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Design and synthesis of imidazolinium salts derived from (L)-valine. Investigation of their potential in chiral molecular recognition†

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Received (in Cambridge, UK) 17th February 2004, Accepted 18th March 2004
First published as an Advance Article on the web 26th April 2004

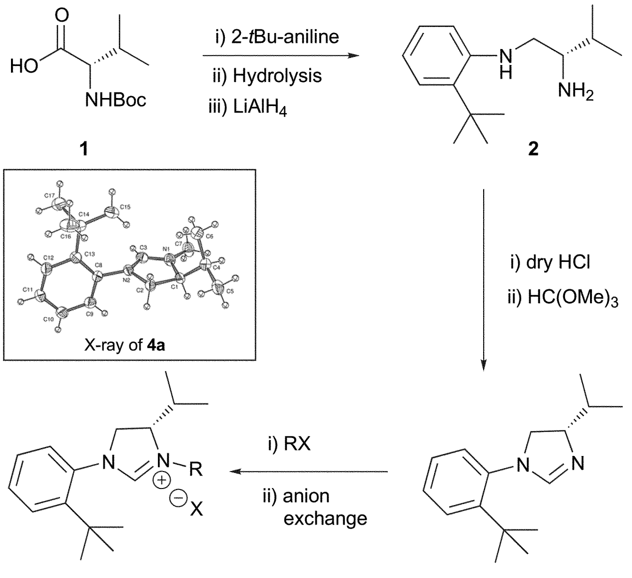
Several imidazolinium salts are synthesized from (L)-valine. A study of the structure relationships is achieved to obtain high diastereomeric interactions with an anionic substrate. High splitting up to 60 Hz of the (*rac*)-potassium Mosher's salt are observed by NMR spectroscopy.

In the context of a sudden awareness of environmental problems, development of new cleaner processes to minimize chemical wastes has became a high priority for chemical industries.[1] In this area, room temperature ionic liquids (RTILs), such as imidazolium, imidazolinium and pyridinium salts, have received considerable attention for their use as novel clean media in organic chemistry.[2] By their interesting properties such as ease to reuse, non-volatility, absence of flammability, these new solvents are promising candidates to replace volatile organic solvents traditionally used in industry.[3] In the area of chiral solvents,[4] because RTILs show a high degree of organisation,[5] their chiral version should be more attractive than classical solvents for a potential application in chiral discrimination, including asymmetric synthesis. However, development of chiral RTILs (cRTILs) is currently in preliminary stage and only few have been reported.[6,7]

Herein, we report the synthesis of new chiral imidazolinium salts **4** derived from natural amino acid (L)-valine. By diastereomeric interactions with a racemic anionic substrate, we have investigated the effect of a hydroxyalkyl side chain in the chiral molecular recognition ability of these new salts.

The synthesis of chiral imidazolinium salts **4** is shown in Scheme 1. Starting from commercially available *N*-Boc-(L)-valine **1**, the aryl group was introduced *via* a classical coupling between substituted aniline and **1** to generate the corresponding amide.[8] After hydrolysis of the carbamate by methanolic hydrochloric acid, the amide function was reduced with $LiAlH_4$ to afford, after chromatography, the diamine **2** in excellent yield. Formation of the diamine chlorhydrate followed by condensation of trimethylorthoformate in toluene delivered the corresponding enantiopure imidazoline **3** (Fig. 1). Finally, the desired chiral imidazolinium salts **4** were obtained by a simple alkylation with various alkyl halides followed by anion exchange. The choice of the counter anion was crucial for the properties of these salts. Indeed, NTf_2 led to a RTIL while PF_6 gave only solid salts. Accordingly, 5 imidazolinium salts have been isolated after purification on silica gel with moderate to good yields. One X-ray structure has been realised with PF_6 imidazolinium salt **4a**.‡

To evaluate the chiral recognition ability of these imidazolinium salts, we have attempted to detect diastereomeric interactions between the enantiopure cations **4** and the racemic anion of Mosher's salt. We modified the NMR experiment developed by Wasserscheid *et al.*[7a] to improve these interactions.§ Indeed, we used the potassium salt **5** instead of the sodium salt and recorded NMR spectra in acetone-d_6, where both salts are completely soluble. This protocol gives a better difference in the chemical shift ($\Delta\delta$ = 10–20 Hz) for both methoxy and CF_3 groups of the two enantiomers of Mosher's carboxylate **5**. This result can be explained by the tightness of the anion pair, which is decreased by a bulky counter cation like potassium, leading to increased diastereomeric interactions. To confirm this, we added the crown ether 18C6 to trap the potassium cation[9] and obtained better interactions, affording a doubling of the chemical shifts difference ($\Delta\delta$ = 20–30 Hz) observed in both ^1H and ^{19}F NMR spectroscopy.



Scheme 1 Synthesis of imidazolinium salts **4a–e**.

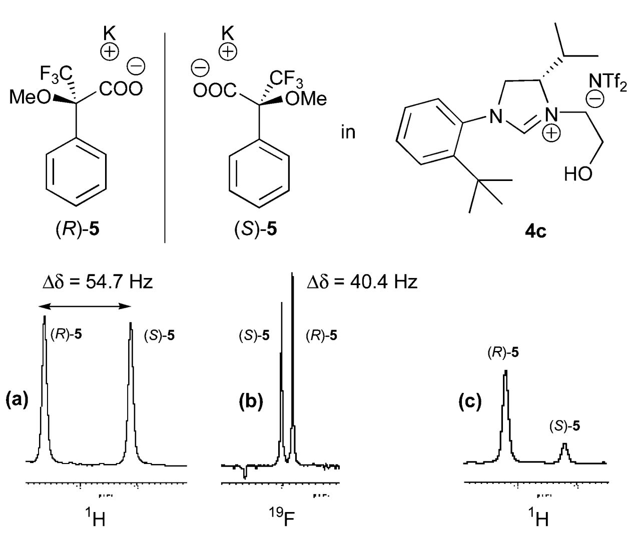


Fig. 1 ^1H (a) and ^{19}F (b) NMR spectra (400 and 376 MHz, respectively, CD_2Cl_2) of (*rac*)-Mosher salt **5** in imidazolinium **4c** in presence of crown ether 18C6. (c) ^1H NMR spectrum of an enantioenriched sample of Mosher salt **5** (60% ee).

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† Electronic supplementary information (ESI) available: preparative details and NMR data for **4a**–**e**. See http://www.rsc.org/suppdata/cc/b4/b402368d/

DOI: 10.1039/b402368d

We then investigated the role of the side chain on the chemical shift difference. If the length of alkyl chain presents a minimal effect (imidazoliniums **4a, b**: $\Delta\delta$ = 20–30 Hz), the introduction of a polar group, such as a hydroxyethyl chain (imidazolinium **4c**), increases considerably the chemical shift difference. Up to 54.7 and 40.4 Hz between the two enantiomers were obtained in ^{1}H and ^{19}F NMR spectroscopy respectively [Fig. 1(a) and (b)]. Consequently, it is thus easy to confirm the enantiomeric excess of an enantioenriched sample of Mosher's salt by a simple integration of NMR signals [81:19, 60% ee, Fig. 1(c)].

Increasing the chain length with a hydroxypropyl chain (imidazolinium **4d**), improved again these splitting up to 60 Hz in proton and 63 Hz in fluorine NMR spectroscopy. However, in the case of longer hydroxyl chain such as a hydroxyoctyl chain (imidazolium **4e**), very small difference was obtained ($\Delta\delta$ = 12 Hz). To explain this, we postulated that diastereomeric interactions were favoured by hydrogen bonding between the hydroxyl group and the anionic substrate, leading to a folding up of the hydroxyl chain toward the cation. The bad splitting observed with the hydroxyoctyl chain showed that this folding up conformation was favoured only for C2 or C3 hydroxyalkyl chain. To prove this folding up conformation, we have added a few drops of water in the NMR solvent, destroying the hydrogen bonds and leading to a diminution of the chemical shift difference.

On the other hand, it is important to note that the presence of a bulky substituent on the *ortho* position of the aromatic ring is also responsible of the chiral discrimination (Fig. 2). Indeed, replacement of the initial bulky 2-*tert*-butyl group by a 2-methyl group decreased considerably the splitting of the NMR signals. In the structure-interaction relationships, a polar group on the lateral side chain and a bulky *ortho* substituent on the aromatic ring were complementary and necessary to obtain high diastereomeric interactions between the chiral cation and the anionic substrate.

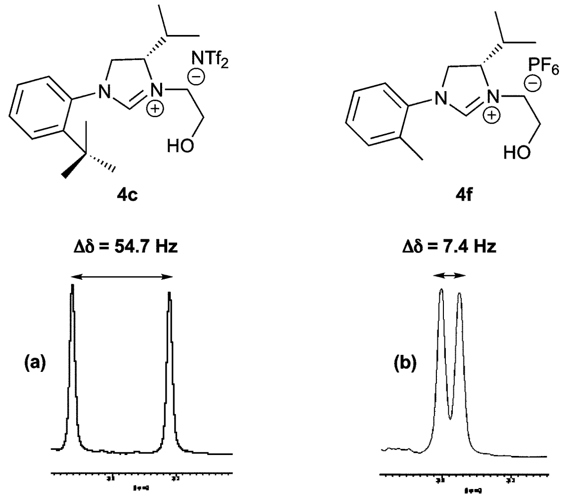

Fig. 2 Influence of the aryl substituent on the chiral discrimination: ^{1}H spectra (400 MHz, CD_2Cl_2) of (*rac*)-Mosher salt **5** in imidazolinium **4c** (a) and **4f** (b) in presence of crown ether 18C6.

In summary, we have designed and synthesized new imidazolinium salts using a simple route starting from (L)-valine. They are water tolerant and stable under acidic conditions. By structure–interaction relationships, we showed the crucial role of the hydroxyalkyl lateral side chain and the bulky aromatic substituents to obtain higher diasteromeric interactions with a racemic anionic substrate. These interactions have been shown by ^{1}H and ^{19}F NMR spectroscopy with high splitting up to 60 Hz of the (*rac*)-potassium Mosher's salt. This study leads us to develop new cRTILs with high molecular recognition ability, based on hydroxyalkyl ammonium, imidazolium or pyridinium salts. The large scale synthesis of these new chiral solvents is under way in our laboratory and their use in asymmetric synthesis will be reported in due course.

Notes and references

‡ *Crystal data* for **4a**: $C_{34}H_{54}F_{12}N_4P_2$, M = 814.78, monoclinic, a = 9.1683(2), b = 20.2115(7), c = 10.8752(3) Å, β = 101.599(2)°, V = 1974.1(1) Å^3, T = 120 K, space group $P2_1$, Z = 2, μ = 1.97 cm^{-1}, 35 228 reflections measured, 5857 unique (R_{int} = 0.078) which were used in all calculations. The final w$R(F^2)$ = 0.204 (all data). CCDC 227054. See http://www.rsc.org/suppdata/cc/b4/b402368d/ for crystallographic data in CIF or other electronic format.

§ Representative procedure for NMR experiment: 12.5 mg of (*rac*)-potassium-2-methoxy-2-(trifluoromethyl)phenylacetate **5** and imidazolinium salt **4c** (3.3 equiv.) were dissolved in 0.4 mL of acetone-d_6 and the spectrum was recorded. Recovery of imidazolium salt can be realised after dilution in dichloromethane following by repeating washing with water. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to afford the pure imidazolium salt without any trace of Mosher salt. With 18C6: the Mosher salt was previously dissolved in 0.4 mL of CD_2Cl_2 in presence of 12.1 mg (1 equiv.) of crown ether 18C6, then imidazolinium salt was introduced and the spectrum was recorded.

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9 NMR spectra were thus recorded in CD_2Cl_2 due to the presence of crown ether, which solubilises the potassium salt in polar aprotic solvent.