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1-Ethyl-3-methylimidazolium tartrate chiral ionic liquids: preparation, characterization and opportunities thereof†

Tessa Castellan,^a Claire Cuyamendous,^b Juliette Fitremann,^c Jean-Marie Galano,^b Camille Oger,^b Thierry Durand,^b Frédéric Guillen^a and Yves Génisson^{*a}

A unified acid/base synthetic access to tartrate-based chiral ionic liquids relying on the generation of cation hydroxide salts with AgOH was challenged with the preparation of sensitive 1-ethyl-3-methylimidazolium derivatives. Systematic variation of the starting tartaric acid stoichiometry and configuration led to eight stereoisomeric 1-ethyl-3-methylimidazolium hydrogen tartrate or di-(1-ethyl-3-methylimidazolium)tartrate entities. These salts were all characterised as proper ionic liquids. An unprecedented influence of the configuration ((2*S*,3*S*), or (2*R*,3*R*) vs. racemic or *meso*) on dynamic viscosity was observed. The relevance of such tartrate salts as task-specific ionic liquids was demonstrated in a synthetically useful base-promoted intramolecular cyclisation of a C₂-symmetrical bis-epoxide *en route* to the total synthesis of phytofuran metabolites.

Introduction

Chiral ionic liquids (CILs) represent an appealing class of ionic liquids (ILs) combining highly diverse structural features¹ with multiple fields of applications. They have for instance been used in physical and materials chemistry,² analytical and separative chemistry,³ catalysis and synthetic chemistry.⁴ Among CILs, bio-sourced derivatives are intended to further address the issue of eco-compatibility and sustainability.⁵ Naturally abundant and renewable precursors obtained from the chiral pool, such as amino or hydroxy acids, carbohydrates and alkaloids, were used to generate either the cation, the anion, or both cation and anion, of such “bio-ionic liquids”.⁶ Direct use of biopolymers such as proteins and polysaccharides has also been explored.⁵

In this context, tartaric acid holds a particular position as an omnipresent source of inspiration in the long-lasting quest for chirality. The field of alternative reaction media naturally came to exploit the potential of tartaric acid as a chiral precursor.⁷ Several deep eutectic solvents combining tartaric acid with

achiral components were for instance reported for synthetic applications.⁸

Since the first report of tetrabutylammonium tartrates by Maschmeyer and colleague in 2006,⁹ tartrate-based CILs have attracted a constant attention, finding applications in various areas ranging from environmental sciences to physico-, nano- and pharmaco-chemistry as well as organometallic catalysis and organic synthesis.

Yuan and colleague described a 1-butyl-3-methylimidazolium hydrogen tartrate as an IL with buffering properties.¹⁰ In the course of a study on stereoselective fluorescence quenching, Petrich and colleague reported a bis(tetrabutylphosphonium)-tartrate.¹¹ Jing and colleague explored the use of several bis(alkylpyridinium)tartrates as chiral additives for asymmetric cycloaddition of CO₂ to epoxides.¹² Bis(tetrabutylammonium)-tartrate proved useful in the development of IL-assisted synthesis of ZnO/Sn₂O¹³ and BaCO₃ nanostructures.¹⁴ Mandal and colleague employed a choline tartrate in an IL-enhanced biodegradation of azo dyes.¹⁵ An enantioselective liquid-liquid extraction process was devised based on bis(tetrabutylphosphonium)tartrate CIL.¹⁶ A commercial 1-octyl-3-methylimidazolium hydrogen tartrate was proposed as a surface active IL able to solubilize pesticides in water.¹⁷ Tartrate-based ILs were prepared from the antifungal drug ketoconazole to try to improve the compound's water solubility.¹⁸ Bouquillon and colleague used both tetrabutylammonium and tetrabutylphosphonium hydrogen tartrates as a co-solvent for aqueous Pd-catalysed hydrogenation reactions¹⁹ or as solvent for a Heck cross-coupling reaction.²⁰ Lately, a commercial choline hydrogen

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† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR and viscosity measurement data. See DOI: 10.1039/c8nj03175d

tartrate CIL was employed in conjunction with a Zn(II)-based catalyst to enhance the stereoselectivity of a Diels–Alder reaction.²¹ In addition, the protic salt obtained from a lauryl monoester of diacetyl tartrate and (*S*)-(-)- α -methylbenzylamine was recently found to be the first CIL forming micelles and reverse micelles.²²

In addition, the potential threat of diverse 1-alkyl-3-methylimidazolium tartrate CILs for aquatic environment was explored by studying their toxicity for the microalgae *Scenedesmus obliquus*. The strong contribution of the cation alkyl chain length²³ was shown to override the influence of chirality of the tartrate anion on toxicity, shorter alkyl residues minimizing cell penetration, growth inhibition rates and oxidative stress.²⁴

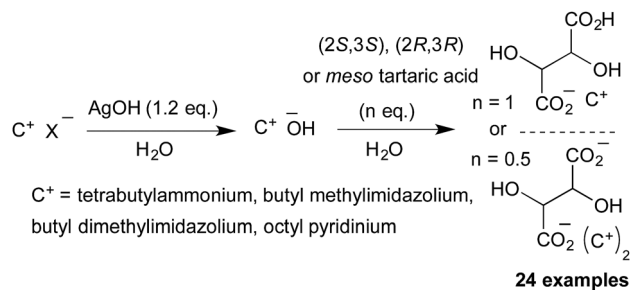
Synthetic access to organic cation-based tartrate salts could appear trivial and these CILs were sometimes employed without proper description.^{13,14,15,25} The relevance of the use of CILs, and *a fortiori* of tartrate-based entities, is however strongly dependent on their chemical integrity, which, in the absence of any practical purification method, directly relies on their preparation procedure. All the reported syntheses are based on the neutralization of tartaric acid with an organic hydroxide salt.^{6,9–12,19,20} This approach,²⁶ popularized by the work of Ohno and colleague,²⁷ avoids potential contamination with the halide salts resulting from anion metathesis. However, it raises the issue of the access to the required hydroxide salt. Most of these studies therefore focus on commercially available tetrabutylammonium and tetrabutylphosphonium hydroxide.^{9,11,19,20}

The imidazolium hydroxide salts required for the preparation of the corresponding tartrate or hydrogen tartrate ionic liquids have been prepared from the corresponding halide salts by treatment with NaOH or KOH in nonpolar organic solvents such as dichloromethane.²⁸ This straightforward method has since been widely used for the preparation and isolation of 1,3-dialkylimidazolium hydroxides, among other ammonium hydroxide salts.²⁹ However, further studies have shown that, as anticipated by calculations,³⁰ the exact nature of the claimed “1,3-dialkylimidazolium hydroxide” species is more akin to an hydrated carbene, due to the acidity of the azolium protons.³¹ These compounds, highly prone to decomposition, can therefore only be isolated as a dilute to moderately concentrated solution in water or protic solvents. The use of an anion exchange resin³² represent an elegant alternative that was applied to the preparation of several tartrate-based CILs,^{6,10} avoiding the generation of stoichiometric amounts of undesired halide salts.³³ Access to these organic hydroxide salts has gained further interest due to the use of 1-butyl-3-methylimidazolium ([BMIM]) hydroxide in catalysis as basic task-specific ionic liquids (TSILs).³⁴

Results and discussion

Optimization of the synthetic approach

We previously developed a unified route to tartrate-based CILs relying on a practical and general access to organic hydroxide salts (Scheme 1).³⁵ This approach relies on the treatment of an



Scheme 1 Unified synthetic access to tartrate-based ILs.

onium halide with the halophilic base AgOH.²⁶ Precipitation of the formed silver halide ensures an irreversible shift of the equilibrium in the course of the anion metathesis. A one pot version of this approach had been mentioned for the preparation of several bis(alkylpyridinium)tartrate CILs.¹² Due to the high added-value of these hydroxide salts as basic TSILs, we systematically isolated and characterized these entities. Clean aqueous solutions of organic hydroxide salts, exempt from halide salts contamination, were readily obtained from ammonium, pyridinium and imidazolium halide precursors. They were used to prepare 24 different tartrate-based ionic liquids from the (2*S*,3*S*), (2*R*,3*R*) or *meso* forms of tartaric acid.³⁵

We wished to challenge this general approach with the preparation of demanding 1-ethyl-3-methylimidazolium (EMIM) derivatives. Due to the reduced steric hindrance generated by the ethyl residue, the cation is indeed particularly sensitive to basic conditions.³¹ These entities have, to the best of our knowledge, never been described in the literature. The use of commercial “1-ethyl-3-methylimidazole tartrates” (Shanghai Chengjie Chemical) were only reported in a study on CIL-modified Au nanoparticle chiral recognition of amino acids enantiomers³⁶ and in the enantiomeric separation of amino acids by chiral ligand exchange capillary electrophoresis.³⁷ Our preliminary work, indicating that EMIM tartrates were, as expected, significantly less viscous than their 1-butyl-3-methylimidazolium counterparts, prompted us to tackle their preparation and characterization. We present here our work along this line.

We started studying the access to the hydroxide precursor. Large scale preparation of dilute aqueous solutions of [EMIM]OH have been reported from [EMIM][EtSO₄] by bipolar membrane electrodialysis³⁸ or employing an anion exchange resin.³⁹ Our first attempts to implement the previously developed procedure using AgOH to generate [EMIM]OH from the corresponding bromide salt in water proved troublesome. Such medium scale reactions (typical concentration 0.3 M) could easily be run in D₂O, allowing direct NMR monitoring of the transformation and product characterization. Treatment of [EMIM]Br with 1.5 equiv. of AgOH led to the apparition of two distinct imidazolium derivatives in ¹H NMR (Fig. 1). The more shielded set of protons could be easily assigned to the silver carbene complex in 2D NMR heteronuclear multiple-bond correlation (HMBC) experiments (Fig. 2 left). All protons from the C3/C4 imidazolium ring as well as the methyl and the

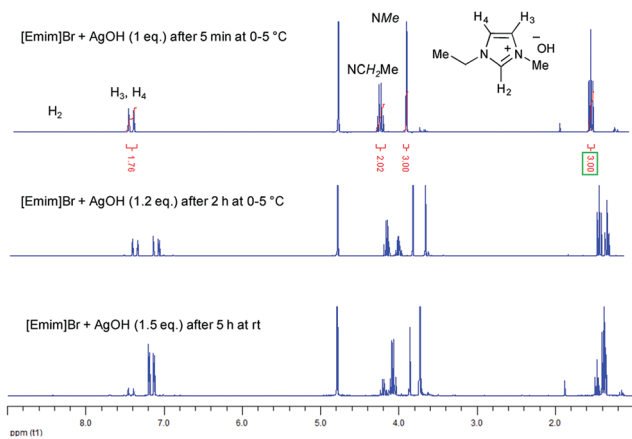


Fig. 1 ^1H NMR spectra (D_2O , 300 MHz) of [Emim]Br + AgOH (1.5 equiv.) after 5 h at RT (bottom), [Emim]Br + AgOH (1.2 equiv.) after 2 h at 0–5 °C (middle) and [Emim]Br + AgOH (1 equiv.) after 5 min at 0–5 °C (top).

methylene of the ethyl residue indeed displayed a strong 3J correlation with a downfield carbon at 179 ppm typical of the carbenic centre.

Optimization of the reaction conditions allowed favouring the formation of the expected [EMIM]OH at the expense of the undesired silver carbene complex. Whereas the use of 1.2 equivalent of AgOH for 2 h at 0–5 °C led to a 1:1 mixture of both compounds, further reducing the amount of base (1 equivalent) and the reaction time (5 min) allowed production of a clean crude mixture. 2D NMR HMBC experiments led to the unambiguous assignment of the structure of [EMIM]OH to this product (Fig. 2 right). In particular, a strong 3J correlation with a carbon at 138 ppm was observed for the C3/C4 imidazolium ring as well as the methyl and the methylene of the ethyl residue.

Preparation

With this facile and reliable preparation of [EMIM]OH in hands, we studied the synthesis of the corresponding tartrate salts. Addition of 0.5 or 1.0 equiv. of tartaric acid to the freshly prepared

ca. 0.05 M aqueous hydroxide solution led to the expected tartrate or hydrogen tartrate ILs, respectively (Scheme 2).

Physicochemical characterization and properties

A total of eight tartrate-based ILs were prepared starting from either (2*S*,3*S*), (2*R*,3*R*), racemic or *meso* tartaric acid. Analytically pure samples were obtained after gentle drying at RT under ca. 10^{-3} mbar for 48 h. Elementary analyses indicated typical water contents comprised between 0.25 and 3.5 molar equivalents, corresponding to 2–15% in weight. They were characterized by standard methods and gave characteristic trends in accord with our previous report (Table 1).³⁵

Typical NMR chemical shifts patterns were observed for the tartrate moieties. Whereas the CO and HCOH carbons display typical signals at 176–177 and 74 ppm, respectively, in all hydrogen tartrate salts, the same carbons were systematically found shifted downfield to 178–179 and 75–76 ppm in all tartrate derivatives. On the other hand, the protons carried by the two stereogenic centres of the hydrogen tartrate anions gave a signal around 4.4 ppm that was shifted to around 4.2 ppm in the more electron-rich tartrate salts, the *meso* derivatives giving a slightly more shielded signal in both cases.⁹

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) analysis showed standard vibrational bands for the O–H, COO–H, C=O and C–O bonds. Aromatic C–H vibration frequencies in 1,3-dialkyl imidazolium ILs have been assigned and studied in details.⁴⁰ In particular, Li and colleague correlated the lowering of the C–2–H stretching frequency in ATR-IR to the electron density of H-bonding with the anion.⁴⁰ A frequency of 3105 cm^{-1} was notably reported for BMIM trifluoroacetate. The assignment of the C–2–H stretching bands of the prepared EMIM ILs can be based on our previous study comparing the C–2–methyl with the C–2–H derivatives.³⁵ Frequencies ranging from 3112 cm^{-1} (for the H-Tart salts) (Fig. 3) to 3086 cm^{-1} (for the Tart derivatives) were typically observed, coherent with the strong H-bonding with the tartrate anions.

The thermal stability of the different tartrate-based ILs was assessed by differential thermal analysis (Table 1). Temperatures

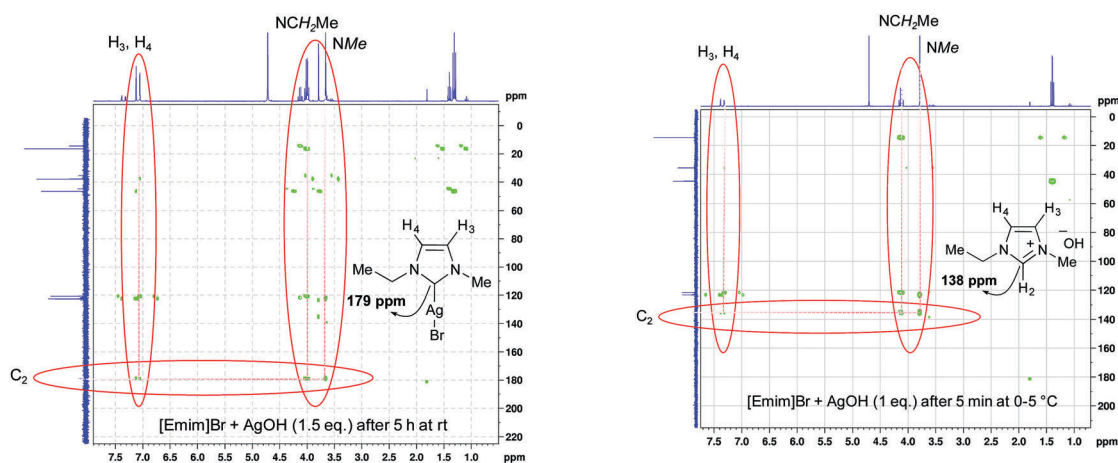
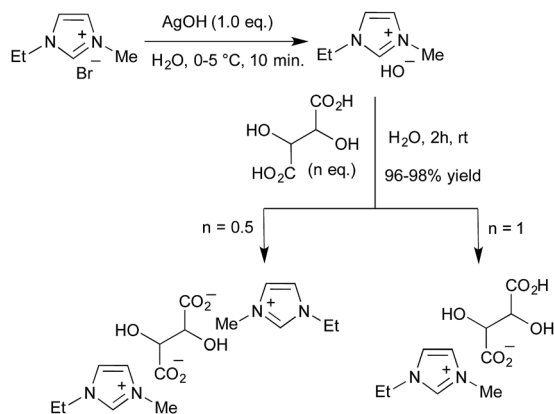


Fig. 2 2D NMR HMBC experiments (D_2O , 300 MHz) of [Emim]Br + AgOH (1.5 equiv.) after 5 h at RT (left) and [Emim]Br + AgOH (1 equiv.) after 5 min at 0–5 °C (right).



Scheme 2 Synthetic route to EMIM tartrate ILs.

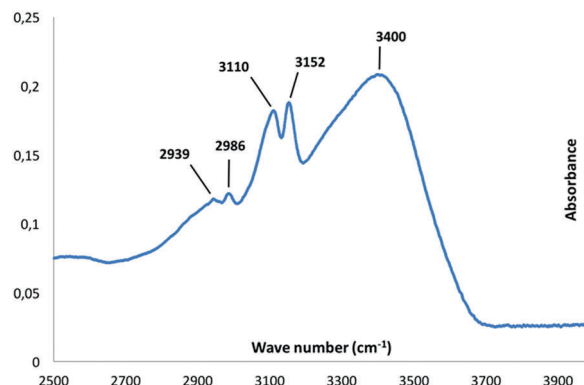


Fig. 3 ATR-IR absorption spectra in the window 2500–4000 cm^{-1} of [EMIM](2*R*,3*R*)-HTart (+)-**1a** showing the characteristic ν C-2-H at 3110 cm^{-1} .

of decomposition (T_d , determined from the onset of weight loss) were found ranging from 188 to 200 $^{\circ}\text{C}$ for the hydrogen tartrates, and from 217 to 240 $^{\circ}\text{C}$ for the tartrates, lacking of acidic proton, demonstrating an overall appreciable degree of thermal stability.

Differential scanning calorimetry (DSC) was then used to analyse the phase behaviour of the eight tartrate salts. Compounds were found to display only a glass transition (T_g , expressed as the

inflection point during the second heating cycle at 5 $^{\circ}\text{C min}^{-1}$) at temperatures ranging from -16 to -52 $^{\circ}\text{C}$ (Table 1), without any other solid-liquid phase transition, in accord with their designation as room temperature ILs (Fig. 4). As in our previous study, all hydrogen tartrate salts gave T_g values higher than their tartrate analogues, in consistence with their stronger capacity to develop cohesive hydrogen bonds.

Table 1 Selected physicochemical data of EMIM tartrate ILs (only the natural chiral enantiopure (2*R*,3*R*)-tartrate series is reported)

<p>[EMIM](2<i>R</i>,3<i>R</i>)-HTart (+)-1</p> <p>Yield: 97% (viscous oil) $[\alpha]_D^{20}$ (c 1, H₂O): +11.6 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 176.50 (CO), 74.03 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.46 (HCOH) ATR-IR, ν (cm^{-1}): 3152 (C-4, 5-H), 3110 (C-2-H), 1732 (CO, acid), 1601, 1336 (carboxylate) T_d ($^{\circ}\text{C}$): 188; T_g ($^{\circ}\text{C}$): -19</p>	<p>[EMIM] <i>rac</i>-HTart (<i>rac</i>)-1</p> <p>Yield: 96% (viscous oil) $[\alpha]_D^{20}$ (c 1, H₂O): 0 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 176.31 (CO), 74.35 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.40 (HCOH) ATR-IR, ν (cm^{-1}): 3149 (C-4, 5-H), 3105 (C-2-H), 1731 (CO, acid), 1607, 1355 (carboxylate) T_d ($^{\circ}\text{C}$): 200, T_g ($^{\circ}\text{C}$): -19</p>	<p>[EMIM] <i>meso</i>-HTart <i>meso</i>-1</p> <p>Yield: 97% (wax) $[\alpha]_D^{20}$ (c 1, H₂O): 0 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 177.08 (CO), 74.26 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.31 (HCOH) ATR-IR, ν (cm^{-1}): 3153 (C-4, 5-H), 3112 (C-2-H), 1732 (CO, acid), 1608, 1343 (carboxylate) T_d ($^{\circ}\text{C}$): 188, T_g ($^{\circ}\text{C}$): -22</p>
<p>[EMIM]₂(2<i>R</i>,3<i>R</i>)-Tart (+)-2</p> <p>Yield: 97% (viscous oil) $[\alpha]_D^{20}$ (c 1, H₂O): +11.1 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 179.12 (CO), 75.21 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.32 (HCOH) ATR-IR, ν (cm^{-1}): 3149 (C-4, 5-H), 3102 (C-2-H), 1604, 1352 (carboxylate) T_d ($^{\circ}\text{C}$): 233, T_g ($^{\circ}\text{C}$): -54 Viscosity at 20 $^{\circ}\text{C}$ (Pa s): 192</p>	<p>[EMIM]₂ <i>rac</i>-Tart (<i>rac</i>)-2</p> <p>Yield: 96% (viscous oil) $[\alpha]_D^{20}$ (c 1, H₂O): 0 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 178.95 (CO), 75.16 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.31 (HCOH) ATR-IR, ν (cm^{-1}): 3144 (C-4, 5-H), 3086 (C-2-H), 1606, 1347 (carboxylate) T_d ($^{\circ}\text{C}$): 240, T_g ($^{\circ}\text{C}$): -39 Viscosity at 20 $^{\circ}\text{C}$ (Pa s): 6</p>	<p>[EMIM]₂ <i>meso</i>-Tart <i>meso</i>-2</p> <p>Yield: 97% (viscous oil) $[\alpha]_D^{20}$ (c 1, H₂O): 0 ¹³C NMR (75 MHz, CD₃OD), δ (ppm): 177.99 (CO), 76.00 (HCOH) ¹H NMR (300 MHz, CD₃OD), δ (ppm): 4.14 (HCOH) ATR-IR, ν (cm^{-1}): 3145 (C-4, 5-H), 3086 (C-2-H), 1606, 1350 (carboxylate) T_d ($^{\circ}\text{C}$): 217, T_g ($^{\circ}\text{C}$): -53 Viscosity at 20 $^{\circ}\text{C}$ (Pa s): 5</p>

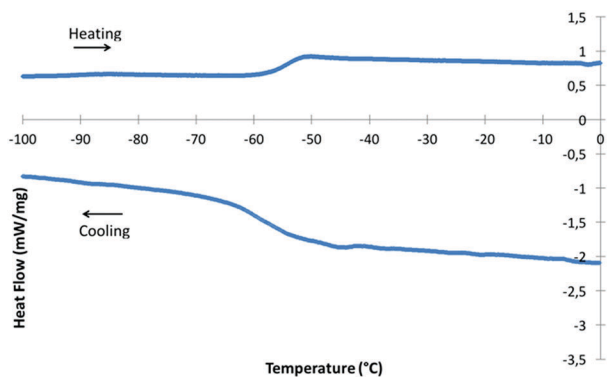


Fig. 4 DSC plot recorded during the second temperature ($5\text{ }^{\circ}\text{C min}^{-1}$) cycle for $[\text{EMIM}]_2(2R,3R)\text{-Tart (+)-2a}$ displaying a T_g of $-54\text{ }^{\circ}\text{C}$.

Despite of the wide panel of CILs reported to date, it is worth noting that studies addressing the influence of chirality on the relationships between their molecular structure and their macroscopic properties remain scarce and, most importantly, limited to crystalline materials. The group of Luis elegantly studied the impact of the chirality of the cationic component of imidazolium ILs on their physical properties.⁴¹ The stereoisomeric composition of such salts was shown to influence their melting points, an effect that was correlated to the pattern of hydrogen bond interactions developed between the ions of the corresponding ILs. More recently, Mochida also showed that racemic CILs, based on a branched cationic ruthenium sandwich complex, exhibited a lower melting point than the corresponding enantiopure derivatives, an outcome that was ascribed to the formation of conglomerates.⁴²

Having in hands a homogenous series of stereoisomeric ILs deriving from tartaric acid, we decided to explore the influence of the chirality of the tartrate moiety on the rheological properties of four different $[\text{EMIM}]_2\text{Tart}$ salts. From the macroscopic point of view, a striking difference in viscosity was observed between the ILs deriving from the chiral enantiopure (2*S*,3*S*)- or (2*R*,3*R*)-tartaric acid and the ones obtained from racemic or achiral *meso*-tartaric acid. The two enantiomeric (2*S*,3*S*)- and (2*R*,3*R*)-tartrate were very viscous liquids that did not flow easily whereas the *meso* IL and the racemic mixture were fluid. In order to quantify this difference in macroscopic behavior, the dynamic viscosity at $20\text{ }^{\circ}\text{C}$ was measured by rheology after 48 h of drying at *ca.* 10^{-3} mbar (Table 1). A water content of 3 molar equivalent, for both enantiopure (2*S*,3*S*) and (2*R*,3*R*) samples, and of 2 molar equivalent, for both racemic and *meso* compounds, was evaluated on the basis of their elementary analyses. Both chiral ILs displayed a viscosity around 200 Pa s , two order of magnitude higher than that of the achiral IL (*meso*) or the racemic mixture (around $5\text{ Pa s} = 5000\text{ mPa s} = 5000\text{ cP}$). These results were in accordance with the macroscopic observations. As a comparison, a viscosity of 38 mPa s was found in the same conditions for $[\text{EMIM}]\text{NTf}_2$, a value identical to the one reported in the literature (38.6 mPa).⁴³

The strong difference of viscosity between the *meso* or racemate IL and the chiral enantiopure (2*S*,3*S*) or (2*R*,3*R*)

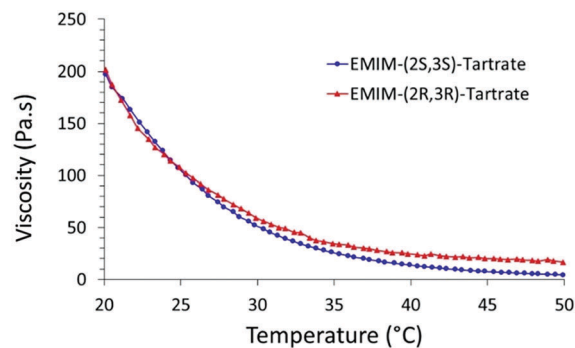


Fig. 5 Temperature dependency of the viscosity of $[\text{EMIM}]_2(2S,3S)\text{-Tart (-)-2}$ and $[\text{EMIM}]_2(2R,3R)\text{-Tart (+)-2}$.

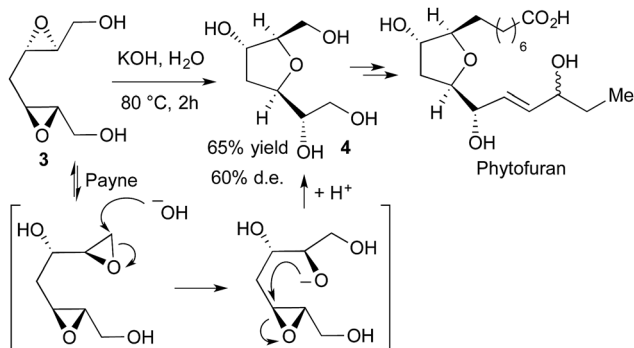
entities could be related to the difference of hydrogen bond network developed by the tartrate units. The impact of the tartrate stereochemistry on hydrogen bond-driven physico-chemical properties is well established, notably regarding tartrate-based crystals.⁴⁴ In the field of ILs, previous studies also focused on the crystalline state.^{41,42} Similar results regarding CILs in the liquid phase remain however, to the best of our knowledge, unprecedented.

In relation with their synthetic application, the temperature dependency of the viscosity was also measured for the two chiral forms (Fig. 5). A quick decrease of the viscosity with temperature was observed, reaching $\approx 100\text{ Pa s}$ at $25\text{ }^{\circ}\text{C}$ and $\approx 10\text{ Pa s}$ at $50\text{ }^{\circ}\text{C}$. The variation of the viscosity with temperature follows a power law (Reynold's model) according to the equation $\mu(T) = 2544 \exp(-0.129 \times T)$, where μ is the viscosity (Pa s) and T the temperature ($^{\circ}\text{C}$). This result showed that those CILs become practical at mild temperature and may be explored as TSILs in organic transformation.

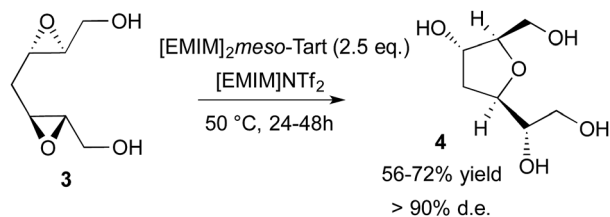
Synthetic application as TSIL

Finally, in order to exploit the intrinsic basicity of the prepared $[\text{EMIM}]$ tartrate salts, their relevance as TSILs was explored to induce a synthetically useful organic transformation. The formation of a high value-added tetraol intermediate in the total synthesis of phytofurans, newly discovered plant lipid metabolites, was selected as a particularly well-suited reaction (Scheme 3).⁴⁵ According to the previous report, treatment of the C_2 -symmetrical bis-epoxide **3** with 5 equiv. aqueous KOH at $80\text{ }^{\circ}\text{C}$ for 2 h lead to the furanic tetraol **4**, isolated as a *ca.* 80 : 20 (according to ^{13}C NMR) mixture with an unknown diastereoisomer.

This cascade reaction is proposed to be triggered by an initial base-catalysed Payne rearrangement followed by the hydrolysis of the terminal epoxide, in turn inducing an intramolecular 5-*exo*-tet cyclisation. Due to the key role of hydroxide anion/water as base/nucleophile, the alternative use of an organic base in non-aqueous conditions is likely to alter the reaction outcome. Yet previous attempts to run this transformation in organic media with a non-nucleophilic base proved unsuccessful, mainly because of the poor solubility of the starting bis-epoxide. The unique properties of ILs as both highly polar and non-protic solvents prompted us to explore their use as alternative reaction media for this transformation.



Scheme 3 The model base-induced intramolecular cyclization cascade of C_2 -symmetrical bis-epoxide **3** into tetrahydrofuran **4** en route to phytofurans.



Scheme 4 Cascade reaction forming the furanic tetraol **4** in IL media.

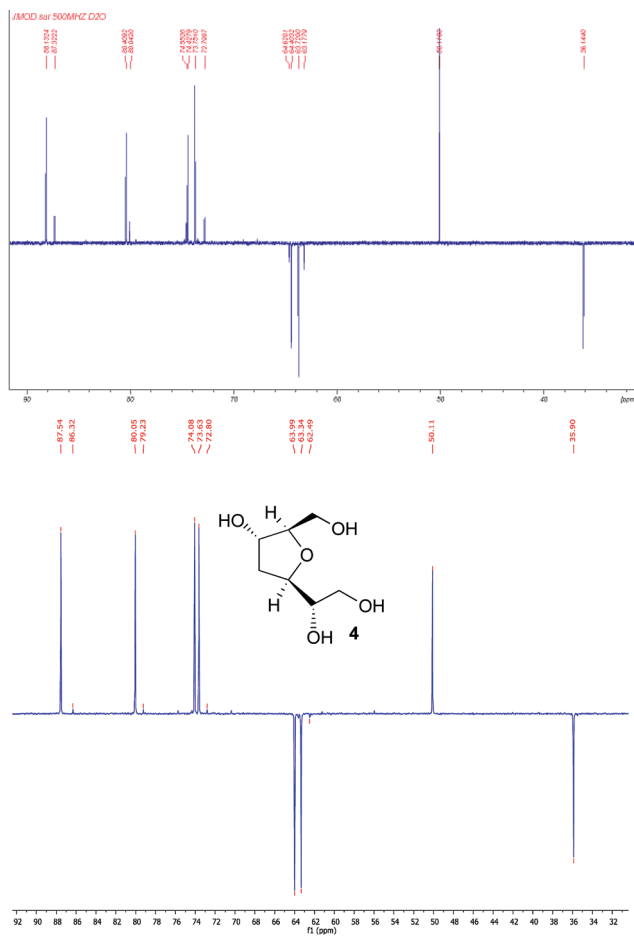


Fig. 6 ^{13}C NMR spectra of tetrahydrofuran **4** as a ca. 80:20 mixture of diastereoisomer (reproduced from ref. 45) and as a >95:5 mixture of diastereoisomer from the reaction in IL media.

In order to ensure optimal contact between reactants while minimizing the amount of tartrate-based IL used, a reaction system combining 2.5 equiv. of a tartrate salt (for 1 equiv. of the starting bis-epoxide) solubilized in the hydrophobic IL [EMIM]NTf₂ was selected (Scheme 4). Since this transformation raised no stereoinduction issues, the less viscous achiral *meso*-tartrate-based IL was selected as a relevant TSIL. Preliminary studies evidenced that, under these alternative conditions, the reaction course was similar to that previously observed in protic media. Gentle heating at 50 °C for 48 h led to the clean formation of the expected tetrahydrofuran **4**. Gratifyingly, the latter was almost formed as a single diastereoisomer, according to the ^{13}C NMR analysis of the crude mixture. Careful drying of the ILs mixture at ca. 10^{-3} mbar before the reaction appeared key to this stereochemical outcome. Minimizing the amount of water in the reaction media might reduce the formation of the unknown minor diastereoisomer by disfavoring a secondary reaction pathway.

The synthetic utility of this procedure was further assessed by carrying out the reaction at 1 mmol scale. Purification of the crude mixture afforded the expected tetrahydrofuran **4** in 56% isolated yield as a >95:5 (according to ^{13}C NMR) mixture of diastereoisomers (Fig. 6). Further optimization showed that the yield could be upgraded to 72% yield without altering the diastereoisomeric ratio when stopping the reaction after only 24 h. These alternative conditions thus favourably compare, in terms of efficiency and diastereoselectivity, to the original experimental procedure under standard conditions.

Conclusions

The previously developed general synthetic access to tartrate-based CILs was successfully applied to the generation of demanding EMIM derivatives. Thanks to the fine optimization of the treatment of [EMIM]Br with AgOH, a clean and reliable access to [EMIM]OH water solution was established. Eight different stereoisomeric [EMIM]H-Tart or [EMIM]₂Tart were obtained as viscous oils by neutralization of the corresponding acid with appropriate amounts of the aqueous [EMIM][OH] solution. Full physicochemical characterisation, including thermal phase behaviour, confirmed their proper designation as ionic liquids. Detailed study of their dynamic viscosity further revealed an unprecedented influence of the chirality on their rheological properties, both enantiopure [EMIM]₂(2*S*,3*S*)- and (2*R*,3*R*)-Tart samples displaying a viscosity 40 times higher than that of the racemic or achiral *meso* forms. Finally, the use of these tartrate salts as basic TSIL was explored in the key step of a recently reported total synthesis of phytofuran metabolites. The reaction in IL media compared favourably in terms of efficiency with the transformation in standard polar protic solvents, the diastereoisomeric excess being notably upgraded from 60 to 90%. This outcome illustrates the relevance of the developed EMIM tartrate derivatives in promoting synthetically useful base-induced organic transformations.

Experimental

General information

NMR spectroscopic data were obtained with Bruker Advance 300. Chemical shifts are quoted in parts per million (ppm) relative to residual solvent peak. J values are given in Hz. Infrared (IR) analysis were recorded with a Nexus-Thermo Nicolet FT-IR using an ATR diamond smart-IR. Mass spectrometry (MS) data were obtained on a ThermoQuest TSQ 7000 spectrometer. Elemental analyses were realized on a Perkin Elmer 2040 series II apparatus. Optical rotations were measured at 20 °C on a Jasco P 2000 polarimeter. $[\alpha]_D^{20}$ values are given in 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. Differential Thermal Analysis (DTA) were run on a Perkin Elmer Diamond TG/DTA apparatus. T_d were determined from the onset of weight loss. Differential Scanning Calorimetry (DSC) plots were recorded with a Netzsch DSC 204 apparatus. T_g were expressed as the inflexion point during the second heating cycle (5 °C min^{-1}). The dynamic viscosity was measured with a rheometer AR1000 (TA instruments) equipped with a cone-plate configuration (diameter 20 or 40 mm, angle 2°, stainless steel) under air.

Synthetic procedures and characterization of [EMIM] tartrates

1-Ethyl-3-methylimidazolium bromide ([EMIM]Br). A neat mixture of bromoethane (2.4 mL, 3.2 mmol) and 1-methylimidazole (2.5 mL, 3.2 mmol) was warm stirred under Ar atmosphere at 40 °C for 3 h. After cooling at RT, EtOAc was added to precipitate the product. The salt was filtered, washed with ethyl acetate and dry under vacuum to obtain the crude [EMIM]Br as a white wax (4.33 g, 94%). ^1H NMR (300 MHz, CD_3OD): δ (ppm) 8.99 (s, 1H), 7.59 (d, $J = 24$, 3 Hz, 2H), 4.29 (q, $J = 7$, 5 Hz, 2H), 3.94 (s, 3H), 1.54 (t, $J = 7$, 5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 137.62, 124.97, 123.34, 46.05, 36.50, 15.61.

Silver hydroxide (AgOH). To a solution of sodium hydroxide (1.00 g, 25 mmol) in distilled water (10 mL) was added silver nitrate (4.25 g, 25 mmol). The solution was stirred 10 min away from light at RT. The resultant mixture was filtered and the solid obtained washed with water. AgOH was dried under vacuum in the dark. The compound was obtained as a fine dark brown powder (2.81 g, 90%).

1-Ethyl-3-methylimidazolium hydroxide ([EMIM]OH). To a solution of [EMIM]Br (100 mg, 0.56 mmol) in distilled water (20 mL g^{-1}) at 0–5 °C was added freshly prepared AgOH (1 equiv.). After 5 minutes of stirring at 0–5 °C and out of direct light, the solution was filtered over 47 mm hydrophilic propylene 0.2 μm membrane filters and washed with distilled water (10 mL). The resulting [EMIM]OH aqueous solution was used directly for the neutralization of tartaric acid. In order to analyze the product solution, the reaction was also performed in D_2O according to the same procedure. ^1H NMR (300 MHz, D_2O): δ (ppm) around 8.4 (s, highly exchangeable, H2), 7.45 (d, $J = 1$, 8 Hz, 1H, H4), 7.38 (d, $J = 1.8$ Hz, 1H, H5), 4.18 (q, $J = 7.2$ Hz, 2H, CH_2Me), 3.85 (s, 3H, NMe), 1.46 (t, $J = 7.2$ Hz, 3H, CH_2Me). ^{13}C NMR (75 MHz, D_2O): δ (ppm) around 138.00 (C2, non-apparent on 1D spectra), 123.34 (C4), 121.76 (C5), 46.69 (CH_2Me), 35.50 (NMe), 14.40 (CH_2Me).

General procedure for the preparation of [EMIM] tartrates.

Tartaric acid (0.5 or 1 equiv.) was rapidly added to an aqueous solution of [EMIM]OH prepared as indicated above. The resulting mixture was stirred away from light for 2 h at RT. After evaporation of water on rotary evaporator (water bath temperature 30 °C), the residue was dissolved in methanol (10 mL) and filtered over a 25 mm Acrodisc[®] syringe filter equipped with a 0.2 μm PTFE membrane to remove the unreacted tartaric acid. The solvent was removed under vacuum and the compound was dried for 2–3 days at RT under *ca.* 10^{-3} bar.

1-Ethyl-3-methylimidazolium hydrogen (2R,3R)-tartrate ([EMIM](2R,3R)-HTart), (+)-1. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.07 g, 5.6 mmol), AgOH (0.71 g, 5.6 mmol) and (2R,3R)-tartaric acid (0.846 g, 5.6 mmol). The compound (+)-1 was obtained as a clear light yellow viscous oil (1.42 g, 97%). $[\alpha]_D^{20} + 11.6$ (*c* 1, H_2O). ^1H NMR (300 MHz, CD_3OD): δ (ppm) 9.04 (s, 1H, H2), 7.66 (d, $J = 1.8$ Hz, 1H, H4), 7.59 (d, $J = 1.8$ Hz, 1H, H5), 4.46 (s, 2H, CHOH), 4.29 (q, $J = 7$, 5 Hz, 2H, CH_2Me), 3.95 (s, 3H, NMe), 1.53 (t, $J = 7$, 2 Hz, 3H, CH_2Me). ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 176.50 (C=O), 137.76 (C2), 124.93 (C4), 123.22 (C5), 74.03 (CHOH), 45.98 (CH_2Me), 36.53 (NMe), 15.67 (CH_2Me). ATR-FTIR: ν_{max} (cm^{-1}) 3400 (O–H, carboxylic acid and hydroxyls), 3152 (C–4, 5–H), 3110 (C–2–H), 2986 (aliph. C–H), 2939 (aliph. C–H), 1732 (C=O, carboxylic acid), 1601 (carboxylate, asym.), 1573 (C=C), 1451 (aliph. C–H), 1389 (aliph. C–H), 1336 (carboxylate, sym.), 1232 (C–OH, carboxylic acid), 1170 (aliph. C–N), 1128 (C–O, hydroxyl), 1083 (C–O, hydroxyl). MS: m/z 111 (IC^+ , NH_3), m/z 149 (IC^- , NH_3). Anal. calc. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_6 + 1.25 \text{H}_2\text{O}$: C, 42.48; H, 6.59; N, 9.91%; found: C, 42.43; H, 6.32; N, 10.28%. DSC: $T_g -19$ °C. ATD: $T_d 188$ °C.

1-Ethyl-3-methylimidazolium hydrogen (2S,3S)-tartrate ([EMIM](2S,3S)-HTart), (–)-1. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.0 g, 5.26 mmol), AgOH (0.66 g, 5.28 mmol) and (2S,3S)-tartaric acid (0.792 g, 5.27 mmol). The compound (–)-1 was obtained as a clear light yellow viscous oil (1.34 g, 98%). It gave analytical data identical to that of its enantiomer except for its optical rotation. $[\alpha]_D^{20} -11.5$ (*c* 1, H_2O). Anal. calc. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_6 + 0.25 \text{H}_2\text{O}$: C, 45.37; H, 6.28; N, 10.58%; found: C, 45.69; H, 6.55; N, 11.13%.

1-Ethyl-3-methylimidazolium hydrogen rac-tartrate ([EMIM]-rac-HTart), (rac)-1. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.0 g, 5.26 mmol), AgOH (0.64 g, 5.3 mmol) and racemic tartaric acid (0.803 g, 5.3 mmol). The compound (rac)-1 was obtained as a clear light yellow viscous oil (1.33 g, 96%). ^1H NMR (300 MHz, CD_3OD): δ (ppm) 9.02 (s, 1H2), 7.64 (d, $J = 1.8$ Hz, 1H, H4), 7.57 (d, $J = 1.8$ Hz, 1H, H5), 4.40 (s, 2H, CHOH), 4.27 (q, $J = 7$, 5 Hz, 2H, CH_2Me), 3.94 (s, 3H, NMe), 1.52 (t, $J = 7$, 5 Hz, 3H, CH_2Me). ^{13}C NMR 75 MHz, CD_3OD : δ (ppm) 176.31 (CO), 137.89 (C2), 124.92 (C4), 123.16 (C5), 74.35 (CHOH), 45.94 (CH_2Me), 36.54 (CH_3 NMe), 15.69 (CH_2Me). ATR-FTIR: ν_{max} (cm^{-1}) 3385 (O–H, carboxylic acid and hydroxyls), 3149 (C–4, 5–H), 3105 (C–2–H), 2984 (aliph. C–H), 2957 (aliph. C–H), 1731 (C=O, carboxylic acid), 1607 (carboxylate, asym.), 1573 (C=C),

1451 (aliph. C-H), 1355 (carboxylate, sym.), 1212 (C-OH, carboxylic acid), 1171 (aliph. C-N), 1111 (C-O, hydroxyls), 1094 (C-O, hydroxyls). MS: m/z 111 (IC⁺, NH₃), m/z 149 (IC⁻, NH₃). Anal. calc. for C₁₀H₁₆N₂O₆ + 0.25 H₂O: C, 45.37; H, 6.28; N, 10.58%; found: C, 45.29; H, 6.16; N, 10.76%. DSC: T_g -19 °C. ATD: T_d 200 °C.

1-Ethyl-3-methylimidazolium hydrogen meso-tartrate ([EMIM]₂-meso-HTart), meso-1. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (0.99 g, 5.21 mmol), AgOH (0.65 g, 5.23 mmol) and meso-tartaric acid (0.78 g, 5.3 mmol). The compound meso-1 was obtained as a pale yellow wax (1.20 g, 83%). ¹H NMR (300 MHz, CD₃OD): δ (ppm) 9.04 (s, 1H, H2), 7.64 (d, J = 1.8 Hz, 1H, H4), 7.57 (d, J = 1.8 Hz, 1H, H5), 4.31 (s, 2H, CHOH), 4.27 (q, J = 7, 5 Hz, 2H, CH₂Me), 3.94 (s, 3H, NMe), 1.52 (t, J = 7, 5 Hz, 3H, CH₂Me). ¹³C-NMR (75 MHz, CD₃OD): δ (ppm) 177.08 (CO), 137.81 (C2), 124.94 (C4), 123.20 (C5), 74.26 (CHOH), 45.96 (CH₂Me), 36.51 (NMe), 15.67 (CH₂Me). ATR-FTIR: ν_{\max} (cm⁻¹) 3419 (O-H, carboxylic acid and hydroxyls), 3153 (C-4, 5-H), 3112 (C-2-H), 2987 (aliph. C-H), 2946 (aliph. C-H), 1732 (C=O, carboxylic acid), 1608 (carboxylate, asym.), 1574 (C=C), 1454 (aliph. C-H), 1343 (carboxylate, sym.), 1222 (C-OH, carboxylic acid), 1170 (aliph. C-N), 1130 (C-O, hydroxyls), 1076 (C-O, hydroxyls). MS: m/z 111 (IC⁺, NH₃), m/z 149 (IC⁻, NH₃). Anal. calc. for C₁₀H₁₆N₂O₆ + 1.75 H₂O: C, 44.04; H, 6.10; N, 10.27%; found: C, 44.25; H, 6.46; N, 10.95%. DSC: T_g -22 °C. ATD: T_d 188 °C.

Bis(1-ethyl-3-methylimidazolium) (2R,3R)-tartrate ([EMIM]₂-(2R,3R)-Tart), (+)-2. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.03 g, 5.41 mmol), AgOH (0.68 g, 5.44 mmol) and (2R,3R)-tartaric acid (0.41 g, 2.68 mmol). The compound (+)-2 was obtained as a clear light yellow viscous oil (0.94 g, 97%). [α]_D²⁰ + 11.1 (c 1, H₂O). ¹H NMR (300 MHz, CD₃OD): δ (ppm) 9.03 (s, 2H, 2 × H2), 7.64 (d, J = 1.2 Hz, 2H, 2 × H4), 7.57 (d, J = 1.2 Hz, 2H, 2 × H5), 4.32 (s, 2H, CHOH), 4.27 (q, J = 7, 2 Hz, 4H, 2 × CH₂Me), 3.94 (s, 6H, 2 × NMe), 1.53 (t, J = 7, 5 Hz, 6H, 2 × CH₂Me). ¹³C NMR (75 MHz, CD₃OD): δ (ppm) 179.12 (CO), 137.91 (C2), 124.91 (C4), 123.20 (C5), 75.21 (CHOH), 45.97 (CH₂Me), 36.44 (NMe), 15.61 (CH₂Me). ATR-FTIR: ν_{\max} (cm⁻¹) 3398 (O-H, carboxylic acid and hydroxyls), 3149 (C-4, 5-H), 3102 (C-2-H), 2985 (aliph. C-H), 1604 (carboxylate, asym.), 1574 (C=C), 1452 (aliph. C-H), 1352 (carboxylate, sym.), 1171 (aliph. C-N), 1119 (C-O, hydroxyls), 1066 (C-O, hydroxyls). MS: m/z 111 (IC⁺, NH₃), m/z 149 (IC⁻, NH₃). Anal. calc. for C₁₆H₂₆N₄O₆ + 2.5 H₂O: C, 46.26; H, 7.52; N, 13.49%; found: C, 46.42; H, 7.58; N, 13.77%. DSC: T_g -54 °C. ATD: T_d 233 °C.

Bis(1-ethyl-3-methylimidazolium) (2S,3S)-tartrate ([EMIM]₂-(2S,3S)-Tart), (-)-2. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.06 g, 5.58 mmol), AgOH (0.697 g, 5.58 mmol) and (2S,3S)-tartaric acid (0.43 g, 2.8 mmol). The compound (-)-2 was obtained as a clear light yellow viscous oil (1.03 g, 98%). It gives analytical data identical to that of its enantiomer except for its optical rotation. [α]_D²⁰ -11.2 (c 1, H₂O). Anal. calc. for C₁₆H₂₆N₄O₆ + 3.5 H₂O: C, 44.33; H, 7.67; N, 12.93%; found: C, 44.61; H, 7.49; N, 12.81%.

Bis(1-ethyl-3-methylimidazolium) rac-tartrate ([EMIM]₂-rac-Tart), (rac)-2. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.00 g, 5.26 mmol), AgOH (0.66 g, 5.27 mmol) and racemic tartaric acid (0.39 g, 2.63 mmol). The compound (rac)-2 was obtained as a clear light yellow viscous oil (0.93 g, 96%). ¹H NMR (300 MHz, CD₃OD): δ (ppm) 9.04 (s, 2H, 2 × H2), 7.64 (d, J = 1.2 Hz, 2H, 2 × H4), 7.57 (d, J = 1.2 Hz, 2H, 2 × H5), 4.31 (s, 2H, CHOH), 4.27 (q, J = 7, 2 Hz, 2H, CH₂Me), 3.94 (s, 3H, NMe), 1.53 (t, J = 7, 5 Hz, 3H, CH₂Me). ¹³C-NMR (75 MHz, CD₃OD): δ (ppm) 178.95 (CO), 137.85 (C2), 124.92 (C4), 123.22 (C5), 75.16 (CHOH), 45.95 (CH₂Me), 36.5 (NMe), 15.70 (CH₂Me). ATR-FTIR: ν_{\max} (cm⁻¹) 3361 (O-H, carboxylic acid and hydroxyls), 3144 (C-4, 5-H), 3085 (C-2-H), 2982 (aliph. C-H), 1606 (carboxylate, asym.), 1573 (C=C), 1452 (aliph. C-H), 1347 (carboxylate, sym.), 1173 (aliph. C-N), 1107 (C-O, hydroxyls), 1060 (C-O, hydroxyls). MS: m/z 111 (IC⁺, NH₃), m/z 149 (IC⁻, NH₃). Anal. calc. for C₁₆H₂₆N₄O₆ + 2.5 H₂O: C, 46.26; H, 7.52; N, 13.49%; found: C, 46.53; H, 7.72; N, 13.92%. DSC: T_g -39 °C. ATD: T_d 240 °C.

Bis(1-ethyl-3-methylimidazolium) meso-tartrate ([EMIM]₂-meso-Tart), meso-2. Synthesized according to the general procedure for the preparation of [EMIM] tartrates using [EMIM]Br (1.01 g, 5.32 mmol), AgOH (0.67 g, 5.34 mmol) and meso-tartaric acid (0.44 g, 2.63 mmol). The compound meso-2 was obtained as a clear light yellow viscous oil (0.95 g, 97%). ¹H NMR (300 MHz, CD₃OD): δ (ppm) 9.04 (s, 2H, 2 × H2), 7.63 (d, J = 2.1 Hz, 2H, 2 × H4), 7.56 (d, J = 1.8 Hz, 2H, 2 × H5), 4.27 (q, J = 7, 5 Hz, 2H, CH₂Me), 4.14 (s, 2H, CHOH), 3.94 (s, 3H, NMe), 1.53 (t, J = 7, 5 Hz, 3H, CH₂Me). ¹³C NMR (75 MHz, CD₃OD): δ (ppm) 177.99 (CO), 138.02 (C2), 124.87 (C4), 123.17 (C5), 76.0 (CHOH), 45.95 (CH₂Me), 36.5 (NMe), 15.65 (CH₂Me). ATR-FTIR: ν_{\max} (cm⁻¹) 3374 (O-H, carboxylic acid and hydroxyls), 3145 (C-4, 5-H), 3086 (C-2-H), 2983 (aliph. C-H), 1606 (carboxylate, asym.), 1574 (C=C), 1452 (aliph. C-H), 1350 (carboxylate, sym.), 1173 (aliph. C-N), 1117 (C-O, hydroxyls), 1063 (C-O, hydroxyls). MS: m/z 111 (IC⁺, NH₃), m/z 149 (IC⁻, NH₃). Anal. calc. for C₁₆H₂₆N₄O₆ + 2.5 H₂O: C, 46.26; H, 7.52; N, 13.49%; found: C, 46.42; H, 7.58; N, 13.77%. DSC: T_g -53 °C. ATD: T_d 217 °C.

Rheology

Before each measurement, the IL was dried for 48 h under a vacuum of 3×10^{-3} mbar, placed rapidly into the geometry gap (diameter 20 mm, 2°) and measured immediately after. For measurements at fixed temperature (20 °C), a logarithmic increase of the shear rate from 0.3 to 10 s⁻¹ has been applied to the sample with a total duration of 5 min. A second measurement starting 5 min after the end of the first measurement provided the same curves and viscosity values for all the samples, indicating that the viscosity was not affected by hydration at the early stage of the measurement. The viscosity was found to be independent of the shear rate applied (Newtonian behavior) (Fig. SI-1, ESI[†]). The viscosity values were extracted for a shear rate = 1 s⁻¹. Observed values were: 192 Pa s ([EMIM]₂(2R,3R)-Tart), 199 Pa s ([EMIM]₂(2S,3S)-Tart), 6 Pa s ([EMIM]₂rac-Tart) and 5 Pa s ([EMIM]₂meso-Tart). For the measurements in function of temperature, a linear temperature ramp

has been applied from 20 °C to 50 °C with a total duration of 5 min (6 °C min⁻¹). The data in Fig. 5 show that the variation of the viscosity with temperature follows a power law (Reynold's model) according to the equation $\mu(T) = 2544 \exp(-0.129 \times T)$, where μ is the viscosity (Pa s) and T the temperature (°C). For comparison, the viscosity of EMIM(NTf)₂ at 20 °C was measured in the same conditions of drying and measurement, except the geometry (diameter 40 mm, 2°).

Use of [EMIM] tartrates as TSIL in the model intramolecular cyclization cascade

General procedure for the reaction in IL. To a mixture of [EMIM]₂Tart (2.5 equiv.) and [EMIM]NTf₂ (80 w%) dried at ca. 10⁻³ mbar for 48 h, was added the bis-epoxydiol 3 (1 equiv.). The reaction was stirred at 50 °C. After cooling to RT, the crude was purified by flash chromatography eluted with DCM/MeOH (90:10 to 85:15) to afford the expected tetrahydrofuran 4.

Tetrahydrofuran 4. Obtained according to the general procedure for the reaction in IL using bis-epoxydiol 3 (170 mg, 1.10 mmol), [EMIM]₂meso-Tart (1.02 g, 2.75 mmol), [EMIM]NTf₂ (800 mg) for 48 h. Purification gave the expected product 4 (110 mg, 56%) in >90% d.e. (according to ¹³C NMR).

Conflicts of interest

There are no conflicts to declare.

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