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Simple and straightforward synthesis of novel enantiopure ionic liquids via efficient enzymatic resolution of (±)-2-(1*H*-imidazol-1-yl)cyclohexanol

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Abstract—Both enantiomers of enantiopure imidazolium ionic liquids were synthesized by a simple and straightforward procedure from (*R*,*R*)- and (*S*,*S*)-2-(1*H*-imidazol-1-yl)cyclohexanol derivatives obtained via lipase-catalyzed resolution. Structural properties and thermal stability of these compounds have been studied to elucidate their potential applications in asymmetric catalysis.

Ionic liquids (ILs) are attracting considerable attention as reaction solvents,[1] extraction liquids,[2] and electrolyte materials[3] as a result of their remarkable properties. ILs are now expected to be designed liquids with controllable physical and chemical properties or even specific functions (task-specific ILs).[4] Structural diversity often plays an important role in ionic liquid physicochemical properties.[5] The introduction of chirality is by far one of the goals mostly pursued by organic chemists. Therefore, the design and synthesis of novel enantiopure ionic liquids with the possibility of easy structural tuneability is highly attractive. In this sense, a great effort is being devoted to design and synthesize chiral ionic liquids (CILs).[6] However, most of the known CILs are derived from chiral pools and provide a very limited scope for structural modifications.[7] Herein, we describe a flexible and simple synthetic approach for the synthesis of chiral imidazolium salts as potential ionic liquids prepared from chiral (1*R*,2*R*)-2-(1*H*-imidazol-1-yl)cyclohexyl acetate and (1*S*,2*S*)-2-(1*H*-imidazol-1-yl)cyclohexanol obtained through lipase-catalyzed resolution.

The chemical synthesis of (±)-2-(1*H*-imidazol-1-yl)cyclohexanol (±)-**3** was developed as described by Yus and co-workers,[8] and the enzymatic resolution of the racemic alcohol **3** was performed by biocatalyzed enantioselective acylation (Scheme 1). Firstly, the reaction was carried out using *Candida antarctica* lipase B (CAL-B) and a 3-fold excess of vinyl acetate as acyl donor in THF at 30 °C (Table 1, entry 1).[9]

The O-acylation of the (*R*,*R*)-**3** enantiomer took place smoothly and a 49% conversion was reached after 39 h. Both the substrate and the product were isolated with very high enantiomeric excesses and an excellent enantioselectivity (E >200). The resolution was faster when *Pseudomonas cepacia* lipase (PSL-C) was used instead of CAL-B finding a 50% of conversion just after 14 h (entry 2). The reaction in *tert*-butyl methyl ether (TBME) using PSL-C at 30 °C led to (*R*,*R*)-**4** in

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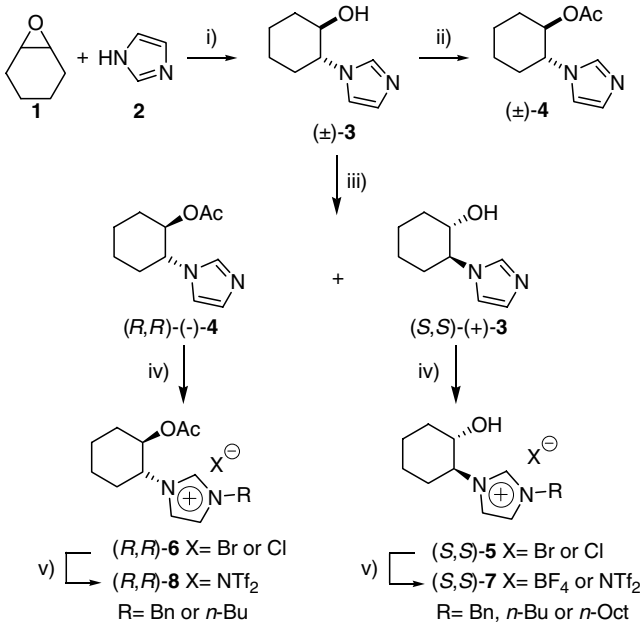

Scheme 1. Synthesis of enantiopure ILs. Reagents and conditions: (i) 60 °C; (ii) Ac_2O (2 equiv), DMAP (0.33 equiv), NEt_3 (3 equiv), CH_2Cl_2, rt; (iii) vinyl acetate (3 equiv), enzyme, solvent, 30 or 45 °C, 250 rpm; (iv) RX, Δ; (v) $NaBF_4$ (2 equiv) or $LiNTf_2$ (1.1 equiv), MeOH–H_2O, rt.

Table 1. Lipase-catalysed resolution of (±)-**3**

Entry	Enzyme	Solvent	T (°C)	t (h)	ee_S[a] (%)	ee_P[a] (%)	c[b] (%)	E[c]
1	CAL-B	THF	30	39	93	98	49	>200
2	PSL-C	THF	30	14	97	98	50	>200
3	PSL-C	TBME	30	13	33	>99	25	>200
4	PSL-C	TBME	45	15	>99	>99	50	>200

[a] Calculated by chiral HPLC analysis, ee_S refers to the enantiomeric excess of the substrate and ee_P for the enantiomeric excess of the product.
[b] $c = ee_S/(ee_S + ee_P)$.
[c] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_P)]$.

enantiopure form. However, the conversion and enantiomeric excess for the substrate were very low, due to the low solubility of this substrate in TBME (entry 3). This problem was overcome by using a higher temperature. Under these conditions (*R*,*R*)-**4** and (*S*,*S*)-**3** were both obtained in their enantiopure forms (>99% ee) and in good isolated yields: 91% and 88%, respectively (entry 4). The assignment of the absolute configuration of (+)-**3** was done on the basis of its X-ray crystal structure (see Supplementary data).

The imidazole salts (**5a**–**d** and **6a**,**b**) derived from both hydroxy (*S*,*S*)-**3** and acetylated (*R*,*R*)-**4** imidazole compounds were obtained in high to excellent isolated yields (88–96%) by heating the chiral imidazole derivatives with the corresponding halogenated reagent (Table 2, entries 1–6). The exchange of imidazolium salts with different anions (BF_4^-, NTf_2^-) led to the corresponding compounds **7a**–**f** and **8a** also in high yields (entries 7–13). Some representative properties of enantiopure IL are summarized in Table 2.

Table 2. Synthesis and structural properties of ILs

Entry	IL	R	Anion	Yield (%)	T_m[c]	$[\alpha]_D$
1	**5a**	Bn	Cl	88[a]	219	+7.0
2	**5b**	Bn	Br	96[a]	188	+6.3
3	**5c**	*n*-Bu	Cl	94[a]	7	+8.1
4	**5d**	*n*-Oct	Cl	94[a]	2	+8.9
5	**6a**	Bn	Br	89[a]	182	−2.7
6	**6b**	*n*-Bu	Cl	91[a]	21	+4.9
7	**7a**	Bn	NTf_2	95[b]	−29	+9.3
8	**7b**	Bn	BF_4	91[b]	6	+8.1
9	**7c**	*n*-Bu	NTf_2	91[b]	−50	+7.9
10	**7d**	*n*-Bu	BF_4	91[b]	−26	+8.3
11	**7e**	*n*-Oct	NTf_2	95[b]	−51	+7.5
12	**7f**	*n*-Oct	BF_4	91[b]	−35	+8.6
13	**8a**	*n*-Bu	NTf_2	93[b]	−42	+9.8

[a] Yield corresponding to quaternization reaction.
[b] Yields corresponding to metathesis reaction.
[c] Melting point calculated at onset.

All organic salts were characterized by spectroscopic analysis of ^1H NMR, ^{13}C NMR, IR, and MS (see Supplementary data). We also obtained suitable crystals for X-ray diffraction analysis of compounds **5a** (R = Bn, X = Cl) and **5b** (R = Bn, X = Br). X-ray analysis unambiguously confirmed the proposed chemical structure and (*S*,*S*)-configuration of the chiral imidazole salts. The structure consists of layers of cations and anions, which are interconnected by a network of hydrogen bonds and π–π interactions between the aromatic rings.

Slight differences in the hydrogen-bond networks between chiral cation and either chloride or bromide lead to a different ionic packing for these two compounds (Figs. 1 and 3). However, in both the cases, the anion showed close contacts with different hydrogen atoms of the chiral cation. Both the hydroxyl and imidazolium moieties are implicated in H-bonding with the anion, being the hydrogen bond established through imidazo-

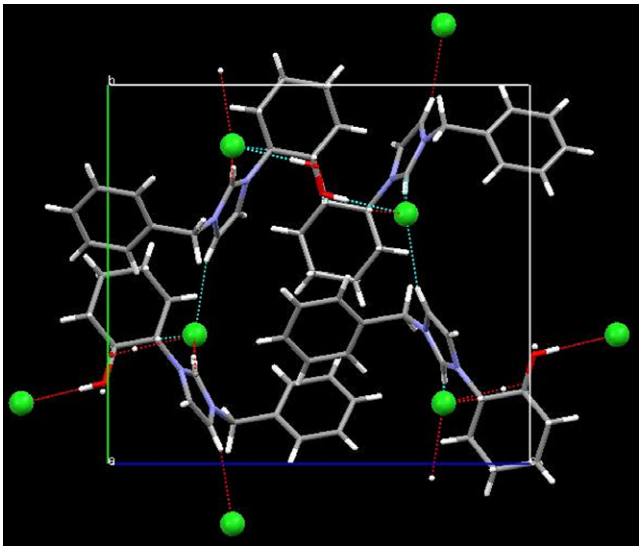

Figure 1. Molecular structures obtained from X-ray analysis. Crystal packing view of **5a** along the *a*-axis.

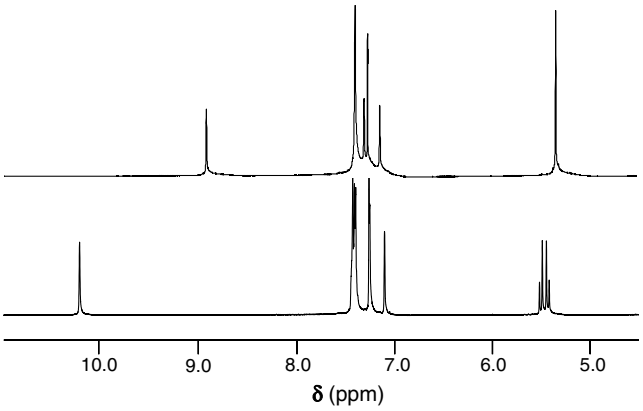

Figure 2. Partial ^{1}H NMR (5 mM, $CDCl_3$, 500 MHz) spectra of **5a** (lower trace) and **7b** (upper trace).

lium C(2)–H atom specially noteworthy. The OH and C(2)–H groups from a given cation are bound to different anions within the crystal lattice (see packing in Figs. 1 and 3).

Cation–anion H-bond interactions for chloride are stronger than for bromide C(2)–H···Cl 2.545 Å versus C(2)–H···Br 2.720 Å O–H···Cl 2.244 Å versus O–H···Br 2.720 Å. Such differences are big enough to produce a change on the T_m observed for either Cl or Br (**5a** 219 °C and **5b** 188 °C). Related H-bond networks have been reported for other imidazole salts.[10] Indeed, hydrogen-bond interactions are by far the most important contribution to the lattice energy in IL compounds. At that point, we wondered if these interactions are retained for the isolated ion pair. Regarding that, the ^{1}H NMR spectra of diluted solutions in deuterochloroform showed very different chemical shifts for C(2)–H hydrogen depending on the anion (see Fig. 2). For instance, this proton resonates at 8.92 ppm for the BF_4, while it is shifted to lower field up to 10.23 ppm for Cl, supporting that the hydrogen bonds observed in the crystals are retained in the isolated ion pair for the more basic anion.[11] Therefore, imidazole salts with lower melting points (**7a** $T_m = -29$ °C and **7b** $T_m = 6$ °C) were obtained by the introduction of less basic anions such as NTf_2^- or BF_4^-, which have less hydrogen-bond capacity reducing the lattice energy and leading to RTILs.

Additionally, other C–H···X interactions involving the methylene hydrogens of the side chain (R = $PhCH_2$–, CH_3–$(CH_2)_2$–CH_2–, and CH_3–$(CH_2)_6$–CH_2–) can be observed. Thus, the anisochrony of the diastereotopic protons at the benzylic position (~5.5 ppm) is much higher for Cl than for the BF_4 suggesting a more rigid structure for the halogen derivative (Fig. 2). Preliminary DFT calculations on the isolated ion pair of **5a** led to minima showing a C(2)–H···Cl···H–O hydrogen-bond pattern in an anion-chelated geometry (see Supplementary data). All these data suggest that the anion must play a fundamental role in the asymmetric environment induced by these new chiral ionic liquids and therefore having an important impact on their physicochemical properties.

However, the characteristics of IL are not only modulated by the hydrogen-bond interactions but also by the cation–cation interactions and hydrophobic effects. In this context, the X-ray showed interactions between the aryl groups of different chiral cations. These interactions will contribute to increase the lattice energy explaining the high melting points for **5a** and **5b**. When aryl groups were substituted by aliphatic chains, which suppress the above-mentioned interactions, significant decreases on the melting temperatures were observed (**5c** 7 °C and **5d** 2 °C).

The thermal stability of the ionic liquids was assessed using thermogravimetric analysis. The TGA showed for temperatures below 200 °C a weight loss lower than 5% for the NTf_2 derivatives. When **7a** was heated at 150 °C for a period of 3 h, the compound after cooling did not show any signals of decomposition by ^{1}H NMR.

In summary, we have designed and synthesized enantiopure room temperature imidazolium ionic liquids. These novel RTILs can be readily prepared by simple and straightforward procedures from non-expensive enantiopure synthons obtained via lipase-catalyzed resolutions. The strategy reported here can be used to obtain a family of chiral RTILs, in which structural diversity can be introduced by varying either the epoxide or the imidazole moieties. We are currently investigating how these modifications can affect the ILs physicochemical properties and further development of these molten salts

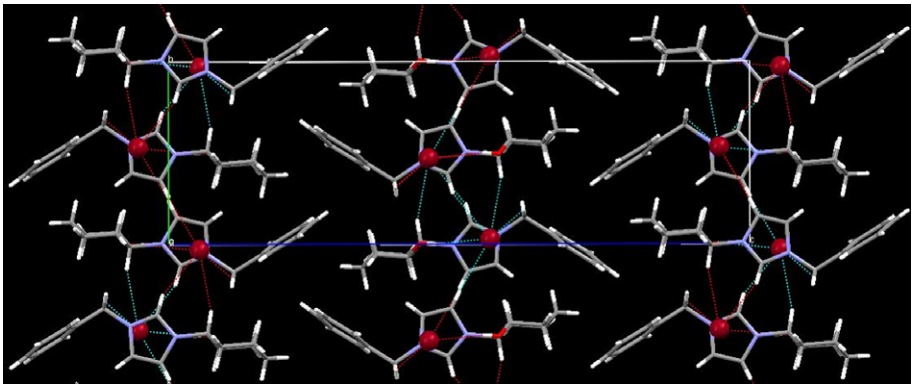

Figure 3. Molecular structures obtained from X-ray diffraction analysis. Crystal packing view of **5b** along the *a*-axis.

as effective solvents, as well as chiral catalysts for a variety of asymmetric reactions.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data for new compounds, and X-ray) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.138.

References and notes

1. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, Germany, 2003; (c) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (d) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459–2477; (e) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2005**, *61*, 1015–1060; (f) Jain, N.; Kumar, A.; Chauhan, S.; Chauan, S. M. S. *Tetrahedron* **2007**, *63*, 2363–2389.
2. (a) Huddleston, J. G.; Rogers, R. D. *Chem. Commun.* **1998**, 1765–1766; (b) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S.; Wierzbicki, A.; Davis, J. H.; Rogers, R. D. *Chem. Commun.* **2001**, 135–136.
3. (a) Bonhôte, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178; (b) Yoshizawa, M.; Narita, A.; Ohno, H. *Aust. J. Chem.* **2004**, *57*, 139–144.
4. Lee, S. *Chem. Commun.* **2006**, 1049–1063.
5. (a) Zhou, Z.-B.; Matsumoto, H.; Tatsumi, K. *Chem. Eur. J.* **2004**, *10*, 6581–6591; (b) Tokuda, H.; Hayamizu, K.; Ishii, K.; Susan, K. M.; Watanabe, M. *J. Phys. Chem. B* **2005**, *109*, 6103–6110; (c) Tokuda, H.; Ishii, K.; Susan, M.; Tsuzuki, S.; Hayamizu, K.; Watanabe, M. *J. Phys. Chem. B* **2006**, *110*, 2833–2839.
6. For general revisions see: (a) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A.-C.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081–3093; (b) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281–292; (c) Baudequin, C.; Brjgeon, D.; Levillain, J.; Guillen, J.; Plaquevent, F.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921–3945.
7. (a) Ni, B.; Headley, A. D. *Tetrahedron Lett.* **2006**, *47*, 7331–7334; (b) Malhotra, S. V.; Wang, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1032–1035; (c) Luıs, C.; Branco, L. C.; Gois, P. M. P.; Lourenço, N. M. T.; Kurteva, V. B.; Afonso, C. A. M. *Chem. Commun.* **2006**, 2371–2372; (d) Guillen, F.; Bregeond, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **2006**, *47*, 1245–1248.
8. Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2007**, *63*, 469–473.
9. For enzymatic studies on related structures: González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1335–1341.
10. (a) Fuller, J.; Carlin, R. T.; De Long, H. C.; Hawotth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299–300; (b) Elaiwi, A.; Hitchcock, P. B.; Seddon, R. K.; Srinivasan, N.; Tan, N. Y.; Welton, T.; Zoraa, J. A. *J. Chem. Soc., Dalton Trans.* **1995**, 3467–3472 ; (c) Holbrey, J. D.; Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133–2139; (d) Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Pitner, K. W. R.; Seddon, R.; Rogers, R. D. *Green Chem.* **2002**, *4*, 407–413.
11. Bonhöte, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178.