Supplementary Material for Chemical Communications

Supplementary data

Protonated N'-benzyl-N'-prolyl Proline Hydrazide as Highly Enantioselective Catalyst for Direct Asymmetric Aldol Reaction

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Generalities: NMR spectra were recorded on a Brucker-600 MHz spectrometer. Optical rotations were measured on a Perkin-Elmer 341 Polarimeter at λ = 589 nm. ESIMS spectra were recorded on BioTOF Q. HPLC analyses were performed on PerkinElmer (Series 200 UV/VIS Detector and Series 200 Pump). Chiralpak AS-H and OJ-H columns were purchased from Daicel Chemical Industries, LTD. Acetone was dried over anhydrous K_2CO_3 and then was distilled by adding P_2O_5. Hexane and ethyl acetate for column chromatography were distilled before use. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Chemical shifts were reported in ppm using the solvent residue signals as reference.

Materials: All starting materials were of the highest commercially available grade and used without further purification.

Procedure for the synthesis of Boc-1: To a solution of Boc-L-Pro (430 mg, 2.0 mmol) in DCM (20 mL) was added 4-nitrophenylhydrazine (370 mg, 2.4 mmol), HOBt (350 mg, 2.4 mmol), N, N-Diisopropylethylamine (DIEA, 700 μL) and EDCI (460 mg, 2.4 mmol) at 0 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 12 h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-1.**

Procedure for the synthesis of 1: After compound **Boc-1** (1.0 g) with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) was stirred for half an hour, the solution was evaporated to dryness and then passed through a H^+ ion-exchange resin column eluted with $NH_3 \cdot H_2O$ (3.0 M). After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 20: 1) to give **1.**

1: Yellow solid; Yield: 60%; $[\alpha]_D^{25}$ = -79.9 (c = 0.244, MeOH); mp 153.0-154.0□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.80-1.91 (m, 3H), 2.20-2.23 (m, 1H), 2.93-2.97 (m, 1H), 3.06-3.10 (m, 1H), 3.76 (dd, *J* =2.82 Hz, 5.7 Hz, 1H), 6.80 (d, *J* = 9.12 Hz, 2H), 8.10 (d, *J* = 9.18 Hz, 2H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 25.6, 30.1, 46.6, 59.2, 110.6, 125.4, 139.5, 154.3, 175.0. ESI HRMS exact mass calcd for $(C_{11}H_{14}N_4O_3 + H)^+$ requires m/z 251.1139, found m/z 251.1122.

Procedure for the synthesis of 2 is similar to that for 1.

2: yellow solid; Yield: 78%; $[\alpha]_D^{25}$ = -39.5 (c = 0.238, MeOH); mp 198-200□; The ^{1}H and ^{13}C NMR spectra showed a double set of peaks due to different conformers. ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.99-2.18 (m, 3H), 1.94 (brs, 1H), 2.43 (m, 1H), 3.34-3.38 (m, 2H), 4.40-4.63 (m, 1H), 6.83 (m, 5H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 23.6, 23.7, 28.9, 29.6, 45.9, 46.0, 58.5, 58.8, 112.6, 112.8, 120.1, 120.7, 128.7, 129.0, 147.5, 148.1, 168.6, 173.0. ESI HRMS exact mass calcd for $(C_{11}H_{15}N_3O_1 + H)^+$ requires m/z 206.1288, found m/z 206.1279.

Procedure for the synthesis of Boc-L-Pro-NHNH$_2$: Compound **Boc-4** (see procedure for the synthesis of Boc-**4**) (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Boc-4** disappeared completely (monitored by TLC), the solution was filtered. Removal of solvent gave Boc-L-Pro-NHNH$_2$.

Procedure for the synthesis of Boc-3: To a mixture of solution of Boc-L-Pro-NHNH$_2$ (460 mg, 2.0 mmol) and TEA (1.4 mL, 10 mmol) in DCM (20 mL) was added benzyl bromide (1.2 mL, 10 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (30 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried over

anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-3.**

Procedure for the synthesis of 3: Compounds **Boc-3** (1.0 g) was treated with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for half an hour and then concentrated under reduced pressure. After saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, the solution was extracted three times with EtOAc (30 mL each). The organic layers were combined, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 20: 1) to give **3**

3: white solid; Yield: 66%; $[\alpha]_D^{25}$ = -19.8 (c = 0.242, MeOH); mp 204-206□; ^{1}HNMR (600 MHz, CD_3OD) The ^{1}H and ^{13}C NMR spectra show a double set of peaks due to different conformers. δ (ppm) 1.12-1.23 (m, 1H), 1.58 (m, 2H), 1.90 (m, 1H), 3.13 (m, 2H), 3.87 (m, 1H), 3.95 (m, 2H), 4.07 (m, 2H), 7.24 (m, 10H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 23.2, 23.4, 28.6, 29.7, 45.8, 46.2, 57.7, 58.4, 60.8, 61.6, 62.3, 127.3, 127.9, 128.3, 129.1, 129.8, 136.0, 136.2, 136.8, 166.8, 171.2. ESI HRMS exact mass calcd for $(C_{19}H_{24}N_3O_1 + H)^+$ requires m/z 310.1914, found m/z 310.1924.

Procedure for the synthesis of Boc-4: To a solution of Boc-L-Pro (430 mg, 2.0 mmo) in DCM (20 mL) was added benzyloxycarbonylhydrazine (400 mg, 2.4 mmol), HOBt (350 mg, 2.4 mmol), N,N-diisopropylethylamine (DIEA, 700 μL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 12 h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-4.**

Procedure for the synthesis of 4: Compound **Boc-4** (1.0 g) was treated with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for half an hour and then concentrated under reduced pressure. After saturated aqueous $NaHCO_3$ (10 mL) was added to the residue, the solution was extracted three times with EtOAc (30 mL each). The organic layers were combined, washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 20: 1) to give **4.**

4: Off-white solid; Yield: 63%; $[\alpha]_D^{25}$ = -33.3 (c = 0.766, EtOAc); ^{1}HNMR (600 MHz, $CDCl_3$) δ(ppm) 1.66-1.75 (brs, 1H), 1.94 (brs, 1H), 2.09 (m, 1H), 2.95 (m, 2H), 3.80 (m, 1H), 5.10-5.16 (m, 2H), 7.31-7.34 (m, 5H); ^{13}CNMR (150 MHz, $CDCl_3$) δ (ppm) 26.0, 30.5, 38.1, 47.2, 59.8, 67.6, 128.2, 128.3, 128.5, 135.7, 156.1, 174.6. ESI HRMS exact mass calcd for $(C_{13}H_{17}N_3O_3 + Na)^+$ requires m/z 286.1162, found m/z 286.1148.

Procedure for the synthesis of 5 is similar to that for 4.

5: Off-white solid; Yield: 70%; $[\alpha]_D^{25}$ = -46.8 (c = 0.434, MeOH); ^{1}HNMR (600 MHz, $CDCl_3$) δ (ppm) 1.76-1.84 (m, 2H), 1.86-1.92 (m, 1H), 1.99 (s, 1H), 2.12-2.17 (m, 1H), 2.90-2.94 (m, 1H), 3.03-3.07 (m, 1H), 3.73 (dd, J = 6.06 Hz, 8.40 Hz, 1H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 19.1, 25.4, 30.5, 46.5, 59.2, 170.3, 174.0. ESI HRMS exact mass calcd for $(C_7H_{13}N_3O_2 + Na)^+$ requires m/z 194.0900, found m/z 194.0910.

Procedure for the synthesis of 6: To a mixture of solution of Boc-L-Pro-$NHNH_2$ (460 mg, 2.0 mmol) and TEA (1.4 mL, 10 mmol) in DCM (20 mL) was slowly added TFAA (600 μL, 4.0 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 0.5 h, quenched with MeOH and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (30 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL),

and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-6.**

Compound **Boc-6** (1.0 g) reacted with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for half an hour and then concentrated under reduced pressure. The residue was purified through column chromatography on silica gel (eluent: DCM: MeOH) = 10:1 to give **6.**

6: white solid; Yield: 66%; $[\alpha]_D^{25}$ = -8.6 (c = 0.51, MeOH); mp 208-210□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 2.08-2.18 (m, 3H), 2.46-2.52 (m, 1H), 3.34-3.38 (m, 1H), 3.40-3.45 (m, 1H), 4.38 (dd, *J* = 6.6 Hz, 8.28 Hz, 1H), 3.03-3.07 (m, 1H), 3.73-3.96 (m, 1H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 23.5, 29.4, 46.0, 58.6, 114.9, 116.8, 156.4, 156.7, 167.6. ESI HRMS exact mass calcd for $(C_7H_{10}F_3N_3O_3 + H)^+$ requires m/z 226.0798, found m/z 226.0789.

Procedure for the synthesis of Z-L-Pro-NHNH$_2$: To a solution of Z-L-Pro (500 mg, 2 mmol) in DMF (20 mL) was added $NH_2NH_2{\cdot}2HCl$ (250mg, 2.4 mmol), HOBt (350 mg, 2.4mol), DIEA (1.4 mL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 24h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: ethyl acetate = 4: 1) to give **Z-L- Pro-NHNH$_2$.**

Procedure for the synthesis of Z-7: To a solution of 1-Z-4-Boc-L-Piperazine-2-carboxylic acid (730 mg, 2 mmol) in DCM (20 mL) was added Z-L-Pro-NHNH$_2$ (631 mg, 2.4 mmol), HOBt (350 mg, 2.4mol), DIEA (1.4 mL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 24h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: Hexane: ethyl acetate = 1: 1) to give **Z-7.**

Procedure for the synthesis of 7: Compound **Z-7** (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Z-7** disappeared completely (monitored by TLC), the solution was filtered. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10:1) to give **7.**

7: off-white solid; Yield: 50%; $[\alpha]_D^{25}$ = +46.6 (c = 0.336, MeOH); mp 64.7-67.7□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm)1.46 (s, 9H), 1.77-1.85 (m, 2H), 1.89-1.94 (m, 1H), 2.13-2.19 (m, 1H), 2.67-2.71 (m, 1H), 2.93-3.10 (m, 5H), 3.37 (dd, *J* = 3.36 Hz, 9.54 Hz, 1H), 3.75-3.78 (m, 2H), 4.06 (brs, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 25.2, 27.2, 30.4, 43.5, 46.4, 56.9, 59.3, 80.1, 94.3, 154.9, 169.9, 172.9. ESI HRMS exact mass calcd for $(C_{15}H_{27}N_5O_4 + Na)^+$ requires m/z 364.1955, found m/z 364.1939.

Procedure for the synthesis of Z-8: To a solution of pyridine-2-carboxylic acid (295 mg, 2.4 mmol) in DCM (20 mL) was added Z-L-Pro-NHNH$_2$ (530 mg, 2 mmol), HOBt (350 mg, 2.4mol), N,N-Diisopropylethylamine (DIEA, 700μL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25^oC for 12 h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal

of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Z-8**

Procedure for the synthesis of 8: Compound **Z-8** (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Z-8** disappeared completely (monitered by TLC), the solution was filtered. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10: 1) to give **8.**

8: Yellow solid; Yield: 55%; $[\alpha]_D^{25}$ = -20 (c = 0.12, MeOH); The ^{1}H and ^{13}CNMR spectra show a double set of peaks in a ratio of about 2: 1 due to different conformers. ^{1}HNMR (600 MHz, CD_3OD)δ (ppm) 1.81-1.96 (m, 2H), 2.02-2.07 (m, 1H), 2.21-2.27 (m, 1H), 2.90 (m, 1H), 3.02 (m, 1H), 3.96 and 4.07 (dd, *J* = 6.06Hz, 8.46 Hz, and q, *J* = 4.62 Hz, 1H), 7.55-7.62 (m, 1H), 7.95-8.00 (m, 1H), 8.09-8.11 (m, 1H), 8.63-8.68 (m, 1H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 24.5, 24.8, 29.3, 30.1, 46.3, 59.7, 61.4, 121.9, 122.4, 126.6, 127.0, 137.4, 148.6, 149.1, 162.5, 164.7, 170.4, 173.8. ESI HRMS exact mass calcd for $(C_{11}H_{14}N_4O_2 + H)^+$ requires m/z 235.1190, found m/z 235.1203.

Procedure for the synthesis of Boc-9: To a solution of Z-L-Phenylalanine (400 mg, 2.4 mmol) in DCM (20 mL) was added L-Boc-Pro-$NHNH_2$ (460 mg, 2 mmol), HOBt (350 mg, 2.4mol), DIEA (700 μL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 24h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-9.**

Procedure for the synthesis of 9 is similar to that for 1.

9: white solid; Yield: 61%; $[\alpha]_D^{25}$ = -48.9. (c = 0.552, MeOH); mp 153.7-154.7□; ^{1}HNMR (600 MHz, CD_3OD and $CDCl_3$) δ (ppm) 1.79-1.87 (m, 2H), 1.91-1.97 (m, 1H), 2.15-2.20 (m, 1H), 2.88 (dd, *J* = 9.9 Hz, 13.86 Hz, 1H), 2.94-2.98 (m, 1H), 3.08-3.12 (m, 1H), 3.22 (dd, *J* = 4.74 Hz, 13.92 Hz, 1H), 3.79 (dd, *J* = 6.12 Hz, 8.70 Hz, 1H), 4.48 (dd, *J* = 4.74 Hz, 9.72 Hz, 1H), 4.99-5.05 (m, 2H), 7.19-7.33 (m, 10H); ^{13}CNMR (150 MHz, CD_3OD and $CDCl_3$)δ(ppm) 25.2, 30.4, 37.8, 46.5, 55.1, 59.3, 66.2, 126.3, 127.3, 127.5, 128.0, 128.3, 129.2, 136.7, 137.1, 156.8, 170.9, 172.7. ESI HRMS exact mass calcd for $(C_{22}H_{26}N_4O_4 + H)^+$ requires m/z 411.2027, found m/z 411.2006.

Procedure for the synthesis of Boc-10: Compound **Boc-9** (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Boc-9** disappeared completely (monitored by TLC), the solution was filtered. After removal of solvent under reduced pressure, the residue was diluted with DCM. The solution was added TEA (1.4mL, 10 mmol) and TFAA (600 μL, 4.0mmol) at 0 ^oC. The reaction mixture was stirred at 0^oC for 0.5h, quenched with MeOH, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (30 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-10.**

Procedure for the synthesis of 10: Compound **Boc-10** (1.0 g) reacted with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for an hour and then concentrated under reduced pressure. The residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10: 1) to give **10.**

10: white solid; Yield: 63%; $[\alpha]_D^{25}$ = -22.6 (c = 0.212, MeOH); mp 194-196□; ^{1}HNMR (600 MHz,

CD_3OD) δ (ppm) 1.97-2.04 (m, 2H), 2.05-2.19 (m, 1H), 2.32-2.38 (m, 1H), 2.99 (dd, *J* = 10.02 Hz, 14.10 Hz, 1H), 3.18-3.22 (m, 1H), 327-3.30 (m, 1H), 4.13-4.14 (brs, 1H), 4.76 (dd, *J* = 5.16 Hz, 9.78 Hz, 1H), 7.21-7.25 (m 1H), 7.26-7.32 (m, 4H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 24.2, 29.8, 37.0, 46.2, 53.4 and 53.5, 58.9, 114.9, 116.8, 126.6, 128.1, 128.9, 136.3, 157.2, 157.4, 169.6, 169.8; ESI HRMS exact mass calcd for $(C_{16}H_{19}F_3N_4O_3\text{- H})^-$ requires m/z 371.13256, found m/z 371.1312.

Procedure for the synthesis of Boc-11: Compound **Boc-9** (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Boc-9** disappeared completely (monitered by TLC), the solution was filtered. After removal of solvent under reduced pressure, the residue was diluted with DMF (30 mL). The solution was added TEA (835 μL, 6 mmol) and $Br(CH_2)_4Br$ (360 μL, 3.0 mmol) at room temperature. After the reaction mixture was stirred at 60 ^oC for 5 h, then cooled to room temperature. The reaction mixture was added saturated aqueous $NaHCO_3$ (40 mL) and was extracted four times with EtOAc (40 mL each).The organic layers were combined, washed with brine (40 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 2) to give **Boc-11.**

Procedure for the synthesis of 11: Compound **Boc-11** (1.0 g) reacted with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for an hour and then concentrated under reduced pressure. After chromatography on a H^+ ion-exchange resin column eluted with $NH_3 \cdot H_2O$ (3.0 M) and removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10: 1) to give **11.**

11: off-white solid; Yield: 45%; $[\alpha]_D^{25}$ = + 13.0 (c = 0.10, MeOH); ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.61-1.74 (m, 1H), 1.81-1.90 (m, 6H), 2.06-2.18 (m, 1H), 2.65-2.71 (m, 1H), 2.79 (brs, 3H), 2.95-2.99 (m, 1H), 3.03-3.13 (m, 3H), 3.25-2.27 (t, *J* = 7.68 Hz, 1H), 3.71-3.78 (m, 1H), 7.16-7.19 (m, 1H), 7.22-7.34 (m, 4H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 22.8, 25.0, 30.2, 37.3, 46.4, 50.7, 59.0, 68.1, 126.1, 128.0, 129.0, 137.7, 170.6, 172.0R ESI HRMS exact mass calcd for $(C_{18}H_{26}N_4O_2 + H)^+$ requires m/z 331.2129, found m/z 331.2117.

Procedure for the synthesis of Boc-12: To a solution of Boc-L-Pro (520 mg, 2.4 mmol) in DMF (20 mL) was added hydrazine dihydrochloride ($NH_2NH_2 \cdot 2HCl$, 106 mg, 1mmol), HOBt (350 mg, 2.4mol), DIEA (1.4 mL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 24h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Boc-12.**

Procedure for the synthesis of 12: Compound **Boc-12** (1.0 g) reacted with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for an hour and then concentrated under reduced pressure. After chromatography on a H^+ ion-exchange resin column eluted with $NH_3 \cdot H_2O$ (3.0 M) and removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH (NH_3) = 10: 1) to give **12.**

12: white solid; Yield: 71%; $[\alpha]_D^{25}$ = -56.0. (c = 0.48, MeOH); mp 155.3-158.3□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.75-1.85 (m, 2H), 1.88-1.93 (m, 1H), 2.13-2.19 (m, 1H), 2.93-297 (m, 1H), 3.04-3.08 (m, 1H), 3.75 (dd, *J* = 5.94 Hz, 8.64 Hz, 1H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 25.3, 30.4, 46.5, 59.3, 172.5. ESI HRMS exact mass calcd for $(C_{10}H_{18}N_4O_2 + Na)^+$ requires m/z 249.1322, found m/z 249.1310.

Procedure for the synthesis of Boc-13: To a solution of **12** (652 mg, 2 mmol) in DMF (20 mL) was added benzaldehyde (245 μL, 2.4 mmol) at room temperature. The reaction mixture was stirred for 0.5h at room temperature, and then $NaBH_3CN$ (265 mg, 4 mmol) was added in portions and the reactions mixture was stirred for another 1 h. The reaction mixture was quenched with H_2O and then concentrated under reduced pressure. After the residue was diluted with EtOAc (30 mL), and the organic phase was washed with aqueous NaOH (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: Hexane: ethyl acetate = 1: 1) to give **Boc-13.**

Procedure for the synthesis of 13: Compound **Boc-13** (1.0 g) was treated with a mixture of TFA: CH_2Cl_2 (1: 2, 20 mL) for an hour and then concentrated under reduced pressure. After chromatography on a H^+ ion-exchange resin column eluted with $NH_3 \cdot H_2O$ (3.0 M) and removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10:1) to give **13.**

13: white solid; Yield: 50%; $[\alpha]_D^{25}$ = -20.8 (c = 0.048, MeOH); ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.78-1.86 (m, 1H), 1.87-1.97 (m, 4H), 2.00-2.04 (m, 1H), 2.18-2.27 (m, 1H), 2.34-2.38 (m, 1H), 2.98-3.01 (m, 1H), 3.07-3.11 (m, 2H), 3.19-3.25 (m, 2H), 3.49 (d, J = 12.8 Hz, 1H), 3.95-3.99 (m, 2H), 7.28 (t, J = 7.26 Hz, 7.44 Hz, 1H), 7.29 (t, J = 7.26 Hz, 2H), 7.37 (d, J = 7.08 Hz, 2H), ^{13}CNMR (150 MHz, CD_3OD)δ (ppm) 23.2, 24.7, 30.0, 46.3, 53.0, 58.9, 59.3, 66.1, 126.9, 127.9, 128.9, 138.2, 170.2, 173.5. ESI HRMS exact mass calcd for $(C_{17}H_{24}N_4O_2 + H)^+$ requires m/z 317.1972, found m/z 317.1982.

Procedure for the synthesis of Z-14: To a solution of Z-L-Pro (600 mg, 2.4 mmol) in DCM (20 mL) was added L-Boc-Pro-$NHNH_2$ (460 mg, 2 mmol), HOBt (350 mg, 2.4 mmol), DIEA (700 μL) and EDCI (460 mg, 2.4 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 12 h, and then concentrated under reduced pressure. After the resulting mixture was diluted with EtOAc (20 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), aqueous HCl (1.0 M, 10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 1: 1) to give **Z-14.**

Procedure for the synthesis of 14: Compound **Z-14** (1.0 g), 5% Pd/C (0.1 g) and methanol (30 mL) were charged in a two-neck flask (100 mL). After stirred under hydrogen (1 atm) until **Z-14** disappeared completely (monitored by TLC), the solution was filtered. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10: 1) to give **14.**

14: white solid; Yield: 66%; $[\alpha]_D^{25}$ = -73.0. (c = 0.104, MeOH); mp 153.7-156.0□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm)1.47 (d, *J* = 11.34 Hz, 9H), 1.82-1.88 (m, 2H), 1.89-1.97 (m, 2H), 2.00-2.10 (m, 2H), 2.19-2.30 (m, 1H), 2.97-3.00 (m, 1H), 3.41-3.45 (m, 1H), 3.52-3.54 (brs, 1H), 3.80 (dd, *J* = 6.06 Hz, 8.46 Hz, 1H), 4.24-4.26 (m, 1H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 23.2, 23.9, 25.2, 27.2, 30.0, 30.4, 31.1, 46.4, 46.8, 48.2, 59.1, 80.1, 154.7, 172.4, 172.7. ESI HRMS exact mass calcd for $(C_{15}H_{26}N_4O_4 - H)^-$ requires m/z 325.1870, found m/z 325.1887.

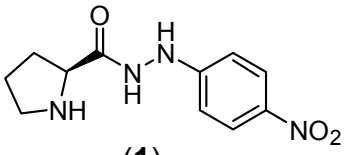
Procedure for the synthesis of Boc-15: To a solution of **Boc-12** (831 mg, 2 mmol) in THF (20 mL) was added benzyl bromide (260 μL, 2.2 mmol) and sodium hydride (250 mg, 4 mmol) at 0^oC. The reaction mixture was stirred at 25 ^oC for 24 h, and then quenched with H_2O. The mixture was added EtOAc (30 mL), and the organic phase was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: hexane: ethyl acetate = 3: 1) to give **Boc-15.**

Procedure for the synthesis of 15: Compound **Boc-15** (1.0 g) was treated with a mixture of TFA: CH_2Cl_2 (1:2, 20 mL) for an hour and then concentrated under reduced pressure. After chromatography on a H^+ ion-exchange resin column eluted with $NH_3 \cdot H_2O$ (3.0 M) and removal of solvent under reduced pressure, the residue was purified through column chromatography on silica gel (eluent: DCM: MeOH = 10: 1) to give **15.**

15: white solid; Yield: 62%; $[\alpha]_D^{25}$ = -56.0 (c = 0.116, MeOH); mp 101.3-103.7□; ^{1}HNMR (600 MHz, CD_3OD) δ (ppm) 1.59-1.64 (m, 1H), 1.67-1.82 (m, 5H), 1.99-2.07 (m, 2H), 2.76-2.80 (m, 1H), 2.81-2.85 (m, 1H), 2.94-2.98 (m, 1H), 3.11-3.15 (m, 1H), 3.55 (dd, *J*= 6.18 Hz, 8.46 Hz, 1H), 3.78 (dd, J = 6.36 Hz, 8.82 Hz, 1H), 4.65-4.93 (brs, 2H), 7.27-7.36 (m, 5H); ^{13}CNMR (150 MHz, CD_3OD) δ (ppm) 25.5, 25.6, 30.1, 30.5, 46.6, 50.5, 57.5, 58.9, 127.6, 128.3, 128.7, 135.5, 174.2, 175.7. ESI HRMS exact mass calcd for $(C_{17}H_{24}N_4O_2 + Na)^+$ requires m/z 339.1791, found m/z 339.1779.

General procedure for aldol reaction in toluene using catalyst 15: To a solution of 15 (0.04 mmol, 20 mol%) in a mixture of acetone (0.4 mL) and toluene (1.6 mL) was added TFA (0.04 mmol). The reaction mixture was stirred at 0 ^oC for 10 minutes, and then aldehyde (0.2 mmol) was added. The reaction mixture was stirred at 0 ^oC for another 4-72 h and then was quenched with saturated ammonium chloride solution (1 mL) and the layers were separated. The aqueous layer was extracted three times (15 mL each) with ethyl acetate. The combined organic layers was washed with brine (5 mL) and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified through flash column chromatography on silica gel (eluent: Hexane: AcOEt = 3:1) to give the pure aldol adducts.

Selected NMR Spectra



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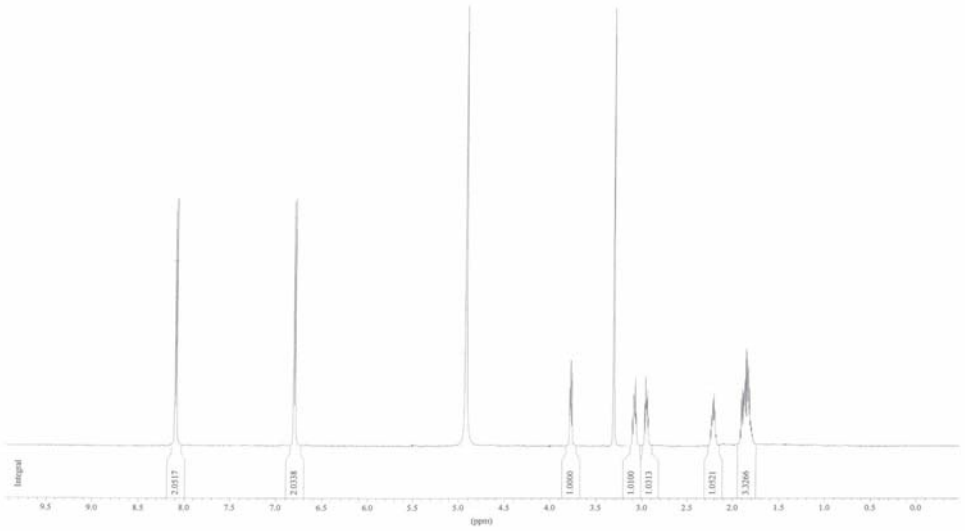

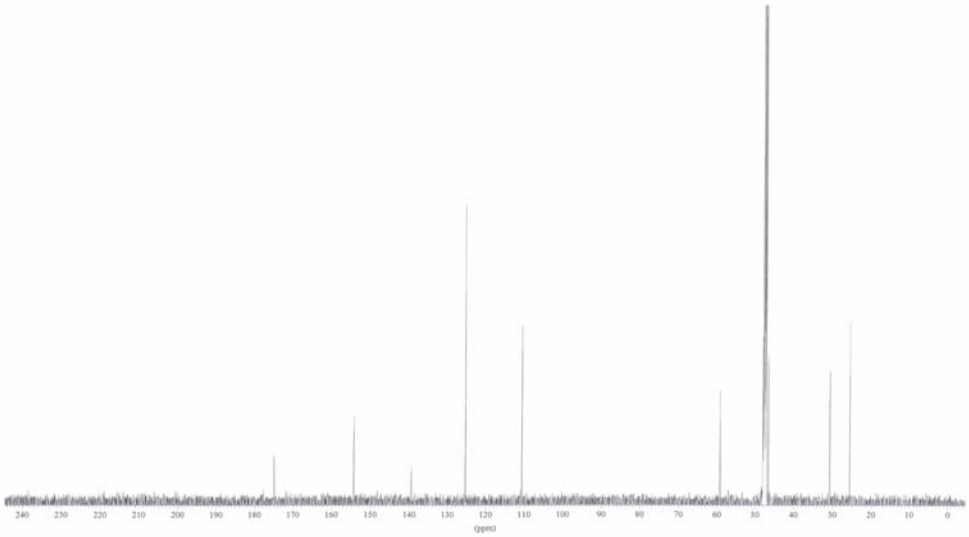

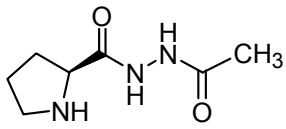

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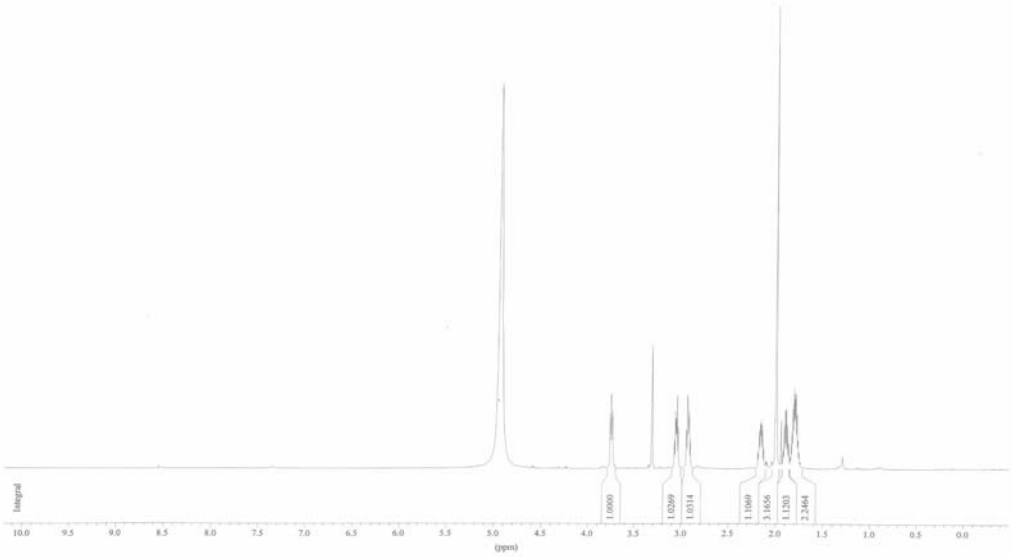
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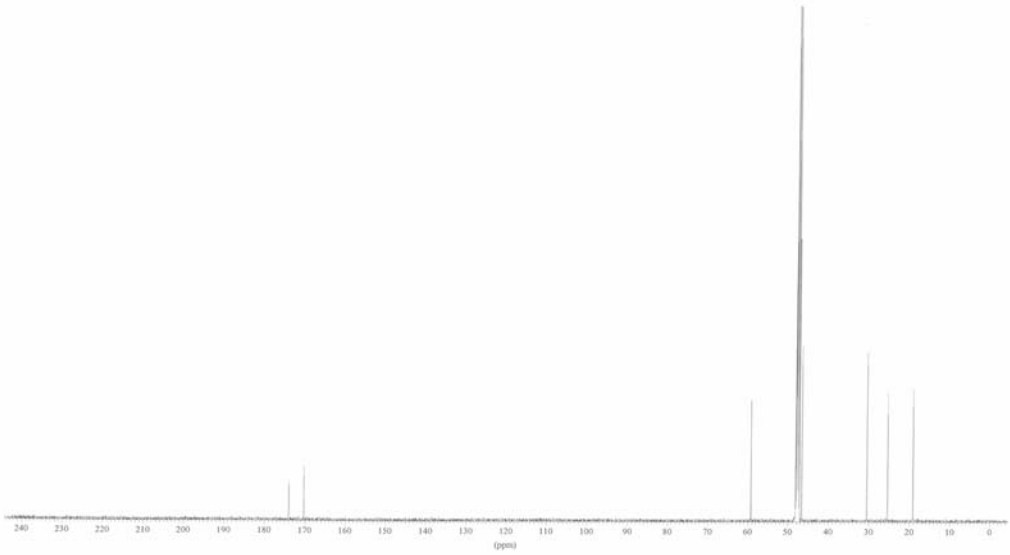
1.1069
3.1656
1.1203
2.2464
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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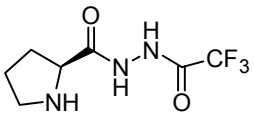

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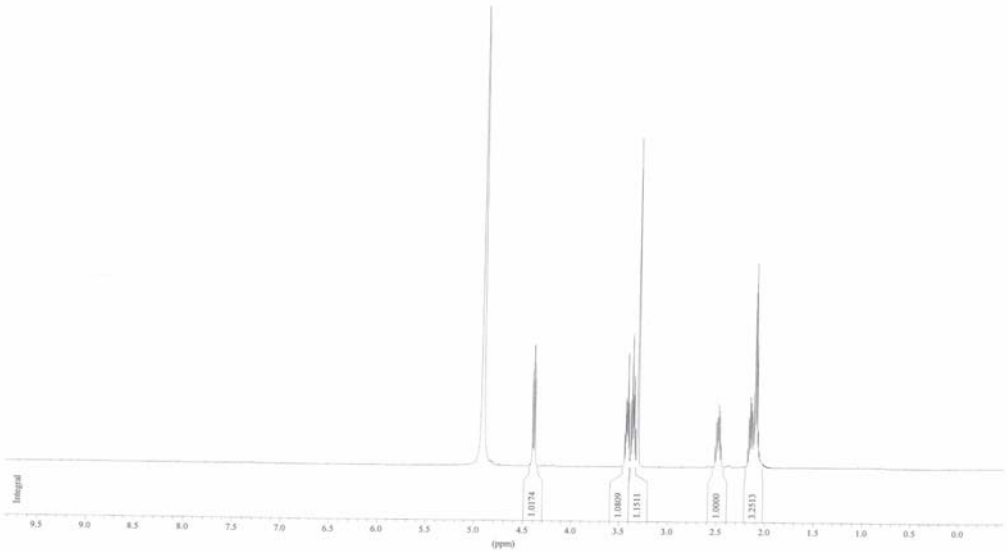
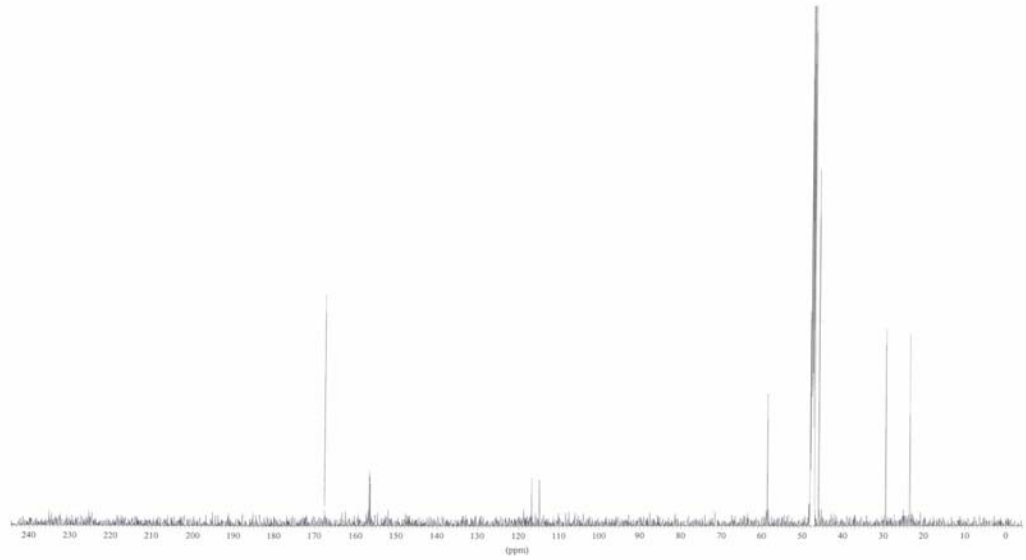
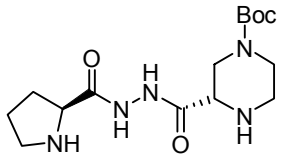
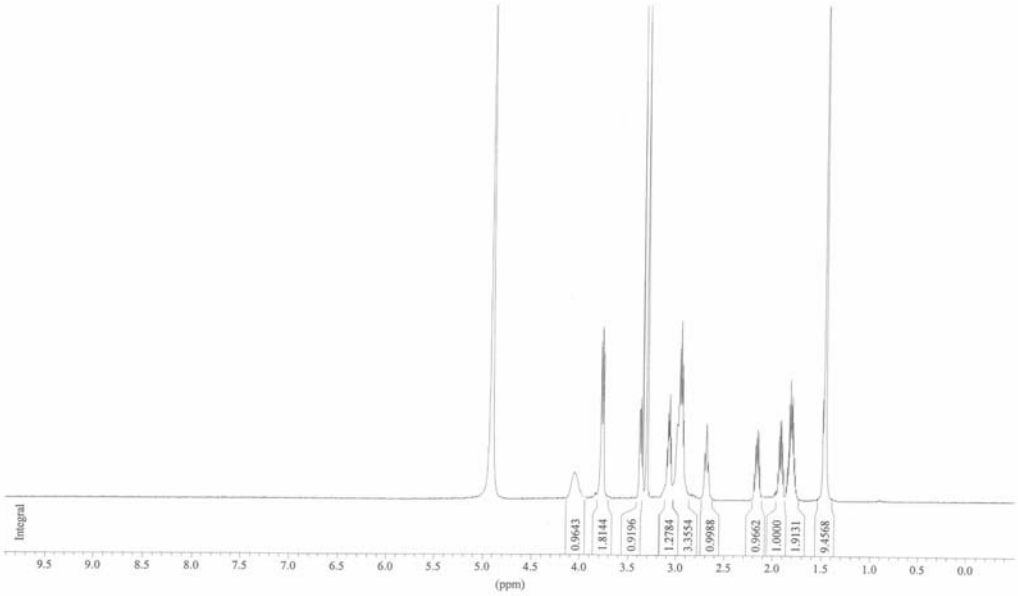





Boc
N
O
H
N
N
H
O
N
H
NH

(**7**)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0.9196
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0.9988
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1.9131
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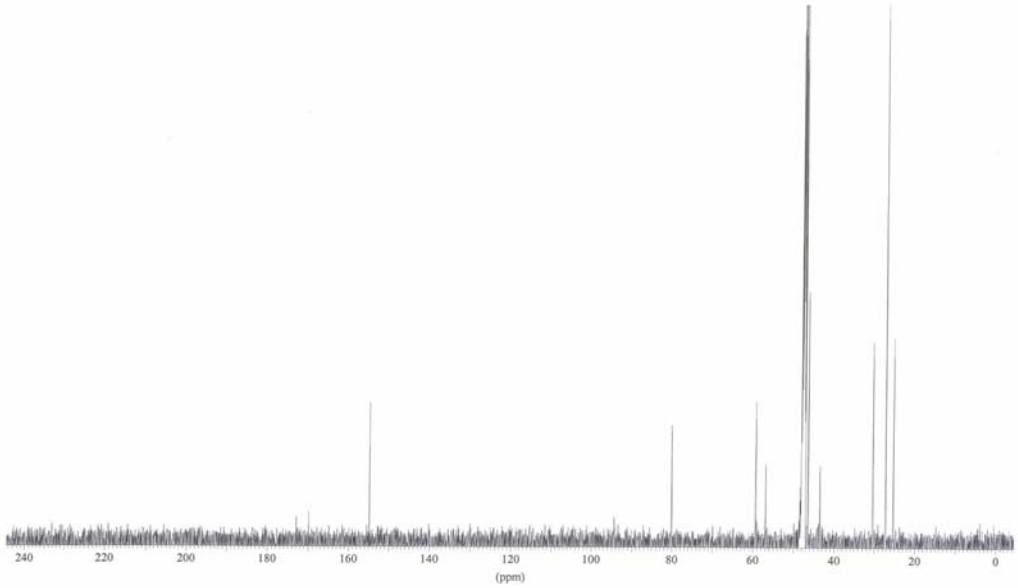
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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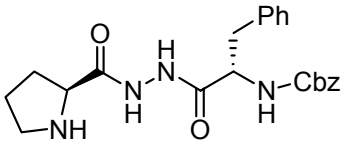
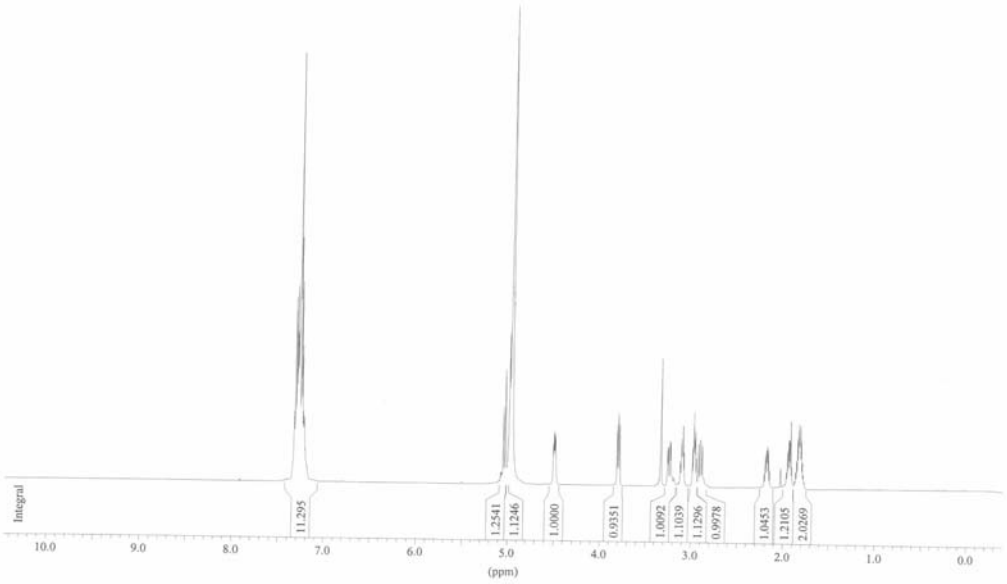
(ppm)


Ph
O
H
N
N
Cbz
N
H
H
NH
O

(**9**)


Integral
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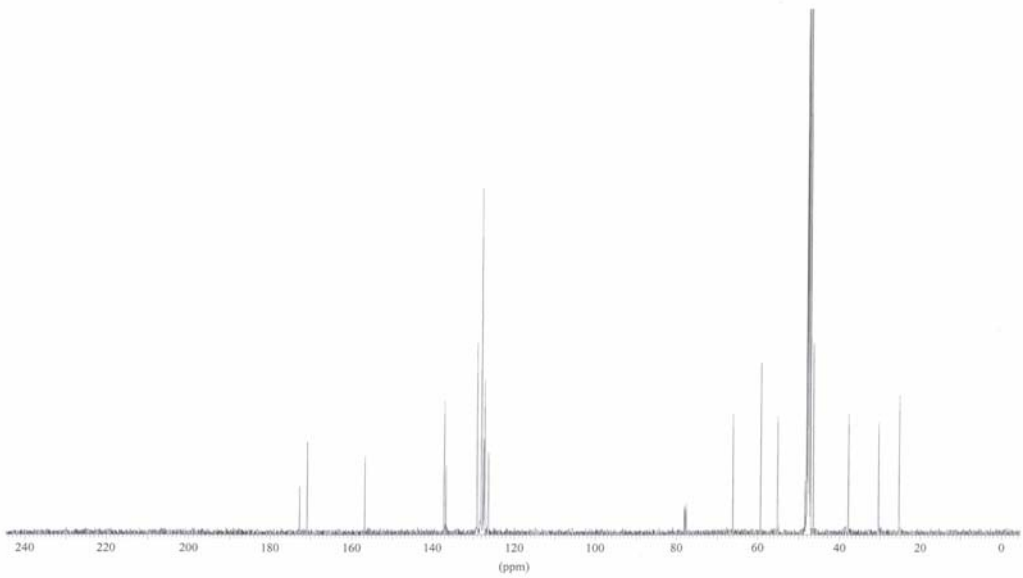
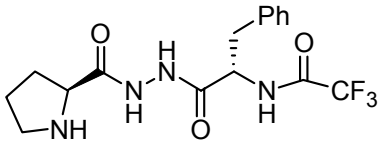
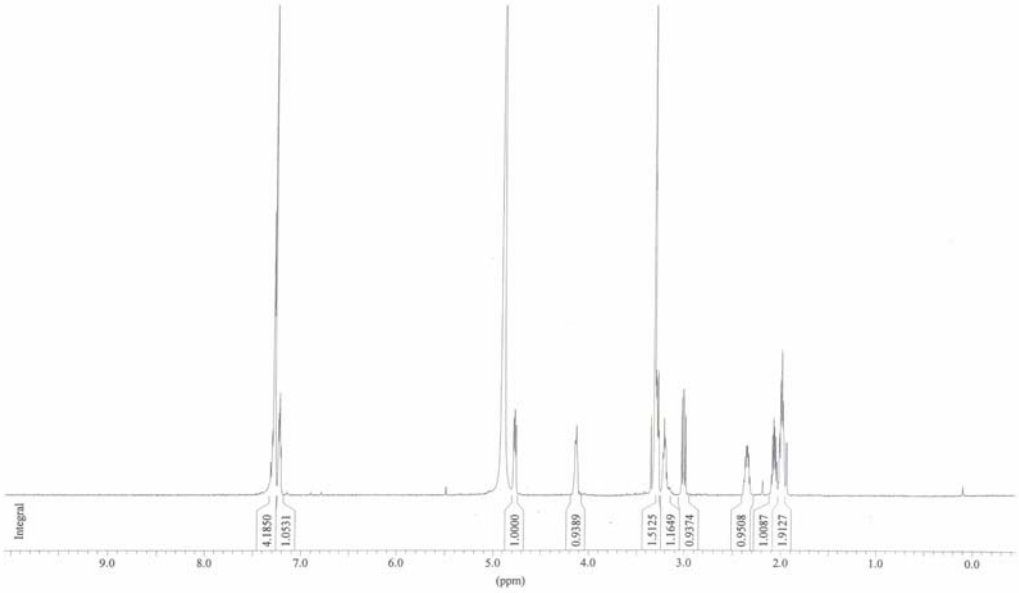
0.9351
1.0092
1.1039
1.1296
0.9978
1.0453
1.2105
2.0269
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


240
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)


Ph
O
H
N
N
O
N
H
O
CF3
NH
H

(**10**)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0.9508
1.0087
1.9127
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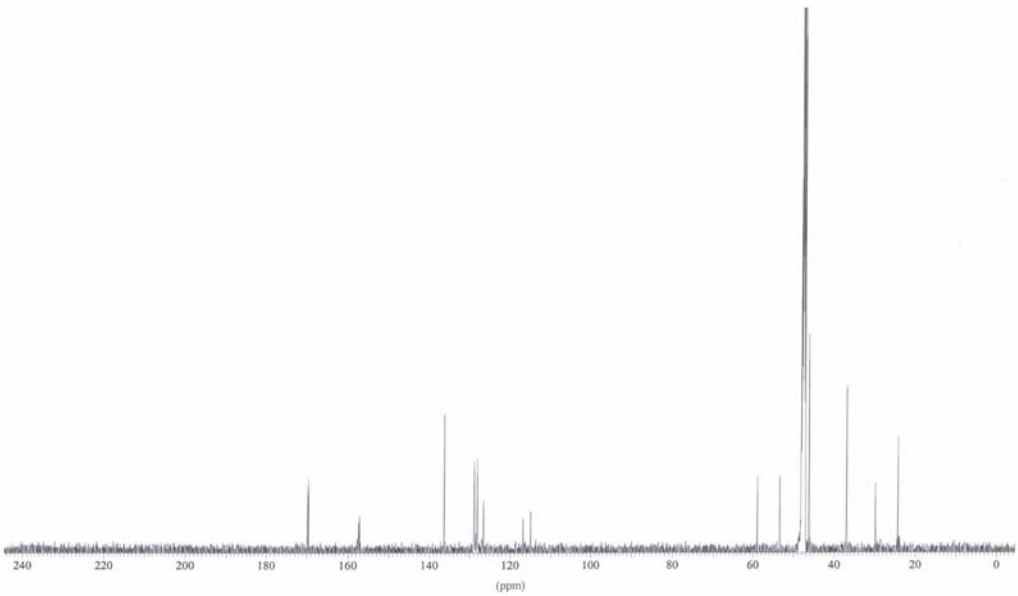
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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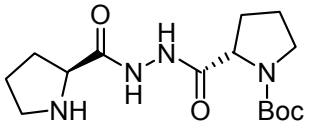
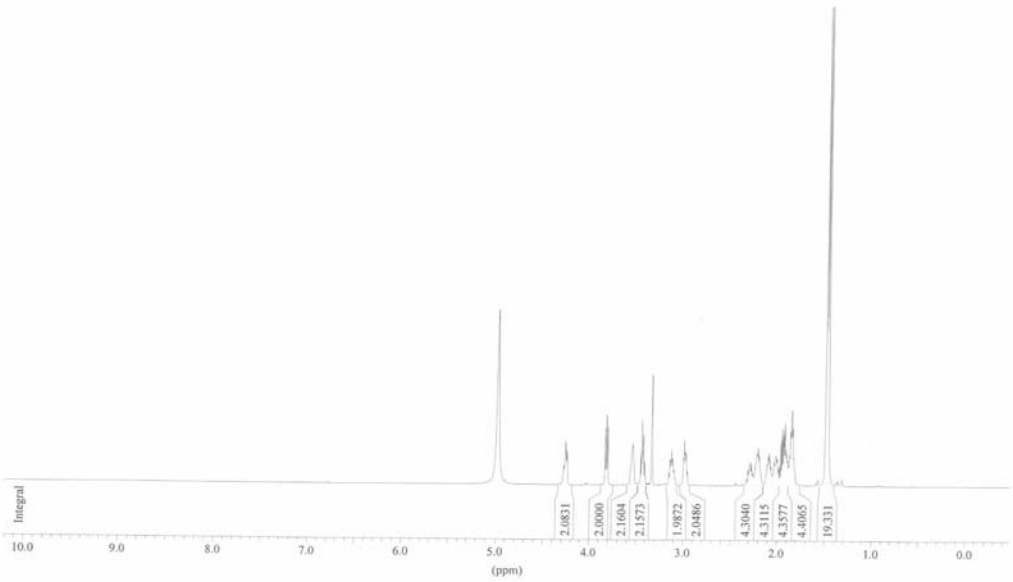
200
180
160
140
120
100
80
60
40
20
0
(ppm)



(**14**)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2.0486
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4.3577
4.4065
19.331
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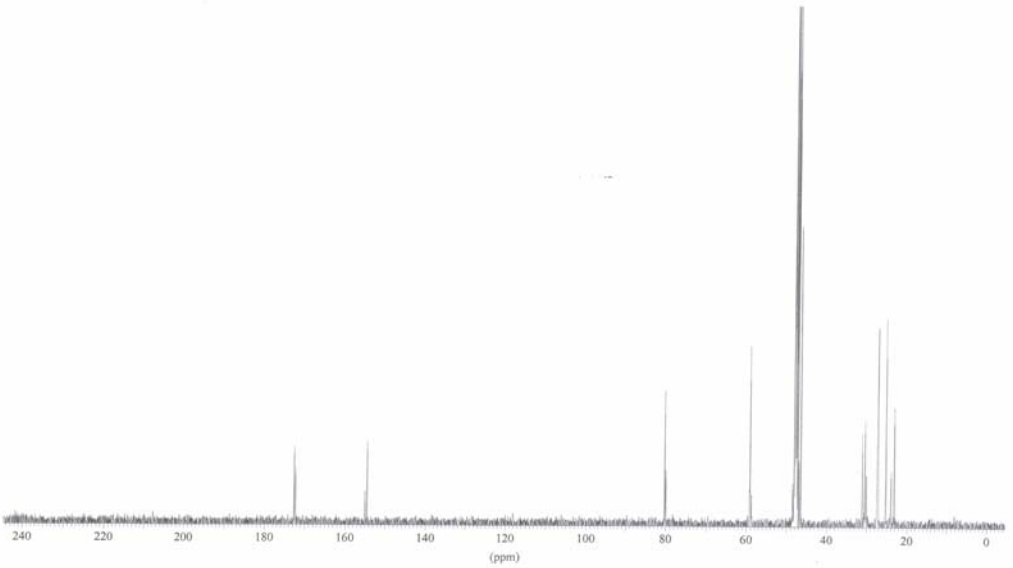
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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200
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160
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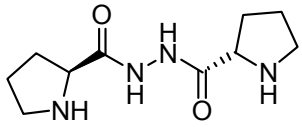
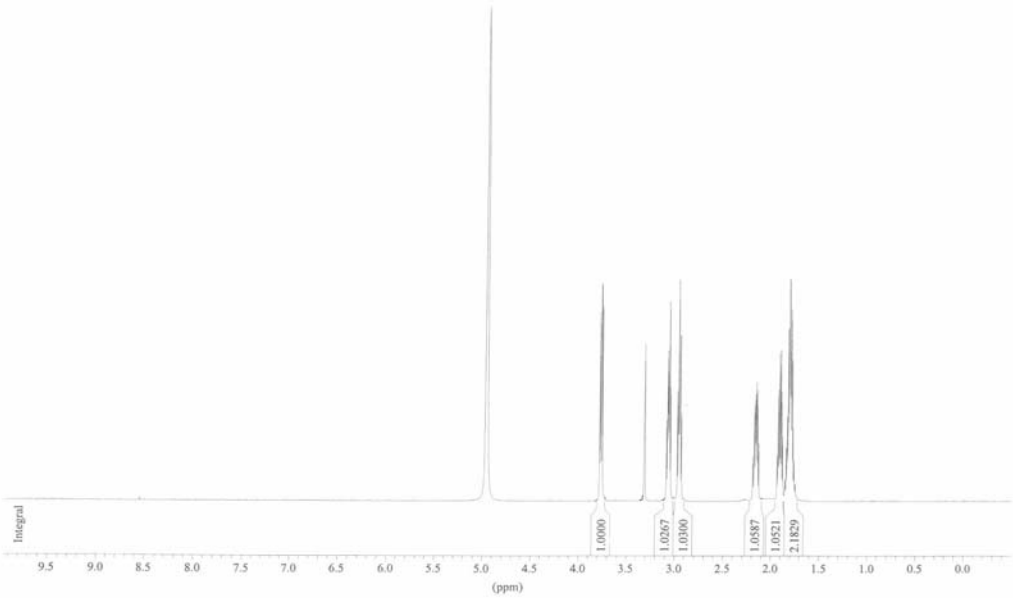
120
100
80
60
40
20
0
(ppm)



(**12**)


Integral
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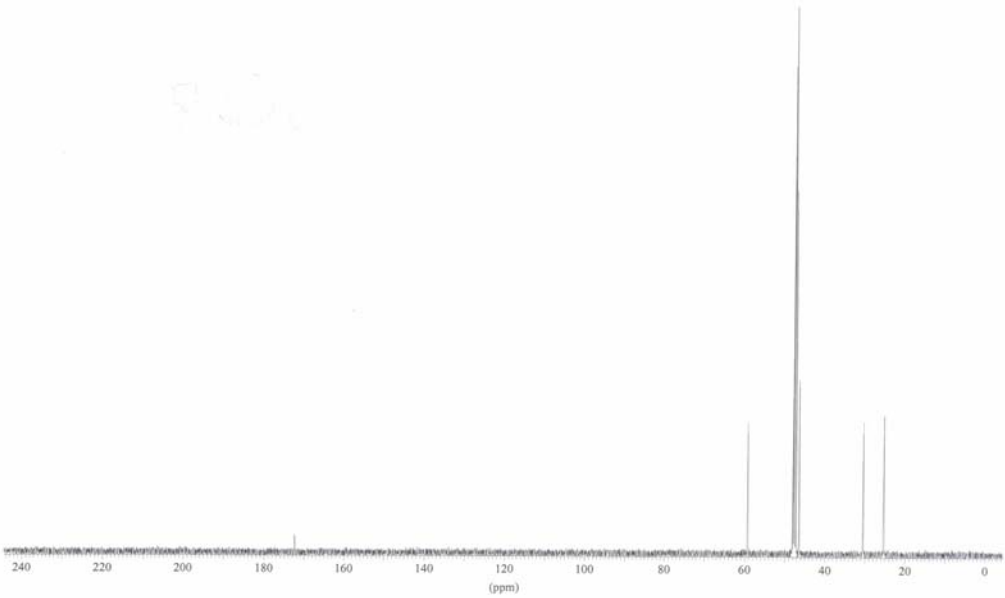
1.0300
1.0587
1.0521
2.1829
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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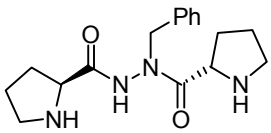
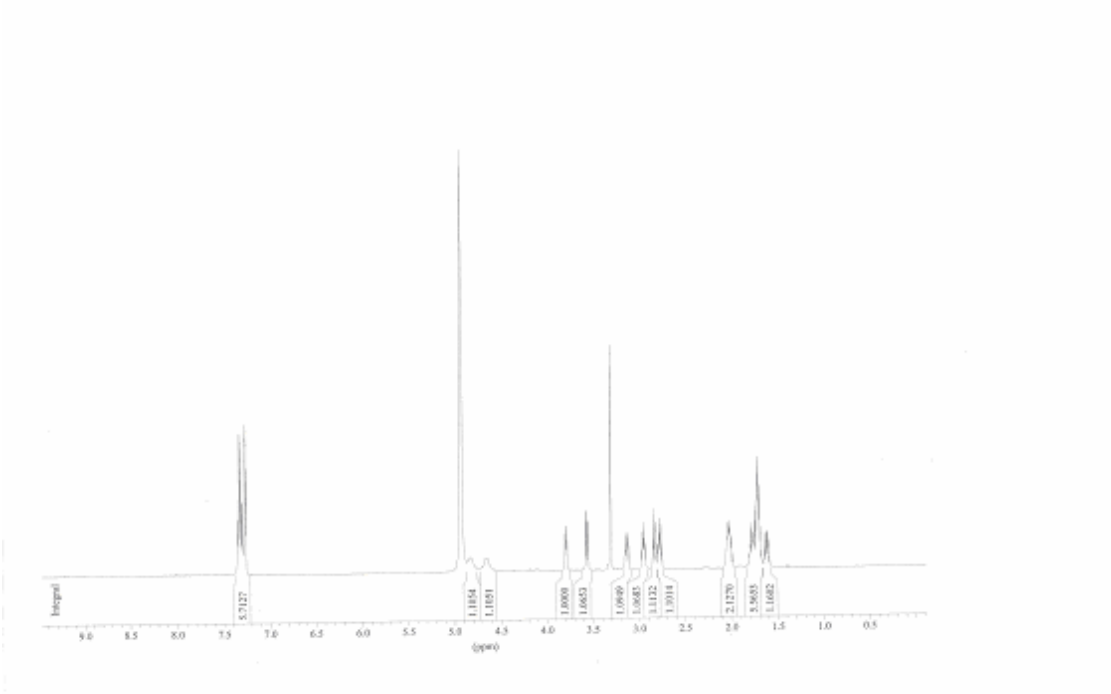
(ppm)


Ph
O
N
N
H
O
NH
N
H

(**15**)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1.0685
1.1172
1.1014
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5.5635
1.1682
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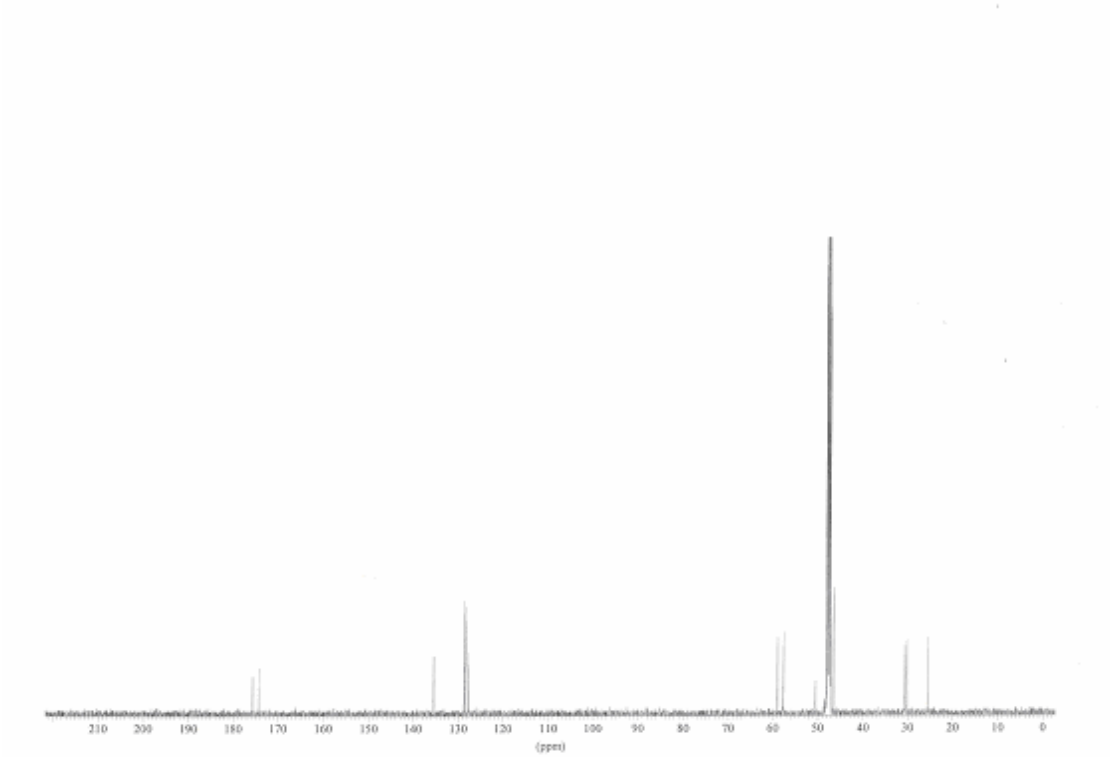
(ppm)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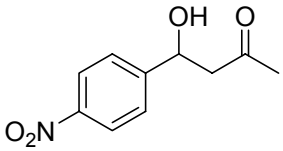
(ppm)

HPLC spectra of 16a-g



(16a)Racemic

Page 1 of 1

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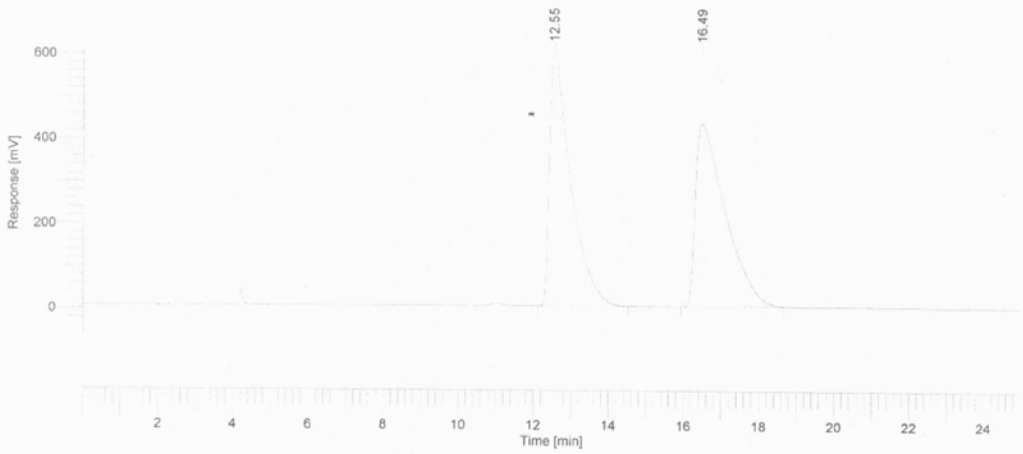
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\wy\as30\2004-10\041018-h2o-ac.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\041018-h2o-ac.seq



REPORT

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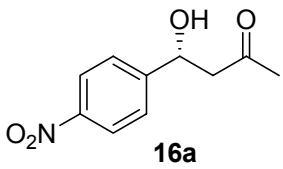
		47173849.57	1.03e+06	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 13.4 min and *S*-isomer, t_R 18.6.

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 16:46:53
Sample Name	: ccl	Data Acquisition Time	: 2005-3-3 12:06:50
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(4'-NO2Ph)-butan-2-one\2005-3\050303.rst
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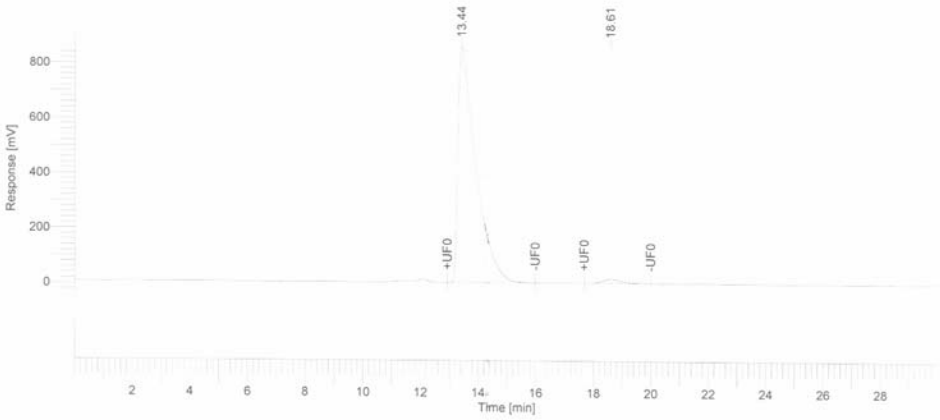

REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
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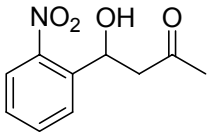
2	18.605	685062.02	15154.17	1.83
		37405531.22	867345.30	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

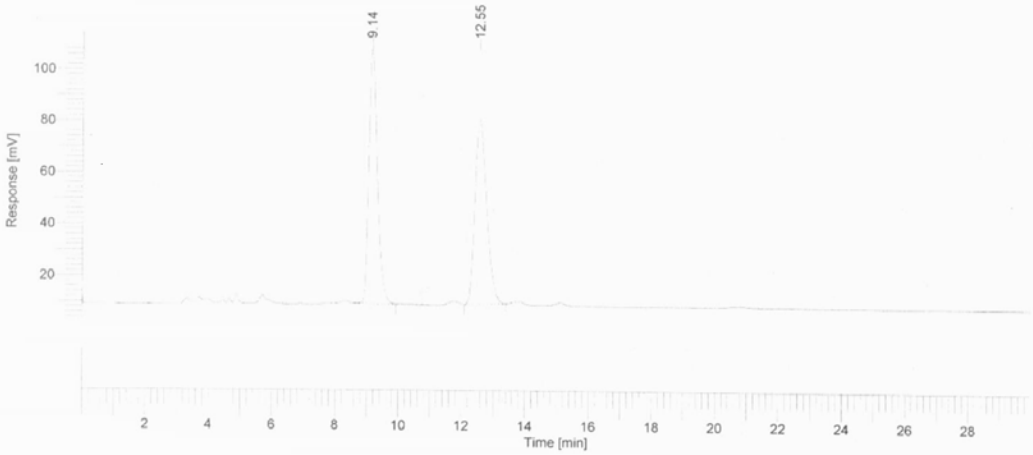
All components were found



(16b)Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 9:29:22
Sample Name	: ccl	Data Acquisition Time	: 2005-3-2 10:54:09
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(2'-NO2Ph)-butan-2-one\050302-7-45-2xx.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050302-7-45-2-20050302-104752.seq



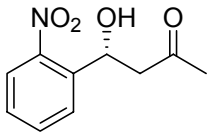
REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	9.138	1843028.46	98589.76	50.11
2	12.553	1834727.19	71195.47	49.89
		3677755.65	169785.23	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found



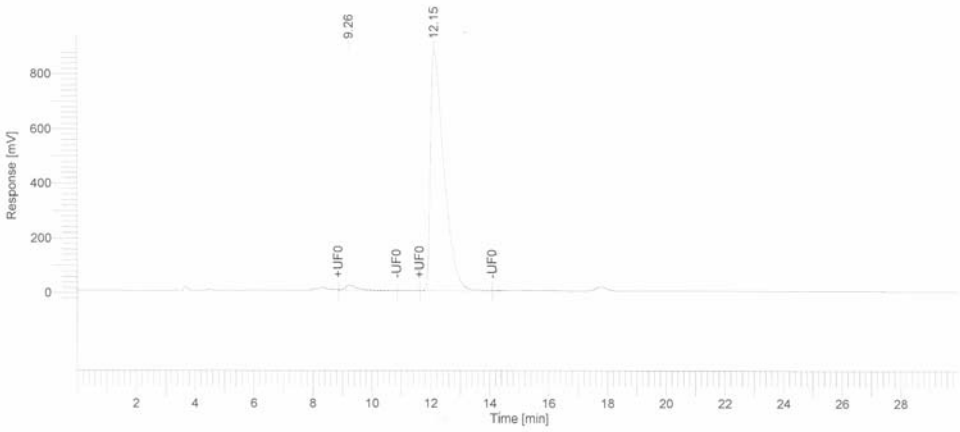
16b

Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 12.1 min and *S*-isomer, t_R. 9.2.

Page 1 of 1

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 16:55:50
Sample Name	: ccl	Data Acquisition Time	: 2005-3-2 12:01:04
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(2'-NO2Ph)-butan-2-one\050302.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050302-7-50-5.seq



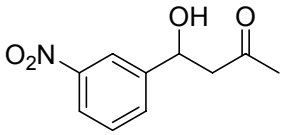
REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	9.255	573781.54	19816.67	2.01
2	12.152	27956671.68	881977.82	97.99
		28530453.22	901794.49	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

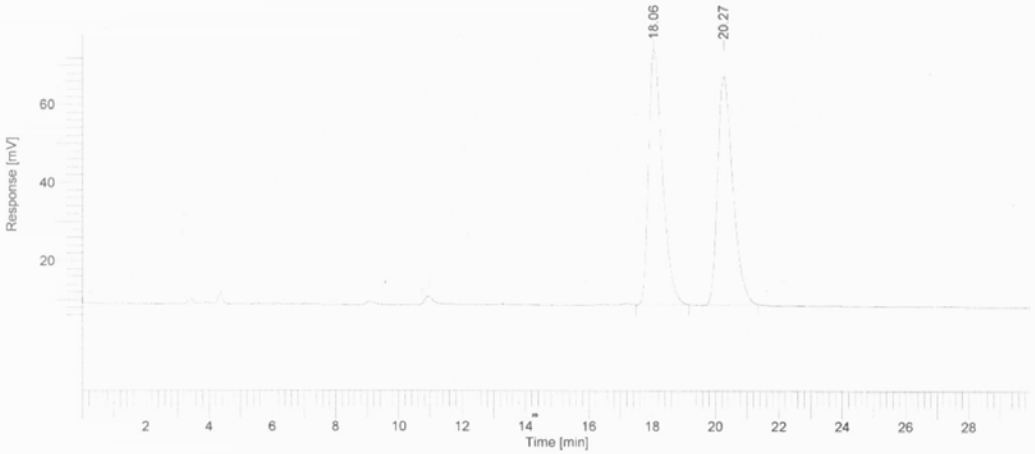
All components were found



(16c)Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 9:37:10
Sample Name	: ccl	Data Acquisition Time	: 2005-3-2 14:48:04
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result Fiie : D:\LC\ccl\4-OH-4-(3'-NO2Ph)-butan-2-one\050302-7-45-1xx.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050302-7-45-1xx.seq

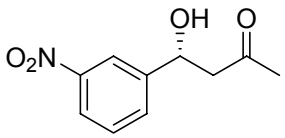


REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	18.063	1994478.81	65312.99	50.50
2	20.269	1955125.98	58671.40	49.50
		3949604.79	123984.40	100.00

Missing Component Report

Component	Expected Retention (Calibration File)
PE serise200	0.001



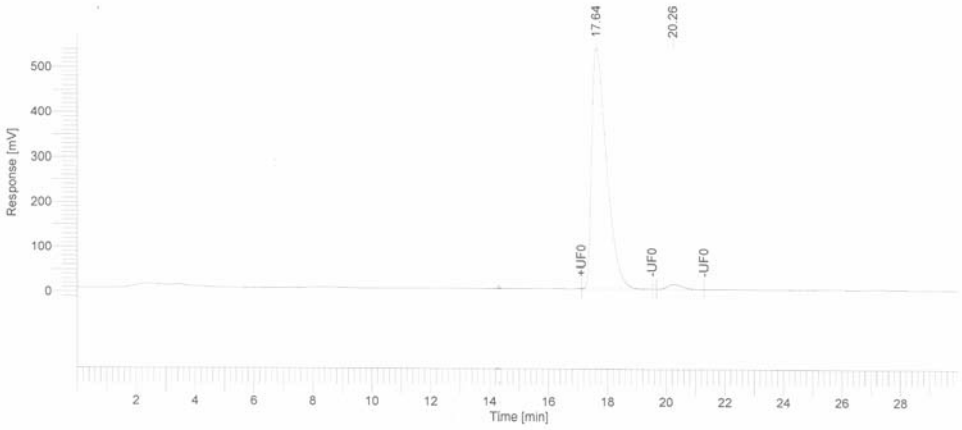
16c

Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak OJ-H, i-PrOH/Hexane = 20/80), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 17.6, min and *S*-isomer, t_R. 20.3.

Page 1 of 1

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 17:00:30
Sample Name	: ccl	Data Acquisition Time	: 2005-3-2 15:58:36
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(3'-NO2Ph)-butan-2-one\050302.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050302-7-45-1xx-20050302-155628.seq

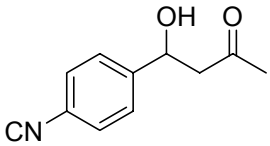


REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	17.643	19007133.73	535886.93	97.98
2	20.260	391466.35	11294.89	2.02
		19398600.09	547181.82	100.00

Missing Component Report

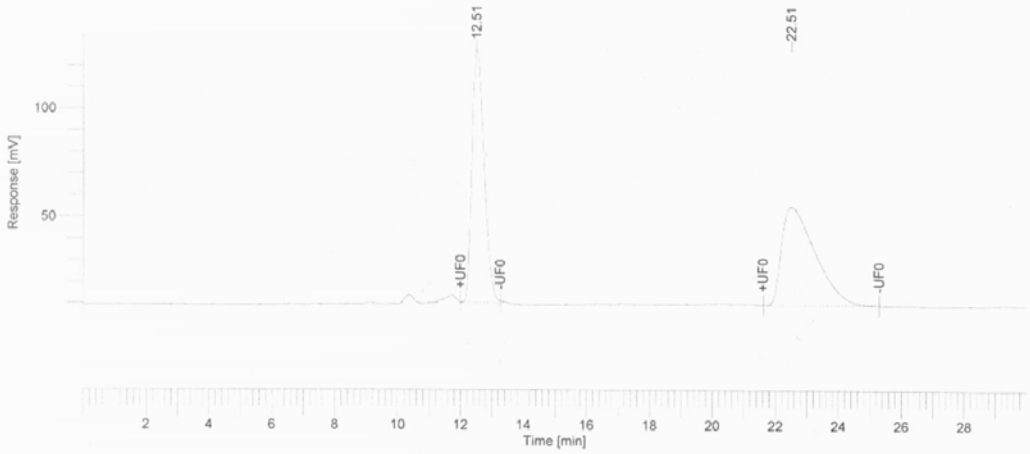
Component	Expected Retention (Calibration File)
PE serise200	0.001



(16d)Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 9:46:17
Sample Name	: ccl	Data Acquisition Time	: 2005-3-3 16:18:49
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(4'-CNPh)-butan-2-one\050303-7-45-5xx.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050303-7-45-5xx.seq



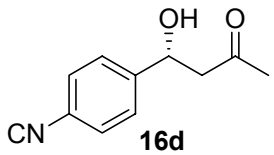
REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	12.507	3157899.87	116934.08	48.08
2	22.508	3410008.99	45858.60	51.92
		6567908.86	162792.67	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

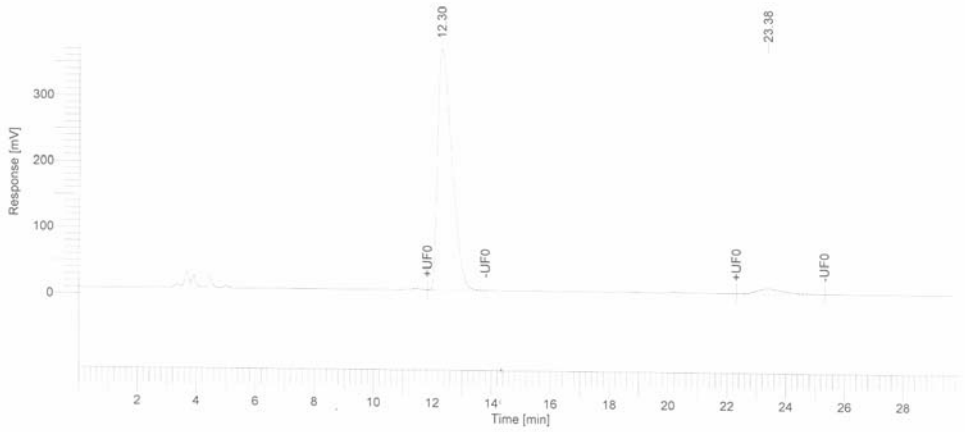
All components were found



Enantiomeric excess: 92%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 12.3, min and *S*-isomer, t_R. 23.4.

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 16:52:09
Sample Name	: ccl	Data Acquisition Time	: 2005-3-3 16:53:54
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(4'-CNPh)-butan-2-one\050303.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050303-7-50-7.seq



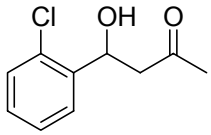
REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	12.297	12188228.75	363823.08	96.20
2	23.375	481727.00	7644.19	3.80
		12669955.76	371467.27	100.00

Missing Component Report

Component	Expected Retention (Calibration File)

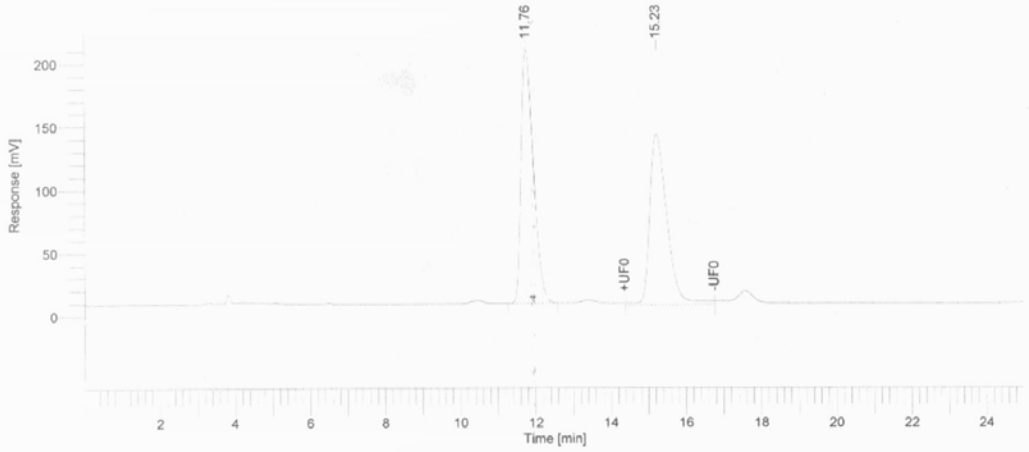
All components were found



(16e)Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 17:54:20
Sample Name	: ccl	Data Acquisition Time	: 2005-6-20 15:59:13
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(2'-ClPh)-butan-2-one\2005\050620-11-4-2.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050620-10-44-1-20050620-155658.seq

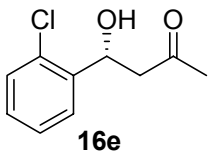


REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	11.760	4557925.99	200657.64	51.26
2	15.227	4334687.92	135058.81	48.74
		8892613.91	335716.45	100.00

Missing Component Report

Component	Expected Retention (Calibration File)
PE serise200	0.001



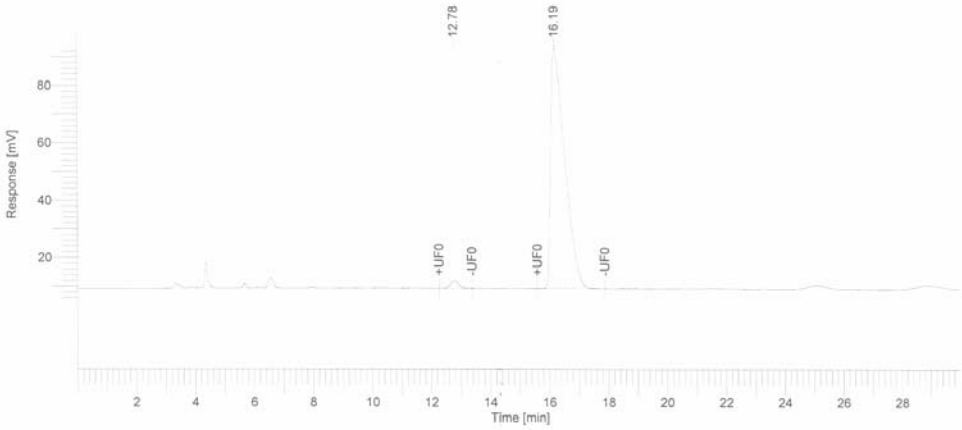
16e

Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 8/92), UV 262 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 16.2, min and *S*-isomer, t_R. 12.8.

Page 1 of 1

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 16:58:03
Sample Name	: ccl	Data Acquisition Time	: 2005-3-7 9:42:32
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(2'-ClPh)-butan-2-one\050307.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050307-7-50-2.seq

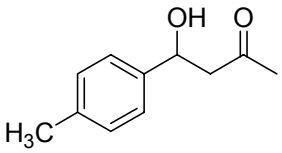


REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	12.778	52770.44	2766.27	1.85
2	16.193	2792474.65	83750.86	98.15
		2845245.10	86517.14	100.00

Missing Component Report

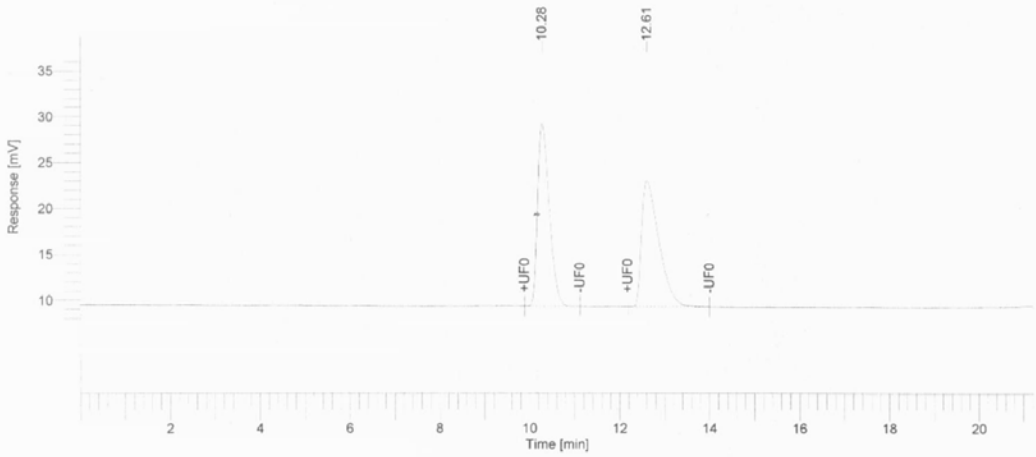
Component	Expected Retention (Calibration File)
PE-SERISE200	0.001



(16f)-Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 9:51:53
Sample Name	: ccl	Data Acquisition Time	: 2005-3-9 18:20:24
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(4-CH3Ph)-butan-2-one\050309
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050309-7-45-6xx.seq

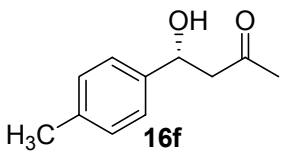


DEFAULT REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	10.280	358545.15	19854.25	49.37
2	12.610	367639.71	13653.70	50.63
		726184.85	33507.96	100.00

Missing Component Report

Component	Expected Retention (Calibration File)
PE serise200	0.001

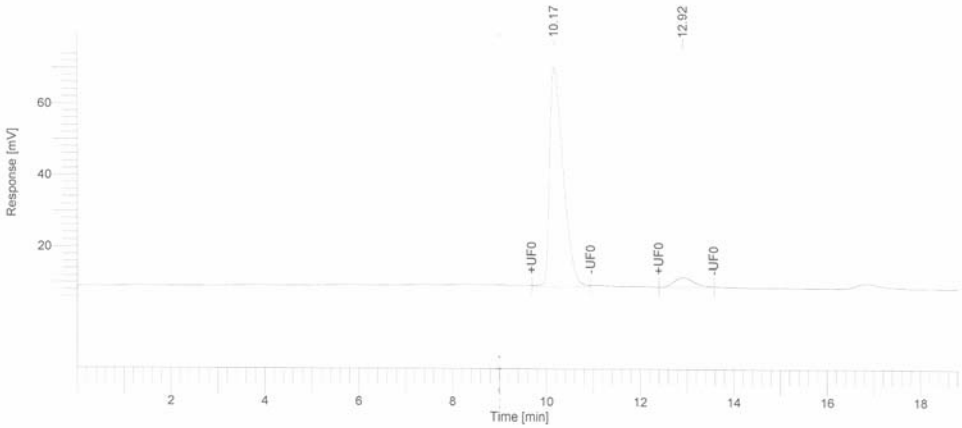


16f

Enantiomeric excess: 87%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 15/85), UV 257 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 10.2, min and *S*-isomer, t_R. 12.9.

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 17:07:06
Sample Name	: ccl	Data Acquisition Time	: 2005-3-10 9:08:00
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-(4-CH3Ph)-butan-2-one\050310.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050310-8 4-1.seq

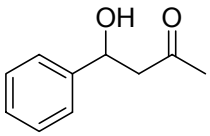


DEFAULT REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	10.168	1221885.08	61058.87	93.62
2	12.918	83329.05	2777.57	6.38
		1305214.13	63836.43	100.00

Missing Component Report

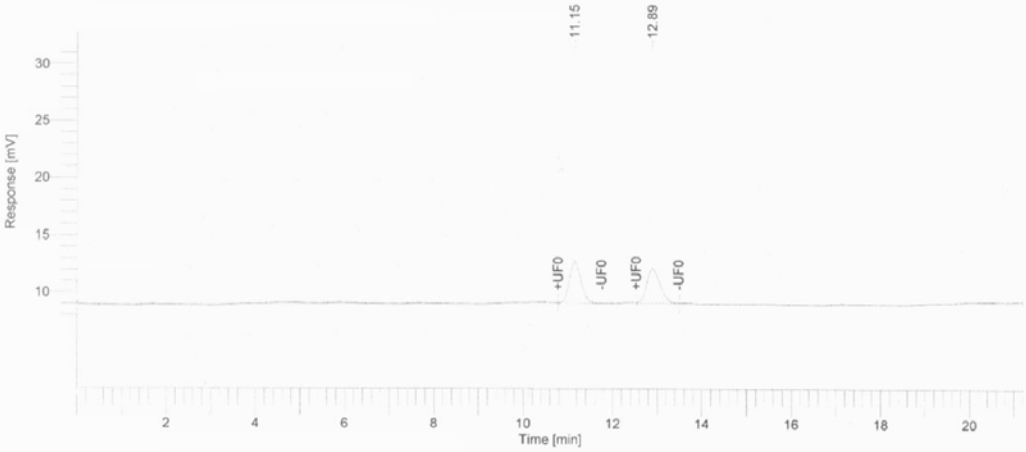
Component	Expected Retention (Calibration File)
PE serise200	0.001



(16g)Racemic

Software Version	: 6.2.1.0.104:0104	Date	: 2005-6-30 10:00:28
Sample Name	: ccl	Data Acquisition Time	: 2005-3-10 9:30:58
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dfiution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-Ph-butan-2-one\050310
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050310-7-43-6xx.seq

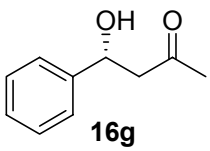


DEFAULT REPORT

Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	11.152	68360.21	3735.33	51.46
2	12.893	64489.30	3072.88	48.54
		132849.51	6808.21	100.00

Missing Component Report

Component	Expected Retention (Calibration File)
PE serise200	0.001

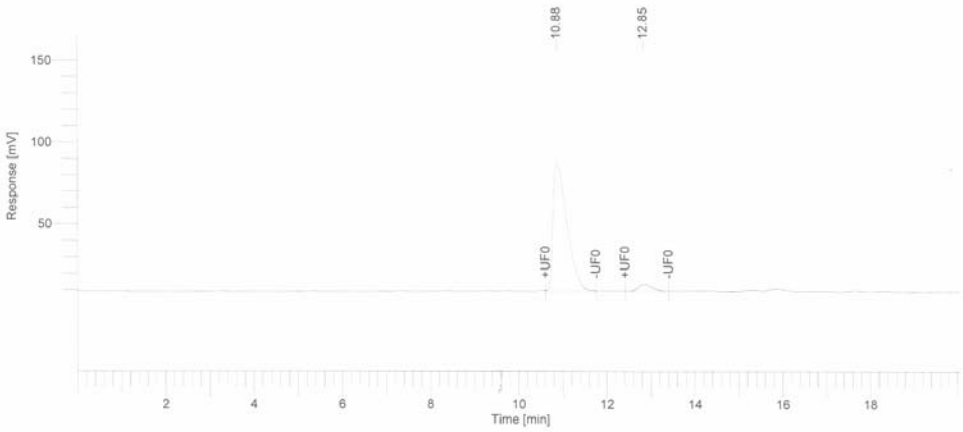


Enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane = 15/85), UV 257 nm, flow rate 1.0 mL/min. *R*-isomer, t_R 10.9, min and *S*-isomer, t_R. 12.8.

Page 1 of 1

Software Version	: 6.2.1.0.104:0104	Date	: 2005-5-23 17:03:29
Sample Name	: ccl	Data Acquisition Time	: 2005-3-10 9:57:24
Instrument Name	: HPLC	Channel	: A
Rack/Vial	: 0/0	Operator	: manager
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 1		

Result File : D:\LC\ccl\4-OH-4-Ph-butan-2-one\050310.rst
Sequence File : C:\PenExe\TcWS\Ver6.2.1\Examples\050310-8-4-6.seq



DEFAULT REPORT

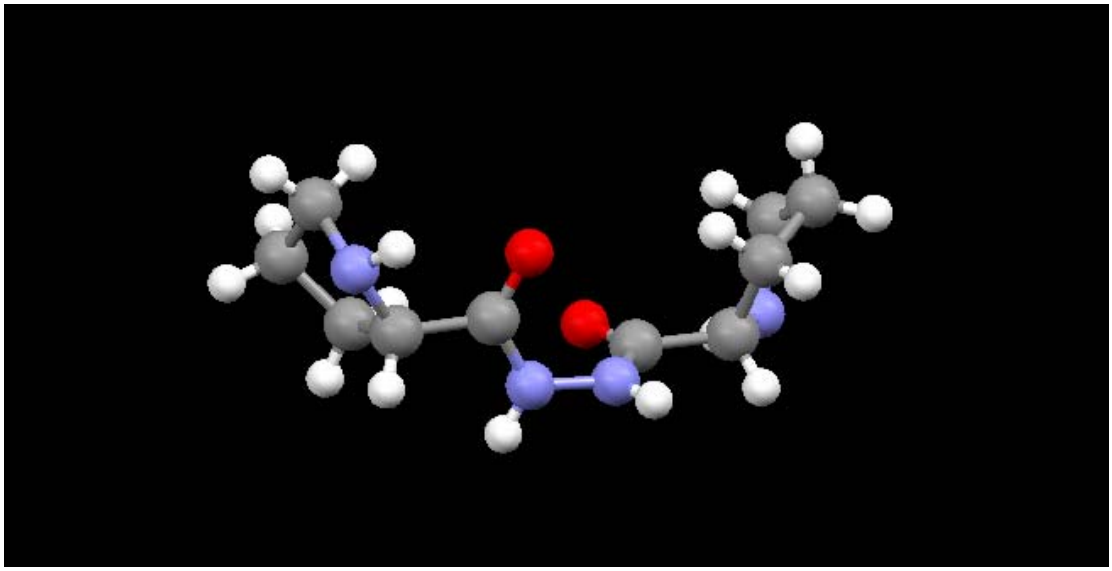
Peak #	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1	10.880	1738107.56	79010.38	95.00
2	12.848	91500.15	4268.42	5.00
		1829607.71	83278.81	100.00

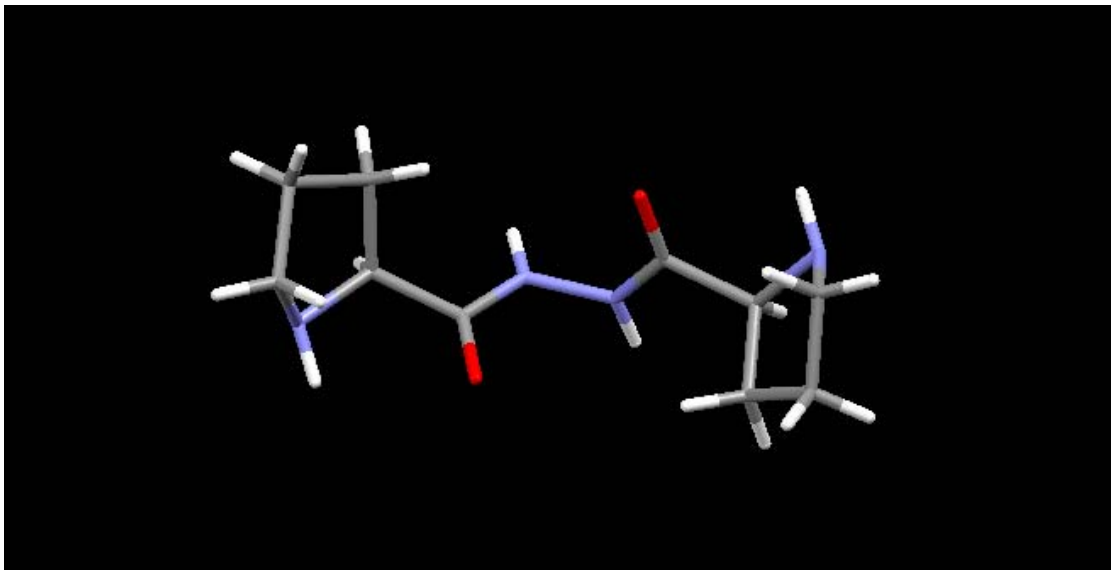
Missing Component Report

Component	Expected Retention (Calibration File)
PE serise200	0.001

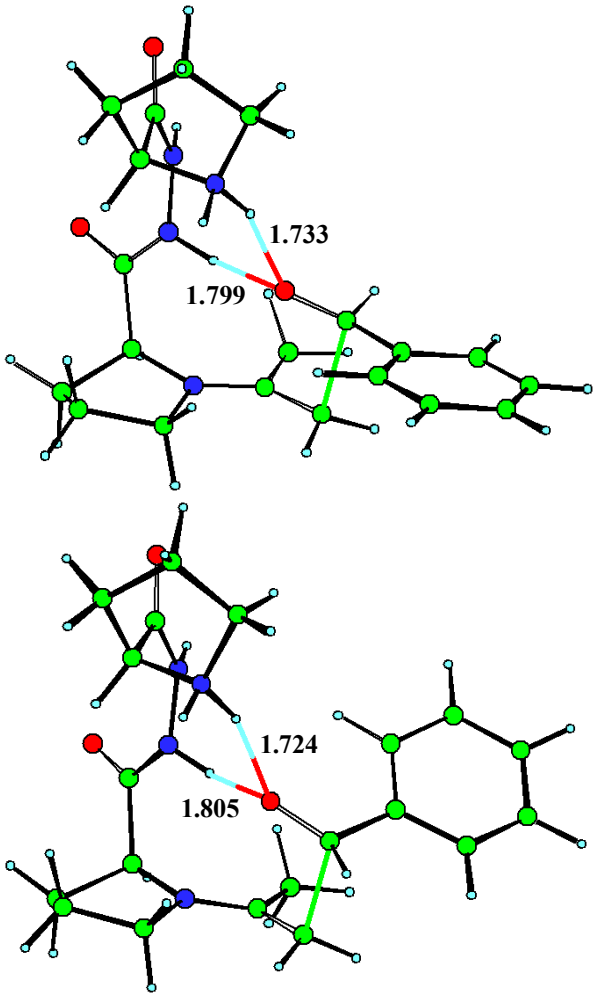
X-ray analysis. Single crystal diffraction data were measured by an Enraf-Nonius CCD single-crystal x-ray diffractometer at 286K. Intensity data were collected with a Siemens P4 four –circle diffractometer with a graphite-monochromated MoK_{α}(λ = 0.71073 Å)radiation. The structure was solved by direct methods using SHELX-97 and refined by full-matrix least-squares with SHELX-97.

Crystal data for 12: $C_{10}H_{18}N_4O_2$ (286K). M = 226.28, orthorhombic, space group $P2_12_12_1$, a = 9.705 (1) Å, b = 7.660 (1) Å, c = 7.818 (1) Å, $\alpha = \beta = \gamma = 90^o$, V = 581.23 (17) $Å^3$, Z = 2, ρ_{calc} = 1.293 mg/m^3, absorption coefficient = 0.093 mm^{-1}, F (000) = 244, total reflections collected 939, unique 823 (R_{int} = 0.0095), final R indices [I>2σ(1)] were R_1 = 0.0351, wR_2 = 0.0751.





Calculations:



TS3 **TS4**

Figure S1. The optimized transition structures for the aldol reaction of benzaldehyde with acetone catalyzed by **12**.

The resulting Cartesian coordinates for the four transition structures **TS1, TS2, TS3** and **TS4**, as well as the enamine intermediate **E1** and **E2** formed by the condensation of acetone with, respectively, catalyst **15** and **12**:

Structure of **TS1**:

C	0.52787100	0.20104600	3.35720400
N	-0.02648300	-0.92083100	2.57070600
C	-1.47989200	-1.02351400	2.75073600
C	-1.71178600	-0.30554700	4.08350300
C	-0.69134800	0.83170200	4.03471900
C	-2.32195400	-0.38435500	1.63380400
O	-3.50846400	-0.31850100	1.75417900
N	-1.64431400	0.05687200	0.54559200
C	0.74185700	-1.79141100	1.93547000
C	2.09542000	-1.53877300	1.68216500

C	1.94437000	-0.51210600	-0.04635900
O	1.08337900	0.41153600	0.11442900
C	0.11003000	-3.02969000	1.35782900
C	3.38832100	-0.15339100	-0.23364300
C	4.23613200	-1.01975900	-0.91067800
C	5.56389800	-0.68345500	-1.12014600
C	6.05360600	0.52395200	-0.65072600
C	5.21154000	1.39537900	0.02600700
C	3.88594900	1.05891600	0.23036200
N	-2.31740700	0.45112700	-0.58801500
C	-2.14129900	1.69595800	-1.07927300
O	-2.49284400	2.02239900	-2.17895400
C	-1.45780700	2.74257400	-0.18386800
C	-1.90468600	4.16427600	-0.54115600
N	0.00970400	2.79274700	-0.50763900
C	-3.04126300	-0.57029400	-1.35439900
C	-1.00423400	4.60569900	-1.71761500
C	0.13826800	3.57725800	-1.78257400
C	-2.15435100	-1.66968300	-1.89888100
C	-1.06116200	-1.37804700	-2.71050500
C	-2.45605300	-2.99808500	-1.63505000
C	-0.28237200	-2.39423900	-3.23441400
C	-1.68011100	-4.02110300	-2.16549900
C	-0.58965900	-3.72108300	-2.96134600
H	0.00872500	-4.51041100	-3.37901800
H	-0.62016000	5.60441600	-1.55732500
H	-0.65060300	-0.06658900	0.44232200
H	1.65171500	-1.36855100	-0.64440500
H	2.69101300	-2.39430200	1.41929100
H	-1.79407600	-2.05531100	2.79933200
H	-1.48192900	-0.98563700	4.89587800
H	-2.73465500	0.02239300	4.18966700
H	1.05722000	0.88280900	2.71136000
H	1.22372700	-0.19722300	4.08573500
H	-1.07663100	1.65472900	3.44045900
H	-0.44829900	1.22464100	5.01293400
H	2.60844800	-0.81852500	2.28995800
H	0.83772300	-3.59052300	0.79141600
H	-0.72082800	-2.79612900	0.70514800
H	-0.25514400	-3.66337200	2.15988400
H	3.85990900	-1.95771400	-1.28209700
H	6.21110900	-1.35892900	-1.64912800
H	7.08341800	0.78631400	-0.81092900
H	5.59148600	2.33239700	0.39162200

H	3.23237300	1.73119200	0.75540500
H	-1.56754500	2.50234000	0.85927500
H	-1.75091000	4.80412900	0.32101600
H	-2.95349100	4.19419500	-0.79253900
H	0.46808900	3.29695600	0.23469900
H	0.47542300	1.87123600	-0.51141300
H	-3.53939200	-0.04813700	-2.15498300
H	-3.79716000	-0.98131500	-0.70199900
H	0.01397300	2.88347400	-2.59722100
H	1.12976300	4.00203500	-1.82446700
H	-1.55077000	4.60041400	-2.64771900
H	-0.83351500	-0.35476900	-2.95184100
H	-3.30894300	-3.24118000	-1.02498200
H	0.55140000	-2.15583300	-3.87034400
H	-1.93422400	-5.04546200	-1.96073700

Structure of **TS2**:

C	-2.39250500	3.12619900	0.38611800
N	-2.11368100	2.25082200	-0.77183800
C	-0.93624000	2.72316300	-1.51284300
C	-0.86298100	4.20344100	-1.12775700
C	-1.29008200	4.18727900	0.33990000
C	0.38038400	2.00964900	-1.16434600
O	1.40421600	2.41808300	-1.62371500
N	0.28033300	0.92579600	-0.35971800
C	-2.93555200	1.28798100	-1.14752600
C	-3.97338000	0.83971100	-0.31586500
C	-3.03206300	-0.50651400	0.84914900
O	-1.86680900	-0.07286900	1.13389400
C	-2.68027500	0.57770000	-2.45000700
N	1.37087400	0.11262900	-0.12719900
C	1.60624800	-0.25529700	1.15862900
O	2.12192100	-1.29446000	1.45031100
C	1.24095100	0.73389600	2.27288900
C	2.31029500	0.75059300	3.37261900
N	0.03790800	0.22664600	3.01728200
C	1.79943800	-0.79826700	-1.20802600
C	1.95994700	-0.42042100	4.31789900
C	0.52385900	-0.84096600	3.95903400
C	-3.18304100	-1.80180500	0.10317600
C	-2.07579400	-2.44291000	-0.43392200
C	-4.43145500	-2.41017000	0.00174900
C	-2.21451700	-3.66016300	-1.08330700
C	-4.57258100	-3.62368200	-0.64458700

C	-3.46193900	-4.25010200	-1.19365500
C	3.30330600	-0.89880200	-1.34867700
C	4.05333200	0.21642200	-1.70881600
C	3.94281900	-2.11523400	-1.16470500
C	5.42232300	0.10930100	-1.87932600
C	5.31356500	-2.22444800	-1.34226800
C	6.05524100	-1.11198300	-1.69881700
H	7.11830900	-1.19392200	-1.83688900
H	-3.56964900	-5.19513700	-1.69395700
H	2.03031000	-0.11466400	5.35333500
H	-0.61042800	0.56985000	-0.05728200
H	-4.74803300	0.28084800	-0.80675000
H	-1.07057000	2.59642200	-2.57654000
H	-1.57645800	4.76042300	-1.72446800
H	0.12104400	4.61287100	-1.29721800
H	-2.39327900	2.54609200	1.29573700
H	-3.37154300	3.57082500	0.25729600
H	-0.45363200	3.90039600	0.96964000
H	-1.64434800	5.14801200	0.68882700
H	-4.33615900	1.51695200	0.43514400
H	-3.34278300	-0.26708600	-2.55050300
H	-1.66001400	0.22248400	-2.52459500
H	-2.86252600	1.25763200	-3.27646600
H	1.01238000	1.70845800	1.87782200
H	2.25478200	1.69799300	3.89767400
H	3.30307100	0.66315000	2.95708000
H	-0.33482500	0.99317200	3.55446200
H	-0.73412800	-0.06532500	2.39417700
H	1.37171500	-0.39194800	-2.11220500
H	1.37290400	-1.77948800	-1.04018200
H	0.49580700	-1.77384200	3.42244300
H	-0.15461200	-0.88795100	4.79753200
H	2.62834500	-1.25350900	4.16651200
H	-3.80287600	-0.38111000	1.60241700
H	-1.10455300	-2.00033800	-0.32496800
H	-5.29628600	-1.93518000	0.43307800
H	-1.34993800	-4.15025500	-1.49331800
H	-5.54096000	-4.08438700	-0.71536200
H	3.56461700	1.16205400	-1.85495800
H	3.37403300	-2.97984900	-0.87238300
H	5.99431400	0.97525200	-2.16047900
H	5.79746200	-3.17359000	-1.19854400

Structure of **TS3**:

C	0.08351600	-2.31718600	1.78665100
N	-0.15565700	-2.57629600	0.35043700
C	-1.55571500	-2.93687100	0.09606000
C	-2.06339300	-3.36275800	1.47935900
C	-1.29999300	-2.43803900	2.42754100
C	-2.41113600	-1.80347000	-0.48286900
O	-3.53245800	-2.01448000	-0.82984000
N	-1.81313600	-0.58349700	-0.57632100
C	0.81698100	-2.59741400	-0.54542500
C	2.09421300	-2.09210000	-0.27194900
C	1.82762700	-0.15088100	-0.73436300
O	0.78021600	0.26596400	-0.14218200
C	0.49945600	-3.06056000	-1.94375900
C	3.16774700	0.37834300	-0.31986200
C	4.23000200	0.36225600	-1.21407100
C	5.46222300	0.88032000	-0.85006500
C	5.63984200	1.41725700	0.41436400
C	4.58165800	1.43834900	1.31214000
C	3.35133000	0.92407100	0.94543900
N	-2.43309700	0.39422800	-1.31718700
C	-2.81503300	1.59200600	-0.81934900
O	-3.46173800	2.36431700	-1.45897600
C	-2.29795200	1.97358400	0.57682100
C	-2.91965600	3.27670300	1.07834500
N	-0.84334400	2.34637100	0.48699000
C	-2.09019100	4.40305900	0.42114000
C	-0.80888000	3.72800500	-0.10370100
H	-2.86458700	0.11598900	-2.17465800
H	-1.85591200	5.18195500	1.13407600
H	-0.81284800	-0.48497700	-0.50759100
H	1.76697600	-0.31646100	-1.80645400
H	2.87388600	-2.40371100	-0.94348900
H	-1.62946000	-3.74760100	-0.61254100
H	-1.78509400	-4.39595200	1.65226200
H	-3.13831800	-3.28493100	1.55426900
H	0.52742000	-1.34434200	1.91912800
H	0.76585500	-3.06877400	2.16581600
H	-1.78147900	-1.46676600	2.47492500
H	-1.24281700	-2.82404300	3.43650000
H	2.40623300	-2.01191700	0.75165700
H	1.35542800	-2.92333000	-2.58685600
H	-0.34045800	-2.52434800	-2.36984100
H	0.25009900	-4.11654500	-1.93561900
H	4.09683600	-0.04909400	-2.20023500

H	6.27735500	0.86756200	-1.55025100
H	6.59524700	1.81852900	0.69929200
H	4.71936800	1.85530900	2.29352100
H	2.52912100	0.94004400	1.63685900
H	-2.39570800	1.14330400	1.25827400
H	-2.83379400	3.31410400	2.15891900
H	-3.96579300	3.33415200	0.82271100
H	-0.47637600	2.37923900	1.42522300
H	-0.23559400	1.66200000	0.01298100
H	-0.81526000	3.61382200	-1.17638100
H	0.11187700	4.20641400	0.19299500
H	-2.62960500	4.85028000	-0.39963000

Structure of **TS4**:

C	0.01032700	2.82283700	-1.70769100
N	0.65009800	2.52119700	-0.40840800
C	-0.15517300	3.02471700	0.71111900
C	-1.03826700	4.09093000	0.05158000
C	-1.30804100	3.50388600	-1.33411600
C	-1.01055600	1.95855500	1.40502900
O	-1.62931900	2.22834400	2.38832700
N	-1.01130700	0.72205700	0.83389600
C	1.85315000	1.98499600	-0.30932300
C	2.49482100	1.40179100	-1.41321200
C	1.74023800	-0.45712700	-1.42371700
O	0.48557500	-0.39682800	-1.20369700
C	2.49950500	1.89710600	1.04745300
N	-1.55068100	-0.32375300	1.54666000
C	-2.58326400	-1.07961600	1.10211100
O	-3.12668900	-1.87685200	1.80309700
C	-2.97053800	-0.94593500	-0.37954200
C	-4.21868000	-1.76079900	-0.71707900
N	-1.93224600	-1.61441800	-1.23817300
C	-3.71332900	-3.20467800	-0.93493500
C	-2.18777800	-3.09056400	-1.11794100
C	2.62884900	-1.22928200	-0.48878500
C	2.15232300	-1.69207100	0.73061600
C	3.93066500	-1.54481900	-0.86784200
C	2.96812300	-2.43907700	1.56660100
C	4.74607900	-2.28995900	-0.03626400
C	4.26616700	-2.73630500	1.18713000
H	-1.40485400	-0.32186500	2.53579400
H	4.89773900	-3.31779100	1.83361200
H	-4.17728700	-3.65426900	-1.80230800

H	-0.28625600	0.45438700	0.18833000
H	3.55530500	1.26441200	-1.31001700
H	0.46734800	3.45172600	1.48206500
H	-0.47368400	5.01262200	-0.02980300
H	-1.92912500	4.28899500	0.62967700
H	-0.12530000	1.91423400	-2.27178900
H	0.65687800	3.48970700	-2.26522400
H	-2.11102700	2.77603500	-1.28468700
H	-1.59148200	4.25358900	-2.06063000
H	2.19184700	1.72645400	-2.39155700
H	3.41283200	1.32702600	0.99039000
H	1.85106700	1.42812400	1.77759200
H	2.73791500	2.89519800	1.40145600
H	-3.02845200	0.09338800	-0.66215800
H	-4.66133400	-1.36535400	-1.62492100
H	-4.95302500	-1.69643300	0.07005200
H	-2.09329800	-1.32736500	-2.19100500
H	-0.95508600	-1.33370900	-1.06453000
H	-1.64220600	-3.43676500	-0.25394200
H	-1.79817300	-3.58036100	-1.99713700
H	-3.93340900	-3.82298800	-0.07820500
H	2.05203500	-0.56528400	-2.45740200
H	1.14076700	-1.48145700	1.02240300
H	4.30737400	-1.21051300	-1.81958600
H	2.58900000	-2.79368100	2.50812100
H	5.74858000	-2.52847800	-0.34137400

Structure of **E1**:

C	0.96847900	3.21408900	-1.45702800
N	1.46981400	2.36464100	-0.37647800
C	0.62475400	2.46815100	0.80414800
C	-0.35974500	3.60852600	0.47949400
C	-0.45953500	3.55634800	-1.04378000
C	-0.14388300	1.18730900	1.12959200
O	-0.74471000	1.05368300	2.15310300
N	-0.17751300	0.22643200	0.13647500
C	2.85801200	2.14300100	-0.28978100
C	3.68532200	2.38400100	-1.29870800
C	3.37457800	1.58072300	1.01233600
N	-0.63494400	-1.03431500	0.45321300
C	-1.85611800	-1.41379000	0.06912600
O	-2.30867200	-2.51883300	0.24812600
C	-2.75005300	-0.38530700	-0.63919700
C	-3.48161200	0.56838600	0.33593600

N	-3.86182500	-1.19632000	-1.26983300
C	0.23313500	-1.92512100	1.23664800
C	-4.84849500	-0.08375200	0.56127400
C	-5.18892800	-0.65534400	-0.80572900
C	1.46889800	-2.36099600	0.47722300
C	2.71485200	-2.29103700	1.08240900
C	1.37338300	-2.88708800	-0.80783000
C	3.84988700	-2.73165400	0.41649800
C	2.50404600	-3.31938700	-1.47662200
C	3.74732300	-3.24128900	-0.86504200
H	4.62519500	-3.58088800	-1.38349900
H	-5.91375600	-1.45497300	-0.81017500
H	0.56805500	0.24811900	-0.52904000
H	4.73083900	2.16742700	-1.19728100
H	1.17577100	2.69730800	1.70379000
H	0.08670900	4.54660600	0.78809000
H	-1.30264600	3.50583900	1.00001600
H	1.01870500	2.69835100	-2.40873700
H	1.57178200	4.11425700	-1.53907400
H	-1.14570500	2.77414700	-1.35845700
H	-0.80086700	4.48688500	-1.47905900
H	3.37077800	2.78786700	-2.24097900
H	4.40141600	1.26608500	0.89418300
H	2.80065300	0.71954800	1.33719500
H	3.34476500	2.31877500	1.80757600
H	-2.21654300	0.13643000	-1.41520700
H	-3.59867600	1.53680600	-0.13587500
H	-2.92397800	0.70525400	1.24955200
H	-3.79113200	-1.22898000	-2.27388400
H	-3.72958300	-2.14495900	-0.92124400
H	0.50035500	-1.39910200	2.14234700
H	-0.37079000	-2.77503400	1.51142400
H	-4.78353100	-0.87787600	1.29605300
H	-5.59561800	0.62324100	0.89458600
H	-5.49110900	0.11235600	-1.50359600
H	2.80473900	-1.90151300	2.08155100
H	0.41117100	-2.97769200	-1.28157100
H	4.80806800	-2.67454900	0.89993800
H	2.41745800	-3.72621800	-2.46788600

Structure of **E2**:

C	-3.98337900	-0.51795100	-0.64124600
N	-2.87961700	0.23720900	-0.04833800
C	-2.08129000	-0.61370700	0.82507600

C	-2.80260600	-1.97866300	0.81397800
C	-3.54654900	-1.97266100	-0.52023300
C	-0.64426600	-0.78069900	0.35006400
O	0.21860700	-1.24938000	1.03926300
N	-0.39258900	-0.42697800	-0.94831400
C	-3.06779700	1.60537200	0.22606300
C	-4.11211900	2.29234900	-0.21933400
C	-1.97631000	2.28828000	1.01631700
N	0.90220500	-0.49193200	-1.38553600
C	1.82219500	0.33350500	-0.84670900
O	1.58605000	1.38051600	-0.31703200
C	3.27195800	-0.14619800	-0.95696400
C	3.60358900	-1.26104900	0.06253000
N	4.12531600	1.02381300	-0.53492100
C	4.13128600	-0.50163800	1.28190400
C	4.95457000	0.61844900	0.66357100
H	1.18934400	-1.40344500	-1.67017400
H	5.10646900	1.48472600	1.28867000
H	-1.02241700	0.16087400	-1.44650200
H	-4.18275700	3.34506900	-0.02555200
H	-2.00589300	-0.23910600	1.83572200
H	-3.51080100	-1.99993900	1.63411600
H	-2.12143900	-2.80910700	0.94508900
H	-4.14853200	-0.20798800	-1.66577700
H	-4.90470600	-0.34587100	-0.08971600
H	-2.88116100	-2.24161300	-1.33473700
H	-4.38492600	-2.65717500	-0.53765000
H	-4.91217400	1.85665400	-0.78454000
H	-2.14304200	3.35622300	1.02259300
H	-0.99440900	2.10554600	0.59165800
H	-1.95676200	1.95596900	2.04938000
H	3.51635500	-0.41330300	-1.97517800
H	4.36751100	-1.91071100	-0.34753700
H	2.73202800	-1.85396400	0.29862100
H	4.69385600	1.37694900	-1.28778200
H	3.47161800	1.76047500	-0.27583200
H	3.31141400	-0.09957600	1.86507800
H	4.73400500	-1.12352500	1.92913000
H	5.90627000	0.26662400	0.29274100

The resulting energies (in atomic unit) of the enamine intermediates and the transition states by various methods, as well as the thermal corrections obtained by the harmonic vibrational frequency analysis:

	HF/6-31G*	B3LYP/6-31G*	B3LYP/6-31G*	B3LYP/6-311+G**	ZPE	H	Gibbs	S
					-			

	optimized	sp gas phase	iefpcm (toluene)	iefpcm (toluene)	corr.	corr.	Corr.	cal/mol·K
E1	-1141.55920	-1148.80456	-1148.83395	-1149.14953	0.51739	0.54155	0.46059	170.39
TS1	-1484.97009	-1494.38182	-1494.39981	-1494.80578	0.63843	0.66861	0.57527	196.46
TS2	-1484.96375	-1494.37592	-1494.39506	-1494.80070	0.63841	0.66854	0.57553	195.76
E2	-872.97962	-878.43855	-878.47927	-878.73199	0.40005	0.41875	0.35201	140.48
TS3	-1216.38764	-1224.01414	-1224.04175	-1224.38634	0.52055	0.54543	0.46474	169.83
TS4	-1216.38696	-1224.01313	-1224.04133	-1224.38540	0.52092	0.54558	0.46584	167.84

Note: the single point energies in solvent contain the non-electrostatic contributions.

The resulting activation energies (in kcal/mol) with the thermal corrections:

	HF/6-31G*	B3LYP/6-31G*	B3LYP/6-31G*	B3LYP/6-311+G**	ZPE	H	Gibbs	S	**H**	**G**
	opt.	sp gas phase	iefpcm (toluene)	iefpcm (toluene)	corr.	corr.	corr.	cal/mol·K	298K	298K
TS1	14.2	-3.9	3.6	8.0	1.7	1.2	16.8	-52.2	9.2	24.8
TS2	18.2	-0.2	6.6	11.2	1.7	1.2	16.9	-52.9	12.4	28.1
TS3	16.0	-2.9	5.7	9.2	1.4	1.0	15.5	-48.9	10.2	24.8
TS4	16.4	-2.3	6.0	9.8	1.6	1.1	16.2	-50.9	10.9	26.0

Full reference 8 from paper b511992h:

All calculations were performed with the Gaussian03 program. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Sealmani, N. Rega, G. A. Petersson, H. Nakatsuij, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Iahida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. F. Startmann, O. Yazyev, J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorv, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanavakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, GAUSSIAN 03 (Revision C.02), Gaussian, Inc., Wallingford, CT, 2004.