Amino Acids (2008) 35: 175–184
DOI 10.1007/s00726-007-0575-3
Printed in The Netherlands

Amino Acids

Thiazolinium and imidazolium chiral ionic liquids derived from natural amino acid derivatives

D. Brégeon[1], **J. Levillain**[1], **F. Guillen**[2], **J.-C. Plaquevent**[2], and **A.-C. Gaumont**[1]

[1] Laboratoire de Chimie Moléculaire et Thioorganique, ENSICAEN, Université de Caen Basse-Normandie, CNRS, Caen, France
[2] UMR-CNRS, IRCOF, rue Tesnière, Rouen, France

Received March 5, 2007
Accepted June 18, 2007
Published online October 2, 2007;

Summary. Starting from commercially available amino acid derivatives, two novel families of chiral ionic liquids having either a thiazolinium or an imidazolium cation were prepared by simple and straightforward procedures in good overall yields. The properties of these new salts can be finely tuned by careful selection of the anion and the cation.

Keywords: Amino acid derivatives – Chiral ionic liquids – Thiazolinium salts – Imidazolium salts

Introduction

The last few years have witnessed a growing interest in research involving room temperature ionic liquids (RTILs), mainly because of their potential to replace volatile organic solvents (VOCs) (Rogers et al., 2002; Wasserscheid and Welton, 2003). In view of the importance of these new media in organic synthesis, several groups have recently focused their attention to chiral ionic liquids (CILs), which could constitute a renewal for the chemistry in chiral solvents (Baudequin et al., 2003, 2005; Ding and Armstrong, 2005). Application of chiral ionic liquids in chirality transfer is not only an opportunity but also a challenge for researchers. Although only a few studies dealing with the use of CILs have been reported until now, the various fields in which they found applications testify to their importance [chromatography (Ding et al., 2004), enantioselective synthesis (Kiss et al., 2003; Pégot et al., 2004; Wang et al., 2005; Branco et al., 2006; Gausepohl et al., 2006; Malhotra and Wang, 2006), kinetic resolution (Kitazume, 2001), polymerization reactions (Biedron and Kubisa, 2003; Ma et al., 2003), chiral recognition (Wasserscheid and Keim, 2000; Zhao et al., 2002; Levillain et al., 2003; Clavier et al., 2004)].

Indeed, a series of seminal successes regarding asymmetric induction promoted by CILs used as solvents were disclosed last year. Branco et al. (2006) prepared new guanidinium salts having a chiral counter-anion. Their use in the enantioselective Sharpless dihydroxylation led to high asymmetric inductions (up to 85% ee). Malhotra and Wang (2006) described the copper catalyzed enantioselective addition of diethylzinc to enones in the presence of CILs derived from α-pinene. Again, a rather high induction was reported (ca. 76% ee). Finally, a conceptually rich approach led Gausepohl et al. (2006) to design a family of bifunctional CILs in the series of ammonium dimalatoborates. When carried out in these CILs, the aza-Baylis-Hilmann reaction was performed with ee as high as 84%. For the first time in the continuing history of asymmetric synthesis, this fascinating series of results demonstrated that, contrarily to popular point of view, the application of chiral solvents (or chiral reaction media) in enantioselective synthesis could be successful!

The interest in CILs in asymmetric synthesis also stands in the use of immobilized chiral catalysts, which belong to the class of TSILs (task specific ionic liquids). For example, among a wide family of structures, one can highlight proline derivatives that were described by Luo et al., in 2006. They were reported to be highly efficient in the Michael additions to nitroolefins.

Nowadays, there is no place for doubt that CILs are promised to be a conceptually new class of chiral auxiliaries and catalysts (and/or solvents) that will induce asymmetry with efficiency in classical enantioselective reactions, but also, owing to their peculiar physico-chem-

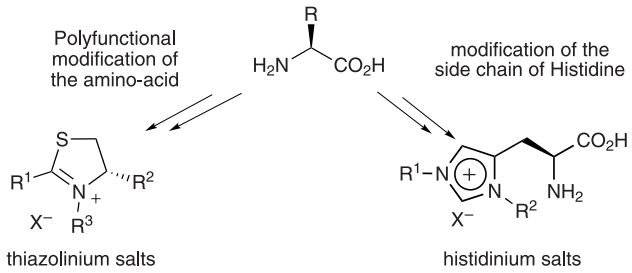


Fig. 1. Thiazolinium and histidinium salts from amino acids

ical properties, in novel applications. In this context, we believe that the construction of various CILs is a topic of main importance.

There are two main strategies to access to chiral ionic liquids: asymmetric synthesis or use of a chiral starting material. This last strategy is highly desirable for both economy and simplicity. As far as the chiral pool is involved, amino acid derivatives are the substrates of choice. The CILs can result from modification of both the amino and the acid functions, from modification of only one function or from alteration of the side chain of an amino acid, thus preserving both functions (Baudequin et al., 2005). We wish to report the synthesis and properties of two series of structurally distinct, enantiomerically pure chiral ionic liquids starting from amino acid derivatives, either by polyfunctional modification or by modification of the side chain (Fig. 1). The preliminary work on these two series has been reported elsewhere (Levillain et al., 2003; Guillen et al., 2006). Herein, we report the detailed synthesis and properties of these new CILs.

Materials and methods

General experimental

THF, CH_2Cl_2 and acetonitrile were purified using an *Innitiative Technologie PURESOL*™ apparatus developed by Innovative Technology Inc. Pentane was dried over CaH_2. All the commercially available starting materials were used as received. The dithioester **1** was prepared according to literature procedure (Westmijze et al., 1979). Thiazolines were prepared according to literature procedure (Abrunhosa et al., 2001).

The NMR spectra were recorded on a *Bruker AC 250* or a *Bruker AC 400* spectrometer. The chemical shifts δ are expressed in ppm, conventional abbreviations are used for the coupling constants (*J*), which are expressed in Hz. The ^1H and ^{19}F NMR spectra for NMR recognition experiments were obtained from a *Bruker AC* 400 MHz instrument. FT-IR spectra were registered with a *Perkin Elmer 16 PC FT-IR* infrared spectrometer. Optical rotation values were measured on a *Perkin-Elmer 241 Polarimeter* for the sodium D line at 20 °C. HRMS were recorded on a *Varian Matt 311 spectrometer* in electronic-impact mode at 70 eV. DSC measurement were performed on *a Perkin-Elmer DSC7* apparatus. TGA analysis were done on *Perkin-Elmer TGA7* apparatus. Elemental analysis were obtained from a *Thermoquest NA 2500* CHNS-O instrument.

*Preparation of (S)-4-benzyl-2-isopropyl-2-thiazoline (**3**)*

To a stirred mixture of the corresponding thioamide (2.62 g, 11 mmol) and mesylchloride (1.90 g, 16.6 mmol) in dichloromethane (20 ml) was added dropwise triethylamine (4.6 ml, 33 mmol) at room temperature. Stirring was maintained for 10 min, then water (20 ml) was added and the mixture was extracted with dichloromethane (2 × 20 ml). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by chromatography on silica gel (pentane/diethylether, 50/50) to provide thiazoline **3** as a yellow oil (2.4 g, 10.9 mmol, 96%). $[\alpha]_D^{20} = -54.7$ (c = 1.5 in $CHCl_3$); IR (NaCl): ν = 3010, 2960, 2920, 2850, 1640, 1490, 1450, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 2.70 (dd, *J* = 13.6, 9.3 Hz, 1H), 2.82 (sept, *J* = 6.9 Hz, 1H), 3.00 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.18 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.19 (dd, *J* = 13.6, 4.8 Hz, 1H), 4.72 (m, 1H), 7.24 (m, 5H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.3, 34.1, 36.8, 40.3, 78.0, 126.6, 128.6, 129.5, 138.7, 176.7 ppm; HRMS for $C_{13}H_{17}NS$, calcd: M^+ 219.1082, found: 219.1099.

General procedure for preparation of thiazolinium iodide salts

In a flammed round-bottomed flask under nitrogen, a solution of thiazoline **3** (1.09 g, 5 mmol) in alkyl iodide (15 mmol) is stirred at 70 °C during 48 h (100 °C during 7 days for compound **8a**). After concentration under reduced pressure, the crude product is washed successively with pentane and diethylether. The resulting powder is recrystallized from ethyl acetate/acetonitrile to afford pure compound.

(*S*)-4-Benzyl-3-butyl-2-isopropyl-2-thiazolinium iodide (**6a**)

White powder (1.35 g, 3.35 mmol, 67%). $[\alpha]_D^{20} = +33$ (c = 1 in acetone); mp 172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.44–1.5 (m, 2H), 1.78–1.90 (m, 1H), 1.95–2.06 (m, 1H), 3.21 (dd, *J* = 14, 8.6 Hz, 1H), 3.32–3.38 (m, 2H), 3.47 (dd, *J* = 12, 3.5 Hz, 1H), 3.82–3.90 (m, 1H), 4.00–4.13 (m, 1H), 4.14 (dd, *J* = 12, 9.5 Hz, 1H), 5.53–5.60 (m, 1H), 7.28–7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 20.2, 21.8, 22.2, 30.9, 32.1, 33.8, 36.8, 51.6, 73.2, 128.0, 129.3, 129.6, 133.8, 200.5 ppm; Anal. calcd. for $C_{17}H_{26}INS$: C, 50.62; H, 6.50; S, 7.95. Found: C, 50.76; H, 6.39; S, 8.35.

(*S*)-4-Benzyl-3-ethyl-2-isopropyl-2-thiazolinium iodide (**7a**)

White crystals (1.29 g, 3.44 mmol, 69%). $[\alpha]_D^{20} = -19$ (c = 1 in $CHCl_3$); mp 175 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 6.7 Hz, 3H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.59 (t, *J* = 7.3 Hz, 3H), 3.16 (dd, *J* = 14, 8.4 Hz, 1H), 3.32 (dd, *J* = 14, 4.6 Hz, 1H), 3.45 (m, 2H), 3.98 (dq, *J* = 7.2, 14.6 Hz, 1H), 4.12 (dd, *J* = 9.6, 12.0 Hz, 1H), 4.26 (dq, *J* = 7.2, 14.6 Hz, 1H), 5.50–5.60 (m, 1H), 7.25–7.40 (m, 5H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.9, 21.6, 22.3, 32.1, 33.6, 36.7, 47.1, 72.8, 128.1, 129.4, 129.6, 133.7, 200.6 ppm; Anal. calcd. for $C_{15}H_{22}INS$: C, 48.00; H, 5.91; S, 8.54. Found: C, 48.25; H, 6.14; S, 8.61.

(*S*)-4-Benzyl-3-dodecyl-2-isopropyl-2-thiazolinium iodide (**8a**)

White crystals (0.376 g, 0.97 mmol, 25%); $[\alpha]_D^{20} = +33.7$ (c = 1.025 in acetone); mp 114 °C; ^1H NMR (400 MHz, CD_3CN): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.20–1.40 (m, 18H), 1.65–1.80 (m, 1H), 1.85–1.95 (m, 1H), 3.06 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.22 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.31 (sept, *J* = 6.7 Hz, 1H), 3.40 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.65–3.75 (m, 2H), 3.90–4.00 (m, 1H), 5.00–5.15 (m, 1H), 7.30–7.40 (m, 5H) ppm; ^{13}C NMR (100 MHz, CD_3CN): δ = 14.2, 21.8, 22.3, 22.7, 26.9, 29.0, 29.1, 29.4, 29.5, 29.6, 29.7, 32.0, 32.1, 33.9, 36.8, 52.0, 73.3, 128.0, 129.4, 129.6, 133.8, 177.7, 200.3 ppm; HRMS for $C_{25}H_{42}NS$, calcd: M^+ 388.3030, found: M^+ 388.3038.

General procedure for the preparation of thiazolinium hexafluorophosphate and tetrafluoroborate salts

To a cold solution of thiazolinium iodide (2.9 mmol) in water (2 ml) was added a 60% aqueous solution of hexafluorophosphoric acid (60%) (325 µl, 4.4 mmol) or a 34% aqueous solution of tetrafluoroboric acid (462 µl, 4.4 mmol). The mixture was stirred at room temperature for 16 h. Then, the aqueous layer was removed. The crude product was diluted in dichloromethane (2 ml), washed with 3 × 1 ml of water, then with 3 × 1 ml of 1N aqueous sodium thiosulfate. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure then washed with diethyl ether. Then the crude product was purified on silica gel by chromatography or by recrystallization in ethyl acetate/acetonitrile yielding **4b** as white crystals (0.937 g, 2.61 mmol, 90%). $[\alpha]_D^{20} = -35.6$ (c = 1 in acetone); mp 130 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3H), 1.05 (t, *J* = 7.4 Hz, 3H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.30–1.50 (m, 2H), 1.60–2.00 (m, 4H), 3.27 (sept, *J* = 6,9 Hz, 1H), 3.37 (dd, *J* = 4, 12 Hz, 1H), 3.70–3.80 (m, 1H), 3.84–3.95 (m, 2H), 4.70–4.90 (m, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.7, 13.4, 19.9, 21.5, 21.6, 23.6, 30.1, 31.8, 49.8, 73.5, 200.1 ppm; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ = −73.35 (d, *J* = 712.4 Hz) ppm; ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = −139.7 (sept, *J* = 712.4 Hz) ppm. Anal. Calcd. for $C_{12}H_{24}F_6NPS$: C, 40.11; H, 6.73; N, 3.90; S, 8.92. Found: C, 39.93; H, 7.40; N, 3.99; S, 8.50. HRMS for the ionisation cluster $2M + PF_6$ ($C_{24}H_{48}N_2F_6PS_2$), calcd: 573.2900, found: 573.2900.

(*R*)-3-butyl-4-ethyl-2-isopropyl-2-thiazolinium tetrafluoroborate (**4d**)

Recrystallization in ethyl acetate/acetonitrile yielded **4d** as a white solid (0.794 g, 2.64 mmol, 91%). $[\alpha]_D^{20} = -32.5$ (c = 1 in acetone); mp 105 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.38–1.52 (m, 2H), 1.70–2.02 (m, 4H), 3.30 (sept, *J* = 6.8 Hz, 1H), 3.37 (dd, *J* = 4.7, 11.9 Hz, 1H), 3.69–4.00 (m, 2H), 4.03 (dd, *J* = 9.7, 11.9 Hz, 1H), 4.96–5.07 (m, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.6, 13.3, 19.8, 21.5, 21.6, 23.6, 30.0, 31.6, 32.2, 50.0, 73.4, 199.7 ppm; ^{19}F NMR (235.35 MHz, $CDCl_3$): δ = −153.1 ppm. HRMS for $C_{12}H_{24}NS$, calcd: 214.1637, found: 214.1629. HRMS for the ionisation cluster $2M + BF_4$ ($C_{24}H_{48}N_2F_4BS_2$), calcd: 515.3288, found: 515.3284.

(*S*)-4-benzyl-3-butyl-2-isopropyl-2-thiazolinium hexafluorophosphate (**6b**)

Purification by chromatography on silica gel (CH_2Cl_2/acetone, 90/10) yielded **6b** as a white solid (0.948 g, 1.97 mmol, 68%). $[\alpha]_D^{20} = +34$ (c = 1 in acetone); mp 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.35 (d, *J* = 6.7 Hz, 3H), 1.30–1.45 (m, 2H), 1.60–1.85 (m, 2H), 1.85–2.00 (m, 1H), 3.08 (dd, *J* = 14.1, 8.3 Hz, 1H), 3.21–3.32 (m, 2H), 3.39 (dd, *J* = 12.2, 3.6 Hz, 1H), 3.62–3.70 (m, 1H), 3.74 (dd, *J* = 12.2, 9.4 Hz, 1H), 3.90–3.98 (m, 1H), 5.06–5.13 (m, 1H), 7.22–7.36 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.0, 21.3, 21.9, 30.3, 31.9, 32.6, 36.4, 50.5, 72.9, 128.1, 129.4, 129.5, 133.8, 201.0 ppm; ^{19}F NMR (235.31 MHz, CD_3CN): δ = 98.19 (6F, d, *J* = 712 Hz) ppm; ^{31}P NMR (101.25 MHz, CD_3CN): δ = −143.2 (1P, sept, *J* = 712 Hz) ppm. HRMS for $C_{17}H_{26}NS$, calcd: 276.1786, found: *M* 276.1791. HRMS for the ionisation cluster $2M + PF_6$ ($C_{34}H_{52}N_2F_6PS_2$), calcd: 697.3214, found: 697.3198.

General procedure for the preparation of 2-substituted thiazolinium bis(trifluoromethanesulfonyl)imide

To a solution of thiazolinium iodide or bromide (1 mmol) in dichloromethane (5 ml) was added lithium bis(trifluoromethanesulfonyl) imide (287 mg, 1 mmol). The resulting suspension was stirred for 12 h at room temperature. The residual mixture was washed successively with water and 1N aqueous solution of sodium thiosulfate (3 × 1 ml). The organic solution was dried over anhydrous $MgSO_4$, after which the solvent was removed in vacuo. The resulting oil was purified by silica gel chromatography (CH_2Cl_2/acetone, 9/1).

(*R*)-3-dodecyl-4-ethyl-2-isopropyl-2-thiazolinium bis(trifluoromethanesulfonyl)imide (**5c**)

Yellow oil (0.509 g, 0.84 mmol, 84%). $[\alpha]_D^{20} = -36.7$ (c = 1 in acetone); $T_g = -68$ °C; ^{1}H NMR (400 MHz, CD_3CN): δ = 0.88 (t, *J* = 7.4 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.25–1.40 (m, 24H), 1.60–1.72 (m, 1H), 1.70–1.90 (m, 3H), 3.28 (sept, *J* = 6.7 Hz, 1H), 3.39 (dd, *J* = 4.3, 12.1 Hz, 1H), 3.55–3.65 (m, 1H), 3.73 (dd, *J* = 9.6, 12.1 Hz, 1H), 3.87 (ddd, *J* = 14, 10.4, 6.1 Hz, 1H), 4.72–4.77 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3CN): δ = 9.0, 14.5, 21.7, 21.9, 23.4, 24.1, 27.1, 28.8, 29.7, 30.1, 30.2, 30.4, 32.4, 32.7, 33.0, 50.6, 73.9, 120.9 (q, *J* = 321 Hz), 200.9 ppm. ^{19}F NMR (376.5 MHz, CD_3CN): δ = −80.48 ppm. HRMS for the ionisation cluster $2M + NTf_2$ ($C_{42}H_{80}N_3F_6O_4S_4$), calcd: 932.4945, found: 932.4936.

(*S*)-4-benzyl-3-butyl-2-isopropyl-2-thiazolinium bis(trifluoromethanesulfonyl) imide (**6c**)

Colourless oil (0.400 g, 0.72 mmol, 72%). $[\alpha]_D^{20} = +29$ (c = 1 in acetone); $T_g = -40$ °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.30–1.50 (m, 2H), 1.65–1.90 (m, 2H), 3.06 (dd, *J* = 14.1, 8.4 Hz, 1H), 3.21 (dd, *J* = 14.1, 4.4 Hz, 1H), 3.3 (sept, *J* = 6.7 Hz, 1H), 3.39 (dd, *J* = 12.3, 3 Hz, 1H), 3.68 (dd, *J* = 12.3, 9.5 Hz, 1H), 3.60–3.73 (m, 1H), 3.95 (m, 1H), 5.00–5.06 (m, 1H), 7.31–7.41 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 20.0, 21.3, 21.8, 30.4, 31.9, 32.6, 36.5, 50.6, 72.8, 120.0 (q, $J_{C\text{-}F}$ = 321 Hz), 128.2, 129.4, 129.5, 133.5, 201.1 ppm; ^{19}F NMR (235.5 MHz, $CDCl_3$): δ = −80.68 ppm; Anal. calcd. for $C_{19}H_{26}F_6N_2O_4S_3$: C, 41.00; H, 4.71; N, 5.03. Found: C, 41.01; H, 5.07; N 4.93.

(*S*)-4-benzyl-2-thiazoline (**9**)

To a solution of 5.13 g (31.8 mmol) of (*S*)-4-benzyl-2-oxazoline (Kamata et al., 1998) in 100 ml of toluene were added 10.61 g (47.7 mmol) of P_4S_{10}. The mixture was stirred vigorously under reflux for 3 h. After cooling, the reaction medium was treated with a 20% aqueous solution of NaOH. The aqueous phase was extracted with diethylether (5 × 20 ml). The combined organic layer were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by distillation and yielded the (*S*)-4-benzyl-2-thiazoline **9** as an orange oil. (3.66 g, 20.7 mmol, 66%). $[\alpha]_D^{20} = -119$ (c = 1.5 in $CHCl_3$); Bp: 130–140 °C/0.25 mbar; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (dd, *J* = 8.6, 13.7 Hz, 1H), 2.97 (dd, *J* = 7.3, 11.1 Hz, 1H), 3.18 (dd, *J* = 8.7, 11.1 Hz, 1H), 3.19 (dd, *J* = 5.9, 13.7 Hz, 1H), 4.68–4.82 (m, 1H), 7.20–7.37 (m, 5H), 7.91 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5, 40.3, 77.9, 126.7, 128.7, 129.3, 138.5, 156.1 ppm.

General procedure for the preparation of 2H-thiazolinium iodide or bromide salts

A mixture of thiazoline **9** (800 mg, 4.5 mmol) and the alkylating agent (4.95 mmol) was irradiated with microwaves at 80 °C for 10 min. The reaction mixture was then brought to room temperature and washed successively with pentane and diethylether to give the thiazolinium salt.

(*S*)-3-butyl-4-benzyl-2-thiazolinium iodide (**10a**)

(1.54 g, 4.2 mmol, 93%). $[\alpha]_D^{20} = -5.79$ (c = 0.95 in $CHCl_3$); T_g = 132 °C; IR (ATR): ν = 2958, 1614, 1492, 1453, 1261, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3H), 1.40–1.55 (m, 2H), 1.85–2.00 (m, 1H), 3.12 (dd, *J* = 8.9, 14.0 Hz, 1H), 3.32 (dd, *J* = 4.8, 14.0 Hz, 1H), 3.55 (dd, *J* = 4.3, 12.4 Hz, 1H), 3.8–3.95 (m, 1H),

4.02 (dd, $J = 9.8$, 12.4 Hz, 1H), 4.15–4.30 (m, 1H), 5.21 (m, 1H), 7.2–7.5 (m, 5H), 10.35 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_3CN): $\delta = 13.7$, 19.8, 30.3, 36.2, 36.3, 53.9, 71.5, 128.3, 129.4, 129.6, 133.6, 178.8 ppm; Anal. calcd. for $C_{14}H_{20}INS$: C, 46.54; H, 5.58; N, 3.88; S, 8.88; Found: C, 46.25; H, 5.26; N 4.32; S, 9.08.

(*S*)-3,4-dibenzyl-2-thiazolinium bromide (**10b**)

(1.49 g, 4.27 mmol, 95%). $[\alpha]_D^{20} = -14.2$ ($c = 1.0$ in $CHCl_3$); $T_g = 136\,^{\circ}C$; IR(ATR): $\nu = 3027$, 1610, 1493, 1458, 1247, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):$\delta = 2.97$ (dd, $J = 13.7$, 9.3 Hz, 1H), 3.20 (dd, $J = 13.7$, 4.7 Hz, 1H), 3.48 (dd, $J = 12.1$, 4.1 Hz, 1H), 3.73, (dd, $J = 12.1$, 9.6 Hz, 1H), 4.85–4.92 (m, 1H), 5.07 (d, $J = 14.3$ Hz, 1H), 5.75 (d, $J = 14.3$ Hz, 1H), 7.11 (d, $J = 6.6$ Hz, 2H), 7.18–7.24 (m, 3H), 7.31–7.33 (m, 3H), 10.73 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_3CN): $\delta =$ 35.9, 36.7, 57.0, 70.2, 127.8, 129.2, 129.3, 129.5, 129.6, 129.8, 131.0, 133.9, 179.6 ppm; Anal. calcd. for $C_{17}H_{28}BrNS$, 0.5 H_2O: C, 57.14; H, 5.36; S, 8.97. Found: C, 57.29; H, 5.71; S, 9.09.

(+)-(7*S*)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine (**11**)

L-Histidine methylester dihydrochloride (10 g, 41.3 mmol) and carbonyldiimidazole (7.37 g, 45.4 mmol) were heated at 80 °C with vigorous mechanical stirring under a flow of nitrogen. After 30 min, the viscous, slightly yellowish liquid obtained was hydrolysed with 10 ml of H_2O, and the aqueous phase was extracted with 5×25 ml of CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo until precipitation of a white solid. Diethylether (200 ml) was then added, and the product was filtered on a sintered glass Büchner, washed with diethylether and dried to give analytically pure **11** as a white crystalline solid (6.61 g, 33.87 mmol, 82%).$[\alpha]_D^{20} = +58$ ($c = 1.2$ in CH_3OH) [lit. (Chivikas and Hodges, 1987; Jain and Cohen, 1996) $[\alpha]_D^{25} = +59$ ($c = 1.1$ in CH_3OH)]; mp 165–167 °C (lit. (Chivikas and Hodges, 1987; Jain and Cohen, 1996); mp 167–168 °C); MS (EI), m/e 195 (*M*, 50%), 152 (100), 136 (51), 81(87); IR (KBr): $\nu = 1755$ (CO_2, Me), 1717 (NCON) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.14$ (ddd, $J = 15.7$, 8.3, 1.0 Hz, 1H), 3.34 (ddd, $J = 15.7$, 5.4, 1.0 Hz, 1H), 3.77 (s, 3H), 4.35 (dd, $J = 8.3$, 5.4 Hz, 1H), 6.68 (s (broad), 1H), 6.85 (d, $J = 1.0$ Hz, 1H), 8.12 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 23.1$ 52.7, 53.3, 123.8, 126.3, 135.2, 147.9, 169.6 ppm.

(*S*)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-2-butyl-5-oxoimidazo-[1,5-c]pyrimidinium iodide (**12b**)

To a suspension of **11** (1.95 g, 10 mmol) in acetonitrile (50 ml) was added butyl iodide (2.28 ml, 20 mmol). The reaction mixture was heated at reflux for 24 h. The mixture was cooled, and butyl iodide in excess was removed by washing with pentane. The mixture was then evaporated to dryness in vacuo. The residual solid was dissolved in CH_2Cl_2 (100 ml), washed with Na_2SO_3 1 M (2×10 ml) and water (20 ml). The aqueous layers were saturated with NaCl and extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give **12b** as a white solid (2.46 g, 6.5 mmol, 65%). ^{1}H NMR (250 MHz, D_2O): $\delta = 1.02$ (t, $J = 7.1$ Hz, 3H), 1.30–1.35 (m, 2H), 1.80–1.86 (m, 2H), 3.50–3.55 (m, 2H), 3.79 (s, 3H), 3.91 (t, $J = 7.1$, 2H), 4.70–4.75 (m, 1H), 7.41 (d, $J = 0.7$ Hz, 1H), 9.37 (s, 1H) ppm; ^{13}C NMR (63 MHz, D_2O): $\delta = 13.8$, 20.4, 22.2, 24.6, 47.0, 54.3, 54.1, 121.6, 128.9, 135.5, 147.2, 172.3 ppm.

General method for the clivage of the cyclic urea

To a solution of **12a** (5 g, 14.8 mmol) in the appropriate alcohol (50 ml) and acetonitrile (5 ml) is added diisopropylethylamine (2.6 ml, 14.8 mmol). The solution is heated at reflux for 1–6 h under argon. The solvents are removed in vacuo and the residue dissolved in ethyl acetate. The solution is washed with water, dried over $MgSO_4$ and concentrated in vacuo to afford an oil which is purified by chromatography on silica gel (CH_2Cl_2/MeOH: 9/1).

N-α-(tert-butoxycarbonyl)-1-methyl-L-histidine methyl ester (**13a**)

Colorless oil (2.89 g, 10.1 mmol, 69%); $[\alpha]_D^{20} = +13.3$ ($c = 1.35$ in $CHCl_3$); HPLC AD-H (250×4.6 mm), hexane/EtOH 50/50, 1 ml/min, 22.31 min for (*R*) and 24.13 min for (*S*). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (s, 9H), 2.99 (m, 2H), 3.58 (s, 3H), 3.66 (s, 3H), 4.51–4.45 (m, 1H), 5.89 (d, $J = 7.9$ Hz, 1H), 6.60 (s, 1H), 7.28 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 28.3$, 30.0, 33.2, 52.1, 53.5, 79.4, 117.6, 137.5, 137.6, 155.6, 172.5 ppm.

N-α-(allyloxycarbonyl)-1-methyl-L-histidine methyl ester (**13c**)

Yellow oil (2.97 g, 11.1 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 3.16 (dd, $J = 5.5$, 14.7 Hz, 1H), 3.38 (dd, $J = 3.2$, 14.7 Hz, 1H), 3.61 (s, 3H), 3.70 (s, 3H), 4.35–4.50 (m, 1H), 4.54–4.60 (m, 2H), 5.15–5.40 (m, 2H), 5.82–6.00 (m, 1H), 6.60 (s (broad), 1H), 7.34 (s (broad), 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 30.0$, 34.5, 52.4, 53.9, 65.8, 117.7, 119.1, 133.0, 136.4, 137.7, 155.7, 172.4 ppm.

N-α-(tert-butoxycarbonyl)-1-butyl-L-histidine methyl ester (**13b**)

To a solution of **12b** (2.02 g, 6.09 mmol) in the appropriate alcohol (50 ml) and acetonitrile (5 ml) was added diisopropylethylamine (1 ml, 6.09 mmol) and the solution was heated at reflux for 2.5 h under argon. The solvents were removed in vacuo and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo to afford an oil, which was purified by chromatography on silica gel (CH_2Cl_2/acetone: 7/3). Colorless oil (793 mg, 2.43 mmol, 40%). $[\alpha]_D^{20} = +6.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.94 (t, $J = 7.1$ Hz, 3H), 1.20–1.35 (m, 2H), 1.42 (s, 9H), 1.60–1.75 (m, 2H), 2.98 (dd, $J = 4.7$, 14.6 Hz, 1H), 3.07 (dd, $J = 5.3$, 14.6 Hz, 1H), 3.68 (s, 3H), 3.84 (t, $J = 7.1$ Hz, 2H), 4.45–4.55 (m, 1H), 5.92 (d broad, $J =$ 7.9 Hz, 1H, NH), 6.65 (s, 1H), 7.34 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.9$, 20.1, 28.7, 30.6, 33.3, 47.1, 52.5, 54.0, 79.7, 116.8, 136.4, 137.7, 155.6, 168.3 ppm.

General method for the synthesis of histidinium bromide salts

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-butyl-1-methyl-1H-imidazolium bromide (**14a**)

To **13a** (6 mmol) was added *n*-butylbromide (5 ml). The reaction medium was heated at 90 °C overnight. The resulting biphasic mixture was concentrated in vacuo to give an off-white foam, which was engaged in the next step without further purification. Pale pink oil (2.37 g, 5.64 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.3$ Hz, 3H), 1.40 (s, 9H), 1.33–1.47 (m, 2H), 1.70–1.95 (m, 2H), 3.15–3.35 (m, 2H), 3.79 (s, 3H), 4.03 (s, 3H), 4.10–4.30 (m, 2H), 4.50–4.65 (m, 1H), 5.75–5.90 (m, 1H, NH), 7.28 (s, 1H), 10.24 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.6$, 19.7, 26.4, 28.3, 32.2, 36.7, 47.3, 52.3, 53.3, 80.9, 121.4, 131.0, 137.6, 155.6, 170.9 ppm.

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-1-butyl-3-methyl-1H-imidazol-3-ium iodide (**14b**)

To a solution of **13c** (1 mmol) in acetonitrile (10 ml) was added methyliodide (0.31 ml, 5 mmol). The reaction medium was heated under nitrogen at 40 °C overnight. The resulting mixture was concentrated in vacuo to give an off-white foam, which was engaged in the next step without further purification. Yellow solid (420 mg, 0.9 mmol, 90%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.38 (s, 9H), 1.30–1.42 (m, 2H), 1.80–1.91 (m, 2H), 3.11 (dd, *J* = 9.0, 15.8 Hz, 1H), 3.25 (dd, *J* = 4.7, 15.8 Hz, 1H), 3.77 (s, 3H), 3.96 (s, 3H), 4.20 (t, *J* = 7.3 Hz, 2H), 4.50–4.60 (m, 1H), 5.59 (d, *J* = 7.7 Hz, 1H, NH), 7.18 (s, 1H), 9.97 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.4, 19.4, 27.5, 28.1, 31.9, 34.4, 49.8, 51.9, 53.2, 80.8, 119.9, 131.6, 136.8, 155.4, 170.6 ppm.

Representative procedure for the anion exchange with LiNTf$_2$

To a solution of histidinium bromide (3.6 mmol) in dichloromethane (7 ml) was added lithium bis (trifluoromethanesulfonyl) imide (1.05 g, 3.65 mmol). The resulting suspension was stirred overnight at room temperature and then filtered. The residual mixture was washed with water (3 × 3 ml) then with a solution of saturated NaCl (3 ml) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the resulting oil was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 95/5).

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-butyl-1-methyl-1H-imidazolium bis(trifluoromethanesulfonyl)imide (**14c**)

White solid (2.01 g, 3.24 mmol, 90%). $[\alpha]_D^{20} = +7.7°$ (c = 1.2 in $CHCl_3$); T_g = 46.2 °C; ESI: *m/e* 340 ($C_{17}H_{30}N_3O_4^+$, 100%), 284 (32), 240 (4); IR (KBr): ν = 2968 (NH), 1744 (CO_2CH_3), 1712 (NCO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7,3 Hz, 3H), 1.41 (s, 9H), 1.30–1.50 (m, 2H), 1.76–1.87 (m, 2H), 3.10 (dd, *J* = 8.2, 16.0 Hz, 1H), 3.21 (dd, *J* = 5.4, 16.0 Hz, 1H), 3.80 (s, 3H), 3.88 (s, 3H), 4.00–4.20 (m, 2H), 4.51–4.56 (m, 1H), 5.45–5.48 (s (broad), 1H, NH), 7.10 (s, 1H), 8.67 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.4, 19.6, 26.5, 28.2, 32.0, 36.3, 47.3, 52.4, 53.2, 80.9, 119.9 (q, *J* = 321 Hz, NTf_2), 121.8, 131.5, 136.0, 155.7, 170.7 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −79.4 ppm; Anal. calcd. for $C_{19}H_{30}F_6N_4O_8S_2$: C, 36.77; H, 4.87; N, 9.03; S, 10.33; Found: C, 36.86; H, 4.34; N,8.98; S, 10.41.

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-1-butyl-3-methyl-1H-imidazolium bis(trifluoromethanesulfonyl) imide (**14f**)

Viscous oil (494 mg, 3.34 mmol, 93%). $[\alpha]_D^{20} = +3.1$ (c = 1.21 in $CHCl_3$); T_g = −33 °C; ^{1}H NMR (300 MHz, CD_3CN): δ = 0.95 (t, *J* = 7.3 Hz, 3H), 1.39 (s, 9H), 1.25–1.40 (m, 2H), 1.70–1.85 (m, 2H), 3.03 (dd, *J* = 9.0, 15.8 Hz, 1H), 3.22 (dd, *J* = 4.7, 15.8 Hz, 1H), 3.74 (s, 3H), 3.75 (s, 3H), 4.08 (t, *J* = 7.3 Hz, 2H), 4.45–4.55 (m, 1H), 5.75–5.80 (m, 1H, NH), 7.21 (s, 1H), 8.36 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, CD_3CN): δ = 12.9, 19.2, 26.0, 27.7, 31.8, 33.8, 49.5, 52.1, 52.6, 79.9, 119.0 (q, *J* = 321 Hz, NTf_2), 120.7, 132.2, 135.9, 155.7, 171.2 ppm; ^{19}F NMR (282.4 MHz, CD_3CN): δ = 80.64 ppm.

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-butyl-1-methyl-1H-imidazolium hexafluorophosphate (**14d**)

To a solution of histidinium bromide (1.86 g, 4.44 mmol) in water (15 ml) and CH_3CN (10 ml) was added potassium hexafluorophosphate (860 mg, 4.67 mmol). After stirring for 72 h at room temperature, the mixture was extracted with dichloromethane (3 × 15 ml). The combined organic layer were washed with water and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo. The resulting oil was purified by chromatography on silica gel (CH_2Cl_2/iPrOH, 95/5). Colorless oil (1.79 g, 3.68 mmol, 83%). $[\alpha]_D^{20} = +1.7°$ (c = 1.01 in $CHCl_3$); T_g = −38 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7,3 Hz, 3H), 1.38 (s, 9H), 1.30–1.45 (m, 2H), 1.76–1.87 (m, 2H), 3.09 (dd, *J* = 7.3, 15.9 Hz, 1H), 3.22 (dd, *J* = 5, 15.9 Hz, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 4.0–4.2 (m, 2H), 4.45 (m, 1H), 5.42 (d, *J* = 7.3 Hz, 1H, NH), 7.10 (s, 1H), 8.44 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.5, 19.7, 26.4, 28.2, 31.8, 36.3, 47.2, 52.5, 53.2, 80.8, 121.8, 131.2, 135.9, 155.6, 170.8 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −72.7 (d, *J* = 712 Hz) ppm; HRMS for $C_{17}H_{30}N_3O_4$, calcd: 340.2232, found: 340.2237.

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-3-butyl-1-methyl-1H-imidazolium tetrafluoroborate (**14e**)

To a solution of histidinium bromide (319 mg, 1.13 mmol) in water (5 ml) was added sodium tetrafluoroborate (132 mg, 1.20 mmol). After stirring overnight at room temperature, the mixture was extracted with dichloromethane (4 × 5 ml). The combined organic layer were dried over anhydrous $MgSO_4$. Solvent was removed in vacuo to give the crude product as a yellow oil, which was purified by chromatography on silica gel (CH_2Cl_2/iPrOH, 90/10). Colorless oil (314 mg, 0.73 mmol, 65%). $[\alpha]_D^{20} = +6.4$ (c = 0.56 in $CHCl_3$); T_g = −29.4 °C; ^{1}H NMR (300 MHz, CD_3CN): δ = 0.95 (t, *J* = 7,3 Hz, 3H), 1.37 (s, 9H), 1.30–1.45 (m, 2H), 1.73–1.85 (m, 2H), 3.05 (dd, *J* = 7.3, 15.9 Hz, 1H), 3.20 (dd, *J* = 5, 15.9 Hz, 1H), 3.71 (s, 3H), 3.78 (s, 3H), 4.0–4.2 (m, 2H), 4.45 (m, 1H), 5.85 (d (broad), *J* = 7.3 Hz, 1H, NH), 7.17 (s, 1H), 8.43 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, CD_3CN): δ = 13.5, 19.9, 26.2, 28.2, 32.1, 36.6, 47.4, 52.5, 53.2, 80.4, 121.8, 131.2, 136.6, 156.3, 171.8 ppm; ^{19}F NMR (282.4 MHz, CD_3CN): δ = −151.6 ppm; HRMS for $C_{17}H_{30}N_3O_4$, calcd. 340.2236, found: 340.2237.

(*S*)-4-(2-(tert-butoxycarbonylamino)-3-hydroxypropyl)-3-butyl-1-methyl-1H-imidazol-3-ium bis (trifluoromethanesulfonyl) imide (**15**)

Lithium borohydride (21 mg, 0.9 mmol) was added in portions to a stirred solution of **14c** (380 mg, 0.6 mmol) in THF (8 ml) at 0 °C under an atmosphere of argon. After stirring for 24 h at rt the mixture was quenched with a saturated solution of ammonium chloride (1 ml). The solvents were evaporated and the residue partitioned between water and dichloromethane. After separation, the aqueous phase was further extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and evaporated to give a colorless residue which was purified on silica gel (dichloromethane/acetone (7/3)), leading to **15** as a colorless oil (210 mg, 0.348 mmol, 58%). $[\alpha]_D^{20} = -4.7°$ (c = 1.45 in CH_3CN); ^{1}H NMR (300 MHz, CD_3CN): δ = 0.96 (t, *J* = 7.3 Hz, 3H), 1.36 (s, 9H), 1.34–1.45 (m, 2H), 1.73–1.83 (m, 2H), 2.71 (dd, *J* = 9.4, 15.8 Hz, 1H), 2.90 (dd, *J* = 5.6, 15.8 Hz, 1H), 3.51 (d, *J* = 5.3 Hz, 2H), 3.70–3.80 (m, 1H), 3.75 (s, 3H), 4.05–4.11 (m, 2H), 5.35 (s (broad), 1H, NH), 7.13 (s, 1H), 8.32 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, CD_3CN): δ = 13.6, 20.0, 26.4, 28.3, 32.3, 36.6, 47.5, 51.7, 63.8, 79.6, 120.7 (q, *J* = 321 Hz, NTf_2), 122.1, 133.5, 136.2, 156.6 ppm; ^{19}F NMR (282.4 MHz, CD_3CN): δ = −80.68 ppm.

Results and discussion

Preparation and properties of chiral thiazolinium salts

Chiral thiazolinium salts are usually prepared from available aminothiols such as cysteine (Undheim and Eidem, 1970; Chikashita et al., 1989). Owing to the lack of availability of chiral aminothiol precursors, these compounds are seldom encountered. To circumvent this problem, our synthetic route was based on the use of commercially available low cost enantiopure 2-amino alcohols and easily accessible dithioesters as sulphur source (Abrunhosa et al., 2001, 2004). The chiral thiazolinium salts were ob-

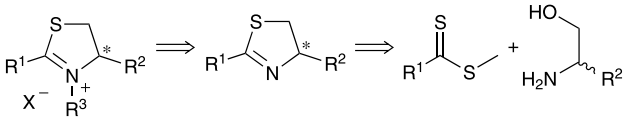


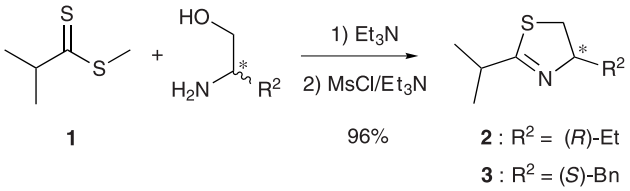
Fig. 2. Retrosynthetic pathway for the synthesis of thiazolinium salts

tained by alkylation of the intermediate thiazoline followed by anion exchange (Fig. 2).

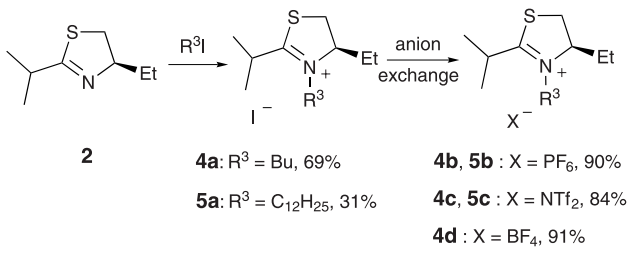
Starting from the two amino alcohols (*R*)-2-aminobutanol and (*S*)-phenylalaninol, and dithioester **1**, we were able to prepare twelve new salts. Thiazoline **2** was prepared from dithioester **1** and (*R*)-2-aminobutanol via a thioacylation/cyclization sequence and obtained with an excellent overall yield (96%). With (*S*)-phenylalaninol, the same protocol afforded thiazoline **3** in similar yield (96%) (Scheme 1).

Chiral salt **4a** was then obtained by refluxing thiazoline **2** in the presence of a slight excess of butyl iodide (Scheme 2). The reaction was completed in 2 days and afforded **4a** in 69% yield after recrystallization (acetonitrile/ethyl acetate). Results from differential scanning calorimetry (DSC) measurements gave a melting point of 137 °C for **4a** (entry 1, Table 1). In order to lower the melting point of the salt, the nature of the anion was modified via an anion exchange procedure using hexafluorophosphoric acid (HPF_6), tetrafluoroboric acid (HBF_4) or lithium bis(trifluoromethanesulfonyl)imide ($LiNTf_2$) (Scheme 2). When a 60% aqueous solution of hexafluorophosphoric acid was used, the reaction proceeded rapidly leading to **4b**. Washing with aqueous sodium bicarbonate or water up to neutrality, then with sodium thiosulfate to remove iodine traces, followed by extraction, drying and filtration over black charcoal afforded **4b** as a pure product in high yield (90% yield). A melting point of 136 °C was measured by DSC for **4b** (entry 2, Table 1). Following a quite similar procedure, salts **4c** and **4d** were prepared. Anion exchange with $LiNTf_2$ afforded salt **4c**, which is liquid at room temperature. DSC measurements showed a glass transition at −68 °C (entry 3, Table 1). Reaction of **4a** with a 34% aqueous solution of HBF_4 gave **4d** in 91% yield. A melting point of 111 °C was measured by DSC (entry 4, Table 1). The length of the alkyl chain was reported to be of importance for the melting point value of imidazolium salts (Mantz and Trulove, 2003). Thus, we replaced the butyl chain by a dodecyl one: salt **5a** was obtained after heating at 80 °C for 3 days a solution of thiazoline **2** and dodecyl iodide (1.6 eq). The melting point measured by DSC was as low as 63 °C (74 °C lower than its butyl analogue), thus allowing the use of **5a** as solvent (entry 5, Table 1). Exchanging the iodide anion of **5a** for an hexafluorophosphate one under conditions reported for **4a** led to salt **5b** having a melting point of 42 °C (entry 6, Table 1). With NTf_2 as counter anion, salt **5c** was liquid at room temperature with a glass transition temperature at −67 °C as measured by DSC (entry 7, Table 1).

We then applied the same procedure to thiazoline **3** derived from (*S*)-phenylalaninol (Scheme 3). Upon refluxing **3** in butyliodide, thiazolinium **6a** was obtained in 67% yield. The replacement, in the thiazolinium salt, of the ethyl group by a benzyl one considerably modifies the



Scheme 1. Synthesis of thiazolines **2** and **3** from amino alcohols

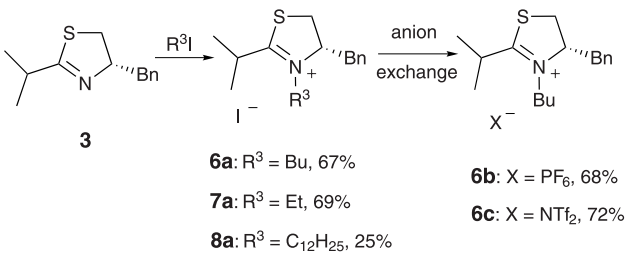


Scheme 2. Synthesis of chiral thiazolinium salts **4** and **5**

Table 1. Thiazolinium salts

Entry	R^2	R^3	X	Salt	Yield (%)[a]	mp or Tg in °C (DSC)
1	(*R*)-C_2H_5	C_4H_9	I	**4a**	66	137
2	(*R*)-C_2H_5	C_4H_9	PF_6	**4b**	60	136
3	(*R*)-C_2H_5	C_4H_9	NTf_2	**4c**	54	−68[b]
4	(*R*)-C_2H_5	C_4H_9	BF_4	**4d**	60	111
5	(*R*)-C_2H_5	$C_{12}H_{25}$	I	**5a**	30	63
6	(*R*)-C_2H_5	$C_{12}H_{25}$	PF_6	**5b**	25	42
7	(*R*)-C_2H_5	$C_{12}H_{25}$	NTf_2	**5c**	25	−67[b]
8	(*S*)-$CH_2C_6H_5$	C_4H_9	I	**6a**	64	172
9	(*S*)-$CH_2C_6H_5$	C_4H_9	PF_6	**6b**	44	115
10	(*S*)-$CH_2C_6H_5$	C_4H_9	NTf_2	**6c**	46	−40[b]
11	(*S*)-$CH_2C_6H_5$	C_2H_5	I	**7a**	66	175
12	(*S*)-$CH_2C_6H_5$	$C_{12}H_{25}$	I	**8a**	24	106

[a] Calcd. from the dithioester precursor
[b] Glass transition temperature



Scheme 3. Synthesis of chiral thiazolinium salts **6**, **7** and **8**

melting point of the salt ranging from 137 °C for **4a** (entry 1, Table 1) to 175 °C for **6a** (entry 8, Table 1). The anion exchange allowed again to lower the melting point of the salt. For instance, the melting point of hexafluorophosphate salt **6b** was measured at 115 °C (entry 9, Table 1) while bis(trifuoromethanesulfonyl)imide salt **6c** showed a glass transition temperature at −40 °C (entry 10, Table 1).

Replacing the butyl chain on nitrogen by a shorter (ethyl group) or a longer one (dodecyl group) led to iodide salts **7a** and **8a** with melting points of 175 and 106 °C, respectively. In agreement with literature data for imidazolium salts (Wasserscheid and Keim, 2000; Zhao et al., 2002) the melting point of the thiazolinium salts strongly depends on the structure of the cation.

The chiral salts **4**–**8** are soluble in dichloromethane, chloroform, acetonitrile, acetone, insoluble in ether, toluene and other weakly polar solvents. All the new salts proved to be poorly or totally insoluble in the aqueous phase except the iodide derivatives. A good thermal stability being an important criterion for the application of CILs, a thermal gravimetric analysis (TGA) was performed on various thiazolinium salts. All remained stable up to 170 °C allowing their use as solvents. All the salts having NTf_2 (**4c**, **5c**, **6c**), BF_4 (**4d**) and PF_6 (**4b**, **5b**, **6b**) counter anions showed a good chemical stability under aqueous basic (1 M K_2CO_3) and acidic (0.1 M HCl) conditions. Ring opening of the cycle was not observed even under acidic conditions contrarily to what was observed with oxazolinium derivatives (Wasserscheid et al., 2002).

Two chiral 2H-thiazolinium salts **10a**, **b** were also prepared by alkylation of thiazoline **9** previously prepared following Meyers procedure by direct sulfuration of the oxazoline precursor in 60% yield (Meyers, 1960). Alkylation was performed with 2 equivalents of butyl iodide or benzyl bromide upon microwaves irradiation and was completed in 15 min leading quantitatively to the new salts **10a** and **10b**. Purification of the new salts was performed by washing with pentane then with diethylether. The new salts were fully characterised by NMR spectroscopy and centesimal analysis. DSC measurements show a glass transition temperature of respectively 132 and 136 °C for **10a** and **10b**. The two salts have a good thermal stability as measured by TGA. They remain stable up to 200 °C.

Worthy of note is that these two new salts constitute the first examples of an unprecedented series of CILs, which could be promising tools in asymmetric synthesis because of the presence of C-2 proton.

Preparation and properties of new chiral histidinium salts

Several recent publications have stressed the critical importance of additional functional group on task-specific chiral ionic liquids in order to achieve high enantiomeric induction in various CIL mediated chemical transformations (Malhotra and Wang, 2006; Gausepohl et al., 2006). We were therefore interested in the synthesis of highly functionalized, chiral ionic liquids starting for naturally available compounds.

In this regard, histidine, a cheap natural amino acid, is an ideal candidate, as it already bears an imidazole ring which can serve as building block for the ionic part of the molecule, leaving both amino and carboxy groups untouched and readily available for further chemical transformations (Fig. 3) (Guillen et al., 2006).

However, in order to access to a family of CIL derived from histidine and possessing tuneable properties, it is highly desirable to develop a robust and versatile method that allows for each alkyl substituent R^1 and R^2 to be selectively introduced. We therefore chose to rely on a reported procedure, which permits the synthesis of N-1 alkylated, N-protected histidines with various carbamate protecting groups (Chivikas and Hodges, 1987; Jain and Cohen, 1996). In order to mimic the widely used [bmim] ionic liquids, we introduce methyl and butyl substituents on position 1 and 3 of the imidazole ring.

Simultaneous protection of the amine function and of the 3-position of the imidazole group was accomplished via an intermediate cyclic urea **11**, which can be subse-

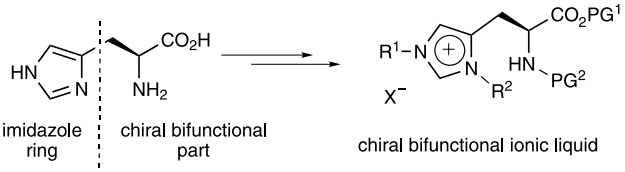
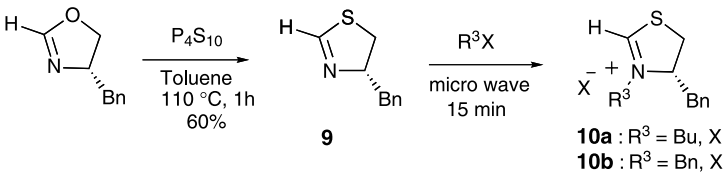
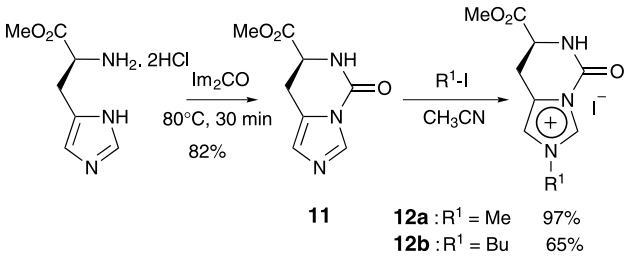


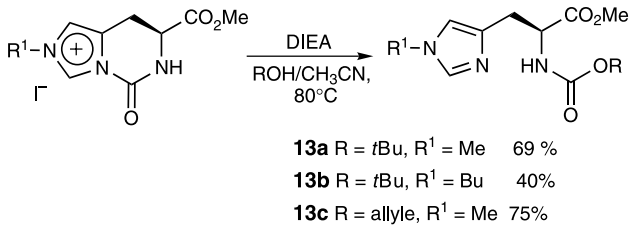
Fig. 3. Chiral bifunctional imidazolium salts from histidine



Scheme 4. Synthesis of 2H-thiazolinium salts **10a** and **10b**



Scheme 5. Protection and alkylation at *N*-1



Eq. 1. Opening of the cyclic urea

quently alkylated at N-1 with methyl or *n*-butyl iodide (Scheme 5).

However, the reported methods for the preparation of the cyclic urea **11** are rather tedious, as they require either prior treatment of the starting material with a stream of gaseous NH_3 to decompose the hydrochloride (Chivikas and Hodges, 1987) or the use of a rather large volume of DMF (Jain and Cohen, 1996). As the only byproduct of the carbonylation reaction is imidazolium hydrochloride which can be considered as the simplest prototype of ionic solvent (although its reported melting point of 158–161 °C is much too high to qualify it as a proper ionic liquid), we reasoned that we could run the reaction without adding solvent, relying on the forming salt to provide an homogeneous reaction medium. Simple mixing of histidine methyl ester dihydrochloride with a slight excess of carbonyldiimidazole at 115 °C with a mechanical stirrer under a stream of nitrogen for 30 min rapidly gave an amber oil, which was worked up as reported for the reaction in DMF to give a modest yield of the desired cyclic urea **11** (49%). We were delighted to find that better yields (82%) could be obtained when the reaction was run for 30 min at a temperature as low as 80 °C without any solvent (Scheme 5). It is worth noting that while the melting points of both starting materials and products are largely over 100 °C, an homogeneous liquid is obtained. Table 2 summarizes the results obtained for various reaction temperatures and durations.

Table 2. Solvent-free synthesis of **11**

Entry	Temp/°C	Duration/min	Isolated yield (%)
1	115	30	49
2	100	10	77
3	80	10	53
4	80	30	82

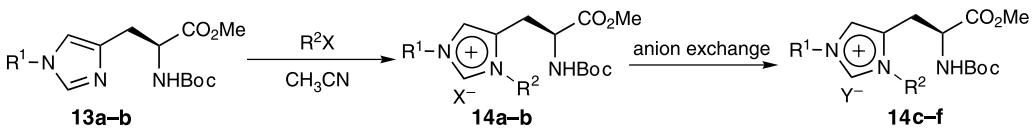
Alkylation of the cyclic urea with methyl iodide or *n*-butyl iodide gave the corresponding iodide salts **12a** and **12b** in 97 and 65% yield, respectively. Whereas the methyl derivative **12a** is only slightly soluble in acetonitrile and can therefore be conveniently isolated by simple filtration in quantitative yield, the butyl salt **12b** is much more soluble and cannot be conveniently precipitated.

Both cyclic ureas can then be opened in the presence of a suitable alcohol to give the corresponding 1-alkyl histidine methyl esters **13a–c** having the amino function protected as a carbamate (i.e. Boc or Alloc protection) (Eq. 1).

The enantiomeric purity of the alkylated histidine was assessed by chiral HPLC at this stage of the synthesis, i.e. on the last ''molecular'' species.

Alkylation at the 3-position proceeded smoothly with *n*-butyl bromide for **13a** or iodomethane for **13b**, giving the corresponding halide salts **14a** and **14b**, respectively. As the protected 1-methylhistidine is soluble in *n*-butyl bromide, the reaction could be conveniently run without any added solvent, whereas reaction of the 1-butylhistidine derivative was conducted in acetonitrile. However, purification of the obtained halide salts proved to be rather tedious, as they are quite hygroscopic low melting salts, which cannot be purified by column chromatography. They were therefore directly engaged in an anion metathesis reaction with various metal salts in order to give the corresponding hexafluorophosphate, tetrafluoroborate or bis (trifluoromethanesulfonyl) imide salt **14c–f** (Scheme 6) that could be obtained analytically pure after column chromatography.

All histidinium derivatives are colourless liquids that display a glass transition at low temperature, except **14c**, which is a low-melting solid (Table 3). They are insoluble

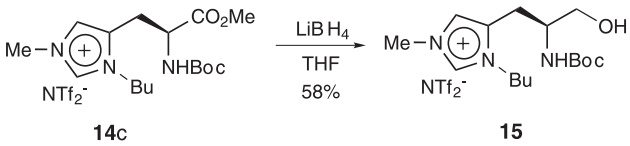


Scheme 6. Alkylation of histidine moiety and anion exchange

Table 3. Histidinium salts, yield, mp or Tg[a]

Entry	No.	R^1	R^2	Y	Yield[a] (%)	Mp/°C (DSC)
1	**14c**	Me	Bu	NTf_2	85	46.2
2	**14d**	Me	Bu	PF_6	78	−38[b]
3	**14e**	Me	Bu	BF_4	61	−29.4[b]
4	**14f**	Bu	Me	NTf_2	82	−33[b]

[a] Yields given for alkylation-metathesis sequence starting from **13a**, **b**
[b] Glass transition



Eq. 2. Reduction of the ester function of **14c**

in water, alkanes or diethyl ether but soluble in most other organic solvents. Thermogravimetric analysis of the bis-(trifluoromethanesulfonyl) imide salt showed thermal stability up to 170 °C. The overall yield of the synthesis, the melting points or the glass temperatures of the protected histidinium salts are listed in Table 3.

As we postulated at the beginning of this work, the substitution pattern of the imidazolium ring is critical for the physical properties of the salts, as shown by the difference between the melting point of the 1-butyl-3-methyl and 1-methyl-3-butyl substituted salts (Table 3, entry 1 and 4).

The protected 1-methyl-3-butylhistidinium bis(trifluoromethanesulfonyl) imide was then selectively deprotected at either *N*- or *C*-terminal position, and engaged in peptide coupling reaction with *C*-protected (respectively *N*-protected) alanine, to give the corresponding ionic dipeptides in good yields (Guillen et al., 2006). In both cases only one diastereomer of the dipeptide was obtained, confirming the enantiomeric purity of the protected histidinium salt and the non-racemizing character of the coupling reaction, even with this unprecedented ionic amino acid. Moreover, the same salt could be reduced to the protected amino alcohol **15** using lithium borohydride (Eq. 2).

This synthesis opens the route to a new family of chiral organocatalysts immobilized into an ionic medium. Further studies in our group will focus on their potential in asymmetric catalysis.

Conclusions

We have designed and prepared two new families of chiral ionic liquids from inexpensive amino acid derivative precursors: thiazolinium and histidinium salts. The enantiopure thiazolinium salts were straightforwardly prepared in multigram scale. They are thermally and chemically stable under acidic or basic conditions. By selecting the appropriate anion and cation, salts with low melting points are obtained. They could find applications in the field of chiral discrimination or for some of them as chiral ligands. Highly functional chiral ionic liquids were conveniently prepared from histidine. Their properties can be tuned by the substitution pattern of the imidazolium ring and the nature of the anion. The amino and carboxyl groups can undergo further transformations such as reduction and peptide coupling. They should find applications in the field of supported peptidic chemistry and in catalysis.

Acknowledgements

This work has been performed within the "PUNCHOrga" interregional network (Pôle Universitaire de Chimie Organique). We gratefully acknowledge financial support from the "Ministère de la Recherche et des Nouvelles Technologies", CNRS (Centre National de la Recherche Scientifique), the "Région Basse-Normandie" and the European Union (FEDER funding). The "Région Basse-Normandie" is also acknowledged for a financial support to D.B. The authors wish to thank Dr. L. LePluart and Dr. I. Dez for DSC measurements.

References

Abrunhosa I, Delain-Bioton L, Gaumont A-C, Gulea M, Masson S (2004) Chiral thiazoline ligands: application in Pd-catalysed allylic substitution. Tetrahedron 60: 9263–9272

Abrunhosa I, Gulea M, Levillain J, Masson S (2001) Synthesis of new chiral thiazoline-containing ligands. Tetrahedron Asymmetry 12: 2851–2859

Baudequin C, Baudoux J, Levillain J, Cahard D, Gaumont A-C, Plaquevent J-C (2003) Ionic liquids and chirality: opportunities and challenges. Tetrahedron Asymmetry 14: 3081–3093

Baudequin C, Brégeon D, Levillain J, Guillen F, Plaquevent J-C, Gaumont A-C (2005) Chiral ionic liquids, a renewal for the chemistry of chiral solvents? Design, synthesis and applications for chiral recognition and asymmetric synthesis. Tetrahedron Asymmetry 16: 3921–3945

Biedron T, Kubisa P (2003) Ionic liquids as reaction media for polymerization processes: atom transfer radical polymerization (ATRP) of acrylates in ionic liquids. Polym Int 52: 1584–1588

Branco LC, Gois PMP, Lourenço NMT, Kurteva VB, Afonso CAM (2006) Simple transformation of crystalline chiral natural anions to liquid medium and their use to induce chirality. Chem Commun: 2371–2372

Chikashita H, Komazawa S, Itoh K (1989) Synthesis of optically active thiazolinium salts. Technol Rep Kansai Univ 31: 81

Chivikas CJ, Hodges JC (1987) Phenacyl-directed alkylation of imidazoles: a new regiospecific synthesis of 3-substituted L-histidines. J Org Chem 52: 3591–3594

Clavier H, Boulanger L, Audic N, Toupet L, Mauduit M, Guillemin J-C (2004) Design and synthesis of imidazolinium salts derived from (l)-valine. Investigation of their potential in chiral molecular recognition. Chem Commun: 1224–1225

Ding J, Armstrong DW (2005) Chiral ionic liquids: synthesis and applications. Chirality 17: 281–292

Ding J, Welton T, Armstrong DW (2004) Chiral ionic liquids as stationary phases in gas chromatography. Anal Chem 76: 6819–6822

Gausepohl R, Buskens P, Kleinen J, Bruckmann A, Lehmann CW, Klankermayer J, Leitner W (2006) Highly enantioselective Aza-Baylis-Hillman reaction in a chiral reaction medium. Angew Chem Int Ed 45: 3689–3692

Guillen F, Brégeon D, Plaquevent J-C (2006) (*S*)-Histidine: the ideal precursor for a novel family of chiral amino acid and peptidic ionic liquids. Tetrahedron Lett 47: 1245–1248

Jain R, Cohen LA (1996) Regiospecific alkylation of histidine and histamine at N-1 (τ). Tetrahedron 52: 5363–5370

Kamata K, Agata I, Meyers AI (1998) An efficient and versatile method for the synthesis of optically active 2-oxazolines: an acid-catalyzed condensation of ortho esters with amino alcohols. J Org Chem 63: 3113–3116

Kiss L, Kurtan T, Antus S, Bruner H (2003) Further insight into the mechanism of Heck oxyarylation in the presence of chiral ligands. Arkivoc 5: 69–76

Kitazume T (2001) Optically active ionic liquid. US Patent 2001031875

Levillain J, Dubant G, Abrunhosa I, Gulea M, Gaumont A-C (2003) Synthesis and properties of thiazoline based ionic liquids derived from the chiral pool. Chem Commun: 2914–2915

Luo S, Mi X, Zhang L, Liu S, Xu H, Cheng J-P (2006) Functionalized chiral ionic liquids as highly efficient asymmetric organocatalysts for Michael addition to nitroolefins. Angew Chem Int Ed 45: 3093–3097

Ma HY, Wan XH, Chen XF, Zhou QF (2003) Design and synthesis of novel chiral ionic liquids and their application in free radical polymerization of methyl methacrylate. Chin J Polym Sci 21: 265–270

Malhotra SV, Wang Y (2006) Application of chiral ionic liquids in the copper catalyzed enantioselective 1,4-addition of diethylzinc to enones. Tetrahedron Asymmetry 17: 1032–1035

Mantz R, Trulove P (2003) Viscosity and density of ionic liquids. In: Wasserscheid P, Welton T (eds) Ionic liquids in synthesis. Wiley-VCH, Weinheim, pp 56–68

Meyers AI (1960) Preparation of 5,6-dihydro-1,3-thiazines and 2-thiazolines from mercaptoalcohols and nitriles. J Org Chem 25: 1147–1151

Pégot B, Vo-Thanh G, Loupy A (2004) First application of chiral ionic liquids in asymmetric Baylis-Hillman reaction. Tetrahedron Lett 45: 6425–6728

Rogers RD, Seddon KR, Volkov S (2002) Green industrial applications of ionic liquids. Kluwer Academic, Dordrecht

Tao GH, He L, Syn Y, Kou Y (2005) New generation ionic liquids: cations derived from amino acids. Chem Commun: 3562–3564

Undheim K, Eidem A (1970) N-quaternary compounds. XVI. 4-Carboxythiazolinium derivatives. Acta Chem Scand 24: 3129–3133

Wang Z, Wang Q, Zhang Y, Bao W (2005) Synthesis of new chiral ionic liquids from natural acids and their applications in enantioselective Michael addition. Tetrahedron Lett 46: 4657–4660

Wasserscheid P, Bösmann A, Bolm C (2002) Synthesis and properties of ionic liquids derived from the 'chiral pool'. Chem Commun: 200–201

Wasserscheid P, Keim W (2000) Ionic liquids – new "solutions" for transition metal catalysis. Angew Chem Int Ed 39: 3772–3789

Wasserscheid P, Welton T (2003) Ionic liquids in synthesis. Wiley-VCH, Weinheim

Westmijze H, Klein H, Meijer J, Vermeer P (1979) Synthesis of dithioesters from organocopper(I) compounds. Synthesis: 432–434

Zhao D, Kou Y, Wu M, Min E (2002) Ionic liquids: applications in catalysis. Catal Today 74: 157–189

Authors' address: Annie-Claude Gaumont, Laboratoire de Chimie Moléculaire et Thioorganique, ENSICAEN, Université de Caen Basse-Normandie, CNRS, 6 Bd Maréchal Juin, F-14050 Caen, France,
Fax: +33-2-31452877, E-mail: gaumont@ensicaen.fr