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Design and synthesis of fused-ring chiral ionic liquids from amino acid derivatives

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Abstract—Six novel imidazolium salts, which contain a chiral moiety as well as a fused-ring system, have been designed, synthesized, and fully characterized. The synthesis of these ionic liquids is concise and practical due to the commercial availability of the starting materials. These imidazolium compounds were readily prepared from 1-methyl-2-imidazoliumcarboxaldehyde and chiral amino alcohols. Salts that contain the PF_6 anion were solids, but salts with the NTf_2 anion were liquids at room temperature. We envision that these new chiral imidazolium compounds can serve as effective reaction media as well as chiral catalysts for asymmetric reactions, which are presently being investigated in our lab.

The interest in using room temperature ionic liquids (RTILs) as potential replacement solvents for organic synthesis,[1,2] extraction,[3] electrochemistry,[4] and material science[5] has increased tremendously in the recent years. Owing to the unique combination of properties that ionic liquids possess, they are rapidly becoming the solvent of choice for a wide variety of reactions; they are recyclable and most are stable over a very wide temperature range.[6] In recent years, the use of chiral RTILs as reaction media for asymmetric organic reactions,[7] chiral discrimination, analytical chemistry, as well as optical resolution of racemic mixtures[8] has increased dramatically. Research into the effects that chiral ionic liquids have on the outcomes of asymmetric reactions is in the preliminary stage; to date there are only a few chiral ionic liquids that have been designed, synthesized and effectively used as solvents for asymmetric reactions.[7,9]

RTILs consist of cations and anions; cations are typically imidazolium or pyridinium species and anions normally include halogen anions, AlX_4^-, BF_4^-, PF_6^-, $CF_3SO_3^-$, or $(CF_3SO_3)_2N^-$.[10] By modifying the structures of the cations or anions, the properties of RTILs can be changed to meet specific solvation requirements in order to influence reaction outcomes.[11] Imidazolium cation-derived chiral RTILs are ideal candidates for solvents due to their facile preparation, their low melting points, and relatively favorable viscosity. As a result, they have gained widespread usage as potential green solvents for a number of reactions. Shown in Figure 1 are some imidazole-derived chiral RTILs that have synthesized. They include imidazolium ionic liquids that contain chiral moieties bonded to one or both of the nitrogen atoms (**I**–**VI**);[7c,d,12] chirality bonded to positions 4 (**VII**)[12f] and 2 (**VIII**);[13] and one that has a sprio skeleton (**IX**).[14]

Owing to the relative acidity of the hydrogen in the 2-position of most imidazolium-based ionic liquids (e.g., **I**–**IV** and **VII** in Fig. 1), they often undergo deprotonation to give undesired side products when used as solvents.[15] For example, Aggarwal and co-workers have reported that when the ionic liquid butylmethylimidazolium chloride is used as the solvent for the Baylis–Hillman reaction, deprotonation of the imidazolium proton results and unwanted side products are produced.[16] Therefore, there is a great urgency to design and synthesize novel chiral ionic liquids to overcome this type of problem. Recently, we designed and synthesized a new class of chiral ionic liquids **VIII** (Fig. 1),[13] which has a chiral moiety bonded to the 2-position of the imidazolium cation. We envisaged that the introduction of a rigid fused skeleton into ionic liquids would produce a novel class of chiral ionic liquids, which would be an efficient class of solvents for asymmetric reactions. Herein, we describe the synthesis of a novel

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Keywords: Ionic liquids; Chirality; Asymmetric reactions; Green solvents.

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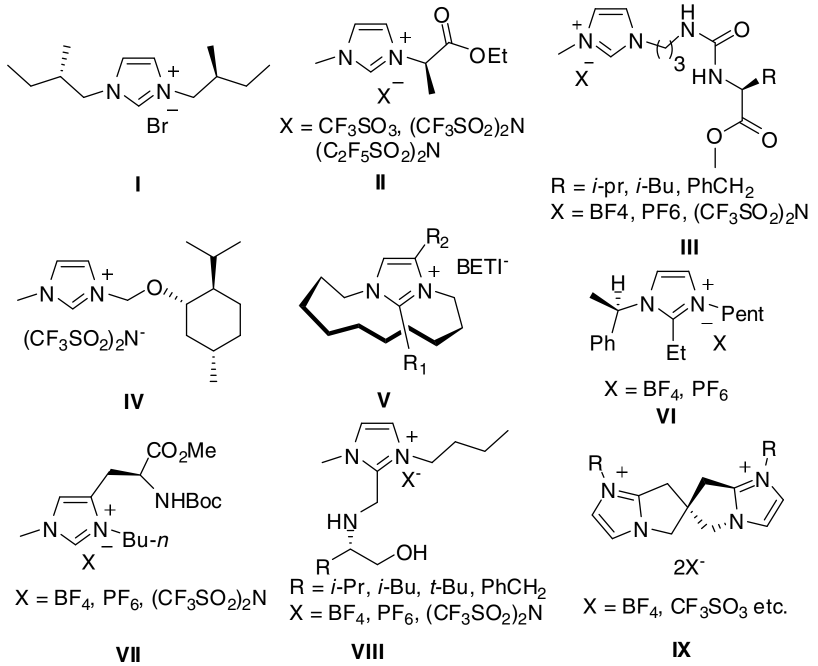


Figure 1. Known chiral imidazolium-based ionic liquids.

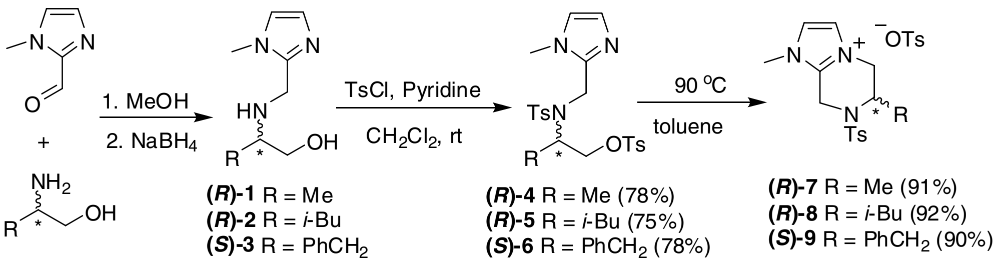
set of chiral RTILs, in which the chiral moiety is bonded to the nitrogen, and most important, there is a substitution at the 2-position. The present design is concise and practical because of the ready availability of the starting materials.

As shown in Scheme 1, the condensation of 1-methyl-2-imidazolecarboxaldehyde with (*R*)-2-amino-1-propanol, (*R*)-leucinol, and (*S*)-3-phenyl-2-amino-propanol in MeOH afforded the corresponding Schiff base precursors, which were reduced with $NaBH_4$ to give the desired imidazole derivatives (***R***)-**1**, (***R***)-**2**, and (*S*)-**3**.[13] Treatment of (***R***)-**1**, (***R***)-**2**, and (*S*)-**3** with *p*-toluenesulfonyl chloride gave the corresponding double tosylate compounds (***R***)-**4**, (***R***)-**5**, and (*S*)-**6**, which were subjected to the ring-closure reaction in toluene by heating to 90 °C to form the chiral tosylate salts (***R***)-**7**, (***R***)-**8**, and (*S*)-**9** in 90–92% yields.

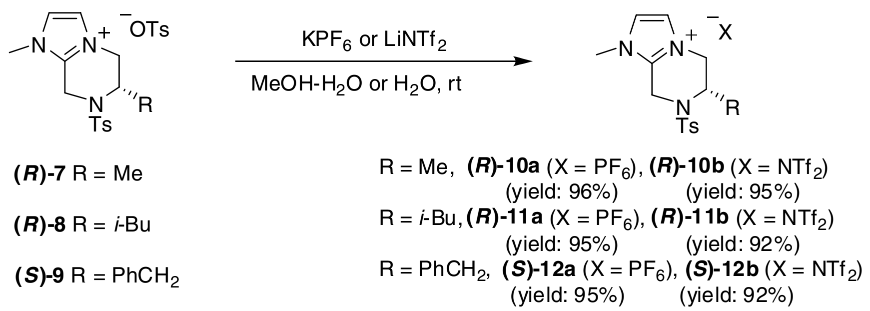
The next set of reactions involves the transformation of the anion tosylate salts via ion exchange to give the PF_6 and NTf_2 chiral ionic liquids (Scheme 2). Chiral imidazolium hexafluorophosphates (***R***)-**10a**, (***R***)-**11a**, and (*S*)-**12a** were prepared by the treatment of their prescursors, imidazolium tosylate (***R***)-**7**, (***R***)-**8**, and (*S*)-**9**, with potassium hexafluorophosphate in methanol and water at room temperature for 12 h to give yields of 95–96%. Similarly, imidazolium bis(trifluoromethanesulfonyl)imides were obtained in 92–95% yields (Scheme 2).[17]

All the fused imidazolium salts were characterized by spectroscopic analysis. Furthermore, to ensure that the ring-closure reaction occurred successfully, X-ray crystallographic analysis was carried out on (***R***)-**11a**.[18] The X-ray crystal structure is shown in Figure 2. ^{1}H NMR deuterium exchange experiments demonstrate that these chiral ionic liquids do not deprotonate at the CH_2 position, adjacent to the 2-position of the imidazolium cation in neutral conditions, such as D_2O, but they do deprotonate in basic media that contain Et_3N.

In conclusion, six novel imidazolium salts, which contain a chiral moiety as well as a fused-ring system, have been designed, synthesized and characterized. The ring-closure reaction was successful as proven by X-ray crystallographic analysis. The synthesis of these ionic liquids is concise and practical due to the commercial availability of the starting materials. These imidazolium compounds were readily prepared from 1-methyl-2-imi-



Scheme 1. Reagents and reaction conditions for the synthesis of fused-ring ionic liquids.



Scheme 2. Reagents and reaction conditions for the ion exchange reaction.

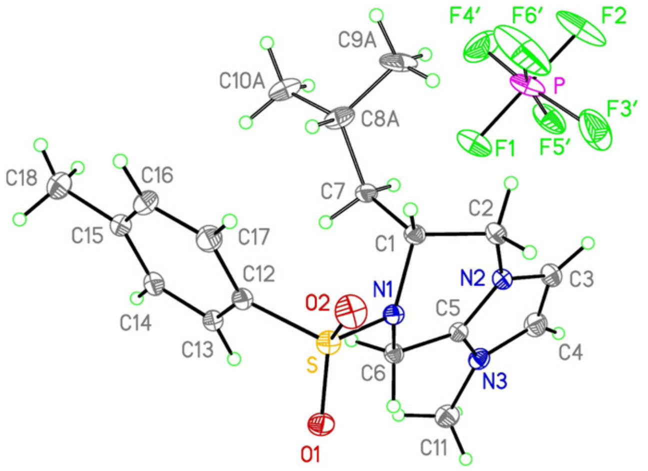


Figure 2. X-ray crystal structure of (***R***)-**11a**.

dazoliumcarboxaldehyde and chiral amino alcohols. Salts that contain the PF_6 anion were solids at room temperature, but salts with the NTf_2 anion were liquids at room temperature. We envision that these new chiral imidazolium compounds can serve as effective reaction media as well as chiral catalysts for asymmetric reactions, which are presently being investigated in our lab.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.072.

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17. For the detailed experimental procedure, see Ref. 13. For analytical data, see Supplementary data.
18. Crystal data for (***R***)-**11a**: $C_{18}H_{26}F_6N_3O_2PS$, $M = 493.45$, orthorhombic, $a = 6.2571(3)$, $b = 15.2826(7)$, $c = 23.1499(1)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2213.70(18)$ Å^3, $T = 223(2)$ K, space group $P2(1)2(1)2(1)$, $Z = 4$, reflections collected/unique: 40784/7842 ($R_{\text{int}} = 0.0276$), final R indices [$I > 2\text{sigma}(I)$] $R_1 = 0.0442$, $wR2 = 0.1092$, CCDC 630998.