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Advances in chiral ionic liquids derived from natural amino acids

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Abstract—Ionic liquids (ILs) possess a number of unique properties; hence they have received much interest as green media for synthesis, analysis, catalysis, separation, and energy provision. More recently, chiral ionic liquids (CILs), which are derived from natural amino acids with chirality, biodegradability, reduced toxicity, and high biocompatibility, have also attracted interest. This report provides an overview of the design, synthesis, properties, and applications of these new CILs derived from natural amino acids. This is a current area of research that is poised for rapid development and expansion.

Contents

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1. Introduction

Ionic liquids (ILs) have attracted increasing interest in the chemical community as green alternatives to classical environmentally-damaging media for synthesis, catalysis, separation, and other various chemical tasks.[1] This is mainly the result of their unique properties, such as non-volatility, wide liquid range, high thermal stability, low toxicity, good solubility, reusability, and incombustibility. Due to their ionic properties, an obvious potential exists for solvent–solute interactions, which may provide a mechanism for substantial improvement over conventional media. In addition to the aforementioned favorable properties, the physical–chemical properties of ILs can also be adjusted for specific applications by varying the structures of their cations and/or anions. Hence, various types of functionalized ionic liquids expressly categorized as 'task-specific' ionic liquids (TSILs) have been designed and synthesized over the last few years. They have also been widely applied in catalysis, organic synthesis, and separation, as well as for the construction of nanostructured materials, etc.[2]

It is well known that chirality has played an important role in chemistry. In the last few years, research for new solvents and materials based on chiral ionic liquids (CILs) has became a topic of increasing importance, and a growing number of CILs have been designed, synthesized, and utilized for potential applications in chiral discrimination, asymmetric synthesis, and the optical resolution of racemates.[3] With the rapid development of CILs, these new solvents have the potential to play a key role in enantioselective organic chemistry, and their role in this field is expected to expand substantially.

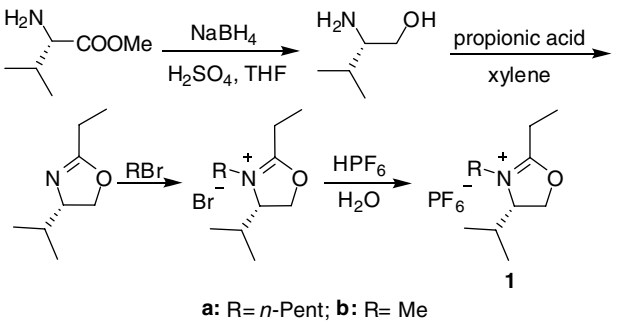
The adoption by the chemical industry of renewable natural sources as starting materials is necessary and topical at present, as our mineral resources continue to be consumed at a prodigious pace. Natural amino acids and their derivatives provide the most abundant renewable natural chiral pool, and can form an efficient, practical, facile precursor for the preparation of chiral compounds.[4] Nevertheless, current studies have also raised doubts over whether traditional ILs are genuine green reagents. For example, some ILs are volatile,[5] combustible,[6] and toxic,[7] and could exert negative effects on the environment.[8] Rogers et al. have previously reported that the decomposition of some ILs could form corrosive HF.[9] As far as we are concerned, the development of environmentally compatible or biodegradable ILs is of paramount importance. Not only are CILs derived from amino acids chiral, but they are also biodegradable with reduced toxicity and high biocompatibility. Hence, 20 natural amino acids and their derivatives are ideal precursor materials for the framework of CILs from environmental and economic viewpoints. Accordingly, increasing interest has been concentrated on the design, synthesis, and application of amino acid-based ILs in the last few years.

Although ILs have been extensively reviewed with particular focus on their synthesis and applications,[1–4] CILs derived from amino acids have always been ignored or reviewed intermittently and incompletely in the literature. Up until now, no review devoted to CILs derived from natural amino acids has been published. Our common interests prompted us to focus attention on the more comprehensive advances in this area. In this report, the design, synthesis, properties, and applications of CILs derived from natural amino acids are reviewed in detail.

2. Chiral cations derived from natural amino acids

2.1. Heterocycles of chiral cations built from natural amino acids or their derivates

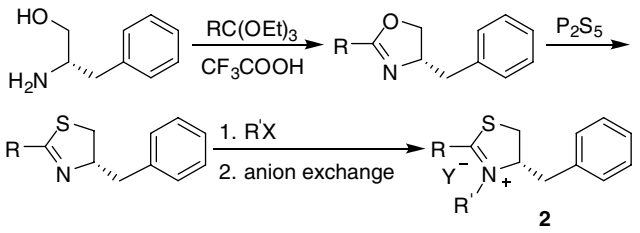
2.1.1. 4,5-Dihydrooxazolium chiral cations built from L-valine methyl ester. In 2001, ILs with chiral 4,5-dihydrooxazolium cations were first reported by Wasserscheid et al. from L-valine methyl ester in 40% overall yield.[10] Reduction of the L-valine methyl ester with $NaBH_4$–H_2SO_4 afforded L-valinol. Then, cyclization of L-valinol with propionic acid produced a 4,5-dihydrooxazole. Finally, alkylation of the corresponding 4,5-dihydrooxazole with bromopentane or bromomethane followed by anion exchange with hexafluorophosphoric acid afforded the expected 4,5-dihydrooxazolium CILs **1** (Scheme 1). The melting points of the CILs synthesized are 63 °C for **1a** and 79 °C for **1b**, respectively. The enantiopurity of **1a** was confirmed by ^{19}F NMR spectroscopy after basic hydrolysis of **1a** and reaction with (*S*)-Mosher's acid chloride. Although this kind of 4,5-dihydrooxazolium CILs can be prepared on a multigram scale, the relatively low overall yield, and especially the low stability of the 4,5-dihydrooxazole ring under acidic conditions limit its practical appli-



Scheme 1. Synthesis of 4,5-dihydrooxazolium CILs from L-valine methyl ester.

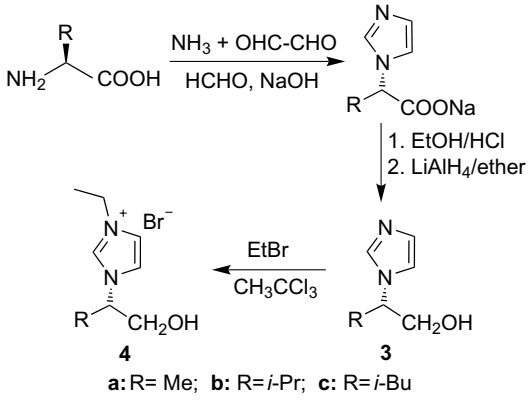
cation. Nevertheless, this was the first report of CILs with chiral cations derived from a natural amino acid.

2.1.2. 4,5-Dihydrothiazolium chiral cations built from L-phenylalaninol. A series of new 4,5-dihydrothiazolium CILs derived from a natural amino acid precursor were also synthesized by Gaumont et al.[11] The 4,5-dihydrothiazolium salts were prepared in a three-step reaction starting from the reaction between orthoester and L-phenylalaninol. The 4,5-dihydrooxazole intermediate produced was then sulfurated by P_2S_5 to afford the corresponding 4,5-dihydrothiazole. Finally, alkylation of the 4,5-dihydrothiazole followed by an anion exchange to afford the 4,5-dihydrothiazolium CILs **2** (Scheme 2), which were obtained in reasonable to good yields on a multigram scale. Furthermore, through a judicious choice of the anion and the cation, salts with low melting points were obtained and tested as chiral shift reagents and new solvents. These CILs were also found to be efficient organocatalysts in the Stetter reaction and were seen to act as ligands in the copper catalyzed addition reaction of diethylzinc to enones. As solvents, these CILs proved to be superior to other traditional ILs in the Mukaiyama aldolization reactions between benzaldehyde and Danishefsky's diene. Unfortunately, no enantioselectivity was observable. Regardless, this report provided a method for forming 4,5-dihydrothiazole from 4,5-dihydrooxazole. 4,5-Dihydrothiazolium CILs **2** are water tolerant and stable under acidic or basic conditions. Thus, they are potential candidates for new chiral solvents.



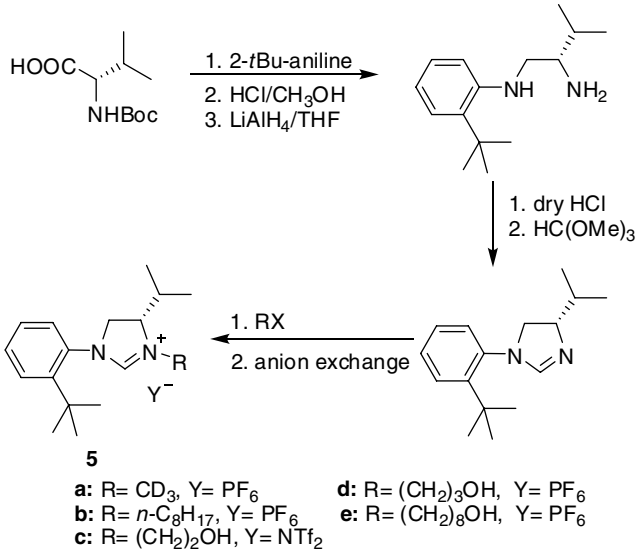
Scheme 2. Synthesis of 4,5-dihydrothiazolium CILs from L-phenylalaninol.

2.1.3. Imidazolium chiral cations built from natural amino acids. In 2003, Bao et al. reported for the first time the synthesis of chiral imidazolium ILs with chiral lateral chains derived from the natural amino acids (L-alanine, L-leucine, and L-valine) in four steps with 30–33% overall yields.[12] L-Alanine was first condensed with aldehydes under basic conditions to form an imidazole ring, which was then esterified by ethyl alcohol to obtain the ester. Subsequently, the reduction of the ester with $LiAlH_4$ afforded the L-2-(1-imidazolyl)-propyl alcohols **3a**. Finally, the desired CIL **4a** was obtained by alkylation of **3a** with bromoethane. CILs **4b** and **4c** were synthesized from L-leucine and L-valine using a similar method (Scheme 3). These CILs have melting points ranging from 5 to 16 °C, which make them potential solvents for asymmetric reactions. Other properties of these CILs are similar to those of usual imidazolium ILs in terms of thermal and chemical stability and solvency.



Scheme 3. Synthesis of imidazolium CILs from natural amino acids.

2.1.4. 4,5-Dihydroimidazolium chiral cations built from L-valine. In 2004, Guillemin et al. reported the synthesis of new chiral 4,5-dihydroimidazolium salts derived from L-valine.[13] The reaction of the *N*-Boc-L-valine with *t*-butylaniline, followed by Boc-deprotection under acidic conditions and then reduction of the amide functional group, yielded the corresponding diamine. The formation of the diamine hydrochloride followed by cyclization with trimethylorthoformate produced the 4,5-dihydroimidazole. The expected 4,5-dihydroimidazolium salts **5** were obtained after classical alkylation of the corresponding 4,5-dihydroimidazole with various alkyl halides and anion exchange (Scheme 4). The 4,5-dihydroimidazolium salts **5b**, **5c**, **5d** were found to be ILs. ILs **5b** and **5c** were liquid, while **5d** was a white solid with a melting point of 88–90 °C. The 4,5-dihydroimidazolium salts are water tolerant and stable under acidic conditions. The effect of a hydroxyalkyl side chain on the chiral molecular recognition ability of these new salts was investigated by diastereomeric interactions with a racemic anionic substrate. It was found that the hydroxyalkyl lateral side chain and the bulky aromatic substituents were crucial for the formation of higher



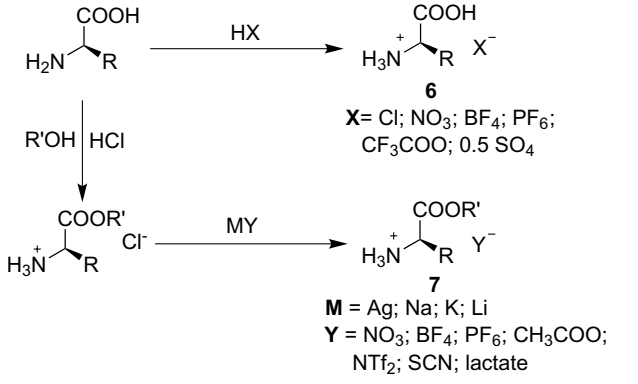
Scheme 4. Synthesis of new 4,5-dihydroimidazolium CILs from L-valine.

diastereomeric interactions with racemic anionic substrates from the viewpoint of structure-interaction relationships.

2.2. Amino acids or amino acid esters employed directly as chiral cations

In 2002, Shan et al. successfully synthesized $[AA]_l[SO_4]_m$ type and $[AA][HSO_4]_n$-type CILs from amino acids (AA) and H_2SO_4.[14,15] These novel CILs could be formulated as $[AA]_l[SO_4]_m$ and/or $[AA][HSO_4]_n$, where $l = 1, 2$, $m = 1$–3, $n = 1$–4. These CILs were simply prepared by the reaction of aqueous L-amino acid solutions with 98% H_2SO_4 and then complete vaporization of H_2O; the stoichiometric molar ratio of these two reactants depends on the valence of the amino acid cation. This routine is quite interesting as many amino acids such as alanine, valine, leucine, glycine, tyrosine, glutamic acid, proline, lysine, histidine, and arginine can all be employed.

In 2005, Kou et al.[16] employed a similar strategy for the synthesis of two new families of CILs (**6** and **7**) charged with cations derived from natural amino acids ([AA]) or amino acid esters ([AAE]). CILs **6** were achieved by a one-step acidification of amino acids with an equimolar ratio of strong acid, which is an atom-economic reaction (water is the reaction medium), while CILs **7**, derived from amino acid esters, were obtained by esterification of the amino acids and then anion exchange (Scheme 5). Due to the strong hydrogen bonds between the carboxylic acid groups, most of the salts **6** have high melting points. Fortunately, not only does esterification provide a great potential for adjusting the structures and properties of these CILs, but it also reduces the amount of hydrogen bonding, which results in a significant decrease in the melting points of these salts. On the other hand, the incorporation of an ester group could increase the biodegradability of these CILs. As a result, a series of CILs with lower melting points and biodegradability were obtained successfully. More than one hundred CILs have been synthesized via this simple route. In all cases, the stereogenic center present in the amino acid precursor has been successfully retained in the final CILs, which also show good thermal stability up to 200 °C.



Scheme 5. Schematic strategy for the synthesis of amino acid-based CILs.

Based on their previous work,[16] Kou et al. reported 'fully green' CILs (Fig. 1), which were combined with suitable, environmentally benign, anions (NO_3^- and Sac^-) and amino

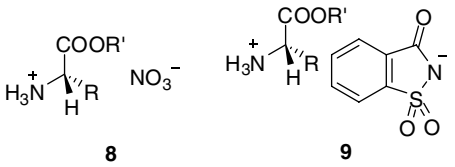


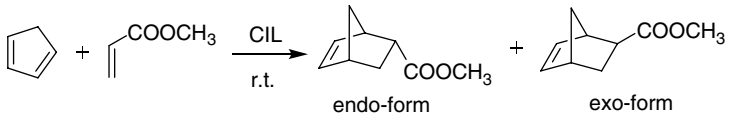
Figure 1. Structures of fully green ionic liquids from natural amino acids.

acid esters cations ($[AAE]^+$).[17] Using a similar synthetic strategy (Scheme 5),[16] $[AAE]NO_3$ **8** was synthesized by the reaction of [AAE]Cl and $AgNO_3$ in methanol, while [AAE]Sac **9** was obtained by the reaction of sodium saccharin and [AAE]Cl in acetone. The stereogenic center existing in the precursors is still retained in the final CILs. Replacement of the traditional anions by non-toxic NO_3^- and saccharide anions increases the 'greenness level' of this new generation of amino acid-based CILs and is the first report about the investigation of 'fully green' CILs, in which both the cations and anions are from non-toxic, renewable materials.

The thermal stabilities, phase behaviors, viscosities, and miscibilities of the above CILs **8** and **9** were investigated in detail. More than half of these products (14 out of 20) were room temperature ionic liquids and almost all of them had melting points lower than 100 °C. All of these CILs have a glass transition temperature (T_g) between −70 and 0 °C. These compounds exhibited differential thermal stability from 150 to 230 °C under N_2 while [AAE]Sac **9** had a better thermal stability than that of $[AAE]NO_3$ **8**. When these salts were heated rapidly to 250 °C in air, an irritating odor was generated, while a very small amount of black residue remained. Compound $[AAE]NO_3$ **8** displayed qualitatively similar viscosity behavior to conventional imidazolium ILs, while [AAE]Sac **9** was a very viscous liquid. With modest heating, the viscosities of most [AAE]-Sac ILs decreased rapidly. Furthermore, the chirality of all these ILs remained unaltered after three months. ^1H NMR chemical shifts of $-NH_3^+$ (or $-NH_2^+-$) in $[AAE]NO_3$ **8** indicate that $[AAE]NO_3$ **8** exhibits acidic behavior. All of these CILs are miscible with high polarity solvents such as water, low molecular weight alcohols, and ketones. Amino acid structure, alkyl chain length, and anions have no strong influence in these cases. All of these CILs are immiscible with non-polar solvents. It has been shown that these 'fully green' CILs have the same physical and chemical properties as those of conventional ILs.

Both the catalysis and solvent effects of these 'fully green' amino acid CILs in the Diels–Alder reactions were investigated through the cycloaddition of cyclopentadiene to methyl acrylate (Scheme 6). The same level of stereoselectivity as that of [bmim][BF_4] was achieved with these CILs system. However, [AAE]Sac **9** showed a much better stereoselectivity than that of $[AAE]NO_3$ **8**. [Methyl 2-aminopropanoate]NO_3 ($AlaC_1NO_3$) also showed catalytic activity though the enantiomeric excesses (ee) of the endo and exo-products were found to be less than 3%.

Maschmeyer et al. also synthesized 23 new CILs with relatively high yields and purity by the reaction of an amino



Scheme 6. Diels–Alder reactions catalyzed by fully green CILs.

acid or a chiral carboxylic acid with tetrabutylammonium hydroxide ([N_{4444}]OH) in water.[18] They gave clear evidence for the deprotonation of the free acid through comparison of chemical shifts of the α-proton in the starting acid and the subsequent CILs. The α-proton in CILs exhibits a clear upfield shift, which is consistent with the increasing electron density in the carboxylate moiety upon deprotonation. The specific rotations for the CILs prepared were also measured in aqueous solutions. In most cases, the magnitude of their specific rotations is smaller than that of the free amino acids except for that of [N_{4444}][*N*-Ac-L-Cys]. For a number of these CILs, the rotation direction of the plane-polarized light was opposite to that of the starting acid. The chiral integrity of these CILs was also tested by comparing the $[\alpha]_D^{20}$ value of the decomposed CIL with that of the parent amino acid at the same concentration. The results showed that no racemization of the stereogenic center had occurred during the formation of CILs. These amino acid-based CILs showed significant darkening when heated to 110 °C or at elevated temperature. However, they showed no signs of decomposition after 24 h at 110 °C.

2.3. L-Proline-derived pyrrolidine-based CILs

Chiral pyrrolidines derived from L-proline and its derivates were successfully used as highly enantioselective organocatalysts.[19] Chiral pyrrolidine structure of these compounds is now regarded as one of the most important backbones for asymmetric catalysis and it has been incorporated into the design of task-specific ionic liquids. As a result, an extensive series of pyrrolidine-type CILs was designed and synthesized from the 'chiral pool' while L-proline and its derivatives were used as starting materials.

2.3.1. Synthesis of L-proline-derived pyrrolidine-based CILs. Luo et al. designed and synthesized a series of chiral pyrrolidine-based CILs (Fig. 2) bonded to an imidazolium ring using L-proline as a starting material.[20,21] Reduction of L-proline with $LiAlH_4$ followed by Boc-protection under basic conditions afforded Boc-protected L-prolinol, which was reacted with *p*-toluenesulfonyl chloride (TsCl) to yield the tosylation product. N-Alkylation of the product to an imidazole followed by classical alkylation with *n*-butyl bromide gave the Boc-protected pyrrolidinylimidazolium bromide. The expected pyrrolidine-type CILs 10 were obtained after Boc-deprotection and anion exchange (Scheme 7). Pyrrolidine-type CILs **11**–**16** were also synthesized via a similar method. The synthetic procedures were quite straightforward and afforded the product (e.g., **10a**) in 45% overall yield from L-proline. The synthetic procedure allows for facile variations of the cations, anions, and side chains of the CILs. All the CILs obtained are viscous liquids at room temperature and soluble in moderately polar solvents, but insoluble in less polar solvents.

2.3.2. Applications of L-proline-derived pyrrolidine-based CILs. These pyrrolidine-type CILs comprise a chiral pyrrolidine unit covalently tethered to an ionic-liquid moiety. The chiral pyrrolidine unit can serve as a catalytically active center: not only can the ionic-liquid moiety act as a phase tag to facilitate the recycling and reuse of the catalyst, but it can also play an important role as an efficient chiral induction group to ensure high selectivity. These types of CILs thus combine both the advantages of organocatalysts and ILs.

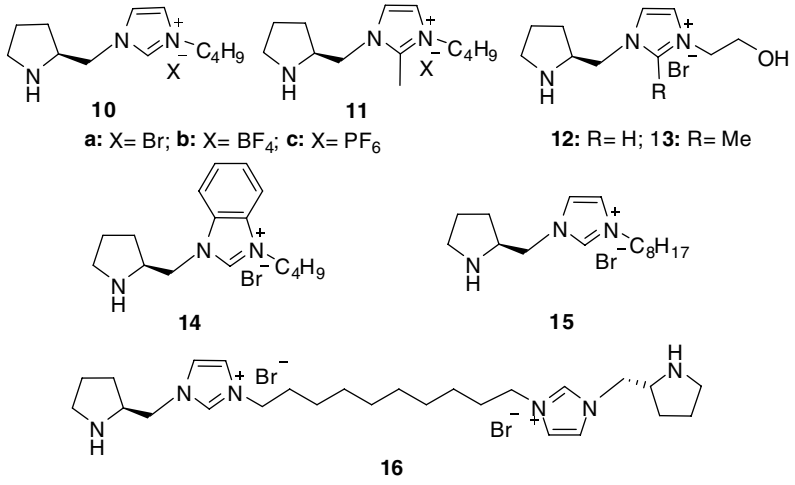
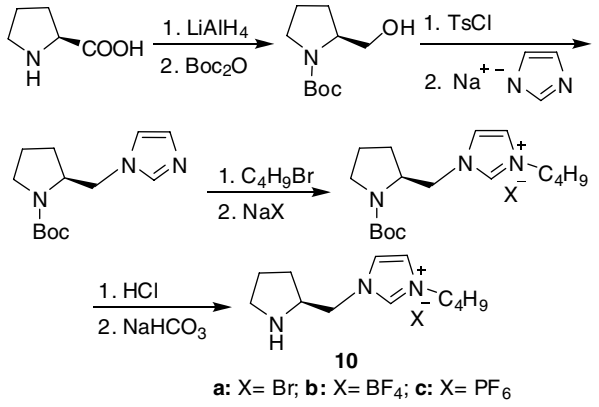
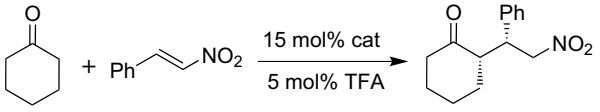


Figure 2. Pyrrolidine-based CILs derived from L-proline.



Scheme 7. Synthesis of pyrrolidine-based CILs **10** from L-proline.

The pyrrolidine-based CILs **10**–**13** (Fig. 2), which were applied as good catalysts in the asymmetric Michael addition reaction, were reported by Luo et al.[20] These functionalized CILs performed much better than previous chiral pyrrolidine catalysis in ILs.[22] Their catalysis was first investigated in the asymmetric Michael addition reaction of cyclohexanone to *trans*-β-nitrostyrene in neat mixtures with 15 mol % of catalyst and 5 mol % of trifluoroacetic acid (TFA) cocatalyst (Scheme 8). The corresponding catalytic and enantioselective activities varied significantly with different ionic-liquid units. Pyrrolidine-imidazolium bromide and tetrafluoroborate **10a** and **10b** demonstrated the best performances with nearly quantitative yields and high diastereoselectivity (*syn*/*anti* = 99:1) and enantioselectivity (98% ee). Excellent yields and ee values could still be achieved although a loss in activity was observed for the third and fourth cycles.



Scheme 8. Asymmetric Michael additions catalyzed by pyrrolidine-based CILs.

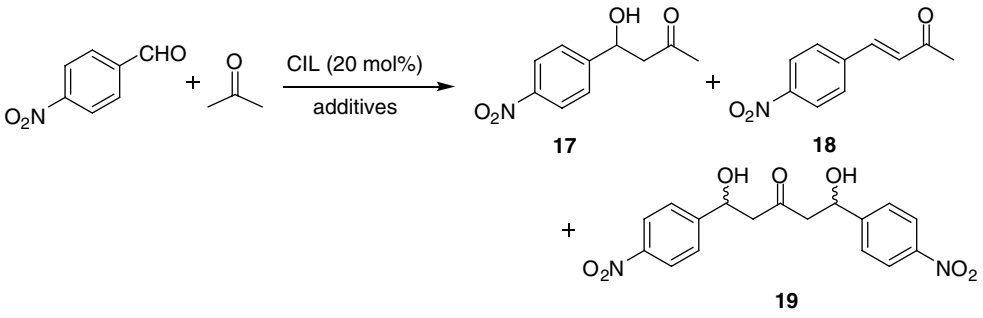
Compounds **10a** and **10b** were employed in the Michael reactions with a variety of Michael donors and nitroalkenes as well. The reactions operated extremely well with cyclohexanone to generate Michael adducts in nearly quantitative yields with high diastereoselectivities and excellent enantioselectivities. When cyclopentanone was employed, the reaction occurred smoothly and showed moderate diastereoselectivity and enantioselectivity for both diastereomers. Moreover, acetone and aldehydes also served as efficient Michael donors to produce the desired adducts with good yield and moderate enantioselectivity.

In summary, pyrrolidine-type CILs can act as highly efficient organocatalysts in asymmetric Michael addition reactions for a broad range of Michael donors (both ketones and aldehydes) and Michael acceptors (nitroolefins) with high yields (up to 100%), excellent enantioselectivity (up to 99% ee), and very good diastereoselectivity (*syn*/*anti* up to 99:1).

After successful application of the pyrrolidine-type CILs in the asymmetric Michael addition reactions, these pyrrolidine-type CILs **10**–**16** (Fig. 2) were then applied as reusable organocatalysts for direct aldol reactions (Scheme 9).[21] They were first screened by the model reaction of *p*-nitrobenzaldehyde and acetone. All the CILs are able to catalyze this reaction and the desired direct aldol products **17** were produced along with some dehydration by-products **18**. CILs **13** and **16** gave the best outcome in terms of the yield of the aldol products. Unfortunately, all the examined CILs demonstrated low enantioselectivities.

It was interesting to see that these CILs could effectively catalyze direct aldol reactions with only 20 mol % loading of the catalyst. Acidic additives also showed some effect on the direct aldol reaction. While the reaction was catalyzed by **10b** in acetone containing 5 mol % of HOAc additive, 88% yield of aldol product **17** was afforded with a trace of the dehydration product **18**. Interestingly, the reaction catalyzed by **13** and **16** only produced (the minor) bisaldol product **19**, as well as the major aldol product **17**, and no dehydration product **18** was detected. Overall, IL **10b** performed better than **13** and **16** under the optimized conditions in terms of yield of the desired aldol product **17**.

CIL **10b** was therefore selected for examination with other substrates. The reactions between acetone and active aromatic aldehydes afforded the desired aldol products in high yields without isolation of dehydration products, while the reactions between acetone and the less reactive aromatic aldehydes produced significant amounts of dehydration products as well as the aldol products. For example, only

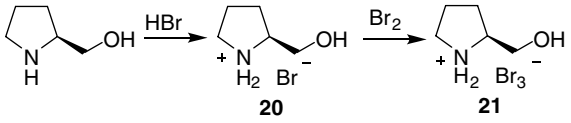


Scheme 9. Direct aldol reactions catalyzed by pyrrolidine-type CILs.

the aldol condensation product was isolated when *p*-hydroxybenzaldehyde was used. Cyclic ketones and other acyclic ketones also worked well in the reactions. Notably, methyl ethyl ketone underwent reaction with *p*-nitrobenzaldehyde with complete regioselectivity favoring the branched product in high yield and with moderate diastereoselectivity and enantioselectivity. The absence of directing the hydrogen bond interaction and electrostatic interaction between the participating aldehyde and enamine intermediate could account for the poor diastereoselectivities observed.

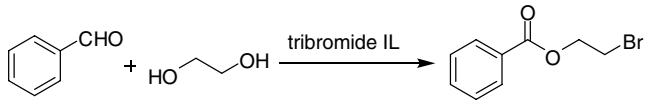
CIL **10b** could be easily recycled by precipitation in diethyl ether. After six cycles, the activity of the CIL is only slightly decreased. The results and observations in this study could also provide useful knowledge for the design of new types of CILs with improved enantioselectivities. The reactions are believed to occur via a *syn*-enamine intermediate and the ionic-liquid moiety would provide certain steric shielding for the participating aldehyde acceptors. This steric effect accounts for the modest enantioselectivities observed in the reactions.

2.3.3. L-Prolinol-derived pyrrolidine-based tribromide CIL. Bao and Wang reported the synthesis of tribromide CIL based on L-prolinol, and this salt was used as reagent and solvent for the chemoselective, regioselective, and stereoselective synthesis of ω-bromoesters at room temperature.[23] CIL **20** was obtained by neutralizing L-prolinol with hydrobromic acid in water. By adding molecular bromine dropwise to **20** with stirring, the red liquid tribromide **21** was formed exothermically (Scheme 10). CIL **21** could be stored for several weeks or with prolonged heated at 60 °C under vacuum without changing in structure and activity. CIL **21** is miscible with polar organic solvents and immiscible with weakly polar organic solvents. It is significant that the stereogenic centers in CILs **20** and **21** were retained and that no racemization was detected under the acidic conditions.



Scheme 10. Synthesis of tribromide CIL from L-prolinol.

The application of tribromide ILs (CIL **21**, [bmim]Br_3 and [butylpyridinium]Br_3) was investigated by mixing tribromide salts with benzaldehyde and ethylene glycol (Scheme 11). When CIL **21** took part in the reaction, the 2-bromoethyl benzoate was obtained after 28 h, in 90% yield at room temperature, while other tribromide ILs gave poor yields even after 40 h at 50 °C. After the reaction, CIL **21** recovered could be readily reused by adding additional amounts of molecular bromine, with only a small decrease in the yield of 2-bromoethyl benzoate being observed after four cycles (90–85% yield). As CIL **21** was the best IL examined, it was then applied in the reaction of ethylene glycol with aromatic aldehydes. Both electron-rich and electron-deficient aromatic aldehydes were suitable for this reaction, giving the desired products in good yields. Unexpectedly, when 3,4,5-trimethoxy benzaldehyde was used,



Scheme 11. Synthesis of bromoester using tribromide ILs reagent and reaction medium.

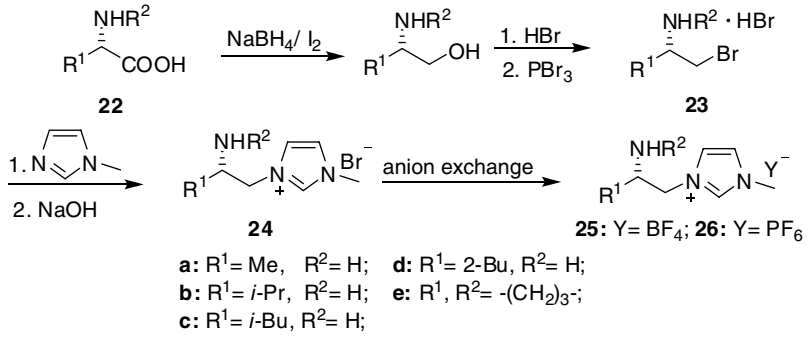
the product was mainly 2-bromo-3,4,5-trimethoxy benzaldehyde rather than 2-bromoethyl 3,4,5-trimethoxybenzoate. When **21** was used in large excess, a 68% yield of 2-bromoethyl 2-bromo-3,4,5-trimethoxybenzoate was obtained. When 2-hydroxybenzaldehyde was used as a starting material, 2-bromoethyl 5-bromo-2-hydroxybenzoate was obtained as the main product.

Regioselectivity was observed in the brominating reactions of benzaldehyde and 1,2-propanediol. The regioselectivity ratios gave a favorable selectivity of regioisomers in the range from 4:1 to 19:1, which are comparable to selectivities reported for other brominating reagents, such as *N*,*N*-bibromobenzenesulfonamide, Br_2. When either 4-nitrobenzaldehyde or 4-methoxybenzaldehyde was used as the reaction material, a favorable ratio of the regioisomers was obtained as 17:1 or 14:1, respectively. Unfortunately, only a 3.7:1.0 ratio of the regioisomers was obtained when 1,3-butanediol was used and a 1.7:1.0 ratio of the *erythreo*/*threo* isomers was detected when 2,3-butanediol was used.

The chiral induction of CIL **21** and other CILs as chiral reagents and reaction medium was also investigated in the reaction of meso-2,3-butanediol with benzaldehyde and 0–17% ee was achieved with different CILs. Only 4% ee was achieved when **21** was used at room temperature and 5% ee at −70 °C. It was shown that the type of cation greatly affected the chiral discrimination. Although the reason for the enantioselectivity is unclear and the enantiomeric excesses are moderate at present, the results of this work could provide meaningful insights in the understanding of the use of chiral ILs in asymmetric induction.

2.4. Amino acid-derived chiral-amine-functionalized ILs

A novel class of chiral-amine-functionalized ILs (CAFILs) had been designed and synthesized efficiently in enantiopure form from natural amino acids by Xu et al.[24] The synthesis of the novel ILs **24**–**26** started from natural amino acids **22a**–**e** (L-alanine, L-valine, L-leucine, L-isoleucine, and L-proline) with fairly good overall yields (66–71% yield) (Scheme 12). The key precursors **23** were synthesized via reduction of the amino acid with $NaBH_4/I_2$ followed by the neutralization of the NaOH solution, and bromination with PBr_3. After *N*-alkylation of **23** to 1-methylimidazole followed by the neutralization to give CILs **24**, anion exchange using $AgBF_4$ or KPF_6 in $MeCN/H_2O$ at room temperature afforded CILs **25** and **26**. CILs **24e**, **25e**, and **26e** belong to the class of pyrrolidinyl-imidazolium-CILs. This report also provided an alternative synthetic pathway for pyrrolidinyl-imidazolium ILs, which were also synthesized by Luo et al.[20,21] Furthermore, low temperature X-ray diffraction analysis of a single crystal of the hydrobromide salt of **24c** unambiguously confirmed the proposed chemical structure and L-configuration.

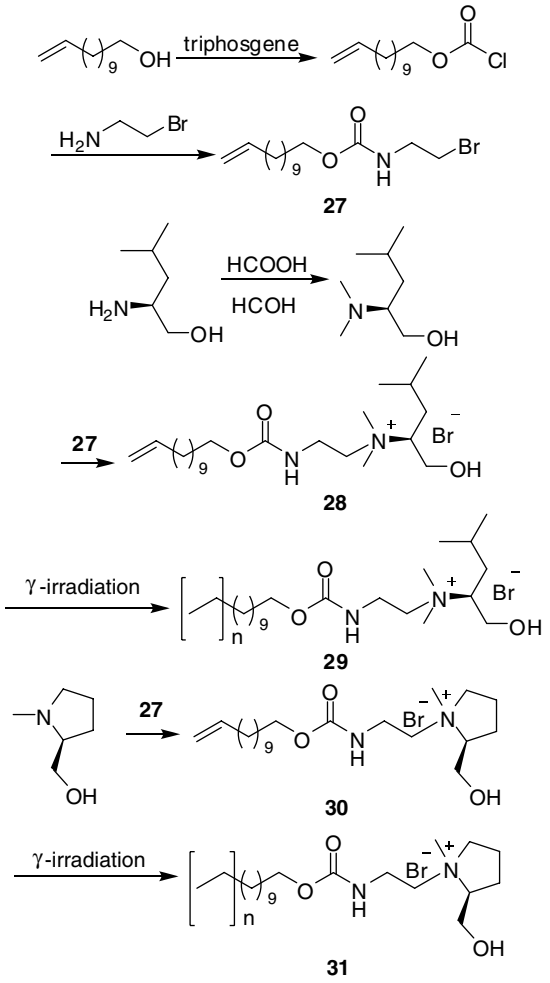


Scheme 12. Synthesis of ILs functionalized with chiral-amine functional groups.

Some representative properties of CAFILs were also reported. The ILs show low melting points or glass transition temperatures ranging from −49 to 145 °C. CAFILs **25** had T_m/T_g values lower than those of other CAFILs, whereas CAFILs **24** had higher values. T_g determinations also revealed that all CAFILs had good thermal stabilities up to at least 210 °C. In addition, all CAFILs showed a trend of being more miscible in polar solvents and much more immiscible in non-polar solvents than non-functionalized imidazolium type ILs. An NMR chiral discrimination study indicated that these novel CAFILs can provide a highly efficient chiral environment.

2.5. Amino acid-derived monomeric and polymeric CILs

The amino acid-derived CILs, both in monomeric and polymeric forms, were synthesized and characterized by Shamsi and Rizvi.[25] The carbamate-functionalized alkenyl bromide intermediate **27** was obtained by the acylation of 2-bromoethylamine with chloroformate, which was synthesized by treating triphosgene with the unsaturated alcohol. The *N*,*N*-dimethyl-leucinol was synthesized by reductive alkylation of the primary amine group of leucinol using the well-known Eschweiler–Clark reaction. The monomeric CILs **28** and **30** were synthesized by refluxing intermediate **27** with *N*,*N*-dimethyl-leucinol and *N*-methylpyrrolidinol, respectively. Furthermore, the polymeric CILs **29** and **31** were obtained by complete polymerization of the monomeric CILs through continuous ^{60}Co γ-irradiation (Scheme 13). The cationic surfactant undecenoxycarbonyl-L-leucinol bromide **28** (L-UCLB) is an IL at room temperature, while undecenoxycarbonyl-L-pyrrolidinol bromide **30** (L-UCPB) is a greasy solid with a melting temperature of 30–35 °C.



Scheme 13. Synthesis of the monomeric and polymeric CILs from amino acids.

The monomeric and polymeric CILs were thoroughly characterized to determine critical micelle concentration (cmc), aggregation number (*A*), polarity, specific rotation, and partial specific volume (V_h). L-UCLB **28** exhibited higher polarity, lower cmc and V_h, significantly higher specific rotation, but a similar *A* value compared with L-UCPB **30**. A similar trend was also observed for poly-L-UCLB **29** and poly-L-UCPB **31**, except that the *A* value was higher for the former polymer.

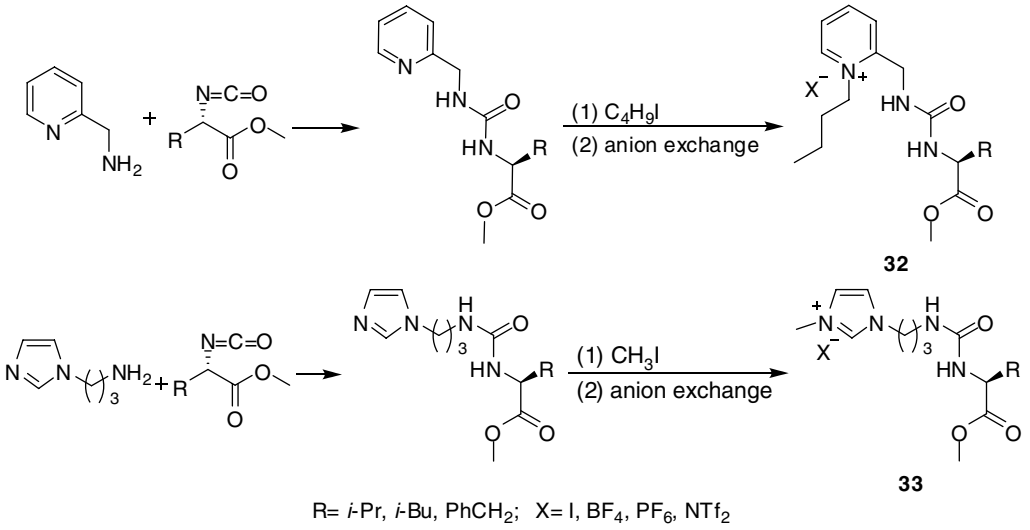
The first enantioseparation using CILs as a pseudostationary phase in capillary electrophoresis has been reported. Chiral separation of two acidic analytes, (±)-α-bromophenylacetic acid and (±)-2-(2-chlorophenoxy)propanoic acid, was achieved with both monomers and polymers of L-UCPB **28** and L-UCLB **30**. Chiral separation of the acidic analyte was compared using polymeric anionic surfactants containing similar headgroups under both acidic and basic pH conditions. The comparison of chiral separation of the anionic and cationic surfactants demonstrates that the electrostatic-interaction between the acidic analyte and the cationic micelle plays a profound role in their enantioseparation.

2.6. Amino acid-derived CILs with a urea functionality

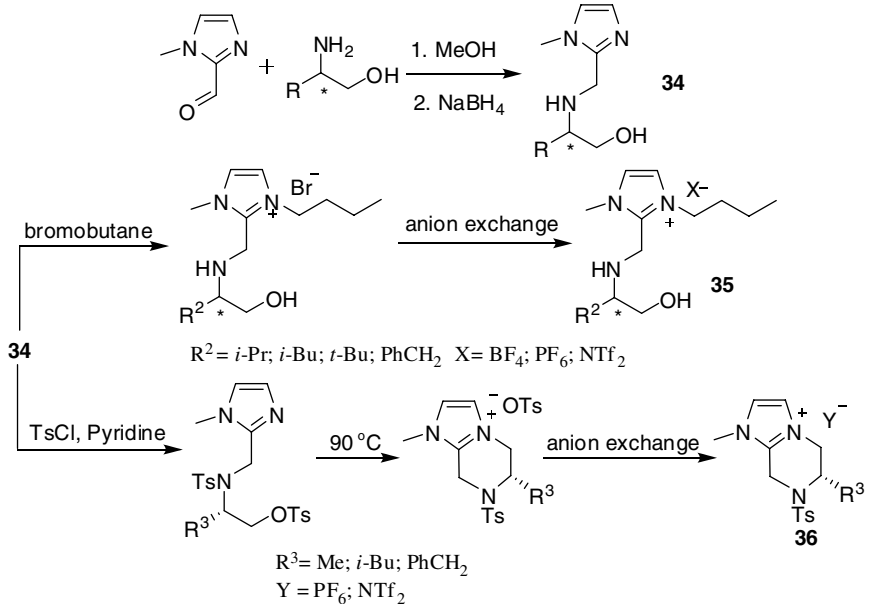
Headley et al. designed and synthesized two series of CILs **32** and **33** tethered to a urea functionality in 2006.[26,27] Urea functional pyridinium CILs **32** contained a chiral moiety and a urea functionality bonded to a pyridinium ring, which were synthesized from amino acid ester derived isocyanates. 2-(Aminomethyl)pyridine was treated with isocyanates to yield the desired ureas. Then, the expected CILs **32** were obtained after classical alkylation and anion exchange (Scheme 14). These CILs were soluble in moderately polar solvents, but insoluble in less polar solvents. Chiral pyridinium tetrafluoroborates were soluble in H_2O, hexafluorophosphates (PF_6^-) partially miscible, and the bis(trifluoromethanesulfonyl)imides (NTf_2^-) immiscible. The thermal stabilities of these CILs range from 151 to 236 °C. The CILs with the PF_6 anion are the least stable and the NTf_2 anion the most stable. CILs charged with the NTf_2 anion exhibit degradation temperatures ranging from 226 to 236 °C. Furthermore, urea functional imidazolium CILs **33**, which contained a chiral moiety and a urea functionality bonded to an imidazolium ring, could also be synthesized in the similar method (Scheme 14).[27]

2.7. Amino acid-derived imidazolium-based CILs with chiral substituents at C-2

Owing to the relative acidity of the hydrogen at the 2-position of the imidazolium-based ILs, they often undergo deprotonation to give undesired side products when used as solvents. To solve this problem, Headley et al. designed and synthesized a series of imidazolium-based ILs bearing a chiral substituent at C-2 (Scheme 15).[28,29] Condensation of 1-methyl-2-imidazolecarboxaldehyde with amino



Scheme 14. Synthesis of urea functionalized CILs from amino acid-derived isocyanates.

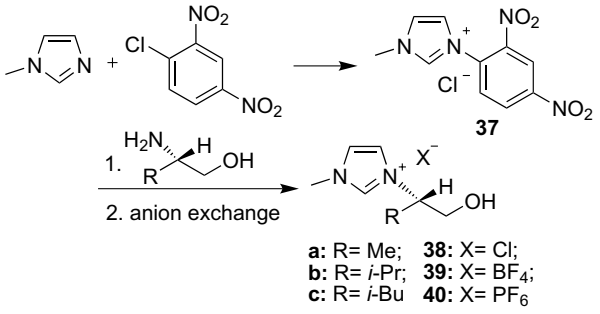


Scheme 15. Synthesis of imidazolium CILs bearing chiral substituents at C-2.

acid-derived chiral amino alcohols followed by reduction by $NaBH_4$ afforded the key intermediate **34**. The expected CILs **35** can be prepared by alkylation of **34** with bromoethane followed by anion exchange. This simple and straightforward procedure resulted in CILs as colorless oils at room temperature in good yields. Subsequently, six novel imidazolium salts **36**, which contain a chiral moiety as well as a fused-ring system, have also been designed and synthesized. Treatment of intermediate **34** with TsCl gave the corresponding double tosylate compounds, which were subjected to the ring-closure reaction to form the chiral tosylate salts. CILs **36** were obtained by anion exchange. However, ^{1}H NMR deuterium exchange experiments demonstrate that CILs **36** do deprotonate at the CH_2 position, adjacent to the 2-position of the imidazolium cation, in basic media containing Et_3N. CILs **36** having PF_6 anions were solids, but with the NTf_2 anion, they were liquids at room temperature.

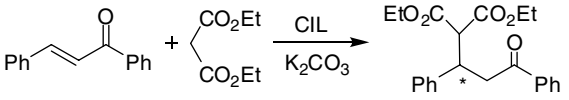
2.8. Amino acid-derived ILs with chiral hydroxyalkyl lateral side chain

Huang and Ou presented an efficient and practical synthetic route to amino acid-derived CILs (Scheme 16).[30] Reaction of 1-methylimidazole with 2,4-dinitrochlorobenzene gave 1-(2,4-dinitro-phenyl)-3-methylimidazolium chloride **37**. The chiral imidazolium ILs **38** could be obtained in good yields by refluxing imidazolium salt **37** with amino acid-derived amino alcohols. Consequently, an anion exchange reaction of chiral imidazolium ILs **38** with fluoroboric acid or potassium hexafluorophosphate gave new chiral imidazolium ILs **39** or **40** (Scheme 16). This route is much better than previous methods[12] for the synthesis of similar chiral imidazolium ILs; the overall yields were 67–81%, making these new CILs suitable for large-scale preparation.



Scheme 16. Efficient synthesis of imidazolium CILs from amino alcohols.

Furthermore, the new chiral imidazolium ILs **38**–**40** were applied to the asymmetric Michael addition (Scheme 17). In the presence of potassium carbonate, 1,3-diphenylprop-2-en-1-one smoothly underwent a Michael addition reaction with ethyl malonate in all of these CILs, giving diethyl 2-(3-oxo-1,3-diphenylpropyl) malonate in moderate to good yields. Most of the new CILs **38**–**40** have chiral discrimination, and the enantioselective effect of the chiral IL **39c** was observed with up to 15% ee in a Michael reaction.

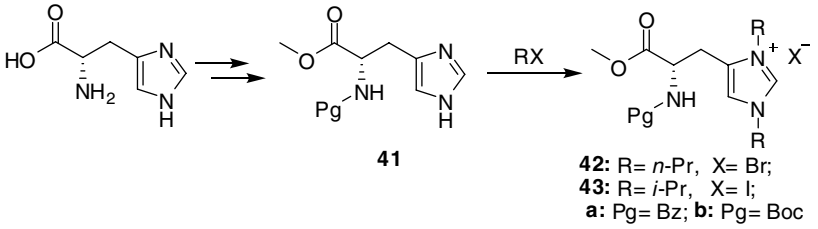


Scheme 17. Michael addition reaction reacted in imidazolium CIL.

2.9. L-Histidine-derived CILs

2.9.1. Imidazolium CILs and imidazol-2-ylidene metal complexes. L-Histidine derived imidazolium CILs, their related chiral imidazol-2-ylidene ligands and their metal complexes were designed and synthesized by Erker et al.[31] L-Histidine was O-protected by ester formation and then *N*-benzoyl (Bz) or *N*-*tert*-butoxycarbonyl (Boc) protected to give the starting materials **41** (Scheme 18). Treatment of Bz-His-OMe **41a** with *n*-propylbromide afforded the [Bz-His(*n*-propyl)$_2$-OMe]Br CIL **42a**, which has a melting point of 39 °C. The stereogenic center in the synthesized precursors is still retained in the final CILs. Furthermore, the CILs do not lose their activity even if heated at 110 °C for 6 h in a two phase system with toluene. Treatment of **41a** with *iso*-propyliodide gave **43a** in excellent yield. Salt **43a** had a melting point of 55 °C. It may potentially serve as a chiral IL as well. Products **42b** and **43b** were obtained by similar dialkylation of the imidazol core of Boc-His-OMe **41b** with *n*-propylbromide and *iso*-propyliodide, respectively (Scheme 18). The hydroxyalkylation of α-naphthol with ethylpyruvate, catalyzed by the Lewis acid $CpZrCl_3$, was successfully carried out in a 1:2 mixture of [Bz-His(*n*-propyl)$_2$-OMe]Br (**2a**)/CH_2Cl_2 at room temperature. Unfortunately, the isolated product, obtained in 60% yield, was racemic.

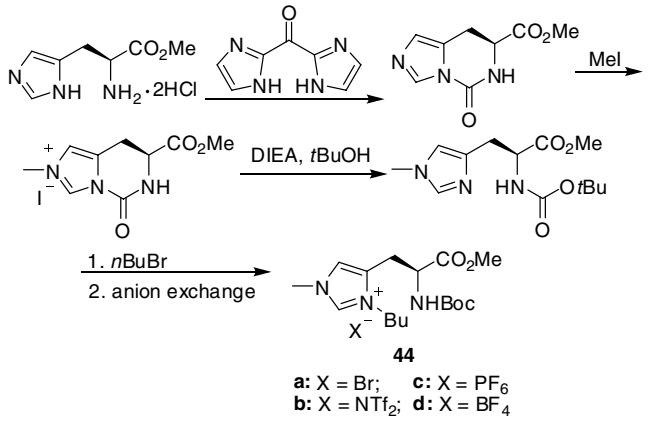
Moreover, treatment of CILs **42** with silver oxide gave the corresponding L-histidine derived chiral *N*-heterocyclic carbene complex. Its subsequent transmetallation by treatment with $Pd(CH_3CN)_2Cl_2$ or $[Rh(cod)Cl]_2$ led to the formation of the respective chiral late metal imidazol-2-yl-



Scheme 18. Synthesis of imidazolium CILs from L-histidine.

idene complexes. Four diastereomers of the square planar palladium system were observed. Due to the additional stereogenic center in the L-histidine derived 'Arduengo-carbene ligand', two diastereomers of the rhodium carbene complex were formed. The derivatives may become useful solvents, reagents or catalysts in reactions proceeding with transfer of their chiral features.

2.9.2. Amino acid and peptidic CILs. A handy access to a novel family of chiral amino acid and peptidic CILs (Fig. 3) starting from L-histidine was reported by Guillen et al.[32] By heating histidine methyl ester dihydrochloride with carbonyldiimidazole in the absence of solvent, the expected cyclic urea could be obtained. After alkylation with methyl iodide, the cyclic urea was then opened by *tert*-butanol to give the Boc-protected N-alkylated histidine methyl ester. Alkylation of the histidine derivative proceeded with *n*-bromobutane to give the desired chiral imidazolium salts **44a**, which then underwent an anion exchange reaction to give CILs **44b–d** (Scheme 19). The Boc-[bmHis][NTf_2]-OMe **44b** was conveniently transformed into various ionic structures (either unprotected **45**, mono O-protected **46** or mono N-protected **47**) using standard procedures. Monoprotected amino acids **46** and **47** combined with *N*-Boc-alanine (respectively, alanine *tert*-butylester) afforded the desired dipeptide **48** (respectively, **49**) in good yield. Peptide coupling of this new amino acid takes place with similar efficiency to that of classical examples, and occurs without racemization.

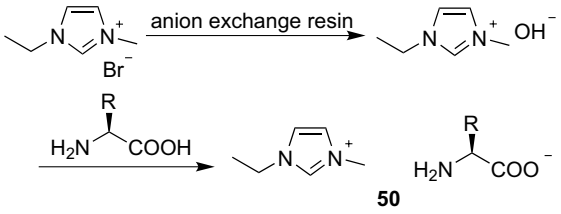


Scheme 19. Synthesis of imidazolium CILs **44** from L-histidine.

3. Chiral anions derived from natural amino acids

3.1. Amino acids employed directly as chiral anions

3.1.1. Chiral amino acid anions charge-compensated by imidazolium cations. ILs have often been designed using a series of cationic derivatives, due to their convenient chemical modification, while there is much less information about the effect of anion structure. The neutralizing reaction is one of the most efficient and atom-economical methods for the synthesis of ILs. In 2005, Ohno et al. developed a method for facile synthesis of CILs **50** containing amino acids as anions with the neutralizing reaction and 20 CILs were prepared by reaction of 1-ethyl- 3-methylimidazolium hydroxide ([emim]OH) aqueous solution with 20 natural amino acids.[33] The [emim]OH aqueous solution was prepared from [emim]Br by passing an aqueous solution of the salt through a column filled with anion exchange resins Amberlite (Scheme 20). The overall yields were fairly good, ranging between 66% and 89%. It was not difficult to obtain CILs with many different anions by this method. These proved quite helpful in analyzing the effect of the anion structure on the properties of the corresponding salts.



Scheme 20. Synthesis of imidazolium CILs possessing natural amino acid-based anions.

Then, the effect of anion structure on the physicochemical properties of the corresponding salts was analyzed. The side chains of the corresponding amino acid anions and hydrogen bonding in the ILs strongly affect the solubility of organic molecules, the glass transition temperature and the ionic conductivity. From the trends found in this study, one can estimate the glass transition temperature, the ionic conductivity, and the miscibility with organic solvents based upon the structure of the side chains on the component ions. These findings should be useful for designing

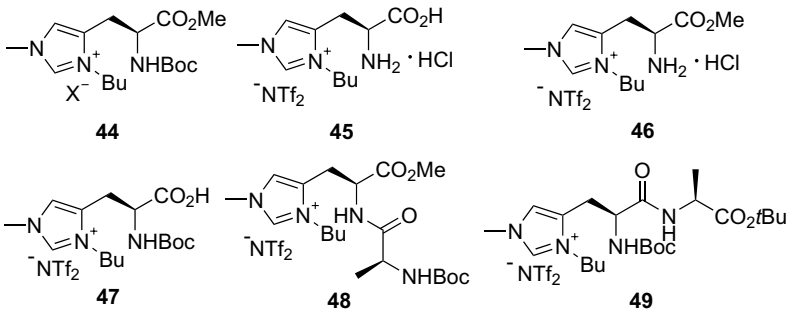


Figure 3. Imidazolium CILs from L-histidine.

suitable ILs for a wide variety of fields, such as intermediates for peptide synthesis, chiral solvents, functional materials, and biodegradable ILs.

3.1.2. Chiral amino acid anions charge-compensated by other cations. Other cations can also be used for preparing CILs with anions derived from amino acids. In 2006, Ohno et al. reported the design, synthesis, and properties of tetraalkylphosphonium-based amino acid ionic liquids.[34] At first, L-alanine-based salts with the cations of tetrabutylammonium ($[N_{4444}]^+$), triethylhexylammonium ($[N_{2226}]^+$), *N*-butyl-*N*-methylpyrrolidinium ($[P_{14}]^+$), butylpyridinium ($[Py_4]^+$), and tetrabutylphosphonium ($[P_{4444}]^+$) (Fig. 4) were investigated by the method[33] reported previously: the corresponding cation hydroxide aqueous solution was prepared with an anion exchange column, and then neutralized with L-alanine. In the case of $[Py_4]OH$, no reaction product was obtained after mixing with L-alanine. The thermal properties of the L-alanine salts obtained were subsequently investigated. $[P_{4444}][Ala]$ showed the best properties with the lowest glass transition temperature (T_g) of −70.2 °C and the highest decomposition temperature (T_{decomp}) of 286 °C. Its T_{decomp} was about 110 °C higher than that of the other salts. In the same way, $[P_{4444}][Ala]$ also had a lower T_g and a higher T_{decomp} than those of [emim][Ala]. In addition, $[P_{4444}]OH$ was quite stable and commercially. As a result, $[P_{4444}]^+$ may be a more appropriate cation to constitute the amino acid CILs.

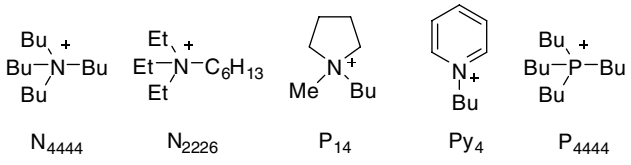


Figure 4. Cations used to prepare CILs with L-alanine.

$[P_{4444}]$-based amino acid CILs with the other 19 natural amino acids as anions have likewise been synthesized, and their physicochemical characteristics examined. The $[P_{4444}][His]$ showed only a melting point (T_m) at 85.9 °C, eleven salts showed only a T_g and eight salts showed both a T_m and a T_g. Sixteen out of 20 phosphonium-based amino acids had a lower T_g value than that of [emim][amino acid]. The T_g value of most $[P_{4444}]$[amino acid]s was about 10 °C lower than that of the corresponding [emim][amino acid]. The fact that all the glass transition temperatures of the phosphonium amino acids are lower than the [emim][amino acid]-type, may be due to the larger volume of the phosphonium cations. The effect of amino acid side chain structures on the T_g of $[P_{4444}]$[amino acid]s was similar to that for [emim][amino acid]s. The thermal stability of $[P_{4444}]$[amino acid]s was generally better than that of [emim][amino acid]s. In particular, the decomposition temperature of [emim][amino acid]s was around 220 °C, while that of several $[P_{4444}]$[amino acid]s was above 300 °C. Additionally, the viscosity of $[P_{4444}]$[amino acid]s was lower than that of the [emim][amino acid]s. Hydrogen bonding should increase the solution viscosity as well as increase the T_g value. Although [emim][Gly] had the lowest viscosity of all the [emim][amino acid]s, $[P_{4444}]$[amino acid]s, containing Ala^-, Met^-, Leu^-, Gly^-, and Val^-, had even lower viscosities. All $[P_{4444}]$[amino acid]s have a linear relationship between viscosity and T_g. Thus, for these ILs, the side chain structure did not affect the general relationship between T_g and viscosity. As far as melting point and viscosities were concerned, the tetrabutylphosphonium cation seemed to be best only for the amino acids.

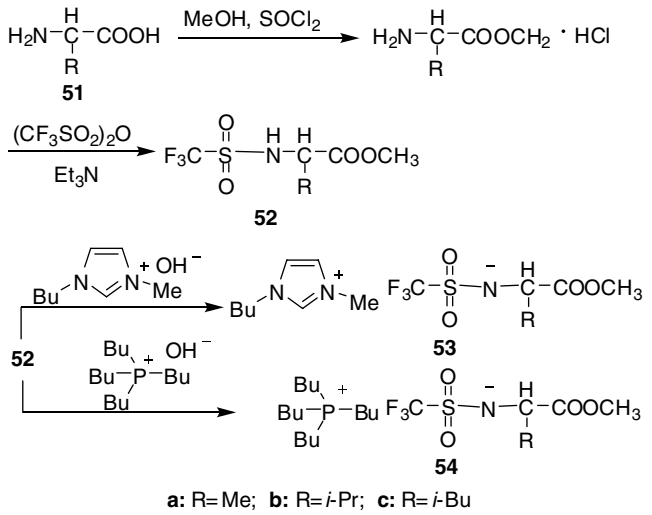
Tetraalkylphosphonium-based amino acid CILs showed good chemical and thermal stabilities, lower T_g values and higher decomposition temperatures than previously reported ammonium-based amino acid ILs;[33] they are expected to be used for various applications.

In 2006, Zhang et al. also reported the synthesis of a series of $[P_{4444}]$-based CILs with glycine, L-alanine, L-serine, and L-lysine as the anion from $[P_{4444}]Br$ by anion exchange and neutralization.[35] The ionic liquids were characterized by NMR, IR, and elemental analysis, and their thermal decomposition temperature, glass transition temperature, electrical conductivity, density, and viscosity were also recorded in detail. These CILs were further supported on porous silica gel and their CO_2 absorption behavior was investigated. The absorption rate of CO_2 by $[P_{4444}]$-based CILs supported over porous SiO_2 is significantly increased due to the large surface area of silica gel. The absorption of CO_2 is fast and reversible with a capacity of 50 mol % of the ionic liquids and the absorption equilibriums can all be reached in less than 100 min. The rates of CO_2 absorption by supported ionic liquids were much higher than those of the viscous ionic liquids themselves. The absorbed CO_2 can be released in a vacuum at room temperature over several hours. Four cycles of absorption/desorption were repeated and no changes in the absorption capacity or the rates were observed. The absorption capacity of these CILs can be improved via the addition of small amounts of water. For example, in the presence of 1 wt % water, equimolar amounts of CO_2 to the ionic liquids could be absorbed. Extensive studies showed that the CO_2 absorption mechanisms by the ionic liquids with and without water were quite different.

3.2. Modified amino acids as chiral anions

Most of these amino acid anions contain functional groups such as amino groups, carboxyls, and hydroxyls. This may open up new applications through the introduction of further functionality on the anions. Ohno and Fukumoto first reported the design and synthesis of new ILs composed of chiral and hydrophilic anions, which were derived from natural amino acids and modified with the trifluoromethane sulfonyl group and methyl ester group.[36] L-Alanine **51a** was treated first with thionyl chloride in methanol to afford a white solid, which was then suspended in dichloromethane. After the addition of triethylamine and trifluoromethanesulfonic anhydride, the mixture was stirred overnight at room temperature. The resulting solution was washed and concentrated to produce an oil-like liquid, which was purified by column chromatography to provide the corresponding *N*-trifluoromethane sulfonyl amino acid

methyl ester **52a**. Finally, the ester was neutralized with $[P_{4444}]OH$ or [bmim]OH to provide the expected CIL **53a** or **54a**. CILs **53b**, **53c**, **54b**, and **54c** were synthesized from L-valine and L-leucine in a similar way (Scheme 21).



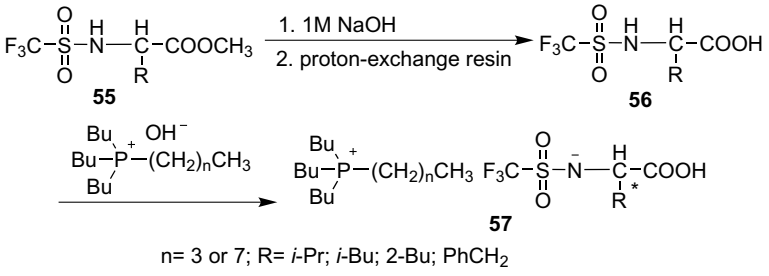
Scheme 21. Synthesis of hydrophilic CILs from natural amino acids.

The T_m and T_g of these CILs were higher than those of typical hydrophobic ILs, such as [bmim][Tf_2N]. However, in the case of CILs **53**, the imide anion derived from the amino acid led to a lower T_m than that of $[P_{4444}][Tf_2N]$. Amino acid-derived imide anions gave superior ILs to Tf_2N anion when partnered with phosphonium cations. The ILs synthesized also showed a gradual increase in T_g according to the length of the side chain of the starting amino acid. The T_{decomp} of these ILs was around 250 °C. The viscosity of the ILs prepared was affected mainly by their T_g, and increased according to the alkyl side chain length. The CILs were less viscous than some other above mentioned CILs. The asymmetric imide anion structure and relatively small formula weight of the anion would generate CILs of less viscosity than other CILs, although the introduction of an imide function on the amino acid can increase the viscosity of these CILs. The chirality of anions and the corresponding CILs was confirmed by specific rotation measurements. No significant racemization of the corresponding CILs was observed when the onium hydroxide was neutralized by an amino acid and followed by drying at 70 °C for 24 h. In addition, the CILs maintained their chiral integrity even after heating at 100 °C for a few hours.

As to the hydrophobicity of the prepared CILs, the [bmim] salts were wholly miscible with water, but $[P_{4444}]$ systems showed two phase separation. When combined with the $[P_{4444}]$ cation, amino acid derivatives yielded hydrophobic CILs. Hydrophobic alkyl chains covering the phosphorus atom may contribute to hydrophobicity. The water content of the CIL-rich phase of the $[P_{4444}]$[L-Ala] system was 5.1 wt %, while for $[P_{4444}]$[L-Leu] the water content was 2.9 wt %. Hence the hydrophobicity of the CILs is easily controllable by changing the side chain of the amino acids used. The use of different amino acids as starting materials allows a choice of the physico-chemical properties of the prepared CILs.

In 2007, Ohno and Fukumoto had also reported the synthesis of new CILs from natural amino acids, which exhibited lower critical solution temperature (LCST)-type phase separation with water.[37] At first, *N*-trifluoromethanesulfonyl amino acid methyl esters **55** were synthesized from amino acids (L-valine, L-leucine, L-isoleucine, and L-phenylalanine) using the reported method.[36] The esters were then hydrolyzed with an NaOH solution and the sodium ions were removed with a proton-exchange resin to obtain *N*-trifluoromethanesulfonyl (Tf) amino acids **56**. Finally, CILs **57** with tetra-*n*-butylphosphonium ($[P_{4444}]$) cations or more hydrophobic tri-*n*-butyloctylphosphonium ($[P_{4448}]$) cations were obtained by neutralization of the corresponding amino acids with $[P_{4444}]OH$ or $[P_{4448}]OH$ (Scheme 22). CILs with $[P_{4444}]$ were solids, with melting points in the range 50–65 °C, while $[P_{4448}]$[Tf-Leu] displayed no melting point but did have a glass transition temperature of −50 °C. The chirality of the resulting ILs was also measured by specific rotation measurements.

As all the CILs synthesized in this study exhibited LCST-type phase behavior with water, the LCST-type phenomenon does not depend on the specific structure of the side chains on the anions. The phase-separation temperature of these mixtures depends reproducibly on the water content and ion structure. An increasing water content in the mixture and an increase in the hydrophobicity of the side chain can lower the phase-separation temperature. These results imply that the phase separation temperature of the mixture can be controlled by the side chain structure on the starting amino acid, by the alkyl chain length of the cation and by the water/IL ratio.



Scheme 22. Synthesis of LCST-type CILs from natural amino acids.

4. Conclusion

In conclusion, natural amino acids, which are readily available at low cost and offer interesting molecular diversity from which could be built a large variety of structures, provide a vast range of new opportunities for the design, synthesis and application of functional CILs. The materials highlighted in this review are only the beginning of what promises to be an exciting new area of creative exploration as chemists design the next generation of ideal solvents. It is a field of tremendous potential that will expand rapidly in the coming years.

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