Recent Advances on Design and Synthesis of Chiral Imidazolium Ionic Liquids and their Applications in Green Asymmetric Synthesis

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Abstract: Over the past decade, catalysis by ionic liquids (ILs) has experienced a tremendous growth in the context of "Green Chemistry", and there are numerous examples of a variety of catalytic reactions that have been successfully carried out in such neoteric media. The great enthusiasm for catalysis in ILs is not only driven by the curiosity of chemists, but also due to the growing awareness of developing greener reactions or process media in catalytic science and greener catalytic technologies due their advantages of unique physical and chemical properties as compared to traditional volatile organic solvents. Recently, development of chiral ionic liquids and their applications in asymmetric synthesis have attracted much attention as these reactions have widespread applications in the synthesis of chiral drugs and pharmaceutical industries. Asymmetric induction is mainly achieved by the use of chiral substrates or reagents, chiral catalysts or enzymes. Owing to the vast number of structurally different room temperature ILS that have been synthesized, this review focuses on imidazolium ionic liquids that possess chirality either in the imidazolium moiety or in the anion moiety. The aim of this review is to highlight the recent breakthrough of Chiral ILs in chirality transfer or chiral recognition when used as solvent or co-solvent: the case of task specific ionic liquids is beyond the scope of this review. In the first part, the synthesis of of CILs has been presented and the second part of the review has been devoted on the applications of such CILs in green asymmetric synthesis as well as various pharmaceutical industries.

Keywords: Chiral Imidazolium Ionic Liquids, Chiral Catalyst and Reaction Medium, Green Asymmetric Synthesis, Recyclable Homogeneous Catalyst, Solvent-free Clean Synthesis.

1. INTRODUCTION

Ionic liquids (ILs) often recognized as molten salts having melting point below 100 °C with entirely ionic character, consisting of both a cationic and anionic parts (Figure **1**) [1].

ILs usually consists of several properties such as low melting organic salts (<100 °C), very low vapor pressure, non-flammable, wide liquid range, moderate to high viscosity, high thermal/mechanical/ electrochemical stability, low toxicity, high Solvating properties etc. Interestingly, physical and chemical properties can be tailored by the modification of cationic and anionic core, hence for this structural diversity ILs are generally termed as designer solvent [2]. The first report of ILs emerged in 1914 [3]; since then, it has been taken tremendous attention in the perspective of green Synthesis for their unique, diverse and tunable properties. There are varieties of examples of catalytic reactions that have been efficiently promoted in presence of such materials as the catalyst and/or reaction media [4]. Now, introduction of chiral building blocks in either in the cationic part or in the anion moiety of ILs make it novel materials because of its promising efficacy as asymmetric catalyst for the fabrication of chiral drugs and biomolecules. Several examples of asymmetric induction by chiral ionic liquids (CILs) have been reported in the literature [5].

Recently, asymmetric catalysis by imidazolium based CILs have concerned much interest predominantly in pharmaceutical industries. This growing interest in the exploitation of CILs for chiral induction has provoked us to commence the review on imidazolium based CILs and their applications in green asymmetric synthesis. The present study focuses on recent advances on design and synthesis of imidazolium based CILs and highlights their applications in green asymmetric synthesis.

2. DEVELOPMENT OF CHIRAL IMIDAZOLIUM IONIC LIQUIDS AND THEIR APPLICATIONS IN GREEN ASYMMETRIC SYNTHESIS

2.1. Chiral Imidazolium Ionic Liquids with Chiral Anions

In 1999, chiral imidazolium ionic liquid was invented by Seddon and co-workers [6]. They prepared chiral 1-*n*-butyl-3-methylimidazolium L-lactate ([bmim][lactate]), **1**, simply by introducing (*S*)-2-hydroxypropionate as the chiral anion (Scheme **1**).

Ohno *et al.* have fabricated a number of bio-based chiral imidazolium ionic liquids, **2**, derived from chiral

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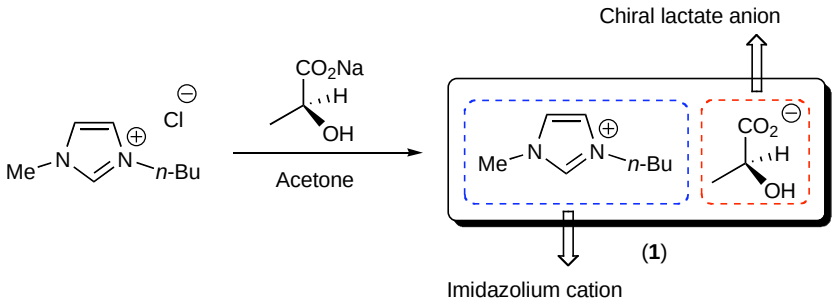


Scheme 1: First report for the synthesis of imidazolium based CIILs.

amino acids *via* anion exchange techniques (Figure **1**) [7].

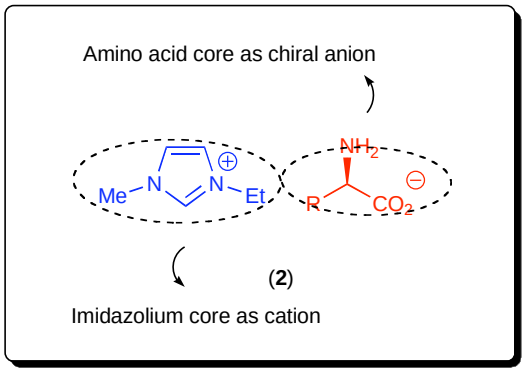
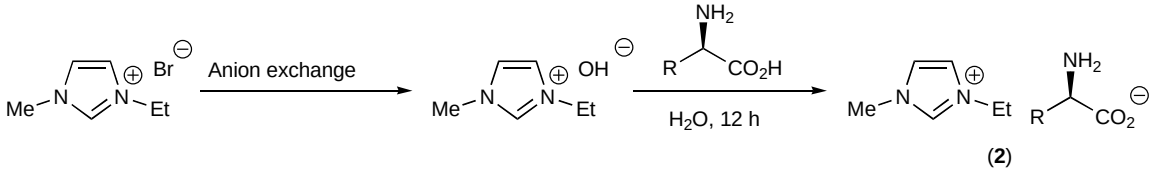


Figure 1: Naturally occurring amino acids derived imidazolium CILs.

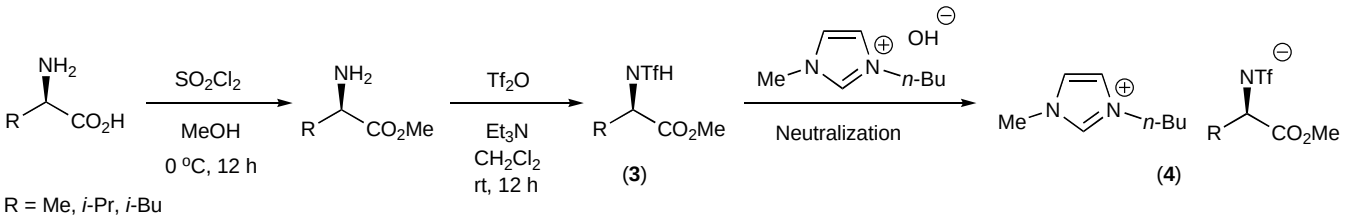
The conversion of 1-ethyl-3-methylimidazolium bromide ([emim][Br]) into 1-ethyl-3-methylimidazolium hydroxide ([emim][OH]) using an anion-exchange resin, subsequently, neutralization of ([emim][OH] with a series of amino acids provide the desired CILs, **2**, as the transparent and almost colorless liquids at room temperature (Scheme **2**). The as prepared CILs except [emim][Glu] and [emim][Asp] (both contain two carboxyl groups) are miscible in different organic solvents such as methanol, acetonitrile, and chloroform etc. Only [emim][Cys] shows thermal stability up to 173 ^{o}C and all the other CILs exhibit good thermal stability (>200 ^{o}C). The effects of different side chains in amino acid residues of the CILs on glass transition temperature (*T*g) have also been investigated. The increase in the length of the alkyl side chain of the amino acid cores in the CILs results gradual increase in *T*g, which was associated to the increase in the van der Waals attraction between the alkyl groups (Scheme **2**).

Recently, Ohno *et al.* synthesized another new imidazolium CIILs containing amino acids modified chiral anions (Scheme **3**) [8]. The synthesis of these



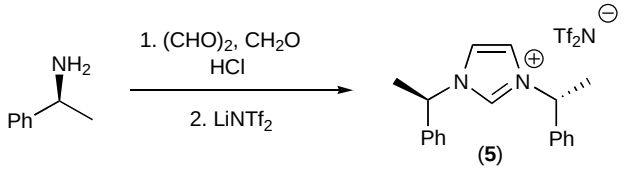
Anionic part of **1**	T_g (^{o} C) of **1**	Yield (%) of **1**	Anionic part in **1**	T_g (^{o} C) of **1**	Yield (%) of **1**
Gly	-62	82	Phe	-36	83
Ala	-57	86	Trp	-31	82
Met	-57	78	His	-24	78
Val	-52	79	Tyr	-23	70
Ile	-52	82	Cys	-19	77
Leu	-51	80	Arg	-18	74
Ser	-49	79	Asn	-16	83
Pro	-48	83	Gln	-12	66
Lys	-47	78	Asp	5	79
Thr	-40	84	Glu	6	80

Scheme 2: Synthesis of bio-based chiral imidazolium ionic liquids.



Scheme 3: Synthesis of amino acids modified imidazolium based CIILs.

CILs involves three steps. Amino acids were converted to corresponding methyl esters by the treatment of thionyl chloride in methanol at 0 ^{o}C, subsequently, reaction with trifluoromethanesulfonic anhydride in presence of triethylamine in dichloromethane produced methyl esters of *N*-trifluoromethanesulfonylamino acid analogous (**3**). Finally, neutralization of [bmim][OH] with the ester (**3**) afforded the desired CIILs (**4**).



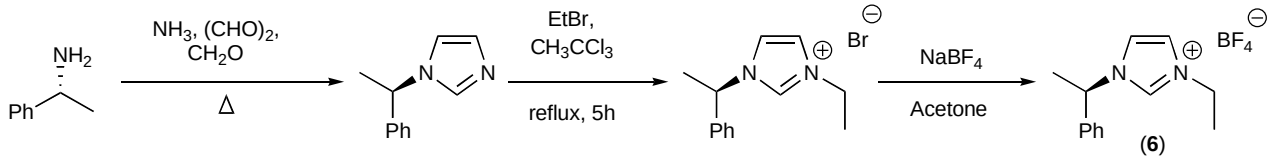
Scheme 4: CILs containing two chiral centers attached to imidazole core.

2.2. Chiral Imidazolium Ionic Liquids with Chiral Cations:

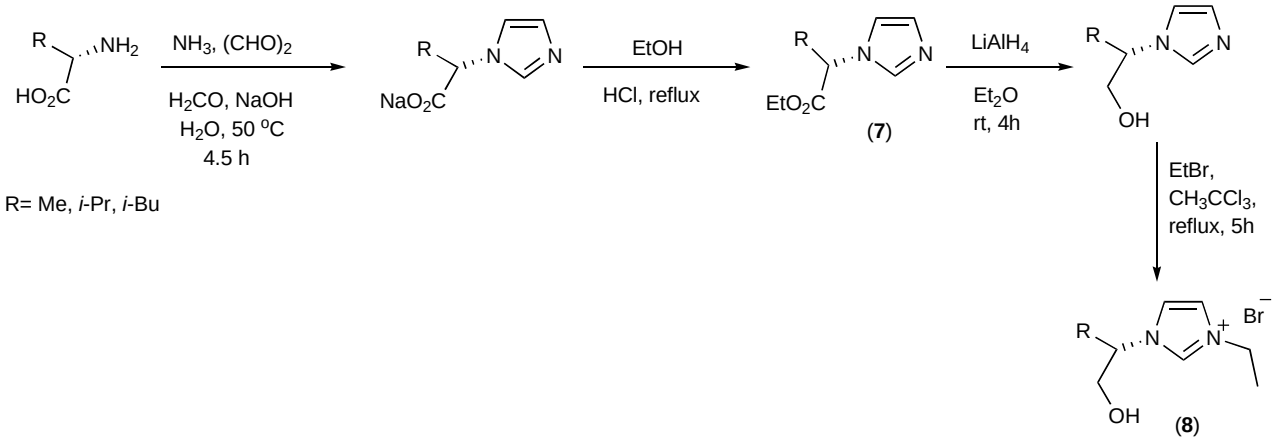
Ding *et al.* have synthesized imidazolium based chiral ionic liquid (**5**) containing chiral imidazolium moiety bearing two chiral centers bonded to a nitrogen atoms of the imidazole centre (Scheme **4**) [9].

Bao *et al.* synthesized of same type of chiral imidazolium ionic liquid (**6**) with single chiral center derived from the (*R*)-(+)-α-methylbenzylamine (Scheme **5**) [10]. This ionic liquid failed to promote asymmetric reactions due to its high melting point (90 ^{o}C).

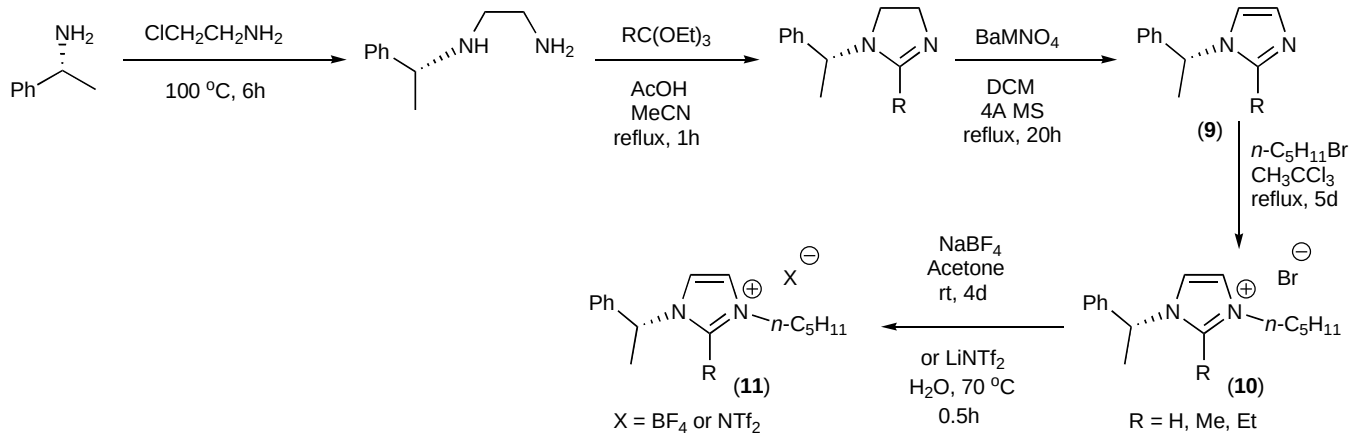
Also, Bao and co-workers have synthesized new imidazolium CILs containing chiral imidazolium moiety as cation modified by amino acids (Scheme **6**) [10]. Chiral imidazolium ring (**5**) was synthesized by four component reaction of amino acid, formaldehyde, glyoxal and ammonia under basic condition. Then, the acid functional groups of amino acids were converted into corresponding ethyl esters (**7**). The ethyl esters (**7**) upon treatment with lithium aluminum hydride ($LiAlH_4$) produced corresponding ethyl alcohol analogous followed by the reaction with bromoethane gave desired CILs (**8**).



Scheme 5: Synthesis of single chiral imidazolium moiety derived CILs.



Scheme 6: CILs containing amino acid modified chiral imidazolium cation.



Scheme 7: Synthesis of imidazolium CILs derived from (*R*)-(+)-α-methylbenzylamine.

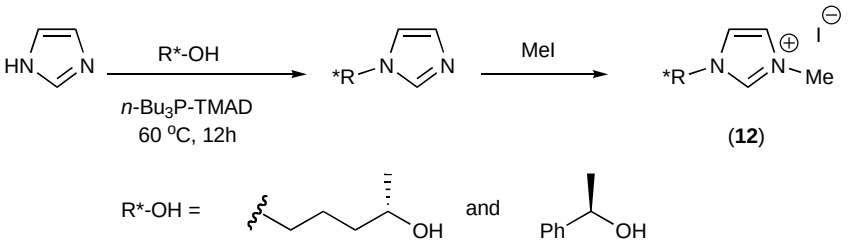
Recently, Génisson *et al.* have synthesized a new series of novel chiral imidazolium ionic liquids starting from (*R*) -(+)-α-methylbenzylamine [11]. First they have prepared chiral imidazole moiety (**7**) *via* alkylation of (*R*)-(+)-α-methylbenzylamine with chloroethylamine followed by the treatment with ortho ester and barium permanganate. Subsequently, compound, **9,** was treated with *n*-pentyl bromide giving CILs, **10**, which was then converted to desire CILs, **11**, *via* anion exchange with $NaBF_4$ or $LiNTf_2$ (Scheme **7**).

Kim *et al.* have prepared a new type of chiral imidazolim ionic liquids (**12**) derived from chiral alcohols (*S*)-2-hexanol and (*R*)-α-methylbenzyl alcohol *via* Mitsunobu alkylation of imidazole moiety (Scheme **8**) [12].

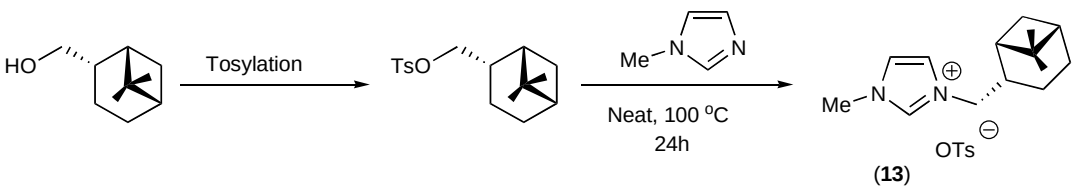
Machado *et al.* have synthesized another new imidazolium CIL (**13**) starting form (1*S*,2*S*,5*S*)-(-)-myrtanol (Scheme **9**) [13].

Tosoni *et al.* have been synthesized chiral citronellol moiety containing imidazolium based CIILs (**16**) [14]. They have prepared CIL, **16**, starting from the bromination of (3*R*)-citronellol with Br_2 and PPh_3 in CH_2Cl_2 at room temperature to produce corresponding citronellyl bromide derivative (**14**) which on heating 1-alkyl-1*H*-imidazoles for few days gave chiral imidazolium bromide salts (**15**). Subsequently, anion exchange with $NaBF_4$ in acetone, led to the corresponding imidazolium tetrafluoroborates as CILs (Scheme **10**). In addition, they have also prepared 1,3-dicitronellyl-1*H*-imidazolium bromide by deprotonation of 1*H*-imidazole (**17**) with $(n\text{-Bu})_4NOH$ and subsequent treatment with 2 equivalents of the chiral bromide (Scheme **10**).

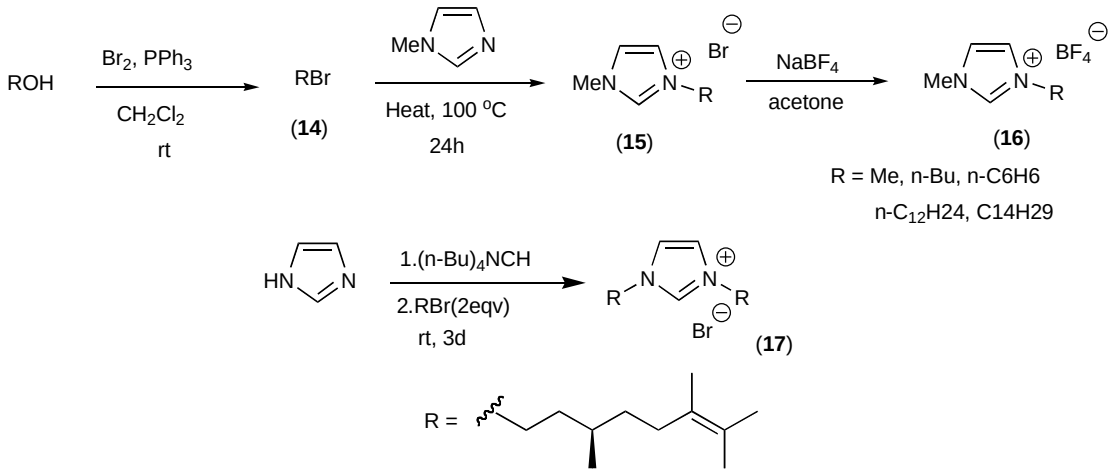
Xu *et al.* prepared chiral amino acids functionalized chiral imidazolium ionic liquids [15]. First, amino acids were reduced to amino alcohols by $NaBH_4/I_2$, followed by neutralized and under goes bromonation with PBr_3.



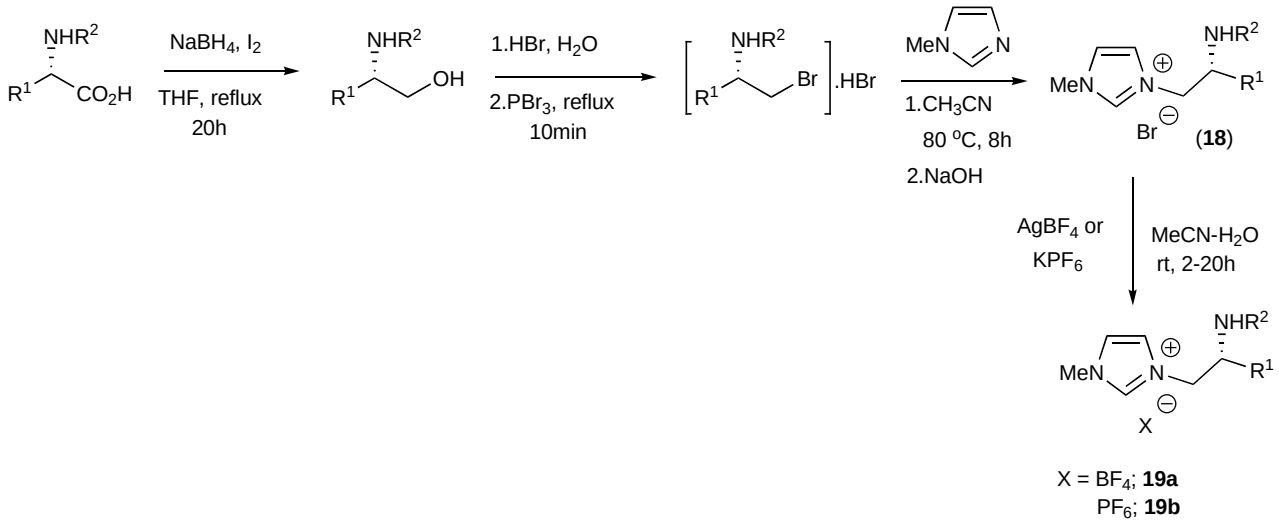
Scheme 8: Synthesis of chiral imidazolium chiral ionic liquids derived form chiral alcohol.



Scheme 9: Synthesis of chiral imidazolium based CILs derived form chiral myrtanol.



Scheme 10: Synthesis of chiral imidazolium CILs derived form chiral citronellol.



Scheme 11: Synthesis of chiral imidazolium CILs derived from amino acids.

Then, N-alkylation with methylimidazole followed by neutralization with NaOH gave chiral imidazolium bromide salts (**18**). Anion exchange of **18** with $AgBF_4$ or KPF_6 produced the desired CILs (**19a and 19b**) with thermal stability up to 210 °C (Scheme **11**). The as prepared CILs, **19b**, exhibit higher melting points and glass-transition temperatures than the CILs, **19a**.

Recently, Ni *et al.* synthesized new novel CIILs, **20**, from chiral amino alcohols (Scheme **12**) [16].

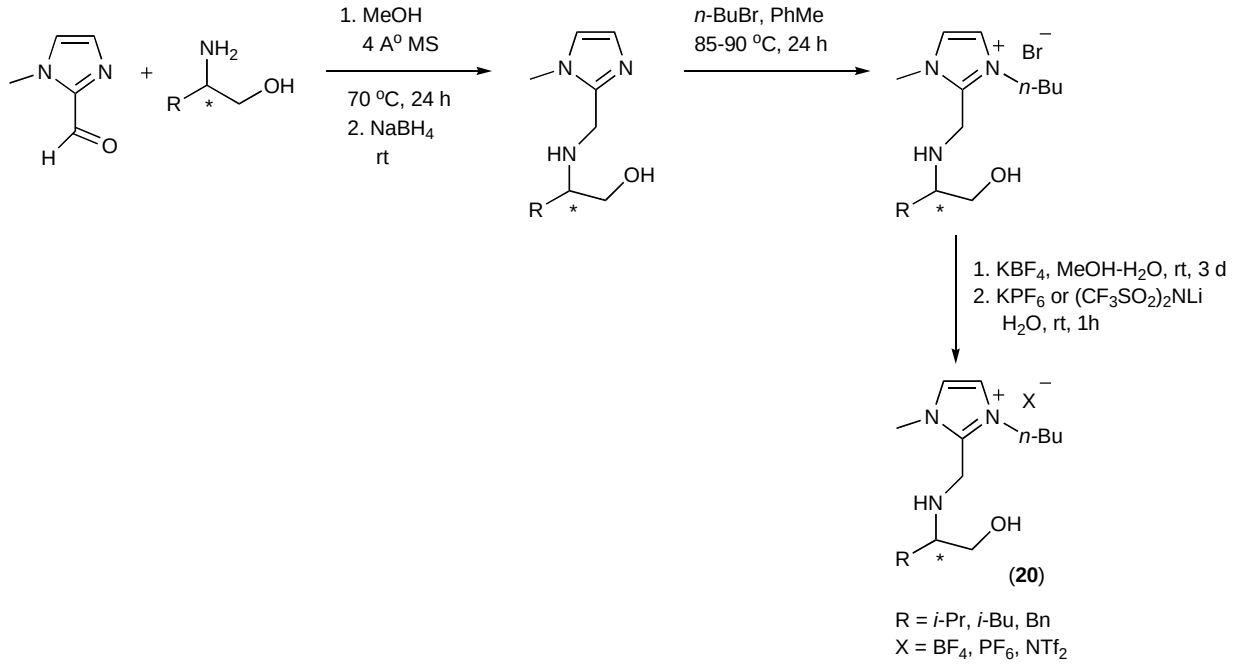
Ou and Huang developed a useful method for synthesizing imidazolium ILs from amino alcohols [17]. The reaction of 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride with chiral primary amino alcohols gave CILs followed by, anionexchange with fluoroboric acid or potassiumhexafluorophosphate produced the CIILs, **21a-c** and **22a-c** (Scheme **13**).

Luo *et al.* synthesized pyrrolidine modified imidazolium CIILs starting from L‑proline (Scheme **14**) [18].

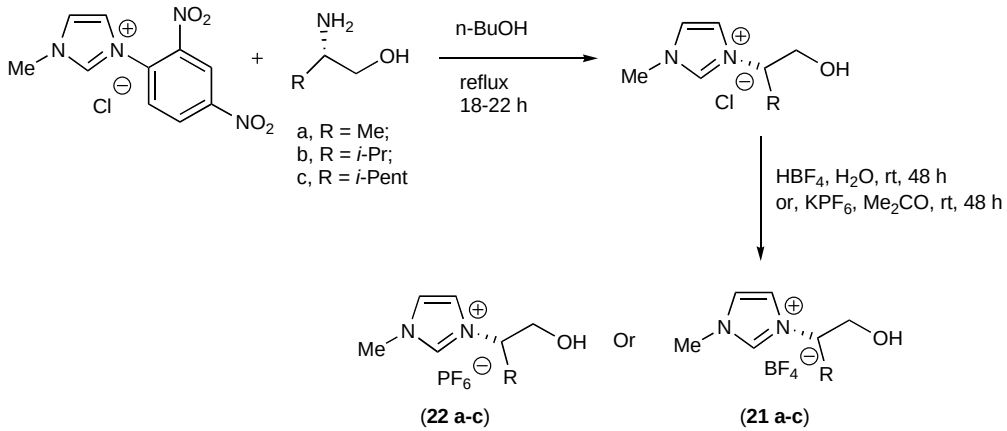
Miao *et al.* [19] have synthesized proline moiety containing imidazolium CIILs (**27** and **30**) (Scheme **15**).

Guillen *et al.* have synthesized histidine functionalized imidazolium chiral ionic liquids **32** [20]. Protection of histidine methyl ester, followed by alkylation with iodomethane and oxidative ring opening of the cyclic urea by *t*‑BuOOH in the presence of (*i*‑Pr)$_2$NEt, resulting histidine derivative, **31**. After that, the reaction of **31**, with *n*-butylbromide, followed by anion exchange resulting desired histidine functionalized imidazolium CIL (Scheme **16**).

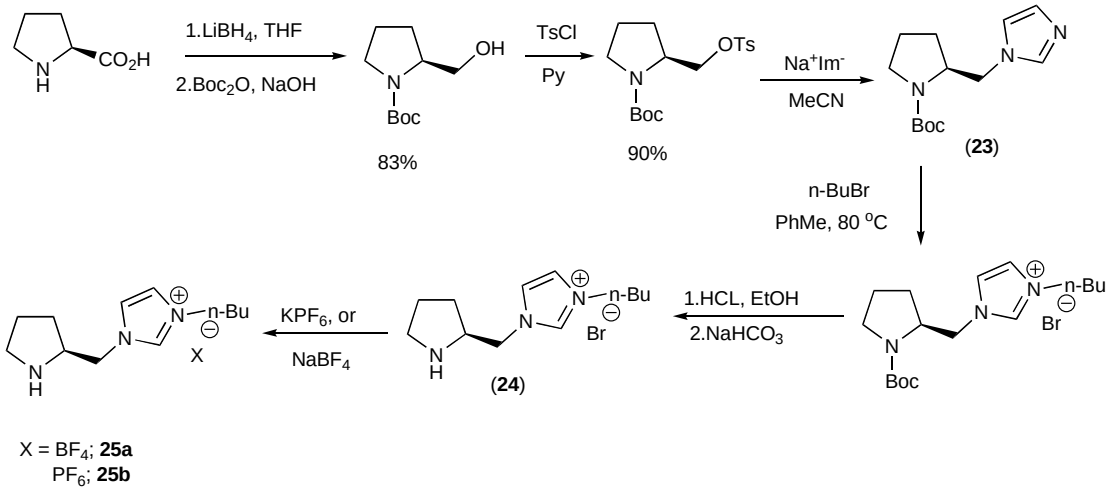
Ni *et al.* have synthesized a new pyrrolidine based CIILfrom L-proline (**35**) [21]. The reaction of 3-chloropropanesulfonyl chloride with (*S*)-2-aminomethyl-



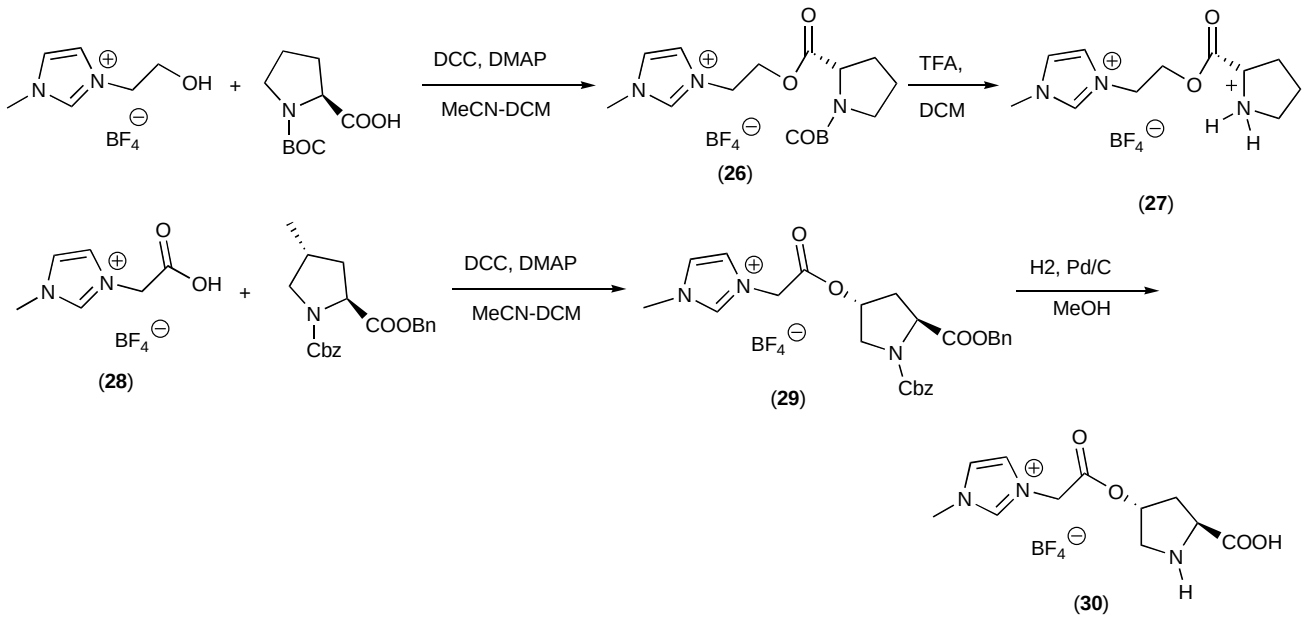
Scheme 12: Synthesis of imidazolium CIILs from amino alcohol.



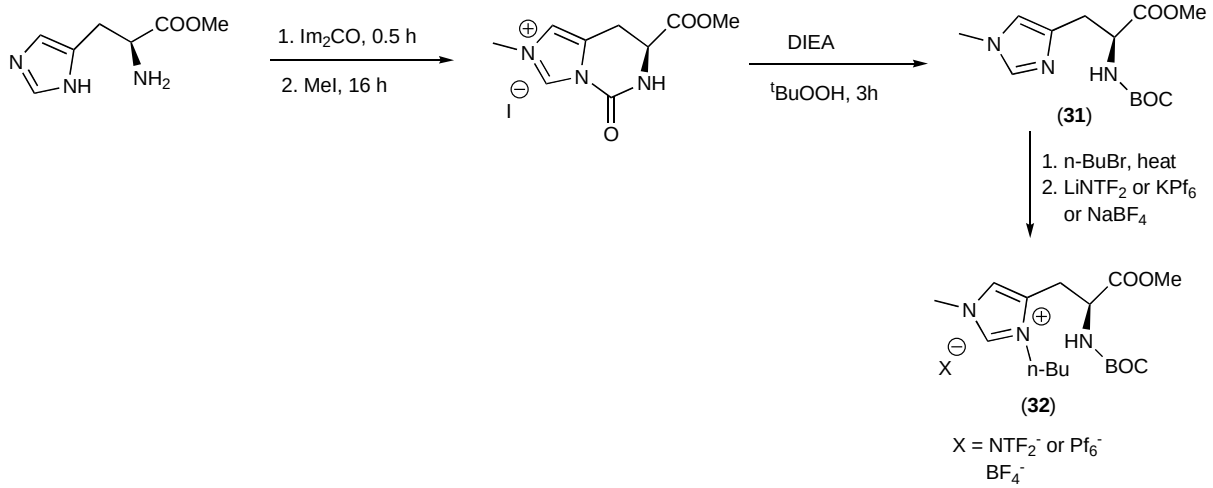
Scheme 13: Synthesis of CIILs from chiral amino alcohols.



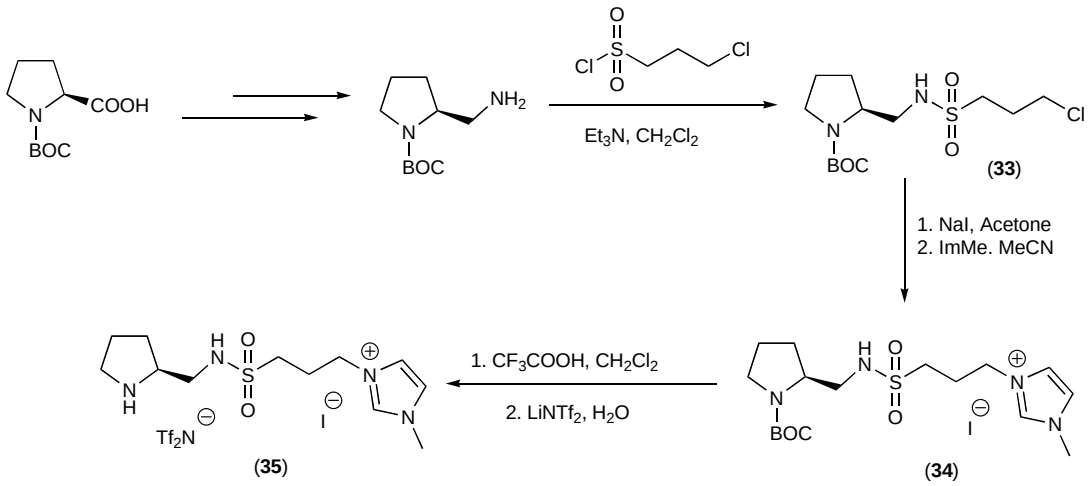
Scheme 14: Synthesis of imidazolium CIILs starting from amino acid.



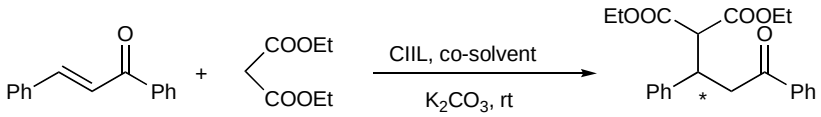
Scheme 15: Synthesis of imidazolium CILs starting from L-Proline derivatives.

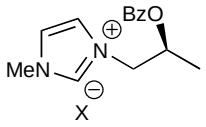


Scheme 16: Synthesis of histidine functionalized imidazolium CIL.



Scheme 17: Synthesis of Pyrrolidine-Based CIILs from l-Proline.





X= Br or BF_4 or PF_6

CIIL	Co-solvent	Time	Yield	ee
Br	PhMe	10 h	96 %	25 %
BF_4	PhMe	10 h	95 %	24 %
BF_4	DMSO	6 h	90 %	17 %
BF_4	DMF	7 h	91 %	16 %
PF_6	PhMe	10 h	93 %	23 %

Scheme 18: Imidazolium CIL as solvent in asymmetric Michael addition.

1-Boc-pyrrolidine obtained from L-proline, gave sulfonamide (**33**). Conversion of **33** into imidazolium iodide was done by iodination with NaI followed by alkylation producing CIL, **34**. After that, BOC deprotection and subsequently, anion exchange with Tf_2N^- resulting the desired CIIL, **35**.

2.3. Applications of CIILs in Asymmetric Organic Reactions

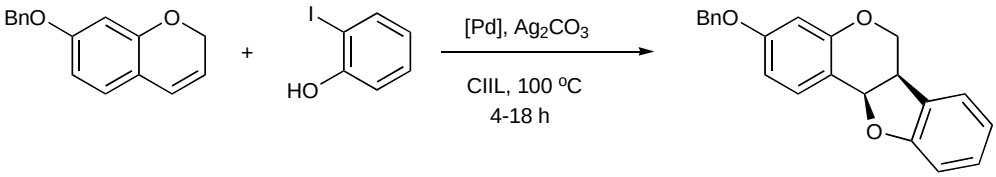
In 1975, Seebach and Oei first applied chiral solvents in asymmetric reactions [22]. Since that time, there have been many attempts to use chiral solvents in asymmetric reactions, but the enantioselectivities have been fairly low. This has led to the conclusion that asymmetric induction effected by chiral solvents. Even though the enantioselectivity observed for the electrochemical reduction of ketones in chiral amino ethers was low, it opened up the field to develop chiral solvents to influence the outcome of asymmetric reactions. Although a large number of chiral ionic liquids have been synthesized, only a limited number have been successful in affecting the outcome of asymmetric reactions.

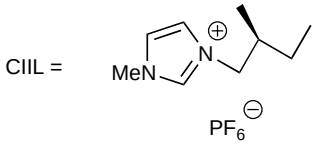
Bao and co-workers have utilized CIILs as chiral solvents in the asymmetric Michael addition of diethyl malonate to 1,3-diphenyl-2-propenone (Scheme **18**) [23]. Better results were obtained in toluene than in DMSO or DMF as the co-solvent. Comparable chemical yields and enantioselectivities were obtained with CIIL bromide giving the best yield and ee of the three.

In 2003, Kiss *et al.* reported the palladium catalyzed Heck oxyarylation of 7-benzyloxy-2*H*-chromene with 2‑iodophenol using CIIL both as a chiral solvent and ligand (Scheme **21**) [24]. The transformation gave low yields (13–28%) and poor enantioselectivities (4–5%) with $Pd(OAc)_2$ and $PdCl_2$ (Scheme **19**).

2.4. As Organocatalysts

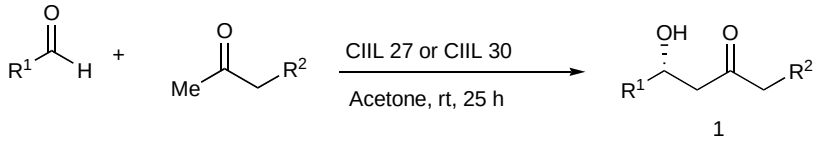
Metal-free catalysis of asymmetric reactions by simple organocatalysts has become an important area of research in recent years [25]. Pyrrolidine catalysts have been used successfully for the direct asymmetric aldol and Michael addition reactions [25], which are regarded as two of the most powerful carbon–carbon-bond-forming reactions inorganic synthesis [25]. For these reactions, the organocatalyst is usually used in substantial quantity, and the efficient recovery and reuse of the organocatalyst are a major concern. Therefore, there is a need to develop new organocatalysts, which are easily recyclable and possess enhanced catalytic abilities. In this regard,





$Pd(OAc)_2$: 13%, 5% ee
$PdCl_2$: 28%, 4% ee

Scheme 19: CIIL promoted asymmetric Heck oxyarylation reaction.



R^1	Yield	ee (%)
4-NCC_6H_4	10 %	11
4-NCC_6H_4	59 %	72
2-Np	50 %	80
Ph	50 %	76
4-$AcNHC_6H_4$	40 %	64
4-BrC_6H_4	58 %	73
2-ClC_6H_4	92 %	71
Cy	43 %	85
4-$NO_2C_6H_4$	51 %	71
4-$NO_2C_6H_4$	64 %	85

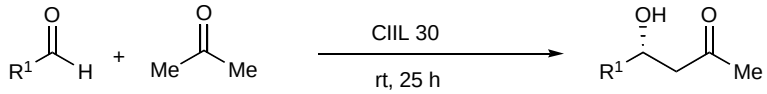
Scheme 20: CIIL promoted asymmetric aldol reaction.

ionic liquids that contain specific functionalities and are capable of acting as organocatalysts have received much attention recently. One advantage of ionic-liquid-based chiral organocatalysts is that they can be recovered easily from the reaction mixtures simply by capitalizing on their solubility characteristics.

Miao and Chan reported proline based CIIL **27** as organo catalyst for the direct asymmetric aldol reaction of 4-cyanobenzaldehyde with acetone, but obtained the aldol product, **1a**, in only 10% yield and 11%ee. CIIL **30** fared better as organocatalyst under the same conditions, leading to **1a** in 59% yield and 72% see (Scheme **20**) [19]. The results indicate that the acidic proton of proline is essential for efficient catalysis to occur. Thus, the aldol reaction of a broad range of aldehyde acceptors, including aromatic and aliphatic aldehydes, and two ketone donors, acetone and 2-butanone, was carried out in good yields and enantioselectivities in the presence of organo catalyst **30** under the same conditions. Furthermore, the authors carried out the reactions of 4‑nitrobenzaldehydein deuterated acetone with CIIL **30** or proline as catalyst, respectively, and proved that CIIL **30** is a more efficient organocatalyst than proline itself. The recyclability of CIIL **30** as organocatalyst was also examined (Scheme **21**) [19]. CIIL **30** was recycled and reused at least four times in the same reaction without significant loss in yield and enantioselectivity.

Functionalized CIILs 32 and 33 have been employed as highly efficient asymmetric organo-catalysts for the Michael addition of cyclohexanone to nitroalkenes (Scheme **22**) [18]. CIILs 32a–c and 33a, lacking a substituent at C-2 of the imidazole ring, were superiorto their 2'-methyl counterparts (32a–c and 33b) in terms of yields and selectivity. Introduction of a protic group (OH) in the side chain did not improve the catalytic activity and selectivity, and CIILs with Br^- and $BF4^-$ were much more active and selective than those with $PF6^-$.

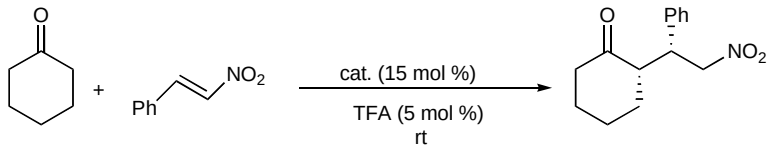
Headly and his co-workers has developed a new type of pyrrolidine based CIIL which catalyzes the Michael addition of various aldehydes to nitrostryenes in Et_2O at 4 ^oC with moderate yields (≤64%), good

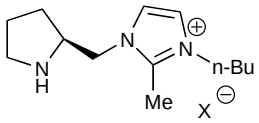


R1 = 4-$NO_2C_6H_4$

Cycle	Yield(%)	ee(%)
1	68	85
2	68	85
3	66	83
4	64	82

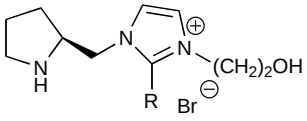
Scheme 21: Recyclability of CIIL **30**.





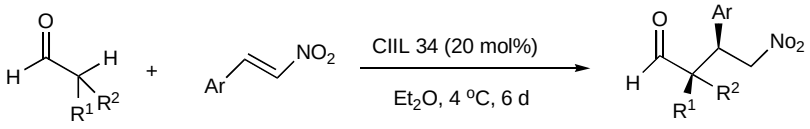
CIIL 32a, X= Br
CIIL 32b, X= BF_4
CIIL 32c, X= PF_6

Cycle	Cat	Time	Yield (%)	Syn/ Anti	ee (%)
1	40a	20 h	97	97:3	97
1	40b	16 h	100	96:4	94
1	40c	12 h	40	96:4	82
1	41a	18 h	86	97:3	89
1	41b	18 h	25	94:6	70



CIIL 33a, R= H
CIIL 33b, R= Me

Scheme 22: CIIL catalyzed Michael addition of cyclohexanone to nitroalkenes.



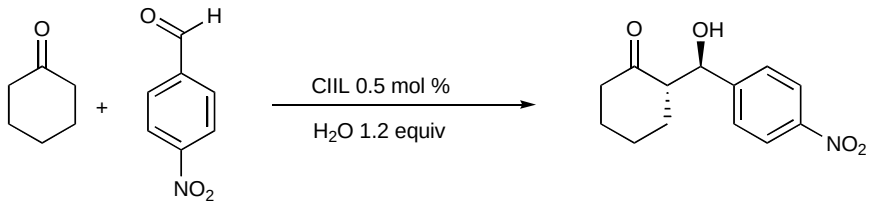
R^1	R^2	Ar	Yield (%)	Syn/ Anti	ee (%)
Me	Me	Ph	58	....	82
n-Bu	H	Ph	64	97:03	68
n-Bu	H	*p*-Tol	60	96:04	67
n-Pr	H	*p*-An	29	92:08	67
i- Pr	H	Ph	53	96:04	66
i- Pr	H	*p*-Tol	64	97:03	73
n-Pr	H	Ph	49	89:11	64
n-Pr	H	*p*-Tol	38	96:04	68
a,b	a,b	Ph	38	95:05	88

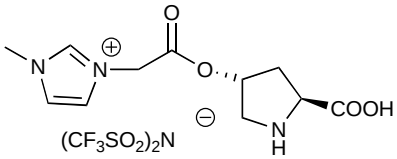
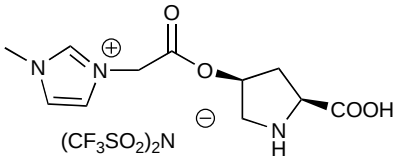
Scheme 23: CIIL catalized asymmetric Michael addition of various aldehydes to nitrostryenes.

enantioselectivities (≤82% ee), and high diastereoselectivities (syn:anti ≤ 97:3) (Scheme **23**) [21]. Moreover, catalyst also catalyzes the Michael addition of cyclohexanoneto *trans*-β-nitrostyrene in acetonitrile at room temperature to give the adduct in moderate yield and high stereoselectivities (syn:anti = 95:5, 88% ee). Our results also demonstrate that the presence of acidic hydrogen is necessary for the selectivity; the acidic N–H adjacent to the electron-withdrawing sulfonyl group plays an important role in the selectivity of the reaction. The catalyst is easily recycled without loss of activity.

2.5. Asymmetric Aldol Reaction

Lombardo *et al.* described the synthesis of ‘‘ion-tagged L-prolines’’ as organo catalysts for asymmetric aldol reactions [26-28]. These are essentially L-proline-based CIILs (Scheme **24**). They observed a higher efficiency with the lipophilic bis(trifluoromethylsulfonyl) imide (NTf_2^-) counter anion as compared with the BF_4^- anion. This was further improved by theuse of aqueous biphasic conditions instead of using the neationic liquid ([bmim][NTf_2]) as the solvent [27]. The final improvement of this L-proline-based catalyst was achieved by using the cis-geometry of the imidazolium ionic moiety toproline as opposed to the trans-geometry present in their previous publications. As shown by the example in Scheme **24**, the yield improved from 37% to 87% by the use of cis-CIIL compared with the trans-CIIL. No organic solvent was used for the reaction. However, 1.2 equivalents of water and 5molar excess of liquid ketone as the aldol

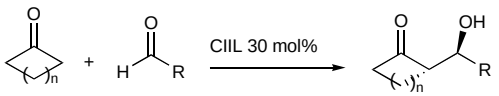


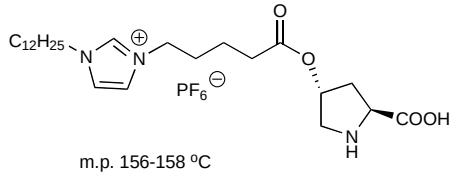
CIIL	Condition	Yield (%)	ee (%)	Syn/ Anti
 $(CF_3SO_2)_2N$ CIIL 35	5 h at 20 °C	37	99	94:6
 $(CF_3SO_2)_2N$ CIIL 36	5 h, 20 °C	87	99	92:8
	24 h, 20 °C	98	99	93:7
	CIIL 2 mol% H_2O 1.2 equiv 2 h, 20 °C	98	99	93:7

Scheme 24: Assymetric aldol reaction catalyzed by L-proline modified CIILs.

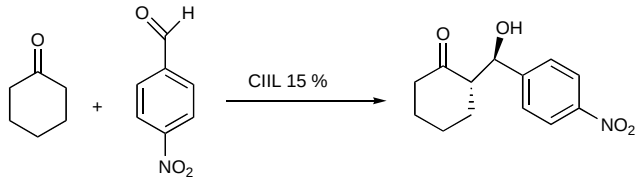
donor were used to ensure homogeneous conditions. Exceptionally, high turnover numbers for most reactive aromatic aldehydes were observed (TON= 196 for the cis-CIIL, 0.5 mol %, and 24 h reaction time). Also, high yields (up to 99%), excellent enantioselectivities (>99% ee), and diastereo- selectivities (anti:syn up to 95:5) were obtained with this organocatalyst.

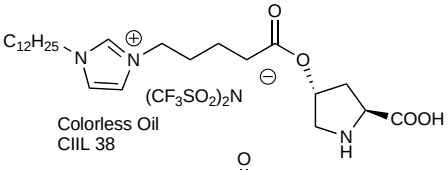
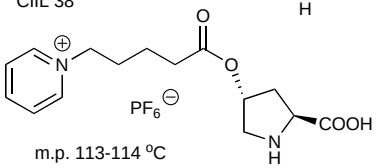
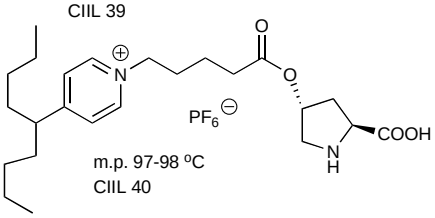
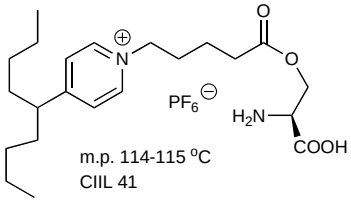
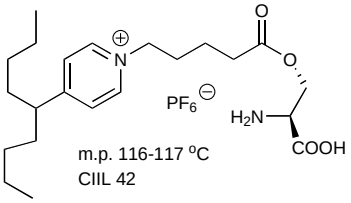
In 2008, Zlotin and coworkers synthesized the amphiphilic chiral imidazolium salts derived from (S)-proline and accompanying anions $BF_4^-$and PF_6^- (Scheme **25**). These are structurally similar to the previously described class but have longer alkane chains on the imidazolium moiety for added hydrophobicity. Organocatalysis by these CIILs between cycloketones and aromatic aldehydes proved to be efficient (up to 95% yield), stereoselective (up to >99% ee) and diastereoselective (anti:syn up to 97:3). Good recover ability for up to 5 cycles was also observed. Following this success, in 2009, they synthesized a series of CIILs with different hydroxyl-α-amino acids such as proline, serine, and threonine and different cationic charge carrying moieties such as imidazolium and pyridinium (Scheme **26**) [29]. The incorporation of the NTf_2^- anion and pyridinium or 4-(5-nolyl)-pyridinium cations instead of imidazolium-based cations were intended to improve the hydrophobicity of the CIIL. These new CIILs are amphiphilic and their catalytic properties in the ‘‘on water" aldol reaction has been examined. It is interesting to note that the CIIL 39 with a pyridinium cation and a PF_6^- anion did not catalyze the aldol reaction under the conditions examined, whereas the CIIL 40 with4-(5-nolyl)-pyridinum cation and same anion displayed high activity (97% yield) and enantioselectivity (99% ee). This was correlated to the hydrophobicity of the ionic liquids. Despite the presence of PF_6^- anion, CIIL 39 was water soluble, whereas CIIL 40 was insoluble in water. This enabled the organocatalyst to reside at the water/organic solvent interface facilitating the reaction. The authors also stated that CIIL 40 retained its catalytic activity and selectivity after eight reaction cycles. In their most recent publication on this topic, Zlotin and coworkers further modified these organocatalysts by removing the free carboxylic acid group on the proline structure by converting it to an amide [30]. This modification optimized the catalyst’s hydrophobic/hydrophilic properties to obtain maximum catalytic efficiency in an aqueous environment compared with the catalysts with free carboxylic groups (Scheme **27**). They obtained almost quantitative yields and good enantioselectivities (up to 99% ee with CIIL



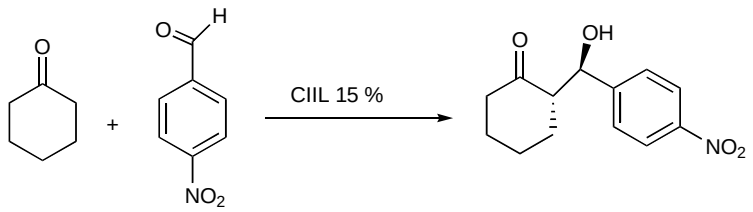
CIIL	Condition	yield %	ee %	Syn/Anti
 m.p. 156-158 °C CIIL 37	n= 3, R=*p*-$NO_2C_6H_4$ CIIL 30 mol % H_2O, 10 h, 20 °C	95	99	97:3
	n= 3, R=*p*-$CO_2HC_6H_4$ CIIL 30 mol % H_2O, 10 h, 20 °C	86	99	97:3
	n= 3, R=C_6H_5 CIIL 30 mol % H_2O, 36 h, 20 °C	67	88	93:7
	n= 2, R=*p*-$NO_2C_6H_4$ CIIL 30 mol % H_2O, 10 h, 20 °C	95	91	85:15

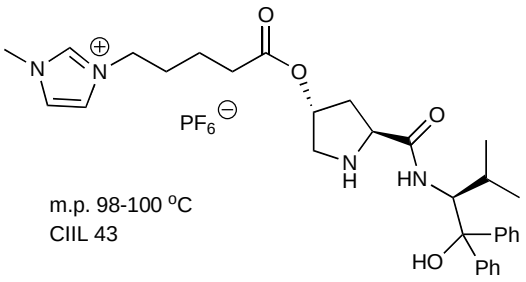
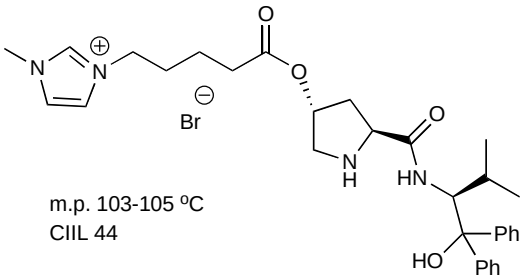
Scheme 25: CIIL promoted asymmetric aldol reation.



CIIL	Condition	yield %	ee %	Syn/Anti
 Colorless Oil CIIL 38	CIIL 15 mol % H_2O, 15 h at rt	99	98	98:2
 m.p. 113-114 °C CIIL 39	CIIL 15 mol % H_2O, 15 h at rt	-	-	-
 m.p. 97-98 °C CIIL 40	CIIL 15 mol % H_2O, 15 h at rt	97	99	97:3
 m.p. 114-115 °C CIIL 41	CIIL 15 mol % H_2O, 20 h at rt	84	91	87:13
 m.p. 116-117 °C CIIL 42	CIIL 15 mol % H_2O, 20 h at rt	89	97	90:10

Scheme 26: Imidazolium and pyridinium based CIL promoted asymmetric aldol reaction.



CIIL	Condition	yield %	ee %	Syn/Anti
 m.p. 98-100 °C CIIL 43	CIIL 1 mol % H_2O (100 eq.), 4.5 h at rt	99	97	97:3
	CIIL 5 mol % H_2O (100 eq.), 4.5 h at rt	99	89	94:6
 m.p. 103-105 °C CIIL 44	CIIL 5 mol % H_2O (100 eq.), 20 h at rt	99	89	85:15

Scheme 27: CIIL catalyzed asymmetric aldol reaction.

58) and diastereoselectivities (anti:syn up to 99:1 with CIIL 43 at 3°C for 15 h) in the presence of large excess of water. Selectivity was notably higher for the more hydrophobic catalyst 43 as compared with 44. Finally, it was noted that CILs containing imidazole moiety exhibited promising catalytic activity that the others.

2.6. Asymmetric Diels-Alder Reaction

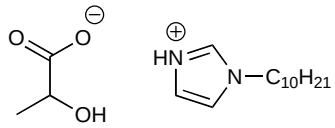
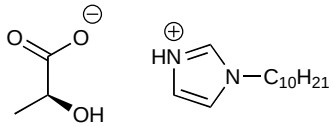
Howarth *et al.* used dialkylimidazoliumsalts (chiral and achiral) as Lewis-acids to catalyze the reaction between crotonaldehyde or methacrolein with cyclopentadiene. The chirality of the ionic liquid did no tseem to have much influence on the stereochemistry as the enantiomeric excess was less than 5%, whereas the endo:exo product ratios were almost the same for both chiral and achiral ILs [31]. Since then ionic liquids have been tried both as acid catalysts and as the solvent in asymmetric Diels-Alder reaction to improve the stereoselectivity.

In 2006, Pernak and coworkers used protic imidazolium ionic liquids as the reaction media for cyclopentadiene and two dienophiles (dimethyl maleate and methyl acrylate) that resulted in good endo/exo selectivities (up to 3.9:1; Scheme **28**) [32]. The racemic DL-lactate ionic liquid **45** chiral L-lactate ionic liquid **46** and both performed almost identically.

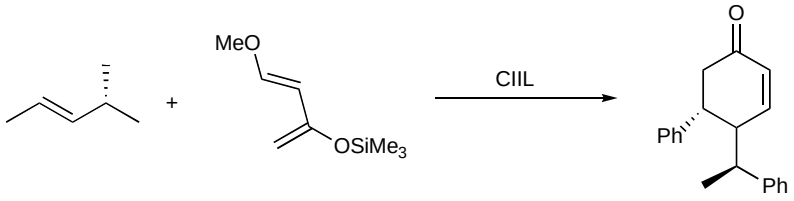
Vo-Thanh and coworkers designed different CIILs to be used as the reaction media in an aza-Diels-Alder reaction between Danishefsky's diene and chiral imine (Scheme **29**). The reactions involved only the diene, chiral imines, and the CIIL, **47** and **48**, whereas no other acid catalyst or organic solvent was used [33].

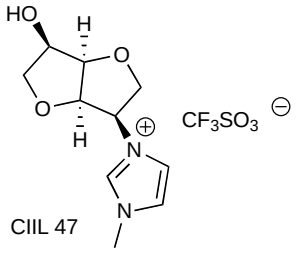
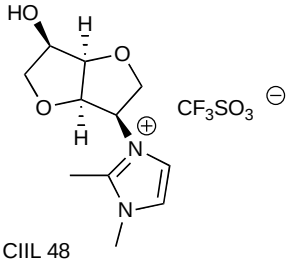
The first enantioselective Diels-Alder reaction with a CIIL was reported by Doherty *et al*. [34]. They used imidazolium modified bis-oxazoline CIIL **49** (Scheme **30**) as a chiral ligand in the copper(II)-catalyzed reaction of N-acryloyl and N-crotonoyloxazolidinones with cyclopentadiene and 1,3-cyclohexadiene. Higher rates were achieved in reactions carried out in anionic liquid [emim][NTf_2] compared with dichloromethane. Higher yields (up to 100%) and enantioselectivities (95% ee) were also achieved with the IL. The catalyst could be recycled 10 times without loss of activity.

In 2010, Wang and coworkers reported the successful application of 2-pyrrolidinecarboxylicacid

CIIL	Condition	Yield (%)	ee (%)	dr(endo;exo)
 CIIL 45	in CIIL 24 h at 25 ^{0}C	90	-	78:21
 CIIL 46	in CIIL 24 h at 25 ^{0}C	90	-	78:21

Scheme 28: Asymmetric Diels-Alder reaction catalyzed by CIILs.



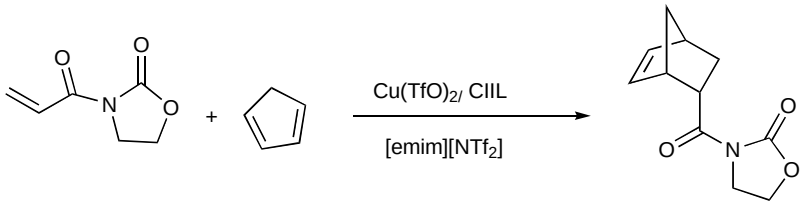
CIIL	Condition	Yield (%)	ee (%)	dr(%)	Ref.
 CIIL 47	CIIL (0.5 equv.) 5 h at 30 ^{o}C	74	-	68	87
 CIIL 48	CIIL (0.5 equv.) 5 h at 30 ^{o}C	40	-	65	87

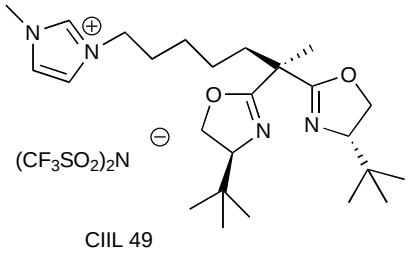
Scheme 29: Aza-Diels-Alder reaction catalyzed by CIILs.

derived CIIL 50 as a catalyst for the aza-Diels-Alder reaction (Scheme **31**) [35]. The products were obtained in good yields (up to 93%) with excellent enantioselectivities (>99% ee) and diastereo-selectivities (endo:exo up to >99:1). The catalytic system could be recycled six times without loss of activity.

2.7. Enantioselective Hydrogenation

Transition metal catalysts consisting of chiral metal complexes are commonly used in enantioselective hydrogenation reactions. Schulz *et al.* reported the first asymmetric synthesis where this reaction was carried out solely via the ion-pairing effect of a CIL as the only source of chirality [36]. The chiral anionic ionic liquid N-



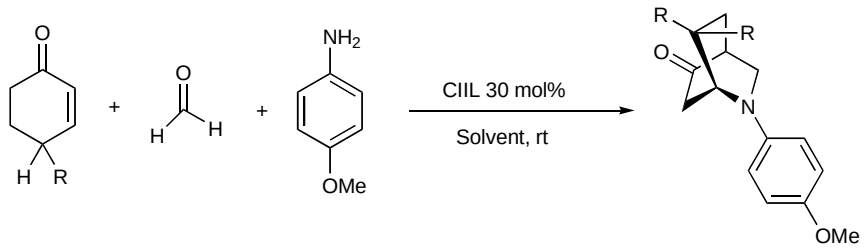
CIIL	Condition	Yield (%)	ee (%)	dr(endo:exo)	Ref.
 CIIL 49	$Cu(TfO)_2$ 10 mol % CIIL 10 mol % in $[emim][NTf_2]$ 2 min	100	84(endo)	88:12	88

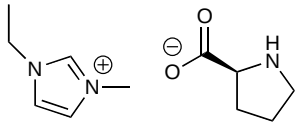
Scheme 30: Bis-oxazoline modified CIILs catalyzed aza-Diels-Alder reaction.

methylimidazolium (*R*)-camphorsulfonate (Scheme **32**) was reacted with methyl vinyl ketone in a Michael-type addition to obtain N-(3 -oxobutyl)-N-methylimi-dazolium (R)-camphorsulfonate. The hydrogenation of this pro-chiral cation under heterogeneous conditions with Ru/C catalyst in ethanol solution yielded the corresponding hydroxybutyl derivative in quantitative yield and up to 80% ee. The importance of the ion-paring effect on enantioselectivity was confirmed by the strong dependence of concentration of the imidazolium salt to the observed enantiomeric excess of the hydrogenated cation as well as the absence of enantioselctivity (<5% ee) for the hydrogenated product of the nonionic substrate acetophenone.

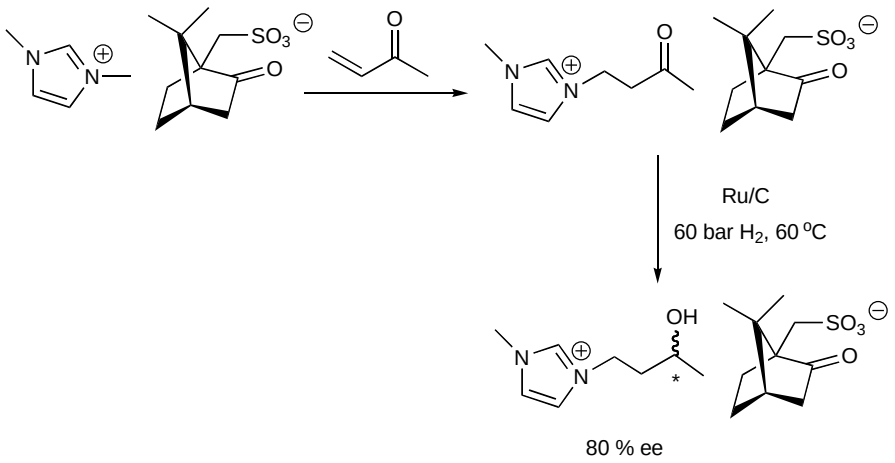
2.8. Enantioselective Aldol Reaction

Natalia and his group have reported a CIIL for asymmetric syn-aldol reactions using (S)-Threonine/α,α-(S)-diphenylvalinol, imidazolium chiral ionic liquid as a efficient catalyst [37]. Chiral ionic liquids containing (S)- or (R)-threonine amide and α,α-(S)-diphenylvalinol units have synthesized in the presence of the (S)-threonine-derived catalyst reactions between ketones with secondary carbon atom(s) at the α-position with respect to the carbonyl group and aromatic (heteroaromatic) aldehydes afforded the corresponding syn-aldols in high yields (up to 99%) and with high diastereo-(syn/anti up to 97:3)

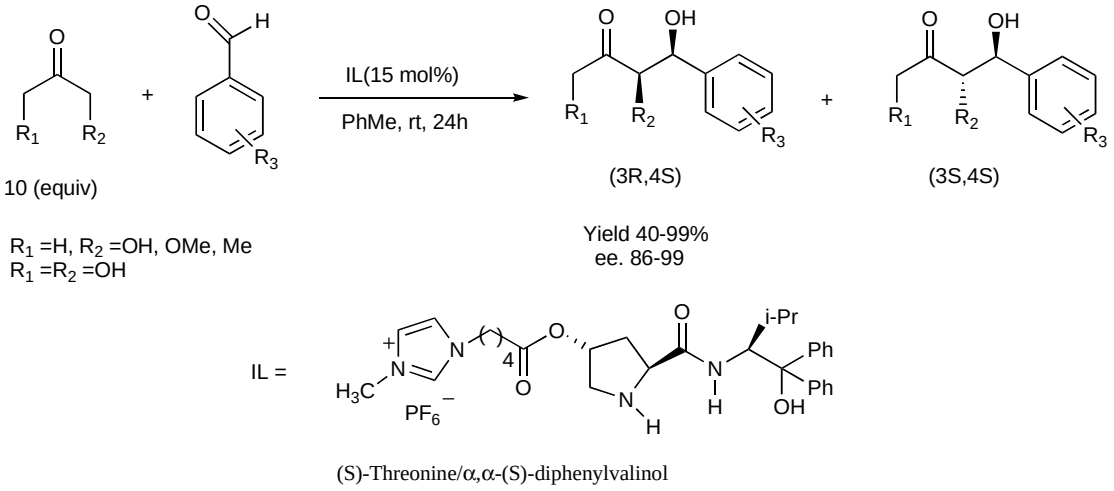


CIIL	Condition	Yield (%)	ee (%)	dr(endo:exo)	Ref.
 CIIL 50	R= H CIIL 30 mol % in DMSO 15 h at rt.	75	98 (endo)	84:16	89
	R= H CIIL 30 mol % in DMSO 15 h at rt.	72	99 (endo)	99:1	

Scheme 31: 2-pyrrolidinecarboxylicacid derived CIIL as a catalyst for the aza-Diels-Alder reaction.



Scheme 32: Enantioselective hydrogenation of keto functionalized ionic liquid.



Scheme 33: Aldol reaction in (S)-Threonine/α,α-(S)-diphenylvalinol chiral ionic liquid.

and enantioselectivity (up to 99% ee), which have maintained over three reaction cycles (Scheme **33**).

3. CONCLUSIONS

The field of task-specific imidazolium based chiral ionic liquids is only in its infancy, but has a very promising future. The main advantage of these types of ionic liquids is that they are easily recovered and recycled without loss of activity when used for asymmetric reactions. Owing to a readily available source of chiral compounds such as naturally occurring amino acids and other compounds, which can serve as precursors in the synthesis of chiral ionic liquids-a new opportunity now exists for the synthesis of a very important class of organic compounds. The past few years have seen a tremendous growth in the number of chiral ionic liquids synthesized, but their effect on the outcome of asymmetric reactions has been limited, with most still giving low enantioselectivities. Therefore, a need exists for the development of additional, improved, and task-specific imidazolium chiral ionic liquids that are better able to influence the outcome of asymmetric reactions.

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