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Design of a New Chiral Ionic Liquids System for the Enantioselective Addition of Diethylzinc to Aldehydes

Mariana Ferrari Bach,[a] Cassiana Herzer Griebeler, [a] Caroline Gross Jacoby[a] and Paulo Henrique Schneider*[a]

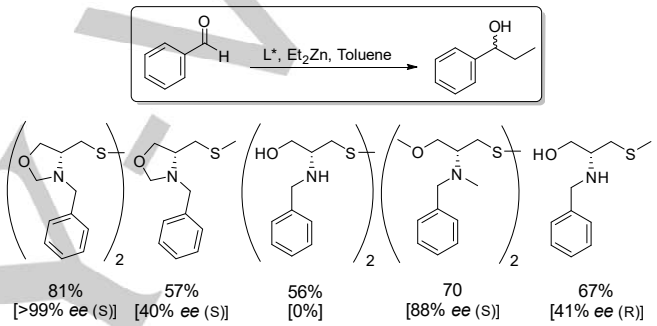
Abstract: An important contribution to the field of asymmetric catalysis is described in this work, as it merges the search for new ligands that can provide high performance in asymmetric catalysis with the extremely important and increasing need for sustainability. New chiral ionic liquids were synthesized from the amino acid L-cysteine by straightforward routes. With these ligands, we could develop a chiral ionic system which included chiral ionic liquids and their immobilization in ionic solvents providing a chiral supramolecular structure. These new catalytic systems were used in the enantioselective addition of alkylzinc to aldehydes and proved to be very efficient, capable of providing chiral secondary alcohols in excellent enantiomeric excesses and yields. This system enabled also the recycling of the ionic media and the ionic ligand, taking into account green chemistry considerations.

Introduction

Carbon–carbon bond formation is one of the most important transformations in organic chemistry and its asymmetrical version is a useful tool in the synthesis of several biologically active molecules.[1] In this context, the enantioselective alkylzinc addition to aldehydes and ketones is a well-established methodology for the synthesis of optically active alcohols, which are important synthetic intermediates towards more complex molecules.[2]

In the literature, a wide range of ligands can be found for the organozinc addition to aldehydes. Ligands derived from amino acids are outstanding due to their easy access from natural sources and to their excellent performance in asymmetric reactions.[3] In this way, our group has described a series of ligands from the amino acid L-cysteine, which have proved to be very efficient in the enantioselective addition of alkylzinc, alkynylzinc and arylzinc to aldehydes, as well as in the palladium-catalysed asymmetric allylations and enantioselective direct aldol reactions.[4] Some examples of the use of these ligands in the asymmetric addition of diethylzinc to aldehydes can be seen in Scheme 1.

The search for methodologies that are environmentally benign, practical and economic has become a target for chemical communities. In this context, ionic liquids play a pivotal role, as they can be used as solvents with high thermal stability and negligible vapor pressure, instead of the commonly used volatile organic solvents.[5] In addition, they provide the possibility of recycling both the reaction medium and the ligands/catalysts, because of their tunable properties through simple structural changes.[6] More important, in asymmetric catalysis, chiral ionic liquids (CILs) have being successfully used as recyclable ligands/catalysts.[7] Despite their potential, there have been only a few examples reported of the asymmetric diethylzinc addition to aldehydes using CILs as ligands, however in conventional organic solvents.[8]



Scheme 1. Ligands derived from L-cysteine applied in the asymmetric addition of diethylzinc to aldehydes.

One example of an enantioselective addition of alkylzinc to aldehydes in an ionic liquid as solvent and using CILs as ligands was reported by Lombardo et al. in 2008.[9] Three diphenylprolinol derivatives containing an ionic moiety were prepared and their activities were evaluated in the enantioselective addition of diethylzinc to benzaldehyde. The CILs were efficient as ligands and furnished the product with 89% *ee* and 96% yield when the reaction was carried out in 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)amide ([BMPy][N(Tf)$_2$]) as solvent at 0 °C for 3 h using 10 mol% of the ligand. Additionally, the ligand and the reaction medium were recycled without decreasing yield and enantioselectivity.

Despite all the advantages and outcome of the use of ILs in the asymmetric alkylzinc addition reaction, there has clearly been a lack of study and development of a chiral ionic system to include the synthesis of chiral ionic liquids and their immobilization in ionic solvents to provide a chiral supramolecular structure, as only a few articles have been reported.[9,10]

As part of our broader programme to explore the preparation and use of chiral catalysts in asymmetric synthesis,[4,11] we describe in this article the design and synthesis of a new class of chiral ionic liquids derived from L-cysteine (Scheme 2) in efficient synthetic routes. In order to prove our new catalytic system reaction we envisioned their application in an organometallic reaction, taking into account the importance of replacing the use of volatile organic solvents with clean ones, such as ionic liquids. We chose as a probe reaction the well-known enantioselective

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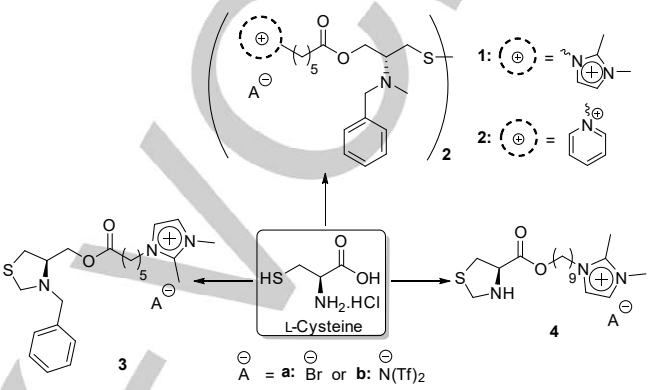
addition of diethylzinc to aldehydes. Additionally, in an important feature of this work, we investigated the possibility of recycling the chiral reaction medium, using a model reaction.

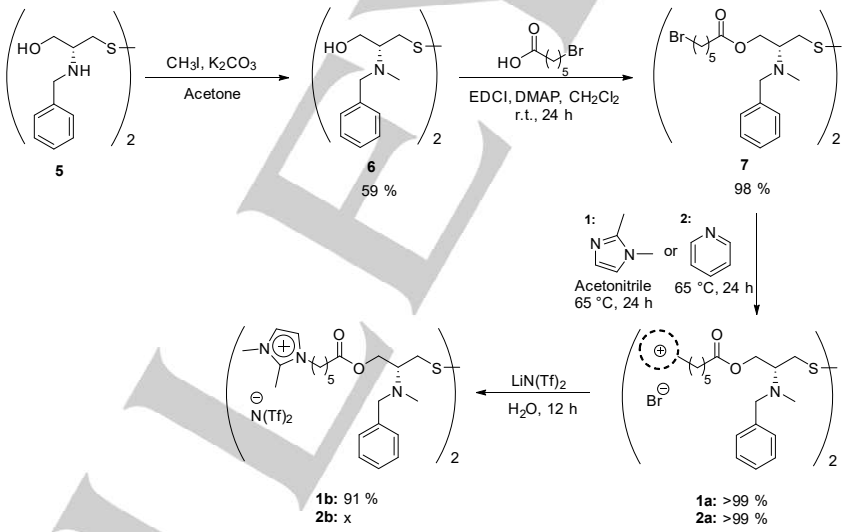
Results and Discussion

According to our objectives, as the starting point we designed four new CILs, **1**–**4** (Scheme 2), from the amino acid L-cysteine, which is an inexpensive and widely available source of chirality. As a general strategy, we used a linear synthesis to obtain chiral molecules of an ionic nature, containing coordinating atoms (O, N and S). 1,2-dimethylimidazolium and pyridinium rings were chosen as cations due to the easy access to these materials and to the absence of acidic hydrogens present in the structure of 1-methylimidazolium, a commonly used cation, as it could react with the Et_2Zn.[8c,10a,12] The $N(Tf)_2$ anion was chosen because of the properties that it confers to ionic liquids, such as good thermal stability, low melting point, good miscibility with polar organic solvents, low miscibility with water and lower viscosity.[10b]

Our strategy to synthesize the CILs **1** and **2** (Scheme 3), started with the disulfide **5**, which was obtained in two steps from L-cysteine, as previously described.[4a] The disulfide **5** was treated with iodomethane and K_2CO_3 to provide the disulfide **6**, which through an esterification with 6-bromohexanoic acid, furnished **7** in excellent yield. To form the ionic pair, compound **7** was treated with 1,2-dimethylimidazole, in acetonitrile, or with pyridine at 65 °C to provide the bromides **1a** or **2a**, respectively, in quantitative yields. Finally, compound **1b** was obtained by the anion exchange of **1a** in water by treatment with $LiN(Tf)_2$. It was not possible to perform the anion exchange for **2a**, as decomposition was observed.



Scheme 2. Chiral ionic liquids synthesised from L-cysteine.



Scheme 3. Synthesis of chiral ionic liquids **1** and **2**.

To synthesize the CIL **3b**, we started from the same disulfide **5**, which was easily converted to the thiazolidine alcohol **8** (Scheme 4) in two steps, as previously described.[4d] The alcohol **8** was used in an esterification with 6-bromohexanoic acid to provide **9** in good yield. The target CIL **3b** was obtained by treatment of **9** with 1,2-dimethylimidazole followed by anion exchange with $LiN(Tf)_2$, in excellent overall yields.

The synthesis of CILs **4** started with the cyclisation of L-cysteine with formaldehyde followed by protection of the amine group with Boc_2O to provide **10** (Scheme 5), as previously described.[4i] After esterification of **10** with 9-bromo-1-nonanol, followed by a deprotection, compound **12** was treated with 1,2-dimethylimidazole to give the CIL **4a**. The anion exchange was performed with $LiN(Tf)_2$ in water to provide the CIL **4b** in excellent yields for all reaction steps.

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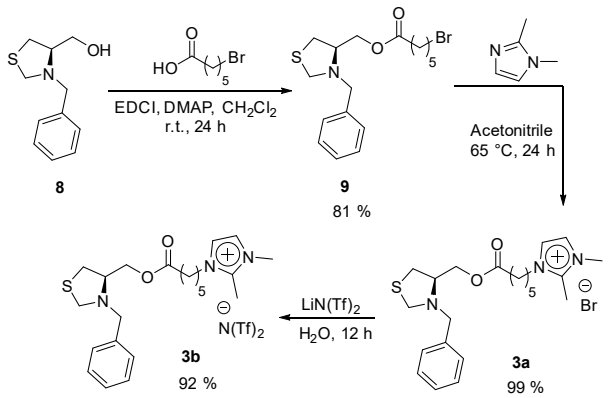
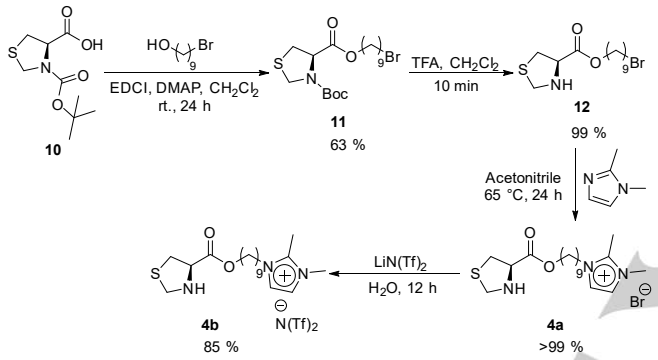


Scheme 4. Synthesis of chiral ionic liquids **3**.



Scheme 5. Synthesis of chiral ionic liquids **4**.

With the target compounds (CILs **1**–**4**) in our hands, we focused our attention on exploring their potential as chiral ligands in the enantioselective addition of diakylzinc to aldehydes. Our studies started by examining the efficiency of these CILs, using as a model reaction the asymmetric addition of diethylzinc to benzaldehyde (Table 1). The CILs chosen for these initial studies were those containing $N(Tf)_2$ as anion to maintain the homogeneous nature of the anions in the system. As solvent, the ionic liquid [BPy][$N(Tf)_2$] was chosen, as it has already been reported in the literature to be an efficient solvent for this reaction.[9,12]

In our first attempt, the test reaction was performed in the presence of 5 mol % of CIL **1b**, 2 equiv diethylzinc, ionic solvent, at 0 °C for 48 h, and whit this conditions, the (*S*)-1-phenylpropan-1-ol was obtained with 72% *ee*; however in low yield (Table 1, entry 1). Due to the high viscosity of the reaction medium, we thought that the addition of a co-solvent could help to increase the yields, so we added a small amount of toluene. With these conditions we could improve the *ee* to 86%, while a similar yield of 30% was obtained (Table 1, entry 2). By increasing the amount of ligand to 10 mol% no significant influence on enantioselectivity and yield was observed (Table 1, entry 3).

After screening the initial experimental parameters, we evaluated the different characteristics of compounds **3b**, **4b** and **7** in regard to their structural diversity, in order to identify the ligands with superior performance. The CIL **3b** provided the best result (45% *ee*, 37% yield, entry 6) using 10 mol% load and 4 equiv diethylzinc. Even increasing the amount of ligand to 20% and the reaction time to 72 h did not increase the enantioselectivity (Table 1, entry 7). When ligand **4b** was used, poor yields and *ee*s were obtained, even when 20 mol % of the ligand was used, as well as 4 equiv diethylzinc, affording 51% *ee* and 16% yield as the best result among the conditions tested (entry 8-10).

Table 1. Enantioselective addition of diethylzinc to benzaldehyde promoted by different CILs.[a]

Entry	Ligand (mol%)	Et_2Zn (eq)	*ee* (%)[b]	Yield (%)[c]
1[d]	**1b** (5)	2	72	27
2	**1b** (5)	2	86	30
3	**1b** (10)	2	88	35
4	**3b** (5)	2	28	18
5	**3b** (10)	2	37	16
6	**3b** (10)	4	45	37
7[e]	**3b** (20)	4	39	66
8	**4b** (10)	2	11	25
9	**4b** (10)	4	31	5
10	**4b** (20)	4	51	16
11	**7** (5)	2	0	23
12	**1a** (5)	2	84	24
13	**2a** (5)	2	77	10

[a] The reactions were carried with 0.25 mmol benzaldehyde in 0.25 mL of ionic solvent; 0.25 mL of toluene was added in addition to the toluene from Et_2Zn solution, and reactions quenched with HCl 1M. [BPy] = 1-butylpyridinium. [b] Determined by HPLC analysis (chiracel OD-H column). [c] Yield of isolated product. [d] No extra toluene added. [e] Reaction time: 72 h.

In order to investigate the necessity for an ionic ligand for this catalytic system, we tested the nonionic disulfide **7**, in IL as solvent, and the resulting product was obtained with 23% yield in its racemic form (entry 11). The low yield and enantiomeric excess could suggest that the CILs are very important for the formation of a highly organized supramolecular structure in IL media.[13]

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Finally, we evaluated the effect of the ionic portion of the ligand (Table 1, entries 12–13). Using the CIL **1a**, containing bromide anion, the enantiomeric excess of the product did not change, but the yield was lower than when **1b** was used (compare entries 2 and 12). Using the CIL **2a**, containing pyridinium as cation and bromide as anion, a slight decrease in enantioselectivity, together with a large decrease in yield was observed (Table 1, entry 13).

Having established the optimum reaction conditions, as well as the most efficient ligand, we turned our attention to study some reaction parameters that we found to be crucial for increasing the yields (Table 2). Our first observation was that the quenching of the reaction had a dramatic influence on the yield. As an example, when the reaction was quenched with $NH_4Cl_{sat.}$ instead of HCl 1M, the yield increased from 30% (entry 1) to 41% (entry 2). Adding oxalic acid at the end of the reaction and using acetone for the precipitation of the inorganic compounds formed increased the yield to 76%, but the *ee* decreased to 79% (Table 2, entry 3). On the other hand, using methanol to quench the reaction and dichloromethane to precipitate the inorganic compounds formed, increased the yield to 78% with the same *ee* of 87% (Table 2, entry 4).

Table 2. Optimisation of the addition of diethylzinc to benzaldehyde promoted by CIL **1b**.[a]

Entry	Solvent	t (h)	*ee*[b] (%)	Yield[c] (%)	Quench
1	[BPy][N(Tf)$_2$][d]	48	86	30	HCl 1M
2	[BPy][N(Tf)$_2$]	48	85	41	$NH_4Cl_{sat.}$
3	[BPy][N(Tf)$_2$]	72	79	76	Oxalic Acid
4	[BPy][N(Tf)$_2$]	72	87	78	MeOH
5	[BMPy][N(Tf)$_2$][e]	48	71	17	$NH_4Cl_{sat.}$
6	[BDMI][N(Tf)$_2$][f]	48	79	54	$NH_4Cl_{sat.}$
7	CH_2Cl_2[g]	48	5	8	$NH_4Cl_{sat.}$
8	[BPy][N(Tf)$_2$]	72	87	61	$NH_4Cl_{sat.}$
9[h]	[BPy][N(Tf)$_2$]	72	50	91	$NH_4Cl_{sat.}$

[a] The reactions were carried out with 0.25 mmol benzaldehyde in 0.25 mL of ionic solvent; 2 equiv of Et_2Zn; 0.25 mL of toluene was added in addition to the toluene from Et_2Zn solution and reactions quenched with HCl 1M. [b] Determined by HPLC analysis (chiracel OD-H column). [c] Yield of isolated product. [d] [BPy] = 1-butylpyridinium. [e] [BMPy] = 1-butyl-1-methylpyrrolidinium. [f] [BDMI] = 1-butyl-2,3-dimethylimidazolium. [g] No extra toluene added. [h] The reaction was performed at room temperature.

The effect of variation of the ionic environment was also verified (entries 5–7). Two other ionic liquids were tested as solvents, containing 1-butyl-1-methylpyrrolidinium (BMPy) or 1-butyl-2,3-dimethylimidazolium (BDMI) as cation and N-triflate as anion. In both cases the enantiomeric excess dropped; nevertheless, the yield was higher when [BDMI][N(Tf)$_2$] was used (Table 2, entry 6). To verify the real influence of the use of an ionic liquid as solvent, a neutral environment was also used. When CH_2Cl_2 was used as solvent, the product was obtained with only 5% *ee* and 8% yield. Thus, we could suggest again that a biphasic reaction medium is essential to promote the ethyl transfer reaction using this system.

The next two parameters examined were the reaction time and the temperature. By increasing the reaction time from 48 to 72 h the yield raised to 61% without loss of enantioselectivity (compare entries 2 and 8). When the reaction was carried out at room temperature the yield increased to 91%, but a large decrease in enantioselectivity was observed (entry 9).

Having established the optimum reaction conditions (Table 2, entry 4), the scope and limitations of the alkylzinc addition to different aldehydes, catalysed by **1b** were also examined (Table 3). Very good enantioselectivities and yields were obtained with aromatic aldehydes substituted at the *para* and *ortho* positions, except for *o*-bromobenzaldehyde which provided the product with 68% *ee*, and for *o*-tolualdehyde which provided the product with 42% yield. Moderate *ee* and yield were obtained with 1-naphtaldehyde and very good results were obtained using the aliphatic aldehyde cyclohexanecarboxaldehyde (Table 3, entry 8).

Table 3. Enantioselective addition of diethylzinc to different aldehydes promoted by CIL **1b**.[a]

Entry	R	*ee* (%)	Yield (%)[d]
1	*p*-Me-C_6H_4	89[b]	78
2	*o*-Me-C_6H_4	87[b]	42
3	*p*-MeO-C_6H_4	85[b]	77
4	*p*-CN-C_6H_4	87[c]	88
5	*p*-Br-C_6H_4	87[c]	85
6	*o*-Br-C_6H_4	68[c]	97
7	1-naphthyl	64[b]	65
8	cyclohexyl	85[c]	71

[a] The reactions were carried out with 0.25 mmol benzaldehyde in 0.25 mL of ionic solvent; 0.25 mL of toluene was added in addition to the toluene from Et_2Zn solution and reactions quenched with MeOH. [b] Determined by HPLC analysis. [c] Determined by GC-FID analysis. [d] Yield of isolated product.

An important feature of these CILs and ionic liquids as solvents is the possibility of recycling, which makes them an excellent choice when considering economic and environmental aspects. Thus, we verified the possibility of reusing the catalytic ionic medium. To generate an efficient recyclable system, it is

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necessary that the product extraction is efficient, that both the ionic solvent and the ligand are not soluble in the extractant solvent and that the inorganic zinc salts formed are efficiently removed from the ionic phase. To perform the recycling, the methanol used to quench the reaction was completely evaporated and the product extraction was carried out with hexane only. After each treatment and extraction method the recovered ionic liquid was dried under vacuum, at 60 °C and stirred for 5 h before the addition of a new portion of benzaldehyde, diethylzinc and toluene for the new catalytic run. To prove our system in these recycling experiments, the model reaction, using 5 mol % of ligand **1b**, was chosen and as we expected, the catalytic system was successfully recycled three times (four catalytic cycles) without significant decrease in chemical yields or enantiomeric excesses (Figure 1).

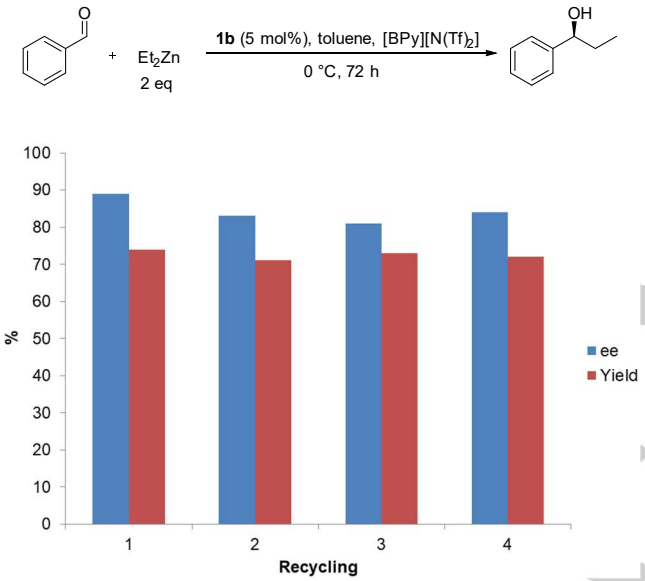

Figure 1. Recycling of the catalytic system [BPy][N(Tf)$_2$] and ligand **1b**.

Conclusions

The results presented in this work are an important contribution to the field of asymmetric catalysis, as the study merges the search for new ligands that can provide high performance of asymmetric catalysis with the extremely important and increasing need for sustainability. We have accomplished the synthesis of new chiral ionic liquids derived from the amino acid L-cysteine by efficient, high-yielding synthetic routes. To test these new ligands, we chose as a probe reaction the enantioselective addition of diethylzinc to aldehydes in ionic media, and all CILs used (**1**, **2b**, **3b** and **4b**) were shown to have catalytic activity, able to furnishing the products in excellent yields and enantioselectivities. A study was carried out to find an efficient recyclable system; the ionic ligand **1b** and the ionic solvent [BPy][N(Tf)$_2$] could be used at least four times, proving here an important concept of catalytic systems.

Experimental Section

General Information

^{1}H NMR, ^{13}C NMR, 2D-COSY NMR and 2D HSQC NMR spectra were recorded on a Varian Inova 300, Varian VNMRS 300, Varian Inova 400, Bruker Avance 400 and Varian VNMRS 500. Chemical shifts (δ) are expressed in ppm with TMS as an internal reference in spectra made in $CDCl_3$ and the deuterated solvents were used like internal references in spectra made in acetone-d_6, DMSO-d_6 and CD_3OD. Coupling constants are reported in Hertz. Optical rotations were measured with a Jasco P-2000 polarimeter. High resolution mass spectra (HRMS) were measured by electrospray (ESI) with Micromass Q-Tof micro spectrometer. Chiral HPLC analysis were performed on a Shimadzu LC-20AT chromatograph with an UV detector using different columns as described in the supporting information. Chiral GC analysis were performed on a Agilent Technologies GC System 6820 chromatograph (Detector: FID, 280 °C; injector: 220 °C; carrier gas: nitrogen) with a chiral Hydrodex-β-3P, 25 m x 0.25 mm capillary column. All the column chromatography separations were done by using silica gel Sigma Aldrich 230–400 Mesh.

SYNTHESIS OF THE IONIC LIGANDS

(*R*,*R*')-bis[2-(*N*-benzyl-*N*-methyl-amino)propan-1-ol]dissulfide (6)

In 25 mL two necked round-bottomed flask under argon atmosphere, 0.39 g (1.0 mmol) of the disulfide **5**, obtained in two steps from L-cysteine as previously described[4a], 3 mL of anhydrous acetone, 0.28 g (2.0 mmol) of potassium carbonate and 0.12 mL (2.0 mmol) of iodomethane were added. This solution was stirred at room temperature for 20 hours. Then, the solvent was evaporated. The obtained material was solubilized in 15 mL of dichloromethane and washed three times with 10 mL of water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified with column chromatography using the mixture ethyl acetate:hexane 20:80 as eluent providing a yellow oil. Yield: 59%. $[\alpha]_D^{20}$ = +79 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.22 (m, 10 H), 3.79-3.73 (m, 2H), 3.76 (d, *J* =13.0, 2H), 3.60 (d, *J* = 13.0, 2H), 3.50-3.42 (m, 2H), 3.20-3.10 (m, 2H), 3.02 (dd, *J* = 4.7 e 13.2, 2 H), 2.51 (dd, *J* = 8.7 and 13.2, 2H), 2.23 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9, 126.2, 125.9, 124.8, 60.5, 57.7, 55.7, 33.4, 32.4. HRMS: calculated for $[C_{22}H_{32}N_2O_2S_2+H]^+$: 421,1985; obtained: 421,1988.

General procedure for esterification

A dry Schlenk tube under argon atmosphere was charged with carboxylic acid, dry CH_2Cl_2, EDCI (*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride) and DMAP (4-(dimethylamino)pyridine). This solution was stirred at room temperature for 30 minutes. The alcohol was added and this solution was stirred at room temperature for 24 hours. Then, additional amount of CH_2Cl_2 was added, the organic layer was washed three times with saturated $NaHCO_{3(aq)}$ solution, was dried over $MgSO_4$ and the solvent was evaporated. The products were purified with column chromatography.

(*R*,*R*')-bis-[2-(*N*-benzyl-*N*-methylamino)-3-(6-bromohexanoate)-propyl]dissulfide (7)

Reagents and amounts used: 6-bromohexanoic acid (0.44 g, 2.25 mmol), dry CH_2Cl_2 (7 mL), EDCI (0.43 g, 2.25 mmol), DMAP (catalytic) and alcohol **6** (0.24 g, 0.56 mmol). The residue was purified with column chromatography using the mixture ethyl acetate:hexane 20:80 as eluent providing a yellow oil. Yield: 98%. $[\alpha]_D^{20}$ = -2 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.19 (m, 10H), 4.33 (dd, *J* = 6.8 and 11.5, 2H),

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4.20 (dd, *J* = 4.8 and 11.5, 2H), 3.71 (d, *J* = 13.6, 2H), 3.66 (d, *J* = 13.6, 2H), 3.39 (t, *J* = 6.5, 4H), 3.29-3.21 (m, 2H), 3.05 (dd, *J* = 7.2 and 13.1, 2H), 2.74 (dd, *J* = 7.2 and 13.1, 2H), 2.35 (t, *J* = 7.4, 4H), 2.25 (s, 6H), 1.92-1.82 (m, 4H), 1.72-1.61 (m, 4H), 1.54-1.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 139.2, 128.5, 128.2, 127.0, 62.6, 60.6, 58.5, 38.3, 37.0, 34.0, 33.5, 32.3, 27.6, 24.0. HRMS calculated for $[C_{34}H_{50}Br_2N_2O_4S_2]^+$: 772,1579; obtained: 772,1593.

(4*R*)-3-benzyl-thiazolidin-4-yl-methyl 6-bromohexanoate (9)

Reagents and amounts used: 6-bromohexanoic acid (0.21 g, 1.09 mmol), dry CH_2Cl_2 (8 mL), EDCI (0.17 g, 0.91 mmol), DMAP (catalytic) and alcohol **8** (0.18 g, 0.91 mmol) obtained in two steps from disulfide **5** as previously described[4a]. The residue was purified with column chromatography using the mixture ethyl acetate:hexane 10:90 as eluent providing a yellow oil. Yield: 81%. $[\alpha]_D^{20}$ = -51 (*c* 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.24 (m, 5H), 4.15 (d, *J* = 10.1, 1H), 4.08 (dd, *J* = 7.6 and 11.2, 1H), 4.00 (d, *J* = 10.1, 1H), 3.88 (dd, *J* = 6.6 and 11.2, 1H), 3.72-3.64 (m, 1H), 3.67 (d, *J* = 13.4, 1H), 3.58 (d, *J* = 13.3, 1H), 3.39 (t, *J* = 6.7, 2H), 3.08 (dd, *J* = 6.8 and 10.9, 1H), 2.77 (dd, *J* = 2.5 and 10.9, 1H), 2.33 (t, *J* = 7.2, 2H), 1.91-1.83 (m, 2H), 1.69-1.60 (m, 2H), 1.52-1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 138.4, 128.8, 128.4, 127.4, 67.0, 63.9, 58.7, 58.4, 33.9, 33.4, 32.3, 31.9, 27.6, 24.0. HRMS calculated for $[C_{17}H_{24}BrNO_2S+H]^+$: 386,0791; obtained: 386,0749.

4-(9-bromononyl) 3-(*tert*-butyl) (*R*)-thiazolidine-3,4-dicarboxylate (11)

Reagents and amounts used: Protected thiazolidinic acid **10** (2.33 g, 10.0 mmol) obtained in two steps from L-cysteine as previously described[4i,j], dry CH_2Cl_2 (20 mL), EDCI (1.91 g, 10.0 mmol), DMAP (catalytic) and 9-bromo-1-nonanol (3.35 g, 15.0 mmol). The residue was purified with column chromatography using the mixture ethyl acetate:hexane 5:95 as eluent providing a colorless oil. Yield: 63%. $[\alpha]_D^{20}$ = -56 (*c* 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, conformers mixture) δ: [4.94-4.84 (m), 4.74-4.62 (m) and 4.57 (d, *J* = 8.5), 2H], [4.48 (d, *J* = 8.8) and 4.41 (d, *J* = 8.4), 1H], 4.25-4.07 (m, 2H), 3.41 (t, *J* = 6.8, 2H), 3.38-3.14 (m, 2H), 1.85 (q, *J* = 6.9, 2H), 1.72-1.59 (m, 2H), 1.55-1.39 (m, 9H), 1.39-1.21 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, conformers mixture) δ: 170.8, 170.4, 153.2, 153.1, 81.08, 65.6, 61.6, 48.9, 48.0, 34.7, 34.0, 33.2, 32.7, 29.2, 29.0, 28.6, 28.5, 28.2, 28.1, 25.7. HRMS calculated for $[C_{18}H_{32}BrNO_4S+Na]^+$: 460.1133; obtained: 460.1146.

9-bromononyl (*R*)-thiazolidine-4-carboxylate (12)

A round-bottomed flask was charged with the protected compound **11** (2.7 g, 6.27 mmol) and TFA:CH_2Cl_2 1:1 solution (20 mL). The reaction was monitored by thin layer chromatography and was completed in 10 minutes. The solvent was evaporated. To the residue was added water and the pH was adjusted to 8 by the addition of $NaHCO_3$. The product was extracted with 3 x 5 mL of CH_2Cl_2, the organic layer was dried over $MgSO_4$ and the solvent was evaporated providing an yellow oil without further purification. Yield: 99%. $[\alpha]_D^{20}$ = -52 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.39 (d, *J* = 9.6, 1H), 4.18 (t, *J* = 6.7, 2H), 4.12 (d, *J* = 9.6, 1H), 3.83 (t, *J* = 7.6, 2H), 3.41 (t, *J* = 6.8, 2H), 3.26 (dd, *J* = 7.2 and 10.4, 1H), 2.87 (dd, *J* = 7.9 and 10.4, 1H), 2.33 (s, 1H), 1.85 (q, *J* = 7.1, 2H), 1.66 (q, *J* = 7.0, 2H), 1.49-1.38 (m, 2H), 1.38-1.27 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 65.6, 65.3, 54.4, 37.0, 33.9, 32.7, 29.2, 29.0, 28.6, 28.4, 28.1, 25.7. HRMS calculated for $[C_{13}H_{24}BrNO_2S+H]^+$: 338,0791; obtained: 338,0816.

General procedure to generate the ionic species containing imidazolium cation

A round-bottomed flask, equipped with reflux condenser, was charged with the bromide, acetonitrile and 1,2-dimethylimidazole. This solution was stirred at 60 °C for 24 hours. Then, the solvent was evaporated and the yellow oil was dried under vacuum.

1-{(*R*,*R*')-bis-[2-(*N*-benzyl-*N*-methylamino)-3-hexanoate-propyl]dissulfide}-2,3-dimethylimidazolium bromide (1a)

Reagents and amounts used: Bromide **7** (0.36 g, 0.46 mmol), 1,2-dimethylimidazole (0.18 g, 1.84 mmol) and acetonitrile (10 mL). The yellow oil obtained consist of a mixture of the ionic product and the unreacted 1,2-dimethylimidazole in the proportion of 1:1.1 (ionic product: 1,2-dimethylimidazole) calculated by ^{1}H NMR. Yield: >99%. $[\alpha]_D^{20}$ = +13 (*c* 1.0, MeOH). *Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 2.0, 2H), 7.64 (d, *J* = 1.8, 2H), 7.42-7.15 (m, 10H), 4.37-4,14 (m, 8H), 3.98 (s, 6H), 3.67 (quart, *J* = 13.6, 4H), 3.28-3.17 (m, 2H), 3.03 (dd, *J* = 6.9 and 13.2, 2H), 2.79 (s, 6H), 2.74 (dd, *J* = 7.4 and 13.2, 2H), 2.39-2.31 (m, 4H), 2.24 (s, 6H), 1.85 (q, *J* = 7.4, 4H), 1.65 (q, *J* = 7.4, 4H), 1.50-1.36 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 143.7, 139.3, 128.6, 128.2, 126.4, 122.9, 121.3, 62.6, 60.5, 58.5, 48.6, 38.3, 37.1, 36.1, 33.8, 29.6, 25.7, 24.1, 10.9. *1,2-dimethylimidazole unreacted: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.81 (d, *J* = 1.1, 1H), 3.57 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 127.0, 120.4, 32.8, 12.8. HRMS calculated for cation $[C_{44}H_{66}N_6O_4S_2]^{2+}$: 403,2288; obtained: 403,2292. HRMS calculated for anion $[Br]^-$: 78,9189; obtained: 78,9154.

1-[(4*R*)-3-benzyl-thiazolidin-4-yl-methylhexanoate]-2,3-dimethylimidazolium bromide (3a)

Reagents and amounts used: Bromide **9** (0.04 g, 0.11 mmol), 1,2-dimethylimidazole (0.02 g, 0.23 mmol) and acetonitrile (2 mL). The yellow oil obtained consist of a mixture of the ionic product and the unreacted 1,2-dimethylimidazole in the proportion of 1:1 (ionic product: 1,2-dimethylimidazole) calculated by ^{1}H NMR. The mixture of the compound **3a** with 1,2-dimethylimidazole was solubilized in 2 mL of water and washed with ethyl ether (6 x 3 mL) to remove the 1,2-dimethylimidazole unreacted. Then, **3a** was extracted with CH_2Cl_2 and the solvent was evaporated providing and yellow oil consisting in a mixture of ionic product:1,2-dimethylimidazole 1:0,15 calculated by ^{1}H NMR. Yield: 99%. $[\alpha]_D^{20}$ = -37 (*c* 0.7, CH_2Cl_2). *Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 2.0, 1H), 7.56 (d, *J* = 2.0, 1H), 7.38-7.24 (m, 5H), 4.24 (t, *J* = 7.4, 2H), 4.13 (d, *J* = 10.1, 1H), 4.07 (dd, *J* = 7.5 and 11.2, 1H), 4.00 (s, 3H), 3.99 (d, *J* = 10.0, 1H), 3.87 (dd, *J* = 6.7 and 11.2, 1H), 3.73-3.65 (m, 1H), 3.67 (d, *J* = 13.3, 1H), 3.58 (d, *J* = 13.0 1H), 3.09 (dd, *J* = 6.8 and 10.9, 1H), 2.80 (s, 3H), 2.77 (dd, *J* = 2.4 and 10.9, 1H), 2.34 (t, *J* = 7.3, 2H), 1.92-1.80 (m, 2H), 1.70-1.59 (m, 2H), 1.46-1.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 143.9, 138.5, 128.9, 128.6, 127.6, 123.2, 121.4, 67.2, 64.2, 58.8, 58.6, 48.8, 36.3, 33.8, 32.1, 29.7, 25.9, 24.2, 11.1. *1,2-dimethylimidazole unreacted: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.89-6.86 (m, 1H), 6.81-6.78 (m, 1H), 3.56 (s, 3H), 2.37 (s, 3H). HRMS calculated for cation $[C_{22}H_{32}N_3O_2S]^+$: 402,2210; obtained: 402,2239.

1-(nonyl (*R*)-thiazolidine-4-carboxylate)-2,3-dimethylimidazolium bromide (4a)

Reagents and amounts used: Bromide **12** (2.09 g, 6,17 mmol), 1,2-dimethylimidazole (1.19 g, 12.3 mmol) and acetonitrile (50 mL). The yellow oil obtained consist of a mixture of the ionic product and the unreacted 1,2-dimethylimidazole in the proportion of 1:1 (ionic product: 1,2-dimethylimidazole) calculated by ^{1}H NMR. Yield: >99%. $[\alpha]_D^{20}$ = -36 (*c* 0.4, CH_2Cl_2). *Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 2.0, 1H), 7.58 (d, *J* = 2.1, 1H), 4.36 (d, *J* = 9.5, 1H), 4.24 (t, *J* = 7.5, 2H), 4.16 (t, *J* = 6.7, 2H), 4.12 (d, *J* = 9.5, 1H), 4.03 (s, 3H), 3.90 (t, *J* = 7.3, 1H),

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3.24 (dd, *J* = 7.2 and 10.3, 1H), 2.89 (dd, *J* = 7.4 and 10.3, 1H), 2.82 (s, 3H), 1.88-1.78 (m, 2H), 1.71-1.60 (m, 2H), 1.42-1.23 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 143.6, 123.0, 121.1, 65.5, 65.3, 54.4, 48.9, 36.9, 36.1, 29.8, 29.1, 28.9, 28.9, 28.4, 26.2, 25.6, 10.9. *1,2-dimethylimidazole unreacted: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (d, *J* = 1.3, 1H), 6.90 (d, *J* = 1.1, 1H), 3.65 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.8, 126.8, 120.3, 32.7, 12.8. HRMS calculated for cation $[C_{18}H_{32}N_3O_2S]^+$: 354,2210; obtained: 354,2258.

{(*R*,*R*')-bis-[2-(*N*-benzyl-*N*-methylamino)-3-hexanoate-propyl]dissulfide} pyridinium bromide (2a)

In a round-bottomed flask, equipped with reflux condenser, was added the bromide **7** (0.15 g, 0.20 mmol) and 2 mL of pyridine (used as reagent and solvent). This solution was stirred at 65 °C for 24 hours. Then, was added 10 mL of toluene to precipitate the product as brown oil. The supernatant solvent was pipetted. The oil was solubilized in methanol and the purification procedure by addition of toluene was repeated two more times. The brown oil was dried under vacuum. Yield: >99%. $[\alpha]_D^{20}$ = +12 (*c* 0.9, MeOH). ^{1}H NMR (500 MHz, methanol-d_4) δ: 9.04 (d, *J* = 6.1, 4H), 8.63 (d, *J* = 7.8, 2H), 8.14 (t, *J* = 7.0, 4H), 7.37 (d, *J* = 7.3, 4H), 7.31 (t, *J* = 7.5, 4H), 7.24 (t, *J* = 6.6, 2H), 4.68 (t, *J* = 7.5, 4H), 4.37 (dd, *J* = 11.6 and 7.2, 2H), 4.26 (dd, *J* = 11.6 and 4.5, 2H), 3.72 (s, 4H), 3.23-3.30 (m, 2H), 3.10 (dd, *J* = 13.4 and 6.4, 2H), 2.77 (dd, *J* = 13.4 and 7.8, 2H), 2.44 (t, *J* = 7.3, 4H), 2.28 (s, 6H), 2.12-2.03 (m, 4H), 1.78-1.69 (m, 4H), 1.51-1.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.3, 145.5, 144.5, 139.3, 128.5, 128.1, 127.9, 126.7, 62.3, 61.4, 60.4, 58.1, 37.0, 36.1, 33.2, 30.7, 25.1, 23.8. HRMS calculated for cation $[C_{44}H_{60}N_4O_4S_2]^{2+}$: 386,2022; obtained: 386,2062. HRMS calculated for anion $[Br]^-$: 78,9189; obtained: 78,9146.

1-{(*R*,*R*')-bis-[2-(*N*-benzyl-*N*-methylamino)-3-hexanoate-propyl]dissulfide}-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (1b)

The mixture of the compound **1a** with 1,2-dimethylimidazole was solubilized in 2 mL of water and washed with CH_2Cl_2 (5 x 2 mL) to remove the 1,2-dimethylimidazole unreacted. Considering that the entire starting amount of the compound **1a** was maintained in the aqueous layer (0.46 mmol), $LiN(Tf)_2$ (0.26 g, 0.92 mmol) was added and this solution was stirred at room temperature for 12 hours. The precipitation of the product as a yellow oil was observed. The product was extracted with CH_2Cl_2 (3 x 3 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated. Yield: 91%. $[\alpha]_D^{20}$ = +3.9 (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.61 (d, *J* = 2.1, 2H), 7.58 (d, *J* = 2.1, 2H), 7.40-7.19 (m, 10H), 4.37 (dd, *J* = 7.2 and 11.6, 2H), 4.28 (t, *J* = 7.5, 4H), 4.22 (dd, *J* = 4.6 e 11.6, 2H), 3.93 (s, 6H), 3.76 (d, *J* = 13.6, 4H), 3.71 (d, *J* = 13.6, 4H), 3.33-3.25 (m, 2H), 3.18 (dd, *J* = 7.1 and 13.1, 2H), 2.85 (dd, *J* = 7.2 and 13.1, 2H), 2.76 (s, 6H), 2.39 (t, *J* = 7.4, 4H), 2.25 (s, 6H), 1.95 (q, *J* = 7.6, 4H), 1.68 (q, *J* = 7.5, 4H), 1.45 (q, *J* = 7.7, 4H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 172.5, 144.7, 139.8, 128.5, 128.1, 126.8, 122.5, 120.9, 120.11 (quart, *J* = 321, CF_3), 62.2, 60.9, 58.1, 48.0, 37.6, 36.4, 34.6, 33.5, 29.2, 25.5, 24.1, 8.8. HRMS calculated for cation $[C_{44}H_{66}N_6O_4S_2]^{2+}$ = 403,2288; obtained = 403,2286. HRMS calculated for anion $[C_2F_6NO_4S_2]^-$ = 279,9178; obtained: 279,9181.

1-[(4*R*)-3-benzyl-thiazolidin-4-yl-methylhexanoate]-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (3b)

A round-bottomed flask was charged with **3a** (0.10 g, 0.21 mmol), $LiN(Tf)_2$ (0.12 g, 0.42 mmol) and 5 mL of water. This solution was stirred at room temperature for 12 hours. The precipitation of the product as a yellow oil was observed. The product was extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated. After this reaction no unreacted 1,2-dimethylimidazole was observed in ^{1}H NMR analysis. Yield: 92%. $[\alpha]_D^{20}$ = -8.0 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCL_3$) δ: 7.36-7.23 (m, 5H), 7.17 (d, *J* = 2.2, 1H), 7.16 (d, *J* = 2.2, 1H), 4.11 (d, *J* = 10.1, 1H), 4.09-3.94 (m, 4H), 3.85 (dd, *J* = 6.7 and 11.2, 1H), 3.76 (s, 3H), 3.71-3.64 (m, 1H), 3.65 (d, *J* = 13.4, 1H), 3.56 (d, *J* = 13.4, 1H), 3.07 (dd, *J* = 6.8 and 10.9, 1H), 2.75 (dd, *J* = 2.5 and 10.9, 1H), 2.56 (s, 3H), 2.32 (t, *J* = 7.4, 2H), 1.84-1.74 (m, 2H), 1.68-1.58 (m, 2H), 1.41-1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 143.7, 138.4, 128.8, 128.4, 127.4, 122.5, 120.8, 119.7 (quart, *J* = 321.4, CF_3), 67.0, 64.0, 58.6, 58.4, 48.4, 35.2, 33.4, 31.8, 29.1, 25.6, 23.9, 9.5. HRMS calculated for cation $[C_{22}H_{32}N_3O_2S]^+$:402,2210; obtained: 402,2238. HRMS calculated for anion $[C_2F_6NO_4S_2]^-$: 279,9178; obtained: 279,9143.

1-(nonyl(*R*)-thiazolidine-4-carboxylate)-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (4b)

The mixture of the compound **4a** with 1,2-dimethylimidazole was solubilized in 5 mL of water and washed with ethyl ether (6 x 10 mL) to remove the 1,2-dimethylimidazole unreacted. Considering that the entire starting amount of the compound **4a** was maintained in the aqueous layer (0.29 g; 0.65 mmol), $LiN(Tf)_2$ (0.13 g; 1.31 mmol) was added and this solution was stirred at room temperature for 12 hours. The precipitation of the product as a yellow oil was observed. The product was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated. After this reaction, the ratio of ionic product:1,2-dimethylimidazole varied from 1:0.4 to 1:0,25. Yield: 78-85%. $[\alpha]_D^{20}$ = -20 (*c* 0.1, DCM). *Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 2.2, 1H), 7.18 (d, *J* = 2.1, 1H), 4.37 (d, *J* = 9.6, 1H), 4.17 (td, *J* = 6.7 and 1.0, 2H), 4.12 (d, *J* = 9.6, 1H), 4.04 (t, *J* = 7.6, 2H), 3.86 (t, *J* = 7.4, 1H), 3.8 (s, 3H), 3.25 (dd, *J* = 7.2 and 10.4, 1H), 2.88 (dd, *J* = 7.7 and 10.4, 1H), 2.6 (s, 3H), 1.84-1.74 (m, 2H), 1.70-1.60 (m, 2H), 1.39-1.24 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 143.7, 122.5, 120.8, 119.4 (quart, *J* = 321.3, CF_3), 65.6, 65.3, 54.4, 48.8, 37.0, 35.3, 29.5, 29.1, 28.9, 28.8, 28.4, 26.2, 25.7, 9.5. *1,2-dimethylimidazole unreacted: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (d, *J* = 1.7, 1H), 7.01 (d, *J* = 1.7, 1H), 3.7 (s, 3H), 2.5 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.8, 124.9, 120.9, 33.1, 12.3. HRMS calculated for cation $[C_{18}H_{32}N_3O_2S]^+$: 354,2210; obtained: 354,2247.

General procedure for asymmetric addition of diethylzinc to aldehydes

A Schlenk tube was charged with the ionic ligand (5-20 mol%) and the ionic solvent (0.25 mL). The ionic compounds were dried under vacuum, heating at 60 °C and stirring for 5 hours. Then, under argon atmosphere, at 0 °C, 0.25 mL of dried toluene (when toluene extra was used), 0.5-1 mmol of diethylzinc (1,5 mol.L^{-1} in toluene, added dropwise) and the aldehyde (0.25 mmol) were added. The mixture was stirred at desired temperature for 24-72 hours. At the end of the reaction time, $HCl_{(aq)}$ 1 mol.L^{-1}, NH_4Cl_{sat}, oxalic acid in acetone or methanol were added. In the case of aqueous solutions ($HCl_{(aq)}$ and NH_4Cl_{sat}) the organic compounds, including the ionic liquids, were separated from the aqueous layer with CH_2Cl_2, dried with $MgSO_4$ and the solvent was evaporated. In the case of oxalic acid in acetone (1:1 oxalic acid:Et_2Zn) and methanol, CH_2Cl_2 was added to aid the precipitation of inorganic zinc compounds, the solutions were filtered and the solvents were evaporated. In all cases, the product was extracted from the ionic layer with a mixture of 0,5 mL of CH_2Cl_2 and 4 mL of hexane. For this, 0,5 mL of CH_2Cl_2 was added to dilute the ionic liquid. Then, hexane was added under stirring and the stirring was continued for 15 minutes. The system was rested in the refrigerator for 10 minutes and the supernatant (containing the product and the other nonionic compounds) was pipetted. This procedure was carried out until

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there was no more product to be extracted (verified by thin-layer chromatography). The organic solvent was evaporated and the products were purified with column chromatography. In the case of reaction carried out in conventional solvent (CH_2Cl_2) the drying step of the ionic compounds for 5 hours under stirring, heating and vacuum was not carried out. The quench of this reaction was carried out with NH_4Cl_{sat} and CH_2Cl_2 was used to the extraction of the product.
The racemic standards were prepared with typical Grignard protocol.

Recycling procedure

It was used the general procedure for asymmetric addition of diethylzinc to aldehydes in ionic liquids described above, modifying only the extraction method to enable recycling. Reactive conditions used: benzaldehyde:Et_2Zn:**1b**:BPy.N(Tf_2):toluene (0.25 mmol:0.5 mmol:0.0125 mmol:0.25 mL:0.25 mL), 0 °C, 72 hours. At the end of the reaction time, at 0 ° C, 2 mL of methanol were added and this mixture was stirred and bubbled with compressed air for 1 hour to oxidize the ionic ligand to their disulfide form. The formed solid was removed by filtration and CH_2Cl_2 was used to wash the solid and the filter. The conventional solvents (methanol and CH_2Cl_2) were completely evaporated. From the remaining material (containing the ionic and nonionic organic compounds) the nonionic compounds were extracted with hexane. For this, 2 mL of hexane were added under stirring and the stirring was continued for 15 minutes. The system was rested in the refrigerator for 10 minutes and the supernatant (containing the product and the other nonionic compounds) was pipetted. This procedure was carried out until there was no more product to be extracted (verified by thin-layer chromatography), 10 times on average. The organic solvent (hexane) was evaporated and the product was purified with column chromatography. To recycling the ionic solvent and the ionic ligand, after each catalytic cycle these compounds were dried under vacuum, heating at 60 °C and stirring for 5 hours and a new charge of benzaldehyde, diethylzinc and dried toluene were added and a new catalytic cycle was performed.

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Keywords: ionic liquids • asymmetric catalysis • amino acids • diethylzinc • L-cysteine

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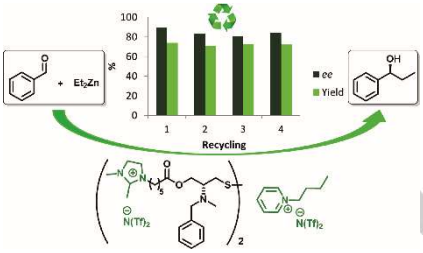

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