

Chiral Imidazolium Ionic Liquids: Their Synthesis and Influence on the Outcome of Organic Reactions



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1. Introduction

Research in the field of ionic liquids (ILs) has grown exponentially in recent years. The need to have alternative solvents that are environmentally friendly, and can serve as effective substitutes for conventional organic solvents, has driven this rapid growth. The first report of a room-temperature ionic liquid appeared in 1914;¹ since then, ionic liquids have been utilized in numerous applications, including as electrolytes for batteries.² Ionic liquids seem to be ideal replacement solvents, since they are typically liquids below 100 °C and are thermally stable over a very wide temperature range; some maintain their liquid state at temperatures as high as 200 °C.³ Ionic liquids consist of cations and anions and, owing to the very strong ion-ion interactions, they exhibit low vapor pressures and high boiling points. The

factors that dictate their physical properties depend on the nature of both the cation and anion. Ionic liquids that contain aromatic heterocyclic cations tend to have lower melting points than those containing aliphatic ammonium ions. Ionic liquids that contain highly electronegative anions, such as organic amides, typically have lower melting points than those containing halide anions. As a result, most ionic liquids that can serve as effective organic solvents consist of imidazolium or pyridinium cations and anions such as AlX_4^- , BF_4^- , PF_6^- , CF_3SO_3^- , $(\text{CF}_3\text{SO}_3)_2\text{N}^-$, or halides.

The modification of the structures of the cations or anions of ionic liquids can result in unique solvent properties that dramatically influence the outcome of various reactions, including asymmetric reactions. Recently, there has been a dramatic increase in the use of room-temperature ionic liquids (RTILs) as solvents for organic synthesis.⁴ RTILs have become the solvents of choice for 'green chemistry' and are employed in a wide variety of reactions.⁵ One of the main advantages of ionic liquids as solvents over conventional ones is that RTILs are typically recyclable.

Ionic liquids that have gained widespread use as solvents for organic reactions can be divided into two categories: chiral and achiral RTILs. Owing to the vast number of structurally different RTILs that have been synthesized, this review focuses on imidazolium ionic liquids that possess chirality either in the imidazolium moiety or in the anion moiety. It discusses first the design and synthesis of chiral imidazolium ionic liquids, and then highlights their influence on the outcome of asymmetric reactions.

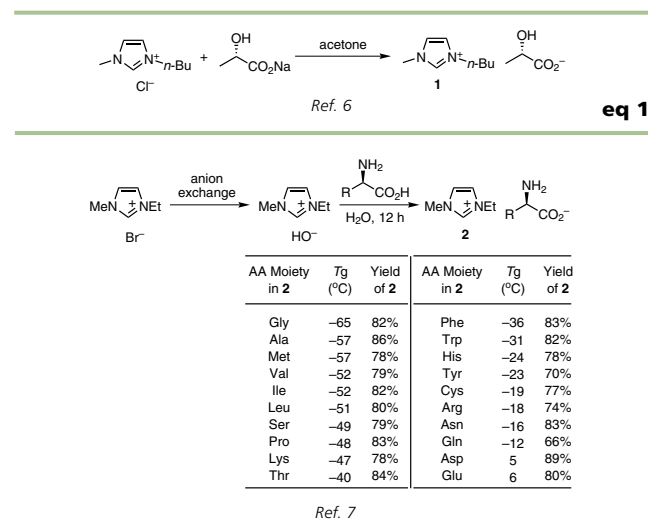
2. Design and Synthesis of Chiral Imidazolium Ionic Liquids (CIILs)

2.1. CIILs of Chiral Anions

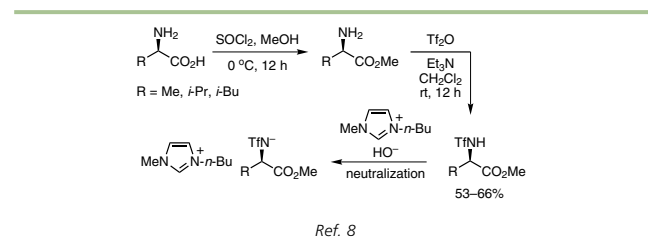
In 1999, Seddon and co-workers reported the first example of a chiral ionic liquid, 1-*n*-butyl-3-methylimidazolium L-lactate ([BMIM][lactate], **1**), prepared simply by reacting sodium (*S*)-2-hydroxypropionate and [BMIM]Cl in acetone, followed by a straightforward workup (eq **1**).⁶

The synthesis of other ionic liquids that contain chiral anions relies on anion-exchange techniques. For example, Ohno's research group synthesized 20 room-temperature chiral ionic liquids (RTCILs) in which the chiral anions were derived from naturally occurring amino acids. The synthesis involved two steps: the conversion of 1-ethyl-3-methylimidazolium bromide ([EMIM][Br]) into 1-ethyl-3-methylimidazolium hydroxide ([EMIM][OH]) using an anion-exchange resin, followed by neutralization with a series of natural amino acids to give amino acid ionic liquids **2** (Scheme 1).⁷

These ionic liquids are transparent and nearly colorless liquids at room temperature; they are miscible with various organic solvents such as methanol, acetonitrile, and chloroform. However, chiral ionic liquids that are similar to **2** and contain two carboxyl groups—[EMIM][Glu] and [EMIM][Asp]—are insoluble in chloroform. Nineteen of the 20 ionic liquids are thermally stable at temperatures above 200 °C; only [EMIM][Cys]



Scheme 1. Synthesis of Ionic Liquids of Chiral Anions from Amino Acids.



Scheme 2. Preparation of CIILs from Amino Acid Derivatives.

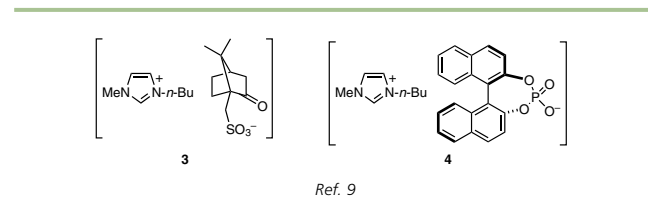
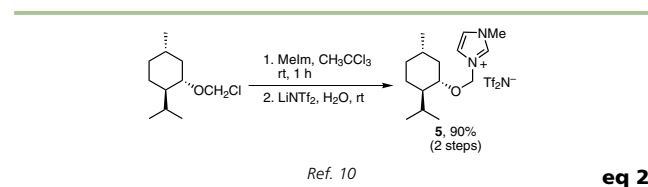


Figure 1. Chiral Imidazolium Ionic Liquids of Chiral Anions.



eq 2

exhibits thermal stability up to 173 °C. The authors also explored the effects different side chains have on the glass transition-temperature (T_g) of ionic liquids in the temperature range -65 °C to 6 °C. It was observed that an increase in the length of the alkyl side chain results in a gradual increase in T_g , which was attributed to an increase in the van der Waals attraction between the alkyl groups.

More recently, Fukumoto and Ohno reported the synthesis of a new category of CIILs, which contain chiral anions derived from amino acid derivatives (Scheme 2).⁸ Conversion of amino acids into their methyl esters with thionyl chloride in methanol, followed by treatment with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane, gave the corresponding methyl esters of *N*-trifluoromethanesulfonylamino acids. An exchange reaction of the ester with an aqueous solution of [BMIM][OH] afforded the desired CIILs as liquids at room temperature. It was observed that the melting points and glass-transition temperatures for these CIILs are higher than those of the typical hydrophobic CIILs shown in Scheme 1.

Other naturally occurring molecules have also served as starting materials for the synthesis of chiral ionic liquids that contain chirality in the anionic moiety. Machado and Dorta described the synthesis of CIILs **3** and **4** on a multigram scale by a simple exchange of commercially available [BMIM]Cl with the potassium salts of (*S*)-10-camphorsulfonate and (*R*)-1,1'-binaphthyl-2,2'-diylphosphate in CH_2Cl_2 - H_2O (Figure 1).⁹ Both salts are hygroscopic; **3** is a very viscous golden oil, while **4** is a white solid with a melting point of 78–80 °C. As the preceding examples demonstrate, anion exchange using chiral anions is a proven technique for synthesizing CIILs that contain the chirality in the anionic moiety.

2.2. CIILs of Chiral Cations

A greater number of known chiral ionic liquids derive their chirality from the cationic moiety. Owing to the ready availability of naturally occurring chiral amines, alcohols, and amino acids, they are typically the most prevalent in CIILs of chiral cations.

2.2.1. CIILs from Chiral Chlorides, Amines, and Alcohols

Commercially available (+)- and (-)-chloromethyl menthyl ethers have been used for the preparation of both enantiomers of CIIL **5** in two steps: alkylation followed by anion exchange (eq 2).¹⁰ In 2003, Bao et al. reported the synthesis of a chiral imidazolium ionic liquid with cationic chirality obtained from the chiral amine (*R*)-(+)- α -methylbenzylamine.¹¹ Imidazolium salt **7** was obtained in three steps involving condensation of the chiral amine with ammonia, glyoxal, and formaldehyde; alkylation with bromoethane in CH_2Cl_2 ; and anion exchange with NaBF_4 in acetone (Scheme 3). Unfortunately, due to the high melting point of this ionic liquid (90 °C), it could not serve as an effective solvent for asymmetric reactions.

A similar strategy was utilized for the preparation of ionic liquid **8**, which contains two chiral centers, each bonded to a nitrogen atom of the imidazolium cation. For this synthesis, two equivalents of α -methylbenzylamine were consumed and an overall yield of 30% was obtained (eq 3).¹⁰

Recently, Génisson et al. also used (*R*)-(+)- α -methylbenzylamine as the starting material for a series of novel chiral imidazolium derivatives (Scheme 4).¹² Alkylation of (*R*)-(+)- α -methylbenzylamine with chloroethylamine gave chiral 1,2-diamines, which were subjected to a ring-closing reaction with an appropriate ortho ester electrophile to obtain

4,5-dihydroimidazoles. Dehydrogenation of the dihydroimidazoles with manganese-based oxidants gave various C-2 substituted and unsubstituted imidazole rings. The target CIILs, **9**, were obtained by N-alkylation with *n*-pentyl bromide and anion exchange with NaBF₄ or LiNTf₂. The resulting BF₄⁻ and Tf₂N⁻ salts are water-immiscible liquids at room temperature, and their glass-transition temperatures are as low as -39 °C and -48 °C, respectively.

The chiral alcohols (*S*)-2-hexanol and (*R*)- α -methylbenzyl alcohol were utilized for the preparation of a similar type of chiral imidazolium ionic liquid.¹³ The Mitsunobu alkylation of imidazole was the key step leading to chiral *N*-alkyl-substituted imidazoles. The configuration of the stereogenic carbinol carbon was confirmed by comparison with authentic samples. The inversion of configuration was virtually complete (>99%) in the case of (*S*)-2-hexanol, but only an 86% selectivity was observed in the case of (*R*)- α -methylbenzyl alcohol. Two of the chiral *N*-alkyl-substituted imidazoles were used as precursors in the synthesis of the corresponding CIILs by N-alkylation with iodomethane (Scheme 5).

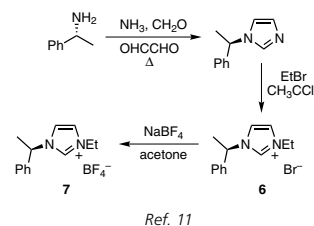
Commercially available (1*S*,2*S*,5*S*)-(-)-myrtanol has also been used as a precursor in the synthesis of another class of CIILs. Imidazolium tosylate salt **11** was formed in 63% yield from the reaction of tosylate **10** and neat imidazole at 100 °C for 24 h (Scheme 6).⁹

Novel, (3*R*)-citronellol-based CIILs have been synthesized starting with the bromination of (3*R*)-citronellol with Br₂ and PPh₃ in CH₂Cl₂ at room temperature to give the corresponding citronellyl bromide (Scheme 7).¹⁴ Heating of this bromide with 1-alkyl-1*H*-imidazoles for several days provided the imidazolium bromide salts which, after anion exchange with NaBF₄ in acetone, led to the corresponding imidazolium tetrafluoroborates in 46–94% yields. In addition, 1,3-dicitronellyl-1*H*-imidazolium bromide was obtained by deprotonation of 1*H*-imidazole with (*n*-Bu)₄NOH and subsequent treatment with 2 equivalents of the chiral bromide. All the (3*R*)-citronellol-based CIILs thus prepared are liquids at room temperature.

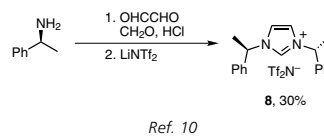
2.2.2. CIILs from Amino Acids and Amino Acid Derivatives

Amino acids form one of the most prominent pools of natural products that can serve as precursors for chiral ionic liquids. In 2003, Bao and co-workers reported, for the first time, the synthesis of CIILs from natural amino acids. Using L-alanine, L-leucine, or L-valine as the chiral starting material, they prepared chiral ionic liquids with one chiral carbon in four steps and in 30–33% overall yields (Scheme 8).¹¹ The imidazole ring was formed by condensation of the amino functionality of the amino acid with formaldehyde, glyoxal, and aqueous ammonia under basic conditions. The initially formed sodium salts were esterified with anhydrous ethanol saturated with dry hydrogen chloride. Reduction of the resulting ethyl esters using LiAlH₄ in anhydrous Et₂O led to the corresponding alcohols, which were subjected to alkylation with bromoethane to afford the desired CIILs possessing melting points in the 5–16 °C range. These CIILs are miscible with water, methanol, acetone, and other very polar organic solvents; they are immiscible with weakly polar organic solvents, such as ether and 1,1,1-trichloroethane.

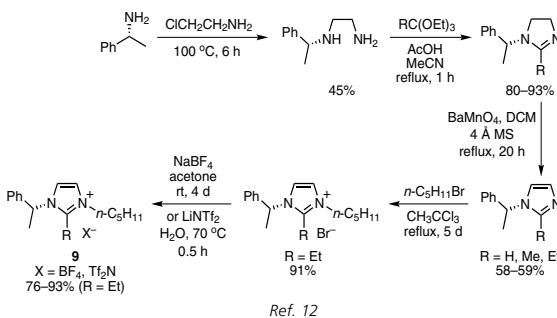
More recently, Xu and co-workers described the synthesis and properties of novel chiral amine-functionalized ionic liquids, which were derived from the natural amino acids L-alanine, L-valine, L-leucine, L-isoleucine, and L-proline in four steps (Scheme 9).¹⁵ The key precursors, **12**, were obtained by reduction of the amino acids with NaBH₄/I₂, followed by a



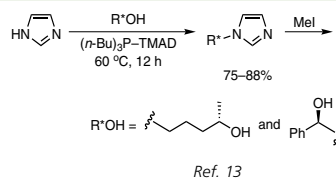
Scheme 3. Bao's Synthesis of CIILs from (*R*)-(+)- α -Methylbenzylamine.



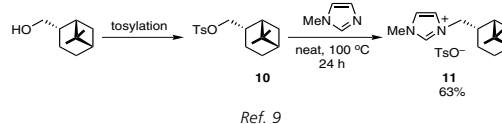
Scheme 4. G nisson's Synthesis of CIILs from (*R*)-(+)- α -Methylbenzylamine.



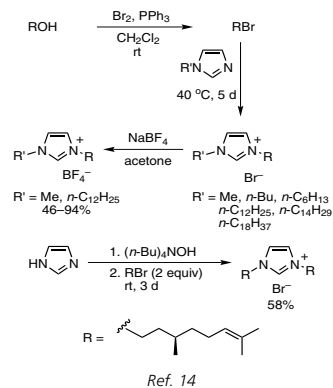
Scheme 4. G nisson's Synthesis of CIILs from (*R*)-(+)- α -Methylbenzylamine.



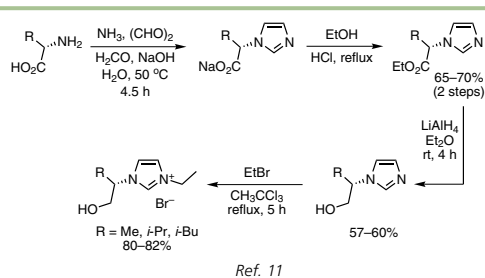
Scheme 5. Synthesis of CIILs by a Mitsunobu Alkylation.



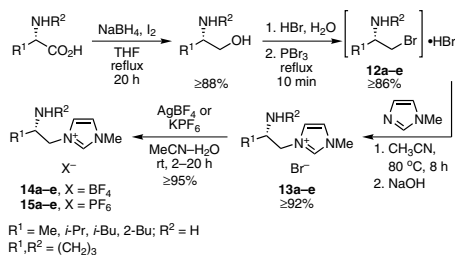
Scheme 6. Synthesis of (-)-Myrtanol-Based, Chiral Imidazolium Tosylate Salt.



Scheme 7. Synthesis of CIILs from (3*R*)-Citronellol.



Scheme 8. CIILs from Naturally Occurring Amino Acids.

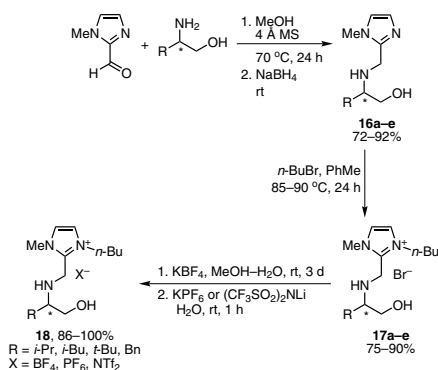


Scheme 9. Chiral-Amine-Functionalized CIILs from Natural Amino Acids.

Table 1. Properties of CIILs **13a–e**, **14a–e**, and **15a–e**.

No.	R ¹	R ²	X	T _m , °C	T _g , °C	T _{dec} , °C
13a	Me	H	Br	131	---	226
13b	<i>i</i> -Pr	H	Br	145	---	270
13c	<i>i</i> -Bu	H	Br	134	---	267
13d	2-Bu	H	Br	135	---	268
13e	-(CH ₂) ₃ -	H	Br	141	---	257
14a	Me	H	BF ₄	---	-46	261
14b	<i>i</i> -Pr	H	BF ₄	---	-49	281
14c	<i>i</i> -Bu	H	BF ₄	---	-47	291
14d	2-Bu	H	BF ₄	---	-35	285
14e	-(CH ₂) ₃ -	H	BF ₄	---	-45	291
15a	Me	H	PF ₆	6	---	218
15b	<i>i</i> -Pr	H	PF ₆	---	38	287
15c	<i>i</i> -Bu	H	PF ₆	69	---	287
15d	2-Bu	H	PF ₆	73	---	281
15e	-(CH ₂) ₃ -	H	PF ₆	---	67	274

^a The melting point (T_m) and glass-transition temperature (T_g) were determined by DSC. ^b T_{dec} was determined by TG.



Scheme 10. Synthesis of CIILs Lacking an Acidic Hydrogen at C-2 of the Imidazolium Ring.

neutralization step and bromination with PBr₃. N-alkylation of **12** with methylimidazole in refluxing acetonitrile followed by neutralization with NaOH gave bromides **13a–e**. Anion exchange with AgBF₄ or KPF₆ in MeCN–H₂O at room temperature afforded **14a–e** or **15a–e** in 66–71% overall yields. Ionic liquid bromides **13a–e** have higher melting points (T_m's) or glass-transition temperatures (T_g's) than the corresponding tetrafluoroborates, **14a–e**. All exhibit thermal stability up to 210 °C (**Table 1**) and are more miscible in polar solvents and less miscible in nonpolar solvents than the related unfunctionalized imidazolium-type ionic liquids.

Amino acid derivatives in the form of amino alcohols are also good starting materials for the synthesis of CIILs. Recently, our group designed and synthesized a new family of CIILs from chiral amino alcohols (**Scheme 10**).¹⁶ This was the first time that CIILs have been synthesized by introducing chiral scaffolds at the C-2 position of the imidazolium cation of ILs. Owing to the relative acidity of the hydrogen in the C-2 position,¹⁷ the introduction of substituents at this position should result in a more inert category of chiral ionic liquids for reactions carried out under basic conditions.

The synthesis involved the condensation of 1-methyl-2-imidazolecarboxaldehyde and chiral amino alcohols [(*S*)-(+)-2-amino-3-methyl-1-butanol, (*S*)-leucinol, (*R*)-leucinol, (*S*)-*tert*-leucinol, or (*S*)-3-phenyl-2-aminopropanol] in MeOH to give the corresponding Schiff base precursors, which were reduced *in situ* with NaBH₄ to give the desired chiral imidazole derivatives **16a–e** in 72–92% yields. N-Alkylation was carried out by heating imidazoles **16a–e** with one equivalent of bromobutane in toluene at 85–90 °C for 24 h to form imidazolium bromides **17a–e**. Anion exchange of these salts with various anions [BF₄⁻, PF₆⁻, (CF₃SO₂)₂N⁻] afforded a series of CIILs, **18**, in good yields as colorless oils at room temperature. These new ionic liquids avoid the shortcomings of their traditional C-2-unsubstituted counterparts, which can participate in deprotonation side reactions at their C-2 position.¹⁸

More recently, Ou and Huang¹⁹ developed a practical and efficient method for synthesizing CIILs from chiral amino alcohols in two or three steps. Chiral imidazolium chlorides, **19**, were obtained in good yields by reacting 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride with chiral primary amino alcohols in *n*-butanol under reflux for 18–22 h. Anion exchange of chlorides **19** with fluoroboric acid or potassium hexafluorophosphate afforded a new category of CIILs, **20** and **21**, in 67–81% overall yields (**Scheme 11**).

2.2.3. CIILs from Proline and Histidine

The amino acid proline is a very versatile starting material for the synthesis of chiral ionic liquids; it is readily available, inexpensive, and chiral. Recently, Luo et al. designed and synthesized a series of pyrrolidine-containing CIILs from L-proline (**Scheme 12**).²⁰ Reduction of L-proline with LiAlH₄ followed by reaction with Boc₂O generated the corresponding N-Boc-protected (*S*)-prolinol. Tosylation followed by nucleophilic substitution with imidazolite anion gave the desired chiral imidazole derivative, **22**. Butylation of **22** and removal of Boc gave the pyrrolidine-based imidazolium bromide salt **24a** in 45% overall yield from L-proline. Anion exchange of **24a** with NaBF₄ or KPF₆ afforded CIILs **24b** and **24c**, respectively. Using a similar procedure, the authors synthesized various other CIILs, **25a–c**, that contain a methyl group at C-2 of the imidazolium moiety, and **26a,b**, that vary in the type of substitution at positions 1 and 2 of the imidazolium

fragment. CIILs **24–26** are viscous liquids at room temperature and soluble in moderately polar solvents such as chloroform, dichloromethane, and methanol; but insoluble in less polar solvents such as diethyl ether, ethyl acetate, and hexane.

Miao and Chan described the synthesis of other types of CIIL from proline (**Scheme 13**).²¹ Coupling of ionic liquid **27** with commercially available Boc-Pro-OH in the presence of DCC–DMAP afforded the ionic-liquid-supported Boc-proline **28** which, upon deprotection with trifluoroacetic acid, gave TFA salt **29**. The synthesis of CIIL **32**, which retains the free carboxylic acid group, utilized a variation of this method. After coupling the ionic liquid carboxylic acid **30** with the readily available *N*-Cbz-(*2S,4R*)-4-hydroxyproline benzyl ester, the resulting supported proline **31** was deprotected by hydrogenation to afford the ionic-liquid-supported proline **32** in very good yield and high purity.

More recently, our group designed and synthesized a new pyrrolidine-based CIIL, **35**, from *L*-proline (**Scheme 14**).²² The reaction of 3-chloropropanesulfonyl chloride with (*S*)-2-aminomethyl-1-Boc-pyrrolidine, readily obtained from *L*-proline, provided sulfonamide **33**. Conversion of **33** into imidazolium iodide **34** was accomplished in 86% yield (2 steps) first by iodination with NaI and then alkylation of the resulting 3-iodopropanesulfonamide with 1-methylimidazole in CH₃CN. CIIL **35** was obtained in 88% yield (2 steps) by cleavage of the Boc group, followed by anion exchange with Tf₂N⁻.

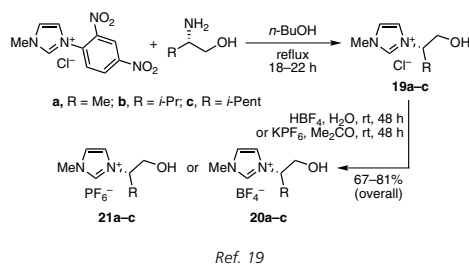
Histidine is a unique amino acid for the synthesis of imidazolium-containing ionic liquids since it is chiral and incorporates an imidazole fragment in its structure. Erker and co-workers were first to exploit histidine as a starting material for CIILs (**Scheme 15**).²³ *L*-Histidine was O-protected by methyl ester formation and then N-protected with benzoyl or Boc to give the CIIL precursors **36a** and **36b**. Treatment of **36a** with *n*-propyl bromide or isopropyl iodide under basic conditions in CH₃CN at reflux for several days gave CIILs **37a** and **37b**, respectively. CIILs **37c,d** were obtained similarly from histidine derivative **36b**. CIILs **37** exhibit high water solubility and have melting points in the range 39–55 °C.

A year later, Guillen et al. employed histidine as the starting material in the synthesis of a new series of imidazolium-containing chiral ionic liquids, in which the bifunctional unit of histidine remained unchanged (**Scheme 16**).²⁴ Protection of histidine methyl ester via a cyclic urea structure, followed by alkylation with iodomethane and opening of the cyclic urea by *t*-BuOH in the presence of (*i*-Pr)₂NEt, gave histidine derivative **38**. Alkylation of **38** with bromobutane followed by anion exchange afforded CIILs **39a–c** in 65–90% yields. CIILs **39a–c**, possessing an ester and a protected amine functional groups, were conveniently transformed into various other chiral ionic liquids by known reactions (**Scheme 17**).²⁴

2.2.4. CIILs from Lactate and Tartrate

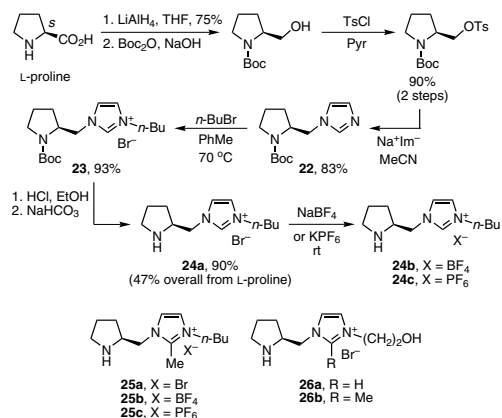
In 2004, Jodry and Mikami reported the synthesis of a new category of hydrophobic CIILs from commercially available and inexpensive (*S*)-ethyl lactate (**Scheme 18**).²⁵ (*S*)-Ethyl lactate was converted into the triflate derivative, which was N-alkylated to give the corresponding imidazolium triflate salt. Exchange of the triflate anion with the anions of HPF₆, LiNTf₂, Li(SO₂C₂F₅)₅, and LiN(SO₂C₄F₉)Tf provided a series of hydrophobic CIILs that are liquid at room temperature.

The research groups of Bao²⁶ and Kubisa²⁷ have also utilized lactate as a starting material for the preparation of CIILs **40a–c** in 5–6 steps and 54–60% overall yields (**Figure 2**). Ethyl tartrate



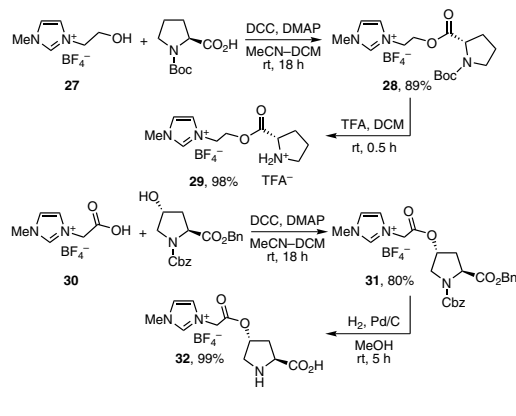
Ref. 19

Scheme 11. Synthesis of CIILs from Chiral Amino Alcohols.



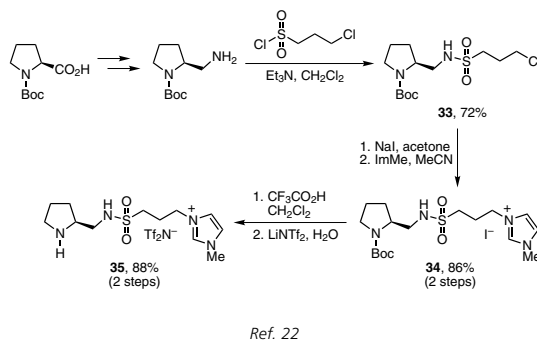
Ref. 20

Scheme 12. Synthesis of Functionalized CIILs from *L*-Proline.



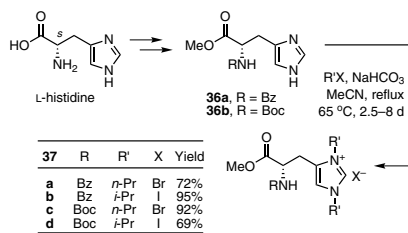
Ref. 21

Scheme 13. Preparation of Ionic-Liquid-Supported *L*-Proline.

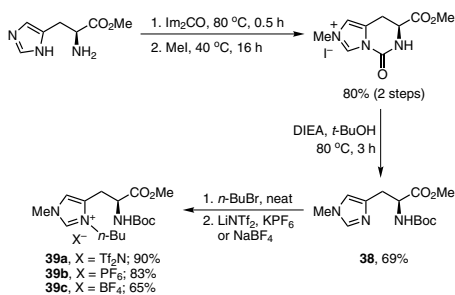


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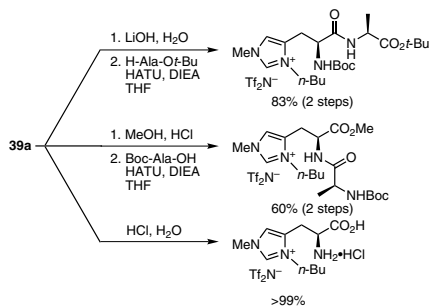
Scheme 14. Synthesis of Pyrrolidine-Based CIILs from *L*-Proline.



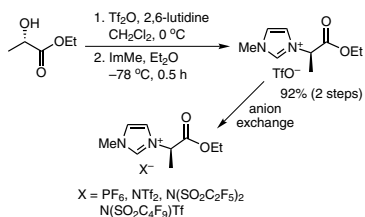
Ref. 23

Scheme 15. Erker's Synthesis of CIILs from Histidine.

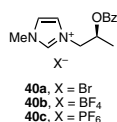
Ref. 24

Scheme 16. Synthesis of O- and N-Protected Histidinium Salts.

Ref. 24

Scheme 17. Transformation of O- and N-Protected Histidinium Salts into Other CIILs.

Ref. 25

Scheme 18. Preparation of Hydrophobic CIILs from (S)-Lactate.

Ref. 26

Figure 2. CIILs from Lactate.

has been employed as a chiral starting material for dicationic CIILs (**Scheme 19**).²⁵ The bis(imidazolium bromide) salt was prepared in five steps from chiral tartrate in 51% overall yield. Anion exchange with NaBF₄ and NH₄PF₆ gave the corresponding bis(imidazolium tetrafluoroborate) and hexafluorophosphate ionic liquids as solids at room temperature with melting points in the 41–90 °C range. Tosyl tartrate has also served as a starting material for the synthesis of a dicationic imidazolium tosylate salt (**eq 4**).⁹

2.2.5. CIILs with Fused and Spiro Rings

The introduction of a rigid skeleton into ionic liquids was envisaged as a method of creating a class of efficient, task-specific solvents capable of inducing asymmetry. Very recently, our group described the synthesis of a novel set of chiral, fused-ring RTILs, in which the chiral moiety is bonded to one of the imidazole nitrogens and, most importantly, in which the 2 position is substituted.²⁸ Treatment of imidazole derivatives **16**¹⁶ with *p*-toluenesulfonyl chloride gave the corresponding double tosylates, **43**, which underwent ring closure at 90 °C in toluene to form fused-ring, chiral tosylate salts **44** (**Scheme 20**). Anion exchange of **44** led to the corresponding PF₆⁻ and NTf₂⁻ CIILs **45a–47** in 63–68% overall yields. At room temperature, CIILs **45a**, **46a**, and **47a** (containing the PF₆⁻ anion) are solids, whereas the NTf₂⁻ anion-containing ones (**45b**, **46b**, and **47b**) are viscous liquids.

Sasai and co-workers synthesized another type of novel, chiral ionic liquid that contains a spiro skeleton (**Scheme 21**).²⁹ The alkylation of diethyl malonate with 2-(chloromethyl)-1-methyl-1*H*-imidazole hydrochloride or 2-(chloromethyl)-1-isopropyl-1*H*-imidazole hydrochloride, followed by reduction with LiAlH₄, produced diols **48** in high yields. Treatment of diols **48** with PBr₃ produced dibromides **49**, which underwent intramolecular N-alkylation smoothly in refluxing toluene to yield spiro imidazolium salts **50**. Anion exchange of the bromide counterions with AgBF₄, AgOTf, LiNTf₂, or bis(heptafluoropropanesulfonyl)imide gave a series of spiro CIILs, **51**. Unfortunately, the melting points of CIILs **50a,b** and **51a,b** are in the neighborhood of 166 °C, while those with the NTf₂⁻ anion (**51c,d**) exhibit lower melting points (68–112 °C). By increasing the length of the fluoroalkyl chain of the counteranion, as in **51e**, CIILs that are liquids at room temperature (*T*_g = –10 °C) were obtained. To obtain CIILs with even lower melting points, Sasai's group prepared unsymmetrical spiro CIILs **52a–d** using a similar synthetic protocol (**Figure 3**). CIIL **52d**, with an *N*-propyl-*N'*-isopropyl substituent and Tf₂N⁻, is a liquid at room temperature with a *T*_g of –20 °C.

2.2.6. CIILs with a Urea Unit

Urea derivatives serve as efficient Lewis acid catalysts in organic reactions due to the effective hydrogen bonds that are formed by their amide hydrogens. Urea compounds that contain electron-withdrawing substituents readily form stable co-crystals with a variety of proton acceptors, including carbonyl compounds.³⁰ Recently, our group synthesized CIILs in which the urea functional group is part of the chiral moiety that is bonded to the imidazolium ring (**Scheme 22**).³¹ Reaction of 1-(3-aminopropyl)imidazole with commercially available isocyanate-substituted amino acid esters in CH₂Cl₂, followed by alkylation with one equivalent of neat iodomethane at 40 °C for 24 h, gave imidazolium iodides **53a–c** in excellent yields. Anion exchange with BF₄⁻, PF₆⁻, and (CF₃SO₂)₂N⁻ produced CIILs **54–56**, all of which are viscous liquids at room temperature.

2.2.7. Other Types of CIIL

In 2002, Saigo's group described the first example of a planar-chiral ionic liquid (**Scheme 23**).³² The cyclophane-type imidazolium salts were obtained in about 40% overall yields by monoalkylation of substituted imidazoles with 1,10-dibromodecane under basic conditions, followed by cyclization of the resulting 1-(10-bromodecyl)imidazoles in refluxing acetonitrile for 8–10 days. The introduction of a substituent at C-4 of the imidazolium ring not only induced planar chirality, but also dramatically lowered the melting point. The substituent at C-2 suppressed the racemization of these planar-chiral cyclophanes.

Using a similar synthetic methodology, planar-chiral imidazolium chlorides with a tris(oxoethylene) bridge were obtained in good yields (81–82%) without any side reactions (**Figure 4**).³³ The high selectivity for the formation of the “crowned” imidazolium salts is most likely due to the conformational preference of the tri(oxoethylene) chain. The vicinal oxygens have a strong tendency to adopt a *gauche* conformation and, as a result, the tri(oxoethylene) chain is expected to form a curved structure that is suitable for the intramolecular cyclization.

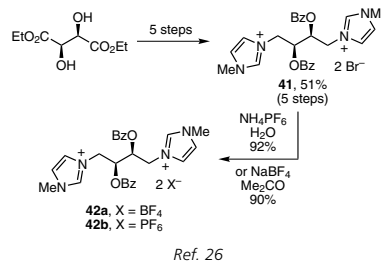
In 2004, Geldbach and Dyson introduced a class of highly active ruthenium catalysts, in which chiral 1,2-diamine or 1,2-amino alcohol ligands are coordinated to ruthenium (**Scheme 24**).³⁴ These new ruthenium complexes also contained η^6 -arenes substituted with 2-(imidazolyl)ethyl groups. Quaternization of 1,2-dimethylimidazole with chloroethylcyclohexadiene and subsequent anion exchange with NaBF_4 yield the functionalized imidazolium ionic liquid **57** as a solid with a melting point of 85 °C. Reduction of RuCl_3 with three equivalents of **57** in methanol under reflux conditions leads to the dinuclear complex **58**, which is insoluble in most common organic solvents, but is highly soluble in water and ionic liquids. Addition of (1*R*,2*R*)-*N*-tosyl-1,2-diphenyl-1,2-ethylenediamine or (1*S*,2*R*)-2-amino-1,2-diphenylethanol to **58** in DMF affords cationic complexes **59** and **60**, respectively, in excellent yields.

3. Applications of CIILs in Asymmetric Reactions

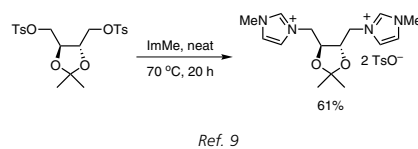
3.1. As Solvents

Seebach and Oei first introduced the idea of using chiral solvents to influence the outcome of asymmetric reactions back in 1975.³⁵ Since that time, there have been many attempts to use chiral solvents to affect the outcome of asymmetric reactions, but the observed enantioselectivities have been fairly low. This has led to the conclusion that asymmetric induction effected by chiral solvents is typically low. 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.

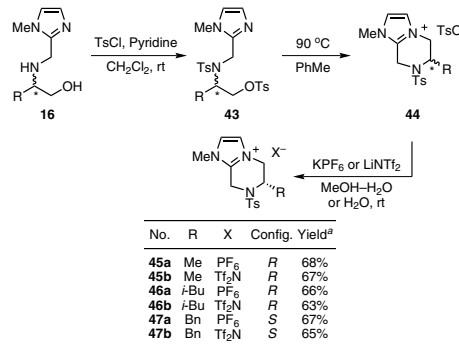
In 2005, Armstrong and co-workers reported the use of CIILs as chiral solvents for the photorearrangement of dibenzocyclo[2.2.2]octatrienes.¹⁰ This was the first report on chiral induction by CIILs for an irreversible, unimolecular photochemical isomerization, with enantioselectivities ranging from 3.3% to 6.8% ee (**eq 5**). The enantioselectivity increased to 11.6% ee when chiral ammonium ionic liquids were used as solvents. The authors did not observe any enantioselectivity when the corresponding methyl or isopropyl diesters were



Scheme 19. Synthesis of Bis(CIILs) from Tartrate.



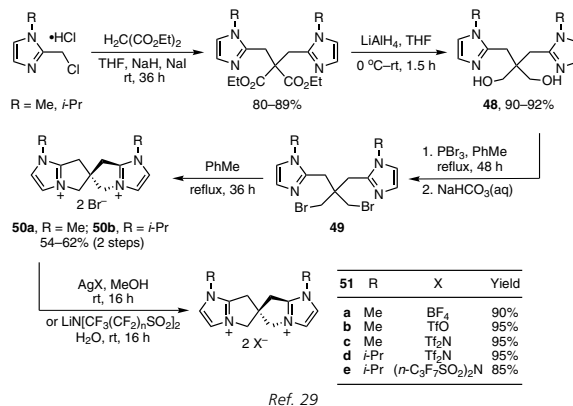
eq 4



^a Overall yield from **16**.

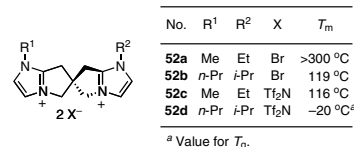
Ref. 28

Scheme 20. Synthesis of Fused-Ring CIILs.



Ref. 29

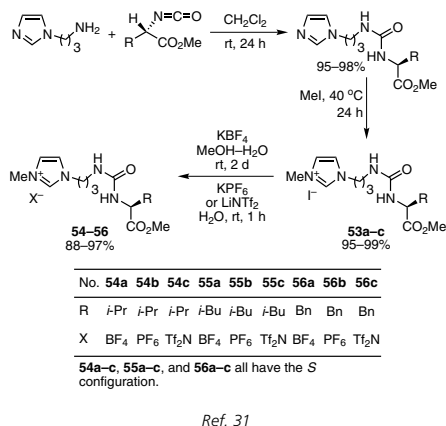
Scheme 21. Synthesis of Symmetric, Spiro Bis(imidazolium) Salts.



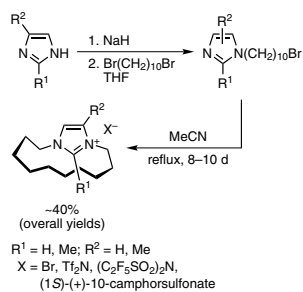
^a Value for T_g.

Ref. 29

Figure 3. Physical Properties of Unsymmetrical Spiro Bis(imidazolium) Salts.



Scheme 22. Chiral, Ionic Liquids Containing a Urea Functionality.



Scheme 23. Cyclophane-Type Chiral Imidazolium Salts.

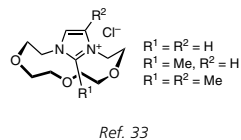
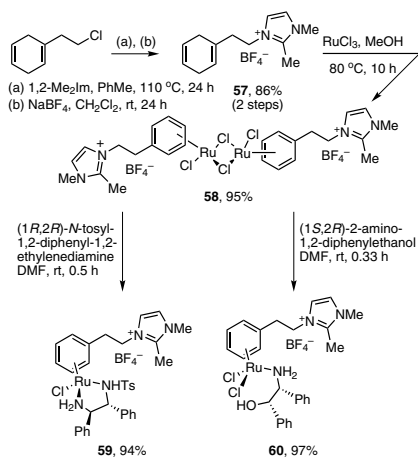


Figure 4. Planar-Chiral Imidazolium Salts with a Tris(oxoethylene) Bridge.



Scheme 24. Synthesis of Ruthenium-Based CIIL Catalysts.

employed, but noted increased enantioselectivities when the diacid was utilized in the presence of NaOH. It is believed that NaOH allows ion-pair formation by deprotonating the diacid; however, more complex interactions with the chiral discriminator may be at play.

Bao and co-workers have utilized CIILs **40a-c** and **42b** as chiral co-solvents in the asymmetric Michael addition of diethyl malonate to 1,3-diphenyl-2-propenone (**eq 6**).²⁶ Except in the case of **42b**, better results were obtained in toluene than in DMSO or DMF. Comparable chemical yields and enantioselectivities were obtained with **40a-c**, which differ only in their anions, with CIIL bromide **40a** giving the best yield and ee of the three.

More recently, Ou and Huang also reported on the same asymmetric Michael addition using CIILs **19-21** and acetonitrile as co-solvent (**eq 7**).¹⁹ They found that most of these CIILs exhibited some chiral discrimination, with CIIL **20c** giving rise to the best ee (15%).

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 (**eq 8**).³⁶ The transformation gave low yields (13–28%) and poor enantioselectivities (4–5%) with Pd(OAc)₂ and PdCl₂. No asymmetric induction was observed when Ph₃P was added as auxiliary ligand.

3.2. As Organocatalysts

Metal-free catalysis of asymmetric reactions by simple organocatalysts has become an important area of research in recent years.³⁷ Among today's organocatalysts, proline and its derivatives are particularly interesting. Pyrrolidine catalysts have been used successfully for the direct asymmetric aldol and Michael addition reactions,³⁷ which are regarded as two of the most powerful carbon-carbon-bond-forming reactions in organic synthesis.³⁷ 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, 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.

Recently, Miao and Chan reported proline-based chiral imidazolium ionic liquid **29** as organocatalyst for the direct asymmetric aldol reaction of 4-cyanobenzaldehyde with acetone, but obtained the aldol product, **61a**, in only 10% yield and 11% ee. CIIL **32** fared better as organocatalyst under the same conditions, leading to **61a** in 59% yield and 72% ee (**eq 9**).²¹ 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 organocatalyst **32** under the same conditions. Furthermore, the authors carried out the reactions of 4-nitrobenzaldehyde in deuterated acetone with CIIL **32** or proline as catalyst, respectively, and proved that CIIL **32** is a more efficient organocatalyst than proline itself. The recyclability of CIIL **32** as organocatalyst was also examined (**eq 10**). CIIL **32** was recycled and reused at least four times in the same reaction without significant loss in yield and enantioselectivity.

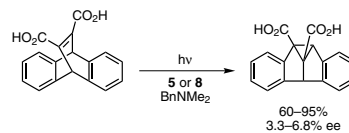
Functionalized CIILs **24a–26b** have been employed as highly efficient asymmetric organocatalysts for the Michael addition of cyclohexanone to nitroalkenes (eq 11).²⁰ CIILs **24a–c** and **26a**, lacking a substituent at C-2 of the imidazole ring, were superior to their 2'-methyl counterparts (**25a–c** and **26b**) in terms of yields and selectivities. Introduction of a protic group (OH) in the side chain (see **26a,b**) did not improve the catalytic activity and selectivity, and CIILs with Br⁻ and BF₄⁻ were much more active and selective than those with PF₆⁻. Overall, catalysts **24a–b** performed best, leading to near-quantitative yields, excellent diastereoselectivities (syn/anti = 99:1), and enantioselectivities (97–99% ee's). These CIILs were easily recycled by precipitation with diethyl ether, and they maintained their high activity albeit with a slightly decreased selectivity, as demonstrated for **24b** over four reaction cycles.

The scope of the preceding reaction was investigated with respect to the ketone and the nitroalkene. Cyclohexanone reacted with a variety of nitroalkenes to generate Michael adducts in near-quantitative yields (94–100%), high diastereoselectivities (dr ≥ 97:3), and excellent enantioselectivities (95–99% ee). Substituting cyclopentanone or acetone for cyclohexanone showed only moderate selectivities, whereas the use of an aldehyde instead of cyclohexanone led to good selectivities (eq 12).

Our group also has developed a new type of pyrrolidine-based CIIL, **35**, which catalyzes the Michael addition of various aldehydes to nitroalkenes in Et₂O at 4 °C with moderate yields (≤64%), good enantioselectivities (≤82% ee), and high diastereoselectivities (syn:anti ≤ 97:3) (eq 13).²² Moreover, catalyst **35** also catalyzes the Michael addition of cyclohexanone to *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 an 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 newly designed ionic-liquid-tethered chiral pyrrolidine catalyst, **35**, is easily recycled without loss of activity.

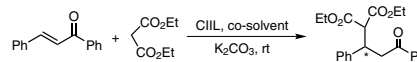
3.3. As Organometallic Catalysts

The transfer-hydrogenation reaction, in which a ruthenium complex is employed as catalyst, has attracted considerable interest.³⁸ Dyson's group has attached a ruthenium complex with chiral ligands onto an ionic liquid, and examined the resulting ruthenium ionic liquids, **59** and **60**, as catalysts for the asymmetric transfer hydrogenation of acetophenone (eq 14).³⁴ The reaction was carried out in 2-propanol with 2 equivalents of KOH and **60** as organometallic catalyst in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [BDMIM][PF₆], as solvent to give the adduct with 95% conversion and 27% ee for the first run. Even under less basic conditions, catalyst **60** was deactivated quickly, and reuse of the ionic liquid phase was not viable. However, catalyst **59** was stable under the reaction conditions for at least 72 h, and recycling of the ionic-liquid phase was feasible, but conversion dropped from 80% in the first cycle to 21% in the fourth cycle. When a formic acid–triethylamine azeotrope was substituted for 2-propanol–KOH as the proton source, catalyst **59** provided essentially quantitative conversion and excellent enantioselectivity (>99%). The product was extracted from the homogeneous phase together with [BDMIM][PF₆] using hexane and Et₂O, and the remaining solution was recharged with ketone and formic acid and reused (eq 15). Furthermore, a range of different substrates including cyclic ketones and aldehydes have been reduced using the same **59**–[BDMIM][PF₆] combination.



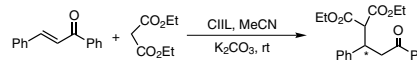
Ref. 10

eq 5



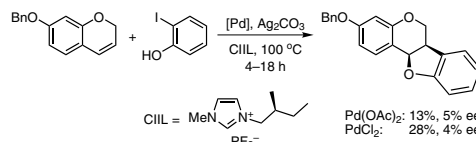
Ref. 26

eq 6



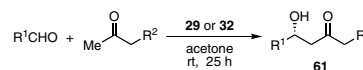
Ref. 19

eq 7



Ref. 36

eq 8

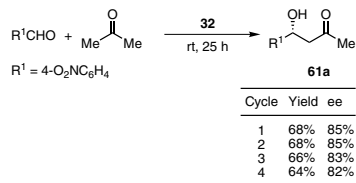


61	R ¹	Yield	ee
a	4-NCC ₆ H ₄	10%	11%
a	4-NCC ₆ H ₄	59%	72%
b	2-Np	50%	80%
c	Ph	50%	76%
d	4-AcNHC ₆ H ₄	40%	64%
e	4-BrC ₆ H ₄	58%	73%
f	2-ClC ₆ H ₄	92%	71%
g	Cy	43%	85%
h	4-O ₂ NC ₆ H ₄	51%	71%
i	4-O ₂ NC ₆ H ₄	64%	85%

^a CIIL **32** was used in all cases, except table entry 1.
^b In all cases, R² = H, except for **61h**, in which R² = Me.

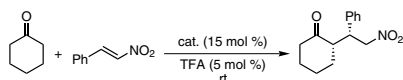
Ref. 21

eq 9



Ref. 21

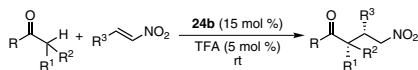
eq 10



Cycle	Cat.	Time	Yield	Syn/Anti	ee
1	24a	10 h	99%	99:1	98%
1	24a	20 h	99%	99:1	97%
1	24b	8 h	100%	99:1	99%
2	24b	8 h	97%	97:3	94%
3	24b	24 h	99%	96:4	91%
4	24b	48 h	96%	97:3	93%
1	24c	12 h	86%	98:2	87%
1	25a	20 h	97%	97:3	97%
1	25b	16 h	100%	96:4	94%
1	25c	12 h	40%	96:4	82%
1	26a	18 h	86%	97:3	89%
1	26b	18 h	25%	94:6	70%

Ref. 20

eq 11

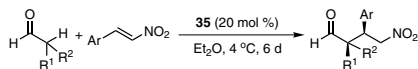


R	R ¹	R ²	R ³	Time	Yield	Syn/Anti	ee
a	a	H	4-ClC ₆ H ₄	10 h	100%	99:01	99%
a	a	H	3-O ₂ NC ₆ H ₄	10 h	94%	98:02	96%
a	a	H	4-MeC ₆ H ₄	12 h	99%	99:01	95%
a	a	H	4-MeOC ₆ H ₄	12 h	99%	99:01	95%
a	a	H	2-Np	10 h	99%	99:01	97%
b	b	H	Ph	60 h	87%	63:37	79% ^c
Me	H	H	Ph	12 h	83%	---	43%
Me	H	H	d	24 h	92%	85:15	76% ^e
H	Me	Me	Ph	96 h	70%	---	86%
H	i-Pr	H	Ph	60 h	100%	90:10	72%

^a R, R¹ = (CH₂)₄. ^b R, R¹ = (CH₂)₅. ^c 82% ee for the anti isomer. ^d 1-nitrocyclohexene used. ^e 80% ee for the anti isomer. ^f The yield is that of the isolated product; the syn/anti ratio was determined by ¹H NMR, while ee was determined by HPLC.

Ref. 20

eq 12

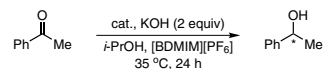


R ¹	R ²	Ar	Yield	Syn/Anti	ee
Me	Me	Ph	58%	---	82%
n-Bu	H	Ph	64%	97:03	68%
n-Bu	H	p-Tol	60%	96:04	67%
n-Pr	H	p-An	29%	92:08	67%
i-Pr	H	Ph	53%	96:04	66%
i-Pr	H	p-Tol	64%	97:03	73%
n-Pr	H	Ph	49%	89:11	64%
n-Pr	H	p-Tol	38%	96:04	68%
a,b	a,b	Ph	38%	95:05	88%

^a R, R¹ = (CH₂)₄. ^b In MeCN. The syn/anti and ee ratios are for the stereoisomer with opposite configurations at the two chiral centers.

Ref. 22

eq 13

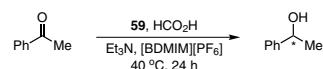


Cat.	Run	Conv. ^a	ee ^b	Leaching ^c
60	1	95%	27	5% Ru
60	2	15%	---	---
59	1	80%	98	8% Ru
59	2	66%	---	---
59	3	57%	---	---
59	4	21%	---	---

^a Determined by GC. ^b Determined by GC using a Chromapack CP-Cyclodex B column. ^c Determined by ICP-OES.

Ref. 34

eq 14



Run	Meth. A ^a	Meth. B ^b	Recovered 59
1	>99%	>99%	^a Product extracted with hexane, ionic liquid washed with H ₂ O and dried in vacuo. ^b Product extracted with hexane and ionic liquid dried in vacuo.
2	68%	>99%	
3	19%	80%	
4	01%	52%	

Ref. 34

eq 15

4. Conclusions and Outlook

The field of task-specific 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 chiral ionic liquids that are better able to influence the outcome of asymmetric reactions.

5. Acknowledgments

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