Simple transformation of crystalline chiral natural anions to liquid medium and their use to induce chirality†

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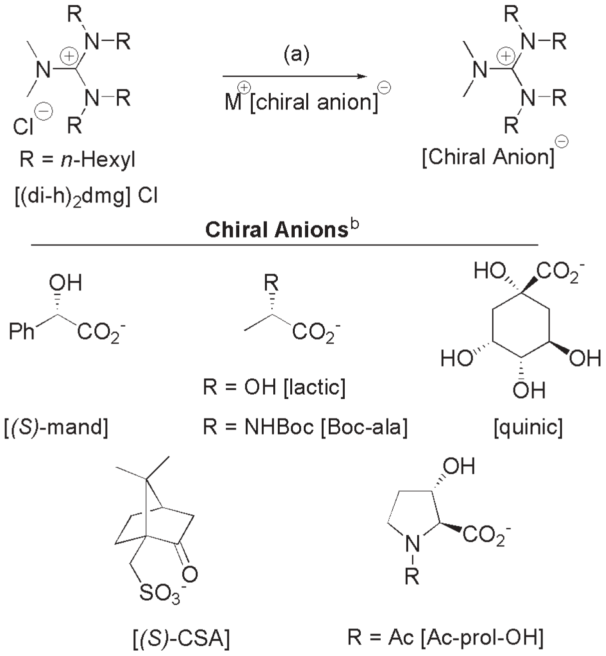
New chiral ionic liquids can be prepared simply by combining the tetra-*n*-hexyl-dimethylguanidinium cation with readily available chiral anions and used as an asymmetric inducing agent as demonstrated for catalytic Rh(II) carbenoid C–H insertion and Sharpless dihydroxylation.

Living systems use chirality as an important tool in biodiversity to create a large range of architecturally sophisticated complex structures. As a result of the large-scale creation of chiral centers by living organisms, they produce a diverse range of chiral organic polyfunctional molecules which become available in the earth in large quantities such as cellulose, starch, carbohydrates, aminoacids and steroids. The creation of chiral molecules *in vivo*, *in vitro* or in the traditional chemical fashion is mainly performed in homogeneous conditions where the solvent used plays an important role not only in the asymmetric induction but also in heat transfer and transport of molecules to the reactive center. Different but complementary strategies have been established for the production of chiral compounds. One of the most popular approaches is the resolution of racemic mixtures in which the traditional crystallization is still one of the most successful procedures.[1] Another important method is based on the chemical manipulation of already existing chiral natural compounds, *chiral synthons*.[2] The creation of chiral centers can be achieved by several chemical reactions where the enantioselectivity is induced using chiral auxiliaries, readily obtained by chemical manipulation of chiral natural and non-natural compounds,[2] by asymmetric catalysis based on organometallic catalysts,[3] organocatalysis[4] and biocatalysis where enzymes and antibodies are used.[5] Such methodologies are highly appealing not only for the high degree of enantioselectivities and atom efficiency achieved, but also due to the possibility of recycling the catalyst and chiral auxiliary. Here is described a new and remarkably simple methodology to generate new chiral centers under homogeneous conditions using non-volatile chiral ionic liquids readily available from the unique combination of crystalline chiral salts, common in nature, used as anion and a guanidinium unit that acts as cation.

In the course of continuous effort in the development and application of room temperature ionic liquids, ILs,[6] based on the combination of organic cations and inorganic and organic anions, we observed that tetra-alkyl-dimethylguanidinium cations [dmg] are potential candidates for the creation of a new generation of ILs due to peculiar solubility properties and a high thermal and chemical stability.[7] Despite containing 27 carbon atoms, the [dmg] cation tetra-*n*-hexyl-dimethylguanidinium [$(\text{di-h})_2$dmg] is less prone to crystallize even in the presence of anions which are persistently solid in combination with different cations. This notable property allows the development of a new, simple and efficient strategy to synthesize new chiral ionic liquids (CILs)[8] by simple exchange of the [$(\text{di-h})_2$dmg] Cl salt with natural or easily functionalized chiral natural anions. In Scheme 1 are presented the chiral ionic liquids (CILs) prepared and the physical properties determined, namely the viscosity and the glass transition temperature (Tg). Noticeably,



Scheme 1 Chiral ionic liquids (CILs) prepared by combination of readily accessible chiral anions with ([$(\text{di-h})_2$dmg]) cation. [a] Salt [$(\text{di-h})_2$dmg] Cl, M^+[chiral anion] (2 eq), dichloromethane, rt, 24 h. [b] Observed glass transition temperature (Tg, °C) and viscosity (η, cP at 25 °C) for [$(\text{di-h})_2$dmg] X^-: X = [(*S*)-mand], Tg = −56.9, η = 1633.3; X = [lactic], Tg = −72.9, η = 247.6; X = [Boc-ala], Tg = −37.5, η = 749.1; X = [quinic], Tg = −63.6, η = 998.2; X = [(*S*)-CSA], Tg = −44.3, η = 417.0; X = [Ac-prol-OH], Tg = −32.7, η = 4913.6.

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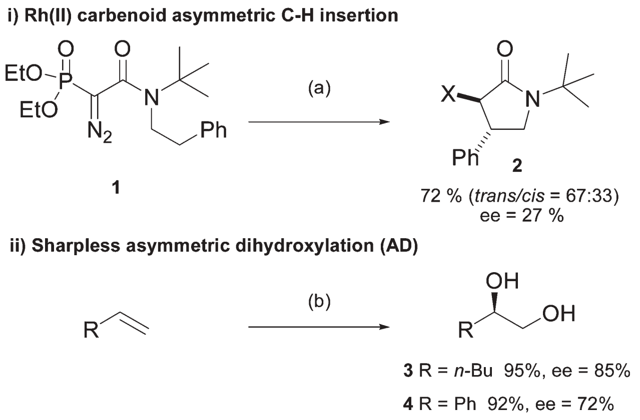

Scheme 2 Induction of chirality by chiral ionic liquids (CILs) in: i) C–H insertion of α-diazo-acetamides catalyzed by $Rh_2(OAc)_4$ and ii) Sharpless AD. [a] $Rh_2(OAc)_4$ (1 mol%), $[(di\text{-}h)_2dmg][(R)\text{-}mand]$ (0.3 g), **1** (0.15 mmol), 110 °C, 3 h. [b] Alkene (0.5 mmol), $K_2OsO_2(OH)_4$ (0.5 mol%), NMO (1 eq), $[(di\text{-}h)_2dmg]$ [quinic] (0.3 mL), rt, 24 h.

the CIL with lactate as anion has low viscosity and has a lower Tg value. All the CILs prepared are stable thermally (up to 220 °C) and are liquids at room temperature.

In order to test the effectiveness in inducing chirality in asymmetric reactions of this new class of chiral ionic liquids,[9] we performed their evaluation as the reaction medium in the following transformations: carbenoid intramolecular C–H insertion of α-phosphono-α-diazo-acetamides catalyzed by $Rh_2(OAc)_4$ and Sharpless asymmetric dihydroxylation (AD) (Scheme 2).

Using the CIL $[(di\text{-}h)_2dmg][(R)\text{-}mand]$ instead of the traditional organic solvent, 1,2-dichloroethane, under routine conditions (110 °C, 3 h) in the presence of $Rh_2(OAc)_4$ catalyst, the *in situ* formation of Rh(II) carbenoid from **1** originates the γ-lactam **2** in 72% yield (*trans*/*cis* 67/33) (Scheme 2i) with a moderate enantiomeric excess (ee 27%), nevertheless, this constitutes an improvement when compared with the result obtained when the chiral $Rh_2((R)\text{-}mandelate)_4$ catalyst (ee 18%) was used.[10] The asymmetric induction probably occurs as a result of *in situ* ligand exchange and the chiral solvent environment.

The Sharpless osmium-catalyzed asymmetric dihydroxylation (AD)[11] is a very powerful methodology for the preparation of chiral vicinal diols and amino alcohols. The success of the asymmetric induction requires the use of one chiral ligand consisting of two *cinchona* alkaloid units attached to one core unit. Generally in the case of 4-methylmorpholine-*N*-oxide (NMO) as co-oxidant, a slow addition of the olefin is required in order to eliminate the secondary catalytic cycle effect. Interestingly, using the CILs $[(di\text{-}h)_2dmg]$[quinic], in the absence of the Sharpless chiral ligand and without slow addition of the olefin, the diols **3** and **4** were obtained in high yields (95 and 92%) and high enantiomeric excesses (ee 85 and 72%) (Scheme 2ii). It should be mentioned that the observed yields and enantioselectivities are similar to the ones obtained using the chiral ligand $[DHQD]_2PHAL$ in $t\text{-}BuOH/H_2O$ (1 : 1) by adding the olefin at once (80% yield and 73% ee for **4**).[12] Using a catalytic amount (5 mol%) of the CIL $[(di\text{-}h)_2dmg]$[quinic] dissolved in $t\text{-}BuOH/H_2O$ (1 : 1) lower yields (81%) and enantioselectivities (40%) were obtained for **4**.

The examples of asymmetric induction described here demonstrate that one simple approach to create new chiral centers can be used to perform established reactions in homogeneous ionic liquid media based on the use of readily available chiral natural anions, usually crystalline, and the appropriate tetra-alkyl-dimethylguanidinium cation which presents a very low tendency to crystallize. This new chiral medium, due to being ionic, moderately viscous and non-volatile, opens new opportunities not only to induce chirality by performing different reactions in this medium but also in other areas such as chiral sensors, chiral selectors for mass spectrometry (*e.g.* matrix for MALDI), chiral resolution based on membrane technology and on different types of chromatographic methods such as GLC or capillary electrophoresis. The possibility to effect simple chemical transformation on other crystalline and readily accessible chiral natural compounds such as carbohydrates in order for them to become anions and then moderately viscous liquids in combination with the appropriate [dmg] cation opens new opportunities in the broad area of chirality.

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