Synthesis of Novel Task Specific Ionic Liquids and their Applications in Selected Organic Transformations

THESIS

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DOCTOR OF PHILOSOPHY

by

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Under the supervision of

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Dedicated to
My beloved mother,
father and sister

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis of Novel Task Specific Ionic Liquids and their Applications in Selected Organic Transformations"** submitted by **Mr. Manoj Kumar Muthyala** ID No **2009PHXF002P** for the award of Ph. D. Degree of the Institute embodies the original work done by him under my supervision.

Signature in full of the Supervisor:

Name in capital block letters: **Dr. ANIL KUMAR**

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ABSTRACT

The thesis entitled "**Synthesis of Novel Task Specific Ionic Liquids and Their Applications in Selected Organic Transformations**" deals with the synthesis of some selected novel task specific ionic liquids with properties for specific chemical tasks. These task specific ionic liquids further have been used as catalysts, scavengers and as reagents in parallel synthesis. The thesis is divided into five chapters.

The first chapter of thesis describes a literature overview of synthesis of task specific ionic liquids and their applications in combinatorial synthesis. The chapter is divided in two parts. In part-A, detailed literature report on the synthesis and applications of ionic liquid supported reagents and scavengers has been described. Part B deals with brief account on recent developments in soluble supported synthesis, especially ionic liquid-supported synthesis and its superiority over other conventional supported synthesis.

The second chapter of the thesis describes synthesis and applications of ionic liquid-supported aldehyde. The chapter is divided in two parts. In part-A, aldehyde functionalized ionic liquid has been synthesized and used as scavenger for primary amines in the reductive amination process. Using this strategy, small library of secondary amines was synthesized in high (82-90%) yields with excellent purity (> 95%), by eradicating chromatographic purification. The reagent can be regenerated and reused several times without much loss in its activity. In part-B, a parallel solution-pahse, multi step synthesis of amides and sulfonamides has been developed. Reductive amination of ionic liquid supported aldehyde resulted in ionic liquid-supported secondary amines, which were further reacted with sulfonyl chlorides and acid chlorides, respectively. Cleavage of ionic liquid-supported sulfonamides and amides using trifluoroacetic acid (TFA) afforded sulfonamides and caboxamides in good yields. Suzuki coupling reaction has also been performed on the ionic liquid support. The advantages of this protocol over solid-phase synthesis are homogeneous reaction medium, high loading, easy separation of products, and characterization of intermediates by various analytical techniques.

The third chapter of the thesis describes synthesis of new class of sulfonyl reagents, their synthetic utility, and their superiority over conventional sulfonyl reagents. The chapter consists of two parts. In part A, a novel nucleophilic ionic liquid 1-butyl-3-methylimidazolium *p*-toluenesulfinate, [bmim][*p*-TolSO_2] has been synthesized and used as a nucleophile for the reaction with alkyl bromides and phenacyl bromides to prepare sulfones and β-ketosulfones in excellent yields (80–93%) in [bmim][BF_4] ionic liquid. The isolated yields were higher in case of [bmim][*p*-TolSO_2] than sodium *p*-toluenesulfinate. In part B, a new safe diazotransfer reagent, ionic liquid-supported sulfonyl azide has been synthesized. Ionic liquid-supported sulfonyl azide converts active methylene containing compounds to corresponding diazocompounds. The reagent has also been used as detrifluoroacetylative diazotransfer reagent to synthesize α-diazoketones. The method offers better and simple purification and high purity of product in short period of time.

The fourth chapter of thesis describes the synthesis of novel ionic liquid supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (IL-TBD) and its ability to act as an active organocatalyst in the Michael addition of active methylene compounds and thiophenols to chalcones under solvent-free conditions. The IL-TBD afforded Michael addition products in excellent yields (82-94%) at room temperature. Moreover catalyst was recycled and reused at least five times without significant loss of catalytic activity.

The fifth chapter of thesis briefly describes an efficient one-pot procedure for synthesis of 2,4-disubstituted thiazoles and oxazoles from the reaction of ketones with thioamides/thiourea and amides/urea using PTT as *in-situ* brominating agent in ionic liquid [bmim][BF_4]. The procedure avoids the handling of lacrymetric compounds, hazardous organic solvents and toxic catalysts.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
Å	Angstrom
ADM	2-Azido-1,3-dimethylimidazolinium
ACN	Acetonitrile
ATP	Adenosine triphosphate
Bt-SO_2N_3	Benzotriazol-1-yl-sulfonyl azide
[bmim][Br]	1-Butyl-3-methylimidazolium bromide
[bmim][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[bmim][N_3]	1-Butyl-3-methylimidazolium azide
[bmim][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
[bmim][*p*-TolSO_2]	1-butyl-3-methylimidazolium p-toluenesulfinate
[bmim][SCN]	1-Butyl-3-methylimidazolium thiocyante
n-BuLi	*n*-Butyl lithium
β	Beta
Bu	Butyl
Calcd.	Calculated
^{13}C	Carbon-13
Cat.	Catalyst
CAN	Cerric ammonium nitrate
Conc	Concentration
°C	Degree centigrade
Δ	Delta
$CDCl_3$	Deuterated chloroform

D	Doublet
dd	Doublet of doublet
DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
EI	Electron ionization
ESI	Electron spray ionization
EtOAc	Ethyl acetate
Equiv	Equivalent
FILs	Functionalized ionic liquids
G	Gram
h	Hours
HDNIB	[Hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene,
HRMS	High resolution mass spectra
ILs	Ionic liquids
Im-SO_2N_3	Imidazole-1-sulfonyl azide
IR	Infrared
Hz	Hertz
J	Coupling constant
Kcal	Kilocalories
Lit.	Literature
MS	Mass spectrometry

M.p.	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MsN_3	Methanesulfonyl azide
MW	Microwave
N_2	Nitrogen gas
NMR	Nuclear Magnetic Resonance
p-CBSA	*p*-Carboxybenzylsulfonyl azide
PEG	Polyethylene glycol
ppm	Parts per million
PS-SO_2N_3	Polymer-supported benzenesulfonyl azide
PTT	Phenyltrimethylammoniumtribromide
%	Percentage
psi	Per square inch
p-TsOH	*p*-Toluenesulfonic acid
p-TsN_3	*p*-Tolylsulfonyl azide
rpm	Revolutions per minute
rt	Room temperature
s	Singlet
Na[*p*-$TolSO_2$]	Sodium *p*-toluenesulfinate
NBS	*N*-bromosuccinimid

TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
t	Triplet
TFA	Trifluoroacetic acid
TfN_3	Trifluoromethanesulfonyl azide
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
TSIL	Task specific ionic liquid
OTf	Triflouromethanesulfonate
δ	Parts per million
μL	Microliter
μM	Micromolar
v	Volume
w	Watt

CHAPTER I

A Brief Overview on Task Specific Ionic Liquids

PART A

Advances in Task Specific Ionic Liquids as Reagents and Scavengers in Organic Synthesis

Part A: Advances in Task Specific Ionic Liquids as Reagents and Scavengers in Organic Synthesis

1.1.1 Introduction

Supported materials have facilitated the organic synthetic process by virtue of their inimitable advantage, such as facile separation and purification of products and making the process environmentally friendly by increasing reusability and recyclability. This branch of chemistry has become a boon to pharmaceutical companies by assisting them to find the new drugs rapidly for high-throughput screening technologies, thus saving a significant amount of money and ultimately changing their fundamental approach towards drug discovery.

Solid-phase organic synthesis (SPOS) is a widely used technique in organic synthesis for the preparation of libraries of molecules for various purposes.[1-11] The advantages of this strategy have been thoroughly described in the literature. Merrifield pioneered the concept of solid-phase synthesis to attain an efficient method for the synthesis of polypeptides.[12] This method was successfully applied for the synthesis of biopolymers such as DNA, RNA and peptides, as the chemistry required for chain extension is consistent for each step. Later, SPOS proved to be an efficient technique in combinatorial synthesis that facilitated the synthesis of many pharmacologically important compounds and made the purification process more facile.[8, 13-16] A broad range of polymer-supported materials[1-11, 17] and silica-supported materials[18-20] have been developed for SPOS. Despite its great success, SPOS suffers from some serious drawbacks, such as inability to purify and characterize the compounds prior to the final cleavage from the solid support, heterogeneous reaction conditions and non-linear kinetics.

To overcome these drawbacks soluble supports such as PEG[21-26] and fluorous phase[27-31] were utilized as an alternative to the solid-phase. The reactions using these soluble supports are performed under conventional solution phase conditions. Another interesting feature of PEG

supports is that a change in the polarity of the solvent leads to precipitation of the support, thus resulting in facile separation by filtration after the completion of the reaction. PEG-supported synthesis often combines the advantage of both product isolation and purification of solid-phase chemistry with the solubility benefits of solution phase chemistry. However, maximum loading capacity of a PEG support is <1 mmol that is even lower than that of polystyrene-supported reagents.[15, 32-35] Moreover, due to its high oxygenating ability, PEG may interfere in certain types of reactions that may lead to degeneration of the support. In case of fluorous-supported synthesis, special solvents requirement and cost are some serious concerns.[36, 37] Thus, search of new soluble support led to the development of ionic liquid as alternative soluble support to PEG and fluorous supports in the last decade.[38, 39] In view of their unique characteristics, ionic liquid-supported reagents and catalyst have attracted great interest both from academia and industry.[40]

Ionic liquids are salts with melting points below the boiling point of water and they are solely composed of ions in their molten state. These materials have been termed as 'designer solvents' as their properties such as thermal stability, vapor pressure, and solvating ability can be tuned by appropriately varying combination of ions. The initial focus of organic chemists has been to use ionic liquids as an alternative to volatile organic compound solvents (VOCs) in various organic transformations.[41-45]

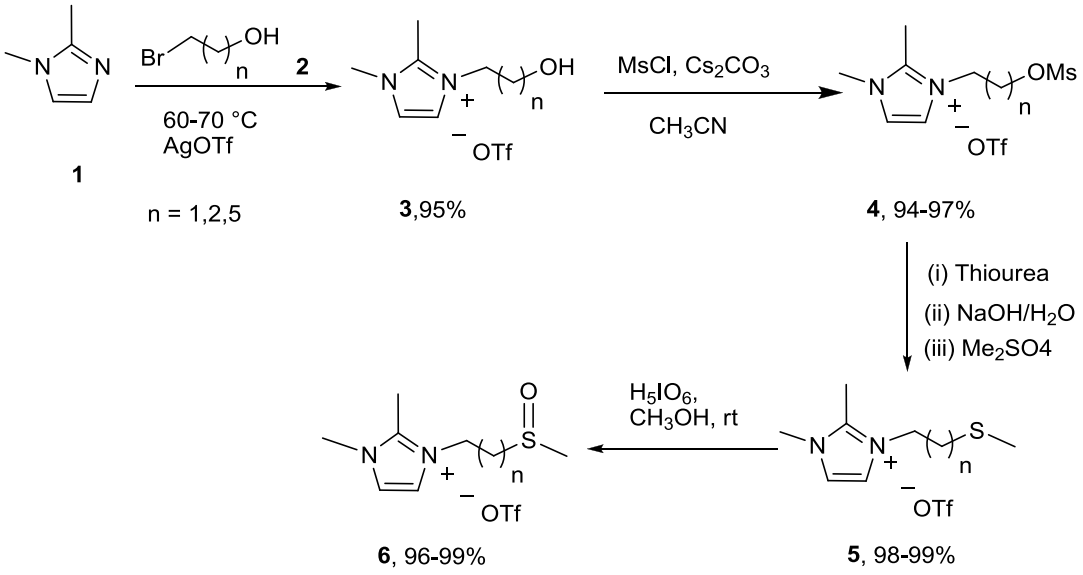
In last decade new class of functionalized ionic liquids (FILs) also known as task-specific ionic liquids (TSILs) have been synthesized with specific desired chemical properties.[46-48] The functional groups in FILs are covalently tethered to the anion, cation or both to get the desired properties for specific chemical tasks.[49-53] A plethora of FILs has been synthesized and used as reagents,[50, 51] catalysts,[52, 53] and scavengers[54-57] in organic synthesis. A number of excellent reviews have appeared on FILs dealing with ionic liquid-supported catalysis.[45, 58-60]. In this

chapter, we have reviewed the synthesis of ionic liquid-supported reagents and their application as reagents and scavengers in organic synthesis. Synthesis of chiral ionic liquids and ionic liquid-supported catalysts[61-65] are not discussed in this chapter. The chapter describes how ionic liquid-supported reagents and scavengers have facilitated the organic synthetic process by virtue of their inimitable advantages such as facile separation and purification of products and thus making the process environmentally friendly.

1.1.2 Ionic liquid-supported reagents

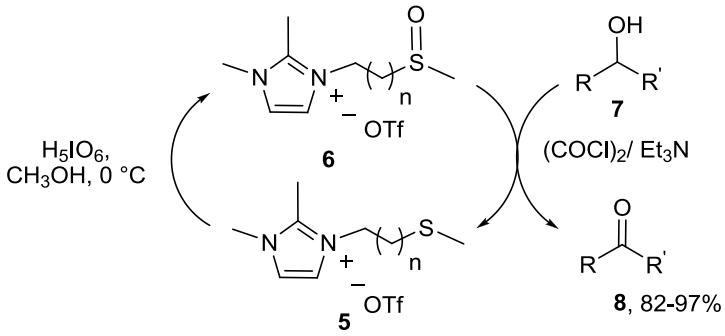
1.1.2.1 Ionic liquid-supported Swern oxidation reagent

Swern oxidation is a well known and widely used process for the oxidation of alcohols to the corresponding carbonyl compounds.[66, 67] Dimethyl sulfide, co-product of Swern oxidation process is volatile, noxious, foul-smelling and difficult to recover. To overcome the drawbacks associated with this protocol, Chan and co-workers prepared non-volatile and odourless ionic liquid-supported sulfoxides **6**.[68] Compound **6** was synthesized by simple reaction sequences as shown in scheme 1.1.1. Alkylation of 1,2-dimethylimidazole **1** with bromo alcohols **2** followed by treatment with AgOTf gave ionic liquid-supported alcohols **3**, which were subjected to mesylation under basic conditions to give mesylated ionic liquid **4**. Sequential reactions involving, treatment of **4** with thiourea, followed by base hydrolysis and quenching the reaction mixture with dimethyl sulphate resulted in ionic liquid-supported sulphide **5**. Controlled oxidation of **5** with periodic acid gave desired ionic liquid-supported sulfoxide **6**. Due to the negligible vapor pressure, these newly synthesized ionic liquid-sulfur compounds **5** and **6** do not possess odor.



Scheme 1.1.1 Synthesis of ionic liquid-supported Swern reagent **6**

Alcohols **7** were successfully oxidized to corresponding carbonyl compounds **8** in excellent yields (82-97%) under the Swern oxidation conditions using **6** (Scheme 1.1.2). In addition to the odorless conditions, simple ether extraction, excellent yields, and high purity without the need of chromatographic purification are silent features of the method. Moreover, the recovered **5** was regenerated and reused up to four cycles with comparable activity.

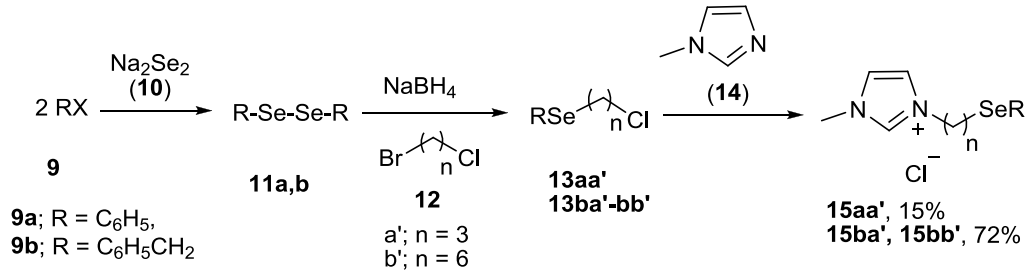


R = C_6H_5, 4-BrC_6H_4, $C_{10}H_7$, $C_6H_5C_2H_2$, 3-$OBnC_6H_4$, 3,4-$(OCH_3)_2C_6H_3$
R' = H, CH_3, C_6H_5,

Scheme 1.1.2 Oxidation of alcohols using ionic liquid-supported Swern reagent **6**

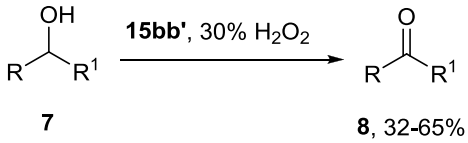
1.1.2.2 Ionic liquid-supported selenium reagent

Ying group reported novel ionic liquid-supported selenium reagents **15** to overcome the purification and handling problems encountered with selenium dioxide and organic selenides in the oxidation reactions.[69] Selenium reagent **15** was synthesized by treating Na_2Se_2 with phenyl halide **9a** or benzyl halide **9b** to give dialkyldiselane **11**. Reduction of **11** with $NaBH_4$ followed by reaction with bromochloroalkane **12** gave alkyl hypochloroselenoite **13**, which upon reaction with 1-methylimidazole gave ionic liquid-supported selenium reagent **15** (Scheme 1.1.3).



Scheme 1.1.3 Synthesis of ionic liquid-supported selenium **15**

Reagent **15b** in the presence of two fold excess of H_2O_2 oxidized alcohols **7** to corresponding carbonyl compounds **8** in good to moderate yields (Scheme 1.1.4). The conventional solubility difference in reagent **15** and carbonyl compounds allowed easy isolation of the product from the reaction mixture. In addition to simplifying purification process, **15** was also recycled and reused effectively up to four times.



R = C_6H_5, 4-$NO_2C_6H_4$, 2-OHC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, C_6H_5CHCH, 4-$CH_3C_6H_4$, C_8H_{13}. R^1 = H, CH_3, C_2H_5, C_6H_5

Scheme 1.1.4 Oxidation of alcohols using ionic liquid-supported selenium **15** in presence of H_2O_2

1.1.2.3 Ionic liquid-supported iodobenzene and hypervalent iodine reagents

Hypervalent iodine reagents have received great interest in organic synthesis in recent years as they are used to carry out several organic transformations under metal free conditions as well as in the presence of transition metals and their reactivity can be tuned accordingly.[70-73] With their increasing use in organic transformations, isolation of co-product and reuse of these reagents is a great challenge for synthetic chemists.

1.1.2.3.1 Ionic liquid-supported iodobenzene

To improve synthetic utility of hypervalent iodine reagents, Togo and co-workers have designed and synthesized several ionic liquid-supported iodobenzenes (Figure 1.1.1).[74-76]

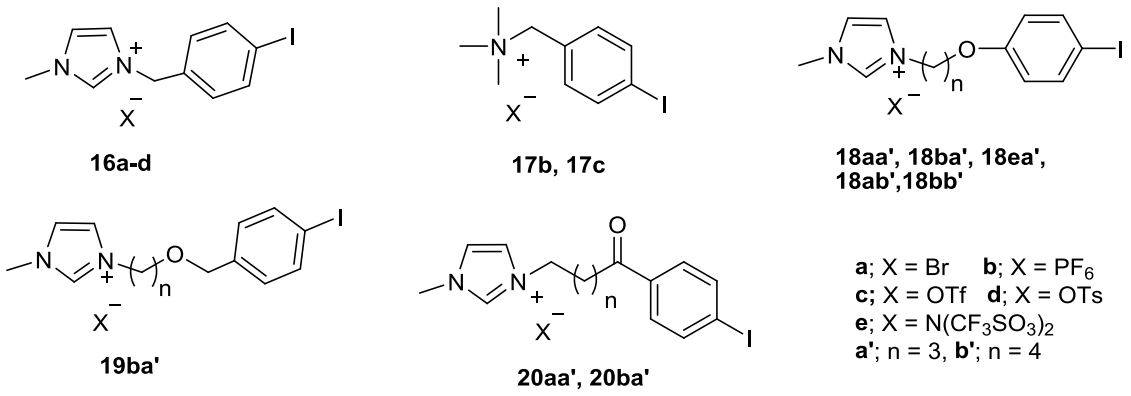
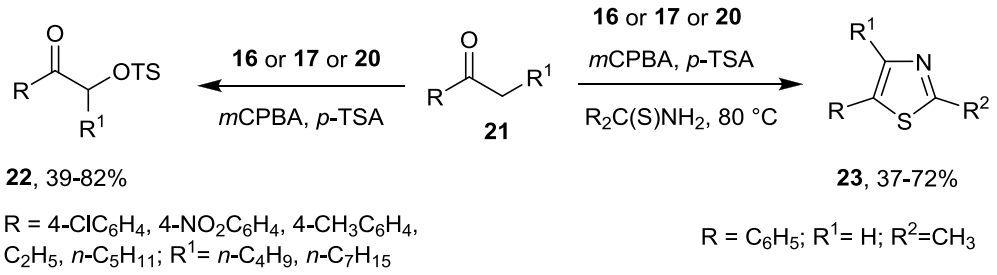


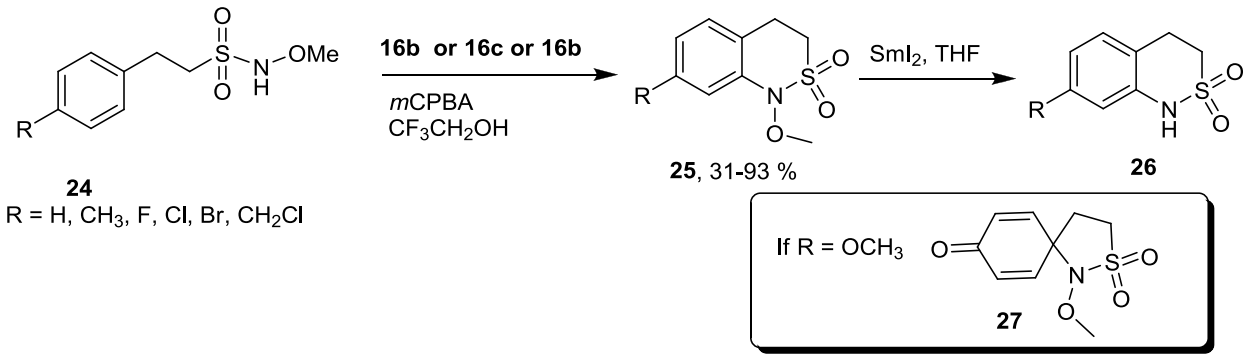
Figure 1.1.1 Structures of various ionic liquid-supported iodobenzenes

Hydroxyl(tosyloxy)iodobenzene (HTIB) also known as Koser's reagent is an excellent reagent for the synthesis of α-tosyloxy ketones from ketones.[77] Togo *et al.* developed an alternative procedure, in which various ketones **21** were converted into corresponding α-tosyloxy ketones **22** using *m*-chloroperbenzoic acid (*m*CPBA) and *p*-toluenesulfonic acid (*p*-TsOH) in the presence of a catalytic amount of ionic liquid-supported iodobenzenes **16a**, **17**, or **20** (Scheme 1.1.5).[76] The scope of this procedure was further extended by synthesizing 2-methyl-5-phenylthiazole **23** directly from **21** without isolating **22** (Scheme 1.1.5). The ionic liquid-supported iodobenzenes were recovered and reused for up to three cycles.



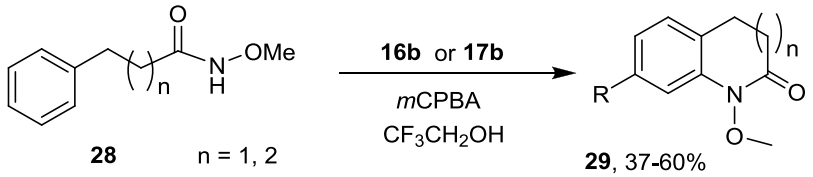
Scheme 1.1.5 Synthesis of α-tosyloxy ketones and thiazoles using ionic liquid-supported iodobenzenes

Inspired by the *in-situ* formation of Koser's reagent, Togo and his group developed an efficient cyclization protocol for the synthesis of *N*-methoxy-3,4-dihydro-2,1-benzothiazine -2,2-dioxide derivatives **25** (Scheme 1.1.6).[74] The ionic liquid-supported iodobenzenes (**16b**, **16c** and **17b**) in the presence of *m*CPBA and *p*-TsOH catalyzed the cyclization of *N*-methoxy-2-arylethanesulfonamide derivatives **24** to give **25**. Among various ion supported-iodobenzenes studied in the synthesis of **25**, **16b** and **16c** were found to be the more efficient than **16a** and **16d**. Replacing *p*-TsOH with trifluoroethanol (TFE) gave better yields of **25** in a shorter period of time. Compound **25** was further reduced to **26** using samarium iodide, however, *p*-methoxy substituted **24** resulted in spiro-sultam derivatives **27**. Recycling of ionic liquid-supported iodobenzenes showed that the reagents could be recycled and reused for at least five cycles.



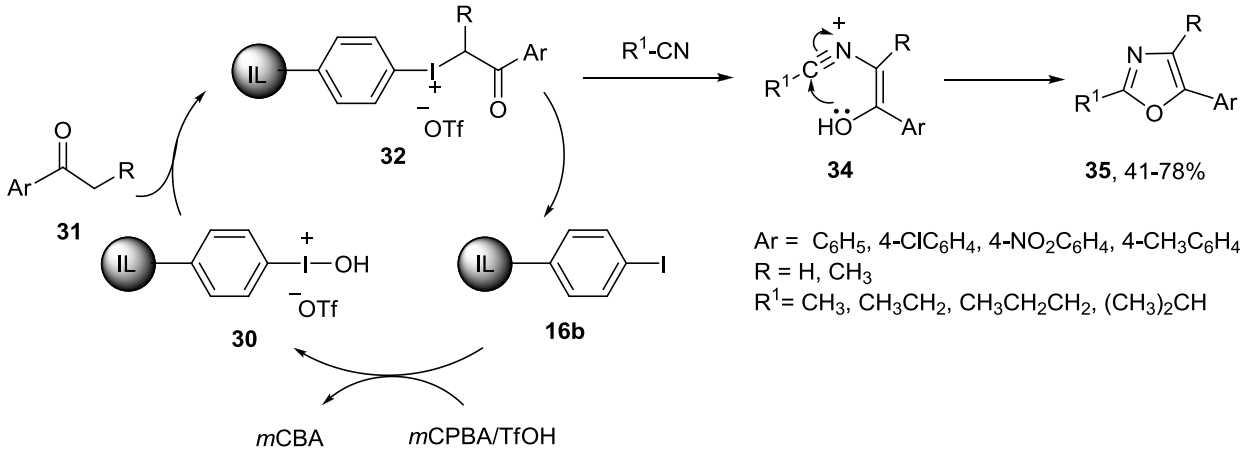
Scheme 1.1.6 Cyclization of sulfonamide **24** using **16**

Same group further explored application of **16b** or **17b** for the cyclization of *N*-methoxy-3-phenylalkanamide **28** to **29** (Scheme1.1.7). Excellent yields of **29** were obtained, and the work-up procedure was quite simple.



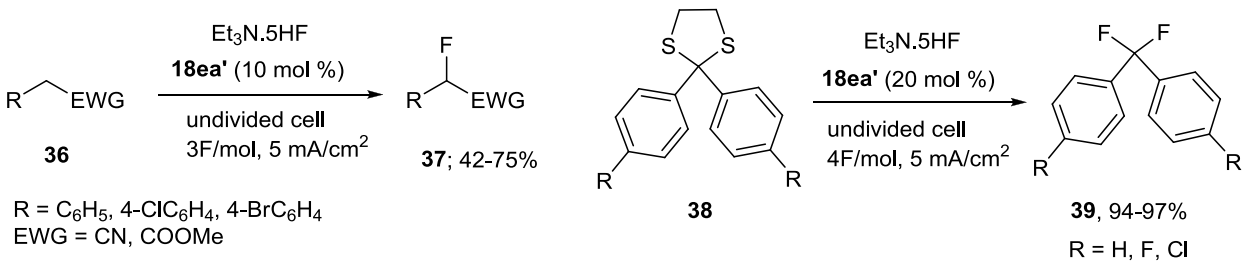
Scheme 1.1.7 Cyclization of *N*-methoxy-3-phenylalkanamides using **16** or **17**

Togo group also compared ionic liquid-supported iodobenzene **16b** with polymer-supported iodobenzene for the synthesis of 2,4,5-trisubstituted oxazoles **35** from corresponding ketones **31** and found that the catalytic activity of ionic liquid-supported iodobenzene is superior over polymer-supported iodobenzene.[75] The reaction proceeded *via in situ* generation of trivalent aryliodonium species **30**, which in turn reacted with aryl ketones **31** to form β-keto-aryliodonium salt **32**. Addition of nitrile **33** to **32** followed by an intermolecular cyclization gave desired oxazoles **35** (Scheme 1.1.8).



Scheme 1.1.8 Proposed mechanism for the synthesis of oxaoles using ionic liquid-supported iodobenzene **16b**

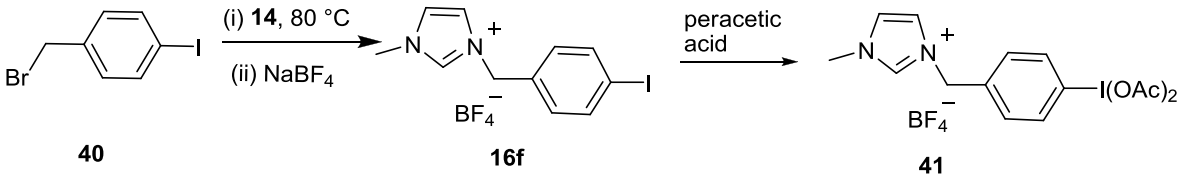
Fuchigami group has reported indirect electrochemical fluorination of active methylene group containing compounds, employing ionic liquid-supported iodobenzene **18ea'** as a mediator and $Et_3N.HF$ as fluoride source.[78] Fluorination of **36**, in the absence of **18ea'** (direct electrochemical fluorination) engendered anode passivation and resulted in poorer yields. Whereas employing **18ea'** as mediator (indirect electrochemical fluorination) significantly enhanced the product yield and overcame the anode passivation (Scheme 1.1.9). The reason for enhanced activity was attributed to the lesser mobility of ionic liquid-supported iodobenzene **18ea'** in $Et_3N.HF$, which enabled the fluorination effectively. The procedure was further extended to cyclic dithioacetals **38** to get corresponding fluorinated product **39** (Scheme 1.1.9). Simple ether extraction gave the products in pure form. It was found that **18ea'** remains intact with $Et_3N.HF$ and can be reused several times without apparent loss in its activity.



Scheme 1.1.9 Electrochemical fluorination using ionic liquid-supported iodobenzene **18ea'**

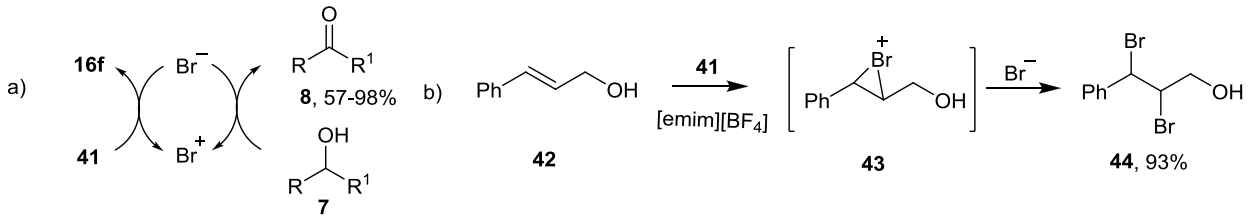
1.1.2.3.2 Ionic liquid-supported iodobenzene diacetate

Zhang group synthesized ionic liquid-supported iodobenzene diacetate **41** by reacting 4-iodobenzylbromide **40** with 1-methylimidazole **14** at 80 °C followed by anion exchange with BF_4^- and oxidation with peracetic acid (Scheme 1.1.10).[79] They further explored the application of **41** for the oxidation of alochols **7** to ketones **8** in ionic liquid [emim][BF_4]. The oxidation of alcohols **7** is believed to be catalyzed by some excess bromide ions present in the [emim][BF_4] ionic liquid (Scheme 1.1.11).



Scheme 1.1.10 Synthesis of ionic liquid-supported iodobenzene diacetate **41**

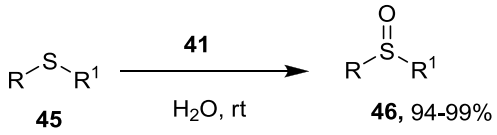
The investigators believed that bromide ions were oxidized by the ionic liquid-supported reagent **41** to form an extremely reactive bromonium ion (Br^+) intermediate which then oxidized the alcohol to its corresponding carbonyl compound. Formation of 2,3-dibromo-3-phenyl propanol **44** from cinnamyl alcohol instead of cinnamaldehyde supported formation of Br^+ ions in the reaction mixture (Scheme 1.1.11). The method provides a high degree of selectivity along with easy workup and the reusability of the reagent. By comparing the reactivities of **41** with $PhI(OAc)_2$, it was found that **41** gives better yields in shorter reaction time. The improved activity is attributed due to the electron withdrawing nature of imidazolium ions. Additionally, the presence of the [emim][BF_4] solvent is believed to have prevented the over oxidation of primary alcohols to carboxylic acids.



Scheme 1.1.11 a) Oxidation of alcohols to carbonyl compounds using **41** b) Reaction of cinnamyl alcohol with **41**

Qian *et al.* reported oxidation of sulphides **45** to sulfoxides **46** using ionic liquid-supported iodobenzene diacetate **41** (Scheme 1.1.12).[80] Reagent **41** selectively oxidized sulfides **45** to the corresponding sulfoxides **46** in excellent yields at room temperature with high tolerance of various functional groups such as ester, nitrile, methoxy, hydroxyl and alkenes. Of the various solvents screened for the reaction, water was found to be the best choice in terms of the yield and

reaction time. It is believed that the phase transfer property of reagent **41** facilitated the solubility of substrates in water and thus accelerated the reaction.

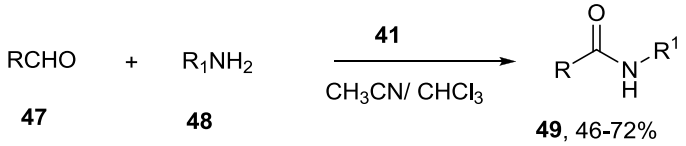


R = C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-$OCH_3C_6H_4$, 4-$(CH_3)_2CHC_6H_4$, $CH_3(CH_2)_3$, $C_6H_5CH_2$, 2-naphthyl

R^1 = C_6H_5, $C_6H_5CH_2$, CH_3, $CH_3(CH_2)_3$, CH_2CHCH_2, $(CH_2)_2OH$, $(CH_2)_2CN$

Scheme 1.1.12 Oxidation of sulphides to sulfoxides using ionic liquid-supported iodobenzene diacetate **41**

Bao group demonstrated oxidative amidation of aldehydes using **41** (Scheme 1.1.13).[81] Although, the yield of amides **49** were found to be lower than those obtained by the conventional reagent $PhI(OAc)_2$ but easy separation of products and recyclability were inherent advantages of this protocol.

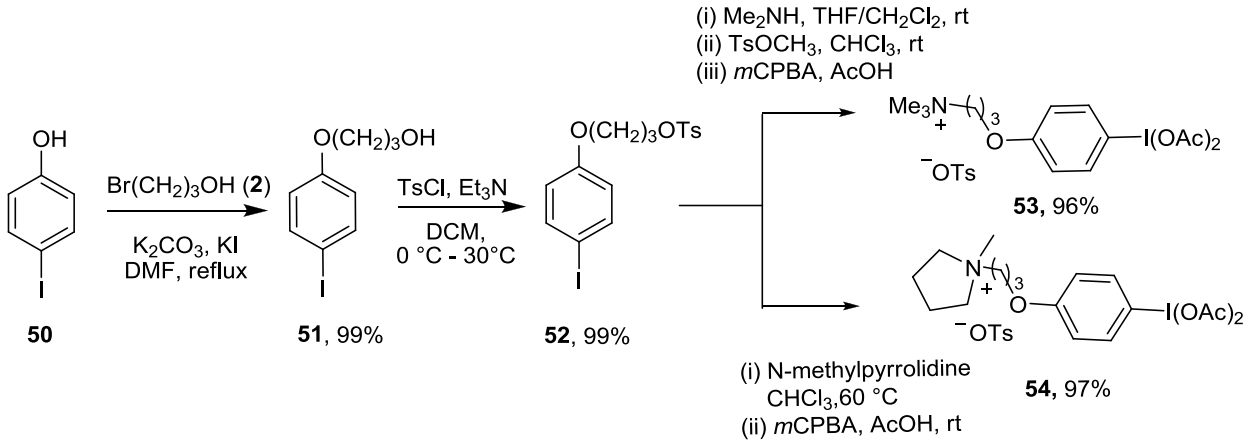


R = C_6H_5, 4-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 3,4,5-$(OCH_3)_3C_6H_2$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 1-naphthyl

R^1 = $CH_3(CH_2)_2$, $CH_3(CH_2)_3$, $C_6H_5CH_2$

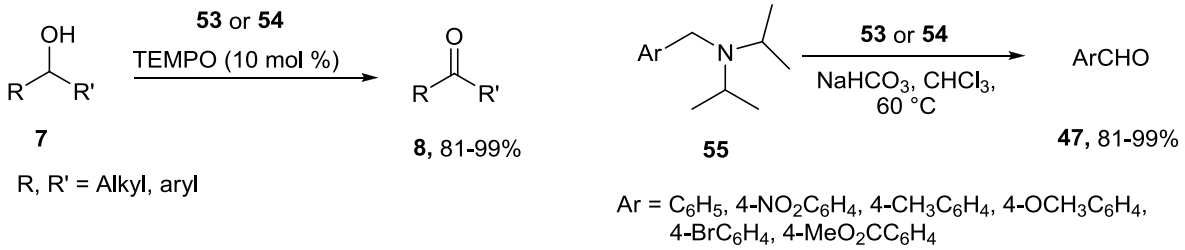
Scheme 1.1.13 Synthesis of amides from aldehydes and amines using ionic liquid-supported iodobenzene diacetate **41**

Togo and co-workers synthesized new class of ionic liquid-supported iodobenzene diacetates **53** and **54** from 4-iodophenol as shown in scheme 1.1.14.[82] The reaction of 4-iodophenol **50** with 1-bromo-3-propanol **2** in the presence of K_2CO_3 and KI afforded **51**, which upon tosylation gave **52**. Reaction of **52** with *N*-methylpyrrolidine followed by oxidation with *m*CPBA gave **54** in excellent yields. In an approach, reaction of **52** with dimethylamine followed by methylation with $TsOCH_3$ and controlled oxidation with *m*CPBA gave **53** in excellent yields (Scheme 1.1.14).



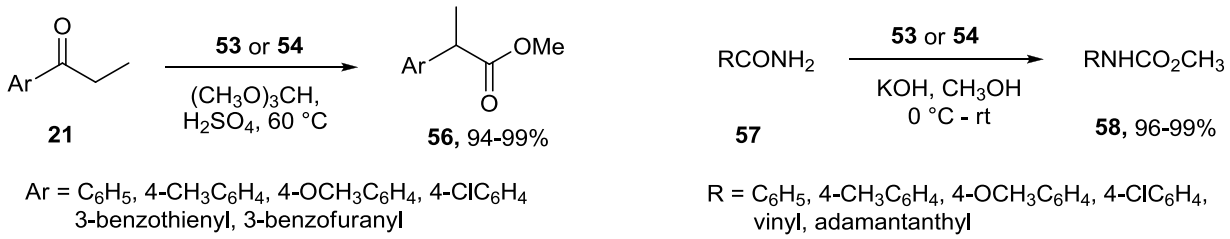
Scheme 1.1.14 Synthesis of ionic liquid-supported iodobenzene diacetates **53** & **54**

Reagents **53** and **54** were used for the oxidation of alcohols **7** to carbonyl compounds **8** in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and oxidation of *N*,*N*-diisopropylbenzylamines to aromatic aldehydes (Scheme 1.1.15).



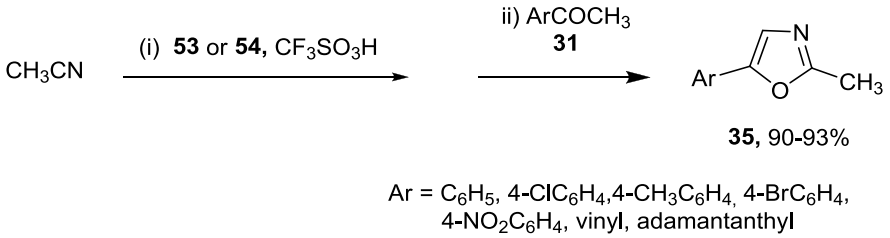
Scheme 1.1.15 Oxidation of alcohols and benzylamines using ionic liquid-supported iodobenzene diacetates **53** and **54**

The reaction of aryl propiophenones **21** with **53** or **54** under acidic conditions underwent 1,2-rearrangement to give methyl-2-arylpropanoates **56** (Scheme 1.1.16). On the other hand, Hofmann rearrangement of primary amides **57** in the presence of **53** or **54** under basic conditions gave carbamates **58** in excellent yields and high purities.



Scheme 1.1.16 1,2-Rearrangement of propiophenones and Hofmann rearrangement of amides using **53** and **54**

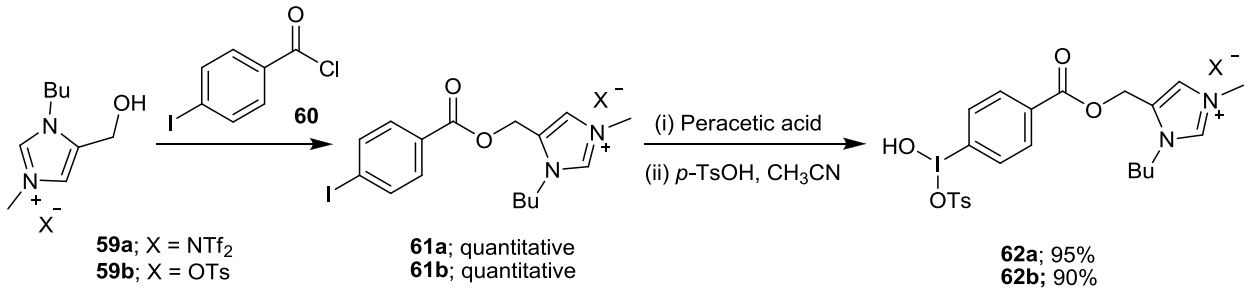
Togo group also developed a new procedure for the synthesis of oxazoles **35** from acetophenones **31** and acetonitrile using **53** or **54** (Scheme 1.1.17). The procedure was quite similar to ionic liquid-supported iodobenzene and *m*CPBA.[75] Use of $PhI(OAc)_2$ in place of **53** or **54** resulted in comparative yields but the purity of the products were poor due to the release of iodobenzene (co-product), and chromatographic separation was required to get pure compounds. On the other hand, when **53** or **54** were used, the products were isolated in high purity by simple ether extraction.



Scheme 1.1.17 Synthesis of oxazoles from nitriles and ketones using ionic liquid-supported iodobenzene diacetates **53** and **54**

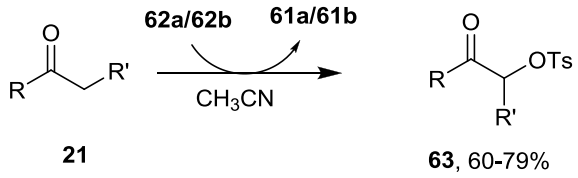
1.1.2.3.3 Ionic liquid-supported HTIB or Koser's salt

Handy and Okello prepared a novel ionic liquid-supported hydroxyl(tosyloxy)iodobenzene (HTIB) or Koser's salt **62** as shown in scheme 1.1.18.[83] Initially, 4-iodobenzoyl chloride **60** was anchored onto the fructose derived ionic liquid alcohol **59**[84, 85] by an ester linkage. Oxidation of **61** with peracetic acid followed by treatment with *p*-TsOH, gave corresponding reagent **62** in good yields.



Scheme 1.1.18 Synthesis of ionic liquid-supported Koser's salt **62**

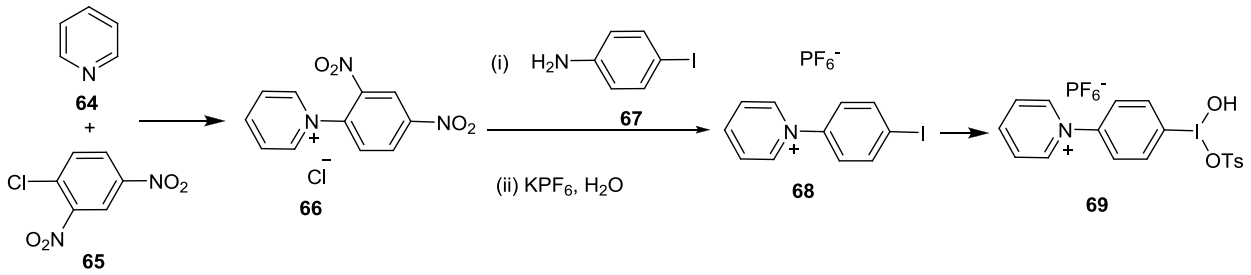
The synthesized ionic liquid-supported Koser's salt was used for the tosyloxyation of ketones (Scheme 1.1.19). The reaction of ketones **21** with **62a** gave tosyloxyketone **63** in good yields. However, chromatographic purification was required to separate the product from the by-product **61a** due to its high solubility in organic solvents such as acetone, ether, ethyl acetate, and dichloromethane. When **62b** in which triflamide ion of **62a** was replaced with harder tosylate ($^-$OTs) ion, tosyloxyketones **63** were isolated by simple ether extraction as the by-product **61b** was less soluble in ether. It is important to note that α-tosylation was faster with **63** compared to Koser's salt due to the electron withdrawing ester linkage.



R = CH_3, CH_3CH_2, C_6H_5, R' = H, CH_3, R-R' = -$(CH_2)_4$-, -$(CH_2)_3$-

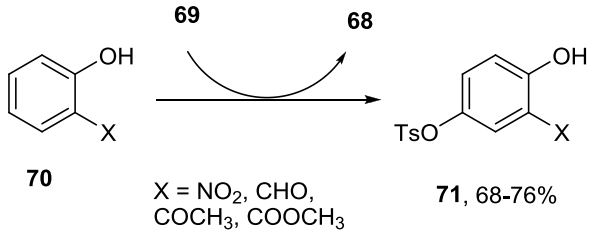
Scheme 1.1.19 Synthesis of α-tosyloxy ketones using ionic liquid-supported Koser's salt **62**

Taking into the account that alteration in the anion or cation may lead to the stability of ionic liquid, Zhang group developed a novel pyridinium salt-supported HTIB **69** (Scheme 1.1.20).[86] Reagent **69** was prepared by using modified Zinckes reaction in three steps. *N*-alkylation of pyridine with 1-chloro-2,4-dinitrobenzene **65** gave **66**, which upon reaction with 4-iodoaniline **66** followed by anion exchange gave **68**. Oxidation of **68** with *m*CPBA followed by the tosylation yielded pyridinum salt-supported HTIB **69** (Scheme1.1.20). Reagent **69** was found to be relatively more stable than previously reported ionic liquid-supported HTIBs.[83]



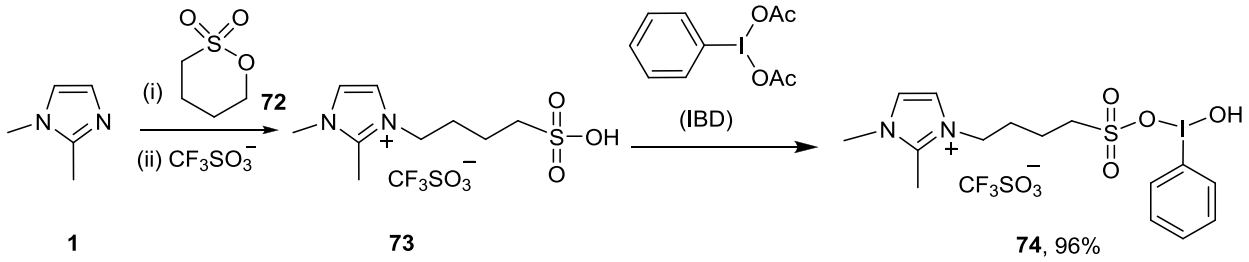
Scheme 1.1.20 Synthesis of pyridinium salt-supported HTIB **69**

Tosyloxylation of various *ortho*-substituted phenolic compounds **70** was explored using **69** (Scheme 1.1.21). The reaction of **69** with phenols bearing electron withdrawing groups at *ortho* positions resulted in desired products **71** but failed to give desired products from simple phenol and electron rich phenols. Reagent **69** can be regenerated from by-product **68** and reused up to 3 cycles without loss in reactivity.



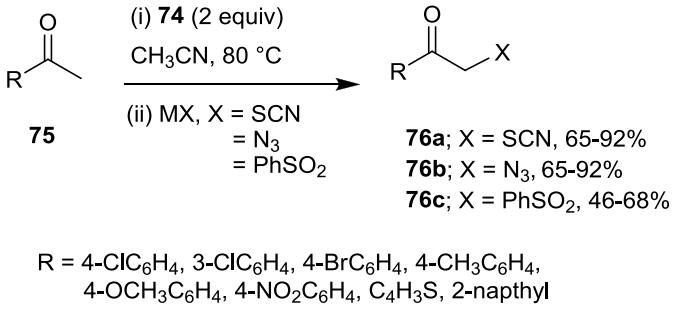
Scheme 1.1.21 Tosyloxylation of phenols using **69**

Recently, we have successfully developed a novel imidazolium based ionic liquid-supported hypervalent iodine reagent **74** and employed it in a 'catch and release' strategy.[87] Synthesis of **74** was achieved by mixing a homogeneous solution of ionic liquid-supported sulfonic acid **73** in CH_3CN with a hot solution of iodobenzene diacetate (IBD) and keeping it at room temperature for one week (Scheme 1.1.22).



Scheme 1.1.22 Synthesis of ionic liquid-supported hypervalent iodine reagent **74**

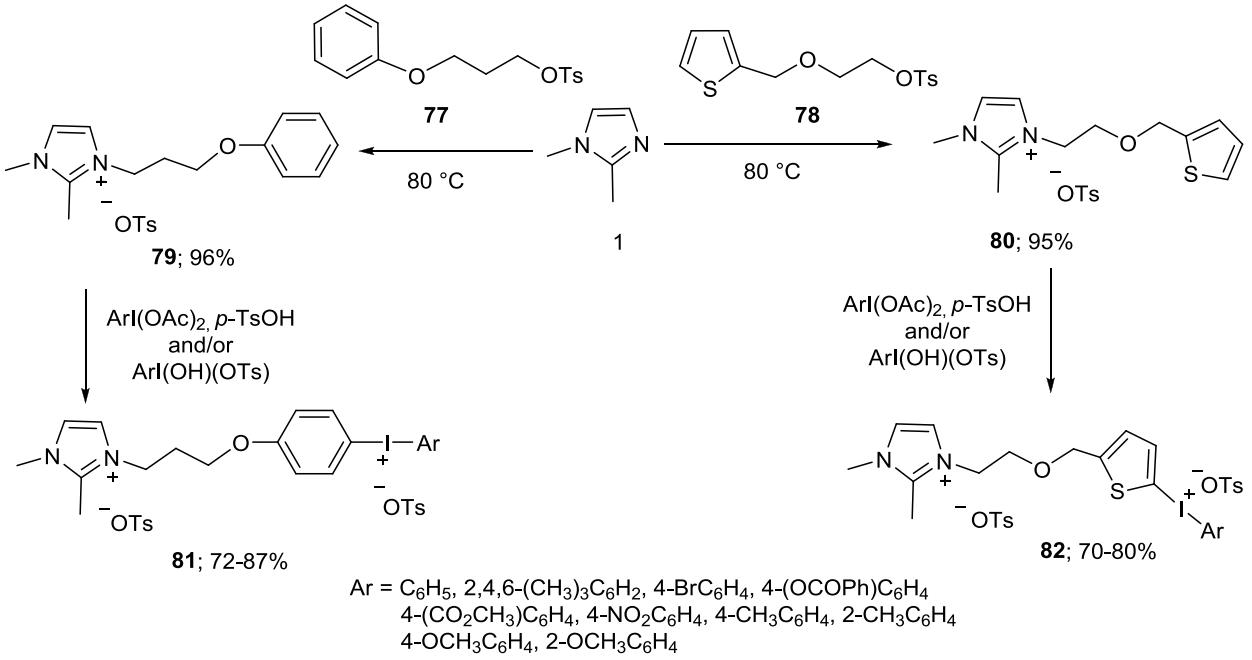
After successfully synthesizing **74**, it was used to develop a chromatographic free protocol for the synthesis of α-substituted acetophenones **76** by first capturing acetophenones **75** on ionic liquid followed by nucleophilic release with KSCN, NaN_3 and $PhSO_2Na$ (Scheme 1.1.23).[87] Small library of α-thiocynato-β-ketones **76a**, α-azido-β-ketones **76b** and β-ketosulfones **76c** have been synthesized in good to excellent yields (46-92%) using this strategy. Superior loading capacity and chromatography-free synthesis are inherent advantages of this process.



Scheme 1.1.23 Synthesis of α-substituted ketones using ionic liquid-supported hypervalent iodine reagent **74**

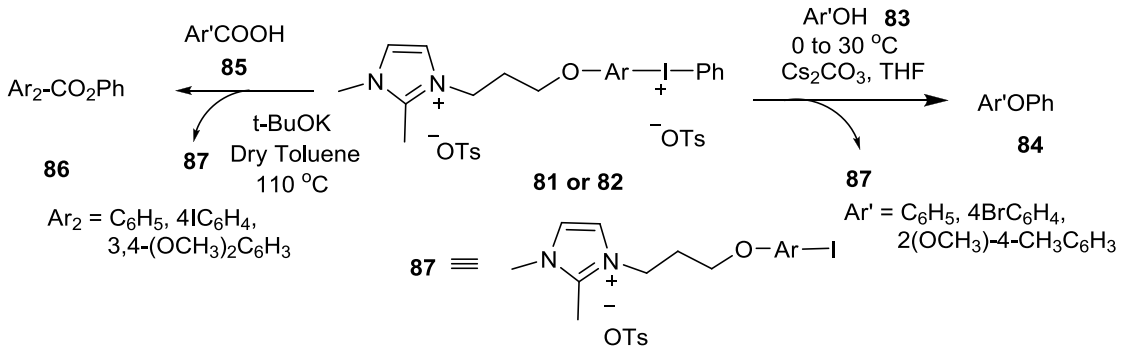
1.1.2.3.4 Ionic liquid-supported diaryliodonium salts

Diaryliodonium salts serves as proficient and potent electrophilic arylating source for the carbon-carbon and carbon-heteroatom bond formation reactions.[88] To deal with the purification, isolation, and loading problems of diaryliodonium salts, recently we have developed new ionic liquid-supported diaryliodonium salts.[89] Electron-rich aryl groups, like alkoxyphenyl and thiophene, have been grafted on ionic liquids for the facile synthesis of ionic liquid-supported diaryliodonium salts as shown in the Scheme 1.1.24. These imidazolium-supported aryls **79** and **80** further reacted with hydroxyl(tosyloxy)iodoarene (HTIA) or (diacetoxyiodo)arenes to give corresponding ionic liquid-supported diaryliodonium salts **81** and **82**. They were isolated in pure form by simple washing with organic solvents like chloroform and tetrahydrofuran, without requiring chromatographic purification; moreover, these salts are quite stable and have not shown any sign of decomposition or loss of reactivity even after one month of storing at 5 °C.



Scheme 1.1.24 Synthesis of ionic liquid-supported diaryliodonium salts

Metal-free electrophilic phenylation of phenols **83** and carboxylic acids **85** was performed using **81** or **82** to give phenyl ether **84** and carboxylic esters **86**, respectively in good yields (Scheme 1.1.25). Products **84** and **86** were isolated simply by evaloparting the reaction solvent followed by extraction with a hexane/ethyl acetate mixture. This left behind the by-product supported on the ionic liquid, which can potentially be reused as a supported reagent in many other organic transformations. Better yields for phenylation were obtained using **81** as compared with **82**.



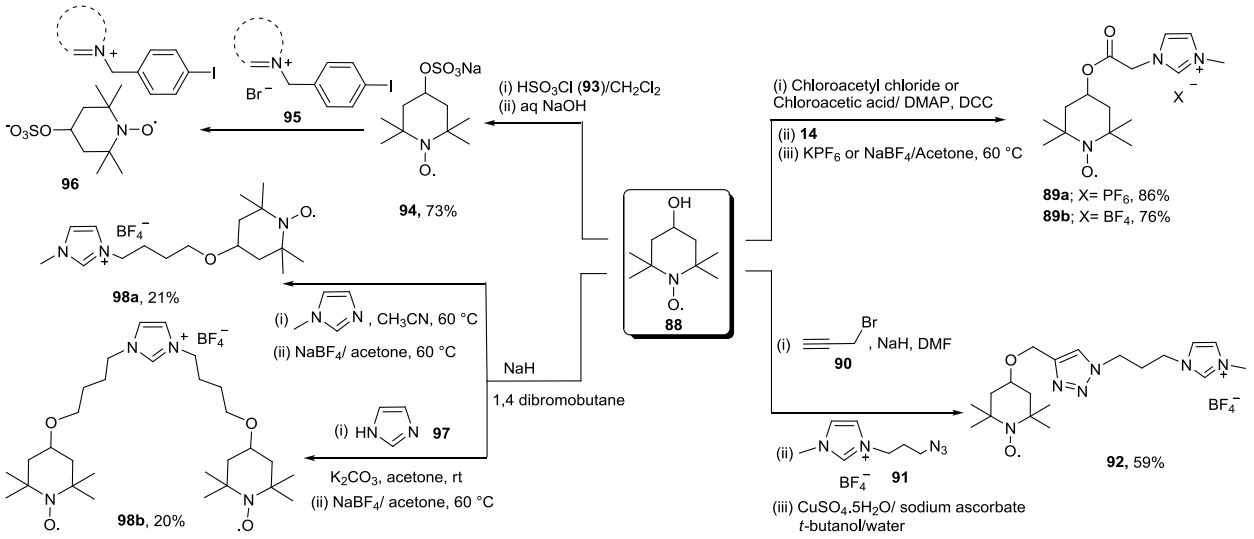
Scheme 1.1.25 Electrophilic phenylation of phenols and carboxylic acids using **81** or **82**

1.1.2.4 Ionic liquid-supported TEMPO

Chemoselective oxidation of alcohols to corresponding carbonyl compounds is an important process in synthetic organic chemistry.[90] TEMPO is widely used co-catalyst along with terminal oxidant for this process due to its non-metallic nature.[91] Although the amount of TEMPO required for the oxidation process is quite less (1-5 mol %), in order to make the whole process cost effective, there is a need to recycle and reuse the co-catalyst. To address the problems associated with recyclability and reusability, TEMPO has been grafted onto various supports.[92]

Wu *et al*. synthesized ionic liquid-supported TEMPO **89** from 4-hydroxy-TEMPO **88** in a two-step process.[93] Coupling of **88** with chloroacetyl chloride or chloroacetic acid followed by quaternization with 1-methylimidazole **14** and anion exchange with KPF_6 or $NaBF_4$ gave **89** in good yields (Scheme 1.1.26). Qian *et al.* also reported the synthesis of various ionic liquid-

supported TEMPO **89b**, **98a** and **98b** by grafting **88** onto an imidazolium ion as shown in scheme 1.1.26.[79] Oxidation of alcohols **7** using **89** along with terminal oxidant sodium hypochlorite ($NaClO_4$) in a biphasic mixture of [bmim][PF_6]-water gave excellent yield (86-96%) of carbonyl compounds **8** (Scheme 1.1.27, method A).[93] Comparable catalytic activity was observed for **89a** to that of TEMPO and efficient recyclability and reusability of **89** were inherent advantages of this process.

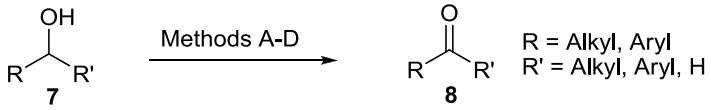


Scheme 1.1.26 Synthesis of various ionic liquid-supported TEMPO

Tong group developed a heterogeneous method for the oxidation of alcohols **7** to carbonyl compounds **8**, by impregnating **89b** and CuCl on to various silica supports including SiO_2, MCM-41 and SBA-15.[94] The heterogeneous catalyst has shown superior catalytic activity compared to ionic liquid-TEMPO/CuCl system (Scheme 1.1.27, method B). Fall *et al.* reported a new ionic liquid-supported TEMPO **92** *via* a click reaction as shown in scheme 1.1.26.[95] Reaction of **88** with propargyl bromide **90** in DMF followed by click reaction with azido functionalized ionic liquid **91** in the presence of $CuSO_4$/sodium ascorbate gave **92** in moderate yield (59%). The catalytic activity of **92** for the oxidation of alcohols **7** was evaluated in various ionic liquids such as [hmim][BF_4], [hmim][Cl], [bmim][BF_4] & [omim][Cl]. Among all these

ionic liquids, [hmim][BF_4] proved to be the solvent of choice for this reaction (Scheme 1.1.27, method C).

Qian *et al.* also studied catalytic activity of **89b** and **98** in the oxidation of alcohols **7** using a stochiometric amount of terminal oxidants like peracetic acid, IBD, [dibmim][BF_4], sodium hypochlorite, and iodine (Scheme 1.1.27, method D). Superior catalytic activity was observed for **98b** due to its higher loading capacity, where as **89b** and **98a** showed similar catalytic activity to TEMPO. Of the various terminal oxidants that were screened, [dibmim][BF_4] gave the best result and this may be attributed to its complete solubility in water.

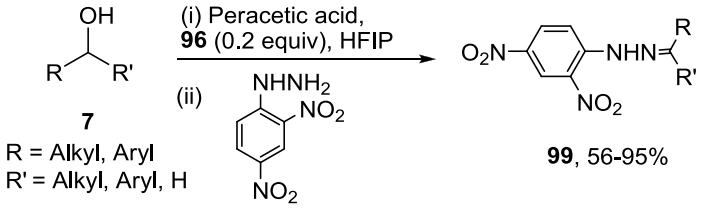


Method A: **89a** (1 mol %), NaOCl (1.2 equiv), KBr (10 mol %), pH = 8.6, [bmim][PF_6], H_2O, 0 °C, 86-96%
Method B: **89a**/$CuCl_2/SiO_2$, O_2, *n*-Octane, 70 °C
Method C: **92** (10 mol %), IBD (1.1 equiv), [hmim][BF_4], H_2O, 30 °C, 86-99%
Method D: **89b**, **98a** or **98b** (5 mol %), [dibmim][BF_4], H_2O, 30 °C, 78-99%

Scheme 1.1.27 Oxidation of alcohols using ionic liquid-supported TEMPO

Zhdankin and group have synthesized a bifunctional hybrid-type ionic liquid-supported TEMPO **96** (Scheme 1.1.26).[96] For the synthesis of **96**, iodobenzene was integrated to the cationic part of ionic liquid by quaternization of 1-methylimidazole or pyridine with 1-(bromomethyl)-4-iodobenzene to generate ionic liquid **95**. TEMPO was introduced as the anion part of ionic liquid by anion metathesis of **95** with Na[TEMPO-OSO_3] **94**. Zhdankin *et al.* has further studied oxidation of alcohols **7** to hydrazone derivatives **99** using catalytic amount of **96** along with stoichiometric amount of peracetic acid (Scheme 1.1.28).[96] Remarkable rate-enhancing effect has been noticed when 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was used as co-solvent in this oxidation process. Due to the presence of both functionalities (iodobenzene and TEMPO) on the same moiety (**96**), oxidation process is believed to be intramolecular rather than intermolecular.

Superior catalytic activities, no apparent loss in catalytic activity even after five cycles, and easy separation of products from the reaction mixture are advantages of this process.

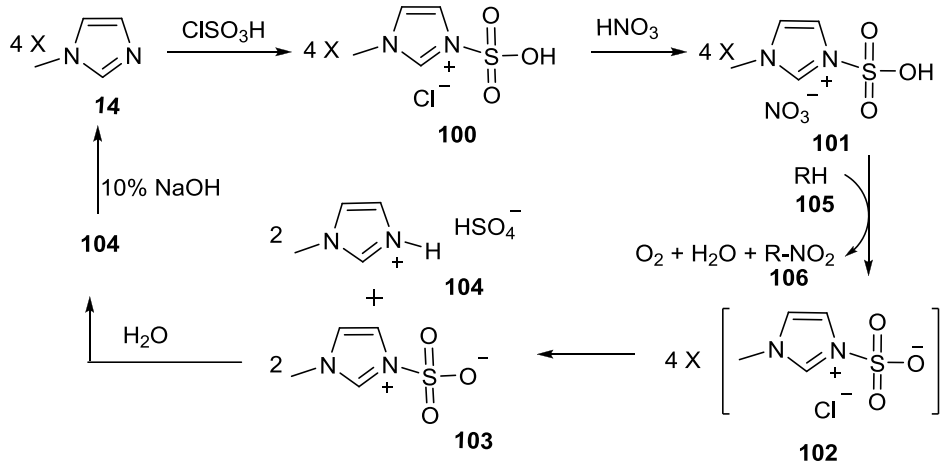


Scheme 1.1.28 Conversion of alcohols to hydrazones **99** using ionic liquid-supported TEMPO **96**

In all these cases, the biphasic system offered easy isolation of products from the reaction mixture, and ionic liquid-supported TEMPO could be reused several times without much loss of catalytic activity. These systems offer clean, convenient and environmentally benign method for the selective oxidation of alcohols.

1.1.2.5 Ionic liquid-supported nitrating reagent

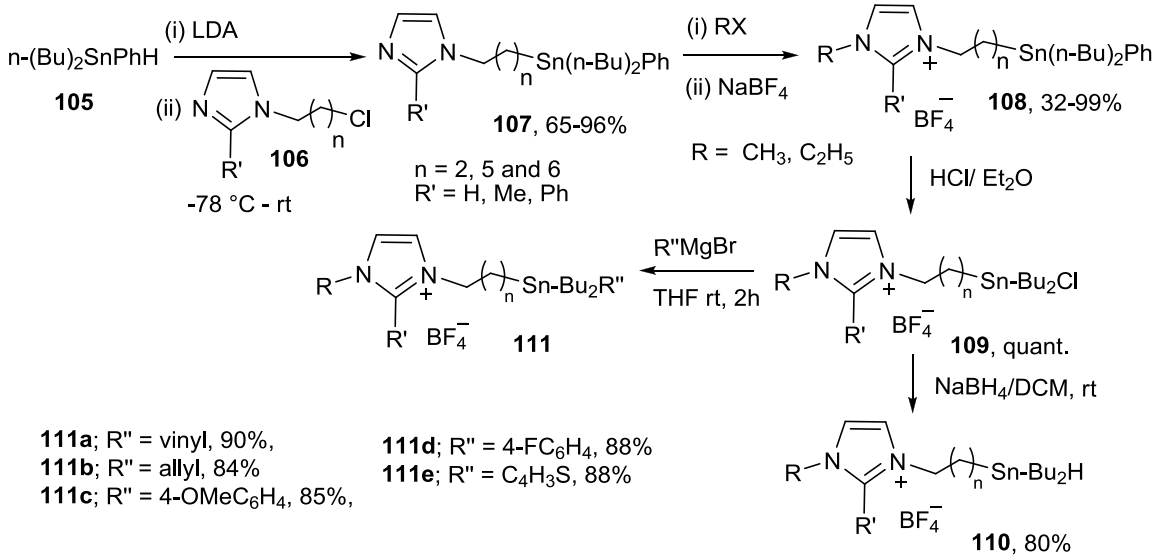
In an interesting study, Zolfigol *et al.* reported a novel bifunctional ionic liquid **101** having sulfonic acid and nitrate ion.[50] Synthesis of **101**, was achieved by the reaction of 1-methylimidazole **14** with chlorosulfonic acid to give **100** followed by addition of nitric acid to **100** under solvent free conditions (Scheme 1.1.29).



Scheme 1.1.29 Synthesis of ionic liquid-supported reagent **101** and aromatic nitration using **101**

Nitration of aromatic compounds was studied using **101** and a wide range of aromatic compounds **105** were nitrated under mild conditions in good to excellent yields. Successful nitration of aniline and a significant decrease in the yield on employing free radicals scavengers (iodine, butylated hydroxytoluene) are clear evidence that nitration occurs due to the generation of NO_2 radical rather than NO_2^+ ion. Moreover, 21% weight loss on heating the reagent **101** from 60 to 160 °C and formation of $Cu(NO_3)_2$ by the reaction of copper metal during the heating process are some other evidences that support that this nitration process proceeds *via* NO_2 radical rather than NO_2^+. The reagent **101** can be regenerated and reused efficiently (Scheme 1.1.29).

1.1.2.6 Ionic liquid-supported organotin reagents

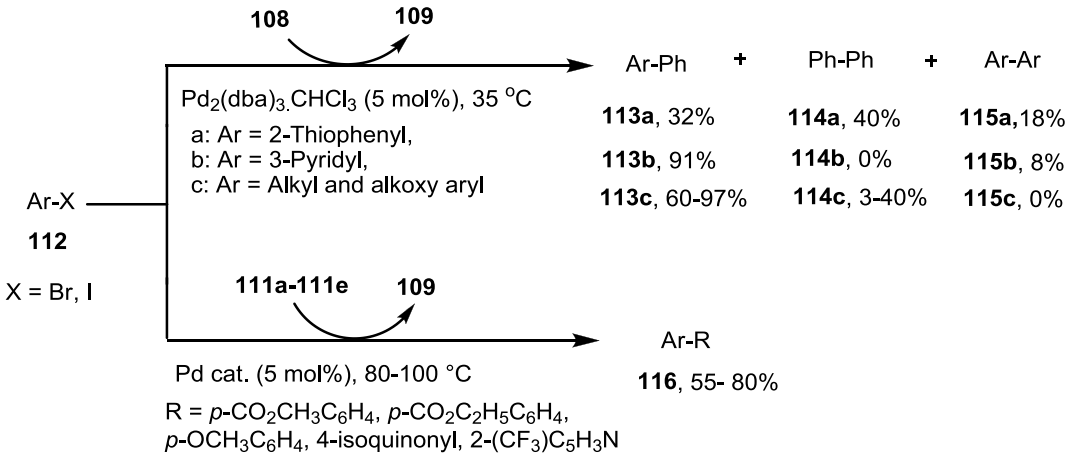


Scheme 1.1.30 Synthesis of ionic liquid-supported organotin reagents

Legoupy and co-workers synthesized ionic liquid-supported organotin reagents **108-111**.[97-100] Substitution reaction of **106** with tributyltin lithium produced **107**, which upon reaction with alkyl iodide gave desired organotin reagent **108**. Reaction of **108** with hydrochloric acid in ether produced ionic liquid-supported chlorostannane **109** that on further reaction with alkyl/arylmagnesium bromides resulted in liquid-supported organotin reagents **111a-e** (Scheme

1.1.30). Different functional groups, such as vinyl, allyl, methoxy, and fluoro, were well tolerated under these conditions.

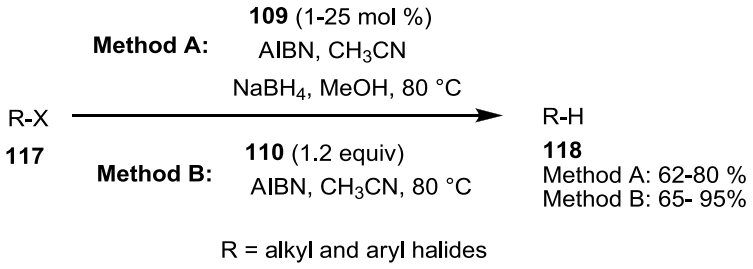
The investigators further studied Stille cross coupling of aryl halides **112** using **108-111**. Dibutyldiphenylstannane was obtained by the reaction of iodobenzene with **108** in the presence of $Pd(PPh_3)$ and CuI instead of expected biphenyl **114**. After optimizing the reaction conditions, it was found that use of $Pd_2(dba)_3.CHCl_3$ gave the desired biphenyl **114** in high yields even in the absence of CuI.[97] Legoupy *et al*. further studied the use of the **108** in other Stille cross coupling reactions using various aryl halides **112** including 4-methoxyiodobenzenes, 3-bromo/iodopyridine and 2-iodothiophene.[99, 100] In most of the cases, along with desired product **113** (Ar-Ph), unwanted homocoupling products **114** and **115** (Ph-Ph, Ar-Ar) were also formed as shown in scheme 1.1.31. The procedure was further extended to various ionic liquid-supported organotin reagents **111a-e**. Surprisingly, there was no homocoupling products formation observed when **111a-e** were reacted with aryl bromides (Scheme 1.1.31).[99] The reagents could be easily regenerated from co-product **109** by the addition of PhLi in THF.



Schem 1.1.31 Stille cross coupling reaction using ionic liquid-supported tin reagent

Legoupy and co-workers also reported the reduction of alkyl and aryl halides using ionic liquid-supported organotin reagents **109** and **110**.[98] Reaction of **109** with $NaBH_4$ resulted in the

formation of ionic liquid-supported stannane **110** in 80% yield (Scheme 1.1.30). A variety of alkyl and aryl halides **117** were reduced to the corresponding hydrocarbons **118** in high to excellent yields using **109** in the presence of AIBN and $NaBH_4$ (Scheme 1.1.32, method A). AIBN was believed to enhance the formation of organotin radical, thus promoting the reduction of alkyl and aryl halides. Similarly, alkyl and aryl halides were reduced to **118** using **110** in the presence of AIBN (Scheme 1.1.32, method B). Reagent **110** was shown to have excellent tolerance to a variety of functional groups including keto and ester. The counter anion (I^-/BF_4^-) of the reagent also played a key role in the yield of the reaction as reagent **110** with counter anion I^- showed enhanced reactivity.



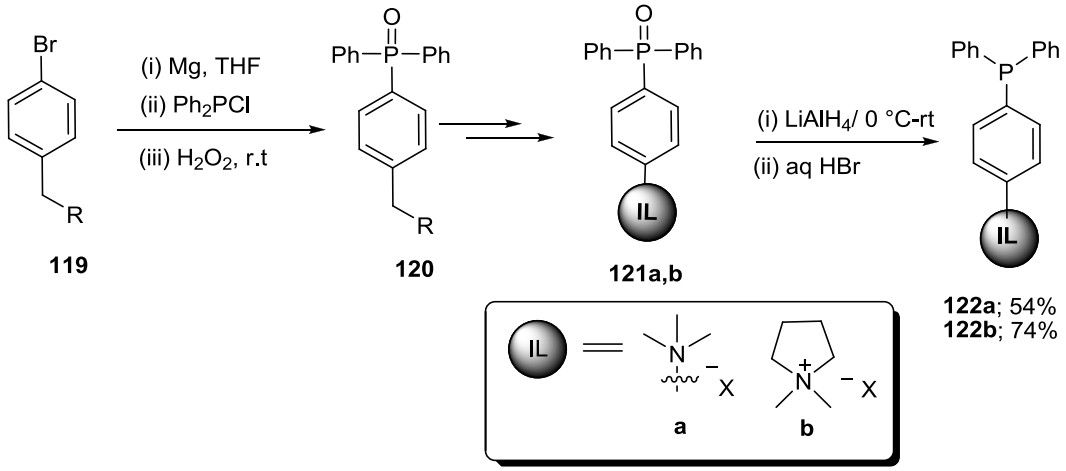
Scheme 1.1.32 Reduction of alkyl/aryl halides using ionic liquid-supported organotin reagents **109** and **110**

1.1.2.7 Ionic liquid-supported phosphine derivatives

1.1.2.7.1 Ionic liquid-supported triphenylphosphine

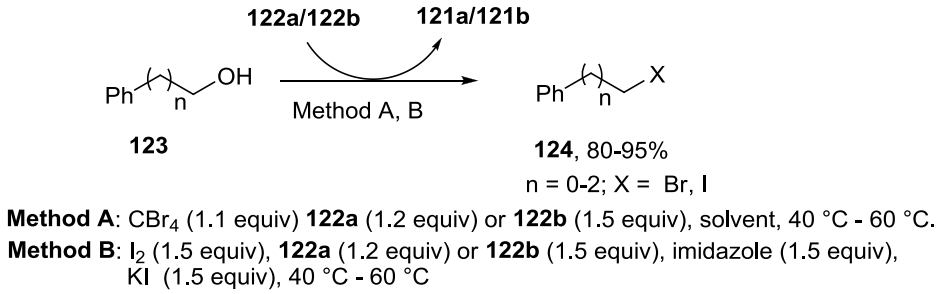
Triphenylphosphine (Ph_3P) is widely used as a ligand in transition metal catalyzed coupling reactions. Removal of Ph_3P and Ph_3PO (co-product in some reactions) from the reaction mixture is very troublesome and requires repetitive column chromatography. Keeping this in view, Togo *et al.* synthesized ionic liquid-supported triphenylphosphines **122**.[101] The reagents **122a** and **122b** were prepared from substituted aryl bromides **119** as shown in scheme 1.1.33. *In situ* generation of Grignard reagent from **119**, followed by reaction with Ph_2PCl and oxidation yielded phosphine oxide **120**, which was anchored onto an ionic liquid by quaternization of

tertiary amines to give **121**. Reduction of **121** using $LiAlH_4$ followed by acidification with HBr gave reagents **122a** and **122b** in good yields (Scheme 1.1.33).



Scheme 1.1.33 Synthesis of ionic liquid-supported triphenylphosphine

Reagent **122a**, **122b** and Ph_3P were screened independently for the halogenation of alcohols **123** to corresponding halides **124** (Scheme 1.1.34).[101, 102] When **122** was employed as a reagent, products were isolated in good yields with high purity (>70%) by simple filtration and by-products **121a** and **121b** were recovered in over 90% yield. The recovered **121** were again reduced to **122** and reused. On the other hand, when Ph_3P was employed, the purity of the products **124** was quite less (<45%) and they were purified by column chromatography.



Scheme 1.1.34 Halogenation of alcohols using **122**

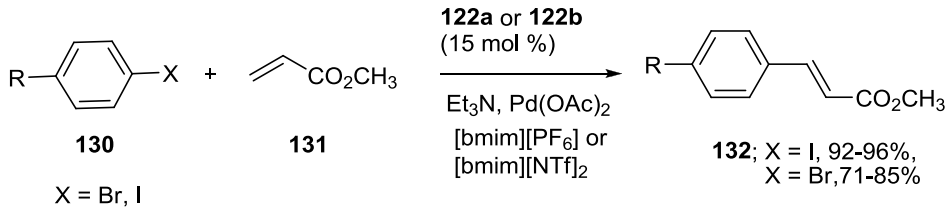
Togo group further explored application of **122** in Mitsunobu and amide bond formation reactions (Scheme 1.1.35). Carboxylic acids **125** were converted to corresponding esters **126** by reaction with alcohols **126** in the presence of **122** in excellent yields, and the ionic liquid-supported phosphine oxide **121** was recovered. Similarly, amides **129** were obtained in excellent yields (83-99%) and high purity by the reaction of **125** with amines **128** in the presence of **122b**.

R = 4-$OCH_3C_6H_4(CH_2)_2$
R' = $C_6H_5(CH_2)_2$

R = C_6H_5, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, $C_6H_5CHCH_2$, 4-$ClC_6H_4CHCH_2$, 4-$CH_3C_6H_4CHCH_2$, $CH_3(CH_2)_7CHCH_2$, $CH_3(CH_2)_{15}CHCH_2$, 2-napthyl, 2-benzofuryl, 2-indolyl,2-benzothienyl.
R'R"NH = $C_6H_4(CH_2)_3NH_2$, $CH_3(CH_2)_{11}NH_2$, 4-$CH_3C_6H_4NH_2$, morpholine, cyclohexylamine, piperidine.

Scheme 1.1.35 Ester and amide bond formation using **122**

The success of these reactions encouraged Togo group to examine **122** as ligands in the Mizoroki-Heck and Sonogashira coupling reaction.[101] A comparative study performed for the reuse of the catalyst for these coupling reactions in the absence and presence of **122** showed that when **122** was employed not only the rate of the reactions were dramatically accelerated but $Pd(OAc)_2$ and CuI could be recovered and reused several times (Scheme 1.1.36). The coupling products **132** and **134** were isolated in pure form by simple extraction with appropriate organic solvents.



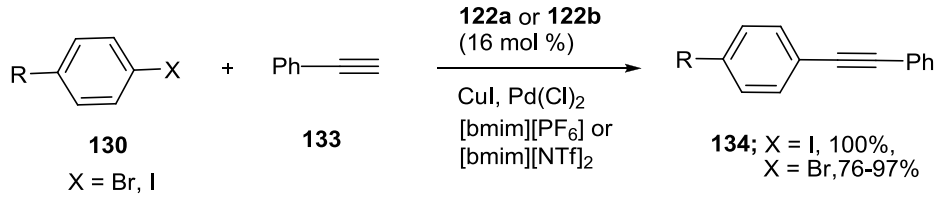
130

X = Br, I

131

132; X = I, 92-96%,
X = Br,71-85%

Solvent	Catalyst	Reuse 0	1	2	Solvent	Catalyst	Reuse 0	1	2
[bmim][PF_6]	-	88	50	14	[bmim][$NTf]_2$	-	92	50	27
	122a	90	91	76		**122a**	95	96	90
	122b	95	83	81		**122b**	96	96	95



130

X = Br, I

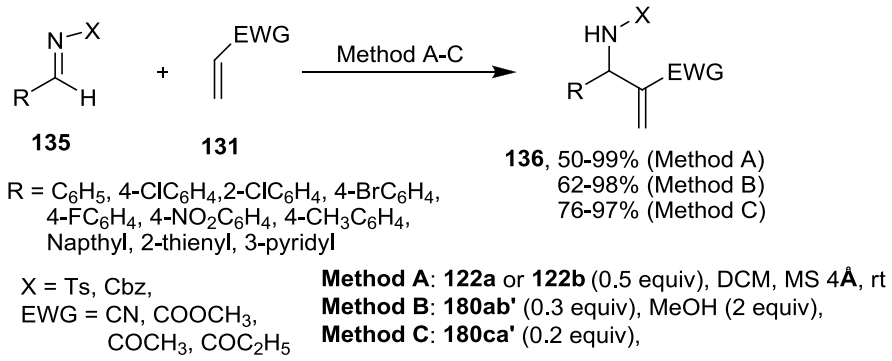
133

134; X = I, 100%,
X = Br,76-97%

Solvent	Catalyst	Reuse 0	1	2	Solvent	Catalyst	Reuse 0	1	2
[bmim][PF_6]	-	75	68	40	[bmim][$NTf]_2$	-	75	73	52
	122a	100	100	97		**122a**	100	100	100
	122b	100	100	100		**122b**	100	100	100

Scheme 1.1.36 Mizoroki-Heck and Sonogashira coupling reactions in the absence and presence of **122**

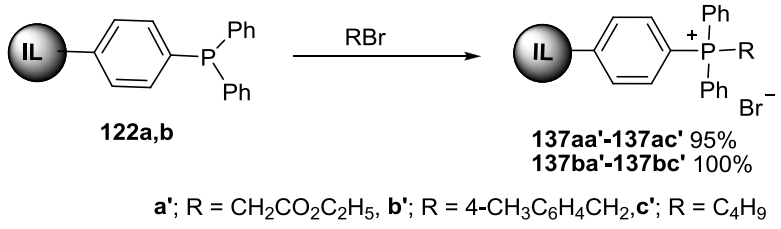
Togo group also developed an efficient procedure for Aza-Morita-Baylis-Hillman reaction using **122** as a reusable catalyst.[102] Various *N*-benzylidinecarbamate imines and *N*-tosylarylimines **135** were reacted alkenes **131** in the presence of **122a** and **122b** to give corresponding Baylis-Hillman adducts **136** in good to excellent (50-99%) yields and high purity (Scheme 1.1.37). Among various solvents that were screened, best yield of **136** was obtained in CH_2Cl_2. Further increase in the yield and purity was observed when molecular sieves (MS 4Å) were added to the reaction mixture. The increase in the yield of products is attributed to the removal of moisture from **122** by MS 4Å.



Scheme 1.1.37 Aza-Morita-Baylis-Hillman reaction using **122**

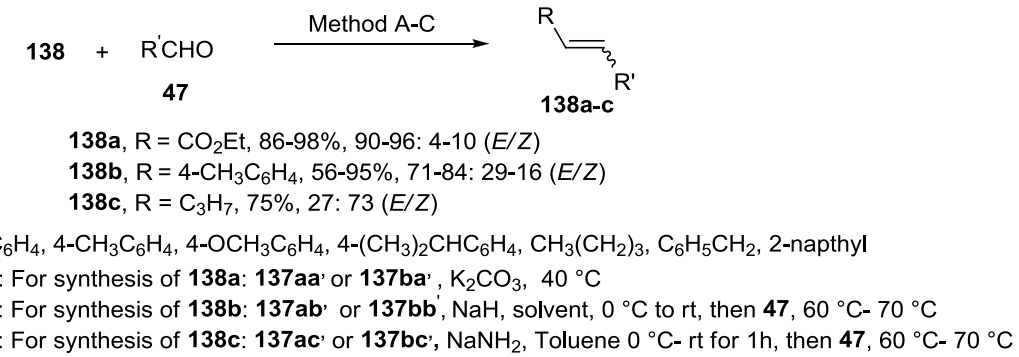
1.1.2.7.2 Ionic liquid-supported phosphonium salts

liquid-supported phosphonium salts **137aa'-ac'** and **137ba'-bc'** were synthesized by the alkylation of **122a** and **122b** with *p*-methylbenzyl bromide, ethyl bromoacetate and *n*-butyl bromide as shown in scheme 1.1.38.[103]



Scheme 1.1.38 Synthesis of ionic liquid-supported phosphonium salts

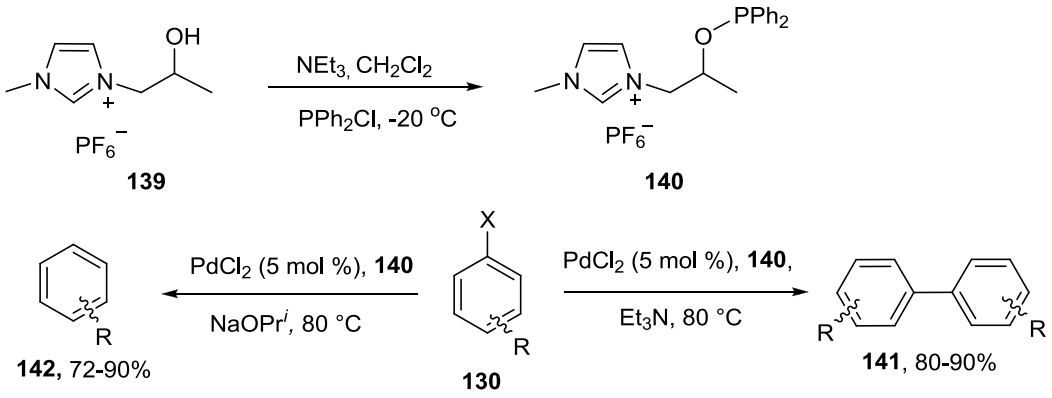
Ionic liquid-supported phosphonium salts **137** were used in Wittig reaction as alkyl source. Aldehydes **47** were converted to corresponding alkenes **138** in high yields and excellent purities by reacting with **137** (Scheme 1.1.39).[103]



Scheme 1.1.39 Wittig reaction using **137**

1.1.2.7.3 Diphenylphosphinite-functionalized ionic liquids

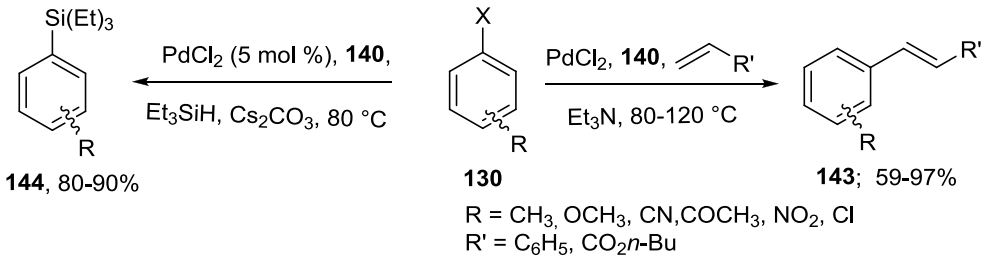
Iranpoor and co-workers have described the synthesis of diphenylphosphinite-functionalized ionic liquids (IL-$OPPh_2$) **140** by the reaction of chlorodiphenylphosphine (PPh_2Cl) with ionic liquid alcohol **139** in the presence of Et_3N (Scheme 1.1.40).[104] Dehalogenation and homocoupling reactions of aryl halides **130** were carried out using **140** both as a reagent and reaction medium (Scheme 1.1.40).[105, 106] The outcome of the reaction relied on the reactants and the bases employed in the reaction. For example, aryl halide **130**, in the presence of reagent **140**, $PdCl_2$ and Et_3N resulted in homocoupled product **141**. On the contrary, replacement of Et_3N with sodium isopropoxide ($NaOPr^i$) resulted in the dehalogenation of aryl halides to give **142**. The method proved to be tolerant to various functional groups, such as nitro, keto, and nitrile.



Scheme 1.1.40 Synthesis of ionic liquid-$OPPh_2$ and its application in homocoupling and dehalogenation reaction of aryl halides

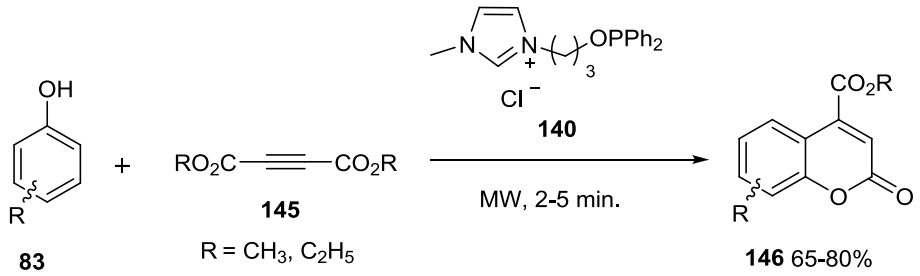
Later, **140** was also used as reusable and recyclable ligand in Heck reactions and silylation of aryl halides (Scheme 1.1.41).[107] Aryl halides **130** in the presence of **140**, $PdCl_2$, and Et_3N reacted with styrene or *n*-butyl acrylate to give corresponding Heck coupled products **143** in good to excellent yields (59-97%). Interestingly, less reactive aryl chlorides also underwent Heck coupling reaction under given reaction conditions. On the other hand, the reaction of aryl halides

with triethylsilanes in the presence of Cs_2CO_3 gave arylsilanes **144**. Surprisingly, in the absence of the base same system resulted dehalogenated products **142**.



Scheme 1.1.41 Heck reaction and silylation of aryl halides using IL-$OPPh_2$

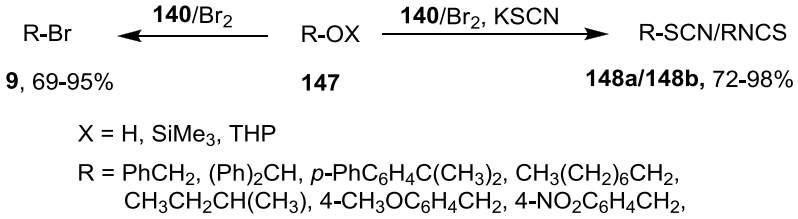
Valizadeh *et al.* has reported an elegant microwave-assisted synthesis of coumarins **146** from phenols and dialkyl but-2-ynedioate using diphenylphosphinite-functionalized ionic liquid **140** (Scheme 1.1.42).[108] **C**oumarins were obtained in good yields (65-80%), and the reagent **140** could be reused at least three times without apparent loss in its activity.



Scheme 1.1.42 Microwave assisted synthesis of coumarins using ionic liquid-$OPPh_2$

Iranpoor and co-workers reported bromination of alcohols, trimethylsilyl and THP-ethers **147** by bromine in the presence of **140** (Scheme 1.1.43).[104] Although the procedure was applicable to all alcohols, trimethylsilyl and THP-ethers, the reagent is highly selective for primary alcohols in the presence secondary alcohols and similarly for primary and secondary alcohols over trimethylsilyl and THP-ethers. The study was further extended to the synthesis of thiocyantes and isothiocyanates by reacting alcohols and their derivatives using ionic liquid-$OPPh_2$(SCN) which is prepared by the reaction of **140** with bromine followed by the reaction of KSCN. It is

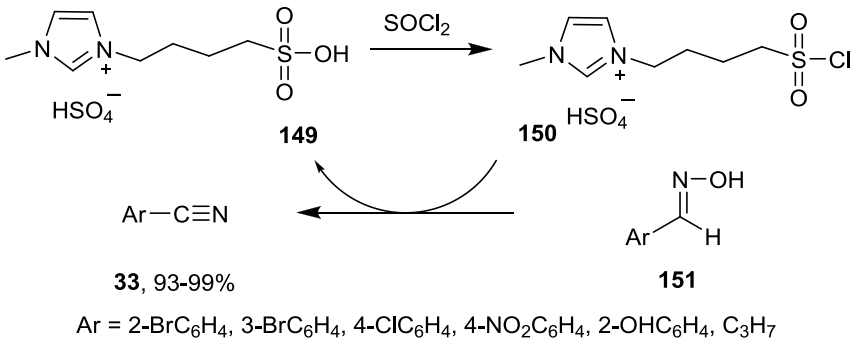
worth to emphasize that primary alcohol selectively gave thiocyanates (**148a**) while tertiary alcohols yielded isothiocyanates (**148b**). A mixture of thiocyanates and isothiocyanates was obtained from secondary alcohols.[104] The products were isolated by simple extraction with diethyl ether.



Scheme 1.1.43 Bromination and thiocyanation using **140**

1.1.2.8 Ionic liquid-supported sulfonyl chloride

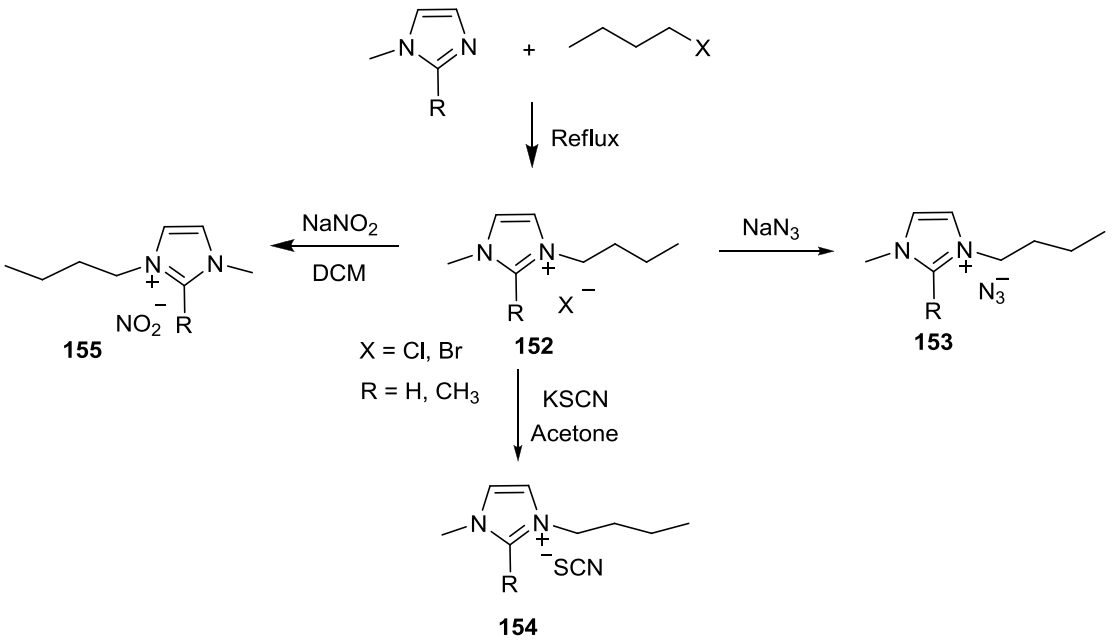
Qiao group synthesized an acidic ionic liquid, 1-4[(chlorosulfonyl)butyl]-3-methylimidazolium chlorosulfate [cbmim][SO_3Cl] **150** from [sbmim][HSO_4] **149** by reacting with $SOCl_2$.[109] Compound **150** features acidic sites on both the anion and cation part of ionic liquid. Dehydration of aldoximes **151** was performed to give nitriles **33** using both **149** or **150** as a catalyst. Reagent **150** was found to be more efficient than **149,** and nitriles were obtained in 93-95% yield using **150**. Moreover, self-induced phase separation of the reaction mixture after completion of the reaction provided simple and effortless isolation of the products from the reaction mixture. Recovered **149** was converted to **150** on reacting with $SOCl_2$ (Scheme 1.1.44).



Scheme 1.1.44 Synthesis of ionic liquid-supported sulfonyl chloride **150** and its application in dehydration of aldoximes

1.1.2.9 Nucleophilic Ionic liquids

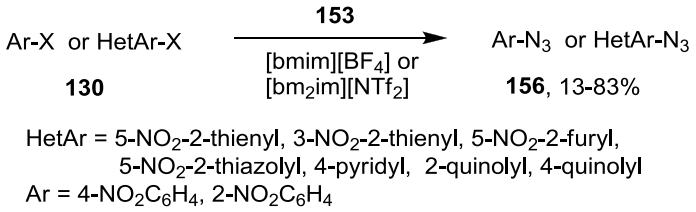
Nucleophilic ionic liquids (NILs)[110] are a unique class of ionic liquid based reagents in which the anion of the ionic liquid acts as nucleophile. One common characteristic amongst these NILs are that the nucleophilicity of these anions is generally higher than that of their inorganic salts. The increase in nucelophilicity may be attributed to the presence of ionic liquid. Similar effect of ionic liquid has been reported for fluorination by nucleophilic substitution,[111] nucleophilic substitution of activated aryl halides with secondary amines[112] and reactivity of anionic nucleophiles in ionic liquids.[113, 114] Synthesis of NILs **153-155** has been achieved by the anion metathesis of halide ion of ionic liquid **152** using corresponding sodium or potassium salts (Scheme 1.1.45).



Scheme 1.1.45 Synthesis of nucleophilic ionic liquids

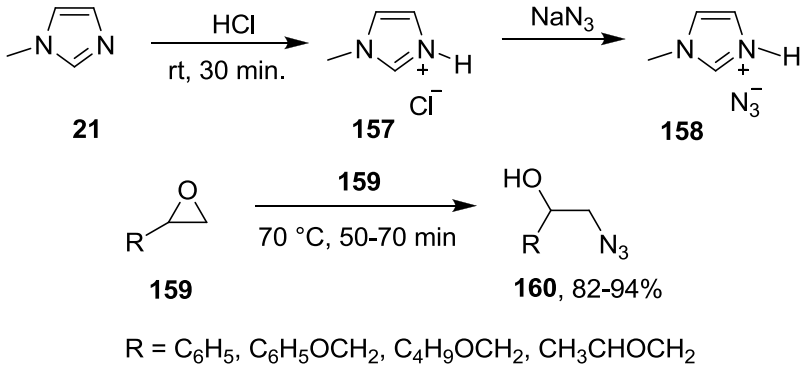
Anna *et al.* were the first to report the use of [bmim][N_3] **153** in aromatic nucleophilic substitution reaction (S_NAr) (Scheme 1.1.46).[51] A comprehensive discussion of solvent effect and substrate scope revealed interesting aspects of the reaction. Hydrogen bond donor ability (α)

of the solvent played a key role in the outcome of the reaction. It was found that high α disfavours the reaction by stabilizing the nucleophile through coordination. Better yield of aryl azides **156** were obtained by using **153** in [bmim][BF_4] compared to NaN_3 in MeOH. Also the acidic C2-proton of [bmim] ion in [bmim][BF_4] coordinates with the N_3^- ion and decrease its nucleophilicity. Replacing, C2-proton with methyl group in [bm_2im][N_3] and using [bm_2im][NTf_2] as solvent improved the yield of aryl azides.



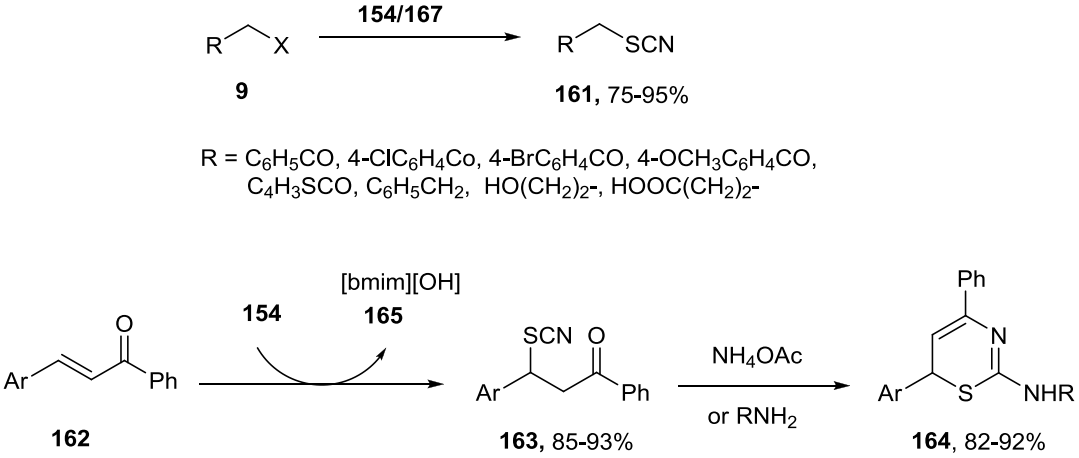
Scheme 1.1.46 Aromatic nucleophilic substitution reaction using [bmim][N_3] & [bm_2im][N_3]

Heidarizadeh *et al.* described synthesis of a novel protic azido functionalized nucleophilic ionic liquid **158** from 1-methylimidazole **21** (Scheme 1.1.47).[115] The reaction of **21** with hydrochloric acid at room temperature gave 1-methyl-*1H*-imidazol-3-ium chloride **157** which on anion exchange with NaN_3 in dry CH_3CN resulted in **158**. The nucleophilic ability of reagent **158** was evaluated for the ring opening of epoxides **159** to 1,2-azidoalcohols **160**.[115] In this reaction multiple-functions such as solvent, reagent and an activator were accomplished by **158**. The acidic hydrogen of **158** activated the reaction and azide anion acted as nucleophilic source.



Scheme 1.1.47 Synthesis of NIL **158**and application in ring opening of epoxides

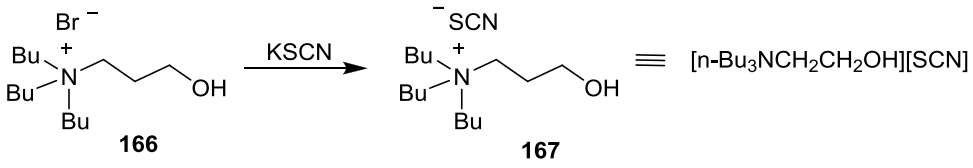
Thiocyanate functionality is generally introduced *via* nucleophilic substitution reaction of alkyl halides with metal thiocyanates.[116] Prolonged heating at 50 °C and the chromatographic purification with silica gel leads to the formation of thermodynamically favoured isothiocyanates. To overcome these difficulties, Kamal and Chouhan reported novel NILs [bmim][SCN] **154**.[117] Reagent **154** was prepared by the anion exchange of **152** with KSCN in acetone. A variety of alkyl halides and substituted phenacyl bromides **9** were converted to corresponding alkyl thiocyanates **161** in high yields at room temperature using **154** under solvent free conditions (Scheme 1.1.48). In this reaction [bmim][SCN] plays dual roles as reagent and solvent that obviates the necessity of additional solvent in the reaction mixture. Comparative study of a nucleophilic displacement reaction of alkyl halides were carried out using reagent **154** and KSCN. Complete conversion of **9** to **161** was observed when **154** was employed as the nucleophilic source whereas only 20-30% of **161** were formed in the case of KSCN.



Scheme 1.1.48 Thiocyanation of alkyl halides and chalcones using [bmim][SCN]

To tune the solubility of nucleophilic ionic liquid with thiocyanate anion, Mohanazadeh and Aghvami synthesized a new ionic liquid 2-hydroxy-*N*,*N*,*N*-tributylethanaminium thiocyanate [n-$Bu_3NCH_2CH_2OH$][SCN], **167** by an anion metathesis from its corresponding bromide salt **166** (Scheme 1.1.49)[118] Reagent **167** is soluble in acetone, chloroform, dichloromethane, and

ethanol but insoluble in water, ether, and hexane. This differential solubility is very useful for the separation of product from the reaction mixture. Compound **167** has been used as a reagent and solvent in the synthesis of **161** from **9**.

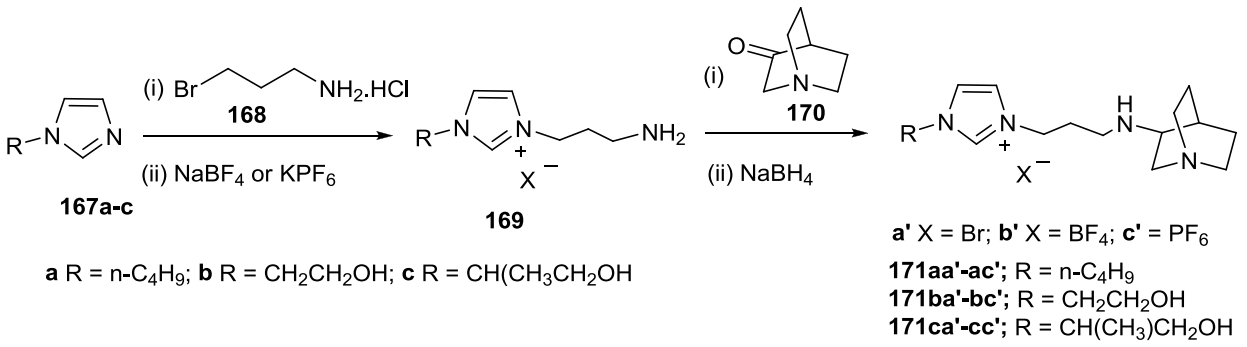


Scheme 1.1.49 Synthesis of [n-$Bu_3NCH_2CH_2OH$][SCN]

Later, Yadav *et al.* developed an efficient method for conjugative hydro thiocyanation of chalcones **162** using **154** (Scheme 1.1.48).[119] The superior nucleophilicity of **154** led to the formation of β-thiocyanato *α,β*-unsaturated ketones **163** in very good yields (85-93%). Compound **163** was further transformed to the pharmaceutically interesting molecule 2-amino-1,3-thiazines **164** by reacting with ammonium acetate or alkyl amines. The advantage of the method is easy purification and it does not require chromatographic separation and thus the possibility of rearrangement of thiocyanate to isothiocyanates was minimized. The reagent **154** could be recycled by treating co-product [bmim][OH] **165** with conc. HCl followed by reaction with KSCN at room temperature.

1.1.2.10 Ionic liquid-supported quinuclidine

Cheng *et al.* have synthesized quinuclidine-functionalized ionic liquids **171**.[120, 121] The target ionic liquids **171** were obtained as shown in scheme 1.1.50. Initially, quaternization of imidazoles **167** with 4-bromobutyl amine **168** gave amino functionalized ionic liquid **169**. Reductive amination of **169** with quinuclidin-3-one **170** gave **171aa′-ac′** that on further anion exchange with $NaBF_4$ or KPF_6 led to **171ba′-bc′** and **171ca′-cc′**, respectively.

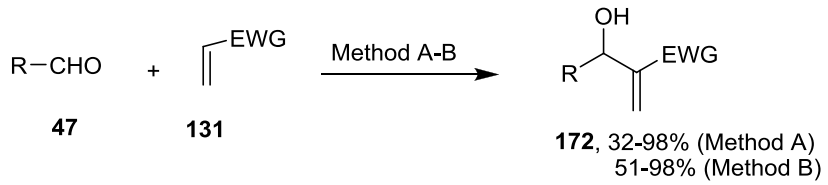


Scheme 1.1.50 Synthesis of quinuclidine-functionalized ionic liquids **172**

Morita-Baylis-Hillman (MBH) reaction is an efficient and simple carbon-carbon bond forming reactions in organic synthesis. Stoichiometric amount of Lewis bases such as DABCO, DBU, DMAP, PPh_3 and imidazole are required to facilitate the MBH reaction.[122, 123] To solve the problems associated with the recovery and reuse of Lewis base **171** was used as homogeneous catalysts in the MBH reaction of aldehydes **47** with alkenes **131** (Scheme 1.1.51). Of all the solvents screened for the MBH reaction, polar protic solvents like methanol proved to be the most efficient. Further examination revealed that the amount of methanol also had a pronounced effect on the yield of **172** and optimal yield was achieved when **171ab′** was employed with two equiv of methanol in the reaction mixture (Scheme 1.1.51, Method A). When ionic liquids [bmim][BF_4], [bmim][PF_6], [bupy][BF_4] and [bmmim][BF_4] were used as solvents the yields of **172** were found to be substantially lower than those in methanol. Remarkably, the catalyst **171ab′** was equally efficient for poor substrates like cyclicenones and *p*-methoxybenzaldehyde. Moreover, **172b** exhibited much better catalytic activity than some well known Lewis bases such as 3-quinuclidinone and DABCO under the given reaction conditions.

Quinclidine functionalized ionic liquid with hydroxyl group in alkyl side chain **171ba′-bc′** and **171ca′-cc′** showed higher catalytic activity as compared to the non hydroxyl counterpart **171aa′-ac′** even at lower catalyst loading (20 mol %) under solvent free conditions (Scheme 1.1.51, method A *vs* method B). This is attributed to hydrogen bond activation and/or the promotion of

intramolecular proton transfer by the hydroxyl group of **171ba′-bc′** and **171ca′-cc′**. As the catalyst offered a homogenous reaction and heterogeneous separation **171** can be easily separated from the products and reused at least six times without significant loss of activity. Moreover, MBH reactions of *N*-sulfonated imines 1**35** with various substrates such as methyl acrylate and acrylonitrile were promoted to give exclusively the desired adducts **136** (Scheme 1.1.37, method B & C).



R = C_3H_7, C_4H_9, C_6H_{13}, C_6H_5, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4
4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, *iPr*C_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$,
3-$NO_2C_6H_4$, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl

EWG = CN, $COOCH_3$, $COOC_2H_5$, $COOC_4H_9$, -$CO(CH_2)_3$-

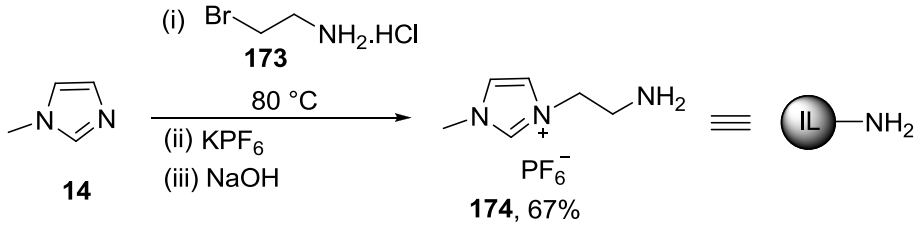
Method A: **171ab'** (0.3 equiv), MeOH (2 equiv), 62-98%
Method B: **171ca'** (0.2 equiv)

Scheme1.1.51 Morita-Baylis-Hillman reaction catalysed by **171**

1.1.3 Functionalized ionic liquid as scavengers

1.1.3.1 Amino functionalized ionic liquids

Song and group synthesized amino functionalized ionic liquid **174** by n-alkylation of 1-methylimidazole **14** with 2-bromoethylamine hydrobromide **173**, followed by anion exchange with KPF_6 and neutralization with NaOH (Scheme 1.1.52).[55] They further demonstrated the application of **174** as scavengers to remove excess of electrophiles like *p*-toluenesulfonyl chloride, acid chlorides, isothiocyanate and isocyanates from the reaction mixture (Figure 1.1.2)



Scheme1.1.52 Synthesis of amino functionalized ionic liquid

Due to the viscous nature of **174**, a longer time (over 9 h was required to scavenge *p*-toluenesulfonyl chloride from a toluene solution (Figure 1.1.2). Addition of conventional ionic liquid [bmim][PF_6] into the reaction mixture dramatically enhanced the scavenging process (35 min). The large difference in special gravity and high interfacial tension between ionic liquid phase ([bmim][PF_6] and **174)** and organic solvents (toluene) caused the phase separation. The electrophile-free organic phase was separated by decantation and the pure compound was extracted using CH_2Cl_2/Et_2O from ionic liquid phase. A small library of aromatic esters has been synthesized from various benzoyl chlorides with different phenols using **174** as scavenger. The products were obtained in high yields (> 97%) and purity (> 97%). Moreover, the reagent **174** was regenerated and reused for three cycles with comparable activity.

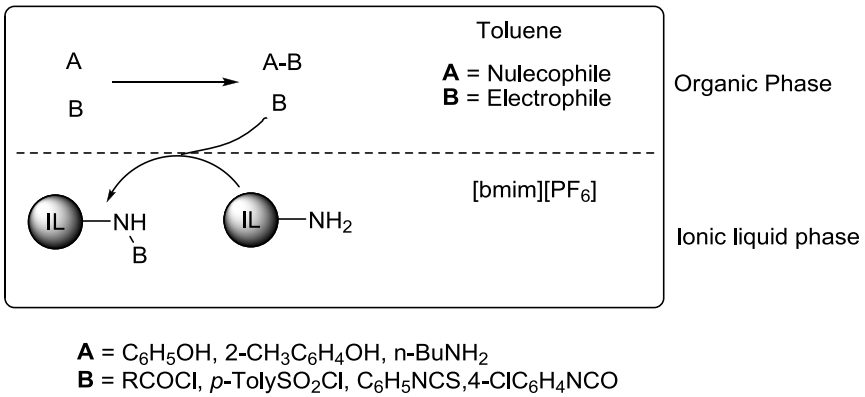
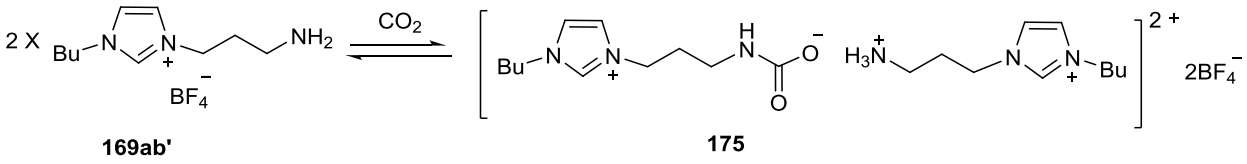


Figure 1.1.2 Scavenging of electrophiles using **174**

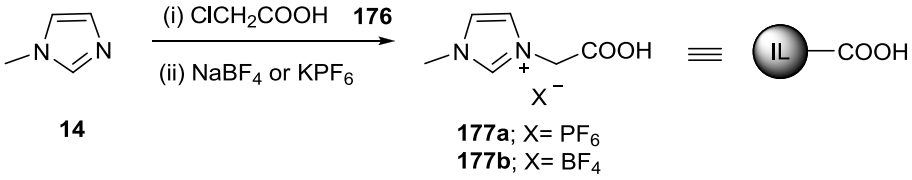
Davis and co-workers have used amino functionalized ionic liquid **169ab′** as a recyclable scavenger for carbon dioxide.[124] In general, aqueous amines are used for the removal of carbon dioxide from natural gas. Conversely, in these systems, the uptake of the volatile amine sequestering agent and water into the gas stream is problematic. To deal with these problems Davis group used **169ab′** to capture CO_2 as carbamate **175** (Scheme 1.1.53). The molar uptake of CO_2 per mole of **169ab′** was close to 0.5, which is the theoretical maximum for CO_2 as an ammonium carbamate. Moreover, the uptake of **169ab′** is comparable to the regular sequestering amines such as diisopropylamine (DIPA), β,β'-hydroxyaminoethyl ether (DGA) and monoethanolamine (MEA). The process is reversible and CO_2 could be expelled from the 1**75** by heating in vacuum. The recovered ionic liquid **169ab′** can be reused for five cycles effectively. FT-IR and NMR spectroscopic techniques were used to analyze the gas-treated ionic liquid.



Scheme 1.1.53 Scavenging of CO_2 as carbamate using **169ab′**

1.1.3.2 Carboxyl functionalized ionic liquids

Song and group have also synthesized a carboxyl functionalized ionic liquid **177** from 1-methylimidazole **14** as shown in scheme 1.1.54. The reaction of **14** with chloroacetic acid **176** followed by anion exchange with KPF_6 or $NaBF_4$ resulted in corresponding carboxyl functionalized ionic liquid **177**. [54]



Scheme 1.1.54 Synthesis of carboxyl functionalized ionic liquid

Reagent **177** was used as a scavenger for the removal of excess of materials present in the reaction mixture of the synthesis of sulfonyl esters, amides and acid anhydrides (Figure 1.1.3).[54] The products were isolated in pure form by simple decantation of toluene, followed by extraction with CH_2Cl_2/Et_2O. The generality of the method was further extended by employing **177** in the synthesis of *N*-acyl-*N*-alkylpiperazines. Also **177** was regenerated by the hydrolysis of the ionic phase and recycled thrice without any marked decrease in activity.

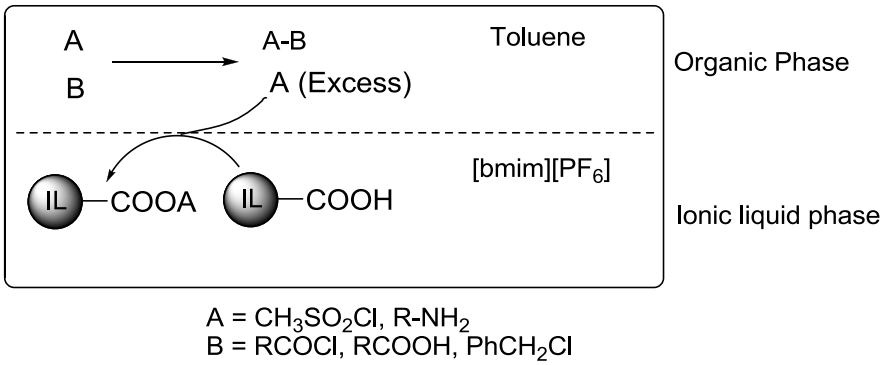
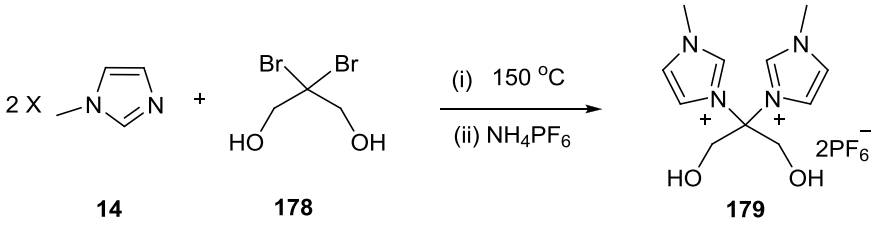


Figure 1.1.3 Scavenging of excess benzyl chlorides, sulfonyl chlorides and amines **177**

1.1.3.3 Diol functionalized ionic liquid

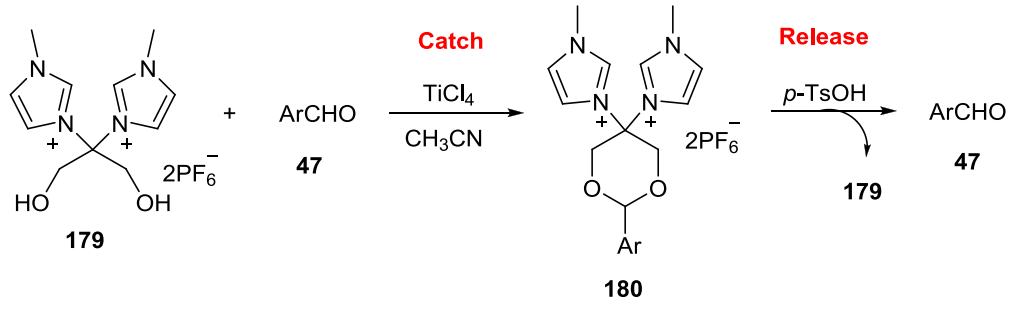
Cai and Liu reported synthesis of a novel diol-functionalized ionic liquid, 2,2-bis(1-(1-methylimidazolium)methylpropane -1,3-diol hexafluorophosphate **179**.[56] Synthesis of **179** has been achived as shown in scheme 1.1.55. Reaction of **14** with 2,2-bis(bromomethyl)-1,3-propanediol **178** at 150 °C, followed by anion exchange with NH_4PF_6 yielded diol functionalized ionic liquid **179**.



14 **178** **179**

Scheme 1.1.55 Synthesis of diol functionalized ionic liquid

The capture and release studies of different aldehydes were studied using **179** (Scheme 1.1.56). The aldehydes were selectively captured as 1,3-dioxane **180** when a mixture of aldehydes and ketones was treated with **179** in the presence of $TiCl_4$ (Table 1.1.1, entry 1-4). The captured aldehydes were further released by the hydrolysis of **180** in the presence of TsOH and recovered **179** was reused four times without significant loss of activity.[56]



179 **47** **180** **179** **47**

Scheme 1.1.56 Capture and release of aldehydes using **179**

Table 1.1.1 Capture and release of aldehydes in the presence of ketones using diol-functionalized ionic liquid **193**

Entry	Mixture	% Capture	% Release	Entry	Mixture	% Capture	% Release
1	C_6H_5CHO	100	92	5	C_6H_5CHO	100	93
	$C_6H_5COCH_3$	0	0		4-$BrC_6H_5OCH_3$	0	0
2	2,6-$(Cl)_2C_6H_3CHO$	100	91	6	2-ClC_6H_4CHO	100	92
	$C_6H_5COCH_3$	0	0		4-$BrC_6H_5OCH_3$	0	0
3	2,6-$(Cl)_2C_6H_3CHO$	100	90	7	2,6-$(Cl)_2C_6H_3CHO$	100	90
	$C_2H_5COC_4H_9$	0	0		4-$BrC_6H_5OCH_3$	0	0
4	2,6-$(Cl)_2C_6H_3CHO$	100	91	8	2,6-$(Cl)_2C_6H_3CHO$	63	92
	Cyclohexanone	0	0		C_6H_5CHO	37	0

1.1.4 Conclusions

In recent years, ionic liquid-supported reagents and scavengers have gained considerable interest as promising alternative supported reagents and scavenge due to their unique tunable physical and chemical properties. They have facilitated the organic synthetic process by virtue of their inimitable advantages such as facile separation and purification of products and thus making the process environmentally friendly. The application of functionalized ionic liquids (FILs) as reagents and scavengers in organic synthesis are still in the early stage of development. A large numbers of structurally distinct ionic liquid-supported reagents and scavengers can be developed. With increased availability of these functionalized ionic liquids, the synthetic process should be distinctly faster, better, and cheaper.

1.1.5 References

[1] Hodge, P., *Chemical Society Reviews*, **1997**, *26*, 417.
[2] Sloan, L. A.; Procter, D. J., *Chemical Society Reviews*, **2006**, *35*, 1221.
[3] Ruck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F., *Chemical Society Reviews*, **2005**, *34*, 507.
[4] C. D. Brown, R., *Journal of the Chemical Society, Perkin Transactions 1*, **1998**, 3293.
[5] Seeberger, P. H.; Haase, W.-C., *Chemical Reviews*, **2000**, *100*, 4349.
[6] Boas, U.; Brask, J.; Jensen, K. J., *Chemical Reviews*, **2009**, *109*, 2092.
[7] Lorsbach, B. A.; Kurth, M. J., *Chemical Reviews*, **1999**, *99*, 1549.
[8] Guillier, F.; Orain, D.; Bradley, M., *Chemical Reviews*, **2000**, *100*, 2091.
[9] Sammelson, R. E.; Kurth, M. J., *Chemical Reviews*, **2000**, *101*, 137.
[10] Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C., *Tetrahedron*, **1998**, *54*, 15385.
[11] Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D., *Tetrahedron*, **1996**, *52*, 4527.
[12] Merrifield, R. B., *Journal of the American Chemical Society*, **1963**, *85*, 2149.
[13] Hlaváč, J.; Soural, M.; Krchňák, V., John Wiley & Sons, Inc.: 2011.
[14] Crowley, J. I.; Rapoport, H., *Accounts of Chemical Research*, **1976**, *9*, 135.
[15] Lu, J.; Toy, P. H., *Chemical Reviews*, **2009**, *109*, 815.
[16] Blaney, P.; Grigg, R.; Sridharan, V., *Chemical Reviews*, **2002**, *102*, 2607.
[17] Varma, R. S., *Green Chemistry*, **1999**, *1*, 43.
[18] Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C., *Journal of Organic Chemistry*, **2001**, *66*, 8154.
[19] Michaud, A.; Gingras, G.; Morin, M.; Béland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M., *Organic Process Research & Development*, **2007**, *11*, 766.
[20] Varma, R. S., *Tetrahedron*, **2002**, *58*, 1235.
[21] Gravert, D. J.; Janda, K. D., *Chemical Reviews*, **1997**, *97*, 489.
[22] Sieber, F.; Wentworth, P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D., *Journal of Organic Chemistry*, **1999**, *64*, 5188.
[23] Toy, P. H.; Janda, K. D., *Accounts of Chemical Research*, **2000**, *33*, 546.
[24] Wipf, P.; Venkatraman, S., *Tetrahedron Letters*, **1996**, *37*, 4659.
[25] Wentworth, A. D.; Wentworth, P.; Mansoor, U. F.; Janda, K. D., *Organic Letters*, **2000**, *2*, 477.
[26] Wentworth Jr, P.; D. Janda, K., *Chemical Communications*, **1999**, 1917.
[27] Miura, T.; Goto, K.; Hosaka, D.; Inazu, T., *Angewandte Chemie International Edition*, **2003**, *42*, 2047.
[28] Chen, C.-T.; Zhang, W., *Molecular Diversity*, **2005**, *9*, 353.
[29] Zong, C.; Venot, A.; Dhamale, O.; Boons, G.-J., *Organic Letters*, **2013**, *15*, 342.
[30] Dobbs, A. P.; Kimberley, M. R., *Journal of Fluorine Chemistry*, **2002**, *118*, 3.
[31] Zhang, W., *Chemical Reviews*, **2009**, *109*, 749.
[32] Thompson, L. A., *Current Opinion in Chemical Biology*, **2000**, *4*, 324.

[33] Ley, S. V.; Leach, A. G.; Storer, R. I., *Journal of the Chemical Society, Perkin Transactions 1*, **2001**, 358.
[34] Ley, S.V.; Schucht, O.; Thomas, A. W; Murray, P. J., *Journal of the Chemical Society, Perkin Transactions 1*, **1999**, 1251.
[35] Dickerson, T. J.; Reed, N. N.; Janda, K. D., *Chemical Reviews*, **2002**, *102*, 3325.
[36] Wolf, E. D.; Koten, G. V.; Deelman, B.-J., *Chemical Society Reviews*, **1999**, *28*, 37.
[37] Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J., *Chemical Society Reviews*, **2011**, *40*, 3496.
[38] Tang, S.; Baker, G. A.; Zhao, H., *Chemical Society Reviews*, **2012**, *41*, 4030.
[39] Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S., *Tetrahedron*, **2005**, *61*, 1015.
[40] Plechkova, N. V.; Seddon, K. R., *Chemical Society Reviews*, **2008**, *37*, 123.
[41] Wasserscheid, P.; Keim, W., *Angewandte Chemie International Edition*, **2000**, *39*, 3772.
[42] Welton, T., *Chemical Reviews*, **1999**, *99*, 2071.
[43] Hallett, J. P.; Welton, T., *Chemical Reviews*, **2011**, *111*, 3508.
[44] Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G., *Chemical Reviews*, **2008**, *108*, 2015.
[45] Zhao. S. V. M. H, *Aldrichimica Acta*, **2002**, *35*, 75.
[46] Davis, J. J. H., *Chemistry Letters*, *33*, 1072.
[47] Giernoth, R., *Angewandte Chemie International Edition*, **2010**, *49*, 2834.
[48] Plaquevent, J.-C.; Levillain, J.; Guillen, F. d. r.; Malhiac, C.; Gaumont, A.-C., *Chemical Reviews*, **2008**, *108*, 5035.
[49] Huo, C.; Chan, T. H., *Chemical Society Reviews*, **2010**, *39*, 2977.
[50] Zolfigol, M. A.; Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Kruger, H. G.; Asgari, Z.; Khakyzadeh, V.; Kazem-Rostami, M., *Journal of Organic Chemistry*, **2012**, *77*, 3640.
[51] D'Anna, F.; Marullo, S.; Noto, R., *Journal of Organic Chemistry*, **2008**, *73*, 6224.
[52] Pârvulescu, V. I.; Hardacre, C., *Chemical Reviews*, **2007**, *107*, 2615.
[53] Rantwijk, F. V.; Sheldon, R. A., *Chemical Reviews*, **2007**, *107*, 2757.
[54] Cai, Y.; Zhang, Y.; Peng, Y.; Lu, F.; Huang, X.; Song, G., *Journal of Combinatorial Chemistry*, **2006**, *8*, 636.
[55] Song, G.; Cai, Y.; Peng, Y., *Journal of Combinatorial Chemistry*, **2005**, *7*, 561.
[56] Cai, Y.; Liu, Y., *Monatshefte für Chemie - Chemical Monthly*, **2008**, *140*, 39.
[57] Muthayala, M. K.; Kumar, A., *ACS Combinatorial Science*, **2011**, *14*, 5.
[58] Dyson, P. J., *Applied Organometallic Chemistry*, **2002**, *16*, 495.
[59] Sawant, A. D.; Raut, D. G.; Darvatkar, N. B.; Salunkhe, M. M., *Green Chemistry Letters and Reviews*, **2011**, *4*, 41.
[60] Yue, C.; Fang, D.; Liu, L.; Yi, T.-F., *Journal of Molecular Liquids*, **2011**, *163*, 99.
[61] Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C., *Tetrahedron: Asymmetry*, **2005**, *16*, 3921.
[62] Ding, J.; Armstrong, D. W., *Chirality*, **2005**, *17*, 281.
[63] Zhang, Q.; Zhang, S.; Deng, Y., *Green Chemistry*, **2011**, *13*, 2619.

[64] Mehnert, C. P., *Chemistry – A European Journal*, **2005**, *11*, 50.
[65] Lee, J. W.; Shin, J. Y.; Chun, Y. S.; Jang, H. B.; Song, C. E.; Lee, S.-g., *Accounts of Chemical Research*, **2010**, *43*, 985.
[66] Mancuso, A. J.; Brownfain, D. S.; Swern, D., *Journal of Organic Chemistry*, **1979**, *44*, 4148.
[67] Mancuso, A. J.; Huang, S.-L.; Swern, D., *Journal of Organic Chemistry*, **1978**, *43*, 2480.
[68] He, X.; Chan, T. H., *Tetrahedron*, **2006**, *62*, 3389.
[69] Cheng, X. Y.; Li, K. F.; Wang, Q. J.; Wang, C. Y.; Ying, T. K., *Chinese Chemical Letters*, **2012**, *23*, 801.
[70] Merritt, E. A.; Olofsson, B., *Angewandte Chemie International Edition*, **2009**, *48*, 9052.
[71] Zhdankin, V. V.; Stang, P. J., *Chemical Reviews*, **2008**, *108*, 5299.
[72] Zhdankin, V. V.; Stang, P. J., *Chemical Reviews*, **2002**, *102*, 2523.
[73] Stang, P. J.; Zhdankin, V. V., *Chemical Reviews*, **1996**, *96*, 1123.
[74] Ishiwata, Y.; Togo, H., *Tetrahedron Letters*, **2009**, *50*, 5354.
[75] Kawano, Y.; Togo, H., *Tetrahedron*, **2009**, *65*, 6251.
[76] Togo, H.; Akiike, J.; Yamamoto, Y., *Synlett*, **2007**, 2168.
[77] Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H., *Journal of Organic Chemistry*, **1982**, *47*, 2487.
[78] Sawamura, T.; Kuribayashi, S.; Inagi, S.; Fuchigami, T., *Organic Letters*, **2010**, *12*, 644.
[79] Qian, W.; Jin, E.; Bao, W.; Zhang, Y., *Tetrahedron*, **2006**, *62*, 556.
[80] Qian, W.; Pei, L., *Synlett*, **2006**, 709.
[81] Fang, C.; Qian, W.; Bao, W., *Synlett*, **2008**, 2529.
[82] Iinuma, M.; Moriyama, K.; Togo, H., *Tetrahedron*, **2013**, *69*, 2961.
[83] Handy, S. T.; Okello, M., *Journal of Organic Chemistry*, **2005**, *70*, 2874.
[84] Handy, S. T.; Okello, M., *Tetrahedron Letters*, **2003**, *44*, 8399.
[85] Handy, S. T., *Chemistry – A European Journal*, **2003**, *9*, 2938.
[86] Yang, J. Z. B.; Zhao. D.; Wang. Y.; Jia. H, *Chemistry Letters*, **2013**, *42*, 930.
[87] Muthyala, M. K.; Choudhary, S.; Kumar, A., *RSC Advances*, **2014**, *4*, 14297.
[88] Ito, M.; Itani, I.; Toyoda, Y.; Morimoto, K.; Dohi, T.; Kita, Y., *Angewandte Chemie International Edition*, **2012**, *51*, 12555.
[89] Muthyala, M. K.; Choudhary, S.; Pandey, K.; Shelke, G. M.; Jha, M.; Kumar, A., *European Journal of Organic Chemistry*, **2014**, 2365.
[90] Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y., *Journal of the American Chemical Society*, **2006**, *128*, 8412.
[91] Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A., *Accounts of Chemical Research*, **2002**, *35*, 774.
[92] Zhu, J.; Wang, P.-c.; Lu, M., *RSC Advances*, **2012**, *2*, 8265.
[93] Wu, X.-E.; Ma, L.; Ding, M.-X.; Gao, L.-X., *Synlett*, **2005**, 607.
[94] Liu, L.; Ma, J.; Sun, Z.; Zhang, J.; Huang, J.; Li, S.; Tong, Z., *Canadian Journal of Chemistry*, **2010**, *89*, 68.

[95] Fall, A.; Sene, M.; Gaye, M.; Gómez, G.; Fall, Y., *Tetrahedron Letters*, **2010**, *51*, 4501.
[96] Zhu, C.; Yoshimura, A.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V., *Tetrahedron Letters*, **2012**, *53*, 1438.
[97] Vitz, J.; Mac, D. H.; Legoupy, S., *Green Chemistry*, **2007**, *9*, 431.
[98] Pham, P. D.; Legoupy, S., *Tetrahedron Letters*, **2009**, *50*, 3780.
[99] Louaisil, N.; Pham, P. D.; Boeda, F.; Faye, D.; Castanet, A.-S.; Legoupy, S., *European Journal of Organic Chemistry*, **2011**, 143.
[100] Pham. P. D.; Vitz, J.; Chamignon, C.; Martel, A.; Legoupy, S., *European Journal of Organic Chemistry*, **2009**, 3249.
[101] Imura, Y.; Shimojuh, N.; Kawano, Y.; Togo, H., *Tetrahedron*, **2010**, *66*, 3421.
[102] Imura, Y.; Shimojuh, N.; Moriyama, K.; Togo, H., *Tetrahedron*, **2012**, *68*, 2319.
[103] Shimojuh, N.; Imura, Y.; Moriyama, K.; Togo, H., *Tetrahedron*, **2011**, *67*, 951.
[104] Iranpoor, N.; Firouzabadi, H.; Azadi, R., *Tetrahedron Letters*, **2006**, *47*, 5531.
[105] Iranpoor, N.; Firouzabadi, H.; Azadi, R., *Journal of Organometallic Chemistry*, **2010**, *695*, 887.
[106] Iranpoor, N.; Firouzabadi, H.; Azadi, R., *Journal of Organometallic Chemistry*, **2008**, *693*, 2469.
[107] Iranpoor, N.; Firouzabadi, H.; Azadi, R., *European Journal of Organic Chemistry*, **2007**, 2197.
[108] Valizadeh, H.; Gholipour, H.; Mahmoudian, M., *Journal of the Iranian Chemical Society*, **2011**, *8*, 862.
[109] Nakajima, K. Q. M.; Kobayashi, N.; Bao, Q.; Tomida, D.; Yokoyam. C., *Chemistry Letters*, **2011**, *40*, 396.
[110] Koguchi, S.; Nakamura, K., *Synlett*, **2013**, *24*, 2305.
[111] Kim, D. W.; Song, C. E.; Chi, D. Y., *Journal of the American Chemical Society*, **2002**, *124*, 10278.
[112] Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V., *Tetrahedron Letters*, **2003**, *44*, 2217.
[113] Betti, C.; Landini, D.; Maia, A., *Tetrahedron*, **2008**, *64*, 1689.
[114] Landini, D.; Maia, A., *Tetrahedron Letters*, **2005**, *46*, 3961.
[115] Heidarizadeh, F.; Saeed, A. B.; Rezaee-Nezhad, E., *Comptes Rendus Chimie*, **2014**, *17*, 450.
[116] Guy, R. G., John Wiley & Sons, Ltd.: 2010.
[117] Kamal, A.; Chouhan, G., *Tetrahedron Letters*, **2005**, *46*, 1489.
[118] Mohanazadeh, F.; Aghvami, M., *Tetrahedron Letters*, **2007**, *48*, 7240.
[119] Yadav, L. D. S.; Patel, R.; Rai, V. K.; Srivastava, V. P., *Tetrahedron Letters*, **2007**, *48*, 7793.
[120] Mi, X.; Luo, S.; Xu, H.; Zhang, L.; Cheng, J.-P., *Tetrahedron*, **2006**, *62*, 2537.
[121] Mi, X.; Luo, S.; Cheng, J.-P., *Journal of Organic Chemistry*, **2005**, *70*, 2338.
[122] Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R., *Tetrahedron*, **1996**, *52*, 8001.

[123] Singh, V.; Batra, S., *Tetrahedron*, **2008**, *64*, 4511.
[124] Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H., *Journal of the American Chemical Society*, **2002**, *124*, 926.

PART B

Advances in Task Specific Ionic Liquids as Soluble support in Organic Synthesis

Part B: Advances in Task Specific Ionic Liquids as Soluble Support in Organic Synthesis

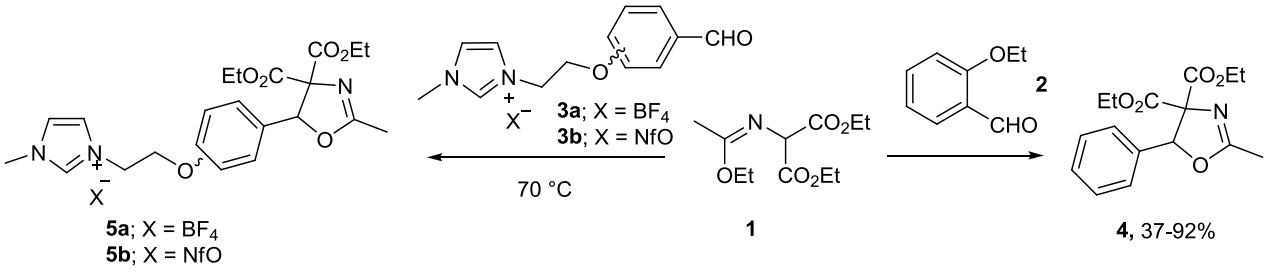
1.2.1 Introduction

Solid-supported synthesis is a widely employed technique that has greatly facilitated the synthesis and purification of many compounds.[1-3] Traditionally, solid-supported synthesis employs a heterogeneous material such as cross-linked polystyrene to support one of the reactants. The primary advantage of such a choice is that the supported material being heterogeneous can be readily separated by simple filtration from the reaction medium. At the same time, this heterogeneity limits the types of reactions and reaction conditions that can be employed and moreover, the maximum loading of polystyrene supports are <2 mmol/g. These limitations have led more recently to the development of a variety of 'soluble' supports.[2, 4, 5] Since the supports are homogeneous in a variety of conventional organic solvents, reactions can be performed under conventional solution-phase conditions. At the same time, by changing the polarity of the solvent (most frequently by the addition of methanol), the support and supported molecule will precipitate, resulting in facile separation by filtration. While this is a major step forward, there are still limitations to the current soluble supports. First, using simple PEG supports, the maximum loading that can be achieved is even lower than that of polystyrene supports (<1 mmol/g).[6] Second, the highly oxygenated nature of the PEG supports can interfere in certain types of reactions or even can be degraded under certain reaction conditions.

Ionic liquid-phase organic synthesis (IoLiPOS) methodology is a new approach in supported synthesis offering several advantages for organic synthesis by retaining the benefits of product isolation and purification of polymer-supported synthesis along with solubility prosperity of traditional solution phase synthesis. In this approach, a preferred molecule is anchored to an ionic liquid by appropriate linker and the synthesis of the desired molecule is carried out without

detaching the ionic liquid. Un-reacted reagents and unwanted compounds can be easily removed from the ionic liquid by simple washings with appropriate solvents and thus avoiding the need for chromatographic purification. Though, the main feature of IoLiPOS resembles the polymer-supported synthesis, however, tunable solubility, homogenous reaction conditions, high-loading capacity, minimal use of solvents and reagents and moreover possibility to monitor the reaction progress by various analytical conditions have made this method an attractive and favorable alternative to solid-phase synthesis.

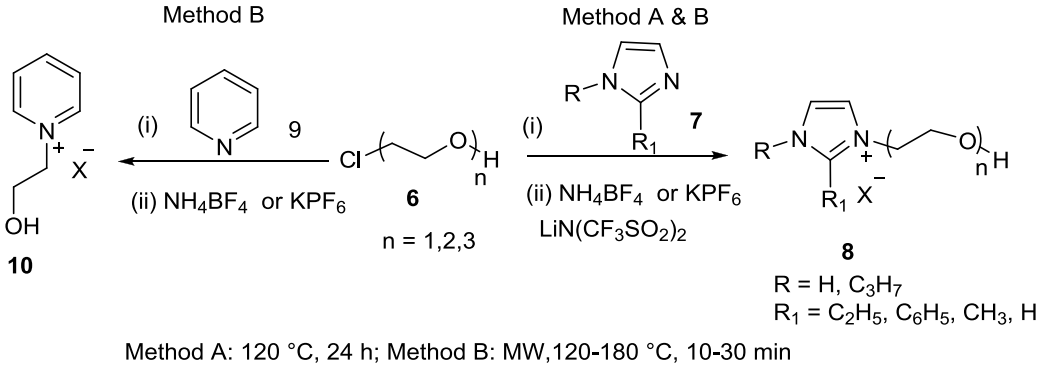
Bazureau was the first to exploit the use of ionic liquids as a soluble support in organic synthesis. Bazureau *et al.* investigated 1,3-dipolar cycloaddition reactions between imidiate **1** and 2-ethoxybenzaldehyde **2** in various ionic liquids including [emim][BF_4], [emim][PF_6] and [emim][NfO].[6] Significant rate enhancement in the 1,3-dipolar cycloaddition reaction was noticed, when ionic liquid-supported aldehyde **3** was employed (Scheme 1.2.1). The rate acceleration was attributed to the intramolecular interaction between the CHO group and the methylimidazolium moiety of **3**. These fascinating results attracted attention of researchers towards IoLiPOS methodology.



Scheme 1.2.1 1,3-Dipolar cycloaddition reactions between **1** and **3**

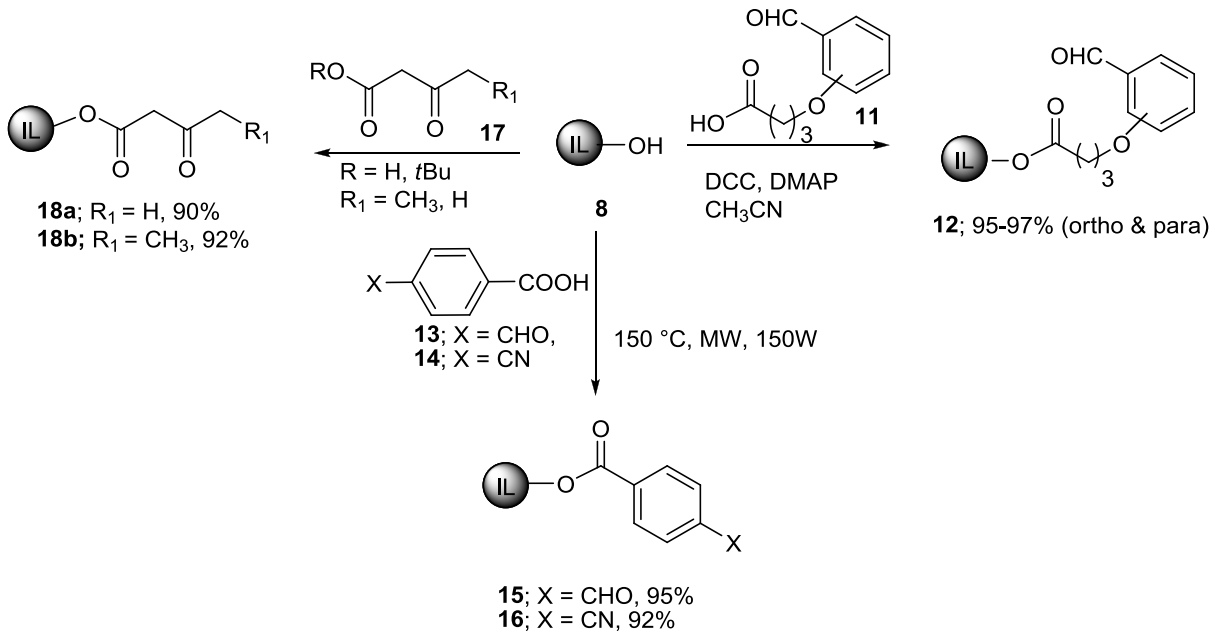
Ionic liquids are very good media for absorbing microwaves due to their unique properties such as high dielectric constants and relatively low heat capacities. Considering these facts into account, Bazureau *et al.* developed clean and efficient protocols for the synthesis of various bio-active organic molecules by combining IoLiPOS methodology with microwave-assisted synthesis.[6-18]

Alcohol functionalized ionic liquids **8** and **10** were prepared from 1-methylimidazole **7** and pyridine **9** by reacting them with chloroalkanes **6**.[8] Investigators noticed that, in contrast to classical synthesis (24 h), microwave heating (10-30 min) afforded ionic liquid alcohols **8** and **10** in a short period of time with excellent yields (Scheme 1.2.2).[8]



Scheme 1.2.2 Synthesis of alcohol-functionalized ionic liquids **8**&**10**

A variety of organic moieties with diverse functional groups like aldehyde,[7, 9, 12] nitrile,[17] 1,3-diketones[13, 14] and isocyanate[11] have been grafted on **8** and **10** as shown in the scheme 1.2.3. Reaction of substituted benzaldehydes **11** and **13** with **8** in presence of dicyclohexylcarbodiimide gave benzaldehyde-functionalized ionic liquid **12** [7, 9] and **15**[12, 18] respectively (Scheme 1.2.3). Using the similar strategy substituted benzonitrile **14** also grafted on **8** to give benzonitrile-functionalized ionic liquid **16**. The active methylene containing 1,3-diketone derivatives **17** have been grafted onto **8** under focused microwave irradiation to yield 1,3-diketone-functionalized ionic liquid **18** in excellent yields (Scheme 1.2.3). [14]



Scheme 1.2.3 Anchoring various functional groups on **8**

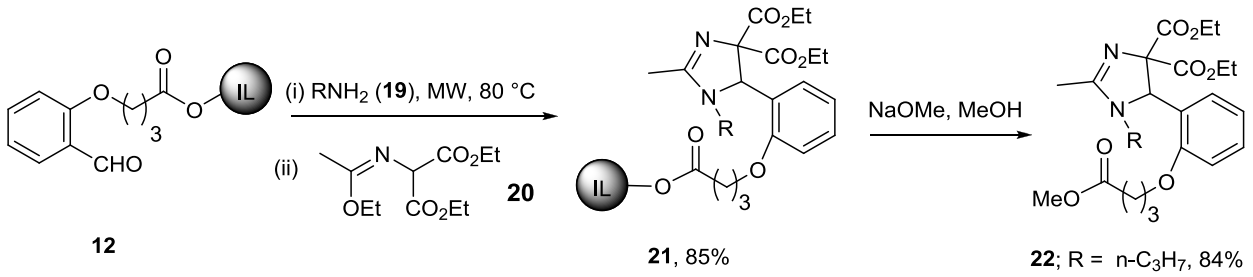
These functionalized ionic liquids further used as soluble supports for various reactions like cycloaddition reactions, Knoevenagel condensation, crossed aldol reaction, Biginelli, Hantzsch condensation and Suzuki coupling reactions.

1.2.2 Cycloaddition reactions

1.2.2.1 1,3-Dipolar cycloaddition reaction

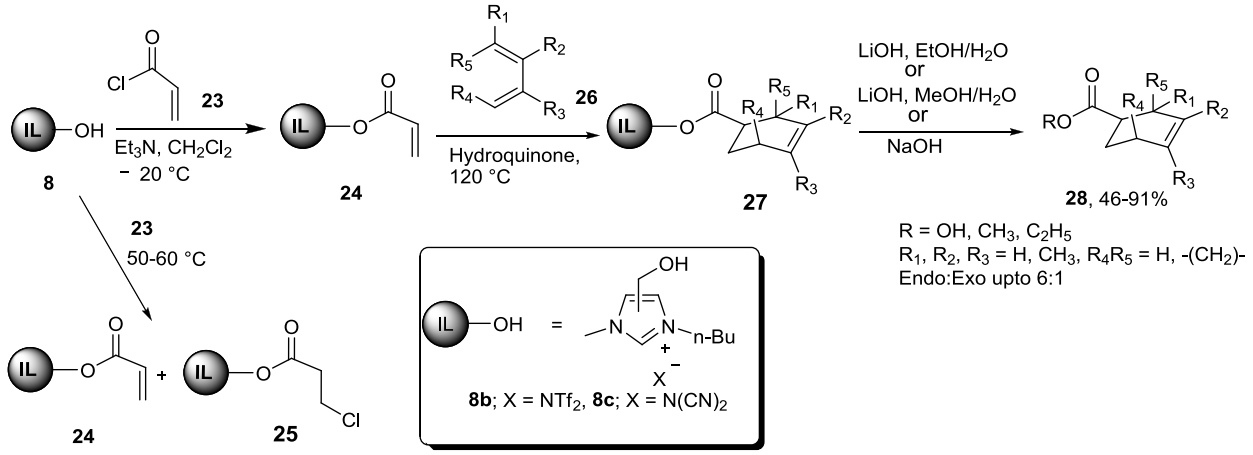
Bazureau *et al.* synthesized a small library of imidazoline derivatives **22** using benzaldehyde-functionalized ionic liquid **12** as soluble support in three steps; First step involves the condensation of **12** with various amines **19**, followed by regioselective 1,3-dipolar cycloaddition with imidate **20** to give ionic liquid-supported imidazoline derivatives **21**.[7] Ionic liquid alcohol is dismantled from **21** by transesterification reaction using **N**aOMe in MeOH to give imidazoline derivatives **22** (Scheme 1.2.4).[7] Using this IoLiPOS methodology, all the side products during the reactions could be removed by simple extraction and no chromatography was necessary throughout the synthesis. Moreover, in contrast to the solid-phase synthesis, IoLiPOS allows the

use of standard analytical methods such as NMR and TLC to monitor the progress of the reaction.



Scheme 1.2.4 Synthesis of imidazoline derivatives **16** using **12**

1.2.2.2 Diels-Alder reaction



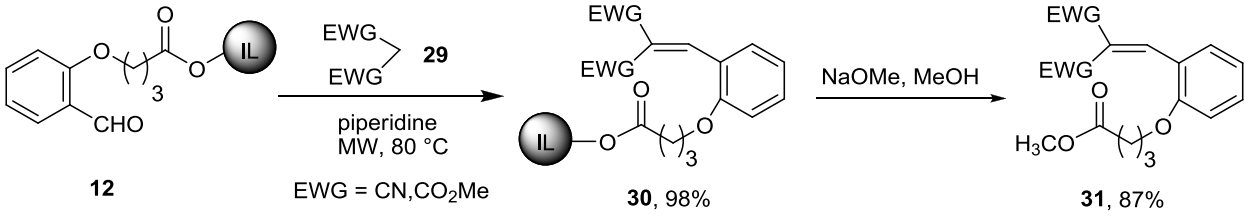
Scheme 1.2.5 Diels-Alder reaction on fructose derived alcoho-functionalized ionic liquid

Handy and Okello[19] developed fructose derived alcohol-functionalized ionic liquids **8b** and **8c** and used them as soluble supports for the synthesis of Diels-Alder adducts. Reaction of **8c** with acryloyl chloride **18** under solvent-free conditions at 50-60 °C resulted in dienophile **24** along with **25** in 3:1 ratio. On the other hand, decreasing the reaction temperature to −20°C and quenching the hydrochloric acid by Et_3N gave exclusively **24**. Compound **24** further reacted with various dienes **26** under solvent free conditions to ionic liquid Diels-Alder adducts **27** in good yields (Scheme 1.2.5). Basic saponification of **27** gave desired products **28** in moderate yields.

The main advantages of this procedure are minimizing the use of hazardous organic solvents and eradicating the chromatographic purification.

1.2.3 Knoevenagel condensation reaction

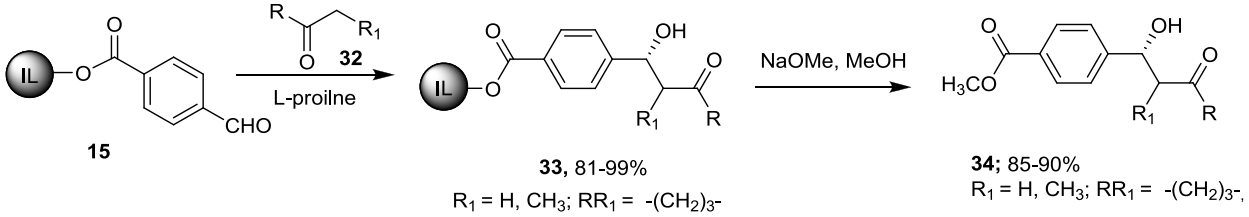
Bazureo *et al.* demonstrated Knoevenagel condensation reaction on **12** using IoLiPOS methodology. Reaction of **12** with various active methylene compounds **29** under focused microwave-irradiation gave ionic liquid bound Knoevenagel adducts **30** in short reaction times.[7] Compounds **30** were further cleaved using NaOMe in methanol to yield desired products **31** in good yields (Scheme 1.2.4). Short reaction times, easy isolation of the products and recyclability are inherent advantages of this protocol (Scheme 1.2.6).



Scheme1.2.6 Knoevenagel condensation reaction on benzaldehyde-functionalized ionic liquid **12**

1.2.4 Crossed aldol reaction

Bazureau and group also utilized benzaldehyde-functionalized ionic liquid **15** in the crossed aldol reaction (Scheme 1.2.7).[18] Proline catalyzed asymmetric intramolecular aldol reaction of **15** with various ketones **32** gave **33,** which upon cleavage with NaOMe afforded alodol adducts **34** in good yields. A moderate enantiomeric excess (49% ee) of **34** was obtained using this methodology.

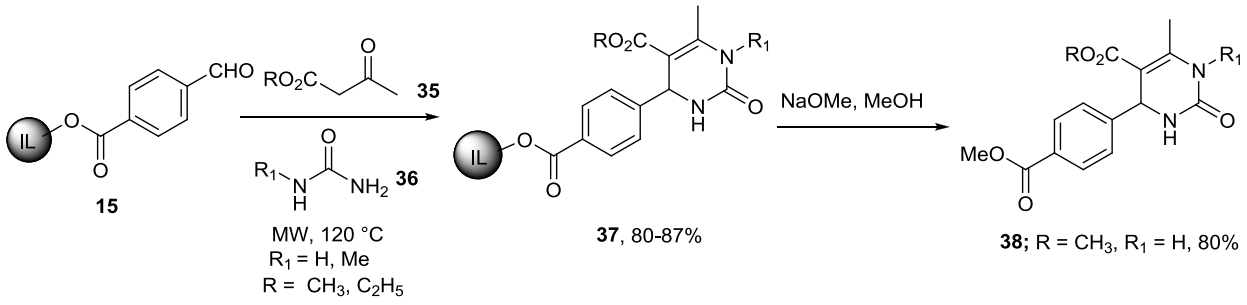


Scheme 1.2.7 Aldol condensation reactions on benzaldehyde-functionalized ionic liquid **15**

1.2.5 Biginelli reaction

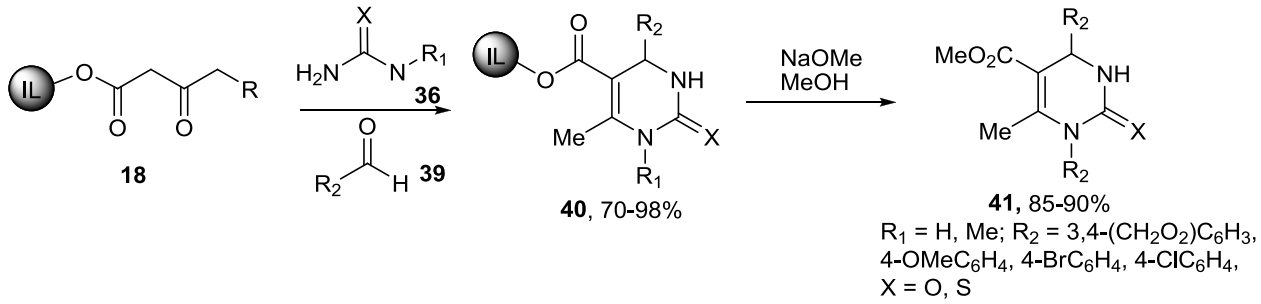
1.2.5.1 Synthesis of 3,4-dihydropyrimidine-2(1*H*)-one

Biginelli reaction is a well known and widely used reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones derivatives.[20-22] Various solid-phase and liquid-phase supported synthesis have been developed for Biginelli condensation reactions. To overcome the purification problems and low yields, Bazureau developed two different IoLiPOS methodologies for Biginelli reaction. In the first approach, benzaldehyde-functionalized ionic liquid **15** was reacted with variety of 1,3-diketone **35** and substituted urea derivatives **36** under focused microwave heating to generate ionic liquid-bound 3,4-dihydropyrimidin-2(1*H*)-ones **37** in very good yields. Excess of urea derivative **34** was removed with cold deionised water. Finally, dismantling of the ionic liquid was performed using NaOMe in methanol to give 3,4-dihydropyrimidin-2(1*H*)-one derivatives **38** (Scheme 1.2.8).[12]



Scheme 1.2.8 Biginelli reaction benzaldehyde-functionalized ionic liquid **15**

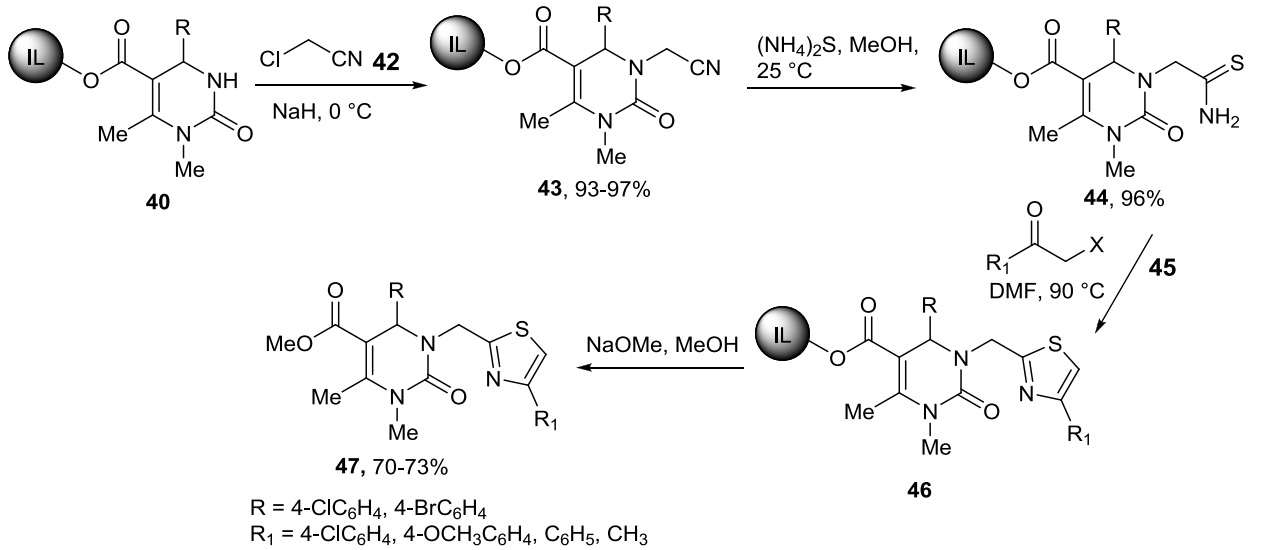
In the second approach, 1,3-diketone-functionalized ionic liquid **18** was reacted with aldehyde **39** and urea derivatives **34** in the presence of a catalytic amount of HCl yielded **40**, which was cleaved using NaOMe in MeOH to give 3,4-dihydropyrimidine-2(1*H*)-one derivatives **41** (Scheme 1.2.9).[14]



Scheme 1.2.9 Biginelli reaction on 1,3-diketone-functionalized ionic liquid **18**

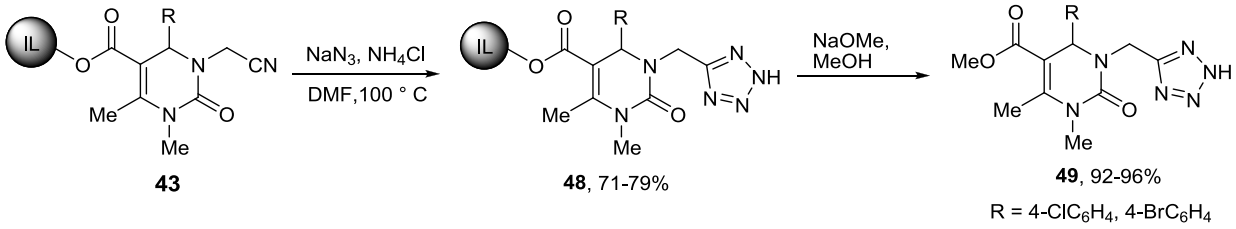
1.2.5.2 Functionalization of 3,4-dihydropyrimidine-2(1*H*)-ones

Diversity in the ionic liquid-phase Biginelli reaction was accomplished by constructing various aza-heterocycles on N-3 position of **40**. The key precursor **43** was obtained by alkylation of **40** with excess of chloroacetonitrile **42** in the presence of NaH. The conversion of nitrile group **43** to thioamide **44** was accomplished by reaction with an excess of ammonium sulfide in methanol. The thiazole ring was constructed by reacting **44** with α-haloacetophenones **45** in DMF. Ionic liquid tags were dismantled from **46** by transesterification reaction using NaOMe in methanol resulted in the desired product **47** in good yields (Scheme 1.2.10).[16]



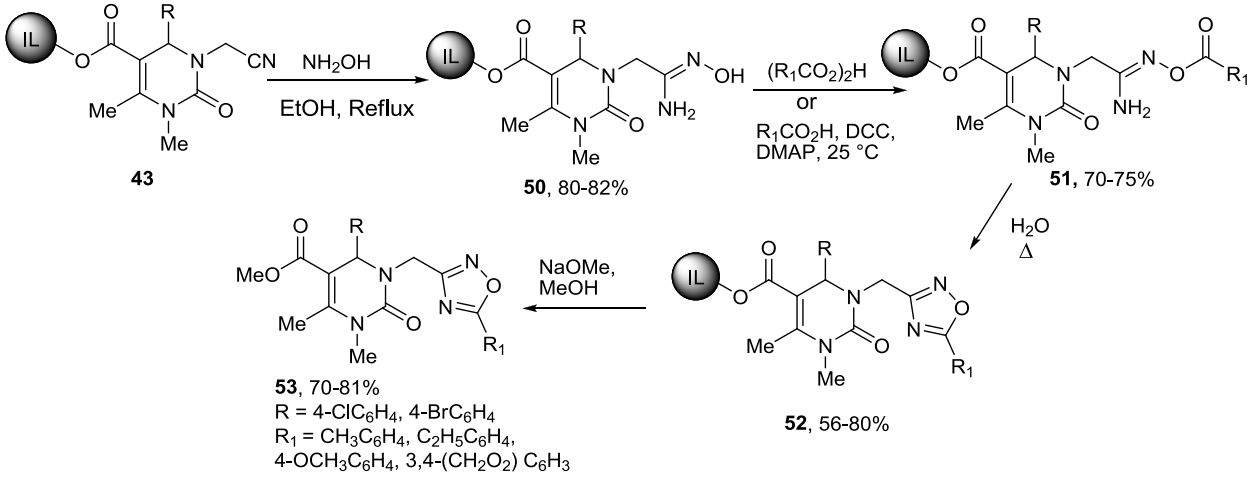
Scheme 1.2.10 Construction of thiazole ring on 3,4-dihydropyrimidine-2(1*H*)-ones

Same group has synthesized tetrazole derivative using IoLiPOS methodology. Desired tetrazoles **49** were synthesized from **43** in two steps as shown in scheme 1.2.11. Initially, tetrazole ring was constructed by the reaction of **43** with NaN_3 and NH_4Cl in DMF under reflux conditions. Finally, Ionic liquid-tags were cleaved using NaOMe in methanol to give **49** in good yields **(**Scheme 1.2.11**).**[16]



Scheme 1.2.11 Construction of tetrazoles on 3,4-dihydropyrimidine-2(1*H*)-ones

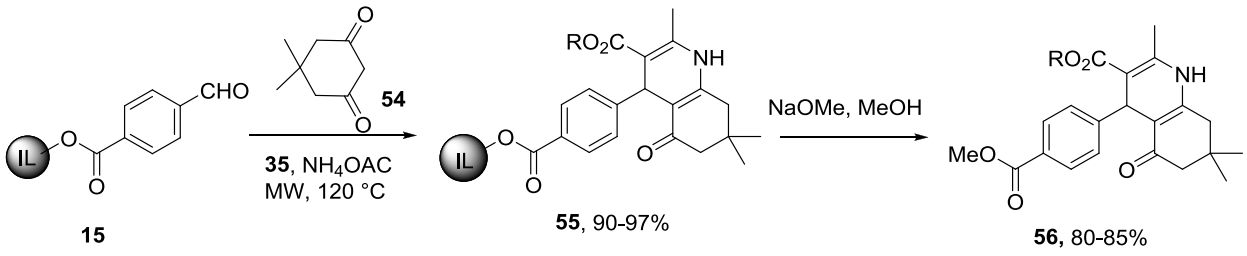
The methodology was further broaden by constructing 1,2,4-oxadiazoles using similar strategy.[15] Ionic liquid-bound nitrile **43** was converted into key intermediate amidoximes **50** as shown in scheme 1.2.12. O-Acylation of amidoximes with acids or acid anhydrides followed by heating in water resulted in ionic liquid-bound 1,2,4-oxadiazoles **52** in good yields. Ionic liquid tags were cleaved by transesterification reaction to get 1,4 oxadiazole derivatives **53** in moderate yields.



Scheme 1.2.12 Consrtuction of on 3,4-dihydropyrimidine-2(1*H*)-ones

1.2.6 Hantzsch condensation

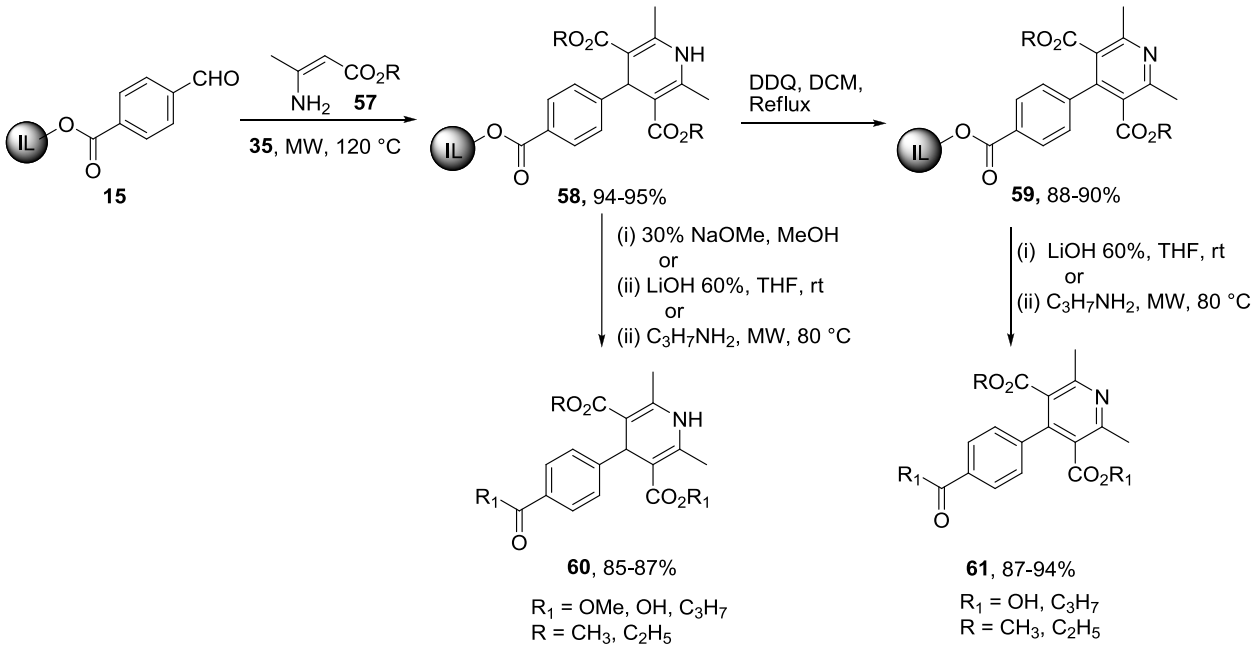
Dihydropyridine derivatives are important structural motifs with wide occurrence in unnatural and natural compounds exhibiting important biological activities.[23, 24] Dihydropyridine derivatives were synthesized *via* Hantzsch condensation reaction.[25] Hantzsch dihydropyridine synthesis is a multi-component organic reaction between an aldehyde, two equivalents of 1,3-diketone and a nitrogen donor. Bazureau developed three different IoLiPOS strategies for the synthesis of 1,4-dihydropyridines.



Scheme 1.2.13 Hantzsch condensation on aldehyde functionalized ionic liquid**15**

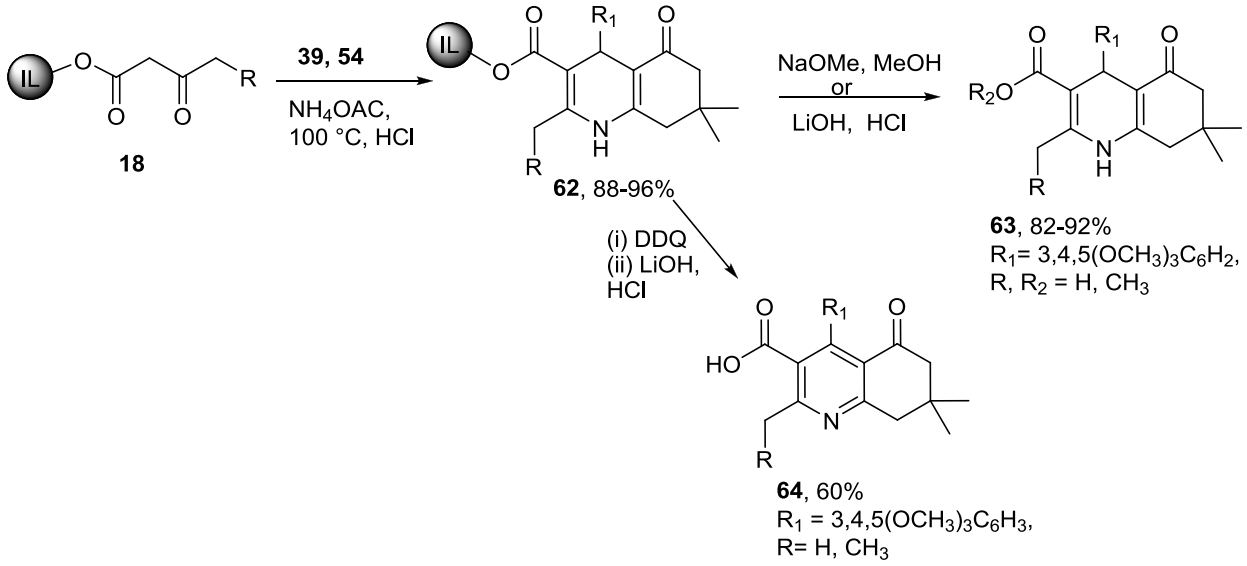
The reaction of **15** with equimolar concentrations of dimedone **54**, ester **35** and NH_4OAc under microwave heating yielded ionic liquid-bound Hantzsch condensation products **55,** which upon cleavage with NaOMe in methanol gave **d**esired compounds **56** (Scheme 1.2.13).[12]

The Hantzsch condensation reaction also worked efficiently when aminocrotonate **57** was employed in place of dimedone **54** and NH_4OAc as shown in scheme 1.2.14.[12] A high degree of chemical diversity was introduced by employing different cleavage conditions. Transesterification reaction with NaOMe, ester aminolysis with various alkyl amines and saponification reaction with LiOH were employed to synthesize wide range of derivatives. Ionic liquid-supported dihydropyridine derivatives **58** were further oxidized and ionic liquid tags were cleaved to give pyridine derivatives **61**.



Scheme 1.2.14 Demonstration of Hantzsch condensation on ionic liquid-supported aldehyde **15**

In a different approach, Bazureau and group demonstrated Hantzsch condensation reaction on 1,3-diketone functionalized ionic liquid **18** as shown in scheme 1.2.15.

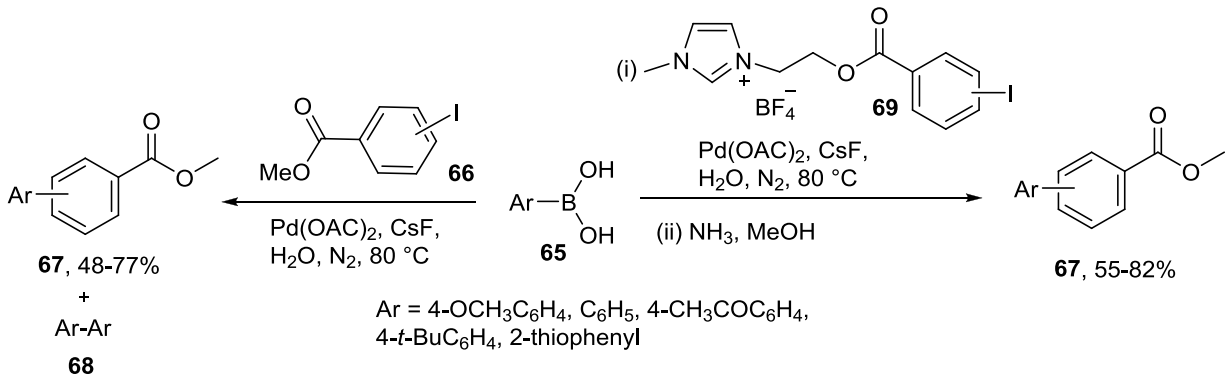


Scheme 1.2.15 Hantzsch condensation reaction 1,3diketone functionalized ionic liquid **18**

Reaction of **18** with dimedone **54**, aldehyde **39**, and NH_4OAc under acidic conditions gave ionic liquid-supported dihydropyridine derivatives **62** in good to excellent yields.[13] Further diversity was introduced into the ionic liquid-phase Hantzsch condensation by oxidizing **62** to pyridine derivatives **64** (Scheme 1.2.15).

1.2.7 Suzuki coupling reaction

In order to demonstrate the superiority of IoLiPOS over the conventional solution-phase synthesis, Chan and Miao demonstrated a series of Suzuki coupling reactions on the ionic liquid-supported iodobenzoates **69** (Scheme 1.2.16).[26] Suzuki coupling reactions of **66** with arylboronic acid **65** gave mixture of products **67** and **68** along with unreacted **66**. Chromatographic purification was mandatory in order to get pure products **67**. On the contrary, employing ionic liquid-supported iodobenzene **69** gave desired products **67** in superior yields in two steps without the need for chromatographic purification. The reason for the higher yield is attributed to the better solubility of the **69** in the reaction media and the possible rate enhancing effect of the positive charge of **69**.

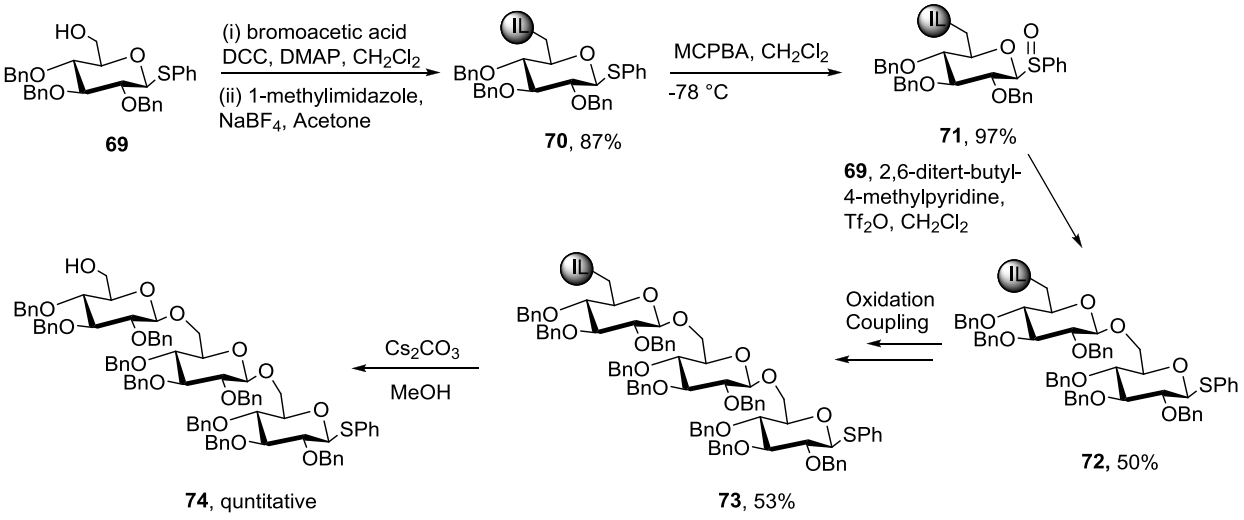


Scheme 1.2.16 Suzuki coupling reaction on ionic liquid-supported iodobenzene **69**

1.2.8 Synthesis of bio-oligomers

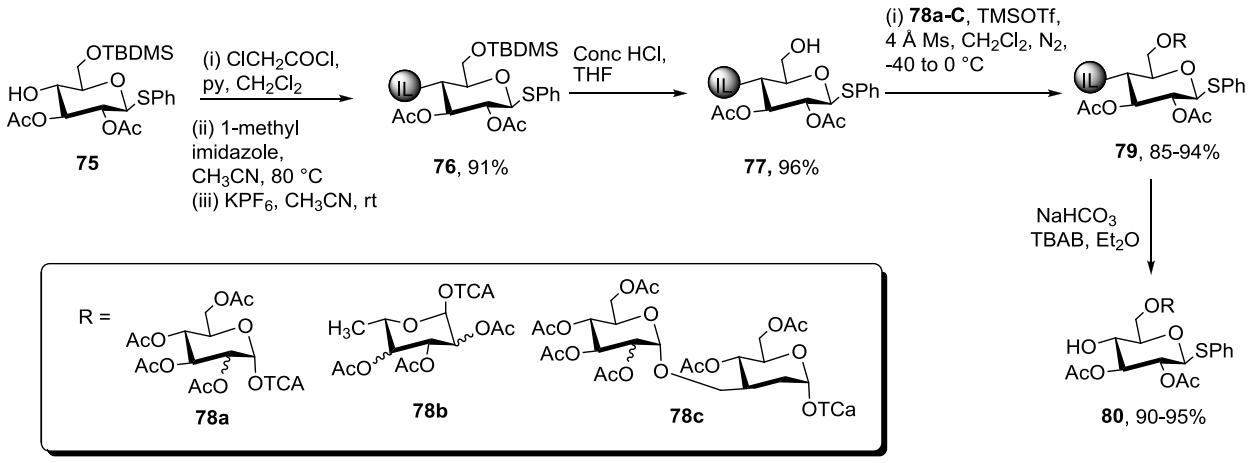
Chan and He were first to apply IoLiPOS strategy for the synthesis of oligosaccharides.[27] This strategy represents proves to be good alternative to the solid and soluble supported oligosaccharides synthesis. Though the fluorous supports have excellent loading capacity, as the number of saccharide unit's increases the solubility of the fluorous support alters, which may cause severe isolation problems.

To overcome the drawbacks of the solid and fluorous supported oligosaccharide synthesis Chan and He demonstrated IoLiPOS for the synthesis of polysacaride **74**. Initially, β-thioglycoside **69** was covalently anchored onto the ionic liquid-support and subsequently oxidized to **71** as shown in scheme 1.2.17. The ionic liquid-supported sulfoxide **71** was thus coupled to the glycosyl alcohol **69** to give the ionic liquid-supported disaccharide **72**. Same sequence of oxidation/coupling repeated to give the trisaccharide **73**. Finally dismantling the ionic liquid from **73** gave the free trisaccharide **74** in good yields and high purity.



Scheme 1.2.17 Ionic liquid supported trisaccharide synthesis

Meanwhile in the same time, Wang and co-workers also used IoLiPOS strategy for the synthesis of oligosaccharides **80**.[28] Initially, β-D-glucopyranose derivative **75** was immobilized to 1-methylimidazole to give ionic liquid-supported **76**. The TBDMS protecting group of **76** was dismantled and polysaccharides synthesis was carried out on **77**. Ionic liquid-supported β-D-glucopyranose **77** was coupled with various glucopyranose **78a-c** to give different ionic liquid-polysaccharides **79** as shown scheme 1.2.18. Excess reagents and by-products could be removed at each stage by washing with diethyl ether and ethyl acetate. Progress of the reaction was easily monitored by ^{1}HNMR and ^{13}CNMR. Finally, Ionic liquid-tags were cleaved using a saturated aqueous $NaHCO_3$ solution with TBAB to give oligosaccharides **80** with high yield and purity.



Scheme 1.2.18 Ionic liquid supported oligosaccharides synthesis

1.2.9 Conclusions

The excellent articles published on the use of TSILs as soluble supports in various organic transformations in the last decade are underpinning their importance and great potential in organic synthesis. TSILs have provided efficient ways of addressing some of the disadvantages of solid-phase synthesis and fluorous phase synthesis. The linker strategy developed for solid-phase synthesis and fluorous phase synthesis can be applied to ionic liquids to generate new functionalized ionic liquids. With increased availability of functionalized ionic liquids, they should find applications in the synthesis of complex molecules and biomolecules.

1.2.10 References

[1] Miao, W.; Chan, T. H., *Accounts of Chemical Research*, **2006**, *39*, 897.
[2] Toy, P. H.; Janda, K. D., *Accounts of Chemical Research*, **2000**, *33*, 546.
[3] Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R., *Bioorganic & Medicinal Chemistry*, **2000**, *8*, 69.
[4] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F., *Chemistry – A European Journal*, **2000**, *6*, 133.
[5] Gravert, D. J.; Janda, K. D., *Chemical Reviews*, **1997**, *97*, 489.
[6] Dubreuil, J. F.; Bazureau, J. P., *Tetrahedron Letters*, **2000**, *41*, 7351.
[7] Fraga-Dubreuil, J.; Bazureau, J. P., *Tetrahedron Letters*, **2001**, *42*, 6097.
[8] Fraga-Dubreuil, J.; Famelart, M.-H.; Bazureau, J. P., *Organic Process Research & Development*, **2002**, *6*, 374.
[9] Fraga-Dubreuil, J.; Bazureau, J. P., *Tetrahedron*, **2003**, *59*, 6121.
[10] Hakkou, H.; Vanden Eynde, J. J.; Hamelin, J.; Bazureau, J. P., *Tetrahedron*, **2004**, *60*, 3745.
[11] Hakkou, H.; Vanden Eynde, J. J.; Hamelin, J.; Bazureau, J. P., *Synthesis*, **2004**, 1793.
[12] Legeay, J.-C.; Vanden Eynde, J. J.; Bazureau, J. P., *Tetrahedron*, **2005**, *61*, 12386.
[13] Legeay, J. C.; Goujon, J. Y.; Vanden Eynde, J. J.; Toupet, L.; Bazureau, J. P., *Journal of Combinatorial Chemistry*, **2006**, *8*, 829.
[14] Jean Christophe Legeay, J. J. V. E., Loic Toupet and Jean Pierre Bazureaua, *ARKIVOC*, **2007**, *iii*, 13.
[15] Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P., *Tetrahedron Letters*, **2007**, *48*, 1063.
[16] Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P., *Tetrahedron*, **2008**, *64*, 5328.
[17] Duchet, L.; Legeay, J. C.; Carrié, D.; Paquin, L.; Vanden Eynde, J. J.; Bazureau, J. P., *Tetrahedron*, **2010**, *66*, 986.
[18] Hakkou, H.; Carrié, D.; Paquin, L.; Bazureau, J. P., *Russian Journal of Organic Chemistry*, **2011**, *47*, 371.
[19] Handy, S. T.; Okello, M., *Tetrahedron Letters*, **2003**, *44*, 8399.
[20] Cepanec, I.; Litvić, M.; Bartolinčić, A.; Lovrić, M., *Tetrahedron*, **2005**, *61*, 4275.
[21] Hazarkhani, H.; Karimi, B., *Synthesis*, **2004**, 1239.
[22] Khodaei, M. M.; Khosropour, A. R.; Jowkar, M., *Synthesis*, **2005**, 1301.
[23] Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F., *Tetrahedron Letters*, **2005**, *46*, 5771.
[24] Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B., *Chemical Reviews*, **2012**, *112*, 2642.
[25] De Paolis, O.; Baffoe, J.; Landge, S. M.; Török, B., *Synthesis*, **2008**, 3423.
[26] Miao, W.; Chan, T. H., *Organic Letters*, **2003**, *5*, 5003.
[27] He, X.; Chan, T. H., *Synthesis*, **2006**, 1645.
[28] Huang, J.-Y.; Lei, M.; Wang, Y.-G., *Tetrahedron Letters*, **2006**, *47*, 3047.

CHAPTER II

Synthesis of Novel Aldehyde Functionalized Ionic Liquid and its Applications in Organic Synthesis

PART A

Ionic Liquid Supported Aldehyde: A Highly Efficient Scavenger for Primary Amines

PART-A: Ionic Liquid-supported Aldehyde: A Highly Efficient Scavenger for Primary amines

2.1.1 Introduction

For the last several years, solid-phase synthesis has been utilized to generate large molecular libraries of small organic molecules in synthetic organic chemistry.[1-3] A significant number of organic reactions on various solid supports and a variety of linkers have been explored for the discovery of active compounds in pharmaceutical research.[4-11] Despite the success of solid-phase approaches for the generation of large libraries in combinatorial or parallel organic synthesis, they are associated with several disadvantages such as low-loading efficiency, difficulty in characterization of intermediates, prolonged validation-time in conversion of solution-phase protocols to solid-phase methods, inability to affect compound purification prior to the final cleavage from the solid support, use of large excesses of reagents, and difficulty and high cost of synthesis of compounds in adequate quantities for biological evaluation. Thus, particularly for smaller focused arrays, more attention has increasingly turned to the identification of new strategies. This has driven to re-evaluation of supported reagents and scavengers in combinatorial synthesis with combined advantages of solid-phase and solution-phase chemistry.[12-17]

Supported scavengers are a class of organic compounds that are used in synthetic chemistry to capture excess reagents, catalysts and metal complexes in a chemical process. Furthermore, if the reactions proceed poorly and generates by-products or impurities, scavengers or catch and release techniques can lead to isolation of pure products in a simple fashion without the need for conventional purification procedures.[18-20] The fact that only simple work-up operations are

necessary, involving filtration and solvent removal or exchange, is a crucial feature for library generation as the chemistry can be suitable for automation using robotic devices.

The use of supported scavengers expedites synthesis and increases productivity as follows:

1) Reagents and by-products can be trapped and separated by a simple filtration or decantation.
2) Purification protocols like chromatography, which are time consuming and difficult to scale up are not required.
3) One-pot multiple step reactions are more feasible to conduct.
4) They are suitable for use in flow-through applications and automated synthesis.

The removal of un-reacted or excess starting materials can be achieved using a range of supported scavengers.

A series of supported nucleophiles and electrophiles have been developed for the selective removal of reaction impurities. Use of these reagents facilitates the clean solution-phase production of small molecule libraries. The choice of scavenger depends on the nature of both the impurity and the desired product. Covalent scavengers are selective for the removal of electrophiles in the presence of non-electrophiles, nucleophiles in the presence of non-nucleophiles.

Secondary amines are important pharmacophores in many biologically active compounds. Reductive amination is a powerful tool for synthesis of structurally diverse secondary amines that are used in high throughput synthesis. Majority of amines in the pharmaceutical industry are made this way. Reductive amination is a form of amination that involves the conversion of a carbonyl group to an amine *via* an imine or an iminium species. This Schiff base formation is usually promoted by the addition of acetic acid and the imine/iminium species are then reduced

using a boron based hydride source, typically sodium cyanoborohydride or sodium triacetoxyborohydride. Over alkylation that leads to the formation of tertiary amine is main concern in the reductive amination process. In order to overcome over alkylation, excess primary amine is usually used.[21,22] The excess amine has to be removed by tedious column chromatography or traditional distillations in order to get pure compounds. These techniques are often time consuming, labor-intensive, expensive process and may not result in pure compound always. Moreover, these purification techniques are impractical task in the combinatorial synthesis where large numbers of compounds are synthesized. Thus it is desirable to develop and use supported scavenging reagents for selective removal of the primary amines in the presence of the secondary amines. PL-CHO **1**[23,24] PL-AAEM **2**,[24, 25] PL-NCO **3**[19,26-28] and PL-MIA **4**[29] are some of the commonly used polymer supported amine scavengers (Figure 2.1.1).

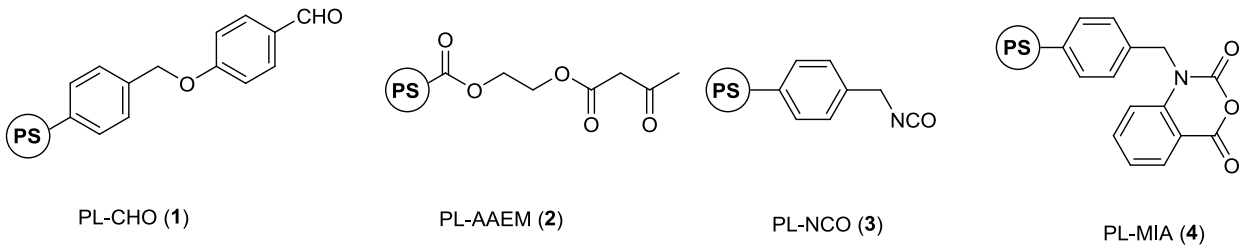
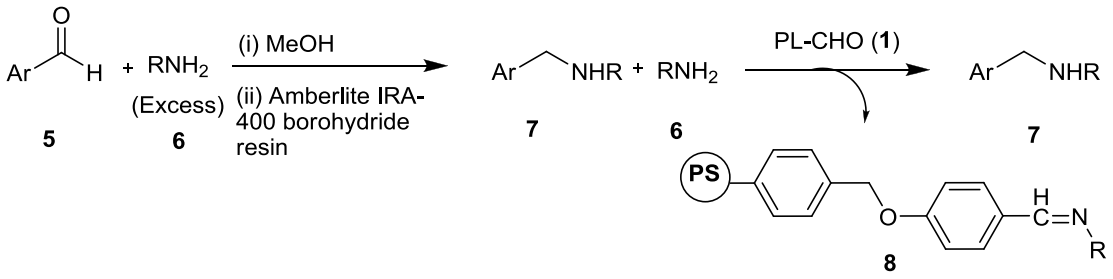


Figure 2.1.1 Polymer-supported amine scavengers **1-4**

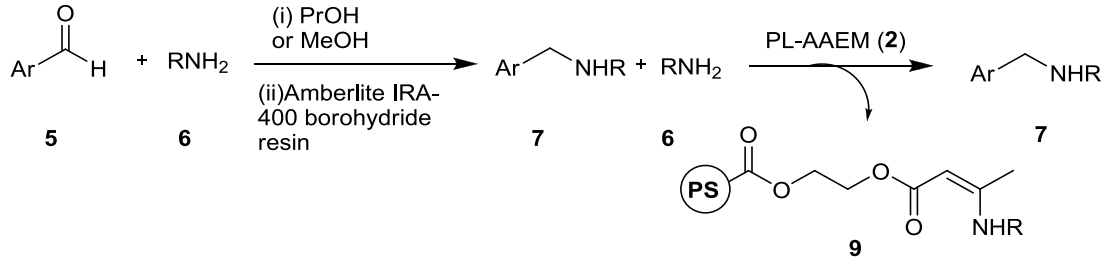
A brief overview of applications of polymer-supported scavengers in the combinatorial synthesis is given below:

Kaldor *et al.*[23, 24] developed a chromatographic free protocol for the synthesis of the secondary amines **7**. In the reductive amination process excess primary amine **6** was readily separated from the desired secondary amine by selective imine **8** formation using a polymer-supported aldehyde **1** (Scheme 2.1.1).



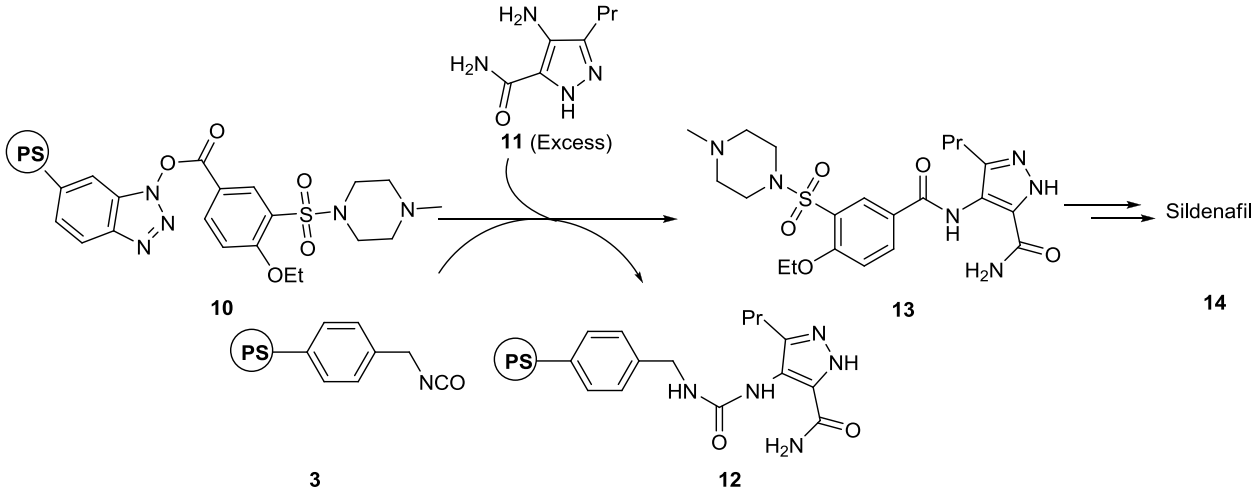
Scheme 2.1.1 Secondary amine synthesis using PL-CHO as scavenger **1**

Bradley and his co-workers demonstrated the application of polymer-supported acetoacetoxyethyl methacrylate (P-AAEM, **2**) in a solution phase library synthesis of secondary amines (**7,** Scheme 2.1.2). P-AAEM resin selectively removed the primary amines in the presence of secondary amines in the reductive amination process (Scheme 2.1.2).



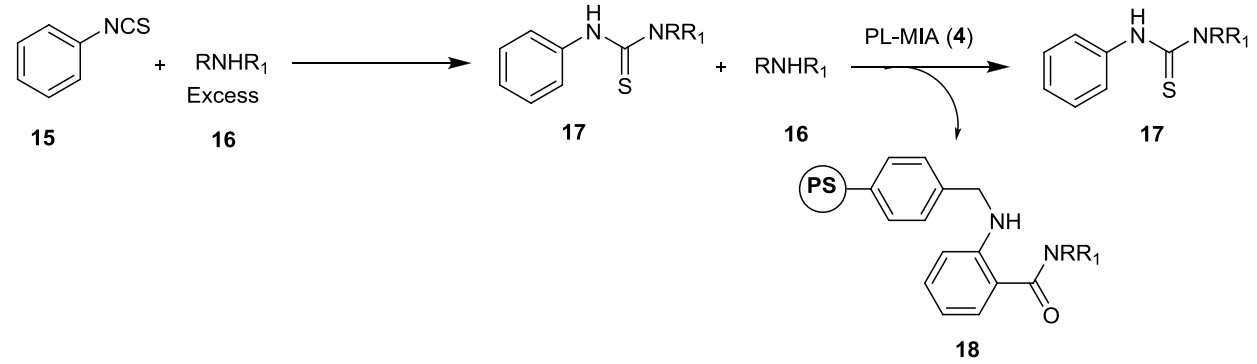
Scheme 2.1.2 Secondary amine synthesis using PL-AAEM **2** as scavenger for primary amines **6**

Ley and Baxendale[30] have demonstrated the application of polymer-supported reagents and scavengers in multi-step organic synthesis of commercially important molecule Sildenafil **14**. In one of the key step, PL-NCO **3** was employed to remove the excess of amino-pyrazole **11** from the reaction mixture as shown in the scheme 2.1.3.



Scheme 2.1.3 Synthesis of Sildenafil using PL-NCO **3** as scavenger

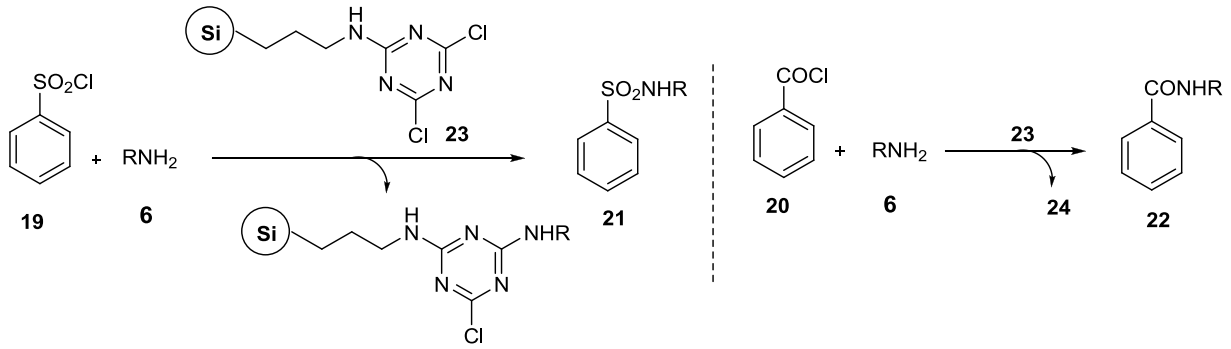
Coppola reported synthesis of novel nucleophilic polymer-supported scavenger **4**.[19,26-28] The carbonyl group of the scavenger **4** is highly susceptible to attack by a variety of nucleophiles. The synthetic utility of scavenger **4** was demonstrated in the synthesis of thioureas **17** by scavenging excess of amines **16** as shown in scheme 2.1.4. The reagent **4** scavenges both primary and secondary amines.



Scheme 2.1.4 Synthesis of thiourea using PL-MIA **4**

Silica has been used as alternative support for immobilization of scavengers and reagents. Reaction kinetics of silica-supported scavengers is superior compare to their polymer-counter parts due to the easy availability of functional groups on the surface of the support. Free flowing nature of silica-supported reagents allows straightforward handling and high mechanical stability allows for conventional methods of stirring. Many functionalized silica gels like supported-

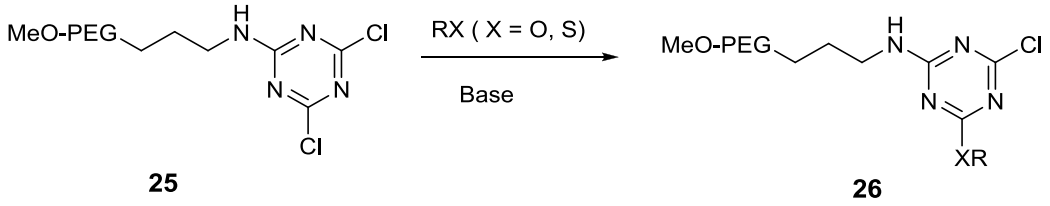
thiocyantes, amines, tosyl chlorides and tosylhydrazines are commercially available for use in synthesis and scavenging. Pattarawarapan and Singhatana[31] illustrated a new method for heterogeneous nucleophilic scavenging of amines with silica-supported dichlorotriazine (Si-DCT, **23**). An excess amine **6** from sulfonamides **21** and amides **22** synthesis was completely removed by simply adding Si-DCT **23**, followed by filtering off the solid (Scheme 2.1.5). Moreover, silica-supported reagent **23** is cheaper than its corresponding polymer-supported reagent.



Scheme 2.1.5 Synthesis of amides & sulfonamides using Si-DCT **23** as scavenger

Despite the great success of polymer-supported reagents, it still suffers from low loading capacity and heterogeneous reaction conditions. Moreover, synthesis of polymer-supported reagents are tricky and it is difficult to find out the amount of reagent that has been grafted on these supports so one has to use excess of these supported reagents to drive the reaction. These deficiencies have prompted the development of alternative supports such as polyethylene glycol (PEG), fluorous materials and ionic liquid for the facile synthesis and purification. PEG-supported scavengers emerged as key alternative to polymer-supported scavengers as it addresses key drawbacks of polymer-supported scavengers, like loading and solubility.[13,22] Once the reaction is completed they are precipitated off and filtered to remove from the reaction mixture. Falchi and Tadde have described a new scavenger system, PEG-dichlorotriazine (PEG-

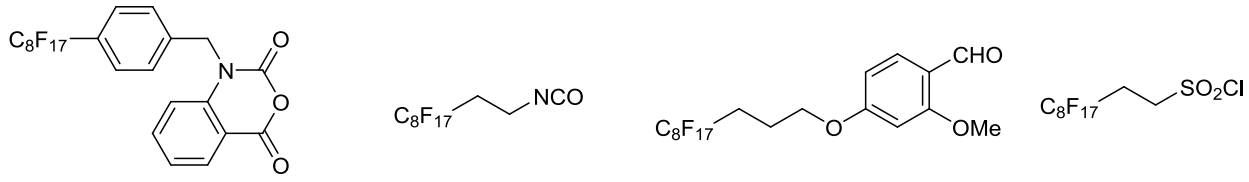
DCT, **25,** Scheme 2.1.6) that was used as a soluble electrophilic scavenger. The PEG-DCT **25** is utilized to remove excess of alcohols, thiols, triphenylphosphine and phosphine oxide from the reaction medium in the synthesis of esters, silyl ethers, acetals, thioacetals and thioglycosides.[22] The main advantage, in this case, is the possibility of working in a homogeneous phase.



25 **26**

Scheme 2.1.6 Scavenging of nucleophiles using PEG-DCT **25**

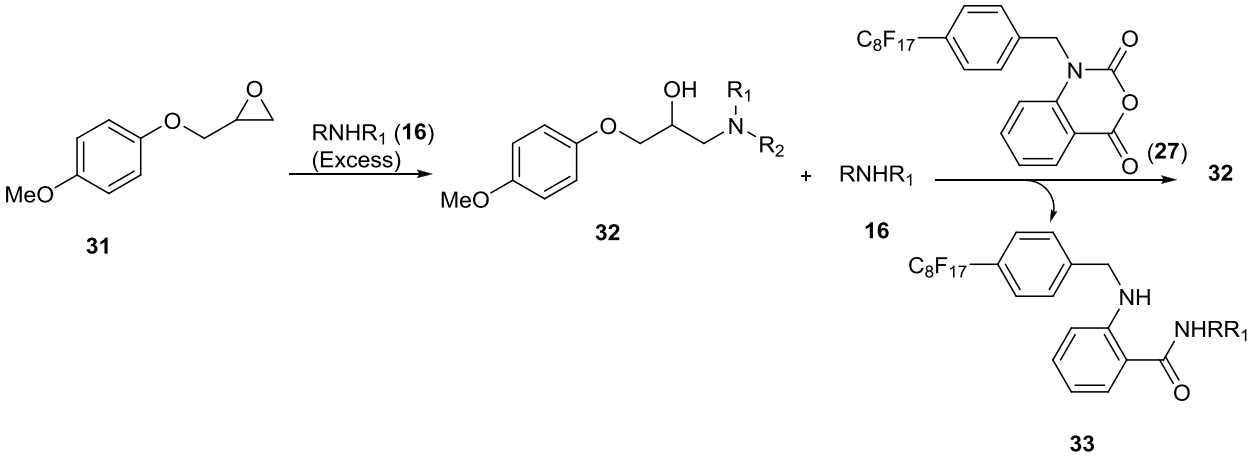
Fluorous-supported reagents and scavengers have gained much prominence over last few years. Fluorous tags do not involve use of polymeric-beads but entails the attachment of perfluroalkyl chain to the reagent and scavengers. Work-up involves the use of liquid-liquid extraction for the separation of fluorous and non-fluorous materials. Reagents **27**-**30** are commonly used fluorous - supported scavengers (Figure 2.1.2).



27 **28** **29** **30**

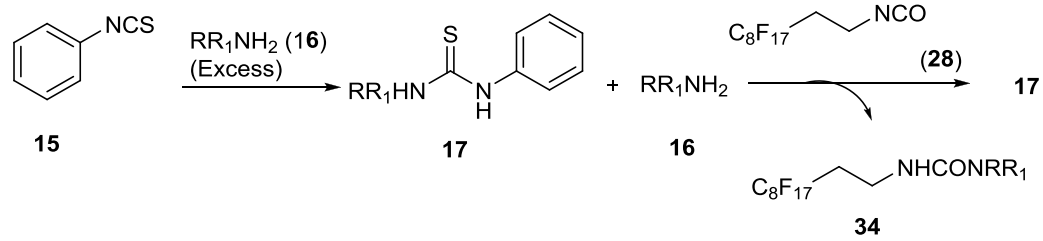
Figure 2.1.2 Fluorous-supported scavengers **27**-**30**

Zhang and his co-workers elegantly demonstrated the use of fluorous-supported scavengers in solution-phase parallel synthesis of hydroxylamine **32**. Excess of amine was readily removed from the reaction mixture by employing functionalised fluorous-supported scavengers isatoic anhydride **27** and isocyanate **28** (Scheme 2.1.7).[32, 33]



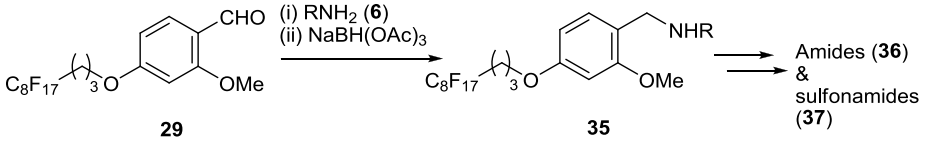
Scheme 2.1.7 Synthesis of hydroxylamine analogs **32** using **27** as scavenger

Zhang and his co-workers further demonstrated the use of fluorous-supported scavengers in solution-phase parallel synthesis of thiourea **17** analogs as shown in scheme 2.1.8.



Scheme 2.1.8 Synthesis of thiourea analogs **17** using **28** as scavenger

Villard *et al.*[34] synthesized a new acid-labile, fluorous-tagged carboxaldehyde **29** to facilitate the rapid parallel solution-phase multistep synthesis of amides **36** and sulphonamides **37**. The reductive amination of **29** resulted in fluorous-tagged amines **35** which were further derivatized to amides **36** and sulphonamides **37** by series of reaction (Scheme 2.1.9).



Scheme 2.1.9 Reaction of fluorous-supported aldehyde **29** with amines **6**

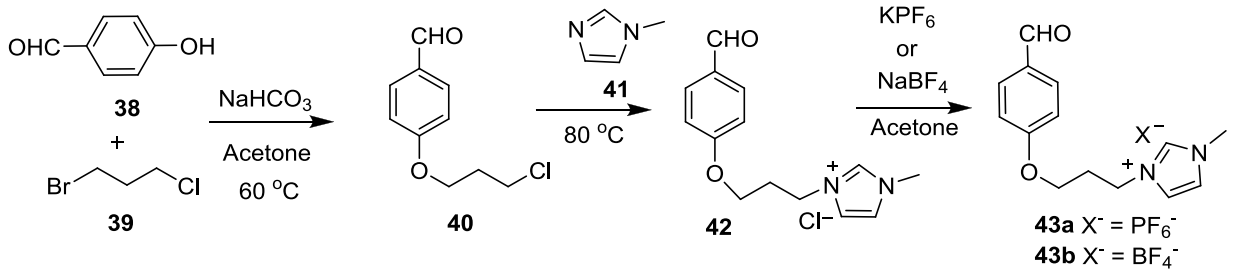
However, synthesis of polymer,[13,14,35] polyethylene glycol (PEG)[36-41] and silica-supported reagents[42-44] are tricky. It is difficult to find out the amount of reagent that has been grafted on these supports so one has to use excess of these supported reagents to drive the reaction. On the other hand fluorous-supported reagents are expensive and need specialized solvents to carry out the reaction.[32,45-47]

In recent years, ionic liquid-supported reagents[48-55] have shown promising alternative to supported reagents due to their high loading capacity, tunable solubility, homogeneity and easy monitoring of the reaction by various analytical techniques such as NMR, IR and mass. Several ionic liquid-supported reagents have been synthesized and used for different organic transformations. With our interest towards the synthesis of novel ionic liquids and to develop ecofriendly reaction methodologies, we have synthesized a novel ionic liquid-supported aldehyde and used as scavenger to remove excess of primary amines in synthesis of secondary amines.

2.1.2 Results and Discussion

Synthesis of two different aldehyde functionalized ionic liquid is achieved as shown in scheme 2.1.10. Reaction of 4-hydroxybenzaldehyde **38** with 1-chloro-3-bromopropane **39** in presence sodium bicarbonate gave monoalkylated aldehyde **40**. Reaction of **40** with *N*-methylimidazole **41** at 80 °C gave corresponding chloride salt **42**. Anion exchange of **42** with KPF_6 and $NaBF_4$ resulted in corresponding ionic liquids **43a** and **43b** respectively.

The structure of **43a** and **43b** is confirmed by ^{1}H NMR and high-resolution mass spectrometry. The ^{1}H NMR of **43a** spectrum showed a singlet at 9.84 ppm for aldehydic proton, a singlet at 3.82 ppm for the methyl protons of *N*-methyl, two triplets and a multiplet at 3.63, 3.34 and 1.67 ppm for OCH_2, NCH_2 and CH_2, respectively along with other aromatic protons of imidazolium and aryl ring as shown in the figure 2.1.3. In ESI-MS a peak appeared at 245.13 $[M - PF_6]^+$ or $[M - BF_4]^+$ for both **43a** and **43b**.



Scheme 2.1.10 Synthesis of ionic liquid-supported aldehydes **43a** and **43b**

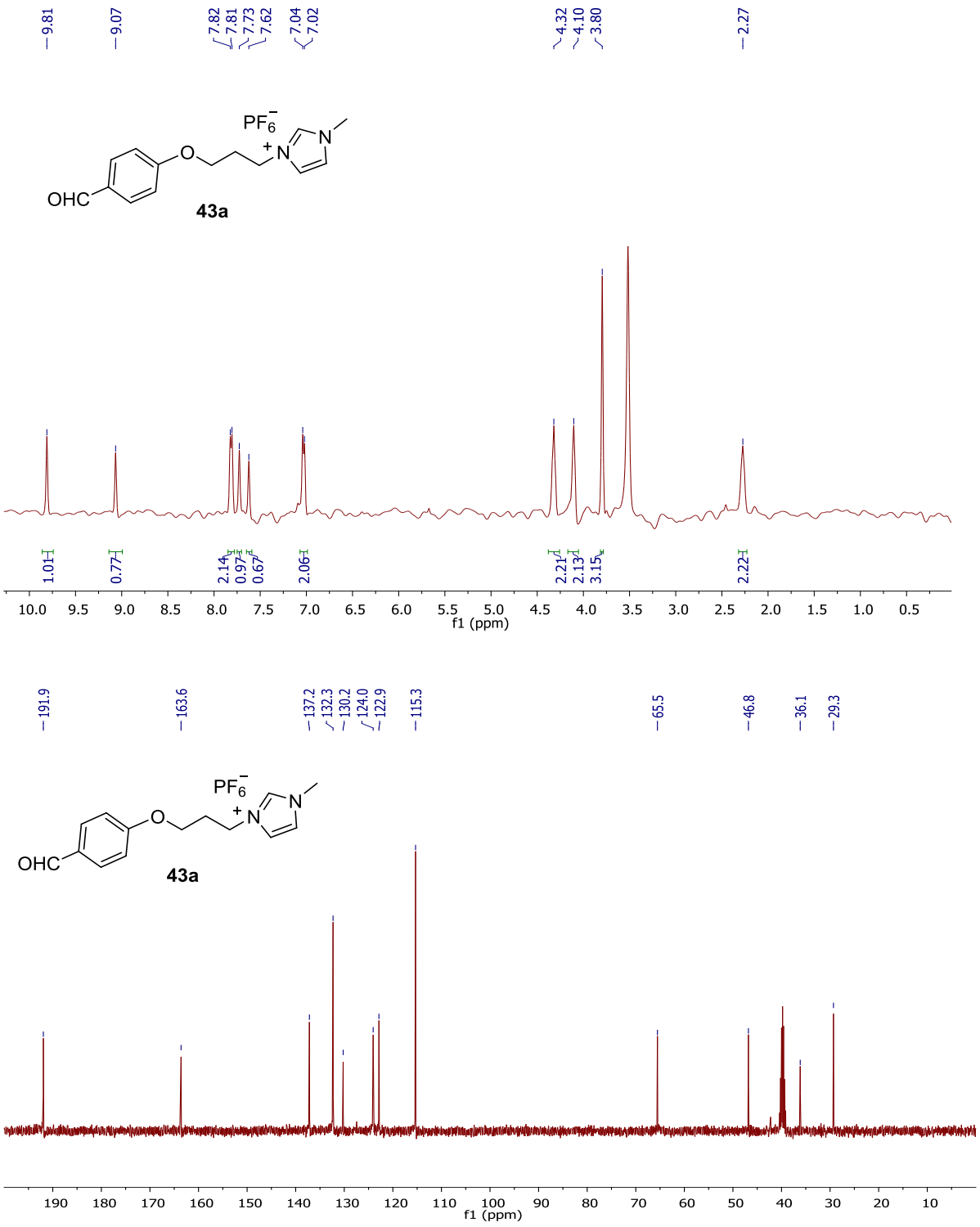
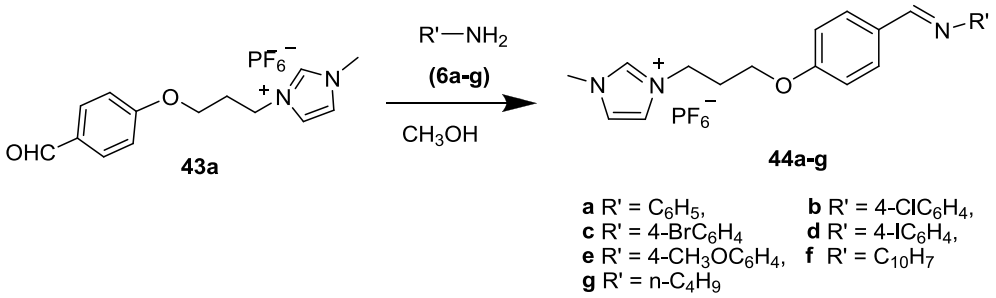


Figure 2.1.3 ^{1}H NMR and ^{13}C NMR spectrum of ionic liquid-supported aldehyde **43a**



Scheme 2.1.8 Synthesis of ionic liquid-supported imines **44** using **43a**

Table 2.1.1: Yields of ionic liquid-supported imines

Entry	R'	Imines	Yield (%)[a]
1	C_6H_5	**44a**	87 (60)[b]
2	4-ClC_6H_4	**44b**	87 (52)[c]
3	4-BrC_6H_4	**44c**	86
4	4-IC_6H_4	**44d**	86
5	4-$CH_3OC_6H_4$	**44e**	89
6	$C_{10}H_7$	**44f**	85
7	n-C_4H_9	**44g**	70

[a]Isolated yield
[b]In absence of 0.1 mol% of acetic acid.
[c]Isolated yield when **43b** was used.

After synthesizing ionic liquid-supported aldehydes **43a** and **43b**, we studied their scavenging properties by reacting with *p*-chloroaniline **6b** under different conditions (Scheme 2.1.11). Only 60% of **44b** was obtained when **43a** was reacted with **6a** in methanol under reflux conditions after 6 h. Adding catalytic amount of acetic acid dramatically increased yield of **44b** to 87% in 4 h at room temperature. The imine of **43a** precipitates out in methanol (Figure 2.1.4, B), whereas

imine of **43b** was completely soluble in methanol (Figure 2.1.4, C). Thus simple filtration and washing with appropriate solvents separates out **44b** from reaction mixture. Reaction of seven different amines **7a-g** with **43a** was studied to give corresponding ionic liquid-supported imines **44a-g** in excellent yields (Table 2.1.1). The structure of ionic liquid-supported imines was confirmed by ^{1}H NMR and ^{13}C NMR analysis. Figure 2.1.5 demonstrates representative ^{1}H and ^{13}C NMR of ionic liquid-supported imine **44a**. In all aromatic amines **6a-f** corresponding ionic liquid-supported imines **44a-f** precipitated in methanol and were removed by filtration, however, for n-butylamine **6g** the ionic liquid supported imine **44g** was liquid and did not precipitate in methanol. In this case methanol was evaporated and excess amine was removed by extraction with ethyl acetate leaving behind **44g**.

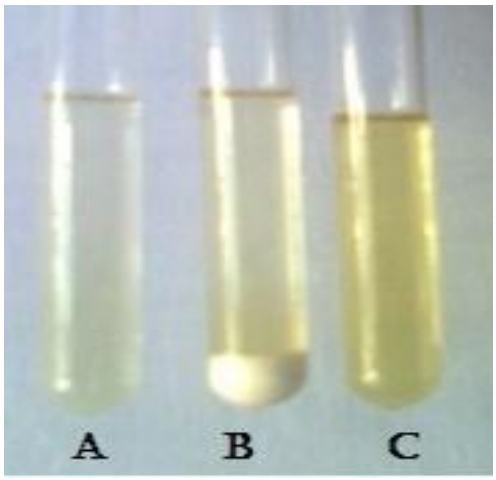


Figure 2.1.4 Capture of **6b** in **43a** and **43b**, A) Only methanol + **6b**, B) methanol + **6b** + **43a**, C) methanol + **6b** + **43b**.

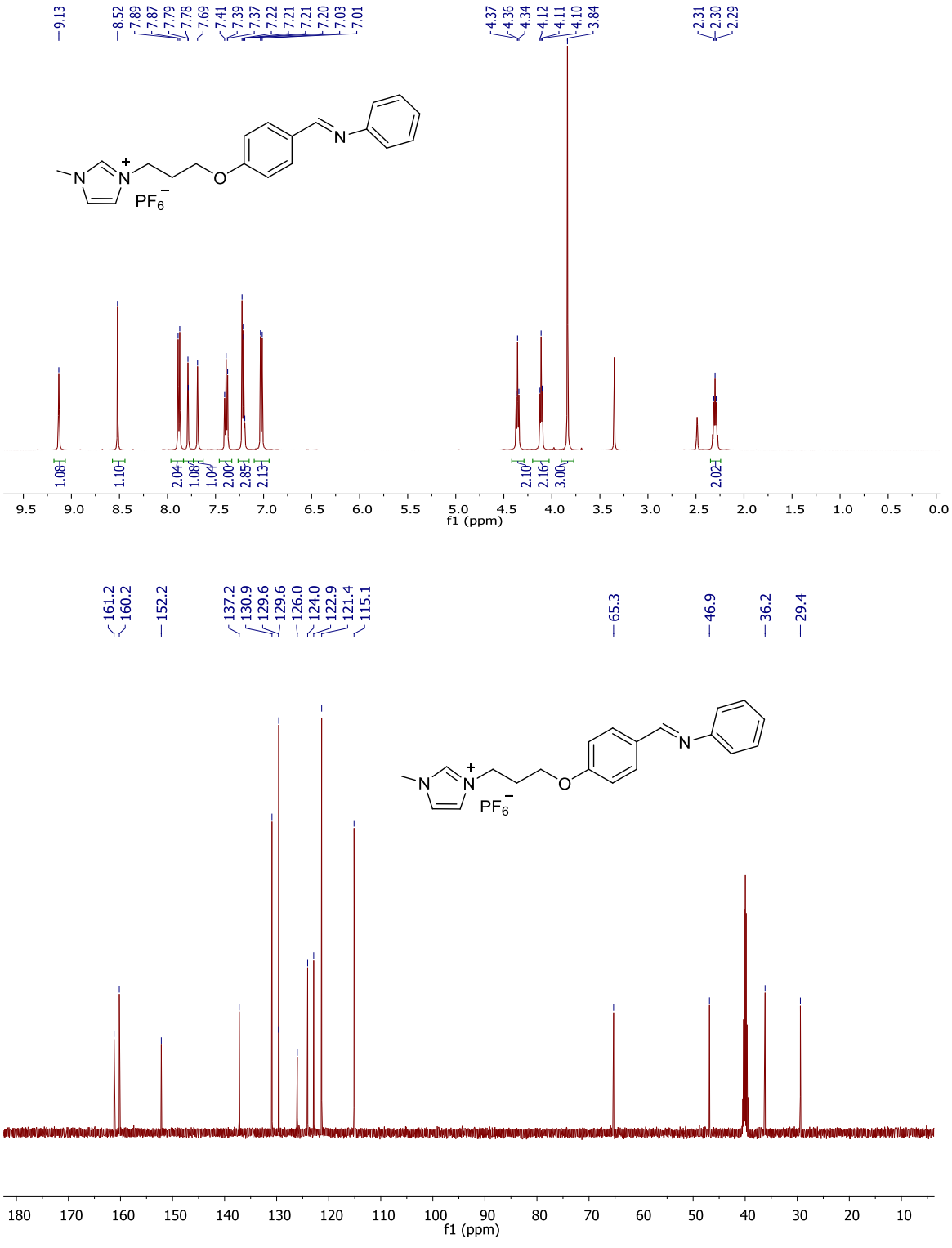
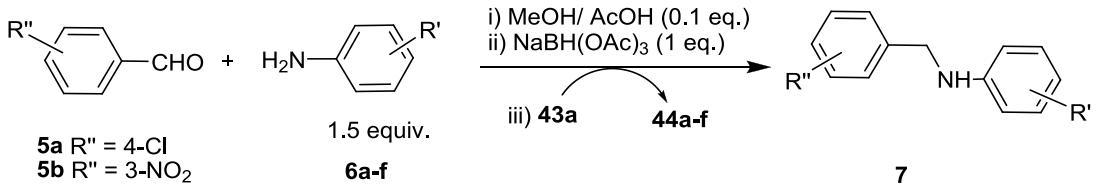


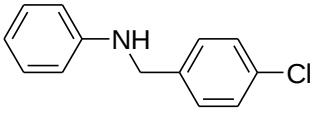
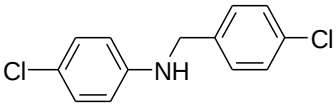
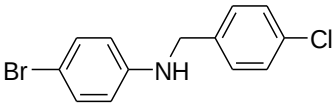
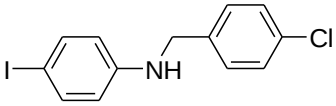
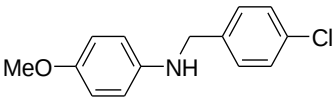
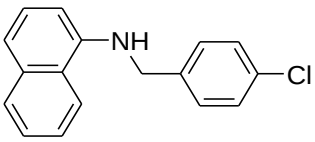
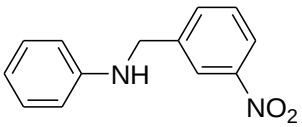
Figure 2.1.5 ^{1}H and ^{13}C NMR spectrum of ionic liquid-supported imine **44a**

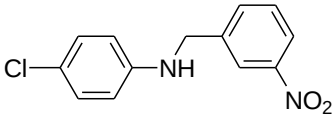
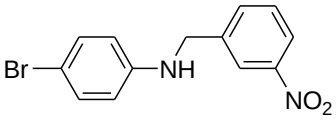
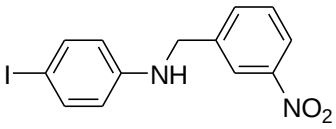
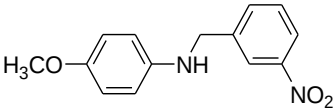
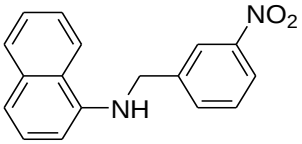
Next, the application of **43a** as scavenger for primary amines was demonstrated in parallel synthesis of secondary amines. 4-Chlorobenzaldehyde **5a** was reacted with excess 4-chloroaniline **6b** in methanol to give imine which was then reduced to *N*-(4-chlorobenzyl)-4-chlorobenzenamine **7b** by adding $NaBH(OAc)_3$. After completion of reduction of imine, excess of **6b** was removed by precipitation of **44b** on reaction with **43a** with **6b** (Scheme 2.1.12). Using this methodology a small library of secondary amines was synthesized. The yield and purity of different secondary amines **7a-l** are shown in table 2.1. 2. All the synthesized secondary amines were characterized by ^{1}H NMR and ^{13}C NMR spectroscopic data. The method is simple and gives high yield of secondary amines with high purity in shorter reaction time. Guinó *et al.* used polymer-supported aldehyde as a scavenger for synthesis of small library of secondary amines and it took around 3 days for complete process,[56] whereas in our method the synthesis and purification process completed in 9-10 h.



Scheme 2.1.9 Synthesis of secondary amines using **43a** as scavenger

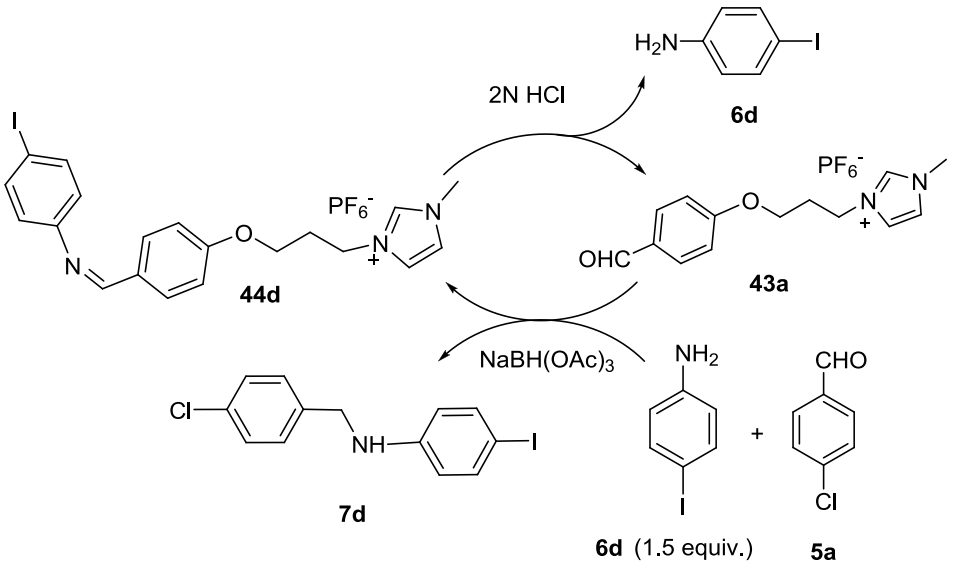
Table 2.1.2: Yields of secondary amines

Entry	Aldehyde	Amine	Secondary amines		%Yield[a] (Purity)[b]
1	**5a**	**6a**		**7a**	84 (96)
2	**5a**	**6b**		**7b**	85 (98)
3	**5a**	**6c**		**7c**	82 (95)
4	**5a**	**6d**		**7d**	83[c] (>94)
5	**5a**	**6e**		**7e**	86 (98)
6	**5a**	**6f**		**7f**	82 (96)
7	**5a**	**6a**		**7g**	92 (99)

8	**5a**	**6b**		**7h**	90 (96)
9	**5a**	**6c**		**7i**	88 (98)
10	**5a**	**6d**		**7j**	87 (99)
11	**5a**	**6e**		**7k**	90 (98)
12	**5a**	**6f**		**7l**	88 (97)

[a]Isolated yield
[b]Purity determined by HPLC.
[c]Yield of **7d** in 2nd and 3rd cycle were 80 and 78%, respectively.

To reuse the ionic liquid-supported aldehyde **43a,** it was regenerated by treating with 2N HCl solution after filtration from reaction mass (Scheme 2.1.13). The regenerated **43a** was reused for scavenging of aniline **6d** for 3 times without much loss of activity (Table 2.1.2, Entry 4).



Scheme 2.1.10 Reuse of **6a** as scavenger

2.1.3 Conclusions

We have synthesized a novel aldehyde functionalized ionic liquid and used it as scavenger for primary amines in the synthesis of secondary amines. The yield of secondary amines are high (82-90%) with high purity. The ionic liquid supported aldehyde is highly efficient scavenger for the primary amines and complete process time using this scavenger is shorter than the polymer supported aldehyde scavenger.

2.1.4 Experimental

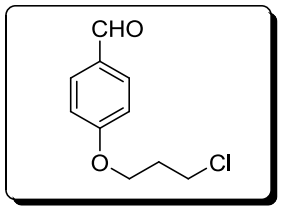
General: The ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 & 500 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 as solvents with ^{1}H resonant frequency of 400 MHz & 500 MHz and ^{13}C resonant frequency of 101 & 126 MHz. The chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants (*J*) in

Hz. The mass spectra were recorded on QSTAR® ELITE LX/MS/MS from Applied Biosystems. Melting points were determined on open capillary tube on MPA-120 automated melting point apparatus and are uncorrected. All chemicals are purchased from Sigma-Aldrich and are used without further purification. Thin-layer chromatography (TLC) was performed on Merck-precoated silica gel 60-F_{254} plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

Synthesis of 4-(3-chloropropoxy)benzaldehyde 40

A mixture of 4-hydroxybenzaldehyde **38** (0.041 mol), 1-bromo-3-chloropropane **39** (0.08 mol) and $NaHCO_3$ (0.06 mol) in dry acetone (30 mL) was stirred at 60 ^oC for 60 h. After completion of the reaction, acetone was evaporated and the viscous residue was washed with water and extracted by ethyl acetate (3 × 50 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure to get crude product which was purified by column chromatography on silica using hexane and ethyl acetate as eluent.

4-(3-Chloropropoxy)benzaldehyde 40



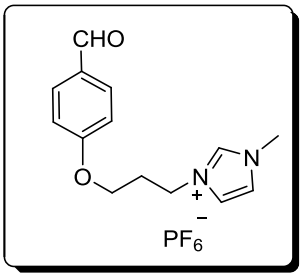
Yield: 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 4.24 – 4.16 (t, *J* = 5.9 Hz, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 2.54 – 2.18 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 163.7, 132.1, 130.1, 114.8, 65.6, 32.1, 29.7; ESI-MS: *m/z* calcd for $C_{10}H_{11}ClO_2$ 198.0448, found 199.0572 $[M + H]^+$.

Synthesis of ionic liquid-supported aldehyde 43a & 43b

A mixture of **40** (0.025 mol) and 1-methylimidazole (0.027 mol) was heated at 80 ^oC for 6 h to give a thick viscous liquid of **42**. The viscous liquid was washed with ethyl acetate (2 × 10 mL) to remove unreacted starting materials to give pure chloride salt. Ion exchange of chloride was

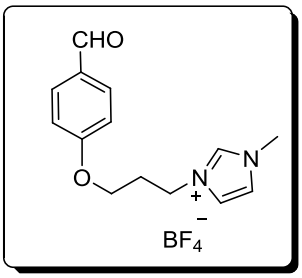
performed in dry acetone (50 mL) using potassium hexafluorophosphate (0.041 mol) for **43a** or sodium tetrafluoroborate (0.041 mol) for **43b** at room temperature for 48 h. After complete exchange of chloride anion as indicated by silver nitrate, acetone was evaporated. In case of **43a** resulting solution was washed with water to remove salts and the ionic liquid was extracted by dichloromethane (DCM) (3 × 50 mL), dried with anhydrous sodium sulfate and evaporated under reduced pressure to get pure **43a** (4.30 g, 90%). In case of **43b** reaction mixture was dissolved in DCM, salts were removed by repeated filtrations through 60-120 mesh silica gel columns. Finally, DCM was evaporated to get pure **43b (**3.86 g, 93%).

Compound 43a



Yield: 96%; M.p. 92-95 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.03 (s, 1H), 7.86 (d, J = 8.78 Hz, 2H), 7.75-7.70 (m, 1H), 7.65-7.59 (m, 1H), 7.05 (d, J = 8.78 Hz, 2H), 4.39 (t, J = 7.0 Hz, 2H), 4.14 (t, J = 6.2 Hz, 1H), 3.85 (s, 3H), 2.35 – 2.26 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.9, 163.6, 137.22, 132.36, 130.18, 124.10, 122.92, 115.31, 65.51, 46.92, 36.07, 29.28; ESI-MS: *m/z* calcd for $C_{14}H_{17}F_6N_2O_2P$ 390.0932, found 245.1302 $[M - PF_6]^+$.

Compound 43b

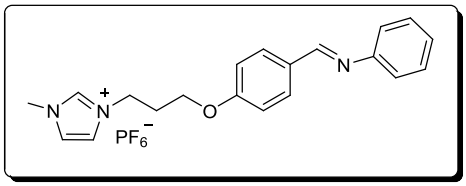


Yield: 93%; M.p. 51-52 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.06 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.64 – 7.56 (m, 1H), 7.08 (d, J = 8.8 Hz, 2H), 4.37 (t, J = 6.9 Hz, 2H), 4.16 (t, J = 6 Hz, 1H), 3.82 (s, 3H), 2.34 – 2.26 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.9, 163.6, 137.2, 132.3, 130.2, 124.0, 122.9, 115.3, 65.5, 46.8, 36.1, 29.3; ESI-MS: *m/z* calcd for $C_{14}H_{17}BF_4N_2O_2$ 332.1319, found 245.1298 $[M - BF_4]^+$.

General procedure for synthesis of ionic liquid-supported imines 44a-g

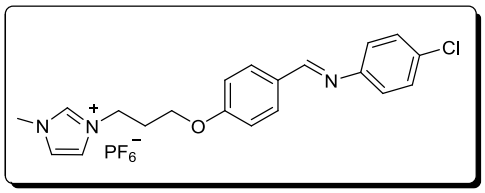
A mixture of ionic liquid-supported aldehyde **43a** or **43b** (0.0025 mol) and amine **6a-g** (0.003 mol) in methanol in presence of 0.1 % of acetic acid was stirred for 4 h at 30 ˚C. In case of **43a** solid precipitated, which was filtered and washed with methanol to get pure compound. Whereas for **43b** it was soluble in methanol and thus solvent was evaporated and residue obtained was washed with ethyl acetate (3 × 15 mL) to get pure compound.

Compound 44a



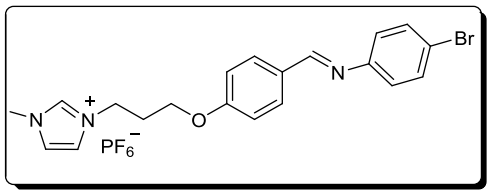
Yield: 87%; M.p. 151-154 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.52 (s, 1H), 7.90 – 7.86 (m, 2H), 7.79 (t, *J* = 2.0 Hz, 1H), 7.69 (t, *J* = 2.0 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.24 – 7.18 (m, 3H), 7.04 – 7.00 (m, 2H), 4.36 (t, *J* = 6.9 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 2.34 – 2.26 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.2, 160.2, 152.2, 137.2, 130.9, 129.6, 129.6, 126.0, 124.0, 122.9, 121.3, 115.1, 65.3, 46.9, 36.28, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{22}F_6N_3OP$ 465.1405, found 320.1789 $[M - PF_6]^+$.

Compound 44b



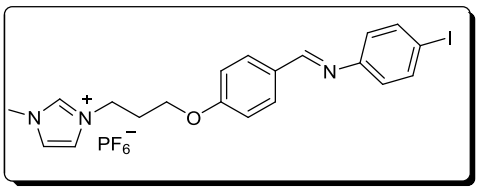
Yield: 87%; M.p. 180-183 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s,1H), 8.53 (s, 1H), 7.89 – 7.86 (m, 2H), 7.79 (t, *J* = 1.9 Hz, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.30 – 7.18 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 2H) 4.35 (t, *J* = 7.0 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 2.35 – 2.25 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 161.0, 150.9, 137.2, 131.0, 130.2, 129.5, 129.4, 124.1, 123.2, 122.9, 115.2, 65.3, 46.8, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{21}ClF_6N_3OP$ 499.1015, found 354.1405 $[M - PF_6]^+$.

Compound 44c



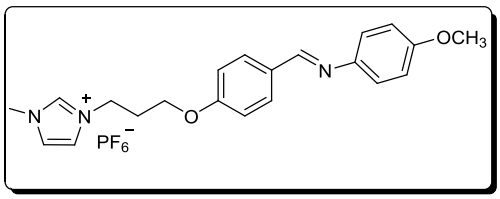
Yield: 86%; M.p. 202-204 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.53 (s, 1H), 7.88 (t, *J* = 10.1 Hz, 2H), 7.79 – 7.74 (m, 1H), 7.70 – 7.63 (m, 1H), 7.56 (t, *J* = 5.9 Hz, 2H), 7.18 (t, *J* = 5.9 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.35 (t, *J* = 6.9 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 2.34 – 2.26 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 161.0, 151.3, 137.2, 132.4, 131.1, 129.4, 124.1, 123.6, 122.9, 118.5, 115.2, 65.3, 46.8, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{21}BrF_6N_3OP$ 543.051, found 398.1012 $[M - PF_6]^+$ and 400.0938 $[M + 2 - PF_6]^+$.

Compound 44d



Yield: 86%; M.p. 220-224 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.53 (s, 1H), 7.89 – 7.85 (m, 2H), 7.79 (t, *J* = 1.9 Hz, 1H), 7.74 – 7.68 (m, 3H), 7.07 – 7.00 (m, 4H), 4.35 (t, *J* = 6.9 Hz, 2H), 4.11 (t, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.35 – 2.25 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 160.9, 151.8, 138.3, 137.2, 131.1, 129.4, 124.1, 123.9, 122.9, 115.2, 90.9, 65.3, 46.8, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{21}F_6IN_3OP$ 591.0371, found 446.0923 $[M - PF_6]^+$.

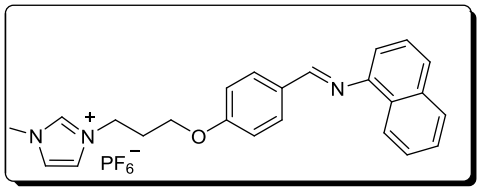
Compound 44e



Yield: 89 %; M.p. 150-153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.54 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.79 (t, *J* = 1.7 Hz, 1H), 7.69 (t, *J* = 1.6 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.97 – 6.94 (m, 2H), 4.35 (t, *J* = 6.9 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.29 (p, *J* = 6.5 Hz, 2H); ^{13}C NMR (126 MHz,

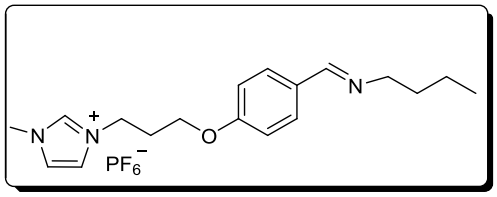
DMSO-d_6) δ 160.9, 158.1, 158.0, 144.8, 137.2, 130.6, 129.9, 124.1, 122.9, 122.6, 115.1, 114.8, 65.2, 55.7, 46.9, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{21}H_{24}F_6N_3OP$ 479.1561, found 334.2016 [M – PF_6]$^+$.

Compound 44f



Yield: 85%; M.p. 149-156 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.62 (s, 1H), 8.31 – 8.25 (m, 1H), 8.04 – 7.98 (m, 2H), 7.92 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 1.9 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 4.37 (t, *J* = 7.0 Hz, 2H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 2.36 – 2.27 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 160.5, 149.0, 137.2, 134.0, 131.1, 129.8, 128.9, 128.1, 126.8, 126.8, 126.2, 125.7, 124.1, 123.9, 122.9, 115.2, 113.4, 65.3, 46.9, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{24}H_{24}F_6N_3OP$ 515.1561, found 370.2031 [M – PF_6]$^+$.

Compound 44g

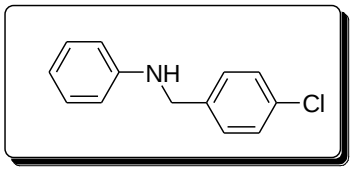


Yield: 70%; Viscous liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.16 (s, 1H), 7.68 (t, *J* = 1.8 Hz, 1H), 7.61 (s, 1H), 7.59 (s, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.36 (t, *J* = 6.9 Hz, 2H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.85 (s, 3H), 2.30 (t, *J* = 6.1 Hz, 2H), 1.62 – 1.52 (m, 2H), 1.38 – 1.25 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.7, 159.2, 136.6, 129.2, 129.1, 123.5, 122.4, 114.1, 64.2, 60.4, 46.46, 35.7, 32.6, 29.0, 19.9, 13.6.

General procedure for solution-phase synthesis of secondary amines 7a-g

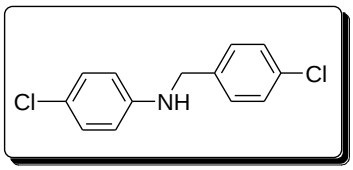
Substituted benzaldehyde (0.001 mol) and amine (0.0015 mol) were added to a round bottom flask containing methanol (3.0 mL) and stirred for 2 h at room temperature. Sodium triacetoxyborohydride (0.00075 mmol) was added to the reaction mixture and stirred for additional 30 min. After completion of reductive amination, **43a** (1 mmol) and 0.1 mol % of acetic acid were added to the reaction mixture and stirred for additional 4 h. After completion of reaction as indicated by TLC, the solid was filtered and resulting solution was evaporated to get pure secondary amine.

N-(4-Chlorobenzyl)benzenamine 7a



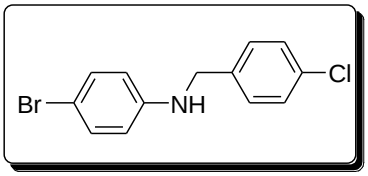
Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 4H), 7.14 – 7.03 (m, 2H), 6.65 (tt, *J* = 7.3, 1.3 Hz, 1H), 6.53 (dd, *J* = 8.7, 1.2 Hz, 2H), 4.23 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 147.8, 138.0, 132.9, 129.3, 128.8, 128.7, 117.8, 112.9, 47.6.

N-(4-Chlorobenzyl)-4-chlorobenzenamine 7b



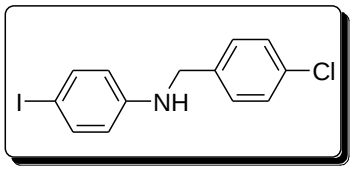
Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.25 (m, 2H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 4.31 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 146.2, 137.4, 133.1, 129.1, 128.8, 128.7, 122.5, 114.1, 47.7.

N-(4-Chlorobenzyl)-4-bromobenzenamine 7c



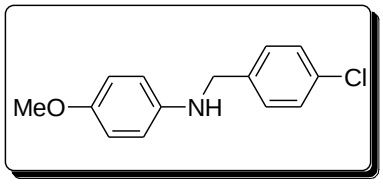
Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.21 – 7.16 (m, 3H), 7.16 – 7.13 (m, 1H), 6.43 – 6.37 (m, 2H), 4.19 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 137.3, 133.1, 132.0, 128.9, 128.7, 114.6, 109.5, 47.6.

N-(4-Chlorobenzyl)-4-iodobenzenamine 7d



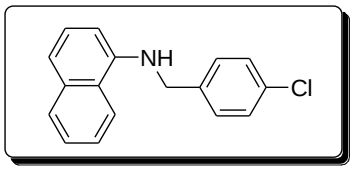
Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.21 – 7.17 (m, 2H), 6.33 (d, *J* = 8.8 Hz, 2H), 4.21 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 137.9, 137.1, 133.1, 128.9, 128.7, 115.4, 100.0, 47.6.

N-(4-Chlorobenzyl)-4-methoxybenzenamine 7e



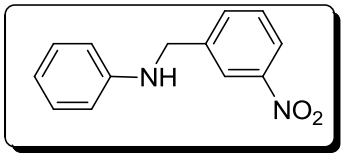
Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.29 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 142.0, 138.2, 132.8, 128.8, 128.7, 114.9, 114.2, 55.8, 48.5.

N-(4-Chlorobenzyl)naphthalen-1-amine 7f



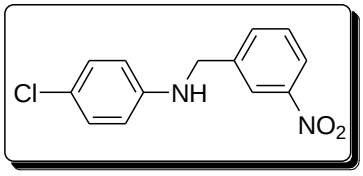
Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 6.9 Hz, 2H), 7.44 – 7.32 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.20 (m, 3H), 7.18 (d, *J* = 9.8 Hz, 1H), 6.47 (d, *J* = 7.1 Hz, 1H), 4.66 (bs, 1H), 4.39 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 137.6, 134.3, 133.1, 128.9, 128.9, 128.8, 126.5, 125.8, 124.9, 123.4, 119.8, 117.9, 104.9, 47.9.

N-(3-Nitrobenzyl)benzenamine 7g



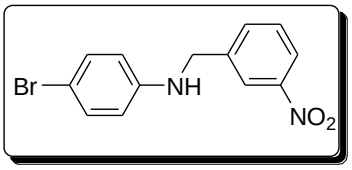
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.97 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.58 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.63 (dt, *J* = 14.7 Hz, 1.0 Hz, 1H), 6.48 (dd, *J* = 8.2, 1.2 Hz, 2H), 4.32 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 147.4, 142.1, 133.4, 129.6, 129.4, 122.3 122.1, 118.2, 113.0, 47.5.

N-(3-Nitrobenzyl)-4-chlorobenzenamine 7h



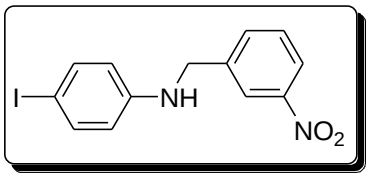
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.13 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.56 – 6.50 (m, 2H), 4.46 (s, 2H), 4.35 (s,1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 145.9, 141.5, 133.2, 129.7, 129.2, 122.7, 122.4, 122.0, 114.1, 47.5.

N-(3-Nitrobenzyl)-4-bromobenzenamine 7i



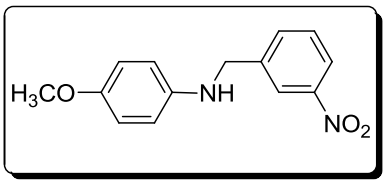
Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.43 – 6.36 (m, 2H), 4.36 (s, 2H), 4.23 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 146.3, 141.4, 133.1, 132.1, 129.7, 122.4, 122.0, 114.5, 109.9, 47.4.

N-(3-Nitrobenzyl)-4-iodobenzenamine 7j



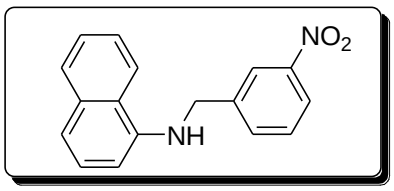
Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 15.0, 7.2 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 8.6 Hz, 2H), 4.45 (d, *J* = 4.4 Hz, 1H), 4.37 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 146.9, 141.4, 137.9, 133.2, 129.7, 122.4, 122.0, 115.2, 47.2.

N-(3-Nitrobenzyl)-4-methoxybenzenamine 7k



Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.03 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 4.33 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 148.5, 142.2, 141.3, 133.4, 129.5, 122.2, 122.2, 115.0, 114.3, 55.8, 48.5.

N-(3-Nitrobenzyl)naphthalen-1-amine 7l



Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.74 (dt, *J* = 8.5, 4.9 Hz, 914.0, 7.6 Hz, 2H), 6.44 (d, *J* = 6.0 Hz, 1H), 4.57 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 144.2, 142.1, 141.4, 134.3, 133.4, 129.7, 128.8, 126.4, 126.0, 125.2, 123.5, 122.5, 122.3, 119.8, 118.7, 47. 9.

General procedure for regeneration of ionic liquid-supported aldehyde 43a

To the ionic liquid supported imines **44d** (50 mg), 2N HCl (1.0 mL) was added and stirred vigorously for 4 h. During the progress of reaction, color of ionic liquid amine changed from colorless to yellowish. After completion of reaction, reaction mixture was neutralized by $NaHCO_3$ and compound was extracted by DCM (3.0 mL). The organic layer was dried with sodium sulfate and evaporated and extracted with hexane and ethyl acetate mixture (1: 1 *v/v*) to remove 4-iodoaniline **7d**. After removal of **7d**, the residue was dried under reduced pressure to get ionic liquid aldehyde **6a**. Yield: 28 mg, 85%.

2.1.5 References

[1] Dörwald, F. Z., Wiley-VCH Verlag GmbH & Co.: Weinheim, **2000**.

[2] Burgess, K., John-Wiley and Sons, Inc.: **2000**.

[3] Kates, S. A.; Albericio, F., Marcel Dekker: New York: **2000**.

[4] Ganesan, A., *Mini-Reviews in Medicinal Chemistry*, **2006**, *6*, 3.

[5] Cironi, A.; Alvarez, M.; Albericio, F., *Mini-Reviews in Medicinal Chemistry*, **2006**, *6*, 11.

[6] Lam, K. S.; Liu, R.; Miyamoto, S.; Lehman, A. L.; Tuscano, J. M., *Accounts of Chemical Research*, **2003**, *36*, 370.

[7] Leznoff, C. C., *Accounts of Chemical Research*, **1978**, *11*, 327.

[8] Cowley, P. M.; Rees, D. C., *Current Medicinal Chemistry*, **1997**, *4*, 211.

[9] Gordon, K.; Balasubramanian, S., *Journal of Chemical Technology and Biotechnology*, **1999**, *74*, 835.

[10] Bergbreiter, D. E., *Current Opinion in Drug Discovery & Development*, **2001**, *4*, 736.

[11] Adang, A. E. P.; Hermkens, P. H. H., *Current Medicinal Chemistry*, **2001**, *8*, 985.

[12] Varma, R. S., *Green Chemistry*, **1999**, *1*, 43.

[13] Thompson, L. A., *Current Opinion in Chemical Biology*, **2000**, *4*, 324.

[14] Ley, S. V.; Schucht, O.; W. Thomas, A.; John Murray, P., *Journal of the Chemical Society, Perkin Transactions 1*, **1999**, 1251.

[15] Kobayashi, S., *Chemical Society Reviews*, **1999**, *28*, 1.

[16] Lu, J.; Toy, P. H., *Chemical Reviews*, **2009**, *109*, 815.

[17] Dickerson, T. J.; Reed, N. N.; Janda, K. D., *Chemical Reviews*, **2002**, *102*, 3325.

[18] Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J., *Journal of the Chemical Society, Perkin Transactions 1*, **2000**, 3815.

[19] Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J., *Tetrahedron Letters*, **1996**, *37*, 7193.

[20] Hodge, P., *Current Opinion in Chemical Biology*, **2003**, *7*, 362.

[21] Robichaud, A.; Nait Ajjou, A., *Tetrahedron Letters*, **2006**, *47*, 3633.

[22] Miriyala, B.; Bhattacharyya, S.; Williamson, J. S., *Tetrahedron*, **2004**, *60*, 1463.

[23] Creswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppen, M., *Tetrahedron*, **1998**, *54*, 3983.

[24] Yu, Z.; Alesso, S.; Pears, D.; Worthington, P. A.; Luke, R. W. A.; Bradley, M., *Tetrahedron Letters*, **2000**, *41*, 8963.

[25] Schön, U.; Messinger, J.; Merayo, N.; Juszkiewicz, G.; Kirschning, A., *Synlett*, **2003**, 983.

[26] Booth, R. J.; Hodges, J. C., *Journal of the American Chemical Society*, **1997**, *119*, 4882.

[27] Dressman, B. A.; Singh, U.; Kaldor, S. W., *Tetrahedron Letters*, **1998**, *39*, 3631.

[28] Hulme, C.; Ma, L.; Romano, J.; Morrissette, M., *Tetrahedron Letters*, **1999**, *40*, 7925.

[29] Coppola, G. M., *Tetrahedron Letters*, **1998**, *39*, 8233.

[30] Baxendale, I. R.; Ley, S. V., *Bioorganic & Medicinal Chemistry Letters*, **2000**, *10*, 1983.
[31] Singhatana, M. P. A. S., *Chiang Mai Journal of Science*, **2006**, *33*, 203.
[32] Chen, C.-T.; Zhang, W., *Molecular Diversity*, **2005**, *9*, 353.
[33] Zhang, W.; Chen, C. H.-T.; Nagashima, T., *Tetrahedron Letters*, **2003**, *44*, 2065.
[34] Villard, A.-L.; Warrington, B. H.; Ladlow, M., *Journal of Combinatorial Chemistry*, **2004**, *6*, 611.
[35] Ley, S. V.; Leach, A. G.; Storer, R. I., *Journal of the Chemical Society, Perkin Transactions 1*, **2001**, 358.
[36] Gravert, D. J.; Janda, K. D., *Chemical Reviews*, **1997**, *97*, 489.
[37] Sieber, F.; Wentworth, P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D., *Journal of Organic Chemistry*, **1999**, *64*, 5188.
[38] Toy, P. H.; Janda, K. D., *Accounts of Chemical Research*, **2000**, *33*, 546.
[39] Wipf, P.; Venkatraman, S., *Tetrahedron Letters*, **1996**, *37*, 4659.
[40] Wentworth, A. D.; Wentworth, P.; Mansoor, U. F.; Janda, K. D., *Organic Letters*, **2000**, *2*, 477.
[41] Wentworth Jr, P.; D. Janda, K., *Chemical Communications*, **1999**, 1917.
[42] Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C., *The Journal of Organic Chemistry*, **2001**, *66*, 8154.
[43] Michaud, A.; Gingras, G.; Morin, M.; Béland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M., *Organic Process Research & Development*, **2007**, *11*, 766.
[44] Varma, R. S., *Tetrahedron*, **2002**, *58*, 1235.
[45] Miura, T.; Goto, K.; Hosaka, D.; Inazu, T., *Angewandte Chemie International Edition*, **2003**, *42*, 2047.
[46] Dobbs, A. P.; Kimberley, M. R., *Journal of Fluorine Chemistry*, **2002**, *118*, 3.
[47] Zong, C.; Venot, A.; Dhamale, O.; Boons, G.-J., *Organic Letters*, **2013**, *15*, 342.
[48] Zolfigol, M. A.; Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Kruger, H. G.; Asgari, Z.; Khakyzadeh, V.; Kazem-Rostami, M., *The Journal of Organic Chemistry*, **2012**, *77*, 3640.
[49] D'Anna, F.; Marullo, S.; Noto, R., *The Journal of Organic Chemistry*, **2008**, *73*, 6224.
[50] Kamal, A.; Chouhan, G., *Tetrahedron Letters*, **2005**, *46*, 1489.
[51] Yadav, L. D. S.; Patel, R.; Rai, V. K.; Srivastava, V. P., *Tetrahedron Letters*, **2007**, *48*, 7793.
[52] Zhu, C.; Yoshimura, A.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V., *Tetrahedron Letters*, **2012**, *53*, 1438.
[53] Qian, W.; Jin, E.; Bao, W.; Zhang, Y., *Angewandte Chemie International Edition*, **2005**, *44*, 952.
[54] Suzuki, Y.; Iinuma, M.; Moriyama, K.; Togo, H., *Synlett*, **2012**, 1250.
[55] Iinuma, M.; Moriyama, K.; Togo, H., *Tetrahedron*, **2013**, *69*, 2961.
[56] Guinó, M.; Brulé, E.; de Miguel, Y. R., *Journal of Combinatorial Chemistry*, **2003**, *5*, 161.

PART B

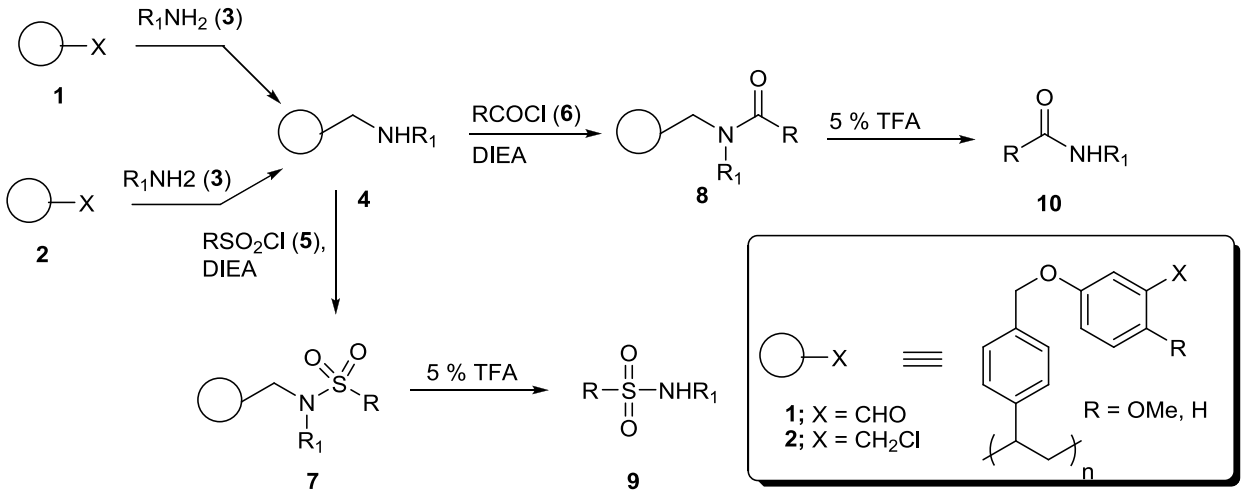
Ionic Liquid-Supported Synthesis of Sulfonamides and Carboxamides

PART-B: Ionic Liquid-Supported Synthesis of Sulfonamides and Carboxamides

2.2.1 Introduction

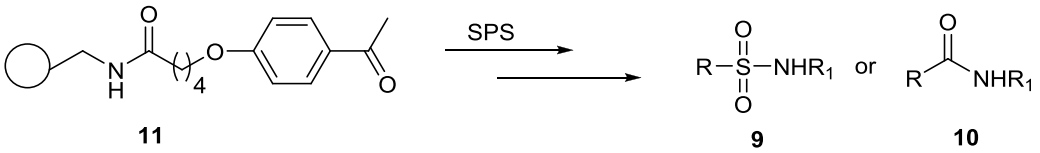
In view of pharmacological importance of sulfonamides and amides, their synthesis has been an area of high interest in medicinal chemistry research. The amide bond is a key building unit in many natural and synthetic compounds. A number of small molecules with amide functionality have been shown to possess various biological activities such as antibacterial,[1] antitumor,[2] antiviral, Kv1.5 channel inhibition,[3] and VEGFR-2 kinase inhibition.[4] Sulfonamide moiety is a common pharmacophore in various biologically important molecules. Sulfonamides are pharmacologically significant as therapeutic agents as shown in sulfa antibiotics, serotonin antagonists, antifungal,[5,6] antibacterial,[7] and antitubercular agents.[8] Isoquinoline sulfonamides inhibit protein kinases by competing with ATP. In view of their importance in drug discovery, several solid-phase routes have been reported for the synthesis of a large number of structurally diversified sulfonamides and amides.[9-11]

Willson and Fivush developed a novel acid sensitive aldehyde functional group resin, AMEBA **1**.[12] Reductive amination of **1** generated resin bound amines **4**, which were further derivatized to polymer-supported sulfonamides **7** and amides **8**. Cleavage of these resins under acidic conditions (5 % TFA/CH_2Cl_2) generated the desired products in moderate yields with high purity (Scheme 2.2.1). Raju and Kogan used, halomethyl equivalents of Wang's resin **2** for the synthesis of amides and sulfonamides. Amines **3** were tethered on the polymer *via* nucleophilic substitution reaction to produce resin **4**. Sulfonylation or acylation followed by resin cleavage under acidic conditions gave amides **10** and sulfonamides **9** in good yields.



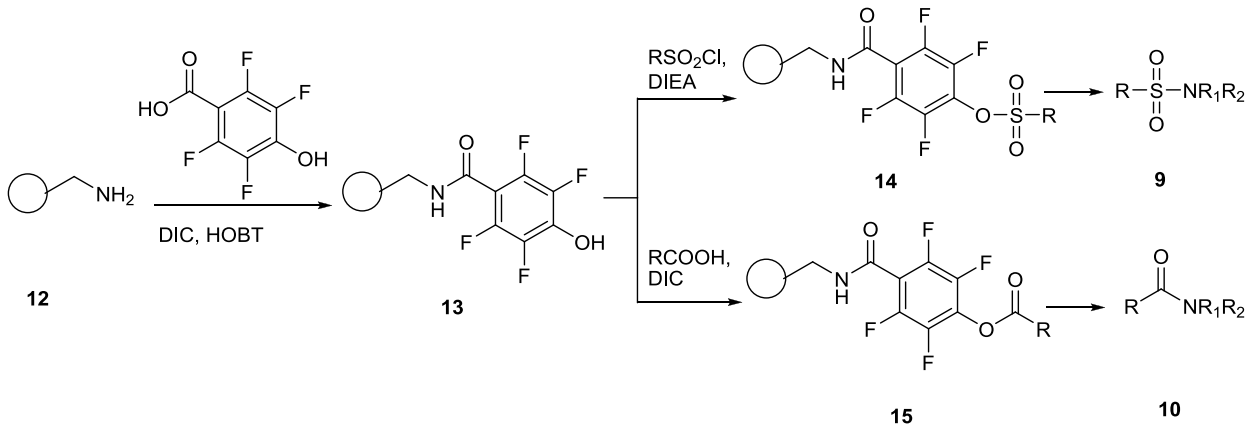
Scheme 2.2.1 Synthesis of sulfonamides and carboxamides using resins **1** and **2**

Bui *et al.*[13] established the use of acetophenone-based linker **11** for solid phase synthesis of sulfonamides **9** and secondary amides **10**. Acetophenone moiety was anchored on the solid support *via* an amide linkage. Sequential reductive amination/acylation or sulfonylation followed by cleavage with TFA resulted in the amides and sulfonamides in excellent yields (Scheme 2.2.2).



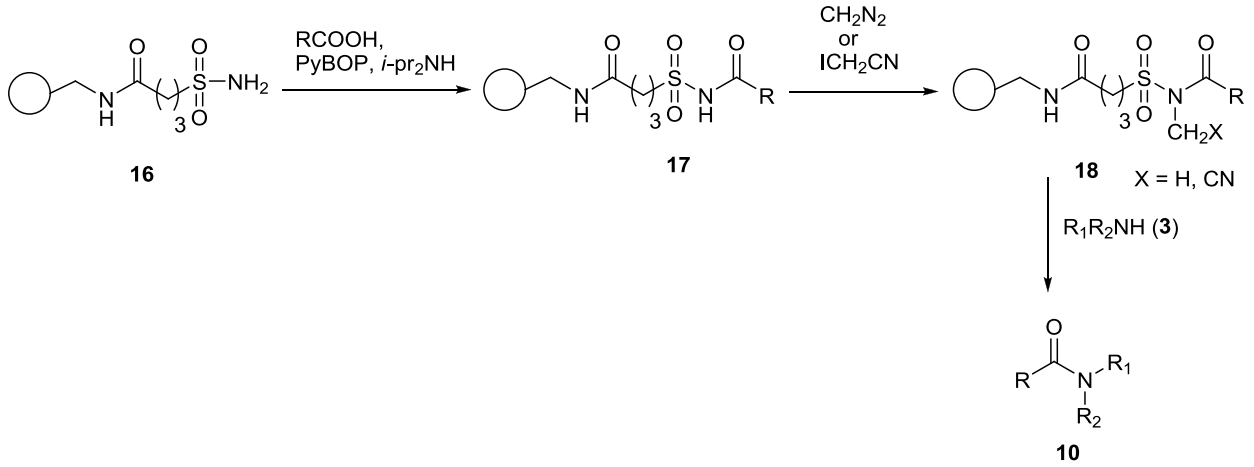
Scheme 2.2.2 Synthesis of sulfonamides and amides using acetophenone based linker **11**

A new polymer-bound tetrafluorophenol resin **13** has been synthesized by Salvino group.[14] Reaction of **13** with sulfonyl chloride or acyl chloride resulted in the formation of activated sulfonate esters **14** and esters **15** respectively (Scheme 2.2.3).These activated resins were allowed to react with a variety of amines including primary and secondary amines, and anilines to generate wide range of sulfonamides **9** and amides **10**. Moreover, **13** facilitate the use of ^{19}F NMR to quantify loading of the polymer.



Scheme 2.2.3 Synthesis of sulfonamides and amides using polymer-bound tetrafluorophenol resin **13**

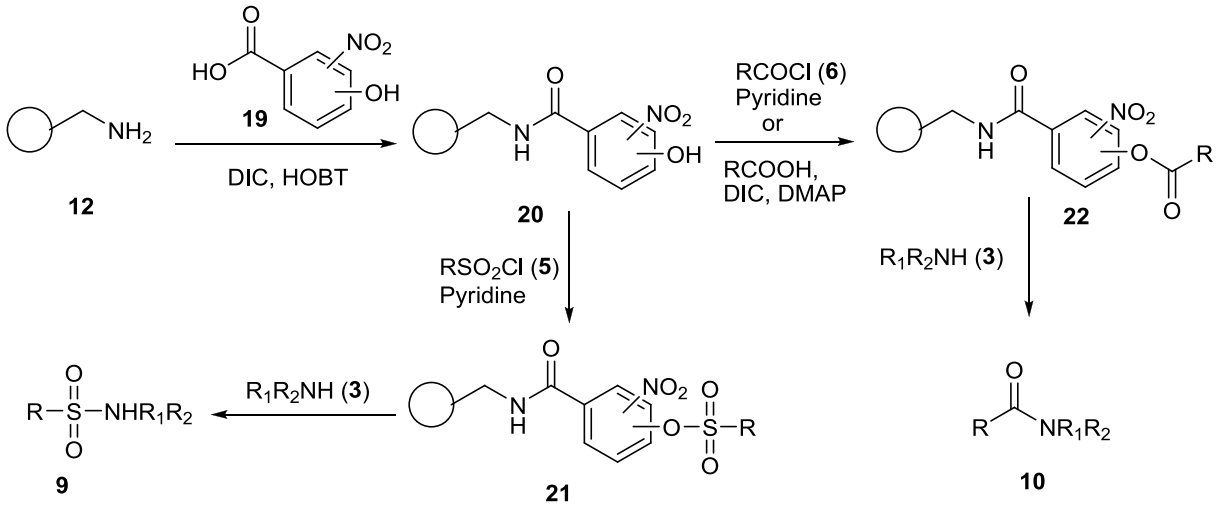
Backes *et al.* used Kenner's acylsulfonamide safety-catch linker **16** for the synthesis of carboxamides (Scheme 2.2.4). Kenner's linker is completely stable to basic and strongly nucleophilic conditions and can only be cleaved by activating with diazomethane or iodoacetonitrile. Diversity can be introduced in the carboxamides synthesis by treating with various amines.



Scheme 2.2.4 Synthesis of amides using Kenner's safety-catch linker **16**

Chang group[11] has reported the synthesis of novel polymer-bound nitrophenol resins **20** by coupling alkylamino resin **12** with hydroxyl nitrobenzoic acid **19**. The broad choice of resin materials were employed like polystyrene, tentagel, macroporous, acryloyl poly(ethylene glycol)

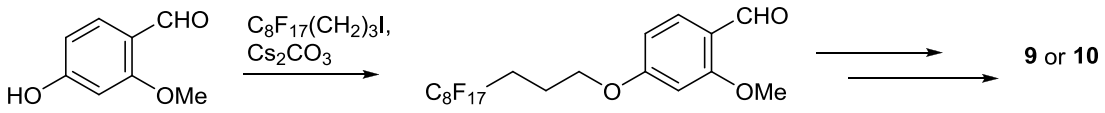
(PEGA) and silica gel to allow the reaction to occur successfully in solvents ranging from nonpolar organic solvents to aqueous media. These polymer-bound nitrophenol resins **20** were converted to active sulfonyl esters **21** and esters **22**, which were reacted with a diverse set of amines under various conditions to generate vast arrays of sulfonamides and amides that are useful in drug discovery (Scheme 2.2.5).



Scheme 2.2.5 Synthesis of amides and sulfonamides using nitrophenol resin **20**

Despite the success of solid-phase approaches for the generation of large libraries of amides and sulfonamides, they are associated with several disadvantages such as low-loading efficiency, difficulty in characterization of intermediates, prolonged validation-time, inability to affect compound purification prior to the final cleavage from the solid support, use of large excess of reagents and high cost of synthesis of compounds in adequate quantities for biological evaluation. Consequently, alternative solution-phase approaches such as fluorous-assisted synthesis,[15-19] PEG-supported synthesis,[20-22] and soluble polymer supported synthesis,[23] that do not suffer from these limitations have been reported.

A rapid fluorous-supported synthesis of sulfonamides and carboxamides was demonstrated by Ladlow and his co-workers.[24] Acid-labile and fluorous-tag **24** accomplished as a soluble support in the multistep solution-phase parallel synthesis (Scheme 2.2.6). The fluorous tag was also found to be compatible with microwave accelerated Suzuki-Miyaura coupling reactions. The purification of all intermediates was done by reversed-phase fluorous silica gel (RPFSG) to afford compounds in good yields and excellent purities without the need for column chromatography.



23 **24**

Scheme 2.2.6 Fluorous-supported synthesis of sulfonamides **9** and carboxamides **10**

Ionic liquid-supported synthesis[25] is a new concept with several advantages for organic synthesis retaining the supremacy of product isolation and purification of solid-phase synthesis along with solubility benefits of traditional solution-phase chemistry. In this method desired molecule is attached to an ionic liquid by an appropriate linker and the multistep synthesis of the target molecule is carried out without detaching the ionic liquid for monitoring reaction progress at every stage. Un-reacted reagents and unwanted compounds are easily separated out from ionic liquid by simple washing with appropriate solvents before the final cleavage. The main feature of ionic liquid-supported synthesis resembles the polymer-supported synthesis, but high-loading efficiency, tunable solubility,[26] possibility to monitor the reaction progress by different analytical techniques, and minimal use of solvents have made this method an attractive and favorable alternative to solid-phase synthesis.

Ionic liquid with a different type of linkers and desired functional group or moiety (Figure 2.2.1) have been synthesized and used for several organic transformations. Bazureau *et al.*[27] were the first to propose the use of ionic liquid as soluble support for the synthesis of small organic molecules. Miao *et al*.[28] demonstrated the application of ionic liquid as a soluble support in Suzuki reaction. They have successfully applied the ionic liquid-supported synthesis strategy in polypeptide synthesis.[29] He *et al.*[30] developed ionic liquid-type imidazolium oligomers and used them as a support in the peptide synthesis. Huang *et al.*[31] have demonstrated the feasibility of oligosaccharide synthesis on ionic liquid. A detailed overview of application of ionic liquids in organic synthesis has been presented in chapter 1.

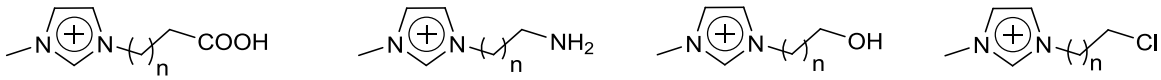
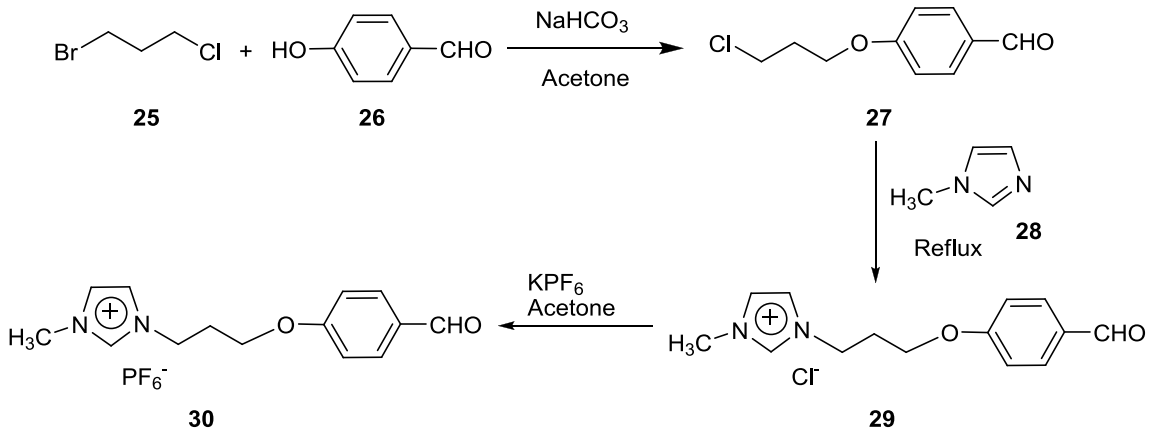


Figure 2.2.1 Various type of linkers used in ionic liquid-supported synthesis

2.2.2 Results and Discussion

With our interest to explore the synthetic utility of the ionic liquid-supported synthesis and to develop new and eco-friendly reaction methodologies using ionic liquid as soluble support, we have synthesized an acid labile ionic liquid-supported aldehyde linker and demonstrated its application in soluble support synthesis of amides and sulfonamides.

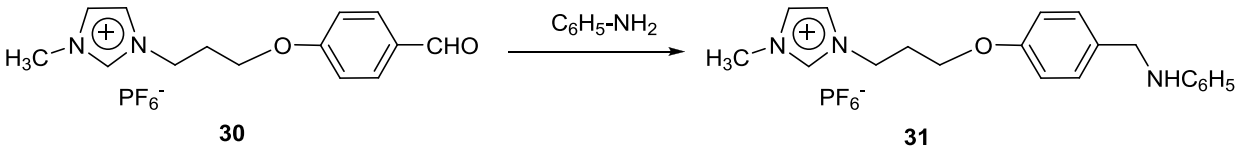
Ionic liquid-supported aldehyde **30** was synthesized from 4-hydroxybenzaldehyde **26** as shown in scheme 2.2.7. A detailed discussion of synthesis of ionic liquid-supported aldehyde **30** is given in part A of chapter 2 under 2.1.2.



Scheme 2.2.7 Synthesis of ionic liquid-supported aldehyde **30**

The application of designed ionic liquid-supported aldehyde **30** has been demonstrated by ionic liquid-supported liquid phase synthesis of sulfonamides and amides are shown in scheme 2.2.8. Initially, reaction conditions were optimized for the reductive amination of ionic liquid-supported aldehyde group **30** with aniline using different borohydrides to afford the intermediate ionic liquid-supported secondary amines **31a-f** as summarized in Table 2.2.1. Among different screened borohydrides, $NaBH(OAc)_3$ was found to give the highest yield of supported amine in [bmim][BF_4] ionic liquid at 40 °C (entry 5, Table 2.2.1). Thus, $NaBH(OAc)_3$ was used with six different amines for the reductive amination reactions.

Table 2.2.1. Optimization of reductive amination conditions[a]



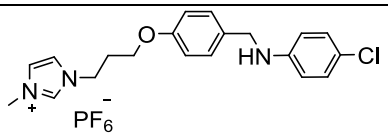
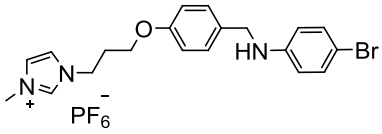
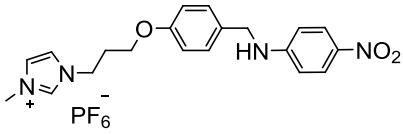
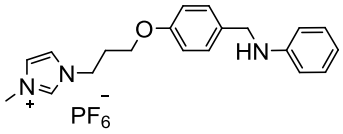
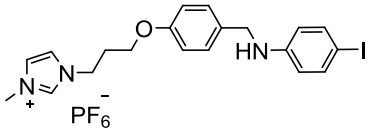
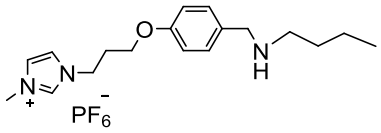
30 **31**

Entry	Reducing agent	Temp (°C)	Time (h)	Yield (%)[b]
1	$NaBH_4$	35	7	66
2	$NaBH_4$	60	7	75
3	$NaBH_4$	60	8	72[c]
4	$NaBH_4$	35	6	60[d]
5	$NaBH(OAc)_3$	40	5	87
6	$NaBH(OAc)_3$	40	5	83[d]
7	$NaBH_3CN$	60	6	85
8	$NaBH_3CN$	60	6	79[d]

[a]Reaction conditions: Ionic liquid-supported aldehyde **30** (1 mmol), aniline (1 mmol), reducing agent (1.1 mmol), room temperature, [bmim][BF_4] (1.0 mL). [b]Isolated yield. [c]Toluene used as a solvent in place of [bmim][BF_4]. [d]Methanol used as a solvent.

Six amines were reacted with **30** to give ionic liquid-supported amines **31a-f** in 70-83% yield (Table 2.2.2). The excess of anilines was removed from the ionic liquid by extraction with ethyl acetate and then $NaBH(OAc)_3$ and [bmim][BF_4] were removed by water washing leaving behind the supported secondary amines **31**. All the ionic liquid-supported anilines were characterized by IR, ^{1}H NMR, and mass spectrometry. In the IR spectra, a peak around 1690-1700 cm^{-1} for stretching of aldehyde carbonyl disappeared and a broad peak appeared in the range of 3100-3200 cm^{-1} for secondary NH stretching. In the ^{1}H NMR, a characteristic peak appeared around 4.10 ppm for CH_2NH group along with other aromatic protons of the phenyl ring. A representative ^{1}H NMR and ^{13}C NMR of **31f** is shown in figure 2.2.2.

Table 2.2.2: Structure of ionic liquid-supported amines and their yield

Compound Number	Ionic liquid-supported amines **31**	%Yield[a]
31a		82
31b		82
31c		80
31d		87
31e		83
31f		70

[a] Isolated yield

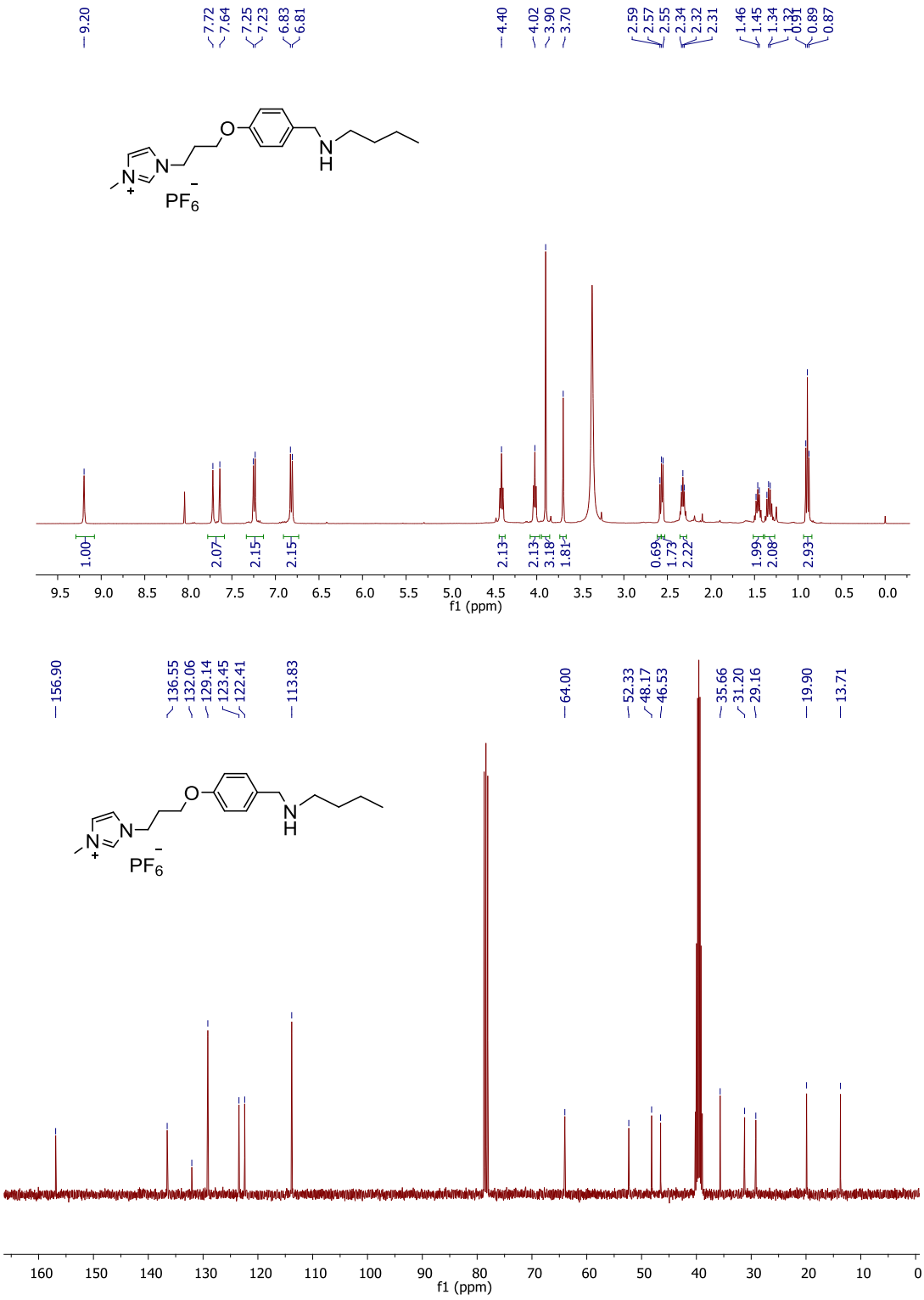
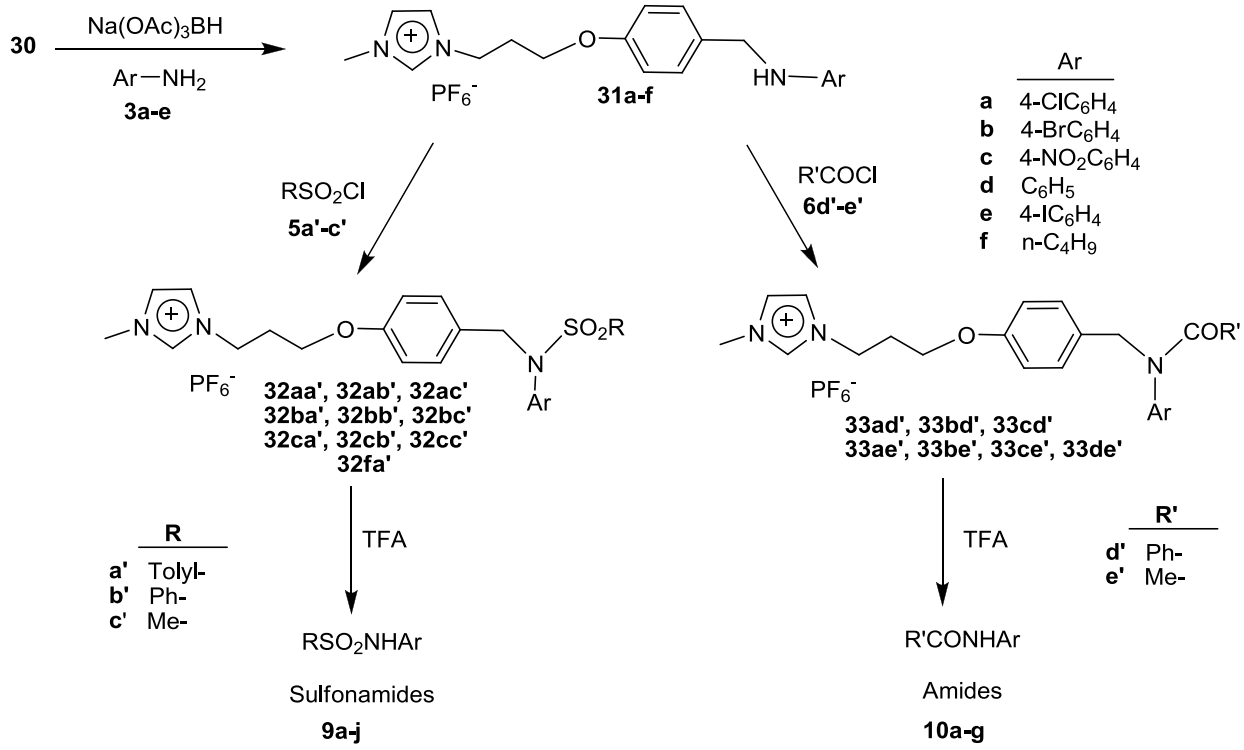


Figure 2.2.2 ^{1}H and ^{13}C NMR NMR spectrums of ionic liquid-supported amine **31f**

Next, ionic liquid-supported secondary amines **31** were reacted with sulfonyl chlorides **5** to give ionic liquid-supported sulfonamides **32**. After removal of excess of sulfonyl chloride from the reaction mixture, the ionic liquid-supported sulfonamides were cleaved using TFA to give sulfonamides **9a-j** in high yields (82–87%) as shown in Table 2.2.3



Scheme 2.2.8 Synthesis of sulfonamides **9** and amides **10** from ionic liquid-supported aldehyde **30**

The reaction could be easily monitored by different spectroscopic techniques. For example ^{1}H NMR and ^{13}C NMR of ionic liquid-supported sulfonamide showed that reaction has progressed. Figure 2.2.3 represents ^{1}H NMR and ^{13}C NMR of **31fa'**.

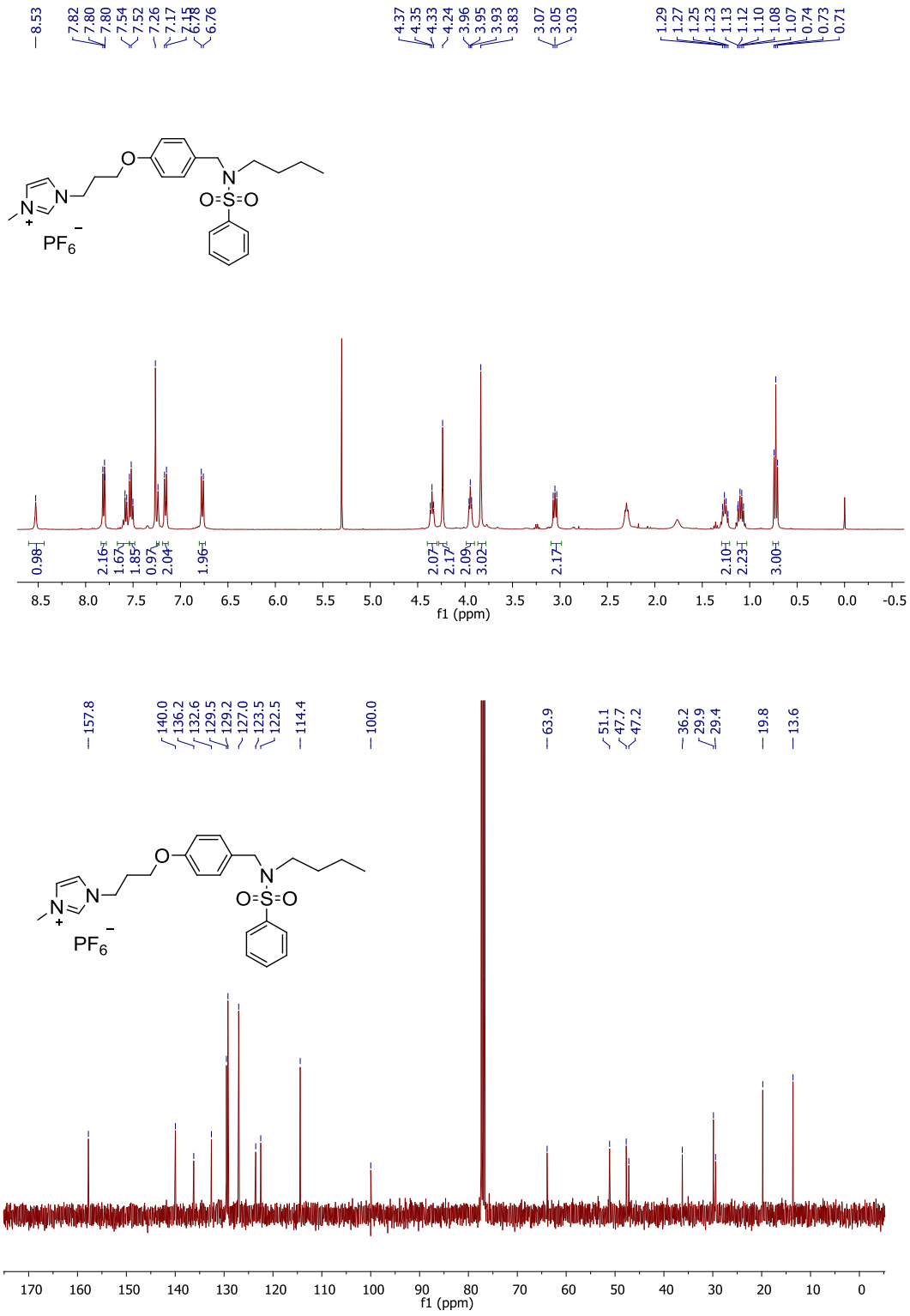
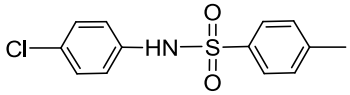
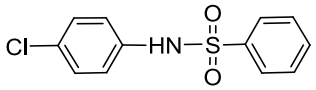
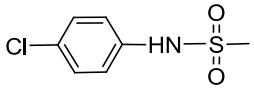
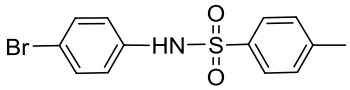
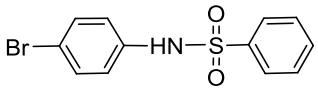
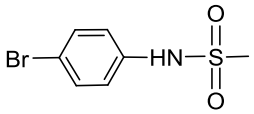
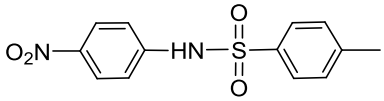
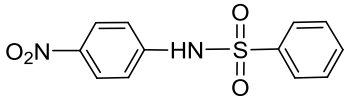
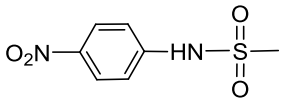
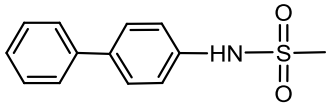
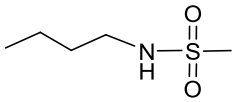


Figure 2.2.3 ^{13}C NMR spectrum of ionic liquid-supported sulfonamide **31fa'**

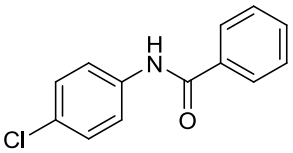
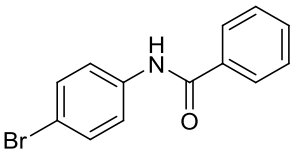
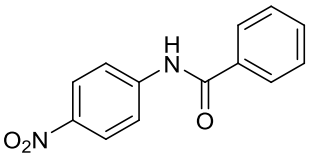
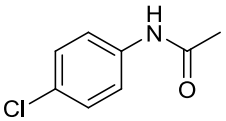
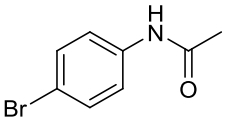
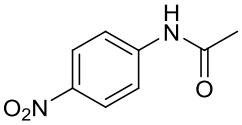
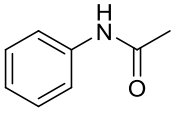
Table 2.2.3 Yields of synthesized sulfonamides **9a-k**

Ar	R	Product		Time (h)	% Yield[a]
4-ClC_6H_4	4-$CH_3C_6H_4$	**9a**		8	87 (66)[b]
4-ClC_6H_4	C_6H_5	**9b**		8	88 (65)[b]
4-ClC_6H_4	CH_3	**9c**		10	86 (64)[b]
4-BrC_6H_4	4-$CH_3C_6H_4$	**9d**		8	89 (64)[b]
4-BrC_6H_4	C_6H_5	**9e**		8	85 (63)[b]
4-BrC_6H_4	CH_3	**9f**		10	84 (61)[b]
4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	**9g**		8	85 (57)[b]
4-$NO_2C_6H_4$	C_6H_5	**9h**		8	83 (55)[b]
4-$NO_2C_6H_4$	CH_3	**9i**		10	82 (54)[b]
4-$C_6H_5C_6H_4$	CH_3	**9j**		10	87 (56)[b]
n-C_4H_9	4-$CH_3C_6H_4$	**9k**		10	91 (59)[b]

[a]Isolated yields after column chromatography. [b]Overall yield (from ionic liquid supported aldehyde **30**).

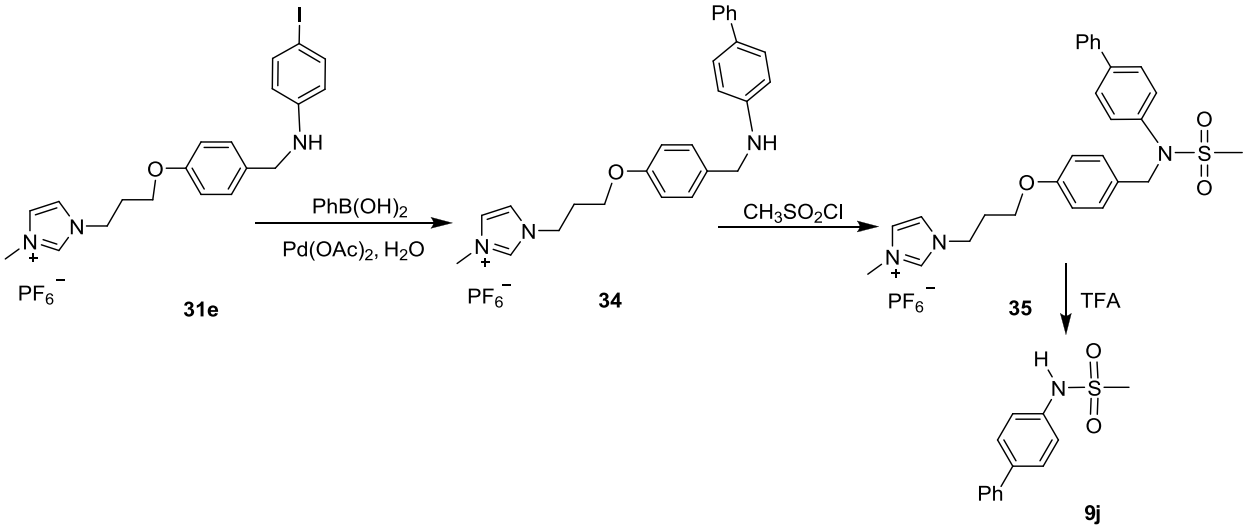
To demonstrate the utility of **30** in supported liquid phase synthesis, ionic liquid-supported secondary amines **31** were reacted with acid chlorides **6** to give ionic liquid-supported amides **33**. The excess of acid chlorides were removed by ethyl acetate extraction followed by cleavage with TFA to afford desired amides **10a-g**. All the amides were isolated in good yields (81-87%, Table 2.2.4).

Table 2.2.4 Yields of synthesized of carboxamides **10a-g**

Ar	R'	Product		Time (h)	% Yield[a]
4-ClC_6H_4	C_6H_5	**10a**		8	85 (63)[b]
4-BrC_6H_4	C_6H_5	**10b**		7	83 (59)[b]
4-$NO_2C_6H_4$	C_6H_5	**10c**		8	81 (55)[b]
4-ClC_6H_4	CH_3	**10d**		8	86 (63)[b]
4-BrC_6H_4	CH_3	**10e**		8	81 (62)[b]
4-$NO_2C_6H_4$	CH_3	**10f**		8	82 (53)[b]
C_6H_5	CH_3	**10g**		7	87 (56)[b]

[a]Isolated yields after column chromatography. [b]Overall yield (from ionic liquid supported aldehyde **30**.

The scope of the ionic liquid-supported aldehyde **30** was further extended to increase functional diversity (Scheme 2.2.9). Compound **30** was converted to ionic liquid-supported iodo-substituted aryl amine **31e**. The ionic liquid-supported aryl amine **31e** was transformed to ionic liquid-supported biaryl secondary amines **34** using Suzuki coupling reaction conditions. The ionic liquid-supported secondary amine with biphenyl was characterized with ^{1}H NMR and mass spectrometry. The resulting secondary amine was transformed to the corresponding sulfonamide by reaction with methanesulfonyl chloride using the standardized reaction conditions and finally cleaved to give sulfonamide **9j**. Structure of both **34** and **35** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.



Scheme 2.2.9 Ionic liquid-supported Suzuki reaction and synthesis of sulfonamide **9j**

2.2.3 Conclusions

A new acid-labile ionic liquid-supported aldehyde was developed to facilitate the rapid and parallel solution-phase synthesis of sulfonamides and carboxamides. The use of ionic liquid-supported aldehyde group avoids the cumbersome conditions and makes the environmentally clean protocol for the synthesis of useful sulfonamides and carboxamides with the experimental ease. Functionalization of substituted ionic liquid-supported secondary amines followed by sulfonylation or acylation can be used to generate library of structurally diversified sulfonamides and carboxamides, respectively. The protocol represented here would improve the paradigm of sulfonamide and carboxamides and provide insights for potential application of ionic liquid-supported aldehydes and amines for generation of other compounds.

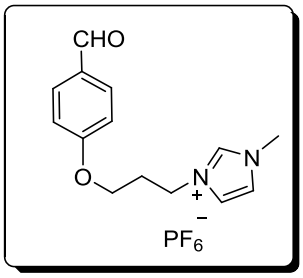
2.2.4 Experimental

General: 1-Methyl imidazole, 1-chloro-3-bromopropane, 4-hydroxybenzaldehyde, KPF_6, and sodium triacetoxyborohydride were purchased from Sigma-Aldrich and were used without further purification. Aryl amines, sulfonyl chlorides, and acid chlorides were purchased from S. D. Fine Chemicals Ltd., Mumbai. Silica gel (100–200 mesh) was used for column chromatography. Thin-layer chromatography (TLC) was performed on Merck-precoated silica gel 60-F_{254} plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 & 500 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 as solvents with ^{1}H resonant frequency of 400 MHz & 500 MHz and ^{13}C resonant frequency of 101 &126 MHz. The chemical shifts are expressed in ppm (δ) and coupling constants (*J*) in Hz. The Mass spectra were recorded on QSTAR® ELITE LX/MS/MS from Applied Biosystems.

Synthesis of ionic liquid-supported aldehyde

1-Methylimidazole, **28** (54 mmol) was mixed with 4-(3-chloropropyloxy)benzaldehyde, **27** (50 mmol) and heated at 80 °C for 6 h. After the completion of the reaction, a thick liquid was obtained. The reaction mixture was cooled down to room temperature, and unreacted 1-methylimidazole and 4-(3-chloropropyloxy)benzaldehyde were removed by extraction with diethyl ether/ethyl acetate (2 × 25 mL, 1:1 *v/v*). The ionic liquid layer was concentrated under vacuum on a rotatory evaporator to give chloride salt **29**. Ion exchange was carried out in dry acetone (50 mL) using potassium hexafluorophosphate (0.06 mol) at room temperature for 48 h. Acetone was evaporated; resulting solution was dissolved in water (25 mL) and extracted with DCM (3 × 50 mL). The DCM layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford pure **30**.

Compound 30

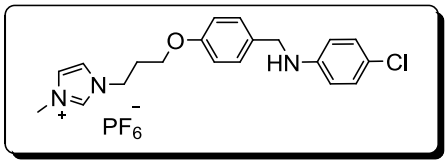


Yield: 96%; M.p. 92-95 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (s, 1H), 9.03 (s, 1H), 7.86 (d, J = 8.78 Hz, 2H), 7.75-7.70 (m, 1H), 7.65-7.59 (m, 1H), 7.05 (d, J = 8.78 Hz, 2H), 4.39 (t, J = 7.0 Hz, 2H), 4.14 (t, J = 6.2 Hz, 1H), 3.85 (s, 3H), 2.35 – 2.26 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.9, 163.6, 137.22, 132.36, 130.18, 124.10, 122.92, 115.31, 65.51, 46.92, 36.07, 29.28; ESI-MS: *m/z* calcd for $C_{14}H_{17}F_6N_2O_2P$ 390.0932, found 245.1302 [M – PF_6]$^{+}$.

General procedure for the synthesis of ionic liquid-supported amines

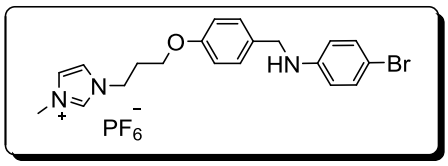
Compound **30** (2.5 mmol) was refluxed with corresponding amine **3** (3 mmol) in methanol or ethanol for overnight. The obtained solid was reduced using sodium triacetoxyborohydride (3.3 mmol) in [bmim][BF_4] for 5 h at 40 °C. The excess of amine was removed by extracting with ethyl acetate (3 × 20 mL). The inorganic impurities were removed by washing with water (2 × 10 mL) and the organic layer was dried on a rotatory evaporator to give ionic liquid-supported amine **31**.

Compound 31a



Yield: 82%; M.p. 156-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.79 – 7. 69 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 6.39 (s, 1H), 4.36 – 4.32 (m, 2H), 4.16 – 4.13 (m, 2H), 4.01 – 3.93 (m, 2H), 3.84 (s, 3H), 2.34 – 2.19 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 146.2, 137.2, 131.1, 129.6, 128.9, 124.1, 123.3, 115.2, 114.7, 114.1, 64.9, 46.9, 46.2, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{23}ClF_6N_3OP$ 501.1171, found 357.1608 $[M - PF_6]^+$.

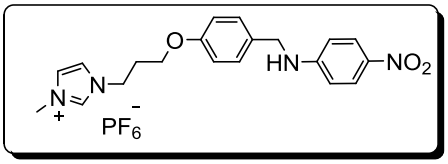
Compound 31b



Yield: 82%; M.p. 175-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H), δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 9.5 Hz, 1H), 7.70 (d, *J* = 6.2 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 1H), 7.28 – 7.11 (m, 3H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 6.9 Hz, 1H), 6.50 (d, *J* = 7.3 Hz, 1H), 6.43 (s, 1H), 4.34 – 4.31 (m, 2H), 4.18 – 4.10 (m, 2H), 4.03 – 3.98 (m, 2H), 3.82 (s, 3H), 2.32 – 2.22 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.5, 148.3, 137.2, 132.4, 131.8, 128.9,

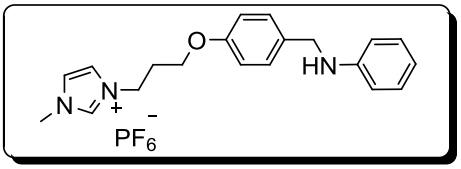
124.1, 123.0, 115.4, 114.7, 114.1, 65.6, 64.9, 46.8, 36.2, 29.5; ESI-MS: m/z calcd for $C_{20}H_{23}BrF_6N_3OP$ 545.0666, found 401.1121 [M – PF6]+.

Compound 31c



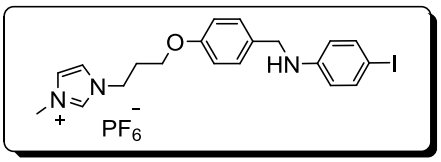
Yield: 80%; Light brown thick liquid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.49–9.28 (m, 3H), 8.08–8.00 (m, 1H), 7.98–7.89 (m, 1H), 7.68 – 7.49 (m, 2H), 7.26 – 6.99 (m, 2H) 6.87 – 6.57 (m, 2H), 6.43 (s, 1H), 4.39 – 4.32 (m, 2H), 4.23 – 4.17 (m, 2H), 4.06 – 3.95 (m, 2H), 4.87 (s, 3H), 2.55 – 2.33 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.8, 148.3, 137.3, 131.2, 130.1, 129.5, 124.3, 123.8, 115.3, 114.6, 114.3, 64.7, 46.8, 46.3, 36.3, 29.5; ESI-MS: *m/z* calcd for $C_{20}H_{23}F_6N_4O_3P$ 512.1412, found 368.1823 $[M + H – PF_6]^+$.

Compound 31d



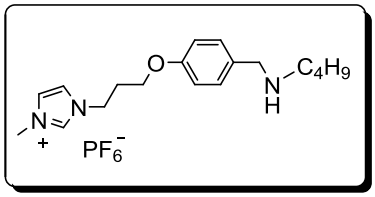
Yield: 87%; Light yellow thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 – 9.18 (m, 1H), 7.85 – 7.80 (m, 1H), 7.76 – 7.69 (m, 1H), 7.37 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 7.15 – 7.11 (m, 2H), 7.08 – 7.02 (m, 1H), 6.84 – 6.63 (m, 2H), 6.41 (s, 1H), 4.76 (s, 2H), 4.32 (t, *J* = 7.35 Hz, 2H), 4.11 – 4.06 (m, 2H), 3.93 (s, 3H), 2.28 – 2.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.7, 143.2, 137.3, 130.4, 128.5, 128.0, 127.7, 124.3, 123.2, 115.7, 114.6, 65.1, 51.7, 45.3, 36.5, 29.4; ESI-MS: *m/z* calcd for $C_{20}H_{24}F_6N_3OP$ 467.1561, found 323.2018 $[M + H – PF_6]^+$.

Compound 31e



Yield 83%; M.p. 156-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.88 – 7.69 (m, 3H), 7.43 (d, *J* = 7.78 Hz, 1H), 7.26 (d, *J* = 7.81 Hz, 2H), 7.05 (d, *J* = 7.69 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 6.39 (s, 1H), 4.72 – 4.67 (m, 2H), 4.26 – 4.18 (m, 2H), 4.03 – 3.94 (m, 2H), 3.86 (s, 3H), 2.36 – 2.17 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 146.3,137.3, 131.5, 129.3, 128.5, 127.6, 123.9, 115.6, 114.8, 114.1, 64.3, 46.7, 46.1, 36.3, 29.5; ESI-MS: *m/z* calcd for $C_{20}H_{23}F_6IN_3OP$ 593.0528, found 449.0983 $[M + H - PF_6]^+$.

Compound 31f



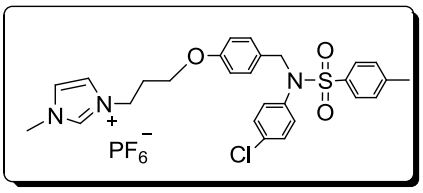
Yield 70%; Yellow thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.72 (s, 1H), 7.64 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.40 (t, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 2H), 2.59 (s, 1H), 2.58 – 2.52 (m, 2H), 2.36 – 2.27 (m, 2H), 1.51 – 1.41 (m, 2H), 1.38 – 1.27 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.90, 136.55, 132.06, 129.14, 123.45, 122.41, 113.83, 64.00, 52.33, 48.17, 46.53, 35.66, 31.20, 29.16, 19.90, 13.71.

General procedure for the synthesis of sulfonamides/carboxamides

To the stirred reaction mixture of **31** (1 mmol) and triethylamine (1.5 mmol) in dichloromethane (3.0 mL) at 0 °C was added sulfonyl chloride/acid chloride (1.2 mmol) drop wise. The reaction mixture was brought to room temperature and stirred for 7-10 h (Table 2.2.1). After completion of the reaction, the mixture was washed with diethyl ether (3 × 10 mL) and water (2 × 10 mL), respectively. The sulfonamide/carboxamide-supported on ionic liquid was cleaved using trifluoroacetic acid (TFA, 1 mL). The resulting solution was neutralized with 10 %

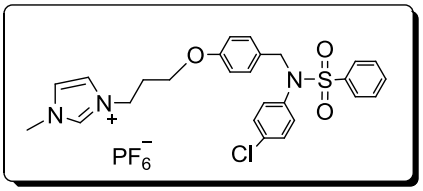
aqueous $NaHCO_3$ solution and extracted with hexane/ethyl acetate (1:1 *v/v*) (2 × 10 mL). The combined organic extracts were concentrated under reduced pressure and purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate as eluents.

Compound 32aa′



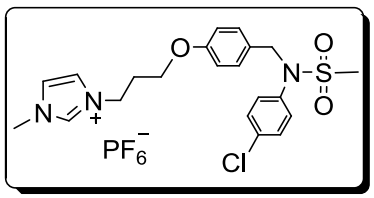
Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H), 7.94 – 7.58 (m, 2H), 7.58 – 7.24 (m, 6H), 7.21 – 6.94 (m, 4H), 6.78 – 6.69 (m, 2H), 4.67 (s, 2H), 4.35 – 4.28 (m, 2H), 3.95 – 3.90 (m, 2H), 3.80 (s, 3H), 2.41 (s, 3H), 2.32 – 2.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 144.3, 137.9, 137.3, 135.0, 132.5, 130.6, 130.4, 130.0, 129.3, 128.4, 127.9, 124.1, 122.9, 115.4, 64.8, 52.9, 46.9, 36.2, 29.5, 21.6; ESI-MS: *m/z* calcd for $C_{27}H_{29}ClF_6N_3O_3PS$ 655.126, found 510.1608 $[M - PF_6]^+$.

Compound 32ab′



Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), δ 7.83 – 7.80 (m, 4H), 7.66 – 7.63 (m, 4H), 7.38 – 7.32 (m, 2H), 7.11 – 7.04 (m, 4H), 6.76 – 6.73 (m, 1H), 4.69 (s, 2H), 4.33 – 4.30 (m, 2H), 3.97 – 3.85 (m, 2H), 3.78 (s, 3H), 2.34 – 2.13 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.0, 137.9, 137.3, 137.2, 133.9, 132.6, 130.6, 130.0, 129.3, 128.3, 127.8, 124.1, 123.3, 122.9, 114.7, 64.8, 53.1, 46.8, 36.1, 29.3; ESI-MS: *m/z* calcd for $C_{26}H_{27}ClF_6N_3O_3PS$ 641.1103, found 496.1425 $[M - PF_6]^+$.

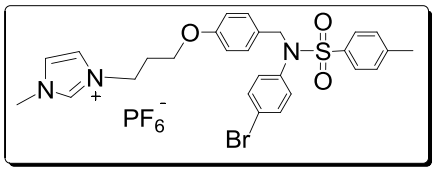
Compound 32ac′



Yield: 91%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.27 (m, 3H),

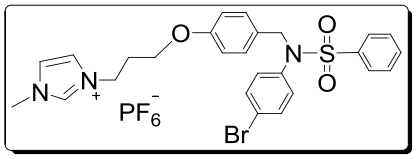
7.21 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.05 – 6.87 (m, 1H), 6.84 – 6.77 (m, 2H), 4.83 – 4.71 (m, 2H), 4.33 – 4.27 (m, 2H), 3.94 (s, 3H), 3.84 – 3.79 (m, 2H), 3.20 (s, 3H), 2.28 – 2.16 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 140.8, 137.3, 136.8, 132.7, 130.3, 130.0, 129.8, 124.2, 122.7, 114.4, 65.3, 51.1, 46.2, 40.2, 36.4, 28.9; ESI-MS: *m/z* calcd for $C_{21}H_{25}ClF_6N_3O_3PS$ 579.0947, found 434.1297 $[M - PF_6]^+$.

Compound 32ba′



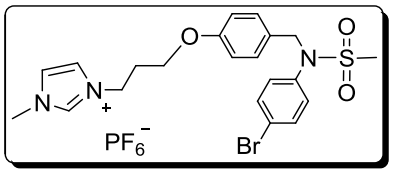
Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.55 – 8.54 (m, 1H), 7.96 – 7.64 (m, 3H), 7.69 – 7.65 (m, 1H), 7.56 – 7.50 (m, 2H), 7.43 – 7.40 (m, 1H), 7.18 – 7.10 (m, 3H), 7.02 – 6.90 (m, 2H), 6.81 – 6.75 (m, 1H), 4.66 (s, 2H), 4.37 – 4.33 (m, 2H), 4.13 – 4.09 (m, 2H), 3.83 (s, 3H), 2.43 (s, 3H), 2.27 – 2.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 151.4, 137.2, 132.5, 132.2, 131.1, 130.4, 130.0, 129.4, 127.9, 124.1, 123.9, 122.9, 115.2, 114.7, 65.3, 46.9, 36.2, 29.4, 21.5; ESI-MS: *m/z* calcd for $C_{27}H_{29}BrF_6N_3O_3PS$ 699.0755, found 554.1097 $[M - PF_6]^+$.

Compound 32bb′



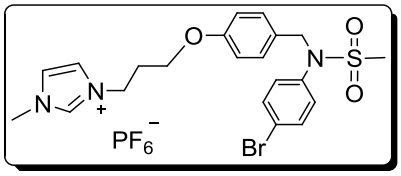
Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H), δ 7.82 – 7.78 (m, 4H), 7.68 -7.61 (m, 4H), 7.38 – 7.32 (m, 2H), 7.12 – 7.06 (m, 4H), 6.75 (s, 1H), 4.69 (s, 2H), 4.29 (d, *J* = 7.23 Hz, 2H), 3.96 – 3.83 (m, 2H), 3.79 (s, 3H), 2.35 – 2.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.2, 138.0, 137.2, 137.0, 134.1, 132.7, 130.3, 129.8, 129.2, 128.5, 127.6, 124.3, 124.2, 122.7, 114.5, 65.1, 52.8, 46.6, 36.1, 29.0; ESI-MS: *m/z* calcd for $C_{26}H_{27}BrF_6N_3O_3PS$ 685.0598, found 540.0914 $[M - PF_6]^+$.

Compound 32bc′



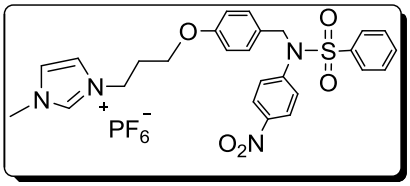
Yield: 89%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.46 – 7. 25 (m, 3H), 7.18 (d, J = 8.76 Hz, 1H), 7.11 (d, J = 8.76 Hz, 1H), 7.08 – 6.84 (m, 1H), 6.84 – 6.74 (m, 2H), 4.81 – 4.67 (m, 2H), 4.29 – 4.19 (m, 2H), 3.92 (s, 3H), 3.85 – 3.81 (m, 2H), 3.18 (s, 3H), 2.28 – 2.13 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 137.2, 132.8, 132.8, 132.3, 130.8, 129.8, 124.1, 122.9, 115.4, 114.7, 65.49, 64.9, 50.1, 46.9, 36.2, 29.5; ESI-MS: *m/z* calcd for $C_{21}H_{25}BrF_6N_3O_3PS$ 623.0442, found 478.0801 $[M - PF_6]^+$.

Compound 32ca′



Yield: 84%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.46 – 9.25 (m, 3H), 8.10 – 7.85 (m, 4H), 7.71 – 7.48 (m, 2H), 7.24 – 6.95 (m, 4H), 6.91 – 6.84 (m, 2H), 4.98 – 4.90 (m, 2H), 4.55 (t, J = 7.0 Hz, 2H), 4.25 (t, J = 5.8 Hz, 2H), 3.97 (s, 3H), 2.41 (s, 3H), 2.57 – 2.32 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.3, 137.5, 137.2, 133.7, 132.5, 131.2, 129.4, 129.0, 128.6, 124.2, 123.3, 123.1, 115.5, 115.1, 114.5, 65.2, 54.7, 46.5, 36.5, 29.6; ESI-MS: *m/z* calcd for $C_{27}H_{29}F_6N_4O_5PS$ 666.15, found 521.1818 $[M - PF_6]^+$.

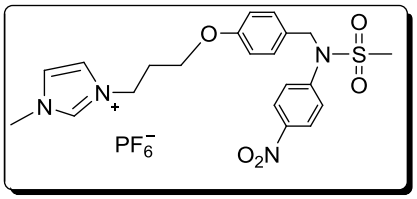
Compound 32cb′



Yield: 83%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.45 – 9.27 (m, 3H), 8.08 – 7.83 (m, 4H), 7.71 – 7.48 (m, 3H), 7.22 – 6.88 (m, 4H), 6.85 – 6.82 (m, 2H), 4.95 – 4.84 (m, 2H), 4.48 (t, J = 7.0 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.97 (s, 3H), 2.49 – 2.28 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.2, 137.2, 136.9, 133.9, 132.6, 131.0, 129.8, 129.1, 128.3, 124.2, 123.4, 122.8,

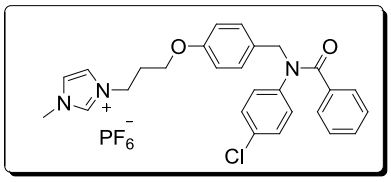
115.3, 114.8, 114.2, 64.7, 53.5, 46.1, 36.5, 29.6; ESI-MS: *m/z* calcd for $C_{26}H_{27}F_6N_4O_5PS$ 652.1344, found 507.1689 $[M - PF_6]^+$.

Compound 32cc′



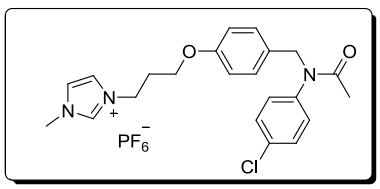
Yield: 82%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.49 – 9.28 (m, 3H), 8.08–8.00 (m, 1H), 7.98 – 7.89 (m, 3H), 7.68 – 7.49 (m, 2H), 7.26 – 6.99 (m, 2H), 5.00 – 4.91 (m, 2H), 4.57 (t, *J* = 6.9 Hz, 2H), 4.26 (t, *J* = 5.9 Hz, 2H), 4.07 (s, 3H), 2.78 (s, 3H), 2.57 – 2.41 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.3, 137.2, 132.4, 130.9, 129.6, 128.9, 124.1, 123.3, 122.9, 115.2, 114.1, 65.3, 64.9, 46.9, 46.2, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{21}H_{25}F_6N_4O_5PS$ 590.1187, found 445.1497 $[M - PF_6]^+$.

Compound 33ad′



Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H), 7.87 – 7.79 (m, *J* = 8.5 Hz, 2H), 7.72 – 7.68 (m, 3H), 7.32 – 7.20 (m, 5H), 7.17 (d, *J* = 7.3 Hz, 2H), 7.12 – 6.99 (m, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 5.02 (s, 2H), 4.39 – 4.24 (m, 2H), 4.03 – 3.90 (m, 2H), 3.82 (s, 3H), 2.37 – 2.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 157.8, 137.2, 132.4, 132.3, 131.2, 130.2, 130.0, 129.8, 129.4, 128.8, 128.4, 124.1, 122.9, 115.4, 114.8, 64.9, 46.9, 46.8, 36.2, 29.5; ESI-MS: *m/z* calcd for $C_{27}H_{27}ClF_6N_3O_2P$ 605.1434, found 461.1813 $[M + H - PF_6]^+$.

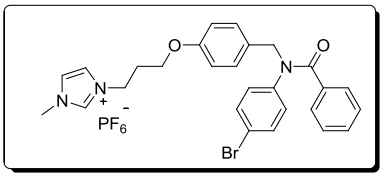
Compound 33ae′



Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 1H), δ 7.79 – 7.69 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.81 – 6.74 (d, *J* = 8.5 Hz, 2H), 4.77 (s, 2H), 4.32 (t, *J* = 7.5 Hz, 2H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 2.30 – 2.16 (m, 2H), 1.81

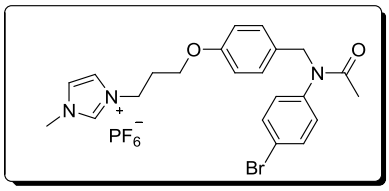
(s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 157.7, 137.2, 132.5, 132.1, 130.4, 130.1, 129.9, 129.6, 124.1, 122.9, 114.7, 64.9, 51.3, 47.1, 36.2, 29.5, 23.0; ESI-MS: *m/z* calcd for $C_{22}H_{25}ClF_6N_3O2P$ 543.1277, found 398.1757 $[M - PF_6]^+$.

Compound 33bd′



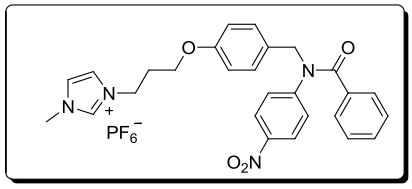
Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.78 – 7.68 (m, 2H), 7.40 -7.35 (m, 2H), 7.31 – 7.27 (m, 4H), 7.23 – 7.18 (m, 4H), 7.01 – 6.93 (m, 2H), 6.79 – 6.68 (m, 1H), 5.01 (s, 2H), 4.42 – 4.20 (m, 2H), 4.02 – 3.93 (m, 2H), 3.81 (s, 3H), 2.23 – 2.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ; 170.3, 157.6, 137.5, 132.8, 132.1, 130.9, 130.1, 129.9, 129.6, 129.4, 128.9, 128.4, 124.2, 123.1, 115.5, 114.7, 65.1, 46.9, 46.5, 36.2, 29.3; ESI-MS: *m/z* calcd for $C_{27}H_{27}BrF_6N_3O_2P$ 649.0928, found 505.1303 $[M + H – PF_6]^+$ and 507.1306 $[M + 2 + H – PF_6]^+$.

Compound 33be′



Yield: 93%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 7.79 – 7.69 (m, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.11 – 7.09 (m, 2H), 6.83 – 6.78 (m, 2H), 4.87–4.68 (m, 2H), 4.42 – 4.24 (m, 2H), 4.05 – 3.89 (m, 2H), 3.82 (s, 3H), 2.32 – 2.16 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 157.8, 137.2, 132.8, 132.3, 130.8, 130.8, 129.8, 124.1, 122.9, 115.4, 114.7, 64.9, 50.1, 46.9, 36.2, 29.5, 23.0; ESI-MS: *m/z* calcd for $C_{22}H_{25}BrF_6N_3O_2P$ 587.0772, found 442.1034 $[M – PF_6]^+$, 444.1034 $[M + 2 – PF_6]^+$.

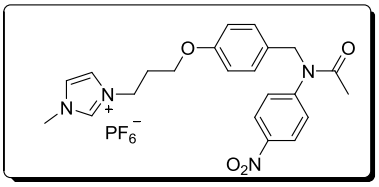
Compound 33cd′



Yield: 85%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H), 7.97 – 7.92 (m, 3H), 7.81 – 7.76 (m, 2H), 7.66 – 7.60 (m, 3H), 7.51 – 7.45 (m, 3H), 7.39 – 7.33 (m, 2H), 6.95 – 6.89 (m, 2H), 5.40 –

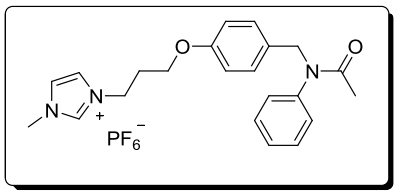
5.08 (m, 2H), 4.34 – 4.29 (m, 2H), 4.18 – 3.91 (m, 2H), 3.82 (s, 3H), 2.51 – 2.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 166.1, 158.6, 137.2, 133.9, 130.5, 130.1, 129.6, 129.4, 129.3, 129.2, 128.8, 124.2, 124.1, 122.9, 114.9, 66.5, 65.0, 46.9, 36.2, 29.4; ESI-MS: *m/z* calcd for $C_{27}H_{27}F_6N_4O_4P$ 616.1674, found 472.2103 $[M + H - PF_6]^+$.

Compound 33ce′



Yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 – 8.99 (m, 3H), 7.86 – 7.60 (m, 4H), 7.11 – 7.05 (m, 2H), 6.93 – 6.85 (m, 2H), 4.37 – 4.31 (m, 2H), 4.08 – 4.00 (m, 2H), 3.98 – 3.93 (m, 2H), 3.83 (s, 3H), 2.25 – 2.18 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.6, 156.8, 137.2, 133.5, 130.5, 130.2, 130.0, 129.7, 124.1, 124.1, 122.9, 114.8, 65.7, 64.8, 46.9, 36.2, 29.6, 21.5; ESI-MS: *m/z* calcd for $C_{22}H_{25}F_6N_4O_4P$ 554.1518, found 409.1798 $[M - PF_6]^+$.

Compound 33de′



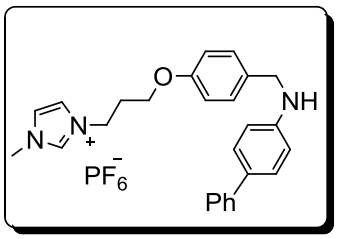
Yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (s, 1H), 7.82 – 7.72 (m, 2H), 7.38 – 7.34 (m, 3H), 7.28 – 7.05 (m, 4H), 6.81 – 6.75 (m, 2H), 4.76 (s, 2H), 4.33 (t, *J* = 8.2 Hz, 2H), 3.95 (t, *J* = 8.2 Hz, 2H), 3.84 (s, 3H), 2.24 – 2.16 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.6, 157.7, 143.1, 137.3, 130.4, 129.9, 129.8, 128.5, 128.0, 124.1, 122.9, 114.6, 64.9, 51.5, 45.7, 36.3, 29.6, 23.0; ESI-MS: *m/z* calcd for $C_{22}H_{26}F_6N_3O_2P$ 509.1667, found 364.1986 $[M - PF_6]^+$.

General procedure for Suzuki coupling on ionic liquid-support

To a solution of ionic liquid-supported 4-iodoaniline (0.67×10^{-3} mol) in water (5.0 mL) at 80 ºC under nitrogen was added phenylboronic acid (0.19×10^{-3} mol) and Cs_2CO_3 (0.00134 mol). The resulting mixture was stirred at 80 ºC for 15 min followed by the addition of $Pd(OAc)_2$

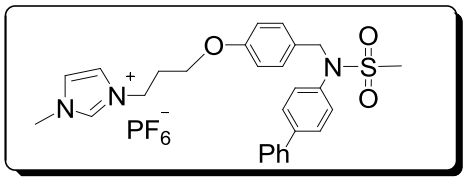
(0.097×10^{-3} mol). The reaction mixture was then stirred vigorously for 23 h at 80 ºC under nitrogen atmosphere. After completion of the reaction, the mixture was washed with water (3 × 15 mL), and finally the residue was dissolved in DCM (10 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **34**. Yield 423 mg (85 %).

Compound 34



Yield: 82%; M. P. 122 – 125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.71 – 7.62 (m, 2H), 7.48 – 7.46 (m, 2H), 7.38 – 7.32 (m, 4H), 7.30 – 7.22 (m, 4H), 7.19 – 7.15 (m, 2H), 6.83 – 6.74 (m, 1H), 5.95 – 5.91 (m, 1H), 4.40 (t, *J* = 6.9 Hz, 2H), 4.31 – 4.25 (m, 2H), 4.07 – 4.01 (m, 2H), 3.89 (s, 3H), 2.36 – 2.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5, 148.3, 141.2, 137.2, 132.7, 129.0, 128.7, 128.0, 127.6, 126.3, 125.4, 124.1, 123.1, 115.1, 114.2, 64.5, 51.2, 46.8, 46.2, 29.5; ESI-MS: *m/z* calcd for $C_{26}H_{28}F_6N_3OP$ 543.1874, found 398.2187 $[M - PF_6]^+$.

Compound 35



Yield: 87%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.11 (s, 1H), 7.76 (t, *J* = 1.7 Hz, 1H), 7.67 (t, *J* = 1.6 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.39 – 7.31 (m, 3H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.21 – 7.16 (m, 1H), 6.86 – 6.81 (m, 2H), 6.66 – 6.61 (m, 2H), 6.35 (t, *J* = 6.1 Hz, 1H), 4.31 (t, *J* = 7.0 Hz, 2H), 4.22 (d, *J* = 6.0 Hz, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 2.27 – 2.20 (m, 2H), 1.78 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.1, 157.4, 148.6, 141.0, 137.2, 132.8, 129.1, 128.8, 127.9, 127.5, 126.1, 125.8, 124.0, 122.9, 114.7, 113.1, 64.9, 50.2, 46.9, 46.1, 36.2, 29.5; ESI-MS: *m/z* calcd for $C_{27}H_{30}F_6N_3O_3PS$ 621.1650, found 476.1989 $[M - PF_6]^+$.

2.2.5 References

[1] Ballard, T. E.; Wang, X.; Olekhnovich, I.; Koerner, T.; Seymour, C.; Hoffman, P. S.; Macdonald, T. L., *Bioorganic & Medicinal Chemistry Letters* **2010,** *20*, 3537.

[2] Asai, A.; Sakai, Y.; Ogawa, H.; Yamashita, Y.; Kakita, S.; Ochiai, K.; Asmzawa, T.; Mihara, A.; Mizukami, T.; Nakano, H., *The Journal of Antibiotics* **2000,** *53*, 66.

[3] Peukert, S.; Brendel, J.; Pirard, B.; Strübing, C.; Kleemann, H.-W.; Böhme, T.; Hemmerle, H., *Bioorganic & Medicinal Chemistry Letters* **2004,** *14*, 2823.

[4] Yang, Y.; Shi, L.; Zhou, Y.; Li, H.-Q.; Zhu, Z.-W.; Zhu, H.-L., *Bioorganic & Medicinal Chemistry Letters* **2010,** *20*, 6653.

[5] Wang, X.-L.; Wan, K.; Zhou, C.-H., *European Journal of Medicinal Chemistry* **2010,** *45*, 4631.

[6] Li, X.-H.; Wu, D.-C.; Qi, Z.-Q.; Li, X.-W.; Gu, Z.-M.; Wei, S.-H.; Zhang, Y.; Wang, Y.-Z.; Ji, M.-S., *Journal of Agricultural and Food Chemistry* **2010,** 58, 11384.

[7] Van de Vijver, P.; Vondenhoff, G. H. M.; Denivelle, S.; Rozenski, J.; Verhaegen, J.; Van Aerschot, A.; Herdewijn, P., *Bioorganic & Medicinal Chemistry* **2009,** *17*, 260.

[8] Talath, S.; Gadad, A. K., *European Journal of Medicinal Chemistry* **2006,** *41*, 918.

[9] Kumar, A.; Ye, G.; Ahmadibeni, Y.; Parang, K., *The Journal of Organic Chemistry* **2006,** *71*, 7915.

[10] Luo, J.; Huang, W., *Molecular Diversity* **2003,** *6*, 33.

[11] Lee, J. W.; Louie, Y. Q.; Walsh, D. P.; Chang, Y.-T., *Journal of Combinatorial Chemistry* **2003,** *5*, 330.

[12] Fivush, A. M.; Willson, T. M., *Tetrahedron Letters* **1997,** *38*, 7151.

[13] Bui, C. T.; Bray, A. M.; Ercole, F.; Pham, Y.; Rasoul, F. A.; Maeji, N. J., *Tetrahedron Letters* **1999,** *40*, 3471.

[14] Salvino, J. M.; Kumar, N. V.; Orton, E.; Airey, J.; Kiesow, T.; Crawford, K.; Mathew, R.; Krolikowski, P.; Drew, M.; Engers, D.; Krolikowski, D.; Herpin, T.; Gardyan, M.; McGeehan, G.; Labaudiniere, R., *Journal of Combinatorial Chemistry* **2000,** *2*, 691.

[15] Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P., *Science* **1997,** *275*, 823.

[16] Zhang, W., *Chemical Reviews* **2004,** *104*, 2531.

[17] Chen, C. H.-T.; Zhang, W., *Organic Letters* **2003,** *5*, 1015.

[18] Curran, D. P., *Synlett* **2001**, 1488.

[19] Zhang, W., *Chemical Reviews* **2009,** *109*, 749.

[20] Bergbreiter, D. E.; Tian, J.; Hongfa, C., *Chemical Reviews* **2009,** *109*, 530.

[21] Barrett, A. G. M.; Hopkins, B. T.; Love, A. C.; Tedeschi, L., *Organic Letters* **2004,** *6*, 835.

[22] Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J., *Chemical Reviews* **2002,** *102*, 3301.

[23] Toy, P. H.; Janda, K. D., *Accounts of Chemical Research* **2000,** *33*, 546.

[24] Villard, A.-L.; Warrington, B. H.; Ladlow, M., *Journal of Combinatorial Chemistry* **2004,** *6*, 611.

[25] Miao, W.; Chan, T. H., *Accounts of Chemical Research* **2006,** *39*, 897.
[26] S. Lee, *Chemical Communications* **2006**, 1049.
[27] Fraga-Dubreuil, J.; Bazureau, J. P., *Tetrahedron Letters* **2001,** *42*, 6097.
[28] Miao, W.; Chan, T. H., *Organic Letters* **2003,** *5*, 5003.
[29] Miao, W.; Chan, T.-H., *The Journal of Organic Chemistry* **2005,** *70*, 3251.
[30] He, X.; Chan, T. H., *Organic Letters* **2007,** *9*, 2681.
[31] Huang, J.-Y.; Lei, M.; Wang, Y.-G., *Tetrahedron Letters* **2006,** *47*, 3047.

CHAPTER III

Synthesis of Novel Sulfonyl Functionalized Ionic Liquids and their Applications in Organic Synthesis

PART A

1-Butyl-3-methylimidazolium *p*-Toluenesulfinate: A Novel Reagent for Synthesis of Sulfones and β-Ketosulfones in Ionic Liquid

PART-A: 1-Butyl-3-methylimidazolium *p*-Toluenesulfinate: A Novel Reagent for Synthesis of Sulfones and β-Ketosulfones in Ionic Liquid

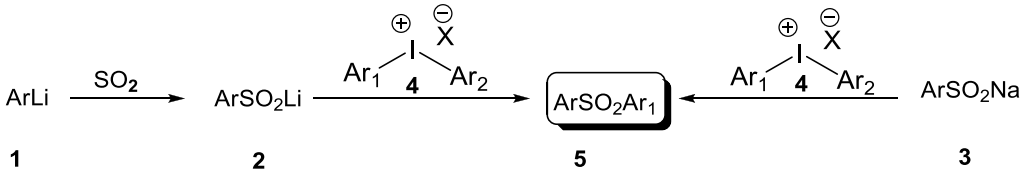
3.1.1 Introduction

Sulfones and β-ketosulfones are important synthetic intermediates in organic synthesis, which are widely utilized in organic transformations. They have been utilized for the synthesis of natural product such as Lycopodine alkaloid,[1] α-halo β-ketosulfones, α-halo methylsulfones, α, α-di-halomethylsulfones, quinolines, allenes, vinyl sulfones and polyfunctionalized 4*H*-pyrans.[2-6] They are useful intermediate for the conversion of ketones to alkynes.[7] β-Ketosulfones can also be transformed to corresponding ketones by reductive desulfonylation. Certain β-ketosulfones exhibit biological activities such as antibacterial, antifungal,[8,9] and inhibition of 11β-hydroxysteroid dehydrogenase type 1.[10,11] Indolyl aryl sulfones are known as potent non-nucleoside inhibitors for the growth of wild-type and drug-resistant human immunodeficiency virus type 1 (HIV-1).[10] Because of their synthetic utility and versatile reactivity several methods have been developed for their preparation.[7,12-17]

A brief overview of various approaches for the synthesis of sulfones and β-ketosulfones is given below

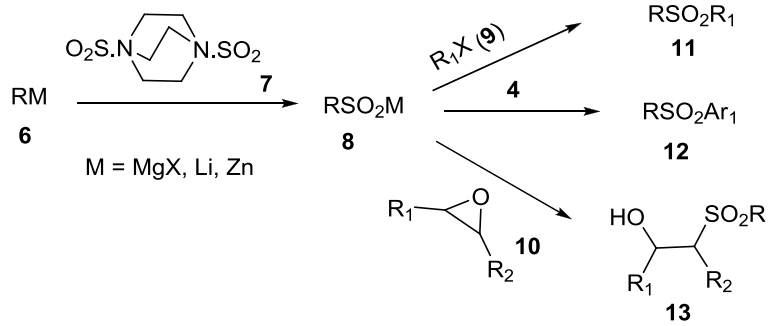
Umierski and Manolikakes developed transition-metal-free synthesis of diaryl sulfones from arylsulfinic acid sodium salts **3** and diaryliodonium salts **4**[18] The scope of method was further extended by employing sulfinic acid lithium salts, which were prepared in a straight forward manner from the reaction of organolithium compounds **1** with sulfur dioxide (Scheme 3.1.1).[19] The reaction conditions are mild, robust and avoid the use of excess reagents or additives. The scope of this reaction is quite broad and includes the synthesis of halogen-substituted or sterically hindered diarylsulfones. Kumar *et al*.[20] developed metal-free, green and facile

protocol for the synthesis of diaryl sulfones from the reaction of diaryliodonium salts with arenesulfinic acid salts. Chemo selective arylation of arenesulfinate with and without metal has been performed. This method gave access to various diaryl sulfones in high yields and shorter reaction times under microwave irradiation.



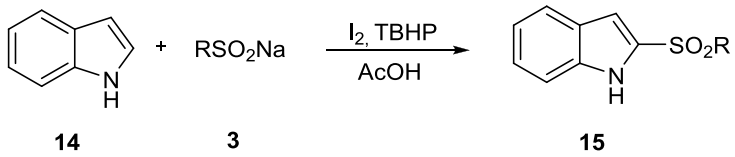
Scheme 3.1.1 Synthesis of diaryl sulfones **5** using diaryliodonium salts **4**

Willis[21] and Rocke[22] independently developed a facile procedure for the synthesis of sulfones using DABCO-bis(sulfur dioxide) (DABSO, **7**) as a convenient source of sulfur dioxide. Grignard reagents or organolithium or organozinc reagents were added to the SO_2-surrogate DABSO to generate a diverse set of metal sulfinates **8**. These metal sulfinates are further trapped *in-situ* with a wide range of carbon-electrophiles, including alkyl halides **9**, diaryliodonium salts **4**, epoxides **10** to generate broad class of sulfones (Scheme 3.1.2). This transformation has broader scope and reaction conditions are compatible with a wide range of structural motifs including nitrile, secondary carbamates and nitrogen-containing heterocycles.



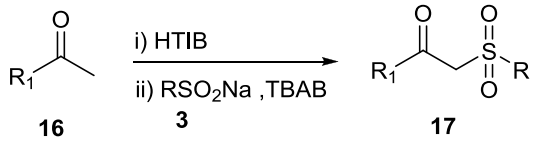
Scheme 3.1.2 Synthesis of diaryl sulfones **11** &**12**using DABSO **7**

Quite recently, Xiao *et al*.[23] developed arylsulfonyl indoles **15** from indoles **14** and sodium sulfinates **3** in the presence of iodine and tert-butyl hydroperoxide (TBHP). Catalytic amount of TBHP promoted the sulfonylation reaction to occur exclusively at the C-2 position of the indole ring. Halogens and other functional groups were well tolerated in this procedure (Scheme 3.1.3).



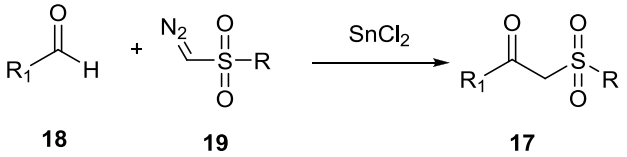
Scheme 3.1.3 Synthesis of arylsulfonyl indoles **15**

An efficient solvent-free, one-pot synthesis of β-ketosulfones **17** from ketones has been reported by Kumar *et al*.[24] *α*-Tosyloxy ketones generated *in-situ* from the readily available methyl ketones **16** upon the action of HTIB were further reacted with sodium arenesulfinate **3** in the presence of tetrabutylammonium bromide (TBAB) at room temperature to give desired products **17** in good to excellent yields (Scheme 3.1.4).



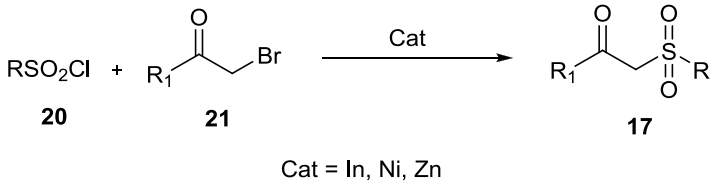
Scheme 3.1.4 Synthesis of β-keto sulfones **17** from methyl ketones **16**

Holmquist and Roskamp employed diazo sulfones **19** as precursors to obtain **17**.[25] The reaction of **19** with aldehydes **18** in the presence of a catalytic amount of tin(II) chloride under mild and non-basic conditions yielded **17** (Scheme 3.1.5) Reactions with primary aldehydes proceed in higher yields, 53–79%, than those of secondary aldehydes, 42–56%. Reactions with tertiary aldehydes, which are more sterically encumbered substrates, give only 5–36% yields.



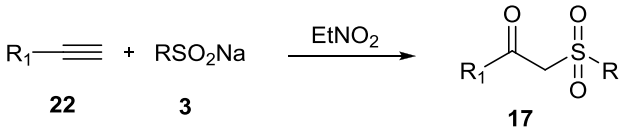
Scheme 3.1.5 Synthesis of β-ketosulfones **17** from diazo sulfones **19**

Another approach to synthesize aryl-containing *β*-ketosulfones **17** involves coupling reactions of aryl sulfonyl chlorides **2** with *α*-haloketones **21** under the promotion of metallic catalysts such as indium, nickel,[26] and zinc[27] (Scheme 3.1.6).



Scheme 3.1.6 Synthesize of *β*-ketosulfones **17** under the promotion of metallic catalysts

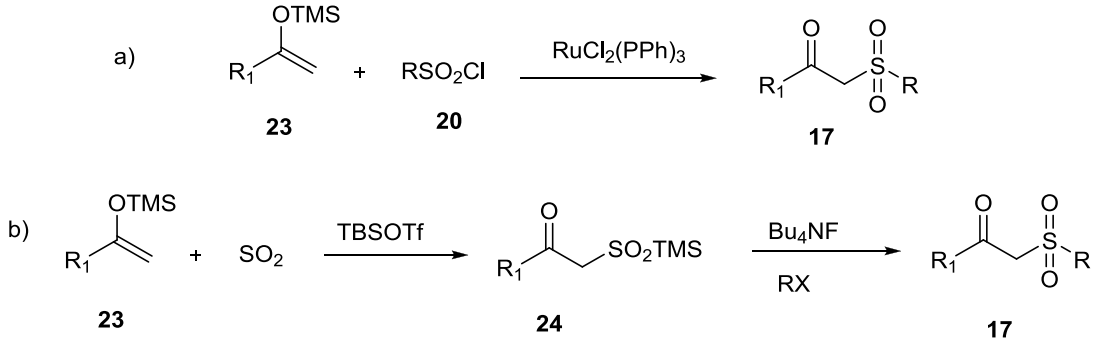
Sreedhar and Rawat [28] developed a facile and regioselective procedure for the preparation of aryl β-ketosulfones **17** from terminal alkynes **22**. The reaction of aryl acetylene **22** and sodium arene sulfinate **3** in presence of nitroethane in water led to the formation of *β*-ketosulfones **17** in good yields (Scheme 3.1.7).



Scheme 3.1.7 Synthesis of β-ketosulfones from terminal alkynes

Bouchez and Vogel reported a one-pot, three-component synthesis of polyfunctional sulfones from silyl enol ethers **23**. [29,30] The reactions of alkane- and arene-sulfonyl chlorides **20** with **23** in the presence of ruthenium(II) phosphine complex gave *β*-ketosulfones in high yields (Scheme 3.1.8a). In addition, silyl enol ethers also underwent ene reaction with SO_2 promoted by *t*-

$BuMe_2SiOSO_2CF_3$ (TBSOTf) to give **24**, which were further desilylated using Bu_4NF and then reacted with corresponding alkyl halides to give *β*-ketosulfones (Scheme 3.1.8b).[31]



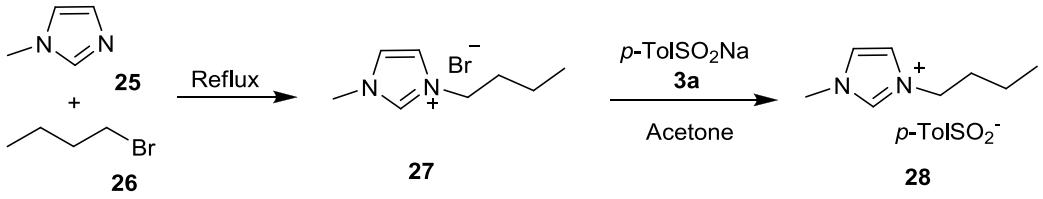
Scheme 3.1.8 Synthesis of β-ketosulfones from Silyl enol ethers

The most general method for synthesis of sulfones and β-ketosulfones is by alkylation of sodium sulphinates with alkyl halide or phenacyl halide, respectively.[32, 33] However, this method suffers from some drawbacks such as long reaction times, tedious reaction conditions, involving high temperature or microwave heating, low yields, use of expensive reagents and the difficulties associated with isolation of sulfones and β-ketosulfones from solvents.

In view of the prominent merits of ionic liquids in organic synthesis and our interest towards the synthesis of ionic liquid-supported reagents, we have designed and synthesized a novel task-specific ionic liquid, 1-butyl-3-methylimidazolium *p*-toluenesulfinate, [bmim][*p*-$TolSO_2$] (Scheme 3.1.9) and successfully used the reagent in synthesis of sulfones and β-ketosulfones from alkyl bromides and phenacyl bromides respectively in [bmim][BF_4] ionic liquid (Scheme 3.1.10).

3.1.2 Results and discussion

Synthesis of [bmim][*p*-TolSO$_2$] **28** was achieved following the reaction sequences shown in Scheme 3.1.9. Initially, the reaction of 1-methylimidazole **25** with 1-bromobutane **26** at room temperature afforded 1-butyl-3-methylimidazolium bromide **27**. Subsequent reaction of **27** with sodium *p*-toluenesulfinate **3a** in acetone at room temperature for 48 h gave **28**.



Scheme 3.1.9 Synthesis of Nucleophilic ionic liquid [bmim][*p*-TolSO$_2$] **28**

The structure of **28** was confirmed by ^{1}H NMR and high-resolution mass spectrometry. The ^{1}H NMR spectrum showed two doublets at 7.38 and 7.12 ppm for aromatic protons of toluenesulfinate ring and a singlet at 2.15 ppm for the methyl protons along with other protons of imidazolium cation (Figure 3.1.1). In HRMS peaks appeared at 294.1463 $[M]^+$ and 139.1246 $[M - p\text{-TolSO}_2]^+$ which confirmed the structure of **28**.

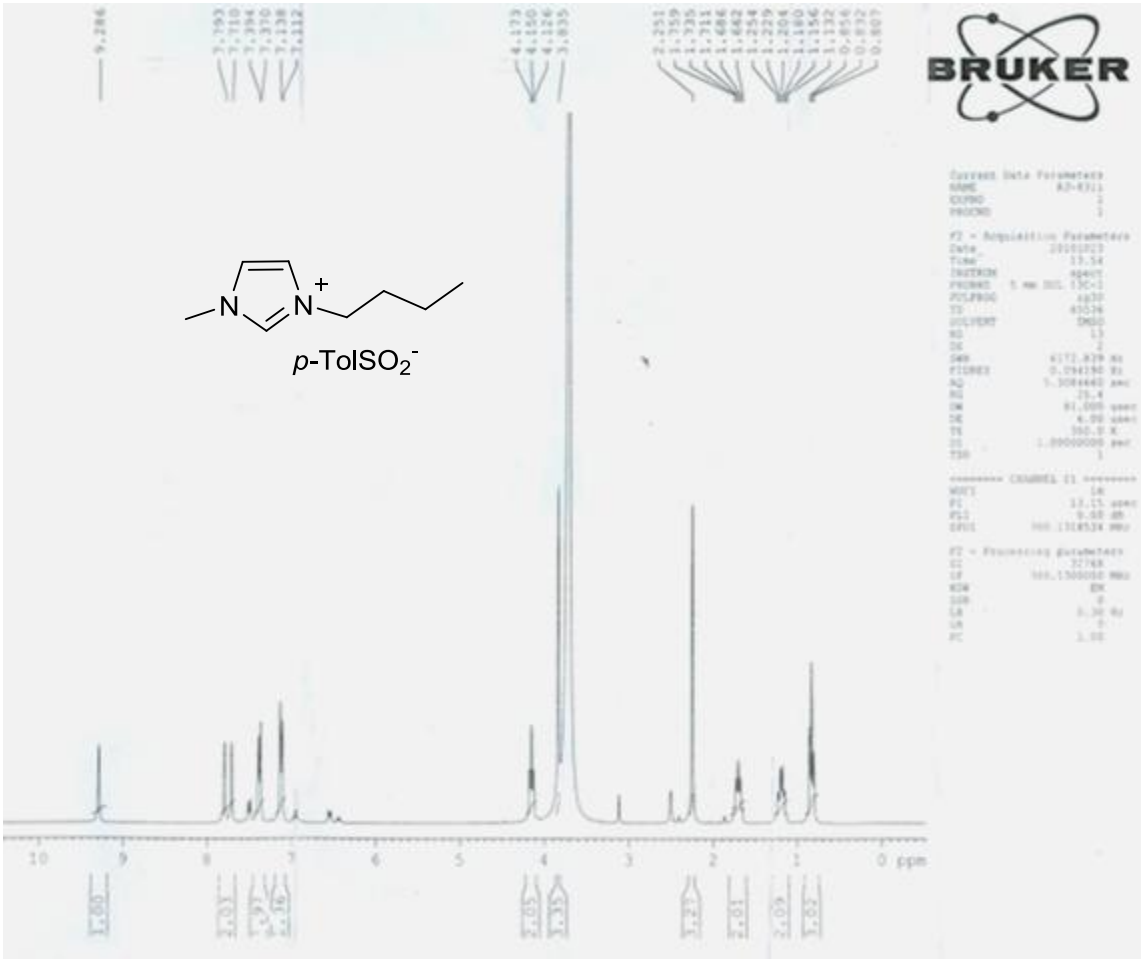


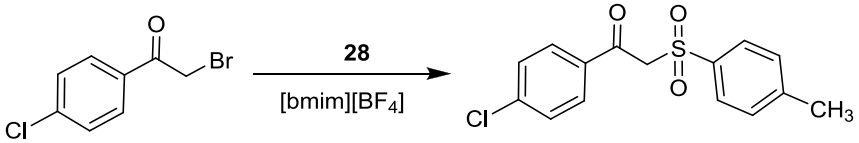
Figure 3.1.1 ^{1}H NMR of [bmim][*p*-TolSO$_2$] **28**

After synthesizing, we studied reaction of **28** with 2-bromo-1-(4-chlorophenyl)ethanone **29a** as model reaction under different conditions. In our initial studies, we tested effect of different solvents such as THF, DMSO, EtOH, MeOH, [bmim][Br] and [bmim][BF_4]. As shown in table 3.1.1, among all the screened solvents, [bmim][BF_4] was found to be the best solvent in terms of yield and reaction time.

The exact reason for higher reactivity in [bmim][BF_4] is not clear, however based on literature reports the increased rate of reaction in [bmim][BF_4] may be attributed to the non-coordinating nature of [bmim][BF_4] which increases effective nucleophilicity of the anion (*p*-TolSO$_2^-$). Similar effect in nuleophilicity has also been observed for the synthesis of sulfones from alkyl

halides using sulfinates in aprotic solvents in presence of tetrabutylammonium salt. Apart from enhancing nucleophilicity, the effect of ionic liquid may well be primarily due to solubility of **28** in [bmim][BF_4]. Further, the increased rate of reaction may also be due to activation of the phenacyl bromide by the acidic nature of the proton H–C(2) of the imidazolium cation (pKa = 22.7 in DMSO).[16] The ionic liquid probably activates the phenacyl bromide through hydrogen bond formation with the carbonyl group.

Table 3.1.1 Optimization of reaction conditions for the synthesis of **30a**



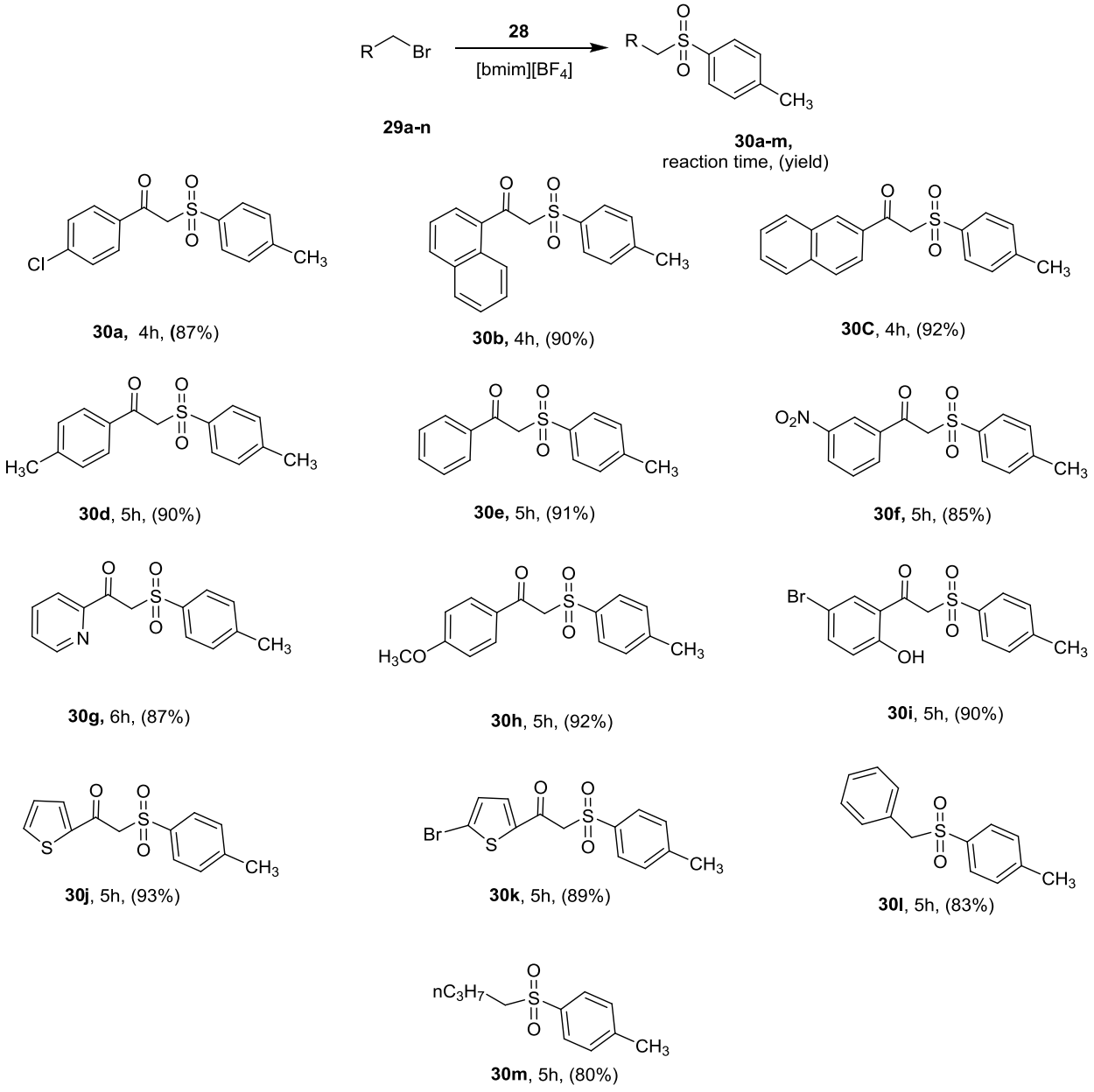
29a **30a**

Entry	Solvent	Reagent	Temp(°C)	Time (h)	Yield (%)[a]
1	-	**28**	60	12	60
2	[bmim][BF_4]	**28**	30	1	87
3	[bmim][BF_4]	*p*-TolSO_2Na	30	4	40
4	[bmim][Br]	**28**	30	1	-[b]
5	Ethanol	**28**	30	1	62
6	Ethanol	*p*-TolSO_2Na	80	10	67
7	Ethanol	**28**	30	1	64
8	DMSO	**28**	30	1	79
9	Acetonitrile	**28**	30	1	-[b]
10	DCM	**28**	30	1	39
11	THF	**28**	30	1	58
12	MeOH	**28**	30	1	38

[a]Isolated yield, [b]No product isolated

For comparison, **30a** was also prepared by the reaction of sodium *p*-toluenesulfinate (*p*-TolSO_2Na) in [bmim][BF_4] ionic liquid (Table 3.1.1, entry 3). The yield of **30a** was 40% at room temperature after 4 h. It is noteworthy to mention that reactivity of sulfinate anion (*p*-TolSO_2^-) in **28** is higher as compared to *p*-TolSO_2Na under these conditions. Moreover,

traditional method for the synthesis of β-ketosulfones by alkylation of *p*-TolSO_2Na with phenacyl bromide **29a** in ethanol required 10 h and resulted **30a** in only 67% yield (Table 3.1.1, entry 6).



Scheme 3.1.10 Synthesis of sulfones and β-ketosulfones using **28**

After establishing the higher reactivity of **28** over sodium sulfinate and optimum reaction condition, we investigated nucleophilic substitution of a variety of alkyl bromides to give corresponding sulfones to validate the general scope of the reaction (Scheme 3.1.11). Excellent yields of sulfones and β-ketosulfones **30a-m** (80-93%) were obtained from different alkyl bromides and phenacyl bromides in short reaction time and the results are summarized in scheme 3.1.10. The products were extracted from the reaction mixture with hexane/ethyl acetate mixture (1: 1, *v/v*) leaving behind [bmim][Br] dissolved in [bmim][BF_4]. Structure of all the compounds **30a-m** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. Figure 3.1.2-3.1.3 demonstrates representative ^{1}H &^{13}C NMR of β-ketosulfones **30f** and sulfone **30l**.

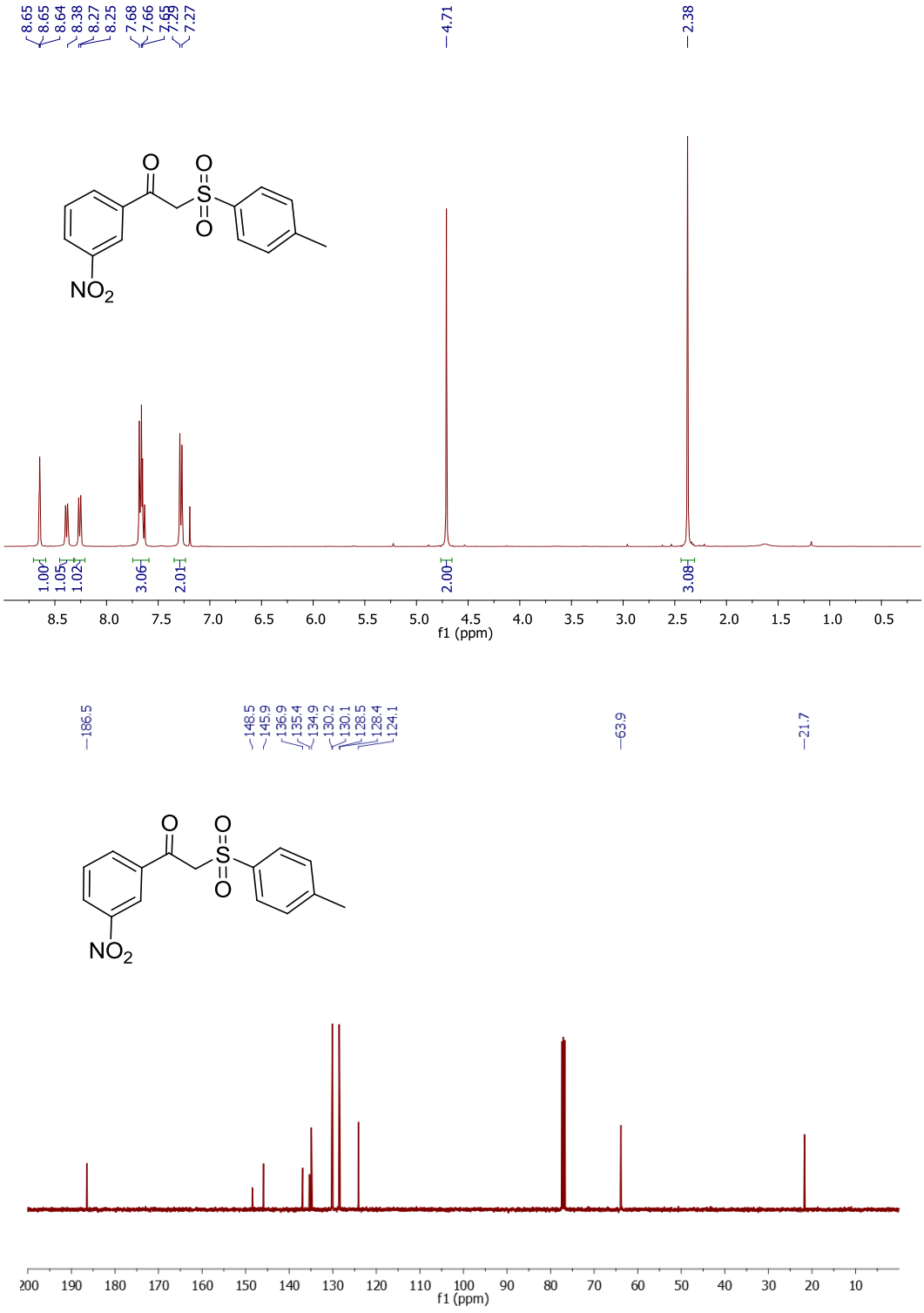


Figure 3.1.2 ^{1}H and ^{13}C NMR spectrums of β-ketosulfones **30f**

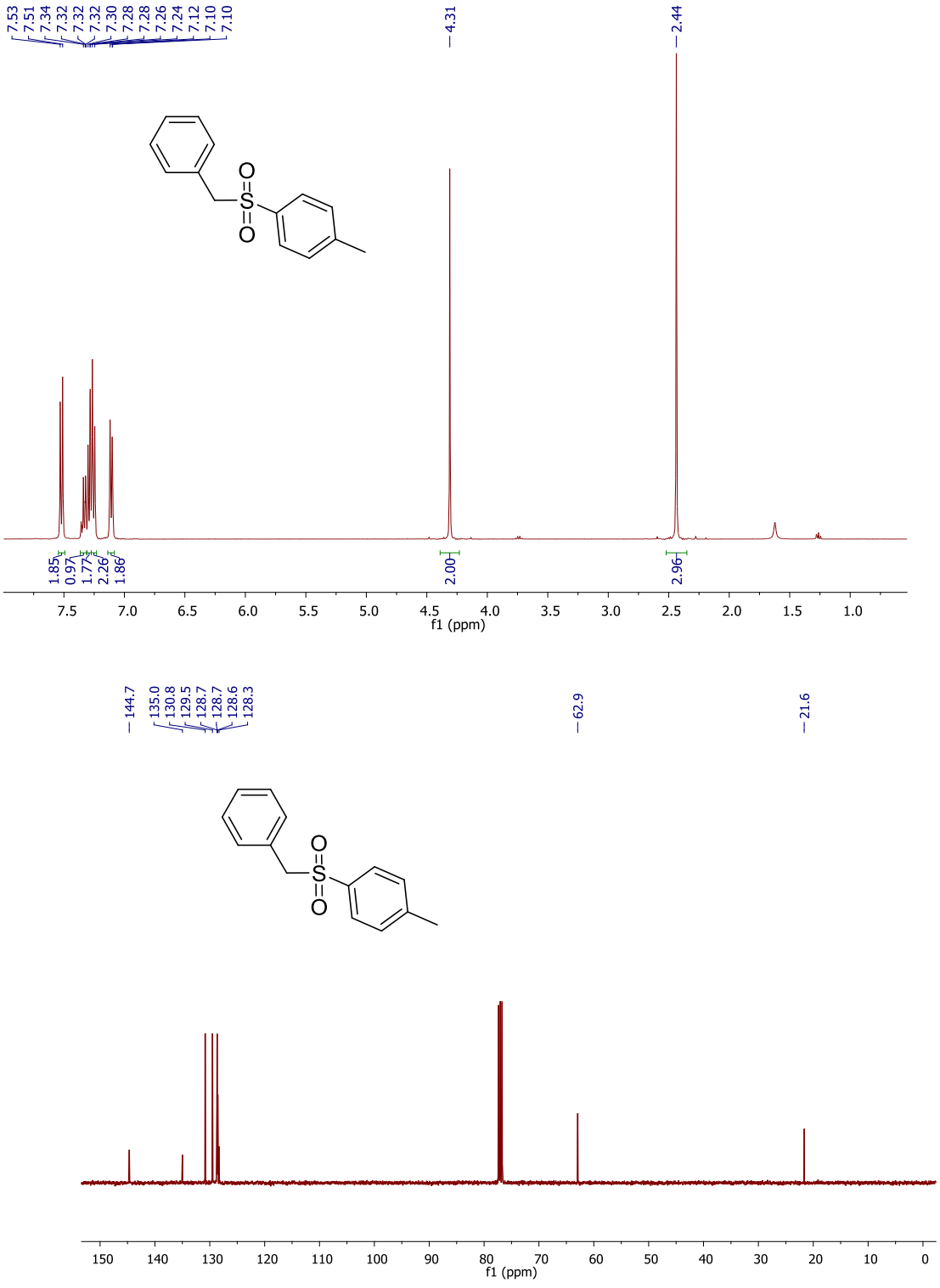


Figure 3.1.3 ^{1}H and ^{13}C NMR spectrums of sulfone **30l**

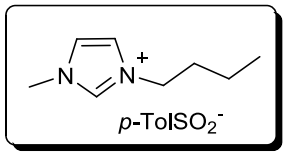
3.1.3 Conclusions

We have described synthesis of novel 1-butyl-3-methylimidazolium *p*-toluenesulfinate ionic liquid [bmim][*p*-TolSO_2] and its ability to act as a nucleophile towards alkyl bromides and phenacyl bromides in ionic liquid [bmim][BF_4]. The [bmim][*p*-TolSO_2] afforded corresponding sulfones and β-ketosulfones in excellent yield (80-93 %) at room temperature. This methodology could be an alternative to the existing methods for the synthesis of sulfones and β-ketosulfones.

3.1.4 Experimental

Synthesis of 1-butyl-3-methylimidazolium p-toluenesulfinate 28

To the solution of [bmim][Br] (**27**, 22.8 mmol) in acetone (20 mL) sodium toluenesulfinate (34.2 mmol) was added and reaction mixture was stirred vigorously at room temperature for 48 h. After completion of reaction, reaction mixture was filtered and acetone was evaporated. The crude product was dissolved in minimum amount of DCM and filtered to remove NaBr. Finally, residual obtained on evaporation of DCM was passed through silica bed (60-120 mesh) to get pure product **28**.



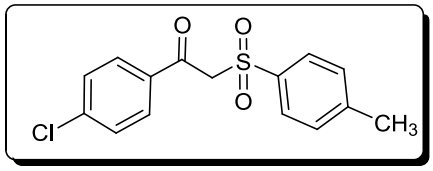
Yield: 92%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.79 – 7.76 (m, 1H), 7.71 – 7.63 (m, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 7.8, 2H), 4.15 (t, *J* = 7.2, 2H), 3.83 (s, 3H), 2.15 (s, 3H), 1.25 – 1.13 (m, 2H), 0.85 – 0.80 (t, *J* = 7.6 Hz, 3H).

General Procedure for the synthesis of Sulfones and β-ketosulfones

Ionic liquid **28** (1.2 mmol) was added to the solution of phenacyl bromide or alkyl bromides (1 mmol) in [bmim][BF_4] (2 mL) and the reaction mixture was stirred vigorously at 30 °C. The progress of reaction was monitored by TLC. After completion of reaction, the product was extracted from ionic liquid by hexane/ethyl acetate mixture (4 × 10 mL, 1: 1 *v/v*) leaving both ionic liquids in the round bottom flask. The organic layers were combined and concentrated to

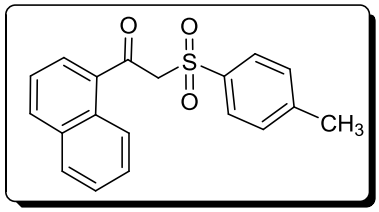
give crude product which was passed through a bed of silica gel (100-120 mesh) to give pure Sulfones or β-ketosulfones.

1-(4-Chlorophenyl)-2-tosylethanone 30a



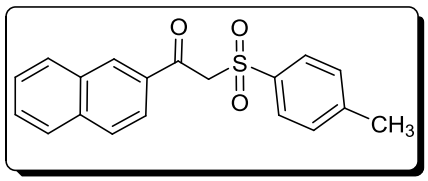
Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (dd, J = 6.7, 2.0 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.55 (dd, J = 6.7, 2.0 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 5.20 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.6, 145.3, 145.3, 134.8, 131.4, 130.1, 129.3, 129.3, 128.5, 62.8, 21.5; ESI-MS: *m/z* calcd for $C_{15}H_{14}ClO_3S$ 308.02, found 309.03 $[M + H]^+$.

1-(Naphthalen-4-yl)-2-tosylethanone 30b



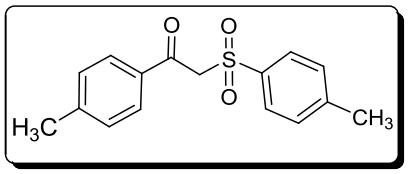
Yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 – 8.46 (m, 1H), 8.06 – 7.96 (m, 2H), 7.89 – 7.86 (m, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.61 – 7.47 (m, 3H), 7.31 – 7.23 (m, 2H), 4.84 (s, 2H), 2.42 (s, J = 5.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 145.3, 135.8, 134.6, 133.9, 133.4, 130.9, 130.4, 129.8, 129.1, 128.8, 128.6, 126.9, 125.6, 124.3, 66.3, 21.7; ESI-MS: *m/z* calcd for $C_{19}H_{17}O_3S$ 324.08, found 325.12 $[M + H]^+$.

1-(Naphthalen-3-yl)-2-tosylethanone 30c



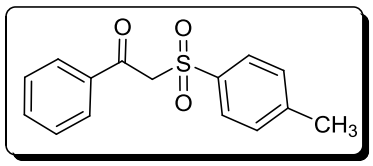
Yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$) 8.43 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.90 – 7.83 (m, 2H), 7.81 – 7.74 (m, 2H), 7.67 – 7.61 (m, 1H), 7.60 – 7.54 (m, 1H), 7.34 – 7.29 (m, 2H), 4.86 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 145.7, 135.9, 134.0, 132.8, 132.4, 131.6, 130.5, 129.9, 129.7, 129.3, 128.4, 127.8, 127.0, 124.2, 66.2, 21.4; ESI-MS (*m/z*): *m/z* calcd for $C_{19}H_{17}O_3S$ 324.08, found 325.12 $[M + H]^+$.

1-p-Tolyl-2-tosylethanone 30d



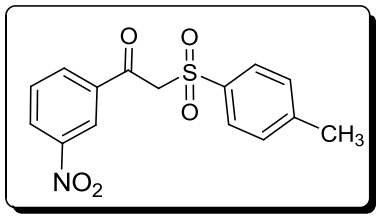
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.67 (t, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 4.61 (s, 2H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 145.6, 145.3, 135.8, 133.4, 129.8, 129.6, 129.5, 128.6, 63.6, 21.8, 21.7; ESI-MS: *m/z* calcd for $C_{16}H_{17}O_3S$ 289.08, found 289.11$[M + H]^+$.

1-Phenyl-2-tosylethanone 30e



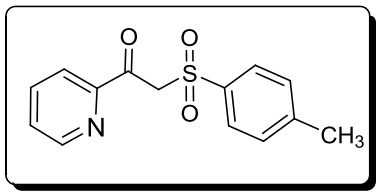
Yield: 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (t, *J* = 8.6 Hz, 2H), 7.77 (t, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 5.9 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.35 (t, *J* = 8.5 Hz, 2H), 4.74 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 134.0, 133.3, 129.8, 129.5, 129.0, 128.9, 128.6, 128.3, 70.5, 21.6; ESI-MS: *m/z* calcd for $C_{15}H_{15}O_3S$ 275.07, found 275.26$[M + H]^+$.

1-(3-Nitrophenyl)-2-tosylethanone 30f



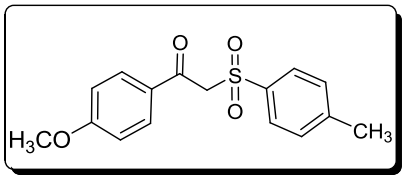
Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (t, *J* = 1.8 Hz, 1H), 8.39 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.26 (d, *J* = 7.8 Hz), 7.69 – 7.63 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.71 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 148.5, 145.9, 136.9, 135.4, 134.9, 130.2, 130.1, 128.5, 128.4, 124.1, 63.9, 21.7; ESI-MS: *m/z* calcd for $C_{15}H_{15}NO_5S$ 320.05, found 320.07 $[M + H]^+$.

1-(Pyridin-2-yl)-2-tosylethanone 30g



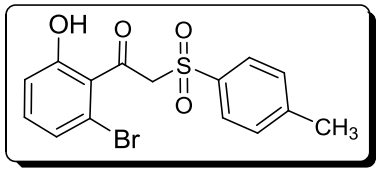
Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.74 (d, *J* = 2.7 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.26 – 7.22 (m, 2H), 5.07 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.83, 151.97, 149.10, 144.95, 137.12, 136.71, 129.66, 128.58, 127.88, 122.55, 61.06, 21.66; ESI-MS: $[M + H]^+$ *m/z* calcd for $C_{14}H_{14}NO_3S$ 276.06, found 276.17 $[M + H]^+$.

1-(4-Methoxyphenyl)-2-tosylethanone 30h



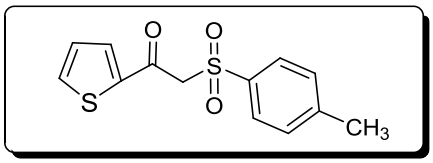
Yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.7, 1.6 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.95 (dd, *J* = 8.7, 1.5 Hz, 2H), 4.66 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 164.1, 145.5, 145.3, 131.9, 130.6, 129.8, 129.7, 128.6, 63.6, 55.6, 21.7; ESI-MS: *m/z* calcd for $C_{16}H_{17}O_4S$ 305.08, found 305.08 $[M + H]^+$.

1-(5-Bromo-2-hydroxyphenyl)-2-tosylethanone 30i



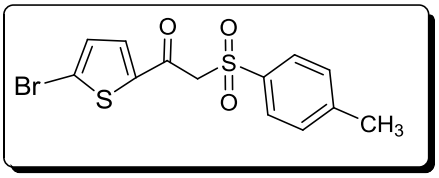
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.61 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 4.70 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 162.2, 155.5, 145.9, 140.5, 140.5, 137.4, 133.4, 130.1, 128.5, 120.7, 63.8, 21.8; ESI-MS: *m/z* calcd for $C_{15}H_{14}NBrO_4S$ 368.97, found 370.98 $[M + 2\ H]^+$.

1-(Thiophen-2-yl)-2-tosylethanone 30j



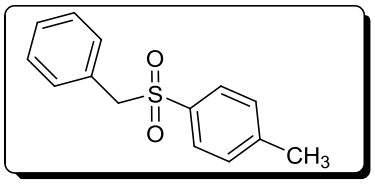
Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.5 Hz, 1H), 7.71 – 7.69(m, 1H), 7.68 – 7.65 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 4.3 Hz, 1H), 4.54 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 145.5, 143.2, 136.4, 135.5, 135.3, 129.9, 128.7, 128.6, 64.7, 21.7; ESI-MS: *m/z* calcd for $C_{13}H_{13}O_4S_2$ 281.03, found 281.14 $[M + H]^+$.

1-(5-Bromothiophen-2-yl)-2-tosylethanone 30k



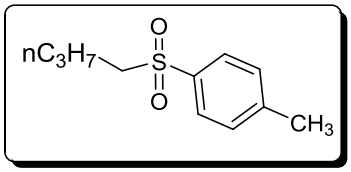
Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 4.1 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 4.1 Hz, 1H), 4.47 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.78, 145.68, 142.90, 139.73, 135.55, 134.48, 131.89, 129.97, 128.60, 64.35, 21.75; ESI-MS: *m/z* calcd for $C_{13}H_{12}BrO_4S_2$ 358.94, found 360.01 $[M + 2 + H]^+$.

1-(Benzylsulfonyl)-4-methylbenzene 30l



Yield: 83%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.31 – 7.27 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.13 – 7.09 (m, 2H), 4.31 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 135.0, 130.8, 129.5, 128.7, 128.6, 128.6, 128.3, 62.9, 21.6; ESI-MS: *m/z* calcd for $C_{14}H_{15}O_2S_2$ 247.07, found 247.21$[M + H]^+$.

1-(Butylsulfonyl)-4-methylbenzene 30m



Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.27 (m, 2H), 3.02 – 2.97 (m, 2H), 2.38 (s, 3H), 1.65 – 1.55 (m, 2H), 1.36 – 1.25 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 132.6, 129.9, 128.1, 56.2, 24.7, 21.6, 21.6, 13.5; ESI-MS: *m/z* calcd for $C_{11}H_{17}O_2S$ 213.09 found 213.09 $[M + H]^+$.

3.1.5 References

[1] Yang, H.; Carter, R. G.; Zakharov, L. N., *Journal of the American Chemical Society*, **2008**, *130*, 9238.

[2] Suryakiran, N.; Reddy, T. S.; Suresh, V.; Lakshman, M.; Venkateswarlu, Y., *Tetrahedron Letters*, **2006**, *47*, 4319.

[3] Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Hill, R. L.; Laffey, T. G., *Tetrahedron Letters*, **1995**, *36*, 7925.

[4] Sengupta, S.; Sarma, D. S.; Mondal, S., *Tetrahedron: Asymmetry*, **1998**, *9*, 2311.

[5] Marco, J.-L.; Fernandez, I.; Khiar, N.; Fernandez, P.; Romero, A., *The Journal of Organic Chemistry*, **1995**, *60*, 6678.

[6] Swenson, R. E.; Sowin, T. J.; Zhang, H. Q., *The Journal of Organic Chemistry*, **2002**, *67*, 9182.

[7] Bartlett, P. A.; Green, F. R.; Rose, E. H., *Journal of the American Chemical Society*, **1978**, *100*, 4852.

[8] Curti, C.; Laget, M.; Carle, A. O.; Gellis, A.; Vanelle, P., *European Journal of Medicinal Chemistry*, **2007**, *42*, 880.

[9] Wolf, W. M., *Journal of Molecular Structure*, **1999**, *474*, 113.

[10] Cancio, R.; Silvestri, R.; Ragno, R.; Artico, M.; Martino, G. D.; Regina, G. L.; Crespan, E.; Zanoli, S.; Hübscher, U.; Spadari, S.; Maga, G., *Antimicrobial Agents and Chemotherapy*, **2005**, *49*, 4546.

[11] Trivedi, S. P., P. C.; Chaurasiya, P. K.; Pawar, R. S.; Patil, U. K.; Singour, P. K., *Der Pharma Chemica*, **2010**, *2*, 369.

[12] Markitanov, Y. M.; Timoshenko, V. M.; Shermolovich, Y. G., *Journal of Sulfur Chemistry*, **2013**, *35*, 188.

[13] Shyshkina, O. O.; Popov, K. S.; Gordivska, O. O.; Tkachuk, T. M.; Kovalenko, N. V.; Volovnenko, T. A.; Volovenko, Y. M., *Chemistry of Heterocyclic Compounds*, **2011**, *47*, 923.

[14] Samakkanad, N.; Katrun, P.; Techajaroonjit, T.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C., *Synthesis*, **2012**, 1693.

[15] Guravaiah, N.; Rao, V. R., *Journal of Chemical Research*, **2009**, 87.

[16] Rawat, V. S.; Reddy, P. L. M.; Sreedhar, B., *RSC Advances*, **2014**, *4*, 5165.

[17] Ibarra, C. A.; Rodriguez, R. C.; Monreal, M. C. F.; Navarro, F. J. G.; Tesorero, J. M., *The Journal of Organic Chemistry*, **1989**, *54*, 5620.

[18] Umierski, N.; Manolikakes, G., *Organic Letters*, **2012**, *15*, 188.

[19] Umierski, N.; Manolikakes, G., *Organic Letters*, **2013**, *15*, 4972.

[20] Kumar, D.; Arun, V.; Pilania, M.; Shekar, K. P. C., *Synlett*, **2013**, 831.

[21] Deeming, A. S.; Russell, C. J.; Hennessy, A. J.; Willis, M. C., *Organic Letters*, **2014**, *16*, 150.

[22] Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A., *Organic Letters*, **2014**, *16*, 154.
[23] Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G.-J., *Organic Letters*, **2013**, *16*, 50.
[24] Kumar, D.; Sundaree, S.; Rao, V. S.; Varma, R. S., *Tetrahedron Letters*, **2006**, *47*, 4197.
[25] Holmquist, C. R.; Roskamp, E. J., *Tetrahedron Letters*, **1992**, *33*, 1131.
[26] Li, H.; Wang, H.; Pan, Y.; Shi, Y., *Synthetic Communications*, **1998**, *28*, 409.
[27] Srinivas, K.; Dubey, P. K., *Synthetic Communications*, **2011**, *41*, 1584.
[28] Sreedhar, B.; Rawat, V. S., *Synlett*, **2012**, 413.
[29] Kamigata, N.; Udodaira, K.; Shimizu, T., *Journal of the Chemical Society*, *Perkin Transactions 1*, **1997**, 783.
[30] Huang, X.; Vogel, P., *Synthesis*, **2002**, 232.
[31] Bouchez, L.; Vogel, P., *Synthesis*, **2002**, 225.
[32] Wildeman, J.; Leusen, A. M. V, *Synthesis*, **1979**, 733.
[33] Vennstra, G. E.; Zwaneburg, B., *Synthesis*, **1975**, 519.

PART B

Synthesis of Ionic Liquid-Supported Sulfonyl Azide and its Application in Diazotransfer Reaction

Part B: Synthesis of Ionic Liquid-Supported Sulfonyl Azide and its Application in Diazotransfer Reaction

3.2.1 Introduction

Diazo compounds are useful industrial and pharmaceutical reagents since they can undergo a wide variety of chemical transformations under mild conditions.[1] They serve as potentially valuable building blocks in the synthesis of complex organic molecules including natural products. Diazo compounds have been widely employed as carbene source in organic synthesis.[2] These important intermediates are used in a variety of chemical transformations such as 1, 3-dipolar cycloadditions and insertion reactions.[2,3]

Regitz diazotransfer method is well known method for the synthesis of diazo compounds from active methylene compounds using sulfonyl azides.[2,3] Commonly used reagents in diazotransfer reaction are methanesulfonyl azide,[4] *p*-tolylsulfonyl azide,[5] pyridinesulfonyl azide,[6] imidazole-1-sulfonyl azide,[7] trifluoromethanesulfonyl azide[8] (TfN_3) and triisopropylbenzenesulfonyl azide[9] (Figure 3.2.1). However, the reaction using these sulfonyl azide frequently raises the problem of isolation of the desired diazo compound from excess sulfonyl azide and sulfonamide (by-product of the diazotransfer reaction). Furthermore, sulfonyl azides like trifluoromethanesulfonyl azide (TfN_3) and methanesulfonyl azide are hazardous, decompose rapidly and are of explosive nature.[4] Because of poor shelf life and explosive nature, these reagents must be generated *in situ* from sodium azide and corresponding sulfonic anhydride. To overcome these problems several reagents have been developed.

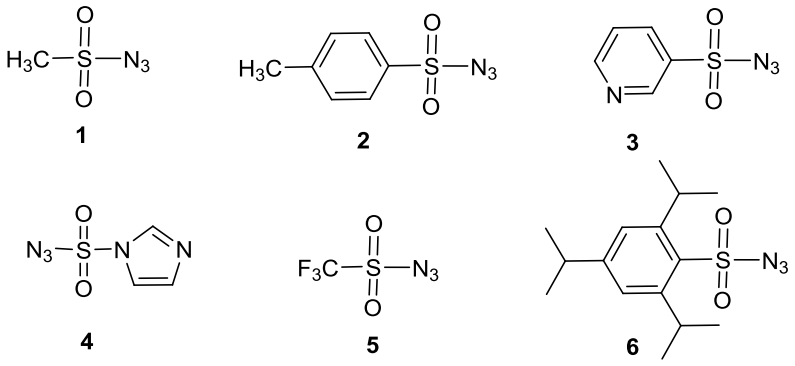
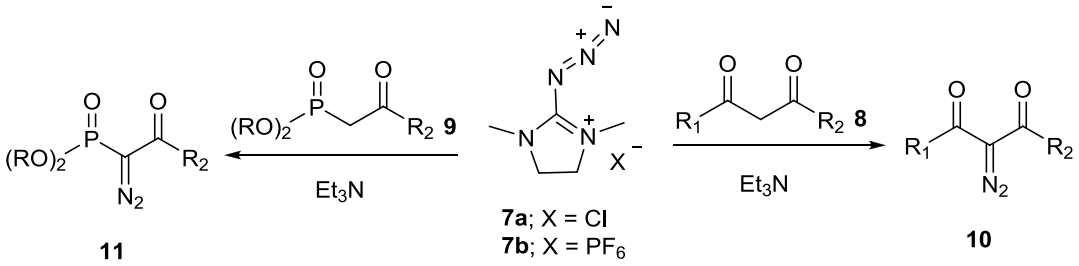


Figure 3.2.1 Commonly used diazotransfer reagents **1-6**

A brief overview of recently developed diazotransfer reagents and methods is presented below

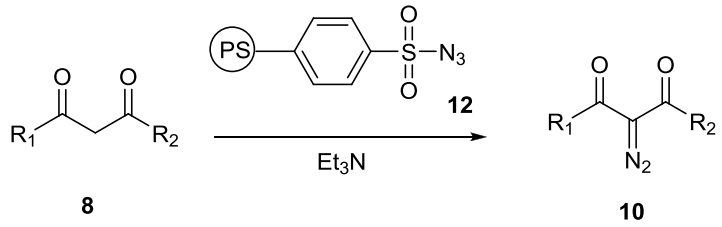
Kitamura group synthesized novel 2-azido-1,3-dimethylimidazolinium salts (ADM) [10] and established its application in diazotransfer reaction (Scheme 3.2.1). 2-Azido-1,3-dimethylimidazolinium chloride (ADMC, **7a**) and its corresponding hexafluorophosphate (ADMP, **7b**) reacts with 1,3-dicarbonyl compounds **8** & **9** under mild basic conditions to give corresponding azido derivatives **10** & **11** in high yields. The products were isolated by simple water work-up as the by-products are highly soluble in water.



Scheme 3.2.1 Diazotransfer reaction of active methylene **8** & **9** compounds using ADM salts **7**

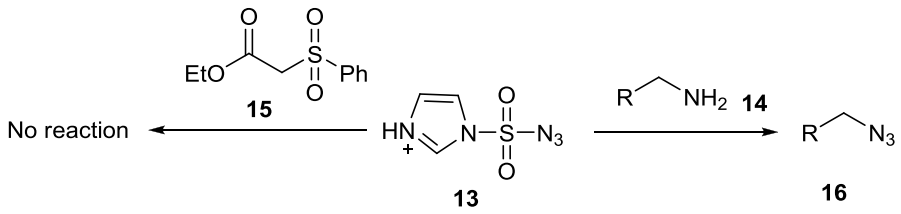
Metz *et al.* has used polymer-supported benzene sulfonyl azide **12**[11] for the synthesis of α-diazo carbonyl compounds. Reagent **12** is thermally stable and non friction sensitive and has reactivity capabilities similar to its solution phase counterpart, benzene sulfonyl azide. Moreover, products were isolated in pure form by simple resin filtration in good to excellent yields without

the necessity of an aqueous workup. On the contrary, the time taken to complete the reaction for aliphatic derivatives is very long (Scheme 3.2.2).



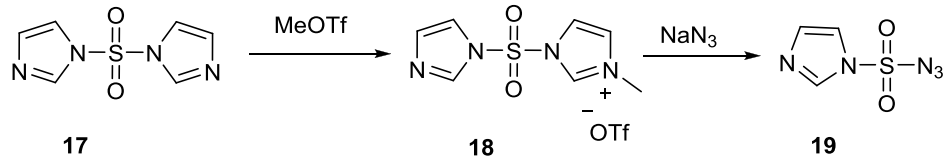
Scheme 3.2.2 Diazo transfer to active methylene compounds using polymer supported benzenesulfonyl azide **12**

Goddard-Borger and his co-workers reported imidazole-1-sulfonyl azide hydrochloride **13**,[12, 13] as an effective reagent for azide transfer to amines than as diazo group transfer (Scheme 3.2.3). Recently, imidazole-1-sulfonyl azide [12] has been found to be highly explosive and it's stability has been improved by altering the Cl^- to BF_4^-, HSO_4^-, TsO^-.[14] Reaction of **13** with β-ketosulfone did not result in corresponding diazo compounds.



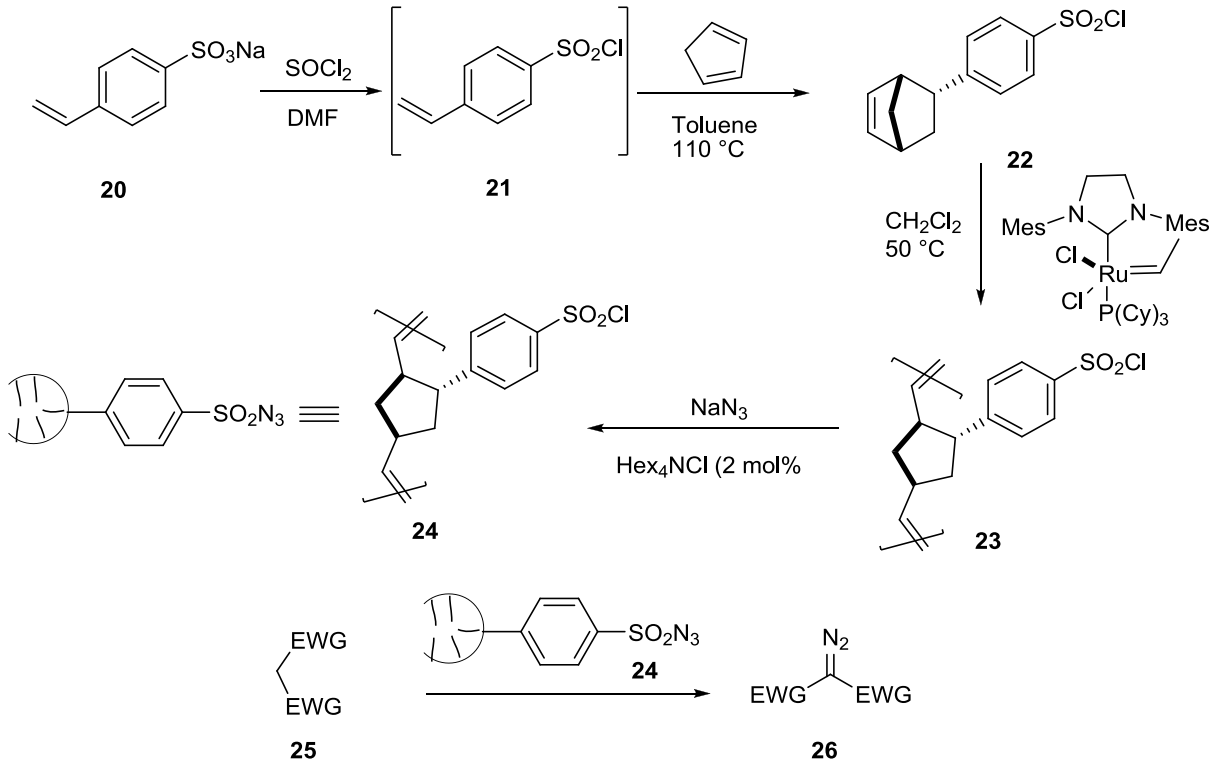
Scheme 3.2.3 Applications of imidazole-1-sulfonyl azide hydrochloride **13**

The synthetic process of imidazole-1-sulfonyl azide hydrochloride **13** often produces toxic hydrazoic acid (HN_3) along with extremely explosive molecule sulfuryl diazide ($N_3SO_2N_3$). To evade these toxic and explosive molecules Wang group demonstrated a safe and facile route for the synthesis of imidazole-1-sulfonyl azide[7] **19** as shown in the scheme 3.2.4. Mono *N*-methylation of sulfuryl diimidazole **17** with methyl trifluoromethanesulfonate, followed by reaction with sodium azide produces reagent **19** in excellent yields without evolving any toxic and explosive compounds (Scheme 3.2.4).



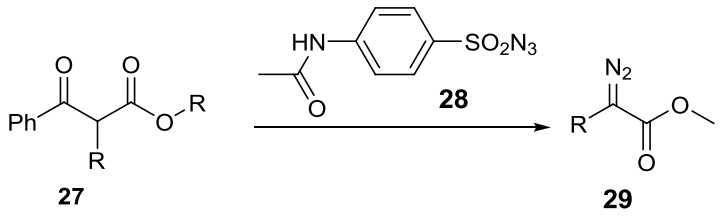
Scheme 3.2.4 Synthesis of diazotranfer reagent imidazole-1-sulfonyl azide **19**

Hanson *et al*. developed soluble oligomeric sulfonyl azide **24**[15] using ring open metathesis (ROM) polymerization and successfully used the reagent for diazotransfer reactions of active methylene compounds (Scheme 3.2.5). Lack of stability and decomposition even at low temperatures made this reagent non user friendly.



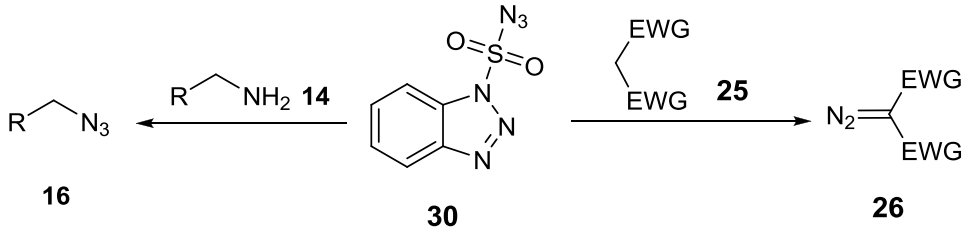
Scheme 3.2.5 Synthesis and diazo transfer reaction of oligomeric sulfonyl azide **24**

Taber *et al.* has reported diazotransfer to the benzoylated ester **28** utilizing *p*-acetamidobenzenesulfonyl azide **27** (Scheme 3.2.6).[16] This procedure allows the preparation of α-diazo esters **29** in gram quantities. However, it becomes very difficult to remove by-product tosylamide generated during the reaction and requires repetitive column chromatography.



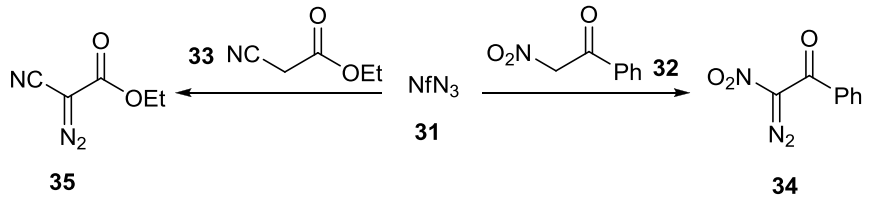
Scheme 3.2.6 Diazo transfer of the benzoylated ester **27** using *p*-acetamidobenzenesulfonyl azide **28**

Katritsky *et al.*[17] developed a crystalline benzotriazol-1-yl-sulfonyl azide **30** and used as convenient and efficient reagent for the synthesis of a wide range of azides **16** and diazo compounds **26** from amines and active methylene compounds respectively (Scheme 3.2.7). Apart from this, reagent **26** has been used in the synthesis of N-(α-azidoacyl)-benzotriazoles, efficient N-, S-, C-, and O-acylating agents.[17] Unfortunately, reagent **26** was found to be highly explosive.



Scheme 3.2.7 Applications of benzotriazol-1-yl-sulfonyl azide **30** in diazotranfer reaction

Chiara *et al.* have synthesized a shelf-stable and cost-effective diazo transfer reagent nonafluorobutanesulfonyl azide (NfN_3) **31**.[18] The reagent is highly effective for the synthesis of *α*-diazo carbonyl compounds from versatile substrates like 2-nitro-1-phenylethanone **32** and ethyl cyanoacetate **33**, which have been reported as poor substrates for diazotransfer reaction (Scheme 3.2.8).



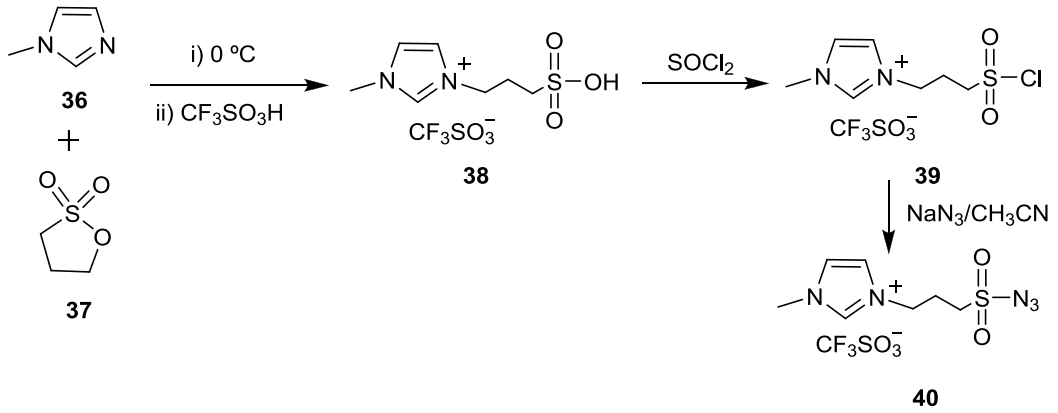
Scheme 3.2.8 Nonafluorobutanesulfonyl azide 31 as diazo transfer reagent

Ramachary *et al.* have developed ionic liquid promoted organocatalytic selective diazotransfer reactions using some well known diazotransfer reagents.[19] Use of ionic liquid as solvent has improved the yield, separation of products and moreover, the solvent could be recycled and reused several times.

Due to wide importance of diazo compounds and problem associated with safety of reagents and separation of sulfonamides generated as side products, prompted us to develop self-stable novel ionic liquid-supported sulfonyl azide **40**. Reagent **40** has been used as a green and safe reagent for diazotransfer reaction under solvent free conditions.

3.2.2 Results and Discussion

Synthesis of **40** was achieved following the reaction sequences as shown in scheme 3.2.9. Initially, the reaction of 1-methylimidazole **36** with 1,3-propanesultone **37** at 0 °C followed by reaction with trifluoromethanesulfonic acid (TfOH) at room temperature for 2 h gave **37**. Reaction of **38** with thionyl chloride under reflux conditions gave **39** which on reaction with sodium azide afforded **40**. Structure of **40** was confirmed by IR, ^{1}H NMR and high-resolution mass spectrometry. IR spectrum of the **40** showed a strong band for the N_3 group at 2130 cm^{-1}. The ^{1}H NMR spectrum showed a triplet and a multiplet at δ 4.28 and δ 3.80 for aliphatic protons adjacent to sulfonyl group and 1-methylimidazole, respectively. Peaks for protons of imidazole moiety were observed at δ 9.07, 7.79 and 7.65. Figure 3.2.2 represents ^{1}H and ^{13}C NMR of ionic liquid-supported sulfonyl azide **40**. In HRMS peak for *m/z* of $[M\text{-}CF_3SO_3]^+$ ion appeared at 230.0714, which confirmed the structure of **40**.



Scheme 3.2.9 Synthesis of ionic liquid-supported sulfonyl azide **40**

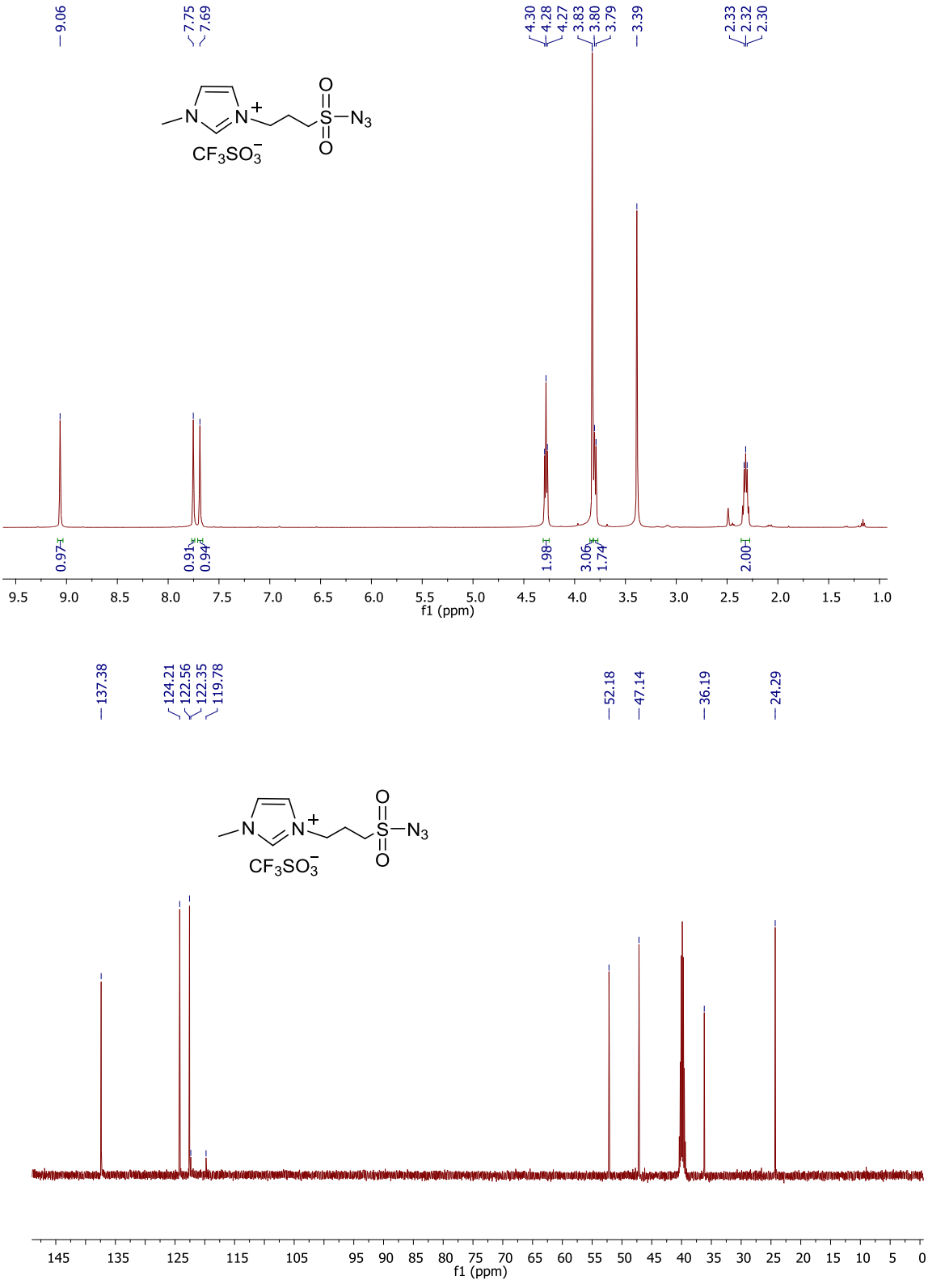


Figure 3.2.2 ^{1}H and ^{13}C NMR spectrum of ionic liquid-supported sulfonyl azide **40**

The differential scanning calorimetry (DSC) experiment showed that exothermic decomposition temperature of pure ionic liquid-supported sulfonyl azide **40** is above 150 °C (Figure 3.2.3) with initiation temperature of 159.69 °C and end point at 213.72 °C. Therefore, it should work without any problem below 100 °C. We recommend use of **40** well below its decomposition temperature, preferably at room temperature. It is worth to mention that **40** has not shown any sign of decomposition or loss of reactivity even after storing for one month at room temperature.

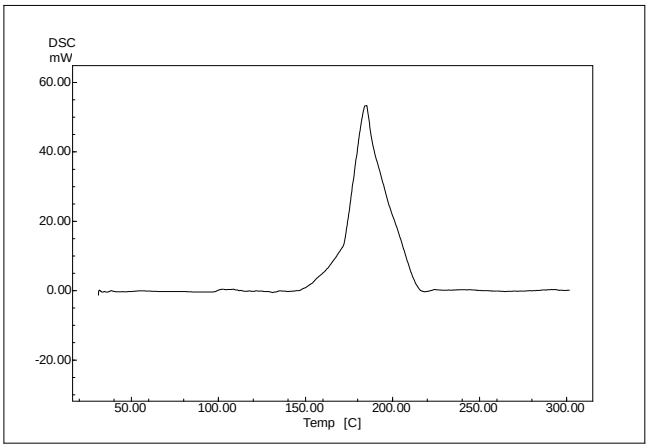
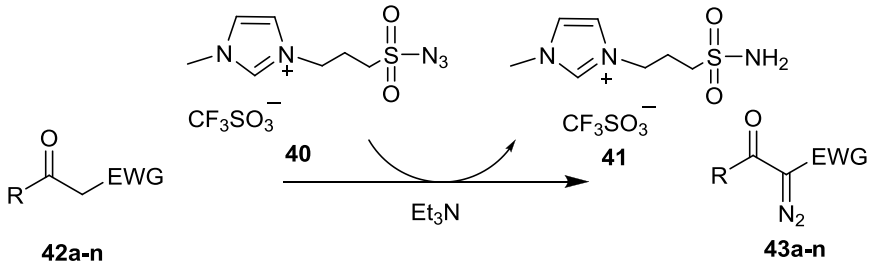


Figure 3.2.3 DSC curve for pure ionic liquid-supported sulfonyl azide **40**

After successfully synthesizing **36**, we studied its reaction as diazotransfer reagent for active methylene compounds (Scheme 3.2.10). Reaction of dimedone (**42h**) with **40** was taken as model reaction to optimize the reaction conditions. In our initial studies, we investigated effect of different solvents. It was observed that the best yield of **43h** (94%) was obtained under solvent free conditions. Among different solvents studied maximum yield of **43h** was obtained in ethanol (92%) whereas good to moderate yield 92% of **43h** was obtained in other solvents such as acetonitrile (70%), ionic liquid [bmim][BF_4] (65%), THF (60%), toluene (35%). No product formation was observed in water.



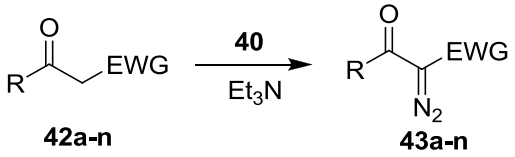
	R	EWG		R	EWG		R	EWG
a	C_6H_5	$COCH_3$	f	CH_3	$COCH_3$	k	4-ClC_6H_4	4-$CH_3C_6H_4SO_2$
b	C_6H_5	COC_2H_5	g	-COC_5H_4CO-		l	4-$CH_3C_6H_4$	4-$CH_3C_6H_4SO_2$
c	CH_3	$CO_2C_2H_5$	h	-$CH_2C(CH_3)_2CH_2CO$-		m	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4SO_2$
d	OC_2H_5	$CO_2C_2H_5$	i	-$CH_2CH_2CH_2CO$-		n	OC_2H_5	$C_6H_5SO_2$
e	CH_3	CO_2CH_3	j	-$N(CH_3)CON(CH_3)CO$-				

Scheme 3.2.10 Diazotransfer to active methylene compounds using **40**

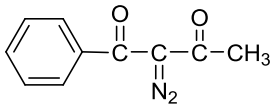
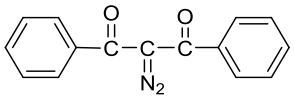
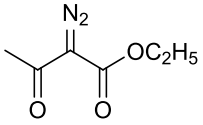
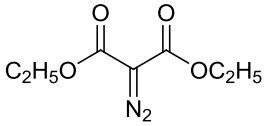
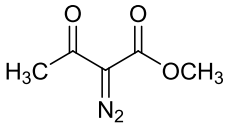
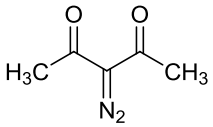
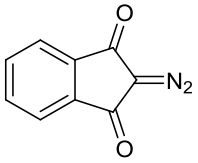
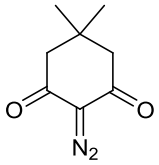
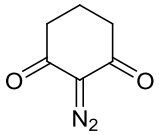
To assess the scope of **40** as diazotransfer reagent structurally diverse 1,3-diketones, β-ketoester and 1,3-diesters were reacted with **40** under the optimized reaction conditions to afford corresponding diazo compounds in excellent yields (Table 3.2.1). There was no appreciable difference in the yield and rate of reaction with different substrates. All the synthesized diazo compounds were well characterized by ^{1}H NMR and ^{13}C NMR (Experimental section).

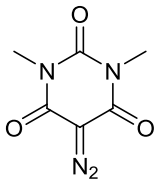
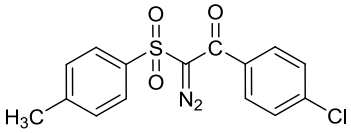
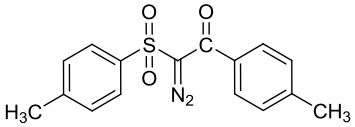
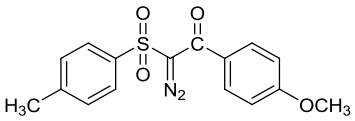
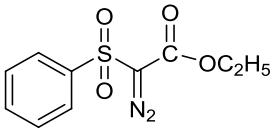
α-Diazo-β-ketosulfones have been employed as carbene source in intramolecular cyclopropanation, insertion reactions. Recently, Kumar and Namboothiri has utilized α-diazo-β-ketosulfone for the synthesis of sulfonylpyrazoles by reacting with nitroalkenes.[20] To further broaden the scope of our reagent **40**, we explored reaction of β-ketosulfones. As expected the reaction went very smooth in short time with excellent yield (82-87%) to give corresponding diazo derivatives of β-ketosulfones (Table 3.2.1, entries k-n). It is worth to mention that β-ketosulfones have been reported poor substrates with several diazotransfer reagents such as Im-SO_2N_3.HCl [13] and Bt-SO_2N_3[17] (Table 3.2.2, entries 7,8).

Table 3.2.1 Synthesis of diazo compounds using **40**



42a-n **43a-n**

Entry	R	EWG	Product	Time (Min.)	Yield (%)[a]
a	C_6H_5	$COCH_3$		2	88
b	C_6H_5	COC_6H_5		2	85
c	CH_3	$CO_2C_2H_5$		3	89
d	C_2H_5O	$CO_2C_2H_5$		3	87
e	CH_3	CO_2CH_3		3	90
f	CH_3	$COCH_3$		3	89
g	-CO- C_6H_4- CO-			2	87[b]
h	$CH_2C(CH_3)_2CH_2CO$			2	94
i	$CH_2CH_2CH_2CO$			2	94

j	$CH_3NCON(CH_3)CO$			2	91
k	4-ClC_6H_4	4-$CH_3C_6H_4SO_2$		4	82
l	4-$CH_3C_6H_4$	4-$CH_3C_6H_4SO_2$		4	87
m	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4SO_2$		4	83
n	C_2H_5O	$C_6H_5SO_2$		5	84

[a]Isolated yields, [b]Product purified by column chromatography over silica-gel.

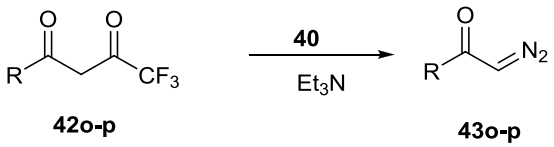
The reactivity and stability of **40** was compared with other traditional diazotransfer reagents (Table 3.2.2). As apparent from Table 3.2.1 and Table 3.2.2, higher yield of diazo products were obtained with **40** in shorter reaction time under optimized reaction conditions in comparison to other traditional reagents such as oligomeric-SO_2N_3, PS-SO_2N_3, *p*-CBSA, Im-SO_2N_3.HCl, ADMP and Bt-SO_2N_3 on similar substrates. Presset *et al.*[21] reported that TsN_3 is better reagent for multi gram scale than other reagents such as MsN_3, Im-SO_2N_3.HCl, ADMC and *p*-CBSA. However, it becomes very difficult to remove tosylamide generated during the reaction and repetitive column chromatography first over silica gel and then over basic alumina is required. We can overcome this problem by using **40**. Simple extraction with hexane-ethyl acetate mixture followed by water wash gave pure product, except in case of **43g**, where purification was performed over silica-gel column. Comparing the DSC experimental data with some of the traditional diazotransfer reagents it was observed that the initiation temperature at which

decomposition started in DSC for **40** (159 °C) was higher or comparable with these diazotransfer reagents (Table 3.2.2). Only for AMDP the initiation temperature at which decomposition started in DSC (200 °C) was higher than **40**.

Table 3.2.2 Comparison of stability and yield for selected substrates between **40** and other sulfonyl reagents

S. No.	Reagent	Stability (°C) [c,d]	Substrate	Product	Time (h)	Yield (%)[a,b]
1	Oligomeric-SO_2N_3	-[e]	**42h**	**43h**	0.5	75[15]
2	NfN_3	120	**42a**	**43a**	0.25	89[18]
3	PS-SO_2N_3	130	**42d**	**43d**	16	63[11]
4	*p*-CBSA	42	**42d**	**43d**	16	76[22]
5	Im-SO_2N_3.HCl	~85	**42d**	**43d**	16	65[13]
6	ADMP	200	**42g**	**43g**	0.15	78[23]
7	Bt-SO_2N_3	85	**42n**	**43n**	14	56[17]
8	Im-SO_2N_3.HCl	85	**42n**	**43n**	48	-[13]

[a]Yields are as reported in literature. [b]Yields for **43a**, **43d, 43g, 43h** and **43n** using **40** are 94, 87, 87, 94 and 84 % respectively (Table 3.2.1). [c]Initiation temperature at which decomposition started in DSC. [d]For reagent **40** initiation temperature is 159 °C. [e]It slowly decomposes at room temperature



42o-p **43o-p**

42o, R = C_6H_5,
42p, R = 2-C_4H_3S

Scheme 3.2.11 Detrifluoroacetylative diazotransfer

Encouraged by these results, we then decided to investigate the suitability of **40** for synthesis of diazo compounds from acetophenone. Reaction did not work under these conditions and we recovered the acetophenone. We also screened this reaction using different strong bases such as sodium hydride and potassium *tert*-butoxide instead of triethylamine but did not get the desired

product. It is also reported that diazotransfer to the simple carbonyl compound usually fails when the methylene group is linked to a single carbonyl group only.[24] Diazo derivative of such compounds can be prepared by employing deacylating diazotransfer strategy.[25] We studied the use of **40** for detrifluoroacetylative diazo group transfer for commercially available 4,4,4-trifluoro-1-phenylbutane-1,3-dione **42o** and 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione **42p** (Scheme 3.2.11). Treating one equivalent of **42o** and **42p** with **40** in the presence of triethyl amine under above conditions gave corresponding α-diazo derivatives **43o** and **43p** in 82% and 80%, respectively. Figure 3.2.4 demonstrates an representative ^{1}H and ^{13}C NMR spectra of **43o**.

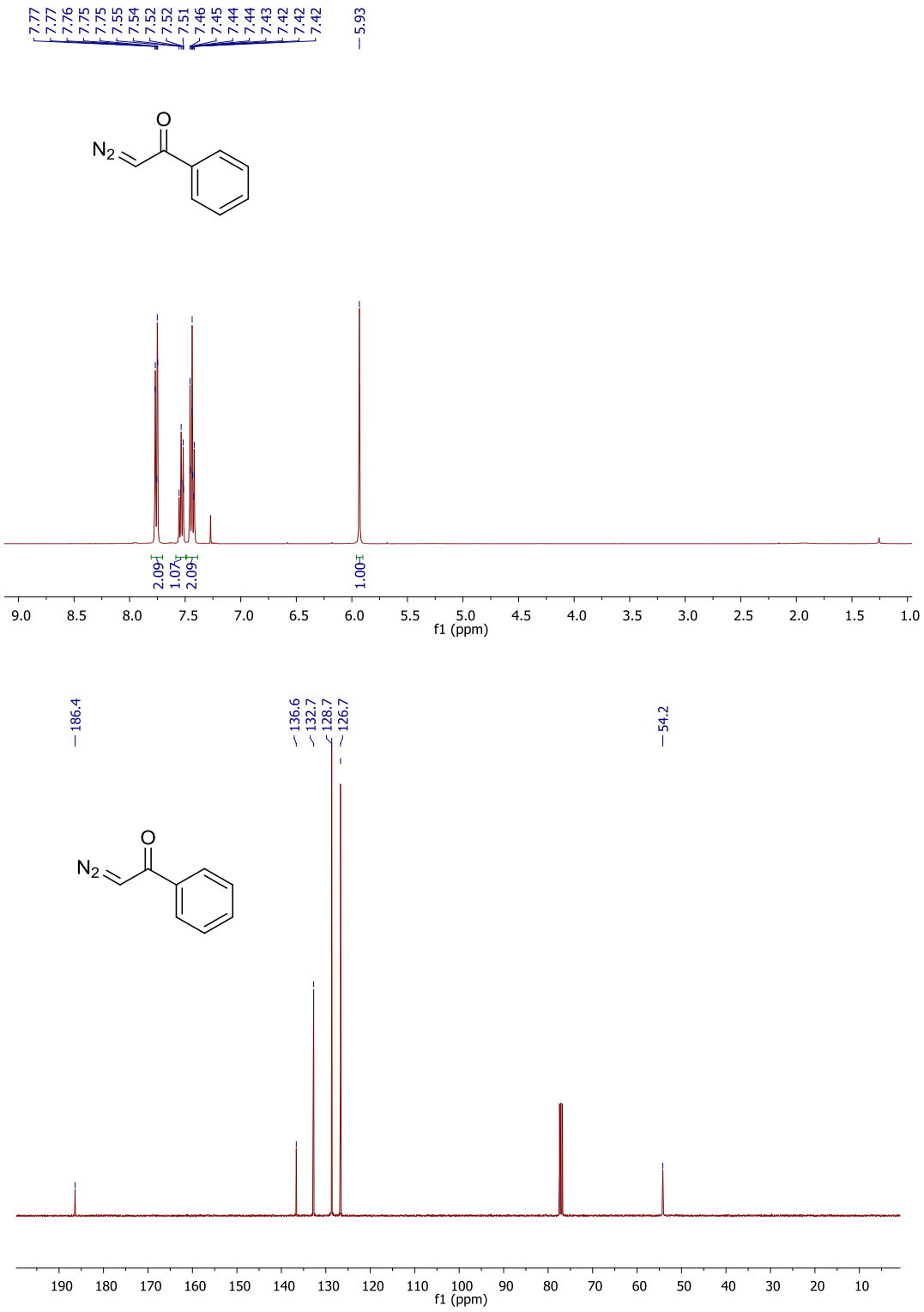


Figure 3.2.4 ^{1}H and ^{13}C NMR spectrum of 2-Diazo-1-(phenyl)ethanone **43o**

3.2.3 Conclusion

We have synthesized a novel ionic liquid-supported sulfonyl azide. The azide is stable and used to develop a green method for diazotransfer reaction using a novel ionic liquid-supported sulfonyl azide under solvent free conditions. Different diazo compounds were synthesized from active methylene compounds in excellent yield (82-94%) and high purity. The reagent is versatile and can be used for detrifluoroacetylative diazotransfer as well. The method offers better and simple purification and high purity of product.

3.2.4 Experimental

Procedure for synthesis of ionic liquid-supported sulfonic acid 38

Propane sultone **37** (12.18 mmol) was added drop wise to 1-methylimidazole **36** (12.18 mmol) at 0 °C. The resulting solution was stirred at room temperature until solid was obtained. After completion of reaction, the product was washed with toluene (3 × 15 mL) and finally with diethyl ether (3 × 15 mL) to remove unreacted starting materials. The compound was dried under reduced pressure to get zwitterionic form. Trifluoromethane sulfonic acid (13.39 mmol) was added dropwise to zwitter ion at 0 °C. The solution was stirred at 40 °C after completion of the addition until thick liquid was obtained. The resulting liquid was washed with diethyl ether to remove excess of triflic acid. The compound was dried under reduced pressure to give **38** as thick liquid in 98% yield.

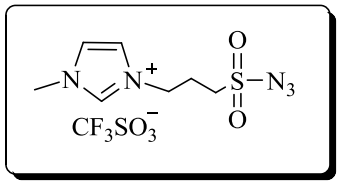
Procedure for synthesis of ionic liquid-supported sulfonyl chloride 39

Thionyl chloride ($SOCl_2$) (35.8 mmol) was added drop wise to the ionic liquid sulfonic acid **38** (11.9 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 8 h and finally heated up to 80 °C for 2 h. Excess of thionyl chloride was removed by rotary evaporator under reduced pressure with nitrogen atmosphere to get ionic liquid-sulfonyl chloride **39** as yellow thick liquid in 96% yield.

Procedure for synthesis of ionic liquid-supported sulfonyl azide 40

Ionic liquid-supported sulfonyl chloride **39** (11.4 mmol) was dissolved in acetonitrile and then treated with NaN_3 (13.68 mmol). Resulting solution was stirred for 12 h at 60 °C. Reaction mixture was filtered to remove sodium salts. The filtrate was concentrated to give crude product which was then washed with DCM and ethyl acetate mixture (4 × 50 mL, 1: 1 *v/v*) to get pure ionic liquid liquid-supported sulfonyl azide **40**. Finally ionic liquid-supported sulfonyl azide **40** was dried under reduced pressure.

Ionic liquid-supported sulfonyl azide 40



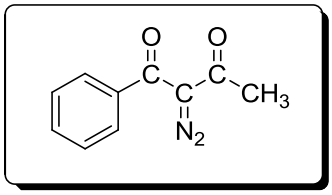
Yield: 96%; Thick pale yellow liquid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.06 (s, 1H), 7.77 – 7.73 (m, 1H), 7.70 – 7.68 (m 1H), 4.28 (t, J = 6.9 Hz, 2H), 3.83 (s, 3H), 3.81 – 3.78 (m, 2H), 2.36 – 2.28 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 137.9, 124.2, 122.6, 121.1 (q, $J_{C\text{-}F}$ = 323.82), 119.8, 52.2, 47.1, 36.2, 24.3; IR (neat): ν_{max} 2145 (diazo), 1366, 1257, 1157, 1034 cm^{-1}; HRMS (ESI-qTOF) $[M\text{-}CF_3SO_3]^+$ *m/z* Calcd for $C_7H_{12}N_5O_2S^+$ 230.0706; found 230.0714

General procedure for diazotransfer using ionic liquid-supported sulfonyl azide 40

(**CAUTION:** Although we never had any accident while using **40** but it may be explosive). Triethylamine (1.5 mmol) was added to the mixture of active methylene compound (1 mmol) and ionic liquid-supported sulfonyl azide **40** (1.2 mmol). The resulting mixture was stirred at room temperature for the time indicated in Table 4.22. The progress of reaction was monitored by TLC. After completion of reaction, the product was extracted with hexane/ethyl acetate mixture (4 × 10 mL, 1: 1 *v/v*) and washed with water. The organic layer were combined, dried with anhydrous sodium sulfate and concentrated to give crude product. In case of **43g** purification was performed over silica-gel column. The side product ionic liquid-supported sulfonylamide **41** does not dissolve in organic layer and thus can be easily removed. Physical and

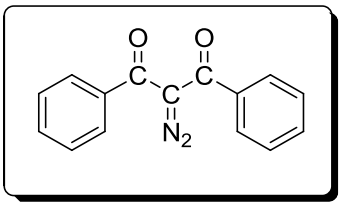
spectral data of synthesized diazo compounds are given below.

2-Diazo-1-phenyl-butane-1,3-dione 43a



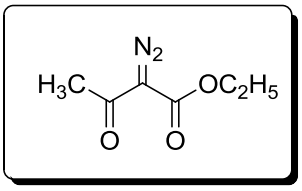
Yield: 88%; M.p. 62–63 °C, (Lit.[26] 60-62 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 5.5, 4.0 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.53 – 7.47 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.9, 185.1, 137.3, 132.7, 128.9, 127.3, 29.2; IR (neat): ν_{max} 2177 (diazo), 1651 (C=O), 1059, 752, 642 cm^{-1}.

2-Diazo-1,3-diphenylpropane-1,3-dione 43b



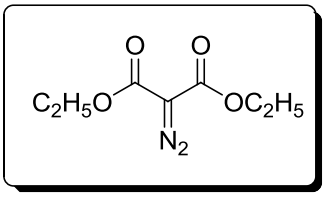
Yield: 85%; M.p. 106-109 °C, (Lit.[22] 107-109 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.5 Hz, 4H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 136.9, 132.6, 128.3, 128.3; IR (neat): ν_{max} 2119 (diazo), 1643, 1317, 1176 cm^{-1}.

2-Diazo-3-oxo-butyric acid ethyl ester 43c



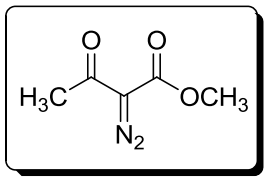
Yield: 89%; Pale yellow liquid;[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 161.6, 61.6, 28.3, 14.5. IR (neat): ν_{max} 2136 (diazo), 1720 (-C=O), 1658 (O-C=O), 1319, 1072 cm^{-1}.

2-Diazomalonic acid diethyl ester 43d



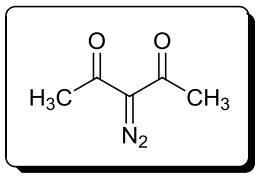
Yield: 87%; Yellow liquid;[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (q, *J* = 7.1 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 61.7, 14.5. IR (neat): ν_{max} 2144 (diazo), 1720, 1373, 1319, 1095 cm^{-1}.

2-Diazo-3-oxo-butyric acid methyl ester 43e



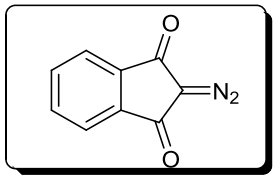
Yield: 90%; Yellow liquid;[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 161.8, 52.2, 28.2; IR (neat): ν_{max} 2142 (diazo), 1687, 1365, 752, 642 cm^{-1}.

3-Diazo-2,4-pentanedione 43f



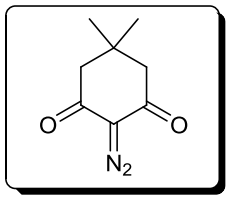
Yield: 89%; Colorless liquid;[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4, 28.5; IR (neat): ν_{max} 2140 (diazo), 1687, 1365, 752, 642 cm^{-1}.

2-Diazoindan-1,3-dione 43g



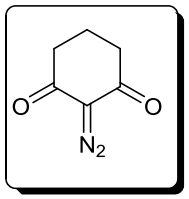
Yield: 87%; M.p. 146-149 °C, (Lit.[28] 148-149 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.82 (m, 2H), 7.77 – 7.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3, 137.3, 135.0, 122.9; IR (neat): ν_{max} 2121 (diazo), 1697, 1357, 1095, cm^{-1}.

2-Diazo-5,5-dimethylcyclohexane-1,3-dione 43h



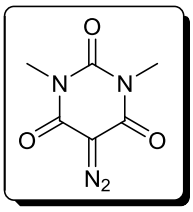
Yield: 94%; M.p. 103-106 °C, (Lit.[15] 105-107 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 4H), 1.12 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 50.5, 31.1, 28.4; IR (neat): ν_{max} 2138, 1738, 1693 cm^{-1}.

2-Diazocyclohexane-1,3-dione 43i



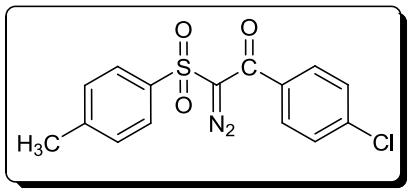
Yield: 94%; M.p. 47-49 °C, (Lit.[21] 48-49 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 – 2.53 (m, 4H), 2.08 – 1.99 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 37.0, 18.7; IR (neat): ν_{max} 2136, 1737, 1695 cm^{-1};

5-Diazo-1,3-dimethylpyrimidine-2,4,6-trione 43j



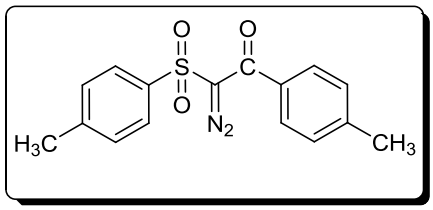
Yield: 91%; M.p. 141-145 ºC, (Lit.[29] 158 °C solvent isopropanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 150.5, 28.6.); IR (neat): ν_{max} 2156 (diazo), 1650, 1303, 1265 cm^{-1}.

2-Diazo-1-(4-chlorophenyl)-2-tosylethanone 43k



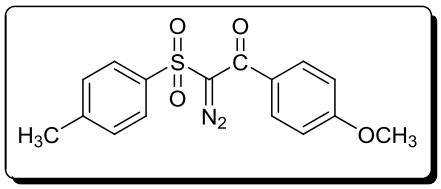
Yield: 82%; M.p. 125-127 °C (Lit.[30] 134 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.6, 145.6, 139.4, 138.5, 138.2, 129.8, 129.2, 129.0, 128.2, 21.7; IR (neat): ν_{max} 2104 (diazo), 1680 (C=O), 1381, 1286, 1072cm^{-1}.

2-Diazo-1-(4-tolyl)-2-tosylethanone 43l



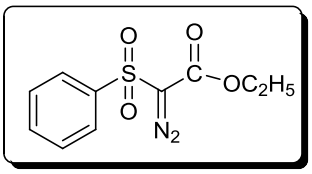
Yield: 87%; M.p. 120-123 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.3, 145.3, 144.0, 138.7, 133.7, 129.7, 129.5, 128.2, 127.6, 21.7, 21.6; IR (neat): ν_{max} 2124 (diazo), 1675 (C=O), 1361, 1276 cm^{-1}.

2-Diazo-1-(4-methoxyphenyl)-2-tosylethanone 43m



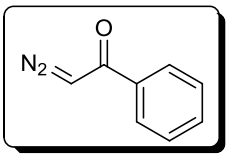
Yield: 83%; M.p. 141-145 ºC (Lit.[30] 124 °C); IR (neat): ν_{max} 2121 (diazo), 1633 (C=O), 1208, 1024, 642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 – 7.54 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.95 – 6.88 (m, 2H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.3, 163.5, 145.3, 138.7, 129.9, 129.7, 128.4, 128.2, 114.1, 55.6, 21.7.

Ethyl 2-diazo-2-(phenylsulfonyl)acetate 43n



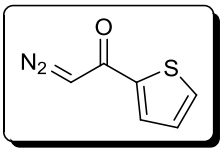
Yield; 84%; M.p. 48-49 °C, (Lit.[17] 52-54 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 2H), 4.25 – 4.18 (q, *J* = 14.1 Hz, 2H), 1.27 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 141.7, 134.1, 129.2, 127.9, 62.4, 14.2; IR (neat): ν_{max} 2129 (diazo), 1727 (C=O), 1371, 1286, 1072cm^{-1}

2-Diazo-1-(phenyl)ethanone 43o



Yield: 82 %; Colorless Liquid, (Lit.[31] 27-28 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.72 (m, 2H), 7.57 – 7.50 (m, 1H), 7.43 (dd, *J* = 6.8, 4.5 Hz, 2H), 5.93 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 136.6, 132.7, 128.7, 126.7, 54.2; IR (neat): ν_{max} 2106 (diazo), 1725, 1371, 1228, 1180 cm^{-1}.

2-Diazo-1-(2-thienyl)ethanone 43p



Yield: 80 %; M.p. 61-64 °C, (Lit.[32] 60 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.50 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.11 (dd, *J* = 4.9, 3.8 Hz, 1H), 5.81 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 142.5, 132.2, 129.0, 128.0, 54.3. IR (neat): ν_{max} 2108 (diazo), 1705, 1415, 1259, 1035 cm^{-1}.

3.2.5 References

[1] Ye, T.; McKervey, M. A., *Chemical Reviews*, **1994**, *94*, 1091.
[2] Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L., *Chemical Reviews*, **2009**, *110*, 704.
[3] Slattery, C. N.; Maguire, A. R., *Organic & Biomolecular Chemistry*, **2011**, *9*, 667.
[4] Taber, D. F.; Ruckle, R. E.; Hennessy, M. J., *Journal of Organic Chemistry*, **1986**, *51*, 4077.
[5] Curphey, T. J., *Organic Preparations and Procedures International*, **1981**, *13*, 112.
[6] Panchaud, P.; Renaud, P., *Advanced Synthesis & Catalysis*, **2004**, *346*, 925.
[7] Ye, H.; Liu, R.; Li, D.; Liu, Y.; Yuan, H.; Guo, W.; Zhou, L.; Cao, X.; Tian, H.; Shen, J.; Wang, P. G., *Organic Letters*, **2012**, *15*, 18.
[8] Cavender, C. J.; Shiner, V. J., *Journal of Organic Chemistry*, **1972**, *37*, 3567.
[9] Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W., *Synthetic Communications*, **1981**, *11*, 947.
[10] Kitamura, M.; Tashiro, N.; Miyagawa, S.; Okauchi, T., *Synthesis*, **2011**, 1037.
[11] Green, G. M.; Peet, N. P.; Metz, W. A., *Journal of Organic Chemistry*, **2001**, *66*, 2509.
[12] Goddard-Borger, E. D.; Stick, R. V., *Organic Letters*, **2011**, *13*, 2514.
[13] Goddard-Borger, E. D.; Stick, R. V., *Organic Letters*, **2007**, *9*, 3797.
[14] Fischer, N.; Goddard-Borger, E. D.; Greiner, R.; Klapötke, T. M.; Skelton, B. W.; Stierstorfer, J., *Journal of Organic Chemistry*, **2012**, *77*, 1760.
[15] Harned, A. M.; Sherrill, W. M.; Flynn, D. L.; Hanson, P. R., *Tetrahedron*, **2005**, *61*, 12093.
[16] Taber, D. F.; Sheth, R. B.; Joshi, P. V., *Journal of Organic Chemistry*, **2005**, *70*, 2851.
[17] Katritzky, A. R.; El Khatib, M.; Bol'shakov, O.; Khelashvili, L.; Steel, P. J., *Journal of Organic Chemistry*, **2010**, *75*, 6532.
[18] Chiara, J. L.; Suárez, J. R., *Advanced Synthesis & Catalysis*, **2011**, *353*, 575.
[19] Ramachary, D. B.; Narayana, V. V.; Ramakumar, K., *Tetrahedron Letters*, **2008**, *49*, 2704.
[20] Kumar, R.; Namboothiri, I. N. N., *Organic Letters*, **2011**, *13*, 4016.
[21] Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J., *Synthesis*, **2011**, 2549.
[22] Hendrickson, J. B.; Wolf, W. A., *Journal of Organic Chemistry*, **1968**, *33*, 3610.
[23] Kitamura, M.; Tashiro, N.; Miyagawa, S.; Okauchi, T., *Synthesis*, **2011**, 1037.
[24] Lombardo, L.; Mander, L. N., *Synthesis*, **1980**, 368.
[25] Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z., *Journal of Organic Chemistry*, **1990**, *55*, 1959.
[26] Rianelli, R. D. S.; de Souza, M. C. B. V.; Ferreira, V. F., *Synthetic Communications*, **2004**, *34*, 951.
[27] Brehm, W. J.; Levenson, T., *Journal of the American Chemical Society*, **1954**, *76*, 5389.
[28] Lu, C.-D.; Chen, Z.-Y.; Liu, H.; Hu, W.-H.; Mi, A.-Q.; Doyle, M. P., *Journal of Organic Chemistry*, **2004**, *69*, 4856.
[29] Kokel, B.; Viehe, H. G., *Angewandte Chemie International Edition*, **1980**, *19*, 716.
[30] Ferdinand, G.; Jeblick, W.; Schank, K., *Justus Liebigs Ann. Chem.*, **1976**, 1713.

[31] Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R., *Organic Letters*, **2010**, *13*, 320.
[32] Regitz, M.; Tawfik, A. M.; Heydt, H., *Synthesis*, **1979**, 805.

CHAPTER IV

Chapter IV: Synthesis of Ionic Liquid-Supported TBD and its Application as Recyclable Organocatalyst for Michael Addition Reaction

4.1 Introduction

Organocatalysis has emerged as new and powerful tools in organic synthesis.[1-4] Lower cost, operational simplicity, easy availability, efficiency and less toxicity make them attractive alternatives to organometallic catalysts in organic synthesis. Major problem associated with most homogeneous organocatalyst systems is high organocatalyst loadings to afford efficient synthesis, long and tedious preparation steps and separation and recycling of these catalysts. To overcome these difficulties, organocatalysts have been immobilized on various solid supports. For example, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [5-8] a versatile bicyclic guanidine, extremely useful catalyst for many organic transformations.[9-11] TBD (Figure 4.1) shows structure of some solid supported TBD.[12, 13] The solid-supported TBD has been utilized in several organic transformations to facilitate separation and recycling process. A brief account of some reactions using supported-TBD is given below.

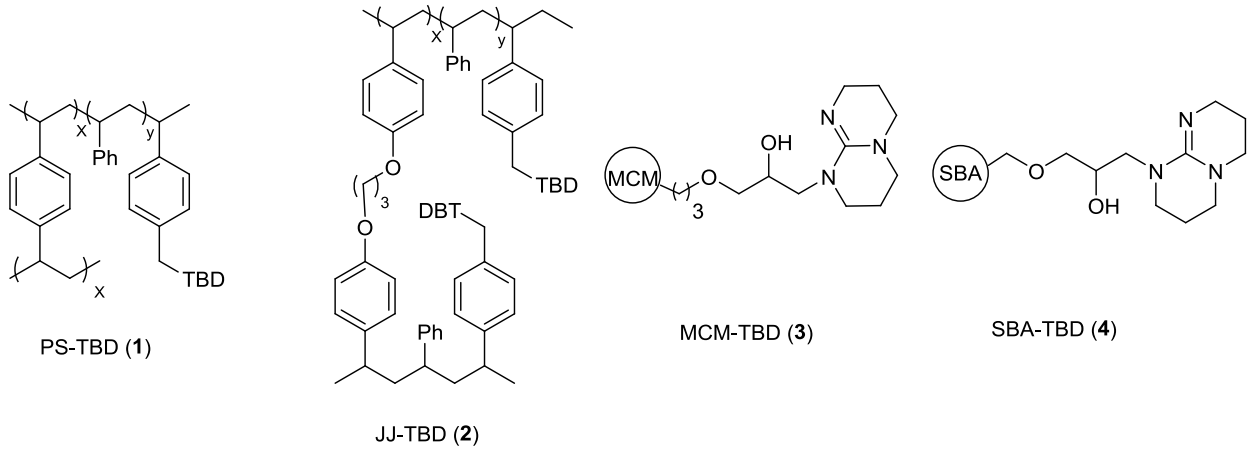
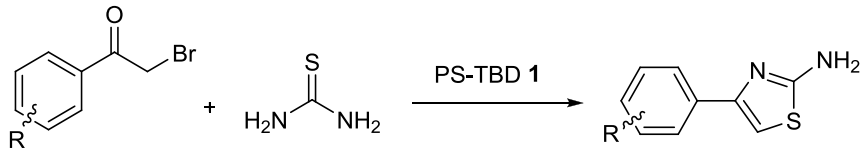


Figure 4.1 Structures of various supported-TBD **1-4**

Habermann and coworkers[12] employed polystrene-supported 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (PS-TBD, **1**) as a base in the synthesis of 2-aminothiazoles **7** (Scheme 4.1). The procedure is simple, straightforward and the desired products were isolated by simple filtration of PS-TBD.



5 **6** **7**

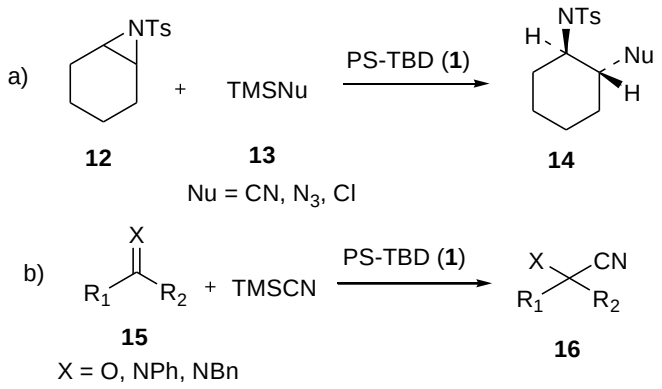
Scheme 4.1 Synthesis of 2-aminothiazoles catalyzed by PS-TBD

Xu *et al.* examined the reaction between substituted phenols **8** and alkyl halides **10** utilizing PS-TBD **1** as a base and acid scavenger.[13] Phenol is deprotonated by the PS-TBD to yield polymeric species $PSTBDH^{+}/ArO^{-}$ **9**. The phenoxide then underwent S_N2 reaction with various alkyl halides **9** to generate the aryl ether (ArOR, **11**). Moreover, by-product HBr was also quenched by PS-TBD (Scheme 4.2).

8 **1** **9** **11**

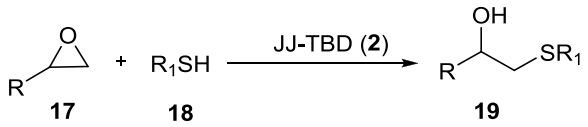
Scheme 4.2 Synthesis of aryl ethers using PS-TBD

PS-TBD has been used as a recoverable and recyclable base in the ring opening reactions of aziridines **12** with silylated nucleophiles **13**, including silyl cyanide, azide and halides (Scheme 4.3a).[14] PS-TBD was found to be better base among various supported-bases such as (Diisopropyl)aminomethyl polystyrene (PS-DIEA), diphenylphosphinopolystyrene (PS-TPP), (Methylpolystyrene)-4-(methylamino)pyridine (PS-DMAP) and PS-TBD) PS-TBD used for this reaction. The procedure was further extended to cyanosilylation of carbonyl and imine compounds **15** to give cyanohydrins or cyanoamines **16** in high yields (Scheme 4.3b).[15] PS-TBD was easily recovered and reused without significant loss in the catalytic activity.



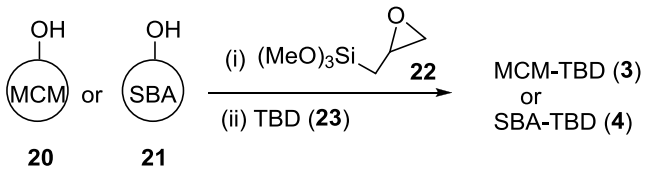
Scheme 4.3 a) PS-TBD catalyzed ring opening reactions of aziridines using silylated nucleophiles b) PS-TBD catalyzed cyanosilylation of carbonyl compounds using TMSCN

To minimize the swelling drawbacks of PS-TBD, recently Lanari *et al.*[16] proposed modifications in the back bone of the polymer support by introducing polytetrahydrofuran and synthesized Jandajel-supported-TBD (JJ-TBD, **2**). The polytetrahydrofuran linker allowed greater spacing between the linear polymeric chains and the reactants, driven to more access to the active sites without the help of a swelling medium. JJ-TBD has been employed as reusable and recyclable catalyst in thiolysis of epoxides **17** under solvent free conditions (Scheme 4.4). JJ-TBD **2** has shown superior catalytic activity compared to PS-TBD **1** under given conditions.



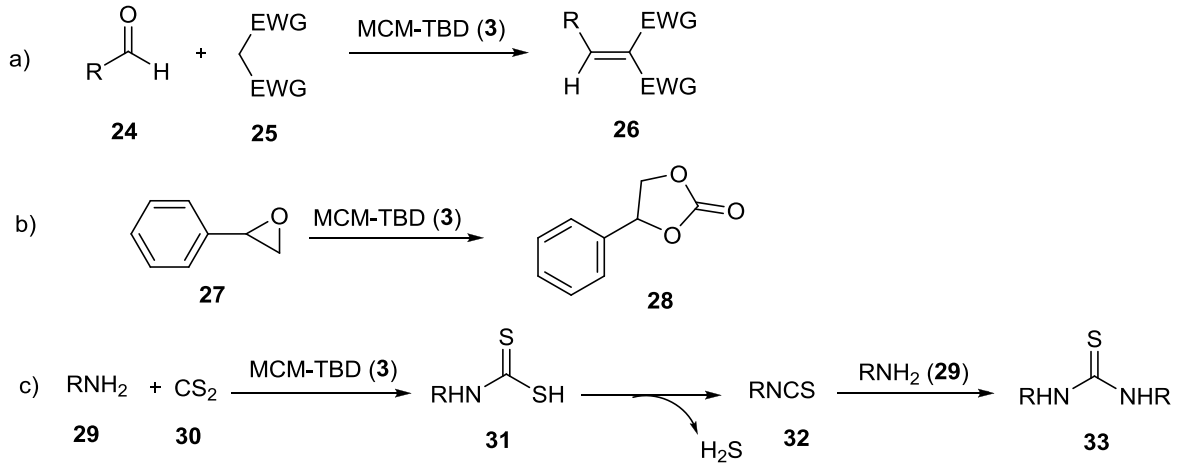
Scheme 4.4 Thiolysis of epoxides catalyzed by JJ-TBD

The surface of mesoporous silica materials are suitable for the grafting of different catalysts in order to obtain highly active and selective heterogeneous catalysts. Considering this fact, Jacobs and co-workers [17, 18] designed and synthesized mesoporous silica-supported MSM-TBD **3** from MSM-41 **20**, [(*3*-(trimethoxysilyl*)*propoxy)methyl]oxirane **22** and TBD **23** as shown scheme 4.5. Same synthetic procedure has been employed by Kaliaguine group to synthesize TBD functionalized SBA-16 **4** (Scheme 4.5).



Scheme 4.5 Synthetic scheme of MCM-TBD & SBA-TBD

MCM-TBD has been used as an efficient catalyst in Knoevenagel condensations (Scheme 4.6 a), selective preparation of carbamtes **28** (Scheme 4.6b) and synthesis of thioureas **33** (Scheme 4.6 c).[20] After completion of the reaction catalyst was recovered by simple filtration and further reused several times without much loss in the catalytic activity.



Scheme 4.6 a) MCM-TBD catalyzed Knoevenagel condensations b) MCM-TBD catalyzed carbmate synthesis c) MCM-TBD catalyzed thiourea synthesis

Although, the solid-supported TBD have efficiently promoted some fundamental base catalyzed organic transformation such as Nef reaction,[19] alkylation,[13] aldol-type condensation,[20] Knoevenagel condensation,[17] Michael addition,[17] synthesis of thioureas,[21] aryl ether synthesis,[22] synthesis of benzofuran,[23] thiazoles,[12] and transesterification of soybean oil,[18] these materials usually suffers from the disadvantage of requirement of compatible solvent for swelling and prolonged reaction times.

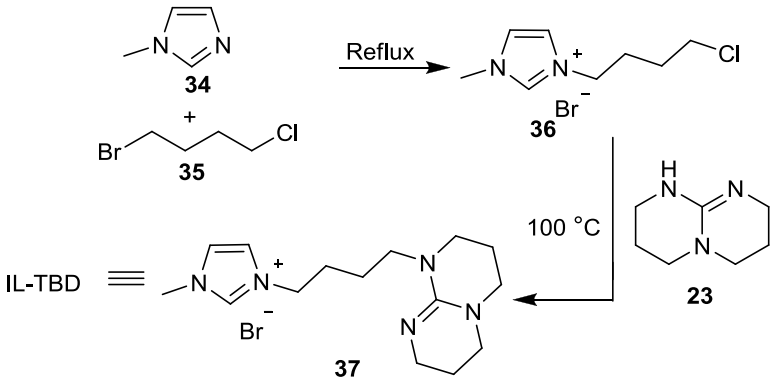
To overcome these problems, a new concept of ionic liquid-supported catalysis[24] in organic catalysis has emanated. This concept has been successfully employed for various catalytic and

separation techniques.[25] Unique properties of ionic liquids such as good solvating ability, low volatility[26] have overcome the main limitations of solid phase catalysis and retain advantages aspects of solution phase chemistry. Especially, basic ionic liquids (BIL) have aroused unprecedented interested because of having more advantages than normal inorganic bases for some base catalyzed process.[27, 28] Due to flexibility, non-volatility , noncorrosive nature and immiscibility with many organic solvents BILs exhibited great potential for the replacement of conventional basic catalysts.[29] Basic nature of BIL is due to anion or cationic part. BILs with anions such as hydroxide,[28, 30] lactate,[31, 32] formate,[33] acetate, dicyanamide[34] and carboxylate anions[35] have been developed and successfully applied in separation and a series of base-catalyzed processes, such as aldol reactions,[36] Knoevenagel reactions,[37] Michael additions,[38] Henry reaction[39] etc. Most of these BILs are thermally unstable. An alternative to the design of ionic liquids utilizing a basic anion is to incorporate a basic site into the cation part of ionic liquid. There are very few such ionic liquids in the literature. One of them is $[C_4dabco][BF_4]$.

With our interest in the development of task specific ionic liquids, we have synthesized a novel BIL, ionic liquid-supported TBD (IL-TBD), and explored its application as organocatalyst in the Michael addition of active methylene compounds and thiophenols to chalcones.

4.2 Results and Discussion

Synthesis of ionic liquid-supported TBD **37** was achieved following the reaction sequences shown in Scheme 4.7. Initially, the reaction of 1-methylimidazole **34** with 1-bromo-4-chlorobutane **35** at room temperature afforded (4'-chlorobutyl)-3-methylimidazolium bromide **36**. Subsequent reaction of **36** with 1.5 equivalents of TBD **23** at 100 °C for 6 h gave ionic liquid-supported TBD **37** with bromide as anion. The excess of TBD was removed by washing with dichloromethane and ionic liquid-supported TBD **37** was purified by column chromatography on silica gel.



Scheme 4.7 Synthesis of ionic liquid-supported TBD **37**

The structure of **37** was confirmed by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry. The ^{1}H NMR spectrum of **37** showed multiplets in the range of 3.24–3.04 representing the methylene protons of TBD adjacent to nitrogens (Figure 4.2). In the ^{13}C NMR, six carbons appeared in the aliphatic region, in addition to methyl and methylene carbons of ionic liquid which corresponds to the methylene carbon of TBD (Figure 4.2). In HRMS peaks appeared at 356.1260, 358.1257 and 276.1889 corresponding to $[M]^{+}$, $[M + 2]^{+}$, $[M – Br]^{+}$ respectively, that further confirmed the structure of **37**.

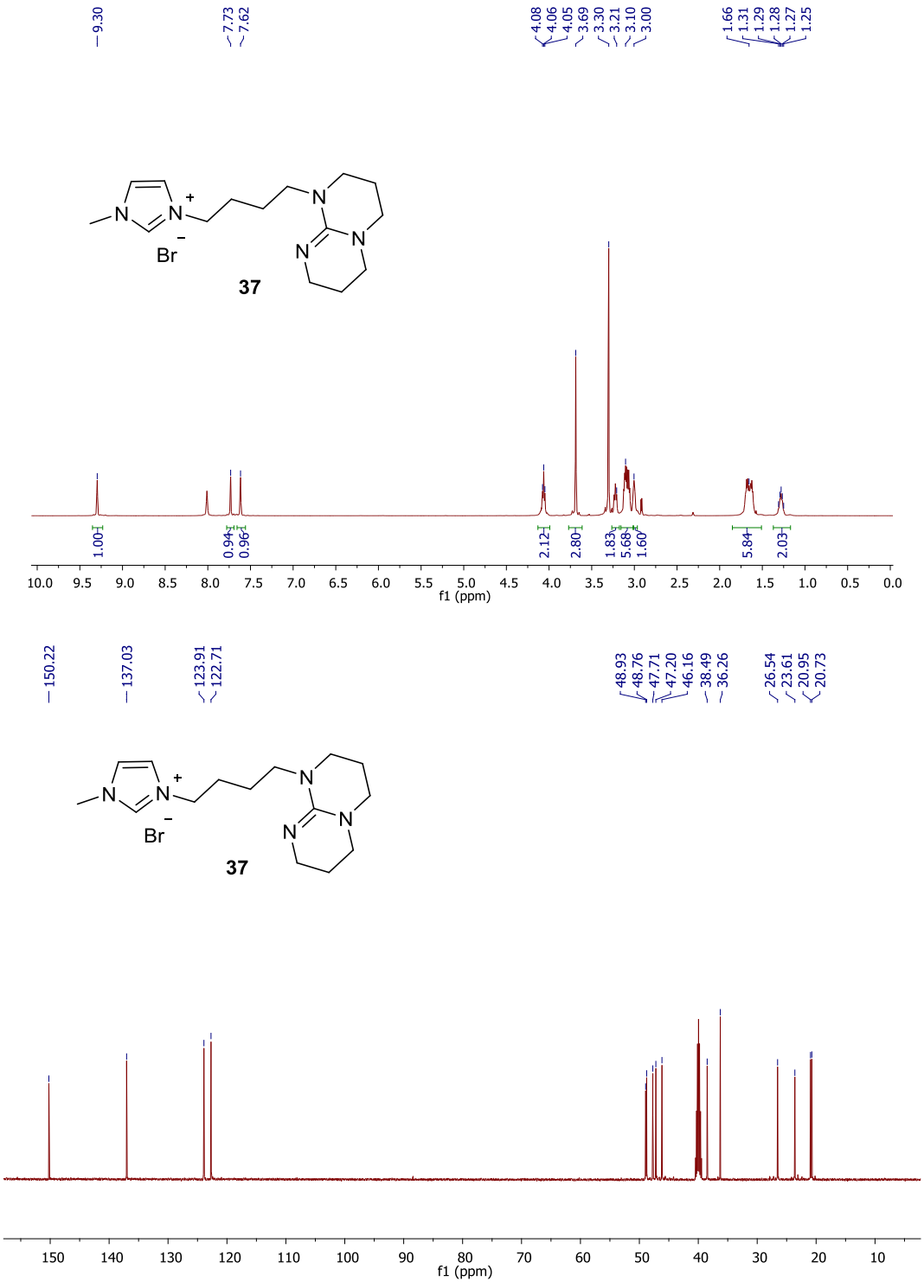
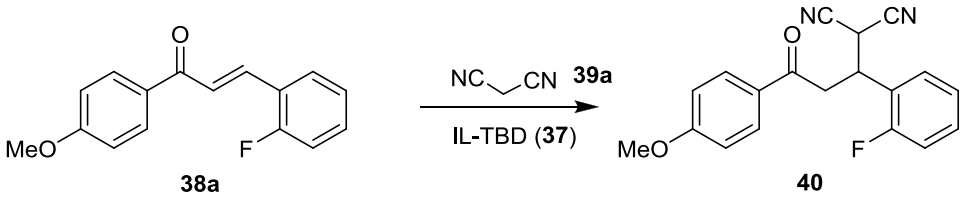


Figure 4.2 ^{1}H and ^{13}C NMR spectrum of ionic liquid-supported TBD **37**

The catalytic activity of ionic liquid-supported TBD as organocatalyst was evaluated for Michael addition of malononitrile to chalcones. The reaction conditions were optimized taking reaction of 3-(2-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one with malononitrile to give **40** (Table 4.1). Loading studies using different concentrations of catalyst showed the requirement of 50 mol% of ionic liquid-supported TBD to catalyze the reaction to maximum yields (Table 4.1, entries 1-4). The yield of Michael addition product was higher in solvent-free conditions (87%, Table 4.1, entry 3) as compared to reaction in different organic solvents (58-85%, Table 4.1, entries 5-9). The aqueous media served as a poor system for this reaction giving no product over the period under similar reaction conditions (Table 4.1, entry 11). This may be due to insolubility of both chalcone and the catalyst in water. The product yield was low (17-20%) when reaction was performed in ionic liquids ([bmim][Br], [bmim][BF_4] and [bmim][PF_6]) as solvent. The low yield in these ionic liquids may be probably due to slight acidic nature of ionic liquids and poor solubility of reactant at room temperature especially in [bmim][Br].

Table 4.1 Optimization of reaction condition for Michael addition

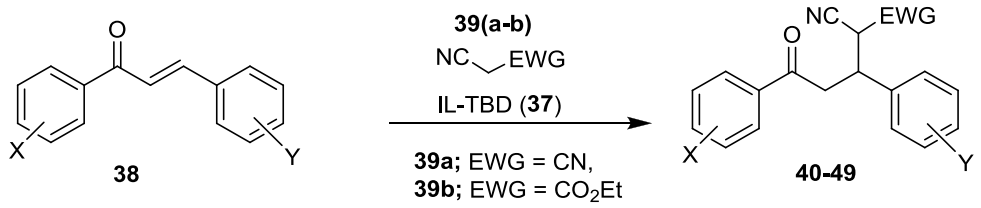


Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[a,b]
1	10	-	24	60
2	30	-	12	75
3	50	-	4	87
4	60	-	4	86
5	50	CH_3CN	4	85
6	50	CH_3OH	4	80
7	50	DMF	8	72
8	50	Ethanol	8	70
9	50	DCM	8	58
10	50	Toluene	36	70
11	50	H_2O	36	-[c]
12	50	[bmim][Br]	12	18
13	50	[bmim][PF_6]	12	17 (10)[d]
14	50	[bmim][BF_4]	12	20

[a]Reaction condition: Chalcone (1 mmol), malononitrile (1 mmol), catalyst **37** (10-50 mol%), room temperature. [b]Isolated yield. [c]No product formation was observed. [d]Yield without catalyst

Furthermore, the catalyst was evaluated for its general application in Michael addition reaction by performing the reaction with different chalcones **38** having electron-releasing and electron-

withdrawing groups in either side as Michael acceptors and malononitrile **39a** and ethyl cyanoacetate **39b** as Michael donors (Table 4.2). The presence of electron-withdrawing or electron-releasing groups on **38** had negligible effect on the yield of the product. Malononitrile was found to be better donor (Table 4.2, entries 1 and 8) compared to ethyl cyanoacetate (Table 4.2, entries 9 and 10). The structure of synthesized compound was confirmed by ^{1}H NMR and ^{13}C NMR (Experimental section). A representative ^{1}H NMR of Michael addition product is shown in figure 4.3.



Scheme 4.8 Michael addition of active methylene compounds to chalcones

Table 4.2: Michael addition of active methylene compounds to chalcones catalyzed by **37**

Product	X	Y	EWG	Time (h)	Yield (%)[a]
40	4-OCH_3	2-F	CN	4	87
41	4-Cl	2-F	CN	1.5	90
42	4-Cl	3-NO_2	CN	2	87
43	4-Cl	4-NO_2	CN	2	87
44	4-Cl	H	CN	2	92
45	4-OCH_3	4-NO_2	CN	4	86
46	4-OCH_3	4-OCH_3	CN	3	86
47	H	4-OCH_3	CN	3	85
48	4-OCH_3	2-F	CO_2Et	6	82
49	4-Cl	H	CO_2Et	3	87

[a]Isolated yield.

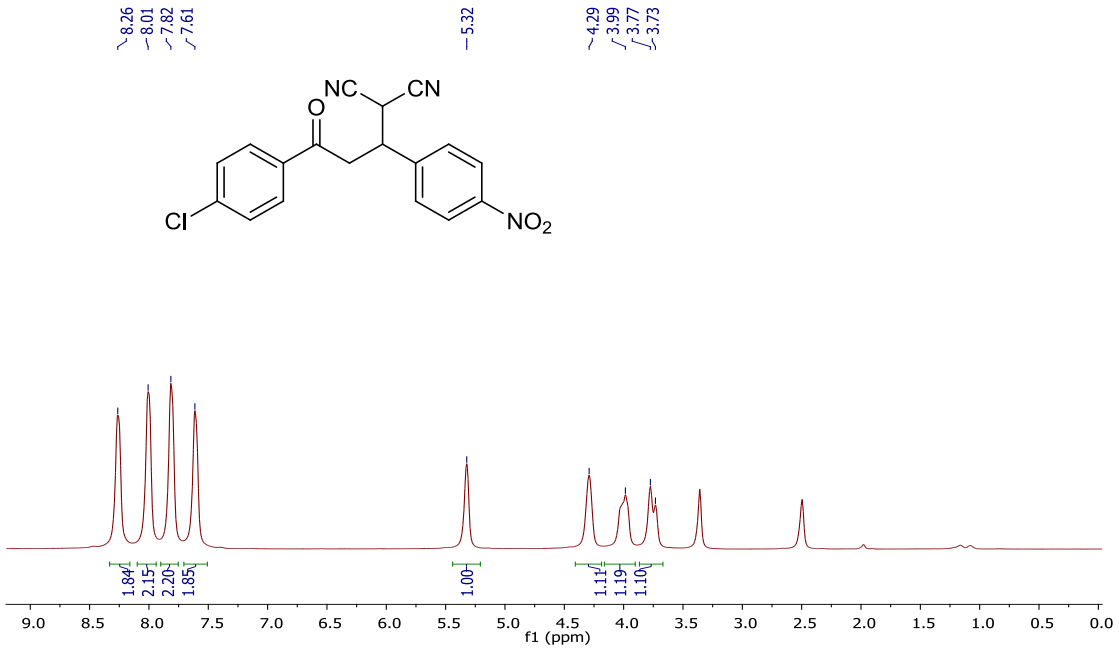
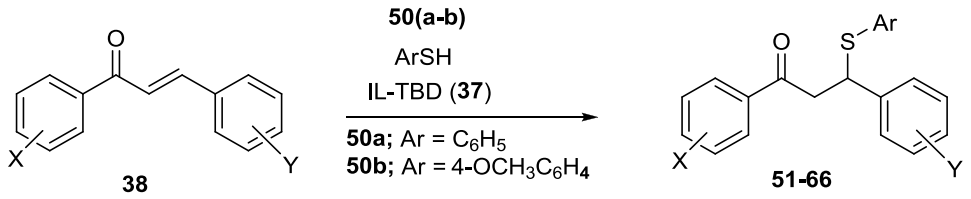


Figure 4.3 ^{1}H NMR spectrum of **43**

The catalytic scope of the ionic liquid-supported TBD was also assessed for the *thia*-Michael addition to chalcones (Scheme 4.9). As expected *thia*-Michael addition of thiophenols **50** to chalcones was extraordinarily fast in the presence of ionic liquid-supported TBD (10 mol %) and gave high yields in short reaction times (3-5 min) at room temperature (Table 4.3). Although the reaction also proceeded in [bmim][PF_6] alone to give **51** in 10% yield but the yield of product was more (87%) and it required shorter reaction time in the presence of the of ionic liquid-supported TBD under solvent-free condition. All the products were characterized by ^{1}H NMR and ^{13}C NMR data (Experimental section). Figure 4.4shows representative ^{1}H NMR for thia-Michael addition product **57**.



Scheme 4.9 Michael addition of thiophenols to chalcones

Table 4. 3 Michael addition of thiophenols **50** to chalcones **38** catalyzed by **37**

Product	X	Y	Ar	Time (min.)	Yield (%)[a]
51	4-OCH_3	2-F	C_6H_5	2	92
52	4-Cl	2-F	C_6H_5	2	93
53	H	4-Cl	C_6H_5	2	91
54	4-CH_3	H	C_6H_5	2	92
55	4-Cl	H	C_6H_5	4	92
56	4-OCH_3	3-NO_2	C_6H_5	5	90
57	4-OCH_3	4-NO_2	C_6H_5	5	92
58	4-CH_3	4-Cl	C_6H_5	3	92
59	4-Cl	4-OCH_3	C_6H_5	2	94
60	4-CH_3	4-OCH_3	C_6H_5	2	93
61	4-OCH_3	4-OCH_3	C_6H_5	2	92
62	4-NO_2	H	C_6H_5	5	90
63	4-OCH_3	H	C_6H_5	2	93
64	4-CH_3	3-NO_2	C_6H_5	5	92
65	H	3-NO_2	C_6H_5	5	91
66	4-Cl	H	4-$CH_3OC_6H_5$	4	90

[a]Isolated yield.

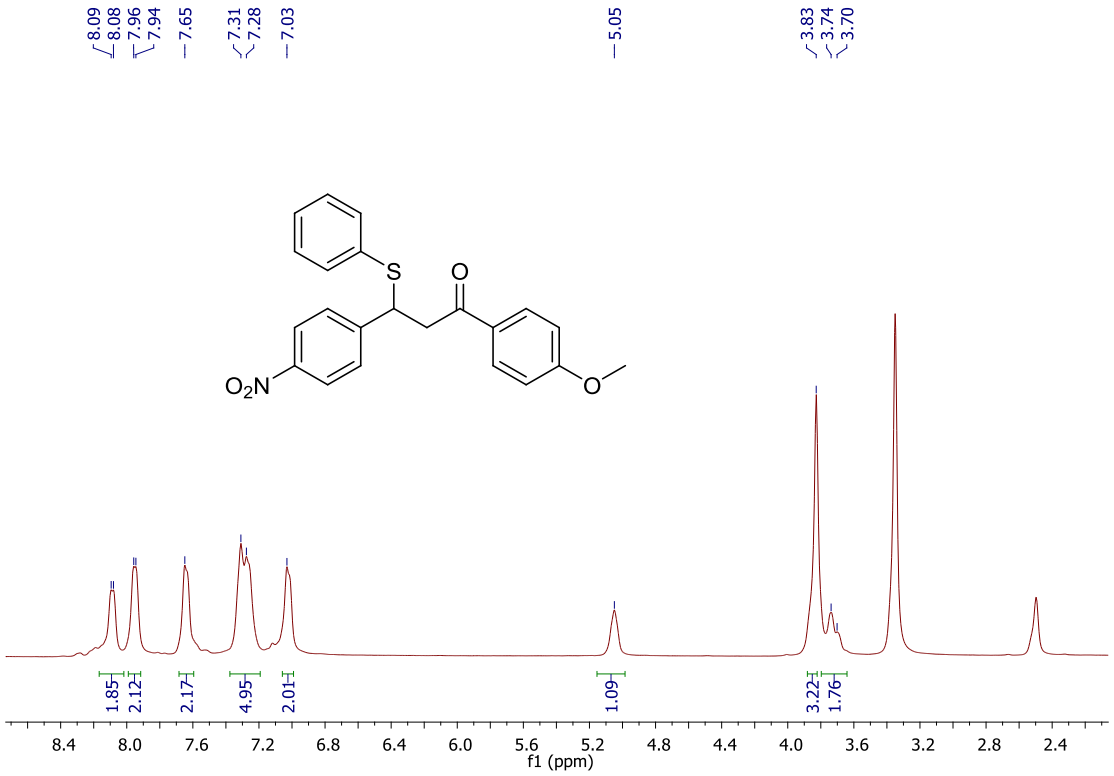
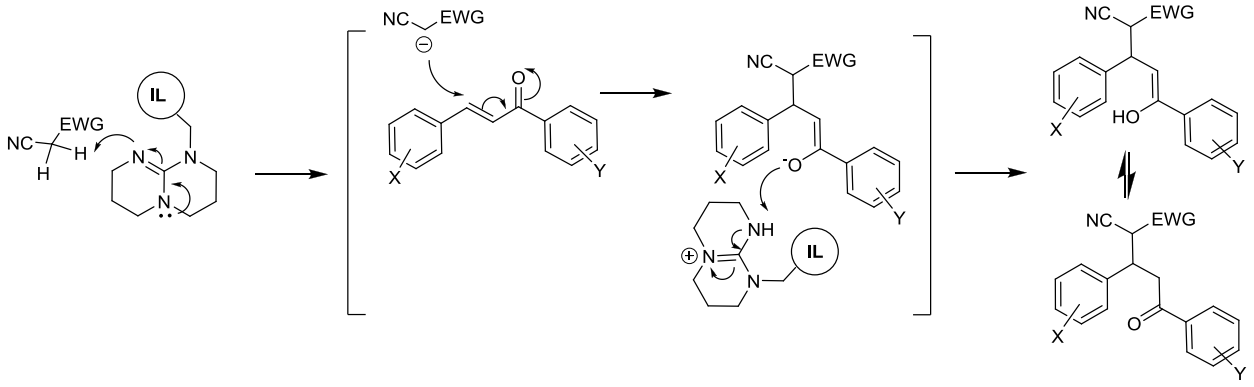


Figure 4.4 ^{1}H NMR spectrum of **57**

The reaction seems to proceed with general base catalyzed pathway. A plausible mechanism is proposed as shown in scheme 4.10.



Scheme 4.10 Plausible mechanism

Finally, the recyclability of the catalyst **37** was investigated in model reaction. Addition of malononitrile to chalcone; 3-(2-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one afforded **40**. After extracting **40** the recovered **37** was again used for model reaction and it was found that the catalyst **37** can be efficiently reused up to five cycles without much loss in the yield of **40** (Figure 4.5).

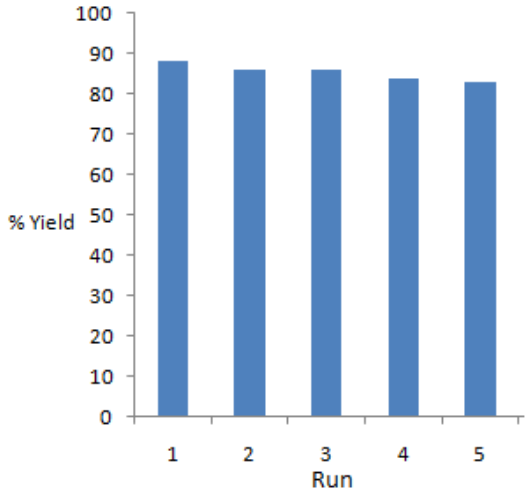


Figure 4.5 Recycling of ionic liquid-supported TBD for Michael addition

4.3 Conclusions

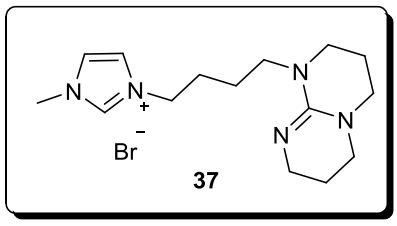
We have described the synthesis of a novel ionic liquid-supported TBD (IL-TBD) and its ability to act as organocatalyst in the Michael addition of active methylene compounds and thiophenols to chalcones under solvent-free conditions. The ionic liquid-supported-TBD afforded Michael addition products in excellent yield (82-94%) at room temperature, and it was easily recycled and reused at least five times without significant loss of catalytic activity. This is the first example of ionic liquid-supported TBD and its use in organic synthesis. The present study shows that high catalytic efficacy can be achieved by functionalizing ionic liquids with organocatalysts under greener reaction conditions.

4.4 Experimental

General: 1-Methylimidazole, 1-bromo-4-chlorobutane and TBD were purchased from Sigma-Aldrich. All other reagents and solvents were purchased from S. D. Fine, India and used without further purification unless otherwise specified. Column chromatography was carried out over xsilica gel (60–120 mesh, S. D. Fine, India). NMR spectra were recorded on a Bruker Heaven Avance 11 400 and Varian (500 MHz) spectrometers using $CDCl_3$ and DMSO-d_6 as solvents and the chemical shifts were expressed in ppm. Mass spectra were recorded on a QSTAR® ELITE LX/MS/MS mass spectrometer from Applied Biosystem. The purity of the products was determined on silica-coated aluminum plates (Merck).

Synthesis of 1-methyl-3-(4'-TBD-butyl)imidazolium bromide (IL-TBD) 37

1-Bromo-4-chlorobutane **35** (12 mmol) was added dropwise to 1-methylimidazole **34** (12 mmol) at room temperature and the reaction mixture was stirred for 4 h. The mixture turned viscous over the time. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3 × 10 mL) to remove unreacted starting materials. The trapped ethyl acetate was removed on rotatory evaporator under reduced pressure to obtain the product **36** in 89% yield. The ionic liquid **36** (10.7 mmol) was added to TBD **23** (17.7 mmol) and the mixture was heated at 100 ^{o}C for 6 h. After completion of reaction, the reaction mixture was cooled to room temperature and washed with DCM (5 × 15 mL) to remove unreacted TBD and TBD salt. The resulting ionic liquid was dried under reduced pressure to form thick light yellow liquid, which was purified by column chromatography on silica gel to give **37**.



37

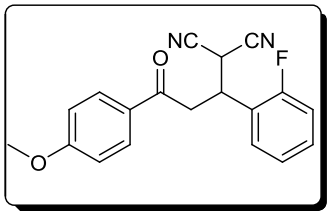
Yield: 92%. Viscous liquid, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.75 – 7.72 (m, 1H), 7.63 – 7.60 (m, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.69 (s, 3H), 3.24 – 3.19 (m, 2H), 3.13 – 3.04

(m, 6H), 3.00 – 2.93(m, 2H), 1.74 – 1.56 (m, 6H), 1.32 – 1.23 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.2, 137.0, 123.9, 122.7, 48.9, 48.7, 47.7, 47.2, 46.1, 38.5, 36.2, 26.5, 23.6, 20.9, 20.7; HRMS *m/z* calcd. for $C_{15}H_{26}N_5Br$ 356.14, found 356.1260 $[M]^+$, 358.1257 $[M + 2]^+$ and 276.1889 $[M – Br]^+$.

General procedure for Michael addition of active methylene compounds and thiophenols to chalcones

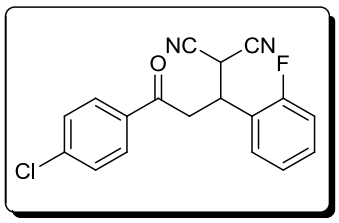
Malononitrile/ethyl 2-cynoacetate/thiophenol (1.0 mmol) was added to the solution of chalcone (1.0 mmol) and **37** (0.5 mmol/ 0.1 mmol in case of thiophenols). The reaction mixture was stirred vigorously until reaction completes (for time as mentioned in Tables 4.2 and 4.3). The progress of reaction was monitored by TLC. After completion of reaction, the product was extracted by ethyl acetate (2 × 5 mL) leaving ionic liquid-supported TBD catalyst in the flask. The ethyl acetate layer was evaporated and washed with diethyl ether to afford the pure product.

2-(1-(2-Fluorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)malononitrile 40



Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, *J* = 7.4 Hz, 2H), 7.68 – 6.68 (m, 6H), 5.32 (d, *J* = 6.3 Hz, 1H), 4.58 – 4.19 (m, 1H), 3.80 (s, 3H), 3.71 – 3.57 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.8, 164.0, 161.9, 159.5, 130.9, 129.3, 125.2, 116.2, 116.0, 114.4, 113.6, 113.4, 56.0, 40.0, 33.7, 28.9; HRMS: *m/z* calcd for $C_{19}H_{16}F\ N_2O_2$ 323.1118, found 323.1016 $[M + H\ ]^+$.

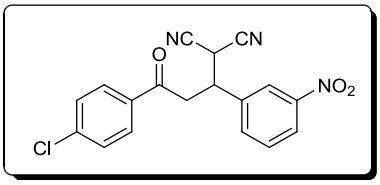
2-(3-(4-Chlorophenyl)-1-(2-fluorophenyl)-3-oxopropyl)malononitrile 41



Yield: 90%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, *J* = 7.28 Hz, 2H), 7.60 – 7.58 (m, 3H), 7.40 – 7.35 (m, 1H), 7.26 – 7.20 (m, 2H), 5.25 (d, *J* = 6.5 Hz, 1H), 4.36 – 4.32 (m, 1H), 3.90 (dd, *J* = 18.3, 8.65 Hz, 1H), 3.69 (dd, *J* = 18.3, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 195.7, 159.6,

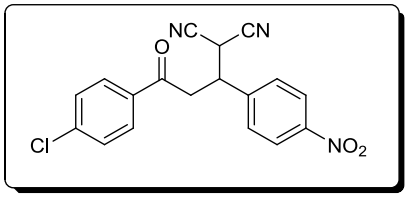
139.0, 135.0, 130.8, 130.7, 130.4, 129.3, 125.3, 116.2, 115.98, 113.5, 40.5, 33.6, 28.8; HRMS: *m/z* calcd for $C_{18}H_{13}ClFN_2O^+$ 327.0622, found 327.0006 $[M + H]^+$.

2-(3-(4-Chlorophenyl)-1-(3-nitrophenyl)-3-oxopropyl)malononitrile 42



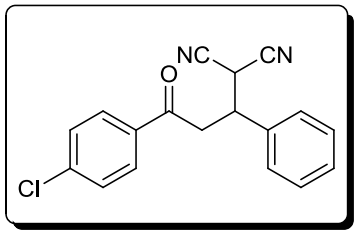
Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J* = 6.8 Hz, 2H), 7.65 – 7.61 (m, 3H), 7. 42 – 7. 38 (m, 1H), 7.26 (d, *J* = 6.68 Hz, 2H), 5.26 (d, *J* = 6.5 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.95 – 3.89 (m, 1H), 3.73 – 3.68 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.7, 139.1, 135.0, 130.8, 130.7, 130.5, 129.4, 125.3, 116.2, 116.0, 113.7, 113.4, 40.9, 33.5, 28.9; HRMS: *m/z* calcd for $C_{18}H_{11}ClN_3O_3Na$ 375.0455, found 375.0487 $[M –H + Na]^+$.

2-(3-(4-Chlorophenyl)-1-(4-nitrophenyl)-3-oxopropyl)malononitrile 43



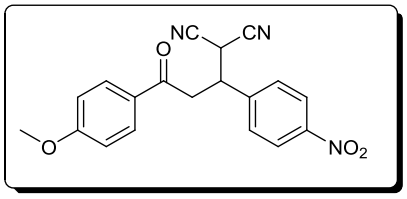
Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 7.27 Hz, 2H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 2H), 5.32 (d, *J* = 6.3 Hz, 1H), 4.32 – 4.26 (m, 1H), 4.06 – 3.96 (m, 1H), 3.81 – 3.69 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.7, 147.9, 145.9, 139.1, 135.0, 130.6, 130.4, 129.4, 124.2, 113.6, 40.5, 40.2, 29.3; HRMS: *m/z* calcd for $C_{18}H_{121}ClN_3O_3Na$ 375.0465, found 375.0484 $[M –H + Na]^+$.

2-(3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl)malononitrile 44



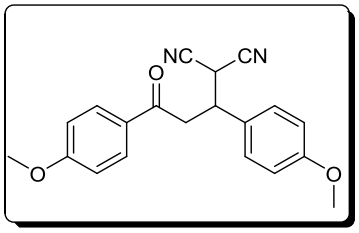
Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.98 (m, 2H), 7.64 – 7.54 (m, 3H), 7.53 – 7.41 (m, 2H), 7.39 – 7.35 (m, 2H), 5.25 – 5.20 (m, 1H), 4.07 – 4.03 (m, 1H), 3.88 – 3.84 (m, 1H), 3.68 – 3.64 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.0, 139.1, 138.2, 135.2, 130.5, 129.4, 129.1, 128.7, 113.9, 113.6, 40.7, 40.5, 29.8; HRMS: *m/z* calcd for $C_{18}H_{14}ClN_2O$ 309.0716, found 309.0701 $[M + H]^+$.

2-(3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-3-oxopropyl)malononitrile 45



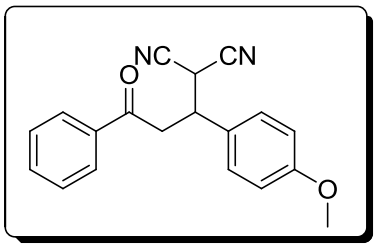
Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 7.12 Hz, 2H), 7.84 (d, J = 6.9 Hz, 2H), 7. 43 (d, J = 6.9 Hz, 2H), 6.89 (d, J = 7.1 Hz, 2H), 5.23 (d, J = 6.5 Hz, 1H), 4.43 – 4.36 (m, 1H), 4.01 – 3.96 (m, 1H), 3.83 – 3.72 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.8, 144.9, 144.0, 139.2, 135.7, 130.6, 130.2, 128.6, 114.6, 113.9, 55.5, 40.9, 41.3, 29.4; HRMS: *m/z* calcd for $C_{19}H_{14}N_3O_4Na$ 371. 0960, found 371.0978 $[M –H + Na]^+$.

2-(1,3-*Bis*(4-methoxyphenyl)-3-oxopropyl)malononitrile 46



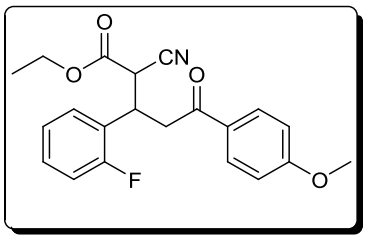
Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 – 7.96 (m, 2H), 7.45 – 7.37 (m, 2H), 7.04 – 7.02 (m, 2H), 7.01 – 6. 98 (m, 2H), 5.21 (d, J = 6.5 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.82 (s, 3H), 3.77 – 3.73 (m, 1H), 3.72 (s, 3H), 3.55 – 3.53 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.2, 163.9, 159.5, 130.9, 130.1, 129.9, 129.5, 114.4, 113.8, 56.0, 55.5, 40.3, 40.3, 30.0; HRMS: *m/z* calcd for $C_{20}H_{19}N_2O_3$ 335.1317, found 335.1187 $[M + H]^+$.

2-(1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl)malononitrile 47



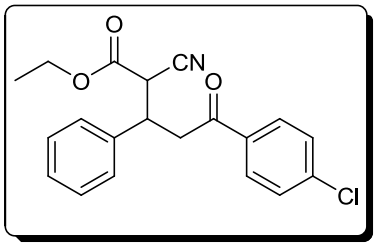
Yield: 85%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 7.3 Hz, 2H), 7.71 – 7.62 (m, 1H), 7. 60 – 7.49 (m, 2H), 7.45 – 7.36 (m, 2H), 7.03 – 6.89 (m, 2H), 5.24 – 5.05 (m, 1H), 4.06 – 3.98 (m, 1H), 3.82 – 3.78 (m, 1H), 3.73 (s, 3H), 3.63 – 3.57 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.9, 159.5, 136.5, 134.1, 130.1, 129.9, 128.6, 114.4, 114.1, 113.8, 55.5, 40.8, 40.6, 30.0; HRMS: *m/z* calcd for $C_{19}H_{15}N_2O_2K$ 343.0849, found 343.1114 $[M –H + K]^+$.

Ethyl 2-cyano-3-(2-fluorophenyl)-5-(4-methoxyphenyl)-5-oxopentanoate 48



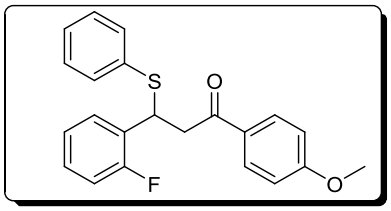
Yield: 82%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, *J* = 5.9, Hz, 2H), 7.62 – 7.58 (m, 2H), 7.53 – 7.45 (m, 1H), 7.35 – 7.30 (m, 1H), 7.18 (d, *J* = 6.6 Hz, 2H), 4.60 (d, *J* = 4.5 Hz, 1H), 4.37 – 4.28 (m, 1H), 4.11 – 4.04 (m, 2H), 3.88 – 3.57 (m, 2H), 1.01 (t, *J* = 6.7 Hz, 3H); 13C NMR (101 MHz, DMSO) δ 196.3, 165.8, 139.2, 135.5, 132.8, 130.5, 130.1, 129.5, 129.4, 125.2, 116.7, 115.9, 114.3, 62.80, 43.49, 43.16, 41.60, 32.61, 14.09; HRMS: *m/z* calcd for $C_{21}H_{21}FNO_4$ 370.1376, found 370.1288 $[M + H]^+$.

Ethyl 5-(4-chlorophenyl)-2-cyano-5-oxo-3-phenylpentanoate 49



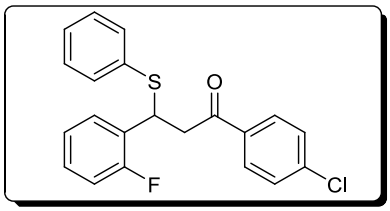
Yield: 87%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.35 – 7.26 (m, 5H), 4.69 – 4.46 (m, 1H), 4.08 – 3.97 (m, 3H), 3.72 – 3.65 (m, 2H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.2, 165.7, 138.9, 135.4, 130.5, 129.4, 128.9, 128.6, 128.4, 128.2, 114.4, 62.6, 44.1, 41.7, 40.9, 14.2; HRMS: *m/z* calcd for $C_{20}H_{19}ClNO_3$ 356.0975, found 356.0798 $[M + H]^+$.

3-(2-Fluorophenyl)-1-(4-methoxyphenyl)-3-(phenylthio)propan-1-one 51



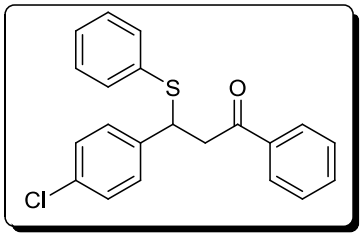
Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* = 6.87 Hz, 2H), 7.54 – 7.46 (m, 1H), 7.36 – 7.18 (m, 6H), 7.15 -7.05 (m, 2H), 7.01 (d, *J* = 6.85 Hz, 2H), 5.21 – 5.08 (m, 1H), 3.83 (s, 3H), 3.83 – 3.78 (m, 1H), 3.72 – 3.58 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.5, 163.8, 161.3, 158.9, 134.2, 132.4, 130.9, 129.7, 129.5, 129.5, 129.0, 128.9, 128.1, 124.9, 115.8, 56.0, 42.8, 41.0; HRMS: *m/z* calcd for $C_{22}H_{20}FO_2S$ 367.1090, found 367.1062 $[M + H]^+$.

1-(4-Chlorophenyl)-3-(2-fluorophenyl)-3-(phenylthio)propan-1-one 52



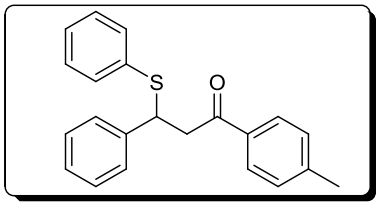
Yield: 93%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 – 8. 13 (m, 1H), 7.97 (d, *J* = 6.9 Hz, 2H), 7.57 – 7.09 (m, 10H), 5.18 – 4.98 (m, 1H), 3.90 – 3.81 (m, 1H), 3.79 – 3.72 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.3, 160.3, 138.9, 135.3, 133.9, 133.4, 132.5, 131.0, 130.5, 129.6, 128.8, 125.4, 124.9, 116.1, 115.6, 43.4, 40.8; HRMS: *m/z* calcd for $C_{21}H_{15}ClFOSNa$ 392.0492, found 392.0561 $[M - H + Na]^+$.

3-(4-Chlorophenyl)-1-phenyl-3-(phenylthio)propan-1-one 53



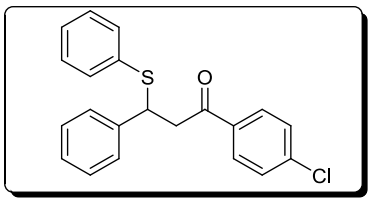
Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.3 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.46 (d, *J* = 7.5, 2H), 7.38 – 7.16 (m, 9H), 4.94 – 4.90 (m, 1H), 3.67 – 3.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 139.6, 136.3, 133.5, 133.2, 132.8, 129.0, 128.8, 128.5, 128.4, 127.8, 127.6, 115.8, 47.4, 44.3; HRMS: *m/z* calcd for $C_{21}H_{18}ClOS$ 353.0689 found, 353.0597 $[M + H]^+$.

3-Phenyl-3-(phenylthio)-1-p-tolylpropan-1-one 54



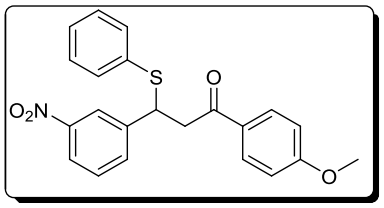
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4, 2H), 7.33 – 7.22 (m, 12H), 4.95 (t, *J* = 7.0 Hz, 1H), 3.63 – 3.50 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 132.5, 129.1, 128.6, 128.2, 128.0, 127.6, 127.3, 127.1, 48.0, 44.3, 21.5; HRMS: *m/z* calcd for $C_{22}H_{21}OS$ 333.1235, found 333.1187 $[M + H]^+$.

1-(4-Chlorophenyl)-3-phenyl-3-(phenylthio)propan-1-one 55



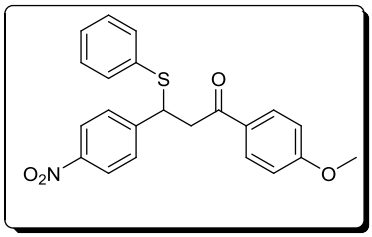
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.42 – 7.24 (m, 12H), 4.94 (t, *J* = 7.8 Hz, 1H), 3.66 – 3.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 140.8, 139.5, 134.8, 133.9, 132.6, 129.3, 128.7, 128.7, 128.3, 127.6, 127.4, 127.3, 48.0, 44.4; HRMS: *m/z* calcd for $C_{21}H_{18}ClOS$ 353.0689, found 353.0582 $[M + H]^+$.

1-(4-Methoxyphenyl)-3-(3-nitrophenyl)-3-(phenylthio)propan-1-one 56



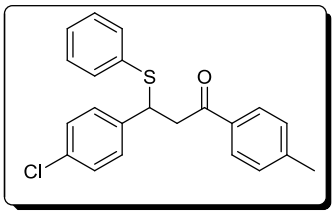
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.04 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 6.7 Hz, 1H), 7.48 – 7.35 (m, 1H), 7.31-7.23 (m, 5H), 6.93 (d, *J* = 7.5 Hz, 2H), 5.01 (t, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 3.63 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 163.7, 148.5, 143.6, 134.1, 133.2, 132.6, 130.2, 129.1, 129.0, 128.9, 128.0, 122.4, 122.1, 115.6, 55.3, 47.6, 43.5; HRMS: [*m/z* calcd for $C_{22}H_{20}NO_4S$ 394.1035, found 394.0985 $M + H]^+$.

1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-3-(phenylthio)propan-1-one 57



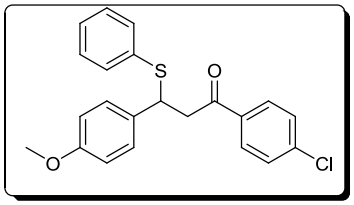
Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, *J* = 5.6 Hz, 2H), 7.95 (d, *J* = 5.2 Hz, 2H), 7.64 (d, *J* = 5.1 Hz, 2H), 7.31 – 7. 19 (m 5H), 7.03 (d, *J* = 5.37 Hz, 2H), 5.07 – 4.98 (m, 1H), 3.83 (s, 3H), 3.73 – 3.68 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 163.8, 150.2, 148.6, 146.8, 133.7, 132.3, 131.0, 129.6, 128.1, 124.3, 123.8, 114.4, 47.4, 42.5; HRMS: *m/z* calcd for $C_{22}H_{20}NO_4S$ 394.1035, found 394.0989 $[M + H]^+$.

3-(4-Chlorophenyl)-3-(phenylthio)-1-p-tolylpropan-1-one 58



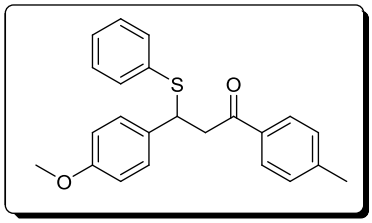
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.42 – 7.14 (m, 11H), 4.91 (dd, *J* = 6.1, 7.8 Hz, 1H), 3.69 – 3.46 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 144.1, 139.7, 133.9, 133.5, 132.7, 130.0, 129.2, 129.0, 128.7, 128.3, 128.0, 127.6, 47.5, 44.1, 21.5; HRMS: *m/z* calcd for $C_{22}H_{20}ClOS$ 367.0845, found 367.0782 $[M + H]^+$.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-3-(phenylthio)propan-1-one 59



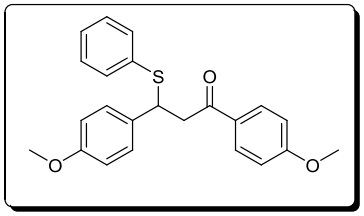
Yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.17 (m, 9H), 6.79 (d, *J* = 8.1 Hz, 2H), 4.98 – 4.82 (m, 1H), 3.76 (s, 3H), 3.63 – 3.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 158.6, 139.5, 136.3, 133.9, 132.5, 130.6, 129.3, 128.7, 128.7, 128.6, 127.3, 113.6, 55.0, 47.4, 44.6; HRMS: *m/z* calcd for $C_{22}H_{19}ClO_2S$ 382.0794, found 383.0703 $[M + H]^+$.

3-(4-Methoxyphenyl)-3-(phenylthio)-1-p-tolylpropan-1-one 60



Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.22 (m, 9H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.94 (dd, *J* = 5.6, 8.4 Hz, 1H), 3.76 (s, 3H), 3.65 – 3.49 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 158.5, 143.9, 136.1, 134.1, 132.9, 132.4, 129.1, 128.7, 128.6, 128.0, 127.2, 113.6, 55.0, 47.4, 44.4, 21.5; HRMS: *m/z* calcd for $C_{23}H_{23}O_2S$ 363.1341, found 363.1274 $[M + H]^+$.

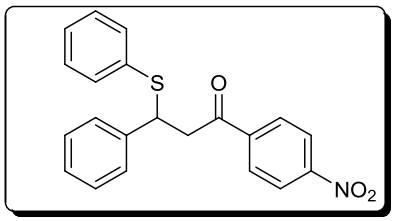
1,3-Bis(4-methoxyphenyl)-3-(phenylthio)propan-1-one 61



Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.13 (m, 7H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 6.4 Hz, 2H), 4.94 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.63 – 3.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 176.4, 163.4, 158.5,

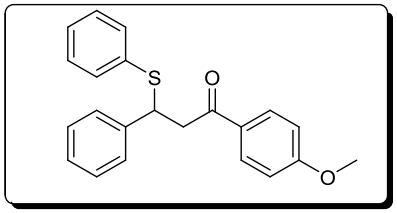
133.0, 132.4, 130.2, 130.0, 128.7, 127.2, 123.2, 113.6, 113.5, 55.3, 55.0, 47.5, 44.2; HRMS: *m/z* calcd for $C_{23}H_{23}O_3S$ 379.129, found 379.1405 $[M + H]^+$.

3-(4-methoxyphenyl)-1-(4-Nitrophenyl)-3-phenyl-3-(phenylthio)propan-1-one 62



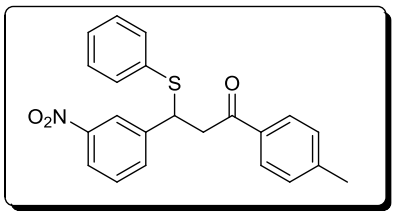
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.80, 2H), 8.00 (d, *J* = 8.74 Hz, 2H), 7.37 – 7.17 (m, 10H), 4.90 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.70 – 3.57 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 141.2, 139.4, 135.0, 134.0, 132.6, 129.6, 128.8, 128.6, 128.5, 127.1, 127.4, 127.3, 48.1, 44.4; HRMS: *m/z* calcd for $C_{21}H_{16}NO_3SNa$ 385.0827, found 385.0879 $[M –H + Na]^+$.

1-(4-Methoxyphenyl)-3-phenyl-3-(phenylthio)propan-1-one 63



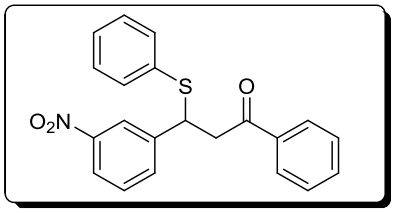
Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.79 (m, 2H), 7.34 – 7.24 (m, 10H), 6.98 – 6.84 (m, 2H), 4.97 (m, 1H), 3.85 (s, 3H), 3.61 – 3.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 163.4, 141.1, 136.2, 132.5, 130.2, 129.6, 128.6, 128.2, 127.6, 127.3, 127.1, 113.5, 55.3, 48.1, 44.0; HRMS: *m/z* calcd for $C_{22}H_{21}O_2S$ 349.1184, found 349.1079 $[M + H]^+$.

3-(3-Nitrophenyl)-3-(phenylthio)-1-p-tolylpropan-1-one 64



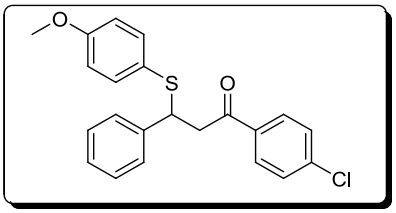
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.04 (d, *J* = 6.1 Hz, 1H), 7.90 – 7.74 (m, 2H), 7.62 (d, *J* = 6.3 Hz, 1H), 7.42 –7.35 (m, 1H), 7.32-7.25 (m, 7H), 5.09 – 4.90 (m, 1H), 3.67 – 3.56 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 148.0, 144.4, 143.6, 134.1, 133.6, 132.6, 129.2, 129.0, 128.9, 128.0, 122.4, 122.1, 47.6, 43.7, 21.5; HRMS: *m/z* calcd for $C_{22}H_{20}NO_3S$ 378.1086, found 378.1023 $[M + H]^+$.

3-(3-Nitrophenyl)-1-phenyl-3-(phenylthio)propan-1-one 65



Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.05 (d, *J* = 7.1 Hz, 1H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.71 – 7.54 (m, 2H), 7.54 – 7.36 (m, 3H), 7.36 – 7.17 (m, 5H), 5.01 (t, *J* = 6.7 Hz, 1H), 3.69 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 148.7, 143.5, 136.0, 134.1, 133.5, 133.1, 131.2, 129.0, 128.9, 128.6, 128.1, 127.9, 122.4, 122.1, 47.1, 43.9; HRMS: *m/z* calcd for $C_{21}H_{18}NO_3S$ 364.0929, found 364.00875$[M + H]^+$.

3-(4-Methoxyphenylthio)-1-(4-chlorophenyl)-3-phenylpropan-1-one 66



Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H,), 7.29 – 7.17 (m, 7H), 6.74 (d, *J* = 8.7 Hz, 2H), 4.70 (m, 1H), 3.75 (s, 3H), 3.53 – 3.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 159.9, 141.2, 139.7, 136.3, 135.1, 129.5, 128.9, 128.4, 127.8, 124.1, 123.5, 114.4, 55.3, 49.4, 44.3; HRMS: *m/z* calcd for $C_{22}H_{18}ClO_2SNa$ 404.0692, found 404.0703 $[M –H + Na]^+$.

General procedure for recycling the catalyst

Malononitrile (1.0 mmol) was added to the solution of chalcone; (3-(2-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one)) and ionic liquid-supported TBD (**37**) (0.5 mmol). The reaction mixture was stirred vigorously until reaction completes. After completion of reaction, the product was extracted from catalyst by ethyl acetate (2 × 5 mL) leaving ionic liquid-supported TBD catalyst in the flask. Ionic liquid-supported TBD was washed with diethyl ether and dried under reduced pressure. The recovered ionic liquid was again used as a catalyst for fresh batch of chalcone and malononitrile (1.0 mmol) under same experimental conditions. The process was repeated five times without much loss in catalytic activity

4.5 References

[1] Dalko, P. I.; Moisan, L., *Angewandte Chemie International Edition*, **2004**, *43*, 5138.
[2] Lee, J.-E.; Yun, J., *Angewandte Chemie International Edition*, **2008**, *47*, 2.
[3] Yu, X.; Wang, W., *Chemistry – An Asian Journal*, **2008**, *3*, 516.
[4] List, B., *Chemical Reviews*, **2007**, *107*, 5413.
[5] Coles, M. P., *Chemical Communications*, **2009**, 3659.
[6] Selig, P.; Turočkin, A.; Raven, W., *Synlett*, **2013**, 2535.
[7] Cota, I.; Medina, F.; Sueiras, J. E.; Tichit, D., *Tetrahedron Letters*, **2011**, *52*, 385.
[8] Bensa, D.; Rodriguez, J., *Synthetic Communications*, **2004**, *34*, 1515.
[9] Ye, W.; Xu, J.; Tan, C.-T.; Tan, C.-H., *Tetrahedron Letters*, **2005**, *46*, 6875.
[10] Schroeder, G.; Leska, B.; Jarczewski, A.; Nowak-Wydra, B.; Brzezinski, B., *Journal of Molecular Structure*, **1995**, *344*, 77.
[11] Iijima, K.; Fukuda, W.; Tomoi, M., *Journal of Macromolecular Science, Part A*, **1992**, *29*, 249.
[12] Habermann, J.; Ley, S. V.; Scicinski, J. J.; Scott, J. S.; Smits, R.; Thomas, A. W., *Journal of the Chemical Society, Perkin Transactions 1*, **1999**, 2425.
[13] Xu, W.; Mohan, R.; Morrissey, M. M., *Tetrahedron Letters*, **1997**, *38*, 7337.
[14] Matsukawa, S.; Harada, T.; Yasuda, S., *Organic & Biomolecular Chemistry*, **2012**, *10*, 4886.
[15] Matsukawa, S.; Fujikawa, S., *Tetrahedron Letters*, **2012**, *53*, 1075.
[16] Lanari, D.; Ballini, R.; Bonollo, S.; Palmieri, A.; Pizzo, F.; Vaccaro, L., *Green Chemistry*, **2011**, *13*, 3181.
[17] Rao, Y. V. S.; De Vos, D. E.; Jacobs, P. A., *Angewandte Chemie International Edition*, **1997**, *36*, 2661.
[18] Nguyen, P.-T.; Nohair, B.; Mighri, N.; Kaliaguine, S., *Microporous and Mesoporous Materials*, **2013**, *180*, 293.
[19] Ballini, R.; Fiorini, D.; Maggi, R.; Oro, C.; Palmieri, A.; Sartori, G., *Synlett*, **2006**, 1849.
[20] Fringuelli, F.; Pizzo, F.; Vittoriani, C.; Vaccaro, L., *Chemical Communications*, **2004**, 2756.
[21] Ballini, R.; Bosica, G.; Fiorini, D.; Maggi, R.; Righi, P.; Sartori, G.; Sartorio, R., *Tetrahedron Letters*, **2002**, *43*, 8445.
[22] Lizarzaburu, M. E.; Shuttleworth, S. J., *Tetrahedron Letters*, **2003**, *44*, 4873.
[23] Habermann, J.; Ley, S. V.; Smits, R., *Journal of the Chemical Society, Perkin Transactions 1*, **1999**, 2421.
[24] Miao, W.; Chan, T. H., *Accounts of Chemical Research*, **2006**, *39*, 897.
[25] S. Lee, *Chemical Communications*, **2006**, 1049.
[26] Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S., *Tetrahedron*, **2005**, *61*, 1015.
[27] Formentín, P.; García, H.; Leyva, A., *Journal of Molecular Catalysis A: Chemical*, **2004**, *214*, 137.
[28] Chen, H.; Justes, D. R.; Cooks, R. G., *Organic Letters*, **2005**, *7*, 3949.

[29] Yavari, I.; Kowsari, E., *Tetrahedron Letters*, **2007**, *48*, 3753.
[30] Ranu, B. C.; Banerjee, S., *Organic Letters*, **2005**, *7*, 3049.
[31] Pernak, J.; Goc, I.; Mirska, I., *Green Chemistry*, **2004**, *6*, 323.
[32] Earle. J.; M.; McCormac, P. B.; Seddon, K. R., *Green Chemistry*, **1999**, *1*, 23.
[33] Bicak, N., *Journal of Molecular Liquids*, **2005**, *116*, 15.
[34] MacFarlane, D. R.; Forsyth, S. A.; Golding, J.; Deacon, G. B., *Green Chemistry*, **2002**, *4*, 444.
[35] MacFarlane, D. R.; Pringle, J. M.; Johansson, K. M.; Forsyth, S. A.; Forsyth, M., *Chemical Communications*, **2006**, 1905.
[36] Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P., *Tetrahedron*, **2007**, *63*, 1923.
[37] Cai, Y.; Peng, Y.; Song G. H., *Catalysis Letters*, **2006**, *109*, 61.
[38] Xu, J.-M.; Qian, C.; Liu, B.-K.; Wu, Q.; Lin, X.-F., *Tetrahedron*, **2007**, *63*, 986.
[39] Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G., *Tetrahedron Letters*, **2004**, *45*, 2699.

CHAPTER V

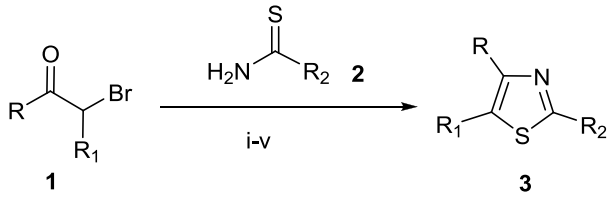
One Pot Synthesis of 2,4-Disubstituted Thiazoles and Oxazoles Using PTT in Ionic Liquid

5.1 Introduction

Thiazoles and oxazoles are common structural motifs found in both natural products and pharmaceuticals with broad spectrum of biological activities.[1-3] Compounds containing these motifs display anti-fungal,[4] anti-bacterial,[4, 5] anti-HIV,[6] anti-inflammatory,[7, 8] anti-tubercular,[9, 10] histone deacetylase inhibition[11] and are ligands for estrogen-receptors (ER).[12] Occurrence of these motifs in natural products and their diverse biological activities has inspired significant interest in their synthesis.[2, 13]

Selected literature reports on the synthesis of oxazoles and thiazoles

The well known method for synthesis of thiazoles **3** skeleton is Hantzsch's method, which involves condensation of α-haloketones **1** with thioamide/thiourea **2**. Several methods were reported in the literature for the synthesis of 2,4-disubstituted thiazoles using ammonium-12-molybdophosphate,[14] β-cyclodextrin in water,[15] microwave irradiation,[16, 17] and in green solvents like [bmim][BF_4],[18] water[19] without any catalyst (Scheme 5.1).

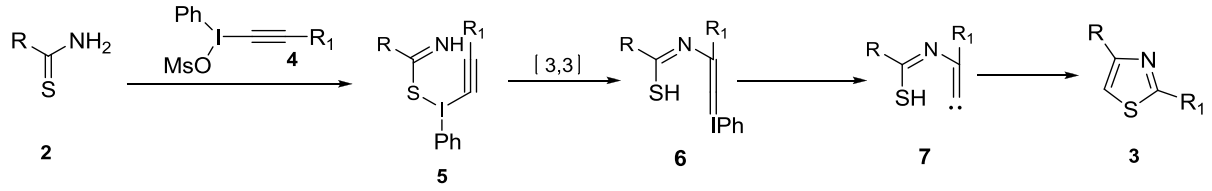


(i) Ammonium-12-molybdophosphate [AMP], MeOH, rt
(ii) -Cyclodextrin, H_2O, 50 °C
(iii) EtOH, MW
(iv) [bmim][BF_4], rt
(v) H_2O, rt

Scheme 5.1 Synthesis of thiazoles **3** from α-haloketones **1**

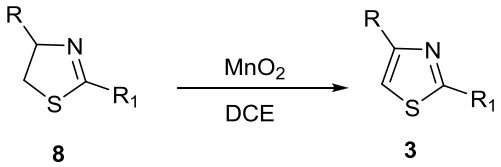
Wipf and Venkatraman developed hypervalent iodine mediated synthesis of thiazoles **3**.[20] Cyclocondensation of thioamides **2** with alkynyl(Aryl)Iodonium reagents **4** resulted in regioselective thiazole synthesis in moderate to good yields. The reaction expected to proceed *via* thiophilic attack of the iodonium atom on **2**, followed by polyhetero-Claisen rearrangement

and 1,1-elimination of iodobenzene resulted in carbene intermediate **7**. The carbene further cyclized to form desired five-membered thiazoles **3** in good yields (Scheme 5.2).



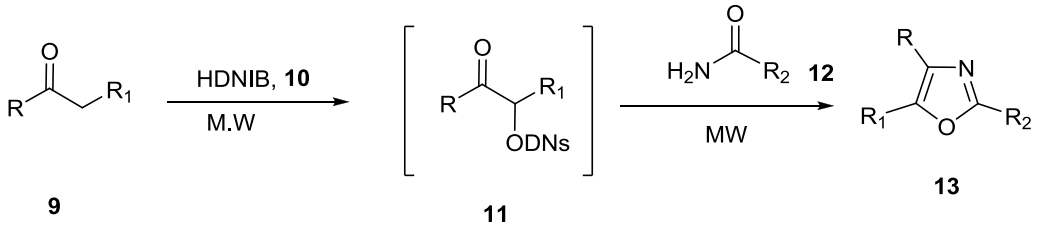
Scheme 5.2 Synthesis of thiazoles **3** from alkynyl(aryl)Iodonium reagents **4**

Fu *et al.*[21] have demonstrated the synthesis of thiazoles **3** from the corresponding thiazolines **8** through manganese dioxide (MnO_2) oxidation (Scheme 5.3). Various aryl substitutes bearing different electron-donating and electron-withdrawing groups at the 2- and 4-position of thiazolines **8** were well tolerated to give corresponding thiazoles in excellent yields.



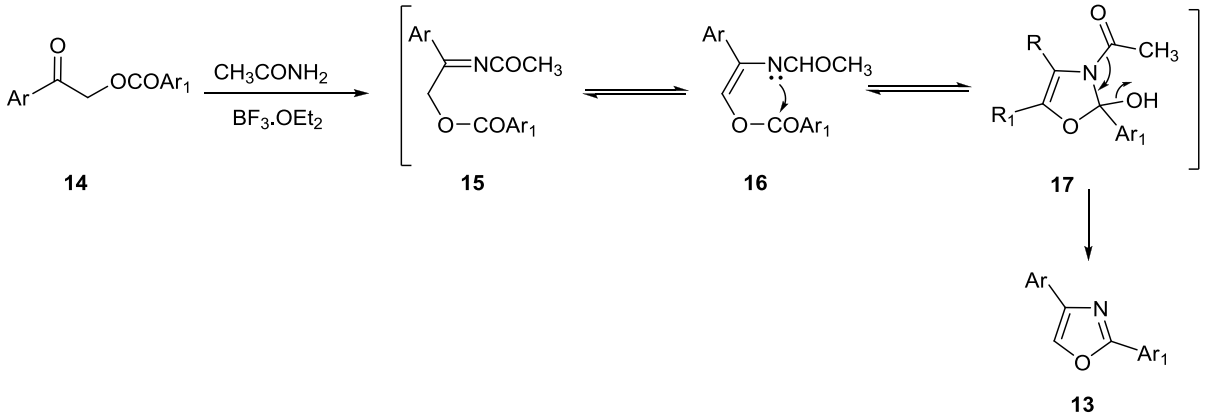
Scheme 5.3 Synthesis of thiazoles **3** from thiazolines **8**

Lee *et al.*[22] have described a rapid and highly efficient method for the synthesis of multi-substituted oxazoles **13** starting from carbonyl compounds **9** under solvent-free microwave irradiation reaction conditions. The reaction of methyl ketones **9** with [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB, **10**) under microwave irradiation provided α–[(2,4-dinitrobenzene)sulfonyl]oxy ketone **11**, which upon reaction with acetamide or benzamide **12** resulted to oxazoles **13** under microwave irradiation for short period of time (1-2 min).



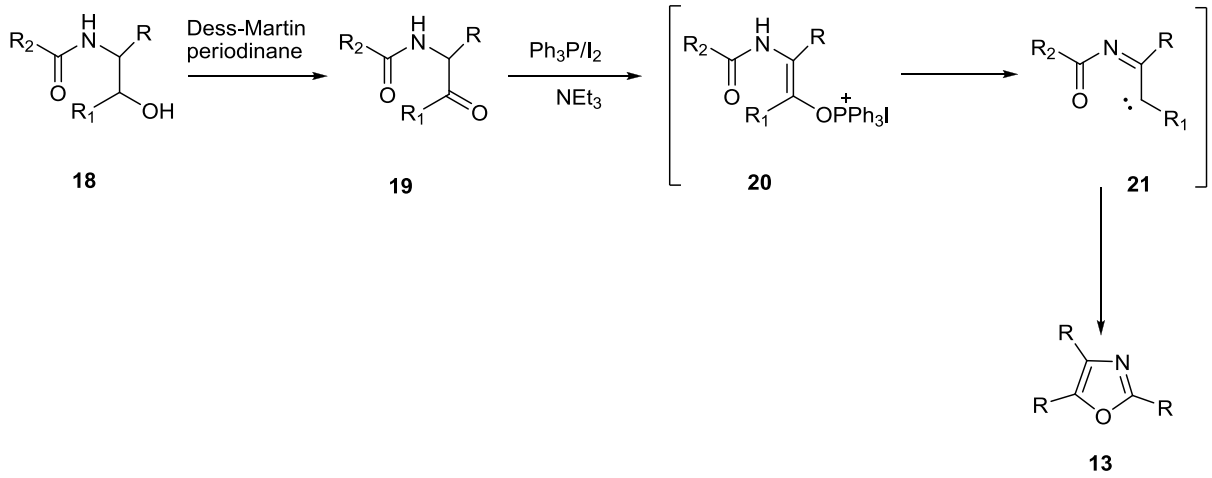
Scheme 5.4 Synthesis of oxazoles**13** from carbonyl compounds using HDNIB **10**

Huang and his co-workers developed a novel procedure for the synthesis of 2,4-diaryl substituted oxazoles **13**. The reaction of phenacyl benzoates **14** with acetamide in presence $BF_3.OEt_2$ produced intermediate **16**, which upon cyclization followed by deacylation gave oxazoles **13** in good to moderate yields (Scheme 5.5).



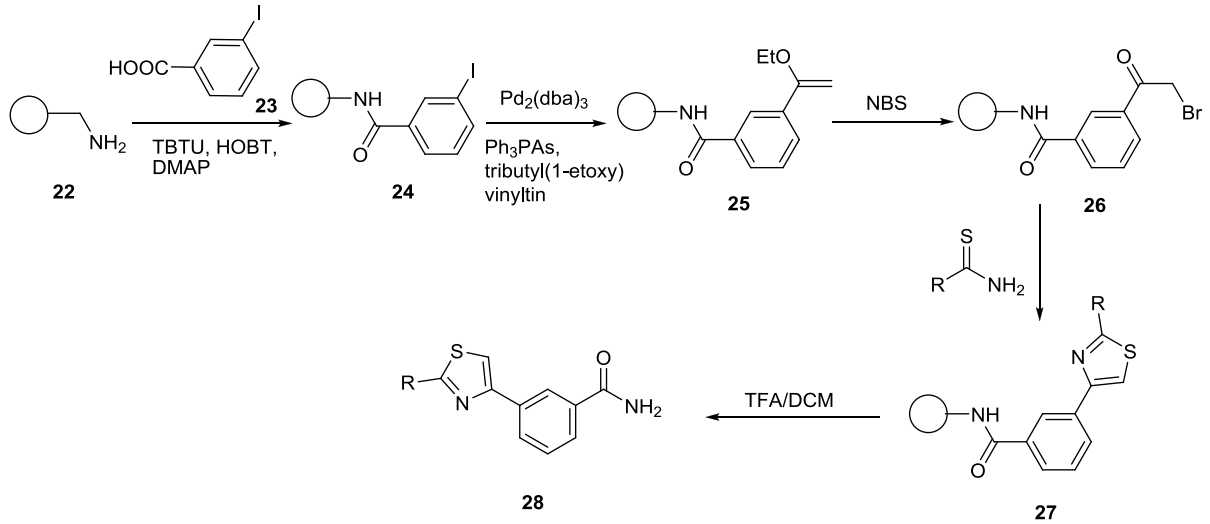
Scheme 5.5 Synthesis of 2,4-diaryl substituted oxazoles from phenacyl benzoates **13**

Wipf and Venkatraman[20] reported a multi step synthesis of oxazoles **13** from β-hydroxy amide **18**. Oxidation of the β-hydroxy amide with Dess-Martin periodinane gave ketone **19**, which upon further exposure to triphenylphosphine/iodine resulted carbene intermediate **21**. Ring closure of the carbene intermediate **21** yielded desired oxazoles **13** in excellent yields (Scheme 5.6).



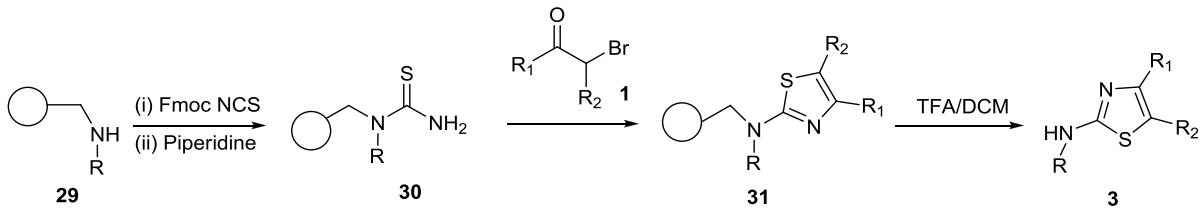
Scheme 5.6 Synthesis of oxazoles from β-hydroxy amide **18**

Owing to the biological importance of the aza-heterocycles derivatives, Raboin and Flygare groups independently developed solid-phase approaches to synthesize diverse library of thiazoles. Raboin *et al.*[23] synthesized α-bromoketone bound acid labile linker on solid-support as shown in the scheme 5.7. Initially, 3-iodobenzoic acid **23** was loaded on Rink amide resin **22**, which upon cross coupling reaction with tributyl(1-ethoxyvinyl)tin, followed by bromination using NBS gave an α-bromoketone bound to a solid support **26**. Condensation of **26** with substituted thioureas, followed by TFA cleavage gave 2,4-disubstituted thiazoles **28** in excellent yields.



Scheme 5.7 Synthesis of 2,4-disubstitued thiazoles on resin **22**

On the other hand, Flygare *et al.*[24] developed a different approach where, thiourea was grafted on acid labile linker **29** and Hantzsch thiazole synthesis was carried out with various α-bromoketones **1** (Scheme 5.8). A large number of diverse thiazoles were synthesized in good to excellent yields using this methodology.



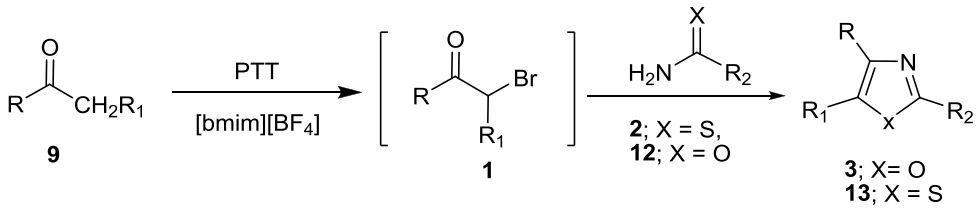
Scheme 5.8 Thiazole synthesis on thiourea grafted solid support **30**

However, many of these methods suffer from one or more drawbacks that include use of reactive or unsafe starting materials such as α-haloketones, use of expensive and corrosive catalysts, use of volatile organic solvents, tedious reaction work-up, long reaction times, low yields, harsh reaction conditions and multistep synthesis. Furthermore, most of these procedure are for the synthesis of thiazoles or oxazole, there have been far fewer methods that describe the synthesis of both thiazoles oxazoles starting directly from ketones.

Due to the wide biological importance of thiazoles and oxazoles and the problems associated in their synthesis impelled us to develop a simple, economical and environmentally friendly one-pot procedure of 2,4-substituted thiazoles and oxazoles from substituted ketones in [bmim][BF_4]. In this one-pot procedure PTT has been used as *in situ* brominating agent.

5.2 Results and Discussion

Initially we tried reaction of *p*-chloroacetophenone and thiourea in the presence of NBS or Br_2 to yield 4-(4'-chlorophenyl)thiazol-2-amine **3b**. The yield of **3b** was very low (< 20%) with both NBS and Br_2. With our earlier experience with phenyltrimethylammoniumtribromide (PTT) as *in situ* brominating agent in ionic liquid,[25] we replaced NBS or Br_2 with PTT in the above reaction and to our delight the yield of **3b** increased to 90%. The added advantage with PTT is that it does not require any acidic conditions or radical initiator like NBS and handling of PTT is very easy as compared to other brominating agents. With PTT *in-situ* bromination of *p*-chloroacetophenone was completed within 2 hours. After bromination, the condensation of *in situ* generated α-bromo-*p*-chloroacetophenone with thiourea was carried out in the same reaction media to give 4-(4'-chlorophenyl)thiazol-2-amine **3b**.



Scheme 5.9 Synthesis of thiazoles **3** and oxazoles **13**

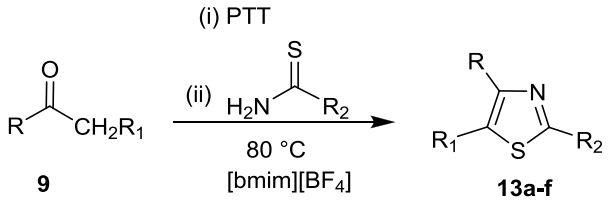
To understand the role of solvent the model reaction was carried out in different solvents such as [bmim][BF_4], [bmim][PF_6], methanol, THF, DMF, DCM, toluene and water. In DMF and toluene no appreciable yield of product was obtained whereas in other organic solvents such as DCM, THF and methanol the yield of **3b** was between 65-80% (Table 5.1). Among two ionic liquids screened, [bmim][BF_4] was found to give the best yield (90%) of **3b** (Table 5. 1). The results are in agreement with previous report on the synthesis of thiazoles from α-bromoketones in ionic liquid where [bmim][BF_4] was found to be better medium over [bmim][PF_6] and other ionic liquids.[18] The ionic liquid [bmim][BF_4] was selected as solvent of choice keeping in view

of its non volatile and environmentally benign nature. The role of ionic liquid to enhance the rate of reaction may be in terms of some Lewis/ Brønsted acidity of the imidazolium cation leading to increased electropositive character of carbonyl group of *in situ* generated α-bromoketone as proposed earlier.[18, 26] The [bmim][BF_4] also enhances the rate of *in-situ* bromination of ketones by PTT as reported earlier.[25]

Table 5.1 Solvent effect on the yield of 4-(4'-chlorophenyl)thiazol-2-amine **3b**

Sr. No.	Solvent	Time (h)	Yield (%)[a]
1	[bmim][BF_4]	4	90
2	[bmim][PF_6]	6	65
3	DCM	4	82
4	Methanol	6	70
5	THF	6	75
6	DMF	24	< 10
7	Toluene	24	-[b]
8	Water	24	-[b]

[a]Isolated yields.
[b]No product observed on TLC.



Scheme 5.10 Outline for synthesis of thiazoles **3**

Table 5.2 Synthesis of 2,4-disubstituted thiazoles in [bmim][BF_4]

R	R_1	R_2	Compound	Time (h)	Yield (%)[a]	Mp °C (Lit. Mp)
Ph	H	NH_2	**3a**	4	92	148-150 (150)[15]
4-ClPh	H	NH_2	**3b**	4	90	163-165 (163-164)[16]
3-NO_2Ph	H	NH_2	**3c**	4	86	187-189 (188-190)[15]
4-OCH_3Ph	H	NH_2	**3d**	4	87	204-207 (204-205)[15]
1-Naphthyl	H	NH_2	**3e**	4	80	157-158
2-Naphthyl	H	NH_2	**3f**	4	80	152-154 (152-153)[15]
4-CH_3Ph	H	NH_2	**3g**	4	85	130 (125-126)[16]
6-OH, 2-BrPh	H	NH_2	**3h**	4	85	209-212
2-Thiazolyl	H	NH_2	**3i**	4	87	186-189
-$CH_2(CH_2)_2CH_2$-		NH_2	**3j**	4	83	87-90 (88-90)[21]
-$CH_2(CH_2)_3CH_2$-		NH_2	**3k**	4	81	63-66
4-ClPh	H	CH_3	**3l**	5	81	112-115 (111-112)[16]
2-Naphthyl	H	CH_3	**3m**	5	78	88-89
3-NO_2Ph	H	CH_3	**3n**	5	80	87-89
4-ClPh	H	Ph	**3o**	6	75	130-132

[a]Isolated yield.

After obtaining optimum reaction conditions, to study the scope of the reaction different substituted ketones **9** and thioamides/thiourea **2** were allowed to react to give corresponding thiazoles **3a-o**. The results for these thiazoles are summarized in table 5.2. The yields of the thiazoles are excellent (75-92 %) and the synthetic strategy allows synthesis of diverse thiazoles. As per the yields of thiazoles (Table 5.2) it can be observed that acetophenones containing both electron withdrawing and electron releasing substituents were tolerated as good substrate for this reaction under these conditions.

The structures of thiazoles were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS data. Figure 5.1 represents ^{1}H and ^{13}C NMR of 2-amino-4-(*p*-tolyl)thiazole. In ^{1}HNMR characteristic peak at δ 6.89 appeared for C_5–proton of the thiazole ring and in ^{13}C NMR characteristic peak appeared at δ 168.5 and δ 101.0 ppm for C_2-carbon and C_4–carbon of the thiazole ring, respectively. The IR spectrum showed two peaks at 3446 and 3216 cm^{-1} corresponding to the NH_2 group.

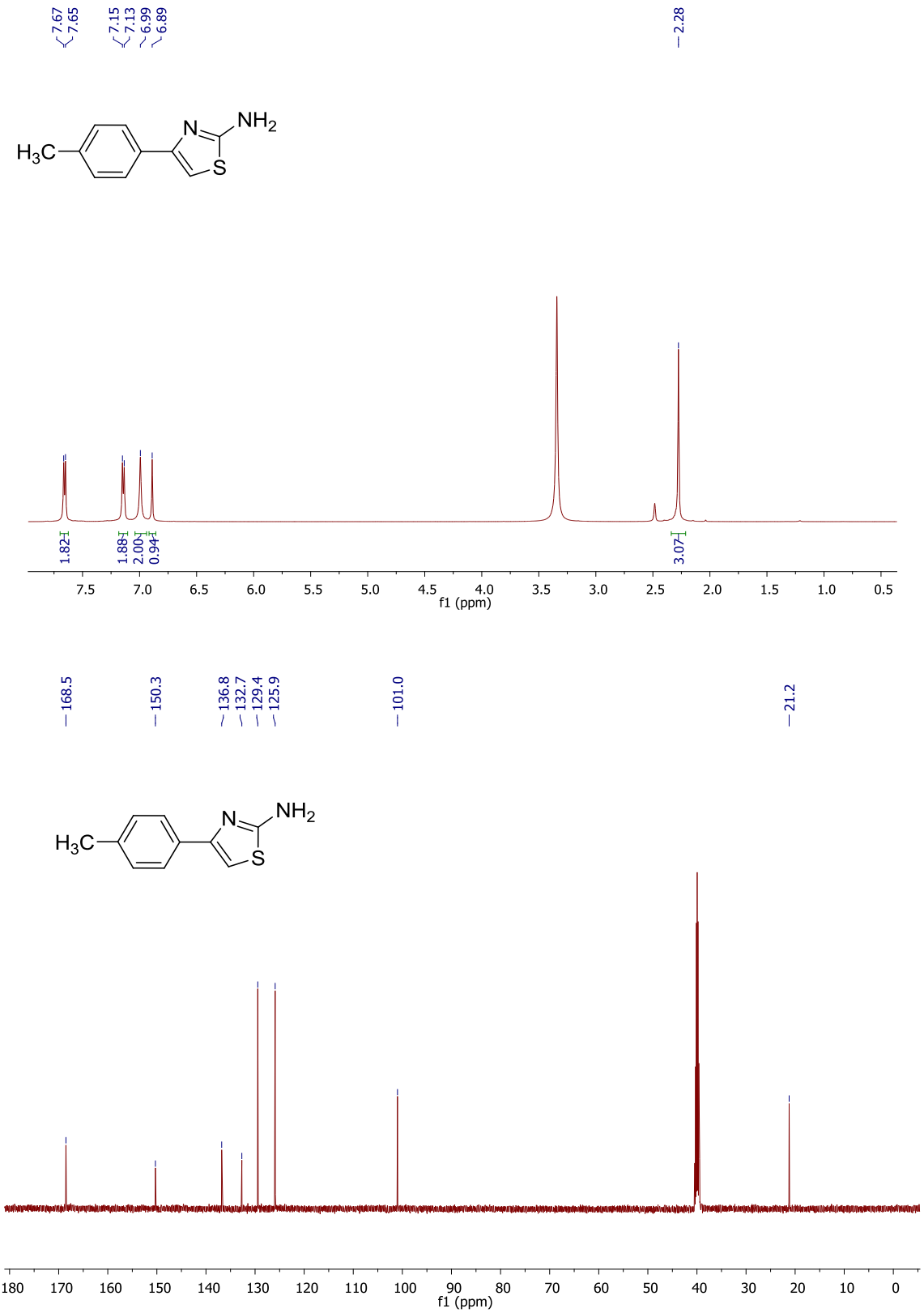


Figure 5.1 ^{1}H and ^{13}C NMR spectra of 2-amino-4-*p*-tolylthiazole **3g**

To explore the generality and increase the utility of the protocol we extended it for the synthesis of 2,4-disubstituted oxazoles **13a-f** from ketones. Initially we failed to achieve the desired 2-methyl-4-phenyloxazole **13a** from the reaction of acetophenone and acetamide using PTT in [bmim][BF_4] at room temperature. After exploring different reaction conditions the best yield of **13a** was obtained when the reaction mixture was heated at 80°C in [bmim][BF_4]. The lower reactivity at room temperature can be attributed to the lower nucleophilicity of oxygen in acetamide as compared to sulfur in thioamides. After obtaining the optimum reaction conditions, the scope of protocol was examined for the synthesis of diversified oxazoles by the reaction of different substituted ketones and amides/ureas in the presence of PTT in [bmim][BF_4]. The results for different oxazoles are summarized in table 5.3. It was observed that yields were lower for oxazoles (68-75%) and reaction required longer time and high temperature as compared to thiazoles. Like thiazoles, in the synthesis of oxazole as well acetophenones containing both electron withdrawing and electron releasing substituents were tolerated as good substrate for this reaction under these conditions.

Table 5.3. Synthesis of 2,4-disubstituted oxazoles in [bmim][BF_4]

Entry	R	R_1	R_2	Product	Time (h)	Yield (%)[a]
1	Ph	H	NH_2	**13a**	8	76
2	3-NO_2Ph	H	NH_2	**13b**	8	75
3	4-CH_3OPh	H	NH_2	**13c**	8	74
4	3-NO_2Ph	H	CH_3	**13d**	9	70
5	2-Naphthyl	H	CH_3	**13e**	10	68
6	Ph	H	CH_3	**13f**	10	71

[a]Isolated yield.

The structures of oxazole **13a-f** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS data. Figure 5.2 represents ^{1}H NMR and ^{13}C NMR of **13a**. A characteristic peak for C_3-proton of oxazole ring was observed at δ 7.85 ppm whereas a peak appeared at δ 6.70 for amine protons in ^{1}H NMR spectrum. Two peaks appeared at δ 162.0 and δ 125.1 ppm for C_2-carbon and C_4-carbon, respectively in ^{13}C NMR spectrum.

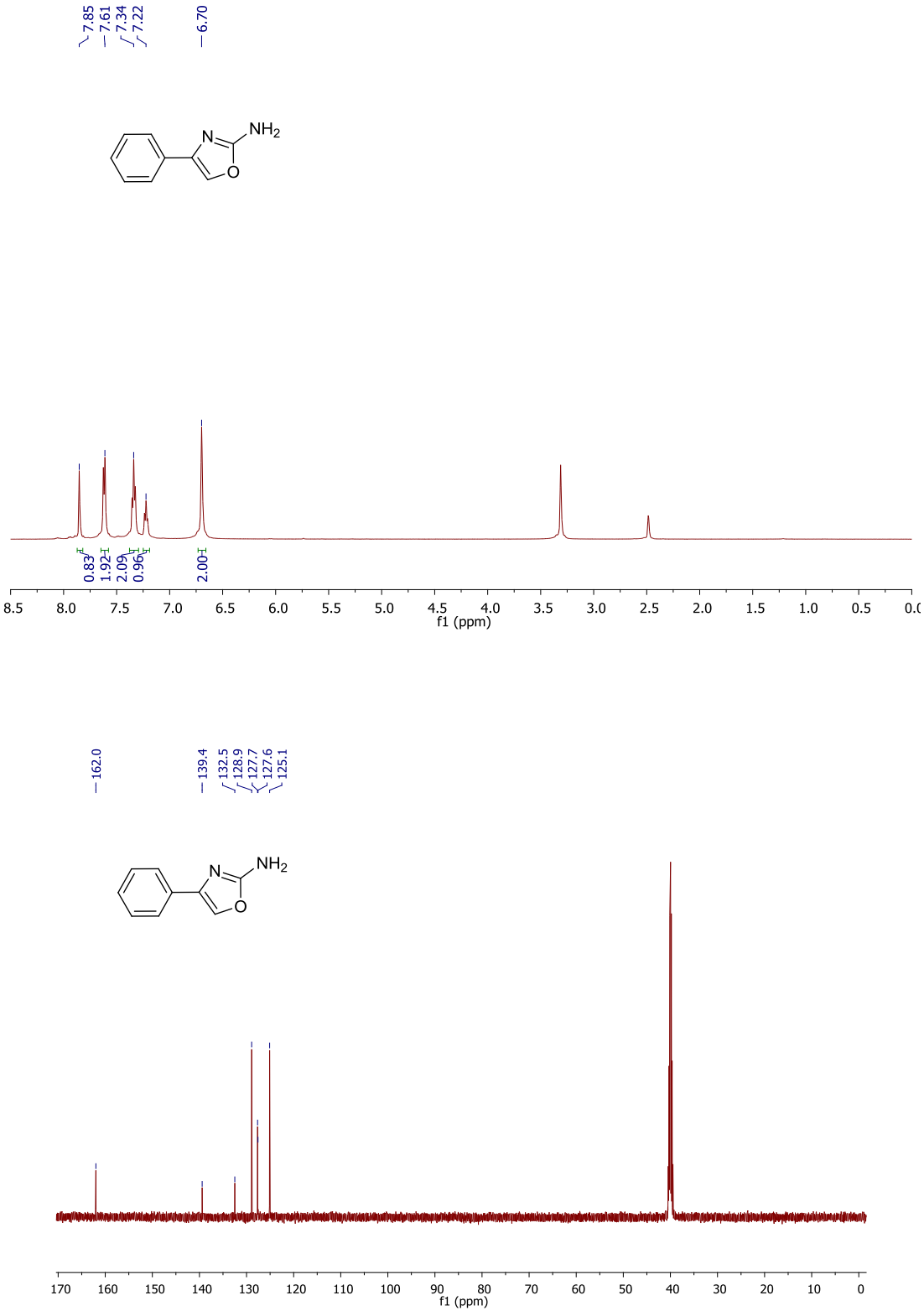


Figure 5.2 ^{1}H and ^{13}C NMR spectra of 4-phenyloxazol-2-amine **13a**

5.3 Conclusions

We have demonstrated a novel, highly efficient one-pot procedure for synthesis of 2,4-disubstituted thiazoles and oxazoles from the reaction of ketones with thioamides/thiourea and amides/urea using PTT as *in-situ* brominating agent in ionic liquid [bmim][BF_4]. The main advantages of this procedure are avoiding the handling of lacrymetric compounds, hazardous organic solvents and toxic catalysts.

5.4 Experimental Section

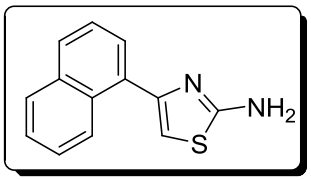
General: 1-Methylimidazole, n-butyl bromide, $NaBF_4$ and KPF_6 were purchased from Sigma-Aldrich. All other reagents and solvents were purchased from S. D. Fine, India and used without further purification unless otherwise specified. Column chromatography was carried out over silica gel (60–120 mesh, S. D. Fine, India). NMR spectra were recorded on a Brucker Heaven Avance 11 400 spectrophotometer using $CDCl_3$ and DMSO-d_6 as solvent and the chemical shifts were expressed in ppm. Mass spectra were recorded on a QSTAR® ELITE LX/MS/MS mass spectrometer from applied biosystem. The purity of the products was determined on silica-coated aluminium plates (Merck). The ionic liquid, [bmim][BF_4] and [bmim][PF_6] were prepared from 1-methylimidazole by minor modification of literature procedure[27, 28].

General procedure for synthesis of 2,4-disubstitutedthiazoles

PTT (1.1 mmol) was added to a mixture of ketone (1.0 mmol) in [bmim][BF_4] (2.0 mL) and reaction mixture was stirred vigorously at room temperature for 2 hour then thioamide/thiourea (1.2 mmol) was added to this reaction mixture and stirred for additional one hour at room temperature. Progress of the reaction was monitored by thin layer chromatography (TLC), after completion of reaction aqueous sodium bicarbonate wash was given to reaction mixture and pH ~ 9 was maintained. The precipitation occurred, which was filtered and washed with diethyl ether. The residue obtained after diethyl wash was percolated through a band of silica gel (60-

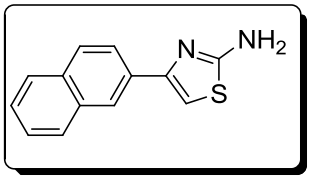
120 mesh) using hexane/ethyl acetate (9: 1 *v/v*) as an eluent to afford corresponding compounds in 75-92 % yield.

4-(Napthalen-1-yl)thiazol-2-amine 3e



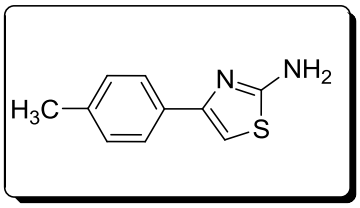
Yield: 80%; M.p. 157-158 °C; ^{1}H NMR (500 MHz, DMSO-d_6) 8.44 (d, J = 8.0 Hz, 1H), 7.97 – 7.82 (m, 2H), 7.62 (d, J = 7.1 Hz, 1H), 7.50 (d, J = 6.5 Hz, 3H), 7.09 (s, 2H, NH_2), 6.75 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) 168.4, 150.5, 133.9, 133.9, 131.2, 128.6, 128.3, 127.0, 126.7, 126.3, 126.2, 125.8, 105.4; HRMS: *m/z* calcd. for $C_{13}H_{11}N_2S$ 227.0643, found 227.0343 $[M + H]^+$.

4-(Naphthalene-2yl)thiazol-2-amine 3f



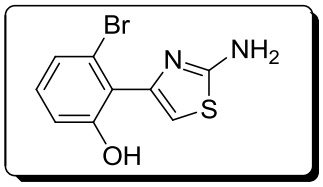
Yield: 80%; M.p. 152-155 °C (Lit.[19] 152-153 °C); ^{1}H NMR (500 MHz, DMSO-d_6) 8.30 (s, 1H), 7.95 – 7.83 (m, 4H), 7.50 – 7.42 (m, 2H), 7.15 (s, 1H), 7.09 (s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) 168.7, 150.2, 133.6, 132.8, 132.7, 128.5, 128.3, 127.9, 126.8, 126.2, 124.5, 124.4, 102.8; HRMS: *m/z* calcd. for $C_{13}H_{11}N_2S$ 227.0643, found 227.0341 $[M + H]^+$.

4-*p*-Tolylthiazol-2-amine 3g



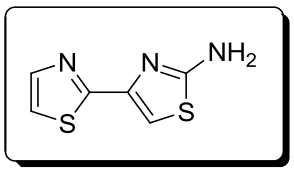
Yield: 85%; M.p. 130-132°C (Lit.[18] 125-126 °C); ^{1}H NMR (500 MHz, DMSO-d_6) 7.70 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.99 (brs, 2H), 6.89 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) 168.5, 150.3, 136.8, 132.7, 129.4, 125.9, 101.0, 21.2; HRMS: *m/z* calcd. for $C_{10}H_{11}N_2S$ 191.0643, found 191.0347 $[M + H]^+$.

2-(2-Aminothiazol-4-yl)-3-bromophenol 3h



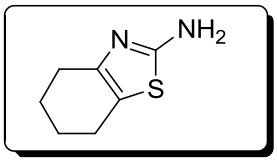
Yield: 85%; M.p. 209-212°C; ^{1}H NMR (500 MHz, DMSO-d_6) 11.93 (s, 1H), 7.92 – 7.90 (m, 1H), 7.45 – 7.39 (m, 2H), 7.24 (brs, 2H,), 7.16 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) 168.6, 155.1, 145.9, 131.5, 129.1, 121.2, 119.5, 110.6, 103.1; HRMS: *m/z* calcd. for $C_9H_8BrN_2OS$ 270.9541, found 270.9342 $[M + H]^+$.

4-(Thiazol-2-yl)thiazol-2-amine 3i



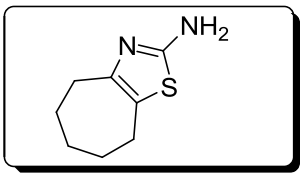
Yield: 87%; M.p. 186-189 °C; ^{1}H NMR (500 MHz, DMSO-d_6) 7.83 – 7.74 (m, 1H), 7.68– 7.58 (m, 1H), 7.28 (brs, 2H), 7.16 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) 169.2, 163.2, 144.5, 143.9, 120.1, 104.5; MS (ESI) *m/z* calcd. for $C_6H_6N_3S_2$ 184.0003, found 183.8932 $[M + H]^+$.

4,5,6,7-Tetrahydrobenzo(d)thiazol-2-amine 3j



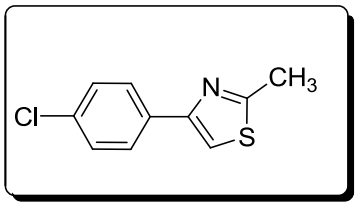
Yield: 83%; M.p. 87-90 °C (Lit.[29] 88-90 °C); ^{1}H NMR (400 MHz, DMSO-d_6) 5.06 (brs, 2H), 3.01 – 2.43 (m, 4H), 2.00 – 1.53 (m, 4H); ^{13}CNMR (101 MHz, DMSO-d_6) 165.2, 145.2, 118.1, 26.5, 23.5, 23.2, 22.9; MS (ESI) *m/z* calcd. for $C_7H_{11}N_2S$ 155.0643, found 155.0235 $[M +H^+]$.

5,6,7,8-Tetrahydro-4H-cyclohepta(d)thiazol-2-amine 3k



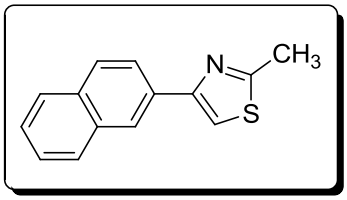
Yield: 81%; M.p. 63-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 4.88 (brs, 2H), 2.63 – 2.56 (m, 4H), 1.78 – 1.55 (m, 6H); ^{13}CNMR (101 MHz, DMSO-d_6) 163.2, 149.7, 121.1, 31.6, 31.3, 28.2, 26.6, 26.0; MS (ESI) *m/z* calcd. for $C_8H_{13}N_2S$ 169.0799, found 169.0452 $[M + H]^+$.

4-(4'-Chlorophenyl)-2-methylthiazole 3l



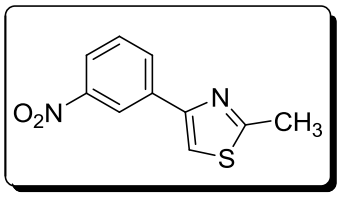
Yield: 81%; M.p. 112-115 °C (Lit.[18] 111-112 °C); ^{1}H NMR (300 MHz, $CDCl_3$) 7.82 – 7.79 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.29 (m, 2H), 7.26 (s, 1H), 2.76 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) 169.3, 150.4, 138.1, 133.0, 128.9, 127.6, 112.6, 19.3; HRMS: *m/z* calcd. for $C_{10}H_9ClNS$ 210.0144, found 209.9316 $[M + H]^+$.

2-Methyl-4-(naphthalene-2'-yl)thiazole 3m



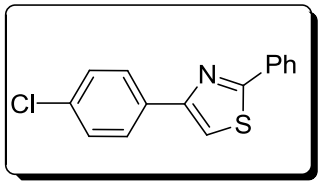
Yield: 78%; M.p. 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 7.94 – 7.81 (m, 4H), 7.47 – 7.42 (m, 3H), 2.80 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) δ = 163.8, 152.8, 131.4, 130.8, 129.5, 126.1, 126.1, 125.4, 124.0, 123.8, 123.0, 121.9, 110.4, 17.1; HRMS: *m/z* calcd. for $C_{14}H_{12}NS$ 226.0690, found 226.0389 $[M + H]^+$.

2-Methyl-(4'-nitrophenyl)thiazole 3n



Yield: 80%; M.p. 87-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.72 (s, 1H), 8.23 – 8.15 (m, 2H), 7.58 (t, *J* = 8.1 Hz, 1H), 7.48 (s, 1H), 2.79 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) 166.7, 152.6, 148.7, 136.1, 132.0, 129.7, 122.5, 121.1, 114.4, 19.3; HRMS: *m/z* calcd. for $C_{10}H_9N_2O_2S$ 221.0385, found 221.0278 $[M + H]^+$.

4-(4'-Chlorophenyl)-2-phenylthiazole 3o

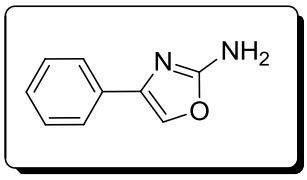


Yield: 75%; M.p. 130-132 °C; ^{1}H NMR (500 MHz, DMSO-d_6) 8.24 (s, 1H), 8.12 – 8.05 (m, 3H), 8.05 – 7.96 (m, 2H), 7.62 – 7.45 (m, 4H); ^{13}CNMR (126 MHz, DMSO-d_6) 167.7, 154.3, 133.4, 133.3, 133.2, 130.9, 129.7, 129.3, 128.3, 126.7, 115.8; HRMS: *m/z* calcd. for $C_{15}H_{11}ClNS$ 272.0301, found 272.0103 $[M + H]^+$.

General procedure for synthesis of 2,4-disubstituted oxazoles

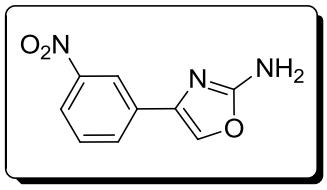
PTT (1.1 mmol) was added portion wise to a mixture of ketone (1.0 mmol) in [bmim][BF_4] (2.0 mL) and the reaction was stirred vigorously at room temperature for 2 hour then acetamide/urea (1.2 mmol) was added to the reaction mixture and stirred it for additional 7-10 hour at 80 °C. Progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction aqueous sodium bicarbonate wash was given to the reaction mixture to maintain pH ~ 9. The compound was extracted using ethyl acetate (3 × 3 mL). The combined organic layer was dried with anhydrous sodium sulphate and concentrated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel (60-120 mesh) using hexane/ethyl acetate (9: 1 *v/v*) as eluent to afford corresponding compounds in 71-85 % yield.

4-Phenyloxazol-2-amine 13a



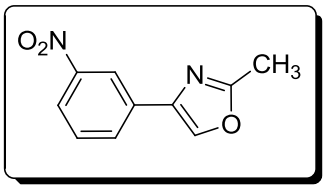
Yield: 76%; M.p. 150-152 °C (Lit.[30] 151-152 °C); ^{1}HNMR (500 MHz, DMSO-d_6) 8.36 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.29 – 7.24 (m, 1H); ^{13}CNMR (126 MHz, DMSO-d_6) 162.0, 139.4, 132.5, 128.9, 127.7, 127.6, 125.1; HRMS: *m/z* calcd. for $C_9H_9N_2O$ 161.0715, found 161.0345 $[M + H]^+$.

4-(3'-Nitrophenyl)oxazol-2-amine 13b



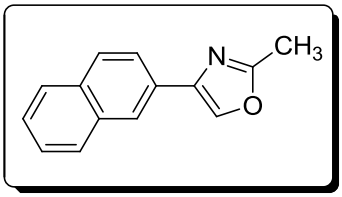
Yield: 75%; M.p. 149-153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) 8.34 (s, 1H), 8.03 – 7.96 (m, 3H), 7.57 (s, 1H), 6.79 (brs, 2H); ^{13}CNMR (126 MHz, DMSO-d_6) 164.4, 150.8, 139.8, 136.4, 133.4, 132.8, 131.7, 124.3, 121.5; HRMS: *m/z* calcd. for $C_9H_8N_3O_3$ 206.0566, found 206.0038 $[M + H]^+$.

2-Methyl-4-(3'-nitrophenyl)oxazole 13d



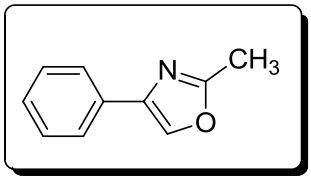
Yield: 70%; M.p. 113-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.54 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 2.55 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) 162.5, 151.0, 146.3, 138.9, 134.4, 131.1, 129.7, 122.5, 120.3, 13.9; HRMS: *m/z* calcd. for $C_{10}H_9N_2O$ 205.0613, found 205.0437 $[M + H]^+$.

2-Methyl-(napthalen-2'-yl)oxazole 13e



Yield: 68%; M.p. 70-72 °C; ^{1}H NMR (300 MHz , $CDCl_3$) 8.26 (s, 1H), 7.91 – 7.88 (m, 2H), 7.83 – 7.81 (m, 2H), 7.74 – 7.71 (m, 1H), 7.50 – 7.43 (m, 2H), 2.56 (s, 3H); ^{13}CNMR (75 MHz, $CDCl_3$) 163.0, 153.2, 141.7, 134.5, 134.0, 129.4, 129.2, 128.7, 127.4, 126.9, 125.1, 124.4, 118.3, 15.0; HRMS: *m/z* calcd. for $C_{14}H_{12}NO$ 210.0919, found 210.0734 $[M + H]^+$.

2-Methyl-4-phenyloxazole 13f



Yield: 71%; M.p. 45- 46 °C (Lit.[31] 45 °C); ^{1}HNMR (500 MHz, DMSO-d_6) 8.36 (s, 1H, ArH), 7.70 (d, *J* = 8.2 Hz, 2H, ArH), 7.46 – 7.35 (m, 3H, ArH), 7.27 (s, 1H), 2.40 (s, 3H); ^{13}CNMR (126 MHz, DMSO-d_6) 162.1, 140.0, 134.9, 131.3, 129.2, 128.2, 125.4, 13.9; HRMS: *m/z* calcd. for $C_{10}H_{10}NO$ 160.0762, found 160.0431 $[M + H]^+$.

5.5 References

[1] Yeh, V. S. C., *Tetrahedron*, **2004**, *60*, 11995.

[2] Jin, Z., *Natural Product Reports*, **2006**, *23*, 464.

[3] Lewis, J. R., *Natural Product Reports*, **1999**, *16*, 389.

[4] George, C.; Martin, N.; Ray, R., *Journal of Medicinal Chemistry*, **1973**, *16*, 1402.

[5] Kaspady, M.; Narayanaswamy, V. K.; Raju, M.; Rao, G. K., *Letters in Drug Design & Discovery*, **2009**, *6*, 21.

[6] Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., *Journal of Medicinal Chemistry*, **1995**, *38*, 4929.

[7] George, C.; Michael, J. F., *Journal of Medicinal Chemistry*, **1971**, *14*, 1075.

[8] Venugopala, K. N.; Jayashree, B. S., *Indian Journal of Heterocyclic Chemistry*, **2003**, *12*, 307.

[9] Wang, W.; Nan, F., *Journal of Organic Chemistry*, **2003**, *68*, 1636.

[10] Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N. S.; Shoemaker, R. H., *Journal of Medicinal Chemistry*, **2008**, *51*, 809.

[11] Anandan, S. K.; Ward, J. S.; Brokx, R. D.; Denny, T.; Bray, M. R.; Patel, D. V.; Xiao, X. Y., *Bioorganic & Medicinal Chemistry Letters*, **2007**, *17*, 5995.

[12] Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A., *Chemistry & Biology*, **1999**, *6*, 205.

[13] Wipf, P., *Chemical Reviews*, **1995**, *95*, 2115.

[14] Das, B.; Reddy, V. S.; Ramu, R., *Journal of Molecular Catalysis A: Chemical*, **2006**, *252*, 235.

[15] Narender, M.; Reddy, M. S.; Sridhar, R.; Nageswar, Y. V. D.; Rao, K. R., *Tetrahedron Letters*, **2005**, *46*, 5953.

[16] Kabalka, G. W.; Mereddy, A. R., *Tetrahedron Letters*, **2006**, *47*, 5171.

[17] Lee, J. C.; Choi, H. J.; Lee, Y. C., *Tetrahedron Letters*, **2003**, *44*, 123.

[18] Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V., *Tetrahedron*, **2007**, *63*, 11066.

[19] Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V., *Tetrahedron*, **2008**, *64*, 5019.

[20] Wipf, P.; Venkatraman, S., *The Journal of Organic Chemistry*, **1996**, *61*, 8004.

[21] Yu, Y.-B.; Chen, H.-L.; Wang, L.-Y.; Chen, X.-Z.; Fu, B., *Molecules*, **2009**, *14*, 4858.

[22] Lee, J. C.; Choi, H. J.; Lee, Y. C., *Tetrahedron Letters*, **2003**, *44*, 123.

[23] El Kazzouli, S. D.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G., *Tetrahedron Letters*, **2002**, *43*, 3193.

[24] Kearney, P. C.; Fernandez, M.; Flygare, J. A., *The Journal of Organic Chemistry*, **1998**, *63*, 196.

[25] Kumar, A.; Ahmed, I.; Rao, M. S.; Patel, G.; Kumar, D., *Indian Journal of Chemistry*, **2009**, *48B*, 416.

[26] Kumar, D.; Patel, G.; Kumar, A.; Roy, R. K., *Journal of Heterocyclic Chemistry*, **2009**, *46*, 791.
[27] Chauhan, S. M. S.; Kumar, A.; Srinivas, K. A., *Chemical Communications*, **2003**, 2348.
[28] Srinivas, K. A.; Kumar, A.; Chauhan, S. M. S., *Chemical Communications*, **2002**, 2456.
[29] Gasteiger, J.; Herzig, C., *Tetrahedron*, **1981**, *37*, 2607.
[30] Nath, J. P.; Dash, M.; Satrusallya, S. C.; Mahapatra, G. N., *Indian Journal of Chemistry*, **1981**, *20B*, 606.
[31] Ang, K. H.; Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M., *Tetrahedron Letters*, **1996**, *37*, 675.

CHAPTER VI

Conclusions

Summary

6.1 General Conclusions

Ionic liquids are organic salts engineered to melt at low temperatures generally below the boiling point of water. They are fascinating materials that have attracted the attention of many chemists as a result of their unique physical and chemical properties such as high thermal stability, non-coordinating nature, very low to negligible vapor pressure, good solvating ability, tunable solubility and ease of recyclability. Due to these distinctive properties ionic liquids were called 'designer green solvents'. The initial focus in the field has been to make use of ionic liquids as an alternative to volatile organic compound solvents (VOCs) in various organic transformations. Now, ionic liquids have advanced far from their reaction media status. A new class of ionic liquids task-specific ionic liquids (TSILs) offering exciting opportunities for achieving desired properties or functions. TSILs are a special class of ionic liquids which are synthesized with desired chemical tasks by covalently tethering specific functional groups to the anion, cation or both. Many researchers synthesized TSILs that have been employed as catalysts, reagents, alternatively supported tools, scavengers and in chiral induction separation science including extractions, gas chromatography.

The current thesis entitled "**Synthesis of Task Specific Ionic Liquids and their Applications in Selected Organic Transformations**" deals with the synthesis of some selected novel task specific ionic liquids with properties for specific chemical tasks. These task specific ionic liquids further have been used as reagents in synthesis, catalysis, solvent and as scavengers in parallel synthesis. The thesis is divided in five chapters.

6.2 Specific Conclusions

The thesis entitled "**Synthesis of Task Specific Ionic Liquids and their Applications in Selected Organic Transformations**" is divided in five chapters. A brief overview of these chapters is presented below.

The first chapter of thesis describes brief literature overview on functionalized liquids. A brief account on the synthesis of functionalized liquids and its applications in combinatorial synthesis has been discussed in this chapter. The chapter is divided in two parts. In part A, synthesis, application of various ionic liquid-supported reagents including hypervalent iodine reagents, tin reagents, triphenylphosphine and sufonyl reagents synthesis and their application in combinatorial synthesis has been discussed. Advantages of ionic liquid-supported reagents over conventional supported reagents have been demonstrated. In addition to these, preparation of some nucleophilic ionic liquids (NILs) and their application has been discussed. In part B a brief account on the use of ionic liquids as soluble supports in organic synthesis has been presented.

The second chapter of the thesis describes synthesis and applications of ionic liquid-supported aldehyde. The chapter is divided in two parts. In part-A, aldehyde functionalized ionic liquid has been synthesized and used as scavenger for primary amines in the reductive amination process. By using this strategy, small library of secondary amines was synthesized in high yields (82-90%) with excellent purity (> 95%). Reducing waste generation, minimizing solvent requirement, short reaction times as compared to the polymer supported counterpart and avoiding the chromatographic purification are clear advantages of the process. In part-B, a parallel solution-phase, multi step synthesis of amides and sulfonamides has been developed. Reductive amination of ionic liquid supported-aldehyde resulted in ionic liquid-supported secondary amines, which were further reacted with sulfonyl chlorides and acid chlorides to give

ionic liquid-supported amides and sulfonamides followed by cleavage using trifluoroacetic acid (TFA) afforded sulfonamides and caboxamides in good yields. To introduce additional diversity in the synthesis of sulfonamides and caboxamides ionic liquid-supported iodo-substituted aryl amine was synthesized using the same strategy and further Suzuki coupling reaction followed by sulfonylation using methanesulfonyl chloride was performed to generate the corresponding biaryl sulfonamide. The advantages of the protocol over solid-phase synthesis are homogeneous reaction medium, high loading and easy separation of products. Moreover, the progress of reaction is monitored by using different spectroscopic techniques such as thin layer chromatography, ^{1}H and ^{13}C NMR without dismantling the ionic liquid-support.

The third chapter of the thesis describes synthesis of new class of sulfonyl reagents, their synthetic utility, and their superiority over conventional sulfonyl reagents. The chapter consists of two parts. In part A, a novel nucleophilic ionic liquid 1-butyl-3-methylimidazolium *p*-toluenesulfinate, [bmim][*p*-TolSO_2] has been synthesized and used as a nucleophile for the reaction with alkyl bromides and phenacyl bromides to prepare sulfones and β-ketosulfones in excellent yields (80–93%) in [bmim][BF_4] ionic liquid. The reactivity of sulfinate anion (*p*-TolSO_2^-) in [bmim][*p*-TolSO_2] is higher as compared to *p*-TolSO_2Na under given conditions. In part B, a new safe diazotransfer reagent, ionic liquid-supported sulfonyl azide has been synthesized. Ionic liquid-supported sulfonyl azide converts active methylene containing compounds to corresponding diazo compounds. The reagent has also been used as deformylative diazotransfer reagent to synthesize α-diazoketones. The method offers better and simple purification and high purity of products in short period of time. The reactivity and the thermal stability of ionic liquid supported sufonyl azide reagent is higher than the most of the recently reported sulfonyl azides such as polymer-supported benzenesulfonyl azide (PS-SO_2N_3),

nonafluorobutanesulfonyl azide (NfN_3), imidazole-1-sulfonyl azide hydrochloride, oligomeric sulfonyl azide, and benzotriazol-1-yl-sulfonyl azide (Bt-SO_2N_3). β-Ketosulfones which have been reported poor substrates for diazotransfer reaction with several diazotransfer reagents such as Im-SO_2N_3.HCl and Bt-SO_2N_3 gave α-diazo-β-ketosulfones in excellent yields with ionic liquid supported sufonyl azide.

The fourth chapter of the thesis describes synthesis of novel ionic liquid-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (IL-TBD) and its ability to act as an active organocatalyst in the Michael addition of active methylene compounds and thiophenols to chalcones under solvent-free conditions. The IL-TBD afforded Michael addition products in excellent yields (82-94%) at room temperature. IL-TBD was simply recycled and reused at least five times without significant loss of catalytic activity.

The fifth chapter of thesis briefly describes the applications of ionic liquids as an efficient reaction medium and catalyst in selected organic transformations. A novel, highly efficient one-pot procedure for synthesis of 2,4-disubstituted thiazoles and oxazoles from the reaction of ketones with thioamides/thiourea and amides/urea using PTT as *in-situ* brominating agent in ionic liquid [bmim][BF_4] has been developed. The advantages of the procedure include avoiding, the handling of lacrymetric compounds, hazardous and toxic organic solvents along with good to excellent yield (68-92%) of the products. Of the various solvents that were screened for the reaction ([bmim][BF_4], [bmim][PF_6], methanol, THF, DMF, DCM, toluene and water [bmim][BF_4] was found to be good choice in terms of the yield and reaction time. The reason for the enhanced rate of reaction in [bmim][BF_4] is attributed to the Lewis/Brønsted acidity of the imidazolium cation leading to increased electropositive character of carbonyl group of *in situ* generated α-bromoketone.

6.3 Future Scope of the Research Work

Ionic liquid-supported reagents have gained considerable interest as promising alternative supported reagents to solid-supported reagents due to their high loading capacity, tuneable solubility, homogeneity and easy monitoring of the reaction by various analytical techniques such as NMR, IR and mass. Several ionic liquid-supported reagents have been synthesized and used for different organic transformations.

Ionic liquid-supported aldehyde has been used as an efficient scavenger for primary amines and soluble supportive tool for the synthesis of amide and sulfonamides. This high loading ionic liquid-supported aldehyde can be used as solule support tool in 1,3-dipolar cycloaddition, aldol condensation reactions, Biginelli and Hantzsch condensation reaction to synthesize diverse molecules. Ionic liquid-supported iodo substituted aryl amine can be used aryl iodide source in various cross coupling reactions such as Suzuki, Heck and Sonogashira reactions.

An environmental friendly protocol for the synthesis of sulfones and β-ketosulfones using 1-butyl-3-methylimidazolium *p*-toluenesulfinate, [bmim][*p*-$TolSO_2$] has been developed. Replacing the *p*-toluenesulfinate with other sulfinate salts including benzenesulfinate, heteroarylsulfinate and alkylsulfinate will lead to the formation of novel nucleophilic ionic liquids. These ionic liquids can be used as sulfinate ion source in various reactions. Different ionic liquid-supported sulfony reagent can be synthesized from ionic liquid supported sulfonyl chloride. Reaction of ionic liquid-supported sulfonyl chloride with hydrazine hydrate and ammonia will provide sulfonyl hydrazine and sulfonyl amine respectively. These sulfonyl reagents can be used as catch and release reagents to synthesize various aza-heterocycles.

Ionic liquid-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (IL-TBD), an effective organocatalyst in the Michael addition reaction, can be used as catalyst, in various base catalyzed reactions including Mortia-Bayils-Hillman reaction, Aldol condensation, Henry reaction, and Knoevenagel

reactions. Easy recyclability of the IL-TBD makes the method simple, convenient, and moreover cost-effective.

In the synthesis of 2,4-disubstituted thiazoles and oxazoles from the reaction of ketones with thioamides/thiourea and amides/urea, urea derivatives can be replaced with guanidine and 2-aminopyridine to synthesize imidazole derivatives. The [bmim][BF_4] can be used as an effective reaction media for the synthesis of various bioactive heterocyclic compounds.

Appendices

Appendices

List of Publications *[A-1]*

1. **MK Muthyala**, K Velisetti, K Parang, Anil Kumar, Advances in functionalized ionic liquids as reagents and scavengers in organic synthesis, *Current Organic Chemistry* **2014** (Communicated).
2. S Choudhary, **MK Muthyala,** K Parang, Anil Kumar, Ionic liquid-supported sulfonyl hydrazine: A useful reagent for traceless synthesis of pyrazoles, *Organic Chemistry Frontiers* **2014** (Communicated).
3. **MK Muthyala,** S Choudhary, K Pandey, GM Shelke, M Jha, Anil Kumar, Synthesis of ionic liquid-supported diaryliodonium salts**,** *European Journal of Organic Chemistry* **2014,** 2365–2370.
4. **MK Muthyala,** S Choudhary, Anil Kumar, Synthesis of ionic liquid-supported hypervalent iodine reagent and its application as 'catch and release' reagent for α-substituted acetophenones, *RSC Advances.* **2014,** *4*, 14297–14303.
5. **MK Muthyala**, S Choudhary, Anil Kumar, Synthesis of ionic liquid-supported sulfonyl azide and its application in diazotransfer reaction, *Journal of Organic Chemistry*, **2012,** *77*, 8787–8791**.**
6. Anil Kumar, **MK Muthyala**, S Choudhary, R. K. Tiwari, K Parang, Ionic liquid as soluble support for synthesis of 1,2,3-thiadiazoles and 1,2,3-selenadiazoles, *Journal of Organic Chemistry*, **2012,** *77*, 9391–9396.
7. **MK Muthyala**, Anil Kumar, A novel and efficient one pot synthesis of 2,4-disubstituted thiazoles and oxazoles using PTT in ionic liquid, *Journal of Heterocyclic Chemistry*, **2012**, *49*, 959–964.
8. Anil Kumar, **MK Muthyala**, BS Chhikara, K Parang, Ionic liquid supported TBD: An efficient and recyclable organocatalyst for Michael addition to α,β-unsaturated ketones, *Canadian Journal of Chemistry*, **2012**, *90*, 290–297.
9. **MK Muthayala**, Anil Kumar, Ionic liquid supported aldehyde: A highly efficient scavenger for primary amines, *ACS Combinatorial Science*, **2012**, *14*, 5-9.
10. **MK Muthayala**, BS Chhikara, K Parang, Anil Kumar, Ionic liquid-supported synthesis of sulfonamides and carboxamides, *ACS Combinatorial Science*. **2012**, *14*, 60−65.

11. Anil Kumar, **MK Muthyala**, 1-Butyl-3-methylimidazolium p-toluenesulfinate: A novel reagent for synthesis of β-ketosulfones in ionic liquid, *Tetrahedron Letters*, **2011**, *52*, 5368–5370.
12. **MK Muthyala,** VK Rao, Anil Kumar, $Cu(OTf)_2$ catalyzed synthesis of bis(5-methyl-2-furyl)methanes by condensation of 2-methylfuran with carbonyl compounds under solvent free conditions, *Chinese Journal of Chemistry*, **2011,** *29*, 1483–1488.
13. VK Rao**, MK Muthyala**, Anil Kumar, An efficient and simple synthesis of tetraketones catalysed by $Yb(OTf)_3$–SiO_2 under solvent free conditions, *Indian Journal of Chemistry*, **2011**, *50B*, 1128-1135.

List of Oral/poster presented in conferences *[A-2]*

Oral presentations

1. **MK Muthyala**, Anil Kumar, An ecofriendly synthesis of 1,2,3-thiadiazoles using ionic liquid as soluble support, Conference on Technological Advancements in Chemical and Environmental Engineering, BITS Pilani (March 23-24, 2012).
2. **MK Muthyala**, Anil Kumar, Ionic liquid-supported synthesis of Aza-heterocycles, Symposium on Recent Trends in Chemical Science, BITS Pilani (March 25, 2012).

Poster presentations

1. **MK Muthyala,** Anil Kumar, Tagged hypervalent iodine(III) reagents: A new liaison between diaryliodonium salts and ionic liquids, 20th ISCB International Conference on Chemistry and Medicinal Plants in Translational Medicine for Healthcare (ISCBC-2014), University of Delhi, Delhi. (March 1-4, 2014).
2. **MK Muthyala,** Anil Kumar, Synthesis of ionic liquid-supported hypervalent iodine reagent and applications in organic synthesis, 14th Tetrahedron Symposium on Challenges in Organic and Bioorganic Medicinal Chemistry, Vienna, Austria (June 25- 28, 2013).
3. **MK Muthyala,** Anil Kumar, Synthesis of ionic liquid-supported hypervalent iodine reagent and applications in organic synthesis, 19th ISCB International Conference on Recent Advances and Current Trends in Chemical and Biological Sciences(ISCBC-2013), Mohanlal Sukhadia University, Udaipur (March 2-5, 2013).
4. **MK Muthyala**, Anil Kumar Ionic liquid-supported synthesis of Aza-heterocycles, Symposium on Recent Trends in Chemical Science, BITS Pilani (March 25, 2012).

5. **MK Muthyala**, Anil Kumar Ionic liquid-supported sulfonyl azide, A green reagent for diazo transfer reaction, Catalyst Technical Conclave, Dr. Reddy's Hyderabad, (December 16-17, 2011).
6. **MK Muthyala**, Anil Kumar, [TBDbmim]Br, An efficient and recyclable organocatalyst for Michael addition to α,β-unsaturated ketones, National Symposium on Organic Synthesis, IIS university, Jaipur (February 18-19, 2011).
7. **MK Muthyala**, Anil Kumar, Ionic liquid-supported synthesis of sulfonamides and carboxamides, 15th ISCB International Conference on Chemical Biology for Discovery for Affordable Health, Wellness and Sustainability (ISCBC-2012), Saurashtra University, Rajkot. (February 7-8, 2011).
8. **MK Muthyala,** Anil Kumar, Ionic liquid-supported synthesis of amides and sulfonamides, National Symposium on Green and Sustainable Chemistry (NSGSC-2010), BITS Pilani (February 19-21, 2010).
9. **MK Muthyala,** V. Kameswara Rao, Anil Kumar, $Cu(OTf)_2$ promoted synthesis of bis(furyl)methanes under solvent free condition, 14th ISCB International Conference on Chemical Biology for Discovery; Perspectives and Challenges (ISCBC-2010), Central Drug Research Institute, Lucknow (January 15-18, 2010).

BRIEF BIOGRAPHY OF THE CANDIDATE ***[A-3]***

Manoj Kumar Muthyala obtained his master degree in Organic Chemistry from Jawaharlal Nehru Technological University, Hyderabad, India. In April 2009, he joined Dr. Anil Kumar's group at BITS Pilani as junior research fellow in CSIR sponsored project. Later he was admitted to the PhD program of the Institute in August 2009. In 2012 he was awarded Senior Research Fellowship by CSIR New Delhi. He has published eleven research articles in peer reviewed international journals and presented papers in ten conferences/symposiums. He attended one international conference (Tetrahedron Symposium-2013, Vienna) and presented his work in the form of poster. His research interest lies in developing new task specific ionic liquids and exploring their applications in various organic transformations to develop efficient and economical methods of synthesis.

BRIEF BIOGRAPHY OF THE SUPERVISOR *[A-4]*

Dr. Anil Kumar is Associate Professor at Department of Chemistry, Birla Institute of Technology and Science, Pilani. He received his PhD degree from Department of Chemistry, University of Delhi in 2004 under the supervision of Prof. SMS Chauhan. During his doctoral studies Dr. Anil Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry. He was postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island in Prof. Keykavous Parang's laboratory. In his postdoctoral studies he has worked on synthesis of novel Src kinase inhibitory agents and solid phase synthesis.

Dr. Anil Kumar joined BITS Pilani in May 2006 as Assistant Professor and was promoted to Associate Professor in February 2013. He has 14 year of research experience and 8 year of teaching experience. He has visited several times University of Rhode Island, Kingston during summer as visiting scientist in Prof. Parang's laboratory. He is recipient of Harrison McCain Foundation award from Acadia University, Canada for 2012. He is supervising eleven PhD students and co-supervising three students. As a result of his research accomplishment he has published 90 research papers in peer reviewed journals, presented papers and delivered lectures in several national and international conferences. Additionally, to his credit he also has one US patent and a book chapter. He has completed three research project as PI and one as Co-PI sponsored by DST, CSIR and UGC. Currently, he has one major project from CSIR and one industry project from Ranbaxy in collaboration with Prof. Dalip Kumar.