The application of "backdoor induction" in bioinspired asymmetric catalysis

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Electronic Supplementary Information (ESI)

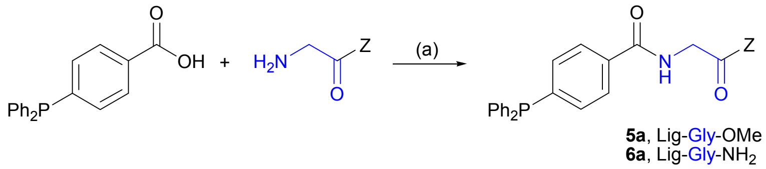
Content.

1. Synthesis, general procedures.

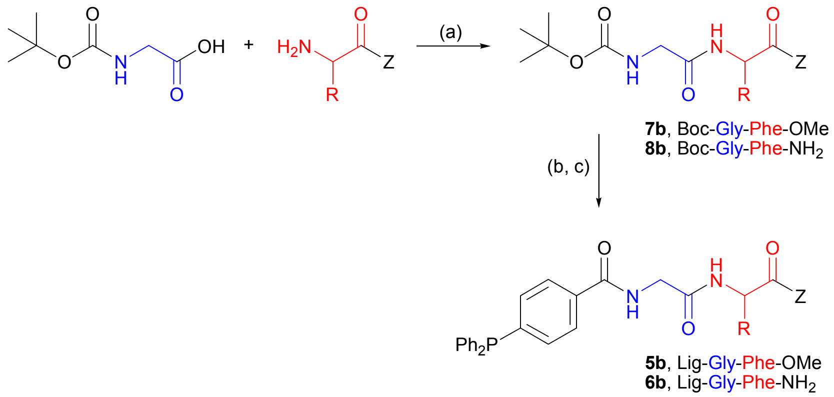
Peptide coupling. 4-(Diphenylphosphino)-benzoic acid, Boc-protected amino acid or peptide, TBTU, HOBt and DIPEA were added to DCM and stirred at room temperature. After 1 h, *N*-unprotected amino acid or peptide was added to the reaction mixture and stirring was continued overnight (approximately 15 h). The reaction mixture was then washed with $NaHCO_3$ (sat., aq.), citric acid (10 %, aq.) and NaCl (sat., aq.), dried over Na_2SO_4, filtered, evaporated in vacuum and purified by automated flash chromatography on a prepacked silica column.

Boc-protecting group removal. The corresponding Boc-protected peptide was dissolved in DCM/trifluoroacetic acid (1:1, 10 mL) and stirred for 2 h at room temperature. The volatile were evaporated under reduced pressure and the viscous residue was dissolved in 15 mL of DCM. The residual trifluoroacetic acid was neutralized with excess of DIPEA (0.5 mL). This solution was used for further coupling.

2. Synthesis of ligands 5a / 6a and 5b / 6b.



Solution phase synthesis of Lig-Aa_1-Z 5a and **6a**. Reaction conditions: (a) TBTU / HOBt, DIPEA, DCM.



Synthesis of Lig-Gly-Phe-Z 5b and **6b**. Reaction conditions: (a) TBTU / HOBt, DIPEA, DCM; (b) TFA / DCM (1:1) (c) Ph_2P-*p*C_6H_4-CO_2H / TBTU / HOBt, DIPEA, DCM.

3. Synthesis of precursors 7-10.

Boc-Gly-Phe-OMe, **7b**. Boc-Gly-OH (876.0 mg, 5.00 mmol), HOBt (676.9 mg, 5.01 mmol), TBTU (1601.6 mg, 4.99 mmol), DIPEA (1.100 mL, 6.66 mmol), H-Phe-OMe × HCl (1089.2 mg, 5.05 mmol), DCM (100 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.38, EtOAc/Hexane = 1/1). Yield: 902.9 mg (54 %). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ/ppm: 1.44 (s, 9H), 3.11 (dd, 1H, J_1 = 14 Hz, J_2 = 6 Hz), 3.15 (dd, 1H, J_1 = 14 Hz, J_2 = 6 Hz), 3.72 (s, 3H), 3.72 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 3.83 (dd, 1H, J_1 = 14 Hz, J_2 = 4 Hz), 4.87–4.90 (m, 1H), 5.02 (s, 1H), 6.46 (d, J = 7 Hz, 1H), 7.09 (d, J = 7 Hz, 2H), 7.23–7.30 (3H).

Boc-Ala-Gly-OMe, **7c**. Boc-Ala-OH (570.1 mg, 3.01 mmol), HOBt (407.0 mg, 3.01 mmol), TBTU (954.6 mg, 2.97 mmol), DIPEA (2.000 mL, 12.10 mmol), H-Gly-OMe × HCl (383.0 mg, 3.05 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient

(TLC: R_f = 0.17, EtOAc/Hexane = 1/1). Yield: 391.0 mg (50 %), ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.38 (d, *J* = 7 Hz, 3H), 1.46 (s, 9H), 3.76 (s, 3H), 3.98–4.13 (m, 2H), 4.17–4.26 (m, 1H), 4.97 (ws, 1H), 6.67 (ws, 1H).

Boc-Val-Gly-OMe, **7d**. Boc-Val-OH (394.5 mg, 1.81 mmol), HOBt (246.1 mg, 1.82 mmol), TBTU (582.6 mg, 1.81 mmol), DIPEA (1.144 mL, 6.92 mmol), H-Gly-OMe × HCl (234.6 mg, 1.87 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.3, EtOAc/Hexane = 2/8). Yield: 430.48 mg (82 %,). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.95 (d, 3H, *J* = 7 Hz), 1.00 (d, 3H, *J* = 7 Hz), 1.45 (s, 9H) 2.13–2.28 (m, 1H), 3.99–4.15 (m, 3H), 5.08 (d, 1H, *J* = 8 Hz), 6.58 (t, 1H, *J* = 5 Hz).

Boc-Leu-Gly-OMe, **7e**. Boc-Leu-OH (657.4 mg, 2.84 mmol), HOBt (359.5 mg, 2.66 mmol), TBTU (851.3 mg, 2.65 mmol), DIPEA (2.000 mL, 12.10 mmol), H-Gly-OMe × HCl (335.7 mg, 2.67 mmol), DCM (100 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.43, EtOAc/Hexane = 1/1). Yield: 600 mg (74 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.94 (d, 3H, *J* = 6 Hz), 0.95 (d, 3H, *J* = 6 Hz), 1.45 (s, 9H), 1.49–1.55 (m, 1H), 1.66–1.76 (m, 2H), 4.05 (d, 2H, *J* = 5 Hz) 4.13–4.19 (m, 1H), 4.86 (d, 1H, *J* = 7 Hz), 6.62 (t, 1H, *J* = 6 Hz).

Boc-Pro-Gly-OMe, **7f**. Boc-Pro-OH (379.6 mg, 1.76 mmol), HOBt (246.6 mg, 1.84 mmol), TBTU (557.0 mg, 1.74 mmol), DIPEA (1.200 mL, 7.26 mmol), H-Gly-OMe × HCl (229.4 mg, 1.84 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.18, EtOAc/Hexane = 1/1). Yield: 469.9 mg (93 %). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ/ppm: 1.47 (s, 9H), 1.85–2.34 (m, 4H), 3.39–3.46 (m, 2H), 3.75 (s, 3H), 3.96–4.14 (m, 2H), 4.32 (ws, 1H), 6.53, 7.29 (ws, two weak signals, 1H).

Boc-Phe-Phe-OEt, **7g**. Boc-Phe-OH (303.9 mg, 1.15 mmol), HOBt (164.8 mg, 1.22 mmol), TBTU (366.6 mg, 1.14 mmol), DIPEA (0.750 mL, 4.54 mmol), H-Phe-OEt × HCl (558.9 mg, 0.99 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.2, EtOAc/Hexane = 2/8). Yield: 358.7 mg (71 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.20 (t, 3H, *J* = 7. Hz), 1.40 (s, 9H), 3.02–3.05 (m, 4H), 4.06–4.17 (m, 2H), 4.29–4.36 (m, 1H), 4.72–4.78 (m, 1H), 4.92 (s, 1H), 6.26 (d, 1H, *J* = 7 Hz), 6.99–7.01 (m, 2H), 7.18–7.31 (m, 8H).

Boc-Val-Phe-OEt, **7h**. Boc-Val-OH (570.8 mg, 2.63 mmol), HOBt (351.0 mg, 2.60 mmol), TBTU (895.1 mg, 2.79 mmol), DIPEA (2.000 mL, 11.637 mmol), H-Phe-OMe × HCl (615.0 mg, 2.68 mmol), DCM (50 mL). *Chromatography*: silica (12 g), DCM/EtOH gradient (TLC: R_f = 0.6, DCM/EtOH = 95/5). Yield: 575.8 mg (56 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.87 (d, 3H, *J* = 6.5 Hz), 0.92 (d, 3H, *J* = 7 Hz), 1.22 (t, 3H, *J* = 7 Hz), 1.44 (s, 9H), 2.03–2.14 (m, 1H), 3.12 (d, 2H, *J* = 6 Hz), 3.89 (dd, 1H, J_1 = 8 Hz, J_2 = 6.5 Hz), 4.15 (q, 2H, *J* = 7 Hz), 4.85 (dt, 1H, J_1 = 8 Hz, J_2 = 6 Hz), 5.00 (d, 1H, *J* = 6.5 Hz), 6.27 (d, 1H, *J* = 6 Hz), 7.11–7.14 (m, 2H), 7.21–7.31 (m, 3H).

Boc-Pro-Phe-OMe, **7j**. Boc-Pro-OH (644.5 mg, 2.99 mmol), HOBt (402.01 mg, 2.98 mmol), TBTU (1009.0 mg, 3.14 mmol), DIPEA (2.000 mL, 11.637 mmol), H-Phe-OMe × HCl (661.1 mg, 3.07 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.4, EtOAc/Hexane = 1/1). Yield: 941.7 mg (84 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.43 (s, 9H), 1.79 (ws, 2H), 1.99 (ws, 1H), 2.26 (ws, 1H), 3.01 (dd, 1H, J_1 = 14 Hz, J_2 = 7 Hz), 3.19 (dd, 1H, J_1 = 14 Hz, J_2 = 5.5 Hz), 3.26–3.38 (m, 2H), 3.72 (s, 3H), 4.24 (ws, 1H), 4.87 (ws, 1H), 6.45 (ws, 1H), 7.10 (d, 2H, *J* = 7 Hz), 7.20–7.30 (m, 3H).

Boc-Gly-Phe-NH_2, **8b**. Boc-Gly-OH (326.9 mg, 1.86 mmol), HOBt (246.5 mg, 1.82 mmol), TBTU (587.2 mg, 1.83 mmol), DIPEA (0.455 mL, 2.75 mmol), H-Phe-NH_2 (205.03 mg, 1.25 mmol), DCM (50 mL). The crude product was used for the next synthetic step without chromatographic purification (due to gelation). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ/ppm: 1.37 (s, 9H), 2.79 (dd, 1H, J_1 = 14 Hz, J_2 = 9 Hz), 3.00 (dd, 1H, J_1 = 14 Hz, J_2 = 4.5 Hz), 3.41 (dd, 1H, J_1 = 16.5 Hz, J_2 = 6 Hz), 3.56 (dd, 1H, J_1 = 16.5 Hz, J_2 = 6 Hz), 4.45 (ddd, 1H, J_1 = J_2 = 8.5 Hz, J_3 = 4.5 Hz), 6.93 (t, 1H, *J* = 6 Hz), 7.11 (s, 1H), 7.15–7,28 (m, 5H), 7.41 (s, 1H), 7.87 (d, 1H, *J* = 8.5 Hz).

Boc-Val-Gly-NH_2, 8d. Boc-Val-OH (397 mg, 1.82 mmol), HOBt (240.9 mg, 1.78 mmol), TBTU (571.9 mg, 1.78 mmol), DIPEA (1.200 mL, 7.26 mmol), H-Gly-NH_2 × HCl (204.4 mg, 1.85 mmol), DCM (50 mL). The crude product was not extracted (since it is soluble in water). *Chromatography*: silica (24 g), DCM/MeOH gradient (TLC: R_f = 0.4, DCM/MeOH = 9/1). Yield: 370 mg (72 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.98 (d, 3H, J = 7 Hz), 1.02 (d, 3H, J = 7 Hz), 1.47 (s, 9H), 2.13–2.24 (m, 1H), 3.84 (pseudo-t, 1H), 3.94 (dd, 1H, J_1 = 17 Hz, J_2 = 5.5 Hz), 4.03 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 5.00 (d, 1H, J = 7 Hz), 5.44 (s, 1H), 6.53 (s, 1H), 6.64 (s, 1H).

Boc-Phe-Phe-NH_2, 8g. Boc-Phe-OH (321.08 mg, 1.21 mmol), HOBt (163.5 mg, 1.21 mmol), TBTU (388.1 mg, 1.21 mmol), DIPEA (0.795 mL, 4.81 mmol), H-Phe-NH_2 (205.03 mg, 1.25 mmol), DCM (50 mL). The crude product was used for the next synthetic step without chromatographic purification (due to gelation). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ/ppm: 1.29 (s, 9H), 2.66 (dd, 1H, J_1 = 13.5 Hz, J_2 = 10.5 Hz), 2.83–2.87 (m, 2H), 3.02 (dd, 1H, J_1 = 13.5 Hz, J_2 = 5 Hz), 4.08–4.11 (m, 1H), 4.45–4.48 (m, 1H), 6.90 (d, 1H, J = 8.5 Hz), 7.07 (s, 1H), 7.16–7,27 (m, 5H), 7.34 (s, 1H), 7.84 (d, 1H, J = 8 Hz).

Boc-Val-Phe-NH_2, 8h. Boc-Val-OH (458.4 mg, 2.10 mmol), HOBt (289.3 mg, 2.14 mmol), TBTU (675.14 mg, 2.10 mmol), DIPEA (1.400 mL, 8.83 mmol), H-Phe-NH_2 (362.2 mg, 2.21 mmol), DCM (50 mL). The crude product was used for the next synthetic step without chromatographic purification (due to gelation). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ/ppm: 0.80 (d, 3H, J = 6 Hz), 0.9 (d, 3H, J = 7 Hz), 1.39 (s, 9H), 2.11–2.16 (m, 1H), 3.09 (dd, 1H, J_1 = 14 Hz, J_2 = 7 Hz), 3.18 (dd, 1H, J_1 = 14 Hz, J_2 = 6 Hz), 3.85 (dd, 1H, J_1 = 6 Hz, J_2 = 5 Hz), 4.73 (pseudo-q, 1H, J = 7 Hz), 4.81 (d, 1H, J = 6 Hz), 5.33 (s, 1H), 6.25 (s, 1H), 6.44 (s, 1H), 7.22–7.25 (m, 3H), 7.29–7.31 (m, 2H).

Boc-Pro-Phe-NH_2, 8j. Boc-Pro-OH (475.6 mg, 2.21 mmol), HOBt (312.08 mg, 2.31 mmol), TBTU (713.3 mg, 2.22 mmol), DIPEA (1.460 mL, 8.47 mmol), H-Phe-NH_2 (348.8 mg, 2.12 mmol), DCM (50 mL). *Chromatography*: silica (24 g), DCM/MeOH gradient (TLC: R_f = 0.35, DCM/MeOH = 9.5/0.5). Yield: 761.5 mg (95 %). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ/ppm: 1.35 (s, 9H), 1.67 (s, 1H), 1.84 (s, 1H), 2.01 (s, 1H), 2.06–2.12 (m, 1H), 3.09 (s, 1H), 3.27–3.33 (m, 3H), 4.18 (dd, 1H, J_1 = 8 Hz, J_2 = 3 Hz), 4.75 (s, 1H), 5.31 (s, 1H), 6.38 (s, 1H), 6.73 (s, 1H), 7.18–7.32 (m, 5H).

Boc-Gly-Ala-Gly-OMe, 9c. Boc-Gly-OH (193.5 mg, 1.11 mmol), HOBt (206.0 mg, 1.52 mmol), TBTU (478.2 mg, 1.49 mmol), DIPEA (1.000 mL, 6.05 mmol), **H-Ala-Gly-OMe** (1.50 mmol), DCM (50 mL). *Chromatography*: silica (24 g), EtOAc/Hexane gradient (TLC: R_f = 0.16, EtOAc/Hexane = 9/1). Yield: 98.4 mg (28 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.42 (d, J = 7 Hz, 3H), 1.45 (s, 9H), 3.75 (s, 1H), 3.81 (d, J = 5.5 Hz, 2H), 3.98 (dd, J_1 = 18 Hz, J_2 = 5.5 Hz, 1H), 4.07 (dd, J_1 = 18 Hz, J_2 = 5.5 Hz, 1H), 4.57 (pseudo quintet, J = 7 Hz), 5.16 (s, 1H), 6.65 (d, J = 7 Hz, 1H), 6.80 (s, 1H).

Boc-Gly-Val-Gly-OMe, 9d. Boc-Gly-OH (367.3 mg, 2.10 mmol), HOBt (283.6 mg, 2.10 mmol), TBTU (670.0 mg, 2.09 mmol), DIPEA (0.520 mL, 3.15 mmol), **H-Val-Gly-OMe** (2.09 mmol), DCM (50 mL). *Chromatography*: silica (12 g), EtOAc/Hexane gradient (TLC: R_f = 0.36, EtOAc/Hexane = 9/1). Yield: 611.6 mg (85 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.95 (d, 3H, J = 7 Hz), 0.98 (d, 3H, J = 7 Hz), 1.45 (s, 9H), 2.21–2.25 (m ,1H), 3.75 (s, 3H), 3.79 (dd, 1H, J_1 = 17 Hz, J_2 = 5 Hz), 3.85 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 4.03 (d, 2H, J = 5 Hz), 4.35 (dd, 1H, J_1 = 8.5 Hz, J_2 = 6 Hz), 5.20 (ws, 1H), 6.69 (dd, 1H, J = 8.5 Hz), 6.69 (ws, 1H).

Boc-Gly-Leu-Gly-OMe, 9e. Boc-Gly-OH (174.5 mg, 1.00 mmol), HOBt (186.2 mg, 1.38 mmol), TBTU (427.6 mg, 1.33 mmol), DIPEA (1.000 mL, 6.05 mmol), **H-Leu-Gly-OMe** (1.35 mmol), DCM (50 mL). *Chromatography*: silica (12 g), DCM/MeOH gradient (TLC: R_f = 0.22, EtOAc/Hex = 9/1). Yield: 189.4 mg (53 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.93 (d, 3H, J = 6 Hz), 0.94 (d, 3H, J = 6 Hz), 1.45 (s, 9H), 1.52–1.78 (m, 3H), 3.75 (s, 3H), 3.73–3.88 (m, 2H), 3.93–4.09 (m, 2H), 4.49–4.57 (m, 1H), 5.19 (s, 1H), 6.58 (d, 1H, J = 8 Hz), 6.83 (s, 1H).

Boc-Gly-Pro-Gly-OMe, 9f. Boc-Gly-OH (204.4 mg, 1.17 mmol), HOBt (154.8 mg, 1.16

mmol), TBTU (362.0 mg, 1.13 mmol), DIPEA (0.280 mL, 1.69 mmol), **H-Pro-Gly-OMe** (1.13 mmol), DCM (50 mL). *Chromatography*: silica (12 g), EtOAc/EtOH gradient (TLC: R_f = 0.36, EtOAc/MeOH = 9/1). Yield: 265.2 mg (66 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.45 (s, 9H), 1.83–2.20 (m, 3H) ,2.39–2.46 (m, 1H), 3.37–3.45 (m, 1H), 3.52–3.59 (m, 1H), 3.94–4.02 (m, 4H), 4.64 (dd, 1H, J_1 = 8 Hz, J_2 = 2 Hz), 5.31 (s, 1H), 7.28 (s, 1H).

Boc-Gly-Phe-Phe-OEt, **9g**. Boc-Gly-OH (80.2 mg, 0.46 mmol), HOBt (60.7 mg, 0.45 mmol), TBTU (142.5 mg, 0.44 mmol), DIPEA (0.300 mL, 3.97 mmol), **H-Phe-Phe-OEt** (0.86 mmol), DCM (50 mL). *Chromatography*: silica (12 g), EtOAc/hexane gradient (TLC: R_f = 0.3, EtOAc/hexane = 9/1). Yield: 276.6 mg (74 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.21 (t, 3H, J = 7 Hz), 1.45 (s, 9H), 2.95–3.11 (m, 4H), 3.69 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 3.77 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 4.08–4.18 (m, 2H), 4.59–4.76 (m, 2H), 4.98 (ws), 6.23 (d, 1H, J = 7 Hz), 6.55 (d, 1H, J = 8 Hz), 7.00–7.03 (m, 2H), 7.17–7.19 (m, 2H), 7.22–7.30 (m, 6H).

Boc-Gly-Val-Phe-OEt, **9h**. Boc-Gly-OH (203.3 mg, 1.16 mmol), HOBt (152.5 mg, 1.13 mmol), TBTU (351.2 mg, 1.11 mmol), DIPEA (0.800 mL, 4.66 mmol), **H-Val-Phe-OEt** (1.12 mmol), DCM (50 mL). *Chromatography*: silica (12 g), DCM/EtOH gradient (TLC: R_f = 0.45, DCM/EtOH = 10/0.5). Yield: 232.1 mg (44 %,). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.88 (d, 3H, J = 7 Hz), 0.92 (d, 3H, J = 7 Hz), 1.24 (t, 3H, J = 7 Hz), 1.46 (s, 9H), 2.03–2.14 (m, 1H), 3.08 (dd, 1H, J_1 = 14 Hz, J_2 = 6 Hz), 3.14 (dd, 1H, J_1 = 14 Hz, J_2 = 5.5 Hz), 3.73 (dd, 1H, J_1 = 17 Hz, J_2 = 5.5 Hz), 3.83 (dd, 1H, J_1 = 17 Hz, J_2 = 6 Hz), 4.17 (q, 2H, J = 7 Hz), 4.24 (dd, 1H, J_1 = 8.5 Hz, J_2 = 6.5 Hz), 4.84 (ddd, 1H, J_1 = 7.5 Hz, J_2 = 6 Hz, J_3 = 5.5 Hz), 5.09 (ws, 1H), 6.28 (d, 1H, J = 7 Hz), 6.58 (d, 1H, J = 8.5 Hz), 7.11–7.14 (m, 2H), 7.24–7.32 (m, 3H).

Boc-Gly-Pro-Phe-OMe, 9**j**. Boc-Gly-OH (164.8 mg, 0.94 mmol), HOBt (138.1 mg, 1.02 mmol), TBTU (307.2 mg, 0.96 mmol), DIPEA (0.650 mL, 3.93 mmol), **H-Pro-Phe-OMe** (0.86 mmol), DCM (50 mL). *Chromatography*: silica (12 g), EtOAc/hexane gradient (TLC: R_f = 0.3, EtOAc/hexane = 9/1). Yield: 276.6 mg (74 %,). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 1.48 (s, 9H), 1.72–1.82 (m, 1H), 1.88–1.98 (m, 2H), 2.33–2.40 (m, 1H), 2.97 (dd, 1H, J_1 = 14 Hz, J_2 = 8 Hz), 3.21 (dd, 1H, J_1 = 14 Hz, J_2 = 5.5 Hz), 3.25–3.30 (m, 2H), 3.72 (dd, 1H, J_1 = 17.5 Hz, J_2 = 4 Hz), 3.75 (s, 3H), 3.90 (dd, 1H, J_1 = 17.5 Hz, J_2 = 4.5 Hz), 4.56 (d, 1H, J = 7 Hz), 4.84 (ddd, 1H, J_1 = J_2 = 8 Hz, J_3 = 5.5 Hz), 5.37 (s, 1H), 7.09–7.12 (m, 2H), 7.22–7.32 (m, 3H).

Boc-Gly-Val-Gly-NH₂, **10d**. Boc-Gly-OH (197.4 mg, 1.13 mmol), HOBt (149.4 mg, 1.11 mmol), TBTU (352.6 mg, 1.10 mmol), DIPEA (0.270 mL, 1.66 mmol), **H-Val-Gly-NH₂** (1.10 mmol), DCM (40 mL). The crude product was not extracted (since it is soluble in water). *Chromatography*: silica (24 g), DCM/MeOH gradient (TLC: R_f = 0.2, DCM/MeOH = 9/1). Yield: 206 mg (55 %). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ/ppm: 0.94 (d, 3H, J = 7 Hz), 0.96 (d, 3H, J = 7 Hz), 1.38 (s, 9H), 2.15–2.25 (m, 1H), 3.78–3.93 (m, 4H), 4.21 (pseudo-t, 1H, J = 7 Hz), 5.85 (s, 1H), 6.07 (s, 1H), 7.01 (s, 1H), 7.26 (s, 1H (under solvent peak)), 7.83 (s, 1H).

Boc-Gly-Phe-Phe-NH₂, 10**g**. Boc-Gly-OH (88.5 mg, 0.51 mmol), HOBt (75.2 mg, 0.56 mmol), TBTU (157.1 mg, 0.49 mmol), DIPEA (0.125 mL, 0.76 mmol), **H-Phe-Phe-NH₂** (0.50 mmol), DCM (40 mL). The crude product was used for the next synthetic step without chromatographic purification (due to gelation). ^{1}H NMR (600.13 MHz, DMSO-d_6) δ/ppm: 1.37 (s, 9H), 2.74 (dd, 1H, J_1 = 14 Hz, J_2 = 9 Hz), 2.83 (dd, 1H, J_1 = 14 Hz, J_2 = 9 Hz), 2.94 (dd, 1H, J_1 = 14 Hz, J_2 = 5 Hz), 3.02 (dd, 1H, J_1 = 14 Hz, J_2 = 5 Hz), 4.41–4.44 (m, 1H), 4.46–4.49 (m, 1H), 6.87 (t, 1H, J = 5.5 Hz), 7.05 (s, 1H), 7.15–7,27 (m, 11H), 7.85 (d, 1H, J = 8 Hz), 8.05 (d, 1H, J = 8 Hz).

Boc-Gly-Val-Phe-NH₂, **10h**. Boc-Gly-OH (165.4 mg, 0.94 mmol), HOBt (132.3 mg, 0.98 mmol), TBTU (301.4 mg, 0.94 mmol), DIPEA (0.235 mL, 1.42 mmol), **H-Val-Phe-NH₂** (0.99 mmol), DCM (40 mL). The crude product was used for the next synthetic step without chromatographic purification (due to gelation). ^{1}H NMR (600.13 MHz, DMSO-d_6) δ/ppm: 0.71 (d, 3H, J = 7 Hz), 0.76 (d, 3H, J = 7 Hz), 1.38 (s, 9H), 1.87–1.98 (m, 1H), 2.80 (dd, 1H, J_1 = 14 Hz, J_2 = 9.5 Hz), 3.18 (dd, 1H, J_1 = 14 Hz, J_2 = 5 Hz), 3.48–3.63 (m, 2H), 4.10–4.14

(m, 1H), 4.40–4.47 (m, 1H), 7.04–7.07 (m, 2H), 7.15–7.28 (m, 6H), 7.59 (d, 1H, *J* = 8.5 Hz), 7.97 (d, 1H, *J* = 8 Hz).

Boc-βAla-Val-Phe-NH$_2$, 10i. Boc-βAla-OH (99.3 mg, 0.53 mmol), HOBt (70.1 mg, 0.52 mmol), TBTU (161.4 mg, 0.52 mmol), DIPEA (0.125 mL, 0.76 mmol), **H-Val-Phe-NH$_2$** (0.54 mmol), DCM (40 mL). *Chromatography*: silica (12 g), DCM/MeOH gradient. Yield: 140 mg (62 %). ^{1}H NMR (600.13 MHz, DMSO-d$_6$) δ/ppm: 0.737 (d, 3H, *J* = 7 Hz), 0.741 (d, 3H, *J* = 7 Hz), 1.37 (s, 9H), 1.83–1.94 (m, 1H), 2.25–2.36 (m, 2H), 2.80 (dd, 1H, J_1 = 14 Hz, J_2 = 9.5 Hz), 3.01 (dd, 1H, J_1 = 14 Hz, J_2 = 5 Hz), 3.07–3.14 (m, 2H), 4.02–4.07 (m, 1H), 4.41–4.49 (m, 1H), 4.70 (t, 1H, *J* = 5 Hz), 7.05 (s, 1H), 7.14–7.27 (m, 5H), 7.29 (s, 1H), 7.82 (d, 1H, *J* = 8.5 Hz), 7.86 (d, 1H, *J* = 8.5 Hz).

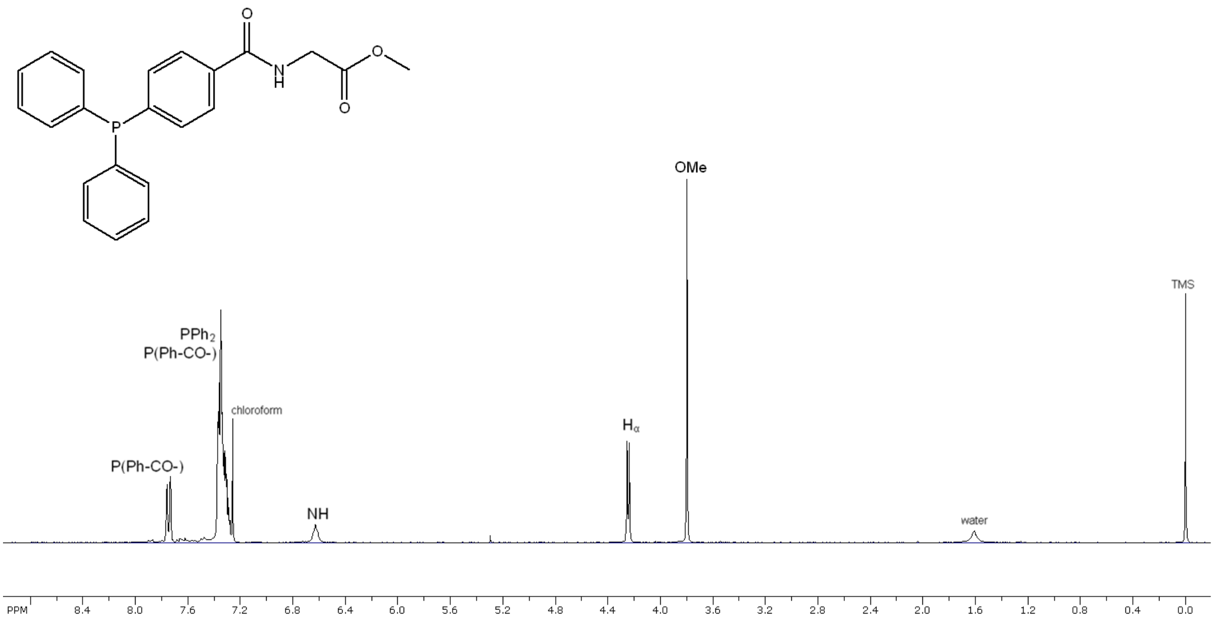
Boc-Gly-Pro-Phe-NH$_2$, 10j. Boc-Gly-OH (137.5 mg, 0.79 mmol), HOBt (100.8 mg, 0.75 mmol), TBTU (239.3 mg, 0.75 mmol), DIPEA (0.185 mL, 1.12 mmol), **H-Pro-Phe-NH$_2$** (0.75 mmol), DCM (40 mL). *Chromatography*: silica (12 g), DCM/MeOH gradient (TLC: R_f = 0.4, DCM/MeOH = 9/1). Yield: 182.4 mg (58 %). ^{1}H NMR (300.13 MHz, CDCl$_3$) δ/ppm: 1.47 (s, 9H), 1.60–1.69 (m, 1H), 1.87–1.95 (m, 2H), 2.03–2.09 (m, 1H), 3.03 (dd, 1H, J_1 = 14 Hz, J_2 = 10 Hz), 3.31–3.37 (m, 2H), 3.42–3.44 (m, 1H), 3.71 (dd, 1H, J_1 = 16.5 Hz, J_2 = 5 Hz), 3.81 (dd, 1H, J_1 = 16.5 Hz, J_2 = 3.5 Hz), 4.46 (dd, 1H, J_1 = 8 Hz, J_2 = 2.5 Hz), 4.66–4.70 (m, 1H), 5.27 (s, 1H), 5.37 (s, 1H), 6.46 (s, 1H), 6.89 (d, 1H, *J* = 8 Hz), 7.21–7.24 (m, 3H), 7.27–7.30 (m, 2H).

Boc-βAla-Pro-Phe-NH$_2$, 10k. Boc-βAla-OH (128.1 mg, 0.68 mmol), HOBt (84.3 mg, 0.62 mmol), TBTU (202.3 mg, 0.63 mmol), DIPEA (0.155 mL, 0.94 mmol), **H-Pro-Phe-NH$_2$** (0.64 mmol), DCM (40 mL). *Chromatography*: silica (12 g), DCM/MeOH gradient (TLC: R_f = 0.45, DCM/MeOH = 9/1). Yield: 205 mg (75 %). ^{1}H NMR (300.13 MHz, CDCl$_3$) δ/ppm: 1.44 (s, 9H), 1.50–2.47 (m, 6H), 3.08–3.42 (m, 6H), 4.41–4.43 (dd, 1H, J_1 = 8.5 Hz, J_2 = 3 Hz), 4.67–4.75 (m, 1H), 5.18 (s, 1H), 5.32 (s, 1H), 5.39 (s, 1H), 6.81 (d, 1H, *J* = 8.5 Hz), 7.17–7.32 (m, 5H).

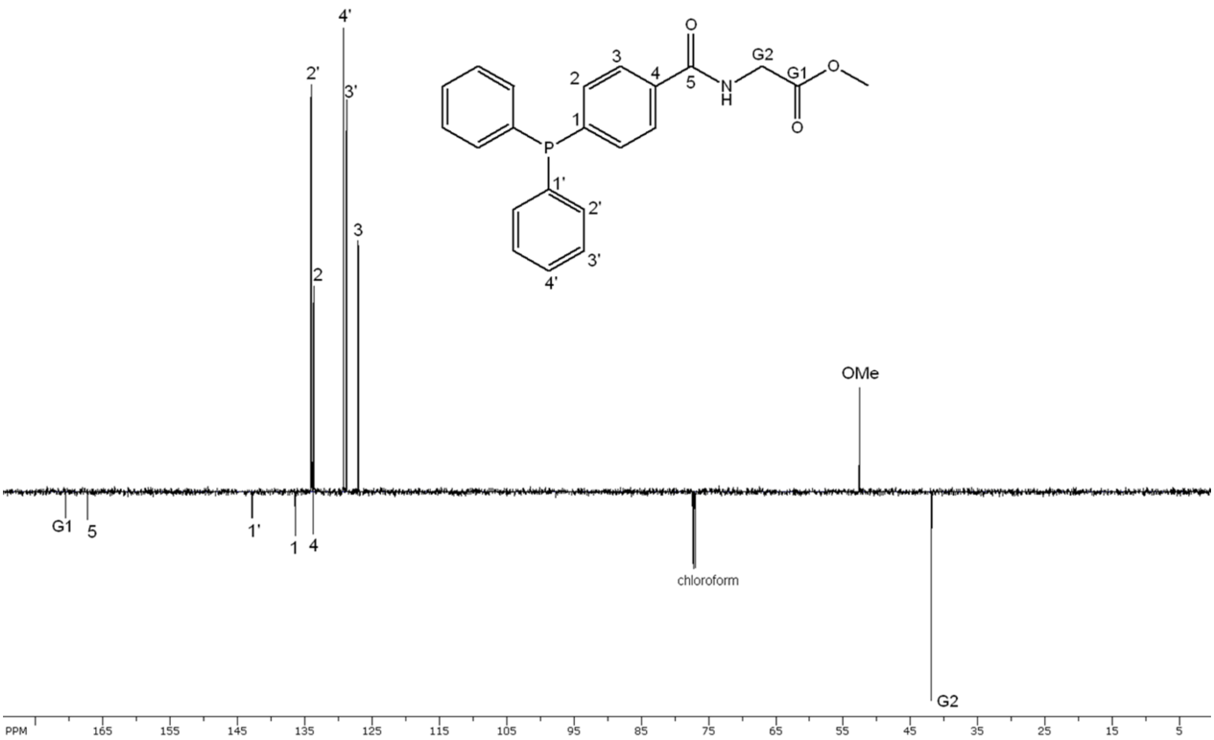
Boc-Gaba-Pro-Phe-NH$_2$, 10l. Boc-Gaba-OH (143.5 mg, 0.71 mmol), HOBt (93.0 mg, 0.69 mmol), TBTU (219.0 mg, 0.68 mmol), DIPEA (0.170 mL, 1.03 mmol), **H-Pro-Phe-NH$_2$** (0.69 mmol), DCM (40 mL). *Chromatography*: silica (12 g), EtOAc/DCM/MeOH gradient (TLC: R_f = 0.15, EtOAc/DCM/MeOH = 9/2/1). Yield: 166 mg (55 %). ^{1}H NMR (300.13 MHz, CDCl$_3$) δ/ppm: 1.46 (s, 9H), 1.70–1.87 (m, 4H), 1.99–2.11 (m, 2H), 2.15–2.24 (m, 1H), 2.34–2.51 (m, 2H), 2.91–2.99 (m, 2H), 3.31–3.56 (m, 4H), 4.34 (dd, 1H, J_1 = 9 Hz, J_2 = 4 Hz), 4.68–4.73 (m, 1H), 4.84–4.92 (m, 1H), 5.39 (s, 1H), 7.17–7.35 (m, 7H).

4. NMR Spectra.

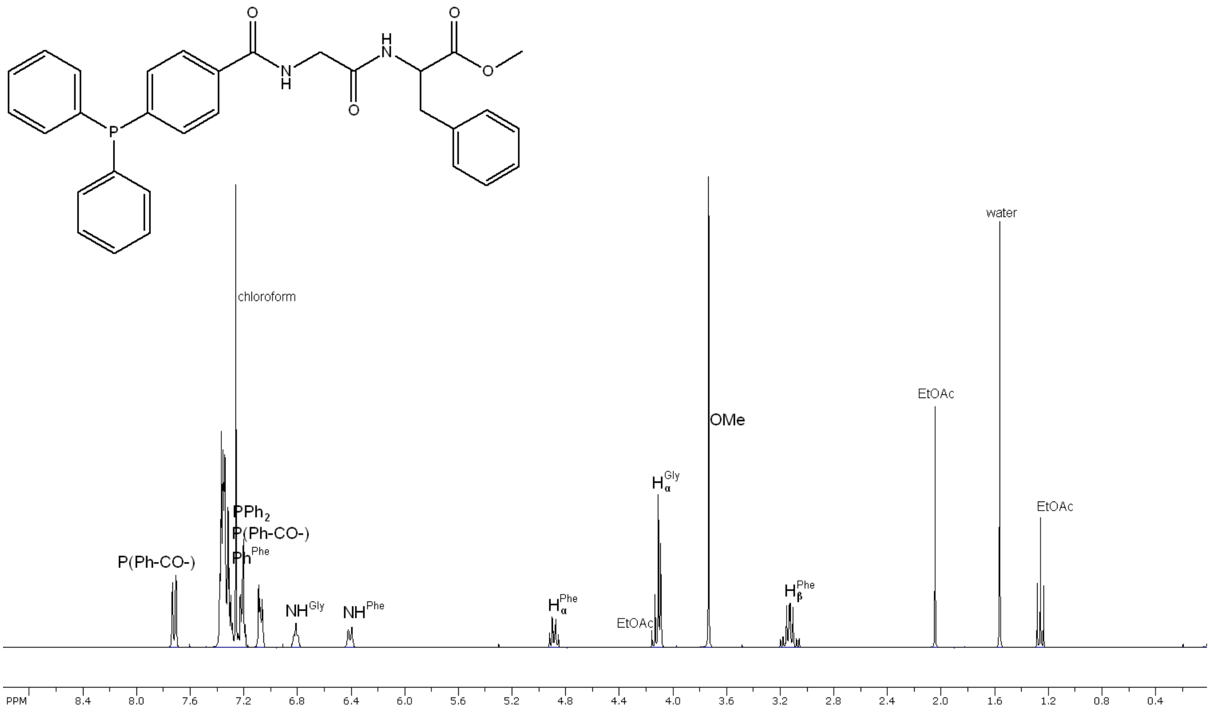
4.01. ^{1}H NMR ($CDCl_3$) **Lig-Gly-OMe 5a**



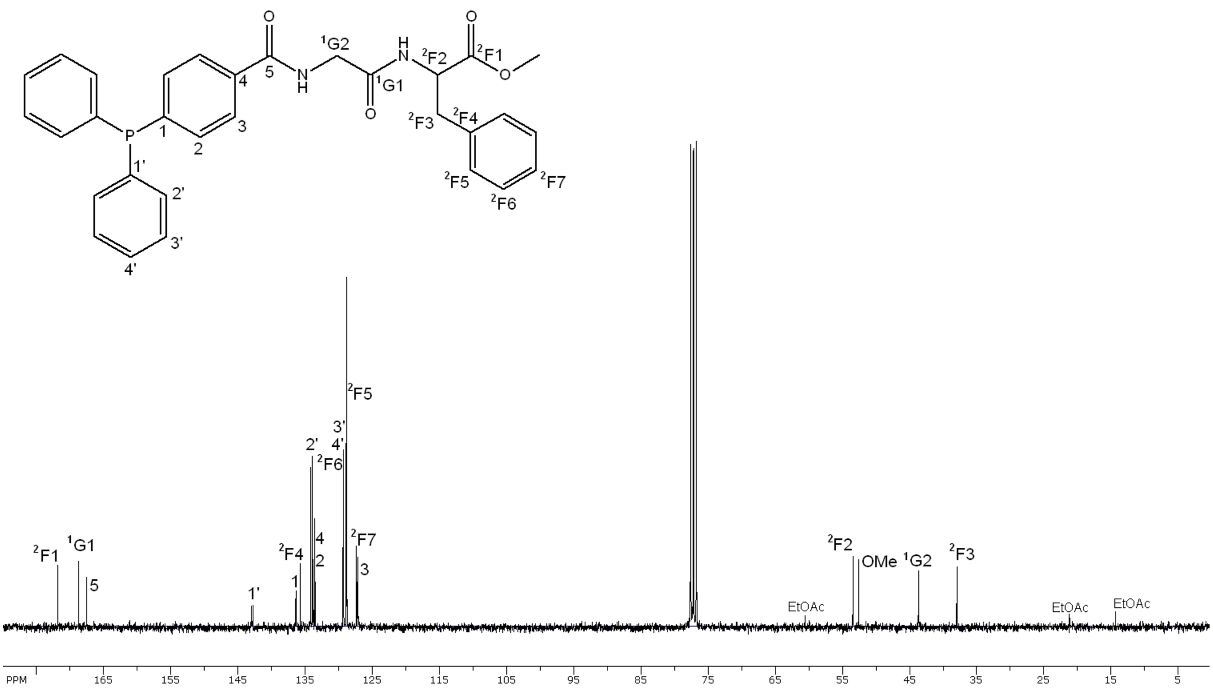
4.02. ^{13}C NMR ($CDCl_3$) **Lig-Gly-OMe 5a**



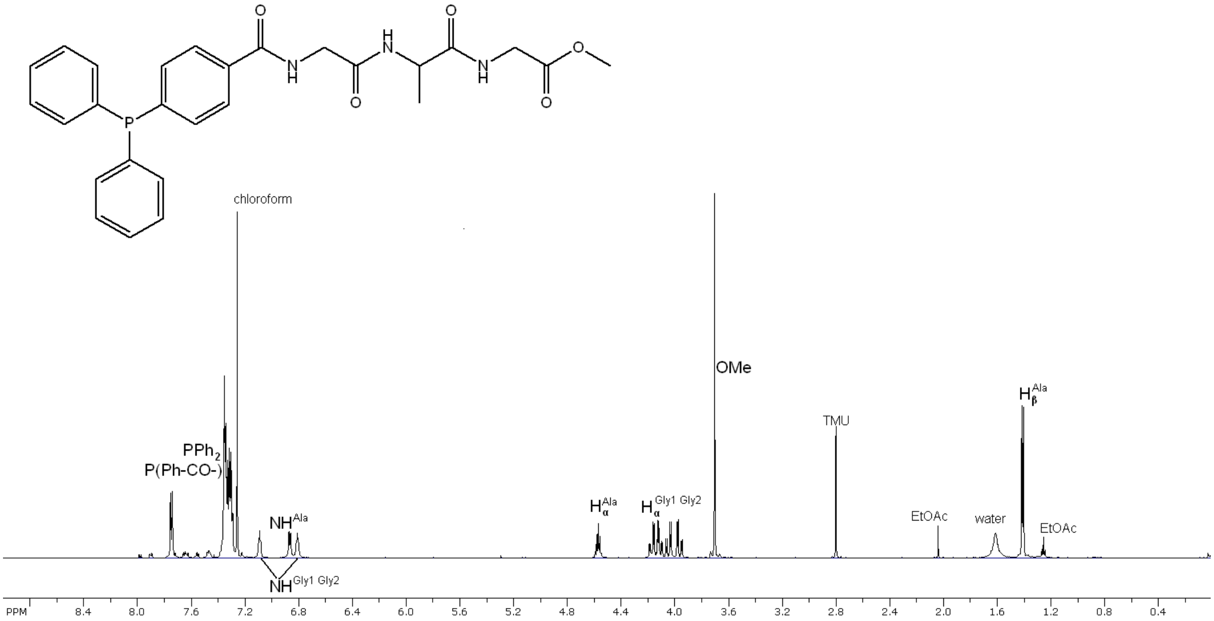
4.03. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Phe-OMe 5b**



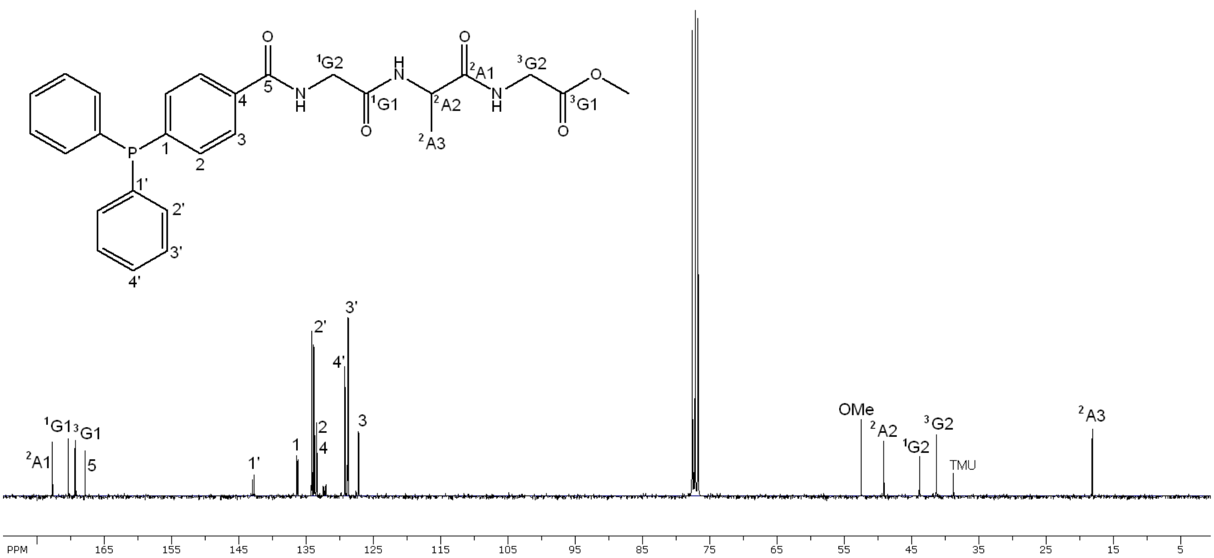
4.04. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Phe-OMe 5b**



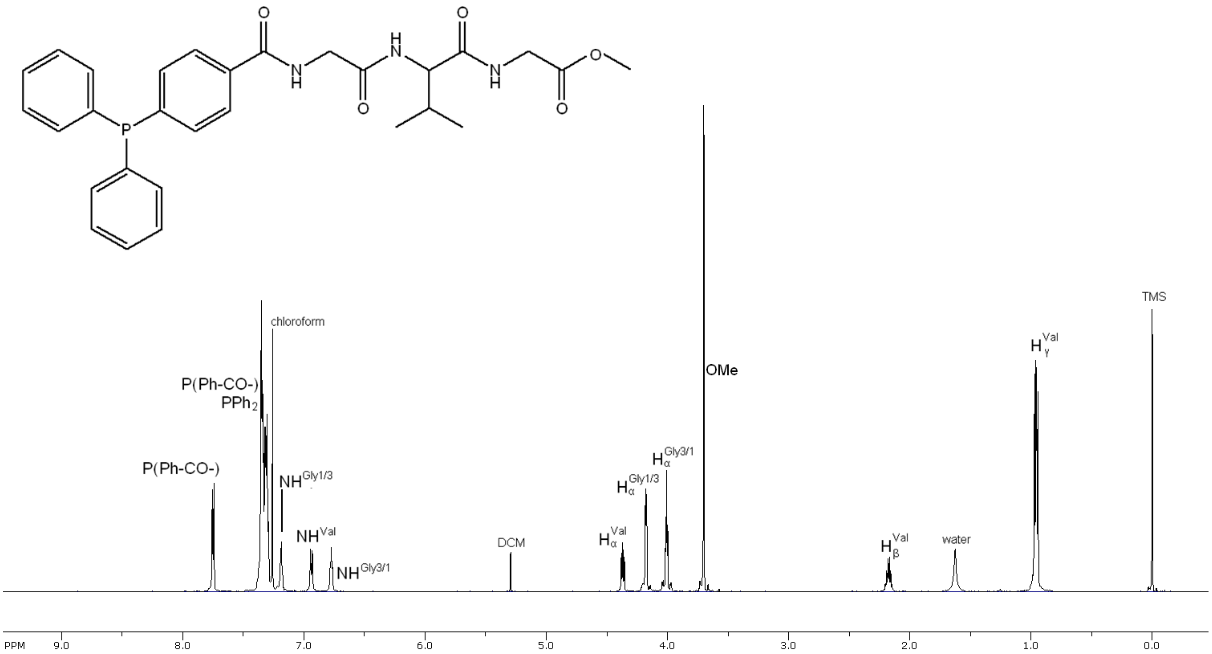
4.05. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Ala-Gly-OMe 5c**



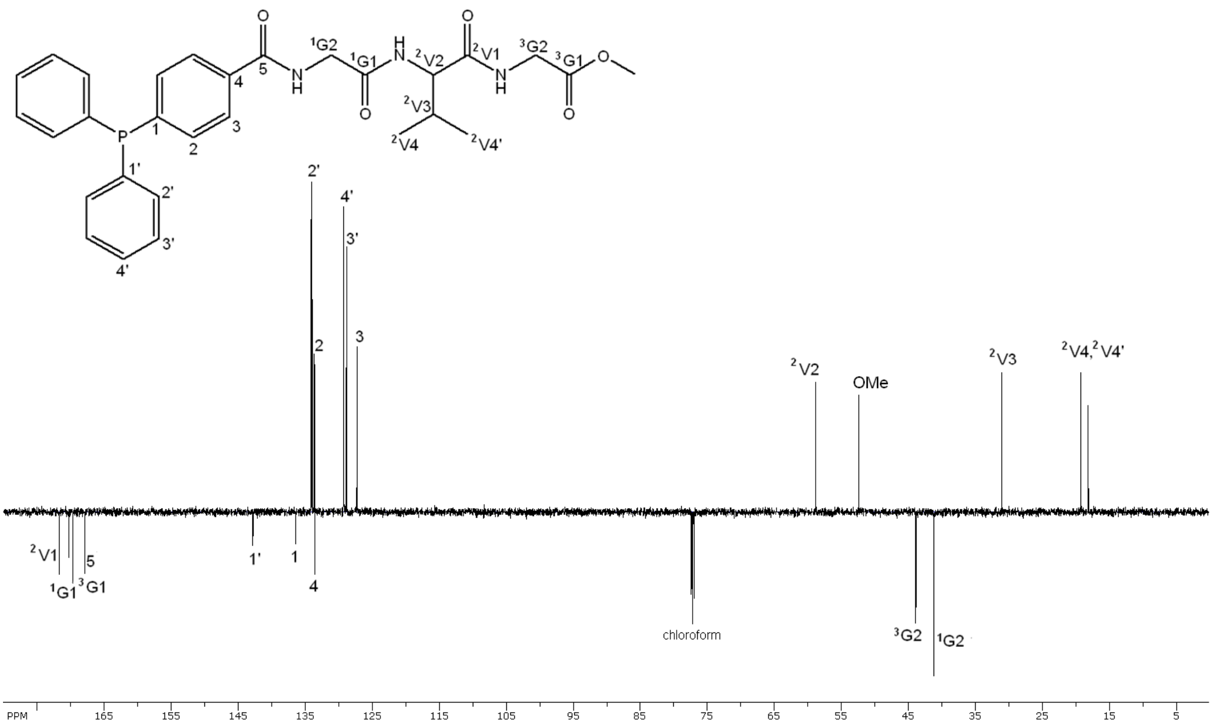
4.06. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Ala-Gly-OMe 5c**



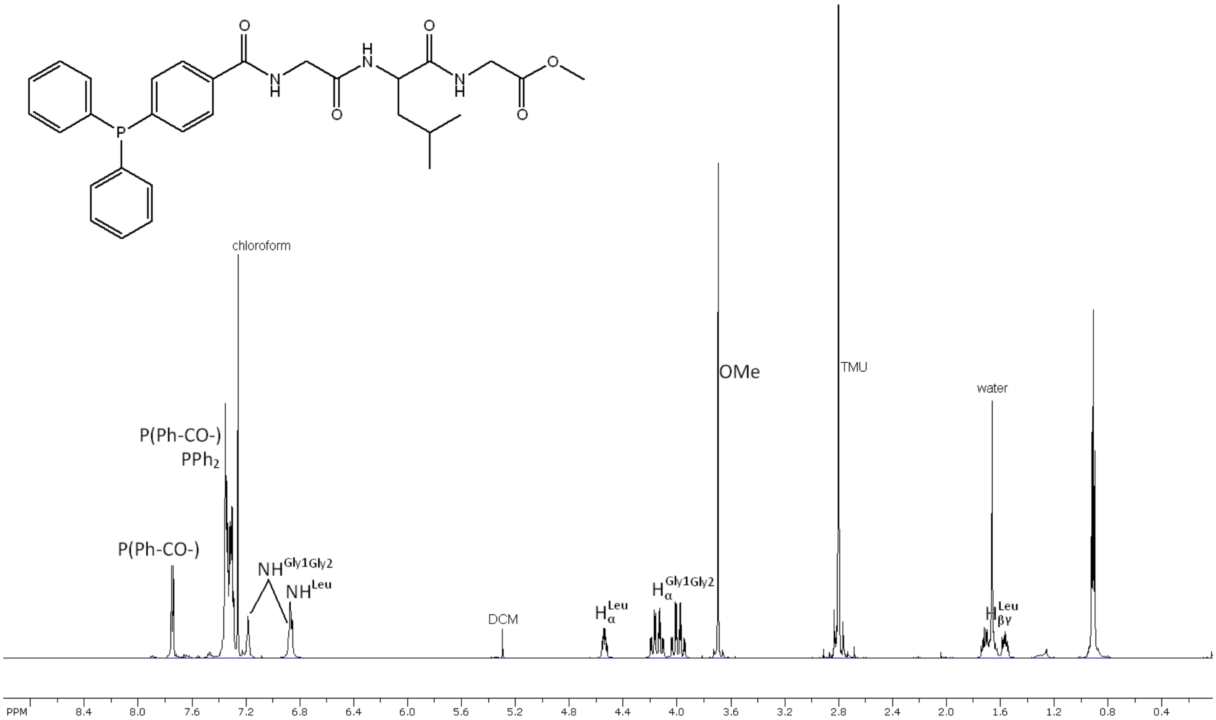
4.07. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Val-Gly-OMe 5d**



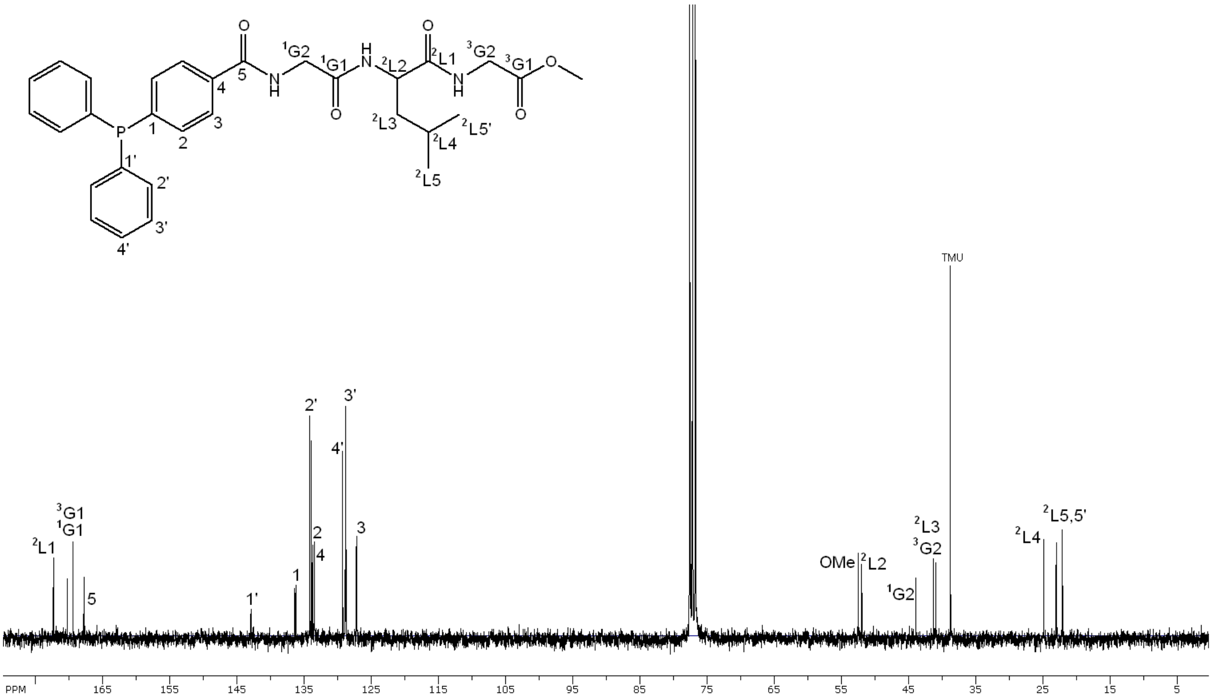
4.08. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Val-Gly-OMe 5d**



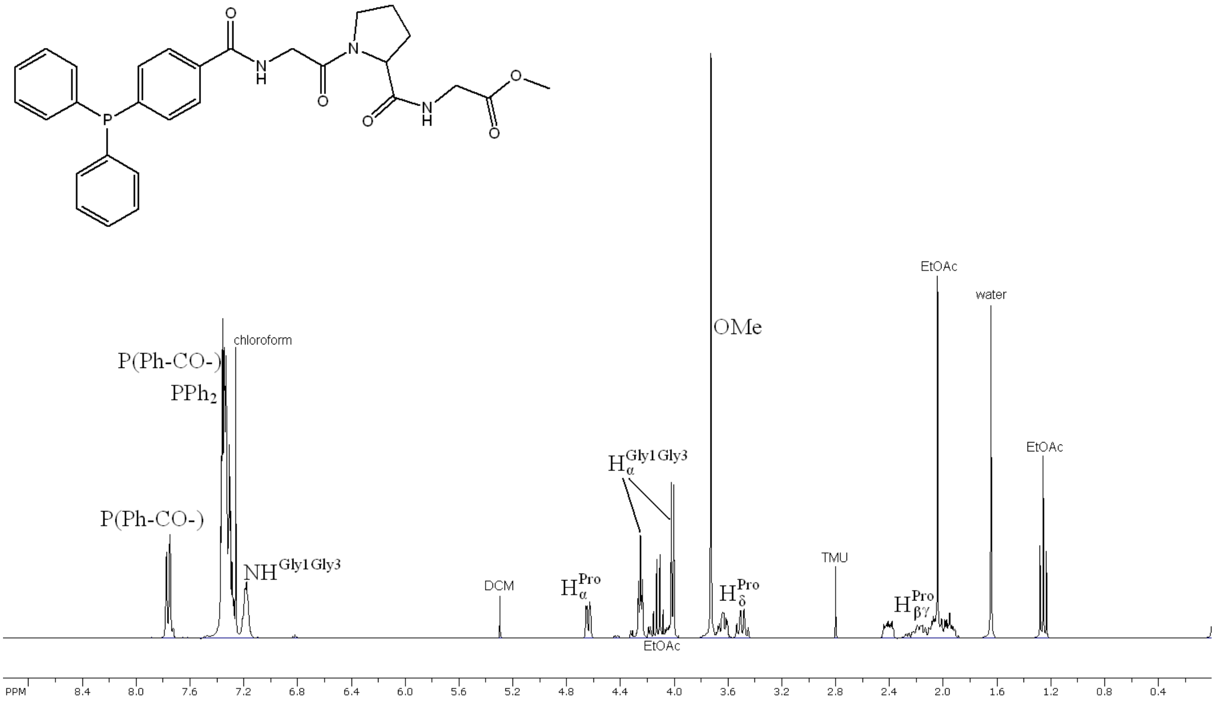
4.09. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Leu-Gly-OMe 5e**



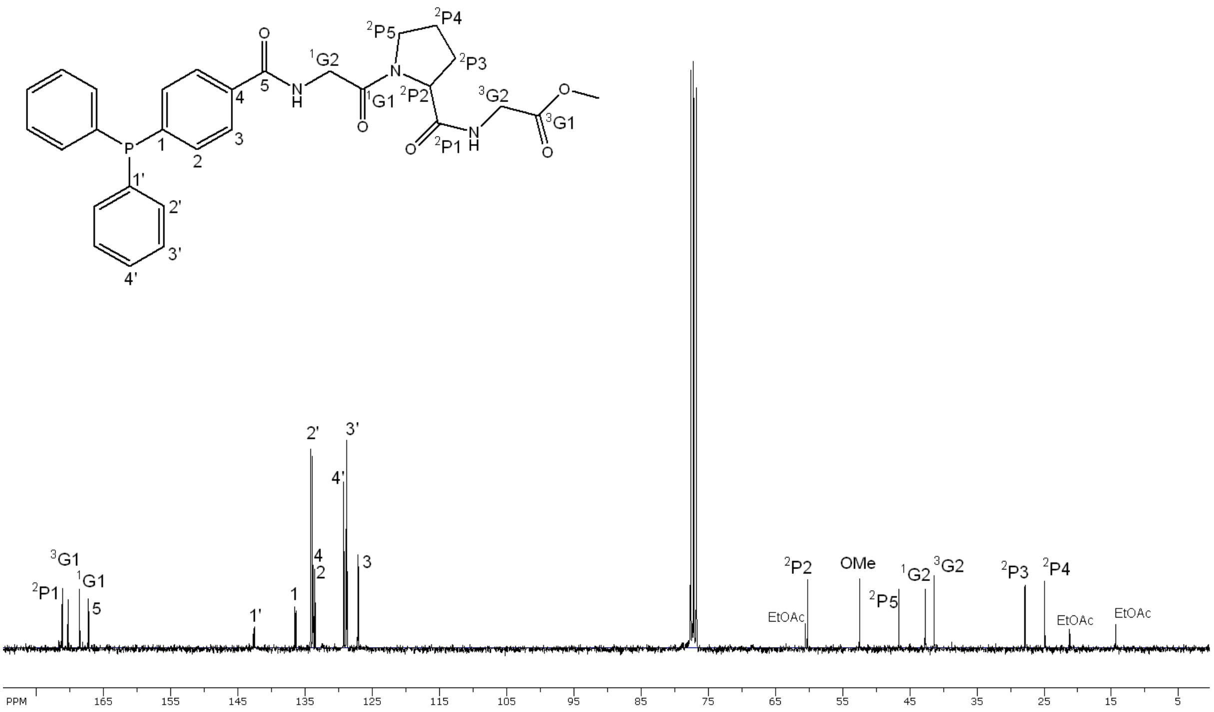
4.10. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Leu-Gly-OMe 5e**



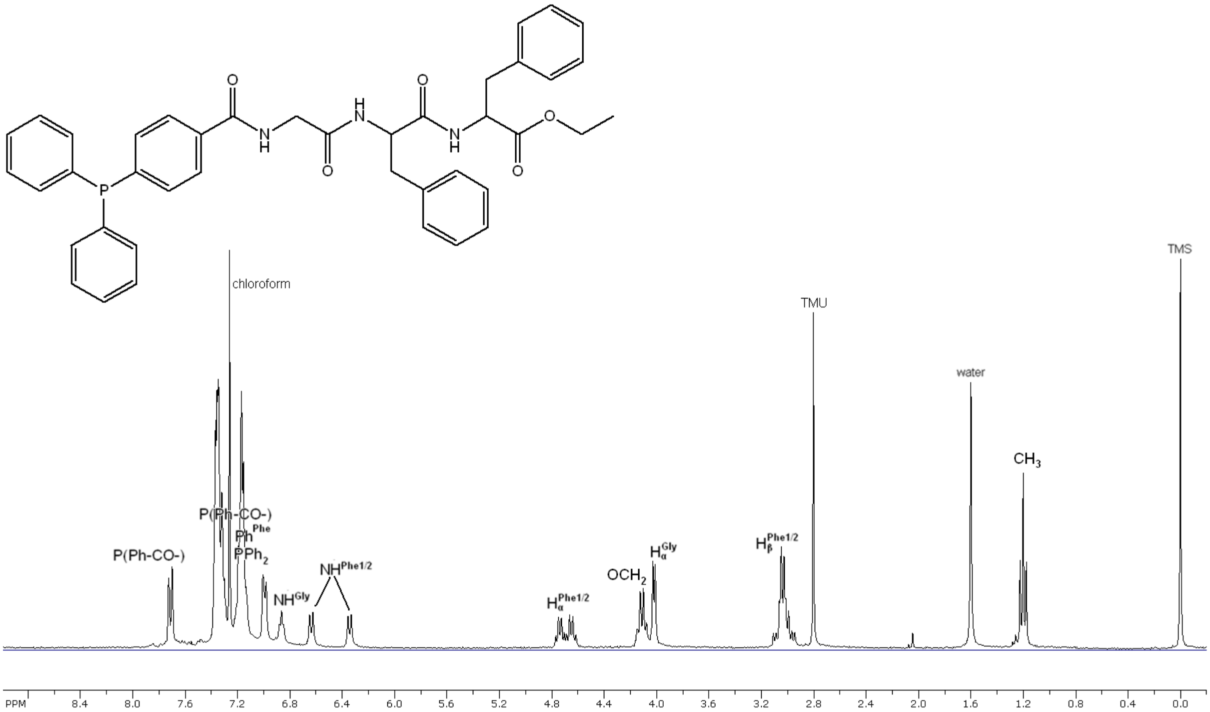
4.11. [1]H NMR ($CDCl_3$) **Lig-Gly-Pro-Gly-OMe 5f**



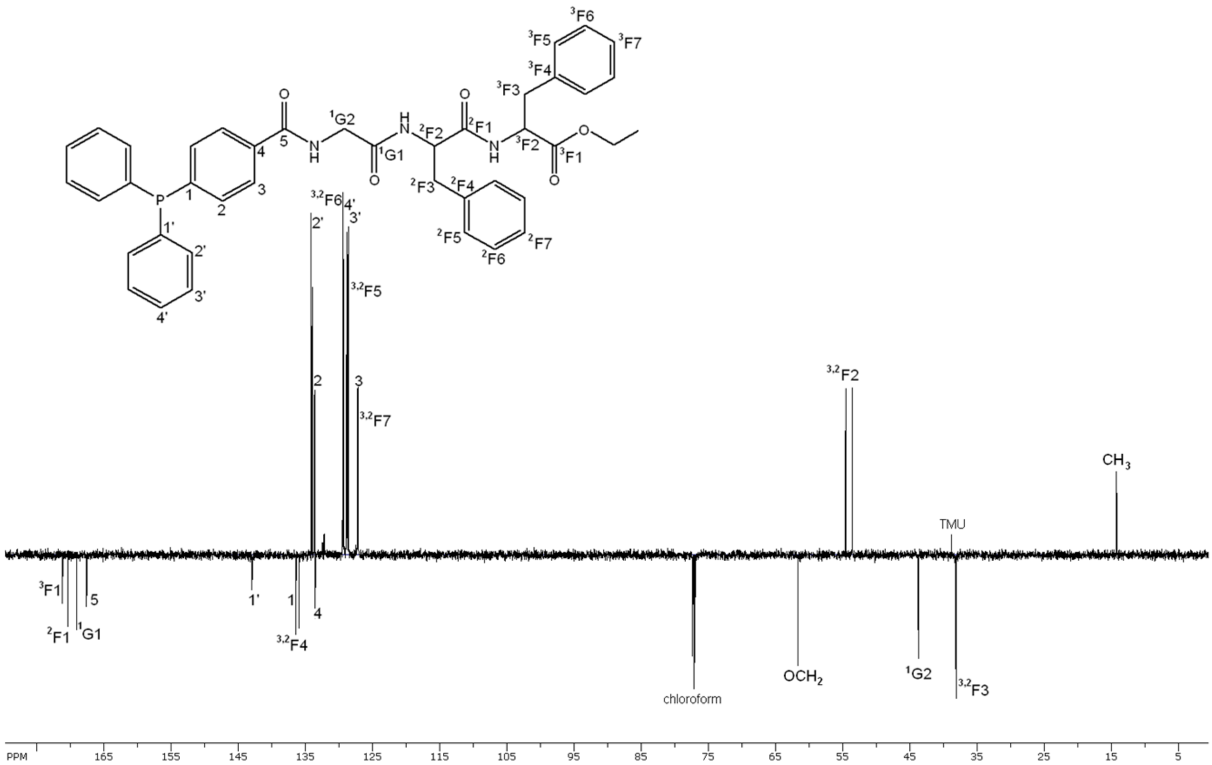
4.12. [13]C NMR ($CDCl_3$) **Lig-Gly-Pro-Gly-OMe 5f**



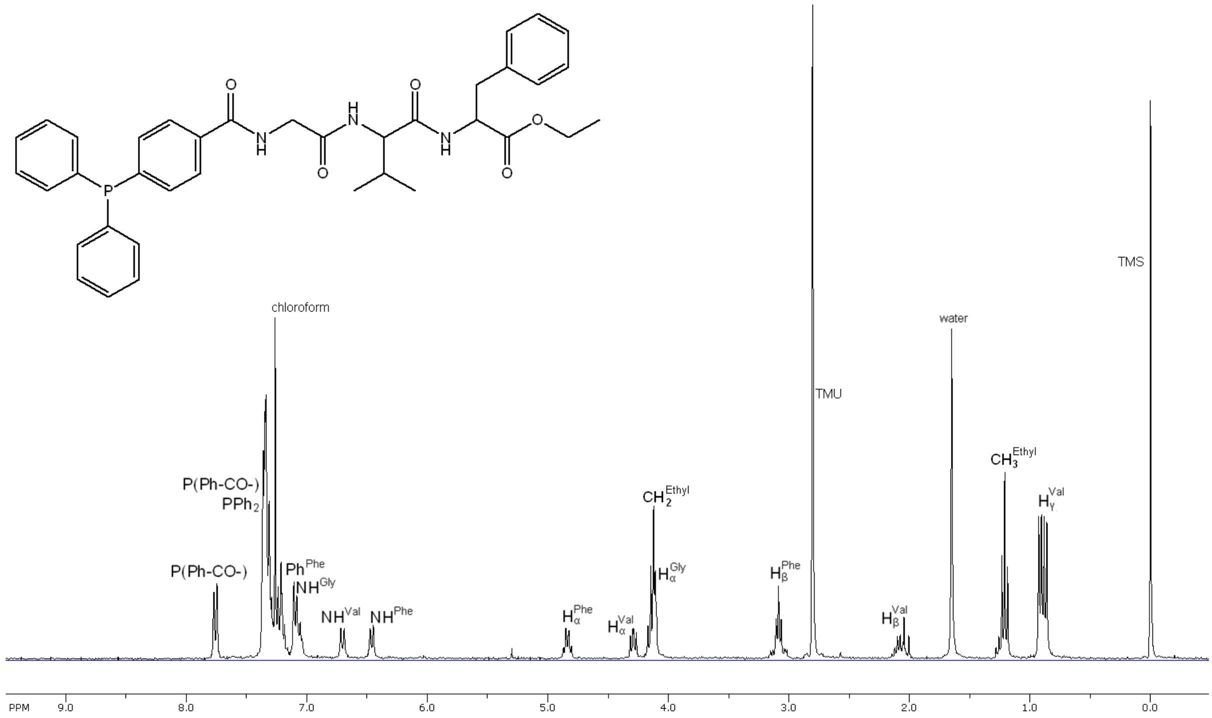
3.13. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Phe-Phe-OEt 5g**



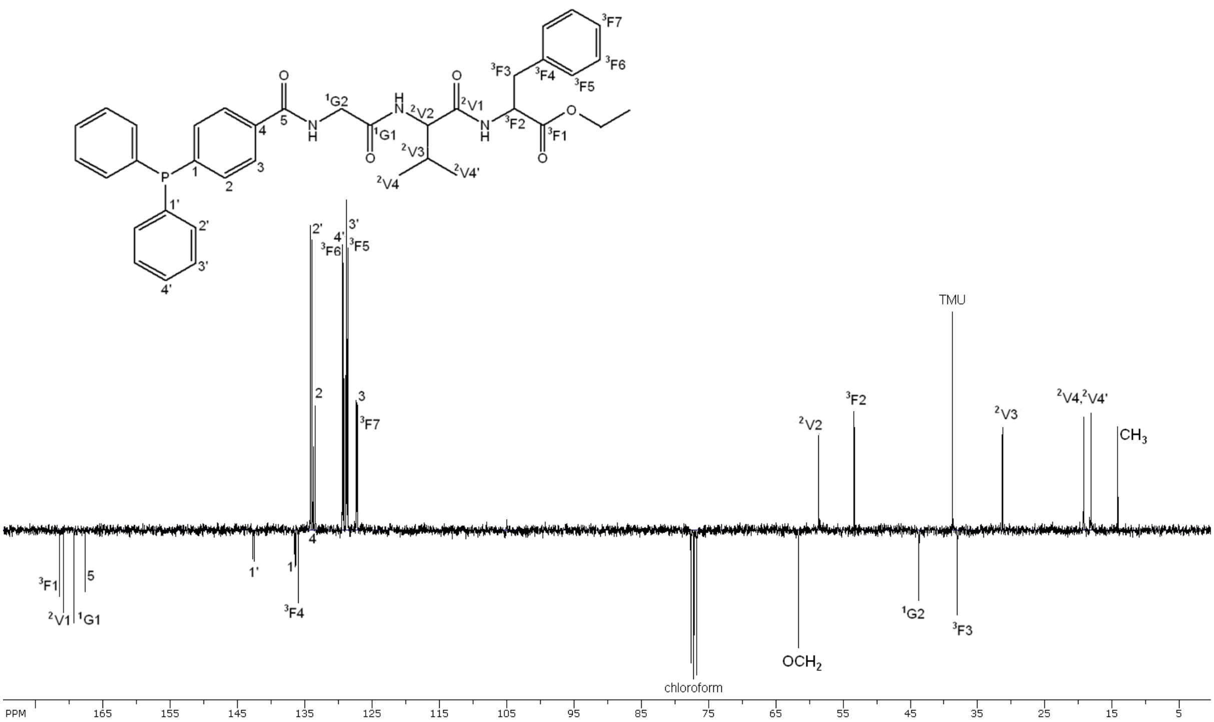
4.14. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Phe-Phe-OEt 5g**



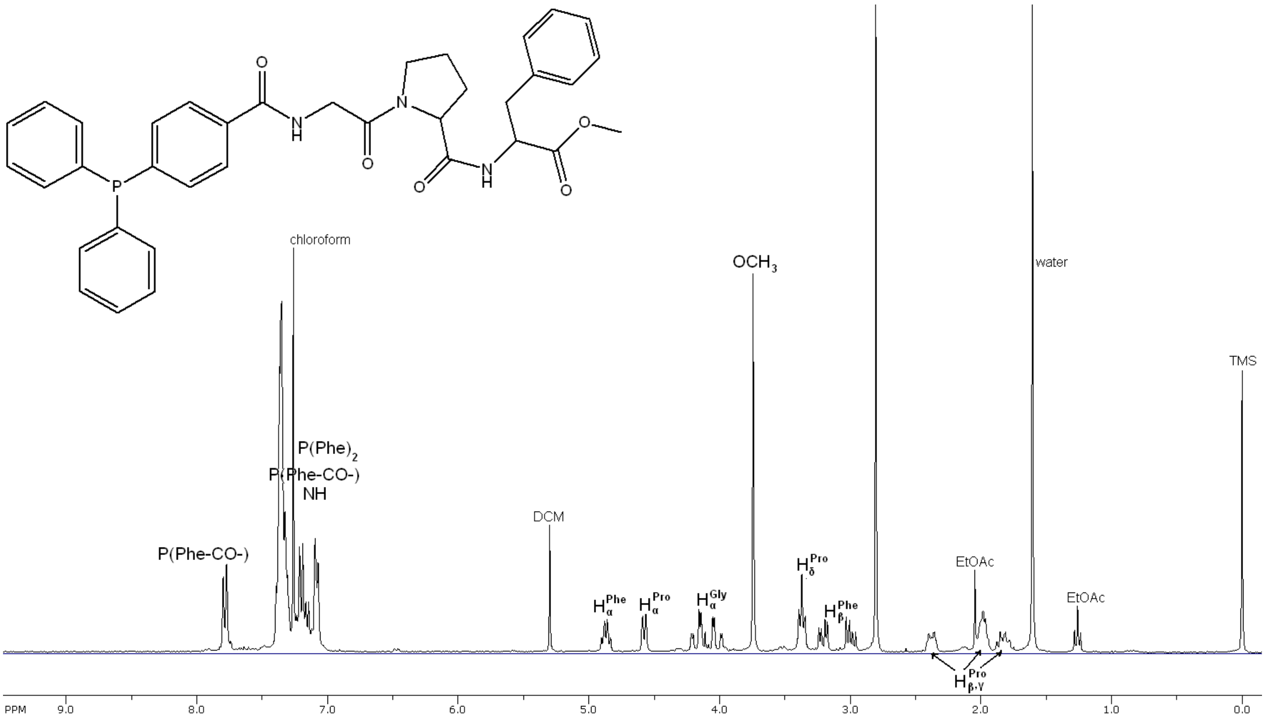
3.15. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Val-Phe-OEt 5h**



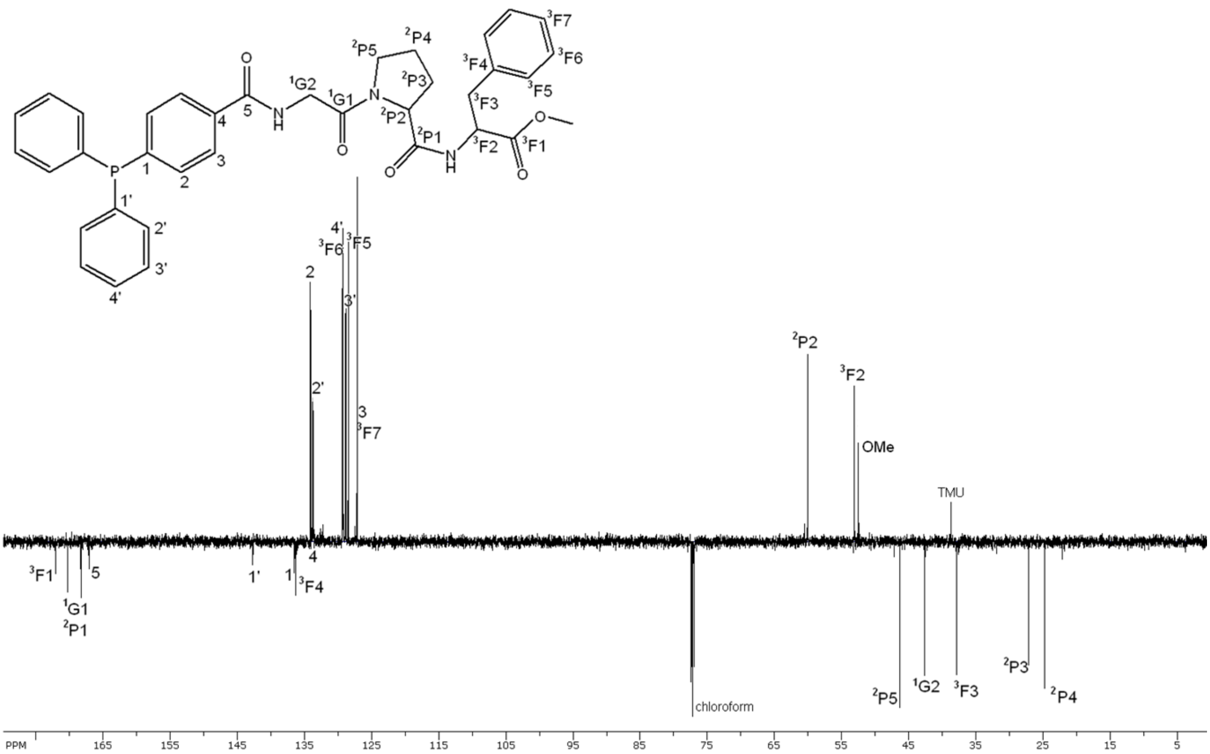
4.16. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Val-Phe-OEt 5h**



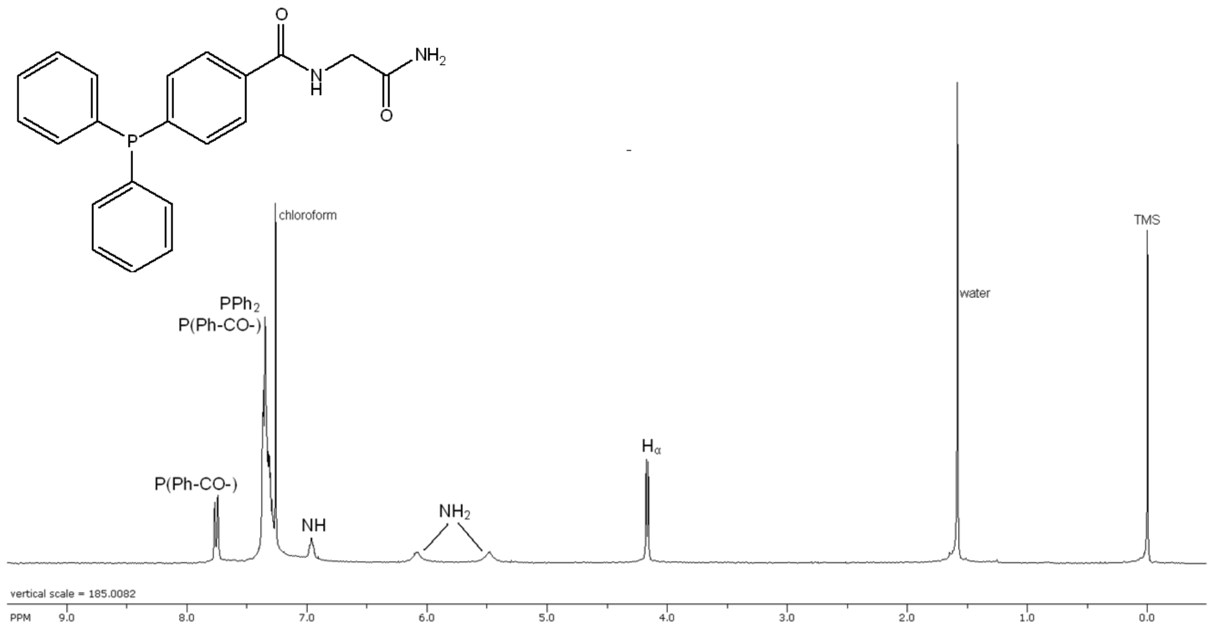
4.17. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Pro-Phe-OMe 5j**



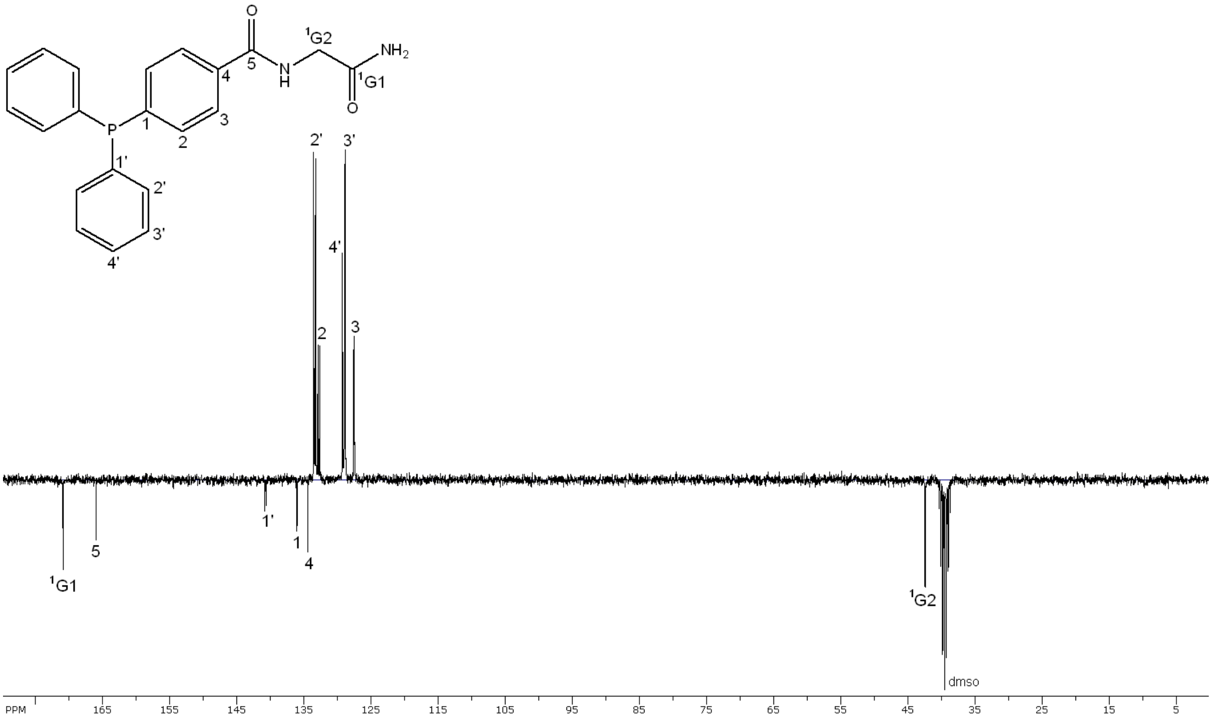
4.18. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Pro-Phe-OMe 5j**



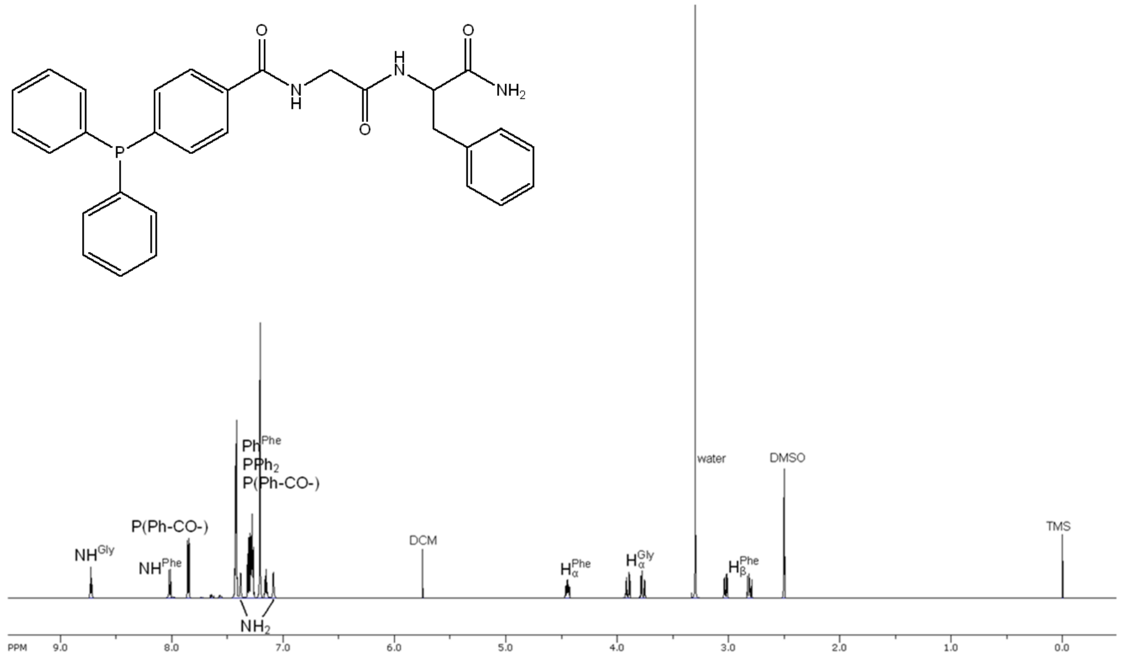
4.19. ^{1}H NMR ($CDCl_3$) **Lig-Gly-NH$_2$ 6a**



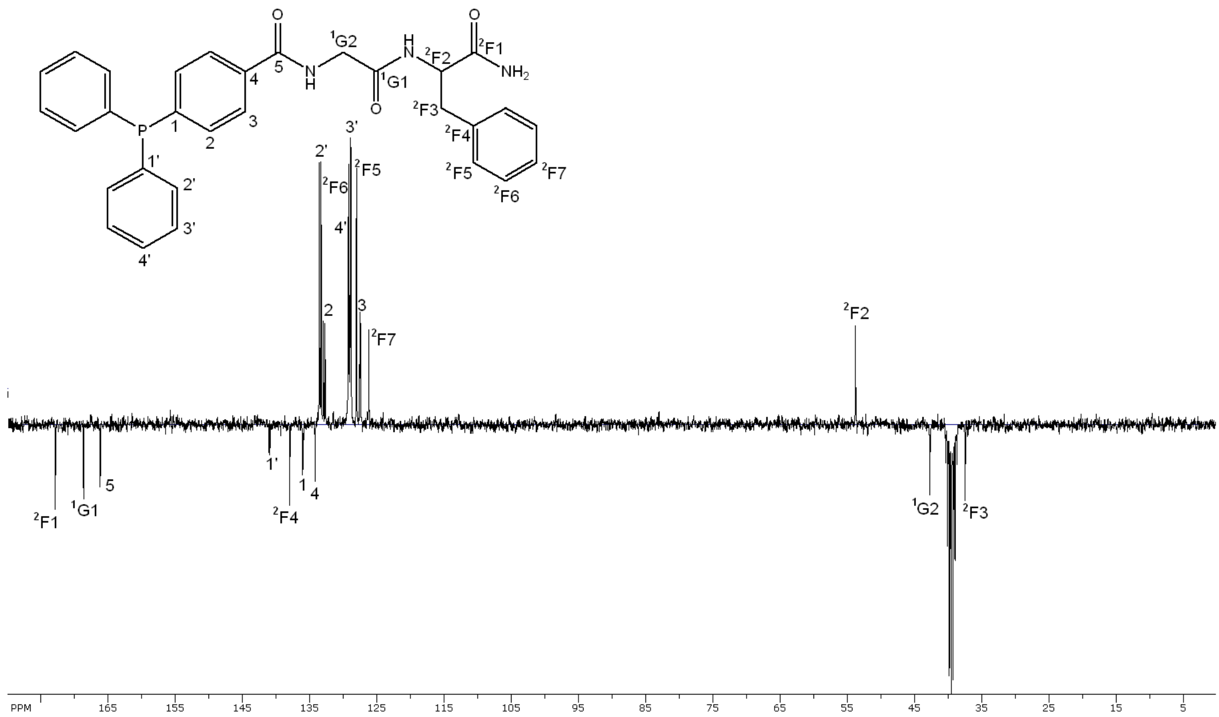
4.20. ^{13}C NMR (DMSO-d$_6$) **Lig-Gly-NH$_2$ 6a**



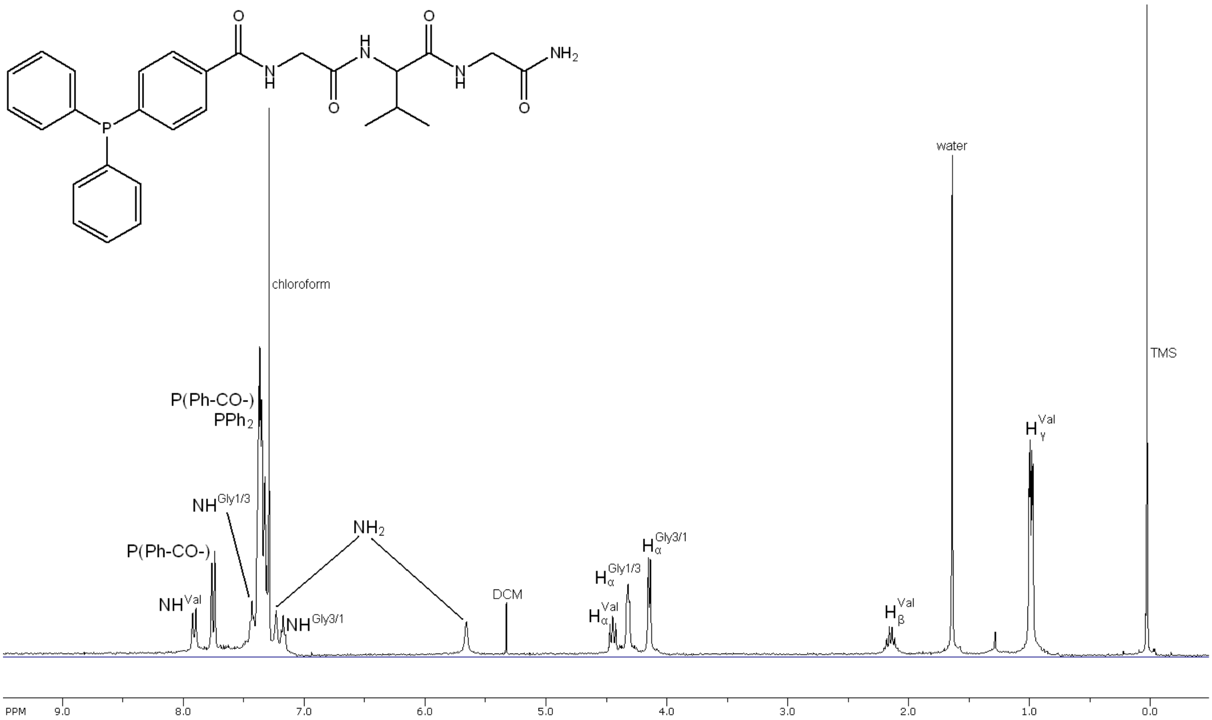
4.21. [1]H NMR ($CDCl_3$) **Lig-Gly-Phe-NH_2 6b**



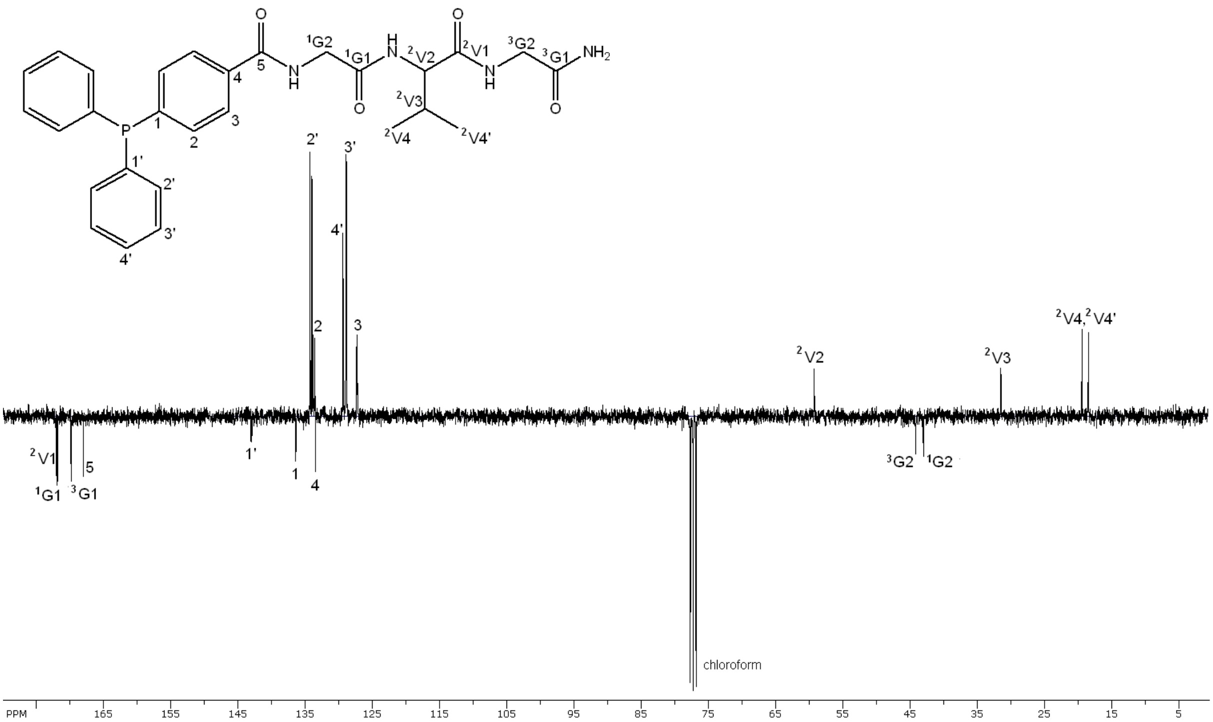
4.24. [13]C NMR (DMSO-d_6) **Lig-Gly-Phe-NH_2 6b**



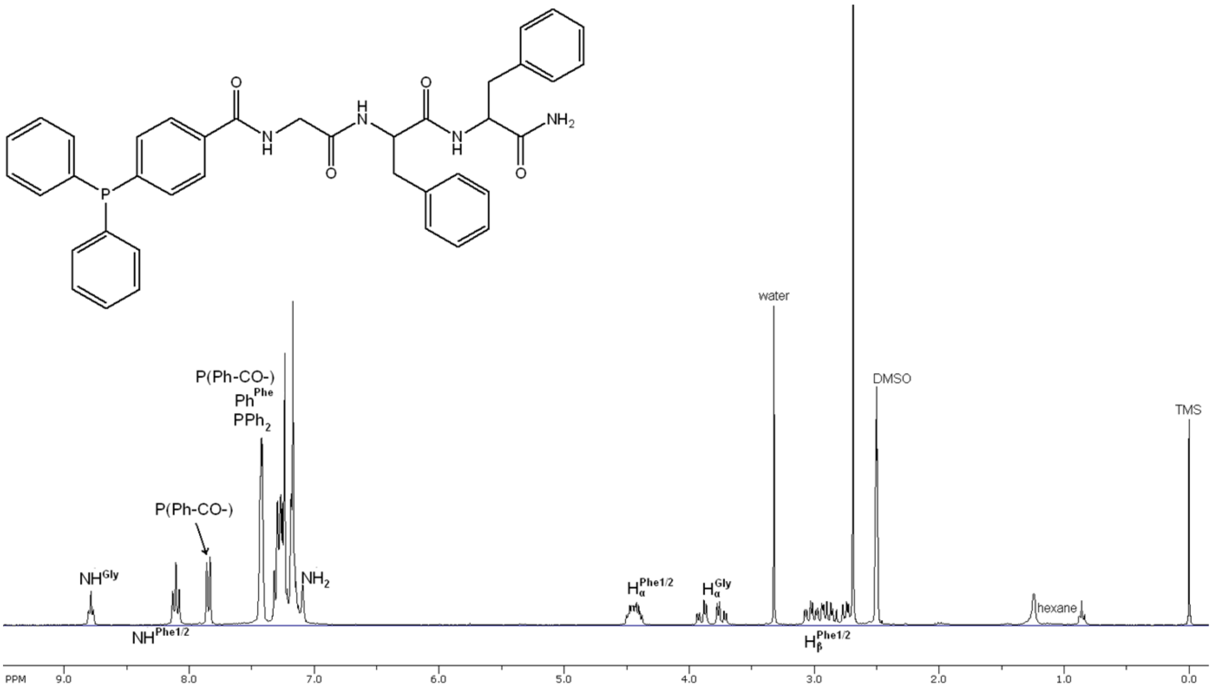
4.25. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Val-Gly-NH$_d$ 6b**



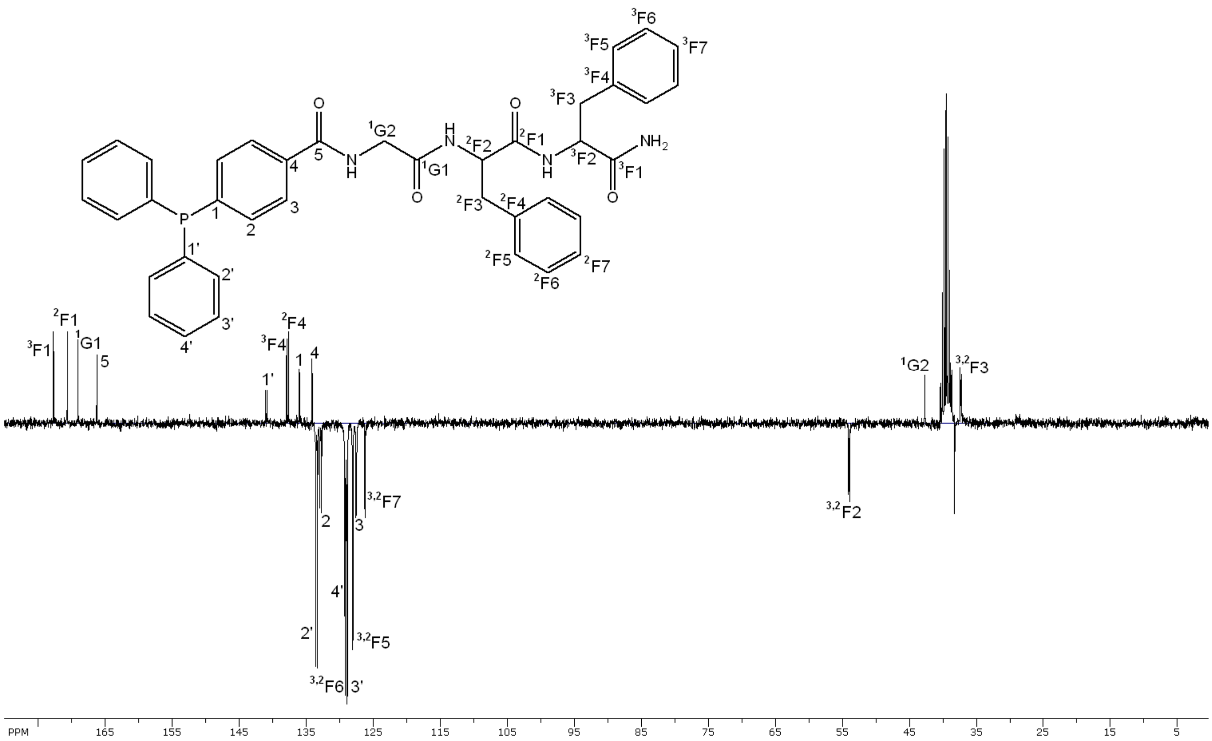
4.26. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Val-Gly-NH$_2$ 6d**



4.27. ^{1}H NMR (DMSO-d$_6$) **Lig-Gly-Phe-Phe-NH$_2$ 6g**

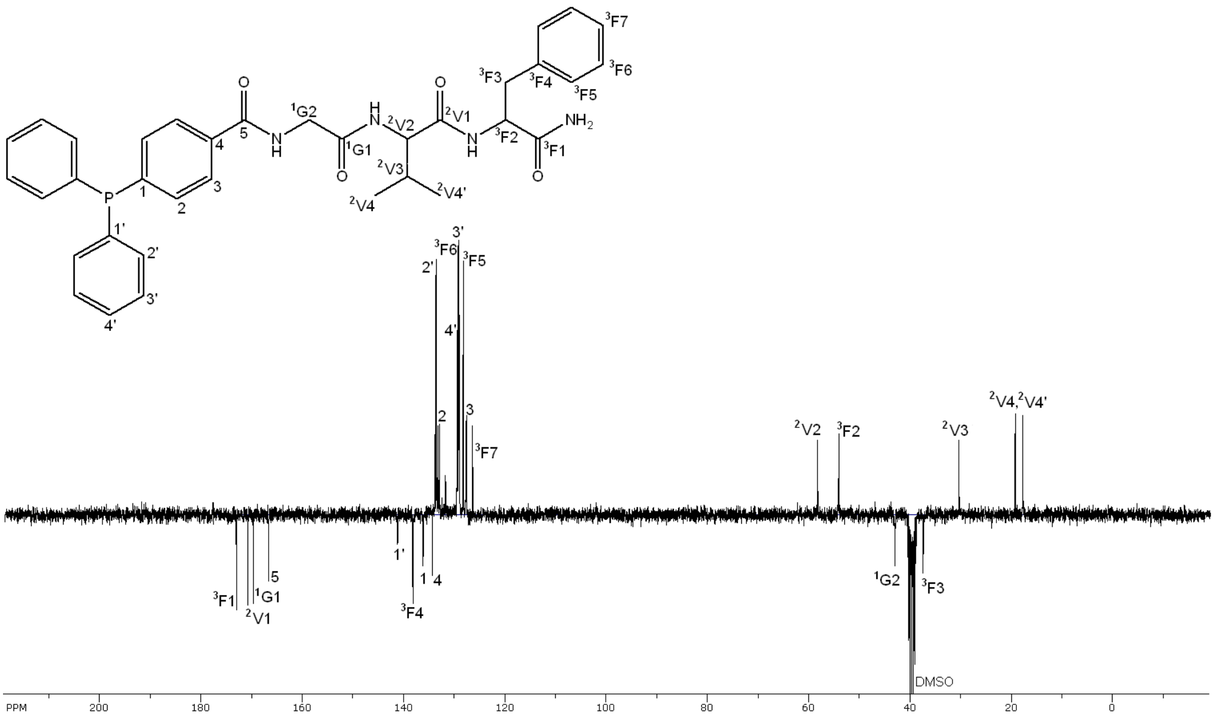


4.28. ^{13}C NMR (DMSO-d$_6$) **Lig-Gly-Phe-Phe-NH$_2$ 6g**

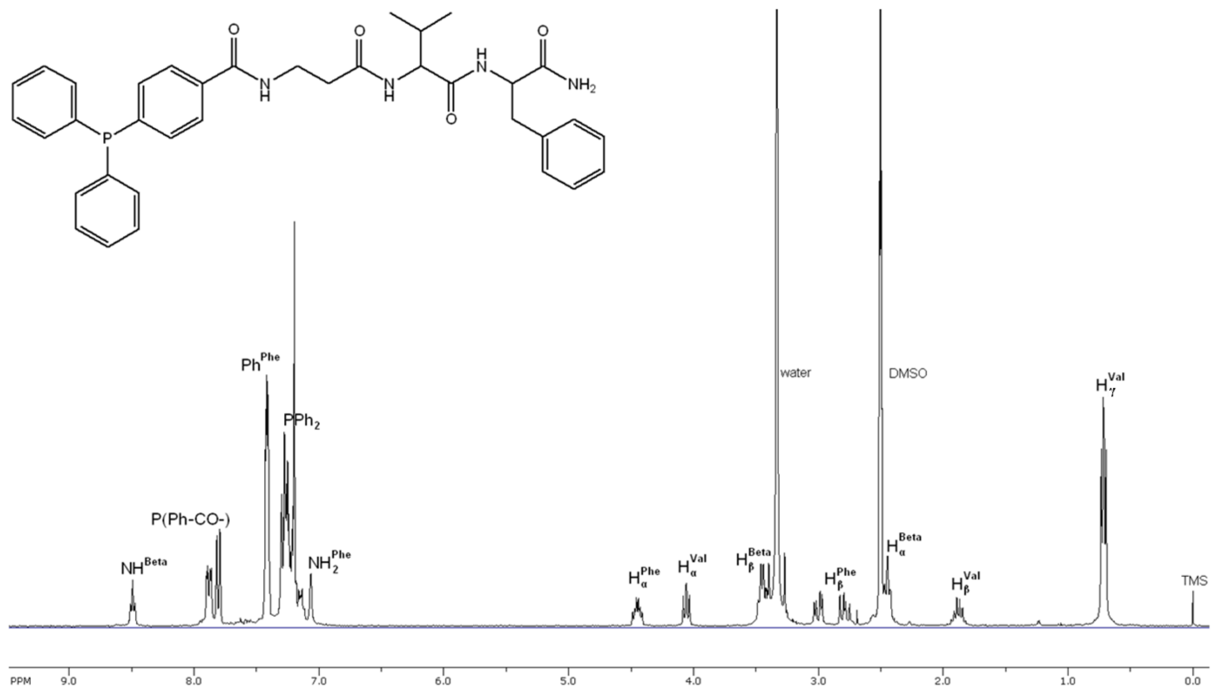


4.29. ^{1}H NMR (DMSO-d$_6$) **Lig-Gly-Val-Phe-NH$_2$ 6h**

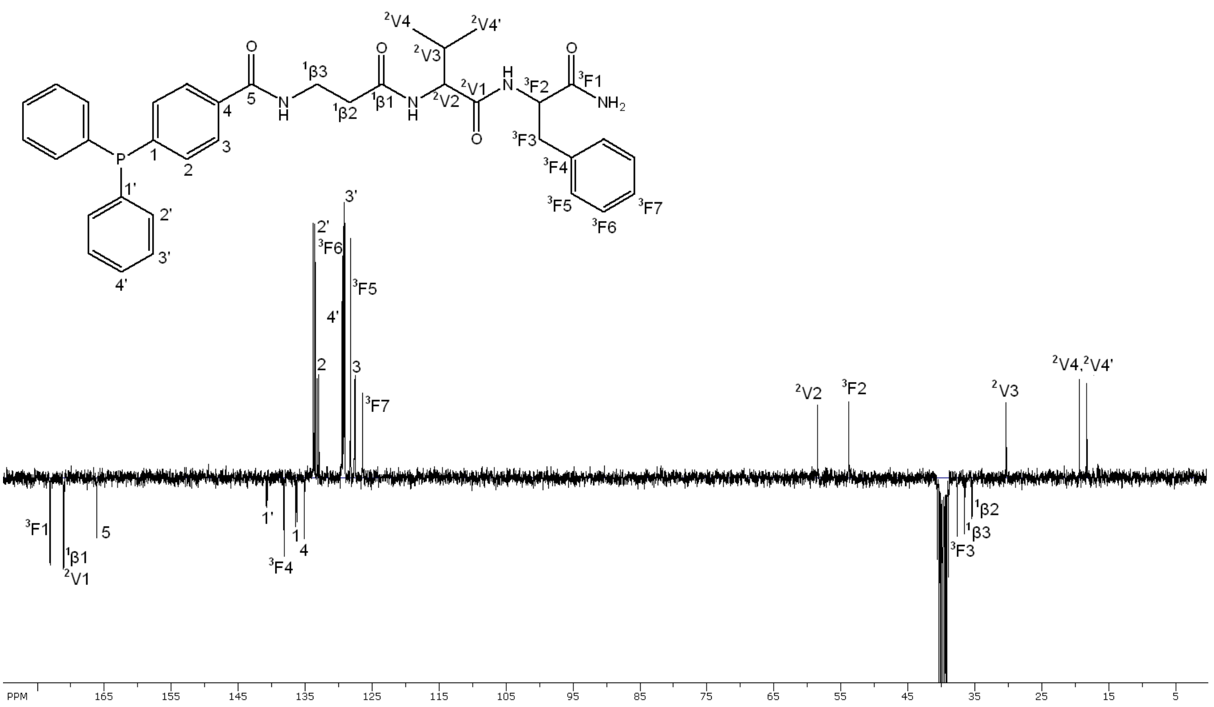
4.30. ^{1}H NMR (DMSO-d$_6$) **Lig-Gly-Val-Phe-NH$_2$ 6h**



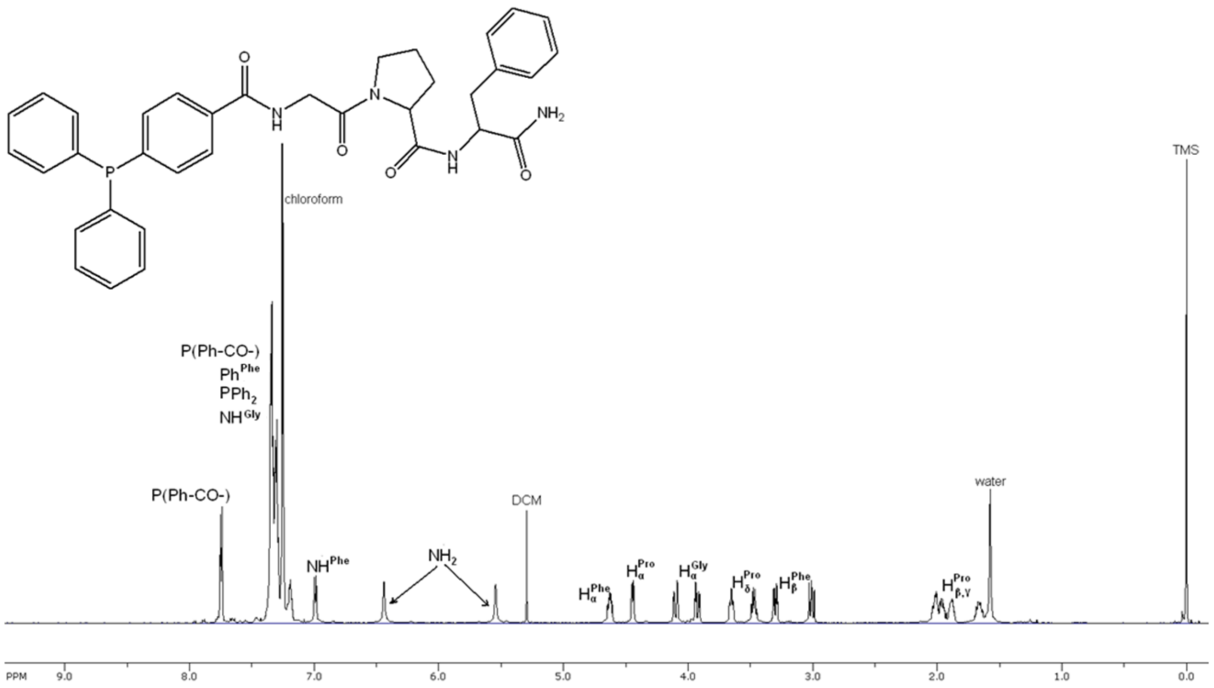
4.31. ^{1}H NMR (DMSO-d$_6$) **Lig-βAla-Val-Phe-NH$_2$ 6i**



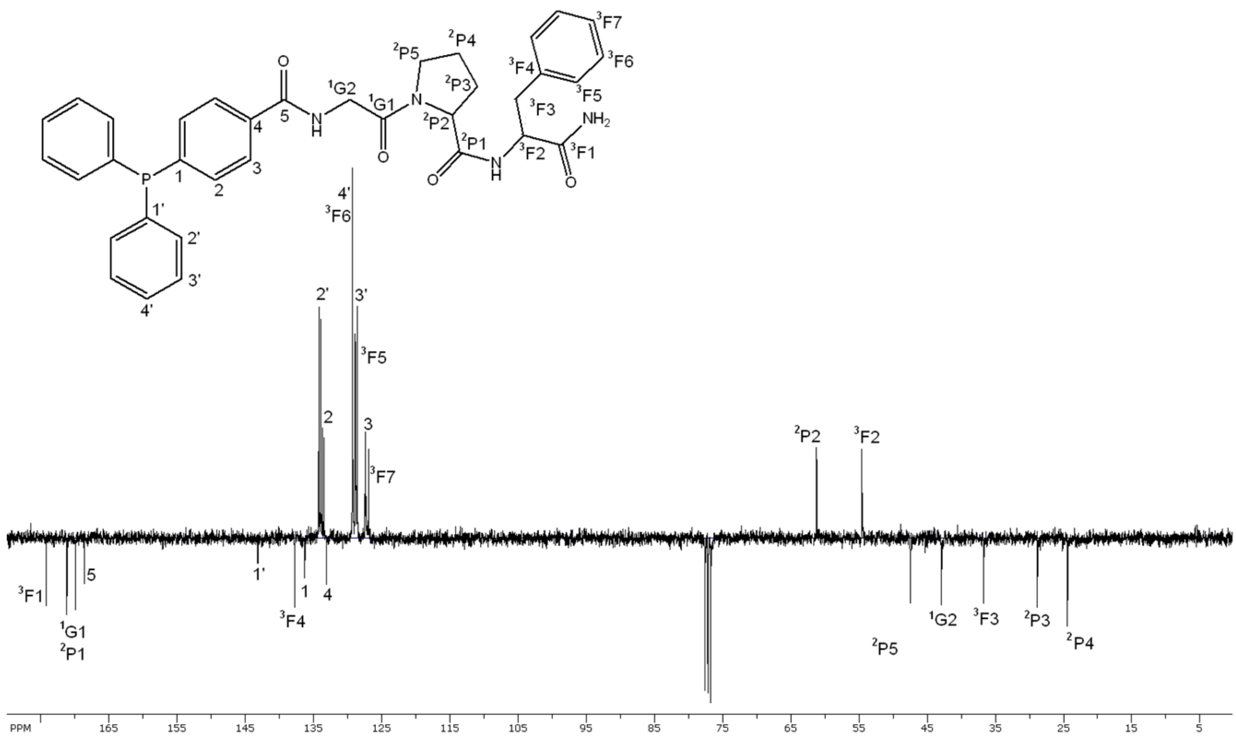
4.32. ^{13}C NMR (DMSO-d$_6$) **Lig-βAla-Val-Phe-NH$_2$ 6i**



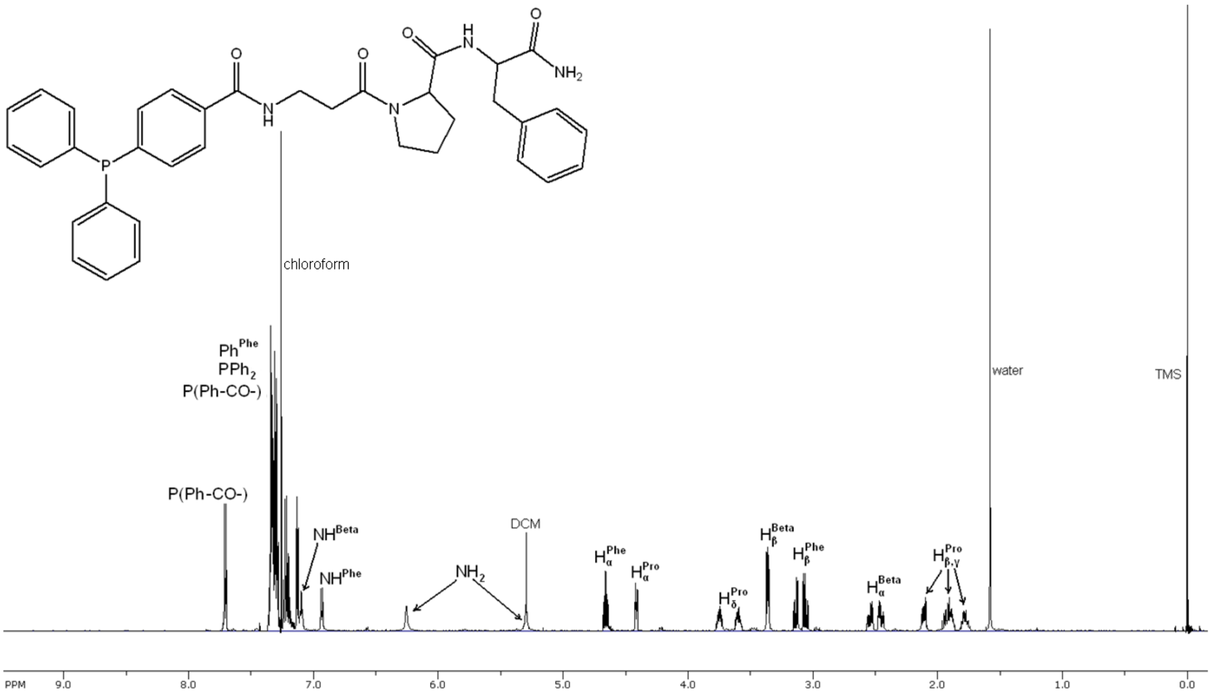
4.33. ^{1}H NMR ($CDCl_3$) **Lig-Gly-Pro-Phe-NH_2 6j**



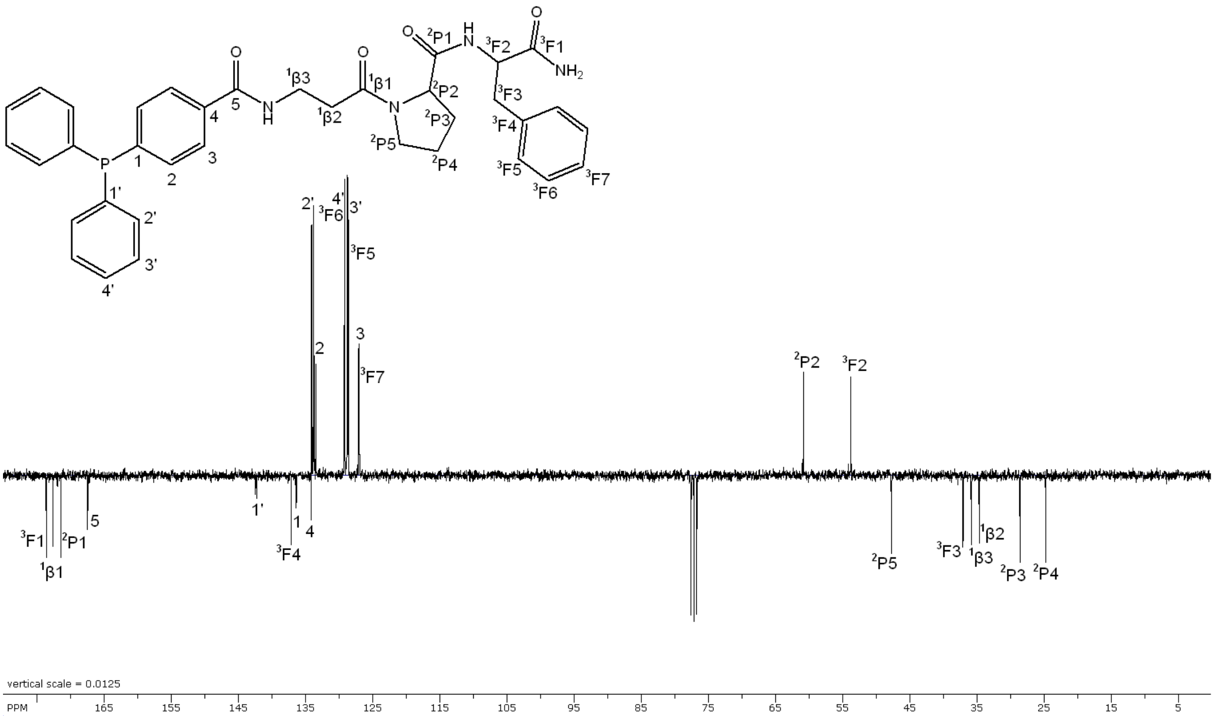
4.34. ^{13}C NMR ($CDCl_3$) **Lig-Gly-Pro-Phe-NH_2 6j**



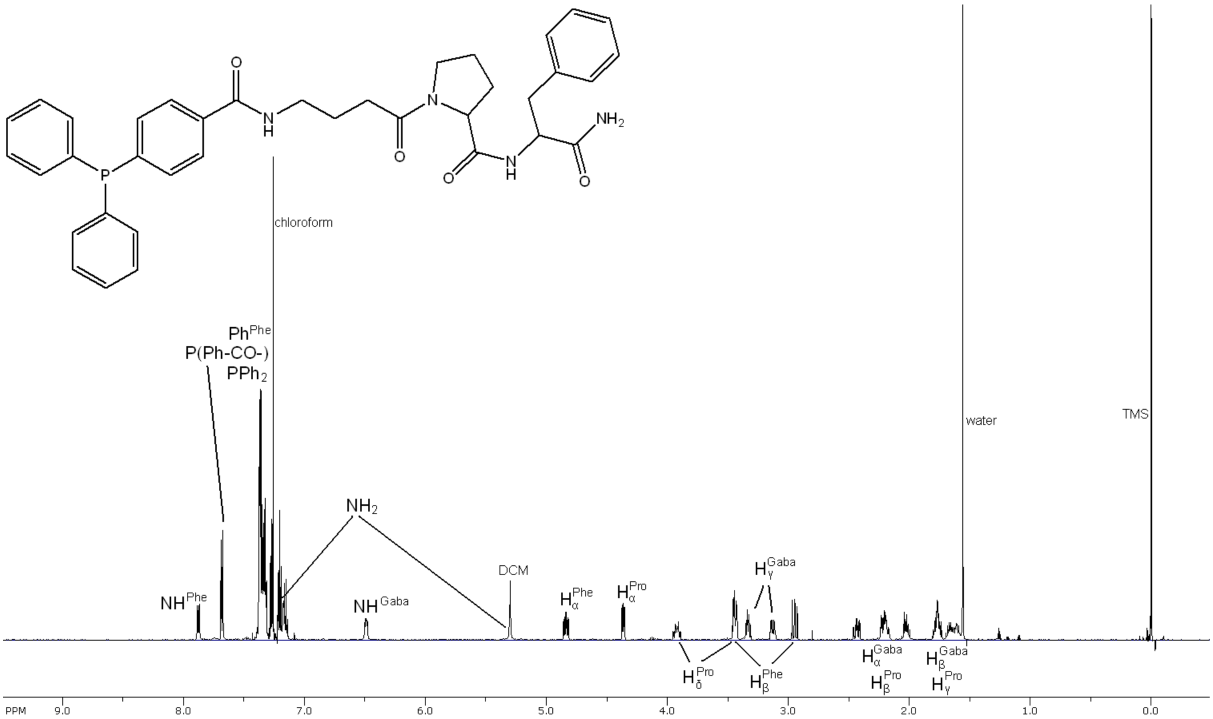
4.35. [1]H NMR ($CDCl_3$) **Lig-βAla-Pro-Phe-NH_2 6k**



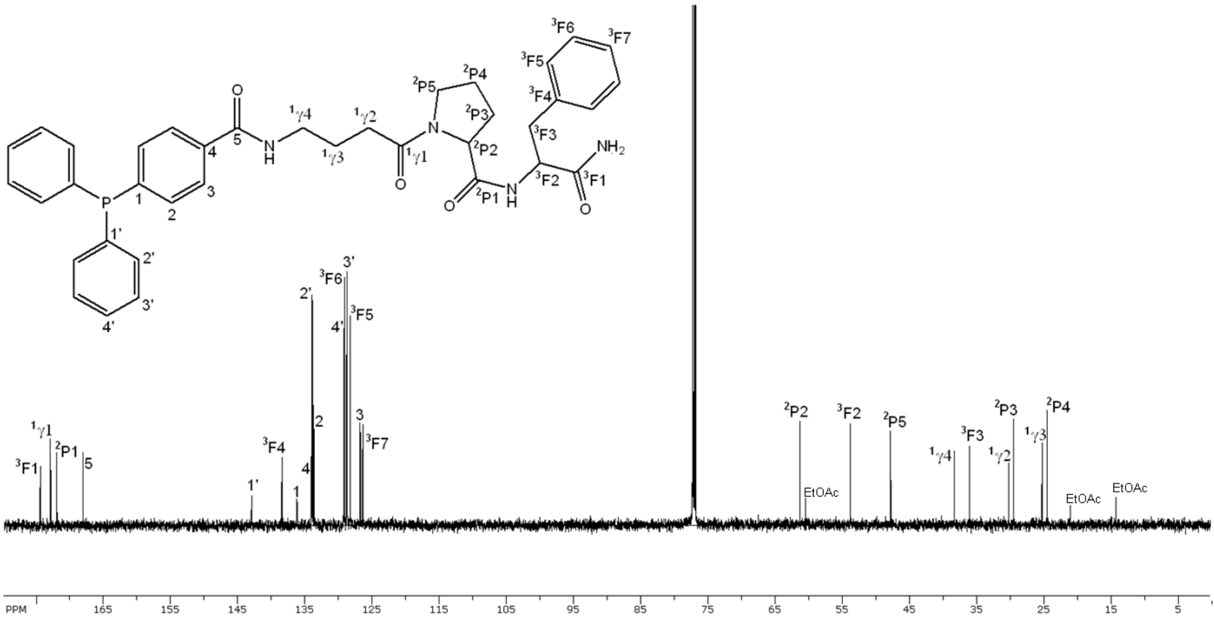
4.36. [13]C NMR ($CDCl_3$) **Lig-βAla-Pro-Phe-NH_2 6k**



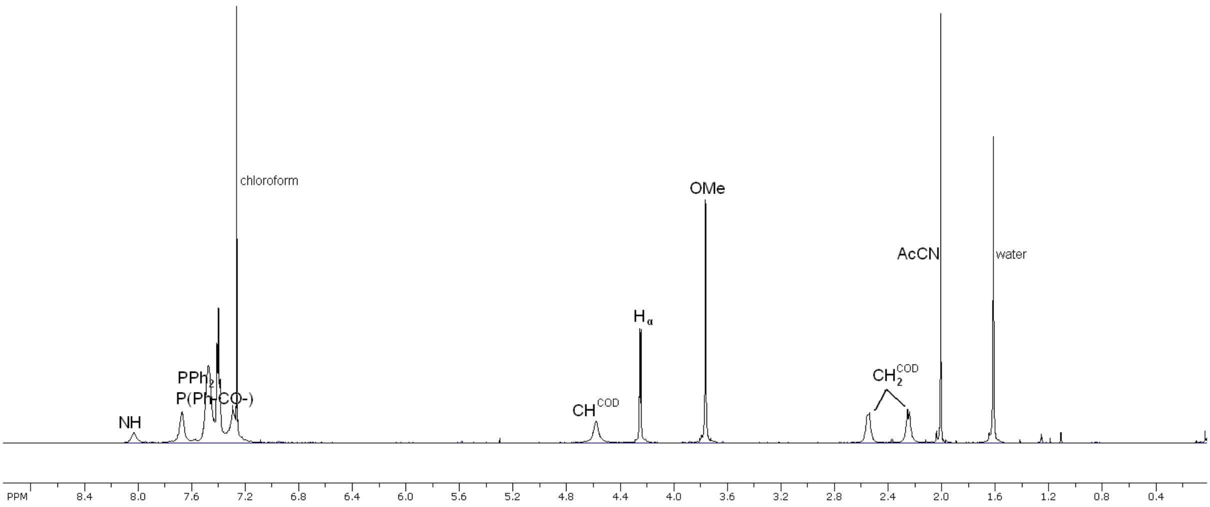
4.37. ^{1}H NMR ($CDCl_3$) **Lig-Gaba-Pro-Phe-NH_2 6l**



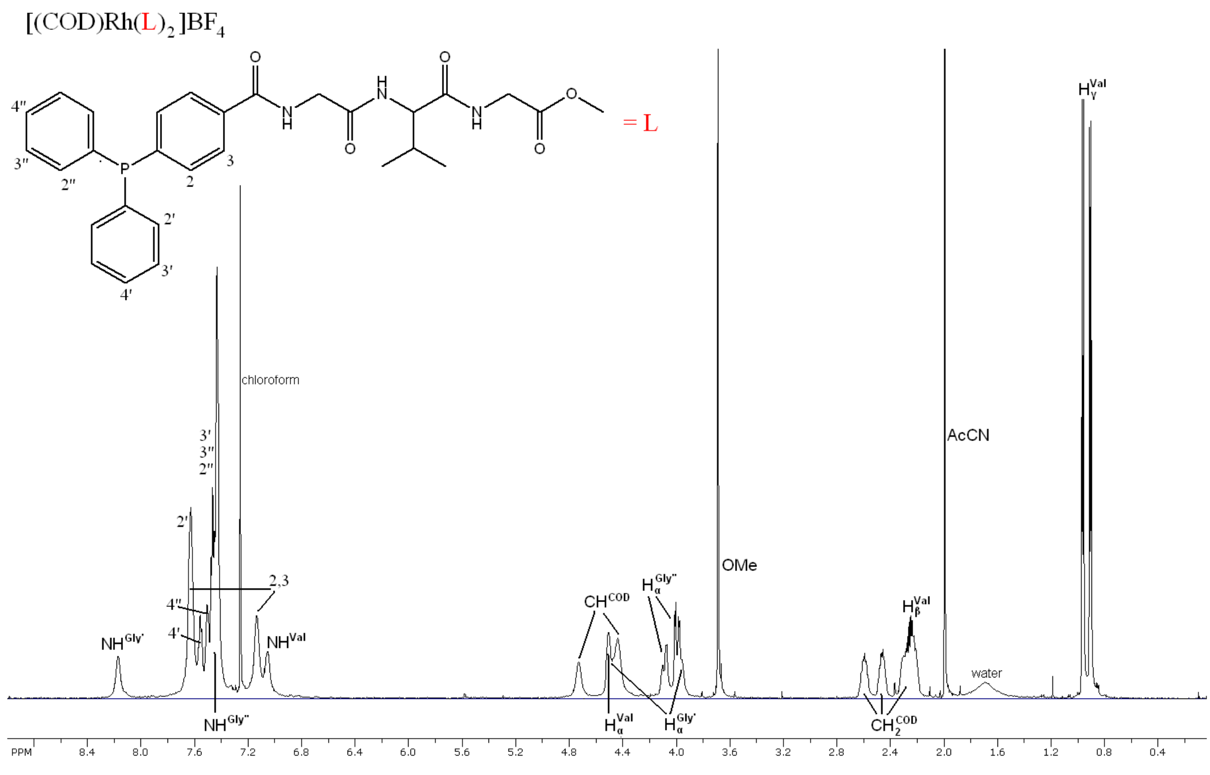
4.38. ^{13}C NMR ($CDCl_3$) **Lig-Gaba-Pro-Phe-NH_2 6l**



4.39. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-OMe)$_2$]BF$_4$ 3a**



4.40. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-Val-Gly-OMe)$_2$]BF$_4$ 3d**



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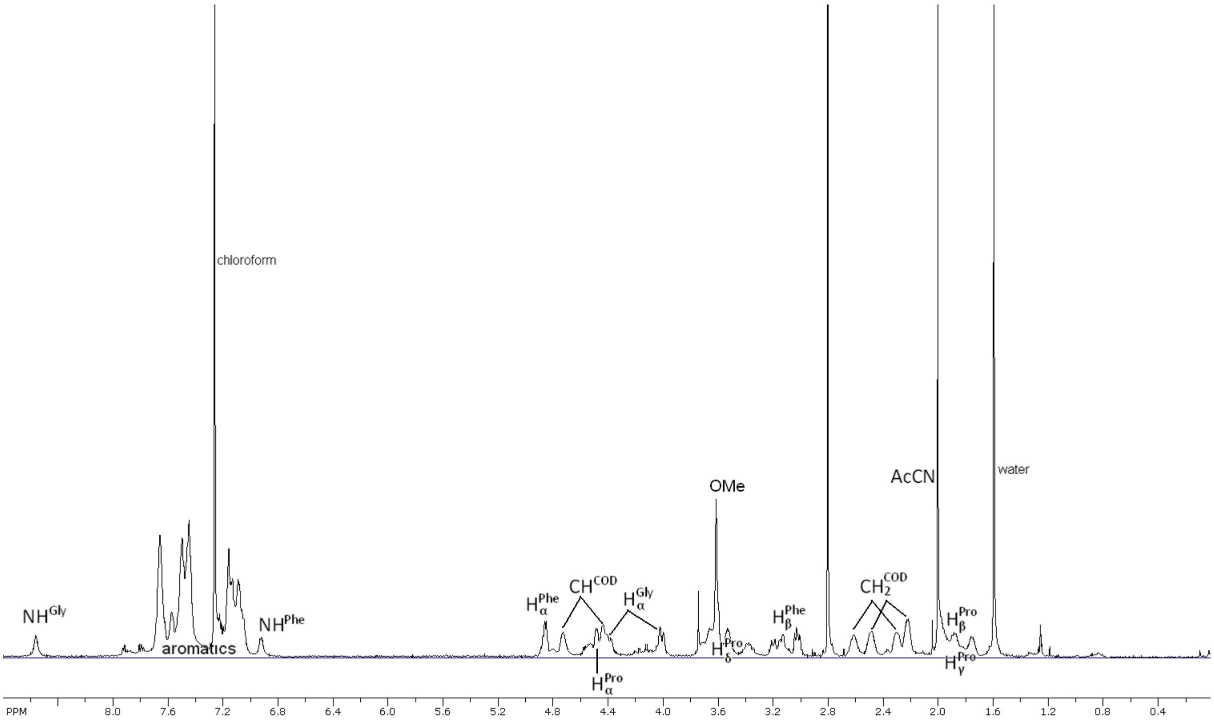
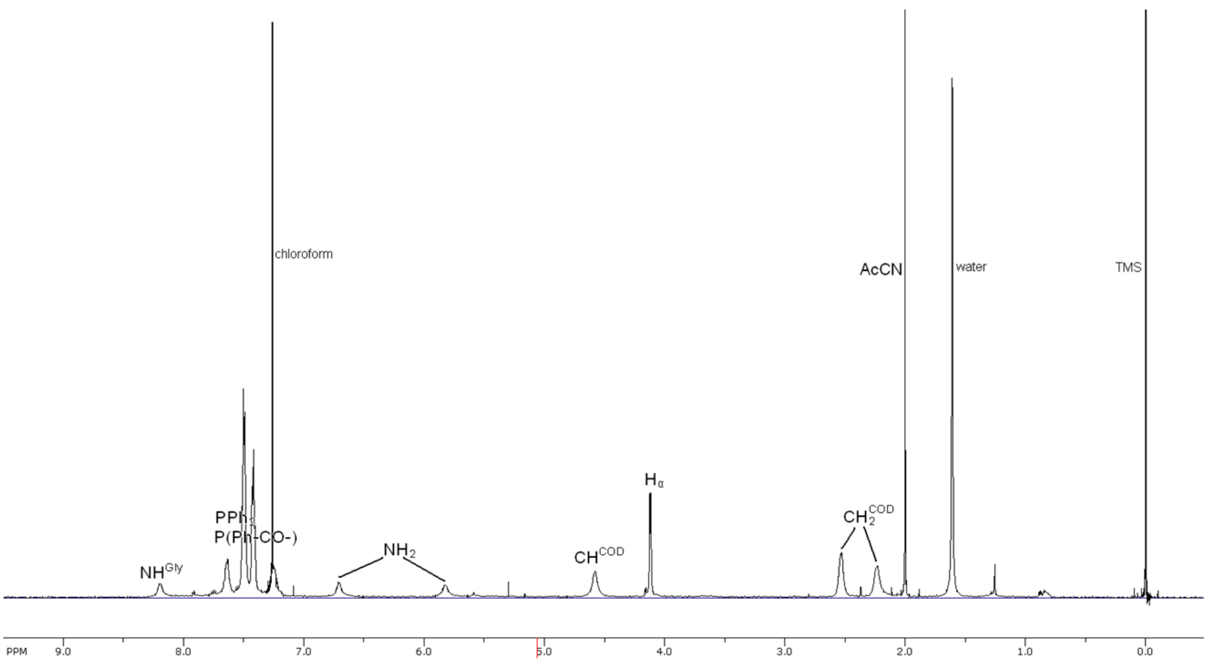
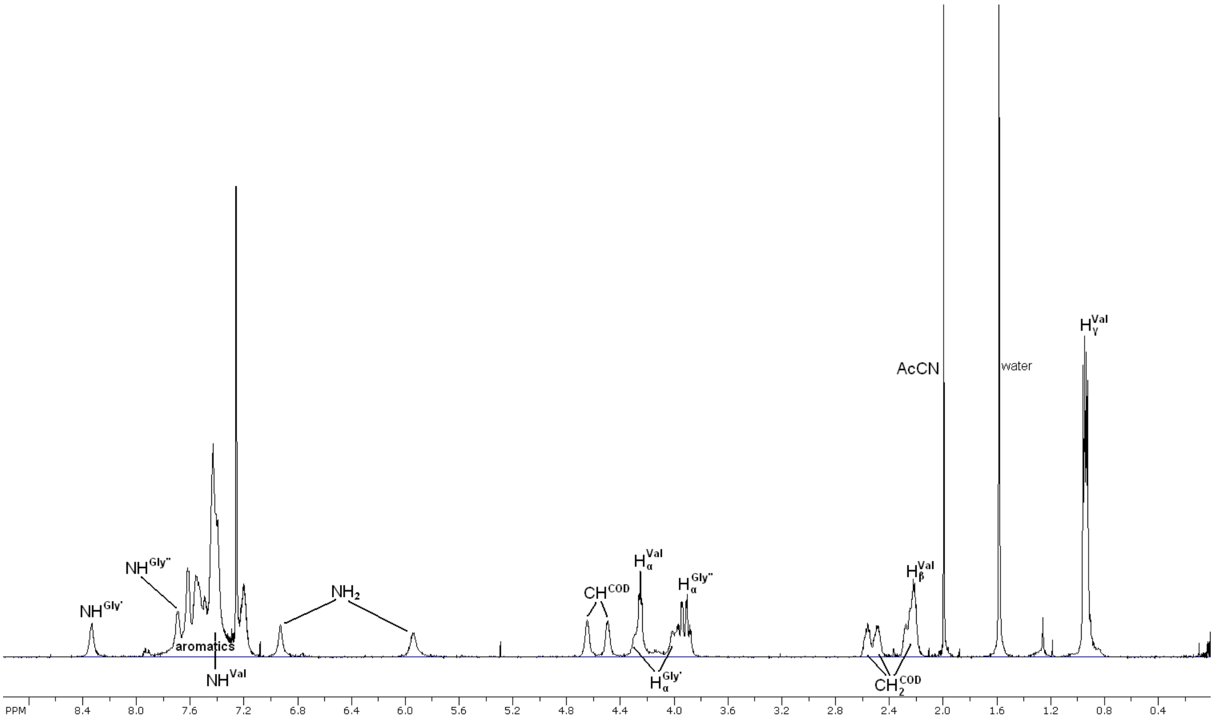
4.41. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-Pro-Phe-OMe)$_2$]BF$_4$ 3j**



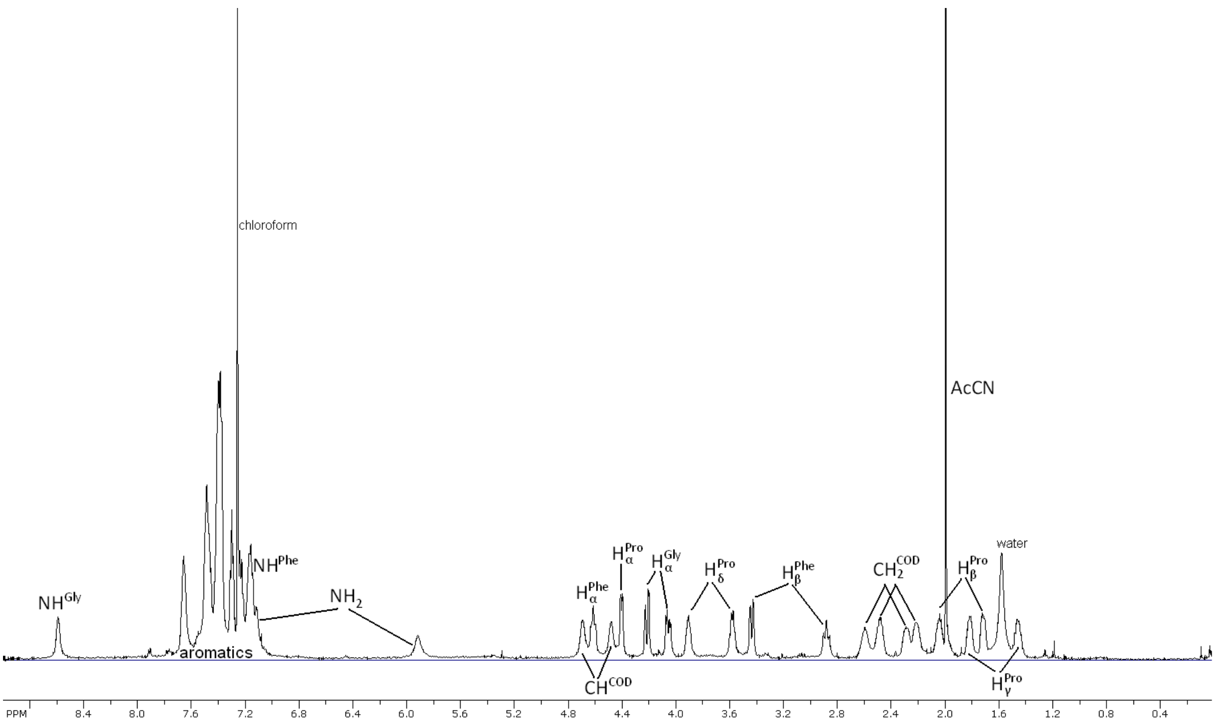
4.42. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-NH$_2$)$_2$]BF$_4$ 4a**



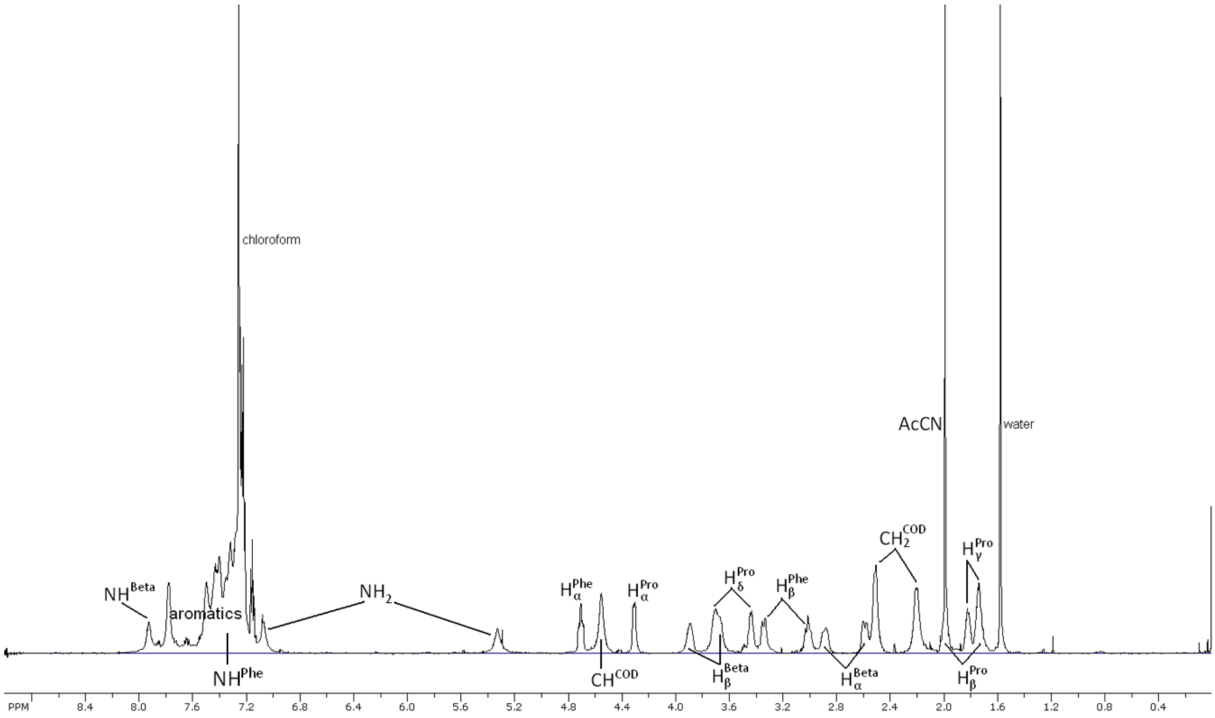
3.43. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-Val-Gly-NH$_2$)$_2$]BF$_4$ 4d**



4.44. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-Gly-Pro-Phe-NH$_2$)$_2$]BF$_4$ 4j**

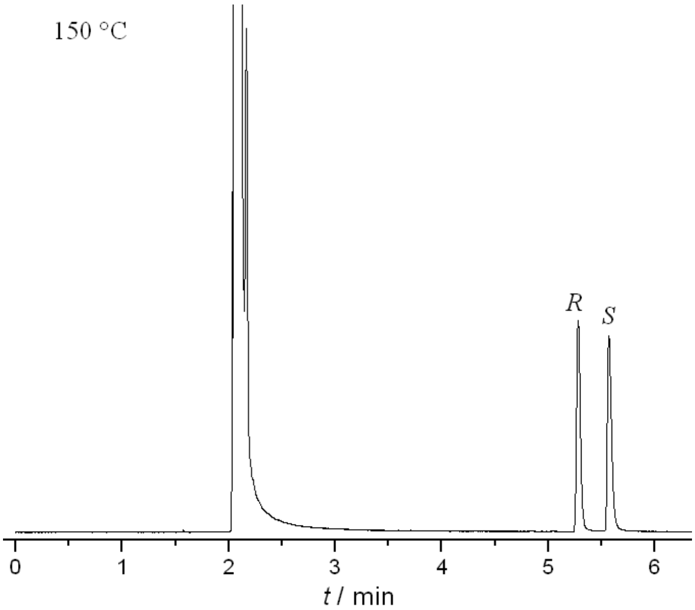


3.45. ^{1}H NMR ($CDCl_3$) **[(COD)Rh(Lig-βAla-Pro-Phe-NH_2)$_2$]BF_4 4k**

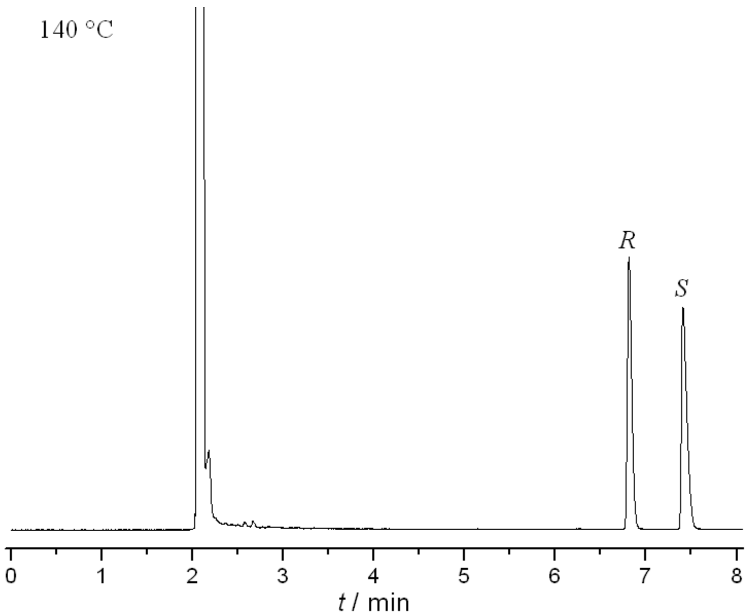


5. Gas chromatograms.

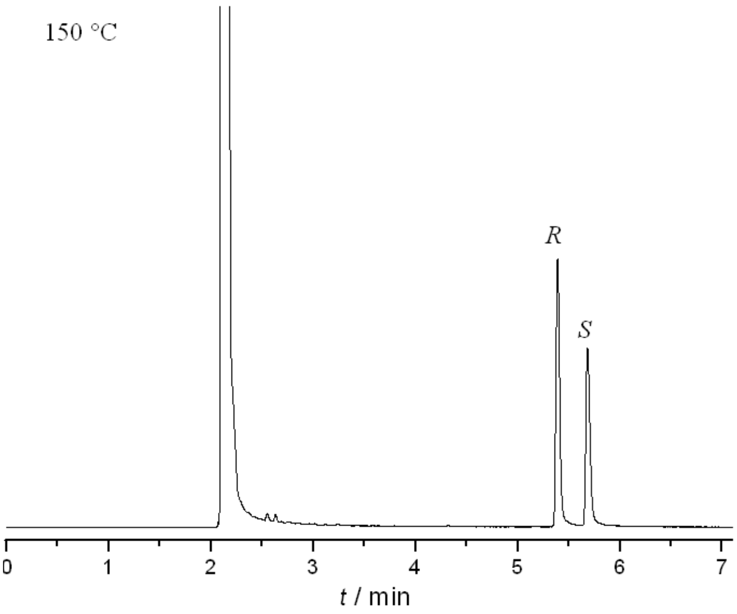
5.01. Catalysis with **Lig-Gly-OMe 5a**, RT



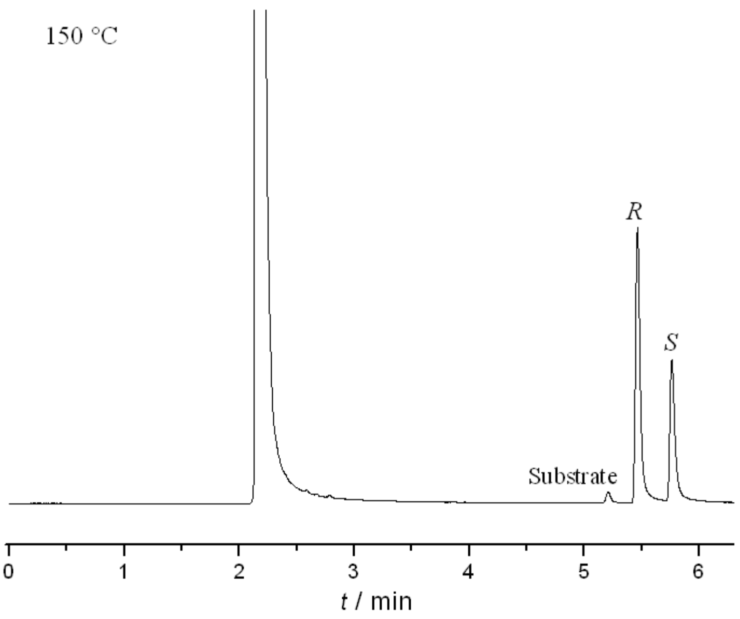
5.02. Catalysis with **Lig-Gly-Phe-OMe 5b**, RT



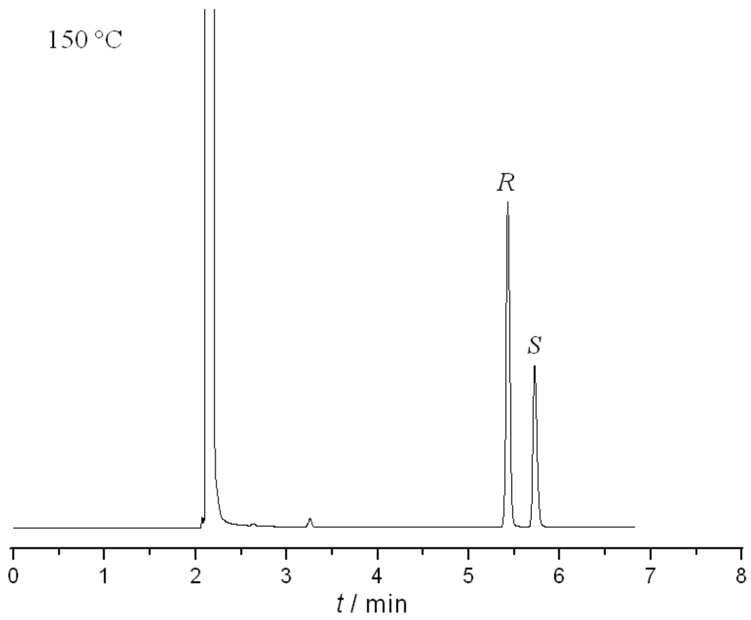
5.03. Catalysis with **Lig-Gly-Ala-Gly-OMe 5c**, RT



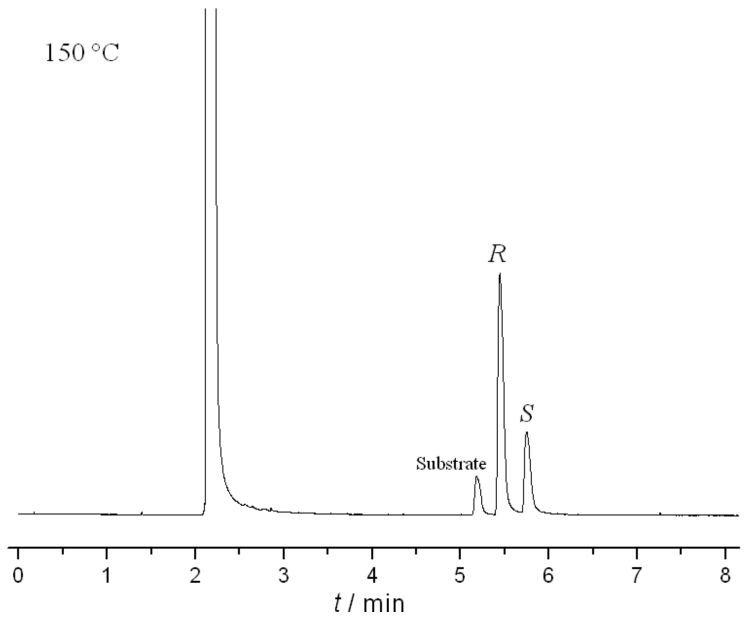
5.04. Catalysis with **Lig-Gly-Ala-Gly-OMe 5c**, –5 °C



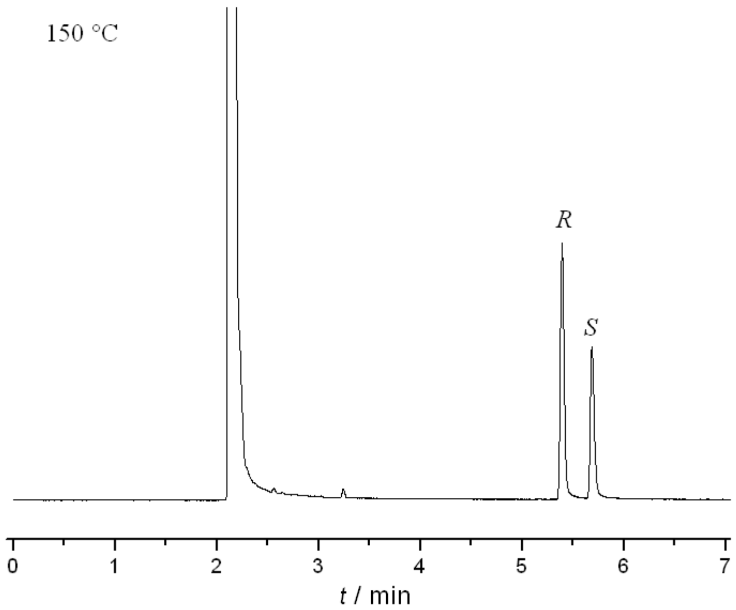
5.05. Catalysis with **Lig-Gly-Val-Gly-OMe 5d**, RT



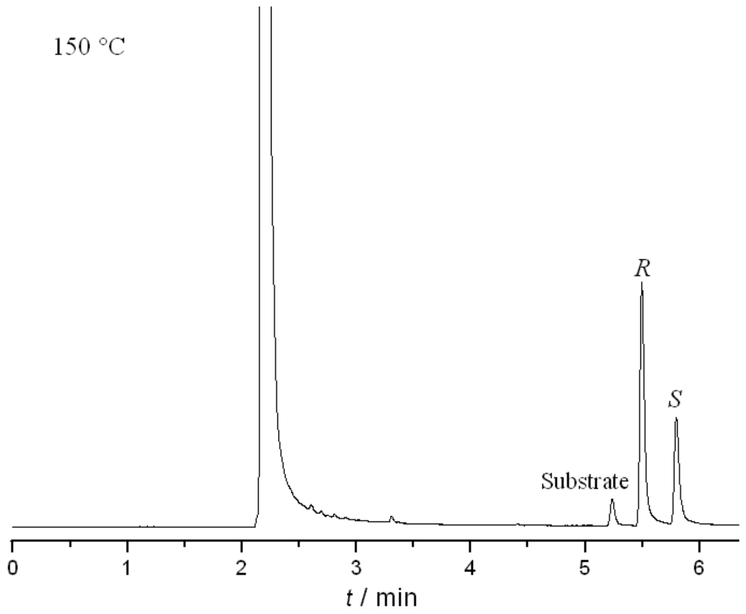
5.06. Catalysis with **Lig-Gly-Val-Gly-OMe 5d**, –5 °C



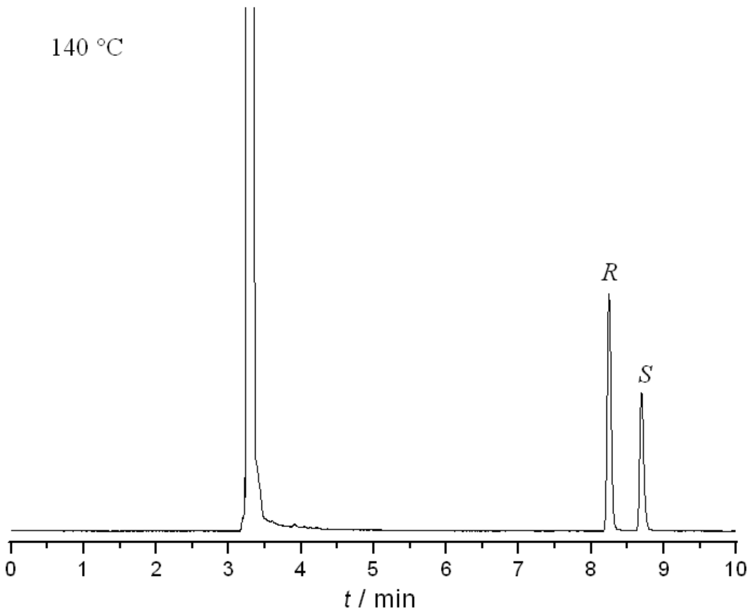
5.07. Catalysis with **Lig-Gly-Leu-Gly-OMe 5e**, RT



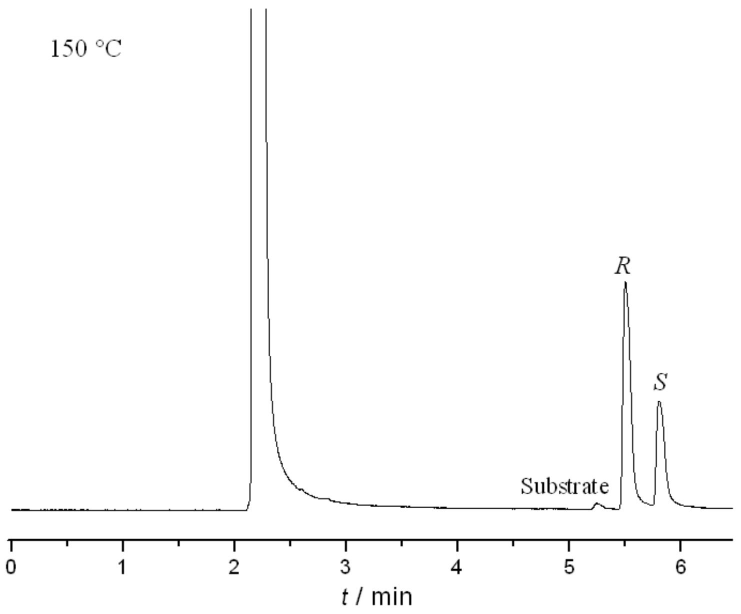
5.08. Catalysis with **Lig-Gly-Leu-Gly-OMe 5e**, –5 °C



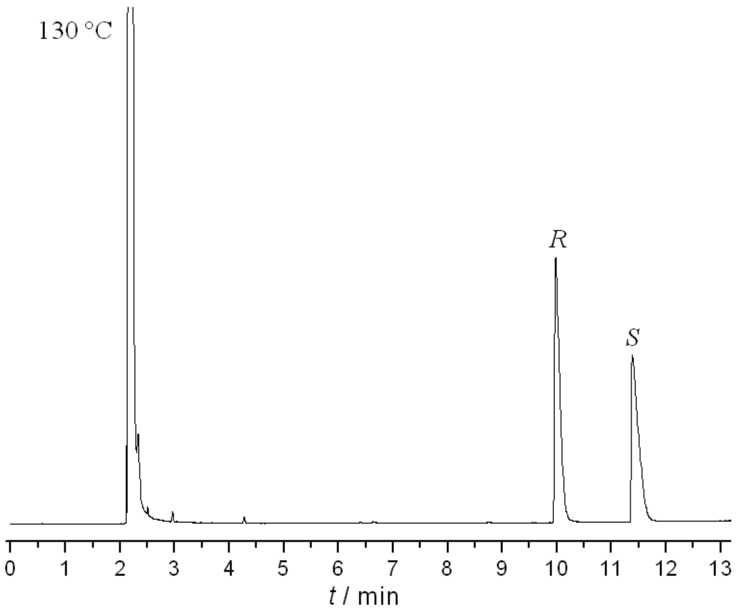
5.09. Catalysis with **Lig-Gly-Pro-Gly-OMe 5f**, RT



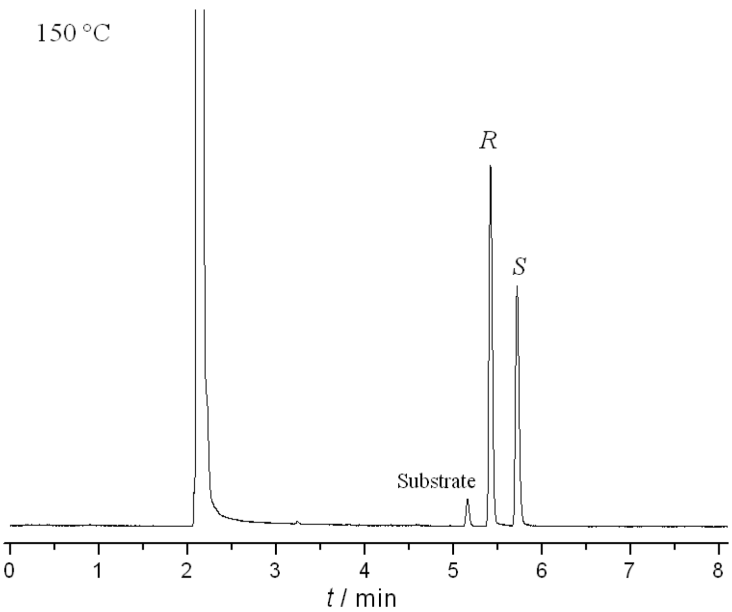
5.10. Catalysis with **Lig-Gly-Pro-Gly-OMe 5f**, –5 °C



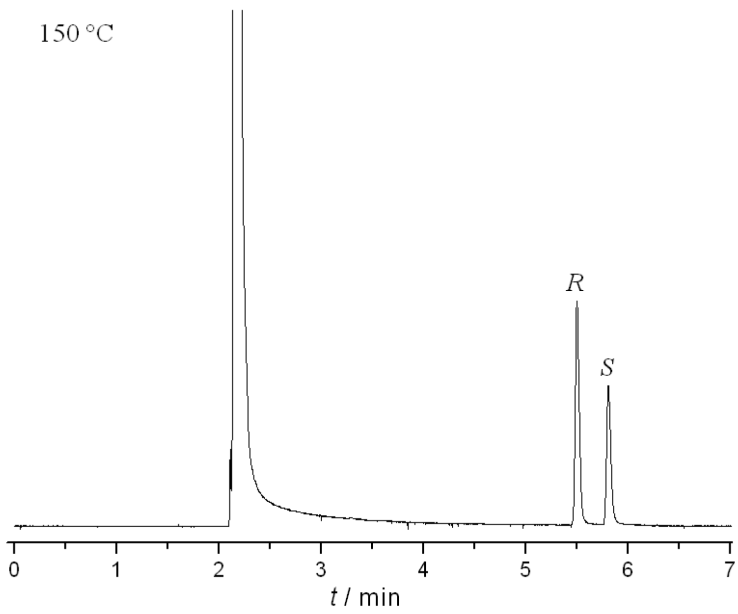
5.11. Catalysis with **Lig-Gly-Phe-Phe-OEt 5g**, RT



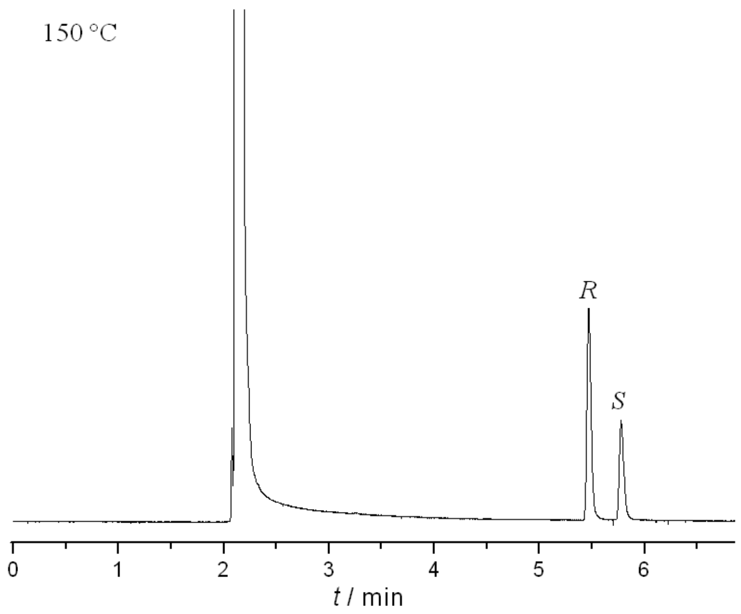
5.12. Catalysis with **Lig-Gly-Phe-Phe-OEt 5g**, –5 °C



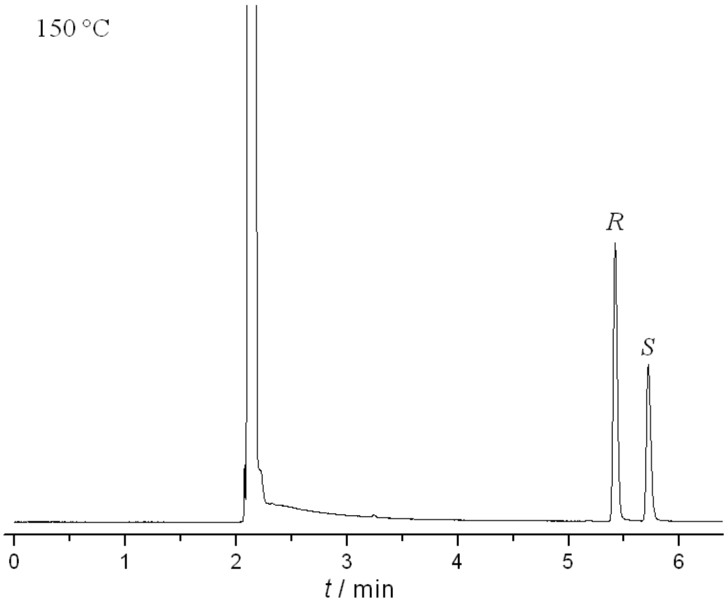
5.13. Catalysis with **Lig-Gly-Val-Phe-OEt 5h**, RT



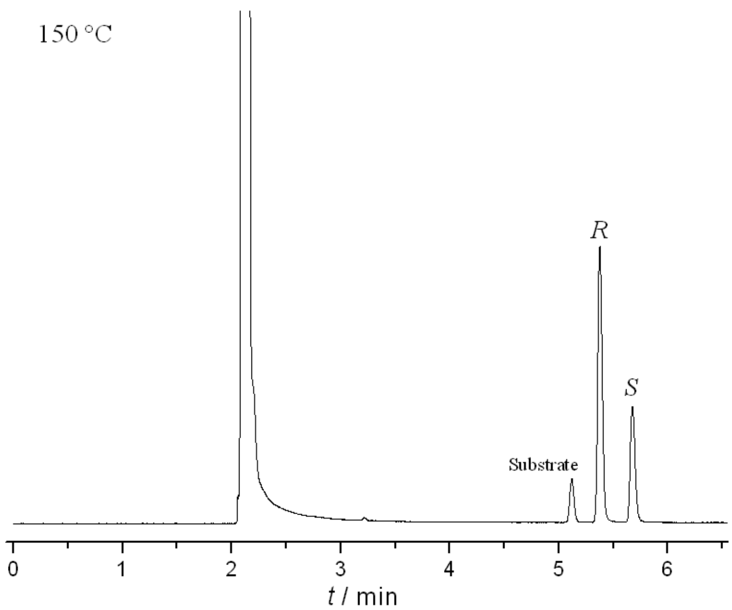
5.14. Catalysis with **Lig-Gly-Val-Phe-OEt 5h**, –5 °C



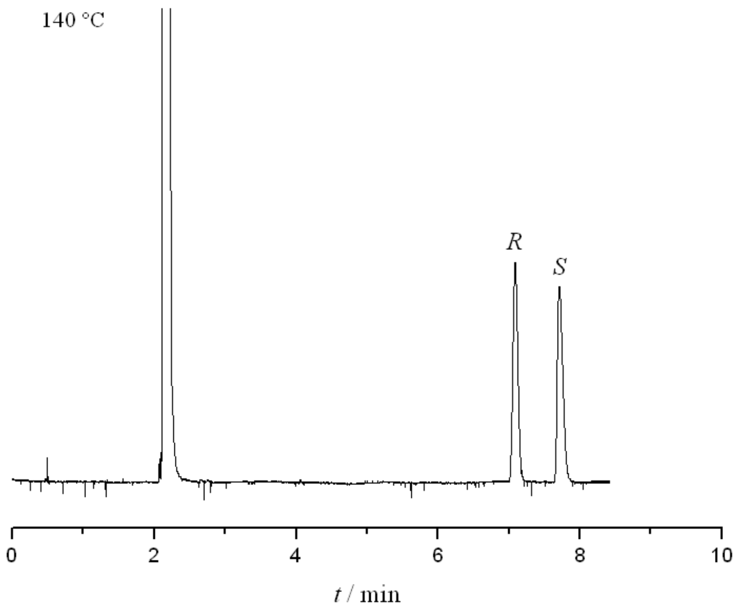
5.15. Catalysis with **Lig-Gly-Pro-Phe-OMe 5j**, RT



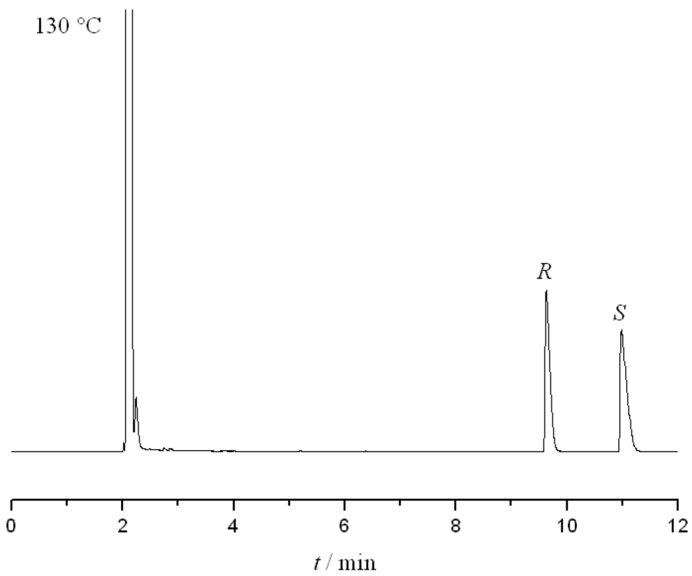
5.16. Catalysis with **Lig-Gly-Pro-Phe-OMe 5j**, –5 °C



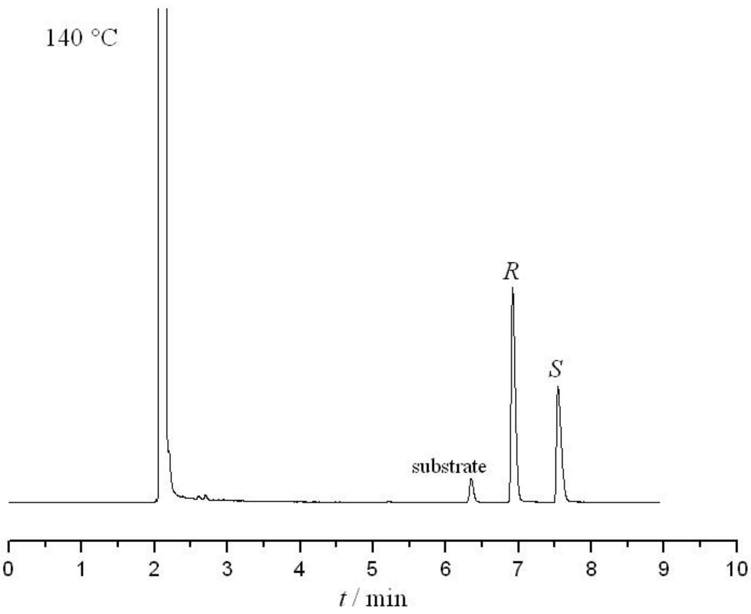
5.17. Catalysis with **Lig-Gly-NH_2 6a**



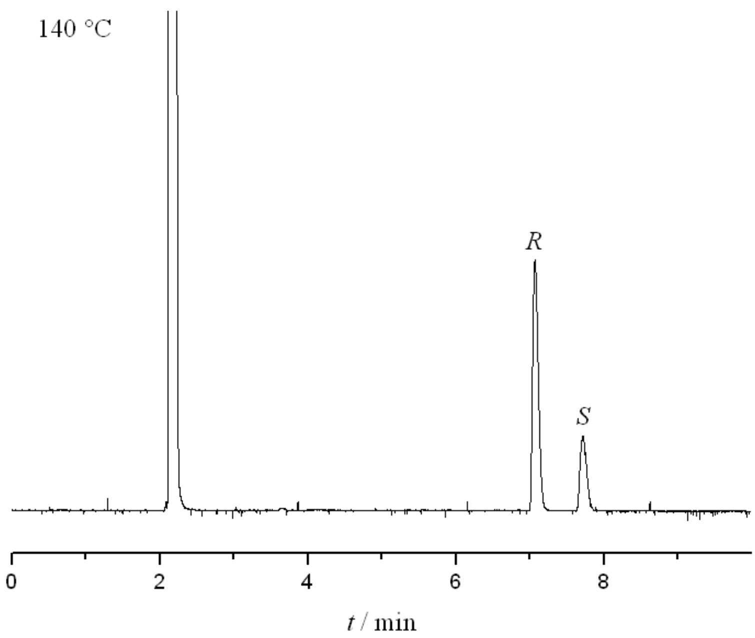
5.18. Catalysis with **Lig-Gly-Phe-NH_2 6b**



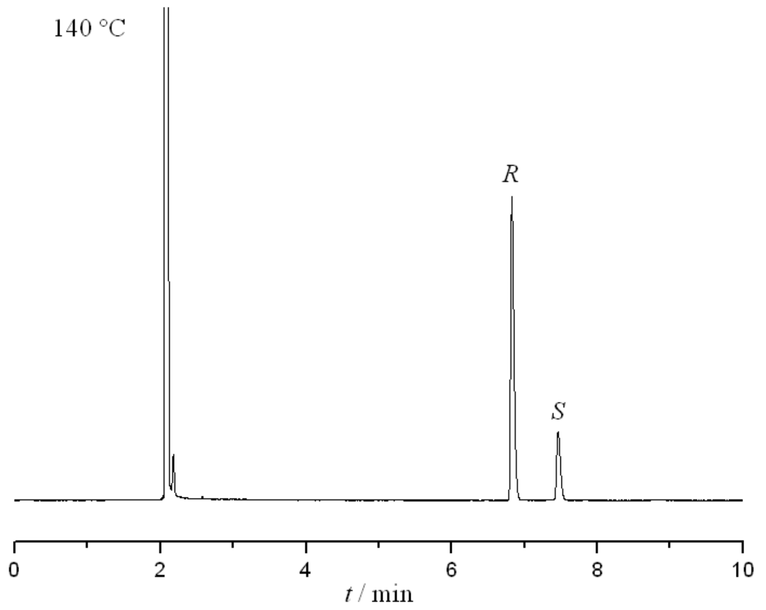
5.19. Catalysis with **Lig-Gly-Val-Gly-NH_2 6d**



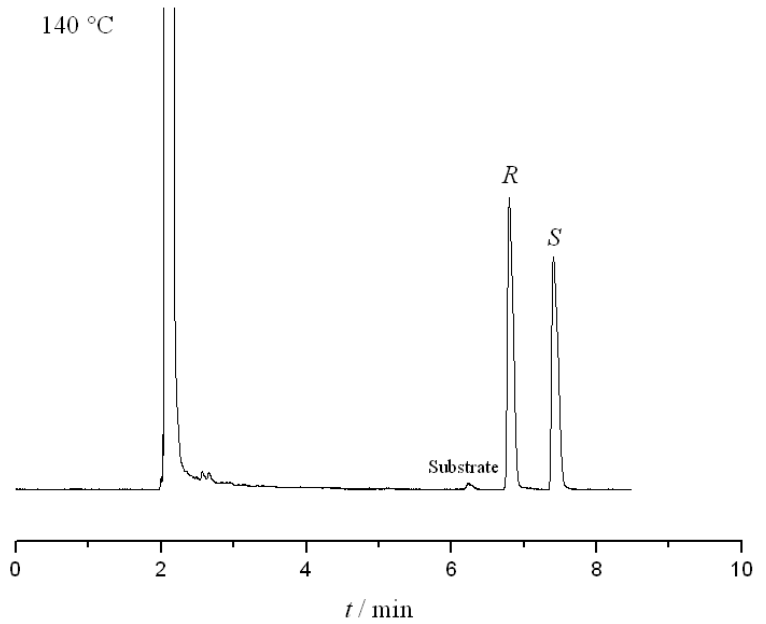
5.20. Catalysis with **Lig-Gly-Phe-Phe-NH_2 6g**



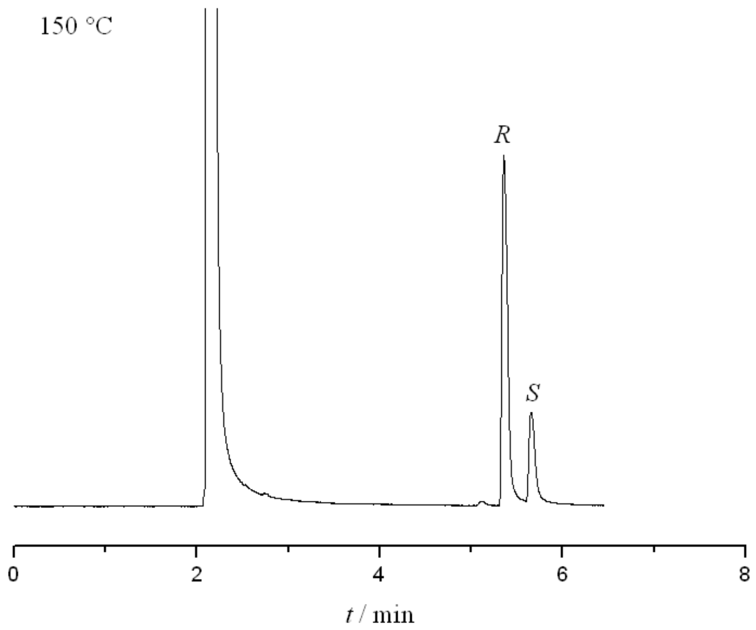
5.21. Catalysis with **Lig-Gly-Val-Phe-NH$_2$ 6h**



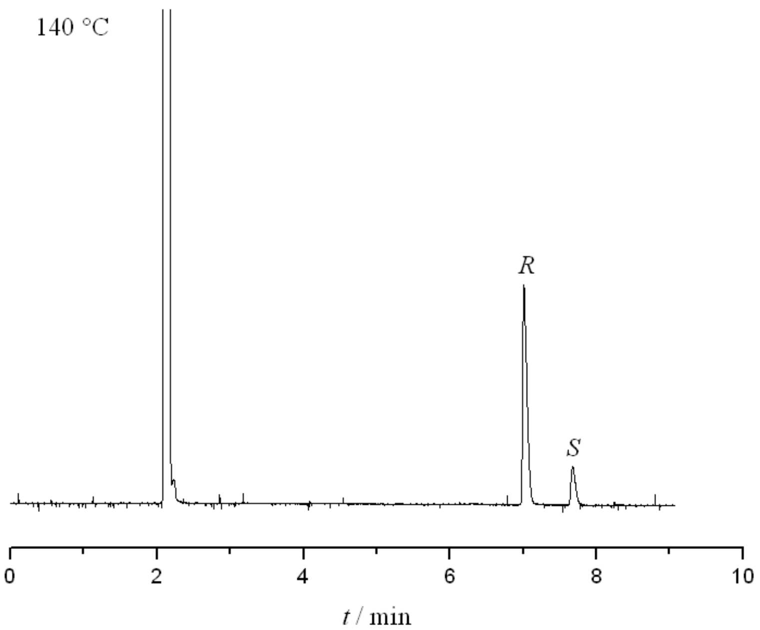
5.22. Catalysis with **Lig-βAla-Val-Phe-NH$_2$ 6i**



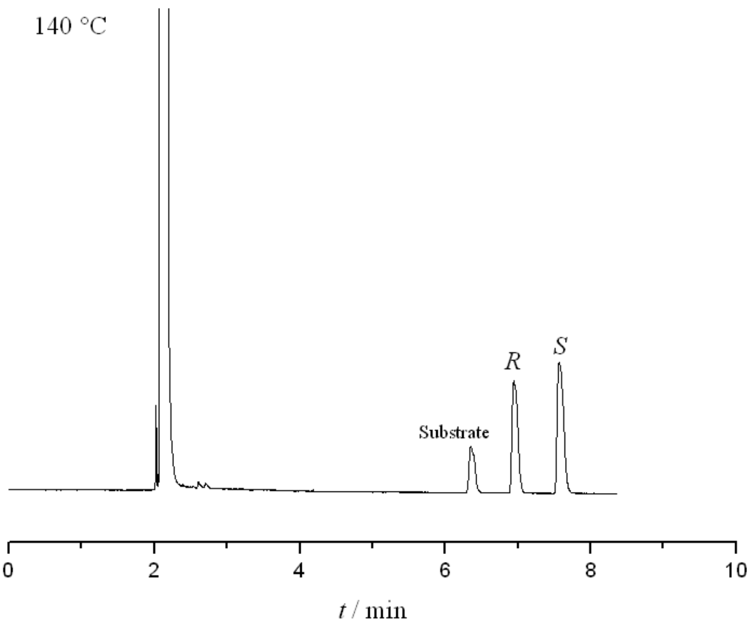
5.23. Catalysis with **Lig-Gly-Pro-Phe-NH_2 6j**



5.24. Catalysis with **Lig-βAla-Pro-Phe-NH_2 6k**



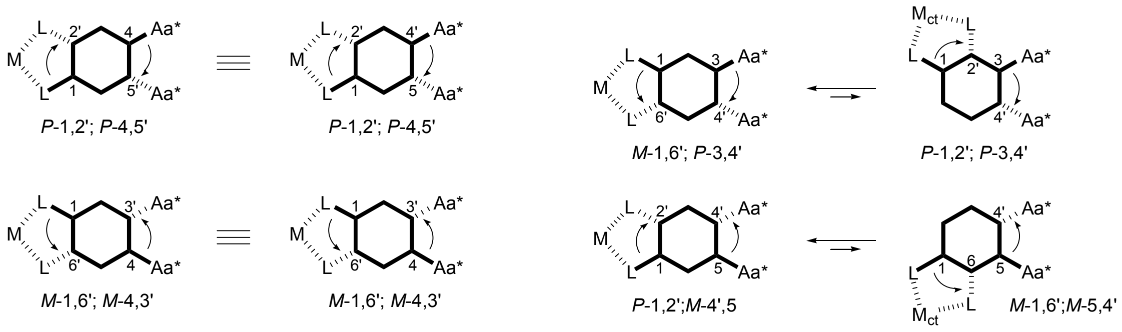
5.25. Catalysis with **Lig-Gaba-Pro-Phe-NH_2 6l**



6. Stereochemical analysis.[1]

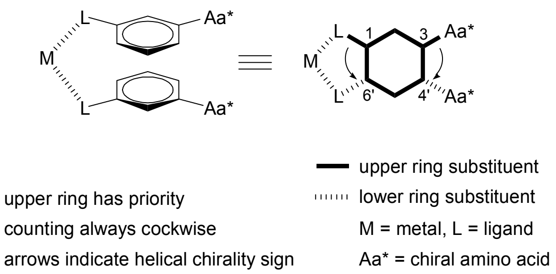
para-substitution, $[M(Ph_2P\text{-}pC_6H_4\text{-}CO\text{-}Aa^*)_2]$

meta-substitution, $[M(Ph_2P\text{-}mC_6H_4\text{-}CO\text{-}Aa^*)_2]$



insensitive to 180° rotation of one ligand

180° rotation of one ligand gives an additional isomer with opposite helical chirality of the prochiral metal



7. Literature.

[1] S. I. Kirin, H.-B. Kraatz and N. Metzler-Nolte, *Chem. Soc. Rev.*, 2006, **35**, 348.