Supporting Information

Engineered Immobilised Organocatalysts for the Synthesis of Chiral Amines

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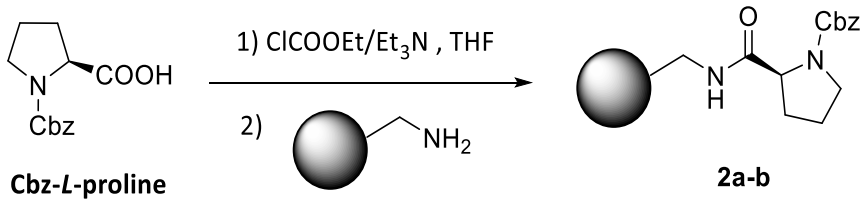
1. General information

All reagents and solvents were obtained from commercial sources (Aldrich, Fluka, Scharlab or Iris-Biotech) and used without further purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an inert atmosphere of nitrogen, using glass material previously dried in the oven and dry solvents supplied by a Pure Solv model solvent dispensing system from Innovative Technology. Moisture-sensitive reagents were handled using syringes under an inert atmosphere. Reactions whose procedure required low temperature for a long time were carried out with the aid of a Neslab model CC-100 II Cryocool. After obtaining synthesized products, they were dried in a Binder vacuum oven at a temperature of 45 °C and then stored in a desiccator or refrigerator according to the needs of the product. The enantiomeric excess of the imine reduction was determined by high-performance liquid chromatography (HPLC) with a Merck HITACHI LaChrom D-7000 chromatograph and a Chiralcel OD-H chiral filler column (4.6 mm Ø × 250 mm L). HPLC conditions: *n*-hexane/MTBE (98/2), 1 mL/min, 30 °C, 254 nm (UV/Vis detection), t_R (*S*-amine): 26 min, t_R (*R*-amine): 27.5 min. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian model INOVA 500 spectrometer (^{1}H-NMR at 500 MHz and ^{13}C-NMR at 125 MHz) in the indicated deuterated solvent. Fourier Transform Infrared (FT-IR) spectra were acquired with a Pike single-reflection ATR diamond/ZnSe accessory in a JASCO FT/IR-4700 instrument.

2. Synthetic procedures

General procedure for the synthesis of 2a-b.[1]

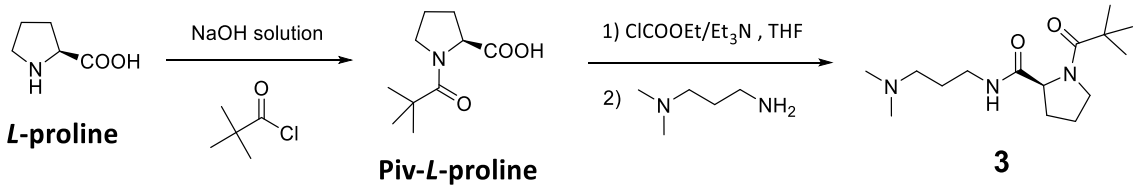


Cbz-*L*-proline

2a-b

Triethylamine (3 equiv.) and ethyl chloroformate (3 equiv.) were added to a solution of Cbz-L-proline (3 equiv.) in dry THF (0.1 M), under inert atmosphere conditions and a temperature of 0 °C. The resulting mixture was stirred for 30 minutes and then the corresponding amine polymer (1 equiv., PS-DVB with benzyl amines (-CH_2NH_2), **1a** = low loading macroporous (0.5 meq/g), **1b** = high loading macroporous (2.0 meq/g)) was added. The mixture was stirred for three hours in an ice bath and then stirred at room temperature overnight. The resulting polymer was separated by filtration, washed with THF and MeOH, and dried under vacuum.

General procedure for the synthesis of 3.



L-proline

Piv-*L*-proline

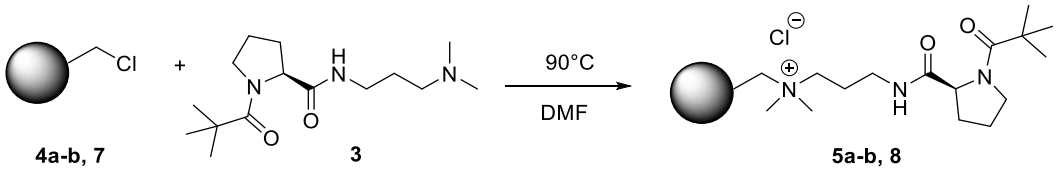
3

Step 1. Synthesis of the Piv-L-proline.[2] L-proline (10 g, 86.86 mmol) was added to a round-bottomed flask and dissolved in 50 mL of NaOH solution (2 M). This mixture was cooled to 0 °C with an ice bath and 10.70 mL (86.86 mmol) of pivalyl chloride and 40 mL of NaOH solution (2 M) were added alternately several times, periodically checking that the pH of the solution remained strongly alkaline during the process. After the addition was complete, the reaction mixture was stirred at room temperature for one hour. Next, the mixture was extracted with CH_2Cl_2 (3 x 25 mL), and the aqueous phase was collected and acidified to pH 1-2 by adding HCl. Finally, it was extracted with CH_2Cl_2 (3 x 25 mL). The resulting organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed by distillation at reduced pressure to obtain the desired product (**Piv-L-proline**).

Step 2. Synthesis of compound 3. Triethylamine (1 equiv.) and ethyl chloroformate (1 equiv.) were added to a solution of the **Piv-L-proline** (1 equiv.) in dry THF (0.63 M),

under inert atmosphere conditions and a temperature of 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C and then *N,N'*-dimethylpropane-1,3-diamine (1 equiv.) was added dropwise. The mixture was stirred for three hours in an ice bath and then stirred at room temperature overnight. The mixture reaction was filtered and the solvent was removed by distillation at reduced pressure. The obtained product was purified by an acid extraction with solution HCl 1 M and CH_2Cl_2. The aqueous phase was collected and basified to pH 10-12 by adding NaOH 2 M. Finally, it was extracted with CH_2Cl_2, the organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed by distillation at reduced pressure to obtain compound **3**.

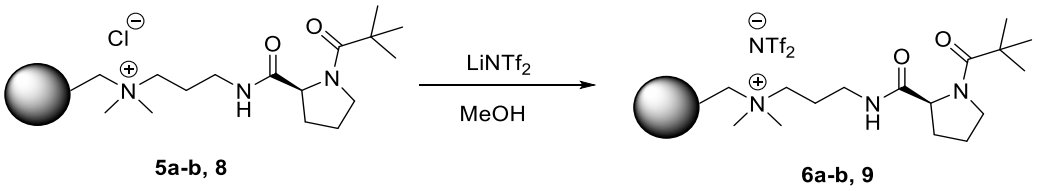
General procedure for the synthesis of 5a-b and 8.



4a-b, 7 **3** **5a-b, 8**

A solution of product **3** (3 equiv.) in DMF (1.27 M) was added to the corresponding Merrifield polymer (1 equiv., PS-DVB with benzyl chloride (-CH_2NH_2), **4a** = low loading macroporous (1.20 meq/g), **4b** = high loading macroporous (6.35 meq/g), **7** = low loading gel type (1.50 meq/g)) and the resulting mixture was stirred at 90 °C for 24 hours. The NBP test (4-(4-nitrobenzyl)pyridine) was performed to follow the reaction by taking a sample of the polymer and adding 300 µL of triethylamine and 9 drops of a solution of NBP in CH_2Cl_2/DMF (the polymer did not acquire any coloration, indicating that the substitution reaction had occurred successfully). The resulting polymer was separated by filtration, washed with THF and MeOH, and dried under vacuum.

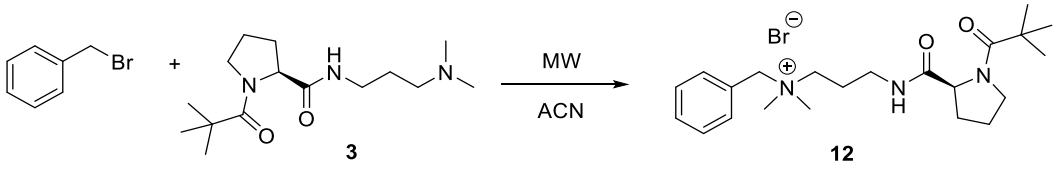
General procedure for the synthesis of 6a-b and 9.



A solution of $LiNTf_2$ (1.1 equiv.) in MeOH (0.17 M) was added to the corresponding polymer (1 equiv., **5a-b** or **8**) and stirred at room temperature for 24 hours. The resulting polymer was separated by filtration, washed with MeOH and dried under vacuum.

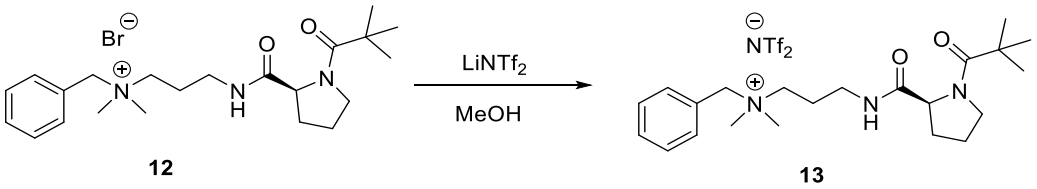
General procedure for the synthesis of imine 10.[3] A mixture of activated 4 Å molecular sieves (35 g), acetophenone (10 mL, 85.73 mmol) and aniline (10.16 mL, 111.44 mmol) in dry CH_2Cl_2 (40 mL) was stirred at room temperature for 24 h under a nitrogen atmosphere. The reaction mixture was filtered and the solvent was removed by distillation at reduced pressure. The crude was distilled by distillation under reduced pressure. The product was obtained in the distillate fraction when the temperature was 175-180°C, which it was solidified after cooling, giving a yellow solid.

General procedure for the synthesis of 12.



The product **3** (140 mg, 0.49 mmol), benzyl bromide (60 µL, 0.59 mmol) and acetonitrile (2 mL) were introduced in a reinforced glass tube of 10 mL of capacity. The resultant mixture was heated in a microwave oven (CEM Discover, CEM Microwave Technology Ltd, USA) at 150°C with low stirring and 120 Ws. The system was run at constant temperature operation mode by using the air-cooling feature of the apparatus and hold at this temperature for 90 minutes according to the experiment. Then, the tube was cooled down to room temperature. The resulting product was washed with MTBE and Et_2O, separated by filtration, and dried in vacuum.

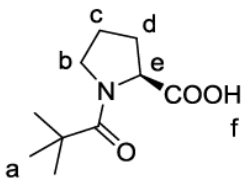
General procedure for the synthesis of 13.



A solution of $LiNTf_2$ (1.2 equiv.) in MeOH (0.27 M) was added to the corresponding compound **12** (1 equiv.) and stirred at room temperature for 24 hours. The solvent was removed by distillation at reduced pressure. Next, the mixture was extracted with ethyl acetate (30 mL) and washed with distilled water (3 x 10 mL). Finally, the organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed by distillation at reduced pressure to obtain compound **13**.

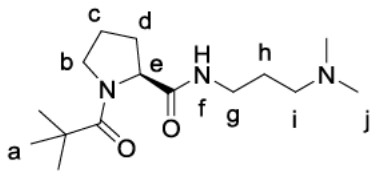
3. Characterization

Compound Piv-L-proline



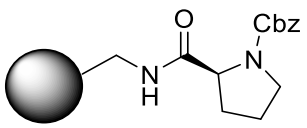
^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.26 (s, 9H, Ha), 1.89 - 2.00 (m, 1H, Hc1), 2.01 - 2.09 (m, 2H, Hc2+d1), 2.09 - 2.15 (m, 1H, Hd2), 3.65 - 3.78 (m, 2H, Hb), 4.50 - 4.60 (m, 1H, He), 11.36 (s, 1H, Hf) ppm.
^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 26.0 (Cc), 27.2 (Cd), 27.3 (Ca), 39.1 (Cquaternary), 48.5 (Cb), 61.6 (Ce), 175.7 (C=O), 178.6 (C=O) ppm.
IR (ATR) $\nu_{máx}$: 1423, 1479, 1508, 1581, 1747, 2877, 2914, 2937, 2978 cm^{-1}.
ESI-MS m/z (CH_3OH): 200.2 [$M+H^+$].

Compound 3



^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.25 (s, 9H, Ha), 1.57-1.67 (m, 2H, Hh), 1.82-1.95 (m, 2H, Hc), 1.96-2.14 (m, 1H, Hd1), 2.15-2.26 (m, 7H, Hd2+j), 2.26-2.36 (m, 2H, Hi), 3.21-3.37 (m, 2H, Hg), 3.58-3.66 (m, 1H, Hb1), 3.66-3.75 (m, 1H, Hb2), 4.50-4.62 (m, 1H, He), 6.92-7.24 (m, 1H, Hf) ppm.
^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 25.9 (Cc), 26.8 (Cd), 27.7 (Ca), 38.7 (Cquaternary), 39.3 (Ch), 45.6 (Cj), 48.4 (Cb), 58.2 (Ci), 62.0 (Ce), 172.2 (C=O), 177.7 (C=O) ppm.
IR (ATR) $\nu_{máx}$: 1232, 1265, 1361, 1373, 1385, 1421, 1451, 1479, 1549, 1599, 1685, 2763, 2777, 2811, 2852, 2875, 2905, 2938, 2961, 2974, 3300 cm^{-1}.
ESI-MS m/z (CH_3OH): 284.4 [$M+H^+$].

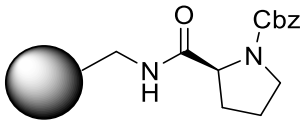
Compound 2a



(0.18 meq/g)

IR (ATR) $\nu_{máx}$: 695, 753, 1450, 1493, 1599, 1690, 2851, 2921, 3026, 3060 cm^{-1}.
Elemental analysis (%): Experimental: C 87.07, H 6.82, N 0.51.

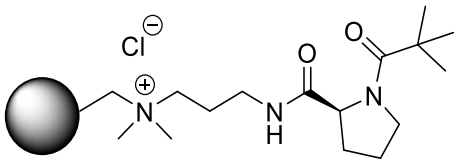
Compound 2b



(1.24 meq/g)

IR (ATR) $\nu_{máx}$: 696, 756, 1246, 1449, 1495, 1511, 1689, 1725, 2851, 2921, 3024, 3057, 3310, 3339 cm^{-1}.
Elemental analysis (%): Experimental: C 82.34, H 7.46, N 3.48.

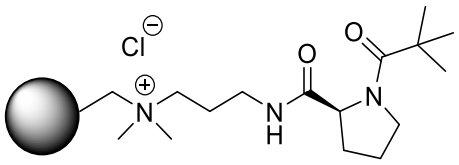
Compound 5a



(0.74 meq/g)

IR (ATR) $\nu_{máx}$: 699, 759, 1364, 1384, 1411, 1452, 1492, 1604, 1669, 2925, 2956, 3026 cm^{-1}.
Elemental analysis (%): Experimental: C 72.54, H 7.13, N 3.10.

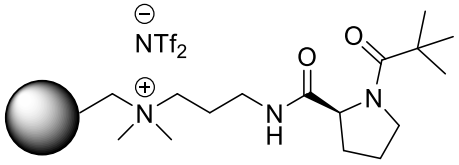
Compound 5b



(2.11 meq/g)

IR (ATR) $\nu_{máx}$: 1233, 1362, 1381, 1409, 1446, 1479, 1523, 1541, 1556, 1607, 1667, 2878, 2957 cm^{-1}.
Elemental analysis (%): Experimental: C 63.79, H 8.89, N 8.88.

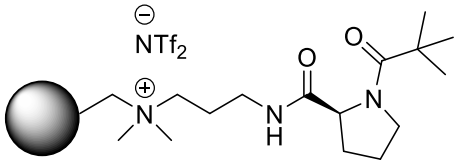
Compound 6a



(0.33 meq/g)

IR (ATR) $\nu_{máx}$: 618, 699, 760, 1058, 1136, 1188, 1226, 1351, 1452, 1492, 1604, 1669, 2925, 3026 cm^{-1}.
Elemental analysis (%): Experimental: C 35.63, H 3.52, N 1.83, S 1.87.

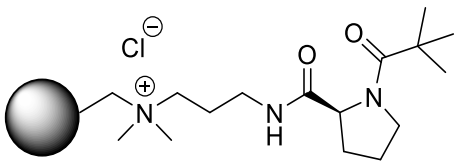
Compound 6b



(1.43 meq/g)

IR (ATR) $\nu_{máx}$: 616, 1056, 1135, 1183, 1227, 1330, 1351, 1412, 1447, 1480, 1525, 1539, 1606, 1668, 2922, 2935, 2975 cm^{-1}.
Elemental analysis (%): Experimental: 48.37, H 6.11, N 8.02, S 7.74.

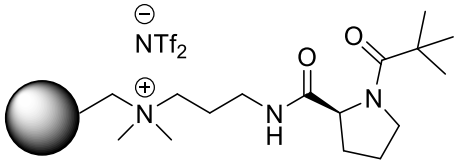
Compound 8



(0.77 meq/g)

IR (ATR) $\nu_{máx}$: 697, 756, 1372, 1411, 1446, 1456, 1607, 1672, 2922, 3025 cm^{-1}.
Elemental analysis (%): C 82.30, H 7.91, N 3.24.

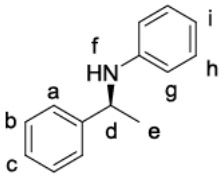
Compound 9



(0.62 meq/g)

IR (ATR) $\nu_{máx}$: 612, 697, 755, 1057, 1139, 1187, 1349, 1414, 1447, 1486, 1529, 1606, 1674, 2854, 2921, 3026, 3056 cm^{-1}.
Elemental analysis (%): C 74.51, H 6.96, N 3.46, S 3.62.

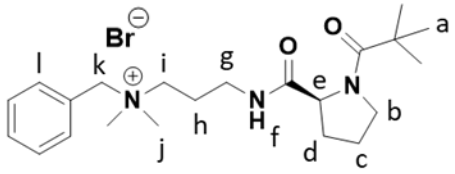
Compound 11



^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.50 (d, *J* = 7.1 Hz, 3H, He), 3.95 (s, 1H, Hf), 4.48 (q, *J* = 6.9 Hz, 1H, Hd), 6.50 (d, *J* = 7.9 Hz, 2H, Hg), 6.65 (t, *J* = 7.4 Hz, 1H, Hi), 7.06 (dd, *J*

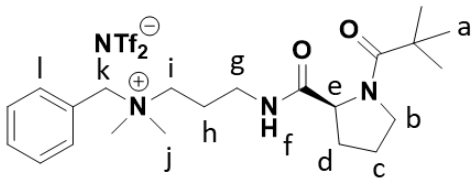
= 8.9 Hz, 7.4 Hz, 2H, Hh), 7.22 (t, *J* = 7.4 Hz, 1H, Hc), 7.33 (t, *J* = 8.1 Hz, 2H, Ha), 7.36 (d, *J* = 7.4 Hz, 2H, Hb) ppm.
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 25.0 (Ce), 53.4 (Cd), 113.2 (Cg), 117.2 (Ci), 125.8 (Ca), 126.8 (Cc), 128.6 (Cb), 129.1 (Ch), 145.2 (Cquaternary), 147.2 (Cquaternary) ppm.
HPLC: t_R (*S*-amine): 26 min.

Compound 12



^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.22 (s, 9H, Ha), 1.78-1.95 (m, 2H, Hh), 2.03-2.24 (m, 2H, Hc+d1), 2.28-2.42 (m, 1H, Hd2), 3.16 (s, 3H, Hj), 3.18-3.28 (m, 4H, Hb1+j), 3.55-3.89 (m, 5H, Hb2+i+g), 4.50 (dd, J = 7.8, 5.8 Hz, 1H, He), 4.77 (q, J = 12.8 Hz, 2H, Hk), 7.42-7.52 (m, 3H, Hl), 7.56 (m, 2H, Hl), 8.09 (m, 1H, Hf) ppm.
^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 23.5 (Cc), 27.7 (Ca), 28.6 (Cquaternary), 35.4 (Cg), 38.9 (Ch), 49.0 (Cj), 49.3 (Cb), 50.1 (Cj) 62.7 (Ci), 62.9 (Ce), 68.3 (Ck), 127.3 (Cquaternary), 129.5 (Cl), 130.9 (Cl), 133.3 (Cl), 173.9 (C=O), 176.9 (C=O) ppm.
IR (ATR) $\nu_{máx}$: 613, 653, 703, 736, 762, 788, 876, 924, 1001, 1053, 1135, 1180, 1349, 1412, 1482, 1532, 1606, 1669, 2974, 3394 cm^{-1}.
ESI-MS m/z (CH_3OH): 374.5 [M^+].

Compound 13



^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.24 (s, 9H, Ha), 1.78-1.99 (m, 2H, Hh), 1.99-2.22 (m, 4H, Hc+d), 2.96 (s, 3H, Hj), 3.01 (m, 3H, Hj), 3.19-3.29 (m, 1H, Hb), 3.41-3-53 (m, 1H, Hb), 3.54-3.68 (m, 2H, Hg), 3.75 (t, J = 6.3 Hz, 1Hi), 4.25 (m, 1H, He), 4.46 (s, 2H, Hk), 6.65 (m, 1H, Hf), 7.42-7.56 (m, 5H, Hl) ppm.
^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 23.3 (Cc), 27.6 (Ca), 28.4 (Cquaternary), 35.3 (Cg), 38.9 (Ch), 49.0 (Cj), 49.1 (Cb), 49.7 (Cj) 62.1 (Ci), 62.3 (Ce), 68.9 (Ck), 115.9 (C-F), 118.8 (C-F), 121.6 (C-F), 124.7 (C-F), 126.7 (Cquaternary), 129.7 (Cl), 131.3 (Cl), 132.9 (Cl), 173.9 (C=O), 177.4 (C=O) ppm.
IR (ATR) $\nu_{máx}$: 618, 709, 739, 786, 867, 935, 1032, 1087, 1178, 1224, 1374, 1403, 1450, 1483, 1525, 1611, 1638, 2873, 2971, 3030, 3220 cm^{-1}.
ESI-MS m/z (CH_3OH): 374.5 [M^+].

4. Supporting figures

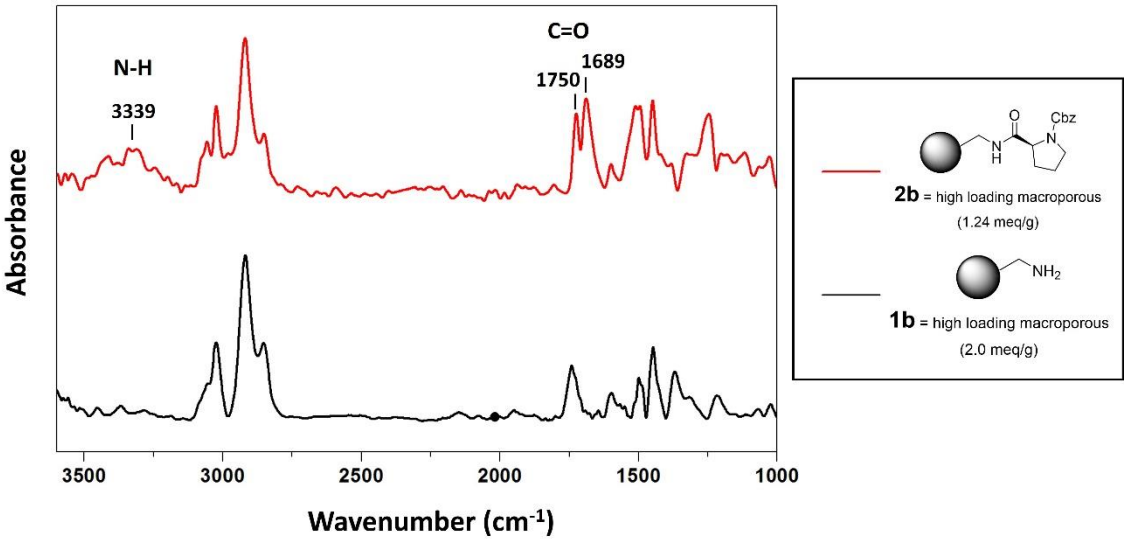


Figure S1: Comparison of FT-ATR-IR spectra for synthesis of **2b**.

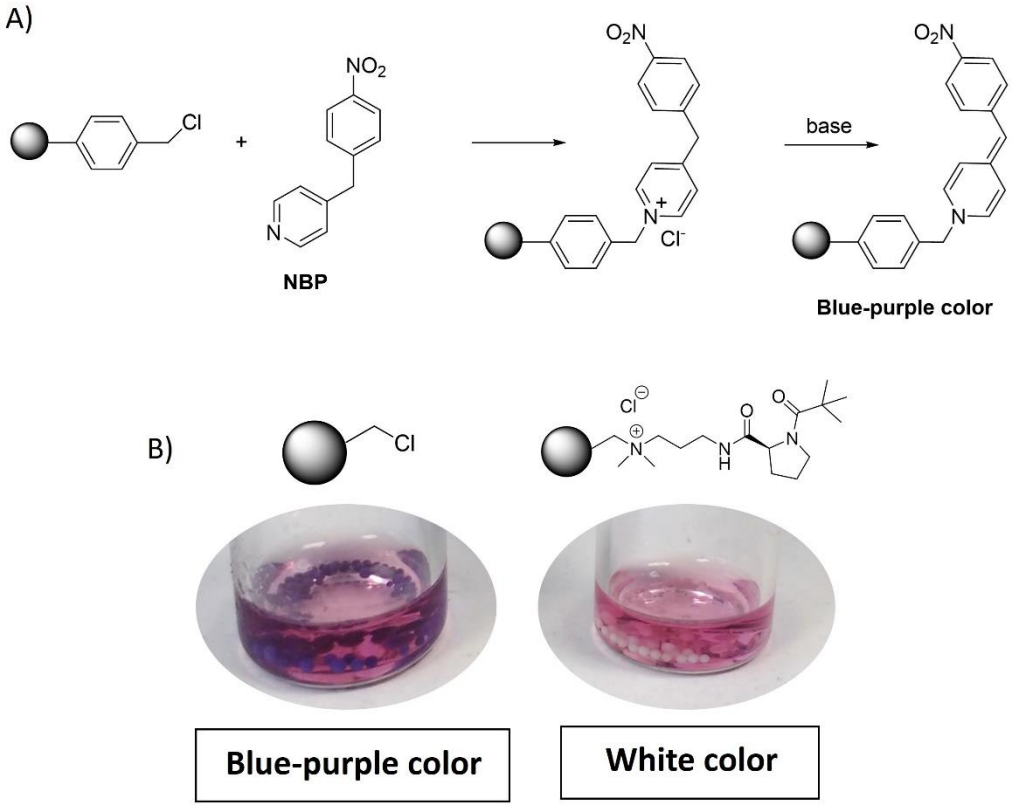


Figure S2: A) Reaction of the NBP test . B) Examples of a positive test (the resin shows blue-purple color) and a negative test (the resin shows white color).

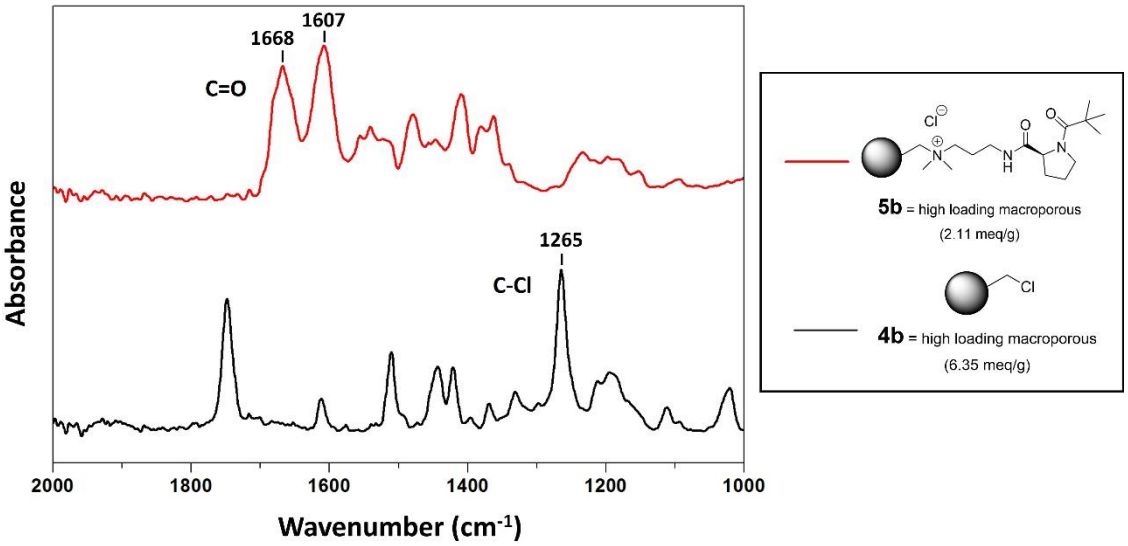


Figure S3: Comparison of FT-ATR-IR spectra for synthesis of **5b**.

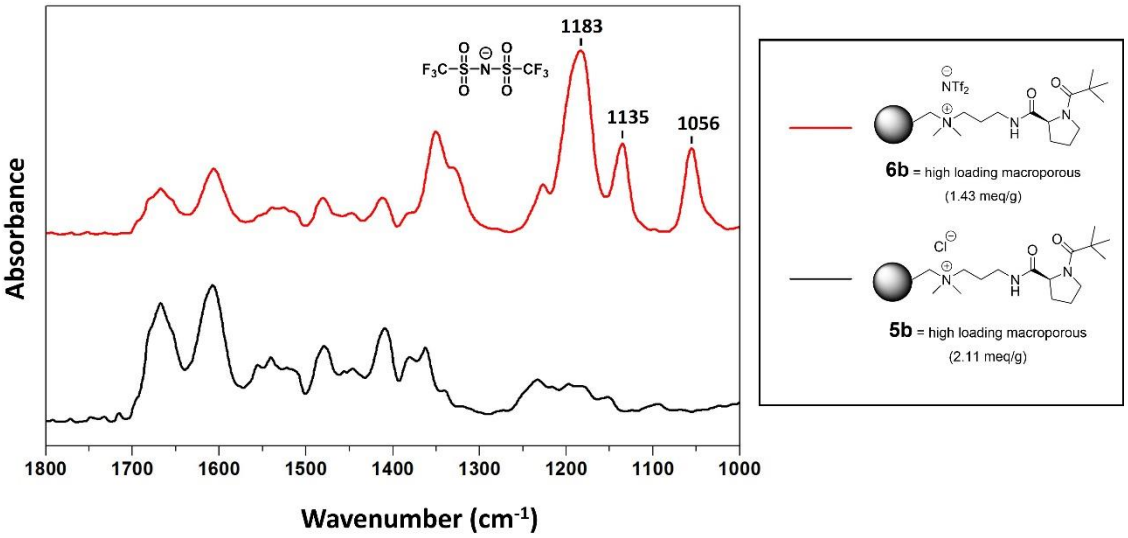


Figure S4: Comparison of FT-ATR-IR spectra for synthesis of **6b**.

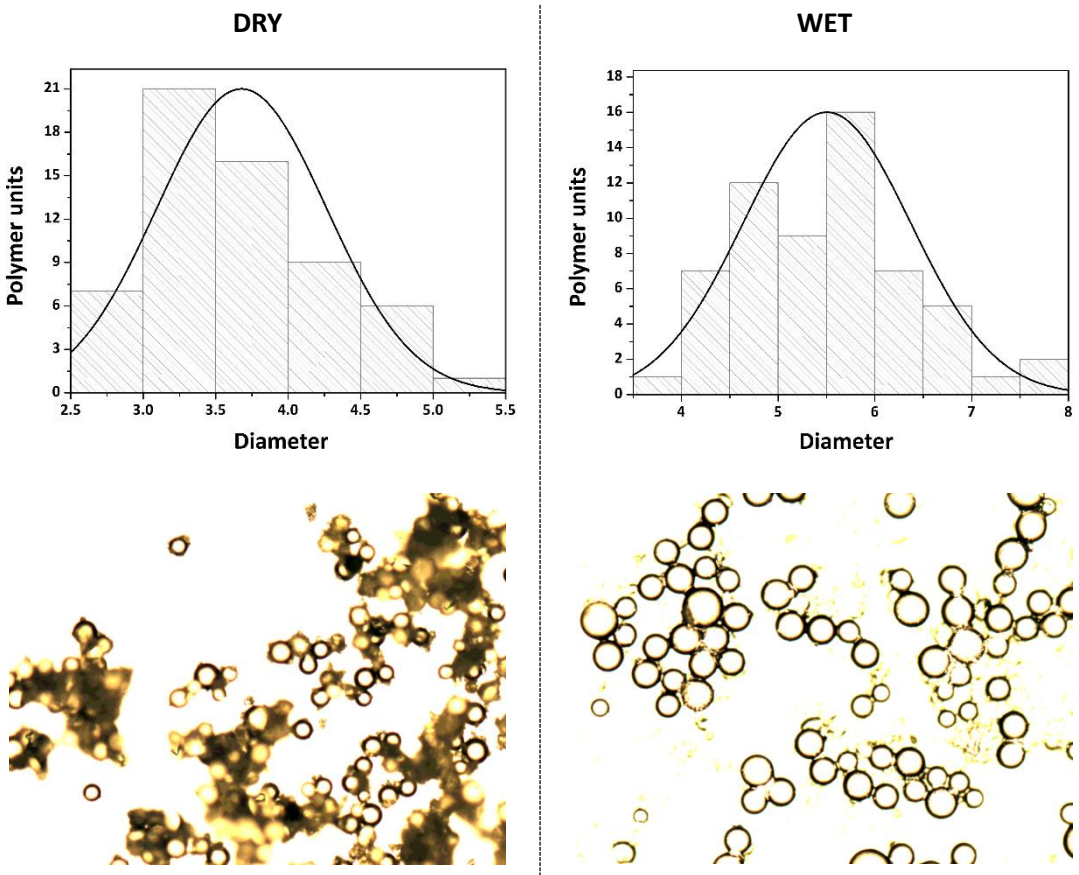


Figure S5: Determination of the swelling of polymer **8** using optical microscopy measurements. Swelling of 49%.

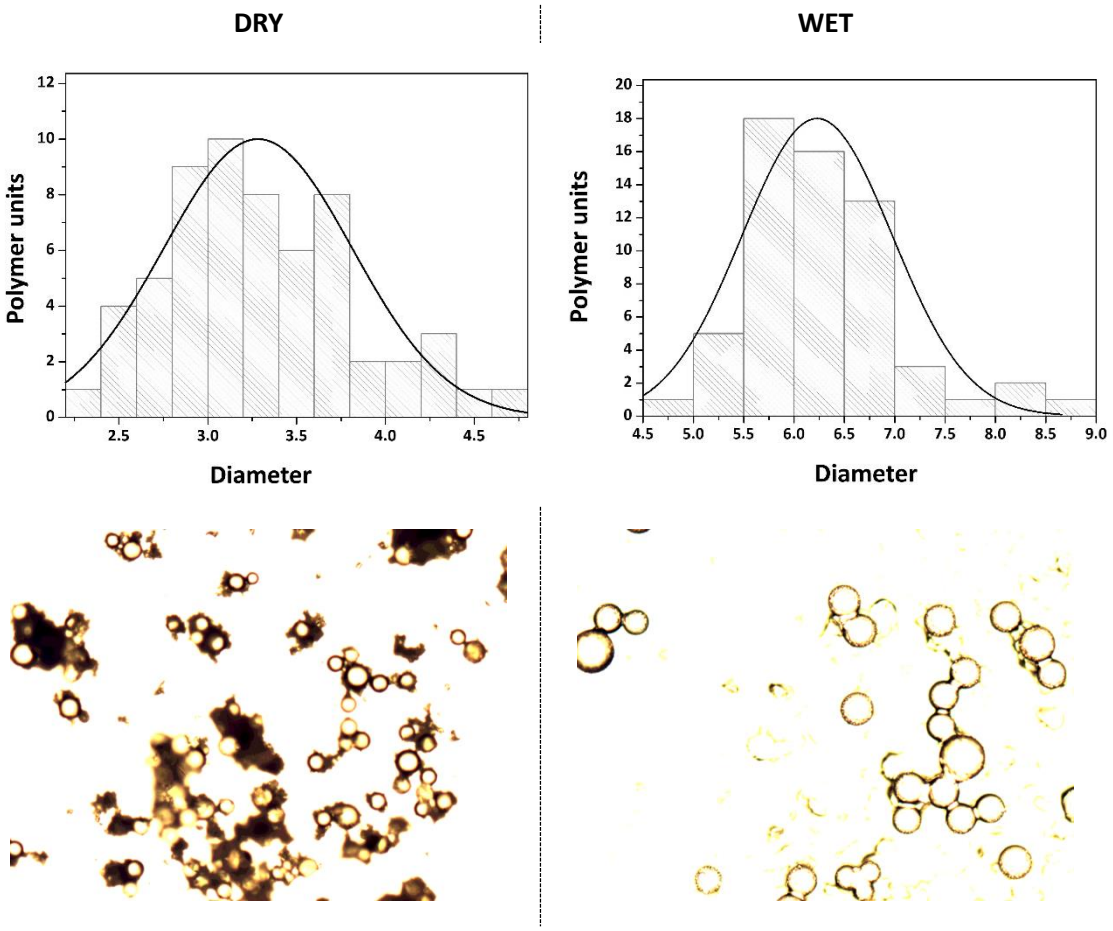


Figure S6: Determination of the swelling of polymer **9** using optical microscopy measurements. Swelling of 90%.

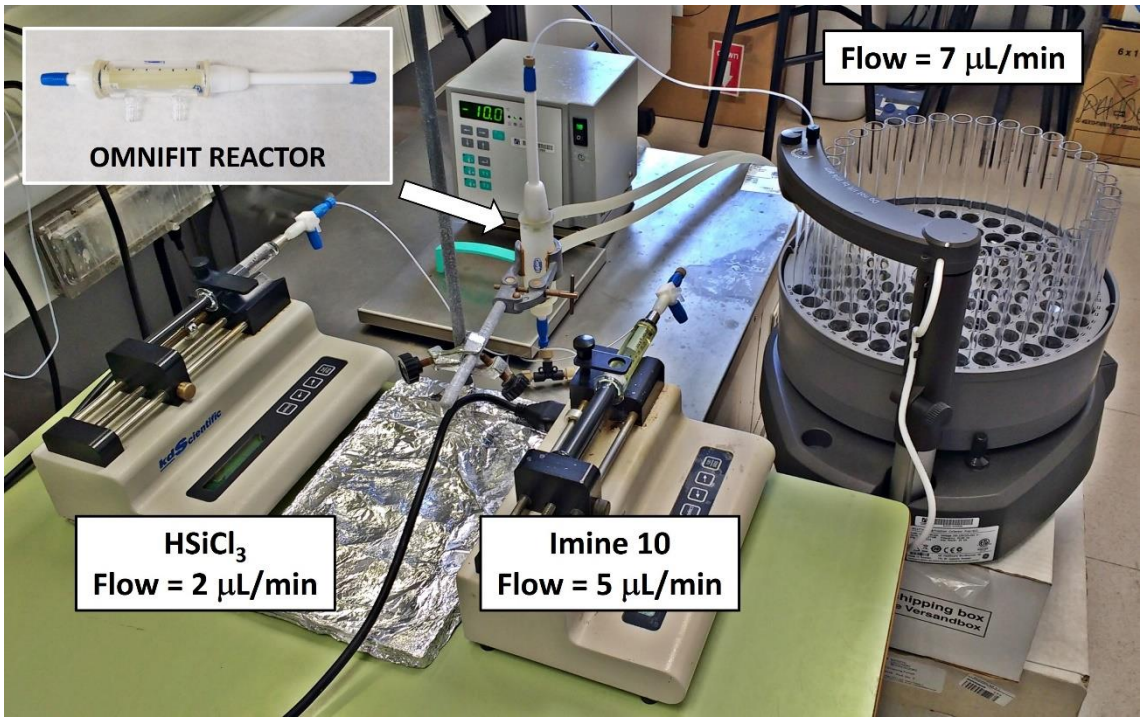


Figure S7: Continuous flow imine reduction system using an Omnifit reactor containing the catalyst **9**.

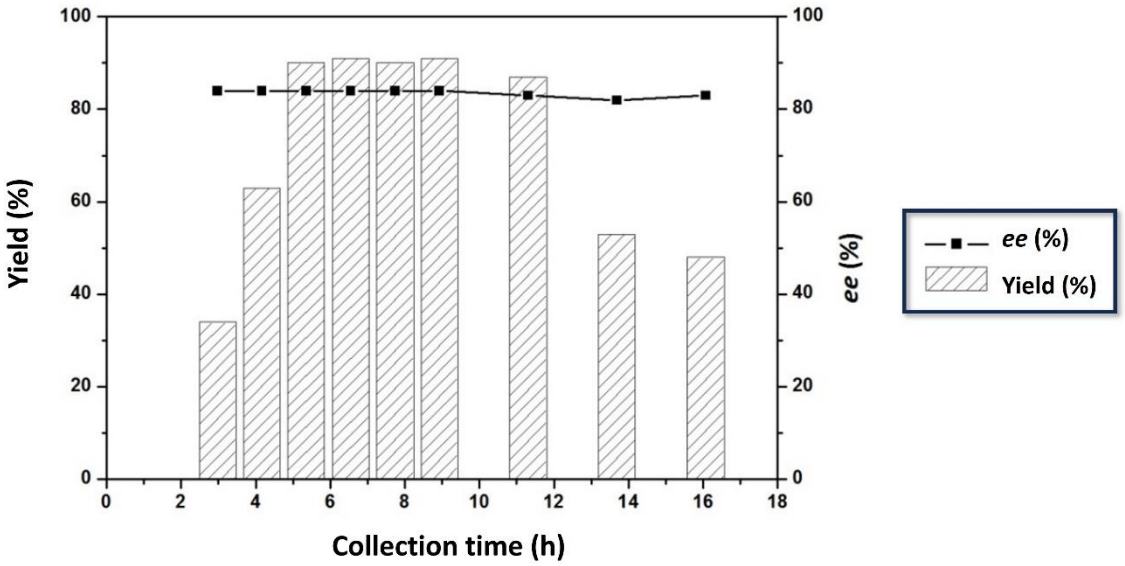
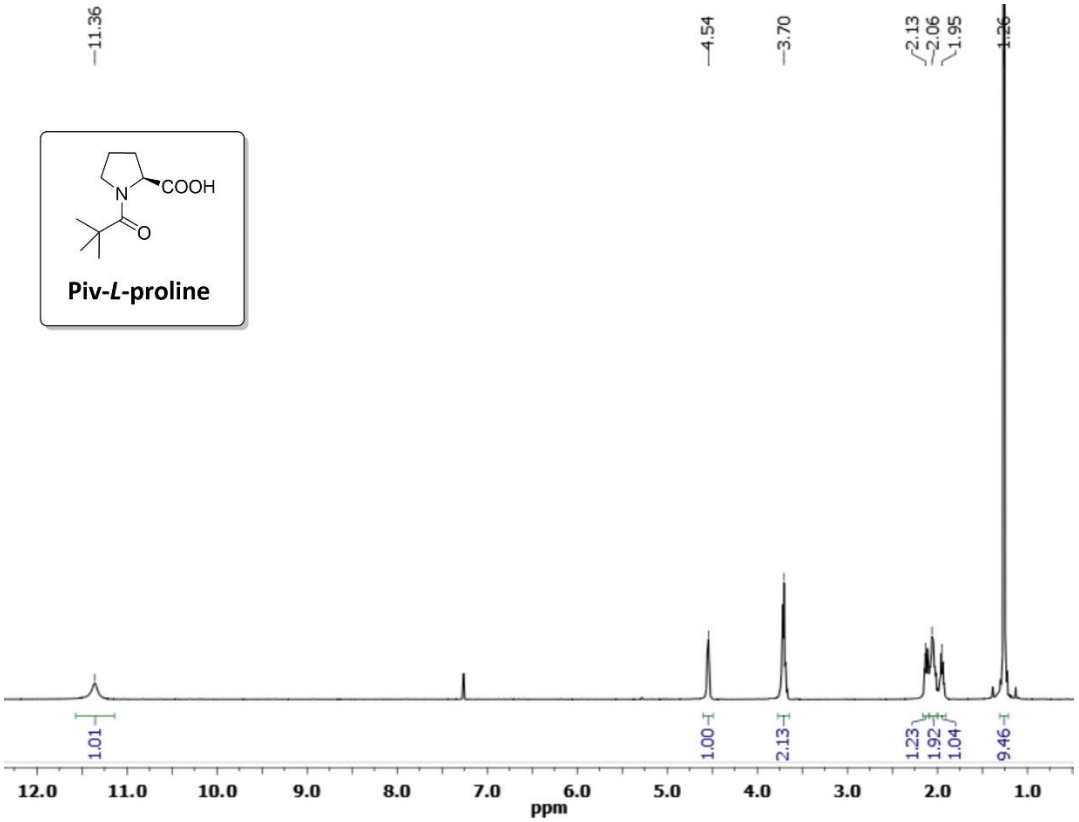


Figure S8: Representation of the yield and the enantiomeric excess obtained in each fraction collected in the continuous flow system.

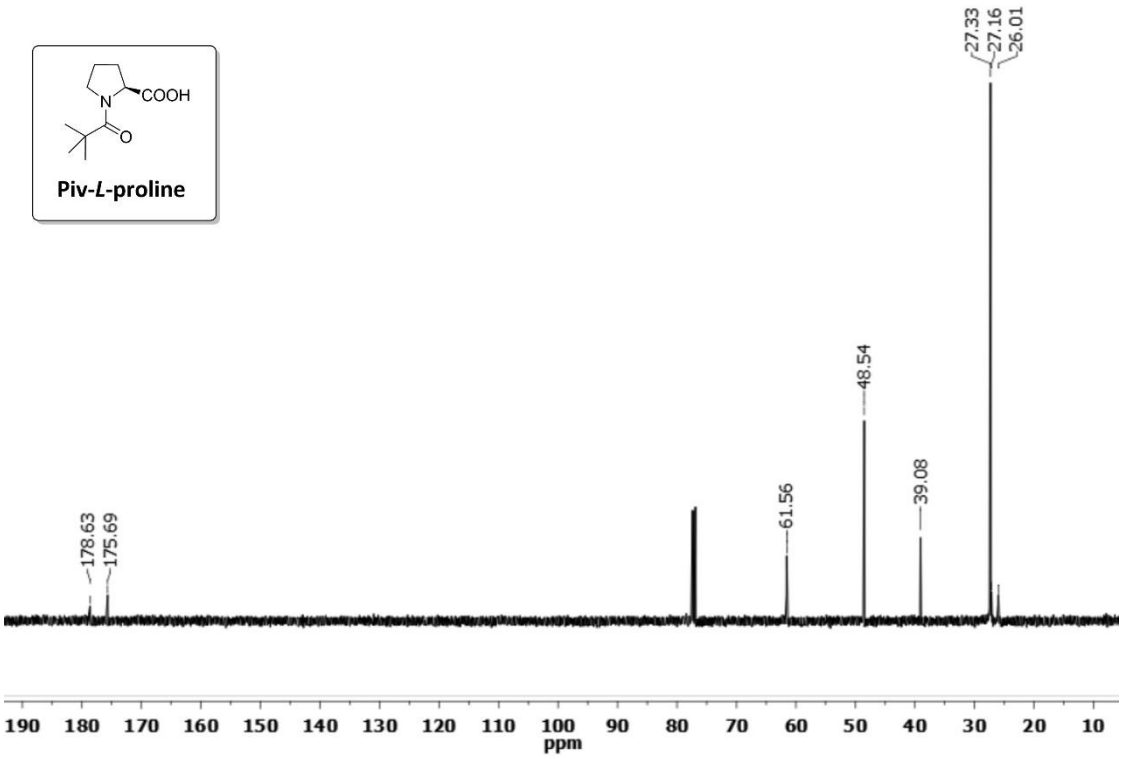
5. NMR spectra

Compound Piv-L-proline

^{1}H-NMR ($CDCl_3$, 500 MHz, rt):

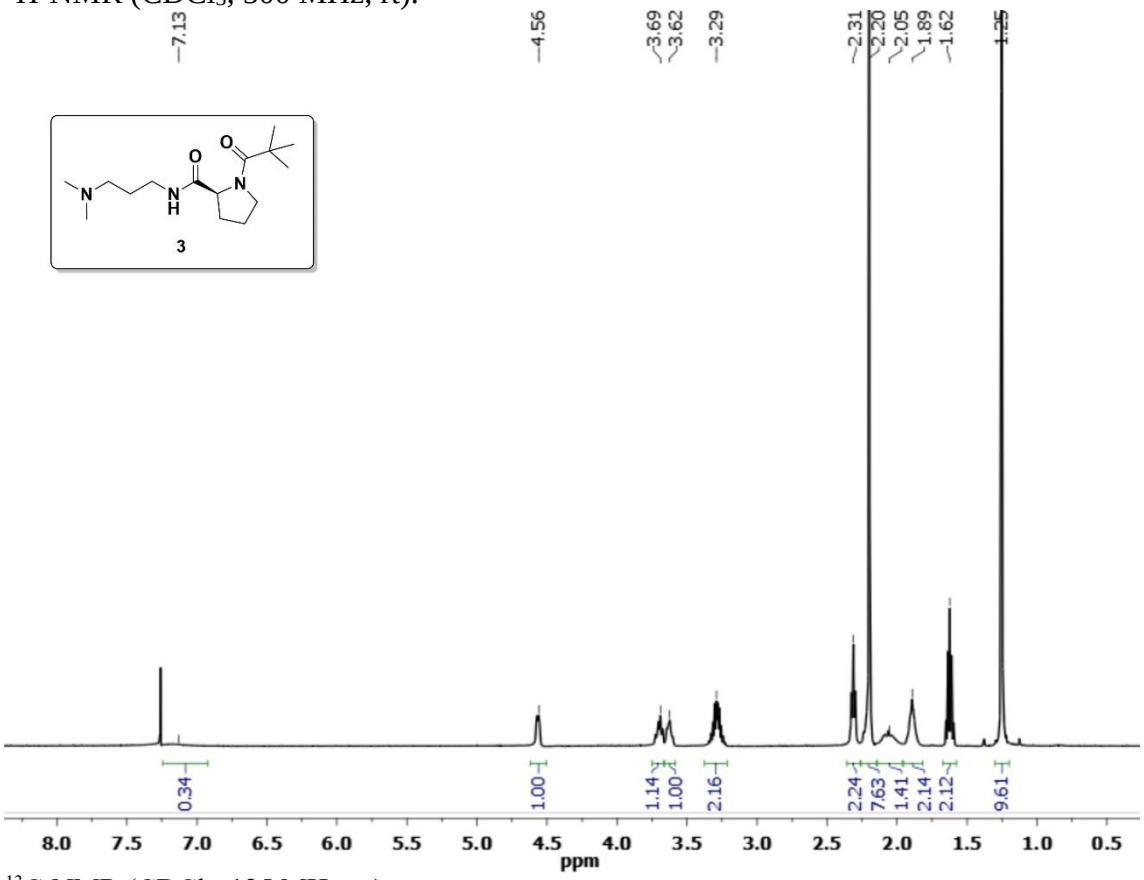


^{13}C-NMR ($CDCl_3$, 125 MHz, rt):

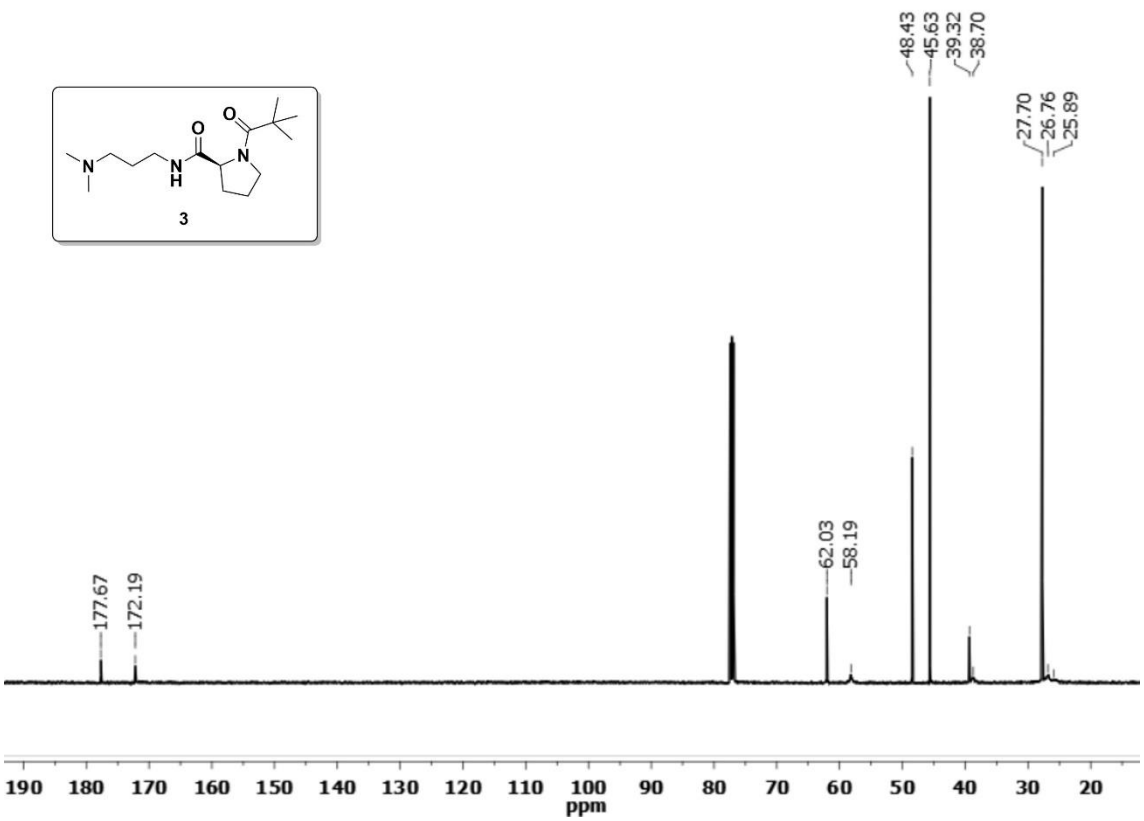


Compound 3

^{1}H-NMR ($CDCl_3$, 500 MHz, rt):

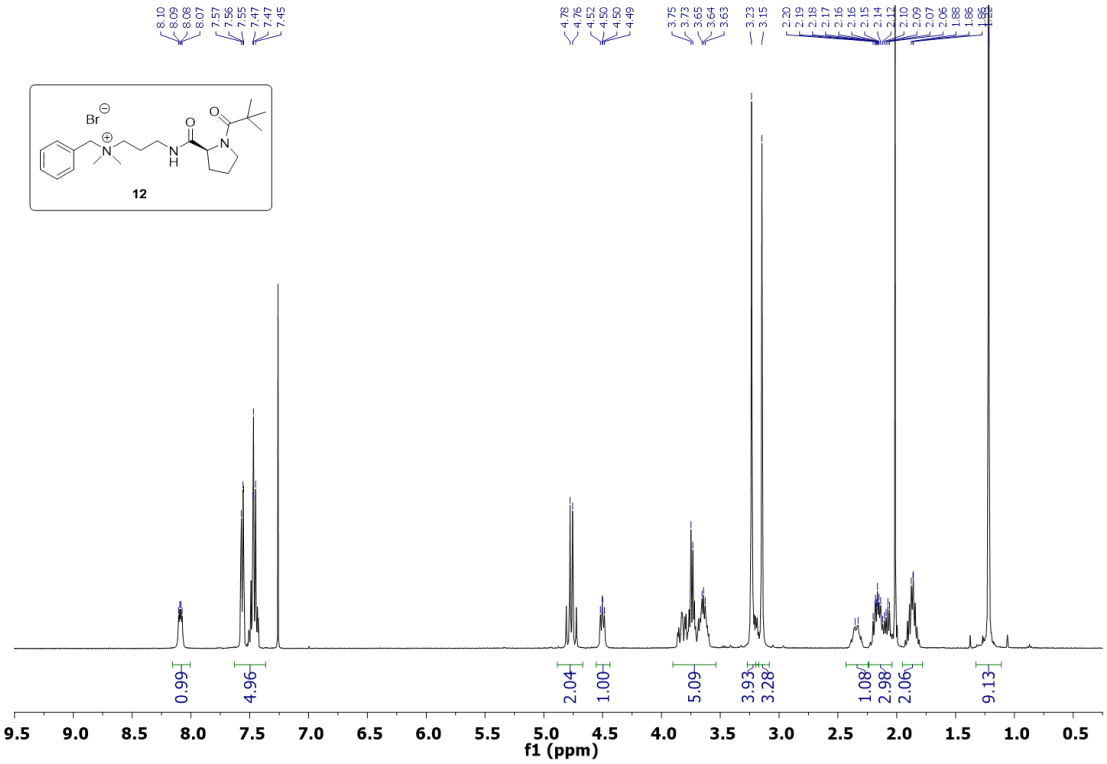


^{13}C-NMR ($CDCl_3$, 125 MHz, rt):

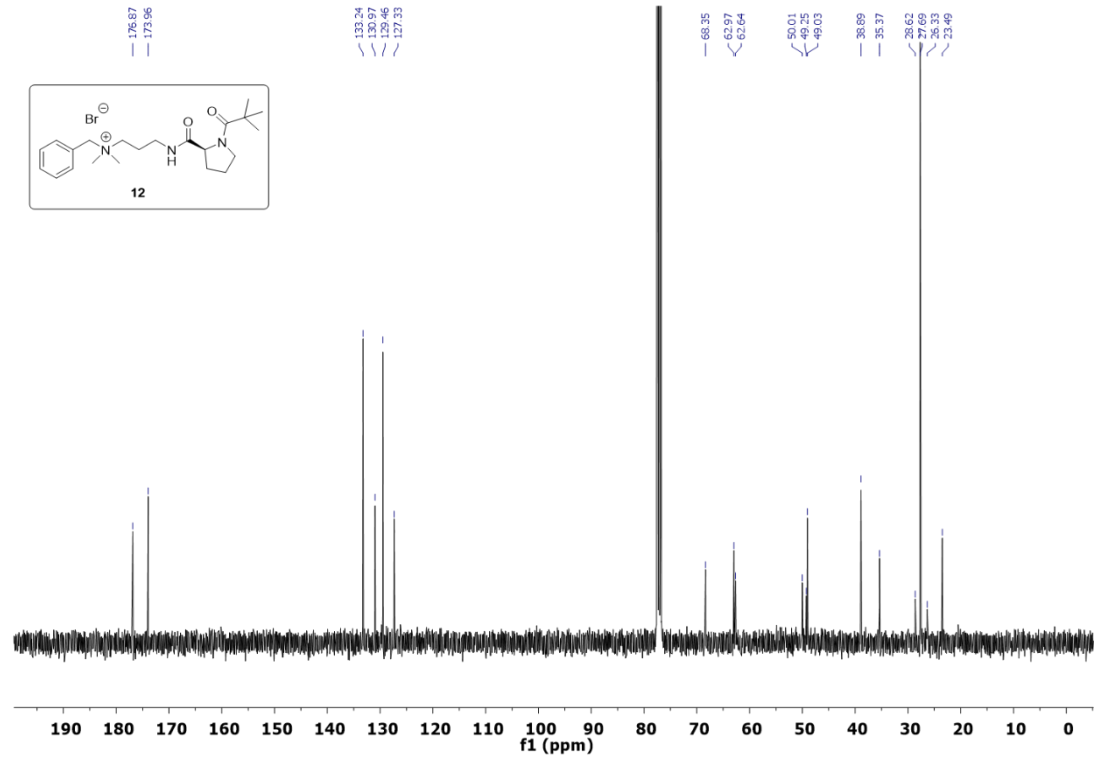


Compound 12

^{1}H-NMR (500 MHz, $CDCl_3$, rt)

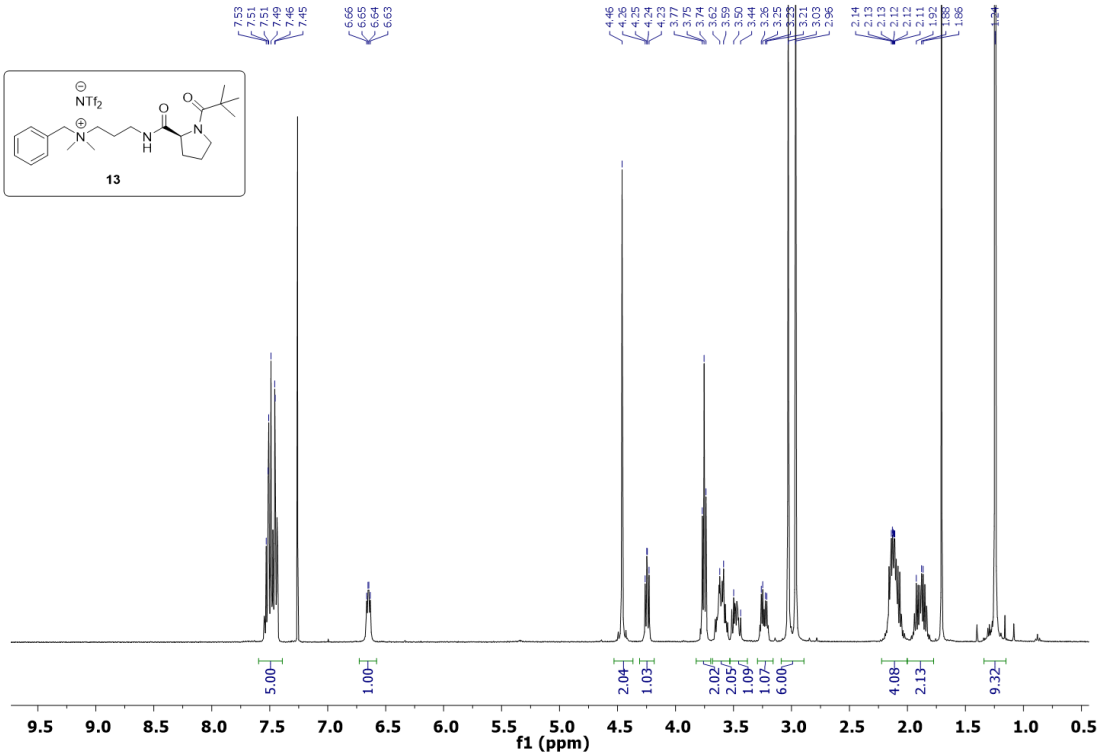


^{13}C-NMR (125 MHz, $CDCl_3$, rt)

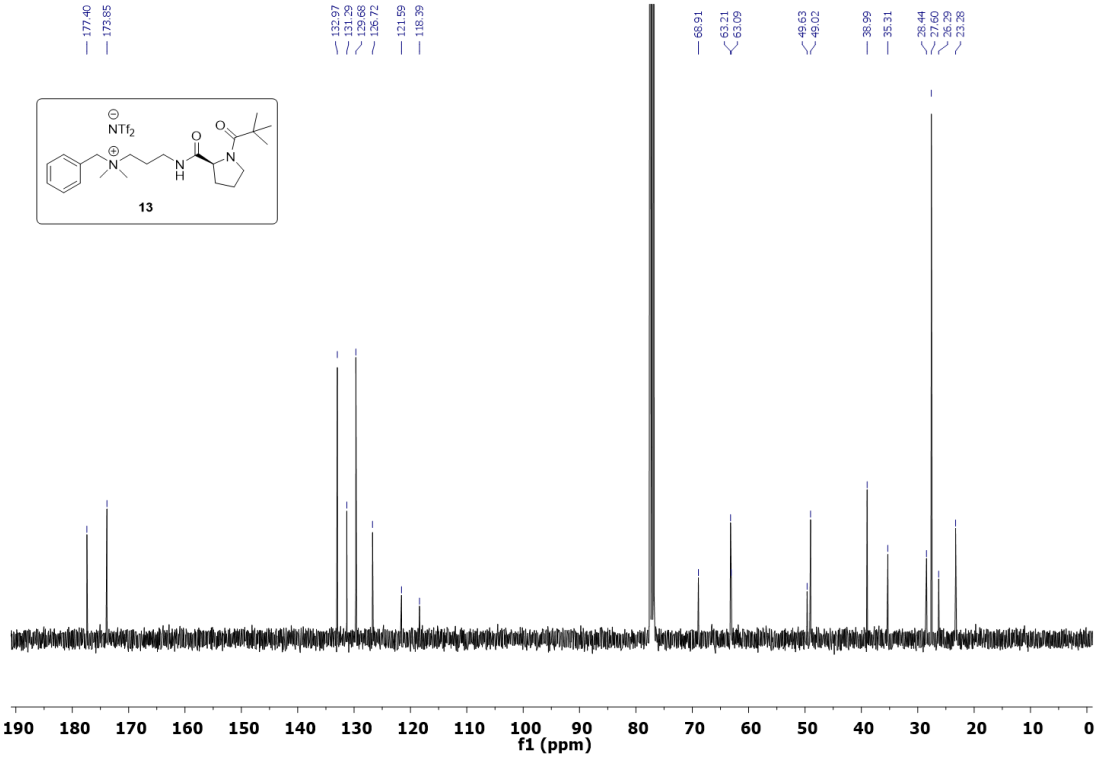


Compound 13

^{1}H-NMR (500 MHz, $CDCl_3$, rt)



^{13}C-NMR (125 MHz, $CDCl_3$, rt)



6. References

[1] Becerril, J.; Bolte, M.; Burguete, M. I.; Galindo, F.; Garcia-Espana, E.; Luis, S. V.; Miravet, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6677.
[2] Pirkle, W. H.; Murray, P. G.; Rausch, D. J.; McKenna, S. T. *J. Org. Chem.* **1996**, *61*, 4769.
[3] F-M. Gautier, S. Jones, S. J. Martin. *Org. Biomol. Chem.* **2009**, *7*, 229-231.