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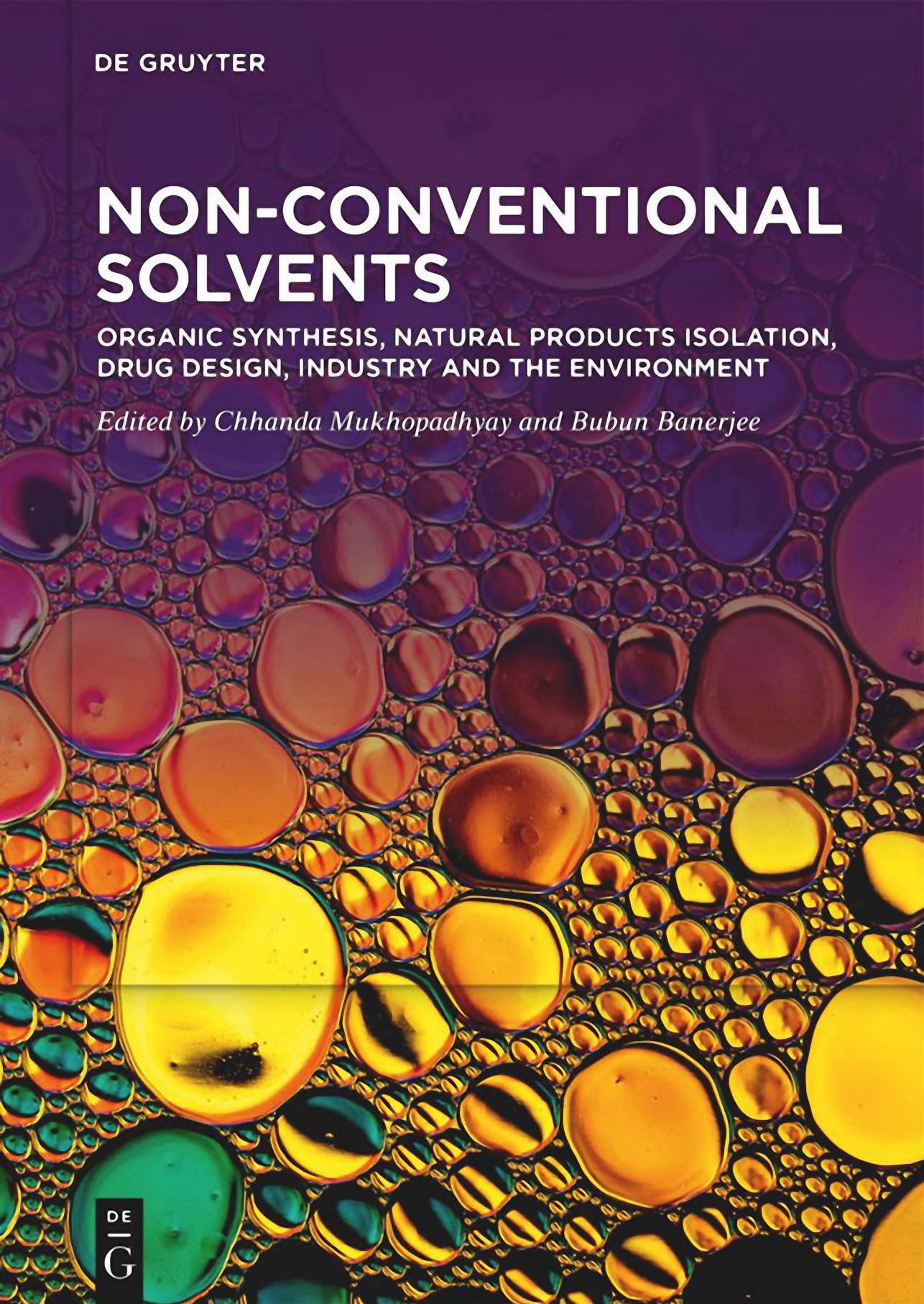
ORGANIC SYNTHESIS, NATURAL PRODUCTS ISOLATION, DRUG DESIGN, INDUSTRY AND THE ENVIRONMENT

Edited by Chhanda Mukhopadhyay and Bubun Banerjee



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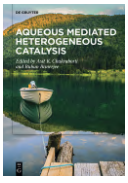

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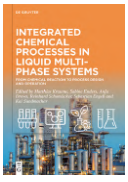

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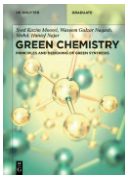

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Non-Conventional Solvents

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Foreword

Nowadays, the reduction in usage of conventional organic solvents in chemical processes is one of the major concerns in terms of green and sustainable development. This is mainly due to the high vapor pressure of conventional solvents resulting in potential risks such as low flash points, higher flammability and toxicity. Conventional volatile organic solvents are harmful to living organisms, and ozone layer destruction is also catalyzed by the vapors of chlorinated volatile solvents. Hence, nonconventional solvents with high recyclability and less volatility, toxicity and flammability are considered as a promising alternative to conventional organic solvents. These solvents have gained more attention in recent decades as a new generation of solvents with applications in various organic transformations, natural products isolation and drug design. Recently, the use of nonconventional solvents has increased significantly in pharmaceutical, chemical, cosmetics, paints and many other industries. However, certain scientific research revealed the risks related to nonconventional solvents which disprove the opinion that nonconventional solvents are fully harmless for the environment. Therefore, further study is highly required to redesign or modify the existing nonconventional solvents to make them more efficient and sustainable. Under this purview, I personally believe that this book, edited by Prof. Chhanda Mukhopadhyay and Dr. Bubun Banerjee, is going to be a valuable resource for the researchers working in the fascinating field of nonconventional solvents.

This book has nine unique chapters that are focused on this crucial contemporary subject. Dr. Reddy and his research group described various triethylamine-mediated synthesis of bioactive heterocycles in Chapter 1. In Chapter 2, Banerjee et al. summarized various organic transformations using nitromethane as solvent. In Chapter 3, Prof. Asish Ranjan Das and his group explored recent advances on tert-butyl hydroperoxide-mediated cross-coupling reactions. In Chapter 4, Prof. Kantharaju Kamanna and Yamanappagouda Amaregouda summarized applications of cyrene and ethyl lactate as bio-based solvents for various organic transformations. In Chapter 5, Animesh Mondal and Prof. Chhanda Mukhopadhyay established solid-phase platform as a nonconventional synthetic route for the synthesis of diversified heterocyclic and carbocyclic frameworks. Dr. Sasadhar Majhi and his group explored the role of nonconventional solvents in the isolation of natural products in Chapter 6. In Chapter 7, Nahid Ahmadi and Prof. Ali Ramazani discussed the utility of nonconventional solvents in drug design. Prof. Suresh C. Ameta and his group demonstrated

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industrial applications of various nonconventional solvents in Chapter 8. In Chapter 9, Prof. Kamla Pathak and her group reported the effects of nonconventional solvents on the environment.

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About Professor Bimal Krishna Banik

Bimal Krishna Banik received his undergraduate, graduate and doctoral studies at Itachuna Bejoy Narayan Mahavidyalaya, Burdwan University and Indian Association for the Cultivation of Science (Jadavpur University). Thereafter, he pursued his postdoctoral research at Case Western Reserve University (Ohio, USA) and Stevens Institute of Technology (New Jersey, USA). Prof. Banik was Assistant Professor in Experimental Molecular Pathology at the University of Texas M. D. Anderson Cancer Center, Houston. He became a tenured Full Professor in Chemistry and First President's Endowed Professor in Science and Engineering at the University of Texas – Pan American (UTPA). Prof. Banik was also affiliated to the University of Texas at San Antonio and the University of Texas Health Science Center at San Antonio as Adjunct Full Professor. Prof. Banik served as the Vice President of Research and Education Development of the Community Health Systems of South Texas. At present, he is a Full Professor and Senior Researcher of the Deanship of Research Development, College of Natural Sciences and Human Studies at the Prince Mohammad Bin Fahd University, Saudi Arabia.

Prof. Banik has taught organic and medicinal chemistry as well as special topics in chemistry and chemistry for engineering for B.S., M.S. and Ph.D. students in the US and Saudi Arabia universities for several years. He has introduced various new courses to render teaching in a most effective and innovative manner. His exceptional teaching skills were reflected from several thousand students', peers' and administrators' outstanding evaluations as well as from independent comments posted at the Rate My Professor Website by the US students. Numerous distinguished leaders and top administrators in the US universities and research institutes rated him as "Truly Exceptional" and "Excellent Teacher" on a scale of excellent, good, average and weak. He has mentored approximately 300 students, 20 postdoctoral fellows, 7 Ph.D. research scientists and 28 university faculties in research activities. Prof. Banik remained as an advisor of two students' organizations and societies in the USA that had 1,400 students of diverse subjects.

Prof. Banik's students have completed higher degrees and education from premier institutes of the USA such as Harvard University, MIT, Northwestern University, Yale University, Stanford University, Rutgers University, University of Texas at San Antonio, Stevens Institute of Technology, New Jersey Institute of Technology, Baylor College of Medicine, University of Texas Southwestern Medical Center, University of Texas M. D. Anderson Cancer Center, University of Texas at Austin, New Jersey Medical University, University of Iowa, University of Texas Health Science Center at San Antonio, University of Texas-Galveston Medical School, University of Philadelphia, State University of New York at Buffalo, University of Reynosa, UTPA and Vanderbilt University. Many of his alumni students are successful as university professors and CEOs/directors/principal scientists/research scientists of chemical and drug companies. Some of them are working at Merck Pharmaceutical Company, Johnson & Johnson, Procter & Gamble, Bristol Myers Pharmaceutical Company, Dow Chemical Company, International University, Polish Academy of Sciences, the University of Mexico, Colgate-Palmolive, the University of Texas at San Antonio, Chemsyn, Syngene Pharmaceutical Company, G. V. Biochemicals and the US University.

Prof. Banik has carried out his research on synthetic chemistry and chemical biology in the ovary, colon, breast, blood, prostate, brain, pancreas and skin cancers; antibiotics; hormones; catalysis; green chemistry; natural products; metal- and salt-mediated processes; and microwave-induced reactions. As the principal investigator (PI), he has been awarded $7.25 million grants from the US National Institute of Health, US National Cancer Institute and Texas Private Foundations.

Importantly, Prof. Banik has already published above 600 peer-reviewed publications along with more than 500 presentation abstracts. He has also penned 75 technical reports. He is the author/editor of 17 books published by Springer Nature, Springer, Nova, Elsevier, CRC (Taylor & Francis), De Gruyter and Prince Mohammad Bin Fahd University. In addition, four "Banik's reactions" were invented by him and named as Banik's cycloaddition, Banik's glycosylation, Banik's nitration and Banik's oxidation. The number of citations

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for his publications has crossed 8,450. Highly prestigious organizations have also published news based on Prof. Banik's outstanding achievements. For example, American Association for the Advancement of Science (*EurekAlert*), Indian Chemical Society, *Times of India*, *Down to Earth*, *American Chemical Society Chemical & Engineering News*, Thomson-Reuters, Bentham Publisher and Royal Society of Chemistry had commented on his research excellence in diverse areas that have been consistent and persistent for the past three decades or more.

Prof. Banik served as PI of a joint green chemistry symposium between the USA and India. He chaired 20 symposiums at the American Chemical Society (ACS) national meetings and over 100 conferences at the state, national and international levels, including one at the Nobel Prize celebration in Germany. He has introduced more than 300 speakers, in the capacity of chair. He is a reviewer of 93 journals, editorial board member of 26 journals, editor in chief of 12 journals, founder of 8 journals, associate editor of 4 journals and guest editor of 10 journals. As the editor in chief, he recruited approximately 200 associate editors, regional editors and editorial board members from different countries. He is an examiner of NSF, NCI, NRC, DOE, ACS and international grant applications; reviewer of promotion and tenure of faculty of national and international universities; examiner of doctoral theses; and panel member of NSF and NCI/NIH grant sections. Over the years, he served as the chair/member of more than 100 scientific committees. Prof. Banik served as the chair of the University of Texas M. D. Anderson Cancer Center's drug discovery symposiums and directed the US NCI-funded analytical chemistry of Core Research Laboratory.

Prof. Banik was promoted to tenured full professor in 2007, which was within a year of his last promotion to associate professor at the University of Texas System. Prof. Banik has been ranked within top 2% of researchers in the world. He has received the Indian Chemical Society's (ICS) Lifetime Achievement Award, the US National Society of Collegiate Scholar's Best Advisor Award, Mahatma Gandhi Honor Medal from the UK Parliament, ICS's Professor P. K. Bose Endowment Medal, Dr. M. N. Ghosh Gold Medal, the University of Texas Board of Regents' Outstanding Teaching Award, five top-cited paper awards by Elsevier, Fifty Certificates of Excellence in his profession, Indian Association Community Service Award, ACS Member Service Award, NCI Webpage Recognition, Bentham Ambassador Recognition, Best Researcher/Mentor Award by the UTPA, Burdwan University Eminent Alumnus Recognition, First President's Endowed Professorship at the UTPA (a single position that was available in 87 years), New Jersey Board of Education Best Mentor Award and UTPA's Award for Excellence in international studies. Prof. Banik was nominated for the US Presidential Award on Teaching/Mentoring twice by the US University. He was the finalist for the University of Texas Chancellor Award successively for 6 years. He has been regarded as a "distinguished scientist" and "distinguished researcher" by scientific societies. Some of his international research presentations were considered as keynote, plenary and inaugural lectures. Prof. Banik received more than 200 invitations to deliver lectures in 35 countries. He received frequent invitations to contribute textbooks by major publishers, including Wiley, Elsevier, Springer, Springer Nature, Taylor & Francis, Cambridge University Press, Cambridge Scholars Publishing, De Gruyter, Bentham, Thompson, Linus, Nova, Pearson, Cengage, Houghton Mifflin, ICS and PMU Press. Notably, Prof. Banik was invited by the Royal Society of Chemistry to participate in scientific discussions with distinguished professionals at Indianapolis (2013), New Orleans (2013), Philadelphia (2012), Boston (2010), Washington, D.C. (2009), Salt Lake City (2009), Philadelphia (2008), New Orleans (2008), Boston (2007), Chicago (2007), San Francisco (2006), Atlanta (2006) and Washington, D.C. (2005). As an educationalist, Prof. Banik hosted a few dignified professionals, including Nobel Prize winners, ACS presidents, the US White House secretary, editors of most reputed journals and US senator/congressmen.

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Chapter 1
Triethylamine-mediated synthesis of bioactive heterocycles

1.1 Introduction

Organic bases typically contain proton acceptors, but this is not always the case, and the use of base-promoted organic reactions has recently gained prominence [1]. They generally have nitrogen atoms that are easy to protonate. In amines and other heterocyclic compounds containing nitrogen, the nitrogen atom has a single pair of electrons that can act as proton acceptors. Triethylamine (TEA), also known as *N*,*N*-diethylethanamine (Et_3N), is a colorless, water-soluble liquid that has a wide range of applications as an organocatalyst in chemical transformations [2]. Thus, the lone pair on nitrogen can act as a base. It functions in a variety of chemical syntheses as a solvent and a basic catalyst. In synthetic organic chemistry, TEA is recognized as a flexible and effective organocatalyst that is also inexpensive, easy to handle, nontoxic and reasonably safe. TEA is a mildly hydrogen-bond basic, dipolar/polarizable, weakly cohesive, non-hydrogen-bond acidic solvent. Compared to the other solvents, TEA has more occurrences of the creation of catalytic transformation products.

TEA should be defined for its first usage as a versatile reagent with applications ranging from photochemistry, electrochemistry and organic reactions. This chapter mainly focuses on applications of TEA photochemically and electrochemically and in organic reactions. It is useful for deprotonation and scavenging protons, for the formation of new compounds, and as a sensitizer photochemically [3]. In electrochemical

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experiments, TEA can be added as a supporting electrolyte to increase the conductivity of the solution and to stabilize the potential of the electrode [4]. It can also function as a solvent and a complexing agent. A typical organic base called TEA is frequently employed in organic chemistry reactions as a catalyst or reagent [5]. Additionally, TEA can also be used to complex metal ions and promote typical organic reactions (Figure 1.1).

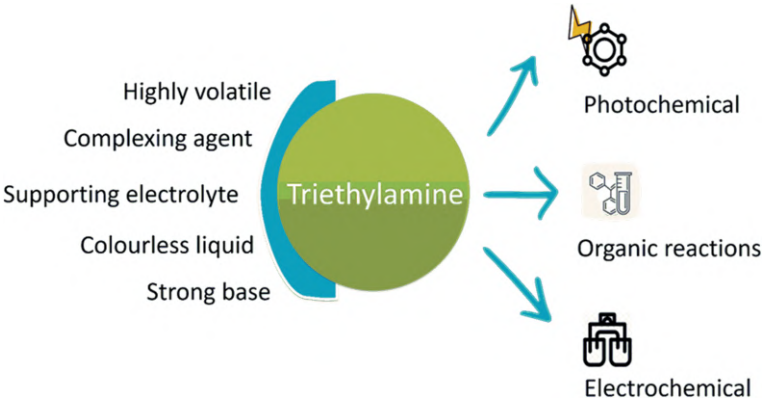


Figure 1.1: Triethylamine properties and main fields of applications.

1.2 Triethylamine-promoted photocatalytic reactions

1.2.1 Photocatalytic triethylamine-mediated synthesis of 1,4-substituted 1,2,3-triazoles

Click chemistry has one of the most effective alternatives to synthesize 1,2,3-triazole. This study by Kumar et al. [6] uses a bipyrimidine-bridging ligand to coordinate the photocatalyst's ruthenium photosensitizer unit with the manganese carbonyl complex. It offers quick electron transfer for a contact-free in situ reduction of Cu(II) to Cu(I) with TEA acting as a sacrificial donor. This led to a faster reaction rate than when the photosensitizer and Mn complex were physically mixed together in the reaction mixture, but the yield was still constrained by alkyne–alkyne homocoupling. $Ru(bpy)_2Cl_2$ and $Mn(bpm)(CO)_3Br$ were combined to create a bimetallic complex, $[Ru(bpy)_2(bpm)Mn(CO)_3Br](PF_6)_2$, which was then precipitated with ammonium hexafluorophosphate to produce an in situ Cu reduction of 1,4-disubstituted 1,2,3-triazole. The [3 + 2] cycloaddition of the azide and alkynes is facilitated by Cu(I) metal coordination. By regenerating the catalyst, the intermediate is then subjected to protonation, producing 1,4-disubstituted-1,2,3-triazoles (Figure 1.2).

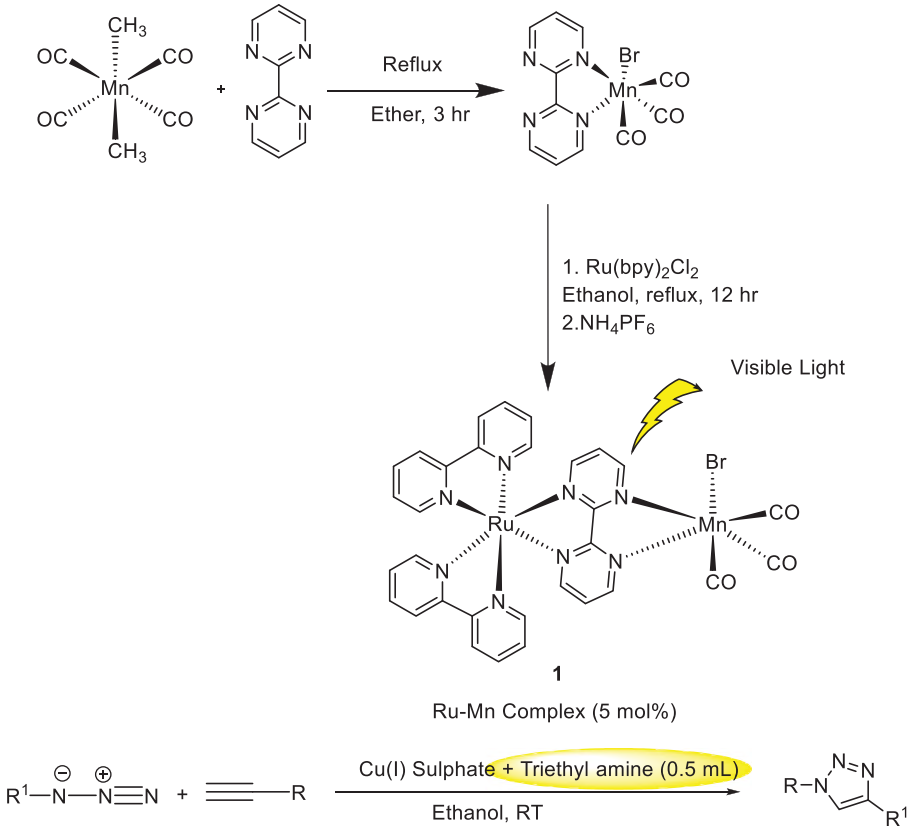


Figure 1.2: Photocatalytic triethylamine-mediated synthesis of 1,4-substituted 1,2,3-triazoles.

The effective electron mobility occurs through Ru–Mn to Cu(II) via the pyrimidine-bridging ligand which is stabilized by $[C_2H_5]_3N$–$[C_2H_5]_3N^{+\bullet}$. The mechanistic steps involved are explained in Figure 1.3.

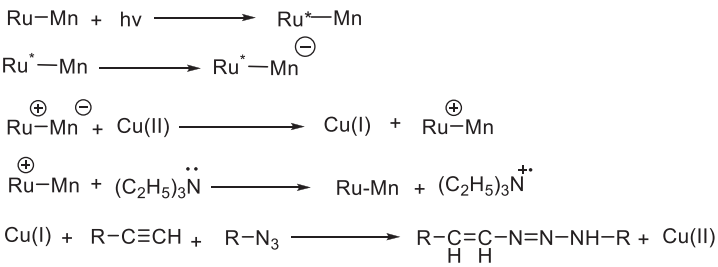


Figure 1.3: Mechanistic details of role of TEA.

1.2.2 Reductive alkylation of difluoroalkyl halides using triethylamine as reductant

Miller et al. [7] described the creation of an improved photocatalytic method for reducing difluoroalkylation for different olefins. Under mild reaction conditions, these alkenes allow access to synthetically relevant noncanonical amino acid scaffolds. The starting materials, commercial difluoroalkyl halides, of experiments allowed the addition of various olefins, such as dehydroalanine residues toward considerable monomers. The currently described procedure uses TEA as the terminal reductant and an iridium photocatalyst to access the orthogonally protected residues in one step. Similar work was previously established using Hantzsch ester [8]. However, due to the problem of reactivity and undesired pathways, an efficient pathway using TEA as reductants is established.

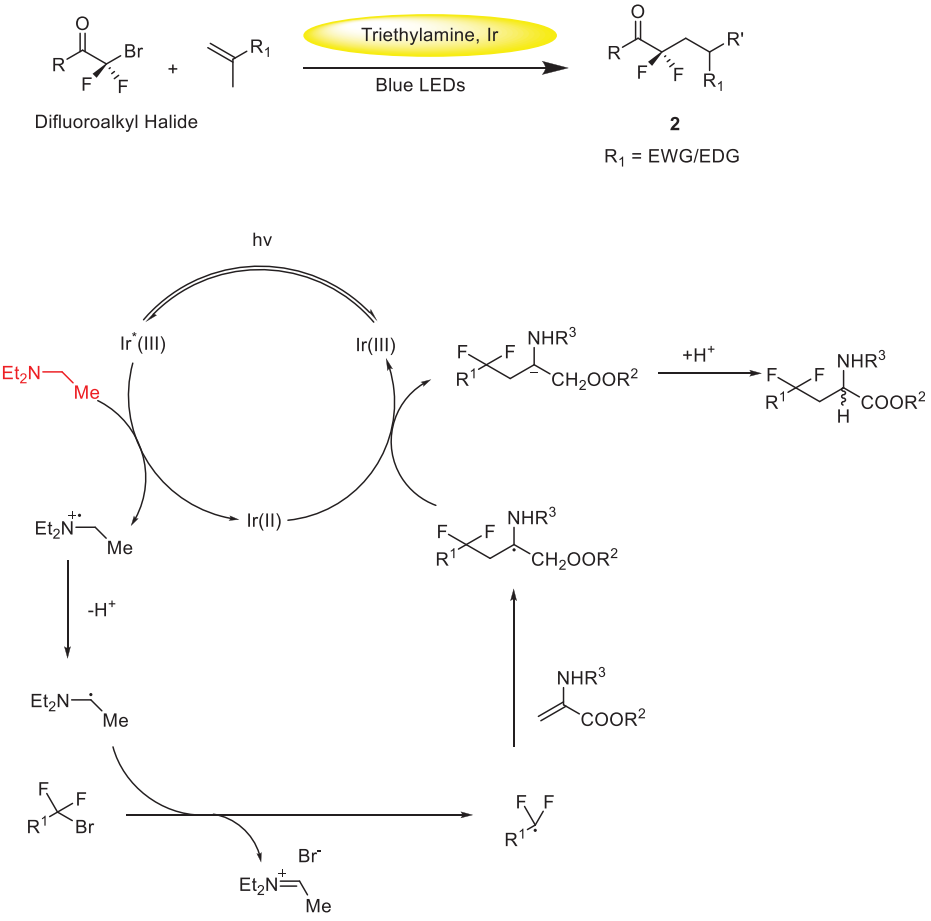


Figure 1.4: Photocatalytic triethylamine-mediated reductive alkylation of difluoroalkyl halides.

When Et_3N is oxidized, a radical cation is created, followed by the loss of a proton, producing the amino radical. Then, this species may engage in simple bromine atom abstraction from the precursor to produce the necessary difluoroalkyl radical and the iminium ion derived from Et_3N. This radical in the presence of highly reducing iridium(II) species undergoes subsequent reactions to give product **2**. Plausible mechanistic aspects are shown in Figure 1.4.

1.2.3 Triethylamine-mediated aerobic oxidation of sulfides

Due to the wide range of applications, selective oxidation of sulfides to sulfoxides has gained a great deal of interest. The most common semiconductor photocatalyst (TiO_2) was found to show high performances. While carbazolic conjugated microporous polymers

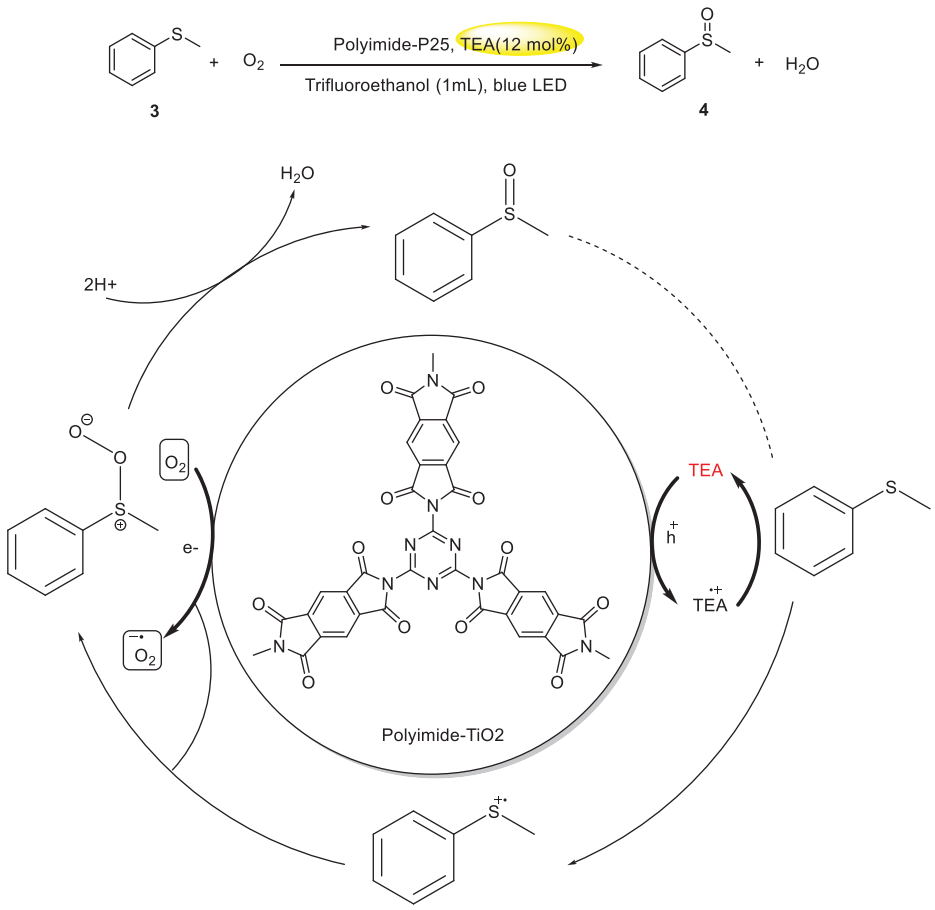


Figure 1.5: Triethylamine-mediated aerobic oxidation of sulfides`.

rose to benefit selective oxidation, pure polyimides [9] or PDA (polydopamine)-modified TiO_2 failed to meet the requirements [10]. Polyimides bearing high lowest unoccupied molecular orbital had no recognizable photocatalytic activity and PDA-modified TiO_2 could not achieve high selectivity. TEMPO (2,2,6,6-tetramethyl-1-piperidine *N*-oxyl) serves no purpose as a redox mediator in this process and is hence incapable. In order to increase the efficacy of the polyimide–TiO_2 photocatalyst, a novel redox mediator was discovered. Lang et al. [11] found that TEA could increase the activity of polyimide–TiO_2 catalysis by threefold. While an irradiation with 460 nm of blue light stimulates the reaction, TEA mediates the electron transfer between polyimide–TiO_2 and sulfides, enabling oxidation of sulfides **3** to product **4** with high stereoselectivity. Detailed mechanistic aspects are demonstrated in Figure 1.5.

1.2.4 Photocatalytic triethylamine-mediated synthesis of 6-β-disubstituted phenanthridines

Rastogi et al. [12] synthesized 6-functionalized phenanthridines by generating enolate vinyl radical intermediates that were then trapped with *o*-aryl vinyl azides. Intramolecular cyclization was then applied to the resulting iminyl radicals. By reducing keto-diazophosphonates and keto-diazocarboxylates, the excited Rh-radical anion, which is created when blue light activates Rh-6G (Rhodamine 6G dye) in the presence of electron donors, created enolate vinyl radicals. It was found that substituting TEA for the electron donor *N*,*N*-diisopropylethylamine (DIPEA) significantly increased the yield to 84%. A 1:2 ratio of substrates **5** and **6** was found to be the best combination, along with 1.0 equivalents of TBAB (Tetrabutylammonium bromide), 2 mol% of Rh-6G and 1.5 equivalents of Et_3N in DCM (Dichloromethane).

The Rh-radical anion is produced by removing one electron from excited Rh-6G by Et_3N. Et_3N transforms into a radical cation. The oxidation of intermediates **7** and **8** is also aided by this. Based on observations made during reaction optimization, the mechanism is described (Figure 1.6).

1.2.5 Photocatalytic triethylamine-mediated synthesis of C_3-alkylated imidazopyridines

Pyridine is regarded as a “drug bias” heterocyclic skeleton due to the wide range of pharmacological properties, such as anti-inflammatory, antiulcer, antiviral and anticancer activities, of heterocyclic molecules containing imidazo[1,2-a]pyridine. In this study, a quick, one-pot condensation and alkylation of 2-aminopyridines with a variety of bromocarbonyl molecules were used to demonstrate the synthesis of C_3-alkylated imidazopyridines under visible light photoredox catalysis. This novel method, short synthetic pathway, readily accessible substrates, eases of operation and favorable reaction conditions are just a few of its outstanding qualities. This technique, which can also be used to create other C_3-functionalized imidazo[1,2-*a*]pyridine derivatives [14], allowed for the

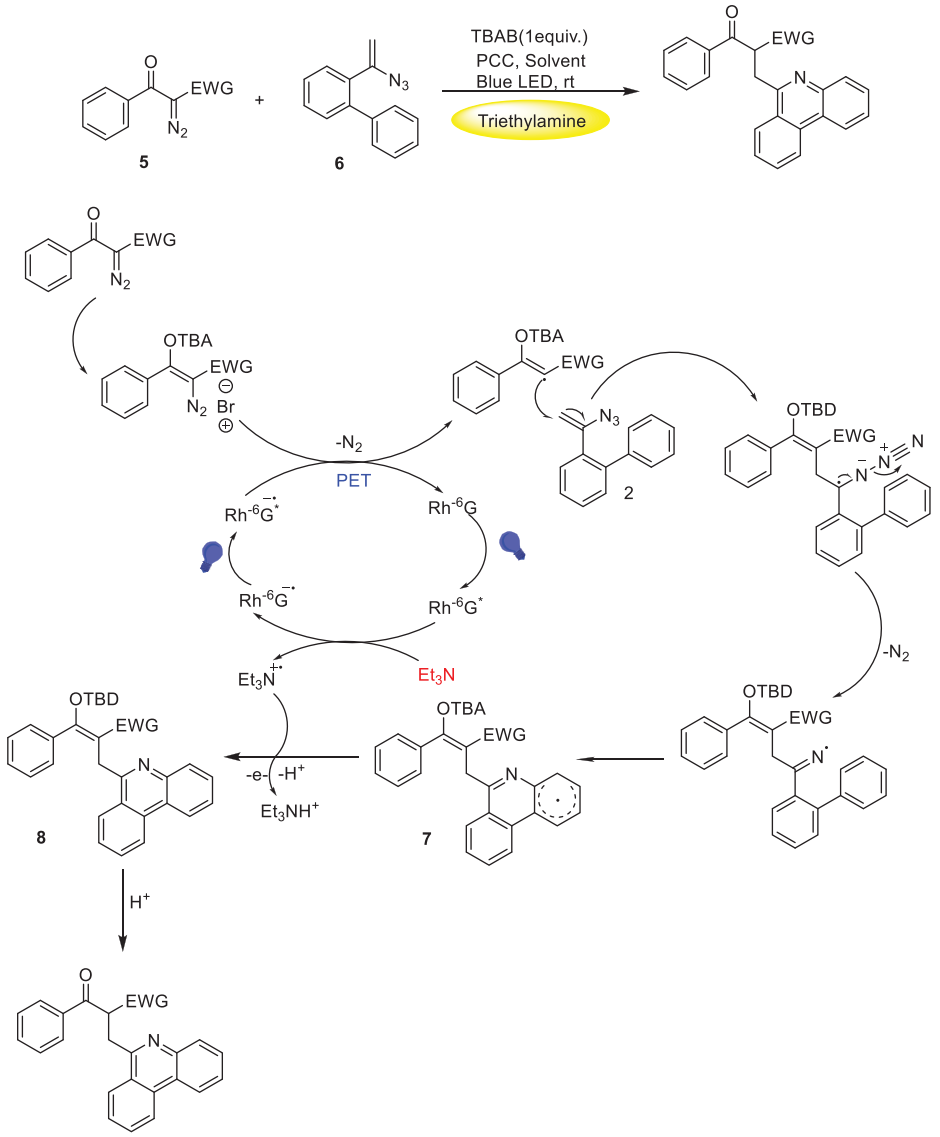


Figure 1.6: Photocatalytic triethylamine-mediated synthesis of 6-β-disubstituted phenanthridines.

quick synthesis of zolpidem [13]. It was observed that the reaction occurred in DCM at room temperature when fac-ir(ppy)$_3$ (2 mol%) was employed as a photocatalyst and Et_3N (2 equiv.) was used as a base. This resulted in the production of C_3-alkylated imidazopyridine **9** in 80% of the reactions. While in the absence of a TEA, photocatalyst or visible light irradiation, no desired product was observed. The scheme and the plausible reaction mechanism are discussed in Figure 1.7.

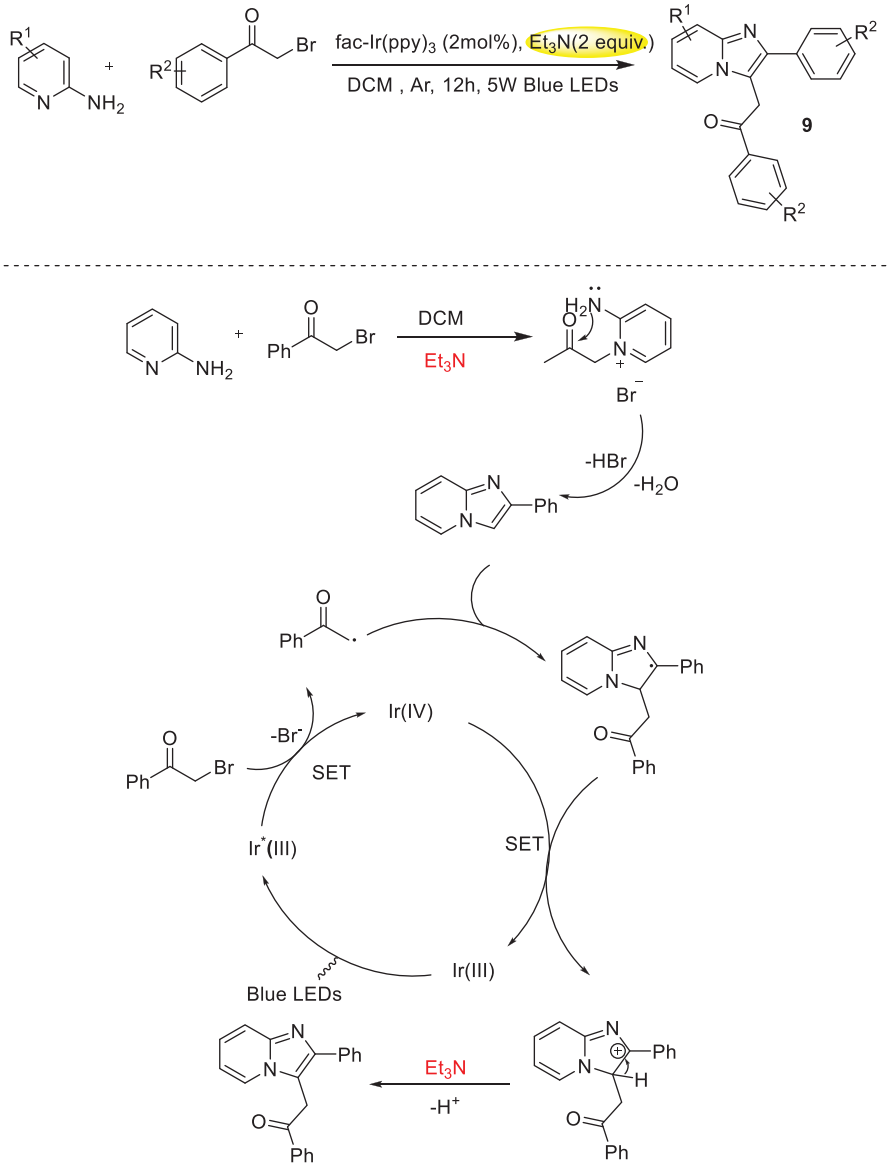


Figure 1.7: Photocatalytic triethylamine-mediated synthesis of C_3-alkylated imidazopyridines.

1.2.6 Visible-light-driven triethylamine-mediated photocatalytic duet reaction

Shimakoshi et al. [15] succeeded in synthesizing ester and amide from trichlorinated reactant **10** with UV light irradiation. Even though it was able to proceed in room temperature, irradiation of UV light corresponding to the band gap excitation of TiO_2 was challenging. Hence, visible-light-mediated pathway was in quest and successful visible-light-responsive hybrid catalyst was synthesized [16].

Surface modification of TiO_2 was required for efficient visible-light-driven reaction. Among various surface modifications with glucose and inorganic compounds, metal ion modification was found to be the most efficient. This was explained by the stability of the catalyst. The B_{12} hybrid catalyst was synthesized using the rhodium-modified TiO_2 (Rh^{3+}–TiO_2). Rhodium(III) ions were attached onto the surface of TiO_2 making it task specific, and vitamin B_{12} complex is covalently immobilized onto TiO_2 through trimethoxysilyl groups which is a visible-light-photoresponsive catalyst. When visible light was irradiated onto the surface-modified TiO_2 catalyst, TEA acts as a sacrificial reagent and underwent oxidation to form diethylamine. Alongside, the electrons were transferred to cobalt catalyst, that is, vitamin B_{12} complex reducing Co(III) to Co(I). Amide **11** was synthesized from diethylamine and benzoyl chloride formed by oxidation with CO(I) (Figure 1.8).

1.2.7 Photocatalytic triethylamine-mediated synthesis of phenols

Iodoarene **12** can be extracted from phenol using a gentle, easy and efficient method [17]. This process uses visible light from white light-emitting diodes (LEDs) as a clean energy source and KI as an inexpensive, widely available catalyst to produce iodine radical reactive species in the presence of atmospheric oxygen. TEA was used as the base and solvent in the reaction, which resulted in a variety of phenols with yields ranging from fair to good and high compatibility with a wide range of functional groups. A catalyst screening was done, and it was found that using I_2 as a photocatalyst produced a good yield of the desired product. According to mechanistic research, breaking of C–I bond takes place, which results in free aryl radicals, advantageously facilitated by the interaction of KI with catalysis. The importance of Et_3N was studied by the use of other bases like CH_3ONa or KOH, DABCO (1,4-diazabicyclo[2.2.2]octane) and DIPEA. Moreover, the reaction was completely inhibited in the absence of TEA, which confirms the role of TEA in the reaction mechanism (Figure 1.9).

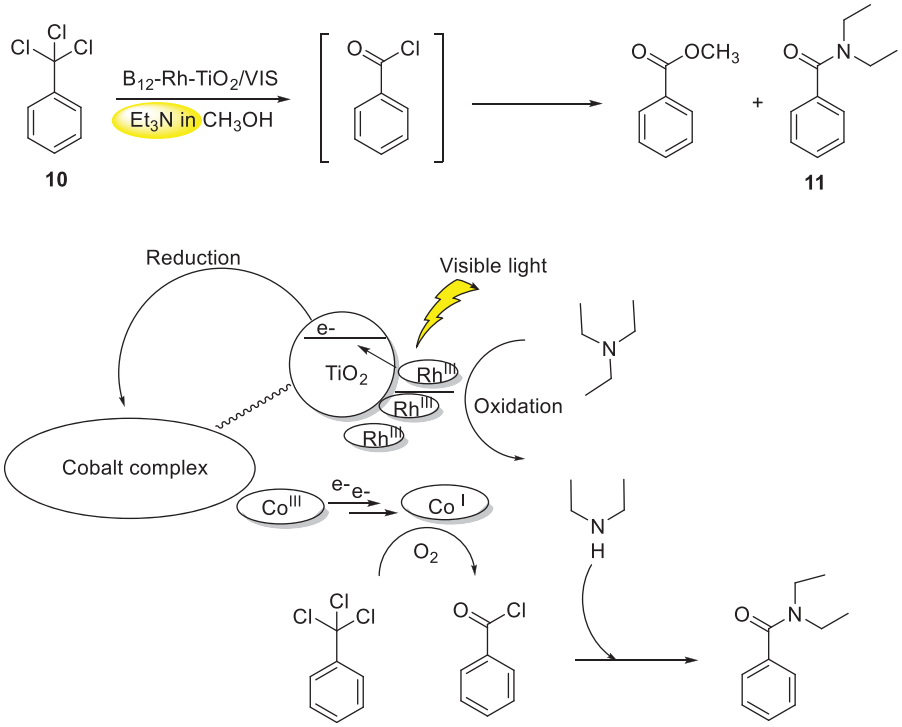


Figure 1.8: Photocatalytic triethylamine-mediated reaction.

1.2.8 Photocatalytic triethylamine-mediated synthesis of indoline

General indoline synthesis involves the formation of either Csp^3–N or Csp^3–Csp^3 bond first, which is followed by cyclization to form a five-membered ring. When the visible light photoredox catalyst ($Ru(bpy)_3(PF_6)_2$) was added, conditions similar to those described by Molander (acetone and 2,6-lutidine) resulted in a significant increase in the amount of indoline product compared to the reaction without the photoredox catalyst [18]. The use of aryl iodides instead of bromides, as well as blue LEDs to decrease reaction time, provided the optimal circumstances for good indoline product yields with high selectivity over the Heck reaction products. Utilizing *N*-heterocyclic carbene ligands, IPr identified the tiny amount of indoline product with remarkable selectivity (>19:1) when compared to other products. This suggests that the alkene migratory insertion had been highly selective for arene insertion at the internal position in addition to suppressing -H elimination. Glorius and coworkers recently reported indole synthesis from 2-haloaniline **13** and alkene **14**, using an internal diazine carboxylate oxidant and Rh(III)-catalyzed directed C–H functionalization to couple arenes with primarily electron-

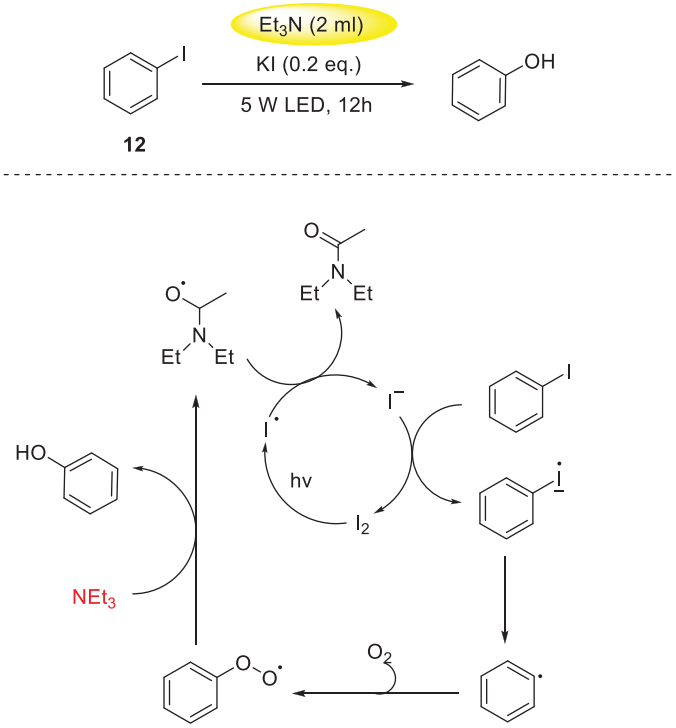


Figure 1.9: Photocatalytic triethylamine-mediated phenol synthesis.

poor alkenes, which tend to result in 2-substituted aminoindolines from which the 1-amino group can be removed to produce NH-indoline [19].

The required oxidation to Ni(III) prior to product formation that is most plausible with stoichiometric oxidants enhances the quantity of C–N bond formation. Et_3N mediates the oxidation of Ni from +2 to +3 oxidation state enabling complex (number) to take up path 1 rather than undergoing beta-hydride elimination through path 2. Path 1 allows the synthesis of indoline product **15** via cyclization reaction which is facilitated by Et_3N acts as a base (Figure 1.10).

1.2.9 Photocatalytic triethylamine-mediated oxidation of alcohols

Due to its importance in organic synthesis, the oxidation of alcohols continues to be one of the most used and researched organic reactions [20]. As an alternative to TiO_2's small size, potassium niobium oxide ($KNbO_3$) is used in this study as a photocatalyst. Niobium oxide perovskites have the advantage of being easier to separate because of their higher particle size and porosity [21]. This study examines the effects of base, H_2O_2 and catalyst on the photooxidation of sec-phenethyl alcohol (SPA) **16**, which was used as

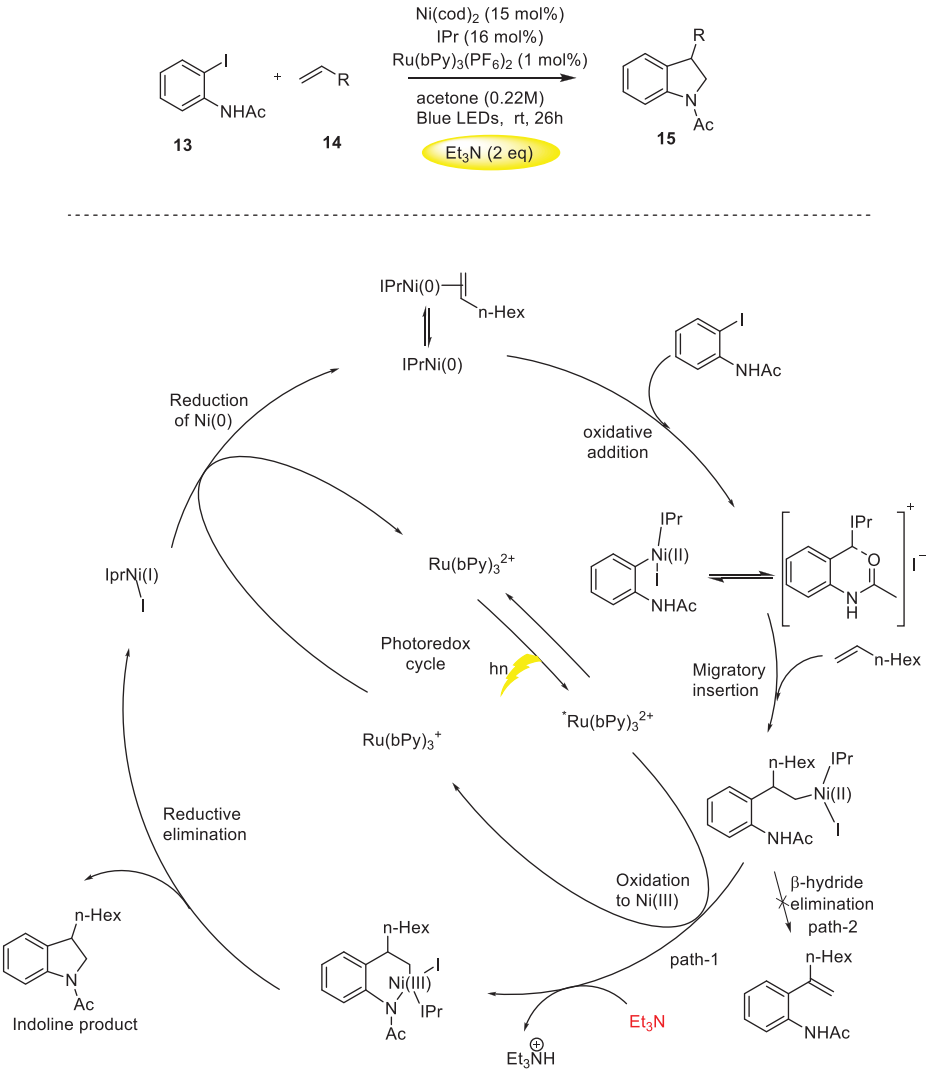
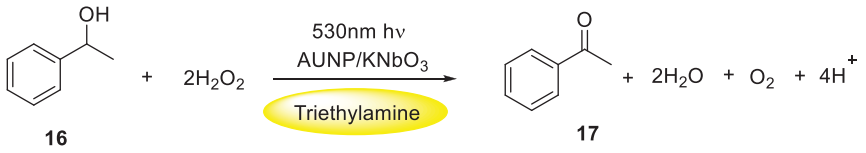


Figure 1.10: Photocatalytic triethylamine-mediated synthesis of indolines.

a probe molecule to investigate the use of AuNP/$KNbO_3$ as a visible-light-activated material in the absence of solvent [22]. Only initially was there a limited conversion of the SPA substrate to the desired acetophenone product **17** (8%) in combination with H_2O_2, AuNP/$KNbO_3$ and LED cubic array as the visible light source. But when TEA is added and the exposure time is increased by an hour, the percentage of conversion to acetophenone jumps to 38%. This increase in the carbonyl product conversion rate demonstrates the significance of the base in the reaction mixture. TEA was chosen to continue the research after the photooxidation of SPA was conducted in the presence of three bases: a strong

base (NaOH), a weak base (Na_2CO_3) and an amine base (TEA). They discovered that NaOH was acting efficiently and that reactions involving the bicarbonate base frequently produce an undetectable by-product, decreasing selectivity. The minimum concentration of TEA was kept constant to preserve the overall effectiveness of SPA photooxidation. Green LED photoreactor lamps provide a superior source of visible light in terms of percent conversion and efficiency compared to high-powered LED apparatus because the amount of carbonyl generated rises with increasing light source power (Figure 1.11).



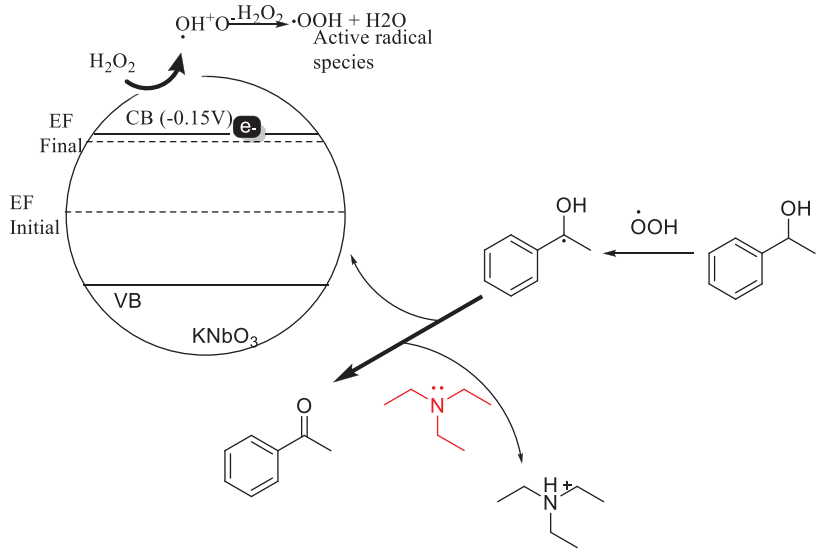


Figure 1.11: Photocatalytic triethylamine-mediated oxidation of alcohols.

1.3 Triethylamine-promoted electrochemical reactions

1.3.1 Triethylamine-mediated electrochemical alcohol oxidation

Activities for converting energy and chemicals are largely focused on the electrochemical oxidation of alcohols, with applications in fuel cells, the use of biomass and fine chemical synthesis. Small-molecule electrocatalysts for these kinds of processes are an intriguing area for further study, as evidenced by recent advancements in nickel catalysts for electrochemical hydrogen production and oxidation. It has been shown that complexes with tethered amines that resemble the active site of hydrogenases can catalyze hydrogen production (from protons and electrons) at rates far exceeding those of such enzymes while also mediating reversible electrocatalytic hydrogen production and oxidation with efficiency similar to that of the enzymes. The most extensively investigated electrocatalysts for alcohol oxidation are organic nitroxyls, such as TEMPO along with nickel complexes are frequently used to promote the reaction for various alcohols. However, the requirement for high electrode potentials sets a major drawback. (2,2′-Bipyridine) Cu/nitroxyl cocatalyst systems for electrochemical alcohol oxidation have been established by Stahl et al. [23] to overcome the drawback.

It undergoes the proton-coupled TEMPO/TEMPOH redox process as opposed to the high-potential TEMPO/$TEMPO^+$ process mechanically. The use of TEA makes this possible. In addition to recycling the catalyst and serving as a base, Et_3N also mediates the oxidation of alcohol **18** (Figure 1.12). These results suggest a novel strategy for the design of non-precious metal electrocatalysts by showing that efficient two-electron electrochemical processes can be achieved by combining mediators of electron–proton transfer, such as TEMPO, with first-row transition metals, such as copper.

1.3.2 Triethylamine-mediated electrochemical reductive decarboxylative coupling

Zeng and coworkers [24] reported the first instance of reductive decarboxylationative coupling of *N*-hydroxyphthalimide (NHP) ester **20** with quinoxalinone **19** that is electrochemically enabled and catalyzed by $NiCl_2$.

It was proposed to decarboxylately couple quinoxalinone to an NHP ester and was based on experimental research and relevant literature publications. At the cathode, Ni(I) is initially created by reducing Ni(II). The resulting Ni(I) species undergoes a single-electron transfer with NHP ester to produce Ni(II) species and a cyclohexyl radical (path a). However, the possibility that an NHP ester could be directly reduced at the cathode to create a cyclohexyl radical cannot be completely disregarded (path b). The radical cation is created by combining the complex and the cyclohexyl radical after which the radical

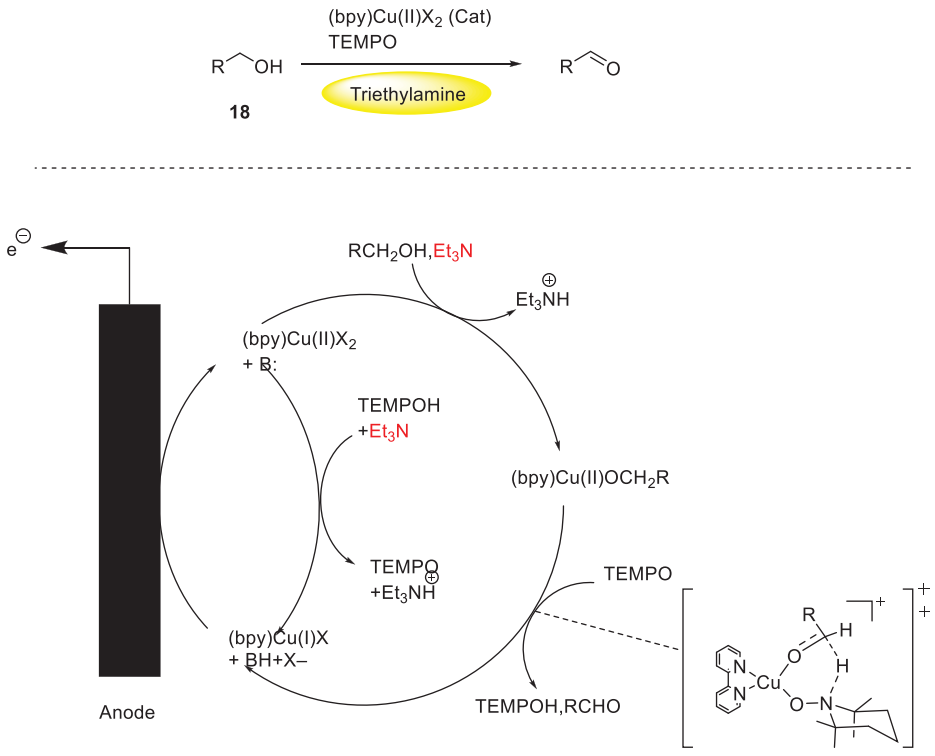


Figure 1.12: Triethylamine-mediated electrochemical alcohol oxidation.

loses one molecule of H^+ to create the radical. Before losing one Ni(II) molecule, the radical undergoes one more round of oxidation to produce the desired product. Meanwhile, Et_3N is oxidized at the anode to create a TEA radical cation (Figure 1.13).

Biochemically significant 3-alkylated quinoxalinones **21** were produced in good to outstanding yields by combining nickel catalysis and electrochemistry. The current approach has a wide range of substrates, gentle conditions, inexpensive catalysts and great functional group tolerance.

1.3.3 Triethylamine-mediated electrocatalyzed mild C–H alkylations

Direct alkylations of carboxylic acid derivatives can be challenging, and nickel catalysis frequently necessitates hot reactions and powerful bases, which limits the range of substrates. In a study by Samanta et al. [25], unactivated 8-aminoquinoline amide **22** was subjected to nickel-catalyzed C–H alkylations at room temperature, using a mild base and a simple electrochemical setup. This C–H alkylation is electrocatalyzed,

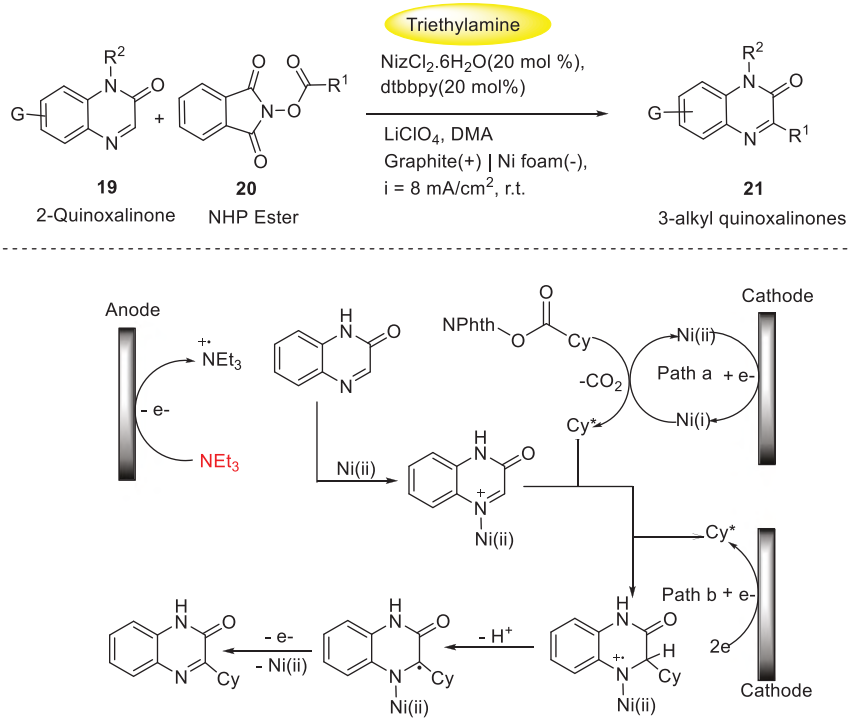
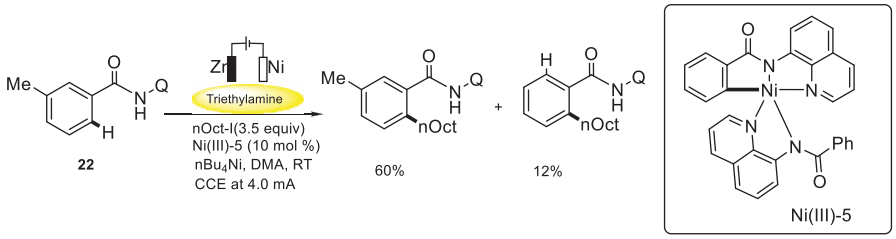


Figure 1.13: Triethylamine-mediated electrochemically reductive decarboxylative coupling.

exhibits excellent functional group tolerance and can be used for both primary and secondary alkylation. A thorough mechanistic analysis has led to the suggestion of a nickel(II/III/I) catalytic manifold.

Therefore, a remarkable mild reaction for this type of reaction is produced by a nickel-catalyzed electrochemical process for directly C–H alkylating quinoline amides with the mild base (Et_3N) at room temperature. It was seen that without the use of TEA, moderate yield of only 55% was observed. This method allows for the conversion of a variety of primary and secondary alkyl iodides, while tolerating a number of delicate functional groups. Comprehensive mechanistic analyses provided strong evidence in favor of a Ni(II/III/I) catalytic cycle through SET mechanisms (Figure 1.14).



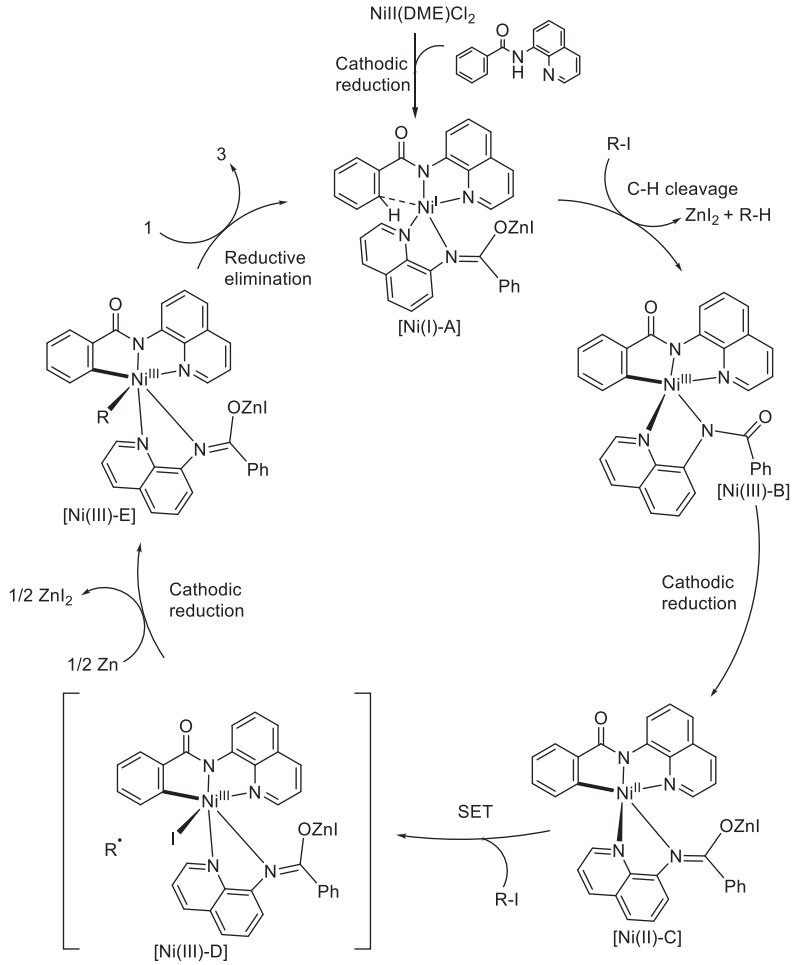


Figure 1.14: Triethylamine-mediated electrocatalyzed mild C–H alkylations.

1.4 Triethylamine-promoted organic reactions

1.4.1 Triethylamine-mediated synthesis of 2-oxazolidinones

One of the most important five-membered heterocycles in medicinal chemistry is 2-oxazolidinones. In drugs such as rivaroxaban, anticoagulants are synthesized from 2-oxazolidinone core. This demands a novel and simple synthetic protocol for their synthesis. Use of triethylamine hydroiodide as a bifunctional organocatalyst led to an efficient synthesis of 2-oxazolidinone **25** free of solvent and metal usage [26]. General reaction of epoxide **23** with phenyl isocyanate **24** for about 100 °C led to their formation of about 83%. The substrate scope of epoxides was expanded from different functional groups attached to epoxides to 2,2-disubstituted epoxide. However, when styrene oxide was used as a reactant, regioisomeric products were obtained. Triethylamine hydroiodide is regarded as a bifunctional organocatalyst as control experiments proved the effect of anion and acidic hydrogen of the catalyst were equally important to drive the reaction. Acidic hydrogen helps to activate the epoxide and iodine involves in a nucleophilic reaction with the activated epoxide. TEA promotes the reaction to obtain the optically pure product with retention of chirality (Figure 1.15).

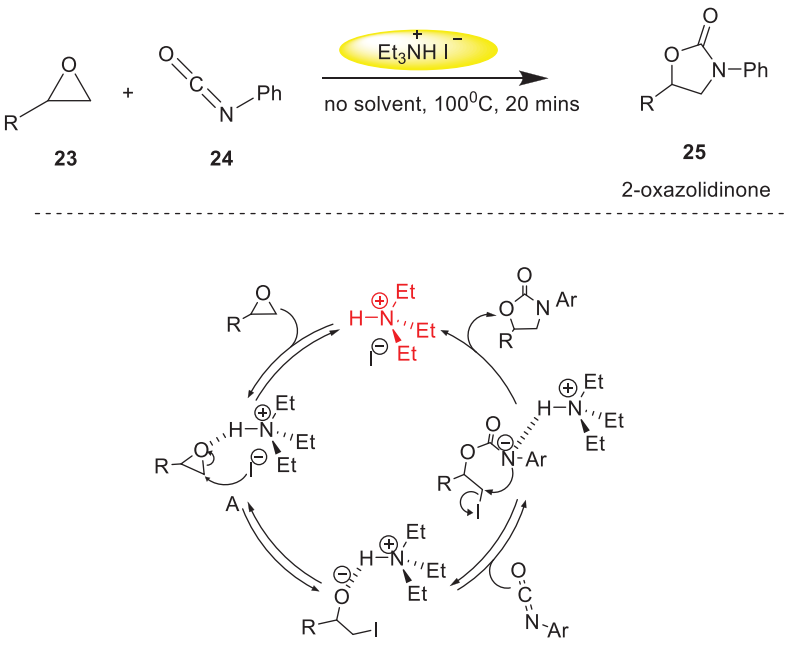


Figure 1.15: Triethylamine-mediated synthesis of 2-oxazolidinones.

1.4.2 Triethylamine-mediated synthesis of dialkyl 2-thiofumarates

One of the main tasks in organic synthesis is the development of straightforward synthetic routes for sulfur-containing compounds using readily available reagents because organosulfur compounds are widely present in many synthetic drugs and bioactive natural products and play a significant role in the biochemistry of almost all living things. Based on the addition reaction between dialkyl acetylene dicarboxylate **27** and aryl(benzyl) thiol **26** in the presence of TEA as a mild base, a mild, effective and stereoselective synthesis of dialkyl 2-thiofumarates **28** is described [27]. Different derivatives of aromatic thiols were added to dialkyl acetylene dicarboxylates with high stereoselectivity toward the synthesis of *Z*-configuration as the major isomer in the presence of TEA as a basic promoter in CH_2Cl_2 at room temperature. Good yields of the corresponding fumarates were obtained. TEA is added to increase the catalytic activity (Figure 1.16).

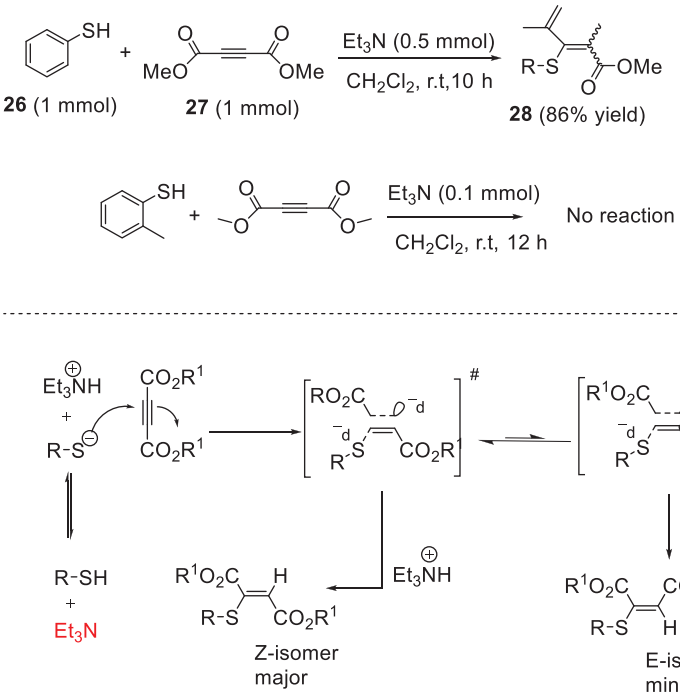


Figure 1.16: Triethylamine-mediated synthesis of dialkyl 2-thiofumarates.

1.4.3 Selective synthesis of multifunctionalized cyclopent-3-ene-1-carboxamides and 2-oxabicyclo[2.2.1]heptane derivatives

2-Oxabicyclo[2.2.1]heptane is one of the intriguing bridged cyclic scaffolds found in numerous biologically active compounds of heptane. By base-promoted reactions of phenacylmalononitriles with *o*-hydroxychalcones and their *o*-enolates, Zheng et al. [28] reported the selective synthesis of cyclopent-1-ene-1,2-dicarboxylates and 2-oxabicyclo-[2.2.1]heptane in good yields and with high diastereoselectivity. The multifunctionalized cyclopent-3-ene-1-carboxamides are produced in good yields and with a high degree of diastereoselectivity by the TEA-promoted cycloaddition reaction. Utilizing TEA (0.5 equiv.) resulted in an 85% increase in the yield of product **29**. A yield of 75% was

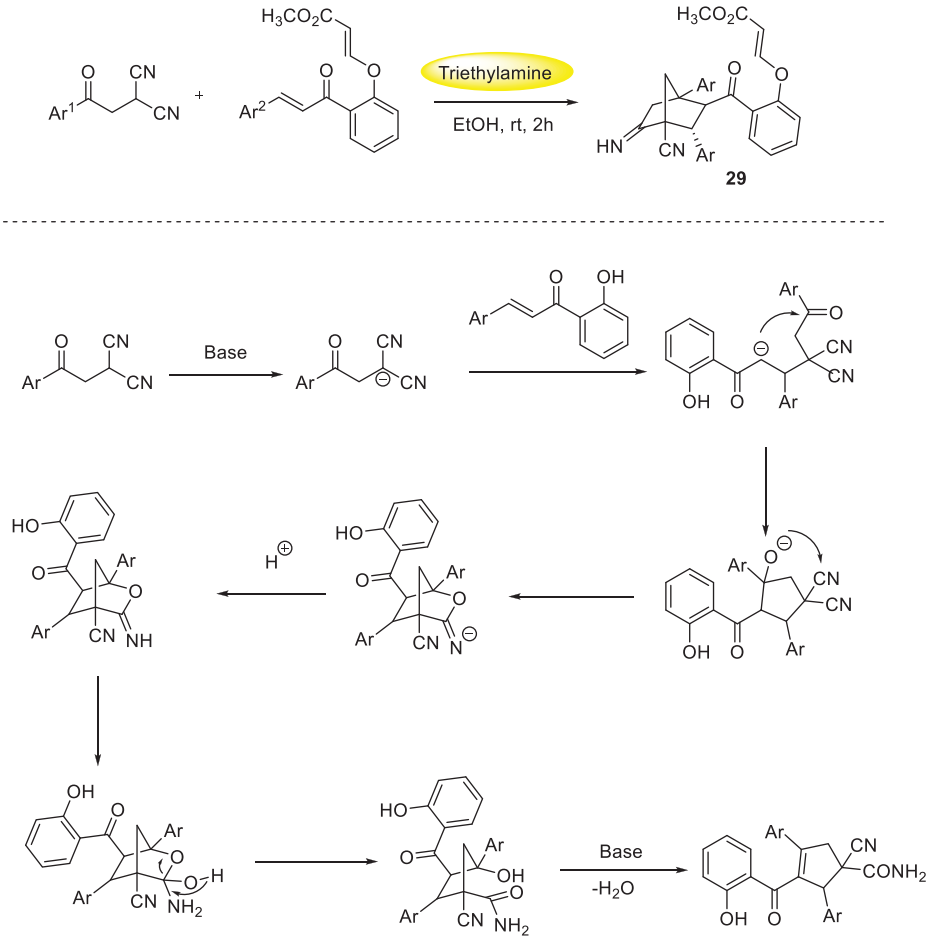


Figure 1.17: Triethylamine-mediated selective synthesis.

obtained with just 0.3 equivalents of TEA. However, in the presence of excess use of TEA, the yield slightly decreased to 70% (2.0 equiv.) (Figure 1.17).

1.4.4 Triethylamine-mediated Knoevenagel condensation

Cinnamic acid is used in a wide range of industrial products, including those for the production of pharmaceutical intermediates, flavors, perfumery goods and cosmetics. Cinnamic acid has antitumor and anti-inflammatory properties. Cinnamic acid and its derivatives are typically made by Knoevenagel condensation with an organic or inorganic base present. Typically, bases included ammonia: primary, secondary and their salts. The most popular Knoevenagel condensation uses piperidine as an organocatalyst with pyridine serving as both a solvent and a base. TEA in toluene was used as the base for this condensation reaction, which resulted in the formation of product **32**, according to Pawar et al. [29]. Pyridine is typically used for this condensation reaction. Of the three different tertiary amines (TEA, tertiary octyl acrylamide and tertiary butyl alcohol), TEA was found to yield well when catalytic amounts of piperidine were present. TEA was discovered to play the dual role of a base and a solubilizing agent for facilitating the reaction in both toluene and TEA itself. TEA and solvent were eliminated following the reaction using vacuum distillation (Figure 1.18).

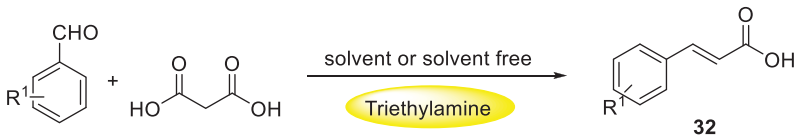


Figure 1.18: Triethylamine-mediated Knoevenagel condensation.

1.4.5 Triethylamine-mediated synthesis of phosphonate diols

Several phosphonate diols (bis-α-hydroxyphosphonates) can be effectively made from aromatic and heteroaromatic dialdehydes in a green, mild environment, according to a method that has been reported [30]. Because they were discovered to be biologically active and valuable synthetic precursors for the synthesis of related organophosphonates, such as α-aminophosphonates, alkoxy- and acyloxy-phosphonates, ketophosphonates and halophosphonates, hydroxyphosphonates have received a great deal of attention. Under solvent-free conditions or in a small amount of tetrahydrofuran at room temperature, a series of aromatic/heteroaromatic dialdehydes react with dialkyl phosphites to yield the corresponding bis-hydroxyphosphonate **33** with a moderate-to-excellent yield (52–95%) (Figure 1.19).

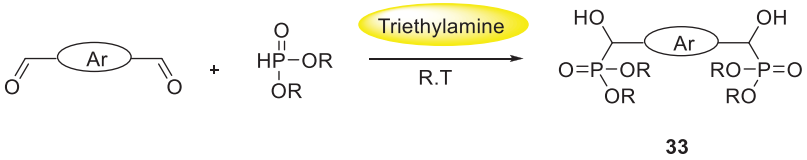


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Figure 1.19: Triethylamine-mediated synthesis of bis-α-hydroxyphosphonates.

1.4.6 Triethylamine-mediated regioselective synthesis of the indolopyrazines

Through a sequential Rh-catalyzed formal [3 + 3] cycloaddition and aromatization reaction of a variety of diazoindolinimines with azirines, Lee et al. [31] demonstrated a regioselective method for the synthesis of indolopyrazines. TEA (1.5 equiv.) is added to generate indolodihydropyrazine in situ, increasing the yield by up to 79%. Additionally, TEA addition causes a TsH elimination reaction, which yields the desired indolopyrazine **34** in 96% of the cases (Figure 1.20).

1.5 Conclusions

Due to its versatility, reactivity and ability to improve reaction efficiency, TEA is a widely used chemical in a variety of applications, including photocatalytic, electrochemical and organic syntheses. TEA is specifically used in the activation of C–X, C–H and C=O bonds, as well as the oxidation of alcohols to produce the corresponding carbonyl compounds. Additionally, it is used in the cascade synthesis of cyclic organic compounds. However, it should be handled with caution because it is toxic, and its high concentrations can cause irritation in the skin, eye and respiratory system. Its ability to act as a base in nucleophilic substitution reactions and to form stable complexes with electrophiles makes it a versatile tool in the synthesis of a wide range of organic compounds.

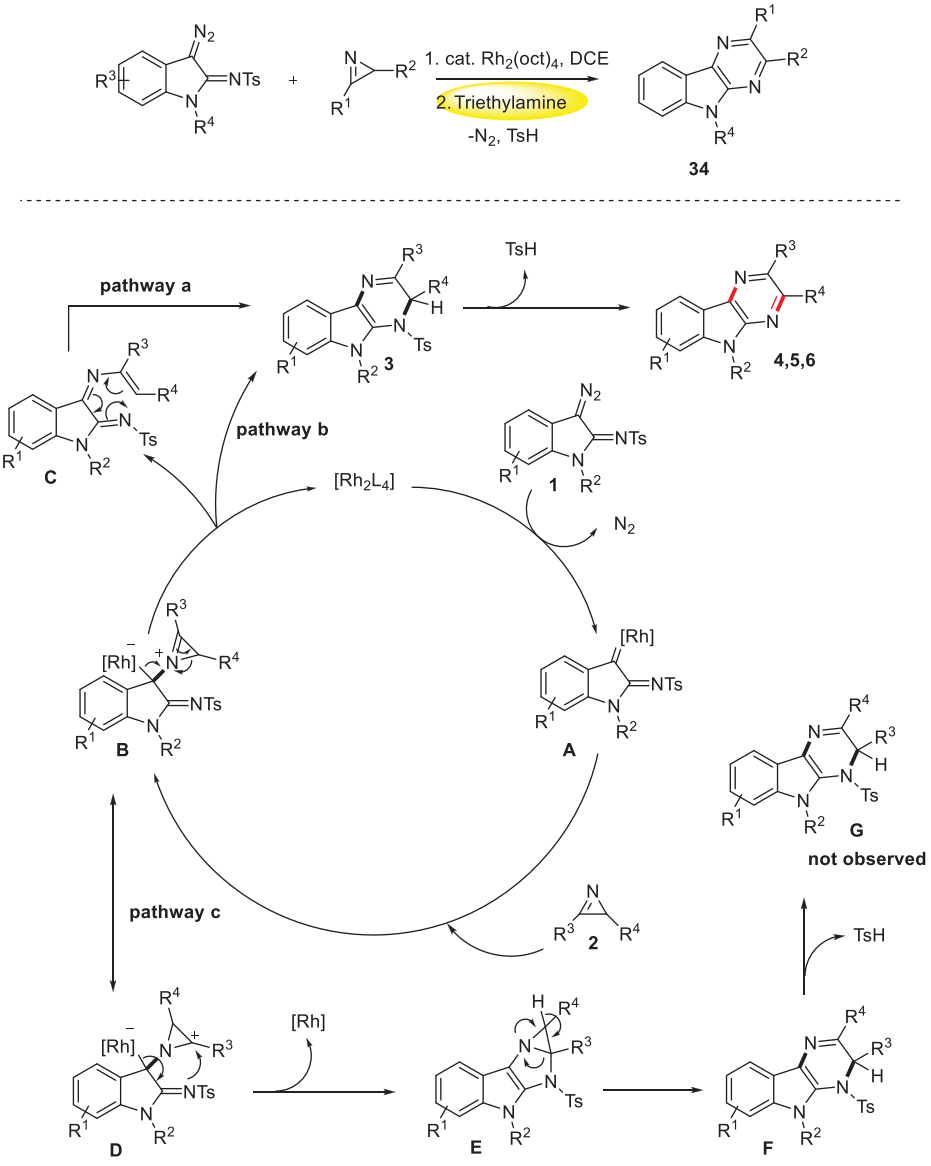

Figure 1.20: Triethylamine-mediated synthesis of indolopyrazines.

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Chapter 2
Organic transformations in nitromethane as solvent

2.1 Introduction

Nitromethane is the simplest nitro-compound. At normal conditions, it is liquid in nature. It is used as a reagent, solvent, stabilizer and fuel in sports car and rockets [1]. It is a highly polar solvent (ε = 37.5) almost comparable to acetonitrile (ε = 36.6) [2]. It has a higher dipole moment (μ = 3.46 D) [2]. These properties make it as an extremely versatile reaction media for various organic transformations, especially for stereoselective carbon–carbon bond formation [3]. It has been extensively used in chemical industries and can also be used for cleaning processes. In many reactions, nitromethane showed a dual character [4] by solving the purposes of both as a solvent and as a source for carbon and nitrogen [5]. Along with solvent, it can also be used simultaneously as a surrogate source of methylamine or nitrile [6]. In many cases, even under mild conditions, it behaves like stabilized carbanions due to the strong electron-withdrawing nature of the nitro group (pK_a $MeNO_2 < 10$) [7]. It is also used as a suitable nucleophilic donor in the Michael addition reaction. Moreover, the nitro group of nitromethane can be converted to ketone by following the pathways of Nef reaction [8]. It is used for the synthesis of nitroalkanols through the Henry reaction [9]. Very recently, in 2020, Liu et al. [10] explored the reactivity of nitromethane as a nitrogen donor in the Schmidt-type synthesis of amides and nitriles. In this chapter, we have summarized various organic transformations which were carried out in nitromethane as a solvent.

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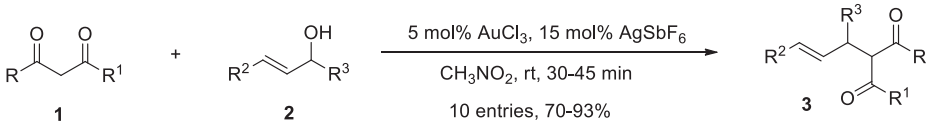
2.2 C–C bond formation in nitromethane

2.2.1 Alkylation of 1,3-dicarbonyl compounds

In 2009, Kothandaraman et al. [11] demonstrated a facile and efficient protocol for allylic alkylation of various 1,3-dicarbonyl compounds (**1**) with allylic alcohols (**2**) which afforded the corresponding adducts (**3**) in good to excellent yields (55–96%) in the presence of a catalytic mixture of $AuCl_3$ and $AgSbF_5$ in nitromethane at room temperature (Figure 2.1). All the reactions were completed within 45 min. During optimization, a number of other solvents such as dichloromethane (DCM), acetonitrile, 1,4-dioxane, benzene and toluene were also screened but afforded lesser products even after few hours.

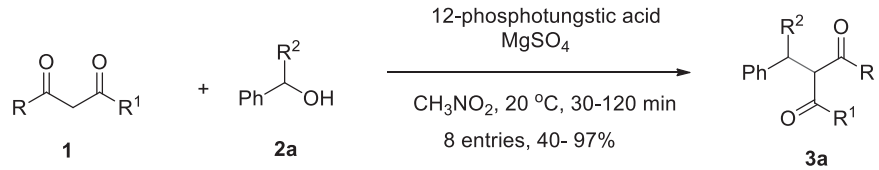


R = CH_3, C_6H_5
R^1 = CH_3, OEt, C_6H_5
R^2 = C_6H_5, 4-BrC_6H_4, 4-$CH_3C_6H_4$
R^3 = H, CH_3, C_6H_5, 4-BrC_6H_4, 4-$CH_3C_6H_4$

Figure 2.1: Nitromethane-mediated allylic alkylation of 1,3-dicarbonyl compounds with allylic alcohols.

2.2.2 Benzylation of 1,3-dicarbonyl compounds

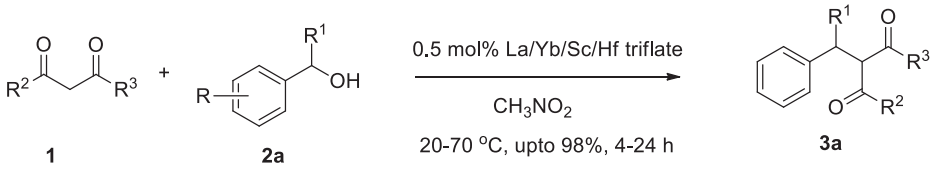
Wang et al. [12] reported a facile protocol for the direct substitution of the hydroxy group of various benzylic and allylic alcohols (**2a**) with diverse 1,3-dicarbonyl compounds (**1**) in the presence of a catalytic amount of 12-phosphotungstic acid and $MgSO_4$ as catalysts in nitromethane at ambient temperature (Figure 2.2). This efficient carbon–carbon bond-forming reaction provides a series of monoalkylated dicarbonyl compounds (**3a**) in high yields.



R = CH_3, C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4
R^1 = CH_3, C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4
R^2 = C_6H_5, CH_3, C_6H_5CH=CH

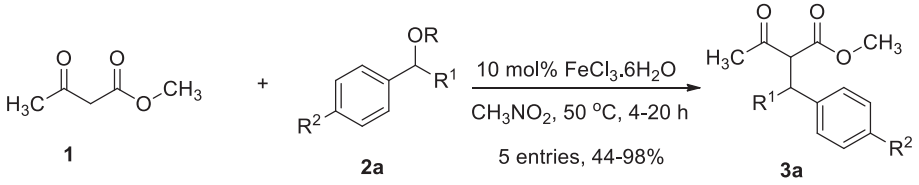
Figure 2.2: Nitromethane-mediated alkylation of 1,3-dicarbonyl compounds with various alcohols.

Noji et al. [13] reported various rare earth metal triflate-catalyzed secondary benzylation of 1,3-dicarbonyl compounds (**1**) in nitromethane as solvent at room temperature (Figure 2.3). A series of benzylated 1,3-dicarbonyl compounds (**3a**) were synthesized in excellent yields. It was proposed that the reaction undergoes through the formation of 1-phenylethyl cations generated from substituted 1-phenylethanols using the catalytic amount of metal triflates in nitromethane. After completion of the reaction, the used catalyst was recovered by water extraction and reused up to five times with almost equal efficiency. In the same year, Motokura et al. [14] also reported another protocol for the benzylation of 1,3-dicarbonyl compounds in nitromethane using montmorillonite as solid Brønsted acidic catalysts at 100 °C. Similar reaction was also achieved in nitromethane by using bismuth triflate as catalyst at 100 °C [15]. Kischel et al. [16] achieved benzylation of β-ketoesters (**1**) using ferric chloride as catalyst in nitromethane as solvent at 50 °C (Figure 2.4).



R = 4-OMe, 2,6-diCH_3, 4-CH_3, 2-CH_3, 4-Cl, 4-CO_2CH_3, 4-NO_2
R^1 = alkyl
R^2 = alkyl, aryl
R^3 = alkyl, aryl, ester, amide

Figure 2.3: Nitromethane-mediated benzylation of 1,3-dicarbonyl compounds.



R = H, CH_3CO
R^1 = H, CH_3, CH_3CH_2, C_6H_5
R^2 = H, OCH_3, Cl

Figure 2.4: Nitromethane-mediated ferric chloride-catalyzed benzylation of 1,3-dicarbonyl compounds.

2.2.3 Friedel–Crafts alkylation of indoles

Jana et al. [17] reported an efficient C_3-selective Friedel–Crafts alkylation of indoles (**4**) using allylic, benzylic and propargylic alcohols (**2**) using a catalytic amount of anhydrous $FeCl_3$ as catalyst in nitromethane at room temperature (Figure 2.5). Under this reaction conditions, the corresponding 3-alkyl substituted indoles (**5**) were synthesized in good to excellent yields within 3 h. It was proposed that the alcohol was activated by coordination with the catalyst $FeCl_3$ and the reaction undergoes through the aromatic electrophilic substitution.

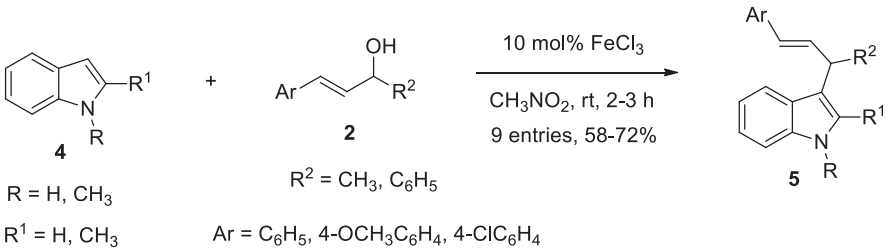


Figure 2.5: Nitromethane-mediated $FeCl_3$-catalyzed Friedel–Crafts alkylation of indoles with alcohols.

In 2010, Silveira et al. [18] demonstrated an efficient anhydrous $CeCl_3$-catalyzed method for the synthesis of several 3-propargyl indoles (**6**) in good yields from the reaction of substituted indoles (**4**) and propargyl alcohols (**2b**) in nitromethane under refluxed conditions (Figure 2.6).

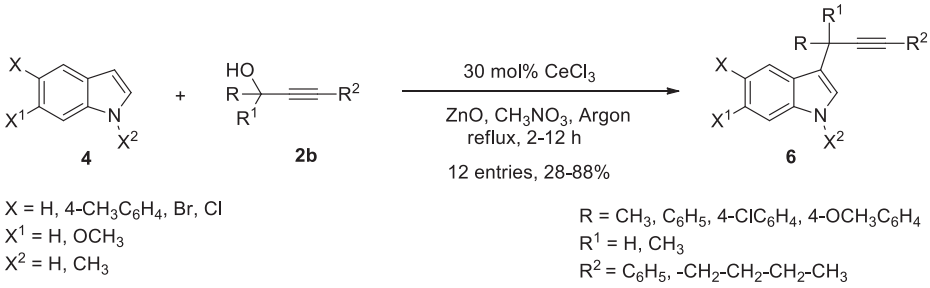


Figure 2.6: Nitromethane-mediated synthesis of 3-propargyl indole derivatives.

2.2.4 Friedel–Crafts alkylation of biaryl alcohols

In 2012, Jana and his research group [19] developed another nitromethane-mediated anhydrous $FeCl_3$-catalyzed protocol for the efficient synthesis of a series of substituted

fluorene derivatives (**8**) in excellent yields via the intramolecular Friedel–Crafts alkylation of biaryl methanol derivatives (**7**) at room temperature (Figure 2.7).

R = H, 3,4-diOCH_3; R^1 = H, 4-OCH_3, 4-CH_3, 4-Cl, 4-Br
R^2 = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, naphthyl, 9-phenanthryl

Figure 2.7: Nitromethane-mediated synthesis of substituted fluorenes at room temperature.

2.2.5 Alkylation of various arenes

In 2008, Rubenbauer and Bach [20] reported a facile gold(III) chloride ($AuCl_3$)-catalyzed protocol for the diastereoselective C–C bond formation of various chiral *para*-methoxybenzylic acetates (**9**) with several arene nucleophiles (**10**) in nitromethane at room temperature (Figure 2.8). It was proposed that the reactions proceeded through the formation of a free carbocation which was facilitated by a preferred conformation. Under the optimized reaction conditions, a variety of arene nucleophiles (**10**) underwent smoothly and afforded the corresponding *anti*-products (**11**) in high yields (63–99%). Li et al. [21] demonstrated an efficient protocol for the addition of electron-rich arenes (**10**) to aryl-substituted alkynes (**12**) which afforded the corresponding 1,1-diaryl alkenes (**13**) in good to excellent yields in the presence of a catalytic amount of $FeCl_3$ as catalyst in nitromethane at room temperature (Figure 2.9). Wang et al. [22] developed an interesting $FeCl_3$-catalyzed approach for Friedel–Crafts reaction between various electron-rich arenes (**10**) and aziridines (**14**) in nitromethane at room temperature. The reactions yielded the desired ring-opening products (**15**) regioselectively in moderate to excellent yields within just 2 min (Figure 2.10). During optimization, other solvents such as DCM, 1,2-dichloroethane (DCE) and tetrahydrofuran (THF) were also screened but found less effective for this reaction.

2.2.6 Tsuji–Trost coupling reaction

In general, the catalytic activation of sp^3 C–N bond of allylic amides is difficult to achieve because of the poor leaving group nature of the amide group. In 2010, Jiang et al. [23] demonstrated a simple and efficient Tsuji–Trost coupling [24, 25]-type

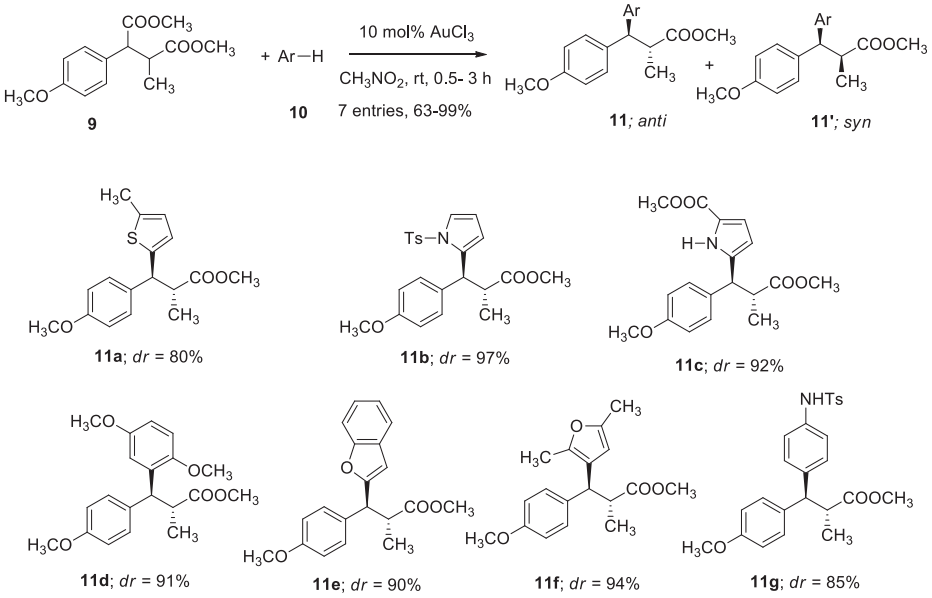


Figure 2.8: Nitromethane-mediated $AuCl_3$-catalyzed alkylation of various arenes with acetate containing nucleophiles.

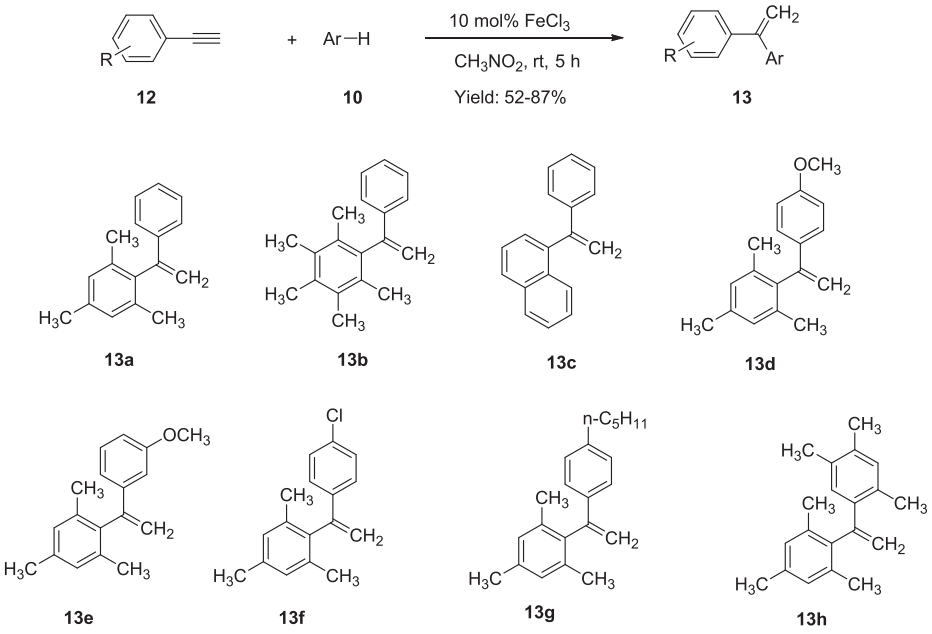


Figure 2.9: Nitromethane-mediated $FeCl_3$-catalyzed alkenylation of various arenes with aryl-substituted alkynes.

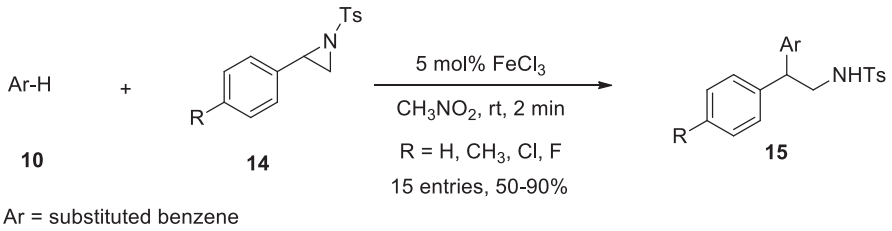


Figure 2.10: $FeCl_3$-catalyzed Friedel–Crafts reactions of electron-rich arenes with aziridines in nitromethane.

reaction between aromatic allylic amides (**16**) and various 1,3-dicarbonyl compounds (**1**)/dimedone (**1a**) using a catalytic amount of $FeCl_3$ as catalyst in nitromethane at room temperature (Figure 2.11). By using this method, the corresponding adducts (**17**, **18**) were synthesized in good to excellent yields. With the same catalyst, a number of other organic solvents such as THF, toluene, acetonitrile and DCM were also tested but failed to produce the desired product.

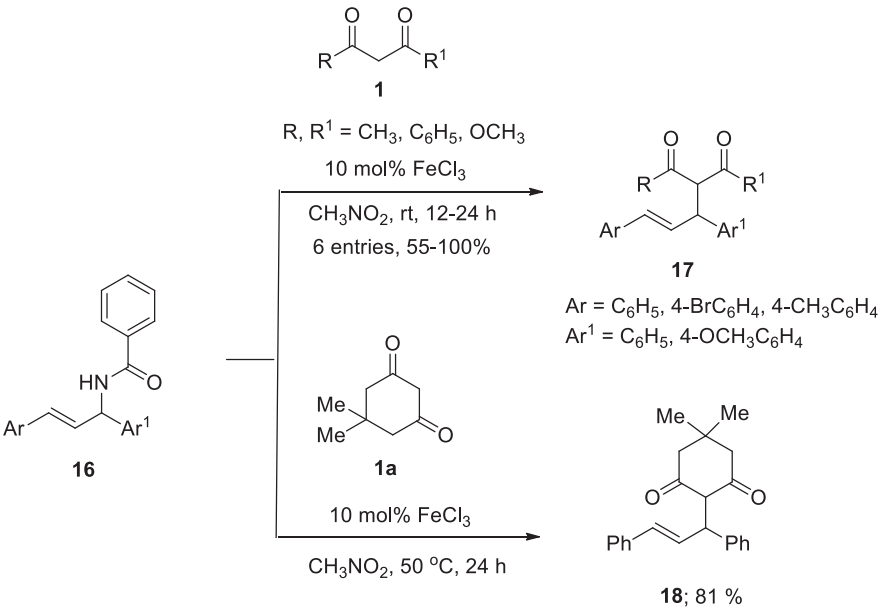


Figure 2.11: Nitromethane-mediated Tsuji–Trost-type coupling reactions of different allylic amides with activated methylated compounds.

2.2.7 Intramolecular Friedel–Crafts reaction

In 2009, Huang et al. [26] reported a simple and efficient approach for the synthesis of a series of new dihydronaphthalenes (**20**) or tetrahydronaphthalenes (**21**) via the intramolecular Friedel–Crafts reactions of aryl-substituted propargylic alcohols (**19**) using $FeCl_3$ as catalyst in nitromethane as solvent (Figure 2.12). By following almost the same strategy, they were also able to synthesize a number of tetrahydroisoquinoline derivatives (**23**) starting with *N*-substituted benzylamino-substituted propargylic alcohols (**22**) (Figure 2.13).

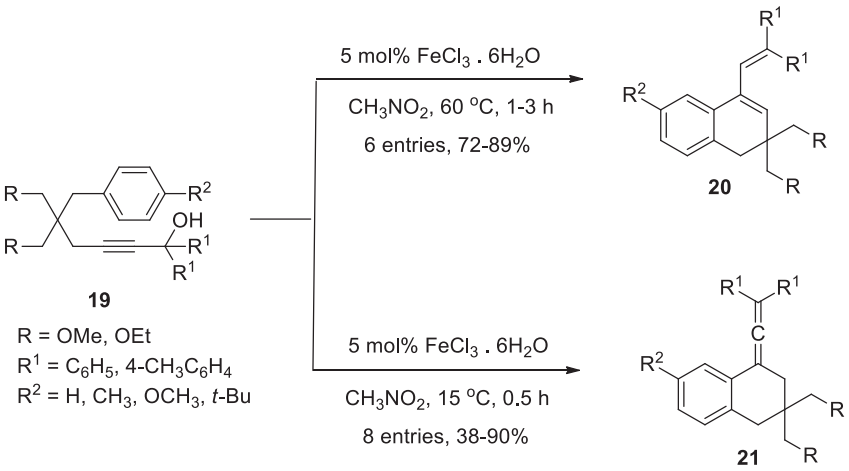


Figure 2.12: Nitromethane-mediated synthesis of dihydronaphthalenes or tetrahydronaphthalenes.

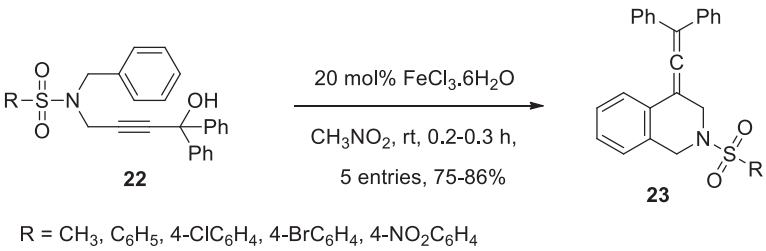
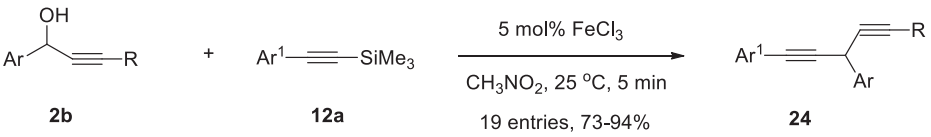


Figure 2.13: Nitromethane-mediated synthesis of tetrahydroisoquinolones.

2.2.8 Synthesis of 1,4-diynes

Lin et al. [27] prepared a series of substituted 1,4-diynes (**24**) in good to excellent yields via nucleophilic substitution of various propargylic alcohols (**2b**) with alkenyl silane (**12a**) in the presence of a catalytic amount of $FeCl_3$ in nitromethane as solvent at 25 °C (Figure 2.14). All reactions were completed within just 5 min. Interestingly, the aryl moiety with electron-withdrawing substituent in propargylic alcohols (**2b**) failed to afford the desired products.

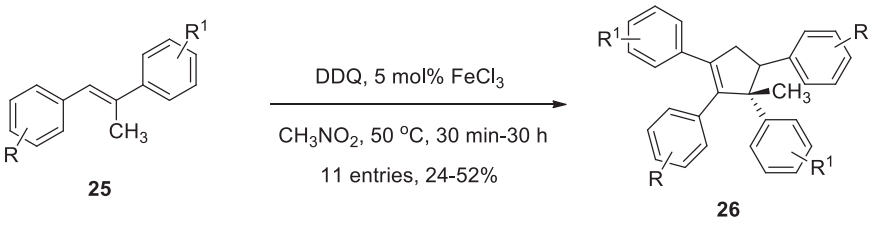


Ar = C_6H_5, 1-napthyl, 4-ClC_6H_4, 4-BrC_6H_4, 2-$CH_3C_6H_4$
R = C_6H_5, cyclopropyl, 1-cyclohexyl, $SiMe_3$, H, n-butyl
Ar^1 = C_6H_5, 4-BrC_6H_4, 4-$OCH_3C_6H_4$, 5-Me-2-furyl

Figure 2.14: Nitromethane-mediated $FeCl_3$-catalyzed synthesis of a series of 1,4-diynes.

2.2.9 Synthesis of tetra-aryl-substituted cyclopentenes

Li et al. [28] designed a simple C(sp^3)–C(sp^2) bond-forming approach to synthesize a series of tetra-aryl-substituted cyclopentenes (**26**) in moderate yields via the DDQ-mediated $FeCl_3$-catalyzed cross-dehydrogenative homo-coupling reactions of (*E*)-1,2-diarylprop-1-enes (**25**) in nitromethane as solvent at 50 °C (Figure 2.15). Under the same catalytic conditions, other organic solvents such as toluene, 1,4-dioxane and acetonitrile failed to afford the desired product. The plausible mechanism of this conversation is depicted in Figure 2.16.



R = H, 4-CH_3, 4-Br
R^1 = H, 4-CH_3, 4-Br, 3-Br, 4-Cl

Figure 2.15: Nitromethane-mediated synthesis of tetra-aryl-substituted cyclopentenes.

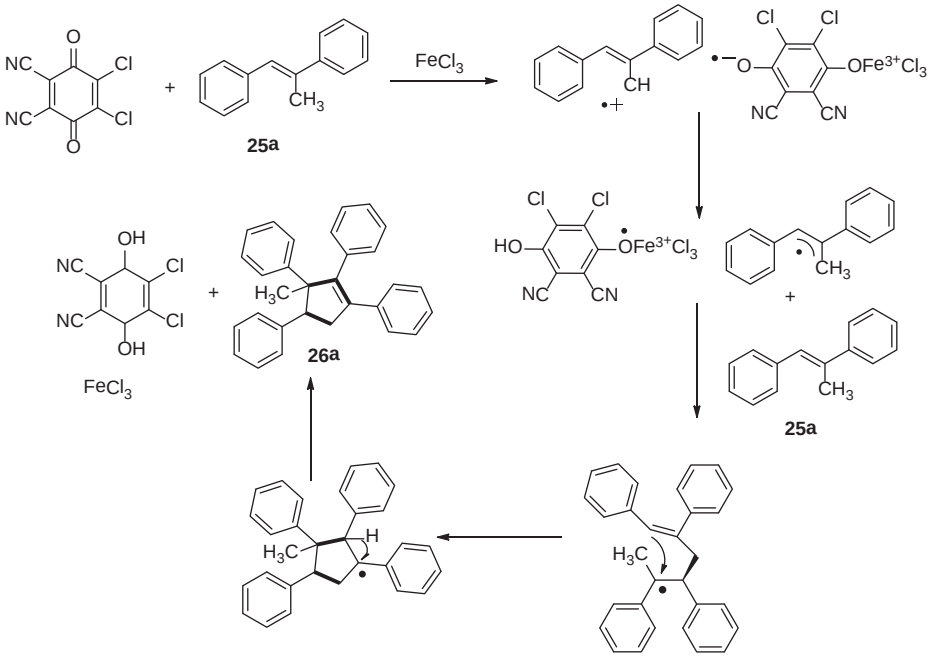


Figure 2.16: Plausible mechanism for the synthesis of tetra-aryl-substituted cyclopentenes.

2.2.10 Synthesis of substituted aryl ketones

In 2008, Jana et al. [29] synthesized a series of substituted aryl ketones (**27**, **27a**) via the direct addition reactions of various benzylic alcohols (**2a**) and several substituted terminal aryl alkynes (**12**) in the presence of $FeCl_3$ as catalyst in nitromethane (Figure 2.17). Anhydrous $FeCl_3$-catalyzed reactions afforded the desired products in higher yields at room temperature, whereas $FeCl_3{\cdot}6H_2O$ as catalyst yielded lower products even at higher temperature (80 °C). It was observed that the electron-rich alkynes underwent more efficiently than the neutral or electron-deficient alkynes. Authors were able to isolate the intermediate (**28**) and proposed the mechanism shown in Figure 2.18.

2.2.11 Synthesis of trisubstituted alkenes

Li et al. [30] reported a highly stereoselective synthesis of trisubstituted alkenes (**29**) via a three-component reaction of terminal alkynes (**12**), benzylic alcohols (**2a**) and substituted benzene or naphthalenes (**10**) in the presence of a catalytic combination of trifluoromethanesulfonyl anhydride (Tf_2O), ferric chloride and silver nitrate in nitromethane at low temperature (Figure 2.19). Under this reaction conditions, at low temperature, *E*-isomer (**29**)

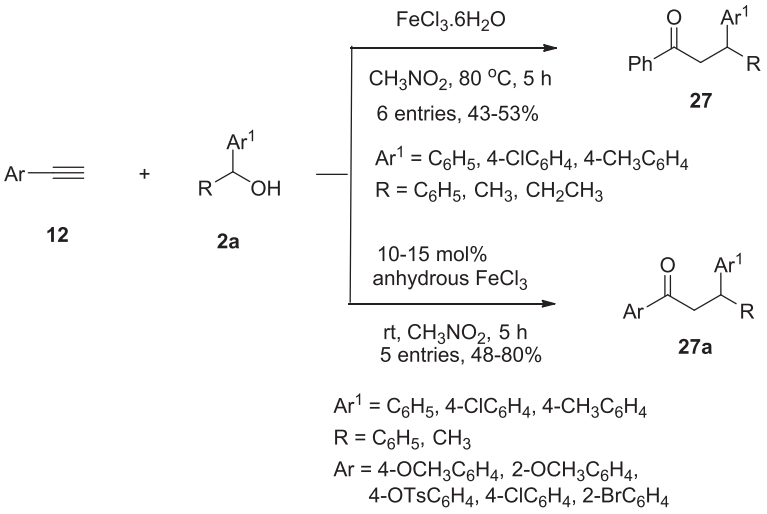


Figure 2.17: Nitromethane-mediated synthesis of substituted aryl ketones starting from terminal alkynes and various substituted benzylic alcohols.

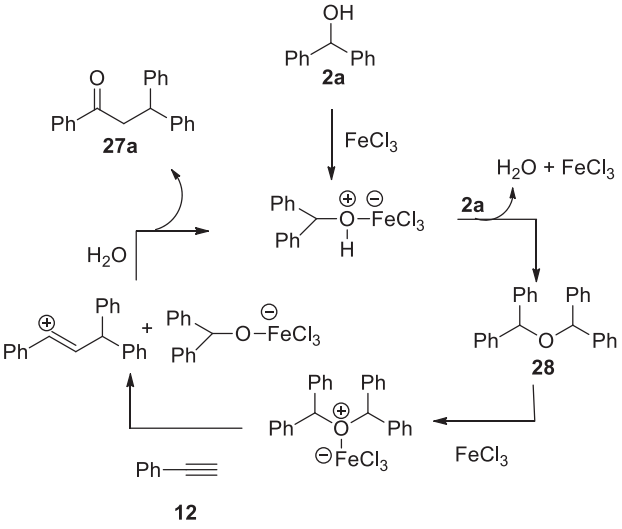
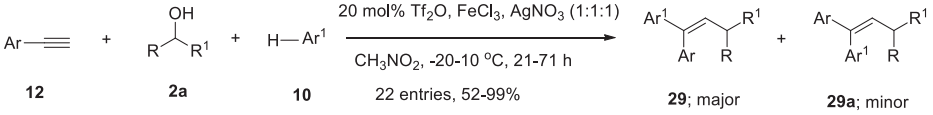


Figure 2.18: Plausible mechanism for the synthesis of substituted aryl ketones.

predominates over *Z*-isomer (**29a**) though it requires longer reaction times. Other organic solvents like DCE, chloroform, DCM, THF, ethyl acetate, acetonitrile and 1,4-dioxane failed to produce the desired products though nitromethane as solvent afforded moderate yield. Interestingly, the same reaction with only ferric chloride as catalyst at higher temperature (80 °C) afforded the *Z*-isomer (**29a**) predominately over *E*-isomer (**29**) within just 5 h.

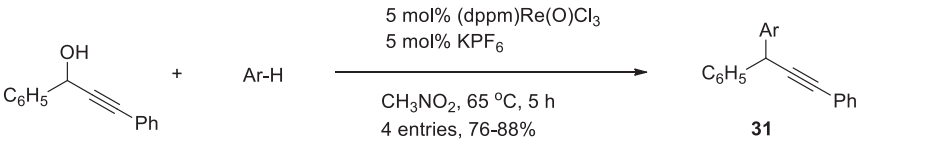


Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-tBuC_6H_4, 4-$OCH_3C_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 2-FC_6H_4
Ar^1 = 2,4,6-tri$CH_3C_6H_2$, 3-I-2,4,6-triCH_3C_6H, 2,4-di$CH_3C_6H_3$, 2,5-di$CH_3C_6H_3$,
3-Br-2,4,6-triCH_3C_6H, 2,3,5,6-tetraC_6H,1-napthyl
R = C_6H_5, 4-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 2-napthyl,
R^1 = C_6H_5, 4-ClC_6H_4, CH_3

Figure 2.19: Nitromethane-mediated synthesis of trisubstituted alkenes.

2.2.12 Synthesis of propargylic arenes

Toste and his group [31] employed diphenylphosphinomethane-functionalized rhenium-oxo complex ((dppm)$ReOCl_3$) as an efficient air- and moisture-tolerant catalyst for the regioselective synthesis of a series of propargylic arenes (**31**) from the reactions of propargyl alcohol (**30**) and various substituted aromatic compounds (**10**) in nitromethane at 65 °C (Figure 2.20). Phenols, naphthols, methoxybenzenes and various heteroaryl compounds also afforded the desired products in excellent yields.



Ar = 2,3,5-tri$OCH_3C_6H_2$, 2,4-di$OCH_3C_6H_3$,
2-$OCH_3C_6H_4$, 2,4-di$OCH_3C_6H_3$

Figure 2.20: Rhenium-catalyzed aromatic propargylation reaction.

2.3 C–N bond formation in nitromethane

Jana et al. [32] reported a simple and facile direct C–N bond forming the reaction protocol between various benzylic and allylic alcohols (**2a**) and primary amides (**32**) in the presence of a catalytic amount of $FeCl_3$ as a catalyst in nitromethane as solvent under refluxed conditions (Figure 2.21). This reaction afforded the corresponding amides (**33**) in excellent yields. Interestingly, sulfonamide and acrylamide also underwent smoothly and afforded the desired products with excellent yields.

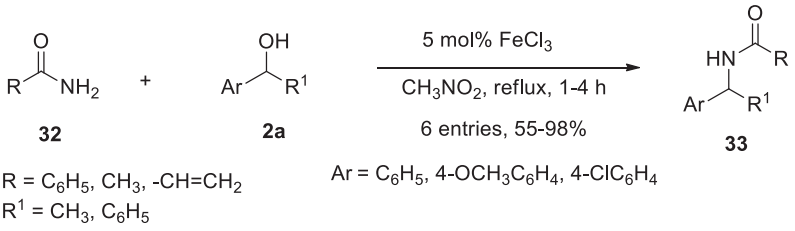
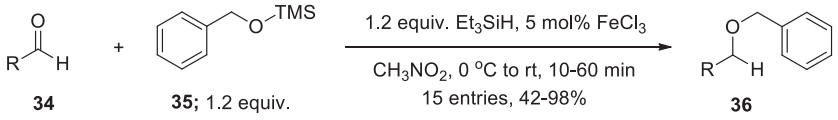


Figure 2.21: $FeCl_3$-catalyzed amidation reaction of secondary benzylic and allylic alcohols.

2.4 Etherification reaction in nitromethane

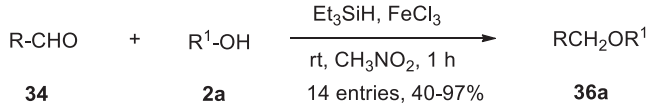
Oriyama and his research group [33] reported a simple, efficient and $FeCl_3$-catalyzed method for the reductive etherification of carbonyl compounds (**34**) by reaction with triethylsilane and alkoxytrimethylsilane (**35**) in nitromethane (Figure 2.22). The corresponding benzyl/ allyl ethers (**36**) were obtained in good to excellent yields within just 1 h at room temperature.



R = $C_6H_5CH_2CH_2$, $C_6H_5CH(CH_3)$, C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2,4,6- $(CH_3)_3C_6H_2$, 4-$OCH_3C_6H_4$,4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3OOCC_6H_4$, 4-$AcOC_6H_4$, 4-AcC_6H_4, 2-napthyl, cinnamyl

Figure 2.22: $FeCl_3$-catalyzed reductive etherification of carbonyl compounds in nitromethane.

The same group [34] reported another nitromethane-mediated $FeCl_3$-catalyzed method for the synthesis of various alkyl ethers (**36a**) through the reductive etherification of carbonyl compounds (**34**) with alcohols (**2a**) (Figure 2.23).

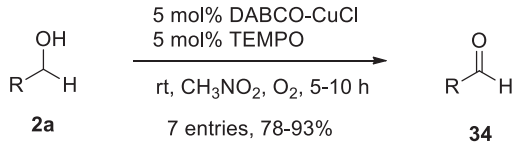


R = C_6H_5, 2-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, 2-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-BrC_6H_5, 4-$COOCH_3C_6H_4$, -$CH_2CH_2C_6H_5$, 4-CH_3OOC-C_6H_4, 4-$CH_3COC_6H_4$, 1-napthyl, 2-napthyl
R^1 = -$CH_2CH_2CH_2C_6H_5$, -$CH_2CH_2CH(CH_3)$, -$CH_2C_6H_4$

Figure 2.23: $FeCl_3$-catalyzed synthesis of various alkyl ethers in nitromethane.

2.5 Oxidation of alcohols in nitromethane

In 2007, Mannam et al. [35] demonstrated a facile method for the oxidation of various alcohols (**2a**) to the corresponding carbonyl compounds (**34**) in the presence of a catalytic mixture of 1,4-diazabicyclo[2.2.2]octane (DABCO), CuCl and 2,2,6,6-tetramethyl-1-piperidinyloxyl radical (TEMPO) in nitromethane as solvent at room temperature (Figure 2.24). Under the same reaction conditions, other solvents such as acetonitrile, dimethyl sulfoxide, dimethyl formamide and 1,4-dioxane afforded poor yields of the desired products.

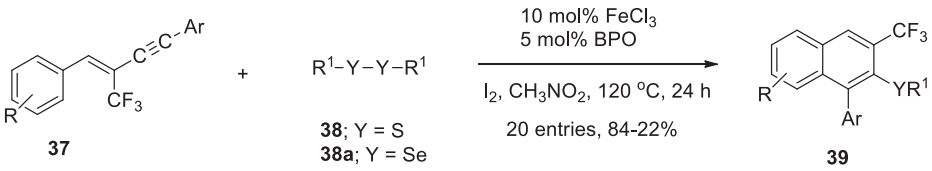


R = 4-$OCH_3C_6H_4$, C_6H_5, 3,4,5-$(OCH_3)_3$-C_6H_2, 4-ClC_6H_4,
4-$NO_2C_6H_4$, 2-furyl, cinnamyl

Figure 2.24: Nitromethane-mediated oxidation of alcohols to carbonyl compounds.

2.6 C–C and C–X (C-heteroatom) bond formation in nitromethane

Yang et al. [36] developed a simple and efficient method for the electrophilic annulations of trifluoromethyl-containing aryl enynes (**37**) with disulfides (**38**) or diselenides (**38a**) in nitromethane, which afford the corresponding polysubstituted naphthalenes (**39**) in good to excellent yields (Figure 2.25). The reaction was promoted by a catalytic mixture of $FeCl_3$ and benzoyl peroxide in the presence of excess molecular iodine at 120 °C.



R = H, 4-CH_3, 4-t-Butyl, 6-Cl, 4-C_6H_5,
R^1 = 4-ClC_6H_4, 4-FC_6H_4, 3-FC_6H_4, CH_3, -CH_2CH_3, C_6H_5,
Ar = C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3C_6H_5$, 4-ClC_6H_5, 4-$NO_2C_6H_4$

Figure 2.25: Iron-promoted electrophilic annulations of aryl enynes with disulfides or diselenides in nitromethane.

Kumamoto et al. [37] reported a simple, facile and efficient method for the synthesis of 2-aryl-2-methoxyacetonitrile derivatives (**42**) from the reactions of aromatic acetals (**40**) with trimethylsilyl cyanide (**41**) in nitromethane under high-pressure conditions at 60–80 °C (Figure 2.26). Authors proposed a mechanism, and the role of nitromethane is shown in Figure 2.27.

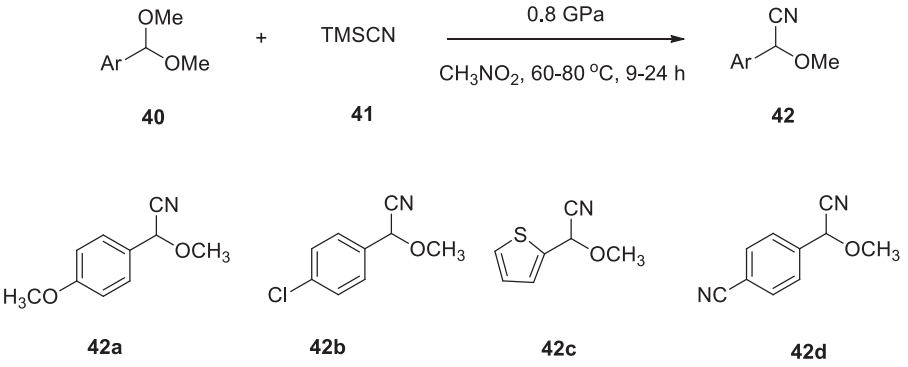


Figure 2.26: Nitromethane-mediated synthesis of 2-aryl-2-methoxyacetonitrile derivatives.

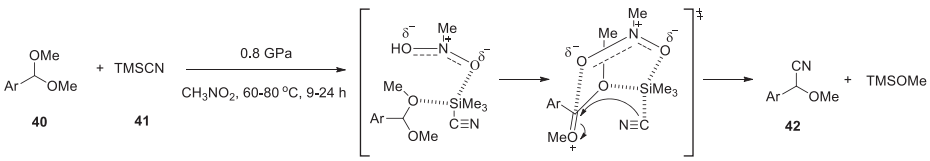


Figure 2.27: Plausible mechanism of nitromethane-mediated synthesis of 2-aryl-2-methoxyacetonitrile derivatives.

Halli and Manolikakes [38] prepared a series of α-amino ester derivatives (**45**) from the reactions of various readily available amides (**43**), glyoxalates (**44**) and arenes or heteroarenes (**10**) using various iron catalysts in nitromethane as solvent under heating conditions (Figure 2.28). By using carbamates as the amide component, various synthetically very useful *N*-protected arylglycine derivatives could be prepared.

2.7 Synthesis of heterocycles

Heterocyclic skeletons are very common in naturally occurring as well as synthetic bioactive molecules. During last few years, we have compiled many literatures for the synthesis of various types of biologically promising heterocycles under diverse reaction conditions [39–48].

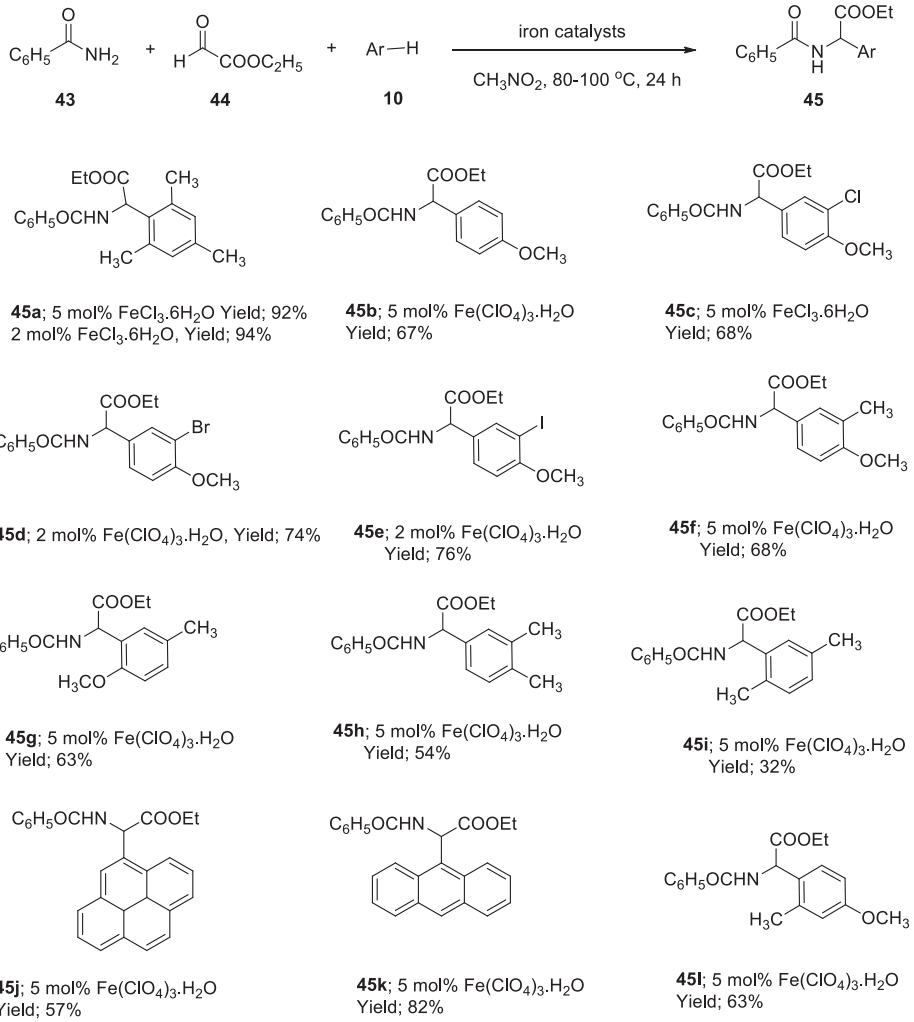


Figure 2.28: Nitromethane-mediated synthesis of α-amino ester derivatives.

2.7.1 Synthesis of *O*-heterocycles

Li and Gu [49] synthesized 12-(4-hydroxy-3-methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[*a*]xanthen-11(12H)-one (**48**) in 76% yield from the reaction of 4-hydroxy-3-methoxybenzaldehyde (**46**), dimedone (**1a**) and 2-naphthol (**47**) in the presence of a catalytic amount of bismuth triflate as catalyst in nitromethane at 80 °C (Figure 2.29). The same group also synthesized 9-(2-hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-

tetrahydro-1H-xanthen-1-one derivatives (**50**) in moderate to good yields via one-pot three-component reactions of salicylaldehydes (**49**), dimedone (**1a**) and 2-naphthol (**47**) in the presence of a catalytic mixture of $FeCl_3$ and triphenylphosphine as catalyst in nitromethane at 100 °C (Figure 2.30). Here, triphenylphosphine plays the role of hydrogen bond acceptor.

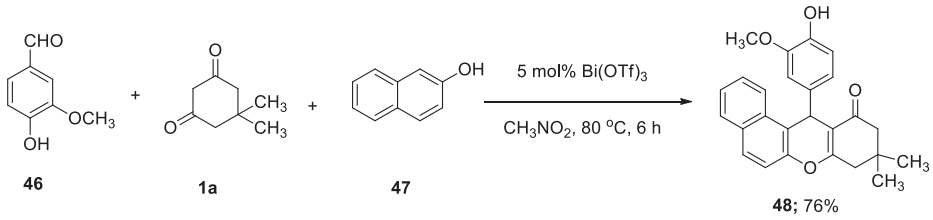


Figure 2.29: Nitromethane-mediated synthesis of 12-(4-hydroxy-3-methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[*a*]xanthen-11(12H)-one.

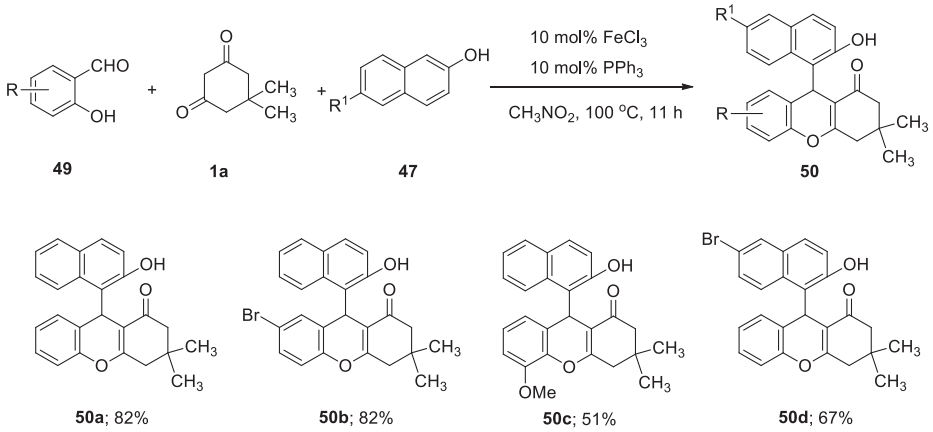
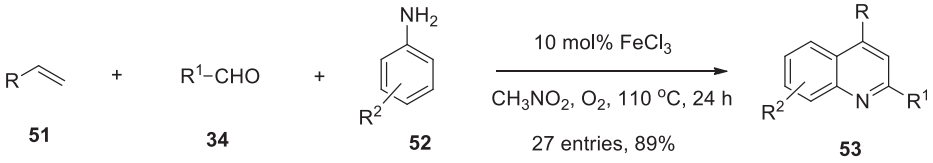


Figure 2.30: Nitromethane-mediated synthesis of 9-(2-hydroxynaphthalen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-ones.

2.7.2 Synthesis of *N*-heterocycles

2.7.2.1 Synthesis of substituted quinolines

In 2014, Gandeepan et al. [50] reported a practical, simple and environmentally benign protocol for the efficient synthesis of a series of substituted quinolines (**53**) via $FeCl_3$-catalyzed one-pot three-component coupling reactions of styrenes (**51**), aldehydes (**34**) and substituted anilines (**52**) in the presence of oxygen in nitromethane as solvent at 110 °C (Figure 2.31).



R = C_6H_5, 3-OCH_3, 4-Cl, 4-Br, 4-F, 4-OCH_3, 4-C_6H_5, napthyl, thiophene
R^1 = 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4,
4-FC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 4-$COOCH_3C_6H_4$, 2-OHC_6H_4, 2-napthyl, 2-thienyl
R^2 = H, 4-CH_3, 3,5-diCH_3, 2-CH_3, 4-Br, 4-F, 4-OCH_3

Figure 2.31: Nitromethane-mediated synthesis of substituted quinolines.

2.7.2.2 Synthesis of substituted isoquinolines

In 2008, Huang et al. [51] developed a simple, efficient and versatile method for the synthesis of a series of structurally diverse substituted dihydro- and tetrahydroisoquinolines (**55**) via the intramolecular Friedel–Crafts allenylation reaction followed by cyclization reaction of various benzylamino-substituted propargylic alcohols (**54**) in the presence of a catalytic amount of $FeCl_3$ as a catalyst in nitromethane (Figure 2.32). All reactions were completed in 1 h.

2.8 Dual role of nitromethane

2.8.1 Asymmetric allylic alkylation

Nemoto et al. [52] achieved the asymmetric allylic alkylation of 1,3-diaryl-substituted allyl carbonates (**56**) with excess nitromethane using palladium as a catalyst in the presence of a catalytic amount of aspartic acid-derived *P*-chirogenic diaminophosphine oxide [(S,R_P)-Ph-DIAPHOX] at room temperature (Figure 2.33). In this protocol, nitromethane played a dual role, both as a solvent and as an alkylating agent. Under this optimized reaction conditions, they successfully prepared (*R*)-preclamol and (*R*)-baclofen enantioselectively.

2.8.2 Synthesis of β-nitro-α-hydroxy esters

Blay et al. [53] prepared a chiral iminopyridine (**60**) starting from (*R*)-(–)-fenchone and picolylamine. Using the synthesized ligands and in the presence of a catalytic amount of copper triflate [$Cu(OTf)_2$] as catalyst, they successfully achieved the enantioselective Henry reaction of α-keto esters (**58**) and excess nitromethane at very low

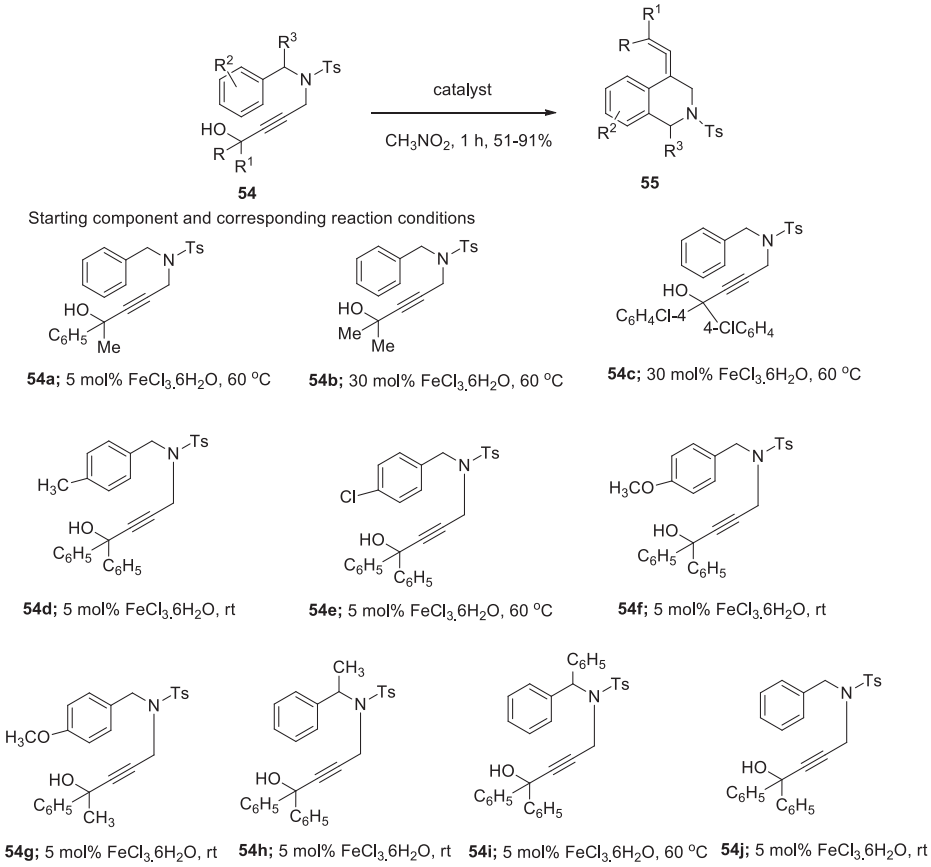
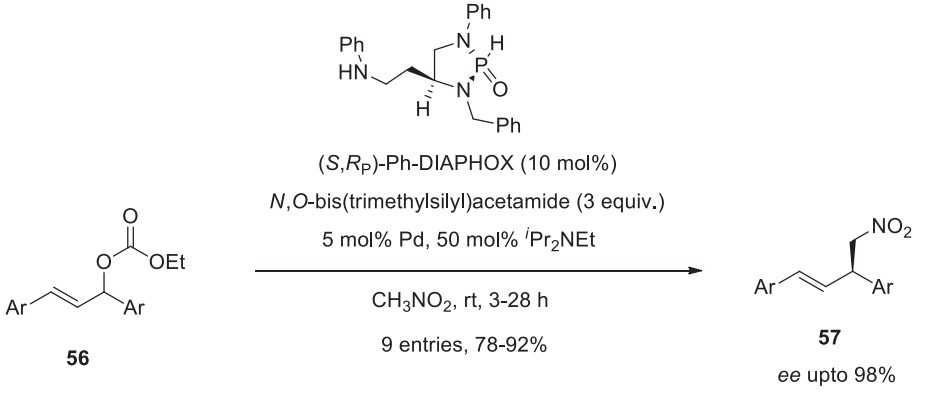


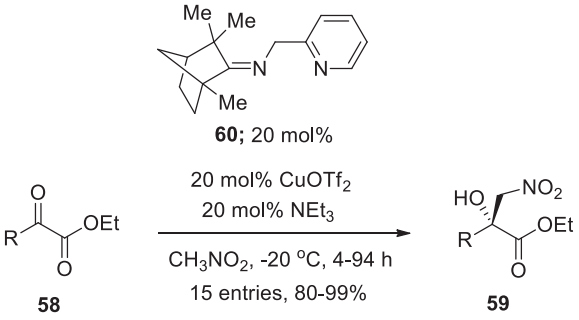
Figure 2.32: Nitromethane-mediated synthesis of various dihydro- and tetrahydroisoquinolines.



Ar = C_6H_5, 4-$CH_3C_6H_4$, 3-ClC_6H_4, 3-FC_6H_4, 3-$OCH_3C_6H_4$, 2-FC_6H_4, 2-$CH_3C_6H_4$, 2-naphthyl

Figure 2.33: Asymmetric allylic alkylation of 1,3-diaryl allyl carbonates in nitromethane.

temperature (Figure 2.34). This reaction afforded the corresponding β-nitro-α-hydroxy esters (**59**) in good yields and modest to good enantioselectivities. A wide variety of α-keto esters, bearing alkyl, aryl or alkenyl groups were well tolerated under this optimized reaction conditions. In this protocol, nitromethane is used both as a solvent and as an alkylating agent. Authors proposed that the addition of nitromethane to α-keto esters proceeded through the transition states as shown in Figure 2.35.



R = CH_3, C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 3,5-diFC_6H_3, 3,5-di$CF_3C_6H_3$, 2-naphthyl, $CH_3(CH_2)_9$-, $C_6H_5(CH_2)_2$-, $(CH_3)_2CH$-, C_6H_{11}, CH_3CH=CH-, $C_6H_4CH_2OCH_2CH$=CH-

Figure 2.34: Synthesis of β-nitro-α-hydroxy esters in nitromethane via the Henry reaction.

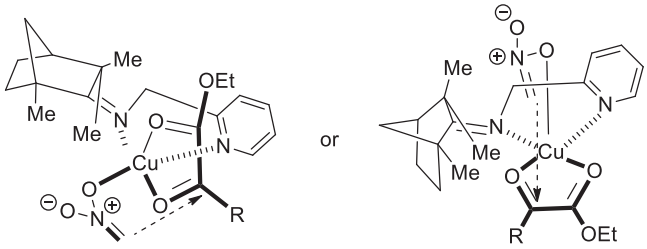


Figure 2.35: Proposed transition states for the synthesis of β-nitro-α-hydroxy esters in nitromethane.

2.8.3 Synthesis of bisarylmethanes and dithioacetals

In 2020, Dethe et al. [54] used nitromethane both as a solvent and as an electrophilic methylene source for the synthesis of symmetrical bisarylmethanes (**61**) starting from various substituted arenes (**10**) in the presence of a catalytic mixture of $Sc(OTf)_3$ and $LiClO_4$ as a catalyst at room temperature (Figure 2.36). By applying this method, they were able to synthesize biologically promising tetramethyl mellotojaponin C (**61h**)

(antimalarial) and dimeric phloroglucinol (**61i**) (anticancer) derivatives. Under the same optimized conditions and starting from various thiol derivatives (**62**), they also synthesized a series of symmetric dithioacetals (**63**) in excellent yields (Figure 2.37).

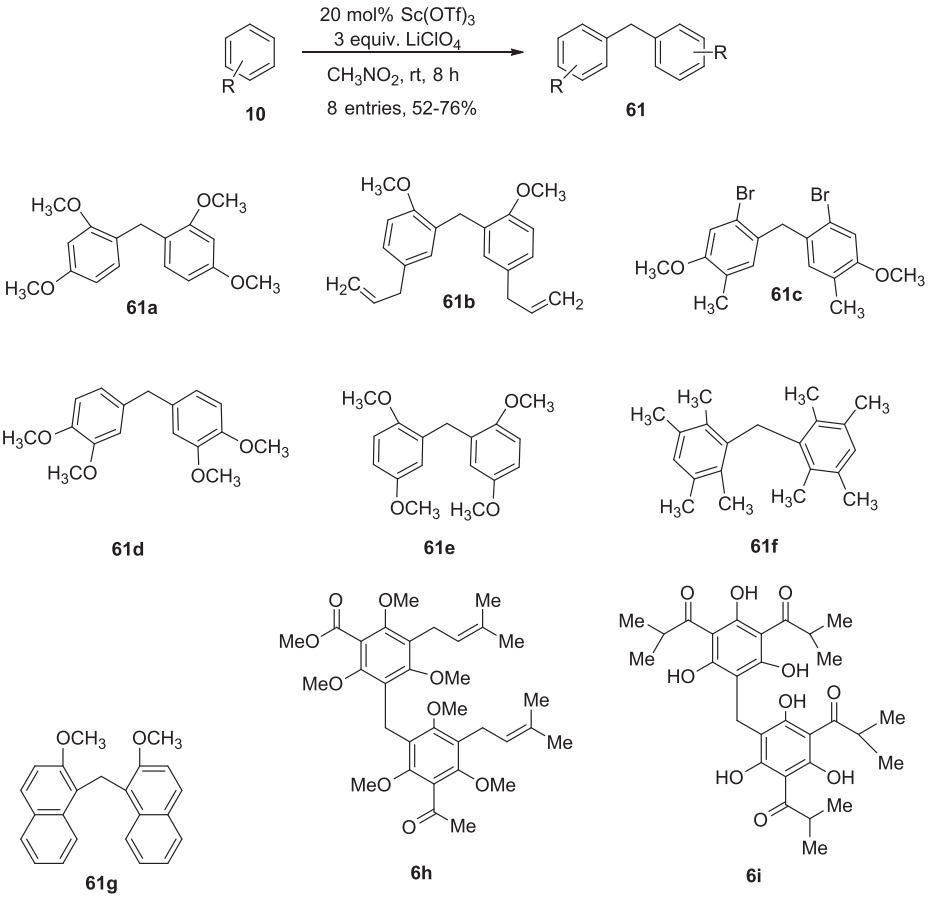
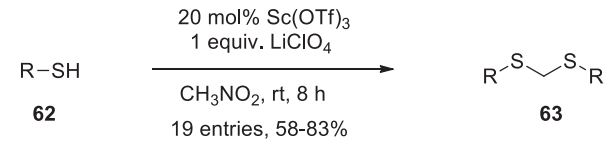


Figure 2.36: Synthesis of bisarylmethanes involving nitromethane.

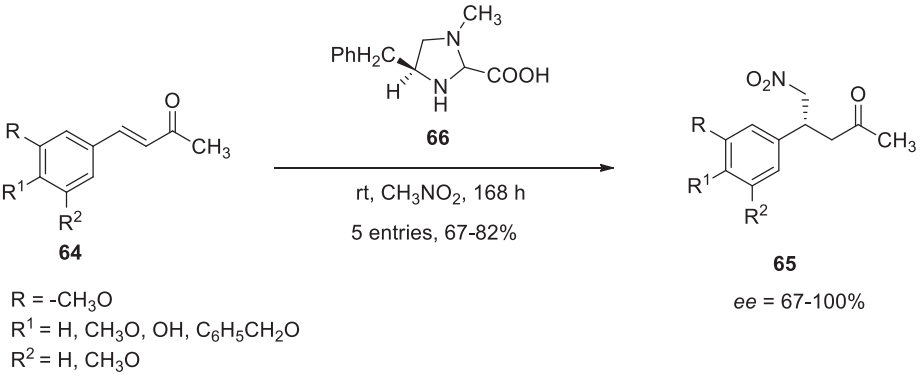
2.8.4 Asymmetric Michael addition reaction

The asymmetric Michael addition of nitromethane to benzylidene acetones (**64**) was achieved by using an imidazolidine-type enantioselective organocatalyst (**66**) at room temperature which yielded the corresponding 4-aryl-5-nitro-pentan-2-ones (**65**) enantioselectively (Figure 2.38) [55]. In this reaction, nitromethane behaved as both nucleophile and solvent.



R = C_6H_5, 4-$CH_3C_6H_5$, 4-*t*BuC_6H_4, 4-BrC_6H_4,2-EtC_6H_4, 2-$OCH_3C_6H_4$, 2-ClC_6H_4, 2-COOMeC_6H_4, 2-BrC_6H_4,2,4-di$CH_3C_6H_3$, 2,4-diFC_6H_3, 2,4-diClC_6H_3, 3,5-di$CH_3C_6H_3$, 2,6-di$CH_3C_6H_3$, 2,6-diClC_6H_3, 2-naphthyl, cyclohexyl, cyclopentyl

Figure 2.37: Synthesis of symmetrical dithioacetals involving nitromethane.



R = -CH_3O
R^1 = H, CH_3O, OH, $C_6H_5CH_2O$
R^2 = H, CH_3O

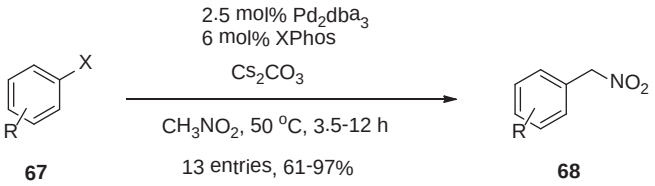
Figure 2.38: Asymmetric Michael addition reaction involving nitromethane.

2.8.5 Coupling reaction

Aryl nitromethanes (**68**) are used as precursors for various useful synthetic compounds. In 2012, Walvoord et al. [56] designed an efficient cross-coupling reaction of aryl halides (**67**) and nitromethane using a catalytic amount of tris(dibenzylideneacetone)dipalladium(0) [Pd_2dba_3] as catalyst in the presence of 2-dicyclohexylphosphino-2,4-6-triisopropylbiphenyl (XPhos) ligand in basic medium at 50 °C (Figure 2.39).

2.8.6 Alkali-cyanide-free synthesis of α-iminonitriles

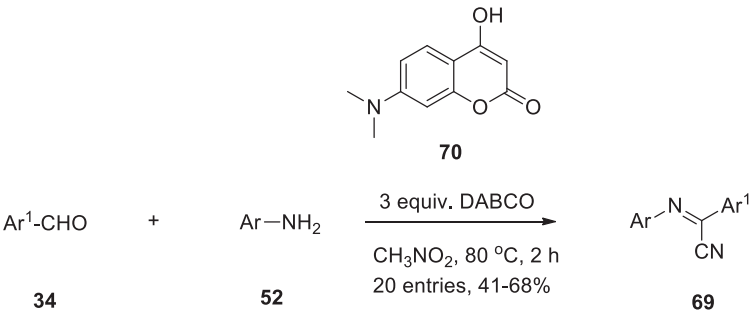
In 2006, Chen et al. [57] first employed nitromethane as a surrogate cyanating source for the copper-mediated, chelate-driven arene cyanation with nitromethane. Then numerous research groups used nitromethane to make nitrile group in the product [58–60]. In 2020, Satyanarayana et al. [61] demonstrated a simple, organocatalyzed alkali-cyanide-free base-mediated kinetically controlled approach for the synthesis of a series of α-



R = H, 4-OCH_3, 4-CF_3, 4-$(CO)C_6H_5$, 4-$COOC_2H_5$, 3-OCH_3, 2-CH_3, 2-$(CO)CH_3$, 2-NO_2, 2,4,6-triCH_3, 3,5-diCH_3, 4-OCH_3, 4-Cl
X = Br, I, OTf

Figure 2.39: Palladium-catalyzed nitromethylation of aryl halides via cross-coupling reaction.

iminonitriles (**69**) via the condensation reactions of aldehydes (**34**) and substituted anilines (**52**) in the presence of 7-*N*,*N*-dimethylamino-4-hydroxycoumarin (**70**) as a promoter in nitromethane at 80 °C (Figure 2.40). In this reaction, nitromethane behaved both as a surrogate cyanating agent and as a solvent. The proposed mechanism including the catalytic role of 7-*N*,*N*-dimethylamino-4-hydroxycoumarin in this reaction is shown in Figure 2.41.



Ar = H, 4-$OCH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 4-BrC_6H_4, 4-$NH_2C_6H_4$,
Ar^1 = C_6H_5, 4-BrC_6H_4, 3,4,6-tri$OCH_3C_6H_2$, 4-$N(CH_3)_2C_6H_4$, 4-$OCH_3C_6H_4$, 2,6-diOCH_3, 3-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, thiophene, isonicotine, picoline
R= -$N(CH_3)_2$

Figure 2.40: Nitromethane-mediated synthesis of α-iminonitriles.

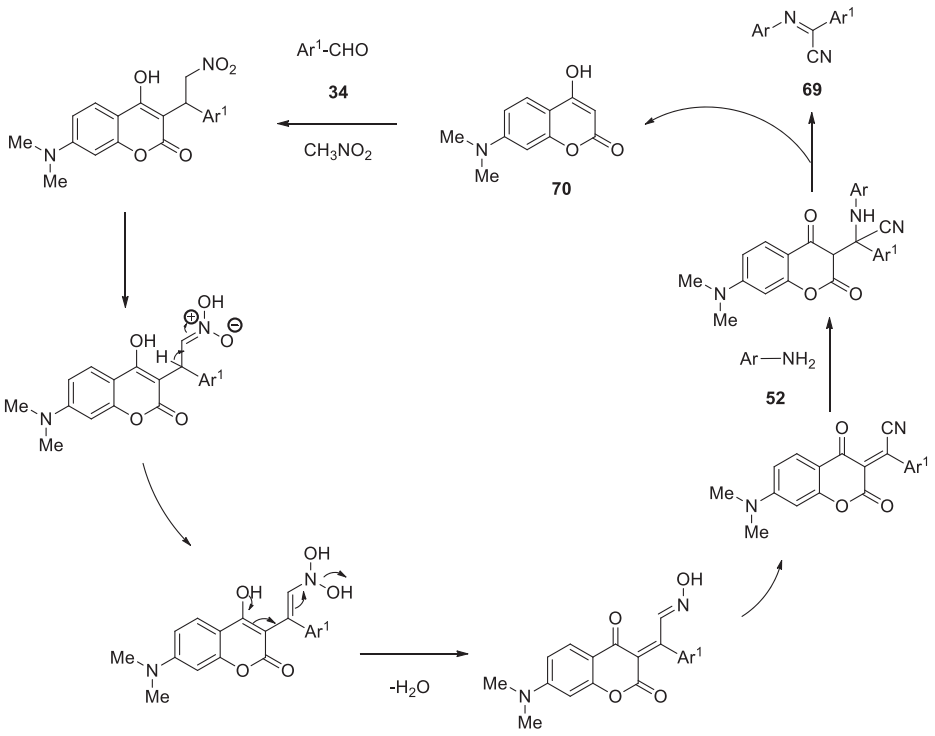


Figure 2.41: Proposed mechanism for the synthesis of α-iminonitriles in nitromethane.

2.9 Conclusions

Nitromethane is a highly polar solvent comparable to acetonitrile. It is used as an extremely versatile reaction media for various organic transformations, including alkylation/benzylation of 1,3-dicarbonyl compounds/arenes, Friedel–Crafts alkylation of indoles/biaryl alcohols and Tsuji–Trost coupling reaction. Synthesis of various biologically promising skeletons such as tetra-aryl-substituted cyclopentenes, substituted aryl ketones, trisubstituted alkenes, 1,4-diynes, propargylic arenas, amides and α-amino esters was accomplished by using nitromethane as solvent. Etherification, oxidation of alcohols and synthesis of some important *N*/*O*-heterocycles are also carried out efficiently in nitromethane as solvent. In some reactions, it was reported to play a dual role.

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Chapter 3
Tert-butyl hydroperoxide (TBHP)-mediated cross-coupling reactions

3.1 Introduction

The fundamental focus for an organic chemist has always been the construction of bonds between carbon–carbon and carbon–heteroatoms. Recently, direct cross-coupling reactions have developed one of the powerful ways for the formation of C–C and C–X (X = heteroatom) bonds because of their enormous importance in green chemistry through the processes of step economy, atom economy, minimization of chemical wastes and also by avoiding pre-functionalization of the starting materials (generally essential for traditional cross-coupling reaction) [1–4]. These cross-coupling reactions often demand the presence of leaving groups [5], such as X, Y = -Br, -I, -OTf, -OTs, -BR_2, -SnR_3 and -SiR_3, attached with the coupling partner (Figure 3.1). Nowadays, these techniques appear to be ineffective and quite unappealing because of involvement of additional processes to create functionalized starting materials.

The three most fundamental rules that need to be followed while developing a reliable synthetic method are: (i) readily available starting materials, (ii) nontoxic reagents or catalysts and (iii) mild reaction conditions. It is difficult to create such necessary ambience every time, but once created, they have a significant influence on contemporary organic chemistry. When two molecules come together to form a new bond with the help of a catalyst or devoid of catalyst, the process is referred to as coupling [6–8]. These reactions are adaptable and helpful for producing several complicated biologically active compounds in ready synthetic sequences rather than through multistep processes. Pro-electrophilic and pro-nucleophilic partners are often the starting materials in C–C cross-coupling reaction processes [9] and sometimes they appear as pericyclic reactions [10] and radical reactions [11–14], respectively.

Different transition metal (TM) catalysts, various organocatalysts and the pairing of metal and organocatalysts and enzymes have been used to enhance diverse cross-

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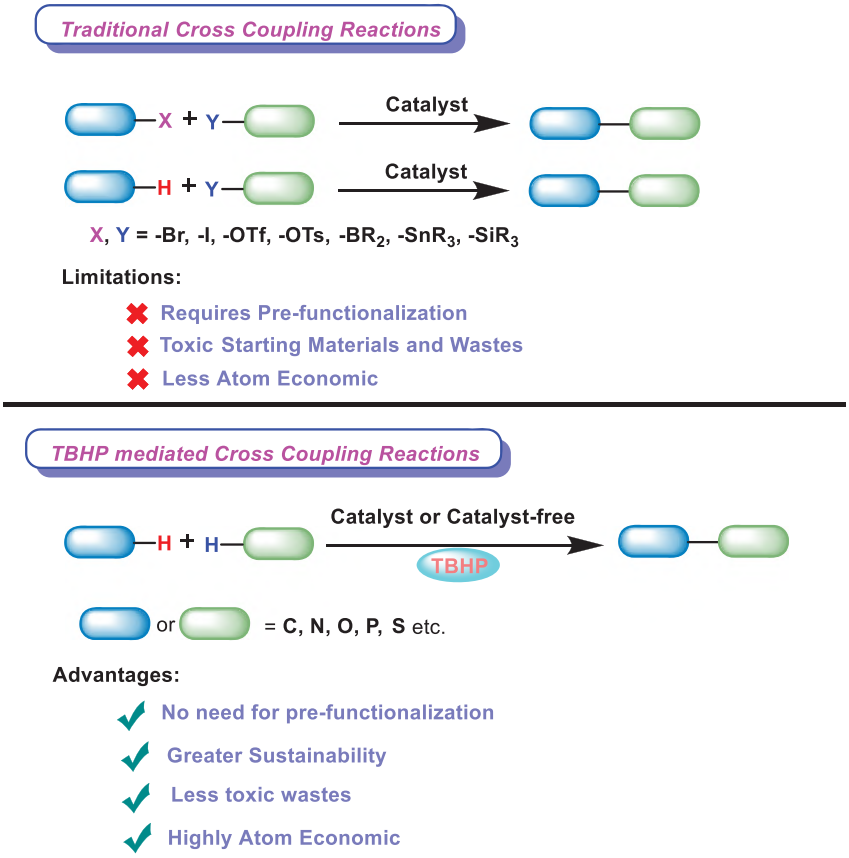

Figure 3.1: Schematic comparison between traditional and TBHP-mediated cross-coupling methods.

coupling processes depending on the pre-activation [15]. However, majority of them suffer from significant problems like the expensiveness of the catalyst and the generation of heavy metal wastes on application of stringent reaction condition. As a result, the TM-free or TM-catalyzed cross-dehydrogenative coupling (CDC) reactions have captivated the attention of various synthetic chemists due to their advantages such as greener approach, atom-economical reaction and easy handling. Tert-butyl hydroperoxide (TBHP) is a handy and easily accessible supply source of active oxygen. It is also appropriate for the varied oxidation mechanisms and also offers advantages of versatility, stereoselectivity, reactivity, regioselectivity and chemoselectivity control with exact catalyst choice, soft reaction condition and major availability [16]. Moreover, TBHP in combination with several iodine(III) and iodine(IV) reagents could perform the role of radical initiators in many radical-based organic transformations, cross-coupling reaction as well as in annulation process. This chapter aims to highlight the recent innovative applications of TBHP alone or in conjunction with other metal-free reagents in C–C and

C–X cross-coupling reactions under mild conditions, which in turn will help the synthetic practitioners to achieve a new course of functionalization in future [17].

3.2 Examples of TBHP in C–C and C–X (X = heteroatom) cross-coupling reactions

3.2.1 TBHP- and Rose-Bengal-mediated C(sp^3)–O cross-coupling of oxy-functionalized *N*-heterocycles

For medicinal chemists, heterocycles containing nitrogen are essential structural components. Among various heterocyclic compounds, phthalazinone, 2-pyridone, pyrimidinone and quinoxalinone show biological activities such as anticonvulsant [18, 19], antidiabetic [20], antihypertensive [21], analgesic, anti-inflammatory [22], antiviral [23], antihistaminic [24] and potent antitumor [25] activities.

Considering synthetic and biological merits of *N*-heterocyclic components, in 2022, Das and coworkers [26] described a simple and straightforward photoinduced C(sp^3)–O cross-coupling of tautomerizable *N*-heterocycles (dihydrophthalazine-1,4-diones, pyridone, quinoxalinone and pyrimidinone) with various coupling partners (ketones, β-dicarbonyl compounds and nitroalkanes) under metal-free condition (Figure 3.2). The best conditions for synthesizing C–O coupling products were found to be Rose Bengal (1 mol%), $NaHCO_3$ (2.2 equiv.), and TBHP (2.0 equiv.) in 2 mL of an acetonitrile–water combination. The combination of Rose Bengal photocatalyst and TBHP features sustainable reaction condition, operational simplicity, high chemoselectivity and regioselectivity with exceptional yields (up to 94%), good functional group tolerance and ample substrate scope. When it comes to asymmetrical ketones, the less substituted end is preferentially functionalized. The *di*-C–O coupling products (**2**) are generally formed with ketones containing three enolizable "H" at the reaction site while ketones with two enolizable "H" furnished only single C–O coupling products (**3**) (Figure 3.3). The results of the control studies using a radical scavenger showed that the radical route is involved in this coupling technique. The coupling products are also scaled up to large scale, making them suitable for even more transformations. An unusual ring contraction providing 2-substituted phthalimides (**4**) was produced without any coupling partners with dihydrophthalazine-1,4-dione (**1**) in good yields. This cross-coupling approach is advantageous in a number of ways, including (i) devoid of costly metal catalysts; (ii) use of readily available *N*-heterocycles; (iii) dry solvents, inert environment or high reaction temperatures not necessary; (iv) use of cheap and greener energy source, that is, visible range LED bulbs; and (v) extraordinary reactivity with high functional group tolerance. Additionally, this reaction is also imperative as TBHP promotes both of C–O cross-coupling and a rare ring fragmentation of dihydrophthalazine-1, 4-diones to various 2-phenyl phthalimides by simultaneous two-bond (C–N and N–N) cleavage under visible light circumstances.

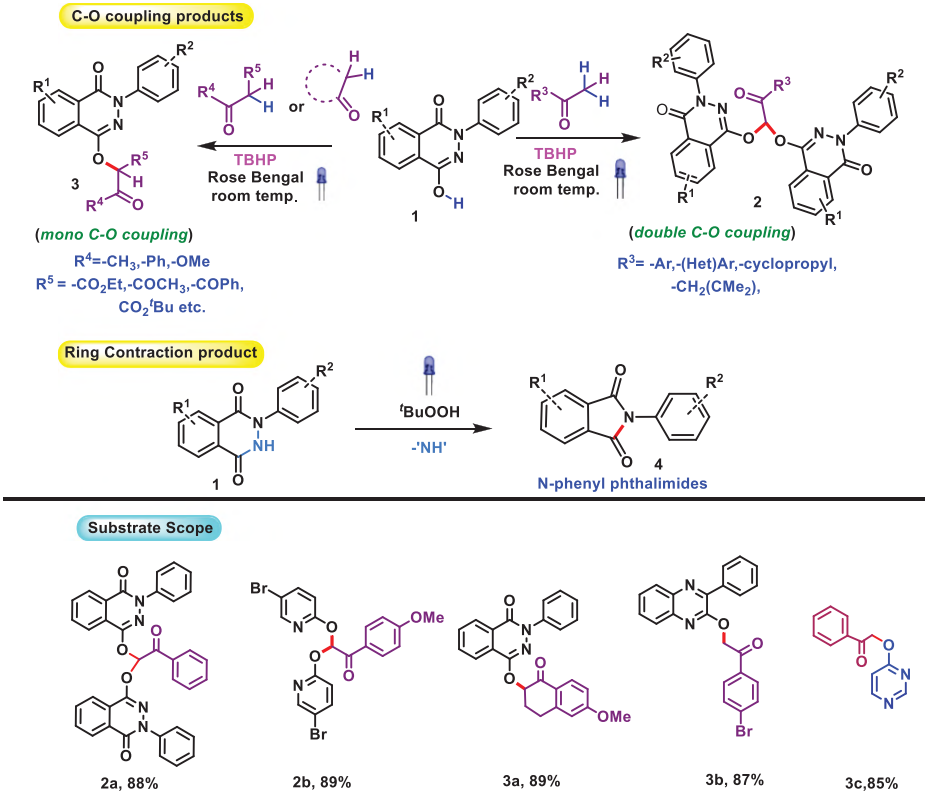

Figure 3.2: Substrate scope of C–O coupling products.

3.2.2 C–S cross-coupling reaction of xanthene with sulfonyl hydrazides

Xanthene is an oxygen-containing tricyclic compound which has recently gained huge synthetic interest due to its wide biological contribution. Particularly, the presence of various substituents in position 9 of xanthones powerfully affects their physical and chemical properties and also biological applications. Xanthene derivatives exposed biological activities such as antitumor, neuroprotector and antimicrobial [27]. Recent interest in the synthesis of functionalized sulfones has concentrated on the formation of carbon–heteroatom bonds, notably the C–H sulfonylation process [28–32].

Deb et al. [33] described an easy and straightforward methodology for the direct addition of sulfonyl units into xanthene (**5**) moiety to access xanthen-9-sulfone (**7**) products via a radical–radical cross-coupling reaction of xanthenes and sulfonyl hydrazides under metal-free condition (Figure 3.4). This method proceeds with a high grade of functional group tolerance with a wide-ranging variety of both xanthenes (**5**)

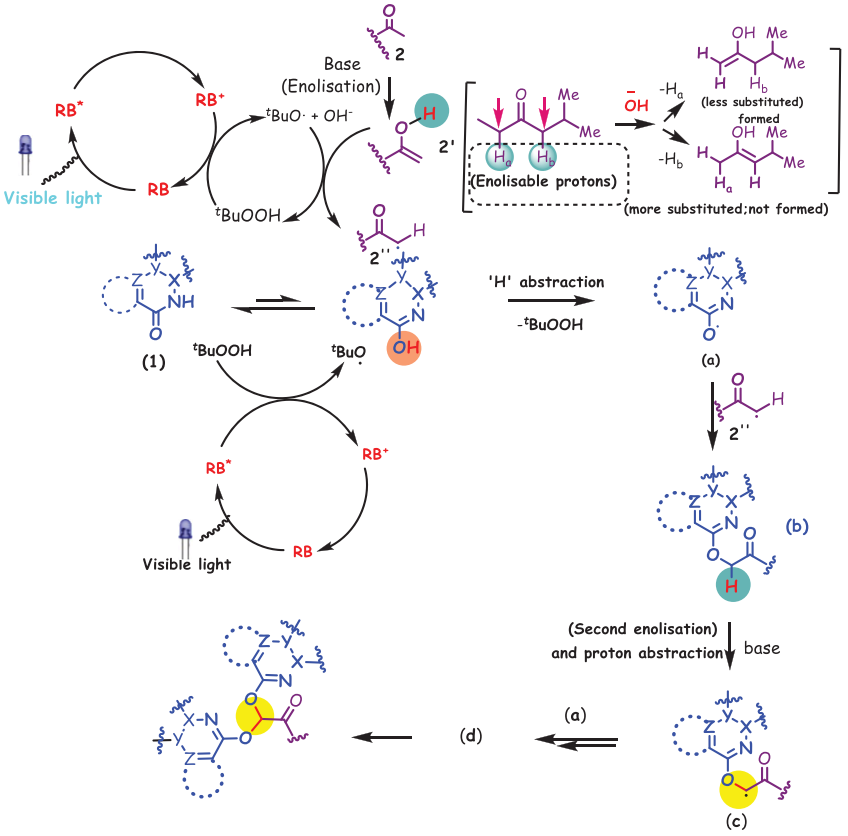

Figure 3.3: Plausible mechanism for C–O coupling reaction between phthalazinone and acetophenone derivatives.

and sulfonyl hydrazides (**6**) under mild condition. The performed mechanistic investigations indicated that sulfonyl radicals were generated from sulfonyl hydrazides on application of TBHP under oxygen atmosphere (Figure 3.5). When the reaction was executed in the presence of argon (both TBHP and O_2 are absent), the reaction did not proceed. Again, moderate yield was obtained when molecular oxygen was used as a sole oxidant. Hence, it was concluded that both oxygen and TBHP conjunctively play the accelerating role in this reaction which favors 45 instances to get yield up to 99%.

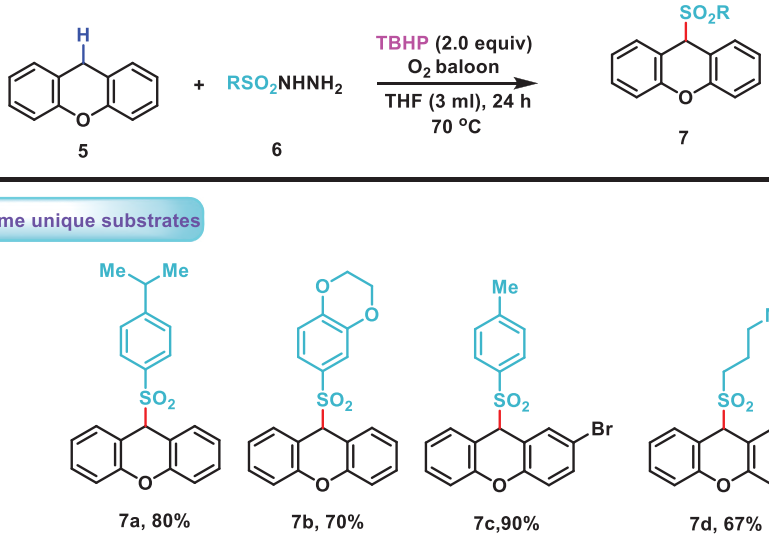

Figure 3.4: Substrate possibility of xanthene-9-sulfonylation products.

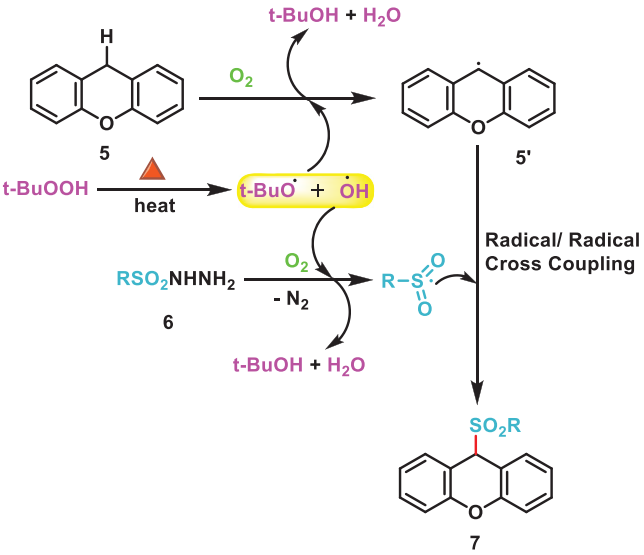

Figure 3.5: Probable mechanistic pathway for the synthesis of 9-sulfonyl xanthene.

3.2.3 TBHP-mediated synthesis of 2,3-diaryl-1,4-diketones via oxidative coupling of benzyl ketones in aqueous medium

In the domain of material science and organic chemistry, 2,3-diaryl-1,4-diketones are crucial intermediates. Using such type of ketone, numerous five-membered heterocycles, including furans [34–36], pyrroles [37, 38] and pyrrolones [39], were synthesized. Furthermore, 2,3-disubstituted-1,4-diketones are important frames in both natural and medicinal chemistry [40–43].

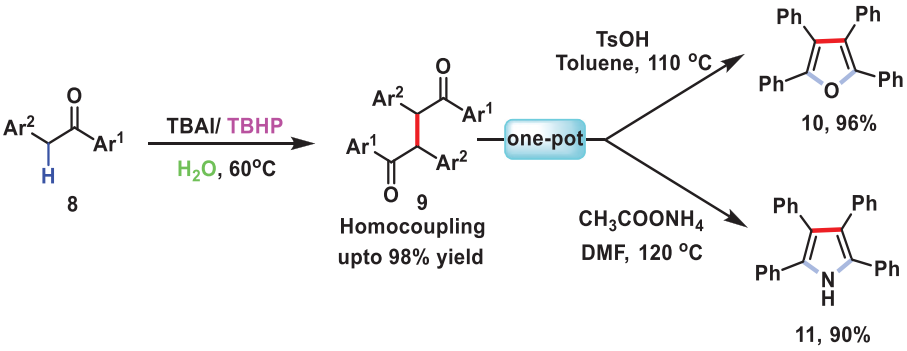

Figure 3.6: Synthetic pathway of 2,3-diaryl-1,4-diketones.

Bai and coworkers [44], in 2022, reported a green and efficient way for the formation of 2,3-diaryl-1,4-diketones (**9**) through dehydrogenative oxidative coupling process using benzyl ketones (**8**), which are easily accessible with TBHP as a sacrificial oxidant under tetrabutylammonium iodide (TBAI) catalysis in water medium (Figure 3.6). The methodology has a wide substrate range, mild reaction condition and a high level of substituent tolerance. Moreover, it is involved in such a catalytic system that seems to be biologically friendly while offering a range of desired products with good to outstanding yields. In this reaction, TBAI was oxidized to $[n\mathrm{Bu}_4\mathrm{N}]^+ [\mathrm{IO}_x]^-$ (where x is 1 and 2) in the presence of TBHP and in turn drives the reaction through hypoiodite pathway. The radical trapping experiments also supported this fact as the reaction proceeded efficiently in the presence of radical scavengers like TEMPO (2,2,6,6-tetramethylpiperidinoxyl) and BHT (butylated hydroxytoluene). The tetrasubstituted furan (**10**) and pyrrole (**11**) were also synthesized following this strategy to occur in one-pot method with a yield of 90–96%.

3.2.4 TBHP-mediated C–O oxidative cross-coupling of phenols and 2-aminoacetophenones

One of the most important processes in the synthesis of organic molecules is the oxidative formation of C–O bonds with enolizable carbonyl compounds [45–49]. Hypervalent iodine compounds have been frequently used as effective mediators for these beneficial conversions in addition to organic peroxides and heavy metal salts [50–55].

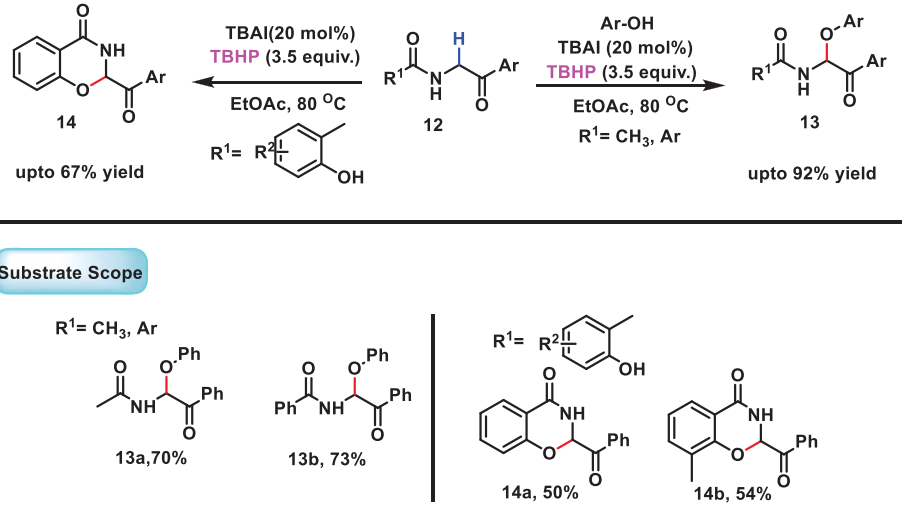

Figure 3.7: Substrate scope of cross-coupling between phenols and 2-aminoacetophenones.

On the basis of this, in 2015, Xu and Nachtsheim [56] described a convenient route for the oxidative cross-coupling between phenols and 2-aminoacetophenones (**12**), via catalytic amounts of TBAI as an iodine-containing catalyst, and aqueous solution of TBHP in stoichiometric amount acted as the co-oxidant (Figure 3.7). In this case, the reaction followed the hypoiodite pathway where $[n\mathrm{Bu_4N}]^+[\mathrm{IO}_x]^-$ (x = 1, 2) acted as the active catalyst. Lower yield was reported in case of other ionic iodides (NaI and KI). Metallic iodides with covalent nature (like CuI) failed to generate the target product as the aggregate does not supply free iodide ion. After very short reaction period (20 min), a diversity of phenoxylated 2-aminoacetophenones (**13**) can be produced in yields up to 92%. This is a quite uncommon instance of an intermolecular cross-coupling involving phenols and an α-enolic carbon atom that was catalyzed by iodide.

3.2.5 TBHP-mediated cross-coupling using aldehyde or alcohol with *N*-chloramine

In peptides and proteins, the amide functionality is widely recognized. The amide bond is the most prevalent motif in a variety of natural and synthetic products because of its stability, strong polarity and variety of morphologies [57]. It is extremely desirable and has received a lot of attention in recent years to develop practical techniques for generation of amide functionality under metal-free, catalytic and chemoselective manner.

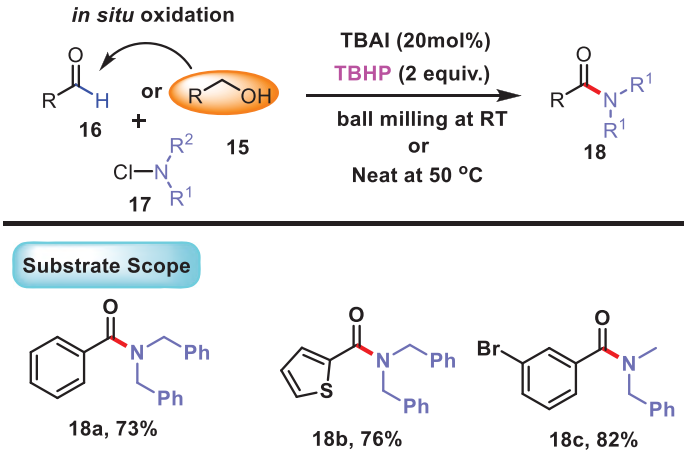

Figure 3.8: Substrate scope of amidation of aldehydes and alcohols with *N*-chloramines.

In 2014, Achar and Mal [58] discovered a mild, effective and metal-free technique for the synthesis of amides from alcohols and aldehydes utilizing TBHP–TBAI in a solvent-free environment (Figure 3.8). As an illustration of the activation of the aldehydic C–H under metal-free condition, the cross-coupling reaction between the aldehyde (**16**) and *N*-chloramine (**17**) is shown either in a ball milling setting at room temperature or under neat condition at 50 °C. The combination of TBAI and TBHP generated TBHP radical which responsively induces the formation of benzoyl and aminyl radicals, respectively, and the target product (**18**) was achieved via the oxidative coupling between benzoyl and aminyl radicals. This technology has been displayed well with a variation of functional groups and just recognized as readily available starting ingredients and can be produced in excellent yields. Executing the reactions in a ball mill might be a significant improvement to mechanochemical synthesis.

3.2.6 TBHP-mediated oxidative cross-dehydrogenative coupling of quinoxalin-2(1H)-ones with 4-hydroxycoumarins, 4-hydroxy-6-methyl-2-pyrone and 2-hydroxy-1, 4-naphthoquinone

A key heterocyclic scaffold with an inclusive range of biological and pharmacological actions is the quinoxalin-2(1H)-one moiety, which is found in many different natural compounds [59]. It has drawn the interest of several scientists due to its encouraging biological activities like antimicrobial, anticancer, protein kinase inhibitory, antithrombotic and benzodiazepine receptor agonist activities [60–63]. Functionalization of the C_3-position of quinoxalin-2(1H)-ones in particular has received the most attention due to its radical addition mode, and the resultants are used in several biological fields.

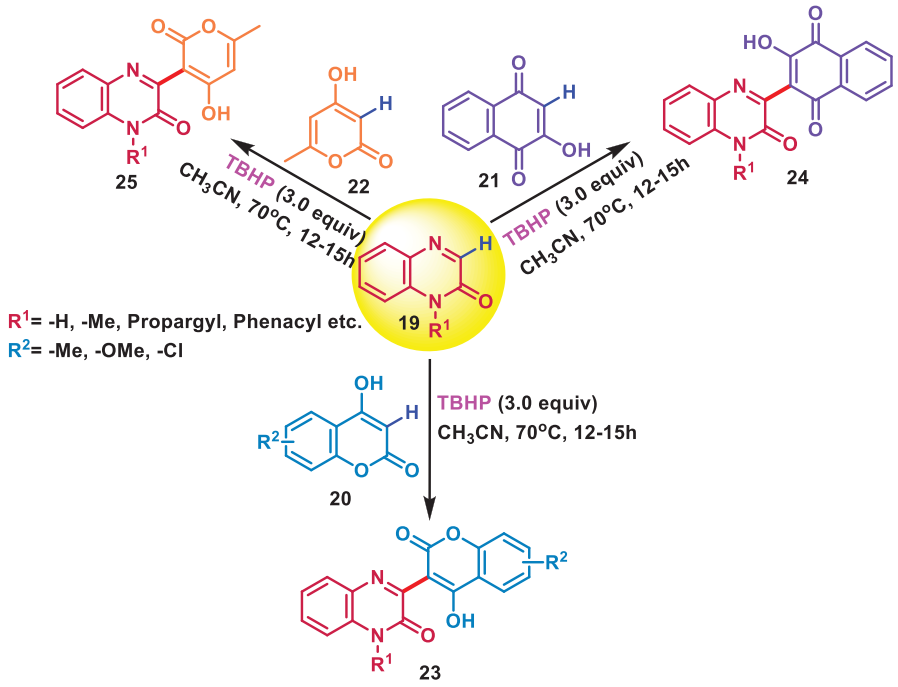

Figure 3.9: Cross-dehydrogenative coupling reaction pathway of quinoxalin-2(1H)-ones.

In 2020, Baishya and coworkers [64] reported an effective and environmentally friendly strategy to functionalize the C_3-position of quinoxalin-2(1H)-ones (19) by combining them with 4-hydroxycoumarins (20), 4-hydroxy-6-methyl-2-pyrones (22) and 2-hydroxy -1,4-naphthoquinones (21), in a metal-free environment (Figure 3.9). The CDC products are produced in very good to outstanding yields as a result of the smooth promotion of the reaction by TBHP. The procedure avoids the use of any hazardous substances or

metal catalysts, and pure products are achievable without performing column chromatography with a reasonably good yield. This procedure involves TBHP-induced radical pathways and was confirmed by radical trapping experiments with TEMPO, BHT and diphenyl ethylene.

3.2.7 TBHP-mediated dehydrogenative cross-oxidative coupling between methylarenes and acetanilides

In pharmaceutical and agricultural applications [65, 66], amides have recently drawn increasing interest as precursors in the synthesis of organic compounds like polymers and natural substances [67, 68]. According to the medicinal chemistry database, the amide moiety is present in around 25% of synthetic drugs [69]. In addition, the amide motif has been used as a crucial intermediate to produce a number of different chemicals with varied activities [70, 71].

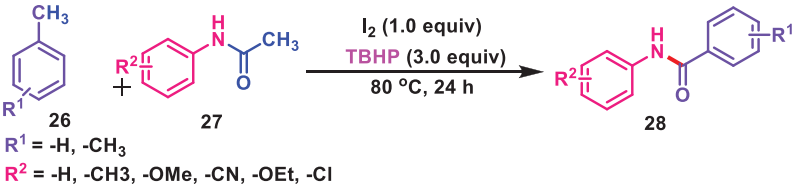

Figure 3.10: Cross-oxidative coupling between methylarenes and acetanilides.

In 2016, Zhou and coworkers [72] reported a synthetic approach using TBHP for the synthesis of *N*-arylbenzamides (28) via a cross-oxidative coupling method between methylarenes (26) and acetanilides (27) (Figure 3.10). This cross-coupling technique demands no additional organic solvent, any TM catalyst or ligands. For the simple formation of C–N bonds, it is a practical and interesting approach to produce the desired product with excellent yield. The traditional C–N bond formation technique needs to be supplemented by this conversion. The reaction was totally suppressed in the radical inhibition experiment with TEMPO and established the radical mechanism for this coupling process.

3.2.8 TBAI/TBHP-mediated oxidative cross-coupling of ketones with phenols and carboxylic acids

Aryloxyketones are useful constructions for the production of organic molecules, drugs and physiologically active substances [73]. In particular, the Pfitzinger reaction [74] makes it simple to turn aryloxyketones into quinolines as well as synthesis of

substituted benzofurans [75]. α-Acyloxycarbonyl compounds are crucial building blocks because they may be converted into α-hydroxyketones, which are found as essential components in a range of physiologically active natural products and medicines [76, 77]. Conventionally, α-halocarbonyl compounds and carboxylic acids have historically been used to fabricate α-acyloxycarbonyl substrate under TM-catalyzed reaction condition by also placing highly toxic heavy metal oxidants. However, the disadvantage of those techniques was the deployment of hazardous chemicals and heavy metals [78].

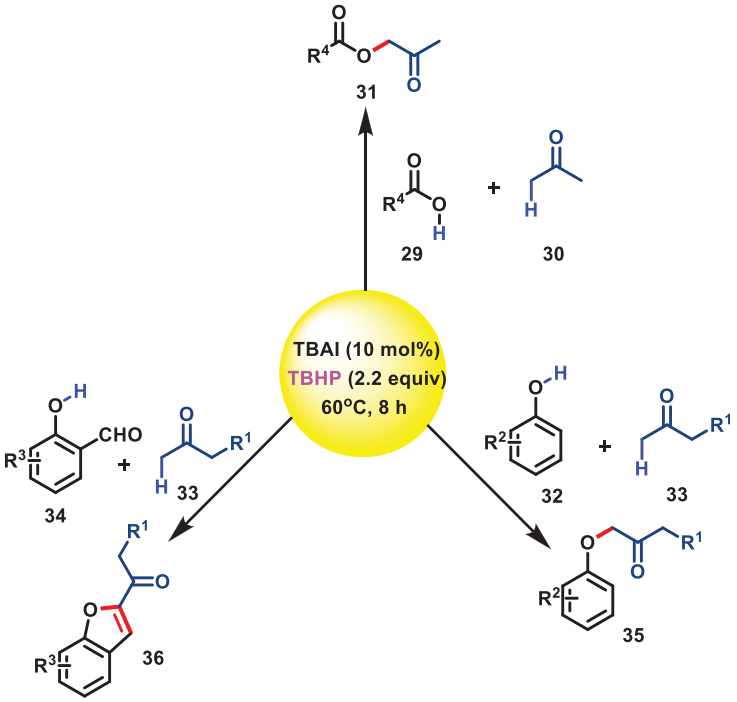

Figure 3.11: Cross-coupling pathway of ketones with phenols and carboxylic acids.

In 2018, Reddy and coworkers [79] described a cross-coupling reaction of phenols (**32**) and carboxylic acids (**29**) with ketones (**30** and **33**) by interacting with TBAI/TBHP catalyst combination and keeping metal and base, as well as solvent-free condition (Figure 3.11), eventually the outcome approached to the synthesis of aryloxyketone (**35**), acyloxyketone (**31**) and benzofurans (**36**). Benzofurans (**36**) were produced in moderate quantities, but phenoxyketone (**35**) and acyloxylcarbonyl (**31**) compounds were produced in excellent to great yields. It is significant to have an easy-to-use approach with a commercially available and less expensive catalyst (TBAI) as well as an oxidant (TBHP). By following this technique, synthetic chemists are able to successfully avoid poisonous metals, toxic chemicals and metal oxidants.

3.2.9 TBHP-mediated oxidative coupling of bisnucleophiles and isocyanides

In bioactive metabolites and natural products, 2-aminobenzoxazinone, 2-aminobenzoxazine and 2-aminoquinozoline are preferred heterocyclic scaffolds [80–83]. In particular, the formation of 2-aminobenzoxazinone has advanced quickly throughout the past few decades, but the Pd(II)-catalyzed reactions were the major focus of the methodologies developed so far.

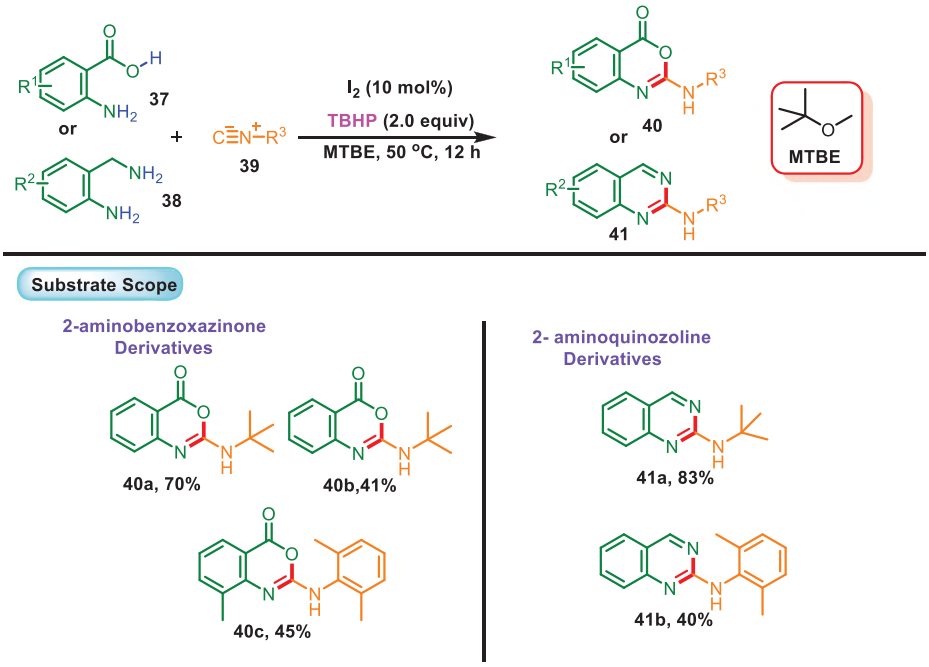

Figure 3.12: Oxidative coupling pathway of amino-based bisnucleophiles and isocyanides.

In 2018, Ji and coworkers [84] proposed a novel, general, reliable, straightforward and atom-efficient approach for the oxidative coupling reaction of isocyanide (39) with an amino-based bisnucleophile for the synthesis of 2-aminobenzoxazinone (40) and 2-aminoquinozoline (41) in moderate to excellent yields in the I_2/TBHP domain via N–H/O–H bond blooming (Figure 3.12). Additionally, this approach offers a straightforward and useful way to build potentially functionalized molecules with biological activity.

3.2.10 TBHP-promoted reaction between quinazoline-3-oxides and primary benzyl amines: C–N bond formation

The starting ingredients to fabricate primary amine are inexpensive, easily accessible and chemically varied. Because of these benefits, primary amines are frequently employed in the synthesis of heterocycles containing nitrogen, including quinolones [85, 86], quinoxalines [87, 88], indoles [89, 90] and quinazolines [91, 92]. A number of initiatives have been made in recent years to synthesize nitrogen-containing heterocycles by reacting readily available *N*-oxides with a variety of primary amines. One of the most significant heterocycles that include nitrogen is the quinazolinone, which is abundantly present in many natural products [93–95]. A wide range of bioactivities, including anticancer, antifungal, antibacterial, antiviral, anti-inflammatory, antiallergic, antihypertensive and the inhibition of HIV-1 integrase, have been seen in quinazolinone derivatives that integrate various functional groups [96–98]. Additionally, several well-known medications are analogues of quinazolinone, which include febrifugine, evodiamine, fiproqualone, cloroqualone and afloqualone [99, 100].

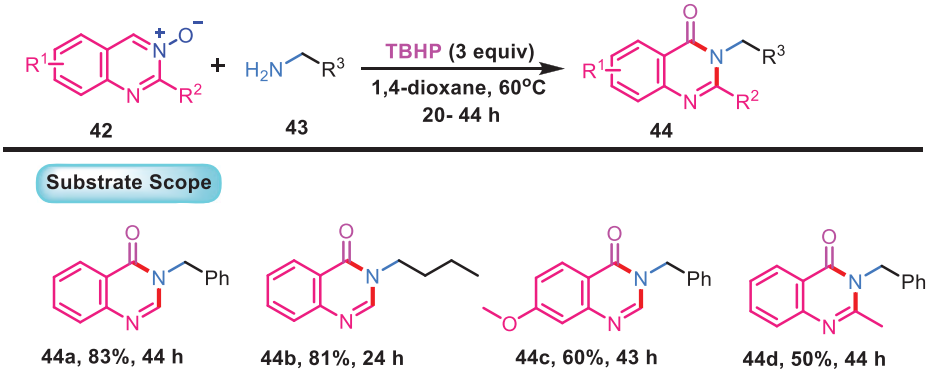

Figure 3.13: Cross-coupling reaction between primary amines and quinazoline-3-oxides.

Due to their immense biological significance, in 2022, Wang and coworkers [101] described a reaction route between quinazoline-3-oxides (**42**) and primary amines (**43**) to form quinazolin-4(3H)-ones (**44**) (Figure 3.13). This method relies on readily accessible TBHP as the oxidant and is shown to work effectively on a wide variety of substrates under moderate reaction conditions, avoiding the use of metal salt. Surprisingly, 3-(2-(1H-indol-3-yl) ethyl)quinazolin-4(3H)-one (**45**), which can be easily prepared by applying this method in 70% yield, becomes a good starting material for the synthesis of beneficial compounds rutaempine (**46**) and (±)-evodiamine (**47**) (Figure 3.14). The optimum reaction condition is set up with quinazoline-3-oxide and low-cost benzyl amine using TBHP (5.5 M in decane, 3 equiv.) as an oxidant in 4 mL of DCM at 60 °C for 44 h.

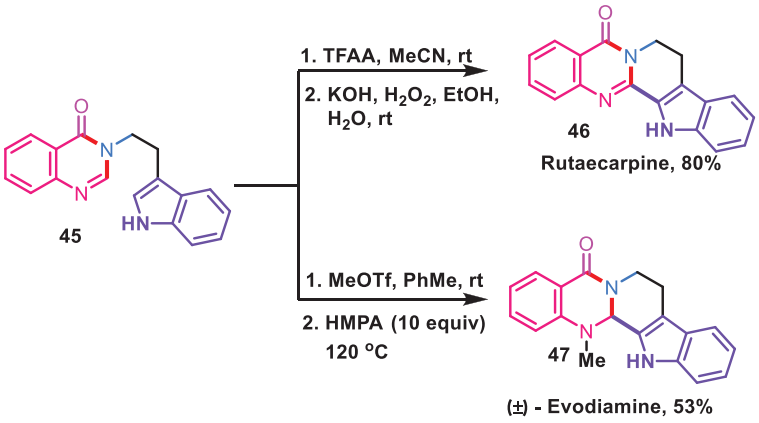

Figure 3.14: Synthesis of rutaecarpine and (±)-evodiamine from 3-(2-(1H-indol-3-yl) ethyl) quinazolin-4(3*H*)-one.

The condition is set up with benzyl amine and quinazoline-3-oxide by the help of TBHP (5.5 M in decane) as an oxidant in 4 mL of dioxane for 24–44 h at 60 °C.

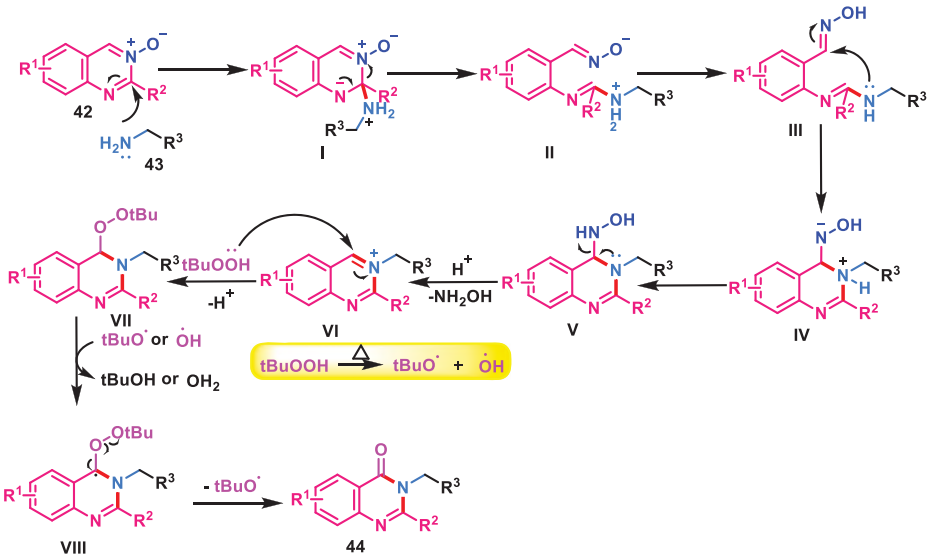

Figure 3.15: Plausible mechanism for cross-coupling reaction between quinazoline-3-oxides and primary amines.

3.2.11 TBHP-mediated direct oxidative aryl–aryl cross-coupling in a regioselective manner

In the field of organic chemistry, the creation of innovative carbon–carbon bond formation techniques is a decisive problem. In-depth research done on C–C bond formation processes that result in dimerization concluded with self-dehydrogenative coupling or cross-dehydrogenative coupling. In keeping track with the series of several carbon–carbon and carbon–nitrogen bond-forming reactions [102–104], it has revealed that it would be extremely intriguing and challenging as well to investigate the regioselective synthesis of biaryls through direct oxidative cross-coupling.

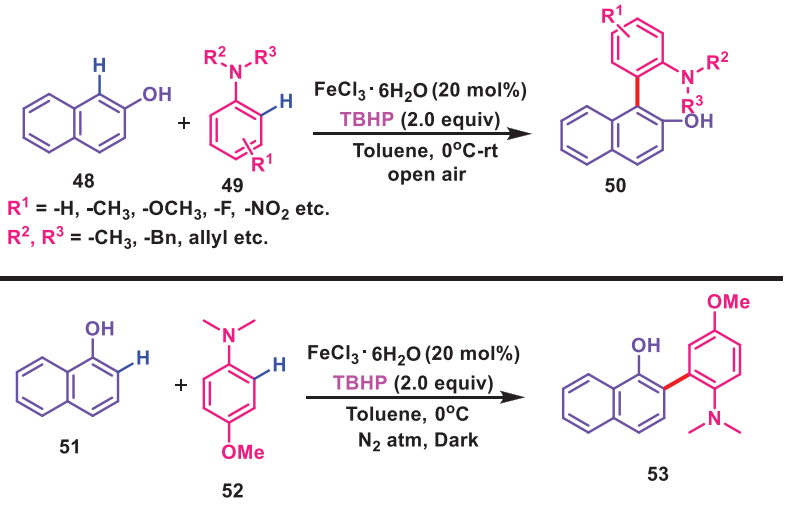

Figure 3.16: Oxidative aryl–aryl cross-coupling.

In 2011, Sridhar and coworkers [105] established an efficient pathway by using a low-cost catalyst oxidant combination, that is, the Fe(III)/TBHP system under a benign environment for the CDC coupling between *N*,*N*-dimethylanilines (**49** and **52**) and 2-naphthol/1-naphthol (**48** and **51**) (Figure 3.16). This cross-coupling process produced a large number of dialkyl amino- and hydroxy-substituted biaryls. It was found that the reaction followed both chemoselective and regioselective pathways since it did not allow any of the homocoupled biaryls to form. In addition, the aryl substrates are not subjected to pre-functionalization and defunctionalization due to the use of suitable reagent combinations in this reaction, which in turn efficiently generated the functionalized biaryls. It is interesting to note that $AlCl_3$ also promotes the cross-coupling process, offering strong catalytic activity in the presence of TBHP, and a wide array of products can be prepared with good to excellent yields.

3.2.12 TBHP-mediated oxidative cross-coupling between sp^3 C–H and sp^2 P–H centers

Direct C–H bond functionalization and ensuing cross-coupling using pro-nucleophile based on heteroatom and electronic nature of carbon to judge the newly discovered carbon–carbon and C–X (X = N, O, P) bond construction in oxidative domain have become notable in synthetic organic chemistry. Specifically, ketone-containing phosphate esters are well-established physiologically important chemical molecules that are employed as sugar analogues and a crucial precursor for the production of phospholipids and nucleotides [106]. To synthesize this moiety, a few synthetic techniques are archived in previous reports [107–109]. Nevertheless, the bulk of these techniques relied on the oxidative cross-coupling approach using in-situ-generated organo-hypervalent iodine reagents [110–112].

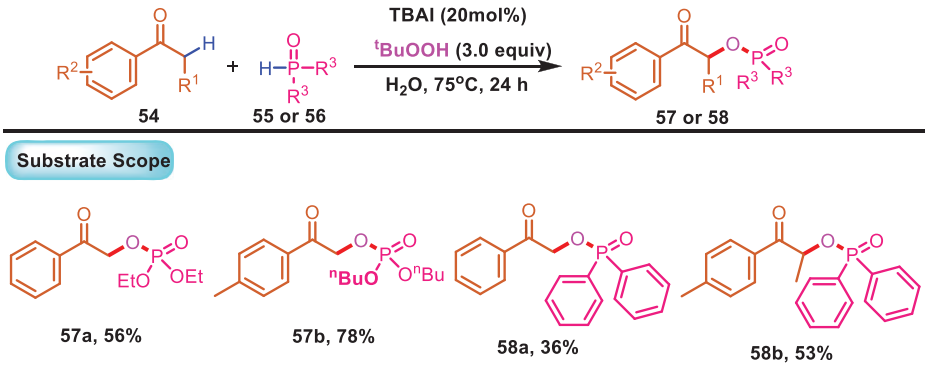

Figure 3.17: Cross-coupling reaction between sp^3 C–H and sp^2 P–H centers.

In 2016, Reddy and coworkers developed [113] a cross-coupling reaction of aryl alkyl ketones (**54**) with alkyl/aryl H-phosphonates (**55**) and H-phosphine oxide (**56**) under metal-free condition in the presence of TBAI catalyst and TBHP as a terminal oxidant in aqueous media (Figure 3.17). This innovative method provides a straightforward and practical way to obtain a variety of β-keto phosphates (**57**) and phosphinates (**58**) with yields ranging from good to excellent.

3.2.13 TBHP-mediated synthesis of β-ketosulfones via oxidative cross-coupling of vinyl acetates with sulfonyl hydrazides

In several kinds of physiologically active chemicals and commercially available medications, the sulfone-containing molecule is the pivotal one. The molecule containing sulfone group plays an important role in many classes of biologically active compounds

and marketed drugs [114, 115]. Due to its electron-withdrawing nature, the sulfone molecule also functions as a multifunctional building block, notably as a carbon nucleophile. Due to their major uses in a wide range of natural goods and critical organic compounds, β-ketosulfones have garnered immense interest [116, 117].

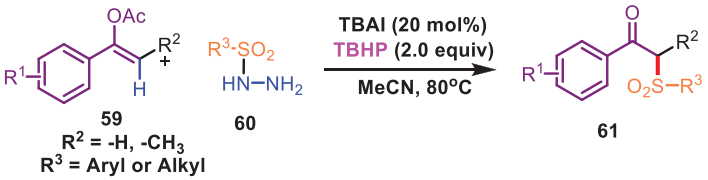

Figure 3.18: Oxidative cross-coupling of vinyl acetates with sulfonyl hydrazides.

In 2015, Xu and coworkers [118] illustrated an efficient way for the oxidative cross-coupling of vinyl acetates (**59**) with sulfonyl hydrazides (**60**) with the aid of TBAI/TBHP combination, following that it has been possible to develop β-ketosulfone derivatives (**61**) (Figure 3.18). Several β-ketosulfone derivatives were successfully produced in yields ranging from excellent to moderate. Studies toward coupling of vinyl acetates with sulfonyl hydrazides were mostly focused on 1-phenylvinyl acetate with *p*-toluenesulfonyl hydrazide in the presence of TBAI as a catalyst in CH_3CN at 80 °C in the presence of TBHP as the oxidant. Furthermore, the scope of sulfonyl hydrazide with 1-phenylvinyl acetate was also inspected under the optimized reaction condition. At the para-position of sulfonyl hydrazide, electron-donating as well as electron-withdrawing groups displayed no obvious difference in the reaction yield of target products.

3.2.14 TBHP-promoted oxidative C–N bond formation

Modern organic synthesis mainly focused in recent years on reactions that involve the formation of carbon–heteroatom bond. Among them, a good number of pharmacologically active heterocycles are produced by direct oxidative C–N bond formation processes [119–122]. Again, among a variety of medicinal components, *N*-heterocycles are the most prevalent and essential scaffold [123]. The varied pharmacological characteristics and therapeutic potential of benzimidazoles, in particular, including their anticancer, antifungal, antibacterial, anti-leishmanial and antiviral effects, prove them to be a significant class of *N*-heterocycles [124–126].

Accordingly, Saha and Das [127] in 2018 established a useful one-flask methodology for the oxidative ring contraction aided by iodine and TBHP to assemble a variety of 2-substituted benzimidazoles (Figure 3.19). In this technique, pre-functionalized or halogenated substrates, oxidants or severe reaction conditions are avoided in favor of readily available 2-aminobenzyl alcohol (**62**) and 2-aminobenzamide (**64**) as representative starting materials. Numerous nitriles (**63**) and aldehydes (**65**) with oxidation-

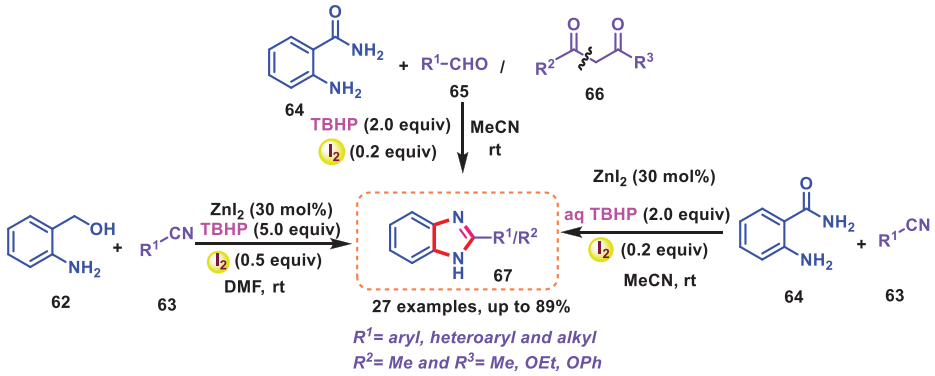

Figure 3.19: Synthesis of benzimidazole via cross-coupling reaction.

prone functional groups were used in the process, and an excellent output has been realized. In this synthetic approach, I_2/TBHP combination is the key reagent.

In 2017, Punniyamurthy and coworkers [128] also devised a cross-coupling reaction protocol with anilines (**68**), methyl arenes (**72**) and $TMSN_3$ using copper(II) as catalyst in the presence of TBHP at a moderate temperature, resulting in 2-aryl benzimidazoles (**71**) via tandem C(sp^3/sp^2)H functionalization and C–N bond formation (Figure 3.20). In 2015, Punniyamurthy and coworkers [129] also developed a one-pot amination protocol for *N*-aryl imine (**70**) leading to benzimidazole (**71**) scaffold under copper (II)/TBHP catalytic system (Figure 3.20).

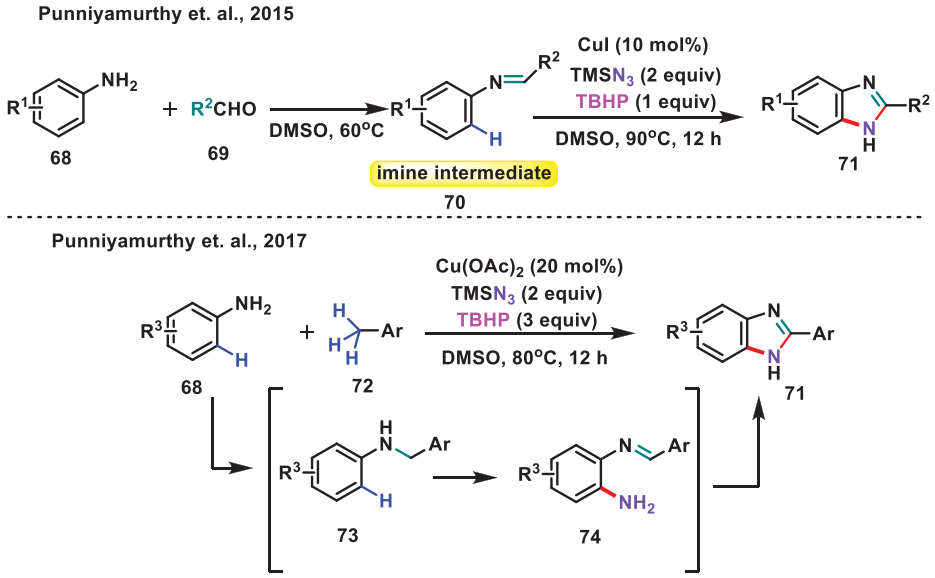

Figure 3.20: Synthesis of benzimidazole via C–H bond amination.

3.2.15 TBHP-promoted various important cross-coupling reactions

Numerous significant cross-coupling reaction protocols were developed using TBHP as the key reagent. These protocols lead us to a vast world of biologically and medicinally active moieties.

3.2.15.1 Oxidative sp^3 C–H bond functionalization

In 2016, Huo et al. [130] described a Fe(II)-catalyzed oxidative sp^3 C–H bond functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones (**75**) with indoles leading to a benzoxazin-2-one-indole hybrid (**77**) heterocyclic scaffold. This protocol was also useful when the electronically rich phloroglucinol trimethyl ether (**78**) was introduced instead of indole (**76**). They have expanded the utility of their devised protocol by synthesizing a natural product Cephalandole A (**81**) in gram scale (Figure 3.21).

3.2.15.2 Cross-coupling reaction of 4-hydroxydithiocoumarin

In 2018, Khan and coworkers [131] reported I_2- and TBHP-mediated oxidative cross-coupling reaction of 4-hydroxydithiocoumarin (**82**) and amines or thiols (**83**, **84** or **85**) leading to various biologically active molecules (Figure 3.22).

3.2.15.3 Synthesis of 5-aminopyrazoles

In 2015, Wang and coworkers [132] synthesized 5-aminopyrazoles (**92** or **93**) involving the oxidative cross-coupling of *N*-sulfonyl hydrazones (**89** or **90**) and isocyanides (**91**) in the presence of I_2/TBHP catalyst (Figure 3.23).

The mechanistic details show that I_2/TBHP-mediated formal [4 + 1]-annulation of *N*-sulfonyl keto-hydrazones with isocyanides was accomplished via in situ generation of azo-alkene intermediate (**94**). Further, conjugate addition of isocyanide to the intermediate **94** (C−C bond formation) and zwitterionic cyclization (C−N bond formation) lead to the product (Figure 3.24).

3.2.15.4 Synthesis of unsymmetrical bis-acyl ketals

In 2014, Patel and coworkers [133] reported a preparation procedure for the generation of unsymmetrically substituted bis-acyl ketals (**97**) from different acetic acid esters (**95**) and benzyl amines (**96**) via TBHP-mediated oxidative cross-coupling (Figure 3.25).

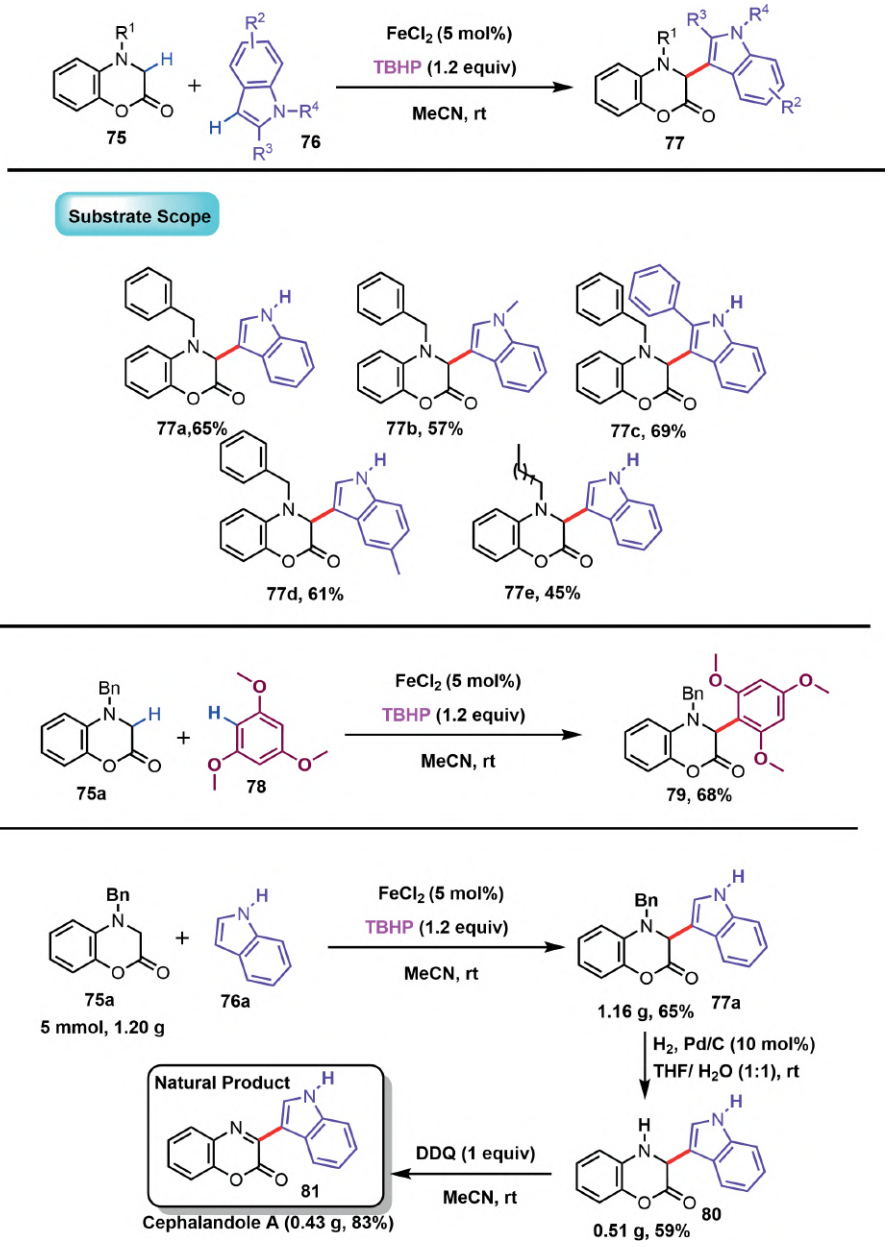

Figure 3.21: Fe(II)-catalyzed oxidative sp^3 C–H bond functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones with indoles.

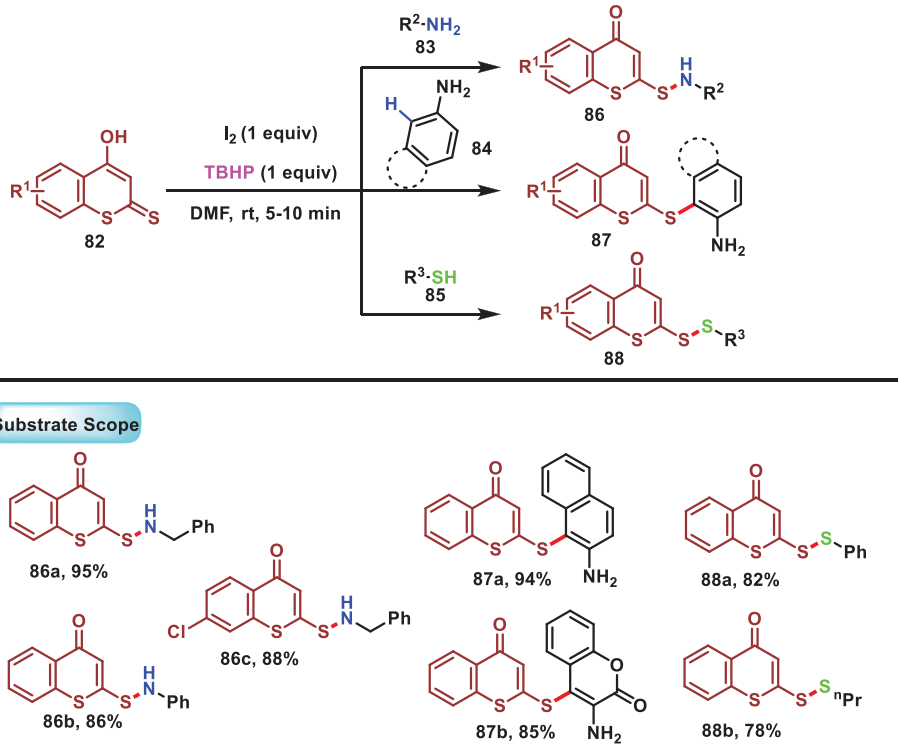

Figure 3.22: I_2- and TBHP-mediated oxidative cross-coupling reaction of 4-hydroxydithiocoumarin and amines or thiols.

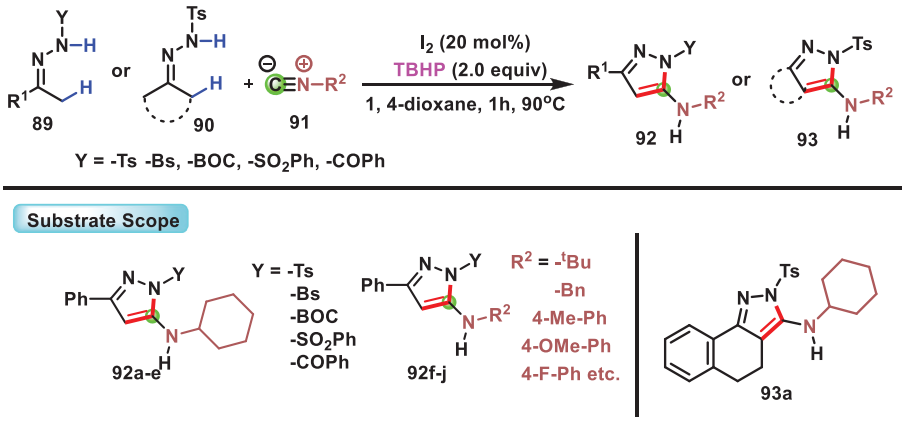

Figure 3.23: Synthesis of 5-aminopyrazoles involving oxidative cross-coupling of *N*-sulfonyl hydrazones.

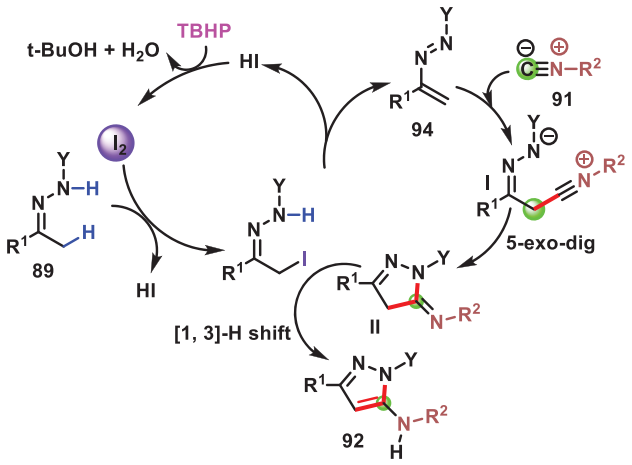

Figure 3.24: Mechanism for the synthesis of 5-aminopyrazoles.

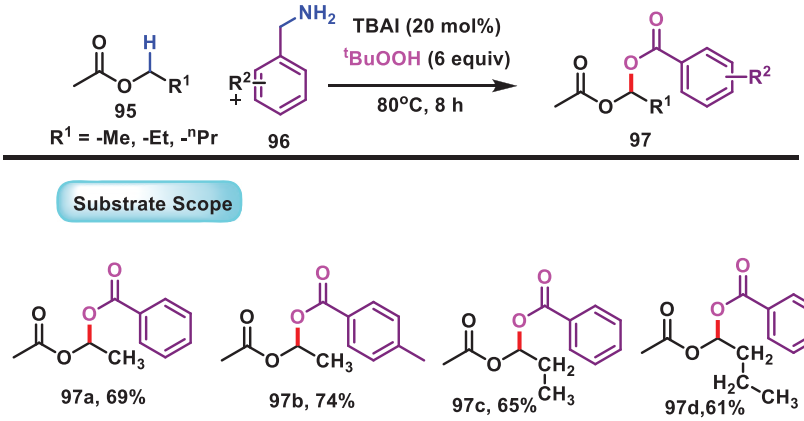

Figure 3.25: Synthesis of bis-acyl ketals from acetic acid esters and benzyl amines via TBHP-mediated oxidative cross-coupling.

3.2.15.5 Synthesis of functionalized 2H-azirine

In 2016, Duan et al. [134] reported a facile synthetic procedure to access functionalized 2H-azirine (**100**) moieties involving a KI/TBHP-promoted oxidative cross-coupling between β-enaminones (**98**) and carboxylic acids (**99**) (Figure 3.26). A plausible mechanism of this conversation is shown in Figure 3.27.

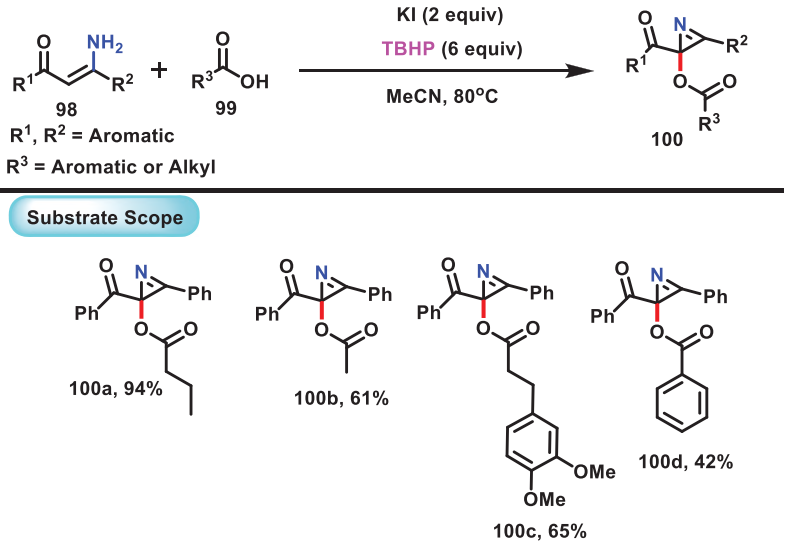

Figure 3.26: Preparation of 2H-azirine via oxidative cross-coupling between β-enaminones and carboxylic acids.

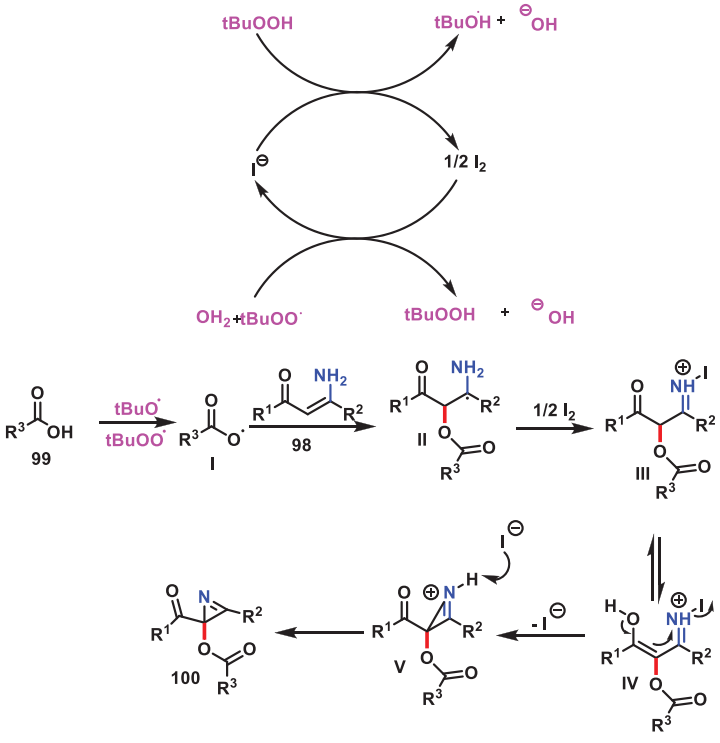

Figure 3.27: Plausible mechanism for the synthesis of 2H-azirine.

3.2.15.6 TBHP mediated synthesis of highly functionalized isoquinolinones and quinolinones

In 2019, Reddy and coworkers [135] described a unique protocol for the generation of highly functionalized isoquinolinones and quinolinones involving the TBHP-mediated oxidative coupling (Figure 3.28).

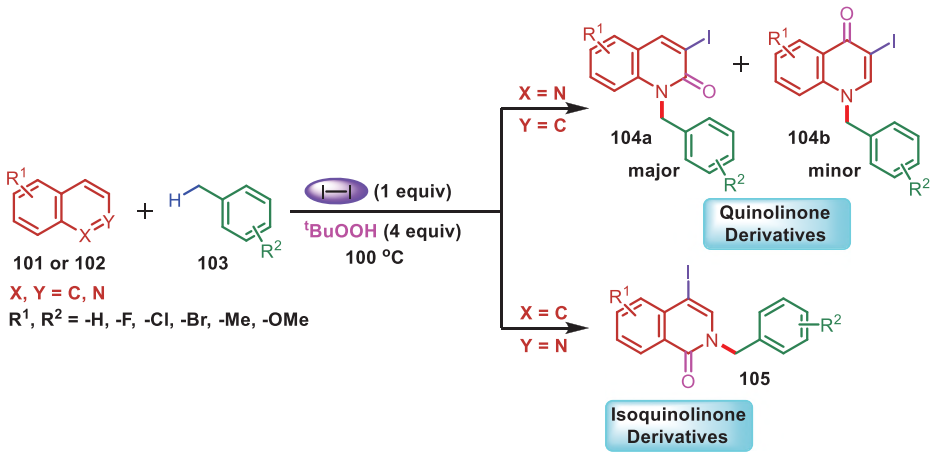

Figure 3.28: Preparation of highly functionalized isoquinolinones and quinolinones involving the TBHP-mediated oxidative coupling.

3.3 Conclusions

In summary, we must say that TBHP-mediated cross-coupling reactions are evolving as complementary to metal-catalyzed cross-coupling protocols. The TBHP-mediated cross-coupling reactions overcome the necessity of pre-functionalization of the starting material being essential in traditional cross-coupling methods. These types of cross-coupling procedures are also efficient and ideal in terms of the number of steps and atom economy. From the last decade, several research groups are exploring this proliferating area and are able to generate several new catalytic system. Each of this catalytic system features their own uniqueness, versatility and applicability. Thus, with respect to oxidants, TBHP has turned out to be an ideal terminal and sacrificial oxidant too in the mentioned reactions Further, TBHP-mediated cross-coupling strategy has gained concern, huge attention and exciting outcome and is still awaited in the coming days.

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Chapter 4
Applications of Cyrene and ethyl lactate bio-based solvents for organic transformations

4.1 Introduction

In recent years, it has been observed that the environmental effect is directly dependent on the chemical processes employed in industries, and it demands the protocol more on sustainable development, and a focus on inexpensive and eco-friendly reaction medium is an important research in modern synthetic chemistry [1, 2]. Organic solvents are playing a pivotal role in many chemical processes, and not just to promote better interaction of reactants or transition-state stabilization but also facilitate product separation [3]. Solvent separation, recycling and purification are critical factors used in reactions that have a direct impact on economy, efficiency and its industrial viability [4]. The statistics showed that 80% of the chemical processes required solvents [5], and volatile organic solvents are used because they allow easier product isolation and recovery or recycling via low-temperature distillation, thereby preventing thermally sensitive compounds from degradation [6]. Unfortunately, these volatile solvents have large number of safety and environmental issues, including flammability, storage and transport, and also health issues on exposure to people [7]. The chemical industry has long been aware of this issue, and is constantly looking for a novel and safety medium to improve the long-term safety, storage and sustainable method [8]. With this background, chemical industries are playing a responsible role to take care of the society and environment [9]. These solvent media are aimed at encouraging chemical companies across the world to improve their environmental, health and safety performance [10]. Researchers demonstrated an alternative procedure of solventless route under the green chemistry principle [11]. However, intrinsic issues like mass transfer limits, viscosity, melting temperature of the reactant and reaction control exothermicity hinder the solventless reaction development popularity in a broader manner [12].

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Furthermore, the commercialization of a solventless technique is highly focused on atom economy and is inexpensive; otherwise, the reaction-influenced organic solvent typically gave significant product yield, but required isolation and purification of products, severely restricting the appeal of this strategy [13]. Hence, most of the academic studies focused on *bio-based solvents* as an alternative solvent for organic synthesis, particularly in the application of pharmaceutical or fine chemical manufacturing (Figure 4.1) [14]. The paint and coating industries are by far the largest users of solvents, accounting for 46% of the overall solvent usage in the European Union [15]. The solvent in paints and coatings dissolves, and suspends paint components before evaporating from the once applied paint. Because the polymer binder makes up the major amount of paint formulations, green solvents are critical in the paint and coating industry [16]. Other industries that use green solvents are: (i) adhesives, where green solvents dissolve the adhesive compounds to allow spreading onto a surface; (ii) cosmetics, where bio-based solvents are used as stiffeners and gelling agents; (iii) household care, where solvents are used in laundry detergent formulations; (iv) polymer manufacturing, where the use of bio-based solvents enhances the physicochemical properties of polymer products; and (iv) industrial cleaning, where bio-based solvents were used to remove the toxicity from the products.

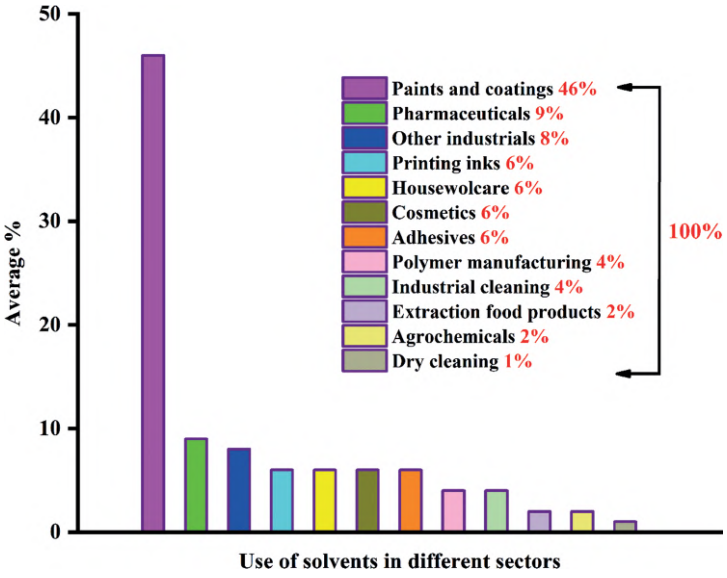


Figure 4.1: Average use of bio-based solvents in different sectors.

A variety of ambitious sustainability plans have been formed by researchers, international organizations and business sectors in response to the grave environmental issues of the past decade [17]. These efforts resulted in a more stringent regulatory environment and a surge in research areas in green chemistry and sustainable technologies [18]. Because the solvent accounts for the biggest amount of the total mass

utilization in chemical manufacturing, they have long been of major importance in green chemistry [19]. A number of green solvents have been discovered and described in the literature to address the environmental, health and safety concerns connected with the use of organic solvents [20]. When compared to their conventional equivalents, these green solvents have reduced acute and chronic toxicity, less environmental impact and fewer safety concerns [21]. Furthermore, they are frequently built on renewable resources, making them more appealing from a sustainability standpoint [22]. Bio-based solvents are the category of chemicals with well-developed market [23], and those made from biowastes are in high demand alternative to several common solvents like aromatic, halogenated and ether derivatives, due to the regulatory restrictions in using these solvents. The use of some of the prominent bio-based solvent systems and their chemical composition structure are given in Figure 4.2 [24]. This chapter provides insights and highlights solvents derived from the bio-based that are employed in organocatalysis and transition metal and biocatalysis-accelerated reactions reported in the literature [17].

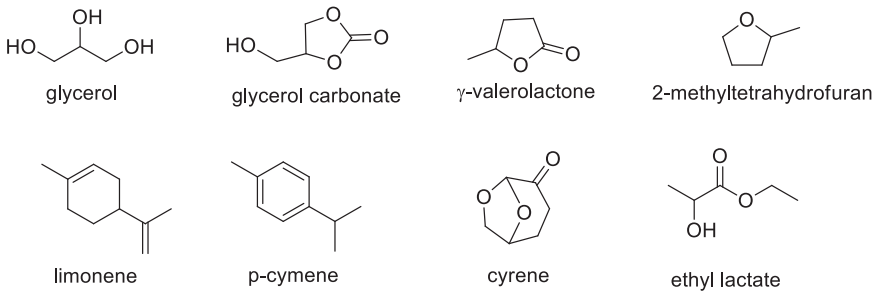


Figure 4.2: Alternative bio-based solvents.

In an effort to replace hazardous solvents with greener solvents, four major developments have been considered [25]: (i) the replacement of solvents dangerous to the environment is replaced with better safety, health and environmental properties; (ii) bio-based solvents derived from recyclable resources are starchy feed, ethanol or lignocellulosic; (iii) the blending of organic solvents with nontoxic green solvents; and (iv) use of stable bio-based solvents. Biomass has recently received a lot of interest as a sustainable carbon feedstock source due to its important properties, thereby replacing the solvent derived from oil refineries [26]. The solvents derived from biomass feedstock such as Cyrene and ethyl lactate (EL) have emerged greater heights of bio-based solvents [27]. Both physical and chemical methods, which are safer to humans and the environment, are employed to create these compounds from vegetable, animal and mineral sources [28, 29]. Further, bio-based solvents are projected to deliver a favorable balanced environment like reduced volatile organic compounds, nontoxicity and biodegradability with improved safety issues because of the compatible concept on sustainable development. The procedures used in the solvent manufacture must be environmentally friendly, cropping cycle, choice of abundant raw materials, cost reduction and physicochemical standards.

Cyrene is a bio-based solvent derived from various biomass (Figure 4.3) [30–33]. In recent years, these solvents, used in academic and industrial research, steadily increased as an alternative to toxic, aprotic and dipolar solvents generated from petroleum, such as *N*-methyl-2-pyrrolidone (NMP) and *N*,*N*-dimethylformamide (DMF) [34]. DMF, NMP and Cyrene have 0.88, 0.90 and 0.93 values on the Kamlet–Abboud–Taft polarity scale, which measures the dipolarity of a solvent π^*. Cyrene was found to have similar solvent properties like DMF and NMP, according to the Hansen solubility relating to polar (*P*), dispersion (*D*) and H-bonding interactions (Table 4.1) [35, 36]. Cyrene was investigated in a wide range of reactions, namely, S_N2 and S_NAr reactions, coupling reaction catalyzed by Pd, nucleophilic addition reaction [37], metal–organic framework (MOF) synthesis and graphene manufacturing [38]. The wide applications of Cyrene is also extended to other research areas such as membrane synthesis and resin swelling techniques [39], acyl substitution processes, due to its physical and solubility properties similar to conventional aprotic dipolar solvents, and with the added benefit of no mutagenicity and being barely ecotoxic [40]. Cacchi-type annulations, a number of biocatalysis applications [41, 42], where it could operate as an electrophile, were incompatible by Cyrene™ as a solvent [43]. Watson et al. described the use of Cyrene™ in hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU)-mediated amide bond formation by amines and carboxylic acid condensation in the presence of base. In addition, *Cyrene™* has been employed as a solvent in a number of studies [44–53]. The various applications of Cyrene™ over other petroleum-derived solvents are described in Figure 4.4.

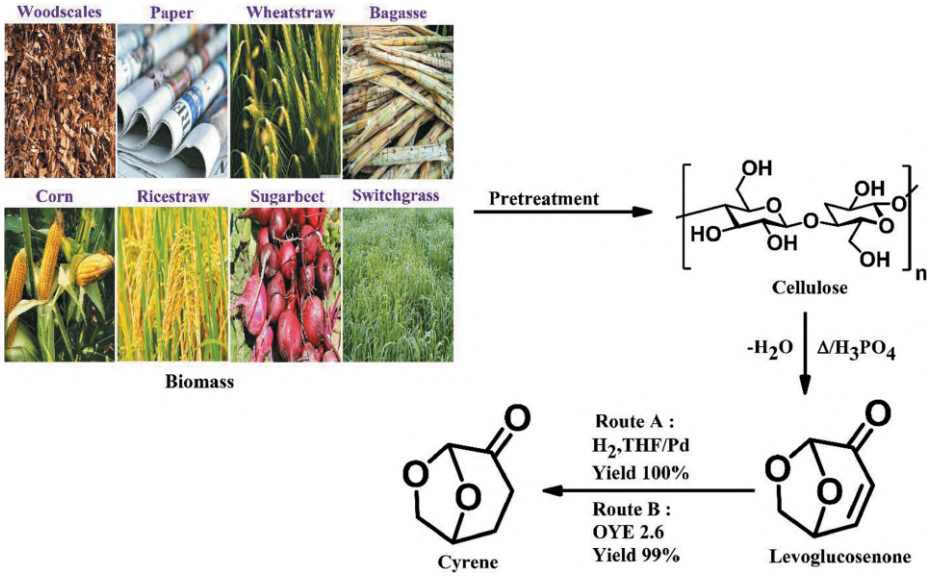


Figure 4.3: Synthesis of Cyrene from biomass.

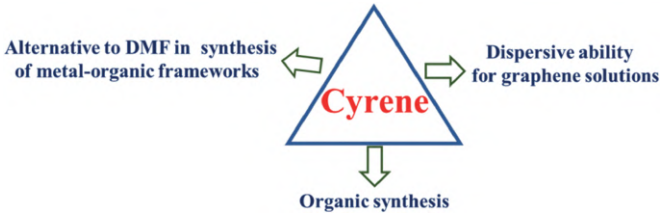


Figure 4.4: Application of Cyrene in various sectors.

EL (Figure 4.5) is extracted from carbohydrate biowaste [54–58] derived from lactic acid and ethanol, which are obtained by biomass fermentation. Alternative solvents have adequate physical properties (Table 4.1). EL is highly abundant in nature and is primarily an optically active ($[\alpha]^{20}D$ = 10.6) [59] L-isomer (ethyl-(*S*)-2-hydroxypropanoate) which emerged as a promising solvent available with added advantages, including complete biodegradability, inexpensive, nontoxicity, low vapor pressure, high boiling point (154 °C) and recyclable with excellent solubility of the organic compounds [60]. EL emerged as an sustainable alternative solvent in organic synthesis, with added benefits such as nontoxicity, high stability, complete degradability and solubility both in organic and water system [61]. EL influenced various types of organic reactions such as Suzuki–Miyaura (SM) reaction, enaminone, thiophenol, 1,3-dipolar cycloaddition, enaminones and 1,3-diketone C = C bond cleavage [62], Glaser-type terminal alkyne preparation, aldehyde thioacetalization, the reaction of amines, furfural and 1,4-dihydropyridines [63] and 4(3H)-quinazolinone synthesis [64]. EL and its dilute solutions showed a wide range of applications due to their sustainable nature, excellent safety and ecotoxicological profile, as well as their strong solvency power [65]. EL has been reported to be an effective solvent system in the treatment of soil contamination

Table 4.1: Physical properties of Cyrene and ethyl lactate.

	Cyrene	Ethyl lactate
BP (°C)	226	153
MP (°C)	−18	−23
FP (°C)	108	61
Density, [ρ (g cm^{-3})]	1.2508	1.0284
Absolute viscosity, η (mPa· s)	14.5	2.3753
Vapor pressure, p (kPa)	14.4	0.436
Refractive index, n_D^{20}	1.4732	1.4107
Kamlet–Taft (dipolarity/polarizability) π^*	0.93	0.82
Reichardt's solvatochromic data, E_T^N	0.333	0.62
Hansen parameter for solubility (MPa$^{1/2}$): dispersion forces, δD	18.8	16.0
Dipole forces, δP	10.6	7.6
Hydrogen bonding interactions, δH	6.9	12.5
Solubility in water	Miscible	Miscible

caused by polycyclic aromatic hydrocarbons [66–68] and heavy metals [69]. Many effective techniques for extracting nonpolar and polar phytochemicals from nature employing EL have been reported [70–72]. The miscibility with water and tunable properties of EL make biphasic development in aqueous medium for polar compound separation [73, 74] and are also used in mobile phase system in chromatographic methods [75, 76]. This is a more efficient liquid embolic agent for precipitation than DMSO [77], replacing NMP in the polyetherimide synthesis [78], and more applications drawn were reported in Figure 4.6.

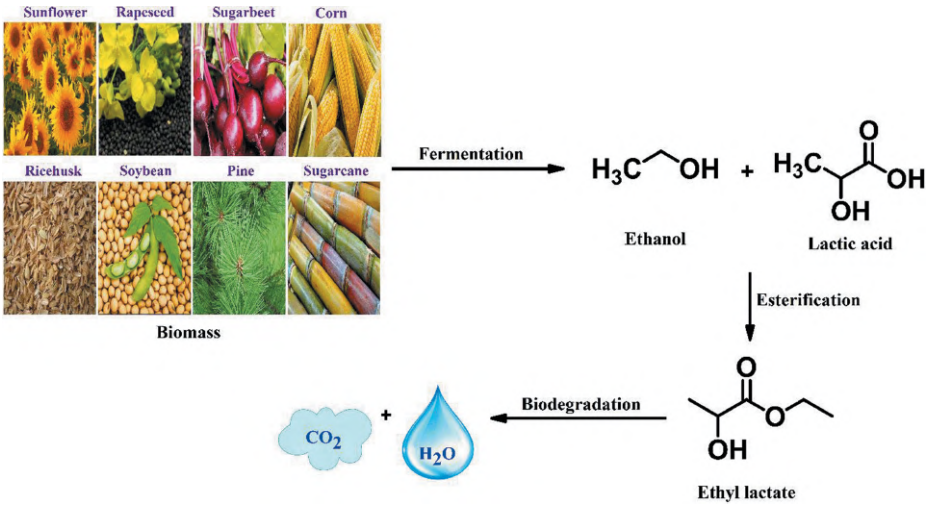


Figure 4.5: Synthesis of ethyl lactate from biomass.

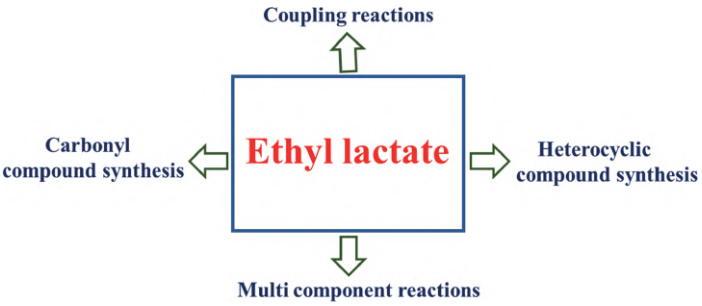


Figure 4.6: Application of ethyl lactate in various sectors.

4.2 Cyrene-mediated organic reactions

Camp and coworkers described the 4-fluorobenzoyl chloride (**1**) reaction with a variety of substituted amines (**2**) for the synthesis of amide derivatives in the presence of Cyrene and triethylamine which afforded desired amides (**3**) (Table 4.2) in good yields. Amides are a class of compounds that has been used in a variety of industries, including pharmaceuticals, agrochemicals and materials research. Amides have a tremendous impact in the practice of clinical research, as evidenced by enormous medicines containing an amide group; hence, the high percentage of amide bond linking synthesis is performed by medicinal chemists [79]. The top 15 bestselling medicines in 2017 featured the amide bond, which has a history of being highest grossing of all time drugs (Figure 4.7). Further, the amide bond-containing molecules are being found in ligands, catalysts, solvents, reagents and substrates in a number of synthetic methods.

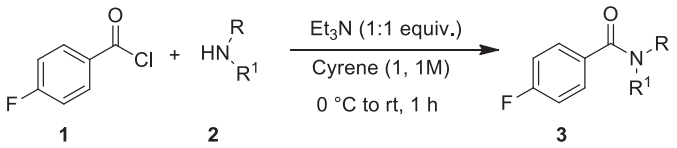


Figure 4.7: Synthesis of amides in Cyrene™.

Table 4.2: Synthesis of amide bonds in Cyrene™ using optimization molar efficiency calculations.

Entry	Amine (2)	Workup condition	% Yield (3)	Relative mol. *E*%
1	Aniline	Direct precipitation	72	24
2	Pyrrolidine	Water, then chromatography	91	1
3	Benzylamine	Direct precipitation	81	28

Amide bonds found in fundamental links to life systems play a critical role in medicine development. Current methods of synthesis found dependent on aprotic dipolar solvents, but, its usage is restricted because laws become more severe, and societal opposition has been increased for more sustainable and safer alternatives. Watson and coworkers [80] investigated the use of Cyrene™ in HATU-mediated amide and peptide synthesis, which showed a good substitute to DMF for numerous dipeptide and lead compound syntheses. Authors also investigated the capacity of Cyrene in amide bond building in the presence of HATU coupling agent for the reaction of aniline (**5a**) and *p*-toluic acid (**4a**) which gave amide bond with a good % yield of 4-methyl-*N*-phenylbenzamide (**6a**) (Figure 4.8).

Further, Watson and coworkers [80] investigated the optimized condition for a wide range of organic carboxylic acids (**7b–p**) and amine derivatives of primary (**8b–p**) and secondary amines (**9b–p**) which gave very good product isolation. Various substituted carboxylic acid and amine derivatives are tolerated by the developed method and gave

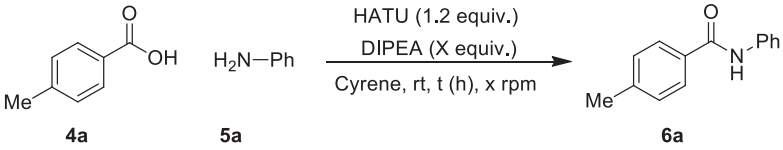


Figure 4.8: Amide bond formation of aniline coupled with *p*-toluic acid.

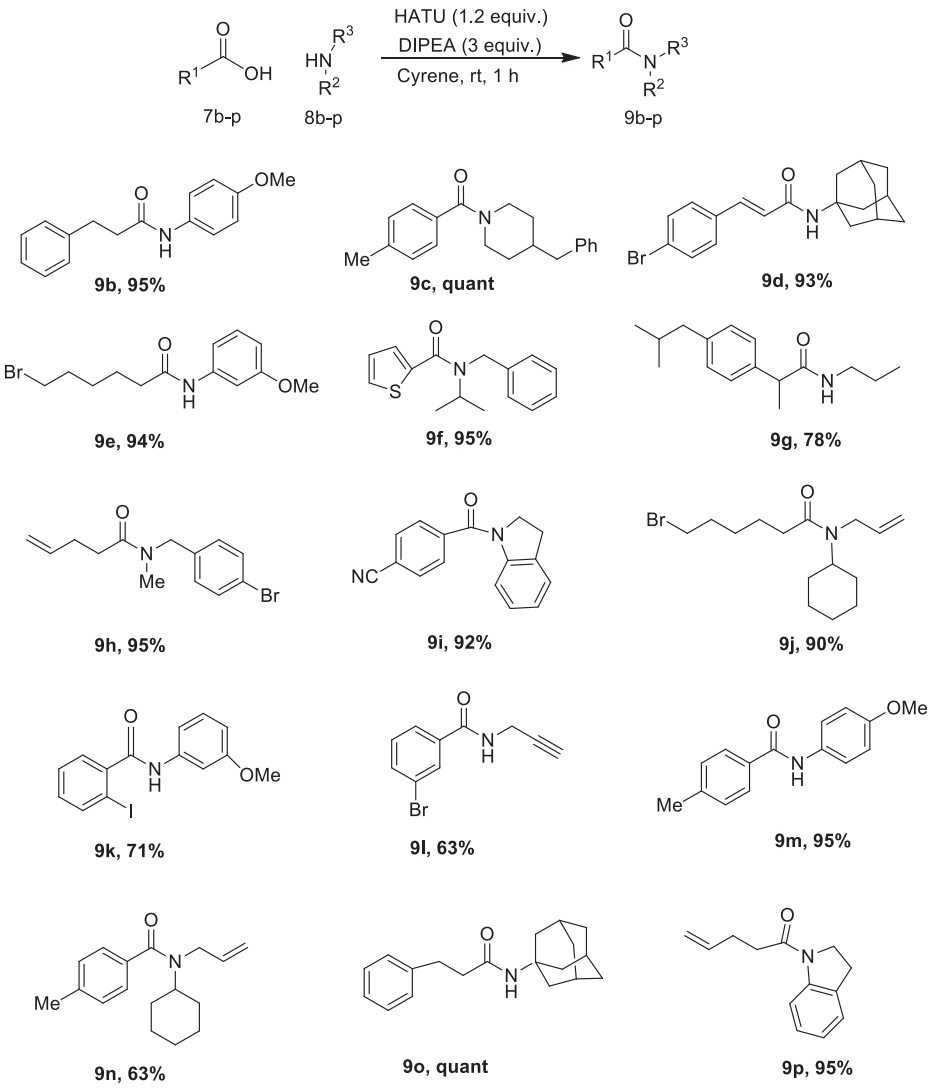


Figure 4.9: Amide bond formation by acid and amine in the presence of HATU, *N*,*N*-diisopropylethylamine and Cyrene.

63–100% of product isolation. Furthermore, authors examined the secondary acyclic (**9f**) and cyclic (**9c** and **9i**) amines which gave excellent product isolation (Figure 4.9).

Moreover, the authors used this approach to peptide synthesis (Figure 4.10) which gave good yield of the product isolation by the reaction of amino acids *N*-protected (**10a–d**) with esters of amino acids (**11a–i**) gave peptide isolation (**12a–i**) in high yield (63–100%). Authors also explain about aryl and alkyl side chains containing (**12a** and **c**) heteroaromatics with protected and unprotected also tolerated this method giving high yields of product isolation (**12e** and **i**). However, in case of product isolation (**12b**, **d** and **h**), authors claimed an increase in HATU equivalents necessary to achieve the improved yield [80].

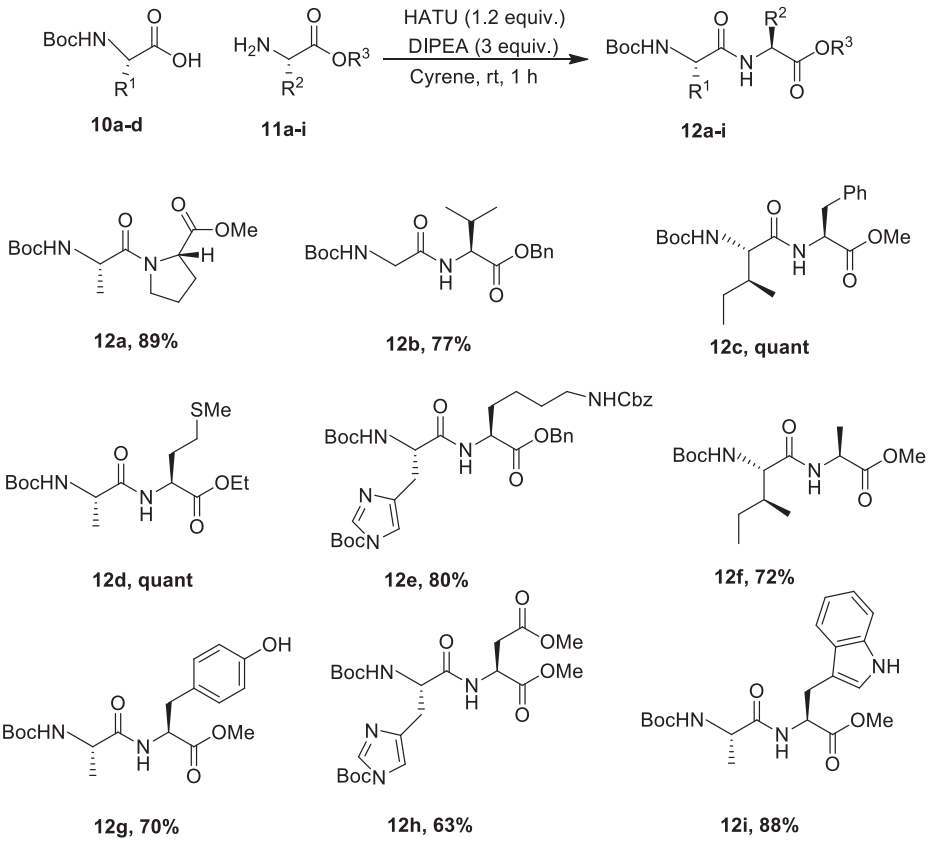


Figure 4.10: Peptide bond formation using HATU, *N*,*N*-diisopropylethylamine and Cyrene.

A cellulose-originated 6,8-dioxabicyclooctanone or dihydrolevoglucosenone (Cyrene™) emerged as an aprotic biogenic solvent. Maria et al. described the application of Cyrene in enzyme *lipase*-catalyzed biotransformation in aqueous cosolvent and nonconventional medium for the synthesis. A typical reaction of benzoic acid (**13**) with glycerol (**14**) as a model reaction in Cyrene in the presence of immobilized *lipase B* from

Candida antarctica gave the product 2,3-dihydroxypropyl benzoate (**15**) in good yield. Authors noticed, lipases cross-linked enzyme aggregates (CLEA) and remain stable in Cyrene, and also enables use in several times [81]. Cyrene is very hygroscopic and, when mixed with water, forms geminal-diol structures, resulting in solvent mixes with a (tailored) gradient of polarities, which may be promising for biocatalysis in aqueous solutions. This displays reactions in various percentages of Cyrene, and CLEA mixtures remain active even after six cycles at 30% v/v (Figure 4.11).

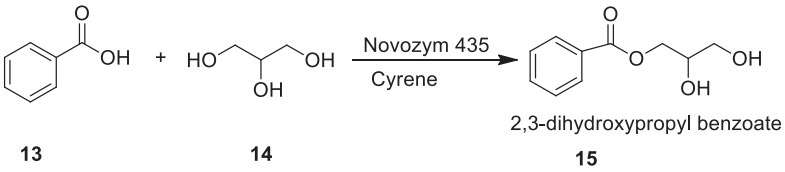


Figure 4.11: Enzyme-catalyzed esterification reaction.

Milescu et al. [82] investigated the binary solvent consisting of Cyrene and its Cygnet derivatives in biocatalytic polyester and membrane synthesis. The blends of Cyrene and Cygnet showed a feasible alternative to harmful polar aprotic solvent employed in the earlier process. The fabrication of flat sheet-like membranes achieved by non-solvents influenced the phase separation of 50 wt% (Cyrene–Cygnet) mixture. The presence of CaLB and solvent, and the reactants DMA (**16**), Doil (**17**) and DEF (**19**) gave aliphatic (**18**) and furan-based (**20**) polyesters (Figure 4.12). A novel membrane polymer from polysulfone, cellulose acetate and polyimides was manufactured by employing Cyrene–Cygnet blend solvent system. Authors noticed that membranes obtained in this method showed a different morphology achieved with a change in temperature, solvent mixture and casting change. Moreover, Cygnet, Cyrene and its blends are explored for diphenyl ether substituents for the synthesis of polyesters. Authors revealed that Cygnet showed a very promising solvent system for the enzymatic molecular weight higher polyester synthesis (Figure 4.13).

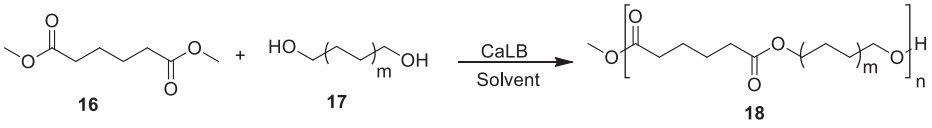


Figure 4.12: Enzymatic synthesis of aliphatic polyesters with Cyrene solvent.

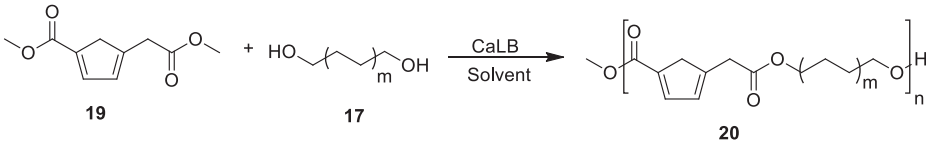


Figure 4.13: Furan-based polyester synthesis by enzymes in Cygnet.

A very effective, less waste-producing technique was described for the synthesis of urea derivatives from secondary amines and isocyanates in Cyrene. Authors compared the standard techniques of industries, and this technology avoids the use of hazardous solvent (DMF) and provides direct Cyrene removal procedure, resulting in 28-fold molar efficiency [83].

Camp and coworkers investigated that the reaction of phenylisocyanate (**21**) with pyrrolidine (**22**) in Cyrene gave urea derivatives (Figure 4.4). Authors optimized the reaction, and to avoid the formation of by-product during reaction, reagents were taken together and kept at 0 °C, and slowly reached the room temperature at 1 h. Further, authors also examined the tolerance of the developed protocol, which allowed both electron-donating and electron-withdrawing substituents on isocyanate derivatives. The previous procedure used product isolation by water and dichloromethane mixture extraction, followed by water wash, dried in magnesium sulfate, and then by column purification (hexanes/ethyl acetate). This method produced a significant quantity of organic and aqueous contaminated wastes [83]. To overcome some of these limits, Cyrene-mediated synthesis of urea derivatives showed benefits in many ways to achieve the pure targeted product and does not require column purification. Authors noticed the addition of water in Cyrene-mediated reaction to give direct precipitation of urea derivatives (**23**), simply filtrated and washed with water to give chromatographically pure *N*-phenylpyrrolidine-1-carboxamide (**23**) in 80% yield (Figure 4.14).

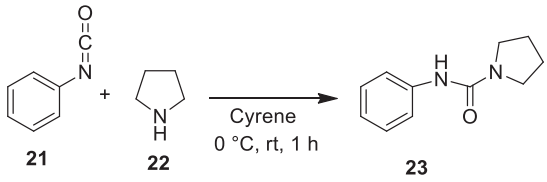


Figure 4.14: Synthesis of urea derivative in Cyrene.

In the chemical industry, the SM cross-coupling reaction is a widely used carbon–carbon bonding catalyzed by Pd [84]. Although dipolar aprotic solvents are used in many SM couplings, contemporary ecological initiatives and increasing severe laws encourage chemists to use novel alternatives with better characteristics. Among these, Cyrene, employed in the cross-coupling of SM reaction, emerged as a benchmark medium to be used in gram scale [84]. Authors claimed that the Cyrene medium was found to be more effective for the coupling of 4-bromotoluene (**24**) with boron species (**25**) in the presence of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol%), Cs_2CO_3 (0.75 mmol, 3 equiv.) and Cyrene:H_2O at about 50 °C for 5 h to give the expected product 4-methyl-1,1′-biphenyl (**26**) in good yield (Figure 4.15).

Further, authors demonstrated the Cyrene application in preparative-scale reaction of 2-bromobenzonitrile (**27**) and boron derivatives (**28**) for the synthesis of biphenyl derivative product (**29**) (Figure 4.16). These types of derivatives act as a key intermediate for the synthesis of antagonists, angiotensin-II receptor inhibitors, and

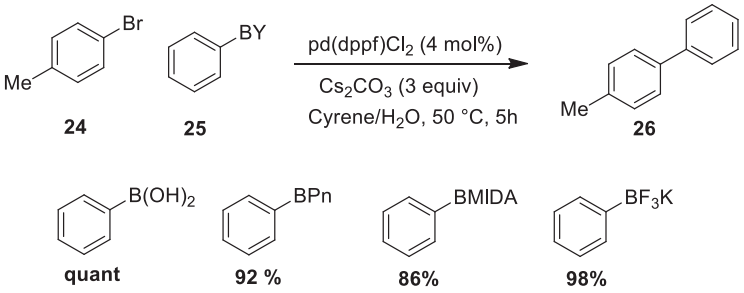


Figure 4.15: Suzuki–Miyaura cross-coupling by bromotoluene and boron derivatives in Cyrene.

can be easily prepared via SM cross-coupling reaction [84]. This method allowed reactions in large scale followed by medium polarity addition of solvent mixture (40% EtOAc in petroleum ether) resulting in the precipitation of the product, and easily separated by filtration, followed by water wash to remove the residual Cyrene present and enable pure product isolation.

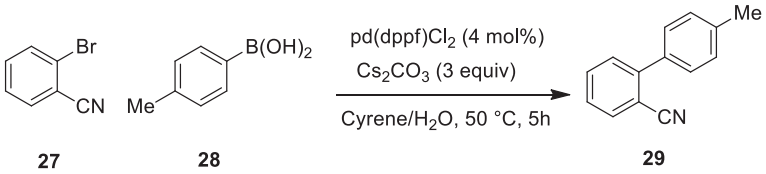


Figure 4.16: Synthesis of 4-methyl-2-biphenylcarbonitrile.

Allais and coworkers [85] reported norbornene–levoglucosenone monomer-based family synthesis using novel bifunctional methacrylate monomer, which is prepared by chemo-enzymatic method. Authors employed Cyrene^{TM} for the first time as an alternative to greener organic solvent for ring-opening metathesis polymerization (ROMP), where the norbornene moiety polymerized selectively by ROMP. Authors compared various common and hazardous solvents like dichloromethane, but the metathesis catalytic activity controlled by Cyrene^{TM} was found superior and gave very functional thermostable polymer P(N-HBO-MA) (**31**) with high T_d and T_g temperatures (Figure 4.17).

Camp et al. [86] reported that Cyrene-mediated reaction of 1,2-dimethylimidazole (**32**) and 1-bromodecane (**33**) gave imidazolium ionic liquid (**34**) (Figure 4.18). Authors revealed that the rate of this reaction is dependent on solvent dipolarities such as NMP, DMF and DMAc, and behaves marginally slow than sulfolane and DMSO. But the reaction in Cyrene carried out by the authors showed significantly better results compared to standard aprotic dipolar solvents [86]. In addition, authors also described fluorination of 2-chloro-5-nitropyridine (**35**) in the presence of KF to give 2-fluoro-5-nitropyridine (**36**) in reasonably good yield (Figure 4.19).

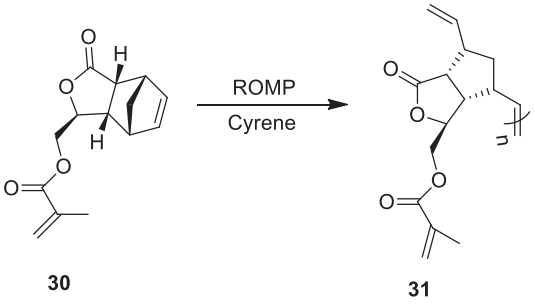


Figure 4.17: Preparation of N-HBO-MA in Cyrene.

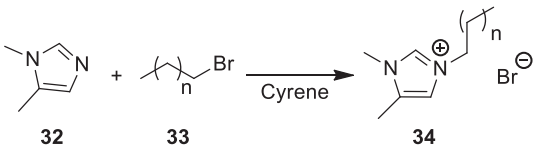


Figure 4.18: Synthesis of imidazolium ionic liquid in S_N2 reaction.

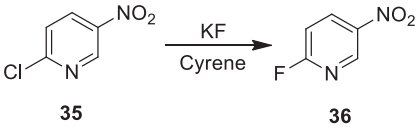


Figure 4.19: Synthesis of 2-fluoro-5-nitropyridine in S_NAr reaction.

Watson and coworkers reported the first time usage of Cyrene in a metal-catalyzed Sonogashira reaction of alkynes **38** and aryl halogen **37**, which gave the internal alkyne product **39** isolated by the standard aqueous workup followed by ethyl acetate extraction and purification by column chromatography (Figure 4.20) [86]. Authors also described that the Cacchi-type annulation of 2-iodoanilines and 2-iodophenols with terminal alkynes gave Cyrene-mediated benzofuran (**39a**) and indole (**40**) derivatives, respectively. Further, authors also demonstrated the SM cross-coupling.

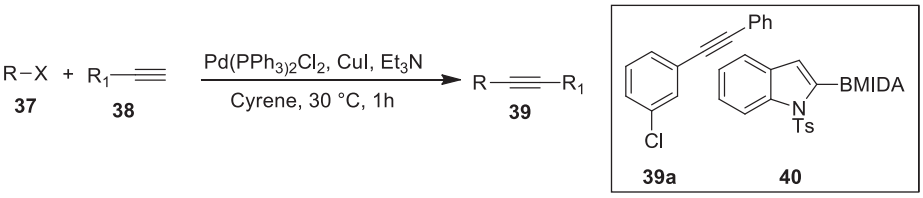


Figure 4.20: Sonogashira- and Cacchi-type annulation in Cyrene.

Reaction of heteroaryl, aryl and vinylhalides **37** with a wide range of organoborane analogs (**40**), which afforded products **41(a–c)** in good to excellent yields (Figure 4.21) [86].

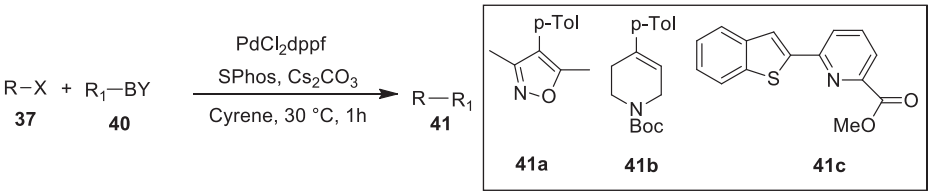


Figure 4.21: Suzuki–Miyaura reaction.

Researchers described that Cyrene-mediated Baylis–Hillman reaction of 4-nitrobenzaldehyde (**42**) and methyl acrylate (**43**) gave methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate product (**44**) in excellent yield (Figure 4.22). Authors claimed that the bio-solvent notably observed the high rate of reaction, and the complete conversion of reaction was noticed due to high dipolarity of the solvent-stabilized zwitterionic intermediate generated during conjugate DABCO addition to methyl acrylate. The reaction rate in Cyrene (**2**) was significantly faster than that of standard dipolar aprotic solvents such as DMF, NMP, and DMAc, and only marginally slower than DMSO and sulpholane. Additionally, sulfolane also emerged as a suitable solvent for the Baylis–Hillman reaction. However, sulfolane and NMP are toxic to the environment and are hazardous. Therefore, authors explained the advantages of Cyrene – an alternative inexpensive solvent used for the conventional Baylis–Hillman reaction [86].

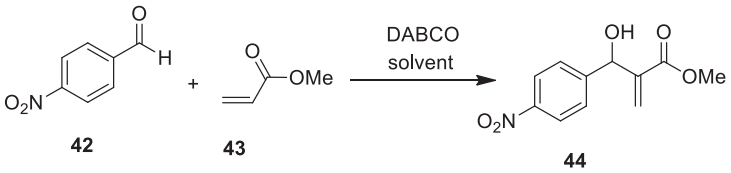


Figure 4.22: Synthesis of hydroxy(4-nitrophenyl)methyl)acrylate via Baylis–Hillman reaction.

Watson and coworkers [87] reported the use of Cyrene in the Sonogashira reaction, which established that a simple reaction of iodobenzene (**45**) and phenylacetylene (**46**) catalyzed by $(Pd(PPh_3)_2Cl_2$ with CuI additive gave diphenylacetylene (**47**) (Figure 4.23). Further, the same authors explored Cacchi-type annulation reaction of *o*-hydroxyaryl iodides (**48**) with alkyne derivatives (**49**) at 60 °C which undergoes 5-endo-dig cyclization to give pharmaceutically functionalized benzofuran, indole and aza-indole derivatives (**50**) [87] (Figure 4.24).

Mention et al. [88] described the sustainable industrially useful synthetic route for selective β,β′- dimerized sinapic acid derivatives (**52**) in excellent yield, and the

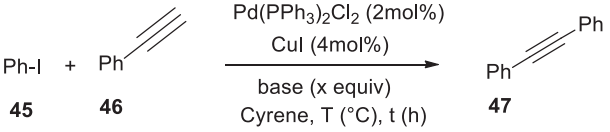


Figure 4.23: Diphenylacetylene synthesis.

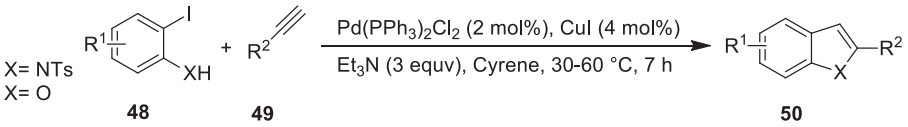


Figure 4.24: Cacchi-type annulation.

product showed valuable commercial applications used in cosmetic additives, food/feed and plastics. The naturally found sinapic acid and its esters showed antiradical and anti-UV properties. The optimized reaction condition of copper(I) catalyzed in pyridine and air oxidation in the presence of Cyrene was reported. Authors revealed that the processes gave dimerization of sinapate esters (**51**) to multigram-scale β–β′-disinapate esters (**52**) in excellent yield (Figure 4.25).

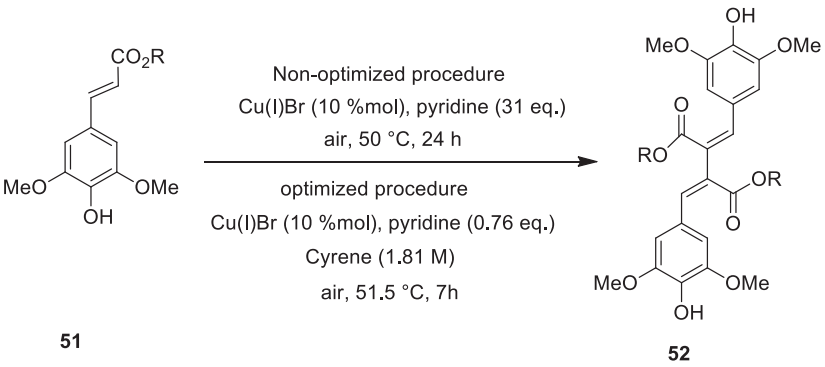


Figure 4.25: Sinapate β–β′ dimer synthesis.

de Gonzalo [89] demonstrated novel eco-friendly reaction media in enzyme catalysis by replacing water medium, due to the requirement of organic cosolvent. Authors described a new route with Cyrene approach reduction reactions in the presence of purified alcohol dehydrogenases. Authors used a set of α-ketoester (**53**) reduction to chiral α-hydroxyesters (**54**) in high optical purities and conversions in aqueous Cyrene contents of 30% v/v. The presence of Cyrene has a beneficial effect on bioreduction conversion at this concentration (Figure 4.26).

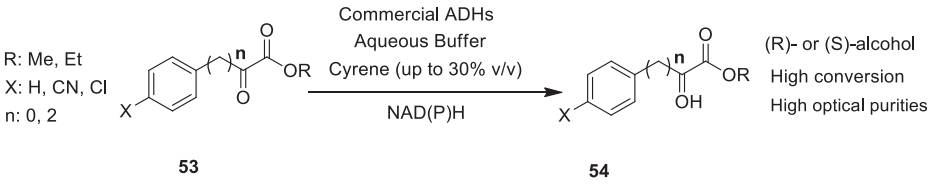


Figure 4.26: Synthesis of α-hydroxyesters.

Cyrene (dihydrolevoglucosenone) extracted in two steps from cellulose behaves similar to DMF and other dipolar aprotic solvents and not showed any noticeable adverse effects. Taking this into account, Watson and coworkers [84] reported that the steam methane-reforming reaction of halides/pseudo-halides (**55**) in boron derivatives (**56**) gave the dimer product (**57**). Authors claimed that the reaction is eco-friendly with an efficient alternative to the conventional solvent employed. THF, DMF and 1,4-dioxane gave excellent functional group tolerance and excellent yields in both small and large scales (Figure 4.27).

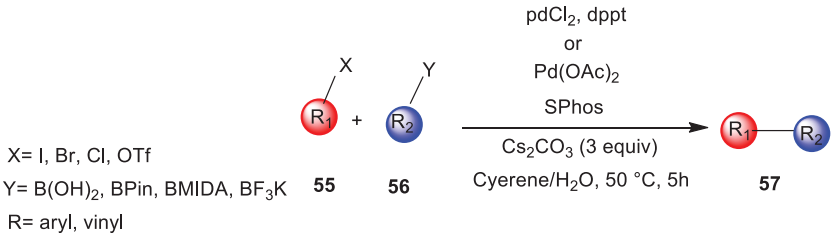


Figure 4.27: Halide/pseudohalide reaction with boron resulted in steam methane-reforming product.

Lee and his coworkers [90] described that the reaction of aldehyde (**59**), pyridine methylene nitrile (**60**) and *o*-substituted aniline (**58**) gave 2,3-bipyridine derivatives (**61**) (Figure 4.28). The reactant **58** contains both electron-donating (2-OMe and 2-Me) and electron-withdrawing (2-Br) substituents to give desired products (2,3-bipyridine

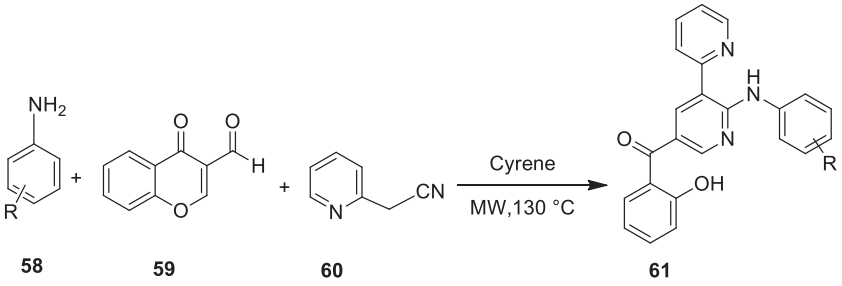


Figure 4.28: 2,3-Bipyridine synthesis by aniline, 3-formylchromone and 2-pyridylacetonitrile.

derivatives, **61**) in excellent (86–94%) yield. Authors also studied the structure-activity relationships of aniline substrate (**58**) substitution at *meta*- and *para*-positions which were also effectively involved in the product formation and gave excellent yields.

Further, the same authors examined that amine derivatives of aliphatic and cyclic of primary amines (benzyl amine, 2-phenylethan-1-amine, diphenylmethanamine, cyclohexanamine and 4-methoxybenzylamine), respectively, gave excellent yields of the desired product (86–96%) (Figure 4.29). Also, pyrrolidine, a secondary amine, gave product isolation in excellent yield (82%). Moreover, the desired products achieved for 4-aminopyridine and 2-aminopyridine heteroaromatic amines gave 62–92% yields. Authors further presented that the reaction of *R*-(+)-1-phenylethylamine (**2**), chiral amine, 3-formylchromone (**59**) and 2-pyridyl acetonitrile (**60**) gave chiral product 2′-(dimethylamino)-[2,3′-bipyridin]-5′-yl-(2-hydroxyphenyl)methanone (**62**) in excellent yield [90].

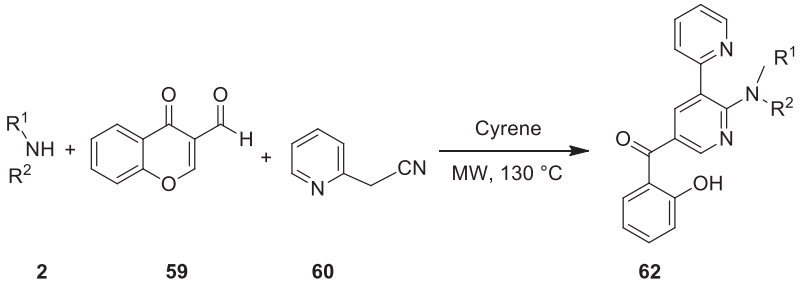


Figure 4.29: Synthesis of 2′-(dimethylamino)-[2,3′-bipyridin]-5′-yl-(2-hydroxyphenyl)methanone.

Furthermore, the same authors extended the methodology to the reaction of 3-formylchromone (**63**) derivatives with aniline derivatives (**64**) and 2-pyridylacetonitrile (**60**) to give highly complex polycyclic product (**65**) in good yield (Figure 4.30). Authors also noticed that the reactants of electron-donating CH_3 and OCH_3 substituents gave excellent yields [90].

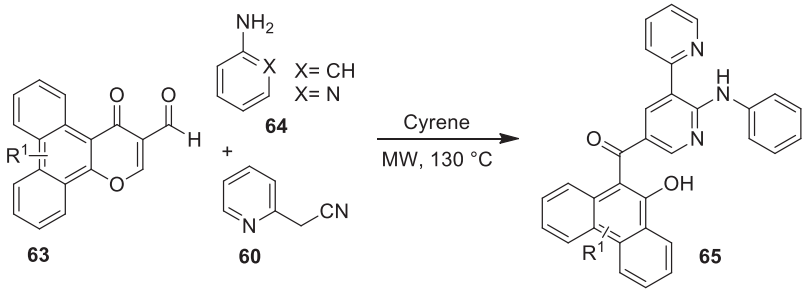


Figure 4.30: Synthesis of polycyclic complex molecule via MCRs.

Moreover, the same authors extended that this method to MCRs of 3-(pyridinyl)acetonitrile (**68**) or 4-(pyridinyl) acetonitrile (**69**), aniline derivative (**66**) and substituted formyl chromones (**67**) afforded 3,3′- and 3,4′-bipyridine products **70** or **71**, respectively (Figure 4.31) [90].

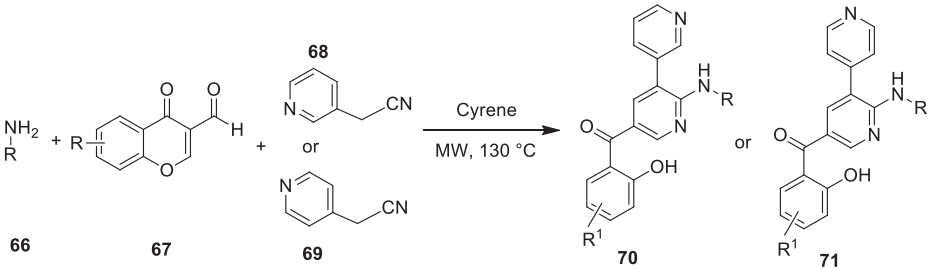


Figure 4.31: Bipyridine derivative synthesis.

Authors also explored that the synthetic utility of this method to the reaction of aryl amine (**72**), 3-formylchromone (**59**) and nitrile derivatives of aryl (**73**) gave interesting bioactive aryl pyridine derivatives (**74**) (Figure 4.32) [90]. The authors also demonstrated that the mechanism and control experiments conducted by the combination of aryl amine (**72**), formyl aldehyde (**59**) and nitrile derivative (**60**) at room temperature in Cyrene™ solvent medium gave the Knoevenagel pyridine adducts (**75**) and (**76**) in excellent yield (Figure 4.33). Authors noticed prior to the nucleophilic substitution of the aryl amine that the active methylene generated condensed with the aldehyde derivative (**59**) to give exclusively product **75** over **76** [90].

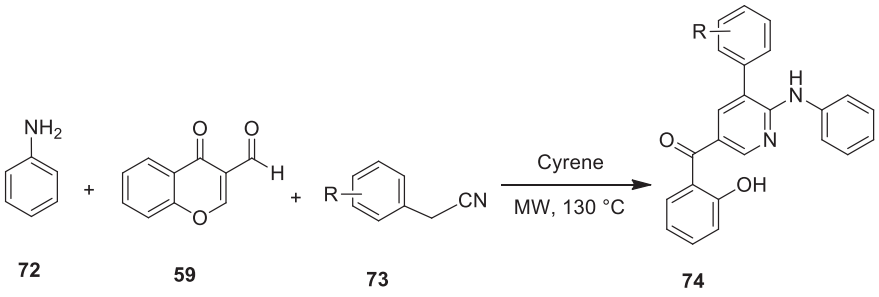


Figure 4.32: Aryl pyridine derivative synthesis.

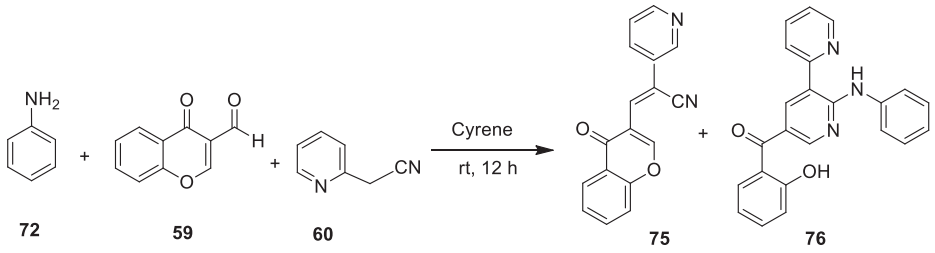


Figure 4.33: MCR Knoevenagel pyridine over nucleophilic substitution.

4.3 Ethyl-lactate-mediated organic transformations

The synthesis carried out in the presence of EL demonstrated various advantages compared to the organic solvent found over the last decades: facile, hazardous free, nontoxic and efficient. The organic transformations reported using EL includes reactions of carbonyl, diverse heterocyclic molecule synthesis, in MCRs and many more organic transformations employed [91]. EL is an amphiphilic bio-based solvent and nontoxicity characteristics; moreover, it is miscible in water, and it is possible to alter the properties of required in aqueous varied concentration reported. The use of EL and aqueous mixture in several coupling reactions of metathesis, heterocyclizations, carbonyl reactions, MCRs and more chemical reactions showed efficient, eco-friendly and inexpensive route. Chemists described the alternative use of nonconventional energy sources, which gave an added advantage in various organic reactions accelerated by ultrasound, visible light and microwave irradiation techniques. In most of these techniques, the yield of product isolated is higher than those isolated by the conventional method, and fewer by-products with high purity advantages were also reported. Herein, we have discussed some of the recent and important organic reactions performed in EL and its aqueous medium for various transformations.

EL was shown to be a good medium for Glaser coupling, and the reaction conditions were tuned using a model reaction of phenyl acetylene (**46**) with terminal aliphatic alkyne (77) (Figure 4.34) [92]. The authors claimed a respectable yield of the product (**78**), however other alkynes with conjugated product detected dependant substrate structure exhibited a range of low to high (26–80%) yield of the product described. In addition to serving as a solvent medium, the authors discovered that EL also acts as a ligand in copper-catalyzed. reactions to facilitate.

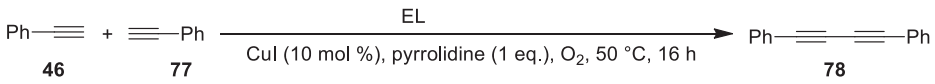


Figure 4.34: Homophenylacetylene coupling reaction in EL.

SM in EL was successfully performed in the absence of ligand condition [93]. The reaction of iodobenzene (**45**) and phenylboronic acid (**79**) in aqueous EL gave biphenyl product (**80**) in high yields compared to other solvent systems screened by the author (93% vs 62% yields) (Figure 4.35). The authors tested the compatibility in a wide range of aryl halides with arylboronic acids which gave low to excellent (43–96%) yields. Authors further noticed that aryl iodide derivatives were found to be more reactive substrates compared to other halide derivatives tested (aryl bromides).

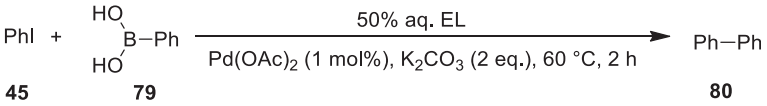


Figure 4.35: Suzuki–Miyaura reaction in aqueous EL.

In another interesting work, authors reported that loading of palladium catalyst during SM coupling was reduced in the presence of melamine ligand by one order [94]. In a typical reaction of phenylboronic acid (**79**) and 4-bromoacetophenone (**81**) in aqueous EL isolated C–C bond product **82** in good yield (Figure 4.36). However, authors observed that starting with 4-chloroacetophenone gave low product isolation (57%) even at 130 °C. Further, authors performed the reaction with various substituted aryl bromide and aryl boronic acids of 10 analog products (**82**) resulting in 64–99% product isolation.

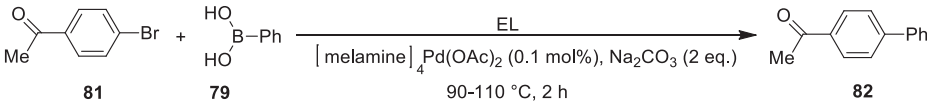


Figure 4.36: Coupling of 4-bromoacetophenone and phenylboronic acid in EL.

Researchers reported the thiol derivative homocoupling via oxidation in the presence of EL in open air, and also revealed the reaction that did not require any other catalyst [95]. In a typical reaction, thiophenol (**83**) in open-air vessel at 60 °C in EL gave excellent disulfide product (**84**) (Figure 4.37). Authors also examined that the reaction in the presence of oxygen atmosphere and noticed the same reaction in 2 h gave excellent (95%) yield. Further, authors extended this protocol to various aliphatic and aromatic thiol derivatives which gave good to excellent product isolation (57–97%). However, *ortho*-substituents of thiols showed high steric hindrance and isolated reduced final product isolation (57–67%).

Figure 4.37: Oxidative homocoupling of thiophenols in EL.

Researchers described that the oxidative coupling of β-enaminones (**85**) and thiophenols (**86**) in the presence of potassium iodate-mediated EL gave very good product **87** isolation [96]. Authors examined superiority of this solvent in model reaction that afforded product **87** in high yield than the reaction performed in hazardous solvents such as DMF, DMSO or any other solvents which were reported to give low to good yields (18–70%) (Figure 4.38). The authors also tested that, various substituted β-enaminones (electron-deficient) coupling to thiophenol was observed tolerable to this protocol.

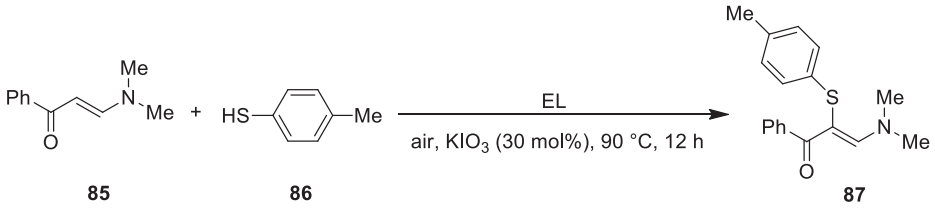


Figure 4.38: Oxidative reaction of *N*,*N*-dimethylaminoacrylophenone and *p*-thiocresol.

4.3.1 Transamination

Authors described that the transamination reaction of *N*,*N*-dimethylenaminones achieved through refluxing 12 h of *N*,*N*-dimethylaminoacrylophenone (**85**) in morpholine (**88**, 4 molar equiv.) gave product **89** in good yield (Figure 4.39). The reaction was reversible, and the authors prepared various secondary amine derivatives to give transamination product in this protocol [97].

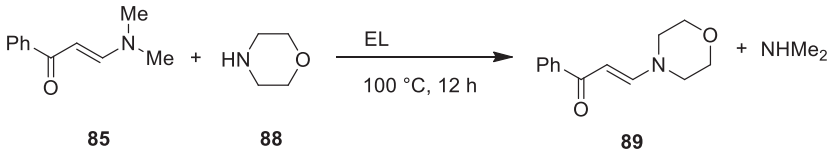


Figure 4.39: Transamination reaction.

4.3.2 Olefin metathesis

In olefin metathesis, the reactant (**90**) and 1,4-dimethyl-2-(prop-1-en-1-yl)benzene (**91**) reacted using catalyst ruthenium complex (**92**) in EL medium (Figure 4.40). This catalyst showed an efficient ring-closing metathesis reaction in EL [98]. Authors conducted the reaction of diethyl 2,2-diallylmalonate (**93**) to give product **94** under argon atmosphere in EL-mediated isolation in excellent yields (95–97%) (Figure 4.41). Further, authors tested a wide range of diene analogues and isolated excellent yields in this method.

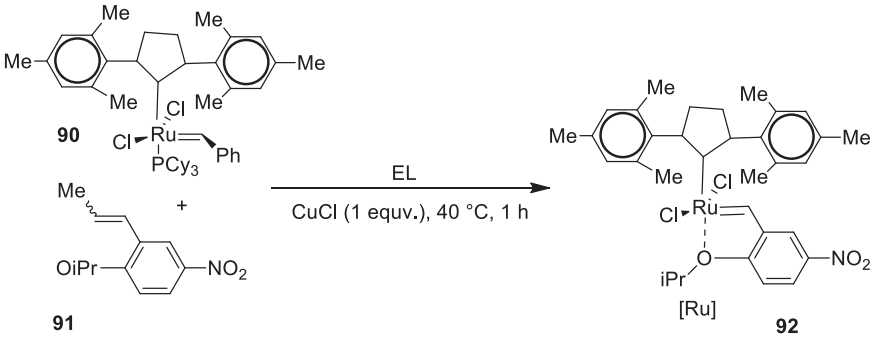


Figure 4.40: Preparation of [Ru] complex catalysts in EL.

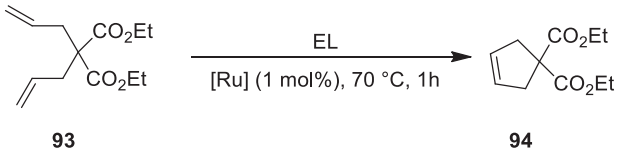


Figure 4.41: Olefin metathesis ring closing in EL.

Authors demonstrated that the combined synergic effect of [Ru] complex catalysts and EL medium in the synthesis of 2,2-diphenyl-4-vinyl-2,5-dihydrofuran (**96**) via 1-(allyloxy)prop-2-yne-1,1-diyl)dibenzene (**95**) enyne cycloisomerization gave excellent product isolation (Figure 4.42) [98].

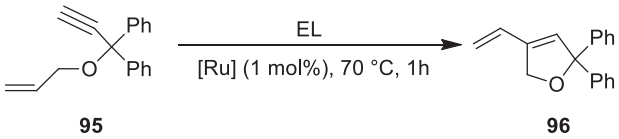


Figure 4.42: Enyne cycloisomerization in ethyl lactate.

Authors extended the synthesis method to various metathesis products like alkene (*E*)-4-phenylbut-2-en-1-yl acetate (**99**) by the reaction of allylbenzene (**97**) and (*Z*)-but-2-ene-1,4-diyl diacetate (**98**) (Figure 4.43) to give a mixture of Z- and *E*-isomers (8:1), and similar product isolation was noticed in open-air or argon atmosphere [98].

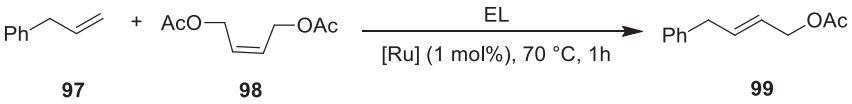


Figure 4.43: Cross-metathesis of olefin-mediated EL.

4.3.3 Carbonyl group transformations

Huttenhain [99] reported the EL-mediated reaction of carbonyl of aldehyde and ketone with a wide range of nucleophiles. Authors employed chiral L-(–)-ethyl lactate for asymmetric reduction of acetophenone (**100**) with $NaBH_4$ gave L-phenylethanol (**101**) without using any other additives, but the method gave low *ee* (15%) for *R*-(+)-isomer. The added Lewis acid played a crucial role in improvement of enantioselectivity to 36% *ee*, but noticed 70% conversion (Figure 4.44). Authors also employed the alternative reducing agent borane to this condition to give high enantioselectivity product isolation (46% *ee*).

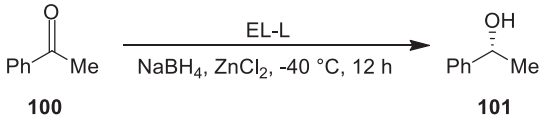


Figure 4.44: Acetophenone reduction.

Researchers described a simple method for the preparation of Schiff's base aldimine (**104**) with cinnamaldehyde (**102**) and aniline (**103**) in aqueous EL [100]. Authors tune the medium by EL alone and in the presence of aqueous EL medium, the reaction gave high yields of the product observed (Figure 4.45). Authors also studied the effect of substituents on the substrates and the reaction time required from a few seconds to hours, but isolated excellent yields (82–99%), except the reaction of 4-phenoxyaniline and 4-hydroxybenzaldehyde which gave lesser yields (54%).

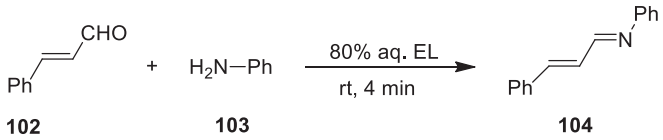


Figure 4.45: Schiff base of cinnamaldehyde in aqueous EL.

Moussallem et al. [102] prepared Schiff's base-derived 2-amino-6-methylbenzothiazole and 2-methoxy-1-naphthaldehyde in aqueous EL at ambient temperature [101]. Authors noticed the best reaction obtained in 4 mol% of ytterbium(III) triflate in EL medium reaction performed in 10 min and isolated excellent yields of the product (90%). This bio-based EL also used in conjugated Schiff base (**106**) synthesis by the reaction of 3,7-*bis*(perfluorophenyl)benzo[1,2-b:4,5-b′]difuran-2,6-diamine (**105**) with furfural gave semiconductor properties of the product (Figure 4.46) [102]. However, the poor reactivity of the amine was noticed, and the reaction took longer time in the presence of P_2O_5.

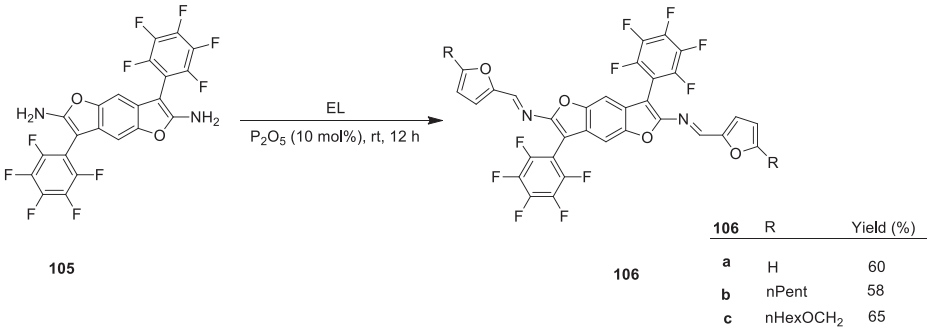


Figure 4.46: Schiff's base synthesis.

Liu and Wen [103] reported oxime synthesis by the reaction of $NH_2OH{\cdot}HCl$ and acetophenone in EL as a solvent for efficient synthesis without any additional catalyst required (Figure 4.47). Authors explained this reaction by taking acetophenone and benzaldehyde as a model reaction, and achieved an excellent product (77–91%). Further, authors employed EL as a medium for the transformation of oxime (**107**) into amide (**108**)-catalyzed ferric chloride and TCT (cyanuric chloride) via Beckmann rearrangement.

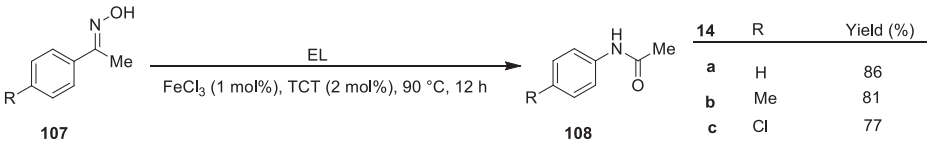


Figure 4.47: Synthesis of *N*-arylacetamides via Beckmann's rearrangement.

Wan et al. [104] reported the synthesis of dithioacetal (**111**) from 4-chlorobenzaldehyde (**109**) and ethanethiol (**110**) in EL to give excellent product isolation (Figure 4.48). Interestingly, authors noticed a trace amount of the product, when the reaction was carried out with *p*-xylene or acetonitrile, and in water, no reaction progress was reported. Authors evaluated substrate compatibility, which enables heteroaromatic, aromatic and aliphatic aldehydes with cyclic, alkyl and thiophenols to give excellent yield (59–84%). Authors observed faster reactivity of S- and N-nucleophiles attached to the carbonyl group in EL medium without any additional catalysts to give activation by H-bonding and keep substrate closer for effective attack.

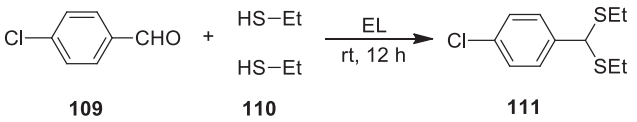


Figure 4.48: Synthesis of dithiolation.

Gao et al. [105] reported 3,3′-(phenylmethylene)*bis*(1H-indole) (**114**) synthesis by the reaction of 2 mol of indole (**112**) and benzaldehyde (**113**) in 60% EL in water under ultrasound irradiation (Figure 4.49). Authors claimed that the protocol developed was efficient than the previously employed solvents (organic). Authors also examined that the reaction in pure EL gave very low product isolation (36%) and in aqueous EL gave excellent product isolation (95%). Further, authors scale up the reaction in aqueous EL medium from 1 to 100 mmol scale and observed nearly the same product yield isolation (93%). The reaction tolerability on indole ring substituents examined and prepared a wide range of representative libraries of derivatives (80–95%). The reaction-compatible wide range of aromatic, aliphatic and heterocyclic aldehydes was reported.

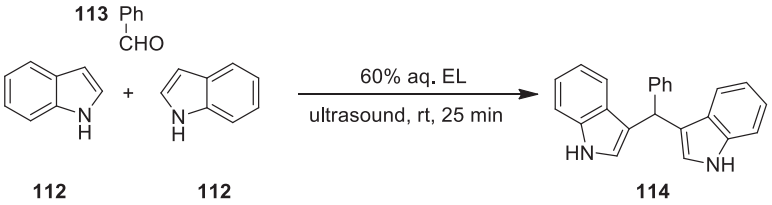


Figure 4.49: Reaction of benzaldehyde with indole.

Further, authors extended that the reaction condition for 1″-[3,3′:3′,3″-terindolin]-2′-one (**116**) synthesis from the reaction of two indoles (**112**) with isatin (**115**) gave excellent yield of the product (95%) (Figure 4.50) [105]. Authors also examined the effect of substituents on heterocyclic benzene ring, and did not affect the substituents on the rate of the reaction in 89–95% yields.

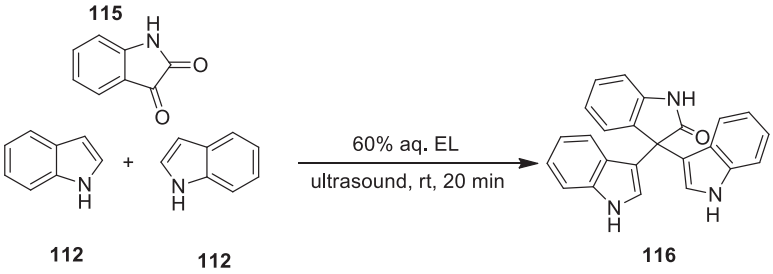


Figure 4.50: MCRs of isatin with indole.

Minkovska et al. [106] described EL-mediated squaraine dye (**119**) synthesis by the reaction of 3,4-dihydroxycyclobut-3-ene-1,2-dione (**118**) and 1,3,3-trimethyl-2-methyleneindoline (**117**) (Figure 4.51). The reaction performed efficiently under microwave irradiation to give the desired product in excellent yield.

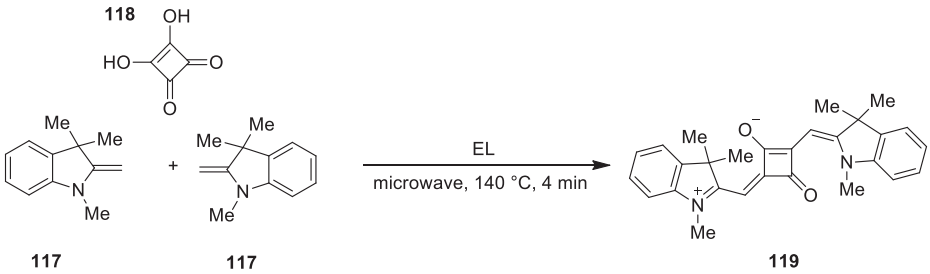


Figure 4.51: Squaraine dye synthesis.

4.3.4 Dehydration of sugars

Selective carbohydrate dehydration (**120**) is performed to obtain 5-hydroxymethylfurfural (**121**) in EL-mediated graphene oxide reaction accelerated by microwave irradiation, and choline chloride as an additive, and this was found to improve the reaction [107]. Authors tested that the D-fructose substrate was found to be most effective and gave 76% yield (Figure 4.52), and other saccharides like D-galactose, D-glucose, D-sucrose and D-mannose were also reported in this method, with lower than 60% product isolation.

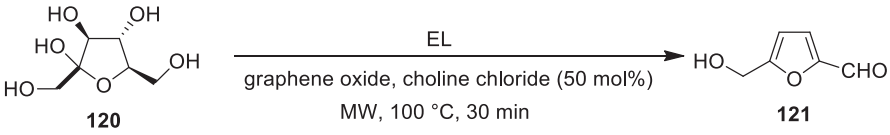


Figure 4.52: Dehydration of D-fructose.

4.3.5 Heterocyclizations

Various fused six- and five-membered heterocyclic compounds via MCRs were prepared in EL medium or in its aqueous solution mixture. Authors demonstrated that aqueous EL-mediated reaction was found to be suitable for the ring closure of pyrazoline in substituted chalcone (**122**) reaction with phenyl hydrazine (**123**) under cerium (III) chloride, and after simple filtration gave pyrazoline (**124**) product in excellent yields, 87% (Figure 4.53). The authors also recycled the catalysts and solvent medium, which produced in each cycle isolation of 86%, 83%, and 78%, respectively, product, revealing that it could be recycled up to three times without any noticeable loss of activity. Authors also studied the role of EL in activation of phenyl hydrazine derivatives with increasing nucleophilicity via H-bonding (Figure 4.53) [108].

Choudhary and Peddinti. [109] reported that thiazolidinone (**127**) derivative synthesis via ring-closure reaction of *N*,*N*′-diphenylthiourea (**125**) and dimethyl

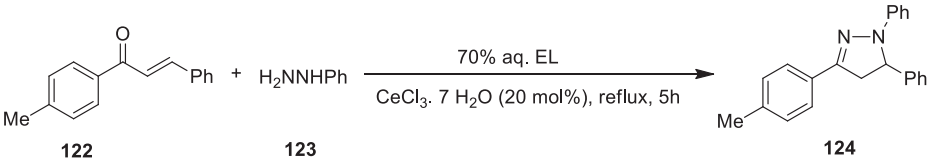


Figure 4.53: Pyrazoline derivative synthesis in aqueous EL.

acetylenedicarboxylate (**126**) gave product in excellent (95%) yield (Figure 4.54). Authors revealed that the reaction proceeds without the need of the catalyst and the reaction was completed in 6 min. Authors revealed that 18 thiazolidinone derivatives synthesized under this protocol isolated excellent yields (91–98%).

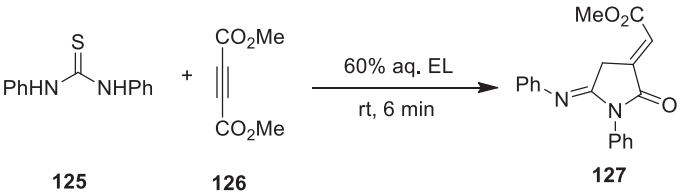


Figure 4.54: Synthesis of thiazolidinone derivatives.

Yu et al. [110] described that the reaction of *o*-aminothiophenol (**128**) with aromatic aldehyde (**129**)-mediated EL gave the product benzothiazoles (**130**) in the presence of ionic liquid-based proline catalyst (Figure 4.55). Authors examined other typical organic solvents for the reaction, but observed to be less effective under this catalyst condition. Expanding the wide range compatibility of present protocol, various substituted aldehydes reacted, and it was noticed that thiophen-2-carboxaldehyde and benzaldehyde gave excellent product isolation (82–92%), but the reaction of valeraldehyde with *o*-aminothiophenol reported dropping of isolated yield (55%).

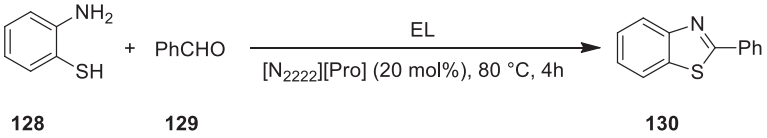


Figure 4.55: Synthesis of benzothiazoles.

Researchers reported that the domino reaction of thiol derivatives (**132**) and enaminone (**131**) in the presence of potassium iodate and EL medium gave chromone ring-closure product (**133**) [96] (Figure 4.56). The reaction produced chromone derivatives (**133**) in EL medium which observed high yield product isolation compared to those obtained in the other organic solvent medium studied. Authors also studied the absence of thiol moiety

and no chromone ring closure was noticed; further, the reaction of thiol and chromone was also unsuccessful. Further authors explained the mode of mechanism of the reaction by radical scavenger TEMPO to model reaction, and not observed any product isolation revealed reaction not involved radical mechanism. Furthermore, authors also extend the reaction condition to various substituents present on aryl ring of enaminone (**131**) and aryl selenol (**134**) which gave 3-phenylselenylated chromone (**135**) in excellent yields (76–88%) [96] (Figure 4.57).

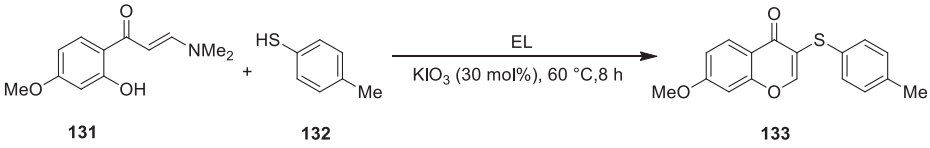


Figure 4.56: Synthesis of chromone.

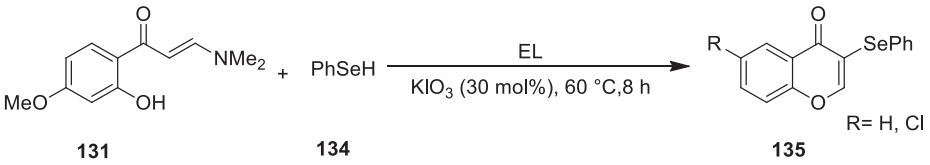


Figure 4.57: Synthesis of 3-phenylselenylated chromones.

Researchers reported similar product synthesis of 3-bromo- and 3-iodo-substituted chromone in EL for in situ oxidation and ring closure of halide derivatives with hypervalent iodine(III) [111]. In a model reaction, oxidation of phenyliododiacetate gave 3-iodochromone isolation in 78% yield (Figure 4.58). The authors also reported that the reaction pathways involved in radical mechanism by TEMPO or butylated hydroxytoluene radical scavengers, but this model reaction does not inhibit the product formation but indicated the reaction not involved in radical mechanism for the transformations. Further, authors tested the formation of 3-iodochromone (**137**) by the reaction of KI (**136**) and phenyliododiacetate (**131**) in molecular iodine isolated good yield. Authors examined that the iodination reaction took place before chromone ring formation, since they reported that the iodination reaction was performed on chromone and not on isolated

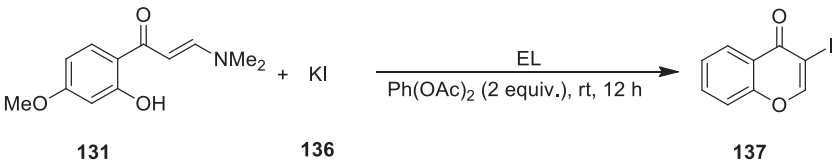


Figure 4.58: 3-Iodochromone synthesis.

product (**137**). Furthermore, authors revealed that 3-halochromone derivatives can be catalyzed equally by either KI or KBr, and wide range of substituents.

In another work, researchers reported the synthesis of quinazolone derivatives (**140**) that mediated effectively in 10% aqueous EL by the reaction of anthranilamide (**138**) and 1,3-diketone (**139**) in the presence of camphor sulfonic acid [112]. They examined anthranilamide and acetylacetone as a model reaction: ketone C–C bond cleavage followed by quinazolone ring formation gave excellent product isolation (Figure 4.59). Authors also examined the tolerance of this method to various substituted anthranilamides (**138**) with 1,3-diketones (**139**), and reported 16 libraries of quinazolone derivatives in good to excellent yields of product isolation (58–98%).

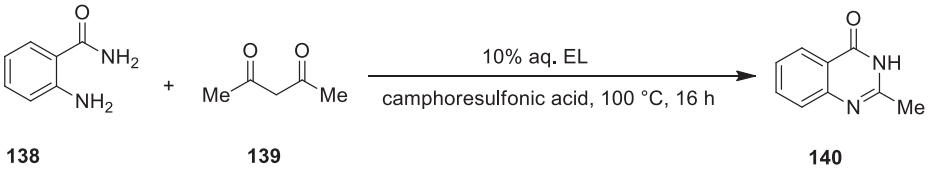


Figure 4.59: Quinazolone derivative synthesis in aqueous EL.

Authors further extended the protocol to cyclic cyclohexane-1,3-dione (**141**) with anthranilamide (**138**) to give quinazolones (**142**) (Figure 4.60) [112]. The protocol is expanded successfully to 10 more substituted derivative synthesis to give 55–98% yields of product isolation. Authors studied the substituted anthranilamides and cyclohexane-1,3-diones having methyl substituents one or more in ring system tolerance and gave product isolation in excellent yield.

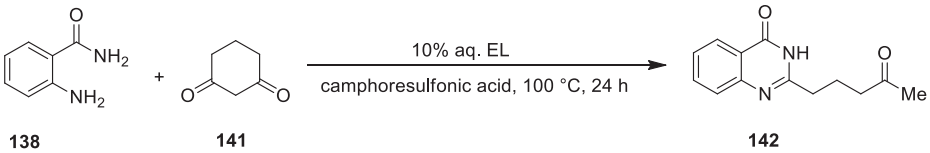


Figure 4.60: Reaction of cyclohexane-1,3-dione and anthranilamide.

Cao et al. [113] described the synthesis of 2,3-diarylquinoxalines (**146**) by *N*,*N*-dimethyl-substituted 1,2-diarylenaminone (**143**) one-pot two-step reaction under photocatalytic condition in EL. They established the optimized reaction condition for the formation of benzyl product (**144**) in EL and isolated high yield compared to that of common organic solvents (Figure 4.61). The subsequent benzyl (**144**) with *o*-phenylenediamine (**145**) in similar condition gave 2,3-diphenylquinoxaline (**146**) derivatives (Figure 4.62). Authors claimed that eighteen 2,3-diarylquinoxalines having aromatic ring substituents were prepared, and the isolated yield was 47–90% [113].

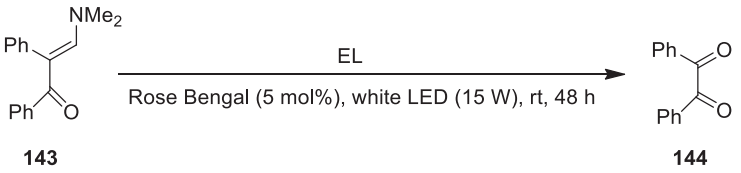


Figure 4.61: Photocatalytic synthesis of benzyl.

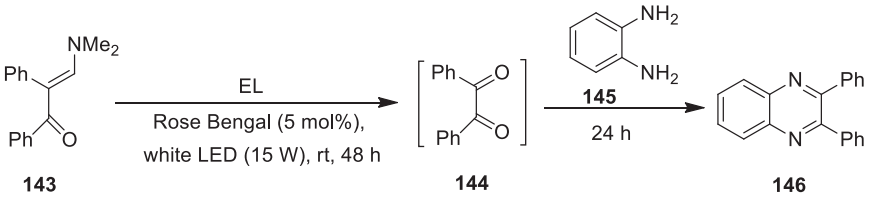


Figure 4.62: Synthesis of 2,3-diphenylquinoxaline.

Wan et al. [114] reported that the EL-mediated synthesis of 2-aryl-1,4-benzothiazines (**148**) by *o*-aminothiophenol (**128**) and *N*,*N*-dimethylaminoacrylophenone (**147**) gave 82% yield (Figure 4.63) in the presence of catalytic amount of iodine. Under the same reaction condition, they examined that various substituents present on aromatic ring isolated 62–92% product yield, except *o*-hydroxyl group positioned on enaminone which gave low yield product.

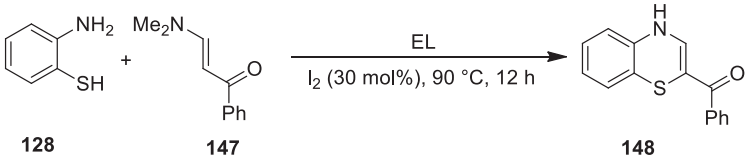


Figure 4.63: Synthesis of 2-aryl-1,4-benzothiazines.

4.3.6 Multicomponent reactions

EL and its aqueous medium emerged as an effective solvent system for various MCR types described. One such reaction catalyzed erbium(III) chloride for furfural (**149**) with morpholine (**88**) to give *trans*-4,5-dimorpholinocyclopent-2-enone (**150**) quantitative product (Figure 4.64) [115]. Authors prepared eight analogues of product **150** and isolated excellent yield by employing the same method using furfural and secondary aromatic and aliphatic amines. Surprisingly, authors noticed the low yield of product isolation, when diisobutylamine bulky group was present. Further, authors showed that the reaction of primary amine is less favorable, and in the reaction of benzylamine

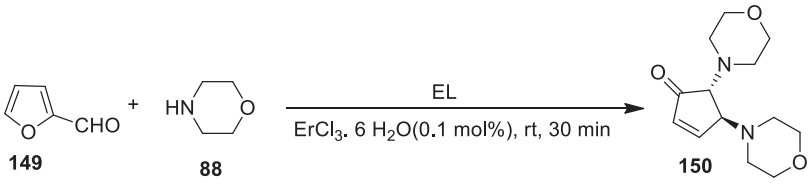


Figure 4.64: Reaction between furfural and morpholine.

with furfural, the formation of only the Schiff base was observed. But authors reported that the reaction of aniline and furfural took twice long reaction time to give *trans*-4,5-bis(phenylamino)cyclopent-2-enone in less yield and purity (25%).

Researchers noticed that EL plays an important role in α-aminophosphonate (**152**) synthesis via three-component aniline (**103**), benzaldehyde (**129**) and triethyl phosphate (**151**) reaction accelerated by ultrasound[116]. The authors adapt the reaction conditions to further improve product yield isolation by adding water to EL and finding a water optimal concentration in EL of 60%, which allowed segregation of the product 32–95% yield (Figure 4.65). Further, authors studied the reaction scope on substituted aniline and various aldehydes, and the best product isolation achieved in benzaldehyde or furfural reactions (89–95%). However, authors reported a decreased yield (79%) for cyclohexane carboxaldehyde reaction.

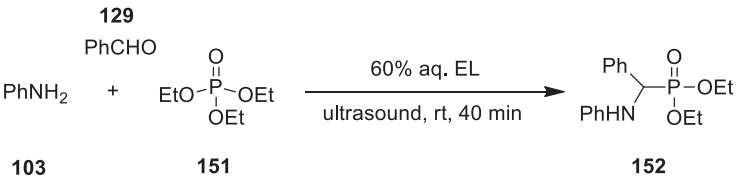


Figure 4.65: Ultrasound-promoted α-aminophosphonate synthesis.

Researchers described MCRs of benzaldehyde (**129**), phthalhydrazide (**153**) and dimedone (**154**) for the synthesis of fused phthalazines (**155**) in EL-accelerated reaction in microwave (CEM) [117]. Authors revealed that *p*-sulfonic acid calix[4]arene (PSAC[4]A) proceeds faster with high yield of product isolation in the reaction (Figure 4.66). Further, authors also examined the scope of this method for various aryl aldehydes, particularly electron-withdrawing groups on benzene ring afforded high yield products (94%), but aliphatic aldehydes gave low yield (30–35%), and 11% product isolated for formaldehyde was reported. Furthermore, authors tested some of these derivatives for antiproliferative activity against cancer cells.

Vaidya et al. [118] described that aqueous EL-mediated MCRs of aryl aldehydes (**156**), ethyl acetoacetate (**157**) and $NH_2OH{\cdot}HCl$ in the presence of cerium(III) chloride afforded isoxazolone derivatives (**158**) (Figure 4.67). Authors studied the tolerance of

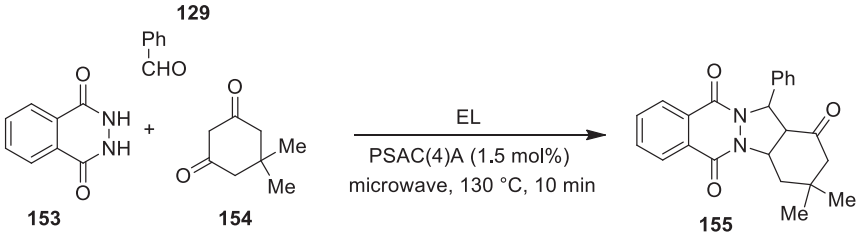


Figure 4.66: Microwave-assisted synthesis of fused phthalazines.

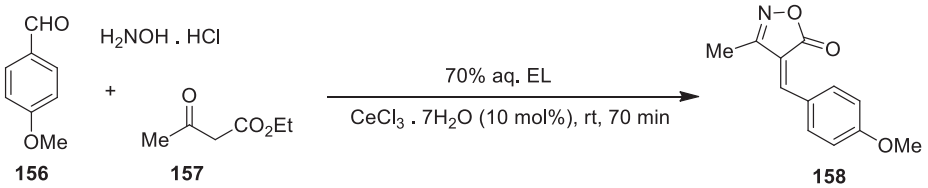


Figure 4.67: Three-component synthesis of isoxazolone derivatives.

various aromatic substituted aldehydes for the reaction, and resulted in a series of isoxazolone derivative isolation in excellent yields (44–85%).

Ghosh et al. [119] demonstrated that EL-mediated reaction under visible light (150 W) conditions emerged as a better choice of the solvent than common solvents employed in Hantzsch 1,4-dihydropyridines (**161**) (Figure 4.68). In a typical reaction, ethyl acetoacetate (**159**), *p*-nitrobenzaldehyde (**160**) and ammonium formate in EL isolated 75% product yield.

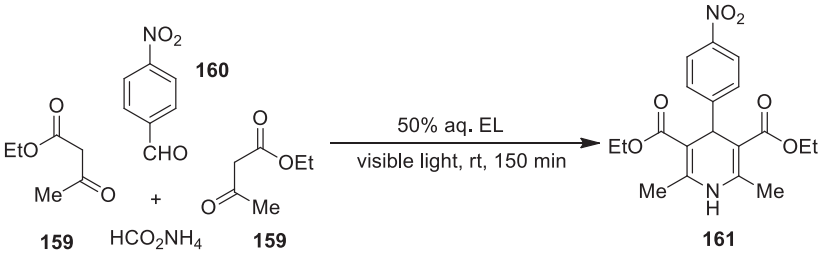
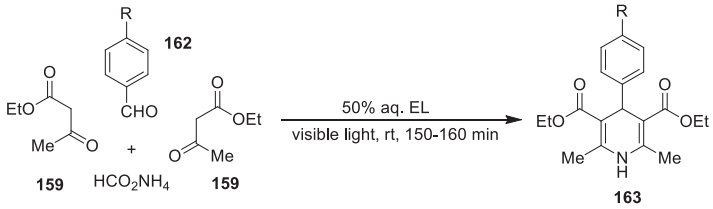


Figure 4.68: Light-induced Hantzsch 1,4-dihydropyridine synthesis.

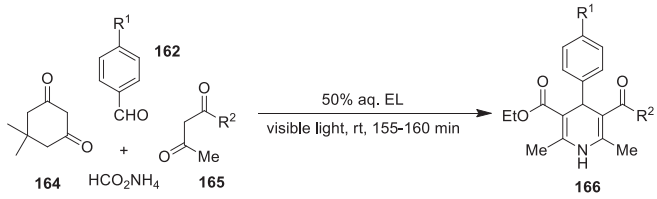
Authors optimized EL in different aqueous percentage, and identified 50% aqueous EL as a best suitable optimal medium for the reaction to give 35–92% product isolation. Authors studied variants of aldehyde structure (aromatic, aliphatic and heterocyclic) (**162**) and ethyl acetoacetate (**159**) allowed 20 symmetrical 1,4-dihydropyridines (**163**) library of derivative synthesis in excellent yields (80–92%). Also, authors prepared unsymmetrical 1,4-dihydropyridines (**163**) by the reaction of acetylacetone and ethyl

acetoacetate (Figure 4.69) [119]. Further, authors also extended this light-induced reaction to the synthesis of tetrahydroquinolones (**166**) via MCRs of aryl aldehyde (**162**), dimedone (**164**), ethyl acetoacetate (**165**) or acetylacetone, and ammonium formate in aqueous EL with excellent product isolation (Figure 4.70) [119].



163	R	Yield (%)
a	F	77
b	MeO	74
c	NO_2	81

Figure 4.69: Light-induced unsymmetrical 1,4-dihydropyridine synthesis.



166	R^1	R^2	Yield (%)
a	MeO	Me	80
b	MeO	EtO	88
c	NO_2	Me	83
d	NO_2	EtO	91

Figure 4.70: Light-induced synthesis of tetrahydroquinolones.

Yang and Wan [120] described the dual role of EL as a building block and medium for the three-component ethyl-2-arylquinoline-4-carboxylate (**169**) synthesis. A model reaction of *p*-toluidine (**167**), ethyl-2-hydroxypropanoate (**168**) and benzaldehyde (**129**) in EL with the catalyst ferric chloride was identified as a suitable system to give the target product in excellent yield (Figure 4.71). Authors also examined the scope of the reaction for various substrates and prepared 23 derivatives in 53–79% product yields of benzaldehyde and aniline derivative combination. The reaction mechanism explained by the author suggested the conversion of EL to ethyl pyruvate reactive species in the reaction course which play an important role.

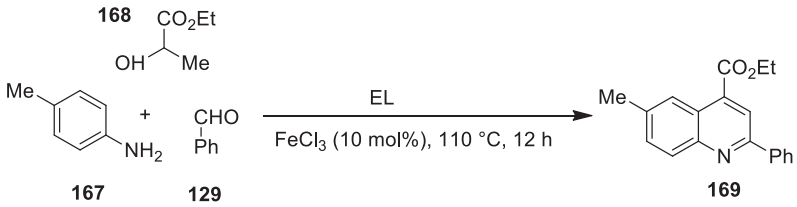


Figure 4.71: Synthesis of ethyl-2-arylquinoline-4-carboxylate.

Chen et al. [121] described the three-component reactions of isatin (**115**), malononitrile (**170**) and ethyl acetoacetate derivatives (**171** and **172**) in photocatalysis, and the presence of EL condition showed to be efficient than in conventional organic solvent employed. Authors also optimized EL water percentage, and 60% EL system emerged as better efficient medium for spiro-fused indoleethyl-2′-amino-3′-cyano-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (**174**) and 2-acetyl-5-amino-3-methyl-2′-oxospiro[cyclohexane-1,3′-indoline]-2,5-diene-6-carbonitrile (**175**) synthesis (Figure 4.72). Further, authors observed slightly high yield under green versus white light, which scale-up reaction up to 10 mmol, and no change in the isolation of the product was reported.

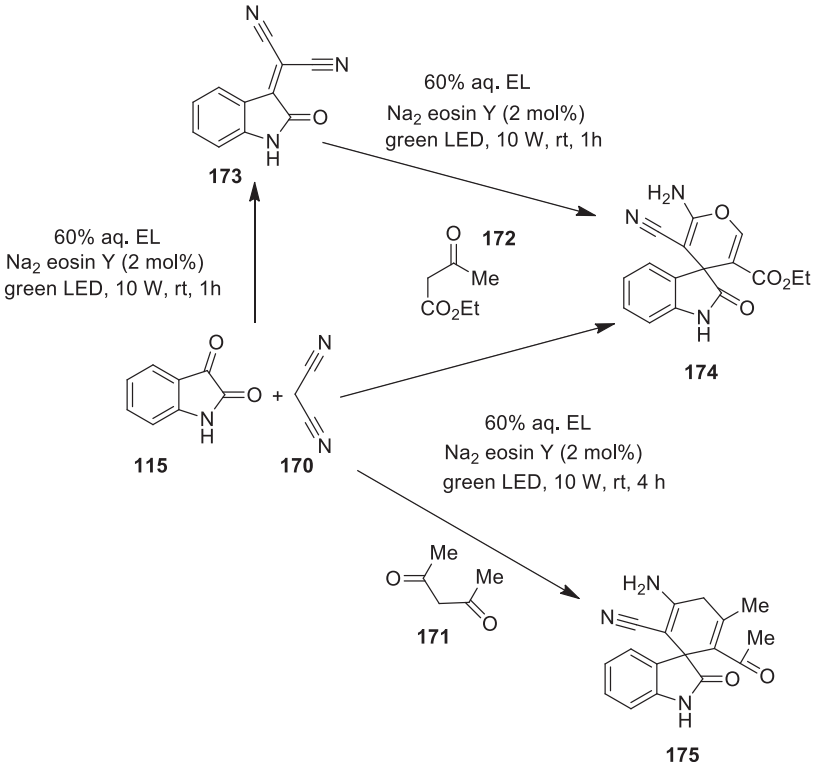


Figure 4.72: Photocatalytic three-component synthesis of spiro-fused indole.

Zhang et al. [122] reported a two-step process for fused spiroindole synthesis in the identical reaction condition reported earlier. The Knoevenagel condensation of malononitrile and isatin, followed by spirocyclization with ethyl acetoacetate gave the product. Authors revealed the reaction mechanism via radical initiated by light, since the reaction was not progressed in dark, and also inhibited the reaction in the presence of TEMPO affording excellent product yield (85–94%). β-Keto esters replaced with acetylacetone gave similar spiro-fused indole. Authors demonstrated the scope

of this reaction using substituted isatins to give product in 85–93% yields. Authors also tested the reaction of 4-hydroxycoumarin (**177**) or 2-hydroxy-1,4-naphthoquinone (**178**) in place of dimedone (**176**) under similar reaction conditions with isolated spiro-fused isatins (**180**) and (**181**) in high yield (95%). Further, authors explained that the reaction scope extension to isatin substituted (**115**) and malononitrile (**170**) for the analogues of spiro-fused isatins (**179**), (**180**) and (**181**) gave libraries of product in three types of derivatives with excellent product isolation (82–96%) (Figure 4.73). The application of the protocol developed was extended to scale up the synthesis of product **181** from 1 to 10 mmol (96% yields) of successfully isolated products. Authors also screened other solvent systems for the reaction (including pure EL) in an identical condition which observed significantly low yield isolation of the product.

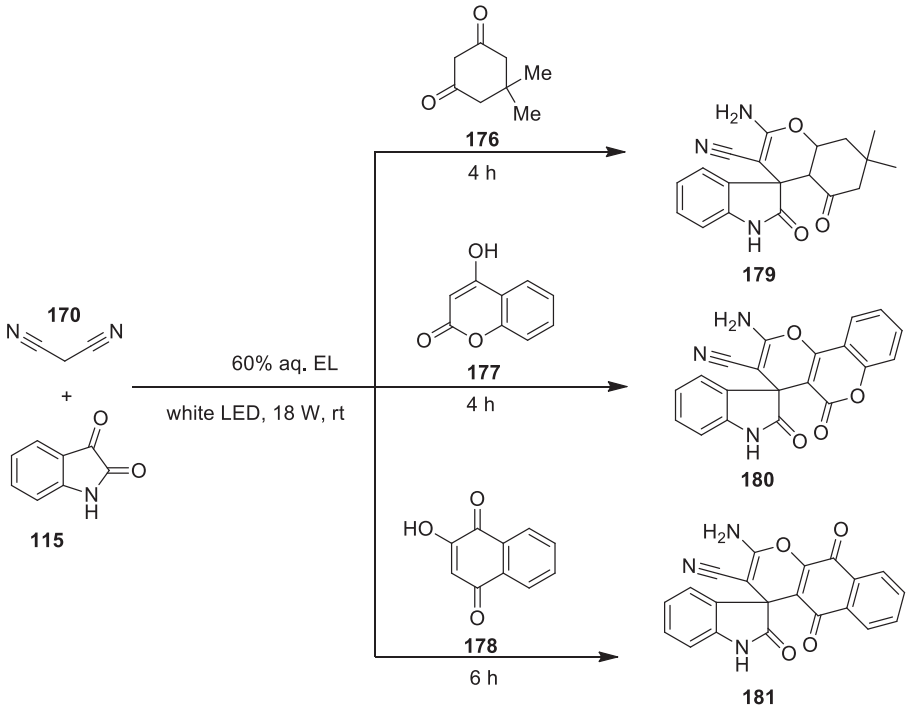


Figure 4.73: Photochemical synthesis of spiro-fused isatins.

Paul and Das [123] reported EL as a preferred choice of the solvent for 3-CRs of 4-aminocoumarin (**182**), aryl aldehyde (**129**) and dimedone (**176**), or 1,3-indandione (**183**) catalyzed lactic acid at heating condition gave product **185** in 87% yield (Figure 4.74). Authors determined the structure of the product **186** by crystallography, and the same product isolated stepwise Knoevenagel condensation, followed by intermediate reaction of 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione (**184**) and 4-aminocoumarin (**182**).

The 3-CRs of 4-aminocoumarin (**182**), benzaldehyde (**129**) and 1,3-indandione (**183**) gave product **187** in good yield. The reaction scope of 3-CRs extended to various aryl aldehydes was prepared by seven derivatives (**186**) in high yield (78–91%), and another seven derivatives of product **187** were isolated in good yield (73–85%). The catalyst loading was found to be high, but authors isolated the solvent–catalyst system and recycled four times for the reaction without any loss in its activity.

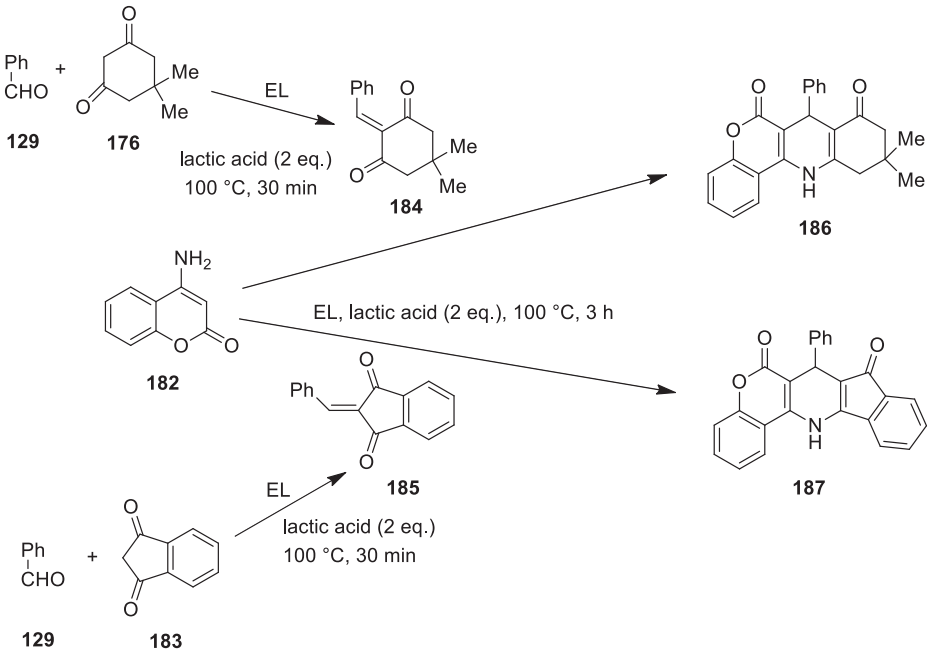


Figure 4.74: Three-component reaction of 4-aminocoumarin and benzaldehyde with dimedone or 1,3-indandione.

The light-induced MCRs of indole (**112**), malononitrile (**170**) and aryl aldehyde (**188**) in aqueous EL gave 2,4-diamino-5-(1H-indol-3-yl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile (**190**) isolation in 92% yield (Figure 4.75) [124]. Authors also examined that the same reaction in blue or white light isolated the low yield product (**190**) (90%), and under UV light, they further noticed the lower yield product (**186**) and a trace amount of product was noticed even after prolonged stirring of reaction mixture at dark. Authors examined the reaction of pseudo 4-CRs via 2-amino-4-(1H-indol-3-yl)chromane-3-carbonitrile (**189**) intermediate which involved the radical mechanism. The synthetic application developed MCRs efficiently scale-up 48 derivatives synthesised 1 mmol-10 mmol scale reported (93%), reaction scope enlarged, and twenty additional salicylaldehyde and/or indole analogues reported (70–93% yields).

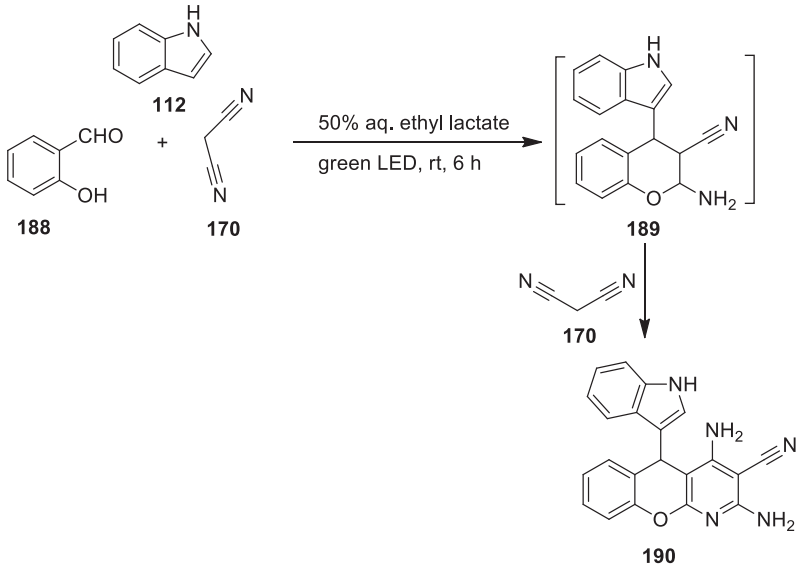


Figure 4.75: Photochemical multicomponent synthesis of chromene derivatives.

Zhang et al. [124] extended the absence of indole MCRs of 2-hydroxy-4-methoxybenzaldehyde (**191**) with malononitrile (**170**) formation of pyridine and chromene rings, and finally gave 2-(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile (**193**), when 3 equivalents of reactant **170** was used (Figure 4.76). However, authors demonstrated the chromene intermediate (**192**) isolated in 95% yield.

In another piece of work, authors described EL-mediated decarboxylative condensation of isatin (**115**), naphthoquinone (**194**), and proline (**195**) gave indole-5-carboxamide (**196**) excellent yield isolation. Dandia et al. [125] described that EL played a crucial role for the efficient reaction compared to routine solvents used . Further, they performed the reaction under mild condition, without using any catalyst, and indole-5-carboxamide (**196**) product was isolated in 82% yield. Then they examined EL with water, and showed that the optimal 80% water in EL gave very good product isolation (**196**, 93%) (Figure 4.77), and also authors assigned the structure of the product **196** by X-ray crystallography.

Xu et al. [126] demonstrated that trimethylsilyl chloride combined with ELmixture emerged as a better medium for Biginelli product isolation. A typical MCR of benzaldehyde (**129**), ethyl acetoacetate (**159**) and thiourea (**197**) gave pyrimidine-2-thione (**198**) in good yield (75%, Figure 4.78). Further, authors extended this reaction condition successfully to various substituted benzaldehyde, and *N*-methylthiourea was used in place of thiourea, but their attempt to use urea as a reactant in the reaction failed.

However, Dias et al. [127] described EL-mediated Biginelli reaction of urea. They demonstrated that the reaction does not require any catalysts and performed the reaction in two steps by heating ethyl acetoacetate (**159**) and urea (**197**) in EL medium to

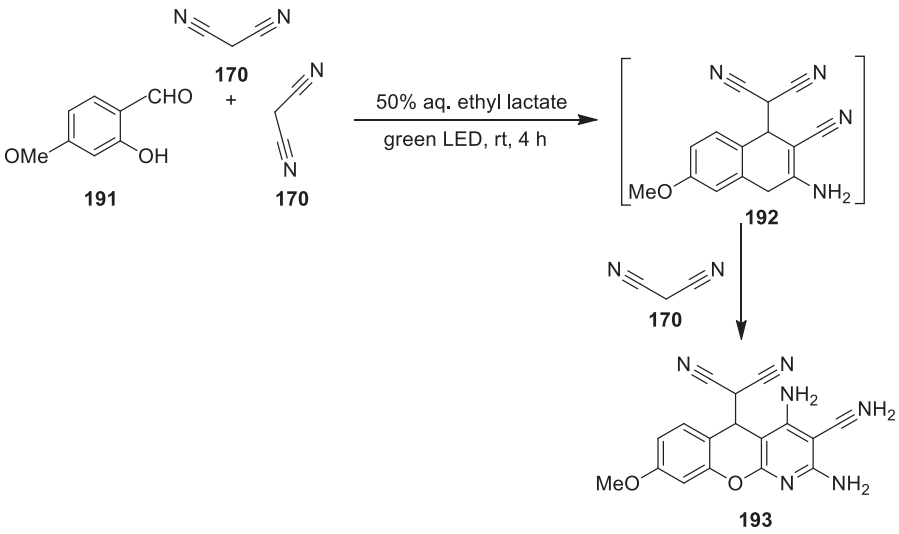


Figure 4.76: Light-induced multicomponent reaction between 2-hydroxy-4-methoxybenzaldehyde and multiple equivalents of malononitrile.

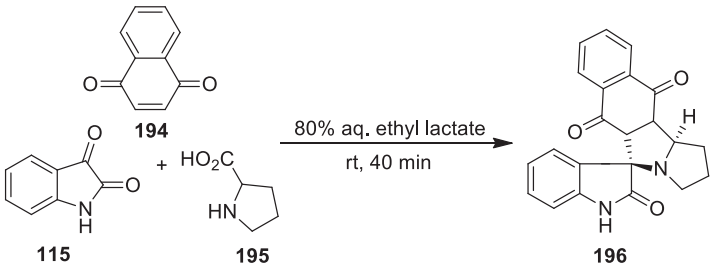


Figure 4.77: Decarboxylative condensation of proline, naphthoquinone and isatin.

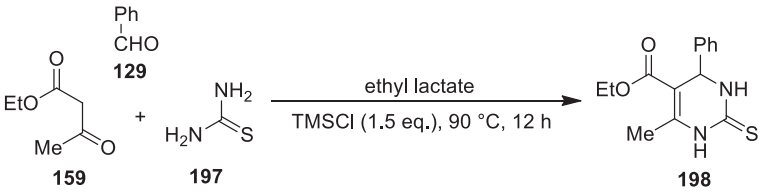


Figure 4.78: Biginelli reaction.

give the intermediate ethyl (*E*)-3-thioureidobut-2-enoate (**199**), and then the reaction with (–)-(1*R*)-myrtenal (**200**) afforded dimethyl-bicyclo-pyrimidine-carboxylate (**201**) single stereoisomer, which is assigned using X-ray diffraction (Figure 4.79).

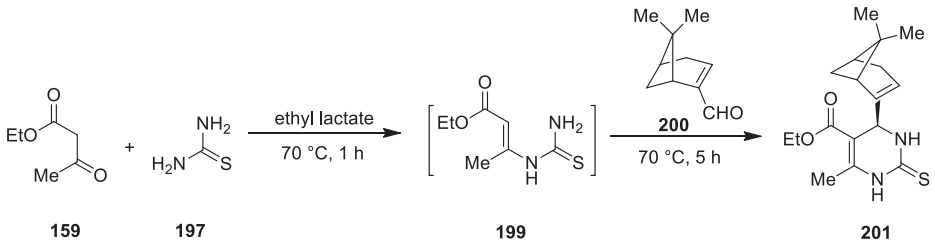


Figure 4.79: Stereospecific Biginelli reaction.

4.4 Conclusions

The sustainable development toward economic and social imperative makes the scientific community to develop an alternative reaction condition over pyrophoricity, volatility, toxicity, environmental toxicity and difficulty in solvent recovery. The solvents derived from bio-based have been recently emerging as next-generation solvents in design of eco-friendly organic synthesis. This chapter discussed the literature reported on Cyrene and EL solvents, which are successfully examined in organic, metal and biocatalysts. Recently, bio-based solvent is increasingly using both academic and industries as alternative solvents to conventional solvents. The environmental effect by the greener solvent is lower than the conventional organic solvents used because these are toxicless and biodegradable. The solvents, prepared in renewable sources, showed a significant role and are referred to as bio-based solvents, which come under green chemistry principles. In spite of high interest and demand, various bio-based solvents recently reported an alternative eco-friendly catalysis, synthesis, isolation and purification. Researchers exclusively focused on solvents such as EL and Cyrene which emerged as a better solvent medium. The molecules derived from animals, vegetables or minerals using physical and chemical processes are safe to the environment and humans.

Cyrene is a bio-based dipolar, is safe for end-of-life disposal and decomposes into CO_2 and H_2O. It is an aprotic alternative to common solvents, which are of environmental concern. Cyrene™ is a trademark representation commercially available in Merck, and an alternative for many solvents classified by REACH as substances of very high concern, such as NMP and DMF. Cyrene has a huge application in (i) dispersive ability for grapheme solutions, (ii) alternative to DMF in the synthesis of MOFs and (iii) organic synthesis: Cacchi-type annulation, synthesis of urea, HATU amide coupling replaced DMF in amide and dipeptide synthesis, SM reaction and Sonogashira reaction.

Another bio-based solvent (EL) also attracted the researcher's attention and is used in various organic transformations. The most advantageous one in using EL is its miscibility in water to open a new avenue for tuning solvent properties to the required

condition. Researchers demonstrated EL and its solutions that emerged as a choice of solvent for a wide range of chemical reactions (coupling, heterocycles and MCRs), in combination with nonconventional acceleration techniques such as ultrasound, microwave and visible irradiation. Further, researchers described significant applications in EL, and its solution (water, employed as a medium) showed safe and sustainable alternatives to the traditional solvent. Another more advantages revealed that due to its miscibility of EL in water allowed solvent properties can be adjusted to the required condition, make more convenient than pure solvent alone. Chemists discovered a synergic effect of nonconventional energy with EL or its solutions employed expedient acceleration of the reaction for diverse molecule synthesis. EL or its solution medium showed a significant progress in the reaction for coupling, heterocyclic and MCRs. The solvents Cyrene and EL are derived from bio-based ones which emerged as a superior choice of solvent medium. This is covered in the green chemistry concept for sustainable development and is used in various organic transformations from laboratory scale to industrial scale.

List of abbreviations

Cpme	Cyclopentyl methyl ether
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EL	Ethyl lactate
2-MeTHF	2-Methyltetrahydrofuran
PhCl	Chlorobenzene
n-BuLi	*n*-Butyllithium
$scCO_2$	Supercritical carbon dioxide
TMEDA	Tetramethylethylenediamine
Cyrene	Dihydrolevoglucosenone
NMP	*N*-Methyl-2-pyrrolidone
MOF	Metal–organic framework
S_NAr	Nucleophilic aromatic substitution
S_N2	Substitution nucleophilic bimolecular
THF	Tetrahydrofuran
LGO	Levoglucosenone
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
CALB	Calcium-dependent lipid binding
ROMP	Ring-opening metathesis polymerization
DCM	Dichloromethane (CH_2Cl_2)
DMAc	Dimethylacetamide
DABCO	1,4-Diazabicyclo[2.2.2]octane
TEDA	Triethylenediamine
NBP	Niobium phosphide
TEMPO	(Tetramethylpiperidin-1-yl)oxyl
TBME	*tert*-Butyl methyl ether

PF_6	Hexafluorophosphate
NMR	Nuclear magnetic resonance
NBS	*N*-Bromosuccinimide
MeOH	Methanol
OTBN	4-Methyl-2-biphenylcarbonitrile
BMIDA	*N*-Methyliminodiacetylboronate
BPin	Bis(pinacolato)diboron
N-HBO-MA	Norbornene-(*S*)-γ-hydroxymethyl-α,β-butenolidemethacrylate

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Chapter 5
Solid-phase platform: a nonconventional synthetic route for the current organic synthesis of diversified heterocyclic and carbocyclic framework

5.1 Introduction

Over the past decade, all researchers of synthetic chemistry are just passionate as their predecessors for making of valuable small organic molecules with advanced properties and enthralling chemical assemblies. In spite of their great success, there are some major issues concerning chemical synthesis with handling of waste materials and exploration for the eco-friendly reaction procedures. Therefore, implementation of cleaner production technique by eliminating serious pollution issues for the synthesis of bioactive molecules is very necessary [1–3]. From the past few decades, chemists are engaged to fulfill these necessities and develop various types of innovative arrays for the bioactive organic framework using eco-friendly conditions [4–8]. Nowadays, solid-phase synthesis (SPS) is one of them that receives great interest to prepare the heterocyclic and carbocyclic libraries of molecules with low molecular mass for drug discovery [9–14]. Small organic pharmacophores are very beneficial for the synthesis of rigid and highly functionalized molecular scaffolds with broad biological relevance in medicinal chemistry as well as in the pharmaceutical industry. In addition, recent reports display that most of the traditional solution-phase reactions have shifted effectively to the solid phase employing solid-supported reagents by the pharmaceutical companies [15, 16]. As a matter of fact, this strategy has delivered large numbers of heterocycles, carbocycles and linear oligomers, such as peptides and oligonucleotides in a short time frame.

SPS is a chemical process where the reactant molecules are chemically bounded to an insoluble support material and react with the reagents in the solution phase to yield the targeted product. At the onset of the evolution of SPS, the concept was first conceived by professor Robert Bruce Merrifield in the 1950s and 1960s in order to construct

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peptide chains on an insoluble polymer support [17]. In 1984, he received the Nobel Prize in Chemistry for his pioneering work. During the last four decades, tremendous interest has been shown in the medicinal field for the synthesis of polyfunctionalized molecules using SPS [18–20]. The advantages of SPS have promoted the development of new resins for scaling up linkers, synthesizers and procedures to monitor reactions. Clean technology with time-consuming step in SPS is one of the most important features for new drug discovery programs [21]. Thus, the most important aspect of this protocol is the use of eco-friendly and sustainable myriad of materials that can be easily recovered and recycled in the reaction medium with an increase in purity and yield of final products.

5.2 Solid-phase synthesis (SPS)

In the current organic chemistry, SPS is a technique in which reagents are either covalently or ionically bound to support materials in the solid state and progressed stepwise in a single reaction vessel applying selective protecting groups (Figure 5.1). Building blocks are used in this SPS technique which has two functional groups where one of them is generally protected by a protective group. Here, the bead of starting materials binds to the building block. Initially, this bead is stirring in the solution of the protected building block. After completion of the reaction of bead with a protected building block, the bead is removed from the solution phase by simple filtration and washing. Finally, the protecting group is separated and performed the abovementioned steps again. After completion of all steps, the desired compound is purified by chemical cleavage from the bead.

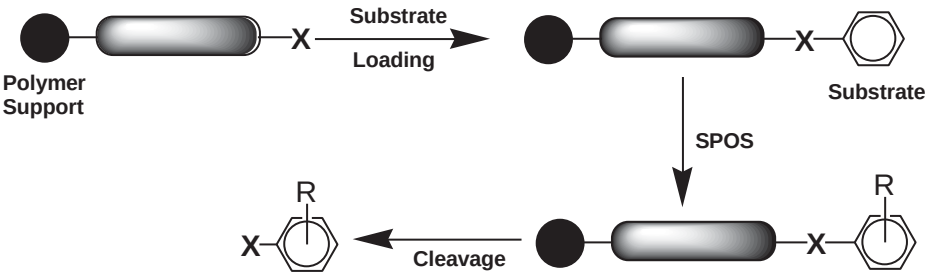


Figure 5.1: Schematic representation of a solid-phase organic synthesis (SPOS).

5.2.1 Advantages of SPS

Over the last decade, development of the SPS route has become a very striking tool in high-throughput synthetic organic chemistry and an integral part of the research methodology and drug discovery. Currently, the SPS of small organic molecules adapted

mostly from solution-phase reactions to solid-state reactions. Chemists paid attention to this methodology because of its several benefits upon the synthesis carried out in the solution phase as follows:

- The SPS often allows the use of excess reagents, and simultaneously solid-supported substrates are elaborated synthetically to force reactions to completion.
- Impurities, excess reagents and support materials can be easily removed from the desired compounds by simple filtration method and washing away of the unreacted reagents and by-products.
- In SPS, the substrate is bound to a chemically inert insoluble support material (resin or lantern) by a simple covalent bond.
- This bond remains stable during the whole synthetic process but at the end of the pathway permits the cleavage of the target product from the support material by hydrolysis or nucleophilic attack.
- The facilities in the purification process are another advantage of the SPS as it can allow the automation of the whole synthesis.
- Additionally, the SPS offered numerous possibilities of products employing excess of reagents to assure the completion of reactions and also by the pseudo-dilution effect.
- Using this mix and split technique, huge numbers of compounds can be created.
- Synthetically it is a very useful procedure for cross-linking or cyclization reactions.

Moreover, SPS can be used as an alternative synthetic route avoiding the use of noxious organic solvents and reduce multistep protocol with high-energy efficiency and atom economy that are common features of green chemistry. In addition, high efficiency with operational simplicity and selectivity of the active reagent sites are the most attractive features for solid-state methodology.

5.2.2 Limitations of SPS

Till date, copious nonconventional SPSs have been achieved successfully and are applied both in biological and environmental aspects for the development of diversified heterocyclic and carbocyclic compounds. Despite these advantages, solid-phase chemistry also suffers from significant limitations as follows:

- The presence of difficulties in adapting some conventional SPS to a solid-phase format.
- It can be tough to monitor the progress of solid-supported reactions in real time.
- Additional labor is also needed to develop a solid-phase route (to link the starting material with the solid support and cleave to the desired molecules from the solid support).

- Sometimes, the presence of a resin vestige along with final compound is observed due to the attachment of the molecule to the solid support.
- A potential scale limitation imposed by the loading level of the solid support.
- A wide range of commercially available support reagents, linkers and cleanup agents (scavengers) are introduced to the substrates to facilitate the reactions in solution.

The aim of this chapter is to discuss the basic concepts and to cover the practices over SPS of the current organic chemist. In this context, we illustrate the choice of support reagents, linkers and development of nonconventional synthetic routes using solid-phase platform for the formation of diversified heterocyclic and carbocyclic organic frameworks from the literature.

5.2.3 Definitions of some expressions associated with SPS

To discuss the application of this solid-phase organic synthesis, different types of phrases, terms and buzzwords have been included in the vocabulary. Hence, it is relevant to define the commonly used expressions during the presentation of this chapter, which will be very helpful or informative to the synthetic chemist.

- ***Supported reagents:*** The reactive substances that convert a substrate into a new chemical product associating with a support material are called supported reagents. After completion of the reaction, excess or spent reagents can be removed by simple filtration.
- ***Supported catalysts:*** The reactive substances that are allied with a support material and required in substoichiometric amounts to convert a substrate (or substrates) to a new chemical product (or products) are known as supported catalysts. At the end of the reaction, they could be removed by filtration and reused for the next cycle via simple washing.
- ***Supported scavengers:*** The reactive substances which are associated with a support material and selectively quench the by-products in the reaction medium or eliminate extra or unreacted starting materials from the desired molecule are called supported scavengers. Finally, they may be removed by using a simple filtration technique. In addition, they are also very familiar as “sequestering agents” or “quenching agents” and variants thereof.
- ***Catch and release:*** The technique that is used in a solution-phase reaction to selectively trap the desired product onto a functionalized support material is referred to as catch and release. The compound can be isolated from the solution-phase contaminants using filtration followed by the washing method, and the desired products may then be easily released from the support material. Alternatively, the method is also known as “capture and release.”

5.3 Solid-phase platform

5.3.1 Polymer-supported solid phase

The first polymeric-supported peptide synthesis based on 2% divinylbenzene (DVB) cross-linked polystyrene (PS) on solid phase was established by Merrifield. PS is a very important polymeric material for various organic transformations since it is readily available, inexpensive, mechanically robust, smoothly functionalizable and chemically inert [22–27]. In addition, cross-linking shows mechanical stability with improved diffusion and having swelling properties to the resin. Based upon these properties, a variety of cross-linking agents with various percentages have been introduced into the PS resins to give different solvation properties, for example, DVB, tetraethylene glycol diacrylate and ethylene glycol dimethylacrylate [28–30].

5.3.2 Clay and clay-supported reagents

In recent times, in various organic transformations, the use of clay minerals constitutes as heterogeneous media offering several opportunities rather than the currently used homogeneous system because of its effective solid surface. Through decades, easily available clay minerals show immense catalytic applications due to their high surface area, ion exchange and sorptive properties [31, 32]. The solid clay-supported catalyst has several advantages; for instance, it can be used as (i) a catalytically active agent (generally as solid acids); (ii) fillers to yield solid catalysts with exciting physical properties such as density, attrition resistance and specific heat capacity; and (iii) also a bifunctional or “inert” support material in academia, industry and organic and medicinal chemistry [33].

5.3.3 Silica gel as solid-state platform

In solid-state synthesis, silica gel is one of the most familiar solid-phase platforms to the synthetic chemist. It is nontoxic, nonflammable, nonreactive and very stable in nature and is a highly used material in chromatographic separation as a stationary phase [34]. Due to its high surface area (5–800 $m^2\ g^{-1}$) and porosity, it is widely used as a support catalyst in numerous chemical reactions and as an absorbent in case of dehydration of fluids and gases. The silica gel promoted operationally simple solid-phase methodology proceeds under mild reaction conditions to afford the desired compound with significant chemoselectivity, regioselectivity and stereoselectivity. In exploration of solid-surface-mediated reaction protocol, here we have illustrated few reactions on the potential surface of silica gel.

5.3.4 Alumina as solid-phase platform

Nowadays, one of the most superior desiccants is alumina which is remarkably used with a wide range of applications in industry such as filler, adsorbent and also solid-supported catalyst along with the reagent [35, 36]. It opens up a world of possibilities for technicians such as in pharmacy and in industry and can be used for biohazard, bioterrorism, research, toxic waste, environmental cleanup and gas and liquid dehydration applications [37, 38]. It is an effective adsorbent and is used in the reaction medium for the moisture-adsorptive purpose because of its higher stability toward cracking and resistant to expand after adsorbing the water molecule [39–41]. Hence, in this context, we report few examples of simple, solvent-free and expeditious technique using reusable alumina as a solid-phase platform.

5.3.4.1 Activated neutral alumina (Al_2O_3)

Neutral alumina is counted in the list of metal oxide which possesses highly porous arrangement of aluminum oxide and tremendous surface area. Alumina displays amphoteric properties and is stable throughout the pH range of 2–13. It has amphoteric properties with both cation- and anion-exchange phenomenon over a broad pH range. The most important feature is that it possesses superior amphoteric properties. It has no special physical feature as it is a completely odorless and tasteless white powder, but this ingredient possesses high stability at high temperature. Moreover, it is insoluble in nature and could be made to dissolve only with either acid or base. No other life science material has provided such stability and versatility, remembering the ease of use and the low cost of alumina. It possesses powerful crushing strength with high resistance to the thermal shock and abrasion. The neutral Al_2O_3 does not shrink, swell, disintegrate or soften when engrossed in the reaction medium. Therefore, it will be very promising to use neutral alumina activating different calcined temperatures as a solid support reagent in the reaction medium.

5.3.4.2 Activated alumina ball

Activated alumina ball is reckoned in the list of effective desiccant and adsorbent. It has no special physical feature as it is a completely odorless and tasteless white sphere along with nontoxic nature, insoluble in water as well as organic solvent and soluble in strong acidic and alkaline solutions (Figure 5.2). These characters make these balls an ideal selection for the study of reaction processes. These balls are used in several applications for the moisture-adsorptive purpose in the reaction medium, and they do not expand and crack after adsorbing the water molecule.

Figure 5.2: Image of activated alumina balls.

These highly porous Al_2O_3 balls are produced by heating at a higher temperature. It works effectively in a range of conditions, which is highly appreciated with its powerful crushing strength and tremendous absorbing quality. Such type of desiccant has the characters of any kind of abrasion and highly resistant to the thermal stock. It can never be disintegrated and, at the same time, will not shrink, swell and soften when engrossed in the reaction. Considering all these advantages, these activated balls could be used as a dehydrating agent in the separation and purification processes by removing the uncontaminated compounds. The characteristic features such as surface area, pore size along with its mechanical strength and adsorption, play the major part in making this activated alumina ball an ideal choice for the solid-state synthesis of heterocyclic and carbocyclic skeleton.

5.3.4.3 KF/alumina

Ando et al. introduced completely different solid-phase strategy [42–45] using alumina doped with potassium fluoride (KF/alumina) for the vast range of organic transformations. Here, solid basic surface of KF/alumina has been extensively used as a reaction platform and can ionize C-acids up to pK_a ~35 [46]. Depending on the temperature, the actual basic site is generated on the surface of the alumina. On the other hand, infrared (IR) spectroscopic and ^{19}F magic angle NMR study indicated that in KF/alumina, the fluoride anion species is more electron rich compared to fluoride anion in pure solid. It displays variable functions and properties under different conditions of KF loading.

5.4 Construction of carbocyclic framework on solid support

The establishment of effective and reliable methods for the construction of carbocyclic skeleton remains a significant goal in SPS to the synthetic chemist. It is not possible to give a complete account of carbocyclic framework-based SPS as it is an ever-growing

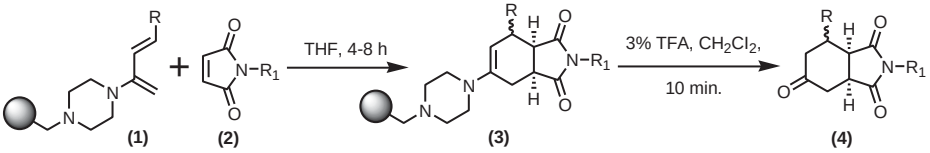
field of the medicinal and synthetic organic chemistry. Only few developments of this field have been included in this section.

5.4.1 Diels–Alder reaction

In recent times, one of the most synthetically advantageous methods for the development of six-membered ring systems is Diels–Alder reaction [47], and its use affords many possibilities in the construction of templates for combinatorial libraries. Particularly, the [4 +2] cycloaddition reaction is a widely used technique for the formation of rigid three-dimensional carbocyclic framework where various types of substituents are attached by directionally constrained carbon–carbon bond linkages. To date, the development and implementation of large libraries with reduced flexibility remains a challenge to explore features of selectivity and specificity for the screening of therapeutic targets and there are few reports of Diels–Alder reactions on the solid surface [48–50]. It is not possible to give a complete account of solid-phase-mediated Diels–Alder reactions as it is an ever-growing field of the medicinal and synthetic chemistry. Only few developments of this field have been covered in this chapter.

5.4.1.1 Synthesis of 3,4,5-trisubstituted cyclohexanones

In 1997, Crawshaw and coworkers developed a solid-supported [4 + 2] cycloaddition reaction of activated maleimides (**2**) and nitrostyrenes with a resin-bound 4-substituted-2-aminobutadienes (**1**) that result in bicyclic adducts (**3**) (Figure 5.3) [51]. Hydrolysis of the bicyclic adducts helps to cleave from the solid support and release several 3,4,5-trisubstituted cyclohexanones (**4**) into solution in moderate to good yields with high purities. The working methodology has been automated on the ACT 496 synthesizer and provides a library of diversely functionalized rigid templates under mild reaction conditions.



Entry	R	R_1	Yield (%)	Entry	R	R_1	Yield (%)
1	C_6H_5	CH_3	87	5	*p*-$MeOC_6H_4$	C_6H_5	53
2	C_6H_5	*p*-BrC_6H_4	81	6	*t*-Bu	(*p*-$MeO_2CC_6H_4$)CH_2	38
3	C_6H_5	*p*-$MeCOC_6H_4$	75	7	*p*-$MeOC_6H_4$	*p*-EtC_6H_4	43
4	*p*-FC_6H_4	*p*-BrC_6H_4	58				

Figure 5.3: Solid-phase synthesis of 3,4,5-trisubstituted cyclohexanones.

5.4.2 Electrocyclic reaction

Electrocyclic reaction is a very familiar class of organic reaction among various synthetic approaches toward structurally complex and biologically active natural products. The reactions exhibit excellent and predictable regio- and stereo-control based upon Woodward–Hoffmann rules in the construction of polycyclic scaffolds [52–54]. Basically, an electrocyclic reaction is a kind of pericyclic rearrangement, where the net outcome is the intramolecular conversion of one π-bond being converted into one σ-bond or vice versa with the highest atom economy. From documentation, it seems that the nature also prefers developing its compounds in such a synthetic manner, for example, electrocyclic biosynthesis of endiandric acids and vitamin D cascades [55]. Over the last few decades, a dramatic increase in its application for the synthesis of complex natural products with heterocyclic and carbocyclic frameworks has been achieved. Herein, we have disclosed few summaries of electrocyclic reaction to construct bioactive heterocyclic and carbocyclic compounds on solid phase.

5.4.2.1 Synthesis of multiple core structure libraries

Armstrong and Tempest [56] have presented a potential method for the construction of libraries of multiple core structure (**11**) via the thermal electrocyclic ring-opening sequence followed by ring-closure sequence of cyclobutenone derivatives (**6**) on the solid support (Figure 5.4). Halogen–metal exchange on aryl iodide yields a resin-bound organolithium reagent (**5**) which reacts with diisopropyl squarate in a 1,2-fashion delivers tertiary alcohol (**6**). Acid-catalyzed rearrangement of this alcohol followed by conjugate addition–elimination of primary amine furnished the diones (**7**). Next, 1,2-addition of a lithiated alkene with reactive carbonyl group (**8**) delivered the corresponding cyclobutene (**9**), which provided compound (**10**) by the electrocyclic ring opening followed by ring closure under refluxing in toluene. At the end, acid-catalyzed cleavage from the Wang resin gave directly the target oxidized 1,4-quinones (**11**).

5.4.3 Oligomerization reaction

Kato et al. [57] investigated a facile oligomerization reaction of styrene derivatives (**12**) under acid-treated montmorillonite resulting in the formation of carbocyclic polymerized compounds (**13**) (Figure 5.5). It is one of the first reports of clay-catalyzed dimerization reaction via protonation and deprotonation steps to give oligomers.

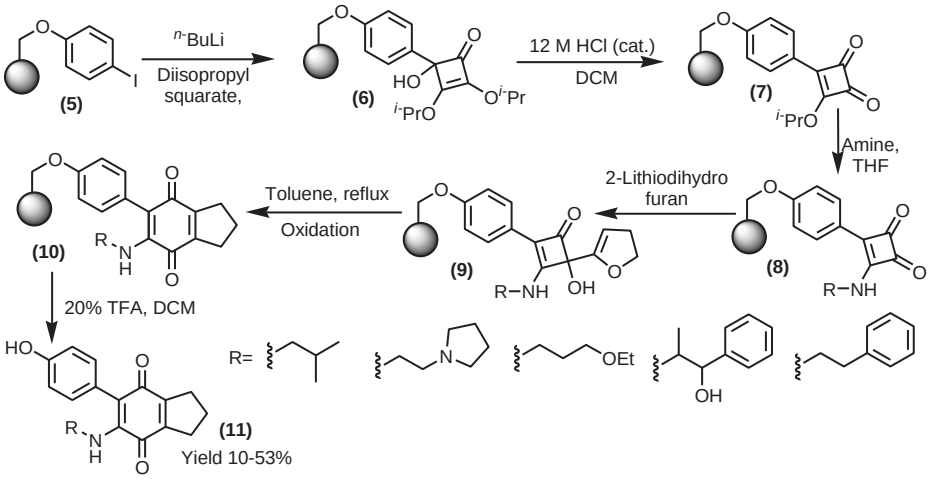


Figure 5.4: Solid-supported protocol toward multiple core structure libraries.

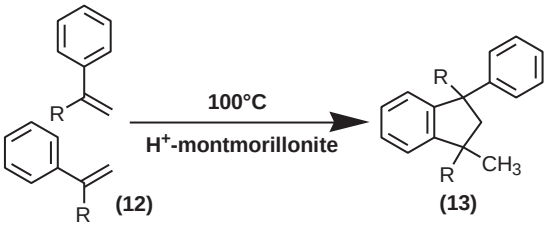


Figure 5.5: Clay-catalyzed solid-state synthesis of polymerized compounds.

5.5 Formation of heterocyclic framework on solid phase

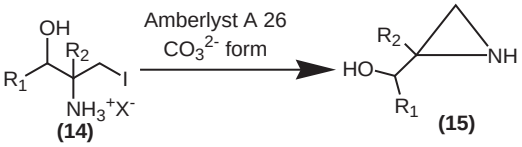
Heterocyclic compounds are the types of cyclic organic compounds which contain at least one heteroatom like nitrogen, oxygen and sulfur (i.e., atom other than carbon in the cyclic ring system). The heterocyclic rings containing other heteroatoms instead of most communal heteroatoms are N, O and S but are also widely known. Heterocyclic rings are one of the most important constituents of almost one half of the biological molecules such as hormones, DNA and RNA, essential amino acids, chlorophyll, hemoglobin, antibiotic, vitamins, alkaloids, dyestuffs and pigments and are frequently abundant in plants and animal goods [58, 59]. Heterocyclic compounds are widely used in the fields of pharmaceuticals, agrochemicals and veterinary and possess several biological activities such as antifungal, antibacterial, anticonvulsant, antioxidants, anti-inflammatory,

antiallergic, herbicidal and anticancer [60–62]. In this section, we have covered most of the SPS procedures for the formation of biologically active heterocyclic compounds.

5.5.1 Nitrogen-containing heterocycle

5.5.1.1 Synthesis of hydroxyaziridines

Giuliana Cardillo and his groups have reported an efficient, polymer-supported strategy for the synthesis of hydroxyaziridines (**15**) (Figure 5.6) [63] via reactions of salt (**14**) ($X^- = Cl^-:CCl_3CO_2^-$ in a 1:1 mixture) with Amberlyst A 26 in the CO_3^{2-} form in methanol at room temperature and give the desired product up to 96% yield. This protocol offered a new synthetic step for the synthesis of variety of natural compounds and amino sugars because it allows different types of functional group pattern incorporation into a chiral target molecule.



Entry	R_1	R_2	Yield (%)
1	H	CH_3	96
2	C_5H_{11}	H	95
3	$CHMe_2$	H	95

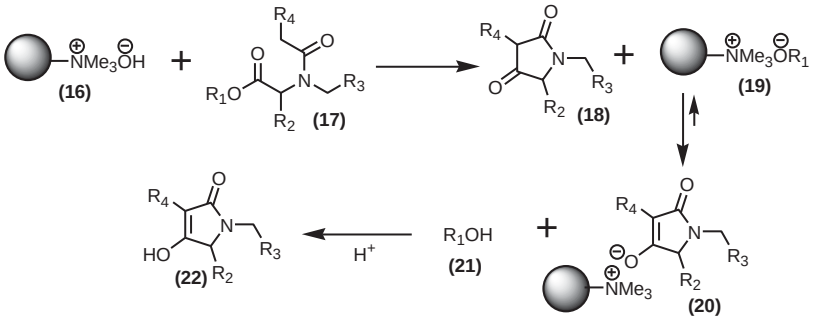
Figure 5.6: Synthesis of hydroxyaziridines on a polymeric support.

5.5.1.2 Synthesis of 2,4-pyrrolidinedionescombinatorial library

In 1997, Kulkarni and Ganesan presented an ion-exchange resin-based reaction to generate combinatorial library of 2,4-pyrrolidinediones (**22**) [64] via the Dieckmann condensation (Figure 5.7). These heterocycles are very useful scaffolds for the development of novel biologically active compounds because they are assembled from three easily available building blocks (amino acids, aldehydes and carboxylic acids) with a high degree of diversity.

5.5.1.3 Synthesis of 2,3-dihydro-4-pyridones derivatives

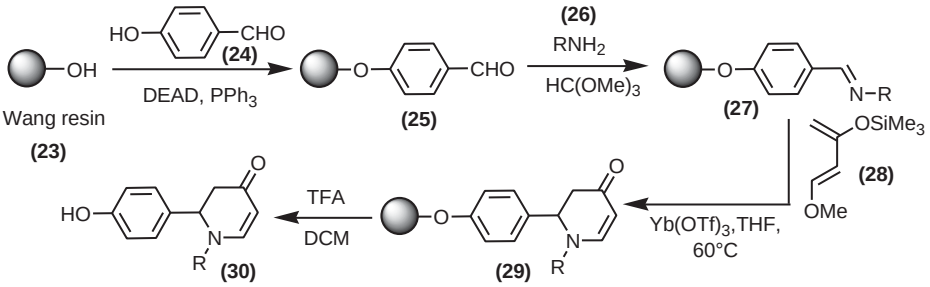
In this context, solid-supported preparation of 2,3-dihydro-4-pyridones employing Danishefsky's diene (**28**) and polymer-bound aldimines (**27**) via tandem Mannich–Michael reaction is illustrated by Wang and Wilson [65] (Figure 5.8). This novel and efficient method provides 2,3-dihydro-4-pyridone derivatives (**30**) with construction of new C–N bond via a [4 + 2] cycloaddition reaction using catalytic amount of $Yb(OTf)_3$ Lewis acid



Entry	R_2	R_3	R_4	Yield (%)	Entry	R_2	R_3	R_4	Yield (%)
1	H	C_6H_5	CN	72	6	$CH_2CH_2SCH_3$	C_6H_5	CN	79
2	H	C_6H_5	*o*-$NO_2C_6H_4$	73	7	$CH_2C_6H_5$	C_6H_5	CN	77
3	H	C_6H_5	$P(O)(OEt)_2$	86	8	$CH_2C_6H_5$	*p*-$MeOC_6H_4$	CN	75
4	H	C_6H_5	SPh	87	9	$CH_2C_6H_5$	*p*-$NO_2C_6H_4$	CN	70
5	*i*-Pr	C_6H_5	CN	80	10	$CH_2C_6H_5$	*p*-*t*BuC_6H_4	CN	71

Figure 5.7: Ion-exchange resin-based combinatorial synthesis of 2,4-pyrrolidinediones.

in moderate to good yields (60–90%). The polymer-bound 2,3-dihydro-4-pyridone analog is a very useful scaffold for synthetic transformations and can be used to prepare a library of various types of alkaloids by the application of solid-phase methodology.

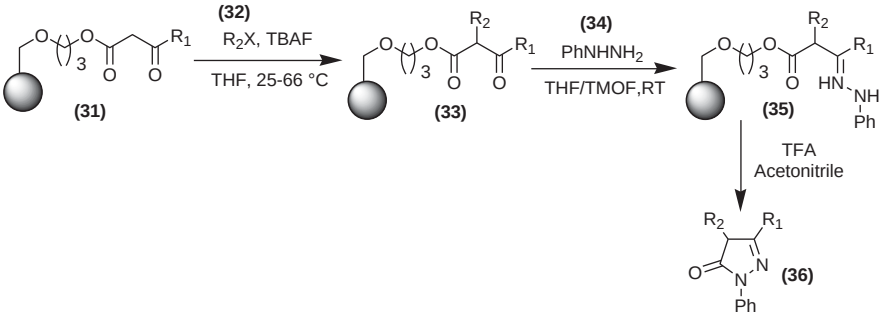


Entry	R	Yield (%)	Entry	R	Yield (%)
1	*n*-Bu	90	5	*p*-$OMeC_6H_4CH_2$	65
2	*i*-Bu	82	6	C_6H_5	60
3	*i*-Pr	85	7	*Cyc*-Pent	75
4	$CH_2C_6H_5$	80	8	*Cyc*-Hept	63

Figure 5.8: Solid-phase preparation of 2,3-dihydro-4-pyridones.

5.5.1.4 Synthesis of structurally diverse pyrazolones

In 1997, Tietze et al. [66] demonstrated a general and straightforward route to structurally diverse pyrazolones (**36**) utilizing cyclization reaction of different polymer-bound β-ketoesters (**33**) with phenylhydrazine (**34**) or hydrazine, and subsequently cleavage from the resin provides good yield in high purity (Figure 5.9). The diversified polymer-bound β-ketoesters (**33**) have been developed from readily available starting acid chlorides and Meldrum's acid followed by α-alkylation using haloalkanes (**32**). The SPS with mild reaction conditions make it amenable for automation and give a way toward the construction of new podium for combinatorial libraries using a wide range of structurally different β-ketoesters as the polymeric starting unit.



Entry	R_1	R_2	Yield (%)	Entry	R_1	R_2	Yield (%)
1	$CH_2C_6H_5$	H	91	7	CH_3	CH_2CHCH_2	52
2	$CH_2CH_2CO_2Me$	H	95	8	CH_3	$CH_2CHC(CH_3)_2$	81
3	$CH_2CH_2CH_2Cl$	H	93	9	CH_3	$(CH_2)_5CH_3$	80
4	Cyclohexyl	H	89	10	CH_3	CH_2CO_2Et	56
5	CH_3	CH_3	64	11	$CH_2C_6H_5$	CH_3	76
6	CH_3	C_2H_5	58	12	$CH_2CH_2CO_2Me$	$(CH_2)_5CH_3$	56

Figure 5.9: Solid-state synthesis of structurally diverse pyrazolones.

5.5.1.5 Synthesis of 2-[[4-chloro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy]-1-phenylethanone

John J. Parlow in 1995 developed a polymeric reagent-supported three-step synthetic procedure in which soluble sec-phenethyl alcohol (**37**) was stirred in a solution containing three different polymeric reagents at once in a single reaction vessel to afford 2-[{4-chloro-l-methyl-5-(trifluoromethyl)-lH-pyrazol-3-yl}oxy]-l-phenylethanone (**41**) in cyclohexane medium at 65 °C (Figure 5.10) [67]. The easily available polymeric reagents (**40**) and substrate alcohol (**37**) successfully provided highly functionalized and synthetically valuable structure (**41**) in 48% yield of the desired product.

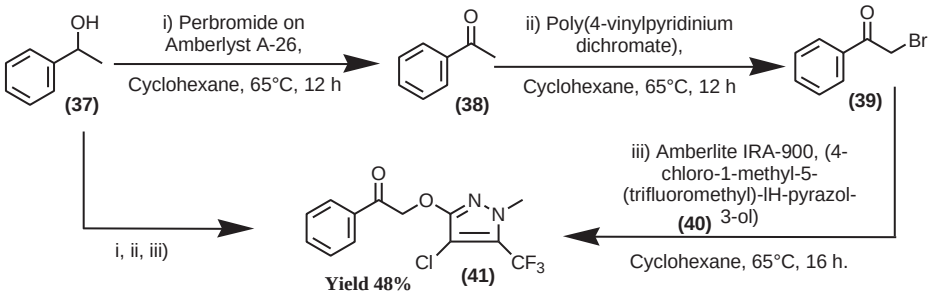
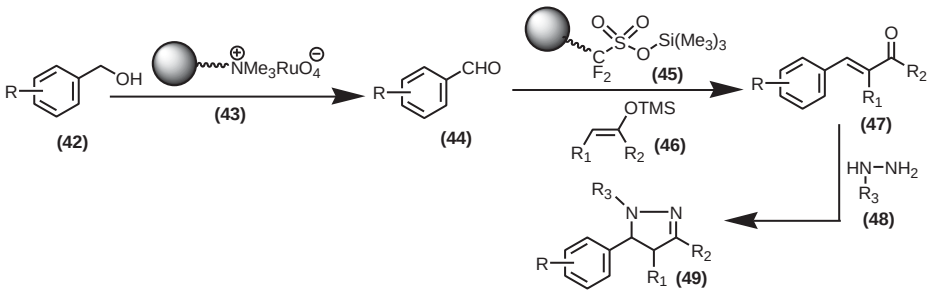


Figure 5.10: Solid-phase preparation of 2-[[4-chloro-l-methyl-5-(trifluoromethyl)-lH-pyrazol-3-yl]oxy]-l-phenylethanone using polymeric reagents.

5.5.1.6 Synthesis of 4,5-dihydro-1H-pyrazoles

A Nafion-TMS-mediated Mukaiyama aldol-type reaction strategy was applied by Ramirez and Gonzalez–Gomez in the reaction of silyl enol ethers (**46**) with aldehydes (**44**) (Figure 5.11) [68]. Polymer-supported perruthenate (PSP) (**43**) yielded corresponding aldehydes (**44**) via mild oxidation of alcohols (**42**) and produces α,β-unsaturated ketones (**47**) in the presence of polymeric reagent (**45**), which upon treatment with hydrazines (**48**) furnishes the desired 4,5-dihydro-1H-pyrazole (**49**). This new clean multistep procedure is suitable for robotic synthesis.



Entry	R	R_1	R_2	R_3	Yield (%)	Entry	R_2	R_1	R_2	R_3	Yield (%)
1	H	H	CH_3	H	95	5	H	H	CH_3	CH_3	95
2	*p*-OMe	H	CH_3	H	92	6	*p*-OMe	H	CH_3	CH_3	94
3	*3,4*-OMe	H	CH_3	H	92	7	*p*-Cl	H	CH_3	CH_3	92
4	*p*-Cl	H	CH_3	H	94						

Figure 5.11: Polymer-supported synthesis of 4,5-dihydro-1H-pyrazoles.

5.5.1.7 Synthesis of aromatic 1,2-diazines

A reverse electron demand Diels–Alder reaction has also been studied by the laboratory of Panek on the solid phase (Figure 5.12) [69]. The functionalized aromatic 1,2-diazines substituted at the C_6 position by a sulfur-based leaving group (**53**, **56**) were constructed by employing unsymmetrically substituted 1,2,4,5-tetrazines (**50**) with diversified electron-rich dienophiles (**51**, **54**) via thermally promoted cycloadditions. This technique is very helpful for the preparation of a diverse set of desired product as it permits the inclusion of four different types of elements on an aromatic scaffold via nucleophilic aromatic substitution (S_NAr) at C_6 position of the methyl sulfide/sulfone and acylation/alkylation of the C_3 amine.

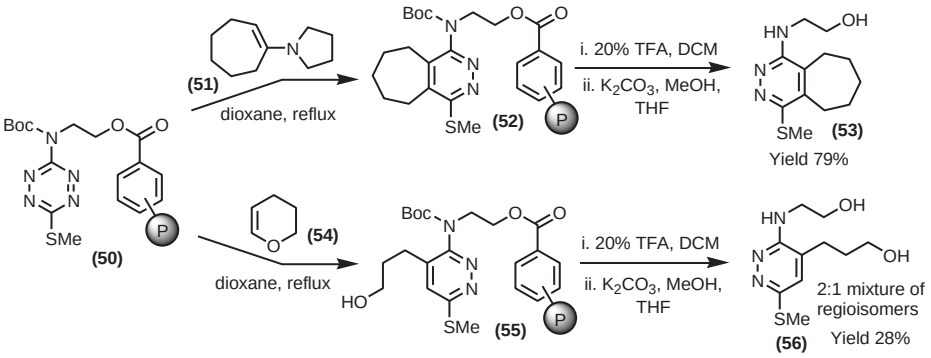
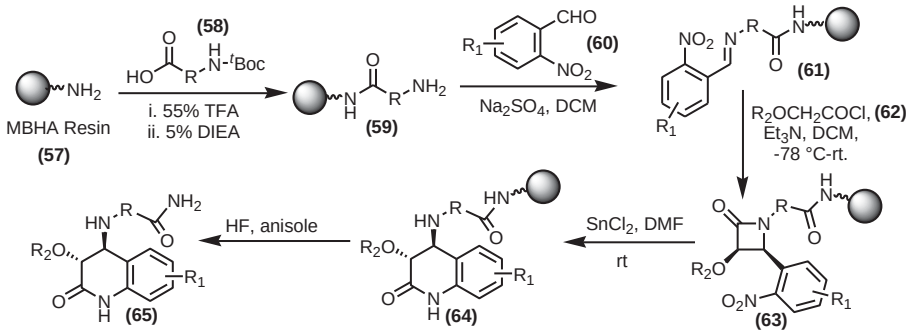


Figure 5.12: Polymer-supported synthesis of aromatic 1,2-diazines.

5.5.1.8 Synthesis of 4-amino-3,4-dihydro-2(1H)-quinolinones

The lab of Pei [70] reported the construction of 3,4-dihydro-2(1H)-quinolinones (**65**) by means of the rearrangement of β-lactam intermediates (**63**) on the solid surface (Figure 5.13). The β-lactam intermediates were derived from ketene-imine (**61**) [2 + 2] cycloaddition reaction.

This transformation is used to globally produce highly valuable bioactive library of 4,140 members of dihydroquinolinone derivatives (**65**) in good to excellent yield (68–100%). This split and mix method allows three diverse types of building blocks to synthesize the structurally different dihydroquinolinone including stereoisomers with a set of substituents at various positions.



R	R_1	R_2	Yield (%)	R	R_1	R_2	Yield (%)
CH_2	H	C_6H_5	96	C_6H_4	6-Cl	*p*-ClC_6H_4	80
CH_3CH	H	C_6H_5	100	CH_3CH	H	*p*-ClC_6H_4	100
$CH_2C_6H_4$	H	C_6H_5	100	$(CH_3)_2CHCH$	8-OMe	C_6H_5	92
C_6H_5CH	6,7-methylendioxy	*p*-ClC_6H_4	100	$(CH_3)_2CHCH$	8-OMe	CH_3CO	80
C_6H_4	6-Cl	CH_3CO	85	$(CH_3)_2CHCH$	8-OMe	*p*-ClC_6H_4	100
C_6H_4	6-Cl	CH_3	75	$CH_2C_6H_4$	6,7-$(OMe)_2$	C_6H_5	92
C_6H_4	6-Cl	C_6H_5	87	$CH_2C_6H_4$	6,7-$(OMe)_2$	*p*-ClC_6H_4	90
C_6H_4	6-Cl	H	68	HO_2CCH_2CH	6-OH	*p*-ClC_6H_4	91

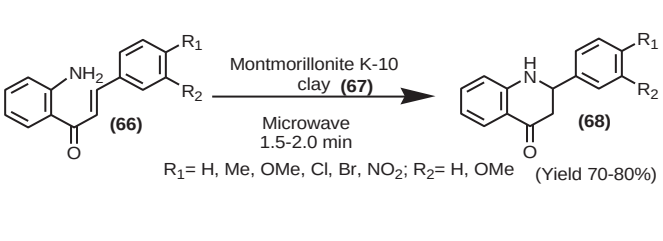
Figure 5.13: Construction of 4-amino-3,4-dihydro-2(1H)-quinolinones on the solid phase.

5.5.1.9 Synthesis of 2-aryl-1,2,3,4-tetrahydro-4-quinolones

In 1997, Varma and Saini [71] proposed a clay-supported C–N bond formation method utilizing microwave-assisted isomerization of 2′-aminochalcones (**66**) to 2-aryl-1,2,3,4-tetrahydro-4-quinolones (**68**) (Figure 5.14). This simple, solvent-free and environmentally benign strategy yields the desired compound in pure form under mild and dry reaction conditions on the surface of montmorillonite K-10 clay (**67**). Moreover, the methods have broad interest to the field of SPS of heterocyclic framework using abundant precursors and operationally easy and efficient reaction conditions.

5.5.1.10 Synthesis of tetrahydroquinolines

Very recently, 80-membered library of tetrahydroquinolines (**76**) were synthesized using a three-component condensation of solid-support aromatic amines (**72**), aldehydes (**73**), alkenes (**74**) and in the presence of trifluoroacetic acid (TFA) as a catalyst by Kiselyov and Armstrong (Figure 5.15) [72]. A number of electron-rich alkenes were established as new olefins and inputs with a variety of aldehydes for the tetrahydroquinoline library on the solid phase. Although a number of styrenes afforded the target compounds in good yields (53–92%), the best results were observed by the use of cyclopentadiene as the dienophile.



R_1	R_2	Yield (%)
H	H	80
CH_3	H	77
OMe	H	78
Cl	H	80
Br	H	72
NO2	H	70
OMe	OMe	72

Figure 5.14: Clay support preparation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones under microwave irradiation.

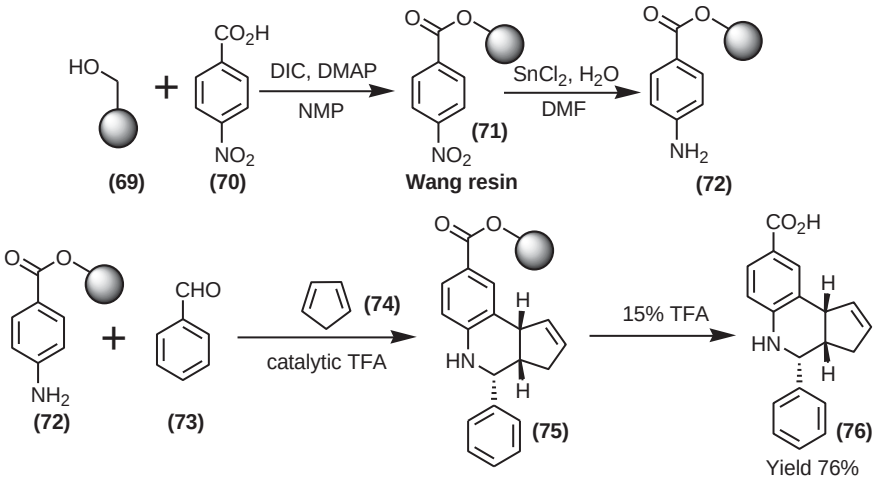


Figure 5.15: Solid-supported synthesis of tetrahydroquinolines.

5.5.1.11 Electrophilic aromatic substitution

The functionalization of PS via electrophilic aromatic substitution toward the formation of PS-based resins is well recognized and a challenge in organic synthesis. Thus, electrophilic aromatic substitution of substrates is integrally complicated on the surface of PS resins by the reactivity of the solid support material itself. Many instances of electrophilic aromatic substitutions are achieved successfully using resin-bound substrates bearing activated aromatic ring or via intramolecular fashion. Here, only few interesting methods including intermolecular electrophilic aromatic substitution have been illustrated.

5.5.1.11.1 Synthesis of 1,2,6-trisubstituted 1,2,3,4-tetrahydroisoquinoline

Rölfing et al. [73] demonstrated an eight-step synthetic route for simultaneous synthesis of 1,2,6-trisubstituted 1,2,3,4-tetrahydroisoquinoline derivatives (**82**) involving intramolecular electrophilic aromatic substitution of **79** (Figure 5.16) in 1996. Key to the success was the use of 2-hydroxyethyl polystyrene (**77**) as solid support to generate the bicyclic core. Further, the iminium ion is produced via the Bischler–Napieralski-type ring closure and subsequently reduced by sodium borohydride prior to trimethylaluminum-induced nucleophilic cleavage from the resin.

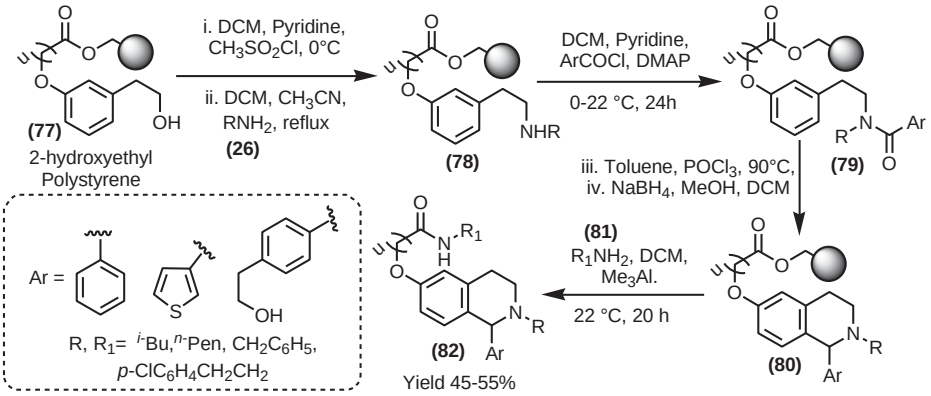


Figure 5.16: Construction of 1,2,6-trisubstituted tetrahydroisoquinoline derivatives on solid surface.

5.5.1.12 Nucleophilic aromatic substitution

From the past few years, heterocyclic skeleton gained from the solid-phase reactions are very attractive synthetic protocols for biological evaluation. Moreover, reports of the analogous synthesis through S_NAr of the resin-bound substrates are very effective to functionalization of electron lacking aromatic rings since this strategy produced the desired heterocycle with the introduction of an inclusive range of readily accessible heteroatomic nucleophiles. In this context, we reported few examples of such environmentally benign methodology.

5.5.1.12.1 Synthesis of 3,4-disubstituted-7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones

Lee et al. [74] produced 3,4-disubstituted-7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-one (**90**) derivatives by the reaction of *R*-amino esters (**86**) with alkyl halides (**85**) on a solid support (Figure 5.17). Initially, 4-fluoro-3-nitrobenzoic acid reacts (**84**) with solid support (**83**) to give resin-bound 4-fluoro-3-nitrobenzoic acid derivatives (**85**). Then compound **85** undergoes a sequential S_NAr reaction with amino acid esters (**86**) followed by

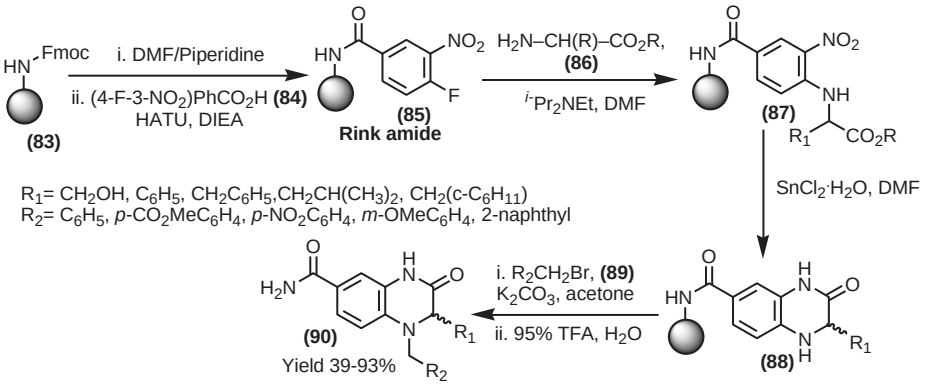


Figure 5.17: Construction of 3,4-disubstituted-7-carbamoyl-1,2,3,4-tetrahydroquinoxalin-2-ones on solid phase.

intramolecular reductive cyclization catalyzed by $SnCl_2{\cdot}H_2O$ which result in the formation of tetrahydroquinoxalin-2-one derivatives (**88**) in DMF. Selective N-4 alkylation of the quinoxalinone derivatives in the presence of K_2CO_3 prevents oxidation of the heterocyclic products and obtained the desired products (**90**) after cleavage from solid supports under acidic conditions in 32–93% isolated yields.

5.5.1.13 Synthesis of quinoxalines

In 2011, Paul and Basu [75] presented facile and expeditious solid-state tandem oxidation–condensation or condensation of a variety of simple α-hydroxy ketones (**92**), α-bromoketones (**94**), or α-dicarbonyl compounds (**96**) with aromatic 1,2-diamines (**91**) prompted by the basic surface of heterogeneous KF alumina (Figure 5.18). In addition, this solvent-free C–N bond-forming reactions offered a direct, rapid and operationally simple synthetic tools for bioactive libraries of quinoxalines (**93**, **95**, **97**), which make the synthetic methodology bio-friendly and economically workable.

5.5.1.14 Synthesis of 2-substituted indole

In 1996, Ian Hughes [76] reported the solid-phase organic synthesis of 2-substituted indole (**104**) using polymer-supported phosphonium salts (**98**) as a traceless linker (Figure 5.19). Easily available phosphonium salts afforded cleaved alkyl, alkenyl and heteroaryl products with up to 82% yield under basic conditions and can be elaborated with reagents of both acids/bases including reducing agents.

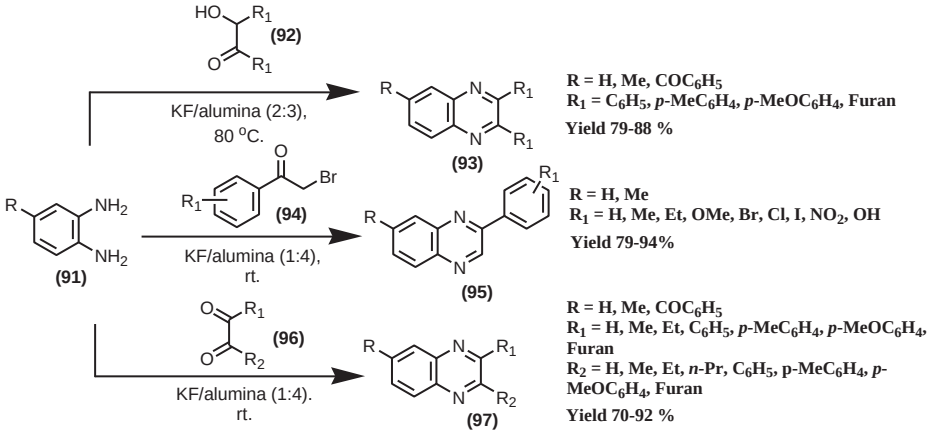


Figure 5.18: Synthesis of quinoxaline libraries on the basic surface of KF alumina.

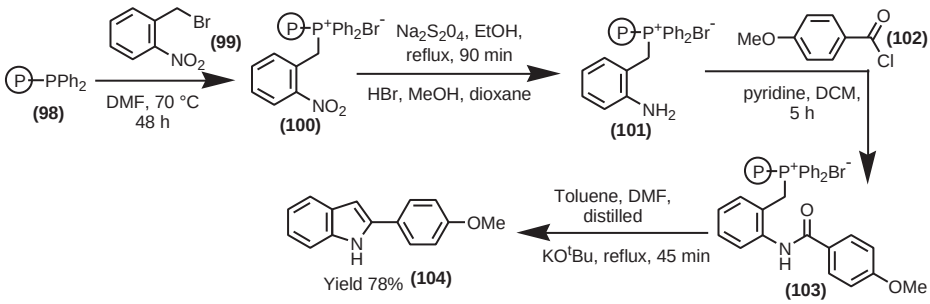
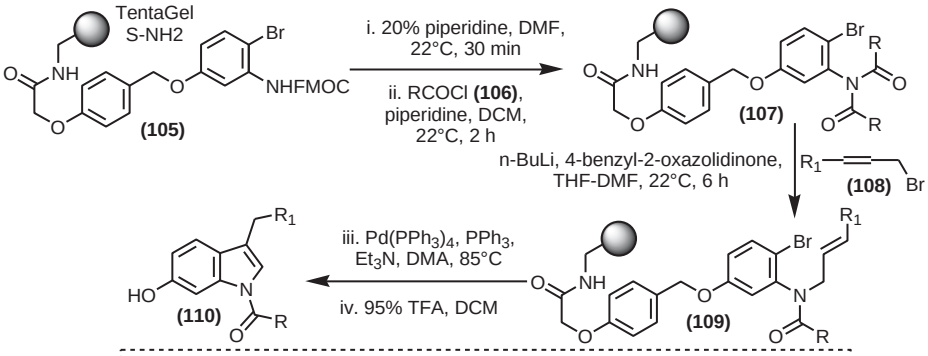


Figure 5.19: Solid-supported synthesis of 2-substituted indole using polymer-bound phosphonium salts.

5.5.1.15 Synthesis of indole analogs

Weiya Yun and Raju Mohan [77] published solid-supported intramolecular Heck reaction to afford indole-based library (**110**) using polymer-bound arylhalides such as **105** in high yields of up to 94% in 1996 (Figure 5.20).

They were successful to develop varied libraries of indole analogs (**110**) from the readily assembled precursor which is constructed by the reaction of commercially available acid chlorides (**106**) with alkylating agent allylic bromides (**108**) under mild reaction conditions.



Entry	R	R_1	Yield (%)	Entry	R	R_1	Yield (%)
1	C_2H_5	H	90	5	C_6H_5	C_6H_5	65
2	C_2H_5	C_6H_5	94	6	C_6H_5	CH_3	90
3	i-Pr	CH_3	92	7	*m*-$OMeC_6H_4$	H	90
4	C_6H_5	H	70	8	*m*-$OMeC_6H_4$	C_6H_5	83

Figure 5.20: Solid-state synthesis of indoleanalogs.

5.5.1.16 Synthesis of trisubstituted indoles

From the past few years, a number of palladium-catalyzed approaches to the solid-supported preparation of bioactive heterocycles have been disclosed. Zhang et al. [78] have proposed a palladium-mediated coupling reaction between alkynes (**113**) and resin-bound aryl iodides (**112**) to synthesize trisubstituted indoles (**115**) (Figure 5.21). This synthetic approach furnished diversified trisubstituted indole derivatives (**115**) in good to excellent yields. The resin-bound heteroannulation of trimethylsilyl alkynes also afforded other 2-substituted indole derivatives with high product purity. In addition, synthesis of this indole-based combinatorial library from the easily obtainable starting internal alkynes makes this technique more attractive and valuable to the current synthetic researcher.

5.5.1.17 Synthesis of 1,2-disubstituted benzimidazoles

In the next year, Paul and Basu [79] introduced an innovative, eco-friendly synthetic platform for C–N bond-forming reaction on the solid surface of ferric sulfate soaked with silica [iron(III)sulfate-silica] at room temperature (Figure 5.22). The study consists of one-pot condensation and subsequently aromatization reaction of *o*-phenylenediamine (**116**) with readily available electronically different aldehydes (**117**) to generate functionalized 1,2-benzimidazole products (**118**) with moderate to good yield under mild conditions. This solvent-free technique needs only inexpensive environmentally friendly

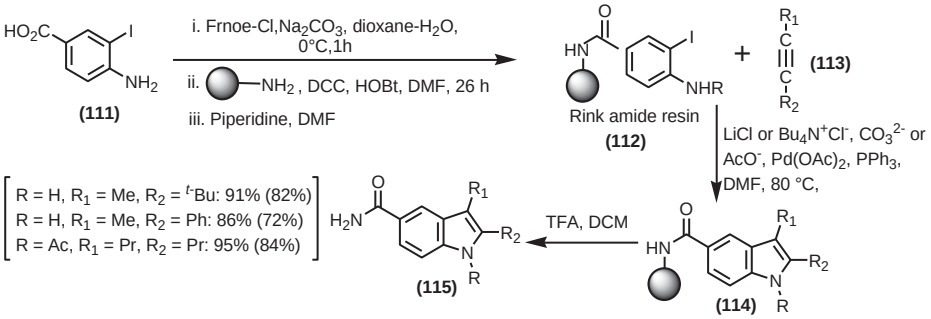
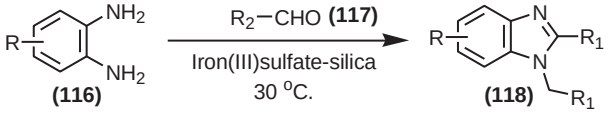


Figure 5.21: Palladium-mediated solid-phase synthesis of trisubstituted indoles.



Entry	R	R_1	Yield (%)	Entry	R	R_1	Yield (%)
1	H	C_6H_5	89	10	H	1-Naphthyl	84
2	H	*p*-$CH_3OC_6H_4$	85	11	H	Furan-2-yl	79
3	H	*p*-ClC_6H_4	87	12	H	5-Bromo-thiophene-2-yl	75
4	H	*p*-$NO_2C_6H_4$	83	13	H	*o*-OHC_6H_4	78
5	H	*p*-$Me_2NC_6H_4$	86	14	3-CH_3	5-Br-thiophene-2-yl	77
6	H	*p*-Isopopyl C_6H_4	84	15	3-CH_3	*o*-ClC_6H_4	75
7	H	*m*-$NO_2C_6H_4$	84	16	3-COC_6H_5	C_6H_5	88
8	H	*m*-OHC_6H_4	86	17	H	Cyclohexyl	84
9	H	*m*-$OPhC_6H_4$	84	18	H	2-Methylpropyl	78

Figure 5.22: Synthesis of 1,2-disubstituted benzimidazoles on silica gel-soaked ferric sulfate.

starting materials and recyclable catalytic system to deliver appreciable yield with high product selectivity.

5.5.1.18 Synthesis of 1H-indazoles

A solid-supported multistep procedure for the preparation of 1H-indazoles (**124**) was investigated by Yan et al. using single-bead Fourier-transform infrared (FTIR) microspectroscopy (Figure 5.23) [80]. Synthesis of the target compound involved an intramolecular electrophilic aromatic substitution reaction. Moreover, oxidation and final cyclization of **122** promoted by Lewis's acid were studied under FTIR to afford the desired heterocycle (**124**) in good yield with high product purity after acid-induced cleavage from the resin. Advantage of this technique is the use of single-bead IR for a

quick and convenient analysis of product formation with remaining starting materials in each synthetic step. This time-consuming solid-phase reaction is also very useful to generate combinatorial chemistry.

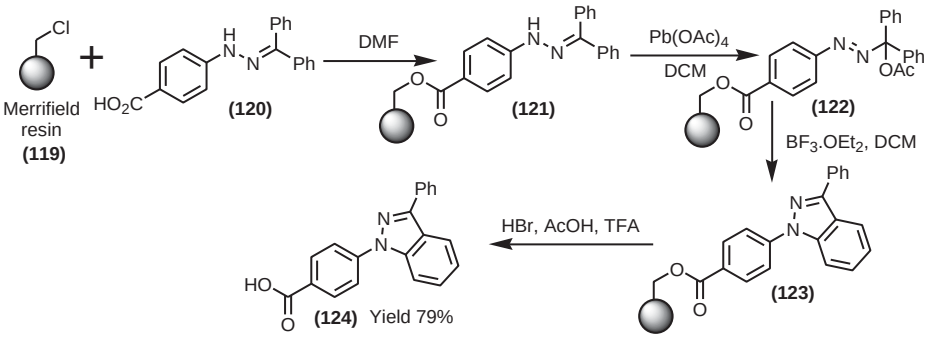
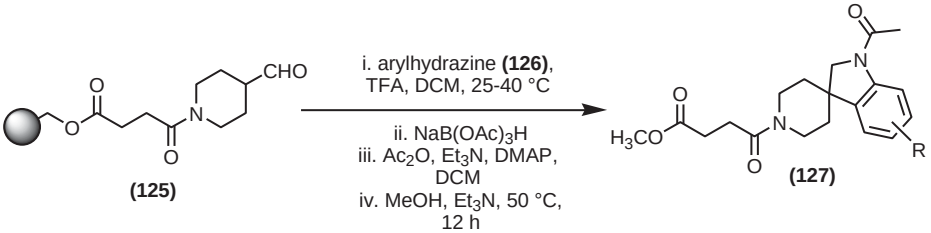


Figure 5.23: Synthesis of indazole on solid support.

5.5.1.19 Synthesis of spiroindoline

Cheng and Chapman [81] invented a completely different strategy to the solid-state synthesis of heterocyclic spiroindoline derivatives (**127**) via a modified Fischer indole reaction (Figure 5.24). A wide range of electron-rich aryl hydrazines (**126**) were employed



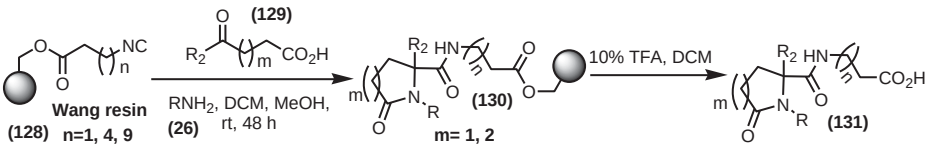
Entry	R	Yield (%)	Entry	R	Yield (%)
1	H	95	9	3, 5-$(CF_3)_2$	95
2	2-Br	93	10	4-^{t}Bu	95
3	4-CF_3	91	11	4--benzyloxy	91
4	3, 5-Cl_2	95	12	2, 5-$(CH_3)_2$	89
5	3-NO_2	87	13	4-OMe	94
6	4-NO_2	94	14	4-OCF_3	87
7	3, 4-Cl_2	94	15	4-(2-oxazoly)	83
8	2, 4-Cl_2	94	16	1-naphthyl	95

Figure 5.24: Solid-phase formation of spiroindoline.

in TFA/CH_2Cl_2 medium and reacted smoothly with polymer-bound piperidine-4-carboxaldehyde (**125**). However, the electron-deficient hydrazine derivatives tolerated the reaction relatively at higher concentration of TFA (10–25%). The protocol is feasible for a large variety of arylhydrazines and amenable for construction of combinatorial libraries of spiroindoline in good to excellent yields with high product purity.

5.5.1.20 Synthesis of five- and six-membered ring lactams

A resin-based solid-phase reaction strategy has been applied to the formation of novel functionalized five- and six-membered ring lactams (**131**) via the condensation of resin-bounded isocyanides (**128**) with ω-ketoacids (**129**) and amines (**26**) by Short and Mjalli [82] (Figure 5.25). At the beginning, the starting isocyanide moiety is attached on the surface of the Wang resin through an ester linkage and provided comparatively pure compounds without applying monotonous chromatographic separation method. A wide range of commercially accessible amines, ω-ketoacids and isocyanide components immobilized on the surface of the Wang resin worked effectively for the construction of a stage for combinatorial library of small-ring lactams. At the end, the desired product (**131**) was isolated from the support material under the treatment of 10% TFA/CH_2CI_2 in moderate to excellent yields.



Entry	n	m	R	R_1	Yield (%)	Entry	n	m	R	R_1	Yield (%)
1	9	1	$CH_2C_6H_5$	CH_3	93	5	1	1	$CH_2C_6H_5$	CH_3	91
2	4	1	*n*-$C_{11}H_{23}$	CH_3	98	6	1	2	$CH_2C_6H_5$	CH_3	60
3	4	1	$CH_2C{\equiv}CH_2$	CH_3	47	7	9	2	$CH_2C_6H_5$	CH_3	96
4	9	1	C_6H_5	CO_2H	84	8	9	1	*n*-Bu	CH_3	94

Figure 5.25: Solid-phase method for the synthesis of five- and six-membered ring lactams.

5.5.1.21 Synthesis of cyclic ureas and thioureas

The laboratory of Nefzi has illustrated a new method to the preparation of cyclic ureas and thioureas (**138**) from linear peptides (**136**) on solid phase (Figure 5.26) [83].

The reaction that proceeded through N-alkylation of methylbenzhydrylamine resin-supported amino acid (**133**) followed by stepwise homologation of this precursor gave triamide derivatives (**136**) via the amide bond formation. Primarily, the acylated

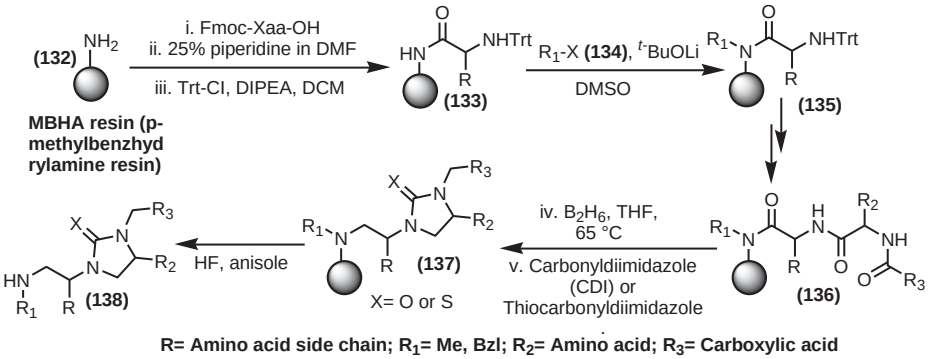


Figure 5.26: Preparation of cyclic ureas and thioureas on solid phase.

dipeptides were reduced by diborane and delivered the corresponding highly pure cyclic compound (**138**) in good yield in the presence of carbonyl diimidazole or thiocarbonyl diimidazole. This solid-phase methodology could be utilized for the synthesis of individual heterocycle and a range of combinatorial libraries.

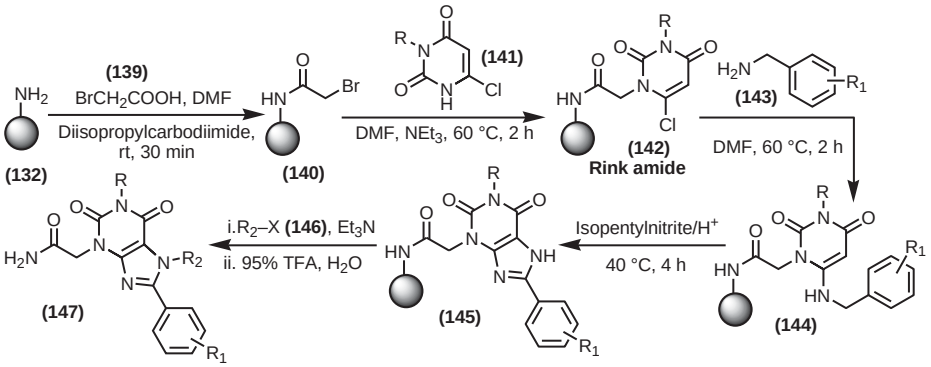
5.5.1.22 Synthesis of xanthines

Heizmann and Eberle [84] adapted xanthine derivatives (**147**) as a novel, versatile scaffold for combinatorial chemistry on solid support. They described a five-step synthetic approach, which includes *N*-alkylations of the uracil system (**141**), a nucleophilic substitution by amine substrate at the heterocycle (**142**) and cyclization via the condensation reaction between activated methylene and nitrosofunctional group (Figure 5.27). The synthetic strategy generates a small xanthine library (**147**) with eight individual entities in 10–32% isolated yields after HPLC purification and allows high molecular diversity. The technique is also expandable to create a library of large number of compounds and is already applied in the library synthesis containing 90 individual compounds and is being tested in several biological assays at present.

5.5.1.23 Multicomponent reactions (MCRs)

The convergent chemical reaction in which more than two reactants combined with each other via well-defined condensation generates a product that possesses significant portions of all atoms of the reactants is called multicomponent reactions (MCRs).

In this one-pot synthesis, three or more reactants react together and furnishes a new compound in a single reaction container (Figure 5.28). Products of this protocol comprises almost all portions of substrates along with no by-products, which is the



Entry	R	R_1	R_2	Yield (%)	Entry	R	R_1	R_2	Yield (%)
1	CH_3	*o*-OMe	$H_2CC{\equiv}CH$	10	6	CH_3	*p*-CH_3	CH_2CONH_2	32
2	$CH_2C_6H_5$	*p*-CF_3	CH_2CONH_2	14	7	C_3H_7	*p*-F	H	23
3	CH_3	*p*-F	H	19	8	C_3H_7	*p*-F	CH_2CONH_2	26
4	CH_3	*p*-F	CH_2CONH_2	32	9	C_3H_7	*p*-CH_3	H	13
5	CH_3	*p*-CH_3	H	25	10	C_3H_7	*p*-CH_3	CH_2CONH_2	11

Figure 5.27: Solid support synthesis of xanthines.

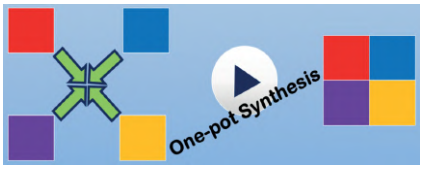


Figure 5.28: Schematic presentation of multicomponent reactions (MCRs).

key characteristics of MCR strategy. This eco-friendly, ideal synthesis offered target compounds in a single synthetic step and paid much attention in the field of biomedicinal, industrial and combinatorial chemistry.

Three-component reactions are very common. Four- and five-component reactions are also familiar nowadays. Six or more than six-component reactions are rare. A + B + C type of reaction is a true three-component reaction where all the three components are different. A + B + B type of reaction is also taken into consideration of MCR where one component is taken twice. This type of reaction should be truly called as pseudo-three-component reaction.

5.5.1.23.1 Features of multicomponent reactions

In the current organic chemistry, one of the most efficient synthetic tools is MCR technique because it possesses all characteristics that contribute to a model synthesis. Usually, productivity is encoded in terms of reaction yield, product selectivity and

number of steps in the mind of synthetic chemists mostly. However, the perspective of MCRs is considerably wider and consists of waste generation, use of hazardous chemicals, reagents and solvents with general safety and energy intensity. All of these characteristics are included in Figure 5.29.

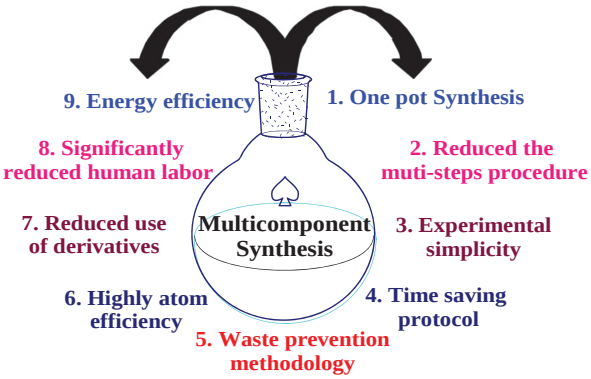


Figure 5.29: Features of multicomponent synthesis.

Hence, the development of a novel MCR strategy toward the biomedicinal and industrial frameworks applying SPS platform is inevitable at the present time.

The advantages of MCRs have endorsed their application in interrelated fields including synthetic podium for natural products, functional molecular libraries and the development of new drug molecules [85, 86]. Thus, the aim is to point out the prospects of the employment of MCRs bringing for the SPS of heterocyclic framework, and the process design is a great challenge to modern synthetic chemists. Few such representative examples of solid-phase MCRs are shown here.

5.5.1.23.2 Synthesis of quinoline derivatives

Nagayama's [87] laboratory constructed a library of high-quality and -quantity quinoline derivatives (**151**) (Figure 5.30) using polymer-supported scandium catalyst. The PA-Sc-TAD (polyallylscandium trifylamide ditriflate) catalysis synthetic procedure provides the desired products from the reaction mixture of different types of aldehyde (**148**), aromatic amine (**149**) and alkene (**150**) in dichloromethane–MeCN (2:1) at ambient temperature for 15 h. This method is also very workable for development of new research projects as well as other compound libraries.

5.5.1.23.3 Synthesis of 2-arylquinoline-4-carboxylic acid

Gopalsamy and Pallai [88] investigated an efficient multicomponent condensation approach by adopting the Doebner quinoline synthetic method for the synthesis of 2-arylquinoline-4-carboxylic acid derivatives (**153**) on the solid surface of the Rink resin

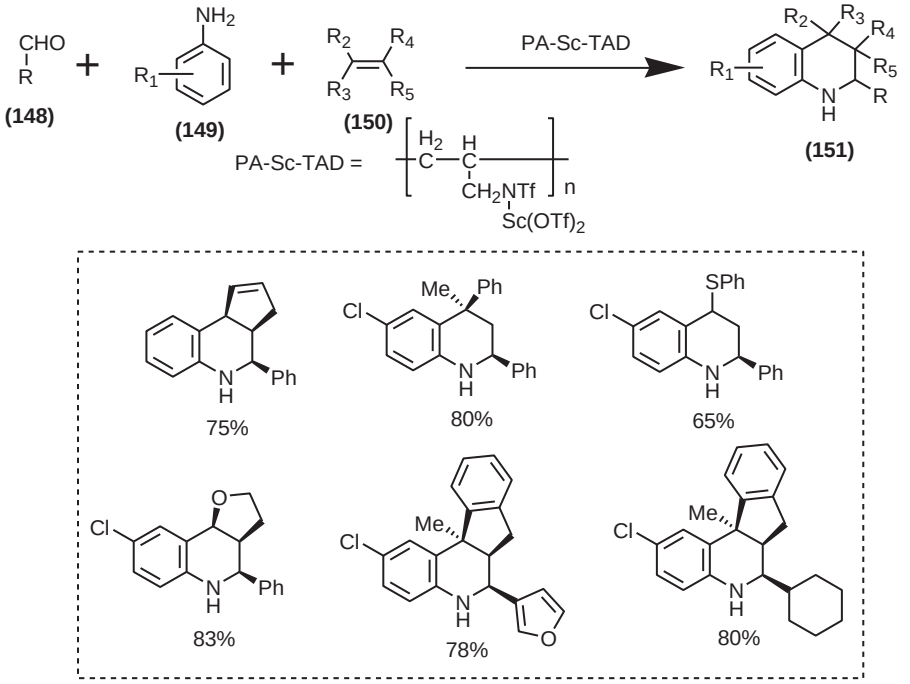
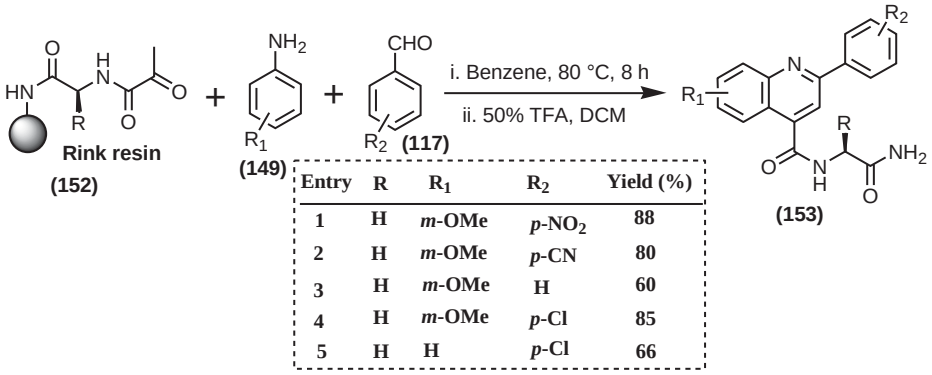


Figure 5.30: Polymer-supported scandium-catalyzed synthesis of quinoline derivatives.



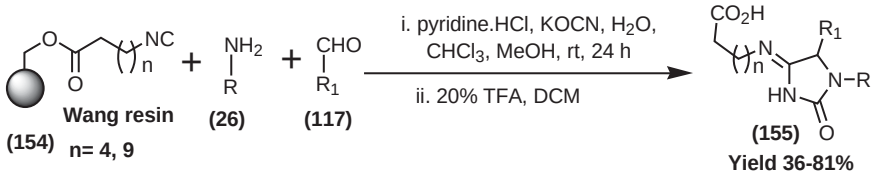
Entry	R	R_1	R_2	Yield (%)
1	H	*m*-OMe	*p*-NO_2	88
2	H	*m*-OMe	*p*-CN	80
3	H	*m*-OMe	H	60
4	H	*m*-OMe	*p*-Cl	85
5	H	H	*p*-Cl	66

Figure 5.31: Solid-phase synthesis of 2-arylquinoline-4-carboxylic acid.

(Figure 5.31). Here, the Rink PS resin-bounded amino acid furnishes corresponding the immobilized amide derivatives (**152**) by acylation with pyruvyl chloride. Further treatment of immobilized pyruvic amide with a mixture of Schiff's base or aldehyde (**149**) and aniline (**117**) offered resin-bound cyclized product under reflux in benzene. The method provides 2-arylquinoline-4-carboxylic acids (**153**) of up to 88% after cleavage from the resin using TFA.

5.5.1.23.4 Synthesis of hydantoin 4-imides

Short et al. [89] presented a new solid-supported platform for hydantoin 4-imides (**155**) by applying the "Ugi" four-component condensation of amines (**26**), aliphatic aldehydes (**117**), Wang resin-supported isocyanides (**154**) and in-situ-generated hydrazoic acid (Figure 5.32). The commercially available starting materials were successfully employed with immobilization of the isocyanide constituent in a combinatorial fashion on the Wang resin. At the end of the synthetic strategy, target molecules were separated upon treatment with 20% TFA from the solid support material in CH_2Cl_2 medium. This solid-phase MCR methodology delivered structurally diverse hydantoin 4-imide derivatives (**155**) in moderate to good yields (36–81%).



R= *n*-C_4H_9, *n*-C_8H_{17}, *sec*-C_4H_9, *i*-C_3H_7, *i*-C_5H_{11}, $CH(CH_3)CH_2CH(CH_3)_2$, *p*-$BrC_6H_4CH_2$, *p*-$ClC_6H_4CH_2$, *m*-F-*o*-$CH_3C_6H_3$; R_1= *n*-C_3H_7, *n*-C_7H_{15}, *sec*-C_4H_9, *trans*-$(CH_2)_2CH{=}CH(CH_2)_4CH_3$, $CH_2CH(CH_3)CH_2C(CH_3)_3$, $CH(C_2H_5)(CH_2)_3CH_3$, *c*-C_6H_{11}

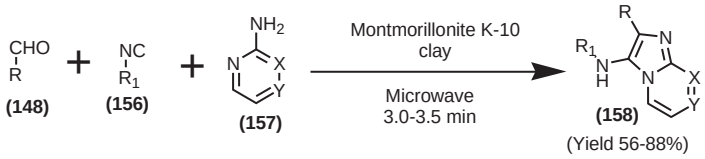
Figure 5.32: Construction of hydantoin 4-imides on solid support.

5.5.1.23.5 Synthesis of imidazo[1,2-a]-annulated pyridines, pyrazines and pyrimidines

In 1999, Varma and Kumar [90] reported a rapid, one-pot and solventless method for imidazo[1,2-a]-annulated pyridines, pyrazines and pyrimidines (**158**) under microwave irradiation using solid surface of reusable montmorillonite K-10 clay (Figure 5.33). Moreover, an economical and eco-friendly condensation of aldehydes (**148**; aliphatic, aromatic and vinylic), amines (**157**; 2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine) and isocyanides (**156**; aliphatic, aromatic and cyclic) give the desired multisubstituted dimidazo [1,2-a]-annulated pyridine, pyrazine and pyrimidine derivatives (**158**) in moderate to excellent yields. Additionally, this new, inexpensive and recyclable clay-supported one-step method is highly complementing for the parallel assembly of the library synthesis.

5.5.1.23.6 Synthesis of spiro[pyrrolo-4,10′-indeno[1,2-b]quinoline] and spiro [indololo-3,4′-indeno[1,2-b]pyridine]

Our laboratory has developed a new efficient and environmentally benevolent MCR approach for the formation of regioselective spiro-heterocyclic scaffolds (**162** and **163**) in moderate to excellent yields (Figure 5.34) [91]. The mixture of amine (**149**), β-keto ester (**159**) and indane-1,3-dione (**160**) treated with isatin moiety (**161**) (either N-substituted or unsubstituted) under neat condition on the solid surface of activated



X	Y	R	R_1	Yield (%)	X	Y	R	R_1	Yield (%)
C	C	C_6H_5	$C_6H_5CH_2$	86	C	N	C_6H_5	$C_6H_5CH_2$	81
C	C	4-MeC_6H_4	$C_6H_5CH_2$	88	C	N	C_6H_5	Cyclohexyl	82
C	C	C_6H_5	Cyclohexyl	86	C	N	4-MeC_6H_4	Cyclohexyl	81
C	C	C_6H_5	$CH(CMe_3)_2$	85	C	N	C_6H_5	$CH(CMe_3)_2$	83
C	C	4-OMeC_6H_4	$C_6H_5CH_2$	82	C	N	C_6H_5CH=CH	$C_6H_5CH_2$	64
C	C	C_6H_5	t-Bu	84	N	C	C_6H_5	Cyclohexyl	58
C	C	$(Me)_2CH$	$C_6H_5CH_2$	85	N	C	C_6H_5	$C_6H_5CH_2$	56

Figure 5.33: Clay-supported solvent-free synthesis of imidazo[1,2-a]-annulated pyridines, pyrazines and pyrimidines.

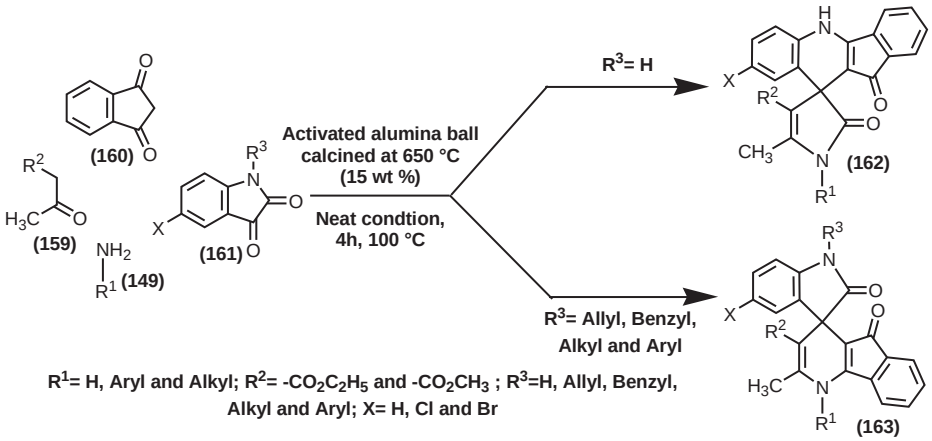


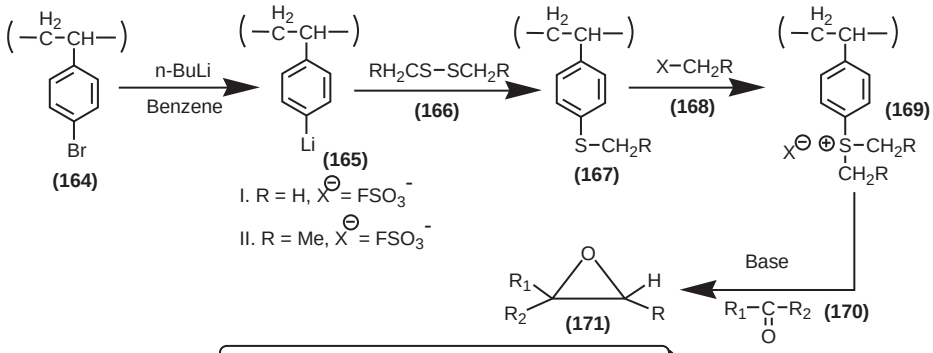
Figure 5.34: Solvent-free solid-phase preparation of spiro[pyrrolo-4,10′-indeno[1,2-b]quinolin] and spiro [indololo-3,4′-indeno[1,2-b]pyridine] derivatives.

alumina balls over a steam bath. Here, the cheap, easily available and environmentally benign activated alumina balls absorb water molecule from the reaction medium which is the main driving force to accelerate the reaction in the forward direction. It was observed that the yield of the reaction increases with increasing pore size of the catalyst but not directly correlated with the surface area or pore volume.

5.5.2 Oxygen-bearing heterocycle

5.5.2.1 Synthesis of epoxide scaffolds

From the very beginning, various types of sulfur ylides were synthesized from soluble sulfonium salts utilizing phase transfer catalyst in the reaction medium. The most important features of the polymeric sulfonium salts are thermally stable and their sulfide by-products are nonvolatile and have no smell. Jean Farrall et al. [92] developed a highly efficient and facile method for the preparation of epoxide scaffolds (**171**) by reaction of regenerable sulfonium ylides (**169**) with carbonyl compounds (**170**) to delivere the desired product in good to excellent yields (94–97%) (Figure 5.35).



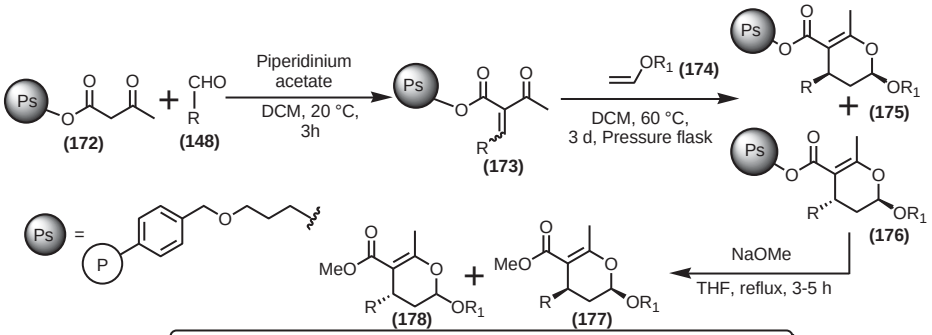
Entry	R	R_1	R_2	Yield (%)
1	H	C_6H_5	H	97
2	H	C_6H_5	CH_3	94
3	H	C_6H_5	C_6H_5	96
4	CH_3	C_6H_5	C_6H_5	96

Figure 5.35: Polymeric reagent-based synthesis of epoxides.

5.5.2.2 Synthesis of substituted 3,4-dihydro-2H-pyrans

In 1996, Tietze et al. [93] introduced a hetero-Diels–Alder reaction of compound **173**, generated via Knoevenagel condensation and with enol ether (**174**) to afford the diastereoisomeric-3,4-dihydropyrans (**177**) and (**178**) in high purity (Figure 5.36).

The solid-supported three-component domino reactions via transesterification released the corresponding methyl esters from the supported resin utilizing THF as solvent under reflux condition and provided overall yields in between 12% and 37%. The method is very effective for generating combinatorial libraries of substituted 3,4-dihydropyrans from the commercially available aldehyde and enol ethers.



Entry	R	R_1	Yield (%)	Entry	R	R_1	Yield (%)
1	C_2H_5	Et	13	6	*i*-Bu	Bu	26
2	*i*-Pr	Et	13	7	*i*-Bu	Me	12
3	*i*-Pr	*i*-Bu	20	8	*n*-Pent	Et	22
4	*n*-Pr	Et	21	9	*n*-Pent	Bu	32
5	*i*-Bu	Et	37				

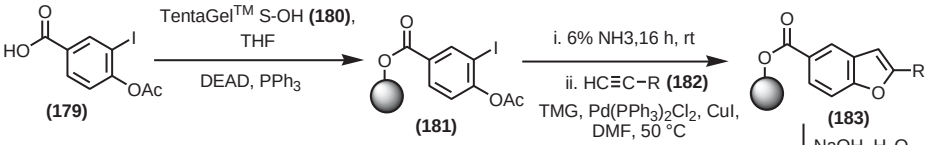
Figure 5.36: Solid-phase three-component approach to substituted 3,4-dihydro-2H-pyrans.

5.5.2.3 Synthesis of 2-substituted benzofurans

Synthetically very important, copper/palladium-promoted heteroannulation of terminal acetylenic compounds have been achieved by Fancelli et al. [94] for construction of C–O and C–C bonds in the presence of resin-bound *ortho*-hydroxy aryl iodides (**181**) (Figure 5.37). The solid-phase process considering mild reaction conditions and commercially available large variety of acetylenic compounds (**182**) produces 2-substituted 5-carboxybenzofuran (**184**) derivatives in good yield and high purity. 4-Acetoxy-3-iodobenzoic acid (**179**) was successfully coupled with TentaGel^{TM} S–OH resin (**180**) using the well-established Mitsunobu reaction and subsequent unmasking of the phenol then offered the stage for the palladium-catalyzed heteroannulation. The method provides an efficient new route to increasing diversity in the design of combinatorial chemistry libraries of small organic molecules.

5.5.2.4 Radical reactions

Recently, researchers of science and technology have focused their practices on the scope and limitations of solid-supported radical chemistry. Various studies on solid support radical reactions offered many advantages over the harsh reaction conditions such as mild protocol, rapid synthesis and easy to perform at room temperature. Herein, we wish to report few interesting examples of solid-state construction of heterocyclic nucleus via radical reaction.



Entry	R	Yield (%)	Entry	R	Yield (%)
1	$(CH_2)_5CH_3$	53	6	$C(OH)(CH_3)_2$	65
2	$C(CH_3)_3$	40	7	CH_2NH_2	not determined
3	C_6H_5	71	8	CH_2NEt_2	42
4	$(CH_2)_3Cl$	61	9	$CH_2NHCONHC(CH_3)_3$	52
5	$(CH_2)_3OH$	55	10	$CH_2NHCOOC(CH_3)_3$	55

Figure 5.37: Palladium-catalyzed synthesis of 2-substituted benzofurans on solid phase.

5.5.2.4.1 Synthesis of dihydrobenzofuran derivatives

A samarium diiodide-mediated mild and efficient synthetic route for the benzofuran derivatives (**190** and **191**) via intramolecular radical reaction of aryl iodides (**189**) and then the TFA-induced cleavage of the target molecule from the polyethylene glycol (PEG)-grafted resin were proposed by Du and Armstrong [95] in 1997 (Figure 5.38).

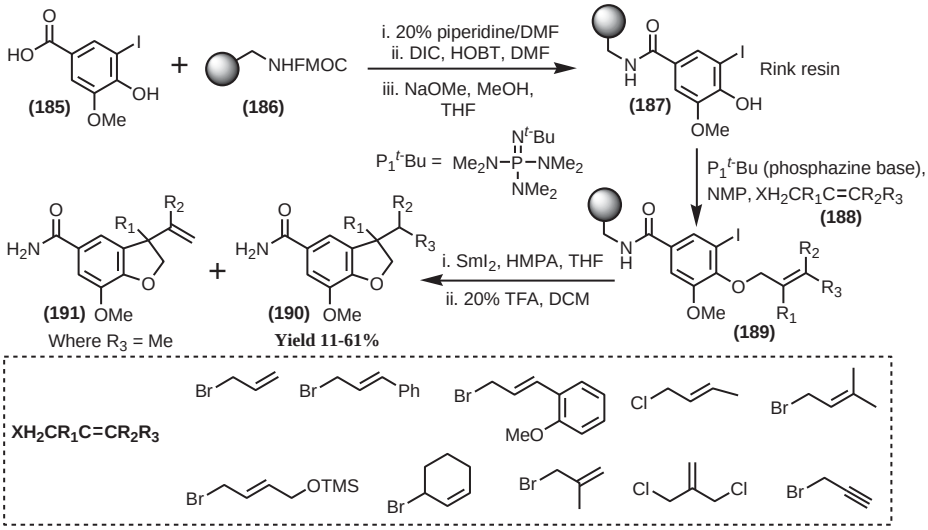


Figure 5.38: Solid-supported synthesis of benzofuran derivatives.

Depending on the substitution in the starting alkene (**188**), the unsaturated by-products were observed in some cases as minor components with the desired compound. On the other hand, Sm^{3+} by-products can be easily removed by the employed PS or PEG-grafted

resins. This coupling method worked well on solid support and provided diverse heterocycles (**190** and **191**) in respectable yields.

5.5.2.4.2 Synthesis of 3-substituted dihydrobenzofuran

Routledge et al. [96] introduced a completely different approach for the formation of dihydrobenzofuran (**195**) using classical radical-generating conditions by the cyclization of bromoalkene derivatives (**194**) on solid supports (Figure 5.39). The reaction only proceeded on TentaGel resin beads (**193**) in the presence of tributyltin hydride with catalytic amounts of α,α′-azobis(isobutyronitrile) and released the desired products in reasonable yields. The analogous reaction has several advantages such as no by-products are detected at high concentrations of Bu_3SnH and it can be easily washed away before cleavage of the target compound from the PEG-grafted resin.

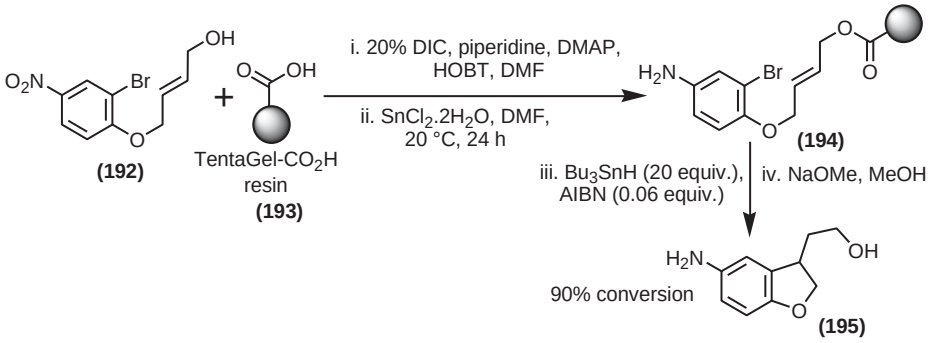
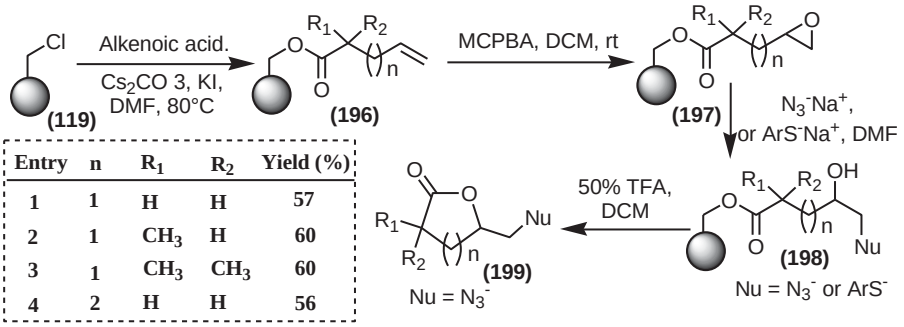


Figure 5.39: Synthesis of furan rings on TentaGel resin beads.

5.5.2.5 Synthesis of functionalized γ- and δ-lactones

In the past few years, application of epoxides in organic synthesis to generate new carbon–carbon or carbon–heteroatom bonds via nucleophilic ring opening has been extensively studied. Knowing the importance, Hetet et al. [97] developed polymer-supported epoxides (**197**) from alkenoic acid derivatives (**196**) and effectively applied as suitable precursors for functionalized γ- and δ-lactones (**199**) (Figure 5.40). Solid-phase epoxidation of resin-bound olefins (**196**), synthesized from alkenoic acids and subsequent ring-opening reactions using sodium azide or thiophenols, afforded secondary alcohols (**198**) which underwent acid-catalyzed lactonization followed by the release from polymeric support reagents gives highly pure functionalized γ- and δ-lactones (**199**) in good yields. The easily accessible chemicals are compatible with this reaction sequence and display their potential in combinatorial synthesis.

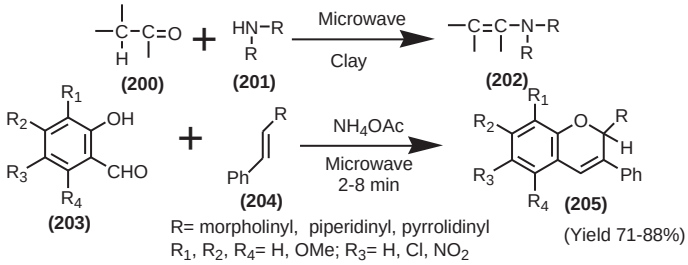


Entry	n	R_1	R_2	Yield (%)
1	1	H	H	57
2	1	CH_3	H	60
3	1	CH_3	CH_3	60
4	2	H	H	56

Figure 5.40: Polymer-supported synthesis of functionalized γ- and δ-lactones.

5.5.2.6 Synthesis of 2-amino-substituted isoflav-3-enes

Varma and Dahiya [98] developed a clay-supported one-pot, expeditious and solvent-free protocol under microwave irradiation via in-situ-generated enamines (**202**) from the mixture of phenyl acetaldehyde (**200**) and morpholine (**201**) and simultaneously their reactions with salicylaldehydes (**203**) to produce pure 2-morpholinoisoflav-3-enes (**205**) in 80% yield (Figure 5.41). The advantage of this methodology is that this environmentally friendly approach offered enamines without necessity of the large excess of organic solvents for the azeotropic removal of water molecule and also does not require any activation of the catalyst.

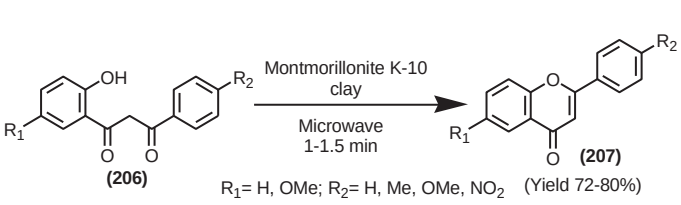


R	R_1	R_2	R_3	R_4	Yield (%)	R	R_1	R_2	R_3	R_4	Yield (%)
morpholinyl	H	H	H	H	80	piperidinyl	H	H	Cl	H	88
morpholinyl	H	H	Cl	H	81	piperidinyl	H	H	NO_2	H	85
morpholinyl	H	H	NO_2	H	82	piperidinyl	H	H	H	H	71
morpholinyl	OMe	H	H	H	73	piperidinyl	H	H	Cl	H	79
morpholinyl	H	OMe	H	OMe	75	piperidinyl	H	H	NO_2	H	83
piperidinyl	H	H	H	H	72						

Figure 5.41: Clay-supported synthesis of 2-amino-substituted isoflav-3-enes under microwave irradiation.

5.5.2.7 Synthesis of flavones

In the same year, a manipulatively simple and mild solid-state method for the formation of flavones (**207**) via dehydrative cyclization of *o*-hydroxydibenzoyl methanes (**206**) on a clay surface under microwaves has been shown by Varma's group (Figure 5.42) [99]. They developed a microwave-irradiated procedure for flavone derivatives (**207**) using montmorillonite K-10 clay as an adsorbent and delivered exclusively cyclized flavones which are easily extractable in good yields of up to 80% from the support catalyst.



R_1	R_2	Yield (%)
H	H	75
H	CH_3	77
H	OMe	76
H	NO2	78
OMe	H	73
OMe	CH_3	80
OMe	OMe	72

Figure 5.42: Formation of flavones on montmorillonite K-10 clay under microwaves.

5.5.3 Sulfur-containing heterocycles

5.5.3.1 Synthesis of substituted thiophenes

In 1997, Stephensen and Zaragoza [100] disclosed a new, robust synthetic procedure for the solid-phase preparation of thiophene molecule (**211**) (Figure 5.43). They applied resin-bounded amine (**208**) appended to isothiocyanates (**209**) or their synthetic equivalents along with base (DBU or amines) to afford the desired product via the subsequent cleavage from the support reagents. These bioactive and pharmaceutically useful thiophene derivatives (**211**) were achieved with very satisfactory results with

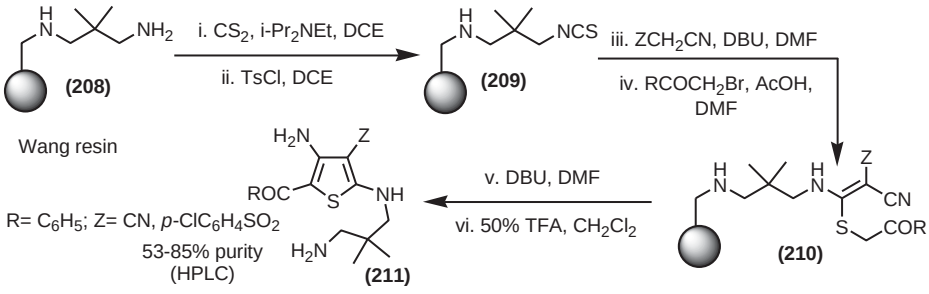


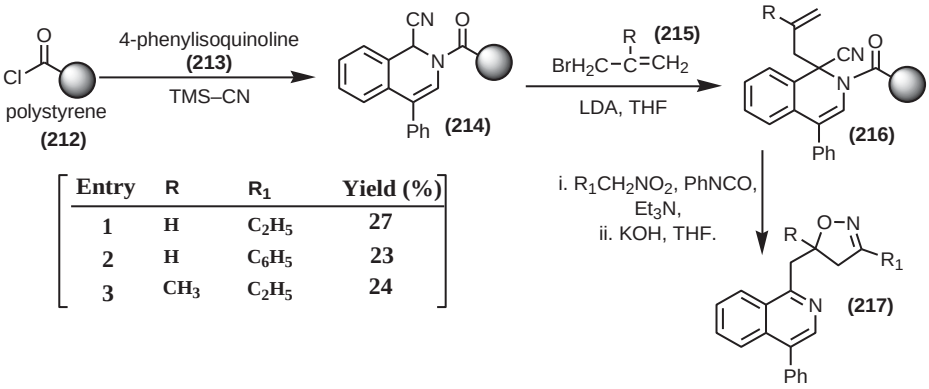
Figure 5.43: Solid-state synthesis of substituted thiophenes from resin-bound intermediates.

no major by-products from the easily available starting materials at ambient temperature. This reaction sequence permits the quick accelerating numerous bioactive compounds and is also very useful for standard peptide synthesizers.

5.5.4 Solid-phase syntheses of miscellaneous heterocycle

5.5.4.1 Synthesis of isoquinoline- and isoxazoline-containing heterocycles

In 1996, Lorsbach et al. [101] prepared novel isoquinoline–isoxazoline heterocycles (**217**) using traceless solid-phase approach by the way of 1,3-dipolar [3 + 2] cycloaddition reactions (Figure 5.44). This solid-supported synthesis is a well-suited application for the discovery of combinatorial programs.



Entry	R	R_1	Yield (%)
1	H	C_2H_5	27
2	H	C_6H_5	23
3	CH_3	C_2H_5	24

Figure 5.44: Synthesis of isoquinoline and isoxazoline-containing heterocycles on solid surface.

5.5.4.2 Synthesis of benzoxazoles

A mild and high productive dehydrative cyclization of solid-supported 2-amidophenol derivatives (**219**) afforded the desired benzoxazole (**220**) in THF at room temperature by treatment of triphenylphosphine and diethyl azodicarboxylate (Figure 5.45) [102]. Very convenient methodology offered the corresponding product after release from the resin via the Mitsunobu reaction conditions. This synthetic procedure has been successfully applied for the formation of combinatorial library with satisfactory results.

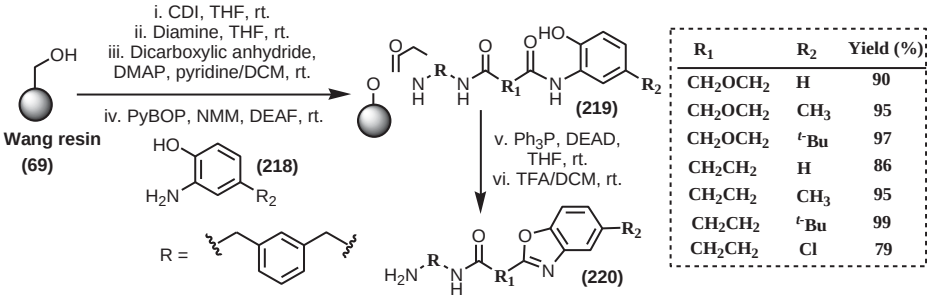


Figure 5.45: Solid-phase synthesis of benzoxazoles by applying the Mitsunobu reaction.

5.5.4.3 Syntheses of cyclic peptides with endocyclic biaryl ether bonds

Over the years, a wide range of easily available heteroatomic nucleophiles were employed for the functionalization of electron-deficient aromatic rings based on S_NAr approach. The laboratory of Burgess [103] reported a rapid and efficient solid-phase protocol for the formation of cyclic peptides, linked by the endocyclic biaryl ether bonds (**222**) via the protection/deprotection of tyrosine side chains (**221**) and afterward S_NAr macrocyclization reactions on a support material (Figure 5.46). This working methodology is very useful to cyclize the starting materials with complex skeleton and generate corresponding compounds in relatively shorter times with reasonable yields (59% for 10 steps).

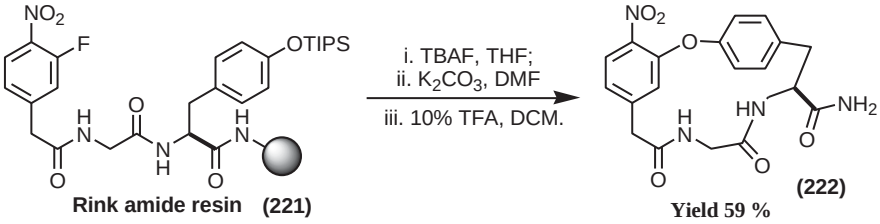


Figure 5.46: Syntheses of cyclic peptides with endocyclic biarylether bonds on solid phase.

5.5.4.4 Synthesis of isoxazolidines

Hinzen and Ley [104] constructed isoxazolidine scaffold (**227**), where one-pot selective oxidations of secondary hydroxylamines (**223**) formed nitrone derivatives (**225**) by PSP (**224**) in 1998 (Figure 5.47). This nitrone combined with electron-deficient dipolarophiles, for instance, acrylonitrile, methyl vinyl ketone and methyl acrylate (**226**) afforded the corresponding isoxazolidine derivatives (**227**) in good to excellent (55–91%)

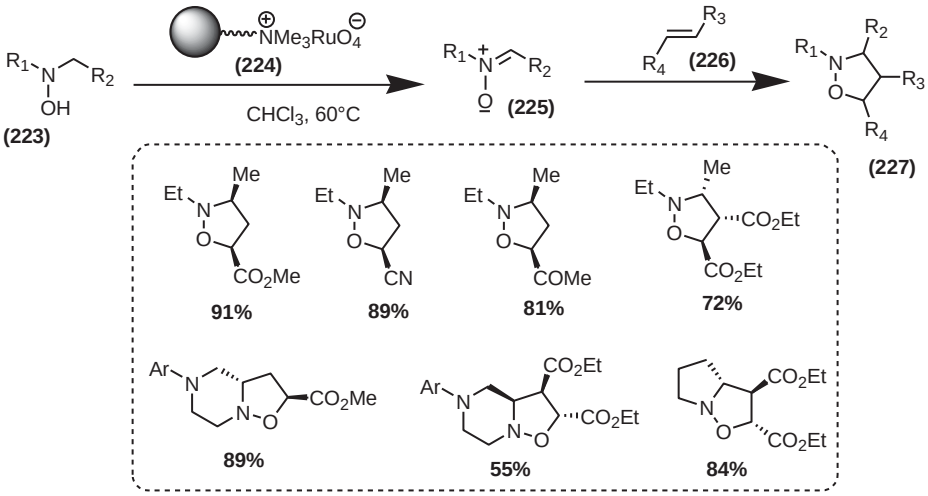


Figure 5.47: Preparation of isoxazolidines using polymer-supported perruthenate.

yields. Here, the process is very useful for automated synthesis and offered various opportunities for the development of chemical libraries.

5.5.4.5 Synthesis of benzoxazinone

A solution-phase five-step synthetic procedure for benzoxazinone derivatives (**234**) is achieved with combinations of molecular reactivity and recognition (CMR/R) purification technique to construct new C–O bond (**10**) by Parlow and Flynn [105] (Figure 5.48). The multistep synthesis produces the target molecule in excellent purities and yields. In addition, the final compounds along with all intermediates were purified in robotic laboratory block apparatus through the postreaction process by introducing reactant as well as sequestering resins and in situ labeling by the reaction-quenching resins and sequestration-enabling reagents.

5.5.4.6 Synthesis of peptidosulfonamides

SPS of peptidosulfonamides (**239**) was presented by de Bont et al. [106] by employing a TentaGel® resin (**235**) (Figure 5.49) in 1996.

The sulfonamide derivatives (**237**) oxidized by OsO_4/NMMO give better results than that of tetra-butylammonium oxone® (**238**) because in the latter condition partial deprotection of Boc-protected dipeptides took place. Further, the acid-catalyzed cyclization of compound (**238**) and concurrent cleavage from resin by Et_3N delivered cyclic peptidosulfonamides which increased the potential molecular diversity of reaction methodology.

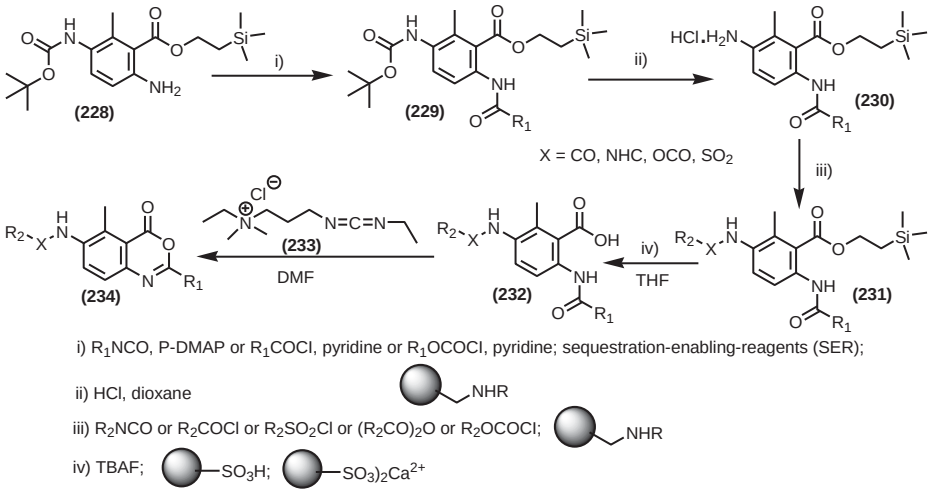


Figure 5.48: Construction of benzoxazinone library on solid phase.

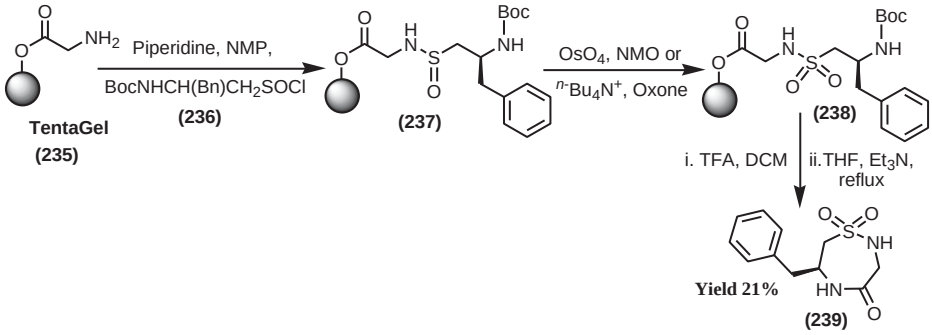


Figure 5.49: Solid-phase formation of peptidosulfonamides.

5.5.4.7 Synthesis of piperidino-thiomorpholine

The earlier literature survey indicated that a polymer-supported material or other solid sequestering reagents might be used to construct a library of piperidino-thiomorpholine (**241**). In 1998, Habermann et al. [107] demonstrated a new clean multistep procedure to prepare a library of piperidino-thiomorpholine derivatives (**241**) and their corresponding sulfones starting from 4-piperidone (**240**) (Figure 5.50). The present catalytic strategy afforded a novel high-yielding approach applying polymer-supported material and solid sequestering reagents in synthetic sequences with no need of chromatographic separation.

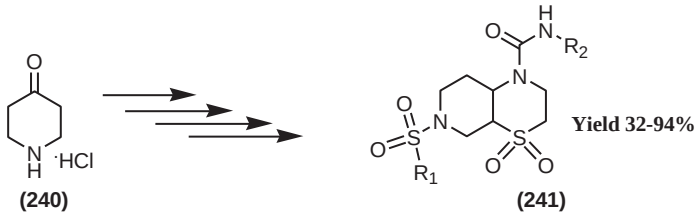


Figure 5.50: Preparation of a piperidino-thiomorpholine library using polymeric reagents.

5.5.4.8 Synthesis of di[benzo(*d*)thiazol-3(2H)-yl]methane

Very recently, our group demonstrated a novel one-pot MCR strategy on solid phase. Here, we executed a reaction strategy employing difunctionalized 2-aminothiophenol which contains both thiol and amine groups (**242**) in the same moiety (2 mmol) with 37–41% aqueous solution of formaldehyde (**243**) (3.5 mmol) (Figure 5.51) [108] to afford di[benzo(*d*)thiazol-3(2H)-yl]methane derivatives (**244**) on the solid surface of neutral Al_2O_3 in 84% yield.

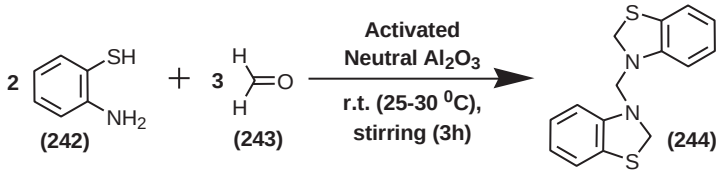
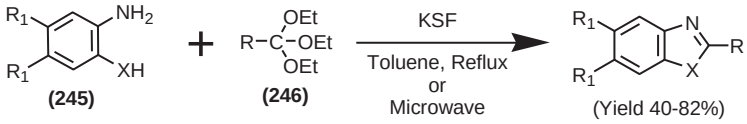


Figure 5.51: Synthesis of di[benzo(*d*)thiazol-3(2H)-yl]methane derivatives on the solid surface of activated neutral Al_2O_3.

5.5.4.9 Synthesis of benzirnidazoles and 1,3-benzothiazole

Villemin et al. [109] reported KSF clay-catalyzed completely different two synthetic routes, that is, under reflux in toluene or solvent-free conditions under microwave irradiation for the condensation of orthoesters (**246**) with *o*-substituted aminoaromatics (**245**) into heterocycles (Figure 5.52). In addition, structurally different *o*-substituted aminoaromatics gave the product (**247**) under nitrogen atmosphere in good yields of up to 92%. Moreover, starting from *o*-diaminobenzene derivatives provided very useful benzirnidazole heterocycles. Similarly, the reaction of 2-arninophenol or 2-aminothiophenol generated the corresponding 1,3-benzoxazole or 1,3-benzothiazole derivatives under the same reaction condition.



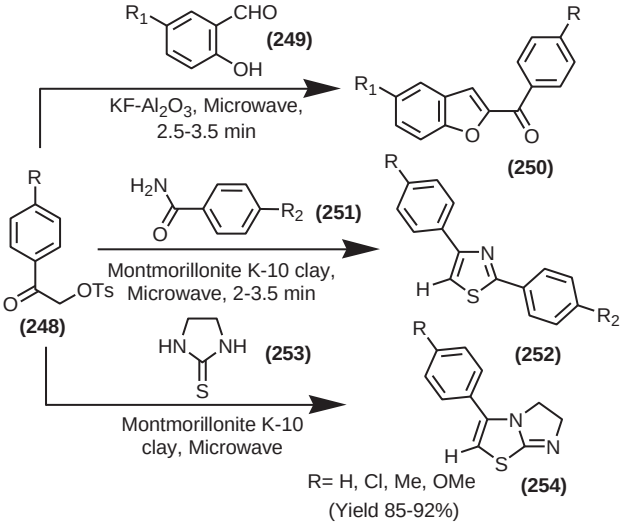
Entry	R	R_1	X	Yield (%)	Entry	R	R_1	X	Yield (%)
1	H	H	NH	74	5	H	H	O	55
2	CH_3	H	NH	79	6	CH_3	H	O	76
3	H	3,4-Me_2	NH	85	7	H	H	S	74
4	CH_3	3,4-Me_2	NH	92	8	CH_3	H	S	70

Reaction under microwave irradiation (6OW. resonance cavity)

Figure 5.52: Clay-supported synthesis of benzirnidazoles, 1,3-benzoxazole and 1,3-benzothiazole.

5.5.4.10 Synthesis of 2-aroylbenzo[b]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-b][1,3]thiazoles

In 1998, Varma et al. [110] developed an expeditious solvent-free synthesis of 2-aroylbenzo[b]furans, thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-*b*][1, 3]thiazoles (**250**, **252** and **254**) from readily obtainable α-tosyloxyketones (**248**) catalyzed by mineral



R	R_1	Yield (%)
H	H	94
Cl	H	94
Me	H	91
OMe	H	89
H	Cl	95
Cl	Cl	92
Me	Cl	96
OMe	Cl	89
R	**R_2**	**Yield (%)**
H	Cl	90
H	OMe	91
Cl	Cl	94
Cl	OMe	96
Me	Cl	92
Me	OMe	92
OMe	Cl	90
OMe	OMe	88

Figure 5.53: Solid-supported synthesis of 2-aroylbenzo[b]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-b][1,3]thiazoles.

oxides under clean energy source of microwave irradiation (Figure 5.53). Specifically, 2-aroylbenzo[*b*]furans (**250**) are delightedly achieved from the reaction mixture of salicylaldehydes (**249**) and α-tosyloxyketones (**248**) in the presence of solid potassium fluoride-doped alumina (KF-Al_2O_3) catalyst. Whereas montmorillonite K-10 clay affords 1,3-thiazoles (**252**) from the reaction of thioamides (**253**) with α-tosyloxyketones (**248**). In the same way, mixture of ethylene thiourea (**251**) and α-tosyloxyketones (**248**) deliver bridgehead nitrogen heterocycles (**254**) in excellent yields.

5.6 Conclusions

Solid-phase platforms have been in use for the construction of heterocyclic and carbocyclic bioactive core structures for decades and have successfully established to be advantageous for a diverse range of transformations to synthetic organic chemists. In this chapter, we summarized a variety of solid-state protocols for the generation of carbocycles and N/O/S-containing three- to seven-membered heterocycles and also their fused analogues from the respective starting materials on the surface of the solid materials. The reasons behind adopting solid-phase organic reactions are environmental friendliness, mild reaction conditions, use of sustainable and traceless solid materials, easy workup procedure, recyclability of the support material or catalyst and selective synthesis of the target compound. Moreover, this platform offered a desired molecule in faster rates, preserving the product purity and with higher yields in comparison to a conventional technique. The examples listed in this chapter are more helpful for the development of newer SPS of bioactive complex molecules to synthetic chemists in future.

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Chapter 6
Nonconventional solvents for the isolation of natural products

6.1 Introduction

Daily life is connected to natural products (NPs), including food, clothes, beverages, fibers and fuel along with fine chemicals, such as pharmaceuticals and cosmetics [1]. These products need comprehensive processing from very large to small scale including cellulose, paper production to medicines and fragrances. Interestingly, all types of regulations for these processes as well as solvents are required [2]. Currently, much attention has been provided to the substitution of conventional organic solvents by using nonconventional solvents to reduce toxic waste and enhance selectivity and/or extraction efficiency. The design of green along with sustainable extraction methods of secondary metabolites is presently a hot research topic in the multidisciplinary field of applied chemistry, technology and biological sciences [3]. The isolation of high-value bioactive NPs including polyphenols, pigments, proteins and dietary fibers involving nonconventional solvents is now broadly investigated to protect Mother Nature [4–12]. Green solvents are eco-friendly solvents that have a profound role in extracting active chemical components from raw materials (plants). NPs and their structural analogues comprise historically a key role in pharmacotherapy, particularly for cancer and infectious diseases [13]. Hence, this chapter concentrates on a brief introduction, features and applications of nonconventional solvents for the isolation of NPs as an alternative media. This chapter provides an extensive application of nonconventional solvents such as subcritical water (SW), ionic liquids (ILs), bio-based solvents and liquefied dimethyl ether and structures of isolated NPs using nonconventional solvents in a brilliant manner.

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6.2 Subcritical water

Subcritical water extraction (SWE) has become an accessible green extraction and separation technique for several types of compounds which are found in diverse types of samples and matrices, including food, environmental and botanical sources [14]. It is a green method based on the application of water as an extractant (extraction solvent) in which temperatures exist between 100 and 374 °C with high pressure to maintain the liquid state [15, 16]. Currently, SWE is an efficient method to extract chemicals selectively having various functional groups in secondary metabolites such as flavonoids, terpenoids, carbohydrates, essential oils, vitamins, organic acids and polyphenolic compounds [14–17]. SWE is a promising alternative compared to the traditional method because it is a nontoxic, inexpensive, easily available, nonflammable and eco-friendly technique [14, 15]. Moreover, this rapid extraction technique avoids the loss along with the degradation of volatile compounds which are found in many herbal materials [18, 19].

6.2.1 Features of subcritical water

Under ambient conditions, water is very polar along with a weak solvent for many organic molecules [20]. Its polarity comprises a dramatic effect with increasing temperature; pressure is employed to retain water in a liquid state. The polarity of SW can be greatly reduced by an increase in temperature which is an unparalleled feature of it. Notably, water becomes less polar with increasing temperature. The polarity of SW is determined by the value of the dielectric constant. Interestingly, when water is heated above 100 °C, its dielectric constant reduces and SW can behave similarly to organic solvents [21]. For example, at 214 °C, the dielectric constant of water (H_2O) obeyed the identical value as methanol (CH_3OH) at room temperature, and H_2O at 295 °C can act similarly to simplest ketone acetone (CH_3COCH_3). It provides SW with an eco-friendly and sustainable extraction fluid employed for a diversity of organic compounds. It is interesting to be noted that optimum conditions for SWE of a supplied substance rely on temperature, pressure, flow rate, pH, water characteristics and extraction kinetics, along with the analyte's chemical structure [22–24].

6.2.2 Applications of subcritical water for the isolation of natural products as a green solvent

6.2.2.1 Alkaloids

In 2020, the nutritional and bioactive content of banana (Musaceae) together with red beetroot (*Beta vulgaris*) peels was assessed by Komes and coworkers [25]. Standard

method of Association of Official Analytical Chemists was applied for the determination of basic macrocomponent composition along with innovative extraction techniques. It includes microwave- and ultrasound-promoted extraction, and SWE was used for the extraction of bioactive compounds including alkaloids. It has been observed that the extract comprises a maximum total reddish to violet betacyanin content (9.81 mg betanin g^{-1} dmb), and the U30 extract contains the maximum betaxanthin content (8.61 mg vulgaxanthin I g^{-1} dmb), as well as extracts of banana peel include highest dopamine content (12.63 mg g^{-1} dmb).

Food industries create huge amounts of residues. Jokíc et al. [26] isolated important compounds from the cocoa shell (normally regarded as "waste") involving SWE as a sustainable green separation process in 2018. Different concentrations of theobromine, theophylline, caffeine and epicatechin were ascertained in the extracts derived from SW, depending on the applied extraction conditions.

Liu and coworkers [27] described an effective and eco-friendly extraction and analysis strategy for the ascertainment of alkaloids such as cytisine, sophocarpine, matrine (**1**), sophoridine, together with oxymatrine in *Sophora flavescens* by applying SWE along with capillary electrophoresis. SWE displayed the maximum extraction efficiency for the yield of the total alkaloid. SWE includes some merits over traditional extraction methods including a short extraction time, no requirement for organic volatile solvent consumption as well as improved extraction efficiency.

6.2.2.2 Flavonoids

Chuna et al. [28] reported SWE of isoflavones (chemoprotective) from soybean byproducts with minimal degradation by applying response surface methodology (RSM) for the standardization of pressure, temperature, along with solid extractant volume in 2019. RSM of the extraction variables with SW (extraction time 5 min) suggested that the optimized conditions would be $P = 3.98$ MPa, $T = 146.23$ °C and $\alpha = 20$ mg (solid) mL (extractant)$^{-1}$. It has also been evident from detailed kinetics modeling that the optimum extraction time was 213.5 ± 8.7 min.

The multitalented technology is the SW hydrolysis with different merits in the processing of important products from biomass [29]. Chun and coworkers [30] demonstrated that this hydrolysis with controlled prolonged reaction time displayed a prominent effect on the composition of bioactive molecules in the hydrolysates. The experimental result indicated that after 215 min, there was a 55% improvement in total phenolic contents from the initial reaction time, reflecting the maximum recovery. Besides, isoflavones, genistein and daidzein were improved by up to 6.5- and 9-folds, from 5 to 245 min, respectively.

In 2018, SW was applied by Wang et al. [31] for the extraction of isoflavones namely puerarin, 3′-methoxypuerarin, daidzein and daidzin from *Pueraria lobata* firstly; the total isoflavones were investigated by employing SW as a green solvent.

The extraction yields of puerarin, 3′-methoxypuerarin and daidzin gained the highest at extraction temperatures of 120, 140 and 200 °C, respectively, having an extraction time of 45 min together with a liquid/solid ratio of 1:20. RSM (extraction time of 45 min, solid/liquid ratio of 1:15 along with extraction temperature of 120 °C) provided the highest extraction yields of the total secondary metabolite isoflavones.

The extraction condition of the SW solvent together with the structure of the flavonoid affected greatly the extraction of a flavonoid, the polyphenolic compound that is frequently appended to nutraceuticals as antioxidants due to bioavailability [32]. An excellent solvent is SW (about 10 MPa) for extracting nonpolar flavonoids by altering the temperature-dependent dielectric constant. Chung and coworkers [33] ascertained the optimum conditions for SWE, including time and temperature, for extracting flavonoids from eight plants, along with their dependence on the chemical structure of flavonoids such as the polarity of side chains and the existence of sugar and double bonds. At lower temperatures, flavonoids containing an OH side chain such as quercetin (**2**) at 170 °C/10 min were optimally extracted compared to O–CH_3, namely, isorhamnetin at 190 °C/15 min and H such as kaempferol (**3**) at 190 °C/15 min side chains. The glycoside forms comprising sugar, namely, quercitrin (110 °C/5 min), isoquercitrin (150 °C/15 min) and spiraeoside (150 °C/15 min) included lower optimal temperatures compared to the less polar aglycones (170 °C/10 min and 190 °C/15 min). In SWE, apigenin (**4**) bearing double bonds was extracted well at a higher temperature (190 °C/15 min) compared to naringenin (**5**) (170 °C/15 min). It has also been also observed that the optimum temperature was greater for a tetrahydroxyflavone luteolin (**6**) from carrots (190 °C/15 min) compared to the plant flavonol quercetin (**2**) (170 °C/15 min).

6.2.2.3 Lignans

A perennial herb *Sinopodophyllum hexandrum* was found efficient in rheumatism treatment and blood activation, along with dehumidification as a valuable traditional Tibetan medicine [34]. Secondary metabolite lignans occur in the roots of this herb in large amounts. Chen and coworkers [35] reported a green extraction of an aryltetralin-type lignan podophyllotoxin (**7**) from this plant using optimized SWE amalgamated with macroporous resin enrichment in 2018. RSM was performed to optimize the SWE conditions for a better extraction yield. An extraction temperature of 180 °C, extraction pressure of 4 MPa, SW flow rate of 2.5 mL min^{-1} and extraction solvent to feed ratio of 18 mL g^{-1} were the maximum extraction efficiencies in this study. The content of podophyllotoxin which is broadly employed in combination therapy of cancer in the final desired product reached 61.5% than that of 8.3% in the crude extract derived by SWE. Moreover, a betterment of 74.6% was established.

Sesame (*Sesamum indicum* L.) seeds consist of a major array of lignans and phenolic molecules with significant biological activities. An optimized methodology to derive these seed components was disclosed by Maestri and coworkers [36] involving

water and ethanol at high temperature and pressure conditions. The highest concentrations of lignans and other phytochemicals were gained at 220 °C extraction temperature and 8 MPa pressure, employing 63.5% ethanol as a cosolvent.

6.2.2.4 Steroids

For thousands of years, ashwagandha (*Withania somnifera* L. Dunal) is an important medicinal herb that has been extensively employed in Ayurvedic along with Chinese medicine and belongs to the Solanaceae family, broadly called Indian ginseng that includes several medicinal properties [37]. Kai and coworkers [38] employed SWE of withanosides and withanolides (**8–20**, Figure 6.1) from this plant in 2019, and SWE was used to analyze the plant's bioactive compounds at varying temperatures (100–200 °C) and extraction time (10–30 min). The plant extract employing SWE displayed high concentrations of withanolide, withanoside and steroidal lactone molecules with potent biological properties. This suggested that the SWE at 160 °C for 20 min could be employed as a novel methodology for extraction of bioactive molecules from this medicinal plant, instead of traditional methods such as maceration, Soxhlet extraction and microwave-assisted extraction (MAE) since these are more time-consuming and needed hazardous solvents. The SWE together with a steroidal lactone withaferin A displayed a potent reduction in cell viability of cervical cancer (HeLa) cells, having half-maximal inhibitory concentration (IC_{50}) values of 10 mg mL^{-1} and 8.5 μM mL^{-1}, respectively.

The main steroid hormone in insects is ecdysone, which is the main steroid hormone in insects that comprises important roles in coordinating developmental transitions including larval molting along with metamorphosis via its active metabolite 20-hydroxyecdysone [39]. Meireles and coworkers [40] reported the extraction of beta-ecdysone using SWE in 2017. Brazilian ginseng roots (BGRs) and aerial parts produced beta-ecdysone using SWE aiming to apply the whole plant in a biorefinery approach. BGRs displayed a beta-ecdysone content of up to 0.7 g/100 g of extract as well as aerial parts provided 0.3 g/100 g of extract.

6.2.2.5 Terpenoids

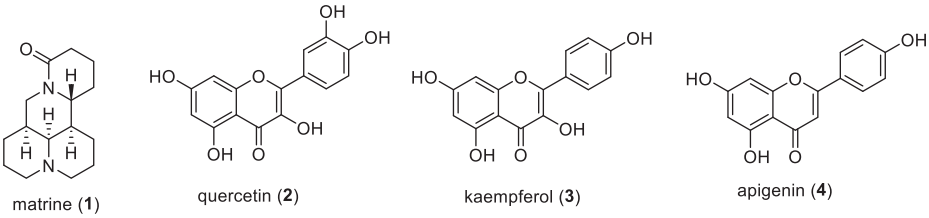
Inula racemosa has long been employed for the treatment of bacterial infections, inflammation and chronic gastritis [41]. Phytochemical investigation of *I. racemosa* disclosed the existence of higher amounts of sesquiterpene lactones [42]. Recently, Chen and coworkers [43] applied the green technique of SWE for the effective extraction of sesquiterpene lactones from *I. racemosa*. The investigators examined several parameters including temperature (190 °C), extraction time (45 min) and SW flow rate (3.0 mL min^{-1}) for the recovery of desired compounds under optimal conditions. Four sesquiterpene lactone isomers

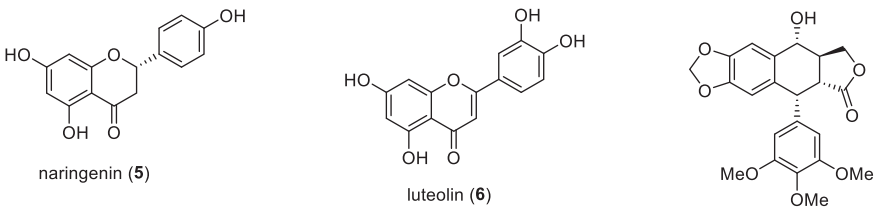
such as igalan, alantolactone, isoalantolactone *etc* were separated by *prep*-HPLC (high-performance liquid chromatography) from the SWE extract.

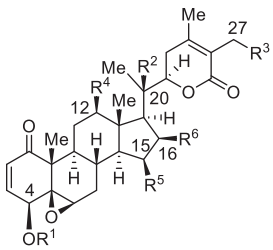
The multiflorane triterpene ester group of compounds includes 3,29-dibenzoylkarounidiol. It is difficult to dissolve in water but dissolves simply in lipophilic organic solvents [44]. Hence, organic solvents such as methanol, ether, dichloromethane and trichloromethane are employed to extract and separate 3,29-dibenzoylkarounidiol from *Semen richonsanthis* (the seeds of *Trichosanthes kirilowii*) frequently [45]. However, most of these organic solvents are poisonous and volatile as well as they require a long extraction time, and the yields are usually low. Besides, saponification is needed generally. So, more efficient and greener routes are essential for the extraction of 3,29-dibenzoylkarounidiol. Xue and coworkers [46] applied green SW technology for the extraction of 3,29-dibenzoylkarounidiol from *Semen richonsanthis* in 2019 [46]. In this green technique, the optimum conditions of 3,29-dibenzoylkarounidiol (0.102 ± 0.004%) were achieved at 130 °C, 10 min and 4.0 mL water loading. Compared with heating reflux and ultrasonic extraction, the three extracts were evaluated by antioxidant property against DPPH (2,2-diphenyl-1-picrylhydrazyl) as well as cytotoxicity toward HeLa cells. The experimental results disclosed that the activities of SW extracts are more encouraging compared to the other extracts and can be safely employed in nutraceuticals along with pharmaceutical products.

Stevia rebaudiana Bertoni leaves have attracted great attention as a noncaloric sweetener called steviol glycosides over the last two decades, and its leaf extracts are valuable sources of bioactive compounds including diterpenic glycosides, carotenoids, chlorophylls, ascorbic acid and polyphenols with antioxidant and antimicrobial activities [47, 48]. Putnik and coworkers [49] developed an effective and multitalented approach for the green recovery of diterpene steviol glycosides from *Stevia rebaudiana* Bertoni leaves through pressurized hot water extraction in 2018. Herein, the main parameter for the extraction is temperature; the most recoveries of all bioactive molecules (excluding carotenoids) were at 160 °C. The experimental results revealed that higher temperatures and cycles, along with static extraction time extracted better levels of stevioside and rebaudioside A, a steviol glycoside that is 240 times sweeter compared to sugar.

Hedyotis diffusa Willd. is a type of herb employed in traditional Chinese medicine and it was also used to treat several types of cancer in combination with other herbal medicines [50]. Phytochemical investigations of this plant revealed a variety of active components such as flavonoids, steroids and triterpene acids namely ursolic acid [51]. A pentacyclic ursolic acid displays various biological activities including antitumor, anti-HIV, anti-inflammatory and antidiabetic [52, 53]. Lei and coworkers [54] developed an efficient and environmentally sound extraction method to isolate triterpenoid ursolic acid from *Hedyotis diffusa* using SWE in 2017. RSM was successfully implemented for the optimization of ursolic acid yield, and the maximum yield of this pentacyclic triterpenoid was 6.45 mg g^{-1} material. SWE was superior than that of ultrasonic extraction, reflux extraction and MAE since it was eco-friendly, cost-saving and time-saving.







$R^1 = R^3 = R^4 = R^5 = R^6 = H$, $R^2 = OH$, **8**
$R^1 = R^2 = R^4 = R^5 = R^6 = H$, $R^3 = OH$, **9**
$R^1 = R^2 = R^4 = R^5 = H$, $R^3 = R^6 = OH$, **10**
$R^1 = R^2 = R^5 = R^6 = H$, $R^3 = R^4 = OH$, **11**
$R^1 = Ac$, $R^2 = R^4 = R^5 = H$, $R^3 = R^6 = OAc$, **12**
$R^1 = R^2 = R^4 = R^6 = H$, $R^3 = R^5 = OH$, **13**
$R^1 = Ac$, $R^2 = OH$, $R^3 = R^4 = R^5$, $R^6 = H$, **14**
$R^1 = Ac$, $R^2 = R^4 = R^5 = R^6 = H$, $R^3 = OAc$, **15**
$R^1 = R^3 = R^4 = R^5 = H$, R^2, $R^6 = OH$, **16**
$R^1 = Ac$, $R^2 = R^5 = R^6 = H$, $R^3 = R^4 = OAc$, **17**
$R^1 = Ac$, $R^2 = OH$, $R^3 = R^4 = R^5 = H$, $R^6 = OAc$, **18**
$R^1 = R^3 = R^4 = R^6 = H$, R^2, $R^5 = OH$, **19**
$R^1 = Ac$, $R^2 = OH$, $R^3 = R^4 = R^6 = H$, $R^5 = OAc$, **20**

Figure 6.1: The structures of various natural products isolated using subcritical water.

6.3 Ionic liquid

Choi and Verpoorte [55] revealed a statement like “What you see is what you extract” in pointing out that solvent extraction is a vital step in the preparation of phytochemical samples. However, we can generalize it to food, cosmetic, perfumery and pharmaceutical production by extracting aromatics, colors, antioxidants, fats and oils, and fine chemicals. Volatile organic compounds used in extraction are usually derived from nonrenewable resources, primarily petroleum, and are suspected to be toxic to humans and the environment. As a replacement for organic solvents (high volatility,

flammability and toxicity), ILs have gained significant interest and growing demand due to the aversion toward green solvents [56]. When organic cations and organic or inorganic anions are combined, a class of nonmolecular solvents known as ILs is created that melts below 100 °C [57].

The green role of ILs has been widely contested due to their low biocompatibility and biodegradability during the past few years [58–60]. Deep eutectic solvents (DESs), a green substitute for ILs, have been gradually appearing since 2004 to address this issue [59]. In addition, they differ from ILs in a few ways, most notably in how simple and inexpensive it is to store and synthesize them [61].

ILs made of bioderived components offer the added benefit in this regard and are excellent options for solvents that are sustainable and environmentally friendly. In order to extract along with promising components of purification from herbal medicines, numerous studies had used IL-based methods.

6.3.1 Features of ionic liquid

In general, several comparison of investigations clearly showed that ILs were superior extractants than typical molecular solvents (such as water, methanol, ethanol, dichloromethane, chloroform and toluene). Since it is well known that the type of anion has a significant impact on properties like polarity, viscosity, density and surface tension for a group of ILs based on the same cation, many studies began by performing a comparison of the extraction abilities of various anions, primarily with $[C_4C_1im]C$ as the cation [62]. There has been an assessment of a wide variety of anions that differ in their complexity and the possibilities for noncovalent interactions. According to these experiments, Br^- anion is preferred over the other anion compounds, except in some instances. Anions like Cl^-, $[BF_4]^-$, $[PF_6]^-$, $[OTs]^-$ and $[C_1CO_2]^-$ were nevertheless successful as well. However, Cl^- and Br^- were chosen because of their superior overall extraction efficiency, in situations where similar compounds need to be extracted, or for more practical or cost-effective reasons. In some cases, $[C_1CO_2]$ and [OTs] anions demonstrated comparable or better extraction ability than Cl^- and Br^-. Among the anions used, saccharinate $[Sac]^-$ and acesulfamate $[Ace]^-$ showed improved performance over Cl^- and Br^-. As a result of the characteristics of anions selected, it can be concluded that hydrogen bonding [63] is the most important factor influencing extraction, but there is also a possibility of synergistic effects due to π–π and n–π interactions offered by some aromatic rings containing anions. It is important to take care of the results obtained with ILs containing $[BF_4]^-$ and $[PF_6]^-$ anions; they are prone to hydrolyzing, particularly at high temperatures, and generating hydrogen fluoride, which for sure decreases the system's initial pH value [64]. In addition, the IL concentration plays a very important role from an application point of view. It is also possible to obtain an incomplete extraction by using ILs in a low concentration, while the use of extra amounts of ILs will essentially increase the overall cost of the process. Many

studies report high IL concentrations that result in higher extraction yields; however, the yields reduce after reaching a maximum as the IL concentration increases. There was also an increase in viscosity, which may have resulted from either the IL itself or from the dissolution of additional compounds from the plant matrix, such as carbohydrates. Since the concentration of IL significantly affects its physicochemical properties [65], fine-tuning the extractive systems could be achieved by increasing or decreasing IL concentrations [62].

6.3.1.1 Sugar containing ionic liquids

In view of the possibility of using ILs to depolymerize carbohydrate polymers which are hard to dissolve, it would be beneficial to develop sugar-based ILs for an application that would require a "closed-loop" method of depolymerizing carbohydrate polymers [66]. ILs based on sugars with potential for use in this area have already been synthesized, although they have been used in other applications. As shown in Figure 2A–C, 1,2,3-triazolium ILs containing glucose linkage were synthesized by copper(I)-catalyzed cycloaddition of glucose azides with glucose alkynes, followed by quaternization with methyl iodide [67]. The ILs were utilized in copper(I)-catalyzed amination of aryl halides with aqueous ammonia as reusable chiral solvents and ligands. The chemicals can be employed as a solvent because the triazolium salt keeps it liquid at room temperature. The free hydroxyl groups in the glucose moiety also help to stabilize copper(I) species during the reaction. A promising IL with solvent potential has also been created using methyl-D-glucopyranoside [68]. The hydroxyl at the main position is shielded throughout the synthesis process using thexyldimethylsilyl chloride. After lowering the anomeric position and further deprotecting the main hydroxyl, the other secondary hydroxyl groups were transformed into methyl ethers. The primary hydroxyl group was first deprotected, and after that, it was changed into a triflate to create an intermediate. Using diethyl sulfide, this triflate intermediate underwent a nucleophilic substitution reaction to produce an IL containing a triflate anion and a sulfonium cation that was liquid at normal temperature (Figure 6.2A–C).

Fructose was employed by Handy et al. [69] to create ILs at room temperature. Copper carbonate, ammonia and formaldehyde were employed in their synthetic procedure to ring close fructose and create hydroxymethylene imidazole. To create an imidazolium cation, this imidazole underwent a series of alkylation processes (with 1-bromobutane and iodomethane). A variety of room-temperature ILs were produced by anion metathesis (Figure 6.2D) and employed as reusable solvents for the Mizoroki–Heck cross-coupling of aryl iodides with alkenes.

In 2018, 2,3,5-tri-*O*-benzyl-D-arabinofuranose [70] was used to begin the synthesis of an arabinose-based imidazolium IL (Figure 6.2E). All of the hydroxyl groups in D-arabinose, with the exception of the one on the carbon next to the ring oxygen atom, were benzylated to create the pentofuranoside starting material. The reaction between

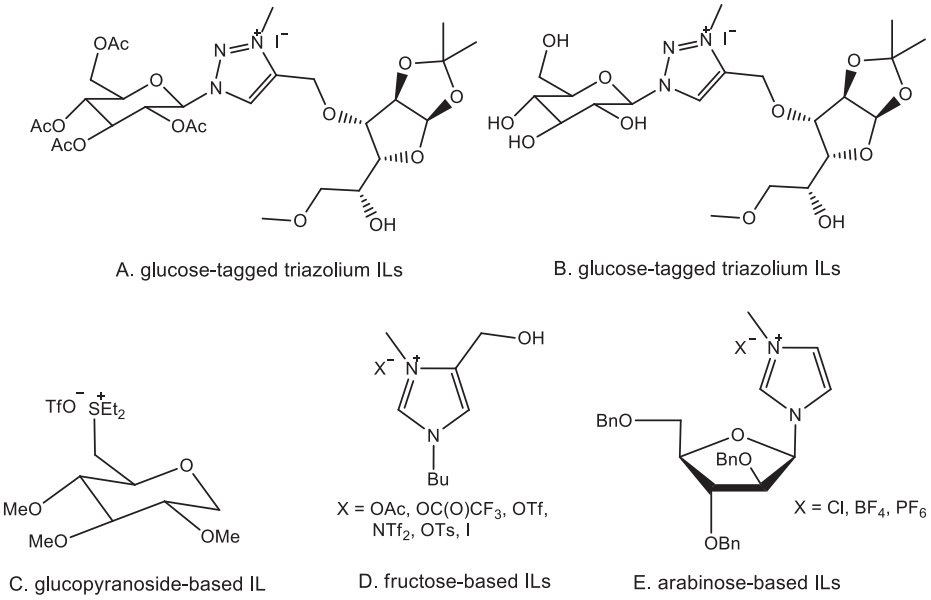


Figure 6.2: (A and B) Glucose-tagged triazolium ILs; (C) glucopyranoside-based IL; (D) fructose-based ILs; and (E) arabinose-based ILs.

the free hydroxyl group and propane-1,3-diyldioxyphosphoryl chloride was then carried out in the presence of 1-methylimidazole to produce a mixture of anomeric phosphates. This was then combined in a catalytic amount with 1-methylimidazolium chloride and trimethylsilyl triflate to create a pure anomeric IL that contains a chloride anion. Two more ILs were produced by anion metathesis processes and employed as cosolvents in the synthesis of alcohols from aromatic aldehydes (Figure 6.2E) [70].

6.3.1.2 Alkaloid containing ionic liquids

Using different organic cation hydroxides to neutralize basic ammonia solutions of ampicillin, Ferraz et al. [71] developed ILs containing ampicillin as active pharmaceutical ingredients. The development of bioactive materials may make use of these ampicillin-based ILs [71]. In a study published in 2002, Wasserscheid and Bolm [72] synthesized chiral ILs by alkylation of ephedrine with dimethyl sulfate followed by ion exchange to form ILs with melting points of 54 °C. ILs have been synthesized from nicotine by quaternizing the pyridine ring with ethyl bromide and methyl iodide as reported by Heckel et al. [73]. The nicotine-based chiral ILs were tested as chiral solvating agents (Figure 6.3).

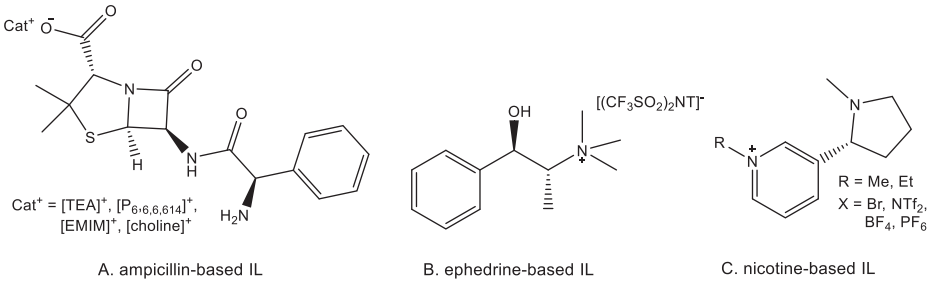


Figure 6.3: Alkaloid-based ILs [(A) ampicillin-based ILs; (B) ephedrine-based IL; and (C) nicotine-based ILs].

6.3.1.3 Lipid-containing ionic liquids

In the synthesis of four ILs with melting points below 21 °C, oleate and linoleate were utilized (Figure 6.4A–D). Initial neutralizing processes with NaOH were used to extract unsaturated fatty acids, and then either tetraoctylammonium chloride or methyltrioctylammonium chloride was used for ion exchange. The extraction of metal ions from aqueous solutions using ILs as solvents was then accomplished satisfactorily [74]. Additionally, Kwan et al. [75] produced ILs from lipids by alkylating a tertiary amine (Figure 6.4E–G). In this case, methyl oleate and methyl stearate were the lipids utilized. In the third case, the tertiary amine was alkylated using diethylzinc and cyclopropanated oleic acid methyl ester to create the reaction between the oleate's double bond and diiodomethane. Alkyl iodide was produced by reacting it with imidazoles, and anion exchange of the iodide with bistriflimide produced imidazolium bistriflimide intermediates (ILs).

6.3.2 Applications of ionic liquid for the isolation of natural products as a green solvent

Traditional methods for purifying single compounds from plants began with extraction, followed by repeated chromatography using macroporous resins, silica gel, Sephadex LH-20 column chromatography and HPLC. There was a waste of time and money involved in these purification processes. Due to their unique chemical functional groups, ILs had been proposed to catch NPs [76, 77].

6.3.2.1 Flavonoids

Flavonoids are different types such as flavones, flavonols, isoflavones, chalcones and anthocyanidins comprising a C_6–C_3–C_6 skeleton [78–80]. Furthermore, the architectures

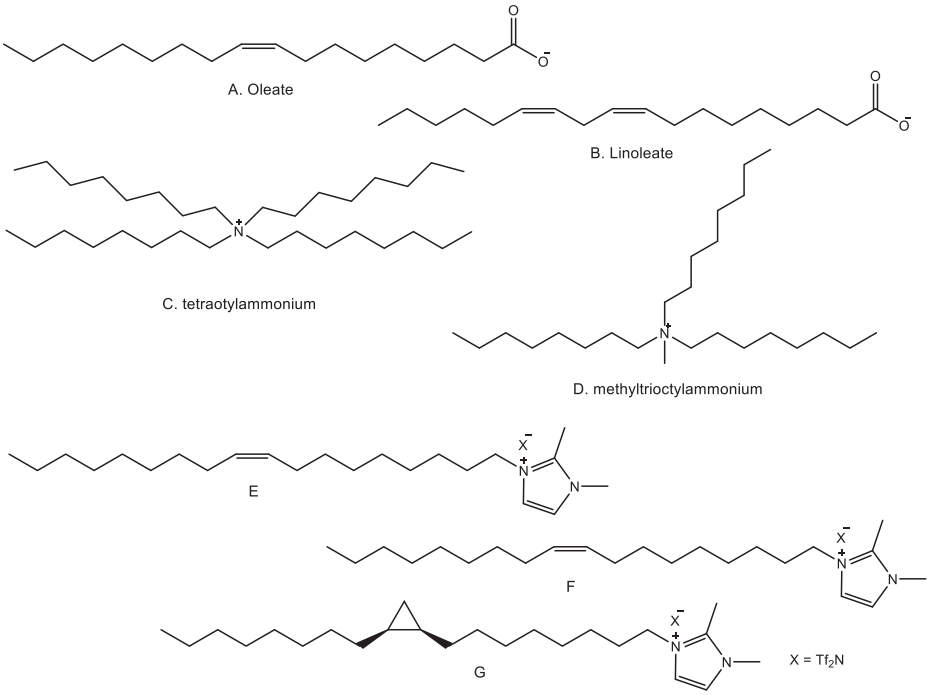


Figure 6.4: Anions and cations used in the syntheses of lipid-based ILs (A–D); lipid-based imidazolyl ILs (E–G).

of flavonoid molecules frequently contained hydroxyl, methoxyl and glycosyl groups. Table 6.1 and Figure 6.5 describe all flavonoids (**21–63**) that were obtained from natural sources by using ILs.

There have been many studies showing rutin (quercetin-3-*O*-rutinoside, **21**) component to be an active component in herbs, such as *Tamarix chinensis* [81], *Sophora japonica* L. and *Abutilon theophrasti* [26]. Depending on its polarity and acidity, it could be extracted using a variety of solvent extraction techniques. As rutin has a polarity, it is usually extracted by refluxing ethanol with water [82]. Moreover, $Ca(OH)_2$ solution could be used to enrich acidic rutin as well [83]. Due to their disadvantages, the traditional methods were unable to be applied further due to their low yield of 8% [82] and long-time requirements. Thus, Zhao et al. [84] developed a new method for extracting rutin from *A. theophrasti* leaves using ultrasonic and microwave-assisted extraction (UMAE) with IL [C_4mim]Br. In contrast to heating reflux extraction with methanol, ILs-UMAE produced 5.49 mg g^{-1} of rutin, an increase of 2.01 times. To further demonstrate the superiority of [Bmim]Br extraction over ultrasonic extraction with methanol, Wang et al. [81] extracted rutin (0.0756%.) from *T. chinensis* using [Bmim]Br, which was 15.1% greater than that of traditional methods.

Table 6.1: Ionic liquids used to extract flavonoids from natural sources.

Type of ionic liquids	Methods of extraction	Compounds	Sources	References
[Bmim]Br, [Hmim]BF, SilprBImCl, [Bmim] BF_4[Hmim]Br, [C_4mim]Br	MAE, SPE, UMAE	Rutin (**21**)	*Saururus chinensis*, *Artemisia capillaris*, *Tamarix chinensis*, *Xanthium sibiricum*	[80–82, 86, 87]
SilprBImCl, SilprIm NH_2, SilprPy, SiImBr, [Hmim] Br, SilmPS, [C_4mim]Br, [$HO_3S(CH_2)_4$mim]-HSO_4, [Bmim] Br, [BPy]Br	UMAE, MDSPE, MAE	Quercetin (**2**)	*Toona sinensis*, *Artemisia capillaris*, *Ginkgo biloba*, *Xanthium sibiricum*	[80, 88, 89]
[$HO_3S(CH_2)_4$mim]HSO_4, Mim, [Bmim]Br, [BPy]Br, [Hmim] Br	MAE	Kaempferol-3-*O*-β-D-glucoside (**22**)	*Hippophae rhamnoides*, *Toona sinensis*, *Ginkgo biloba*	[88, 89]
[C_6MIM]Br, [C_4MIM]Br, [C_8mim]Br	CAE, MAE	Orientin (**23**), vitexin (**24**), genistin (**25**), isovitexin (**26**), luteolin-6-*C*-β-D-glucopyranosyl-8-*C*-α-L-arabinopyranoside (**27**), luteolin-6-*O*-β-L-arabinopyranosyl-8-*O*-β-D-glucopyranoside (**28**), apigenin-8-*O*-α-L-arabinoside (**29**), apigenin-6,8-di-*O*-α-L-arabinopyranoside (**30**)	*Cajanus cajan*, *Glycine max*	[90, 91]
[Omim][PF_6], $BMImBF_4$, [Hmim][PF_6], [Bmim][PF_6], [C_8mim]Br, [Bmim][NTf_2], [C_6min]Br, 1-butyl-3-methylimidazolium bromide	Liquid–liquid extraction, MAE, CAE, UAE	Ononin (**31**), daidzin (**32**), biochanin A (**33**), formononetin (**34**), puerarin (**35**), genistein (**36**), daidzein (**37**)	*Pueraria lobata*, *Glycine max*, *Cajanus cajan*	[90–92]
[$HO_3S(CH_2)_4$mim]HSO_4	MAE	Isorhamnetin (**38**)	*Ginkgo biloba*	[89]
1-Butyl-3-methyl-imidazolium bromide, [C_6mim][PF_6], C_4mim][PF_6], [C_8mim][PF_6]	MAE, TPME	Fisetin (**39**), kaempferide (**40**)	*Pueraria lobata*, *Rheum officinale*, *Coptis chinensis*	[92, 93]
[C_4mim][PF_6]	Aqueous two-phase system	Baicalein-7-*O*-diglucoside (**41**), baicalein-7-*O*-glucoside (**42**)	*Veratrum stenophyllum*	[85]

Table 6.1 (continued)

Type of ionic liquids	Methods of extraction	Compounds	Sources	References
$[C_2mim]OAc$	Aqueous two-phase systems	Pelargonin (**43**), cyanidin (**44**), peonidin (**45**), petunidin (**46**), malvidin (**47**)	*Vitis vinifera*	[92]
$[C_{12}mim]Br$, [Bmim][MS], $[C_8mim]Br$	CAE, UAE	Luteolin (**6**), apigenin (**4**)	*Apium graveolens*, *Chrysanthemum morifolium*, *Cajanus cajan*	[84, 91, 94]
1-Vinylimidazole, [Dmim]Br, 1-oxyl-3-methylimidazolium bromide, [Hmim][Cl, 1-bromodecane, [Emim][Cl], [Omim][Cl], [Bmim][Cl]	SPE, MPDE, UAE	Myricetin (**48**)	*Chamaecyparis obtusa* (hinoki cypress)	[95]
EMIMB, [BMIM]Cl	UAE, ATPS	Rhodiosin (**49**), rhodionin (**50**)	*Rhodiola rosea*	[96, 97]
[Emim][Cl, 1-vinylimidazole, [Bmim][Cl, 1-bromodecane, [Hmim][Cl], [DMIM]Br, [Omim][Cl]	SPE, MPDE	Quercitrin (**51**)	*Chamaecyparis obtusa*	[95, 98]
1-Ethyl-3-methyl-imidazoliumbromide	SPE	Herbacetin-8-*O*-β-D-glucopyranoside (**52**), herbacetin-3-*O*-β-D-glucopyranosyl-7-*O*-α-L-rhamnopyranoside (**53**), kaempferol 3-*O*-β-D-glucopyranoside-(2→1)-α-D-xylopyranoside (**54**), kaempferol-3-*O*-β-D-glucopyranosyl-7-*O*-α-L-rhamnopyranoside (**55**)	*Rhodiola rosea*	[99]
$[C_{12}mim]Br$	UAE	Acacetin (**56**)	*Chrysanthemum morifolium*	[94]
$[C_8mim]Br$	UAE	Baicalein (**57**), wogonin (**58**)	*Scutellaria baicalensis*	[100]

Table 6.1 (continued)

Type of ionic liquids	Methods of extraction	Compounds	Sources	References
$[sC_4mim][HSO_4]$, $[C_4mim][Br]$, $[mim][HSO_4]$, $[C_2mim][Br]$	Liquid–liquid extraction	Anthocyanin-3-(6-*O*-*p*-coumaroyl) monoglucosides (**59**), anthocyanin-3-*O*-acetylmonoglucosides (**60**)	*Vitis vinifera*	[101]
$[C_4mim]BF_4$	MAE	Hyperin (**61**)	*Populus euphratica*	[102]
[Emim][Cl], [Prmim][Cl], [B mim][Cl], $[C_5mim][BF_4]$, $[C_5mim][Cl]$, $[EMIM][BF_4]$, [Emim][Br], [Prmim][Br], $[Prmim][BF_4]$, [Bmim][Br], $[C_5mim][Br]$, $[Bmim][BF_4]$	ATPS	Kaempferol-3,4′-di-*O*-β-D-glucoside (**62**), kaempferol-3-*O*-β-D-(2-*O*-β-D-glucosyl)-glucopyranoside (**63**)	*Brassica napus*	[103]

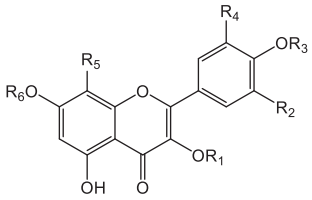
MAE, microwave-assisted extraction; SPE solid-phase extraction; UMAE, ultrasonic and microwave-assisted extraction; MDSPE, magnetic-dispersive SPE; CAE, collagenase-assisted extraction; UAE, ultrasound-assisted extraction; TPME, three-phase microextraction; ATPS, aqueous two-phase systems.

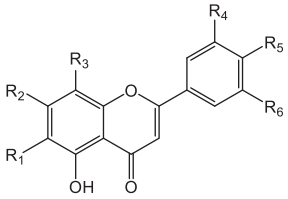
6.3.2.2 Alkaloids

Alkaloids comprise basic nitrogen atoms and one or more carbon rings (Figure 6.6) [104]. Alkaloids are classified as tryptophan-derived, phenylalanine-derived and terpenoid alkaloids, among others, based on their chemical component and biosynthesis process. Figure 6.6 and Table 6.2 provide descriptions of alkaloids (**64–89**) that were obtained from natural sources by using ILs [105–107].

A magnetic IL (MIL) was developed by Li et al. [108] based on ultrasound-assisted extraction (UAE) for the extraction of sinomenine (**64**) from *S. acutum*. The yield of this bioactive alkaloid (**64**) was enhanced by 2.4 and 2.8 times with MILs than that of reflux extraction using 70% ethanol–water (v:v) and pure water, respectively. Notably, the extraction time course was also decreased by ILs by 4 h.

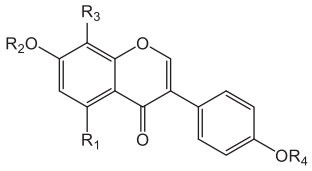
Dong et al. [109] extracted five alkaloids (**65–69**) from *Physochlaina infundibularis* by a similar approach. The investigators observed that the amount of IL and the solid–liquid ratio affect the yield of alkaloids; IL aqueous solution required lower time (55 min compared to 80 min) than that of water [110].

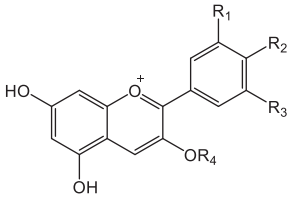




21. R1=Rut, R2=R3=R5=R6=H, R4=OH
2. R1=R3=R4=R5=R6=H, R2=OH
22. R1=Glc, R2=R3=R4=R5=R6=H
38. R1=R3=R4=R5=R6=H, R2=OMe
39. R1=R3=R4=R5=R6=H, R2=OH
40. R1=R2=R4=R5=R6=H, R3=Me
48. R1=R3=R4=R5=R6=H, R2=OH
49. R1=R2=R3=R4=H, R5=OH, R6=Rha(3-1)Glc
50. R1=R2=R3=R4=H, R5=OH, R6=Rha
51. R1=Rha, R2=OH, R3= R4=R5=R6=H
52. R1=R2=R3=R4=R6=H, R5=OGlc
53. R1=Glc, R2=R3=R4=H, R5=OH, R6=Rha
54. R1= Glc(2-1)Xyl, R2=R3=R4=R5=R6=H
55. R1=Glc, R2=R3=R4=R5=H, R6=Rha
61. R1=Glc, R2=OH, R3= R4=R5=R6=H
62. R1=R3=Glc, R2=R4=R5=R6=H
63. R1= Glc(2-1)Glc, R2=R3=R4=R5=R6=H

23. R1=R4=H, R2=R5=R6=OH, R3=OGlc
24. R1=R4=R6=H, R2=R5=OH, R3=OGlc
26. R1=Glc, R2=R5=OH, R3=R4=R6=H
27. R1=Glc, R2=R5=R6=OH, R3=Ara, R4=H
28. R1=Ara, R2=R5=R6=OH, R3=Glc, R4=H
29. R1=R2=R5=OH,R3=Ara, R4=R6=H
30. R1=R3=Ara, R2=R5=OH, R4=R6=H
41. R1=OH,R2=OGlc(1-1)Glc, R3=R4=R5=R6=H
42. R1=OH,R2=OGlc, R3=R4=R5=R6=H
6. R1=R3=R6=H, R2=R4=R5=OH
4. R1=R3=R4=R6=H, R2=R5=OH
56. R1=R3=R4=R6=H, R2=OH, R5=OMe
57. R1=R2=OH, R3=R4=R5=R6=H
58. R1=R4=R5=R6=H, R2=OH, R3=OMe





25. R1=R3=R4=H, R2=Glc
31. R1=R3=H, R2=Glc, R4=Me
32. R1=OH, R3=R4=H, R2=Glc
33. R1=OH, R2=R3=H, R4=Me
34. R1=R2=R3=H, R4=Me
35. R1=R2=R4=H, R3=Glc
36. R1=OH, R2=R3=R4=H
37. R1=R2=R3=R4=H

43. R1=R3=R4=H, R2=OH
44. R1=R2=R3=OH, R4=H
45. R1=OMe, R2=OH, R3=R4=H
46. R1=OMe, R2=R3=OH, R4=H
47. R1=R3=OMe, R2= OH, R4=Me
59. R1=R2=R3=H, R4=GlcAc
60. R1=R2=R3=H, R4=(6-coumaryacyl)Glcc

Figure 6.5: The structures of different flavonoids (**21–63**) extracted using ionic liquid.

6.3.2.3 Terpenoids

Secondary metabolite terpenoids are different types such as monoterpenes, sesquiterpenes, diterpenes, sesterpenes and triterpenes [118]. ILs were used to extract all terpenoids from natural sources. Terpenoids (**90–119**) are listed in Table 6.3 and Figure 6.7. A diterpenoid called paclitaxel (**90**) existed in several *Taxus* species [119, 120]. This compound was used as an antitumor drug in clinical trials. Paclitaxel is usually extracted

Table 6.2: Ionic liquids used to extract alkaloids from natural sources.

Type of ionic liquids	Methods of extraction	Compounds	Sources	References
$[C_2OHmim]FeCl_4$	Ultrasound-assisted extraction	Sinomenine (**64**)	*Adenia chevalieri*	[108]
$[C_3tr][PF_6]$	Maceration	Anisodamine (**65**), atropine (**66**), scopolamine (**67**), aposcopolamine (**68**), scopoline (**69**)	*Physochlaina infundibularis*	[109]
1-Ethyl-3-methylimidazolium tetrafluoroborate	Ultrasound-assisted extraction	Aconitine (**70**), mesaconitine (**71**), hypaconitine (**72**)	*Aconitum carmichaelii*	[112]
1-Butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium, bromide1-butyl-3-methylimidazole tetrafluoroborate	Infrared-assisted extraction, ultrasound-assisted extraction	Coptisine (**73**), palmatine (**74**), berberine (**75**), boldine (**76**)	*Coptis chinensis*, *Dicranostigma leptopodum*, *Phellodendron amurense*	[108, 113]
$[C_4mim][BF_4]$	Aqueous two-phase system	*N*-Nornuciferine (**77**), nuciferine (**78**), roemerine (**79**)	*Nelumbo nucifera*	[114]
$[C_4C_1im]$[Ace, 1-butyl-2,3-dimethyl-imidazolium tetrafluoroborate	Infrared-assisted extraction, maceration	Glaucine (**80**)	*Glaucium flavum*	[111, 115]
$[C_4mim][PF_6]$	Aqueous two-phase systems	Liensinine (**81**), isoliensinine (**82**), romerine (**83**), neferine (**84**)	*Nelumbo nucifera*	[116]
$[C_6mim]Br$	Aqueous two-phase system	Benzoylmesaconine (**85**), benzoylaconine (**86**), mesaconitine (**87**), hypaconitine (**88**), aconitine (**89**)	*Aconitum carmichaelii*	[117]

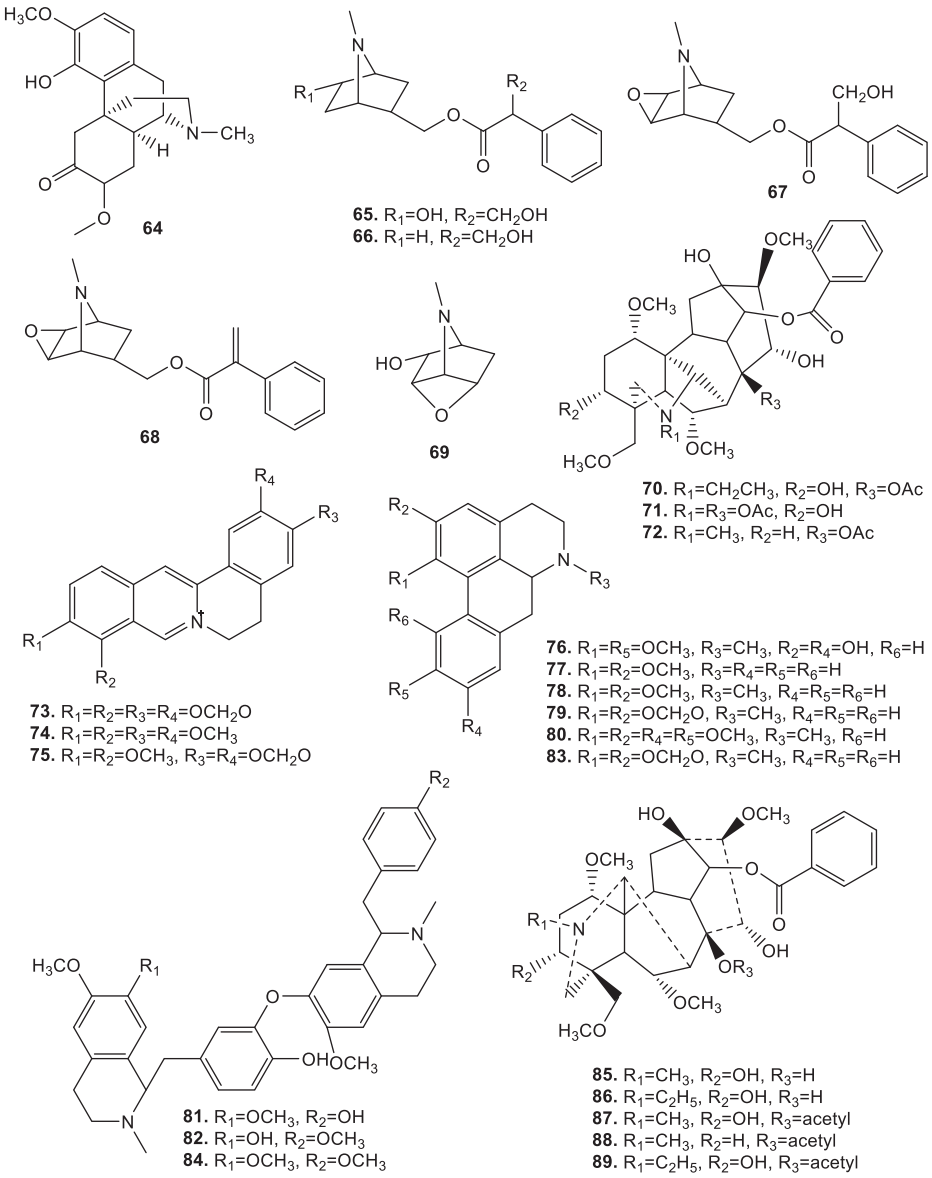


Figure 6.6: The structures of various alkaloids (**64–89**) extracted using ionic liquids.

from the original plant by two different methods [121, 122]. Tian et al. [123] dissolved paclitaxel in methanol alongside MIL $[C_4mim]FeCl_3Br$ during the extraction process of *Taxus* species to provide improved yield with significant time savings (16 h vs 30 min).

Table 6.3: Ionic liquids used to extract terpenoids from natural sources.

Type of ILs	Methods of extraction	Compounds	Sources	References
MIL $[C_4mim]FeCl_3Br$	Ultrasound-assisted extraction	Paclitaxel (**90**)	*Taxus chinensis*	[123]
Tetramethyl guanidium lactate	Ultrasound-assisted extraction	Forskolin (**91**)	*Coleus forskohlii*	[124]
Didecyldimethyl lactate, Tris (2-hydroxyethyl) methylammonium methylsulfate, benzalconium nitrate, didecyldimethyl nitrate, benzalconium lactate	Ultrasound-assisted extraction	α-Pinene (**92**), cadina-1,4-diene (**93**), 1,8-cineole (**94**), calamenene (**95**), linalool (**96**), humulene (**97**), terpinen-4-ol (**98**), β-caryophyllene (**99**), borneol (**100**), bergamotene (**101**), α-terpineol (**102**), bornyl acetate (**103**), α-copaene (**104**), cubebene (**105**)	*Cinnamomum cassia*	[125]
$[BMIM][BF_4]$	Ultrasound-assisted extraction	Scroside B (**106**), picroside II (**107**), hemiphroside A (**108**), picroside (**109**), scroside A (**110**), scroside I (**111**), scroside C (**112**), scroside D (**113**), picroside III (**114**), picroside I (**115**), specioside (**116**), 6-*O*-*E*-feruloyl catalpol (**117**)	*Picrorhiza scrophulariiflora*	[126]
$[C_4C_1im][N(CN)_2]$, $[C_4C1pyr]Cl$, $[C_4C_1im][TOS]$, $[C_4C_1im][SCN]$, $[C_4C_1py][N(CN)_2]$, $[C_4C_1im][C_2H_5SO_4]$	Liquid–liquid extraction	Ursolic (**118**), betulinic acids (**119**)	*Malus pumila*	[127]

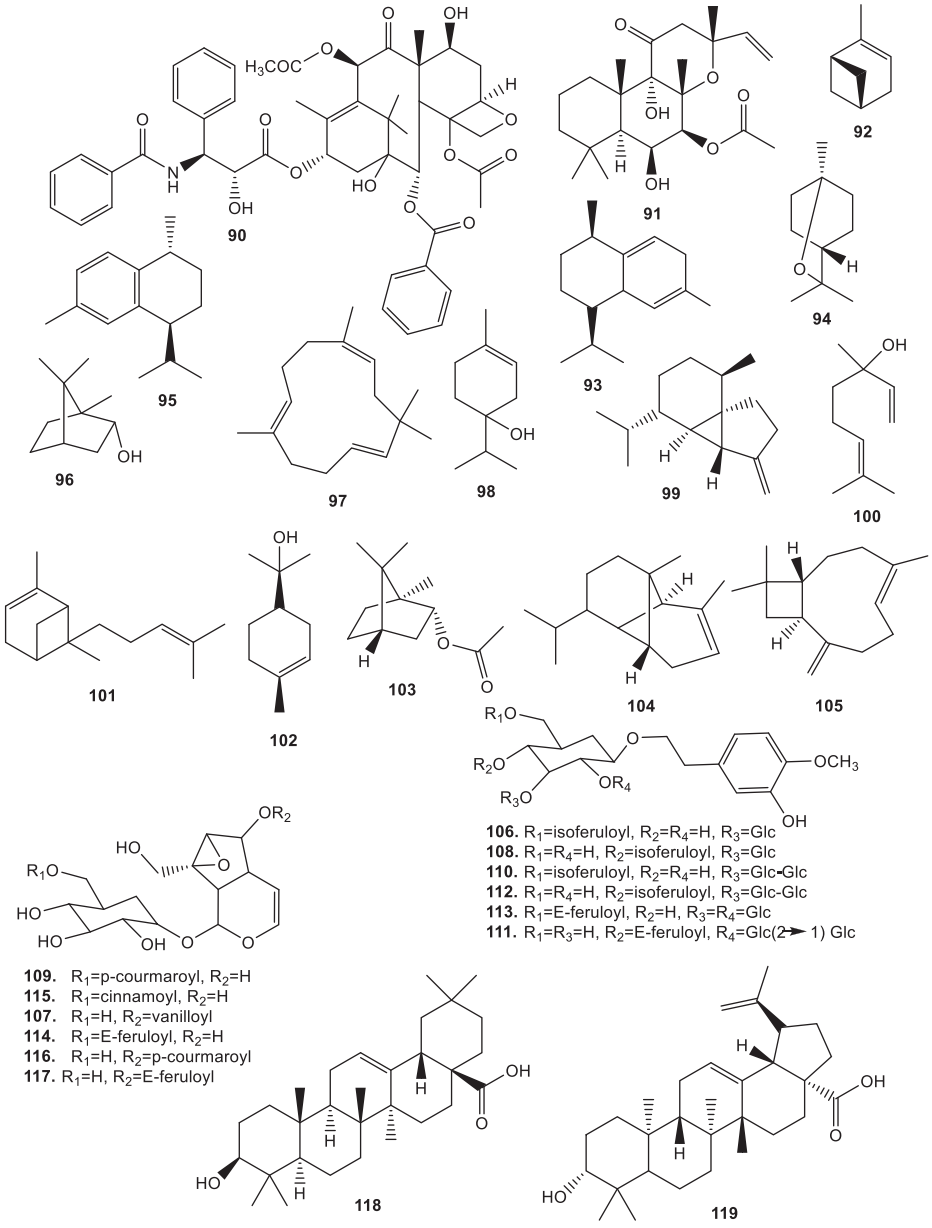


Figure 6.7: The structures of various terpenoids (**90–119**) extracted by employing ionic liquids.

6.3.2.4 Phenylpropanoids

NPs like coumarins and lignans are composed of C_6–C_3 units, which are the general skeleton of phenylpropanoids [128]. Figure 6.8 and Table 6.4 show phenylpropanoids (**120–138**) obtained from natural sources using ILs.

Compound psoralen (**124**) is the main active component of *Ficus carica* L. and *Psoralea corylifolia* L. [129], which are usually purified using multiple chromatographic steps after being extracted from the plant materials [130, 131]. Based on pH-dependent ILs, Wang et al. [129] turned *F. carica* L. leaves into psoralen using [Bmin]Br. By using this procedure, 30.21 mg g^{-1} of psoralen was obtained, which is 2.44-fold higher than that of using ethanol–citric acid in the absence of ILs in conventional methods. Additionally, the proposed method is more environmentally friendly than previous ones since no organic solvents, such as methanol or ethanol, were used in the extraction process.

Furthermore, aesculin (**131**) is another compound obtained from *Cortex fraxini* by applying IL extraction [C_4mim]Br, described by Liu and Yang [132]. As a result of optimal conditions, extracting aesculin (**131**) with 75% ethanol and water furnished 18.70 mg g^{-1}. Interestingly, it is 6-fold higher compared to conventional refluxing [133].

Table 6.4: Ionic liquids used to extract phenylpropanoids from natural sources.

Type of ionic liquids	Methods of extraction	Compounds	Sources	References
Bmim-BF_4	Aqueous two-phase system	Schisandrin (**120**), schisantherin (**121**), deoxyschisandrin (**122**), γ-schisandrin (**123**)	*Schisandra chinensis*	[129]
[Bmim]Br	Liquid–liquid extraction	Psoralen (**124**)	*Ficus carica*	[131]
[C_4mim][BF_4]	Ultrasound-assisted extraction	Schisanhenol (**125**), deoxyshisandrin (**126**), schisandrin C (**127**)	*Schisandra chinensis*	[134]
[C_4mim]Ac	Maceration	Schizandrin (**128**), schisantherin A (**129**), γ-schizandrin (**130**)	*Schisandra chinensis*	[135]
[C_4mim]Br	Ultrasound-microwave synergistic extraction	Aesculin (**131**), aesculetin (**132**)	*Fraxinus chinensis*	[132, 136]
[C_6mim][PF_6]	Liquid–liquid microextraction	Bergapten (**133**), isobergapten (**134**), oxypeucedanin (**135**), imperatorin (**136**), osthole (**137**), isoimperatorin (**138**)	*Angelica dahurica*	[137]

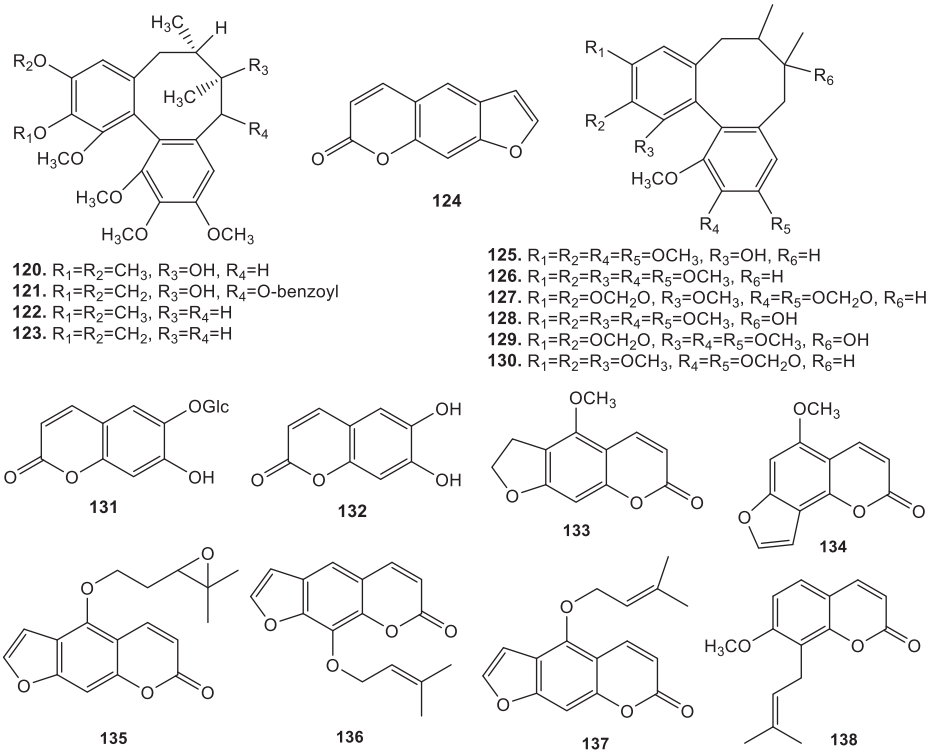


Figure 6.8: The structures of different phenylpropanoids (**120–138**) extracted using ionic liquids.

6.3.2.5 Quinones

There are several types of quinones, all of which consist of a fully conjugated cyclic dione structure such as benzoquinone, phenanthraquinone, naphthoquinone and anthraquinone. Figure 6.9 and Table 6.5 represent (**139–153**) quinones obtained from natural sources.

The purpose of Tian et al. [138] was to use mild and effective techniques for isolating and purifying quinone aloe-emodin (**144**) from *Aloe vera* L. In the extraction of aloe-emodin (**144**), the effects of IL anions (Br^-, BF_4^- and $N[CN]_2^-$) and side chain lengths of alkyl cations in the $[CnC_1im]^+$ series were examined. As compared to heating reflux extraction with toluene, aloe-emodin extraction efficiency (92.34%) enhanced 3-fold under optimal conditions [139, 140].

Danshen (*Salvia miltiorrhiza*) is composed of tanshinone IIA (**153**) [140]. Usually, tanshinone IIA was extracted using ethanol under reflux. The high temperature may, however, break down the structure [141]. Liu et al. [142] obtained tanshinone IIA from Danshen by utilizing ultra-high-pressure extraction through the selection of 0.5 MIL (1-octyl-3-methylimidazolium hexafluorophosphate) in solvent ethanol. It produced

Table 6.5: Ionic liquids used to extract quinones from natural sources.

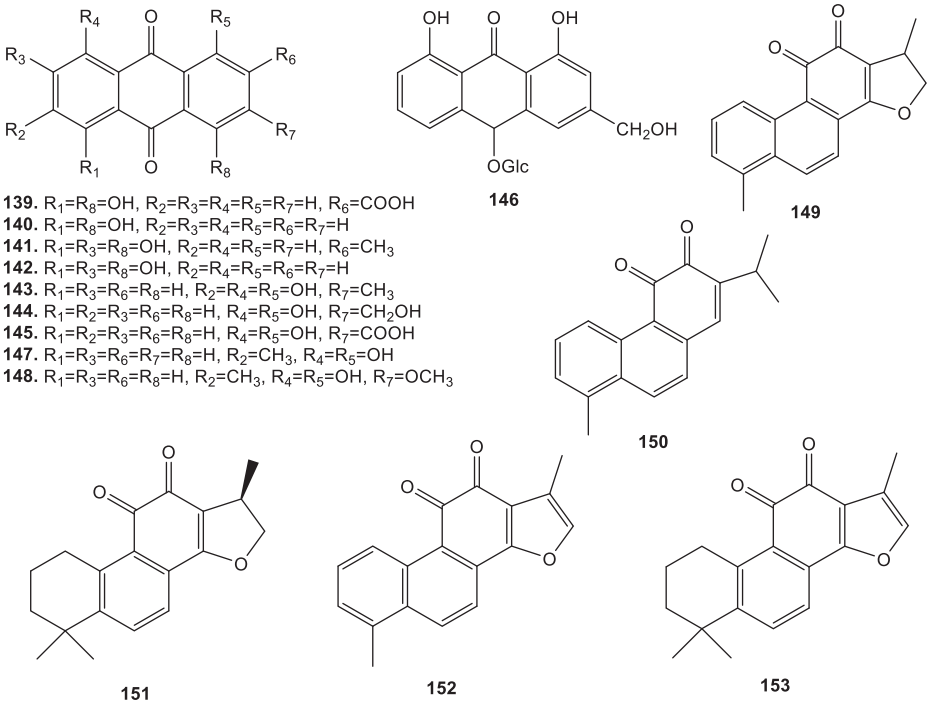
Type of ILs	Methods of extraction	Compounds	Sources	References
[Bmim]Br, [Bmim]Cl, $[Bmim]BF_4$	Ultrasound-assisted extraction, microwave-assisted extraction	Rhein (**139**), danthron (**140**), emodin (**141**), chrysophanol (**142**)	*Rheum officinale*	[137]
$[C_4mim]BF_4$	Liquid–liquid extraction	Emodin (**143**), aloe-emodin (**144**), rhein (**145**), aloin (**146**)	*Aloe vera*	[138, 143]
1-Hexyl-3-methylimidazolium hexafluorophosphate	Liquid–liquid microextraction	Chrysophanol (**147**), physcion (**148**)	*Rheum officinale*	[144]
1-Octyl-3-methylimidazolium hexafluorophosphate	Ultra-high-pressure extraction	Dihydrotanshinone (**149**), miltirone (**150**)	*Salvia miltiorrhiza*	[142]
(3-Aminopropyl) trimethoxysilane	Imprinted functionalized ionic liquid-improved silica	Cryptotanshinone (**151**), tanshinone I (**152**)	*Salvia miltiorrhiza*	[145]
1-Octyl-3-methylimidazolium hexafluoro-phosphate, (3-aminopropyl)-trimethoxysilane	Imprinted functionalized ionic liquid-improved silica	Tanshinone IIA (**153**)	*Salvia miltiorrhiza*	[142, 145]

37.4 mg g^{-1} more tanshinone IIA when ILs were included in the extraction process than when it was not. As a result, this approach significantly reduced the duration of the experiment from 120 min (with methanol) to 2 min (with ILs).

6.3.2.6 Fats

Li and Li [146] published their groundbreaking research in 2008 on the use of ILs and silver salts to recover omega-3 polyunsaturated fatty acid methyl esters (FAMEs) (**154**) from fish oil, as shown in Figure 6.10A. Hexane served as the primary solvent in the initial tests' standard combinations of five FAMEs, with the silver salts and ILs serving as the extraction phases. The most effective ILs were those that were hydrophobic and had big anions with low lattice energies [146]. In comparison to $[C_6C_1im][BF_4]$ alone or with $AgBF_4$ in water or ethylene glycol, the $[C_6C_1im][BF_4] + AgBF_4$ system was found to be significantly more effective. Furthermore, IL and silver salt mixtures removed lipids more easily from higher unsaturation degrees.

An approach to selectively extract fat from chocolate was developed by Lateef et al. [147] to minimize food disposal in landfill. A total of four ILs were screened, and



139. $R_1=R_8=OH$, $R_2=R_3=R_4=R_5=R_7=H$, $R_6=COOH$
140. $R_1=R_8=OH$, $R_2=R_3=R_4=R_5=R_6=R_7=H$
141. $R_1=R_3=R_8=OH$, $R_2=R_4=R_5=R_7=H$, $R_6=CH_3$
142. $R_1=R_3=R_8=OH$, $R_2=R_4=R_5=R_6=R_7=H$
143. $R_1=R_3=R_6=R_8=H$, $R_2=R_4=R_5=OH$, $R_7=CH_3$
144. $R_1=R_2=R_3=R_6=R_8=H$, $R_4=R_5=OH$, $R_7=CH_2OH$
145. $R_1=R_2=R_3=R_6=R_8=H$, $R_4=R_5=OH$, $R_7=COOH$
147. $R_1=R_3=R_6=R_7=R_8=H$, $R_2=CH_3$, $R_4=R_5=OH$
148. $R_1=R_3=R_6=R_8=H$, $R_2=CH_3$, $R_4=R_5=OH$, $R_7=OCH_3$

146 **149** **150** **151** **152** **153**

Figure 6.9: The structures of different quinones (**139–153**) extracted using ionic liquid.

only $[C_3C_1im]Br$ and $[(NC)C_2C_1im]Br$ could separate sugars from cocoa butter fats. The cyano group at the cation is crucial to the increased capability of ILs to form hydrogen bonds with sugars. A Lewis acidic chloroaluminate IL catalyst was used as a catalyst in situ transesterification of soy flake lipids by Bollin and Viamajala [148]. In a solution of $[C_2C_1im]Cl•2AlCl_3$, methanol and dichloromethane, triglycerides were reactively extracted as FAMEs. Liquid–liquid extraction (LLE) with hexane was then used to recover the solubilized FAMEs and glycerides. It was found that >90% of soy flour lipids were recovered as FAMEs under optimum conditions [148].

In recent years, algae biomass has been studied for its potential to produce biodiesel. ILs possess a remarkable capability of dissolving biomass and disrupting cellular processes as an excellent substituent for volatile organic solvents. The dissolution of algal biomass for lipid extraction has been discussed in the literature in several studies. Teixeira [149] reported that dissolution of algal biomass belongs to *Chlorella*, *Chlorococcum*, *Scenedesmus*, *Selenastrum* and *Neochloris* genera using ILs in addition to conceptualizing a process to recover sugars, proteins and lipids using ILs.

Cosolvent combinations of $[C_2C_1im][C_1SO_4]$ and methanol were employed by Cooney and coworkers [150] to extract lipids from several forms of biomass, including microalgae and oil seeds. Similar approaches were used in other papers from the same research group who addressed the co-extraction of substances, including (i) bio-oil from

safflower and jatropha biomass was extracted simultaneously with fermentable sugars utilizing $[C_2C_1im][C_1CO_2]$ and methanol as cosolvents [151]; (ii) in this study, $[C_2C_1im][C_1SO_4]$ and methanol were used as cosolvents in the co-recovery of jatropha oils and phorbol esters [152]; (iii) in order to separate the lipid and fermentable sugar from *Rhodosporidium toruloides*, the carbohydrates were recycled to be consumed by the yeast via $[C_2C_1im]$–$[C_1CO_2]$–methanol mixtures [153]. Kim et al. [154] also accomplished ultrasound-promoted techniques for improved lipid extraction including the $[C_4C_1im][C_1SO_4]$ as a superior IL.

6.3.2.7 Essential oils

Figure 6.10B represents essential oils such as limonene (**155**) and linalool (**156**) which are isolated from natural matrices [155]. Zhai et al. [156] disclosed the IL-based MAE of essential oils from *Cuminum cyminum* and *Illicium verum*. Ma et al. [157] and Liu et al. [158] also successfully extracted essential oils, carnosic, rosmarinic acids and lignans.

Jiao et al. [159, 160] presented a novel method, which is the combination of hydrodistillation and microwave-assisted IL treatment utilizing $[C_2C_1im][C_1CO_2]$ as the best IL. The optimal conditions for essential oil extraction (0.91% over 14.2 min from *Dryopteris fragrans* and 9.58% over 29.3 min from *Fructus forsythiae*) were found to be comparable to other techniques (0.33% over 94 min from *Dryopteris fragrans* by solvent-free MAE, 4.08% over 100 min from *Fructus forsythiae* by hydrodistillation and 5.43% over 45 min from *Fructus forsythiae* by microwave) [159, 160].

The separation of terpenes applying ILs is a topic of interest since oxygenated terpene derivatives are more desirable due to their organoleptic characteristics. Arce et al. [161] were pioneers in this field; their work is related to the addition of $[C_2C_1im–C_1SO_3]$ to ethylene glycol and 2-butene-1,4-diol for deterpenation of citrus oil, which was replicated by means of a synthetic mixture of limonene and linalool.

6.3.2.8 Carotenoids

Carotenoids are fat-soluble pigments having several health benefits as well as wide industrial applications [162]. ILs have also been considered as efficient solvents for the sustainable recovery of carotenoids (**157–160**) from diverse sources (shown in Figure 10C). The work of Bi et al. [163] relates to the environmental concerns surrounding shrimp waste and the potential recovery of bioactive components from such a matrix, including astaxanthin, a very important carotenoid. UAE) was the technique studied, in a first attempt using molecular solvents (e.g., methanol, ethanol, *n*-hexane, ethyl acetate, acetone, dichloromethane and water) and then using the best molecular solvent (i.e., ethanol) in combination with ILs. The maximum astaxanthin recovery was achieved with $[(NH_2)C_3C_1im]Br$ out of the seven ILs examined.

Haematococcus pluvialis, a naturally occurring source of astaxanthin, has a tough cell wall, which inspired Desai et al. [164] to create a different method of astaxanthin extraction. The aqueous solution of $[C_2C_1im][(C_4)_2PO_4]$ displayed the best permeabilization ability under the ideal conditions (40 wt% in water and 40 °C), giving 77.04% of astaxanthin in micrograms per milligram of dry biomass, in the subsequent phase of extraction with ethyl acetate.

For the extraction of lycopene from tomato-based matrices, ILs were also used, either in pure form or as ethanol solutions [165]. The highest amount of recovered lycopene (5.56 g of lycopene per gram of tomato) was produced by pure $[C_4C_1im][PF_6]$, which compares favorably to the outcomes obtained with acetone (3.65 g of lycopene per gram of tomato), ethanol (0.34 g of lycopene per gram of tomato) or IL–ethanol solutions (1.23–2.37 g of lycopene carotenoids were also separated using ABS made from ILs) [166, 167]. In two publications published by Coutinho and colleagues [167], the separation of β-carotene in ABS (Aqueous Biphasic Systems) made of (i) phosphonium-based ILs + K_3PO_4 [77] and (ii) ILs + carbs, was assessed.

6.3.2.9 Saponins

A saponin is an interesting compound because of its versatility, both from the perspective of its chemical structure and from the standpoint of its biological activity. Marrucho and coworkers [168] reported that IL solutions were used to extract saponins and polyphenols from *Ilex paraguariensis* and *Camellia sinensis* followed by saponin recovery by ABS. According to the first study [168], the IL structure, solid–liquid ratio, temperature and contact time were studied in systematic detail. To extract saponins and polyphenols from the two matrices, $[N_{111}(2OH)]Cl$ (at 30 wt%) was selected as the best solvent for pursuing saponin purification using ABS under optimal conditions. As shown in Figure 10D, the saponins (**161–164**) were recovered almost free of $[N_{111}(2OH)]Cl$ by employing $[N_{111}(2OH)][NTf_2]$.

As part of their extraction approach, Wang et al. [169] combined ultrasound and microwave technology to achieve steroidal saponin extraction from *Dioscorea zingiberensis* using ILs as a solvent. Water was compared with six ILs for their aptitude to extract diosgenin, and six were found to be superior. There was a noticeable improvement in diosgenin yields from all ILs when compared with water. $[C_2C_1im][BF_4]$ was responsible for the higher performance [169].

6.3.2.10 Vitamins

Vitamin E is made up of tocopherols, which are fat-soluble antioxidants. Tocopherols are derived as a mixed mixture of four homologues when extracted from natural sources, namely α-, β-, γ- and δ-tocopherol. Figure 6.10E provided the structures of vitamin

obtained from natural sources. Although they share a similar structure, they differ in biological activity, highlighting the need to find fractionation approaches (α-tocopherol possesses the strongest biological activity). This purpose can be achieved using efficient techniques, but it is very difficult to scale them up. The authors developed new platforms based on ILs to separate tocopherol isomers selectively to overcome this limitation [170–172]. In several papers, (i) the use of hexane plus IL and methanol mixtures was reported [170], (ii) hexane plus IL cosolvent mixtures were used in selective LLE [171] and (iii) theoretical studies were conducted to uncover the optimum solvents by understanding the molecular mechanisms at work. In addition, the roles of IL anion in separation of these homologues were inspected, which varied in the order as follows: $[BF_4]-$ (6.7) < $[CF_3SO_3]-$ (7.8) < $Cl-$ (21.3), following the hydrogen bond basicity of ILs [170]. There is another paper of particular interest in this framework by Ren and collaborators [173], which attempted to selectively LLE vitamin D_3 and tachysterol$_3$ (having different double bond structures) in this framework. A higher distribution coefficient was induced by organic solvents while a higher selectivity was induced by ILs among the seven substances investigated. There is a preference for the use of ILs containing anions [NTf_2] and [CF_3SO_3], cations [C_4C_1pyr] and [C_4C_1pyrr], and functionalized alkyl chains with CN or OH groups.

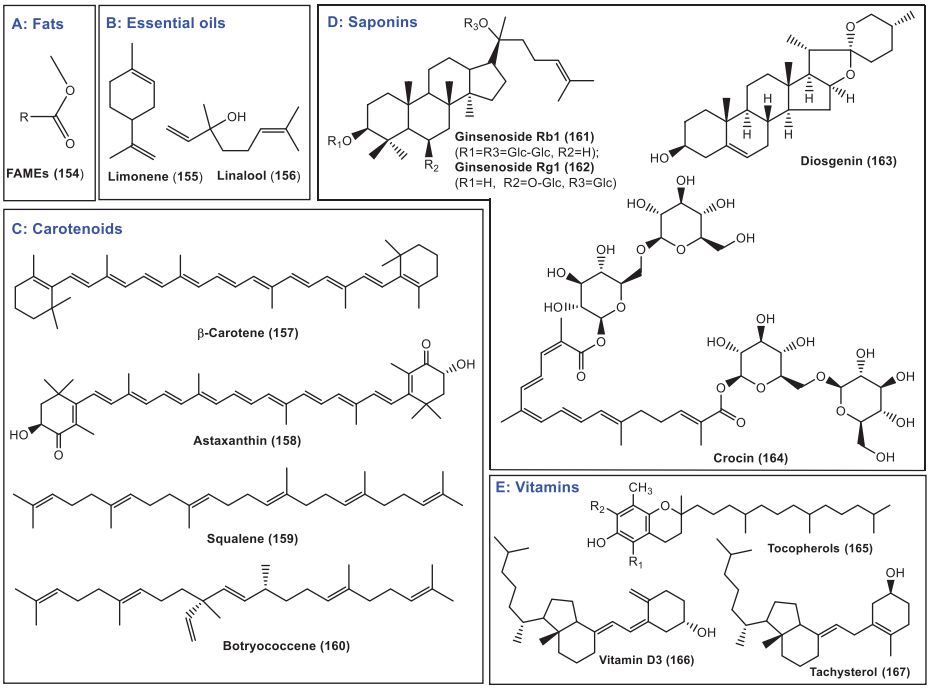


Figure 6.10: The structures of (A) fats, (B) essential oils, (C) carotenoids, (D) saponins and (E) vitamins extracted from natural sources using ILs.

6.4 Bio-based solvents

The ongoing processing of feedstocks derived from fossil fuels to create chemical products like fuels and solvents has given rise to major concerns due to deteriorating air quality as well as environmental, health and safety (ESH) hazards. As a result, several attempts are being undertaken to limit waste formation in chemical processes as well as the usage of hazardous compounds, especially volatile organic solvents. A fundamental tactic to promote sustainability, as well as green and safer chemical processes in both academia and industry, is to switch from the presently employed fossil-based solvents to sustainable ones generated from renewable resources [174, 175].

Numerous organic solvents are combustible, poisonous and volatile; as a result, they are not suitable for the environment, including human beings. This method seeks to make it easier to choose and employ solvents with low ESH hazards and favorable green profiles [176–178]. The current situation demands novel and inventive solvents, namely, bio-based solvents in both academia and industry [179, 180].

6.4.1 Features of bio-based solvents

Generally, solvents based on agricultural biomass are known as bio-based solvents. There are several types of solvents that can be obtained from these categories, including alcohols, alkanes, aromatics, esters, ethers and terpenes, as well as solvents intended to replace petroleum-based solvents. Figure 6.11 presented bio-based ((A) aprotic and (B) protic) solvents (**155**, **168**–**189**). The typical characteristic solvents must possess a number of parameters and prerequisites to qualify as a green solvent [181, 182].

A bio-based solvent can be produced and synthesized in a number of ways without having any negative effects on the environment. Biochemical and thermochemical conversion are the two main processing methods [179]. The manufacture of bio-based solvents (such as alcohols [183], esters [184], ethers [185], alkanes, aromatics [186] and neoterics [187]) is possible using these techniques or a combination of them.

2-Metoxolane, also called 2-methyltetrahydrofuran (2-MeTHF), was developed in the late 2000s [188]. This solvent is composed of three steps: (1) the liberation of pentose and hexose sugar units on the acid treatment of lignocellulosic material; (2) the biorefining process for making furfural and levulinic acid from sugars; and (3) hydrogenation with excess hydrogen of levulinic acid. In a similar way, cyclopentyl methyl ether is synthesized by two different methods. A nucleophilic substitution is used for one where cyclopentanol is methylated by dimethyl sulfate. The second one involves adding methanol to cyclopentane in an addition reaction (Table 6.6) [189].

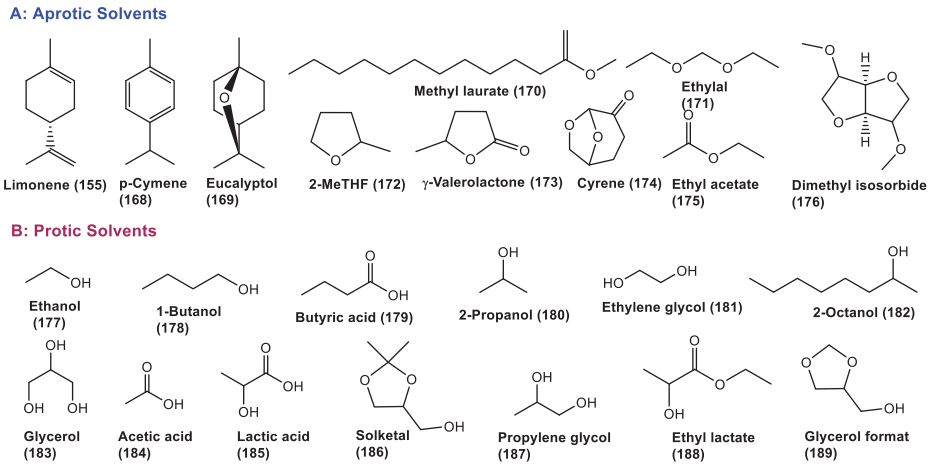


Figure 6.11: Bio-based ((A) aprotic and (B) protic) solvents.

Table 6.6: Extraction of various analytes using bio-based solvents.

Bio-based solvent	Method	Materials	Analyte	Reference
CPME	Hot reflux	*Yarrowia lipolytica*	Oil	[190]
D-Limonene	Pressurized liquid extraction (PLE)	*Anabaena planctonica*	Oil	[191]
DMC	Maceration	*Jatropha curcas*	Oil	[192]
	Three-phase partitioning	*Momordica charantia*	Peroxidase enzyme	[193]
Ethyl acetate	Reflux	*Betula pendula*	Triterpenoids	[194]
	Microwave	*Hura crepitans*	Oil	[195]
	Maceration	*Curcuma longa*	Curcuminoids	[196]
	Pressurized liquid extraction	*Camellia sinensis*	Caffeine	[197]
MeTHF	Soxhlet	*Pistacia lentiscus*	Oil	[198]
α-Pinene	Soxhlet	*Arachis hypogaea*	Fatty acids	[199]

CPME, cyclopentyl methyl ether; DMC, dimethyl carbonate; MeTHF, 2-methyl tetrahydrofuran.

6.4.2 Synthesis and applications of bio-based solvents

6.4.2.1 Alcohols

Bio-based ethanol, which is produced by biological transformation of sugars, is the most commonly produced of all biosolvents. Sugarcane and corn (edible feedstocks) or cellulose (nonedible feedstocks) are used in these processes [200, 201]. At this plant located in Milan, Italy, agricultural waste is pretreated with Proesa^{TM} technology for ethanol production at 60,000 tons per year from rice straw, giant cane and wheat straw [202]. The most widely used applications for ethanol are as a biofuel and solvent in consumer goods such as perfumes, food coloring and flavoring, alcoholic beverages and some types of mediation. Both natural and manufactured drugs may contain the latter. A highly effective method of extracting the active antimalarial drug, artemisinin, from *Artemisia annua* has been demonstrated [203].

It is currently possible to produce large amounts of methanol by hydrogenating carbon monoxide in the presence of catalysts such as ZnO/Cr_2O_3 and $Cu/ZnO/Al_2O_3$ [204]. Because methanol and ethanol have similar structural properties, the former is used in synthetic procedures in place of the latter. As a result of its toxicity, it is not widely used as a solvent in consumer products. Furthermore, methanol has many other applications other than a solvent, such as a reagent and fuel [205]. In addition to methyl levulinate synthesis from bioderived furfural alcohol (FA) and 2,5-hydroxymethylfurfurals, it is also utilized to produce methyl levulinate using acid catalyzation [206]. It is also known that glycerol's (**183**) raw materials can be used in the thermochemical synthesis of alcohols (**190**–**197**) such as methanol, ethanol and propanol (1-propanol and 2-propanol) (Figure 6.12). Catalysts are commonly used in hydrogenolysis reactions to promote this process [207].

The first commercial production of *n*-butanol took place in the early 1900s using the Weizmann method (ABE fermentation). Herein, *Clostridium acetobutylicum* is used to convert the starch feedstock into *n*-butanol, acetone and trace levels of ethanol [208]. Some ABE fermentation units exist today, but the majority of *n*-butanol is still primarily created from petroleum using either (1) the oxo synthesis, in which propene is hydroformylated and butyraldehyde is hydrogenated, while rhodium or cobalt homogeneous catalysts serve as homogeneous catalysts, (2) the Reppe synthesis (which involves oxidizing propene with CO and H_2O with iron as a catalyst or (3) a multistep, catalytic hydrogen borrowing, cascade process that involves hydrogenation of the resulting croton aldehyde after dehydration and self-aldol condensation of acetaldehyde [209]. *n*-Butanol is applied as a valuable solvent for paints as well as for coatings and it produces many solvents such as butyl propanoate, dibutyl ether, butyl acetate and plasticizers [210].

As the first step in the production of furfuryl alcohol, pentosan is hydrolyzed to produce pentoses, such as xylose; and then the pentoses are cyclohydrated into furfuryl alcohol by cyclohydration. Steam distillation and fractionation are used to recover furfuryl alcohol after the reaction is catalyzed by dilute sulfuric acid or phosphoric acid.

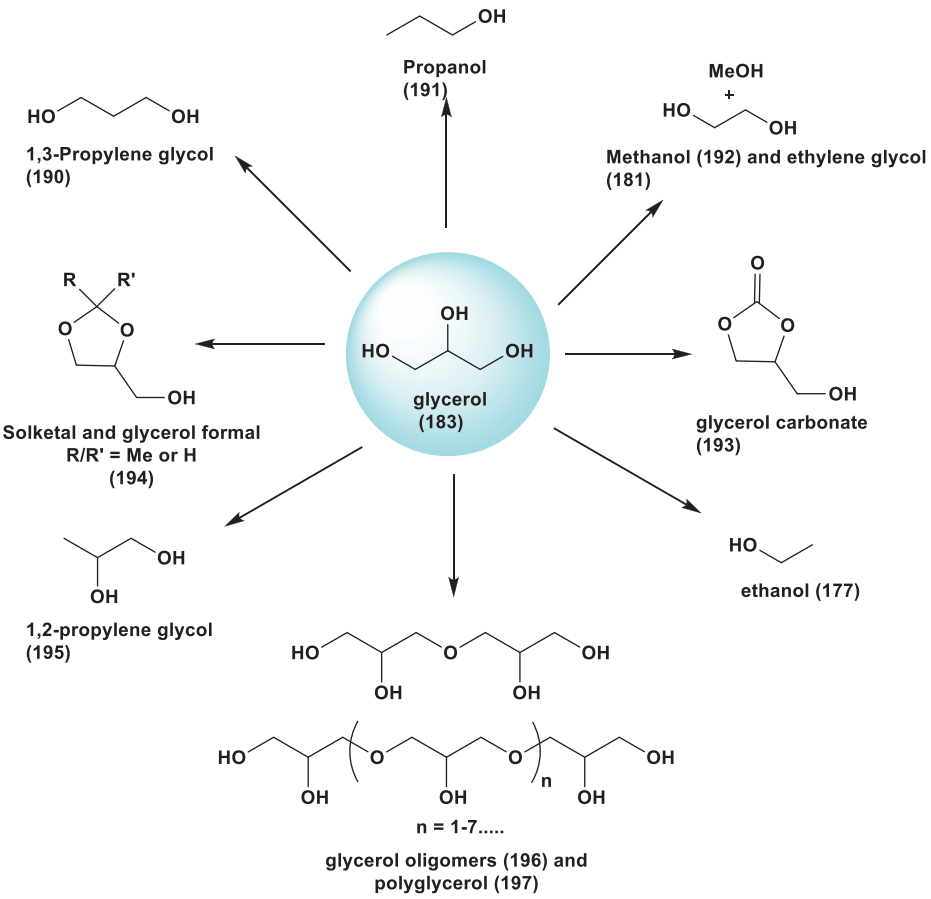


Figure 6.12: Bio-based solvents originated from glycerol.

Furfuryl alcohol can be used to modify high phenolic molding resins to increase corrosion resistance by crystallizing and modifying anthracene oils [211].

The worldwide production of biodiesel rose from 0.78 billion liters in 2000 to 32.6 billion liters in 2016 [212]. As a result, glycerol is widely available with biodiesel production producing 10,000 L of chemicals for every 100,000 L of fuel manufactured. In the past few decades, glycerol's oversupply and low toxicity have led to attempts to increase its use, both directly and indirectly (by accessing its value-added products). The use of glycerol in extractive distillation to purify bioethanol has been proposed in recent years as a viable replacement for fossil-derived polyethylene glycol.

The recovery of bioethanol is possible with as much as 99% purity using glycerol [213]. Glycerol has been used successfully in a number of *aza*-Michael addition, Suzuki–Miyaura and Mizoroki–Heck reactions, despite its high viscosity and boiling point complicating reaction workups [213]. The hydrophilic heads of glycerol oligomers

and polymers make them suitable for use in surfactant applications. Additionally, they have been designated as solvent replacements for glycol ethers made from fossil fuels in paints, inks and cleaning products [214].

Historically, diols have been used to dehumidify and treat antifreeze. They serve important functions as solvents in the cosmetic as well as coating industries as well as monomer production of polyester [215, 216].

6.4.2.2 Esters

A class of environmentally friendly, nontoxic solvents known as lactates is produced by reacting lactic acid with different alcohols including ethanol, propanol and butanol. Both biochemical and thermochemical methods can be used to obtain lactic acid feedstock needed to produce these solvents. The biological process uses microbial fermentation technology and is more selective than the latter, which is more cost-effective but produces a racemic combination of lactic acid and poisonous hydrogen cyanide. Triglycerides from vegetable or animal fats are transesterified with methanol to create FAMEs, which are used in biodiesel production. Furthermore, FAMEs have also been found to possess high solvent power, making them suitable for use as bio-based solvents. During the dissolution or cleaning of industrial components, evaporation is aided by combining ethyl lactate with the formulation [217].

There are direct and indirect ways of synthesizing glycerol carbonate. With direct approaches, glycerol is used to process carbon monoxide and oxygen [218] or carbon dioxide [219] using metal catalysts like Pd or Sn, if appropriate. A polar protic solvent, electrolyte liquid carrier, detergent solvent, humectant and nail polish/gel stripper can be used with glycerol carbonate because of its high polarity, boiling (110–115 °C) and flash (109 °C) points, along with low vapor pressure [220].

In order to produce γ-valerolactone, 5-hydroxymethylfurfural and FA are dehydrated and hydrolyzed, respectively, into levulinic acid. After levulinic acid is obtained, hydrogen and a suitable catalyst should be added to produce γ-valerolactone [221, 222]. Lignocellulose and carbohydrates were dehydrated into furans using this solvent after being pretreated and hydrolyzed. A number of cross-coupling reactions have been conducted using it, including those conducted by Sonogashira [223], Hiyama [224] and Mizoroki–Heck [225].

Dihydrolevoglucosenone or 6,8-dioxabicyclo[3.2.1]octanone, also known as Cyrene™, is a solvent with ketone functionality that may be made from cellulose in two steps [226]. Levoglucosenone is commonly used as a starting material for its synthesis, which can be obtained from a variety of plant materials, including Bilberry press cake, corn cob, poplar wood or bagasse [227]. As a result of levoglucosenone production, Cyrene™ was obtained by hydrogenating it. Figure 6.13 presented the synthetic steps of Cyrene™ (**193**) from cellulose (**191**). Cyrene™ is being investigated as a possible alternative due to worries about the industry's use of harmful solvents like *N*-methyl-2-pyrrolidone,

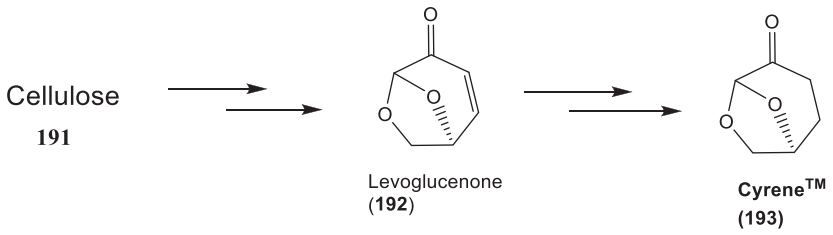


Figure 6.13: Synthetic steps of Cyrene™ from cellulose.

dimethylformamide (DMF) and dimethyl sulfoxide. Cyrene™ solvent has been successfully used to synthesize metal–organic frameworks previously synthesized in DMF [228]. Additionally, Cyrene™ has been utilized in amide bond-forming processes [229].

6.4.2.3 Alkanes and aromatics

Aldol-condensed products bearing longer carbon chains can be obtained by reacting furfural and hydroxymethylfuran in the presence of acetone (derived from fermentation). Following the condensation of aldols with acetic and/or Lewis acid cocatalysts, hydrodeoxygenation of the aldol condensation products produces alkane (**197**) as shown in Figure 6.14 [230, 231].

Due to their nonpolarity, alkanes are ideal for nonpolar reactions. Drugs, pesticides and other chemicals have been synthesized using them as reaction medium. Depending on the carbon chain length, they can be used as fuels. Liquefied petroleum gas made from C_3 and C_4 alkanes is used to cook and in cigarette lighters, while gasoline, diesel and aviation fuel are made from C_5–C_{18} alkanes.

Wood waste and agricultural waste can be used to create benzene, toluene and xylene (BTX) [232]. Anellotech, a US-based business, has scaled up a method for turning biomass into BTX mixes using its Bio-TCat™ technology. The characteristics of BTX are the same as those of their fossil-derived equivalents [233]. The production of resins, rubber lubricants, synthetic textiles, detergents, insecticides, medicines and plastics all involve the use of benzene.

Natural solvents like terpenes are produced by plants through the action of essential oils. By steam distillation and alkali treatment, D-limonene can be extracted from citrus peels and pulp [234]. Various halogenated hydrocarbons can be replaced with limonene as a solvent in industry. It is estimated that the demand for D-limonene will reach 65 kton per year in 2023 [61]. Additionally, it dissolves cholesterol stones better than chloroform and diethyl ether (DEE) in the dissolution of wool and cotton wool while also being used as a solvent to clean wool and cotton wool. When *p*-cymene is catalytically isomerized and dehydrogenated from D-limonene, it becomes an aromatic hydrocarbon with similar solvent properties as D-limonene [235].

There are many sources of pinene, but it is mostly found in essential oils extracted from coniferous trees, and it can also be recovered from paper pulp by-products, for example, crude sulfate turpentine [236]. Household cleaning solvents and insect repellents made from α-pinene are used in home and industrial cleaning as well as in perfume production.

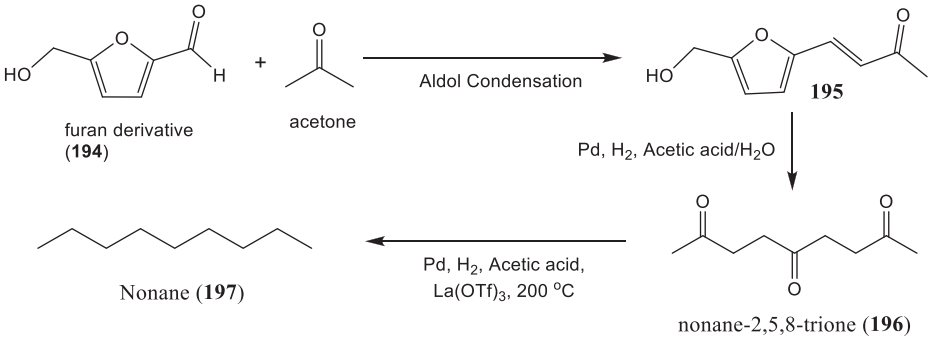


Figure 6.14: Synthetic steps for straight-chain alkane (nonane) from bio-obtained furan derivative.

6.4.2.4 Ethers

DEE and dimethyl ether are produced from ethanol and methanol when they are dehydrated to form bioderived ethers. Fuel additives are usually made with these ethers in order to enhance the octane rating and diminish emissions (NO_x and ozone) along with wear on engines.

An excellent preliminary toxicity assessment has been provided for 2-MeTHF, a biodegradable, environmentally safe, and easily recyclable ether solvent [237]. Through catalytic procedures, it is made from either furfural or levulinic acid. Figure 6.15 illustrates how furfural (**198**) is hydrogenated successively over Cu–Zn, Ni–Cu, Fe–Cu or Cu–Cr to produce 2-MeTHF (**172**) [238]. Despite the poor solubility of water in 2-MeTHF, Pfizer (USA) reports that 2-MeTHF can be used to solve problems in two-phase reactions [239]. The low boiling point of this bioderived solvent makes it difficult to contain on a large scale, which makes it an alternative to dichloromethane. With 2-MeTHF (**172**), amidation, alkylation and nucleophilic aromatic substitution reactions were achieved with

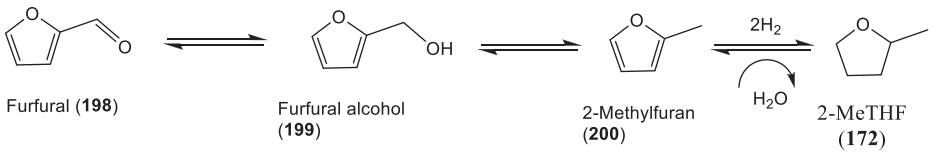


Figure 6.15: Stepwise hydrogenation of furfural to 2-MeTHF.

high yields as well as the synthesis of the intermediate 5-phenylbicyclo[2.2.2]oct-5-en-2-one [240].

6.5 Liquefied dimethyl ether

The use of liquefied dimethyl ether in the extraction of natural resources is popular due to its sturdy extraction capacity of organic compounds and water. Besides, this liquefied dimethyl ether is economical, nature-friendly and requires small power along with little extraction temperature, security and good compressibility [241]. The implementation of liquefied dimethyl ether commences its journey since two decagons ago and is employed to isolate various types of NPs. Liquefied dimethyl ether isolates water, oil and specific ingredients (organics) from natural resources. The disadvantages of this solvent are firetraps and loss of solvent. The feedstock of liquefied DME extraction is being constantly extended, and the liquefied DME technology itself is projected to be explored in novel application areas. Extensive investigations on liquefied dimethyl ether isolation methods are still going on for the betterment and optimization in both laboratory and commercial purposes in connection with the separation of NPs [241, 242].

6.5.1 Features of liquefied dimethyl ether

At room temperature, dimethyl ether is a colorless gas and possesses a slight ether-like smell. The vapor pressure of DME is 0.59 MPa at 298 K which indicates its easy compressibility into the liquid phase at room temperature. Moreover, DME is noncarcinogenic, nonreactive, nontoxic and unable to change the pH in the water solution. The density of liquefied DME is 0.667 g cc^{-1}. The critical temperature, pressure and boiling point of DME are 401 K, 5.4 MPa and 248.8 K, respectively. DME has a dissolving capacity of 7–8% by weight of water at room temperature [243, 244]. The advantages of liquefied dimethyl ether as an excellent extractant are its high extraction rate, the strong extraction capacity of water and organic compounds, environment-friendly, low extraction temperature, small energy requirement safety, better compressibility and the cheap price [245].

6.5.2 Applications of liquefied dimethyl ether for the isolation of natural products as a green solvent

Liquefied dimethyl ether started its journey as an extractant for NPs in the middle of 1970s. The US patents report that at first it is employed to isolate water and lipid

synchronously from the food staff and egg yolk. To date, this solvent is used to isolate various types of natural resources, mainly liquid or oil, water and specific ingredients as organics. Liquefied DME isolates two xanthin-type compounds such as fucoxanthin from macroalgae *Undaria pinnatifida* and astaxanthin from microalgae *Haematococcus pluvialis* [246, 247]. It also isolates the carotenoid lutein from macroalgae *Monostroma nitidum* [248]. Figure 6.16 presented the structures of xanthin- and carotenoid-type compounds **(201–203)** using liquefied DME.

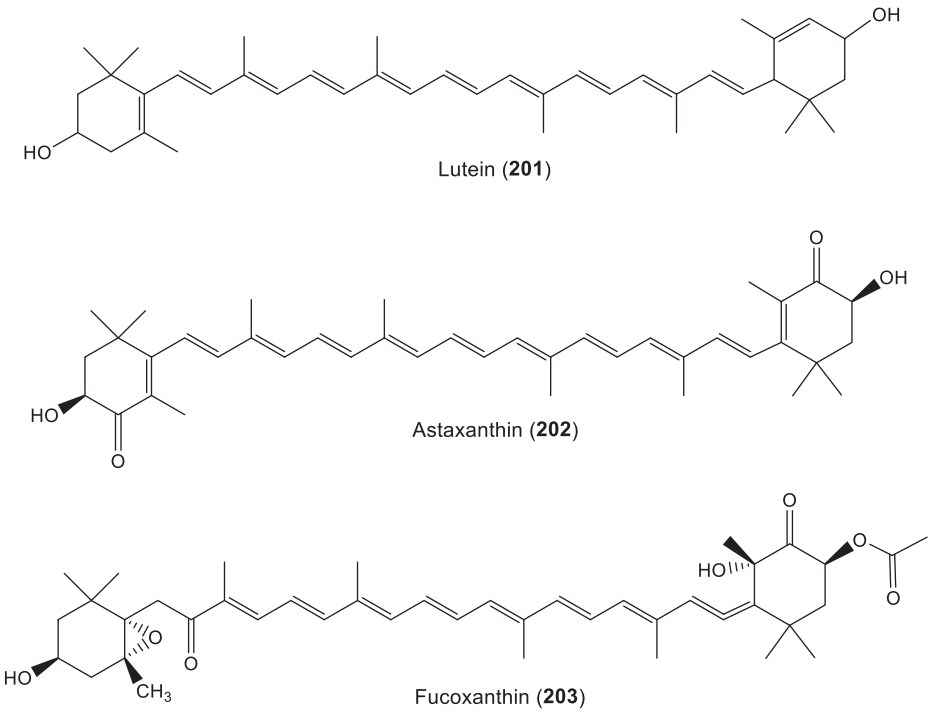


Figure 6.16: Structures of xanthin- and carotenoid-type compounds using liquefied DME.

Low-temperature liquefied DME isolates chlorophylls a and b from the green peel and of Japanese squash, spinach leaves and carotenoids from the yellow cortex of carrot roots and all kinds of vegetable samples [249]. Liquefied DME separates a number of proteins from carrot roots and also from juicy or relatively dry vegetable tissues. DME as a solvent can be efficiently employed to extract water-soluble protein from crude protein samples [250]. Three types of nutraceuticals, namely, γ-oryzanol, phytosterol and policosanol are extracted and purified from by-products of rice bran oil by green technique with low pressure using subcritical DME [251]. Figure 6.17 presented the structures of γ-oryzanol **(204)** and phytosterol **(205)** from rice bran oil by-products.

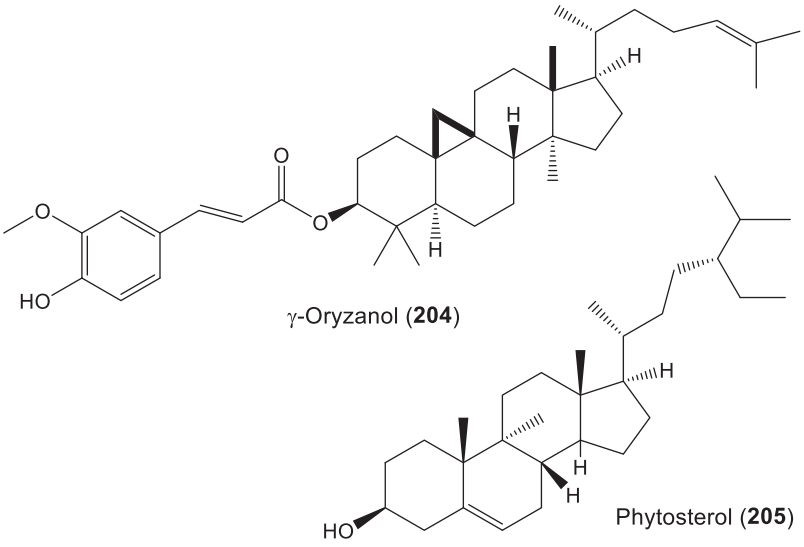


Figure 6.17: Structures of γ-oryzanol and phytosterol from rice bran oil by-products.

6.6 Conclusions

Plants comprise various active compounds such as alkaloids, terpenoids, steroids, phenols, tannins, flavonoids, volatile oils, resins and fixed oils that are accumulated in different parts of plants. These promising molecules are responsible to exhibit biological as well as pharmacological activities. The key step is extraction which is related to the separation of active chemical components from raw materials (plants) using suitable solvents through selective and standard procedures. For solvent extraction, the selection of a solvent is vital because solubility, market price and selectivity together with safety should be examined in the selection of solvents. For this purpose, conventional solvents suffer from various demerits such as it needs for a large amount of solvents and prolonged extraction time with a low yield of product. Besides, volatile organic solvents are harmful to living organisms, and ozone-layer destruction is also catalyzed by vapors of the volatile solvents from short-wavelength ultraviolet solar radiation. Hence, we need alternative and green solvents for the isolation of NPs and include some advantages such as a lower amount of solvent consumption and lower extraction time with a safe and high-quality extract or targeted product. SW, ILs, bio-based solvents, liquefied dimethyl ether and DESs became the most actively explored as potential green solvents. Future research priorities in the field of green technology should concentrate on the application of nonconventional solvents as this has been proven to work on an industrial scale for the extraction/separation of promising NPs.

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Chapter 7
Role of nonconventional solvents in drug design

7.1 Introduction

There are two classes of solvents: conventional and nonconventional. Conventional solvents are organic solvents that include two classes: polar and nonpolar. Examples of polar solvents are methanol, hexane, cyclohexanol, dipropyl methyl, chloroform, chlorobenzene, xylene, *n*-heptane, cyclopentanol, 1-octanol, benzyl alcohol, dibenzyl ether, 1,2-dichloroethane, methyl isobutyl ketone and methylcyclohexanol [1–3].

Nonconventional solvents contain ionic liquids and deep eutectic solvents (DESs). Ionic liquids are a class of solvents that, as a salt, possess an ion structure and are also referred to as nonaqueous solvents. The solvents are liquids at temperature below 100 °C. Some of them even melt at room temperature. Ionic liquids often have high viscosity, low vapor pressure, poor conductivity, high chemical stability, high electrochemical stability and various solubilities and are colorless. Carbon monoxide is less soluble in ionic liquids less than other organic solvents, but carbon dioxide has good solubility in many ionic liquids. Since ionic liquids have many various types, they have varying miscibility with water and organic solvents. These solvents are found as salts of unsymmetrical cations and symmetrical anions [4]. The cations of ionic liquids at room temperature include 1-methylimidazole, 1-alkyl-3-methylimidazolium, 1-ethyl-3-methyl-imidazolium, 1-butyl-3-methyl-imidazolium, 1-octyl-3-methylimidazolium [5], 1-decyl-3-methylimidazolium, 1-dodecyl-3-methyl-docecylimidazolium, 1-butyl-2,3-dimethylimidazolium, 1,3-di(*N*,*N*-dimethylaminoethyl)-2-methylimidazolium, methyl-*N*-butyl-pyridinium, *N*-octylpyridinium, tetraethylammonium and tetrabutylammonium. The anions of ionic liquids contain tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), bis-trifluoromethanesulfonimide (NTf_2), trifluoromethanesulfonate, dicyanamide ($N(CN)_2$), hydrogen sulfate (HSO_4^-), ethyl sulfate ($EtOSO_3$) and 1-butyl-3-methylimidazolium tetrachloroferrate (Table 7.1), and magnetic ionic liquids are synthesized as paramagnetic anions [6].

Brønsted and Lewis acids and bases produce a eutectic mixture, which is called DES. These solvents have wide applications in electrochemistry, separation and catalysis. Eutectic solvents have different generations which consist of a quaternary ammonium salt and a metal salt or hydrogen bond donor forming a complex together (Table 7.2).

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Table 7.1: The molecular structure, name and abbreviation of some of the anionic and cationic ionic liquids.

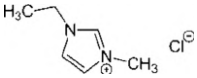
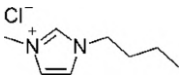
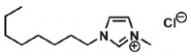
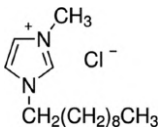
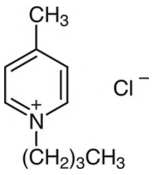
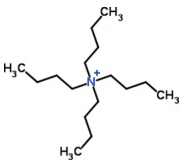
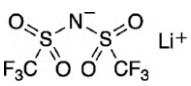
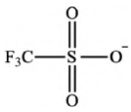
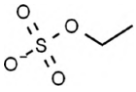
Molecular structure	Name	Abbreviation
	1-Ethyl-3-methylimidazoliumchloride	[EMIM]Cl
	1-Butyl-3-methylimidazoliumchloride	[BMIM]Cl
	1-Octyl-3-methylimidazoliumchloride	[OMIM]Cl
	1-Decyl-3-methylimidazolium	[DecMIM]Cl
	Methyl-*N*-butyl-pyridinium	[MBPy]Cl
	Tetrabutylammonium	TBA
	Bis-trifluoromethanesulfonimide	$[NTf_2]$
	Trifluoromethane sulfonate	[OTf]
	Ethyl sulfate	$[EtOSO_3]$

Table 7.2: The classification of deep eutectic solvents.

Type	Complex	Complex compound	Metal
Type I	$C^+X^-MCl_n$	Quaternary ammonium salts + metal chloride	M = Zn, Fe, Ga, In, Al
Type II	$C^+X^-MCl_n.H_2O$	Quaternary ammonium salts + metal chloride hydrate	M = Co, Cu, Fe, Ni, Cr
Type III	C^+X^-RY	Quaternary ammonium salts + hydrogen bond donor	Y = -$CONH_2$, COOH, OH
Type IV	MCl_n. RY	Metal chloride hydrate + hydrogen bond donor	M = Al, Zn Y = -$CONH_2$, COOH, OH

The first generation of DES is prepared from quaternary ammonium salts and a metal halide where the majority of which is chloride, as well as imidazolium compounds, such as $AlCl_3$ and 1-ethyl-3-methylimidazolium chloride. Type II of the eutectic mixture can be a combination of quaternary ammonium salts and choline chloride (Figure 7.1A), and hydrated metal halide. Choline chloride and hydrogen bond donors, such as urea, carboxylic acids, amides and ethylene glycol (Figure 7.1B), are from another class of eutectic mixture known as type III. This class of solvents is mainly used in metal extraction and electropolishing.

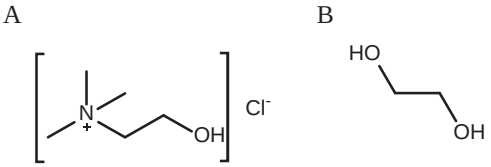


Figure 7.1: The structure of (A) choline chloride and (B) ethylene glycol.

Eutectic solvents of type IV are similar to type III, which employed metal chloride instead of quaternary ammonium salts. In general, phosphonium and sulfonium salts can be used instead of ammonium salts. DES has advantages over ionic liquids; for example, they are cheap, available, easy to prepare and less chemically inert.

Both of these solvent classes, ionic liquids and EDS, are employed in organic synthesis, industry and environment. Further, we discuss the role of these solvents in drug design, drug delivery and drug discovery.

7.2 Drug design

Drug design is a process that leads to the production of a novel drug. The aim of drug design is to influence a biological target. Synthesized drugs are usually small organic molecules, but there are biopharmaceuticals that contain peptides, proteins and antibodies [7]. When designing a drug, molecules are chosen based on the biomolecule

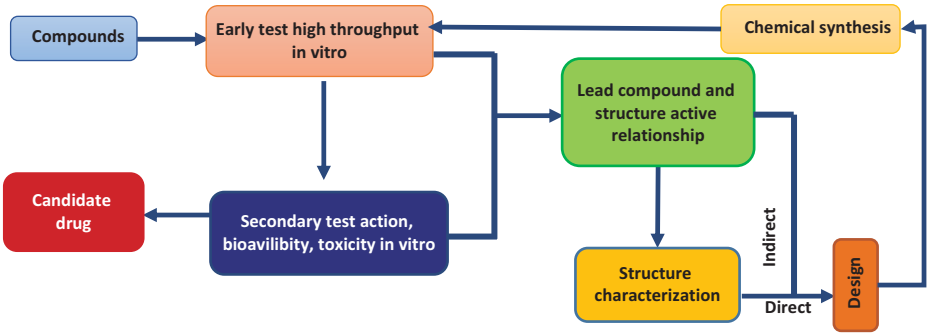


Figure 7.2: The drug discovery process is based on two strategies: ligands (indirect) and structures (direct).

target. These molecules are chosen based on their shape and charge in relation to the targeting molecules. Drug design often utilizes computer techniques and evaluated their selectivity, stability and affinity through computational methods, especially for large molecules [8]. In general, there are two methods for drug design: ligand-based (indirect) and structure-based (direct) approaches (Figure 7.2) [9].

Ligand-based drug design is often designed to join a biological target that has the minimum necessary structural features for deriving a pharmacophore model. Structure-based drug design is usually designed as a three-dimensional structure that is characterized via X-ray crystallography and NMR spectroscopy. Using the target structure, drugs are designed with high selectivity and affinity for binding to the target [4, 5]. Generally, drug design based on the structure includes three methods: identification of new ligands [10], designs of new ligands and the optimization of known ligands [11].

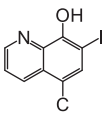
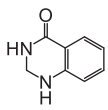
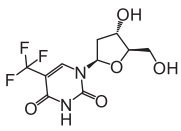
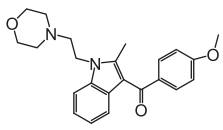
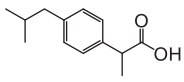
A synthesis is usually controlled by a solvent, so it can affect the rate and result of the reaction. However, some syntheses are performed as solvent-free. On the other hand, some of the drugs have low water solubility [12]. In this case, there are ways to improve water solubility constraints. One of them is the use of ionic liquids and DESs. Both of them have high potential in the pharmaceutical industry. The high versatility of ionic liquids allows for the design of their chemical structure to target specific applications. Ionic liquids possess unique properties, such as high chemical and thermal stability and strong solubility, which are suitable for the wide diversity of drug designs. The appropriate selection of cation and anion in ionic liquids can enable solid active pharmaceutical ingredients to be converted to liquid form. This function improved bioavailability and increased therapeutic properties. In addition, ionic liquids are also employed for drug delivery and development. In fact, ionic liquids are used as solvents, catalysts, reagents, cosolvents, crystallizers, additives [13] and emulsifiers for modifying drug solubility.

7.3 The ionic liquids' role in the pharmaceutical combination synthesis

In the pharmaceutical industry, most waste is produced in relation to solvents. To reduce and minimize this waste, replacing solvents is necessary for a sustainable process and development. According to the results, ionic liquids have been investigated to play multiple roles such as solvents, reagents, catalysts and enantioselective in the synthesis, as observed in Table 7.3. Using compounds containing diverse alcohols, amines and drugs based on chiral ionic liquids will lead to the design and development of new drugs [14]. Ionic liquids have been employed in preparing imidazoles [15], pyrazoles [16], esters [17], thiazolidines [18], thiazoles [19] and lactams [11, 15].

Ionic liquids can provide heating for microwave as quickly as they can be useful for organic reactions in the presence of ultrasound irradiation. The yield is usually over 80% when ionic liquids are present [20].

Table 7.3: Role of ionic liquids in the synthesis of active pharmaceutical ingredients with a sample.

Reagent	Catalyst	Reaction media		Enzyme stability and enantioselective
Antifungal	Precursors	Antiviral	Anti-inflammatory	Anti-inflammatory
Clioquinol	2,3-Dihydroquinazolin-4(1H)	Trifluridine	Pravadoline	Ibuprofen
				

In some cases, when a synthesis is carried out, you have to use three-component solvents (dispersive solvent, extraction solvent and water) for separation. Therefore, dispersive liquid–liquid microextraction is the best method for extraction [21]. In such systems, there is no need to add a step, and the workup is performed by centrifuge and the used solvents are magnetic ionic liquids, [C_4MIM^+] [$FeCl_4^-$], [C4MIM$^+$] [$FeBrCl_3^-$] and so on [22]. Liquid–liquid equilibria from three-component biphasic systems [22–24] such as [BMIM]BF_4, fructose and water are employed to evaluate correlation coefficients [24]. Biphasic systems are also employed in chemical synthesis, recycling and recovery of catalysts. Since enzymes have lower solubility in organic solvents, biphasic water–organic solvents (DMF and dioxane) can be so useful in organic syntheses such as acylation [25, 26]. In biphasic systems, supercritical CO_2 [2, 4, 27, 28] can also be utilized with long ionic liquid or polymers as one of the phases [29].

7.3.1 Ionic liquids as catalyst

Ionic liquids are suitable media for chemocatalytic and biocatalytic reactions [30]. According to the literature, even the synthesis of magnetic amphiprotic catalysts is performed in such solvents [31]. These solvents are liquids at temperatures below 100 °C and are entirely composed of ions. They have special chemical–physical properties such as low vapor pressure, high ionic conductivity, nonflammability, good solubility, high thermal and chemical stability. Organic cations such as dialkylimidazolium and tetraalkyl ammonium, which are paired with anions, are usually used in biocatalyst processes, for example, [PF_6] and bistriflimide. Ionic liquids are employed as the main media in reactions due to their unique properties. Ionic liquids have also been show to improve the catalytic activity of catalysts. One of their applications is affecting the esterification of carboxylic acids. The obtained ester had a high yield in the ionic liquid media, which can act as either a catalyst or a solvent (Figure 7.3). Recycling such catalysts is convenient, and their reuse produced products with high efficiency [17].

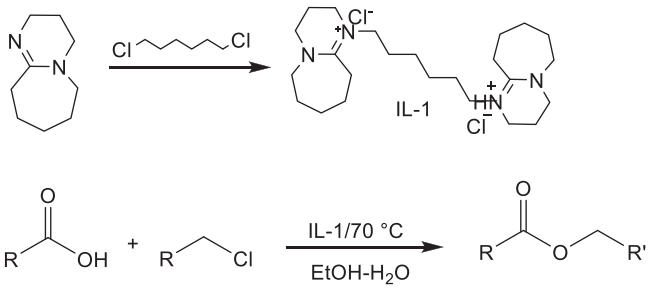


Figure 7.3: Esterification of carboxylic acids in the presence of ionic liquids as a catalyst as well as a solvent.

In the extraction of organic compounds (glucosinolates, their derivatives and isothiocyanates) from plants and vegetables (broccoli, Brussels sprouts, cabbage, kohlrabi, cauliflower, horseradish, collards, turnip, kale, mustard species and vegetable seeds), nonconventional solvents, hexane and supercritical carbon dioxide have also been utilized. On the other hand, the ionic liquids can support the extraction of different organic compounds which are used for various purposes. For example, the peptides are extracted from tobacco leaves and enriched by phosphorylation for analysis (Figure 7.4) [32]. The extraction technique plays a key role in separation and extraction, in actuality. The extraction techniques such as immersion, soxhlet, maceration, steam distillation, ultrasound-assisted extraction and microwave are used for the extraction of essential oils from plants [33].

The derivative of *S*-alkyl tetrahydrothiophene is synthesized in the presence of [NTf_2^-] and tetraphenylborate salts (Figure 7.5), which determined the viscosity and density decrease of the prepared *S*-alkyl with changing temperatures [34]. Aldehydes,

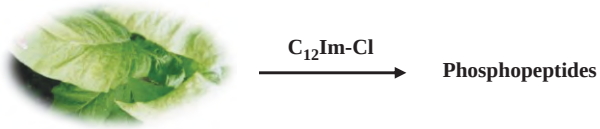


Figure 7.4: Preparing phosphopeptides in the presence of ionic liquid.

Claisen–Schmidt and Knoevenagel condensation, Michael addition, Paal–Knorr and Hantzsch synthesis, cross-coupling reactions and three-component reactions are organic reactions that lead to generating dioxo derivatives under ultrasonic irradiation and an ionic liquid solvent. The solvent plays a pivotal role in this process [35]. In continuing organic synthesis, the Friedel–Crafts acylation reaction is subjected under ionic liquid and pyridine [36]. The presence of Lewis acids like $FeCl_3$ as a suitable catalyst with a long ionic liquid solvent is used for the synthesis of *S*-alkyl derivatives (Figure 7.6).

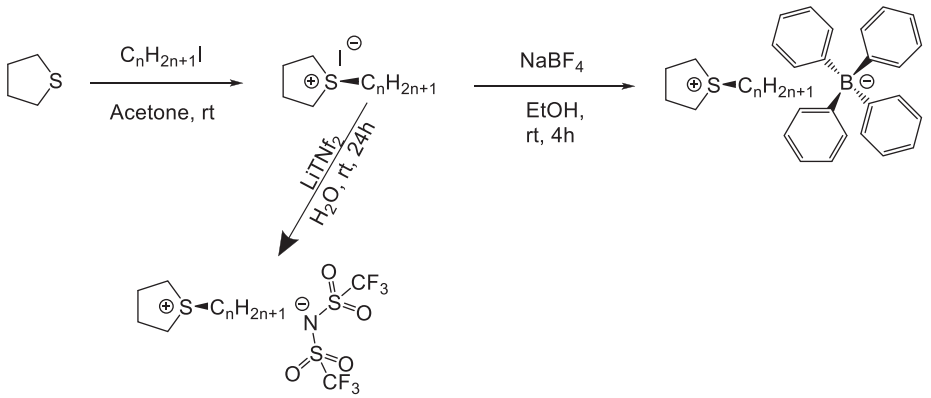


Figure 7.5: Synthesis of *S*-alkyltetrahydrophenium iodide with TNf_2^- and tetraphenylborate salts.

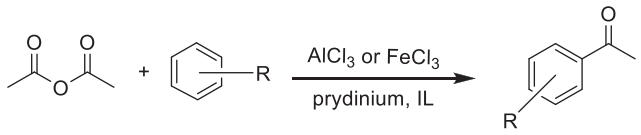


Figure 7.6: Friedel–Crafts acylation of anhydride acetic acid and benzene derivatives.

Ionic liquids are referred to as green chemical solvents due to their nonvolatile nature, which allows for full recycling and major reuse. When suitable cations and anions are selected, their polarity and miscibility with molecular solvents can be modified in biphasic systems, which have been used to develop useful approaches to

product recovery. Ionic liquids, even those that are not miscible with water, are polar solvents that can absorb some of the water. The presence of water molecules in ionic liquids is essential for protecting existing protein complexes in biocatalysts [28, 37].

Biocatalytic methods are often utilized in nonconventional media [4, 28, 38, 39]. Such environments can be beneficial for the sustainable chemical industry, technological applications and enzymatic transformations. Recently, chemoenzymatic synthesis of phosphonic acid with a polar side chain has been reported [40]. However, enzymes are also used as industrial catalysts in the end syntheses. In the industry, enzymes have more applications in esterification and peptidization. Nonconventional solvents may impact the enzyme's properties, as enzymes lose their activity in high concentration, especially at concentrations over 25%. One of the ways in which such solvents are effective is through interaction with the hydration part of enzymes and hydrophobic sites of proteins [41]. However, enzymes can carry out reactions in both hydrophilic and hydrophobic solvents [42]. The various parameters investigated in enzymatic syntheses [26] in nonconventional media are pH, temperature, enzyme quantity and water, which influence the enzyme activity [43]. It is a fact the nonaqueous solvent determines the stability of the enzyme [44]. These cases have been studied for the majority of synthesis.

7.3.2 Ionic liquids as solvent, cosolvent and surfactant

The therapeutic properties of drugs are mainly described by their solubility and bioavailability, as the high solubility in water can facilitate the attainment of the desired drug concentration. Many drugs are poorly soluble in water, so solvents such as ethanol, dimethylsulfoxide, methanol and ionic liquids are used as cosolvents [45] or solvents in organic reactions to improve the solubility of drugs [12, 46]. To address this issue, using ionic liquids is a good idea [47]; the high solubility of ionic liquids increases the drug solubility in aqueous solutions through micellization and hydrotropic phenomena. If the anion and cation of ionic liquids are chosen correctly, it affects the solubility mechanism of drugs with low-water solubility significantly. Another method that can be used to increase the solubility of drugs in water is a surfactant. Modifying the hydrophilic–hydrophobic nature of ionic liquids requires changing the length of carbon chains and the type of cations. Ionic liquids are often known as surface-active liquids due to surfactant treatment [48].

7.3.3 Ionic liquids in crystallization of drugs

In drug development and production, it is necessary to design polymorphs because they influence the produced drug's shelf life and bioavailability. Moreover, the crystallization of drugs depends on the rate of solubility and structural stability. Crystallization is a key step in the separation and purification of pharmaceuticals [49]. In

addition, the solvent, the saturation of the solution, the temperature of the reaction system and the increasable material can impact crystallization. Ionic liquids are not only used as an aid in the crystallization of new drug design but also to modify the crystal form and enhance the separation and purification properties of crystals that cannot be obtained through conventional solvent. It is important to use the correct techniques in crystallization such as solvents and cooling.

7.3.4 Ionic liquids in drug delivery

One more application of ionic liquids in the field of pharmaceuticals is acting as solvents or monomers for polymerization (emulation and suspension) in the preparation of drug delivery systems [50]. In these cases, ionic liquids are employed in the structure of nanocarriers, nanofibers, nanoparticles, membranes, polymerization [51, 52], vesicles, ionogels and permission enhancers. They are excellent solvents for biopolymers such as proteins, DNA [53, 54] and polysaccharides. On the other hand, ionic liquids have displayed special properties in the drug release. Ionic liquid-based forms can be used for intravenous, oral, transdermal [55] and topical [56] delivery. Tanner et al. [57] employed 16 types of ionic liquids to prepare a novel drug delivery system. When they used choline and geranic acid with a ratio of 1:2, they obtained the maximum yield in transdermal delivery. They found that when they had ionic liquids in the drug carrier with the fewest interionic interaction [58], transdermal drug delivery was performed with maximum success. In addition, adhesive patches based on ionic liquids were designed and synthesized for the treatment of neurodegenerative diseases [59]. In the patches, donepezil and ionic liquids were linked via hydrogen bond or ionic bonds and developed for the treatment of Alzheimer's disease [60].

7.3.5 Ionic liquids and biological activity

Ionic liquids illustrate the biological activities as they have a variety of anions and cations [61]. Some of the biological activities of ionic liquids include anticancer [62, 63], antibacterial [64], antiviral [65], anti-inflammatory [66], antioxidant and antitumor [18]. Ionic liquids including imidazolium, pyridinium or the alkyl chain length of cation display antibacterial properties. However, the alkyl chain length of both the anion and cation in the structure of ionic liquids affects the designed drug such as fluorinated ionic liquids: ($[C_2C_1Im]^+$, $[C_2C_1py]^+$, $[C_4C1pyr]^+$, $[N_{1112}(OH)]^+$ or $[N_{4444}]^+$) and ($[C_4F_9SO_3]^-$, $[C_8F_{17}SO_3]^-$ or $[N(C_4F_9SO_3)_2]^-$) [67].

7.4 Deep eutectic as catalyst and solvent in the organic reactions

DES is used to synthesize novel combinations. In this case, many reactions can be performed using traditional and old methods or new and modern methods. Often, reactions require catalysts such as esterification [68], transesterification and acylation. A new C–C bond is formed by an acylation reaction (Figure 7.7A–B). The catalyst present in the reaction is Grubs II (Figure 7.7C). Using Grubbs II as a catalyst in the presence of DES led to a product with low yield. However, employing biocatalysts resulted in an increase in the yield of products [69].

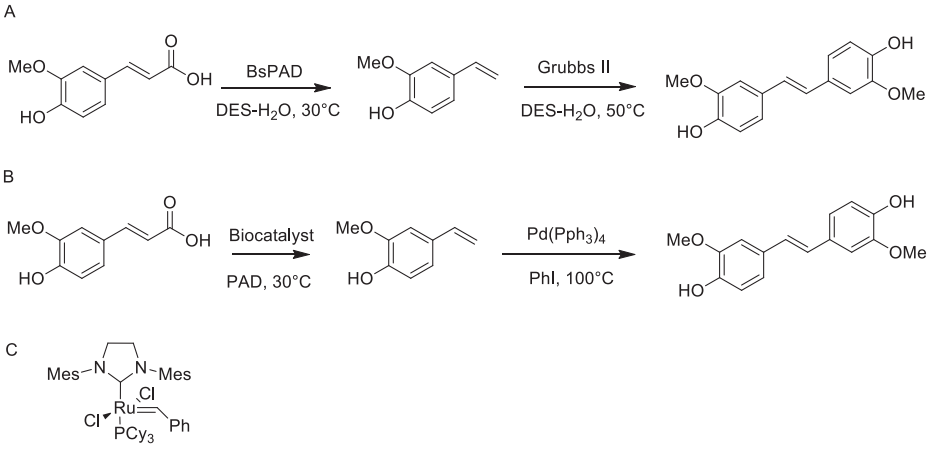


Figure 7.7: Formation of a new C–C bond in the presence of DES. (A) The reaction catalyzed Grubbs II, (B) the reaction carried out in the presence of biocatalysts and (C) the structure of Grubbs II.

Stereoselective synthesis is applied for preparing nitrostyrene and hydrolysis of ketones [70] in the presence of organic catalysts and DES. At both 20 and 50 °C temperatures, Michael addition was enforced and a complete conversion was observed, as shown in Figure 7.8. The yield was more than 90% in all syntheses, and recycling of the chiral catalyst was easy and possible due to the type of solvent [71].

DES can be applied either as a catalyst or as a solvent. In preparing azoles and indoles, DES acts in both these cases via click chemistry (Figure 7.9). The yield of 1H-tetrazole is lower than other azoles and indoles at such reactions. That is why sodium azide has low stability [16].

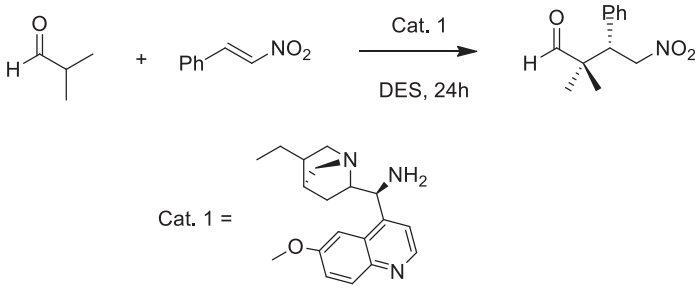


Figure 7.8: Synthesis of stereoselective nitrostyrene in the presence of DES and organic catalyst.

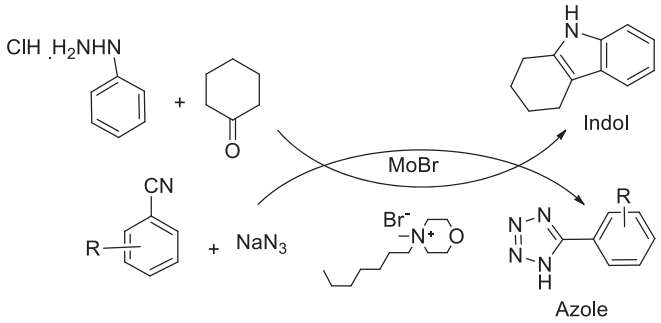


Figure 7.9: Synthesis of azoles and indoles via click chemistry and DES as catalyst and solvent.

7.5 Conclusions

Nonconventional solvents are organic solvents that involved compounds with short and long chains, polar and nonpolar structures and cyclic and noncyclic. Two important classes of these solvents are DES and ionic liquids, which have unique properties. Both of them have many applications in experimental and industry due to their unique features. They have the most application in the pharmaceutical industry. Nonconventional solvents are employed as catalysts, reagents and carriers in drug delivery, additives and biological activities. They increased the drug solubility in aqueous solutions and can develop new drugs with different therapeutic properties. Modifying the surface of nonconventional solvents will produce a number of new drugs that can influence and control diseases.

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Chapter 8
Industrial applications of nonconventional solvents

8.1 Introduction

Solvents are crucial platforms in the synthesis of organic compounds. The choice of a solvent is therefore critical in order to develop eco-friendly and sustainable synthetic methodologies of these solvents. Various organic solvents are used for carrying out different organic transformations on lab scale and industrial level also, but these are associated with demerits like toxicity, generation of hazardous fuels and low boiling. Therefore, a search is necessary for nonconventional solvents or green solvents for developing eco-friendly routes in organic synthesis. Here, many solvents have been tried to replace traditional solvents like ionic liquids and supercritical solvents (water and carbon dioxide), but the list is not complete. Here, polyethylene glycol (PEG), glycerol, cyclopentylmethyl ether, 2-methyltetrahydrofuran (2-MeTHF), ethyl lactate, and so on have been used successfully as solvents in various processes, and all these are discussed in this chapter. Nowadays, different eco-friendly solvents are used, which can find eco-friendly applications in fine chemical syntheses, particularly from large-scale industrial manufacture point of view.

8.2 Polyethylene glycol (PEG)

PEG is a polyether, which was derived from petroleum. It is used in many industrial applications (pharmaceuticals, cosmetics, lubricants, ink, surfactants, cleansing agents, emulsifiers, skin conditioners and humectants). PEG is also called polyoxyethylene (POE). PEG is produced by the reaction of ethylene oxide with water, ethylene glycol or ethylene glycol oligomers. It is a hydrophilic polymer of ethylene oxide.

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PEG has proved its worth in different biological and chemical studies. It has found a variety of applications such as phase transfer catalysis, peptide synthesis, cell and protein purifications, pharmaceutical modification, binding assays and polymer-bound reagents. The preparation of various PEG derivatives was excellently reviewed by Harris [1]. PEG and its esters and ethers are normally used as starting materials of these compounds. PEGs are POEs having hydroxyl end groups with molecular weight in the range of 20,000 Da or less.

Some low-molecular-weight PEG-plasticizing polylactides (PLAs) were prepared by Hassouna et al. [2] to improve the ductility of PLA, but retaining the content plasticizer at maximum 20 wt% of PLA. A reactive blending of anhydride-grafted PLA (MAG-PLA) copolymer was done with PEG, having chains terminated with hydroxyl groups. It was reported that the anhydride-functionalized PLA chains were grafted onto a fraction of PEG during the melt-processing, which will improve the compatibility between PLA and PEG. The presence of MAG-PLA does not influence the behavior of plasticized PLA much with reference to viscoelastic and viscoplastic properties. It was observed that elastic modulus and yield stress decrease with or without MAG-PLA, but the ultimate strain was found to be increased on adding PEG into PLA.

A method has been reported by Li et al. [3] for immobilization of lipase through polylactic acid (PLA) modified with PEG. It was found that lipase from *Candida rugosa* (type VII) can be easily immobilized on the PLA/PEG film (biocompatible) in the presence of glutaraldehyde and 1,6-hexamethylene diamine. It was revealed that the presence of 1,6-hexylenediamine maintains the enzymatic activity (maximum) with 8% w/w, while on immobilization, the optimum temperature of lipase shifted from 45 to 50 °C. The immobilized lipase was found to retain its original activity of up to 63% on treatment at 50 °C in buffer for 2 h, which was significantly higher when compared to control (33%). The optimum pH value of as-prepared lipase was also shifted from 6.5 to 7.5 on immobilization. It was interesting to note that the immobilized lipase maintained up to 70% of its original activity even on storage for 30 days while free lipase can maintain only 23%. It was also found that the lipase (immobilized) exhibited excellent reusability (82%) even after six cycles.

Su et al. [4] prepared TiO_2/Ag nano-antibacterial material at low temperature. They used PEG-600 as reducing as well as stabilizing agent. It was reported that the average particle size of TiO_2 among these nanomaterials was found to be 50–150 nm, while it was around 20 nm in case of silver. It was revealed that the growth inhibition rates against *E. coli* was 99.99%, when concentration of nanoparticle dispersion solution was kept at 10 ppm, and the minimum UV-protective effect could be achieved at the concentration of 290 ppm.

A composite phase change material was obtained by Qian et al. [5], which was PEG/SiO_2 shape-stabilized using oil shale ash (hazardous waste). Here, PEG served for thermal energy storage as a phase change material, while SiO_2 acts as the carrier matrix which provided structural strength, and as a consequence, the leakage of PEG (melted) was prevented. It was revealed that the extraction efficiency of silica could

reach 60.36%, with the following optimal conditions: reaction time (4 h); sodium hydroxide concentration (20 wt%); calcination temperature (900 °C); time 60 min; and liquid/solid ratio (4 mL g^{-1}). It was indicated that the composite had encapsulation ratio and efficiency, high phase change enthalpy and thermal storage capability. It was reported that the melting time, the solidifying time and the supercooling extent of the composite were 26.5, 22.6 and less than 22.3% than pristine PEG, respectively.

Khan and Jiabi [6] prepared solid dispersions of ibuprofen (IBF) by solvent evaporation method. They used PEG 10000, talc and PEG–talc as dispersion carriers. No important and well-defined chemical interaction was observed between the ingredients. An increase in the dissolution rate of IBF from solid dispersions with the carriers may be due to factors like local solubilization, improved wettability and drug particle size reduction.

Morita et al. [7] prepared biodegradable microspheres loaded with protein via solid-in-oil-in-water emulsion process using PEG. PEG lyophilized a protein solution resulting in spherical protein microparticles with diameter <5 μm, which are dispersed in a continuous PEG phase. They used a conventional in-water drying method in the second step. It was observed that horseradish peroxidase was effectively entrapped into microspheres (monolithic type) of poly(DL-lactic-co-glycolic acid) (PLGA), without any significant loss in its activity. It was also revealed that another model protein, bovine superoxide dismutase, could be encapsulated by the "polymer–alloy method" into reservoir-type microspheres using both poly(DL-lactic acid) (PLA) and PLGA.

Firouzabadi et al. [8] carried out thioarylation of structurally different alkyl bromides such as *n*-octyl benzyl, cyclohexyl, cyclopentyl, cinnamyl, *tert*-butyl bromides and benzyl with aryl bromides, iodides and an activated chloride using thiourea in wet PEG 200 (eco-friendly medium) catalyzed by copper(I) iodide in the presence of potassium carbonate under an inert atmosphere at 80 and 100 °C. It was reported that this process has no foul-smelling thiols.

Idris et al. [9] prepared asymmetric polyethersulfone (PES) ultrafiltration flat sheet membranes by the phase inversion process from a casting solution containing *N*,*N*-dimethylformamide as solvent, PES as polymer and PEG of different molecular weights as additives (PEG 200, PEG 400 and PEG 600). As-prepared membranes were characterized in terms of molecular weight cutoff (MWCO), flux, pure water permeation (PWP), solute separation and membrane morphology. It was revealed that membranes with PEG have higher molecular weights with larger pores and higher PWP. It was revealed that MWCO of membranes increased from 26 to 45 kDa with the increase in molecular weight of PEG from 200 to 600. It was also revealed that significant changes were also there in solute separation, PWP and flux, when the concentration of additives was increased from 5 to 25 wt% in casting solution.

Wolcott et al. [10] reported the synthesis of ultrathin WO_3 nanodisks via wet chemical route using PEG as a surface modulator. It was revealed that as-prepared structures have dimensions on the order of 350–1,000, 200–750 and 7–18 nm in length,

width and thickness, respectively. It was suggested that large flat surface area and high aspect ratio of as-prepared WO_3 nanodisks have a potential for use in Photoelectrochemical (PEC) cells for production of hydrogen through water splitting of water.

8.3 Glycerol

It is a colorless, odorless and viscous liquid, which is sweet and nontoxic in nature. It is quite commonly used as a sweetener in the food industry and as a humectant in pharmaceutical formulations. It has three hydroxyl groups, and is therefore miscible with water and is also hygroscopic in nature. Glycerol is used in different medical, pharmaceutical and personal care products.

Transportation and electricity generation require fossil fuels (hydrocarbons) at present but their reserves are regularly declining. It has been predicted that the present global dependency on fossil fuels will not be economically or environmentally sustainable for a long term in future. As a result, an interest in biodiesel has increased in recent times. The use of crude glycerol as a by-product for production of biodiesel is still an existing challenge from an environmental and economic point of view. But crude glycerol can be used as an organic carbon substrate for the production of some high-value chemicals such as 1,3-propanediol, polyols or organic acids using some microorganisms [11].

Glycerol carbonate (GC) can be prepared from glycerol through transesterification of glycerol using dimethyl carbonate (DMC) in the presence of coal fly ash, which was K-zeolite derived via hydrothermal treatment [12]. The effect of different operational parameters such as catalyst loading, reaction temperature and time and molar ratio of DMC to glycerol on the transesterification reaction was observed. It was reported that when DMC–glycerol molar ratio (3:1), catalyst loading (4 wt.%) and reaction temperature (75 °C) were maintained, then 100% and 96% could be achieved for glycerol conversion and GC by this process, respectively. It has been suggested that the as-prepared GC can be used as a green electrolyte solvent, in lithium batteries and as bio-based fuel additive.

Pradhan and Sharma [13] suggested a clean approach for preparation of CaO/TiO_2 nanoparticles using waste chicken eggshells and TiO_2 as inorganic support. Then it was used for the synthesis of GC. It was reported that at the optimal conditions (temp = 90 °C; time = 180 min; catalyst loading = 3 wt% of glycerol–DMC:glymolar ratio = 4:1; and CaO/TiO_2 (3:1) mixed oxide) the reaction exhibited 99.3% glycerol conversion and 93.7% yield of GC. It was revealed that green metrics like environmental factor (E-factor) was 0.082, which indicated the transesterification reaction with 100% atom utilization. It was claimed that this designed catalyst possesses green chemistry metrics to be used in the manufacturing process of GC in both industrial and lab scales. The use of

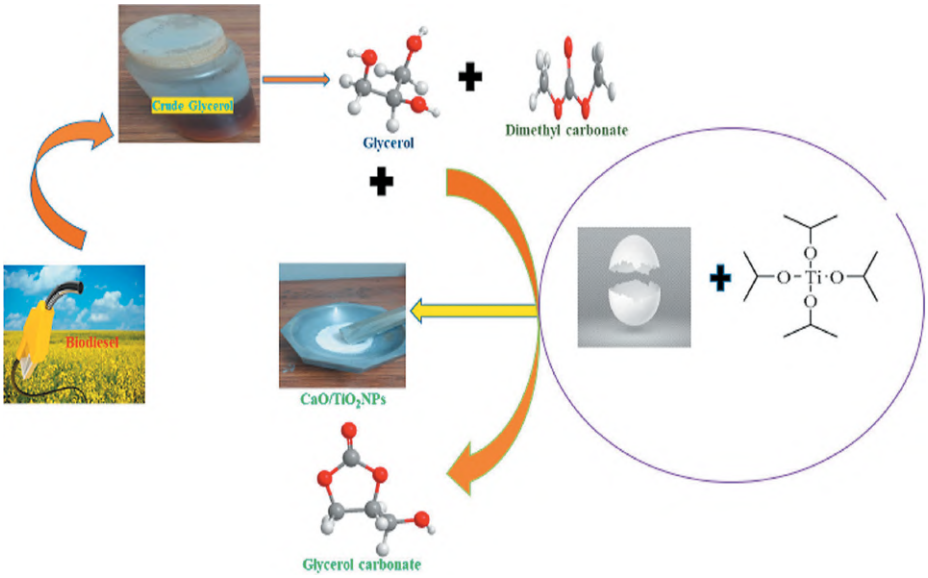

Figure 8.1: Synthesis of glycerol carbonate from biowaste glycerol (adapted from [13] with permission).

eggshell (waste) is low cost and green. This reduced the waste generation and the cost of its treatment, which makes it relatively economic and eco-friendly.

Mantzouridou et al. [14] investigated the use of glycerol as a carbon source (supplementary) to glucose for β-carotene production by *Blakeslea trispora.* It was reported that the highest β-carotene production (15.0 mg g^{-1} of dry biomass) could be obtained at a glycerol concentration of 60.0 g L^{-1}. It was observed that glycerol (industrial)-stimulated β-carotene synthesis was more than 10 and 8 times of soap by-product and biodiesel by-product when compared to the control medium. It was also revealed that the maximum β-carotene contents were 10 and 8 mg g^{-1} of dry biomass, respectively, and its content (relative) in the carotenoid fraction was good (86–88%).

Existing biodiesel manufacturing processes produced crude glycerol as a side fraction. Biodiesel will generate a large quantity of glycerol, suggesting that this type of conversion to a fuel is not a viable route. Sabourin-Provost and Hallenbeck [15] reported that the photosynthetic bacterium *Rhodopseudomonas palustris* is capable of converting glycerol via photofermentation, as both pure and crude glycerol fraction to hydrogen, a fuel of future. They could obtain relatively high yields, up to 6 mol of H_2 mol^{-1} glycerol (75% of theoretical, 8 mol of H_2 mol^{-1} glycerol). Even the crude glycerol fraction was converted to hydrogen with no evidence of toxicity or inhibition. It was also revealed that the concentration of added nitrogen can be used to modify both rates of hydrogen production and its yields. It was suggested that some factors may be identified, which can be examined in future to increase rates and/or yields.

González-Pajuelo et al. [16] evaluated growth inhibition of *Clostridium butyricum* VPI 3266 by raw glycerol obtained from the biodiesel production process. It was reported that *C. butyricum* presents the same tolerance to raw and commercial glycerol of similar grade, 87% (w/v). It was observed that a 39% increase of growth inhibition was there in the presence of 100 g L^{-1} of a lower grade raw glycerol (65% w/v). They also found that 1,3-propanediol production from two raw glycerol types (65% w/v and 92% w/v; without any prior purification) was there in batch and continuous cultures. It was revealed that there was no significant difference in *C. butyricum* fermentation patterns on raw and commercial glycerol as the sole carbon source, and the yield of 1,3-propanediol was about 0.60 mol mol^{-1} glycerol consumed in both these cases.

Bhatti et al. [17] used waste tallow as a low-cost sustainable and potential feedstock for the production of biodiesel. The effect of different reaction parameters on biodiesel production such as temperature, time and amount of catalyst was investigated. The optimal conditions obtained for processing of 5 g tallow were: temperature = 50 and 60 °C; oil/methanol molar ratio = 1:30 and 1:30, amount of H_2SO_4 = 1.25 and 2.5 g for chicken and mutton tallow, respectively. They could obtain the formation of chicken and mutton fat esters under optimal conditions as 99.01 ± 0.71 and 93.21 ± 5.07% in 24 h in the presence of acid. It was revealed that a total of 98.29% and 97.25% fatty acids were found in chicken and mutton fats, respectively. It was also suggested that both these fats were found suitable for producing biodiesel with deserved fuel properties.

8.4 Cyclopentylmethyl ether (CPME)

Cyclopentyl methyl ether (CPME) is also called methoxycyclopentane. It is a hydrophobic ether solvent. CPME is not used as a reaction solvent only but as an extraction as well as a crystallization solvent because it has higher hydrophobicity, lower peroxide formation and relatively higher boiling point. Cyclopentylmethyl ether is used in organic synthesis mainly as a solvent. Easy separation and recovery from water are added advantages of CPME. The CPME is a green and sustainable solvent of choice for many chemical transformations.

Normally, diethyl ether (Et_2O) and tetrahydrofuran (THF) are organic solvents used for Grignard reactions, but these solvents have certain issues, when applied for the synthesis on a large scale in manufacturing chemicals. The disadvantage of Et_2O is that it is highly flammable and has properties such as anesthetics, while THF is slowly converted into explosive peroxides and its recovery becomes very difficult due to its miscibility in water.

Kobayashi et al. [18] use CPME (green solvent) in Grignard reactions. They indicated that its recycling is possible, which makes these more eco-friendly, particularly, tramadol and tamoxifen. It was reported that diisobutylaluminum hydride is a proper activator of magnesium, and as a result, some Grignard reagents may be prepared in

heterogeneous or homogeneous media using CPME. It was revealed that CPME can be easily recycled after use in the Grignard reaction without any adverse effect of the reaction yield in consecutive experiments. The CPME was found to be stable under the conditions of Grignard reaction as it can be recovered. It was also reported that some Grignard reagents were found to be stable in CPME for a number of months, and as a result, these solutions can be used as a substitute of existing reagents. It was observed that tramadol hydrochloride (analgesic) and tamoxifen (an antiestrogenic drug used for treatment of breast cancer) can be successfully prepared by Grignard reactions using CPME as a solvent.

They also evaluated the potential of CPME as a solvent in a number of radical reactions such as hydrosilylation, hydrostannation, hydrothiolation and tributyltin hydride-mediated reductions [19] (Figure 8.2). It was indicated that CPME degraded into cyclopentanone, methyl pentanoate, cyclopentanol and 2-cyclopenten-1-ol under thermal radical conditions, but only slightly. They could achieve radical-containing one-pot reactions in CPME for its applicability to multistep reactions.

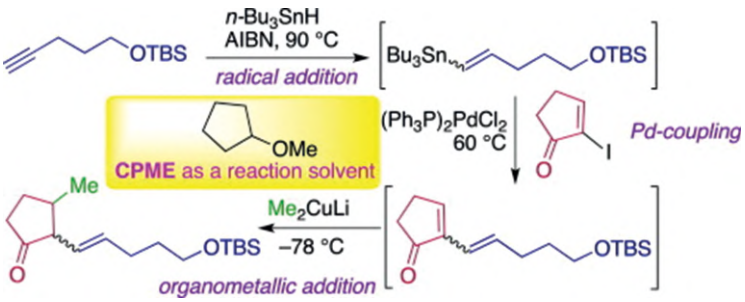

Figure 8.2: Cyclopentyl methyl ether as solvent for radical reaction (adapted from [19] with permission).

It is known that darifenacin is a potent and competitive M_3-selective receptor antagonist. Its hydrobromide salt is also an active ingredient of pharmaceutical formulations for oral treatment of urinary incontinence. Pramanik et al. [20] carried out an efficient, commercial manufacturing process for the synthesis of darifenacin hydrobromide using CPME–water as a solvent in the presence of K_2CO_3 followed by a reaction with aq. HBr (Figure 8.3).

Probst et al. [21] evaluated CPME for extracting triacylglycerol (TAG) or oil from wet cells of the oleaginous yeast *Lipomyces starkeyi*. CPME is considered a greener alternative of chloroform, which is a promising solvent for oil recovery at present. It was reported that a monophasic system of CPME or biphasic system of CPME:water (1:0.7) has poor extraction efficiency of TAG and its selectivity. Multiphasic systems of CPME:water:alcohol with different alcohols (methanol/ethanol/1-propanol) were evaluated, and it was found that methanol could achieve the best oil extraction efficiency

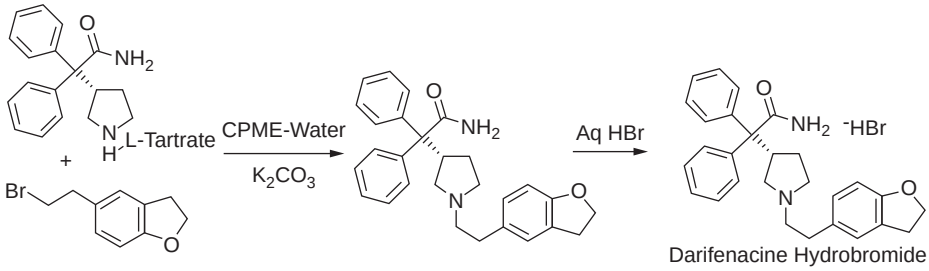

Figure 8.3: Cyclopentyl methyl ether for the synthesis of darifenacine hydrobromide (adapted from [20] with permission).

as compared to other two alcohols: ethanol and 1-propanol. It was revealed that highest extraction efficiency and TAG selectivity of 9.9 mg mL^{-1} and 64.6%, respectively, could be achieved using a starting ratio of 1:1.7:0.6 and a final ratio of 1:1:0.8 (CPME: methanol:water).

The separation of some monocarboxylic acids (formic acid (FA), acetic acid (AA) and propionic acid (PA)) from aqueous solutions is still a problematic issue. Türk et al. [22] reported the recovery of FA, AA and PA from aqueous solutions using tributyl phosphate as an extractant and green solvents such as CPME and 2-MeTHF. It was revealed that the distribution coefficient (*D*), extraction efficiency (*E*%) and loading factor (*Z*) were found to be in the range of 0.289–4.003, 22.41–78.41% and 0.198–2.218, respectively. It was observed that when the extractant concentration was increased, it was formed to be effective on using CPME as the diluent, but not on using 2-MeTHF. It was indicated that the extraction efficiency in both these diluents followed the same order: PA > AA ≥ FA.

Direct arylation polymerization (DArP) is a developing method for conjugated polymer synthesis. Pankow et al. [23] reported the application of green and sustainable solvents like 2-MeTHF, CPME, diethylcarbonate and γ-valerolactone for DArP toward the preparation of poly(3-hexylthiophene) (P3HT) and poly[(2,5-bis(2-hexyldecyloxy)phenylene)-*alt*-(4,7-di(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazole) (PPDTBT). It was observed that CPME provided the higher polymerization products with M_n up to 41 kDa for PPDTBT with significant yields (98%). It was interesting to note that the application of CPME to P3HT resulted in M_n values of 12 kDa with 93% regioregularity (RR) and that too with no detectable β-defects.

Oshima et al. [24] used CPME as an extractant for Au(III) in acidic chloride media. They compared the extraction behavior of Au(III) using CPME with other extractants such as dibutyl carbitol (DBC) and methyl isobutyl ketone (MIBK). It was reported that the order of extractability for Au(III) followed the order:

MIBK > DBC > CPME

It was revealed that the extraction selectivity of these extractants was similar for metal ions, but MIBK exhibited relatively a lower metal selectivity.

8.5 2-Methyltetrahydrofuran (2-MeTHF)

2-MeTHF is a highly flammable and mobile liquid. It is mostly used as a substitute for THF for better performance, such as higher reaction temperatures and easier separations, and it is not miscible with water. 2-MeTHF is considered a good solvent for low-temperature lithiation reactions because of low m.p. and less viscosity at lower temperatures. It has been promoted as an eco-friendly alternative to conventional solvent THF, although 2-MeTHF is little expensive, but it can be compensated with greater overall process economy. 2-MeTHF is a biomass-derived chemical that can find use as a green solvent for organic reactions in industries. It has applications in organocatalysis, organometallics, biotransformations as well as biomass processing. 2-MeTHF is a readily available, neoteric, less expensive and bio-based solvent.

The benefits of 2-MeTHF as green solvents are:

- Benign and sustainable
- Broad tolerance
- Mild conditions
- Large scale
- Fe-NHC catalysis
- HetAr arylation
- Application to API

Lei et al. [25] reported Suzuki–Miyaura cross-coupling of esters and amides catalyzed by palladium–NHC through chemoselective O−C(O) and N−C(O) cleavage with aryl boronic acids using an eco-friendly, green and sustainable solvent, 2-MeTHF. They could couple a variety of aryl esters and amides with aryl boronic acids with higher yields. It was claimed that the use of 2-MeTHF gave highest turnover number (TON) in amide N−C(O) bond cross-coupling. This simple protocol can be utilized in synthesizing a bioactive ketone intermediate with 2-MeTHF as a green solvent.

Englezou et al. [26] combined a series of metal-free and enzymatic ring-opening polymerizations (ROPs) with free radical and controlled reversible addition fragmentation chain transfer (RAFT) polymerizations (separately or tandem) in 2-MeTHF so as to tune the chemistry as well as the architecture of final polymers. The amphiphilic polymers were therefore formulated into nanoparticles and evaluated for their cytocompatibility in three different model cell lines so as to assess their application as possible polymeric excipients for nanomedicines. The suitability of 2-MeTHF as a green solvent was tested for different organo- and enzymatically catalyzed ROP of simple diblocks and also in the production of A–B–C block copolymers with a single-

or double-catalyst system. Two labile ester ROP initiators (hydroxyethyl methacrylate (HEMA)) and (polyethylene glycol methacrylate (PEGMA)) were utilized to initiate lactic acid (LA) macromonomers. To test the versatility of 2-MeTHF as "multipolymerization" green solvent, the macromonomers formed were tested in FRP and RAFT tandem polymerization.

Bisz and Szostak [27] reported that iron-catalyzed cross-coupling of tosylates and aryl chlorides with organometallic reagents having β-hydrogen gave good to excellent yields by using 2-MeTHF as a green, eco-friendly and sustainable solvent. It was observed that this reaction has excellent functional group tolerance under mild conditions also. Such cross-coupling reactions (iron-catalyzed) permit the formation of C−C bonds in the syntheses of fine chemicals, pharmaceuticals and natural products catalyzed by the earth-abundant base metal. Apart from it, large-scale cross-coupling, cross-coupling of challenging aryl tosylates and heteroaromatic substrates, and carbamates mediated with Fe–N-heterocyclic carbene catalysts are also possible:

$$(\mathrm{Het})\mathrm{Ar}-\mathrm{X}+\mathrm{R}-\mathrm{MgX}\xrightarrow[\text{2-MeTHF}]{\text{Fe catalysis}}(\mathrm{Het})\mathrm{Ar}-\mathrm{R}$$

Bannock et al. [28] reported the synthesis of P3HT by Grignard metathesis (GRIM) polymerization. They used a bio-derived "green" solvent, 2-MeTHF. It was observed that the product yield, molecular weight distribution and RR were similar to as obtained with THF. They used a catalyst derived from nickel(II) bromide ethylene glycol dimethyl ether complex ($Ni(dme)Br_2$) and 1,3-bis(diphenylphosphino)propane at 65 °C with almost fourfold increase in the reaction rate and that too with complete conversion within 1 min as compared to THF-based synthesis at 55 °C. It was reported that polymer had an Mw of 46 kg mol^{-1}, with a low PDI (1.4) and an RR of 93%, which indicates that flow-based GRIM polymerization in 2-MeTHF is suitable for high-throughput synthesis of P3HT (high quality).

Smoleń et al. [29] examined the application of 2-MeTHF as a solvent for olefin metathesis using a series of second-generation ruthenium Hoveyda-type catalysts (Figure 8.4). They studied the effect of temperature, and the results were compared with conventional solvents (dichloromethane and toluene) for metathesis. Olefin metathesis is important from industrial manufacturing point of view. Therefore, there is a pressing demand to search for eco-friendly solvents applicable on large scale. This solvent has wide range of applications in synthetic organic chemistry as well as pharmaceutical chemistry.

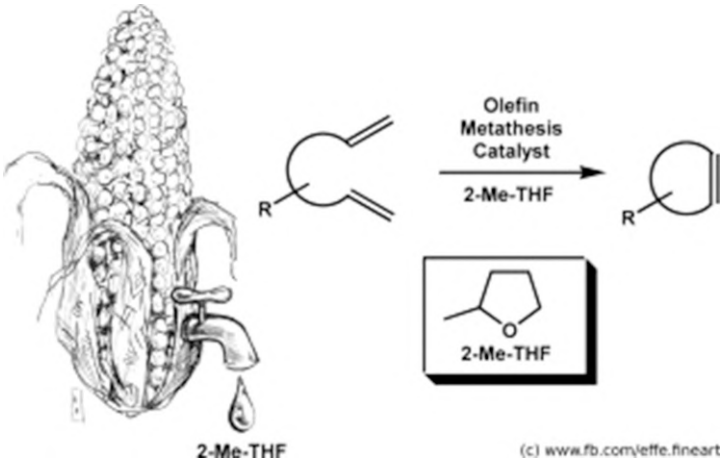

Figure 8.4: 2-Methyltetrahydrofuran as a solvent in olefin metathesis catalyzed by ruthenium (adapted from [29] with permission).

8.6 Ethyl lactate

Ethyl lactate is an ethyl ester of lactic acid with formula $CH_3CH(OH)CO_2CH_2CH_3$. It is a colorless liquid, which is a chiral ester. It is available as a single enantiomer and can be used as a water-rinsible degreaser. It is also biodegradable. Ethyl lactate is present naturally in inmate quantities in a wide range of foods, including chicken, wine and different fruits. It is an eco-friendly solvent and is effective when comparable to petroleum-based solvents.

The advantages of using ethyl lactate as green solvents are:

- Visible-light irradiation
- One-pot procedure high yields
- Broad scope of substrate
- Easy scalability for room-temperature reaction
- Eco-friendly solvents
- No any additional promoter
- Avoiding thermal energy

Zhang et al. [30] developed an efficient and eco-friendly method for the synthesis of spirooxindole–pyran derivatives using the three-component reaction of malononitrile, isatins and enolizable C–H-activated compounds such as dimedone, 2-hydroxynaphthalene-1,4-dione and 4-hydroxycoumarin (Figure 8.5). They carried out this reaction in water–ethyl lactate at room temperature in the presence of visible light. This solvent has certain advantages such as high yield, clean and mild

reaction conditions, absence of catalyst, visible light as a source of energy and ethyl lactate/water as a green solvent, apart from one-pot multicomponent reaction at ambient temperature, which needs no chromatographic separation, and it is also applicable on large scale.

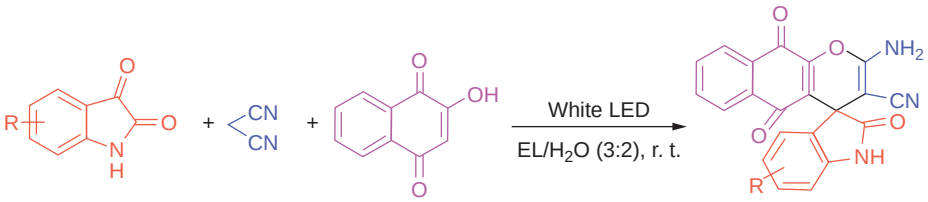

Figure 8.5: One-pot synthesis of spirooxindole–pyran derivatives in aqueous ethyl lactate (adapted from [30] with permission).

The effect of various green cosolvents such as ethanol, ethyl acetate and ethyl lactate extraction of caffeine from green tea leaves was observed by Bermejo et al. [31] using supercritical carbon dioxide. They reported highest caffeine yield with ethyl lactate in both the approaches: static and dynamic extractions as 13.0 and 14.2 mg g^{-1} of tea, respectively. It was followed by ethanol (10.8 and 8.8 mg g^{-1}), while the yield with ethyl acetate was lower than 7 mg g^{-1}.

Golmakani et al. [32] used two extraction techniques and two green solvents for the extraction of γ-linolenic acid (GLnA)-enriched fractions using *Arthrospira platensis* (spirulina). The two approaches used were expanded ethanol with CO_2 (gas-expanded liquid extraction, GXL) and pressurized liquid extraction (PLE) with a mixture of ethanol:ethyl lactate. It was reported that total yields up to 20.7% (w/w) could be obtained under optimal conditions in case of PLE as follows: pressure = 20.7 MPa, temperature = 180 °C, extraction time = 15 min and ethanol:ethyl lactate (50:50, v/v), where 68.3% recovery of GLnA was achieved. The GXL method provided total yields of 7.4% (w/w) with a GLnA recovery of 35.3%, and both these values are lower than the PLE method.

Karthika et al. [33] observed crystallization of IBF using ethyl lactate as a green solvent (Figure 8.6). They investigated crystallization of IBF grown in 50% aqueous ethyl lactate. It was reported that IBF can be crystallized from aqueous ethyl lactate, where the system does not pass through two-phase separation.

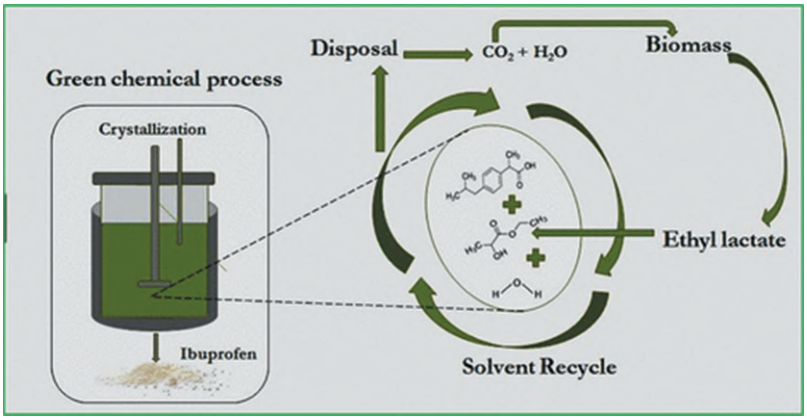

Figure 8.6: Crystallization of ibuprofen using ethyl lactate as green solvent (adapted from [33] with permission).

8.7 Conclusions

The traditional solvents used in laboratories and industries generate harmful vapors on use; therefore, there is a pressing demand all over the globe to replace such toxic solvents by some green solvents. There are many alternate solvents suggested in the last few decades for use at industrial level, but search is still on for some more effective eco-friendly solvents. Such solvents in common use are PEG, glycerol, cyclopentyl-methyl ether, 2-MeTHF, ethyl lactate and so on. This list is not complete as other possibilities are also there such as supercritical solvents (water and carbon dioxide), ionic liquids, *p*-cymene, limonene and gamma-valerolactone. Many more eco-friendly solvents will replace the existing harmful solvents in years to come.

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Chapter 9
Impact of nonconventional solvents on environment

9.1 Introduction

The chemical industry has a major role in increased pollution and is thus degrading the quality of air, water and soil. Under such conditions, green chemistry has been the guide to eradicate toxic substances [1]. Chemical reactions are manifold and occur at different conditions of temperature and pressure having three components, namely, solvent, reagent and energy input. Every component has its own role and affects the outcome of reaction [2]. Solvent is the main concern as its improper selection can be a hurdle in the manufacturing of pure products and may cause health and environmental toxicity. Solvents are ubiquitous and have a significant share in everyday life from making a cup of tea to synthesize a compound in the laboratory. These are crucial synthetic products, with a multimillion ton yearly market. They are consolidated by their job of being inert liquids having the role of dissolving the solute. Before the existence of petrochemical industry, water, naturally derived oil and substances were used as solvents. The numbers of solvents presently available are stupendous in an effort to fulfill the purpose of various processes and formulations. Solvents have different chemical functionalities because water, alcohol, amines, acids and other solvents having these as chemical groups come under protic solvents, whereas aprotic solvents are more diverse which include aliphatic, olefinic, ethers, ester, ketones, nitriles and amides [3]. Certain factors influence the action of the solvent, which includes how smoothly a solvent evaporates at encompassing temperature conditions, chemical nature of solvent, water miscible or immiscible and concentration of solvents [4]. The fate of solvent in the environment depends on the physicochemical properties such as volatility, chemical structure, water and lipid solubility, flammability and explosiveness.

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9.1.1 Volatility

It is an important parameter for considering the health and environmental impact. Higher the volatility of a solvent, higher is its concentration of vapor in the air. The vapor pressure and rate of evaporation are two measurements of volatility. Both are temperature sensitive and rise as the temperature rises [5].

9.1.2 Chemical properties

The functional group attached to solvents decides the toxicological properties. The number of carbon atoms and the presence or absence of saturation determines the toxicity of solvent and how atoms are arranged (straight chain or branched).

9.1.3 Flammability and explosiveness

These are two important determinants of hazards. For instance, some solvents can be explosive and there is a risk of fire or explosion due to exothermic reaction. Some solvents have the tendency to evaporate at atmospheric temperature and enter the human body and cause birth defects as they are carcinogenic. Since water is such an excellent solvent, much of the harmful pollution produced by humans eventually ends up in the ocean. Many chemical compounds accumulate in the sediment and the sea surface microlayer solvents after entering the marine environment, polluting water and posing a serious threat to aquatic creatures [5].

Solvents have a negative impact on our environment because their paths infiltrate the air, water and soil. Long-term exposure to products that involve hazardous environments can cause a slew of issues for humans, animals and the environment. Solvents are frequently utilized in the industry and they can be found in consumer products that people come into contact with on a regular basis [6]. Organic solvents generated from oil are hazardous and have negative health, environmental and safety consequences. The chemicals can cause different types of hazards which include physical hazards (flammability and explosive properties), toxicity and environmental hazards (decrease in ozone layer, climate change and overheating) [7]. It can also be harmful to the animals' liver and kidneys when released into the drinking water by industries. Meanwhile, despite their toxicity, researchers are hesitant to utilize green solvents instead of conventional solvents, and the industries and laboratories continue to use hazardous solvents, regardless of whether they produce high yields or not.

Green chemistry, on the other hand, provides methods for synthesis that reduce pollution and avoid the use of derivatives in reactions. Green chemistry also aims to employ ecologically friendly solvents that produce good results. Because of the emissions that harm the environment, it is necessary to remove volatile organic compounds

(VOCs) [8]. For example, tetrachloroethylene (PERC) is used as a solvent in dry cleaning and metal degreasing [8]. It is emitted from the industry which results in increased quantity of PERC in air, soil and water, and in particular, when it is mixed into the soil. It is not evaporated and thus migrates into groundwater. It also contributes in the formation of photochemical smog through its breakdown into phosgene (toxic chemical) and chloroacetylchlorides in air [9]. Most of the commonly used solvents such as chloroform, carbon tetrachloride and benzene pose threats to the environment. Therefore, the use of solvent should be reduced to wherever required and it should be nontoxic, nonflammable and compatible to the environment [2]. Solvent revelation occurs through different routes: inhalation, transdermal or ingestion. Individuals working in industries such as metal degreasing and painting, involved in mixing solvents, are at higher risk to exposure to harmful solvents. Some categories of population which include children and elderly are more prone to exposure to solvent's deleterious effects causing dysfunctioning of gastrointestinal and respiratory functions. The toxicokinetics of the given solvent depend on the lipophilicity and volatility of chemicals. The rate of uptake depends on the partition coefficient of blood and air for each solvent. The mechanism of toxicity varies with the specific solvent. There are two toxicity types: acute and chronic. In short-term and acute toxicity, the solvent follows a conventional approach of increase in effect with an increase in dose. On the other hand, chronic exposure to high doses can lead to cancer [10].

Incessant agglomeration of these solvents in the environment as well as inappropriate waste handling is the fundamental cause of pollution and is accountable for severe toxicity to land, air and marine life. Depletion of ozone layer, contamination of groundwater, increased biological oxygen demand and chemical oxygen demand are consequences of consumption of conventional solvents [11]. Some of the risks associated with conventional solvents are summarized in Table 9.1.

Table 9.1: Common solvents and their impact on environment.

Solvent	Risk to health	Risk to environment	References
Benzene	Causes acute myeloid leukemia, acute nonlymphocytic leukemia and myelodysplastic syndromes	Photochemical smog	[11, 12]
Toluene	On exposure causes eye and nose irritation, tiredness, dizziness, anxiety, insomnia, liver and kidney damage	Membrane damage to leaves and chronic toxicity to marine life	[11, 13]
Zinc	Causes lethargy, neuronal deficits, immune dysfunction, copper deficiency	Contamination and pose risk to aquatic life	[14, 15]

Table 9.1 (continued)

Solvent	Risk to health	Risk to environment	References
Lead	Affects the central nervous system and kidney	Negative impact on the plant vegetative growth	[16, 17]
Ammonia gas	Vapor irritates the skin, eye and respiratory tract	Impacts species composition and damage to leaves	[5, 18]
Acetic acid	Exposure causes eye irritation, chest tightness, fever, confusion and headache	Harmful to animals and aquatic life	[19, 20]
Acetonitrile	Irritation of mucous membrane and chronic exposure causes headache, numbness and tremors	Toxicity to microorganisms (bacteria, protozoans, cyanobacteria and green algae)	[21, 22]
Dimethyl formamide (DMF)	Cardiac injury, liver and kidney disorder	Enter into the marine system and converted into the precursor, which is the main source of greenhouse gases	[23, 24]
Hexane	Dizziness, polyneuropathy, numbness in the extremities and blurred vision	Affects aquatic organisms	[25, 26]

9.2 Solvent selection methods

Despite being widely used, solvent is neither the active component of a formulation nor it is directly responsible for the composition of a reaction result. As a result, the utilization of toxic, combustible or environmentally hazardous solvents would appear to be superfluous, as these properties have no bearing on the system function. These unfavorable outcomes of solvent use are frequently linked to the solvent's good properties. Solvent volatility allows for solvent recovery and purification by distillation, but it also produces undesirable air pollutants and poses a danger of worker's exposure [27]. For instance, hydrocarbon solvents have audacity to dissolve oils in extractions and conduct separations [28, 29] but they are also very flammable, and their low water solubility (high log *P*) is associated with bioaccumulation and aquatic toxicity [30, 31]. In order to eliminate the disagreeable solvents, different organizations introduce restriction on such solvents and propose alternative solvents, which are structurally related. The Montreal Protocol has prohibited the use of carbon tetrachloride due to its ozone-depleting nature and suggested halogenated solvents such as chloroform and dichloromethane (DCM) [32]. It is critical to note that these efforts have proven to be short-sighted in the face of more stringent chemical restrictions around the world. Furthermore, even as a short-lived halogenated chemical, DCM has now been demonstrated to deplete ozone [33].

Solvents with similar structural similarities can be easily supplied as drop-in replacements, but they are likely to cause many of the same environmental, health and safety (EHS) issues as previous solvent substitutions. Environmental agencies have their own techniques to regulating hazardous substances, with solvents being particularly affected due to their VOC status and hence the increased risk of exposure [34]. Solvent selection tools have been developed to turn down the economic and environmental influence. Solvent performance on reaction along with EHS aspects has been taken into account by these tools. The performance of a solvent is largely determined by its physicochemical and thermodynamic properties, which can be predicted using a variety of methodologies [35].

Different guides have been developed by pharmaceutical industries for ranking the solvent on the basis of greenness which can be referred from Table 9.2. They have developed their own hierarchy to rank solvent, which leads to minimization of use of solvent or use of more greener alternatives [36]. The first guide was developed by SmithKline Beecham. Thirty-five solvents were ranked based on the environmental impact, waste, health and safety parameters [37]. Later, it was updated by GSK by adding two more parameters, namely, life cycle assessment (LCA) and regulatory concerns [36]. Pfizer developed a solvent selection guide which was inspired from traffic light consisting of three categories: preferred, usable and undesirable. Its criteria was based on the safety of workers such as toxicity, carcinogenicity, mutagenicity; safety of processes such as flammability, vapor pressure and peroxide formation; and environmental and regulatory concerns such as ecotoxicity, groundwater contamination and ozone depletion [38]. The guide developed by Sanofi evaluates solvents from various chemical types (alcohols, ketones, esters, ethers, hydrocarbons, halogenated, polar aprotic, bifunctional and miscellaneous) and ranks them as forbidden, substitution requested, indicated and recommended. This ranking was based on safety, occupational health, the environment, quality and industrial restrictions [39].

Table 9.2: List of solvent selection guide as provided by different pharmaceutical companies [40].

Class	Solvent	Pfizer (conclusion)	GSK (conclusion)	Sanofi (conclusion)
Alcohols	Methanol	Preferred	Some issues	Recommended
	Ethanol	Preferred	Some issues	Recommended
	Ethylene glycol	Usable		Substitution advisable
Hydrocarbons	Hexane(s)	Undesirable	Major issues	Substitution requested
	Cyclohexane	Usable	Some issues	Substitution advisable
	Benzene	Undesirable	Major issues	Banned
	Toluene	Usable	Some issues	Substitution advisable

Table 9.2 (continued)

Class	Solvent	Pfizer (conclusion)	GSK (conclusion)	Sanofi (conclusion)
Dipolar aprotic	DMSO	Usable	Some issues	Substitution advisable
	Acetonitrile	Usable	Major issues	Recommended
	DMF	Undesirable	Major issues	Substitution requested
	NMP	Undesirable	Major issues	Substitution requested
Esters	Ethyl acetate	Preferred	Some issues	Recommended
	Methyl acetate	Preferred	Some issues	Substitution advisable
	n-Propyl acetate		Few issues	Recommended
	i-Propyl acetate		Few issues	Recommended
Ethers	THF	Usable	Major issues	Substitution advisable
	TBME	Usable	Some issues	Substitution advisable
	Diethylether	Undesirable	Major issues	Banned
	Di-i-propyl ether	Undesirable	Major issues	Substitution advisable
Ketones	Acetone	Preferred	Some issues	Recommended
	Methylethyl ketone	Preferred	Major issues	Recommended
Halogenated	Dichloromethane	Undesirable	Major issues	Substitution advisable
	Chloroform	Undesirable	Major issues	Banned
	CCl_4	Undesirable	Major issues	Banned
Miscellaneous	Water	Preferred	Few issues	Recommended
	Acetic acid	Usable		Substitution advisable
	Pyridine	Undesirable		Substitution advisable

The CHEM21 consortium reviewed the findings obtained from different selection guides and developed their own guide, which was a three-tiered system of assessment of safety, health and environmental (SHE) impact [40]. Nowadays, to select the solvent, in silico approaches have been utilized, which is based on computational similarity clustering of solvents. This approach involves grouping of solvents on the basis of physicochemical attributes such as melting point, surface tension and boiling point [32]. The triumph of solvent selection depends upon definitive prediction of thermodynamic attributes, compartmentalized into three groups [41]: molecular scale (interaction between atoms at the molecular level, namely, density functional theory and molecular dynamics), macroscale (bulk solvent attributes which include viscosity and density) [42] and large data-based methods (involves semiempirical methods and quantitative structure–property relationship models) [43]. Following the estimation of molecular descriptors, these are used to determine the different parameters such as global warming potential and cumulative energy demand. This leads to more accurate and reliable environmental impact prediction, easing the selection and designing of solvent when experimental data is meager [44].

Durand et al. [45] have developed a computational method to classify 153 solvents into 10 categories, in which descriptors are generated through a modeling tool COSMO-RS (conductor-like screening model for real solvents), which allows to make comparison

between concerned and alternative solvents. Artificial intelligence has also been employed to cluster 500 solvents based on the physical attributes, which allows to explore alternative solvents from solvent space and ranked using SHE criteria [46].

9.3 Methods to evaluate greenness of solvents

To determine how green a solvent is, two methods are available: EHS method [47] and LCA method [48]. The former one takes into account the EHS concerns while the latter deals with emissions during the life cycle of solvents at different stages from production, utilization to disposal. Solvents are evaluated in nine effective areas by implementing the EHS method: release potential, fire/explosion, reaction/decomposition (representing safety threats), acute toxicity, inflammation, chronic toxicity, persistency, air hazard and water hazard are all examples of risks (representing environmental hazards). An index is created for each effective category and the score between zero and one is calculated, yielding an overall score. The scale range is from zero to nine [49]. LCA of solvents is like different pieces of jigsaw puzzle considering the whole life cycle of solvent from cradle to grave, that is, from manufacturing, distribution use to disposal [50]. A systematic tool helps in making decision regarding the impact of solvent on environment by tracing the discharge and resource use. The flowchart for LCA can be referred from Figure 9.1.

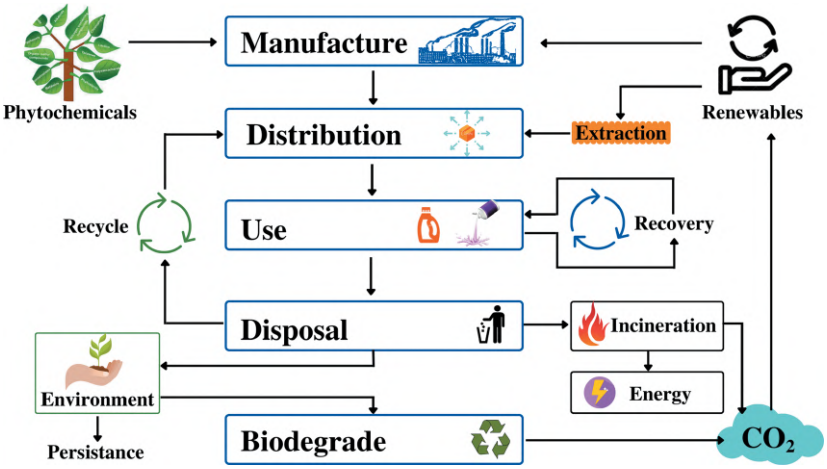

Figure 9.1: Flowchart of LCA of solvent.

More intricacy in how solvents are selected on the basis of a sustainable supply chain will unavoidably be required in the future of solvent selection, and there is scope for more studies in the field of LCA [40].

9.4 Restorative actions to reduce hazards due to conventional solvents

Conventional solvents contribute toward a considerable amount of environmental and health concerns. Consequently, to reduce hazards, the search for better alternatives has always been an area of engrossment. Three directives have been developed to decrease the use of conventional solvents which includes: (a) replacement with the solvent showing comparatively better EHS profile, (b) usage of biosolvents (produced from renewable resources) [49] and (c) swapping of solvents with supercritical fluids (SCFs) [51] or ionic liquids (ILs) [52]. Around 20 years ago, the concept of green chemistry came into existence and was defined as "designing of chemicals and solvents so as to reduce or eliminate the use and generation of hazardous chemicals." The reduction of use of solvent or replacing them with alternate solvent with less toxicity is the major aim of green chemistry [11].

Paul Anastas and John Warner presented the 12 standards of green science in 1998. They are the directing systems for the plan of new chemical compounds and processes, applying to all parts of the interaction of life cycle from the unrefined components utilized to the productivity and impregnability of the change, the toxicity and biodegradability of products and reagents utilized [53]. The principles of green chemistry are depicted in Figure 9.2.

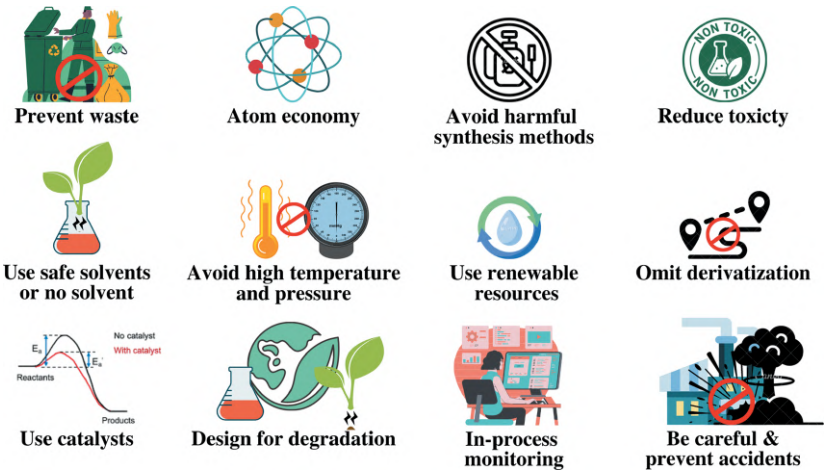

Figure 9.2: Principles of green chemistry.

On similar lines, there is a criterion which needs to be followed in order to be a green solvent, which was proposed by Gu and Jerome. It includes:

1. Attainability: A green solvent must be widely accessible, and productivity should not fluctuate much in order to ensure that the solvent is always available commercially.

2. Cost: Green solvents must nevertheless be aggressive in terms of cost but also stable over time in order to assure the sustainability of chemical processes.
3. Recyclability: A green solvent must be entirely recycled throughout all chemical processes, utilizing eco-friendly practices.
4. Grade: Technical-grade solvents are put forward to prevent the energy-intensive purification operations necessary for extremely unadulterated solvents.
5. Synthesis: It must be produced in an energy-efficient manner and chemical reactions ought to have a high atom economy.
6. Toxicity: To eliminate any hazards when handled by human or emitted into the environment, green solvents must have insignificant toxicity.
7. Biodegradability: It should be biodegradable and not emit hazardous by-products.
8. Performance: A green solvent must function similarly, if not better, than currently utilized conventional solvents in terms of viscosity, polarity, density and so on.
9. Stability: A green solvent must be thermally and electrochemically robust in order to be used in a chemical reaction.
10. Combustibility: A green solvent should not be combustible for safety concerns during operation.
11. Storage: It should be undemanding to store and comply with all regulations in order to carry securely by any mode of transportation.
12. Renewability: The utilization of sustainable unprocessed materials for the development of green solvents ought to be advocated [54].

Catastrophically, no solvent exists that comply with all the twelve criteria. Various green solvents have been proposed over the decade, which include water, SCFs, bio-based solvents, surfactant-based solutions, deep eutectic solvent (DES) and ILs [11, 54]. These solvents along with their applications and limitations have been discussed further.

9.4.1 Water

Water is a universal solvent. All biochemical reactions in the body occur in water and are nontoxic. It can be used in a variety of chemical reactions, separations and organic synthesis as it has polar groups such as alcohols and carboxylic acids. Paint industry has switched from VOCs to water as vapors are released when vehicles are spray-painted [55]. Water can also be used by modifying the temperature and pressure conditions, which is known as subcritical water (liquid water at temperature and pressure below its critical point, i.e., T_c = 374.15 °C, P_c = 217.75 atm) [54]. Physicochemical characteristics of subcritical water vary dramatically as the temperature rises. The viscosity, dielectric constant and surface tension drop consistently with temperature, but its diffusion coefficient increases [56]. Thus, by modifying the extraction temperature and pressure conditions, less polar substances can be recovered by subcritical

water at high temperatures. Water, for example, has a dielectric constant comparable to that of acetonitrile, methanol or ethanol around 200–300 °C, allowing it to dissolve high hydrophobic substances such as polycyclic aromatic hydrocarbons and polychlorinated biphenyls around its critical conditions [57].

Todd et al. [58] carried out a study comparing the economic, technical and environmental aspects by using extraction of subcritical water as a technique to extract medicinally important food-derived compounds. As per studies, subcritical water extraction does not perform well as compared to conventional solvents for extracting components, having persistently huge demand of energy combined with emissions, huge expenditures and overall low economics. Even though subcritical water produced the highest quality compound, it resulted in an energy-exhaustive process, which negated most of the ecological benefits of employing water as a solvent. SWE had higher potential environmental impacts than solvent extraction and higher greenhouse emissions due to its high energy consumption [58]. Further restriction of subcritical water technology is the requirement of specialized technology and reactors, as well as large energy requirements in order to manage the required high pressure as well as high temperature.

9.4.2 Supercritical fluids (SCFs)

SCFs exist as either liquid or gas, and these two phases coexist above critical temperature and pressure [59]. They have unusual qualities that are not observed in either gases or liquids under normal conditions, such as a liquid-like density and gas-like transport capabilities [60]. The advantages of SCFs include that they can be tweaked as per the standard operating temperature and pressure due to their thermophysical properties [61]. Numerous studies on various implementations of SCF extraction have been published. The frequently employed compound for SCF is CO_2. CO_2 has a low polarity, which enables it to dissolve/extract out nonpolar chemicals, while it is not much successful at extracting polar compounds. In such circumstances, small fraction of organic alterant can be added to prevent the issue [62]. The most commonly employed cosolvent is ethanol; it has been widely employed in most of the SCF extraction investigations. Alterants such as ethyl acetate, water and methanol have been employed to improve chemical miscibility. A lot of interest has been received recently by water used as cosolvent, since it is more successful than ethanol at extracting phenolic chemicals [63].

The major drawback of SCF technology is the high energy demand and the necessity for complex equipment. SCF extraction necessitates a significant amount of power to pressurize as well as to heat up the SCF, which is worsened by the overall increasing trajectory in energy prices. Furthermore, the sixth green chemistry principle is violated by SCF extraction: “Energy demands should be acknowledged for their environmental and economic implications and should be avoided. Artificial procedures should be carried out at room pressure and temperature.” This drawback has

been manifested in a study conducted by Rodríguez-Meizoso et al., in which antioxidants have been extracted from rosemary leaves with respect to LCA, and a comparison study has been carried out between two extraction processes, such as subcritical water and SCF. The findings of the study suggested that energy consumption is undoubtedly the most detrimental component of both investigated approaches in terms of environmental impact and associated expenses [64]. Subsequently, instead of introducing a cosolvent to supercritical CO_2, liquid CO_2 was added to an organic solvent, yielding a solvent known as CO_2 expanded liquid with a lowered relative permittivity, ability to form a hydrogen bond, density closer to pure organic solvents and lower viscosity [65]. The equipment was found to be easier to handle and less expensive in comparison to the extraction of SCF, owing to the substantially lower pressures required. However, no commercial equipment is available for extraction of CO_2 expanded liquid, and in few circumstances, it has been extracted using a commercial SCF extraction technology. Furthermore, the usage of CO_2 expanded liquids can result in a decrease in solvent use of about 80% [54].

9.4.3 Bio-based solvent

Bio-based solvents are those derived from renewable resources [66]. The most prevalent feedstock for bio-based solvents is agriculture, although they can be produced from industrial wastes and marine biofuel as well. The most common biosolvent is bio-based ethanol, which is manufactured through the biotransformation of sugars using either consumable or nonconsumable feedstock. Although issues about consumable feedstock show a rise in the cost of food, the industry has made a shift toward refining cellulosic ethanol production techniques [67]. Another notable bio-based solvent is ethyl lactate, which is manufactured by fermenting corn and soybean feedstock and coupling two fermentation products such as ethanol and lactic acid. Ethyl lactate is utilized to extract phytochemicals since it is biodegradable and nontoxic and has a low volatility [66]. Some of the applications of bio-based solvents including D-limonene (monoterpene hydrocarbon) have been utilized in lieu of *n*-hexane for the estimation of fats and oils in olive seeds [68], carotenoids from tomato [69], extraction of lovastatin, simvastatin and their metabolites from plasma [70]. The major drawback of D-limonene is that it is categorized as problematic according to CHEM21 selection guide due to high toxicity for marine species [71].

There are two types of bio-based solvents: polar and nonpolar. Polar includes methanol, ethanol and acetonitrile, in which the latter one has some environmental concerns. Methanol and ethanol confer acceptable results in majority of extractions. Nevertheless, it is difficult to find appropriate nonpolar bio-based solvent for extraction. Terpenes, which are related to some environmental difficulties such as toxicity for fish, are the key possibilities in this field. The key problem here is their great potential for facilitating photochemical smog creation, which prompts us that a solvent

generated from a biological source is not always green. The synthesis of bio-based solvents frequently surges the agricultural environmental consequences such as depletion of abiotic resources, acidification of soil and water eutrophication [72]. Another downside involves purity. Purification of bio-based solvents would increase the separation steps such as deoxygenation, dehydration or distillation which consequently decrease the bio-based solvent's green character [73].

9.4.4 Surfactant-based solutions

When surfactants are added to aqueous solutions, structures such as micelles, microemulsions and vesicle forms provide interesting nonpolar areas. As a result, the use of surfactants in lieu of conventional solvents has been regarded as a positive component. However, during this substitution procedure, the toxicity to aquatic organisms of particular surfactants should be considered. It has previously been observed except the compounds generated from aromatic, the cationic surfactants have higher toxicity than that of anionic surfactants, which is higher than that of nonionic surfactants [74]. Some of the examples of nonionic surfactants include Triton X-45, Triton X-100, Triton X-114, Tween 80 and Tween 20 [54]. These include supramolecular solvents (SUPRAS) and hydrotropes. SUPRAS are nanostructured liquids formed by the uncontrolled, simultaneous mechanisms of self-assembly and coacervation in colloidal solutions of amphiphilic chemicals [75]. These are noncombustible and nonvolatile solvents with tweakable qualities based on the surfactant's hydrophobic or polar groups that can be used as an alternative to organic solvents in liquid-phase microextraction. These were used to measure the level of benzodiazepines and zolpidem in blood and urine [76] and antifungal establishment from plasma and urine [77]. These comply with some of the green criteria such as less energy consumption, less volatility and flammability. The surfactants available currently are petroleum-based and partly biodegradable which offset the advantages. Furthermore, organic solvents (methanol and tetrahydrofuran) are used in their synthesis process. However, few ongoing researches created SUPRAS having low toxicity utilizing synthetic alkyl-carboxylic acids and fatty alcohols in ethanol and water mixtures to lessen the detrimental impact of SUPRAS. The evolution of bio-SUPRASs through coacervation of bio-surfactants has boosted the greenness of these solvents [78]. Another type includes hydrotropes, which are composed of short-chain alkyl (less than or equal to four carbons) and/or aromatic rings and ionic groups [79]. These are often solids; however, some are liquids, such as the short-chain ethers of mono-/di-/tripropylene glycols. Glycol ethers, on the other hand, have documented or probable toxicity, notably reproductive toxicity [80].

9.4.5 Deep eutectic solvent (DES)

DES is a eutectic mixture of Lewis or Bronsted acids and bases and is widely used in the identification of analyte including lithium and sodium ions [81] and as an adsorbent for VOCs [11]. It has characteristics such as low vapor pressure, increased tweakable properties and nonflammability, and are thermally and chemically stable and highly biodegradable. However, even after having such precedence, there is still the requirement of further studies before recognizing DES as "green solvent" as cholinium- and phosphonium-based DES found to be toxic to different biological species [82]. An in silico model was recently utilized to speculate the toxicity of various DESs. According to this research, sugar alcohols and alcohols with a straight chain are the most innocuous hydrogen bond givers. Furthermore, because of their low toxicity, amides such as acetamide and urea can be used as hydrogen bond givers in DES. Sugars might have moderate level of toxicity, and all acids contribute the most positively to DES toxicity [83].

DES can also be obtained from biological sources, namely, organic acids, amino acids and choline derivatives. A recent study used LCA to evaluate the sustainability level of phenolic compound extraction utilizing DES and ethanol. According to the LCA analysis, the typical extraction solvent, ethanol, had the least environmental impact, particularly concerning power utilization. Nevertheless, the authors conclude that several areas remain unclear, indicating the need for additional research [84].

9.4.6 Ionic liquids (ILs)

ILs are salts which are liquids at room temperature and are composed of cations (mostly *N*-alkylpyridinium, PR^{4+} and NR^{4+}), anions (tosylate, alkyl sulfate, NO^{3-} and Cl^{-}) and alkyl chains (ethyl, butyl, hexyl and octyl) [7]. These are also known as "designer solvents" as by varying the length as well as branching of the alkyl chain of cationic and anionic nucleus. They can be made fit for different applications [85]. As numerous cation and anion combinations are possible, IL has a variety of physicochemical properties, and few of which are dangerous while others are perfectly safe. Hydrophobic ILs are heavily adsorbed on debris and constitute incessant pollutants in the surroundings, whereas hydrophilic ILs are more expected to reach the marine habitat. Furthermore, abiotic resources change mechanisms of BF_4 and PF_6 anions from some of the produced ILs, such as photolysis, hydrolysis and oxidation, which result in the emission of toxic hydrogen fluoride [86]. It has been observed that as per the model framework employed for acute toxicity tests and the chemical structure of ILs, they exhibit moderate to severe toxicity, which can be two to four significant degrees greater than the standard organic solvents [87]. Harmfulness of ILs appears to be significantly influenced by the composition of the cation than the anion and alkyl

chain length being the key factor controlling toxicity [88]. Scientists suggest utilizing LCA method to evaluate the greenness of ILs.

Tobiszewski and coworkers utilized a multicriteria decision tree in their study to assess the sustainability level of ILs. The findings suggested that while it is difficult to make conclusive judgments, ILs containing fluorinated anions should be avoided, and the bald assumption that ILs are green solvents is completely unsuitable and ought to be stayed away from [89]. One reason to be skeptical about the greenness of ILs is that their amalgamation includes the utilization of organic solvents. The implementations of ILs include natural product extraction in replacement for *n*-hexane and *n*-butane [11] and extraction of cortisol and cortisone from the saliva sample [90].

9.4.7 Magnetic ionic liquids (MILs)

Magnetic ILs (MILs) are a subclass of ILs, which possess paramagnetic properties in the presence of external magnetic particles. These are metal-containing ILs having strong response to magnetic field combined with the properties of room-temperature ILs (RTILs). RTILs are salts consisting of cation and anion, and exhibit slight vapor pressure, high thermal and chemical stability and high conductivity, and these properties can be tweaked by changing the cation and anion [91] and usually consist of iron, manganese, cobalt, gadolinium and lanthanide in the anion structure. Due to their magnetic properties, these can be easily extracted from the reaction media with the help of magnet. The revelation of MILs exhibiting magnetic characteristics opened up a new field of study. These have applications in various reactions such as preparation of heterocycles, oxidation–reduction reactions, polymerization and coupling reactions [92]. The increased usage of MILs necessitates the consideration of human health and environmental consequences of their discharge. Because of their low vapor pressure and nonflammability, they diminish or eliminate the danger of air emissions. However, some of them are soluble in water and may cause risks to the aquatic ecosystem. Many groups have conducted a study regarding how the structure of different substituents on MILs affect the toxicity. It was concluded that iron-containing RTILs increase the toxicity. Similarly Alvarez-Guerra and Irabien estimated the ecotoxicity using partial least squares discriminant analysis method. It was found that $[FeCl_4]$ anion has been more toxic than the volatile solvent reference (toluene). In vitro studies conducted for different anions suggested that $[CoCl_4]$ and $[MnCl_4]$ cause more toxicity as compared to $[FeCl_4]$ and $[GdCl_6]$ [93]. The properties of nonconventional solvents are summarized in Table 9.3.

Table 9.3: Properties of nonconventional solvents.

Solvent	Properties
Subcritical water	– Less contaminated – High-cost equipment – High temperature and pressure
Supercritical fluids (SCFs)	– Nontoxic – Easily volatilized – Low polarity
Bio-based solvents	– Biodegradable – Toxic to aquatic life – Low volatility
Surfactant-based solutions	– Nonvolatile – Nonflammable – Partially biodegradable
Ionic liquids	– Complex synthesis – Expensive – Inferior biodegradable
Deep eutectic solvent	– Nontoxic – Easy to prepare – Low price – Biodegradable

9.4.8 No solvent approach

This is also an approach and it may appear alien that a reaction can be carried out without a solvent. There are many examples from human history where reactions were done without solvent such as formation of mercury by grinding the cinnabar with acetic acid in a copper vessel. The terms “no solvent” and “solvent free” delineate when solvent is not added intentionally or small fraction of solvent is employed to ease the mechanical (grinding) process. This method has been utilized in the production of tetrahydridoborates and tetrahydridoaluminates. The restriction which diminishes the utilization of this method include scalability, design of equipment and energy consumption [94].

9.5 Conclusions

Considering the abovementioned discussion, it is evident that no solvent or extraction technique is holistically green or environment-friendly regardless of the intensive research. The alternatives or nonconventional solvents, which are available, may be

better as compared to conventional in complying with the criteria proposed by Gu and Jerome; however, each of them has their own limitations. LCA is the best way to evaluate the greenness of solvent. There is a horizon of augmentation to develop better sustainable solvents in lieu of presently available solvents, which can be ephemeral or switchable. Further, there is not only a requirement of green solvent but also a green cosolvent as a hydrotrope which does not comply with the criteria of greenness.

Abbreviations

VOC	Volatile organic compound
EHS	Environment, health and safety
COSMO-RS	Conductor-like screening model for real solvents
LCA	Life cycle assessment
SCF	Supercritical fluids
DES	Deep eutectic solvents
SUPRA	Supramolecular solvents
IL	Ionic liquids

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