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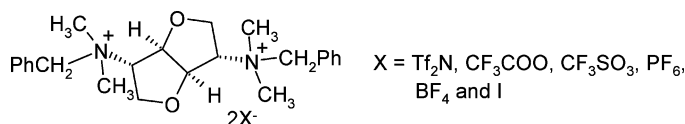
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ABSTRACT



Carbohydrate-based novel bis(ammonium) chiral ionic liquids have been synthesized by following a straightforward protocol using isomannide as the substrate. Their applications in chiral discrimination and optical resolution of racemates have been established.

Ionic liquids (ILs) have shown tremendous applications in modern organic chemistry due to their inimitable physical and chemical properties, which allow them to enhance the reaction kinetics and selectivity and to facilitate catalyst recovery, etc.¹ Significant progress along this line has been made with the development of chiral ionic liquids (CILs).² Although, CILs are at a premature phase of development, they have already found promising applications in asym-

metric synthesis,³ stereoselective polymerization,⁴ chromatography,⁵ liquid crystals,⁶ and chiral resolution and as NMR shift reagents.⁷ The studies so far reveal the prospective of such media and further encourage the synthesis of novel CILs

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(1) (a) Sheldon, R. A. *Green Chem.* **2005**, 7, 267. (b) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, 68, 351. (c) Welton, T. *Chem. Rev.* **1999**, 99, 2071. (d) Wasserchied, W.; Kim, W. *Angew. Chem., Int. Ed.* **2000**, 39, 3772. (e) Sheldon, R. A. *Green Chem.* **2001**, 2399. (f) Zhao, H.; Malhotra, S. V. *Aldrichimica Acta* **2002**, 35, 75. (g) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, 60, 1015.

(2) (a) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A.-C.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2003**, 14, 3081. (b) Ding, J.; Armstrong, D. W. *Chirality* **2005**, 17, 281. (c) Baudequin, C.; Bregeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, 16, 3921.

(3) (a) Pegot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, 45, 6425. (b) Ding, J.; Desikan, V.; Han, X.; Xiao, T. L.; Ding, R.; Jenks, W. S.; Armstrong, D. W. *Org. Lett.* **2005**, 7, 335. (c) Wang, Z.; Wang, Q.; Zhang, Y.; Bao, W. *Tetrahedron Lett.* **2005**, 46, 4657. (d) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, 38, 3097. (e) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, 45, 3093. (f) Malhotra, S. V.; Wang, Y. *Tetrahedron: Asymmetry* **2006**, 17, 1032.

(4) (a) Biedron, T.; Kubisa, P. *Polym. Int.* **2003**, 52, 1584. (b) Biedron, T.; Kubisa, P. *J. Polym. Sci. Part A: Polym. Chem.* **2005**, 43, 3454. (c) Ma, H.-Y.; Wan, X.-H.; Chen, X.-F.; Zhou, Q.-F. *Chin. J. Polym. Sci.* **2003**, 21, 265.

(5) (a) Ding, J.; Welton, T.; Armstrong, D. W. *Anal. Chem.* **2004**, 76, 6819. (b) Rizvi, S. A. A.; Shamsi, S. A. *Anal. Chem.* **2006**, 78, 7061.

(6) (a) Baudoux, J.; Judeinstein, P.; Cahard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **2005**, 46, 1137. (b) Tosoni, M.; Laschat, S.; Baro, A. *Helv. Chim. Acta* **2004**, 87, 2742.

(7) (a) Wasserscheid, P.; Bosmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200. (b) Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* **2004**, 1224. (c) Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A.-C. *Chem. Commun.* **2003**, 2914. (d) Ishida, Y.; Miyauchi, H.; Saigo, K. *Chem. Commun.* **2002**, 2240. (e) Ishida, Y.; Sasaki, D.; Miyauchi, H.; Saigo, K. *Tetrahedron* **2004**, 45, 9455. (f) Jurcik, V.; Wilhelm, R. *Tetrahedron: Asymmetry* **2006**, 17, 801.

from easily available sources, especially from biorenewable sources.

Isosorbide and isomannide are renewable, inexpensive, and commercially available chiral carbohydrates derived by dehydration of glucose derivatives sorbitol and mannitol, respectively, which are major components of corn oil and obtained as byproducts of the starch industry. Major applications of these compounds are in the polymer, cosmetic, and pharmaceutical industries. They are used as monomers for the synthesis of biodegradable and high T_g polymers⁸ and as starting materials for pharmaceutically important compounds including vasodilators^{9a,b} and Xa-inhibitors.^{9c} Their catalytic utilities as chiral ligands or as phase transfer catalysts have also been reported in a variety of important reactions such as alkylations,¹⁰ Diels–Alder reactions,¹¹ and asymmetric hydrogenations,¹² etc. Nevertheless, very few studies have investigated their synthetic utility as valuable chiral pool compounds.¹³

Recently, in a continuation of our efforts in the production and applications of new CILs from readily available natural chiral auxiliaries,^{3f} we have used isomannide for the synthesis of a series of monoammonium CILs. In that approach, one of the hydroxyl groups of isomannide was protected as the ethyl ether and the other hydroxyl was converted to an ammonium salt in combination with different anions to form a series of CILs (Figure 1). These CILs were utilized for

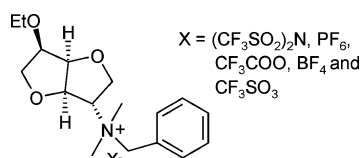
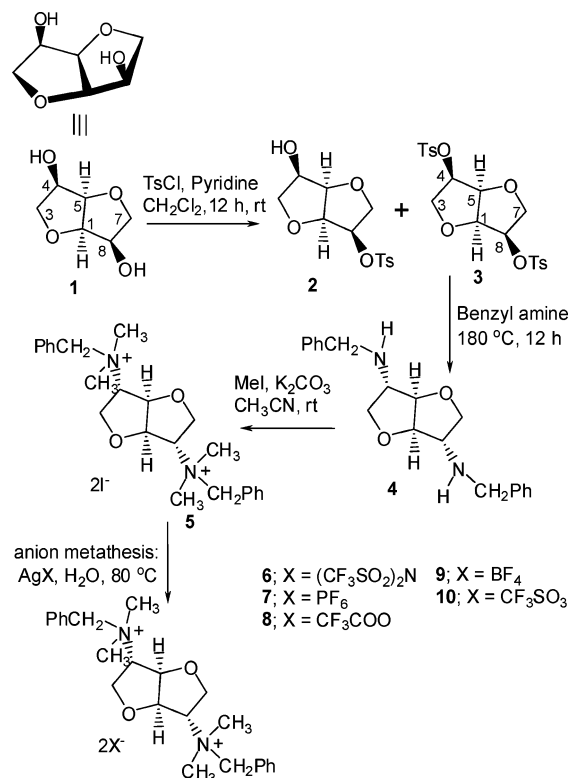


Figure 1. Monoammonium CILs derived from isomannide.

chiral resolution of racemic Mosher's acid and showed remarkable results. This prompted us to synthesize bis-(ammonium) CILs by functional group interconversion of both the hydroxyl groups of isomannide to ammonium salts. D-Isomannide, also known as (1*R*,4*R*,5*R*,8*R*)-2,6-dioxabicyclo-[3.3.0]octan-4,8-diol (**1**) was first tosylated with *p*-toluene-

sulfonyl chloride using pyridine as base to give the monotosyl derivative **2** as the major and ditosyl derivative **3** as the minor product. Because the two hydroxyl groups and also the two heterocyclic rings of isomannide are cis-oriented (Scheme 1) formation of the ditosyl derivative is sterically unfavorable

Scheme 1. Synthesis of Bis(ammonium) CILs from Isomannide



and obtained only as a minor product even when using an excess of *p*-toulensulfonyl chloride.

The monotosyl derivative **2** was utilized for the synthesis of monoammonium CILs. The isomannide ditosylate **3** was reacted with an excess of benzylamine at 180 °C under an atmosphere of nitrogen to get the bis-secondary amine **4** (Scheme 1). It is essential to use benzylamine in excess, so that it is sufficient for the substitution reaction as well as to trap the tosylate. Also, on the basis of literature reports,^{11,14} it is important to carry out the reaction above 165 °C to avoid chances of incomplete substitution and the possibility of elimination reactions to give unsaturated products. As a result of S_N2 substitution of the ditosylate **3** to bis-secondary amine **4**, the inversion in configuration at both centers occurs, converting the isomannide nucleus to an isoidide nucleus where both amino groups are pointing downward. The quaternization of bis-secondary amine **4** was carried out with methyl iodide to get the bis(ammonium iodide) **5**. The structure and stereochemistry of **5** were established by ¹H and ¹³C NMR spectroscopy and further confirmed by X-ray studies (Figure 2). The bis(ammonium iodide) **5** was used

(8) (a) Kricheldorf, H. R.; Gomourachvili, Z. *Macromol. Chem. Phys.* **1997**, *198*, 3149. (b) Adelman, D. J.; Charbonneau, L. F.; Ung, S. United States Patent 6656577. (c) Okada, M.; Okada, Y.; Aoi, K. *J. Polym. Sci.: Part A Polym. Chem.* **1995**, *33*, 2813. (d) Okada, M.; Tsunoda, K.; Tachikawa, K.; Aoi, K. *J. Appl. Polym. Sci.* **2000**, *77*, 338.

(9) (a) Bidoggia, H. *Curr. Med. Res. Opin.* **1987**, *10*, 601. (b) Walker, J. M.; Curry, P. V.; Bailey, A. E.; Steare, S. E. *Int. J. Cardiol.* **1996**, *53*, 117. (c) Vogler, M.; Koert, U.; Harms, K.; Dorsch, D.; Gleitz, J.; Raddatz, P. *Synthesis* **2004**, 8, 1211. (d) Osterkamp, F.; Wehlan, H.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L. *Tetrahedron* **1999**, *55*, 10713.

(10) Kumar, S.; Ramachandran, U. *Tetrahedron* **2005**, *61*, 4141.

(11) De Coster, G.; Vandyck, K.; Van der Eycken, E.; Van der Eycken, J.; Elseviers, M.; Roperb, H. *Tetrahedron: Asymmetry* **2002**, *13*, 1673.

(12) Carcedo, C.; Dervisi, A.; Fallis, I. A.; Ooi, L.; Abdul Malik, K. M. *Chem. Commun.* **2004**, 1236.

(13) (a) Cera, V.; Mazzini, C.; Paolucci, C.; Pollicino, S.; Fava, A. *J. Org. Chem.* **1993**, *58*, 4567. (b) Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, *54*, 3113. (c) Loupy, A.; Mountex, D. A. *Tetrahedron* **2002**, *58*, 1541.

(14) Cope, A.; Shen, T. Y. *J. Am. Chem. Soc.* **1956**, *78*, 3177.

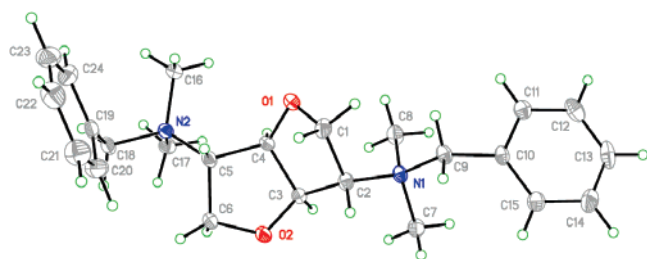


Figure 2. X-ray structure of the cationic part of compound **5**.

for anion exchange reactions in an aqueous medium to obtain other chiral salts with different anions. The solubility of iodide salt **5** is low in water at room temperature, and the reactions were, therefore, carried out at 80 °C. Thus, the desired bis(ammonium) CILs **5–10** have been synthesized following a simple protocol involving functional group interconversions followed by anion exchange (Scheme 1).

The melting point comparison of all these bis(ammonium) CILs is mentioned in Table 1. As reported in the literature,¹⁵

Table 1. Melting Points of Bis(ammonium) CILs

entry	CIL	anion	mp (°C)
1	5	[I]	190
2	6	[Tf ₂ N]	60
3	7	[PF ₆]	251
4	8	[TFA]	65
5	9	[BF ₄]	240
6	10	[TfO]	75

the nature of the anions was found to have a profound effect on the melting points. The CILs with [Tf₂N], [TFA], and [TfO] anions have low melting points due to delocalization of charge through the S–N–S, O–C–O, and O–SO₂ core, respectively. This delocalization results in a decreased Coulombic interaction between the cation and the anion compared to the salts with more localized anion charges, such as the [I], [PF₆], and [BF₄].

After their successful synthesis, the chiral recognition ability of these new CILs was tested by investigating the diastereomeric interaction between the CILs and racemic Mosher's acid silver salt. The iodide salt **5** was mixed with racemic Mosher's acid silver salt in CD₃CN, and the resulting solution containing Mosher's acid chiral ammonium salt **A** was measured by ¹⁹F NMR spectroscopy. High splitting of the CF₃ signal [Figure 3, spectrum (a)] shows an excellent diastereomeric interaction between Mosher's carboxylate and the bis(ammonium) cation. When the same NMR solution was mixed with 1 equiv of CIL **6**, the splitting was further

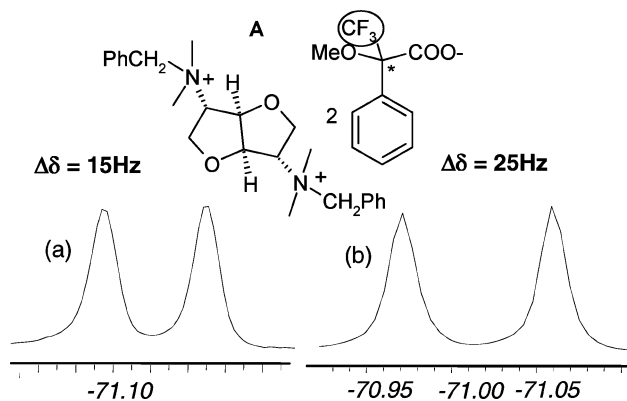


Figure 3. ¹⁹F NMR (282.4 MHz) signals of CF₃ of salt **A** (a) and salt **A** in the presence of 1 equiv of CIL **6** (b).

enhanced [Figure 3, spectrum (b)]. Similar experiments were carried out in the presence of 4 equiv of each of the CILs, and the results are summarized in Table 2. As expected, the

Table 2. Enhanced $\Delta\delta$ Values of CF₃ Signals of Racemic Mosher's Carboxylate of Salt **A** in the Presence of 4 equiv of CILs

entry	CILs	CIL anions	$\Delta\delta$ (Hz) ^a
1	5	[I]	9
2	6	[Tf ₂ N]	23
3	7	[PF ₆]	21
4	8	[TFA]	8
5	9	[BF ₄]	17
6	10	[TfO]	15

^a Recorded by ¹⁹F NMR at 282.4 MHz.

anions of CILs were found to have a profound effect on the chiral discrimination ability as indicated by the enhancement in the chemical shift dispersion (Table 2).

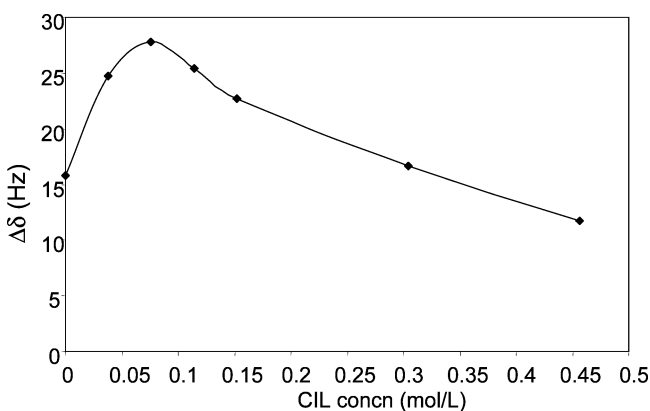


Figure 4. Concentration effect of CIL **6** on the chemical shift of the CF₃ signal (¹⁹F NMR, 282.4 MHz) of racemic Mosher's carboxylate.

(15) (a) Kim, K.; Lang, C. M.; Kohl, P. A. *J. Electrochem. Soc.* **2005**, *152*, E56. (b) Pringle, J. M.; Golding, J.; Baranyai, K.; Forsyth, C. M.; Deacon, G. B.; Scotta, J. L.; MacFarlane, D. R. *New J. Chem.* **2003**, *27*, 1504.

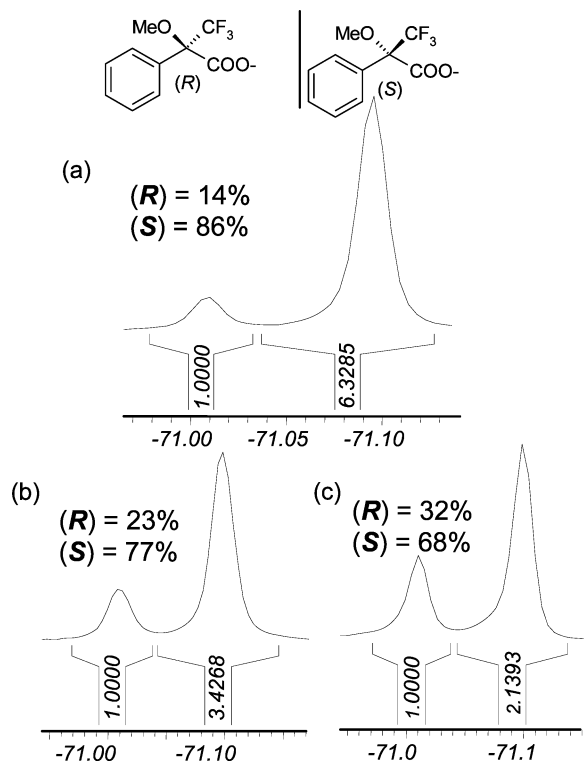


Figure 5. Determination of ee values of Mosher's carboxylate with (*R/S*) = 1:6 (a); 1:3 (b); and 1:2 (c) using CIL **6**.

The concentration effect of CIL **6** on the chemical shift difference of two diastereomeric $-\text{CF}_3$ groups was also studied (as indicated by the $\Delta\delta$ values) and is demonstrated in Figure 4. Interestingly, the increase in the $\Delta\delta$ values with increased CIL concentration reaches a saturation point with 2 equiv (0.076 mol/L) of **6**. Further increase in CIL **6**

concentration results in a gradual decrease in CF_3 signal splitting (Figure 4).

Due to its high chiral discrimination ability, CIL **6** was then utilized in determination of the ee values of three different enantiomerically enriched mixtures of Mosher's carboxylate with approximately *R/S* = 1:6 (Figure 5a), 1:3 (Figure 5b), and 1:2 (Figure 5c), which were prepared by mixing the silver salt of racemic Mosher's acid and (*S*)-Mosher's acid. The exact amount of enantiomers can easily be calculated by integration of the CF_3 signal of each enantiomer of Mosher's carboxylate.

In conclusion, we have synthesized a new class of isomannide-based CILs. The diastereomeric interactions between these CILs and racemic substrates during NMR spectroscopy prove their excellent chiral recognition ability. The high chemical shift dispersion induced by CILs indicate their potential applications in optical resolution of racemates, as chiral shift reagents, and in determining the enantiomeric excess of enantiomerically enriched carboxylates by NMR spectroscopy. Further research into applications of these CILs as reaction media and as a phase transfer catalyst in asymmetric synthesis is in progress in our laboratory.

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Supporting Information Available: Detailed experimental procedures, ^1H (300 MHz), ^{13}C (75.5 MHz), and ^{19}F NMR (282.4 MHz) data, and X-ray data. This material is available free of charge via the Internet at <http://pubs.acs.org>. The X-ray data of compound **5** can be accessed from <http://www.ccdc.cam.ac.uk> (deposition number CCDC 656175).

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