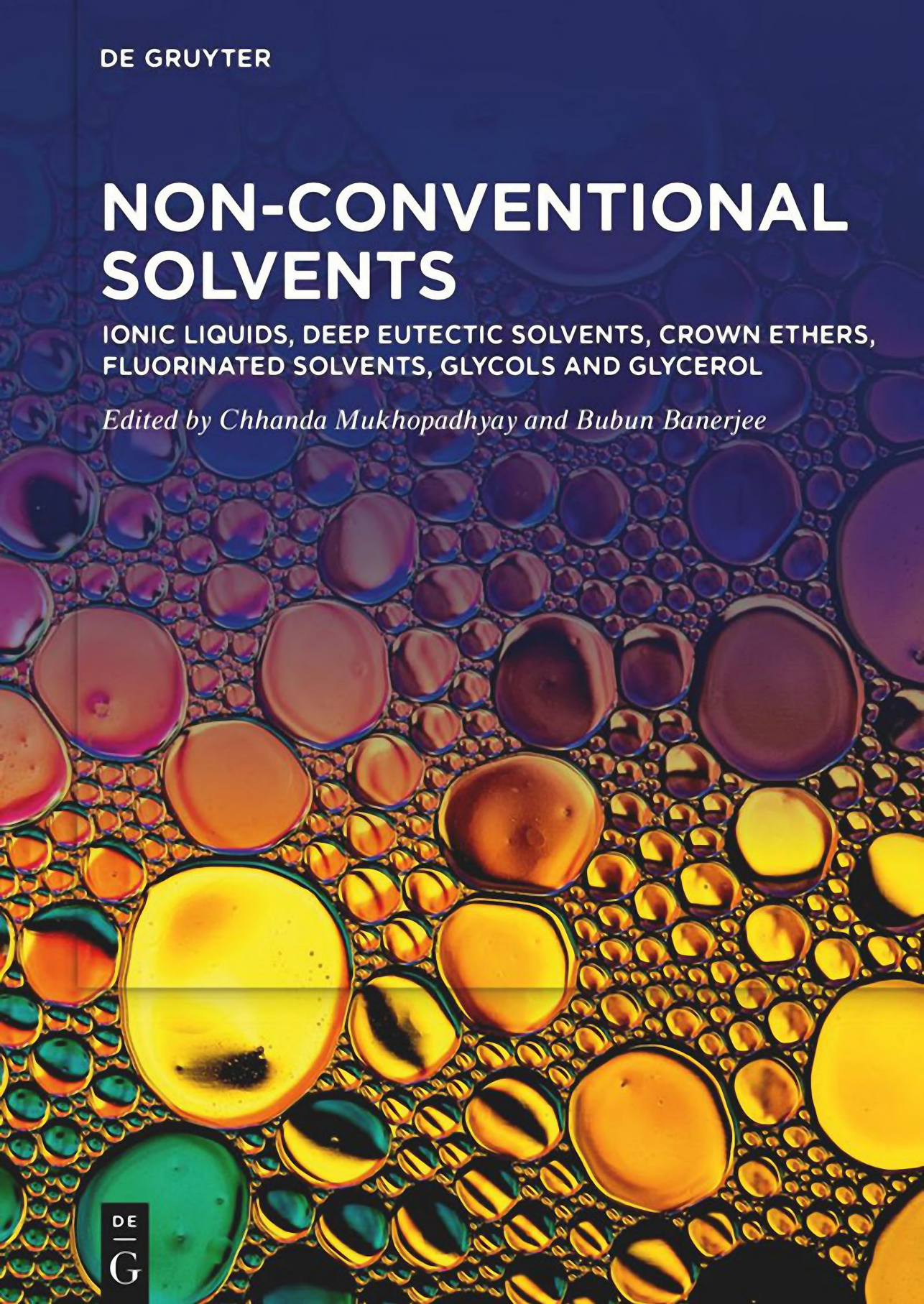
DE GRUYTER

NON-CONVENTIONAL SOLVENTS

IONIC LIQUIDS, DEEP EUTECTIC SOLVENTS, CROWN ETHERS, FLUORINATED SOLVENTS, GLYCOLS AND GLYCEROL

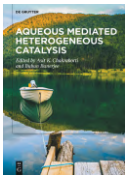
Edited by Chhanda Mukhopadhyay and Bubun Banerjee



Chhanda Mukhopadhyay and Bubun Banerjee (Eds.)
Non-Conventional Solvents

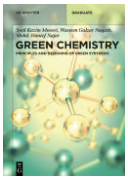
Also of interest

Non-Conventional Solvents.
Volume 2: Organic Synthesis, Natural Products Isolation, Drug Design, Industry and the Environment
Chhanda Mukhopadhyay and Bubun Banerjee (Eds.), 2023
ISBN 978-3-11-124374-0, e-ISBN 978-3-11-124399-3



Aqueous Mediated Heterogeneous Catalysis
Asit K. Chakraborti and Bubun Banerjee (Eds.), 2022
ISBN 978-3-11-073845-2, e-ISBN 978-3-11-073384-6

Integrated Chemical Processes in Liquid Multiphase Systems.
From Chemical Reaction to Process Design and Operation
Matthias Kraume, Sabine Enders, Anja Drews, Reinhard Schomäcker, Sebastian Engell and Kai Sundmacher (Eds.), 2022
ISBN 978-3-11-070943-8, e-ISBN 978-3-11-070985-8



Green Chemistry.
Principles and Designing of Green Synthesis
Syed Kazim Moosvi, Waseem Gulzar Naqash and Mohd. Hanief Najar, 2021
ISBN 978-3-11-075188-8, e-ISBN 978-3-11-075189-5

Industrial Green Chemistry
Serge Kaliaguine and Jean-Luc Dubois (Eds.), 2021
ISBN 978-3-11-064684-9, e-ISBN 978-3-11-064685-6

Non-Conventional Solvents

Volume 1: Ionic Liquids, Deep Eutectic Solvents, Crown Ethers, Fluorinated Solvents, Glycols and Glycerol

Edited by
Chhanda Mukhopadhyay and Bubun Banerjee

DE GRUYTER

Editors
Prof. Chhanda Mukhopadhyay
Department of Chemistry
University of Calcutta
92 Acharya Prafulla Chandra Road
Kolkata 700009
West Bengal
India
cmukhop@yahoo.co.in

Dr. Bubun Banerjee
Department of Chemistry
Akal University
Talwandi Sabo
Bathinda 151302
Punjab
India
banerjeebubun@gmail.com

ISBN 978-3-11-078793-1
e-ISBN (PDF) 978-3-11-078812-9
e-ISBN (EPUB) 978-3-11-078824-2

Library of Congress Control Number: 2023933242

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the internet at http://dnb.dnb.de.

Cover image: Igor Antipin/iStock/Getty Images Plus
Typesetting: Integra Software Services Pvt. Ltd.
Printing and binding: CPI books GmbH, Leck

www.degruyter.com

Foreword

At the outset, I wish with deep sense of gratitude to congratulate the editors and the authors for bringing out this volume on nonconventional solvents, which continue to attract a great deal of attention owing to their unique solvent properties, and more importantly due to much warranted and unavoidable global focus on discovering, developing and practicing sustainable synthetic methodologies for molecular synthesis and chemical processing industries. Today, it has become imperative to move fast toward eco-friendly synthetic methodologies, and desirably so the recent years have witnessed feverish endeavors toward design and development of solvent alternatives for applications in organic synthesis. In this perspective, this volume on *Non-conventional Solvents: Ionic Liquids, Deep Eutectic Solvents, Crown Ethers, Fluorinated Solvents, Glycols and Glycerol* (edited by Chhanda Mukhopadhyay and Bubun Banerjee) is a welcome addition.

Organized in nine chapters, the narrative of the book is built on sustainable chemistry, with a lot of acumen and with global perspectives based on the contributions made by different researchers. I believe that this book will prove to be a valuable resource for researchers in chemical sciences, both in academia and in industry, and in particular to those working toward discovering and developing new and improved eco-friendly methodologies for organic synthesis.

Chapter 1, “Synthesis of Bio-active Heterocycles Using Ionic Liquids,” presents the use of ionic liquids (ILs) as reaction medium as well as catalyst for the efficient formation of C–N, C–O and C–S bonds. It also provides several examples of the synthesis of various heterocyclic molecules of biological importance using room temperature ILs avoiding toxic organic solvents, catalysts and ligands.

Chapter 2, “Synthesis of *Oxygen* and *Sulfur* Heterocycles Mediated by Ionic Liquids,” presents an account of the utility and role of ILs as catalysts, medium and solvent in synthesizing various heterocyclic molecules containing sulfur and oxygen atoms. Also are presented in the chapter a brief history, importance, select methods of preparation and properties of ILs.

https://doi.org/10.1515/9783110788129-202

Chapter 3, “Supported Ionic Liquids for Advanced Catalytic Applications,” is an account of some of the most recent and progressive developments concerning supported ILs, from their elemental characteristics to their utilization in the synthesis of industrially significant organic compounds via catalytic pathways.

Chapter 4, “Recent Updates on Chiral Ionic Liquid-Mediated Asymmetric Organic Synthesis,” specifically deals with the chiral ILs and gives a nice account of their role in asymmetric reactions such as reductions, Michael addition, Aldol condensation, Diels–Alder reaction, etc.

Chapter 5, “Deep Eutectic Solvent-Mediated Organic Transformations,” articulates the superior and significant catalytic activity of eco-friendly and inexpensive deep eutectic solvents toward several organic transformations, reported particularly in the last ten years.

Chapter 6, “Role of Crown Ethers as Mediator in Various Chemical Reactions,” is devoted to a discussion of different roles the crown ethers play in effecting a wide range of chemical reactions and processes.

Chapter 7, “Fluorinated Alcohol-Assisted Preparation of Functional and Biologically Active Compounds,” discusses examples of various organic transformations performed in fluorinated alcohols, which promote the reactions due to their high ionizing power, low nucleophilicity and strong hydrogen-bonding ability, and are considered promising alternatives to conventional organic solvents.

Chapter 8, “PEG-Assisted Organic Transformation,” specifically discusses the merits of using different types of polyethylene glycols as reaction medium and also as catalyst and additive in organic reactions and synthesis.

Finally, Chapter 9, “Glycerol-Mediated Organic Transformations,” explores the uses of glycerol as an eco-friendly recyclable medium for developing environment-friendly synthetic procedures for the synthesis of various organic compounds.

Overall, presented in a reader-friendly manner, the book is an authoritative high-quality treatise of an important subject. A comprehensive and to-the-point account of various chemical aspects of select nonconventional solvents is described in the book. The technical material is presented with a reasonable degree of depth and breadth. Desirably, the book focuses both on the necessary basic concepts and on the application aspects together with numerous examples of the synthesis of organic molecules. The materials presented in the chapters will be very useful to readers for grasping facts clearly and understanding the issues of applications in the proper perspective. This book will also lift the academic spirit, standard and enthuse of the readers, particularly the young students toward learning and practicing more of the sustainable chemistry. The availability of this book will greatly facilitate easy learning, and I hope the book will reach the hands of all concerned stakeholders.

The editors and the authors of this volume deserve the heartfelt thanks of the community of researchers in chemical and allied sciences for making available well-

discerned and discussed materials on a subject of much contemporary interest. I convey my best wishes to the editors, the authors and all the readers.

Prof. Anil Kumar Singh,
Formerly Professor and Head, Department of Chemistry,
Indian Institute of Technology Bombay,
Powai, Mumbai – 400 076, India
Email: retinal@chem.iitb.ac.in

A brief professional profile of Prof. Anil Kumar Singh

A former Professor in the Department of Chemistry, Indian Institute of Technology Bombay (IIT-B), Prof. Anil Kumar Singh embodies a great wealth of expertise and experience in chemical and allied sciences education and research, policy formulation and administration. During a career spanning over four decades, Prof. Singh has worked in several senior key capacities at IIT-B and participated in drawing up and developing academic policies and programs of education and research, as well as expansion of collaborations both in India and abroad. He has also been associated in multiple capacities with other national and international educational institutions, R&D organizations, government bodies, prestigious science academies and societies, and policy-making entities to drive organizational excellence. He has held the position of Director, CSIR-Regional Research Laboratory, Jorhat, India, and Vice-Chancellor of two major universities, the Bundelkhand University (Jhansi, India) and the University of Allahabad (a central university in Prayagraj, India). Recently, Prof. Singh has also shouldered the responsibility as Independent Director of the Rashtriya Chemicals and Fertilizers Ltd., Mumbai (a public sector undertaking of the Ministry of Chemicals and Fertilizers, Government of India).

Prof. Singh's research interests are multidisciplinary, broadly spanning the areas of organic and bioorganic chemistry, photochemistry and photobiology, with a focus on developing molecular understanding of the photocontrol of structure and functions of photoreceptor proteins involved in vision and biological energy transductions; excited state chemistry of linear polyenes; and transformative biomolecular and light-mediated sustainable chemical approaches toward design and development of novel molecules and speciality chemicals including fluorescent probes, new-age agrochemicals, retinoids-based anticancer compounds, radioprotectants, design and development of nanoparticles of low-molecular-weight organic molecules for optoelectronic and medical applications, and smart photoswitches and phototriggers for biomolecular caging and other chemical and biological applications.

Prof. Singh is widely traveled and delivered a large number of talks in prestigious gatherings of academicians and scientists in conferences, and in teaching and research centers of higher learning in India and abroad. His endeavors and contributions have been duly recognized by the academic and research organizations, government and corporate bodies, prestigious science academies, and professional societies with awards and honors.

https://doi.org/10.1515/9783110788129-203

Contents

List of contributors

Sabir Ahammed
Department of Chemistry
Bankura Sammilani College
Kenduadihi
Bankura 722102
West Bengal
India

Brindaban C. Ranu
School of Chemical Sciences
Indian Association for the Cultivation of Science
Jadavpur
Kolkata 700032
West Bengal
India

Vaidya Jayathirtha Rao
Emeritus Scientist CSIR & Honorary
Professor AcSIR
Organic Synthesis and Process Chemistry
Department and AcSIR–Ghaziabad
CSIR–Indian Institute of Chemical Technology
Uppal Road Tarnaka
Hyderabad 500007
Telangana
India

Radhika Gupta
Department of Chemistry
Shyam Lal College
University of Delhi
New Delhi
India
and
Green Chemistry Network Centre
Department of Chemistry
University of Delhi
New Delhi
India

Yukti Monga
Department of Chemistry
Shyam Lal College
University of Delhi
New Delhi
India
and
Green Chemistry Network Centre
Department of Chemistry
University of Delhi
New Delhi
India

Ashu Gupta
Department of Chemistry
Shyam Lal College
University of Delhi
New Delhi
India

Rakesh Kumar Sharma
Green Chemistry Network Centre
Department of Chemistry
University of Delhi
New Delhi
India
e-mail: rksharmagreenchem@hotmail.com

Avtar Singh
Department of Chemistry
Sant Longowal Institute of Engineering and
Technology
Longowal 148106
Distt. Sangrur
Punjab
India

Nirmaljeet Kaur
Department of Chemistry
Baba Farid College
Bathinda 151001
Punjab
India

https://doi.org/10.1515/9783110788129-205

Rohini
Department of Chemistry
Baba Farid College
Bathinda 151001
Punjab
India

Anupama Parmar
PG Department of Chemistry
M. M. Modi College
Patiala 147001
Punjab
India

Payal Malik
Department of Chemistry
Sant Longowal Institute of Engineering and Technology
Longowal 148106
Distt. Sangrur
Punjab
India

Harish Kumar Chopra
Department of Chemistry
Sant Longowal Institute of Engineering and Technology
Longowal 148106
Distt. Sangrur
Punjab
India
e-mail: hk67@rediffmail.com

Yadavalli Venkata Durga Nageswar
Retired Chief Scientist
Indian Institute of Chemical Technology – IICT
Tarnaka
Hyderabad
India
e-mail: dryvdnageswar@gmail.com

Katla Ramesh
Foreign Visiting Professor
Organic Chemistry Laboratory 4
School of Chemistry and Food
Federal University of Rio Grande – FURG
Rio Grande
RS
Brazil

Katla Rakhi
Organic Catalysis and Biocatalysis
Laboratory – LACOB
Federal University of Grande Dourados – UFGD
Dourados/MS
Brazil
Tel.: +55(67) 3410 2081

Simranpreet K. Wahanan
Department of Pharmaceutical Chemistry
ISF College of Pharmacy
Moga 142001
Punjab
India

Gaurav Bhargava
I. K. Gujral Punjab Technical University
Kapurthala 144603
Punjab
India

Pooja A. Chawlaa
Department of Pharmaceutical Chemistry
ISF College of Pharmacy
Moga 142001
Punjab
India
e-mail: pvchawla@gmail.com

Arruje Hameed
Department of Biochemistry
Government College University Faisalabad
Faisalabad
Pakistan

Razia Noreen
Department of Biochemistry
Government College University Faisalabad
Faisalabad
Pakistan

Muhammad Sami Ullah Khan Niazi
Department of Applied Chemistry
Government College University Faisalabad
Faisalabad
Pakistan

Shaheera Batool
Department of Biochemistry
CMH Institute of Medical Sciences Multan
Multan
Pakistan

Anwar Ahmad
Department of Applied Chemistry
Government College University Faisalabad
Faisalabad
Pakistan

Tanzeela Khalid
Department of Applied Chemistry
Government College University Faisalabad
Faisalabad
Pakistan

Tahir Farooq
Department of Applied Chemistry
Government College University Faisalabad
Faisalabad
Pakistan
e-mail: tahirfarooqfsd@gmail.com

Bijeta Mitra
Department of Chemistry
University of North Bengal
West Bengal
India

Pranab Ghosh
Department of Chemistry
University of North Bengal
West Bengal
India
e-mail: pizy12@yahoo.com

Gyan Chandra Pariyar
Department of Food Technology
University of North Bengal
Dist. Darjeeling
West Bengal
India

Bijeta Mitra
Department of Chemistry
University of North Bengal
Dist. Darjeeling
West Bengal
India

Pranab Ghosh
Department of Chemistry
University of North Bengal
Dist. Darjeeling
West Bengal
India
Tel.: +91 (0353) 2776381; fax: +91 (0353) 2699001
e-mail: pizy12@yahoo.com

Sabir Ahammed and Brindaban C. Ranu*

Chapter 1
Synthesis of bio-active heterocycles using ionic liquids

1.1 Introduction

The ionic liquids are compounds that are composed of ions generally, an organic heterocyclic cation and an inorganic anion and are liquids at room temperature. The room temperature ionic liquids (RTIL) have received much interest as benign alternatives to volatile and toxic organic solvents because of their nonvolatility, noninflammability, controlled miscibility, thermal stability and reusability [1–3]. An attractive feature of ionic liquids is flexibility of their tuning of effectiveness and specificity by changing the counter ion of ionic liquids. A particular counter ion often enhances the efficiency of an ionic liquid toward catalysis of certain organic reactions. Recently, various modified ionic liquids are employed for the synthesis of a broad spectrum of organic molecules due to their distinctive chemical and physical properties [4–6]. The task-specific RTIL (TSIL) has emerged as powerful alternatives to organic solvents for their mild and environmentally benign nature [7–9]. Imidazolium ionic liquids are widely used in various reactions and are of considerable interest because of their efficiency as catalyst and green reaction media [10–13].

Heterocycles are of much importance in pharmaceutical industries because of their biological activities [14]. Many heterocyclic compounds have been used as drugs for the treatment of cancer [15], Perkinson's disease [16], malaria [17], etc. They also have antimicrobial [18], anti-inflammatory [19] and antioxidant [20] properties. Therefore, the demand of various bioactive heterocyclic compounds is continuously increasing. The large-scale synthesis of potent heterocyclic drugs by industries is of prime importance. However, large-scale synthesis often produces a large amount of

Acknowledgments: B.C. Ranu is pleased to acknowledge the support of Indian National Science Academy, New Delhi with the offer of INSA Honorary Scientist (Grant no. INSA/SP/HS/2019/291). S. Ahammed thanks Sandipan Ghosal, Bankura Sammilani College for his help and acknowledges WBDSTBT, West Bengal, India (Project No. 1933 (Sanc.)/ST/P/S&T/15G-9/2019) for financial support.

*__Corresponding author: Brindaban C. Ranu,__ School of Chemical Sciences, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, West Bengal, India, e-mail: bcranu@gmail.com
Sabir Ahammed, Department of Chemistry, Bankura Sammilani College, Kenduadihi, Bankura 722102, West Bengal, India

https://doi.org/10.1515/9783110788129-001

harmful waste. In this context, the benign ionic liquids play important role as green reaction media and catalyst for the synthesis of heterocyclic compounds as they produce less waste being recyclable.

This chapter provides an overview of the synthesis of selected heterocyclic molecules of biological interest using RTIL avoiding toxic organic solvents, catalysts and ligands by greener approaches.

1.2 Synthesis of bioactive heterocycles

1.2.1 Synthesis of dihydropyrimidinone and perhydropyrimidine derivative

The dihydropyrimidinones are of much interest due to their therapeutic and pharmacological properties and act as important building blocks in chemical synthesis [21]. It was observed that several biologically active marine alkaloids contain perhydropyrimidine and dihydropyrimidine units [22]. Thus, the dihydropyrimidinone and perhydropyrimidine derivatives are of much utility and are usually obtained by one-pot Biginelli condensation reaction.

Deng and coworkers [23] reported a mild solvent-free Biginelli condensation under room temperature and neutral condition involving the ionic liquid, *n*-butyl-3 methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$) as a catalyst to produce dihydropyrimidines in high yields (Figure 1.1). When quarternary ammonium salts were employed as catalyst, the yield was low. So, it was evident that cation and anion part of an ionic liquid played an important role as catalyst in Biginelli reaction. The best yield of dihydropyrimidines was obtained by the reaction of benzaldehyde, acetylacetone and urea using ionic liquid $BMImBF_4$.

Zuliang and coworkers [24] also reported an environmentally benign method for Biginelli reaction using an SO_3H-functionalized, Bronsted-acidic, TSIL (3-tri-*n*-butylammonio propanesulfonate IL) as a catalyst (Figure 1.2). The best result was achieved by using benzaldehyde, ethyl acetoacetate and urea (1:1:1 mole ratio) as substrates. The ionic liquid was recyclable and reused six times without significant loss of the catalytic activity. Several substituted benzaldehydes and β-keto esters were subjected to this reaction. It was found that both β-ketoester and β-diketone participated in the reaction providing uniform yield. Thiourea can also be used in the place of urea to provide the corresponding thiodihdropyrimidines.

Aromatic aldehydes containing electron donating and electron withdrawing groups provided good-to-moderate yield of DHPM with high purity. A variety of functional groups such as ester, ether, nitro, hydroxyl and halide were tolerated under the reaction conditions. The ionic liquid donates hydrogen ion which assists the dehydration process and enolizes the 1,3-dicarbonyl compound to form the enolate intermediate.

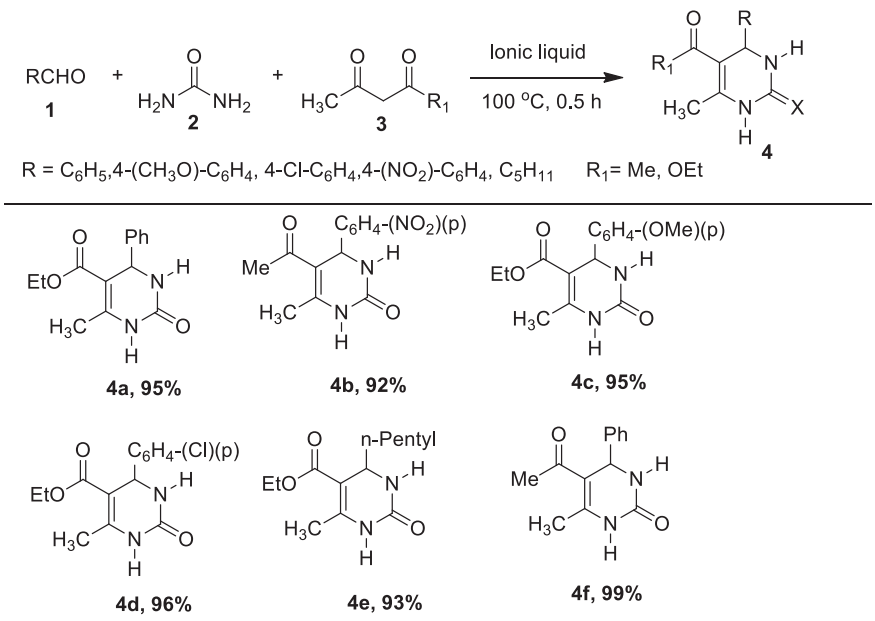


Figure 1.1: Reaction of aryl aldehyde with urea and ester or dicarbonyl compound.

Laali and coworkers reported Biginelli reaction of aldehydes for the synthesis of dihydropyrimidinones and thiones using Bronsted acidic ionic liquid [bmim(SO_3H)[OTf] or $Zn(NTf)_2$ which is recyclable (Figure 1.3) [25]. The [BMIm(SO_3H)(OTf)] provided high yield under mild conditions and short reaction time. Various aromatic aldehydes and both urea and thio urea were used to produce the corresponding products. It was observed that electron-withdrawing group at *para* position provided relatively low yield of the product. It was found that the Lewis acid served as pre-catalyst leading to in situ formation of the actual catalytic species.

Yadav et al. [26] have investigated Biginelli reaction with oxathiolan-5-one/oxazole -5-one as active methylene building block with aromatic aldehyde and urea or thio urea (Figure 1.4). Here, chiral ionic liquid L-proliniumsulfate (Pro_2SO_4) plays an important role by catalyzing the reaction and reducing the reaction time to provide an efficient one-pot synthesis of enantio- and diastereoselective poly-functionalized perhydropyrimidine products. During the reaction, acetophenones are used to activate mercaptoacetic acid as active methylene building block which was mechanically removed during the reaction without hampering the progress of the process.

It was suggested that intramolecular nucleophilic attack of nitrogen atom of urea/thiourea moiety at the carbonyl carbon (C-5) of oxathiolane-5-one or oxazol-5-one nuclei leads to the final product (Figure 1.5).

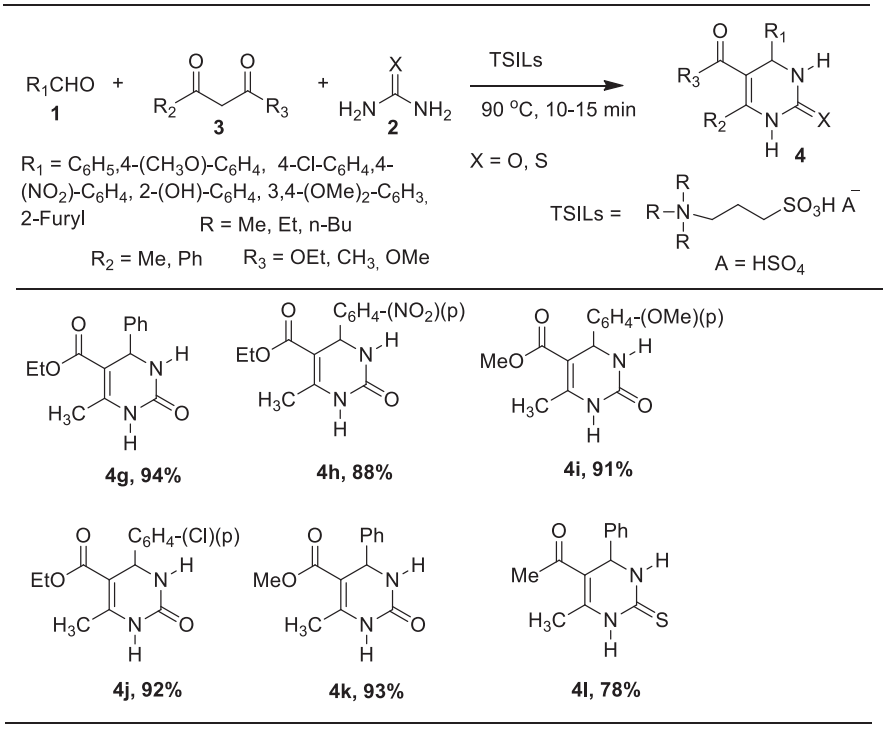


Figure 1.2: Reaction of aryl aldehyde (benzaldehyde) with acetoacetate and urea (thiourea).

1.2.2 Synthesis of substituted furan derivative

Substituted furan derivatives are considered as important scaffolds in medicinal chemistry due to their antiulcer and antibacterial properties [27]. Our group [28] reported that an ionic liquid promoted Feist–Benary reaction to produce dihydrofuran derivatives involving several cyclic and acyclic β-diketones and β-keto carboxylic ester (Figure 1.6). During the condensation reaction, basic ionic liquid, 1-butyl-3-methylimidazolium hydroxide [bmim]OH acts as an effective catalyst to produce the substituted hydroxy dihydro furan derivative with high diastereoselectivity.

In another experiment, it was observed that a neutral ionic liquid [pmim]Br catalyzed the condensation reaction to produce the corresponding furan derivative as a final product. High yield of the product was obtained with higher stereoselectivity using substituted α-bromo carbonyl compound.

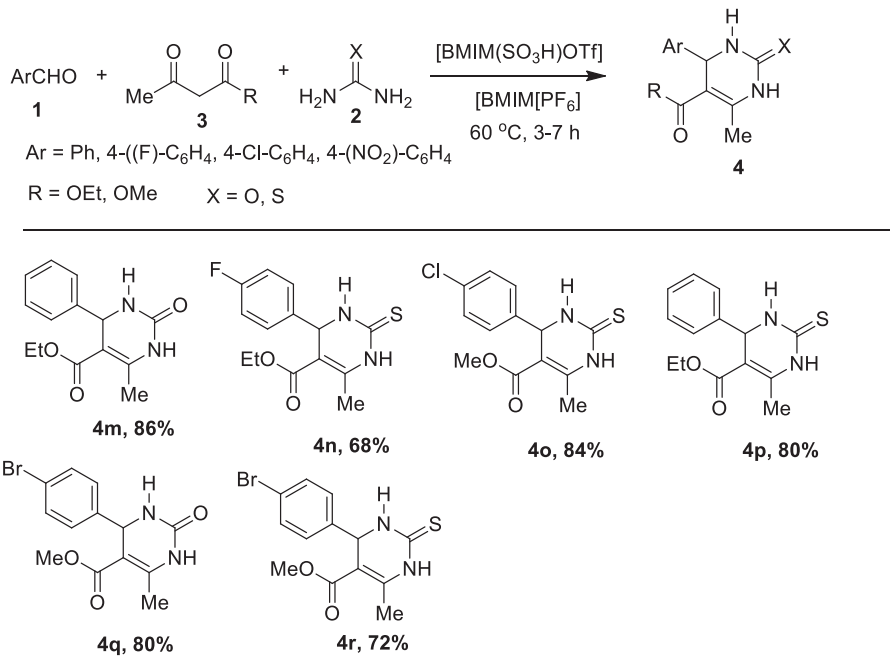


Figure 1.3: Reaction of aryl aldehyde with acetoacetate and urea (thio urea).

1.2.3 Synthesis of pyridine derivative

Pyridine and its derivatives are common structural motifs in many natural products and drugs [29]. Therefore, a considerable attention has been given to the development of the synthesis of derivatives containing pyridine nucleus. Our group [30] reported a one-pot three-component condensation of aromatic aldehyde, malononitrile and alkane thiols for the synthesis of highly substituted pyridine derivatives by using [bmIm]OH ionic liquid in ethanol under room temperature (Figure 1.7). In this reaction different types of diversely substituted aryl aldehyde condensed with malononitrile and thiophenols to produce the corresponding products in moderate-to-high yields. During the optimization process, it was observed that without using ionic liquid the reaction does not proceed at all.

1.2.4 Synthesis of indole derivative

Indole and its derivatives are of much interest due to their diverse biological activities. Sumatriptan and Ondansetron are the indole-based potent drugs which are

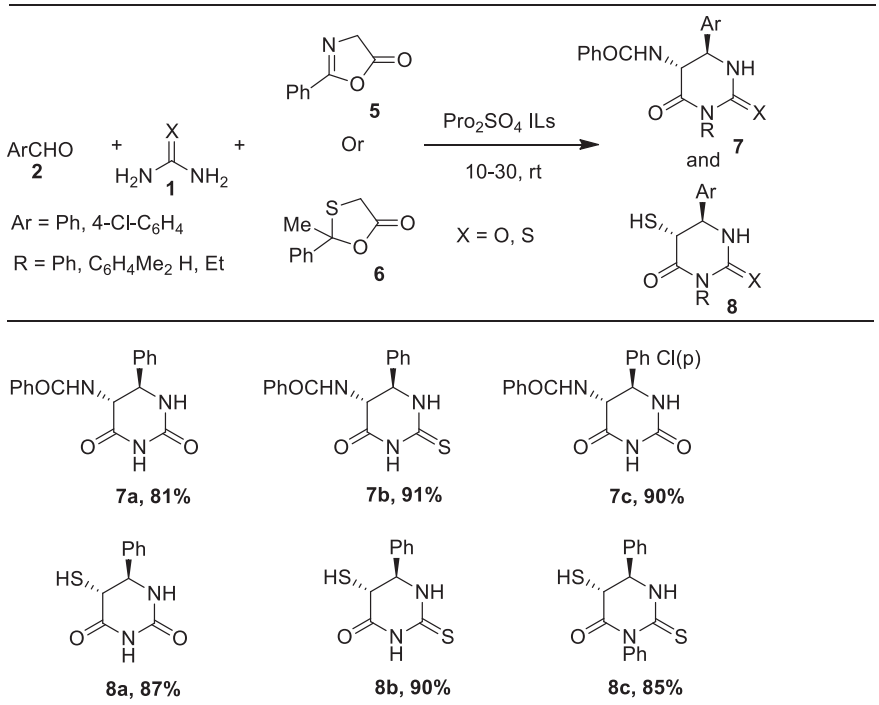


Figure 1.4: Reaction of urea, thiourea moiety with aromatic aldehyde and oxathiolan-5-one and oxazol-5-one nuclei.

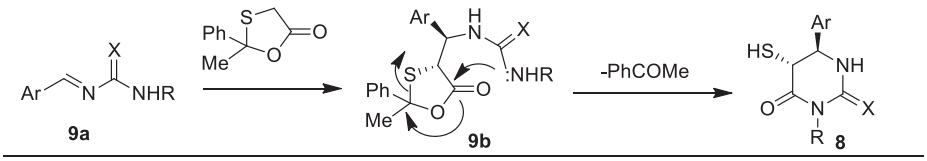


Figure 1.5: Plausible mechanism for the formation of 5-mercaptoperhydropyridines.

used for the treatment of migraine and nausea and vomiting caused by cancer chemotherapy and radiotherapy [31]. Jenkins et al. [32] demonstrated a Fischer indole synthesis using ionic liquid, choline chloride, 2 $ZnCl_2$ to produce 2,3-disubstituted indoles (Figure 1.8). One of the important features of the reaction is that the products readily sublime from the ionic liquid. So, there is no need to purify the product by chromatography or other techniques. The reaction of phenyl hydrazine and ketones provided indoles with a yield ranging from 48% to 88%. Another important aspect of the reaction is the regioselectivity. When an unsymmetrical dialkyl ketone is used,

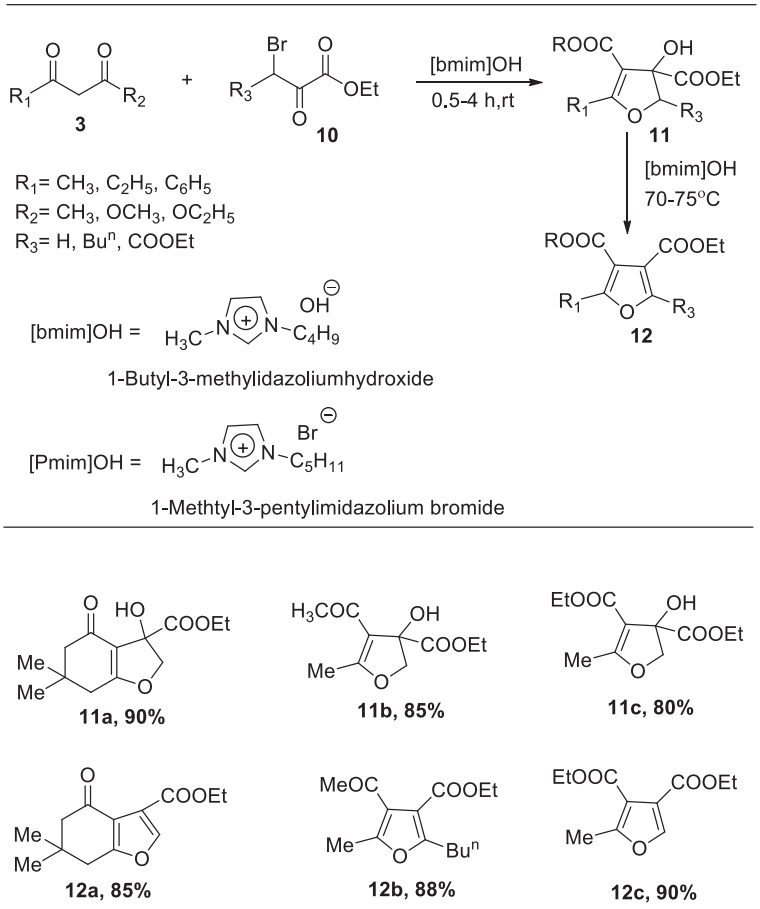


Figure 1.6: Synthesis of hydroxydihydrofurans and substituted furans catalyzed by the ionic liquid.

regiospecific formation of a single product was observed via the intermediacy of a more substituted enamine.

1.2.5 Synthesis of quinoline derivative

The quinoline nucleus is an important moiety of many natural and synthetic molecules with significant biological activity [33]. Heydari et al. [34] developed an SO_3H functionalized ionic liquid as a water-tolerant acidic catalyst for the one-pot synthesis of quinoline derivatives (Figure 1.9). In this protocol of Friedlander quinoline synthesis, 2-aminobenzophenone was subjected to reaction with ethyl acetoacetate in the

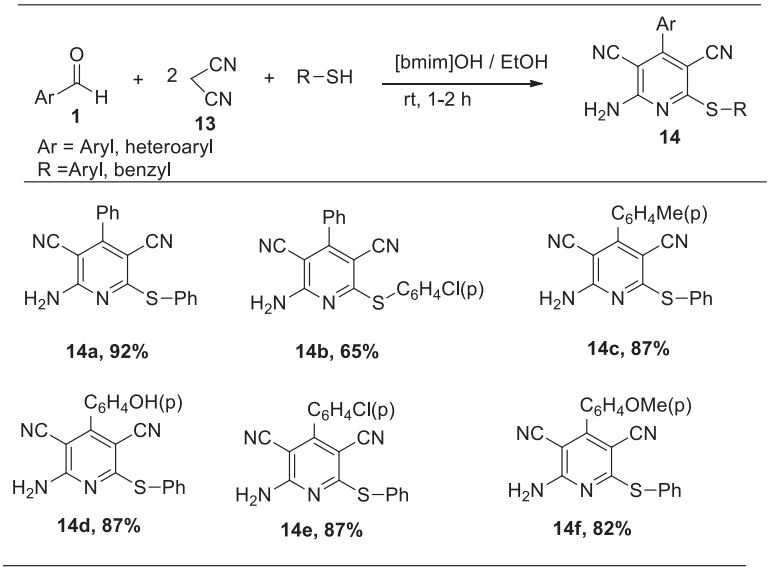


Figure 1.7: Synthesis of substituted pyridines catalyzed by [bmIm]OH.

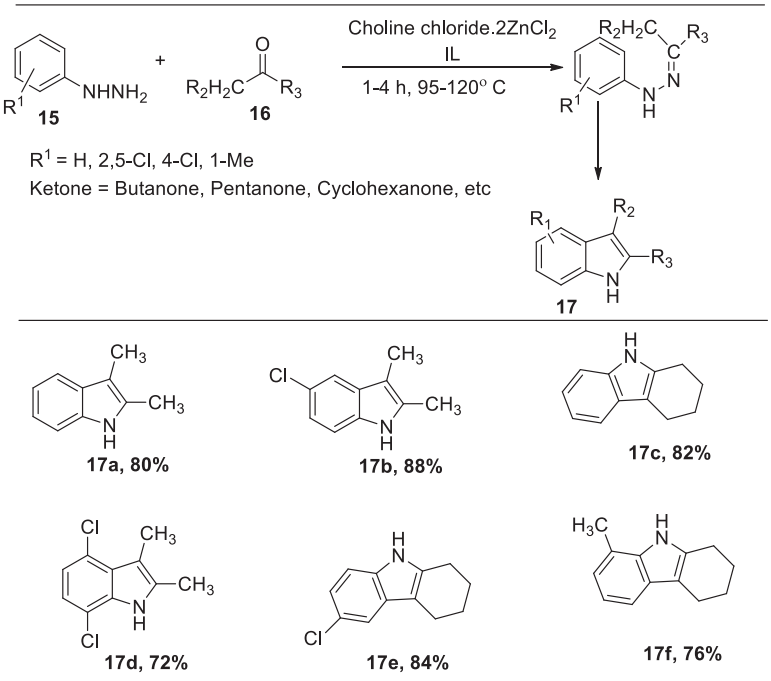


Figure 1.8: Reaction of hydrazine with ketone formation of substituted indole.

presence of SO_3H-functionalized TSIL (SO_3H-functionalized TSIL) as catalyst in water under room temperature to provide the product in good yield. Interestingly, water has important and decisive role as no product was formed in the absence of water. Hence it is suggested that water has the determining effect on the activity of TSILs. TSIL is a green catalyst which is reusable for at least five cycles in this condensation reaction without loss of the catalytic efficiency. This protocol of Friedlander synthesis is simpler compared to other methods and has broad substrate scope using various 1,3-di ketones and 2-aminoaryl ketones to give the corresponding quinolines with good yield avoiding toxic catalyst and solvents.

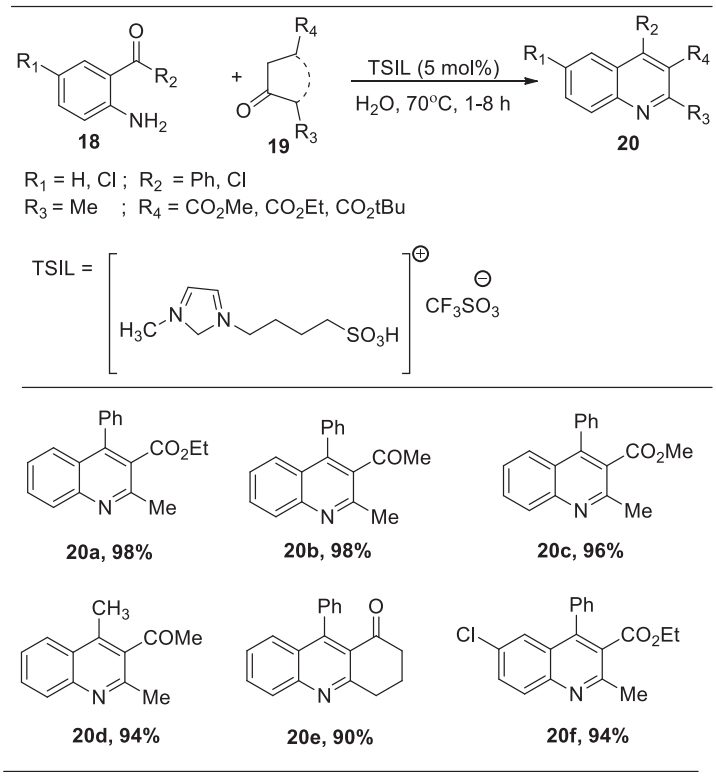


Figure 1.9: Reaction of 2-aminobenzophenone with ethyl acetoacetate or cyclic diketone.

Perumal and coworkers [35] also reported bmimCl:$ZnCl_2$ ionic liquid catalyzed Friedländer condensation to synthesize quinoline derivatives (Figure 1.10). The ionic liquid bmimCl:$ZnCl_2$ acts as solvent as well as catalyst due to its high polarity and Lewis acidic character. Various *o*-amino substituted aromatic ketones were reacted with 1,3-dicarbonyl compounds in bmimCl:$ZnCl_2$ at room temperature to produce the corresponding quinoline derivatives. The product was formed via the formation of *N*-(*O*-acyl-phenyl)-β-enaminones. The reaction avoids hazardous condition and toxic organic solvents.

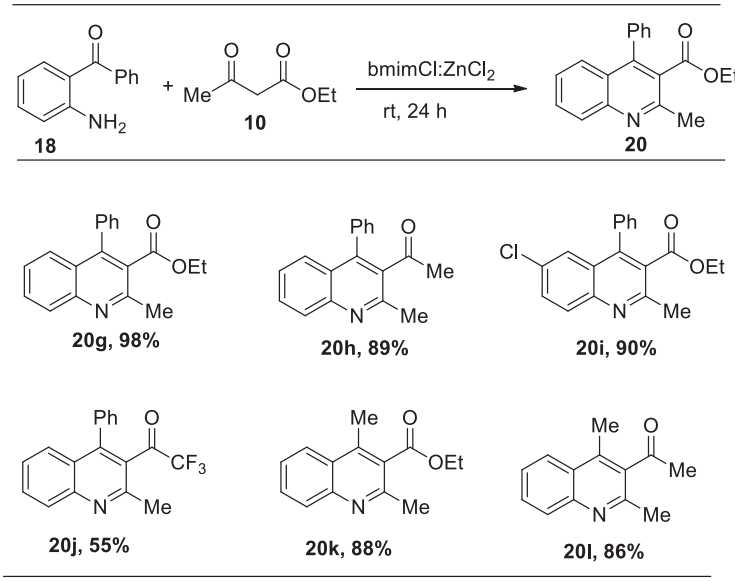


Figure 1.10: Reaction of *o*-amino aromatic ketone with 1,3-dicarbonyl compound.

Kumar and Rao [36] reported the synthesis of substituted quinolines by a three-component reaction of aldehydes, alkynes and amines catalyzed by $Yb(OTf)_3$ under microwave irradiation in $[BMIM]BF_4$ as reaction medium (Figure 1.11). The combined effect of Lewis acidic ionic liquid $[BMIM]BF_4$ and microwave irradiation influences the reaction rate with greater selectivity. The catalyst used in these procedures was recycled for four cycles.

The reaction proceeds through four-step domino sequence (Figure 1.12). The first step involves the formation of ionine which undergoes nucleophilic attack by phenyl acetylene to give the propargyl amine derivative which participates in an intramolecular cyclization and aromatization to give the corresponding quinoline.

1.2.6 Synthesis of pyrazole and imidazole derivative

The derivatives of pyrazole and imidazole molecules are pharmaceutically important because these molecules exhibit a broad spectrum of biological activities and are used as antimicrobial, analgesics, anticancer and antitubercular agent [37, 38]. So, there has been a considerable interest to develop simple and environmentally benign methods for the synthesis of functionalized pyrazole and imadazole molecules. Parmar et al. reported a three-component domino intermolecular Knoevenagel hetero-Diels–Alder reaction to afford the bioactive indonyl and quinolyl pyrano[2,3-*c*] pyrazoles by the

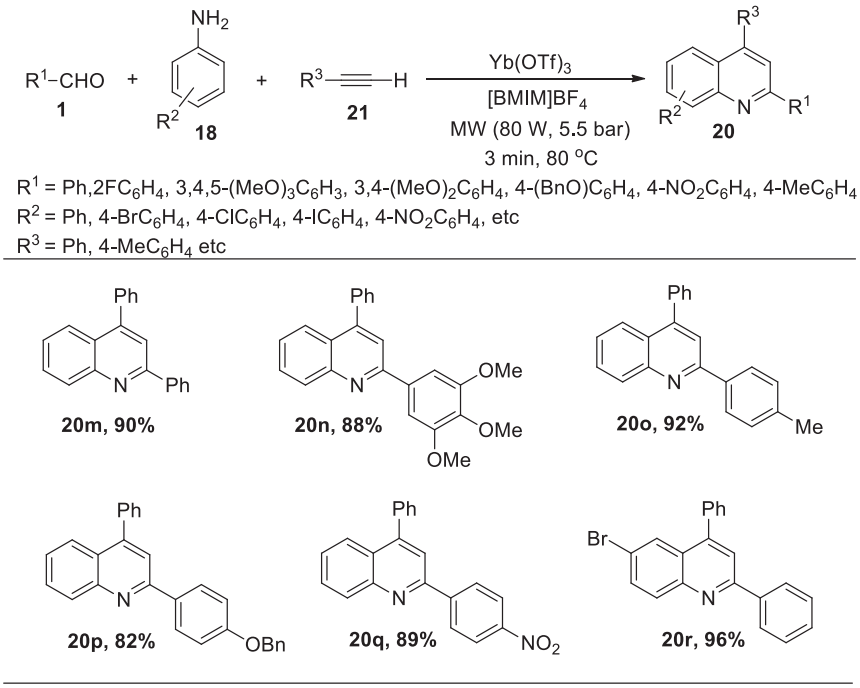


Figure 1.11: Reaction of aromatic aldehydes with phenyl acetylenes and aniline to produce quinoline.

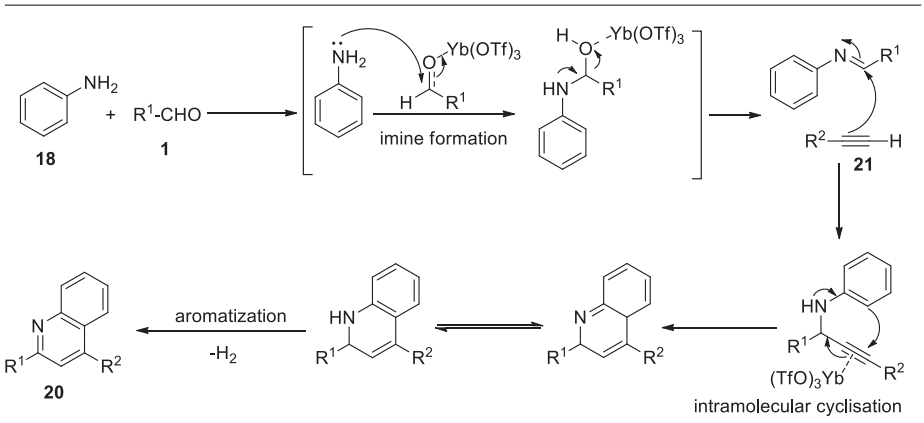


Figure 1.12: Proposed mechanism for the synthesis of quinolines by three-component reaction.

reaction of heteroaryl aldehyde, pyrazolone and enol ether using triethyl ammonium acetate (TEAA) ionic liquid under microwave irradiation (Figure 1.13) [39].

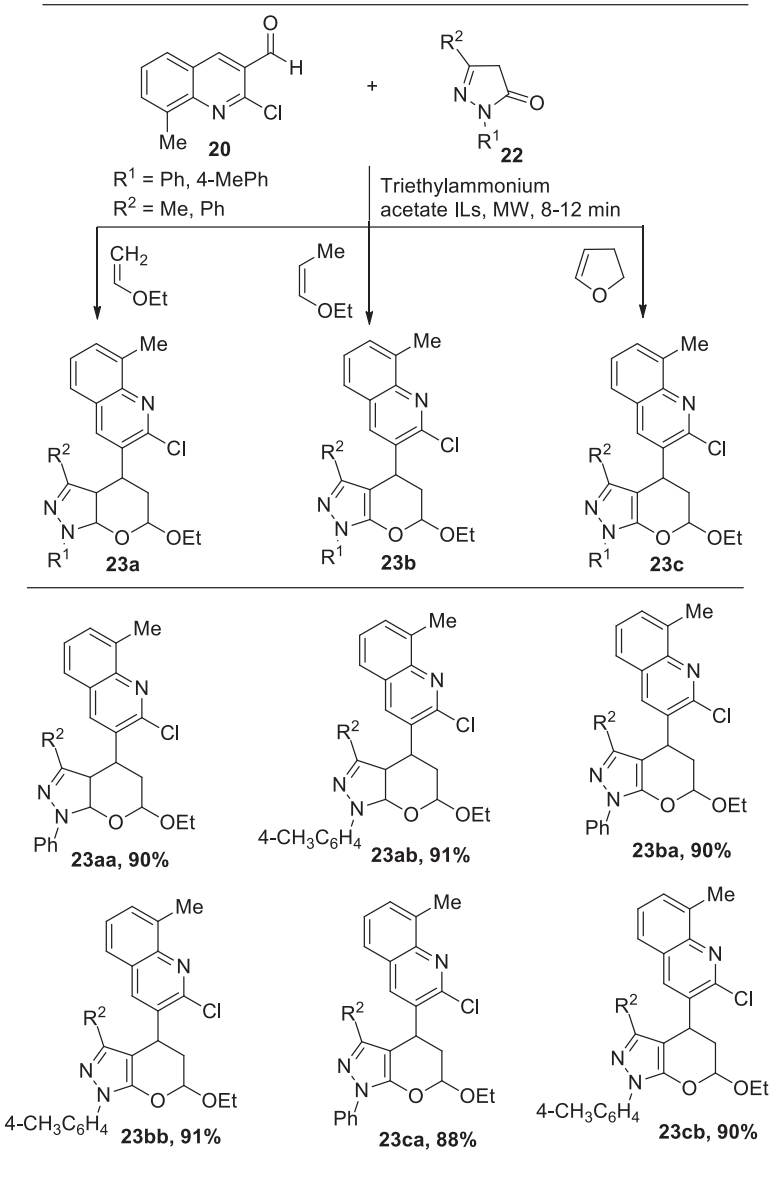


Figure 1.13: Synthesis of quinolyl pyrano[2,3-*c*]pyrazoles.

Various pyrazolone derivatives reacted with a variety of heteroaldehydes and dienophiles, ethyl vinyl ether, dihydrofuran, etc. to provide the corresponding products in good yields. TEAA ionic liquid has dual role as reaction medium as well as catalyst and it was reused further. It was observed that minor amount of Michael adduct was formed besides the major Knoevenagel adduct in this reaction.

Laali's group reported the Van Leusen imidazole-Suzuki and oxazole-Suzuki reaction using [bmim]*X* [where $X = {}^{-}PF_6$ and ${}^{-}BF_4$] as solvent and [PAIM][NTf_2] as a basic catalyst (Figure 1.14) [40]. The reaction proceeded smoothly to provide the products in high yield under mild reaction conditions. The reaction used readily available starting materials and thus enhanced the utility of the method. The ionic liquid was recycled for several runs.

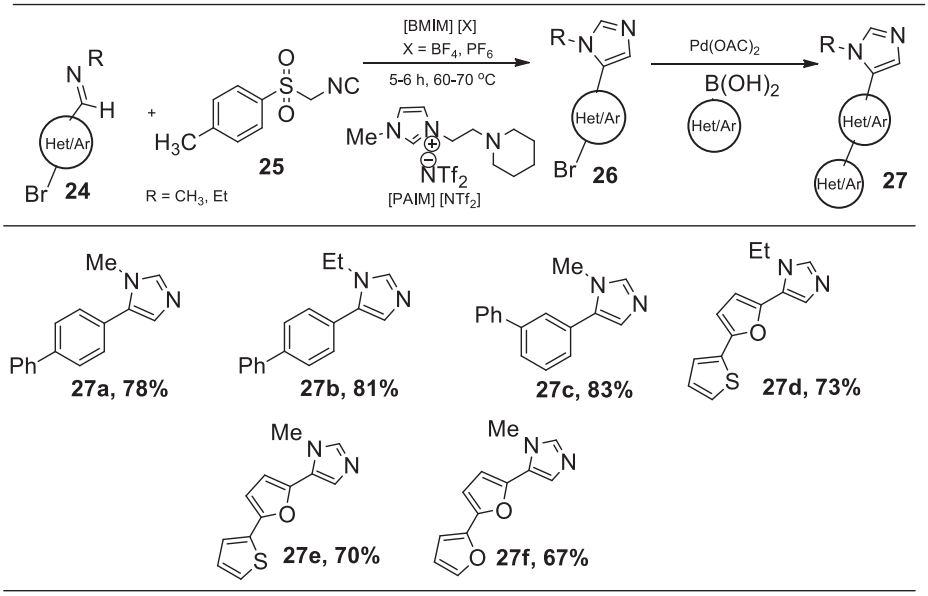


Figure 1.14: Van Leusen imidazole Suzuki reaction to produce different substituted product.

Hasaninejad et al. [41] developed the synthesis of 1,2,4,5-*tetra*-substituted imidazoles using ionic liquid [BMIM]Br under microwave irradiation or simply by heating condition (Figure 1.15). This one-pot four-component condensation reaction proceeds in [BMIM]Br (a neutral reaction medium) without using any additional catalyst. Aromatic aldehydes, aliphatic and aromatic amines were condensed with benzil and ammonium acetate under conventional heating or microwave irradiation to give the product. Electronic effect plays a vital role in the reaction. Aromatic aldehydes having electron withdrawing groups reacted with faster rate while aromatic aldehydes containing electron donating group reacted with the slower one. The methodology is also successful for heteroaromatic aldehydes to furnish *tetra*-substituted imidazoles in excellent yield without any side product.

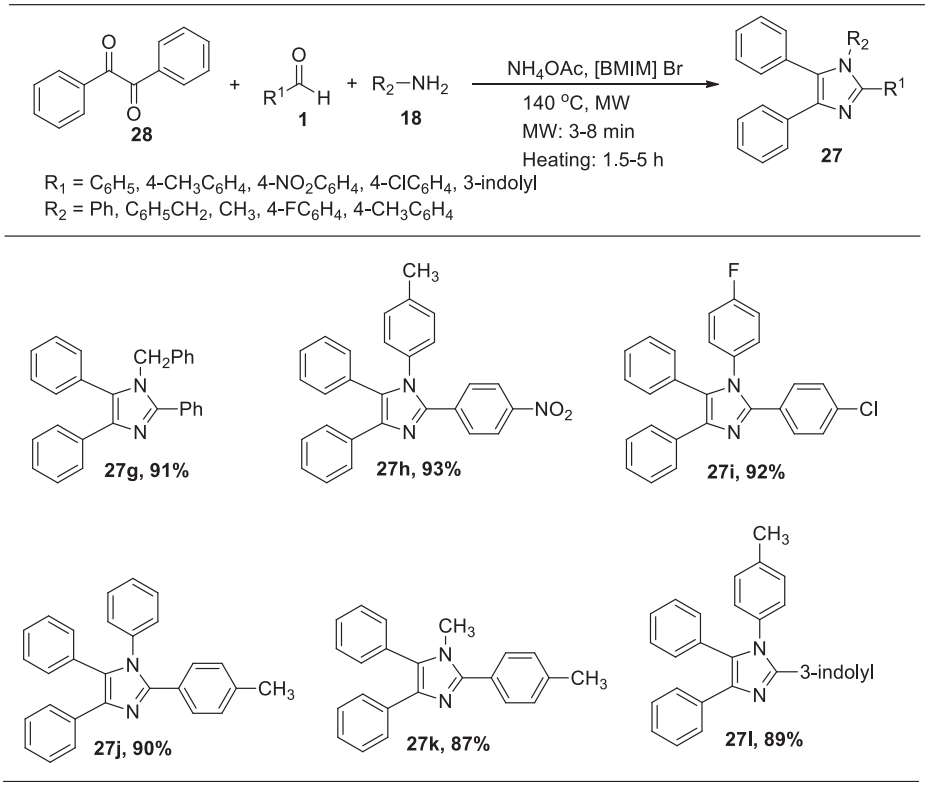


Figure 1.15: Reaction of aromatic aldehyde with aromatic or aliphatic amine and benzil.

1.2.7 Synthesis of quinoxaline derivative

Quinoxalines are important class of molecules having effectiveness in the treatment of various bacterial infections [42]. Meshram et al. [43] described the synthesis of quinoxaline-2-carboxylate derivative by using [bmim]BF_4 as reaction media (Figure 1.16). The catalyst free reaction of α-halo-β-keto ester and 1,2-diamines opened a wide scope for the synthesis of a variety of quinoxaline derivatives which are of much importance as biologically active compound.

The electronic effect of substituted 1,2-diamines plays an important role in the reaction. The electron donating groups increase the rate of the reaction while electron withdrawing groups decrease the rate; however, only one product was formed in all cases.

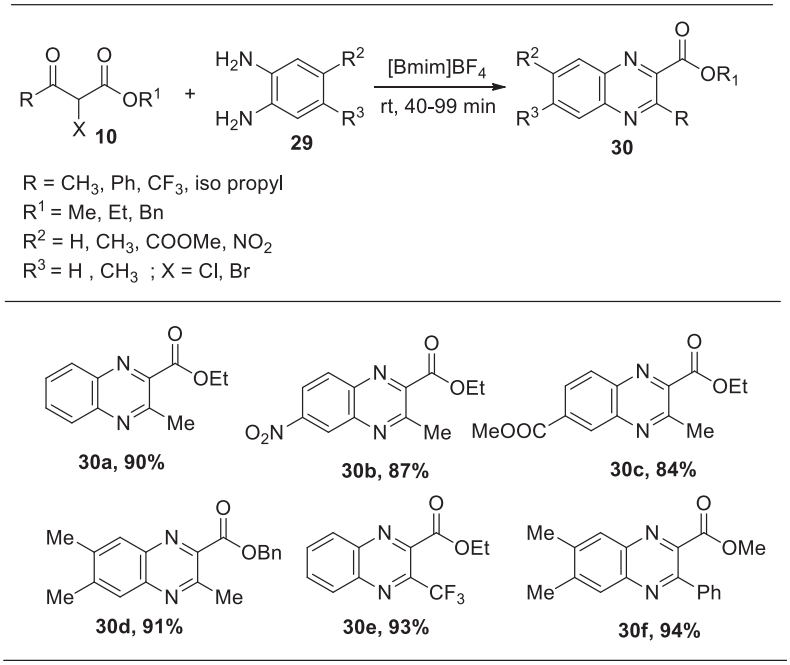


Figure 1.16: Reaction of α-halo, β-keto ester with 1,2-phenylene diamine using [Bmim]BF_4 IL.

1.2.8 Synthesis of thiochromone derivative

Thiochromone derivatives are usually known as privileged scaffolds in pharmaceutical industry due to their promising biological activities [44]. Wang et al. [45] demonstrated the synthesis of thiochromene derivatives (aromatic and nonaromatic) using ionic liquid [BMIM]BF_4 and [BMIM]Br (Figure 1.17). It was observed that by changing the counter ion of the ionic liquid, the IL shows an enhanced activity toward kinetics of the reaction to give good yields of the product.

BF_4^- gives the best result in terms of yield (98%) compared to the counter ion PF_6^- and HSO_4^- while Br^- gives better (83%) yield than that of Cl^-, OH^-, etc. So the counter ion of ionic liquid has determining role in this reaction too. The reaction temperature also has profound effect. The higher temperature leads to elimination reaction and it was found that 50 °C is the optimum to have the product, 9-amino-7-phenyl-6*H*-benzo[*c*]thiochromene-8,10-dicarbonitrile derivative in good yield.

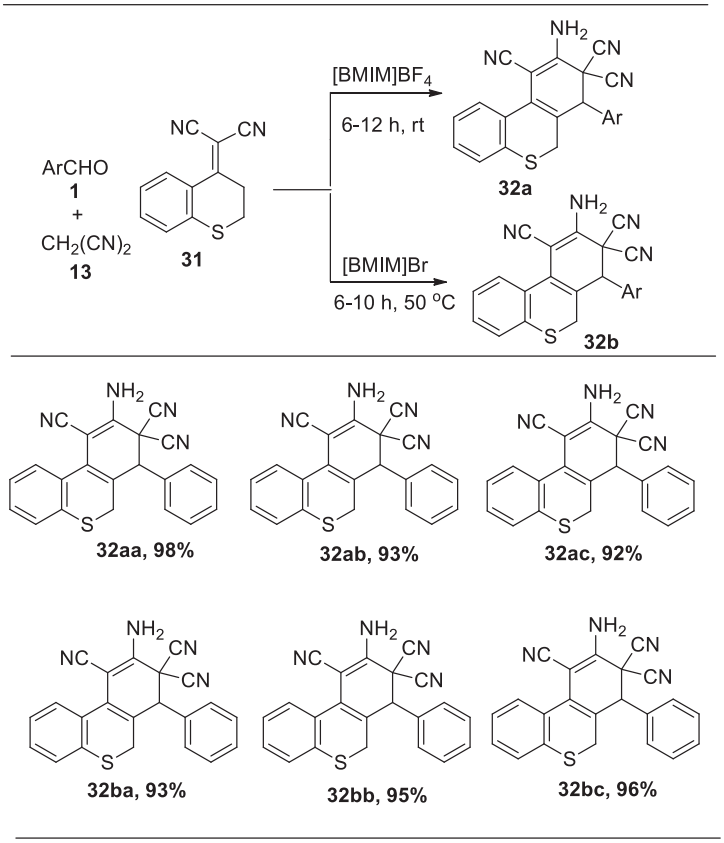


Figure 1.17: Reaction of aromatic aldehyde with malononitrile and 2-(2,3-dihydro thiochromen-4-ylidene) malononitrile.

1.2.9 Synthesis of phthalazine derivative

Nitrogen heterocycles containing phthalazine moiety are of much interest showing diverse activities such as anticonvulsant, cardiotonic and vasorelaxant [46]. Shekouhy and Hasaninejad [47] demonstrated a catalyst-free one-pot four-component synthesis of 2*H*-indazole [2,1-*b*]phthalazine-triones by using neutral ionic liquid 1-butyl-3-methylimidazolium bromide ([Bmim]Br) under ultrasonic irradiation (Figure 1.18). The reaction of dimedone, benzaldehyde, hydrazinium hydroxide and phthalic anhydride under ultrasonic irradiation led to the formation of the corresponding products. Notably, the efficiency of ultrasonic irradiation is due to cavitation phenomena [48].

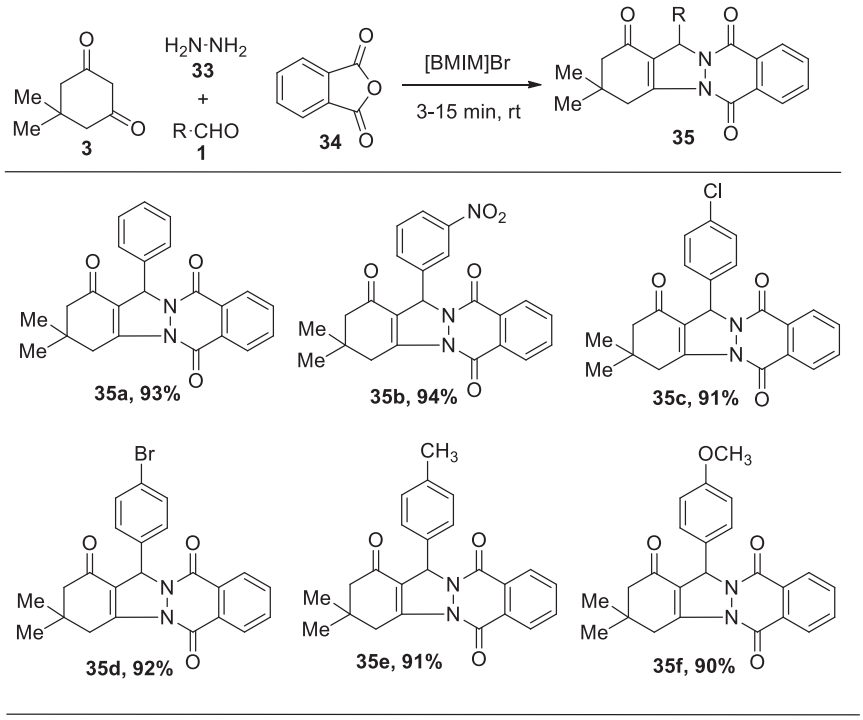


Figure 1.18: Reaction of dimedone, benzaldehyde, hydrazinium hydroxide with phthalic anhydride.

1.2.10 Synthesis of benzodiazepine derivative

Benzodiazepines are known for their wide range of biological activities and therapeutic functions. Most commonly, benzodiazepine derivatives are used as antimicrobial and anthelmintic agents [49]. Kim and coworkers demonstrated a synthesis of 1,5-benzodiazepine derivative using ecofriendly, less-expensive and recyclable di-cationic ionic liquid ([tetra EG(mim)$_2$(OAc)$_2$]) as catalyst under solvent-free condition (Figure 1.19) [50]. It was observed that 5 wt % of tetraethylene glycol-bis (3-methylimidazolium)diacetate ([tetra EG(mim)$_2$(OAc)$_2$]) acts best for the synthesis of benzodiazepine derivative and the reaction proceeds without any cocatalyst and solvent. The ionic liquid is recycled over six times without losing catalytic activity.

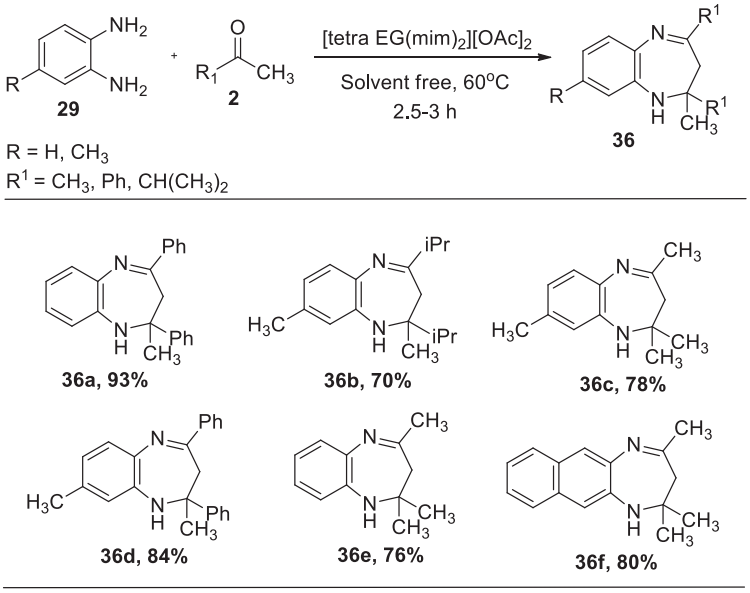


Figure 1.19: Synthesis of 1,5-benzodiazepine derivative.

1.2.11 Synthesis of benzoxazole, benzthiazole and benzimidazole derivative

Benzoxazoles, benzthiazoles and benzimidazoles are of much importance in organic synthesis as well as in pharmaceutical industries showing diverse biological activities [51, 52]. Kalkhambkar and Laali reported a ligand-free, high yielding method for the synthesis of 2-aryl and 2-heteroaryl benzoxazoles and benzthiazoles from readily available Schiff's base using imidazolium ionic liquid in combination with $Pd(OAc)_2$ without any additives (Figure 1.20) [53].

In this reaction, Pd coupled with imine nitrogen of Schiff bases followed by cyclization and elimination to provide 2-aryl and 2-heteroaryl benzoxazoles and benzothiazoles. No oxidant, ligand, additive or hazardous solvent was used in this protocol. The product obtained by this procedure was isolated easily and the ionic liquid is also recyclable being reused three times.

Our group also demonstrated a unique one-pot procedure for the synthesis of 2-substituted benzimidazole derivative by the reaction of an aryl aldehyde with *o*-phenylenediamine in the presence of $[pmIm]BF_4$ ionic liquid at room temperature without any organic solvent (Figure 1.21) [54].

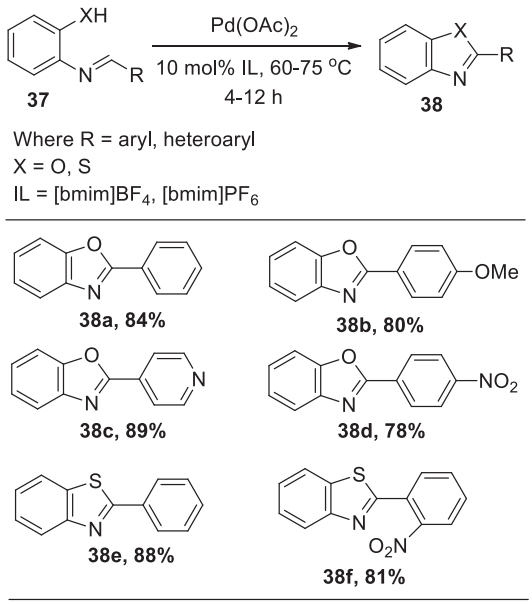


Figure 1.20: Pd-catalyzed synthesis of 2-aryl and 2-heteroaryl benzoxazoles and benzothiazole derivatives.

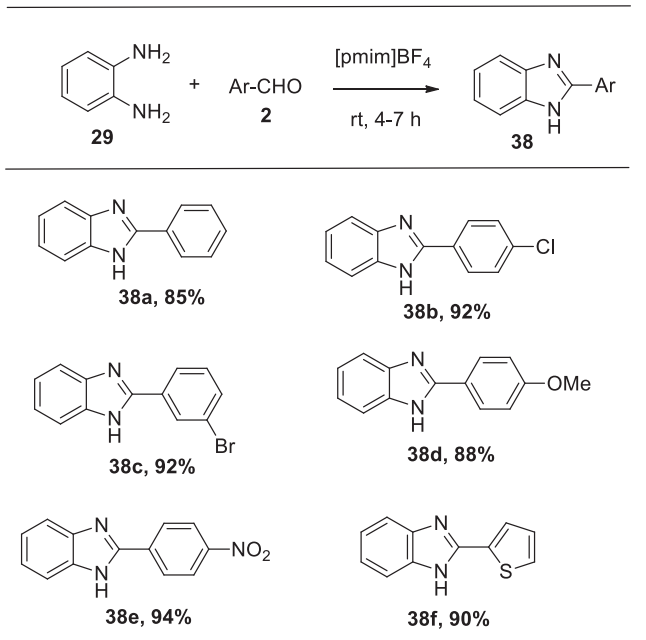


Figure 1.21: Synthesis of substituted benzimidazoles.

It was observed that aromatic aldehyde with electron withdrawing group performs better in terms of product yield compared to those having electron donating group. Sterically hindered as well as heterocyclic aldehydes underwent smooth reaction under the optimized condition. Ionic liquid was recycled up to two cycles without any loss of yield whereas in the next two cycles slight loss of efficiency was observed.

1.3 Conclusions

In this article we have discussed the application of ionic liquids for the synthesis of various heterocyclic molecules of biological importance. Under this discussion it was demonstrated that the carbon–nitrogen, carbon–oxygen and carbon–sulfur bond formations have been efficiently achieved by the catalysis of ionic liquids avoiding any toxic organic solvent. Ionic liquids act here as reaction medium as well as catalysts. Ionic liquids are relatively benign, inexpensive and recyclable. The reactions are usually performed at room temperature under ligand-free conditions. Thus, these procedures involving ionic liquids provide alternative green routes for the access of a variety of bioactive heterocycles. We believe that this review will attract the attention of a wide section of chemists in the academia as well as pharmaceutical industries.

References

[1] Litschauer, M, Neouze, MA. Nanoparticles connected through an ionic liquid-like network. J Mater Chem 2008, 18, 640–646.
[2] Jiang, YY, Wang, GN, Zhou, Z, Wu, YT, Geng, J, Zhang, ZB. Tetraalkylammonium amino acids as functionalized ionic liquids of low viscosity. Chem Commun 2008, 44, 505–507.
[3] Wang, Z, Zhang, Q, Kuehner, D, Ivaska, A, Niu, L. Green synthesis of 1–2 nm gold nanoparticles stabilized by amine-terminated ionic liquid and their electrocatalytic activity in oxygen reduction. Green Chem 2008, 10, 907–909.
[4] Welton, T. Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev 1999, 99, 2071–2083.
[5] Wilkes, JS. Properties of ionic liquid solvents for catalysis. J Mol Catal A: Chem 2004, 214, l1–17.
[6] Andrade, CKZ, Alves, LM. Environmentally benign solvents in organic synthesis: Current topics. Curr Org Chem 2005, 9, 195–218.
[7] Wasserscheid, P, Keim, W. Ionic liquids-new solutions for transition metal catalysis. Angew Chem Int Ed Engl 2000, 39, 3772–3789.
[8] Smith, MB, March, J. March's advanced organic chemistry. New York: Wiley-Interscience, 2001, Chapter 8.
[9] Macfarlane, DR, Pringle, JM, Johansson, KM, Forsyth, SA, Forsyth, M. Lewis base ionic liquids. Chem Commun 2006, 42, 1905–1917.
[10] Wilkes, JS. A short history of ionic liquids-from molten salts to neoteric solvents. Green Chem 2002, 4, 73–80.
[11] Parvulescu, VI, Hardacre, C. Catalysis in ionic liquids. Chem Rev 2007, 107, 2615–2665.

[12] Namboordiri, VV, Varma, RS. Microwave-assisted preparation of dialkylimidazolium tetrachloroaluminates and their use as catalysts in the solvent-free tetrahydropyranylation of alcohols and phenols. Chem Commun 2002, 38, 342–343.
[13] Sun, W, Xia, C-G, Wang, H-W. Synthesis of aziridines from imines and ethyl diazoacetate in room temperature ionic liquids. Tetrahedron Lett 2003, 44, 2409–2411.
[14] Brahmachari, G. Handbook of pharmaceutical natural products, 1st edn. Weinheim: Wiley-VCH, 2010.
[15] Wu, JY, Fong, WF, Zhang, JX, Leung, CH, Kwong, HL, Yang, MS, Li, D, Cheung, HY. Reversal of multidrug resistance in cancer cells by pyranocoumarins isolated from Radix Peucedani. Eur J Pharmacol 2003, 473, 9–17.
[16] Foye, WO. Principi di Chemico Farmaceutica. Padora, Italy: Piccin, 1991.
[17] De Andrade-Neto, VF, Goulart, MO, Da Silva Filho, JF, Da Silva, MJ, Pinto, MDC, Pinto, AV, Zalis, MG, Carvalho, LH, Krettli, AU. Antimalarial activity of phenazines from lapachol, β-lapachone and its derivatives against Plasmodium falciparum in vitro and *Plasmodium berghei* in vivo. Bioorg Med Chem Lett 2004, 14, 1145–1149.
[18] El-Wahab, AHFA. Synthesis, reactions and evaluation of the antimicrobial activity of some 4-(p-Halophenyl)-4H-naphthopyran, pyranopyrimidine and pyranotriazolopyrimidine derivatives. Pharmaceuticals 2012, 5, 745–757.
[19] Moon, DO, Kim, KC, Jin, CY, Han, MH, Park, C, Lee, KJ, Park, YM, Choi, YH, Kim, GY. Inhibitory effects of eicosapentaenoic acid on lipopolysaccharide-induced activation in BV2 microglia. Int Immunopharmacol 2007, 7, 222–229.
[20] Gurunanjappa, P, Ningappa, MB, Kariyappa, AK. Synthesis of pyrazole fused pyran analogues: Antimicrobial, antioxidant and molecular docking studies. Chem Data Collect 2016, 5–6, 1–11.
[21] Atwal, KS, Rovnyak, GC, O′Reilly, BC, Schwartz, J. Substituted 1,4-dihydropyrimidines. 3.[1] synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidine. J Org Chem 1989, 54, 5898–5907.
[22] Kappe, CO. 4-Aryldihydropyrimidines via the Biginelli condensation: Aza-analogs of nifedipine-type calcium channel modulators. Molecules 1998, 3, 1–9.
[23] Peng, J, Deng, Y. Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. Tetrahedron Lett 2001, 42, 5917–5919.
[24] Dong, F, Jun, L, Xinli, Z, Zhiwen, Y, Zuliang, L. One-pot green procedure for Biginelli reaction catalyzed by novel task-specific room-temperature ionic liquids. J Mol Catal A: Chem 2007, 274, 208–211.
[25] Savanur, HM, Kalkhambkar, RG, Aridoss, G, Laali, KK. [bmim(SO_3H)][OTf]/[bmim][X] and Zn(NTf_2)$_2$/[bmim][Xl (X = PF_6 and BF_4); Efficient catalytic systems for the synthesis of tetrahydropyrimidin-ones (-thiones) via the Biginelli reaction. Tetrahedron Lett 2016, 57, 3029–3025.
[26] Yadav, LDS, Rai, A, Rai, VK, Awasthi, C. Chiral ionic liquid-catalyzed Biginelli reaction: Stereoselective synthesis of polyfunctionalized perhydropyrimidines. Tetrahedron 2008, 64, 1420–1429.
[27] Andrade, MMS, Protti, ÍF, Maltarollo, VG, da Costa, YFG, de Moraes, WG, Moreira, NF, Garcia, GG, Caran, GF, Ottoni, FM, Alves, RJ, Moreira, CPS, Martins, HR, Alves, MS, de Oliveira, RB. Synthesis of arylfuran derivatives as potential antibacterial agents. Med Chem Res 2021, 30, 1074–1086.
[28] Ranu, BC, Adak, L, Banerjee, S. Ionic liquid promoted interrupted Feist-Benary reaction with high diastereoselectivity. Tetrahedron Lett 2008, 49, 4613–4617.
[29] Ma, X, Gang, DR. The lycopodium alkaloids. Nat Prod Rep 2004, 21, 752–772.
[30] Ranu, BC, Jana, R, Sowmiah, S. An improved procedure for the three-component synthesis of highly substituted pyridines using ionic liquid. J Org Chem 2007, 72, 3152–3154.
[31] Kaushik, NK, Kaushik, N, Attri, P, Kumar, N, Kim, CH, Verma, AK, Choi, EH. Biomedical importance of indoles. Molecules 2013, 18, 6620–6662.

[32] Morales, RC, Tambyrajah, V, Jenkins, PR, Davies, DL, Abbott, AP. The regiospecific Fischer indole reaction in choline chloride.2$ZnCl_2$ with product isolation by direct sublimation from the ionic liquid. Chem Commun 2004, 40, 158–159.
[33] Kumar, S, Bawa, S, Gupta, H. Biological activities of quinoline derivatives. Mini Rev Med Chem 2009, 9, 1648–1654.
[34] Akbari, J, Heydari, A, Kalhor, HR, Kohan, SA. Sulfonic acid functionalized ionic liquid in combinatorial approach, a recyclable and water tolerant-acidic catalyst for one-pot Friedlander quinoline synthesis. J Comb Chem 2010, 12, 137–140.
[35] Karthikeyan, G, Perumal, PT. A mild, efficient and improved protocol for the Friedländer synthesis of quinolines using Lewis acidic ionic liquid. J Heterocyclic Chem 2004, 41, 1039–1041.
[36] Kumar, A, Rao, VK. Microwave-assisted and $Yb(OTf)_3$,-promoted one-pot multicomponent synthesis of substituted quinolines in ionic liquid. Synlett 2011, 2011, 2157–2162.
[37] Srivalli, T, Satish, K, Suthakaran, R. Synthesis, characterization and analgesic evaluation of some pyrazolone derivatives. Int J Innov Pharm Res 2011, 2, 172–174.
[38] Chopra, PN, Sahu., JK. Biological significance of imidazole-based analogues in new drug development. Curr Drug Discov Technol 2020, 17, 574–584.
[39] Parmar, NJ, Barad, HA, Pansuriya, BR, Talpada, NP. A highly efficient, rapid one-pot synthesis of some new heteroarylpyrano[2,3-c]pyrazoles in ionic liquid under microwave-irradiation. RSC Adv 2013, 3, 8064–8070.
[40] Savanur, HM, Kalkhambkar, RG, Laali, KK. Libraries of C-5 substituted imidazoles and oxazoles by sequential Van Leusen (VL)–Suzuki, VL–Heck and VL–Sonogashira in imidazolium-ILs with piperidine-appended-IL as base. Eur J Org Chem 2018, 38, 5285–5288.
[41] Hasaninejad, A, Zare, A, Shekouhy, M, Rad, JA. Catalyst-free one-pot four component synthesis of polysubstituted imidazoles in neutral ionic liquid 1-butyl-3-methylimidazolium bromide. J Comb Chem 2010, 12, 844–849.
[42] Brown, DJ, Taylor, EC, Ellman, JA, editors. The chemistry of heterocyclic compounds, quinoxalines: Supplements II. New Jersey: John Wiley and Sons, 2004.
[43] Meshram, HM, Ramesh, P, Kumar, GS, Reddy, BC. One-pot synthesis of quinoxaline-2-carboxylate derivatives using ionic liquid as reusable reaction media. Tetrahedron Lett 2010, 51, 4313–4316.
[44] Vargas, E, Echeverri, F, Vélez, ID, Robledo, SM, Quiñones, W. Synthesis and evaluation of thiochroman-4-one derivatives as potential leishmanicidal agents. Molecules 2017, 22, 2041.
[45] Wang, X-S, Wu, J-R, Zhou, J, Zhang, M-M. A green method for the synthesis of thiochromene derivatives in ionic liquids. J Heterocyclic Chem 2011, 48, 1056–1060.
[46] Lichtenthaler, FW. Unsaturated O- and N-heterocycles from carbohydrate feedstocks. Acc Chem Res 2002, 35, 728–737.
[47] Shekouhy, M, Hasaninejad, A. Ultrasound-promoted catalyst-free one-pot four component synthesis of 2H-indazolo[2,1-b]phthalazine-triones in neutral ionic liquid 1-butyl-3-methylimidazolium bromide. Ultason Sonochem 2012, 19, 307–313.
[48] Gogate, PR, Mujumdar, S, Pandit, AB. Sonochemical reactors for waste water treatment: Comparison using formic acid degradation as a model reaction. Adv Environ Res 2003, 7, 283–299.
[49] Kumar, R, Joshi, YC. Synthesis, spectral studies and biological activity of 3H-1, 5-benzodiazepine derivatives. Arkivoc 2007, 13, 142–149.
[50] Jadhav, AH, Chinnappan, A, Patil, RH, Kostjuk, SV, Kim, H. Short oligo ethylene glycolic tailor-made ionic liquids as highly efficient and reusable catalyst for one-pot synthesis of 1,5-benzodiazepine derivatives under solvent free condition. Chem Eng J 2014, 240, 228–234.
[51] Razavi, H, Palaninathan, SK, Powers, ET, Wiseman, RL, Purkey, HE, Mohamedmohaideen, NN, Deechongkit, S, Chiang, KP, Dendle, MTA, Sacchettini, JC, Kelly, JW. Benzoxazoles as transthyretin amyloid fibril inhibitors: Synthesis, evaluation, and mechanism of action. Angew Chem Int Ed 2003, 42, 2758–2761.

[52] Gravalt, GL, Baguley, BC, Wilson, WR, Denny, WA. DNA-directed alkylating agents. 6. synthesis and antitumor activity of DNA minor groove-targeted aniline mustard analogs of pibenzimol (Hoechst 33258). J Med Chem 1994, 37, 4338–4345.

[53] Kalkhambkar, RG, Laali, KK. $Pd(OAc)_2$ catalyzed synthesis of 2-aryl- and 2-heteroaryl-benzoxazoles and benzothiazoles in imidazolium ionic liquids (ILs) without additives and with recycling/reuse of the IL. Tetrahedron Lett 2012, 53, 4212–4215.

[54] Saha, D, Saha, A, Ranu, BC. Remarkable influence of substituent in ionic liquid in control of reaction: Simple, efficient and hazardous organic solvent free procedure for the synthesis of 2-aryl benzimidazoles promoted by ionic liquid, $[pmim]BF_4$. Green Chem 2009, 11, 733–737.

Vaidya Jayathirtha Rao

Chapter 2
Synthesis of *oxygen* and *sulfur* heterocycles mediated by ionic liquids

2.1 Introduction

Generally liquids contain neutral molecules, whereas ionic liquids (ILs) are made of ions or charged species and are in liquid state. Interestingly these ILs have different names like ionic fluids or deep eutectic solvents or liquid electrolytes or liquid salts or ionic melts or ionic glasses or fused salts. These ILs have become prominent because of their very, very low vapor pressure and can substitute organic solvent to be used in organic chemical reactions. ILs have a role to play in carbon capturing, batteries, waste recycling, solar and thermal energy, nuclear fuel processing, catalysis and may be many more.

2.2 History of ionic liquids

Compounds made of ions that are in the liquid state are called as ionic liquids (ILs). Ramsay was one of the first researchers to make ILs [1] by mixing acids with picoline and use them for scientific purpose. Ethylamine-nitric acid [Et-NH_3][NO_3] mixture has 12 °C melting point and it was another ionic liquid reported during 1914 [2]. Fused metal salts (ILs) were prepared by Sugden and Wilkins [3] for parachor studies during 1929. Hurley and Weier [4] reported making alkyl-pyridinium salts mixed with inorganic salts (in 1951) on the usage of molten salts for the purpose of electro-metallation. They noticed that 1-ethylpyridinium bromide-aluminum chloride ([C2py]Br-$AlCl_3$) prepared in 2:1 M ratio was found to be liquid (IL) at room temperature. The same was observed by Zhang and Etzold [5] that a 1:1 ratio and 2:1 ratio of 1-ethylpyridinium bromide-aluminum chloride prepared were having melting point of 45 and 88 °C. Reaction of triethylamine with Cu(I) and (II) salts produced [6] liquid instead of expected solid as reported by Yoke et al. [6], and this triggered a lot of enthusiasm for others to get into the research [7–10]. Then a review article published by Hussey [11, 12] in 1983

Acknowledgment: VJR thanks AcSIR–Ghaziabad for Honorary Professorship and CSIR–New Delhi for Emeritus Scientist Honor.

Vaidya Jayathirtha Rao, Emeritus Scientist CSIR & Honorary Professor AcSIR, Organic Synthesis and Process Chemistry Department and AcSIR–Ghaziabad, CSIR–Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500007, Telangana, India, e-mail: vaidya.opv@gmail.com

https://doi.org/10.1515/9783110788129-002

provided a trigger for the research area of ILs. Also, these ILs entered into different domains like catalysis [13], electrochemistry [14], analytical studies, sensors [15, 16] and analytical biochemistry [17].

2.3 Importance of ionic liquids

Ionic salts having melting point below 100 °C can be called as ILs [18]. These ILs have very low vapor pressure (do not vaporize), high boiling point, low volatility, good thermal stability and nonflammable [18, 19] compared to organic solvents and therefore can act as a substitute for organic solvents in conducting chemical transformations and polymerizations [18–20]. ILs can be recovered and reused after conducting chemical reactions and are considered as green solvents. Interestingly, the properties of these ILs can be varied by changing the cation and anion counter parts for the purpose of possible various applications. ILs can be used for dissolving polymers like cellulose [21], silk fiber [22] and starch [23] and this solubilization of polymers can create composite polymers [24], plasticizers [25] and also gels [26]. ILs have found possible application in space propulsion, space lubrication and space telescopes [27]. Ionic liquid can trigger or initiate a crystallization process, acting as medium or solvent [28], particularly a metal-organic framework was crystallized. Heterocycles were synthesized in a fabricated flow micro reactor using IL as immobilized catalyst over a surface of silicon nano-wires (SiNWs), with CO_2 and amines as starting materials [29], indicating utilization of CO_2 leading to fine chemicals. Oleyl-amine-based IL was prepared and used for converting H_2S into sulfur nano particles in a simple fashion; further the same system was utilized to make metal-sulfide nano particles in preparative [30] level and making the entire chemistry as green and also a viable chemical process. ILs can be adopted for liquid electronics purposes [31], where the IL will be a freestanding system within a crystalline IL. The developed system does not require any mechanical support or external encapsulation. These are known as flexible, self-healing and reconfigurable electronics. IL and polymer composites taken and distributed/placed over formaldehyde-melamine resin and these irregularly placed IL-P composites [32] can adsorb particulate matter of size ~1.2–10 nM. Further these fabrications can be applied to voltage to improve the efficiency of the particulate matter or polluted air to be filtered off and to be predicted to be useful for ultrafiltration purposes. Conversion of CO_2 into value-added chemicals is a much-wanted chemistry and this helps us to reduce the CO_2 in the environment. ILs act as buffer and basic catalyst to convert CO_2 to formic acid [33], with high efficiency. ILs absorb water when treated with sea water and leaving behind salts. The salts left out by the ILs can be recovered and the water absorbed by the ILs can be recovered [34] at lower temperature, thus effecting “desalination” of sea water. ILs provide a great opportunity to study and understand the mechanism involved in liquid–liquid transitions (LLT) and further provide the structure–property relationships involved in this LLT [35] phenomenon.

2.4 Synthesis (preparation) and properties of ILs

Many researchers were thinking that ILs are rare and may not be possible to make them, particularly room temperature ionic liquids. But now there are several room temperature ionic liquids that have been synthesized and characterized. The following part is the description on the preparation and properties of some of the ionic liquids. ILs are generally made of organic salts, a mixture of organic cation and organic anion or organic cation and inorganic anion. Many times, cation part of the IL originates from an amine and the anion may be inorganic or organic.

Generally, ILs are synthesized by quaternization of amines with alkyl-halide (Figure 2.1). Reacting *N*-alkyl-imidazole or pyridine with alkyl or tetraphenylborate or benzyl or allyl halides in a suitable solvent [36–39] provides ILs. The anion is prepared from quaternary amines and cation can be exchanged with other anions to make newer analogs.

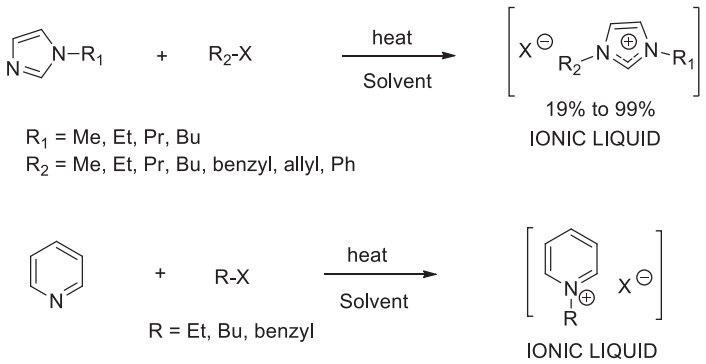


Figure 2.1: Preparation of ILs by amine–alkyl-halide coupling.

The chemical reaction between 1-methylimidazole and dimethyl-carbonate produces zwitterion [40–42] to give 1,3-dimethylimidazolium carboxylate (Figure 2.2). Reaction sequence involves alkylation resulting in cation and followed by carboxylation of this cation leading to 1,3-dimethylimidazolium carboxylate. This interesting zwitterionic intermediate was converted into various ionic liquids (Figure 2.2) by decarboxylation and also differing in their anion part [43] by reacting with various acids. Anion-exchange method – metathesis – can be applied [44, 45] to make ILs (Figure 2.3). Six alkylammonium salts were synthesized [46] among several and were found to be liquid at room temperature. These were prepared by mixing amine with acid for an appropriate time, then water was removed by distillation, and the impurities were removed by extracting with suitable nondissolvable solvent with IL.

The purpose of making these ILs occurred during testing them for chromatography mobile phase and also for liquid–liquid extraction. Tetra-alkyl-borides were prepared

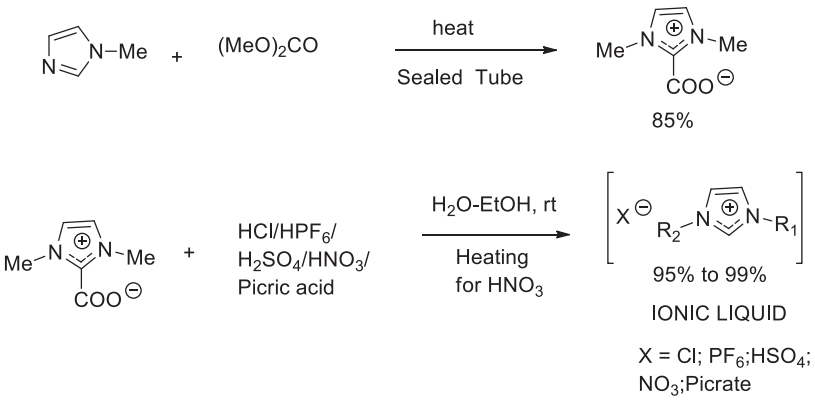


Figure 2.2: Preparation of ILs using zwitterion and acids.

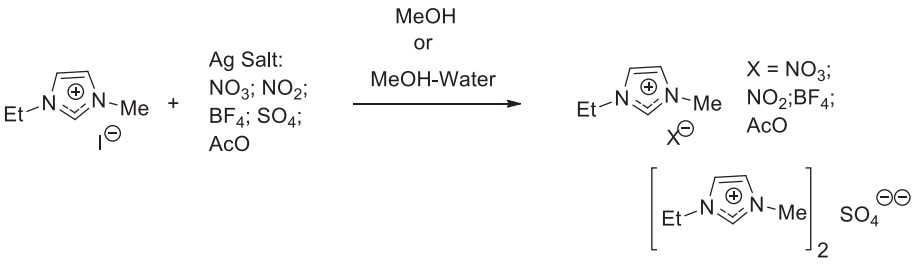


Figure 2.3: Preparation of ILs using anion exchange method.

[47, 48] from alkyl lithium or alkyl sodium compounds reacting with trialkyl-boron compounds (Figure 2.4). These tetra-alkyl-borides were allowed to react with tetra-alkyl ammonium bromides [48] to give corresponding alkylammonium ILs (Figure 2.4).

Thiazolium-based several ILs (Figure 2.5) were synthesized by Hillesheim et al. [49] for the purpose of gas separations. Suitable thiazole moiety was taken and reacted with *n*-butyl bromide (or other bromide) to get corresponding ammonium bromide. Resulting solid ammonium bromide is treated with activated carbon, and after removal of carbon, it is then mixed with lithium *bis*(trifluoromethyl-sulfonamide) to form required ILs (Figure 2.5).

Phosphate-based ILs (Figure 2.6) were reported by Kuhlman et al. [50]. It is a mixture of one equivalent of phosphorous compound to one equivalent amine under controlled conditions and followed by stirring at given temperature to provide fantastic yields of the corresponding imidazolium phosphates (Figure 2.6). The lipophilic imidazolium-phosphate ILs are more interesting that they improve solubility of organic compounds and thereby improving the efficiency of the catalyst.

Phosphonium-based ILs (Figure 2.7) were synthesized by Bradaric et al. [51]. Nucleophilic addition of tertiary phosphine to alkyl halides gives entry to phosphonium-

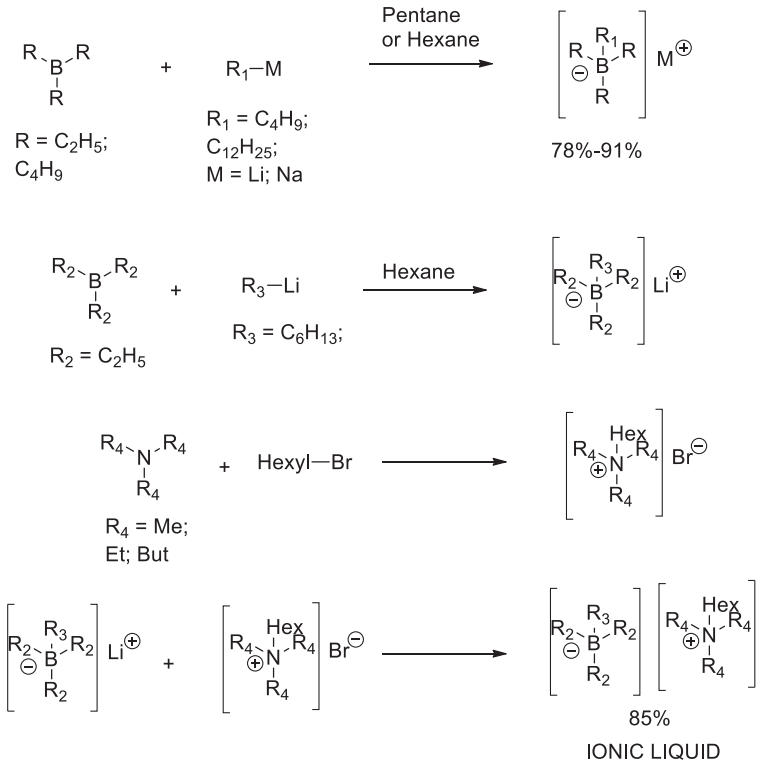


Figure 2.4: Preparation of alkylammonium ILs using metathesis procedure.

based ILs. The halide ion remaining in the above-mentioned ILs preparation is a problem that it interferes in the catalytic reaction and therefore authors have designed a different pathway to avoid residual halogen contaminations (Figure 2.7). Tertiary phosphine was added to the corresponding alkyl ester in a 1:1 ratio, stirred and heated to appropriate temperature to get the phosphonium-based ILs. Alkyl group of alkyl ester used in these reactions has a role to play in the yields of these reactions.

Chiral ILs are becoming more and more important because of their role in catalysis to generate chiral residues and also in chiral separations although its use is still at the beginning stage. These chiral ILs can be constructed using available chiral molecules – chiral pool or adopting asymmetric synthesis. Some of the chiral ILs synthesized are given below in Figure 2.8. *N*-methylation of ephedrine provides entry for ephedrinium (alkaloid)-based chiral IL and this was prepared for a purpose of using it as a gas chromatography (GC) stationary phase [52] and indeed authors have reported the chiral separations. Carbohydrates are known for natural chiral pool compounds and one can use them for making chiral ILs [57]. D-Glucose was transformed into D-glutaric acid, protected the remaining hydroxy groups, reacted with 4,5-dimethyl-1,2-diaminobenzene to make corresponding benzimidazole and then alkylated to make chiral IL with variation

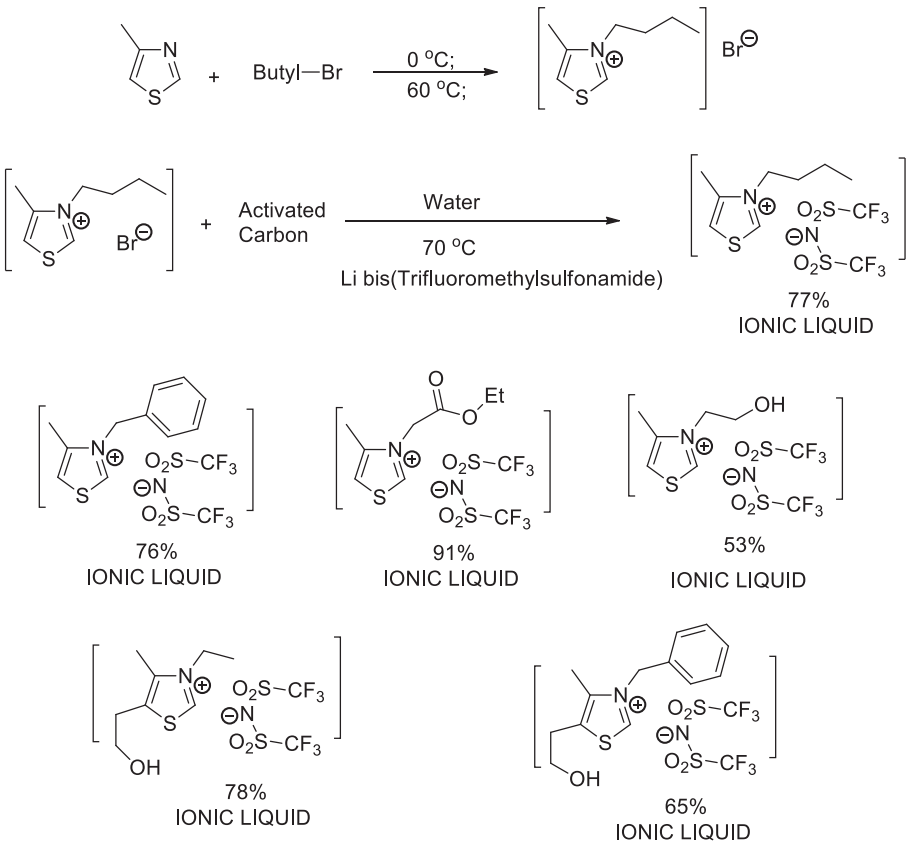


Figure 2.5: Synthesis of various thiazolium-based ILs.

in anion [53]. These chiral ILs were synthesized to use them for stationary phases in GC, liquid chromatography (LC), electrophoresis for enantio-separation [54] and also using them as chiral catalysts for making chiral compounds [55–57].

2.5 Typical procedure to make imidazolium-based ILs

Dimethyl-carbonate and *N*-methylimidazole were taken in a 1.5:1 (–*v*/*v*) ratio and heated in a sealed tube for 24 h [41]. The solid separated out was filtered to get 85% yield of zwitterion, 1,3-dimethylimidazolium carboxylate (Figure 2.2). The authors claim that the procedure can be scaled up to ~35 g level.

1,3-Dimethylimidazolium carboxylate of 10 mmol was taken in 20 mL of 50% ethanol-water medium and added slowly 10 mmol of corresponding acid [43]. The complete

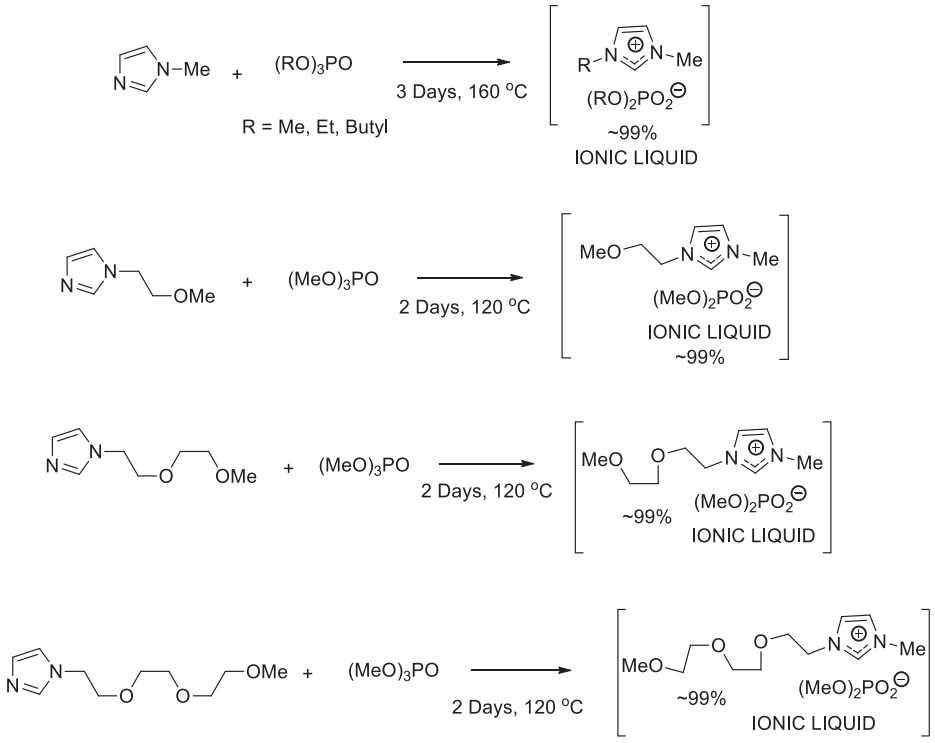


Figure 2.6: Synthesis of various phosphate-based ILs.

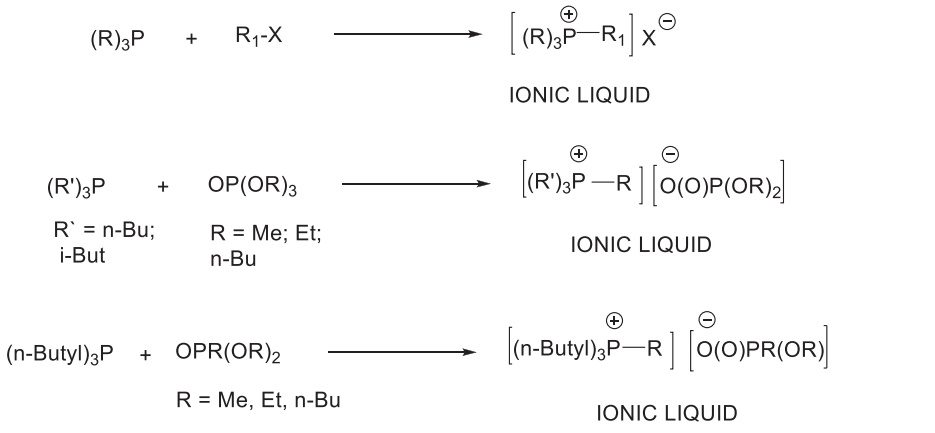


Figure 2.7: Synthesis of various phosphonium-based ILs.

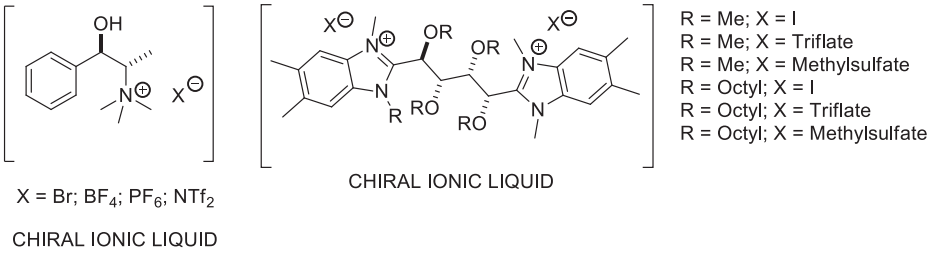


Figure 2.8: Chiral ILs based on alkaloid and carbohydrate chiral pool.

solution was stirred in a closed flask for 24 h at room temperature (Figure 2.2). The solvent was removed using rotary evaporator and the solid obtained was checked for the presence of starting material using NMR spectroscopy. Several acids are employed to make corresponding ILs (Figure 2.2) yielding in the range of 95–99%.

N-Methylimidazole (1.0 equivalent) was taken and to this added slowly (to control the reaction temperature) over a period the 1.0 equivalent of trimethyl/triethyl/tributyl phosphate. Then the reaction mixture was stirred at proper temperature [54] and time to get the corresponding imidazolium-phosphate ILs. The unreacted starting material can be easily removed by washing properly with suitable solvent to get almost 99% yield of ILs.

Properties of ILs like nonvolatility is making it as green alternative solvent, good thermal and chemical stability, a good range of solubility for several organic substances, low nucleophilicity, very less flammability, viscosity, UV–visible absorption, conductivity, density, surface tension, liquid range, heat capacities, dipole moment and polarity/polarizability are some of them, where many researchers have contributed to understand these properties of ILs. These are the few properties that have become important to understand to conduct a chemical reaction and use ILs as efficiently as possible. There are several things to be addressed to understand the properties of these ILs to be exploited for conducting chemical reactions in a desired way. Some studies reported that by increasing the chain length of alkyl group [58, 59] the melting point decreases, improves hydrophobicity and also brings changes in solubility toward substrates. Introduction of fluorine atom [60, 61] in the ILs structure brings lesser hydrogen bonding capabilities, thereby making ILs as less moisture absorbing species. Based on their properties and functions, ILs are designated with names [62] such as (i) high-energetic ILs; (ii) task-specific ILs; (iii) supported ILs; (iv) chiral ILs; (iv) polymeric ILs; (v) acidic ILs; (vi) basic ILs; (vii) surface ionic active ILs; (viii) switchable polarity ILs; (ix) bio ILs; (x) neutral ILs; (xi) metallic ILs.

2.6 Organic transformations leading to sulfur heterocycles – mediated by ILs

2.6.1 Synthesis of thiophene derivatives

Gewald synthesis of tetra and tri-substituted 2-aminothiophene derivatives reported by Rao et al. [63] using basic IL and also by others [64, 65]. The authors reported several 2-aminothiophene derivatives (**3**, **8**, **10**, **11**) by adopting tricomponent chemistry with basic IL [bmIm] and also stepwise chemistry. Three component reactions involved carbonyl compound **1**, reactive methylene compound **2** and sulfur and were mixed in the presence of basic IL [bmIm] and heated to get tetrasubstituted 2-aminothiophene derivatives (**3**) in good yields (Figure 2.9). The stepwise chemistry is to make first olefin compound 7 using trimethyl-orthoacetate (**4**), malanonitrile (**5**) and alcohol (**6**) (Figure 2.9) and then treating the olefin formed with sulfur and basic IL [bmIm] to get trisubstituted 2-aminothiophene derivatives (**8**) in good yields (Figure 2.9). Chemistry conducted without IL (Figure 2.9) involving tri-ethyl-orthoacetate (**4**) and malononitrile (**5**) produced corresponding olefin (**9**); further the olefin was reacted with sulfur and KOH leading to 2-amino-3-cyano-4-hydroxythiophene (**10**) and its equilibrated keto-product **11**, indicating the role of IL in the selectivity of reaction. Another report indicates that Gewald synthesis of 2-aminothiophenes was achieved using task-specific IL [2-hydemim][BF_4]

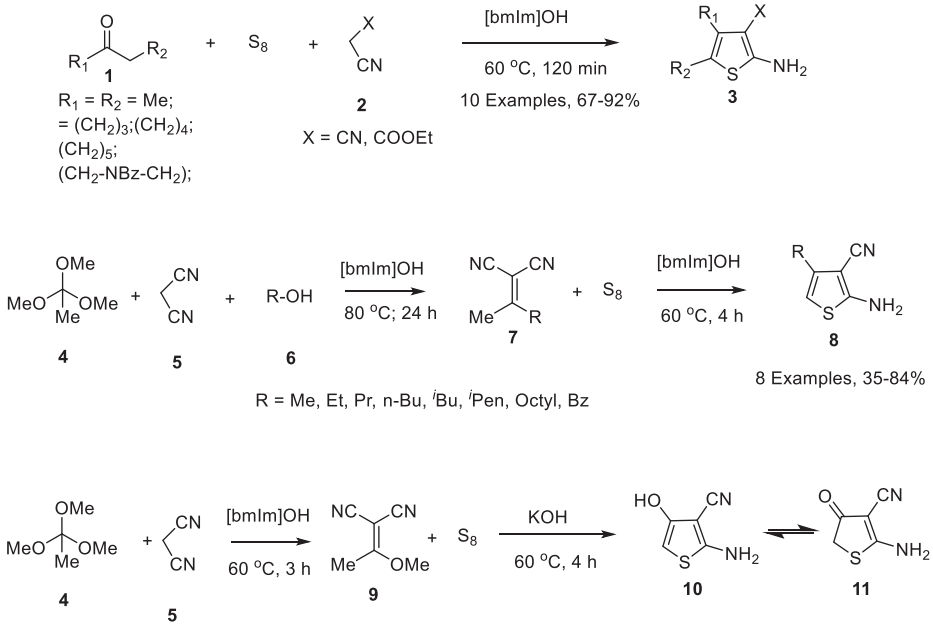


Figure 2.9: IL-mediated tricomponent and stepwise chemistry for making thiophene derivatives.

and assisted by microwave irradiation. The authors claim that this method [66] is simple, efficient, high yielding and does not require chromatographic purification.

2.6.2 Synthesis of tetrazoloquinolinyl-based thiazolidinones

Tetrazoloquinolinyl-based thiazolidinones (**15a-l**) were synthesized by Deshmukh et al. [67] for evaluating their biological activities. It is a three-component one-pot reaction involving tetrqazoloquinolinyl aldehyde (**12**), thioloacetic acid (**13**) and substituted aniline (**14**) along with dicationic IL (Figure 2.10) leading to tetrazoloquinolinyl-thiazolidinone derivatives (**15a-l**). Aniline (**14**) reacts with aldehyde group of tetrazoloquinolinyl (**12**) to form Schiff base, which undergoes the addition of thioloacetic acid (**13**), followed by cyclization to provide thiazolidinone derivatives (**15a-l**). This entire bond forming promotion activity is taking place in the presence of dicationic IL, without any solvent. The substitution on aniline residue introduces 12 compounds with yields of 81–92% range (Figure 2.10). Tetrqazoloquinolinyl aldehyde (**12**) was prepared as per Figure 2.11. 2-Chloroquinolin-3-aldehyde (**16**) reacts with azide to produce tetrazolo compound (**18**), which was reduced using borohydride to get corresponding alcohol (**19**). Alcohol (**19**) was mesitylated to form **21** and further mesitylated compound was converted, upon treatment with K_2CO_3 and 4-hydroxybenzaldehyde into tetrqazoloquinolinyl aldehyde (**12**). Thus synthesized thiazolidinone derivatives (**15a-l**) were taken for bioactivity studies.

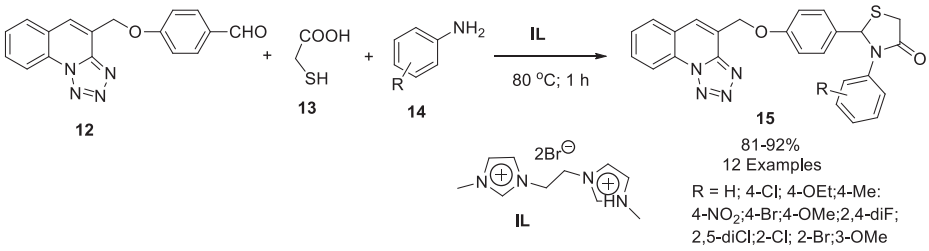


Figure 2.10: Dicationic IL-mediated tricomponent one-pot synthesis of tetrazoloquinolinyl-based thiazolidinones.

2.6.3 Synthesis of substituted thiophene derivatives

Substituted thiophene compounds (**24**, **26** and **28**) were synthesized by Yadav et al. [68] using l,4-diketones (**23**, **25** and **27**), Lawsons reagent and IL (Figure 2.12). Diketones react with Lawsons reagent and then undergoes cyclization followed by aromatization leading to thiophene derivatives (**24**, **26,** and **28)** in good yields (Figure 2.12). The demonstrated chemistry informs that a decent method is given to make trisubstituted thiophenes in an elegant way.

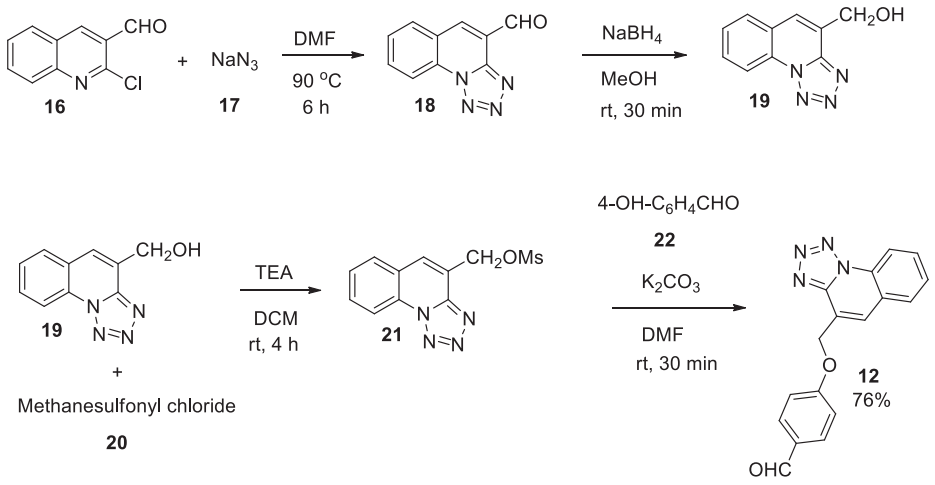


Figure 2.11: Procedure for the preparation of tetrazoloquinolinyl aldehyde derivative **12**.

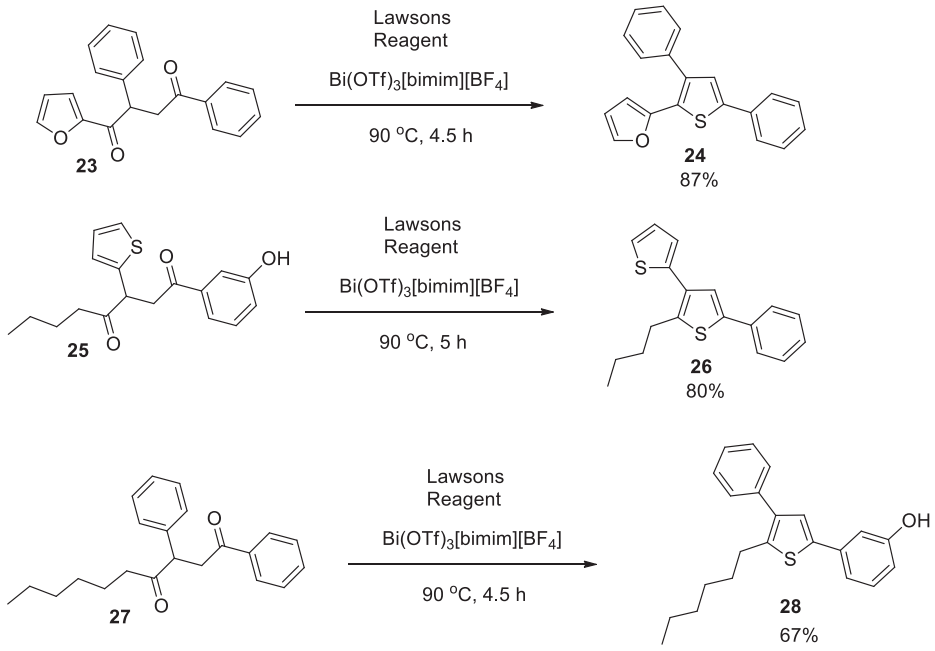


Figure 2.12: Synthesis of substituted thiophene compounds **24, 26** and **28.**

2.6.4 Synthesis of benzothiazepines

IL–[BMIM][BF_4] prepared earlier was found to be thermally deteriorating or charring upon microwave-induced reaction [69]. Then Arya and Prabhakar [69], from the same group, prepared zeolite-encapsulated IL–[BMIM][BF_4]-ZSM-5 and used for making spiro[pyrazolo[3,4-*e*]benzothiazepines] in an IL protected manner. Known amount of IL-[BIMIM][BF_4] was taken in aluminosilicate gel (4.5 Na_2O:Al_2O_3:60SiO_2:2568H_2O) and was crystallized at 150 °C. Thus obtained solid powder was washed with water, dried and analyzed for confined IL-ZSM-5 zeolite [70]. The confined IL [BIMIM][BF_4]-ZSM-5 was utilized as catalyst for making spiro[pyrazolo[3,4-*e*]benzothiazepines] (**34**, **35** and **36)** (Figure 2.13). The reaction parameters were tuned by conducting several experiments to arrive at a very good procedure. The chemistry is a tricomponent reaction involving ketone (isatins (**29**), cyclohexanone (**30**), indanone (**31**), pyrazalone (**32**) and 4-substituted-2-mercaptoaniline and catalyzed by zeolite-confined catalyst [BIMIM][BF_4]-ZSM-5 in the presence of water as medium (Figure 2.13). The authors claim it as green chemistry because of excellent yields and use of water as solvent. Ketone (**29** or **30** or **31**) reacts with active methylene part of pyrazalone to form a double bond, and then amino group of 2-mercaptoaniline forms a Schiff base and this intermediate undergoes cyclization to provide spiro[pyrazolo[3,4-*e*]benzothiazepines] (**34**, **35**, **36**). The IL-confined catalyst [BIMIM][BF_4]-ZSM-5 is found to be recovered and recycled several times.

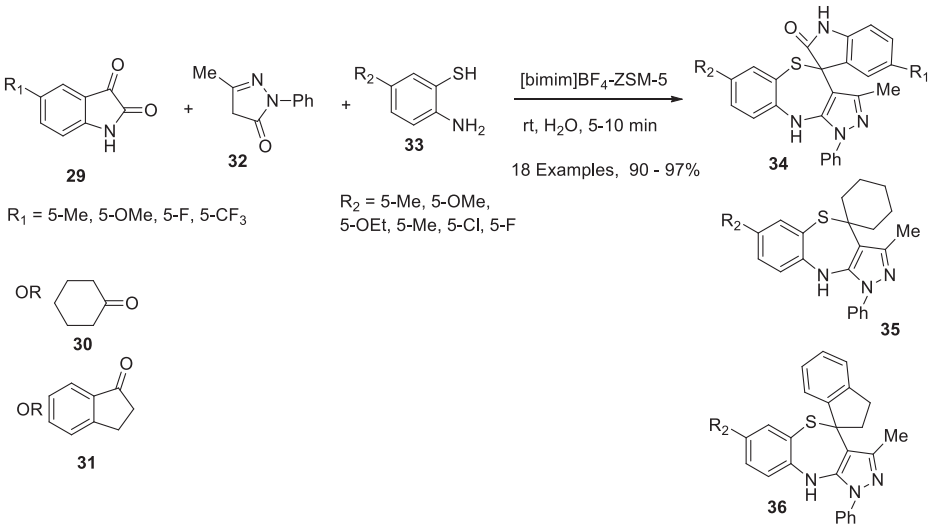


Figure 2.13: Synthesis of spiro[pyrazolo[3,4-*e*]benzothiazepines] (**34**, **35**, **36**).

2.6.5 Synthesis of substituted benzothiazoles

Chandramouli and coworkers [71] reported a very nice way of synthesizing substituted benzothiazoles starting from 4-substituted-2-mercaptoaniline and substituted benzoic acid in the presence of IL [bimim][BF_4] and upon heating without any solvent. Isolation and purification procedures are simple with good yields of products (Figure 2.14).

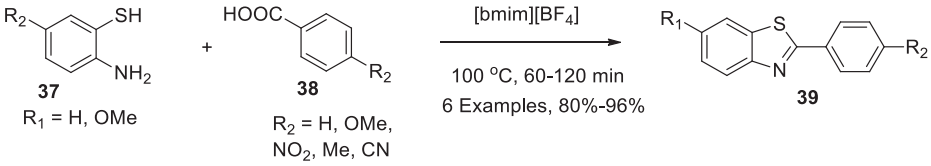


Figure 2.14: Synthesis of substituted benzothiazoles **39**.

2.6.6 Synthesis of thiapyranopyrazoles

Knovenagal condensation, followed by hetero Diels–Alder cyclization, was arranged by Narsidas et al. [72] as catalyzed by IL–[Hmim]HSO_4 leading to *cis*-fused rings (Figure 2.16). Thioketones (**41**) and *allyl*-phenolethers carrying aldehyde group (**44**, **45**) are the starting materials (Figure 2.15). Starting material thioketone **41** was prepared from the corresponding *N*-phenyl-5-methylpyrazalone (**40**), upon treating it with Lawson's reagent (Figure 2.15).

2-Allyloxybenzaldehydes (**44**) and 2-allyloxynaphthaldehydes (**45**) were prepared from the salicyaldehyde (**42**) and 2-hydroxynaphthaldehyde (**43**), upon treatment with suitable *allyl* compound in the presence of base K_2CO_3 (Figure 2.15). Various *allyl* groups, alkenyl-ester groups and propargyl group are used to make a variety of aldehyde-*allyl* compounds (**44**, **45**).

The reaction between aldehyde-*allyl* compounds (**44**, **45**) and pyrazalone thione (**41**) in the presence of IL–[Hmim]HSO_4 and heating produces tetracyclic, pentacyclic and hexacyclic compounds (**47–62)** with excellent diastereoselectivity (Figure 2.16) and yields in the range of 43–84%. Active methylene part of pyrazalonethione compound (**41**) undergoes Knovenegal condensation to form a double bond, whose arrangement is quickly oriented into the form of *endo-E-syn* state (Figure 2.16), and this state undergoes cyclization to give entry to tetracyclic, pentacyclic and hexacyclic compounds. The *cis*-fused rings are perfectly explained based on the *endo-E-syn* transition state (Figure 2.16). The stereochemistry of the products established using H-nmr, 2D-NMR, NOESY, DQY-COSY and crystal structure analysis. The *exo-E-anti* transition state leading to *trans* fusion is ruled out because of high energetic considerations. The *O*-cinnamylatedsalicylaldehyde product upon Knovenegal condensation and hetero Diels–Alder cyclization gave both *cis* and *trans* ring-fused products indicating the possible two transition states.

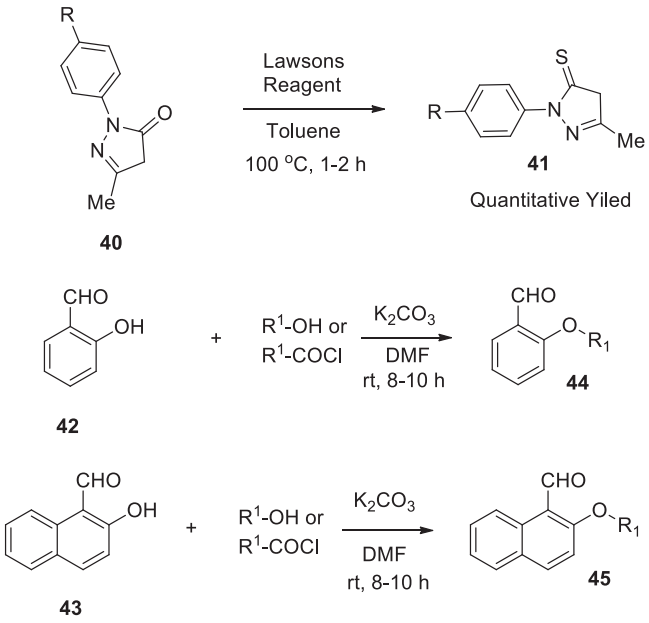


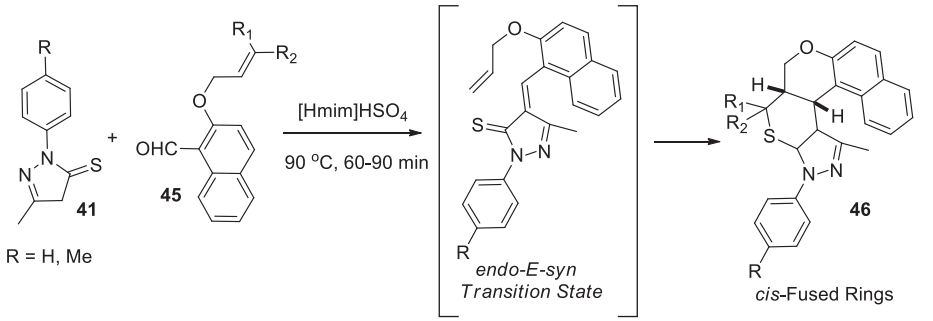
Figure 2.15: Synthesis of thioketones and *allyl*-ethers **41, 44** and **45**.

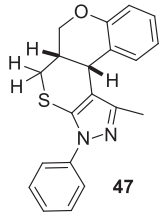
2.6.7 Synthesis of benzothiazine-2-ones

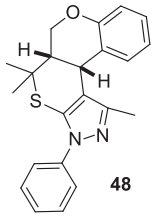
Vibha Tandon and coworkers [73] reported an interesting way of making 1,4-benzothiazine-2-one (**65**) using various starting materials (Figure 2.17), ethylbromoacetate and KF-alumina-IL-[bmim]BF_4 complex. Product isolation, purification, recovery of catalyst and reuse of catalyst are some of the advantages of the methodology. Catalyst is a multicomponent complex of [KF-alumina-[bmim]BF_4].

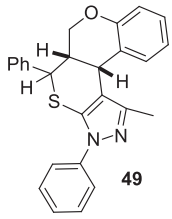
2.6.8 Synthesis of thiazoles

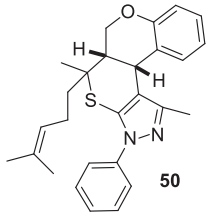
α-Tosyloxy ketones (**73**) reacted with thiobenzamide (**74**) in the presence of IL–[bmim]PF_6 to make trisubstituted thiazoles (**75**) (Figure 2.18) as reported by Hou et al. [74]. Variation in the groups attached with α-Tosyloxy ketones (**73**) produced 10 examples with good yields (Figure 2.18). Isolation and purification of reaction products are very simple and recovery and recycle of the IL catalyst was achieved. Iminothiol form of thiobenzamide substitutes tosyl group by forming C–S bond, and then imino group of thiobenzamide reacts with carbonyl group to form thiazole moiety.

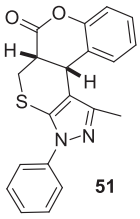


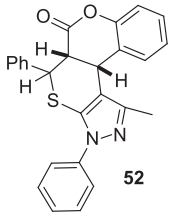


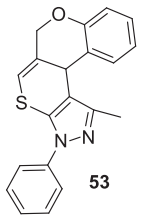


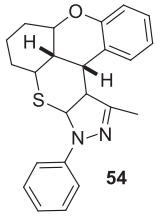


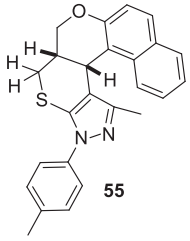


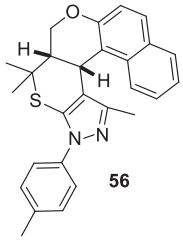


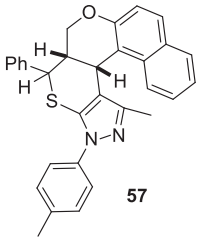


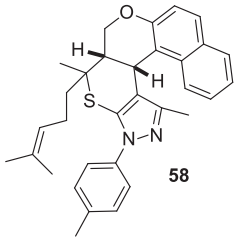


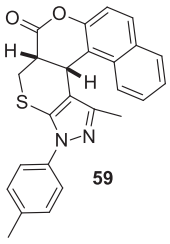


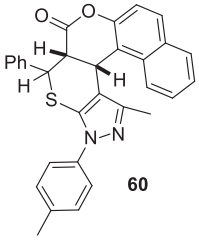


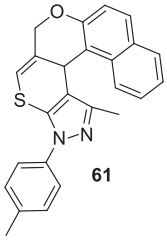












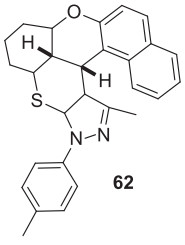


Figure 2.16: Synthesis of various thiapyranopyrazole derivatives **47–62.**

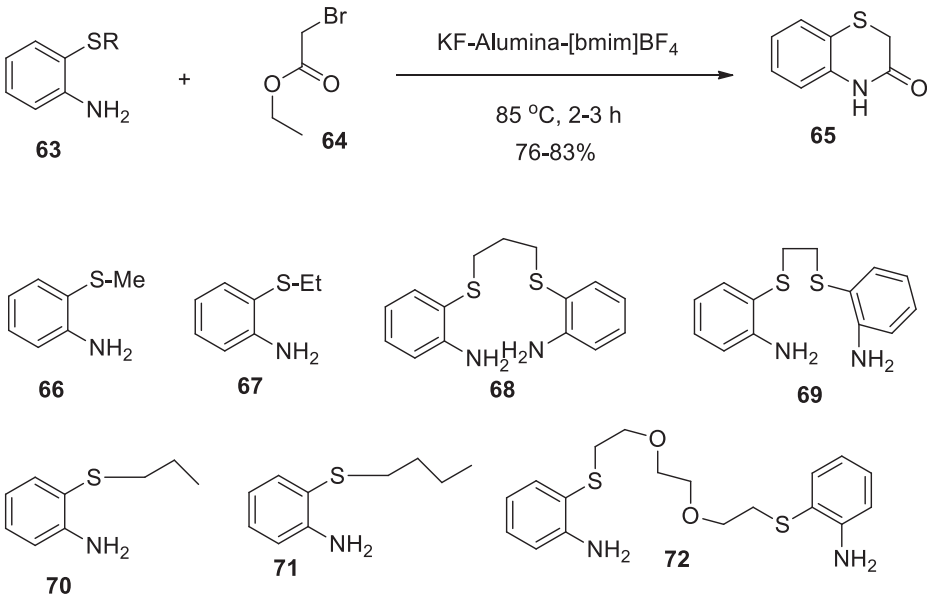
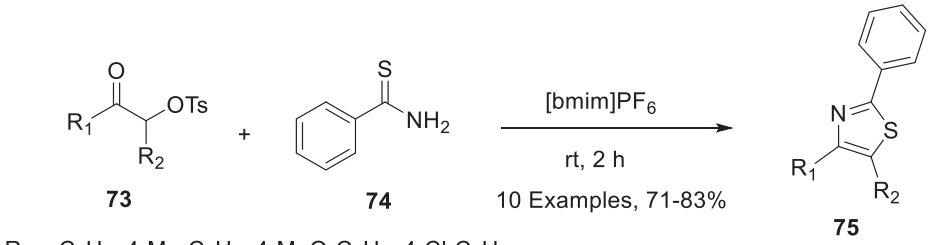


Figure 2.17: Synthesis of 1,4-benzothiazine **65** from various substrates **66–72**.



R_1 = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-furyl, 3-thienyl, Me, EtO
R_2 = H; COOEt

Figure 2.18: Synthesis of trisubstituted thiazoles **75**.

2.6.9 Synthesis of thiazolidinones

A three-component one-pot reaction catalyzed by IL–Pyridinium-Tosylate and reported by Yadav [75] and also Lingampalle et al. [76] leading to thiazolidinones **78** (Figure 2.19). Ketone (**76**), amine (**77**) and thioacetic acid (**13**) are mixed with IL at room temperature for ~2 h to synthesize thiazolidinones (**78**) in very good yields. Ketone reacts with amine to form Schiffs base and then reacts with thioacetic acid to produce thiazolidinones (**78**) (Figure 2.19).

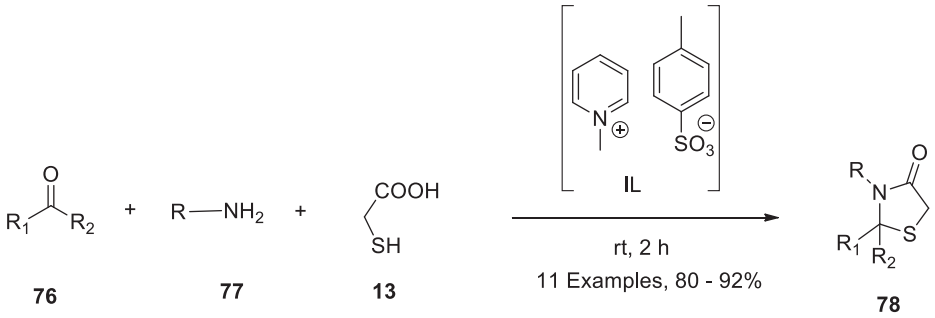


Figure 2.19: Tricomponent one-pot synthesis of substituted thiazolidinones **78**.

2.6.10 Synthesis of thiazoles and bis-thiazoles

Noei and Khosropour [77] described the synthesis of thiozoles (**81**) (Figure 2.20) in excellent yields, in the absence of solvent, using IL [bmim]BF_4 and ultrasound. 4-Substituted thiobenzamide (**79**) and 4-substituted α-bromoacetophenone (**80**) were taken in [bmim]BF_4 IL and irradiated with ultrasound for a few minutes to get 2,5-substituted thiazoles (**81**) (Figure 2.20). Interestingly, bis-thiobenzamide (**82**) was prepared and used as a starting material to make aryl-substituted bis-thiazole (**83**) compound obtained (Figure 2.20). The reaction is facile, and isolation and purification of products are simple; furthermore the IL can be recovered and reused. Similar studies are also reported by Izumisawa and Togo [78].

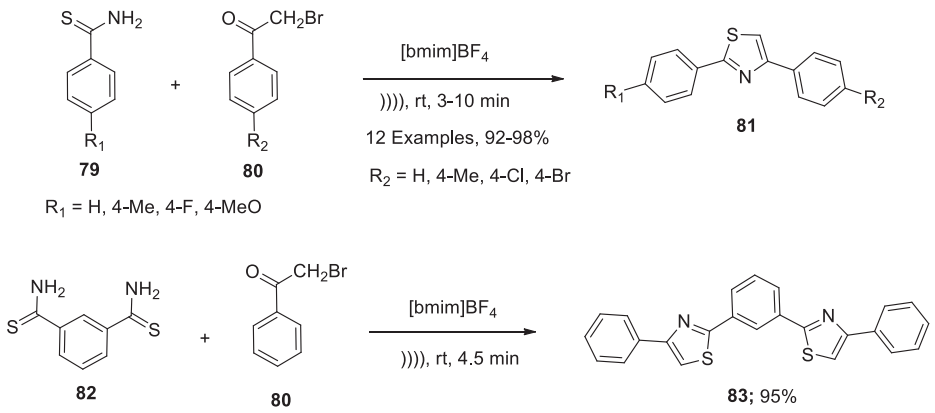


Figure 2.20: Synthesis of substituted thiazoles **81** and bis-thiazole **83**.

2.6.11 Synthesis of benzthiazoles

Srinivasan and coworkers [79] developed a method to make benzthiazoles (**85**) involving ILs (Figure 2.21). 2-Mercaptoaniline (**37**) and substituted benzoylchloride (**84**) were mixed with ILs [bbim]BF_4 and [Hbim]BF_4 separately at room temperature to observe formation of benzthiazoles (**85**) in very good yields (Figure 2.21). Catalyst IL can be easily recovered and reused and the isolation and purification of products are found to be very simple.

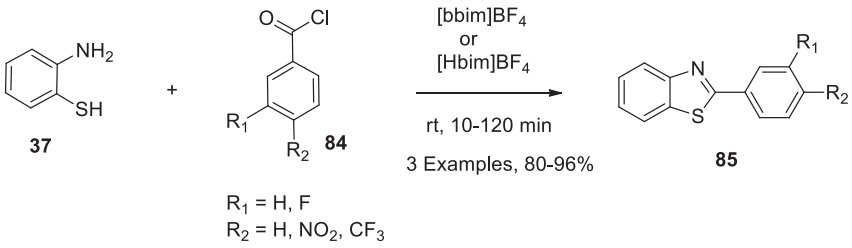


Figure 2.21: Synthesis of substituted benzthiazoles **85.**

2.6.12 Synthesis of thiazine-4-ones and thiapyran compounds

Yadav et al. [80] reported a three-component one-pot reaction, catalyzed by IL, leading to 1,3-thiazine-4-one cyclic structures (**89** and **91**) (Figure 2.22). Chemistry involves, as predicted, Knoevenegal condensation (**92**) and Michael addition (**93**) and followed by cyclization provides the 1,3-thiazine-4-ones (**89** and **91**) (Figure 2.22) compounds. Diastero-selectivity with very high *trans* arrangement is introduced during Michael addition (Figure 2.22). Tricomponent reaction involves 4-substituted benzaldehyde (**87**), 2-Me-2-phenyl-1,3-oxathiolan-5-one (**86**), and *N*-substituted thiourea (**88**) and were mixed with the catalyst IL [Bmim]Br in the presence of acetonitrile as solvent at room temperature to obtain thiazine-cyclized product (**89**). Same reaction was conducted by replacing **86** with 2-phenyl-1,3-oxazol-5-one (**90**) to get thiazine-cyclized product (**91**). Variation in substitution in the starting materials introduced 16 examples with very good yields and also diasteroselectivity. The Knoevenegal condensation product and Michael addition products were isolated to prove the sequential formation mechanism. The Michael addition product was further subjected to cyclization to get thiazine-one compounds (**89** and **91)**. 4*H*-Thiapyran residues (**96, 98** and **100**) are synthesized [81] as a three-component one-pot reaction catalyzed by IL [bmim]BF_4 (Figure 2.23). Starting materials aldehyde (**94**, **97**, **99)**, malanonitrile (**5**) and cyanothioacetamide (**95**) were mixed with IL [bmim]BF_4 and heated to 80 °C to generate the 4H-thiapyran residues. Aldehyde undergoes condensation with malononitrile to form a double bond, then addition of cyano-thioacetamide to double bond and followed by

cyclization generates 4H-thiapyran compounds (**96, 98** and **100**) (Figure 2.23). Interestingly, the methodology is applied to pyrimidine nucleoside to synthesize pyrimidine nucleoside-thiapyran hybrids (**98** and **100**) (Figure 2.23). Various substituted aldehydes employed provides entry to 10 examples of **96** (Figure 2.23) and also some generality of the methodology. The catalyst IL-[bmim]BF_4 can be easily recovered and recycled to conduct the chemistry.

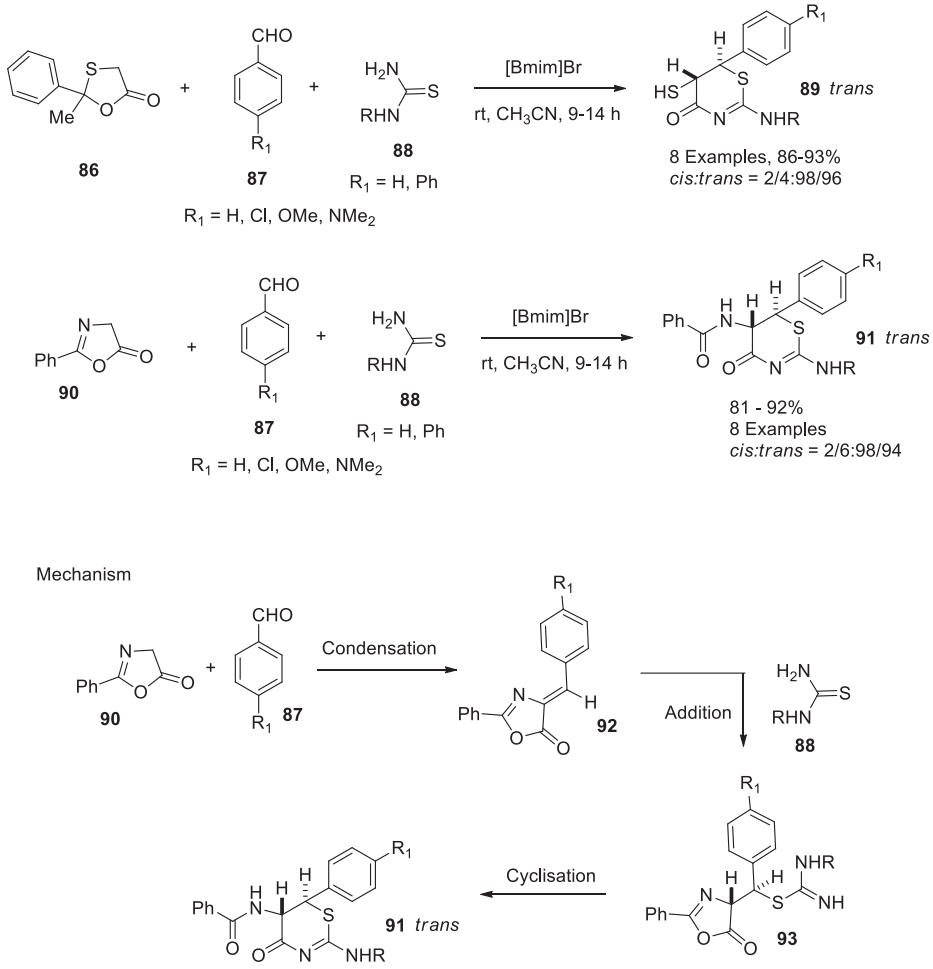
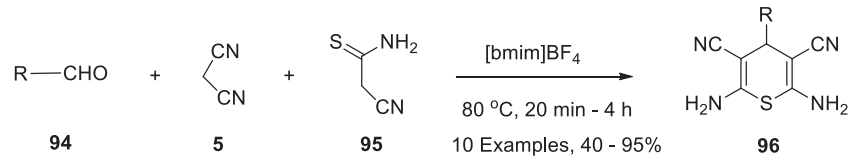
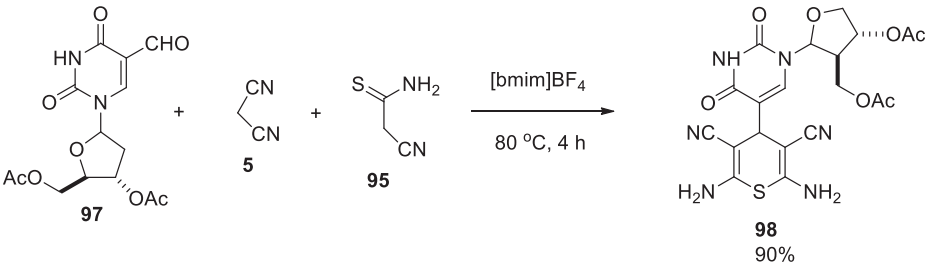


Figure 2.22: Synthesis and mechanism of formation of substituted 1,3-thiazine-4-ones **89** and **91.**



R = C_6H_5, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-F-C_6H_4, 4-Me-C_6H_4, 4-OH-3-OMe-C_6H_4, Pr, Hexyl



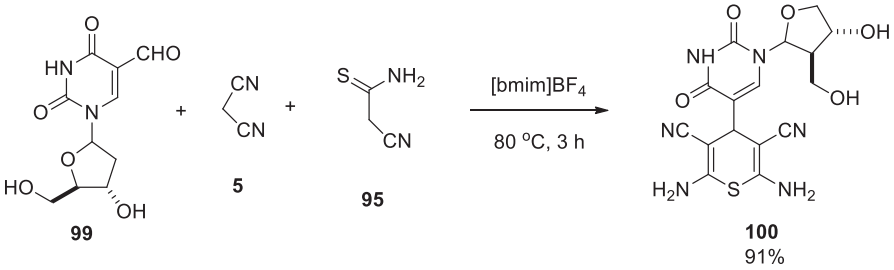


Figure 2.23: Synthesis of 4*H*-thiopyran and pyrimidine nucleoside-thiopyran hybrid **96**, **98** and **100.**

2.7 Organic transformations leading to oxygen heterocycles – mediated by ILs

2.7.1 Synthesis of epoxides

The formation of epoxide is accelerated with high efficiency by using ILs as catalyst [82] to epoxygenate the chromones to **102**, isoflavones to **104** and chalcones to **106** (Figure 2.24). Bernini et al. [82] produced epoxides using chromones (**101**), isoflavones (**103**) and chalcones (**105**) with IL [bmim]BF_4, H_2O_2 and NaOH in high yields (Figure 2.24). Reaction conditions adopted are conducive like at 0 °C and time of ~120 min. The isolation and purification of products and recovery and recycling of IL catalyst are very simple and convenient; further it is a clean and green reaction for not producing

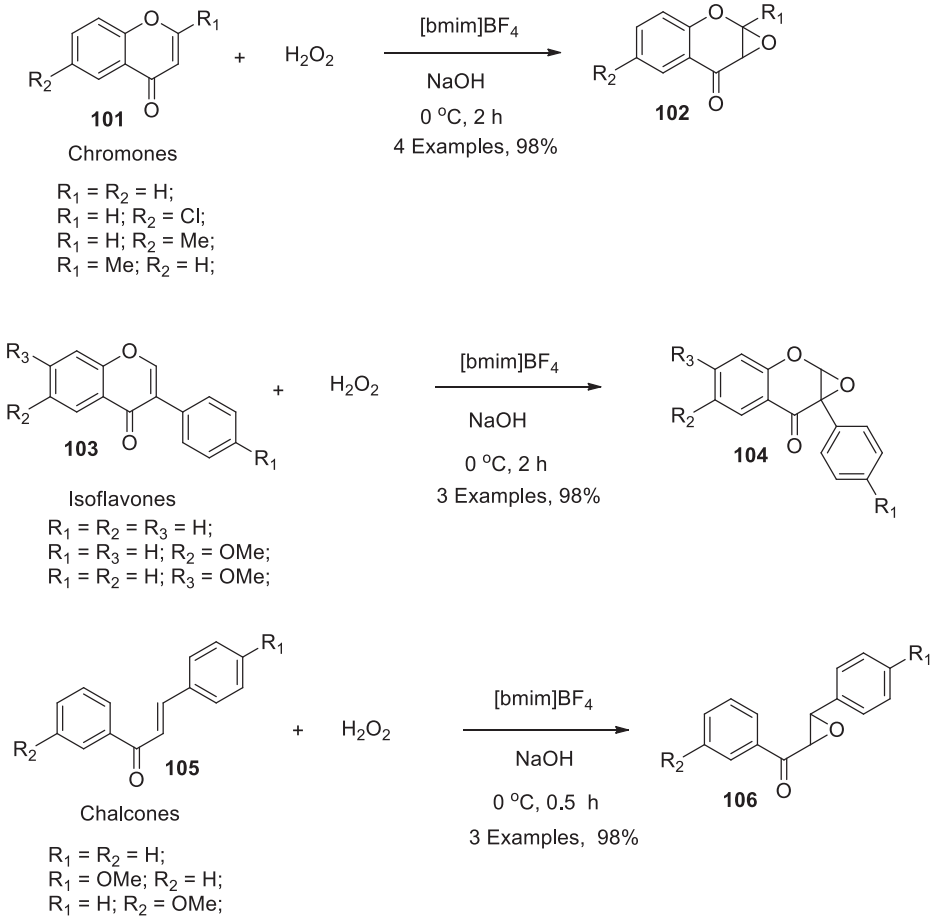


Figure 2.24: Conversion of chromones, isoflavones and chalcones into the corresponding epoxides **102, 104** and **106**.

unwanted waste materials. Excellent yields of epoxide rule out the possibility of formation of epoxide ring-opened product.

Song and Roh [83] prepared a catalyst immobilized on the IL for asymmetric epoxidations and also successfully demonstrated that the prepared immobilized chiral catalyst can be recovered and reused. The Jacobsons chiral catalyst (**107**) (Figure 2.25) was immobilized over IL [bimim]PF_6, which is a stable IL toward air and moisture. Chiral catalyst immobilized hybrid IL, mixed with olefin substrate (**108**), NaOCl, DCM solvent, pH maintained at 11.3, was stirred at 0 °C for 2 h to get good yields and enantiomeric excess (Figure 2.26). Chiral catalyst worked very well to obtain the range of 84–96% for the substrates selected (Figure 2.26). The generality of the asymmetric epoxidation of olefin is further substantiated in isolating different epoxide products

(**109**, **110**, **111**, **112**, **113**) arising from the corresponding olefin substrates and the data is shown in Figure 2.26. The reactions are carried out at 5 g laboratory bench level.

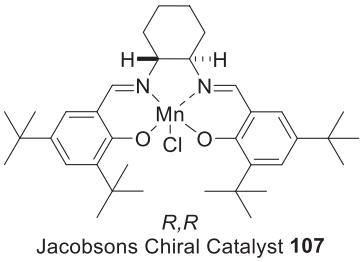


Figure 2.25: Jacobsons chiral catalyst (**107)** used for immobilization with IL [bmim]PF_6.

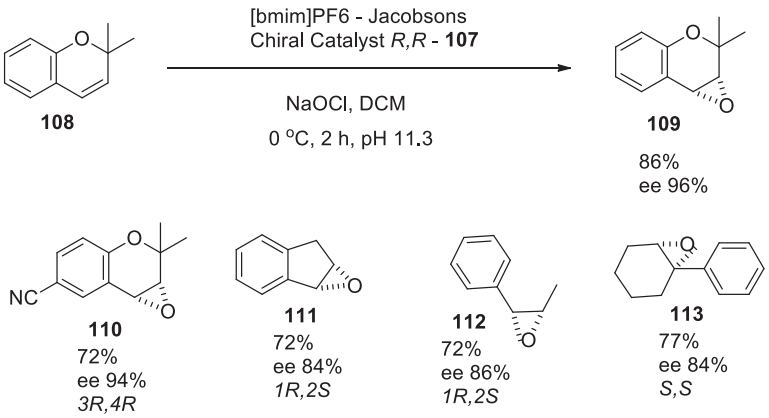


Figure 2.26: Asymmetric epoxidation using chiral catalyst immobilized with [bmim]PF_6.

2.7.2 Synthesis of dihydrofuran derivatives

Manganese III-mediated organic transformations can be conducted in IL medium as solvent and also as a cosolvent. Bar et al. [84] demonstrated that [bmim]BF_4 mixed with $Mn(OAc)_3$ acted as catalyst in the conversion of 1,3-diketones, β-ketoesters and hydroxyquinoline reacting with olefin to form dihydrofuran derivatives (**116**, **119**, **122**, **124** and **125**) (Figure 2.27). 1,3-Cycloheanedione (**114**) and α-methylstyrene (**115**) in DCM along with [[bmim]BF_4-$Mn(OAc)_3$] conducted as a model reaction to generate the bicyclic dihydrofuran (**116**) (Figure 2.27). The β-ketoesters (**117**) can be served as substrates in reacting with olefin (**118**) catalyzed by the [[bmim]BF_4-$Mn(OAc)_3$] to yield trisubstituted dihydrofuran derivatives (**119**) (Figure 2.27). In another instance *N*-Me-4-hydroxy-2-quinolone (**120**) reacted with olefin styrene (**121**) in the presence of catalyst

gave a tricyclic compound having furan residue (**122**) (Figure 2.27). The 2,4-dihydroxy quinolone (**123**) compound exhibited further interesting results that it reacted with olefin **115** to give two types of quinoline-fused dihydrofurans (**124**, **125**) (Figure 2.27). The manganese-III metal becomes manganese-II during the reaction and this Mn-II can be isolated and reconverted back to Mn-III and also can be recycled as catalyst.

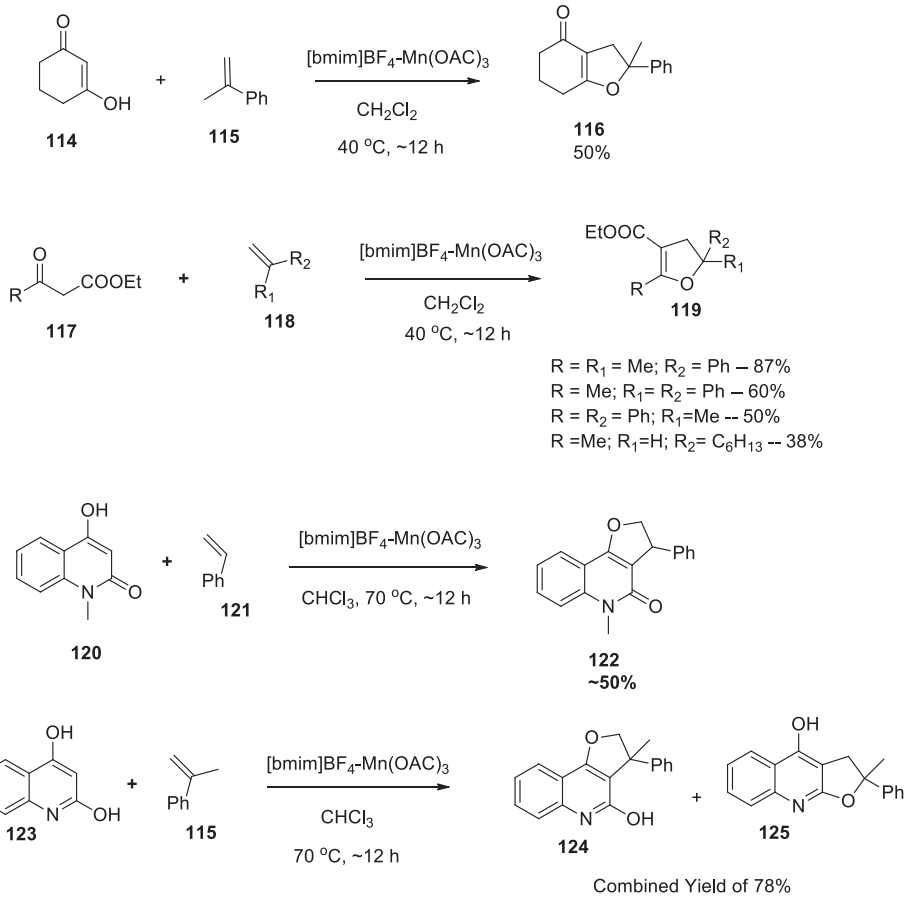
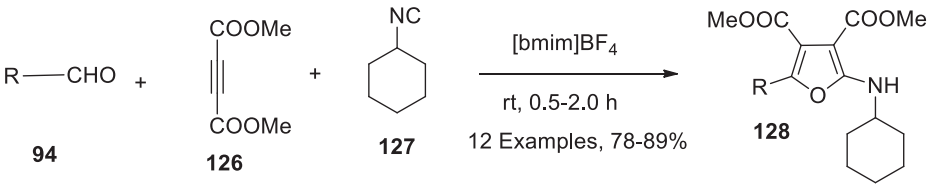


Figure 2.27: Synthesis of dihydrofuran derivatives catalyzed by [$Mn(OAc)_3$-[bmim]BF_4].

2.7.3 Synthesis of tetra-substituted furans

Yadav et al. [85] demonstrated a three-component one-pot reaction to synthesize tetra-substituted furans (**128**) in very good yield (Figure 2.28) using air and moisture stable IL [bmim]BF_4. Aldehyde (**94**), dimethylacetylenedicarboxylate (**126**) and cyclohexylisocyanide (**127**) were mixed together in the presence of IL [bmim]BF_4 at room

temperature (Figure 2.28) to provide various tetra-substituted furans (**128**) in very good yields. The enhanced activity, or increase in the rate of reaction, of formation of furan products is catalyzed by [bmim]BF_4 IL; in this three-component reaction compared to the absence of IL is explained due to the formation of polar intermediates as promoted by the IL [bmim]BF_4. The authors claim that simple reaction conditions, simple isolation and purification of reaction products, recovery and reuse of IL and absence of solvent in the chemistry stand as a Green method. Cyclohexylisocycanide (**127**) reacts with dimethylacetylene dicarboxylate (**126**) to form a C–C bond, leading to a polar or zwitterionic intermediate, which reacts with aldehyde (**94**) in [3 + 2] cyclization fashion to form tetra-substituted furan derivatives (**128**).



R = C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 3-NO_2-C_6H_4, 3-Br-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4, 2-Naphth, cyclohexyl, nonyl, 2-furyl, 2-thienyl

Figure 2.28: Three-component one-pot synthesis of tetra-substituted furan derivatives catalyzed by [bmim]BF_4.

2.7.4 Synthesis of butenolides

Importance of butenolides in organic chemistry is well known and its framework is found to be available in vitamin C, annonaceous acetogenins, digitoxin and other cardenolides. These butenolides (**130**) were synthesized by Villemin et al. [86] involving IL catalysis (Figure 2.29). α-Hydroxy ketones (**129**), ethylcyanoacetate (**2**), K_2CO_3 as a base and IL [bmim]BF_4 as catalyst were taken together at 20 °C for ~12 h to get trisubstituted butenolides (**130**) in very good yields (Figure 2.29). Initially, Knovenegal condensation leads C=C bond formation and followed by lactonization provide butenolide framework. The catalyst IL [bmim]BF_4 was recovered and recycled to conduct the chemistry over four times.

2.7.5 Synthesis of hydroxymethyl-furfural

Conversion of fructose (**131**) to hydroxymethyl furfural (**132**) was affected by the use of [HMIM]Cl, as reported by Moreau et al. [87] (Figure 2.30). The IL–[HMIM]Cl acts as catalyst as well as solvent. The product hydroxymethyl furfural (**132**) can be extracted in a simple way of ether extraction method. Other IL catalysts employed were found to be not that effective and there was some decomposition of the starting material or

$R_1 = R_2 = Me$
$R_1 = Me$; $R_2 = Et$;
$R_1 = R_2 = Cyclohexyl$
$R_1 = Me$; $R_2 = Allyl$
$R_1 = Me$; $R_2 = Bn$

Figure 2.29: Synthesis of trisubstituted butenolides.

product during the reaction. The authors determined kinetics for the fructose **(131)** to hydroxymethyl furfural **(132)** conversion reaction catalyzed by IL–[HMIM]Cl. The absence of decomposition in this conversion is interpreted that the less free energy of activation associated in this fructose **(131)** to HMF **(132)** (Figure 2.30). Further the authors report the conversion of sucrose **(133)**, a disaccharide of fructose-glucose, to HMF **(132)** and glucose recovered in almost in a quantitative way (Figure 2.30).

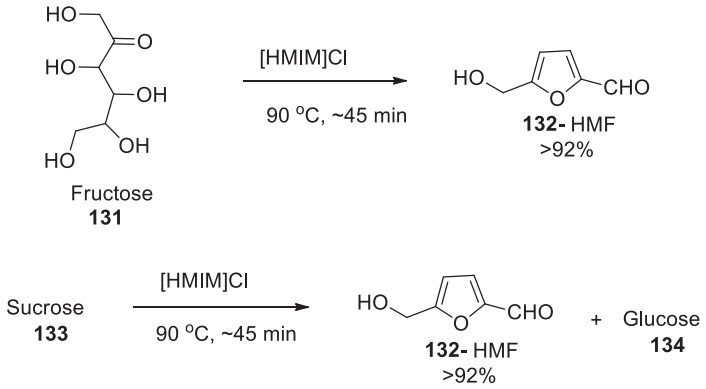
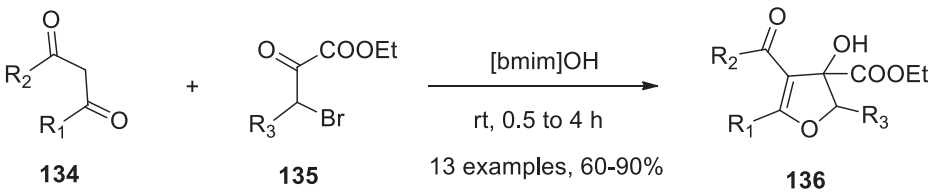


Figure 2.30: Synthesis of hydroxymethyl furfural (HMF) from fructose and sucrose.

2.7.6 Synthesis of interrupted Feist–Benary products and dihydrofurans

Basic IL [bmim]OH catalyzed, interrupted Feist–Benary products, dihydrofuran derivatives were synthesized by Ranu et al. [88, 89] and others. 1,3-Diones (**134**) and 3-bromo-α-ketoethylester (**135**) were mixed with basic IL [bmim]OH at room temperature to obtain

dihydrofuran derivatives, the interrupted Feist–Benary products (**136**) (Figure 2.31). Structural variation in starting compounds produced 13 examples of **136** in very good yields (Figure 2.31). X-ray crystal structure for the compound **137** (Figure 2.32) is solved to know the relative alignments of groups within the dihydrofuran moiety. Stereochemical analysis was carried out on some compounds only (Figure 2.32). Diastereoselectivity observed in the formation of interrupted Feist–Benary products is given in Figure 2.32. Two compounds showed good diastereoselectivity of 88:12 in **137:138** and 93:07 in **139:140** (Figure 2.32). The other dihydrofuran derivatives (**141**, **142**, **143)** exhibited excellent diasteroselectivity (Figure 2.32). Conversion of interrupted Feist–Benary products, upon dehydration, to tri and tetra-substituted furans (Figure 2.33) was observed using another IL [HMIM]Br. The dehydration process conducted using [HMIM]Br for eight examples (**145**–**152**), with good yields (Figure 2.33). The method developed to make dihydrofurans and furans involves two different ionic liquids, with its task defined, as one [bmim]OH for condensation and cyclization and another [HMIM]Br for dehydration process. The IL-catalyzed reactions reported in the present studies are very fast not involving longer reaction times, ambient temperature conditions and involvement of interrupted Feist–Benary diasteroselective products.



R_1 = Me, Et, *n*Pr, Ph, 1,3-Cyclohexanedione, Di-Me-Cyclohexanedione
R_2 = Me, OMe, OEt
R_3 = H, *n*-Bu, COOEt

Figure 2.31: Synthesis of dihydrofuran derivatives **136** using IL [bmim]OH.

2.7.7 Synthesis of 2,5-dihydrofurans

Aksin and Krause [90] used hydroxy allenes as substrates and gold-doped ionic liquid as catalyst to make 2,5-dihydrofurans (Figure 2.34). Allyl-hydroxy allenes (**153**), 1 mol% $AuBr_3$-doped [bmim]PF_6 were mixed at room temperature for short times (Figure 2.34) to undergo cyclo-isomerization to form 2,5-dihydrofurans (**154**) in good yields and with axis to center chirality transfer. [bmim]PF_6 is air-stable, relatively hydrophobic and less viscous, which makes it a better choice of IL catalyst among the various catalysts tried. The $AuBr_3$-doped [BMIM]PF_6 catalyst was recovered and recycled for five times, without much change in its efficiency.

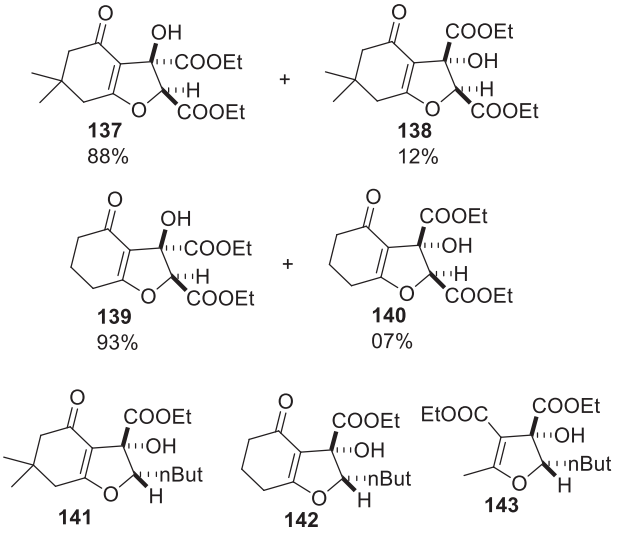


Figure 2.32: Synthesis of dihydrofuran derivatives **137–143** using IL-[bmim]OH and their diastereoselectivity.

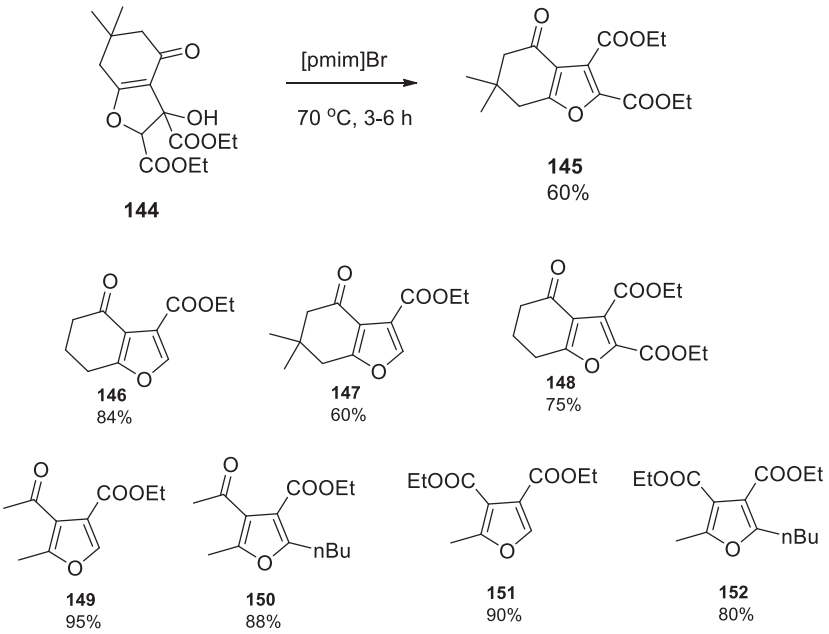


Figure 2.33: Synthesis of fused furan derivatives **145–152** using IL [pmim]Br acting as catalyst for dehydration.

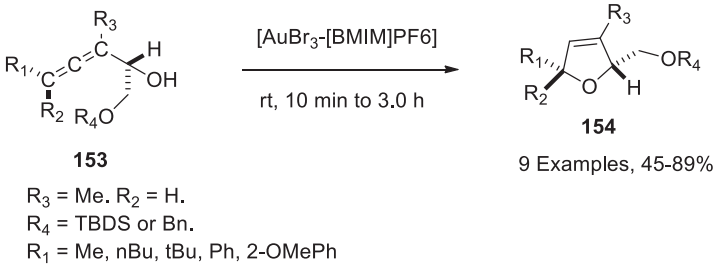


Figure 2.34: Synthesis of 2,5-dihydrofuran derivatives **154** using gold-doped [BMIM]$MeSO_3$.

2.7.8 Synthesis of dihydrobenzofurans

Claisen migration, protonation and followed by cyclization leading to dihydrobenzofuran synthesis reported by Zulfiqar and Kitazume [91]. Allyl phenylether (**155**) heated to 200 °C in the presence of IL–[$Sc(OTf)_3$-[EtDBU]OTf] leading to dihydrobenzofuran (**156**) (Figure 2.35). Task-specific IL is prepared by doping with $Sc(OTf)_3$ of 5 mol% with IL–[EdDBU]OTf. High temperature 200 °C affects Claisen migration in allyl phenylether (**155**), giving 2-allyl phenol formed, then complexation with doped Lewis acid, protonation of double bond and followed by cyclization provides the formation of dihydrobenzofuran (**156**) (Figure 2.35). This is a consecutive sequential reaction catalyzed by "Sc"-doped ionic liquid. Recovery, stability and recyclability of the "Sc"-doped IL catalyst is notable.

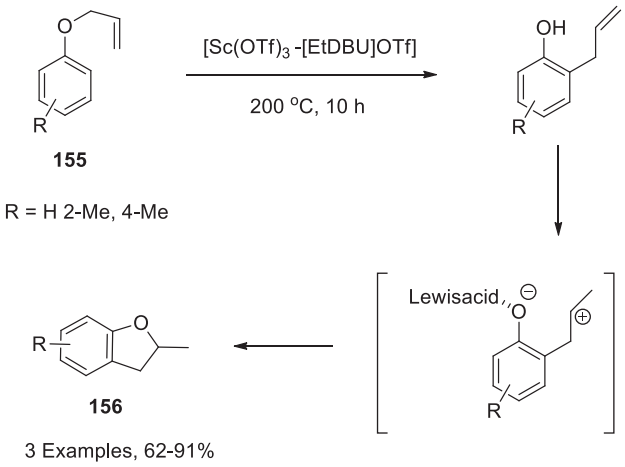


Figure 2.35: Synthesis of 2,3-dihydrobenzofuran **156** using $Sc(OTf)_3$-doped [EtDBU]OTf.

2.7.9 Synthesis of benzofurans

Ionic liquid-mediated Heck reaction [92] was successfully conducted to make variety of benzofurans (Figure 2.36). Substituted phenol *O*-allyethers (**157**), *n*-butylamine, ammonium formate, and $PdCl_2$ (5 mol%) were mixed in IL-[bmim]BF_4 at 60 °C for 24 h to obtain various substituted benzofuran derivatives (**159**–**167**) (Figure 2.36). The benzofurans synthesized indicate the tolerance of different substituents toward efficiency of product formation. The IL catalyst with $PdCl_2$ can be recovered and reused many times.

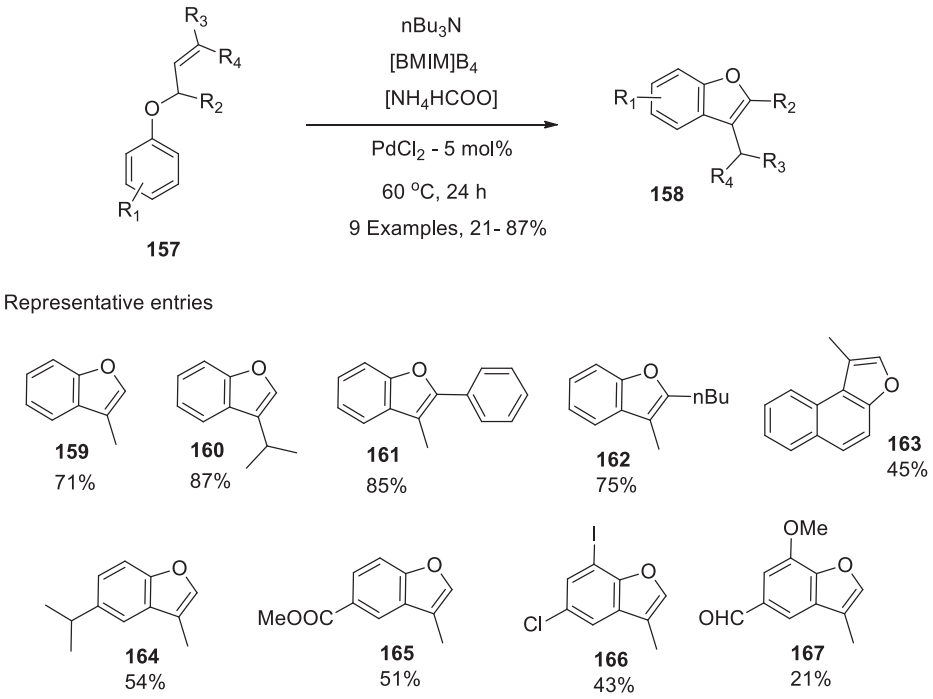
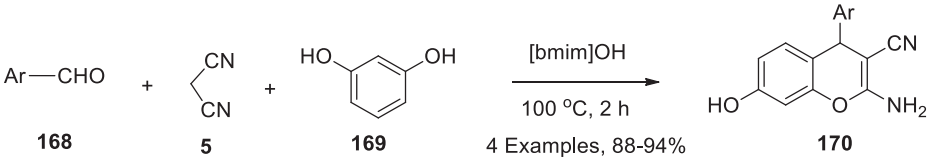


Figure 2.36: Synthesis of benzofurans **159**–**167** using Heck reaction and IL [BMIM]BF_4.

2.7.10 Synthesis of 4H-pyranderivatives

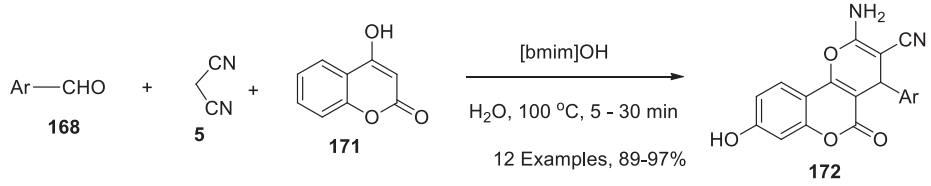
Various substituted, fused, polyfunctional 4*H*-pyrans (**170, 172** and **174**) synthesized by Gong et al. [93], and also by others [94, 95], using IL as catalyst and or medium and in a multicomponent single-pot chemistry (Figures 2.37–2.39). Arylaldehyde (**168**), malanonitrile (**5**) and 1,3-dihydroxybenzene (**169**) were mixed with IL–[bmim]OH in water medium and heated to get polyfunctional/substituted benzo-4*H*-pyrans (**170**) in very good yields (Figure 2.37). To increase the complexity and versatility of the tricomponent reaction, the authors replaced resorcinol (**169**) with 4-hydroxy coumarin (**171**),

and other components arylaldehyde (**168**) and malanonitrile (**5**) were the same to conduct the chemistry with basic IL-[bmim]OH in water medium to obtain (Figure 2.38) various angularly fused tricyclic compounds (**172**) (4H pyran derivatives). Variation in the aryl aldehyde structure provided 12 examples in very good yields (Figure 2.38). The authors replaced the aromatic ring present in one of the starting materials (**169** or **171**) with alicyclic system – dimedone (**173**) – and conducted the multicomponent reaction using basic IL and water as medium (Figure 2.39). Aryl aldehyde (**168**), malanonitrile (**5**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**173**) with basic IL-[bmim]OH in water to make multisubstituted alicyclic ring fused 4*H*-pyran compounds (**174**) (Figure 2.39). Change in the aldehyde structure provided 12 examples in very good yields. All these multicomponent reactions conducted (Figures 2.37–2.39) in the presence of basic IL involve first active methylene group condensation with aldehyde component and then the other bond formation takes place. The chemistry reported by the authors has several merits, that it is a multicomponent chemistry, catalyst is recoverable, recyclable, water as solvent, reaction conditions; product yields and ease of isolation of products make it a green chemistry.



Ar = C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-OMe-C_6H_4

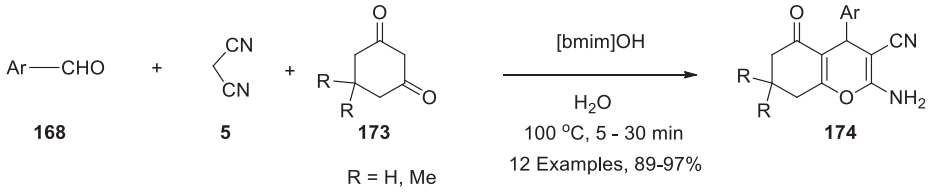
Figure 2.37: Synthesis of 4*H*-benzopyrans **170** using IL [bmim]OH and water.



Ar = C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-diCl-C_6H_3, 4-F-C_6H_4, 4-Br-C_6H_4, 2-NO_2-C_6H_4. 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-OH-C_6H_4

Figure 2.38: Synthesis of 4*H*-pyrano-coumarins **172** using IL [bmim]OH and water.

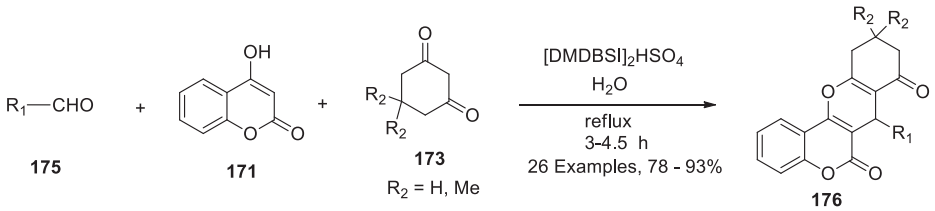
Tricomponent reaction carried out to make angularly fused tetracyclic 4*H*-pyran derivatives using IL medium is reported by Chen et al. [96]. Figure 2.40 illustrates the chemistry, where aldehyde (**175**), 4-hydroxycoumarin (**171**) and dimedone (**173**) were mixed with IL-$[DMDBSI]_2HSO_4$ in water medium at reflux gave entry to angularly fused tetracyclic 4*H*-pyran derivatives (**176**) (Figure 2.40). Structural variations present in aldehyde provided generality of the method and influence on product yields,



Ar = Ph, 2-Cl-Ph, 4-Cl-Ph, 2,4-diCl-Ph, 4-F-Ph, 2-NO_2-Ph, 3-NO_2-Ph, 4-NO_2-Ph, 4-Me-Ph, 4-MeO-Ph, 4-OH-Ph, 4-Me_2N-Ph,2-Furyl

Figure 2.39: Synthesis of cylcohexanone fused 4*H*-pyrans **174** using [bmim]OH and water.

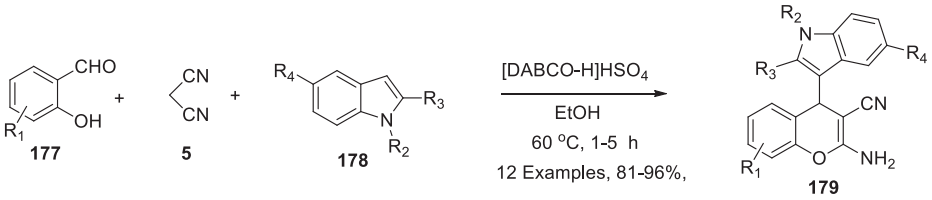
presenting 26 examples (Figure 2.40). The catalyst IL-$[DMDBSI]_2HSO_4$ was synthesized by the authors and also evaluated its recovery and recyclability to a great extent. The authors claim that the chemistry demonstrated is in the green category.



R_1 = Ph; 2-Cl-Ph; 2-OMe-Ph; 3-OMe-Ph; 3-OH-Ph; 3-NO_2-Ph;4-OMe-Ph; 4-Cl-Ph; 4-NO_2-Ph; 3,4-diMe-Ph; 2-F-6-Cl-Ph; 2,4-diCl-Ph; 3-OMe-4-OH-Ph; 2-Furyl; 2-Thienyl; 2-Etyl; 2-Propyl

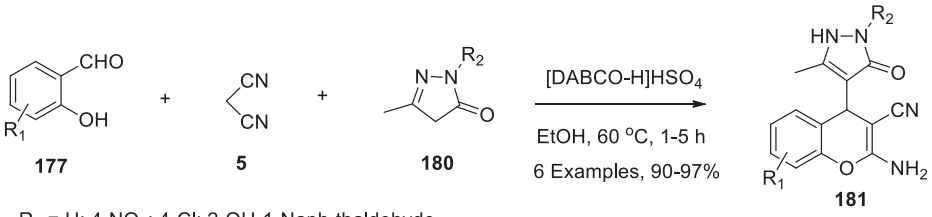
Figure 2.40: Synthesis of fused tetracyclic-4*H*-pyrano-coumarins **176** using IL $[DMDBSI]_2HSO_4$ and water.

DABCO-based IL was used by Li et al. [97] to conduct tricomponent reaction to make benzo-4*H*-pyrans linked with indole moiety (**179**) (Figure 2.41). Hydroxybenzaldehyde (**177**), malanonitrile (**5**), indole moiety (**178**), and ethanol solvent with IL-[DABCO-H] HSO_4 were mixed to heat for generating benzo-4*H*-pyrans linked with indole moiety (**179**). Various hydroxy aldehydes employed gave 12 examples of (**179**), with yields 78–93% range (Figure 2.41). The indole moiety was substituted in the reaction sequence with 1,2-diazalone having active methylene (**180**) (Figure 2.42) to make corresponding 1,2-diazolone-linked benzo-4*H*-pyrans (**181**). Chemistry first involves Knovenegal condensation, then Michael cyclization and followed by C–C linking with indole or 1,2-diazalone moiety.



R_1 = H; 4-NO_2; 4,6-diBr; 4-Cl; 2-OH-1-Naph-thaldehyde.
R_2 = H; Me. R_3 = H; Me. R_4 = OMe; Br; NO_2.

Figure 2.41: Synthesis of indole-substituted benzo-4*H*-pyrans linked with indole moiety **179** using IL [DABCO-H]HSO_4 and ethanol.



R_1 = H; 4-NO_2; 4-Cl; 2-OH-1-Naph-thaldehyde.
R_2 = H; Ph

Figure 2.42: Synthesis of indole-substituted benzo-4*H*-pyrans linked with 1,2-diazole moiety **180** using IL [DABCO-H]HSO_4 and ethanol.

2.7.11 Synthesis of cyclic carbonates

IL–[BIMM]$PhSO_3$ was doped with CuCl with a purpose to use it for making α-methylene cyclic carbonates (**183**) [98] from propargyl alcohols (Figure 2.43). Propargyl alcohol (**182**), CuCl-doped IL–[BMIm]$PhSO_3$ was mixed and held at 10 atm of carbon dioxide pressure at 120 °C to make α-methylene cyclic carbonates (**183**) (Figure 2.43). Cuprous ion bound with IL interacts with triple bond of propargyl moiety to form a complex which facilitates CO_2 addition under pressure and temperature conditions. Four substrates are employed to show the generality of the chemistry of formation of α-methylene cyclic carbonates (**183**) (Figure 2.43) in high yields. The [CuCl] [BMIm]$PhSO_3$ catalyst is conveniently recovered and reused for more than three times. Isolation of products formed is possible through direct distillation too. Hydrolysis of these α-methylene cyclic carbonates (**183**) provides entry to α-hydroxy ketones, and the resulting stereochemistry of these keto-alcohols will be more interesting to follow further.

$InCl_3$-doped IL–[BMIm]Cl catalyst was synthesized to effect carbon dioxide fixation onto epoxides to synthesize cyclic carbonates (**185**) [99]. Microwave irradiation of $InCl_3$ mixed with IL produced metal-doped [$InCl_3$-BMIm]Cl, which was utilized for conducting carbon dioxide fixation to epoxide leading to cyclic carbonates (**185**) (Figure 2.44). Metal-doped IL [$InCl_3$-BMIm]Cl, epoxide and carbon dioxide were mixed

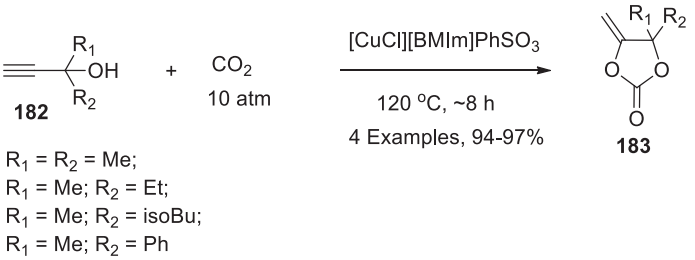


Figure 2.43: Synthesis of α-methylene cyclic carbonates **183** from propargyl compounds using IL [CuCl][BMIm]$PhSO_3$.

under 100 psi pressure and held at 120 °C to effect fixation of carbon dioxide onto the epoxide to form cyclic carbonates (**185**) (Figure 2.44). Other doped catalysts prepared and used for catalysis are found to be inferior to the [$InCl_3$-BMIm]Cl catalyst. Reaction parameters like effect of temperature, mole ratios, pressure and reaction time were studied to fine-tune the conditions to obtain high yields. Indium metal of the catalyst interacts with oxygen of the epoxide leading to the opening of epoxide and then chlorination takes place, then CO_2 enters into the reaction to make C–O bond and followed by nucleophilic substitution of chloride provides cyclic carbonate (**185**). The mechanism was monitored by "C-13" labeling experiments using NMR spectroscopy [99]. Catalyst prepared is stable to higher temperatures, air and moisture, performs very well and easily recoverable and recyclable. The cyclic carbonate products upon hydrolysis produce vicinal diol and carbon dioxide, where the vicinal diols stereochemistry has high relevance.

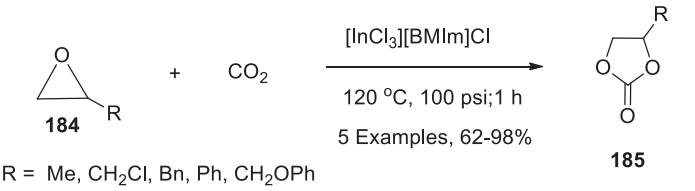


Figure 2.44: Synthesis of cyclic carbonates **185** from epoxides using IL [$InCl_3$–BMIm]Cl.

2.8 Limitations in using ILs

ILs are being increasingly used as substitutes for the common organic solvents used in conducting chemistry and this is because of their (ILs) property of very less volatile in nature. ILs also have other applications like in solar cells, fuel cells, electrode position, supercapacitors and more. But there are some suitability issues or limitations in using these ILs in organic synthesis as reaction solvent or medium or catalyst:

(i) toxicity of these ILs must be verified; (ii) cost, preparation and affordability of these ILs to be considered; (iii) stability of these ILs toward temperature, air and moisture; (iv) biodegradability; (v) recovery and reusability of ILs without any compromise; (vi) catalyzing further consecutive reactions leading different chemistry; (vii) solubility of these ILs in common organic extractable solvents with leaching effect; (viii) utility of ILs for large-scale industrial purposes; (ix) the interaction of IL with solute to effect a chemical transformation is poorly understood. Some of the points are listed and there may be more too. Nevertheless, these points definitely make a researcher to think, advance and come up with more innovations or discoveries to make these ILs more suitable to replace present-day use of volatile solvents.

2.9 Conclusions

This chapter is on the utility and role of ionic liquids as catalysts, medium and solvent in making various "Sulfur" and "Oxygen" atom-containing heterocycles. The accumulated and reported information in this chapter is not exhaustive, but selective to bring the important approach to readers. The chapter starts with brief introduction to history and importance of ILs. Quite a few methods of synthesis or preparation of ILs and their properties are discussed to a level. Imidazole, pyridine, boron, thiazole, phosphonium and chiral ILs synthesis are highlighted. Typical procedures for making couple of ILs are provided. Importance of properties like air stability, thermal stability, solubility, low nucleophilicity, less flammability and other important properties of ILs is brought to the notice of the reader. Several figures dedicated for the display of the synthesis of "S"-containing and "O"-containing heterocycles. Construction of thiophene and substituted thiophenes, thiazole compounds, thiazalones, sulfur-containing seven-membered rings, thiazine derivatives and thiapyran moieties involving ILs as medium, solvent and as catalyst are described. Synthesis of "Oxygen"-containing heterocycles are described in several figures like epoxide (three-membered ring-containing oxygen), 2,4-dihydrofurans, 2,3-dihydrofurans, fused dihydrofurans, multisubstituted furans, fused furans, butenolides, 4*H*-pyrans, monofused-4*H*-pyrans, bifused-4*H*-pyrans, 4-substituted 4*H*-pyrans, α-methylene cyclic carbonates and cyclic carbonates. Few examples given in figures are highlighted with stereochemistry part. The chemistry described clearly indicates that a wide range of "Sulfur" and "Oxygen" heterocycles can be easily synthesized by employing ILs, which are acting as solvent or medium and/or catalyst and informing that the more of GREEN chemistry to be adopted. The limitations in using ILs highlight that there are certain research domains to be attended to unravel the facts to make the ILs more efficient and more logical.

References

[1] Ramsay, W. Philos Mag Ser 5 1876, 24, 269.

[2] Walden, P. Über die. Molekulargrösse und elektrische Leitfähigkeiteinigergeschmolzener Salze. Bull Acad Imper Sci (St Petersburg) 1914, 8, 405–422.

[3] Sugden, S, Wilkins, H. The parachor and chemical constitution. Part XII. Fused metals and salts. J Chem Soc 1929, 1291–1298. DOI: https://doi.org/10.1039/JR9290001291.

[4] Hurley, FH, Wier, TP. Electrodeposition of metals from fused quaternary ammonium salts. J Electrochem Soc 1951, 98, 203–206. DOI: https://doi.org/10.1149/1.2778132.

[5] Zhang, GR, Bjm, E. Ionic liquids in electrocatalysis. J Energy Chem 2016, 25, 199–207. DOI: https://doi.org/10.1016/j.jechem.2016.11.003.

[6] Yoke, JT, Weiss, JF, Tollin, G. Reactions of Triethylamine with copper(I) and copper(II) halides. Inorg Chem 1963, 2, 1210–1216. DOI: https://doi.org/10.1021/ic50010a028.

[7] Axtel, DT, Goo, BW, Porterfield, WW, Yoke, JT. "Fused salts"atroom temperature. Spectroscopic and other studies of liquidChlorocuprates(I). J Am Chem Soc 1973, 95, 4555–4559. DOI: https://doi.org/10.1021/ja00795a016.

[8] Ford, WT, Hauri, RT, Hart, DJ. Syntheses and properties of molten Tetraalkylammonium Tetraalkylborides. J Org Chem 1973, 38, 3916–3918. DOI: https://doi.org/10.1021/jo00962a020.

[9] Ford, WT, Hauri, RT, Smith, SG. Nucleophilic reactivities of halideions in molten Triethyl-n-hexylammonium Triethyl-n-hexylboride. J Amer Chem Soc 1974, 96, 4316–4318. DOI: https://doi.org/10.1021/ja00820a044.

[10] Rosenthal, KS, Storm, DR, Ford, WT. Triethyl-n-HexylammoniumTriethyl-n-Hexylboride: A new antimicrobial showing activity against *Candida albicans* and gram-positive bacteria. Antimicrob Agents Chemother 1975, 8, 510–512. DOI: https://doi.org/10.1128/AAC.8.4.510.

[11] Hussey, CL. Room temperature molten salt systems. Adv Molten Salt Chem 1983, 5, 185–230.

[12] Wilkes, JS, Zaworotko, MJ. Air and water stable 1-ethyl-3-methylimidazolium based ionic liquids. J Chem Soc Chem Commun 1992, 965, DOI: 10.1039/C39920000965.

[13] Welton, T. Ionic liquids in catalysis. Coord Chem Rev 2004, 248, 2459–2477. DOI: https://doi.org/10.1016/j.ccr.2004.04.015.

[14] Buzzeo, MC, Evans, RG. Non-haloaluminate room-temperature ionic liquids in electrochemistry – a review. Compton Chem Phys Chem 2004, 5, 1106. DOI: https://doi.org/10.1002/cphc.200301017.

[15] Liu, JF, Jonsson, JA, Jiang, JB. Application of ionic liquids in analytical chemistry. Trends Anal Chem 2004, 24, 20–27. DOI: https://doi.org/10.1016/j.trac.2004.09.005.

[16] Wang, R, Okajima, T, Kitamura, F, Ohsaka, T. A novel amperometric O_2 gas sensor based on supported room-temperature ionic liquid porous polyethylene membrane-coated electrodes. Electroanalysis 2004, 16, 66–72. DOI: https://doi.org/10.1002/elan.200302919.

[17] Park, S, Kazlauskas, RJ. Biocatalysis in ionic liquids – Advantages beyond green technology. CurrOpinBiotechnol 2003, 14, 432–437. DOI: https://doi.org/10.1016/S0958-1669(03)00100-9.

[18] Wasserscheid, P, Welton, T, Editors. Ionic liquids in synthesis, New York: Wiley-VCH, 2008, ISBN 978-3-527-31239–9.

[19] Holbrey, JD, Seddon, KR. Ionic liquids. In: Clean products processes, 1st edn. Belfast: Springer-Verlag, 1999, 223–236. DOI: 10.1007/s100980050036.

[20] Rynkowska, E, Fatyeyeva, K, Kujawski, W. Application of polymer-based membranes containing ionic liquids in membrane separation processes: A critical review. Rev Chem Eng 2018, 34(3), 341–363. DOI: 10.1515/revce-2016-0054.

[21] Sun, N, Rahman, M, Qin, Y, Maxim, ML, Rodriguez, H, Rogers, RD. Complete dissolutionand partial delignification of wood in the ionic liquid 1-ethyl-3-methylimidazolium acetate. Green Chem 2009, 11, 646–655. DOI: 10.1039/B822702K.

[22] Phillips, DM, Drummy, LF, Conrady, DG, Fox, DM, Naik, RR, Stone, MO, Trulove, PC, DeLong, HC, Mantz, RA. Dissolution and regeneration of *Bombyx mori* silk fibroin using ionic liquids. J Amer Chem Soc 2004, 126, 14350–14351. DOI: 10.1021/ja046079f.

[23] Biswas, A, Shogren, RL, Stevenson, DG, Willett, JL, Bhownik, PK. Ionic liquids as solventsfor biopolymers: Acylation of starch and zein protein. Carbohydr Polym 2006, 66, 546–550. DOI: 10.1016/j.carbpol.2006.04.005.

[24] Regmi, BP, Speller, NC, Anderson, MJ, Brutus, JO, Merid, Y, Das, S, El-Zahab, B, Hayes, DJ, Murray, KK, Warner, IM. Molecular weight sensing properties of ionic liquid-polymercomposite films: Theory and experiment. J Mater Chem 2014, 2, 4867–4878. DOI: 10.1039/C3TC32528H.

[25] Lu, X, Huang, J, He, G, Yang, L, Zhang, N, Zhao, Y, Qu, J. Preparation and characterization of cross-linked poly(butylene succinate) by multifunctional toluene diisocyanate–trimethylol- propane polyurethane prepolymer. Ind &engchem Res 2013, 52, 13677–13684. DOI: 10.1021/ie4020342.

[26] Yuan, J, Schlaad, H, Giordano, C, Antonietti, M. Double hydrophilic diblock copolymers containingapoly(ionic liquid) segment: Controlled synthesis, solution property, and applications carbon precursor. Eur Polymer J 2011, 47, 772–781. DOI: 10.1016/j.eurpolymj.2010.09.030.

[27] Nancarrow, P, Mohammed, H. Ionic liquids in space technology – current and future trends. Chem Bioeng Rev 2017, 4, 1–15. DOI: 10.1002/cben.201600021.

[28] Sang, X, Zhang, J, Xiang, J, Cui, J, Zheng, L, Zhang, J, Wu, Z, Li, Z, Mo, G, Xu, Y, Song, J, Liu, C, Tan, X, Luo, T, Zhang, B, Han, B. Ionic liquid accelerates the crystallization of Zr-based metal–organic frameworks. Nat Commun 2017, 8, 175–181. DOI: 10.1038/s41467-017-00226-y.

[29] Vishwakarma, NK, Singh, AK, Hwang, Y-H, Ko, D-H, Kim, J-O, BabuA, G, Kim, D-P. Integrated CO_2 capture-fixation chemistry via interfacial ionic liquid catalyst in laminar gas/liquid flow. Nat Commun 2017, 8, 1476–1483. DOI: 10.1038/ncomms14676.

[30] Yuan, B, Egner, TK, Venditti, V, Cademartiri, L. Sustainable scalable synthesis of sulfide nanocrystals at low cost with an ionic liquid sulphur precursor. Nat Commun 2018, 9, 4078–4084. DOI: 10.1038/s41467-018-06549-8.

[31] Gao, N, He, Y, Tao, X, Xu, X-Q, Wu, X, Wang, Y. Crystal-confined freestanding ionic liquids for reconfigurable and repairable electronics. Nat Commun 2019, 10, 547–558. DOI: https://doi.org/10.1038/s41467-019-08433-5.

[32] Zhang, G-H, Zhu, Q-H, Zhang, L, Yong, F, Zhang, Z, Wang, S-L, Wang, Y, He, L, Tao, G-H. High-performance particulate matter including nanoscale particle removal by a self-powered air filter. Nat Commun 2020, 11, 1653–1662. DOI: https://doi.org/10.1038/s41467-020-15502-7.

[33] Weilhard, A, Argent, S, Sans, V. Efficient carbon dioxide hydrogenation to formic acid with buffering ionic liquids. Nat Commun 2021, 12, 231–237. DOI: https://doi.org/10.1038/s41467-020-20291-0.

[34] Guo, J, Tucker, Z, Wang, Y, Ashfeld, B, Luo, T. Ionic liquid enables highly efficient low temperature desalination by directional solvent extraction. Nat Commun 2021, 12, 437–443. DOI: https://doi.org/10.1038/s41467-020-20706-y.

[35] Wojnarowska, Z, Cheng, S, Yao, B, Swadzba-Kwasny, M, McLaughlin, S, McGrogan, A, Delavoux, Y, Paluch, M. Pressure-induced liquid-liquid transition in a family of ionic materials. Nat Commun 2022, 13, 1342–1351. DOI: https://doi.org/10.1038/s41467-022-29021-0.

[36] Benedict KM, C, Chang, N-H, Ross Grimmett, M. The synthesis and thermolysis of imidazole quaternary salts. Aust J Chem 1977, 30, 2005–2013. DOI: https://doi.org/10.1071/CH9772005.

[37] Hurley, FH, WIer, TP, Jr. Electrodeposition of metals from fused quaternary ammonium salts. J Electrochem Soc 1951, 98, 203–206. DOI: 10.1149/1.2778132.

[38] Bonhôte, P, Dias, A-P, Papageorgiou, N, Kalyanasundaram, K, Grätzel, M. Hydrophobic, highly conductive ambient-temperature molten salts. Inorg Chem 1996, 35, 1168–1178. DOI: https://doi.org/10.1021/ic951325x.

[39] Wilkes, JS, Levisky, JA, Wilson, RA, Hussey, CL. Dialky-limidazolium chloroaluminate melts: A new class of room-temperature ionic liquids for electrochemistry, spectroscopy and synthesis. Inorg Chem 1982, 21, 1263–1264. DOI: https://doi.org/10.1021/ic00133a078.
[40] Fischer, J, Siegel, W, Bomm, V, Fischer, M, Mundinger, K. Process for the preparation of 1,3-dimethylimidazolium-4-carboxylate. US Patent 6,175,019, 2001.
[41] Holbrey, JD, Matthew Reichert, W, Tkatchenko, I, Bouajila, E, Walter, O. Immacolata Tommasi and Robin D. Rogers. 1,3-Dimethylimidazolium-2-carboxylate: The unexpected synthesis of and ionic liquid precursor and carbene-CO_2 adduct. Chem Commun 2003, 28–29. DOI: 10.1039/B211519K.
[42] Bridges, NJ, Hines, CC, Smiglak, M, Rogers, R. An intermediate for the clean synthesis of ionic liquids: Isolation and crystal structure of 1,3-dimethylimidazolium hydrogen carbonate monohydrate. Chem Eur J 2007, 13, 5207–5212. DOI: https://doi.org/10.1002/chem.200700055.
[43] Smiglak, M, Holbrey, JD, Griffin, ST, Reichert, WM, Swatloski, RP, Katritzky, AR, Yang, H, Zhang, D, Kirichenko, K, Rogers, RD. Ionic liquids via reaction of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate with protic acids. Overcoming synthetic limitations andestablishing new halide free protocols for the formation of ILs. Green Chem 2007, 9, 90–98. DOI: 10.1039/b610421e.
[44] Wilkes, JS, Zaworotko, MJ. Air and water stable I-ethyl-3-methylimidazolium based ionic liquids. J Chem Soc Chem Commun 1992, 965, DOI: 10.1039/C39920000965.
[45] Fuller, J, Carlin, RT, Osteryoung, RA. The room temperature ionic liquid 1 - Ethyl-3-methylimidazolium tetrafluoroborate: Electrochemical couples and physical properties. J Electrochem Soc 1997, 144, 3881. DOI: 10.1149/1.1838106.
[46] Poole, CF, Kerstaen, BR, HO, SSJ, Coddens, ME, Furton, KG. Organic salts, liquid at roomtemperature, as mobile phases in liquid chromatography. J Chromatography 1986, 352, 407–425. DOI: https://doi.org/10.1016/S0021-9673(01)83397-5.
[47] Damico, R. Preparation, characterization, and reactions of lithium and sodium tetraalkylboron compounds. J Org Chem 1964, 29, 1971–1976. DOI: 10.1021/jo01030a077.
[48] Ford, WT, Kauri, RJ, Hart, DJ. Syntheses and properties of molten tetraalkylammonium tetraalkylborides. J Org Chem 1971, 38, 3916–3918. DOI: https://doi.org/10.1021/jo00962a020.
[49] Hillesheim, PC, Mahurin, SM, Fulvio, PF, Yeary, JS, Oyola, Y, Jiang, D-E, Dai, S. Synthesis and characterization of thiazolium-based room temperature ionic liquids for gas separations. Ind Eng Chem 2012, 51, 11530–11537. DOI: 10.1021/ie3015632.
[50] Kuhlmann, E, Himmler, S, Giebelhaus, H, Wasserscheid, P. Imidazolium dialkylphosphates – A class of versatile, halogen-free and hydrolytically stable ionic liquids. Green Chem 2007, 9, 233–242. DOI: https://doi.org/10.1039/B611974C.
[51] Bradaric, CJ, Downard, A, Kennedy, C, Robertson, AJ, Zhou, Y. Industrial preparation of phosphonium ionic liquids. Green Chem 2003, 5, 143–152. DOI: 10.1039/b209734f.
[52] Ding, J, Welton, T, Armstrong, DW. Chiral ionic liquids as stationary phases in gas chromatography. Anal Chem 2004, 76, 6819–6822. DOI: https://doi.org/10.1021/ac049144c.
[53] Ghirardello, M, Costantini, M, Vecchi, A, Pacifico, S, Pazzi, D, Castiglione, F, Mele, A, Marra, A. Synthesis of chiral ionic liquids from natural monosaccharides. Eur J Org Chem 2022, e202200100. DOI: 10.1002/ejoc.202200100.
[54] Flieger, J, Feder-Kubis, J, Tatarczak-Michalewska, M. Chiral ionic liquids: Structural diversity, properties and applications in selected separation techniques. Intl J Mol Sci 2020, 21, 4253. DOI: 10.3390/ijms21124253.
[55] Janus, E, Gano, M, Feder-Kubis, J, Sosnicki, J. Chiral protic imidazolium salts with a (–)-menthol fragment in the cation: Synthesis, properties and use in the Diels–Alder reaction. RSC Adv 2018, 8, 10318–10331. DOI: 10.1039/c7ra12176h.
[56] Gausepohl, R, Buskens, P, Kleinen, J, Bruckmann, A, Lehmann, CW, Klankermayer, J, Leitner, W. Highly enantioselective Aza-Baylis–Hillman reaction in a chiral reaction medium. Angew Chem Int Ed 2006, 45:, 3689–3692. DOI: https://doi.org/10.1002/anie.200600327.

[57] Ding, J, Armstrong, DW. Chiral ionic liquids: Synthesis and applications. Chirality 2005, 17, 281–292. DOI: https://doi.org/10.1002/chir.20153.
[58] Prabhakara H Shetty, P, Brian R Kersten, C. Solvent properties of liquid organic salts used as mobile phases in microcolumn reversed-phase liquid chromatography. J Chromatogr 1987, 411, 61. DOI: https://doi.org/10.1016/S0021-9673(00)93960-8.
[59] GFurton, K, Morales, R. Effect of anion chain length on the solvent properties of liquid tetrabutylammonium alkylsulfonate salts studied by gas – Liquid chromatography. Anal Chimica Acta 1991, 246, 171–179. DOI: https://doi.org/10.1016/S0003-2670(00)80674-1.
[60] Pomaville, RM, Poole, CF. Changes in retention and polarity accompanying the replacement of hydrogen by fluorine in tetraalkylammonium alkyl and arylsulfonate salts used as stationary phases in gas chromatography. J Chromatogr A 1989, 468, 261–278. DOI: https://doi.org/10.1016/S0021-9673(00)96321-0.
[61] Pomaville, RM, Poole, CF. Gas chromatographic study of the solution thermodynamics of organic solutes in tetraalkylammonium alkanesulfonate and perfluoroalkane sulfonate solvents. J Chromatography 1990, 499, 749–759. DOI: https://doi.org/10.1016/S0021-9673(00)97017-1.
[62] Singh, SK, Savoy, AW. Ionic liquids synthesis and applications: An overview. J Mol Liq 2019, e112038. DOI: https://doi.org/10.1016/j.molliq.2019.112038.
[63] Kaki, VR, Akkinepalli, RR, Deb, P, Pichika, MR. Basic ionic liquid [bmIm]OH mediated Gewald reaction as green protocol for the synthesis of 2-aminothiophenes. Synthetic Commun 2014, 45, 119–126. DOI: http://dx.doi.org/10.1080/00397911.2014.951898.
[64] Hu, Y, Chen, Z-C, Le, Z-G, Zheng, QG. Organic reactions in ionic liquids: Gewald synthesis of 2-aminothiophenes catalyzed by ethylenediammonium diacetate. Synthetic Commun 2004, 34, 3801–3806. DOI: 10.1081/scc-200032526.
[65] Chavan, SS, Pedgaonkar, YY, Jadhav, AJ, Degani, MS. Microwave accelerated synthesis of 2-aminothiophenes in ionic liquid via three component Gewald reaction. Indian J Chem Sect B 2012, 43, 657.
[66] Yi, H, Ping, W, He, H, Han, S-Q, Ouyang, P-K. Microwave-assisted Gewald synthesis of 2-aminothiophenes using functional ionic liquid as soluble support. Heterocycles 2006, 68, 375–380. DOI: 10.3987/COM-05-10628.
[67] Deshmukh, AR, Dhumal, ST, Nawale, LU, Khedkar, VM, Sarkar, D, Mane, RA. Dicationic liquid mediated synthesis of tetrazoloquinolinyl methoxy phenyl 4-thiazolidinones and their antibacterial and antitubercular evaluation. Synth Commun 2019, 49, 587–601. DOI: https://doi.org/10.1080/003979911.2018.1564928.
[68] Yadav, JS, Subba Reddy, BV, Eshwaraiah, B, Gupta, MK. $Bi(OTf)_3$[bmim][BF_4] as novel and reusable catalytic system for the synthesis of furan, pyrrole and thiophene derivatives. Tetrahedron Lett 2004, 45, 5873–5876. DOI: 10.1016/j.tetlet.2004.05.152.
[69] Arya, K, Prabhakar, B. Ionic liquids confined zeolite system: An approach towards water mediated room temperature synthesis of spiro[pyrazolo[3,4-*e*]benzothiazepines]. Green Chem 2013, 15, 2885–2894. DOI: 10.1039/C3GC40553B.
[70] Arya, K, Sarkar, B, Ravichandran, G, Prabhu, M, Choudhury, SP, Makhija, S, US Patent 7968079, 2011.
[71] Maradolla, MB, Allam, SK, Mandha, A, Chandramouli, GVP. One pot synthesis of benzoxazoles, benzthiazoles and benzimidazoles from carboxylic acids using ionic liquids. Arkivoc 2008, 42–46.
[72] Parmar, NJ, Parmar, BD, Sutariya, TR, Kant, R, Gupta, VK. An efficient synthesis of some thiopyranopyrazole-heterocycles viadomino reaction in a Brønsted acidic ionic liquid. Tetrahedron Lett 2014, 55, 6060–6064. DOI: http://dx.doi.org/10.1016/j.tetlet.2014.09.026.
[73] Bhupender, SC, Anil, KM, Vibha, T. KF-alumina immobilized ionioc liquids: A novel heterogenous base for heterocyclization of alkylsulfanylphenylamines into 1,4-benzothiazine. Heterocycles 2004, 63, 1057–1065. DOI: 10.3987/COM-04-10003.

[74] Hou, R-S, Wang, H-M. Synthesis of 2-phenylthiazoles from Tosyloxyketones and Thiobenzamide in [Bmim][PF_6]ionic liquid at ambient temperature. J Chinese Chem Soc 2006, 53, 863–866. DOI: 10.1002/jccs.200600114.
[75] Yadav, AK, Kumar, M, Yadav, T, Jain, R. An ionic liquid mediated one-pot synthesis of substituted thiazolidinones and benzimidazoles. Tetrahedron Lett 2009, 50, 5031–5034. DOI: 10.1016/j.tetlet.2009.06.091.
[76] Lingampalle, D, Jawale, D, Waghmare, R, Mane, R. Ionic liquid-mediated, one-pot synthesis for 4-thiazolidinones. Synth Commun 2010, 40, 2397–2401. DOI: 10.1080/00397910903245174.
[77] Noei, J, Khosropour, AR. Ultrasound-promoted a green protocol for the synthesis of 2,4-diarylthiazoles under ambient temperature in [Bmim]BF_4. Ultrason Sonochem 2009, 16, 711–717. DOI: 10.1016/j.ultsonch.2009.04.001.
[78] Izumisawa, Y, Togo, H. Preparation of α-bromoketones and thiazoles from ketones with NBS and thioamides in ionic liquids. Green Sustain Chem 2011, 1, 54–62. DOI: 10.4236/gsc.2011.13010.
[79] Nadaf, RN, Siddiqui, SA, Daniel, T, Lahoti, RJ, Srinivasan, KV. Room temperature ionic liquid promotedregioselective synthesis of 2-aryl benzimidazoles,benzoxazoles and benzthiazoles under ambient conditions. J Mol Catal A Chem 2004, 214, 155–160. DOI: 10.1016/j.molcata.2003.10.064.
[80] Yadav, LDS, Rai, V, Yadav, B. The first ionic liquid-promoted one-pot diastereoselective synthesis of 2,5-diamino-/2-amino-5-mercapto-1,3-thiazin-4-ones using masked amino/mercapto acids. Tetrahedron 2009, 65, 1306–1315. DOI: 10.1016/j.tet.2008.12.050.
[81] Zhang, X, Li, X, Fan, X, Wang, X, Li, D, Qu, G, Wang, J. Ionic liquid promoted preparation of 4H-thiopyran andpyrimidine nucleoside-thiopyran hybrids through one-pot multi-component reaction of thioamide. Mol Divers 2009, 13, 57–61. DOI: 10.1007/s11030-008-9098-4.
[82] Bernini, R, Mincione, E, Coratti, A, Fabrizi, G, Battistuzzi, G. Epoxidation of chromones and flavonoids in ionic liquids. Tetrahedron 2004, 60, 967–971. DOI: https://doi.org/10.1016/j.tet.2003.11.032.
[83] Song, CE, Roh, E. Practical method to recycle a chiral (Salen)Mn epoxidation catalyst by using an ionic liquid. Chem Commun 2000, 837–838. DOI: https://doi.org/10.1039/B001403F.
[84] Bar, G, Parsons, AF, Thomas, BC. Manganese(III) acetate mediated radical reactions in the presence of an ionic liquid. Chem Commun 2001, 1350–1351. DOI: 10.1039/b103544b.
[85] Yadav, JS, SubbaReddy, BV, Shubashree, S, Sadashiv, K, Naidu, JJ. Ionic liquids-promoted multi-component reaction: Green approach for highly substituted 2-Aminofuran derivatives. Synthesis 2004, 2376–2380. DOI: 10.1055/s-2004-831181.
[86] Villemin, D, Mostefa-Kara, B, Bar, N, Choukchou-Braham, N, Cheikh, N, Benmeddah, A, Hazimeh, H, Ziani-Cherif, C. Base-promoted reactions in ionic liquid solvent: Synthesis of butenolides. Lett Org Chem 2006, 3, 558–559. DOI: 10.2174/157017806778341807.
[87] Moreau, C, Finiels, A, Vanoye, L. Dehydration of fructose and sucrose into 5-hydroxymethylfurfural in the presence of 1-H-3-methyl imidazolium chloride acting both as solvent and catalyst. J Mol Catal A Chem 2006, 253, 165–169. DOI: 10.1016/j.molcata.2006.03.046.
[88] Ranu, BC, Adak, L, Banerjee, S. Ionic liquid promoted interrupted Feist–Benary reaction with high diastereoselectivity. Tetrahedron Lett 2008, 49, 4613–4617. DOI: 10.1016/j.tetlet.2008.05.083.
[89] Hajipoura, AR, Rafiee, F. Basic ionic liquids – a short review. J Iran Chem Soc 2009, 6, 647–678. DOI: https://doi.org/10.1007/BF03246155.
[90] Aksina, O, Krause, N. Gold-catalyzed synthesis of 2,5-dihydrofurans in ionic liquids. Adv Synth Catal 2008, 350, 1106–1112. DOI: 10.1002/adsc.200800050.
[91] Zulfiqar, F, Kitazume, T. Lewis acid-catalyzed sequential reaction in ionic liquids. Green Chem 2000, 2, 296–297. DOI: 10.1039/b006684m.
[92] Xie, X, Chen, B, Lu, J, Han, J, She, X, Pan, X. Synthesis of benzofurans in ionic liquid by a $PdCl_2$-catalyzed intramolecular Heck reaction. Tetrahedron Lett 2004, 45, 6235–6237. DOI: 10.1016/j.tetlet.2004.06.110.

[93] Gong, K, Wang, H-L, Luo, J, Liu, Z-L. One-pot synthesis of polyfunctionalized pyrans catalyzed by basic ionic liquid in aqueous media. J Heterocycl Chem 2009, 46, 1145. DOI: 10.1002/jhet.193.
[94] Kumbhar, A, Jadhav, S, Shejwal, R, Rashinkar, G, Salunkhe, R. Application of novel multi-cationic ionic liquids in microwave assisted 2-amino-4*H*-chromene synthesis. RSC Adv 2016, 6, 19612–19619. DOI: 10.1039/C6RA01062H.
[95] Sharma, H, Srivastava, S. Anion–cation co-operative catalysis by artificial sweetener saccharine-based ionic liquid for sustainable synthesis of 3,4-dihydropyrano[c]chromenes, 4,5-dihydropyrano [4,3-b]pyranandtetrahydrobenzo[b]pyrans in aqueous medium. RSC Adv 2018, 8, 38974–38979. DOI: 10.1039/c8ra06889e.
[96] Chen, Z, Zhu, Q, Su, W. A novel sulfonic acid functionalized ionic liquid catalyzed multicomponent synthesis of 10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives in water. Tetrahedron Lett 2011, 52, 2601. DOI: https://doi.org/10.1016/j.tetlet.2011.3.059.
[97] Li, C-B, Li, Y-W, Xu, D-Z. An efficient and ecofriendly three-component reaction for the rapid synthesis of 2-Amino-4*H*-chromenes catalyzed by a DABCO-based ionic liquid. Synthesis 2018, 50, 3708–3714. DOI: 10.1055/s-0037-1610123.
[98] Gu, Y, Shi, F, Deng, Y. Ionic liquid as an efficient promoting medium for fixation of CO2: Clean synthesis of ɤ-methylene cyclic carbonates from CO_2 and propargyl alcohols catalyzed by metal salts under mild conditions. J Org Chem 2004, 69, 391–394. DOI: 10.1021/jo0351365.
[99] Kim, YJ, Varma, RS. Tetrahaloindate(III)-based ionic liquids in the coupling reaction of carbon dioxide and epoxides to generate cyclic carbonates: H-bonding and mechanistic studies. J Org Chem 2005, 70, 7882–7891. DOI: 10.1021/jo050699x.

Radhika Gupta, Yukti Monga, Ashu Gupta and Rakesh Kumar Sharma*

Chapter 3
Supported ionic liquids for advanced catalytic applications

3.1 Introduction

Since the last few decades, there has been an expanding interest in the domain of ionic liquids (ILs) [1–4]. They are defined as ionic compounds having a melting temperature below 100 °C. They contain asymmetric and flexible ions of variable shapes and sizes which are involved with different kinds of interactions (Figure 3.1). They have attracted a diversified range of researchers due to their targeted properties and widespread advantages [5, 6]. One of the prime features of ILs includes diversity: in anion–cation combinations, modes of preparation, of properties and of usage. They have negligible vapor pressure and nonflammable nature which distinguishes them from conventionally used volatile organic solvents. They generally have high thermal stability, broad range of conductivities, and multifunctional sites. Their tunable and versatile nature has allowed them to be used in a plethora of assorted applications such as fuel cells, sensors, lubricants, plasticizers, thermal fluids and many others. In organic synthesis and analysis, they are widely being used as solvents and extractants due to their ability to dissolve the active species within; however, being partially miscible with the reactant and with the corresponding product it allows their separation simply via decantation without any influence over the catalyst. Also, in the field of catalysis they have been used as catalysts or as supporting phase for attaching other catalytic species [7–10].

However, some of the ILs have poor thermal stability and are prone to decomposition. They give highly viscous melts which give rise to transport complications such as diffusion, stirring and mixing barriers in catalytic processes and also, they are not easily biodegradable which produces major obstacles during industrial chemical disposal [11]. Besides, requirement of large amounts of IL, which many a times are costly, raises key concerns toward economic viability of processes. These practical disadvantages have given birth to the concept of supported ionic liquids (SILs) where the concerned ILs are bound onto a suitable support material. It merges the properties of ILs with advantages of heterogeneous catalytic support materials. This process eradicates

*Corresponding author: Rakesh Kumar Sharma, Green Chemistry Network Centre, Department of Chemistry, University of Delhi, New Delhi, India, e-mail: rksharmagreenchem@hotmail.com
Ashu Gupta, Department of Chemistry, Shyam Lal College, University of Delhi, New Delhi, India
Radhika Gupta, Yukti Monga, Department of Chemistry, Shyam Lal College, University of Delhi, New Delhi, India; Green Chemistry Network Centre, Department of Chemistry, University of Delhi, New Delhi, India

https://doi.org/10.1515/9783110788129-003

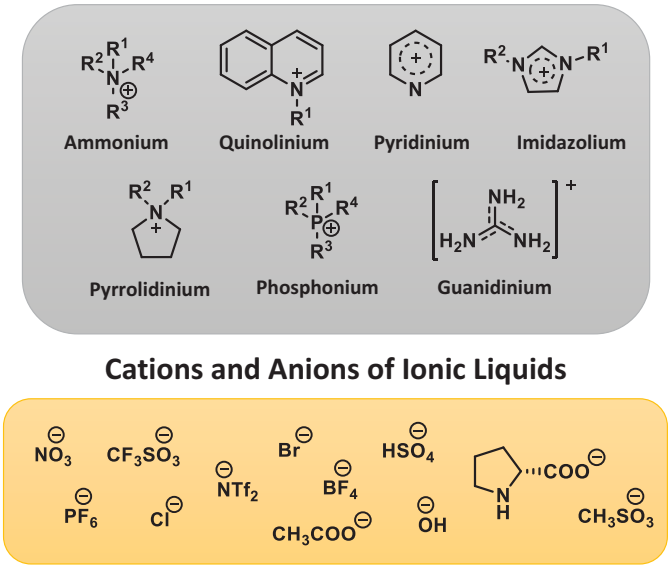


Figure 3.1: Some of the various possible cations and anions of ILs.

most of the above-mentioned shortcomings besides offering additional benefits including but not limited to enhanced selectivity, accelerated reaction kinetics, simplified work-up procedures and improved recyclability [12–15]. This chapter highlights some of the most recent and progressive developments concerning supported ILs from their elemental characteristics to their utilization in the synthesis of industrially significant organic compounds via catalytic pathways.

3.2 Supported ionic liquids catalysis

Different methodologies have been developed in the past for supporting ILs (Figure 3.2): (i) impregnation approach where a preformed IL is fixed on a suitable support by the means of physisorption forming a thin layer over the support [16]; (ii) encapsulation approach where IL is trapped inside the pores of a solid support [17]; (iii) covalent immobilization where IL is attached with the support via strong covalent bonds [18]. Third being the most popular and widely used because of the lowest leaching potential even under vigorous reaction conditions.

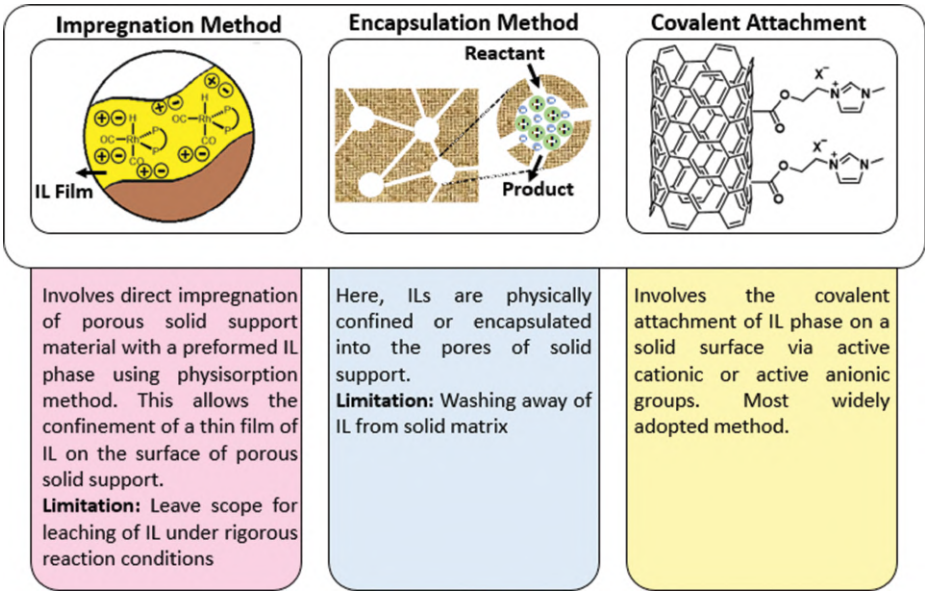


Figure 3.2: Different methodologies for the immobilization of IL.

3.2.1 Supported ionic liquids as support for other catalysts

Catalysis through metal nanoparticles has garnered immense attention in the domain of organic synthesis. Metals in their nano dimensions exhibit astonishing properties due to their large surface area-to-volume ratio and higher activity-selectivity when compared with their bulk counterparts. However, their application is often hampered due to uncontrollable agglomeration tendency which converts nanoparticles into their bulk phase over time. SILs have been widely explored for the stabilization of metal NPs electrostatically or by forming coordination bonds with the active metal. In the work described by Luska et al. [19], ruthenium NPs were attached over a silica-supported acid-functionalized imidazolium ionic liquid which was utilized as a stabilizing medium for the nanoparticles. Silica is one of the widely explored inorganic supporting phase for metal NPs immobilization and addition of an extra-stabilizing agent, which is anchored to its surface, results in improved catalytic performance of the nanoparticles. For the preparation, [1-(4-sulfobutyl)-3-(3-triethoxysilylpropyl)imidazolium]NTf_2, an acid functionalized IL was condensed with dehydroxylated SiO_2. Further, [Ru(2-methylallyl)$_2$(cod)] was added till it transformed the white color of SIL phase to bright yellow illustrating the adsorption of ruthenium precursor. This powder was thereafter subjected to reduction under H_2 atmosphere which converted the powder into black confirming the formation of ruthenium nanoparticles (Figure 3.3). The as-synthesized material was then used as a bifunctional catalyst for the selective deoxygenation of 4-(2-tetrahydrofuryl)-2-butanol and of 4-(5-

(hydroxymethyl)-2-tetrahydrofuryl)-2-butanol to give various valuable products such as ethers and alcohols. Numerous control experiments were conducted to study the utility of the bifunctionality: under Ru free-acid catalyst, the substrate decomposed into humins; under Ru-acid free catalyst, no reaction was observed. However, it was only Ru-acid catalytic composition, the desired products were obtained which confirmed the synergistic role of the two functionalities. High catalytic activities, selectivities as well as catalyst recyclability offer tremendous opportunities in the evolution of continuous flow processes for the selective deoxygenation of biomass-derived substrates.

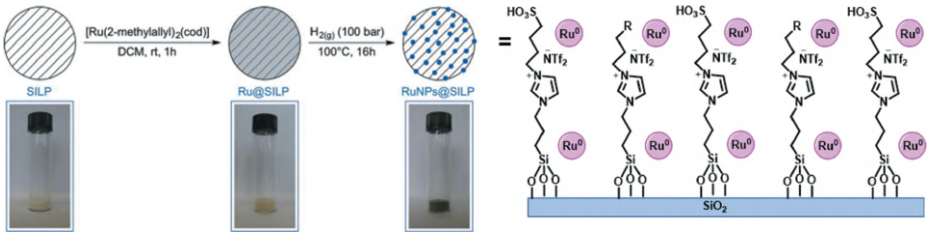


Figure 3.3: Synthesis of ruthenium nanoparticles immobilized silica supported acid-functionalized imidazolium ionic liquid (reproduced with permissions from ref. [19]).

Another work described the decoration of palladium nanoparticles over hybrid organo-silica-immobilized IL [20]. The support was synthesized using a sol–gel approach and further the nanoparticles were deposited using a simple and efficient sputtering-deposition technique (top-down method). This allows uniform deposition of nanoparticles onto the solid support which would ultimately result in efficient and improved catalytic performance. SILs with different anions, hydrophilic (sgB1 and sgB2) and hydrophobic (sgB3 and sgB4), were synthesized (Figure 3.4a). The catalytic ability of above-mentioned materials was evaluated in the selective hydrogenation of 1,3-cyclohexadiene and was found in the order $TOF_{Pd/sgB3} > TOF_{Pd/sgB4} > TOF_{Pd/sg0} > TOF_{Pd/sgB2} > TOF_{Pd/sgB1}$; SILs with hydrophobic anions demonstrated higher activities than the catalyst bearing no IL than with SILs having hydrophilic anions. Also, the catalyst showed high selectivity toward the formation of cyclohexene with very low amounts of benzene. It was observed that the nature of IL did not influence the size distribution of nanoparticles. However, the author found that the hydrophilicity and hydrophobicity of ILs impacted the pore size diameter of the supported phase; a higher palladium concentration was found in small pore diameters obtained with hydrophobic ILs and lower palladium concentration was found in larger pore diameters obtained with hydrophilic ILs. This justified the variation in catalytic performance obtained with different kinds of active anions.

Very recently, Shaikh et al. [21] designed a nano hybrid-bimetallic heterogeneous catalytic system by supporting mixed Au-Pd nanoparticles using imidazolium chloride IL on silica derived from rice husk ash, a natural waste, according to the procedure depicted in Figure 3.5. The combination of the mixed metallic system was chosen as per

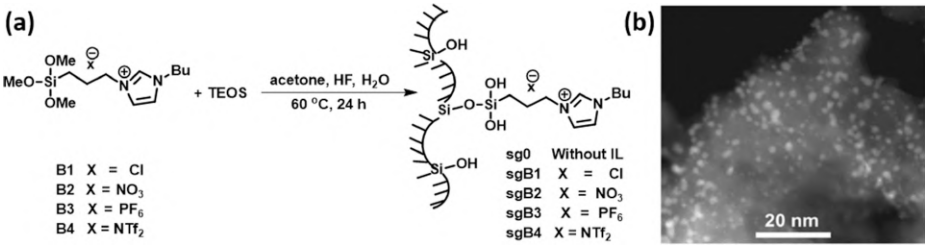


Figure 3.4: (a) Synthesis of support materials and (b) TEM image of Pd/sgB4 (reproduced with permissions from ref. [20]).

the synergistic advantages it offers. According to the earlier reports as well, enhanced catalytic activities of the Au-Pd nanohybrid were observed which was attributed to serial electronic transference among Au and Pd. Taking into account these benefits, the authors checked the catalytic performance in Suzuki reaction, a significant C–C bond forming reaction. After optimizing the reaction parameters, various kinds of halobenzenes were reacted with phenylboronic acid to give the corresponding coupling products with excellent yields. Also, the catalyst was separated by centrifugation and reused successfully for five catalytic cycles without losing much catalytic activity. The same group also developed Ag-Pd nanoparticles supported silica this time derived from sugarcane bagasse ash through immobilized 1-[3-(dimethylamino) propyl] -3-(3-trimethoxysilylpropyl)-1,4-diazabicyclo [2.2.2] octan1-ium hydroxide]ionic liquid [22]. The material was synthesized as per in Figure 3.6. Here, Ag NPs were applied to stabilize highly active Pd nanoparticles over immobilized basic IL on silica support. The catalytic performance was again checked in Suzuki coupling reaction and products were obtained with good yields including its successive repeatability till seven runs.

Amongst other supports, dendritic fibrous nanosilica has particularly received tremendous attention due to its fascinating properties including biocompatibility and non-toxicity. Unlike SBA-15 and MCM-41, it is easily achievable from all sides due to its filamentous morphology which enhances accessibility and loading of active catalytic species. On controlling the dendritic nanosilica fiber density, pore size and pore volume can also be modified. Additionally, it offers easy adsorption and diffusion of the catalytic species and other reactants inside the fibrous spheres with minimal constraints. Taking into accounts these benefits which dendritic fibrous nanosilica offers and the diversity which ruthenium provides in catalyzing organic reactions, Li and coworkers [23] anchored ruthenium nanoparticles on IL-modified dendritic fibrous nanosilica nanoparticles. The schematic procedure for its synthesis is shown in Figure 3.7 wherein first the dendritic fibrous nanosilica nanoparticles were surface functionalized with 3-chloropropyl groups which were further suspended in a preformed IL phase and finally metalation was carried out to form the final catalyst. Figure 3.8 depicts the TEM images of respective stages during the formation of the catalyst. Also, no morphological changes were observed even after surface modification with either IL or Ru nanoparticles. The catalyzed was then

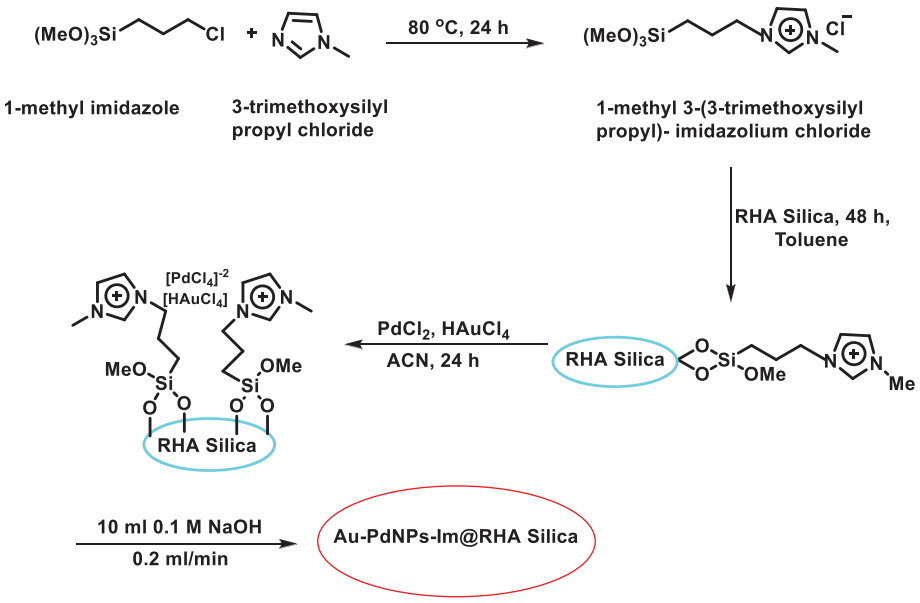


Figure 3.5: Schematic illustration for the formation of nano hybrid-bimetallic heterogeneous catalyst by supporting mixed Au-Pd nanoparticles using imidazolium chloride IL on silica derived from rice husk ash.

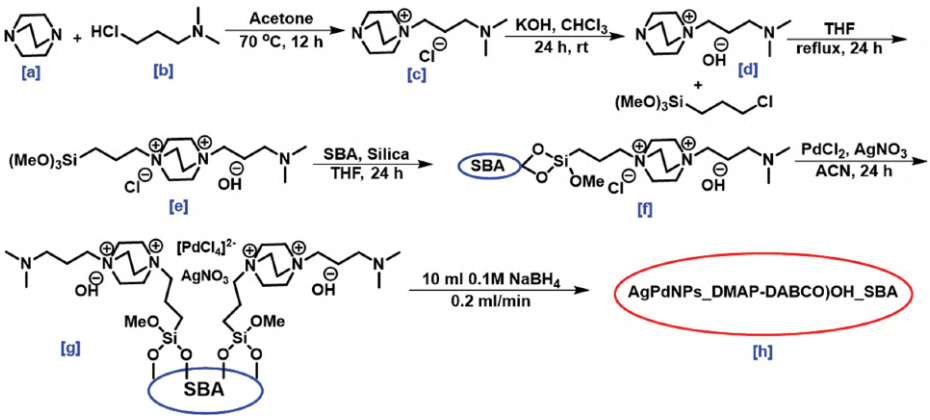


Figure 3.6: Synthesis of Ag-Pd nanoparticles supported silica derived from sugarcane bagasse ash through immobilized IL.

utilized in the single-pot hydroformylation of alkenes using H_2 and CO_2. Hydroformylation using CO_2 also imparts additional greener and sustainable benefits such as nontoxicity, easy availability, low cost and waste utilization. The yield of corresponding products was excellent and reusability of catalyst was for 10 cycles.

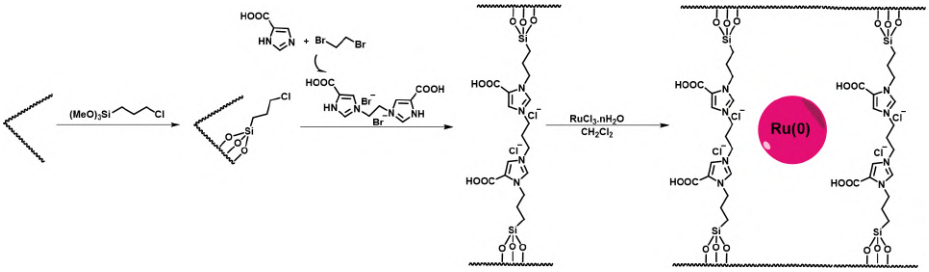


Figure 3.7: Schematic procedure for the synthesis of IL-modified dendritic fibrous nanosilica nanoparticles anchored ruthenium nanoparticles.

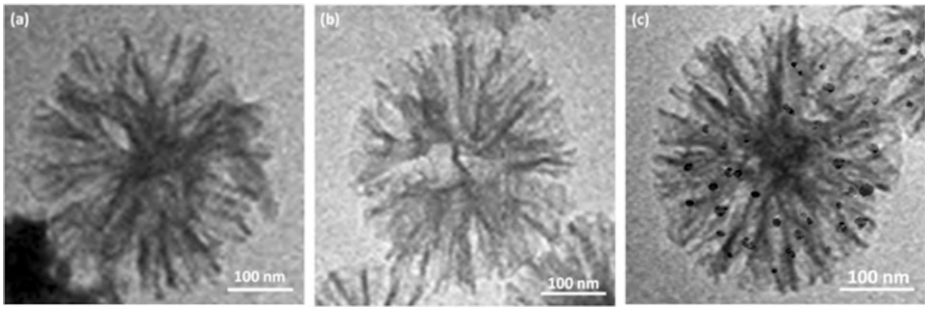


Figure 3.8: TEM images of successive formation of catalyst: (a) dendritic fibrous nanosilica, (b) IL-functionalized nanosilica and (c) ruthenium nanoparticles supported IL functionalized nanosilica (reproduced with permissions from ref. [23]).

Lately, Sadjadi and Koohestani [24] fabricated halloysite nanoclay supported epoxy functionalized imidazolium IL as a support for the stabilization of palladium nanoparticles (Figure 3.9). Halloysite has a tubular morphology with large lumen space. The resultant catalyst was utilized for the hydrogenation of nitro derivatives in aqueous medium under 1 bar H_2 pressure. The catalyst selectivity was evaluated in the presence of carbonyl compounds as well and high selectivity was obtained for hydrogenation of nitro compounds. The recycled catalyst was used for five consecutive runs without losing catalytic activity. Figure 3.10 depicts the TEM image of the catalyst wherein fine Pd NPs with average particle size of 3.5 ± 0.5 nm are homogeneously dispersed.

Another group designed and developed PEG-modified phosphine oxide functionalized styrene-based polymer @ IL on which ruthenium nanoparticles were impregnated (Figure 3.11) [25]. Here, IL was used for the stabilization of ruthenium nanoparticles through electrostatic interactions. However, to reinforce stabilization against aggregation of nanoparticles, to supplement electrostatic stabilization and to increase their long-term stability, phosphine oxide as heteroatom donors were incorporated into the IL. The functionalization might also help in improving the activity and selectivity approach of the

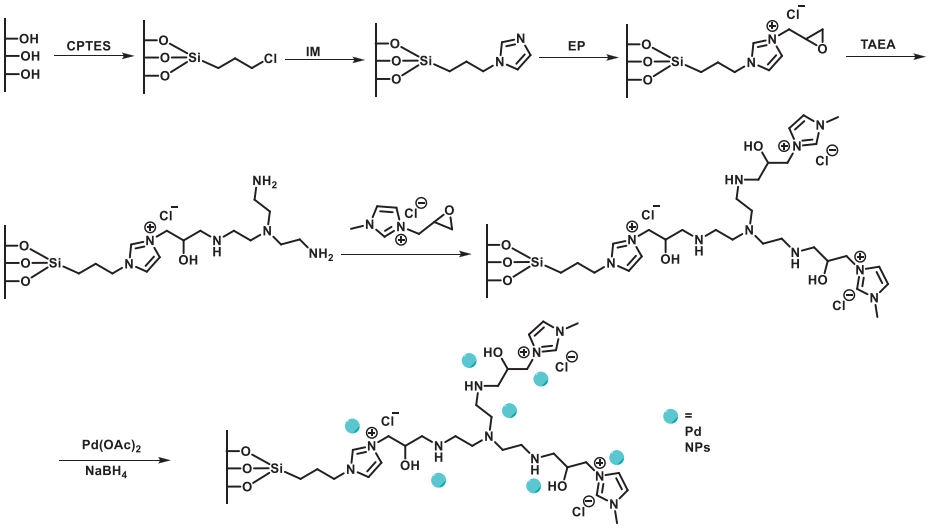


Figure 3.9: Synthesis of halloysite nanoclay-supported epoxy-functionalized imidazolium IL as a support for the stabilization of palladium nanoparticles.

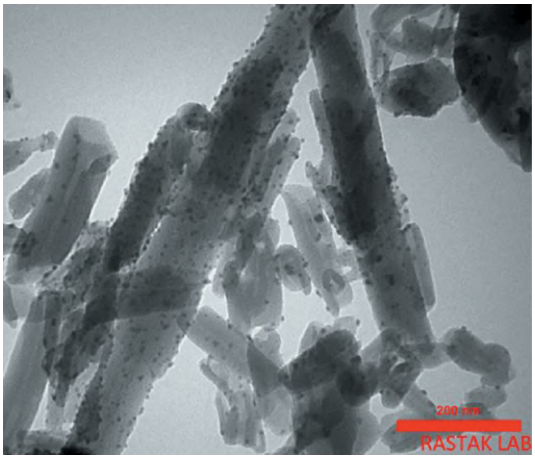


Figure 3.10: TEM image of Pd-supported halloysite nanoclay (reproduced with permission from ref. [24]).

nanoparticle. Further, obtained material was used to selectively reduce the carbonyl group of aryl and heteroaryl ketones, aldehydes and biomass-derived carbonyl compounds to the corresponding aromatic alcohol using water as a reaction medium. PEG-unit present in the catalyst helped for better dispersibility of the catalyst in water and assisted aqueous phase hydrogenation. The catalyst was reused for 10 runs which offers its large-scale utility in continuous flow reactor platform. It is also foreseen that

heteroatom functionalized polymer immobilized IL could act as a versatile support by facilitating the modification of surface electronic structure and steric environment and a control over nanoparticle size and morphology which would enable the development of new catalyst technology.

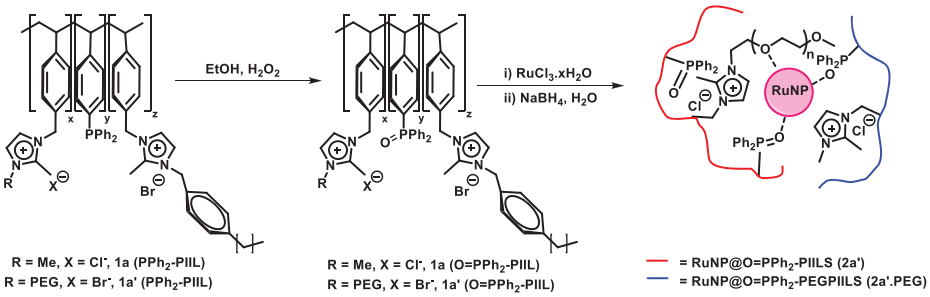


Figure 3.11: Synthesis of modified phosphine oxide functionalized styrene-based polymer immobilized ionic liquid supported ruthenium nanoparticles.

Nowadays, magnetic nano supports are particularly being used in heterogeneous catalysis due to facile magnetic recovery using external magnet field thereby minimizing time and energy usage required during separation of catalysts through other conventional approaches such as filtration or centrifugation [26, 27]. Recently, Rajabzadeh et al. [28] amalgamated the properties of Fe_3O_4 magnetic nanoparticles with hydrotalcite materials. This consists of alternating cationic (having Al^{3+}, Fe^{3+}, Fe^{2+}, Mg^{2+}, etc.), water and anionic $A^{n-}\cdot zH_2O$ layers with many attractive properties. This magnetic hydrotalcite was further utilized as a solid support for anchoring tricationic IL-immobilized CuI. Figure 3.12 illustrates the stepwise formation of the above catalyst. TEM image in Figure 3.13 also illustrates the plate-like morphology with ~50 nm size. Further the catalyst was utilized in Ullmann-type C–N coupling reaction and a variety of substituted aryl halides were reacted well with N(H)-heterocycles. The chemical transformation performed showed good functional group tolerance under mild reaction. The catalyst was utilized for six consecutive runs without affecting much loss of catalytic activity.

3.2.2 Supported ionic liquids as catalysts

Till now we have explained the utility of immobilized ILs as support for metal salts or metal nanoparticles. In the present section application of supported ILs as catalysts is being discussed. When the cationic and anionic moieties of ILs are tethered with entities such as hydrogen bond donors/acceptors, Lewis acids/bases or other functionalized groups, they can behave as catalysts. Even metal ions can be incorporated in the structure of ILs leading to metal-containing ILs. These can be utilized for conducting

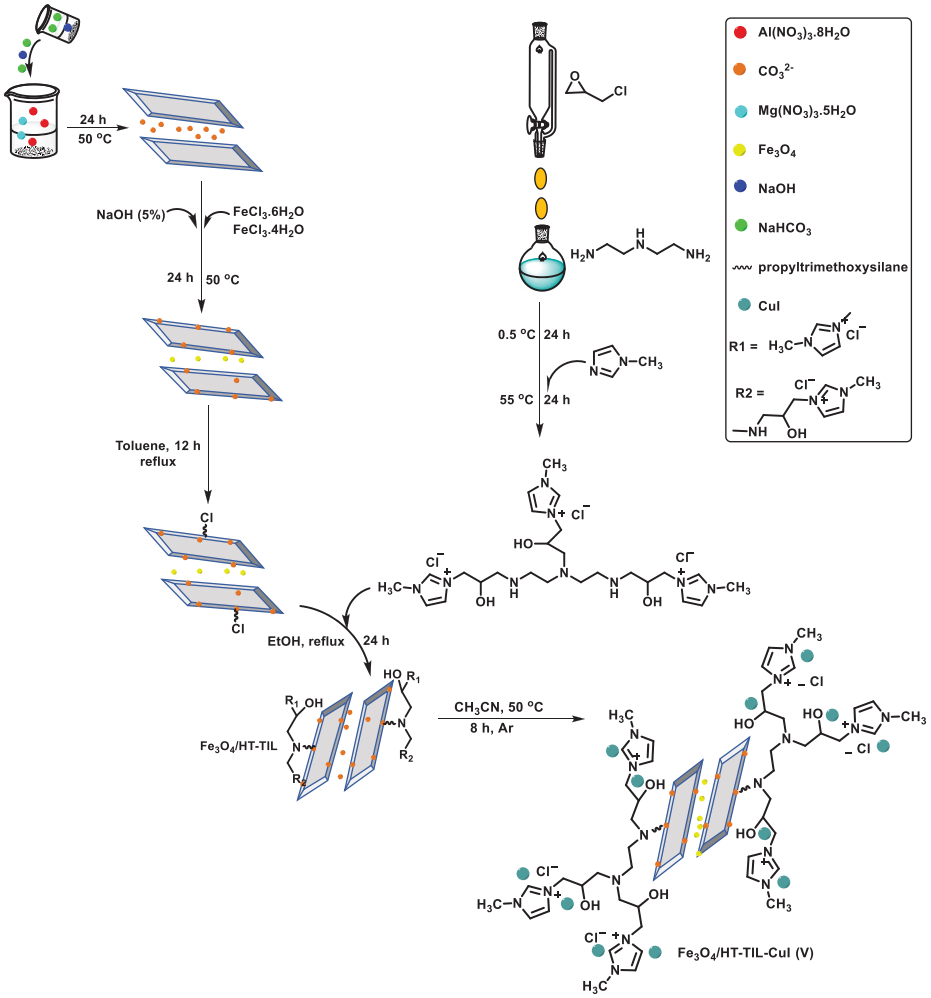


Figure 3.12: Schematic illustration for the synthesis of magnetic hydrotalcite supported tricationic IL immobilized CuI.

metal-catalyzed organic transformations giving combined benefits of metals and ILs [29]. The following are some of the recent works reported in the field of supported metal-free and metal-containing ILs as catalytic entities for industrially significant organic reactions.

Recently, Sadjadi et al. [30] developed a metal-free biocompatible catalyst. In this work, a dendritic moiety was developed through repeated reactions of 2,4,6-trichloro -1,3,5-triazine and ethylenediamine on chitosan. Further, functional groups at the terminal position of dendron were modified with 1-methylimidazolium chloride (Figure 3.14). Chitosan is a natural biopolymer having excellent mechanical, chemical and

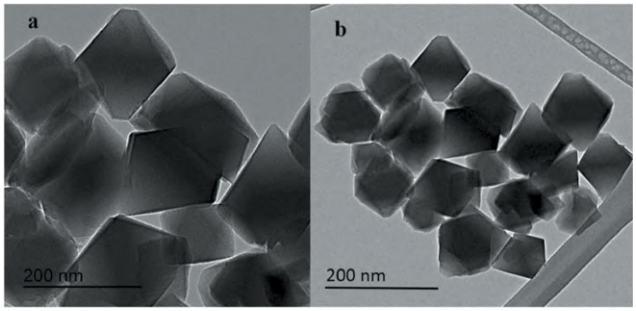


Figure 3.13: TEM images of (a) magnetic hydrotalcite supported tricationic IL and (b) magnetic hydrotalcite supported tricationic IL immobilized CuI (reproduced with permissions from ref. [28]) .

chelating properties. Its high chemical reactivity is attributed to the presence of surface hydroxyl and amino groups. Developed catalyst was confirmed with various characterization techniques such as SEM, EDS, TGA, FTIR, XRD and other mapping techniques. The resultant catalyst was used for the synthesis of xanthene derivatives and for Knoevenagel condensation in aqueous media under mild reaction conditions. The reported results showed high catalytic activity of the catalyst even superior to IL-free counterpart and bare chitosan. This observation was ascribed to the instinct catalytic activity of IL. Moreover, authors also performed the test using control catalyst and results further confirmed that presence of the dendritic moiety could enhance the IL loading on the backbone of the catalyst which automatically leads to enhanced catalytic activity.

Another group discussed single-step synthesis method of *bis*(indolyl)methane derivatives by condensation of indole with various kinds of benzaldehydes employing [DSIM][$AlCl_3$]$_x$-@CS chitosan-supported ionic liquid (CSIL) as catalyst in ethanolic medium (Figure 3.15) [31]. These are imperative class of nitrogen heterocyclic compounds having biologically activity and pharmaceutical value. The authors reported that attachment of IL over chitosan is an effective way for chemical transformations under optimized condition. The supporting effects of cationic and anionic parts of the IL lead to improved catalytic activity. Imidazolium cation made the catalyst acidic, $AlCl_4$ provided Lewis acidic sites to bind with hydroxyl and amine groups and chitosan made the catalyst heterogeneous. The authors claimed that they have simple catalyst synthesis, smaller reaction time, easy work-up procedure, and high chemoselectivity in the described work.

Lately, carbon nanotubes have developed as outstanding catalytic support owing to some fascinating properties such as easy tailorable shapes, chemical resistance, high thermal and mechanical stability and controllable surface chemistry. In view of this, Lina Han and coworkers [32] synthesized multiwalled CNT supported with imidazolium-based IL (CNT-ILs) and used them as easily recoverable catalyst for cycloaddition reaction of epoxides and CO_2 to form cyclic carbonates. For this work, various imidazolium ILs with different alkyl chain lengths and counter halogenic anions were synthesized and imported on oxidized MWCNTs (Figure 3.16). All of these were investigated

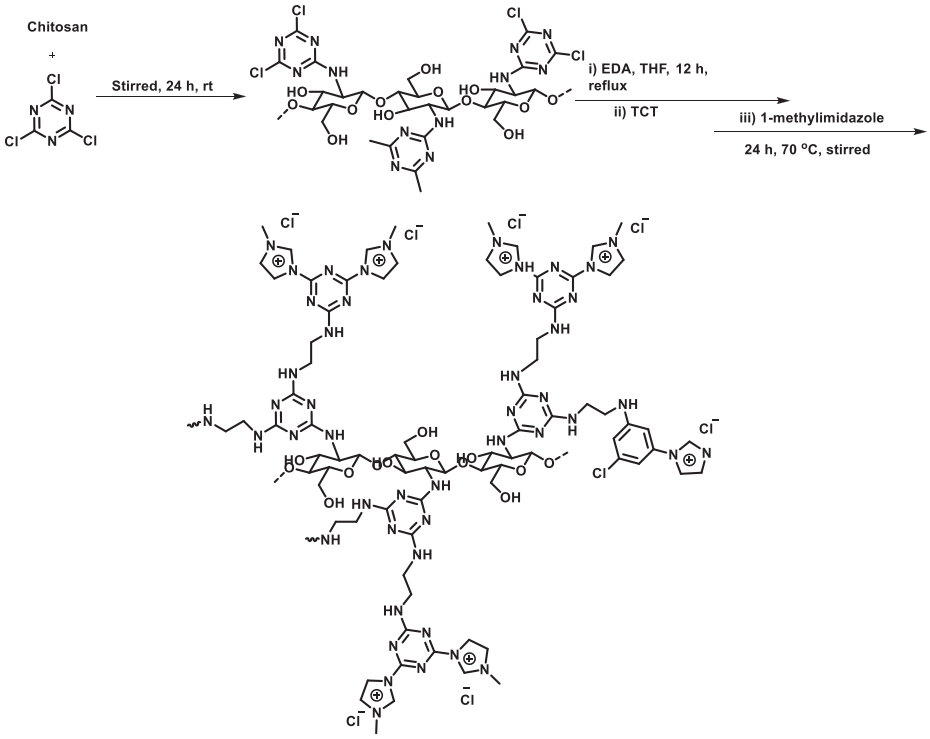


Figure 3.14: Synthesis of dendrimer-decorated chitosan-supported IL.

during the optimization of product yield and showed moderate conversions but excellent selectivities. However, amongst all the halides, it was CNT-HMImI which gave maximum value of turnover number possibly due to its highest nucleophilicity. Further, it was studied that on growing the alkyl chain length from one to four carbons in the attached ILs, carbonate conversion was improved. The authors predicted that on growing the size of alkyl chain makes the halide ions away from the imidazolium cation, which causes electrostatic attraction to gradually decrease between the anion and cation and their availability is accordingly increased. When compared with the other supports such as IL-grafted commercial silica, silicate MCM-41, polymer beads and even pristine CNT and oxidized CNT either the catalytic activity was low or even negligible (in case of pristine CNT and oxidized CNT). Hence, it was concluded that it was the joint effects of the immobilized IL and intrinsic properties of oxidized CNT support which maximized the epoxide yield. Some of those properties were well-defined nanostructure of the catalyst which enabled good dispersion and thereby promoted diffusion of reactants, surface hydroxyl and epoxide groups over the catalyst which acted as co-catalyst and marvelous conductivity which facilitated transfer of electrons during catalytic reaction. Apart from these advantages the catalyst was recyclable for over five runs.

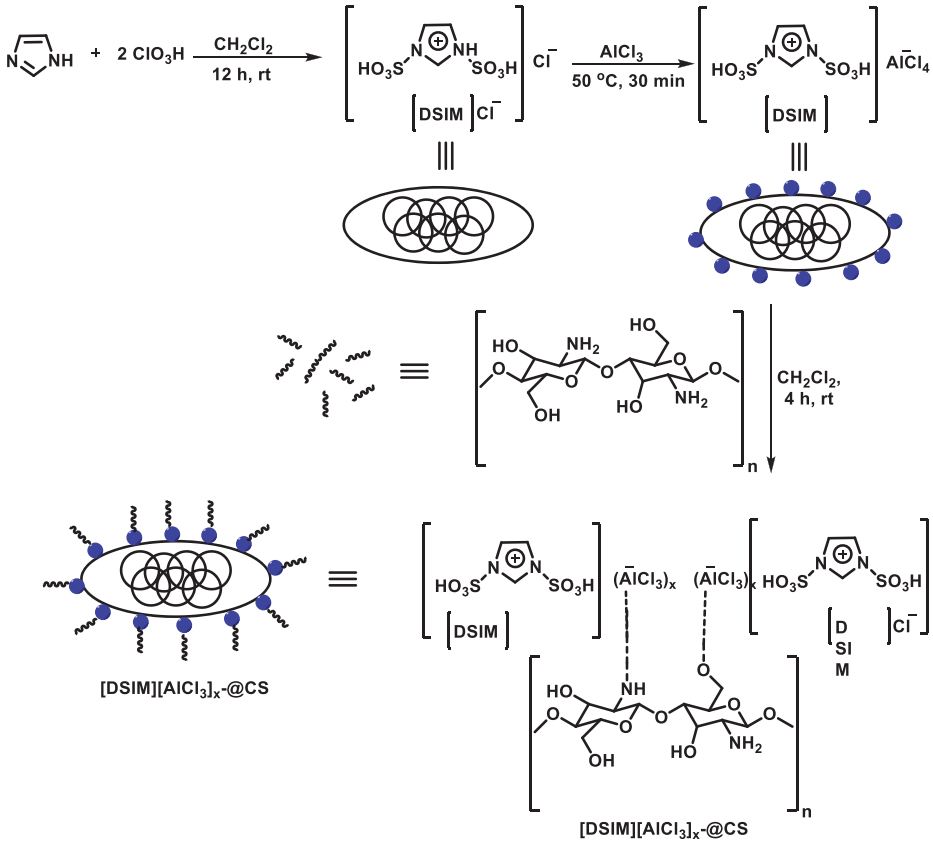


Figure 3.15: Synthesis of chitosan-supported IL.

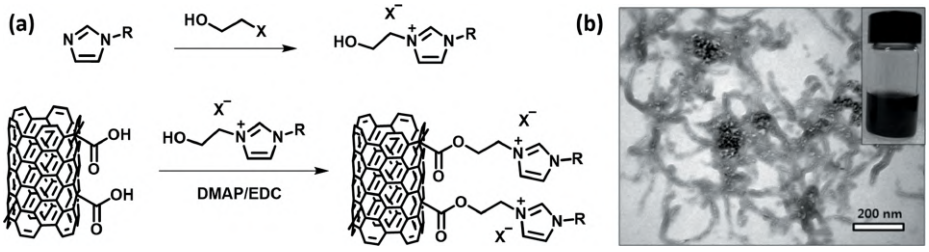


Figure 3.16: (a) Synthesis of CNT supported IL and (b) TEM image of CNT-HMImBr heterogeneous catalyst (reproduced with permissions from ref. [32]).

As described earlier, silica gel is another widely explored supports. Wu and coworkers [33] investigated silica gel-supported (3-sulfobutyl-1-(3-propyltriethoxysilane) imidazolium hydrogen sulfate dual acidic IL as catalyst (Figure 3.17). The characterization

of reported catalyst was performed using all important characterization techniques. The catalytic efficacy for immobilized IL and the free IL (1-butylsulfonate-3-methylimidazolium bisulfate, [MIM-BS][HSO_4^-]) was checked for the synthesis of polyoxymethylene dimethyl ethers (DMM) from methylal and trioxane. The authors reported that covalently bonded ionic liquids have performed excellent in contrast to [MIM-BS][HSO_4^-]. The effective catalyst amount was optimized in the work. The authors also mentioned that IL acid content was a major factor responsible for the good catalytic activity.x

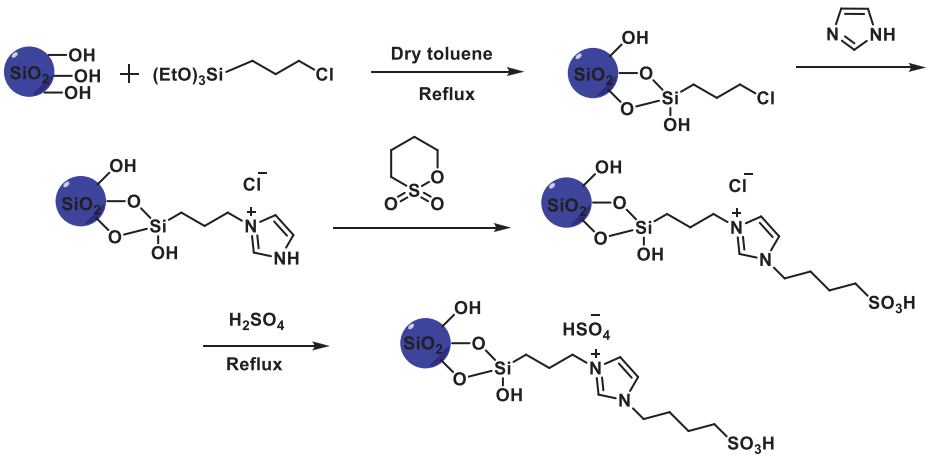


Figure 3.17: Synthesis of silica gel supported dual acidic ionic liquid (3-sulfobutyl-1-(3-propyltriethoxysilane) imidazolium hydrogen sulfate.

In continuation of utilizing silica as a support material, Zhang et al. [34] developed a series of Brønsted acidic ILs immobilized on hollow organosilica nanospheres as a support. Hollow organosilica nanospheres possess many usable properties such as excellent porosity and controlled interior and shell sizes. These properties led to high active sites distribution and thereby capable of exhibiting enhanced catalytic activity. Figure 3.18 depicts the schematic illustration for the synthesis of the above-said catalyst. Initially, toluene swollen Pluronic F127 micelle was reacted with 1,2-*bis*(trimethoxysilyl)ethane and 3-chloropropyltriethoxysilane, using a series of hydrolysis and condensation reactions, which was subsequently functionalized with IL precursors to impart IL over hollow nanospheres. The hollow structure is driven by F127 which acted as a structure-directing agent and toluene which acted as micelle-expanding agent. This immobilized IL catalyst was then used in fructose to 5-hydroxymethylfurfural and 5-ethoxymethylfurfural conversion using microwave irradiation. On one side the catalyst provided a nanoreactor space for conducting organic reaction, strong Brønsted acidity and surface hydrophobicity which increased the accessibility of acidic sites while on the other hand microwave coupling drastically reduced the high temperature and pressure requirement, provided

uniform temperature distribution and also diminished large time duration. The cooperative effect of both the above-mentioned factors resulted in improved catalytic activity and selectivity at a fast reaction rate. Also, connections between the IL site and supporting framework helped by preventing leaching acid as well as ensuring good reusability of the catalyst.

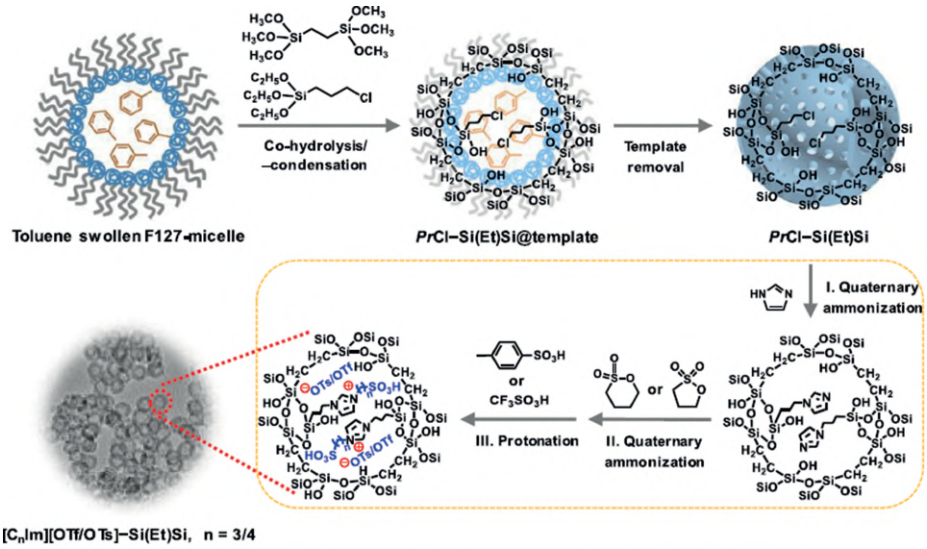


Figure 3.18: Schematic synthesis of Brønsted acidic IL functionalized hollow organosilica nanospheres using toluene swollen Pluronic F127 micelle (reproduced with permissions from ref. [34]).

To study the effect of support morphology on the distribution of immobilized IL, lately Yao and group members supported [1-(trimethoxysilyl)propyl-3-methylimidazolium] ionic liquid on three mesoporous silica materials (MCM-41, MSN and BMMs) having variable morphologies but similarly arranged mesopores with similar pore size [35]. The comparable studies were done by investigating the product yield obtained in the cycloaddition reaction of CO_2 with epoxides. Zn(II) functionality was also incorporated into the catalyst because of its role in promoting CO_2 fixation. All of the three silica supports were functionalized with Zn(II) followed by the addition of IL. SEM and TEM results presented a bulky morphology of MCM-41/Zn-IL, a well-dispersed nanosphere morphology of MSN/Zn-IL and an aggregated dispersion of spherical-shaped BMM/Zn-IL. When talked about distribution of ILs because of the long pore channel and bulkymorphology of MCM-41, grafting of Zn and IL mainly occurred on the outer surface and pore entrance, leading to blockage of pores. In case of MSN, grafting occurred inside the channels. In BMM, the aggregated particles and large accumulated pores led to both internal and external grafting (Figure 3.19). As a result of the above findings, MCM-41/Zn-IL showed minimum conversion percentage and the remaining two showed similar performances.

Hence, it was concluded that the morphology of support, on which immobilization of IL is being carried, out plays a vital role in promoting catalytic activity. Using these results, utilization of active sites in nanopores can be improved significantly.

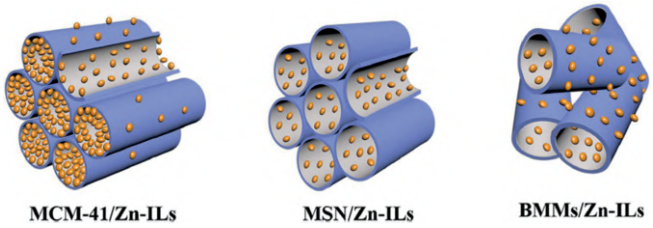


Figure 3.19: Distribution of supported IL on various mesoporous silica materials (reproduced with permissions from ref. [35]).

Out of the recently emerged supports, metal organic frameworks (MOFs) stand out amongst the rest because of their rich metal sites, tunable pore structure, flexible functionalities and large surface area. In recent years, apart from other useful applications, they are also being used as carriers to incorporate ILs. Chen et al. [36] modified MIL-101 (Cr) with an $–SO_3H$ functionalized IL for biodiesel production. To integrate the IL with MOF unit, authors used phosphotungstic acid (HPW) as a bridge (Figure 3.20). HPW was first infused inside the cages of MIL-101 (Cr) and then the $–SO_3H$ functionalized IL was introduced into the cavities through anion exchange. Reactants diffusion and easy access to active sites were some of the major contributions of the hybrid composite toward high conversion percentage. Besides, synergistic effect of Brønsted acid functionalities present in IL, Lewis acidic MIL-101 (Cr) and polyoxometalate anions were the key entities which accelerated the reaction between oleic acid and methanol (biodiesel synthesis). The catalyst also imparted reusability for five successive runs.

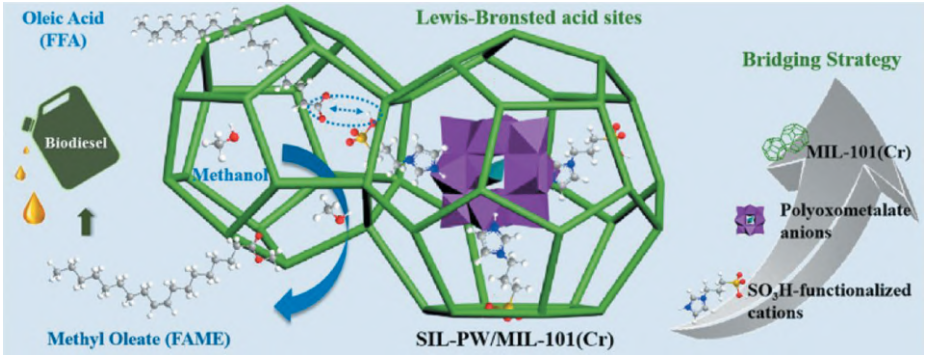


Figure 3.20: Use of MIL-101 (Cr) supported acid functionalized IL for biodiesel production (reproduced with permissions from ref. [36]).

Lately, covalent organic frameworks (COF) have evolved as a novel class of porous organic materials with widely utility in catalysis, gas storage, adsorption, sensing and various different useful applications [37, 38]. These are composed of H, B, C, N and O lighter elements, which are connected by robust covalent bonds including condensation of 2D and 3D organic building precursors and have hydrogen bonding and π–π stacking interactions. They have low densities, long-range ordered crystalline structure, and better chemical stability. Besides, large specific surface area, high porosity and controllable pore-size help in easy and speedy diffusion of reactants/products in/out from the skeleton. Considering the above benefits of COF in heterogeneous catalysis [39] and their immense capability toward CO_2 uptake, Du et al. supported poly(IL) on COF for the epoxides synthesis using cycloaddition of CO_2 [40]. Figure 3.21 shows the preparation of such hybrid material. It initially involves a hard template methodology wherein the COF precursors, 1,3,5-triformylphloroglucinol (Tp) and benzidine (BD) were condensed using *p*-toluenesulfonic acid (acted as catalyst) and polystyrene spheres (used as hard template). Further via free radical polymerization, reaction of the above porous support and linear vinyl IL yielded PIL-HPCOF hybrid. Figure 3.22 clearly depicts the porous morphology of PIL-HPCOF-320-10-100, wherein 320 indicates average diameter of PSs, 10 indicates mass fraction of PSs and 100 denotes mass of ILs monomer added. The hybrid catalyst displayed excellent catalytic performance with high yields of cyclic carbonates and broad substrate scope. The catalyst also offered high catalytic reusability without significant loss of catalytic activity.

The advantages of using magnetic supports have already been discussed in the previous section. Considering the rising number of publications in this area and in progression of our work on the design and synthesis of silica-based organic–inorganic hybrid nanocatalysts for various chemical transformations, we have also compiled the utility of using magnetically supported ILs for the execution of organic synthesis in a recent review article [41]. Table 3.1 depicts a few of such works and the kind of reaction for which they have been used for.

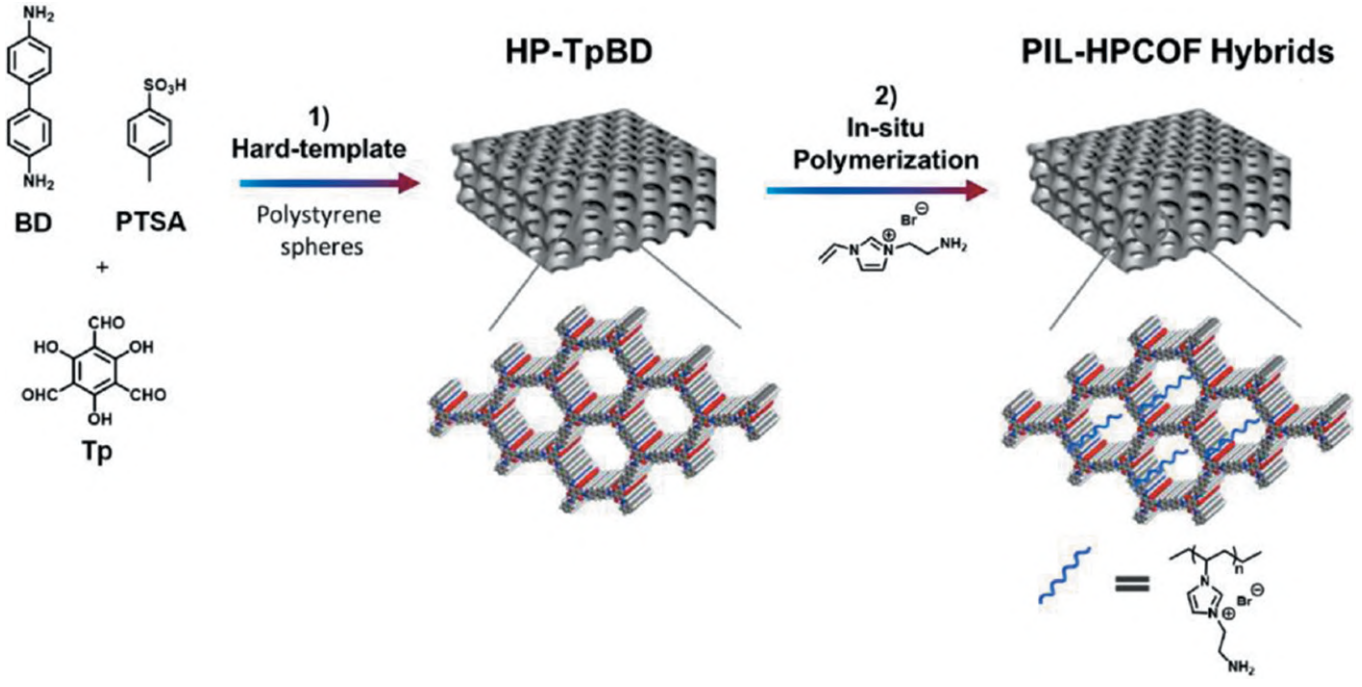


Figure 3.21: Schematic illustration for the synthesis of PI-HPCOF hybrids (reproduced with permissions from ref. [40]).

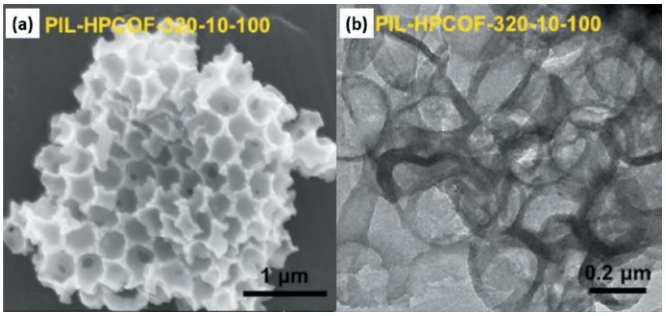
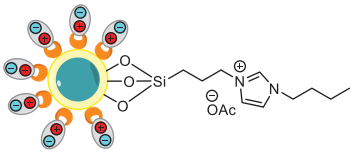
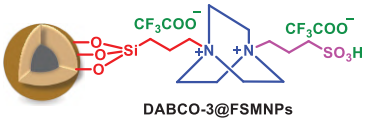
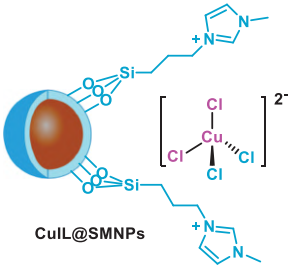


Figure 3.22: (a) SEM and (b) TEM image of PIL-HPCOF-320-10-100 (reproduced with permissions from ref. [40]).

Table 3.1: Some examples of recently developed silica-coated magnetic nanoparticles supported ILs as catalysts for various organic transformations.

Catalyst	Reaction performed	Characteristic features	Ref.
 IL-OAc@FSMNP (⊖ = acetate)	*N*-aryl oxazolidin-2-ones synthesis using coupling of anilines and ethylene carbonate	Excellent conversion and selectivity percentage, under metal-, solvent-, ligand-free conditions, nontoxic reactants, water as only byproduct, less reaction time, low amount of catalyst, large substrate scope and reused for eight runs	[42]
 DABCO-3@FSMNPs	Bioactive 3,3-di(indolyl) indolin-2-ones synthesis via pseudo three-component reaction	Better yields, ecofriendly and simple conditions, water as solvent, wide substrate scope, low catalyst amount and reused for eight runs	[43]
 CuIL@SMNPs	Tandem cyclization and oxidative synthesis of 2-phenylquinazolin-4(3*H*)-ones *viao*-aminobenzamide and benzaldehydes reaction	Ecofriendly solvent, gentle reaction conditions, reduced reaction times, broad substrate scope with excellent yields and without any additional purification, reused for six runs	[44]

3.3 Conclusions

The chapter thoroughly discussed the role of immobilized ionic liquids as support for different catalysts and as catalysts themselves. The chapter fully justified that ILs are not only finest and ecofriendly solvents but they can be excellent materials for catalytic applications as well. These are versatile, can be manipulated easily by scientists to use in different ways of catalysis and have capability to support other entities. However, when they are combined with other heterogeneous supports, their properties are further enhanced; most importantly their recoverability and recyclability become easy and efficient. The chapter tried to exemplify most of the recent supports that are being utilized for the immobilization of ILs such as different kinds of silica, chitosan, carbon nanotubes, polymers, MOFs, COF and even magnetic nanoparticles. Each support provides its own benefits and special characteristics to the immobilized IL which ultimately helped in enhancing the catalytic performance. In the near future, it is anticipated that supported ILs will emerge as excellent and potent tool for effective, efficient and ecofriendly synthetic conventions.

References

[1] Rogers, RD, Seddon, KR. Ionic liquids: Industrial applications for green chemistry. Washington DC: American Chemical Society, 2002.
[2] Seddon, KR. A taste of the future. Nat Mater 2003, 2, 363–365.
[3] Wasserscheid, P, Welton, T. Ionic liquids in synthesis, 2nd edn. Germany: Wiley-VCH, 2007.
[4] Shiflett, MB. Commercial applications of ionic liquids. Switzerland: Springer International Publishing, 2020.
[5] Lei, Z, Chen, B, Koo, Y-M, MacFarlane, DR. Introduction: Ionic liquids. Chem Rev 2017, 117, 6633–6635.
[6] Welton, T. Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev 1999, 99, 2071–2084.
[7] Welton, T. Ionic liquids in catalysis. Coord Chem Rev 2004, 248, 2459–2477.
[8] Chakraborti, AK, Roy, SR. On catalysis by ionic liquids. J Am Chem Soc 2009, 131, 6902–6903.
[9] Vekariya, RL. A review of ionic liquids: Applications towards catalytic organic transformations. J Mol Liq 2017, 227, 44–60.
[10] Zhang, P, Wu, T, Han, B. Preparation of catalytic materials using ionic liquids as the media and functional components. Adv Mater 2014, 26, 6810–6827.
[11] Wu, B, Liu, W, Zhang, Y, Wang, H. Do we understand the recyclability of ionic liquids? Chem Eur J 2009, 15, 1804–1810.
[12] Valkenberg, MH, deCastro, C, Hölderich, WF. Immobilisation of ionic liquids on solid supports. Green Chem 2002, 4, 88–93.
[13] Xin, B, Hao, J. Imidazolium-based ionic liquids grafted on solid surfaces. Chem Soc Rev 2014, 43, 7171–7187.
[14] Campisciano, V, Giacalone, F, Gruttadauria, M. Supported ionic liquids: A versatile and useful class of materials. Chem Rec 2017, 17, 918–938.
[15] Zhang, S, Zhang, J, Zhang, Y, Deng, Y. Nanoconfined ionic liquids. Chem Rev 2017, 117, 6755–6833.

[16] Haumann, M, Dentler, K, Joni, J, Riisager, A, Wasserscheid, P. Continuous gas-phase hydroformylation of 1-butene using supported ionic liquid phase (SILP) catalysts. Adv Synth Catal 2007, 349, 425–431.
[17] Shi, F, Zhang, Q, Li, D, Deng, Y. Silica-gel-confined ionic liquids: A new attempt for the development of supported nanoliquid catalysis. Chem Eur J 2005, 11, 5279–5288.
[18] Giacalone, F, Gruttadauria, M. Covalently supported ionic liquid phases: An advanced class of recyclable catalytic systems. Chem Cat Chem 2016, 8, 664–684.
[19] Luska, KL, Julis, J, Stavitski, E, Zakharov, DN, Adams, A, Leitner, W. Bifunctional nanoparticle–SILP catalysts (NPs@SILP) for the selective deoxygenation of biomass substrates. Chem Sci 2014, 5, 4895–4905.
[20] Luza, L, Gual, A, Rambor, CP, Eberhardt, D, Teixeira, SR, Bernardi, F, Baptista, DL, Dupont, J. Hydrophobic effects on supported ionic liquid phase Pd nanoparticle hydrogenation catalysts. Phys Chem Chem Phys 2014, 16, 18088–18091.
[21] Shaikh, NM, Sawant, AD, Bagihalli, GB, Challa, M, Adimule, VM. Highly active mixed Au–Pd nanoparticles supported on RHA silica through immobilised ionic liquid for Suzuki coupling reaction. Top Catal 2022.
[22] Shaikh, NM, Adimule, V, Bagihalli, GB, Keri, RS. A novel mixed Ag–Pd nanoparticles supported on SBA silica through [DMAP-TMSP-DABCO]OH basic ionic liquid for Suzuki coupling reaction. Top Catal 2022.
[23] Li, Y, Song, S, Sadeghzadeh, SM. Ruthenium nanocatalysts immobilized on DFNS-IL heterogeneous catalyst for hydroformylation of alkenes with CO_2 and H_2. Catal Lett 2023, 153, 95–103.
[24] Sadjadi, S, Koohestani, F. Pd on imidazolium ionic liquid modified halloysite: A potent catalyst for the hydrogenation of nitro-compounds under mild reaction condition. Inorg Chem Commun 2022, 137, 109205.
[25] Doherty, S, Knight, JG, Backhouse, T, Tran, TST, Paterson, R, Stahl, F, Alharbi, HY, Chamberlain, TW, Bourne, RA, Stones, R, Griffiths, A, White, JP, Aslam, Z, Hardare, C, Daly, H, Hart, J, Temperton, RH, O'Shea, JN, Rees, NH. Highly efficient and selective aqueous phase hydrogenation of aryl ketones, aldehydes, furfural and levulinic acid and its ethyl ester catalyzed by phosphine oxide-decorated polymer immobilized ionic liquid-stabilized ruthenium nanoparticles. Catal Sci Technol 2022, 12, 3549–3567.
[26] Gawande, MB, Monga, Y, Zboril, R, Sharma, RK. Silica-decorated magnetic nanocomposites for catalytic applications. Coord Chem Rev 2015, 288, 118–143.
[27] Sharma, RK, Dutta, S, Sharma, S, Zboril, R, Varma, RS, Gawande, MB. Fe_3O_4 (iron oxide)-supported nanocatalysts: Synthesis, characterization and applications in coupling reactions. Green Chem 2016, 18, 3184–3209.
[28] Rajabzadeh, M, Najdi, N, Zarei, Z, Khalifeh, R. CuI immobilized on tricationic ionic liquid anchored on functionalized magnetic hydrotalcite (Fe_3O_4/HT-TIL-CuI) as a novel, magnetic and efficient nanocatalyst for Ullmann-type C–N coupling reaction. J Inorg Organomet Polym Mater 2022, 32, 2696–2711.
[29] Gholinejad, M, Zareh, F, Sheibani, H, Nájera, C, Yus, M. Magnetic ionic liquids as catalysts in organic reactions. J Mol Liq 2022, 367, 120395.
[30] Sadjadi, S, Koohestani, F, Heravi, MM. Fabrication of a metal free catalyst for chemical reactions through decoration of chitosan with ionic liquid terminated dendritic moiety. Sci Rep 2020, 10, 19666.
[31] Patel, GM, Kure, AS, Mandawad, GG, Hote, BS, Konda, SG. Chitosan supported ionic liquid (CSIL): An excellent catalyst for one-pot synthesis of bis(indolyl)methanes. Results Chem 2022, 4, 100436.
[32] Han, L, Li, H, Choi, S-J, Park, M-S, Lee, S-M, Kim, Y-J, Park, D-W. Ionic liquids grafted on carbon nanotubes as highly efficient heterogeneous catalysts for the synthesis of cyclic carbonates. Appl Catal A 2012, 429–430, 67–72.

[33] Wu, Y, Li, Z, Xia, C. Silica-gel-supported dual acidic ionic liquids as efficient catalysts for the synthesis of polyoxymethylene dimethyl ethers. Ind Eng Chem Res 2016, 55, 1859–1865.
[34] Zhang, Q, Ren, M, Liu, Y, Zhang, C, Guo, Y, Song, D. Fabrication of Brønsted acidic ionic liquids functionalized organosilica nanospheres for microwave-assisted fructose valorization. Sci Total Environ 2022, 818, 151761.
[35] Yao, J, Sheng, M, Bai, S, Su, H, Shang, H, Deng, H, Sun, J. Ionic liquids grafted mesoporous silica for chemical fixation of CO_2 to cyclic carbonate: Morphology effect. Catal Lett 2022, 152, 781–790.
[36] Chen, C, Wang, F, Li, Q, Wang, Y, Ma, J. Embedding of SO_3H-functionalized ionic liquids in mesoporous MIL-101(Cr) through polyoxometalate bridging: A robust heterogeneous catalyst for biodiesel production. Colloids Surf A 2022, 648, 129432.
[37] Sharma, RK, Yadav, P, Yadav, M, Gupta, R, Rana, P, Srivastava, A, Zbořil, R, Varma, RS, Antonietti, M, Gawande, MB. Recent development of covalent organic frameworks (COFs): Synthesis and catalytic (organic-electro-photo) applications. Mater Horiz 2020, 7, 411–454.
[38] Yadav, P, Yadav, M, Gaur, R, Gupta, R, Arora, G, Srivastava, A, Goswami, A, Gawande, MB, Sharma, RK. Chemistry of magnetic covalent organic frameworks (MagCOFs): From synthesis to separation applications. Mater Adv 2022, 3, 1432–1458.
[39] Yadav, P, Gupta, R, Arora, G, Srivastava, A, Sharma, RK. Synthesis of phenol esters by direct C–H activation of aldehydes using a highly efficient and reusable copper-immobilized polyimide covalent organic framework (Cu@PI-COF). New J Chem 2022, 46, 4715–4723.
[40] Du, Y-R, Yang, X, Wang, Y-F, Guan, P-X, Wang, R, Xu, B-H. Immobilization poly(ionic liquid)s into hierarchical porous covalent organic frameworks as heterogeneous catalyst for cycloaddition of CO_2 with epoxides. Mol Catal 2022, 520, 112164.
[41] Gupta, R, Yadav, M, Gaur, R, Arora, G, Yadav, P, Sharma, RK. Magnetically supported ionic liquids: A sustainable catalytic route for organic transformations. Mater Horiz 2020, 7, 3097–3130.
[42] Gupta, R, Yadav, M, Gaur, R, Arora, G, Sharma, RK. A straightforward one-pot synthesis of bioactive N-aryl oxazolidin-2-ones *via* a highly efficient Fe_3O_4@SiO_2-supported acetate-based butylimidazolium ionic liquid nanocatalyst under metal- and solvent-free conditions. Green Chem 2017, 19, 3801–3812.
[43] Gupta, R, Yadav, M, Gaur, R, Arora, G, Rana, P, Yadav, P, Adholeya, A, Sharma, RK. Silica-coated magnetic-nanoparticle-supported DABCO-derived acidic ionic liquid for the efficient synthesis of bioactive 3,3-di(indolyl)indolin-2-ones. ACS Omega 2019, 4, 21529–21539.
[44] Gupta, R, Arora, G, Yadav, P, Dixit, R, Srivastava, A, Sharma, RK. A magnetically retrievable copper ionic liquid nanocatalyst for cyclooxidative synthesis of 2-phenylquinazolin-4(3*H*)-ones. Dalton Trans 2021, 50, 890–898.

Avtar Singh, Nirmaljeet Kaur, Rohini, Anupama Parmar, Payal Malik and Harish Kumar Chopra*

Chapter 4
Recent updates on chiral ionic liquid–mediated asymmetric organic synthesis

4.1 Introduction

Ionic liquids (ILs), often called as liquid salts or ionic melts, consist of a cluster of compounds having anions and cations and are liquid at room temperature (melting point < 100 °C). The physical properties of ILs can be tuned by changing the nature of ionic moieties present in a particular IL; this led to the synthesis of tailored ILs. ILs exhibit a wide range of applications including electrolytes (batteries), biotechnology, LCD, analytical chemistry and also in liquid–liquid extractions. Moreover, ILs are replacing conventional organic solvents in organic reactions due to their nonvolatile nature. So the research related to synthesis and application of ILs gained considerable acceleration in the past two decades as evident from plethora of reports published over the period [1–5]. Among the various classes of ILs, chiral ionic liquids (CILs) are those which have some sort of chirality in their structure and can be used to induce asymmetry. CILs can be prepared chiral pool or by using asymmetric synthesis methodologies, the synthetic procedures have already been reviewed and we will not discuss the synthesis of CILs in this chapter. CILs are employed as catalysts and solvents to carry out asymmetric reactions and can also be used as chiral discriminators [6, 7]. Moreover, CILs can also be used as stationary phase or chiral additives in separation techniques of chiral compounds such as liquid chromatography, gas chromatography and capillary electrophoresis [8–10]. CILs can also be utilized in some other important fields like optical differentiation of racemic mixtures, chiral shifting reagents using NMR spectroscopy, fluorescence spectroscopy, etc. [11]. We have reviewed in this chapter the role of CILs in some important asymmetric reactions such as reductions, Michael addition reaction, aldol condensation reaction and Diels–Alder reaction. The

*Corresponding author: Harish Kumar Chopra, Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal 148106, Distt. Sangrur, Punjab, India, e-mail: hk67@rediffmail.com
Avtar Singh, Payal Malik, Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal 148106, Distt. Sangrur, Punjab, India
Nirmaljeet Kaur, Rohini, Department of Chemistry, Baba Farid College, Bathinda, 151001, Punjab, India
Anupama Parmar, PG Department of Chemistry, M. M. Modi College, Patiala 147001, Punjab, India

https://doi.org/10.1515/9783110788129-004

most fascinating thing about the CIL catalysts is their recyclability without any dramatic change in catalytic efficiency or selectivity [12–14].

4.2 Applications in asymmetric synthesis and catalysis

4.2.1 Asymmetric reduction reactions

Asymmetric reduction reactions of C═O, C═N and C═C containing compounds are important for the preparation of organic compounds having frequent industrial applications specially in chemicals, pharmaceutics, fragrance and agrochemical industries [15, 16]. Metal (Ru, Rh, Ir) and organocatalysts as well as biocatalysts have been found to be efficient to deliver the high enantiomeric excess in these reactions [17, 18]. In case of metals, the chiral phosphine ligands such as BINAP are commonly used for asymmetric induction [19]. Besides phosphine ligands, some N–N and P–N ligands have also been reported in the literature [20].

Hajipour et al. [21] reported the use of nicotinium CILs for the asymmetric reduction of acetophenone derivatives using sodium borohydride as reducing agent. CIL (–)-*N*,*N*-dibutylnicotinium bromide was used to deliver chirality and a variety of acetophenone substrates **(1a–1p)** were reduced to secondary alcohols **(2a–ap)** affording moderate enantiomeric excess (*ee* = 24–65%) (Figure 4.1).

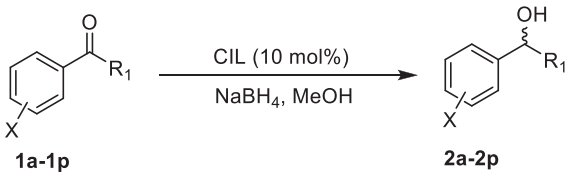


Figure 4.1: Asymmetric reduction of prochiral ketones using nicotinium-based CILs.

Just like the CIL **(3a)** they have also tested (–)-nicotine hydrogen tartrate salt **(3b)** in the reaction but the *ee* obtained was satisfactory (*ee* = 7–43%, Figure 4.1). The lower *ee* value obtained in this case may be because of the less solubility of the reactants in this salt which led to reduced interactions between chiral catalyst and reactants.

Singh and Chopra [22] reported the application of the benzimidazolium-based CILs derived from (–)-menthol (or borneol) in sodium borohydride reduction of some aromatic ketones (Figure 4.2). The CIL was recycled and reused for three cycles without noticeable change in activity or enantioselectivity. The *ee*% of the synthesized compounds was determined by using HPLC analysis (*ee* 6–92%). The authors proposed

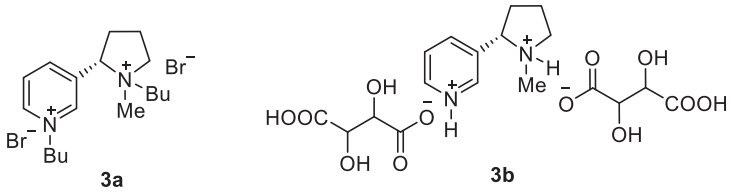


Figure 4.2: (**3a**) Nictonium-bromide-based CIL (**3b**) the CIL precursor.

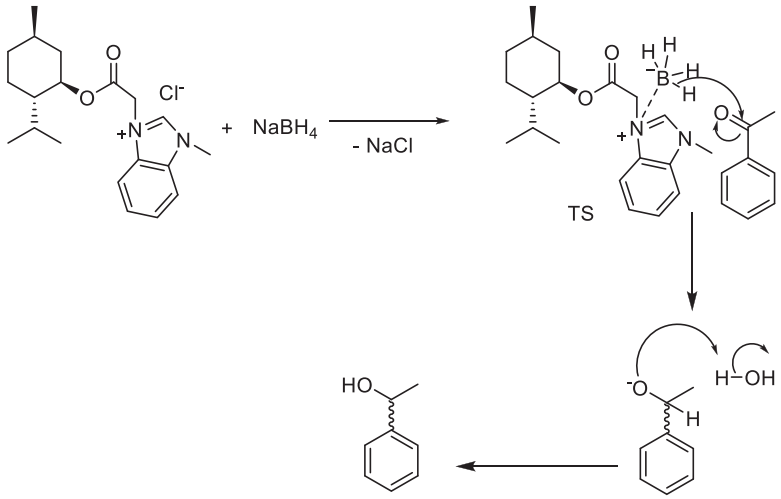


Figure 4.3: The proposed mechanism for the reduction reaction using menthol-based CILs.

a transition state showing ionic interactions between the substrates and CIL to deliver chiarlity (Figure 4.3).

This ionic intermediate can exist as the 10 mol% concentration of the CIL is sufficient to form ion pairs. The same group has synthesized a series of *S*-substituted-2-mercaptobenzthiazolium-based CILs for their application in asymmetric reduction of prochiral ketones. Using these CILs the *ee* was found to be higher than the previous case (up to 99% *ee* was obtained) [23].

Schulz et al. [24] reported another example of chirality transfer via ion pairing in imidazolium CILs containing cation and enantiomerically pure anion. The asymmetric reduction the cation produced enantiomers of this prochiral cation in 80% enantiomeric excess (*ee*) (Figure 4.4). As both the ions were chiral in this case, the enantioselectivity of the cation was determined by anion exchange with *bis*(trifluoromethylsulfonyl) imidate. The introduction of the achiral anion, the CIL was reacted with *R*-Mosher's acid chloride which leads to the formation of a diastereomeric complex with each other and in this way the enantiomeric excess (*ee*) was determined. Further, authors explained that the enantioselectivity decreases as the concentration of the substrate

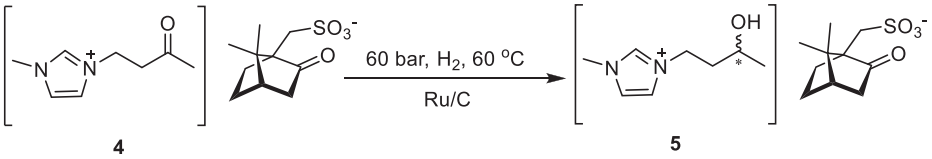


Figure 4.4: Chirality transfer in imidazolium CILs via ion pairing.

decreases in ethanol which leads to solvated ions. As a result, the formation of ion pairs in the solution diminishes and enantioselectivity decreases.

This group [25] further extended this work to synthesize more CILs having prochiral cations and bearing camphor sulfonate anion and the keto group of the cation in **6a–6c** was reduced to alcoholic group with high enantioselectivity (Figure 4.5). In this case the enantioselectivity of the products obtained was a function of the substrate concentration as already discussed in the previous report. Further, it was also observed that the *ee* decreases when water is used as solvent instead of ethanol as water weakens the ion pairing effect by dissociating the ions because of its polarity.

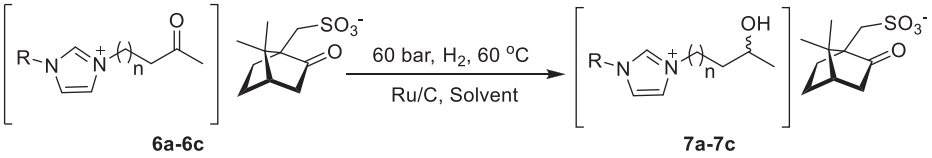


Figure 4.5: Transfer of chirality in imidazolium CILs through ion pairing.

Similarly, CILs based on ephedrine and having prochiral carboxylate anions (**8a–8b**) (Figure 4.6) were also reduced by the same group [26].

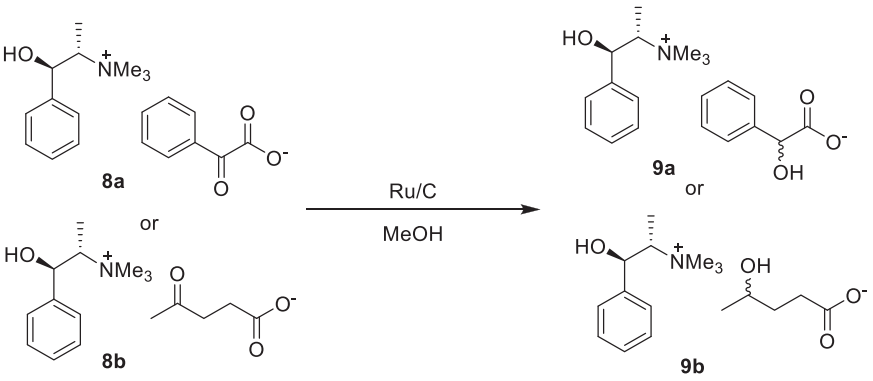


Figure 4.6: Chirality transfer in ephedrine-based CILs.

Vasiloiu et al. [27] reported amino alcohol-based CILs which can coordinate with Ru catalyst to deliver the enantioselectivity in reduction reaction of acetophenone **10** to give corresponding alcohol **11** (Figure 4.7).

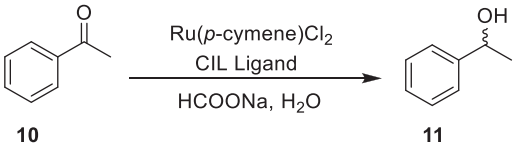


Figure 4.7: Asymmetric reduction of ketones derivatives using CIL ligand.

They compared the efficacy of the CILs and the neutral ephedrine-based ligand and observed that *ee* was higher in case of CILs (*ee* 68–75%) [28]. They expected a transition state **12** which is very similar to the conventional Ru (II) TS **13** (Figure 4.8).

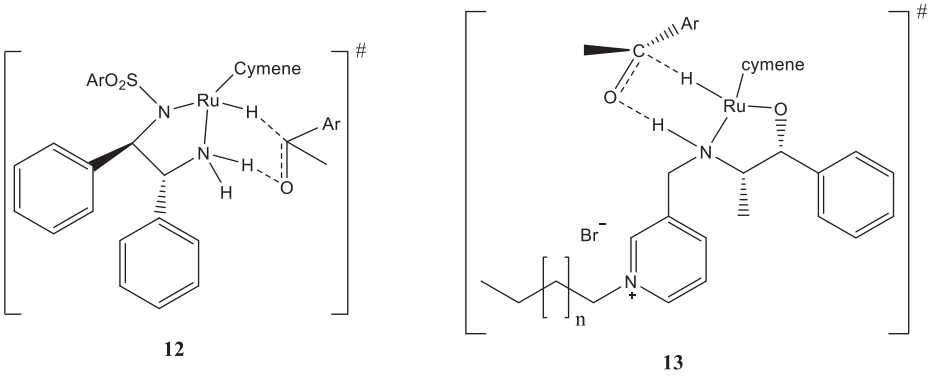


Figure 4.8: (**a**) Conventional Ru (II) TS; (**b**) TS in case of amino alcohol CILs.

Uchimoto et al. [29] prepared chiral ionic ligands which is similar to the chiral catalyst used in the hydrogenation reaction (Figure 4.9). The catalyst can be re-extracted from the reaction mixture and reused for five times. The results reflect that ionic ligand exhibit better activity than the conventional catalyst (Figure 4.10).

Kaur and Chopra [30] employed (*S*,*R*)-noscapine-based CILs as organocatalyst in the reduction of acetophenone and its derivatives (**18a–18f**) using $NaBH_4$ (Figure 4.11). Highest *ee* was obtained in case of PF_6^- than with BF_4^- and minimum with I^-.

Kaur and Chopra [31] also reported D-galactose-based CIL as a catalyst to prepare chiral secondary alcohols (**21a–21g**) from aromatic chiral ketones (**20a–20g**) in the presence of $NaBH_4$ shown in Figure 4.12.

Ferlin et al. [32] used *tetra*-butylammonium-based CILs having chiral anion derived from proline in asymmetric reduction of C=C double bonds. As depicted in Figure 4.13 the reduction of trimethyl cyclohexenol **22** was carried out with moderate *ee*. Among the

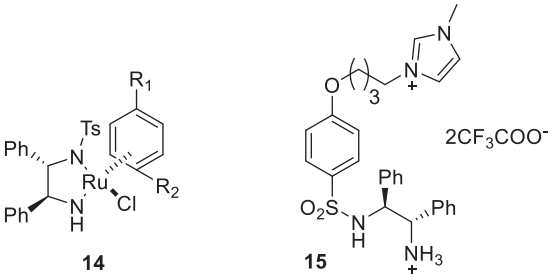


Figure 4.9: Conventional Ru complexes (**14**) and (**15**) ammonum-based chiral ionic ligand salts.

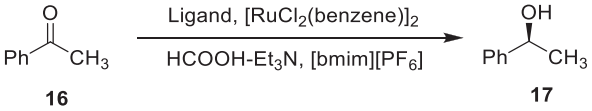


Figure 4.10: Enantioselective reduction of prochiral ketones using chiral ligands.

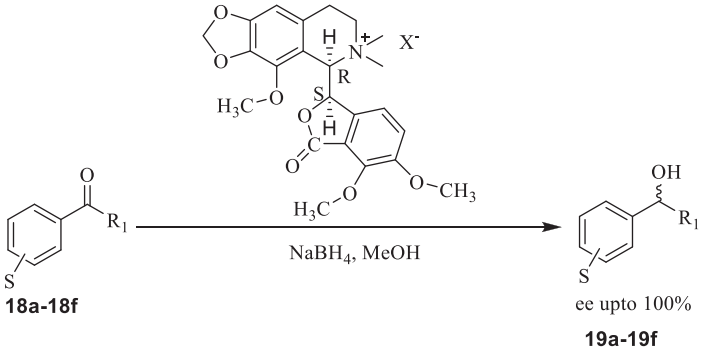


Figure 4.11: Reduction of acetophenone derivatives using noscapine-based CILs.

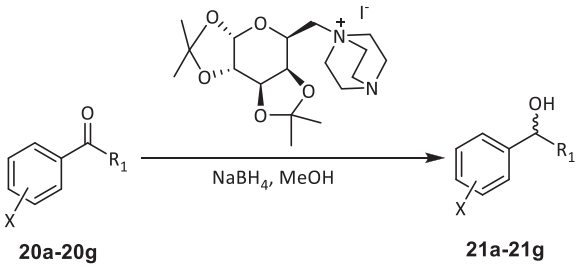


Figure 4.12: Carbohydrate-based CILs for asymmetric reduction of acetophenone derivatives.

various solvents, the maximum *ee* was obtained in isopropyl alcohol and no *ee* was obtained in case of water. This methodology was also used for the reduction of natural products and their analogs.

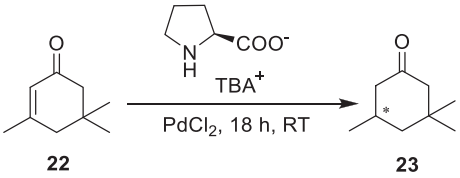


Figure 4.13: Reduction of double bond using tetrabutylammonium-based CILs with prolinate ion.

Schmitkamp et al. [33] employed amino acid-based ILs and achiral tropos ligands to carry out the asymmetric reduction reactions. In this protocol, the CILs were the only species to produce chirality. Enantioselective reduction of methyl-2-acetamidoacrylate and dimethyl itaconate (**24a–24b**) was carried out to obtain high yields and good stereoselectvity (Figure 4.14). The authors also found that the CIL derived more effective catalyst from proline as compared to the CIL derived from valine.

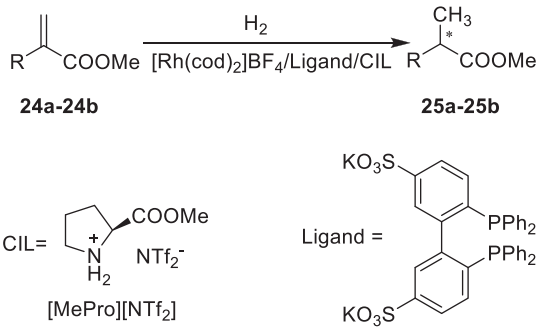


Figure 4.14: Enantioselective reduction of double bond using proline-based CILs.

Also, the same group established that the CILs can induce chirality in the presence of chiral as well as *rac*-BINAP ligands. Amino acid-based CIL [MePro][NTf_2] was used along with the enantio pure as well as *rac*-BINAP ligand for the reduction of dimethyl itaconate and methyl *N*-acetamido acrylate, and it was observed that *R*-BINAP gave *R*-stereoisomer; *S*-BINAP gave *S*-stereoisomer and *rac*-BINAP also gave *S*-product. So, even in the presence of *rac*-BINAP formation of product was solely through *S*-BINAP rhodium complex [34].

4.2.2 Michael addition reaction

Michael addition is widely used for C–C bond formation between different numerous compounds. Numerous organocatalysts have been designed for their application in this reaction; CILs also gained considerable attention in this direction. Wang et al. [35] employed imidazolium based salts for the enantioselective Michael addition of diethyl malonate to 1,3-diphenyl-prop-2-en-1-one in toluene (Figure 4.15). Although Michael adducts were obtained in remarkable yields but *ee* was very low (10–25%). Ou et al. [36] and Suzuki et al. [37] also tried another kind of imidazolium-based salt as an organocatalyst in the above reaction but *ee* was disappointing again (up to 15% *ee*).

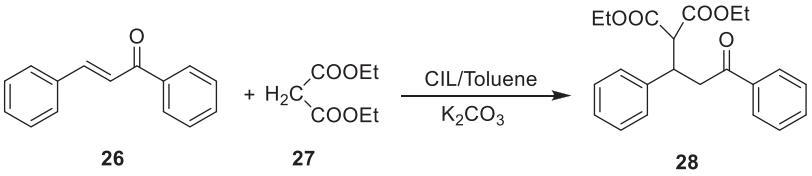


Figure 4.15: Michael addition reaction of diethyl malonate with 1,3-diphenyl-prop-2-en-1-one.

Jayachandra et al. [38, 39] tested some carbohydrate-based CILs in the Michael addition reaction between chalcones and diethylmalonate but ends up with low-to-moderate enantioselectivity only. Sun et al. [40] tested the catalytic potential of pyrrolidine-based CIL in the asymmetric Michael addition of cyclohexanone to *trans*-nitrostyrenein DMSO in the presence of chiral catalyst (Figure 4.16). This catalytic system shows good stereoselectivity and was recovered from the reaction mixture and reused but the catalytic efficacy decreases in successive cycles. Luo et al. [41] reported alkyl chain carried imidazolium-based surfactant-type ILs having pyrrolidine moiety to catalyze asymmetric Michael addition reaction of substrates cyclohexanone to nitrostyrenes. This catalytic system was found to deliver high *ee* in aqueous medium. Li et al. [42] used silica supported pyrrolidine-based CIL as organo-catalyst the same reaction and obtained high enantioselectivity by loading 10 mol% catalyst. Moreover, due to heterogeneous nature of this catalyst, it was reused for five times without any marked failure in its performance. Nobuoka et al. [43] in 2014 described the application of proline pyrrolidine-based recyclable CIL derived from (*S*)-for asymmetric Michael addition reaction and obtained excellent enantioselectivities (up to 95% *ee*) and diastereoselectivities (syn/anti 96/4). Similarly, Liu et al. [44] used functionalized chiral ionic liquids (FCIL) organocatalyst derived from L-proline in asymmetric Michael reaction of cyclohexanone with alkyl as well as aryl nitroolefins. The conversion and *ee* were excellent in this case and catalyst was reused for six times without any loss in its activity and selectivity.

Li et al. [45] used polymer-based CIL immobilized with pyrrolidine organocatalyst in enanioselective Michael addition under neat condition. Asymmetric Michael addition

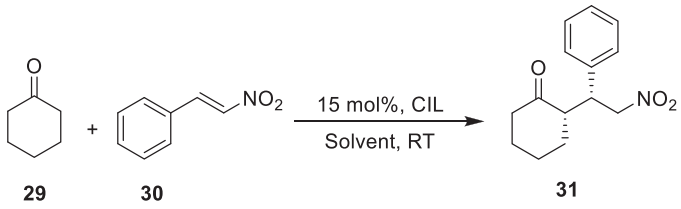


Figure 4.16: Michael addition of cyclohexanone to nitrostyrene using CIL.

of variety of aldehyde/ketone substrates to the nitrostryenes has been studied to analyze its catalytic activity (Figure 4.17). The catalyst was recycled for eight times.

Xu et al. [46] used DABCO-pyrrolidine CIL in asymmetric Michael addition reaction of numerous carbonyl compounds to nitroolefins. Almost quantitative yields and excellent stereocontrol (up to 97% *ee*; up to 99/1 *dr*) has been observed. Further, the catalyst system was reused for six times without any loss in its catalytic efficacy.

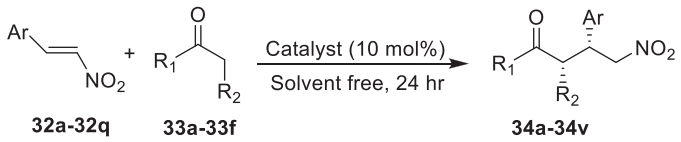


Figure 4.17: Asymmetric Michael addition of carbonyl compounds to nitroolefins using CILs.

Luo et al. [47] used FCIL-containing imidazolium or benzimidazolium in enantioselective desymmetrizations of some prochiral ketones via Michael addition reaction using TFA or salicylic acid as additives (Figure 4.18).

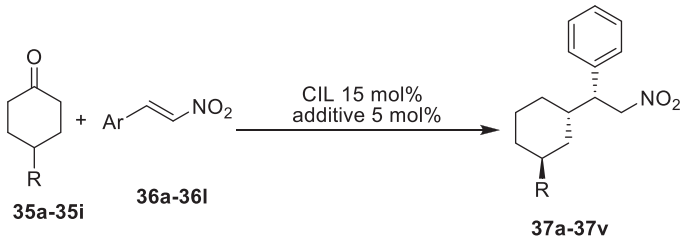


Figure 4.18: Desymmetrization of prochiral ketones via Michael addition reaction in CIL.

Ni et al. [48] demonstrated the use of pyrrolidine-derived chiral imidazolium ionic liquids in asymmetric Michael addition of aldehydes and nitrostyrenes (Figure 4.19).

The derived catalyst was reused twice and was found to deliver high *ee* but lower yields. Same group has used pyrrolidine-based FCILs for the asymmetric Michael addition reaction involving various aldehydes and nitrostyrenes derivatives to get the

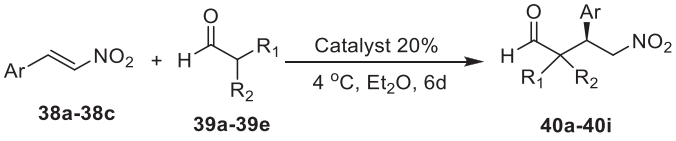


Figure 4.19: Michael addition of aldehydes to nitrostyrenes using imidazolium-based CILs.

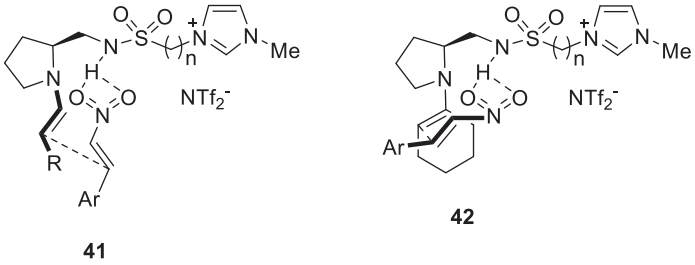


Figure 4.20: H-bonding activation by imidazole ionic liquids bearing an *N*-(pyrrolidine-2ylmethyl) sulfonamide moiety.

addition product in good enantioselectivities (up to 85% *ee*), and high diastereoselectivities (*syn*/*anti* ratio up to 97:3).

As shown in Figure 4.20, the reaction proceeds via enanmine intermediate and the CIL catalyst activates the nitrostyrene derivatives through H-bonding [49].

Kucherenko et al. [50] used (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine derivative modified with an *N*-(4-carboxybutyl)imidazolium cation and PF_6^- anion CIL as an organocatalyst for the asymmetric 1,4-conjugate addition of 4-hydroxy-2*H*-chromen-2-one to 1-substituted buten-3-ones or cyclohexen-3-one to afford corresponding Michael adducts in excellent yields and high enantioselectivities (up to 90% *ee*). This catalyst was reused five times without any loss in its catalytic activity (Figure 4.21).

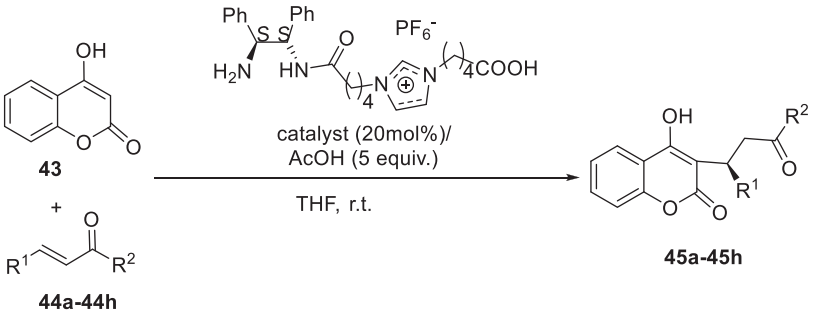


Figure 4.21: Asymmetric 1,4-conjugate addition of 4-hydroxy-2*H*-chromen-2-one to 1-substituted buten-3-ones or cyclohexen-3-one.

4.2.3 Asymmetric aldol reaction

Asymmetric aldol reaction is most fundamental reaction to construct C–C bond in an enantioselective manner. The enantiopure β-hydroxyketones thus produced can be used as building blocks in the synthesis of natural products and other important compounds [51, 52]. Miao et al. [53] in 2006 reported the ionic liquids supported (*2S,4R*)-4-hydroxyproline as an organo-catalyst for asymmetric aldol reactions of a number of aldehydes and ketones (Figure 4.22).

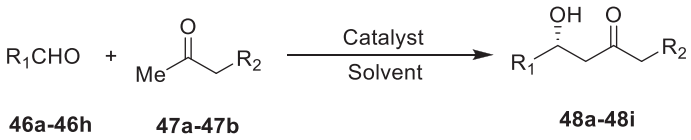


Figure 4.22: Asymmetric aldol reaction using CIL.

From low-to-high enanto-selectivity was observed and catalyst was reused to analyze the efficiency of the catalyst. Zhou et al. [54] synthesized an imidazolium-based CIL having camphor sulfonic acid anion. This CIL was used as an additive to improve the optical yield of L-proline-based CIL in asymmetric aldol reactions of cyclohexanone with 4-nitrobenzaldehyde (Figure 4.23). Almost quantitative yields and good enantioselectivity (94% *ee*) was obtained by using 5 eq. of CIL.

Zhang et al. [55] also reported the proline-based CIL to boost the stereoselectivity in asymmetric aldol reactions catalyzed by L-proline. In this procedure, CIL additive (10 mol%) was used to enhance the yield and *ee* of the reaction. Similarly, Zhang et al. [56] also performed the asymmetric aldol reaction between substituted benzaldehydes and cyclohexanone using FCIL (doubly chiral or *bis*-functional) but in this case only moderate enantioselectivities have been obtained.

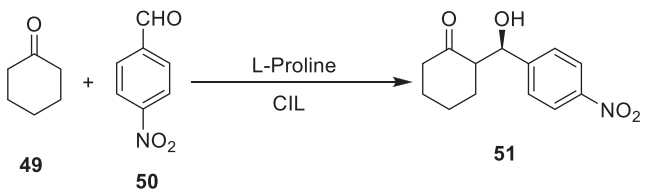


Figure 4.23: Asymmetric aldol condensation using FCIL.

Gonzalez et al. [57] used amino acid-based CILs as an additive or reaction medium in (*S*)-proline-mediated asymmetric aldol reaction (Figure 4.24). The CIL was able to deliver moderate enantioselectivity and has been reused for four times without any loss in its catalytic potential.

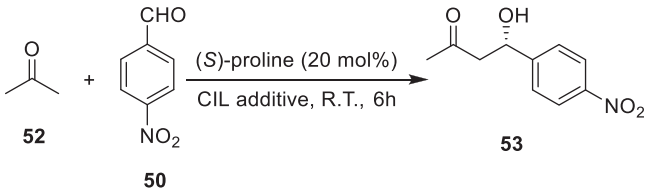


Figure 4.24: Asymmetric aldol reaction catalyzed by amino acid-based CILs.

Vasiloiu et al. [58] showed the potential of basic CILs extracted from (*S*)-proline to achieve acid-free enamine-organo-catalysis for enantioselective C–C bond construction. The aldol reaction between acetone derivatives and 4-nitrobenzaldehyde has been carried out using this catalyst (Figure 4.25). Very good yields and high *ee* (up to 80%) have been obtained and catalyst was recovered though its catalytic activity was affected.

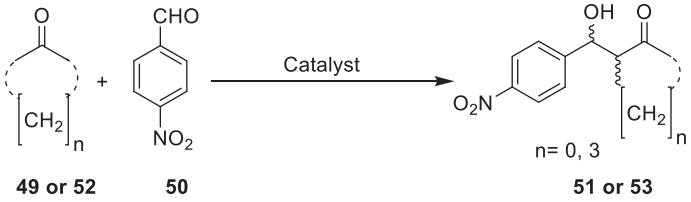


Figure 4.25: Enantioselective aldol reaction using (*S*)-proline-based CILs.

Kui and Guillen [59] reported the synthesis and organocatalytic activity of ionic liquid supported amino catalyst by the peptide coupling of proline on a ring-dialkylated histidine salt used as ionic support. The dipeptide catalyst was used in the enantioselective cross aldol reaction of some substituted benzaldehyde derivatives with acetone, in organic solvent as well as in ionic liquids, the yield and *ee* was found to be significantly higher in ionic liquids as compared to the organic solvents (Figure 4.26).

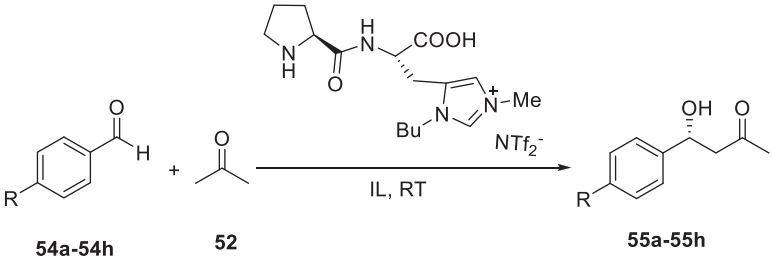


Figure 4.26: Aldol reaction mediated by ionic liquid-supported amino-catalyst.

Porcar et al. [60] explained the use of chiral imidazolium L-prolinate salts, having a complex network of spatial supramolecular interactions, have been tested as an efficient organo-catalyst for direct asymmetric aldol reactions at ambient temperature. The aldol products were obtained in high yield and enantioselectivities. The effect of the presence of chirality in both the cation and the anion on chirality transfer from the organo-catalyst to the aldol products has been thoroughly studied.

Zalewska et al. [61] recently reported that the CILs derived from amino acids (L-cysteine derivatives) have been synthesized and reported in the asymmetric aldol condensation of various aldehyde substrates with ketones. The best results were obtained for CILs composed of *S*-methyl-L-cysteine cation and *bis*(trifluoromethane)sulfonimide anion in the reaction of 2- or 4-nitrobenzaldehyde with acetone or cyclohexanone, giving the aldol product in good yields and very high *ee* values (up to 96%) (Figure 4.27).

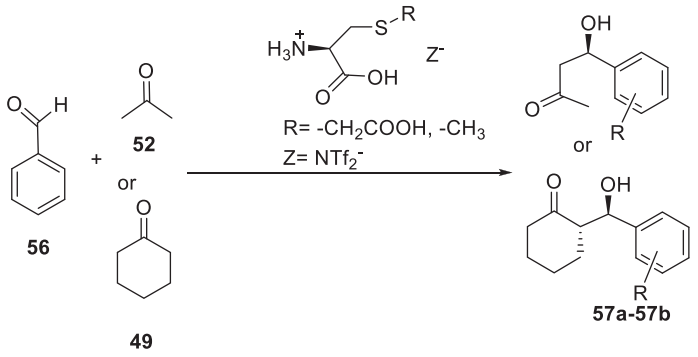


Figure 4.27: Aldol reaction catalyzed by CILs prepared from cysteine derivatives.

4.2.4 Other important reactions

Garre et al. [62] reported a new imidazolium-based bistereogenic salts as a solvent in asymmetric Baylis–Hillman reaction of aldehydes and acrylates and obtained in high yields although the optical yields were not that good (Figure 4.28).

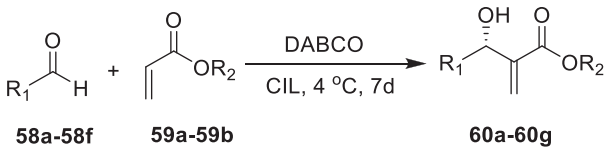


Figure 4.28: Asymmetric Baylis–Hillman reaction catalyzed by imidazolium-based CILs.

Rupini et al. [63] employed the recyclable ammonium-based CIL as a reducing agent as well as reaction medium in reductive amination of ketones to get the amines in high yields (Figure 4.29).

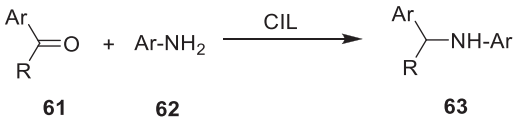


Figure 4.29: Asymmetric reductive amination using quaternary ammonium-based CIL.

Yadav et al. [64] carried out stereoselective synthesis of polyfunctionalized perhydropyrimidines via Biginelli protocol using amino acid-based CILs (Figure 4.30). A wide variety of perhydropyrimidines were obtained with high yields (up to 93%) and enantioselectivities (95% *ee*).

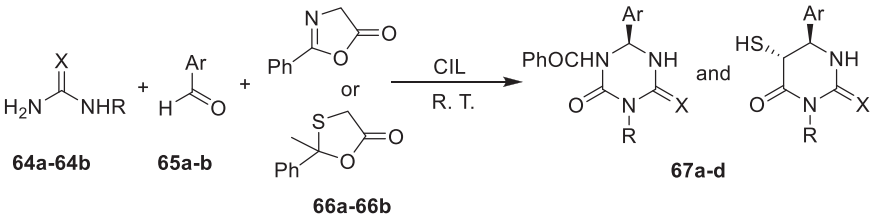


Figure 4.30: Enantioselective Biginelli reaction catalyzed by CILs.

Ahmadkhani et al. [65] in 2019 defined the synthesis of new CIL by the neutralization reaction between (1*S*)-(+)-camphor-10-sulfonic acid and *N*,*N*-dimethyl-*n*-octylamine. This ionic liquid was used as efficient organo-catalyst in the multicomponent reaction between isatin derivatives, pyrimidine-4,6-diol and malononitrile/ethyl cyanoacetate to synthesize some spiro[indoline-3,5′-pyrano[2,3-d]pyrimidine] derivatives in a highly enantioselective manner (Figure 4.31).

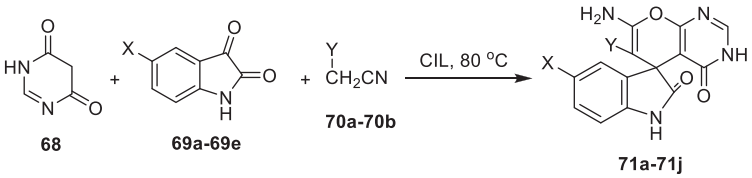


Figure 4.31: (1*S*)-(+)-camphor-10-sulfonic acid-based CIL catalyzed multicomponent reaction.

Zhang et al. [66] used the amino acid-derived CIL along with Co complex to carry out asymmetric reaction of epoxides and CO_2 (cycloaddition) (Figure 4.32). Moderate yields and high stereoselectivities were obtained with this catalytic system. Moreover, the catalyst system was reused for three times with almost same efficiency. Recently, this group also reported the imidazolium-based bifunctional CILs as co-catalyst in asymmetric cycloaddition of CO_2 to epoxides [67].

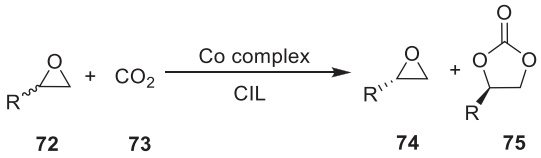


Figure 4.32: Asymmetric cycloaddition reaction using imidazolium-based bifunctional CILs.

Van Buu et al. [68] report the use of isosorbide-based CILs bearing imidazolium moiety in the asymmetric aza Diels–Alder reaction of diene with imines (Figure 4.33).

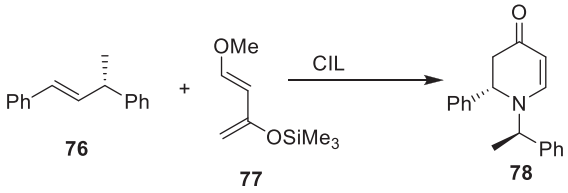


Figure 4.33: Asymmetric Diels–Alder reaction using carbohydrate-based CILs.

Zheng et al. [69] reported the use of 2-pyrrolidinecarboxylic acid-based CILs as an organocatalyst in asymmetric aza Diels–Alder reaction of wide variety of α,β-unsaturated ketones (Figure 4.34). This catalyst delivered very high yields (up to 93%) as well as excellent enantioselectivities (>99% *ee*) and diastereoselectivities (endo/exo > 99/1) and can be reused for six times.

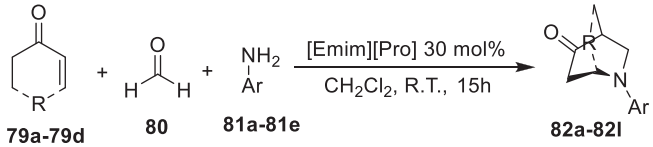


Figure 4.34: Pyrrolidine-based CILs catalyzed asymmetric aza Diels–Alder reaction.

4.3 Conclusions

The literature discussed in the above sections highlights the potential of CILs in asymmetric synthesis and catalysis. Because of their low vapor pressure, excellent thermal stability and solvent potential, CILs gained much attention from the researchers as evident from the literature published in the past decade. The utilization of CILs as a reaction solvent and/or catalyst in asymmetric synthesis started a revolution in organic synthesis. In the near future, there is a massive scope of the design and synthesis of new CILs starting from different precursors, investigation of their structural features and evaluation of their physicochemical properties to make their use in asymmetric organic synthesis. Moreover, due to easy availability and cost effectiveness of natural chiral reactants like amino acids, terpenes and alkaloids to synthesize more CILs and said species can be considered as the future solvents in organic reactions.

Abbreviations

ILs	ionic liquids
CILs	chiral ionic liquids
FCILs	functionalized chiral ionic liquids
ee	enantiomeric excess
dr	diastereomeric ratio
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
TFA	trifluoroacetic acid
DABCO	1,4-diazabicyclo[2.2.2]octane

References

[1] Welton, T. Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev 1999, 99, 2071–2083.
[2] Zhao, H, Malhotra, SV. Applications of ionic liquids in organic synthesis. Aldrichimica Acta 2002, 35, 75–83.
[3] Olivier-Bourbigou, H, Magna, L. Ionic liquids: Perspectives for organic and catalytic reactions. J Mol Catal A: Chemical 2002, 182-183, 419–437.
[4] Zhang, Q, Zhang, S, Deng, Y. Recent advances in ionic liquid catalysis. Green Chem 2011, 13, 2619–2637.
[5] Kaur, G, Kumar, H, Singla, M. Diverse applications of ionic liquids: A comprehensive review. J Mol Liq 2022, 351, 118556.
[6] Baudequin, C, Baudoux, J, Levillain, J, Cahard, D, Gaumont, A-C, Plaquevent, J-C. Ionic liquids and chirality: Opportunities and challenges. Tetrahedron Asymm 2003, 14, 3081–3093.
[7] Ding, J, Armstrong, DW. Chiral ionic liquids: Synthesis and applications. Chirality 2005, 17, 281–292.
[8] Ding, J, Welton, T, Armstrong, DW. Chiral ionic liquids as stationary phase in gas chromatography. Anal Chem 2004, 76, 6819–6822.

[9] Yujiao, W, Guoyan, W, Wenyan, Z, Hongfen, Z, Huanwang, J, Anjia, C. Chiral separation of phenylalanine and tryptophan by capillary electrophoresis using a mixture of β-CD and chiral ionic liquid ([TBA] [L-ASP]) as selectors. Biomed Chromatogr 2014, 28, 610–614.
[10] Singh, A, Kaur, N, Chopra, HK. Chiral recognition methods in analytical chemistry: Role of the chiral ionic liquids. Crit Rev Anal Chem 2019, 49(6), 553–569.
[11] Baudequin, C, Bregeon, D, Levillain, J, Guillen, F, Plaqueventa, J-C, Gaumont, A-C. Chiral ionic liquids, a renewal for the chemistry of chiral solvents?Design, synthesis and applications for chiral recognition and asymmetric synthesis. Tetrahedron Asymm 2005, 16, 3921–3945.
[12] Singh, A, Chopra, HK. Chiral ionic liquids: Design, synthesis and applications in asymmetric synthesis. Curr Org Synth 2017, 4, 488–510.
[13] Van Buu, ON, Aupoix, A, Vo-Thanh, G. Synthesis of novel chiral imidazolium-based ionic liquids derived from isosorbide and their applications in asymmetric aza Diels-Alder reaction. Tetrahedron 2009, 65, 2260–2265.
[14] Ni, B, Zhang, Q, Headley, AD. Pyrrolidine-based chiral pyridinium ionic liquids (ILs) as recyclable and highly efficient organo-catalyst for the asymmetric Michael addition reactions. Tetrahedron Lett 2008, 49, 1249–1252.
[15] Etayo, P, Vidal-Ferran, A. Rhodium-catalyzed asymmetric hydrogenation as a valuable synthetic tool for the preparation of chiral drugs. Chem Soc Rev 2013, 42, 728–754.
[16] Drommi, D, Arena, CG. Recent advances on chiral catalysts for asymmetric hydrogenation of C═C, C═N and C═O bonds. Curr Org Chem 2016, 20, 2552–2590.
[17] Singh, A, Kaur, N, Chopra, HK. Enantioselective reduction reactions using chiral ionic liquids: An overview. Curr Org Synth 2018, 15(5), 578–586.
[18] Foubelo, F, Najera, C, Yus, M. Catalytic asymmetric transfer hydrogenation of ketones: Recent advances. Tetrahedron Asymm 2015, 26, 769–790.
[19] Roszkowski, P, Maurin, JK, Czarnocki, Z. New N,N-diamine ligands derived from (-)-menthol and their application in the asymmetric transfer hydrogenation. Tetrahedron Asymm 2017, 28, 532–538.
[20] Ohkuma, T, Takeno, H, Honda, Y, Noyori, R. Asymmetric hydrogenation of ketones with polymer-bound BINAP/diamine ruthenium catalysts. Adv Synth Catal 2001, 343, 369–375.
[21] Hajipour, AR, Karimi, F. Synthesis of novel chiral ionic liquid and its application in reduction of prochiral ketones to the corresponding chiral alcohols using $NaBH_4$. Synth Commun 2010, 40, 1784–1793.
[22] Singh, A, Chopra, HK. New benzimidazolium-based chiral ionic liquids:synthesis and application in enantioselective sodium borohydride reductions in water. Tetrahedron Asymm 2016, 27, 448–453.
[23] Singh, A, Chopra, HK. S-Substituted-2-mercaptobenzthiazolium based chiral ionic liquids: Efficient organo-catalysts for enantioselective sodium borohydride reductions of prochiral ketones. Tetrahedron Asymm 2017, 28, 414–418.
[24] Schulz, PS, Muller, N, Bosmann, A, Wasserscheid, P. Effective chirality transfer in ionic liquids through ion pairing effects. Angew Chem Int Ed 2007, 46, 1293–1295.
[25] Schneiders, K, Bosmann, A, Schulz, PS, Wasserscheid, P. Chirality transfer in imidazolium camphorsulfonate ionic liquids through ion pairing effects. Adv Synth Catal 2009, 351, 432–440.
[26] Wagner, V, Schulz, PS, Wasserscheid, P. Asymmetric hydrogenation catalysis via ion-pairing in chiral ionic liquids. J Mol Liq 2014, 192, 177–184.
[27] Vasiloiu, M, Gaertner, P, Zirbas, R, Bica, K. Coordinating chiral ionic liquids: Design, synthesis, and application in asymmetric transfer hydrogenation under aqueous conditions. Eur J Org Chem 2015, 2374–2381.
[28] Dub, PA, Gordon, JC. The mechanism of enantioselective ketone reduction with Noyori and Noyori-Ikariyabifuctional catalysts. Dalton Trans 2016, 45, 6756–6781.

[29] Uchimoto, H, Tsuji, T, Kawasaki, I, Arimitsu, K, Yasui, H, Yamashita, M, Ohta, S, Nishide, K. Preparation of chiral ligands connected with quaternary ammonium group for recyclable catalytic asymmetric transfer hydrogenation in ionic liquid. Chem Pharm Bull 2015, 63, 200–209.
[30] Kaur, N, Chopra, HK. Synthesis, characterization and organocatalytic application of chiral ionic liquids derived from (*S*,*R*)-noscapine. Synth Commun 2018, 48, 26–31.
[31] Kaur, N, Chopra, HK. Synthesis and applications of carbohydrate based chiral ionic liquids as chiral recognition agents and organocatalysts. J Mol Liq 2020, 298, 111994.
[32] Ferlin, N, Courty, M, Nhien, ANV, Gatard, S, Pour, M, Quilty, B, Ghavre, M, Hai, A, Kummerer, K, Gathergood, N, Bouquillon, S. Tetrabutylammonium prolinate-based ionic liquids: A combined asymmetric catalysis, antimicrobial toxicity and biodegradation assessment. RSC Adv 2013, 3, 26241–26251.
[33] Schmitkamp, M, Chen, D, Leitner, W, Klankermayer, J, Francio, G. Enantioselective catalysis with tropos ligands in chiral ionic liquids. Chem Commun 2007, 4012–4014.
[34] Chen, D, Schmitkamp, M, Francio, G, Klankermayer, J, Leitner, W. Enantioselective hydrogenation with racemic and enantiopure BINAP in the presence of a chiral ionic liquid. Angew Chem 2008, 47, 7339–7341.
[35] Wang, Z, Wang, Q, Zhang, Y, Bao, W. Synthesis of new chiral ionic liquids from natural acids and their applications in enantioselective Michael addition. Tetrahedron Lett 2005, 46, 4657–4660.
[36] Ou, W-H, Huang, -Z-Z. An efficient and practical synthesis of chiral imidazolium ionic liquids and their application in an enantioselective Michael reaction. Green Chem 2006, 8, 731–734.
[37] Suzuki, Y, Wakatsuki, J, Tsubaki, M, Sato, M. Imidazolium-based chiral ionic liquids: Synthesis and application. Tetrahedron 2013, 69, 9690–9700.
[38] Jayachandra, R, Reddy, SR. Balakrishna, natural sugars derived chiral ionic liquids for asymmetric michael addition reaction. Chem Sel 2016, 1, 2341–2343.
[39] Jayachandra, R, Reddy, SR. Synthesis of D-ribose and D-galactose derived chiral ionic liquids as recyclable chiral solvent for michael addition reaction. Trends Carbohyd Res 2015, 7, 60–67.
[40] Sun, H, Wang, G, Yan, X, Chen, L. Chiral pyrrolidine quaternary derivatives as organocatalysts for asymmetric Michael additions. Res Chem Intermed 2012, 38, 1501–1509.
[41] Luo, S, Mi, X, Liu, S, Xu, H, Cheng, J-P. Surfactant-type asymmetric organo-catalyst: Organocatalytic asymmetric Michael addition to nitro-styrenes in water. Chem Commun 2006, 3687–3689.
[42] Li, P, Wang, L, Zhang, Y, Wang, G. Silica gel supported pyrrolidine-based chiral ionic liquid as recyclable organocatalyst for asymmetric Michael addition to nitrostyrenes. Tetrahedron 2008, 64, 7633–7638.
[43] Nobuoka, K, Kitaoka, S, Kojima, T, Kawano, Y, Hirano, K, Tange, M, Obata, S, Yamamoto, Y, Harran, T, Ishikawa, Y. Proline based chiral ionic liquids for enantioselective Michael reaction. Org Chem Int 2014, 1–9.
[44] Liu, L, Li, J. Synthesis of new functionalized chiral ionic liquid and its organocatalytic asymmetric Michael addition. Synth Commun 2013, 43, 476–485.
[45] Li, P, Wang, L, Wang, M, Zhang, Y. Polymer-immobilized pyrrolidine-based chiral ionic liquids as recyclable organocatalysts for asymmetric Michael additions to nitrostyrenes under solvent-free reaction conditions. Eur J Org Chem 2008, 1157–1160.
[46] Xu, D-Z, Liu, Y, Shi, S, Wang, Y. Chiral quaternary alkylammonium ionic liquid [Pro-dabco][BF4]: As a recyclable and highly efficient organocatalyst for asymmetric Michael addition reactions. Tetrahedron Asymm 2010, 21, 2530–2534.
[47] Luo, S, Zhang, L, Mi, X, Qiao, Y, Cheng, J-P. Functionalized chiral ionic liquid catalyze denantioselective desymmetrizations of prochiral ketones via asymmetric Michael addition reaction. J Org Chem 2007, 72, 9350–9352.
[48] Ni, B, Zhang, Q, Headley, AD. Functionalized chiral ionic liquid as recyclable organocatalyst for asymmetric Michael addition to nitrostyrenes. Green Chem 2007, 9, 737–739.

[49] Zhang, Q, Ni, B, Headley, AD. Asymmetric Michael addition reactions of aldehydes with nitrostyrenes catalyzed by functionalized chiral ionic liquids. Tetrahedron 2008, 64(22), 5091–5097.
[50] Kucherenko, AS, Lisnyak, VG, Chizhov, AO, Zlotin, SG. Primary amine attached to an *N*-(carboxyalkyl) imidazolium cation: A recyclable organocatalyst for the asymmetric Michael reaction. Eur J Org Chem 2014, 18, 3808–3813.
[51] Trost, BM, Brindle, CS. The direct catalytic asymmetric aldol reaction. Chem Soc Rev 2010, 39, 1600–1632.
[52] Inani, H, Singh, A, Bhati, M, Kumari, K, Kucherenko, AS, Zlotin, SG, Easwar, S. Proline-Histidine Dipeptide: A Suitable Template for Generating Ion-Tagged Organocatalysts for the Asymmetric Aldol Reaction. Synthesis 2021, 53(15), 2702–2712.
[53] Miao, W, Chan, TH. Ionic-liquid-supported organo-catalyst: Efficient and recyclable ionic-liquid-anchored proline for asymmetric aldol reaction. Adv Synth Catal 2006, 348, 1711–1718.
[54] Zhou, W, Xu, L-W, Qiu, H-Y, Lai, G-Q, Xia, C-G, Jiang, J-X. Synthesis of a novel chiral ionic liquid and its application in enantioselective aldol reactions. Helvetica Chimica Acta 2008, 91, 53–59.
[55] Zhang, L, Zhang, H, Luo, H, Zhou, X, Cheng, G. Novel chiral ionic liquid (CIL) assisted selectivity enhancement to (L)-prolinecatalyzed asymmetric aldol reactions. J Braz Chem Soc 2011, 1–6.
[56] Zhang, L, Luo, S, Mi, X, Liu, S, Qiao, Y, Xu, H, Cheng, J-P. Combinatorial synthesis of functionalized chiral and doubly chiral ionic liquids and their applications as asymmetric covalent/non-covalent bifunctionalorganocatalysts. Org Biomol Chem 2008, 6, 567–576.
[57] Gonzalez, L, Escorihuela, J, Altava, B, Burguete, MI, Luis, SV. Chiral room temperature ionic liquids as enantioselective promoters for the asymmetric aldol reaction. Eur J Org Chem 2014, 5356–5363.
[58] Vasiloiu, M, Rainer, D, Gaertner, P, Reichel, C, Schroder, C, Bica, K. Basic chiral ionic liquids: A novel strategy for acid-free organo-catalysis. Catal Today 2013, 200, 80–86.
[59] Kui, T, Guillen, F. Histidine-based salt as an ionic tag for proline: Application in enantioselective cross aldol reaction in ionic liquids. Synth Commun 2020, 50(10), 1512–1522.
[60] Porcar, R, García-Verdugo, E, Altava, B, Burguete, MI, Luis, SV. Chiral ImidazoliumProlinate Salts as Efficient Syn-zymaticOrganocatalysts for the Asymmetric Aldol Reaction. Molecules 2021, 26, 4190.
[61] Zalewska, K, Zakrzewska, ME, Branco, LC. Chiral ionic liquids based on L-cysteine derivatives for asymmetric aldol reaction. Catalysts 2022, 12, 47.
[62] Garre, S, Parker, E, Ni, B, Headley, AD. design and synthesis of bis-tereogenic chiral ionic liquids and their use as solvents for asymmetric Baylis-Hillman reaction. Org Biomol Chem 2008, 6, 3041–3043.
[63] Rupini, B, Pasricha, S, Rathi, B. Asymmetric reductive amination of carbonyl compounds by using *N, N,N*-Tributyl propananium based novel chiral ionic liquid. Int J Org Chem 2013, 3, 190–193.
[64] Yadav, LDS, Rai, A, Rai, VK, Awasthi, C. Chiral ionic liquid-catalyzed Biginelli reaction: Stereoselective synthesis of polyfunctionalized per-hydropyrimidines. Tetrahedron 2008, 64, 1420–1429.
[65] Ahmadkhani, A, Rad-Moghadam, K, Roudsari, ST. A Highly enantioselective and efficient synthesis of new pyrimidine-fused spiro [indoline-3, 4′-pyran]s Promoted by a novel chiral ionic liquid. Chem Sel 2019, 4(35), 10442–10446.
[66] Zhang, S, Huang, Y, Jing, H, Yao, W, Yan, P. Chiral ionic liquids improved the asymmetric cycloaddition of CO_2 to epoxides. Green Chem 2009, 11, 935–938.
[67] Duan, S, Jing, X, Li, D, Jing, H. Catalytic asymmetric cycloaddition of CO_2 to epoxides via chiral bifunctional ionic liquids. J Mol Catal A Chem 2016, 411, 34–39.
[68] Van Buu, ON, Aupoix, A, Vo-Thanh, G. Synthesis of novel chiral imidazolium-based ionic liquids derived from isosorbide and their applications in asymmetric aza Diels-Alder reaction. Tetrahedron 2009, 65, 2260–2265.
[69] Zheng, X, Qian, Y, Wang, Y. Direct asymmetric aza Diels–Alder reaction catalyzed by chiral 2-pyrrolidinecarboxylic acid ionic liquid. Catal Commun 2010, 11, 567–570.

Yadavalli Venkata Durga Nageswar*, Katla Ramesh and Katla Rakhi

Chapter 5
Deep eutectic solvent-mediated organic transformations

5.1 Introduction

Deep eutectic solvents (DES), solutions of Lewis or Bronsted acids and bases forming a eutectic mixture, are nonflammable, cost-effective highly tunable with low vapor pressures and toxicities. These have emerged as safe, alternate, eco-friendly, efficient, recyclable and simple solvents. Their properties can be fine-tuned by appropriately changing the components [1–3]. As they resemble ionic liquids in many of their characteristics and properties, they are considered as ionic liquid analogues, even though both differ in their chemical properties. In general, DES can be easily prepared by simply mixing of the components and heating moderately. These exhibit a wide variety of potential applications in a diverse range of catalytic, separation and electrochemical processes.

Based on composition, DESs can be classified into four types [3]:
Type 1. Quaternary ammonium salt + metal chloride
Type 2. Quaternary ammonium salt + metal chloride hydrate
Type 3. Quaternary ammonium salt + hydrogen bond donor (HBD)
Type 4. Metal chloride hydrate + HBD

From the sustainable chemistry point of view, DESs [4, 5] have attracted the attention of researchers across the world during the last decade, finding new applications in a wide variety of chemical processes [6–10]. The broad range of applications cover the areas such as alternative solvents and/or catalysts for organic transformations in general [11–13], biomass processing [14], biodiesel synthesis [15], biotransformations [16, 17], polymerization reactions [18], metal-catalyzed organic reactions

Acknowledgment: Author Ramesh Katla (foreign visiting professor – Edital No. 03/2020) thanks the PROPESP/FURG, Rio Grande-RS, for visiting professorship. Author Rakhi Katla thanks "CNPq-TWAS fellow."

*__Corresponding author: Yadavalli Venkata Durga Nageswar,__ Retired Chief Scientist, Indian Institute of Chemical Technology – IICT, Tarnaka, Hyderabad, Telangana, India,
e-mail: dryvdnageswar@gmail.com
Katla Ramesh, Foreign Visiting Professor, Organic Chemistry Laboratory 4, School of Chemistry and Food, Federal University of Rio Grande – FURG, Rio Grande, Rio Grande do Sul, Brazil
Katla Rakhi, Organic Catalysis and Biocatalysis Laboratory – LACOB, Federal University of Grande Dourados – UFGD, Dourados, Mato Grosso do Sul, Brazil

https://doi.org/10.1515/9783110788129-005

[19], metal processing applications [20, 21] and separation processes [22–24]. Every year, many new applications of DESs are reported in the literature [4], after the first research paper on this topic appeared in 2001 [5], as any number of new DES can be prepared easily by varying the components of the DES as well as their molar ratios. In the last couple of decades, considerable research has been done for the development of green chemical protocols involving unconventional media and catalysts, among which DESs played a significant and potential role. DESs were effectively used in organic reactions, including oxidation reactions, reduction reactions, addition reactions, replacement reactions, cyclization reactions, condensation reactions and multicomponent reactions. Many comprehensive reviews appeared on DES and their applications [25–28]. This chapter showcases the role of eco-friendly and inexpensive DES as solvent as well as catalyst in the organic transformations reported during the last 10 years.

5.2 Recent DES-mediated organic transformations

5.2.1 DES-mediated formation of C–C bond through conjugate addition

Saavedra et al. [29] described an efficient sustainable process for DES-mediated C–C bond formation through multicomponent radical conjugate addition of disubstituted (**1**) and trisubstituted simple olefins (**2**) (Figure 5.1a and b). Authors screened several catalysts like $Co(acac)_2$, $Ni(acac)_2$, $Pd(acac)_2$, $FeCl_3$, $CoCl_2$, $NiCl_2{\cdot}6H_2O$, $PdCl_2$, and $Fe(acac)_3$ and observed that inexpensive $Fe(acac)_3$ provided encouraging results. An air-stable, moisture-stable, cost-effective, nontoxic poly(methyl hydrosiloxane)-PMHS was used as an efficient reducing agent. During optimization, authors examined the effect of different solvents as well as DESs and observed that choline chloride–ethylene glycol (1:2) provided excellent yields. The methodology was also compatible for varied functional groups.

5.2.2 DES-mediated Negishi cross-coupling reaction

A scalable Pd-catalyzed Negishi cross-coupling process between (hetero)aryl bromides (**5**) and organozinc (**6**) compounds “on water” or in biodegradable choline chloride/urea eutectic mixture under mild condition was efficiently demonstrated by Dilauro et al. [30] (Figure 5.2). The eco-friendly methodology was compatible with a broad range of substrates with varied functional group settings. Eutectic mixture and catalyst as well as water medium were recyclable.

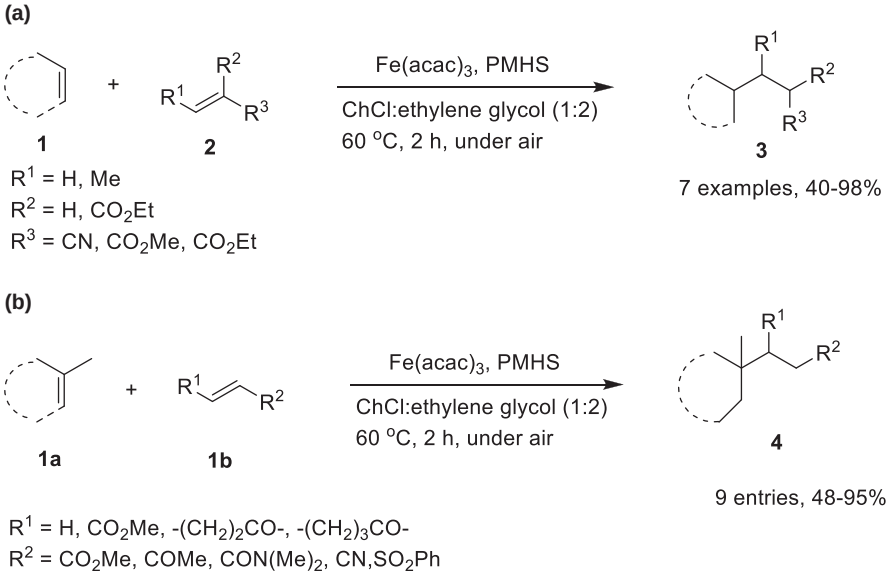


Figure 5.1: Reactions using (a) mono/disubstituted donor olefins and (b) trisubstituted donor olefins.

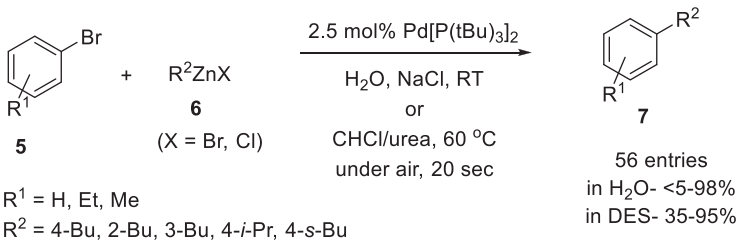
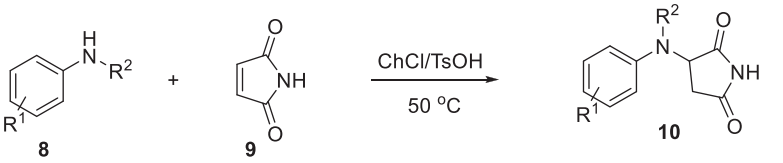


Figure 5.2: General representation of Pd-catalyzed cross-coupling between (hetero)aryl bromides and organozinc halides.

5.2.3 DES-mediated aza-Michael addition reaction

Gutiérrez-Hernández et al. [31] studied systematically the influence of DES-choline chloride/PTSA as well as PTSA/H_2O on aza-Michael addition of aryl amines (**8**) to maleimide (**9**) affording aminopyrrolidine-2,5-diones (**10**) under mild conditions (Figure 5.3). During initial studies, authors examined the effect of reaction conditions like temperature and reactant ratios. Authors investigated to understand kinetics and thermodynamics of interactions between ChCl/TSOH and the reagents as well as the effect of H_2O on supramolecular network of DES. The reaction of aniline (**8**) with maleimide (**9**) as a model reaction was screened for the effect of different polar or nonpolar solvents such as toluene, THF and methanol as well as DES like ChCl/urea, ChCl/$ZnCl_2$ and ChCl/tartaric acid.



R^1 = H, Me, 4-Me, 3-OH, 4-OH, 4-Cl, 2-Br, 4-I, 3,4-Cl_2, 4-COPh, 2-NO_2, 3-NO_2
R^2 = H, Me

Figure 5.3: Aza-Michael addition in DES.

5.2.4 DES-mediated Groebke-Blackburne-Bienayme process

Shaabani and Hooshmand [32] investigated a three-component eco-friendly synthesis of 3-aminoimidazo-fused heterocycles (**11**) via Groebke-Blackburne-Bienayme process involving aldehydes (**12**), isocyanide (**13**) and 2-amino heterocycles (**14**) assisted by recyclable choline chloride–urea and organocatalyst (Figure 5.4a and b). Authors during screening studies verified the suitability of choline chloride/urea, choline chloride/malonic acid, choline chloride/citric acid, choline chloride/TSOH, choline chloride/$ZnCl_2$ and choline chloride/$SnCl_2$ systems at different reaction temperatures. It was observed that alkyl isocyanides (**13**) provided better yields. Aromatic aldehydes (**12**) having both electron-withdrawing and electron-donating groups afforded good yields. Moreover, following the same procedure, imidazo[1,2-*a*]pyridine-chromones (**15**) were also prepared in encouraging yields.

5.2.5 DES-mediated Friedel–Crafts alkylation reaction

Wang et al. [33] utilized reusable DESs for the Friedel–Crafts alkylation of electron-rich arenes (**17**/**17a**) with aldehydes (**12**) under mild reaction conditions and reported that CHCl–$[ZnCl_2]_2$ provided the best results (Figure 5.5a and b). During initial studies, various factors like system temperature, reaction time and amount of DES were investigated. Different diarylalkanes (**18**) and triarylmethanes (**19**) were produced in the research work in encouraging yields.

5.2.6 DES-mediated synthesis of *N*,*N*^{1}-diaryl amidines

Azizi and coauthors [34] described CHCl/$SnCl_2$ promoted environmentally benign practical method for the preparation of *N*,*N*^{1}-diaryl amidines (**20**) and formamides (**21**) from aromatic amines (**8b**) and HCO_2H (**22**) or $HC(OMe)_3$ (**23**) at 70 °C (Figure 5.6a and b).

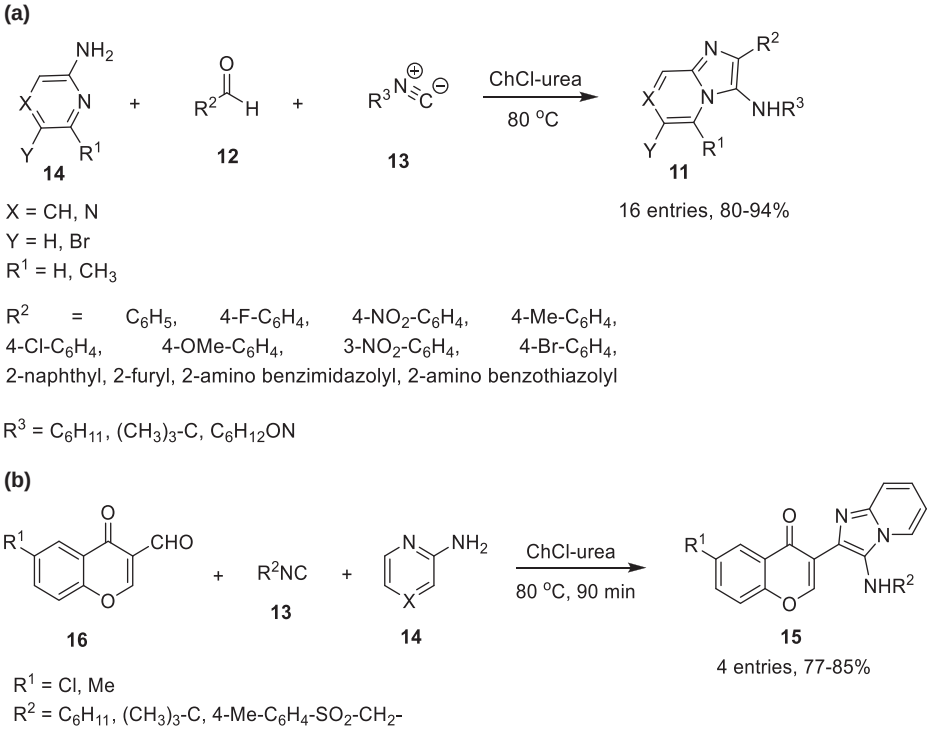


Figure 5.4: (a) 3-Aminoimidazo-fused heterocyclic derivatives using choline chloride–urea and (b) synthesis of imidazo[1,2-a]pyridine-chromones.

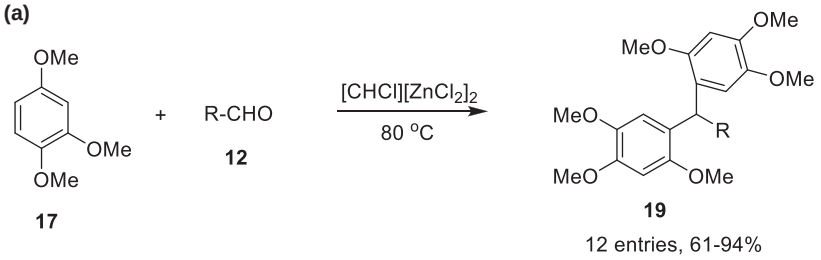
Authors examined the efficiency of different DESs like Ch/$SnCl_2$, Ch/gly, Ch/$ZnCl_2$, Ch/urea and Ch/$ZnCl_2$·$SnCl_2$.

5.2.7 DES-mediated bromination of anthra-9,10-quinones

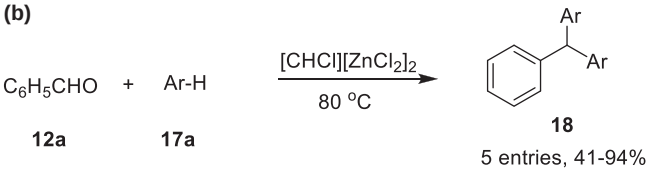
Phadtare and Shankarling [35] reported the preparation of brominated derivatives of substituted 1-amino-anthra-9,10-quinone (**24**) via an eco-friendly method using simple ammonium DES both as a catalyst and reaction medium at 50–60 °C for 2–3 h (Figure 5.7). Authors also compared the reaction results obtained with DES as well as organic solvents and concluded that DES provided best results in shorter reaction times.

5.2.8 DES-mediated synthesis of 2-amino-4H-pyran derivatives

Tavakol and Keshavarzipour [36] developed a novel hybrid magnetic nanoparticles-MAG/iodopropyl trimethoxy silane (IPS)/DES by immobilizing ChCl–urea on Fe_3O_4



R = H, C_6H_5, 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 3-CF_3-C_6H_4, 2-OH-C_6H_4, $CH_3(CH_2)_4$-, $CH_3(CH_2)_2$-, $(CH_3)_2$-CH_2-



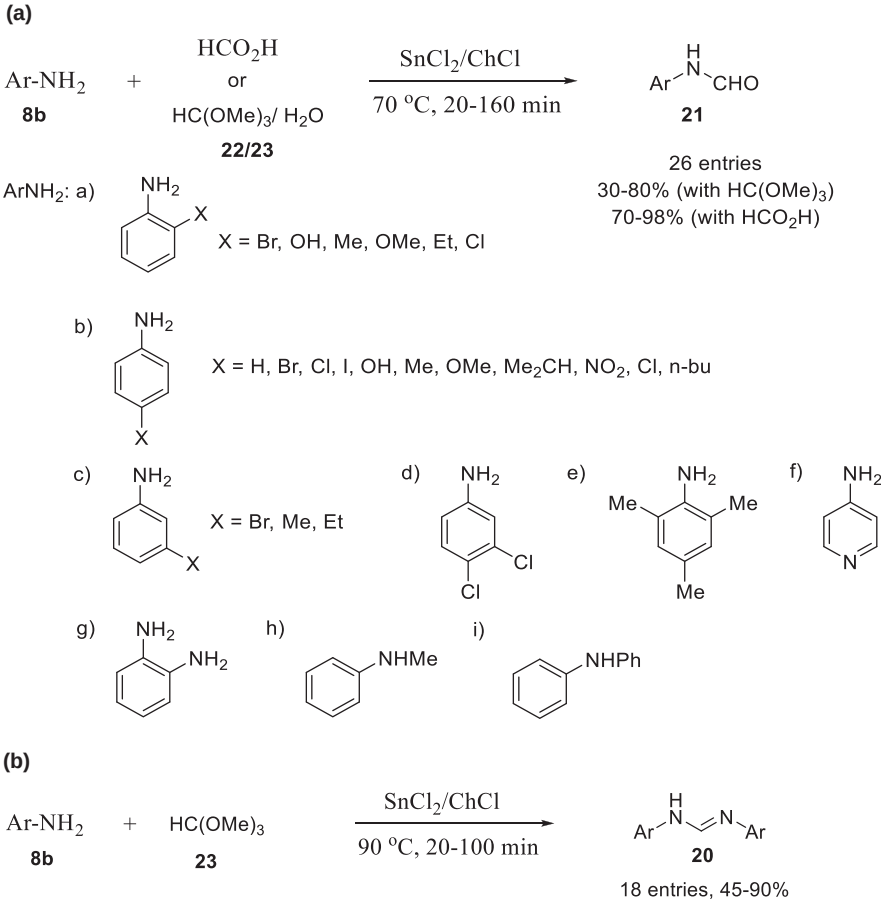
Ar H = 1,2,4-$(OMe)_3$-C_6H_3, 1,3-$(OMe)_2$-C_6H_4, 2-OH-methoxy benzene, phenol (hydroxy benzene)

Figure 5.5: Reaction of (a) 1,2,4-trimethoxy benzene with aldehydes and (b) benzaldehyde with nucleophiles.

(MAG) coated with IPS (Figure 5.8). After thoroughly characterizing these particles with the help of transmission electron microscopy (TEM), scanning electron microscopy (SEM), X-ray diffraction (XRD) and Fourier-transform infrared (FT-IR) spectroscopy, they were applied as reusable catalysts in the synthesis of 2-amino-4H-pyran derivatives (**26**) in water medium in high yields via a three-component reaction strategy involving malononitrile (**27**), aromatic aldehydes (**12**) and enolizable carbonyl compounds (**28**). The catalyst was efficiently recycled for five cycles with just 8% reduction in yields.

5.2.9 DES-mediated preparation of CAPE

Fischer et al. [37] reported the synthesis of caffeic acid phenethyl ester (CAPE) (**29**) via in situ formation of DES made of choline chloride and caffeic acid, which was used both as solvent and as reactant (Figure 5.9). Authors examined the efficiency of different acidic catalysts like sulfuric acid, *p*-toluene sulfonic acid, Amberlite IR 120 and Amberlyst 15.

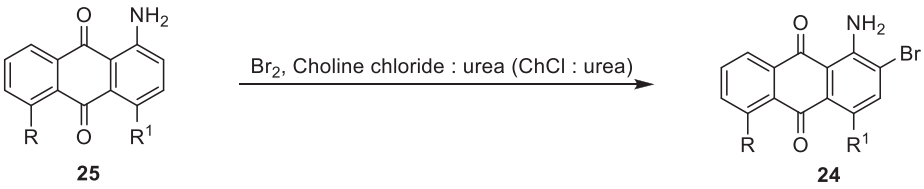


Ar = Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 4-Me-C_6H_4, 4-$CH(CH_3)_2$-C_6H_4, 2-Me-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 2-Br-C_6H_4, 4-n butyl-C_6H_4, 4-OMe-C_6H_4, 2-OMe-C_6H_4, 3-Cl, 4-Me-C_6H_3, 3, 4-Cl_2-C_6H_3, 4-CF_3-C_6H_4, 3-NO_2-C_6H_4, C_6H_5N

Figure 5.6: Synthesis of (a) formamides and (b) symmetrical formamidines.

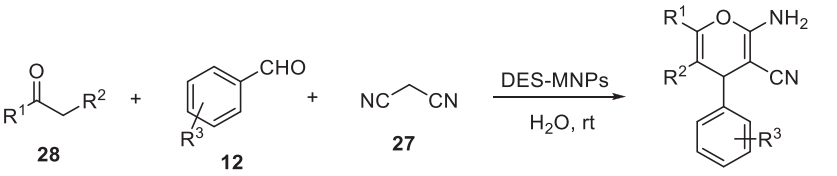
5.2.10 DES-mediated oxidative Ugi reaction

Singh and coauthors [38] unveiled a novel, eco-friendly, operationally simple and metal-free organocatalytic oxidative Ugi reaction promoted by iodine (Figure 5.10a and b). Natural DES choline chloride–urea was used as a solvent. Both solvent and oxidant were recycled up to five cycles. During optimization studies, different oxidants like *o*-iodoxy-benzoic acid (IBX), phenyliodonium diacetate (PIDA), phenyliodine bis(triflouroacetate) (PIFA) and Des-Martin periodinane (DMP) were screened



R = H, Cl, NH_2
R^1 = H, OMe, NHCOPh, OH, Br

Figure 5.7: Synthesis of brominated derivatives of 1-amino-anthra-9,10-quinone compounds in choline chloride/urea.



R^1 = Ph, 4-MePh, Me
R^2 = H, Ph, CO_2Et
R^3 = H, Ph, 2-naphthyl, 4-BrPh, 4-MePh, 4-OMePh, 4-NO_2Ph, 4-ClPh

Figure 5.8: Eco-friendly approach to 2-amino-4H-pyrans assisted by MAG/IPS/DES.

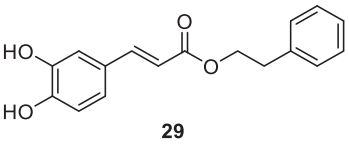


Figure 5.9: Caffeic acid phenethyl ester.

for their efficiency. Agents such as DMP, PIDA, PIFA and IBX as well as solvents such as CH_2Cl_2, CH_3CN, toluene, CH_2Cl_2/HFIP, urea/ChCl, DMO/ChCl, imidazole/ChCl, CA/ChCl and urea/ChCl were investigated for their suitability and efficacy. It was reported that a combination of IBX in ChCl/urea (1:2) at room temperature for 12 h with a catalytic amount of carboxylic acid was very effective for the conversion of benzylamines (**30**) to imines (**31**). Based on the findings, authors extended this four-component Ugi reaction. Several diversely substituted carboxylic acids (**32**) and primary amines (**30**) were employed in the protocol. Both DES and IBX were recycled for five times.

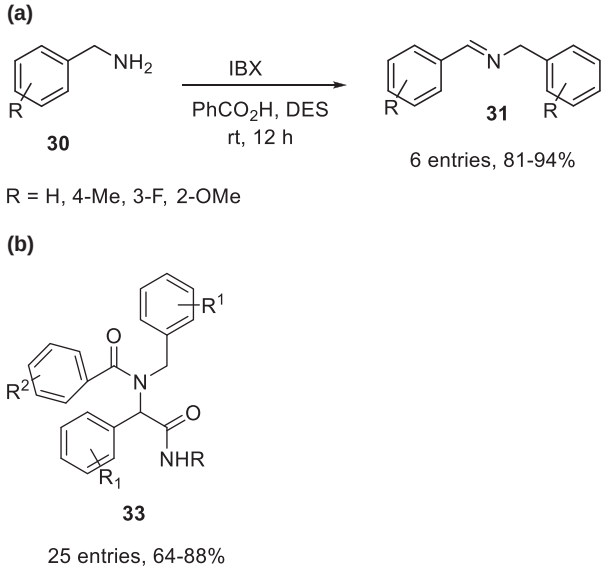


Figure 5.10: (a) Oxidation of primary amines to imines with IBX and (b) general representation of the Ugi reaction product.

5.2.11 DES-mediated synthesis of 2,3-dihydroquinazolines

Molnar et al. [39] described an environmentally benign, rapid, selective and catalyst-free synthesis of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones (**34**) from anthranilic acid (**35**) or 5-iodoanthranilic acid (**35a**) and appropriate isothiocyanates (**36**) in choline chloride/urea (Figure 5.11).

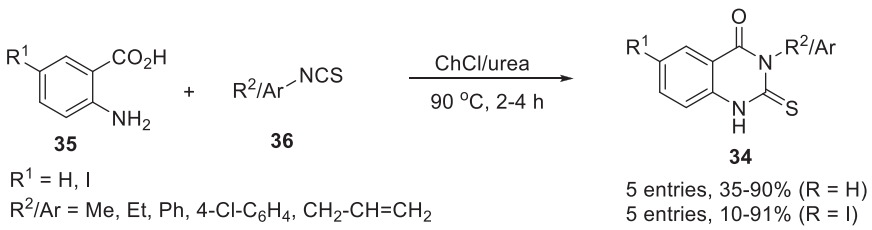


Figure 5.11: Choline chloride/urea-assisted preparation of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones and 6-iodo-2-thioxo derivatives.

5.2.12 DES-mediated epoxidation

Ranganathan et al. [40] developed an eco-friendly, solvent-free lipase-mediated epoxidation process for monoterpenes like 3-carene (**37**), limonene (**38**) and α-pinene (**39**) using choline chloride and HBDs (Figure 5.12). The process was standardized by controlling various parameters such as the type of substrate, peroxide amount, enzyme amount and reaction temperature as well as DES medium. Even though glycol:choline chloride (GL/Ch) and sorbitol:chlorine chloride (So/Ch) provided better results to overcome the formation of ester impurity problem, authors designed cosubstrate incorporation into the DES system. Finally, ChCl and urea–H_2O_2 (ChCl:U:H_2O_2) system was proved to be ideal. The new system converted the reactants in 2–3 h. Good and simple recovery of terpene epoxides was enabled by using water/ethyl acetate. In the first round of screening, valeric acid, malonic acid, levulinic acid, 4-OH phenylacetic acid, glycerol, ethylene glycol, urea, D-glucose, D-fructose, D-xylitol, D-sorbitol, L(+)-tartaric acid and L-glutamic acid were examined as HBDs: 3-carene 87.2 ± 2.4%; limonene 77.0 ± 5.0%; α-pinene 84.6 ±3.7%.

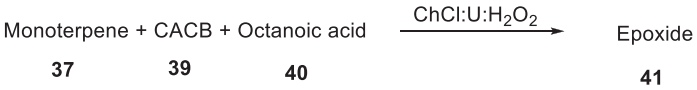


Figure 5.12: Epoxidation process under ChCl–urea–H_2O_2.

5.2.13 DES-mediated preparation of spiroquinazoline-4(3H) one derivatives

Maleki et al. [41] reported the synthesis of a sulfonic acid-functionalized titanium dioxide [42], quasi-superparamagnetic nanocatalyst (Fe_3O_4@SiO_2@TiO_2–OSO_3H) and after characterizing the catalyst was applied in the preparation of 2,3-dihydroxyquinazolin-4(1H)one (**43**) and spiroquinazoline-4(3H)one derivatives (**44**) obtained by the reaction of isatoic anhydride (**45**) and primary aromatic amine (**8c**)/ammonium chloride (**46**) with aromatic aldehydes (**12**)/ketones (**12b**) in the presence of DES–choline chloride–urea (1:2) system at 60 °C (Figure 5.13). Both catalyst and DES were recovered and reused. During initial studies, authors examined other catalysts as well as solvents for the process. The efficiency of the newly synthesized catalyst was compared with other reported works.

5.2.14 DES-mediated azidation/click reaction

Kafle and Handy [42] unveiled a versatile and scalable one-pot, eco-friendly copper-mediated azidation/click reaction of aryl/heteroaryl bromides (**5a**) in DES affording 1,4-disubstituted triazoles (**48**) (Figure 5.14). *N*-*N*^{1}-Dimethyl ethylene diamine (DMEDA) was

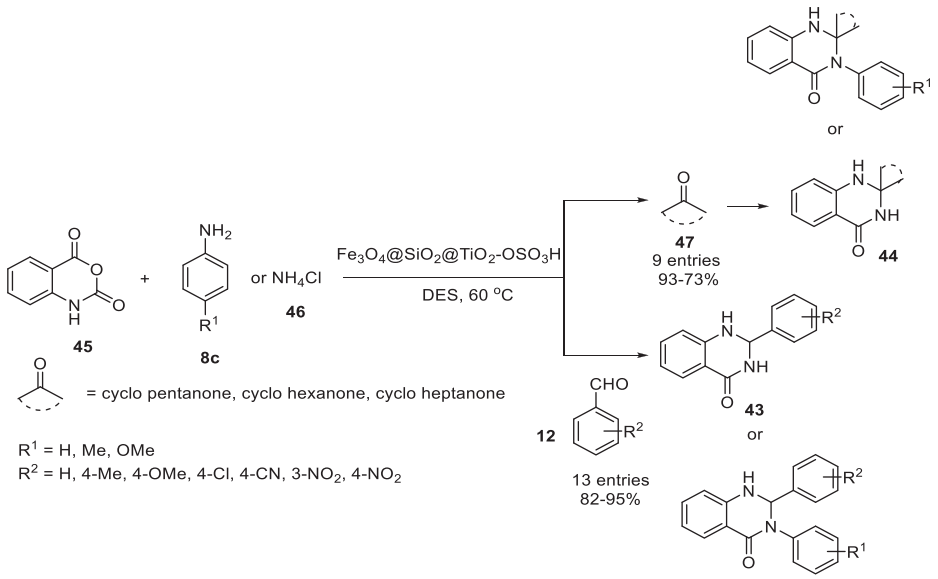


Figure 5.13: Fe_3O_4@SiO_2@TiO_2–OSO_3H-assisted synthesis of 2,3-dihydroquinazolin-4(1H)one and spiroquinazoline-4(3H)one derivatives in choline chloride–urea system.

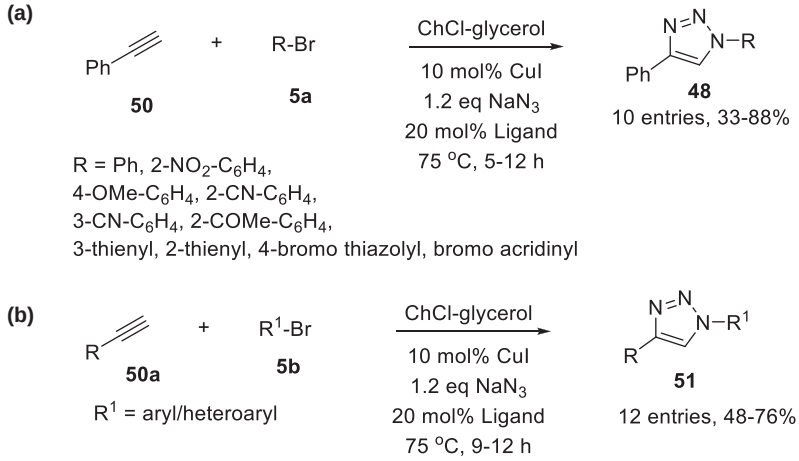


Figure 5.14: Preparation of 1,4-disubstituted triazoles.

used as a ligand. Recyclability of the catalyst, ligand and solvent is the important feature of this protocol. During the initial studies, the authors screened different ligands such as proline, phenanthroline and DMEDA. Reaction with a wide range of electron-rich, electron-deficient, *ortho*-substituted dibromoarenes (**49**) and heteroaromatic bromides (**5a**)

was explored. Various functionalized alkynes (**50**) were examined as reactants, and ChCl–glycerol was used as DES in this study.

5.2.15 DES-mediated preparation of tetrazole derivatives

Xiong and coauthors [43] developed a practical, efficient and environmentally benign multigram-scale method for 5-substituted 1H-tetrazoles (**52**) from arylaldehydes (**12**), hydroxyl amine hydrochloride (**53**) and sodium azide (**54**) catalyzed by 20 mol% $Cu(OAc)_2$ in DES (choline chloride/urea) (Figure 5.15). After initial studies, the applicability of the methodology was extended to a broad range of aryl/alkyl aldehydes (**12a**). The efficiency of various catalysts like $FeCl_3$, $Zn(OAc)_2$, $ZnCl_2$, $CuCl_2{\cdot}2H_2O$, Cu_2O, $Cu(NO_3)_2{\cdot}3H_2O$ and $Cu(OAc)_2$ was evaluated. It was observed that 20 mol% $Cu(OAc)_2$ provided best yields. Solvents such as EtOH, H_2O, CH_3CN, DMF, sorbitol–urea–NH_4Cl, ChCl–glycerol and ChCl–urea were evaluated for their suitability and ChCl–urea gave promising results.

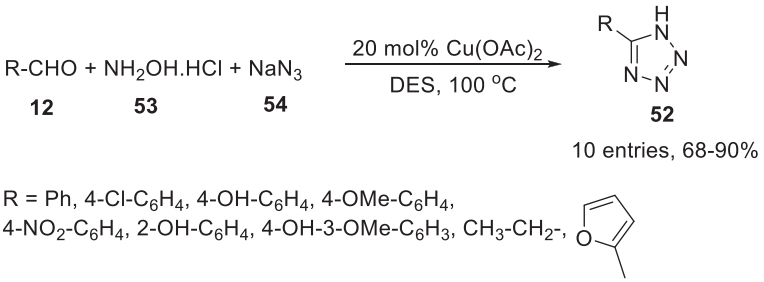
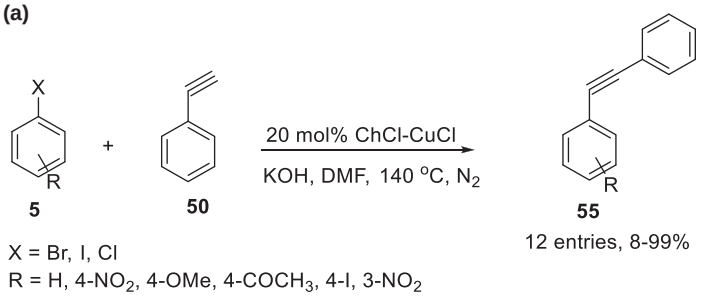


Figure 5.15: Practical preparation of 5-substituted 1H-tetrazoles.

5.2.16 DES-mediated palladium-free Sonogashira-type cross-coupling

Hajipour et al. [44] employed ChCl–CuCl as an effective homogeneous catalytic system for palladium-free Sonogashira-type cross-coupling reaction of phenyl acetylene (**50**) with a broad range of aryl halides (**5**) (Figure 5.16a and b). During optimization, the efficiency of different bases like KOH, t-BuOK and K_2CO_3 and the suitability of various solvents such as DMF, DMSO and NMP were investigated. The reactions proceeded with best yields in the presence of 20 mol% ChCl–CuCl and KOH/DMF system at 140 °C under N_2 atmosphere.



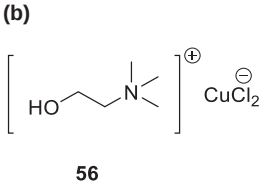


Figure 5.16: (a) Reactions of phenyl acetylene with aryl halides and (b) catalyst.

5.2.17 DES-mediated synthesis of tetrahydroisoquinolines

Marset and coauthors [45] prepared a library of tetrahydroisoquinolines (**57**) from 2-(4-flourophenyl)-1,2,3,4-tetrahydroisoquinoline (**58**) and phenyl acetylene (**50**) by cross-dehydrogenative coupling promoted by copper oxide impregnated on magnetite in choline chloride–ethylene glycol as DES, employing biorenewable air as the only oxidizing agent (Figure 5.17a and b). During initial studies, the efficiency of catalyst concentrations and suitability of different DES on the protocol were examined. Ethylene glycol, ChCl:EG, ChCl:resorcinol, ChCl:urea, AcChCl:urea, ChCl:glycerol and $Ph_3P^+MeBr^-$:glycerol were evaluated at different concentrations for the study. To prove the importance of DES, other organic solvents like MeOH, DMSO, PhMe, H_2O, THF, DMF, DCE and 1,4-dioxane were also evaluated in the comparative study. The activities of various metal oxides impregnated on magnetite were screened for the methodology. The scope of the reaction with diversified pro-electrophiles was also taken up for the study. The protocol was extended to a diverse range of alkynes (**50a**) as well as pro-nucleophiles.

5.2.18 DES-mediated preparation of benzimidazole-based scaffolds

Piemontese Luca et al. [46] designed and developed the synthesis of 2-hydroxyphenyl benzimidazole (**61**)-based scaffolds including a medicinally important hit compound PZ-1 (**62**), based on the framework of acetyl cholinesterase inhibitor Donepezil (Figure 5.18a and b). During the initial investigations on the preparation of 2-hydroxyphenyl

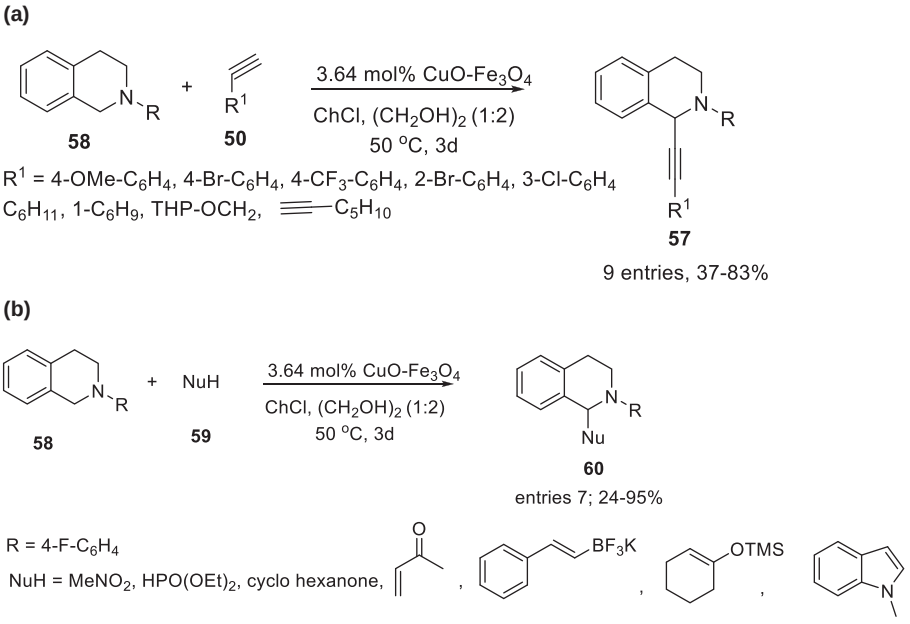


Figure 5.17: Synthesis of tetrahydroisoquinolines (a) assisted by Cuo–Fe_3O_4 in ChCl–$(CH_2OH)_2$, involving different alkynes (**50a**) and (b) employing various pronucleophiles.

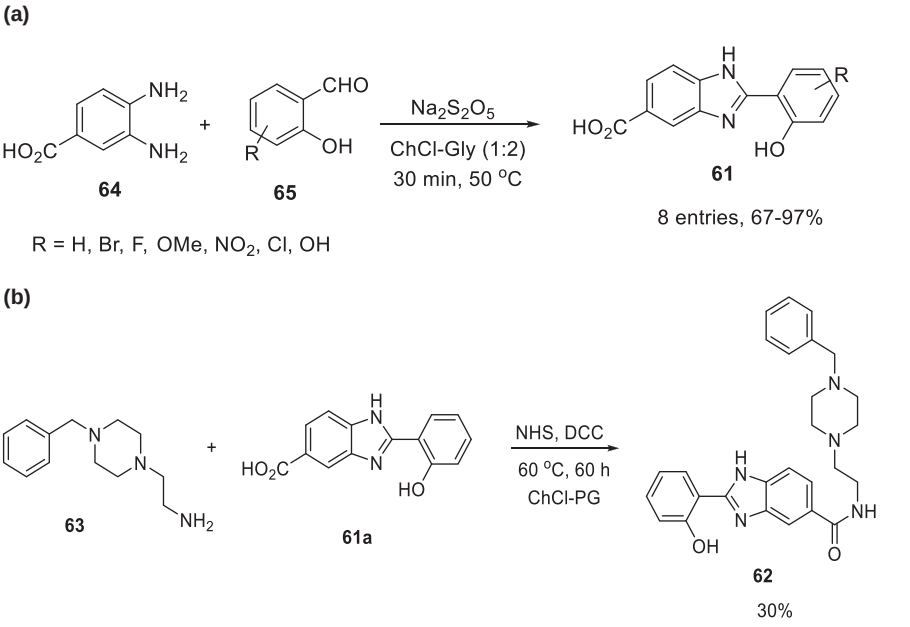


Figure 5.18: Synthesis of (a) 2-OH-phenylbenzimidazole and (b) PZ-1.

benzimidazole (**61**), oxidants like $Na_2S_2O_5$ and urea–H_2O were evaluated. Solvents such as ChCl–urea, ChCl–gly, ChCl–LA and DMA were investigated for achieving best results. Other parameters like suitable bases, molecular equivalents, reaction temperatures and reaction times were examined. Preparation of PZ-1 (**62**) was reported in a one-pot two-step methodology by the reaction of 2-hydroxyphenyl benzimidazole derivatives (**61**) with *N*-benzylated adduct (**63**) in the presence of *N*, N^1-dicyclohexylcarbodiimide, *N*-hydroxysuccinimide and ChCl–PG (1:3) at 60 °C for 60 h in an overall yield of 30%.

5.2.19 DES-mediated Ullmann coupling

Shaabani and Afshari [47] demonstrated the catalytic efficiency of newly designed and developed CuNP-carboxamide-f-Go@Fe_3O_4 nanocomposite by applying for the Ullmann coupling of the *N*-heterocycles and primary amines (**8c**) with aryl halides (**5**) by following the successful completion of the synthesis of 1-(4-methoxyphenyl) piperidine (**66**) (Figure 5.19). The effects of the engineering aspects, reaction temperature, solvents and bases on the kinetics of the reaction of the protocol were investigated. Authors successfully designed and prepared carboxamide-functionalized graphene oxide-decorated copper nanoparticles via a four-component Ugi reaction (Cu Np-carboxamide-f-Go@Fe_3O_4-nanocomposite). For the Ullman reaction, several solvents such as DMF, DMSO, H_2O, EtOH, ChCl–urea, ChCl–malonic acid, ChCl–EG, $ChCl_3$–$FeCl_3$, ChCl–citric acid and Ch–glycerol, and bases like K_2CO_3, Cs_2CO_3, NaOH, NH_4Cl and Cs_2CO_3 were screened. The authors reported recyclability of the catalyst as well as DES.

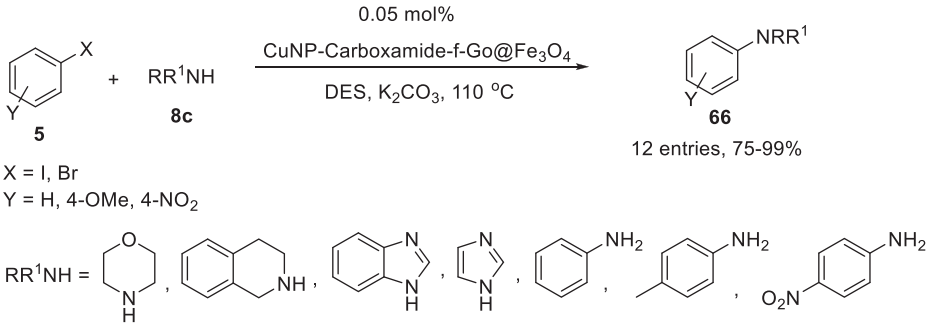


Figure 5.19: Ullman coupling assisted by the new catalyst.

5.2.20 DES-mediated preparation of *N*-acyl ureas

Abbasi and coauthors [48] described an efficient preparation of *N*-aryl ureas (**67**) from the reaction of carbodiimides (**68**) with carboxylic acids (**32**) by employing magnetically separable, reusable copper oxide, supported on magnetic nanoparticles-CuO@γ-Fe_2O_3 in ChCl–urea at 60 °C in 6 h (Figure 5.20).

During initial investigations, different parameters like reaction times, temperatures and suitability of several solvents were examined. Among solvents such as ChCl–urea ChCl–gly, CH_2Cl_2, *n*-hexane, toluene, THF, H_2O and Gly/K_2CO_3, ChCl–urea was observed to provide best results. The catalyst can be used up to five cycles without any significant loss of activity. DES is recovered and reused up to four cycles.

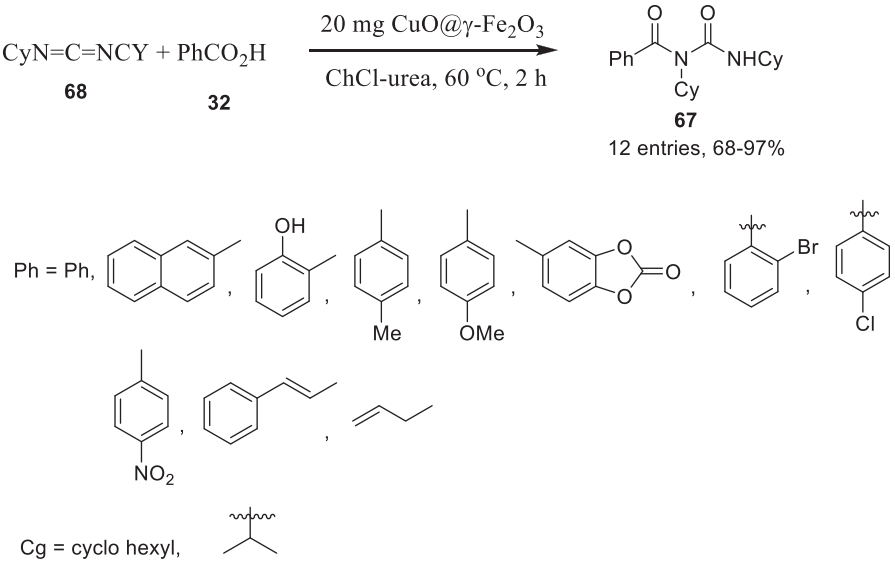


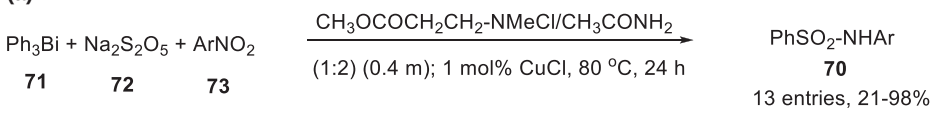
Figure 5.20: Synthesis of *N*-acyl ureas.

5.2.21 DES-mediated preparation of sulfonamides from triarylbismuthines

Marset et al. [49] narrated a suitable one-pot one-step multicomponent synthesis of sulfonamides (**70**) from triarylbismuthines (**71**), sodium metabisulfite ($Na_2S_2O_5$) (**72**) and aromatic nitro compounds (**73**) catalyzed by 1 mol% copper chloride (CuCl) in the presence of AcCh–Cl:acetamide (1:2) at 80 °C in 24 h (Figure 5.21a–c). The protocol was applied to generate a library of sulfonamides (**70**) from diverse range of triarylbismuthines (**71**) and

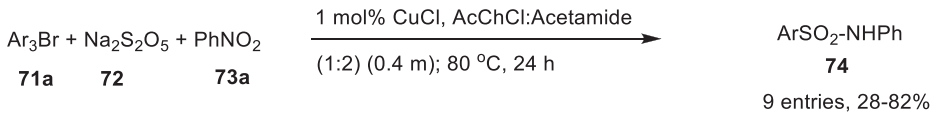
aromatic nitro derivatives (**73**). Solvents such as MeOH, toluene, ChCl–urea, ChCl–acetamide, AcChCl–urea and AcChCl–acetamide were screened, and it was observed that AcChCl–acetamide provided excellent yields. An anti-leprosy compound (**75**) was reportedly prepared using the new methodology.

(a)



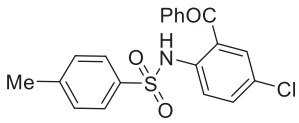
Ar = H, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NH_2-C_6H_4, 4-OH-C_6H_4, 4-Cl-C_6H_4, 4-Ac-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4, 2-Br-C_6H_4, 3-$PhSO_2NH$-C_6H_4, 2-naphthyl, cyclohexyl

(b)



Ar = 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NMe_2-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 2-CF_3-C_6H_4, 3-CF_3-C_6H_4, 3,4,5-OMe_3-C_6H_2, 1-naphthyl

(c)



75

Figure 5.21: Scope of (a) diversified nitro compounds in the methodology, (b) triaryl bismuthines and (c) anti-leprosy compound.

5.2.22 DES-mediated C–S bond formation reactions

Marset et al. [50] discussed the scope and mechanistic studies where recyclable, biodegradable and cost-effective DES were used as media for the Pd-catalyzed new C–S bond formation reactions (**78**/**79**), starting from aryl boronic acids (**76**) and sodium metabisulfite (**72**) (Figure 5.22a–c). The catalytic system is reusable up to three runs without reduction in the yields of the products.

The course of the reaction was observed by employing hydroxyl-functionalized alkene as a radical scavenger.

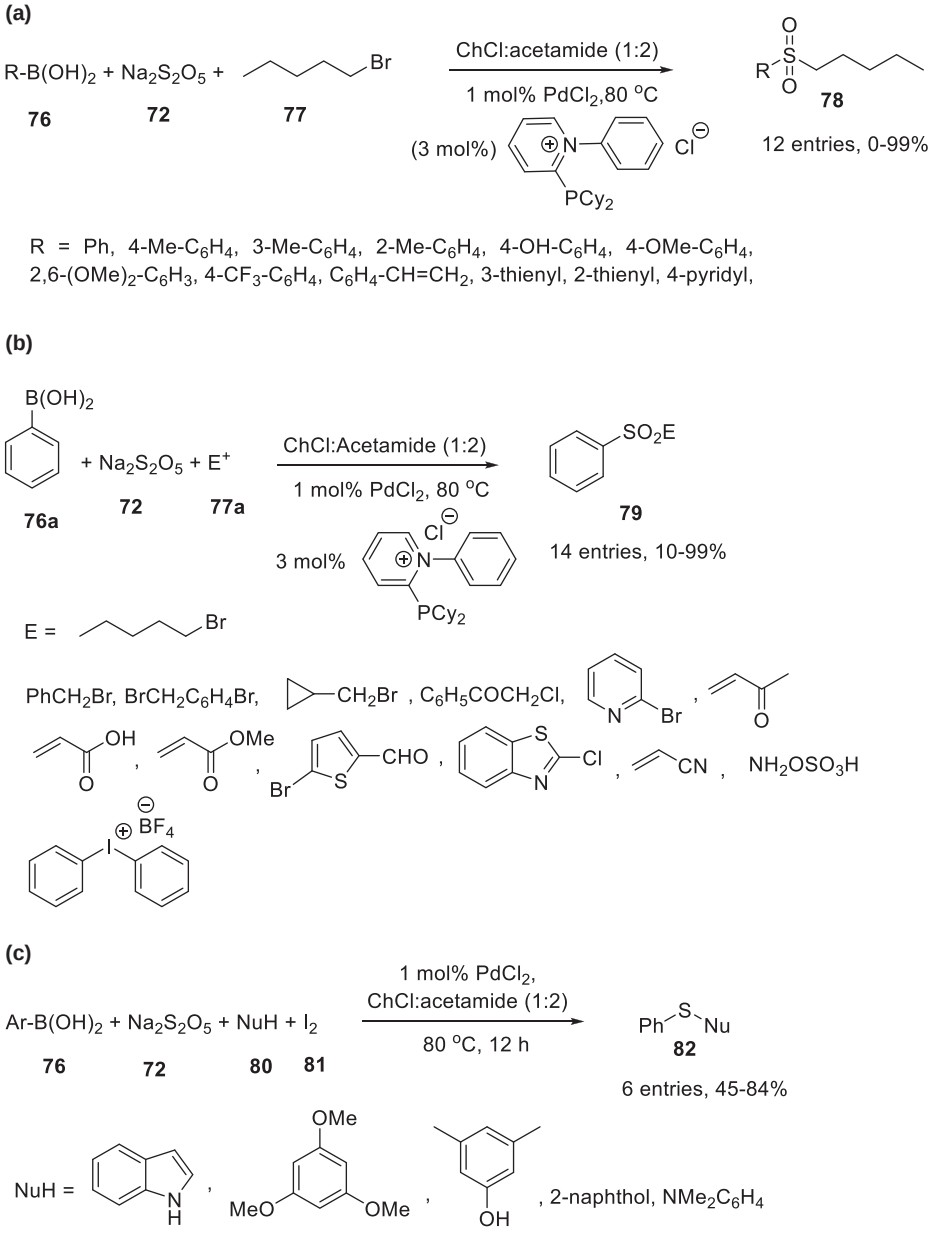


Figure 5.22: Scope of (a) boronic acids in the C–S bond formation reactions, (b) electrophiles in the C–S bond formation reactions and (c) aryl sulfides.

5.2.23 DES-mediated Ullman-type C–O bond formations

Quivelli and coauthors [51] established an efficient and ecofriendly novel protocol involving ligand-free Cu-catalyzed Ullman-type C–O bond formation (aryl allyl ethers) (**83**) accomplished by the reaction of various hetero/aryl halides (Cl, Br and I) (**5**) with alcohols (**84**) using choline chloride-based eutectic solvents at 80 °C in the absence of any ligand system (Figure 5.23). The new methodology was applied to the valorization of naturally occurring polyols for the synthesis of some bioactive aryloxy propane diols (**85**). In this method, catalyst, DES and base are recyclable up to several cycles, with an *E*-factor 5.76. While working on initial optimization studies, authors examined the scope of the catalysts like CuI, CuO, $CuCl_2$ and $Pd(OAc)_2$ as well as bases such as K_2CO_3, Cs_2CO_3 and t-BuOK. Gly, ChCl-gly, Pro-Gly and betaine-gly were tested for their suitability as a reaction medium.

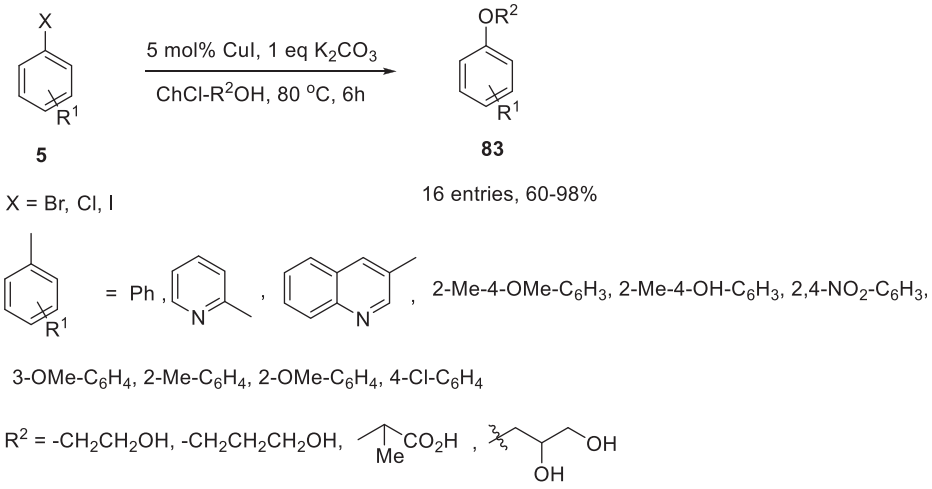


Figure 5.23: Synthesis of aryl alkyl ethers via Cu-catalyzed cross-coupling reactions of hetero/aryl halides with alcohols of ChCl-based eutectic mixtures.

5.2.24 DES-mediated synthesis of highly substituted pyridine compounds

Vadagaonkar et al. [52] unveiled an eco-friendly, economical synthesis of a library of partly and fully substituted pyrimidines (**86**) via [3 +3] tandem annulation–oxidation approach from α,β-unsaturated ketones (**87**) and benzamidine hydrochloride (**88**) employing reusable choline hydroxide (ChOH) as both medium and catalyst under mild reaction conditions and in short reaction times (Figure 5.24). While working on a model reaction between 1,3-diphenyl-2-en-1-one (**89**) and benzamidine hydrochloride

(**88**), authors exhaustively examined the effect of different bases, solvents as well as reaction temperatures. K_2CO_3/CH_3CN, K_3PO_4/CH_3CN, Cs_2CO_3/CH_3CN, NaOH/EtOH, CsOH/DMF, NaH/THF, KtBuO/THF, DBU/CH_3CN, pyridine/THF, piperidine/EtOH, NEt_3/CH_3CN, ChCl/urea, ChCl/PTSA, ChOH, H_2O, EtOH, CH_3CN, THF, DCE, 1,4-dioxane and toluene were evaluated for suitability and promising results. DES-ChOH was reused up to four times without significant loss of activity.

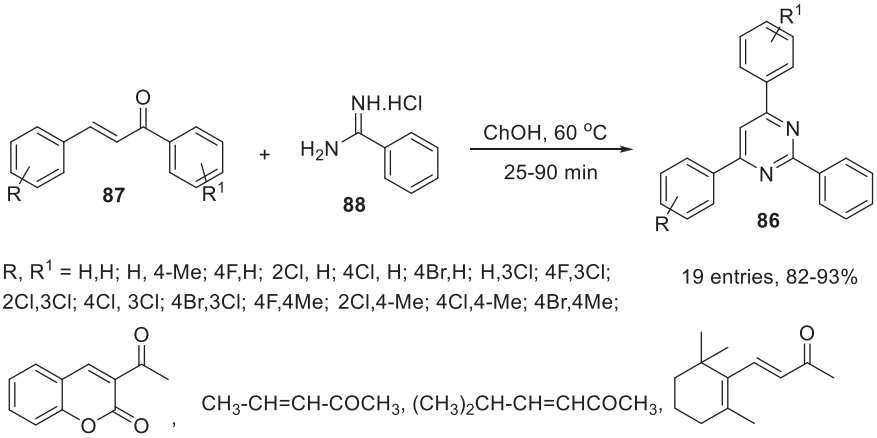


Figure 5.24: Synthesis of pyrimidine derivatives via [3 +3] tandem annulation–oxidation process promoted by ChOH.

5.2.25 DES-mediated synthesis of substituted quinazolinones

Ghosh and Nagarajan [53] developed cost-effective green protocol for a series of substituted quinazolinones (**90/97**) and dihydroquinazolinones (**91/95/96**) via DES L-(+)-tartaric acid–*N*-*N*^{1}-dimethyl urea (DMU) (3:7)] supported by cyclization with a broad range of aliphatic/aromatic/heteroaromatic aldehydes/ketones (**12/12b**) (Figure 5.25a–d). The strategy was extended to build several biologically important natural products as well as drug molecules containing quinazolinone (**90**) frameworks. Citric acid–DMU, D(–)-fructose–DMU, mannose–DMU–NH_4Cl and L(+)-tartaric acid–DMU were screened for their efficiency. L(+)-Tartaric acid–DMU (3:7) mixture at 90 °C provided excellent results. It was noted that with variation of time, both dihydroquinazolinone (**91**) and quinazolinone (**90**) products were obtained.

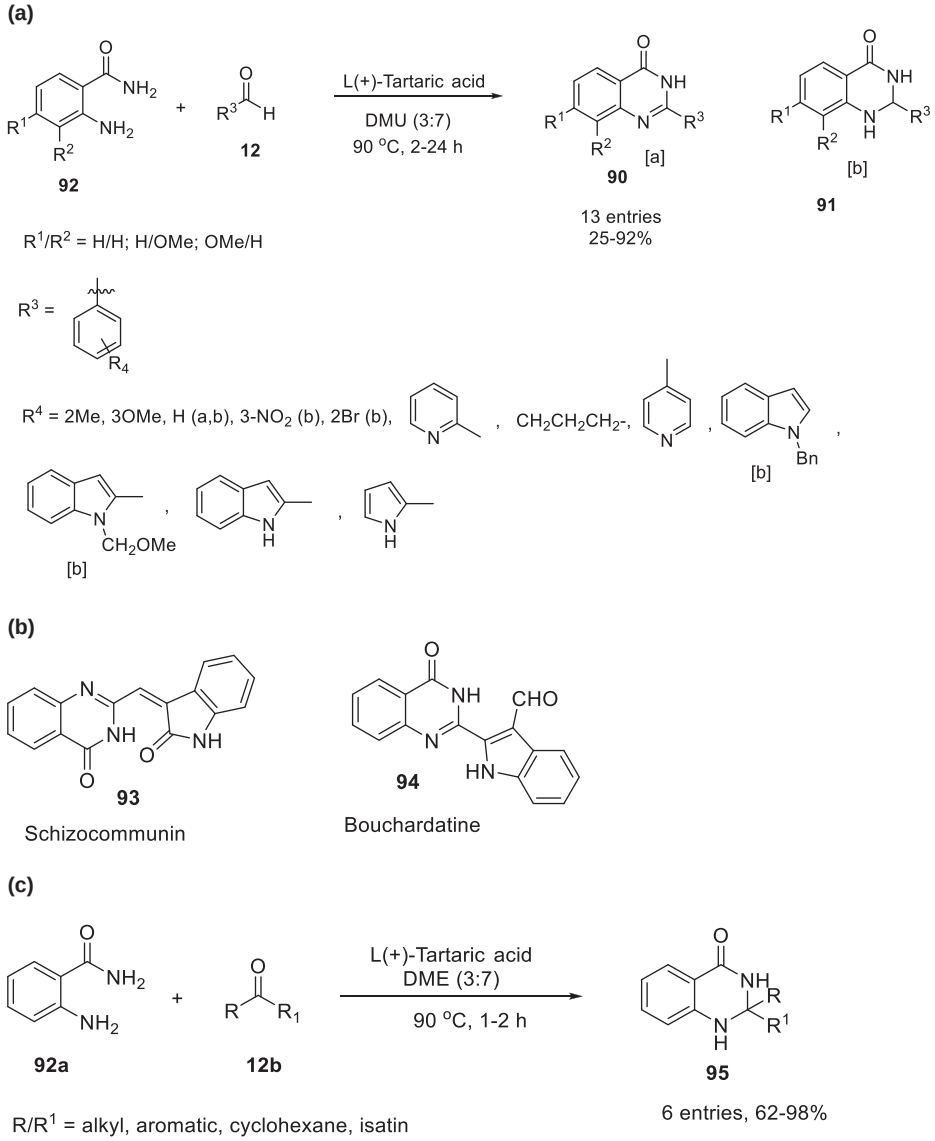


Figure 5.25: Synthesis of (a) 2-substituted quinazolinones, (b) alkaloid molecules, (c) 2,2[1]-disubstituted quinazolinones and (d) 2,3-disubstituted quinazolinones.

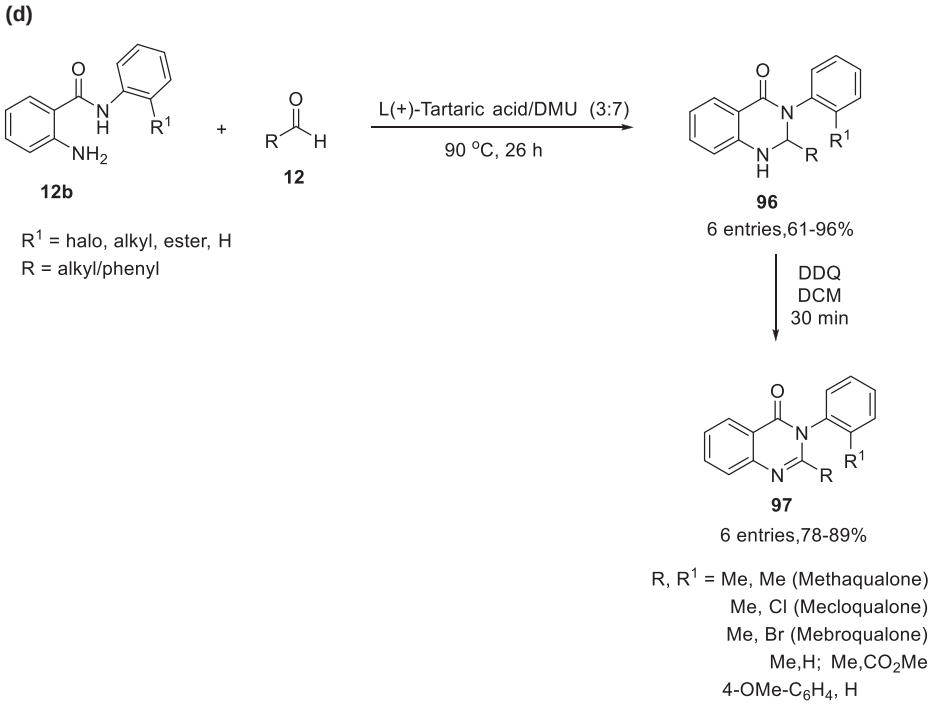
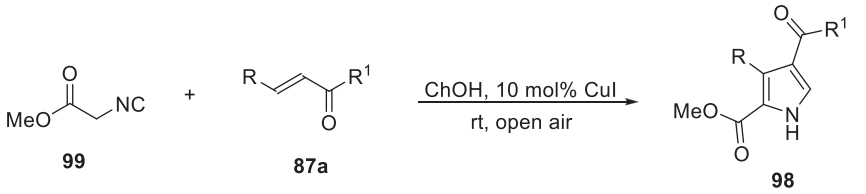


Figure 5.25 (continued)

5.2.26 DES-mediated synthesis of 2,3,4-trisubstituted-1H-pyrroles

Kalmode et al. [54] successfully utilized recyclable choline chloride as a base and reaction medium for an eco-friendly regioselective synthesis of 2,3,4-trisubstituted-1H-pyrroles (**98**), by the reaction of α,β-unsaturated ketones (**87a**) and methyl-2-isocyanoacetate (**99**) via the 1,4-conjugate addition of methyl-2-isocyanoacetate (**99**) with α,β-unsaturated ketones (**87a**) followed by the intramolecular cyclization oxidation reaction (Figure 5.26). During optimization studies, authors screened several bases like Cs_2CO_3, K_2CO_3, NaOMe, K*t*BuO, NaH, DBU, NEt_3, pyridine, 2,6-lutidine, ChCl–PTSA, ChCl–urea and ChOH for their efficiency. CuI, CuCl, CuBr, $CuBr_2$ and $Cu(OAc)_2$ were examined for their catalytic efficacies. CH_3CN, DMF, MeOH, THF, DCM and H_2O were checked for their suitability as solvents. The authors reused DES up to four runs without significant loss of activity.



R = Me, OEt, Ph, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 4-OMe-C_6H_4
R^1 = Me, OEt, Ph, 3-Cl-C_6H_4, 4-Me-C_6H_4,

Figure 5.26: ChOH/CuI-assisted preparation of 2,3,4-trisubstituted 1H-pyrroles.

5.2.27 DES-mediated oxidation reactions

Gadilohar et al. [55] employed choline peroxydisulfate (ChPS) as an environmentally benign biodegradable oxidizing task-specific ionic liquid for selective and faster oxidation of alcohols (**84**) to aldehydes (**100**)/ketones (**101/102**) under solvent-free mild reaction conditions without the reactants being overoxidized to the corresponding acids (**103**) (Figure 5.27). Authors compared the efficiencies of ChPS with other peroxydisulfates for the model reaction taking benzyl alcohol (**104**) as the substrate and other standardized reaction parameters.

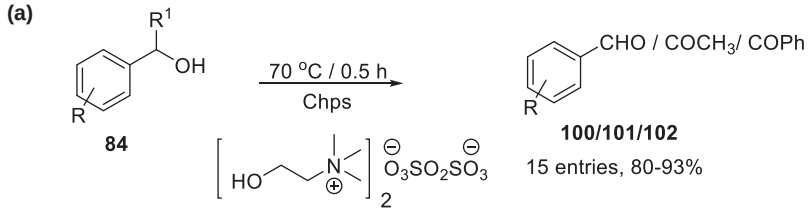


Figure 5.27: ChPS-promoted oxidation of alcohols.

Zhang et al. [56] prepared a novel DES-supported TEMPO containing *N*-*N*^{1}-dimethyl-4^1-(2,2,6,6-tetramethyl-1-oxyl-4-piperidoxyl) butyl)dodecyl ammonium salt ([Quaternium-Tempo]$^+$Br$^-$) (**105**) and urea (**106**). The DES-TEMPO/$Fe(NO_3)_3$ was used as an efficient catalytic system for the selective oxidation of a wide range of alcohols (**84**) to aldehydes (**107**)/

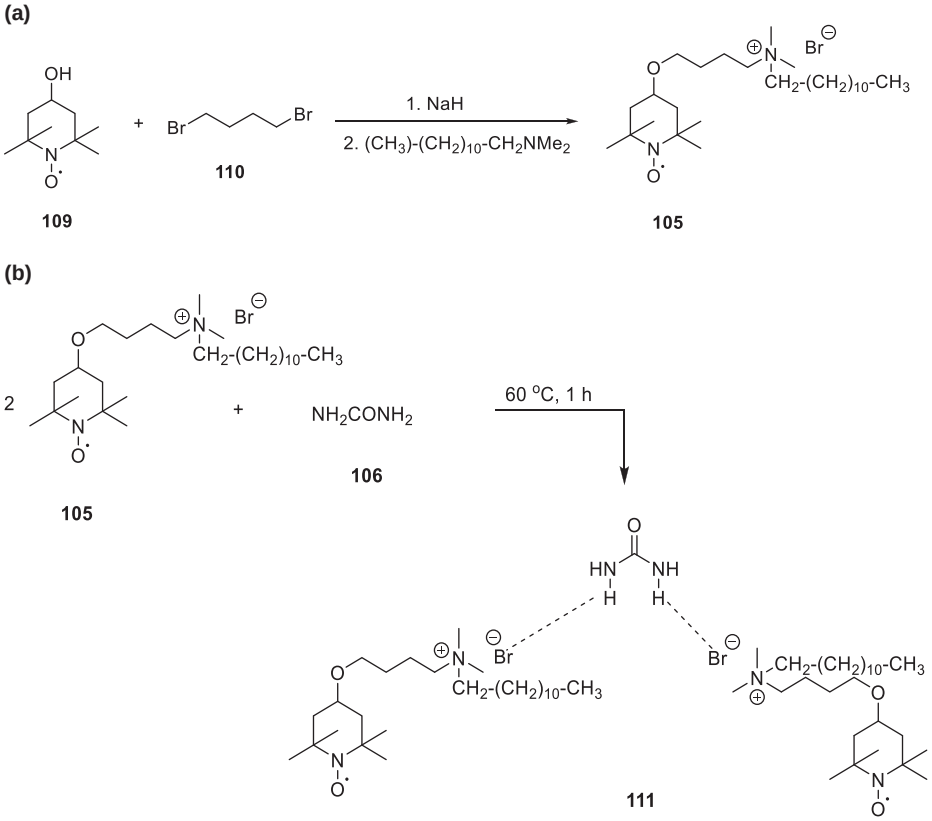


Figure 5.28: Preparation of (a) [Quaternium-TEMPO]$^{+}$Br^{-} and (b) DES-supported TEMPO and (c) oxidation of alcohols by Tempo-supported DES/$Fe(NO_3)_3{\cdot}9H_2O$.

ketones (**108**) under solvent-free mild reaction conditions (Figure 5.28a–c). The authors reused DES system five times without significant loss of activity.

Wagh et al. [57] successfully employed ChCl–urea as a green solvent and H_2O_2 as an oxidant for the oxidation of aldehydes (**12a**) to carboxylic acids (**112**) at ambient temperatures (Figure 5.29). Initially, the authors examined the efficiency of various solvents like MeCN, MeOH, EtOAc, pet ether, H_2O and toluene, apart from ChCl–urea (DES). Oxone, *m*-CPBA, UHP, H_2O_2 and 70% TBHP were investigated for their ability as oxidants for this protocol. ChCl–malonic acid, ChCl–glycerol, ChCl–acetamide, ChCl–citric acid and $ZnCl_2$–urea were evaluated as DES systems. DES system was successfully recycled for about four cycles without any significant loss. Scale-up studies were also conducted. This operationally simple method is tolerant toward a broad range of aldehydes.

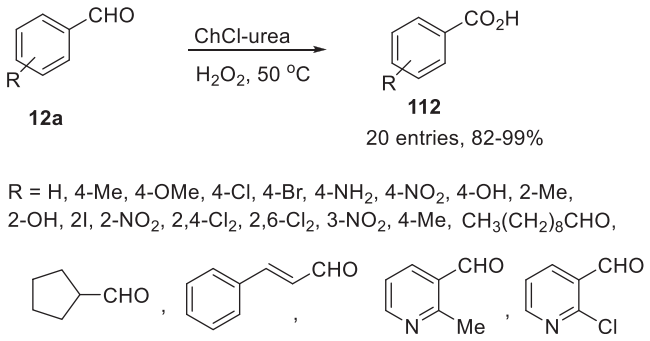


Figure 5.29: ChCl–urea/H_2O_2-promoted oxidation reactions.

5.2.28 DES-mediated conversion of furfural

Ni et al. [58] reported an efficient conversion of furfural (**12c**) to valuable chemicals like maleic acid (**113**) and fumaric acid (**114**) using a mixture of oxalic acid and choline chloride as a DES wherein oxalic acid acted as solvent as well as acidic catalyst (Figure 5.30). The authors reported 100% conversion of furfural (**12c**) at 50 °C with hydrogen peroxide as an oxidizer. The total yield of MA (**113**) and FA (**114**) is reported as 95.7%.

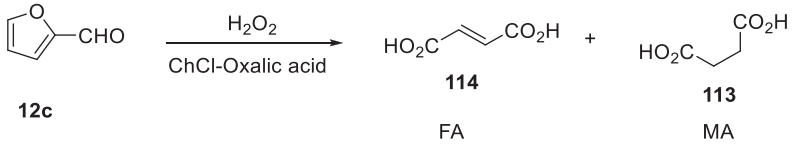


Figure 5.30: Conversion of furfural to maleic acid and fumaric acid.

5.2.29 DES-mediated synthesis of cyclic carbonates

Vagnoni et al. [59] utilized choline-based eutectic mixtures as cost-effective, nontoxic, bio-based catalysts for the synthesis of cyclic carbonates (**115**) from CO_2 (**116**) and various epoxides (**117**), under mild conditions at 80 °C in 7–22 h. The catalysts can be recycled and reused up to four runs without any significant loss of activity. Synergistic activity of the halide in opening the epoxy moiety and stabilization of alkoxide intermediate by HBD are important features of this process, wherein choline chloride and choline iodide are coupled with different HBDs. Urea, ethylene glycol, glycerol, oxalic acid, citric acid, malonic acid, tartaric acid, malic acid, fumaric acid, 3-OH-butyric acid, α-OH isobutyric acid, crotonic acid, benzoic acid, butanoic acid, octanoic acid and acetic acid were evaluated as HBDs. Most of these are bio-based and nontoxic. The authors examined the effect of variations of pressures, time and amounts of catalysts on the protocol. The terminal epoxides (**117**) were easily transformed to cyclic carbonates (**115**) with appreciable yields.

5.2.30 DES-mediated preparation of cyanohydrins

Azizi et al. [60] developed a facile and highly efficient preparation of cyanohydrins (**118**/**120**) from aldehydes (**12a**) and epoxides (**117**) using TMSCN (**119**) catalyzed by magnetically recoverable Fe_3O_4 nanoparticles in urea–ChCl DES system under mild reaction conditions (Figure 5.31a–c). Magnetic DES was reused up to three runs.

5.2.31 DES-mediated preparation of pyridine-5-carbonitriles

Zhang et al. [61] designed and developed a novel, recyclable, highly efficient heterogeneous magnetically separable graphene oxide-anchored sulfonic acid catalyst and applied it in an eco-friendly preparation of 3,6-di(pyridin-3-yl)1H-pyrazolo [3,4-b] pyridine-5-carbonitriles (**123**) via a one-pot three-component approach employing 1-phenyl-3(pyridine-3yl) propane nitrile (**124**) and aldehydes (**12**/**12a**) as reactants in choline chloride/glycerol as DES under microwave conditions (Figure 5.32). The catalyst was characterized by SEM, TEM, XRD and vibrating sample magnetometer techniques. The catalytic system was reused successfully for eight cycles.

The catalyst $CoFe_2O_4$-Go-SO_3H was prepared in a three-step procedure from graphene powder, $FeCl_3$, $CoCl_2$ and chlorosulfonic acid. ChCl/glycerol (1:3) ChCl/itaconic acid (1:1), ChCl/citric acid (1:2), ChCl/urea (1:2), ChCl/glucose, ChCl/L-(+)-tartaric acid (2:1), glucose, H_2O and EtOH as well as solvent-free conditions were examined for the smooth conduct of the process.

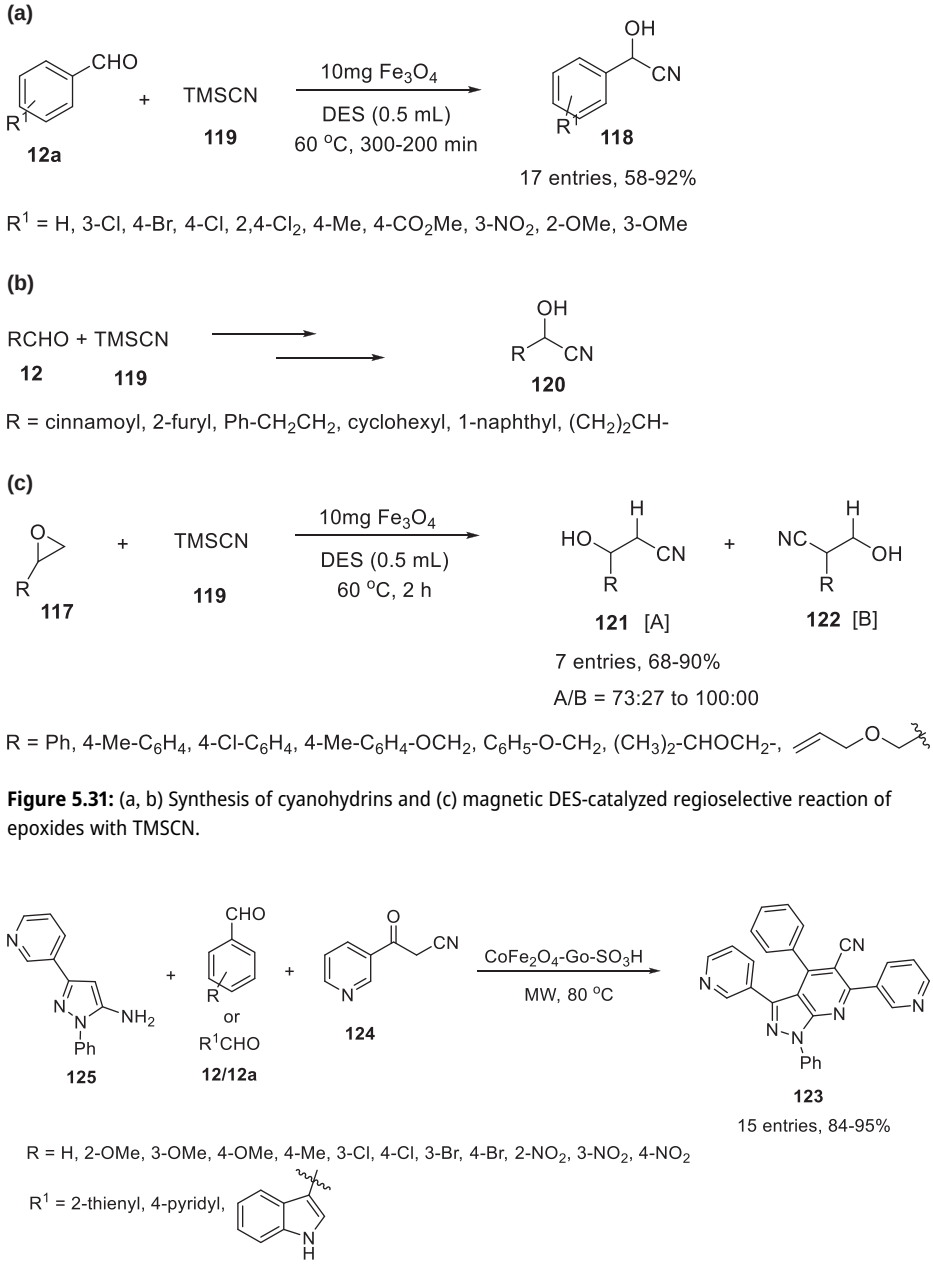


Figure 5.31: (a, b) Synthesis of cyanohydrins and (c) magnetic DES-catalyzed regioselective reaction of epoxides with TMSCN.

Figure 5.32: $CoFe_2O_4$-Go-SO_3H-assisted approach for the preparation of 3,6-di(pyridine-3yl)-1H-pyrazolo [3,4-b] pyridine-5-carbonitriles.

5.2.32 DES-mediated preparation of thiophene derivatives

Choline chloride–glycerol was successfully employed as a non-conventional green solvent by Mancuso et al. [62] for heterocyclodehydration and iodo-cyclization of readily available 1-mercapto-3yn-2-ols (**126**) at 50 °C in 8 h in the presence of PdI_2/KI or with I_2 at RT for 5 h affording thiophenes (**127**) in ChCl–glycerol (Figure 5.33a and b). The catalytic system was recycled for six runs without appreciable loss of activity.

The authors also carried out the addition reaction of lithium acetylides (**129**) to 3-mercapto butan-2-one (**130**) in different DES mixtures such as ChCl–gly (1:2), ChCl–urea (1:2), ChCl–D-sorbitol (1:1) and ChCl-D-fructose (1:1).

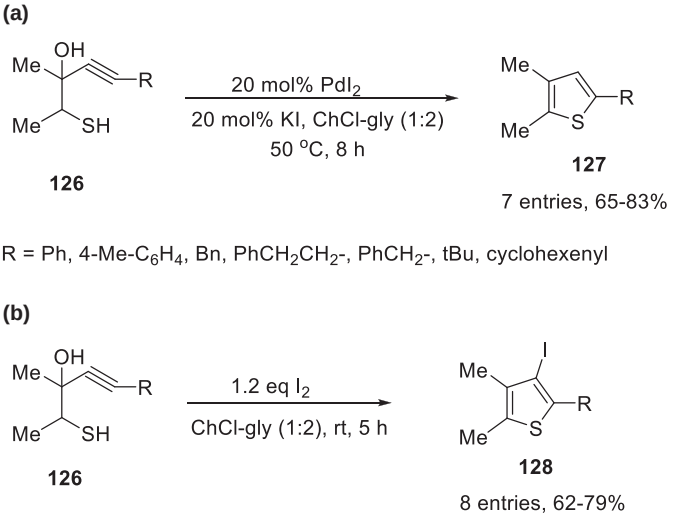
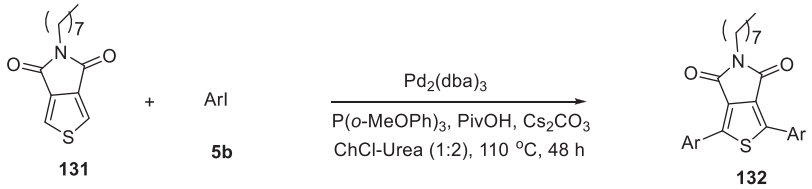


Figure 5.33: (a) Preparation of thiophenes in ChCl–glycerol and (b) base-free synthesis of 3-iodothiophenes in ChCl–glycerol.

5.2.33 DES-mediated direct arylation

Punzi et al. [63] demonstrated direct arylation of 5-octyl-thieno[3,4-c]pyrrole-4,6-dione (**131**) with a series of functionalized aryl iodides (**5b**) via C–H bond activation in eco-friendly medium ChCl–urea (1:2) at 110 °C (Figure 5.34). During optimization, authors exhaustively investigated the efficiencies of different catalysts, additives, solvents as well as ligands for the protocol. Small amounts of cyclopentyl methyl ether produced remarkable enhancement in the yields. The methodology was convenient and practical with functional group tolerance.



Ar = 4-Me-C_6H_4, 3-Me-C_6H_4, 3,5 Me-C_6H_3, 2-Me-C_6H_4, 1-naphthyl, 4-NO_2-C_6H_4, 4-$COCH_3$-C_6H_4, 4-OMe-C_6H_4, 4-CO_2Me-C_6H_4, 4-F-C_6H_4

Figure 5.34: Direct arylation with ChCl–urea.

5.2.34 DES-mediated preparation of primary amides

Several primary amides (**133/135/137–141**) were prepared in an environmentally benign approach from aldehydes (**12a/87a/87b**) and nitriles (**134/134a/134b**) by Patil et al. [64], employing choline chloride/$ZnCl_2$ system (Figure 5.35a–g). DES was recycled for three runs.

5.2.35 DES-mediated isomerization of γ-alkynoic acids

Rodríguez-Álvarez et al. [65] unveiled reusable new air-stable iminophosphorane–Au(I) complex (**142**)-assisted isomerization of γ-alkynoic acids (**143**) using ChCl–urea (1:2) at room temperatures under aerobic conditions (Figure 5.36a and b). The authors prepared iminophosphorane–Au(I) complex (**142**) by the treatment of PTA (PTA= 1,3,5-triaza-7-phosphaadamantane)-based iminophosphorane ligand with [$AuCl(SMe)_2$] in dichloromethane at room temperature. The complex obtained was analyzed using elemental analysis, IR and multinuclear NMR spectroscopy. Initially, the authors screened catalysts such as Au_2O_3, [$AuCl(PPh_3)_3$] and iminophosphorane–Au(I) complex for the efficiency. Solvents like H_2O, glycerol, toluene, ChCl–gly (1:2), ChCl–EG (1:2), ChCl–Lac (1:2) and ChCl–urea (1:2) were tested for suitability. The catalytic system was recycled up to four runs. The green protocol displayed broad substrate scope and functional compatibility.

5.2.36 DES-mediated cyclo-isomerization/DA reaction

Vidal et al. [66] conveniently conducted cyclo-isomerization reactions of (*Z*)-enynols (**145**) into furans (**146**) in ChCl–gly (1:2) at room temperature conditions, employing newly designed recyclable air-stable *bis*(iminophosphorane–AuI complex catalyst (**147**) (Figure 5.37a–c). Following the intermolecular one-pot atom-economical tandem process, cyclo-isomerization of (*Z*)-enynols (**145**)/Diels–Alder reaction using activated

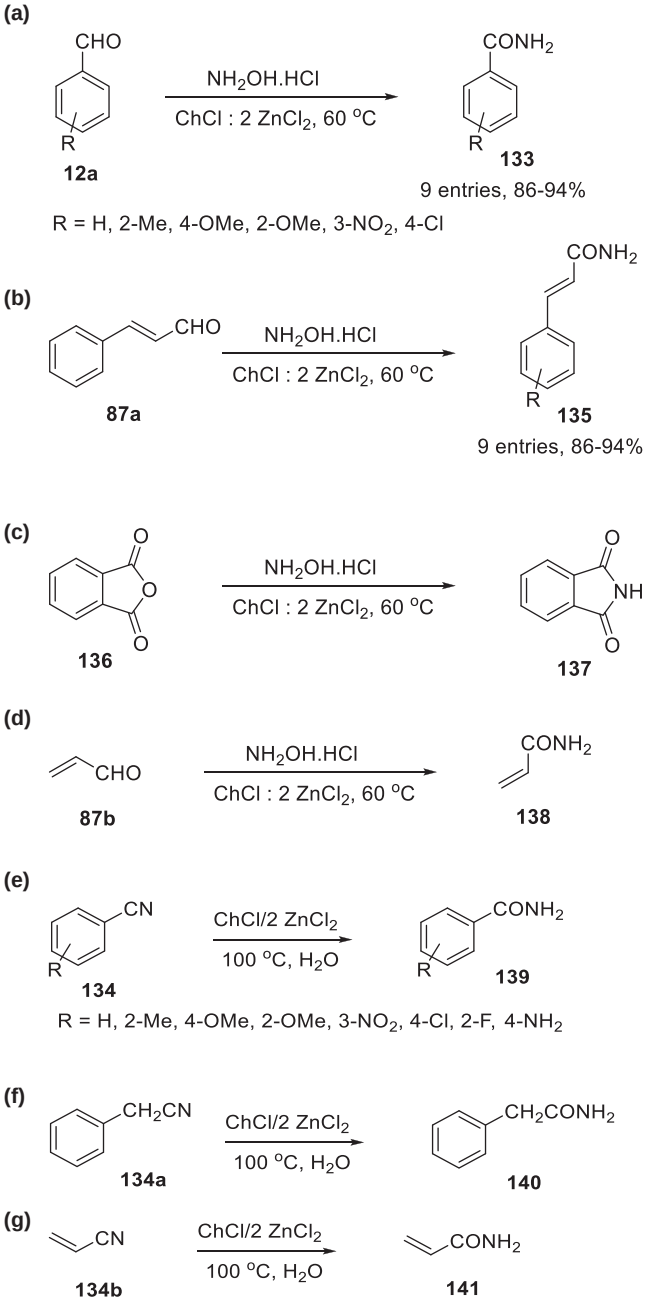


Figure 5.35: (a–d) Preparation of amides and (e–g) conversion of nitriles to amides.

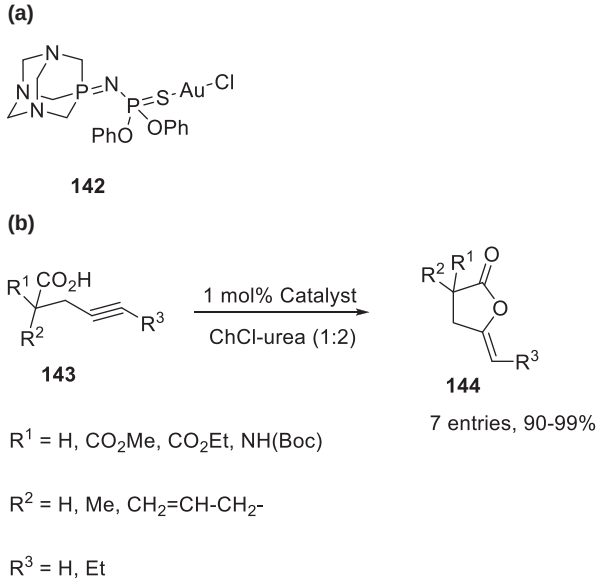


Figure 5.36: (a) Iminophosphorane–Au(I) complex and (b) cyclo-isomerization of gamma-alkynoic acid in ChCl–urea (1:2).

alkynes (**50a**) or alkenes (**50b**) in the absence of cocatalysts and 7-oxonorbornenes was described, affording 1-oxanorbornadienes (**148**). $CH_2[P\{=Np(=S)(OPh)_2\}Ph_2]_2$ was treated with $[AuCl(SMe)_2]$ in CH_2Cl_2 at room temperature, leading to the formation of bimetallic complex catalyst $[Au_2Cl_2(\mu^2\text{-S, S-}CH_2\{P(=Np(=S)(OPh)_2)Ph_2\}_2)]$. The catalyst was characterized using elemental analysis, multinuclear NMR spectroscopy and XRD. The catalytic activity of the new catalyst was assured in the present research work. ChCl–gly (1:2), ChCl–lac (1:2), ChCl–H_2O (1:2), ChCl–urea (1:2), glycerol, H_2O and $[BMIM][BF_4]$ were screened as solvent media for suitability and excellent results. The process displayed broad substrate scope and functional compatibility. The model reaction involving preparation of 2,3-dimethyl furan (**146**) was observed to be showing recyclability of the catalyst in about 10 runs.

5.2.37 DES-mediated synthesis of tetrasubstituted imidazoles

Azizi et al. [67] developed a robust simple one-pot four-component synthesis of tetrasubstituted imidazoles(**149/153**) from aryl/heterocyclyl aldehydes (**12/12a**), arylamines (**8b**), 1,2-diphenyl ethane (**150**), 1,2-dione (**151**) and ammonium acetate (**152**) in the presence of eutectic mixture stabilized by iron nanoparticles at 60 °C (Figure 5.38a and b). Urea–choline chloride and catalysts were prepared under ultrasound irradiation and identified by SEM, XRD and FT-IR.

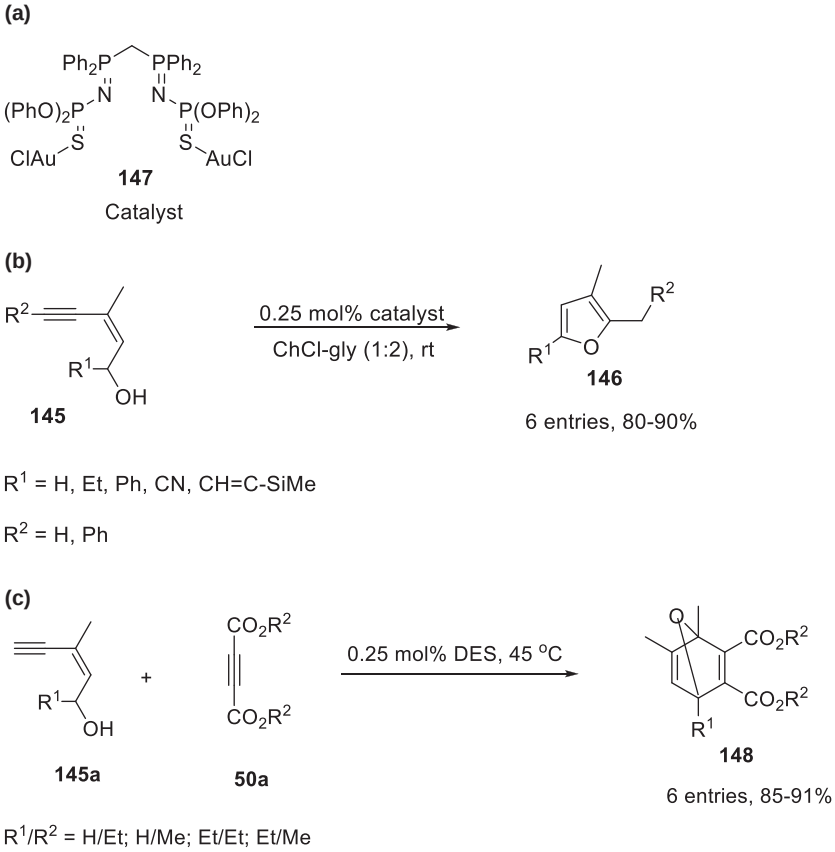
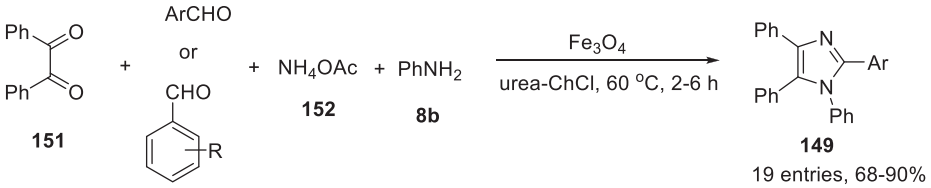


Figure 5.37: (a) Catalyst structure, (b) cyclo-isomerization of several (*Z*)-enynols in ChCl–gly (1:2) and (c) one-pot tandem cyclo-isomerization/DA reaction catalyzed by the bis(iminophosphorane)–AuI complex.

5.2.38 DES-mediated Biginelli reaction

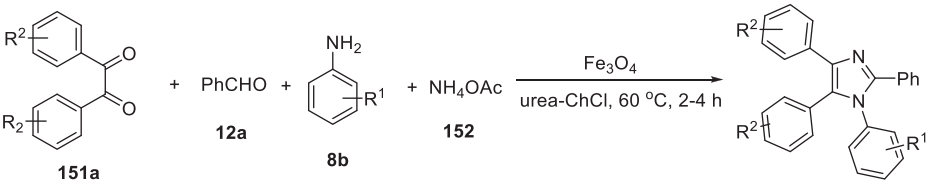
Azizi et al. [68] conducted the Biginelli reaction affording 3,4-dihydropyridine-2(1H)-one derivatives (**154**) from 1,3-dicarbonyl compounds (**155**), aromatic/aliphatic aldehydes (**12/12a**) and urea (**156**) in a simple, environmentally benign, cost-effective, recyclable eutectic solvent based on tin(II) chlorides (Figure 5.39). Initially, DES mixtures such as ChCl/gly (1:3), ChCl/$ZnCl_2$ (1:2), ChCl/urea (1:2), ChCl/$ZnCl_2$/$SnCl_2$ (1:1:1) and Ch/$SnCl_2$ (1:2) were assessed for efficiency. The protocol offers high yields, simple procedure, short reaction times, functional group tolerance and also applicable to structurally diverse substrates. DES is recycled four times without significant loss of activity.

(a)



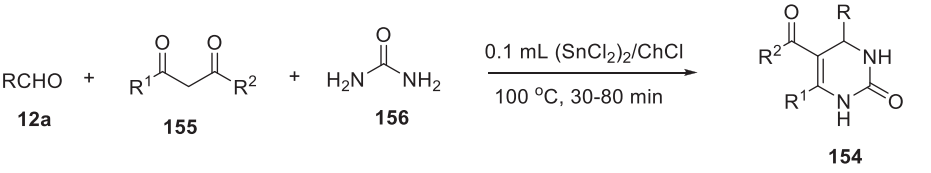
R = H, 4-Br, 4-Cl, 4-OH, 4-Me, 4-OMe, 4-$COCH_3$, 4-NO_2, 2-Me, 2-Cl, 2,4-Cl_2
Ar = 2-phenyl, 1-naphthyl, 2-naphthyl

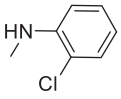
(b)



R^1 = 4-OMe, 4-Cl, 4-Br, 4-Me, 3-Me, 4-Cl
R^2 = 4-Cl, 4-OMe, H

Figure 5.38: Synthesis of (a) 1,2,4,5-tetrasubstituted imidazoles in the presence of ChCl–urea and (b) tetrasubstituted imidazoles.



R = Ph, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OMe-C_6H_4, 2,4-$(OMe)_2$-C_6H_3, 4-NO_2-C_6H_4, 3-Br-C_6H_4, 3-NO_2-C_6H_4, 2-furyl, 2,4-Cl_2-C_6H_3, 4-OH-$(Me)_2$-CH-
R^1 = Me, Ph
R^2 = OMe, OEt, Me, 

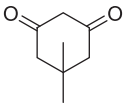
R^1 /R^2 = 

Figure 5.39: $(SnCl_2)_2$/ChCl-promoted green synthesis of dihydropyrimidinones.

5.3 Conclusions

DESs, as alternate environmentally benign solvent media, have the future potential to play a significant role in green processes. This chapter highlights the superior and significant catalytic activities of various DESs toward several organic transformations, particularly reported in the last decade. The authors wish that this chapter stimulates further research and applications of DESs to a diverse range of synthetic applications, resulting in the discovery of new and improved eco-friendly methodologies. The authors of this chapter sincerely appreciate and acknowledge the research groups of the publications cited herein. All the figures are redrawn and are representative. The readers are advised to go through the original research articles for detailed information and learning.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Conflict of interest statement: The authors declare no conflicts of interest regarding this chapter.

References

[1] Zhang, Q, Vigier, KDO, Royer, S, Jérôme, F. Deep eutectic solvents: Syntheses, properties and applications. Chem Soc Rev 2012, 41, 7108–7146.
[2] García-Álvarez, J. Deep eutectic mixtures: Promising sustainable solvents for metal-catalysed and metal-mediated organic reactions. Eur J Inorg Chem 2015, 5147–5157.
[3] Alonso, DA, Baeza, A, Chinchilla, R, Guillena, G, Pastor, IM, Ramón, DJ. Deep eutectic solvents: The organic reaction medium of the century. Eur J Org Chem 2016, 612–632.
[4] Abbott, AP, Capper, G, Davies, DL, Rasheed, RK, Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. Chem Commun 2002, 70–71.
[5] Abbott, AP, Boothby, D, Capper, G, Davies, DL, Rasheed, RK. Deep eutectic solvents formed between choline chloride and carboxylic acids: Versatile alternatives to ionic liquids. J Am Chem Soc 2004, 126, 9142–9147.
[6] García-Álvarez, J. Deep eutectic solvents and their applications as new green and biorenewable reaction media. In: Wypych, G, editor. Handbook of solvents, use, health, and environment. Toronto, Canada: ChemTec Publishing, 2019, 3e, vol. 2.
[7] Francisco, M, van den Bruinhorst, A, Kroon, MC. Low-transition-temperature mixtures (LTTMs): A new generation of designer solvents. Angew Chem Int Ed 2013, 52, 3074–3085.
[8] Avalos, M, Babiano, R, Cintas, P, Jiménez, JL, Palacios, JC. Greener media in chemical synthesis and processing. Angew Chem Int Ed 2006, 45, 3904–3908.
[9] Tang, B, Row, KH. Recent developments in deep eutectic solvents in chemical sciences. Monatsh Chem 2013, 144, 1427–1454.
[10] Paiva, A, Craveiro, R, Aroso, I, Martins, M, Reis, RL, Duarte, ARC. Natural deep eutectic solvents – solvents for the twenty-first century. ACS Sustain Chem Eng 2014, 2, 1063–1071.

[11] Liu, P, Hao, JW, Mo, LP, Zhang, ZH. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. RSC Adv 2015, 5, 48675–48704.
[12] Alonso, DA, Baeza, A, Chinchilla, R, Guillena, G, Pastor, IM, Ramón, DJ. Deep eutectic solvents: The organic reaction medium of the century. Eur J Org Chem 2016, 2016, 612–632.
[13] Khandelwal, S, Tailor, YK, Kumar, M. Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations. J Mol Liq 2016, 215, 345–386.
[14] Vigier, KO, Chatel, G, Jérôme, F. Contribution of deep eutectic solvents for biomass processing: Opportunities, challenges, and limitations. Chem Cat Chem 2015, 7, 1250–1260.
[15] Zhao, H, Baker, GA. Ionic liquids and deep eutectic solvents for biodiesel synthesis: A review. J Chem Technol Biotechnol 2013, 88, 3–12.
[16] Durand, E, Lecomte, J, Villeneuve, P. Deep eutectic solvents: Synthesis, application, and focus on lipase-catalyzed reactions. Eur J Lipid Sci Technol 2013, 115, 379–385.
[17] Guajardo, N, Muller, CR, Schrebler, R, Carlesi, C, María, PD. Deep eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations. Chem Cat Chem 2016, 8, 1020–1027.
[18] Del Monte, F, Carriazo, D, Serrano, MC, Guitiérrez, MC, Ferrer, ML. Deep eutectic solvents in polymerizations: A greener alternative to conventional syntheses. Chem Sus Chem 2014, 7, 999–1009.
[19] García-Álvarez, J. Deep eutectic mixtures: Promising sustainable solvents for metal-catalysed and metal-mediated organic reactions. Eur J Inorg Chem 2015, 2015, 5147–5157.
[20] Chakrabarti, MH, Mjalli, FS, AlNashef, IM, Hashim, MA, Hussain, MA, Bahadori, L, Low, CTJ. Prospects of applying ionic liquids and deep eutectic solvents for renewable energy storage by means of redox flow batteries. Renew Sustain Energ Rev 2014, 30, 254–270.
[21] Abo-Hamad, A, Hayyan, M, AlSaadi, MA, Hashim, MA. Potential applications of deep eutectic solvents in nanotechnology. Chem Eng J 2015, 273, 551–567.
[22] Pena-Pereira, F, Namiesnik, J. Ionic liquids and deep eutectic mixtures: Sustainable solvents for extraction processes. ChemSusChem 2014, 7, 1784–1800.
[23] Tang, B, Zhang, H, Row, KH. Application of deep eutectic solvents in the extraction and separation of target compounds from various samples. J Sep Sci 2015, 38, 1053–1064.
[24] García, G, Aparicio, S, Ullah, R, Atilhan, M. Deep eutectic solvents: Physicochemical Properties and gas separation applications. Energy Fuels 2015, 29, 2616–2644.
[25] Zhang, Q, Vigier, KO, Royer, S, Jérôme, F. Deep eutectic solvents: Syntheses, properties and applications. Chem Soc Rev 2012, 41, 7108–7146.
[26] Smith, EL, Abbott, AP, Ryder, KS. Deep eutectic solvents (DESs) and their applications. Chem Rev 2014, 114, 11060–11082.
[27] Khandelwal, S, Tailor, YK, Kumar, M. Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations. J Mol Liq 2016, 215, 345–386.
[28] Liu, P, Hao, J-W, Mo, L-P, Zhang, Z-H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. RSC Adv 2015, 5(60), 48675–48704.
[29] Saavedra, B, Ramón, DJ. Deep eutectic solvent as a sustainable medium for C-C bond formation *via* multicomponent radical conjugate additions. ACS Sustain Chem Eng 2021, 9, 7941–7947.
[30] Dilauro, G, Azzollini, CS, Vitale, P, Salomone, A, Perna, FM, Capriati, V. Scalable Negishi coupling between organozinc compounds and (hetero)aryl bromides under aerobic conditions when using bulk water or deep eutectic solvents with no additional ligands. Angew Chem Int Ed 2021, 60, 10632–10636.
[31] Gutiérrez-Hernández, A, Richaud, A, Chacón-García, L, Cortés-García, CJ, Méndez, F, Contreras-Celedón, CA. Deep eutectic solvent choline chloride/p-toluenesulfonic acid and water favor the enthalpy-driven binding of arylamines to maleimide in Aza-Michael addition. J Org Chem 2021, 86, 223–234.

[32] Shaabani, A, Hooshmand, SE. Choline chloride/urea as a deep eutectic solvent/organocatalyst promoted three-component synthesis of 3-aminoimidazo-fused heterocycles via Groebke-Blackburn -Bienayme process. Tetrahedron Lett 2016, 57, 310–313.
[33] Wang, A, Xing, P, Zheng, X, Cao, H, Yang, G, Zheng, X. Deep eutectic solvent catalyzed Friedel-Crafts alkylation of electron-rich arenes with aldehydes. RSC Adv 2015, 5, 59022–59026.
[34] Azizi, N, Gholibeglo, E, Babapour, M, Ghafuri, H, Bolourtchian, SM. Deep eutectic solvent promoted highly efficient synthesis of N, N'-diarylamidines and formamides. C R Chim 2012, 15, 768–773.
[35] Phadtare, SB, Shankarling, GS. Halogenation reactions in biodegradable solvent: Efficient bromination of substituted 1-aminoanthra-9,10-quinone in deep eutectic solvent (choline chloride: Urea). Green Chem 2010, 12(3), 458–462.
[36] Tavakol, H, Keshavarzipour, F. Preparation of choline chloride-urea deep eutectic solvent-modified magnetic nanoparticles for synthesis of various 2-amino-4H -pyran derivatives in water solution. Appl Organomet Chem 2017, 31, e3811.
[37] Fischer, V, Touraud, D, Kunz, W. Eco-friendly one pot synthesis of caffeic acid phenethyl ester (CAPE) via an in-situ formed deep eutectic solvent. Sustain Chem Pharm 2016, 4, 40–45.
[38] Singh, K, Kaur, A, Mithu, VS, Sharma, S. Metal-free organocatalytic oxidative Ugi reaction promoted by hypervalent iodine. J Org Chem 2017, 82, 5285–5293.
[39] Molnar, M, Klenkar, J, Tarnai, T. Eco-friendly rapid synthesis of 3-substituted-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones in choline chloride based deep eutectic solvent. Synth Commun 2017, 47, 1040–1045.
[40] Ranganathan, S, Zeitlhofer, S, Sieber, V. Development of a lipase-mediated epoxidation process for monoterpenes in choline chloride-based deep eutectic solvents. Green Chem 2017, 19, 2576–2586.
[41] Maleki, A, Kari, T, Aghaei, M. Fe_3O_4@SiO_2@TiO_2-OSO_3H: An efficient hierarchical nanocatalyst for the organic quinazolines syntheses. J Porous Mater 2017, 24, 1481–1496.
[42] Kafle, A, Handy, ST. A one-pot, copper-catalyzed azidation/click reaction of aryl and heteroaryl bromides in an environmentally friendly deep eutectic solvent. Tetrahedron 2017, 73, 7024–7029.
[43] Xiong, X, Yi, C, Liao, X, Lai, S. A practical multigram-scale method for the green synthesis of 5-substituted-1H-tetrazoles in deep eutectic solvent. Tetrahedron Lett 2019, 60, 02–406.
[44] Hajipour, AR, Nazemzadeh, SH, Mohammadsaleh, F. Choline chloride/CuCl as an effective homogeneous catalyst for palladium-free Sonogashira cross-coupling reactions. Tetrahedron Lett 2014, 55, 654–656.
[45] Marset, X, Pérez, JM, Ramón, DJ. Cross-dehydrogenative coupling reaction using copper oxide impregnated on magnetite in deep eutectic solvents. Green Chem 2016, 18, 826–833.
[46] Luca, P, Roberta, S, Federica, R, Leonardo, B, Filippo, MP, Amélia, SM, Vito, C. Deep eutectic solvents as effective reaction media for the synthesis of 2-Hydroxyphenylbenzimidazole-based scaffolds en route to donepezil-like compounds. Molecules 2020, 25, 574–587.
[47] Shaabani, A, Afshari, R. Magnetic Ugi-functionalized graphene oxide complexed with copper nanoparticles: Efficient catalyst toward Ullman coupling reaction in deep eutectic solvents. J Colloid Interface Sci 2018, 510, 384–394.
[48] Abbasi, S, Miraki, MK, Radfar, I, Karimi, M, Heydari, A. Efficient synthesis of N-acylureas using copper oxide supported on magnetic nanoparticles in deep eutectic solvent. Chemistry Select 2018, 3, 77–80.
[49] Marset, X, Torregrosa-Crespo, J, Martínez-Espinosa, RM, Guillena, G, Ramón, DJ. Multicomponent synthesis of sulfonamides from triarylbismuthines, nitro compounds and sodium metabisulfite in deep eutectic solvents. Green Chem 2019, 21, 4127–4132.
[50] Marset, X, Guillena, G, Ramón, DJ. Deep eutectic solvents as reaction media for the palladium-catalysed C-S bond formation: Scope and mechanistic studies. Eur J Chem 2017, 23, 10522–10526.

[51] Andrea, FQ, Manuela, M, Paola, V, Joaquín, G-Á, Filippo, MP, Ligand-Free Copper-Catalyzed, VC. Ullmann-type C-O bond formation in non-innocent deep eutectic solvents under aerobic conditions. ChemSusChem 2022, 15, e202102211.
[52] Vadagaonkar, KS, Kalmode, HP, Prakash, S, Chaskar, AC. Greener [3+3] tandem annulation-oxidation approach towards the synthesis of substituted pyrimidines. New J Chem 2015, 39, 3639–3645.
[53] Ghosh, SK, Nagarajan, R. Deep eutectic solvent mediated synthesis of quinazolinones and dihydroquinazolinones: Synthesis of natural products and drugs. RSC Adv 2016, 6, 27378–27387.
[54] Kalmode, HP, Vadagaonkar, KS, Murugan, K, Prakash, S, Chaskar, AC. Deep eutectic solvent: A simple, environmentally benign reaction media for regioselective synthesis of 2,3,4-trisubstituted 1H-pyrroles. RSC Adv 2015, 5, 35166–35174.
[55] Gadilohar, BL, Kumbhar, HS, Shankarling, GS. Choline peroxydisulfate: Environmentally friendly biodegradable oxidizing TSIL for selective and rapid oxidation of alcohols. Ind Eng Chem Res 2014, 53, 19010–19018.
[56] Zhang, Y, Lü, F, Cao, X, Zhao, J. Deep eutectic solvent supported TEMPO for oxidation of alcohols. RSC Adv 2014, 4, 40161–40169.
[57] Wagh, R, Nerurkar, G, Nagarkar, J. Highly efficient and selective method for oxidation of aldehydes to carboxylic acids. ChemistrySelect 2018, 3, 9654–9657.
[58] Ni, Y, Bi, Z, Su, H, Yan, L. Deep eutectic solvent (DES) as both solvent and catalyst for oxidation of furfural to maleic acid and fumaric acid. Green Chem 2019, 21, 1075–1079.
[59] Vagnoni, M, Samorì, C, Galletti, P. Choline-based eutectic mixtures as catalysts for effective synthesis of cyclic carbonates from epoxides and CO_2. J CO_2 Util 2020, 42, 101302–101308.
[60] Azizi, N, Rahimi, Z, Alipour, M. A magnetic nanoparticle catalyzed eco-friendly synthesis of cyanohydrins in a deep eutectic solvent. RSC Adv 2015, 5, 61191–61198.
[61] Zhang, M, Liu, P, Liu, Y-H, Shang, Z-R, Hu, H-C, Zhang, Z-H. Magnetically separable graphene oxide anchored sulfonic acid: A novel, highly efficient and recyclable catalyst for one-pot synthesis of 3,6-di(pyridin-3-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitriles in deep eutectic solvent under microwave irradiation. RSC Adv 2016, 6, 106160–106170.
[62] Mancuso, R, Maner, A, Cicco, L, Perna, FM, Capriati, V, Gabriele, B. Synthesis of thiophenes in a deep eutectic solvent: Heterocyclodehydration and iodocyclization of 1-mercapto-3-yn-2-ols in a choline chloride/glycerol medium. Tetrahedron 2016, 72, 4239–4244.
[63] Punzi, A, Coppi, DI, Matera, S, Capozzi, MAM, Operamolla, A, Ragni, R, Babudri, F, Farinola, GM. Pd-catalyzed thiophene-aryl coupling reaction via C–H bond activation in deep eutectic solvents. Org Lett 2017, 19(18), 4754–4757.
[64] Patil, UB, Singh, AS, Nagarkar, JM. Choline chloride based eutectic solvent: An efficient and reusable solvent system for the synthesis of primary amides from aldehydes and from nitriles. RSC Adv 2014, 4, 1102–1106.
[65] Rodríguez-Álvarez, MJ, Vidal, C, Díez, J, García-Álvarez, J. Introducing deep eutectic solvents as biorenewable media for Au(I)-catalysed cycloisomerisation of γ-alkynoic acids: An unprecedented catalytic system. Chem Commun 2014, 50, 12927–12929.
[66] Vidal, C, Merz, L, García-Álvarez, J. Deep eutectic solvents: Biorenewable reaction media for Au(I)-catalysed cycloisomerisations and one-pot tandem cycloisomerisation/Diels-Alder reactions. Green Chem 2015, 17, 3870–3878.
[67] Aziizi, N, Manochehri, Z, Nahayi, A, Torkashvand, S. A facile one-pot synthesis of tetrasubstituted imidazoles catalyzed by eutectic mixture stabilized ferrofluid. J Mol Liq 2014, 196, 153–158.
[68] Azizi, N, Dezfuli, S, Hahsemi, MM. Eutectic salt catalyzed environmentally benign and highly efficient Biginelli reaction. Sci World J 2012, 2012, 1–6.

Simranpreet K. Wahan, Gaurav Bhargava and Pooja A. Chawla*

Chapter 6
Role of crown ethers as mediator in various chemical reactions

6.1 Introduction

The accidental discovery of crown ethers by Pedersen generated a new field of research for scientists [1–8]. Crown ethers are macrocyclic polyethers ranging from 3 to 20 oxygen atoms and having at least 2 carbon atoms between each pair of oxygen atoms, that is, containing repeated $–CH_2CH_2O$ units [9, 10]. Crown ethers are hydrophobic from outside, as the oxygen atoms are excellently positioned to connect with an interior cation. Crown ethers are recognized for their unusual characteristics of forming stable complexes with alkali metals due to the snug fit of cation to the crown cavity and a nearly planar arrangement of oxygen atoms surrounding the central cation. The name "crown" alludes to the similarity between the structure of crown ether linked to a cation and a crown worn by humans. 18-Crown-6 is highly attracted to potassium cation, 15-crown-5 to sodium cation and 12-crown-4 to lithium cation. The strong affinity of 18-crown-6 for potassium ions contributes to its toxicity [11]. The smallest crown ether that can still bind cations is 8-crown-4, whereas the largest crown ether experimentally proven is 81-crown-27 (Figure 6.1). Initially, crown ethers were known to play an important role in phase transfer catalysis, and are favorable because the resulting cations usually form salts that are soluble in nonpolar solvents [12–20]. Guests from a variety of backgrounds, increased activity in the identification of molecules, greater restriction placed on the guests and stimulus-responsive crown ethers that involve molecular aggregate-supramolecular chemistry are latest areas of interest for chemists [21–25]. The variables regulating the cation recognition, stability and selectivity include macrocyclic cavity size, shape, substituent impact, conformational flexibility, kind of donor atom and the solvent utilized. Also, Cram provided the groundwork for host–guest chemistry by the methodological development of investigations on asymmetric recognition, including optical resolution, optically selective transport and asymmetric reaction using a series of chiral crown ethers containing optically active binaphthyl groups [26–30]. In

Acknowledgment: The authors are heartily thankful to the management of ISF College of Pharmacy for constant encouragement, support and motivation.

*__Corresponding author: Pooja A. Chawla,__ Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga 142001, Punjab, India, e-mail: pvchawla@gmail.com
Simranpreet K. Wahan, Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga 142001, Punjab, India; I. K Gujral Punjab Technical University, Kapurthala 144603, Punjab, India
Gaurav Bhargava, I. K Gujral Punjab Technical University, Kapurthala 144603, Punjab, India

https://doi.org/10.1515/9783110788129-006

addition, a substantial amount of studies have been devoted to achieving a more rigorous identification of biomimetic chemistry and its practical applications such as the separation of diastereomers by column chromatography [31–39]. An electron donating group at para locations in substitution enhances the binding ability of crown ether to provide stable cation–polyether complexes produced via ion–dipole interaction between metal cation and the negatively charged oxygen atom of crown ethers. Crown ether compounds, calix crown derivatives, antibiotic valinomycin and nonactin-based ionophores have been extensively employed in building potassium ion-selective electrodes [40–43]. Also, fluorescent probes containing a simple crown ether or an aza-crown ether structure, fluorescent probes containing an aza-thia crown ether, fluorescent

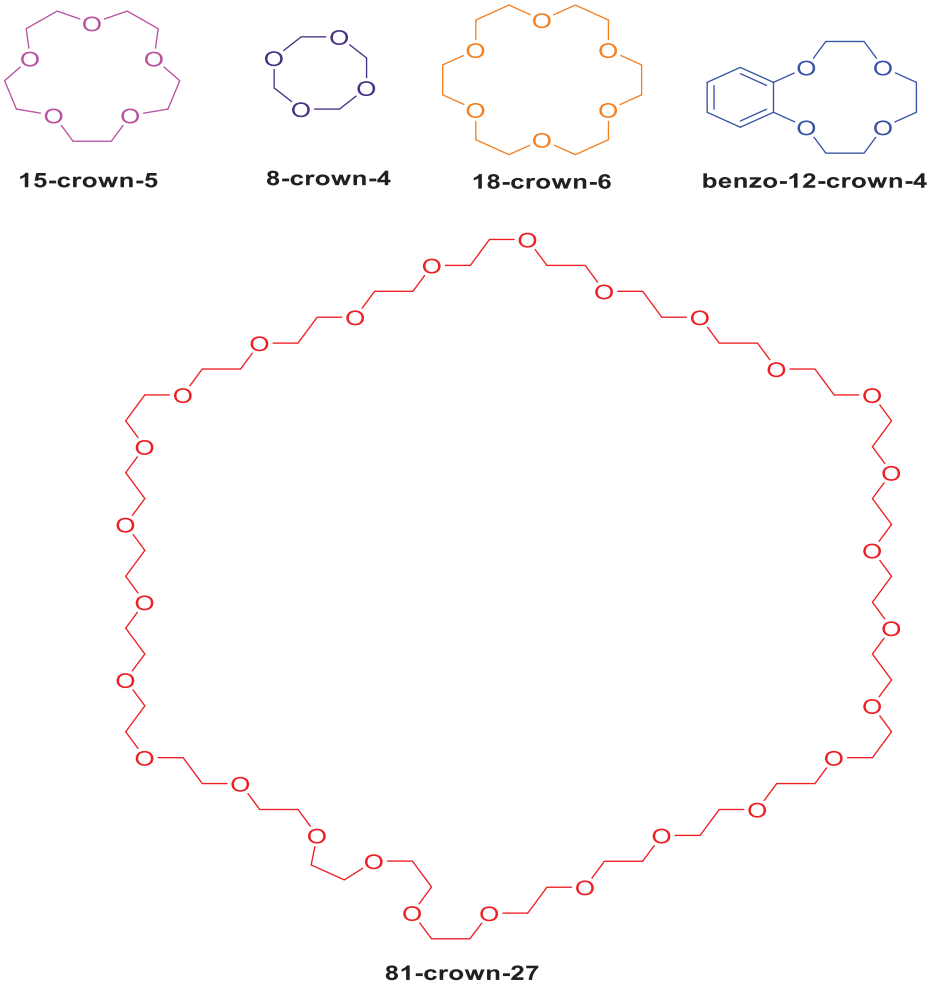


Figure 6.1: Various crown ethers.

probes containing a cryptand, fluorescent probes containing two or more binding sites, and fluorescent probes containing crown ether derivatives and metal complex-assisted chemosensing of bioactive species are areas of great interest. It was recently studied that crown compounds could either induce toxicities that are different from those of conventional antitumor drugs or complement drugs that are currently being used, providing a valuable adjunct to therapy. Moreover, various uses and the ever-increasing biological potentials of these fascinating compounds show a special focus on the possibilities of these compounds' significance as anticancer agents [44–49]. Therefore, in addition to their conventional function in the field of chemistry, crown ethers are presently the subject of research and are employed in a wide variety of applications. We believe that encouraging further research in this direction should be encouraged, as crown compounds play a remarkable role as a mediator in a number of useful organic reactions.

6.2 Crown-ether-mediated chemical reactions

6.2.1 Effect of crown ether on synthetic reactions

In order to reduce the high reaction conditions of Ullmann coupling, Venkatraman and team examined the effect of 18-crown-6 on Ullmann-type coupling in the presence of zinc in air and water. The effect of crown ether on Ullman coupling was determined by carrying coupling of different aromatic iodides and bromides **1** in the presence of catalytic amount of palladium/carbon to yield coupled product **2** (Figure 6.2). The reaction resulted in better product yield even at ambient temperature and in the presence of atmosphere of air which is attributed to the stabilization of arylpalladium intermediate or the effect of surfactant. However, an increase in steric hindrance diminished the product yield. Also, an appreciable amount of volatile halogenated product was reported to be formed and lost during the reaction. The proposed mechanism involves the direct electron transfer between zinc and palladium(II) which is believed to complete the catalytic pathway. Therefore, 18-crown-6 was reported to exhibit remarkable effects on Ullmann coupling of various iodides and bromides [50].

Fernandez-Perez et al. [51] revisited catalytic hydrogenation exhibited by Rh complexes, and therefore, developed a class of enantiopure bisphosphine ligands **3** containing an array of distinct crown ethers which acted as meditator sites through supramolecular chemistry. The developed class of ligands displayed appreciable catalytic activity even at low concentration, whereas enantioselectivity remained low. The developed class of bisphosphine (**3**) was examined by carrying out enantioselective hydrogenation of dimethyl itaconate (**4**) in dichloromethane at room temperature for 24 h under a pressure of 20 bar of hydrogen gas to yield hydrogenated product **5** (Figure 6.3). As expected, strong binding interactions were reported between alkali metal salts and crown ether

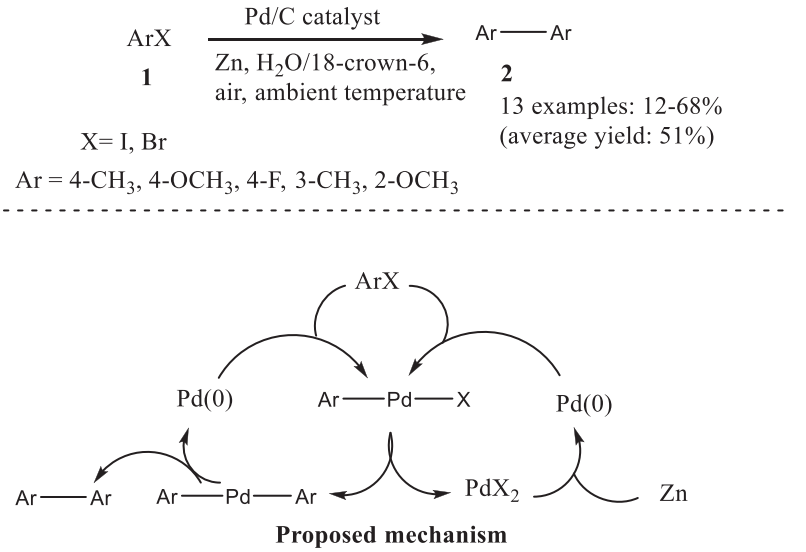
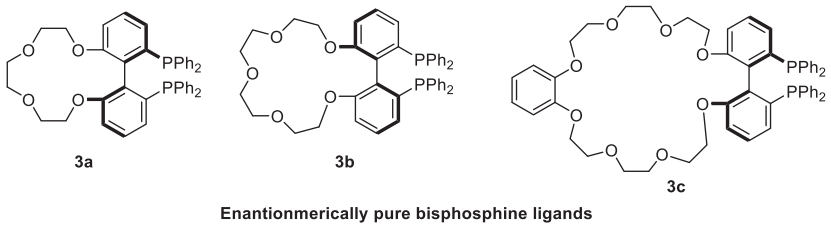


Figure 6.2: 18-Crown-6-mediated Ullmann coupling.

molecules, resulting in remarkable activity of bisphosphine ligands even at lower catalytic concentration of 0.5 mol%. However, use of any regulating agents like NaBArF and CsBArF resulted in mild positive effect toward hydrogenation. Surprisingly, the best catalytic hydrogenation was found to be shown by **3c** without the use of any regulating agent.



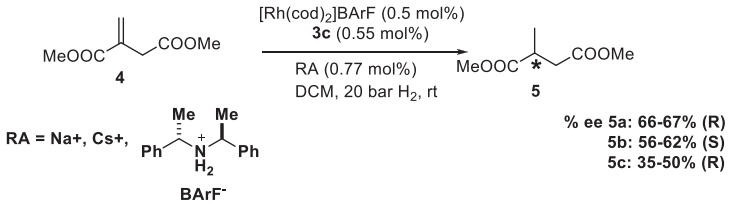


Figure 6.3: Hydrogenation mediated by enantiopure bisphosphine ligands.

Various applications of arynes engrossed Yoshida and team [52] toward the synthesis of arynes using *ortho*-silylaryl triflates and cesium carbonate in the presence of 18-crown-6. The synthetic approach involved mixing 2-(trimethylsilyl)phenyl triflate (**6,** 0.503 mmol) and benzyl azide (**7,** 2.50 mmol) in tetrahydrofuran at room temperature using cesium carbonate (1.0 mmol) and 18-crown-6 ether (1.0 mmol). After vigorously stirring the reaction mixture for 24 h, the mixture was extracted using ethyl acetate, brine solution followed by filtration under reduced pressure to obtain 1-benzyl triazole derivative as a final product (**8**) (Figure 6.4). The method proved to be highly efficient for the reaction between variety of arynes and arynophiles. Interestingly, the aryne formation was reported to be strongly dependent on alkali metal counter cation of carbonate.

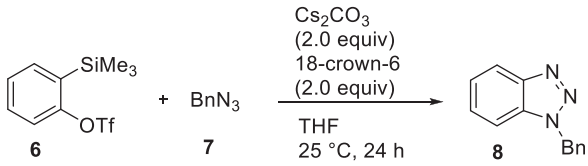


Figure 6.4: Synthesis of benzyl triazole derivatives mediated by 18-crown-6.

Gregor and coauthors [53] synthesized a series of 11 iridium pincer-crown ether complexes. The prepared iridium pincer-crown ether complexes were employed for carrying out salt-promoted methanol carbonylation. The synthetic approach for carrying out methanol carbonylation involved taking methanol with methyl iodide (**10**) (0.5 M) and iridium pincer catalyst **9** (0.34 mM) having temperature of 150 °C while maintaining pressure of 25 bar CO for 3 h in a six-vessel multireactor to obtain methyl acetate (**11**) (Figure 6.5). Later on, tertiary butanol was added into the reaction chamber, which exhibited a dual role as an internal standard as well as an emulsifying agent. Interestingly, maximum reaction rates were reported for lithium chloride and hafnium(IV) chloride, whereas La(III) and Ce(III) showed marked inhibition. Therefore, pincer-crown ether complexes acted as a great precatalyst by carrying out carbonylation at low temperature and pressure.

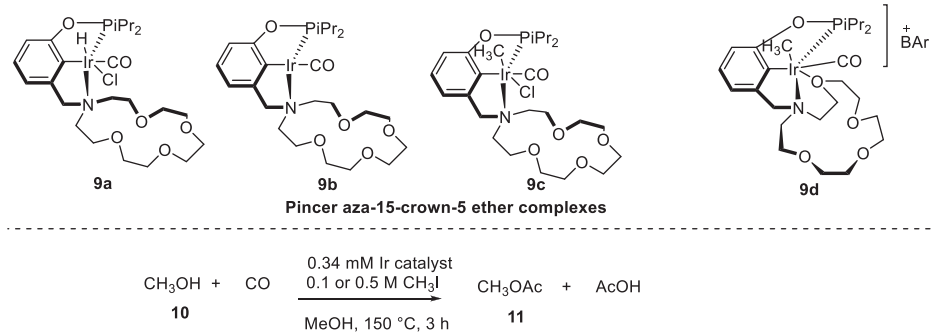


Figure 6.5: Use of iridium pincer-crown ether complexes for methanol carbonylation.

Kumbhat et al. [54] designed and fabricated potassium ion containing electrochemical sensor based on 18-crown-6 ether. The newly developed sensor shows detection even at 1 μM to 10 mM potassium ions and selectivity over lithium ions, ammonium ions and in excess sodium ions in the solution. The interactions between potassium ions and ionophore resulting in complex formation were confirmed through various studies like conductivity, UV–visible and Fourier-transform infrared spectrometric studies. The brown cation–crown ether complex was prepared by gently mixing the equimolar amount of crown ether derivatives (0.1 M) and metal thiocyanate (0.1 M) in methanol (100 mL) in nitrogen atmosphere for 5–7 min. Further, self-assembled sensor surface was prepared by cleaning gold electrode through ultrasonication technique and leaving it overnight in 11-MUA/ethanol (2 mM) followed by activation with the introduction of NHS-EDC reagent (equimolar concentration 1:1 v/v), immobilization of ionophore and finally covering with aminobenzo-18-crown-6 methanol.

Two novel selective deprotection approaches of diphenylmethylsilyl (DPMS) were described by Akporji and coworkers [55]. The first method involved deprotection under mild water micellar reaction conditions using catalytic amount of perfluoro-1-butanesulfonyl fluoride while the second method involved the use of stoichiometric amount of 18-crown-6 ether in aqueous ethanol. The best deprotection results of DPMS ether were obtained by carrying out the reaction in the presence of stoichiometric amount of crown ether using ethanol and water in the ratio of 2:1 at 45 °C for 4 h (Figure 6.6). Water was reported to be responsible for marked chemoselectivities in the two methods for selective unmasking. However, the exact mechanism behind 18-crown-6 ether in facilitating high selective unmasking remains to be unknown. Compellingly, both the methods turned out as beneficial in terms of high recyclability, safer aqueous reaction medium and economically friendly conditions.

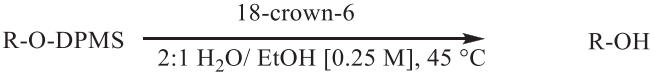


Figure 6.6: Deprotection of diphenylmethylsilyl ether using 18-crown-6 ether.

Le Coz et al. [56] carried out the synthesis of a two nitrogen-containing iminoanilidine and amidine proligands tethered with 15-membered aza-ether crown rings **12 and 13**. Compounds 12 and 13 were reported to completely mediate the intermolecular hydrophosphination of styrene **14** with primary and secondary phosphines to give desired product **15.** Also, compounds **12** and **13** were found to have high coordination numbers, were stabilized by Ba···H–Si bonding, follow anti-Markovnikov rule and exhibit chemoselectivity (Figure 6.7). The proposed mechanism for intermolecular hydrophosphination consists of 2,1-insertion leading to the formation of transient barium alkyl complex followed by rapid protonation of $HPPh_2$ to form the final desired product.

Mediation of asymmetric synthesis by crown ethers pushed Zhang et al. [57] and Cram and Sogah [58] toward asymmetric supramolecular catalysis. The authors

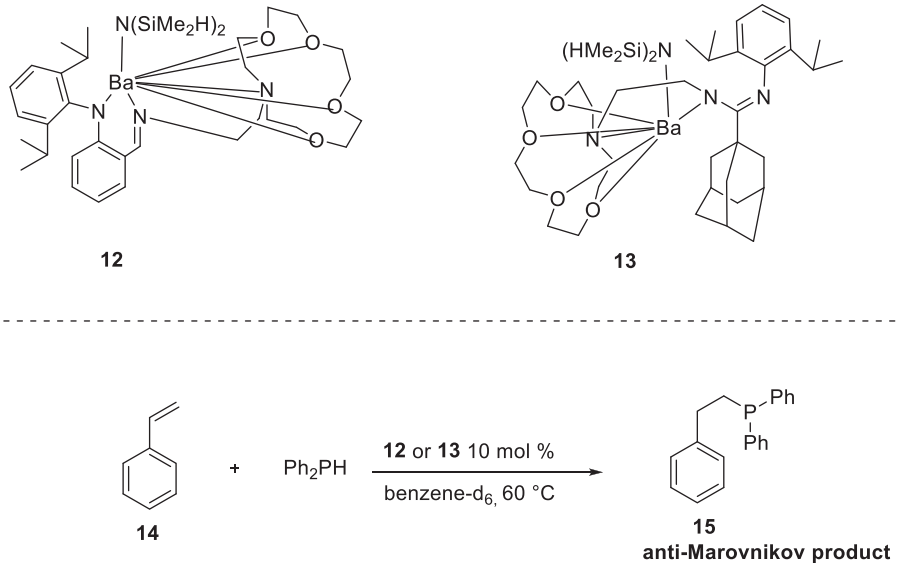


Figure 6.7: Crown-ether-mediated intermolecular hydrophosphination of styrene.

investigated supramolecular asymmetric catalysis on Michael's addition reactions in order to prepare two chiral BINOL-based crown ethers **16** and **17**. Compounds **16** and **17** were reported to combine with potassium salts as the catalysts and aid in the formation of enolates that attack on an α,β-unsaturated ketone or ester resulting in the formation of chiral products with 99% ee (Figure 6.8). The synthesized chiral crown ethers **16** and **17** were proved to form complex with potassium cation which helps in the activation of β-ketoester.

Kobayashi et al. [59] synthesized three chiral crown ether complexes (**18–20**) and rarely used metal ions showing asymmetric supramolecular catalysis. The synthesized chiral crown ethers (**18–20**) have different hole sizes along with different metal salts in order to exhibit supramolecular catalysis. The approach involved treatment of $Pb(OTf)_2$ and **20** with (*Z*)-silyl enol ether of propiophenone in a solvent mixture of water and ethanol in the ratio 1:9 (Figure 6.9). Compound **20** was proved to act as an appreciable chiral catalyst in asymmetric aldol condensation reactions while other prepared chiral crown ether complexes with other metal ions showed almost no enantioselectivity. Among different aldehydes used, isovaleraldehyde displayed remarkable results with high yield (99%) and best enantioselectivity (syn/anti = 94:6).

Maddock's group [60] explored the effect of crown ether mediation in carrying out ferration of unreactive aromatic compounds. Aromatic compounds were found to undergo Na–H exchange, intramolecular transmetallation with Fe, thereby resulting in stabilization of aryl molecule. Therefore, the effect of sodium/iron partnership aiding in chemical reactions was well proved, whereas neither sodium nor iron amides

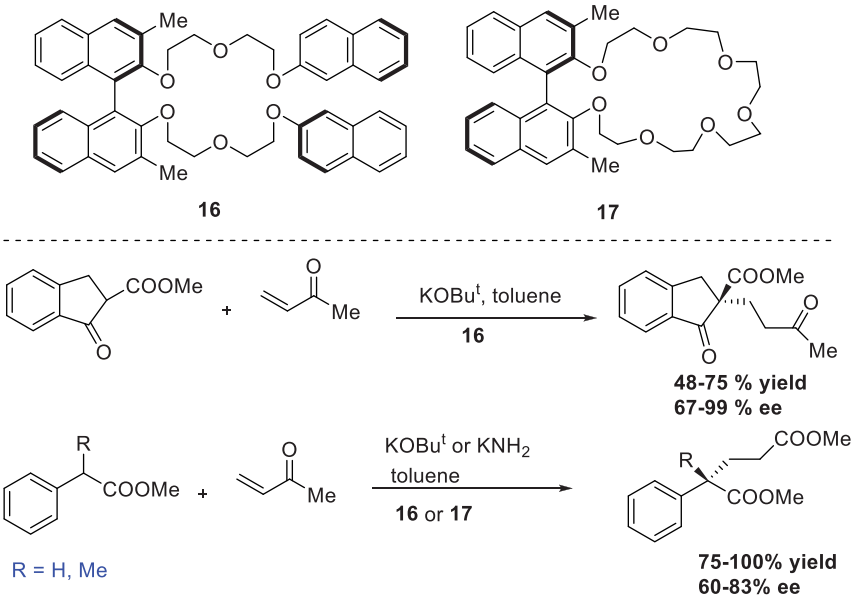


Figure 6.8: The Michael addition reactions mediated by chiral BINOL-based crown ethers.

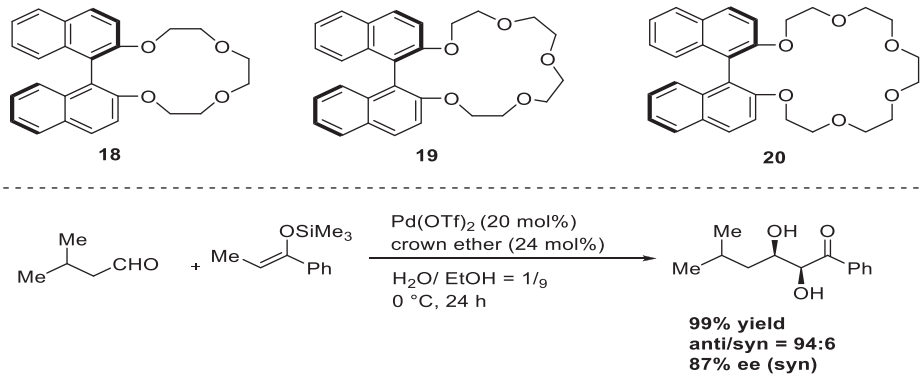


Figure 6.9: Chiral crown-ether-mediated asymmetric aldol reactions.

were able to undergo the reaction alone. When pentafluoroaryl compound forms a complex with Fe, F at C_4 position binds to the neighboring sodium resulting in the formation of polymeric unit (Figure 6.10). Also, Na and Fe bind through two amide N bridges with Na resulting in an increase of coordination number by undergoing interaction antagonistically with methyl group from each HMDS ligand.

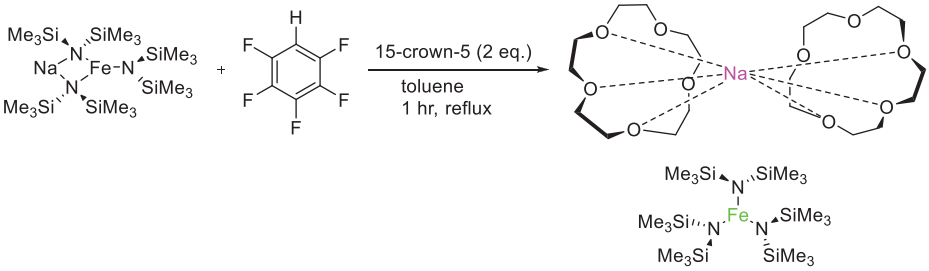


Figure 6.10: Crown-ether-mediated ferration of aromatic compounds.

6.2.2 Crown ether complexes

The immense therapeutic importance of fullerenol fascinated Haung et al. [61] toward the synthesis of fullerenol crown ether conjugates. A group of alkynyl-substituted fullerenol was prepared by epoxy ring opening using Lewis's acid catalyst and nucleophilic substitution of fullerene peroxide. Further, the terminal alkynyl groups were converted into triazoles through copper-catalyzed cycloaddition reaction followed by intramolecular oxidative coupling with alkyne resulting in the formation of fullerenol crown ether derivatives. Interestingly, the terminal alkyne groups present in fullerenol conjugates exhibited similar reactivity to organic alkynes as in Hay coupling and click reactions. Compound **21** was treated with silver perchlorate to undergo S_N1 reaction, and this results in the formation of **22**. Compound **22** was reduced by using stannous chloride to form **23** followed by treatment with azidomethyl benzene, which led to the formation of bis-triazole derivative **25**. Also, compound **23** underwent the Hay coupling reaction in the presence of cuprous iodide and tetramethyl ethylenediamine to form fullerenol crown ether derivative **24** (Figure 6.11).

Considering important therapeutic importance of silver nanoparticles, Berdnikova et al. [62] established a novel approach for synthesizing silver nanoparticles under mild reaction conditions using conjugated silver-based crown ether in order to avoid secondary side reactions associated with ultraviolet or laser light. The novel approach involved photochemically induced electron transfer between energetically excited DNA-bounded molecule **26** which upon irradiation resulted in the oxidation of Ag^+ ions to form oxidized DNA base and electrically neutral quinolizinyl radical **27**. Ag^+ ions complexed with crown ether resulted in closer juxtaposition to **27**, which resulted in the formation of Ag nanoparticles stabilized by associated nucleic acid (Figure 6.12). It has been suggested that the creation of Ag nanoparticles is caused by a synergistic interaction between light-capturing, excited cationic DNA, crown ether coupled with Ag+, and stability caused by DNA on Ag nanoparticles.

Zhang et al. [63] synthesized a supramolecular polymeric adhesive material by carrying water-participant hydrogen bonding of two nonviscous monomers. The approach

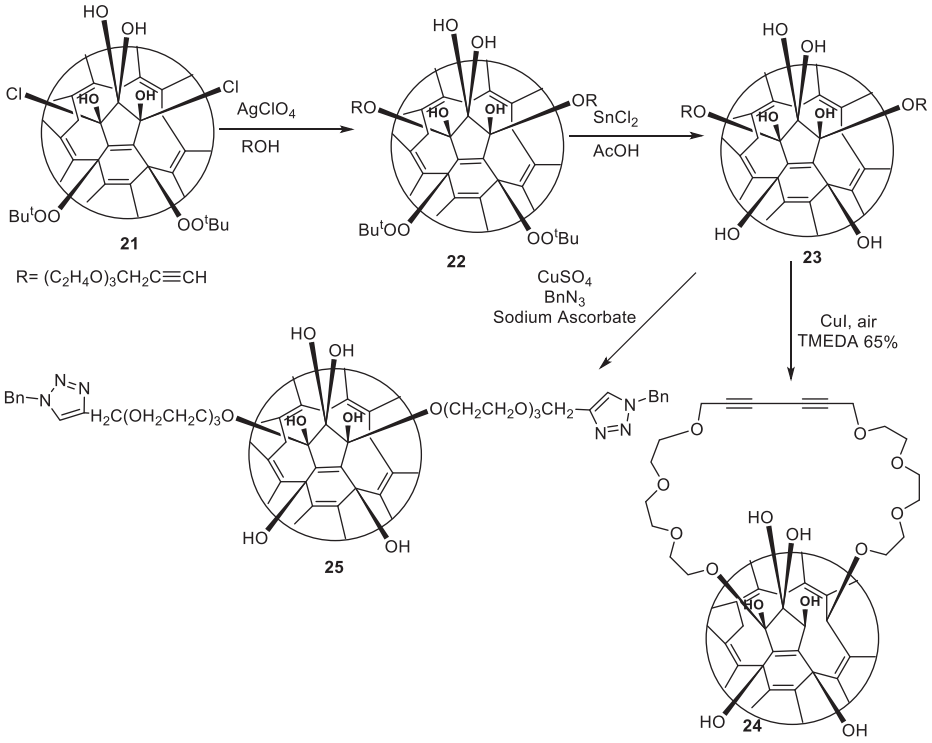


Figure 6.11: Synthesis of fullerenol crown ether complexes.

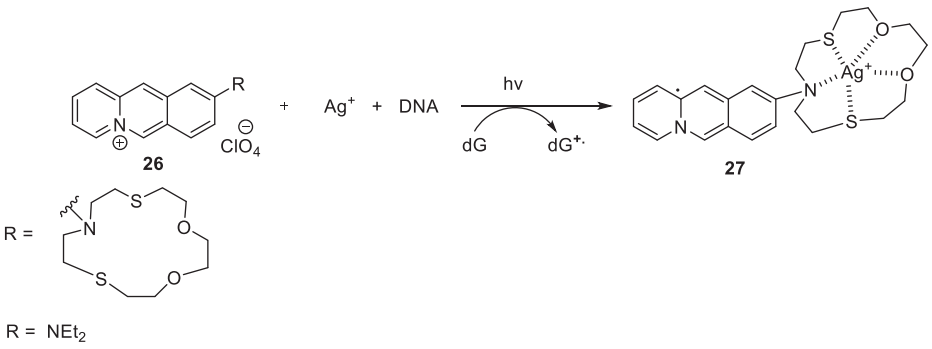


Figure 6.12: Crown-ether-mediated synthesis of Ag nanoparticles.

involved the reaction between trisubstituted **28** and $Pt(Et_3)_2(OTf)_2$ in dichloromethane for 10 h in order to yield 1:2 platinum-coordinated product **29** (Figure 6.13). The structure of product **29** was verified using ^{1}H NMR, ^{31}P NMR, COSY and NOESY and mass spectrometry. Interestingly, coordination between platinum and pyridine along with hydrogen bonding between water and crown ether was found to be responsible for

polymerization. The synthesized compound **29** exhibited appreciable strength, reversible adhesion toward hydrophilic centers, high viscosity and low fluidity. Also, water was reported to be essential for the formation of supramolecular polymer. Therefore, this research will be quite beneficial in the synthesis of crown-ether-based supramolecular materials exhibiting adhesive properties.

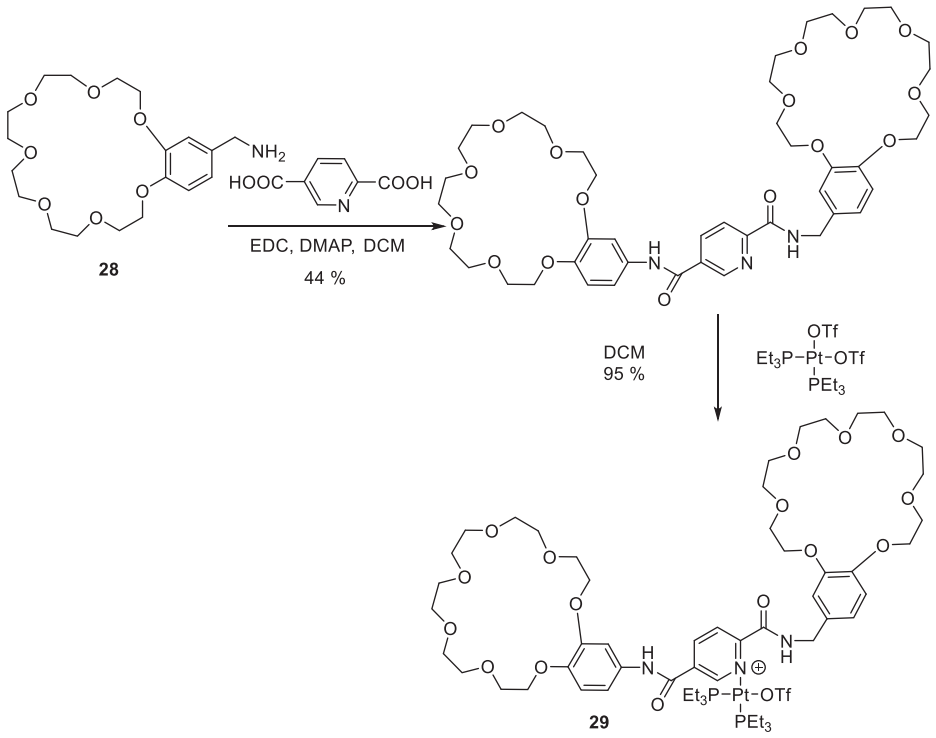


Figure 6.13: Synthesis of crown-ether-based adhesive system.

6.2.3 Application of crown ethers in electrochemical reactions

Lithium anodes in spite of their high energy density due to greater capacity and low potential show poor compatibility with most of the carbonate-based electrolytes. The addition of nitrate to the electrolyte solution results in enhanced effectiveness of electrolyte solution. However, nitrates show poor solubility in carbonate electrolyte solution. The use of crown ether appreciably increased the solubility of nitrate in carbonate solution, and therefore, enhanced its property. The use of rubidium nitrate with 18-crown-6 ether as reported to aid in the stabilization of lithium metal anodes in carbonate electrolyte by promoting dissolution of nitrate ions helped in the formation of solid electrolyte interface layer rich in lithium nitrate. The lithium nitrate layer was found to

be responsible for uniform lithium metal deposition. Moreover, Rb(18-crown-6)$^+$ complex (Figure 6.14) formed gets adsorbed on the dendrite tips halting in further lithium decomposition on the tips of dendrites. Interestingly, the uplifted Coulombic efficiency with the addition of nitrate (97.1%) is compared with the electrolyte in the absence of any additive (92.2%) in a half-cell. Also, 18-crown-6 ether as additives displays high compatibility with nickel-based electrolytes with average Coulombic efficiency value of 99.8% [64].

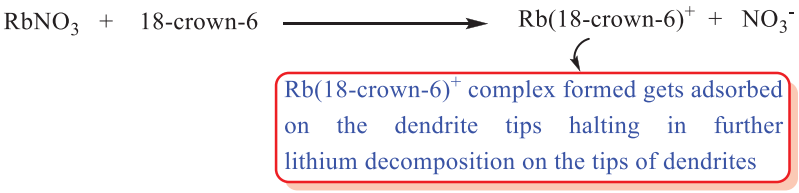


Figure 6.14: Formation of Rb(18-crown-6)$^+$ complex on treatment of rubidium nitrate in 18-crown-6 ether.

In order to detect pollutants like hydroquinone (HQ), catechol (CC) and resorcinol (RC) in the water bodies and other environment samples, Atta et al. [65] fabricated a novel electrochemical sensor based on fusion of benzo-12-crown-4 and poly-hydroquinone (PHQ)/carbon. The development of sensor consists of three steps: coating of carbon nanotubes (CNTs) on graphite/carbon followed by deposition of PHQ layer over the surface of CNTs using a 1.0 mM HQ solution prepared in 0.1 M NaOH under suitable potential for five cycles under optimized conditions, and lastly depositing benzo-12-crown-4 ether over the prepared surface using the electropolymerization technique using a solution of 2.0 mM under suitable potential for three cycles. The increasing order of various carbon nanostructures toward oxidation follows the trend as CNTs > reduced graphite oxide > graphite oxide > graphite. The developed sensor showed a remarkable electrocatalytic detection having the detection limits of 0.156, 0.118 and 0.427 nM for HQ, CC and RC, respectively (Figure 6.15).

Mousavi et al. [66] fabricated two benzopyrylium crown-ether-fused compounds **30** and **31** (Figure 6.16). The synthesized fused crown ether derivatives were coupled with TiO_2 nanoparticles and employed as dye-sensitized solar cells (DSCs) after optimization using density functional theory, UV–Vis, IR and NMR approaches. Further, the sensitivity of prepared DSCs as photoanodes was determined experimentally and through computational approaches which may aid toward the development of solar cells having desired photovoltaic characteristics. Interestingly, the fabricated solar cells **30** and **31** exhibited power conversion efficiency with values 1.63% and 2.93%, respectively, as sensitizers. Also, the developed DSCs acted as an electrolyte in I^-/I_3^- electrolysis, photoanode as well as platinum nanoparticle-based counter electrode.

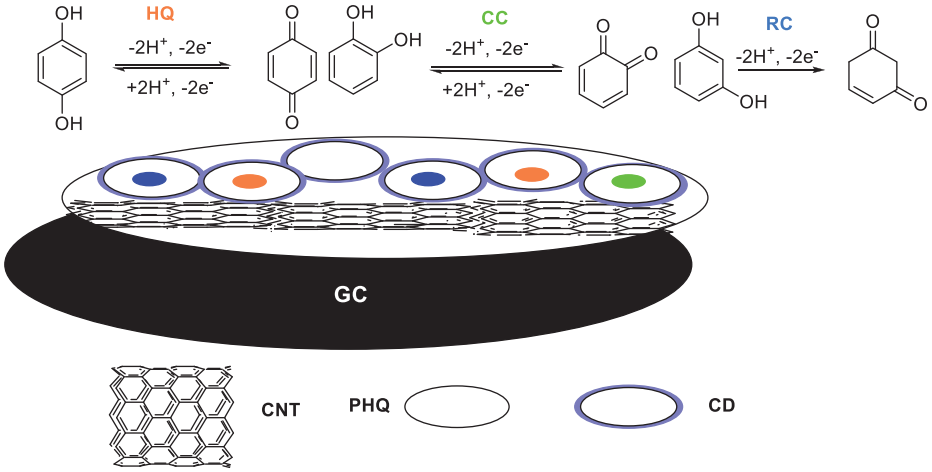


Figure 6.15: Determination of hydroquinone, catechol and resorcinol using crown-ether-based electrode.

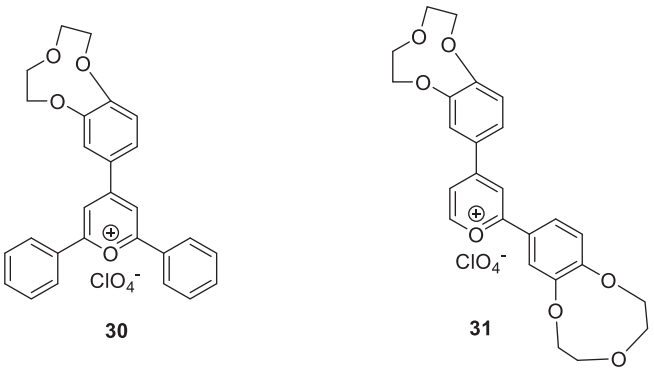


Figure 6.16: Benzopyrylium crown-ether fused compounds as dye-sensitized solar cells.

6.3 Conclusions

The extraordinary chemistry of crown ethers as mediator in various chemical reactions has been a keen area of interest for many chemists. The remarkable roles played by crown ethers are as follows: as phase transfer catalysts, as stimulus-responsive crown ethers that involve molecular aggregate-supramolecular chemistry, in ferration of unreactive aromatic compounds, as optically selective transport, in the asymmetric reaction using a series of chiral crown ethers containing optically active binaphthyl groups, in chiral crown-ether-mediated asymmetric aldol reactions, in the Michael addition reactions mediated by chiral BINOL-based crown ethers, benzopyrylium crown ether fused compounds as DSCs, crown-ether-mediated intermolecular

hydrophosphination of styrene, carbonylation of methanol mediated by crown ethers, synthesis of various heterocyclic compounds, hydrogenation mediated by rhodium-based catalyst, hydrogenation mediated by enantiopure bisphosphine crown-ether-based ligands and in the synthesis of various therapeutically important nanoparticles. Therefore, in addition to their conventional functions in the field of chemistry, crown ethers are presently the subject of research and are employed in a wide variety of applications.

References

[1] Pedersen, CJ. The discovery of crown ethers (Noble Lecture). Angew Chem Int Ed Engl 1988, 27(8), 1021–1027.
[2] Pedersen, CJ. The discovery of crown ethers. Science 1988, 241(4865), 536–540.
[3] Gokel, GW, Leevy, WM, Weber, ME. Crown ethers: Sensors for ions and molecular scaffolds for materials and biological models. Chem Rev 2004, 104(5), 2723–2750.
[4] Stoddart, JF. Chiral crown ethers. Top Stereochem 1988, 17, 207–288.
[5] Ouchi, M, Inoue, Y, Kanzaki, T, Hakushi, T. Molecular design of crown ethers. 1. Effects of methylene chain length: 15-to 17-crown-5 and 18-to 22-crown-6. J Org Chem 1984, 49(8), 1408–1412.
[6] Gokel, GW. Crown ethers. CRC Press, 2004.
[7] Hiraoka, M, editor. Crown ethers and analogous compounds. Elsevier, 2016.
[8] Yoshio, M, Noguchi, H. Crown ethers for chemical analysis: A Review. Anal Lett 1982, 15, 1197–1276.
[9] Chehardoli, G, Bahmani, A. The role of crown ethers in drug delivery. Supramol Chem 2019, 31(4), 221–238.
[10] Stoddart, JF. Chiral crown ethers. Top Stereochem 1988, 17, 207–288.
[11] Kaller, M, Laschat, S. Liquid crystalline crown ethers. Liq Cryst 2011, 109–192.
[12] Rapi, Z, Nemcsok, T, Pálvölgyi, Á, Keglevich, G, Grün, A, Bakó, P. Synthesis of L-threitol-based crown ethers and their application as enantioselective phase transfer catalyst in Michael additions. Chirality 2017, 29(6), 257–272.
[13] Landini, D, Montanari, F, Pirisi, FM. Crown ethers as phase-transfer catalysts in two-phase reactions. J Chem Soc Chem Commun 1974, 21, 879–880.
[14] Mathias, LJ, Carraher, CE, editors. Crown ethers and phase transfer catalysis in polymer science. New York: Plenum Press, 1984.
[15] Mathias, LJ. Crown ethers and phase transfer catalysis in polymer chemistry. J Macromol Sci – Chem 1981, 15(5), 853–876.
[16] Nakamura, K, Nishiyama, S, Tsuruya, S, Masai, M. Oxidation of catechol with $KMnO_4$ by using crown ethers as phase transfer catalysts. J Mol Catal 1994, 93(2), 195–210.
[17] Cinouini, M, Colonna, S, Molinari, H, Montanari, F, Tundo, P. Heterogeneous phase-transfer catalysts: Onium salts, crown ethers, and cryptands immobilized on polymer supports. J Chem Soc, Chem Commun 1976, 11, 394–396.
[18] Maruoka, K, editor. Asymmetric phase transfer catalysis. John Wiley & Sons, 2008.
[19] Vander Zwan, MC, Hartner, FW. Solid-liquid phase-transfer catalysis by a quaternary ammonium salt. A comparison with crown ethers and polyalkylamines. J Org Chem 1978, 43(13), 2655–2657.
[20] Joshi, DR, Adhikari, N. Phase transfer catalyst in organic synthesis. World J Pharm Res 2019, 8(8), 508–515.

[21] Huszthy, P, Tóth, T. Synthesis and molecular recognition studies of crown ethers. Period Polytech 2007, 51(2), 45–51.
[22] Shahgaldian, P, Pieles, U. Cyclodextrin derivatives as chiral supramolecular receptors for enantioselective sensing. Sensors 2006, 6(6), 593–615.
[23] Ren, C, Shen, J, Zeng, H. Combinatorial evolution of fast-conducting highly selective K^+-channels via modularly tunable directional assembly of crown ethers. J Am Chem Soc 2017, 139(36), 12338–12341.
[24] Van Leeuwen, PW, editor. Supramolecular catalysis. John Wiley & Sons, 2008.
[25] Luk'yanenko, NG, Lobach, AV, Leus, ON, Titova, NY. Synthesis and enantiomeric selectivity of chiral crown ethers. Russ J Org Chem 2002, 38(6), 895–899.
[26] Aoki, S, Sasaki, S, Koga, K. Simple chiral crown ethers complexed with potassium tert-butoxide as efficient catalysts for asymmetric Michael additions. Tetrahedron Lett 1989, 30(51), 7229–7230.
[27] Sawamura, M, Nagata, H, Sakamoto, H, Ito, Y. Chiral phosphine ligands modified by crown ethers: An application to palladium-catalyzed asymmetric allylation of beta-diketones. J Am Chem Soc 1992, 114(7), 2586–2592.
[28] Bakó, P, Bajor, Z, Toke, L. Synthesis of novel chiral crown ethers derived from D-glucose and their application to an enantioselective Michael reaction. J Chem Soc Perkin Trans 1999, 1, 3651–3655.
[29] Kanakamma, PP, Mani, NS, Maitra, U, Nair, V. Chiral crown ethers incorporating D-glucose. J Chem Soc Perkin Trans 1995, 1, 2339–2344.
[30] Rapi, Z, Nemcsok, T, Bagi, P, Keglevich, G, Bakó, P. Synthesis of chiral crown ethers derived from d-galactose and their application in enantioselective reactions. Tetrahedron 2019, 75(30), 3993–4004.
[31] Paik, MJ, Kang, JS, Huang, BS, Carey, JR, Lee, W. Development and application of chiral crown ethers as selectors for chiral separation in high-performance liquid chromatography and nuclear magnetic resonance spectroscopy. J Chromatogr A 2013, 1274, 1–5.
[32] Berkecz, R, Németi, G, Péter, A, Ilisz, I. Liquid chromatographic enantioseparations utilizing chiral stationary phases based on crown ethers and cyclofructans. Molecules 2021, 26(15), 4648.
[33] Nishi, H, Nakamura, K, Nakai, H, Sato, T. Separation of enantiomers and isomers of amino compounds by capillary electrophoresis and high-performance liquid chromatography utilizing crown ethers. J Chromatogr A 1997, 757(1–2), 225–235.
[34] Yazdi, AS, Es'haghi, Z. Liquid–liquid–liquid phase microextraction of aromatic amines in water using crown ethers by high-performance liquid chromatography with monolithic column. Talanta 2005, 66(3), 664–669.
[35] Attallah, MF, Borai, EH, Hilal, MA, Shehata, FA, Abo-Aly, MM. Utilization of different crown ethers impregnated polymeric resin for treatment of low-level liquid radioactive waste by column chromatography. J Hazard Mater 2011, 195, 73–81.
[36] Jin, Y, Fu, R, Huang, Z. Use of crown ethers in gas chromatography. J Chromatogr A 1989, 469, 153–159.
[37] Yamini, Y, Shamsipur, M. Extraction and determination of crown ethers from water samples using a membrane disk and gas chromatography. Talanta 1996, 43(12), 2117–2122.
[38] Kimura, K, Harino, H, Hayata, E, Shono, T. Liquid chromatography of alkali and alkaline-earth metal ions using octadecyl silanized silica columns modified in situ with lipophilic crown ethers. Anal Chem 1986, 58(11), 2233–2237.
[39] Walbroehl, Y, Wagner, J. Enantiomeric resolution of primary amines by capillary electrophoresis and high-performance liquid chromatography using chiral crown ethers. J Chromatogr A 1994, 680(1), 253–261.
[40] Chehardoli, G, Bahmani, A. The role of crown ethers in drug delivery. Supramol Chem 2019, 31(4), 221–238.
[41] Sharghi, H, Beni, AR. One-pot synthesis of novel thioxanthone crown ethers. Arkivoc 2007, 13, 1–7.

[42] Ullah, F, Khan, TA, Iltaf, J, Anwar, S, Khan, MF, Khan, MR, Ullah, S, Fayyaz, RM, Mustaqeem, M, Kotwica-Mojzych, K, Mojzych, M. Heterocyclic crown ethers with potential biological and pharmacological properties: from synthesis to applications. Appl Sci 2022, 12(3), 1102.
[43] Gharib, A, Jahangir, M, Roshani, M, Scheeren, JW. A method for catalytic synthesis of convenient thioxanthone crown ethers using Wells-Dawson, H_6 [$P_2W_{18}O_{62}$] and Preyssler H_{14} [$NaP_5W_{30}O_{110}$. Bulg Chem Commun 2010, 42, 217–221.
[44] Xie, J, Ménand, M, Maisonneuve, S, Métivier, R. Synthesis of bispyrenyl sugar-aza-crown ethers as new fluorescent molecular sensors for Cu (II). J Org Chem 2007, 72(16), 5980–5985.
[45] De Silva, AP, de Silva, SA. Fluorescent signalling crown ethers; 'switching on' of fluorescence by alkali metal ion recognition and binding in situ. J Chem Soc Chem Commun 1986, 23, 1709–1710.
[46] Bourson, J, Pouget, J, Valeur, B. Ion-responsive fluorescent compounds. 4. Effect of cation binding on the photophysical properties of a coumarin linked to monoaza-and diaza-crown ethers. J Phys Chem 1993, 97(17), 4552–4557.
[47] Peng, MS, Cai, J. Synthesis and fluorescence of crown ethers containing coumarin. Dyes Pigm 2008, 79(3), 270–272.
[48] Wolfbeis, OS, Offenbacher, H. The effects of alkali cation complexation on the fluorescence properties of crown ethers. Monatshefte Für Chem/Chem Mon 1984, 115(5), 647–654.
[49] Rapi, Z, Bakó, P, Keglevich, G, Baranyai, P, Kubinyi, M, Varga, O. Synthesis and recognition properties of α-D-glucose-based fluorescent crown ethers incorporating an acridine unit. J Inclusion Phenom Macrocyclic Chem 2014, 80(3), 253–261.
[50] Venkatraman, S, Li, CJ. The effect of crown-ether on the palladium-catalyzed Ullmann-type coupling mediated by zinc in air and water. Tetrahedron Lett 2000, 41(25), 4831–4834.
[51] Fernandez-Perez, H, Mon, I, Frontera, A, Vidal-Ferran, A. Enantiopure bisphosphine ligands with appended crown ether groups as regulation sites for Rh-mediated hydrogenations. Tetrahedron 2015, 71(26–27), 4490–4494.
[52] Yoshida, S, Hazama, Y, Sumida, Y, Yano, T, Hosoya, T. An alternative method for generating arynes from ortho-silylaryl triflates: Activation by cesium carbonate in the presence of a crown ether. Molecules 2015, 20(6), 10131–10140.
[53] Gregor, LC, Grajeda, J, White, PS, Vetter, AJ, Miller, AJ. Salt-promoted catalytic methanol carbonylation using iridium pincer-crown ether complexes. Catal Sci Technol 2018, 8(12), 3133–3143.
[54] Kumbhat, S, Singh, U. A potassium-selective electrochemical sensor based on crown-ether functionalized self-assembled monolayer. J Electroanal Chem 2018, 809, 31–35.
[55] Akporji, N, Lieberman, J, Maser, M, Yoshimura, M, Boskovic, Z, Lipshutz, BH. Selective Deprotection of the diphenylmethylsilyl (DPMS) hydroxyl protecting group under environmentally responsible, aqueous conditions. Chem Cat Chem 2019, 11(23), 5743–5747.
[56] Le Coz, E, Roueindeji, H, Roisnel, T, Dorcet, V, Carpentier, JF, Sarazin, Y. Barium complexes with crown-ether-functionalised amidinate and iminoanilide ligands for the hydrophosphination of vinylarenes. Dalton Trans 2019, 48(25), 9173–9180.
[57] Zhang, Z, Shao, Y, Tang, J, Jiang, J, Wang, L, Li, S. Supramolecular asymmetric catalysis mediated by crown ethers and related recognition systems. Green Synth Catal 2021, 2(2), 156–164.
[58] Cram, DJ, Sogah, GD. Chiral crown complexes catalyse Michael addition reactions to give adducts in high optical yields. J Chem Soc Chem Commun 1981, 13, 625–628.
[59] Nagayama, S, Kobayashi, S. A novel chiral lead (II) catalyst for enantioselective aldol reactions in aqueous media. J Am Chem Soc 2000, 122(46), 11531–11532.
[60] Maddock, LC, Mu, M, Kennedy, AR, García-Melchor, M, Hevia, E. Facilitating the ferration of aromatic substrates through intramolecular sodium mediation. Angew Chem Int Ed 2021, 60(28), 15296–15301.
[61] Huang, H, Zhang, G, Liang, S, Xin, N, Gan, L. Selective synthesis of fullerenol derivatives with terminal alkyne and crown ether addends. J Org Chem 2012, 77(5), 2456–2462.

[62] Berdnikova, DV, Ihmels, H, Schönherr, H, Steuber, M, Wesner, D. Photoinduced formation of stable Ag-nanoparticles from a ternary ligand-DNA-Ag^{+} complex. Org Biomol Chem 2015, 13(12), 3766–3770.
[63] Zhang, Q, Li, T, Duan, A, Dong, S, Zhao, W, Stang, PJ. Formation of a supramolecular polymeric adhesive via water–participant hydrogen bond formation. J Am Chem Soc 2019, 141(20), 8058–8063.
[64] Gu, S, Zhang, SW, Han, J, Deng, Y, Luo, C, Zhou, G, He, Y, Wei, G, Kang, F, Lv, W, Yang, QH. Nitrate additives coordinated with crown ether stabilize lithium metal anodes in carbonate electrolyte. Adv Funct Mater 2021, 31(28), 2102128.
[65] Atta, NF, Galal, A, El-Gohary, AR. New insight for simultaneous determination of hazardous di-hydroxybenzene isomers at crown ether modified polymer/carbon nanotubes composite sensor. J Hazard Mater 2020, 388, 122038.
[66] Mousavi, F, Shamsipur, M, Taherpour, AA, Moghimi, A. Feasibility of using two benzo-substituted pyrilium-based compounds in dye-sensitized solar cells. Mater Sci Semicond Process 2021, 123, 105468.

Arruje Hameed, Razia Noreen, Muhammad Sami Ullah Khan Niazi, Shaheera Batool, Anwar Ahmad, Tanzeela Khalid and Tahir Farooq*

Chapter 7
Fluorinated alcohol-assisted preparation of functional and biologically active compounds

7.1 Introduction

Over the last two decades, there has been a great interest to find alternative reaction media under the concepts of green chemistry and cleaner production strategy. The alternative reaction media are expected to modify the course of reactions avoiding the application of metallic catalysts, chemical additives and harsh conditions. In this connection, fluorinated compounds have emerged as attractive reaction media with the potential to replace conventional organic solvents for synthetic applications. The fluorinated compounds show high ionizing power, low nucleophilicity and high hydrogen bonding ability [1]. Such unique physicochemical properties could dramatically alter the course of any reaction due to the presence of one or more fluoroalkyl groups as their constituents. The highly fluorinated solvents are often immiscible with generally used organic solvents termed as the fluorous phase. Usually, they act as common organic solvents but their fluorous nature helps to control the selectivity and reactivity in synthetic applications. The fluorous compounds produced biphasic systems with organic solvents at room temperature and become homogeneous mixtures at elevated temperatures. The two phases get separated when the reaction is cooled down, facilitating the separation of catalyst and products with minimum workup requirements.

Considering the unique properties of fluorinated solvents, they have been employed as solvents for various synthetic transformations in different combinations:

a) As pure fluorous solvents
b) As cosolvents with other organic solvents
c) Fluorous solvents as a phase screen
d) As hybrid solvents

*Corresponding author: **Tahir Farooq**, Department of Applied Chemistry, Government College University Faisalabad, Faisalabad, Pakistan, e-mail: tahirfarooqfsd@gmail.com
Arruje Hameed, Razia Noreen, Department of Biochemistry, Government College University Faisalabad, Faisalabad, Pakistan
Muhammad Sami Ullah Khan Niazi, Anwar Ahmad, Tanzeela Khalid, Department of Applied Chemistry, Government College University Faisalabad, Faisalabad, Pakistan
Shaheera Batool, Department of Biochemistry, CMH Institute of Medical Sciences Multan, Multan, Pakistan

https://doi.org/10.1515/9783110788129-007

Accordingly, the fields of synthetic organic chemistry have been revolutionized with the application of fluorinated alcohols as reaction-promoting media. Over the last few decades, they have been used as reaction-promoting solvents in a number of synthetic organic transformations, owing to their hydrogen bonding ability and electron withdrawing properties. In this regard, hexafluoro-2-propinol (HFIP) and trifluoroethanol (TFE) have shown remarkable reaction-promoting effects being solvents in a variety of synthetic reactions. They have high hydrogen bonding ability, high ionizing power, and high polarity (Figure 7.1) [2]. Such unique physicochemical property renders them to be counted as superior solvents compared to non-fluorinated alcohols. The fluorinated alcohols participate in chemical reactions by at least two different ways [3, 4]:

1. Fluorinated alcohols assist the metallic catalysts and other chemical additives for the promotion of reactions.
2. The fluorinated alcohols directly promote the chemical reactions without the involvement of any catalyst or chemical additives.

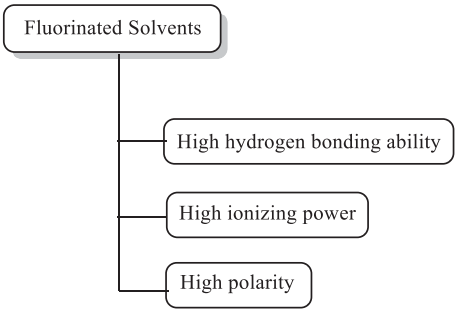


Figure 7.1: Unique properties of fluorinated solvents.

In recent years, the synthetic chemicals have utilized fluorinated alcohols for redox-neutral reactions, metal-free synthesis and reactions under mild conditions. According to the emerging concepts of cleaner production strategies and green chemistry, reaction-promoting solvents must provide higher yield and minimize the byproduct formation and workup requirements. Therefore, fluorinated solvents do support the cleaner production, owing to their unique reaction-promoting properties. Due to the presence of more fluorine atoms, fluorinated solvents generally have higher densities (1.67–1.96) than non-fluorous molecules. The hybrid solvents have relatively low density ranging from 1.27 to 1.66. Due to the low polarizability of carbon fluorine bonds, the fluorinated solvents show small refractive indexes.

Herein, we highlighted the examples of various organic transformations performed in fluorinated alcohols as follows:

a) Reactions have been promoted due to high ionizing power of the fluorinated solvents.
b) Reactions promoted by the acidic character of the fluorinated solvents.
c) The chemical transformations promoted by the strong hydrogen bonding ability of the fluorinated solvents.

The unique physicochemical properties of fluorinated alcohols could modify the course of reactions resulting in short-time reactions with great regioslectivity and enantiopure products [5, 6]. The subsequent section of the chapter illustrates the influence of fluorinated solvents in electrophilic reactions, nucleophilic substitutions, cycloadditions and carbon functionalization reactions (Figure 7.2). The examples also highlight the reaction-promoting role of fluorinated alcohols in metal-catalyzed, metal-free, heterocyclic synthesis and other important green reactions.

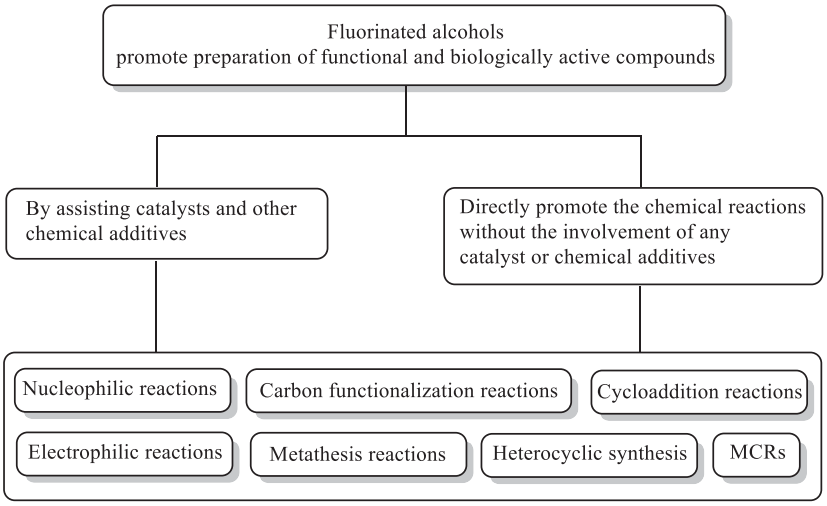


Figure 7.2: Fluorinated alcohol-mediated synthetic transformations.

7.2 Fluorinated alcohol-mediated synthetic transformations

7.2.1 Fluorinated solvent-assisted oxidation reactions

A recent report describes the selective oxidation of secondary alcohols to ketones in the presence of an activating fluorinated solvent [7]. The aerobic oxidation of secondary alcohols proceeds in the presence of HNO_3 and $FeCl_3$ as reaction catalysts. Initially, alkyl nitrile is produced from alcohol due to the in situ formation of NOCl as active species. The alkyl nitrile subsequently decomposes to the corresponding ketone (Figure 7.3).

Over the century, there has been an immense interest to develop methodologies for the selective oxidation of aliphatic C–H bonds. Generally, they are known for their inert behavior and are least susceptible to oxidation conditions. Therefore, notable efforts have always been made to tune the properties of the C–H bond to achieve predictable oxidation products.

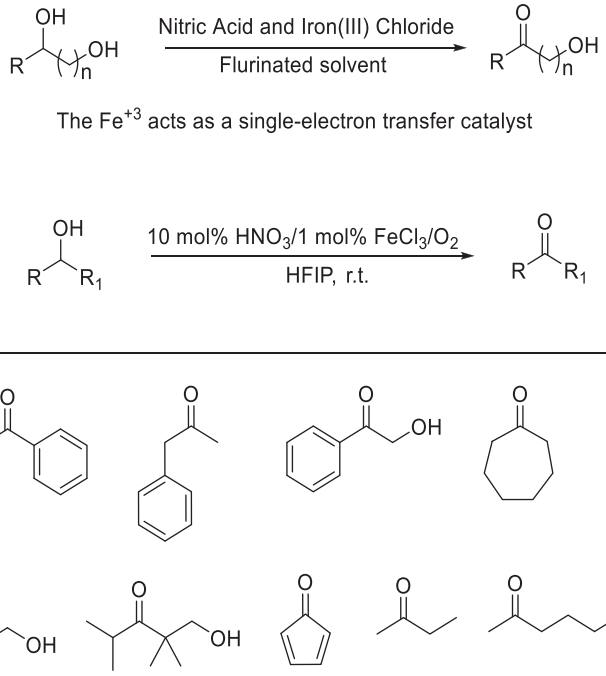


Figure 7.3: Selective oxidation of secondary alcohols in activating fluorinated solvent.

In 2017, a remarkable method described the polarity reversal of electron-rich functional groups, enabling the predictable oxidation of remote aliphatic C–H bonds (Figure 7.4) [8]. The manganese- and iron-catalyzed approach utilized the hydrogen bonding potential of fluorinated solvents for polarity reversal and chemoselective oxidation of methylenic sites in amines, amides, ethers and alcohols. The selective hydroxylation of hydrocarbons was achieved using H_2O_2 as the oxidant in HFIP.

A recent report describes an environment-friendly preparation of quinones and hydroxylated arenes by the straightforward oxidation of electron-rich arenes (Figure 7.5) [9]. Fluorinated solvents were used for the oxidation of naphthol, phenol, and anisole derivatives under milder reaction conditions. The reaction process avoids the use of metallic catalysts and relies on UHP (adduct of urea and hydrogen peroxide) as the source of H_2O_2. The reaction shows high atom economy and provides moderate-to-good yields with the formation of biodegradable byproduct.

Recently, a variety of aldehydes have been prepared from substituted styrenes using HFIP as a fluorinated solvent. The molecular oxygen was used as an oxidant and *N*-hydroxyphthalimide as a catalyst under normal reaction conditions. The reaction offers high functional group tolerance and practical convenience with a cheaper catalyst (Figure 7.6) [10].

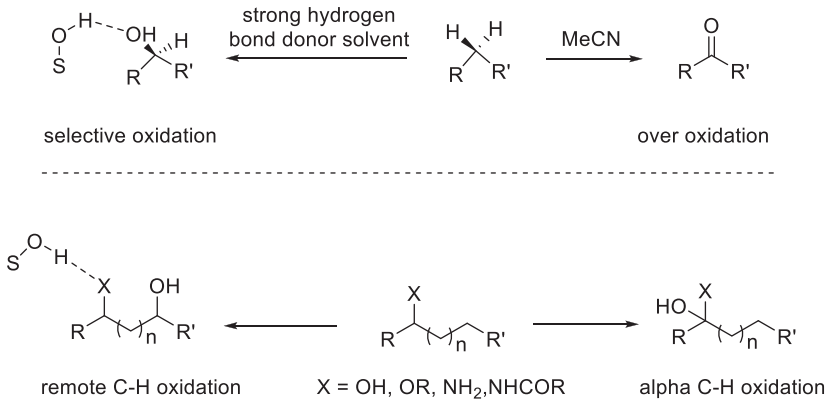
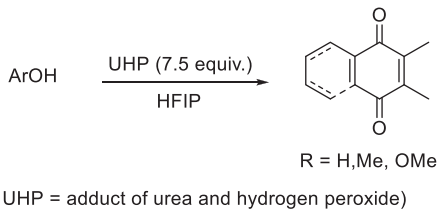


Figure 7.4: Selective C–H oxidation directed by solvent hydrogen bonding.



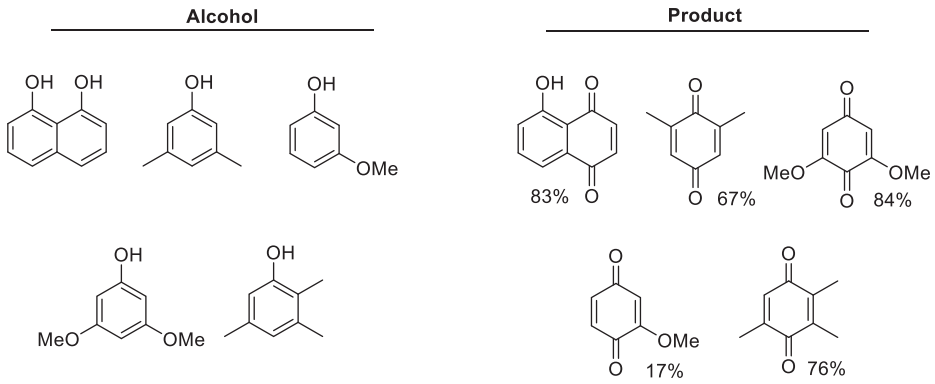


Figure 7.5: Fluorinated solvent-assisted oxidation of electron-rich arenes.

7.2.2 Fluorinated solvent-assisted electrophilic reactions

The HFIP mediated a Friedel-Crafts alkylation reaction of arenes and β-nitroalkenes in a cleaner and more effective way under normal conditions. The hydrogen bonding capacity of HFIP motivated the formation of the product (Figure 7.7) [11].

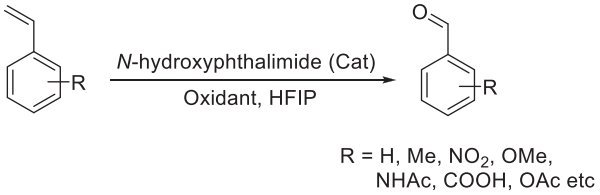


Figure 7.6: Fluorinated alcohol promotes oxidation of substituted styrenes.

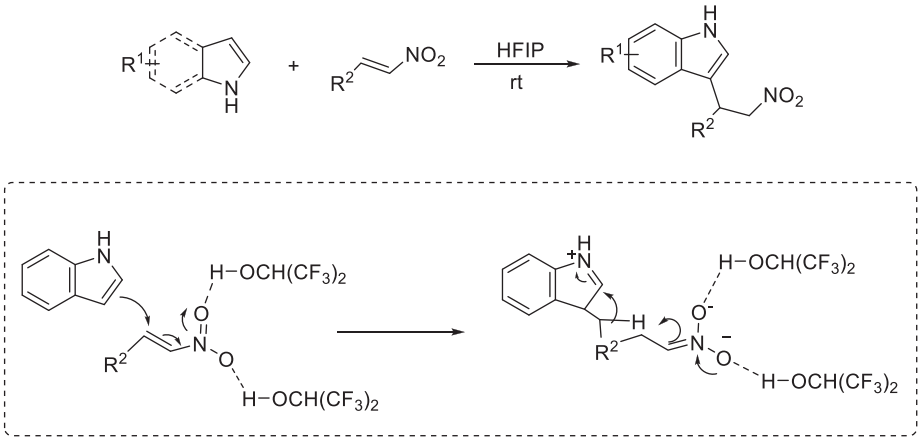


Figure 7.7: Friedel-Crafts alkylation reaction of arenes in fluorinated alcohol.

An earlier report described the alkylation of unprotected indoles using α-haloketones as electrophilic agents. A variety of oxyallyl cations were generated in situ in the presence of a base. The enol formation was stabilized by the fluorinated solvent via hydrogen bond formation (Figure 7.8) [12].

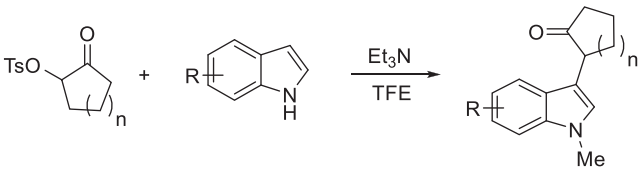


Figure 7.8: Alkylation of unprotected indoles using α-haloketones in fluorinated media.

Electron-rich arenes with epoxides were made to undergo intramolecular stereoselective Friedel-Crafts alkylation. The reaction was supported by the hydrogen bonding capacity of HFIP (Figure 7.9) [13].

Very recently, a report describes the applications of epoxides and alcohols for the direct preparation of substituted arenes (Figures 7.10 and 7.11) [14]. Generally, epoxides

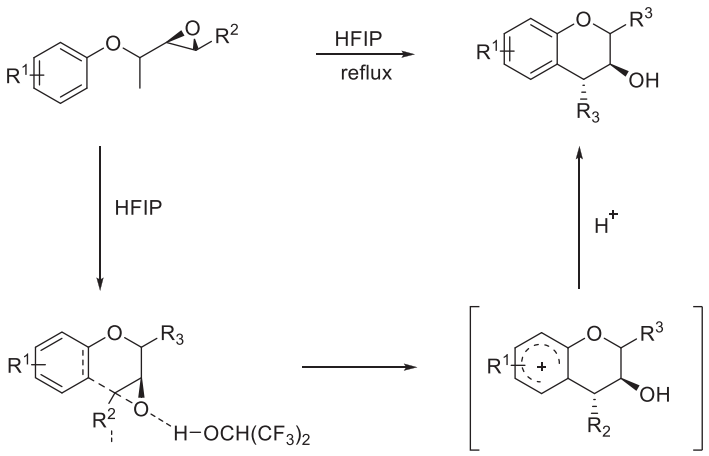


Figure 7.9: Fluorinated alcohol promotes intramolecular stereoselective Friedel-Crafts alkylation.

and alcohols are considered as effective electrophiles because they do not need any preactivation. They participate in Friedel-Crafts alkylation without the generation of waste. Stereospecifically, alcohols are produced from aliphatic epoxides and electron-poor epoxides. Subsequently, they undergo nucleophilic substitution reactions with different arenes in the presence of HFIP. The reported procedure widens the applications of Friedel-Crafts reactions for the preparation of important scaffolds under meta-free conditions of cross-coupling reactions.

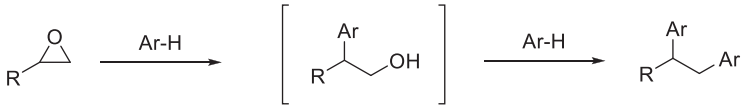


Figure 7.10: Regioselective ring-opening arylation of epoxides and dehydroarylation.

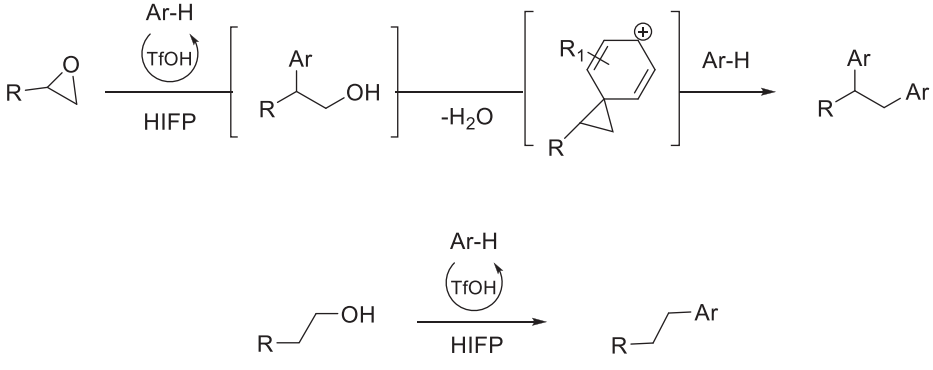


Figure 7.11: Dehydroarylation of epoxides and aliphatic amines.

An intramolecular Friedel-Crafts acylation of aryl–alkyl acid chlorides was promoted by HFIP without the use of any additive. The operationally facile reaction procedure requires no catalyst, reagent and workup (Figure 7.12) [15].

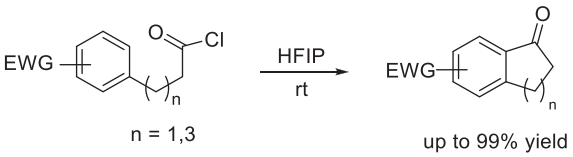


Figure 7.12: Chemical-free intramolecular Friedel-Crafts acylation of aryl–alkyl acid chlorides.

A variety of aryl ketones were also prepared using intermolecular Friedel-Crafts acylation under normal conditions in HFIP. The reaction procedure requires no chemical additives, and product isolation needs no workup (Figure 7.13) [16].

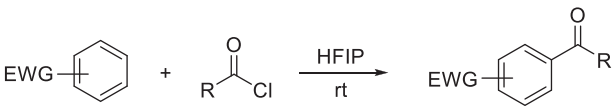


Figure 7.13: Preparation of aryl ketones in fluorinated alcohol.

7.2.3 Fluorinated solvent-assisted nucleophilic addition reaction

Over the years, it has been observed that the fluorinated alcohols could successfully promote a number of organic transformations avoiding the use of any catalysts of chemical additives. According to one report, the fluorinated alcohols promoted the preparation of tetrahydroquinones without the addition of any catalyst. The one-pot domino reaction procedure involves the nucleophilic addition reaction between vinyl ethers and anilines (Figure 7.14) [17].

On the same pattern, the HFIP promotes its nucleophilic addition to vinyl ethers in the absence of any chemical additive. The rate and extent of the reaction showed dependence on the hydrogen bonding capacity of fluorinated alcohol. It helps the formation of an intermediate species with cationic character and causes the liberation of an anionic conjugated base (Figure 7.15) [18].

Over the last two decades, the photochromic molecules have attracted considerable attention of the synthetic chemists, owing to their tunable physicochemical properties, high temporal and spatial resolution. In this connection, the field of molecular machines has been revolutionized with the incorporation of photoresponsive molecules into the materials. Structural modification of photochromics helps to control their thermal stability, quantum yields and absorption properties for desired applications [19]. In

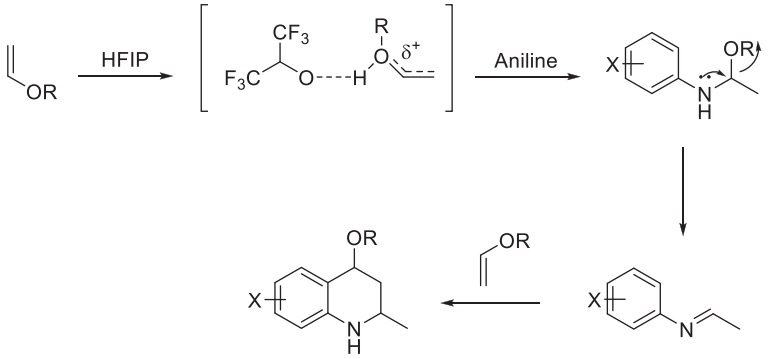


Figure 7.14: Nucleophilic addition reaction of vinyl ethers and anilines in fluorinated media.

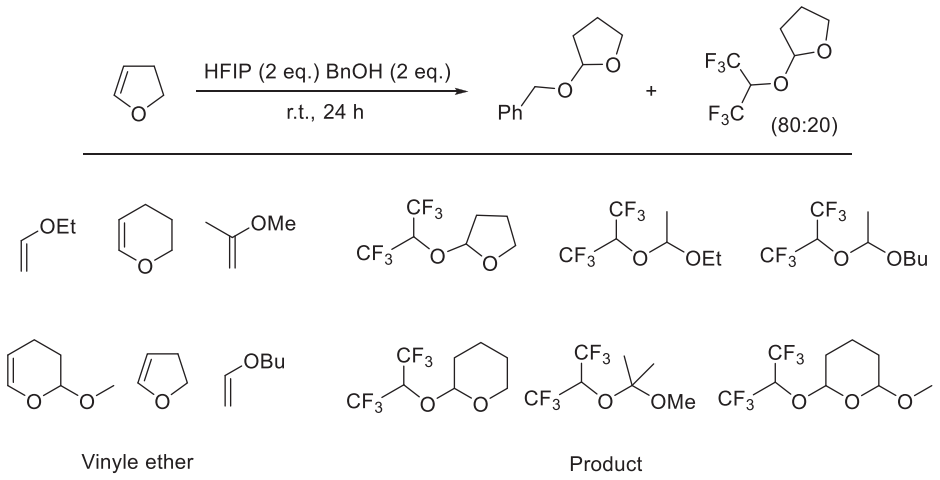


Figure 7.15: Nucleophilic addition of fluorinated alcohol to vinyl ethers.

recent years, a special class of photoresponsive materials called donor-acceptor Stenhouse adducts (DASAs) has shown promising applications as visible-light-responsive photoswitches. They are accessible through an approach which involved nucleophilic ring-opening reactions of activated furans. However, the known synthetic method represents limitations of slow process with low yields, owing to the use of less reactive donors or acceptors. A very recent report described the use of fluorinated alcohol as a promoter of ring-opening reaction with high yield and reduced reaction time. The methodology provided access to a variety of DASA-based photoswitches (Figure 7.16) [20].

Highly complex and chemically diverse molecules are efficiently obtained through multicomponent reaction (MCR) strategy. All the reactants are essentially incorporated into the MCR products.

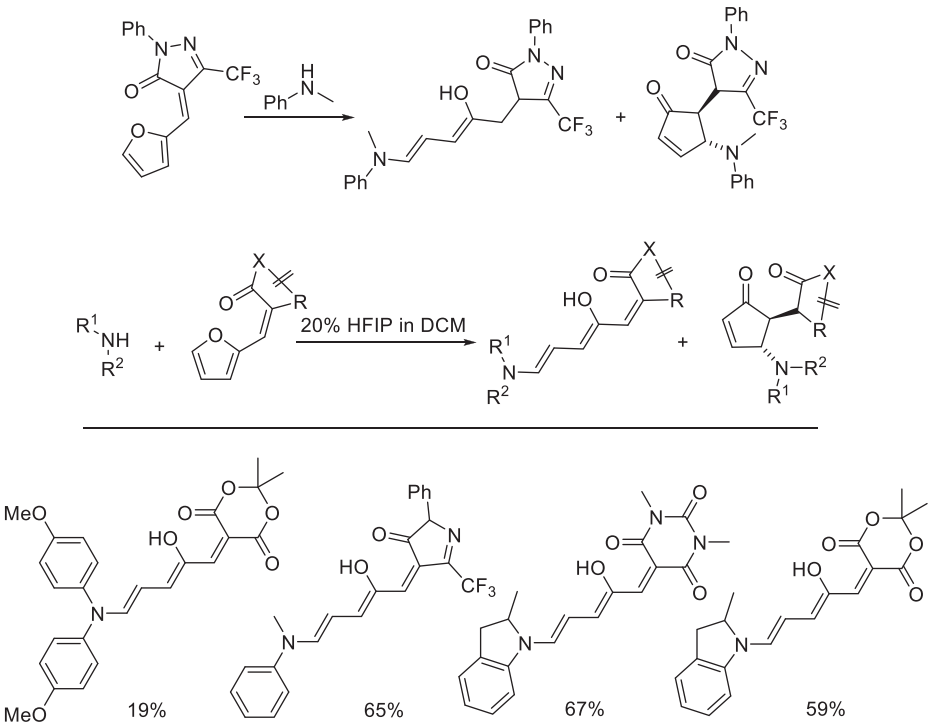


Figure 7.16: Preparation of donor-acceptor Stenhouse adducts in fluorinated alcohol.

In one of the recently reported MCRs, the HFIP acts as an acidic component in Passerini-type reaction tolerating a range of aldehydes and isocyanides. Under metal-free milder conditions, the as-produced imidates were further reduced to β-amino alcohols in the one-pot reaction (Figure 7.17) [21].

The single electron transfer processes do heavily rely on free radical species produced from closed-shell organic molecules. Over the last few years, there has been a great interest in the application of organic radical cations due to exceptional developments in electrosynthesis and photoredox reactions. The reactivity of radical cations is strongly influenced by the solvents as well as anions. However, until recently there has not been any comprehensive study explaining the influence of anions on the reactivity of radical cations. In this context, a recent study described the effects of HFIP and anions on the reactivity of radical cations under hole catalysis. A significant decrease in whole catalytic efficiency was observed with the addition of salts in radical cation Diels-Alder reaction. The common anions caused reduction in efficiency in photoredox catalysis. However, the negative impact of anions on the reaction rate has been counterbalanced by the fluorinated solvent by reducing their nucleophilic strength. This improved the efficiency of electrolytic reactions under hole catalysis (Figure 7.18) [22].

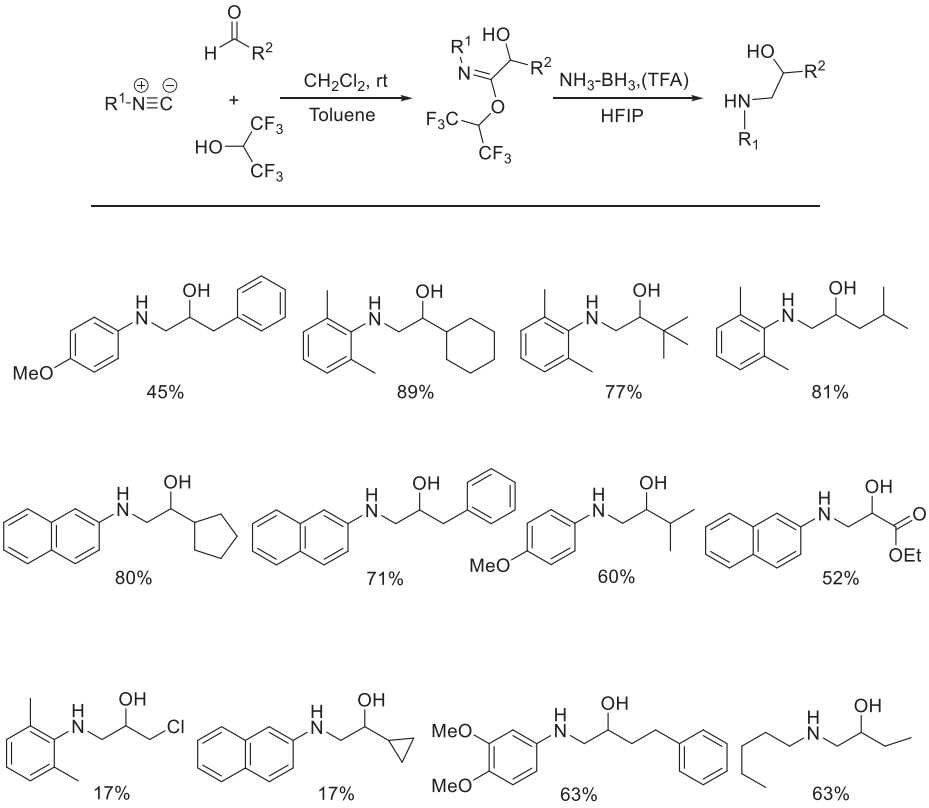
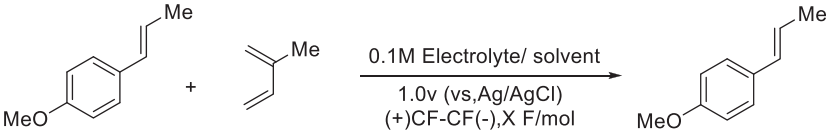


Figure 7.17: Fluorinated solvent-mediated preparation of β-amino alcohols.



Electrolyte = Bu_4NOTf, CF (Carbon felt), X = Charge (0.1, 0.2), solvent = HFIP

Figure 7.18: Fluorinated solvent-mediated electrolytic Diels–Alder reaction.

7.2.4 Fluorinated solvent-assisted nucleophilic substitution reactions

The TFE acted as a favorable reaction media for intramolecular α-alkylation of aldehydes. The reactions proceeded without any additives and enantioselectively provided highly functionalized primary alcohols. The fluorinated solvent with its ability

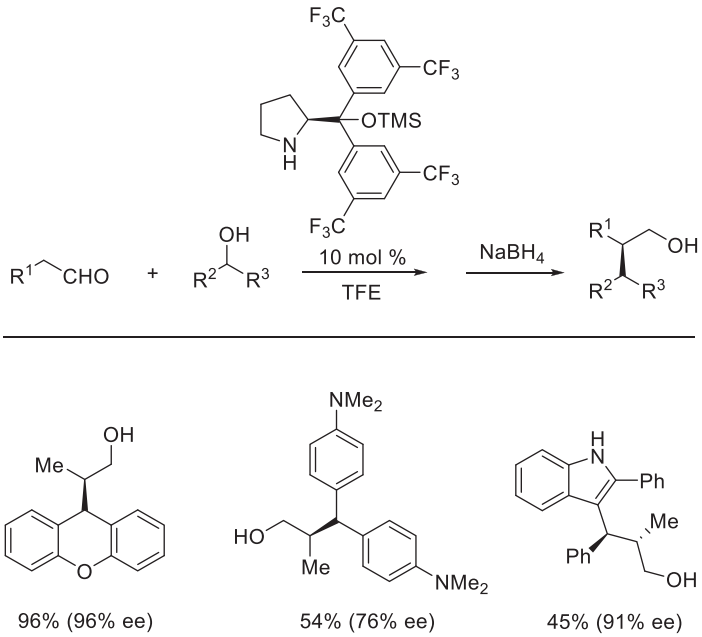


Figure 7.19: Enantioselective intramolecular α-alkylation of aldehydes in fluorinated media.

of strong hydrogen bonding and high ionizing power favors enantioenriched product formation (Figure 7.19) [23].

Fluorinated alcohols also promoted the direct substitution reactions of allylic alcohols with carbanions and silylated and nitrogenated nucleophiles. The application of arenes as nucleophiles also provided Friedel–Crafts products, and the higher hydrogen bonding potential of fluorinated solvents controls the chemoselectivity of the reaction (Figure 7.20) [5].

Electron-rich nucleophiles could attack epoxides with great ease in the presence of fluorinated alcohols. The HFIP promotes the ring-opening reactions of epoxides due to the attack of aromatic amines. Again the hydrogen bonding ability of HFIP favored the formation of amino alcohols in excellent yield. Another report describes the use of TFE as a favorable reaction media for ring-opening reactions of epoxides (Figure 7.21) [24].

The S_N2-type reaction method reports the use of pyrroles and indoles as nucleophiles for a highly stereoselective and regioselective product formation (Figure 7.22) [25].

The epoxides were used for the alkylation of arenes through S_N2 reactions promoted by HFIP as fluorinated reaction media. The highly ionizing solvent stabilized the polar transition state and assisted the concerted C–C bond development (Figure 7.23) [13].

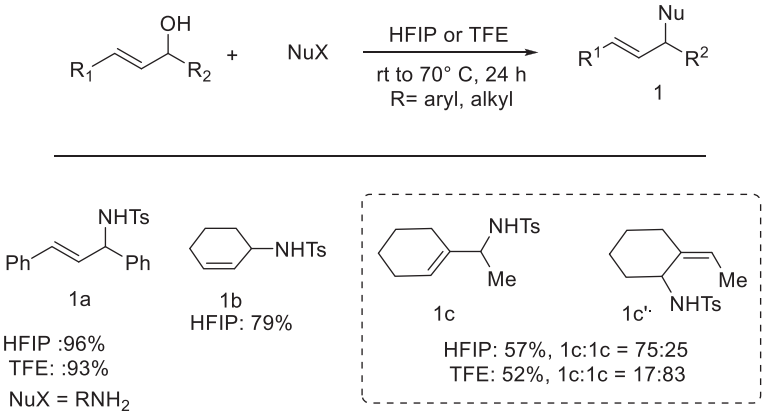


Figure 7.20: Fluorinated alcohol promotes the direct substitution reactions of allylic alcohols.

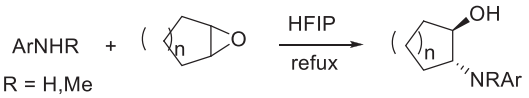


Figure 7.21: HFIP-promoted ring-opening reactions of epoxides.

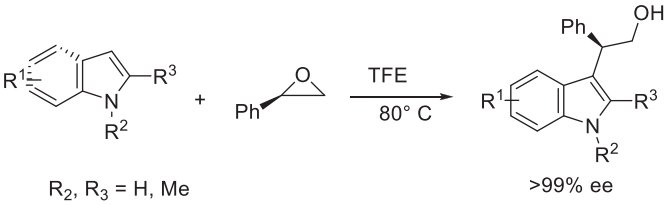


Figure 7.22: Highly stereoselective and regioselective epoxide ring opening in fluorinated medium.

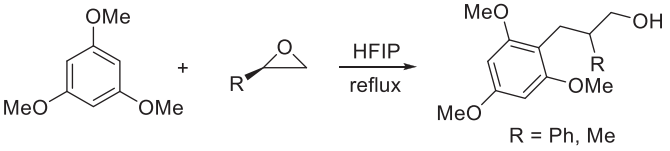


Figure 7.23: Alkylation of arenes through S_N2 reactions promoted by HFIP.

7.2.5 Fluorinated solvent-assisted cycloaddition reactions

In chemical synthesis, functionalized ring formation has been made possible through atom-economy procedure known as cycloaddition reactions. The use of fluorinated solvents like HFIP in cycloaddition reaction resisted the production of solubolysis-based side products improving the yield of major product. Accordingly, the report described the application of fluorinated alcohols for the promotion of intramolecular aza-cycloadditions (Figure 7.24) [26].

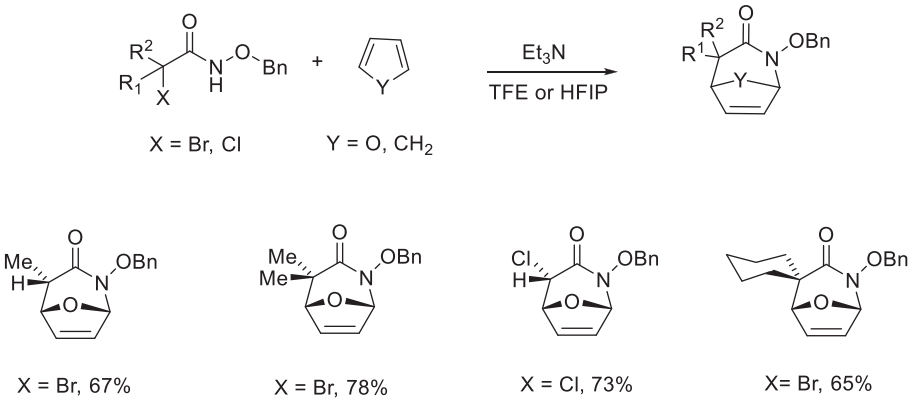


Figure 7.24: Fluorinated alcohol promotes intramolecular aza-cycloadditions.

7.2.6 Fluorinated solvent-assisted C–H functionalization reaction

Over the last few decades, a lot many efforts have been made to manage C–H activations for various synthetic transformations. The emergence of fluorinated solvents as effective reaction media has revolutionized the C–H activation field. They play important roles in C–H functionalization with respect to reactivity and selectivity. They mediate to control site selectivity and stereoselectivity of the reaction with and without chemical additives due to their hydrogen bonding capacity [27].

The application of HFIP as a fluorinated solvent promoted C–H functionalization of α-amino acids. The pyridine-type ligands mediate acid-directed β-C(sp^3)–H arylation in the absence of any directing group. The Pd-catalyzed arylation allowed the preparation of non-natural amino acids. The scalable procedure has also been applied for the C–H functionalization of aliphatic acids and carboxylic acid rings (Figure 7.25) [28].

Owing to the inherent electron deficiency of the benzene ring of benzoic acids, activation of aromatic C−H bonds of benzoic acids is difficult at ambient temperature. To date, no example of C−H bond arylation of benzoic acids at ambient temperature is known (Figure 7.26). Finally, a report came up describing the *ortho*-C–H arylation of

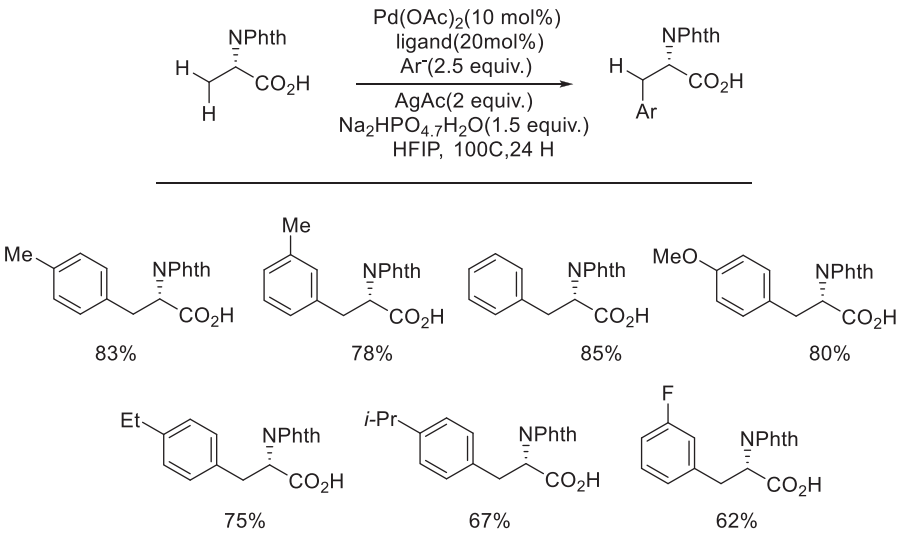


Figure 7.25: Fluorinated solvent promoted C–H functionalization of α-amino acids.

benzoic acids at ambient temperature [29]. The application of fluorinated solvent assisted the C–H activation and improved the catalytic efficiency of Pd catalyst.

The 2,2′-functional biaryl serves as an important structural entity in many naturally occurring and synthetic bioactive compounds. Therefore, there has been a continuous effort to develop new greener and high-yielding methodologies for their facile synthesis. In recent years, the activation of functionalized C–H bonds and direct dehydrogenative arene coupling has become a forefront approach for the preparation of aforesaid biaryls. However, this cross-coupling approach still has some major limitations, which challenge its effective large-scale applications. In 2015, a report described the preparation of various 2,2′-difunctional biaryl compounds through a weak coordination-assisted method under Pd-catalyzed dehydrogenative cross-coupling. The carbonyl oxygen with its weak coordination favors *o*-C–H bond cleavage under Pd-catalyzed acidic conditions. The reaction showed high dependence on oxidants and the use of fluorinated solvents for functional group tolerance and better reactivity (Figure 7.27) [30].

In the area of C–H functionalization and activation, the similarity of electronic features and strength of C–H bond offers great challenges for regioselective activation of positionally diverse C–H bonds. Especially for metal-mediated reactions, it is hard for metals to distinguish between primary and secondary C–H bonds. Therefore, developing site-specific activation of C–H has really been under great focus over the last few decades.

Recently, a report described a preferential activation of distal γ-C(sp^3)–H bond over the proximate β-C(sp^3)–H using 2-pyridone and pyruvic acid as ligands (Figure 7.28) [31]. According to this new protocol, the introduction of geometrically strained directing group helped to achieve six-membered cyclopalladation from five-membered cyclopalladation

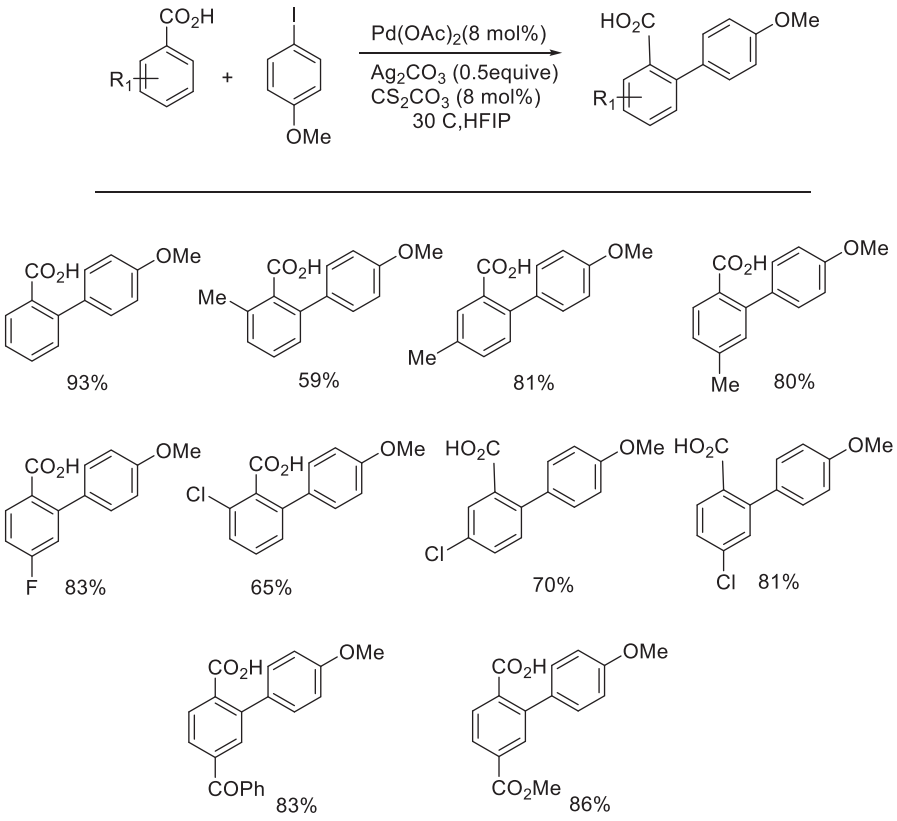


Figure 7.26: Ortho-C–H arylation of benzoic acids at ambient temperature in HFIP.

tolerating a wide range of functional groups. This highly convenient method allows the removal and installation of directing groups with selective functionalization of distal C(sp^3)–H leading to the generation of biologically potent compounds.

The emergence of concepts of transient directing groups has given new dimensions to C–H bond functionalization. The concept involves the installation and subsequent removal of directing group for the C–H functionalization. In 2017, the C–H arylation reaction was promoted by the use of reversible imine formation as a transient directing group. According to the reported method, the aliphatic aldehydes undergo direct β-C–H arylation in Pd-catalyzed reactions promoted by HFIP as cosolvents. The transient imine formation from simple and diamines as directing group promotes the reaction progress (Figure 7.29) [32].

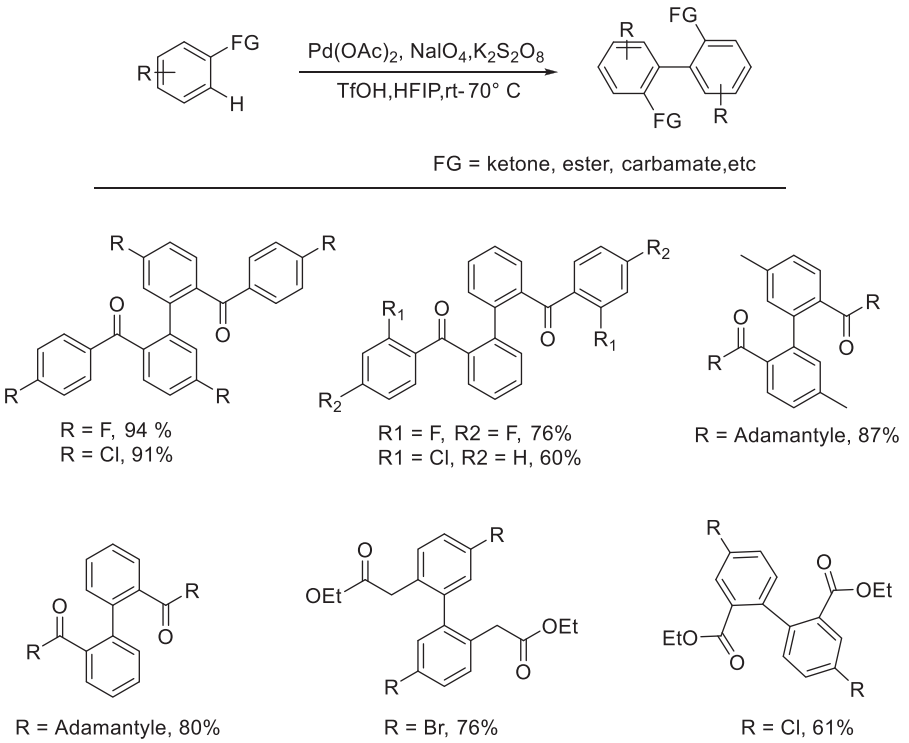


Figure 7.27: Pd-catalyzed dehydrogenative cross-coupling in fluorinated media.

7.2.7 Fluorinated solvent-assisted olefin metathesis

Over the last few decades, olefin metathesis has become a forefront chemical approach for the preparation of various bioactive and natural compounds. The available Ru-based catalysts are generally inefficient in olefin metathesis for the total synthesis of natural products. To avoid such limitations, there has been a great interest in the development of new efficient catalysts or reaction-promoting chemical additives. In one such attempt, aromatic fluorinated hydrocarbons were used as reaction-promoting media for Ru-catalyzed olefin metathesis reactions (Figure 7.30) [33]. The solvent-promoted reactions provided higher yields of biologically active and complex natural compounds.

The sulfur-containing olefins produce challenges in the process of olefin metathesis although they are of high value in various synthetic transformations. The fluorinated solvents have also been employed as reaction-promoting media in order to overcome such reactivity challenges. In this connection, the reactivity of sulfoxides, sulfones and sulfides was evaluated in aromatic fluorinated hydrocarbons as reaction media (Figure 7.31) [34].

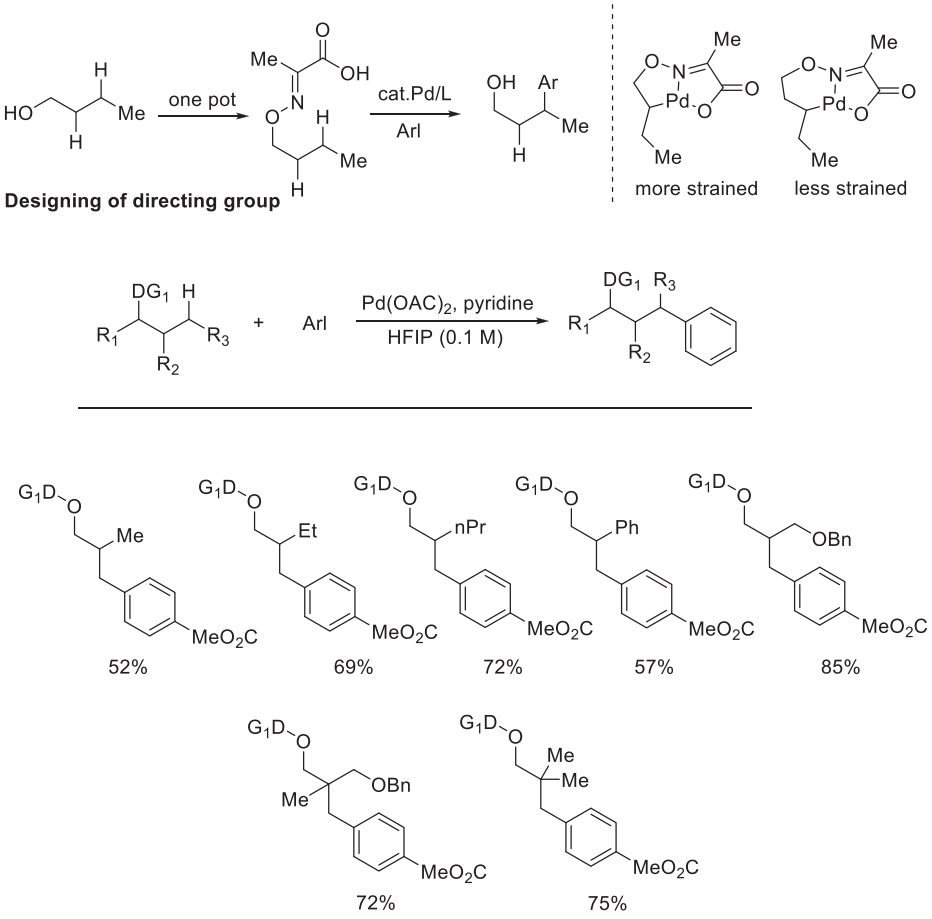
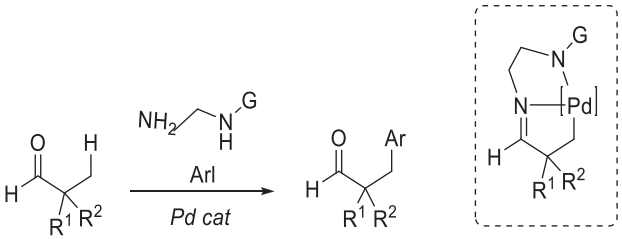


Figure 7.28: HFIP-assisted selective functionalization of distal C(sp^3)–H.

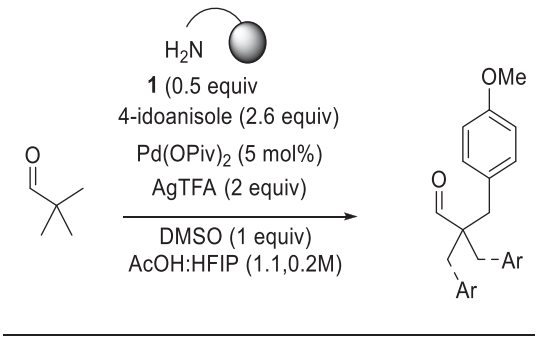
As described earlier, the fluorinated solvents have high polarity, high ionizing power and low nucleophilicity; thus, they are capable of stabilizing the cationic species through hydrogen bonding. In a recent report, the TFE promoted intramolecular alkyne–aldehyde metathesis under metal-free conditions. The boron trifluoride–etherate-mediated reaction provided 3-aroyl-2H-chromenes in high yield (Figure 7.32) [35].

Generally, cyclic alkenes are produced from olefin-carbonyl metathesis. A recent report combined gallium-catalyzed transfer hydrogenation with ring-closing carbonyl–olefin metathesis (COM) as a tandem approach for the successful preparation of cycloalkanes (Figure 7.33) [36].

The Brønsted acid-catalyzed COM has extensively been studied for the preparation of a wide range of functional molecules; however, the methodology remained underexplored due to the limitations of poor reaction yield. Recently, the fluorinated alcohols



Transient directing groups for C-H arylation of aldehydes



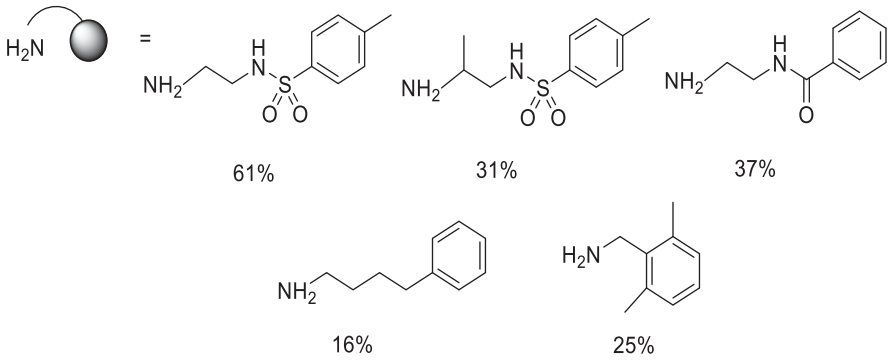


Figure 7.29: Direct β-C–H arylation in Pd-catalyzed reactions promoted by HFIP.

have been evaluated to assist Brønsted acid-catalyzed COM for high yield. The report described the COM reaction efficiently catalyzed by *para*-toluenesulfonic acid in HFIP, owing to its hydrogen bonding capacity for a stable transition state (Figure 7.34) [37].

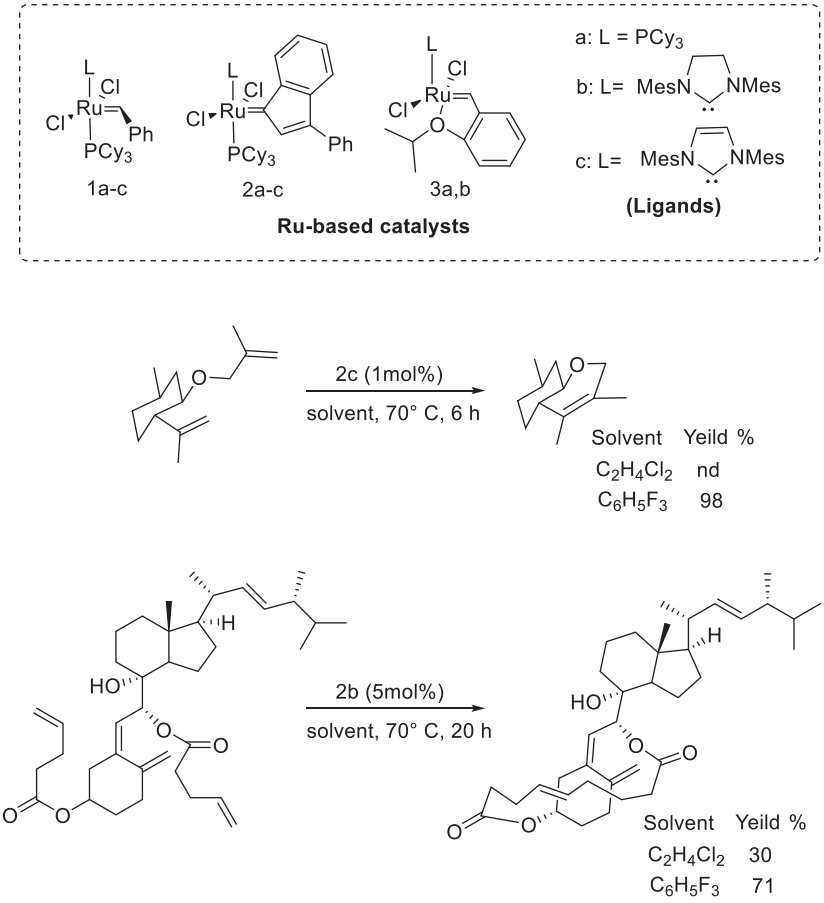


Figure 7.30: Ru-catalyzed olefin metathesis in fluorinated solvent.

7.2.8 Fluorinated alcohol-assisted multicomponent reactions

Highly substituted α-amino tetrazoles are generally produced by employing well-established Ugi tetrazole reaction methodology. During the reaction, a primary amine reacts with an aldehyde or a ketone generating a Schiff base, which subsequently reacts with isocyanide. Then nitrilium ion as an intermediate reacts with an azide to furnish corresponding tetrazoles.

A variety of natural and synthetic pharmacologically potent compounds are recognized as 2,5-diketopiperazines. They are important structural motifs in a variety of bioactive compounds and drug molecules. A new approach describes the fluorinated solvent-assisted synthesis of diketopiperazine tetrazoles. The classical intramolecular Ugi 4CR and Ugi tetrazole 4CR were combined as TFE-assisted MCR (Figure 7.35) [38].

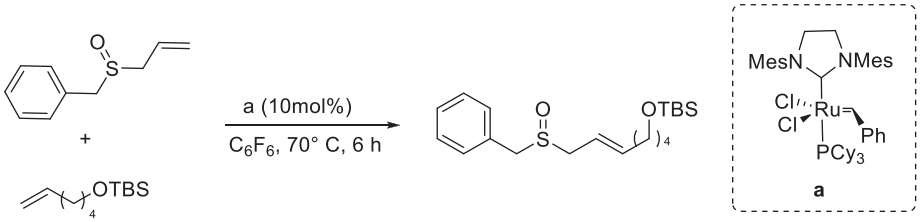


Figure 7.31: Olefin metathesis reactions of sulfur-containing alkenes in fluorinated solvent.

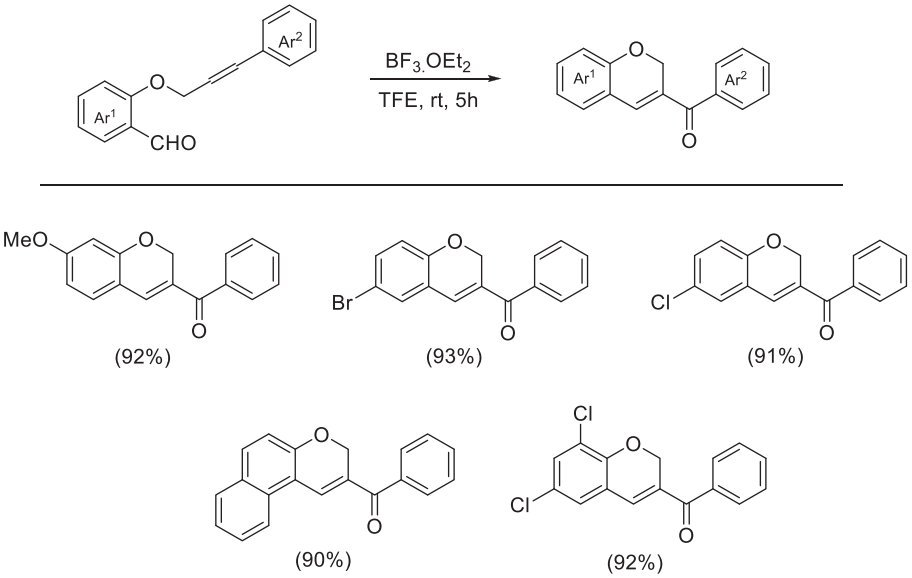


Figure 7.32: Intramolecular alkyne–aldehyde metathesis in fluorinated alcohol.

Although the Ugi reactions are useful for the practical preparation of a variety of substituted tetrazoles, the use of amines put a limit to its scope. A recent report describes the use of $TMSN_3$ with hydrazine compounds as alternatives to extend the scope of MCRs for the preparation of tetrazoles (Figure 7.36) [39].

A large number of biologically potent compounds, drug molecules and functional materials carry sulfonate esters as central functional moieties. Traditionally, they are prepared by reacting chlorosulfonic acid with arenes under harsh conditions. The known methods present a number of limitations, thus challenging the large-scale wide applications of sulfonate esters. A recent study came up with an alternative approach for the preparation of alkyl arylsulfonates. The HFIP-mediated methodology describes the anodic oxidation of electron-rich arenes in an MCR using an alcohol and excess of

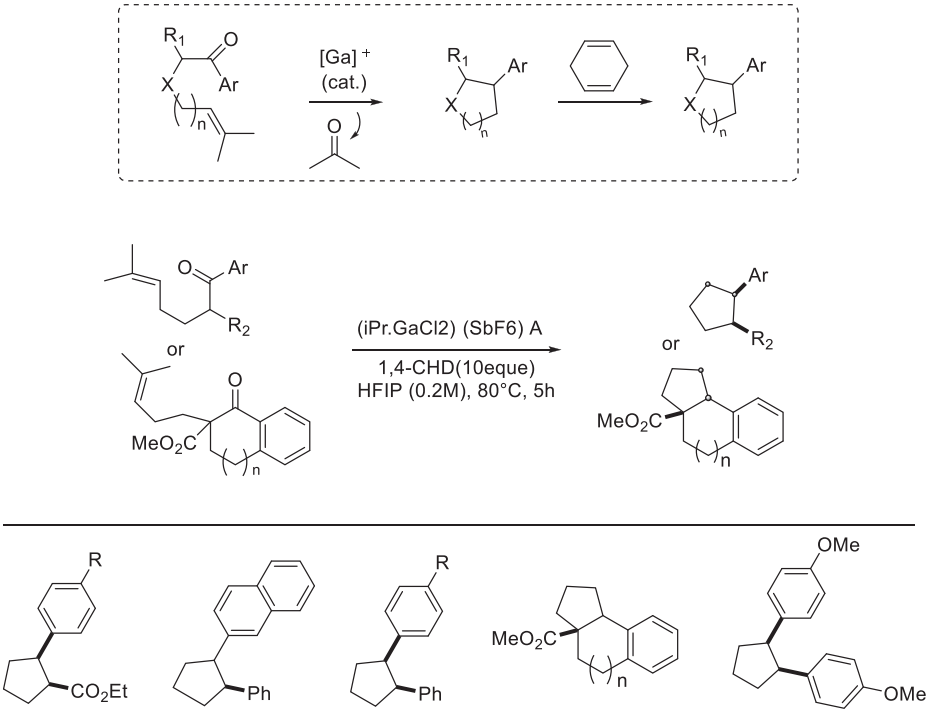
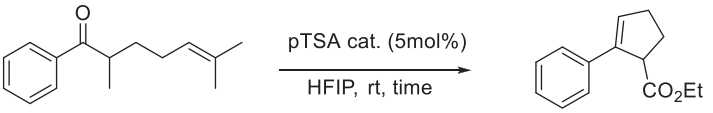


Figure 7.33: Gallium-catalyzed tandem carbonyl–olefin metathesis in HFIP.



Fluorinated solvent	Yield
HFIP (50 μL)	56%
HFIP (75 μL)	62%
HFIP (200 μL)	60%

Figure 7.34: Brønsted acid-catalyzed carbonyl–olefin metathesis in fluorinated media.

SO_2 (Figure 7.37) [40]. During the course of the reaction, a bifunctional intermediate is produced with high conductivity and nucleophilicity. The diamond electrodes execute the oxidation of a variety of electron-rich arenes using differently substituted alcohols providing good-to-excellent yields of alkyl arylsulfonates.

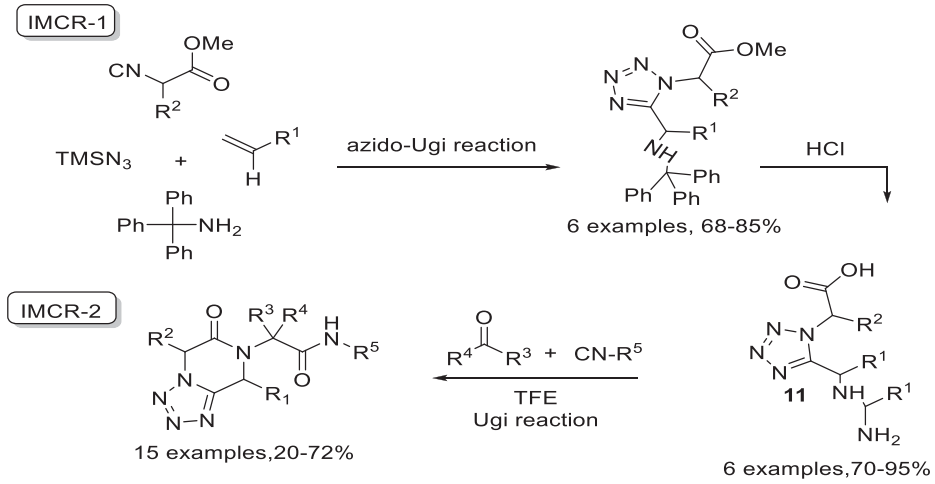


Figure 7.35: Fluorinated solvent-assisted synthesis of diketopiperazine tetrazoles.

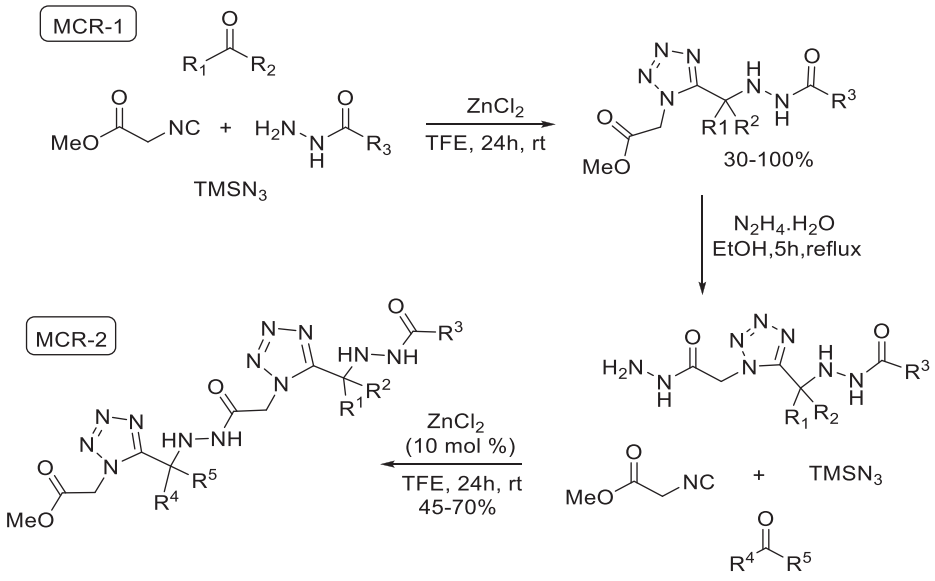


Figure 7.36: TFE-assisted MCRs for the preparation of tetrazoles.

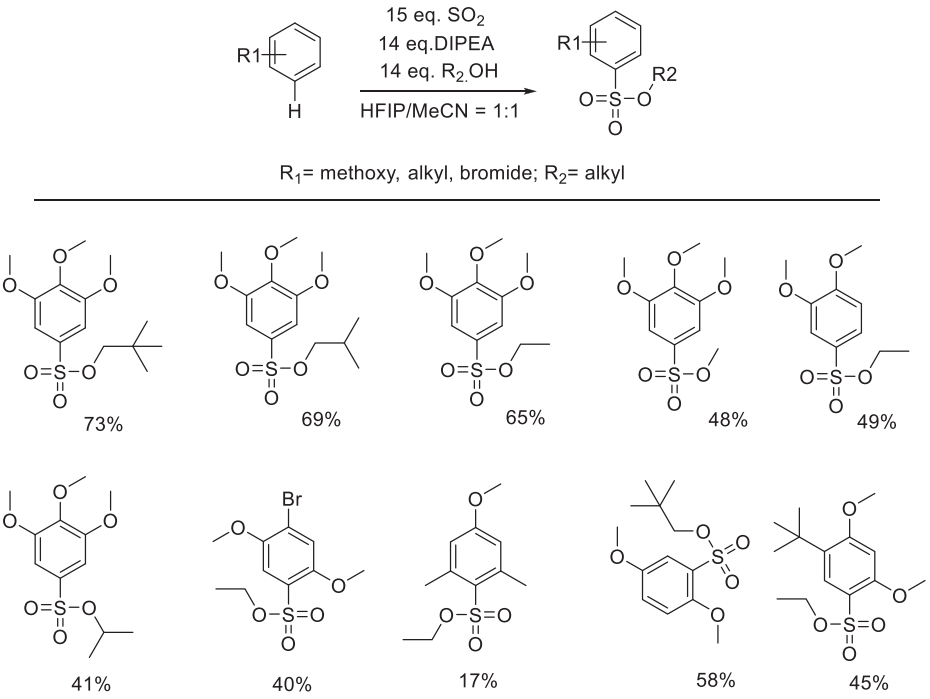


Figure 7.37: HFIP-mediated anodic oxidation of electron-rich arenes.

7.2.9 Fluorinated alcohol-assisted synthesis of biologically potent heterocycles

Heterocyclic compounds have a wide range of applications in chemical biology, drug synthesis, polymer sciences and material sciences. Most of the known methodologies for the synthesis of heterocycles are low yielding, require harsh conditions and require metallic salts as catalysts. Over the last few decades, there has been a great interest to develop new methodologies with high efficiency and environment-friendly protocols. Accordingly, there is an upsurge of reports showing the application of fluorinated solvents as efficient and green reaction media for the synthesis of heterocycles.

The benzimidazole derivatives were prepared using HFIP as a reaction media for *ortho*-esters and *o*-phenylenediamines under standard conditions. This operationally simple procedure and the use of nontoxic HFIP provided a diverse range of desired products in excellent yield in a shorter time (Figure 7.38) [41].

The 1,2-disubstituted benzimidazoles were also prepared from aldehydes and *o*-phenylenediamines. This cyclocondensation reaction was promoted by HFIP and TFE at room temperature. The fluorinated solvents were found superior over the conventional solvents in their capacity to control the reaction selectivity (Figure 7.39) [42].

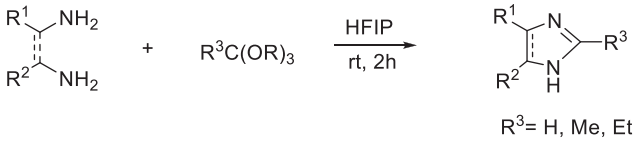


Figure 7.38: Preparation of benzimidazole derivatives using HFIP as a reaction media.

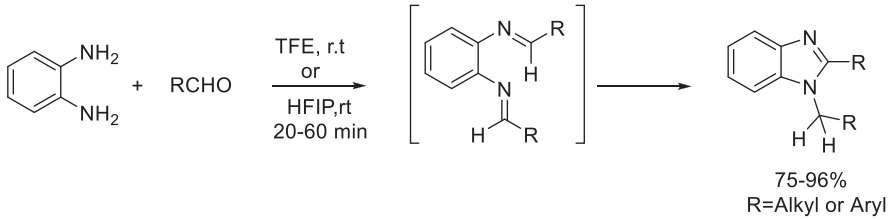
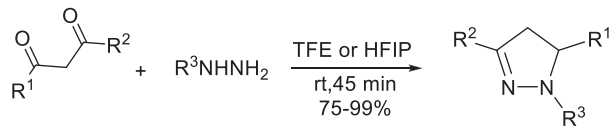


Figure 7.39: Cyclocondensation reaction in fluorinated solvents.

The hydrazine derivatives, *N,N*-dimethylformamide dimethyl acetal and β-dicarbonyls, were reacted in TFE in additive-free conditions to furnish 1,4,5-trisubsituted pyrazoles in excellent yield. The hydrogen bond donating ability of fluorinated solvents controlled the regioselectivity of the reaction (Figure 7.40) [43, 44].



R^1=2-Furyl, Ph, 4-MeO-Ph,CH_3,4-Cl-Ph,2,4-Cl_2-Ph
R^2=CF_3,CF_2CF_3,CF_2CH_3,CO_2Et
R^3=CH_3,Ph,H

Figure 7.40: Regioselective preparation of 1,4,5-trisubsituted pyrazoles in fluorous media.

Tetrahydroquinolines were prepared in excellent yields by TFE- and HFIP-promoted imino-Diels–Alder reactions. Under neutral conditions, the alkyl vinyl ethers reacted with *N*-aryl aldimines and provided a range of products without the use of Lewis acids (Figure 7.41) [45].

A catalyst-free three-component-type metathesis reaction provided excellent yields of 2,3-disubsituted aminoquinolines in HFIP as solvent. In this tandem approach, aromatic aldehydes successfully reacted with alkynes and provided aminoquinolines with complete trans-selectivity (Figure 7.42) [46].

Under mild reaction conditions, the 1,2-dicarbonyl compounds react with 1,2-diamines in fluorinated alcohols furnishing quinoxalines in good-to-excellent yield.

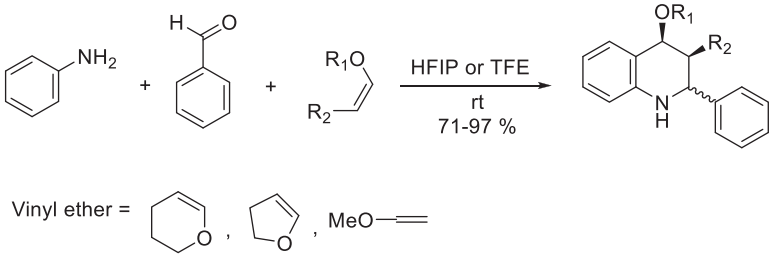
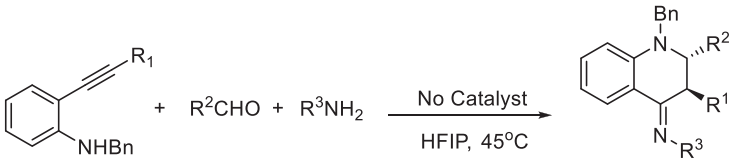


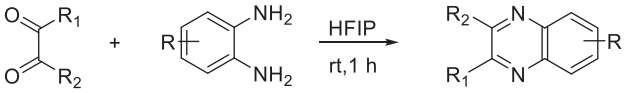
Figure 7.41: One-pot imino-Diels–Alder reactions in fluorinated media.



R_1=*n*Bu,Ph
R_2=Ph, 4-MeO-Ph, 3-MeO-Ph,2-MeO-Ph, 4-Me-Ph, 4-F-Ph,4-NO_2-Ph
R_3=Ph,4-MeO-Ph,4-F-Ph,4-Cl-Ph,4-NO_2-Ph,4-CN-Ph

Figure 7.42: Preparation of disubstituted aminoquinolines in fluorinated solvent.

This was a green and facile reaction procedure requiring no catalyst and aqueous workup (Figure 7.43) [47].



Dicarbonyls= Benzil, Furil, Isatin, Acenaphthene-1,2-quinone

Figure 7.43: Preparation of quinoxalines in fluorinated media.

The fluorinated solvent favors the reaction between ammonium acetate, malononitrite, ketones and aldehydes for the preparation of 2-amino-3-cynopyridines in a four-component one-pot reaction. The highly ionizing TFE as solvent favors the cyclocondensation reactions (Figure 7.44) [48].

The fluorinated HFIP solvent promoted intermolecular and intramolecular Friedel–Crafts alkylation of arenes with epoxides and provided 3-chromanol derivatives regioselectively. The enantiopure substrates provided highly endoselective and enantioselective product due to the use of fluorinated solvent (Figure 7.45) [13].

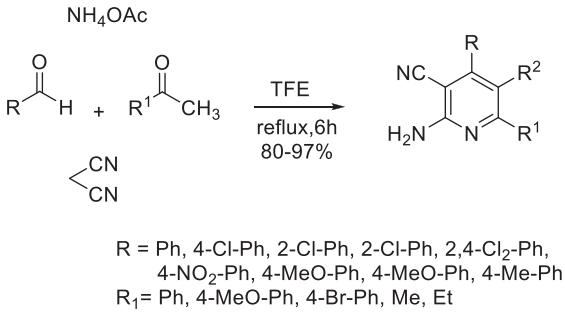


Figure 7.44: Preparation of 2-amino-3-cynopyridines in a four-component one-pot reaction.

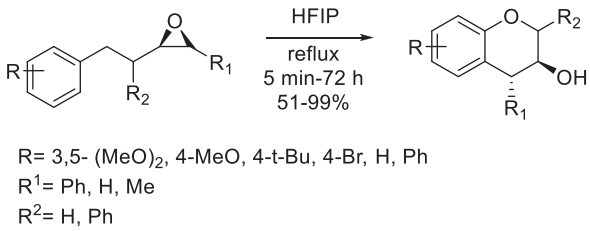


Figure 7.45: Cyclialkylation in fluorinated alcohol.

The use of TFE favors the annulation of 5, 5-dimethyl 1,3-cyclohexandione, arylglyoxals and β- ketothioamides for the regioselective synthesis of thiophene derivatives. This efficient and simple one-pot procedure provided products in moderate-to-good yields in short reaction time (Figure 7.46) [49].

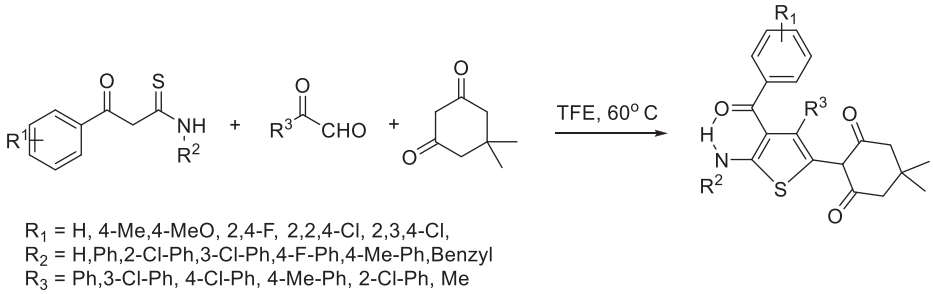


Figure 7.46: Regioselective synthesis of thiophene derivatives in fluorinated alcohol.

A range of substituted morpholine derivatives were prepared from various carboxylic acids, isocyanides and cyclic amines using TFE as reaction media. The fluorinated solvent promoted this Ugi three-component reaction under normal conditions. However, the conventional solvents were failed to favor the product formation (Figure 7.47) [50].

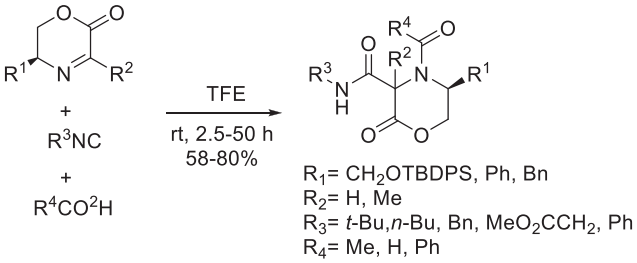


Figure 7.47: TFE-mediated synthesis of substituted morpholine derivatives.

Paal-Knorr pyrrole synthesis was adopted for the preparation of *N*-substituted aryl pyrroles using HFIP as the reaction-promoting solvent. This additive-free methodology employed poorly soluble 1,4-diketones furnishing an excellent yield of products. The reported procedure provided an opportunity to prepare highly substituted pyrroles in a simple manner (Figure 7.48) [51].

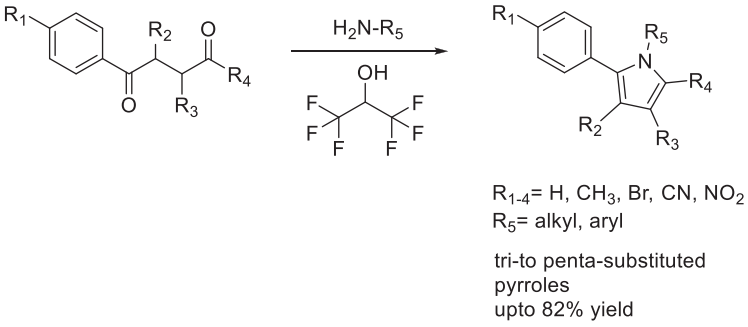


Figure 7.48: Preparation of *N*-substituted aryl pyrroles using HFIP as reaction media.

The azo-ene reactions have served as a powerful synthetic tool for the preparation of valuable allylic amine derivatives with wide applications in biochemical and polymer sciences. Generally, unsaturated hydrocarbons react with highly reactive 1,2,4-triazoline -3,5-diones (TADs) and provides products with allylic C–H amination. However, inactivated terminal alkenes provide low yields in TAD-ene reactions due to reactivity issues.

In a very recent report, the use of unconventional organic solvents has been replaced with fluorinated solvents to address aforesaid inherent limitations of TAD-ene reactions (Figure 7.49) [52]. The use of HFIP facilitated the reaction between TAD and alkene through hydrogen bonding interactions and provided allylic urazoles in an excellent yield.

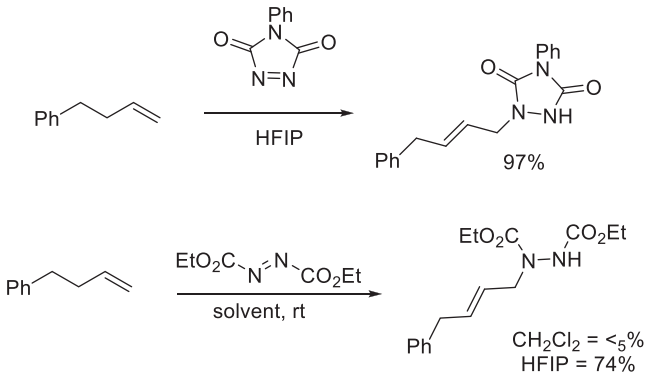


Figure 7.49: Preparation of allylic urazoles in fluorinated alcohol.

7.3 Conclusions

Fluorinated solvents have shown unique physicochemical properties and thus serve as promising alternatives to conventional organic solvents. The fluorinated alcohols exhibit high ionizing power, low nucleophilicity and high hydrogen bonding ability. Owing to these features, they modify the course of reactions, avoiding the application of metallic catalysts, chemical additives and harsh conditions. They could directly promote the chemical reactions without the involvement of any catalyst or chemical additives. Accordingly, they have established a reaction-promoting role in catalyzed and uncatalyzed organic transformations. Due to the presence of high fluorine density, they also control the stereoselectivity of reactions and enantiopure synthesis of biologically active heterocyclic compounds.

References

[1] Matsubara, H. Reactions in fluorous solvents. In: Wang Z, editor. Encyclopedia of physical organic chemistry. John Wiley & Sons, 2017, 1–60.

[2] Hameed, A, Hameed, A, Hussain, G, Qayyum, MA, Farid, MF, Farooq, T. In: Phillips AMMMF, editor. More synthetic approaches to nonaromatic nitrogen heterocycles. United Kingdom: John Wiley & Son, 2022, 649–670.

[3] Motiwala, HF, Armaly, AM, Cacioppo, JG, Coombs, TC, Koehn, KR, Norwood, IV VM. HFIP in organic synthesis. Chem Rev 2022, 122(15), 12544–12747.

[4] Pozhydaiev, V, Power, M, Gandon, V, Moran, J, Lebœuf, D. Exploiting hexafluoroisopropanol (HFIP) in Lewis and Brønsted acid-catalyzed reactions. Chem Comm 2020, 56(78), 11548–11564.

[5] Trillo, P, Baeza, A, Najera, C. Fluorinated alcohols as promoters for the metal-free direct substitution reaction of allylic alcohols with nitrogenated, silylated, and carbon nucleophiles. J Org Chem 2012, 77(17), 7344–7354.

[6] Pérez, JM, Maquilón, C, Ramón, DJ, Baeza, A. Hexafluoroisopropanol-promoted metal-free allylation of silyl enol ethers with allylic alcohols. Asian J Org Chem 2017, 6(10), 1440–1444.
[7] Možina, St, Iskra, J. Aerobic oxidation of secondary alcohols with nitric acid and iron (III) chloride as catalysts in fluorinated alcohol. J Org Chem 2019, 84(22), 14579–14586.
[8] Dantignana, V, Milan, M, Cussó, O, Company, A, Bietti, M, Costas, M. Chemoselective Aliphatic C–H bond oxidation enabled by polarity reversal. ACS Cent Sci 2017, 3(12), 1350–1358.
[9] Llopis, N, Baeza, A. Oxidation of electron-rich arenes using HFIP-UHP system. J Org Chem 2020, 85(9), 6159–6164.
[10] Zhang, Z, Chen, W, Luo, J. 1, 1, 1, 3, 3, 3-Hexafluoroisopropanol as an efficient medium for the room temperature oxidation of styrenes to benzaldehydes. Tetrahedron Lett 2020, 61(46), 152527.
[11] Tang, R-J, Milcent, T, Crousse, B. Friedel–Crafts alkylation reaction with fluorinated alcohols as hydrogen-bond donors and solvents. RSC Adv 2018, 8(19), 10314–10317.
[12] Tang, Q, Chen, X, Tiwari, B, Chi, YR. Addition of indoles to oxyallyl cations for facile access to α-indole carbonyl compounds. Org Lett 2012, 14(7), 1922–1925.
[13] Li, G-X, Qu, J. Friedel–Crafts alkylation of arenes with epoxides promoted by fluorinated alcohols or water. Chem Comm 2010, 46(15), 2653–2655.
[14] Zhang, S, Vayer, M, Noël, F, Vuković, VD, Golushko, A, Rezajooei, N. Unlocking the Friedel-Crafts arylation of primary aliphatic alcohols and epoxides driven by hexafluoroisopropanol. Chem 2021, 7(12), 3425–3441.
[15] Motiwala, HF, Vekariya, RH, Aube, J. Intramolecular Friedel–Crafts acylation reaction promoted by 1, 1, 1, 3, 3, 3-hexafluoro-2-propanol. Org Lett 2015, 17(21), 5484–5487.
[16] Vekariya, RH, Aube, J. Hexafluoro-2-propanol-promoted intermolecular Friedel–Crafts acylation reaction. Org Lett 2016, 18(15), 3534–3537.
[17] Di, Salvo, A, Spanedda, MV, Ourevitch, M, Crousse, B, Bonnet-Delpon, D. Uncatalysed domino reaction in hexafluoroisopropanol: A simple protocol for the synthesis of tetrahydroquinoline derivatives. Synthesis 2003, 2003(14), 2231–2235.
[18] Di Salvo, A, David, M, Crousse, B, Bonnet-Delpon, D. Self-promoted nucleophilic addition of hexafluoro-2-propanol to vinyl ethers. Adv Synth Catal 2006, 348(1–2), 118–124.
[19] Goulet-Hanssens, A, Eisenreich, F, Hecht, S. Enlightening materials with photoswitches. Adv Mater 2020, 32(20), 1905966–1905988.
[20] Clerc, M, Stricker, F, Ulrich, S, Sroda, M, Bruns, N, Boesel, LF. Promoting the furan ring-opening reaction to access new donor–acceptor Stenhouse adducts with hexafluoroisopropanol. Angew Chem Int Ed 2021, 60(18), 10219–10227.
[21] Saya, JM, Berabez, R, Broersen, P, Schuringa, I, Kruithof, A, Orru, RV. Hexafluoroisopropanol as the acid component in the Passerini reaction: One-pot access to β-amino alcohols. Org Lett 2018, 20(13), 3988–3991.
[22] Shida, N, Imada, Y, Nagahara, S, Okada, Y, Chiba, K. Interplay of arene radical cations with anions and fluorinated alcohols in hole catalysis. Comm Chem 2019, 2(1), 1–8.
[23] Xiao, J, Zhao, K, Loh, T-P. The acid free asymmetric intermolecular α-alkylation of aldehydes in fluorinated alcohols. Chem Comm 2012, 48(29), 3548–3550.
[24] Das, U, Crousse, B, Kesavan, V, Bonnet-Delpon, D, Bégué, J-P. Facile ring opening of oxiranes with aromatic amines in fluoro alcohols. J Org Chem 2000, 65(20), 6749–6751.
[25] Westermaier, M, Mayr, H. Regio- and stereoselective ring-opening reactions of epoxides with indoles and pyrroles in 2,2,2-trifluoroethanol. Chem Eur J 2008, 14(5), 1638–1647.
[26] Liu, J, Wang, L, Wang X, Xu, L, Hao, Z, Xiao, J. Fluorinated alcohol-mediated [4 + 3] cycloaddition reaction of indolyl alcohols with cyclopentadiene. Org Biomol Chem 2016, 14(48), 11510–11517.
[27] Bhattacharya, T, Ghosh, A, Maiti, D. Hexafluoroisopropanol: The magical solvent for Pd-catalyzed C–H activation. Chem Sci 2021, 12(11), 3857–3870.

[28] Chen, G, Zhuang, Z, Li, GC, Saint-Denis, TG, Hsiao, Y, Joe, CL. Ligand-enabled β-C–H arylation of α-amino acids without installing exogenous directing groups. Angew Chem Int Ed 2017, 56(6), 1506–1509.
[29] Zhu, C, Zhang, Y, Kan, J, Zhao, H, Su, W. Ambient-temperature ortho C–H arylation of benzoic acids with aryl iodides with ligand-supported palladium catalyst. Org Lett 2015, 17(14), 3418–3421.
[30] Zhang, C, Rao, Y. Weak coordination promoted regioselective oxidative coupling reaction for 2, 2′-difunctional biaryl synthesis in hexafluoro-2-propanol. Org Lett 2015, 17(18), 4456–4459.
[31] Xia, G, Weng, J, Liu, L, Verma, P, Li, Z, Yu, J-Q. Reversing conventional site-selectivity in C (sp3)–H bond activation. Nat Chem 2019, 11(6), 571–577.
[32] St, John-Campbell, S, White, AJ, Bull, JA. Single operation palladium catalysed C (sp^3)–H functionalisation of tertiary aldehydes: Investigations into transient imine directing groups. Chem Sci 2017, 8(7), 4840–4847.
[33] Samojłowicz, C, Bieniek, M, Zarecki, A, Kadyrov, R, Grela, K. The doping effect of fluorinated aromatic hydrocarbon solvents on the performance of common olefin metathesis catalysts: Application in the preparation of biologically active compounds. Chem Comm 2008, 47, 6282–6284.
[34] Grela, K, Samojlowicz, C. Olefin metathesis reactions of sulfur containing alkenes and dienes. ARKIVOC 2011, 2011(4), 71–81.
[35] Das, AJ, Devi, R, Das, SK. Boron trifluoride–etherate in fluorinated alcohols: A powerful promoter system for intramolecular alkyne–aldehyde metathesis of o-(3-arylpropargyloxy) benzaldehydes. Tetrahedron Lett 2018, 59(48), 4263–4266.
[36] Djurovic, A, Vayer, M, Li, Z, Guillot, R, Baltaze, J-P, Gandon, V. Synthesis of medium-sized carbocycles by gallium-catalyzed tandem carbonyl–olefin metathesis/transfer hydrogenation. Org Lett 2019, 21(19), 8132–8137.
[37] Anh, To, T, Pei, C, Koenigs, RM, Vinh, Nguyen, T. Hydrogen bonding networks enable Brønsted acid-catalyzed carbonyl-olefin metathesis**. Angew Chem Int Ed 2022, 61(13), e202117366.
[38] Zarganes-Tzitzikas, T, Patil P, Khoury, K, Herdtweck, E, Dömling, A. Concise synthesis of tetrazole–ketopiperazines by two consecutive Ugi reactions. Eur J Org Chem 2015, 2015(1), 51–55.
[39] Barreto, AdFS, Dos, VS, Andrade, CKZ. Consecutive hydrazino-Ugi-azide reactions: Synthesis of acylhydrazines bearing 1, 5-disubstituted tetrazoles. Beilstein J Org Chem 2017, 13, 2596–2602.
[40] Blum, SP, Schollmeyer, D, Turks, M, Waldvogel, SR. Metal-and reagent-free electrochemical synthesis of alkyl arylsulfonates in a multi-component reaction. Chem Eur J 2020, 26(38), 8358–8362.
[41] Khaksar, S. Fluorinated alcohols: A magic medium for the synthesis of heterocyclic compounds. J Fluor Chem 2015, 172, 51–61.
[42] Chebolu, R, Kommi, DN, Kumar, D, Bollineni, N, Chakraborti, AK. Hydrogen-bond-driven electrophilic activation for selectivity control: Scope and limitations of fluorous alcohol-promoted selective formation of 1, 2-disubstituted benzimidazoles and mechanistic insight for rationale of selectivity. J Org Chem 2012, 77(22), 10158–10167.
[43] Alinezhad, H, Tajbakhsh, M, Zare, M. Catalyst-free one-pot synthesis of 1, 4, 5-trisubstituted pyrazoles in 2, 2, 2-trifluoroethanol. J Fluor Chem 2011, 132(11), 995–1000.
[44] Fustero, S, Román, R, Sanz-Cervera, JF, Simón-Fuentes, A, Cunat, AC, Villanova, S. Improved regioselectivity in pyrazole formation through the use of fluorinated alcohols as solvents: Synthesis and biological activity of fluorinated tebufenpyrad analogs. J Org Chem 2008, 73(9), 3523–3529.
[45] Spanedda, MV, Hoang, VD, Crousse, B, Bonnet-Delpon, D, Bégué, J-P. Aza-Diels–Alder reaction in fluorinated alcohols. A one-pot synthesis of tetrahydroquinolines. Tetrahedron Lett 2003, 44(2), 217–219.
[46] Saito, A, Kasai, J, Konishi, T, Hanzawa, Y. Tandem synthesis of 2, 3-dihydro-4-iminoquinolines via three-component alkyne-imine metathesis. J Org Chem 2010, 75(20), 6980–6982.

[47] Khaksar, S, Rostamnezhad, F. A novel one-pot synthesis of quinoxaline derivatives in fluorinated alcohols. Bull Korean Chem Soc 2012, 33(8), 2581–2584.
[48] Khaksar, S, Yaghoobi, M. A concise and versatile synthesis of 2-amino-3-cyanopyridine derivatives in 2, 2, 2-trifluoroethanol. J Fluor Chem 2012, 142, 41–44.
[49] Wen, L-R, He, T, Lan, M-C, Li, M. Three-component cascade annulation of β-ketothioamides promoted by CF3CH2OH: A regioselective synthesis of tetrasubstituted thiophenes. J Org Chem 2013, 78(21), 10617–10628.
[50] Zhu, D, Chen, R, Liang, H, Li, S, Pan, L, Chen, X. An efficient procedure for the synthesis of morpholin-2-one-3-carboxamide derivatives in good diastereoselectivity by the Ugi reaction. Synlett 2010, 2010(06), 897–900.
[51] Schirmacher, RH, Rösch, D, Thomas, F. Hexafluoroisopropanol as solvent and promoter in the Paal-Knorr synthesis of N-substituted diaryl pyrroles. Tetrahedron 2021, 83, 131985.
[52] Kuroda, Y. Remarkable solvent effect of fluorinated alcohols on azo–ene reactions. Chem Pharm Bull 2022, 70(5), 359–361.

Bijeta Mitra and Pranab Ghosh*

Chapter 8
PEG-assisted organic transformation

8.1 Introduction

Nowadays, most of the organic synthesis is trying to follow the basic principle of "green chemistry" [1–3]. However, sources of most of the solvents that are used in the organic reaction are nonrenewable like petroleum, which is not congruous to environment and create a harmful effect toward our mother earth. So, for the development of eco-benign and sustainable reaction protocol, switching of volatile organic compounds as solvents and reaction media is highly essential [4]. In modern organic chemistry, solvents and reaction media with properties like nonvolatile, high boiling, harmless, inflammable, inexpensive, eco-benign and recyclable are highly appreciating to make a methodology-friendly toward mother nature [5, 6]. Taking this point in mind, there is exploration of unconventional solvents that is advanced for creature as well as environment.

Employment of unconventional [7] reaction medium in organic synthesis is obstruction for making nature greener. Further, water is the most common green solvent but main drawback of water is poor solubility of organic compounds in it. Besides, ethanol is also considered as eco-benign solvent but it has low boiling point (78 °C). Other popular greener solvent includes ionic liquids and fluorous solvents but owing to their high price, anonymous toxicity and poor biodegradability make them quite unsuitable. In the past decades, exploration of ethyl lactate and gluconic acid aqueous solution is interesting for many organic synthetic protocols.

In this chapter, we anchor on the organic transformation using nonconventional benign solvents, the polyethylene glycols (PEGs). Utilization of bio-based solvent is a contemporary paragon of green chemistry [8, 9]. Solvents originated from biomass are helpful for the recovery of expensive transition metal catalysts [10] and have vast prospective for employing in medicinal chemistry and pharmaceutical industry than conventional organic solvents [11]. PEG is a polymer of ethylene oxide, liquid or solid depending on its molecular weight. PEG is easily soluble in water, methanol, ethanol and many solvents. The structure of PEG is commonly expressed as $H–(O–CH_2–CH_2)_n–OH$. PEG has diverse array of application in industrial, commercial, biological, chemical, and medical field. It has an important application in industrial manufacturing of medicine. So, in this chapter we will briefly discuss about the reaction carried out in different types of PEG solvent.

*Corresponding author: **Pranab Ghosh**, Department of Chemistry, University of North Bengal, West Bengal, India, e-mail: pizy12@yahoo.com
Bijeta Mitra, Department of Chemistry, University of North Bengal, West Bengal, India

https://doi.org/10.1515/9783110788129-008

8.2 Organic synthesis in PEG-400

Among variation of PEG, PEG-400 is the most popular and frequently used variant. In this section we have discussed about the reaction reported in literature with PEG-400.

8.2.1 Metal-assisted organic synthesis in PEG-400

In 2022, Costa et al. [12] demonstrated a stereoselective, base-free Heck coupling reaction between 1,4-naphthoquinone (**1**) and 1*H*-1,2,3-triazole derivatives (**2**) utilizing $Pd(OAc)_2$ as a catalyst in the presence of green solvent PEG-400 at 90 °C only for 20 min in good-to-excellent yields (Figure 8.1). This study shows that 1,4-naphthoquinone is enough for this reaction without the use of an additional base to produce the naphthoquinone-triazole conjugates (**3**). This is the first example of a Heck coupling of these two skeletons without using a base as an additive. The reaction mechanism discussed in that paper was based on density functional theory (DFT) CAM−B3LYP calculations. This newly developed methodology opens a new technique to synthesize potential bioactive compounds.

A magnetically recoverable copper catalyst was successfully fabricated through the immobilization of $Cu(NO_3)_2$ on the surface of silica-coated magnetic Fe_3O_4 nanoparticles (Fe_3O_4@SiO_2) functionalized with *S*-benzylisothiourea ligand by Riadi et al. [13] in 2022 (Figure 8.2). The nanocomposite was fully analyzed by FTIR spectroscopy, SEM, EDX, TGA, XRD, VSM, AAS and ICP-OES techniques. The designed nanocomposite exhibited its catalytic activity for the preparation of biorelevant quinazoline derivatives (**6**) by the reaction of functionalized benzamide (**4**) and 2-bromobenzylamine (**5**) using K_2CO_3 as a base in green solvent PEG-400 for 12 h in open air. This method has several advantages

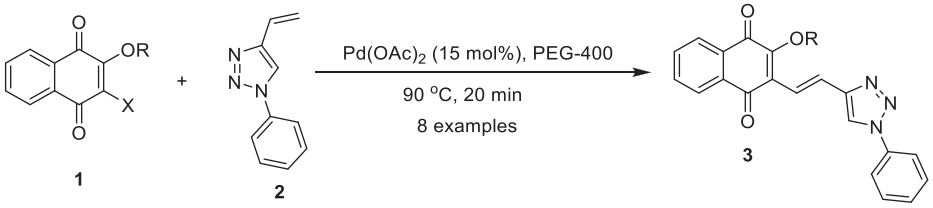


Figure 8.1: A base-free palladium-catalyzed Heck coupling.

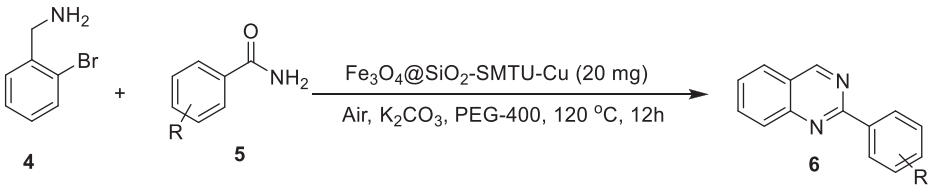


Figure 8.2: Fe_3O_4@SiO_2-SMTU-Cu catalyzed synthesis of quinazolines.

such as easy separation of the catalyst by external magnetic field, good to excellent yields and use of nontoxic metal catalyst.

Pawar et al. [14] reported a microwave-assisted one-pot three-component reaction for the synthesis of fluorescent active quinozolino[4,3-*b*]quinazolin-8-ones (**9**) via C–N bond formation using aldehyde or alcohol or methyl arene (**7**), 2-substituted quinazolin-4(3*H*)-one (**8**) and $TMSN_3$ as an nitrogen source using CuI salt in PEG-400 (Figure 8.3). The main advantages of this protocol are absence of base and ligand, microwave irradiation and environmentally benign solvent PEG-400. DFT and ESI/MS studies were carried out to justify the proposed mechanism.

Nandwana et al. [15] in 2021 developed a ligand-free copper (I) catalyzed one-pot three-component reaction for the synthesis of imidazo[1,2-*c*]quinazolines (**12**) from 2-(2-bromophenyl)-1*H*-imidazoles (**10**), benzyl alcohol or benzylamine (**11**) and sodium azide as nitrogen source in green solvent PEG-400 with TEMPO as a radical initiator in moderate-to-good yields with an assortment of functional groups (Figure 8.4). The reaction mechanism involves copper-catalyzed sequential azidation of 2-(2-bromophenyl)-1*H*-imidazoles through S_NAr reaction and reductive amination followed by oxidative condensation with benzyl alcohols or benzylamines.

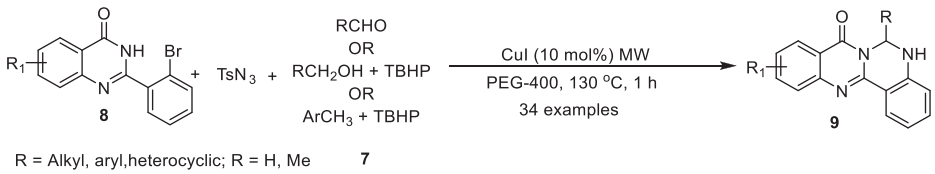


Figure 8.3: CuI-catalyzed synthesis of quinazolino[4,3-*b*]quinazolin-8-ones.

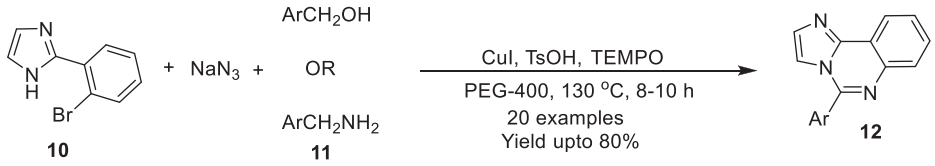


Figure 8.4: Copper-catalyzed synthesis of imidazo[1,2-*c*]quinazolines.

A vigorous Co(III)-assisted oxidative annulations of aromatic aldehydes (**13**) with internal alkynes (**14**) for the generation of derivative (**15**) was described by Tao et al. [16] (Figure 8.5). The formation of diverse array of isocoumarins (**15**) derivative was accomplished by oxidation, C–H functionalization and cascades annulation using harmless solvent PEG-400. This is the first reported Co(III)/CuO/PEG-400 system with excellent recyclability for annulation of internal alkynes with aromatic aldehydes embracing C–H functionalization with tremendous selectivity.

Deshmukh et al. [17] developed an external oxidant and additive free protocol for the synthesis of isoquinolines (**17**) through annulations of *N*-Cbz hydrazone (**14**) with symmetrical and unsymmetrical substituted internal alkynes (**16**) through C–H/N–N activation using ruthenium catalyst under microwave in PEG-400 with lower catalyst loading than previously reported protocol (Figure 8.6). Furthermore, *N*-Cbz hydrazone has been implemented as a rarely explored directing group and higher functional group tolerance and wide substrate are main superiority of this protocol.

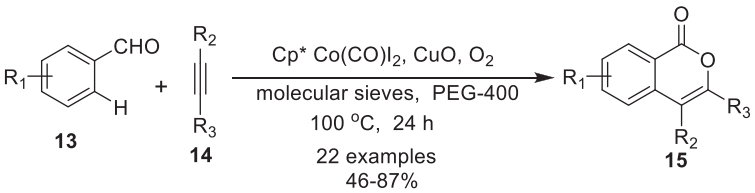


Figure 8.5: Cobalt (III) catalyzed oxidative annulation.

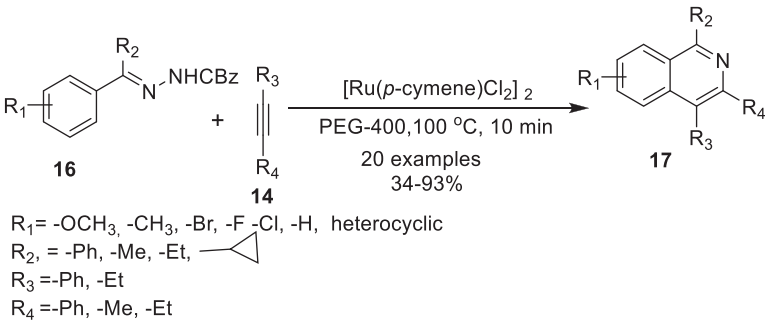
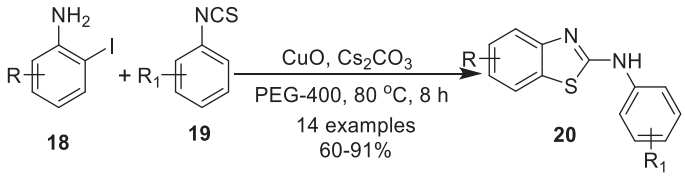


Figure 8.6: Ruthenium catalyzed annulation of *N*-Cbz hydrazones via C–H/N–N bond activation for the synthesis of isoquinolines.

Gaddam et al. [18] reported a ligand-free superficial method for the synthesis of *N*-substituted-2-aminobenzothiazoles (**20**) via a cross-coupling reaction of 2-iodo anilines (**18**) with isothiocyanates (**19**) utilizing nano copper (II) oxide as a recyclable catalyst and Cs_2CO_3 as a base in PEG-400, as a bio-degradable, affordable and safe reaction medium (Figure 8.7). The present tandem protocol emphasizes environmental acceptability to access an ample range of *N*-substituted-2-aminobenzothiazoles in good amount.

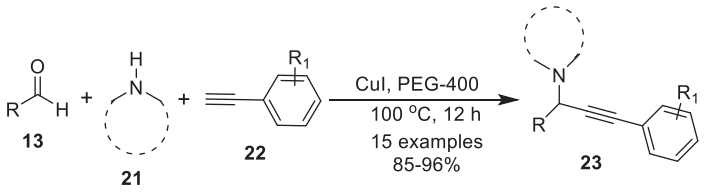
A^3-coupling reaction of amine (**21**), aldehyde (**13**) and alkyne (**22**) via C–H activation with utilizing CuI as catalyst in PEG-400 (Figure 8.8) provide a broad range of propargylamines (**23**) with moderate-to-good yield as demonstrated by Zhang et al. [19]. Additionally, the catalyst system was recovered and reused several times without

evident loss in activity. CuI-PEG-400 is the best couple for this reaction in terms of yield and feasibility of the reaction.



R= -H, -F, $-CF_3$, $-CH_3$
R_1= -H, -Br, -Cl, $-OCH_3$, $-NO_2$

Figure 8.7: Synthesis of *N*-substituted-2-aminobenzothiazoles in PEG-400.



R= aryl, heterocyclic, aliphatic
R_1= -H, $-OCH_3$,$-CH_3$

Figure 8.8: Copper catalyzed A^3-coupling reaction for the synthesis of propargylamines.

Liang et al. [20] designed an direct oxidative amidation reaction for one-pot synthesis of amide derivatives (**25**) by the reaction of aldehydes (**13**) with amines (**24**) using NaOCl/Bu_4NHSO_4 as an oxidant system in PEG-400 medium (Figure 8.9). They have demonstrated a mechanism for this protocol. Initially, the imine intermediates were produced through condensation of aldehydes and amines and then imine was oxidized to provide oxaziridine intermediates by the action of oxidant followed by tautomerization of oxaziridine intermediate finish up to the final products.

Kidwai et al. [21] reported a one-pot, three-component Mannich reaction for the formation of functionalized β-amino carbonyl compounds (**28**) through the reaction of functionalized aromatic aldehydes, (**13**) acetophenone (**26**) and functionalized aromatic amines (**27**) in the presence of ceric ammonium nitrate as a catalyst and PEG-400 as a recyclable solvent (Figure 8.10). The structures of all the synthesized products were recognized on the basis of their IR, ^{1}H NMR and GC/MS mass spectral data.

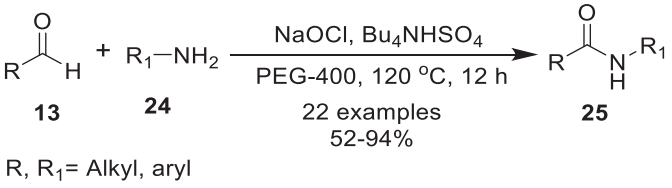


Figure 8.9: PEG-400-assisted synthesis of amides by oxidative amidation.

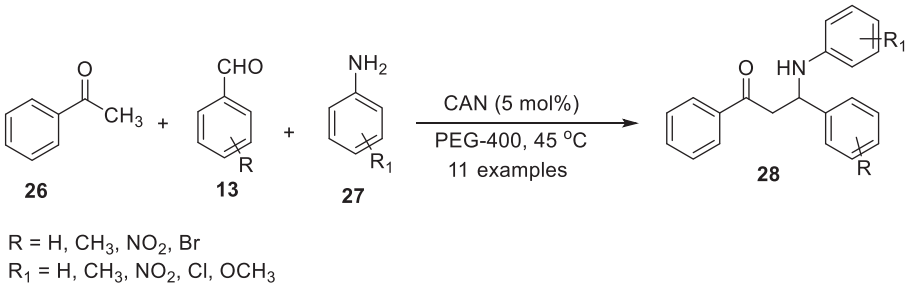


Figure 8.10: CAN-catalyzed Mannich reaction in PEG-400.

8.2.2 Metal-free organic synthesis in PEG-400

Batalin et al. [22] designed a reaction methodology for the preparation of fluorescent active-substituted 2-(ortho-hydroxyaryl)cyclopenta[*b*]pyridines (**31**) by Krönke-type reaction through one-pot pseudo five-component reaction of cyclopentanone (**30**), two molecules of aromatic aldehyde (**13**), Kröhnke salt of ortho-hydroxy-substituted aromatic ketone (**29**) and ammonium acetate in PEG-400 in the absence of any class of additional catalyst (Figure 8.11).

Sujatha et al. [23] in 2020 depicted a reaction methodology for the preparation of (*E*)-ethyl2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene) acetates (**36**) through one-pot multi-component reaction between anilines (**27**), ammonium thiocyanate (**34**), 3-chloropentane-2,4-dione (**32**), dialkylacetylene dicarboxylate (**35**) and thiosemicarbazide (**33**) using PEG-400 as green and recyclable solvent with high yield (Figure 8.12). This is a domino-type reaction with several advantages such as meta-free, shorter reaction time, avoidance of hazardous reaction media and recyclability of solvent.

Patil et al. [24] have designed a schematic protocol for the synthesis of pyrrolo[1,2-*a*]quinoxalines (**38**) by the reaction of benzylamine derivatives (**11**) and 1-(2-aminoaryl) pyrrole (**37**) (Figure 8.13). This methodology entails transformation of benzylamine derivatives into aldehydes derivative through oxidation followed by condensation with 1-(2-aminoaryl)pyrrole with $K_2S_2O_8$ as an oxidant in PEG-400. The transition metal as well

as ligand-free synthesis and broad substrate scope make this methodology environmentally and economically viable. All the synthesized compounds were characterized by NMR technique and recyclability of solvent was also examined.

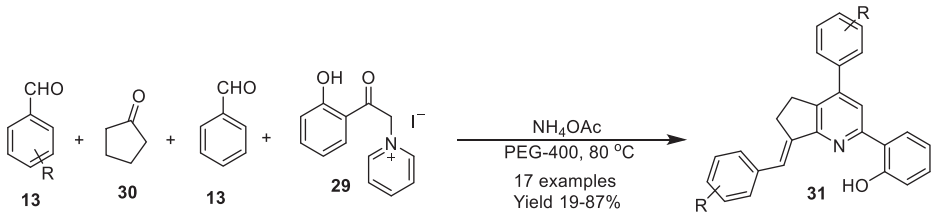


Figure 8.11: PEG-400-mediated synthesis of substituted 2-(*o*-hydroxyaryl) cyclopenta[*b*] pyridines.

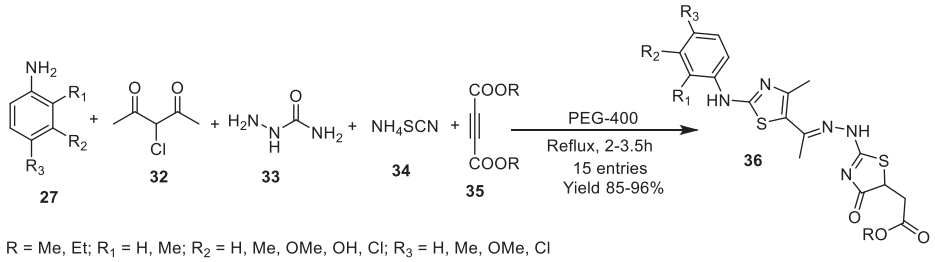


Figure 8.12: PEG-400 promoted one-pot five-component synthesis of (*E*)-ethyl-2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates.

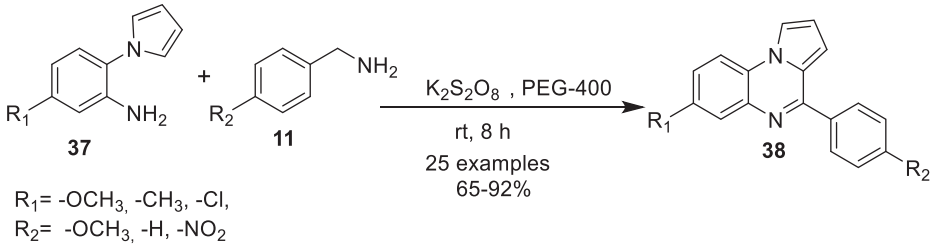
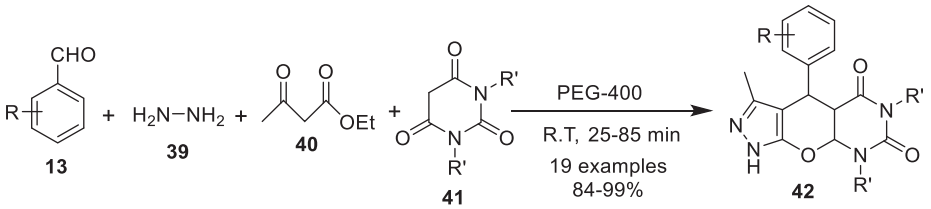


Figure 8.13: Synthesis of pyrrolo [1,2-*a*] quinoxalines in PEG-400.

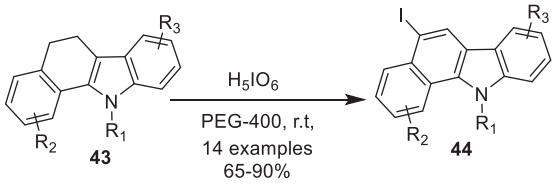
Kardooni and Kiasat [25] described a simplistic approach for the preparation of pyrazolopyrano pyrimidines derivative (**42**) through one-pot multi-component reaction of aromatic aldehydes (**13**), hydrazine hydrate (**39**), ethyl acetoacetate (**40**) and barbituric acid (**41**) in greener solvent PEG-400 in the absence of supplementary catalyst (Figure 8.14). Modest reaction conditions, good yields and biodegradable reaction medium make this innovative route attractive to current methodologies. All these synthesized compounds were characterized by IR and NMR techniques.

One-pot direct iodination and dehydrogenation of dihydrobenzo[*a*]carbazoles (**43**) for conversion into respective iodized product (**44**) using periodic acid in PEG-400 with high regioselectivity in the absence of ant metal was first designed by Ghom et al. [26] (Figure 8.15). A plausible mechanism was suggested in this work. The dihydrobenzo[*a*] carbazole was prone to reduce the oxidation state of periodic acid and converted to iodic acid through the dehydrogenation route.



R= -OCH_3, -CH_3, -Br, -Cl, -H, -F, -NMe_2 -NO_2
R'=-H, -CH_3

Figure 8.14: PEG-400-mediated synthesis of pyrazolopyranopyrimidines.



R_1= -H, -Bn, -Bu, -Me, -Et, -Allyl
R_2=-H, -OMe
R_3=-H, -Cl, -F, -CN,-Cl, -Br, COOMe

Figure 8.15: A metal-free one-pot direct iodination using periodic acid in PEG-400.

Kumar et al. [27] developed a synthetic protocol for designing diaryl selenium compounds (**46**) from phenyl boronic acid (**45**) as precursor in PEG-400. After going through literature, it has been found that the use of selenium dioxide as selenium resource for the synthesis of diaryl selenides was first established in this work. This novel source of selenium, SeO_2, gives an advanced cheaper synthetic route (Figure 8.16).

In 2016, Mohebat et al. [28] described *p*-toluenesulfonic acid-assisted synthesis of 11*H*-benzo[*a*]benzo[6,7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-dione derivatives (**49**) through one-pot four-component condensation of *o*-phenylenediamine, (**47**) 2-hydroxynaphthalene-1,4-dione (**48**) and aromatic aldehydes (**13**) using PEG-400 (Figure 8.17). This protocol designed biorelavant heterocycles with the formation of C–C, C=C, C–N, C=N and C–O bonds in a single operation. Furthermore, this methodology produces bioactive molecules

that exhibit interesting pharmacology activities and may act as potential drug candidates since both phenazine and chromene motifs have enormous range of biological activities.

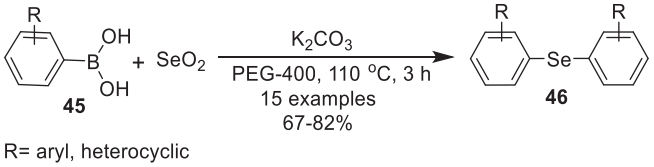


Figure 8.16: PEG-400-assisted metal-free synthesis of diaryl selenides.

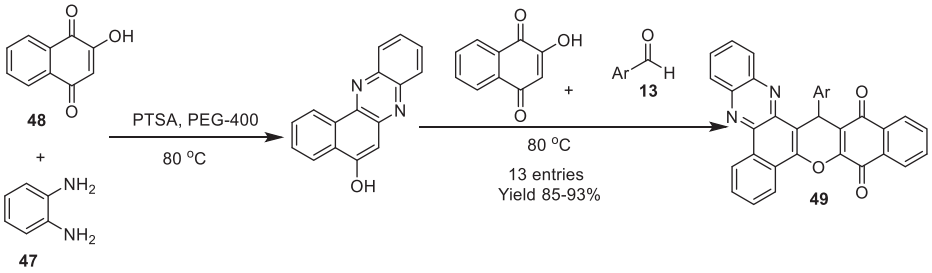


Figure 8.17: PTSA-assisted one-pot four-component domino reactions for the synthesis of functionalized (11*H*)benzo[*a*]benzo[6, 7]chromeno[2,3-*c*]phenazine-11,16(17*H*)-diones.

A novel and robust one-pot multi-component procedure for the synthesis of diverse array of 2-aminoselenopyridine derivatives (**52**) from three reactants including benzeneselenol (**51**), aldehydes (**13**) and malononitrile (**50**) in PEG-400 using ultrasonic radiation was described by Khan et al. [29] (Figure 8.18). In this process, the total four new bonds were formed. No column chromatography was required for the purification of the isolated products and the structure of the products was characterized by XRD, IR, NMR and elemental analysis.

Bi et al. [30] established a reaction methodology for the construction of diverse array of α-mono-fluorinated acetoacetamides (**54**) through selective α-electrophilic mono-fluorination from acetoacetamides (**53**) under modest reaction condition utilizing industrialized selectfluor as the F^+ resource in PEG-400 (Figure 8.19). This protocol circumvents any class of base or metal catalyst. The structure of all the synthesized compounds was signified by NMR and elemental analysis.

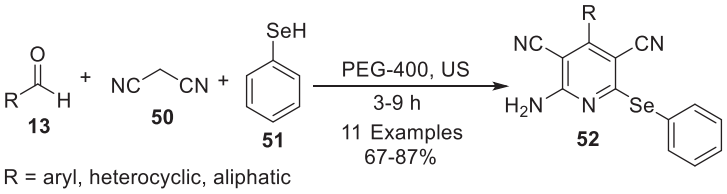


Figure 8.18: PEG-400-mediated synthesis of selenopyridines.

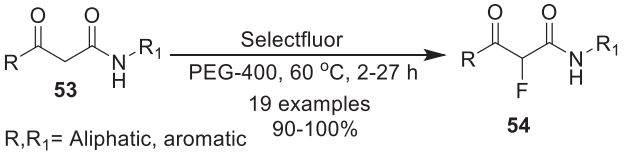


Figure 8.19: Mono fluorination in PEG-400.

8.3 Organic transformation in other PEG variants

In the previous section, we have discussed about the most popular and useful variant of PEG, that is, PEG-400. But there are many other variants of PEG like PEG-200, PEG-300, PEG-600, PEG-3400, PEG-6000 and PEG-8000. In this section, we will discuss about the other variant of PEG.

In 2022, Raya et al. [31] prepared a new and greener zinc catalyst which describes through immobilization of zinc (II) complex on the surface of magnetic nanoparticles modified with phenanthroline (MNPs-Phen-Zn(II)). The structure of this nanomaterial was characterized by FT-IR spectroscopy, SEM, TEM, EDX, XRD, VSM and ICP-OES. The catalytic activity of this nanomaterial was applied for the synthesis of disubstituted alkynes (**56**) via C(sp^2)–C(sp) cross-coupling reactions of alkynes (**22**) with aryl iodides (**55**) with K_2CO_3 as base in recyclable solvent PEG at 120 °C for 12 h (Figure 8.20). It is the first reported Sonogashira-type cross-coupling reaction in the absence of Pd and Cu sources and utilization of zinc nanomagnetic catalyst was found.

Again in 2022, Sarraf et al. [32] introduced a reusable zinc catalyst (Fe_3O_4@SiO_2-imine/thio-Zn$(OAc)_2$) constructed by immobilizing Zn(II) complex on the surface of magnetic nanoparticles functionalized with imine/thio group. The structure of the newly designed nanomaterial was analyzed by FT-IR, SEM, TEM, EDX, XRD, VSM, AAS and ICP-OES. This Fe_3O_4@SiO_2-imine/thio-Zn$(OAc)_2$ nonmaterial is nicely performed by the catalytic role required for the synthesis of diverse array of nitriles (**58**) via cyanation of aryl iodides (**55**) in PEG at 120 °C for 12 h (Figure 8.21) using formamide. This nanocatalyst can be simply recovered from the reaction mixture by an external magnet and reused seven cycles without considerable loss in catalytic activity.

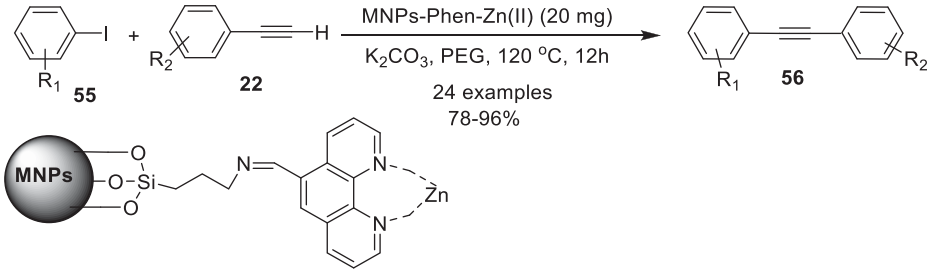


Figure 8.20: MNPs-Phen-zinc (II)-assisted Sonoghasira cross-coupling reaction of aryl iodides with terminal aromatic alkynes.

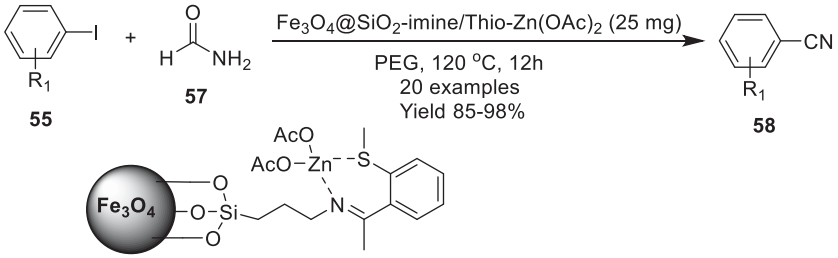


Figure 8.21: Fe_3O_4@SiO_2-imine/thio-Zn$(OAc)_2$-mediated synthesis of nitriles via cyanation of aryl iodides.

Moghaddam et al. [33] in 2022 designed an one-pot four-component protocol for the synthesis of rhodanine-oxindole (**62**) derivatives by the reaction between primary amines, (**24**) ethyl chloroacetate, (**60**) carbon disulfide (**59**) and cyano-substituted alkenyl oxindoles (**61**) in polyethenelyne glycol as green solvent at room temperature using KOH as a base in high yield (Figure 8.22).

Akbarzadeh et al. [34] described another greener protocol for the preparation of broadly functionalized 2-aminothiophene derivatives (**65**) through one-pot three-component reaction of enolizable carbonyl compounds (**63**), malononitrile or ethyl cyanoacetate (**64**) and elemental sulfur in PEG-600, without any additional basic catalyst under ultrasonic irradiation with recyclability of the solvent at least five times without considerable loss of its action (Figure 8.23). The intrinsic worth of this protocol is dearth of any basic catalyst and employment of molecular sulfur as a resource of sulfur of thiophene.

A simple microwave-assisted copper catalyzed reaction protocol for *N*-arylation of benzimidazole and indole (**66**) with iodobenzene (**55**) to produce *N*-arylated product (**67**) in the presence of cesium carbonate as a base in PEG-3400 with no complementary ligands at 150 °C was depicted by Colacino et al. [35] (Figure 8.24). *N*-arylated product was separated from reaction mixture by simple filtration and catalyst was characterized by TEM analysis and it can be easily collected after evaporation and recovery of the catalytic system as a precipitate making this protocol environmentally benign.

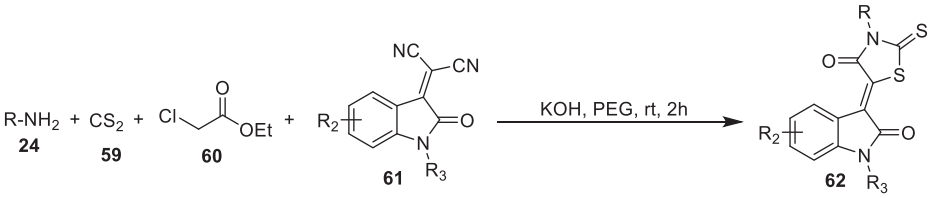


Figure 8.22: One-pot four-component synthesis of (*Z*)-isomer of rhodanine-oxindole derivatives in PEG.

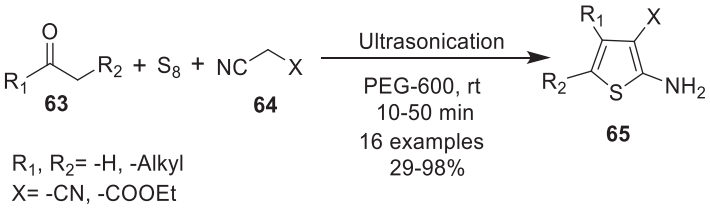


Figure 8.23: PEG-600-mediated synthesis of 2-aminothiophene derivatives.

Declerck et al. [36] demonstrated Heck arylation for the synthesis of various substituted *tert*-butyl cinnamates (**70**) using copper salt as a catalyst, potassium carbonate as a base in greener solvent PEG-3400 under microwave at 150 °C (Figure 8.25). Copper iodide provides the best outcome in the absence of any phosphine ligand. Time required for this reaction to occur is shorter than the previously reported reaction methodology. Recovery of the copper catalyst is facilitated by precipitation and filtration of the solvent.

Winter et al. [37] synthesized densely functionalized 4′-substituted 2, 2′:6′, 2′ terpyridines (**72**) through one-pot pseudo three-component protocol using substituted aldehyde (**13**) and ketone derivative (**71**) sodium hydroxide, PEG-300 and aqueous ammonia as solvents (Figure 8.26). Terpyridine structure was recognized by XRD. The crystallographic data reveal the influence of the 4′-aryl substituent on the molecular structure and *p*-stacking behavior of the respective terpyridines.

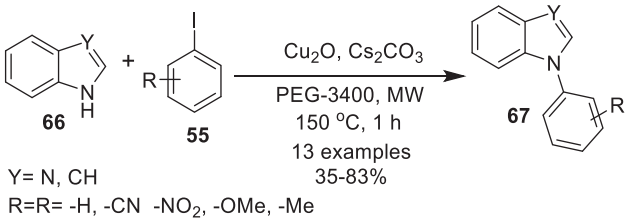
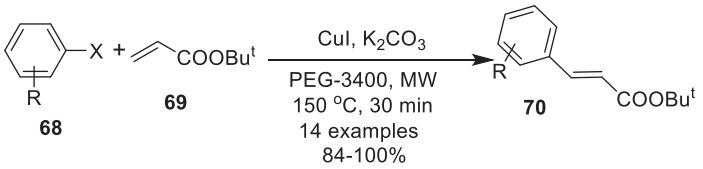
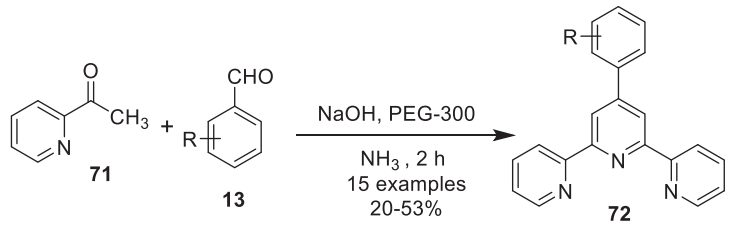


Figure 8.24: Phosphine-free Ullmann arylation in PEG-3400.



R= -H, -F, -Br, -Cl, -CHO,
-CN, -NO_2, -OMe
X= -Cl, -Br, -I

Figure 8.25: Copper-assisted Heck reaction in PEG-3400.



R= -CH_3, -H, -OCH_3 -Cl, -OH, -Br, -SMe, -COOMe

Figure 8.26: Synthesis of terpyridines in PEG-300.

8.4 Conclusions

In conclusion, owing to making our mother earth safe from hazardous material, it is necessary to discover a perfect solvent as a reaction medium. This chapter will help to gain knowledge about the goodness of bio-based greener solvent PEG. It performs as an eco-benign reaction medium and in some cases act as catalyst due to its hydrogen-bonding capacity and also as additive in organic synthesis with the endeavor to diminish the environment hazard making the mother earth pollution-free.

References

[1] Bryan, MC, Dillon, B, Hamann, LG, Hughes, GL, Kopach, ME, Peterson, EA, Pourashraf, M, Raheem, I, Richardson, P, Richter, D, Sneddon, HF. Sustainable practices in medicinal chemistry: Current state and future directions. J Med Chem 2013, 56, 6007–6021.

[2] Dunn, P. The importance of green chemistry in process research and development. Chem Soc Rev 2012, 41, 1452–1461.

[3] Adam, D. Clean and green . . . but are they mean?. Nature 2000, 407, 938–940.

[4] Andrade, CKZ, Alves, LM. Environmentally benign solvents in organic synthesis: Current topics. Curr Org Chem 2005, 9, 195–218.

[5] Capello, C, Fischer, U, Hungerbuhler, K. What is a green solvent? A comprehensive frame work for the environmental assessment of solvents. Green Chem 2007, 9, 927–934.
[6] Alfonsi, K, Colberg, J, Dunn, PJ, Fevig, T, Jennings, S, Johnson, TA, Kleine, HP, Knight, C, Nagy, MA, Perry, DA, Stefaniak, M. Green chemistry tools to influence a medicinal chemistry and research chemistry based organization. Green Chem 2008, 10, 31–36.
[7] Henderson, RK, Jimenez-Gonzalez, C, Constable, DJC, Alston, SR, Inglis, GGA, Fisher, G, Sherwood, J, Binks, SP, Curzons, AD. Expanding GSK's solvent selection guide- embedding sustainability into solvent selection starting at medicinal chemistry. Green Chem 2011, 13, 854–862.
[8] Sheldon, RA. Green and sustainable manufacture of chemicals from biomass: State of the art. Green Chem 2014, 16, 950–963.
[9] Corma, A, Iborra, S, Velty, A. Chemical routes for the transformation of biomass into chemicals. Chem Rev 2007, 107, 2411–2502.
[10] Yan, N, Xiao, C, Kou, Y. Transition metal nanoparticle catalysis in green solvents. Coord Chem Rev 2010, 254, 1179–1218.
[11] Gu, Y, Jérôme, F. Bio-based solvents: An emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. Chem Soc Rev 2013, 42, 9550–9570.
[12] Costa, DCS, Forezi, LSM, Lessa, MD, Delarmelina, M, Matuck, BVA, Freitas, MCR, Ferreira, VF, de C. Resende, JAL, Carneiro, JWM, Silva, FC. A stereoselective, base-free, palladium-catalyzed heck coupling between 3-halo-1,4-naphthoquinones and vinyl-1*H*-1,2,3-triazoles. Chemistry Select 2022, 7, e202201334.
[13] Riadi, Y, Kadhim, MM, Shoja, SJ, Ali, MH, Mustafa, YF, Sajjadi, A. Copper (II) complex supported on the surface of magnetic nanoparticles modified with *S*-benzylisothiourea (Fe_3O_4@SiO_2-SMTU-Cu): A new and efficient nanomagnetic catalyst for the synthesis of quinazolines and amides. Synth Commun 2022, 52, 875–887.
[14] Pawar, G, Ghouse, SM, Joshi, SV, Rana, P, Kar, S, Sarma, PM, Dannarm, SR, Sonti, R, Nanduri, S. Cu(I)-catalyzed microwave-assisted multicomponent reaction towards synthesis of diverse fluorescent quinazolino[4,3-*b*]quinazolin-8-ones and their photophysical study. Chemistry Select 2022, 7, e202200500.
[15] Nandwana, NK, Bhawani, Shinde, VN, Kumar, A. Copper-Catalyzed One-pot, three-component synthesis of imidazo[1,2-*c*]quinazolines and benzimidazo[1,2-*c*]quinazolines. Chemistry Select 2021, 6, 12205–12208.
[16] Tao, L-M, Li, C-H, Chen, J, Liu, H. Cobalt(III)-catalyzed oxidative annulation of benzaldehydes with internal alkynes via c-h functionalization in poly(ethylene glycol). J Org Chem 2019, 84, 6807–6812.
[17] Deshmukh, DS, Bhanage, BM. Ruthenium-catalyzed annulation of *n*-cbz hydrazones via c–h/n–n bond activation for the rapid synthesis of isoquinolines. Synthesis 2019, 51, 2506–2514.
[18] Gaddam, S, Kasireddy, HR, Konkala, K, Katla, R, Durga, NYV. Synthesis of N-substituted-2-aminobenzothiazoles using nano copper oxide as a recyclable catalyst under ligand-free conditions, in reusable PEG-400 medium. Chin Chem Lett 2014, 25, 732–736.
[19] Zhang, Q, Chen, J-X, Gao, W-X, Ding, J-C, Wu, H-Y. Copper-catalyzed one-pot synthesis of propargylamines via C–H activation in PEG. Appl Organometal Chem 2011, 24, 809–812.
[20] Liang, J, Lv, J, ZShang, Z. Metal-free synthesis of amides by oxidative amidation of aldehydes with amines in PEG/oxidant system. Tetrahedron 2011, 67, 8532–8535.
[21] Kidwai, M, Bhatnagar, D, Mishra, NK, Bansal, V. CAN catalyzed synthesis of β-amino carbonyl compounds via Mannich reaction in PEG. Cat Commun 2008, 9, 2547–2549.
[22] Batalin, SD, Golikova, MA, Khrustaleva, AA, Bakal, AA, Ponomareva, TS, Goryacheva, IY. Substituted 2-(ortho-hydroxyaryl)cyclopenta[*b*]pyridines: Synthesis and fluorescent properties under neutral, acidic medium and solid state. Chemistry Select 2021, 6, 11375–11380.

[23] Sujatha, K, Vedula, RR. Polyethylene glycol (PEG-400) promoted one-pot, five-component synthesis of (*E*)-ethyl2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5 (4*H*)-ylidene)acetates. Mol Divers 2020, 24, 413–421.

[24] Patil, BN, Lade, JJ, Pardeshi, SD, Patil, P, Chaskar, AC. Polyethylene-glycol-(peg-400) mediated environmentally benign protocol for the synthesis of pyrrolo[1,2-*a*] quinoxalines from benzyl amines at room temperature. Chemistry Select 2019, 4, 11362–11366.

[25] Kardooni, R, Kiasat, AR. A green, catalyst-free synthesis of pyrazolopyrano pyrimidines in polyethylene glycol as a biodegradable medium at ambient temperature. Mol Divers 2019, 23, 639–649.

[26] Ghom, MH, Naykode, MS, Humne, VT, Lokhande, PD. A one-pot direct regioselective iodination of Fischer-Borsche product using periodic acid in PEG-400. Tetrahedron Lett 2019, 60, 1029–1031.

[27] Kumar, RU, Reddy, KHV, Satish, G, Swapna, GK, Nageswar, YVD. Metal free synthesis of diaryl selenides using SeO_2 as a selenium source. Tetrahedron Lett 2016, 57, 4138–4141.

[28] Mohebat, R, Abadi, AYE, Maghsoodlou, M–T, Mohammadi, M. PTSA-catalyzed four-component domino reactions for the one-pot synthesis of functionalized 11*H*benzo[*a*]benzo[6,7]chromeno[2,3-*c*] phenazine-11,16(17*H*)-diones in PEG. Res Chem Intermed 2016, 42, 5915–5926.

[29] Khan, MN, Karamthulla, S, Choudhury, LH, Faizi, MSH. Ultrasound assisted multicomponent reactions: A green method for the synthesis of highly functionalized selenopyridines using reusable polyethylene glycol as reaction medium. RSC Adv 2015, 5, 22168–22172.

[30] Bi, J, Zhang, Z, Liu, Q, Zhang, G. Catalyst-free and highly selective electrophilic mono-fluorination of acetoacetamides: Facile and efficient preparation of 2-fluoroacetoacetamides in PEG-400. Green Chem 2012, 14, 1159–1162.

[31] Raya, I, Jasim, SA, Abdulkadhim, AH, Abbud, LH, Sharma, H. Zinc (II) complex immobilized on the surface of magnetic nanoparticles modified with phenanthroline: A novel and efficient nanomagnetic reusable catalyst for cross-coupling reaction of aryl iodides with terminal aromatic alkynes. Synth Commun 2022, 52, 602–1613.

[32] Sarraf, AAMA, Alsultany, FH, Mahmoud, ZH, Shafik, SS, Al, ZI, Sajjadi, A. Magnetic nanoparticles supported zinc (II) complex (Fe_3O_4@SiO_2-Imine/Thio-Zn$(OAc)_2$): A green and efficient magnetically reusable zinc nanocatalyst for synthesis of nitriles via cyanation of aryl iodides. Synth Commun 2022, 52, 1245–1253.

[33] Moghaddam, FM, Aghamiri, B, Jalalinik, M. A facile one-pot, four-component synthesis of (*Z*)-isomer of rhodanine-oxindole derivatives under environmentally benevolent conditions. Synth Commun 2022, 52, 175–184.

[34] Akbarzadeh, A, Dekamin, MG. A facile and environmentally benign polyethylene glycol 600-mediated method for the synthesis of densely functionalized 2-aminothiophene derivatives under ultrasonication. Green Chem Lett Rev 2017, 10, 315–323.

[35] Colacino, E, Villebrun, L, Martinez, J, Lamaty, F. PEG3400-Cu_2O-Cs_2CO_3: An efficient and recyclable microwave-enhanced catalytic system for ligand-free Ullmann arylation of indole and benzimidazole. Tetrahedron 2010, 66, 3730–3735.

[36] Declerck, V, Martinez, J, Lamaty, F. Microwave-assisted copper-catalyzed heck reaction in peg solvent. Synlett 2006, 18, 3029–3032.

[37] Winter, A, van den Berg, AMJ, Hoogenboom, R, Kickelbick, G, Schubert, US. A green and straightforward synthesis of 4′-substituted terpyridiness. Synthesis 2006, 17, 2873–2878.

Gyan Chandra Pariyar, Bijeta Mitra and Pranab Ghosh*

Chapter 9
Glycerol-mediated organic transformation

9.1 Introduction

Glycerol is generated as a by-product in enormous amounts in biodiesel industry. Hence, a large amount of glycerol is entering the chemical market and is causing a threat for the existing glycerol plants. Further, the increasing demand of biodiesel will also put an extra pressure in future on the glycerol market. Therefore, the use of glycerol in various processes is gaining much attention recently.

Nowadays, focus on the areas of developing an alternate way to synthesize compounds from glycerol as the starting material has gained much attention. Through literature survey, various examples have been found, where glycerol has been successfully utilized as the starting material. Though some of the developed methodologies have a promising approach, large-scale synthesis of compounds starting from glycerol requires systematic toxicity evaluation, stability and capacity of the synthesized products, which will ultimately cost a lot of hard work as well as valuable time for the research purpose. Considering from the industrial perspective, synthesis of compounds from glycerol is somewhat a not-so-favorable approach. Again, considering the pressure from biodiesel industries, efforts are essential for the development of innovative methods for the utilization of glycerol [1–3].

Development of green solvents in organic synthesis has been gaining much attention these days from the environmental point of view. At the same time, production of glycerol in huge amounts has offered a good opportunity for chemists to use it as a renewable solvent. Some of the properties of glycerol such as long liquid range, solubility of organic compounds and noninflammability make it an important green solvent in the field of organic synthetic methodologies.

Major emphasis is given in designing eco-friendly processes, where solvents play a key role from both environmental and economic aspects. The European Union is also taking measures to regulate the use of solvents in relation to the volatile organic compounds and hazardous air pollutants. Designing of green solvents is now becoming a crucial factor in chemical industries. A solvent that fulfills criteria such as renewability, low volatile organic compound emissions, functional group compatibility and nonflammability fits well in the requirement. In this context, glycerol comes up as an innovative solvent.

*Corresponding author: **Pranab Ghosh,** Department of Chemistry, University of North Bengal, Darjeeling, West Bengal, India, e-mail: pizy12@yahoo.com
Gyan Chandra Pariyar, Department of Food Technology, University of North Bengal, Darjeeling, West Bengal, India
Bijeta Mitra, Department of Chemistry, University of North Bengal, Darjeeling, West Bengal, India

https://doi.org/10.1515/9783110788129-009

9.2 Catalyst-free reaction in glycerol

He et al. [4] proved glycerol to be an efficient medium for the promotion of electrophilic activity of aldehydes. Instead of using the conventional system comprising acid catalyst and organic solvents, glycerol was used as the medium for the reaction of aldehydes (**1**) with indoles (**2**) and 1,3-cyclohexanedione (**3**) to form the corresponding bis(indolyl) methane derivatives (**4**), 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(2*H*)-diones (**5**) and 1-oxo hexahydroxanthenes (**6**) in the absence of any catalyst (Figures 9.1 and 9.2). The yield of the products so obtained was good to excellent. The use of glycerol not only made the separation of products easier but also showed higher environmental compatibility and sustainability. The fact that the quenching steps were avoided results in minimal amount of waste, glycerol being the by-product of biodiesel industry was used in this methodology added to the environmental sustainability. Though the exact role of glycerol was not known, they suspected that the strong hydrogen bond formation between the aldehyde and alcoholic solvents may be the reason behind the effect of glycerol in this reaction.

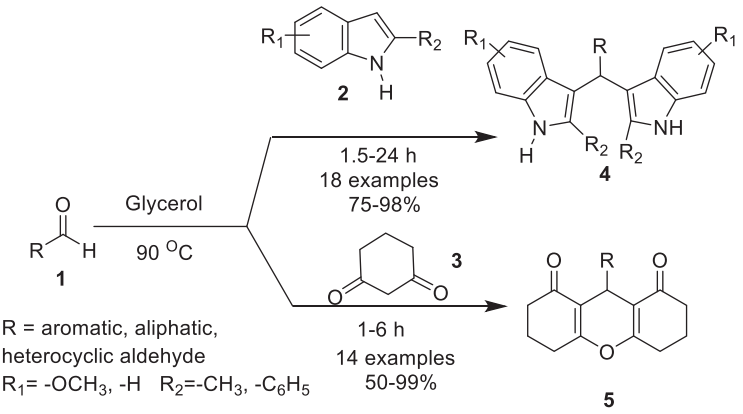


Figure 9.1: Synthesis of bis(indolyl)methanes and xanthene-1,8(2*H*)-diones in glycerol.

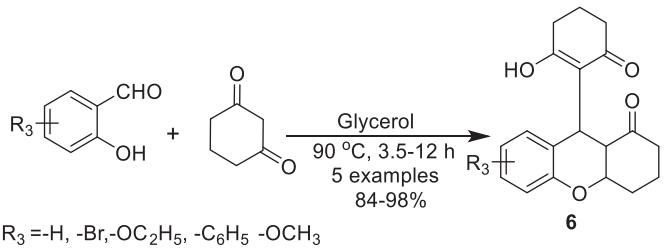


Figure 9.2: Catalyst-free synthesis of 1-oxo-hexahydroxanthenes in glycerol.

Thioacetalization of aldehydes or ketones (**7**) (Figure 9.3) using thiol (**9**) and 1,2-ethanedithiol (**8**) is regarded as an important tool for protection of carbonyl groups. The thioacetals thus formed were then used as a synthetic route for the synthesis of various organic compounds. Perin et al. [5] reported a simple strategy of thioacetalization for the synthesis of protected carbonyl compounds (**10**) and (**11**) using glycerol as a green and recyclable solvent. Without the use of any catalyst, the reaction took place smoothly in glycerol, and the corresponding products were reported to be obtained in good yield. Further, they were able to recover and recycle glycerol for further thioacetalization reactions.

In the absence of any supplementary catalyst, catalyst-free synthetic protocol for the synthesis of benzodiazepines (**14**) and benzimidazoles (**15**) was published by Radatz et al. [6] (Figure 9.4). In this glycerol-mediated reaction, condensation of *o*-phenylenediamine (**12**) with libraries of aldehydes (**1**) and ketones (**13**) was reported to furnish the corresponding 1,2-disubstituted benzimidazoles and 1*H*-1,5-benzodiazepines, respectively, in good yields. Further, glycerol was recovered and reutilized, and no loss of activity was observed up to four times while carrying out further condensation reactions.

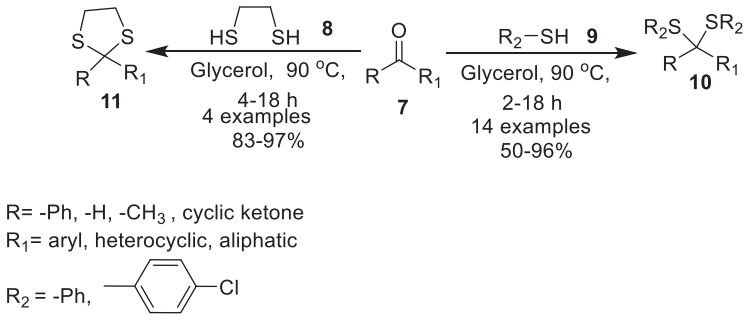


Figure 9.3: Glycerol-assisted thioacetalization of carbonyl compounds.

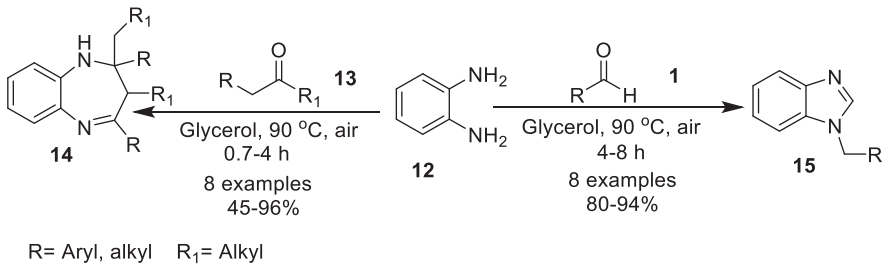


Figure 9.4: Glycerol-catalyzed synthesis of benzimidazoles and benzodiazepines.

Nandre et al. [7] designed an environment-friendly protocol mediated by glycerol where the usual [3 + 2] cycloaddition reaction was used for the synthesis of 5-substituted 1*H*-

tetrazoles (**17**) from organic nitriles (**18**) and sodium azide (Figure 9.5). Where easily available solvents such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), dioxane, acetic acid, water and isopropanol did not give the product, glycerol was an exception and gave good yield of substituted tetrazoles during the reaction. The reaction was reported to yield the products from not only aryl nitriles and benzyl nitriles but also the sterically hindered nitriles.

β-Amino carbonyl compounds (**20**) were designed by Ying et al. [8] by exploring glycerol for aza-Michael addition of aromatic amines (**18**) to α,β-unsaturated ketones (**19**) in the absence of any additional promoter (Figure 9.6). Here, unsaturated ketone and amines act as an acceptor and electron donor, respectively. The pure desired molecule was isolated through column chromatography and analyzed by the spectroscopic technique. A broad array of aromatic amines can react smoothly to accomplish the good yield of target molecule.

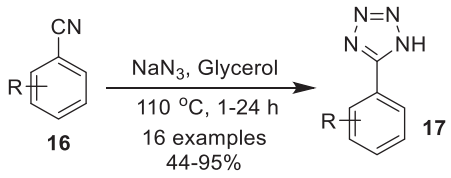


Figure 9.5: Synthesis of 5-substituted 1*H*-tetrazole in glycerol.

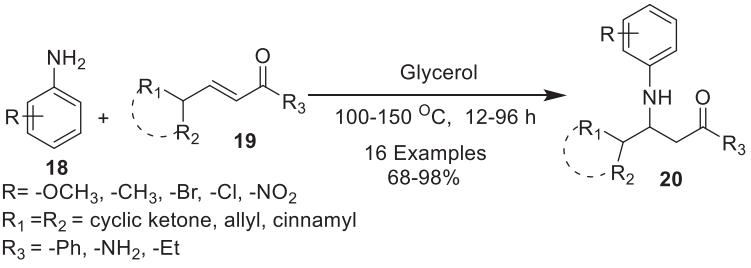
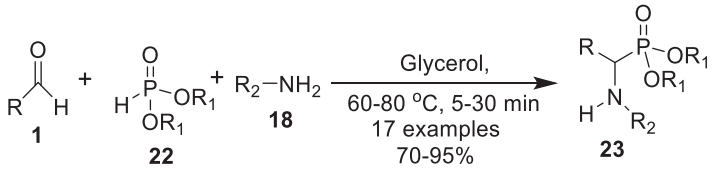


Figure 9.6: Glycerol-assisted aza-Michael reaction.

Azizi et al. [9] utilized the combined advantages of glycerol for being nontoxic, economical, easily available and renewable like water and low vapor pressure, high boiling point like ionic liquids for the synthesis of α-aminophosphonates (**23**). This catalyst-free multicomponent Kabachnik–Fields reaction was reported to combine amines (**18**), carbonyl compound (**1**) and phosphites (**22**) for the synthesis of α-aminophosphonates in high purity (Figure 9.7). The use of glycerol in place of acid as catalysts was reported by them to be more advantageous because it made the workup procedure more simplified, the waste generation was

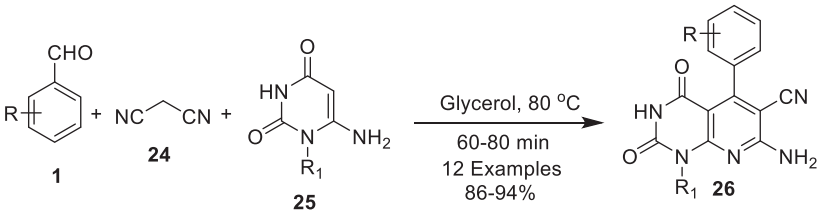
minimized and also allowed the use of reactants that were acid-sensitive. Further, they added that the protocol led to easy separation of the products, and the use of volatile organic solvents was also not required for the procedure to take place.

Singh et al. [10] were successful in the synthesis of pyrido[2,3-*d*]pyrimidines (**26**). The biologically active motif was thus prepared by the reaction between malononitrile (**24**), aldehydes (**1**) and 6-amino-1-methyluracil (**25**) (Figure 9.8) in the presence of recyclable environmentally friendly glycerol medium. In addition to the use of non-hazardous conditions, cheap starting reactants, isolation of pure products without the need of use of column chromatography, 100% atom economical and high yield of the products were the highlights of their reaction. The reactions were also tried using other green solvents like ethanol, PEG-400 and water; however, results were not satisfactory. NMR spectroscopy was used for the identification of isolated compounds.



R= -Ph, -Bu, heterocycle, cyclohexanone
R_1 = -Me, -Et, -Ph
R_2 = -Ph, -Bu,

Figure 9.7: Catalyst-free glycerol-assisted Kabachnik–Fields reaction.



R= OCH_3, CH_3, Br, F,Cl, NO_2
R_1= CH_3, H

Figure 9.8: Glycerol-catalyzed synthesis of pyrido[2,3-*d*]pyrimidines.

Nagasundaram et al. [11] published the synthesis of diverse array of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one (**28**) (Figure 9.10) and 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) (**14**) (Figure 9.9) in a catalyst-free glycerol-mediated conditions. At first, hydrazine hydrate (**29**), aromatic aldehydes (**1**) and ethyl acetoacetate (**30**) furnished 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) (**31**) while under the same conditions, aromatic aldehyde or ketones (**1**) and anthranilamide (**27**) gave 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one. They were able to separate pure glycerol after the reaction by evaporating the

aqueous layer under reduced pressure. The recovered glycerol was then reused for next reaction under similar conditions, and the products were isolated with negligible loss of the product.

6-Amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-*c*]pyrazoles (**32**) and 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[*b*]pyrans (**33**) were prepared by Hamid et al. [12] via multicomponent reaction of aldehydes (**1**), 1,3-dicarbonyl compounds (**3**), hydrazine hydrate or phenyl hydrazine (**32**), ethyl acetoacetate (**30**) and malononitrile (**24**), exploring the catalytic role of glycerol at room temperature without any supplementary catalyst (Figure 9.11). With any other solvent, no targeted product was formed even after a long reaction period. From this, it can be concluded that glycerol performed the required catalytic role smoothly and also as a good reaction medium for designing the compounds.

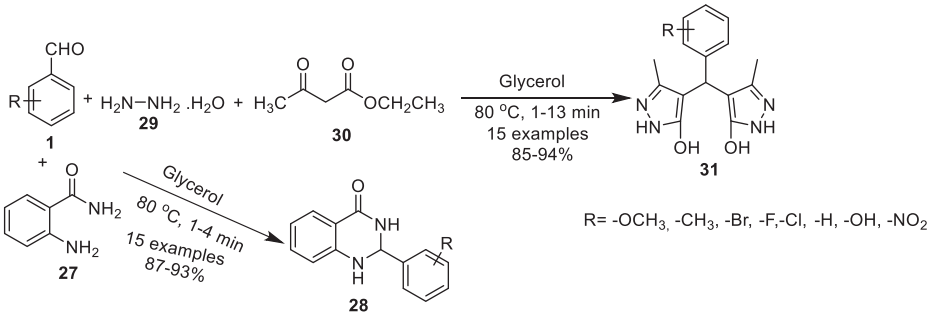


Figure 9.9: Glycerol-assisted pseudo-five-component synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol

Figure 9.10: Glycerol-assisted two-component synthesis of 2,3-dihydro-4(1*H*)-quinazolinones.

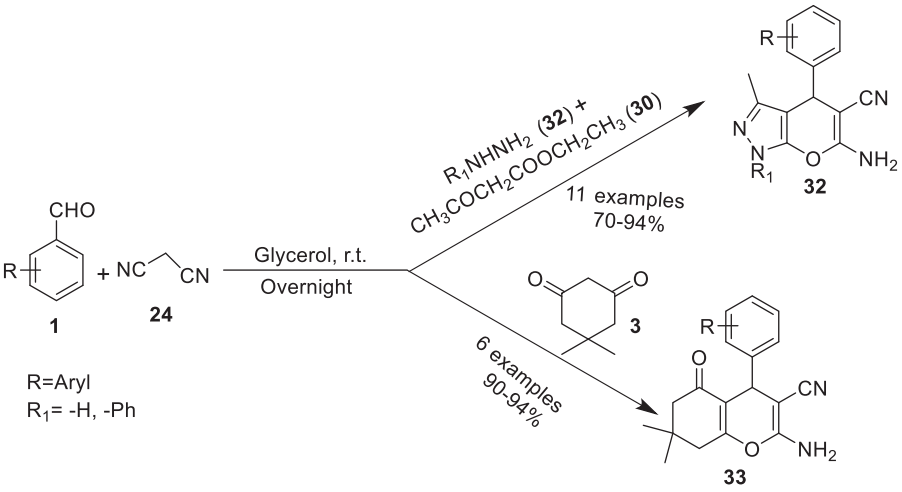
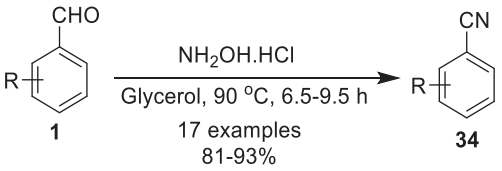


Figure 9.11: Glycerol-mediated synthesis of pyrano[2,3-*c*]pyrazoles and tetrahydro-benzo[*b*]pyrans.

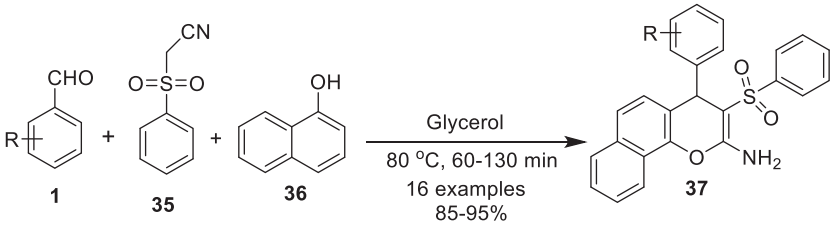
A diverse array of nitrile derivative (**34**) was generated by a robust and facile one-pot catalyst-free methodology by the reaction of aldehydes (**1**) by using hydroxyl amine hydrochlorides only in the presence of glycerol by Ingale et al. [13] (Figure 9.12). All the desired products were analyzed by IR, NMR and GC-MS. This catalyst-free protocol was very competent for the conversion of aromatic aldehydes with both electron-withdrawing and electron-donating groups.

Morshedi and Shaterian [14] demonstrated a greener solvent, glycerol-mediated one-pot, three-component reaction between aldehydes (**1**), (phenylsulfonyl)acetonitrile (**35**) and α-naphthol (**36**) for the synthesis of 4-(aryl)-3-(phenylsulfonyl)-4*H*-benzo[*h*]chromen-2-amine (**37**) derivatives in the absence of any other additional catalyst (Figure 9.13). All the desired compounds were analyzed by IR, ^{1}H-NMR, ^{13}C-NMR and MS. The reaction mechanism involves domino Knoevenagel condensation/Michael addition and cyclization cascade.



R= aromatic, heterocyclic

Figure 9.12: Synthesis of nitriles from aldehydes using glycerol.



R= heterocycles, -OCH_3, -CH_3, -Br, -CN, -F,-Cl, -H, -OH, -NO_2

Figure 9.13: Synthesis of 4-(aryl)-3-(phenylsulfonyl)-4*H*-benzo[*h*]chromen-2-amine derivatives in glycerol.

Mitra et al. [15] demonstrated one-pot multiple-component methodology for designing a vast array of biologically active thioamide (**40**) derivatives (Figure 9.14) and 4*H*-thiopyran (**43**) (Figure 9.15) in the absence of any supplementary catalyst. Both the products, thioamide and thiopyran, were reported to be synthesized in good yield by using easily available reactants, aldehydes (**1**) having benzene substituent, heterocyclic, polynuclear hydrocarbon as well as aliphatic moiety. Thioamide was synthesized using one-pot three-component reaction between amines (**39**), aldehydes (**1**) and molecular sulfur (**38**), whereas one-pot four-component reaction between malononitrile (**24**), aldehyde (**1**),

carbon disulfide (**41**) and butylamine (**42**) furnished the respective thioamides. The synthesized compounds were identified using NMR spectroscopy.

Kordnezhadian et al. [16] depicted catalyst-free and diastereoselective one-pot four-component protocol by the reaction of aldehyde (**1**), 1,3-thiazolidinedione (**44**), amine (**39**) and malononitrile (**24**) to produce diverse array of 2-(*N*-carbamoylacetamide)-substituted 2,3-dihydrothiophenes (**45**) in good yield in glycerol reaction medium in both conventional heating and microwave (Figure 9.16). The time necessary for this conversion is shorter than the formerly reported protocol. Besides, the reported reaction medium, glycerol, was recycled several times without any loss of effectiveness.

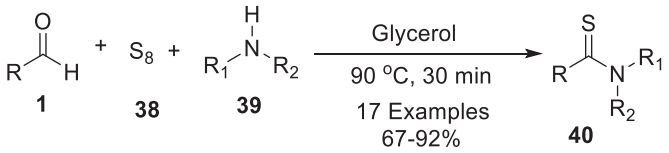


Figure 9.14: Glycerol-mediated metal-free synthesis of thioamide.

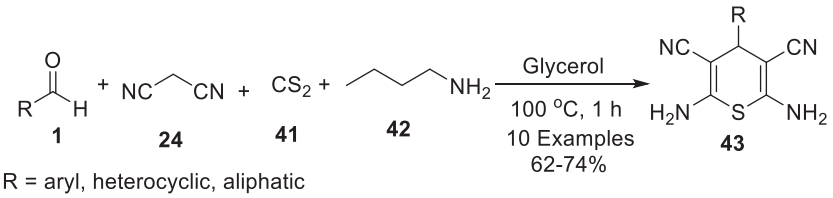


Figure 9.15: One-pot pseudo-five-component synthesis of 4*H*-thiopyran in glycerol.

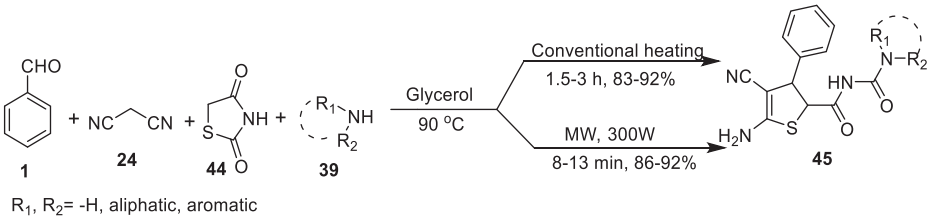


Figure 9.16: Glycerol-catalyzed synthesis of 2-(*N*-carbamoylacetamide)-substituted 2, 3-dihydrothiophenes.

Cabrera et al. [17] demonstrated the synthesis of organic disulfides (**8**) using thiols (**9**), where glycerol was chosen as a solvent (Figure 9.17). This glycerol-mediated oxidation of functionalized thiols was carried out under microwave irradiation where good-to-

excellent yields of the products were reported by them. Further, they were successful in recovering the glycerol and were utilized for further oxidation reactions.

Safaei et al. [18] explored inexpensive, easily available, biodegradable solvent glycerol for the synthesis of 4*H*-pyran derivatives (**33**) (Figure 9.18). This one-pot three-component reaction was performed using aldehydes (**1**), malononitrile (**24**) and dimedone (**3**) in the absence of any catalyst and the method not only resulted in substantial improvement in reaction rates and yields but also avoided the use of hazardous solvents. High yield of the products, short reaction time, easy product isolations, cleaner reaction profile and recycling ability of the reaction medium were important factors of their protocol as reported by them. When compared with the earlier reported methods which composed of utilization of acid or base catalyst and organic solvents, the application of glycerol made not only the product separation easier but also contributed in environmental compatibility and sustainability.

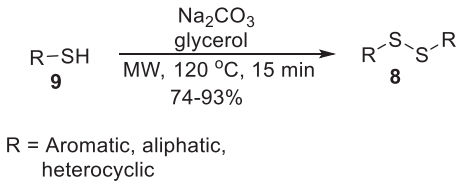


Figure 9.17: Glycerol-mediated microwave-assisted synthesis of disulfides.

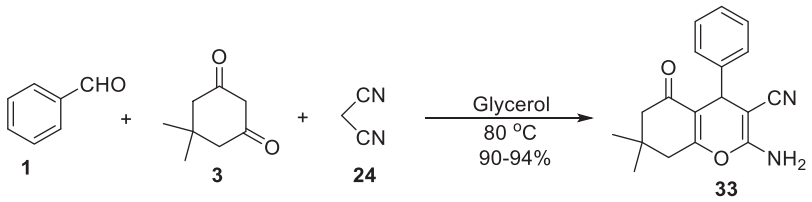


Figure 9.18: Glycerol-promoted catalyst-free synthesis of 4*H*-pyrans.

9.3 Metal-catalyzed organic synthesis in glycerol

Gonçalves et al. [19] demonstrated a convenient methodology for the preparation of vinyl sulfides and vinyl tellurides, where Cu catalyst was used for the coupling of vinyl bromide with diphenyl disulfide and diphenyl ditellurides (**46**) (Figure 9.19). They stated that the advantages of the reaction were the applicability to a wide variety of the substrates, simple process of recovery of the catalyst, reusability of the catalyst for up to four cycles without the loss of its activity and stereoselectivity for *Z*-styryl bromide (**48**) and *E*-styryl bromide (**47**) for the synthesis of Z-isomer (**50**) and E-isomer (**49**) of the respective products. Further, the procedure was also described as environmental-friendly,

economical with the reaction being performed in the absence of any toxic solvents and heavy metals.

Glycerol was used as a medium for N-arylation of indole (**2**) (Figure 9.20) as described by Yadav et al. [20]. Using copper as the catalyst and DMSO as an additive, the cross-coupling of indoles with aryl halides (**51**) was described by them to give good yield of *N*-aryl indole derivatives (**52**) with a vast array of substrates. They recycled the catalyst combination and used up to four runs without the loss of its catalytic activity. They proposed the methodology to be environment-friendly, highly efficient and economical in nature.

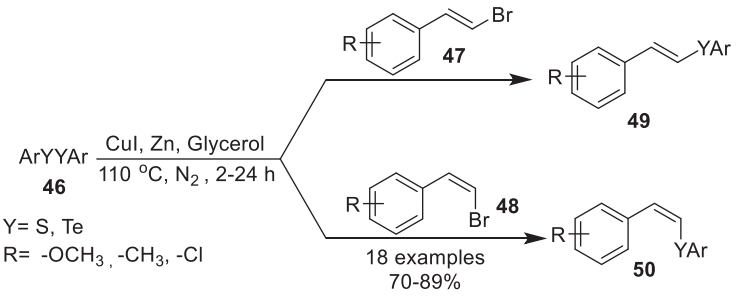


Figure 9.19: Glycerol-assisted synthesis of vinyl sulfides and tellurides.

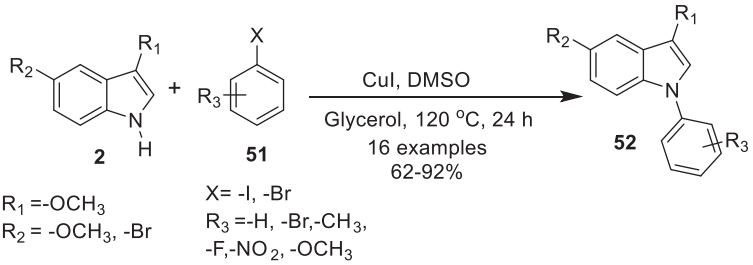


Figure 9.20: Copper-catalyzed N-arylation of indoles.

Bhojane et al. [21] published the Suzuki coupling reaction between phenyl boronic acids (**53**) and aryl diazonium salts (**54**) for the preparation of respective aryl derivatives (**55**). This nickel-catalyzed reaction was carried out in the presence of environmentally friendly solvent glycerol as a medium where varieties of aryl diazonium salts were efficiently converted into the respective diaryl compounds (Figure 9.21) in good yield.

Dubey et al. [22] described an inexpensive, clean and efficient method in which thiols (**56**) and aryl halides (**51**) in the presence of CuI in glycerol combined together to yield aryl sulfides (**57**) (Figure 9.22). The presence of environmentally friendly solvent and use of various aryl, heteroaryl and even sterically hindered substrates for

the formation of the desired products in moderate-to-good yields of diversified functionalized thiols are some of the features of the protocol. Further, the catalyst system was reported to be recycled which gives it an extra edge over previously reported protocols. They further reported that the methodology was used for the synthesis of Gemmacin drug precursor and Gemmacin B.

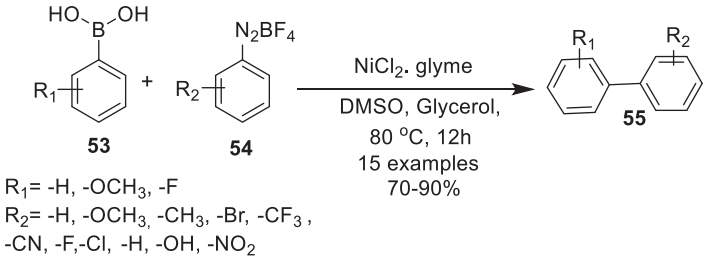


Figure 9.21: Nickel-catalyzed Suzuki cross-coupling reactions.

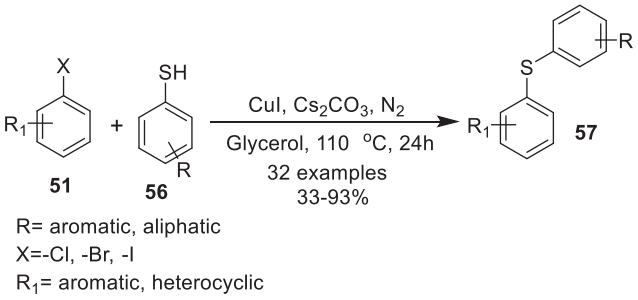


Figure 9.22: Copper-mediated ligand-free C–S cross-coupling reaction in glycerol.

Click reaction involves the synthesis of 1,4-disubstituted 1,2,3-triazoles (**60**) from alkyne (**59**) and alkyl azide (**58**) by the use of CuAAC as a catalyst. The transfer of Cu(I) to thermodynamically stable Cu(II) by aerial oxidation or by disproportionation has been one of the major issues for this conversion. Hence, in order to stabilize Cu(I) species, the reaction is usually carried out under inert atmosphere in the presence of various additives like alcohols, thiols, amines or aldehydes. Pasupuleti and Bez [23] (Figure 9.23) reported the use of CuI/L-proline system in glycerol, where unprecedented Cu(I)-catalyzed click reaction was carried out in the absence of inert atmosphere. The approach may be helpful in the industrial production of triazole moiety.

Wolfson and Dlugy [24] successfully utilized glycerol as a green solvent in both Heck coupling and Suzuki cross-coupling reactions (Figure 9.24). As both the inorganic bases and organic bases were soluble in glycerol, a high yield of the product, namely, styrene derivatives (**62**) and biphenyls (**63**) was reported by the reaction of aryl halide (**51**) with alkene (**61**) and phenyl boronic acid (**53**), respectively. In addition, extraction of the

product with glycerol-immiscible solvents made it an easy process. Further, the catalyst was recycled without much loss of its activities. They also made a comparison between the reactions in glycerol and DMF under similar conditions, and they found that the product recovery was much simpler in case of glycerol than in DMF. Glycerol being an environmentally friendly further added on the advantages of glycerol over DMF.

Gonçalves et al. [25] described the use of glycerol as a solvent in CuI-catalyzed cross-coupling reaction between vinyl bromide (**47**) and diaryl diselenides (**64**) (Figure 9.25). During the reaction, (*Z*)- or (*E*)-vinyl bromides bearing electron-donating groups or electron-withdrawing groups gave good-to-excellent yields of vinyl selenides (**65**). They added that the glycerol/CuI/Zn during the reaction was easily recovered and was further used for the reaction to give good yields even after five successive cycles.

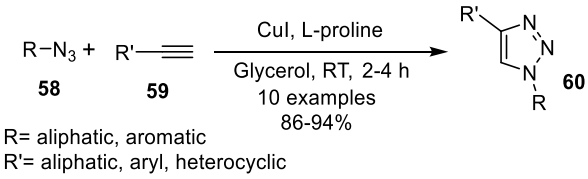


Figure 9.23: Synthesis of 1, 4-disubstituted 1,2,3-triazoles.

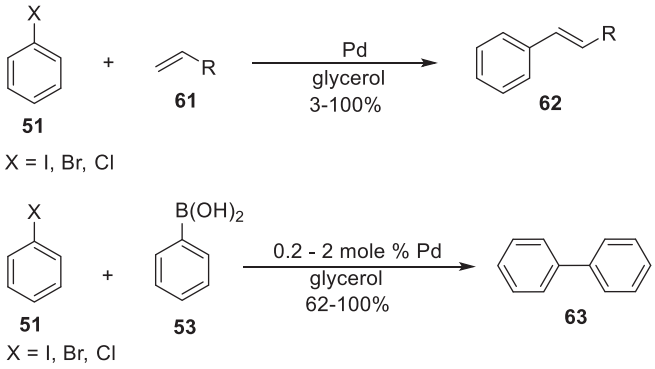


Figure 9.24: Glycerol-mediated Heck and Suzuki Coupling reaction.

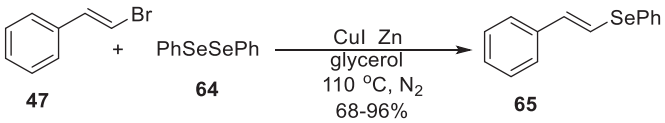


Figure 9.25: Glycerol-promoted cross-coupling reactions of diaryl diselenides with vinyl bromides.

Ricordi et al. [26] reported the use of glycerol as an efficient solvent for cross-coupling reactions of aryl boronic acids (**53**) and diaryl diselenides (**64**) for the synthesis of diaryl

selenides (**66**) (Figure 9.26). The reaction was catalyzed by CuI, where DMSO was used as an additive and was carried out in open air at 110 °C. Diarylboronic acids and diaryl diselenides containing electron-withdrawing groups or electron-donating groups were reported to deliver well-to-excellent yields of the products.

Wolfson et al. [27] successfully employed glycerol (**67**) as a green solvent and as a hydrogen donor for the catalytic transfer hydrogenation–dehydrogenation reaction (Figure 9.27). Glycerol was found to donate hydrogen to several organic compounds for the formation of alcohols (**71**), alkanes (**72**) and aniline (**69**), respectively, from carbonyl compound (**70**), alkenes (**61**) and nitrobenzene (**68**) under mild conditions. Glycerol allows not only the easy separation of the products but also the recyclization of catalyst.

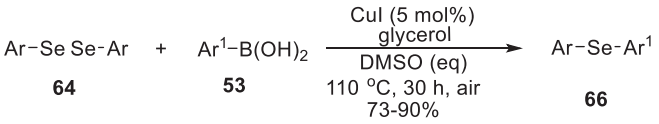


Figure 9.26: Glycerol-mediated cross-coupling reactions of diaryl diselenides with aryl boronic acids.

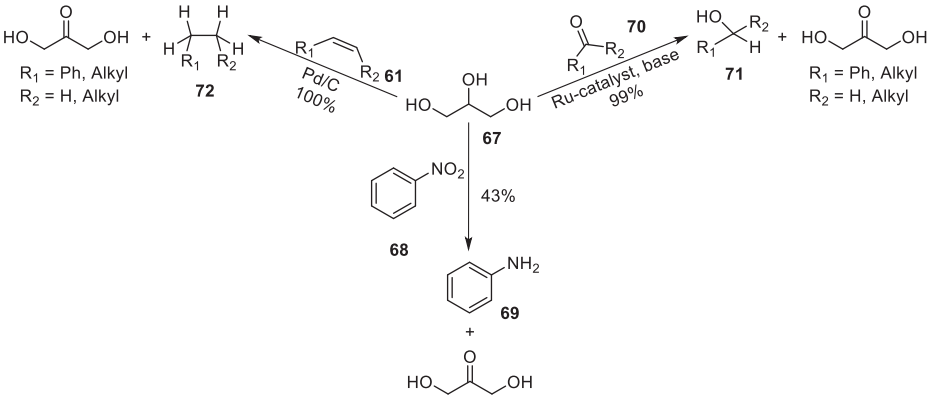


Figure 9.27: Glycerol-mediated hydrogenation–dehydrogenation reactions.

Díaz-Álvarez et al. [28] were successful in demonstrating that pharmaceutical and technical-grade glycerol can act both as a solvent and a hydrogen source in the catalytic reduction of allylic alcohols (**73**) in the presence of arene–ruthenium(II) complexes (Figure 9.28). The tandem process involved initial redox isomerization of the allylic alcohols, which on subsequent hydrogen transfer resulted in the formation of the corresponding saturated alcohols (**74**). The use of glycerol as a solvent gave added advantages on catalyst recycling and easy product separations. They declared that the results reported by them illustrated new examples where glycerol was used as a solvent for synthesis in organic chemistry and stated that it would be an emerging field

of research where the main objectives were revalorization of the waste that was generated in numerous biodiesel industries.

Tavor et al. [29] published a protocol where NaOH promoted hydrogenation of nitrobenzene (**68**) for the synthesis of substituted anilines (**69**), and this was carried out using Raney nickel as a catalyst, and glycerol (**67**) was explored as a green solvent and a source of hydrogen (Figure 9.29). The amount of the base and the reaction temperature had a significant effect on the rate of the reaction. Just as in the case of other reactions, glycerol helped in allowing easy separation of the product and catalyst recycling. However, fresh NaOH additions were necessary during all the processes of catalytic recyclization. During the reaction, glycerol itself was transferred to dihydroxyacetone by dehydrogenation, which is regarded as a valuable product and has a huge utilization on sunless tanning product industries.

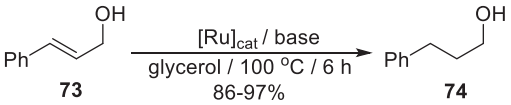


Figure 9.28: Glycerol-assisted reduction of allylic alcohols.

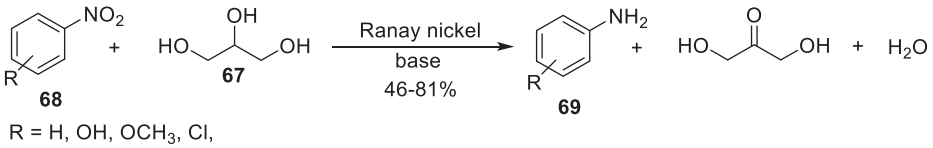


Figure 9.29: Transfer hydrogenations of nitrobenzene in glycerol.

Azua et al. [30] explored iridium and ruthenium *N*-heterocyclic carbene (NHC)-based catalysts for the reduction of numerous organic carbonyl compounds (**70**) into alcohols (**71**) (Figure 9.30). During their synthetic procedure, they found that glycerol (**67**) served as a green solvent and also helped in hydrogen donation. Due to the better solubility in glycerol, Ir(III) complexes with the chelating bis-NHC ligand, and a sulfonate group served as the most efficient catalyst for the reaction. Glycerol was reported to have never been used before them for the chemoselective reduction of alkenic double bond of α,β-unsaturated ketones and suggested that in the presence of appropriate catalyst, glycerol can be utilized as a potent hydrogen source for the process of reduction of numerous organic substrates.

Azua et al. [31] further used glycerol in the synthesis of novel iridium NHC-based complexes which was then fully characterized (Figure 9.31). The synthesized complexes were then used as a catalyst under ultrasound, microwave and oil bath conditions and were compared with their previous work for the synthesis of alcohols (**76**) from ketones (**75**). The same solvent glycerol (**67**) here also acted as a hydrogen donor. In comparison, the ultrasound technique was found to gain a special position as a

capable heating procedure for the development of new catalytic system in glycerol. Using ultrasound of microwave heating, the formation of spherical Ir(0)-containing nanoparticles in glycerol was demonstrated during their work.

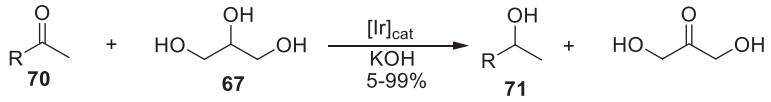


Figure 9.30: Glycerol-mediated transfer hydrogenation processes.

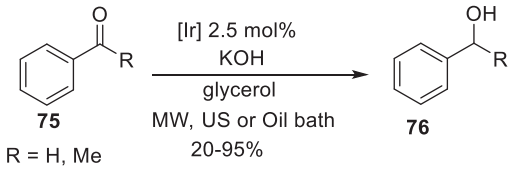


Figure 9.31: Glycerol-assisted transfer hydrogenation.

Carmona et al. [32] reported a combination of zinc(II) acetate and glycerol as an efficient catalyst in the synthesis of 2-pyridyl-2-oxazolines (**79**) by the reaction of 2-cyanopyridines (77) and 2-amino alcohols (**78**) under microwave conditions (Figure 9.32). As compared to the conventional heating method, their procedure was said to furnish good-to-excellent yields of the desired products in less reaction time. They were further able to isolate the glycerol-zinc(II) acetate catalytic system and utilize them up to four times for the same reaction without significant loss of the yield of the product. Further, glycerol provided a medium where pure form of the product was obtained by simple filtration done with short silica pad column.

Aziz et al. [33] successfully obtained 9*H*-fluoren-9-amine derivatives by using one-pot combination of anilines and 2′-bromo-biarylhydrazones (**80**) in glycerol as a solvent and copper as a catalyst (Figure 9.33). The reaction facilitated the formation of a large number of 9*H*-fluoren-9-amine derivatives (**81**) containing various substitution patterns in a very easy way resulting in a novel versatile synthetic procedure. Further, unprecedented generation of C–N and C–C bonds resulting in the same carbonic

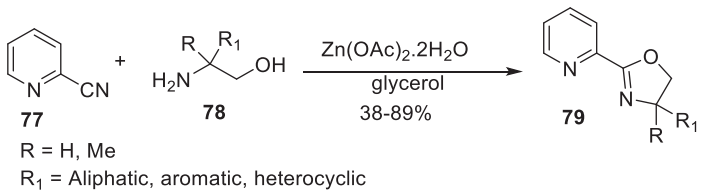


Figure 9.32: Glycerol-zinc(II) acetate-catalyzed synthesis of 2-pyridyl-2-oxazolines.

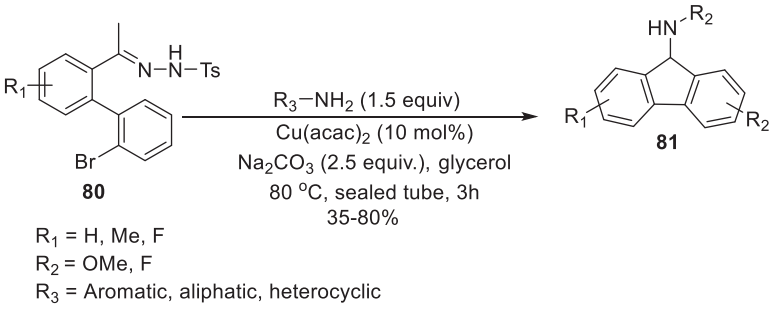


Figure 9.33: Glycerol-mediated copper-catalyzed synthesis of fluorene derivatives.

center from 2′-bromo-biaryl-*N*-tosylhydrazones is the highlight of the procedure and probably represents an example of the evolution of carbenoid moieties into complex structures with the help of original transformation reactions.

Hamel et al. [34] utilized glycerol micellar conditions for the ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (**82**) for the synthesis of the cyclic product (**83**) under microwave irradiation conditions (Figure 9.34). On their investigation on micellization of various cationic surfactants in glycerol, they found out that the results obtained showed superior micellar catalysis for the RCM reaction as compared to only glycerol due to the limitation of by-product formations. As compared to the conventional solution synthesis, the reported method allowed less hazardous chemical synthesis, safe reaction conditions and the utilization of renewable feedstock.

González-Liste et al. [35] published a protocol where commercially available bis (allyl)-ruthenium(IV) dimer [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] was used as a catalyst for selective rearrangement to obtain large number of primary amides (**84**) from respective aldoximes (**85**) (Figure 9.35). In a mixture of water/glycerol (1:1), good yields of the products were reported using either conventional heating process or microwave irradiation in the absence of assistance from any other cocatalyst. The use of microwave irradiation was found to be more appropriate in the rearrangement of aliphatic, aromatic or heteroaromatic aldoximes while it was observed that thermal heating was profitable for α,β-unsaturated aldoximes. They were also able to reutilize the catalyst for up to six times without much reduction in its efficiency.

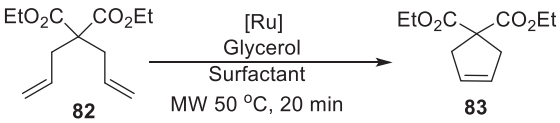


Figure 9.34: Glycerol-assisted ring-closing metathesis of diethyl diallylmalonate.

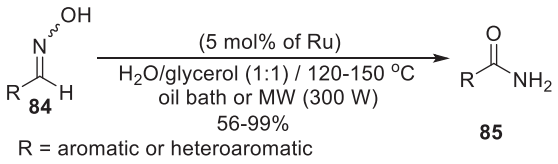


Figure 9.35: Water/glycerol-mediated rearrangement of aldoximes to primary amides.

9.4 Conclusions

In conclusion, glycerol has been widely explored as an eco-friendly recyclable medium in the synthesis of various organic compounds. Either in the presence or in the absence of a catalyst, glycerol has served as a promising medium furnishing good-to-excellent yields of the desired products. Long liquid range, solubility of organic compounds, noninflammability, and recyclability are some of the features that give glycerol an extra edge when compared to other solvents in various synthetic methodologies. Glycerol is, therefore, a solvent showing promising properties for developing environmental-friendly procedures and is likely to remain as a field of interest among chemists working in organic synthesis.

References

[1] Yang, F, Hanna, MA, Sun, R. Value-added uses for crude glycerol-a byproduct of biodiesel production. Biotechnol Biofuels 2012, DOI: 10.1186/1754-6834-5-13.

[2] Tan, HW, Aziz, ARA, Aroua, MK. Glycerol production and its applications as a raw material: A review. Renew Sust Energ Rev 2013, 27, 118–127.

[3] Díaz-Álvarez, AE, Francos, J, Lastra-Barreira, B, Crocheta, P, Cadierno, V. Glycerol and derived solvents: New sustainable reaction media for organic synthesis. Chem Commun 2011, 47, 6208–6227.

[4] He, F, Li, P, Gu, Y, Li, G. Glycerol as a promoting medium for electrophilic activation of aldehydes: Catalyst-free synthesis of di(indolyl)methanes, xanthene-1,8(2*H*)-diones and 1-oxo-hexahydroxanthenes. Green Chem 2009, 11, 1767–1773.

[5] Perin, G, Mello, LG, Radatz, CS, Savegnago, L, Alves, D, Jacob, RG, Lenardão, EJ. Green, catalyst-free thioacetalization of carbonyl compounds using glycerol as recyclable solvent. Tetrahedron Lett 2010, 51, 4354–4356.

[6] Radatz, CS, Silva, RB, Perin, G, Lenardão, EJ, Jacob, RG, Alves, D. Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent. Tetrahedron Lett 2011, 52, 4132–4136.

[7] Nandre, KP, Salunke, JK, Nandre, JP, Patil, VS, Borse, AU, Bhosale, SV. Glycerol mediated synthesis of 5-substituted 1*H*-tetrazole under catalyst-free conditions. Chin Chem Lett 2012, 23, 161–164.

[8] Ying, A, Zhang, Q, Li, H, Shen, G, Gong, W, He, M. An environmentally benign protocol: Catalyst-free Michael addition of aromatic amines to α,β-unsaturated ketones in glycerol. Res Chem Intermed 2013, 39, 517–525.

[9] Azizi, K, Karimi, M, Heydari, A. A catalyst-free synthesis of α-aminophosphonates in glycerol. Tetrahedron Lett 2014, 55, 7236–7239.
[10] Singh, S, Saquib, M, Singh, M, Tiwari, J, Tufail, F, Singh, J. A catalyst free, multicomponent-tandem, facile synthesis of pyrido[2,3-*d*]pyrimidines using glycerol as a recyclable promoting medium. New J Chem 2016, 40, 63–67.
[11] Nagasundaram, RRN, Meignanasundar, D, Vadivel, P, Lalitha, A. Glycerol assisted eco-friendly strategy for the facile synthesis of 4,40-(arylmethylene)bis(3-methyl-1*H*pyrazol-5-ols) and 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones under catalyst-free conditions. Res Chem Intermed 2017, 43, 1767–1782.
[12] Hamid, AA, Abd-Elmonem, M, Hayallah, AM, Elsoud, FAA, Sadek, KU. Glycerol: A promising benign solvent for catalyst-free one-pot multi-component synthesis of pyrano[2,3-*c*]pyrazoles and tetrahydro-benzo[*b*]pyrans at ambient temperature. Chemistry Select 2017, 2, 10689–10693.
[13] Ingale, AP, Patil, SM, Shinde, SV. Catalyst-free, efficient and one pot protocol for synthesis of nitriles from aldehydes using glycerol as green solvent. Tetrahedron Lett 2017, 58, 4845–4848.
[14] Morshedi, A, Shaterian, HR. Green approaches to synthesis of novel and broad-range diversity of 4-(aryl)-3-(phenylsulfonyl)-4*H*benzo[*h*]chromen-2-amine derivatives. Res Chem Intermed 2018, 44, 7219–7230.
[15] Mitra, B, Pariyar, GC, Ghosh, P. Glycerol: A benign solvent-assisted metal-free one-pot multi-component synthesis of 4*H*-thiopyran and thioamides from easily accessible precursors. Chemistry Select 2019, 4, 5476–5483.
[16] Kordnezhadian, R, Shekouhy, M, Khalafi-Nezhad, A. Microwave-accelerated diastereoselective catalyst-free one-pot four-component synthesis of 2-(*N*-carbamoylacetamide)-substituted 2,3-dihydrothiophenes in glycerol. Mol Divers 2020, 24, 737–751.
[17] Cabrera, DML, Lı'bero, FM, Alves, D, Perin, G, Lenarda˜o, EJ, Jacob, RG. Glycerol as a recyclable solvent in a microwave-assisted synthesis of disulfides. Green Chem Lett Rev 2012, 5, 329–336.
[18] Safaei, HR, Shekouhy, M, Rahmanpur, S, Shirinfeshan, A. Glycerol as a biodegradable and reusable promoting medium for the catalyst-free one-pot three component synthesis of 4*H*-pyrans. Green Chem 2012, 14, 1696–1704.
[19] Gonçalves, LCC, Lima, DB, Borba, PMY, Perin, G, Alves, D, Jacob, RG, Lenardão, EJ. Glycerol/CuI/Zn as a recyclable catalytic system for synthesis of vinyl sulfides and tellurides. Tetrahedron Lett 2013, 54, 3475–3480.
[20] Yadav, DKT, Rajak, SS, Bhanage, BM. N-arylation of indoles with aryl halides using copper/glycerol as a mild and highly efficient recyclable catalytic system. Tetrahedron Lett 2014, 55, 931–935.
[21] Bhojane, JM, Sarode, SA, Nagarkar, JM. Nickel–glycerol: An efficient, recyclable catalysis system for Suzuki cross coupling reactions using aryl diazonium salts. New J Chem 2016, 40, 1564–1570.
[22] Dubey, AV, Gharat, SB, Kumar, AV. Glycerol as a recyclable solvent for copper-mediated ligand-free C-S cross-coupling reaction: Application to synthesis of Gemmacin precursor. Chemistry Select 2017, 2, 4852–4856.
[23] Pasupuleti, BG, Bez, G. CuI/L-proline catalyzed click reaction in glycerol for the synthesis of 1,2,3-triazoles. Tetrahedron Lett 2019, 60, 142–146.
[24] Wolfson, A, Dlugy, C. Palladium-catalyzed Heck and Suzuki coupling in glycerol. Chem Pap 2007, 61, 228–232.
[25] Gonçalves, LC, Fiss, GF, Perin, G, Alves, D, Jacob, RG, Lenardão, EJ. Glycerol as a promoting medium for cross-coupling reactions of diaryl diselenides with vinyl bromides. Tetrahedron Lett 2010, 5, 6772–6775.
[26] Ricordi, VG, Freitas, CS, Perin, G, Lenardão, EJ, Jacob, RG, Savegnago, L, Alves, D. Glycerol as a recyclable solvent for copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids. Green Chem 2012, 14, 1030–1034.
[27] Wolfson, A, Dlugy, C, Shotland, Y, Tavor, D. Glycerol as solvent and hydrogen donor in transfer hydrogenation–dehydrogenation reactions. Tetrahedron Lett 2009, 50, 5951–5953.

[28] Díaz-Álvarez, AE, Crochet, P, Cadierno, V. Ruthenium-catalyzed reduction of allylic alcohols using glycerol as solvent and hydrogen donor. Cat Commun 2011, 13, 91–96.
[29] Tavor, D, Gefen, I, Dlugy, C, Wolfson, A. Transfer hydrogenations of nitrobenzene using glycerol as solvent and hydrogen donor. Synth Commun 2011, 1, 3409–3416.
[30] Azua, A, Mata, JA, Peris, E. Iridium NHC based catalysts for transfer hydrogenation processes using glycerol as solvent and hydrogen donor. Organometallics 2011, 30, 5532–5536.
[31] Azua, A, Mata, JA, Peris, E, Lamaty, F, Martinez, J, Colacino, E. Alternative energy input for transfer hydrogenation using iridium NHC based catalysts in glycerol as hydrogen donor and solvent. Organometallics 2012, 31, 3911–3919.
[32] Carmona, RC, Schevciw, EP, Petrarca de Albuquerque, JL, Wendler, EP, Dos Santos, AA. Joint use of microwave and glycerol-zinc (II) acetate catalytic system in the synthesis of 2-pyridyl-2-oxazolines. Green Process Synth 2013, 2, 35–42.
[33] Aziz, J, Frison, G, Gómez, M, Brion, J-D, Hamze, A, Alami, M. Copper-catalyzed coupling of *N*-tosylhydrazones with amines: Synthesis of fluorene derivatives. ACS Catal 2014, 4, 4498–4503.
[34] Hamel, A, Sacco, M, Mnasri, M, Lamaty, F, Martinez, J, Angelis, FD, Colacino, E, Charnay, C. Micelles into glycerol solvent: Overcoming side reactions of glycerol. ACS Sustain Chem Eng 2014, 2, 1353–1358.
[35] González-Liste, PJ, García-Garrido, SE, Cadierno, V. Catalytic rearrangement of aldoximes to primary amides in environmentally friendly media under thermal and microwave heating: Another application of the bis(allyl)-ruthenium(iv) dimer [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$]. ACS Sustain Chem Eng 2015, 3, 3004–3011.

Index

https://doi.org/10.1515/9783110788129-010