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Supporting Information

Thiourea fused γ-amino alcohol organocatalysts for asymmetric Mannich reaction of β-keto active methylene compounds with imines

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1.General Information

Reagents and dry solvents were of the commercially available maximum grade and used without further purification. Reactions were performed under an inert atmosphere in flame dried and cooled glassware. The reaction progress was monitored by thin layer chromatography (TLC) using Merk silica plate gel 60 F_{254} aluminum sheet. Also, the purification of products were carried out using column chromatography techniques in silica gel 60 N (40–50 μm) purchased from Kanto Chemical Company and PLC was performed on silica gel 70 F_{254} purchased from FUJIFILM Wako Pure Chemical Corporation. Visualization of the products was confirmed by ultraviolet light, iodine vapor and ninhydrin stain. Infrared (IR) spectra were measured with a FT-IR spectro-photometer (JASCO FT/IR-400). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA500 (^{1}H for 500 MHz and ^{13}C for 125 MHz). All the spectra were recorded at 21 °C. Chemical shifts (δ) are reported in parts per million (ppm) relative to the signals of tetramethylsilane (TMS) using the residual solvents signals. Report data for ^{1}H NMR spectroscopy was reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet and br = broad, coupling constants (J) and assimilation were measured in hertz (Hz). Optical rotation was measured by JASCO DIP-360 polarimeter. The melting point was measured using a Yanaco micro melting point apparatus. High resolution mass spectra (HRMS) data was collected by electron impact (EI) using Hitachi RMG-GMG and JEOL JNK-DX303 sector instruments. The enantiomeric excess (*ee*) was determined using high pressure liquid chromatography (HPLC) principle by DAICEL CHIRALCEL AD-H, OD-H column, CHIRALPAK IC column.

2.Experimental procedure

2.1 General procedure for the synthesis of β-amino alcohol organocatalysts X5-7.

To a solution of methyl ester hydrochloride (2.0 mmol) in Et_2O (3 mL) was added dropwise phenylmagnesium bromide (3.0 M in Et_2O, 1.8 mmol) at 0 °C under an argon atmosphere. After stirring the reaction mixture for 24 h at room temperature, the solvent was removed under reduced pressure and residue was purified by flash chromatography (n-hexane/EtOAc = 9:1) to provide β-amino alcohol organocatalysts **X5-7**.

(2*S*,3*S*)-2-Amino-3-methyl-1,1-diphenylpentan-1-ol (X5)

White solid. 27% yield. mp 135-136 °C. $[\alpha]_D^{20}$ = -81.567 (c = 0.3, $CHCl_3$). IR (neat) 3648, 2969, 2956, 1216, 754, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.61 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.47-7.49 (m, 2H), 7.25-7.33 (m, 4H), 7.15-7.21 (m, 2H), 3.84 (d, *J* = 2.3 Hz, 1H), 1.79-1.86 (m, 1H), 1.42-1.48 (m, 1H), 0.92-1.03 (m, 4H), 0.70 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 148.11, 144.94, 128.47, 128.05, 126.71, 126.36, 126.13, 125.70, 79.81, 61.12, 35.02, 22.67, 18.92, 12.36. MS (FAB): m/z = 269 $[M+1]^+$, HRMS calculated for $C_{18}H_{23}NO$ $[M+1]^+$: 269.3880; found 270.1855.

(*S*)-2-Amino-4,4-dimethyl-1,1-diphenylpentan-1-ol (X6)

White solid. 18% yield. mp 98-100 °C. $[\alpha]_D^{20}$ = -106.14 (c = 0.5, $CHCl_3$). IR (neat) 3438, 2968, 2946, 1216, 761, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.64 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.50-7.52 (m, 2H), 7.25-7.33 (m, 4H), 7.13-7.20 (m, 2H), 4.00 (d, *J* = 7.4 Hz, 1H), 1.45 (d, *J* = 14.9 Hz, 1H), 1.26-1.32 (m, 1H), 1.08 (dd, *J* = 14.6, 8.3 Hz, 1H), 0.86-0.94 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 147.38, 144.59, 131.01, 128.91, 128.54, 128.04, 126.66, 126.45, 125.97, 125.82, 80.07, 68.25, 53.78, 44.64, 38.80, 30.44, 30.25, 29.03, 23.83, 23.11, 14.20, 11.08. MS (FAB): m/z = 283 $[M+1]^+$, HRMS calculated for $C_{19}H_{25}NO$ $[M+1]^+$: 283.4150; found 284.2015.

(*S*)-2-Amino-2-cyclohexyl-1,1-diphenylethan-1-ol (X7)

White solid. 63% yield. mp 213-216 °C. $[\alpha]_D^{20}$ = -139.54 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2932, 2922, 1216, 743, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.60 (dt, *J* = 8.3, 1.6 Hz, 2H), 7.43-7.48 (m, 2H), 7.15-7.32 (m, 6H), 4.53 (d, *J* = 13.7 Hz, 1H), 3.75 (d, *J* = 2.0 Hz, 1H), 1.96 (d, *J* = 12.9 Hz, 1H), 1.60-1.68 (m, 2H), 1.54-1.56 (m, 1H), 1.49 (t, *J* = 11.9 Hz, 1H), 1.34-1.42 (m, 1H), 0.92-1.27 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 148.07, 144.88, 128.45, 128.07, 126.65, 126.35, 126.06, 125.61, 79.94, 60.80, 38.37, 33.22, 26.97, 26.95, 26.46, 26.35. MS (FAB): m/z = 295 $[M+1]^+$, HRMS calculated for $C_{20}H_{25}NO$ $[M+1]^+$: 295.4260; found 296.2010.

2.2 General procedure for the synthesis of 4b-4e.

A 50 mL flask was charged with Mg (43 mmol) and a small crystal of I_2 and 10 mL of anhydrous Et_2O. Solution of aryl bromide (14 mmol) was added dropwise at 0 °C. After addition, the reaction mixture stir for 30 minutes at r. t. Heat the reaction mixture to reflux for 3 hours to obtain Grignard Reagent. A 50 mL flask was charged with N-(tert-Butoxycarbonyl)-L-serine Methyl Ester (1.4 mmol) and 4 mL of anhydrous Et_2O. Solution of Grignard Reagent was added dropwise at 0 °C. After addition, the reaction mixture stir for 24 h at room temperature. The reaction mixture was quenched with 1M HCl at 0 ℃

and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water (3 × 10 mL) and brine and then dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (n-hexane/EtOAc = 9:1 to 7:3) as the eluent to give the pure compound **4b-e**.

***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-o-tolylpropan-2-yl)carbamate (4b)**

White solid. 32% yield. mp 157-158 °C. $[\alpha]_D^{20}$ = -86.00 (c = 0.5, $CHCl_3$). IR (neat) 3524, 2975, 1698, 1233, 1159, 1052, 763 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.82 (s, 1H), 7.54 (d, *J* = 4.6 Hz, 1H), 7.14-7.21 (m, 4H), 7.00-7.03 (m, 2H), 5.75 (s, 1H), 4.72 (s, 1H), 4.45 (s, 1H), 3.68 (s, 1H), 3.40 (s, 1H), 2.66 (s, 1H), 1.93-2.15 (m, 6H), 1.46 (d, *J* = 37.2 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.06, 141.41, 133.07, 132.72, 127.79, 127.60, 125.52, 124.86, 79.90, 64.24, 28.47, 21.95, 21.52. MS (FAB): m/z = 371 $[M+H]^+$, HRMS calculated for $C_{22}H_{29}NO_4$ $[M+H]^+$: 371.4770; found 372.2178.

***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-m-tolylpropan-2-yl)carbamate (4c)**

White solid. 64% yield. mp 127-128 °C. $[\alpha]_D^{20}$ = -86.00 (c = 0.5, $CHCl_3$). IR (neat) 3522, 2989, 1681, 1177, 1161, 1066, 772, 707 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.25-7.31 (m, 4H), 7.15-7.21 (m, 2H), 6.99 (t, *J* = 7.7 Hz, 2H), 5.42 (d, *J* = 7.7 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.49 (s, 1H), 3.68-3.84 (m, 2H), 2.30 (d, *J* = 4.3 Hz, 6H), 2.20 (s, 1H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.09, 145.45, 144.60, 138.22, 137.84, 128.47, 128.20, 127.79, 127.76, 126.17, 125.72, 122.57, 122.11, 81.75, 79.77, 64.10, 55.46, 28.36, 21.75, 21.71. MS (FAB): m/z = 371 $[M+H]^+$, HRMS calculated for $C_{22}H_{29}NO_4$ $[M+H]^+$: 371.4770; found 372.2174.

***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-p-tolylpropan-2-yl)carbamate (4d)**

White solid. 39% yield. mp 160-162 °C. $[\alpha]_D^{20}$ = -50.12 (c = 0.5, $CHCl_3$). IR (neat) 3585, 3437, 2969, 1681, 1365, 1166, 1055, 807, 766 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.33-7.35 (m, 4H), 7.09 (q, *J* = 7.8 Hz, 4H), 5.41 (d, *J* = 8.0 Hz, 1H), 4.61 (d, *J* = 7.7 Hz, 1H), 4.41 (s, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.72 (qd, *J* = 5.6, 2.5 Hz, 1H), 2.27 (d, *J* = 7.7 Hz, 6H), 2.17 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.12, 142.72, 141.93, 136.59, 136.48, 129.29, 129.00, 125.40, 124.99, 81.54, 79.77, 64.04, 55.49, 28.38, 21.02. MS (FAB): m/z = 371 $[M+H]^+$, HRMS calculated for $C_{22}H_{29}NO_4$ $[M+H]^+$: 371.4770; found 372.2172.

***tert*-Butyl (*S*)-(1,1-bis(3,5-dimethylphenyl)-1,3-dihydroxypropan-2-yl)carbamate (4e)**

White solid. 67% yield. mp 96-98 °C. $[\alpha]_D^{20}$ = -78.00 (c = 0.5, $CHCl_3$). IR (neat) 3647, 2969, 1738, 1228, 1216, 849 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.09 (d, *J* = 6.3 Hz, 4H), 6.82 (s, 2H), 5.50 (d, *J* = 8.3 Hz, 1H), 4.63 (d, *J* = 8.3 Hz, 1H), 4.56 (s, 1H), 3.77 (d, *J* = 10.9 Hz, 1H), 3.66 (dt, *J* = 8.8, 2.4 Hz, 1H), 2.72 (s, 1H), 2.26 (d, *J* = 4.6 Hz, 13H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.27, 145.51, 144.81, 137.96, 137.61, 128.63, 128.43, 123.32, 122.82, 81.83, 79.70, 63.96, 60.64, 55.54, 31.71, 28.36, 22.77, 21.62, 21.59, 21.44, 21.11, 14.24. MS (FAB): m/z = 399 $[M+1]^+$, HRMS calculated for $C_{24}H_{33}NO_4$ $[M+1]^+$: 399.5310; found 400.2482.

2.3 General procedure for the synthesis of 5b-5e.

A 50 mL flask was charged with **4b-e** (3.2mmol) and 24 mL of anhydrous CH_2Cl_2. Solution of Et_3N (4.8 mmol, 1.5eq.) and methanesulfonyl chloride (3.8 mmol, 1.2eq.) were added dropwise at 0 °C. After addition, the reaction mixture stir for 2 h at

room temperature. The reaction mixture was quenched with water at 0 °C and extracted with $CHCl_3$ (3 × 15 mL). The organic layer was washed with water (3 × 15 mL) and brine and then dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (n-hexane/EtOAc = 7:3) as the eluent to give the pure compound **5b-e**.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-o-tolylpropyl methanesulfonate (5b)

White solid. 79% yield. mp 122-126 °C. $[\alpha]_D^{20}$ = -74.00 (c = 0.5, $CHCl_3$). IR 3648, 2969, 1737, 1364, 1228, 1216, 1165, 855, 751 (neat) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.68 (d, *J* = 6.6 Hz, 2H), 7.14-7.24 (m, 4H), 7.02-7.06 (m, 2H), 5.29 (s, 1H), 5.06 (s, 1H), 4.08 (s, 1H), 2.81-3.00 (m, 4H), 1.94 (s, 6H), 1.60 (s, 1H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.93, 140.05, 133.30, 132.95, 128.15, 127.17, 125.79, 125.40, 80.24, 69.90, 37.55, 28.39, 21.71, 21.42. MS (FAB): m/z = 449 $[M+H]^+$, HRMS calculated for $C_{23}H_{31}NO_6S$ $[M+H]^+$: 449.5620; found 450.1951.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-m-tolylpropyl methanesulfonate (5c)

White solid. 80% yield. mp 56-58 °C. $[\alpha]_D^{20}$ = -62.00 (c = 0.5, $CHCl_3$). IR (neat) 3650, 2969, 1738, 1365, 1228, 1216, 776, 717 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.27 (d, *J* = 11.7 Hz, 2H), 7.16-7.24 (m, 4H), 7.03 (t, *J* = 7.4 Hz, 2H), 5.14 (d, *J* = 8.9 Hz, 1H), 4.84-4.88 (m, 1H), 4.24-4.30 (m, 2H), 3.54 (s, 1H), 2.90 (d, *J* = 6.0 Hz, 3H), 2.30-2.33 (m, 6H), 1.31-1.42 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.15, 144.53, 143.86, 138.53, 138.07, 128.71, 128.38, 128.31, 128.08, 126.16, 125.76, 122.67, 122.15, 80.23, 80.10, 69.73, 55.84, 37.40, 28.28, 21.73, 21.69. MS (FAB): m/z = 367 $[M+H]^+$, HRMS calculated for $C_{23}H_{31}NO_6S$ $[M+H]^+$: 449.1872; found 450.1954.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-p-tolylpropyl methanesulfonate (5d)

White solid. 79% yield. mp 132-135 °C. $[\alpha]_D^{20}$ = -52.00 (c = 0.5, $CHCl_3$). IR (neat) 3673, 2969, 1738, 1364, 1228, 1216, 1169, 815, 700 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.31 (dd, *J* = 8.2, 1.9 Hz, 4H), 7.11 (dd, *J* = 14.2, 7.9 Hz, 4H), 5.15 (d, *J* = 8.9 Hz, 1H), 4.81-4.85 (m, 1H), 4.28 (d, *J* = 5.2 Hz, 2H), 3.50 (s, 1H), 2.89 (s, 3H), 2.28 (d, *J* = 5.4 Hz, 6H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.09, 141.70, 141.12, 137.26, 137.00, 129.53, 129.19, 125.47, 125.04, 80.27, 79.90, 69.66, 55.76, 37.42, 28.29, 21.04, 21.02. MS (FAB): m/z = 449 $[M+H]^+$, HRMS calculated for$C_{23}H_{31}NO_6S$ $[M+H]^+$: 449.5620; found 450.1947.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl methanesulfonate (5e)

White solid. 85% yield. mp 122-126 °C. $[\alpha]_D^{20}$ = -52.92 (c = 0.5, $CHCl_3$). IR (neat) 3579, 2917, 1670, 1250, 1167, 1110, 954, 816, cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.05 (d, *J* = 10.6 Hz, 4H), 6.84 (d, *J* = 0.9 Hz, 2H), 5.17 (d, *J* = 9.2 Hz, 1H), 4.85-4.89 (m, 1H), 4.20-4.25 (m, 2H), 3.34 (s, 1H), 2.90 (d, *J* = 6.0 Hz, 3H), 2.27 (d, *J* = 4.9 Hz, 12H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 156.06, 144.51, 143.81, 138.35, 138.00, 129.21, 129.04, 123.25, 122.76, 80.10, 69.86, 55.58, 37.43, 28.27, 22.43, 21.60, 21.57, 14.16. MS (FAB): m/z = 477 $[M+H]^+$, HRMS calculated for $C_{25}H_{35}NO_6S$ $[M+H]^+$: 477.6160; found 478.2270.

2.4 General procedure for the synthesis of 6a,b,6f-i.

A sealed tube was charged with **5a**,**5b-f** (1.5 mmol) and amine (3 mL). The reaction mixture stir for 12-24 h at 50-90 °C. After the completion of the reaction, solvent was evaporated. The residue was purified by column chromatography (n-hexane/EtOAc = 1:1) as the eluent to give the pure compound **6a,b**,**6f-i**.

***tert*-Butyl (*S*)-(3-(dimethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)carbamate (6a)**

White solid. 19% yield. mp 114-117 °C. $[\alpha]_D^{20}$ = -54.72 (c = 0.5, $CHCl_3$). IR (neat) 3734, 2933, 1683, 1356, 1161, 749, 698 cm^{-1}: ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.55 (d, *J* = 7.4 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.25-7.30 (m, 4H), 7.15 (q, *J* = 7.2 Hz, 2H), 5.24 (d, *J* = 8.0 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 2.70 (dd, *J* = 13.9, 2.4 Hz, 1H), 2.53 (dd, *J* = 13.9, 2.4 Hz, 1H), 2.16 (s, 7H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 146.69, 144.99, 128.41, 128.23, 126.73, 126.57, 126.13, 126.02, 125.68, 78.96, 60.44, 54.16, 46.17, 29.81. MS (EI): m/z = 370 $[M]^+$, HRMS calculated for $C_{22}H_{30}N_2O_3$ $[M]^+$: 370.4930; found 370.2248.

***tert*-Butyl (*S*)-(3-(diethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)carbamate (6b)**

White solid. 79% yield. mp 109-114 °C. $[\alpha]_D^{20}$ = -19.72 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2969, 1705, 1364, 1159, 748, 697 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.23-7.30 (m, 4H), 7.11-7.17 (m, 2H), 5.19 (d, *J* = 7.7 Hz, 1H), 4.69 (d, *J* = 8.0 Hz, 1H), 2.90-2.92 (m, 1H), 2.66 (dd, *J* = 14.2, 3.0 Hz, 1H), 2.49-2.54 (m, 2H), 2.42 (q, *J* = 6.8 Hz, 2H), 1.34 (d, *J* = 15.2 Hz, 9H), 0.85 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.84, 146.89, 145.54, 128.42, 128.22, 126.75, 126.54, 125.52, 125.22, 81.39, 79.44, 54.79, 53.96, 47.25, 28.41, 10.53. MS (EI): m/z = 398 $[M]^+$, HRMS calculated for $C_{24}H_{34}N_2O_3$ $[M]^+$: 398.5470; found 398.2560.

***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-o-tolylpropan-2-yl)carbamate (6f)**

White solid. 29% yield. mp 128-132 °C. $[\alpha]_D^{20}$ = -88.53 (c = 0.3, $CHCl_3$). IR (neat) 3455, 2969, 1737, 1365, 1228, 1216, 795, 754 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.46 (s, 1H), 7.22-7.25 (m, 1H), 6.99-7.15 (m, 6H), 4.75 (d, *J* = 6.9 Hz, 1H), 2.46-2.73 (m, 6H), 1.95-2.09 (m, 6H), 1.74 (s, 4H), 1.44 (t, *J* = 17.8 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.58, 142.48, 132.91, 132.64, 128.80, 127.33, 125.10, 124.38, 83.19, 79.44, 68.24, 56.78, 55.71, 52.72, 38.81, 30.45, 29.79, 29.02, 28.57, 23.84, 23.70, 23.08, 21.93, 21.60, 14.16, 11.06. MS (EI): m/z = 424 $[M]^+$, HRMS calculated for $C_{26}H_{36}N_2O_3$ $[M]^+$: 424.5850; found 424.2729.

***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-m-tolylpropan-2-yl)carbamate (6g)**

White solid. 48% yield. mp 50-54 °C. $[\alpha]_D^{20}$ = -47.20 (c = 0.5 , $CHCl_3$). IR (neat) 3452, 2969, 1737, 1365, 1228, 771, 709 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.26-7.34 (m, 4H), 7.14-7.19 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 2H), 5.22 (d, *J* = 7.7 Hz, 1H), 4.60 (d, *J* = 8.0 Hz, 1H), 2.75 (t, *J* = 2.7 Hz, 2H), 2.64 (s, 2H), 2.37 (d, *J* = 6.0 Hz, 2H), 2.29 (d, *J* = 4.0 Hz, 6H), 1.73 (s, 4H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.58, 146.53, 144.86, 137.64, 137.42, 128.00, 127.79, 127.09, 125.82, 125.61, 122.07, 121.90, 81.44, 79.02, 56.05, 55.42, 54.08, 28.13, 23.46, 21.42. MS (EI): m/z = 424 $[M]^+$, HRMS calculated for $C_{26}H_{36}N_2O_3$ $[M]^+$: 424.5850; found 424.2727.

***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-p-tolylpropan-2-yl)carbamate (6h)**

White solid. 82% yield. mp 100-104 °C. $[\alpha]_D^{20}$ = -44.53 (c = 0.3, $CHCl_3$). IR (neat) 3427, 2929, 1707, 1363, 1168, 818, 808, 753 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.9 Hz, 4H), 5.21 (d, *J* = 8.0 Hz, 1H), 4.57 (d, *J* = 8.0 Hz, 1H), 2.76-2.78 (m, 2H), 2.64 (s, 2H), 2.37 (d, *J* = 5.4 Hz, 2H), 2.26 (d, *J* = 4.9 Hz, 6H), 1.69-1.73 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.87, 144.15, 142.49, 136.07, 136.02, 129.15, 128.94, 125.22, 125.04,

81.51, 79.33, 56.26, 55.72, 54.29, 28.45, 23.76, 21.04, 21.01. MS (EI): m/z = 424 $[M]^+$, HRMS calculated for $C_{26}H_{36}N_2O_3$ $[M]^+$: 424.5850; found 424.2732.

***tert*-Butyl (*S*)-(1,1-bis(3,5-dimethylphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)carbamate (6i)**

White solid. 75% yield. mp 56-59 °C. $[\alpha]_D^{20}$ = -56.20 (c = 0.3, $CHCl_3$). IR (neat) 3463, 2969, 1737, 1228, 1216, 899cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.10 (d, *J* = 23.2 Hz, 4H), 6.79 (d, *J* = 0.6 Hz, 2H), 5.22 (d, *J* = 7.7 Hz, 1H), 4.55 (d, *J* = 8.0 Hz, 1H), 2.64-2.72 (m, 4H), 2.37 (d, *J* = 6.3 Hz, 2H), 2.25 (s, 12H), 1.73 (s, 4H), 1.39 (d, *J* = 11.2 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 155.90, 146.80, 145.12, 137.74, 137.50, 129.12, 128.33, 128.23, 125.39, 123.21, 122.97, 81.72, 79.24, 56.35, 55.68, 54.44, 34.22, 29.80, 28.43, 23.77, 22.43, 21.60, 14.16. MS (EI): m/z = 452 $[M]^+$, HRMS calculated for $C_{28}H_{40}N_2O_3$ $[M]^+$: 452.6390; found 452.3035.

2.5 (*S*)-2-Amino-3-(dimethylamino)-1,1-diphenylpropan-1-ol (Y1)

A 6 mL vial was charged with **6a** (1.0 mmol) and 4M HCl/EtOAc (1 mL). The reaction mixture stir for 3 h at room temperature. The reaction mixture was quenched with 2M NaOH at 0 ℃ and extracted with EtOAc (3 × 3 mL). The organic layer was washed with water (3 × 3 mL) and brine and then dried with Na2SO4, and the solvent was evaporated, to provide di-amino alcohol **Y1**. White solid. 79% yield. mp 103-108 °C. $[\alpha]_D^{20}$ = −95.87 (c = 0.3, $CHCl_3$). IR (neat) 3735, 2921, 1035, 746, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.59-7.61 (m, 2H), 7.48-7.50 (m, 2H), 7.25-7.33 (m, 4H), 7.15-7.21 (m, 2H), 3.98 (q, *J* = 4.1 Hz, 1H), 2.43 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.19 (s, 6H), 2.01 (dd, *J* = 12.7, 3.9 Hz, 1H), 1.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 146.69, 144.99, 128.41, 128.23, 126.73, 126.57, 126.13, 126.02, 125.68, 78.96, 60.44, 54.16, 46.17, 29.81. MS (FAB): m/z = 270 $[M+H]^+$, HRMS calculated for $C_{17}H_{22}N_2O$ $[M+H]^+$: 270.3760; found 271.1820.

2.6 General procedure for the synthesis of Thiourea fused γ-amino alcohol organocatalysts Z1-16.

To a solution of amino alcohol (1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise isothiocyanate (1.8 mmol) at 0 °C under an argon atmosphere. After stirring the reaction mixture for 18 h at room temperature the solvent was removed under reduced pressure and residue was purified by flash chromatography (CHCl3/MeOH, 98:2) to provide Thiourea fused γ-amino alcohol organocatalysts **Z1-16**.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)thiourea (Z1)

White solid. 57% yield. mp 115-119 °C. $[\alpha]_D^{20}$ = -113.53 (c = 0.3, $CHCl_3$). IR (neat) 3627, 2949, 1273, 1521, 1472, 1123, 765, 699 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.67 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 4H), 7.44 (d, *J* = 5.4 Hz, 2H), 7.29-7.34 (m, 3H), 7.19 (q, *J* = 7.7 Hz, 3H), 5.46 (s, 1H), 3.03 (d, *J* = 14.3 Hz, 1H), 2.61 (d, *J* = 14.0 Hz, 1H), 2.05 (s, 7H), 1.25 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.36, 145.55, 144.39, 138.55, 128.73, 127.19, 125.09, 124.04, 123.87, 119.67, 82.31, 58.78, 58.42, 47.33, 32.02, 29.80. MS (EI): m/z = 541 $[M]^+$, HRMS calculated for $C_{26}H_{25}F_6N_3OS$ $[M]^+$: 541.5564; found 541.1616.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(diethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)thiourea (Z2)

White solid. 71% yield. mp 68-72 °C. $[\alpha]_D^{20}$ = -56.87 (c = 0.3, $CHCl_3$). IR (neat) 3566, 2969, 1507, 1472, 1375, 1275, 747, 701 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.71 (s, 1H), 7.39-7.56 (m, 6H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.13-7.23 (m, 4H), 5.49 (s, 1H),

3.22 (d, *J* = 12.0 Hz, 1H), 2.79 (d, *J* = 14.0 Hz, 1H), 2.34 (s, 4H), 1.27 (d, *J* = 23.5 Hz, 2H), 0.76-0.89 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.27, 145.67, 144.84, 138.45, 132.91, 128.68, 128.60, 127.17, 127.02, 125.20, 124.70, 124.57, 123.91, 121.72, 119.90, 81.80, 58.61, 54.03, 47.65, 29.80, 10.53. MS (EI): m/z = 569 $[M]^+$, HRMS calculated for $C_{28}H_{29}F_6N_3OS$ $[M]^+$: 569.6104; found 569.1941.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)thiourea (Z3)

White solid. 71% yield. mp 149-151 °C. $[\alpha]_D^{20}$ = -86.00 (c =0.5, $CHCl_3$). IR (neat) 3648, 2970, 1508, 1456, 1274, 1133, 884, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.69 (s, 1H), 7.42-7.51 (m, 7H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.23-7.25 (m, 3H), 7.14-7.20 (m, 2H), 5.44 (s, 1H), 3.10 (d, *J* = 13.5 Hz, 1H), 2.86 (d, *J* = 13.7 Hz, 1H), 2.39 (d, *J* = 74.0 Hz, 4H), 1.67 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.31, 145.60, 144.41, 138.54, 133.13, 132.86, 128.69, 128.57, 127.10, 124.99, 124.37, 123.87, 121.70, 119.79, 82.20, 58.83, 55.82, 55.48, 23.76. MS (EI): m/z = 567 $[M]^+$, HRMS calculated for $C_{28}H_{27}F_6N_3OS$ $[M]^+$: 567.5944; found 567.1769.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-1,1-diphenyl-3-(piperidin-1-yl)propan-2-yl)thiourea (Z4)

White solid. 71% yield. mp 149-152 °C. $[\alpha]_D^{20}$ = -80.92 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2969, 1520, 1448, 1365, 1216, 745, 701 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.36 (s, 1H),7.70 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 4H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.12-7.22 (m, 4H), 5.44 (s, 1H), 1.99-3.09 (m, 6H), 1.22-1.48 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.37, 145.73, 144.52, 138.59, 133.08, 132.81, 128.68, 128.55, 127.12, 124.96, 124.50, 123.90, 121.73, 119.83, 81.77, 76.86, 58.62, 57.88, 56.48, 26.14, 23.44. MS (EI): m/z = 581 $[M]^+$, HRMS calculated for $C_{29}H_{29}F_6N_3OS$ $[M]^+$: 581.6214; found 581.1938.

(*S*)-1-(3-(Azepan-1-yl)-1-hydroxy-1,1-diphenylpropan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (Z5)

White solid. 49% yield. mp 150-152 °C. $[\alpha]_D^{20}$ = -48.12 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2948, 1508, 1456, 1273, 1131, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.72 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.48 (s, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.13-7.31 (m, 7H), 5.41 (s, 1H), 3.30 (d, *J* = 14.0 Hz, 1H), 2.67 (d, *J* = 13.7 Hz, 1H), 2.29-2.48 (m, 6H), 1.36-1.53 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.19, 145.76, 144.71, 138.17, 133.32, 133.06, 128.64, 128.57, 127.11, 125.05, 124.82, 123.83, 121.66, 120.19, 81.88, 58.95, 58.31, 57.84, 27.80, 26.52. MS (EI): m/z = 595 $[M]^+$, HRMS calculated for $C_{30}H_{31}F_6N_3OS$ $[M]^+$: 595.2032; found 595.2087.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-o-tolylpropan-2-yl)thiourea (Z6)

White solid. 39% yield. mp 77-81 °C. $[\alpha]_D^{20}$ = -124.53 (c = 0.3, $CHCl_3$). IR (neat) 3669, 2968, 1508, 1456, 1275, 1132, 741, 701, 680 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.97-8.44 (1H), 8.17-7.76 (1H), 7.60 (d, *J* = 38.7 Hz, 3H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.16 (q, *J* = 7.0 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 5.53 (s, 1H), 3.03 (dd, *J* = 13.6, 2.7 Hz, 1H), 2.27-2.54 (m, 4H), 1.94-2.02 (m, 6H), 1.68 (s, 4H), 1.23-1.31 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 178.86, 141.11, 133.24, 132.88, 132.77, 127.79, 125.16, 124.51, 123.84, 55.86, 55.66, 29.79, 23.71, 22.00, 21.44, 14.21. MS (EI): m/z = 595 $[M]^+$, HRMS calculated for $C_{30}H_{31}F_6N_3OS$ $[M]^+$: 595.6484; found 595.2096.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-m-tolylpropan-2-yl)thiourea (Z7)

White solid. 69% yield. mp 90-95 °C. $[\alpha]_D^{20}$ = -86.87 (c = 0.3, $CHCl_3$). IR (neat) 3648, 2968, 1507, 1456, 1276, 1229, 788, 699, 682 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.67 (s, 1H), 7.47 (s, 2H), 7.28-7.31 (m, 2H), 7.13-7.24 (m, 3H), 6.97-7.08 (m, 3H), 5.38 (s, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 2.84 (d, *J* = 13.5 Hz, 1H), 2.31-2.61 (m, 7H), 2.19-2.24 (m, 3H), 1.71 (d, *J* = 45.5 Hz, 5H), 1.26-1.36 (m, 1H), 0.81-0.86 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.29, 145.59, 144.32, 138.75, 138.26, 133.07, 132.80, 128.54, 128.25, 127.93, 127.83, 126.14, 125.64, 124.09, 123.90, 122.04, 121.74, 119.55, 82.28, 60.62, 58.87, 55.80, 55.46, 29.80, 23.76, 21.73, 21.56, 21.16, 14.25, 14.16. MS (EI): m/z = 595 $[M]^+$, HRMS calculated for $C_{30}H_{31}F_6N_3OS$ $[M]^+$: 595.6484; found 595.2095.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-p-tolylpropan-2-yl)thiourea (Z8)

White solid. 32% yield. mp 96-98 °C. $[\alpha]_D^{20}$ = -64.52 (c = 0.5, $CHCl_3$). IR (neat) 3668, 2967, 1508, 1473, 1275, 1130, 808, 700, 681 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.64 (d, *J* = 37.2 Hz, 3H), 7.26-7.36 (m, 5H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 5.40 (s, 1H), 3.07 (d, *J* = 13.7 Hz, 1H), 2.87 (d, *J* = 13.5 Hz, 1H), 2.51 (s, 1H), 2.32 (s, 2H), 2.28 (s, 4H), 2.23 (s, 4H), 1.65 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.23, 142.91, 141.71, 138.92, 136.60, 133.21, 132.95, 132.67, 132.41, 129.36, 129.23, 128.86, 126.13, 124.93, 124.83, 124.15, 123.95, 121.79, 119.45, 82.19, 58.67, 55.82, 55.49, 34.22, 29.80, 23.72, 22.44, 21.03, 20.94, 14.16. MS (EI): m/z = 595 $[M]^+$, HRMS calculated for $C_{30}H_{31}F_6N_3OS$ $[M]^+$: 595.6484; found 595.2082.

(*S*)-1-(1,1-Bis(3,5-dimethylphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (Z9)

White solid. 75% yield. mp 97-100 °C. $[\alpha]_D^{20}$ = -97.53 (c = 0.3, $CHCl_3$). IR (neat) 3648, 2968, 1508, 1455, 1216, 1131, 884, 852, 700 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.65 (s, 1H), 7.52 (s, 2H), 7.07 (d, *J* = 16.6 Hz, 4H), 6.81 (d, *J* = 7.4 Hz, 2H), 5.34 (s, 1H), 3.07 (d, *J* = 12.6 Hz, 1H), 2.82 (d, *J* = 12.9 Hz, 1H), 2.15-2.49 (m, 17H), 1.67 (s, 5H), 1.25 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.33, 145.53, 144.24, 138.94, 138.06, 137.84, 133.04, 132.77, 128.82, 128.71, 123.79, 122.93, 122.75, 121.76, 119.32, 82.34, 60.59, 58.98, 55.78, 55.44, 29.80, 23.75, 21.61, 21.48, 14.26. MS (EI): m/z = 623 $[M]^+$, HRMS calculated for $C_{32}H_{35}F_6N_3OS$ $[M]^+$: 623.7024; found 623.2414.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-phenylthiourea (Z10)

White solid. 88% yield. mp 164-168 °C. $[\alpha]_D^{20}$ = -22.00 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2965, 1515, 1447, 1290, 1126, 746, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.91 (s, 1H), 7.64 (s, 1H), 7.57 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.52 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.29-7.35 (m, 4H), 7.15-7.23 (m, 5H), 6.71 (d, *J* = 7.4 Hz, 1H), 6.49-6.51 (m, 2H), 5.36 (q, *J* = 2.4 Hz, 1H), 3.21 (dd, *J* = 13.9, 2.4 Hz, 1H), 2.85 (dd, *J* = 14.0, 2.6 Hz, 1H), 2.31 (s, 3H), 1.63 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.42, 145.89, 145.28, 135.48, 130.16, 128.61, 128.53, 127.46, 126.98, 126.96, 125.14, 125.10, 81.89, 59.45, 55.51, 55.31, 23.84, 22.43, 14.16. MS (EI): m/z = 431 $[M]^+$, HRMS calculated for $C_{26}H_{29}N_3OS$ $[M]^+$: 431.5980; found 431.2037.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(naphthalen-1-yl)thiourea (Z11)

White solid. 80% yield. mp 92-95 °C. $[\alpha]_D^{20}$ = -22.00 (c =0.5, $CHCl_3$). IR (neat) 3647, 2969, 1508, 1447, 1228, 1216, 783, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.95 (s, 1H), 7.78-7.84 (m, 3H), 7.46-7.50 (m, 3H), 7.33-7.37 (m, 3H), 7.20-7.27 (m, 5H), 7.12-7.17 (m, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.43 (d, *J* = 7.2 Hz, 1H), 5.38 (q, *J* = 2.5 Hz, 1H), 3.09 (dd, *J* = 13.6, 2.7 Hz, 1H), 2.79 (dd, *J* = 13.6, 2.4 Hz, 1H), 2.17 (d, *J* = 16.8 Hz, 3H), 1.47-1.49 (m, 4H), 1.24-1.32 (m, 1H), 0.86-0.89 (m, 1H). ^{13}C NMR (125

MHz, $CDCl_3$, ppm): δ 180.56, 145.92, 145.00, 134.52, 131.28, 130.18, 129.01, 128.51, 128.37, 127.28, 126.88, 126.82, 125.72, 125.40, 125.16, 125.10, 122.22, 81.73, 59.04, 55.45, 55.39, 34.22, 23.68, 22.44, 14.18. MS (EI): m/z = 481 $[M]^+$, HRMS calculated for $C_{30}H_{31}N_3OS$ $[M]^+$: 481.6580; found 481.2196.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(2-(trifluoromethyl)phenyl)thiourea (Z12)

White solid. 91% yield. mp 77-82 °C. $[\alpha]_D^{20}$ = -5.87 (c = 0.3, $CHCl_3$). IR (neat) 3669, 2968, 1507, 1456, 1230, 767, 704 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (qd, *J* = 8.2, 1.1 Hz, 4H), 7.36-7.39 (m, 3H), 7.24-7.32 (m, 4H), 7.16-7.20 (m, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 5.4 Hz, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.36 (d, *J* = 6.0 Hz, 1H), 3.25 (dd, *J* = 13.9, 2.4 Hz, 1H), 2.84 (dd, *J* = 13.9, 2.4 Hz, 1H), 2.31 (s, 3H), 1.62 (s, 4H), 1.23-1.30 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.80, 145.67, 145.47, 133.66, 133.54, 128.65, 128.28, 127.53, 127.22, 127.18, 127.09, 127.04, 125.98, 125.74, 125.09, 124.98, 124.29, 122.12, 81.87, 77.40, 77.15, 76.90, 59.65, 55.47, 55.06, 31.68, 23.87, 22.75, 22.43, 14.16. MS (EI): m/z = 499 $[M]^+$, HRMS calculated for $C_{27}H_{28}F_3N_3OS$ $[M]^+$: 499.5962; found 499.1914.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(3-(trifluoromethyl)phenyl)thiourea (Z13)

White solid. 70% yield. mp 73-76 °C. $[\alpha]_D^{20}$ = -43.2 (c = 0.3, $CHCl_3$). IR (neat) 3669, 2969, 1507, 1447, 1345, 1228, 747, 701 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.13 (s, 1H), 7.54-7.56 (m, 2H), 7.49 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.27-7.32 (m, 5H), 7.15-7.21 (m, 3H), 6.86 (s, 1H), 6.64 (d, *J* = 7.4 Hz, 1H), 5.39 (s, 1H), 3.18 (dd, *J* = 13.9, 1.9 Hz, 1H), 2.87 (dd, *J* = 14.0, 2.3 Hz, 1H), 2.37 (d, *J* = 49.0 Hz, 4H), 1.65 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.35, 145.73, 144.99, 136.67, 132.58, 132.33, 130.66, 128.64, 128.59, 128.23, 127.08, 127.01, 125.04, 124.49, 123.73, 122.33, 121.74, 81.93, 59.31, 55.65, 55.34, 34.21, 23.81, 22.43, 14.16. MS (EI): m/z = 499 $[M]^+$, HRMS calculated for $C_{27}H_{28}F_3N_3OS$ $[M]^+$: 499.5962; found 499.1915.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (Z14)

White solid. 86% yield. mp 95-97 °C. $[\alpha]_D^{20}$ = -15.54 (c = 0.5, $CHCl_3$). IR (neat) 3668, 2969, 1507, 1365, 1228, 805, 700 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.79 (d, *J* = 201.6 Hz, 2H), 7.48-7.58 (m, 4H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.32 (q, *J* = 7.5 Hz, 4H), 7.15-7.25 (m, 2H), 7.02 (d, *J* = 38.1 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 2H), 5.38 (s, 1H), 3.25 (dd, *J* = 13.9, 1.9 Hz, 1H), 2.88 (dd, *J* = 13.7, 2.3 Hz, 1H), 2.33 (s, 4H), 1.64 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 179.01, 145.59, 145.27, 139.46, 128.69, 128.28, 128.02, 127.24, 127.10, 125.10, 124.99, 124.89, 123.51, 122.72, 81.92, 59.57, 55.66, 55.19, 23.82, 22.42, 14.16. MS (EI): m/z = 499 $[M]^+$, HRMS calculated for $C_{27}H_{28}F_3N_3OS$ $[M]^+$: 499.5962; found499.1914.

(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(4-nitrophenyl)thiourea (Z15)

White solid. 86% yield. mp 100-104 °C. $[\alpha]_D^{20}$ = -20.00 (c = 0.5, $CHCl_3$). IR (neat) 3648, 2968, 1507, 1365, 1228, 803, 702 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.99 (d, *J* = 8.9 Hz, 3H), 7.58-7.61 (m, 4H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.25-7.29 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 2H), 5.37 (s, 1H), 3.29 (d, *J* = 13.7 Hz, 1H), 2.89 (dd, *J* = 14.0, 2.3 Hz, 1H), 2.33 (s, 3H), 1.62 (d, *J* = 39.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 178.78, 145.37, 144.59, 142.30, 128.87, 128.78, 127.45, 127.20, 125.86, 125.05, 124.90, 122.20, 81.94, 59.84, 55.72, 54.86, 23.83. MS (FAB): m/z = 476 $[M]^+$, HRMS calculated for $C_{26}H_{28}N_4O_3S$ $[M]^+$: 4765.5950; found 477.1965.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-yl)thiourea (Z16)

White solid. 99% yield. mp 146-147 °C. $[\alpha]_D^{20}$ = 9.68(c = 0.5, $CHCl_3$). IR (neat) 3648, 2969, 1507, 1366, 1228, 702 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.82 (s, 1H), 7.66-7.70 (m, 3H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.18-7.31 (m, 6H), 7.11-7.15 (m, 1H), 6.81 (d, *J* = 9.5 Hz, 1H), 5.58 (d, *J* = 9.5 Hz, 1H), 2.75 (s, 1H), 1.60 (s, 1H), 0.88 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 180.74, 146.19, 145.03, 138.16, 133.33, 133.05, 132.78, 128.43, 128.40, 127.27, 127.17, 126.06, 125.27, 124.94, 124.31, 123.88, 121.71, 119.70, 119.54, 83.78, 66.28, 38.66, 29.98. MS (EI): m/z = 540 $[M]^+$, HRMS calculated for $C_{27}H_{26}F_6N_2OS$ $[M]^+$: 540.1670; found 540.1682.

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1,1-diphenyl-3-(pyrrolidin-1-yl)-1-((trimethylsilyl)oxy)propan-2-yl)thiourea (Z17)

To a solution of **Z3** (0.1 mmol) in $CHCl_3$(1.5 mL) was added dropwise chlorotrimethylsilane (0.12 mmol) and Et_3N (0.13 mmol) at -30 °C under an argon atmosphere. After stirring the reaction mixture for 24 h at room temperature., the solvent was removed under reduced pressure and residue was purified by flash chromatography (CHCl3/MeOH, 98:2) to provide Thiourea fused γ-amino alcohol organocatalysts **Z17**. White solid. 74% yield. mp 63-66 °C. $[\alpha]_D^{20}$ = -47.23 (c = 0.3, $CHCl_3$). IR (neat) 3648, 2969, 1507, 1446, 1365, 1216, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.05 (s, 2H), 7.59 (s, 1H), 7.33-7.39 (m, 10H), 6.56 (d, *J* = 4.3 Hz, 1H), 4.63 (dd, *J* = 8.0, 5.2 Hz, 1H), 2.81-2.88 (m, 3H), 2.49-2.64 (m, 3H), 1.79-1.85 (m, 4H), -0.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 183.34, 142.44, 142.37, 142.17, 131.89, 131.62, 128.53, 128.45, 128.36, 128.18, 127.97, 126.60, 124.43, 123.04, 122.26, 117.57, 82.41, 61.97, 60.31, 54.22, 23.60, 1.94. MS (EI): m/z = 639 $[M]^+$, HRMS calculated for $C_{31}H_{35}F_6N_3OSSi$ $[M]^+$: 639.7764; found 639.2166.

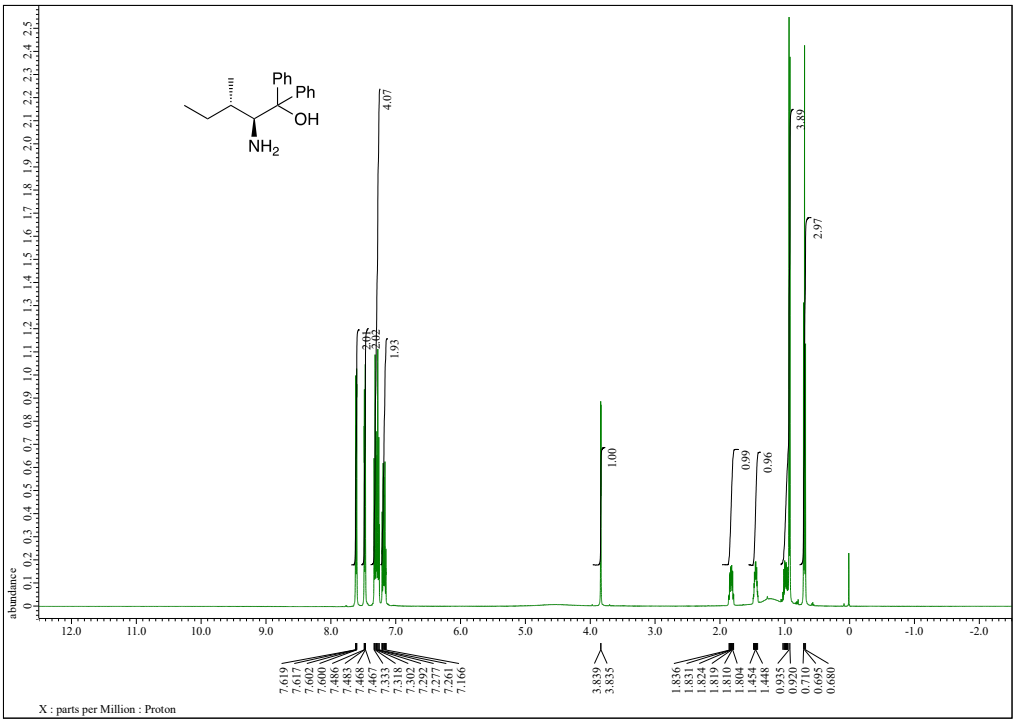
2.7 General Procedure for the catalytic asymmetric Mannich reaction of β-Keto carbonyl compounds with N-Boc imines.

To a solution of the corresponding catalyst (15 mol%) in solvent (1.0 mL) was added N-Boc imine (0.10 mmol) and β-keto carbonyl compounds (0.12 mmol) at -60 ℃ under an argon atmosphere and the solution was stirred at same temperature. After 16 h, the solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography. (n-hexane/EtOAc = 25:1 to 8:1 to 6:1) to give the chiral Mannich products **12**-**18**. Compounds **12**-**18** are the known compounds and the structures were identified by spectral data which were in good agreement with those reported. The enantiomeric excess (ee) and diastereomieric ratio of the product was determined by using HPLC.

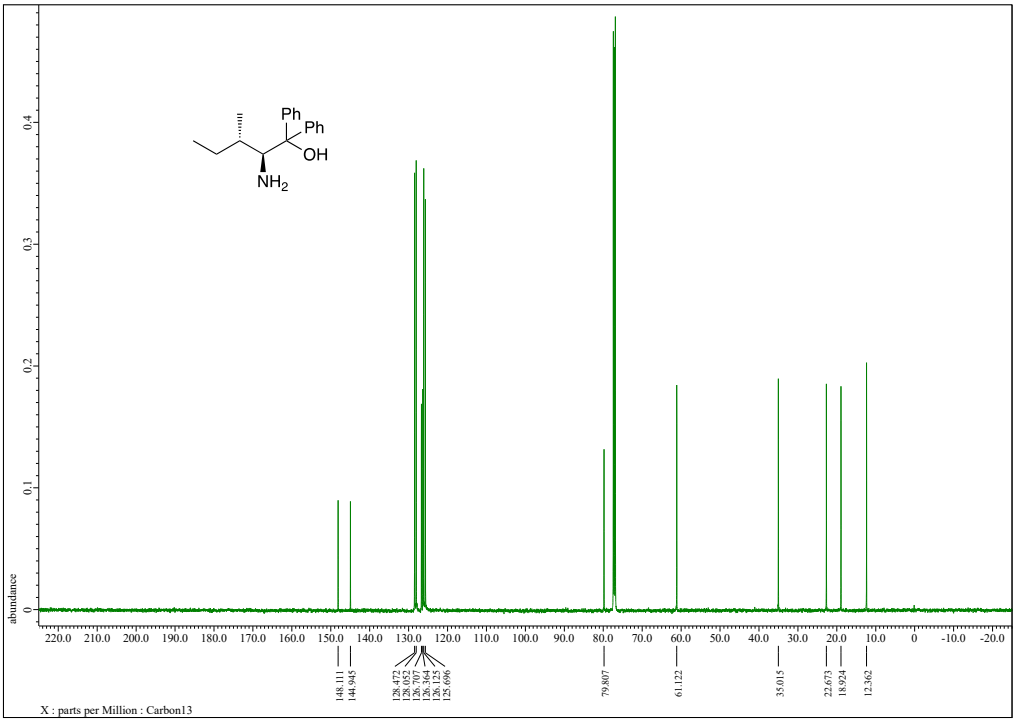
^{1}H-NMR and ^{13}C-NMR Spectra

(2*S*,3*S*)-2-Amino-3-methyl-1,1-diphenylpentan-1-ol (X5)

^{1}H-NMR

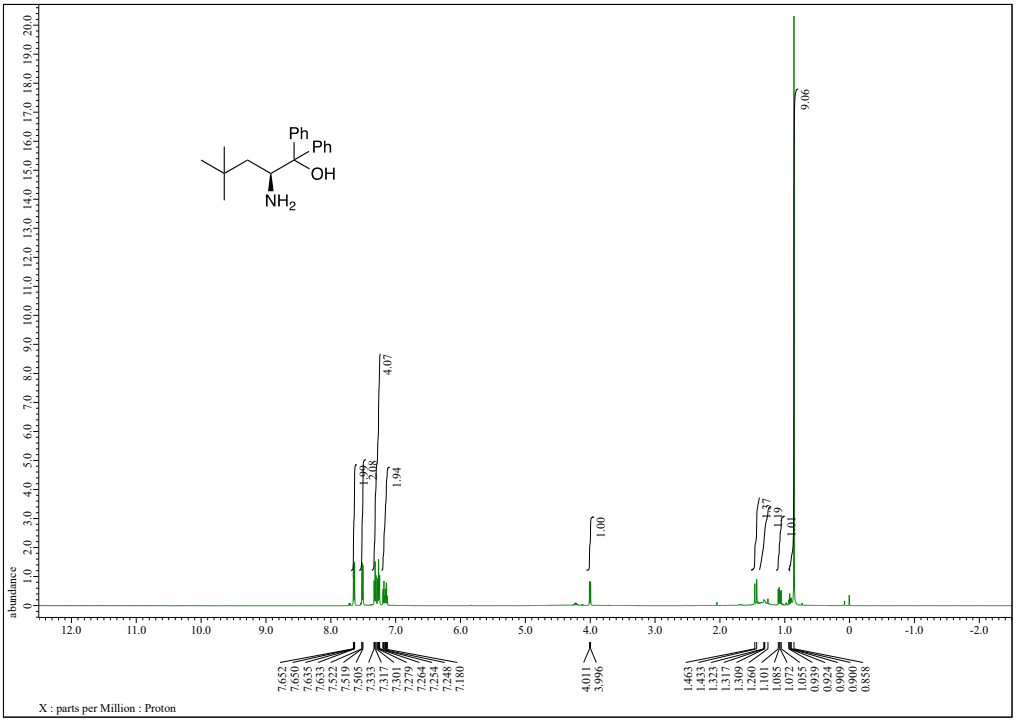


^{13}C-NMR

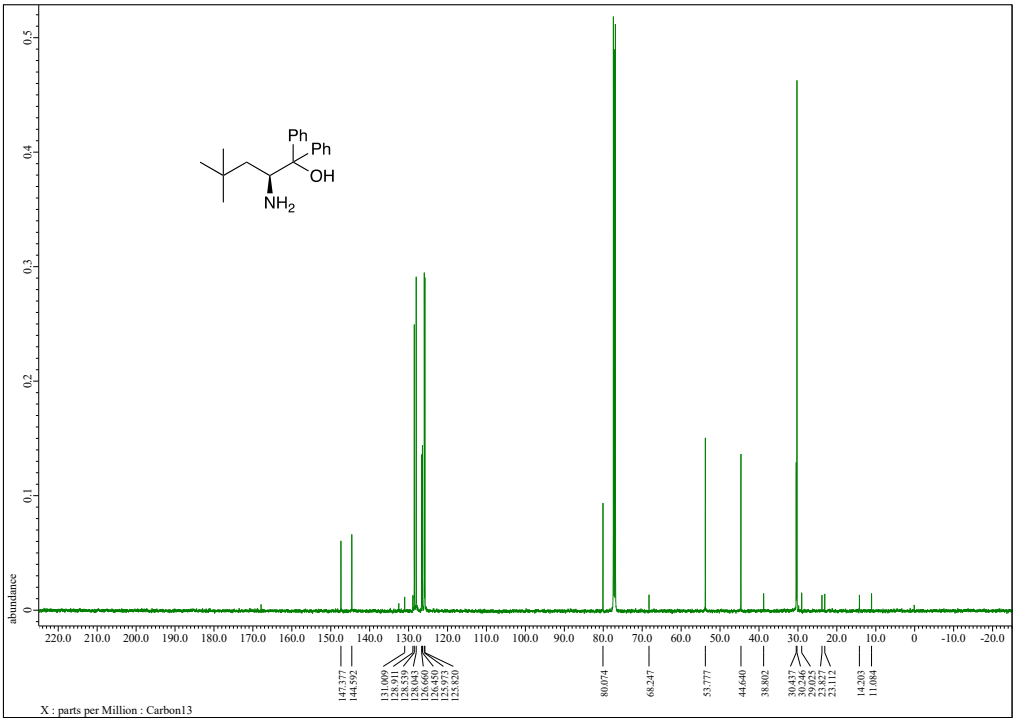


(*S*)-2-Amino-4,4-dimethyl-1,1-diphenylpentan-1-ol (X6)

^{1}H-NMR

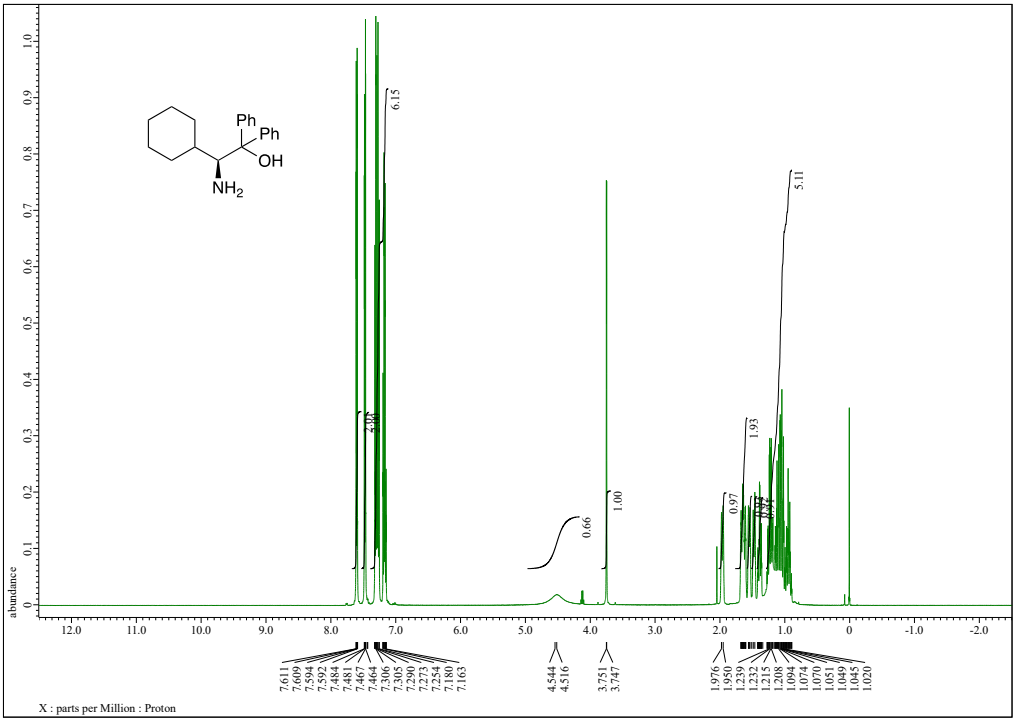


^{13}C-NMR

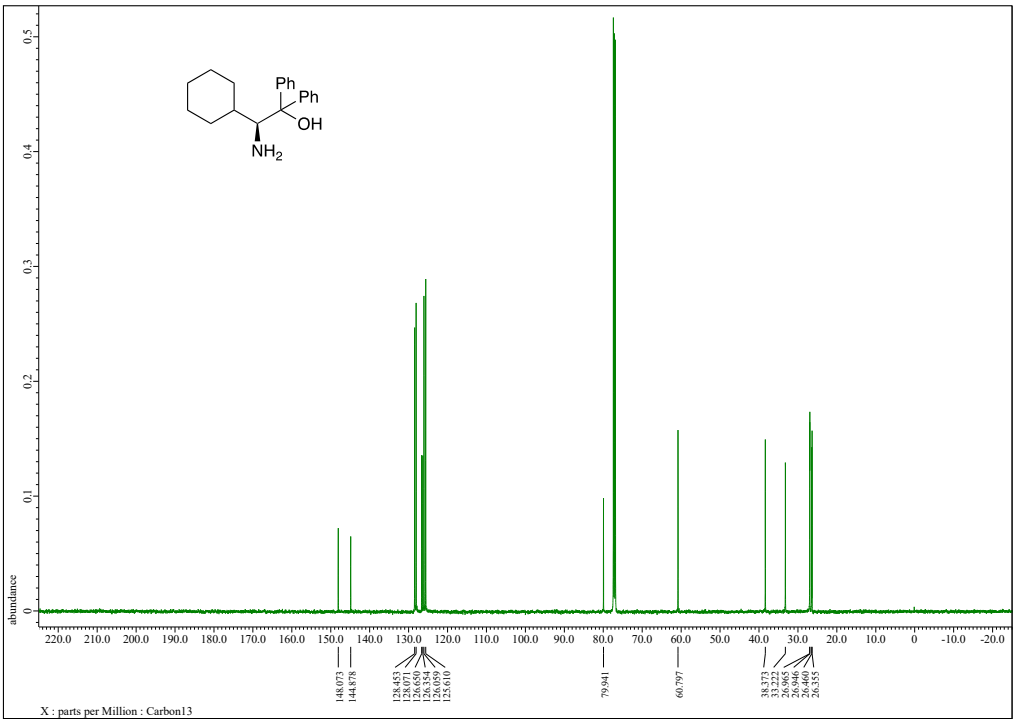


(*S*)-2-Amino-2-cyclohexyl-1,1-diphenylethan-1-ol (X7)

^{1}H-NMR

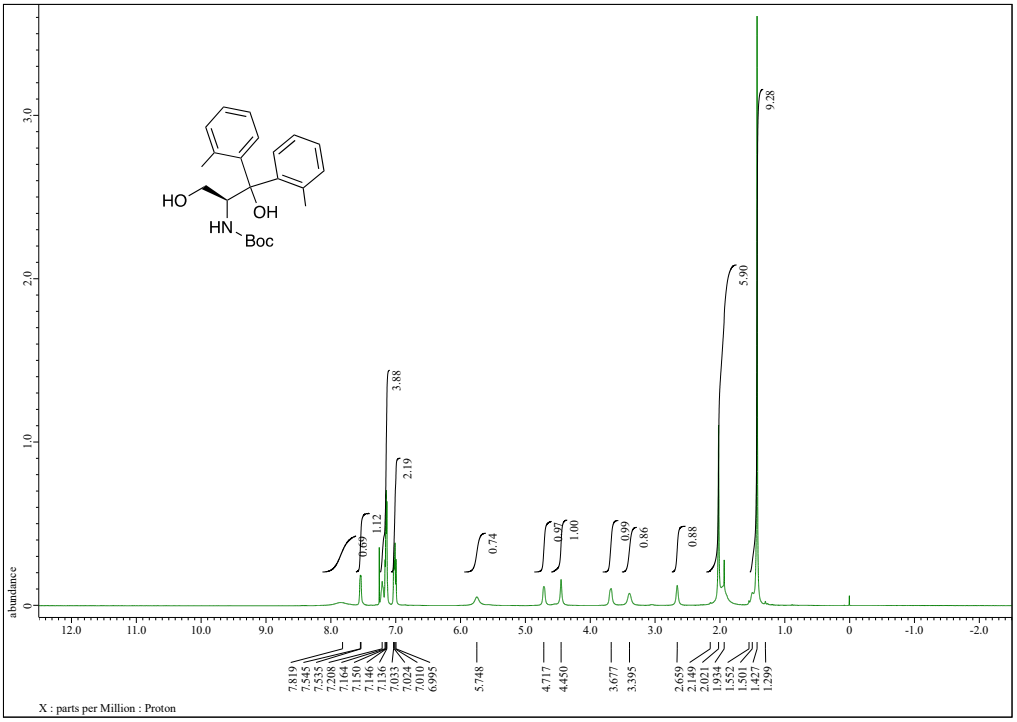


^{13}C-NMR

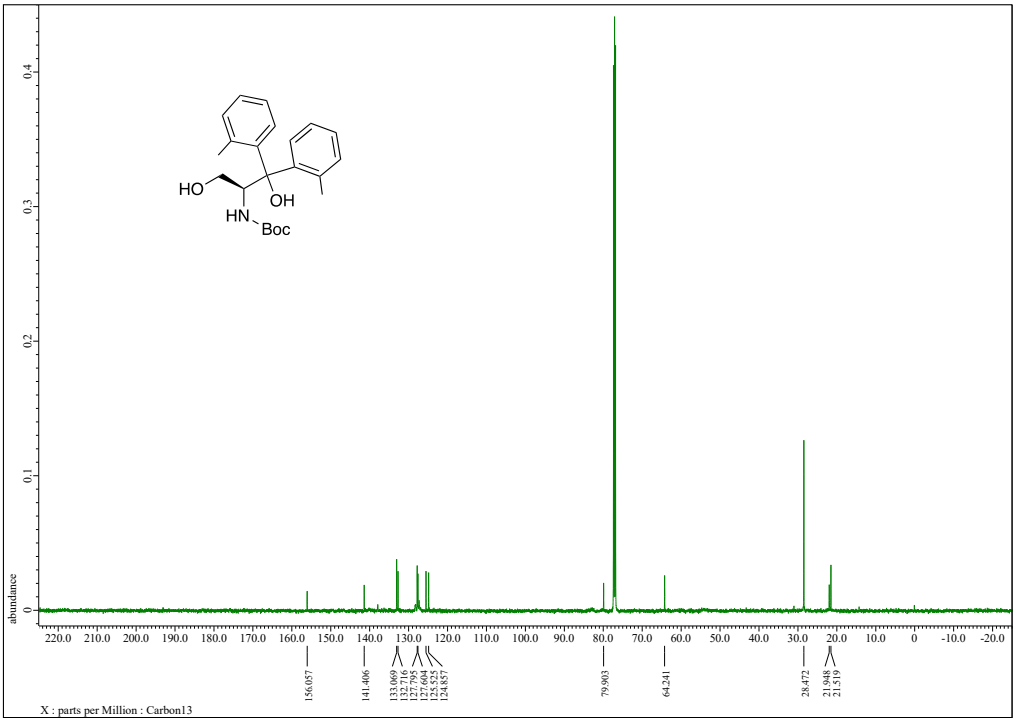


***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-o-tolylpropan-2-yl)carbamate (4b)**

^{1}H-NMR

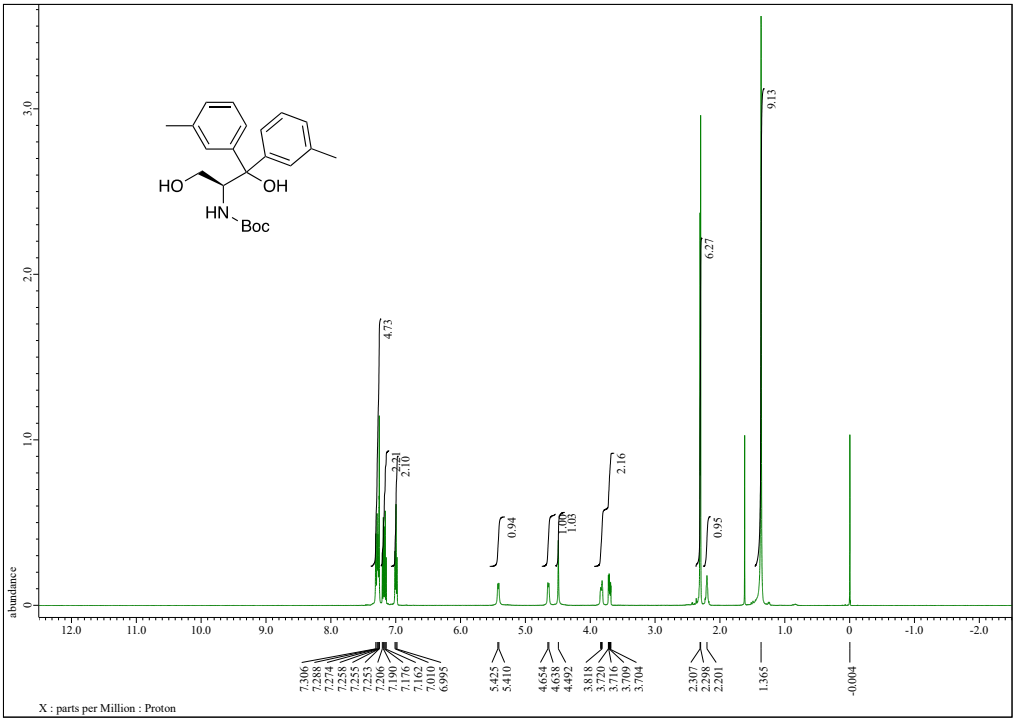


^{13}C-NMR

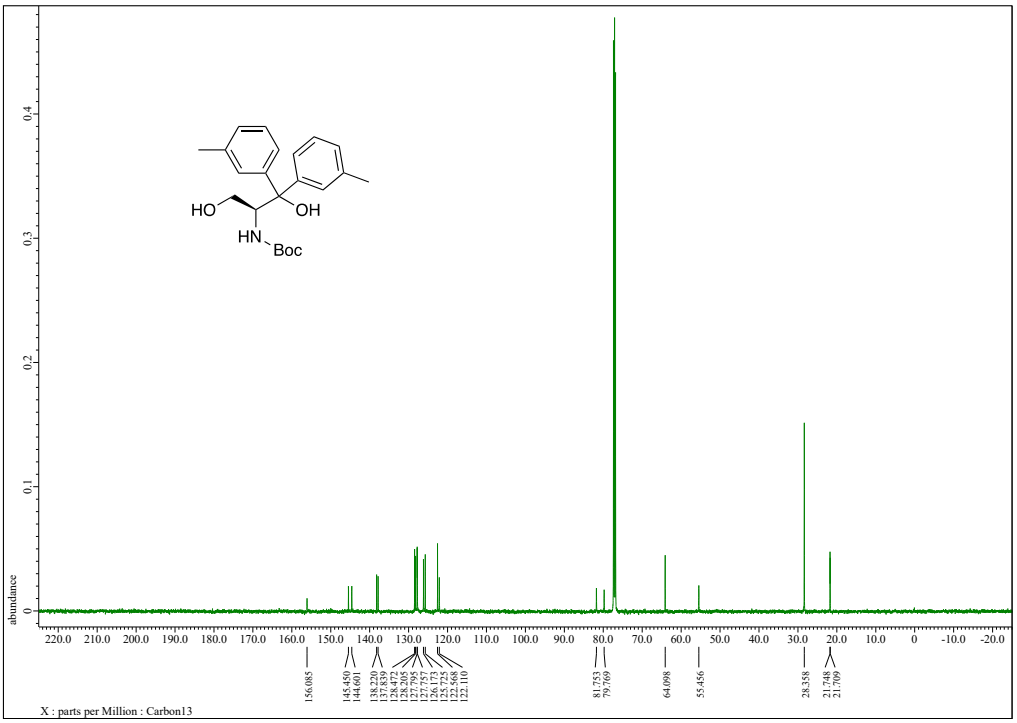


***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-m-tolylpropan-2-yl)carbamate (4c)**

^{1}H-NMR

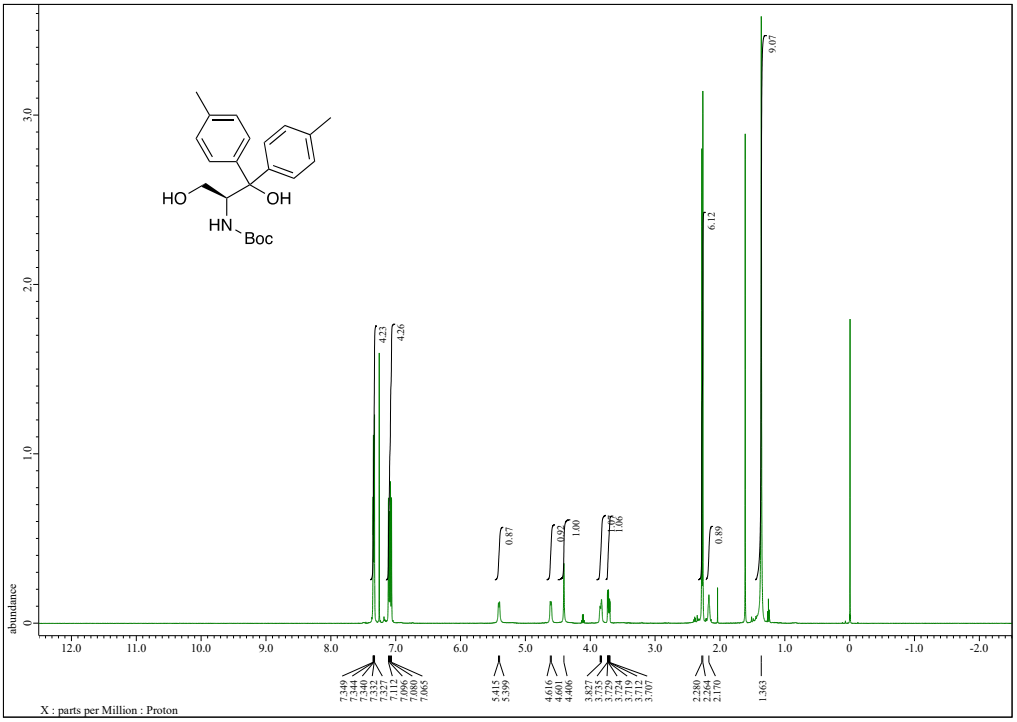


^{13}C-NMR

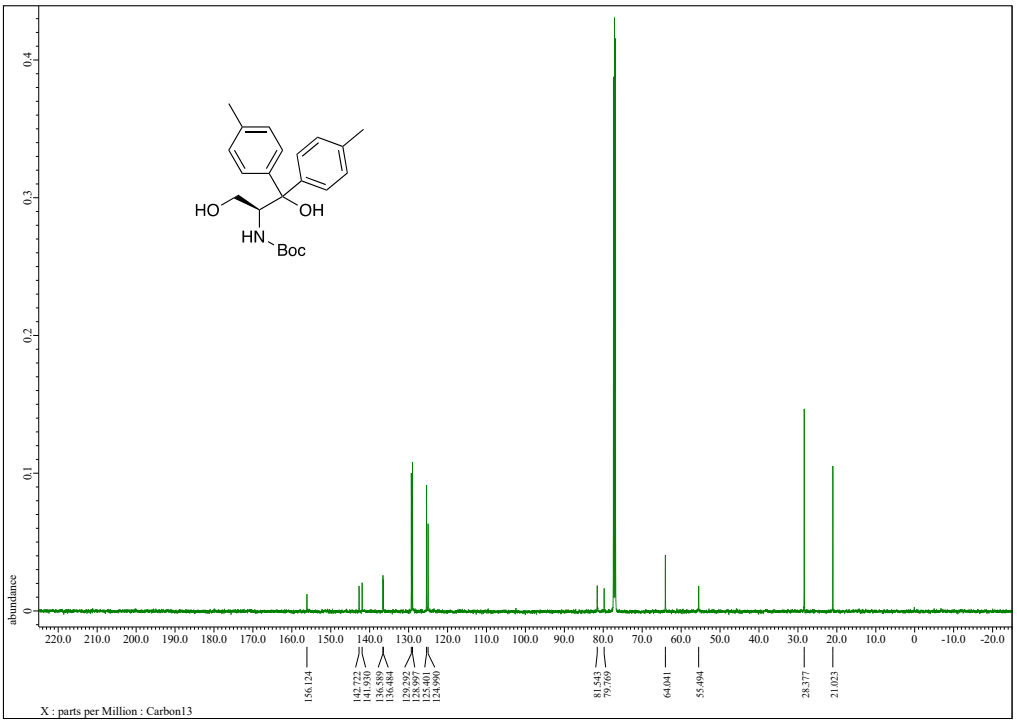


***tert*-Butyl (*S*)-(1,3-dihydroxy-1,1-di-p-tolylpropan-2-yl)carbamate (4d)**

^{1}H-NMR

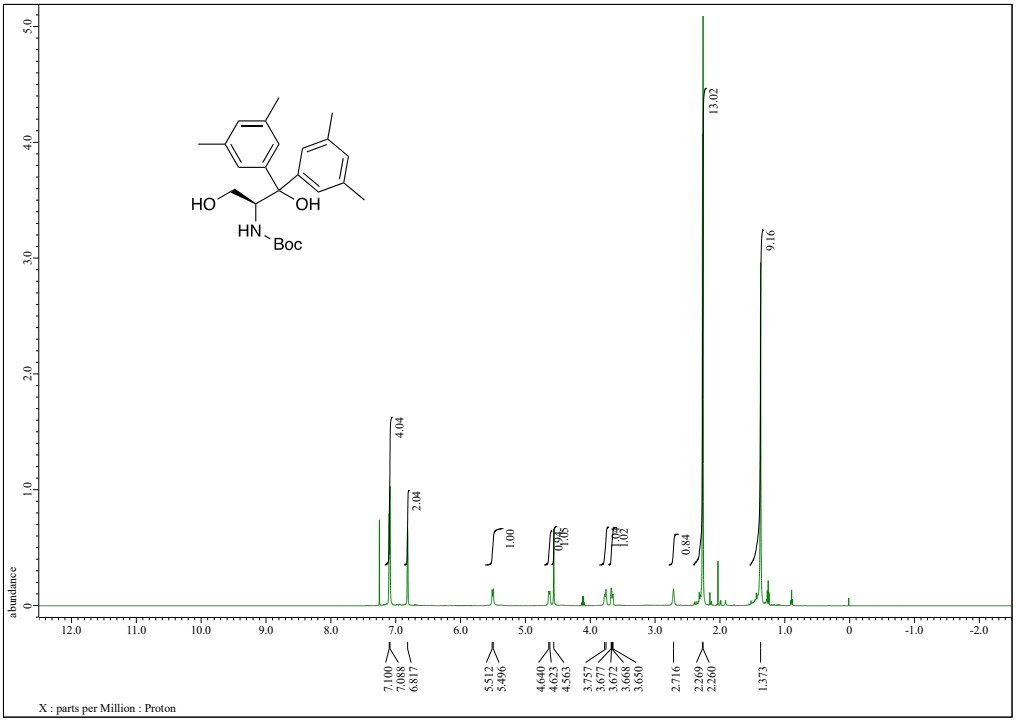


^{13}C-NMR

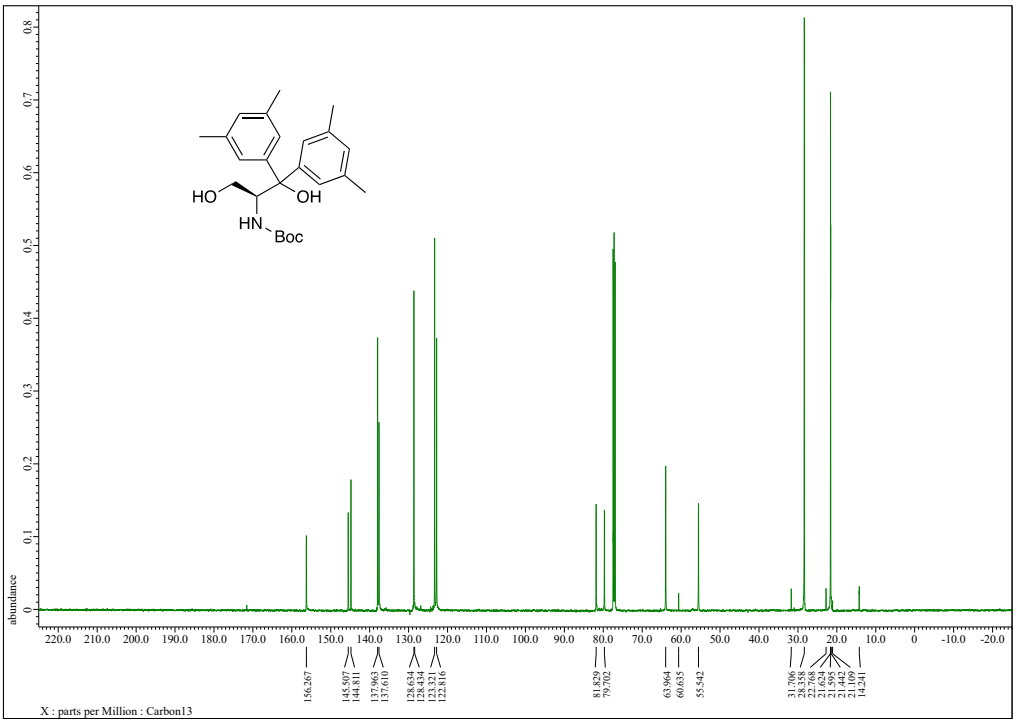


***tert*-Butyl (*S*)-(1,1-bis(3,5-dimethylphenyl)-1,3-dihydroxypropan-2-yl)carbamate (4e)**

^{1}H-NMR

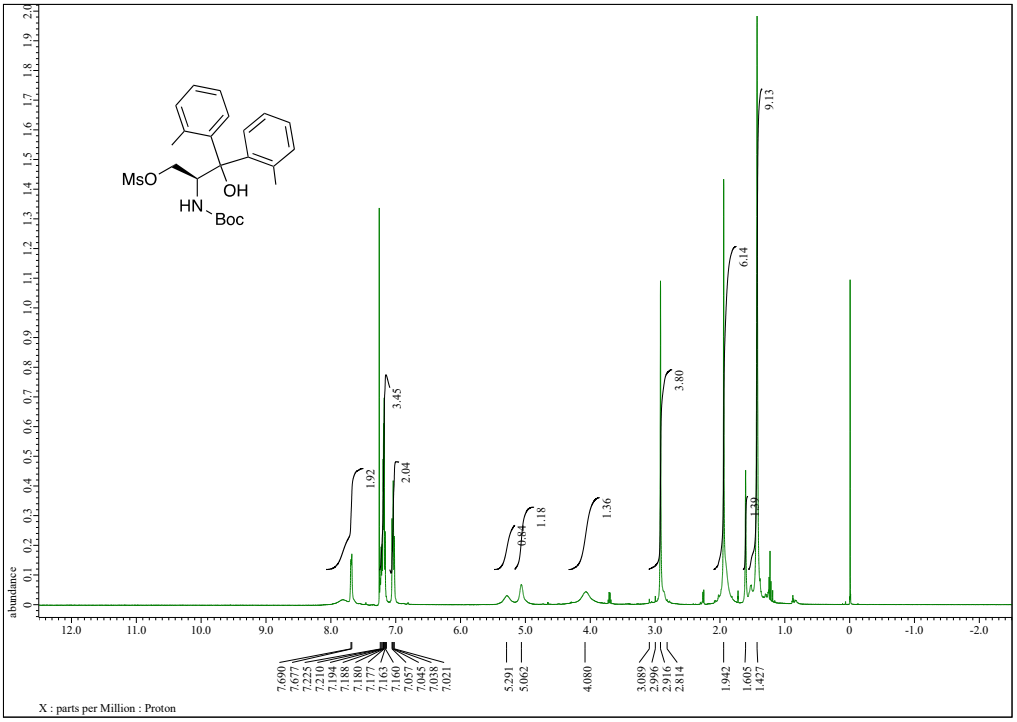


^{13}C-NMR

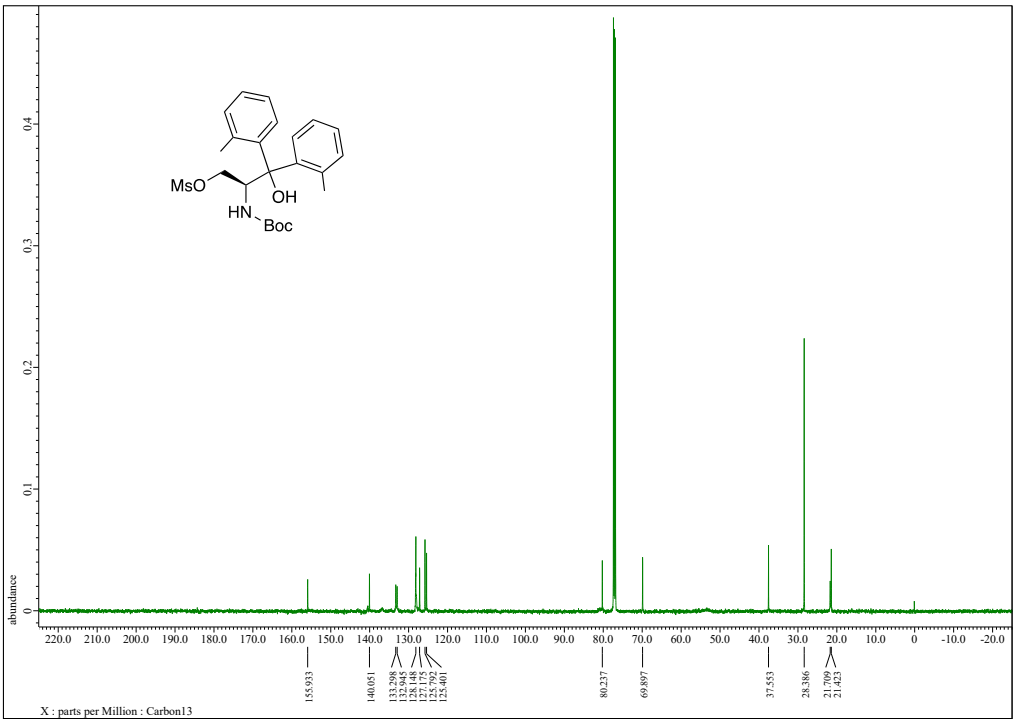


(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-o-tolylpropyl methanesulfonate (5b)

^{1}H-NMR

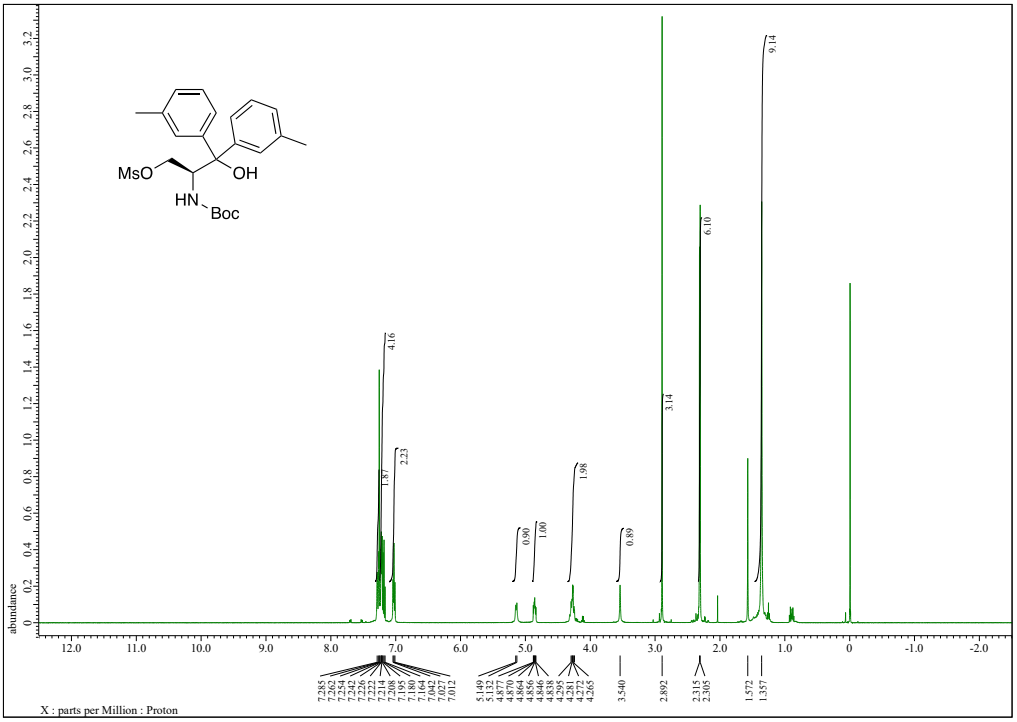


^{13}C-NMR

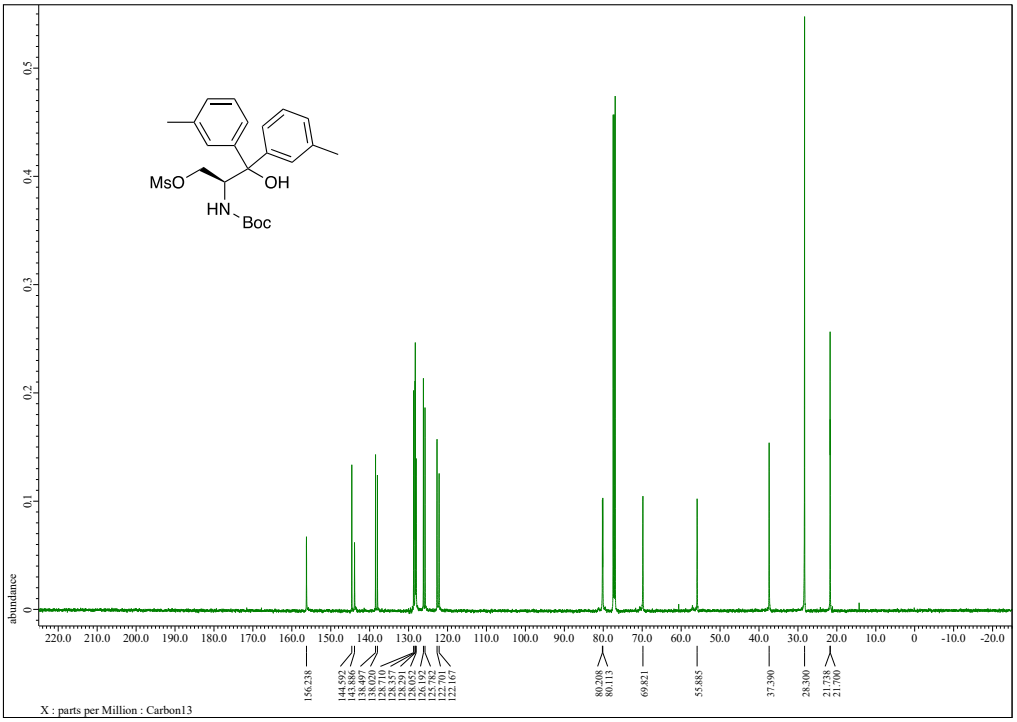


(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-m-tolylpropyl methanesulfonate(5c)

^{1}H-NMR

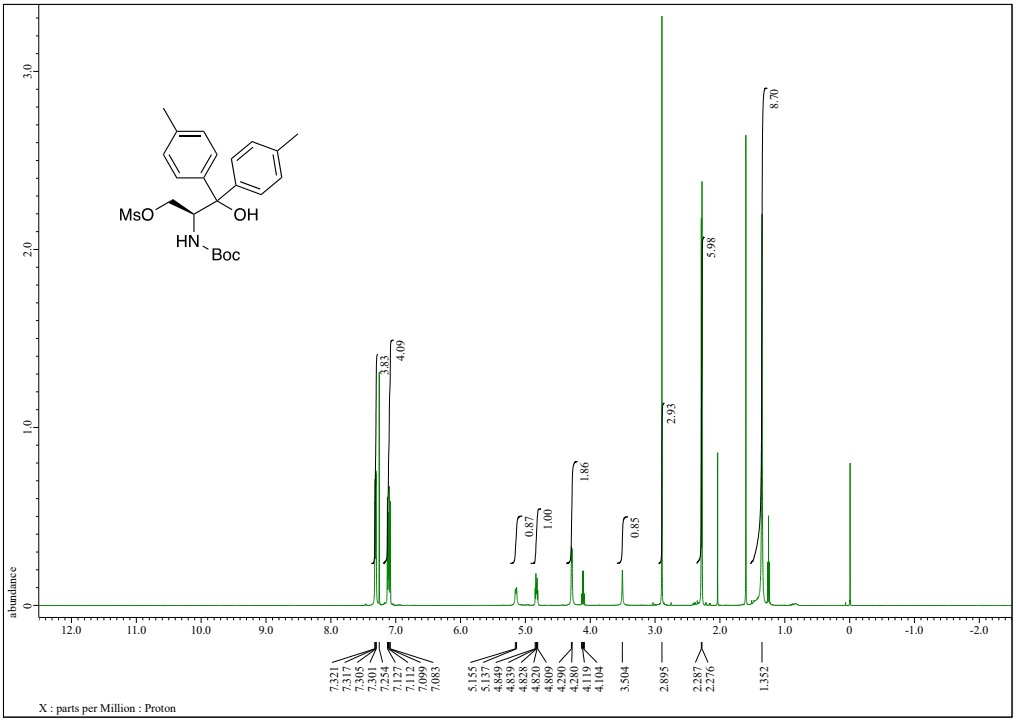


^{13}C-NMR

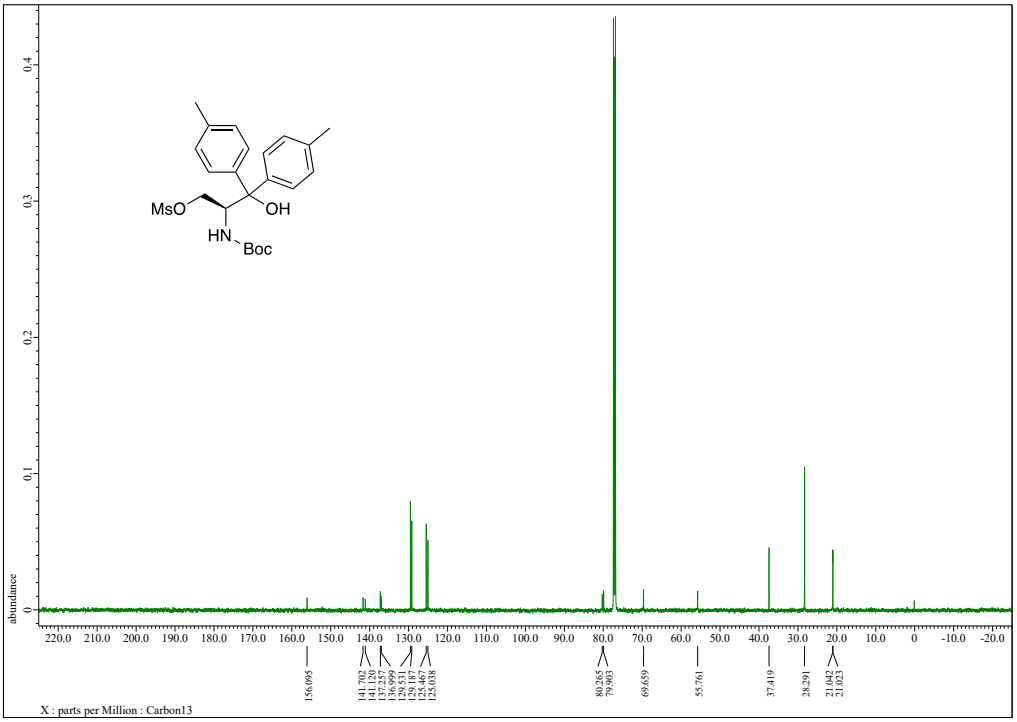


(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3,3-di-p-tolylpropyl methanesulfonate (5d)

^{1}H-NMR

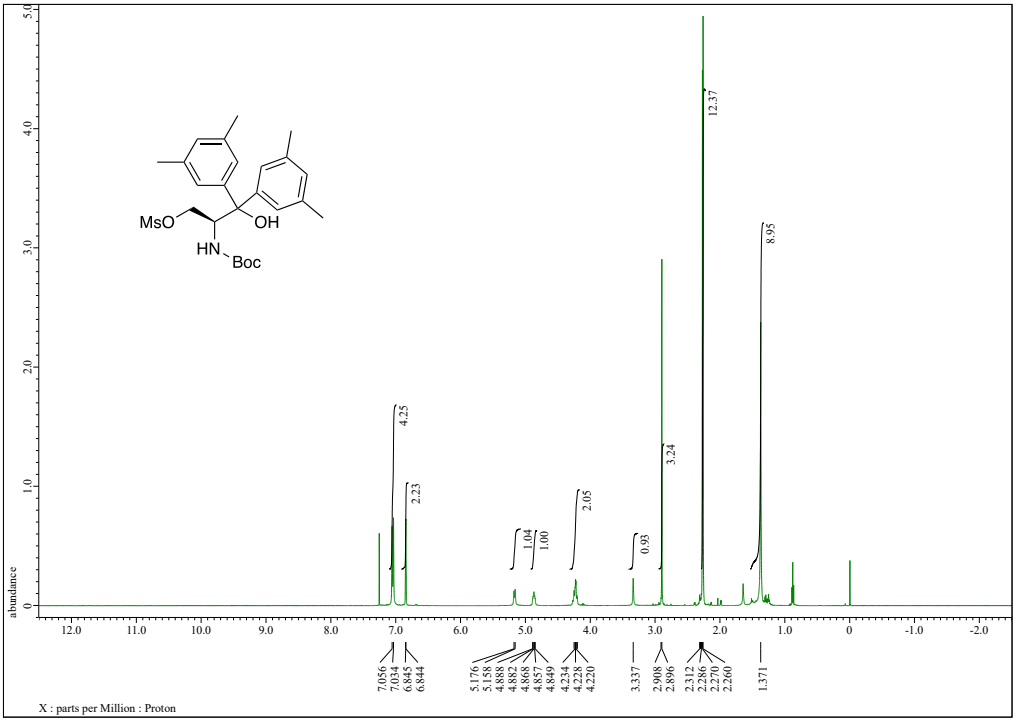


^{13}C-NMR

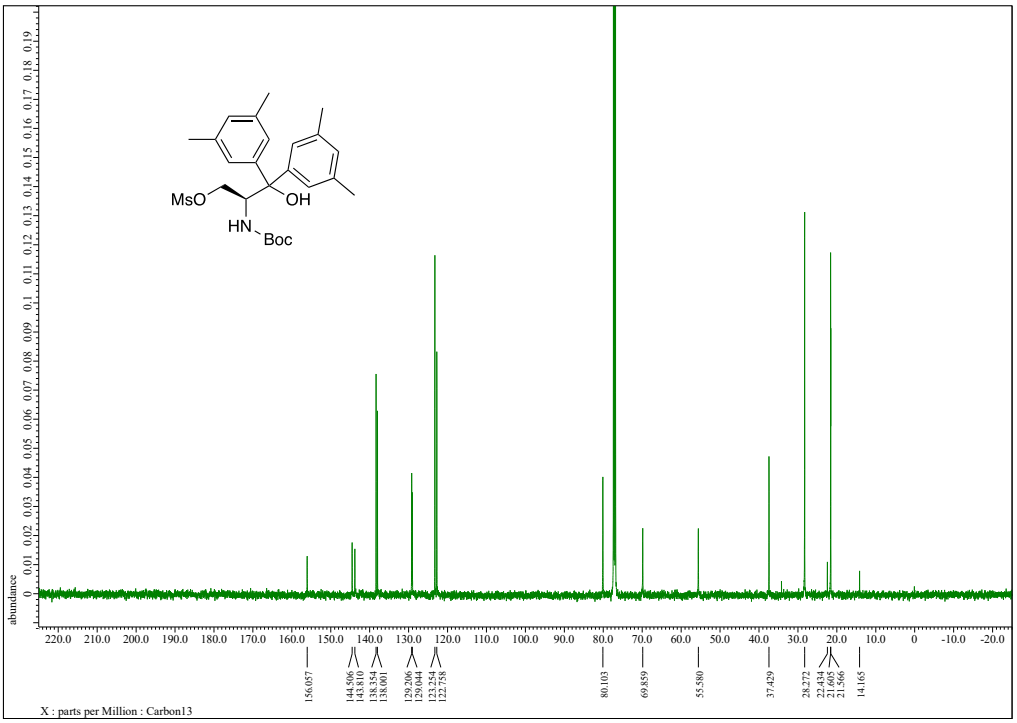


(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-bis(3,5-dimethylphenyl)-3-hydroxypropyl(5e)

^{1}H-NMR

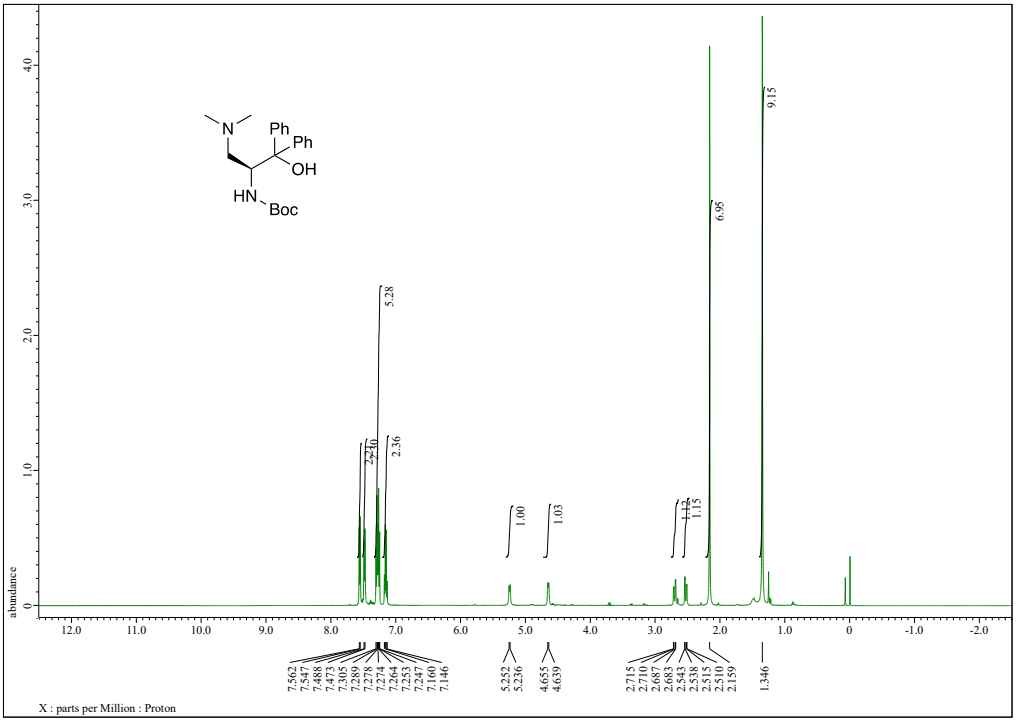


^{13}C-NMR

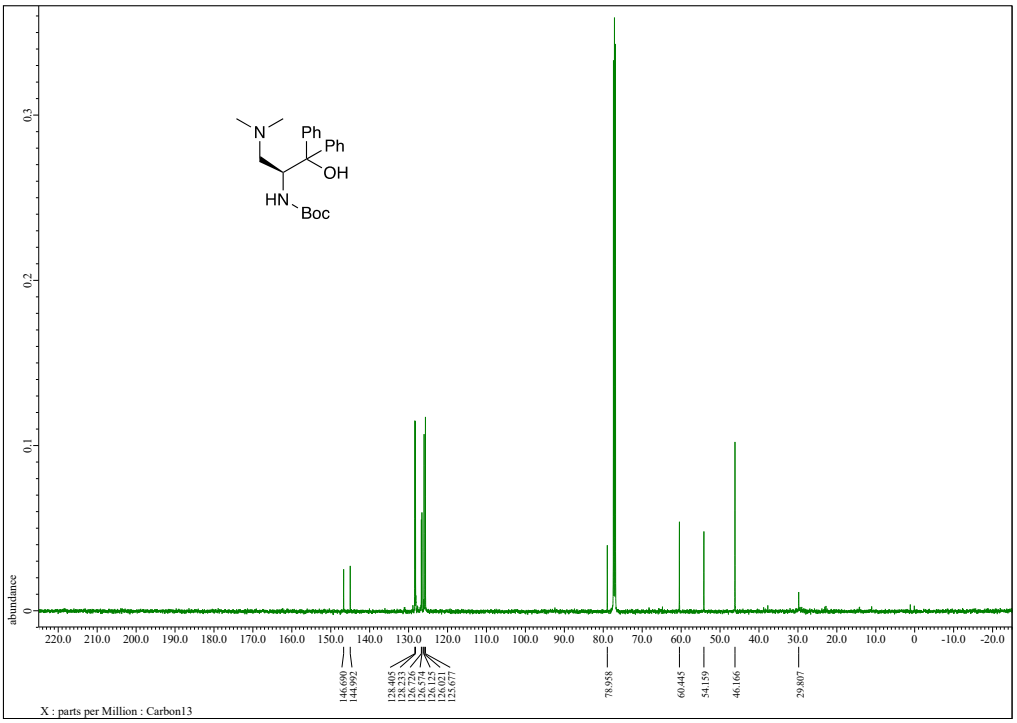


***tert*-Butyl (*S*)-(3-(dimethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)carbamate (6a)**

^{1}H-NMR

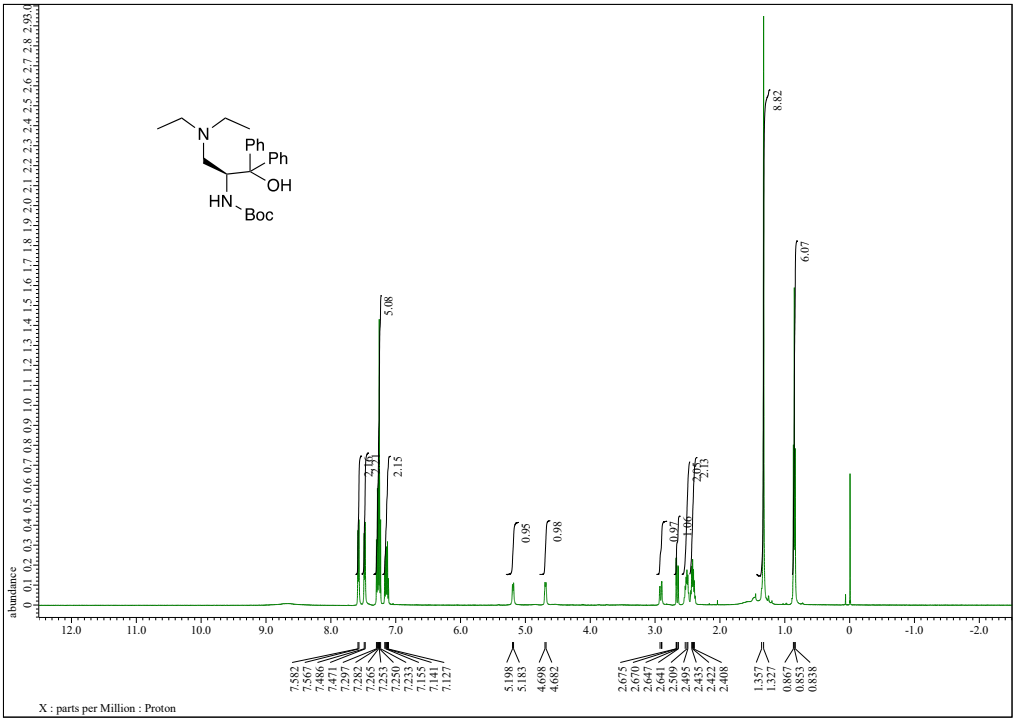


^{13}C-NMR

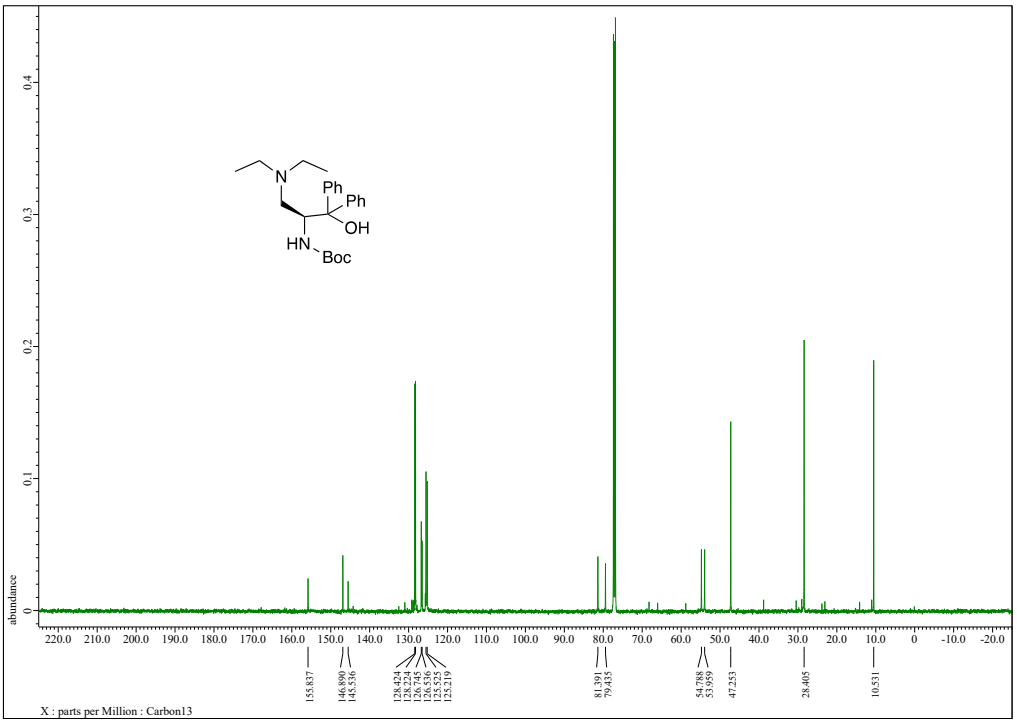


***tert*-Butyl (*S*)-(3-(diethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)carbamate (6b)**

^{1}H-NMR

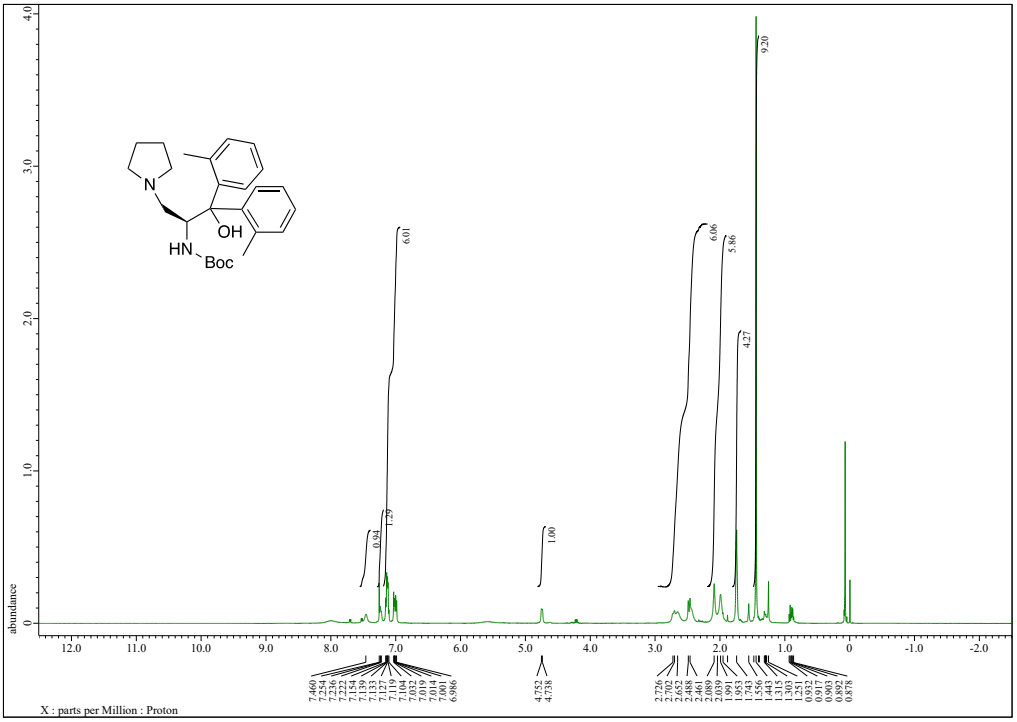


^{13}C-NMR

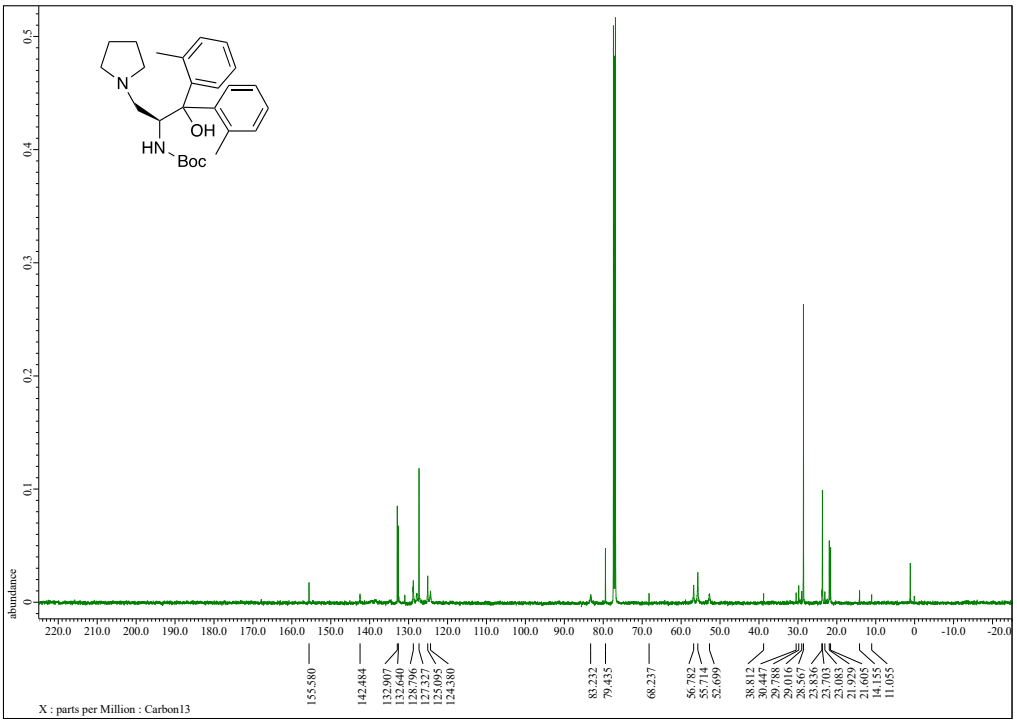


***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-o-tolylpropan-2-yl)carbamate (6f)**

^{1}H-NMR

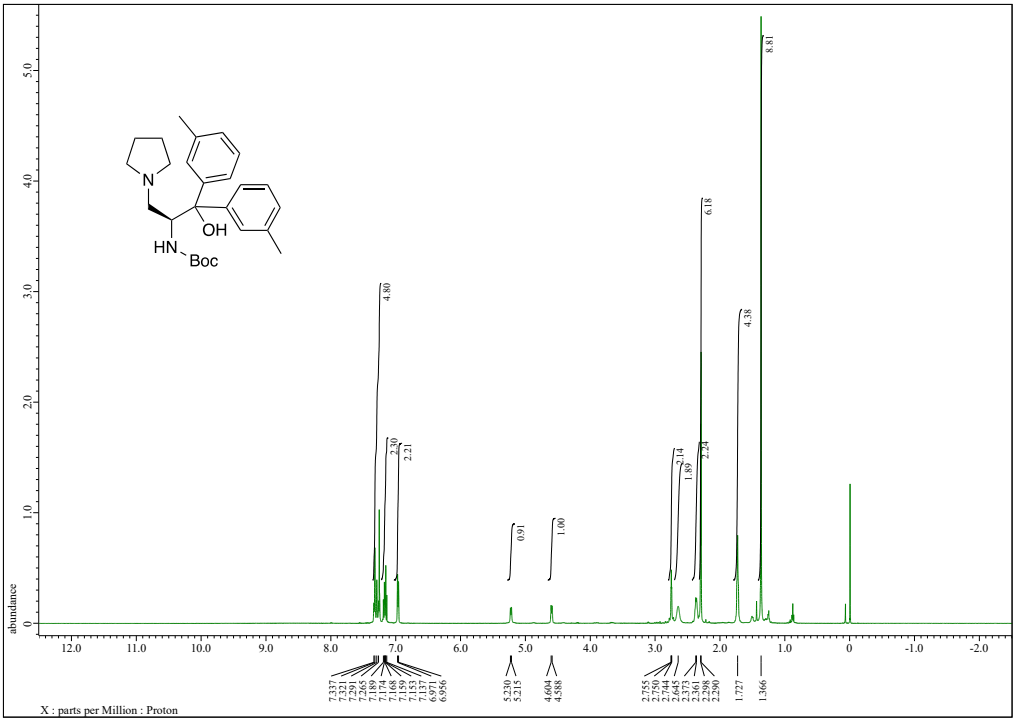


^{13}C-NMR

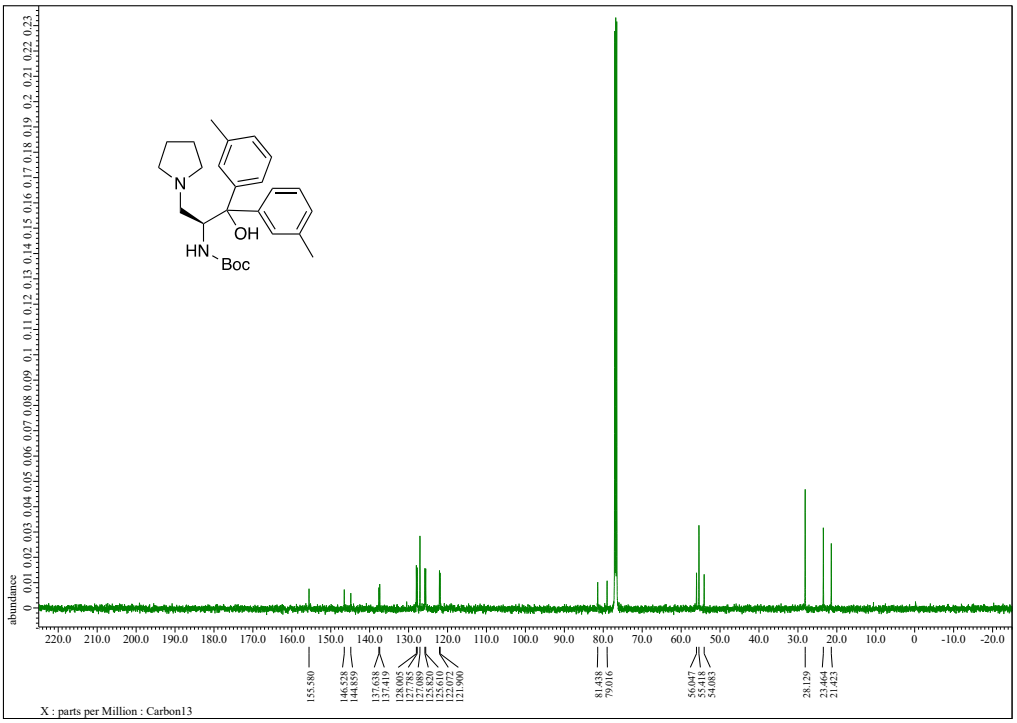


***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-m-tolylpropan-2-yl)carbamate (6g)**

^{1}H-NMR

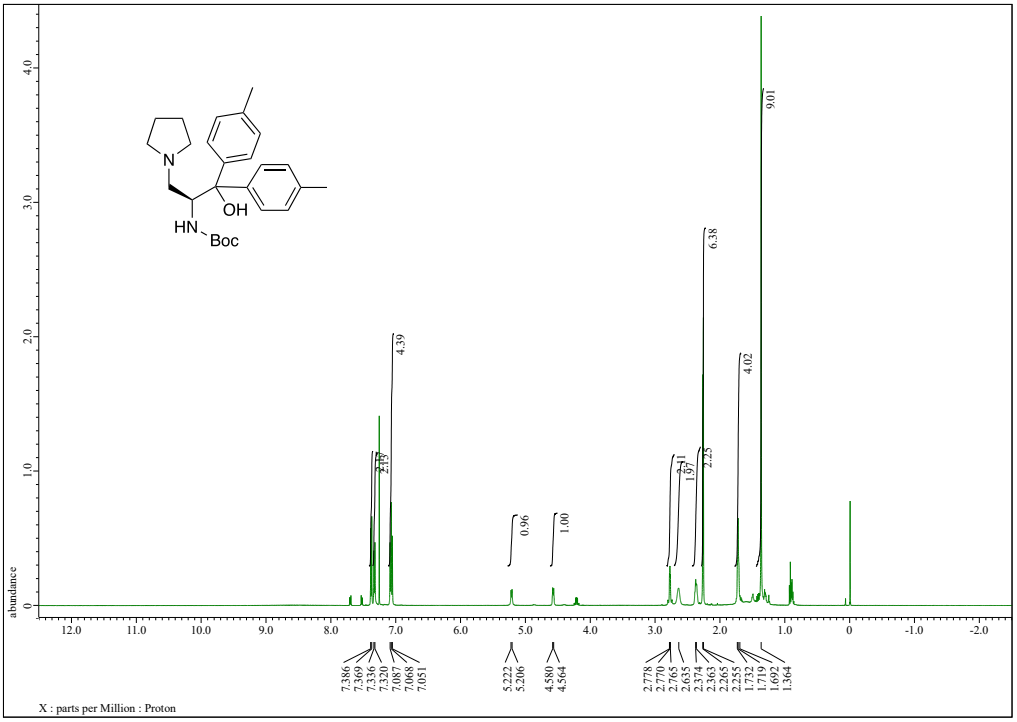


^{13}C-NMR

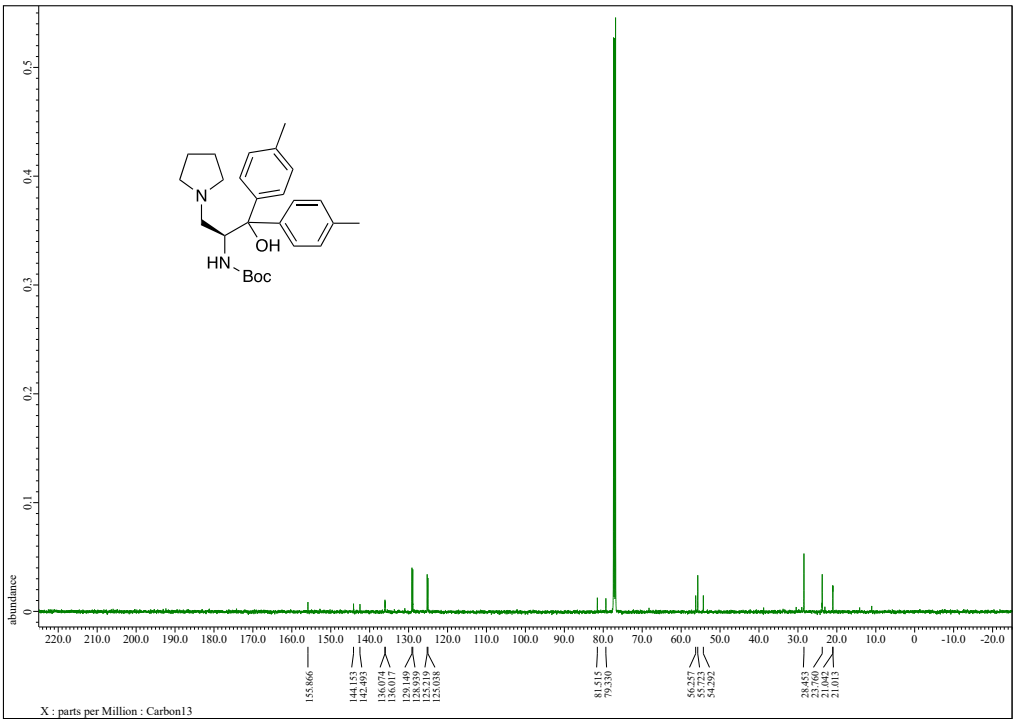


***tert*-Butyl (*S*)-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-p-tolylpropan-2-yl)carbamate (6h)**

^{1}H-NMR

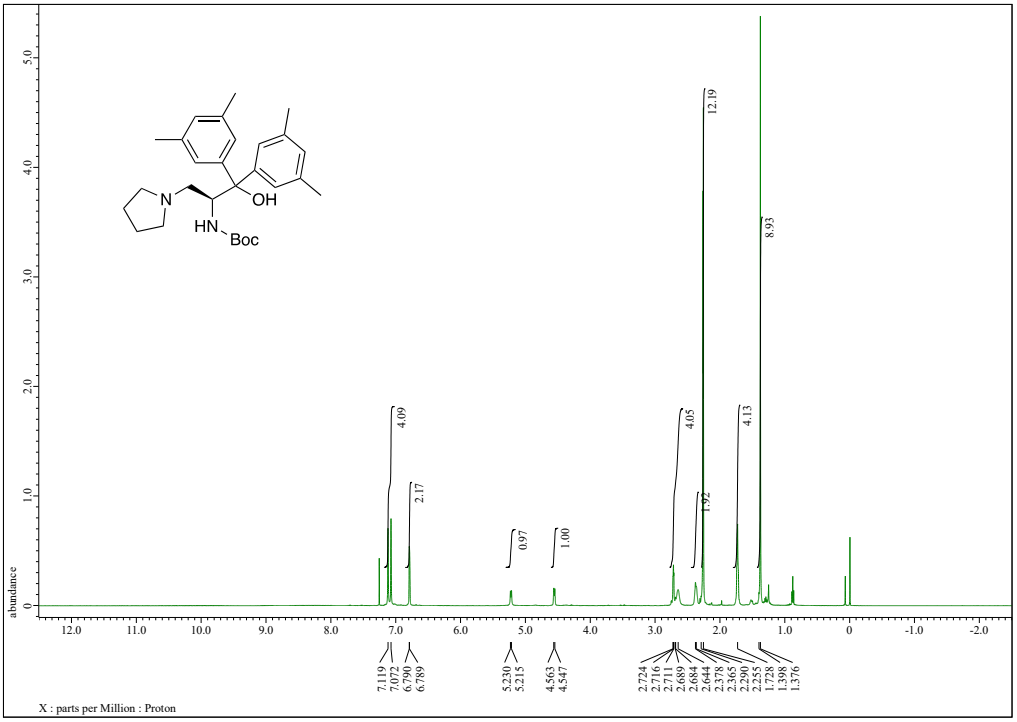


^{13}C-NMR

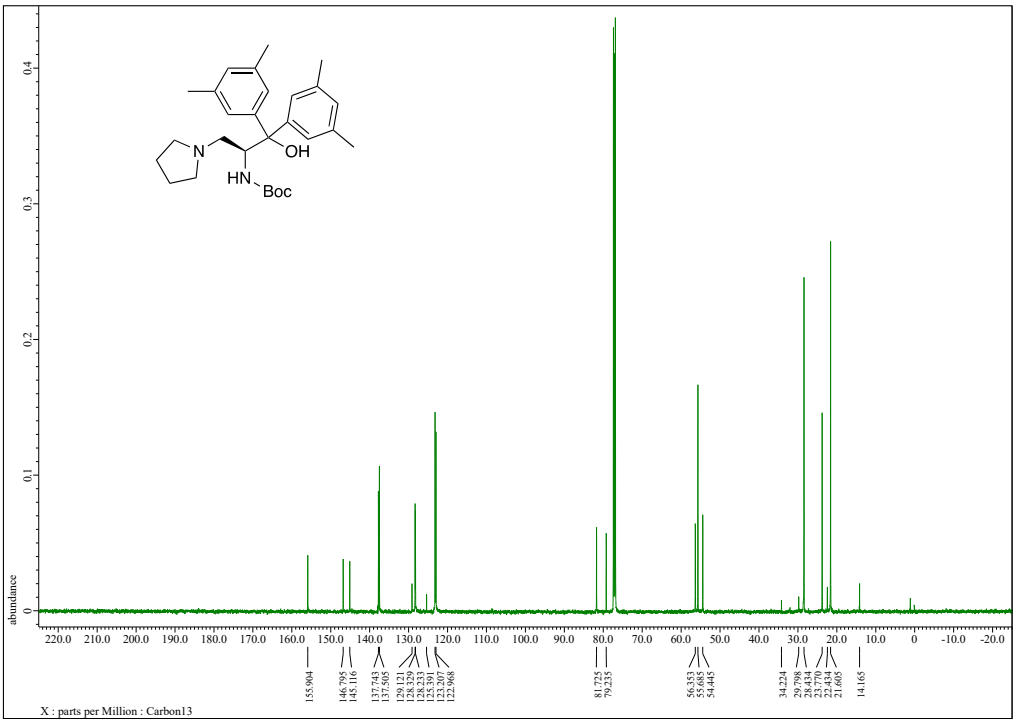


***tert*-Butyl (*S*)-(1,1-bis(3,5-dimethylphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)carbamate (6i)**

^{1}H-NMR

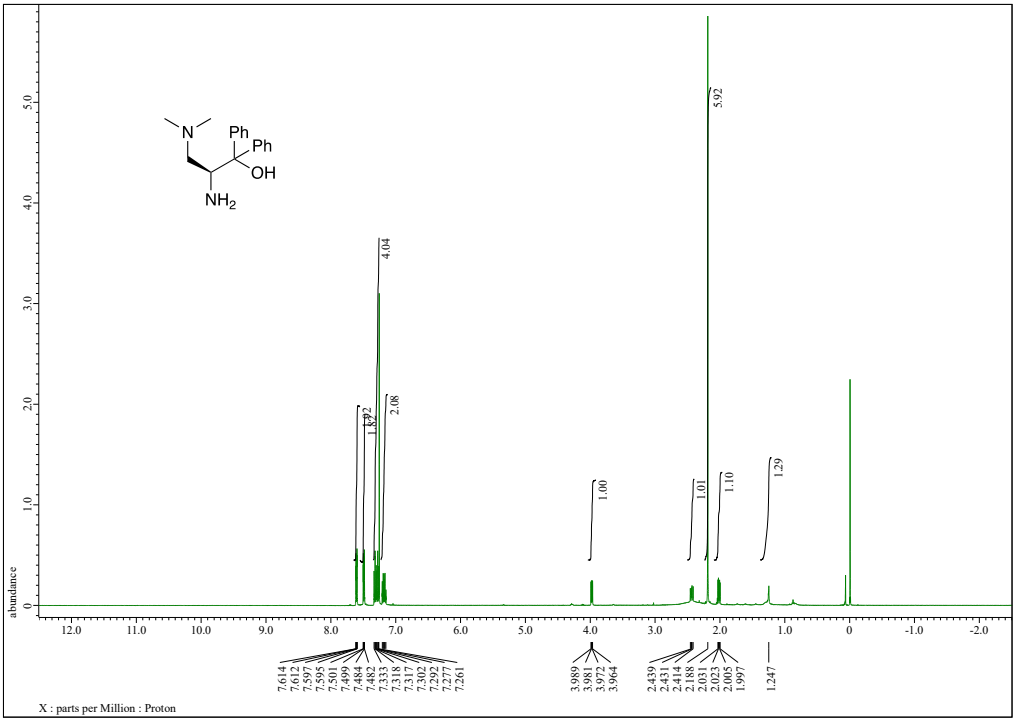


^{13}C-NMR

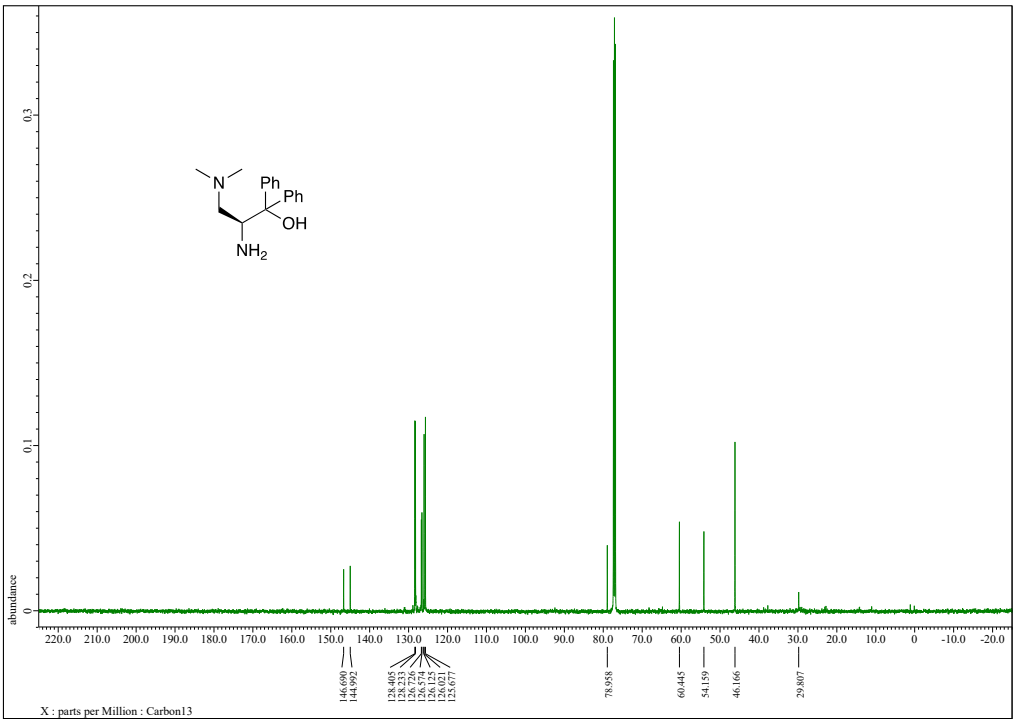


(*S*)-2-Amino-3-(dimethylamino)-1,1-diphenylpropan-1-ol (Y1)

^{1}H-NMR

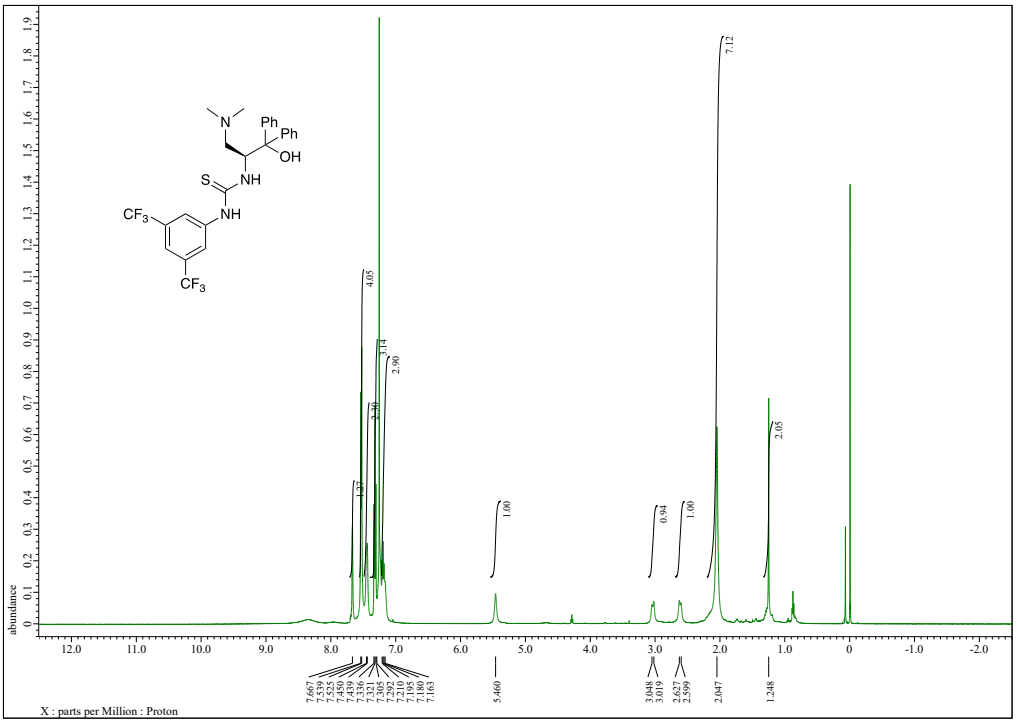


^{13}C-NMR

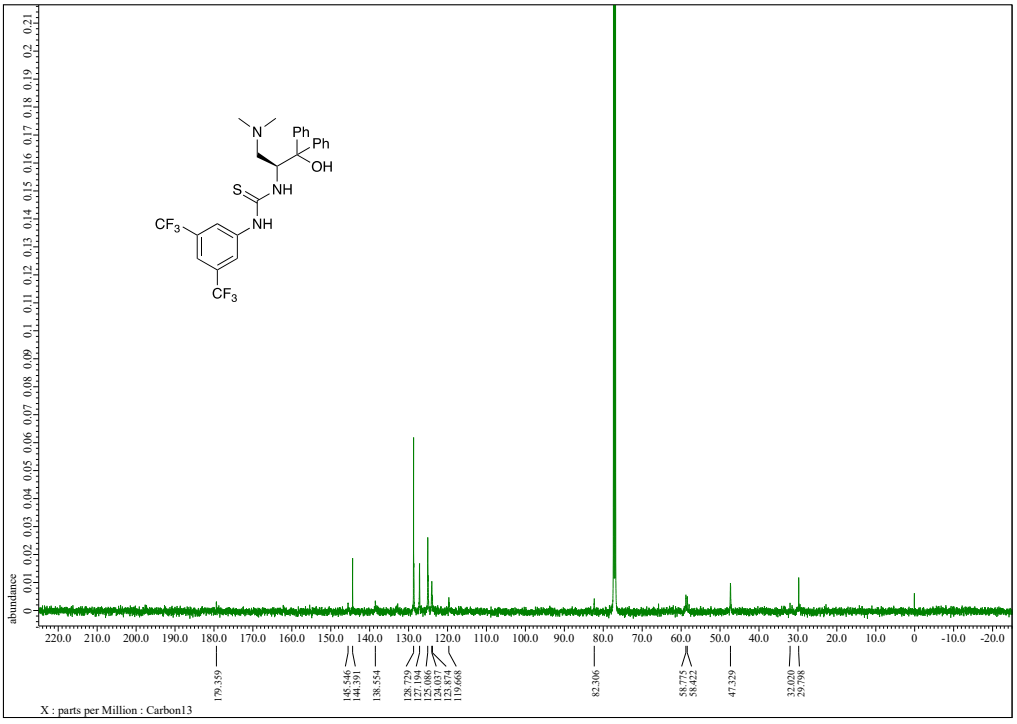


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(dimethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)thiourea (Z1)

^{1}H-NMR

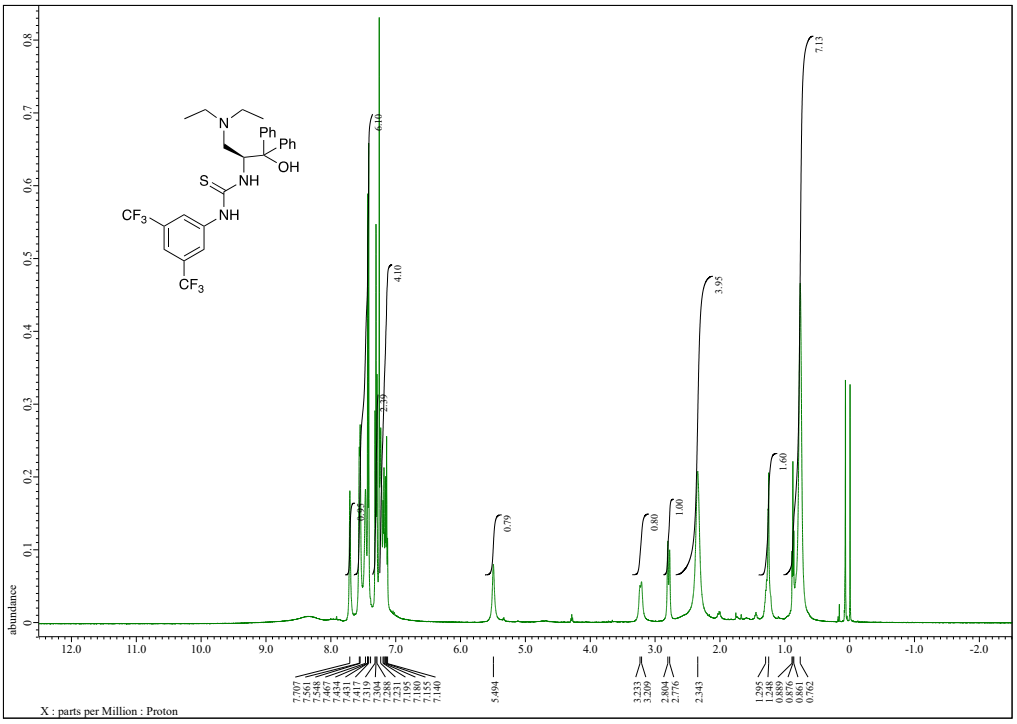


^{13}C-NMR

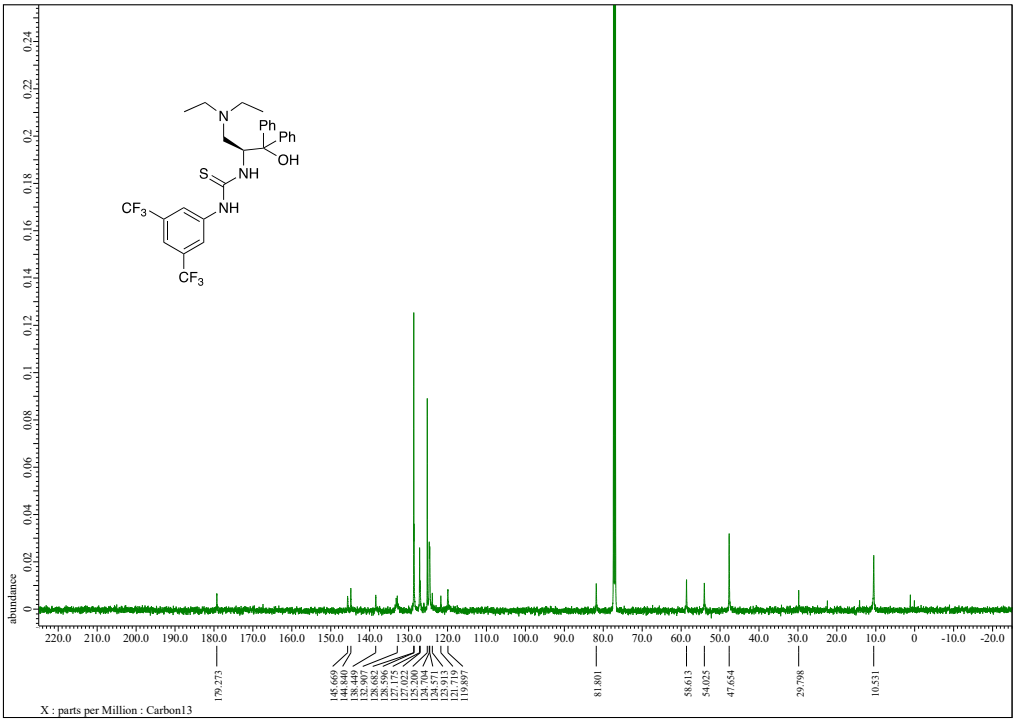


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-(diethylamino)-1-hydroxy-1,1-diphenylpropan-2-yl)thiourea (Z2)

^{1}H-NMR

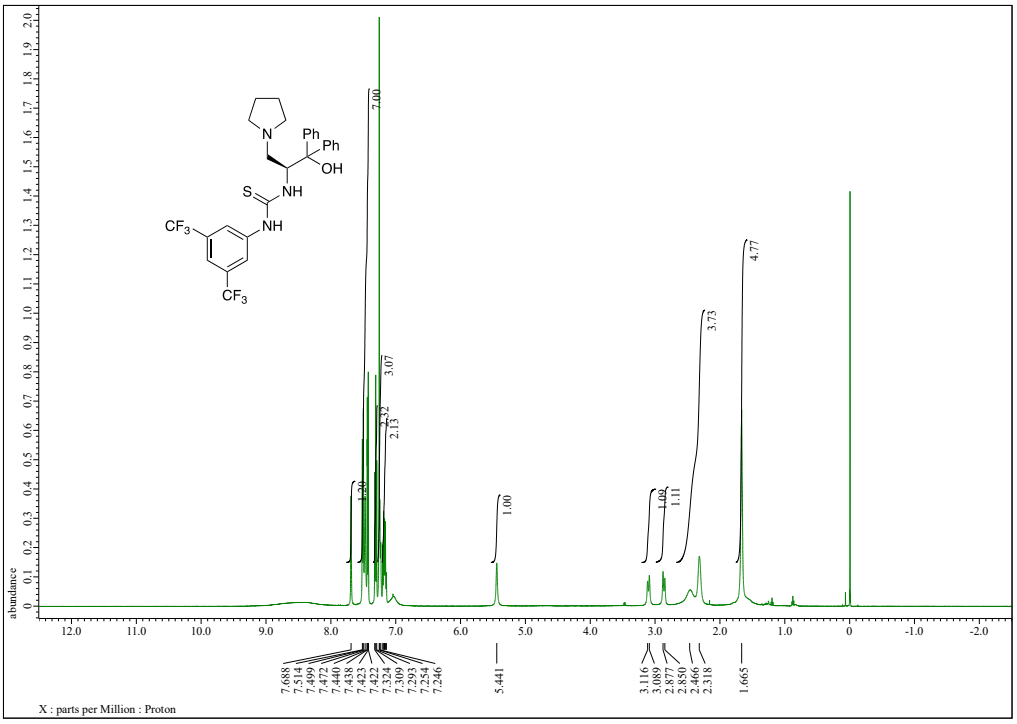


^{13}C-NMR

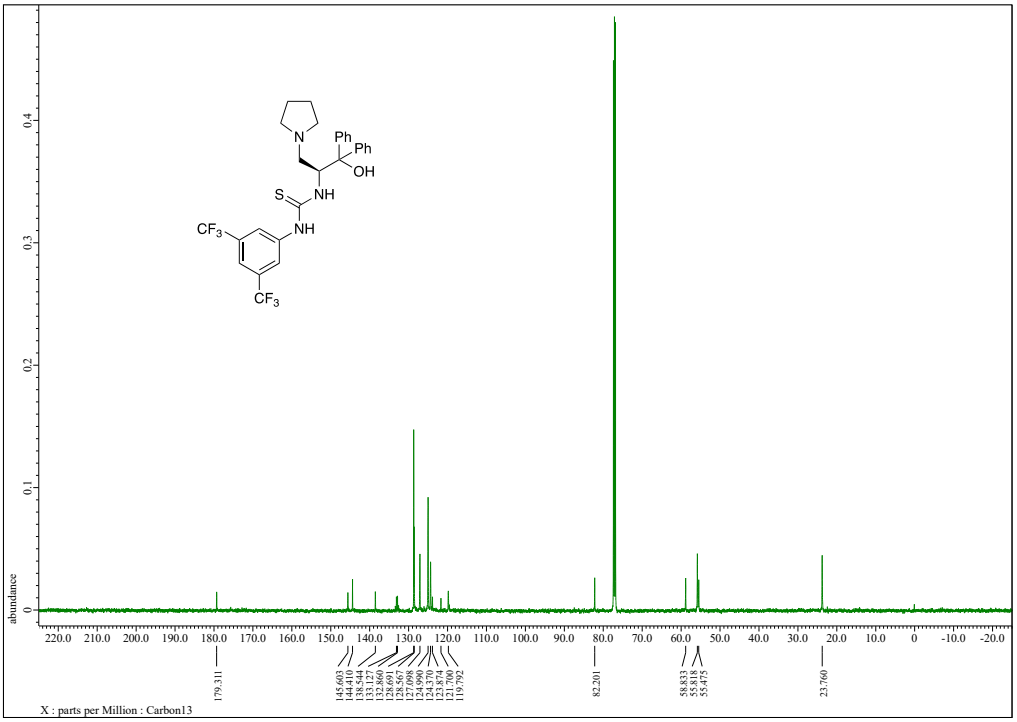


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)thiourea (Z3)

^{1}H-NMR

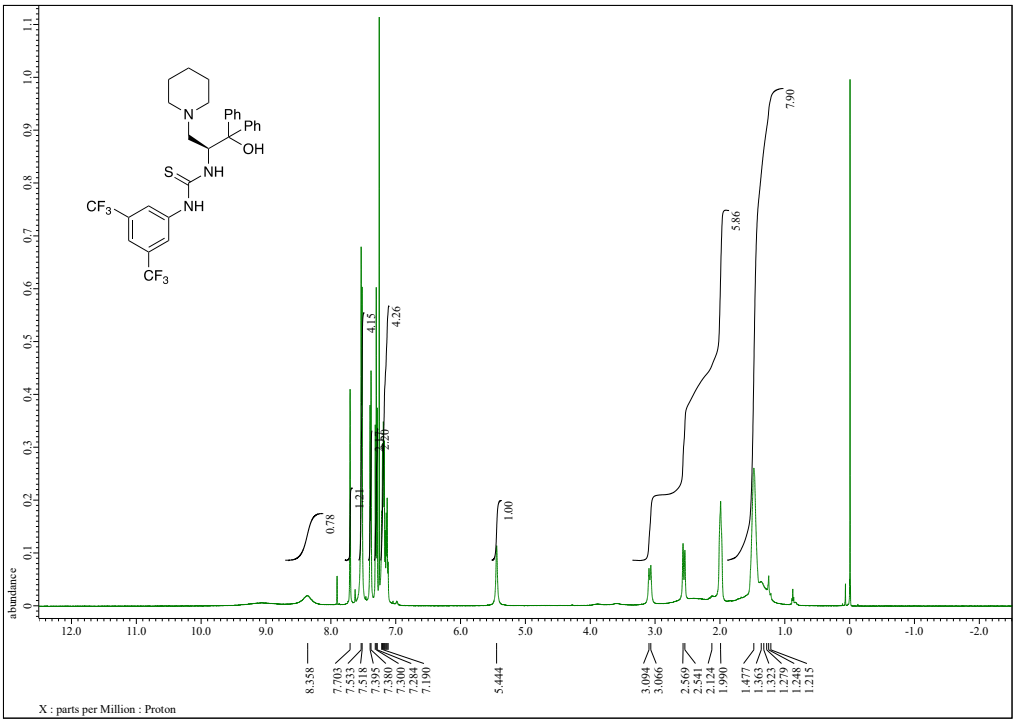


^{13}C-NMR

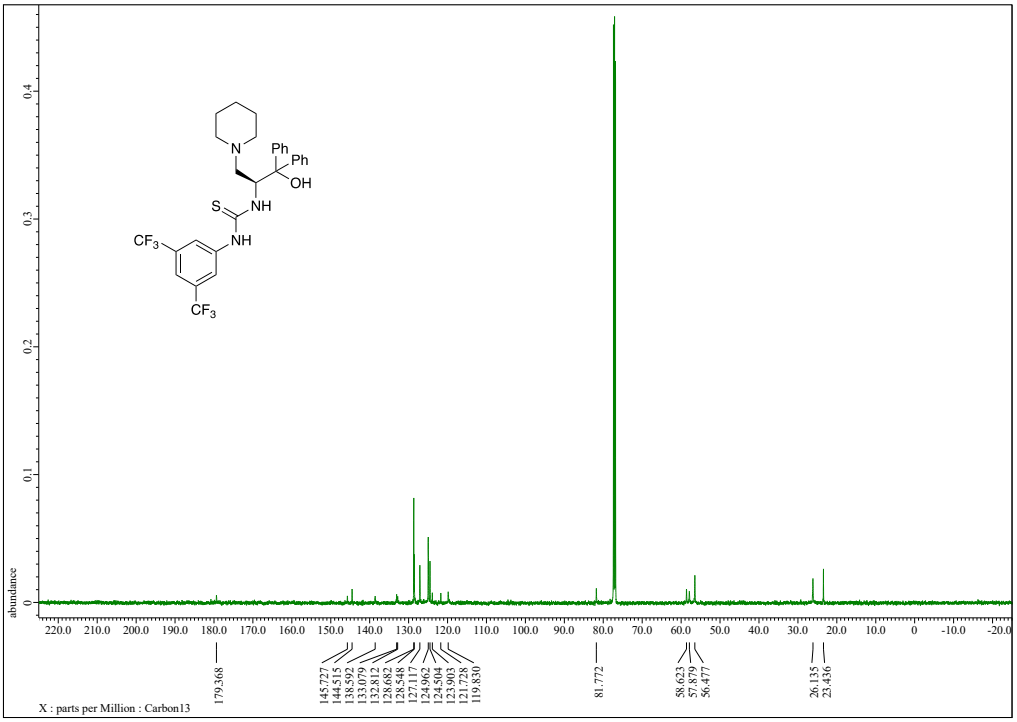


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-1,1-diphenyl-3-(piperidin-1-yl)propan-2-yl)thiourea (Z4)

^{1}H-NMR

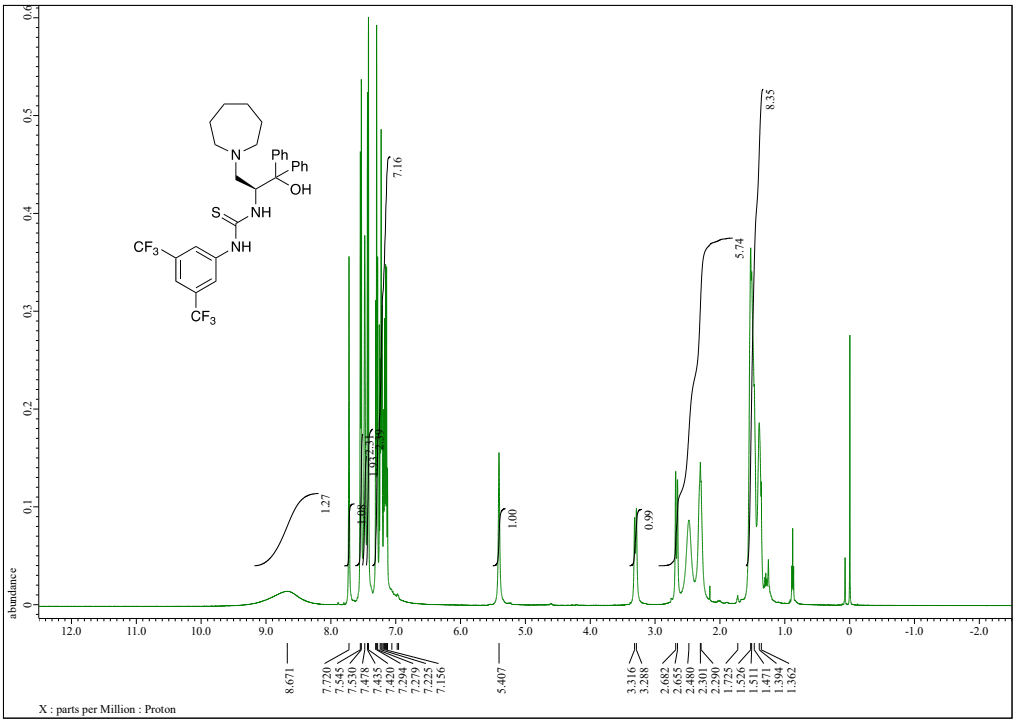


^{13}C-NMR

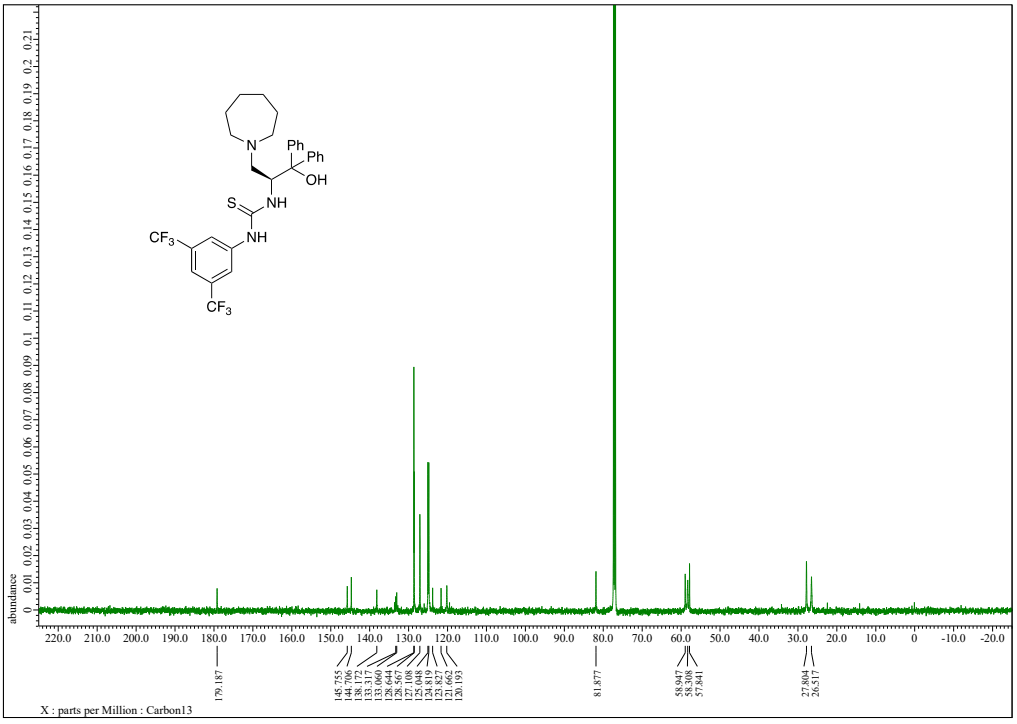


(*S*)-1-(3-(Azepan-1-yl)-1-hydroxy-1,1-diphenylpropan-2-yl)-3-(3,5-bis(trifluoromethyl) phenyl) thiourea (Z5)

^{1}H-NMR

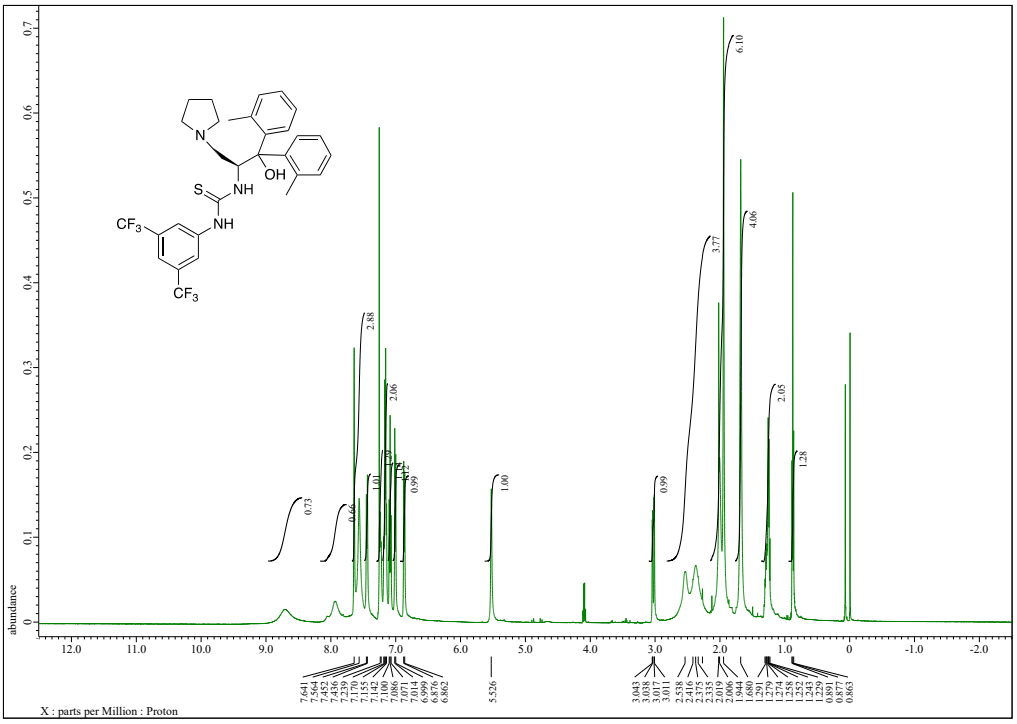


^{13}C-NMR

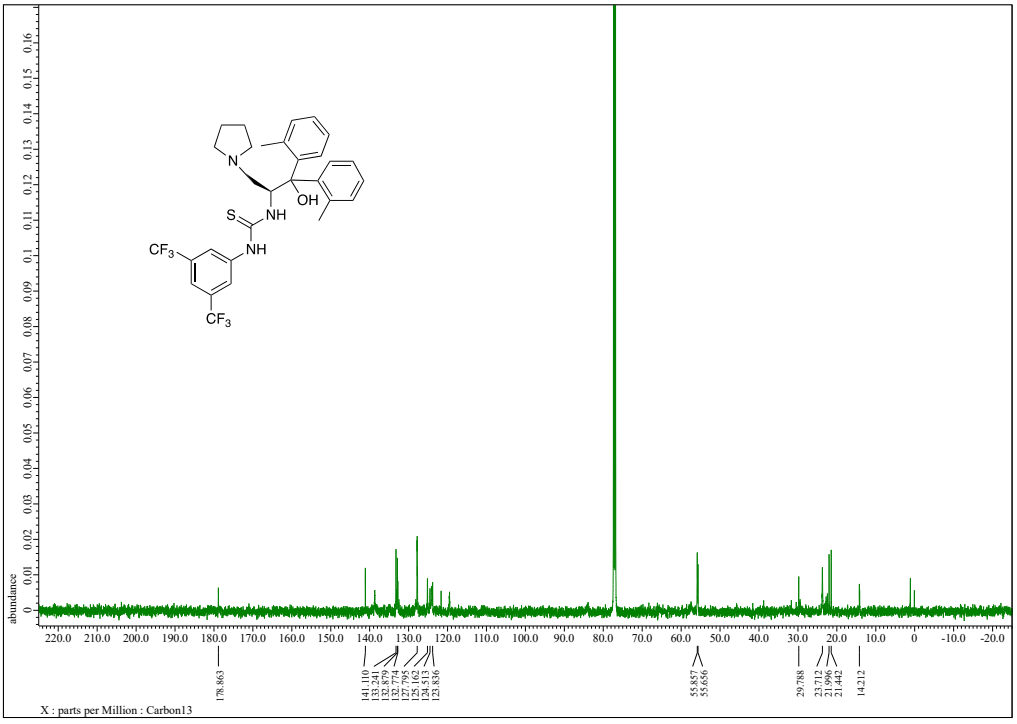


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-o-tolylpropan-2-yl)thiourea (Z6)

^{1}H-NMR

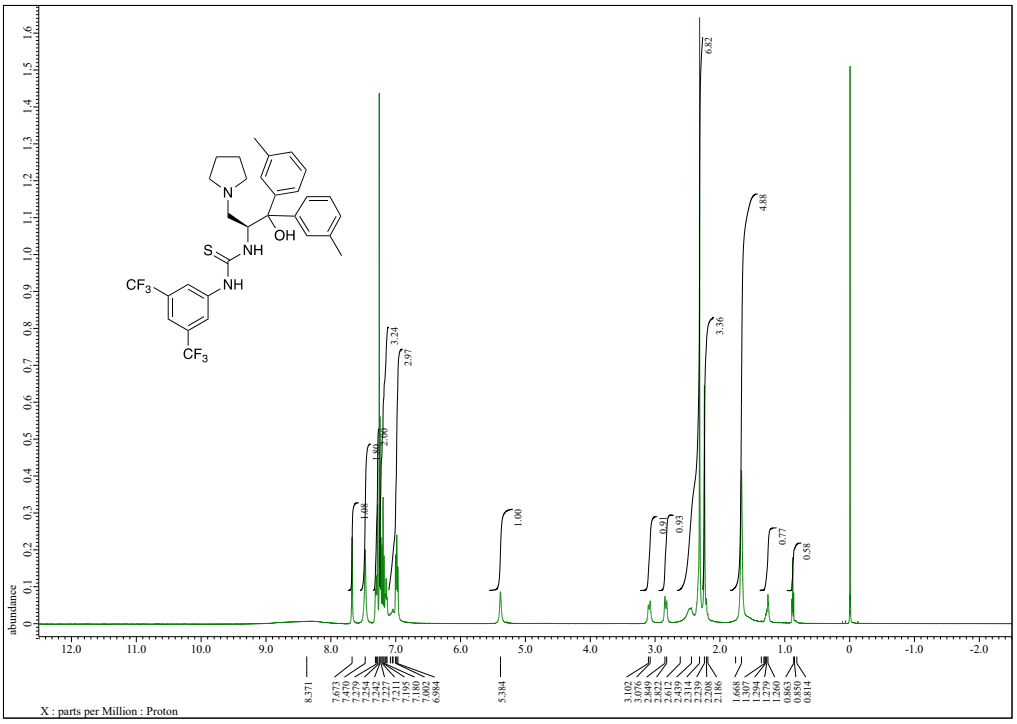


^{13}C-NMR

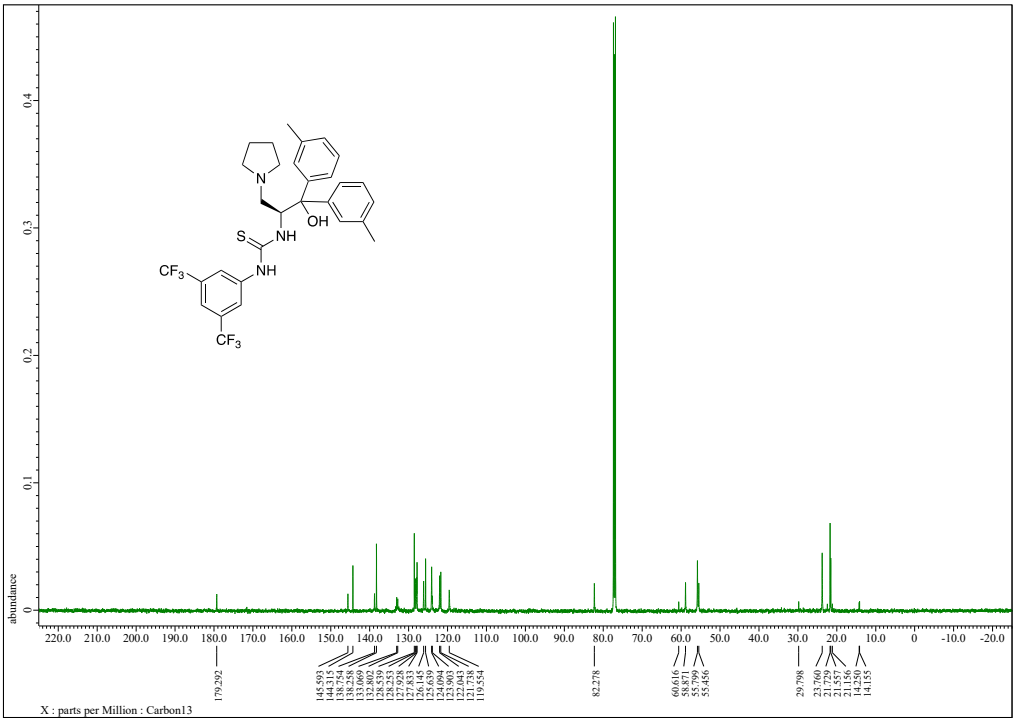


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-m-tolylpropan-2-yl)thiourea (Z7)

^{1}H-NMR

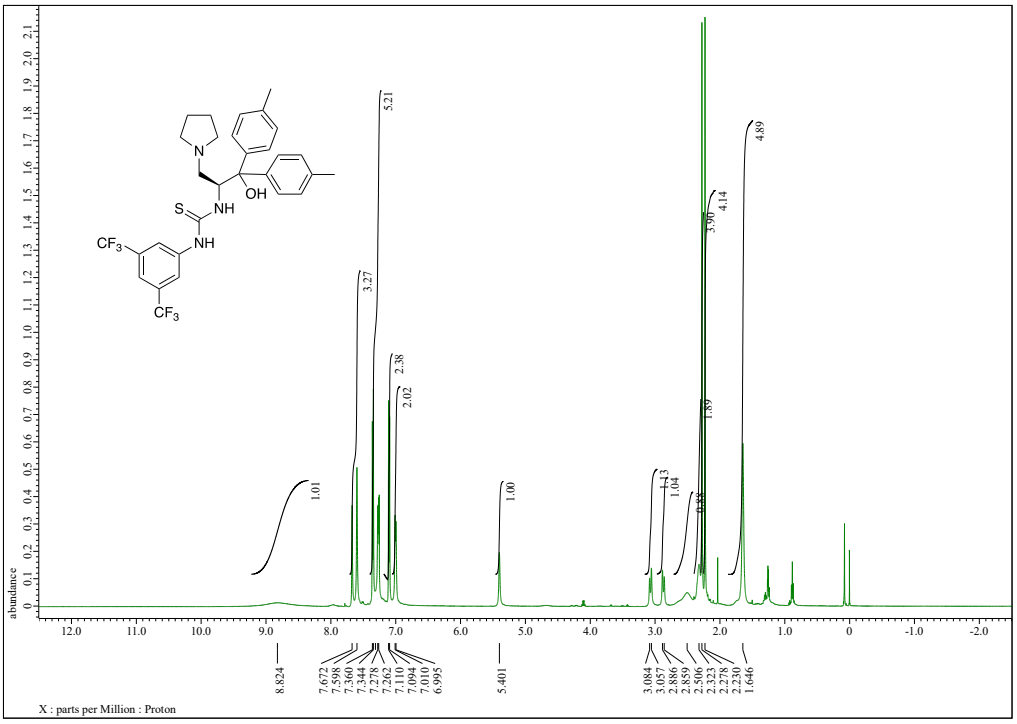


^{13}C-NMR

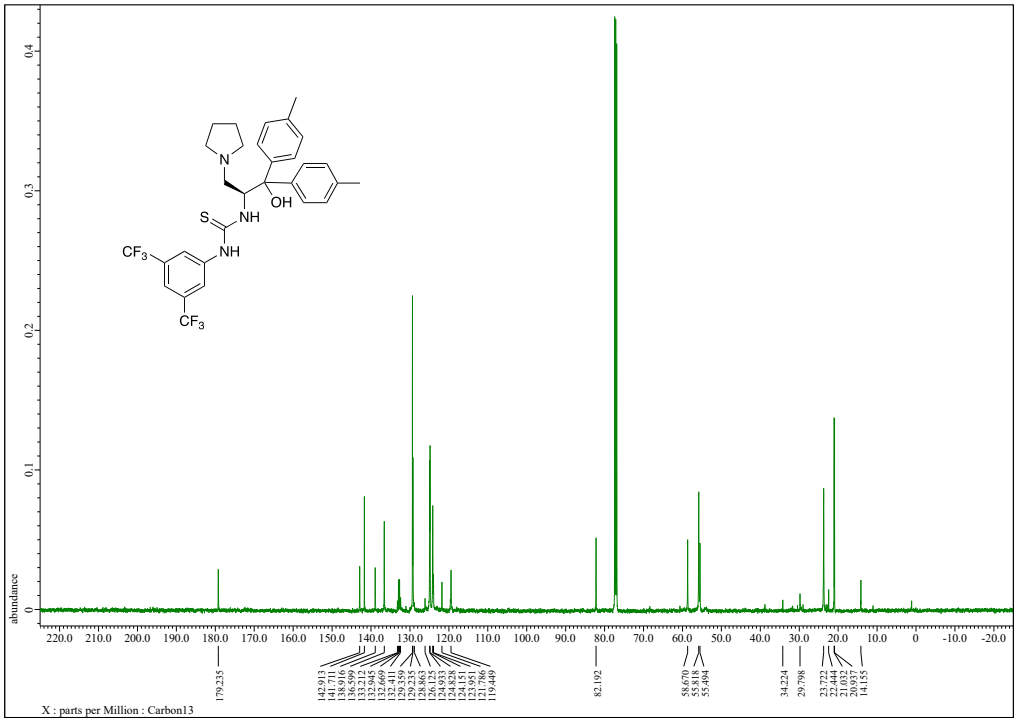


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3-(pyrrolidin-1-yl)-1,1-di-p-tolylpropan-2-yl)thiourea (Z8)

^{1}H-NMR

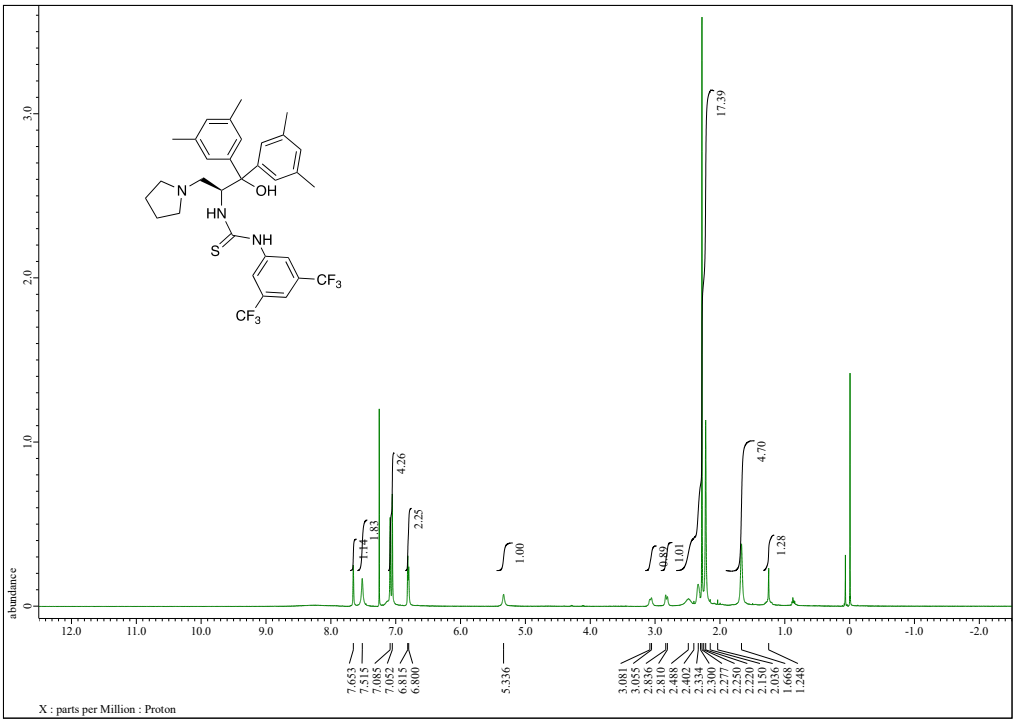


^{13}C-NMR

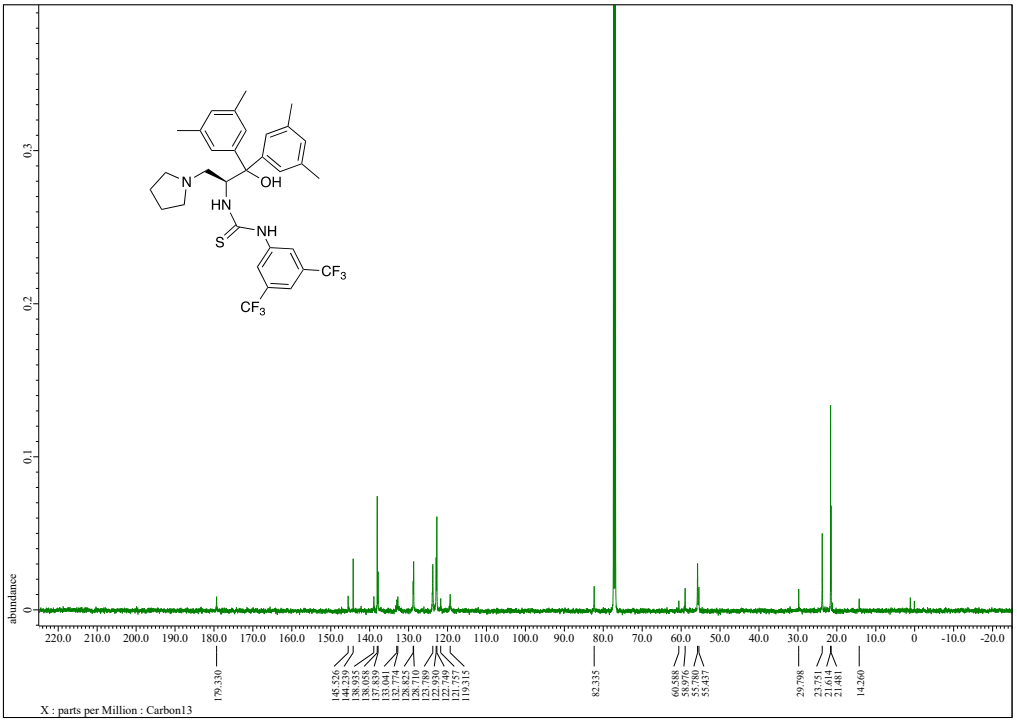


(*S*)-1-(1,1-Bis(3,5-dimethylphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-(3,5-bis (trifluoromethyl)phenyl)thiourea (Z9)

^{1}H-NMR

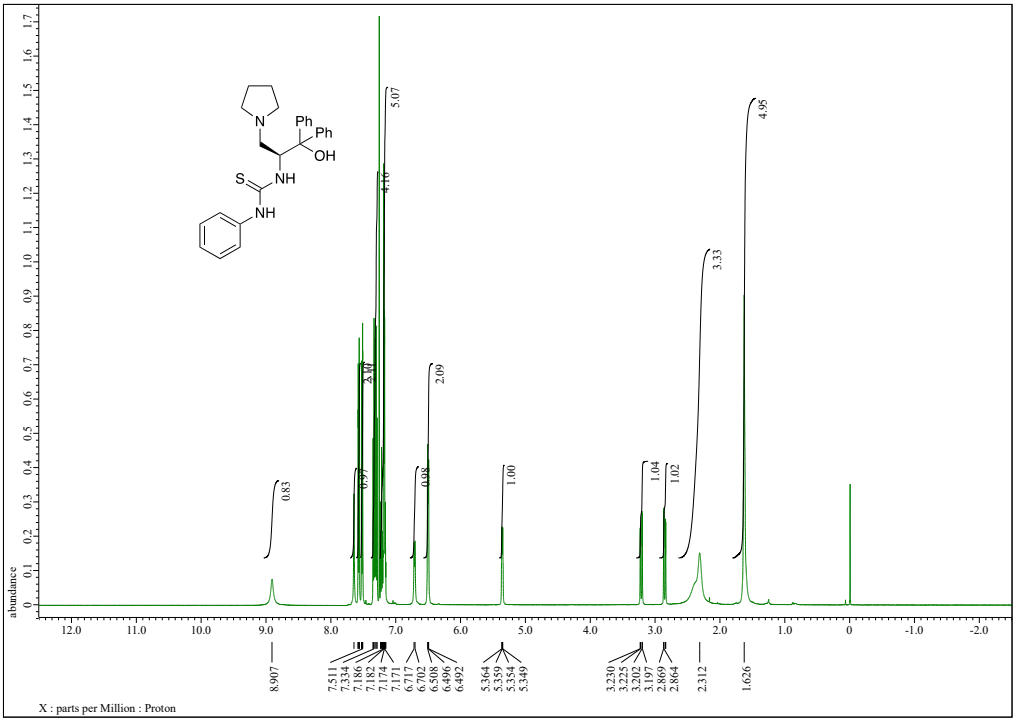


^{13}C-NMR

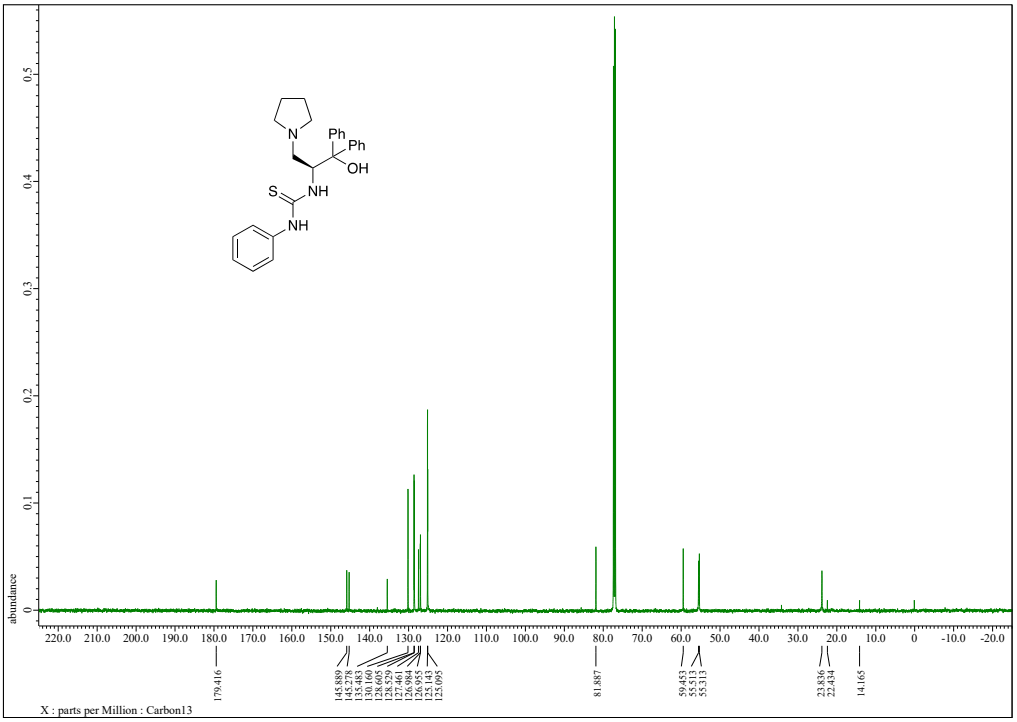


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-phenylthiourea (Z10)

^{1}H-NMR

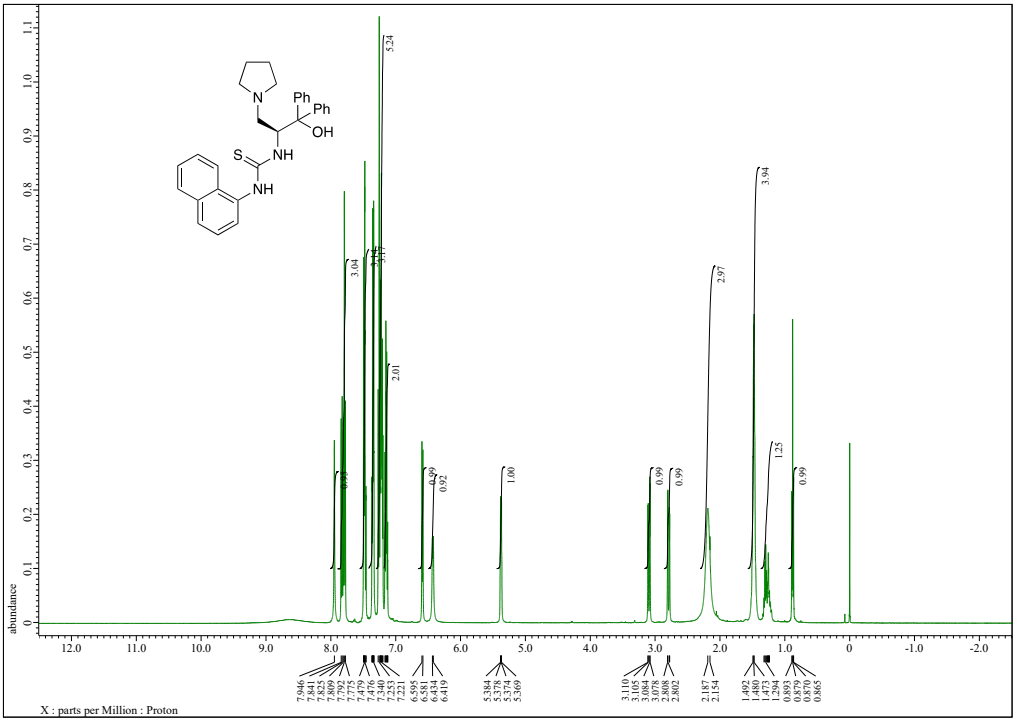


^{13}C-NMR

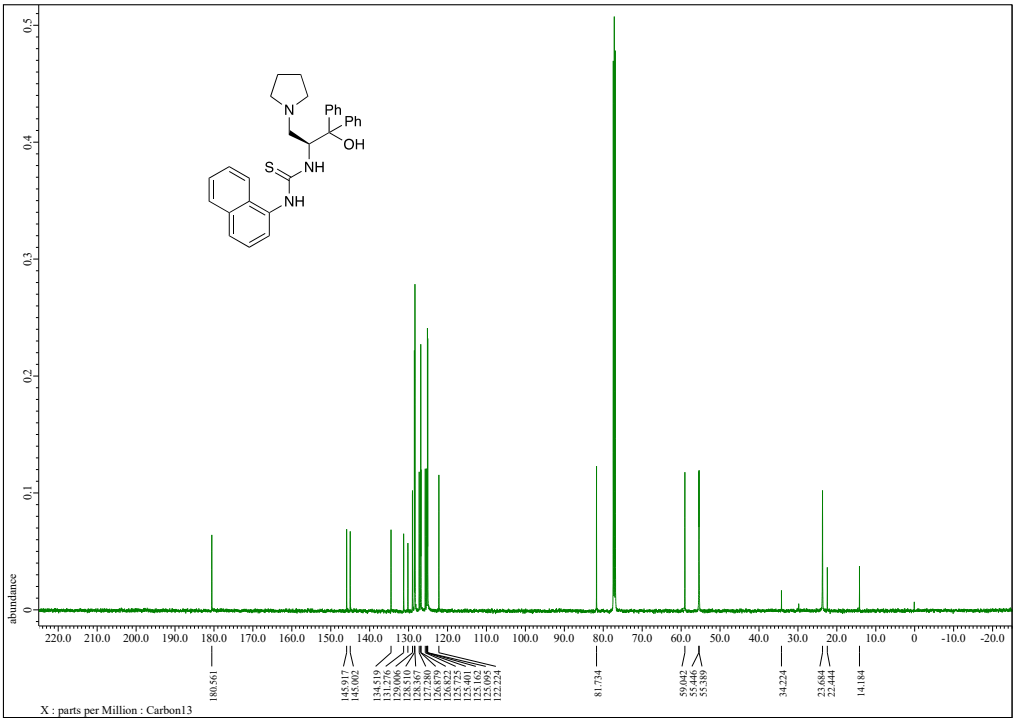


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(naphthalen-1-yl)thiourea (Z11)

^{1}H-NMR

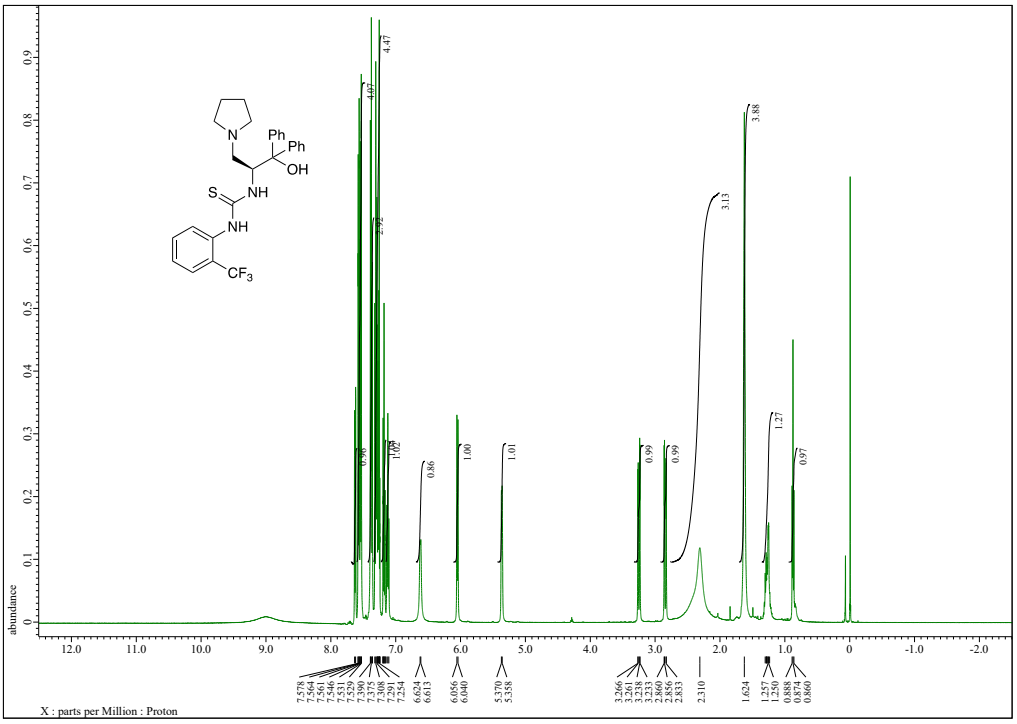


^{13}C-NMR

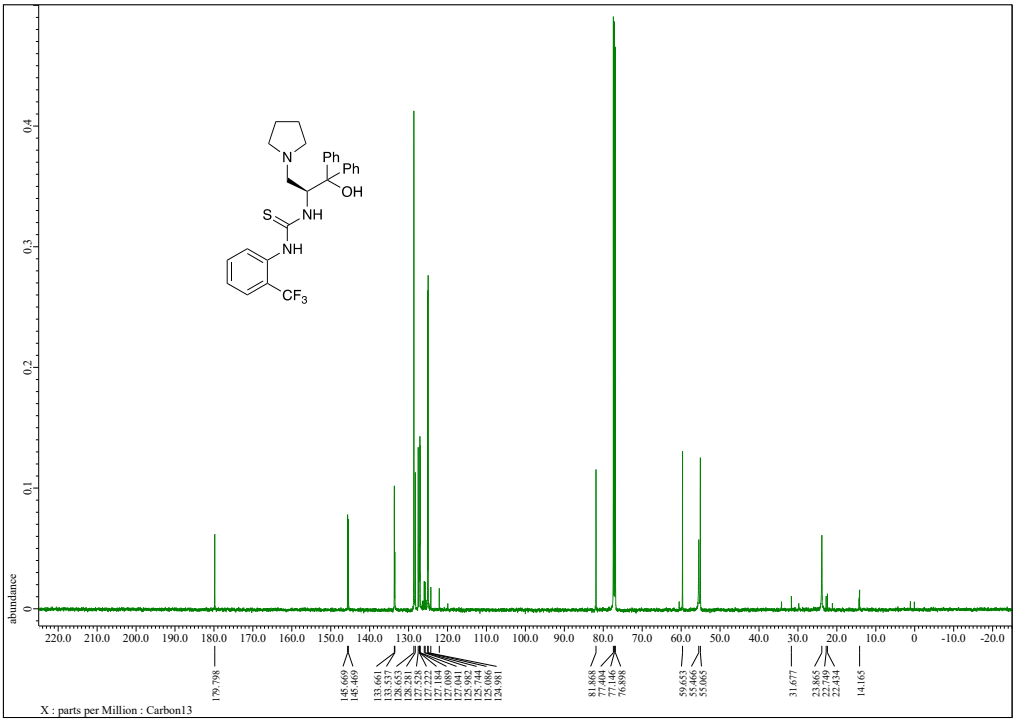


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(2-(trifluoromethyl)phenyl) thiourea (Z12)

^{1}H-NMR

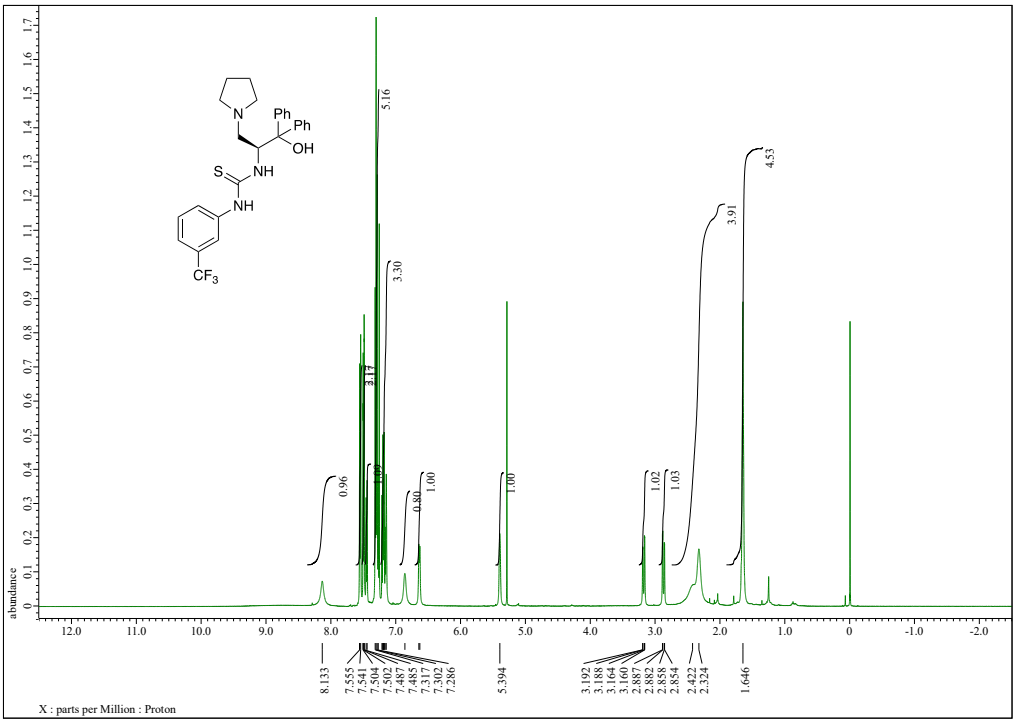


^{13}C-NMR

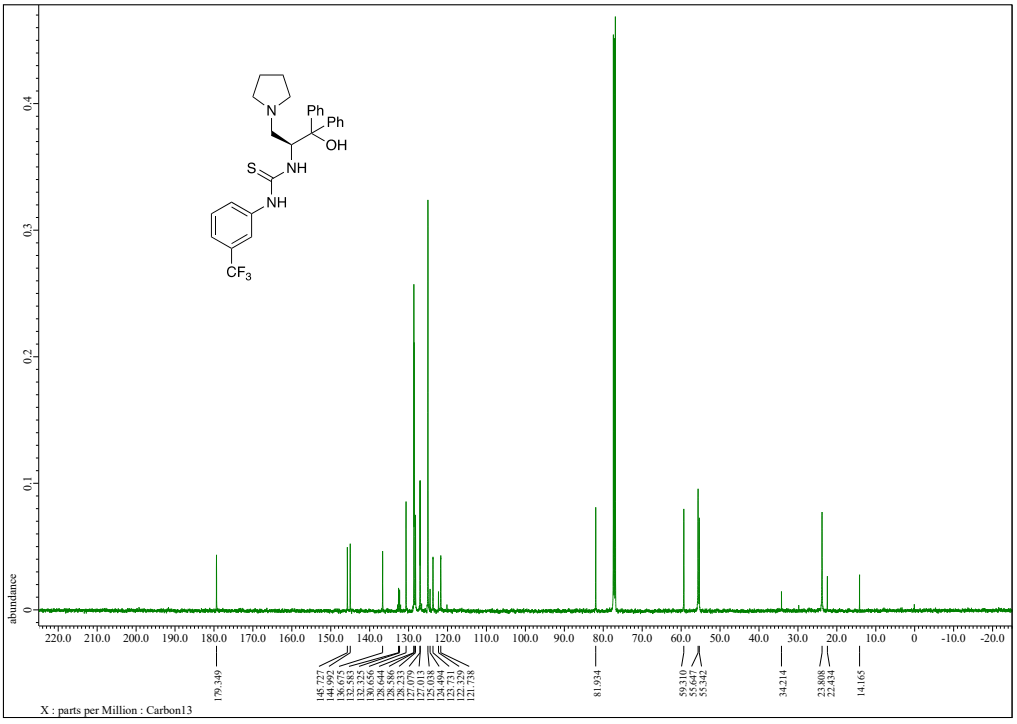


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(3-(trifluoromethyl)phenyl) thiourea (Z13)

^{1}H-NMR

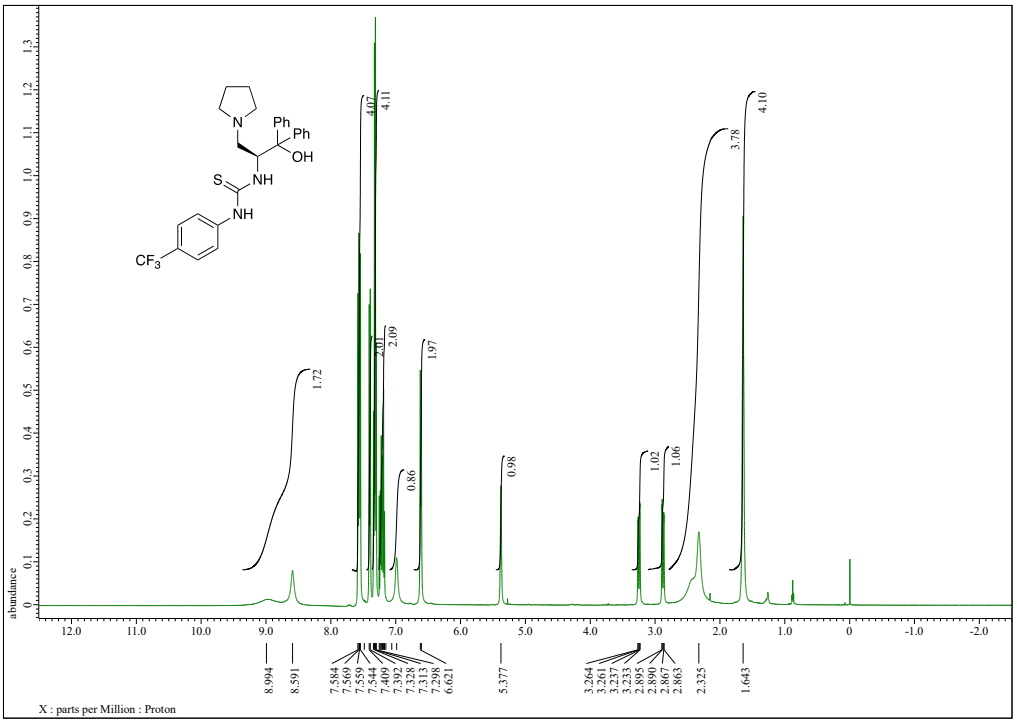


^{13}C-NMR

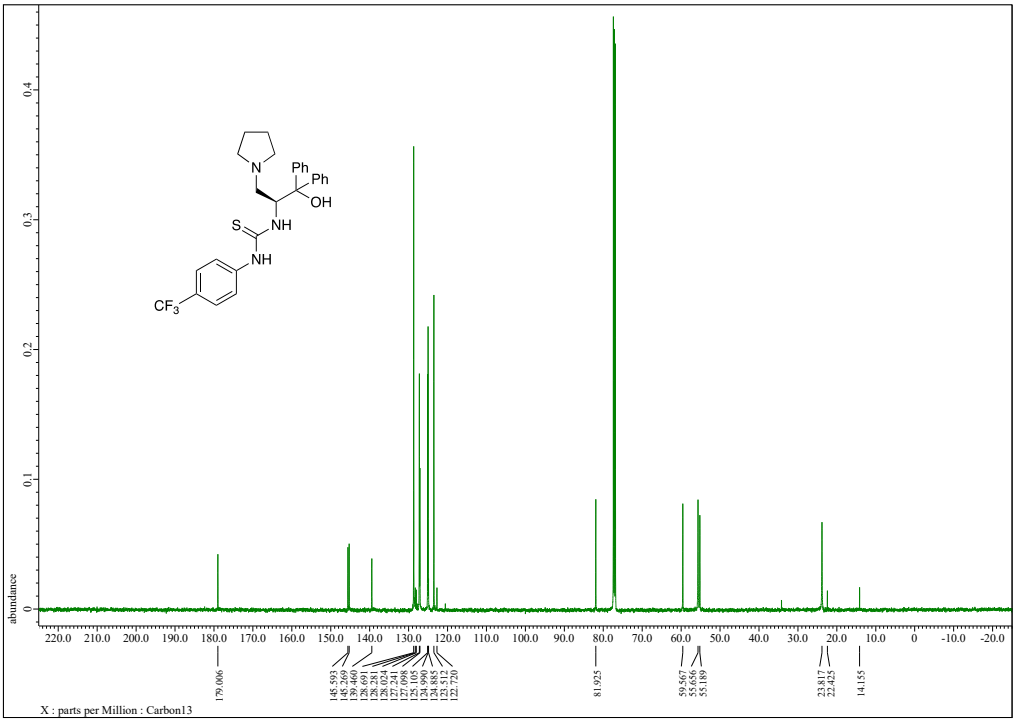


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(4-(trifluoromethyl)phenyl) thiourea (Z14)

^{1}H-NMR

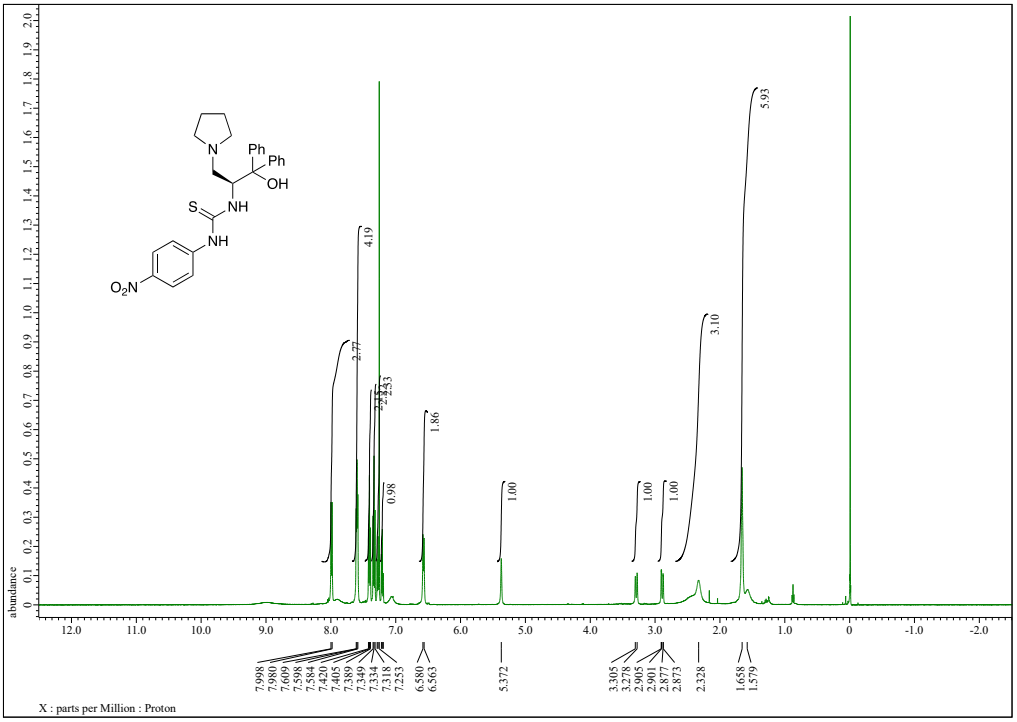


^{13}C-NMR

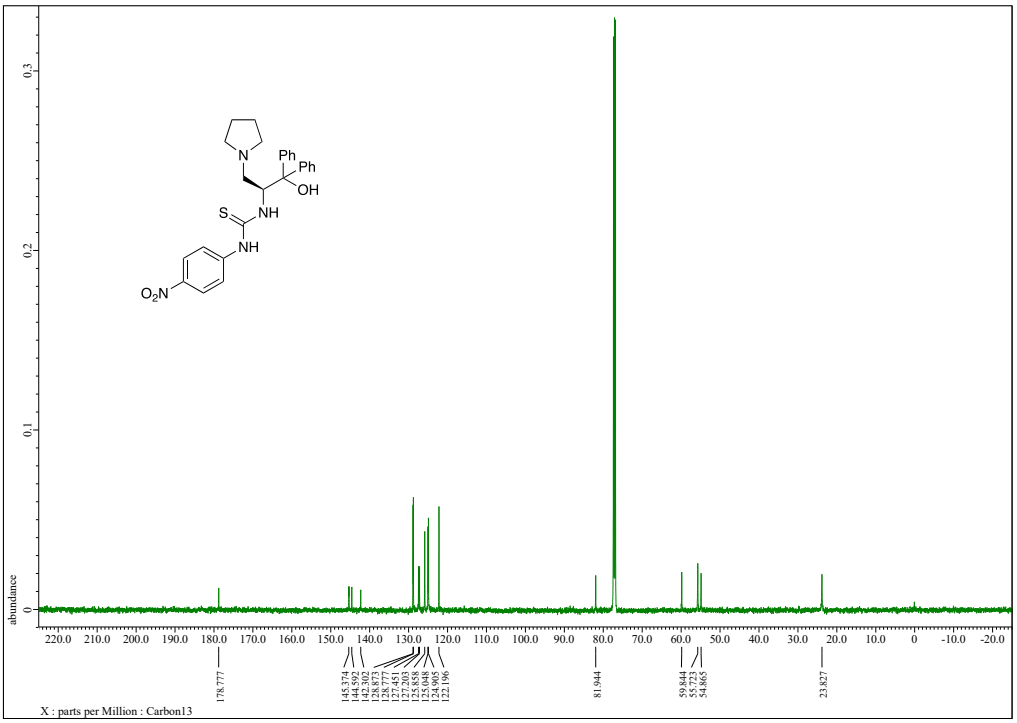


(*S*)-1-(1-Hydroxy-1,1-diphenyl-3-(pyrrolidin-1-yl)propan-2-yl)-3-(4-nitrophenyl)thiourea (Z15)

^{1}H-NMR

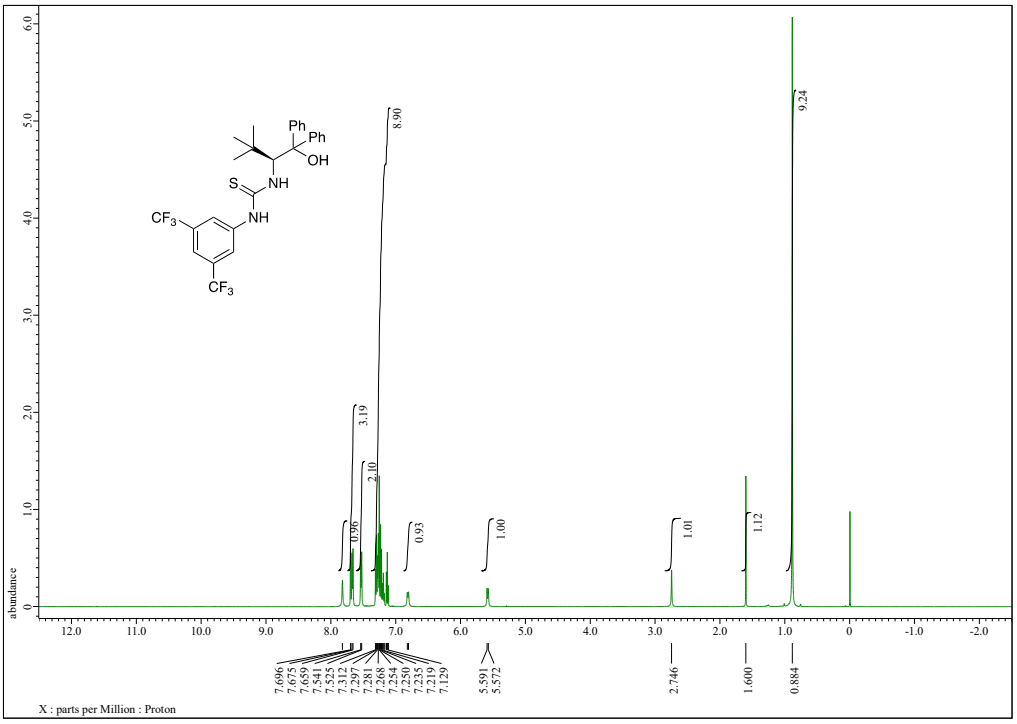


^{13}C-NMR

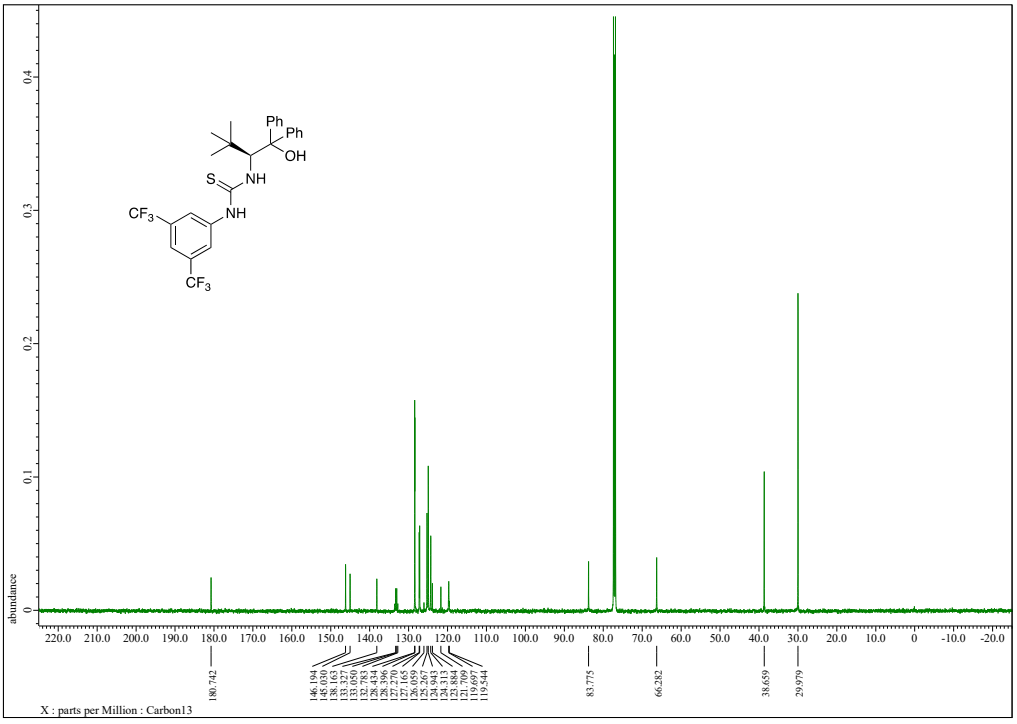


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-yl)thiourea (Z16)

^{1}H-NMR

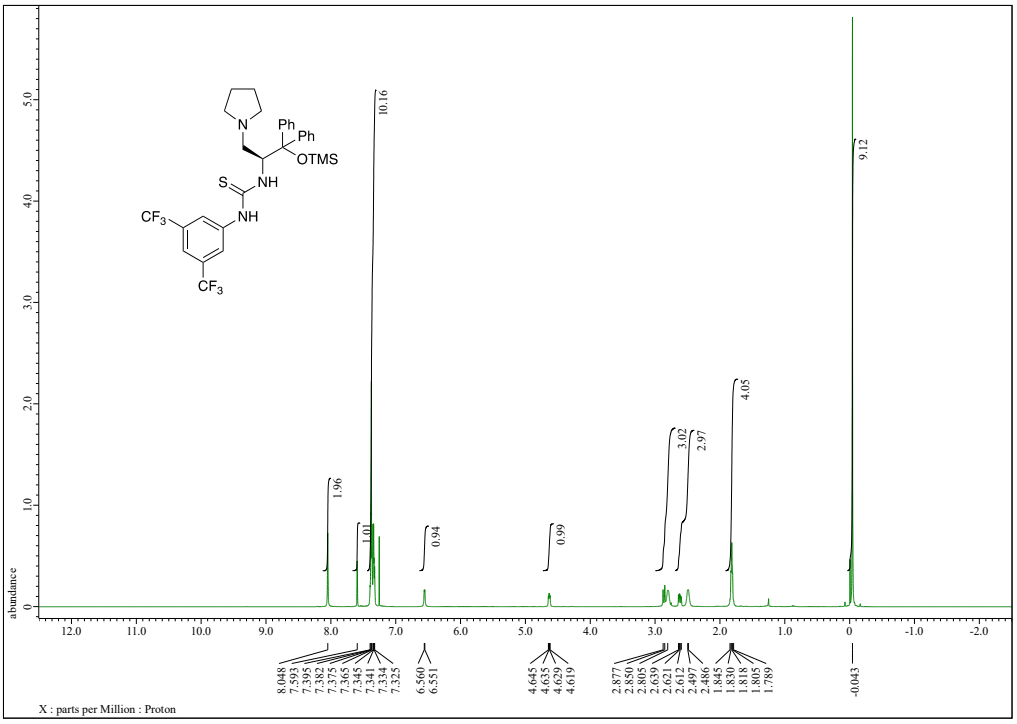


^{13}C-NMR

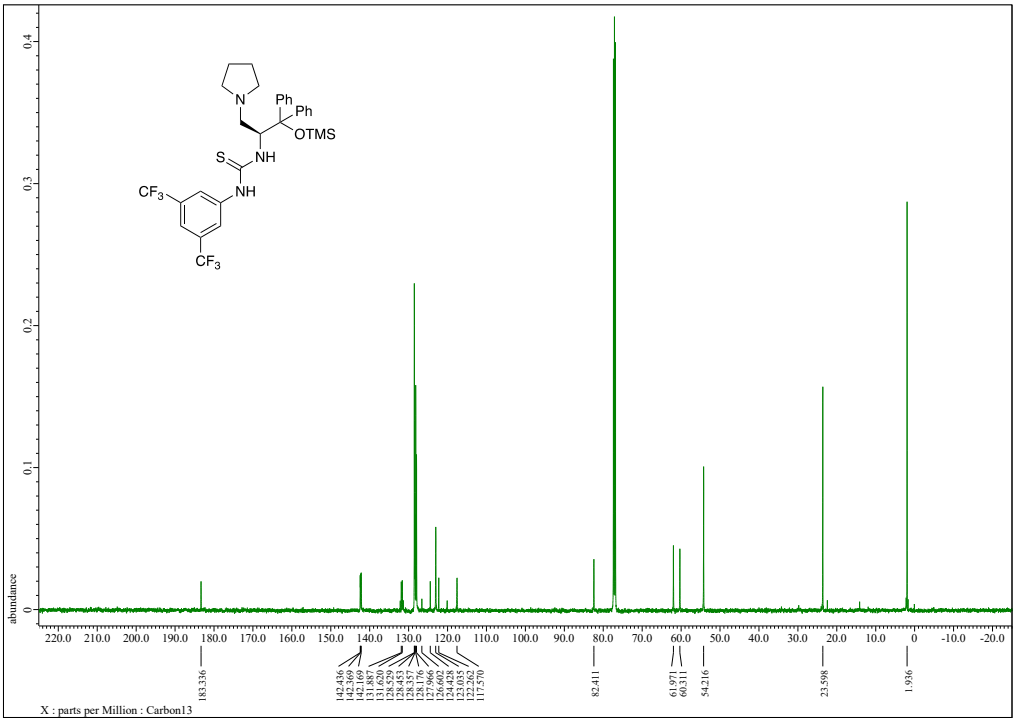


(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1,1-diphenyl-3-(pyrrolidin-1-yl)-1-((trimethylsilyl)oxy) propan-2-yl)thiourea (Z17)

^{1}H-NMR

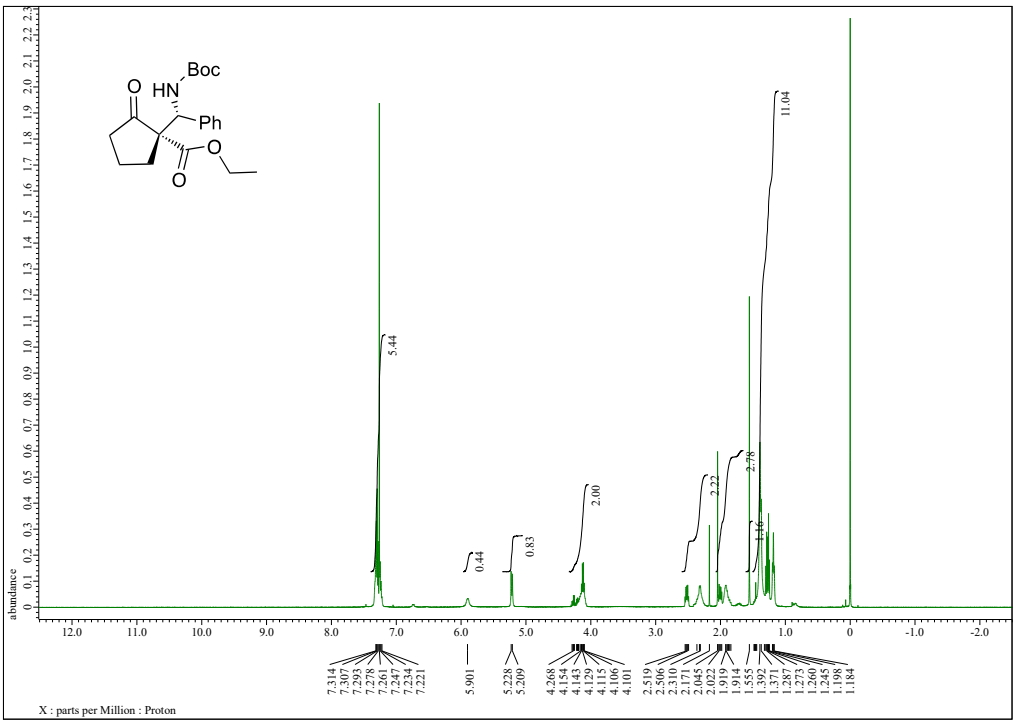


^{13}C-NMR

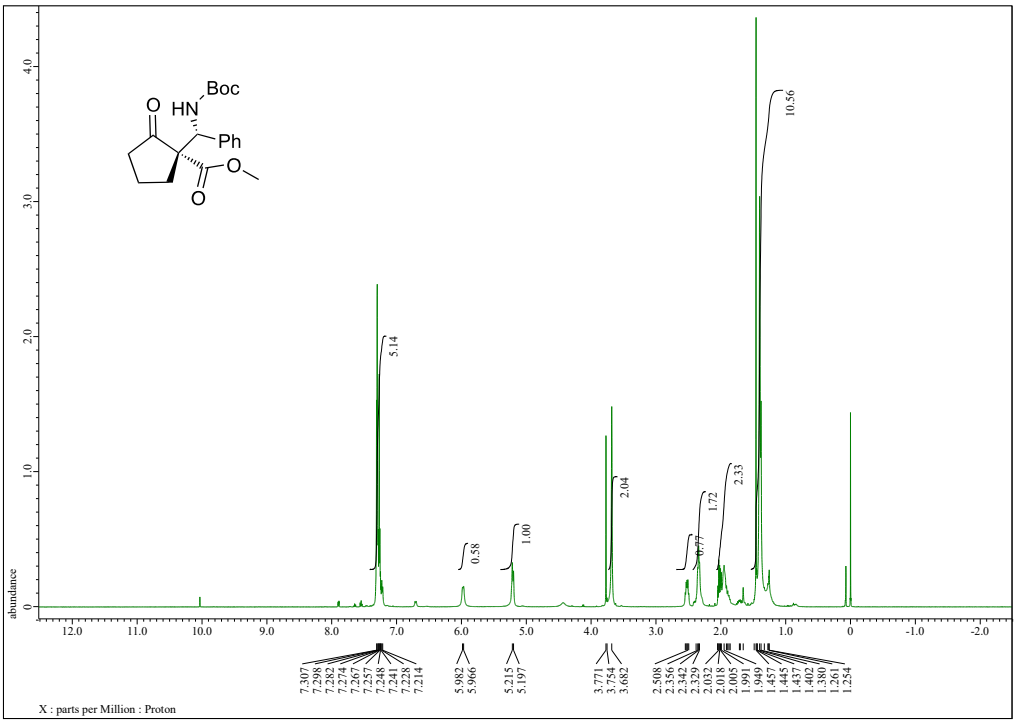


H[1] NMR spectra of the Mannich products

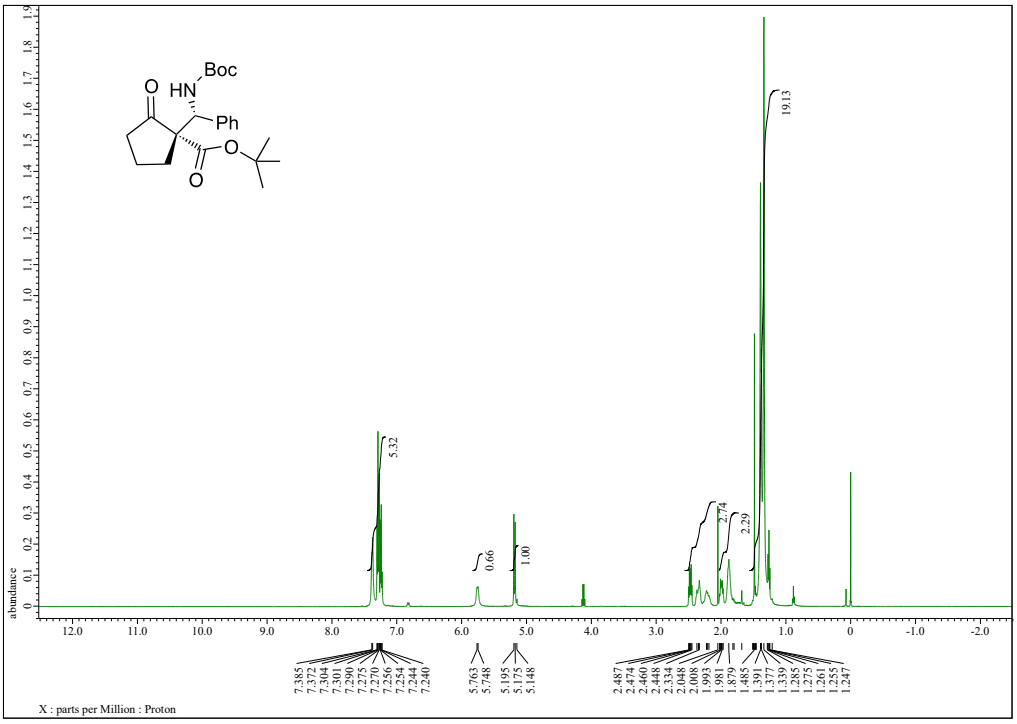
Ethyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (12a'-1)



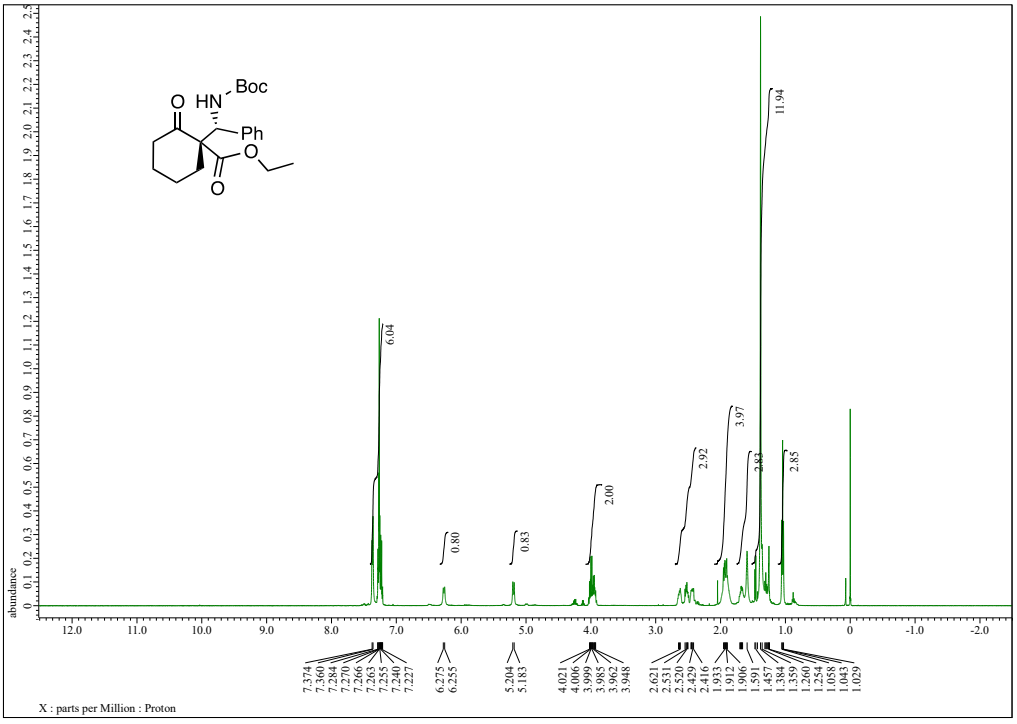
Methyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (12a'-2)



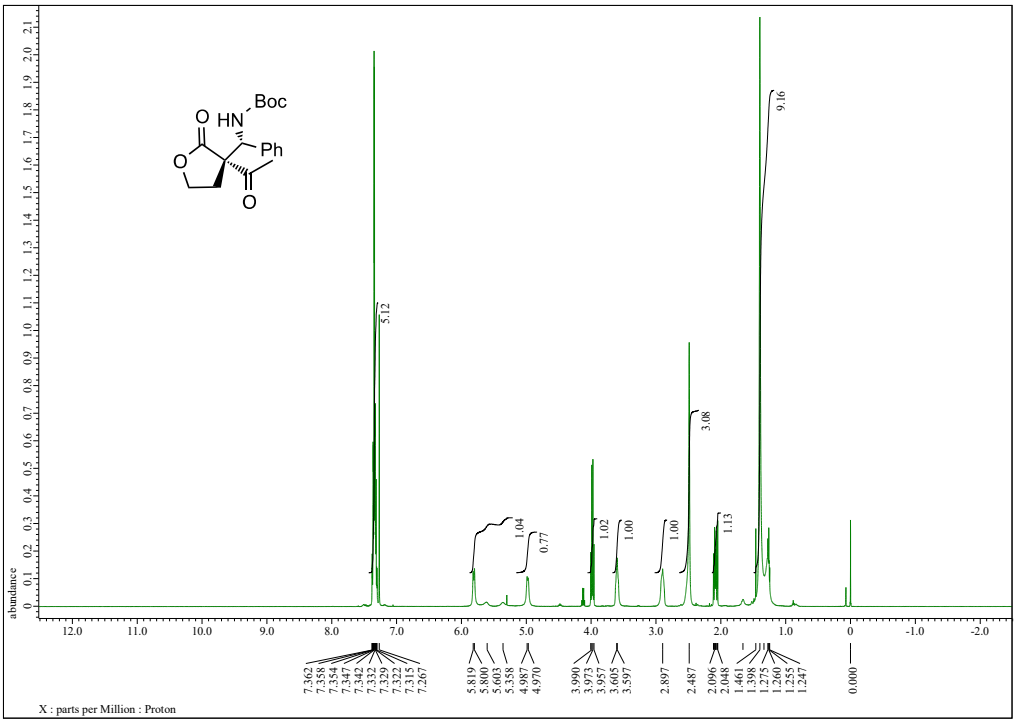
***tert*-Butyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (12a'-3)**



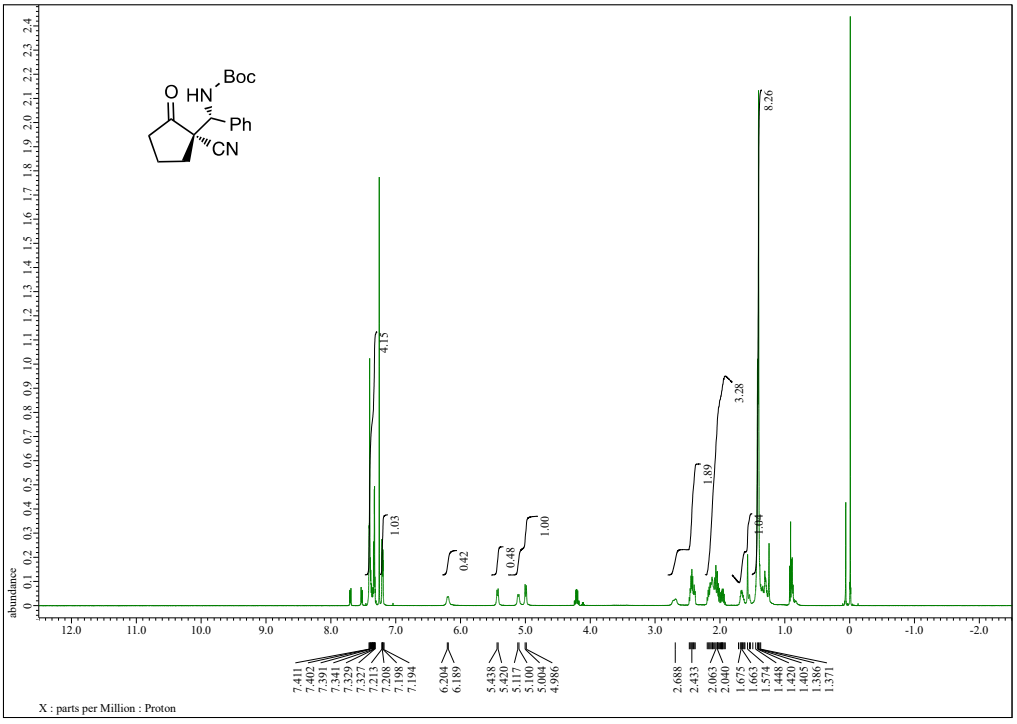
Ethyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclohexane-1-carboxylate (13)



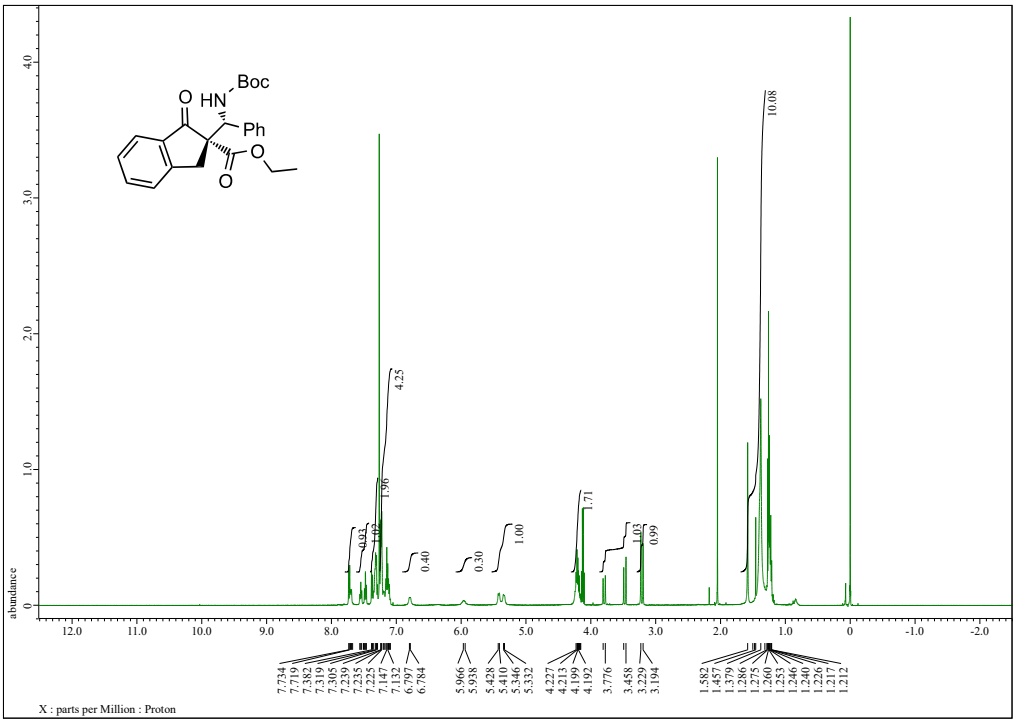
Ethyl (*R*)-3-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxotetrahydrofuran-3-carboxylate (14)



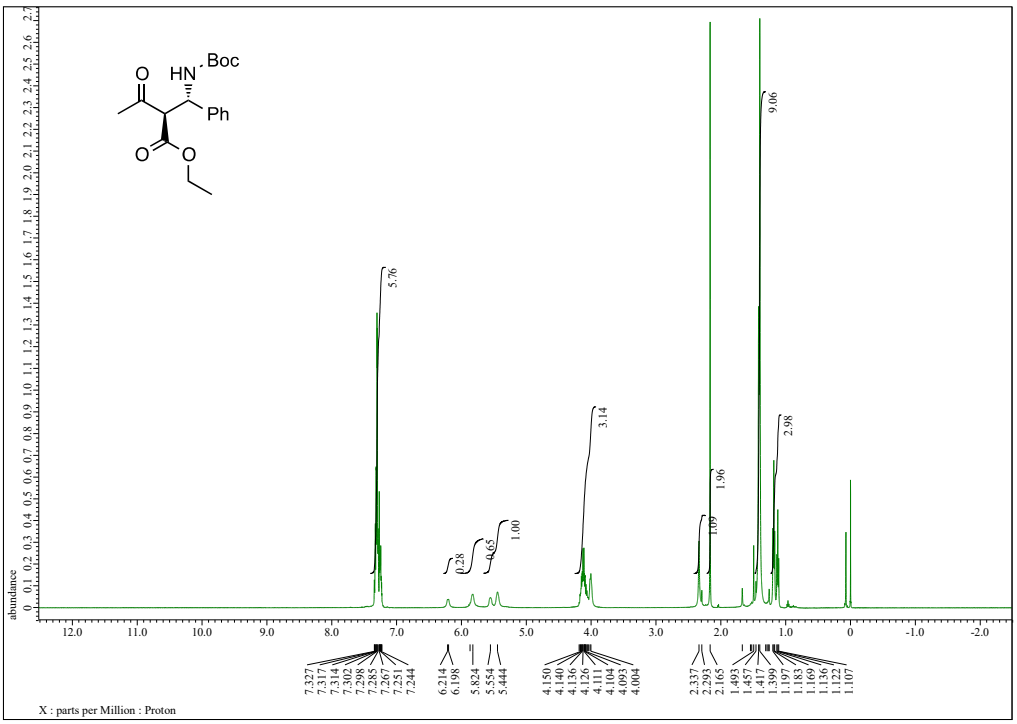
***tert*-Butyl ((*S*)-((*R*)-1-cyano-2-oxocyclopentyl)(phenyl)methyl)carbamate (15)**



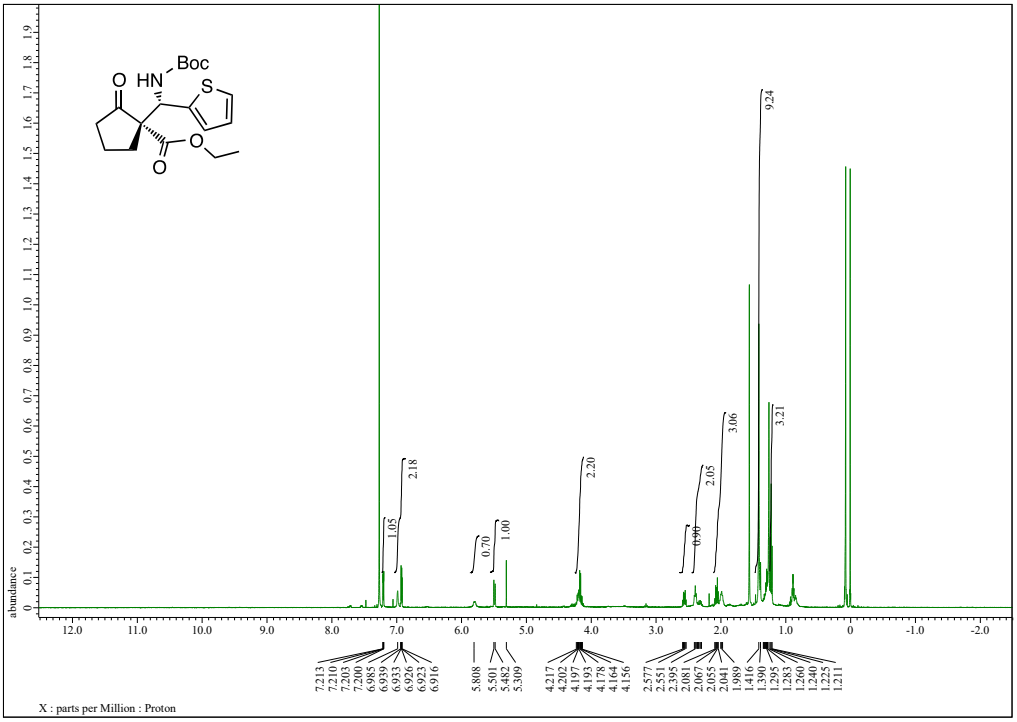
Ethyl (*S*)-2-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (16)



Ethyl (*R*)-2-((*R*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-3-oxobutanoate (17)



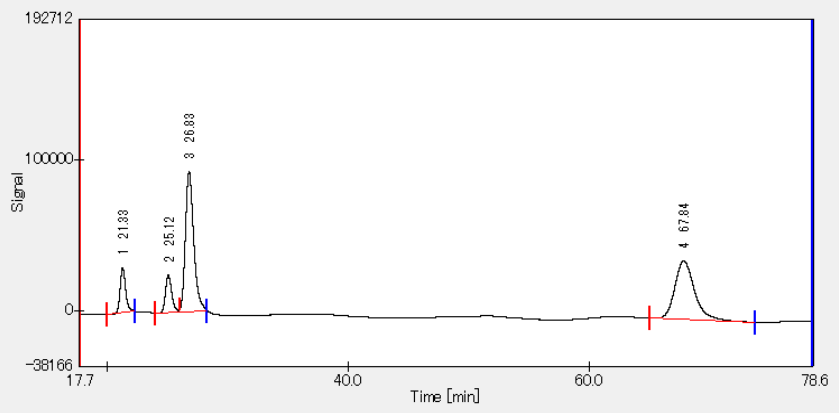
Ethyl (*S*)-1-((*R*)-((*tert*-butoxycarbonyl)amino)(thiophen-2-yl)methyl)-2-oxocyclopentane-1-carboxylate (18)



5. HPLC SPECTRA OF MANNICH PRODUCTS

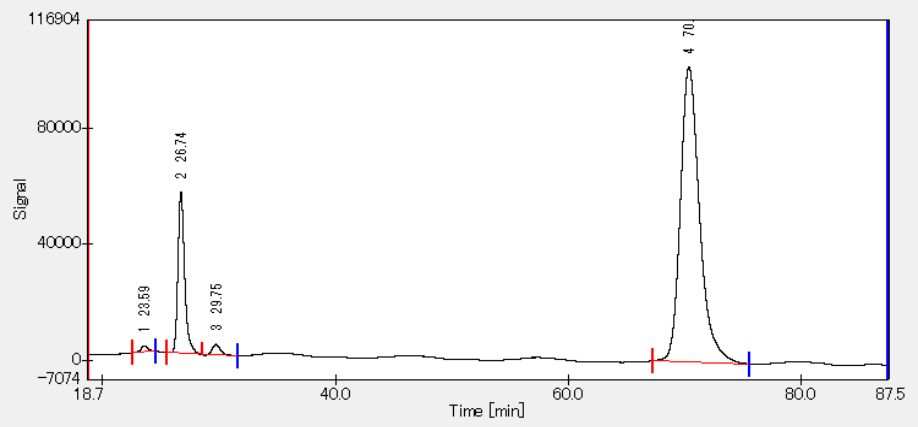
Ethyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (**12a'-1**): *AD-H column, n-hexane/iso-propanol = 98 : 2, flow rate = 1.0 mL/min, λ=210 nm, 98% ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	21.33	958525.3	8.9536	29961	9421.6	1.297	4.083
2	25.12	888978.341	8.304	24605	10934.2	1.217	1.529
3	26.83	4457404.86	41.6369	92925	7076.6	1.318	19.103
4	67.84	4400505.8	41.1054	38777	7853.3	1.314	*****
		10705414.3	100	186268			

Chiral

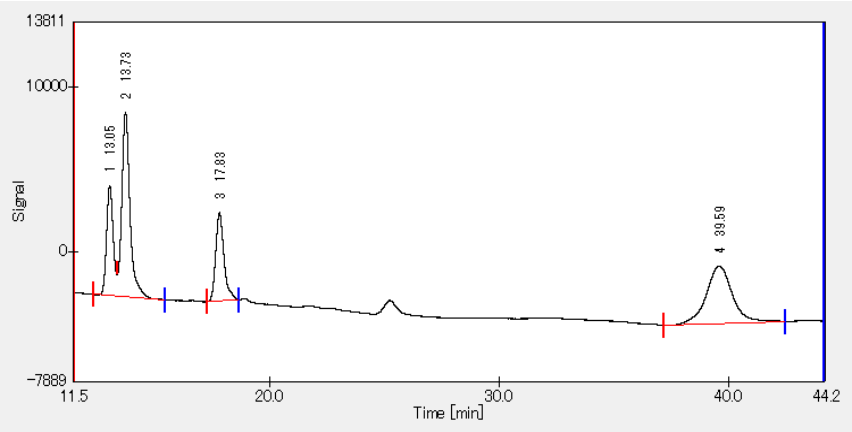


No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	23.59	88535.2	0.6292	2102	5617.8	1.086	2.696
2	26.74	2198580	15.626	55562	10332	1.333	2.859
3	29.75	138863.9	0.9869	3515	12827.1	1.247	19.819
4	70.33	11644073	82.7579	101722	8312.6	1.309	*****

	14070053	100	162901

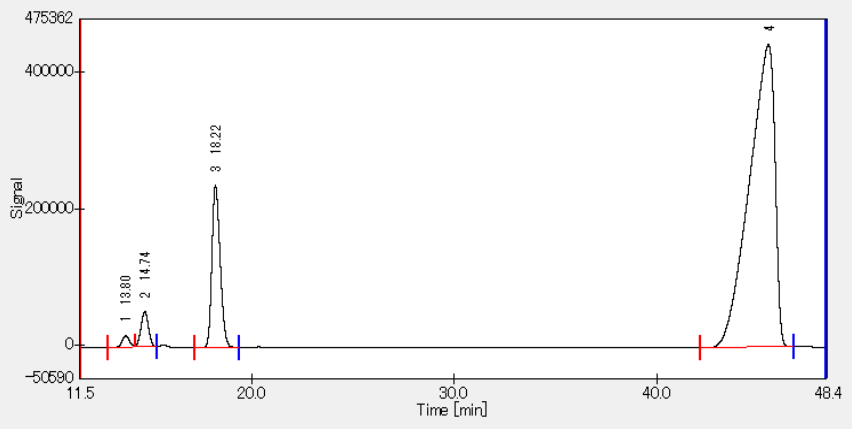
Methyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (**12a'-2**): *AD-H column, n-hexane/iso-propanol = 95 : 5, flow rate = 1.0 mL/min, λ=220 nm, 93% ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.05	135295.4	16.5167	6627	9237.4	*****	1.141
2	13.73	276791.3	33.7904	11149	6921.5	*****	6.147
3	17.83	134613.4	16.4335	5323	10293.8	1.343	15.085
4	39.59	272441.4	33.2594	3459	5267.2	1.03	*****
		819141.5	100	26558			

Chiral

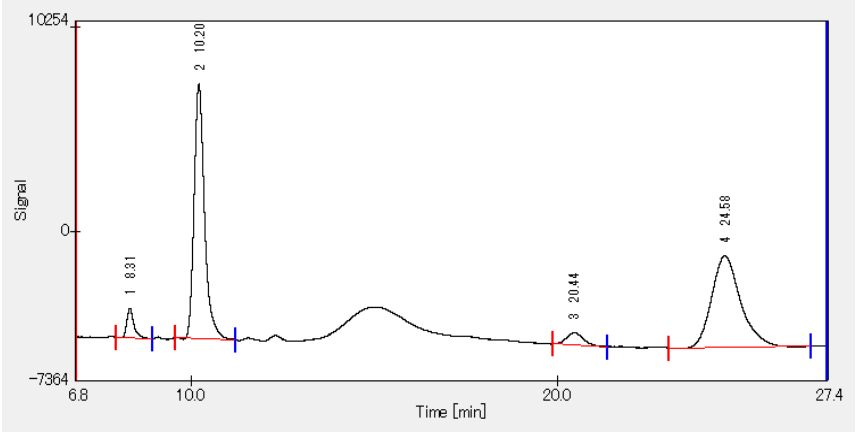


No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.8	388975.2	0.8271	16482	7738	*****	1.435
2	14.74	1319521	2.8058	51767	7564	1.003	4.896

3	18.22	6627609	14.0929	236638	9438.6	1.243	17.428
4	45.49	38691966	82.2742	441723	5852.2	0.653	*****
		47028071	100	746610			

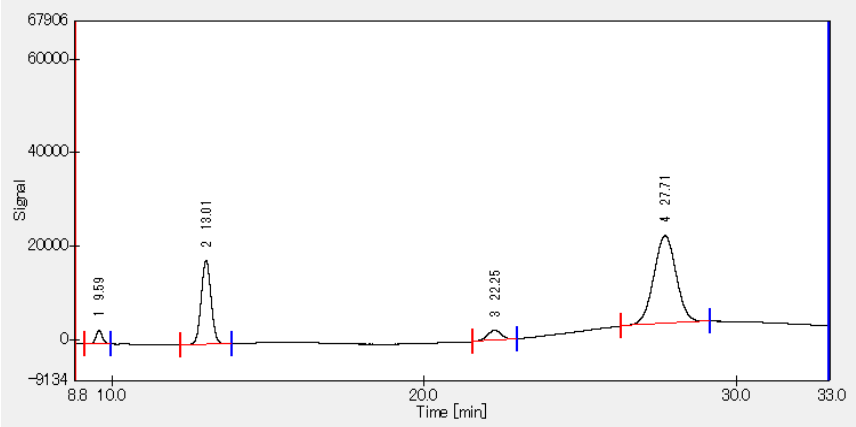
tert-Butyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclopentane-1-carboxylate (**12a'-3**) *AD-H column, n-hexane/iso-propanol = 95 : 5, flow rate = 1.0 mL/min, λ=220 nm, 41 % ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	8.31	19054.8	3.614	1438	7544.1	1.591	4.112
2	10.2	246334	46.7201	12452	5780.1	1.33	14.658
3	20.44	19246	3.6502	599	9021.3	1.163	3.443
4	24.58	242620.4	46.0157	4467	4055.6	1.229	*****
		527255.2	100	18956			

Chiral



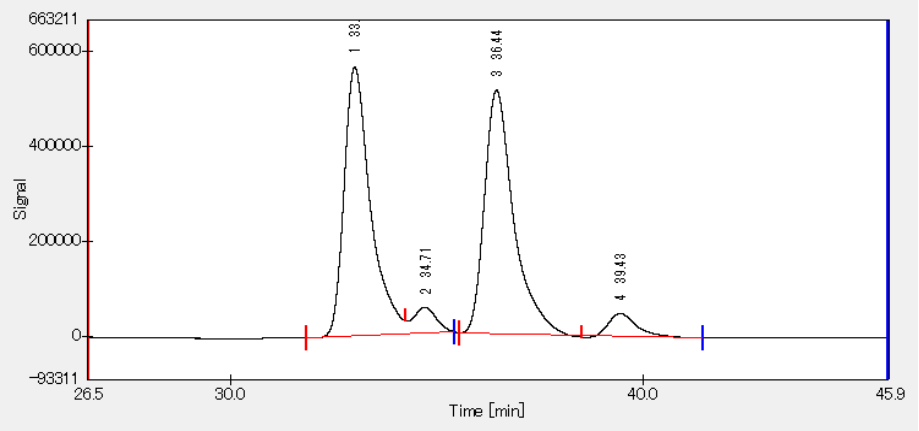
No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution

1	9.59	40400.9	2.8059	2984	11017.3	1.098	7.235
2	13.01	392496.2	27.2593	17985	8000.7	1.053	13.124
3	22.25	64297.1	4.4655	2094	11618.1	0.987	5.059
4	27.71	942668.2	65.4693	18872	6902.9	1.019	*****
		1439862	100	41935			

Ethyl (*S*)-1-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxocyclohexane-1-carboxylate (**13**):

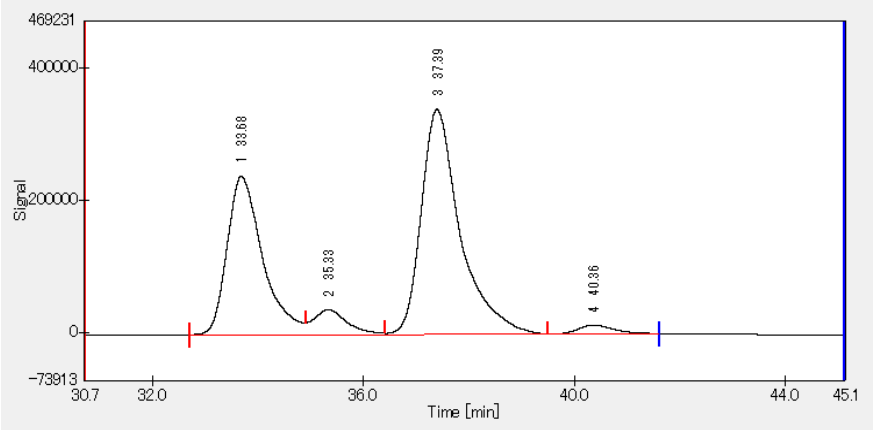
AD-H column, n-hexane/iso-propanol = 96 : 4, flow rate = 0.3 mL/min, λ=210 nm, 22% ee

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	33.01	25235297	46.0606	566161	12406.1	1.605	1.525
2	34.71	2150810	3.9258	54761	17665.7	*****	1.47
3	36.44	25186108	45.9709	511898	12407.5	1.525	2.366
4	39.43	2214901	4.0427	48322	16738.5	1.616	*****
		54787116	100	1181142			

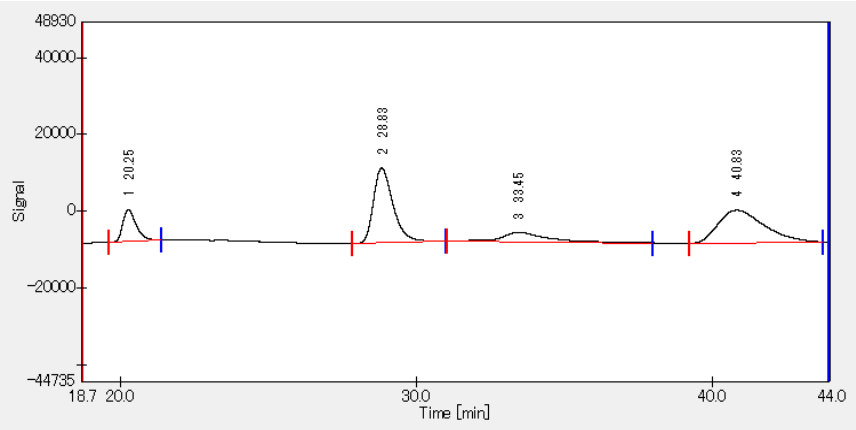
Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	33.68	11195875.3	36.386	238956	11690.5	*****	1.376
2	35.33	1621286.03	5.2691	37414	15038.4	*****	1.64
3	37.39	17341358.7	56.3585	339186	12099.9	1.564	2.304
4	40.36	611228.352	1.9865	13342	17558.7	1.398	*****
		30769748.4	100	628898			

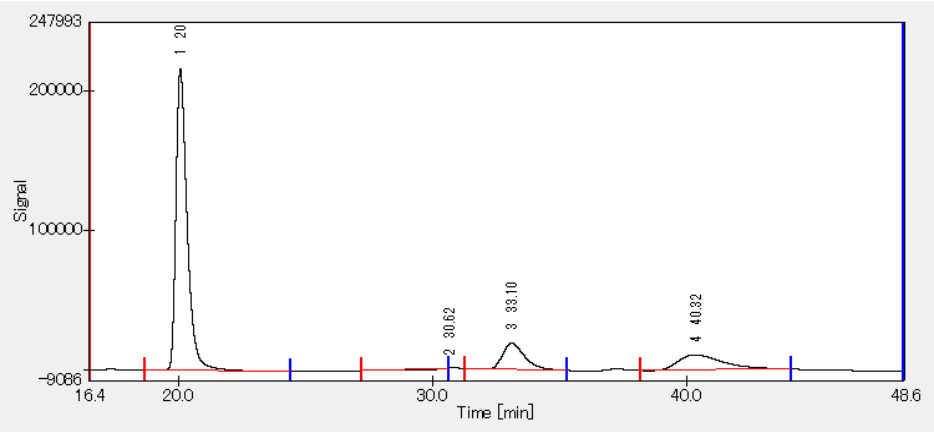
Ethyl (*R*)-3-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-2-oxotetrahydrofuran-3-carboxylate (**14**): *OD-H colum, n-hexane/iso-propanol = 80 : 20, flow rate = 0.5 mL/min, λ=210 nm, 71% ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	20.25	260642.2	11.201	8294	8886.7	1.428	8.174
2	28.83	887447.2	38.1376	19410	8668.9	1.388	2.161
3	33.45	248224.8	10.6673	2366	1933.3	1.502	2.441
4	40.83	930644.6	39.994	8556	2958.7	1.445	*****
		2326958.8	100	38626			

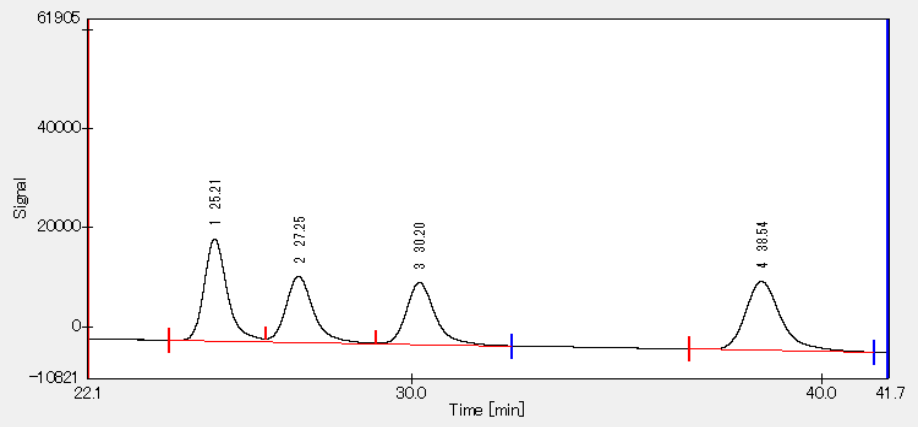
Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	20.04	6581029	73.3153	216070	9639.6	1.504	*****
2	30.62	0	0	0	*****	*****	*****
3	33.1	1120441	12.4822	18638	6357.7	1.482	2.819
4	40.32	1337830	14.904	10852	2170	1.752	*****
		8976341	100	245560			

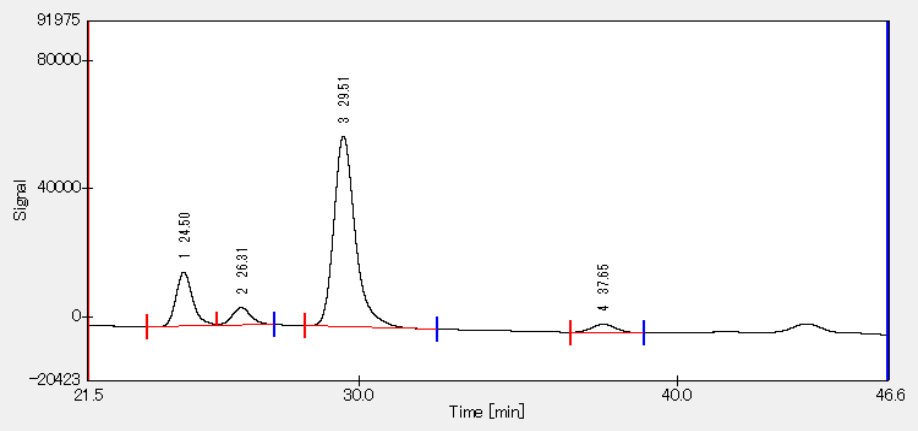
tert-Butyl ((*S*)-((*R*)-1-cyano-2-oxocyclopentyl)(phenyl)methyl)carbamate (**15**): *AD-H column, n-hexane/iso-propanol = 95 : 5, flow rate = 1.0 mL/min, λ=220 nm, 85 % ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	25.21	808378.9	28.1425	20647	9375.6	1.334	1.793
2	27.25	623461.4	21.7048	13352	7705.4	1.237	2.323
3	30.2	607848.1	21.1613	12509	8734.8	1.317	5.788
4	38.54	832764.4	28.9914	13914	9098	1.315	*****
		2872453	100	60422			

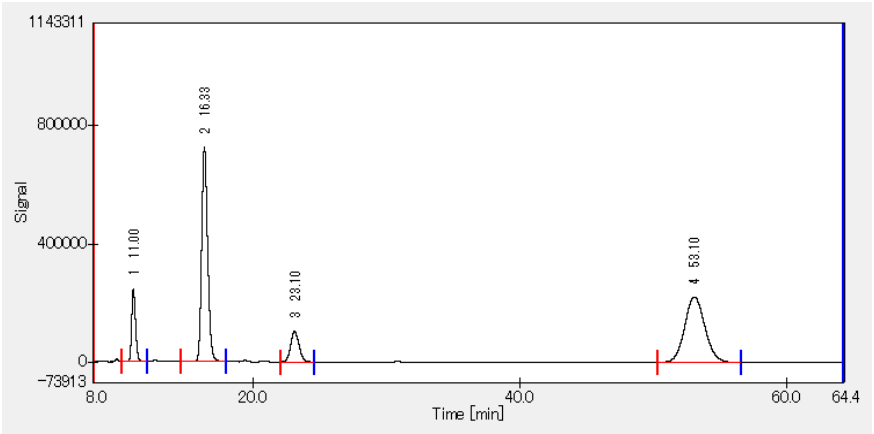
Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	24.5	614756.4	16.3252	16929	10296.1	1.292	1.737
2	26.31	228414.2	6.0657	5453	8921.5	*****	2.717
3	29.51	2785356	73.9668	59563	8688.9	1.337	6.083
4	37.65	137157.4	3.6423	2607	11425.5	1.113	*****
		3765684	100	84552			

Ethyl (*S*)-2-((*S*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**16**): *IC column, n-hexane/iso-propanol = 70 : 30, flow rate = 0.7 mL/min, λ=214 nm, 99% ee*

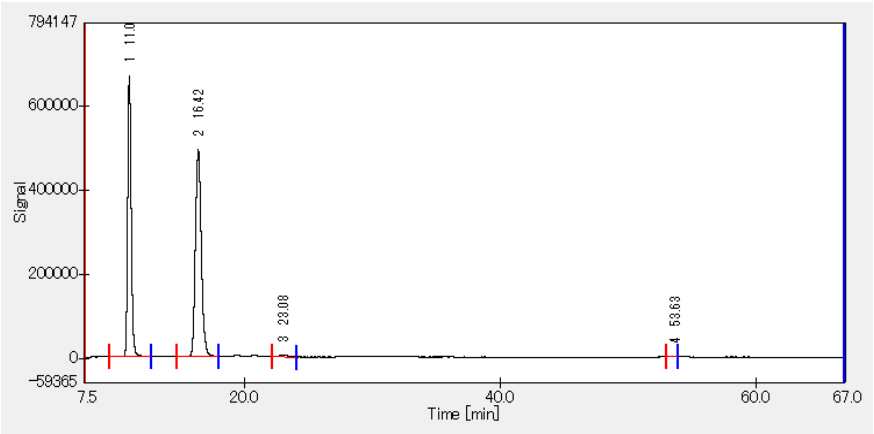
Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	11	4943201	8.937	245463	6643.7	1.234	7.769
2	16.33	22689689.2	41.0218	727393	6148	1.173	6.748
3	23.1	4500302	8.1363	102871	6204.6	1.109	15.038

4	53.1	23178143.5	41.9049	220731	5689.3	1.097	*****
		55311335.7	100	1296458			

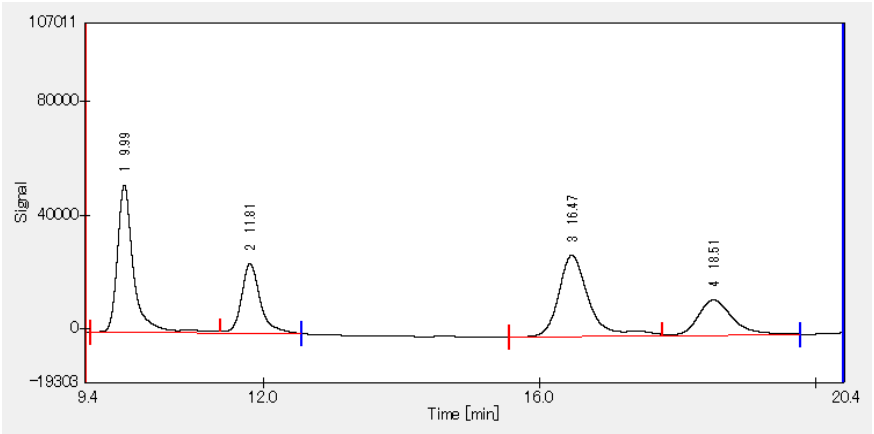
Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	11.03	12816258.4	44.5285	665753	7563.8	1.196	7.964
2	16.42	15745454.4	54.7056	492210	6013.9	1.168	6.522
3	23.08	209497.8	0.7279	4774	5986.5	1.1	31.253
4	53.63	10947.3	0.038	482	79206.3	0.77	*****
		28782157.9	100	1163219			

Ethyl (*R*)-2-((*R*)-((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-3-oxobutanoate (**17**): *AD-H column, n-hexane/EtOH = 90 : 10, flow rate = 1.0 mL/min, λ=210 nm, 91% ee*

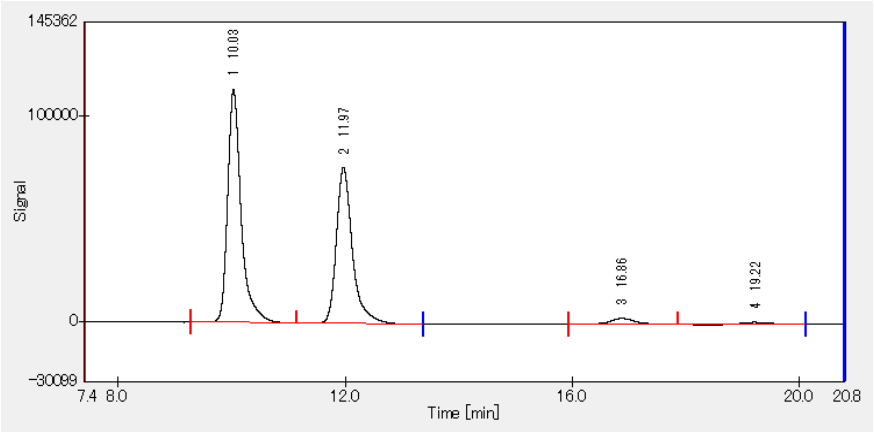
Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	9.99	853616.192	32.8635	51649	8264.4	1.505	3.873

2	11.81	460190.208	17.7169	24463	8915.1	1.329	7.15
3	16.47	859869.886	33.1042	28507	6741.1	1.708	2.384
4	18.51	423784.814	16.3153	12360	6592.4	1.314	*****
		2597461.1	100	116979			

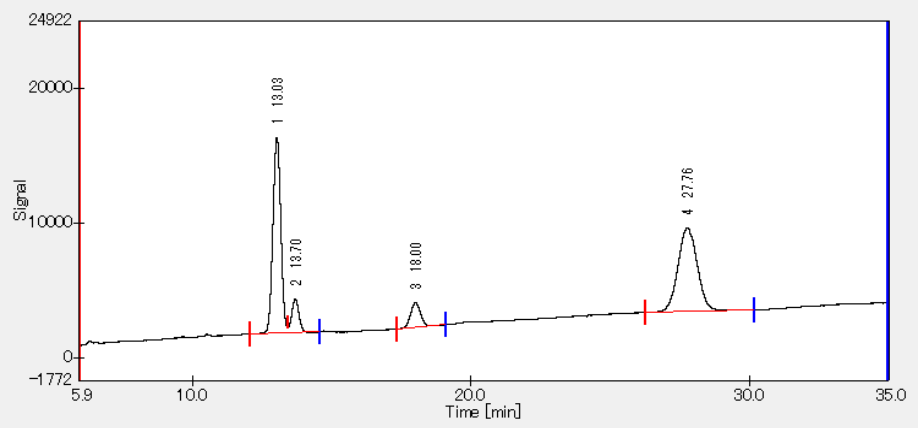
Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	10.03	1889541.9	54.3043	113609	8226.2	1.468	4.008
2	11.97	1501402.3	43.1494	76211	8345.8	1.417	7.274
3	16.86	85404.333	2.4545	2762	6727.5	1.036	5.087
4	19.22	3193.667	0.0918	826	558752.5	1.132	*****
		3479542.2	100	193408			

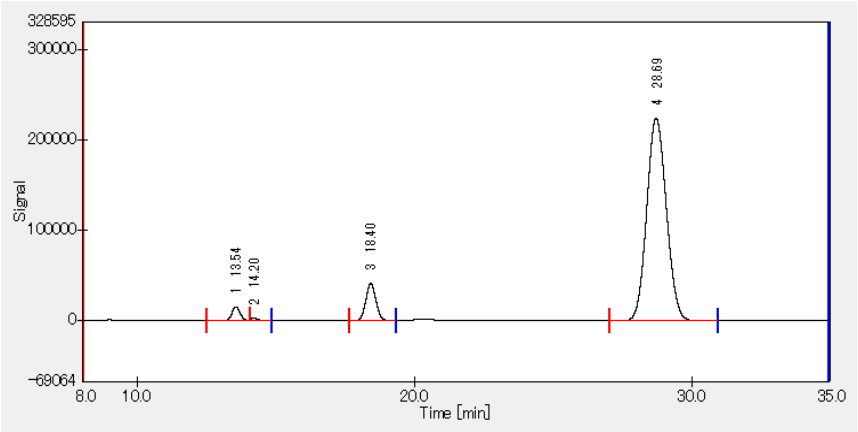
Ethyl (*S*)-1-((*R*)-((*tert*-butoxycarbonyl)amino)(thiophen-2-yl)methyl)-2-oxocyclopentane-1-carboxylate (**18**): *IC column, n-hexane/iso-propanol = 95 : 5, flow rate = 1.0 mL/min, λ=220 nm, 94% ee*

Racemic



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.03	286551.7	42.5083	14539	9891.4	1.017	1.331
2	13.7	44052.17	6.5349	2479	13437.9	*****	7.714
3	18	44189.4	6.5552	1825	12094.5	1.058	10.077
4	27.76	299314.1	44.4015	6222	7513.8	1.04	*****
		674107.4	100	25065			

Chiral



No	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.54	326865.586	2.6227	15417	9229.9	1.094	1.277
2	14.2	49018.614	0.3933	2777	14645.1	*****	7.311
3	18.4	1054185.9	8.4584	41260	11622.1	1.067	10.314
4	28.69	11033076.8	88.5256	224288	7646.7	1.082	*****
		12463146.9	100	283742			

6. Theoretical Calculations

The DFT method (at the B3LYP/6-31G(d) level of theory) was used to perform the conformational analysis with Gaussian 16 program package. The Gas phase geometry optimizations were performed using the B3LYP hybrid density functional and the 6-31G(d) basis set as implemented in the Gaussian 16. Vibrational mode analysis was performed for all structures to ensure that they have zero imaginary frequency.

1) Gaussian 16, Revision A.03,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov,

J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

Table S1. Cartesian coordinates (Angstroms) for **10a** in gas phase.
Point Group: C1
Imaginary Freq: 0
Sum of electronic and thermal Free Energies = −537.608004 hartree

Symbol	X	Y	Z
C	0	0	0
C	0	0	1.546319
C	1.485759	0	1.948413
C	2.211424	0.682513	0.746007
C	1.195296	0.885495	-0.37851
H	0.16156	-1.02175	-0.35817
H	-0.94614	0.357683	-0.41692
H	-0.54107	-0.85515	1.958553
H	-0.47342	0.914457	1.924109
H	1.716127	0.570852	2.852017
H	0.920291	1.950745	-0.3783

H	1.651498	0.672608	-1.34984
O	3.37871	0.991215	0.727259
C	2.053821	-1.40186	2.110925
O	1.608371	-2.39173	1.565488
O	3.131508	-1.39017	2.915085
C	3.846309	-2.64271	3.069609
H	4.345621	-2.54635	4.036558
H	3.120531	-3.4584	3.113963
C	4.845361	-2.84487	1.940969
H	5.437784	-3.74818	2.126906
H	4.328408	-2.96493	0.984647
H	5.525907	-1.99083	1.86904

Table S2. Cartesian coordinates (Angstroms) for **11a** in gas phase.
Point Group: C1
Imaginary Freq: 0
Sum of electronic and thermal Free Energies = −671.316624 hartree

Symbol	X	Y	Z
C	0.115806	0.070538	-0.10651
C	-0.00457	0.162563	1.28533
C	1.127835	0.109931	2.090005

C	2.398968	-0.03747	1.507936
C	2.511364	-0.12564	0.112113
C	1.374454	-0.07341	-0.69279
H	-0.77211	0.113366	-0.73163
H	-0.98544	0.277356	1.738378
H	1.055744	0.183898	3.170353
H	3.49466	-0.23749	-0.33949
H	1.469478	-0.1436	-1.77271
C	3.611422	-0.10547	2.330251
H	4.556245	-0.20455	1.779123
N	3.581653	-0.05222	3.608982
C	4.786847	-0.11486	4.331687
O	5.069754	0.689626	5.193525
O	5.514609	-1.19563	3.973196
C	6.783681	-1.52413	4.654511
C	7.22026	-2.80486	3.93929
H	8.167698	-3.16364	4.355137
H	6.467958	-3.59085	4.060135
H	7.359351	-2.6225	2.86858

C	7.801064	-0.4004	4.433037
H	8.772756	-0.69936	4.842083
H	7.929784	-0.20824	3.361858
H	7.482466	0.521165	4.922526
C	6.522729	-1.79087	6.140326
H	7.443663	-2.1485	6.614515
H	6.193549	-0.88545	6.652437
H	5.75648	-2.56466	6.259128

Table S3. Cartesian coordinates (Angstroms) for **Z3** in gas phase.
Point Group: C1
Imaginary Freq: 0
Sum of electronic and thermal Free Energies = −2319.530637 hartree

Symbol	X	Y	Z
S	-0.02214	-0.01687	0.004489
O	-0.03808	-0.02499	5.307451
H	0.955432	-0.01502	5.356323
N	-0.88764	2.185785	1.198985
H	-1.3067	2.300308	0.285192
C	-1.83837	-0.93108	4.028858
F	-5.19445	4.323623	2.72116

F	-4.62053	5.748215	4.268548
F	1.405373	5.772295	4.094177
F	-4.85683	3.645871	4.759744
F	-0.00757	6.131659	5.713981
N	2.538163	-0.02261	4.445799
N	0.091326	0.640893	2.620405
H	-0.24358	1.22535	3.380111
F	1.088897	4.252893	5.611817
C	0.509966	-0.68959	3.060499
H	0.269982	-1.37361	2.243539
C	-0.02258	-2.62277	6.288186
H	-0.23737	-1.77358	6.927636
C	0.273351	-3.53554	4.080148
H	0.299625	-3.42874	2.999351
C	-0.00211	-2.43098	4.90009
C	-0.6347	4.582226	4.030307
C	-1.25688	3.087037	2.229143
C	-0.33234	-1.03351	4.340428
C	-1.97528	4.863469	4.281164

H	-2.25381	5.548647	5.072426
C	-2.60701	3.367558	2.477745
H	-3.3754	2.874467	1.892306
C	-0.27168	3.71511	2.997406
H	0.774176	3.531314	2.776386
C	-2.62543	0.04379	4.654365
H	-2.16825	0.701668	5.383743
C	2.03599	-0.77529	3.284087
H	2.285785	-1.8273	3.44613
H	2.535094	-0.45682	2.354212
C	0.525332	-4.7928	4.633016
H	0.740816	-5.63245	3.977369
C	4.213744	0.509472	6.002579
H	3.60663	0.465146	6.913664
H	5.264172	0.413294	6.292855
C	2.803613	1.418572	4.214722
H	1.890974	1.996375	4.384315
H	3.120582	1.593721	3.17433
C	0.50336	-4.97024	6.016384

H	0.699704	-5.94862	6.446603
C	3.766797	-0.58453	5.034188
H	4.540057	-0.76124	4.264026
H	3.545345	-1.54137	5.517895
C	-3.98251	0.172112	4.346436
H	-4.56816	0.950537	4.828126
C	3.922112	1.806657	5.215482
H	3.617021	2.631165	5.866024
H	4.814954	2.134888	4.673356
C	0.227105	-3.87872	6.841286
H	0.2041	-4.00358	7.920922
C	-4.41176	4.498184	3.8053
C	-0.27245	0.955772	1.357364
C	0.459087	5.195715	4.866231
C	-2.44556	-1.78468	3.097785
H	-1.86449	-2.55563	2.601694
C	-4.57526	-0.67857	3.413862
H	-5.63053	-0.58021	3.173
C	-2.95652	4.257343	3.491655

C	-3.80032	-1.66051	2.793006
H	-4.24859	-2.33134	2.06498

7. X-Ray Crystallography

Single crystals suitable for X-ray crystallography were obtained by recrystallization from CH_2Cl_2/hexane.

Crystallographic data of **Z3** has been deposited with Cambridge Crystallographic Data Center, deposition no. CCDC 2179025.

Table S4. Crystal data and structure refinement for **Z3**.

Empirical formula	C28H27F6N3OS
Formula weight	567.58
Temperature/K	100(1)
Crystal system	triclinic
Space group	*P*1
a/Å	9.2836(7)
b/Å	10.9381(7)
c/Å	13.6479(10)
α/°	98.031(6)
β/°	98.938(6)
γ/°	90.963(6)
Volume/Å^3	1354.57(17)
Z	2
ρ calcg/cm^3	1.392
μ/mm^{-1}	1.671
F(000)	588.0
Crystal size/mm^3	0.17 × 0.03 × 0.02
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.624 to 133.962
Index ranges	−11 ≤ h ≤ 11, −12 ≤ k ≤ 13, −16 ≤ l ≤ 16
Reflections collected	15416
Independent reflections	8669 [Rint = 0.1467, Rsigma = 0.1511]
Data/restraints/parameters	8669/519/716
Goodness-of-fit on F2	0.998
Final R indexes [I>=2σ (I)]	R1 = 0.0826, wR2 = 0.1954
Final R indexes [all data]	R1 = 0.1264, wR2 = 0.2257
Largest diff. peak/hole /eÅ^{-3}	0.55/−0.42
Flack parameter	0.10(3)