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Synthesis of Chiral Room Temperature Ionic Liquids from Amino Acids – Application in Chiral Molecular Recognition

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A series of structurally new room temperature chiral ionic liquids based on an imidazolium group and derived from natural amino acids have been synthesized and studied as chiral shift agents for the chiral discrimination of enantiomeric carboxylate salts. This family of imidazolium salts can be prepared by a simple synthetic approach and most of the components are liquid at room temperature. The solid to liquid transformation temperatures can be as low as –49 °C. The analysis of the supramolecular structure of the resulting CILs can be used advantageously to understand the potential for the selective recognition of different hosts.

Introduction

Ionic liquids (ILs) are attracting considerable attention as green reaction solvents,[1] extraction liquids[2] and electrolyte materials,[3] as well as structured media for other technological applications such as their use for enhancing the sensitivity of thermal lens measurements.[1g,4] Most of those applications involve the use of the so-called room-temperature Ionic Liquids (RTILs) that have melting temperatures below 100 °C,[5] and were described in the work of Walden in 1914. The potential applications of ILs are closely related to their physicochemical properties, and those depend on the interaction established between both the cation and the anion.[6] The nature of these components can be easily varied and, thus, the large structural diversity available for ILs plays an important role in our ability to define their final properties, such as electrochemical stability,[7] miscibility with water and/or organic solvents,[8] melting point,[9] viscosity,[10] and so on. In this regard much work has been carried out to understand the influence of the different structural parameters, such as the nature of side chains or the presence of additional functional groups, on the intrinsic properties of ILs. On the other hand, chirality plays a key role in organic chemistry. Therefore, the design and synthesis of enantiopure ILs with the possibility of easy structural tuneability is highly attractive and a continued effort is being currently devoted to the preparation of chiral ionic liquids (CILs).[11] CILs have additional potential as chiral solvents,[12] shift reagents,[13] or enantioselective catalysts.[14] Furthermore, it has recently been shown that the configuration of the resulting CILs plays an important role in defining their final physical properties.[15]

Within this context, our group has been involved in the preparation and study of CILs prepared either from racemic materials,[15] or from enantiomerically pure materials obtained from the chiral pool.[16] Here we report on the preparation of a new family of CILs using natural amino acids as the source of chirality and containing an amide group as an essential structural feature.

The use of a flexible and simple synthetic approach allows the preparation of a large variety of configurationally and structurally diverse CILs (see Figure 1 for the general structure). An analysis of the structure-properties relationship has been carried out. The main structural variables considered were the amino acid side chain residue (R), the moiety attached to the nitrogen atom of the imidazolium ring (R^2), the fragment attached to the amide nitrogen atom (R^1) and the counterion. The resulting salts have also been investigated as chiral shift reagents (CSR) for chiral carboxylates.

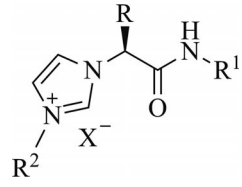

Figure 1. General structure for CILs **7**–**12**.

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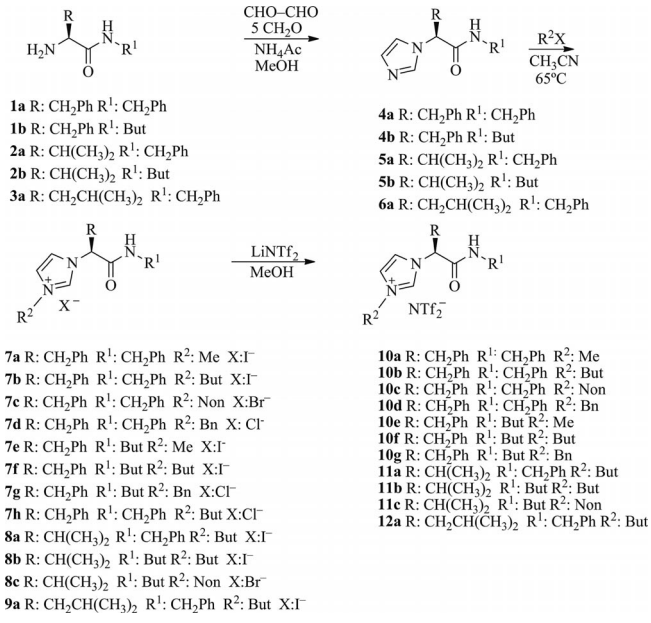
Results and Discussion

Synthesis of CILs

Chiral α-amino amides **1**–**3**, described previously by our group,[17] were used as precursors for the synthesis of chiral ILs **7**–**12** having an imidazolium cation. Here, L-valine, L-phenylalanine and L-leucine were used as starting materials for introducing chirality [R = $CH(CH_3)_2$, CH_2Ph and $CH_2CH(CH_3)_2$]. The imidazole ring was formed by reacting formaldehyde, ammonium acetate, glyoxal and the chiral α-amino amide to obtain compounds **4**–**6**.[18] The chiral imidazoles were then alkylated by using different alkyl chlorides, bromides or iodides to give the corresponding imidazolium salts **7**–**9**. Finally, compounds **7**–**9** were converted into the corresponding bistriflamides by anion exchange using $LiNTf_2$. In general, it has been observed that the presence of this anion is more appropriate for the preparation of RTILs and for recognition studies.[16] Thus, following the general procedure depicted in Scheme 1, the imidazolium chiral salts **10**–**12** were obtained in moderate yields. CILs **10**–**12** were liquid at room temperature with melting points ranging from 2 to –49 °C.



Scheme 1. Synthesis of CILs.

The structures of the new CILs were characterized by ^1H NMR, ^{13}C NMR, IR, MS, DSC, TGA and elemental analysis.

Study of the Structure on the Solid and Solution States

The strong interaction between the imidazolium cation and the corresponding anion through electrostatic forces and hydrogen bonding gives tightly associated ion pairs with well-defined structures, as well as defined supramolecular structures in the solid and liquid states and, in some cases, also in solution.[6c,7,19] In order to analyze those structures, different methodologies such as thermal analysis, IR and NMR can be used.[20]

TGA and DSC Analyses

As show in Table 1, all 23 compounds **7**–**12** are ionic liquids showing a phase transition temperature ranging from 61 °C for **7d** to –49 °C for **11c**, and thermal stability over 250 °C. As expected, substituting the halide anions for the less coordinating NTf_2^- anion is accompanied by a decrease in the melting point, in particular when the substitution of Cl^- takes place. This change in the anion also gives a clear increment in the thermal stability with values of $T_d >$ 300 °C. In the same way, the tendency for formation of solid ionic salts for the different anions decreases in the order $Cl^- > I^- > NTf_2^-$ (Table 1, Entries 2, 8 and 14). Indeed, organic salts containing NTf_2^- are RTILs for all the cases studied with $T_m <$ 20 °C, showing a phase transition temperature ranging from 2 °C for **10d** to –49 °C for **11c**.

Table 1. Phase transition temperature (T_m) and decomposition temperature (T_d) obtained for CILs **7**–**12**.

Entry	CILs	L-aa	R^1	R^2	X^-	T_m [°C][a]	T_d [°C][b]
1	**7a**	Phe	Bn	Me	I	51	280
2	**7b**	Phe	Bn	*n*But	I	35	320
3	**7c**	Phe	Bn	Non	Br	24	322
4	**7d**	Phe	Bn	Bn	Cl	61	327
5	**7e**	Phe	*n*But	Me	I	32	285
6	**7f**	Phe	*n*But	*n*But	I	18	290
7	**7g**	Phe	*n*But	Bn	Cl	48	250
8	**7h**	Phe	Bn	*n*But	Cl	43	325
9	**8a**	Val	Bn	*n*But	I	17	320
10	**8b**	Val	*n*But	*n*But	I	–2	315
11	**8c**	Val	*n*But	Non	Br	–8	305
12	**9a**	Leu	Bn	*n*But	I	17	310
13	**10a**	Phe	Bn	Me	NTf_2	–1	400
14	**10b**	Phe	Bn	*n*But	NTf_2	–12	375
15	**10c**	Phe	Bn	Non	NTf_2	–20	400
16	**10d**	Phe	Bn	Bn	NTf_2	2	355
17	**10e**	Phe	*n*But	Me	NTf_2	–16	380
18	**10f**	Phe	*n*But	*n*But	NTf_2	–23	380
19	**10g**	Phe	*n*But	Bn	NTf_2	–9	380
20	**11a**	Val	Bn	*n*But	NTf_2	–20	340
21	**11b**	Val	*n*But	*n*But	NTf_2	–45	310
22	**11c**	Val	*n*But	Non	NTf_2	–49	330
23	**12a**	Leu	Bn	*n*But	NTf_2	–19	395

[a] Data obtained from DSC. [b] Data obtained from TGA.

The size and nature of the alkylating agent (R^2), the substituent at the amide moiety (R^1) and the side chain derived from the amino acid (R) also play a key role in determining the melting point of the different enantiopure chiral imidazolium salts. An increase in the length of the alkylating agent leads to a small decrease of the transition temperature (T_m) (Table 1, Entries 21, 22 for L-valine derivatives, Entries 13–15 for L-phenylalanine derivatives). On the contrary, the substitution of an alkyl group by a group containing an aromatic ring always induces an increase in the T_m. This increase is observed independently of the counterion and is valid for changes at the alkylating agent (R^2), the substituent at the amide fragment (R^1) or at the side chain

(R). The decrease in T_m with the length of the alkyl chain can be associated with the higher degree of disorder associated to the alkyl chain. However, the increase in T_m for benzylimidazolium salts must involve the presence of π–π interactions (i.e. in **10b**), CH–π interactions or solvophobic forces (i.e. in **10f** or **11a**). The X-ray crystal structure obtained for **7b** (details follow) confirms the presence of an intramolecular CH–π interaction between the butyl alkylating agent and the aromatic ring from the Phe moiety. In the same way, the presence of a side chain, R, containing an aromatic ring also produces an increase in T_m, independently of the anion (See, for example, Table 1, Entries 2 versus 9 or 12, and 9 versus 21). A similar effect is observed when the N-substituent at the amide moiety (R_1) is considered. For instance, the substitution of the *n*-butyl group in **10e** by a benzyl group in **10a** is accompanied by an increase in the T_m of 15 °C (Table 1, Entries 13 and 17).

Experimental attenuated total reflectance (ATR)-FTIR and ^{1}H NMR studies obtained for **7b**, **7i** and **10b** strongly support the stabilization effect of the amide NH-anion hydrogen-bonding interactions, although secondary inter-cationic interactions (such as additional H bonding, π-stacking or C–H–π bonding involving benzyl aromatic rings), as observed in the crystal structures, could also contribute significantly to the global stability of the salts. The stabilization effect decreases in all the CILs studied in the order halide < NTf_2^-. It has been recognized that the presence of additional functionalities in the CILs, which are able to form hydrogen-bond interactions with the counterion, have a significant influence on their final macroscopic properties.[21]

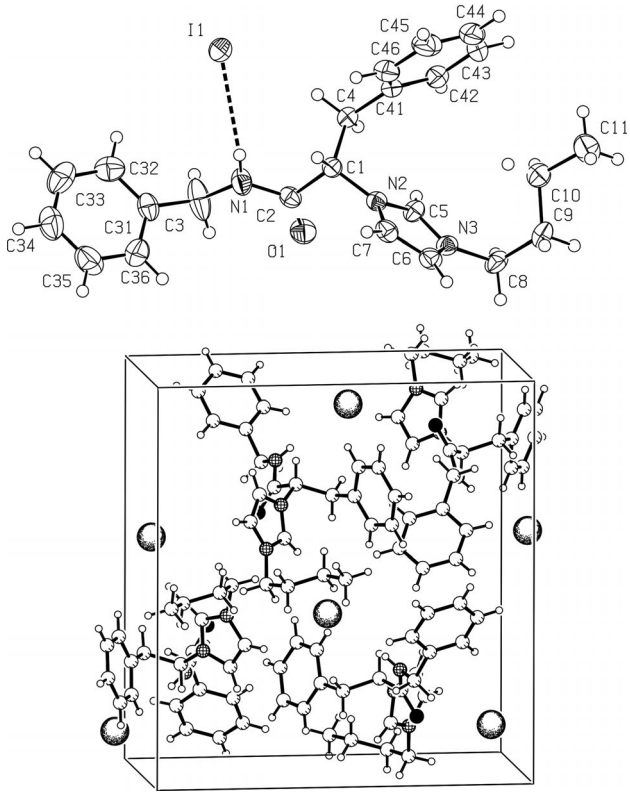


Figure 2. Molecular structure (top) and crystal packing (bottom) for compound **7b**, obtained by X-ray diffraction analysis.

The three-dimensional molecular structure of **7b** was unambiguously determined by using single-crystal X-ray diffraction analysis (Figure 2). As expected, the iodide anion was in proximity to one amide N1–H proton and one imidazolium moiety, and thus able to interact through hydrogen bonding.[22] In the crystal packing it can be observed that the hydrogen-bonding distances with the anion increase in the sequence NH < C5–H < C6–H. It should be noted that the N1–H and the imidazolium protons from a given cation are bound to different anions within the crystal lattice.

In the crystal packing structure an intramolecular CH–π interaction between the butyl group from the alkylating agent and the aromatic ring from the Phe moiety can be seen (C10–H to C43 distance 3.061 Å). Furthermore, different intermolecular edge-to-face π–π interactions can be detected, involving the aromatic ring from the substituent at the amide fragment of a molecule and the aromatic rings derived from the Phe moieties of two additional molecules (π–π distances 2.897 and 2.899 Å).

Computational Studies

To understand the importance of the structural factors, which were observed in the X-ray diffraction study, for the molecule in solution, **7b** was studied using the Monte Carlo conformational search available in Spartan '08.[23] The resulting minimum energy conformer was optimized at a semi empirical level (PM6) in Gaussian 09.[24] The optimized structure obtained for **7b** is shown in Figure 3. Similarly to the crystal structure, the most stable conformer for **7b** presents a predominant hydrogen bonding interaction between the amide NH and the anion (iodide) (NH and anion distance 2.399 Å). A hydrogen-bond interaction between C5–H and the anion is also present (C5–H and anion distance 2.755 Å).

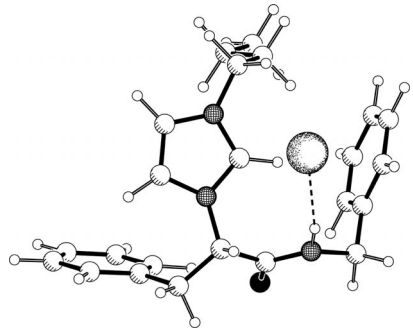


Figure 3. Most stable conformer obtained for **7b** using Gaussian 09 (semiempiric level PM6). Hydrogen bonds are denoted by dotted lines.

ATR-FTIR Vibrational Spectroscopy and NMR Solution Studies

ATR-FTIR spectroscopy was used to study the supramolecular structure of the CILs **7a**–**12a**.[25] NMR spec-

troscopy provides an average chemical shift for imidazolium protons and NH protons interacting with the anion, whereas ATR-FTIR gives separate vibrational bands for distinct species, such as ion pairs. The differences are owing to the different time scales of these techniques.

In the ATR-FTIR spectra of **7a**–**12a**, the bands between 3150 and 3000 cm^{-1} are considered diagnostic of the C–H stretching modes of the aromatic rings.[6b,15] In this region, for the imidazolium aromatic ring, the vibrational bands at higher wavenumbers correspond to C6–H and C7–H stretching modes, whereas vibrational bands at lower wavenumbers correspond to the C5–H stretching mode.

In the partial ATR-FTIR spectra for **7b**, **7h** and **10b**, shown in Figure 4, vibrational bands observed at 3124 cm^{-1} for **7b**, 3096 cm^{-1} for **7h**, and 3147 cm^{-1} for **10b** can be assigned to C6–H and C7–H stretching modes. For **10b**, the vibrational band corresponding to C5–H is observed at 3110 cm^{-1}, whereas for **7b** and **7h** this band appears below 3075 and 3059 cm^{-1} and overlap with the bands corresponding to the benzene ring.[26]

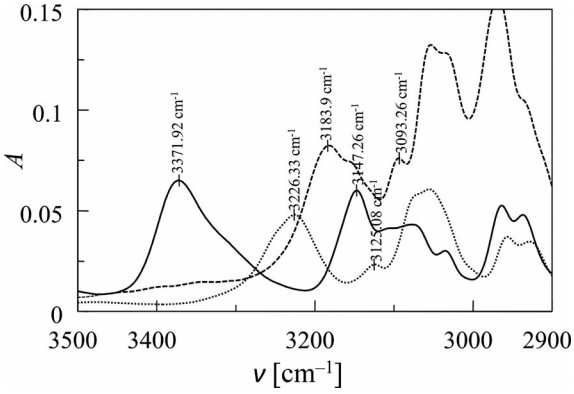


Figure 4. Partial ATR-FTIR spectra for **7b** (dotted line), **7h** (discontinuous line) and **10b** (continuous line) at 25 °C.

Vibrational bands observed at higher wavenumbers (> 3150 cm^{-1}) can be assigned to N–H stretching modes (3225 cm^{-1} for **7b**, 3185 cm^{-1} for **7h** and 3375 cm^{-1} for **10b**, Figure 4).

As can be seen, an increase in the Brønsted basicity of the anion is accompanied by significant variations of the NH stretching bands. Upon formation of the hydrogen bond, the N–H bond is weakened and, thus, the frequency of its stretching vibration normally decreases.[27] Therefore, the frequency observed for the vibrational N–H band follows the order Cl < I < NTf_2 (Figure 4). According to the ATR-FTIR data, the hydrogen from the amide NH is the one more strongly involved in hydrogen bonding with the anion (Δν for the couple NTf_2/I, 150 cm^{-1}), followed by the hydrogen at the C5 (Δν for the couple NTf_2/I >35 cm^{-1}), whereas protons at C6 and C7 are much less affected (Δν for the couple NTf_2/I, 23 cm^{-1}).

Several techniques, including variable-temperature infrared spectroscopy, have been used to monitor the change of the intramolecular order and the supramolecular ordering of different molecules.[28] In this context, the ATR-FTIR spectra of **7b** at different temperatures were measured. Figure 5 displays the changes observed in the wavenumbers of the different bands as a function of the temperature. When the temperature is increased, most of the bands shift to lower wavenumbers except the signal corresponding to C–H asymmetric deformation at approximately 1450 cm^{-1}, which remains essentially unaltered, and the amide I band (approximately 1678 cm^{-1}), which shifts to higher values. This change suggests the presence of a significant degree of order based on H-bonding involving the amide N–H that is partly relieved upon heating.

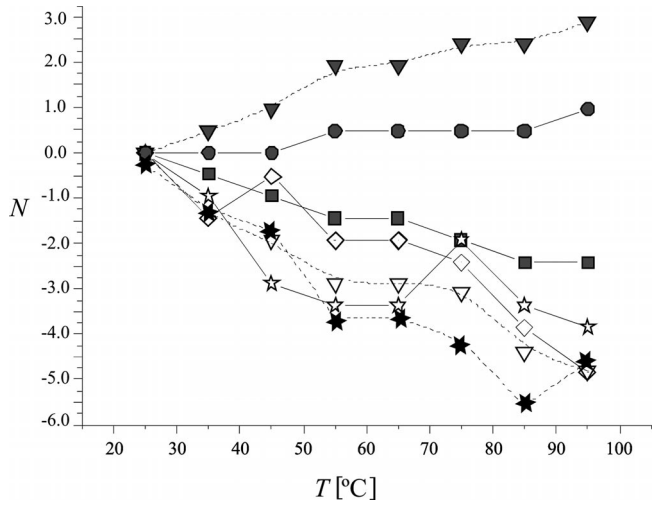


Figure 5. Variation with the temperature of the wavenumbers for the different bands of **7b**. Grey triangle for amide I; grey circle 1453 cm^{-1}, grey square 1557.5 cm^{-1}; white square 3229.9 cm^{-1}; black star 3059 cm^{-1}; white star 3213 cm^{-1}; white triangle amide II.

For **7b**, **7h** and **10b**, the hydrogen-bonding interactions between the imidazolium protons and the anion was also studied by ^1H NMR spectroscopy, by using 10 mM solutions of the different CILs in $CDCl_3$ (Figure 6). As can be observed, with an increase in the Brønsted basicity of the anions, significant and simultaneous downfield shifts were observed for the imidazolium C5–H signal and that of the amide proton (NH), indicating that both are strongly bound to the anion. These data suggest a strong involve-

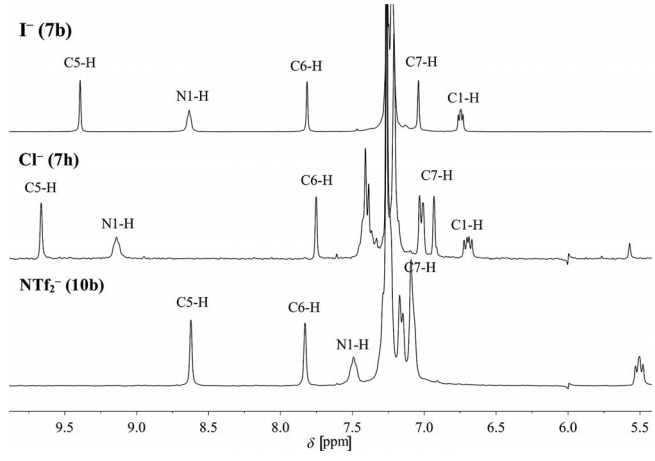


Figure 6. Partial ^1H NMR spectra for **7b**, **7h** and **10b**.

ment of the NH and the C5–H in hydrogen bonding with the anion, which is in good agreement with results from other experimental techniques.[29] For **10b** a significant upfield chemical shift for the chiral proton (C1–H) is observed indicating the presence of a very different conformation for this CIL containing bistriflamide as the anion.

Finally, the formation of supramolecular structures in solution was studied obtaining the ^{1}H NMR spectra of the CILs at various concentrations in various solvents. The analysis of the resulting data shows the existence of a critical aggregation concentration in solution.[17b,30] These spectra provide important data for a detailed study of the nature of the intra- and intermolecular interactions taking place in solution. Both of these aspects are critical for proper understanding of any experiments in which the corresponding CILs are used for recognition and discrimination purposes. Figure 7 shows the variations observed for the ^{1}H NMR signals of **7b** at various concentrations in both $CDCl_3$ and CD_3CN. When the experiments were carried out in $CDCl_3$, very small concentration-dependent changes in the ^{1}H NMR chemical shifts were observed for the aromatic imidazolium protons C5–H, C7–H, and for the amide NH proton (Figure 7a). For example, when increasing the global concentration of **7b** from 1 to 58 mM, the corresponding ^{1}H NMR spectra showed no significant shifts for the signals of the amide NH ($\Delta\delta$ = –0.035 ppm) and the acidic C5–H from the imidazolium moiety ($\Delta\delta$ = 0.063 ppm). Slightly larger variations were observed for the signals of C7–H and the chiral proton, the proton at the stereogenic carbon ($\Delta\delta$ = –0.107 and 0.171 ppm, respectively). The data in $CDCl_3$ are consistent with a situation in which the low polarity of the solvent favors a very strong association of the ion pair in which the hydrogen bonding between the anion and the amide hydrogen is prevalent (as indicated by the very low field observed for the signal corresponding to this hydrogen atom, $\delta > 9.3$ ppm). This strong ion-pair interaction hinders any additional intermolecular associations upon increasing the concentration.

On the contrary, when the experiments were carried out in CD_3CN the chemical shift variations observed with the changes in concentration were much more significant (Figure 7b). For example, when increasing the concentration of **7b** from 1 to 64 mM, very significant variations in the shifts for the signals of the amide N–H ($\Delta\delta$ = –0.812 ppm) and the C1–H ($\Delta\delta$ = –0.519 ppm) were observed. $\Delta\delta$ values were smaller for the aromatic protons of the imidazolium ring ($\Delta\delta_{C5-H}$ = –0.255 ppm and $\Delta\delta_{C7-H}$ = –0.1 ppm; Figure 7b). The higher polarity of this solvent seems to produce solvent separated ion pairs, particularly at lower concentrations. In addition, the amide N–H seems to be involved to a larger extent in the interaction with the anion. The $\Delta\delta$ values observed for higher concentrations, in particular for amide protons, could be ascribed either to a strengthening of the ion pairs or to the increase in the formation of hydrogen-bonded aggregates. In order to better understand this situation, an additional experiment was carried out in which the concentration of the iodide anion was increased by adding $INBut_4$ to a diluted solution of **7b** (10 mM in CD_3CN). This

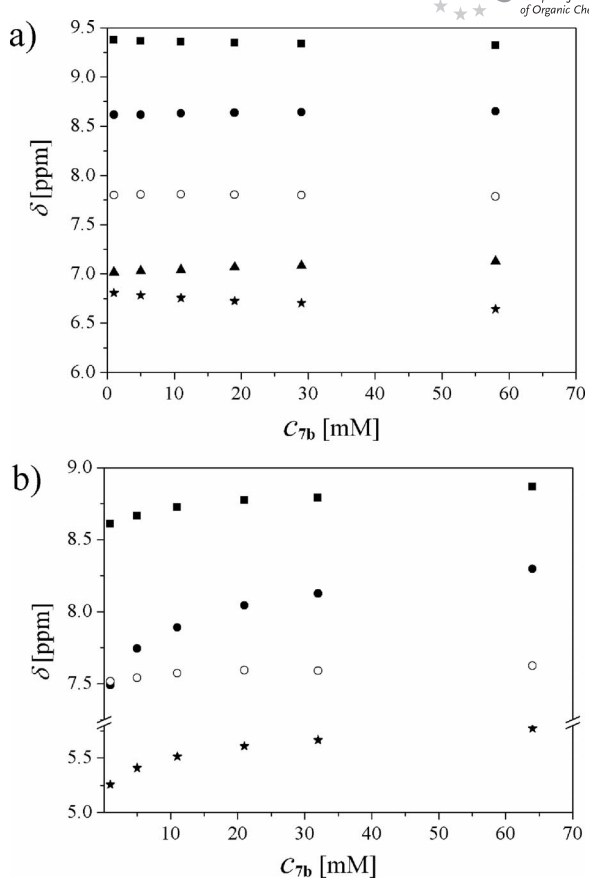


Figure 7. Observed chemical shift changes with changing concentration for a number of signals in the ^{1}H NMR spectra of **7b** in $CDCl_3$(a) and CD_3CN (b). (C5–H square, amide N1–H black circle, C6–H white circle, C7–H triangle and C1–H star).

addition induced significant downfield ^{1}H NMR chemical shift variations for all the protons, similar to those observed when increasing the concentration of **7b**. Thus, the observed concentration-dependence of the chemical shifts (Figure 7b) can be mainly assigned to the normal changes in the association between the anion and the cation in the ion pair.

When the experiments were carried out in CD_3OD, no concentration dependence was observed for C5–H, C6–H and C7–H signals. This polar and hydrogen bonding solvent can clearly compete with cation-anion interactions and is able to achieve complete solvation of the components of the ion pair (see Supporting Information).

The chemical shift variation with concentration for these protons was also studied for **10b** and, as expected for the lower coordinating ability of the anion, very small changes were observed when experiments were carried out in $CDCl_3$. For example, when increasing the global concentration of **10b** from 4 to 60 mM in $CDCl_3$, the corresponding ^{1}H NMR spectra showed no variation for the signals of the amide NH ($\Delta\delta$ = 0.0 ppm) and no significant shifts for the acidic C5–H from the imidazolium moiety ($\Delta\delta$ = 0.05 ppm) and for the signals of C6–H and the chiral proton ($\Delta\delta$ = 0.07 and 0.08 ppm, respectively). On the other hand, when the studies were carried out in CD_3CN, again no ^{1}H chemical shift variations with concentration were observed for

10b ($\Delta\delta$ = 0 ppm for C5–H, C1–H, C7–H and C6–H; see Supporting Information). Thus, with the substitution of the iodide anion by the less coordinating NTf_2^- anion, no additional intermolecular interactions were observed in both $CDCl_3$ and CD_3CN, besides the ion pair association.

The ^1H NMR spectra for **7b** in CD_3CN, CD_3Cl and CD_3OD under the same conditions (Figure 8), show a broad dispersion of the chemical shifts for C5–H, NH, C7–H and C1–H signals is observed. The C5–H, C6–H, C7–H and N1–H signals are shifted downfield as the polarity of non-protic solvents decrease [see Figure 8(a) and (c)]. These variations can be ascribed to the degree of intimate ion-pair interactions between N1–H, C5–H, C6–H and C7–H hydrogen atom with the anion. In the protic solvent [CD_3OD, Figure 8(b)] the cation is completely solvated through polar and hydrogen bonding interactions, therefore chemical shifts for C5–H, C7–H and C6–H appear at higher chemical shifts than in CD_3CN. Simultaneously, the less polar non-protic solvent [$CDCl_3$, Figure 8(a)] produces larger downfield shifts for most of the signals, in particular for the hydrogen bonded N1–H signal. This is explained by the formation of a very strong intimate ion pair in this poorly solvating solvent. The important shift observed for the C1–H chiral proton suggests the involvement of an important conformational change that could locate this proton in two very different environments.

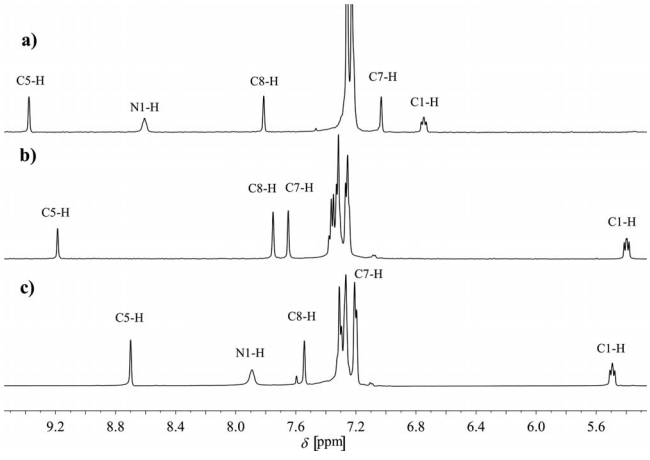


Figure 8. Partial ^1H NMR spectra for **7b** (10 mM) in $CDCl_3$ (a), CD_3OD (b) and CD_3CN (c).

Finally, the ^1H NMR spectra for a 10 mM solution of **7b** at various temperatures were obtained in CD_3CN (Figure 9).[31] Small chemical shift variations with temperature for the amide NH and C5–H signals were observed. The values obtained for $\Delta\delta/T$ were approximately –2.3 ppb for the amide NH. This is indicative of an intramolecular association phenomenon connected to the formation of a more or less tightly bound ion pair. Nevertheless, whereas the NH signal moves upfield, the C5–H signal moves downfield when increasing the temperature. This can be explained by considering the formation of two major conformers, one of them involving a hydrogen bonding interaction between the NH and the C5–H with the anion and the second one presenting just an intermolecular H-bond interaction between C5–H and the anion (see Figure 10). The first one should be favored in the tighter ion pair, whereas the second one would predominate at higher temperatures and dilutions, being entropically more favorable. In general, downfield chemical shift variations were observed for the other aromatic and aliphatic protons of **7b** (see Supporting Information).

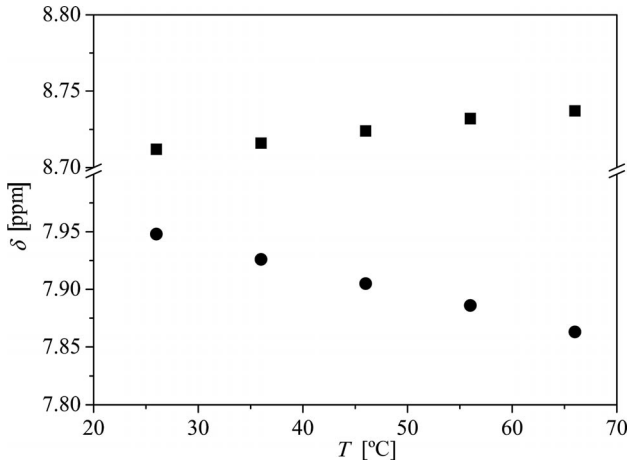


Figure 9. Variation in δ values C5–H (square), N1–H (circle) proton signals of **7b** at different temperatures in CD_3CN at 10 mM.

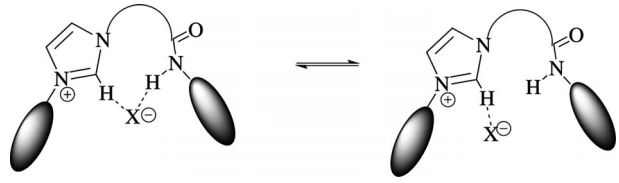


Figure 10. Proposed conformational equilibrium for the intermolecular interactions of NH, C5–H and anion.

Overall, the structural data obtained by X-ray diffraction, ATR-FTIR and NMR spectroscopy, and computational calculations suggest the presence of very strongly intermolecular associated cation–anion ion-pairs, which correlates well with the observed physical (T_m) properties of these ionic liquids. Apart from anion–cation interactions, X-ray diffraction data for **7b** shows the presence of C–H–π and π–π interactions, which can also have an important influence on the macroscopic properties.

CILS as Chiral Shift Agents

To explore the potential of the new chiral ionic liquids for chiral recognition, the prepared ionic liquids were tested as chiral shift agents (CSA) for racemic triethylamine (TEA) mandelate salt. Mandelic acid has important medicinal applications; owing to its bacteriostatic properties it is employed for the treatment of urinary tract infections, using either its calcium or ammonium salts.[32] The pure form of (*R*)-mandelic acid is also used as a precursor for the synthesis of cephalosporin and penicillin.[33–35]

^{1}H NMR spectroscopy was used to investigate the chiral recognition ability of compound **10b**. For this purpose, different mixtures of the corresponding CIL and the TEA salt of the mandelate were examined. As shown in Figure 11, upon addition of the imidazolium receptor, the signal of the methyl proton of the mandelate was downfield shifted and splits into two peaks due to the formation of two diastereomeric complexes between the CIL and the enantiomers of the guest, which confirms that chiral recognition has occurred. When binding **10b**, chemical shift values of the TEA salt of the (*R*)- and (*S*)-mandelic acid exhibit 0.309 and 0.313 ppm downfield shifts, respectively. These results suggest a different chemical environment for the two enantiomers of the mandelate TEA salt, and that host-guest complexes instantaneously formed.

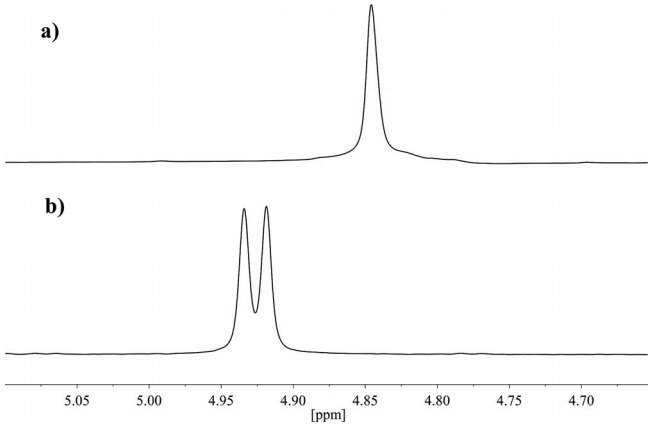


Figure 11. Partial ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of (a) TEA salt of mandelic acid. (b) TEA salt of mandelic acid after the addition of 4 equiv. of **10b** Showing the splitting of the signal corresponding to the CαH group.

To evaluate the chiral discrimination abilities of the different chiral imidazolium salts **10**–**12**, we measured the corresponding ^{1}H NMR spectra for the 2:1 mixtures of the corresponding imidazolium salt and the TEA salt of the mandelic acid in $CDCl_3$. The results are summarized in Table 2 in which the shifts of the methylic hydrogen atoms for the TEA salt of the mandelic acid are shown. Chemical shift nonequivalences were observed in many cases. Chiral imidazolium salts derived from L-phenylalanine, L-valine and L-leucine with benzyl amide groups were the best CSAs, with ^{1}H chemical shift nonequivalences of 0.020 ppm for the methylic proton. In all cases, for the CILs studied, when R^1 does not have an aromatic moiety, $\Delta\Delta\delta$ observed is 0, which means that the aromatic amide moiety has an important role in the recognition abilities of these compounds.

In general, for the supramolecular complexes formed in solution, after the addition of the mandelate TEA salt, the amide NH and C5–H proton signals from the receptors studied moved downfield ($\Delta\delta > 0$), suggesting the interaction between the CILs and the TEA salt of the mandelic acid by formation of supramolecular complexes.

For example, after the addition of 1 equiv. of the (*R*)-madelate TEA salt to a 10 mM solution of **10b** in $CDCl_3$, a

Table 2. Selected ^{1}H chemical shift nonequivalences of the racemic mandelate TEA salt in the presence of imidazolium salts **10**–**12** by NMR (500 MHz) in $CDCl_3$ at 30 °C.

Entry	CILs	L-aa	R^1	R^2	$\Delta\Delta\delta$ (ppm)[a,b]
1	**10e**	Phe	*n*But	Me	0
2	**10f**	Phe	*n*But	*n*But	0
3	**10g**	Phe	*n*But	Non	0
4	**10h**	Phe	*n*But	Bn	overlapped
5	**10a**	Phe	Bn	Me	0
6	**10b**	Phe	Bn	*n*But	0.016[c]
7	**10b**	Phe	Bn	*n*But	0.026[d]
8	**10c**	Phe	Bn	Non	0.020
9	**10d**	Phe	Bn	Bn	0.020
10	**11a**	Val	Bn	*n*But	0.020
11	**11b**	Val	*n*But	*n*But	0.007
12	**11c**	Val	*n*But	Non	0
13	**12a**	Leu	Bn	*n*But	0.022

[a] All samples were prepared by mixing 1 equiv. of racemic TEA mandelate salt and 2 equiv. of the chiral host (0.01 M in $CDCl_3$) in NMR tubes. [b] ^{1}H chemical shift nonequivalences of the methylic protons of the TEA salt of mandelic acid. [c] Samples prepared by mixing 1.5 equiv. of racemic TEA mandelate salt and 1 equiv. of chiral host (0.01 M in $CDCl_3$) in NMR tubes. [d] Sample prepared by mixing 1 equiv. of racemic TEA mandelate and 4 equiv. of chiral host (0.01 M in $CDCl_3$) in an NMR tube.

significant downfield shift variation was observed for the amide NH, the imidazolium C5–H and the chiral C1–H proton signals ($\Delta\delta$ = 1.783, 0.632 and 0.576 ppm, respectively). This indicates the formation of complexes involving strong hydrogen bonding interactions between the TEA salt of the mandelic acid and **10b** with the participation of the amide NH and C5–H protons. On the other hand, small chemical shift variations were observed for the C6–H and C7–H proton signals, moving upfield ($\Delta\delta$ = –0.073 and –0.084 ppm), suggesting the interactions with anion involving these protons are less significant (see Supporting Information). Finally, the stoichiometries of the complexes were investigated by the Job plot method.[36] The Job plot for the complexation of **10b** with the TEA salt of the (*R*)-mandelic acid exhibits a maximum at 0.5 molar fraction of guest, indicating a 1:1 complexation (see Supporting Information).

The clear observation of non-equivalent chemical shifts for the two enantiomers of mandelic acid in the presence of some of the CILs **10**–**12** prompted us to explore the enantiomeric discriminating ability for other α-chiral carboxylic acids. For this study we selected as receptors **10b**, **11a** and **12a** because these were the best CSAs for mandelate. As shown in Table 3, all assayed CILs showed chemical shift nonequivalences for the TEA salt of *p*-methoxy mandelic acid (Table 3, Entries 4–6) ranging from 0.016 to 0.028 ppm. On the other hand, receptor **11a** was the best CSA for the enantiodiscrimination of some pharmacologically active propionic acids, such as ibuprofen (Table 3, Entries 1–3). Moreover, chemical shift nonequivalence was observed for the racemic TEA salt of N-CBz-Phe when CILs **10b**, **11a** and **12a** were used as CSAs (Table 3, Entries 7–9).

Table 3. ^{1}H chemical non-equivalencies ($\Delta\Delta\delta$) of racemic carboxylate TEA salts using CILs as CSAs [500 MHz, CD_3Cl/CD_3OD (1%), 303 K].

Entry	Carboxylate racemic TEA salt	CILs	L-aa	R^1	R^2	$\Delta\Delta\delta$ (ppm)[a]
1		**10b**	Phe	Bn	*n*But	0.0[b]
2	ibuprofen	**11a**	Val	Bn	*n*But	0.014[b]
3		**12a**	Leu	Bn	*n*But	0.010[b]
4		**10b**	Phe	Bn	*n*But	0.016[b]
5	*p*-methoxy mandelic acid	**11a**	Val	Bn	*n*But	0.028[b]
6		**12a**	Leu	Bn	*n*But	0.027[b]
7		**10b**	Phe	Bn	*n*But	0.010[c]
8	*N*-CBz-Phe	**11a**	Val	Bn	*n*But	0.008[c]
9		**12a**	Leu	Bn	*n*But	0.009[c]

[a] All samples were prepared by mixing 1 equiv. of the racemic acid (0.01 M in $CDCl_3$) and 2 equivalents of the chiral host (0.01 M in $CDCl_3$) in NMR tubes. [b] ^{1}H chemical shift nonequivalences of the α-methyl signal of the guest. [c] ^{1}H chemical shift nonequivalences of the CBz methyl signal of the guest.

Conclusions

In conclusion, we have designed and synthesized a new family of chiral room temperature ionic liquids based on imidazolium salts derived from natural amino acids. Different studies have established the influence of the nature of the side chain as well as the presence of additional functional groups in the final CILs on their intrinsic physical properties. Some of those CILs have been efficient as CSAs for the discrimination of racemic mandelate salt and other carboxylate salts by ^{1}H NMR spectroscopy. The formation of diastereomeric complexes is fast and quantitative, and can be analyzed in situ in a 500 MHz NMR spectrometer. Further studies towards the application of these chiral ionic liquids as chiral solvents and as organocatalysts are in progress.

Experimental Section

General Experimental Methods: All reagents were purchased from commercial suppliers and used as received. Chiral α-amino amides were synthesized as described previously[17a] whereas all the *N*-protected amino acids were commercially available. The NMR spectroscopic experiments were carried out at 500 or 125 MHz for ^{1}H and ^{13}C NMR, respectively. The chemical shifts are reported using trimethylsilane as the internal standard. For chiral shift experiments, samples were prepared by mixing CSA with several carboxylic acids salts in $CDCl_3$. FTIR spectra were acquired with a MIRacle single-reflection ATR diamond/ZnSe accessory. Melting points were measured by using a differential scanning calorimeter (DSC). The instrument was calibrated for temperature and heat flow with zinc and indium reference samples. Samples were placed in a 40 mL, hermetically sealed aluminium pan with a pinhole in the top. An empty aluminium pan was used as the reference. Samples were exposed to a flowing N_2 atmosphere. Before the DSC test, each sample was dried at 60 °C in a vacuum oven for 12 h, and was further dried in situ in the differential scanning calorimeter by holding the sample at 100 °C for 60 min because the presence of volatiles, especially water, can affect the melting temperatures. Melting transition temperatures were determined by using multiple cycles (typically three) involving heating the sample from –70 to 150 °C followed by cooling from 150 to –70 °C, both at a rate of 5 °C/min. The melting temperatures were determined at the onset of the transition. Decomposition temperatures were measured using a TG-STDA, heating samples from 20 to 400 °C at a rate of 5 °C/min. The reactions under microwave conditions were carried out using a CEM Discover System Microwave, model 908010, the temperature control was carried out using a surface infrared sensor. CCDC-867607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Synthesis of Imidazole Derivatives 4a, 4b, 5a, 5b, 6a: To a mixture of glyoxal (40% aq., 1 equiv.) and formaldehyde (37% aq., 5 equiv.), the corresponding α-amino amide (1 equiv.) and ammonium acetate (1 equiv.) were dissolved previously in CH_3OH and added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the resulting crude residue was treated with saturated Na_2CO_3 solution, extracted with CH_2Cl_2 (3×), dried with anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by using flash chromatography ($MeOH/CH_2Cl_2$, 1:10) to yield the corresponding imidazole derivatives **4a**, **4b**, **5a**, **5b**, **and 6a**.

(*S*)-*N*-Benzyl-2-(1*H*-imidazol-1-yl)-3-phenylpropanamide (4a): The reaction between glyoxal, formaldehyde, ammonium acetate and *N*-benzyl amide of L-Phe gave a yellow oil (2.98 g, 49%). M.p. 21 °C. $[a]_D^{25}$ = –42.3 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3217, 3032, 2931, 1670, 1554, 1496, 1226, 1076 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.34 (s, 1 H, Im-H), 7.32–7.18 (m, 6 H, Ar-H), 7.12–6.97 (m, 6 H, Ar-H), 6.10 (br., 1 H, N-H), 4.74 (t, J = 7.1 Hz, 1 H, C*-H), 4.42 (dd, J = 14.6, 5.4 Hz, 1 H, CH_2Ph), 4.35 (dd, J = 14.6, 5.4 Hz, 1 H, CH_2Ph), 3.62 (dd, J = 14.0, 5.3 Hz, 1 H, CH_2Ph), 3.19 (dd, J = 13.3, 9.8 Hz, 1 H, CH_2Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 168.3, 137.4, 136.9, 136.8, 136.1, 129.7, 128.8, 128.7, 127.6, 127.2, 117.9, 117.99, 62.89, 43.7, 39.3 ppm. MS (ESI$^+$): *m*/*z* (%) = 306 (100) [M + H]$^+$. $C_{19}H_{19}N_3O$ 0.5H_2O (315.4): calcd. C 72.59, H 6.41, N 13.37; found C 72.2, H 6.6, N 13.0.

(*S*)-*N*-Butyl-2-(1*H*-imidazol-1-yl)-3-phenylpropanamide (4b): The reaction between glyoxal, formaldehyde, ammonium acetate and *N*-butyl amide of L-Phe gave a yellow oil (3.96 g, 84%). M. p. 8 °C. $[a]_D^{25}$ = –45.8 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3228, 3035, 2931, 2870, 1662, 1554, 1500, 1454, 1226, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.36 (s, 1 H, Im-H), 7.32 (s, 1 H, Ar-H), 7.30–7.15 (m, 3 H, Ar-H), 7.10–6.99 (m, 4 H, Ar-H and Im-H), 6.09 (br., 1 H, N-H), 4.8 (dd, J = 8.8, 6.0 Hz, 1 H, C*-H), 3.64 (dd, J = 14.0, 5.5 Hz, 1 H, CH_2Ph), 3.33–3.17 (m, 3 H, CH_2Ph, NHCH_2Pr), 1.48–1.39 (m, 2 H, NHCH$_2$CH_2Et), 1.34–1.20 (m, 2 H, NHCH$_2$CH$_2$CH_2CH$_3$), 0.92 (t, J = 7.2 Hz, 3 H, NHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 168.3, 136.9, 136.2, 129.5, 128.8, 128.6, 127.1, 117.9, 62.8, 39.4, 39.3, 31.2, 19.9, 13.6 ppm. MS (ESI$^+$): *m*/*z* (%) = 272 (100) [M + H]$^+$. $C_{16}H_{21}N_3O$ H_2O (289.4): calcd. C 66.44, H 7.95, N 14.53; found C 66.4, H 7.9, N 14.3.

(*S*)-*N*-Benzyl-2-(1*H*-imidazol-1-yl)-3-methylbutanamide (5a): The reaction between glyoxal, formaldehyde, ammonium acetate and *N*-benzyl amide of L-Val gave a yellow oil (0.99 g, 80%). M. p. 5 °C. $[a]_D^{25}$ = –14.7 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3218, 3150, 3061, 2967, 2877, 1669, 1560, 1496, 1337, 1189, 1126, 1064 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.50 (s, 1 H, Im-H), 7.32–7.27 (m, 3 H, Ar-H), 7.19 (d, J = 6.9 Hz, 2 H, Ar-H), 7.13 (s, 1 H, Im-H), 7.03 (s, 1 H, Im-H), 6.60 (br., 1 H, NH), 4.47 (dd, J =

14.6, 5.5 Hz, 1 H, NHCH_2Ph), 4.36 (dd, J = 14.6, 5.1 Hz, 1 H, NHCH_2Ph), 4.11 (d, J = 9.3 Hz, 1 H, C*-H), 2.57–2.46 (m, 1 H, CH), 1.00 (d, J = 6.5 Hz, 3 H, CH_3), 0.77 (d, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 168.4, 137.4, 137.0, 129.5, 128.8, 127.8, 127.7, 118.33, 67.9, 43.8, 31.4, 19.5, 18.6 ppm. MS (ESI$^+$): m/z (%) = 258.0 (100) [M + H]$^+$. $C_{15}H_{19}N_3O$ 1.5H_2O (283.3): calcd. C 63.38, H 7.75, N 14.78; found C 63.1, H 7.9, N 14.4.

(*S*)-*N*-Butyl-2-(1*H*-imidazol-1-yl)-3-methylbutanamide (5b): The reaction between glyoxal, formaldehyde, ammonium acetate and *N*-butyl amide of L-Val gave a yellow oil (0.53 g, 30%). M. p. –23 °C. $[\alpha]_D^{25}$ = +5.8 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3229, 3109, 3067, 2961, 2932, 2873, 1658, 1562, 1495, 1466, 1226 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.55 (s, 1 H, Im-H), 7.13 (s, 1 H, Im-H), 7.07 (s, 1 H, Im-H), 6.02 (br., 1 H, NH), 4.06 (d, J = 9.2 Hz, 1 H, C*-H), 3.35–3.10 (m, 2 H, NHCH_2Pr), 2.60–2.45 (m, 1 H, CH), 1.53–1.39 (m, 2 H, $NHCH_2CH_2$Et), 1.37–1.20 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 1.00 (d, J = 6.4 Hz, 3 H, CH_3), 0.89 (t, J = 7.1 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$), 0.79 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 168.8, 136.7, 128.6, 118.7, 67.7, 39.4, 31.4, 31.2, 20.0, 19.4, 18.6, 13.6 ppm. MS (ESI$^+$): m/z (%) = 224.2 (100) [M + H]$^+$. $C_{12}H_{21}N_3O$·0.4H_2O (230.5): calcd. C 62.40, H 9.67, N 18.48; found C 62.8, H 9.4, N 18.1.

(*S*)-*N*-Benzyl-2-(1*H*-imidazol-1-yl)-4-methylpentanamide (6a): The reaction between glyoxal, formaldehyde, ammonium acetate and *N*-benzyl amide of L-Leu gave a yellow solid (0.63 g, 18%). M. p. 98 °C. $[\alpha]_D^{25}$ = –9.0 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3256, 3063, 2955, 2869, 1676, 1556, 1498, 1453, 1224, 1078 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 7.54 (s, 1 H, Im-H), 7.34–7.25 (m, 3 H, Ar-H), 7.16 (d, J = 7.2 Hz, 2 H, Ar-H), 7.11 (s, 1 H, Im-H), 7.01 (s, 1 H, Im-H), 5.93 (br., 1 H, NH), 4.70 (dd, J = 10.6, 4.8 Hz, 1 H, C*-H), 4.39 (d, J = 5.7 Hz, 2 H, NHCH_2Ph), 2.2–1.9 (m, 2 H, CH_2), 1.32–1.46 (m, 1 H, CH), 0.93 (d, J= 1.2 Hz, 3 H, CH_3), 0.91 (d, J= 1.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 169.4, 137.5, 136.9, 129.8, 128.7, 127.6, 127.6, 117.8, 59.6, 43.6, 40.9, 24.5, 22.8, 21.4 ppm. MS (ESI$^+$): m/z (%) = 272.2 (100) [M + H]$^+$. $C_{16}H_{21}N_3O$·0.5H_2O (280.4): C 68.57, H 7.86, N 15.00; found C 68.5, H 8.2, N 14.7.

General Procedure for the Synthesis of Imidazolium Salts 7a–h, 8a–c, 9a

Method A: A mixture of the imidazole derivative (1 equiv.) and the corresponding alkyl halide (5 equiv.) in CH_3CN was stirred for 48 h at 60 °C. The solvent was evaporated under reduced pressure and the resulting gummy product washed with hexane/diethyl ether (2:1). The corresponding imidazolium halide salts **7a**–**c**, **7e**–**h**, **8a**–**c** were obtained following liquid-liquid extraction.

Method B: The corresponding imidazole derivative (1 equiv.) and an excess of alkyl halide (10 equiv.) were stirred in a microwave (potency = 120 W; pressure = 250 psi; T = 150 °C) during 30 min. After reaction a mixture of hexane/diethyl ether was added, to allow deposition of the product, which was filtered off and washed with additional hexane/diethyl ether to obtain the corresponding imidazolium halide salts **7d** and **9a**.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-methyl-1*H*-imidazol-3-ium Iodide (7a): The reaction between **4a** and methyl iodide (Method A) gave a yellow solid (0.33 g, 95%). M. p. 51 °C. $[\alpha]_D^{25}$ = –13.9 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3217, 3060, 2925, 2860, 1681, 1549, 1454, 1161 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.53 (s, 1 H, Im-H), 8.54 (br., 1 H, NH), 7.82 (s, 1 H, Im-H), 7.16–7.30 (m, 10 H, Ar-H), 7.06 (s, 1 H, Im-H), 6.74 (t, J = 7.9 Hz, 1 H, C*-H), 4.48 (dd, J = 14.8, 6.5 Hz, 1 H, NHCH_2Ph), 4.26 (dd, J = 14.8, 5.3 Hz, 1 H, NHCH_2Ph), 3.84 (s, 3 H, CH_3), 3.50–3.44 (dd, J = 13.5, 7.1 Hz, 1 H, CH_2Ph), 3.26 (dd, J = 13.7, 9.3 Hz, 1 H, CH_2Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.6, 137.1, 135.9, 133.8, 129.2, 129.0, 128.5, 127.7, 127.3, 122.3, 121.9, 62.2, 43.4, 39.2, 36.7 ppm. MS (ESI$^+$): 320.2 (100) [M$^+$]. MS (ESI$^-$): m/z (%) = 0 126.9 (100) [I$^-$]. $C_{20}H_{22}IN_3O$·0.6H_2O (458.1): calcd. C 52.43, H 5.10, N 9.17; found C 52.8, H 5.5, N 9.5.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-butyl-1*H*-imidazol-3-ium Iodide (7b): The reaction between **4a** and butyl iodide (Method A) gave an orange solid (1.06 g, 96%). M. p. 35 °C. $[\alpha]_D^{25}$ = –27.4 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3225, 3054, 2956, 2871, 1693, 1543, 1455, 1160 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.39 (s, 1 H, Im-H), 8.63 (br., 1 H, NH), 7.81 (s, 1 H, Im-H), 7.30–7.20 (m, 10 H, Ar-H), 7.04 (s, 1 H, Im-H), 6.75 (dd, J = 9.3, 6.7 Hz, 1 H, C*-H), 4.50 (dd, J = 14.8, 6.5 Hz, 1 H, NHCH_2Ph), 4.29 (dd, J = 14.8, 5.4 Hz, 1 H, NHCH_2Ph), 4.06–3.95 (m, 2 H, $CH_2CH_2CH_2CH_3$), 3.48 (t, J = 10 Hz, 1 H, CH_2Ph), 3.25 (dd, J = 13.8, 10.0 Hz, 1 H, CH_2Ph), 1.77–1.67 (m, 2 H, CH_2CH_2Et), 1.21–1.14 (m, 2 H, $CH_2CH_2CH_2CH_3$), 0.92 (t, J = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 167.3, 137.8, 135.8, 134.6, 129.8, 129.6, 129.1, 128.3, 128.2, 127.9, 122.4, 121.7, 62.8, 50.6, 44.0, 39.9, 32.4, 19.8, 13.9 ppm. MS (ESI$^+$): 362.3 (100) [M$^+$]. MS (ESI$^-$): m/z (%) = 126.9 (100) [I$^-$]. $C_{23}H_{28}IN_3O$. 0.4H_2O (497.8): calcd. C 55.63, H 5.85, N 8.46; found C 55.9, H 6.3, N 8.3.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-nonyl-1*H*-imidazol-3-ium Bromide (7c): The reaction between **4a** and nonyl bromide (Method A) gave a white solid (0.26 g, 82%). M. p. 24 °C. $[\alpha]_D^{25}$ = –34.1(c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3202, 3061, 2923, 2854, 1681, 1550, 1454, 1173 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.54 (s, 1 H, Im-H), 9.23 (br., 1 H, NH), 7.83 (s, 1 H, Im-H), 7.31 (s, 2 H, Ar-H), 7.28–7.20 (m, 8 H, Ar-H), 7.09 (s, 1 H, Im-H), 6.82 (t, J = 7.8 Hz, 1 H, C*-H), 4.55 (dd, J = 14.9, 6.2 Hz, 1 H, NHCH_2Ph), 4.31 (dd, J = 14.9, 4.6 Hz, 1 H, NHCH_2Ph), 4.10–3.95 [m, 2 H, C$H_2(CH_2)_7CH_3$], 3.51 (dd, J = 14.0, 6.3 Hz, 1 H, CH_2Ph), 3.36–3.18 (m, 1 H, CH_2Ph), 1.80–1.71 [m, 2 H, $CH_2CH_2(CH_2)_6CH_3$], 1.30 [br., 10 H, $CH_2CH_2(CH_2)_5CH_2CH_3$], 1.25–1.15 [m, 2 H, $(CH_2)_7CH_2CH_3$], 0.93 [t, 3 H, $(CH_2)_8CH_3$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.7, 135.9, 134.1, 132.8, 129.0, 129.0, 128.5, 127.7, 127.5, 127.2, 121.3, 120.7, 62.0, 50.3, 43.5, 38.8, 31.7, 29.9, 29.1, 29.1, 28.8, 26.0, 22.6, 14.0 ppm. MS (ESI$^+$): 432.3 (100) [M$^+$]. MS (ESI$^-$): m/z (%) = 78.9 (100) [Br$^-$]. $C_{28}H_{38}BrN_3O$. 0.5H_2O (522.5): calcd. C 64.61, H 7.50, N 8.08; found C 64.9, H 7.1, N 8.2.

3-Benzyl-1-[(1*S*)-1-(benzylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Chloride (7d): The reaction between **4a** and benzyl chloride (Method B) gave an orange solid (0.38 g, 86%). M. p. 61 °C. $[\alpha]_D^{25}$ = –3.6 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3366, 3186, 3031, 1681, 1555, 1455, 1154 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.73 (s, 2 H, Im-H, NH), 7.73 (s, 1 H, Im-H), 7.45–7.19 (m, 13 H, Ar-H), 7.03 (d, J = 6.9 Hz, 2 H, Ar-H), 6.93 (s, 1 H, Im-H), 6.77–6.70 (m, 1 H, C*-H), 5.20 (d, J = 14.6 Hz, 1 H, CH_2Ph), 5.13 (d, J = 14.6 Hz, 1 H, CH_2Ph), 4.49 (dd, J = 14.9, 6.3 Hz, 1 H, NHCH_2Ph), 4.28 (dd, J = 14.7, 5.1 Hz, 1 H, NHCH_2Ph), 3.49 (dd, J = 14.2, 5.6 Hz, 1 H, CH_2Ph), 3.24 (dd, J = 13.5, 10.5, Hz 1 H, CH_2Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.9, 137.6, 136.6, 134.3, 132.0, 129.7, 129.6, 129.1, 128.9, 128.4, 128.1, 127.6, 127.4, 127.1, 121.7, 120.8, 62.3, 53.5, 43.5, 38.7 ppm. MS (ESI$^+$): m/z (%) = 396.2 (100) [M$^+$]. $C_{26}H_{26}ClN_3O$. H_2O (450.0): calcd. C 69.40, H 6.27, N 9.34; found C 69.8, H 6.2, N 9.0.

1-[(1*S*)-1-(Butylcarbamoyl)-2-phenylethyl]-3-methyl-1*H*-imidazol-3-ium Iodide (7e): The reaction between **4b** and methyl iodide

(Method A) gave a brown solid (1.03 g, 92%). M. p. 32 °C. $[\alpha]_D^{25}$ = –16.2 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3248, 3063, 2956, 1675, 1549, 1455, 1160 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.42 (s, 1 H, Im-H), 8.01 (br., 1 H, NH), 7.82 (s, 1 H, Im-H), 7.27–7.12 (m, 5 H, Ar-H), 7.19 (s, 1 H, Im-H), 6.56 (t, J = 8.0 Hz, 1 H, C*-H), 3.88 (s, 3 H, CH_3), 3.50–3.05 (m, 4 H, CH_2Ph,$NHCH_2Pr$), 1.50–1.36 (m, 2 H, $NHCH_2CH_2Et$), 1.30–1.15 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 0.84 (t, J = 7.2 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$) ppm. 13C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 166.4, 135.8, 133.9, 129.2, 129.0, 127.7, 122.3, 122.0, 62.2, 39.6, 39.2, 36.8, 30.8, 20.1, 13.6 ppm. MS (ESI^+): 286.2 (100) $[M^+]$. MS (ESI^-): m/z (%) = 126.9 (100) $[I^-]$. $C_{17}H_{24}IN_3O$ (413.3): calcd C 49.40, H 5.85, N 10.17; found C 49.8, H 6.2, N 10.0.

3-Butyl-1-[(1*S*)-1-(butylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Iodide (7f): The reaction between **4b** and butyl iodide (Method A) gave an orange oil (0.61 g, 84%). M. p. 18 °C. $[\alpha]_D^{25}$ = –54.4 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3288, 3062, 2958, 2871, 1675, 1549, 1456, 1158 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.28 (s, 1 H, Im-H), 8.13 (br., 1 H, NH), 7.80 (s, 1 H, Im-H), 7.30–7.1 (m, 6 H, Ar-H, Im-H), 6.57 (t, J = 9.6 Hz, 1 H, C*-H), 4.07 (t, J = 6.9 Hz, 2 H, CH_2Pr), 3.48 (dd, J = 14.0, 6.1 Hz, 1 H, CH_2Ph), 3.31–3.07 (m, 3 H, CH_2Ph, $NHCH_2Pr$), 1.72 (m, J = 14.8, 7.3 Hz, 2 H, CH_2CH_2Et), 1.57–1.39 (m, 2 H, $NHCH_2CH_2Et$), 1.37–1.05 (m, 4 H, $CH_2CH_2CH_2CH_3$, $NHCH_2CH_2CH_2CH_3$), 0.97–0.80 (m, 6 H, $CH_2CH_2CH_2CH_3$, $NHCH_2CH_2CH_2CH_3$) ppm. 13C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.5, 134.9, 134.1, 129.1, 128.9, 127.5, 121.8, 121.5, 62.3, 50.0, 39.6, 39.3, 31.8, 30.8, 20.0, 19.2, 13.6, 13.3 ppm. MS (ESI^+): m/z (%) = 328.2 (100) $[M^+]$. MS (ESI^-): m/z (%) = 126.9 (100) $[I^-]$. $C_{20}H_{30}IN_3O$ (455.4): calcd. C 52.75, H 6.64, N 9.23; found C 53.3, H 6.3, N 9.24.

3-Benzyl-1-[(1*S*)-1-(butylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Chloride (7g): The reaction between **4b** and benzyl chloride (Method A) gave a brown solid (0.84 g, 67.9%). M. p. 48 °C. $[\alpha]_D^{25}$ = –48.2 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3215, 3031, 2959, 1673, 1556, 1456, 1155 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.66 (s, 1 H, Im-H), 9.14 (br., 1 H, NH), 7.75 (s, 1 H, Im-H), 7.50–7.30 (m, 3 H, Ar-H), 7.21 (s, 5 H, Ar-H), 7.02 (d, J = 6.4 Hz, 2 H, Ar-H), 6.93 (s, 1 H, Im-H), 6.69 (dd, J = 10.1, 6.1 Hz, 1 H, C*-H), 5.16 (d, J = 14.7 Hz, 1 H, CH_2Ph), 5.11 (d, J = 14.7 Hz, 1 H, CH_2Ph), 3.47 (dd, J = 14.4, 6.0 Hz, 1 H, CH_2Ph), 3.31–3.13 (m, 3 H, CH_2Ph, $NHCH_2Pr$), 1.54–1.46 (m, 2 H, $NHCH_2CH_2Et$), 1.33–1.26 (m, 2 H, $NHCH_2CH_2CH_2CH_3$), 0.87 (t, J = 7.2 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$) ppm. 13C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.6, 136.6, 134.4, 132.0, 129.7, 129.6, 129.0, 1289, 128.1, 127.4, 121.6, 120.8, 62.4, 39.6, 38.9, 30.9, 29.7, 20.1, 13.6 ppm. MS (ESI^+): m/z (%) = 362.2 (100) $[M^+]$. $C_{23}H_{28}ClN_3O{\cdot}0.5H_2O$ (407.0): calcd. C 67.90, H 7.13, N 10.33; found C 67.8, H 7.2, N 10.4.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-butyl-1*H*-imidazol-3-ium Chloride (7h): The reaction between **4a** and butyl chloride (Method A) gave a yellow solid (0.05 g, 40%). M. p. 43 °C. $[\alpha]_D^{25}$ = –38.8 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3181, 3094, 3054, 2969, 1680, 1558, 1452, 1297, 1173 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.66 (br., 1 H, NH), 9.58 (s, 1 H, Im-H), 7.75 (s, 1 H, Im-H), 7.24–7.17 (m, 10 H, Ar-H), 7.02 (s, 1 H, Im-H), 6.7–6.77 (m, 1 H, C*-H), 4.51 (dd, J = 14.2, 6.3 Hz, 1 H, $NHCH_2Ph$), 4.28 (dd, J = 14.3, 4.9 Hz, 1 H, $NHCH_2Ph$), 4.01 (m, 2 H, CH_2Pr), 3.49 (dd, J = 14.1, 6.0 Hz, 1 H, CH_2Ph), 3.25 (dd, J = 13.9, 10.3 Hz, 1 H, CH_2Ph), 1.75 (s, 2 H, CH_2CH_2Et), 1.20–1.16 (m, 2 H, $CH_2CH_2CH_2CH_3$), 0.94 (d, J = 6.6 Hz, 3 H, CH_2CH_2-CH_2CH_3) ppm. 13C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.9, 137.6, 136.4, 134.3, 129.1, 128.9, 128.5, 127.6, 127.5, 127.1, 121.5, 121.0, 62.3, 50.0, 43.5, 38.8, 31.8, 19.2, 13.3 ppm. MS (ESI^+): m/z (%) = 362.3 (100) $[M^+]$. $C_{23}H_{28}ClN_3O{\cdot}0.5H_2O$ (407.0): calcd. C 67.79, H 7.13, N 10.33; found C 67.7, H 7.1, N 10.2.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-methylpropyl]-3-butyl-1*H*-imidazol-3-ium Iodide (8a): The reaction between **5a** and butyl iodide (Method A) gave a brown oil (0.22 g, 74%). M. p. 17 °C. $[\alpha]_D^{25}$ = –18.7 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3221, 3061, 2963, 2934, 2873, 1681, 1549, 1459, 1160 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.70 (s, 1 H, Im-H), 8.65 (br., 1 H, NH), 7.83 (s, 1 H, Im-H), 7.38–7.18 (m, 6 H, Ar-H, Im-H), 5.91 (d, J = 10.3 Hz, 1 H, C*H), 4.52 (dd, J = 14.8, 6.5 Hz, 1 H, $NHCH_2Ph$), 4.28 (dd, J = 14.8, 5.4 Hz, 1 H, $NHCH_2Ph$), 4.20 (t, J = 7.3 Hz, 2 H, CH_2Pr), 2.52–2.40 (m, 1 H, CH), 1.91–1.86 (m, 2 H, CH_2CH_2Et), 1.40–1.37 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.05 (d, J = 6.5 Hz, 3 H, CH_3), 0.97 (t, J = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 0.82 (d, J = 6.6 Hz, 3 H, CH_3) ppm. 13C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 167.1, 137.4, 135.1, 128.5, 127.9, 127.3, 122.1, 121.3, 67.4, 50.2, 43.5, 31.9, 31.9, 19.4, 18.7, 18.3, 13.3 ppm. MS (ESI^+): m/z = 314.0 (100) $[M^+]$. MS (ESI^-): m/z (%) = 127.0 (100) $[I^-]$. $C_{19}H_{28}IN_3O$ (441.4): calcd. C 51.71, H 6.39, N 9.52; found C 52.1, H 6.6, N 9.7.

3-Butyl-1-[(1*S*)-1-(butylcarbamoyl)-2-methylpropyl]-1*H*-imidazol-3-ium Iodide (8b): The reaction between **5b** and butyl chloride (Method A) gave a yellow oil (0.53, g, 98%). M. p. –2 °C. $[\alpha]_D^{25}$ = +3.6 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3233, 3065, 2959, 2932, 2873, 1671, 1548, 1463, 1157 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = (ppm): 9.70 (s, 1 H, Im-H), 8.08 (br., 1 H, NH), 7.85 (s, 1 H, Im-H), 7.32 (s, 1 H, Im-H), 5.89 (d, J = 10.3 Hz, 1 H, C*-H), 4.23 (t, J = 7.2 Hz, 2 H, CH_2Pr), 3.38–3.23 (m, 1 H, $NHCH_2Pr$), 3.22–3.07 (m, 1 H, $NHCH_2Pr$), 2.56–2.39 (m, 1 H, CH), 1.99–1.85 (m, 2 H, CH_2CH_2Et), 1.58–1.51 (m, 2 H, $NHCH_2CH_2Et$), 1.42–1.30 (m, 4 H, $CH_2CH_2CH_2CH_3$, $NHCH_2CH_2CH_2CH_3$), 1.10 (d, J = 6.3 Hz, 3 H, CH_3), 0.98 (t, J = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 0.88 (t, J = 7.4 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$), 0.83 (d, J = 6.5 Hz, 3 H, CH_3) ppm. 13C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.9, 134.6, 122.1, 121.9, 67.6, 50.2, 39.4, 31.9, 31.8, 30.8, 20.0, 19.3, 18.7, 18.3, 13.5, 13.3 ppm. MS (ESI^+): 280.2 (100) $[M^+]$. MS (ESI^-): m/z (%) = 127.1 (100) $[I^-]$. $C_{16}H_{30}IN_3O$ (407.3): calcd. C 47.18, H 7.42, N 10.32; found C 47.6, H 7,8, N 10.2.

1-[(1*S*)-1-(Butylcarbamoyl)-2-methylpropyl]-3-nonyl-1*H*-imidazol-3-ium Bromide (8c): The reaction between **5b** and nonyl bromide (Method A) gave a brown oil (0.37 g, 88%). M. p. –8 °C. $[\alpha]_D^{25}$ = –4.4 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3221, 3064, 2958, 2926, 2856, 1672, 1551, 1465, 1158 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 9.85 (s, 1 H, Im-H), 8.62 (br., 1 H, NH), 7.81 (s, 1 H, Im-H), 7.21 (s, 1 H, Im-H), 5.83 (d, J = 10.7 Hz, 1 H, C*-H), 4.18 [t, J = 7.4 Hz, 2 H, $CH_2(CH_2)_7CH_3$], 3.37–3.24 (m, 1 H, $NHCH_2Pr$), 3.17–3.05 (m, 1 H, $NHCH_2Pr$), 2.51–2.39 (m, 1 H, CH), 2.00–1.90 [m, 2 H, $CH_2CH_2(CH_2)_6CH_3$], 1.64–1.49 (m, 2 H, $NHCH_2CH_2Et$), 1.37–1.24 [m, 14 H, $NHCH_2CH_2CH_2CH_3$, $CH_2CH_2(CH_2)_6CH_3$], 1.09 (d, J = 6.5 Hz, 3 H, CH_3), 0.9–0.84 [m, 6 H, $(CH_2)_8CH_3$, $NHCH_2CH_2CH_2CH_3$], 0.80 (d, J = 6.6 Hz, 3 H, CH_3) ppm. 13C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 167.3, 136.0, 122.0, 121.2, 67.8, 50.6, 39.8, 31.9, 31.5, 31.2, 30.2, 29.4, 29.3, 29.0, 26.4, 22.8, 20.4, 19.0, 18.5, 14.2, 13.9 ppm. MS (ESI^+): 350.3 (100) $[M^+]$. MS (ESI^-): m/z (%) = 79 (100) $[Br^-]$. $C_{21}H_{40}BrN_3O$. $0.8H_2O$ (445.3): calcd. C 56.7, H 9.43, N 9.45; found C 56.7, H 9.3, N 9.6.

1-[(1*S*)-1-(Benzylcarbamoyl)-3-methylbutyl]-3-butyl-1*H*-imidazol-3-ium Iodide (9a): The reaction between **6a** and butyl iodide (Method B) gave a brown oil (0.56 g, 98%). M. p. 17 °C. $[\alpha]_D^{25}$ = –12.6 (c = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3214, 3127, 3057, 2871, 1679, 1547, 1455, 1160 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.78 (s, 1 H, Im-H), 8.67 (br., 1 H, NH), 7.80 (s, 1 H, Im-H),

7.34–7.20 (m, 6 H, Ar-H, Im-H), 6.33 (t, J = 7.6 Hz, 1 H, C*-H), 4.49 (dd, J = 14.8, 6.4 Hz, 1 H, NHCH_2Ph), 4.29 (dd, J = 14.8, 5.5 Hz, 1 H, NHCH_2Ph), 4.18 [t, J = 7.3 Hz, 2 H, CH_2(CH$_2$)$_2$CH$_3$], 2.12–2.04 (m, 1 H, CH$_2$), 1.92–1.80 (m, 3 H, CH$_2$, CH$_2$CH_2CH$_2$CH$_3$), 1.46–1.32 (m, 3 H, CH, CH$_2$CH$_2$CH_2CH$_3$), 0.99–0.95 (m, 9 H, CH$_3$, CH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 30 °C): δ = 167.3, 137.4, 134.9, 128.5, 127.9, 127.3, 121.8, 121.2, 60.2, 50.3, 43.5, 41.5, 31.8, 24.9, 22.6, 22.6, 19.5, 13.4 ppm. MS (ESI$^+$): 328.1 (100) [M$^+$]. . MS (ESI$^-$): m/z (%) = 127.1 (100) [I$^-$]. C$_{20}$H$_{30}$IN$_3$O·0.8H$_2$O (469.8): calcd. C 51.13, H 6.78, N 8.94; found C 50.9, H 6.3, N 8.5.

General Procedure for the Synthesis of Imidazolium Salts 10a–h, 11a–c, 12a: A solution of lithium bis(trifluoromethane) sulfonimide (1.1 equiv.) in MeOH was added to a solution of the corresponding halide salt (1 equiv.) in MeOH, and the resulting mixture stirred for 48 h. The solvent was then evaporated at reduced pressure, further H_2O added, and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried with $MgSO_4$, and the solvent evaporated under reduced pressure to afford the corresponding imidazole salt **10a**–**h**, **11a**–**c** and **12a**.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-methyl-1*H*-imidazol-3-ium Triflamide (10a): The reaction between **7a** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.36 g, 90%). M. p. –1 °C. $[\alpha]_D^{25}$ = –6.6 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3375, 3153, 2932, 1684, 1551, 1456, 1348, 1182, 1133, 1053 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$, 30 °C): δ = 8.69 (s, 1 H, Im-H), 7.74 (s, 1 H, Im-H), 7.36 (br., 1 H, NH), 7.33–7.20 (m, 6 H, Ar-H), 7.17 (s, 1 H, Im-H), 7.12–7.02 (m, 2 H, Ar-H), 5.45 (t, J = 7.6 Hz, 1 H, C*-H), 4.47 (dd, J = 14.8, 6.4 Hz, 1 H, NHCH_2Ph), 4.24 (dd, J = 14.8, 5.1 Hz, 1 H, NHCH_2Ph), 3.83 (s, 3 H, CH$_3$), 3.44 (dd, J = 13.8, 7.1 Hz, 1 H, CH$_2$Ph), 3.24 (dd, J = 13.6, 8.5 Hz, 1 H, CH$_2$Ph) ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.19, 136.78, 135.74, 133.5, 129.1, 128.9, 128.6, 127.9, 127.5, 127.5, 122.8, 122.0, 119.7 (CF$_3$), 63.5, 43.8, 40.0, 36.4 ppm. MS (ESI$^+$): 320.2 (100) [M$^+$]. MS (ESI$^-$): m/z (%) = 280.0 (100) [NTf$_2^-$]. C$_{22}$H$_{22}$F$_6$N$_4$O$_5$S$_2$ (600.5): calcd. C 44.00, H 3.69, N 9.33; found C 44.3, H 3.4, N 9.2.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-butyl-1*H*-imidazol-3-ium Triflamide (10b): The reaction between **7b** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.1 g, 75%). M. p. –12 °C. $[\alpha]_D^{25}$ = –16.2 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3375, 3147, 2964, 2877, 1682, 1550, 1456, 1348, 1185, 1133, 1054 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$, 30 °C): δ = 8.62 (s, 1 H, Im-H), 7.83 (s, 1 H, Im-H), 7.49 (br., 1 H, NH), 7.30–7.05 (m, 11 H, Ar-H, Im-H), 5.58–5.39 (m, 1 H, C*H), 4.48 (dd, J = 14.7, 6.2 Hz, 1 H, NHCH_2Ph), 4.28 (dd, J = 14.7, 5.1 Hz, 1 H, NHCH_2Ph), 4.10–3.92 (m, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 3.43 (dd, J = 13.7, 6.3 Hz, 1 H, CH$_2$Ph), 3.21 (dd, J = 13.4, 9.8 Hz, 1 H, CH$_2$Ph), 1.74–1.65 (m, J = 14.4, 7.1 Hz, 2 H, CH$_2$CH_2Et), 1.19–1.12 (m, J = 14.6, 7.2 Hz, 2 H, CH$_2$CH$_2$CH_2CH$_3$), 0.91 (t, J = 7.2 Hz, 3 H, CH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.3, 136.8, 135.3, 133.5, 129.1, 128.8, 128.6, 127.8, 127.6, 127.5, 121.8, 121.4, 119.7 (CF$_3$), 63.3, 50.0, 43.9, 40.1, 31.7, 19.1, 13.1 ppm. MS (ESI$^+$): 362.3 (100) [M$^+$]. MS (ESI$^-$): m/z (%) = 280.1 (100) [NTf$_2^-$]. C$_{25}$H$_{28}$F$_6$N$_4$O$_5$S$_2$ (642.63): calcd. C 46.72, H 4.39, N 8.72; found C 47.1, H 4.8, N 8.4.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-phenylethyl]-3-nonyl-1*H*-imidazol-3-ium Triflamide (10c): The reaction between **7c** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.24 g, 79%). M. p. –20 °C. $[\alpha]_D^{25}$ = –16.7 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3373, 3147, 2928, 2857, 1683, 1550, 1456, 1348, 1187, 1133, 1055 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C): δ = 8.62 (s, 1 H, Im-H), 7.82 (s, 1 H, Im-H), 7.5 (s, 1 H, NH), 7.32–7.04 (m, 11 H, Ar-H, Im-H), 5.58–5.43 (m, 1 H, C*H), 4.48 (dd, J = 14.6, 6.3 Hz, 1 H, NHCH_2Ph), 4.27 (dd, J = 14.7, 5.2 Hz, 1 H, NHCH_2Ph), 4.08–3.86 [m, 2 H, CH_2(CH$_2$)$_7$CH$_3$], 3.43 (dd, J = 13.8, 6.2 Hz, 1 H, CH$_2$Ph), 3.22 (dd, J = 13.7, 9.5 Hz, 1 H, CH$_2$Ph), 1.75–1.65 [m, 2 H, CH$_2$CH_2(CH$_2$)$_6$CH$_3$], 1.26 [br., 10 H, CH$_2$CH$_2$(CH_2)$_5$CH$_2$CH$_3$], 1.19–1.11 [m, 2 H, (CH$_2$)$_7$CH_2CH$_3$], 0.89 [t, J = 6.6 Hz, 3 H, (CH$_2$)$_8$CH_3] ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.3, 136.8, 135.34, 133.5, 129.1, 128.8, 128.6, 127.9, 127.6, 127.5, 121.8, 121.3, 119.7 (CF$_3$), 63.3, 50.3, 43.9, 40.1, 31.7, 29.9, 29.1, 29.1, 28.7, 25.9, 22.6, 14.0 ppm. MS (ESI$^+$): 432.3 [M$^+$, 100]. MS (ESI$^-$): m/z (%) = 280.0 (100) [NTf$_2^-$]. C$_{30}$H$_{38}$F$_6$N$_4$O$_5$S$_2$ (712.76): calcd. C 50.55, H 5.37, N 7.86; found C 50.6, H 5.7, N 7.9.

3-Benzyl-1-[(1*S*)-1-(benzylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Triflamide. (10d): The reaction between **7d** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.49 g, 71%). M. p. 2 °C. $[\alpha]_D^{25}$ = –26.0 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3375, 3146, 2934, 1683, 1549, 1456, 1348, 1185, 1132, 1054 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C): δ = 8.69 (s, 1 H, Im-H), 7.80 (s, 1 H, Im-H), 7.49 (br., 1 H, NH), 7.46–7.00 (m, 16 H, Ar-H, Im-H), 5.49 (dd, J = 9.0, 6.8 Hz, 1 H, C*H), 5.17 (d, J = 14.6 Hz, 1 H, CH_2Ph), 5.11 (d, J = 14.6 Hz, 1 H, CH_2Ph), 4.48 (dd, J = 14.7, 6.3 Hz, 1 H, NHCH_2Ph), 4.27 (dd, J = 14.7, 5.2 Hz, 1 H, NHCH_2Ph), 3.41 (dd, J = 13.6, 6.0 Hz, 1 H, CH_2Ph), 3.19 (dd, J = 13.8, 9.6 Hz, 1 H, CH_2Ph) ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.2, 136.8, 135.3, 133.5, 131.7, 129.9, 129.7, 129.1, 128.8, 128.6, 128.4, 127.8, 127.6, 127.5, 122.0, 121.4, 119.7 (CF$_3$), 63.4, 53.7, 43.8, 40.1 ppm. MS (ESI$^+$): 396.2 [M$^+$, 100]. MS (ESI$^-$): m/z (%) = 280.0 (100) [NTf$_2^-$]. C$_{28}$H$_{26}$F$_6$N$_4$O$_5$S$_2$·0.5H$_2$O (685.7): calcd. C 49.05, H 3.97, N 8.17; found C 49.4, H 4.3, N 8.3.

1-[(1*S*)-1-(Butylcarbamoyl)-2-phenylethyl]-3-methyl-1*H*-imidazol-3-ium Triflamide. (10e): The reaction between **7e** and bis(trifluoromethane) sulfonamide gave a brown oil (1.12 g, 84%). M. p. –16 °C. $[\alpha]_D^{25}$ = –5.6 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3378, 3152, 2962, 2875, 1681, 1551, 1457, 1183, 1133, 1054 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C): δ = 8.65 (s, ^{1}H: Im-H), 7.69 (s, 1 H, Im-H), 7.30–7.10 (m, 6 H, Ar-H, Im-H), 6.87 (br., 1 H, NH), 5.31 (t, J = 7.7 Hz, 1 H, C*H), 3.83 (s, 3 H, CH$_3$), 3.39 (m, J = 13.0, 7.7 Hz, 1 H, CH$_2$Ph), 3.22 (m, J = 13.5, 7.7 Hz, 2 H, NHCH_2Pr), 3.12–3.02 (m, 1 H, CH$_2$Ph), 1.35 (m, J = 14.1, 7.0 Hz, 2 H, NHCH$_2$CH_2Et), 1.18 (m, J = 14.4, 7.0 Hz, 2 H, NHCH$_2$CH$_2$CH_2CH$_3$), 0.83 (t, J = 7.2 Hz, 3 H, NHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.1, 135.6, 133.6, 129.0, 129.0, 127.9, 122.9, 122.0, 119.7 (CF$_3$), 63.6, 40.0, 39.7, 36.4, 30.7, 19.7, 13.5 ppm. MS (ESI$^+$): 286.2 [M$^+$, 100]. MS (ESI$^-$): m/z (%) = 280.1 (100) [NTf$_2^-$]. C$_{19}$H$_{24}$F$_6$N$_4$O$_5$S$_2$ (566.53): calcd. C 39.96, H 4.32, N 9.81; found C 40.4, H 4.9, N 9.6.

3-Butyl-1-[(1*S*)-1-(butylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Triflamide (10f): The reaction between **7f** and bis(trifluoromethane) sulfonamide gave a brown oil (0.45 g, 77%). M. p. –23 °C. $[\alpha]_D^{25}$ = –18.2 (c = 0.01, CHCl$_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3379, 3147, 2962, 2875, 1678, 1550, 1457, 1348, 1185, 1133, 1055 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C): δ = 8.58 (s, 1 H, Im-H), 7.78 (s, 1 H, Im-H), 7.37–7.10 (m, 6 H, Ar-H, Im-H), 7.02 (br., 1 H, NH), 5.37 (t, J = 9.2 Hz, 1 H, C*H), 4.06 (t, J = 7.1 Hz, 2 H, CH$_2$Pr), 3.47–3.38 (m, 1 H, CH$_2$Ph), 3.33–3.10 (m, 3 H, CH$_2$Ph, NHCH_2Pr), 1.72 (m, J = 14.5, 7.2 Hz, 2 H, CH$_2$CH_2Et), 1.44 (m, J = 14.1, 7.0 Hz, 2 H, NHCH$_2$CH_2Et), 1.31–1.12 (m, 4 H, CH$_2$CH$_2$CH_2CH$_3$, NHCH$_2$CH$_2$CH_2CH$_3$), 0.95–0.85 (m, 6 H, CH$_2$CH$_2$CH$_2$CH_3, NHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, CDCl$_3$, 30 °C): δ = 166.2, 135.3, 133.7, 129.0, 128.8, 127.8, 121.8, 121.4, 119.7 (CF$_3$), 63.4, 50.0, 40.1, 39.7, 31.7, 30.7,

19.8, 19.1, 13.5, 13.1 ppm. MS (ESI$^+$): 328 (100) [M$^+$]. MS (ESI$^-$): *m*/*z* (%) = 280.1 (100) [NTf$_2^-$]. $C_{22}H_{30}F_6N_4O_5S_2$ (608.61): calcd. C 43.42, H 4.97, N 9.21; found C 43.8, H 5.2, N 9.2.

3-Benzyl-1-[(1*S*)-1-(butylcarbamoyl)-2-phenylethyl]-1*H*-imidazol-3-ium Triflamide (10g): The reaction between **7g** and bis(trifluoromethane) sulfonamide gave a brown oil (1.02 g, 83%). M. p. –9 °C. $[\alpha]_D^{25}$ = –21.6 (*c* = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3378, 3144, 2961, 2875, 1678, 1550, 1456, 1348, 1185, 1133, 1054 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 8.66 (s, 1 H, Im-H), 7.78 (s, 1 H, Im-H), 7.43–7.38 (m, 3 H, Ar-H), 7.25–7.21 (m, 3 H, Ar-H), 7.15–7.04 (m, 5 H, Ar-H, Im-H), 7.02 (br., 1 H, NH), 5.39 (dd, *J* = 9.0, 6.6 Hz, 1 H, C*H), 5.18 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 5.13 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 3.39 (dd, *J* = 14.0, 6.5 Hz, 1 H, CH_2Ph), 3.28–3.11 (m, 3 H, CH_2Ph, NHCH_2Pr), 1.40 (m, *J* = 14.3, 7.2 Hz, 2 H, NHCH$_2$CH_2Et), 1.23 (m, *J* = 15.0, 7.4 Hz, 2 H, NHCH$_2$CH$_2$CH_2CH$_3$), 0.86 (t, *J* = 7.3 Hz, 3 H, NHCH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.1, 135.3, 133.6, 131.7, 129.9, 129.6, 129.0, 128.8, 128.4, 127.8, 122.0, 121.4, 119.7 (CF_3), 63.5, 53.7, 39.7, 30.7, 19.8, 13.5 ppm. MS (ESI$^+$): 362.2 (100) [M$^+$]. MS (ESI$^-$): *m*/*z* (%) = 280.1 (100) [NTf$_2^-$]. $C_{25}H_{28}F_6N_4O_5S_2$ (642.63): calcd. C 46.72, H 4.39, N 8.72; found C 47.0, H 4.4, N 8.5.

1-[(1*S*)-1-(Benzylcarbamoyl)-2-methylpropyl]-3-butyl-1*H*-imidazol-3-ium Triflamide (11a): The reaction between **8a** and bis(trifluoromethane) sulfonamide gave a brown oil (0.25 g, 76%). M. p. –20 °C. $[\alpha]_D^{25}$ = +3.3 (*c* = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3378, 3146, 2967, 2878, 1684, 1551, 1468, 1353, 1196, 1058 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 8.99 (s, 1 H, Im-H), 7.80 (s, 1 H, Im-H), 7.62 (br., 1 H, NH), 7.35–7.20 (m, 6 H, Ar-H, Im-H), 4.79 (d, *J* = 10.2 Hz, 1 H, C*H), 4.50 (dd, *J* = 14.6, 6.1 Hz, 1 H, NHCH$_2$Ph), 4.30 (dd, *J* = 14.6, 5.2 Hz, 1 H, NHCH$_2$Ph), 4.17 (t, *J* = 7.2 Hz, 2 H, CH_2Pr), 2.45–2.31 (m, 1 H, CH), 1.86 (m, *J* = 14.5, 7.2 Hz, 2 H, CH$_2$CH_2Et), 1.33 (m, *J* = 14.3, 7.3 Hz, 2 H, CH$_2$CH$_2$CH_2CH$_3$), 1.06–0.94 (m, 6 H, CH$_3$, CH$_2$CH$_2$CH$_2$CH_3), 0.78 (d, *J* = 6.5 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 166.7, 137.0, 135.2, 128.6, 127.8, 127.6, 122.2, 121.5, 119.7 (CF_3), 68.5, 50.2, 43.9, 32.4, 31.8, 19.3, 18.5, 18.0, 13.1 ppm. MS (ESI$^+$): *m*/*z* (%) = 314.0 (100) [M$^+$]. MS (ESI$^-$): *m*/*z* (%) = 280.0 (100) [NTf$_2^-$]. $C_{21}H_{28}F_6N_4O_5S_2$ (594.58): calcd. C 41.66, H 4.86, N 9.25; found C 42.0, H 5.2, N 9.6.

3-Butyl-1-[(1*S*)-1-(butylcarbamoyl)-2-methylpropyl]-1*H*-imidazol-3-ium Triflamide (11b): The reaction between **8b** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.1 g, 72%). M. p. –45 °C. $[\alpha]_D^{25}$ = +8.8 (*c* = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3381, 3145, 2965, 2936, 2877, 1677, 1551, 1469, 1348, 1133, 1053 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 8.98 (s, 1 H, Im-H), 7.80 (s, 1 H, Im-H), 7.26 (s, 1 H, Im-H), 7.15 (s, 1 H, NH), 4.71 (d, *J* = 10.3 Hz, 1 H, C*H), 4.18 (t, *J* = 7.3 Hz, 2 H, CH_2Pr), 3.30 (m, *J* = 13.2, 6.6 Hz, 1 H, NHCH_2Pr), 3.15 (m, *J* = 12.8, 6.7 Hz, ^{1}H NHCH_2Pr), 2.43–2.27 (m, 1 H, CH), 1.88 (m, *J* = 14.9, 7.4 Hz, 2 H, CH$_2$CH_2Et), 1.49 (m, *J* = 14.4, 7.1 Hz, 2 H, NHCH$_2$CH_2Et), 1.41–1.27 (m, 4 H, NHCH$_2$CH$_2$CH_2CH$_3$, CH$_2$CH$_2$CH_2CH$_3$), 1.07 (d, *J* = 6.5 Hz, 3 H, CH$_3$), 0.98 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH$_2$CH$_2$CH_3), 0.90 (t, *J* = 7.2 Hz, 3 H, NHCH$_2$CH$_2$CH$_2$CH_3), 0.79 (d, *J* = 6.6 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 166.8, 135.5, 122.4, 122.1, 120.0 (CF_3), 68.9, 50.4, 39.9, 32.5, 32.1, 31.0, 20.1, 19.6, 18.8, 18.3, 13.7, 13.4 ppm. MS (ESI$^+$): *m*/*z* (%) = 280.2 (100) [M$^+$]. MS (ESI$^-$): *m*/*z* (%) = 280.1 (100) [NTf$_2^-$]. $C_{18}H_{30}F_6N_4O_5S_2$ (560.57): calcd. C 38.57, H 5.39, N 9.99; found C 39.0, H 5.7, N 9.6.

1-[(1*S*)-1-(Butylcarbamoyl)-2-methylpropyl]-3-nonyl-1*H*-imidazol-3-ium Triflamide (11c): The reaction between **8c** and bis(trifluoromethane) sulfonamide gave a yellow oil (0.1 g, 70%). M. p. –49 °C. $[\alpha]_D^{25}$ = +6.6 (*c* = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3382, 3146, 2929, 2877, 1678, 1550, 1468, 1349, 1185, 1054 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 8.95 (s, 1 H, Im-H), 7.77 (s, 1 H, Im-H), 7.26 (s, 1 H, Im-H), 7.13 (t, *J* = 5.2 Hz, 1 H, NH), 4.72 (d, *J* = 10.3 Hz, 1 H, C*H), 4.18 [t, *J* = 7.4 Hz, 2 H, CH_2(CH$_2$)$_7$CH$_3$], 3.3 (m, *J* = 13.3 Hz, 7 MHz, 1 H, NHCH_2Pr), 3.15 (m, *J* = 12.9 Hz, 7 MHz, 1 H, NHCH_2Pr), 2.47–2.28 (m, 1 H, CH), 1.92–1.84 [m, 2 H, CH$_2$CH$_2$(CH$_2$)$_6$CH$_3$], 1.50 (m, *J* = 14.9 Hz, 2 H, NHCH$_2$CH$_2$Et), 1.20–1.4 [m, 14 H, NHCH$_2$CH$_2$CH$_2$CH$_2$CH$_3$, CH$_2$CH$_2$(CH$_2$)$_6$CH$_3$], 1.08 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 0.83–0.95 [m, 6 H, (CH$_2$)$_8$CH$_3$, NHCH$_2$CH$_2$CH$_2$CH$_3$], 0.79 (d, *J* = 6.7 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C): δ = 166.8, 135.5, 122.4, 122.1, 120.0 (CF_3), 68.9, 50.7, 39.9, 32.5, 31.9, 31.0, 30.2, 29.4, 29.2, 29.0, 26.3, 22.8, 20.1, 18.8, 18.3, 14.2, 13.7 ppm. MS (ESI$^+$): 350.3 [M$^+$, 100]. MS (ESI$^-$): *m*/*z* (%) = 279.9 (100) [NTf$_2^-$]. $C_{23}H_{40}F_6N_4O_5S_2$ (630.70): calcd. C 43.80, H 6.39, N 8.88; found C 44.1, H 6.8, N 9.0.

1-[(1*S*)-1-(Benzylcarbamoyl)-3-methylbutyl]-3-butyl-1*H*-imidazol-3-ium Triflamide (12a): The reaction between **9a** and bis(trifluoromethane) sulfonamide gave a brown oil (0.12 g, 76%). M. p. –19 °C. $[\alpha]_D^{25}$ = –5.0 (*c* = 0.01, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3372, 3145, 3077, 2962, 2876, 1681, 1548, 1459, 1346, 1185, 1136, 1054 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.07 (s, 1 H, Im-H), 7.74 (s, 1 H, Im-H), 7.66 (br., 1 H, NH), 7.34–7.23 (m, 5 H, Ar-H), 7.21 (s, 1 H, Im-H), 5.34 (t, *J* = 7.6 Hz, 1 H, C*H), 4.48 (dd, *J* = 14.7, 6.1 Hz, 1 H, NHCH_2Ph), 4.30 (dd, *J* = 14.7, 5.2 Hz, 1 H, NHCH_2Ph), 4.17 [t, *J* = 7.3 Hz, 2 H, CH_2(CH$_2$)$_2$CH$_3$], 2.06–1.96 (m, *J* = 14.0, 7.1 Hz, 1 H, CH$_2$), 1.91–1.80 (m, 3 H, CH$_2$, CH$_2$CH_2CH$_2$CH$_3$), 1.42–1.29 (m, 3 H, CH$_2$, CH$_2$CH$_2$CH_2CH$_3$), 0.99–0.92 (m, 9 H, CH$_3$, CH$_2$CH$_2$CH$_2$CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C): δ = 167.0, 137.1, 135.1, 128.6, 127.7, 127.5, 121.8, 121.5, 119.7 (CF_3), 61.0, 50.2, 43.9, 42.2, 31.8, 24.8, 22.1, 21.9, 19.3, 13.2 ppm. MS (ESI$^+$): 328.1 [M$^+$, 100]. MS (ESI$^-$): *m*/*z* (%) = 280.1 (100) [NTf$_2^-$]. $C_{22}H_{30}F_6N_4O_5S_2$ (608.61): calcd. C 43.42, H 4.97, N 9.21; found C 43.8, H 5.4, N 9.4.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of the prepared compounds. ^{1}D ROESY spectra for **7b**, gCOSY spectra for **11a**, variation of ^{1}H chemical shifts with concentration for **7b** in CD_3OD, variation of ^{1}H chemical shifts with concentration for **10b** in $CDCl_3$, partial FTIR spectra for **7b** at different temperatures, variation of ^{1}H chemical shifts for **7b** at different temperatures in CD_3CN, ^{1}H NMR spectra for **10b** after the addition of 1 equiv. of the TEA salt of (*R*)-mandelic acid, Job-plot for the complexation of **10b** with the TEA salt of the (*R*)-mandelic acid and crystallographic data for **7b**.

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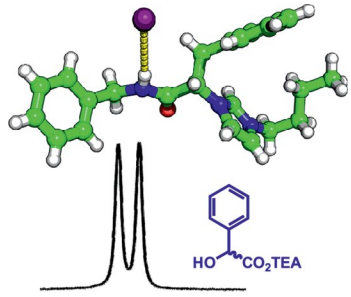
Ionic Liquids

New chiral room temperature ionic liquids, based on an imidazolium group and derived from natural amino acids, have been synthesized and studied as chiral shift agents for the chiral discrimination of enantiomeric carboxylate salts.



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Synthesis of Chiral Room Temperature Ionic Liquids from Amino Acids – Application in Chiral Molecular Recognition

Keywords: Ionic liquids / Chiral shift agents / Amino acids / Carboxylic acids / Molecular recognition

