Supporting information

Iridium-Catalyzed Diastereoselective Amination of Alcohols with Chiral *tert*-Butanesulfinamide by the Use of Borrowing Hydrogen Methodology

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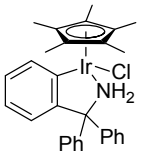
I. General Information

All reactios were carried out under nitrogen atmosphere in the tube and other glassware, and all the solvents employed in the reaction were toluene and *tert*-amyl alcohol, which we bought from Sinopharm Reagent Company and drought it through the activated Na-4Å molecular sieve under nitrogen atmosphere for 20 min. Organic solutions were concentrated under pressure on a rotary evaporate. (*R*)-(+)-*tert*-Butylsulfinamide and KOH were purchased from J&K Scientific LTD, which was grinded by a mortar and pestle. Some of alcohols used in this study were purchased without further purification and others were got through the corresponding ketones were reduced by $NaBH_4$. All the iridium catalysts were prepared as described in the literature. ^1H and ^{13}C NMR spectra were obtained on a Bruker spectrometer (600 MHz) or Mercury-Vx300-NMR spectrometer (300 MHz). $CDCl_3$ were purchased from J&K Scientific LTD. Colum chromatography was performed on silica gel (200-300 mesh) using petroleum ether / ethyl acetate = 2:1.

All new products were characterized by ^1H NMR, ^{13}C NMR, high-resolution mass spectrometry (HRMS). All ^1H NMR and ^{13}C NMR are reported in ppm relative to tetramethylsilane (0.00 ppm) unless otherwise noted. HRMS were obtained on an Agilent Q-TOF 6540. For known compound, we have cited the literature which we used to compare to our synthesized compounds, and we also have included a ^1H NMR spectrum to establish the diastereomeric ratio of unpurified products.

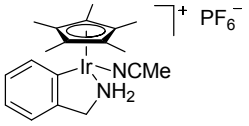
II. Synthises of iridium catalyst

Cp*IrCl[κ^2(N,C)-{$NH_2C(C_6H_5)_2$-2-C_6H_4}] (**4**)



(known compound: see Sachiko Arita, Takashi Koike, Yoshihito Kayaki, and Takao Ikariya*, *organometallics.* **2008**, 27, 2795-2802) A mixture of $[Cp^*IrCl_2]_2$ (199.2 mg, 0.25 mmol), the appropriate benzylamine (130 mg, 0.5 mmol), and NaOAc (0.051 g, 0.625 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 20 h. The solvent was removed under reduced pressure. After the reaction mixture in toluene was filtered through filter paper, evaporation of the filtrate to dryness gave the iridacycle product (249 mg, 75.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 15 H), 4.94 (d, *J* =10.2 Hz, 1 H), 5.77 (d, *J* =10.2 Hz, 1 H), 7.60-6.25 (m, 14 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 8.77, 80.0, 86.8, 122.0, 126.6, 127.3, 127.4, 128.2, 128.3, 128.5, 128.8, 128.9, 129.0, 136.4, 144.5, 147.5, 152.6 ppm.

[Ir(η^5-C_5Me_5)(C_6H_4-2-$CH_2N(CH_3)_2$)($NCCH_3$)](PF_6) (**5**)

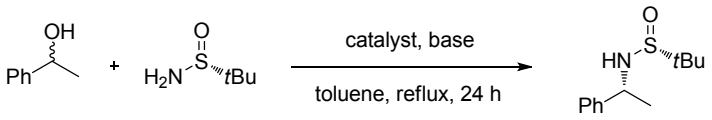


(known compound: see Thomas Jerphagnon, Arnaud J. A. Gayet, Florian Berthiol, Vincent Ritleng, Nataša Mršić, Auke Meetsma, Michel Pfeffer, Adriaan J. Minnaard, Ben L. Feringa, and Johannes G. de Vries*, *Chem. Eur. J.* **2009**, 15, 12780-12790) In a typical experiment, a 50 mL Schlenk tube was thoroughly flame dried and put under an atmosphere of nitrogen, after which the following compounds were added, respectively, in acetonitrile (5 mL): $[Cp^*IrCl_2]_2$ (159 mg, 0.2 mmol), benzylamine (0.40 mmol), NaOH (16 mg,0.4 mmol) and KPF_6 (147 mg, 0.8 mmol). This mixture was stirred at 45℃ for 16 to 50 h. The mixture was

then cooled down to RT, washed with hexane and filtered over neutral aluminium oxide (eluent: MeCN). The resulting solution was concentrated in vacuo. Subsequent stripping with dry Et_2O yielded the desired iridacycle complex.

III. Synthesis and Characterization of compounds

Table 1 Optimization of the reaction conditions



1a **2** **3a**

Entry	Catalyst	Base (mol %)	Solvent	Yield[b]	dr[c]
1	$[Cp^*IrCl_2]_2$	-	toluene	NR	-
2	$[Cp^*IrCl_2]_2$	KOH (20)	toluene	NR	-
3	**4**	-	toluene	NR	-
4	**5**	-	toluene	NR	-
5	**4**	KOH (20)	toluene	98%	>19:1
6	**5**	KOH (20)	toluene	< 5%	-
7	**4**	NaOH (20)	toluene	95%	>19:1
8	**4**	Cs_2CO_3(20)	toluene	95%	>19:1
9	**4**	KO^{t}Bu (20)	toluene	90%	>19:1
10	**4**	K_2CO_3 (20)	toluene	29%	>19:1
11	**4**	CH_3CH_2ONa (20)	toluene	13%	>19:1
12	**4**	KOH (20)	*tert*-amyl alcohol	94%	>19:1
13	**4**	KOH (20)	mesitylene	NR	-

[a]Reaction condition: **1a**(0.6 mmol), **2 (**0.5 mmol), [Cp*Ir^{III}] catalyst (5 mol%), in a solvent (1.5 mL) at 111 ^{o}C under N_2 for 24 h. [b]Yields was measured by ^{1}H NMR with interstandard. [c]The dr-valuewas determined by ^{1}H NMR analysis.

General procedure for examples in Table 1

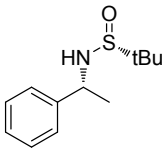
An oven dried tube equipped with a stir bar, then (R)-(+)-*tert*-Butylsulfinamide **2** (0.5 mmol, 1.0 equiv.), 1-phenylethanol **1a** (0.6 mmol, 1.2 equiv.), catalyst (0.025 mmol, 5 mol%), base (0.1 mmol, 20 mol%), and dried solvent (1.5 mL) were added in the tube. The Schlenk tube was further equipped with a condenser. After that, the reaction mixtures were heated at 111 ℃ under N_2 atmosphere for 24 h. We analyze the ^1H NMR of the unpurified resulting mixture to determine the diastereomeric ratio and conversion yield with internal standard.

General procedure for examples in Table 2

An oven dried tube equipped with a stir bar, then (R)-(+)-*tert*-Butylsulfinamide **2** (0.5 mmol, 1.0 equiv.), alcohols **1a-m** (0.6 mmol, 1.2 equiv.), Cp*IrCl[κ^2(N,C)-{$NH_2C(C_6H_5)_2$-2-C_6H_4}] (0.025 mmol, 5 mol%), KOH (0.1 mmol, 20 mol%), toluene (1.5 mL) in the Schleck tube. The Schlenk tube was further equipped with a condenser. After that, the reaction mixtures were heated at 111 ℃ under N_2 atmosphere for 24 h. We analyze the ^1H NMR of the unpurified resulting mixture to determine the diastereomeric ratio, and the dr values were compared with previous literature. The isolated yields were determined by the purified products. The crude products were purified by column chromatography (petroleum ether / ethyl acetate= 2:1).

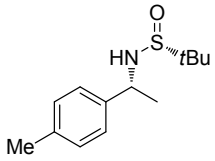
Characterizations of Compounds

(*R*)-2-methyl-N-((*R*)-1-phenylethyl)propane-2-sulfinamide. **(3a)**



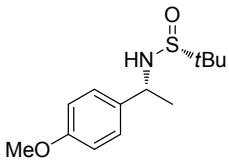
(Known compound compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J.* Am. Chem. Soc. **2014**, 136, 12548-12551) Light yellow oil, 80% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.51 (d, *J* = 6.6 Hz, 3 H), 3.42 (s, 1 H), 4.51-4.59 (m, 1 H), 7.27-7.36 (m, 5 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 22.6, 22.8, 53.9, 55.5, 126.6, 127.8, 128.8, 144.1 ppm.

(*R*)-2-methyl-N-((*R*)-1-(p-tolyl)ethyl)propane-2-sulfinamide. (3b)



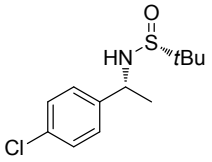
(Known compound: see Anna Adamkiewicz and Jacek Mlynarski*, *Eur. J. Org. Chem.* **2016**, 5, 1060-1065) Light yellow oil, 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23(s, 9 H), 1.49 (d, *J* = 6.6 Hz, 3 H), 2.34 (s, 3 H), 3.37 (s, 1 H), 4.48-4.55 (m, 1 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 7.23-7.25 (m, 2 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 21.0, 22.5, 22.7, 53.6, 55.3, 126.4, 129.3, 137.4, 141.0 ppm.

(*R*)-N-((*R*)-1-(4-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide. (3c)



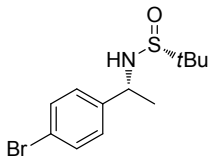
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 82% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.15 (s, 9 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 3.29 (s, 1 H), 3.73(s, 3 H), 4.40-4.46 (m, 1 H), 6.80 (d, *J* = 8.7 Hz, 2 H), 7.17-7.23 (m, 2 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 22.4, 22.6, 53.1, 55.0, 55.1, 113.8, 127.5, 135.9, 158.8 ppm.

(*R*)-N-((*R*)-1-(4-chlorophenyl)ethyl)-2-methylpropane-2-sulfinamide. (3d)



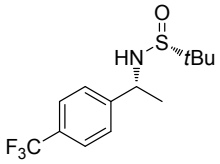
(Known compound: see Anna Adamkiewicz and Jacek Mlynarski*, *Eur. J. Org. Chem.* **2016**, 5, 1060-1065) Light yellow oil, 71% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23(s, 9 H), 1.49 (d, *J* = 3.3 Hz, 3 H), 3.37 (s, 1 H), 4.50-4.54 (m, 1 H), 7.27-7.32 (m, 4 H)ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 22.6, 22.8, 53.5, 55.6, 128.0, 128.9, 133.5, 142.5 ppm.

(*R*)-N-((*R*)-1-(4-bromophenyl)ethyl)-2-methylpropane-2-sulfinamide. (3e)



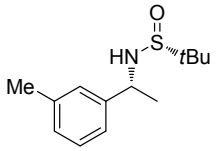
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 83% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.49 (d, *J* = 6.6 Hz, 3 H), 3.42 (s, *J* = 2.1 Hz, 1 H), 4.47-4.54 (m, 1 H), 7.22-7.28 (m, 2 H), 7.45-7.49 (m, 2 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 22.5, 22.7, 53.5, 55.5, 121.5, 128.3, 131.8, 143.0 ppm.

(*R*)-2-methyl-N-((*R*)-1-(4-(trifluoromethyl)phenyl)ethyl)propane-2-sulfinamide. (3f)



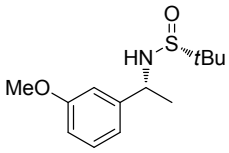
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 70% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 1.53 (dd, *J* = 1.5 Hz, 6.6, 3 H), 3.54 (s, 1 H), 4.56-4.64 (m, 1 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.61 (d, *J* = 8.1 Hz, 2 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 22.4, 22.8, 53.8, 55.6, 122.1, 125.6 (q, *J* = 3.8 Hz), 126.9, 129.9 (q, *J* = 25.6 Hz), 147.9 ppm.

(*R*)-2-methyl-N-((*R*)-1-(m-tolyl)ethyl)propane-2-sulfinamide. (3g)



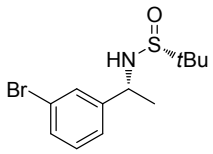
(Known compound: see Marumoto Shinji, Nishimata Toyoki, Ebisawa Masayuki, Asoh Yusuke, Fukushima Yasuo, Kato Mikio Assignee, **WO 2010/021351 A1**) Light yellow oil, 72% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.22 (s, 9 H), 1.48 (d, *J* = 3.3 Hz, 3 H), 2.34 (s, 3 H), 3.43 (d, *J* = 1.2 Hz, 1 H), 4.47-4.51 (m, 1 H), 7.08 (d, *J* = 10.8 Hz, 1 H), 7.12-7.13 (m, 2H), 7.20-7.23 (m, 1 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 21.5, 22.6, 22.8, 53.9, 55.4, 123.6, 127.4, 128.6, 128.7, 138.4, 144.0 ppm.

(*R*)-N-((*R*)-1-(3-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide. (3h)



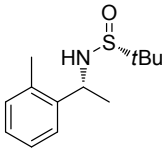
(Known compound: see Veera Reddy.Arava*, Laxminarassimhulu.Gorentla and P.K.Dubey, *Der Pharma Chemica*, **2011**, 3(1), 426-433) Light yellow oil, 94% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.16(s, 9 H), 1.42 (d, *J* = 6.6 Hz, 3 H), 3.39 (s, 1 H), 3.72 (s, 3 H), 4.44 (m, 1 H), 6.72-6.76 (m, 1 H), 6.82-6.87 (m, 2 H), 7.18 (t, *J* = 7.8 Hz, 1 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 22.5, 29.5, 53.7, 55.1, 55.3, 112.3, 112.8, 118.7, 129.6, 145.6, 159.6 ppm.

(*R*)-N-((*R*)-1-(3-bromophenyl)ethyl)-2-methylpropane-2-sulfinamide.(3i)



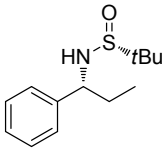
(Known compound: see Anna Adamkiewicz and Jacek Mlynarski*, *Eur. J. Org. Chem.* **2016**, 5, 1060-1065) White solid, 72% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.50 (d, *J* = 6.6 Hz, 3 H), 3.51 (d, *J* = 2.7 Hz, 1 H), 4.46-4.54 (m, 1 H), 7.18-7.23 (m, 1 H), 7.27-7.31 (m, 1 H), 7.38-7.42 (m, 1 H), 7.48-7.49 (d, *J* = 1.2, 1 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 22.4, 22.7, 53.4, 55.4, 122.6, 125.2, 129.4, 130.2, 130.7, 146.2 ppm.

(*R*)-2-methyl-N-((*R*)-1-(o-tolyl)ethyl)propane-2-sulfinamide. (3j)



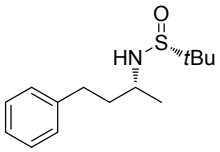
Light yellow oil, 50% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.48 (d, *J* = 6.1 Hz, 3 H), 3.38 (s, 1 H), 4.75-4.83 (m, 1 H), 7.13-7.24 (m, 3H), 7.38-7.41 (m, 1 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 19.1, 21.8, 22.5, 49.2, 55.3, 125.4, 126.4, 127.3, 130.6, 134.9, 141.9 ppm. **HRMS**: $[M+H]^+$ calculated for $C_{13}H_{22}NOS^+$: 240.1417, found 240.1417.

(*R*)-2-methyl-N-((*R*)-1-phenylpropyl)propane-2-sulfinamide.(3k)



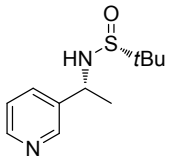
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.5 Hz, 3 H), 1.23 (s, 9 H), 1.69-1.84 (m, 1 H), 1.98-2.12(m, 1 H), 3.43 (d, *J* = 2.1 Hz, 1 H), 4.25-4.31 (m, 1 H), 7.25-7.31 (m, 5 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 9.85, 22.5, 29.2, 55.5, 60.2, 127.1, 127.6, 128.4, 142.1 ppm.

(*R*)-2-methyl-N-((*R*)-4-phenylbutan-2-yl)propane-2-sulfinamide.(3l)



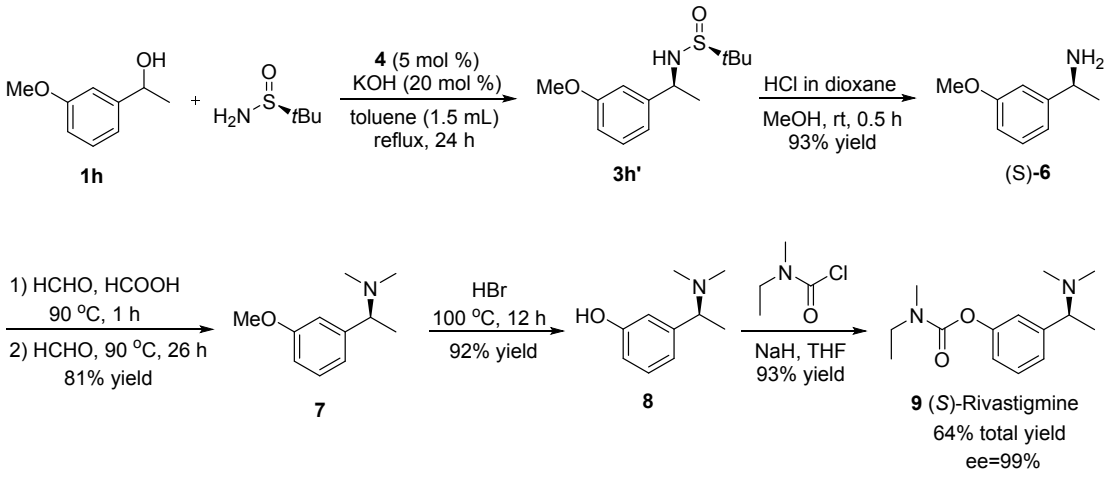
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 70% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.18 (s, 9 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 1.74-1.98 (m, 2 H), 2.63-2.79 (m, 2H), 3.11 (d, *J* = 4.2 Hz, 1 H), 3.39-3.47 (m, 1 H), 7.16-7.31 (m, 5 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 21.6, 22.5, 32.0, 39.8, 51.0, 55.2, 125.9, 128.3, 128.4, 141.4 ppm.

(*R*)-2-methyl-N-((*R*)-1-(pyridin-3-yl)ethyl)propane-2-sulfinamide.(3m)



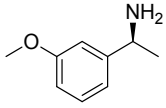
(Known compound: see Nathan J. Oldenhuis, Vy M. Dong*, Zhibin Guan*, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551) Light yellow oil, 84% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.23 (s, 9 H), 1.55 (d, *J* = 6.6 Hz, 3 H), 3.47 (s, 1 H), 4.54-4.62 (m, 1 H), 7.28-7.31 (m, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 8.54 (d, *J* = 4.5 Hz, 1 H), 8.61 (s, 1 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 21.6, 21.7, 51.1, 54.7, 122.7, 133.5, 138.4, 147.3, 148.1 ppm.

IV. Synthesis of (*S*)-Rivastigmine and NPS *R*-568



Scheme 1. Synthesis of (S)-Rivastigmine

(*S*)-1-(3-methoxyphenyl)ethanamine ((*S*)-6)


(S)-6

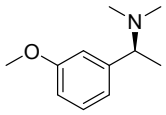
To a solution of (S)-N-((S)-1-(3-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (4 mmol, 1 equiv.) in methanol (2 mL) was add hydrochloric acid/1,4-dioxane solution (8 mmol, 2 equiv.), the mixture was stirred at room temperature for 0.5-1 h. All this procedure was under nitrogen atmosphere. The crude product was concentrated under reduced pressure to remove methanol, then washed with a saturated solution of sodium bicarbonate. The resulting mixture was extracted with dichloromethane (3*10 mL), the organic phases were combined, filtered, and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH/NH_3OH=30:1:0.1) to obtain 6 as light yellow oil with 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.6 Hz, 3 H), 1.60 (s, 2 H), 3.80 (s, 3 H), 4.07* (q, *J* = 6.6 Hz, 1 H), 6.74-6.78 (m, 1 H), 6.90-6.92 (m, 2 H), 7.21-7.25 (t, *J* = 7.5, 4.5 Hz, 1 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 25.4, 51.1, 54.9, 111.2, 111.9,

117.9, 129.3, 149.4, 159.6 ppm.

The enantiomeric ratio of **(S)-6 (as *N*-acetyl derivative)** was determined by HPLC analysis on a ChiralCel OD-H column; n-hexane/isopropanol (90:10), flow rate = 0.8 mL/min, UV = 254 nm, t_R(major) = 33.462 min and t_R(minor) = 16.918 min. 99% ee.

Optical Rotation: $[\alpha]^{20}_D$ = -16.3 (c = 1.0, MeOH). The absolute configuration of **(*S*)-6** was assigned by comparing its specific rotation with that of the same compound reported in the literature.[16c]

(*S*)-1-(3-methoxyphenyl)-N,N-dimethylethanamine (7)



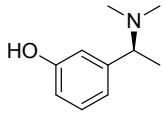
7

To a solution of (S)-1-(3-methoxyphenyl)ethanamine (0.5 mmol, 1 equiv.) in formic acid (57.5 mmol, 115 equiv.) was added a 37% solution of formaldehyde in water (15 mmol, 30 equiv.), and then the mixture was heated to 90 ℃ for 1 h. Then 37% solution of formaldehyde in water (14.5mmol, 29 equiv.) was added and the reaction mixture continued for 26 h. All this procedure was under nitrogen atmosphere. NaOH (3 mol/L) was added until basic pH and the mixture extracted with CH_2Cl_2 (3*15 mL). The organic layers were combined and dried under Na_2SO_4, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash chromatography (DCM/MeOH/NH_3OH=96:4:0.4) on silica gel to obtain 7 as yellow oil with 81% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.6 Hz, 3 H), 2.20 (s, 6 H), 3.20* (q, *J* = 6.6 Hz, 1 H), 3.81 (s, 3 H), 6.76-6.81 (m, 1 H), 6.86-6.89 (m, 2 H), 7.22 (t, J = 7.8 Hz, 1 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 20.5, 43.4, 55.2, 66.2, 112.3, 112.9, 119.9, 129.2, 145.9, 159.6 ppm.

The enantiomeric ratio of **(7)** was determined by HPLC analysis on a Chiralpak OD-

3 column; n-heptane/iPrOH/DEA (97:3:0.1), flow rate = 1.0 mL/min, UV = 277 nm, t_R(major) = 15.584 min and t_R(minor) = 12.579 min. 95% ee.

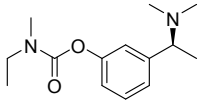
(*S*)-3-(1-(dimethylamino)ethyl)phenol (8)


8

A HBr (0.5 mL) solution was added over (S)-1-(3-methoxyphenyl)-N,N-dimethylethanamine (0.5 mmol, 1 equiv.) in a sealed tube. The reaction was heated at 100 ℃ for 12 h. Cooled the reaction mixture to room temperature, and an aqueous K_2CO_3 saturated solution was added until basic pH. The resulting mixture was extracted with EtOAc (3*15 mL), the organic layers were combined, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (DCM/MeOH/NH_3OH=96:4:0.4) to afford 8 as a white solid with 92% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.38 (d, *J* = 6.6 Hz, 3 H), 2.23 (s, 6 H), 3.24* (q, *J* = 6.6 Hz, 1 H), 6.74 (dd, *J* = 1.8, 1.8 Hz, 1 H), 6.81-6.83 (m, 2 H), 7.17 (t, *J* = 7.8 Hz, 1 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 19.5, 43.0, 66.0, 115.0, 115.3, 119.8, 129.4, 144.0, 156.8 ppm.

The enantiomeric ratio of **(8)** was determined by HPLC analysis on a Chiralpak OD-3 column; n-heptane/iPrOH/DEA (97:3:0.1), flow rate = 1.0 mL/min, UV = 277 nm, t_R(major) = 8.757 min. 99% ee.

(*S*)-Rivastigmine (9)

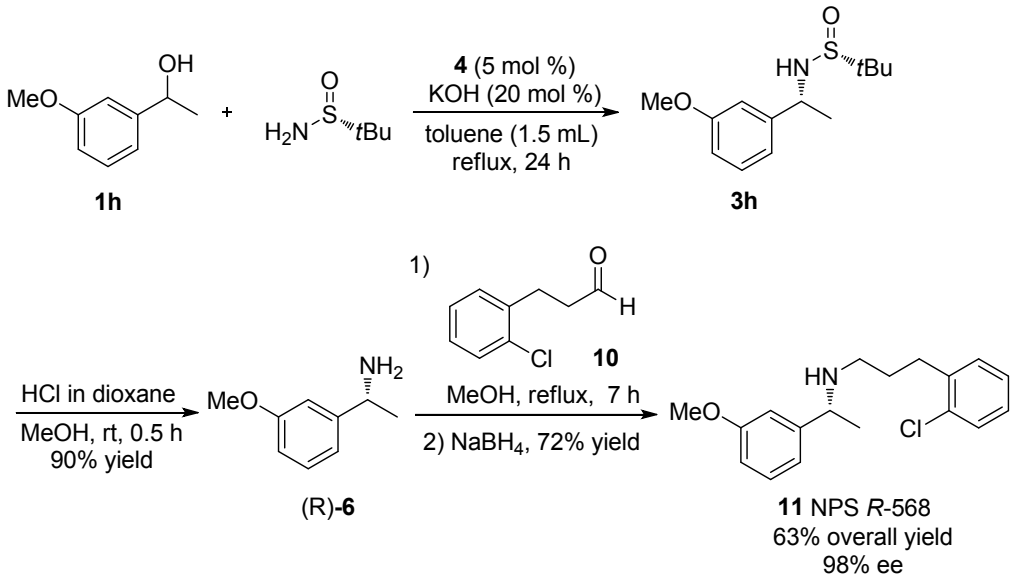

(S)-Rivastigmine

Sodium hydride (1 mmol, 2 equiv.) was suspened in dry THF, (S)-3-(1-(dimethylamino)ethyl)phenol (0.5 mmol, 1 equiv.) was added and the suspension stirred for 30 min at room temperature. A solution of N-ethyl-N-

methylcarbamoyl Chloride (1 mmol, 2 equiv.) in dry THF was add dropwise and the mixture was stirred for 5 h at room temperature. H_2O was added followed by 6 mL of K_2CO_3 saturated solution until basic pH. The resulting mixture was extracted with EtOAc, the organic layers were combined, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (DCM/MeOH/NH_3OH=94:6:0.5) to afford the (S)-Rivastigmine as colorless oil with 93% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.17-1.24 (m, 3 H), 1.39 (d, *J* = 6 Hz, 3 H), 2.23 (s, 6 H), 2.98 (s, 1.5 H), 3.05 (s, 1.5 H), 3.32* (br s, 1 H), 3.38-3.48 (m, 1 H), 7.02(t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 12.5, 13.2, 19.9, 33.8, 34.2, 42.9, 44.0, 65.7, 120.6, 120.9, 124.4, 129.0, 144.6, 151.6, 154.4, 154.6 ppm.

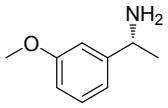
The enantiomeric ratio of **(*S*)-Rivastigmine (9)** was determined by HPLC analysis on a CHIRAL Cellulose-SB column; Hex(0.3%TFA):EtOH=85:15, flow rate = 1.0 mL/min, UV = 254 nm, t_R(major) = 3.851 min and t_R(minor) = 2.940 min. 99% ee.

Optical Rotation: $[\alpha]^{20}_D$ = -32.6 (c = 1.0, CH_2Cl_2). The absolute configuration of **(*S*)-Rivastigmine (9)** was assigned by comparing its specific rotation with that of the same compound reported in the literature.[16a]



Scheme 2. Synthesis of NPS *R*-568

(R)-1-(3-methoxyphenyl)ethanamine ((R)-6)



(R)-6

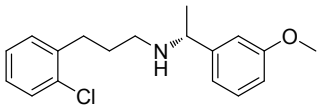
To a solution of (R)-N-((R)-1-(3-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (4 mmol, 1 equiv.) in methanol (2 mL) was add hydrochloric acid/1,4-dioxane solution (8 mmol, 2 equiv.), the mixture was stirred at room temperature for 0.5-1 h. All this procedure was under nitrogen atmosphere. The crude product was concentrated under reduced pressure to remove methanol, then washed with a saturated solution of sodium bicarbonate. The resulting mixture was extracted with dichloromethane (3*10 mL), the organic phases were combined, dried over Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH/NH_3OH=30:1:0.1) to obtain 4 as a light yellow oil with 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.6 Hz, 3 H), 1.60 (s, 2 H), 3.80 (s, 3 H), 4.07* (q, *J* = 6.6 Hz, 1 H), 6.74-6.78 (m, 1 H), 6.90-6.92 (m, 2 H), 7.21-7.25 (t, *J* =

7.5, 4.5 Hz, 1 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 25.4, 51.1, 54.9, 111.2, 111.9, 117.9, 129.3, 149.4, 159.6 ppm.

The enantiomeric ratio of **(R)-6 (as *N*-acetyl derivative)** was determined by HPLC analysis on a ChiralCel OD-H column; n-hexane/isopropanol (90:10), flow rate = 0.8 mL/min, UV = 254 nm, t_R(major) = 16.821 min and t_R(minor) = 33.869 min. 98% ee.

Optical Rotation: $[\alpha]^{20}_D$ = +16.3 (c = 1.0, MeOH). The absolute configuration of **(R)-6** was assigned by comparing its specific rotation with that of the same compound reported in the literature.[16c]

NPS *R*-568 (11)



NPS *R*-568

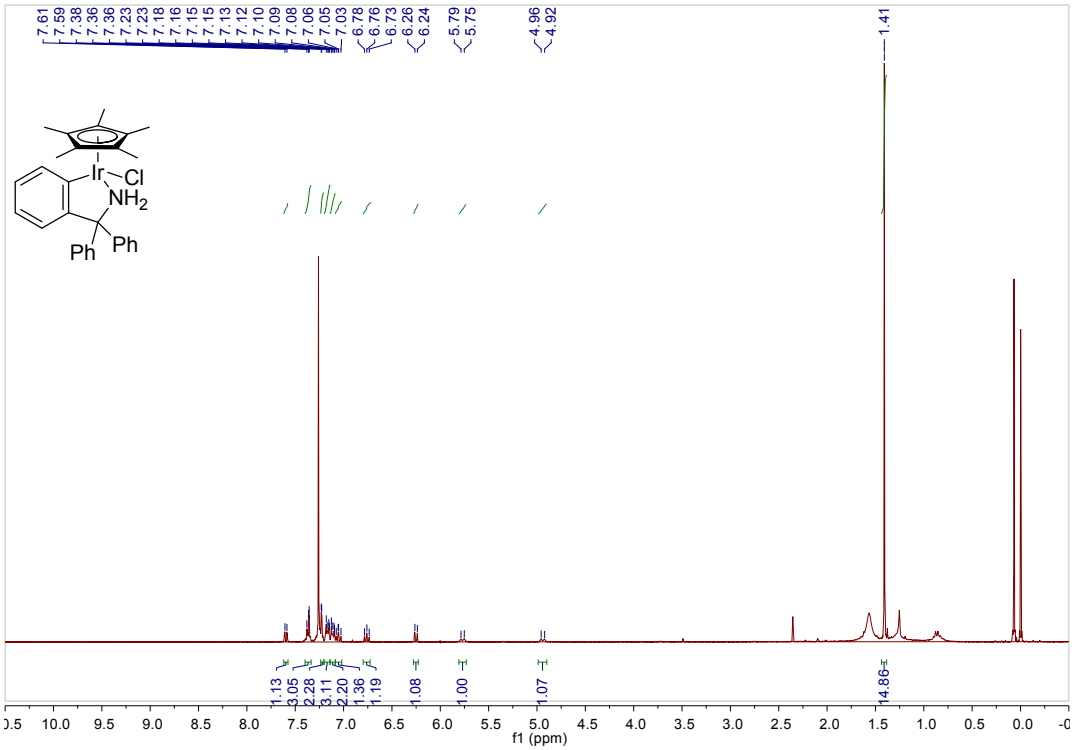
(R)-1-(3-methoxyphenyl)ethanamine (0.5 mmol, 1 equiv.) and 3-(2-chlorophenyl)propanal (0.6 mmol, 1.2 equiv.) were dissolved in 3 mL of MeOH and reflux for 7h. After that time the reaction mixture was allowed to cool down to room temperature and treated with $NaBH_4$. That followed the mixture was quenched with aqueous NH_4Cl solution and extracted three times with ethyl acetate. The Organic solution was collected, dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography (PE/EA=15:1) to obtain NPS *R*-568 as colorless oil with 72% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.6 Hz, 3 H), 1.72-1.83 (m, 2 H), 2.49-2.53 (m, 1 H), 2.55-2.59 (m, 1 H), 2.67-2.72 (m, 1 H), 2.74-2.79 (m, 1 H), 3.74 (q, *J* = 6.6 Hz, 1 H), 3.81(s, 3 H), 4.46-4.54 (m, 1 H), 6.76-6.80 (m, 1 H), 6.87-6.91 (m, 2 H), 7.09-7.17 (m, 3H), 7.22-7.25 (m, 1 H), 7.29-7.32 (m, 1 H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 24.4, 30.2, 31.4, 47.3, 55.2, 58.3, 112.1, 112.2, 119.0, 126.7,

127.3, 129.41, 129.44, 130.3, 133.9, 139.8, 147.7, 159.8 ppm.

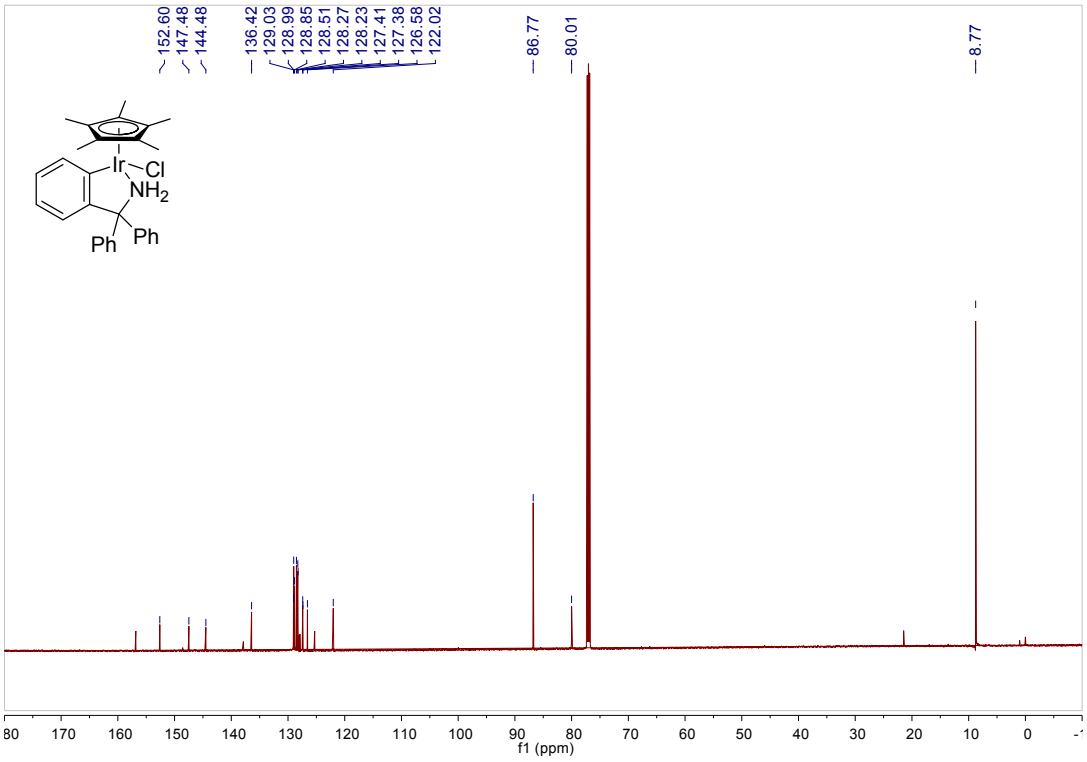
The enantiomeric ratio of **NPS *R*-568 (11)** was determined by HPLC analysis on a CHIRALPAK IG-3 column; Hex(8mMNH_3):EtOH=98:2, flow rate = 1.0 mL/min, UV = 273 nm, t_R(major) = 1.744 min and t_R(minor) = 1.503 min. 99% ee.

Optical Rotation: $[\alpha]^{20}_D$ = +38.9 (c = 0.5, $CHCl_3$). The absolute configuration of **NPS *R*-568 (11)** was assigned by comparing its specific rotation with that of the same compound reported in the literature.[16a]

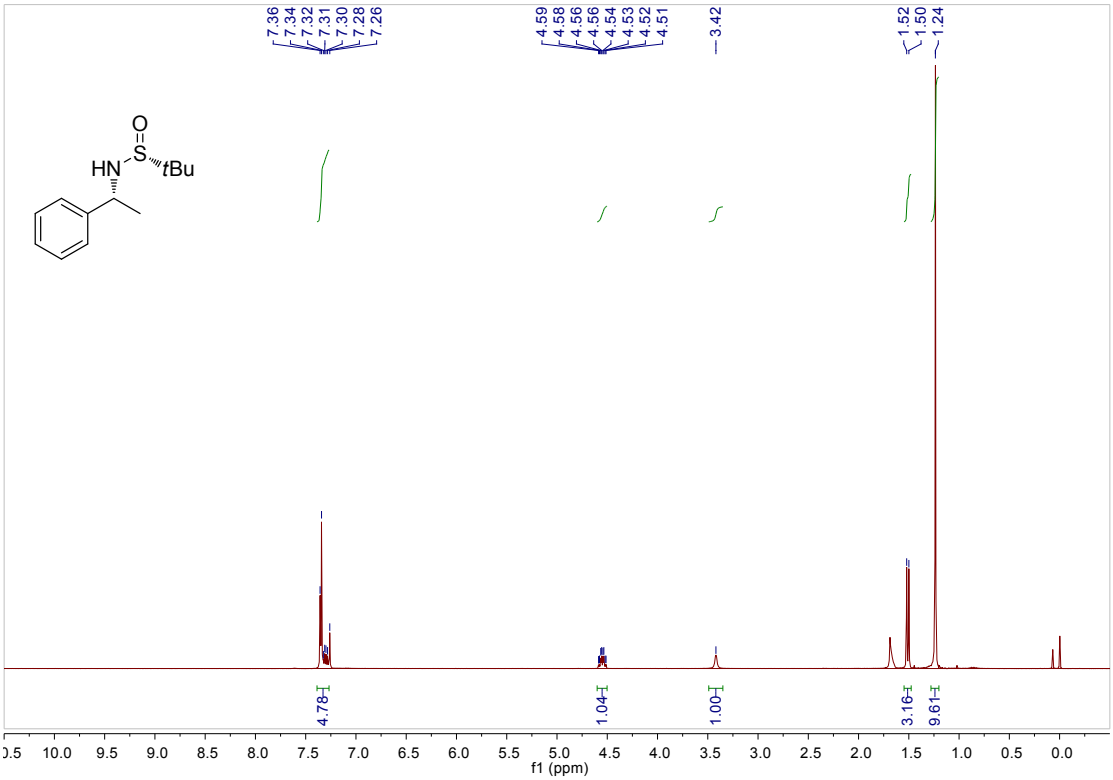
V. ^{1}H and ^{13}C spectra



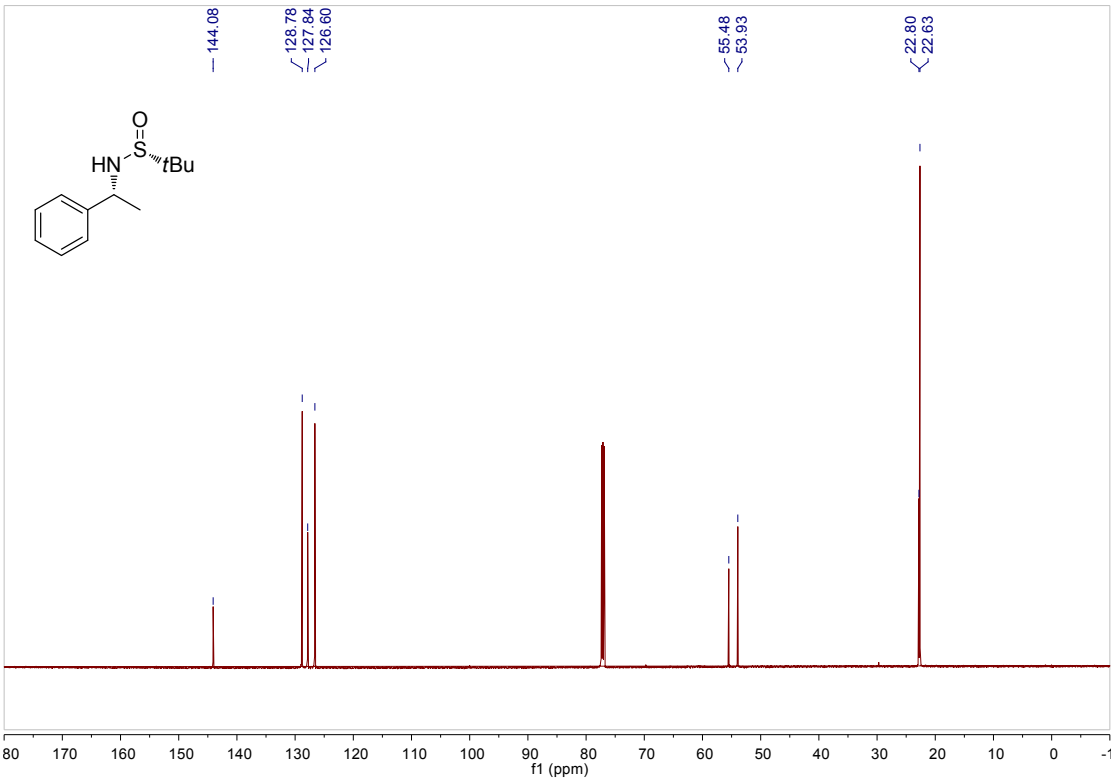
^{1}H NMR spectra of catalyst **4**



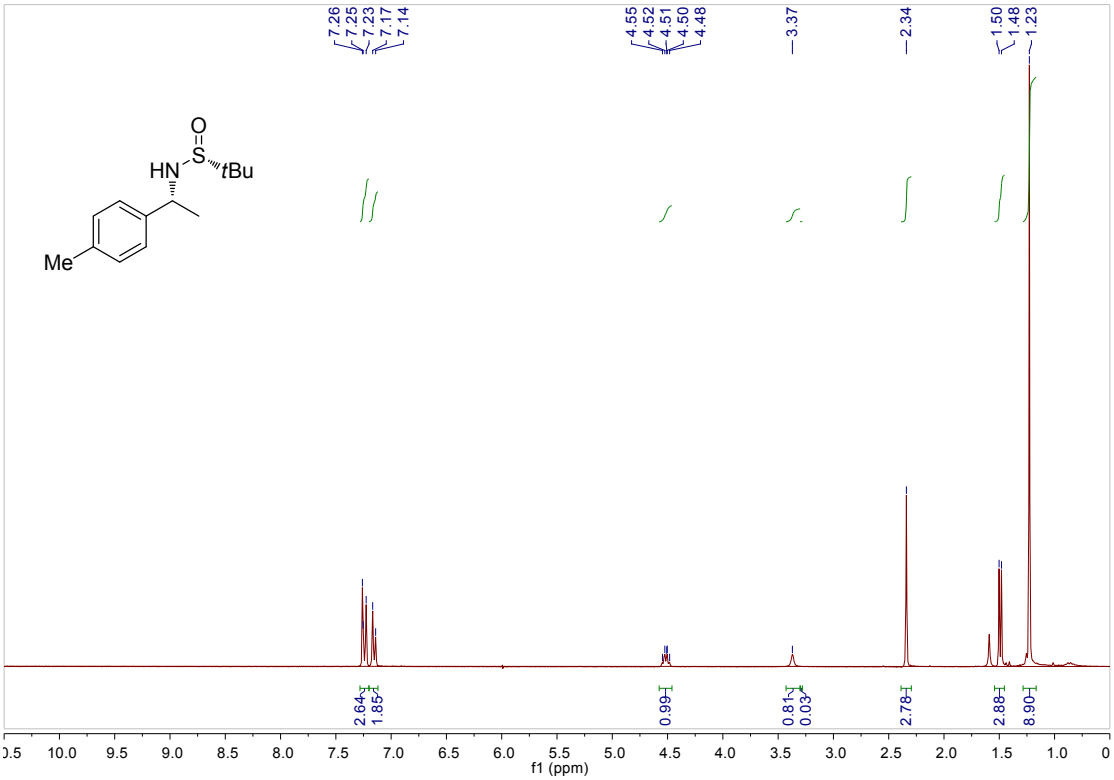
^{13}C NMR spectra of catalyst **4**



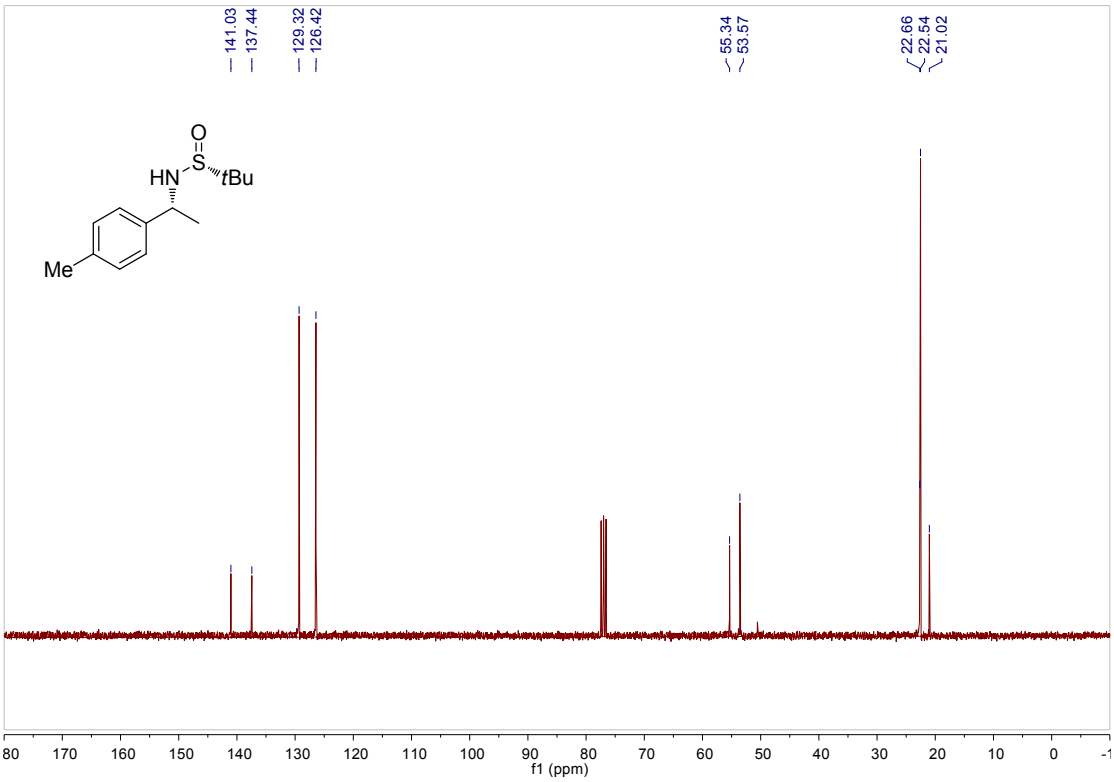
^{1}H NMR spectra of **3a**



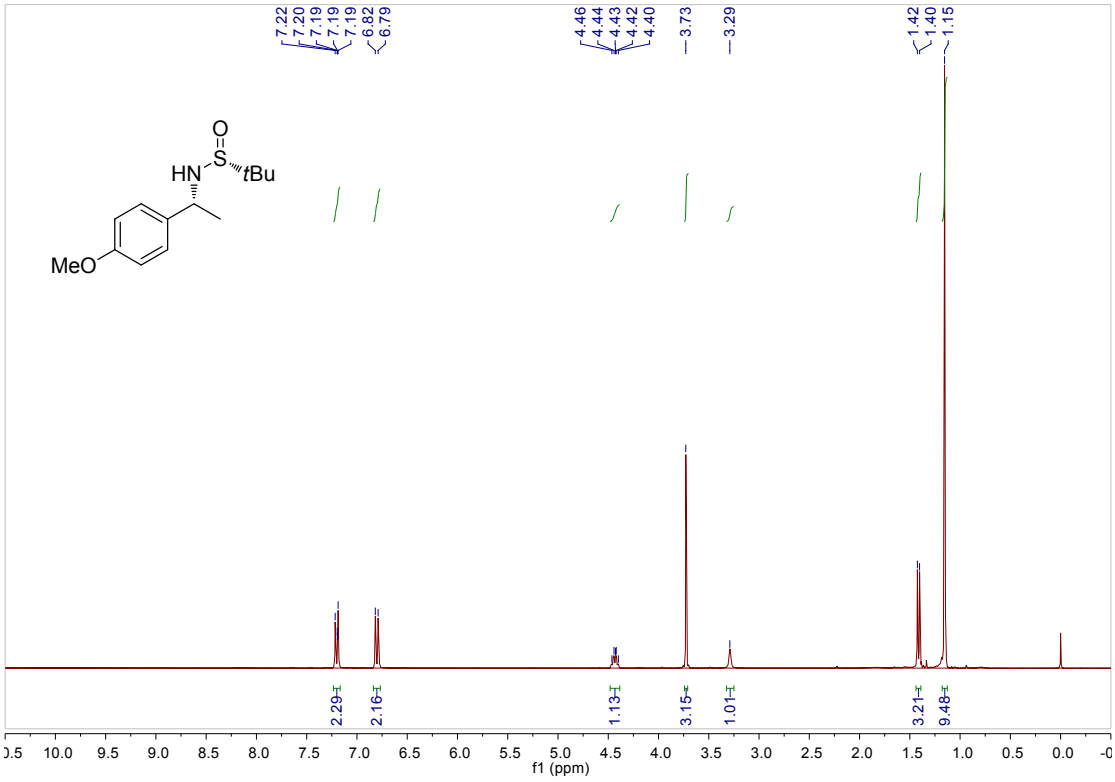
^{13}C NMR spectra of **3a**



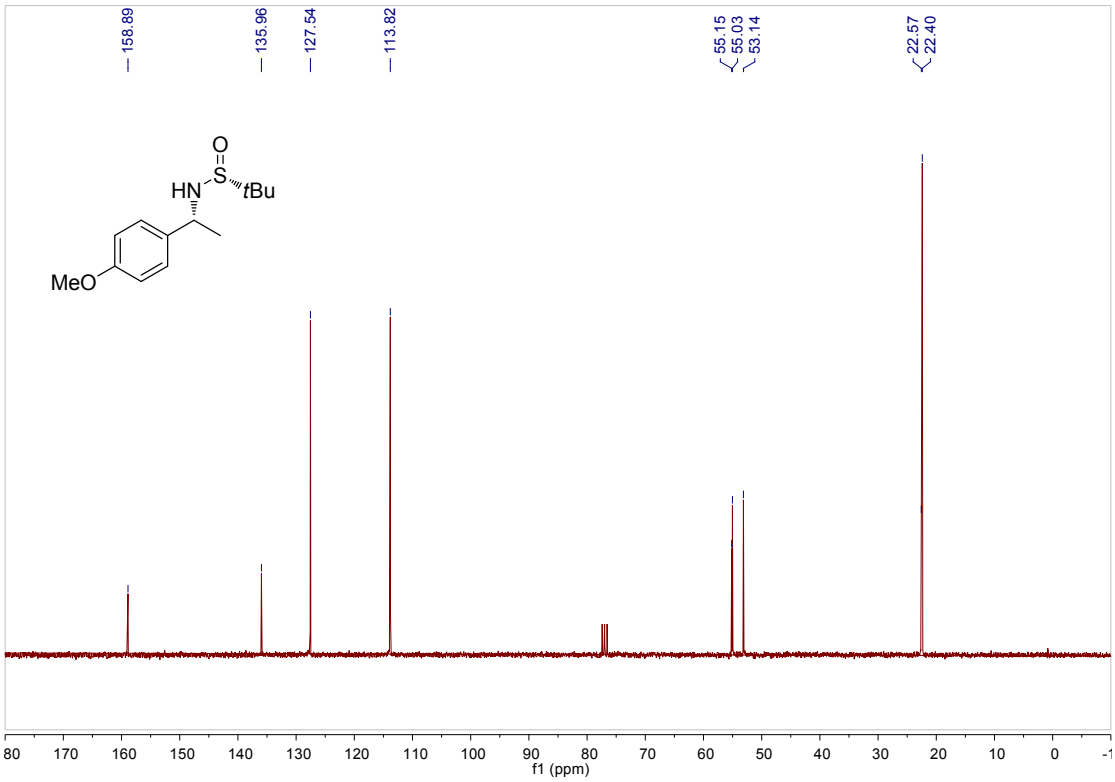
^{1}H NMR spectra of **3b**



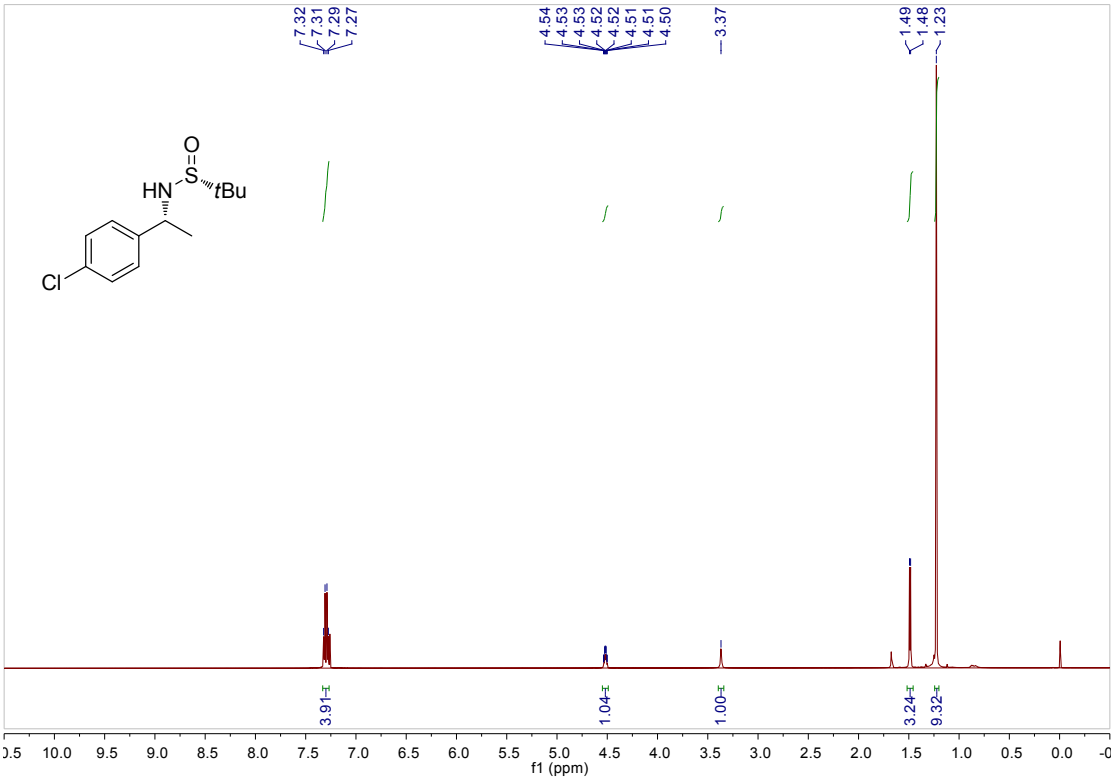
^{13}C NMR spectra of **3b**



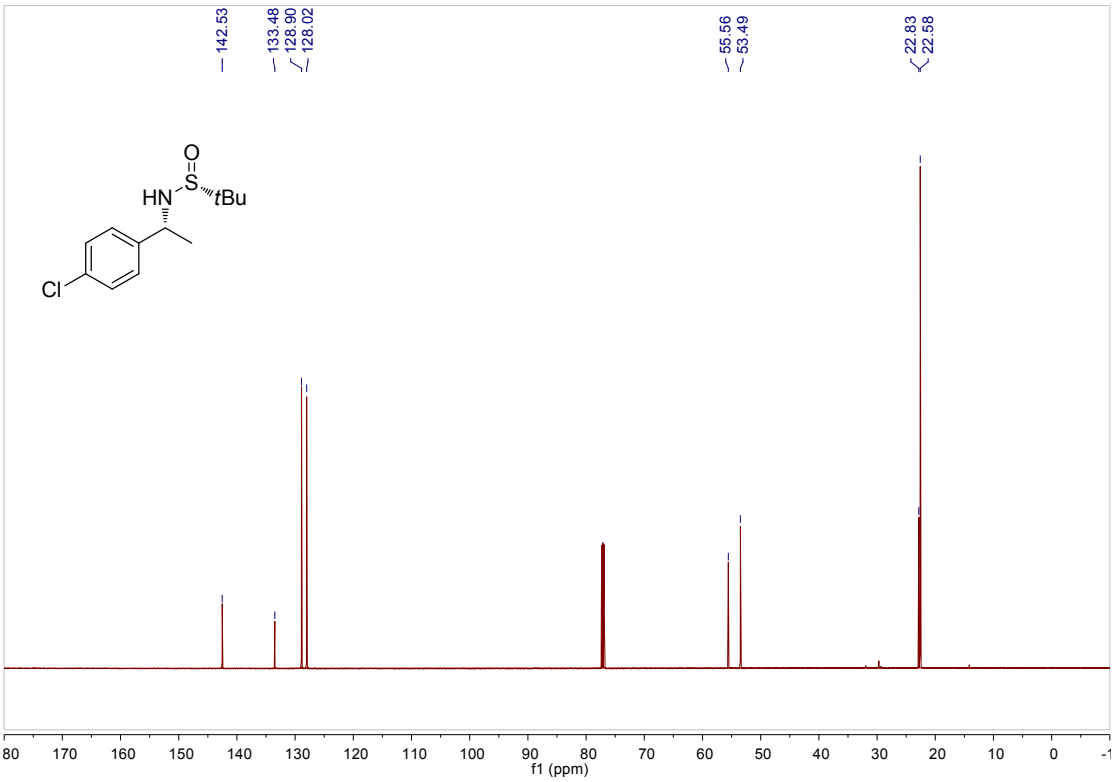
^{1}H NMR spectra of **3c**



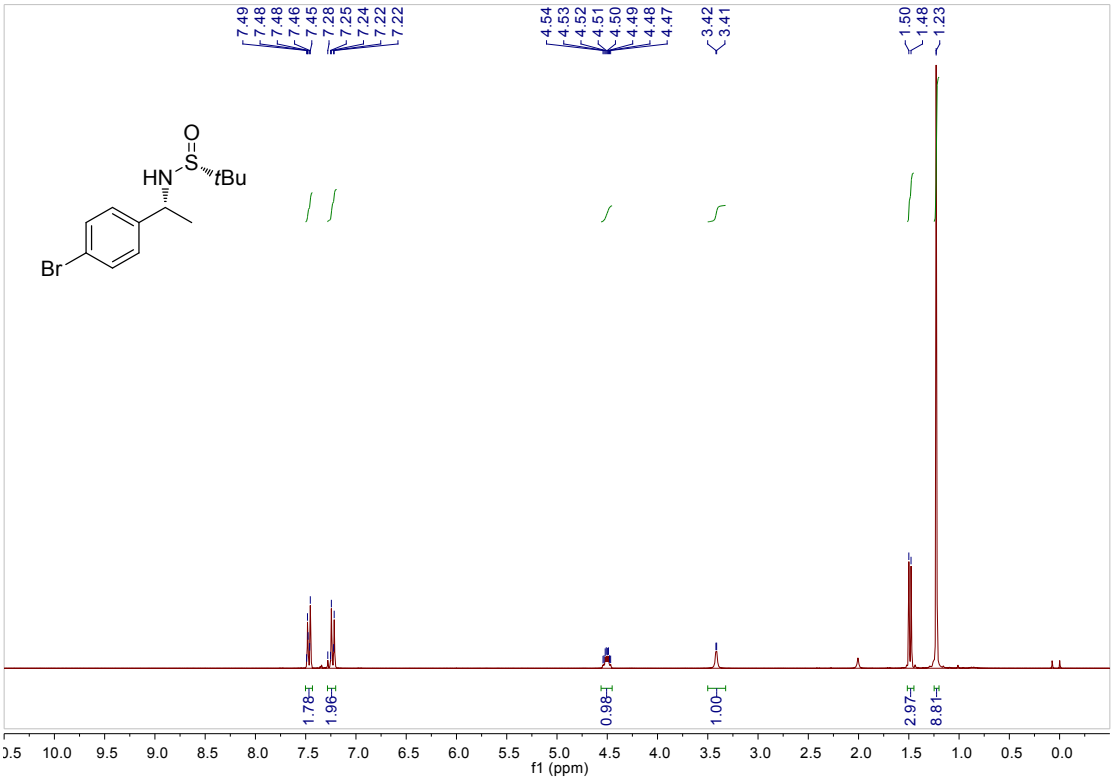
^{13}C NMR spectra of **3c**



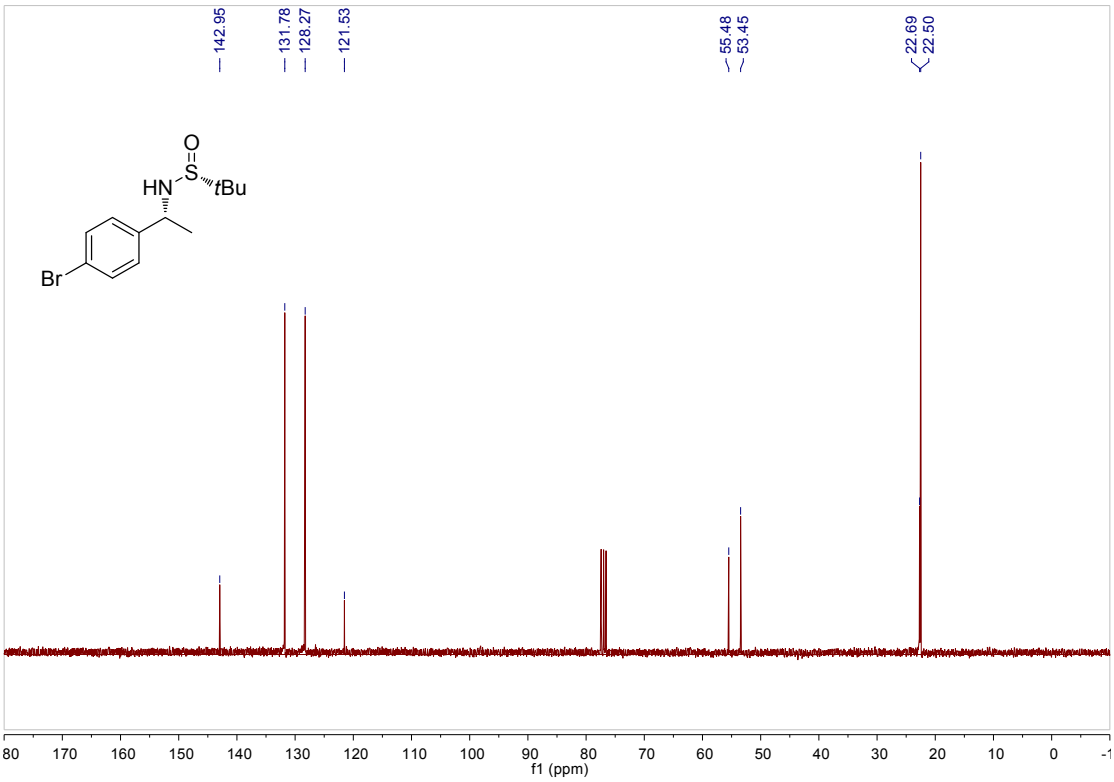
^{1}H NMR spectra of **3d**



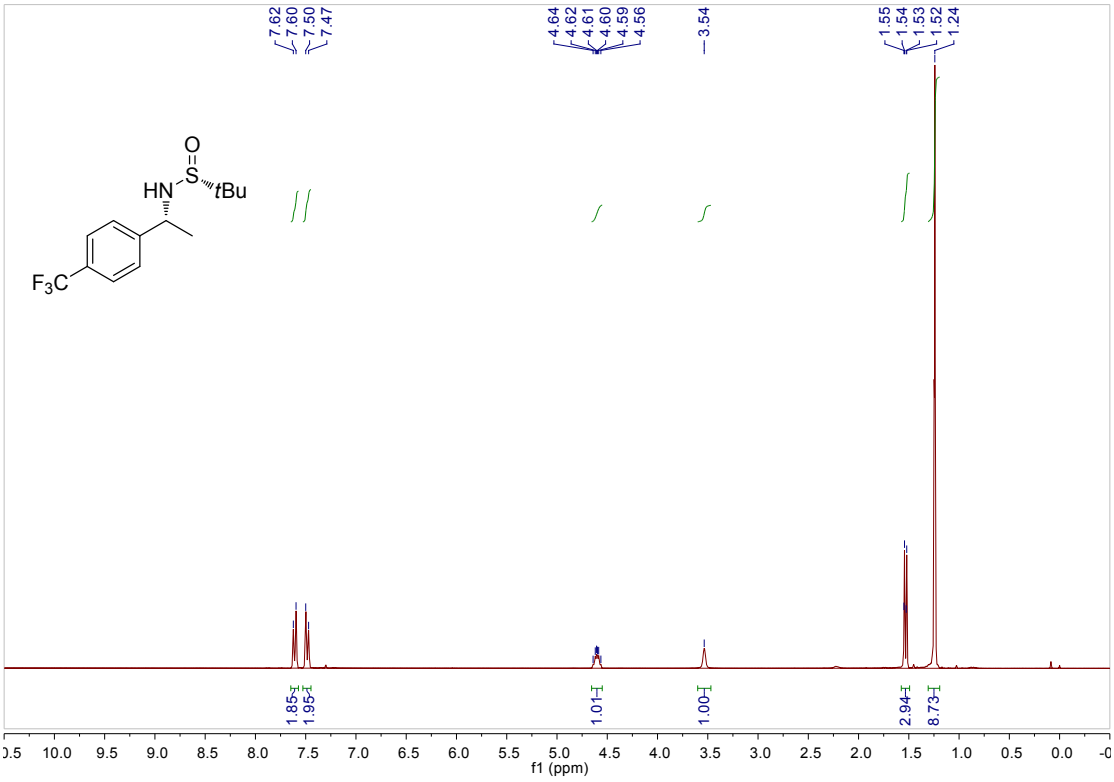
^{13}C NMR spectra of **3d**



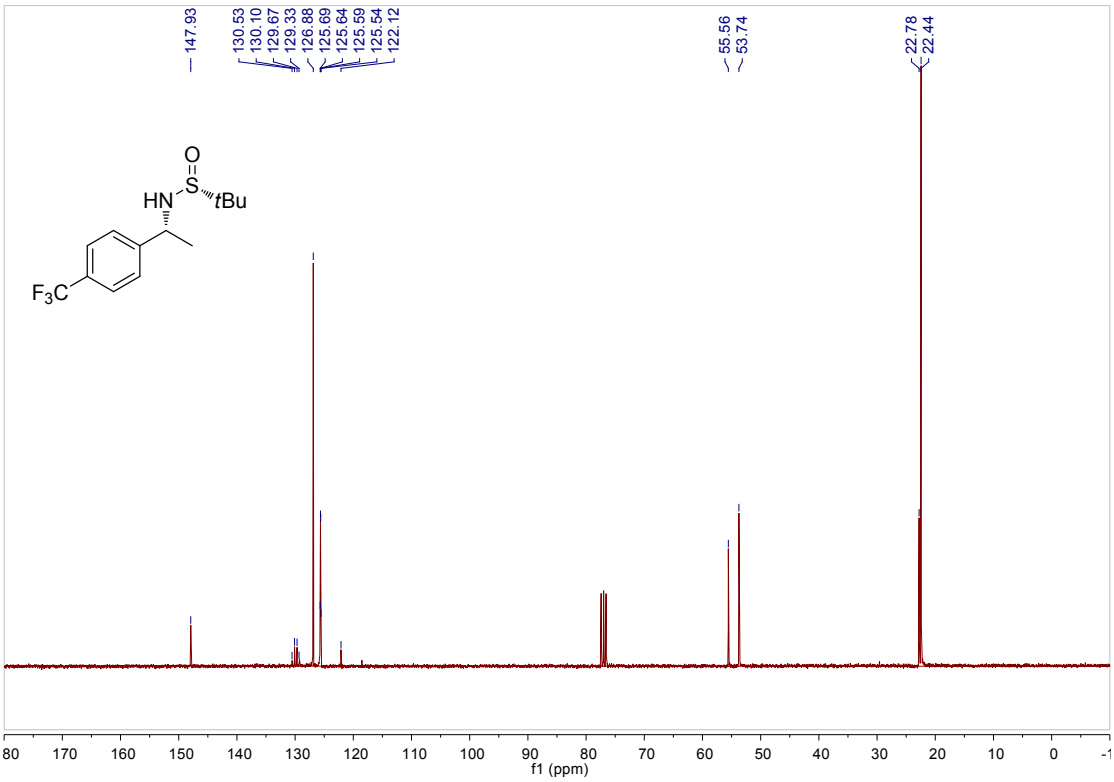
^{1}H NMR spectra of **3e**



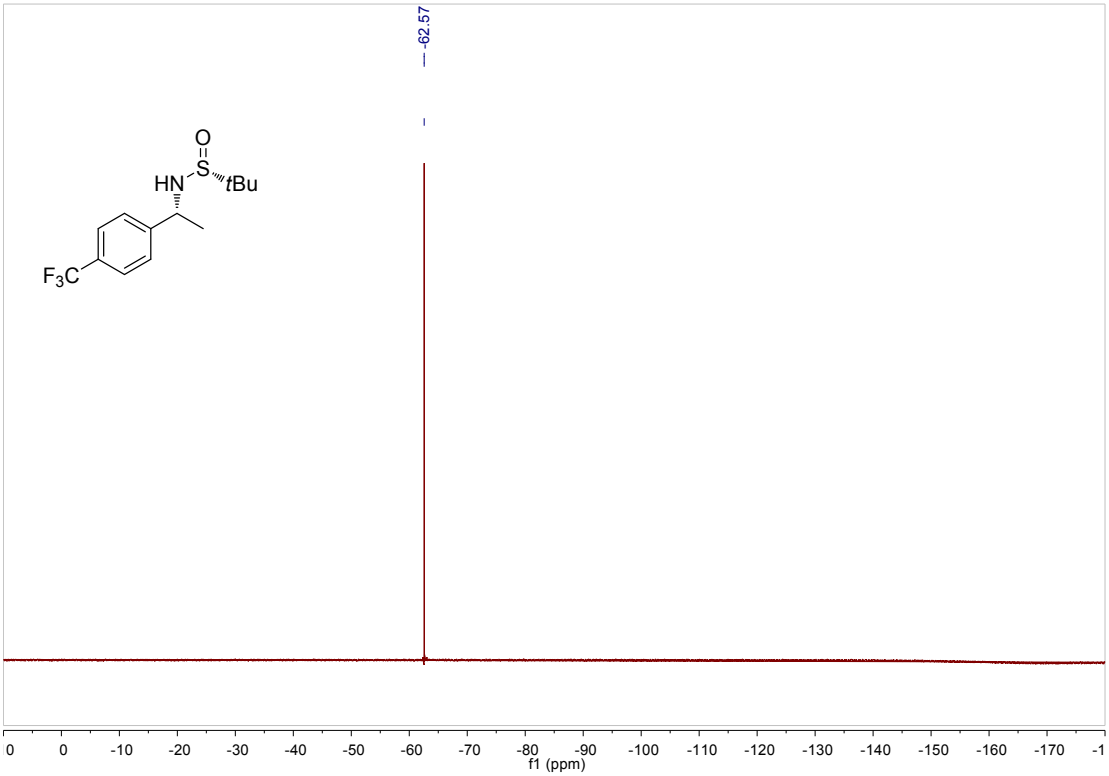
^{13}C NMR spectra of **3e**



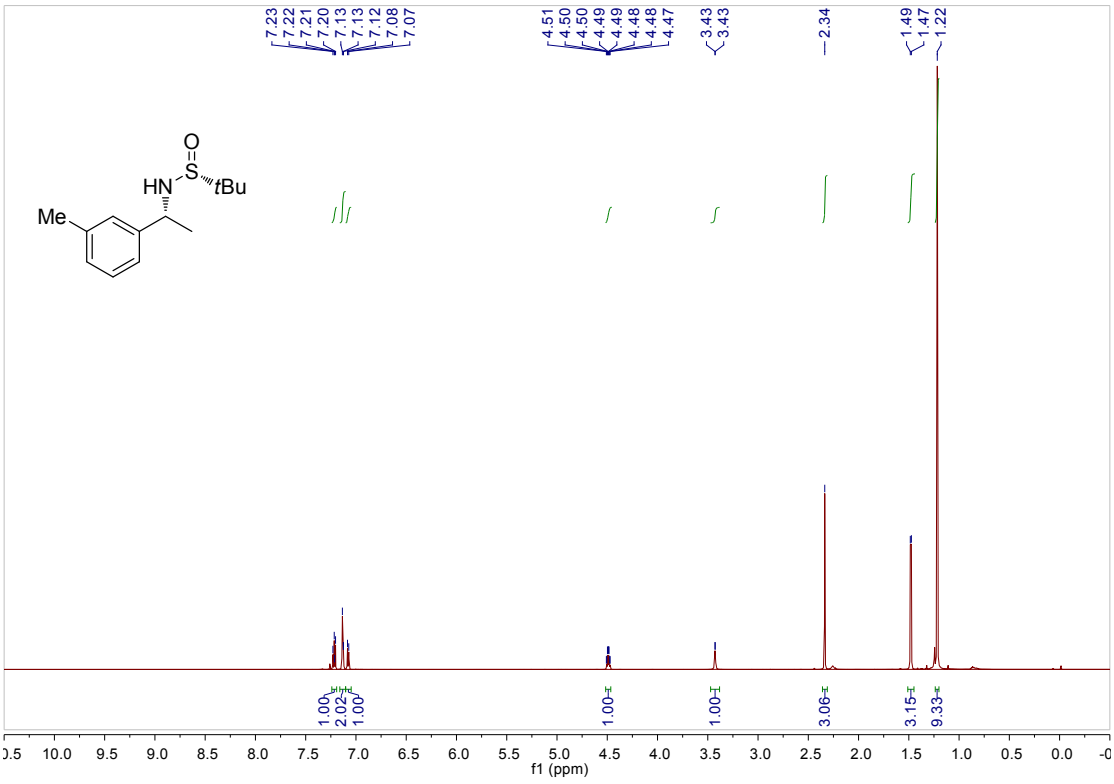
^{1}H NMR spectra of **3f**



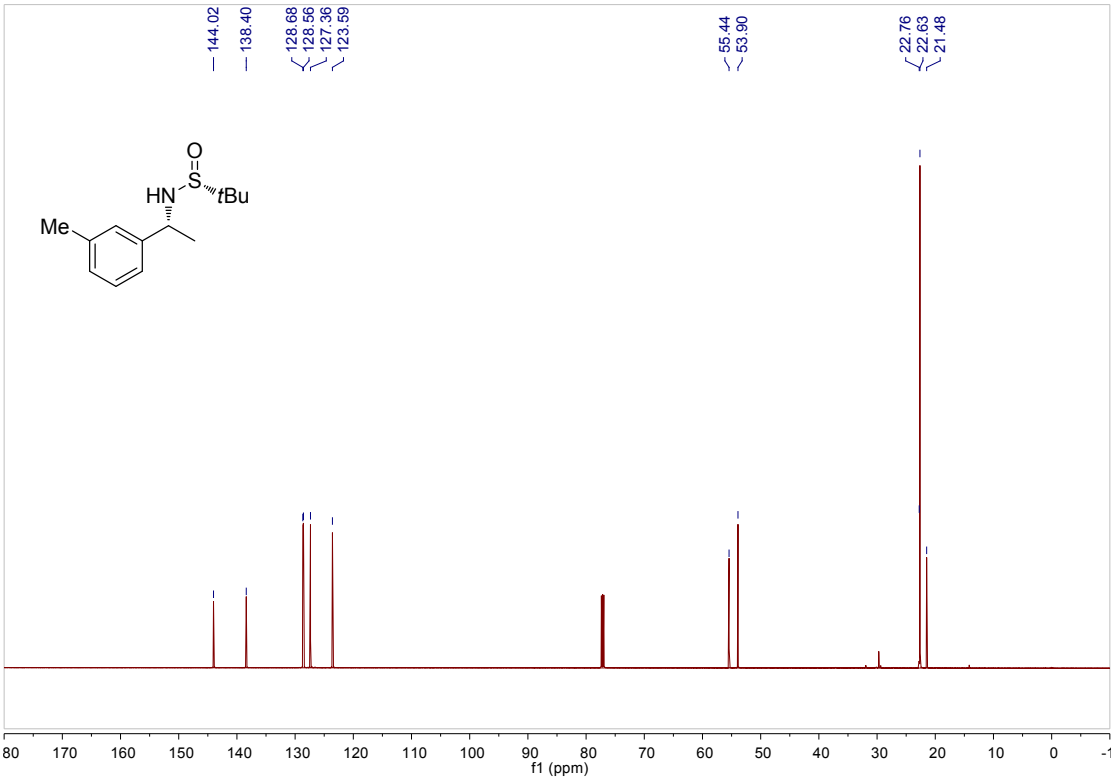
^{13}C NMR spectra of **3f**



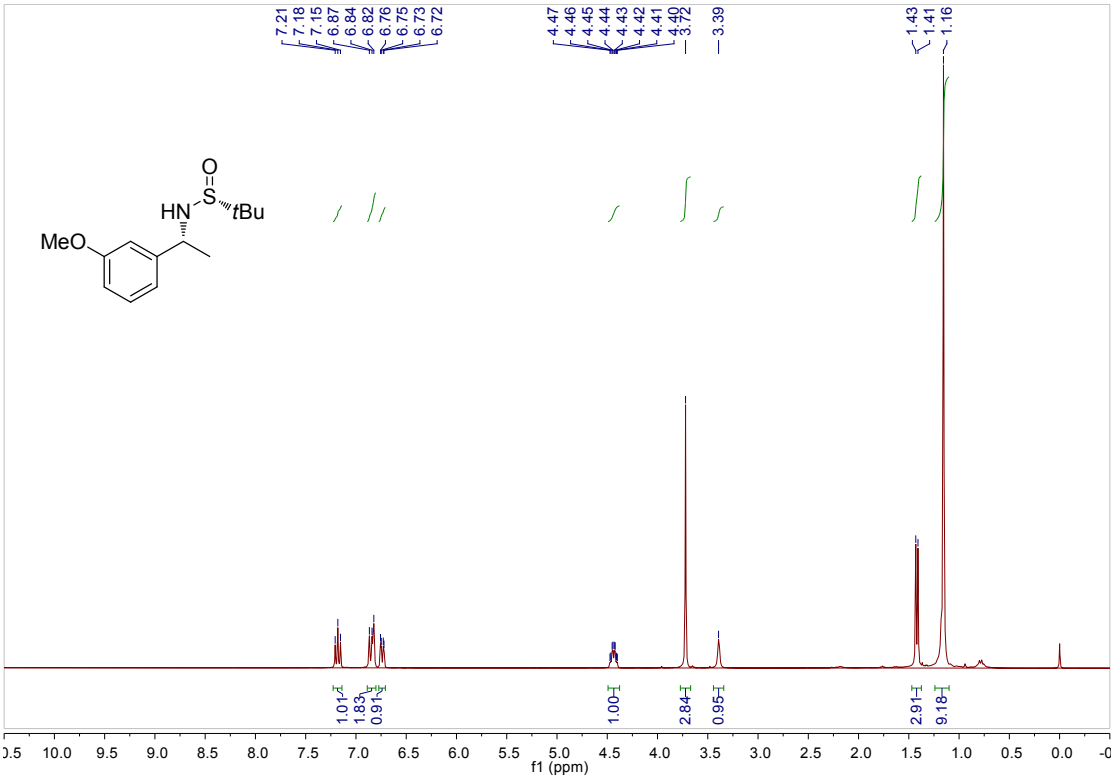
^{19}F NMR spectra of **3f**



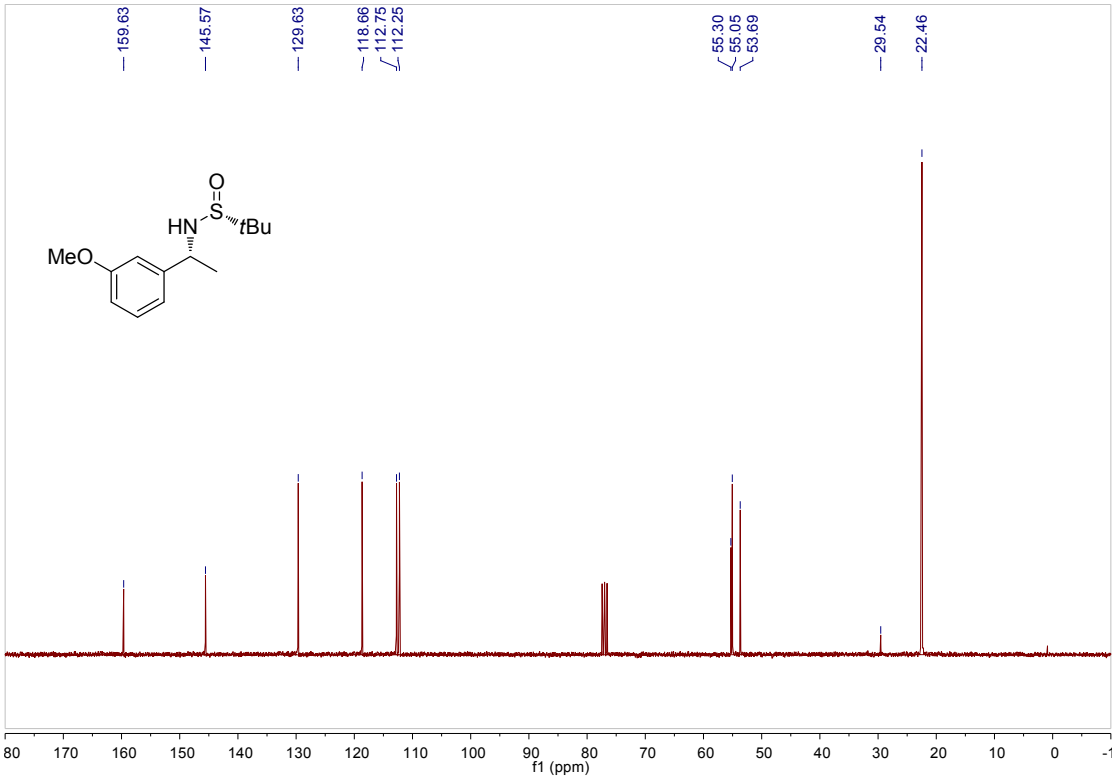
^{1}H NMR spectra of **3g**



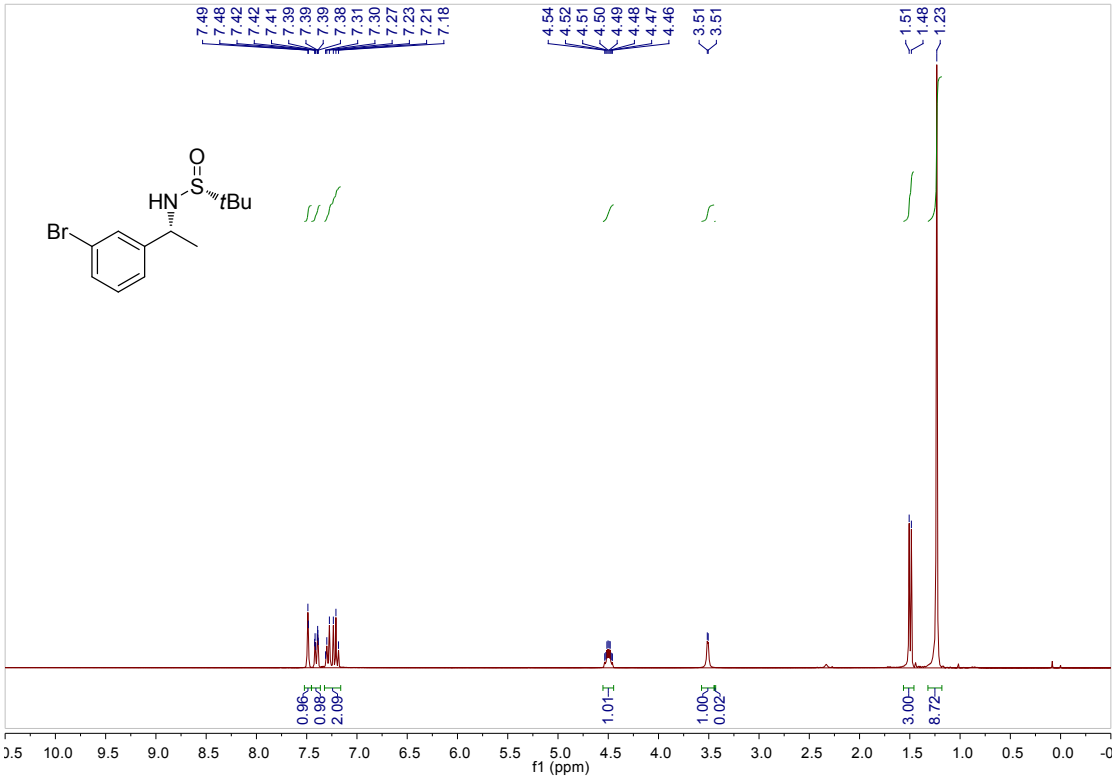
^{13}C NMR spectra of **3g**



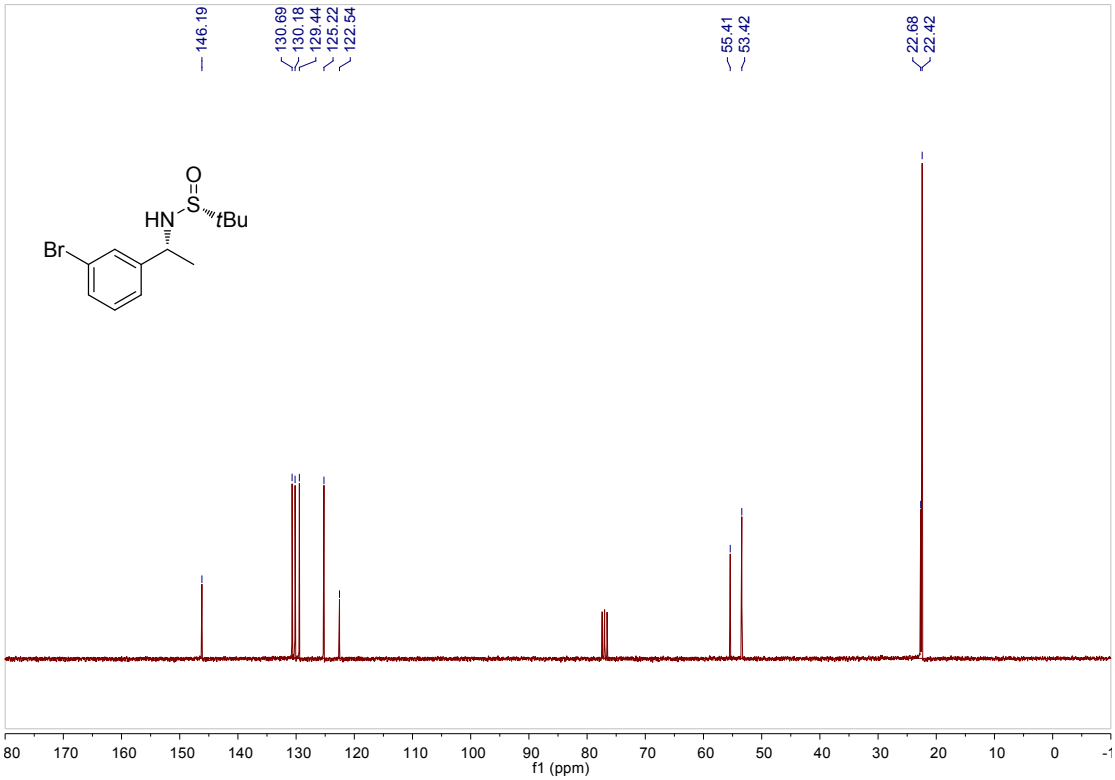
^{1}H NMR spectra of **3h**



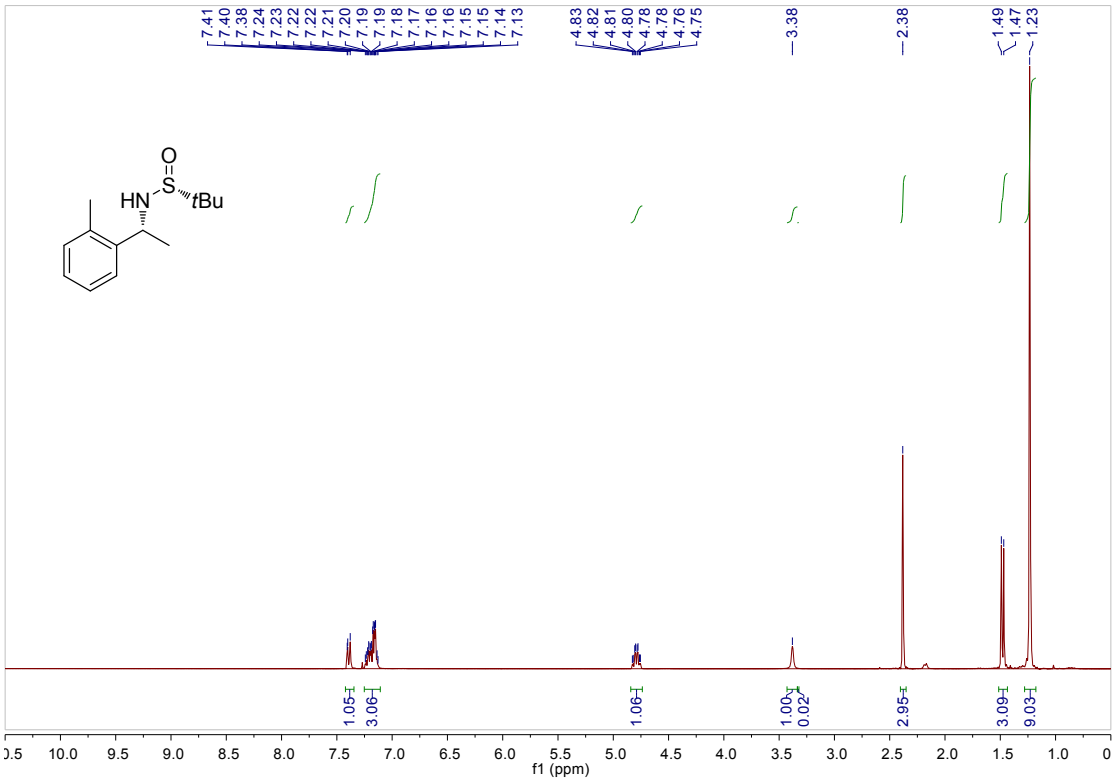
^{13}C NMR spectra of **3h**



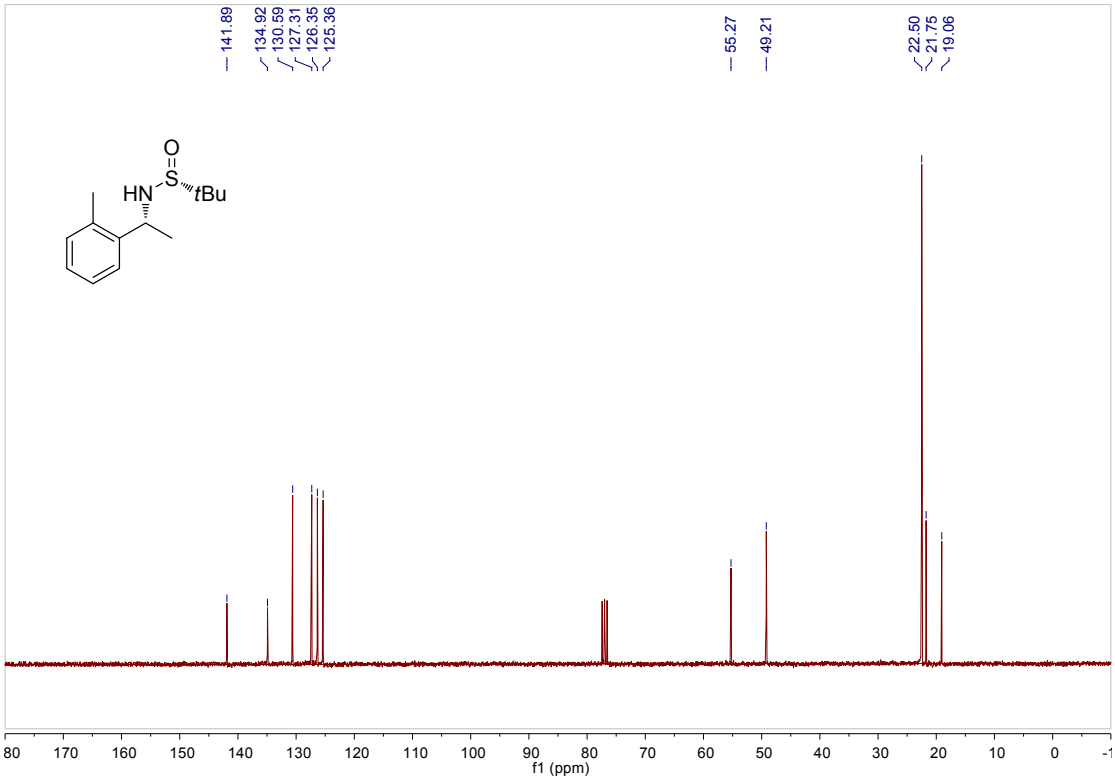
^{1}H NMR spectra of **3i**



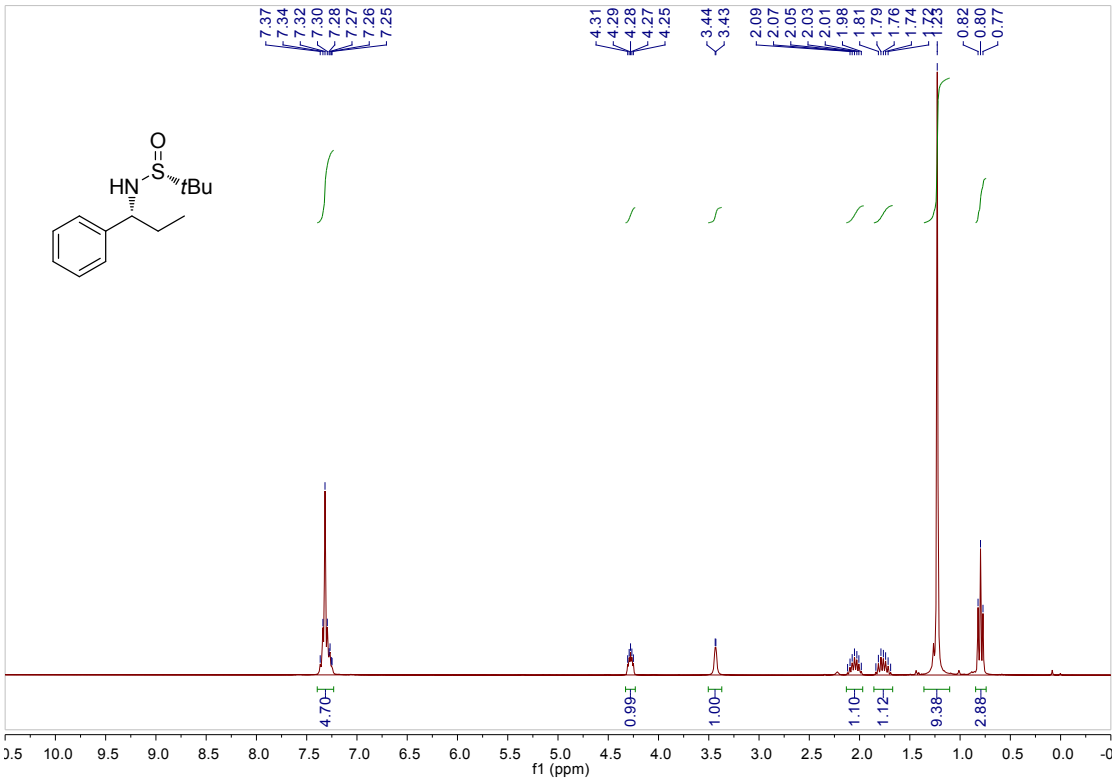
^{13}C NMR spectra of **3i**



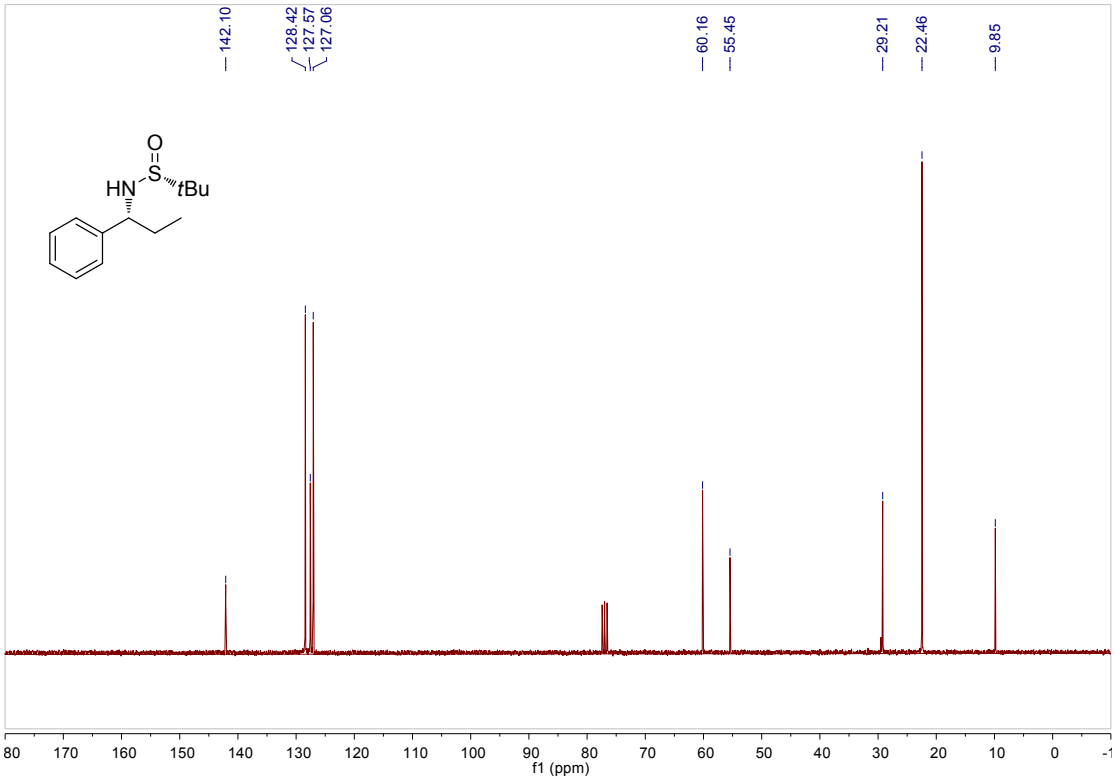
^{1}H NMR spectra of **3j**



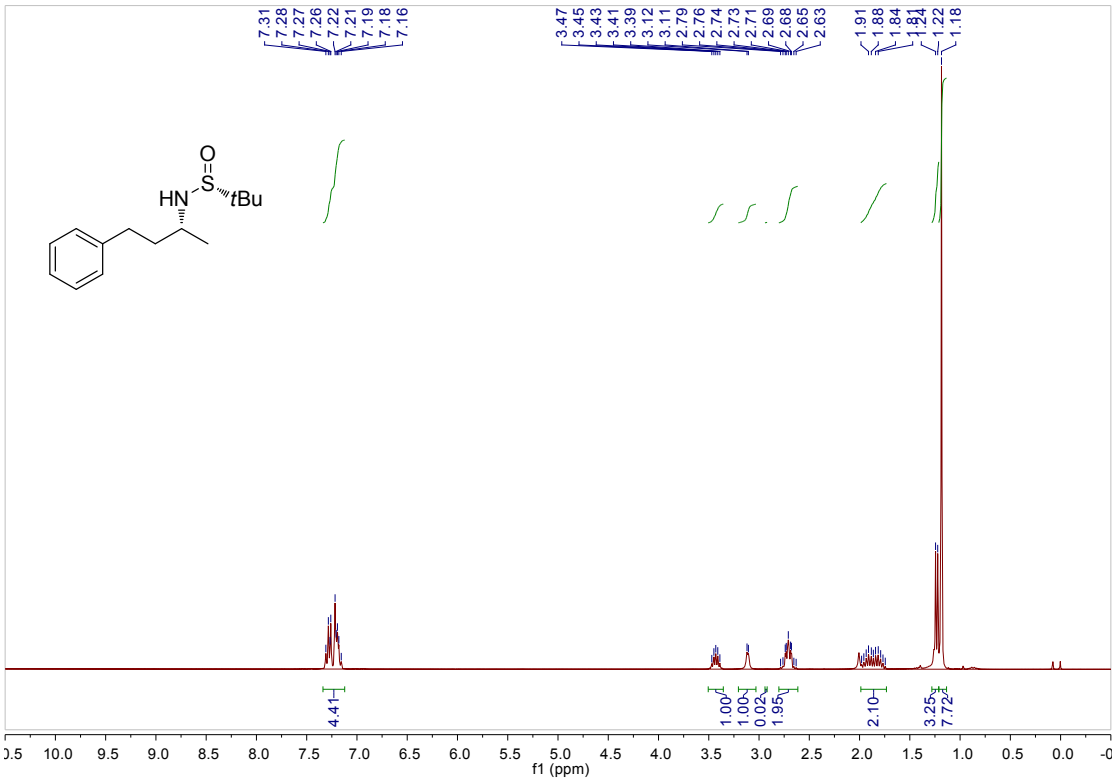
^{13}C NMR spectra of **3j**



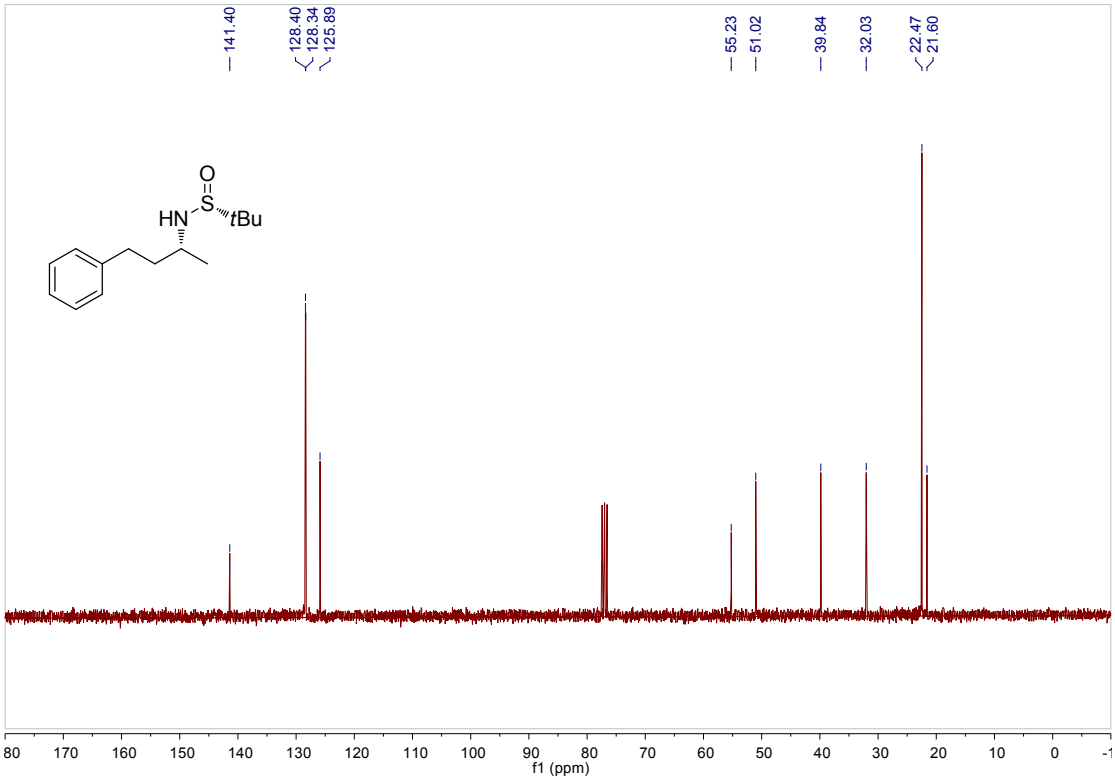
^{1}H NMR spectra of **3k**



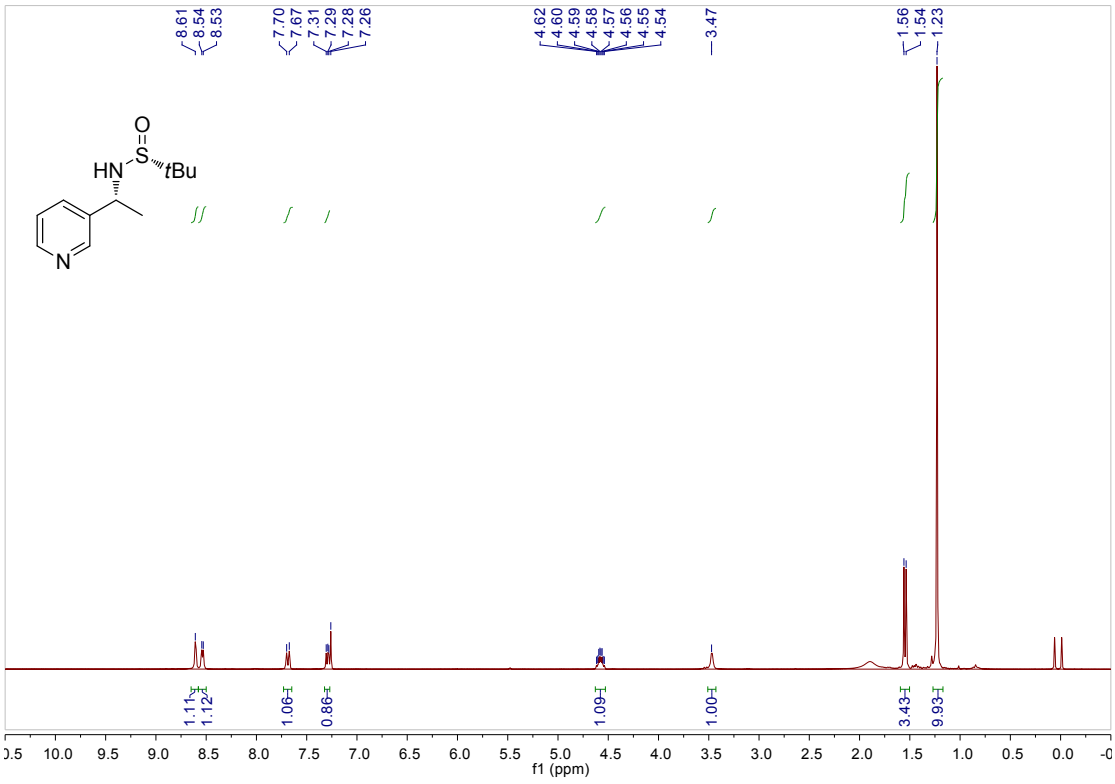
^{13}C NMR spectra of **3k**



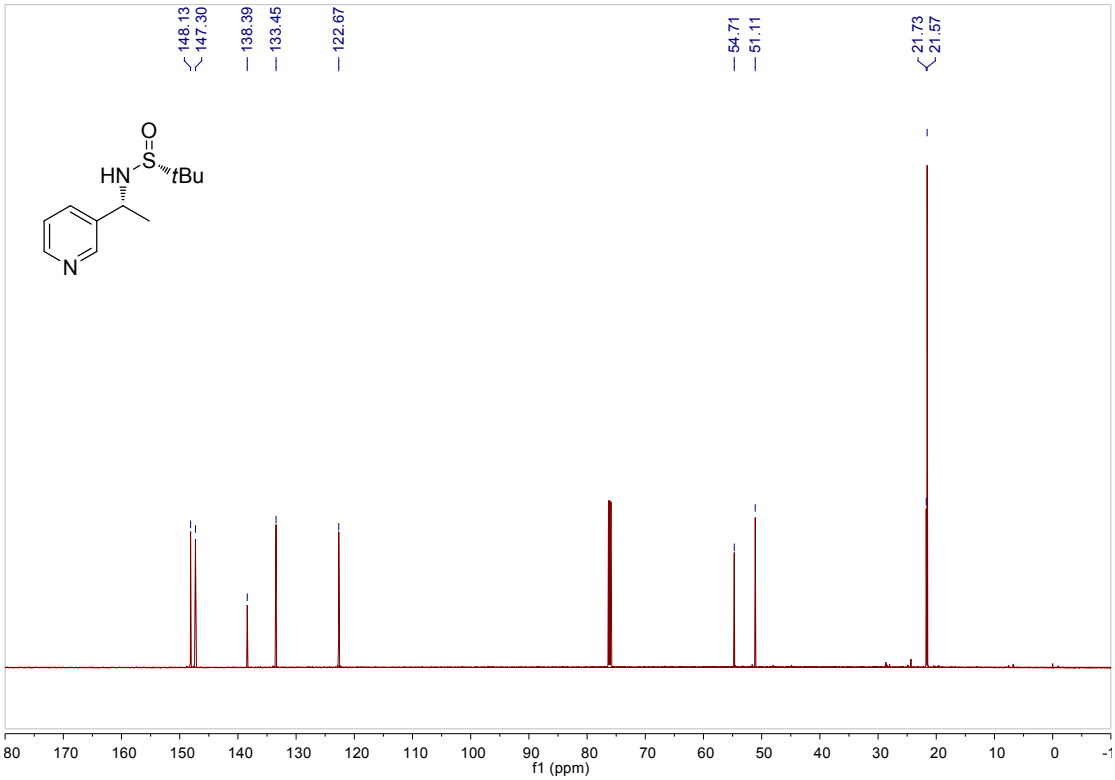
^{1}H NMR spectra of **3l**



^{13}C NMR spectra of **3l**

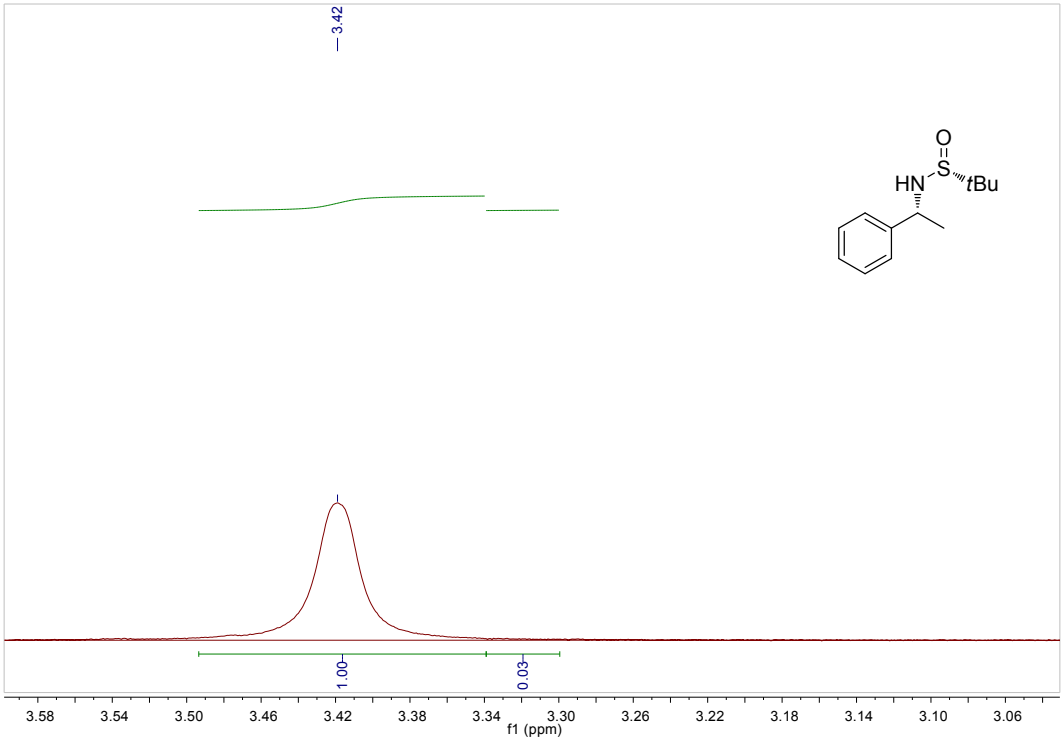


^{1}H NMR spectra of **3m**

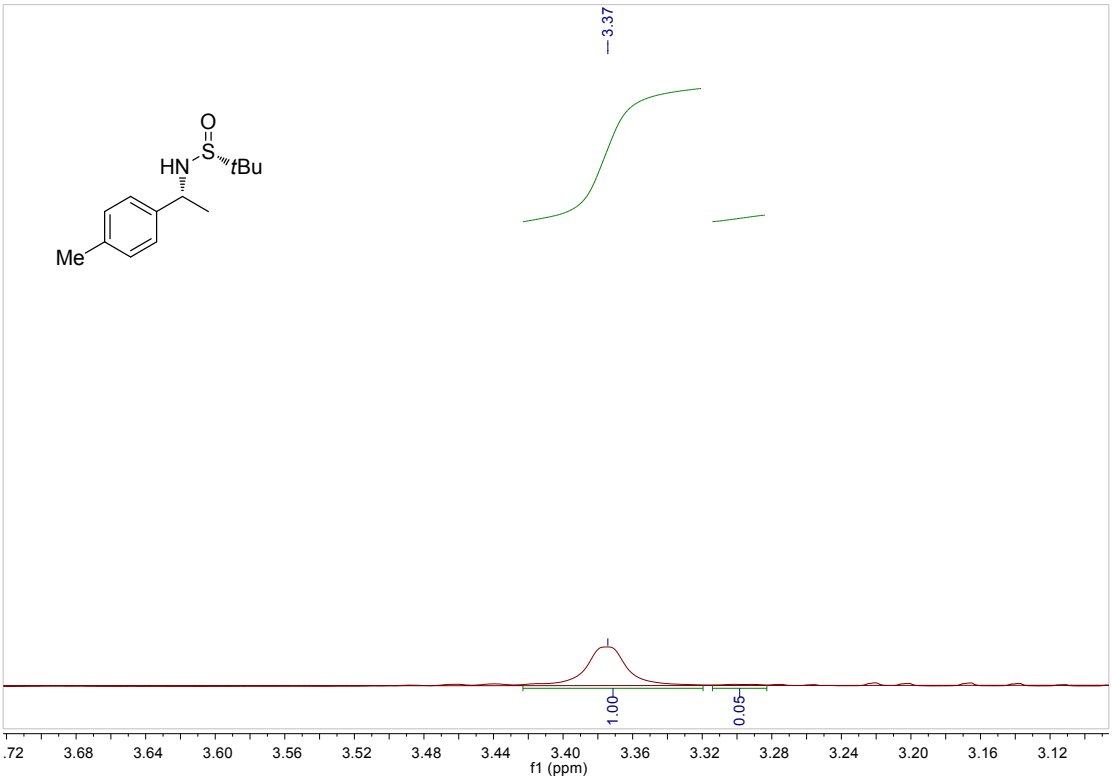


^{13}C NMR spectra of **3m**

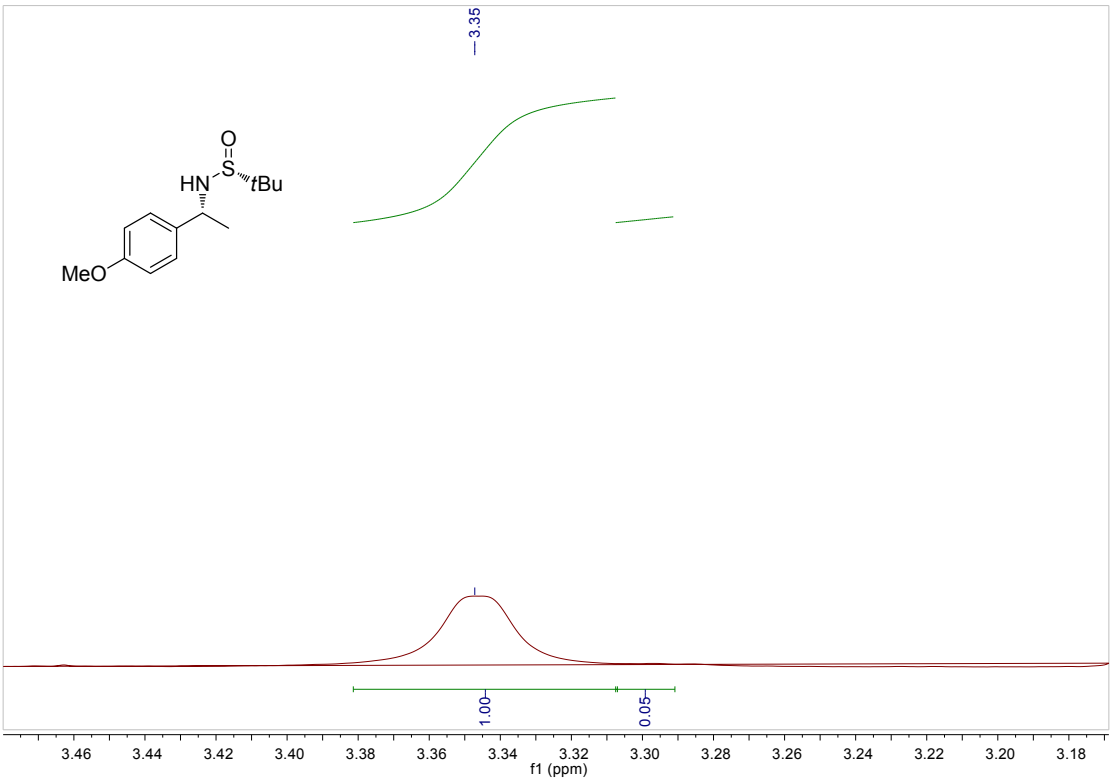
^{1}H NMR of reaction mixture used for dr calculations



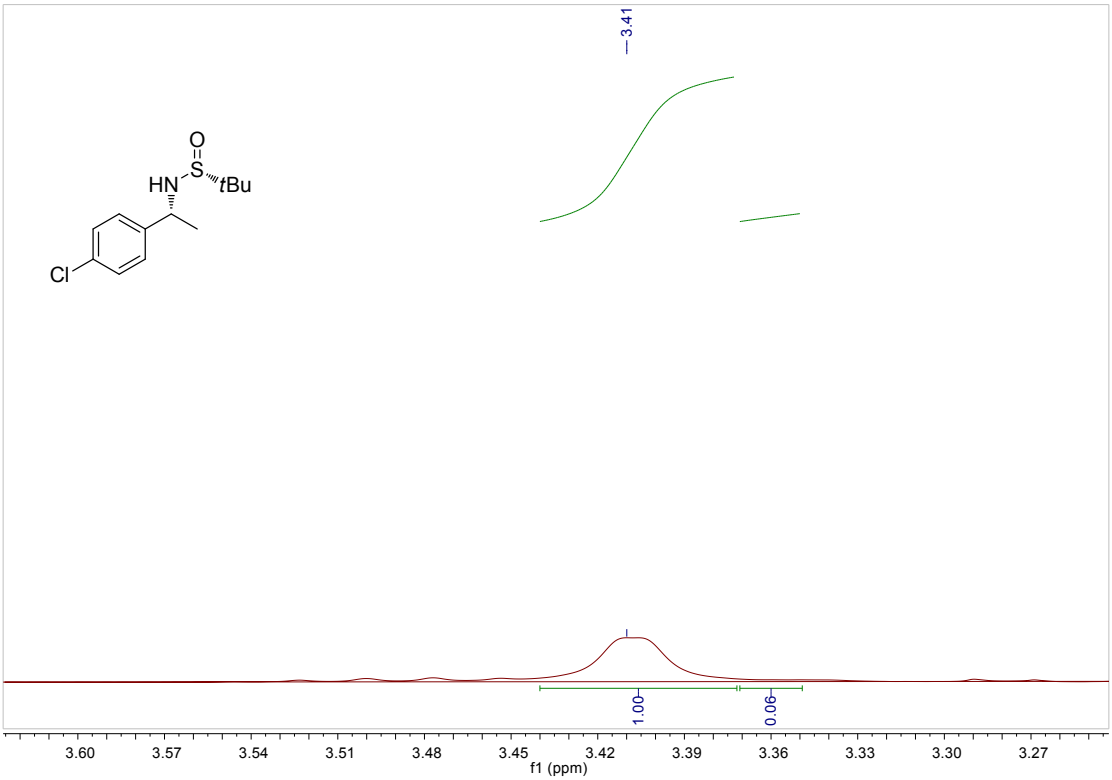
^{1}H NMR spectra of crude product **3a**



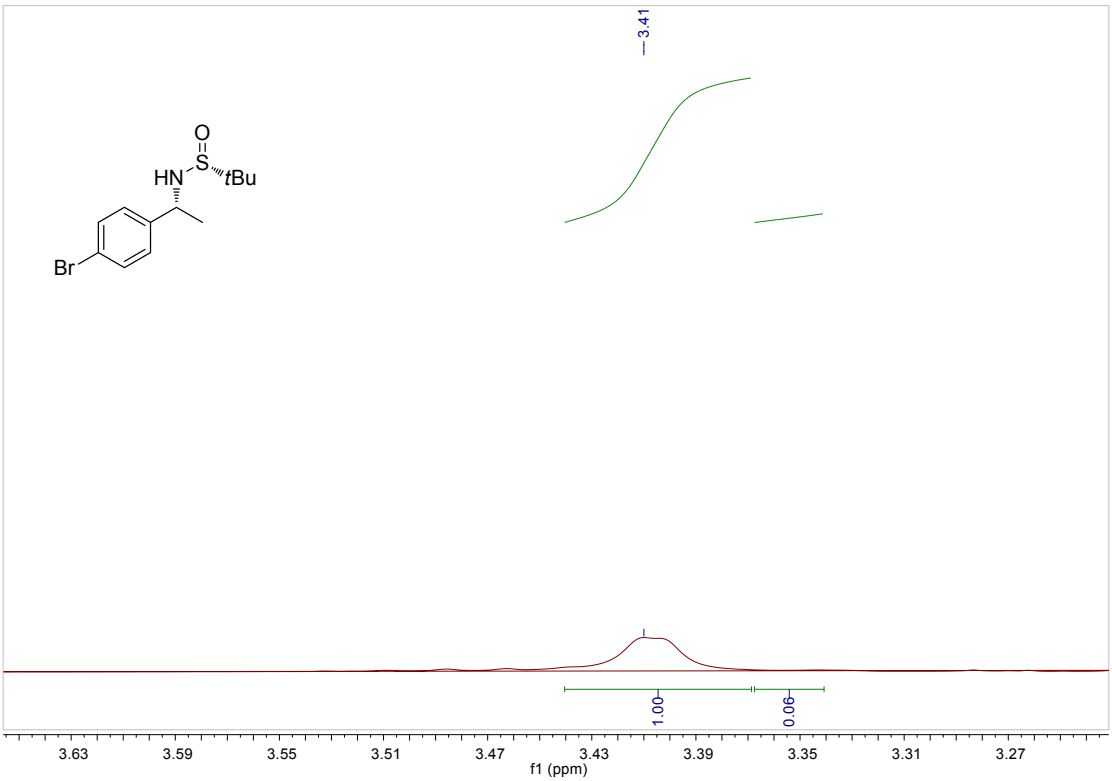
^{1}H NMR spectra of crude product **3b**



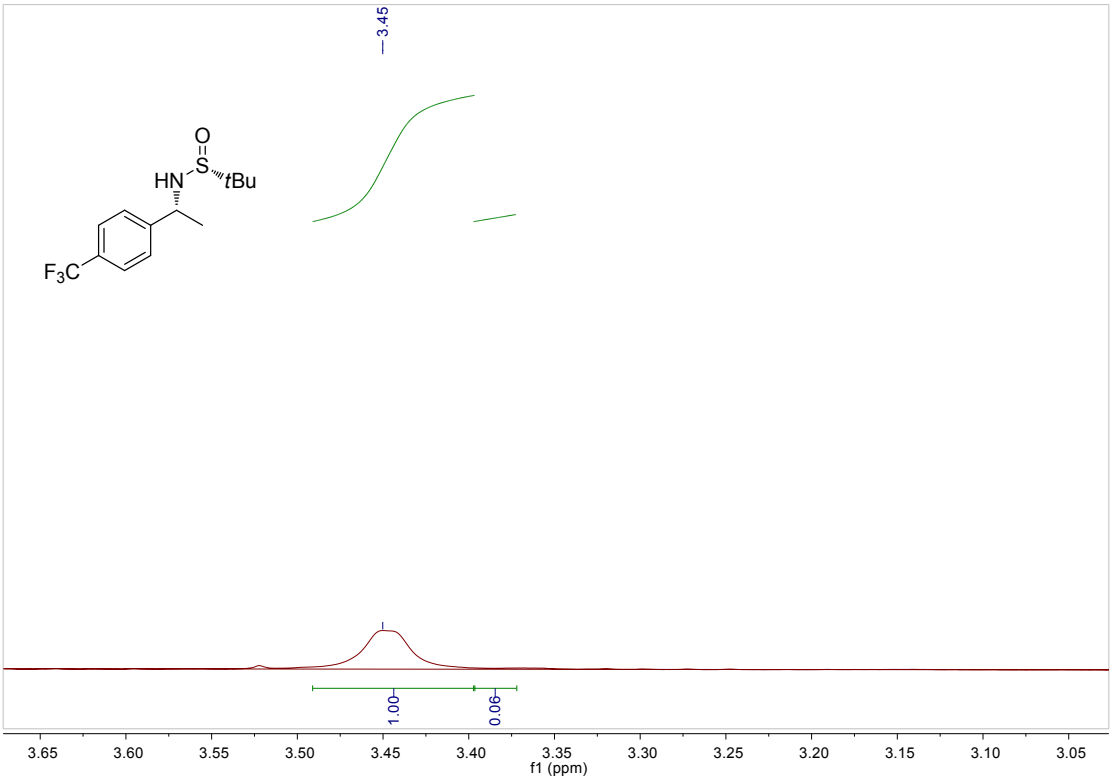
^{1}H NMR spectra of crude product **3c**



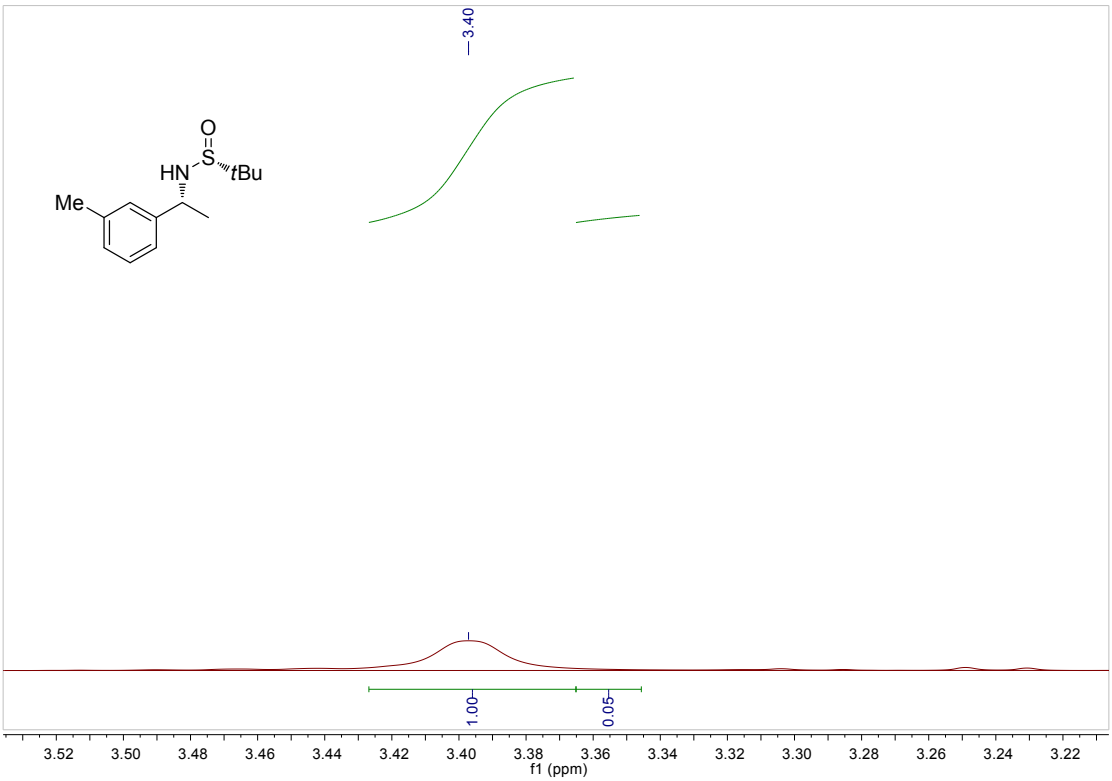
^{1}H NMR spectra of crude product **3d**



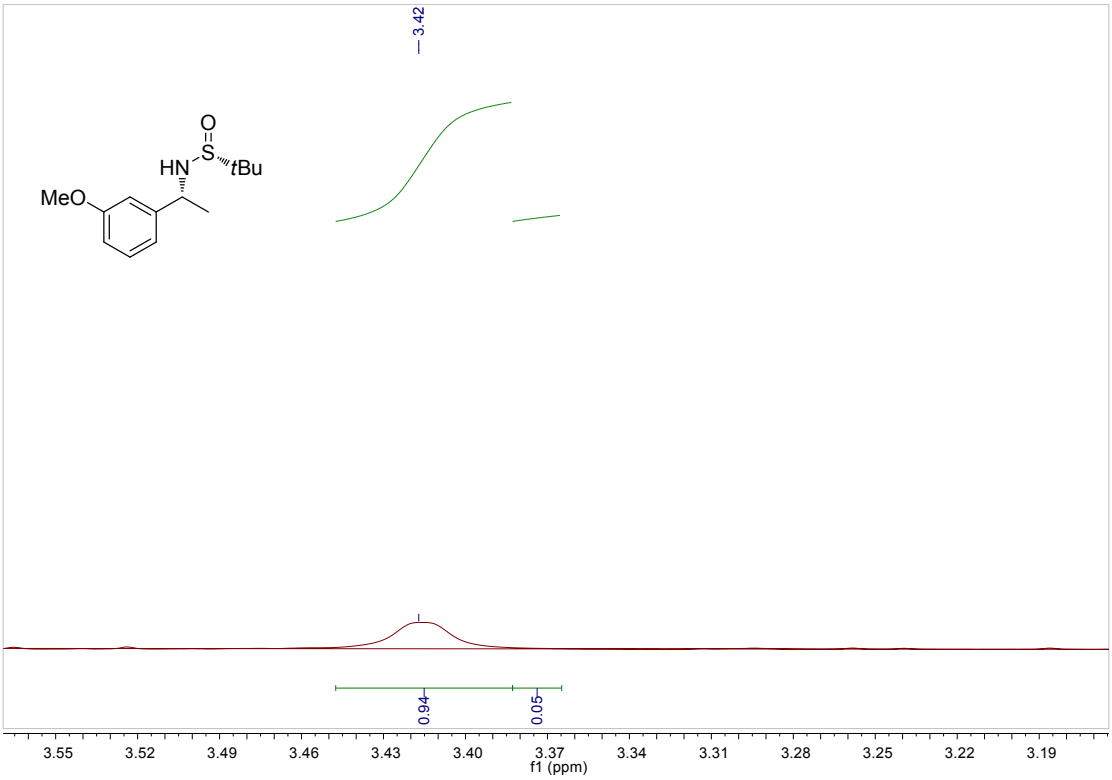
^{1}H NMR spectra of crude product **3e**



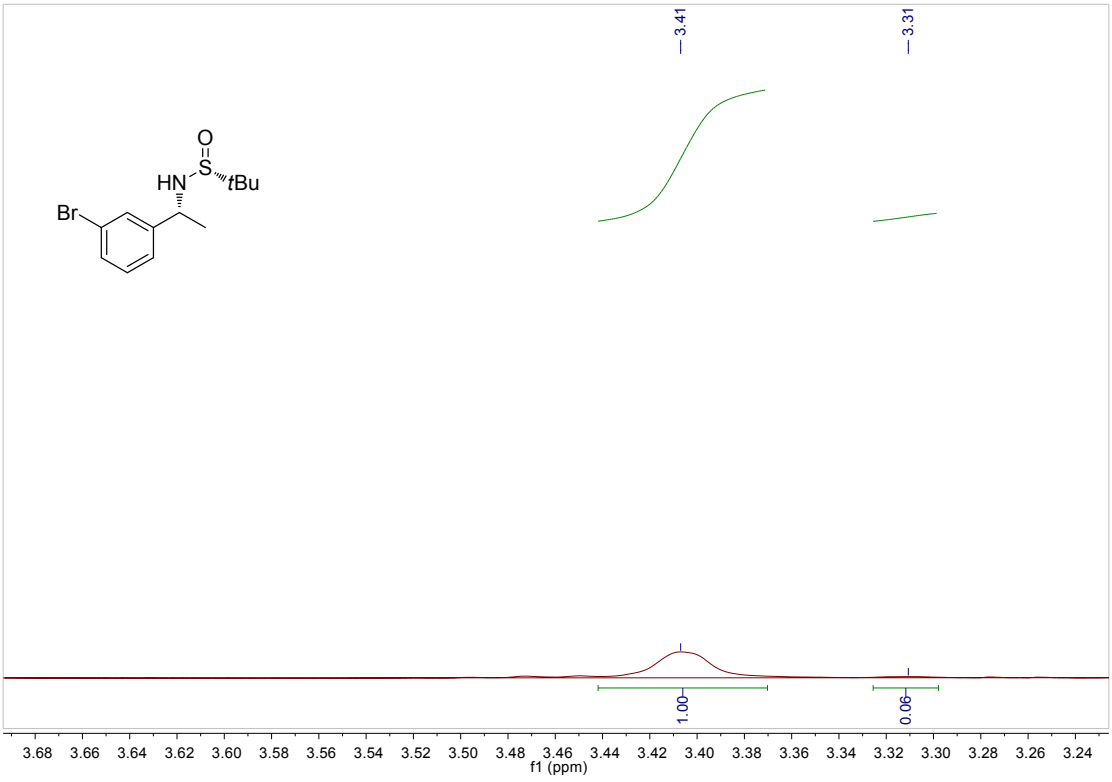
^{1}H NMR spectra of crude product **3f**



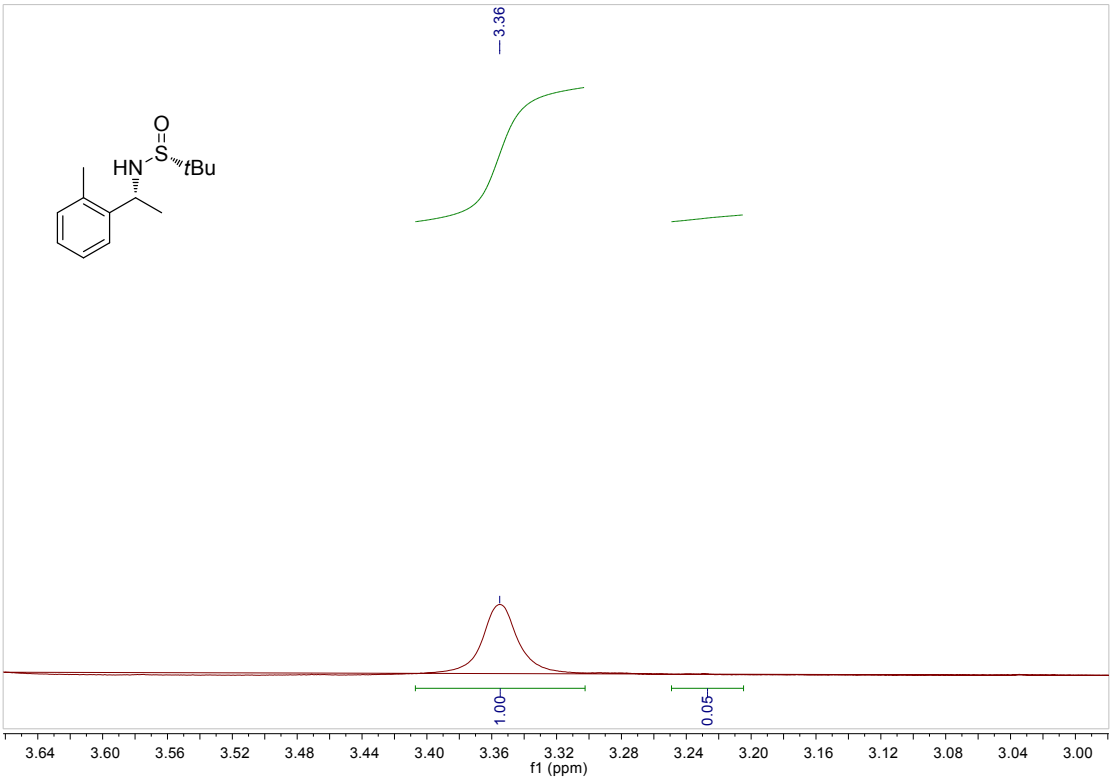
^{1}H NMR spectra of crude product **3g**



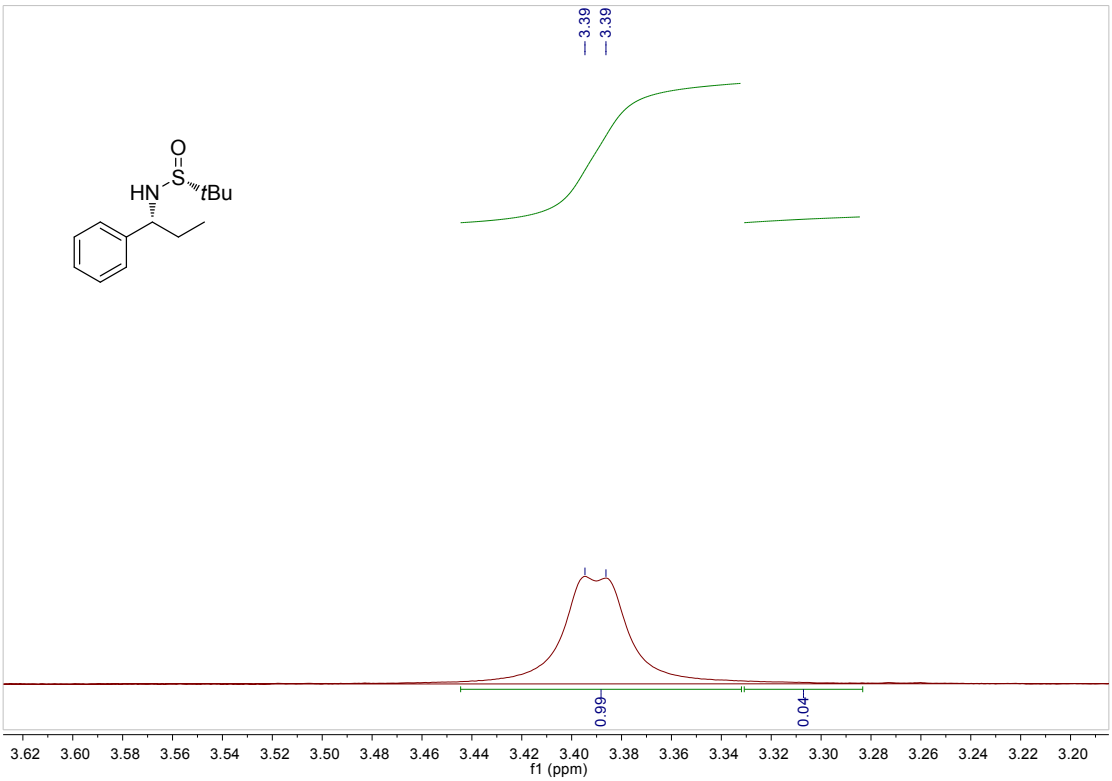
^{1}H NMR spectra of crude product **3h**



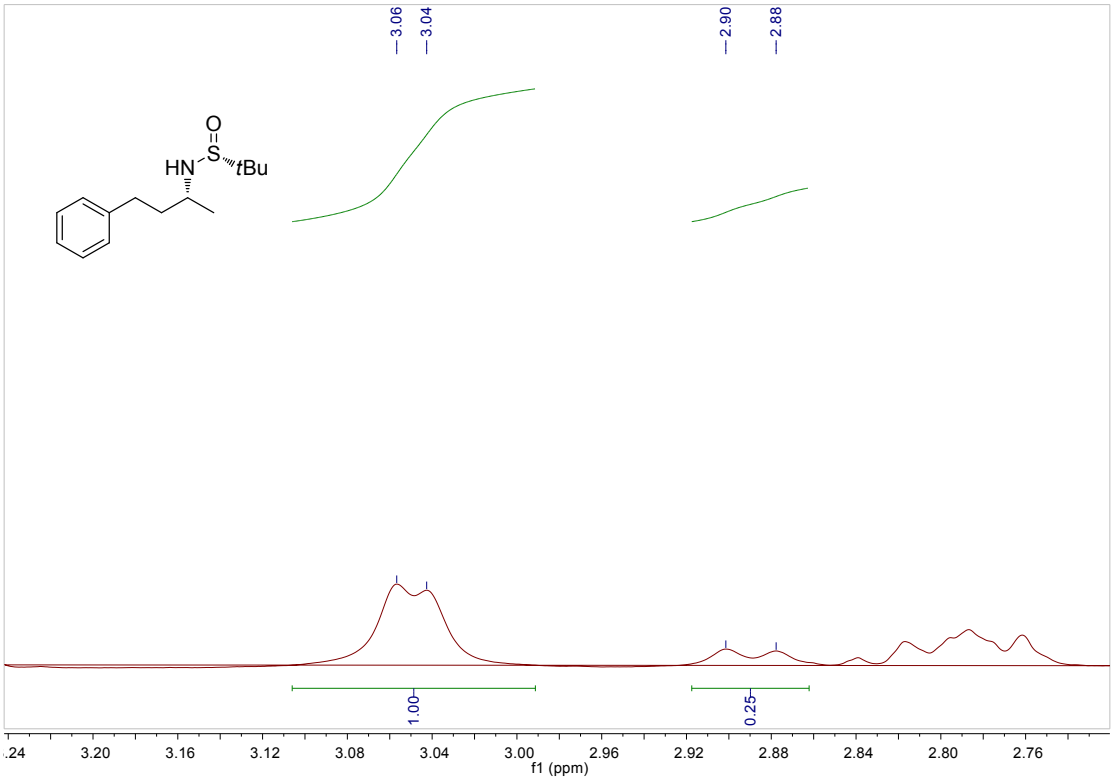
^{1}H NMR spectra of crude product **3i**



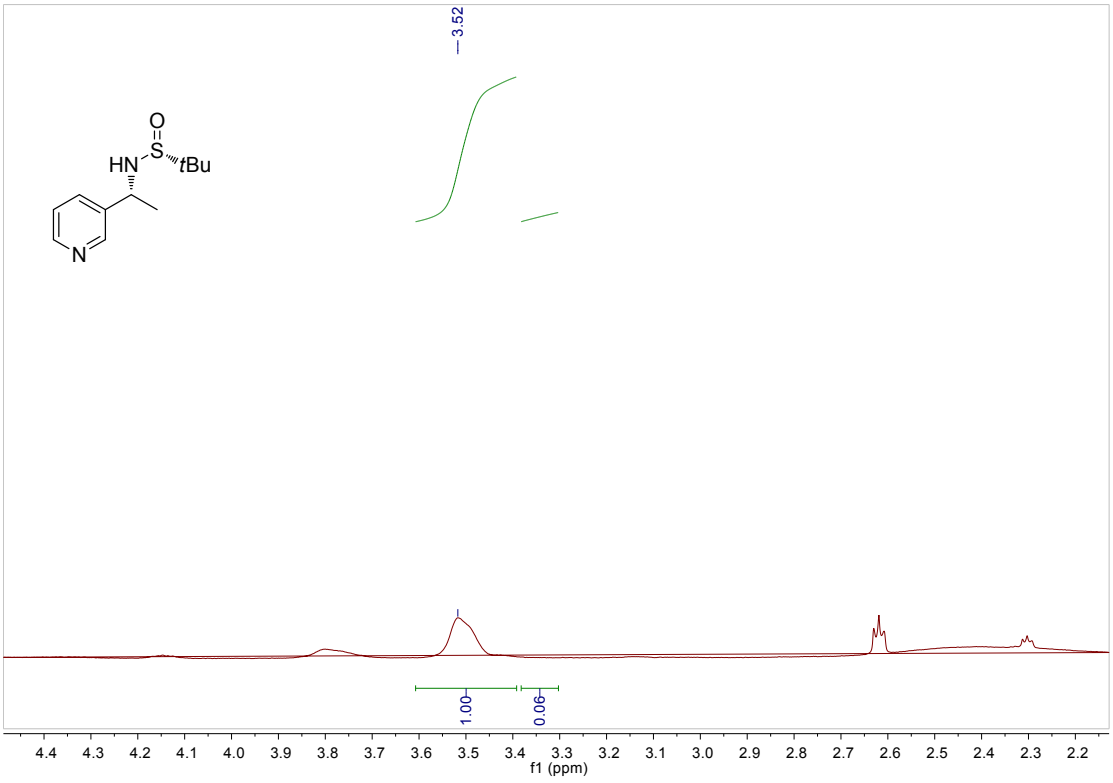
^{1}H NMR spectra of crude product **3j**



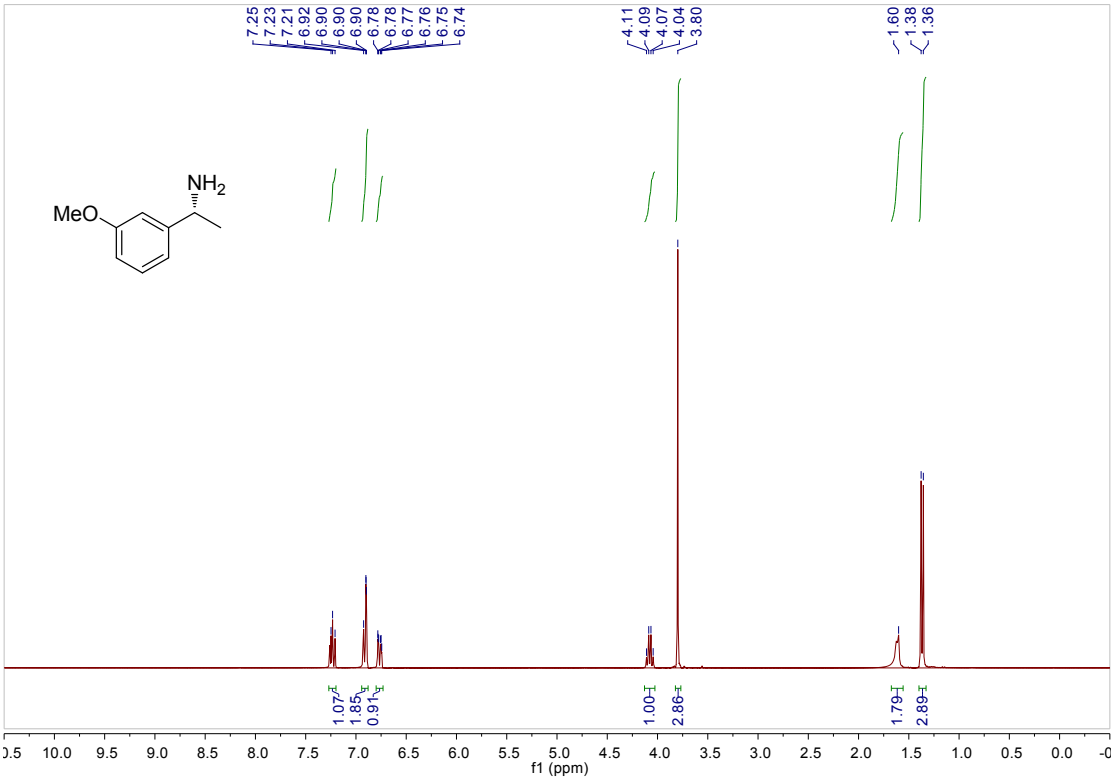
^{1}H NMR spectra of crude product **3k**



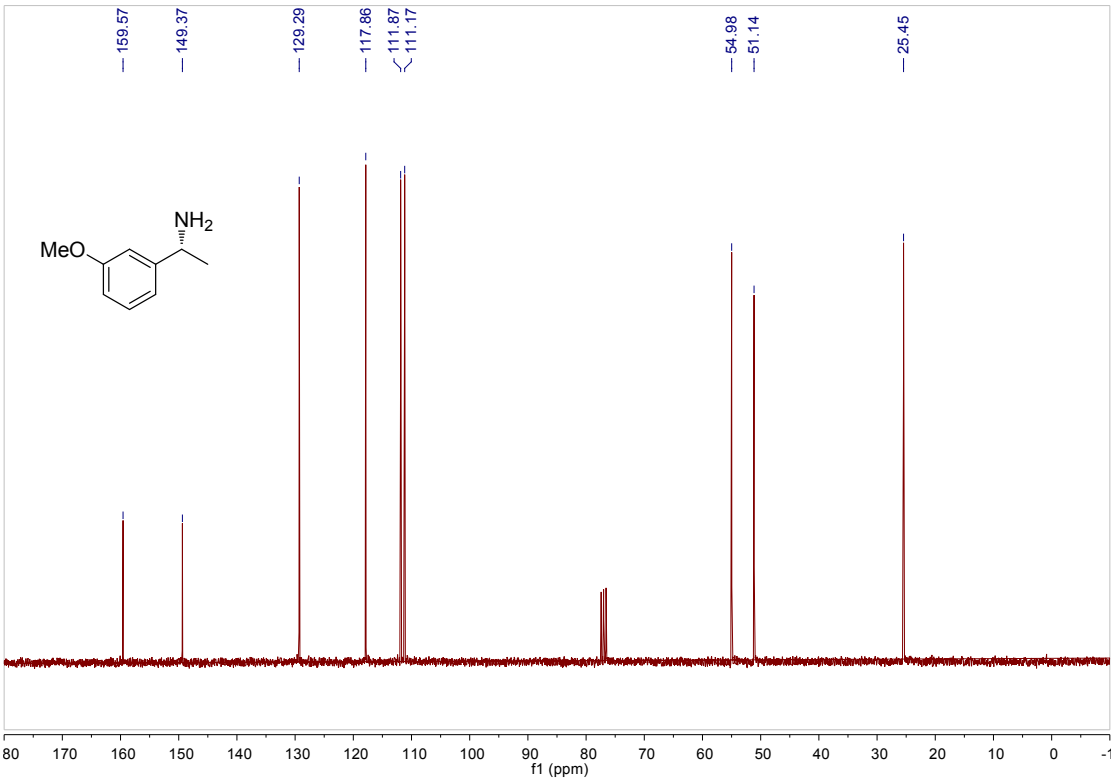
^{1}H NMR spectra of crude product **3l**



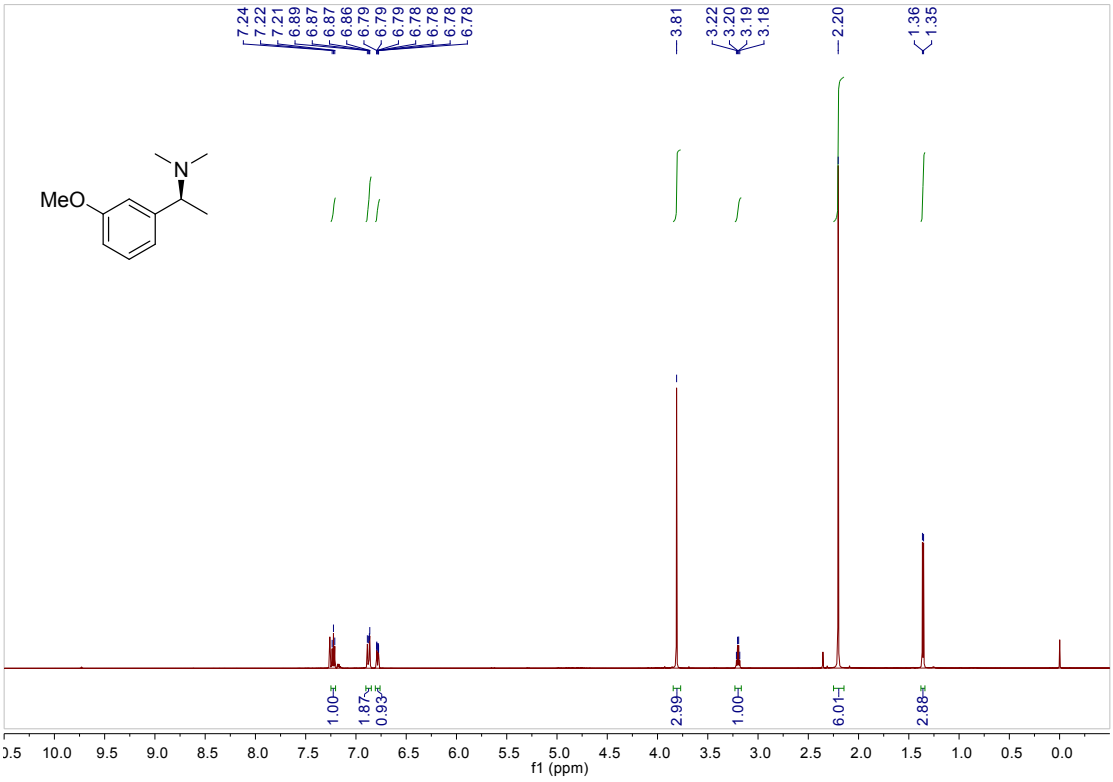
^{1}H NMR spectra of crude product **3m**



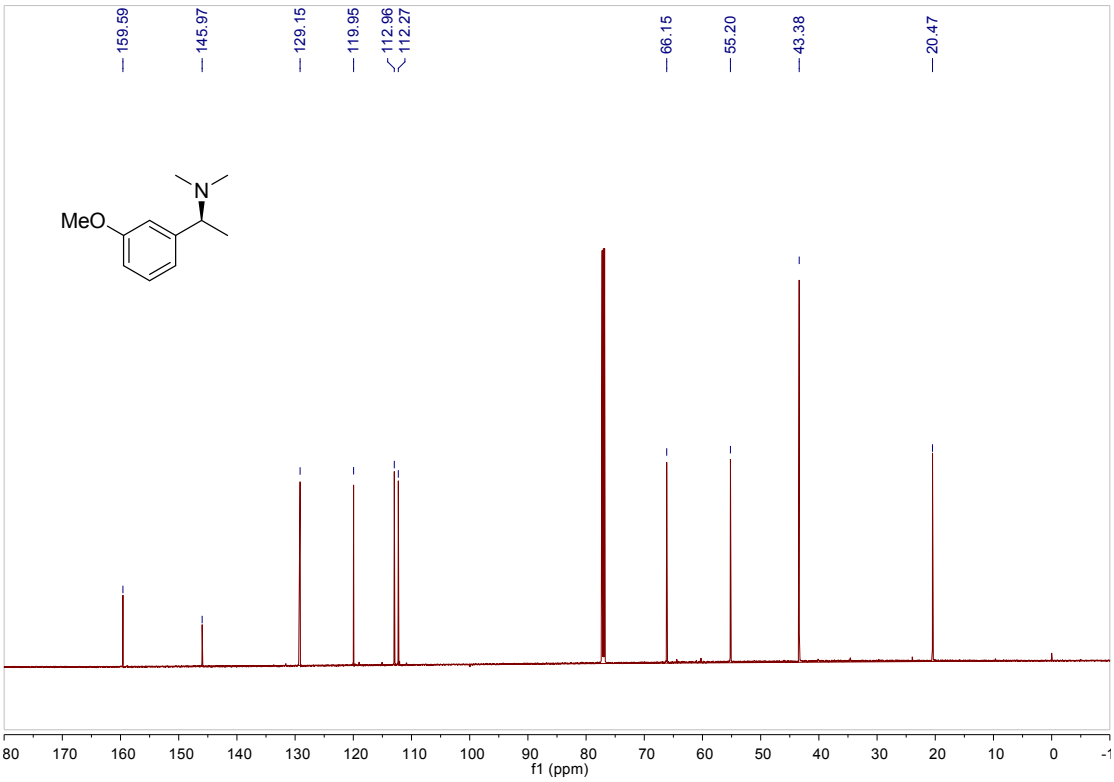
^{1}H NMR spectra of **6**



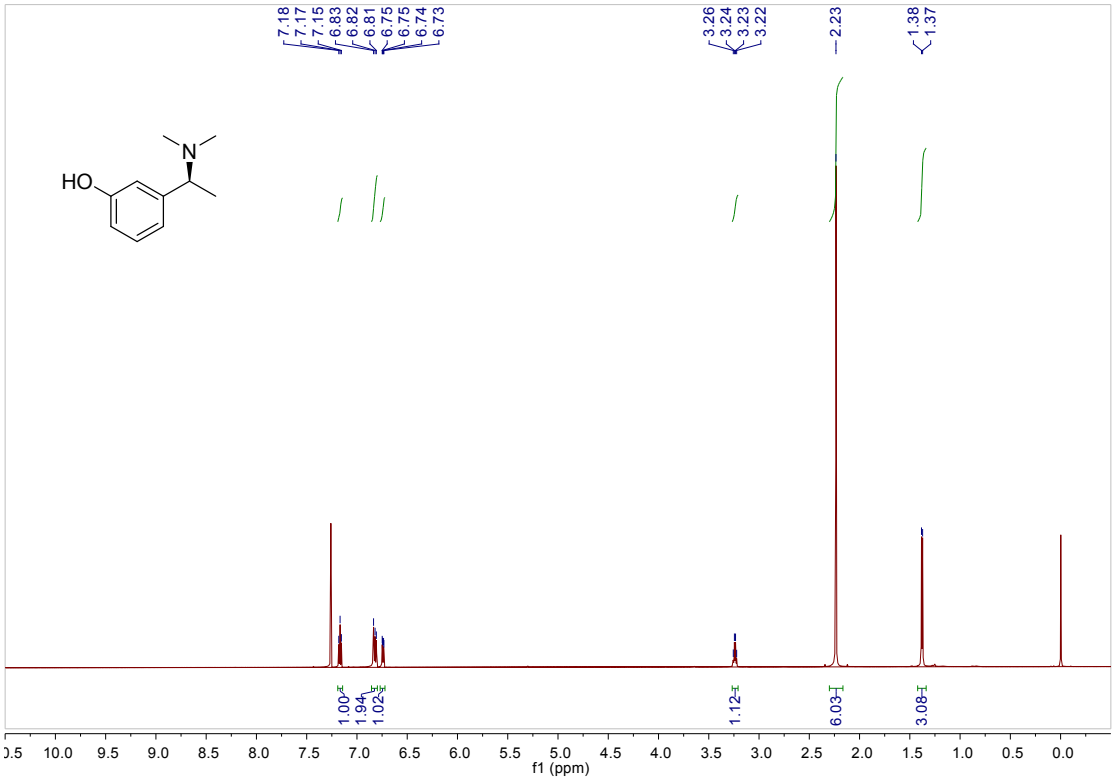
^{13}C NMR spectra of **6**



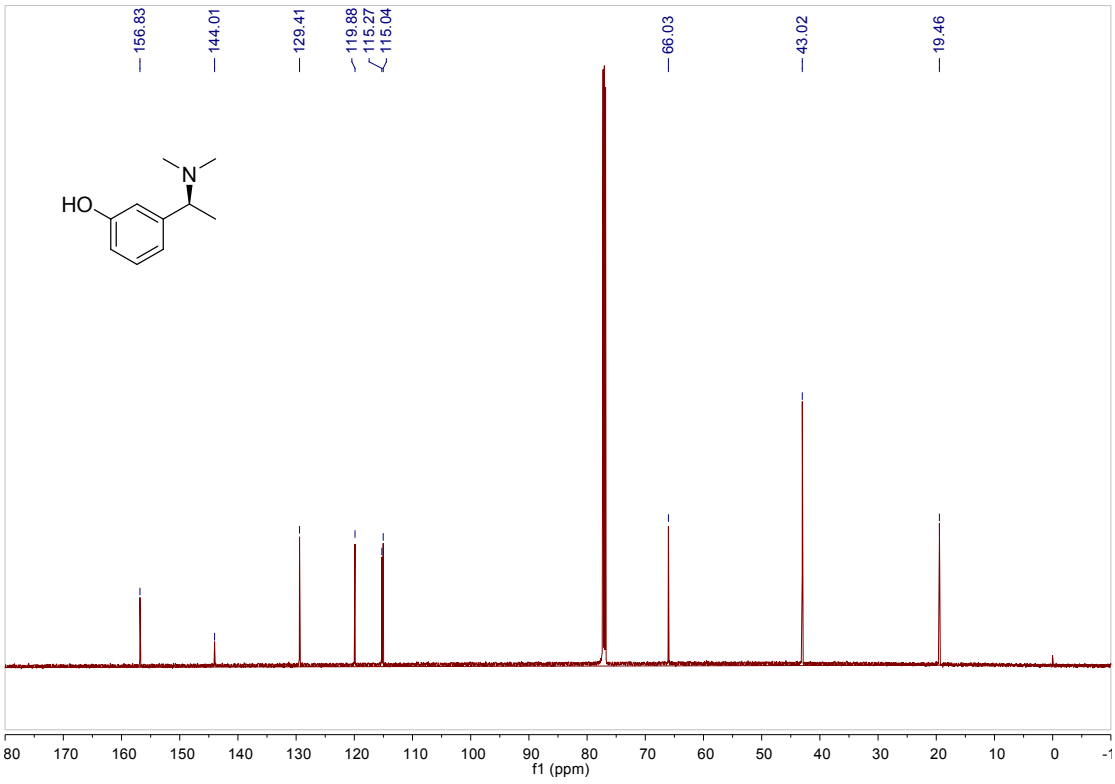
^{1}H NMR spectra of **7**



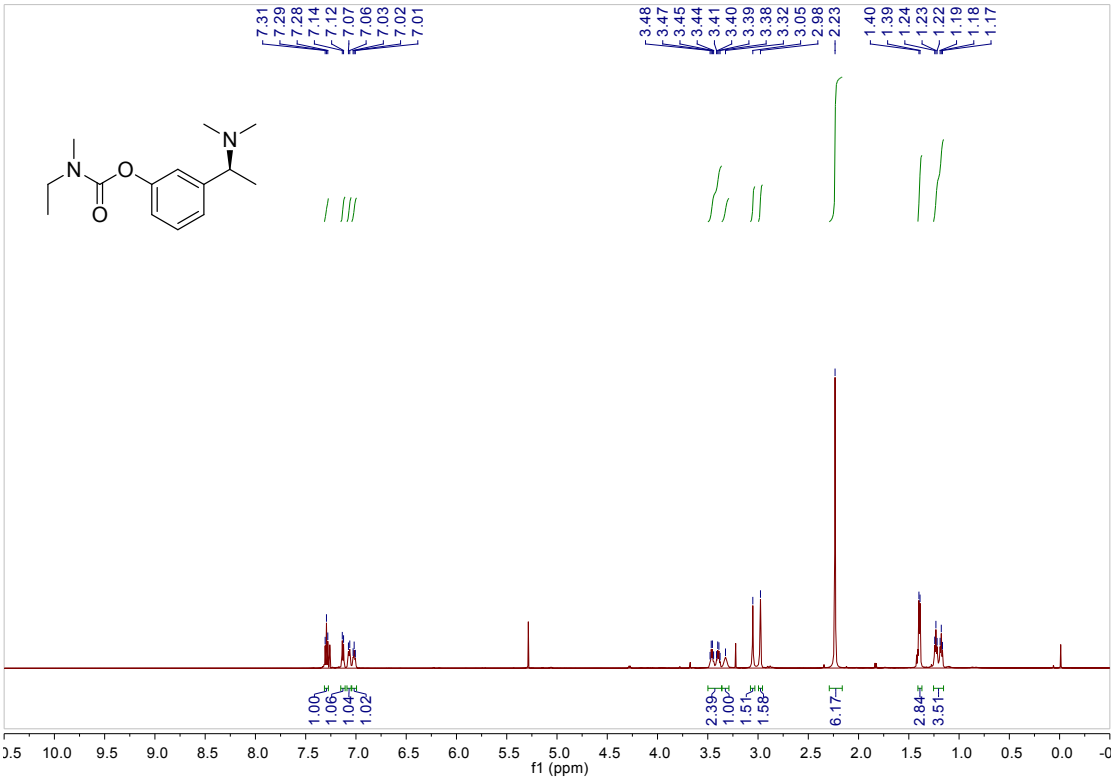
^{13}C NMR spectra of **7**



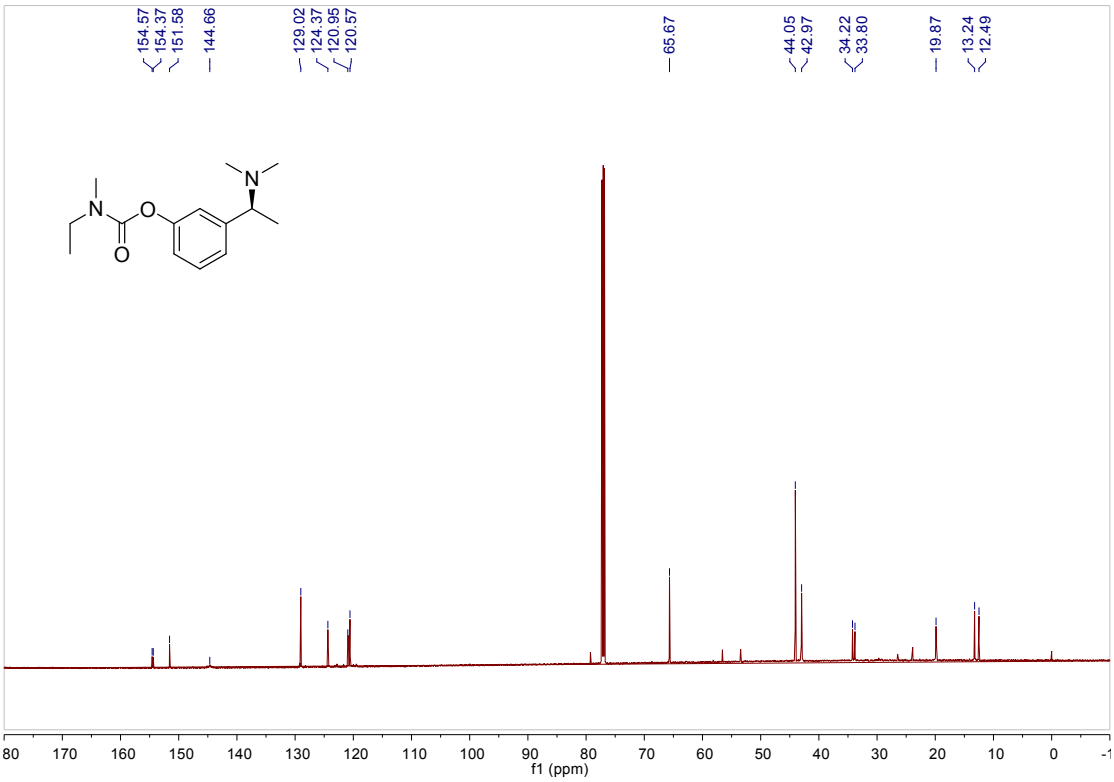
^{1}H NMR spectra of **8**



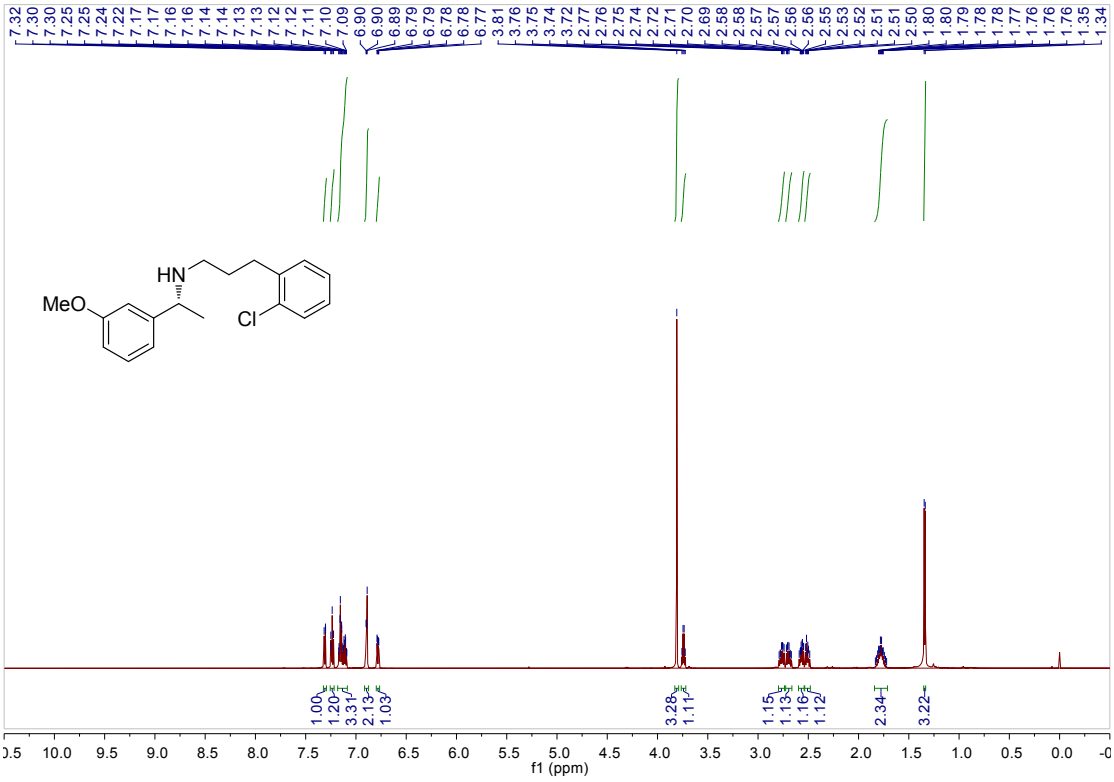
^{13}C NMR spectra of **8**



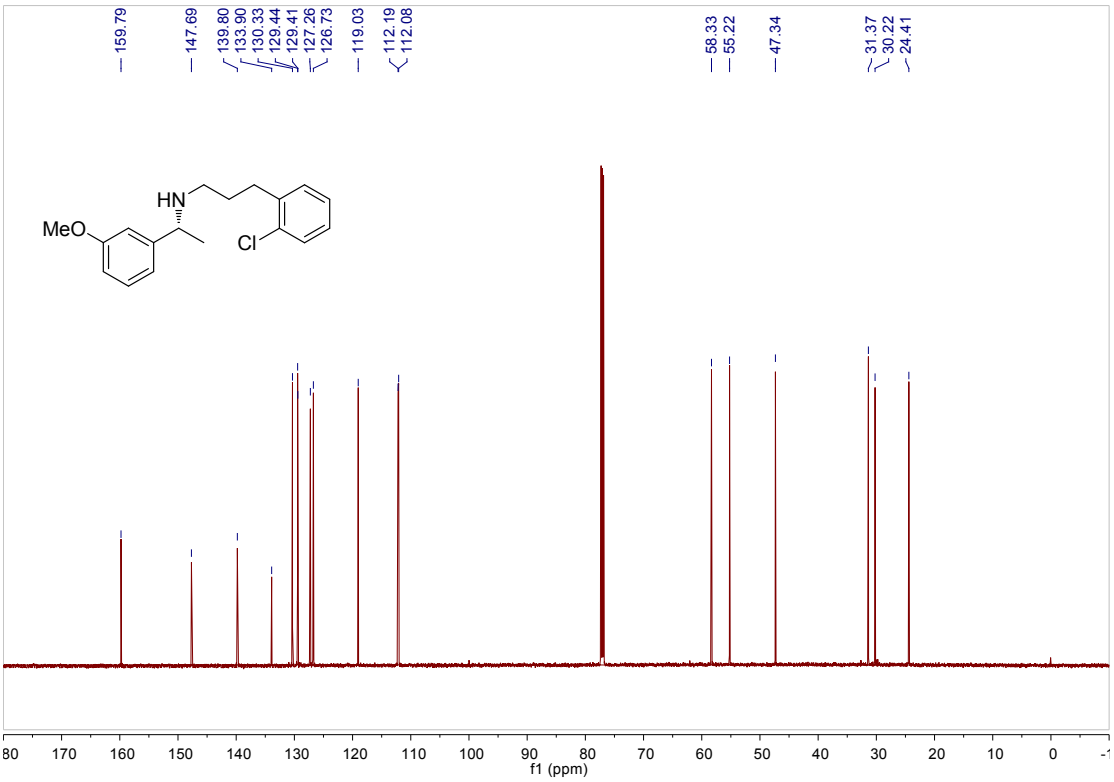
^{1}H NMR spectra of (*S*)-Rivastigmine



^{13}C NMR spectra of (*S*)-Rivastigmine



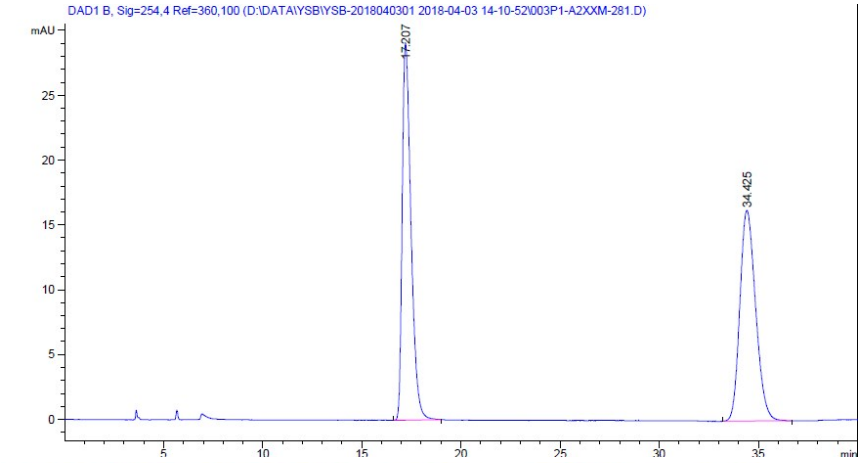
^{1}H NMR spectra of NPS *R*-568



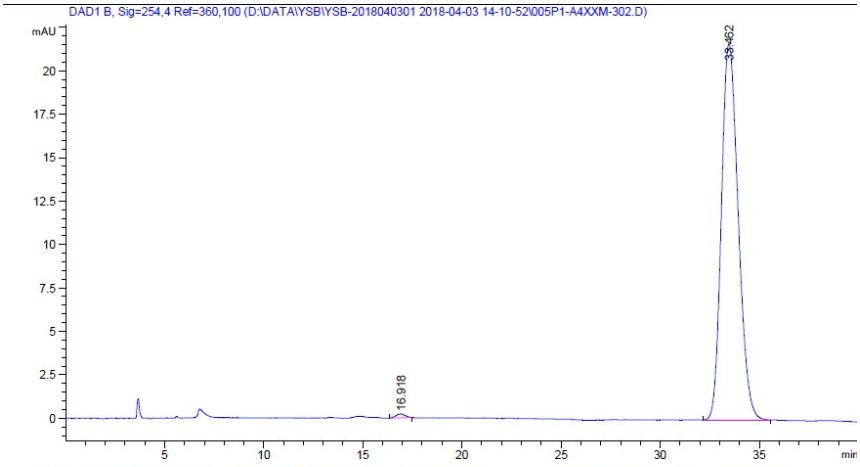
^{13}C NMR spectra of NPS *R*-568

VI. HPLC analysis of Compound (S)-6 (as *N*-acetyl derivative)

Column: ChiralCel OD-H; eluent: n-hexane/isopropanol (90:10); flow rate: 0.8 mL/min; detector 254 nm



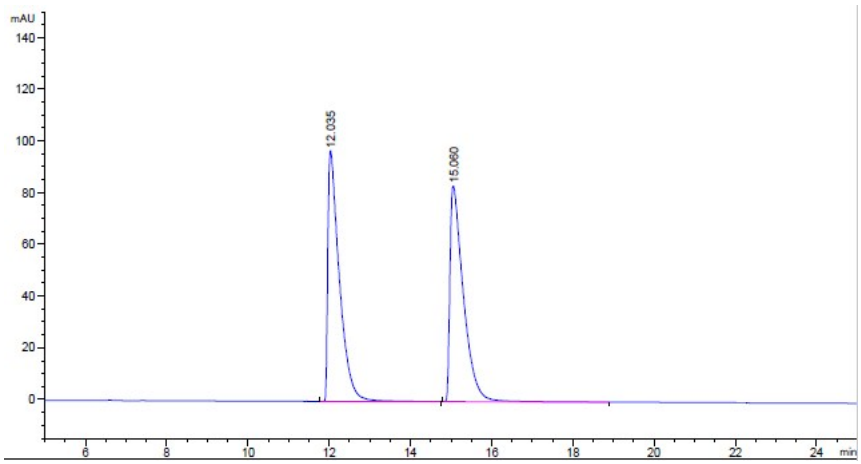
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.207	BB	0.4677	897.32782	29.10148	49.9803
2	34.425	BB	0.8344	898.03625	16.25831	50.0197



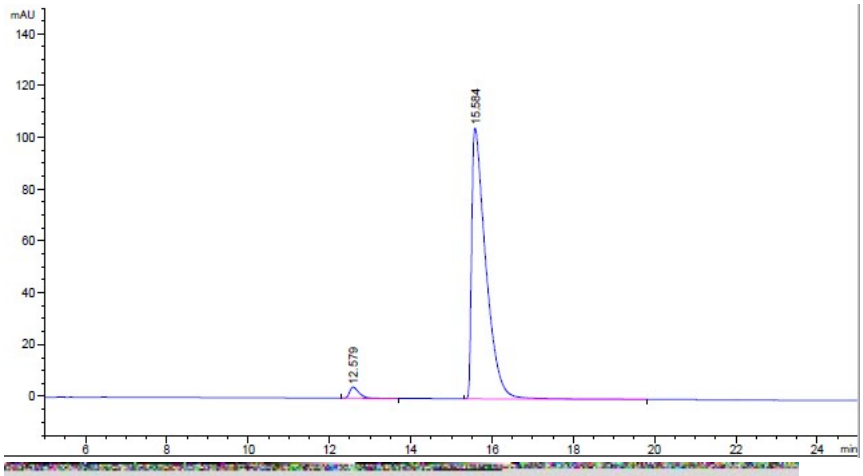
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.918	BB	0.3960	7.34329	2.23090e-1	0.5725
2	33.462	BB	0.8990	1275.29492	21.65708	99.4275

HPLC analysis of Compound 7

Column: Chiralpak OD-3; eluent: n-heptane/iPrOH/DEA (97:3:0.1); flow rate: 1.0 mL/min; detector 277 nm



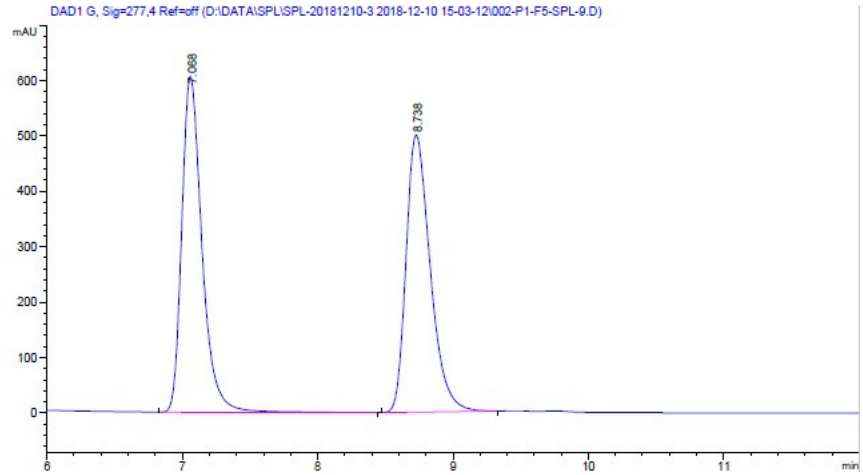
1	12.035	BB	0.2836	1907.61816	96.93793	49.8631
2	15.060	BB	0.3342	1918.09241	83.43602	50.1369



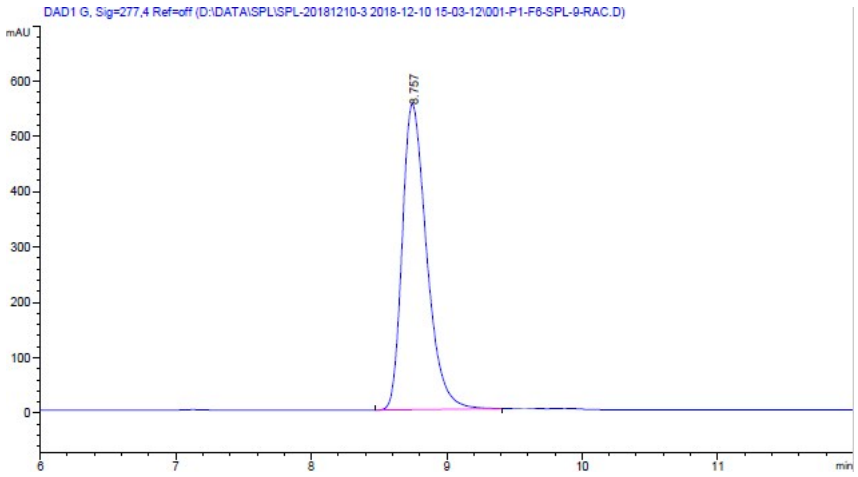
1	12.579	BB	0.2444	69.00205	4.27219	2.6571
2	15.584	BB	0.3520	2527.92993	104.57432	97.3429

HPLC analysis of Compound 8

Column: Chiralpak OD-3 eluent: n-heptane/iPrOH/DEA (97:3:0.1); flow rate: 1.0 mL/min; detector 277 nm



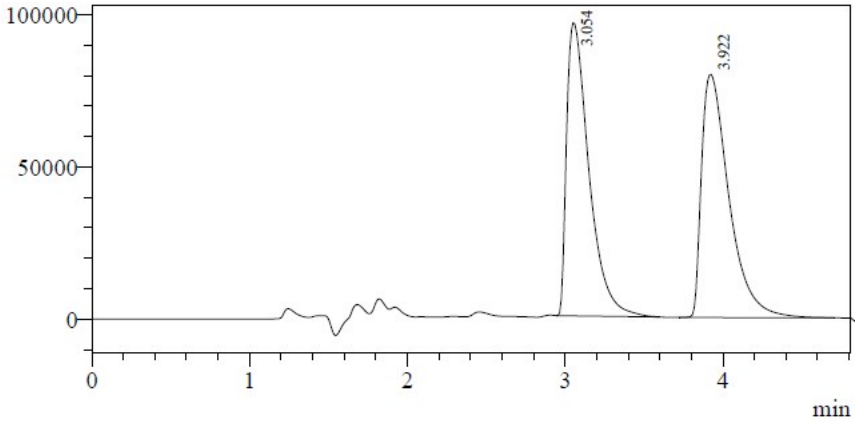
1	7.068	BB	0.1728	6278.58008	586.76691	50.2804
2	8.738	BB	0.2014	6208.54004	498.26944	49.7196



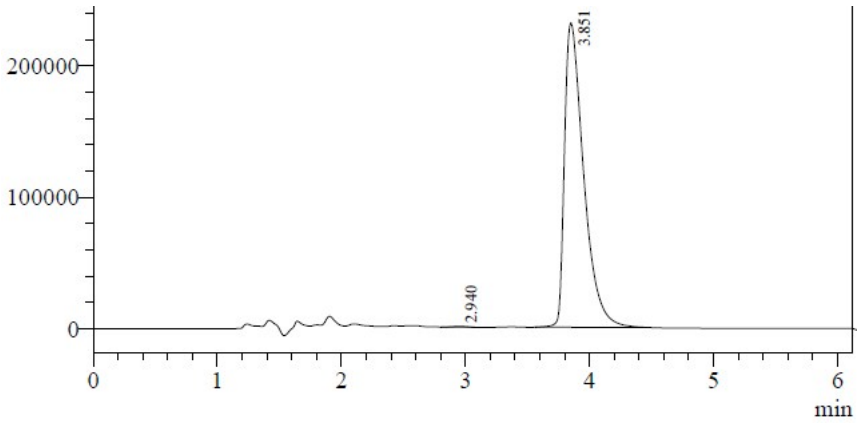
1	8.757	BB	0.2037	6913.33594	545.99457	100.0000

HPLC analysis of Compound 9

Column: CHIRAL Cellulose-SB; eluent: Hex(0.3%TFA):EtOH=85:15; flow rate: 1.0 mL/min; detector 254 nm



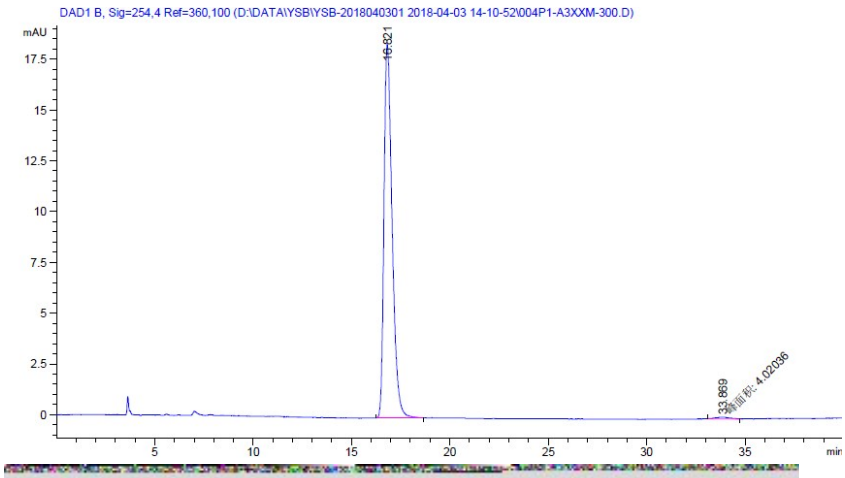
Peak#	Ret. Time	Height	Area	Height %	Area %
1	3.054	96280	946237	54.653	49.468
2	3.922	79886	966607	45.347	50.532
Total		176166	1912845	100.000	100.000



Peak#	Ret. Time	Height	Area	Height %	Area %
1	2.940	576	4153	0.248	0.166
2	3.851	231982	2495200	99.752	99.834
Total		232558	2499353	100.000	100.000

HPLC analysis of Compound (R)-6 (as *N*-acetyl derivative)

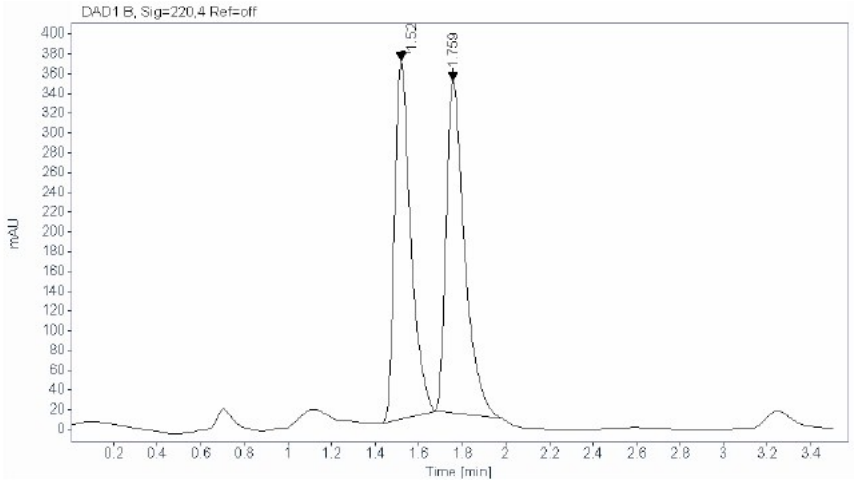
Column: ChiralCel OD-H; eluent: n-hexane/isopropanol (90:10); flow rate: 0.8 mL/min; detector 254 nm



1	16.821	BV R	0.4403	530.10645	18.39173	99.2473
2	33.869	MM	0.8954	4.02036	7.48354e-2	0.7527

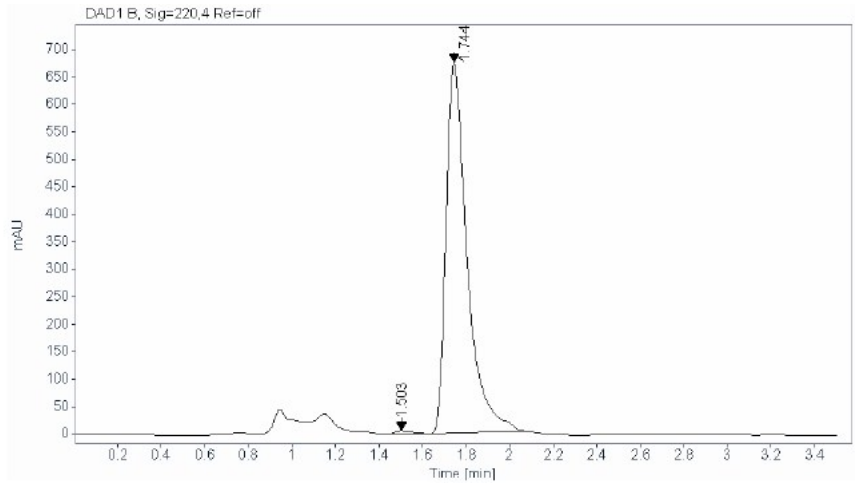
HPLC analysis of Compound 11

Column: CHIRALPAK IG-3; eluent: Hex(8mMNH_3):EtOH=98:2; flow rate: 1.0 mL/min; detector 273 nm



Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Height	Area%
1.520	1864.23926	364.24725	48.49
1.759	1980.60266	336.70343	51.51



Signal: DAD1 B, Sig=220,4 Ref=off

RT [min]	Area	Height	Area%
1.503	28.16728	5.56223	0.62
1.744	4545.67969	674.95563	99.38