Electronic Supplementary Material (ESI) for Polymer Chemistry

Towards an enzymatic biomimetic system: enhancement of catalytic efficiency with new polymeric chiral ionic liquids synthesised by controlled radical polymerisation.

Erno Karjalainen,[a] Diana F. Izquierdo,[b] Vicente Martí-Centelles[b], Eduardo García-Verdugo,*[a,b] Heikki Tenhu,*[a] María I. Burguete[b], Santiago V. Luis[b].

[a] Laboratory of Polymer Chemistry, Department of Chemistry, University of Helsinki, Finland E-mail: heikki.tenhu@helsinki.fi

[b] Universidad Jaume I, Departamento de Química Inorgánica y Orgánica, Campus del Riu Sec, E-12071 Castellón, Spain E-mail: cepeda@uji.es

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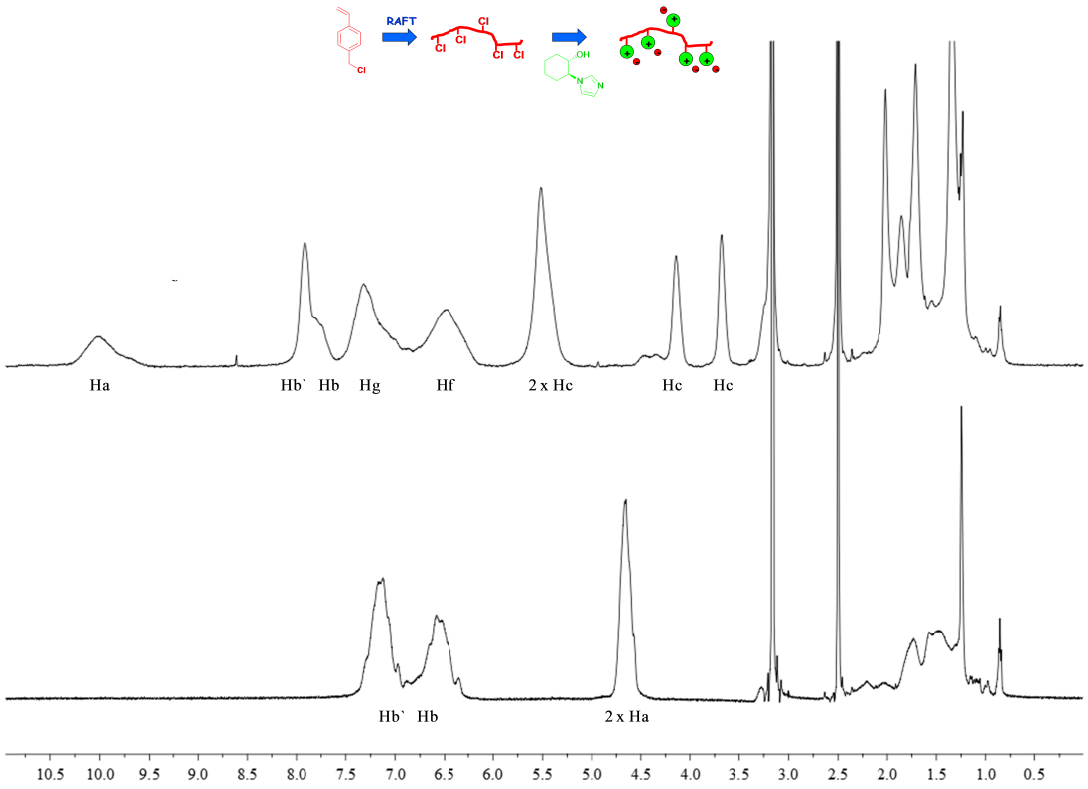


Figure S.I.-1. ^{1}H-NMR-(DMSO-d_6) of the polymer PClSt-**1** before (down) and after (up) the chemical modification with ((+)-**4**) to yield PCIL-RAFT-*graf*-(+)-**6**

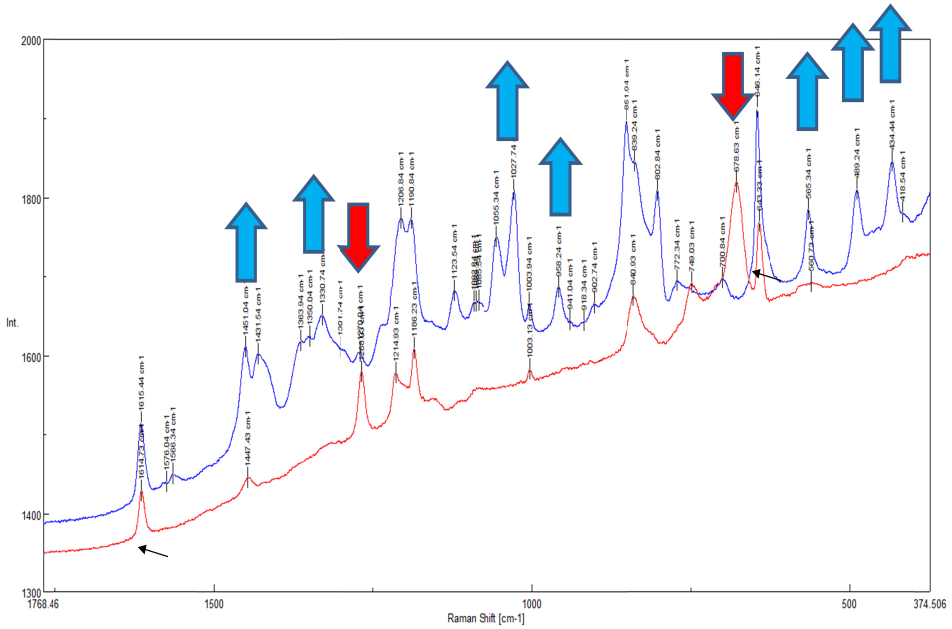


Figure S.I.2. Raman microscopy spectra of the polymer PClSt-**1** before (down) and after (up) the chemical modification with ((+)-**4**) to yield PCIL-RAFT-*graf*-(+)-**6**

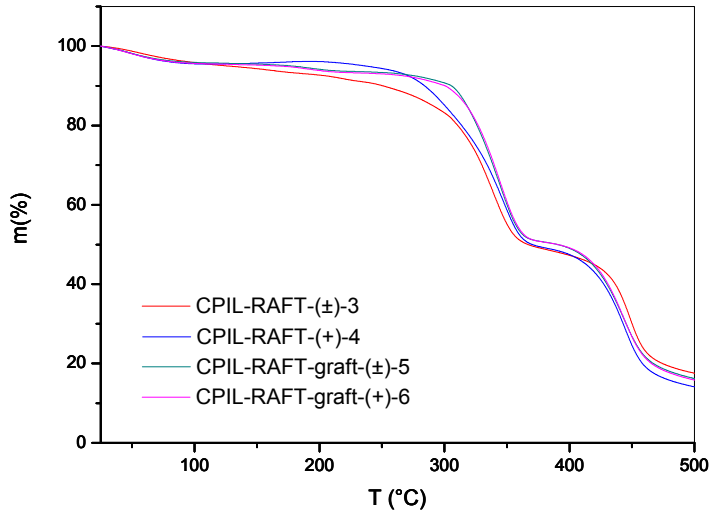


Figure S.I.3. Normalized sample weight as function of temperature under nitrogen. From top-to-bottom at 800 °C: PCIL-RAFT-(±)-**3**, PCIL-RAFT-(+)-**4**, PCIL-RAFT-*graf*-(±)-**5** and PCIL-RAFT-*graf*-(+)-**6**.

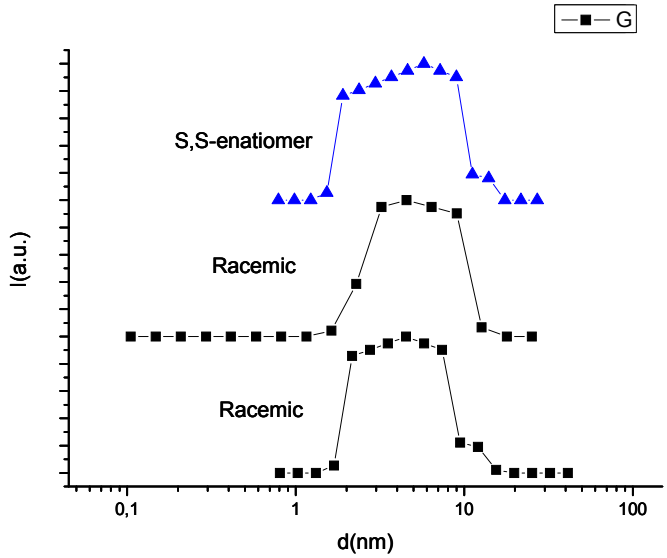


Figure S.I.4 Particle sizes of PCIL-RAFT-(±)-**3** (red) and PCIL-RAFT-(+)-**4** (blue) by DLS as 1 mg/ml solutions in 0.2 M aqueous NaCl measured with a DLS with angle of 30°.

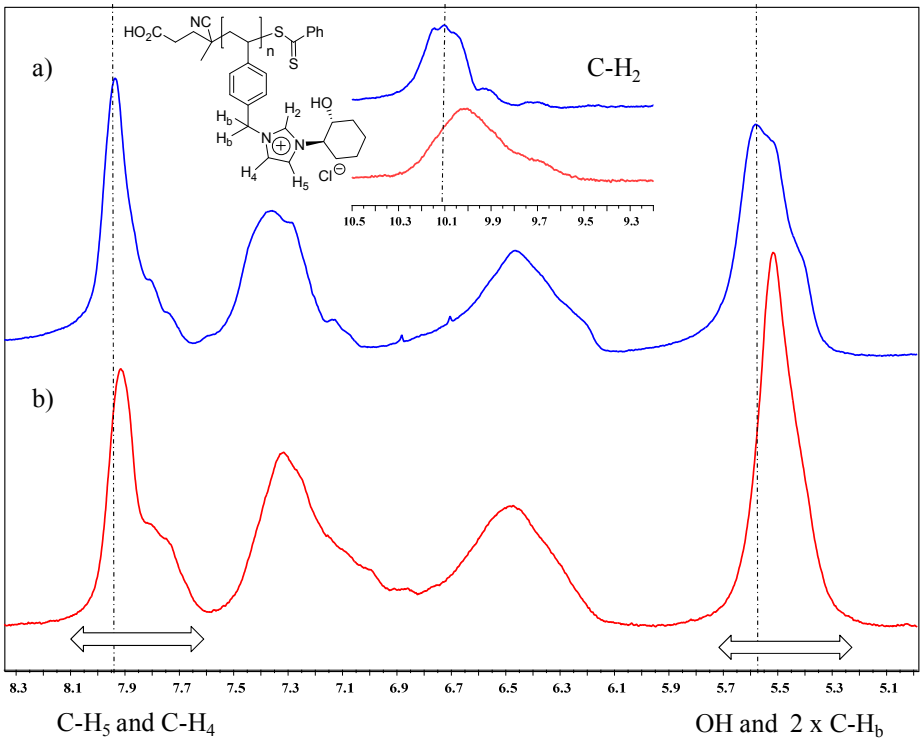


Figure S.I.5. ^{1}H-NMR (DMSO-d_6) 10 mg/mL a): PCIL-RAFT-(+)-**4** blue; b) PCIL-RAFT- *graft*-(+)-**6** (red).

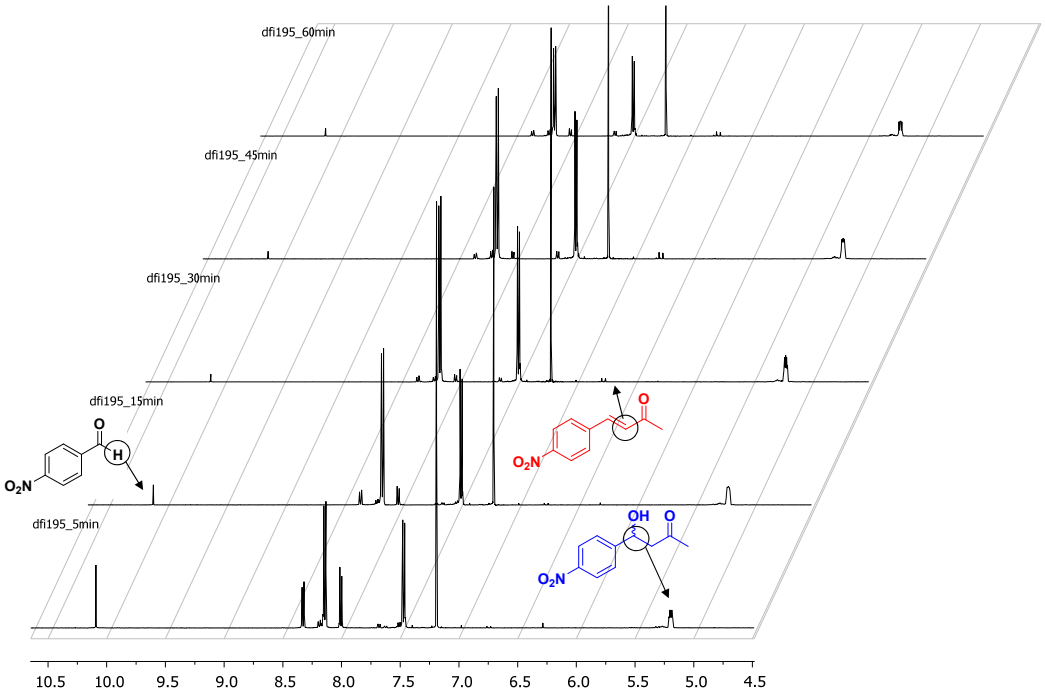


Figure S.I.6. Kinetic study of the aldol reaction by ^{1}H-NMR (D_2O) 1:30:0.1 RCHO:acetone-d_6:catalyst molar ratio, 0.38 M solution, 24 mg polymer/mL, r.t., acetone:D_2O 4:1.

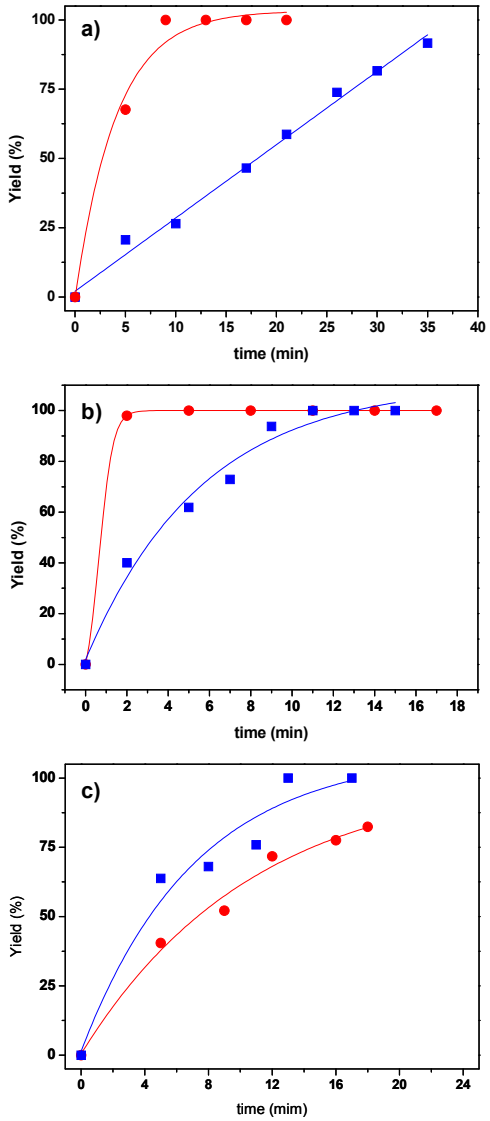


Figure S.I.7. Aldol yield (%) *vs* time for the aldol reaction catalyzed by polymeric catalysts. D_2O:acetone (4:1); RCHO:acetone:cat 1:10:0.1. a) PCIL-ATRP-(±)-**1**-L-Pro (square) or PCIL-ATRP-(+)-**2**-L-Pro (dot). b) PCIL-RAFT-(±)-**3**-L-Pro (square) or PCIL-RAFT-(+)-**4**-L-Pro (dot). c) PCIL-RAFT-*graft*-(±)-**5**-L-Pro (square) or PCIL-RAFT- *graft*-(+)-**6**-L-Pro.

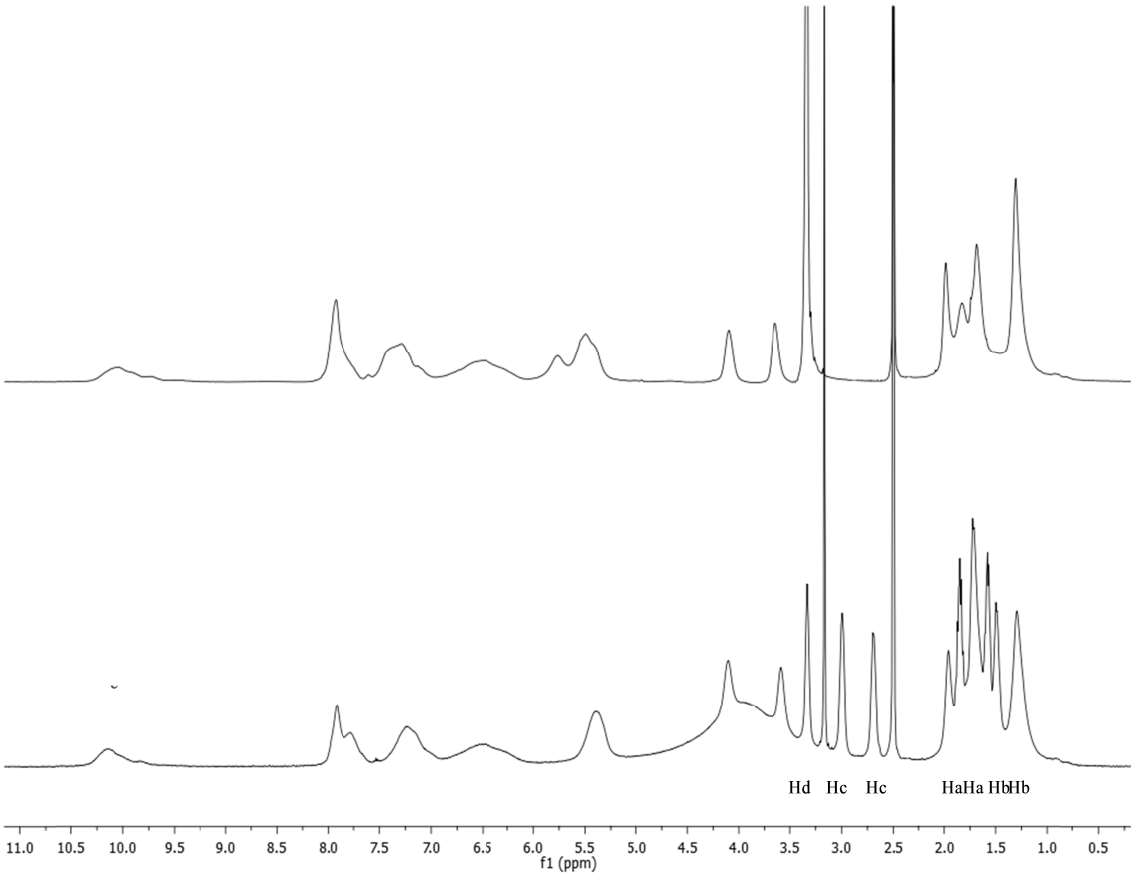


Figure S.I.8. ^{1}H-NMR-(DMSO-d_6) of the polymer PCIL-RAFT-(±)-**3** before (up) and after (down) the ion exchange modification with L-proline to yield PCIL-RAFT-(±)-**3**-L-Pro.

Materials.

Azobisisobutyronitrile (AIBN) (Fluka, 98 %) and azobiscyanopentanoic acid (ACPA) (Fluka, 98 %) were recrystallized from methanol. Dimethyl formamide (DMF) (Lab-Scan, HPLC-grade) and p-choloromethylstyrene (ClMeSt) (Aldrich, 90 %) were purified by vacuum distillation. Methanol (MeOH) (Lab-Scan, HPLC-grade) and Dimethyl sufoxide (DMSO) (Lab-Scan, HPLC-grade) were dried over 3 Å molecular sieves. (4-cyanopentanoic acid)-4-dithiobenzoate (CPA) and 2-cyano-2-propyl-dithiobenzoate were synthesized as described in literature.[1, 2] Tris(2-Dimethylaminoethyl)amine (Me_6TREN) was synthesized following a literature procedure.[3] Ethyl 2-bromopropanoate (E2PrBr) (Aldrich, 99 %), Methylimidazole (Adrich, 99 %), $CuBr_2$ (Aldrich. 99.99 %) and 2,5-dihydroxy benzoic acid (DHB) (Fluka, 98 %) 2-Cyano-2-propyl dodecyl trithiocarbonate (Aldrich, 97 %) were used as received. Deuterated solvents were received from C.E. Saclay and used as received.

Instrumentation

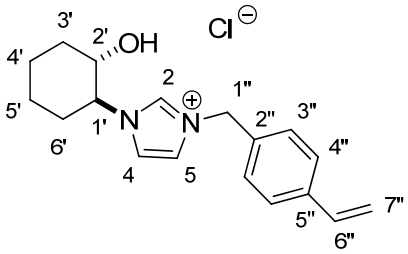
Nuclear magnetic resonance (NMR)-spectra were recorded with 300 MHz Varian Unity INOVA-spectrometer or Bruker Avance III 500-spectrometer. Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI) was measured with Bruker MicroFlex-spectrometer.

MALDI-TOF. MALDI-TOF samples were prepared by first preparing solutions of DHB with concentration of 40 mg/ml and solutions of the polymers with concentration of 10 mg/ml in methanol. These solutions were mixed with 4:1 ratio of DHB solution to polymer solution and injected to a sample plate of stainless steel.

Experimental

Synthesis of (±)-trans-1-(2'-hydroxicyclohexyl)-3-(4'-vinylbenzyl)-1H-imidazol-3-ium Chloride [(±)-7]. A flask was charged with 1g (6.016 mmol) of imidazole derivative **(±)-3** and this was solved with 10ml of CH_3CN heating and stirring until 80°C. Once this temperature was reached, 0.942ml of 1-(chloromethyl)-4-vinylbenzene was added (6.016mmoles, 90%purity). The reaction was allowed at 80°C for 16 hours. The precipitate product was filtered and washed with CH_3CN (3x20mL). Yield 99%.

Characterization



White solid.

Formula: $C_{18}H_{23}ClN_2O$

Molecular Weight: 318.84 g/mol

MP: 201°C.

IR (ATR) : ν 3212, 3054, 3002, 2941, 2927, 2859, 1753, 1624, 1557, 1418, 1357, 1335, 1327, 1165, 1142, 1165, 1075, 996, 871 cm^{-1}.

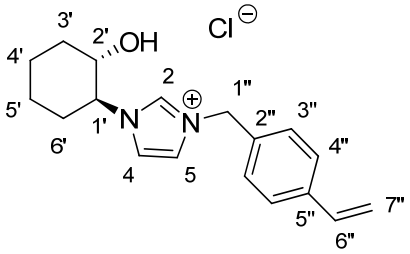
^{1}H-NMR (CD_3OD, 500 MHz) δ 1.37 – 1.51 (m,3H, $H_{3'}$+ $2H_{5'}$), 1.81-1.93 (m, 3H+ $2H_{4'}$, $H_{6'}$), 2.08-2.18 (m, 2H, $H_{3'}$+ $H_{6'}$), 3.61-3.68 (m, 1H, $H_{2'}$), 3.98 – 4.11 (m, 1H, $H_{1'}$), 5.29 (d,1H, d,$H_{7''}$), 5.41 (s, 2H, $H_{1''}$), 5.82 (d, 1H, $H_{7''}$), 6.75 (m,1H, $H_{6''}$), 7.38 (d, 2H, $H_{3''}$), 7.50 (d, 2H, $H_{4''}$), 7.62 (s,1H, H_4), 7.74 (s,1H, H_5) ppm.

^{13}C-NMR (CD_3OD, 125 MHz): δ 25.2 ($C_{5'}$), 25.9 ($C_{4'}$), 32.4 ($C_{6'}$), 35.8 ($C_{3'}$), 54.0 ($C_{1''}$), 67.8 ($C_{2'}$), 73.3 ($C_{1'}$), 114.7 ($C_{6''}$+ $C_{7''}$), 122.6 (C_4), 123.7 (C_5), 128.2 ($C_{3''}$), 130.1 ($C_{4''}$), 134.7 ($C_{5''}$), 137.4 ($C_{2''}$), 140.3 (C_2) ppm.

Elemental Analysis for $C_{18}H_{23}ClN_2O$: C, 67.81; H, 7.27; Cl, 11.12; N, 8.79; O, 5.02.

Synthesis of (*S,S*)-trans-1-(2'-hydroxicyclohexyl)-3-(4'-vinylbenzyl)-1H-imidazol-3-ium Chloride [(+)-(*S,S*)-8].

A flask was charged with 1g (6.016 mmol) of imidazole derivative **(+)-(*S,S*)-4** and this was solved with 10ml of CH_3CN heating and stirring until 80°C. Once this temperature was reached, 0.942ml of 1-(chloromethyl)-4-vinylbenzene was added (6.016mmol, 90%purity). The reaction was allowed at 80°C for 16 hours and was stopped for cooling down into the freezer to form crystals which were filtered and washed with CH_3CN (3x20mL). Yield 99%.



White solid.

Formula: $C_{18}H_{23}ClN_2O$

Molecular Weight: 318.84 g/mol

MP: 206°C

IR (ATR): ν 3250, 3116, 3056, 3010, 2936, 2858, 1554, 1515, 1455, 1413, 1275, 1236, 1158, 1137, 1073, 988, 861 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD) δ 1.36-1.52 (m, 3H, $H_{3'}$+ $2H_{5'}$), 1.79 – 1.97 (m, 3H, $2H_{4'}$+ $H_{6'}$), 2.13-2.2 (m, 2H, $H_{3'}$+ $H_{6'}$), 3.54 – 3.74 (m, 1H, $H_{2'}$), 3.95 – 4.15 (m, 1H, $H_{1'}$), 5.30 (d,1H, $H_{7''}$), 5.41 (s, 2H, $H_{1''}$), 5.83 (d, 1H, $H_{7''}$), 6.76 (m,1H, $H_{6''}$), 7.38 (d, 2H, $H_{2''}$+ $H_{4''}$), 7.51 (d, 2H, $H_{3''}$ +$H_{5''}$), 7.63 (s,1H, H_4), 7.74 (s,1H, H_5) ppm.

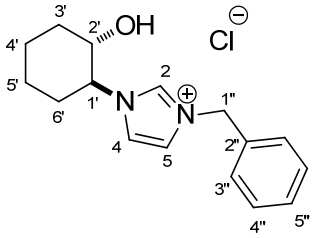
^{13}C NMR (CD_3OD, 125 MHz): δ 23.6 ($C_{5'}$), 24.3 ($C_{4'}$), 30.9 ($C_{6'}$), 34.2 ($C_{3'}$), 52.4 ($C_{1''}$), 66.2 ($C_{2'}$), 71.8 ($C_{1'}$), 114.1 ($C_{6''}$+ $C_{7''}$), 121.1 (C_4), 122.1 (C_5), 126.7 (Cx) 128.5 ($C_{3''}$), 133.2 ($C_{5''}$), 135.9 ($C_{2''}$), 138.7 (C_2) ppm.

Elemental Analysis for $C_{18}H_{23}ClN_2O$, Calculated: C, 67.81; H, 7.27; Cl, 11.12; N, 8.79; O, 5.02.

$[\alpha]_D^{20}$ = +10.6 (c = 0.01, CH_3OH) for > 99% *ee*.

Synthesis of 3-benzyl-1-((±)-*trans*)-(2'-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(±)-8].

A solution of imidazole derivative **(±)-3** (2.41 mmol) in CH_3CN (10 mL) was added benzyl chloride (2.65 mmol). The mixture was stirred for 24 h at 85 ºC. After this time, the reaction was allowed for cooling at room temperature, the solvent was removed by distillation under reduced pressure and the resulting gum was washed with Et_2O (5 × 10 mL), giving the corresponding imidazolium salts as white solids (96%).



White solid

Formula: $C_{16}H_{21}ClN_2O$

Molecular Weight: 292.80g/mol

MP: 181 ºC

IR (KBr): ν 3300, 3225, 3054, 3050, 1681, 1576, 1489, 1469, 1369, 1305, 1155, 991, 875 cm^{-1}

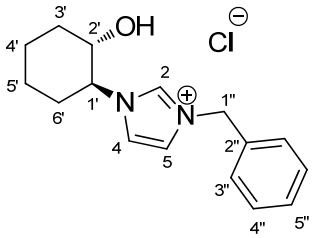
^{1}H-RMN (CD_3OD, 500 MHz): δ 1.36-1.54 (m, 3H, $H_{3'}$+$2H_{5'}$), 1.78-1.95 (m, 3H, $2H_{4'}$+$H_{6'}$), 2.12-2.17 (m, 2H, $H_{3'}$+$H_{6'}$), 3.63-3.71 (m, 1H, $H_{2'}$), 4.02-4.10 (m, 1H, $H_{1'}$), 5.43 (2H, $H_{1''}$), 7.36-7.48 (m, 5H, $2H_{3''}$+$2H_{4''}$+$H_{5''}$), 7.62(s, 1H, H_4), 7.74 (s, 1H, H_5) 9.13 (s, 1H, H_2) ppm.

^{13}C-NMR (CD_3OD, 126 MHz): δ 23.6 ($C_{5'}$), 24.3 ($C_{4'}$), 31.0 ($C_{6'}$), 34.2 ($C_{3'}$), 52.8 ($C_{1'}$), 66.2 ($C_{1''}$), 71.8 ($C_{2'}$), 121.2 (C_4), 122.1 (C_5), 128.2 ($C_{5''}$), 129.0 ($2C_{3''}$+$2C_{4''}$) 133.9 ($C_{2''}$), 135.6 (C_2) ppm.

Elemental Analysis for $C_{16}H_{21}ClN_2O$, calculated: C, 65.63; H, 7.23; N, 9.57. Found: C, 65.7; H, 7.2; N, 9.6

Synthesis of 3-benzyl-1-((*S,S*)-*trans*)-(2'-hydroxycyclohexyl)-1*H*-imidazol-3-ium chloride [(+)-(*S,S*)-10]

A solution of imidazole derivative **(+)-(*S,S*)-4** (2.41 mmol) in CH_3CN (10 mL) was added benzyl chloride (2.65 mmol). The mixture was stirred for 24 h at 85 ºC. After this time, the reaction was allowed for cooling at room temperature, the solvent was removed by distillation under reduced pressure and the resulting gum was washed with Et_2O (5 × 10 mL), giving the corresponding imidazolium salts as white solids (96%).



White solid.

Formula: $C_{16}H_{21}ClN_2O$

Molecular Weight: 292.80g/mol)

IR (KBr): ν 3300, 3225, 3054, 3050, 1681, 1576, 1489, 1469, 1369, 1305, 1155, 991, 875 cm^{-1}

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.38-1.55 (m, 3H, $H_{3'}$+$2H_{5'}$), 1.79-1.84 (m, 3H, $2H_{4'}$+$H_{6'}$), 2.13-2.15 (m, 2H, $H_{3'}$+$H_{6'}$), 3.50 (s, 1H, OH), 3.62-3.83 (m, 1H, $H_{2'}$), 4.25-4.39 (m, 1H, $H_{1'}$), 5.50 (AB system, $^2J_{HH}$ = 15.0 Hz, 2H, $H_{1''}$), 7.19 (s, 1H, H_4), 7.32-7.45 (m, 6H, H_5+$2H_{3''}$+$2H_{4''}$+$H_{5''}$), 9.90 (s, 1H, H_2) ppm.

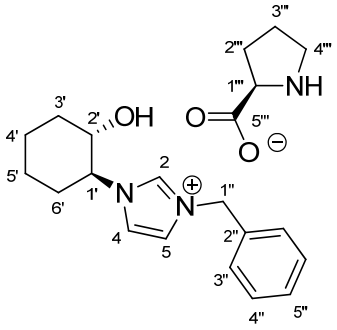
^{13}C-NMR ($CDCl_3$, 125 MHz): δ 23.9 ($C_{5'}$), 24.4 ($C_{4'}$), 31.2 ($C_{6'}$), 34.2 ($C_{3'}$), 53.2 ($C_{1''}$), 65.9 ($C_{2'}$), 71.9 ($C_{1'}$), 121.0 (C_4), 121.4 (C_5), 129.0 ($2C_{3''}$+$2C_{4''}$+$C_{5''}$), 132.9 ($C_{2''}$), 135.8 (C_2) ppm.

Elemental Analysis for $C_{16}H_{21}ClN_2O$, calculated: C, 65.63; H, 7.23; N, 9.57. Found: C, 65.7; H, 7.2; N, 9.6

$[\alpha]_D^{20}$ = +27.3 (c = 0.01, CH_3OD) for > 99% ee.

Synthesis of 3-benzyl-1-((S,S)-*trans*)-(2'-hydroxycyclohexyl)-1*H*-imidazol-3-ium (R)-pyrrolidine-2-carboxylate.

A solution of imidazolium derivative **(+)-(*S,S*)-10** (0,298 mmol) in CH_3OH (5 mL) was added L-proline (0,298 mmol). The mixture was stirred for 24 h at room temperature. After this time, the reaction was concentrated and dried (99%).



White solid.

Formula: $C_{21}H_{29}N_3O_3$

Molecular Weight: 371.47 g/mol

MP: 174°C

IR (ATR): ν 3275, 3127, 3089, 3016, 2935, 2851, 2368, 1612, 1556, 1454, 1370, 1293, 1268, 1260, 1159, 1090, 1037, 957 cm^{-1}.

^{1}H-NMR (CD_3OD, 500 MHz): δ 1.34-1.49 (m, 3H, $H_{3'}$+$2H_{5'}$), 1.76-1.87 (m, 3H, $2H_{4'}$+$H_{6'}$), 1.87-1.99 (m, 2H, $H_{3'''}$+$H_{2'''}$), 2.03-2.15 (m, 3H, $H_{3'}$, $H_{6'}$+$H_{3'''}$), 2.22-2.31 (m, *J* = 7.5, 15.8 Hz, 1H, $H_{2'''}$), 3.18 – 3.25 (m, *J* = 7.3, 11.5 Hz, 1H, $H_{4'''}$), 3.32 – 3.38 (m, 1H, $H_{4'''}$), 3.60 – 3.69 (m, 1H, $H_{2'}$), 3.92-3.98 (dd, *J* = 6.2, 8.7 Hz, 1H, $H_{1'''}$), 4.00-4.09 (m, 1H, $H_{1'}$), 5.39-5.43 (s, 2H, $2H_{1''}$), 7.34 – 7.44 (m, *J* = 4.5, 12.9 Hz, 5H, $2H_{3''}$, $2H_{4''}$, $H_{5''}$), 7.57-7.61 (d,1H, H_4), 7.69-7.73 (d, 1H, H_5) ppm.

^{13}C-NMR (CD_3OD, 126 MHz): δ 25.0 ($C_{3'''}$ +$C_{5'}$), 25.6 ($C_{4'}$), 30.4 ($C_{6'}$), 32.2 ($C_{2'''}$), 35.6 ($C_{3'}$), 47.0 ($C_{4'''}$), 54.1 ($C_{1''}$), 62.6 ($C_{1'}$), 67.6 ($C_{1'''}$), 73.1 ($C_{2'}$), 122.5 (C_4), 123.5 (C_5), 129.5 ($C_{5''}$),130.3 ($2C_{4''}$+ $2C_{3''}$), 135.3 ($C_{2''}$), 137.0 (C_2), 173.9 ($C_{5'''}$) ppm.

Elemental Analysis for $C_{21}H_{29}N_3O_3$, Calculated: C, 67.90; H, 7.87; N, 11.31.

$[\alpha]_D^{20}$ = -14.5 (c = 0.01, CH_3OH) for > 99% ee.

Solution polymerization of IL-monomer by RAFT. A representative synthesis of PIL (PCIL-RAFT-(±)-**3**) is presented here; the other polymerizations were conducted in similar manner and the conditions are shown in table 1.

A flask was charged with 0.3828 g (1.20 mmol) of racemic monomer ((±)-**3**) 0.0013 g (0.00464 mmol) of ACPA, 0.0067 g (0.0240 mmol) of CPA, 2 mL of DMSO and 2 mL of water. The flask was subjected to five freeze-thaw cycles and filled with nitrogen. The reaction was allowed to proceed at 100 °C for 24 hours, after which the reaction was stopped by freezing the reaction mixture with liquid nitrogen. The product was purified by dialysis against water and isolated by lyophilization.

Bulk Polymerization of p-choloromethylstyrene. A flask was charged with 88.5 mg (0.256 mmol) of 2-Cyano-2-propyl dodecyl trithiocarbonate, 4.2 mg (0.0256 mmol) of azobis(isobutyronitrile) (AIBN) and 3.9044 g (25.6 mmol) of p-choloromethylstyrene (**6**). The flask was subjected to five freeze-thaw cycles and filled with nitrogen. The polymerization was allowed to proceed for 24 hours at 100 °C, after which the reaction was quenched with liquid nitrogen. The product was purified by two precipitations from acetone to hexane and one precipitation from acetone to methanol-water mixture (10:1 vol.). The product was dried in a vacuum oven

Derivatization of PClMeSt

PCIL-RAFT-*graft*-(±)-5 and **PCIL-RAFT-*graft*-(+)-6** were synthesized by dissolving 0.1279 g (0.838 mmol of repeating units) of PClMeSt and 0.1715 g (1.03 mmol) of (±)-3 or (+)-(*S,S*)-4 to a solvent mixture containing 2 mL of DMF and 1 mL of methanol. The mixture was allowed to react at 80 °C fo 25 hours and the product was purified by dialysis against water. The product was isolated by lyophilization. **PCIL-RAFT-*graft*-(+)-7** was synthesized in a similar manner, but by using methyl imidazole and with reaction time of 30 hours.

Solution Polymerization of IL-monomer by ARGET-ATRP

Synthesis of **PCIL-RAFT-(±)-3** and **PCIL-RAFT-(+)-4** is represented here; experimental details for the rest of the polymerizations are given in table 1.

In the first flask, 0.2836 g (0.889 mmol) of **(±)-3** or **(+)-(*S,S*)-4** monomer and 0.0031 g (0.0171 mmol) of E_2PrBr were dissolved to 2 mL of methanol. A copper chip of 0.0136 g (0.207 mmol) was added and the flask was bubbled with nitrogen for 30 minutes. A second flask was charged with 0.0040 g (0.0179 mmol) of $CuBr_2$, 11 µL of Me_6TREN and 1 mL of methanol. The second flask was bubbled with nitrogen for 20 minutes. The first flask was immersed to oil bath at 60 °C and the contents of the second flask were transferred to the first flask via a nitrogen-flushed syringe. The first flask was briefly bubbled with nitrogen while heating, to avoid pressure build-up. The reaction was continued at 60 °C for 15 hours. The reaction was stopped by sudden cooling with liquid nitrogen; the product was purified by dialysis against and isolated by freeze-drying the contents of the dialysis tube.

Counter-anion Exchange from Chloride to L-Proline of PCILs In a flask, 50.0 mg (0.1568 mmol) of **PCIL**s (**PCIL**-ATRP-(±)-**1**-L-Pro, **PCIL**-ATRP-(+)-**2**-L-Pro, **PCIL**-RAFT-(±)-**3**-L-Pro or **PCIL**-RAFT-(+)-**4**-L-Pro was solved with 5 mL of methanol and 1g of Amberlite-OH, previously washed, was added and the resultant mixture was stirred slowly for 2h. The mixture was filtered and the solution was solved with 19.9 mg of L-proline (0.1725 mmol) and stirred for 16 h. This solution was concentrated and dried under vacuum.