive enzymes: a review. Crit Rev Environ Sci Technol. 2007;38:1–42. https://doi.org/10.1080/10643380701501213.

Imamura C, Shigemori Y. Enhancement of thermal stabilization of formaldehyde dehydrogenase from *Pseudomonas putida* by directed evolution. Biosci Biotechnol Biochem. 2010;74:1462–5. https://doi.org/10.1271/bbb.100026.

Imran M, Crowley DE, Khalid A, Hussain S, Mumtaz MW, Arshad M. Microbial biotechnology for decolorization of textile wastewaters. Rev Environ Sci Biotechnol. 2014;14:73–92.

Irshad M, Bahadur BA, Anwar Z, Yaqoob M, Ijaz A, Iqbal HMN. Decolorization applicability of sol-gel matrix-immobilized laccase produced from *Ganoderma leucidum* using agro-industrial waste. Bioresources. 2012;7:4249–61.

Jaiswal N, Pandey VP, Dwivedi UN. Immobilization of papaya laccase in chitosan led to improved multipronged stability and dye discoloration. Int J Biol Macromol. 2016;86:288–95. https://doi.org/10.1016/j.ijbiomac.2016.01.079.

Jeganathan J, Bassi A, Nakhla G. Pre-treatment of high oil and grease pet food industrial wastewaters using immobilized lipase hydrolyzation. J Hazard Mater. 2006;137:121–8. https://doi.org/10.1016/j.jhazmat.2005.11.106.

Jochens H, Aerts D, Bornscheuer UT. Thermostabilization of an esterase by alignment-guided focussed directed evolution. Protein Eng Des Sel. 2010;23:903–9. https://doi.org/10.1093/protein/gzq071.

Johannes TW, Zhao H. Directed evolution of enzymes and biosynthetic pathways. Curr Opin Microbiol. 2006;9:261–7. https://doi.org/10.1016/j.mib.2006.03.003.

Jorgensen, A., Le Bocq, A., Nazarkina, L., et al. (2008) Methodologies for social life cycle assessment. Int J LCA 13: 96–103

Kabumoto H, Miyazaki K, Arisawa A. Directed evolution of the actinomycete cytochrome P450moxA (CYP105) for enhanced activity. Biosci Biotechnol Biochem. 2009;73:1922–7. https://doi.org/10.1271/bbb.90013.

Kaiser JP, Feng YC, Bollag JM. Microbial metabolism of pyridine, quinoline, acridine, and their derivatives under aerobic and anaerobic conditions. Microbiol Rev. 1995;60:483–98.

Karam J, Nicell JA. Potential applications of enzymes in waste treatment. J Chem Technol Biotechnol. 1997;69:141–53. https://doi.org/10.1002/(SICI)1097-4660(199706)69:2<141::AID-JCTB694>3.0.CO;2-U.

Kashefi S, Borghei SM, Mahmoodi NM. Covalently immobilized laccase onto graphene oxide nanosheets: preparation, characterization, and biodegradation of azo dyes in colored wastewater. J Mol Liq. 2019;276:153–62. https://doi.org/10.1016/j.molliq.2018.11.156.

Khan AA, Husain Q. Decolorization and removal of textile and non-textile dyes from polluted wastewater and dyeing effluent by using potato (*Solanum tuberosum*) soluble and immobilized polyphenol oxidase. Bioresour Technol. 2007;98:1012–9. https://doi.org/10.1016/j.biortech.2006.04.008.

Khersonsky O, Rothlisberger D, Wollacott AM, Murphy P, Dym O, Albeck S, Kiss G, Houk KN, Baker D, Tawfik DS. Optimization of the in-silico-designed kemp eliminase KE70 by computational design and directed evolution. J Mol Biol. 2011;407:391–412. https://doi.org/10.1016/j.jmb.2011.01.041.

Khlifi R, Belbahri L, Woodward S, Ellouz M, Dhouib A, Sayadi S, Mechichi T. Decolourization and detoxification of textile industry wastewater by the laccase-mediator system. J Hazard Mater. 2010;175:802–8. https://doi.org/10.1016/j.jhazmat.2009.10.079.

Khmelnitsky YL, Welch SH, Clark DS, Dordick JS. Salts dramatically enhance activity of enzymes suspended in organic solvents. J Am Chem Soc. 1994;116:2647–8. https://doi.org/10.1021/ja00085a066.

Kim HJ, Uhm TG, Kim SB, Kim P. Escherichia coli arabinose isomerase and *Staphylococcus aureus* tagatose-6-phosphate isomerase: which is a better template for directed evolution of nonnatural substrate isomerization? J Microbiol Biotechnol. 2010;20:1018–21.

Kittl R, Withers SG. New approaches to enzymatic glycoside synthesis through directed evolution. Carbohydr Res. 2010;345:1272–9. https://doi.org/10.1016/j.carres.2010.04.002.

Klibanov AM. Asymmetric transformations catalyzed by enzymes in organic solvents. Acc Chem Res. 1990;23:114–20. https://doi.org/10.1021/ar00172a004.

Klibanov AM. Why are enzymes less active in organic solvents than in water. Trends Biotechnol. 1997;15:97–101. https://doi.org/10.1016/S0167-7799(97)01013-5.

Koch DJ, Chen MM, van Beilen JB, Arnold FH. In vivo evolution of butane oxidation by terminal alkane hydroxylases AlkB and CYP153A6. Appl Environ Microbiol. 2009;75:337–44. https://doi.org/10.1128/AEM.01758-08.

Kosjek T, Andersen HR, Kompare B, Ledin A, Heath E. Fate of carbamazepine during water treatment. Environ. Sci. Technol. 2009;43:6256e6261.

Kourist R, Bornscheuer UT. Biocatalytic synthesis of optically active tertiary alcohols. Appl Biochem Biotechnol. 2011;91:505–17. https://doi.org/10.1007/s00253-011-3418-9.

Kumar A, Singh S. Directed evolution: tailoring biocatalysis for industrial application. Crit Rev Biotechnol. 2013;33:365–78. https://doi.org/10.3109/07388551.2012.716810.

Kumar S, Mathur A, Singh V, Nandy S, Kumar K, Negi S. Bioremediation of waste cooking oil using a novel lipase produced by *Penicillium chrysogenum* SNP5 grown in solid medium containing waste grease. Bioresour Technol. 2012;120:300–4. https://doi.org/10.1016/j.biortech.2012.06.018.

Kurnik K, Treder K, Skorupa-Kłaput M, Tretyn A, Tyburski J. Removal of phenol from synthetic and industrial wastewater by potato pulp peroxidases. Water Air Soil Pollut. 2015;226:254–71. https://doi.org/10.1007/s11270-015-2517-0.

Lagesson A, Fahlman J, Brodin T, Fick J, Jonsson M, Bystrom P, Klaminder J. Bioaccumulation of five pharmaceuticals at multiple trophic levels in an aquatic food web – insights from a field experiment. Sci Total Environ. 2016;568:208–15. https://doi.org/10.1016/j.scitotenv.2016.05.206.

Le TT, Murugesan K, Lee CS, Vu CH, Chang YS, Jeon JR. Degradation of synthetic pollutants in real wastewater using laccase encapsulated in core-shell magnetic copper alginate beads. Bioresour Technol. 2016;216:203–10. https://doi.org/10.1016/j.biortech.2016.05.077.

Li N, Ma D, Zong MH. Enhancing the activity and regioselectivity of lipases for 3′-benzoylation of floxuridine and its analogs by using ionic liquid-containing systems. J Biotechnol. 2008;133:103–9. https://doi.org/10.1016/j.jbiotec.2007.09.003.

Li Y, Peng X, Chen H. Comparative characterization of proteins secreted by *Neurospora sitophila* in solid-state and submerged fermentation. J Biosci Bioeng. 2010;116:493–8. https://doi.org/10.1016/j.jbiosc.2013.04.001.

Lienert J, Güdel K, Escher BI. Screening method for ecotoxicological hazard assessment of 42 pharmaceuticals considering human metabolism and excretory routes. Environ Sci Technol. 2007;41:4471–8. https://doi.org/10.1021/es0627693.

Lima-Ramos J, Tufvesson P, Woodley JM. Application of environmental and techno-economic metrics to biocatalytic process development. Green Process Synth. 2014;3:195–213. https://doi.org/10.1515/gps-2013-0094.

Littlechild JA. Archaeal enzymes and applications in industrial biocatalysts. Archaea. 2015. 10 pages. https://doi.org/10.1155/2015/147671

Liu QB, Janssen MHA, van Rantwijk F, Sheldon RA. Room-temperature ionic liquids that dissolve carbohydrates in high concentrations. Green Chem. 2005;7:39–42. https://doi.org/10.1039/B412848F.

Liu L, Schmid RD, Urlacher VB. Engineering cytochrome P450 monooxygenase CYP 116B3 for high dealkylation activity. Biotechnol. Lett. 2010a; 32(6):841–845.

Liu YH, Ye M, Lu Y, Zhang X, Li G. Improving the decolorization for textile dyes of a metagenome-derived alkaline laccase by directed evolution. Appl Biochem Biotechnol. 2011;91:667–75. https://doi.org/10.1007/s00253-011-3292-5.

Liu C, Luo J, Xu L, Huo Z. Synthesis of 2-substituted pyridines from pyridine N-oxides. Arkivoc. 2013;1:154–74. https://doi.org/10.3998/ark.5550190.0014.105.

López E, Deive FJ, Longo M, Sanromán A. Strategies for utilisation of food- processing wastes to produce lipases in solid-state cultures of *Rhizopus oryzae*. Bioprocess Biosyst Eng. 2010;33:929–35. https://doi.org/10.1007/s00449-010-0416-8.

López JA, Lázaro CC, Castilho LR, Freire DMG, Castro AM. Characterization of multienzyme solutions produced by solid-state fermentation of babassu cake, for use in cold hydrolysis of raw biomass. Biochem Eng J. 2013;77:231–9. https://doi.org/10.1016/j.bej.2013.06.006.

Ma Y, Wei Y, Qiu J, Wen R, Hong J, Liu W. Isolation, transposon mutagenesis, and characterization of the novel nicotine-degrading strain *Shinella sp.* HZN7. Appl Microbiol Biotechnol. 2014;98:2625–36. https://doi.org/10.1007/s00253-013-5207-0.

Macedo GA, Pastore GM, Park YK. Partial purification and characterization of an extracellular lipase from a newly isolated strain of *Geotrichum* sp. Rev Bras Microbiol. 1997;28:90. Available in: http://repositorio.unicamp.br/handle/REPOSIP/59086

MacPherson IS, Rosell FI, Scofield M, Mauk AG, Murphy ME. Directed evolution of copper nitrite reductase to a chromogenic reductant. Protein Eng Des Sel. 2010;23:137–45. https://doi.org/10.1093/protein/gzp084.

Madeira JV Jr, Ferreira LR, Macedo J, Macedo GA. Efficient tannase production using brazilian citrus residues and potential application for orange juice valorization. Biocatal Agric Biotechnol. 2015;4:91–7. https://doi.org/10.1016/j.bcab.2014.11.005.

Mahadik ND, Puntambekar US, Bastawde KB, Khire JM, Gokhale DV. Production of acidic lipase by *Aspergillus niger* in solid state fermentation. Process Biochem. 2002;38:715–21. https://doi.org/10.1016/S0032-9592(02)00194-2.

Marco-Urrea E, Perez-Trujillo M, Vicent T, Caminal G. Ability of white-rot fungi to remove selected pharmaceuticals and identification of degradation products of ibuprofen by *Trametes versicolor*. Chemosphere. 2009;74:765–72. https://doi.org/10.1016/j.chemosphere.2008.10.040.

Market and Market, Industrial enzymes market by type, application, brands and by region-global trends and forecasts to 2020. 2018. https://www.prnewswire.com/news-releases/industrialenzymes-market-by-type-application-brands%2D%2Dby-region%2D%2D-global-trends-and-forecasts-to-2020-300240612.html/. Accessed 15 Dec 2018.

Masse L, Kennedy KJ, Chou S. Testing of alkaline enzymatic hydrolysis pretreatment for fat particles in slaughterhouse wastewater. Bioresour Technol. 2001;77:145–55. https://doi.org/10.1016/S0960-8524(00)00146-2.

Masse L, Massé DI, Kennedy KJ. Effect of hydrolysis pretreatment on fat degradation during anaerobic digestion of slaughterhouse wastewater. Process Biochem. 2003;38:1365–72. https://doi.org/10.1016/s0032-9592(03)00020-7.

Matsuda T. Recent progress in biocatalysis using supercritical carbon dioxide. J Biosci Bioeng. 2013;115:233–41. https://doi.org/10.1016/j.jbiosc.2012.10.002.

Matsuda T, Kanamaru R, Watanabe K, Kamitanaka T, Harada T, Nakamura K. Asymmetric synthesis using hydrolytic enzymes in supercritical carbon dioxide. Tetrahedron: Asymmetry. 2005;16:905–15. https://doi.org/10.1016/j.tetasy.2005.01.004.

Matto M, Husain Q. Decolorization of textile effluent by bitter gourd peroxidase immobilized on concanavalin A layered calcium alginate-starch beads. J Hazard Mater. 2009;164:1540–6. https://doi.org/10.1016/j.jhazmat.2008.09.069.

Maugeri Z, Dominguez de Maria P. Novel choline-chloride based deep-eutectic solvents with renewable hydrogen bond donors: levulinic acid and sugar-based polyols. RSC Adv. 2012;2:421–5. https://doi.org/10.1039/C1RA00630D.

Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88:5–7. https://doi.org/10.1007/s00204-013-1127-0.

Mazutti MA, Zabot G, Boni G, Skovronski A, de Oliveira D, di Luccio M, Rodrigues MI, Treichel H, Maugeri F. Optimization of inulinase production by solid-state fermentation in a packed bed bioreactor. J Chem Technol Biotechnol. 2010;85:109–14. https://doi.org/10.1002/jctb.2273.

McEvoy FJ, Wright WB, Birnberg GH, Albright JD. Inventors; American Cyanamid Company, assignee. ω –Heteroaroyl (propionyl or butyryl)-L-prolines. 1981; United States patent US 4:299,769.

Miele A, Giardina P, Sannia G, Faraco V. Random mutants of a *Pleurotus ostreatus* laccase as new biocatalysts for industrial effluents bioremediation. J Appl Microbiol. 2010;108:998–1006. https://doi.org/10.1111/j.1365-2672.2009.04505.x.

Mir-Tutusaus J, Sarra M, Caminal G. Continuous treatment of non-sterile hospital wastewater by *Trametes versicolor*: how to increase fungal viability by means of operational strategies and pretreatments. J Hazard Mater. 2016;318:561–70. https://doi.org/10.1016/j.jhazmat.2016.07.036.

Monhemi H, Housaindokht MR, Moosavi-Movahedi AA, Bozorgmehr MR. How a protein can remain stable in a solvent with high content of urea: insights from molecular dynamics simulation of *Candida antarctica* lipase B in urea: choline chloride deep eutectic solvent. Phys Chem Chem Phys. 2014;16:14882–95. https://doi.org/10.1039/c4cp00503a.

Mugdha A, Usha M. Enzymatic treatment of wastewater containing dyestuffs using different delivery systems. Sci Rev Chem Commun. 2012;2:31–40.

Murugesan A, Umarani C, Subramanian R, Nedunchezhian N. Bio-diesel as an alternative fuel for diesel engines-A review. Renew Sust Energy Rev. 2009;13:653–62. https://doi.org/10.1016/j.rser.2007.10.007.

Naghdi M, Taheran M, Brar SK, Kermanshahi-pour A, Verma M, Surampalli R. Immobilized laccase on oxygen functionalized nanobiochars through mineral acids treatment for removal of carbamazepine. Sci Total Environ. 2017;15:584–5. https://doi.org/10.1016/j.scitotenv.2017.01.021.

Naghdi M, Taheran M, Brar SK, Kermanshahi-pour A, Verma M, Surampalli RY. Removal of pharmaceutical compounds in water and wastewater using fungal oxidoreductase enzymes. Environ Poll. 2018;234:190–213.

Nazaret S, Aminov R. Role and prevalence of antibiosis and the related resistance genes in the environment. Front Microbiol. 2014;5:520e520. https://doi.org/10.3389/fmicb.2014.00520.

Neoh CH, Lam CY, Yahya A, Ware I, Ibrahim Z. Utilization of agro-industrial residues from palm oil industry for production of lignocellulolytic enzymes by *Curvularia clavata*. Waste Biomass Valoriz. 2015;6:385–90. https://doi.org/10.1007/s12649-015-9357-4.

Nguyen LN, Hai FI, Yang S, Kang J, Leusch FD, Roddick F, Price WE, Nghiem LD. Removal of trace organic contaminants by an MBR comprising a mixed culture of bacteria and white-rot fungi. Bioresour Technol. 2013;148:234–41. https://doi.org/10.1016/j.biortech.2013.08.142.

Nguyen LN, van de Merwe JP, Hai FI, Leusch FD, Kang J, Price WE, Roddick F, Magram SF, Nghiem LD. Laccase-syringaldehyde-mediated degradation of trace organic contaminants in an enzymatic membrane reactor: removal efficiency and effluent toxicity. Bioresour Technol. 2016;200:477–84. https://doi.org/10.1016/j.biortech.2015.10.054.

Nigam PS, Gupta N, Anthwal A. In: Nigam PS, Pandey A, editors. Pre-treatment of agro-industrial residues. In biotechnology for agro-industrial residues utilisation. Dordrecht: Springer; 2009. p. 13–33.

Novelli PK, Barros MM, Fleuri LF. Novel inexpensive fungi proteases: production by solid state fermentation and characterization. Food Chem. 2016;198:119–24. https://doi.org/10.1016/j.foodchem.2015.11.089.

Nwobi BE, Ofoegbu O, Adesina OB. Extraction and qualitative assessment of African sweet orange seed oil. Afr J Food Agric Nutr Dev. 2006;6:1–11. https://doi.org/10.4314/ajfand.v6i2.71747.

Okino-Delgado CH, Fleuri LF. Obtaining lipases from byproducts of orange juice processing. Food Chem. 2014;163:103±107. https://doi.org/10.1016/j.foodchem.2014.04.090

Okino-Delgado CH, Fleuri LF. Orange and mango by-products: agro-industrial waste as source of bioactive compounds and botanical versus commercial description – a review. Food Rev Int (Print). 2015;1:15±20. https://doi.org/10.1080/87559129.2015.1041183

Okino-Delgado CH, Fleuri LF. Obtaining concentrated extract of lipases from orange waste. Protocols IO. 2017; https://doi.org/10.17504/protocols.io.j3rcqm6.

Okino-Delgado CH, do Prado DZ, Facanali R, Marque MMO, Nascimento AS, da Costa Fernandes CJ, William Fernando Zambuzzi WF, Fleuri LF. Bioremediation of cooking oil waste using lipases from wastes. PLoS ONE. 2017;12:e0186246. https://doi.org/10.1371/journal.pone.0186246.

Okrasa K, Levy C, Wilding M, Goodall M, Baudendistel N, Hauer B, Leys D, Micklefield J. Structure-guided directed evolution of alkenyl and arylmalonate decarboxylases. Angew Chem Int Ed Engl. 2009;48:7691–4. https://doi.org/10.1002/anie.200904112.

Pandey A. Solid-state fermentation. Biochem Eng J. 2003;13:81–4. https://doi.org/10.1016/S1369-703X(02)00121-3.

Papadakis E, Tula AK, Gani R. Solvent selection methodology for ph pharmaceutical processes: solvent swap. Chem Eng Res Des. 2016;115:443–61. https://doi.org/10.1016/j.cherd.2016.09.004.

Paques FW, Macedo GA. Lipases de laÂtex vegetais: propriedades e aplicacËões industriais. QuõÂmica Nova. 2006;29: 93–99. Available in: http://www.scielo.br/pdf/%0D/qn/v29n1/27863.pdf.

Park S, Kazlauskas RJ. Improved preparation and use of room-temperature ionic liquids in lipase-catalyzed enantio- and regioselective acylations. J Org Chem. 2001;66:8395–401. https://doi.org/10.1021/jo015761e.

Park YS, Kang SW, Lee JS, Hong SI, Kim SW. Xylanase production in solid state fermentation by *Aspergillus niger* mutant using statistical experimental designs. Appl Microbiol Biotechnol. 2002;58:761–6. https://doi.org/10.1007/s00253-002-0965-0.

Patel RN. Biocatalysis: synthesis of key intermediates for development of pharmaceuticals. ACS Cata. 2011;1:1056–74. https://doi.org/10.1021/cs200219b.

Patil SR, Dayanand A. Optimization of process for the production of fungal pectinases from deseeded sunflower head in submerged and solid-state conditions. Bioresour Technol. 2006;97:2340–4. https://doi.org/10.1016/j.biortech.2005.10.025.

Petkovic M, Ferguson JL, Nimal Gunaratne HQ, Ferreira R, Leitão MC, Seddon KR, Rebelo LPN, Pereira CS. Novel biocompatible cholinium-based ionic liquids−toxicity and biodegradability. Green Chem. 2010;12:643–9. https://doi.org/10.1039/B922247B.

Piotrowska-Cyplik A, Olejnik A, Cyplik P, Dach J, Czarnecki Z. The kinetics of nicotine degradation, enzyme activities and genotoxic potential in the characterization of tobacco waste composting. Bioresour Technol. 2009;100:5037–44. https://doi.org/10.1016/j.biortech.2009.05.053.

Prasad S, Bocola M, Reetz MT. Revisiting the lipase from *Pseudomonas aeruginosa*: directed evolution of substrate acceptance and enantioselectivity using iterative saturation mutagenesis. Chemphyschem. 2011;12:1550–7. https://doi.org/10.1002/cphc.201100031.

Quartinello F, Vajnhandl S, Valh JV, Farmer TJ, Voncina B, Lobnik A, Acero EH, Pellis A, Guebitz GM. Synergistic chemo-enzymatic hydrolysis of poly (ethylene terephthalate) from textile waste. Microb Biotechnol. 2017;10:1376–83. https://doi.org/10.1111/1751-7915.12734.

Rajagopal R, Saady NMC, Torrijos M, Thanikal JV, Hung YT. Sustainable agro-food industrial wastewater treatment using high rate anaerobic process. Water. 2013;5:292–311. https://doi.org/10.3390/w5010292.

Ramachandran S, Patel AK, Nampoothiri KM, Francis F, Nagy V, Szakacs G, Pandey A. Coconut oil cake—A potential raw material for the production of -amylase. Bioresour. Technol. 2004; 93, 169–174.

Ramachandran S, Singh SK, Larroche C, Soccol CR, Pandey A. Oil cakes and their biotechnological applications-A review. Bioresour Technol. 2007;98:2000–9. https://doi.org/10.1016/j.biortech.2006.08.002.

Reetz MT, Wu S. Laboratory evolution of robust and enantio-selective Baeyer-Villiger monooxygenases for asymmetric catalysis. J Am Chem Soc. 2009;131:15424–32. https://doi.org/10.1021/ja906212k.

Reetz MT, Soni P, Fernandez L, Gumulya Y, Carballeira JD. Increasing the stability of an enzyme toward hostile organic solvents by directed evolution based on iterative saturation mutagenesis using the B-FIT method. Chem Commun (Camb). 2010;46:8657–8. https://doi.org/10.1039/c0cc02657c.

Ribitsch D, Winkler S, Gruber K, Karl W, Wehrschutz-Sigl E, Eiteljorg I, Schratl P, Remler P, Stehr R, Bessler C, Mussmann N, Sauter K, Maurer KH, Schwab H. Engineering of choline oxidase from *Arthrobacter nicotianae* for potential use as biological bleach in detergents. Appl Biochem Biotechnol. 2010;87:1743–52. https://doi.org/10.1007/s00253-010-2637-9.

Rodarte-Morales A, Feijoo G, Moreira M, Lema J. Operation of stirred tank reactors (STRs) and fixed-bed reactors (FBRs) with free and immobilized Phanerochaete chrysosporium for the continuous removal of pharmaceutical compounds. Biochem Eng J. 2012;66:38–45. https://doi.org/10.1016/j.bej.2012.04.011.

Roduit JP, Wellig A, Kiener A. Renewable functionalized pyridines derived from microbial metabolites of the alkaloid (S)-nicotine. Heterocycles. 1997;45:1687–702.

Ruggaber TP, Talley JW. Enhancing bioremediation with enzymatic processes: a review. Pract Period Hazard Toxic Radioact Waste Manag. 2006;10:73–85. https://doi.org/10.1061/(asce)1090-025x(2006)10:2(73).

Sathishkumar P, Kamala-Kannan S, Cho M, Kim JS, Hadibarata T, Salim MR, Oh BT. Laccase immobilization on cellulose nanofiber: the catalytic efficiency and recyclic application for simulated dye effluent treatment. J Mol Catal B Enzym. 2014;100:111–20. https://doi.org/10.1016/j.molcatb.2013.12.008.

Savile CK, Janey JM, Mundorff EC, Moore JC, Tam S, Jarvis WR, Colbeck JC, Krebber A, Fleitz FJ, Brands J, Devine PN, Huisman GW, Hughes GJ. Biocatalytic asymmetric synthesis of chiral amines from ketones applied to sitagliptin manufacture. Science. 2010;329:305–9. https://doi.org/10.1126/science.1188934.

Schmid A, Dordick JS, Hauer B, Kiener A, Wubbolts M, Witholt B. Industrial biocatalysis today and tomorrow. Nature. 2001;409:258–68. https://doi.org/10.1038/35051736.

Schmidt M, Bottcher D, Bornscheuer UT. Protein engineering of carboxyl esterases by rational design and directed evolution. Protein Pept Lett. 2009;16:1162–71. https://doi.org/10.2174/092986609789071216.

Schwarzbauer J, Heim S, Brinker S, Littke R. Occurrence and alteration of organic contaminants in seepage and leakage water from a waste deposit landfill. Water Res. 2002;36:2275–87. https://doi.org/10.1016/S0043-1354(01)00452-3.

Selwal MK, Yadav A, Selwal KK, Aggarwal NK, Gupta R, Gautam SK. Tannase production by *Penicillium atramentosum* KM under SSF and its applications in wine clarification and tea cream solubilization. Braz J Microbiol. 2011;42:374–87. https://doi.org/10.1590/S1517-83822011000100047.

Senthivelan T, Kanagaraj J, Panda R. Recent trends in fungal laccase for various industrial applications: an eco-friendly approach-A review. Biotechnol Bioprocess Eng. 2016;21:19–38. https://doi.org/10.1007/s12257-015-0278-7.

Sheldon RA, Woodley JM. Role of biocatalysis in sustainable chemistry. Chem Rev. 2018;118:801–38. https://doi.org/10.1021/acs.chemrev.7b00203.

Shon HK, Tian D, Kwon DY, Jin CS, Lee TJ, Chung WJ. Degradation of fat, oil, and grease (FOGs) by lipase producing bacterium Pseudomonas sp. strain D2D3. J Microb Biotechnol. 2002;12:583–91.

Sivaperumal P, Kamal K, Rajaram R. Chapter 8-Bioremediation of industrial waste through enzyme producing marine microorganisms. In: Advances in food and nutrition research, marine enzymes biotechnology: production and industrial applications, Part III-Application of marine enzymes, vol. 80; 2017. p. 165–79. https://doi.org/10.1016/bs.afnr.2016.10.006.

Slack RJ, Gronow JR, Voulvoulis N. Household hazardous waste in municipal landfills: contaminants in leachate. Sci Total Environ. 2005;337:119–37. https://doi.org/10.1016/j.scitotenv.2004.07.002.

Soares VF, Castilho LR, Bon EPS, Freire DMG. High-yield *Bacillus subtilis* protease production by solid-state fermentation. Appl Biochem Biotechnol. 2005;121–124:311–9.

Solís M, Solís A, Pérez HI, Manjarrez N, Flores M. Microbial decolouration of azo dyes: a review. Process Biochem. 2012;47:1723–48. https://doi.org/10.1016/j.procbio.2012.08.014.

Stacke J, Graff T, Rempel C, Dal-Bosco SM. Perfil de aÂcidos graxos no oÂleo de soja, apoÂs diferentes tempos de uso, no processo de fritura. Revista de Destaque Acadêmico. 2009;1:71–79. Available in: https://www.researchgate.net/profile/claudete_rempel/publication/263735208_perfil_de_acidos_graxos_no_oleo_de_soja_apos_diferentes_tempos_de_uso_no_processo_de_fritura/links/02e7e53bc9e7854d0e000000.pdf.

Stackelberg PE, Gibs J, Furlong ET, Meyer MT, Zaugg SD, Lippincott RL. Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci Total Environ. 2007;377:255–72. https://doi.org/10.1016/j.scitotenv.2007.01.095.

Steinrück HP, Wasserscheid P. Ionic liquids in catalysis. Catal Lett. 2015;145:380–97.

Straathof AJJ. Transformation of biomass into commodity chemicals using enzymes or cells. Chem Rev. 2014;114:1871–908. https://doi.org/10.1021/cr400309c.

Suzuki Y, Asada K, Miyazaki J, Tomita T, Kuzuyama T, Nishiyama M. Enhancement of the latent 3-isopropylmalate dehydrogenase activity of promiscuous homoisocitrate dehydrogenase by directed evolution. Biochem. J. 2010; 431:401–410.

Tadkaew N, Hai FI, McDonald JA, Khan SJ, Nghiem LD. Removal of trace organics by MBR treatment: the role of molecular properties. Water Res. 2011;45:2439–51. https://doi.org/10.1016/j.watres.2011.01.023.

Talukder MMR, Tamalampudy S, Li CJ, Le YL, Wu JC, Kondo A. An improved method of lipase preparation incorporating both solvent treatment and immobilization onto matrix. Biochem Eng. 2007;33:60–5. https://doi.org/10.1016/j.bej.2006.10.004.

Tang WL, Li Z, Zhao HM. Inverting the enantioselectivity of P450pyr monooxygenase by directed evolution. Chem Commun (Camb). 2010;46:5461–3. https://doi.org/10.1039/c0cc00735h.

Tang H, Wang L, Wang W, Yu H, Zhang K, Yao Y, Xu P. Systematic unraveling of the unsolved pathway of nicotine degradation in pseudomonas. PLoS Genet. 2013;9:e1003923. https://doi.org/10.1371/journal.pgen.1003923.

Urano N, Fukui S, Kumashiro S, Ishige T, Kita S, Sakamoto K, Kataoka M, Shimizu S. Directed evolution of an aminoalcohol dehydrogenase for efficient production of double chiral aminoalcohols. J Biosci Bioeng. 2011;111:266–71. https://doi.org/10.1016/j.jbiosc.2010.11.005.

Valladão ABG, Cammarota MC, Torres AG, Freire DMG. Profiles of fatty acids and triacylglycerols and their influence on the anaerobic biodegradability of effluents from poultry slaughterhouse. Bioresour Technol. 2011;102:7043–50. https://doi.org/10.1016/j.biortech.2011.04.037.

van Rantwijk F, Sheldon RA. Biocatalysis in ionic liquids. Chem Rev. 2007;107:2757–85. https://doi.org/10.1021/cr050946x.

Velmurugan P, Hur H, Balachandar V, Kamala-Kannan S, Lee K, Lee S, Chae JC, Shea PJ, Oh BT. Monascus pigment production by solid-state fermentation with corn cob substrate. J Biosci Bioeng. 2011;112:590–4. https://doi.org/10.1016/j.jbiosc.2011.08.009.

Villegas LGC, Mashhadi N, Chen M, Mukherjee D, Taylor KE, Biswas N. A short review of techniques for phenol removal from wastewater. Curr Pollut Rep. 2016;2:157–67.

Vishwanatha KS, Rao AGA, Singh SA. Acid protease production by solid-state fermentation using *Aspergillus oryzae* MTCC 5341: optimization of process parameters. J Ind Microbiol Biotechnol. 2010;37:129–38. https://doi.org/10.1007/s10295-009-0654-4.

Wandrey C, Liese A, Kihumbu D. Industrial biocatalysis: past, present, and future. Org Process Res Dev. 2000;4:286–90. https://doi.org/10.1021/op9901011.

Wang LX, Huang W. Enzymatic transglycosylation for glycoconjugate synthesis. Curr Opin Chem Biol. 2009;13:592–600. https://doi.org/10.1016/j.cbpa.2009.08.014.

Wang J, Wan W. Factors influencing fermentative hydrogen production: A review. Int J Hydrog Energy 2009;34:799–811.

Wang QY, Yang GY, Liu YL, Feng Y. Discrimination of esterase and peptidase activities of acylaminoacyl peptidase from hyperthermophilic *Aeropyrum pernix* K1 by a single mutation. J Biol Chem. 2006;281:18618–25. https://doi.org/10.1074/jbc.m601015200.

Wang M, Si T, Zhao H. Biocatalyst development by directed evolution. Bioresour Technol. 2012;115C:117–25. https://doi.org/10.1016/j.biortech.2012.01.054.

Wang JH, He HZ, Wang MZ, Wang S, Zhang J, Wei W, Xu HX, Lv ZM, Shen DS. Bioaugmentation of activated sludge with *Acinetobacter sp.* TW enhances nicotine degradation in a synthetic tobacco wastewater treatment system. Bioresour Technol. 2013;142:445–53. https://doi.org/10.1016/j.biortech.2013.05.067.

Wang W, Xu P, Tang H. Sustainable production of valuable compound 3-succinoyl-pyridine by genetically engineering *Pseudomonas putida* using the tobacco waste. Scientific Reports. 2015;5:16411. https://doi.org/10.1038/srep16411.

Westerhoff P, Moon H, Minakata D, Crittenden J. Oxidation of organics in retentates from reverse osmosis wastewater reuse facilities. Water Res. 2009;43:3992–8. https://doi.org/10.1016/j.watres.2009.04.010.

Woodyer RD, Christ TN, Deweese KA. Single-step bioconversion for the preparation of L-gulose and L-galactose. Carbohydr Res. 2010;345:363–8. https://doi.org/10.1016/j.carres.2009.11.023.

Wu BP, Wen Q, Xu H, Yang Z. Insights into the impact of deep eutectic solvents on horseradish peroxidase: activity, stability and structure. J Mol Catal B: Enzym. 2014;101:101–7.

Xia L, Cen P. Cellulase production by solid state fermentation on lignocellulosic waste from the xylose industry. Process Biochem. 1999;34:909–12. https://doi.org/10.1016/S0032-9592(99)00015-1.

Yu H, Tang H, Xu P. Green strategy from waste to value-added-chemical production: efficient biosynthesis of 6-hydroxy-3-succinoyl-pyridine by an engineered biocatalyst. Sci Rep. 2014;4:5397. https://doi.org/10.1038/srep05397.

Zaks A, Klibanov AM. Enzymatic catalysis in organic degrees media at 100 degrees C. Science. 1984;224:1249–51. https://doi.org/10.1126/science.6729453.

Zhang YD, Luo CR, Wang HL, Lu GF. Advances in microbial degradation of nicotine and its application. Tob Sci Technol. 2003;197:3–7.

Zhao HM. Highlights of biocatalysis and biomimetic catalysis. ACS Catal. 2011;1:1119–20. https://doi.org/10.1021/cs200425r.

Zhao HM, Giver L, Shao Z, Affholter JA, Arnold FH. Molecular evolution by staggered extension process (StEP) in vitro recombination. Nat Biotechnol. 1998;16:258–61.

Zhao H, Baker GA, Holmes S. Protease activation in glycerol-based deep eutectic solvents. J Mol Catal B: Enzym. 2011;72:163–7. https://doi.org/10.1016/j.molcatb.2011.05.015.

Zheng F, Cui BK, Wu XJ, Meng G, Liu HX, Si J. Immobilization of laccase onto chitosan beads to enhance its capability to degrade synthetic dyes. Int Biodeter Biodegr. 2016:69–78. https://doi.org/10.1016/j.ibiod.2016.03.004.

# Green Synthesis of Biodiesel Using Microbial Lipases

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_15

## 1 Introduction

The fuel obtained by the oil and fat's transesterification is called as biodiesel. Biodiesel can be directly utilized in the unaltered engines or different blends of biodiesel with conventional diesel fuel may be used due to similar characteristics to that of conventional petro-diesel. The clash between food production and bioenergy is the main hurdle in the biodiesel production which is also called as food vs fuel debate. So, this issue can be resolved by using nonedible feedstock like oleaginous microbes, i.e., oleaginous bacteria, oleaginous yeast, and microalgae, or oil-producing crops which are nonedible, i.e., *Pongamia pinnata*, *Jatropha curcas*, *Ricinus communis*, etc. (Hill et al. 2006).

Biodiesel is advantageous than existing fossil-based diesel fuel because of its biodegradability and less harmful releases of smoke and gases (Fukuda et al. 2001). Biodiesel reduces up to 78% of net carbon dioxide emissions in comparison with fossil-based diesel fuel (Harvey et al. 2007). Similarly, biodiesel combustion decreases 66.7% of particulate matter emissions, 46.7% of carbon monoxide (CO) emissions, and 45.2% of hydrocarbon emissions. Moreover, due to its biodegradability and clean burning biodiesel is perfect for use in highly sensitive environments like mining area and marine ecosystems (Abede et al. 2019).

Some reaction parameters like catalyst type, molar ratio of oil to alcohol and concentration, quantity of free fatty acids in the feedstock, temperature and reaction time, etc. affect both enzymatic and chemical transesterification reactions for biodiesel production, so these parameters should be optimized to get maximum biodiesel production (Freedman et al. 1984).

Different catalysts which can be utilized for the biodiesel production include acids, bases, and biocatalysts; however, base catalysts are more common but base-catalyzed biodiesel requires those feedstocks which are of high quality and purity. So, the chemistry of alkali-catalyzed transesterification reaction and unnecessary side reactions like neutralization reactions along with limited choice of feedstocks make it unattractive choice for biodiesel production. While during the process of acid-catalyzed transesterification, water molecules are generated which reduce the amount of alkyl esters due to the carboxylic acid production and slow down the reaction process. Acid catalysts also require higher reaction temperature and recovery of glycerol is also difficult. Due to these drawbacks associated with chemical catalysts for the fatty acid methyl ester production, the interest has been increased in the lipase-catalyzed process of transesterification. Lipases are recognized as biocatalysts which are noteworthy alternatives to chemical catalysts for the synthesis of fatty acid methyl esters (Mukhtar et al. 2016). Animal as well as microbial sources can be used for obtaining the lipases. However, due to the difficulty of extraction and purification of animal lipases, these are not suitable for commercial applications (Colla et al. 2015). So, microbial sources are preferred for lipase production and its utilization for biodiesel production at industrial scale (Table 4).

Significant advantages which make lipases ideal for biodiesel production comprise of easy recovery of the product, lesser temperature and energy requirement,

ease of catalyst recovery, reuse of lipase for several times, continuous biodiesel production, higher tolerance for various alcohols and flexibility for various substrates, ease of reaction with acceptable water and free fatty acids' amount in the feedstock, and utilization of lipases as natural agents catalyzing the green reactions (Casimir et al. 2007; Al-Zuhair et al. 2007; Park and Mori 2005; Wang et al. 2006 and Nie et al. 2006).

## 2 Biodiesel Feedstocks

The demand on energy is increasing globally. The utilization of total energy is growing gradually. Fossil fuels are the main sources to deliver 80% of this energy which increase greenhouse gas emissions in the atmosphere and aggravate serious climate changes which cause global warming. Moreover, the fossil fuel provisions are decreasing continuously. So to cope with these issues, environment friendly alternative energy sources are required and these sources are divided into first-, second-, and third-generation feedstock oils as explained below.

### *2.1 First-Generation Feedstock Oils*

First-generation feedstock oils are directly related to a biomass that is generally edible like sunflower, coconut, olive, almond and corn oil, etc. The quality parameters and fatty acid profiles of some commonly used feedstock are given in the Table 1 and 2, respectively. Oil price on the international market varies among vegetable sources which is another drawback of first-generation feedstock oils for the fatty acid methyl ester production. Due to increasing prices and use of edible plants for fatty acid methyl ester production, first-generation feedstock oils are not a good option for biodiesel production (Armah et al. 2011). The use of plant oils is considered as advantageous for the biodiesel production because they are readily available, portable, renewable, having higher heat values, lesser sulfur content, biodegradable, and lesser aromatic content (Demirbas et al. 2015). The major drawbacks of using plant oils for biodiesel production include more viscosity, lesser volatility, reaction of unsaturated hydrocarbon chains, and more cost (Demirbas 2009a, b).

Researchers are also working on including mustard oil, sunflower oil, and cotton seed oil for FAME synthesis. In the USA, commonly used oil is soybean and in Europe, rapeseed oil is used for the production of biodiesel whereas, in Indonesia and Malaysia, palm oil and coconut oil are used for biodiesel production (Ghadge and Raheman 2005; Srivastava and Verma 2008). Almost 80% of the Europe's total production of biofuel consists of biodiesel which is synthesized from sunflower and rapeseed oil (Ahmad et al. 2010; Balat and Balat 2010).

**Table 1** Quality parameters of some feedstock oils

| | Feedstock oil | Quality parameters | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Density (g/cc) | Specific gravity | Viscosity ($mm^2/s$) | Acid value (mg KOH/g) | Iodine value | Peroxide value (meq/Kg) | Saponification value | Unsaponifiable matter | References |
| **First-generation feedstock oils** | Sunflower oil | 0.68 | – | 6 | 0.36 | – | – | 192.4 | – | Thirumarimurugan et al. (2012) |
| | Almond oil | – | 0.92 | – | 0.78 | 121.19 | 4.07 | 168.27 | – | Barku et al. (2012) |
| | Coconut oil | – | – | – | – | 0.97 | 2.2 | 259 | – | Ghani et al. (2018) |
| | Corn oil | – | – | 56 | 2.32 | 98.3 | 9.29 | 205 | 1.44 | Aydeniz et al. (2017) |
| | Olive oil | – | – | – | – | 85.60 | 4.5 | 188 | – | Ashokkumar et al. (2018) and Abdalla et al. (2014) |
| | Peanut oil | 1.18 | – | – | 5.89 | – | 83 | 32 | – | Hussain et al. (2015) |
| | Soybean oil | – | – | – | 1.5 | – | 17 | 252 | – | Makni et al. (2015) |
| | Mustard oil | 0.96 | – | 117.27 | – | 8.1 | 0.83 | 125.6 | – | Zahir et al. (2014) |
| | Canola oil | – | – | – | – | 114.47 | 5.73 | – | – | Roiaini et al. (2015) |
| | Sesame oil | – | 0.91 | – | 0.5 | 103 | 8 | 189 | – | Roiaini et al. (2015) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Second generation feedstock oils** | Jatropha oil | 0.98 | | 35.4 | 11.0 | 101.0 | | 194 | | Patel et al. (2013) |
| | Ricinus oil | 0.96 | – | 9.6 | 0.85 | 84 | – | 181.83 | – | Akhabue and Okwundu (2017) |
| | Pongamia oil | – | – | 4.8 | 0.62 | – | – | – | – | Karmee and Chadha (2005) |
| | Palm oil | – | 0.86 | 69 | 19.1 | 53.1 | | 200.6 | 0.31 | Japir et al. (2017) |
| | Neem oil | – | 0.31 | – | 13.94 | 132.23 | | 211.15 | – | Jibril et al. 2012 |
| | Hemp oil | – | 0.89 | – | 2.15 | 163.5 | 7.2 | 190.2 | 0.26 | Borhade (2013) |
| | Butter tree oil | – | – | – | 1.76 | 70.0 | 1.03 | 227.94 | 0.95 | Samuel et al. (2017) |
| | Rubber seed oil | – | 0.91 | 40.86 | 83.76 | 118.8 | 3.42 | – | – | Singh et al. (2016) |
| | Linseed oil | 0.92 | – | – | 0.88 | 139.53 | 0.34 | – | – | Pita and Zadernowski (2010) |
| **Third-generation feedstock oils** | *Phormidium autumnale* (algae oil) | 880.5 | – | 3.16 | 0.50 | – | – | – | – | Karmakar et al. (2018) |
| | *C. vulgaris* (algae oil) | – | – | – | 31.46 ± 2.1 | 63 ± 2 | – | 173.12 ± 3.4 | – | Ahmad et al. (2013) |
| | R. hieroglyphicum (algae oil) | – | – | – | 34.5 ± 1.8 | 75 ± 1 | – | 168.3 ± 4.1 | – | |

**Table 2** Major fatty acid profiles of different feedstock oils

| | Feedstock oil | Fatty acid composition | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Palmitic acid (C16:0) | Oleic acid (C18:1) | Linoleic acid (C18:2) | Linolenic acid (C18:3) | Stearic acid (C18:0) | Palmitoleic acid (C16:1) | Arachidic acid (C20:0) | Myristic acid (C14:0) | References |
| **First-generation feedstock oils** | Sunflower oil | 6.99 | 34.51 | – | 52.38 | 4.16 | – | 0.33 | – | Skowyra et al. (2014) |
| | Almond oil | 6.7 | 78.7 | 33.9 | – | 1.7 | 0.6 | – | – | Roncero et al. (2014) |
| | Coconut oil | 17.2 | 4.5 | 1.1 | – | 2.4 | – | – | 19.2 | Seneviratne and Jayathilaka (2016) |
| | Corn oil | 11.81 | 29.90 | 53.89 | 1.11 | 2.07 | 12.41 | 0.30 | – | Aydeniz et al. (2017) |
| | Olive oil | 16.88 | 70.96 | 6.08 | 0.16 | 2.06 | 0.80 | 0.52 | – | Abdalla et al. (2014) |
| | Peanut oil | 19.46 | | 59.91 | 0.07 | 2.10 | 0.58 | 0.18 | 0.63 | Liu et al. (2014) |
| | Soybean oil | 14.69 | 26.80 | 44.40 | 8.0 | 5.40 | – | 0.35 | | Kushak et al. (2000) |
| | Mustard oil | 1.87 | 15.70 | 12.99 | 6.18 | 1.52 | 0.1 | | 1.13 | Althomali 2015 |
| | Canola oil | 52.9 | 35.42 | 0.63 | 6.61 | 0.06 | 3.37 | 0.74 | 0.82 | Roiaini et al. (2015) |
| | Sesame oil | 8.96 | 40.98 | 42.06 | 0.33 | 6.16 | 0.15 | 0.67 | 0.11 | Zannikos et al. (2011) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Second-generation feedstock oils** | Jatropha oil | 12.7 | 39.1 | 41.6 | – | 5.5 | 0.7 | 0.2 | – | Madhuri et al. (2015) |
| | Ricinus oil | 0.9 | 90.2 | 4.4 | 0.2 | 2.8 | – | – | 0.7 | Knothe (2001) |
| | Pongamia oil | 10.6 | 49.4 | 19.0 | | 6.8 | – | 4.1 | – | Knothe (2001) |
| | Palm oil | 16.85 | 58.07 | 16.93 | 5.45 | 0.42 | 0.76 | 0.99 | 0.34 | Roiaini et al. (2015) |
| | Soapnut oil | 5.0 | 52.0 | 4.0 | – | 1.0 | 1.0 | 7.0 | – | Kankia et al. (2012) |
| | Neem oil | 14.9 | 61.9 | 7.5 | – | 14.4 | – | – | – | Knothe (2001) |
| | Hemp oil | 15 | 15 | 5 | – | 65 | – | – | – | Knothe (2001) |
| | Butter tree oil | 4.1 | 42.5 | 6.1 | – | 45.8 | – | – | 0.3 | Samuel et al. (2017) |
| | Rubber seed oil | 10.2 | 24.6 | 39.6 | – | 8.7 | – | – | 2.2 | Madhuri et al. (2015) |
| | Linseed oil | 5.03 | 17.33 | 22.73 | 50.0 | 4.10 | 0.10 | – | 0.10 | Pitat and Zadernowski (2010) |
| **Third-generation feedstock oils** | *P. autumnale* (algae oil) | 22.5 | 26.2 | 17.8 | 2.10 | 10.5 | 8.5 | – | 7.3 | Siqueira et al. (2016) |
| | *B. braunii* (algae oil) | 36.60 | 6.70 | 7.40 | 22.30 | 2.70 | 11.90 | – | 9.10 | Kushak et al. (2000) |
| | *Schizochytrium* sp. (algae oil) | 51 | 20.91 | 19 | – | 4 | – | – | – | Hossain (2015) |
| | *Y. lipolytica* (yeast oil) | 14.9 | 55.1 | 18.5 | 0.3 | 11.1 | – | – | – | Niehus et al. (2018) |

## 2.2 Second-Generation Feedstock Oils

The use of first-generation oils as feedstock for biodiesel production started a debate at global level that edible crops were consumed for fuel production while the world was running out of food resources, which is called as food versus fuel debate. So, to overcome this issue, researchers found alternative feedstock oils for the biodiesel production which are called as second-generation feedstocks. Second-generation feedstock oils include oils from nonedible plants like *Jatropha curcas*, *Ricinus communis*, and *Pongamia pinnata*, linseed oil, etc. (Table 3). The monoculture, requirement of land, water, and seasonal availability of second-generation feedstock plants make it an unattractive option for the fatty acid methyl ester production (Haas et al. 2006).

The animal fats which are nonedible and are typically utilized for the production of biodiesel are highly saturated, due to which these fats solidify at a relatively high temperature. This high saturation of animal fats means a high cloud point; i.e., biodiesel produced from lard and beef tallow has a cloud point between 55 °F and 60 °F. So, keeping in view the saturation level and cloud point of fatty acid methyl esters produced from animal fat, B100 (100% biodiesel) synthesized from animal fat can only be utilized in a very hot weather.

**Table 3** Comparison of different transesterification catalysts

| | | Chemical catalysts | |
|---|---|---|---|
| Variable | Lipase | Acid catalyst | Base catalyst |
| Temperature required (C°) | 30–60 | 55–80 | 60–70 |
| Biodiesel yield | Higher | Moderate | Moderate |
| By-product (glycerol) recovery | Easy | Difficult | Difficult |
| Purification process | Easy | Several washing required | Several washing required |
| Cost of catalyst | High | Low | Low |
| Recovery of catalyst | Easy for immobilized lipase | Difficult | Difficult |
| Impact on environment | Low | High | High |
| Effect of water presence in feedstock | Reaction is not affected | Interfere in reaction | Interfere in reaction |
| Presence of free fatty acids in feedstock oil | FFA are converted to methyl esters | Ester is formed | Saponification of free fatty acids occurs |

Liu et al. (2012) and Earle et al. (2009)

**Table 4** Various types of lipases used for biodiesel synthesis

| Sr. No. | Lipase source | Feedstock oil | Free lipase/ immobilization support | Biodiesel yield | References |
|---|---|---|---|---|---|
| 1. | *Candida antarctica* lipase | Olive oil | Amphiphilic matrix | 90% | Shagufta et al. (2017) |
| 2. | *Burkholderia cepacia* lipase | Jatropha oil | Silica monolith | 90% | Kawakami et al. (2011) |
| 3. | *Aspergillus niger* lipase | Palm oil | Polyurethane biomass support particles | 90% | Xiao et al. (2011) |
| 4. | *Candida* sp. lipase | Lard | – | 87.4% | Thangaraj et al. (2019) |
| 5. | *Candida rugosa* lipase | Rapeseed oil | Chitosan | 63.6% | Shao et al. (2008) |
| 6. | *Chromobacterium viscosum* lipase | Jatropha oil | Celite 545 | 71% | Shah et al. 2004 |
| 7. | *Thermomyces lanuginosus* lipase | Crude palm oil | Silica gel | 96.15% | Sim et al. (2010) |
| 8. | *Rhizopus oryzae* lipase | Soybean oil | Amberlite IRA-93 | 90.5% | Wang et al. (2010) |
| 9. | *Penicillium expansum* lipase | Corn oil | Free lipase | 86.9% | Zhang et al. (2011) |
| 10. | *Pseudomonas fluorescens* lipase | Soybean oil | Free lipase | 83.8% | Yang et al. (2009) |
| 11. | *Ralstonia* sp. CS274 | Palm oil | Free lipase | 90% | Xiao et al. (2011) |
| 12. | *Photobacterium lipolyticum* M37 | Olive oil | Free lipase | 70% | Ryu et al. (2006) |
| 13. | *Thermomyces lanuginose* lipase | Soybean oil | Magnetic $Fe_3O_4$ | 90% | Yi et al. (2017) |
| 14. | Porcine pancreas lipase | Soybean oil | Magnetic $Fe_3O_4$ | 100% | Ahmad and Sardar (2015) |
| 15. | *Aspergillus niger* lipase | Soybean oil | Silica-coated $Fe_3O_4$ nanoparticles | 92% | Thangaraj et al. (2019) |

## *2.3 Third-Generation Feedstock Oils*

To combat the disadvantages of first- and second-generation feedstock oils, algal and microbial sources for oil production are preferred. Algae are very high oil-yielding feedstock for the biodiesel production (Gude et al. 2013, Ahmed et al. 2012). Microalgae and other microorganisms are the most attractive feedstocks for biodiesel in the future (Folaranmi 2013). Yeast and microbial oils are also considered as third-generation biofuels. Like algae, oleaginous yeasts can also produce lipids to levels more than 20 or even 26% of their dry cell mass (Santamauro et al. 2014). The oil is stored in the oil droplet forms which act as energy deposits. About 600 yeast species are known so far and less than 30 of these are found to be oleaginous. The best-known oleaginous yeasts are usually found in the genera like

**Table 5** Advantages and disadvantages of lipase as catalyst for biodiesel production

| Catalyst type | Advantages | Disadvantages |
|---|---|---|
| Biocatalyst/ lipases | Extremely specific free fatty acids are used for biodiesel synthesis<br>Moderate temperature of reaction<br>Insensitivity to water<br>Simplicity of separation of end products<br>Superior conversion rate than alkaline catalysts<br>Can be used as homogeneous or heterogeneous catalysts | Costly<br>Denaturation of enzyme due to the addition of organic solvent<br>Extra supportive solvents may be required to be used as a medium |

*Cryptococcus*, *Candida*, *Rhodotorula*, *Trichosporon*, *Yarrowia*, *Rhizopus*, and *Lipomyces* (Sitepu et al. 2014). Oleaginous bacteria store excessive carbon in the form of polysaccharides and excessive lipids most of the times in the form of wax esters or polyhydroxyalkanoates. So, yeasts are considered to be the most adapted microorganisms for oil production which can be utilized for the synthesis of biodiesel as yeasts store carbon as glycogen and lipids mostly in the form of triacylglycerols (Ageitos et al. 2011).

Algal, yeast, and microbial oils are also considered as third-generation biofuels (Table 5). The exploitation of microalgae as feedstock for biodiesel synthesis has multiple benefits over traditional oil-producing crops, for example, its rapid rate of growth, high photosynthetic and $CO_2$ fixation competency, high productivity of biomass, higher oil content, simple nutritional necessities, and no requirement for land for development (Wahlen et al. 2013).

## 3 Characteristics of Feedstock

The chemical and physical characteristics of oil feedstocks are much significant because they determine the choice of best feedstock for the synthesis of biodiesel. The physical properties of fats and oils comprise of viscosity, color, refractive index, melting point, specific gravity, and flash and fire point. Mostly oils obtained from plants are transparent having a yellowish color indicating the occurrence of carotenoids. The estimation of color is mostly performed by the Lovibond spectrophotometric colorimeter. The specific gravity of oils and fats is in the range of 0.90–0.92 at 25 °C. The refractive index depends on the variety of oils which mostly falls between 1.44 and 1.47. The refractive index of palm oil is usually between 1.44 and 1.45, whereas all the other plant oils have 1.47 at 25 °C. Some oils are rich in oleic acid (18:1), i.e., olive and rapeseed oils which have ≥0 °C melting points, whereas soybean and corn oils are abundant in linoleic acid (18:2) having melting points ≤ 0 °C. Coconut and palm oil have higher melting points

because they are high in fatty acids which are saturated, particularly palmitic acid (16:0). Viscosity is the standard which is used to estimate the degree of thermal denaturation and oxidation of oils as polymer formation makes the rancid oils highly viscous. Viscosity of oils and fats at 210 °F (98.9 °C) ranges from 6 to 10 mPas. Cleveland open cup tester is used to measure the fire and flash point. Regardless of the variety of oils, the flash point of plant oils is almost 320 °C (Demirbas et al. 2016).

Acid value, saponification value, iodine value, unsaponifiable matter, fatty acid composition, triacylglycerol composition, tocopherols, sterols, phospholipids, and fatty acid esters are the chemical properties of oils. The determination of the quantity of free fatty acids in oils and fats is called as acid value. The titration method is used for finding the acid value. Acid value determines the purification of oils and fats and its desirable value is ≤0.1 for edible fats and oils. The composition of fatty acids of oils determines the saponification value and iodine value. Saponification value tells about the average molecular weight of triacylglycerols. A higher saponification value means lower molecular weight triacylglycerols of oils and fats. Both saponification and iodine values are estimated by the titration methods. Most of the plant oils like corn, soybean, and rapeseed oils have a saponification value of about 190, while coconut and palm oils are rich in myristic acid (14:0), lauric acid (12:0), and palmitic acid (16:0) so these two oils have a saponification value of 200. Iodine value depends on the level of unsaturation of fatty acids which are present in triacylglycerol. Iodine value is a valuable standard for characterizing plant and animal oils. The corn and soybean oils are high in polyunsaturated fatty acids (18:2) which have iodine values that lie between 120 and 140. Different oils and fats can be distinguished by their fatty acid composition. Gas-liquid chromatography with a flame ionization detector (FID) and a capillary column is used to estimate the fatty acid composition (Yasushi 2018; Sayyed et al. 2013). The physical characteristics like freezing and melting points of oils and fats may be affected by the composition of triacylglycerol. Most of the oils contain insignificant components like unsaponifiable matters, containing which contain tocopherols besides triacylglycerols. β-Sitosterol is the main sterol in plant oils; however in animal fats it is cholesterol. The fats and oils' oxidative stability can be found out mostly by the active oxygen method. Peroxide value is a well-known standard to determine the oxidation of oils. The degree of oxidation and rancidity of fats and oils can be estimated by the measurement of peroxide value, p-anisidine value, as well as the number of polar compounds, polymerized triacylglycerols, and carbonyl value. However, hydroperoxides are quickly decomposed at temperature more than 100 °C so the determination of peroxide value is not used for heated oils. Estimation of frying oil polar compounds can be done by a portable digital oil tester by measuring the dielectric constant. In the process of deep frying, polymerized triacylglycerols are often produced. Gel permeation chromatography is used to measure these triacylglycerols. The acceptable range of polymerized triacylglycerols in heated oils is 10–16% (Gebremariam and Marchetti 2017).

## 4 Methods of Biodiesel Production

The principal techniques, which allow scientists to use oil as feedstock for biodiesel production, include pyrolysis, microemulsion, and transesterification.

### *4.1 Microemulsion*

The process of microemulsion is performed by using the organic solvents like methanol and ethanol, etc., to reduce the thickness of biodiesel. These microemulsions are clear and isotropic and are stable at high temperature, which are in the form of scatterings of oil, a surfactant, and water; a cosurfactant is regularly scattered utilizing amphiphilic mixes. After performing this process, the fuel which is obtained is of lesser thickness. This procedure yields a fuel with lower consistency but its usage in the engines is not so productive, and a coarse deposit and combustion is resulted.

### *4.2 Pyrolysis*

Applying the heat energy accompanying oxygen to produce a modification chemically is called as pyrolysis. When triglycerides are decomposed by heat treatment then it yields alkanes, alkenes, alkadienes, aromatic compounds, and carboxylic acids. Due to availability of a varied selection of reaction pathways, different products are obtained after completion of the reaction. Even though the products obtained are same as the conventional diesel chemically, exclusion of oxygen in thermal cracking reduces some of the ecological benefits of these renewable oils (Ma and Hanna 1998) (Figs. 1, 2 and 3).

### *4.3 Transesterification*

Various researchers have reported transesterification as the most attractive technique because improved quality of biodiesel is produced by using this technique (Nasreen et al. 2012). The chemically most similar biodiesel is obtained by performing the transesterification method, so it is the highly suitable technique for biodiesel production. By using this method fats (triglycerides) and oils are converted to their alkyl esters with viscosity level near to diesel fuel. Biodiesel is comparable to existing diesel and it can be used in the conventional diesel engines without any alteration. In general, the process of transesterification is reversible, in which reactants are mixed and heated under high temperatures. However, in the

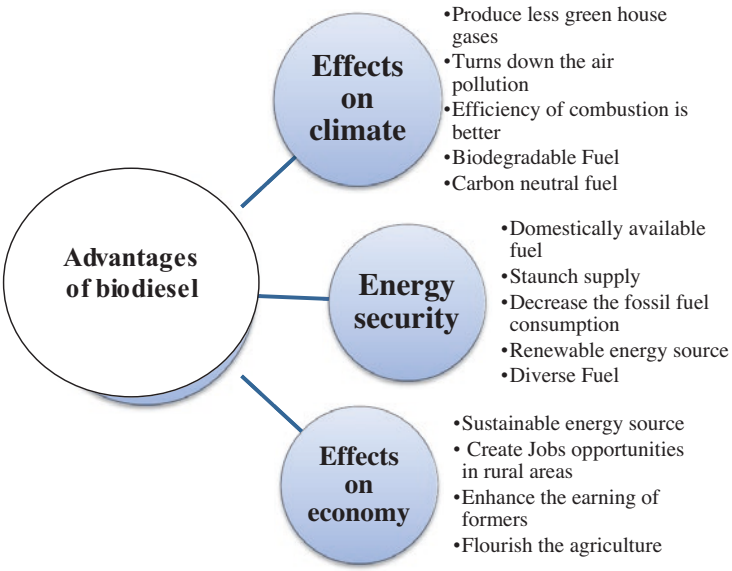


**Fig. 1** Advantages of using biodiesel (Demirbas 2009a, b; Zah and Ruddy 2009)

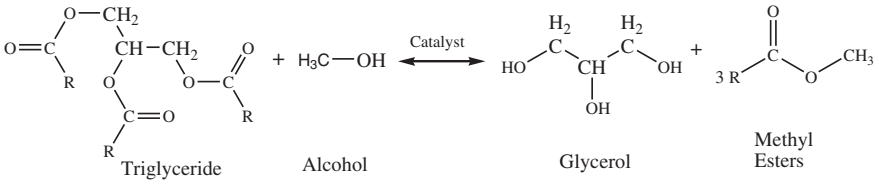


**Fig. 2** Conversion of triglycerides into biodiesel

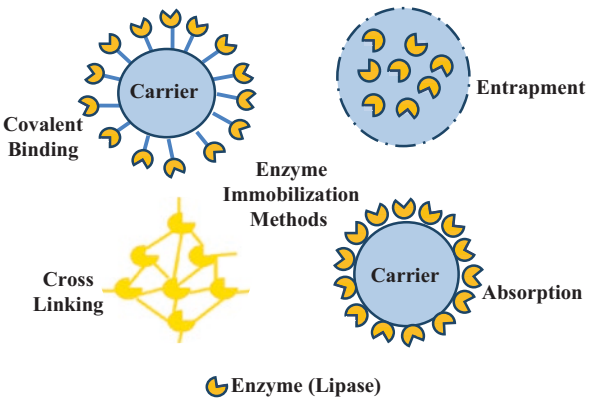


**Fig. 3** An overview of lipase immobilization methods (Hwang and Gu 2013)

presence of some catalyst, i.e., acid, alkali, or enzyme, it will proceed at a higher rate (Chincholkar et al. 2005).

All the transesterifications start by the reaction of a triglyceride (oil or fat) with an alcohol along with some catalyst to form glycerol and esters. A triglyceride is with three long-chain fatty acids and one glycerol molecule attached at its base. The properties of the fat or oil are estimated by the type of the fatty acids linked with glycerol. As a result, the fatty acids can influence the biodiesel properties. A good transesterification reaction for the production of biodiesel is that in which after the completion of the reaction, ester and glycerol layers are easily and effectively separated. Glycerol is the heavier coproduct which can be purified for different industrial uses, e.g., cosmetics and pharmaceutical, etc. (Demirbas et al. 2016).

## *4.4 Transesterification Methods*

The process of transesterification can be carried out by two methods which are chemical and enzymatic transesterification as explained below.

### 4.4.1 Chemical Methods

The chemical methods of transesterification include acid esterification and alkali-catalyzed transesterification. Purity of the feedstock oil and specially the quantity of free fatty acids is important in chemical transesterification. At an acid value higher than 2 mg KOH/g, the transesterification reaction stops while reacting on high FFA feedstocks. Pretreatment with an acid is important for those oils which have high FFA content. In case of very high FFA content, single-step acid treatment with hydrochloric acid may not be enough and two- or three-step pretreatment procedure may be needed. After pretreatment, alkaline transesterification will be performed for biodiesel production. Most common base catalysts which are used for the biodiesel synthesis include sodium hydroxide and potassium hydroxide (Enweremadu and Mbarawa 2009).

The highly recognized biodiesel synthesis process is chemical-catalyzed transesterification. But an alternating biodiesel synthesis process is needed due to the high production cost and complication in the steps.

### 4.4.2 Enzymatic Methods

Easy recovery of glycerol and purification of biodiesel has made the use of lipases as catalyst more attractive. Many research reports support the use of lipase as catalyst for the biodiesel synthesis but due to high cost of enzyme, this idea has not got much attention. To overcome this drawback of high production cost of free lipases,

recent researches have been carried out for the immobilization of lipases on solid supports which include zeolite, Celite, nanoparticles (inorganic) and textile membrane, etc. The immobilization of lipase decreases the cost due to their reusability. Covalent bonding, cross-linking, entrapment, and adsorption are the most known techniques that are used in lipase immobilization on the support (Jegannathan and Abang 2008). The immobilization technique is an important technique to enhance nearly all characteristics of enzyme like activity, specificity, stability, and selectivity along with the decrease in inhibition that positively influences the reaction order with a noteworthy rise in yield (Fjerbaek et al. 2009).

## 5 Immobilization of Lipase

The enzyme cost can be reduced by immobilizing the lipase on different supports like activated charcoal, silica gel, magnetic and nonmagnetic nanoparticles, etc. This method of enzyme immobilization is called as adsorption while other method of immobilization is entrapment in which enzyme is usually entrapped in some gel matrix like calcium alginate and can be reused several times. Magnetic nanoparticles have many advantages like low mass transfer resistance, more specific surface area/volume ratio for binding with high quantity of enzyme, and less effort for separation of immobilized enzyme from the biodiesel (Zhao et al. 2014).

The intrinsic catalytic activity of immobilized lipase can be affected by the physical properties of nanoparticles like particle mobility and increased diffusion. Magnetic nanoparticles present on an iron oxide interior and silica shell are less toxic, a distinctive magnetic reactivity, and a chemically treated surface. Nanoparticles which are coated with silica ($SiO_2$ & $Fe_3O_4$) are better modified to act as enzyme immobilization solid carriers.

Many researchers used enzymes as biocatalyst for biodiesel production; for example, *Candida antarctica*, *Rhizomucor miehei*, *Pseudomonas fluorescens*, *Chromobacterium viscosum*, and *Rhizopus oryzae* lipase (Hama et al. 2006) have been used as biocatalysts in transesterification reactions. Many immobilization techniques are found in literature to increase the stability of lipase in biodiesel synthesis. Some scientists have reported the use of immobilized *Candida antarctica* lipase (Novozyme 435) for feedstock with high free fatty acids for the biodiesel synthesis. The 95% biodiesel yield by using 4% of this lipase and molar ratio of methanol to aggregates of unsaturated fats 1:2 was reported (Winayanuwattikun et al. 2011).

The lipase activity is often affected by mainly two factors which are temperature and pH. After immobilization, lipase remains active in a wide range of pH and temperature than free lipase. It has been reported in many researches that immobilized lipase remains functional at pH up to 8.0 while the free lipase has an activity limit of 7.5 pH (Lei et al. 2004).

Many researchers have examined the effect of temperature on lipase immobilization. Some researchers have reported that at 50 and 60 °C, the activity of free lipase was 88.46 and 75.38%, respectively, while the immobilized lipase gave 95.86 and 81.26%, respectively (Nie et al. 2006). At higher temperatures, free lipase easily gets denatured while immobilized lipase is more stable and well confined due to its inflexible conformation. So due to all these advantages of immobilized lipases, these are used as catalysts for the biodiesel synthesis. The concentration of catalyst from 1.5 to 3.5% at a methanol/oil molar ratio of 4:1, temperature 40 °C, at a speed of 200 rpm for 12 h, and, by following these variables, a biodiesel yield changeable from 73 to 90% can be achieved as reported in the literature. Many researchers have suggested using the DNA recombinant technology to produce high amounts of lipases (Arumugam and Ponnusami 2017).

## 6 Latest Trends

To prevent the enzyme activity loss by not altering the reactive groups in the binding site of the enzyme or by not changing its chemical nature is very important while selecting the mode of immobilization. Nanoparticles have become potent carriers for immobilization of enzyme because many advanced techniques are used in the preparation of nanoparticles which have distinctive physicochemical characteristics like due to their significantly increased surface/bulk atom ratio high specific surface area and reactivity is resulted. Due to fixed conformations of the immobilized enzymes on nanoparticles, they are typically steadier and more active than free enzymes (Lee and Duong 2018).

Nanoparticles have ideal properties for harmonizing the important factors which determine the enzyme's efficiency like resistance to mass transfer, efficient enzyme loading, and specific surface area. All these factors make nanoparticles best choice for enzyme immobilization (Ansari and Husain 2012). To deal with diffusion problem which is caused while using macromolecules, nanoparticles are the perfect candidates (Hwang and Gu 2013). Moreover, nanoparticles having enzyme immobilized on them show Brownian movement when they are in aqueous media which show that the activities of enzymes are relatively enhanced than that of the free enzyme. The use of magnetic nanoparticles has an added benefit that they can be easily separated by magnetic decantation. Protein unfolding is also reduced by the nanoparticles' immobilization of enzymes which can improve stability and performance. Various studies have been performed on enzyme immobilization on nanoparticles like metal, metal oxide, magnetic, polymeric, and porous nanoparticles (Gupta et al. 2011). Nonmagnetic nanoparticles form well-dispersed collide and thus give high enzyme activity but recovery of nonmagnetic nanoparticles is difficult as it requires high-speed centrifugation for long time (Chen et al. 2008). The use of magnetic nanoparticles has more advantages as the catalyst is easily recoverable using external magnet, has better biocompatibility, and does not form aggregates at room

temperature. That is why nanoparticles of iron oxides are the most potent and widely used nanomaterials for lipase immobilization (Ziegler et al. 2017). Some of the methods of immobilization are given below.

## 6.1 Adsorption

As compared to other strategies, adsorption of lipases on the insoluble supports is an old and basic technique which has a number of applications and high capacity enzyme stacking. Enzyme immobilization can be performed by essentially blending the enzymes with a reasonable adsorbent, under proper conditions (Spahn and Minteer 2008). Physical interactions that cause adsorption of lipase require ambient process conditions and give high lipase loading on support; however, the problem is leaching of enzyme during the reaction or purification due to weak interactions among the support and lipase (Eş et al. 2015; Hwang and Gu 2013).

## 6.2 Covalent Binding

The arrangement of covalent bonds between the support framework and enzyme is called as covalent binding. The functional groups present in the lipases are not responsible for catalysis, so these are connected to support framework. The coupling action should be carried out under those environments that do not cause enzymatic activity loss and the active site of the catalyst must be unaltered by the chemicals utilized. Covalent relationship of enzyme to supports happens inferable from their side chain amino acids and level of reactivity dependent on various functional groups and so forth (Fu et al. 2011).

## 6.3 Entrapment

It is characterized as the limited mobility of enzyme in a permeable gel while maintaining them as free molecules in media. Entrapment of enzyme inside gel is an advantageous strategy for use in procedures including lesser molecular weight substrates and products. But the complexity which large molecules face in moving toward the catalytic positions of entrapped enzymes blocks the utilization of these with high molecular weight substrates (Grosova et al. 2008). Overall entrapment is an easy process and protects the activity of lipase but low enzyme loading and less mass transfer and the problems associated with entrapment of lipase (Kim and Grate 2003).

### *6.4 Cross-Linking*

This strategy includes connection of catalysts to one another by two or multifunctional chemicals or ligands. By doing this, extremely high molecular weight, insoluble clusters are framed. Cross-linking is a straightforward procedure. It is not a favored strategy for immobilization as it doesn't utilize any support framework. So, they are generally in gel form and not especially firm. Since it includes a covalent bond, biocatalysts immobilized like this often experience changes which result in loss of activity. Even then it is of great use in combination with other support dependent immobilization techniques, like reduction of leakage of catalysts previously immobilized by adsorption (Verma et al. 2013).

## 7 Limitations of Nanomaterials as Enzyme Immobilization Support

Nanomaterials are advantageous because of their monodispersed and Brownian movement, but at specific pH and temperature levels the nanoparticles form aggregates so, the activity of lipase is reduced another problem is the toxicity of some nanoparticles. These problems can be easily tackled by coating the nanoparticles with suitable polymers. Polymer coating helps to make the stable collides of nanoparticles, makes the nanoparticles biocompatible by reducing the surface energy, and also gives functionality to the surface to afford the strong immobilization of lipase (Cui et al. 2005; Pavlidis et al. 2010).

## 8 Variables Affecting the Transesterification Reaction

### *8.1 Reaction Time*

As the time of reaction increases the biodiesel yield also improves as reported by Freedman et al. (1986). At the start, the speed of the reaction is low due to dispersion and mixing of alcohol and oil but afterward reaction runs at a higher rate. The most oil conversion into biodiesel is obtained in 90 min but additional reaction time does not improve the biodiesel yield (Leung and Guo 2006; Alamu et al. 2008). Because biodiesel production is a reversible reaction so increased time may lead to decreased biodiesel resulting in more soap formation and loss of esters (Eevera et al. 2009). By using lipase as catalyst, a reaction time of 24–96 h is reported for biodiesel production.

## 8.2 Reaction Temperature

Temperature is another significant cause that affects the biodiesel quantity. For example, at high temperature, the thickness of the oils decreases, and it results in increased reaction rate. Higher temperature also decreases the reaction time. However, some scientists have reported that rise in temperature past the most favorable level lowers the biodiesel yield, because at higher temperature soap formation of triglycerides also increases (Leung and Guo (2006) and Eevera et al. (2009). For preventing the loss of alcohol by evaporation during reaction, it is recommended to perform transesterification at a temperature below the alcohol's boiling point. The optimum temperature for the biodiesel production may fluctuate from 50 to 60 °C depending on the fats or oils used (Leung and Guo 2006; Freedman et al. 1984). However, when lipase is used for biodiesel production, the reaction temperature should be at that level which is safe for the activity of enzyme because at higher temperature enzyme may be denatured which can in turn disturb the reaction. The optimum temperature for a transesterification reaction in which lipase is used as a catalyst relies on the kind of enzyme and alcohol used. By using lipase as catalyst for transesterification reactions, optimum temperature ranges between 30 and 50 °C (Mathiyazhagan and Ganapathi 2011).

## 8.3 Alcohol/Oil Molar Ratio

The ratio of alcohol to oil is very important in biodiesel synthesis (Leung and Guo 2006; Freedman et al. 1986). The limitation of both esterification and transesterification reactions is equilibrium and to advance the reaction toward biodiesel synthesis, an excessive quantity of alcohol is usually required. Normally the transesterification reaction requires 3 moles of alcohol for one mole of triglycerides to three moles of fatty acid esters and one mole of glycerol. Excessive quantity of alcohol improves biodiesel production, hence saving time. So, a certain amount of alcohol reduces the conversion time. However, beyond this level, biodiesel yield does not increase but it increases the difficulty of alcohol recovery from the reaction mixture which in turn increases the cost of process (Leung and Guo 2006). Other than this, the alcohol's quantity may differ according to the catalyst used; e.g., when alkali is used as a catalyst the alkali requirement for reaction is 6:1 to speed up the transesterification (Zhang et al. 2003; Freedman et al. 1986). If the feedstock contains high free fatty acids (FFA), then reaction does not respond to alkaline catalysts. So, to overcome this difficulty, acid catalyst is efficient, and the reaction requires higher concentration of alcohol than base catalyst. The reason is that acid tolerates the free fatty acids and excessive water quantity present in the oil feedstock; i.e., used cooking oil needs higher ratio of alcohol; i.e., 15:1 acid catalyst is used for biodiesel production (Leung and Guo 2006; Ali et al. 1995: Zhang 1994). The optimum quantity of alcohol to oil widely varies in the previous studies.

It ranges from 3.5 to 12 depending on the biodiesel production feedstock, enzyme source, and molecular weight of alcohol used during biodiesel production reaction.

It is also reported that an excess quantity of alcohol reduces the viscosity of the feedstock by minimizing diffusion limitations and enhances mass transfer rate and in turn enhances overall reaction rate. But too much excessive alcohol can emulsify the glycerol and decrease the conversion into biodiesel because a recombination of ester and glycerol takes place. A high quantity of alcohol ahead of a specific level may denature lipase by structural changes in enzyme (Thangaraj et al. 2019).

### *8.4 Agitation Speed*

For the formation of biodiesel, agitation speed is very important because by agitating the oil and catalyst mixture, rate of reaction increases. Many researchers reported that at 400 rpm, highest biodiesel production was obtained. But a speed higher than 400 rpm may lead to excessive saponification and a speed lower than this may reduce the reaction rate. The reduction in biodiesel synthesis at slow speed of reaction is due to the reversal of transesterification reaction (Knothe et al. 2005; Demirbas 2008; Eevera et al. 2009; Rashid and Anwar 2008) The summary of the variables affecting the transesterification reaction is given in the Table 6.

## 9 Future Perspective

Transportation will always be needed by the world so the exploration for nonconventional and greener sources of fuel is poised to become stronger. Second- and third-generation biodiesel, and biofuels in general, will have lesser clash with food provision. Since 1985 when biodiesel was first time reported, in situ transesterification has developed significantly. Feasibility has been established for a variety of feedstocks, alcohols, and catalysts. Latest challenges in this field now are to design strategies of making this procedure cost-effective. Biodiesel production should be applied on a large scale to comprehend economies. However, some properties of the production process may permit farmers in countryside to synthesize their own fuel. Due to the ease of the process it will reduce the dependence of farmers and seed growers on large-scale crushing and solvent extraction services. In situ transesterification has been successful but it presents scientists with enormous challenges for making it economical and commercial. The most significant challenges will be to minimize the enzyme production cost and to decrease the concentration of alcohol in the reaction.

**Table 6** Variables affecting the transesterification reaction

| Feed stock | Lipase | Biodiesel yield (%) | Catalyst conc. (%) | Reaction temp. (°C) | Reaction time (hrs) | Methanol to oil ratio | Agitation speed (rpm) | References |
|---|---|---|---|---|---|---|---|---|
| Rubber seed oil | *C. antarctica* lipase | 81.18 | 4 | 37 | 30 | 4:1 | 200 | Bharathiraja (2014) |
| Palm oil | *T. lanuginosus* lipase | 96 | 0.75 | 35 | 24 | 1.5:1 | – | Hama and Kondo (2013) |
| Microalgae | Novozyme 435 | 97 | 5 | 45 | – | 5:1 | 300 | Chen et al. (2016) |

## 10 Conclusions

The synthesis and use of biodiesel have seen a quantum leap in this century because of enormous benefits linked with its ability to reduce ozone-reducing gases. There are many nonconventional, nonedible oils which can be utilized for the production of biodiesel. A steady catalyst based on its catalytic life, its reusability, and lesser cost is vital as they affect the cost of the whole biodiesel production process. A slower rate of reaction and unnecessary side reactions limit the use of catalysts. So, acid and enzymatic catalysts are very useful because they have the capacity to work in single step and are capable of converting high quantities of free fatty acids (FFA) present in the feedstock into biodiesel. Simultaneous esterification and transesterification by using acid-base catalysts is very important while working with those oils which have high fatty acid content. Enzymatic catalysts are highly promising on the other hand because they complete the task in single step and high temperature is also not required. Many researches were done in the past for exploiting, exploring and use of novel catalysts, and using these catalysts for biodiesel synthesis. Some of the causes for the current increase of biocatalysts among others include a 98% biodiesel yield, high-purity by-products, ease of catalyst separation, low energy consumption, and less cost of separation.

## References

Abdalla IIH, Khaddor M, Boussab A, Garrouj DE, Souhial B. Physical and chemical characteristics of olive oils from cooperatives for olive growers in the North of Morocco. Intl J Basic Appl Sci. 2014;14:02.

Abeda KA, Gadb MS, El Morsic AK, Sayedd MM, Abu Elyazee S. Effect of biodiesel fuels on diesel engine emissions. Egypt J Pet. 2019;28:183–8.

Ageitos JM, Vallejo JA, Crespo PV, Villa TG. Oily yeasts as oleaginous cell factories. Appl Microbiol Biotechnol. 2011;90(4):1219–27.

Ahmad M, Ahmed S, Hassan FU. Base catalyzed transesterification of sunflower oil biodiesel. Afr J Biotechnol. 2010;9(50):8630–5.

Ahmad F, Khan AU, Yasar A. Transesterification of oil extracted from different species of algae for biodiesel production. Afr J Environ Sci Technol. 2013;7(6):358–64.

Ahmed AS, Khan S, Hamdan S, Rahman R, Kalam A, Masjuki H, Mahli TMI. Biodiesel production from macro algae as a green fuel for diesel engine. 2012

Akhabue CE, Okwundu OS. Monitoring the transesterification reaction of castor oil and methanol by ultraviolet visible spectroscopy. Biofuels. 2017;(10):729–736.

Alamu OJ, Akintola TA, Enweremadu CC, Adeleke CE. Characterization of palm-kernel oil biodiesel produced through NaOH-catalysed transesterification process. Sci Res Essay. 2008;3(7):308–11.

Ali Y, Hanna M, Cuppett S. Fuel properties of tallow and soybean oil esters. J Am Oil Chem Soc. 1995;72:1557–64.

Althomali A. Effects of mustard oil on oxidative stress parameters of male mice. Adv Food Sci. 2015;36(2):78–85.

Al-Zuhair S, Ling FW, Jun LS. Proposed kinetic mechanism of the production of biodiesel from palm oil using lipase. Process Biochem. 2007;42:951–60.

Ansari SA, Husain Q. Potential applications of enzymes immobilized on/in nano materials: a review. Biotechnol Adv. 2012;30:512–23.
Armah P, Archer A, Philips GC. Drives leading to higher food prices: biofuels are not the main factor. In: Global impact on renewable energy production agriculture and technological advancements. New York: Springer; 2011. p. 19–36.
Arumugam A, Ponnusami V. Production of biodiesel by enzymatic transesterification of waste sardine oil and evaluation of its engine performance. 2017;3(2017):1–18.
Ashokkumar C, Murugan B, Baskaran D, Veerapandian V. Physicochemical properties of olive oil and its stability at different storage temperatures. Intl J Chem Stud. 2018;6(2):1012–7.
Aydeniz B, Yılmaz E, Ok S. Cold pressed versus refined winterized corn oils: quality, composition and aroma. Grasas Aceites. 2017;68(2):194.
Balat M, Balat H. Progress in biodiesel processing. Appl Energy. 2010;87(6):1815–35.
Barku VYA, Nyarko HD, Dordun P. Studies on the physicochemical characteristics, microbial load and storage stability of oil from Indian almond nut Terminalia Catappa L. Food Sci Qual Manag. 2012;8:2012.
Bharathiraja B, Chakravarthy M, Kumar RR, Yuvaraj D, Jayamuthunagai J, Kumar RP, Palani S. Biodiesel production using chemical and biological methods–a review of process, catalyst, acyl acceptor, source and process variables. Renew Sust Energ Rev. 2014;38:368–82.
Borhade SS. Chemical composition and characterization of hemp seed oil and essential fatty acids by HPLC method. Arch Appl Sci Res. 2013;5(1):5–8.
Casimir C, Akoh C, Chang SW, Lee GC, Shaw JF. Enzymatic approach to biodiesel production. J Agric Food Chem. 2007;55(22):8995–9005.
Chen YZ, Yang CT, Ching CB, Xu R. Immobilization of lipases on hydrophobilized zirconia nanoparticles: highly enantioselective and reusable biocatalysts. Langmuir. 2008;24(16):8877–84.
Chen JZ, Wang S, Zhou B, Dai L, Liu D, Du D. A robust process for lipase-mediated biodiesel production from microalgae lipid. RSC Adv. 2016;54:2016.
Chincholkar SP, Srivastava S, Rehman A, Dixit S, Lanjewar A. Biodiesel as an alternative fuel for pollution control in diesel engine. Asian J Exp Sci. 2005;19(2):13–22.
Colla LM, Ficanha AMM, Rizzardi J, Bertolin TE, Reinehr CO, Costa JAV. Production and characterization of lipases by two new isolates of *Aspergillus* through solid-state and submerged fermentation. BioMed Res Intl. 2015;2015:1–9.
Cui T, Zhang J, Wang J, Cui F, Chen W, Xu F, Yang B. CdS nanoparticle/polymer composite shells grown on silica nanospheres by atomic transfer radical polymerization. Adv Funct Mater. 2005;15(3):481–6.
Demirbas A. Biodiesel: a realistic fuel alternative for diesel engines. London: Springer Verlag; 2008.
Demirbas A. Progress and recent trends in biodiesel fuels. Energy Conver Manag. 2009a;50(1):14–34.
Demirbas A. Political, economic and environmental impacts of biofuels: a review. Appl Energy. 2009b;86:S108–17.
Demirbas A, Bafail A, Ahmad W, Sheikh M. Biodiesel production from non-edible plant oils. Energy Explor Exploit. 2016;34(2):290–318.
Demirbas A, Bafail A, Ahmad W, Sheikh M. Biodiesel production from non-edible plant oils. Energy Explor Exploit. 2015;34(2):290–318.
Earle MJ, Plechkova NV, Seddon KR. Green synthesis of biodiesel using ionic liquids. Pure Appl Chem. 2009;81(11):2045–57.
Eevera T, Rajendran K, Saradha S. Biodiesel production process optimization and characterization to assess the suitability of the product for varied environmental conditions. Renew Energy. 2009;34:762–5.
Enweremadu CC, Mbarawa MM. Technical aspects of production and analysis of biodiesel from used cooking oil—a review. Renew Sustain Energy Rev. 2009;13(9):2205–24.
Es I, Vieira JDG, Amaral AC. Principles, techniques, and applications of biocatalyst immobilization for industrial application. Appl Microbiol Biotechnol. 2015;99(5):2065–82.

Fjerbaek L, Christensen VK, Norddahl B. A review of the current state of biodiesel production using enzymatic transesterification. Biotechnol Bioeng. 2009;102:1298–315.
Folaranmi J. Production of Biodiesel (B100) from Jatropha oil using sodium hydroxide as catalyst. J Pet Eng. 2013:1–7.
Freedman B, Rayden OB, Everett HP. Transesterification kinetics of soybean oil. JAOCS. 1986;63:1275–380.
Freedman BH, Pryde EH, Mounts TL. Variable affecting the yields of fatty esters from transesterified vegetable oils. J Am Oil Chem Soc. 1984;61(10):1638–43.
Fu J, Reinhold J, Woodbury NW. Peptide-modified surfaces for enzyme immobilization. PLoS One. 2011;6:e18692.
Fukuda H, Kondo A, Noda H. Review biodiesel production by transesterification of oils. J Biosci Bioeng. 2001;92(5):405–16.
Gebremariam SN, Marchetti JM. Biodiesel production technologies: review. AIMS Energy. 2017;5(3):425–57.
Ghadge SV, Raheman H. Biodiesel production from mahua (*Madhuca indica*) oil having high free fatty acids. Biomass Bioenergy. 2005;28(6):601–5.
Ghani NAA, Channip AA, Hwa PCH, Ja'afar F, Yasin HM, Usman A. Physicochemical properties, antioxidant capacities, and metal contents of virgin coconut oil produced by wet and dry processes. Food Sci Nutr. 2018;6(5):1298–306.
Grosova Z, Rosenberg M, Rebros M, Sipocz M, Sedlackova B. Entrapment of beta-galactosidase in polyvinylalcohol hydrogel. Biotechnol Lett. 2008;30:763–7.
Gude VG, Patil P, Guerra EM, Deng S, Nirmalakhandan S. Microwave energy potential for biodiesel production. Sustain Chem Proc. 2013;1:5.
Gupta MN, Kaloti M, Kapoor M, Solanki K. Nanomaterials as matrices for enzyme immobilization. Artif Cells Blood Substit Immobil Biotechnol. 2011;39:98–109.
Haas MJ, McAloon AJ, Yee WC, Foglia TA. A process model to estimate biodiesel production costs. Bioresour Technol. 2006;97(4):671–8.
Hama S, Kondo A. Enzymatic biodiesel production: an overview of potential feedstock and process development. Bioresour Technol. 2013;135:386–95.
Hama S, Tamalampudi S, Fukumizu T. Lipase localization in *Rhizopus oryzae* cells immobilized within biomass support particles for use as whole-cell biocatalysts in biodiesel-fuel production. J Biosci Bioeng. 2006;101(4):328–33.
Harvey AP, Khurana R, Lee R. In-situ transesterification of jatropha seeds to produce biodiesel using alcohol mixture. Presented at: 4th International Biofuels Conference. New Dehli, India; 2007. p 1–2
Hill J, Nelson E, Tilman D, Polasky S, Tiffany D. Environmental, economic, and energetic costs and benefits of biodiesel and ethanol biofuels. Pro Nat Acad Sci USA. PNAS. 2006;103(30):11206–10.
Hossain ABMS. Alkaline and acid catalyzed transesterification bioprocess in biodiesel preparation from fresh water algae. Asian J Biochem. 2015;10(5):205–13.
Hussain R, Asadullah AH, Sattar S, Zeb M, Hussain A, Nafees M. Physico-chemical properties and assessment of edible oil potential of peanuts grown in Kurram Agency, Parachinar. Pak J Anal Environ Chem. 2015;16(1):45–51.
Hwang ET, Gu MB. Enzyme stabilization by nano/microsized hybrid materials. Eng Life Sci. 2013;13:49–61.
Japir AA, Salimon J, Derawi D, Bahadi M, Shujaa SA, Yusop MR. Physicochemical characteristics of high free fatty acids crude palm oil. EDP Sci. 2017;24(5):1–9.
Jegannathan KR, Abang S. Production of biodiesel using immobilized lipase—a critical review. Crit Rev Biotechnol. 2008;28:253–64.
Jibril M, Joel AS, Edith U, Audu AA. Production and characterization of biodiesel from *Jatropha* oil and neem oil. Intl J Emerg Trends in Eng Dev. 2012;2(2):313–320.
Kankia AI, Abubaka AM, Ishaq DU. Production, characterization and process variables of biodiesel from non-edible plant oil (Neem & Soapnut): a review. Intl J Sci Res. 2012;3(11):456–60.

Karmakar R, Kundu K, Rajor A. Fuel properties and emission characteristics of biodiesel produced from unused algae grown in India. Pet Sci. 2018;15(2):385–95.
Karmee SK, Chadha A. Preparation of biodiesel from crude oil of *Pongamia pinnata*. Bioresour Technol. 2005;96(2005):1425–9.
Kim J, Grate JW. Single-enzyme nanoparticles armored by a nanometer-scale organic/inorganic network. Nano Lett. 2003;3(9):1219–22.
Knothe G, Gerpen V, Krahl JHJ. The biodiesel handbook. Champaign: AOCS Press [CRC Press]; 2005.
Knothe G. Analytical methods used in the production and fuel quality assessment of biodiesel. Trans ASAE. 2001;44(2):193–200.
Kushak R, Drapeau CJ, Cott EMV, Winter HH. Favorable effects of blue-green algae *Aphanizomenon flosaquae* on rat plasma lipids. J Am Nutraceutical Assoc. 2000;2(3):59–65.
Lee CK, Duong ANA. Enzyme immobilization on nanoparticles: recent applications. Emerg Areas Bioeng. 2018:67–80.
Lei J, Fan J, Yu C, Zhang L, Jiang S, Tu B, Zhao D. Immobilization of enzymes in mesoporous materials: controlling the entrance to nanospace. Micropor Mesopor Mat. 2004;73:121–8.
Leung DYC, Guo Y. Transesterification of neat and used frying oil: optimization for biodiesel production. Fuel Process Technol. 2006;87(10):883–90.
Liu M, Niu S, Chunmei L, Li H, Huo MJ. A study on the catalytic performance of carbide slag in transesterification and the calculation of kinetic parameters. Sci China Technol Sci. 2014;58(2):258–65.
Liu CZ, Wang F, Stiles AR, Guo C. Ionic liquids for biofuel production: opportunities and challenges. Appl Energy. 2012;92:406–14.
Ma FCLD, Hanna MA. The effects of catalyst, free fatty acids, and water on transesterification of beef tallow. Trans Am Soc Agric Eng. 1998;41:1261–4.
Madhuri RVS, Rao PV, Alekhya KRM, Kumari AS. Properties of vegetable oils and their influence on performance and exhaust emissions of di-diesel engine- a review. Intl J Mech Eng Technol. 2015;6(11):89–101.
Makni M, Haddar A, Fraj AB, Zeghal N. Physico-chemical properties, composition, and oxidative stability of olive and soybean oils under different conditions. Intl J Food Prop. 2015;18:194–204.
Mathiyazhagan M, Ganapathi A. Factors affecting biodiesel production. Res Plant Biol. 2011;1(2):01–5.
Mukhtar H, Khursheed S, Haq I, Mumtaz MW, Rashid U, Resayes SIA. Optimization of lipase biosynthesis from Rhizopus oryzae for biodiesel production using multiple oils. Chem Eng Technol. 2016;39:9.
Nasreen S, Nafees M, Qureshi LA, Asad MS, Sadiq A, Ali SD. Review of catalytic transesterification methods for biodiesel production. In: Biofuels- state of development. London: InTech; 2012. p. 93–119.
Nie K, Xie F, Tian FW, Tan T. Lipase catalyzed methanolysis to produce biodiesel: optimization of the biodiesel production. J Mol Catal B Enzym. 2006;43(1–4):142–7.
Niehus X, Godoy LC, Valadez FJR, Sandoval G. Evaluation of *Yarrowia lipolytica* oil for biodiesel production: land use, oil yield, carbon and energy balance. J Lipids. 2018;2018:1–6.
Pavlidis I, Tsoufis T, Enotiadis A, Gournis D, Stamatis H. Functionalized multi wall carbon nanotubes for lipase immobilization. Adv Eng Mater. 2010;12(5):B179–83.
Park EY, Mori M. Kinetic study of esterification of rapeseed oil contained in waste activated bleaching earth using Candida rugosa lipase in organic solvent system. J Mol Catal B Enzym. 2005;37:95–100.
Patel NK, Nagar P, Shah SN. Identification of non-edible seeds as potential feedstock for the production and application of bio-diesel. Energy Power. 2013;3(4):67–78.
Pitat B, Zadernowski R. Physicochemical properties of linseed oil and flour. Pol J Nat Sci. 2010;25(1):106–13.
Rashid U, Anwar F. Production of biodiesel through optimized alkaline catalyzed transesterification of rapeseed oil. Fuel. 2008;87:265–73.

Roiaini M, Ardiannie T, Norhayati H. Physicochemical properties of canola oil, olive oil and palm olein blends. Intl Food Res J. 2015;22(3):1227–33.
Roncero JM, Alvarez-Ortí M, Pardo-Gimenez A, Gomez R, Rabadan A, Pardo JE. Virgin almond oil: extraction methods and composition. Grasas Aceites. 2014;67(3):1–9.
Samuel CB, Brine KDD, Joy EV. Physicochemical properties and fatty acid profile of shea butter and fluted pumpkin seed oil, a suitable blend in bakery fat production. Intl J Nutr Food Sci. 2017;6(3):122–8.
Santomauro F, Whiffin F, Scott RJ, Chuck C. Low cost lipid production by oleaginous yeast cultured in non sterile conditions using model waste resources. Biotechnol Biofuels. 2014;7(34):34–43.
Sayyed SR, Gitte BM, Joshi SD, Dharmadhikari HM. Characterization of biodiesel: a review. Intl J Eng Res Technol. 2013;2(10):2077–82.
Seneviratne K, Jayathilaka N. Coconut oil: chemistry and nutrition. Battaramulla: Lakva Publishers; 2016.
Singh G, Yusup S, Wai CK. Physicochemical properties of crude Rubber seed oil for biogasoline production. Procedia Eng. 2016:426–31.
Siqueira SF, Francisco CE, Queiroz MI, De Menezes CR, Zepka LQ, Jacob-Lopes E. Third generation biodiesel production from microalgae. Phormidium Autumnale. 2016;33(3):427–33.
Sitepu IR, Jin M, Fernandez JE, Sousa LC, Balan V, Mills LB. Identification of oleaginous yeast strains able to accumulate high intracellular lipids when cultivated in alkaline pretreated corn Stover. Appl Microbiol Biotechnol. 2014;98(17):7645–57.
Skowyra M, Falguera V, Azman NAM, Segovia F, Almajano MP. The effect of Perilla frutescens extract on the oxidative stability of model food emulsions. Antioxidants. 2014;3:38–54.
Spahn C, Minteer SD. Enzyme immobilization in biotechnology. Recent Pat Eng. 2008;2:195–200.
Srivastava PK, Verma M. Methyl ester of karanja oil as an alternative renewable source energy. Fuel. 2008;87(8):1673–7.
Thirumarimurugan M, Sivakumar VM, Xavier AM, Prabhakaran D, Kannadasan T. Preparation of biodiesel from sunflower oil by transesterification. Intl J Biosci Biochem Bioinform. 2012;2(6):441–4.
Verma ML, Barrow CJ, Puri M. Nanobiotechnology as a novel paradigm for enzyme immobilisation and stabilisation with potential applications in biodiesel production. Appl Microbiol Biotechnol. 2013;97:23–39.
Wahlen D, Morgan R, McCurdy T, Willis M, Morgan D, Dye J, Bugbee B, Wood D, Seefeldt C. Biodiesel from microalgae, yeast, and bacteria: engine performance and exhaust emissions, energy fuels. Am Chem Soci. 2013;27:220–8.
Wang Y, Ou S, Liu P, Zhang Z. Preparation of biodiesel from waste cooking oil via two-step catalyzed process. Energy Convers Manag. 2006;48(1):184–188.
Winayanuwattikun P, Kaewpiboon C, Piriyakananon K, Chulalaksananukul K, Yongvanich T, Svasti J. Immobilized lipase from potential lipolytic microbes for catalyzing biodiesel production using palm oil as feedstock. Afr J Biotechnol. 2011;10(9):1666–73.
Yasushi E. Analytical methods to evaluate the quality of edible fats and oils: the JOCS standard methods for analysis of fats, oils and related materials (2013) and advanced methods. J Oleo Sci. 2018;67(1):1–10.
Zahir E, Saeed R, Hameed MA, Yousuf A. Study of physicochemical properties of edible oil and evaluation of frying oil quality by Fourier Transform-Infrared (FT-IR) Spectroscopy. Arab J Chem. 2014;10(2):S3870–6.
Zah R, Ruddy TF. International trade in biofuels: an introduction to the special issue. J Clean Product. 2009;17:S1–3.
Zannikos FE, Dodos GS, Lois E. Utilization of sesame oil for the production of bio based biofuels and lubricants. Proceedings of 3rd international conference Skiathos; 2011. p 19–2.
Zhang D. Crystallization characteristics and fuel properties of tallow methyl esters. Master thesis, Food Science and Technology. USA: University of Nebraska–Lincoln; 1994.
Ziegler-Borowska M, Chelminiak-Dudkiewicz D, Siodmiak T, Sikora A, Wegrzynowska-Drzymalska K, Skopinska-Wisniewska, Kaczmarek H, Marszall M. Chitosan–collagen coated

magnetic nanoparticles for lipase immobilization—new type of "enzyme friendly" polymer shell crosslinking with squaric acid. Catalysts. 2017;7(1):26.
Zhang Y, Dube MA, McLean DD, Kates M. Biodiesel production from waste cooking oil: 2. Economic assessment and sensitivity analysis. Bioresour Technol. 2003;90:229–40.
Zhao X, Qi F, Yuan C, Du W, Liu D. Lipase-catalyzed process for biodiesel production: enzyme immobilization: process simulation and optimization. Renew Sustain Energy Rev. 2014;44:182–97.
Thangaraj B, Pravin RS, Bagavathi M, Srinivasan R, Lin L. Catalysis in biodiesel production—a review. Clean Energy. 2019;3(1):2–23. https://doi.org/10.1093/ce/zky020.
Ahmad R, Sardar M. Enzyme immobilization: an overview on nanoparticles as immobilization matrix. Biochem Anal Biochem. 2015;4:1–8.
Yi S, Dai F, Zhao C. A reverse micelle strategy for fabricating magnetic lipase-immobilized nanoparticles with robust enzymatic activity. Sci Rep. 2017;7:1–9.
Shagufta, Ahmad I, Dhar R. Sulfonic acid-functionalized solid acid catalyst in esterification and transesterification reactions. Catal Surv Jpn. 2017;21:53–69.
Ryu HS, Kim HK, Choi WC, Kim MH, Park SY, Han NS. New cold adapted lipase from Photobacterium lipolyticum sp. nov. that is closely related to filamentous fungal lipases. Appl Microbiol Biotechnol. 2006;70:321–6.
Xiao M, Qi C, Obbard JP. Biodiesel production using Aspergillus niger as a whole-cell biocatalyst in a packed-bed reactor. GCB Bioenergy. 2011;3:293–8.
Kawakami K, Oda Y, Takahashi R. Application of a Burkholderia cepacia lipase-immobilized silica monolith to batch and continuous biodiesel production with a stoichio-metric mixture of methanol and crude Jatropha oil. Biotechnol Biofuels. 2011;4:31–42.
Shao P, Meng X, He J, Sun P. Analysis of immobilized Candida rugosa lipase catalyzed preparation of biodiesel from rapeseed soapstock. Food Bioprod Process. 2008;86:283–9.
Yang KS, Sohn J-H, Kim HK. Catalytic properties of a lipase from Photobacterium lipolyticum for biodiesel production containing a high methanol concentration. J Biosci Bioeng. 2009;107:599–604.
Wang X, Dou P, Zhao P. Immobilization of lipases onto magnetic $Fe_3O_4$ nanoparticles for application in biodiesel production. ChemSusChem. 2010;2:947–50.
Zhang KP, Lai JQ, Huang ZL, Yang Z. Penicillium expansum lipase-catalyzed production of biodiesel in ionic liquids. Bioresour Technol. 2011;102:2767–72.
Sim JH, Kamaruddin AH, Bhatia S. Biodiesel (FAME) productivity, catalytic efficiency and thermal stability of lipozyme TL IM for crude palm oil transesterification with methanol. J Am Oil Chem Soc. 2010;87:1027–34.
Shah S, Sharma S, Gupta MN. Biodiesel preparation by lipase-catalyzed transesterification of Jatropha oil. Energy Fuel. 2004;18:154–9.

# Industrial Applications of Green Solvents for Sustainable Development of Technologies in Organic Synthesis


**Maryam Meshksar, Fatemeh Afshariani, and Mohammad Reza Rahimpour**

**Contents**



## Abbreviations

| | |
|---|---|
| **IL** | Ionic liquid |
| **$SCO_2$** | Supercritical carbon dioxide |
| **VOCs** | Volatile organic compounds |

## 1 Introduction

Nowadays almost all chemical industries and manufactures use extensive amount of solvents. It is reported that nearly fifteen billion kilograms of hollow and organic generated solvents were produced yearly worldwide (DeSimone 2002). Solvents

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_16

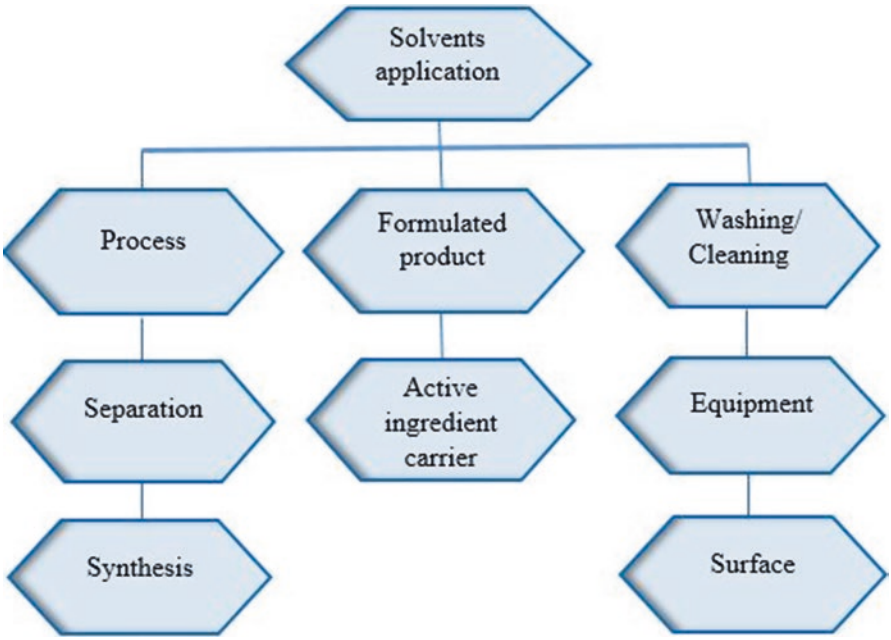



**Fig. 1** Types of solvent applications in the chemical operations

are applicable in both domestic and commercial operations. Solvent applications in different chemical processes are listed in Fig. 1. Solvents are used for chemical synthesis as well as purification or separation of chemicals in industries. The role of solvents in the process is to make the energy and mass transformation easier, modify the reactivity, form a homogeneous dispersion, and allow solid deposition (Lomba et al. 2011).

Solvent selection for defining the chemical selectivity, reactivity, and process yield is an important parameter in synthesis operations. The most commonly used organic solvents such as halogenated compounds, esters, ethers, aromatic and aliphatic hydrocarbons, and ketones cause significant safety, health and environmental concerns because of their toxic, volatile, flammable, and air pollutant nature (DeSimone 2002).

The horrendous amount of produced traditional solvents which are not safe for humans, plants, and animals lead to the definition of sustainable technology or green chemistry by the United Nations in 1987 (DeSimone 2002). According to green chemistry, the industries were obligated to decrease or eliminate their wastes and emissions and avoid using hazardous and toxic solvents. In addition, the highest amount of product selectivity should be achieved by minimizing the solvent, promoter, and reagent in an economical process. In the 1990s, P. Anastas and J. Warner laid down twelve principles of green chemistry for guiding chemical processes toward safer, less energy requirement as well as more economical and more envi-


**Fig. 2** Major aims of green chemistry for improving the environmental, social, and economic benefits

ronmentally friendly ones (Marion et al. 2017; Shanab et al. 2013; Suresh and Sandhu 2011a). The main goals of green chemistry are illustrated in Fig. 2. These twelve principles as a coercive handbook help scientists for designing new working procedures and compounds and preparing their experiments.

In other words, as can be seen in Fig. 3, green chemistry can be taken into account as series of reductions like costs, wastes, energy, materials, and non-renewable and hazardous substances. Therefore, green chemistry improves the environmental, social, and economic benefits. By reducing the consumption of materials and energy along with decreasing wastes, the process becomes more efficient and economical. The reduction of hazardous substances provides social benefits to plant operators, chemical users, and local communities. Here we could conclude that green chemistry actuates us toward ideal synthesis which its features are illustrated in Fig. 4 (Clark 2005).

Generally, there are three different methods for decreasing the amount of contaminated water and solvents which are released into the environment. The first approach is recycling or reducing the consumed solvent. The second one is switching the reaction under solvent-free process. Many reactions which are called dry media or solventless reactions have been performed without solvent. Numerous examples of solventless reactions can be seen in literature (Kidwai 2001). As some reactions cannot be performed in the solvent-free condition, the third method is using environmentally friendly solvents. In the last 20 years, alternative solvents have slowly started to replace conventional ones.


**Fig. 3** Green chemistry reduction effects

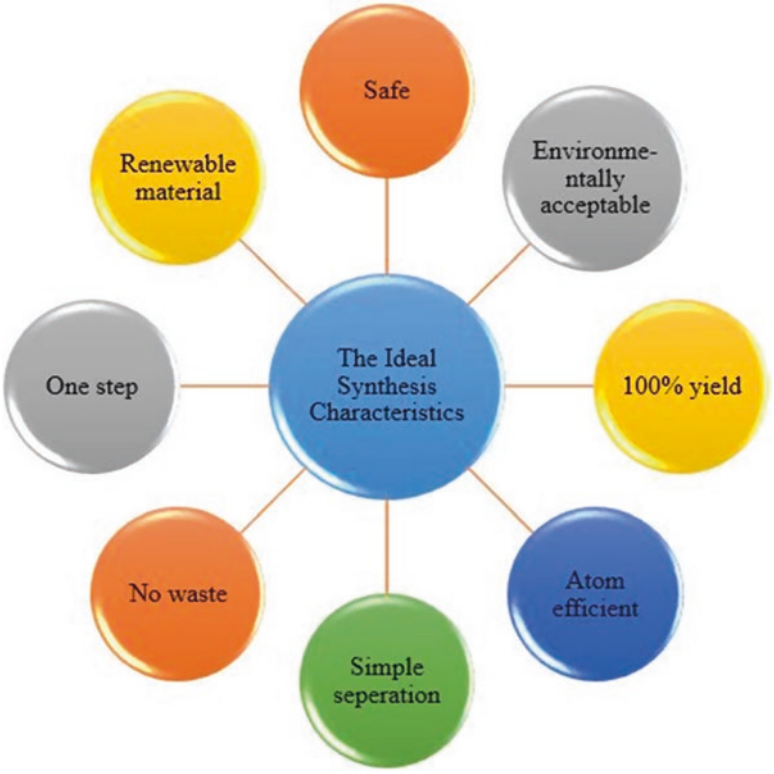



**Fig. 4** The ideal synthesis features

## 2 Solvent Selection

Selection of an appropriate solvent for a specific chemical reaction is an important issue for the process to carry out successfully. Some points should be investigated before choosing a solvent for a reaction. The first property is that products and reagents should have chemical compatibility. In many cases, solvent has been chosen due to the redox or acidic properties of products and reagents. The second one is that solvent should dissolve reactants to form a homogeneous media in conventional reactions. In this case, the polarity or nonpolarity characteristics of solutes and solvents should be considered. The last item which should be considered is the reaction temperature and the melting and boiling points of solvents and reagents (Byrne et al. 2016).

Also, we can explain the twelve principles of green chemistry for the solvent properties as in the following (Gu and Jérôme 2013):

1. Availability: green solvents should be available in a large scale.
2. Recyclability: green solvents should be fully recyclable.
3. Price: the price of green solvents should not change during the chemical process.
4. Grade: for avoiding energy using in purification processes, technical grade solvents are preferred to obtain extremely pure solvents.
5. Toxicity: green solvents should have low toxicity for decreasing all risks for human and environment.
6. Synthesis: green solvents should be produced through an economical process.
7. Biodegradability: green solvents should be completely biodegradable and should not produce toxic materials.
8. Stability: green solvents have to be electrochemically and thermally stable in a chemical process.
9. Performance: green solvents should present similar or even better performances (polarity, viscosity, and density) compared with conventional solvents.
10. Flammability: green solvents should be nonflammable.
11. Renewability: green solvents should be generated from renewable raw materials.
12. Storage: green solvents should be safe for transporting on roads, train, and plane. Also, they should be easy to store.

## 3 Green Solvents

The green chemistry says that utilization of auxiliary materials like solvents should become unnecessary wherever it is possible and harmless. In regard to raw materials, many of solvent resources are coming from fossil reserves like petroleum, natural gas, or coal. The fossil resources' main problem is their non-renewability and their rapid diminishing availability (Lomba et al. 2011).

Solvents which are prepared from sustainable resources like water, bio-solvents, and supercritical carbon dioxide are some of green solvents that can be applied as alternatives for harmful traditional ones. Ionic liquids, organic carbonate, and fluorous solvents are also classified as green solvents due to their special properties which are discussed in the following. It should be noted that each of these solvents has their own drawbacks and advantages and they do not compete with each other but they partly complete one another.

## *3.1 Water*

Water is one of the most useful green solvents which can be used not just in liqter and supercritical phase (DeSimone 2002). Water as an available component is not expensive, not toxic, and not flammable. Due to the polar and protic nature of water, it is an important solvent not just in green chemistry, but also in other fields. Polar and ionic compounds can be dissolved in water at ambient temperature and less polar materials are dissolvable at higher temperatures (Shanab et al. 2013; Sheldon 2005; Hartonen and Riekkola 2017).

Actually, water is the solvent that biochemical reactions in nature are carried out in it. However, water is not applicable for a group of chemical reactions which is a challenge for synthetic chemists. Researchers showed that the reactions which are occurred in water may be inclined to favor transition states by achieving the unique and unusual selectivity in organic reactions. The favor transition states of water cause optimization of hydrophobic interactions (Otto and Engberts 2003).

As supercritical water suffers from loss of hydrogen bonding, it behaves as a nonpolar solvent which can solve nonpolar materials and oxygen but cannot solve salts. Supercritical water exists at temperatures above 370 °C and pressures above 220 bar, which has been used in oxidation reactions, commonly for organic waste disposal. Unfortunately, supercritical water has not been used as a commercial solvent yet due to the corrosion problem which is the result of halogen traces (DeSimone 2002).

Water can be used as a unique green solvent or a mixture with other solvents in a two-phase or homogenous system (Laird 1998). The mix of water and organic solvents is used in many separation processes and also is applied for increasing the solvation of analyte materials with less polarity. In contrast to “in water” reactions in which reactants are soluble or partially soluble in water, in “on water” reactions the reaction occurs in water-based emulsion or in aqueous suspension. So, the on water reactions have an unusual rate of reaction compared with the same reactions using an organic solvent (Shapiro and Vigalok 2008).

High polarity of water has lots of selectivity and reactivity advantages in many processes like in organometallic catalysis. Catalyst can be recovered and recycled in an aqueous biphasic reaction by phase extraction while the product remains dissolved

in organic phase which causes increase in the reaction's greenness. Pt(II) bathophenanthroline complex has been utilized as a recyclable catalyst for primary and secondary alcohol oxidation which can be recovered and recycled back to the process by phase extraction method. The reaction becomes interesting in both environmental and economic points by using water and air as a solvent and oxidant, respectively (ten Brink et al. 2000).

Breslow et al. studied the application of hydrophobic borohydride for controlling the region-selective sulfate reduction. The selectivity was significantly increased (83:13) for 17-Krto group by using $LiBH_4$ in a watery reaction region (Breslow et al. 2002).

In biocatalysis, the reaction conditions are mild. Therefore, water is applicable as a solvent and enzymes are used as a catalyst in biocatalysis reaction field. Today enzymes are applied in commercial processes not just in water, but also in other green solvents like ionic liquids. As an example, the synthesis of cephalosporin, APA (6-aminopenicillanic acid 3), aspartame, and glycolic acid is based on enzymatic biocatalysis method (Wegman et al. 2001; Oyama 1992; Gavagan et al. 1995).

## *3.2 Ionic Liquids*

Ionic liquids (ILs) are comprised from a larger organic cations and a smaller inorganic anions. The asymmetry in the ionic liquid structure reduces their melting points as a result of their low crystalline lattice energy. Therefore, ionic liquids have near-zero vapor pressure and exist in liquid phase below 100 °C. Also, many of ILs are electrically conductive, have high thermal and chemical stability, and have low combustibility.

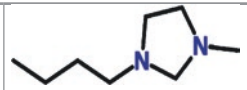
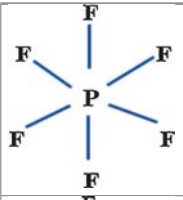
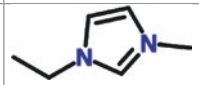
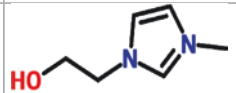
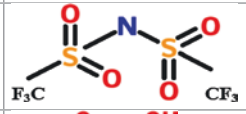
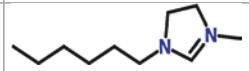
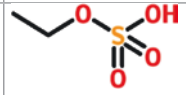
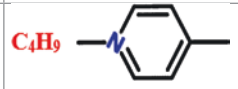
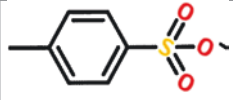
Some examples of most common anions and cations in conventional ionic liquids are demonstrated in Table 1. Figure 5 shows most used ionic liquids in experimental and industrial applications (Marciniak 2010).

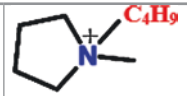
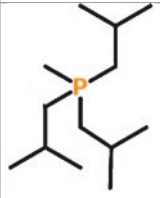
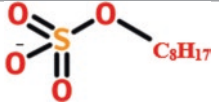
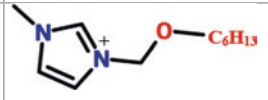
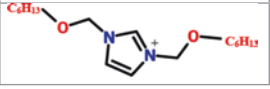
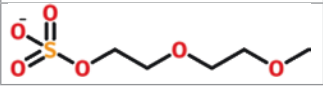
ILs are being used in many researches as solvents due to their some special properties that are not comparable to other solvents. Some researchers postulate that as the production steps of ionic liquids are intricate, they are not greener solvents than other used ones to be replaced. Jessop expressed that ionic liquids cannot be assumed as green solvents but they can be supposed as solvents that are capable to lead the whole reaction into greener pathway. Also, he declares that ionic liquids do not obey most of greenness categories except the ozone layer depletion (Jessop 2011).

Ionic liquids are stable in a wide temperature ranges. As ILs are immiscible with several organic solvents, they can be utilized in biphasic reactions. The used catalyst after extraction can be used again in the reaction. As well as solvent application, ionic liquids are able to be used as ligands or catalysts (Shanab et al. 2013).

Due to the mentioned characteristics of ionic liquids, they are applicable for a wide range of processes such as electrochemical applications, hydrogenation

**Table 1** The most used cationic and anionic parts of ionic liquids

| Cationic | | | Anionic | | |
|---|---|---|---|---|---|
| [bmim] |  | 1-Butyl-3-methylimidazolium | [$PF_6$] |  | Hexafluorophosphate |
| [emim] |  | 1-Ethyl-3-methylimidazolium | [$BF_4$] |  | Tetrafluoroborate |
| [hemim] |  | 1-(2-Hydroxyethyl)-3-methylimidazolium | [$Tf_2N$] |  | Bis(trifluoromethanesulfonyl) imide |
| [hmim] |  | 1-Hexyl-3-methylilmidazolium | [$EtSO_4$] |  | Ethyl sulfate |
| [1,4bmPY] |  | 1-Butyl-4-methylpyridinium | [TOS] |  | Tosylate |

| | | | | | |
|---|---|---|---|---|---|
| [bmPYR] |  | 1-Butyl-1-methylpyrrolidinium | $[CF_3SO_3]$ |  | Trifluoromethanesulfonate |
| $[P_{1,i4,i4,i4}]$ |  | Triisobutyl-methylphosphonium | $[OcSO_4]$ |  | Octyl sulfate |
| $[C_6OCmim]$ |  | 1-Hexyloxymethyl-3-methyl-imidazolium | [SCN] |  | Thiocyanate |
| $[(C_6OC)_2im]$ |  | 1,3-Dihexyloxymethylimidazolium | $[MDEGSO_4]$ |  | 2-(2 Methoxyethoxy)ethyl sulfate |

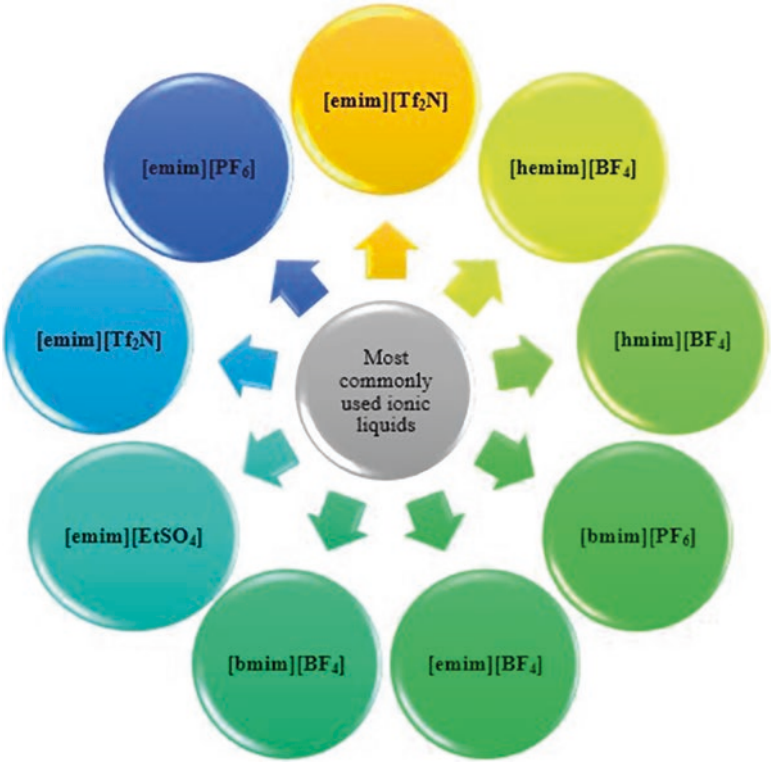



**Fig. 5** Most common ionic liquids

reactions, and biocatalysis reactions. Ionic liquids are also used as a catalyst for production of thiazoles which are significant substances in medical and organic chemistry for condensing ketones, aldehydes, or indoles (Haviv et al. 1988; Tsuji and Ishikawa 1994; Bell et al. 1995).

[bmim]Cl-$AlCl_3$ (1-butyl-3-methylimidazolium chloride-aluminum chloride) as an inorganic liquid Lewis acid is used for Friedel-Crafts acylations. [bmim]$BF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) is applied for halomethylated ß-enaminone production at 50 °C as shown in Fig. 6 (Xin-hua et al. 2009; Bonacorso et al. 2006).

In some standard reactions like aldol reaction, Michael reaction, Knoevenagel reaction, Doebner modification of Knoevenagel reaction, or Biginelli and Hantzsch reaction, reaction occurs at lower pressures and temperatures than conventional process by using ionic liquids. The used IL in such reactions reduces capital costs and consumed energy. Table 2 shows some important reactions which are able to be modified by using ionic liquids to obey the green chemistry requirements.

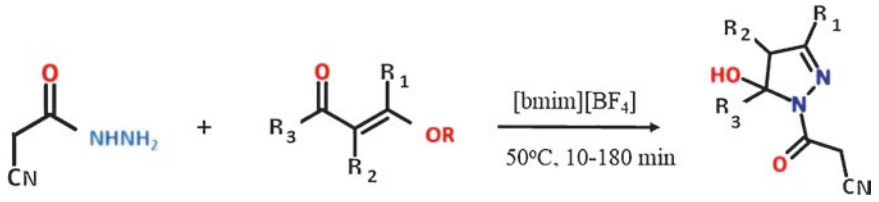



**Fig. 6** Halomethylated ß-enaminone production via [bmim]$BF_4$ ionic liquid

## *3.3 Fluorous Solvents*

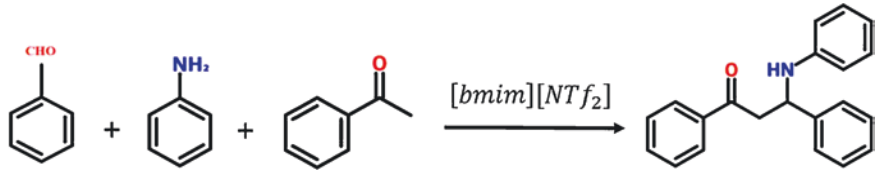
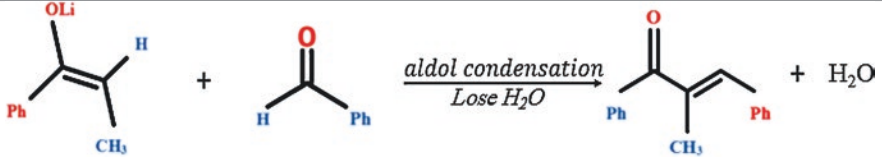
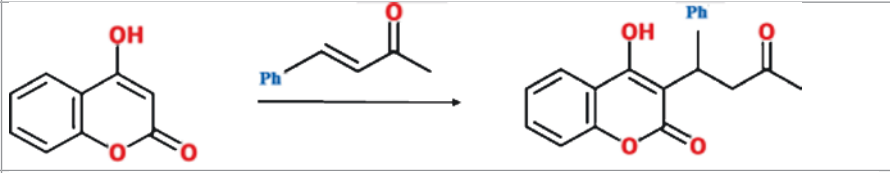
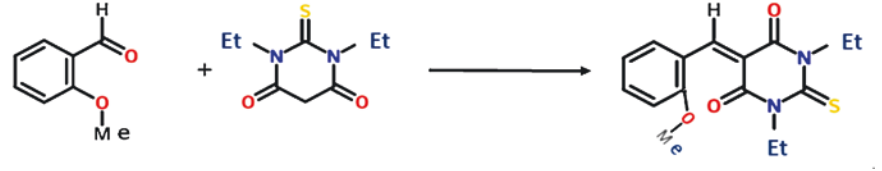
Fluorous solvents were first presented in a Horváth and Rabai paper, who envisioned that the term fluorous could be used analogously to "aqueous" or "aqueous media" in 1994 (Horváth 1998; Horváth and Rábai 1994). In the 1950s, perfluorinated compounds (PFCs) have been created and applied for industrial applications as firefighting foams, cosmetics, water and grease repellents, food packaging, and fabric coatings. A large number of fluorous solvents are commercially available today. The most common fluorous solvents are perfluorinated alkanes, perfluorinated dialkyl ethers, polyethers, and perfluorinated trialkyl amines. Actually, a perfluorinated alkyl group is combined of a conventional organic reagent as an affinity tag. It should be noted that the lone pairs in amines and ethers have extremely low energy and they do not have any residual basicity.

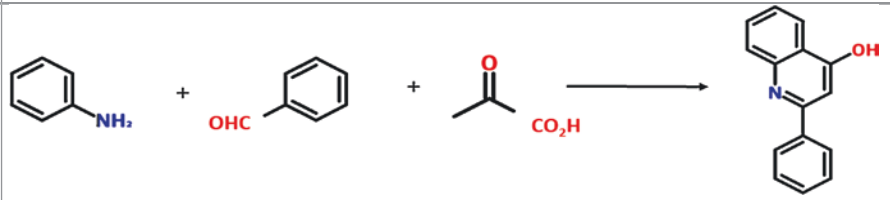
The mentioned perfluorinated liquids have some attractive properties including chemical inertness, nonflammability, high thermal stability, excessive nonpolar characteristics, and weak intermolecular attraction. The immiscibility of perfluorinated liquids in organic solvents and water causes the biphasic system formation at room temperature (Shanab et al. 2013). However, the biphasic fluorous systems become miscible at higher temperatures forming a homogenous liquid media. Therefore, by adjusting the reaction temperature, both reaction and product separation media are achievable (Sheldon 2005; Horváth 1998). In biphasic catalysis reactions, the used catalyst should be soluble into the fluorous phase. As fluorous solvents are expensive and they have high biological half-lives, they are not yet being widely used commercially (Sheldon 2005; Dobbs and Kimberley 2002).

As an example, recyclable 1,1,1-trifluoroethanol is used to produce high yield α-amino phosphonates or α-amino nitriles from the reaction of trimethyl phosphate or trimethylsilyl cyanide, ketones or aldehydes, and amines without any base or acid catalyst requirement as shown in Fig. 7 (Heydari et al. 2009).

It is reported that the functionalization of various branched and linear alkanes has been efficient by putting the carbene group of ethyl diazoacetate in the presence of TpBr3M [Ag; $Tp^{Br3}$ = hydrotris (3,4,5-tribromopyrazolyl)] borate as a catalyst using fluorous media. The advantage of this method is that the used catalyst can be recycled back easily and employed in the reaction several times without activity loss (Shanab et al. 2013).

**Table 2** Examples of some modified standard reactions

| Reactions | Example | Reference |
|---|---|---|
| Mannich reaction |  | Suresh and Sandhu (2011b) |
| Aldol reaction |  | Matsui and Hayashi (2004) |
| Michael reaction |  | Yuan et al. (2017) |
| Knoevenagel reaction |  | Asiri et al. (2004) |

| | | |
|---|---|---|
| Doebner modification of Knoevenagel reaction |  | Heravi (2014) |
| Hantzsch reaction |  | Kumar and Maurya (2007) |

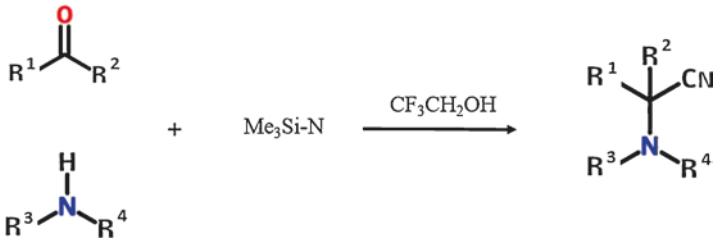



**Fig. 7** Formation of α-amino nitriles in 1,1,1-trifluoroethanol

### *3.4 Supercritical Carbon Dioxide*

Supercritical carbon dioxide ($SCO_2$) is by far the most commonly used supercritical fluid. Supercritical carbon dioxide is a fluid state in which $CO_2$ is at higher pressure and temperature than its critical point. In supercritical state, $CO_2$ has liquid-like density and gas-like viscosity. The changes in its pressure and temperature cause the changes in its dielectric properties, density, and viscosity. Therefore, supercritical $CO_2$ is considered as a multipurpose and selective solvent. Due to some prominent properties of carbon dioxide, such as nonflammability, nontoxicity, renewability, chemically inert to a wide range of substances, and easily evaporating, it is widely used in green chemistry (DeSimone 2002; Sheldon 2005).

Supercritical carbon dioxide demonstrates the properties of nonpolar substances. Therefore, $SCO_2$ is more appropriate for dissolution of materials with weak polarity. Generally, $SCO_2$ is an appropriate solvent for nonpolar molecules that have low molecular weights. It is a poor solvent for high molecular weight polymers under readily accessible conditions. Moreover, the addition of some cosolvents such as ethanol, methanol, and acetone to supercritical carbon dioxide can improve the solubility of the polar substances in $SCO_2$. Actually, the addition of cosolvents to supercritical carbon dioxide can enhance the exploitation efficiency in many cases (Wu and Han 2013).

$SCO_2$ is being utilized in different areas such as nutrition and food industries, dry cleaning, polymer modification, pharmaceutical processing, and metal degreasing. It is also been used for organometallic catalysis and heterogeneous hydrogenation reactions (Leitner 2002).

The high miscibility of $SCO_2$ with gases is useful for hydrogenation with hydrogen, hydroformylation with syngas, and oxidation with oxygen which causes higher efficiency and sometimes higher selectivity (Schaeffner et al. 2008; Ren et al. 2009; Koeken et al. 2008; Roukoss et al. 2007). Moreover supercritical $CO_2$ can be easily separated from products and catalysts by using depressurization and recapture method because of its swelling and plasticizing effects. So, this method is repeatedly used for catalysis as a green reaction medium (Li and Trost 2008).

Some catalyzed carvone hydrogenation methods by varying the supercritical $CO_2$ pressure have been reported by Melo et al. as illustrated in Fig. 8. Results showed that high conversion and high product selectivity were achieved at mild reaction conditions. Furthermore, the reaction time which depends on the used cata-

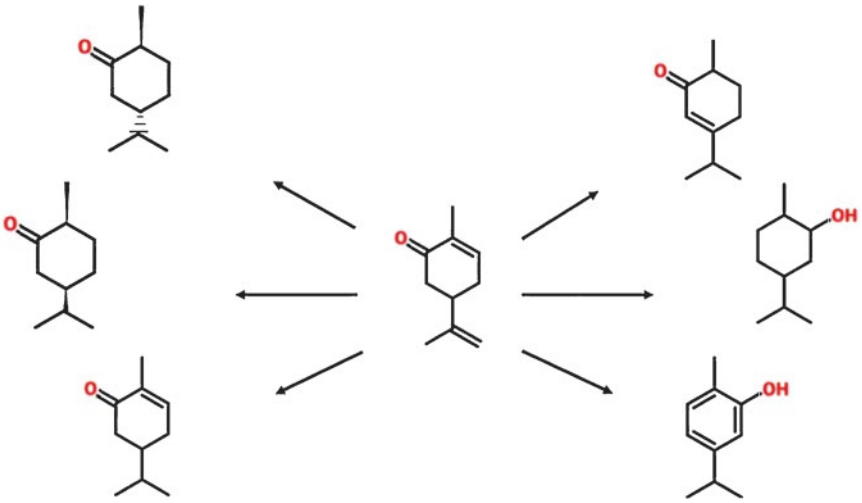



**Fig. 8** Carvone hydrogenation via supercritical $CO_2$

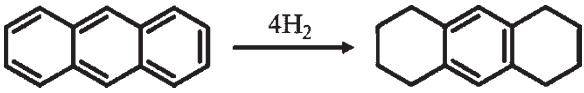



**Fig. 9** Anthracene hydrogenation via supercritical $CO_2$

lyst was decreased significantly in $SCO_2$ media compared with hydrogenation in conventional organic solvents (Melo et al. 2011).

The catalytic anthracene hydrogenation over Hβ-zeolite supported on Ni was done by Endalkachew et al. using $SCO_2$ as shown in Fig. 9. The achieved results demonstrate 100% product conversion which is the result of increment in substrate and hydrogen solubility and reduction in mass transfer limitations in dense carbon dioxide media (Sahle-Demessie et al. 2012).

## *3.5 Organic Carbonates*

Actually, synthesis of organic carbonates from $CO_2$ as a raw material is one of the greatest chances for applying $CO_2$ in industrial chemistry. Organic carbonates are the ester form of carbonic acid which are mostly immiscible or at least partially miscible in water (Calvo-Flores et al. 2018). Organic carbonates are usable in a wide range of applications such as medical applications, in batteries, and also for extraction purposes. Organic carbonates are inexpensive and completely biodegradable and have low toxicity. Carbonates have high industrial potential for being utilized as environmentally friendly and sustainable reactants and solvents. However, they are not synthesized in industrial scales currently (Heyn 2015).

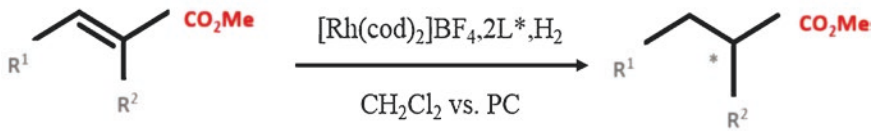



**Fig. 10** Asymmetric olefin hydrogenation in propylene carbonate using rhodium catalyst

Organic carbonates are divided into two groups of cyclic and linear carbonates. While the first group are made from the reaction of diol and carbon dioxide or a cyclic ether like epoxide and carbon dioxide, the second group are made from carbon dioxide and two equivalents of an alcohol like methanol (Heyn 2015). The cyclic form of carbonates has low volatility, flammability, and toxicity and also they stay in liquid phase in a wider temperature range than linear ones. Therefore, cyclic organic carbonates are more suitable for being used as green solvents (Vollmer et al. 2012). Propylene carbonate as a cyclic organic carbonates has low viscosity, large range of temperature in liquid state from −49 °C to 243 °C, and high molecular dipole moment of 4.9 D. So, propylene carbonate is a suitable solvent for organic synthesis using microwave (Shanab et al. 2013).

Organic carbonates are being used as reaction medium in a few references (Shanab et al. 2013). As can be seen in Fig. 10, asymmetrically hydrogenation of some functionalized olefins over rhodium as a catalyst was done in conventional solvents, butylene carbonate and propylene carbonate. Better results were achieved by using both carbonate solvents than standard reagents like $CH_2Cl_2$, THF, and MeOH. At longer reaction times, enantioselectivity was increased over butylene carbonate compared with propylene carbonate (Schäffner et al. 2008; Schäffner et al. 2009).

Allylic substitution reaction over Pd catalyst was done in propylene carbonate, diethyl carbonate, and butylene carbonate by using different types of phosphorous ligands as shown in Fig. 11. The achieved results showed the increment in the enantioselectivity and yields by using carbonate solvents compared with $CH_2Cl_2$ usually used as an environmentally unfriendly solvent (Schaeffner et al. 2008).

Propylene carbonate has been applied successfully as a stabilizing solvent for synthesis and stabilizing of metal nanoparticles without using additional agents. Ionic liquids, organic ligands, or ionic supports are usually required because of their propensity to aggregate metal nanoparticles due to their high surface energy and large specific surface area (Vollmer et al. 2012).

## *3.6 Bio-solvents*

In recent years, bio-solvents have been used as a substitute for volatile organic compounds that are harmful for human, animal, and plant health. The most significant groups of bio-solvents are bioethanol, glycerol and its derivatives, esters, terpenic

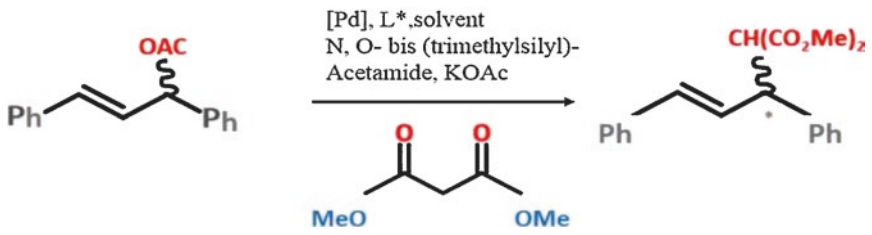



**Fig. 11** Allylic substitution reaction in different organic carbonate solvents using Pd catalyst

compounds, fatty acids, and isosorbide. The advantage of bio-solvents is their renewable production sources including mineral, animal, and vegetable raw materials. These solvents are produced from biomass in three different ways such as (Calvo-Flores et al. 2018):

1. Fermentation
2. Using other process waste materials
3. Transforming the biomass derivatives chemically

Bio-solvents have been used in cleaning agents, cosmetics, inks, agricultural chemicals, and paint. There are some factors which should be considered to choose a bio-solvent for a special process:

1. Optimal technical characteristics including volatility, dissolution capability, and flash point
2. Environmental safety
3. The cost and availability of the renewable raw materials
4. Eco-compatible production

Bio-solvents have been applied in multicomponent reactions. As an example, Li et al. used glycerol as a superior yield solvent in comparison with standard solvents such as water, nitromethane, acetic acid and toluene for three-component dimedone, styrene, and formaldehyde condensation as illustrated in Fig. 12. Their results showed a promising effect on glycerol in the methylene dimedone and styrene oxo-Diels-Alder reaction because of its protic and polar properties (Li et al. 2010).

It was proven that the existence of glycerol in two sequential one-pot reactions of four-component arylhydrazine, styrene, formaldehyde, and β-ketoesters and in another reaction of indole, β-ketoester, arylhydrazine, and paraformaldehyde is indispensable. These two sequential reactions are shown in Fig. 13 (Tan et al. 2010).

It should be noted that the required technologies for using bio-solvents at industrial applications are the same as other green solvents like fluorous solvents, ILs, and supercritical fluids, but they need lower economical costs. Therefore, some bio-solvents have replaced traditional industrial ones more quickly comparing with other environmentally friendly alternatives (Lomba et al. 2011).

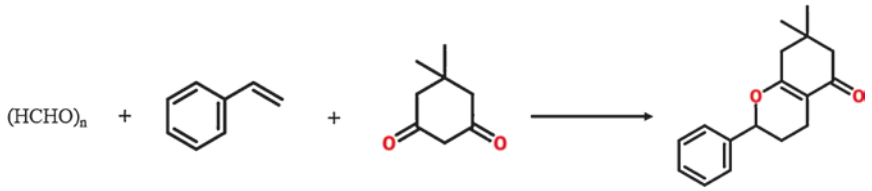



**Fig. 12** Three-component dimedone, styrene, and formaldehyde condensation in glycerol

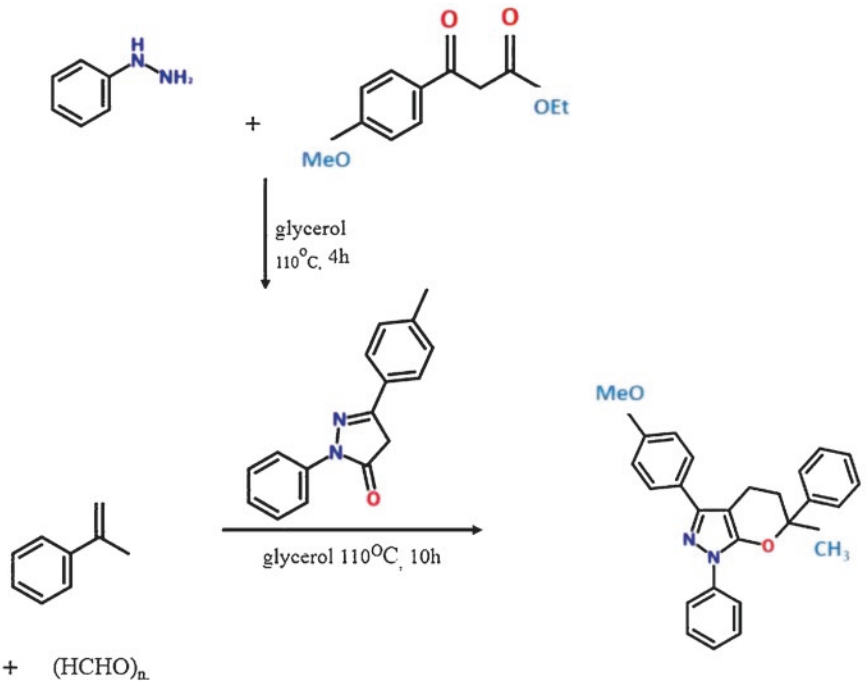



**Fig. 13** Two sequential one-pot reactions of arylhydrazine, styrene, formaldehyde, and β-ketoester in glycerol

## 4 Conclusion

The discussion in this chapter relating to the six alternative solvents including water, ionic liquids, organic carbonates, fluorous solvents, supercritical carbon dioxide, and bio-solvents shows that the results are the same or sometimes better than the results of conventional synthesis using organic solvents. Water, as an available, cheap, nonflammable, and nontoxic solvent, shows an ideal medium for occurring the reaction of many processes such as hydroformylation processes, organometallic catalysis, and oxidations. Ionic liquids and fluorous solvents are suitable alternatives for reactions which cannot accomplish in supercritical carbon dioxide or water.

The reactions in ionic liquids are often carried out easier and quicker than those using conventional organic solvents that is of exceptional importance because of safety concerns and strengthening arrangement of the environment. Supercritical carbon dioxide as another attractive alternative in place of traditional organic solvents exhibits prominent characteristics for being used in green chemistry like its easy separation from reaction products via simple pressure drop. Because of intermediate properties of supercritical carbon dioxide between liquid and gas state, rates of reactions are so high. Organic carbonates have some feature characteristics such as complete biodegradability, inexpensiveness, and low toxicity which are applicable for medical and pharmaceutical applications and extraction purposes.

Generally, the ideal basis is provided by green approach for a chemical industries which leads to basic innovations in chemical science. In other words, sustainable chemistry helps the society for producing more and better environmentally friendly products.

## References

Asiri A, et al. 1, 3-Diethyl-5-(2-methoxybenzylidene)-2-thioxodihydropyrimidine-4, 6 (1H, 5H)-dione. Mol Ther. 2004;2004(1):M359.

Bell FW, et al. Phenethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors. 1. Synthesis and basic structure-activity relationship studies of PETT analogs. J Med Chem. 1995;38(25):4929–36.

Bonacorso HG, et al. Trifluoromethyl-containing pyrazolinyl (p-tolyl) sulfones: the synthesis and structure of promising antimicrobial agents. J Fluor Chem. 2006;127(8):1066–72.

Breslow R, Groves K, Mayer MU. Antihydrophobic cosolvent effects for alkylation reactions in water solution, particularly oxygen versus carbon alkylations of phenoxide ions. J Am Chem Soc. 2002;124(14):3622–35.

Byrne FP, et al. Tools and techniques for solvent selection: green solvent selection guides. Sustain Chem Process. 2016;4(1):7.

Calvo-Flores FG, et al. Green and bio-based solvents. Top Curr Chem. 2018;376(3):18.

Clark JH. Green chemistry and environmentally friendly technologies. In: Green separation processes: fundamentals and applications. Weinheim: Wiley; 2005. p. 1–18.

DeSimone JM. Practical approaches to green solvents. Science. 2002;297(5582):799–803.

Dobbs AP, Kimberley MR. Fluorous phase chemistry: a new industrial technology. J Fluor Chem. 2002;118(1–2):3–17.

Gavagan JE, et al. Glyoxylic acid production using microbial transformant catalysts. J Org Chem. 1995;60(13):3957–63.

Gu Y, Jérôme F. Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. Chem Soc Rev. 2013;42(24):9550–70.

Hartonen K, Riekkola M-L. Water as the first choice green solvent. In: The application of green solvents in separation processes. Amsterdam: Elsevier; 2017. p. 19–55.

Haviv F, et al. 3-[1-(2-Benzoxazolyl) hydrazino] propanenitrile derivatives: inhibitors of immune complex induced inflammation. J Med Chem. 1988;31(9):1719–28.

Heravi M, Asadi S, Azarakhshi F. Recent applications of Doebner, Doebner-von Miller and Knoevenagel-Doebner reactions in organic syntheses. Curr Org Synth. 2014;11(5):701–31.

Heydari A, Khaksar S, Tajbakhsh M. Trifluoroethanol as a metal-free, homogeneous and recyclable medium for the efficient one-pot synthesis of α-amino nitriles and α-amino phosphonates. Tetrahedron Lett. 2009;50(1):77–80.

Heyn RH. Organic carbonates. In: Carbon dioxide utilisation. Amsterdam: Elsevier; 2015. p. 97–113.
Horváth IT. Fluorous biphase chemistry. Acc Chem Res. 1998;31(10):641–50.
Horváth IT, Rábai J. Facile catalyst separation without water: fluorous biphase hydroformylation of olefins. Science. 1994;266(5182):72–5.
Jessop PG. Searching for green solvents. Green Chem. 2011;13(6):1391–8.
Kidwai M. Dry media reactions. Pure Appl Chem. 2001;73:147.
Koeken AC, et al. Selectivity of rhodium-catalyzed hydroformylation of 1-Octene during batch and semi-batch reaction using Trifluoromethyl-substituted ligands. Adv Synth Catal. 2008;350(1):179–88.
Kumar A, Maurya RA. Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts. Tetrahedron. 2007;63(9):1946–52.
Laird T. Organic synthesis in water. Edited by Paul A Grieco. Blackie/Thomson Science: London, UK, 1998. 320 pp.£ 75. ISBN 0 7514 0410 1: ACS Publications; 1998.
Leitner W. Supercritical carbon dioxide as a green reaction medium for catalysis. Acc Chem Res. 2002;35(9):746–56.
Li C-J, Trost BM. Green chemistry for chemical synthesis. Proc Natl Acad Sci. 2008;105(36):13197–202.
Li M, et al. Multicomponent reactions of 1, 3-cyclohexanediones and formaldehyde in glycerol: stabilization of paraformaldehyde in glycerol resulted from using dimedone as substrate. Adv Synth Catal. 2010;352(2–3):519–30.
Lomba L, et al. Physicochemical properties of green solvents derived from biomass. Green Chem. 2011;13(8):2062–70.
Marciniak A. The solubility parameters of ionic liquids. Int J Mol Sci. 2010;11(5):1973–90.
Marion P, et al. Sustainable chemistry: how to produce better and more from less? Green Chem. 2017;19(21):4973–89.
Matsui HKK, Hayashi H. Aldol reactions of propanal using MgO catalyst in supercritical CO2. In: Studies in surface science and catalysis. Amsterdam: Elsevier; 2004. p. 363–8.
Melo CI, et al. Advantageous heterogeneously catalysed hydrogenation of carvone with supercritical carbon dioxide. Green Chem. 2011;13(10):2825–30.
Otto S, Engberts JB. Hydrophobic interactions and chemical reactivity. Org Biomol Chem. 2003;1(16):2809–20.
Oyama K. In: Collins AN, Sheldrake GN, Crosby J, editors. Chirality in Industry. Chichester: Wiley; 1992.
Ren W, Rutz B, Scurto AM. High-pressure phase equilibrium for the hydroformylation of 1-octene to nonanal in compressed CO2. J Supercrit Fluids. 2009;51(2):142–7.
Roukoss C, et al. Emerging strategies in catalysis. Dalton Trans. 2007;5572:5581.
Sahle-Demessie E, Devulapelli VG, Hassan AA. Hydrogenation of anthracene in supercritical carbon dioxide solvent using Ni supported on Hβ-zeolite catalyst. Catalysts. 2012;2(1):85–100.
Schaeffner B, et al. Organic carbonates as alternative solvents for palladium-catalyzed substitution reactions. ChemSusChem. 2008;1(3):249–53.
Schäffner B, et al. Rhodium-catalyzed asymmetric hydrogenation with self-assembling catalysts in propylene carbonate. Tetrahedron Lett. 2008;49(5):768–71.
Schäffner B, et al. Organic carbonates as alternative solvents for asymmetric hydrogenation. Chirality. 2009;21(9):857–61.
Shanab K, et al. Green solvents in organic synthesis: an overview. Curr Org Chem. 2013;17(11):1179–87.
Shapiro N, Vigalok A. Highly efficient organic reactions “on water”, “in water”, and both. Angew Chem Int Ed. 2008;47(15):2849–52.
Sheldon RA. Green solvents for sustainable organic synthesis: state of the art. Green Chem. 2005;7(5):267–78.
Suresh, Sandhu JS. Recent advances in ionic liquids: green unconventional solvents of this century: part I. Green Chem Lett Rev. 2011a;4(4):289–310.

Suresh, Sandhu JS. Recent advances in ionic liquids: green unconventional solvents of this century: part II. Green Chem Lett Rev. 2011b;4(4):311–20.

Tan J-N, Li M, Gu Y. Multicomponent reactions of 1, 3-disubstituted 5-pyrazolones and formaldehyde in environmentally benign solvent systems and their variations with more fundamental substrates. Green Chem. 2010;12(5):908–14.

ten Brink G-J, Arends IW, Sheldon RA. Green, catalytic oxidation of alcohols in water. Science. 2000;287(5458):1636–9.

Tsuji K, Ishikawa H. Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7. Bioorg Med Chem Lett. 1994;4(13):1601–6.

Vollmer C, Thomann R, Janiak C. Organic carbonates as stabilizing solvents for transition-metal nanoparticles. Dalton Trans. 2012;41(32):9722–7.

Wegman MA, et al. Towards biocatalytic synthesis of β-lactam antibiotics. Adv Synth Catal. 2001;343(6–7):559–76.

Wu T, Han B. Supercritical carbon dioxide (CO 2) as green solvent. In: Innovations in green chemistry and green engineering. New York: Springer; 2013. p. 297–326.

Xin-hua Y, et al. Friedel–Crafts acylation of anthracene with oxalyl chloride catalyzed by ionic liquid of [bmim] cl/AlCl3. Chem Eng J. 2009;146(2):266–9.

Yuan Y, et al. Enzyme-catalyzed Michael addition for the synthesis of warfarin and its determination via fluorescence quenching of L-tryptophan. Spectrochim Acta A Mol Biomol Spectrosc. 2017;176:183–8.

# Boric Acid: A Versatile Catalyst in Organic Synthesis

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0_17

# 1 Introduction

In recent years, a paradigm of chemical synthesis has shifted towards green chemistry approach as environmental safety is compromised with the use of organic solvents. Thus, to implement an environment-friendly approach, researchers stand in a need of water-compatible catalysts to establish a library compound of pharmacologically important moieties with distinct properties.

Over the past decade, boric acid has earned exceptional interest by playing a role of catalyst in organic synthesis because of commercial availability, its excellent solubility in water, environmental stability, ease of handling, inexpensiveness and eco-friendly nature. It is recently proven to be a good substitute for conventional acidic catalytic materials (Tu et al. 2003; Maki et al. 2005).

Boric has displayed its catalytic efficiency in various organic transformations such as amidation, esterification, Michael addition, transesterification, ipso-hydroxylation, Biginelli reaction, decarboxylation, halogenation reaction, condensation reactions, Friedel-Crafts reactions, Tishchenko reactions, reactions involving protection and deprotection of functional groups and multicomponent reactions involved in the synthesis of nitrogen and oxygen heterocycles. This review highlights application of boric acid in green chemistry with prominence on recent synthetic applications.

# 2 Synthetic Application of Boric Acid

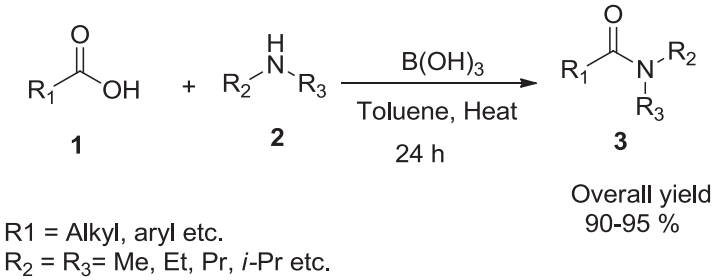
## *2.1 Amidation Reactions*

Amidation reactions are defined as the condensation of amines with carboxylic acids with or without catalysts under thermal conditions. Amide derivatives were known as a precursor in the synthesis of numerous pharmaceutically active drugs of synthetic as well as natural origin (Ghose et al. 1999; Bhattacharya and Bandichhor 2011).

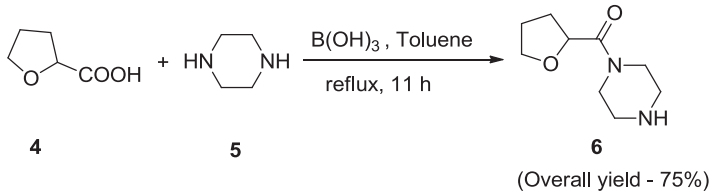
The classical approach to carry out amidation reactions requires extremely harsh conditions in the absence of catalysts which render it as an unattractive approach.

Sabatini et al. recently reported boric acid-catalysed protocol for amidation reaction. The process involves refluxing of carboxylic acid **1** with amine **2** in toluene for 24 h to get amide product **3** with 90–95% overall yield (Scheme 1). Following this approach, efficiency of the reaction is improved over other catalytic amidation methods (Sabatini 2017). Further exploration of above studies revealed that boric acid catalysts were found highly efficient in scale-up of amidation reactions even at kilo scale (Sabatini 2019).

Mylavarapu and co-workers reported approach which involves refluxing of **4** and **5** in toluene for 11 hours to obtain carboxamide derivative **6** in good yield under the influence of boric acid catalyst (Scheme 2) (Mylavarapu 2007).




**Scheme 1** Boric acid promoted amidation reaction




**Scheme 2** Boric acid promoted amidation reaction for the synthesis of terazosin

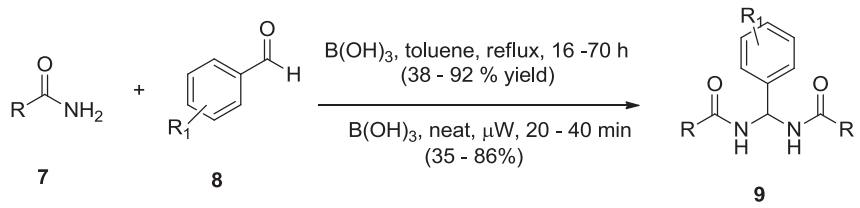
Literature review suggests bisamides as an important element of biologically useful scaffold. A suitable scheme for the synthesis of symmetrical α-bisamides **9** involves condensation reaction between amide **7** and aromatic aldehyde **8** under the influence of boric acid. This reaction was carried out with classical thermal approach as well as in microwave conditions free from solvent. This protocol resulted into moderate to good yields of the product (Scheme 3) (Harichandran 2011).

## *2.2 Esterification Reactions*

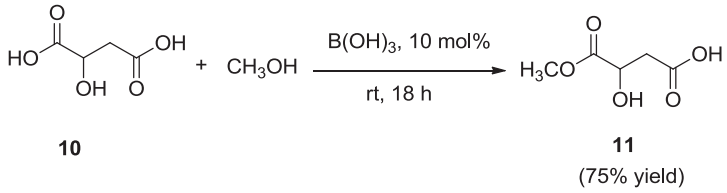
Esterification reactions are the most common and widely used reactions in organic synthesis, for the synthesis of pharmaceuticals, perfumes and cosmetics. In preparation of lactones, esterification reaction is important. Also, these reactions are utilized in natural product synthesis, in reactions of carboxylic acids. Boric acid-catalysed esterification reactions are listed below.

### 2.2.1 Carboxylic Acids

The esterification of α-hydroxy bearing carboxylic acid was catalysed by boric acid to yield monoester. This process involves the reaction of malic acid (**10**) (possessing an α-hydroxyl group) and methanol under the influence of boric acid at




**Scheme 3** Boric acid-catalysed synthesis of bisamides




**Scheme 4** Esterification of carboxylic acid catalysed by boric acid

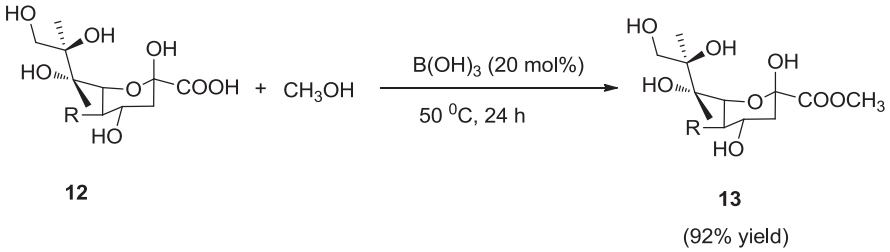
room temperature for overnight to obtain monoester **11** (Scheme 4). The carboxylic group concerning with β-hydroxy group remains unchanged during the reaction (Houston et al. 2004).

### 2.2.2 Sugar Acids

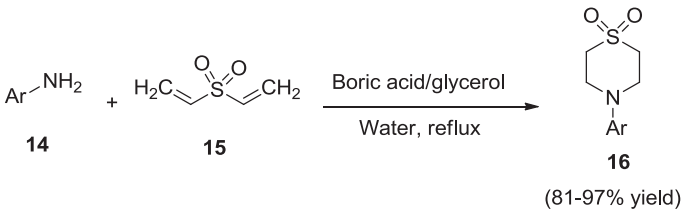
The esterification of sugar acids with methanol was brought about with the help of boric acid. This approach is highly substrate specific and can proceed efficiently in certain sugar acid molecules. As depicted in Scheme 5, a sugar acid substrate **8** reacted with methanol in the presence of boric acid catalyst at 50 °C. The reaction resulted into 90% yield of methyl ester (Levonis 2014).

## *2.3 Michael Addition Reactions*

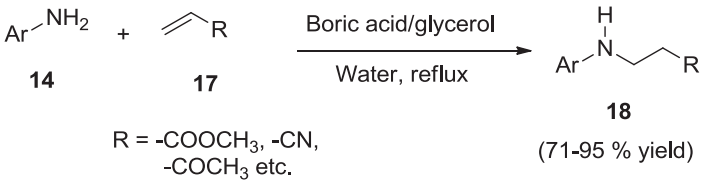
The α,β-unsaturated carbonyl compound undergoes nucleophilic addition by following Michael addition reaction mechanism (Lowrance 1971; Houston et al. 2004). There are two types of Michael addition reported in the literature represented below.




**Scheme 5** Boric acid-catalysed esterification




**Scheme 6** Aza-Michael addition reaction catalysed by boric acid



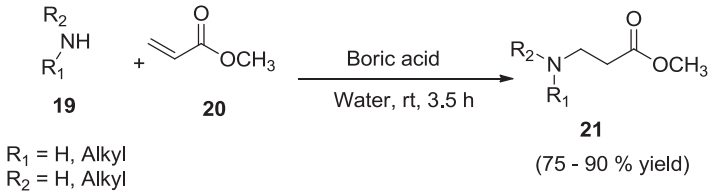

**Scheme 7** Boric acid promoted aza-Michael addition reaction of alkenes

### 2.3.1 Aza-Michael Addition Reaction

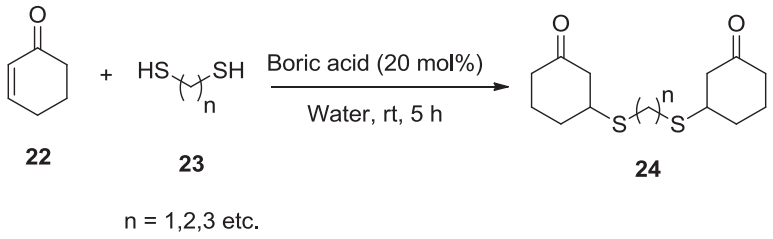
When Michael addition took place via nitrogen atom it is termed as Aza-Michael addition. For example, aromatic amines **14** refluxed with divinyl sulfone **15** with water to yield N-substituted thiomorpholine-1,1-dioxides **16** in good to excellent amount (Scheme 6).

However, the terminal alkenes **17** added to aromatic amines also follow a similar type of reaction to yield β-amino esters/ketones/nitriles **18** (Scheme 7) (Halimehjnai 2013).

Chaudhuri et al. also reported synthetic procedure in which primary/secondary alkyl amine **19** reacted with acrylate esters **20** in water under catalytic influence of




**Scheme 8** Aza-Michael addition of amine in presence of boric acid




**Scheme 9** Boric acid-catalysed thia-Michael addition reaction

boric acid. The corresponding addition product **21** was obtained in good to excellent yield (Scheme 8) (Chaudhuri 2005).

Conversely when Michael addition takes place with addition of sulphur it is known as thia-Michael addition reaction. Generally, aliphatic or aromatic thiols undergo this type of reaction with α,β-unsaturated compounds to yield the corresponding product.

For example, addition to cyclohexenone **22** by dithiol analogues **23** in water catalysed by boric acid is a type of thia-Michael addition reaction. Good yields of the corresponding product **24** were obtained with this approach (Scheme 9). A similar type of reactions can be observed with esters, nitriles and aldehydes (Chaudhuri and Hussain 2007).

## *2.4 Condensation Reactions*

Boric acid can effectively catalyse crossed aldol condensation of aldehydes with ketones to yield α,β-unsaturated carbonyl compounds, which tend to exhibit numerous biological activities (Wang 2003; Das 2010). Also they find application in the synthesis of agrochemicals, pharmaceuticals and perfumes as an intermediate (Pal 2009; Pal et al. 2011). Boric acid also catalyses the condensation of carbonyl compounds with indoles to give bis-(3-indolyl)methane as well as pyrrole to yield dipyrromethanes which are very well known for the biological activities (Shiri et al. 2009).

### 2.4.1 Condensation with Methylene

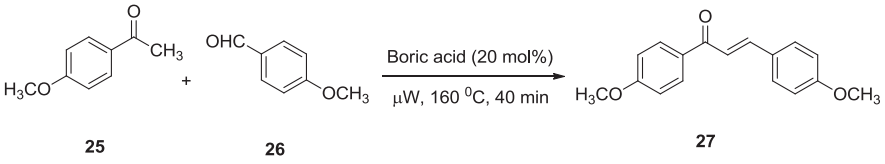
Example of condensation reaction involves microwave irradiated conversion of **25** and **26** catalysed by Lewis acid catalyst without solvent. In this reported reaction boric acid functions as catalyst. The product obtained was **27** in very good yields (Scheme 10) (Brun 2015).

Offenhauer and Nelsen reported a similar type of condensation reaction to form α,β-unsaturated ketones (Offenhauer and Nelsen 1968).

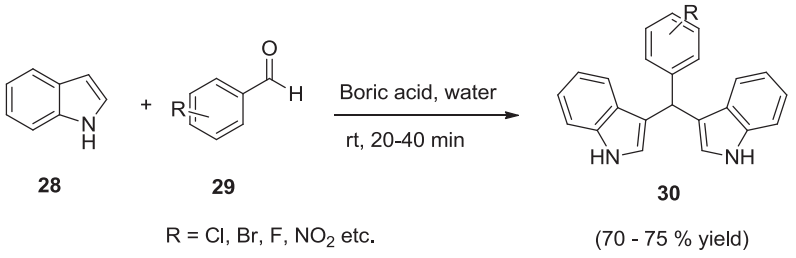
### 2.4.2 Condensation with Indoles

Meshram et al. explored the utility of boric acid in the condensation of **28** with **29** for the synthesis of diindolylmethane **30**. They reported that aromatic aldehyde was stirred with indole at room temperature using water under the influence of boric acid; the desired product **30** was formed within 20–40 min in high yield (Scheme 11) (Meshram et al. 2013). Yadav et al. reported the same condensation reaction under solvent-free conditions (Yadav 2010).

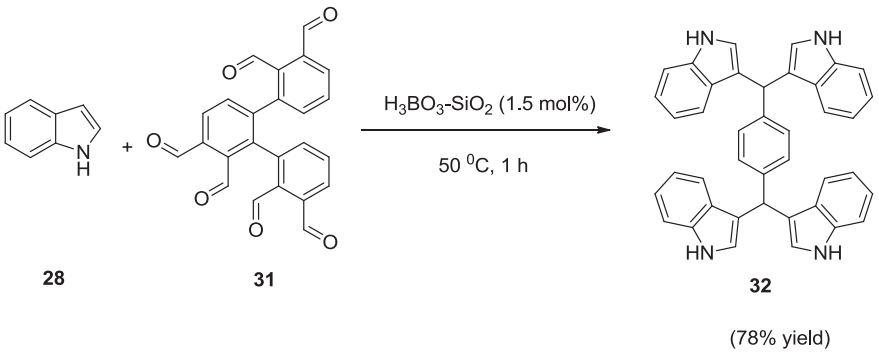
Kumar and his group reported the synthesis of bisindolylmethane and tetra-indolyl derivatives by the condensation of indoles **28** with dialdehydes such as terephthalaldehyde **31**, at room temperature catalysed by silica-supported boric acid to give tetra-indole derivative **32**, respectively (Scheme 12) (Kumar et al. 2014a, b).



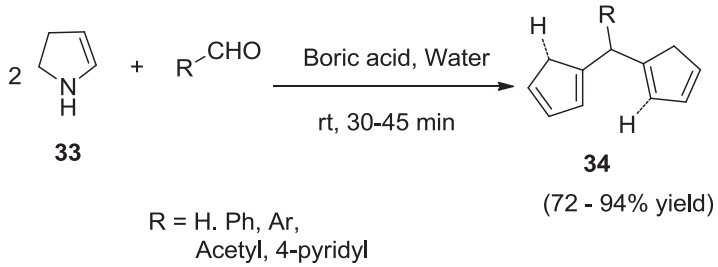

**Scheme 10** Crossed aldol condensation reaction catalysed by boric acid




**Scheme 11** Boric acid-catalysed crossed aldol condensation reaction




**Scheme 12** Silica supported boric acid-catalysed condensation reaction



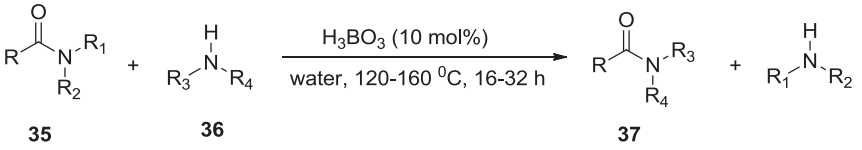

**Scheme 13** Boric acid-catalysed synthesis of dipyrromethane

### 2.4.3 Condensation with Pyrrole

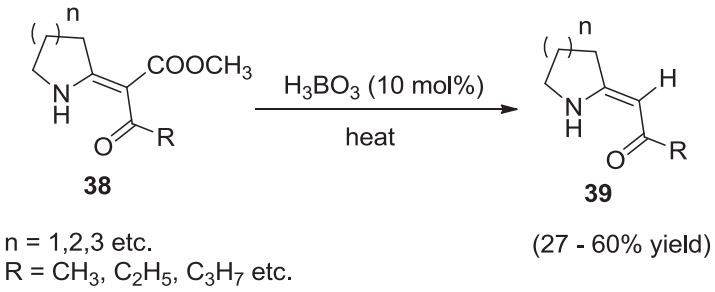
Pratibha and co-workers reported another effortless and well-organized methodology for the synthesis of dipyrromethane **34** where boric acid found useful (Pratibha 2014). Under this protocol, one equivalent of aldehyde was reacted with pyrrole in the water at room temperature under the influence of boric acid to obtain **34** in good yield (Scheme 13). Singhal et al. also reported the same protocol in an aqueous medium, using boric acid (Singhal et al. 2016).

## *2.5 Transamidation Reactions*

Transamidation reactions are the type of a chemical conversion in which an amide reacts with an amine to generate a new amide moiety. This type of conversion typically takes a longer time for its completion. However, use of the catalyst can accelerate transamidation reaction (Baker 2016). Reaction protocol involves mixing up




**Scheme 14** Boric acid-catalysed transamidation reaction




**Scheme 15** Boric acid–catalysed decarboxylation reaction

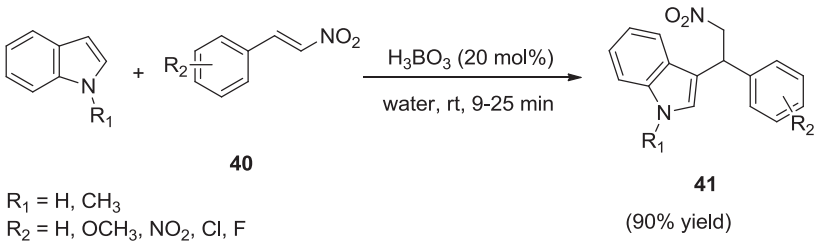
of **35** and **36** in water with boric acid in stoichiometric amount which was heated for a sufficient time to obtain transamidation products **37** with 42–90% yields (Scheme 14) (Nguyen et al. 2012).

## *2.6 Decarboxylation Reactions*

In organic chemistry, the reactions involving the replacement of a carboxyl group (-COOH) with a hydrogen atom are known as decarboxylation reactions. Simple carboxylic acid does not undergo decarboxylation since the presence of β-carbonyl group facilitates decarboxylation at relatively low temperatures (Ouelette and Rawn 2014). One of the reported methods for the synthesis of cyclic β-enaminone **39** was decarboxylation of β-enaminoketoester **38** catalysed by boric acid. In this method, decarboxylation of β-enaminoketoesters **38** was carried out with the help of thermolysis under catalytic influence of boric acid (Scheme 15) (Delbecq et al. 1990).

## *2.7 Friedel-Crafts Reactions*

Aromatic and heteroaromatic compounds undergo carbon-carbon bond-forming reaction through Friedel-Crafts reactions (Marsi and Wilen 1963). There are two types of FC reactions reported in the literature, i.e. Friedel-Crafts alkylation and




**Scheme 16** Boric acid–catalysed Friedel-Crafts alkylation reaction

acylation reactions. Interestingly, both types of reactions have been reported using boric acid catalyst in the literature.

### 2.7.1 Alkylation Reactions

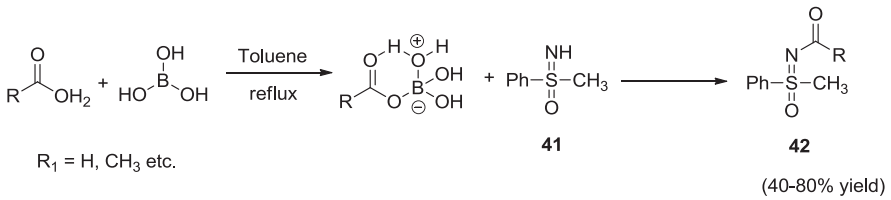
When an alkyl group added to the aromatic or heteroaromatic ring forming C-C bond with the loss of a C-H bond is known as Friedel-Crafts alkylation reactions. Meshram and co-workers reported the utility of boric acid for the substitution of alkyl group on activated nitrostyrene. They reported boric acid-catalysed Friedel-Crafts alkylations of indoles using various nitrostyrene **40** in water to yield the nitroalkylated product **41** with good yield (Scheme 16) (Meshram et al. 2010).

### 2.7.2 Acylation Reactions

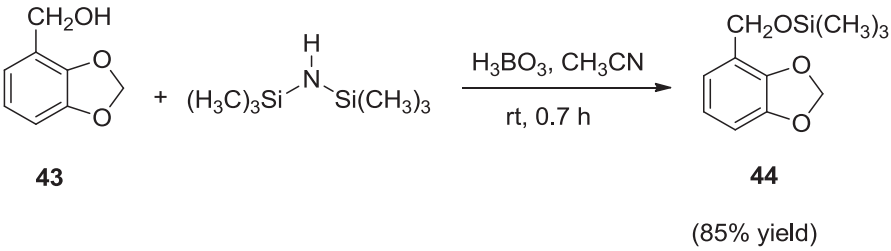
Friedel-Crafts acylation reactions are the electrophilic aromatic substitution type of reaction which allows the synthesis of monoacylated products from the reaction between arenes and acyl donor. Reported literature reveals boric acid-catalysed synthesis of a series of N-acylsulfoximines **42** by acylation of sulfoximines **41** in toluene under reflux conditions (Scheme 17) (Garimallaprabhakaran and Harmata 2011). In this reaction, carboxylic acid acts as an acyl donor. Boric acid catalyses formation of reactive acyl group from the carboxylic acid, which gets substituted on **41** to yield acylation products **42** with yield in the range of 40–80%.

## *2.8 Protection and Deprotection Reactions*

In organic chemistry, protection and deprotection of reactive functional groups such as amines, alcohols, thiols and phenols are widely used strategies for multistep synthesis of various bioactive natural products (Green and Wuts 1991; Kocienski 1994).




**Scheme 17** Boric acid–catalysed Friedel-Crafts acylation reaction



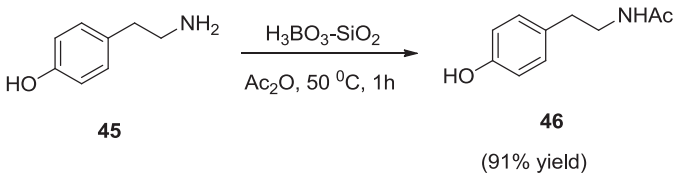

**Scheme 18** Boric acid–catalysed trimethylsilylation of alcohol

Examples highlighted below explain application of boric acid as an eco-friendly catalyst in the protection of alcohols and amines and deprotection of ethers to corresponding alcohols and phenols.

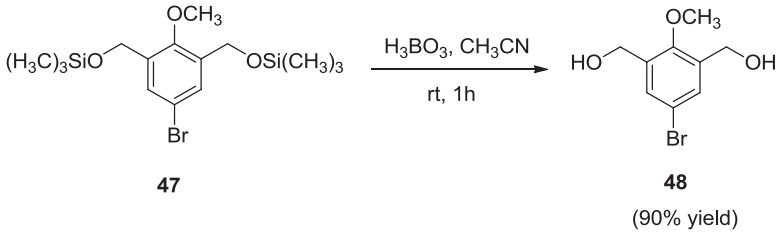
### 2.8.1 Protection Reactions

Rostami et al. reported that protection of -OH, -SH and $–NH_2$ groups can be achieved through trimethysilylation under the influence of boric acid in a catalytic amount. Thus, treating of compound **43** with hexamethyldisilazane (HMDS) in acetonitrile at room temperature under the catalytic influence of boric acid, the corresponding product **44** was obtained in 85% yield as depicted in Scheme 18 (Rostami et al. 2010). Similar reaction protocol was followed, in order to achieve protection of thiols and amines through silylation.

Kumar et al. demonstrated the chemoselective acetylation of amines efficiently achieved under the influence of silica-supported boric acid. Under this protocol, when tyramine **45** was treated with acetic anhydride in the presence of silica-supported boric acid at 50 °C, acetylated product **48** was obtained in excellent yields (Scheme 19) (Kumar et al. 2014a). Similarly, acetylation of 2-aminoethanol can be achieved.




**Scheme 19** Boric acid–catalysed acetylation of amine




**Scheme 20** Boric acid-catalysed deprotection of trimethylsilyl ether

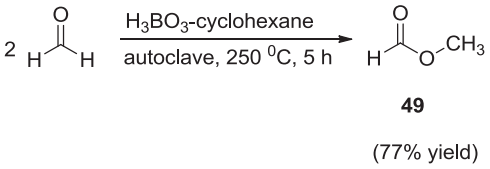
### 2.8.2 Deprotection of Alcohols and Phenols

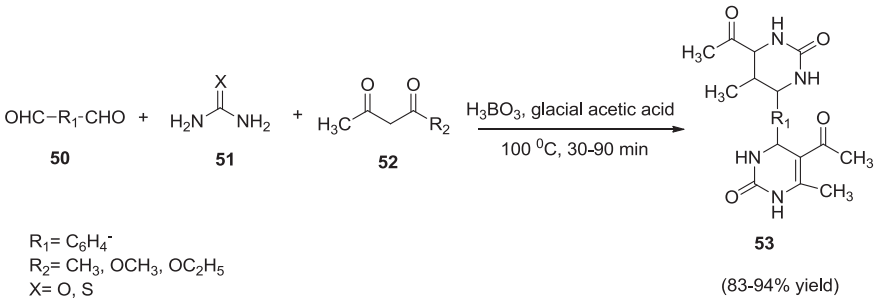
Deprotection reactions are the procedures by which a protecting group is modified into a functional group. Boric acid has been reported as a catalyst to achieve deprotection with good yields. For example: **47** was selectively undergone deprotection reaction to yield the corresponding phenol **48** under the catalytic influence of boric acid at room temperature using water with 90% yield as depicted in Scheme 20 (Rostami et al. 2010).

## *2.9 Tishchenko Reactions*

The Tishchenko reaction is an organic disproportionation reaction that involves preparation of esters from an aldehyde in the presence of catalyst. It is named after the Russian organic chemist Vyacheslav Tishchenko. Esters have been effectively formed from corresponding aldehydes by employing boric acid catalyst. For example, boric acid acts as a catalyst in conversion of paraformaldehyde at 250 °C in cyclohexane, to obtain a methyl formate **49** with a 77% yield (Scheme 21) (Stapp 1973).

**Scheme 21** Boric acid–catalysed Tishchenko reaction




**Scheme 22** Boric acid–catalysed one-pot synthesis of bis-dihydropyrimidinones

## *2.10 Multicomponent Reactions*

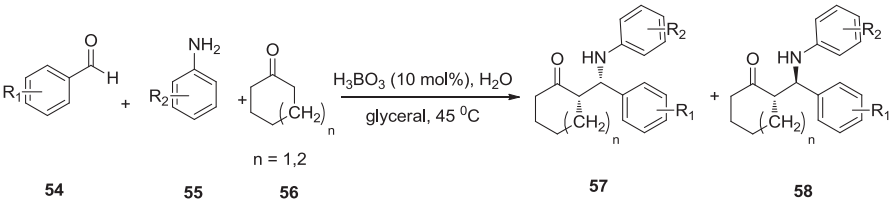
Multicomponent reactions (MCRs) are a highly preferred synthesis approach owing to their efficiency, speed and diversity (Lu and Bai 2002; Sarada et al. 2009). MCRs are useful for creating a library of bioactive heterocycles conveniently in drug discovery programmes, which may deliver drug-like properties in the future (Eckert 2012). Some of the boric acid-catalysed MCRs has been listed below.

### 2.10.1 Biginelli Reactions

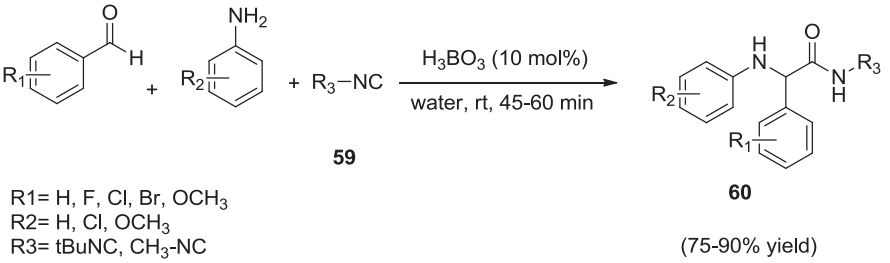
Boric acid also finds its application in carrying out of Biginelli reactions. It involves reaction of dialdehydes **50** and urea or thiourea **51** with β-dicarbonyl compounds **52** to afford bis-dihydropyrimidinone derivatives **53** using glacial acetic acid as a solvent (Scheme 22) (Tu et al. 2005). Another reported Biginelli reaction where boric acid functions as a catalyst involves synthesis of dihydropyrimidinone derivatives (Tu 2003).

### 2.10.2 Mannich Reactions

Mannich reaction can be successfully utilized in the synthesis of β-aminocarbonyl compounds (**57**, **58**) via one-pot synthesis approach involving aromatic amines, aromatic aldehydes and cyclic ketones under the influence of catalyst boric acid




**Scheme 23** Boric acid–catalysed Mannich reaction




**Scheme 24** Boric acid–catalysed Ugi three-component reactions

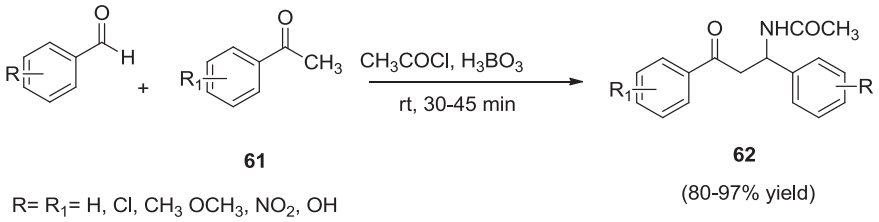
and glycerol mixture in water at ambient temperature with good yields (Scheme 23) (Mukhopadhyay et al. 2009). Boron chelate complex (BCC) formed by the interaction of boric acid and glycerol in water tends to release hydrogen ion, thereby increasing the acidic character of the medium which ultimately results in increased yield of the Mannich reactions.

### 2.10.3 Ugi Three-Component Reaction

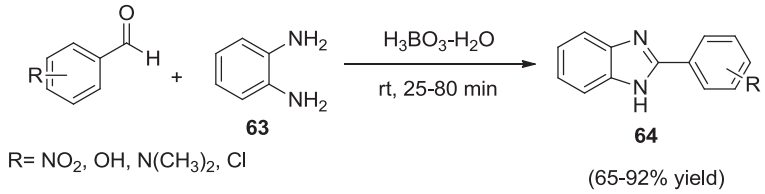
Kumar and co-workers reported Ugi approach for the synthesis of 2-arylamino-2-phenylacetamide **60**. The desired compound **60** has been synthesized efficiently through boric acid–catalysed one-pot reaction of isocyanide, aldehydes and amine in water as depicted in Scheme 24 (Kumar et al. 2013).

### 2.10.4 Synthesis of β-Acetamido Ketones

A synthesis of β-acetamido ketones **62** via one-pot boric acid-catalysed reaction of aromatic aldehydes, acetophenones **61** and acetonitrile has been reported. Researchers for the first time reported boric acid–catalysed preparation of β-acetamido ketones (Scheme 25) (Karimi-Jaberi and Mohammadi 2012).




**Scheme 25** β-Acetamido ketone synthesis catalysed by boric acid




**Scheme 26** Boric acid–catalysed synthesis of benzimidazoles

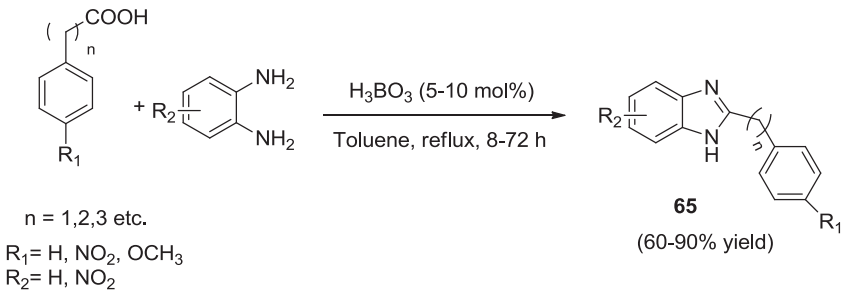
## *2.11 Development of Nitrogen Heterocycles*

Nitrogen heterocycles function as the pharmacophore of most of biologically important compounds. Numerous pharmaceutical and agrochemical products possess benzimidazole (Roth et al. 1997) and benzodiazepine (Schutz 1982) systems as an important constituents. Vasorelaxant activity associated with fused pyrimidines has been well known in the reported literature (Atwal and Moreland 1991). Quinazolinone derivatives have been known for their anticancer and anti-HIV properties (Alagarsamy et al. 2004). A number of natural products which are pharmacologically active possess mostly imidazole (Hunkeler et al. 1981) and pyridine (Reddy et al. 2006) systems as a core structure. Interestingly, boric acid is a well-established catalyst for the synthesis of these important nitrogenous heterocycles as represented below.

### 2.11.1 Synthesis of Benzimidazoles

Rajale and Patil reported a synthesis of substituted benzimidazoles **76** catalysed by boric acid as shown in Scheme 26 (Rajale and Patil 2015).

The same approach was also reported by Heravi and Ashori (Heravi and Ashori 2013).




**Scheme 27** Boric acid–catalysed cyclocondensation reaction

Maras and Kocevar reported a boric acid–catalysed synthesis of a series of 2-substituted benzimidazoles **65** via a cyclocondensation reaction between substituted carboxylic acids and *o*-phenylenediamine in toluene under reflux conditions as represented in Scheme 27 (Maras and Kocevar 2011).

### 2.11.2 Synthesis of Benzodiazepines

Researchers have reported excellent catalytic efficiency of boric acid in the synthesis of benzodiazepine derivatives **66**. This reaction proceeds with refluxing enolizable ketones with *o*-phenylenediamine in n-hexane under the influence of boric acid to obtain **66** in excellent yields as represented in Scheme 28 (Zhou et al. 2009). Both aromatic and aliphatic ketones respond to this approach with same efficiency.

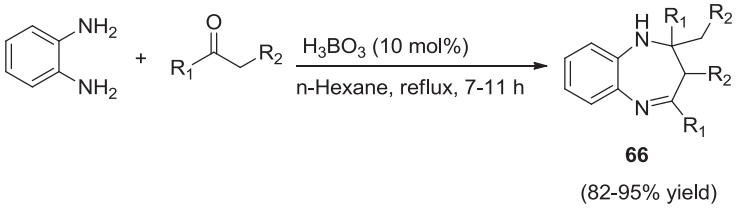
Gholap and Tambe previously reported the same approach at room temperature using boric acid catalyst (Gholap and Tambe 2008).

### 2.11.3 Synthesis of Fused Thiazolopyrimidines

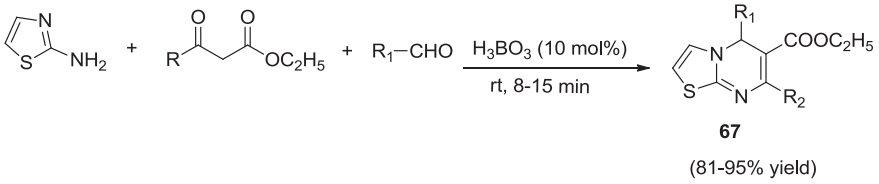
Meshram et al. reported a simplistic and proficient protocol for the synthesis of fused thiazolopyrimidines (**81**) under eco-friendly conditions by employing aldehydes, heterocyclic amine and β-keto ester to undergo reaction under the influence of boric acid. The product is obtained in moderate to excellent yields as represented in Scheme 29 (Meshram et al. 2012).

### 2.11.4 Synthesis of Quinazolinones

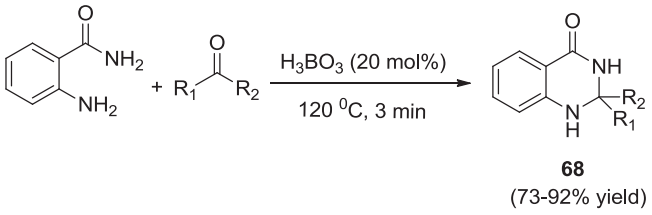
Karimi-Jaberi and Zarei reported an efficient method to synthesize 2-substituted-2,3-dihydro-4(*1H*)-quinazolinones **68** as represented in Scheme 30 (Karimi-Jaberi and Zarei 2012).




**Scheme 28** Boric acid–catalysed synthesis of benzodiazepines




**Scheme 29** Boric acid–catalysed synthesis of fused thiazolopyrimidines

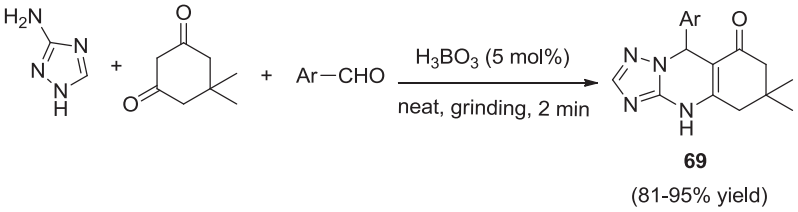



**Scheme 30** Boric acid–catalysed synthesis of 2,3-dihydro-4(1H)-quinazolinones

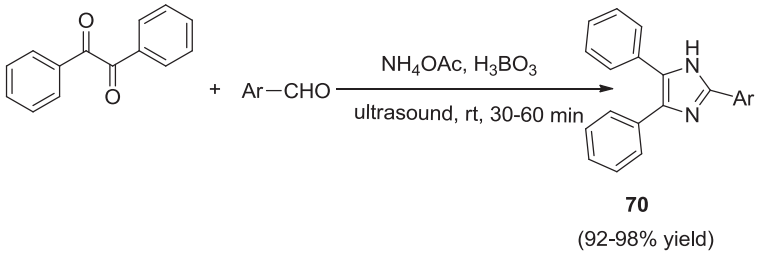
Shaikh et al. reported condensation of dimedone, 3-amino-1,2,4-triazole and aldehydes under the catalytic influence of boric acid to yield [1,2,4]triazoloquinazolinone derivatives **69** as represented in the Scheme 31 (Shaikh et al. 2014).

### 2.11.5 Synthesis of Imidazoles

Imidazole derivatives have also been synthesized by boric acid catalysis. Shelke and co-workers synthesized a library of 2,4,5-triaryl-1*H*-imidazole derivatives **70** by the reaction of benzil with ammonium acetate and aldehydes in aqueous medium at room temperature as represented in Scheme 32. However, benzoin reacts slowly with aldehyde in somewhat lesser yield (Shelke et al. 2009).




**Scheme 31** Boric acid–catalysed synthesis of triazoloquinazolinones




**Scheme 32** Boric acid–catalysed synthesis of imidazoles under ultrasound irradiation

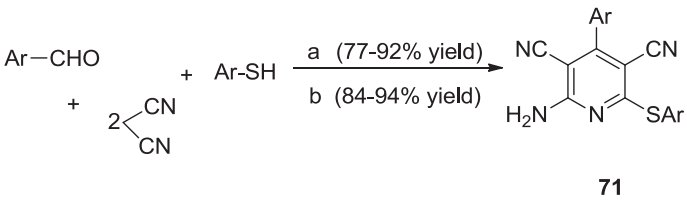
### 2.11.6 Synthesis of Pyridines

Boric acid along with CTAB promotes synthesis of substituted pyridines **71** through the condensation of an aldehyde, malononitrile and thiophenol in water as represented in Scheme 33 (Shinde et al. 2010).

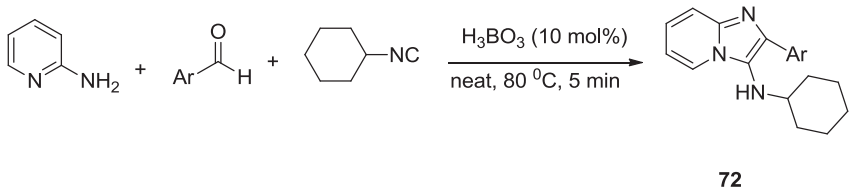
Karimi-Jaberi and Ghasemi reported boric acid–catalysed one-pot three-component synthesis of imidazo[1,2-*a*]pyridine derivatives **72** from the condensation of aromatic aldehydes, 2-aminopyridines and cyclohexyl isocyanide under solvent-free conditions as represented in Scheme 34 (Karimi-Jaberi and Ghasemi 2017).

## *2.12 Development of Oxygen Heterocycles*

Oxygen heterocycles represent another important class of biologically important compounds. Numerous oxygen heterocycles function as a pharmacophore for biological activities for example benzopyrans serves as the backbone of several natural products also mark their presence in a recently discovered class of benzotripyrans functions as HIV inhibitory compounds (Tang et al. 2006) as well as xanthenes possessing antibacterial and antiviral activities (Ion et al. 1998). Interestingly, boric




**Scheme 33** Synthesis of 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles




**Scheme 34** Boric acid–catalysed synthesis of imidazo[1,2-α]pyridine derivatives

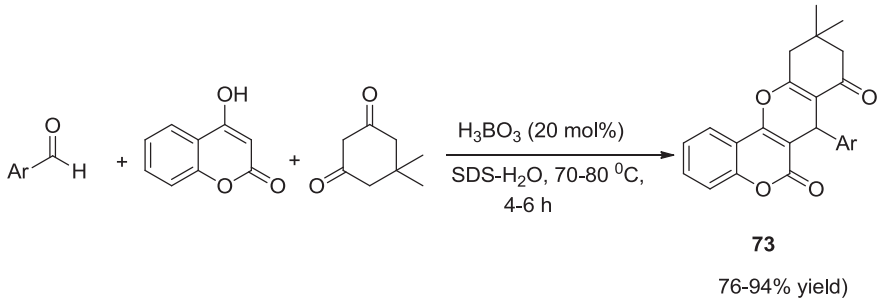
acid functions as an efficient catalyst for the synthesis of oxygen heterocycles as presented below.

### 2.12.1 Synthesis of Benzopyrano-benzopyrans

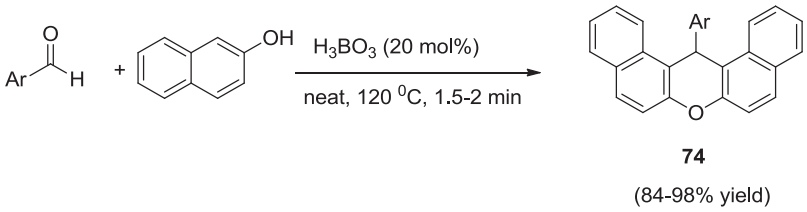
Ganguly and his group reported synthesis of 7-arylbenzopyrano derivative **73** via reaction of an aromatic aldehyde, 4-hydroxycoumarin and dimedone catalysed by boric acid under aqueous micellar conditions as depicted in Scheme 35 (Ganguly et al. 2014). The attractive features of this procedure include high selectivity, good to excellent yields and avoidance of organic solvent in the reactions as well as the use of a Lewis acid catalyst, rendering it a green highly acceptable protocol.

### 2.12.2 Synthesis of Dibenzoxanthenes

Karimi-Jaberi and Keshavarzi reported a simple and reliable solvent-free one-pot synthesis of biologically important 14-substituted-14*H*-dibenzo[*a,j*]xanthenes **74** from a condensation of aldehydes with β-naphthol in the presence of boric acid with high yield as represented in Scheme 36 (Karimi-Jaberi and Keshavarzi 2010).




**Scheme 35** Boric acid–catalysed synthesis of benzopyrano-benzopyrans



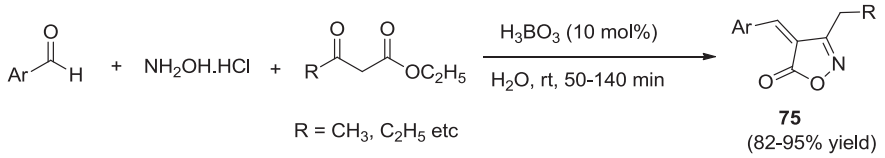

**Scheme 36** Synthesis of dibenzoxanthenes

## *2.13 Synthesis of Isoxazolinones*

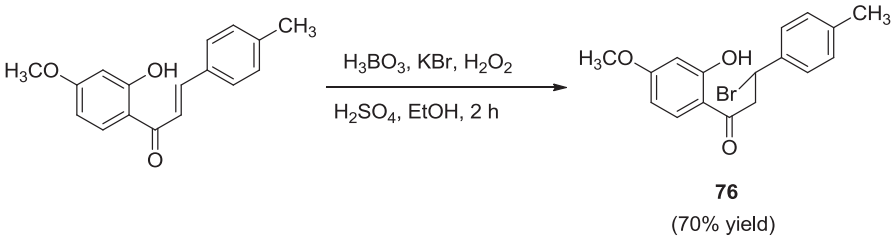
Very recently, Klyani and Ghorbani demonstrated boric acid–catalysed preparation of 4*H*-isoxazol-5-ones **75** from aryl aldehyde, hydroxylamine hydrochloride and β-keto ester in water as represented in Scheme 37 (Klyani and Ghorbani 2015).

## *2.14 Bromination Reactions*

Nath and Chaudhury reported the synthesis of bromo-organic derivatives with very high selectivity towards product formation yielding products in excellent quantity (Nath and Chaudhury 2008). Under this protocol, substituted anilines, phenols, aromatic ketones, styrene, imidazole and dibenzylideneacetone compounds undergo bromination. For example, as represented in Scheme 37, selective bromination of 4,4′-dimethoxy-2′-hydroxychalcone was carried out in the presence of very small amount of $H_2SO_4$ and 30% $H_2O_2$ under the influence of boric acid with KBr (Scheme 38).




**Scheme 37** Synthesis of isoxazolinones




**Scheme 38** Boric acid–catalysed selective bromination

## *2.15* Ipso *Substitution Reactions*

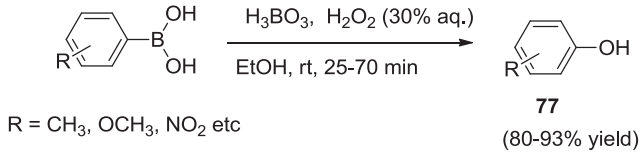
Boric acid–catalysed *Ipso* substitution reactions have also been reported in the literature. Gogoi et al. reported a simplistic one-pot boric acid–catalysed synthetic procedure for *ipso* hydroxylation of arylboronic acids to afford corresponding phenols in ethanol at room temperature as represented in Scheme 39 (Gogoi et al. 2014).

## *2.16 Synthesis of 1-Amidoalkyl-2-naphthols*

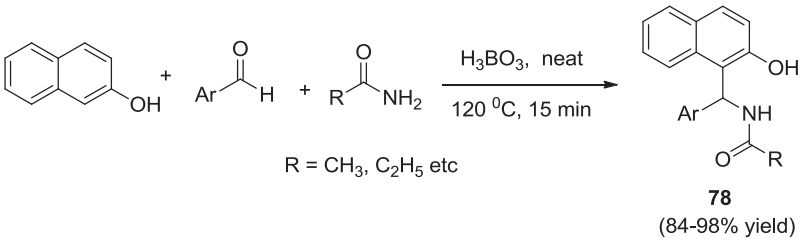
A boric acid-catalysed synthesis of 1-amidoalkyl-2-naphthols **78** through one-pot solvent-free condensation of 2-naphthol, amides and aldehydes in the presence of boric acid with good yields as represented in Scheme 40 (Karimi-Jaberi and Fakhraei 2012).

## *2.17 Synthesis of α-Aminophosphonates and α-Aminonitriles*

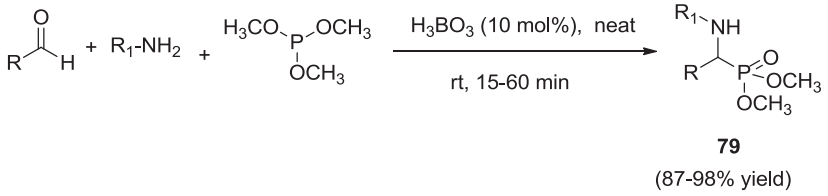
Karimi-Jaberi and Amiri reported a facile one-pot solvent-free condensation between aldehydes, amines and trimethyl phosphite catalysed by boric acid for the synthesis of α-aminophosphonates **79** at room temperature as represented in Scheme 41 (Karimi-Jaberi and Amiri 2010).




**Scheme 39** Boric acid–catalysed *ipso* substitution reactions




**Scheme 40** Boric acid–catalysed synthesis of 1-amidoalkyl-2-naphthols

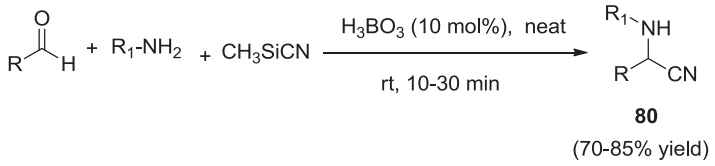



**Scheme 41** Boric acid–catalysed synthesis of α-aminophosphonates

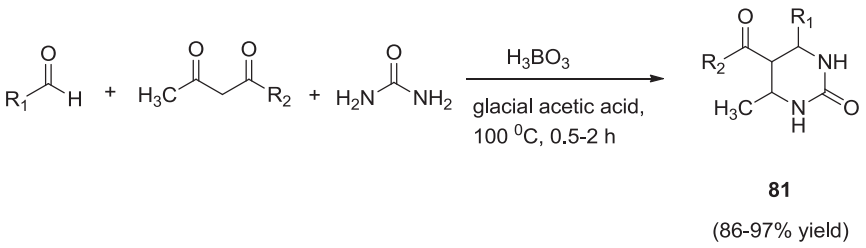
Karimi-Jaberi et al. reported one-pot solvent-free condensation of aromatic amine, aldehyde and trimethylsilyl cyanide catalysed by boric acid to synthesize α-aminonitriles **80** as represented in Scheme 42 (Karimi-Jaberi and Abdolaziz 2012).

## *2.18 Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones*

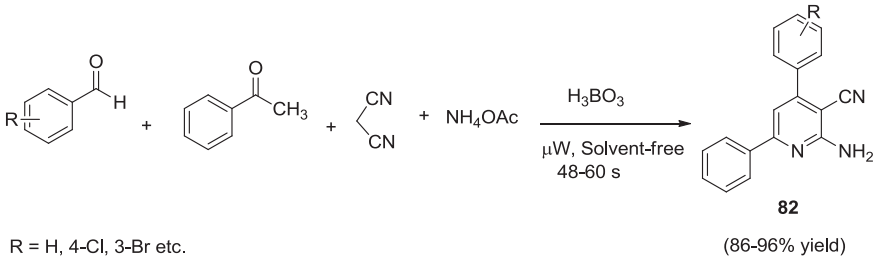
Researchers also reported a simple effective synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives **81** catalysed by boric acid as depicted in Scheme 43. It involves reaction of urea, aromatic aldehydes and 1,3-dicarbonyl compounds under the influence of boric acid catalyst using glacial acetic acid as a solvent.




**Scheme 42** Synthesis of α-aminonitriles




**Scheme 43** Boric acid–catalysed synthesis of 3,4-dihydropyrimidin-2(1H)-ones




**Scheme 44** Boric acid–catalysed synthesis of 2-amino-4,6-diarylnicotinonitrile

## *2.19 Synthesis of 2-Amino-4,6-diarylnicotinonitrile*

Zahra et al. reported boric acid–catalysed synthesis of substituted 2-amino-4,6-diarylnicotinonitrile under solvent-free microwave irradiation conditions within 48–60 s as depicted in Scheme 44. The synthetic procedure involves reaction of substituted aromatic aldehyde, acetophenone, ammonium acetate and malononitrile under the catalytic influence of boric acid without any solvent in microwave condition for a minute to yield the desired product **82** in excellent yield (Hosseinzadeh et al. 2019).

## 3 Conclusions

To date, very few reviews are available in the literature on the use of boric acid as a catalyst. Moreover, there is no report available signifying the utility of boric acid catalysis in green chemistry. This is the primary inspiration behind this review to highlight the importance of boric acid catalysis in green chemistry, which can re-energize researchers to utilize boric acid in green synthesis. This review covers synthetic utility of boric acid catalysis in the formation of C-C, C-N, C-O and C-S bonds. The acidic properties of boric acid along with its cost-effectiveness, commercial availability and hydrophilic properties make it most useful acidic catalyst in green synthesis.

## References

Alagarsamy V, Revathi R, Meena S, Ramasheshu KV, Rajashekam S, De Clercq E. AntiHIV, antibacterial and antifungal activities of some 2, 3-disubstituted quinazolin-4 (3H)-ones. Indian J Pharm Sci. 2004;66:459–62.

Atwal KS, Moreland S. Dihydropyrimidine calcium channel blockers 51: bicyclic dihydropyrimidines as potent mimics of dihydropyridines. Bioorg Med Chem Lett. 1991;1:291–4. https://doi.org/10.1016/S0960-894X(01)80810-6.

Baker EL, Yamano MM, Zhou Y, Anthony SM, Garg NK. A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. Nat Commun. 2016;7:11554.

Bhattacharya A, Bandichhor R. Chapter 14, Green Technologies in the Generic Pharmaceutical Industry. In: Dunn P, Wells A, Williams MT, editors. Green chemistry in the pharmaceutical industry. Weinheim: Wiley-VCH; 2011. p. 289–309.

Brun E, Safer A, Carreaux F, Bourahla K, L'Helgoua'Ch JM, Bazureau JP, Villalgordo J. Microwave-assisted condensation reactions of acetophenone derivatives and activated methylene compounds with aldehydes catalysed by boric acid under solvent-free conditions. Molecules. 2015;20(6):11617–31. https://doi.org/10.3390/molecules200611617.

Chaudhuri MK, Hussain S. Boric acid catalysed thia-Michael reactions in water or alcohols. J Mol Catal A Chem. 2007;269(1–2):214–7. https://doi.org/10.1016/j.molcata.2007.01.014.

Chaudhuri MK, Hussain S, Kantam ML, Neelima B. Boric acid: a novel and safe catalyst for aza-Michael reactions in water. Tetrahedron Lett. 2005;46(48):8329–31. https://doi.org/10.1016/j.tetlet.2005.09.167.

Das BC, Mariappan G, Sudip S, Debjit B. Anthelmintic and anti-microbial activity of some novel chalcone derivatives. J Chem Pharm Res. 2010;2(1):113–20.

Delbecq P, Celerier J-P, Lhommet G. Decarboxylation of cyclic β-enaminoketoesters with boric acid. Tetrahedron Lett. 1990;31:4873–4. https://doi.org/10.1016/S0040-4039(00)97756-6.

Eckert H. Diversity oriented syntheses of conventional heterocycles by smart multi component reactions (MCRs) of the last decade. Molecules. 2012;17:1074–102. https://doi.org/10.3390/molecules17011074.

Ganguly NC, Roy S, Mondal P. Boric Acid–Catalyzed One-Pot Access to 7-Aryl-benzopyrano [4,3-b] benzopyran-6,8-diones Under Aqueous Micellar Conditions. Synth Commun. 2014;44:433–40. https://doi.org/10.1080/00397911.2013.813546.

Garimallaprabhakaran A, Harmata M. Boric acid mediated N-acylation of Sulfoximines. Synlett. 2011:61–4.

Gholap SS, Tambe GB. RJC Rasayan J Chem. 2008;1:862–4.

Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Comb Chem. 1999;1(1):55–68. https://doi.org/10.1021/cc9800071.

Gogoi K, Dewan A, Gogoi A, Borah G, Bora U. Boric acid as highly efficient catalyst for the synthesis of phenols from arylboronic acids. Heteroat Chem. 2014;25(2):127–30. https://doi.org/10.1002/hc.21138.

Green TW, Wuts PGM. Protective groups in organic synthesis. 2nd ed. New York: Wiley; 1991.

Halimehjnai AZ, Hosseyni S, Gholami H, Hashemi MM. Boric acid/glycerol as an efficient catalyst for synthesis of thiomorpholine 1, 1-dioxide by double Michael addition reaction in water. Synth Commun. 2013;43(2):191–7. https://doi.org/10.1080/00397911.2011.594930.

Harichandran G, Amalraj SD, Shanmugam P. Boric acid catalysed efficient synthesis of symmetrical N, N′-alkylidene bisamides. J Iran Chem Soc. 2011;8(1):298–305. https://doi.org/10.1007/BF03246228.

Heravi, M. R. P.; Ashori, M. Boric acid catalyzed convenient synthesis of benzimidazoles in aqueous media. J Chem. 2013, Article ID: 496413, 5 pages.

Hosseinzadeh Z, Ramazani A, Razzaghi-Asl N, Slepokura K, Lis T. Boric acid as an efficient and green catalyst for the synthesis of 2-amino-4, 6-diarylnicotinonitrile under microwave irradiation in solvent-free conditions. Turk J Chem. 2019;43(2):464–74.. URL: http://journals.tubitak.gov.tr/chem/abstract.htm?id=24617

Houston TA, Wilkinson BL, Blanchfield JT. Boric acid catalysed chemoselective esterification of α-hydroxycarboxylic acids. Org Lett. 2004;6(5):679–81. https://doi.org/10.1021/ol036123g.

Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Cumin R, Schaffner R, Haefely W. Selective antagonists of benzodiazepines. Nature. 1981;290:514–6. https://doi.org/10.1038/290514a0.

Ion R-M, Planner A, Wiktorowicz K, Frackowiak D. The incorporation of various porphyrins into blood cells measured via flow cytometry, absorption and emission spectroscopy. Acta Biochim Pol. 1998;45:833–45.

Karimi-Jaberi Z, Abdolaziz BJ. Boric acid catalysed synthesis of α-aminonitriles by a three-component reaction at room temperature. Chem Res. 2012;36:326–7. https://doi.org/10.3184/174751912X13352842814921.

Karimi-Jaberi Z, Amiri M. One-pot synthesis of α-aminophosphonates catalyzed by boric acid at room temperature. Heteroat Chem. 2010;21:96–8. https://doi.org/10.1002/hc.20577.

Karimi-Jaberi Z, Fakhraei H. Synthesis of 1-amidoalkyl-2-naphthols based on a three-component reaction catalyzed by boric acid as a solid heterogeneous catalyst under solvent-free conditions. Bull Chem Soc Ethiop. 2012;26:473–8. https://doi.org/10.4314/bcse.v26i3.18.

Karimi-Jaberi Z, Ghasemi E. Boric acid-accelerated, one-pot three-component synthesis of imidazo [1, 2-a] pyridine derivatives. Chem Biol Interface. 2017;7:224–9.

Karimi-Jaberi Z, Keshavarzi M. Efficient one-pot synthesis of 14-substituted-14H-dibenzo[a,j] xanthenes using boric acid under solvent-free conditions. Chin Chem Lett. 2010;21:547–9. https://doi.org/10.1016/j.cclet.2010.01.014.

Karimi-Jaberi, Z.; Mohammadi, K. One-pot synthesis of β-acetamido ketones using boric acid at room temperature. Sci World J. 2012; Article ID: 925617, 4 pages.

Karimi-Jaberi Z, Zarei LS. Rapid synthesis of 2-substituted-2, 3-dihydro-4 (1 H)-quinazolinones using boric acid or sodium dihydrogen phosphate under solvent-free conditions. Afr J Chem. 2012;65:36–8.

Klyani H, Ghorbani F. Boric acid-catalyzed multi-component reaction for efficient synthesis of 4H-isoxazol-5-ones in aqueous medium. Res Chem Intermed. 2015;41:2653–64. https://doi.org/10.1007/s11164-013-1411-x.

Kocienski PJ. Protecting groups. 3rd ed. Stuttgart/New York: Georg Thieme Verlag; 1994. p. 50–71.

Kumar A, Saxena D, Gupta MK. Boric acid catalyzed Ugi three-component reaction in aqueous media. RSC Adv. 2013;3:4610–2. https://doi.org/10.1039/c3ra23087b.

Kumar V, Singh C, Sharma U, Verma U, Singh B, Kumar N. Silica-supported boric acid catalyzed synthesis of dihydropyrimidin-2-ones, bis(indolyl)methanes, esters and amides. Indian J Chem. 2014a;53B:83–9.

Kumar V, Singh C, Sharma U, Verma U, Singh B, Kumar N. Silica-supported boric acid catalyzed synthesis of dihydropyrimidin-2-ones, bis(indolyl)methanes, esters and amides. Indian J Chem. 2014b;53B:83–9.

Levonis SM, Pappin BB, Sharp A, Kiefel MJ, Houston TA. Boric acid catalysed methyl esterification of sugar acids. Aust J Chem. 2014;67(3):528–30. https://doi.org/10.1071/CH13459.

Lowrance WW. Boric acid-catalysed esterification of phenols. Tetrahedron Lett. 1971;37:3453–4. https://doi.org/10.1016/S0040-4039(01)97203-X.

Lu J, Bai Y. Catalysis of the Biginelli reaction by ferric and nickel chloride hexahydrates. One-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones. Synthesis. 2002:466–70. https://doi.org/10.1055/s-2002-20956.

Maki T, Ishihara K, Yamamoto H. N-Alkyl-4-boronopyridinium halides versus boric acid as catalysts for the esterification of α-hydroxycarboxylic acids. Org Lett. 2005;7(22):5047–50. https://doi.org/10.1021/ol052061d.

Maras N, Kocevar M. Boric acid-catalyzed direct condensation of carboxylic acids with benzene-1,2-diamine into benzimidazoles. Hel Chimica Acta. 2011;94:1860–74. https://doi.org/10.1002/hlca.201100064.

Marsi KL, Wilen SHJ. Boric acid: A highly efficient catalyst for transamidation of carboxamides with amines. Chem Edu. 1963;40:214–5. https://doi.org/10.1021/ed040p214.

Meshram HM, Rao NN, Kumar GS. Boric acid–mediated mild and efficient friedel–crafts alkylation of indoles with nitro styrenes. Synth Commun. 2010;40:3496–500. https://doi.org/10.1080/00397910903457316.

Meshram HM, Kumar AS, Kumar GS, Sweta A, Reddy BC, Ramesh P. Boric acid promoted an efficient and practical synthesis of fused pyrimidines in aqueous media. Der Pharm Chemica. 2012;4:956–60.

Meshram HM, Rao NN, Thakur PB, Reddy BC, Ramesh P. Boric acid promoted convenient synthesis of bis (indolyl) methane in aqueous medium. Indian J Chem Section B Org Med Chem. 2013;52(6):814–7.

Mukhopadhyay C, Datta A, Butcher RJ. Highly efficient one-pot, three-component Mannich reaction catalysed by boric acid and glycerol in water with major 'syn'diastereoselectivity. Tetrahedron Lett. 2009;50:4246–50. https://doi.org/10.1016/j.tetlet.2009.04.135.

Mylavarapu RK, Kolla N, Veeramalla R, Koilkonda P, Bhattacharya A, Bandichhor R. Boric acid catalysed amidation in the synthesis of active pharmaceutical ingredients. Org Process Res Dev. 2007;11(6):1065–8. https://doi.org/10.1021/op700098w.

Nath J, Chaudhuri MK. Boric acid catalyzed bromination of a variety of organic substrates: an eco-friendly and practical protocol. Green Chem Lett Rev. 2008;1:223–30. https://doi.org/10.1080/17518250902758887.

Nguyen TB, Sorres J, Tran MQ, Ermolenko L, Al-Mourabit A. Boric Acid: A Highly Efficient Catalyst for Transamidation of Carboxamides with Amines. Org Lett. 2012;14:3202–5. https://doi.org/10.1021/ol301308c.

Offenhauer RD, Nelsen SF. Aldehyde and ketone condensation reactions catalysed by boric acid. J Org Chem. 1968 Feb;33(2):775–7. https://doi.org/10.1021/jo01266a059.

Ouellette RJ, Rawn JD. 1-structure and bonding in organic compounds. Organic chemistry. Boston: Elsevier; 2014. p. 1–39.

Pal R, Mandal TK, Mallik AK. Base-catalysed cyclocondensation of α, α'-bis (arylmethylene) cyclohexanones with thiourea: formation of E-8-(arylmethylene)-4-aryl-1, 2, 3, 4, 5, 6, 7, 8-octahydrobenzo [d] pyrimidine-2-thiones. J Indian Chem Soc. 2009;86(4):402–5.

Pal R, Mandal TK, Samanta S, Mallik AK. An Efficient Synthesis of E-2-Amino-4-aryl-8-(arylmethylene)-5, 6, 7, 8-tetrahydrobenzo [d] pyrimidines and Their Lower Analogues. ChemInform. 2011;42:711–5.

Pratibha K. Boric acid Catalyzed efficient Synthesis of Dipyrromethanes in Water. Res J Chem Sci. 2014;4:58–62.

Rajale T, Patil DDJ. Boric acid catalysed synthesis of Benzimidazoles in aqueous medium. Pharm Sci Biosci Res. 2015;5:479–86.

Reddy TRK, Mutter R, Heal W, Guo K, Gillet VJ, Pratt S, Chen BJ. Library design, synthesis, and screening: pyridine dicarbonitriles as potential prion disease therapeutics. Med Chem. 2006;49:607–15. https://doi.org/10.1021/jm050610f.

Rostami A, Akradi J, Ahmad-Jangi FJ. Boric acid as cost-effective and recyclable catalyst for trimethylsilyl protection and deprotection of alcohols and phenols. Bra Chem Soc. 2010;21:1587–92. https://doi.org/10.1590/S0103-50532010000800026.

Roth T, Morningstar ML, Boyer PL, Hughes SH, Buckheit W Jr, Michejda CJJ. Synthesis and biological activity of novel nonnucleoside inhibitors of HIV-1 reverse transcriptase. 2-Arylsubstituted benzimidazoles. Med Chem. 1997;40:4199–207. https://doi.org/10.1021/jm970096g.

Sabatini MT, Boulton LT, Sheppard TD. Borate esters: simple catalysts for the sustainable synthesis of complex amides. Sci Adv. 2017;3(9):e1701028. https://doi.org/10.1126/sciadv.1701028.

Sabatini MT, Boulton LT, Sneddon HF, Sheppard TD. A green chemistry perspective on catalytic amide bond formation. Nat Catal. 2019;2(1):10. https://doi.org/10.1038/s41929-018-0211-5.

Sarada T, Kobayashi F, Sakai N, Konakahara T. An unprecedented approach to 4,5-disubstituted pyrimidine derivatives by a ZnCl2-catalyzed three-component coupling reaction. Org Lett. 2009;11:2161–4.

Schutz H. Benzodiazepines, vol. 2. Heidelberg: Springer; 1982. p. 240. https://doi.org/10.1007/978-3-642-68426-5.

Shaikh KA, Kande SR, Khillare CB. Boric acid catalyzed one-pot synthesis of [1, 2, 4] triazolo quinazolinone Derivatives. IOSR J Appl Chem. 2014;7:54–8.

Shelke KF, Sapkal SB, Sonar SS, Madje BR, Shingate BB, Shingare MS. An efficient synthesis of 2, 4, 5-triaryl-1H-imidazole derivatives catalyzed by boric acid in aqueous media under ultrasound-irradiation. Bull Kor Chem Soc. 2009;30:1057–60. https://doi.org/10.5012/bkcs.2009.30.12.2883.

Shinde PV, Sonar SS, Shingate BB, Shingare MS. Boric acid catalyzed convenient synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in aqueous media. Tetrahedron Lett. 2010;51:1309–12. https://doi.org/10.1016/j.tetlet.2009.12.146.

Shiri M, Zolfigol MA, Kruger HG, Tanbakouchian Z. Bis-and trisindolylmethanes (BIMs and TIMs). Chem Rev. 2009;110(4):2250–93. https://doi.org/10.1021/cr900195a.

Singhal A, Singh S, Chauhan SMS. Synthesis of dipyrromethanes in aqueous media using boric acid. Arkivoc. 2016;vi:144–51. https://doi.org/10.24820/ark.5550190.p009.847.

Stapp PRJ. Boric acid catalyzed Tishchenko reactions. Org Chem. 1973;38:1433–4. https://doi.org/10.1021/jo00947a049.

Tang Y, Oppenheimer J, Song Z, You L, Zhang X, Hsung RP. Strategies and approaches for constructing 1-oxadecalins. Tetrahedron. 2006;62:10785–813. https://doi.org/10.1016/j.tet.2006.08.054.

Tu S, Fang F, Miao C, Jiang H, Feng Y, Shi D, Wang X. One-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones using boric acid as catalyst. Tetrahedron Lett. 2003 Aug 4;44(32):6153–5. https://doi.org/10.1016/S0040-4039(03)01466-7.

Tu S-J, Zhu X-T, Fang F, Zhang X-J, Zhu S-L, Li T-J, Shi D-Q, Wang X-S, Ji S-J. One-pot Synthesis of Bis (dihydropyrimidinone-4-yl) benzene Using Boric Acid as a Catalyst Chin J Chem. 2005;23:596–8. https://doi.org/10.1002/cjoc.200590596.

Wang SY, Ji SJ, Loh TP. The Michael addition of indole to α, β-unsaturated ketones catalysed by iodine at room temperature. Synlett. 2003;2003(15):2377–9. https://doi.org/10.1055/s-2003-42105.

Yadav JS, Gupta MK, Jain R, Yadav NN, Reddy BVS. A practical synthesis of bis(indolyl) methanes employing boric acid. Monatsh Chem. 2010;141:1001–4. https://doi.org/10.1007/s00706-010-0355-8.

Zhou X, Zhang MY, Gao ST, Ma JJ, Wang C, Liu C. An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by boric acid. Chin Chem Lett. 2009;20:905–8. https://doi.org/10.1016/j.cclet.2009.03.033.

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Inamuddin, A. M. Asiri (eds.), *Applications of Nanotechnology for Green Synthesis*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-44176-0