Supporting Information for

ADDP facilitate C-S bond formation from sulfonyl chloride with alcohols

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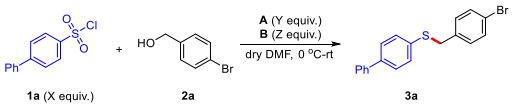
1. General Information

Reagents were purchased from commercial sources and were used without further purification. Reactions were monitored by TLC on silica gel 60 F254 plates. Column chromatography was carried out on silica gel (200-300 mesh). Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on an ACF* 300Q, 400Q, 500Q and 600Q Bruker spectrometer operating at 300 MHz (500 MHz or 600 MHz) for proton and 75 MHz (125 MHz or 150 MHz) for carbon nuclei using $CDCl_3$ [or DMSO-d_6] as solvent, respectively. Chemical shifts are expressed as parts per million (δ, ppm) and are referenced to 7.26 ($CDCl_3$) or 2.50 (DMSO-d_6) for ^{1}H NMR and 77.23 ($CDCl_3$) or 39.51 (DMSO-d_6) for ^{13}C NMR. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet or unresolved). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High Resolution Mass Spectrometry was performed on an Agilent Technologies 6520 Q-TOF LC/MS under the conditions of electrospray ionization (ESI) or atmospheric-pressure chemical ionization(APCI) in positive mode. Analytical HPLC was recorded on a HPLC machine equipped with Quaternary Solvent Manager and PDA Detector (ACQUITY HPLC H-CLASS). The chiral stationary phase was CHIRALCEL OJ-H column (Ø = 0.46 cm, length = 25.0 cm). Melting points were recorded on Tianjin Analysis Instrument Factory RY-1G.

2. Optimization reaction conditions [a)]

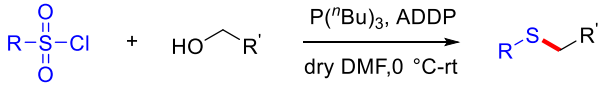


entry	X:Y:Z	**A**	**B**	solvent	yield (%)
1	1:4.5:1	P(^{n}Bu)$_3$	DIAD	DMF	56
2	1:5.0:1	P(^{n}Bu)$_3$	DIAD	DMF	81
3	1:5.5:1	P(^{n}Bu)$_3$	DIAD	DMF	78
4	1:6.0:1	P(^{n}Bu)$_3$	DIAD	DMF	80
5	1.5:7.5:1	P(^{n}Bu)$_3$	DIAD	DMF	73
6	1.5:7.5:1.5	P(^{n}Bu)$_3$	DIAD	DMF	91

Table S1. [a] Reaction conditions: **1a** (X equiv.), **2a** (1.0 mmol), **A** (Y equiv.), **B** (Z equiv.), solvent, 0 ºC-rt.

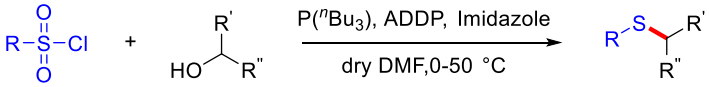
3. Experimental details and characterization data

Method A for primary alcohols



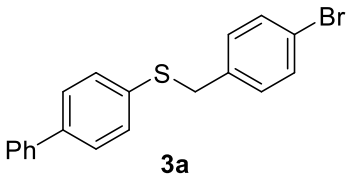
A Schlenk tube was charged with the sulfonyl chloride (1.50 mmol), and alcohol (1.00 mmol) under an argon atmosphere. The mixture was cooled to 0 °C and added anhydrous DMF (3.0 mL). A solution of P(^{n}Bu)$_3$ (7.5 mmol) in anhydrous DMF (1.0 mL) and ADDP (1.5 mmol) in anhydrous DMF (2.0 mL) was slowly added dropwise by syringe in turn. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography.

Method B for secondary alcohols



A Schlenk tube was charged with the sulfonyl chloride (1.50 mmol), and alcohol (1.00 mmol) under an argon atmosphere. The mixture was cooled to 0 °C and added anhydrous DMF (3.0 mL). A solution of P(^{n}Bu)$_3$ (7.5 mmol) in anhydrous DMF (1.0 mL) and ADDP (1.5 mmol) in anhydrous DMF (2.0 mL) was slowly added dropwise by syringe in turn. The mixture was stirred for 15 min and a solution of Imidazole (1.5 mmol) in anhydrous DMF (0.5 mL) was added. The resulting mixture was heated at 50 °C for 24 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with brine (50 mL), dried

over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography.



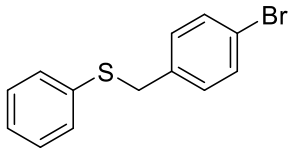
3a

Following method **A**, **[1,1'-biphenyl]-4-yl(4-bromobenzyl)sulfane (3a)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (330.4 mg, 0.93 mmol, 93%); m.p.: 144-145 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.38 (m, 4H), 7.38 – 7.30 (m, 3H), 7.17 (d, *J* = 8.3 Hz, 2H), 4.08 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.30, 139.63, 136.66, 134.76, 131.63, 130.54, 130.51, 128.85, 127.57, 127.45, 126.92, 121.11, 38.65.

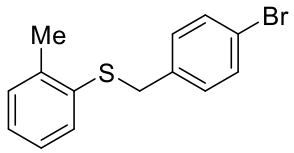
MS (APCI): m/z 355.28 $[M+H]^+$.



3b

Following method **A**, **(4-bromobenzyl)(phenyl)sulfane (3b)** was prepared from benzenesulfonyl chloride (264.9 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (176.7 mg, 0.63 mmol, 63%). ^{1}H NMR data for thioether **3b** prepared in this way were in agreement with the literature.[1]

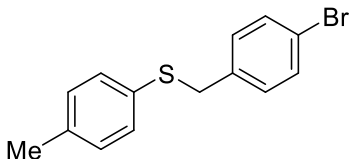
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.19 (m, 5H), 7.14 (d, *J* = 8.3 Hz, 2H), 4.05 (s, 2H).



3c

Following method **A**, **(4-bromobenzyl)(o-tolyl)sulfane (3c)** was prepared from 2-methylbenzenesulfonyl chloride (286.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a colorless oil (205.9 mg, 0.71 mmol, 71%). ^{1}H NMR data for thioether **3c** prepared in this way were in agreement with the literature.[2]

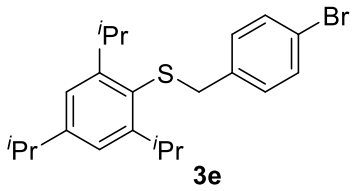
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.08 (m, 6H), 4.01 (s, 2H), 2.32 (s, 3H).



3d

Following method **A**, **(4-bromobenzyl)(p-tolyl)sulfane (3d)** was prepared from 4-methylbenzenesulfonyl chloride (286.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a light pink solid (273.5 mg, 0.93 mmol, 93%). ^{1}H NMR data for thioether **3d** prepared in this way were in agreement with the literature.[3]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.99 (s, 2H), 2.31 (s, 3H).



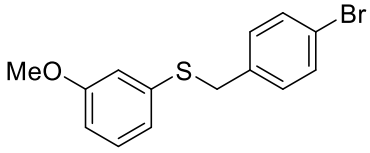
3e

Following method **A**, **(4-bromobenzyl)(2,4,6-triisopropylphenyl)sulfane (3e)** was prepared from 2,4,6-triisopropylbenzenesulfonyl chloride (454.3 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a colorless oil (308.8 mg, 0.76 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2H), 6.98 (s, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 3.83 – 3.72 (m, 2H), 3.70 (s, 2H), 2.88 (hept, *J* = 7.0 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.25, 149.95, 137.22, 131.36, 130.50, 127.44, 121.72, 120.82, 41.71, 34.28, 31.47, 24.36, 23.93.

MS (APCI): m/z 405.12 $[M+H]^+$.



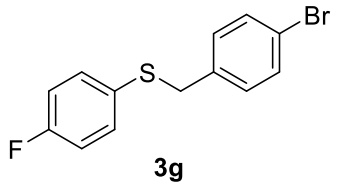
3f

Following method **A**, **(4-bromobenzyl)(3-methoxyphenyl)sulfane (3f)** was prepared from 3-methoxybenzenesulfonyl chloride (310.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a yellowish oil (241.2 mg, 0.78 mmol, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.20 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.05 (s, 2H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.79, 137.00, 136.63, 131.59, 130.48, 129.73, 122.15, 121.06, 115.29, 112.48, 55.25, 38.38.

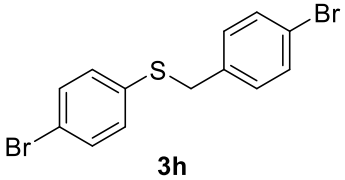
MS (APCI): m/z 308.99 $[M+H]^+$.



3g

Following method **A**, **(4-bromobenzyl)(4-fluorophenyl)sulfane (3g)** was prepared from 4-fluorobenzenesulfonyl chloride (291.9 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (270.8 mg, 0.91 mmol, 91%). ^{1}H NMR data for thioether **3g** prepared in this way were in agreement with the literature.[4]

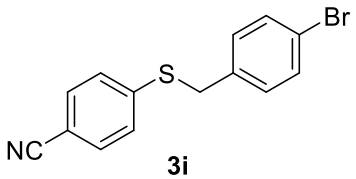
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.2 Hz, 2H), 7.28 (dd, J = 8.6, 5.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 7.03 – 6.89 (m, 2H), 3.98 (s, 2H).



3h

Following method **A**, **(4-bromobenzyl)(4-bromophenyl)sulfane (3h)** was prepared from 4-bromobenzenesulfonyl chloride (383.3 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (192.8 mg, 0.57 mmol, 57%). ^{1}H NMR data for thioether **3h** prepared in this way were in agreement with the literature.[5]

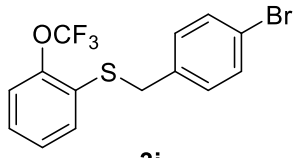
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5, 2H), 7.12 (d, J = 8.4, 2H), 4.01 (s, 2H).



3i

Following method **A**, **4-((4-bromobenzyl)thio)benzonitrile (3i)** was prepared from 4-cyanobenzenesulfonyl chloride (302.4 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 0.5% ethyl acetate in petroleum ether). The product was obtained as a white solid (199.0 mg, 0.66 mmol, 66%). ^{1}H NMR data for thioether **3i** prepared in this way were in agreement with the literature.[6]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.14 (s, 2H).



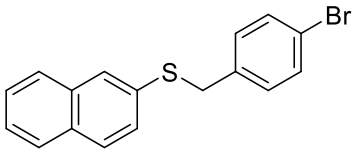
3j

Following method **A**, **(4-bromobenzyl)(2-(trifluoromethoxy)phenyl)sulfane (3j)** was prepared from 2-(trifluoromethoxy)benzenesulfonyl chloride (390.9 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (263.6 mg, 0.73 mmol, 73%); m.p.: 36-37 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.2 Hz, 2H), 7.32 – 7.21 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 4.08 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.83, 135.76, 131.67, 131.32, 130.51, 129.44, 127.80, 127.09, 121.30, 120.55 (q, J_{C-F} = 258.3 Hz), 120.88, 37.11.

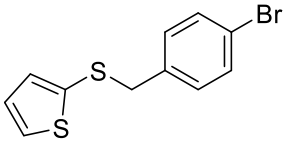
MS (APCI): m/z 360.95 $[M-H]^-$.



3k

Following method **A**, **(4-bromobenzyl)(naphthalen-2-yl)sulfane (3k)** was prepared from naphthalene-2-sulfonyl chloride (340.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (279.9 mg, 0.85 mmol, 85%).[1]H NMR data for thioether **3k** prepared in this way were in agreement with the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.68 (m, 4H), 7.51 – 7.35 (m, 5H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.15 (s, 2H).



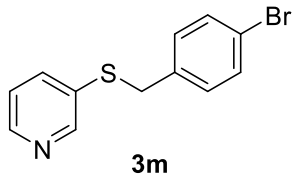
3l

Following method **A**, **2-((4-bromobenzyl)thio)thiophene (3l)** was prepared from thiophene-2-sulfonyl chloride (274.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a yellowish oil (209.0mg, 0.73 mmol, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 3.8 Hz, 2H), 3.88 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.80, 134.70, 132.91, 131.49, 130.62, 130.06, 127.52, 121.17, 43.13.

MS (APCI): m/z 284.94 $[M+H]^+$.



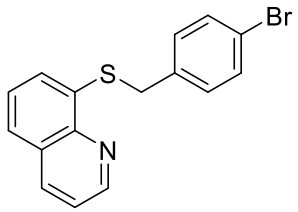
3m

Following method **A**, **3-((4-bromobenzyl)thio)pyridine (3m)** was prepared from pyridine-3-sulfonyl chloride (266.4 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 10% to 20% ethyl acetate in petroleum ether). The product was obtained as yellowish oil (99.0 mg, 0.35 mmol, 35%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.44 (d, *J* = 4.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.03 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.50, 148.00, 138.47, 136.00, 132.41, 131.74, 130.48, 123.59, 121.40, 38.78.

MS (ESI): m/z 279.98 $[M+H]^+$.



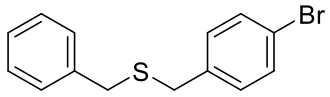
3n

Following method **A**, **8-((4-bromobenzyl)thio)quinoline (3n)** was prepared from quinoline-8-sulfonyl chloride (341.5 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 5% to 7% ethyl acetate in petroleum ether). The product was obtained as a light red white solid (268.0 mg, 0.81 mmol, 81%); m.p.: 142-144 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.50 – 7.38 (m, 5H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.26 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.44, 145.71, 137.65, 136.46, 135.89, 131.61, 130.62, 128.34, 126.56, 125.47, 124.76, 121.73, 121.10, 35.65.

MS (APCI): m/z 330.00 $[M+H]^+$.



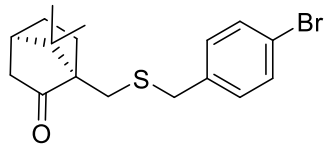
3o

Following method **A**, **benzyl(4-bromobenzyl)sulfane (3o)** was prepared from naphthalene-2-sulfonyl chloride (340.0 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as colorless oil (129.0 mg, 0.44 mmol, 44%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.27 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 2H), 3.59 (s, 2H), 3.53 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.84, 137.23, 131.57, 130.70, 128.98, 128.54, 127.09, 120.80, 35.61, 34.93.

MS (APCI): m/z 293.00 $[M+H]^+$.



3p

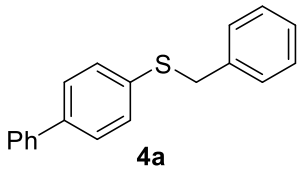
Following method **A**, **(1S,4R)-1-(((4-bromobenzyl)thio)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (3p)** was prepared from ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonyl chloride (376.1 mg, 1.50 mmol, 1.50 equiv.) and (4-bromophenyl)methanol (187.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 1% to 20% ethyl

acetate in petroleum ether). The product was obtained as a yellowish oil (144.0 mg, 0.41 mmol, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.70 (s, 2H), 2.71 (d, *J* = 13.2 Hz, 1H), 2.41 (d, *J* = 13.2 Hz, 1H), 2.32 (dd, *J* = 5.2, 2.1 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.98 – 1.91 (m, 2H), 1.85 (d, *J* = 18.4 Hz, 1H), 1.45 (t, *J* = 9.8 Hz, 1H), 1.37 (t, *J* = 9.5 Hz, 1H), 0.98 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 217.41, 137.62, 131.51, 130.70, 120.75, 60.96, 47.82, 43.53, 43.13, 37.87, 28.42, 26.92, 26.88, 20.21, 20.16.

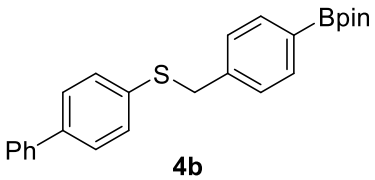
MS (APCI): m/z 353.06 $[M+H]^+$.



4a

Following method **A**, **[1,1'-biphenyl]-4-yl(benzyl)sulfane (4a)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and phenylmethanol (108.1 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (212.0 mg, 0.77 mmol, 77%). ^{1}H NMR data for thioether **4a** prepared in this way were in agreement with the literature. [8]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.24 (m, 14H), 4.16 (s, 2H).



4b

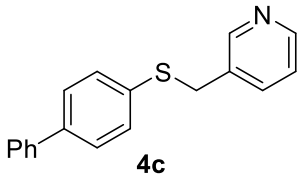
Following method **A**, **2-(4-(([1,1'-biphenyl]-4-ylthio)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4b)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (234.1 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 12% to 30% ethyl

acetate in petroleum ether). The product was obtained as a white solid (311.0 mg, 0.77 mmol, 77%); m.p.: 129-131 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.29 (m, 5H), 4.15 (s, 2H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.70, 140.43, 139.31, 135.31, 135.02, 130.19, 128.81, 128.22, 127.50, 127.35, 126.92, 83.81, 77.36, 77.24, 77.04, 76.72, 39.20, 24.89.

MS (APCI): m/z 403.19 $[M+H]^+$.



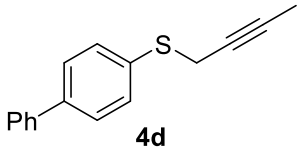
4c

Following method **A**, **3-(([1,1'-biphenyl]-4-ylthio)methyl)pyridine (4c)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and pyridin-3-ylmethanol (109.1 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 10% to 20% ethyl acetate in petroleum ether). The product was obtained as a white solid (67.2 mg, 0.24 mmol, 24%); m.p.: 90-91 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.29 (m, 3H), 7.25 – 7.18 (m, 1H), 4.11 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.97, 148.56, 140.22, 139.99, 136.26, 134.05, 133.49, 131.03, 128.85, 127.67, 127.51, 126.94, 123.41, 36.58.

MS (APCI): m/z 276.09 $[M-H]^-$.



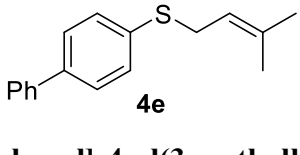
4d

Following method **A**, **[1,1'-biphenyl]-4-yl(but-2-yn-1-yl)sulfane (4d)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and but-2-yn-1-ol (75 µL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a yellowish oil (206.0 mg, 0.87 mmol, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 4H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 3.64 (t, *J* = 2.6 Hz, 2H), 1.82 (t, *J* = 2.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.44, 139.47, 134.86, 129.89, 128.84, 127.56, 127.41, 126.95, 79.65, 74.65, 23.06, 3.74.

MS (APCI): m/z 239.09 $[M+H]^+$.



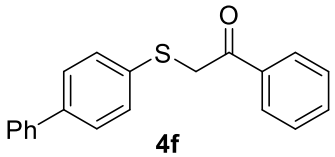
4e

Following method **A**, **[1,1'-biphenyl]-4-yl(3-methylbut-2-en-1-yl)sulfane (4e)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and 3-methylbut-2-en-1-ol (102 µL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (221.5 mg, 0.87 mmol, 87%); m.p.: 78-80 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 7.0 Hz, 3H), 7.40 (d, *J* = 8.4 Hz, 4H), 7.37 – 7.30 (m, 1H), 5.41 – 5.27 (m, 1H), 3.58 (d, *J* = 7.7 Hz, 2H), 1.73 (s, 3H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.54, 138.90, 136.54, 136.07, 129.89, 128.82, 127.39, 127.30, 126.91, 119.29, 32.24, 25.71, 17.77.

MS (APCI): m/z 255.12 $[M+H]^+$.



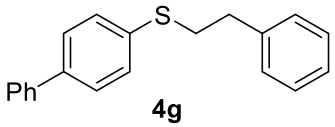
4f

Following method **A**, **2-([1,1'-biphenyl]-4-ylthio)-1-phenylethan-1-one (4f)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and 2-hydroxy-1-phenylethan-1-one (136.2 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 0.5% to 2% ethyl acetate in petroleum ether). The product was obtained as a white solid (127.0 mg, 0.42 mmol, 42%); m.p.: 98-100 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.64 – 7.51 (m, 4H), 7.50 (s, 2H), 7.48 – 7.40 (m, 5H), 7.38 – 7.30 (m, 1H), 4.32 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.08, 140.29, 140.10, 135.44, 133.80, 133.54, 130.90, 128.85, 128.74, 127.75, 127.50, 126.98, 41.24.

MS (APCI): m/z 305.10 $[M+H]^+$.



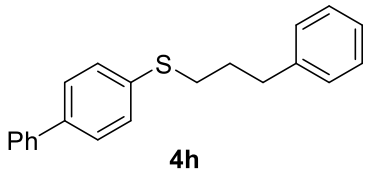
4g

Following method **A**, **[1,1'-biphenyl]-4-yl(phenethyl)sulfane (4g)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and 2-phenylethan-1-ol (120 µL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (188.8 mg, 0.65 mmol, 65%); m.p.: 78-79 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.32 (m, 4H), 7.31 – 7.18 (m, 4H), 7.15 (d, *J* = 7.6 Hz, 2H), 3.14 (dd, *J* = 9.4, 6.3 Hz, 2H), 2.90 (dd, *J* = 9.4, 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.47, 140.22, 138.97, 135.53, 129.53, 128.85, 128.56, 127.62, 127.35, 126.92, 126.52, 35.71, 35.17.

MS (APCI): m/z 291.12 $[M+H]^+$



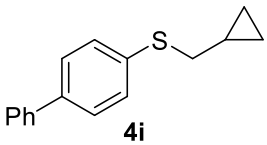
4h

Following method **A**, **[1,1'-biphenyl]-4-yl(3-phenylpropyl)sulfane (4h)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and 3-phenylpropan-1-ol (140 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (153.0 mg, 0.50 mmol, 50%); m.p.: 99-101 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.40 – 7.26 (m, 5H), 7.25 – 7.15 (m, 3H), 2.96 (t, *J* = 7.3 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.00 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.29, 140.51, 138.82, 135.74, 129.40, 128.83, 128.55, 128.45, 127.55, 127.31, 126.90, 126.03, 34.72, 32.93, 30.67.

MS (APCI): m/z 305.14 $[M+H]^+$.



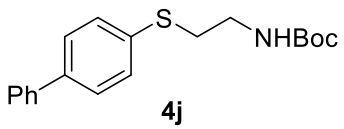
4i

Following method **A**, **[1,1'-biphenyl]-4-yl(cyclopropylmethyl)sulfane (4i)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and cyclopropylmethanol (81 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (174.0 mg, 0.72 mmol, 72%); m.p.: 93-95 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 4H), 7.35 (d, *J* = 7.3 Hz, 1H), 2.91 (d, *J* = 7.0 Hz, 2H), 1.18 – 1.00 (m, 1H), 0.66 – 0.54 (m, 2H), 0.35 – 0.20 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.53, 138.79, 136.27, 129.56, 128.82, 127.47, 127.29, 126.89, 39.65, 10.70, 5.68.

MS (APCI): m/z 241.12 $[M+H]^+$.



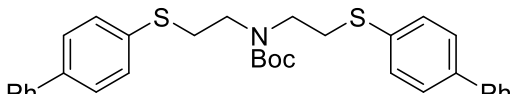
4j

Following method **A**, **tert-butyl (2-([1,1'-biphenyl]-4-ylthio)ethyl)carbamate (4j)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and tert-butyl (2-hydroxyethyl)carbamate (161.2 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 0% to 4% ethyl acetate in petroleum ether). The product was obtained as a white solid (245.0 mg, 0.74 mmol, 74%); m.p.: 102-103 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 4H), 7.48 – 7.27 (m, 5H), 4.92 (s, 1H), 3.37 (q, J = 6.3 Hz, 2H), 3.08 (t, J = 6.2 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.74, 140.36, 139.47, 134.28, 130.12, 128.85, 127.74, 127.42, 126.93, 79.52, 39.71, 34.23, 28.41.

MS (APCI): m/z 328.14 $[M-H]^-$.



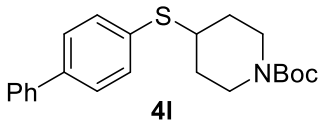
4k

Following method **A**, **tert-butyl bis(2-([1,1'-biphenyl]-4-ylthio)ethyl)carbamate (4k)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 3.00 mmol, 3.00 equiv.) and tert-butyl bis(2-hydroxyethyl)carbamate (205.3 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 0% to 10% ethyl acetate in petroleum ether). The product was obtained as a white solid (360.0 mg, 0.67 mmol, 67%); m.p.: 100-103 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 8H), 7.46 – 7.29 (m, 10H), 3.46 (q, J = 5.9 Hz, 4H), 3.18 – 3.01 (m, 4H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.04, 140.32, 139.36, 138.98, 134.93, 134.58, 129.74, 129.26, 128.85, 127.69, 127.41, 127.34, 126.88, 80.26, 48.62, 48.20, 32.20, 31.73, 28.45.

MS (APCI): m/z 442.16 $[M\text{-Boc}]^+$.



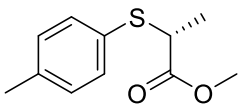
4l

Following method **B**, **tert-butyl 4-([1,1'-biphenyl]-4-ylthio)piperidine-1-carboxylate (4l)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and tert-butyl 4-hydroxypiperidine-1-carboxylate (201.3 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 0% to 7% ethyl acetate in petroleum ether). The product was obtained as a yellowish solid (219.8 mg, 0.59 mmol, 59%); m.p.: 125-127 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.39 – 7.31 (m, 1H), 3.98 (dt, *J* = 13.3, 3.4 Hz, 2H), 3.30 – 3.20 (m, 1H), 2.94 (ddd, *J* = 13.7, 10.7, 3.0 Hz, 2H), 1.96 (dd, *J* = 13.4, 3.7 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.72, 140.31, 140.28, 133.01, 132.88, 128.86, 127.62, 127.52, 126.98, 79.63, 44.63, 43.30, 32.16, 28.44.

MS (APCI): m/z 270.14 $[M\text{-Boc}]^+$.

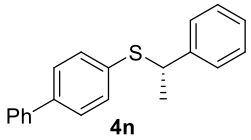


4m

Following method **B**, **methyl (R)-2-(p-tolylthio)propanoate (4m)** was prepared from *p*-toluenesulfonyl chloride (286 mg, 1.50 mmol, 1.50 equiv.) and methyl (S)-2-hydroxypropanoate (95 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a

yellowish oil (186 mg, 0.88 mmol, 88%).[1]H NMR data for thioether **4m** prepared in this way were in agreement with the literature. [9]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.76 – 3.65 (m, 4H), 2.34 (s, 3H), 1.45 (d, *J* = 7.1 Hz, 3H).



4n

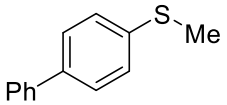
Following method **B**, **(S)-[1,1'-biphenyl]-4-yl(1-phenylethyl)sulfane (4n)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and (R)-1-phenylethan-1-ol (201.3 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (226.5 mg, 0.78 mmol, 78%); m.p.: 85-86 ℃.

^{1}H NMR (300 MHz, CDCl3) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.38 – 7.31 (m, 5H), 7.29 (s, 2H), 7.25 – 7.19 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 1H), 1.66 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.23, 140.41, 139.96, 134.27, 132.70, 128.82, 128.46, 127.43, 127.33, 127.20, 126.96, 48.04, 22.42.

MS (ESI): m/z 313.10 $[M+Na]^+$.

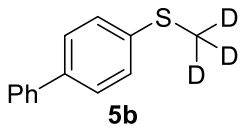
$[\alpha]_D^{20}$ = +210.2° (c=1, acetone).



5a

Following method **A**, **[1,1'-biphenyl]-4-yl(methyl)sulfane (5a)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and methanol (41 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a yellowish solid (198.3 mg, 0.99 mmol, 99%). [1]H NMR data for thioether **5a** prepared in this way were in agreement with the literature.[10]

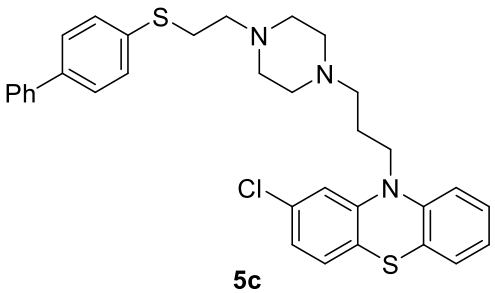
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 3H), 2.53 (s, 3H).



5b

Following method **A**, **[1,1'-biphenyl]-4-yl(methyl-d3)sulfane (5b)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and methanol-d4 (41 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with petroleum ether). The product was obtained as a white solid (189.0 mg, 0.93 mmol, 93%). ^{1}H NMR data for thioether **5b** prepared in this way were in agreement with the literature.[11]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.39 – 7.27 (m, 3H).



5c

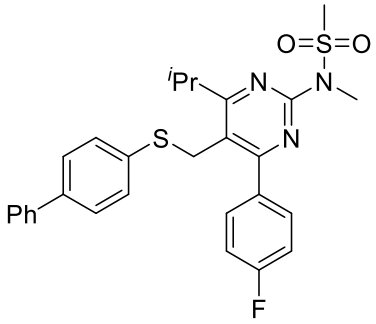
Following method **A**, **10-(3-(4-(2-([1,1'-biphenyl]-4-ylthio)ethyl)piperazin-1-yl)propyl)-2-chloro-10H-phenothiazine (5c)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and 2-(4-(3-(2-chloro-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)ethan-1-ol (404.0 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 1% to 2% methanol in dichloromethane). The product was obtained as a yellow oil (233.0 mg, 0.41 mmol, 41%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.38 (m, 5H), 7.18 – 7.07 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.95 – 6.80 (m, 4H), 3.89 (t, *J*

= 6.8 Hz, 2H), 3.12 – 3.04 (m, 2H), 2.69 – 2.62 (m, 2H), 2.47 (t, *J* = 6.8 Hz, 8H), 1.98 – 1.88 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.49, 144.52, 140.42, 138.92, 135.49, 133.22, 129.31, 128.83, 127.89, 127.58, 127.51, 127.42, 127.34, 126.89, 124.79, 123.52, 122.90, 122.25, 115.87, 115.83, 57.62, 55.46, 53.16, 53.02, 45.33, 30.76, 24.21.

MS (APCI): m/z 572.19 $[M+H]^+$.



5d

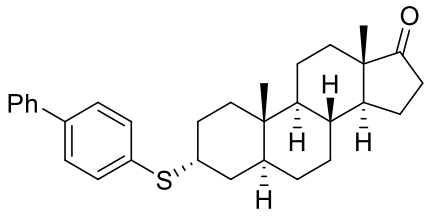
Following method **A**, **N-(5-(([1,1'-biphenyl]-4-ylthio)methyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (5d)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and N-(4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl)-N-methylmethane sulfonamide (353.4 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 3% to 7% ethyl acetate in petroleum ether). The product was obtained as a white solid (345.0 mg, 0.66 mmol, 66%); m.p.: 145-146 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 8.4 Hz, 3H), 7.13 (t, *J* = 8.6 Hz, 2H), 4.13 (s, 2H), 3.57 (s, 3H), 3.54 (s, 1H), 3.52 (s, 3H), 1.36 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.26, 165.97, 163.55 (d, *J* = 250.1 Hz), 157.74, 140.18, 140.02, 134.64, 134.09 (d, *J* = 3.3 Hz), 131.01 (d, *J* = 8.4 Hz), 130.15, 128.92,

127.83, 127.61, 126.95, 115.45 (d, *J* = 21.7 Hz), 117.91, 42.54, 33.14, 32.90, 31.70, 22.35.

MS (APCI): m/z 522.18 $[M+H]^+$.



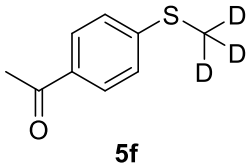
5e

Following method **B**, **(3R,5S,8R,9S,10S,13S,14S)-3-([1,1'-biphenyl]-4-ylthio)-10,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (5e)** was prepared from [1,1'-biphenyl]-4-sulfonyl chloride (379.1 mg, 1.50 mmol, 1.50 equiv.) and (3S,5S,8R,9S,10S,13S,14S)-3-hydroxy-10,13-dimethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-one (209.5 mg, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 2% to 6% ethyl acetate in petroleum ether). The product was obtained as a white solid (242.0 mg, 0.53 mmol, 53%); m.p.: 199-200 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 8.1, 3.0 Hz, 4H), 7.38 – 7.29 (m, 1H), 3.74 – 3.69 (m, 1H), 2.44 (dd, *J* = 19.0, 8.7 Hz, 1H), 2.08 (dt, *J* = 18.6, 8.9 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.84 – 1.66 (m, 6H), 1.54 – 1.42 (m, 4H), 1.33 – 1.23 (m, 5H), 1.08 (td, *J* = 11.7, 6.0 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.56, 140.47, 139.24, 135.53, 131.22, 128.82, 127.54, 127.34, 126.91, 54.26, 51.50, 47.84, 45.55, 40.74, 36.54, 35.88, 35.07, 33.29, 33.19, 31.57, 30.74, 28.15, 26.41, 21.78, 20.10, 13.85, 11.88.

MS (APCI): m/z 459.27 $[M+H]^+$.



5f

Following method **A**, **1-(4-((methyl-d3)thio)phenyl)ethan-1-one (5f)** was prepared from 4-acetylbenzenesulfonyl chloride (328.0 mg, 1.50 mmol, 1.50 equiv.) and methanol-d4 (41 μL, 1.00 mmol, 1 equiv.). The residue was purified by column chromatography (eluting with a gradient of 10% to 20% ethyl acetate in petroleum ether). The product was obtained as a white solid (132.9 mg, 0.79 mmol, 79%). ^{1}H NMR data for thioether **5f** prepared in this way were in agreement with the literature.[12]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 2.57 (s, 3H).

Chiral HPLC analysis

Methyl (*S*)-2-hydroxypropanoate was reacted with TsCl following method **B** to afford the product thioether **4m** in 88% yield (Figure S1). The reaction could produce either of the two possible enantiomers (*R*)-**4m** or (*S*)-**4m**, or a racemic mixture of both.

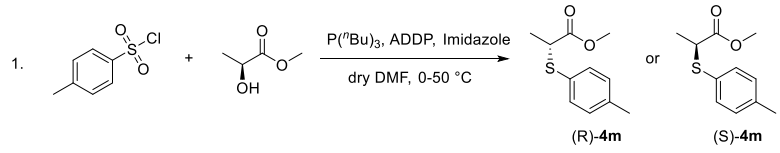


Figure S1. Thioether from TsCl with methyl (S)-2-hydroxypropanoate following method **B**.

To determine the stereochemical configuration of the thioether, single configuration and racemate were prepared using an established method (Figure S2).[13, 14] The thioethers (*rac*)-**4m** and (*R*)-**4m** were analyzed by chiral HPLC (Figure S3-A, S3-B). The peaks were assigned to each respective enantiomer by comparison with the enantio-enriched (*R*)-**4m** (Figure S3-B, 66% ee). Analysis of the thioether synthesized using our method, revealed that the product was (*R*)-**4m** (Figure S3-C, 77% ee).

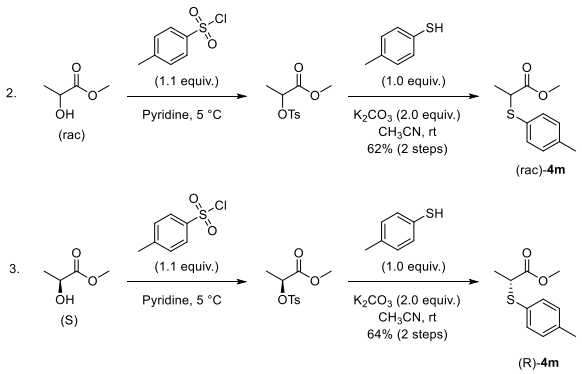
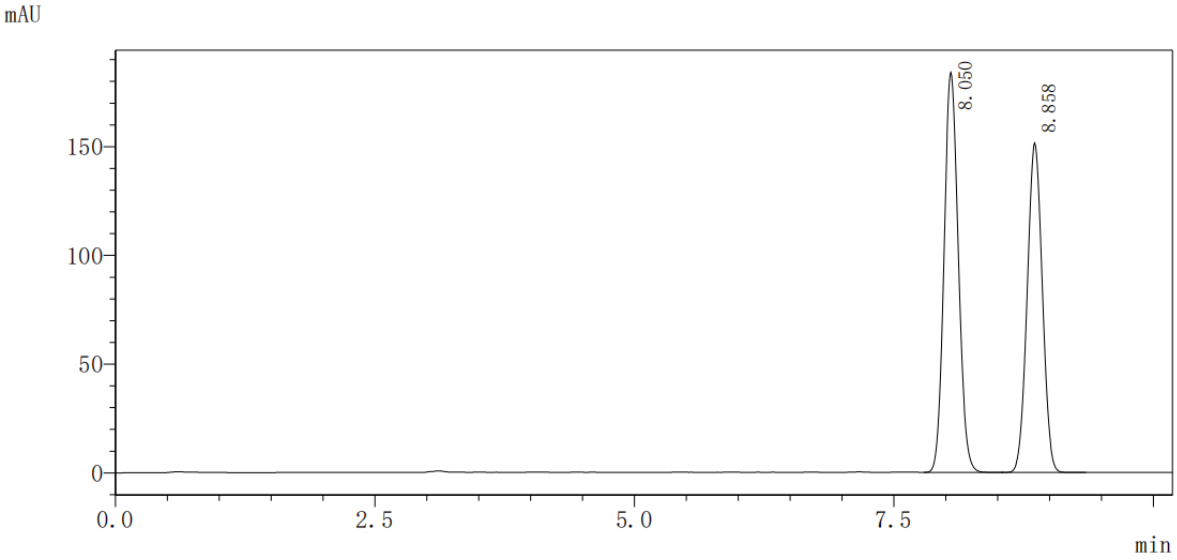


Figure S2. (*rac*)-**4m** and (*R*)-**4m** using a literature procedure.

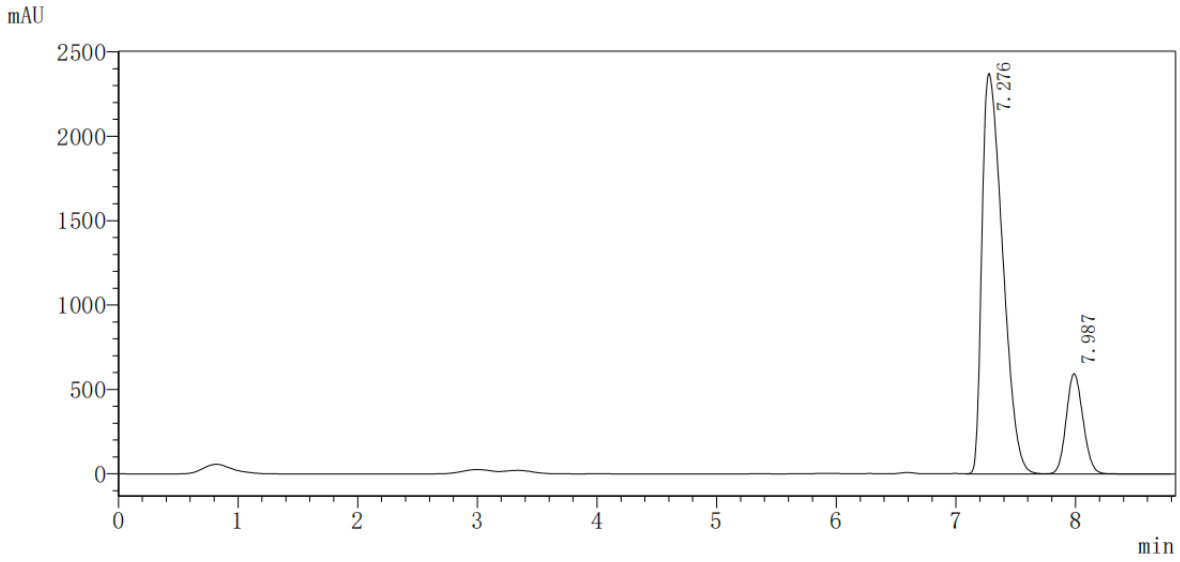
A.(*rac*)-**4m**, 62% yield. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 8.050 min, 8.858 min]



Peak Results

	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	8.050	1762144	183875	53.36
2	8.858	1540479	151574	46.64

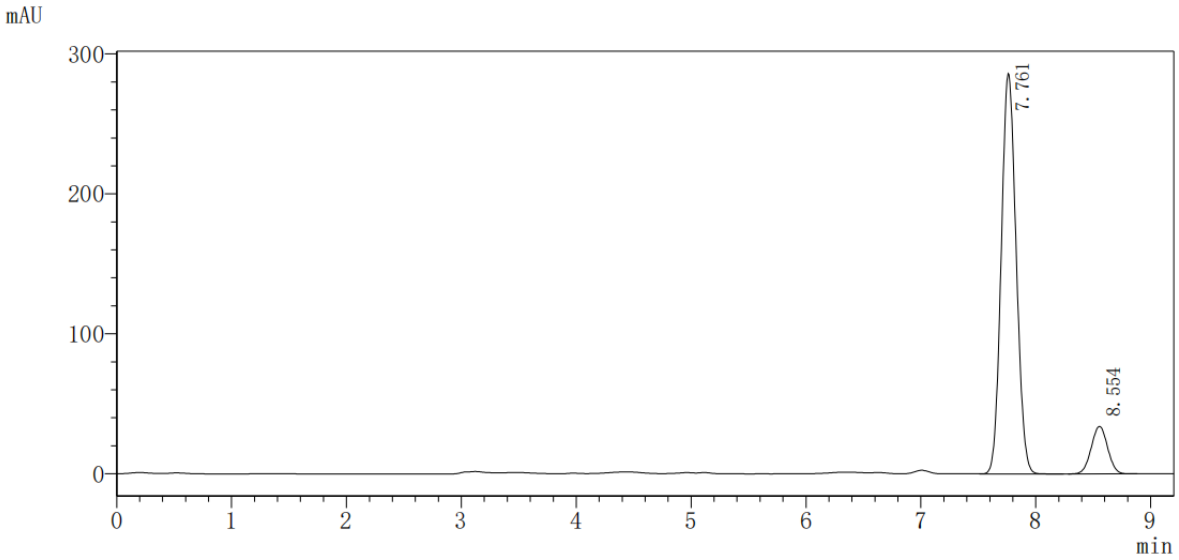
B.(*R*)-**4m**, 66% yield, 66% ee. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 7.276 min(major), 7.987 min (minor)], $[\alpha]_D^{20}$ = +76.9° (c=1, acetone)



Peak Results

	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	7.276	28440168	2371693	83.08
2	7.987	5791148	593103	16.92

C. (*R*)-**4m**, P(^{n}Bu)$_3$, ADDP, Imidazole, 0-50 ℃, 88% yield, 77% ee. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 7.761 min(major), 8.554 min (minor)], $[\alpha]_D^{20}$ = +85.1° (c=1, acetone).



Peak Results

	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	7.761	2585648	286111	88.48
2	8.554	336776	33952	11.52

Figure S3. (A) Chiral HPLC analysis of (*rac*)-**4m**. (B) Chiral HPLC analysis of (*R*)-**4m**. (C) The product of reaction 1 (Figure S1) was determined to be (*R*)-**4m** by chiral HPLC analysis.

To increase enantioselectivity, an improved method was utilized that maintained reaction temperature at 0 ℃. Expectly, enantioselectivity had a moderated elevated, although the yield decreased at the same range.

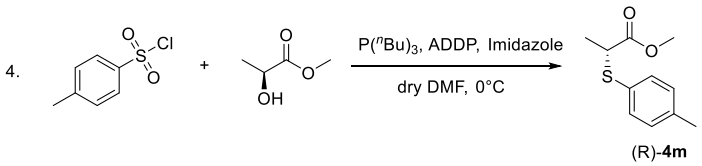
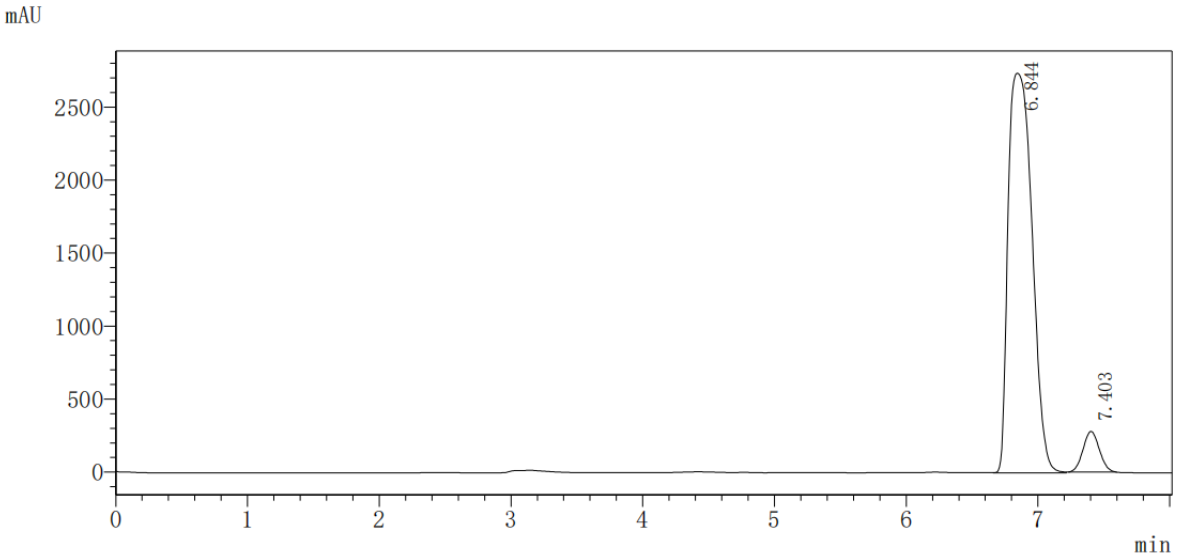


Figure S4. (R)-**4m** using an improved procedure.

P(^{n}Bu)$_3$, ADDP, Imidazole, 0 ℃, 79% yield, 87% ee. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 6.844 min(major), 7.403 min (minor)], $[\alpha]_D^{20} = +113.4^\circ$ (c=1, acetone).



Peak Results

	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	6.844	34542564	2736186	93.54

2	7.403	2384418	277596	6.46

Figure S5. The product of reaction 4 (Figure S4) followed an improved procedure was determined to be (*R*)-**4m** by chiral HPLC analysis.

In addition, to determine the effect of imidazole, control experiments were performed (Figure S6). The results of control experiments showed that imidazole has a significant effect in yield but not enantioselectivity (Figure S7).

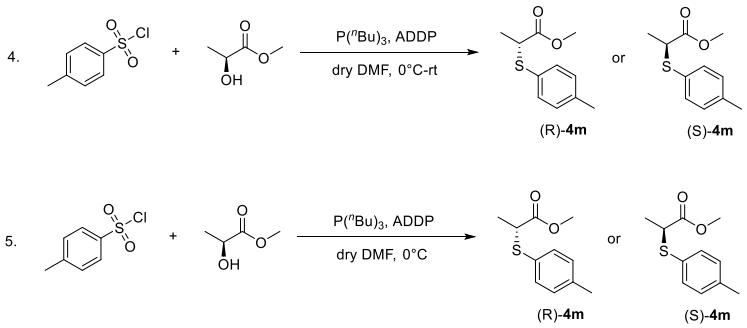
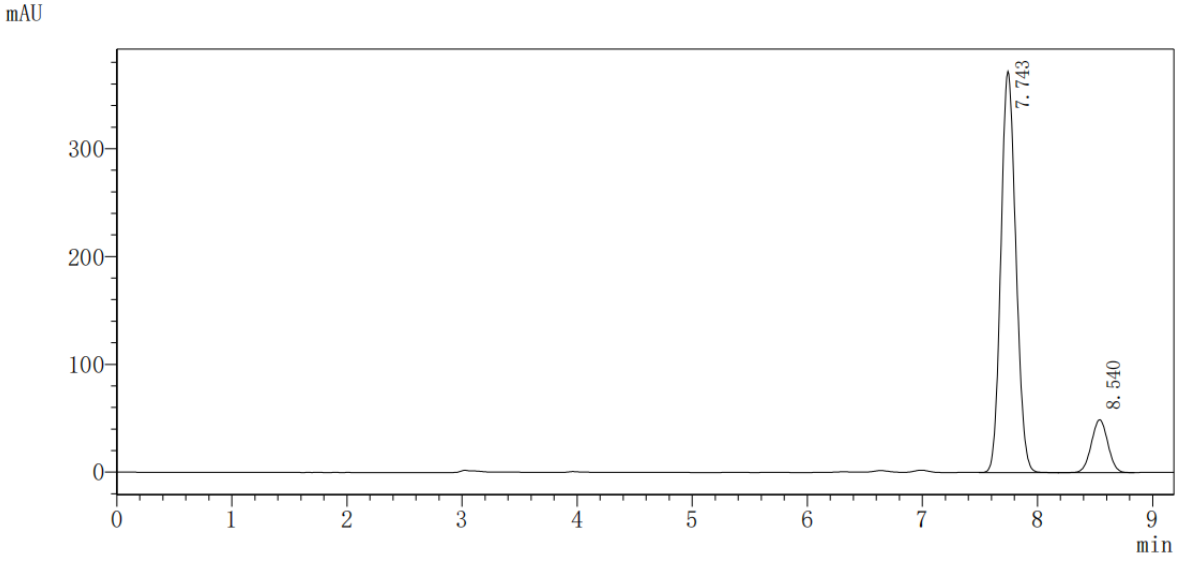


Figure S6. Thioether from TsCl with methyl (*S*)-2-hydroxypropanoate following method **A** (reaction 4) and an improved procedure (reaction 5).

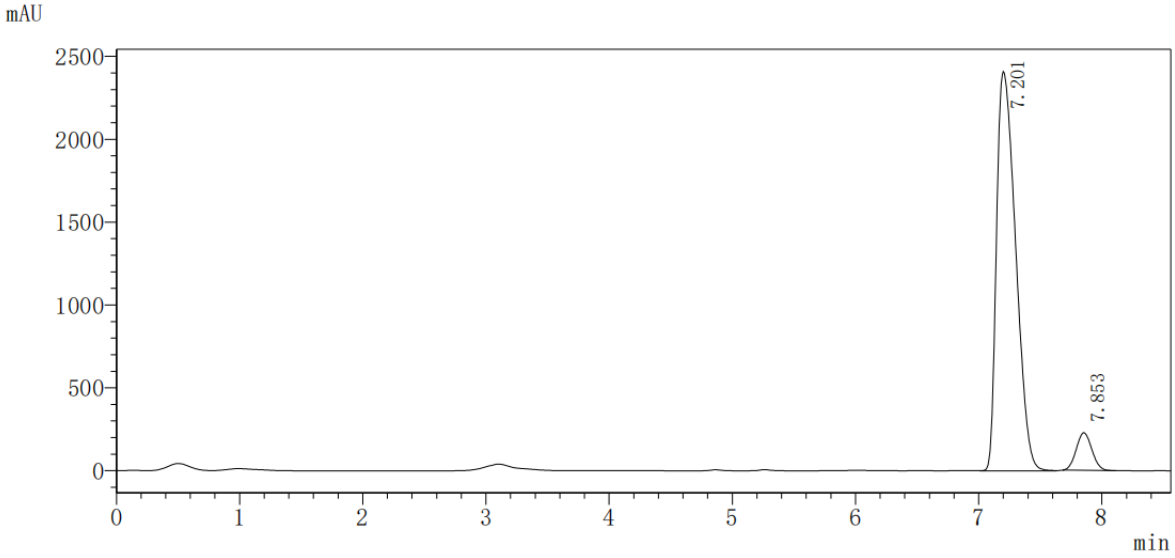
A.P(^{n}Bu)$_3$, ADDP, 0 ℃-rt, 69% yield, 75% ee. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 7.743 min (major), 8.540 min (minor)], $[\alpha]_D^{20}$ = +98.0° (c=1, acetone).



Peak Results

	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	7.743	3373099	371955	87.41
2	8.540	485973	49055	12.59

B.P(^{n}Bu)$_3$, ADDP, 0 ℃, 49% yield, 86% ee. [HPLC analysis of the product: CHIRALCEL OJ-H column; 10% *i*-PrOH in hexanes; 1.0 mL/min; λ = 254 nm; retention times: 7.201 min (major), 7.853 min (minor)], $[\alpha]_D^{20}$ = +112.7° (c=1, acetone).

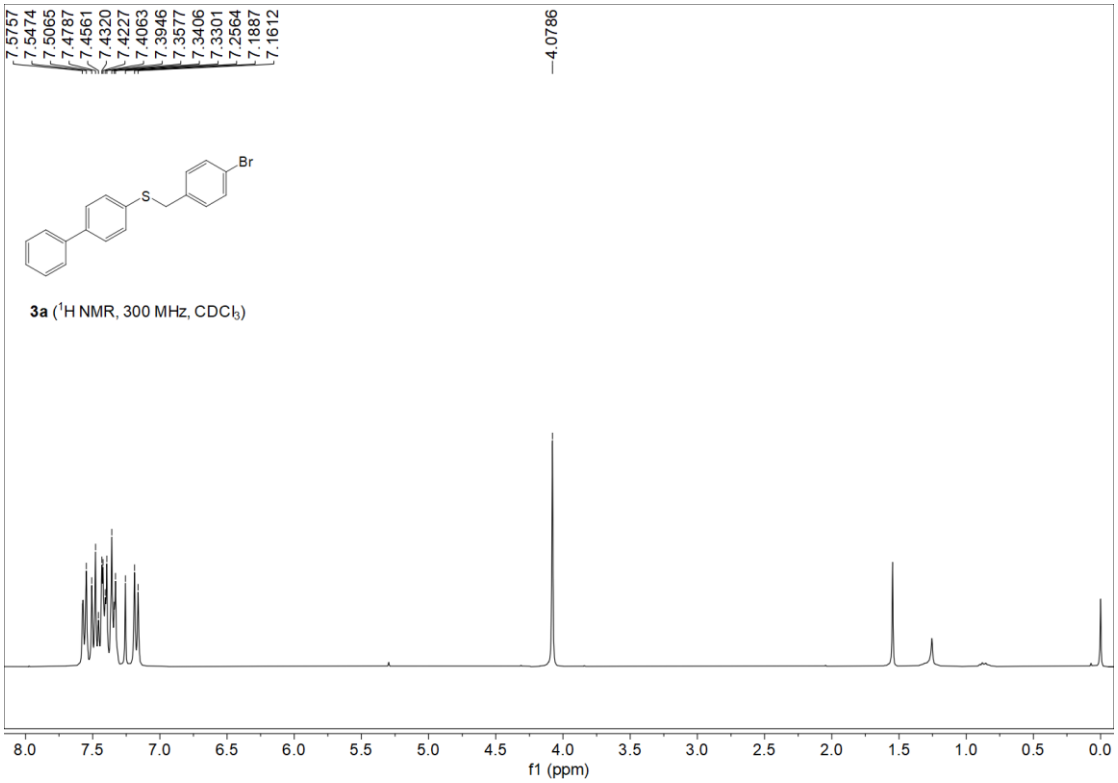


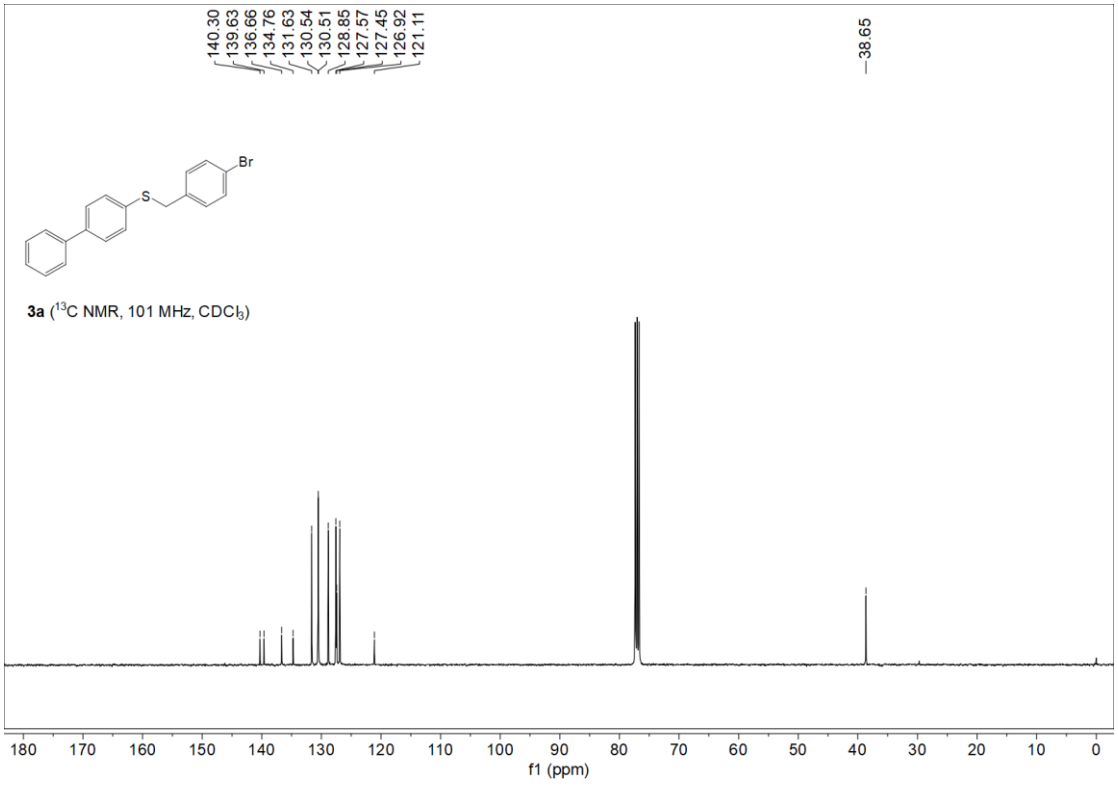
Peak Results

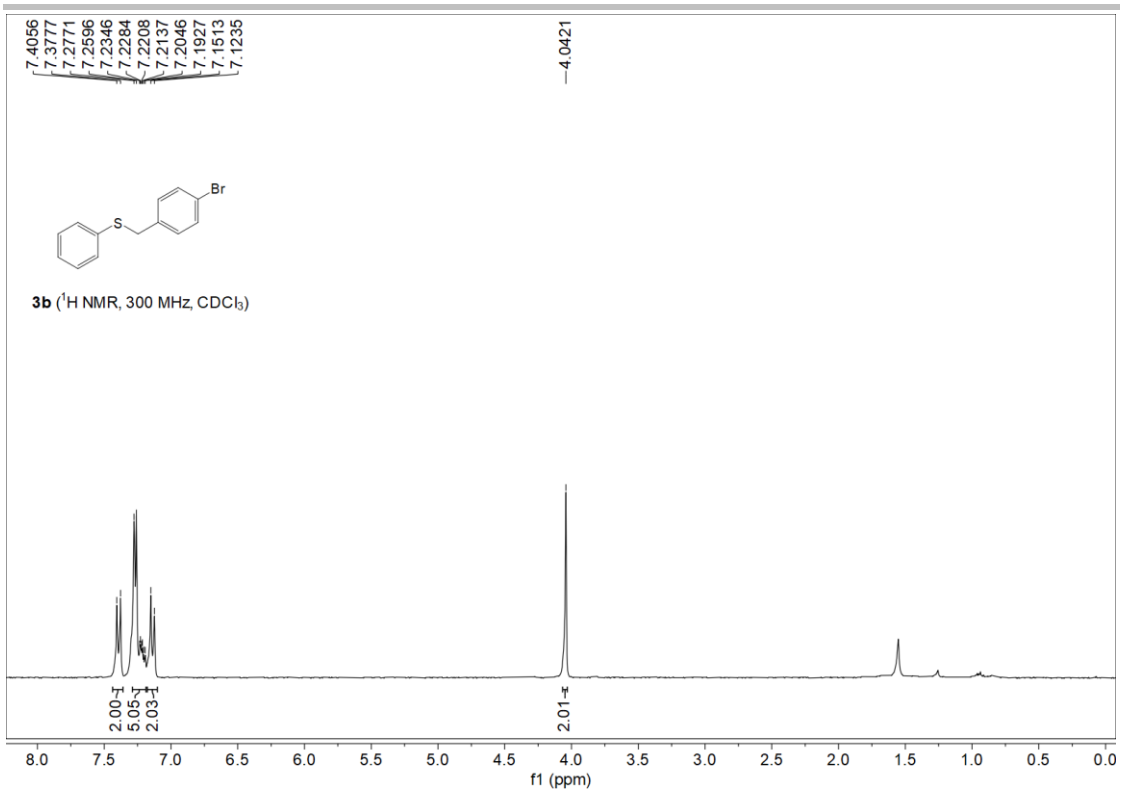
	RT (min)	Area (μV*sec)	Height (μV)	% Area
1	7.201	25962852	2408786	92.82
2	7.853	2008589	227097	7.18

Figure S7. (A) Chiral HPLC analysis following method **A** . (B) Chiral HPLCanalysis following an improved method.

4. Copies od NMR Spectra



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7.1235
4.0421
Br
S
3b (1H NMR, 300 MHz, CDCl3)
2.00
5.05
2.03
2.01
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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2.5
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1.5
1.0
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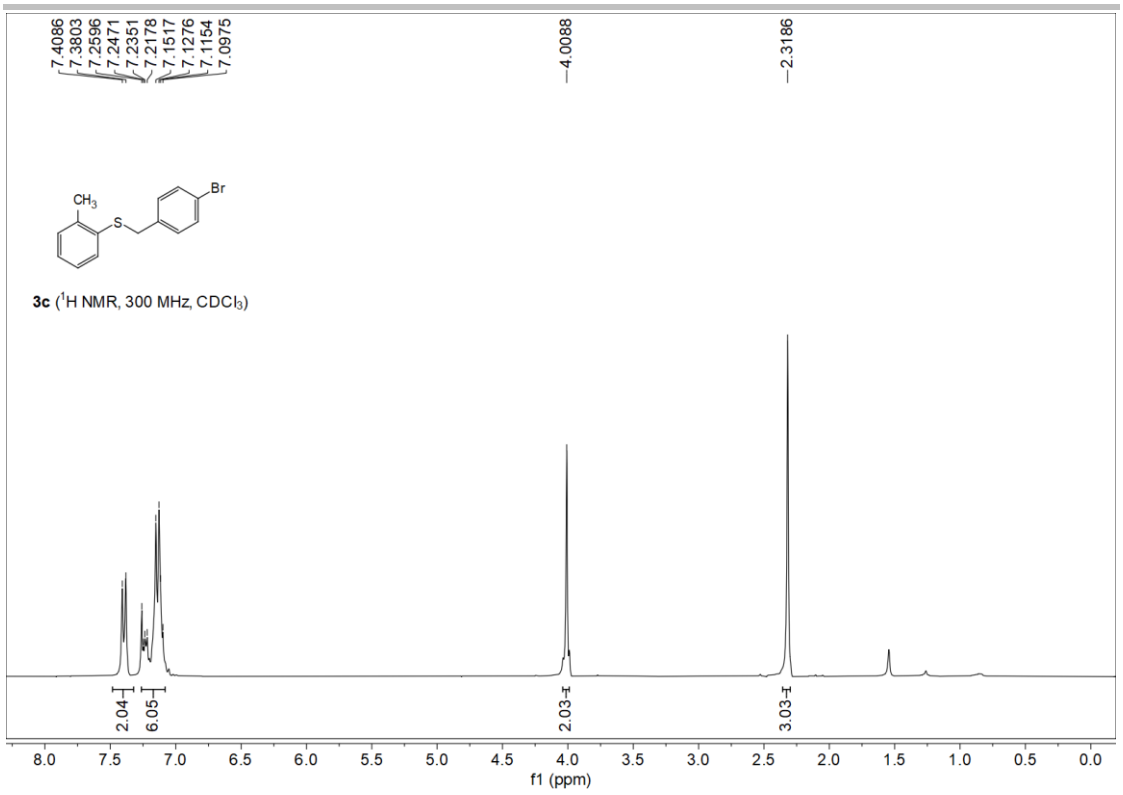
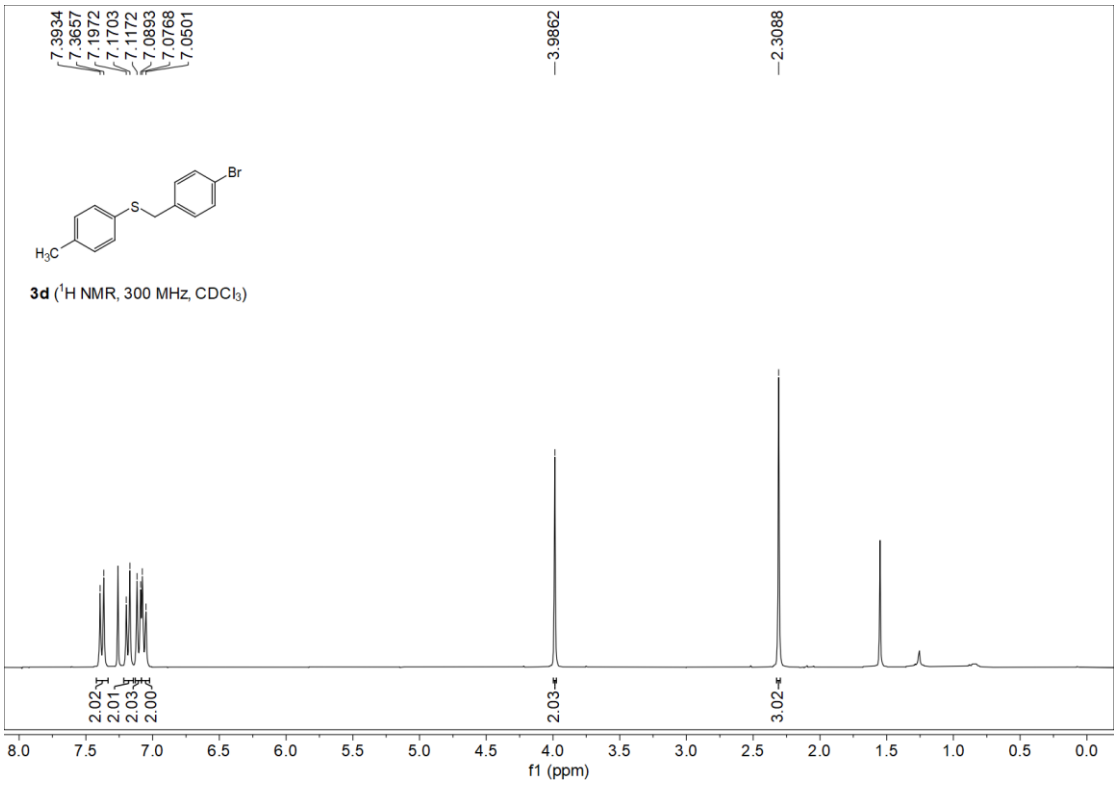
0.0
f1 (ppm)



3c (^{1}H NMR, 300 MHz, $CDCl_3$)



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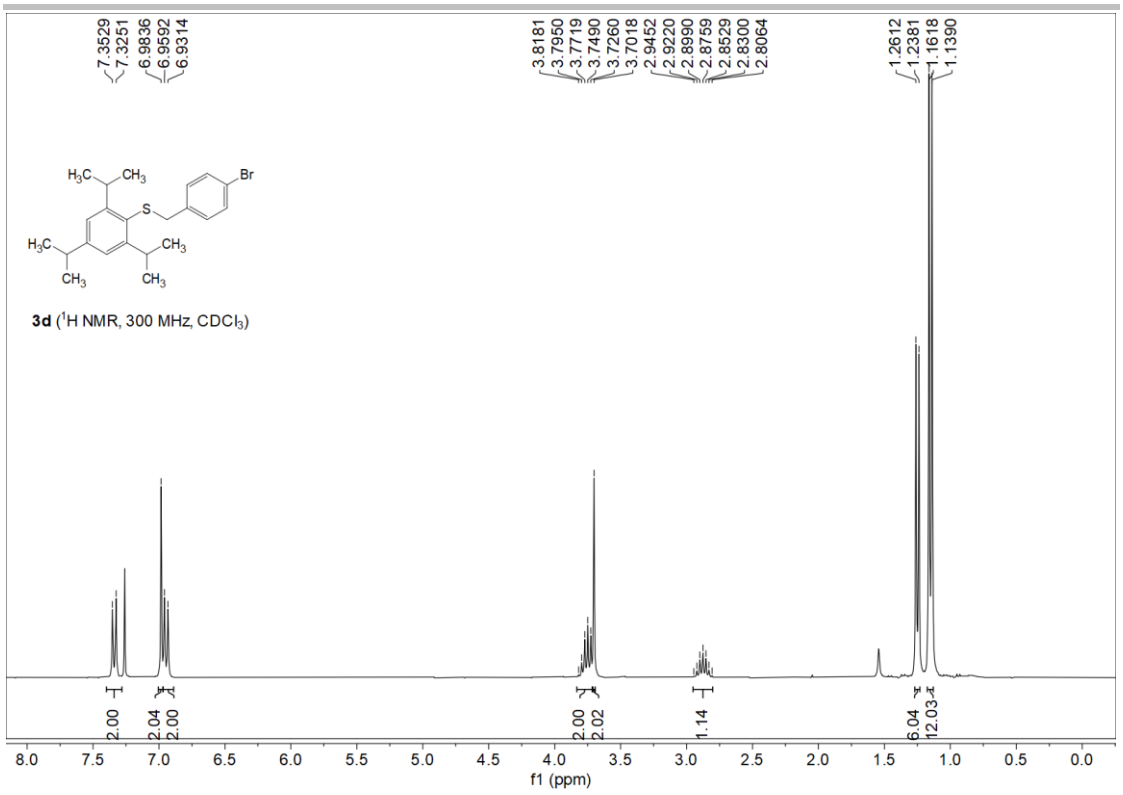
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2.8064
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1.2381
1.1618
1.1390
Br
S
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2.00
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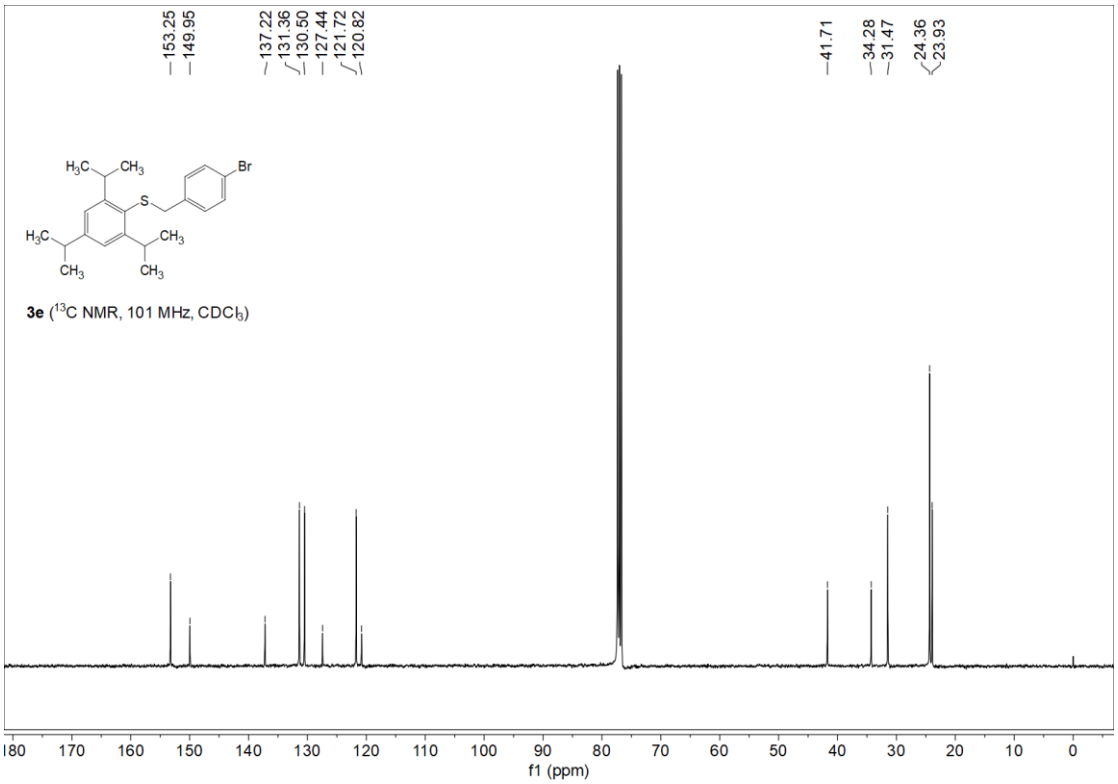
1.14
6.04
12.03
f1 (ppm)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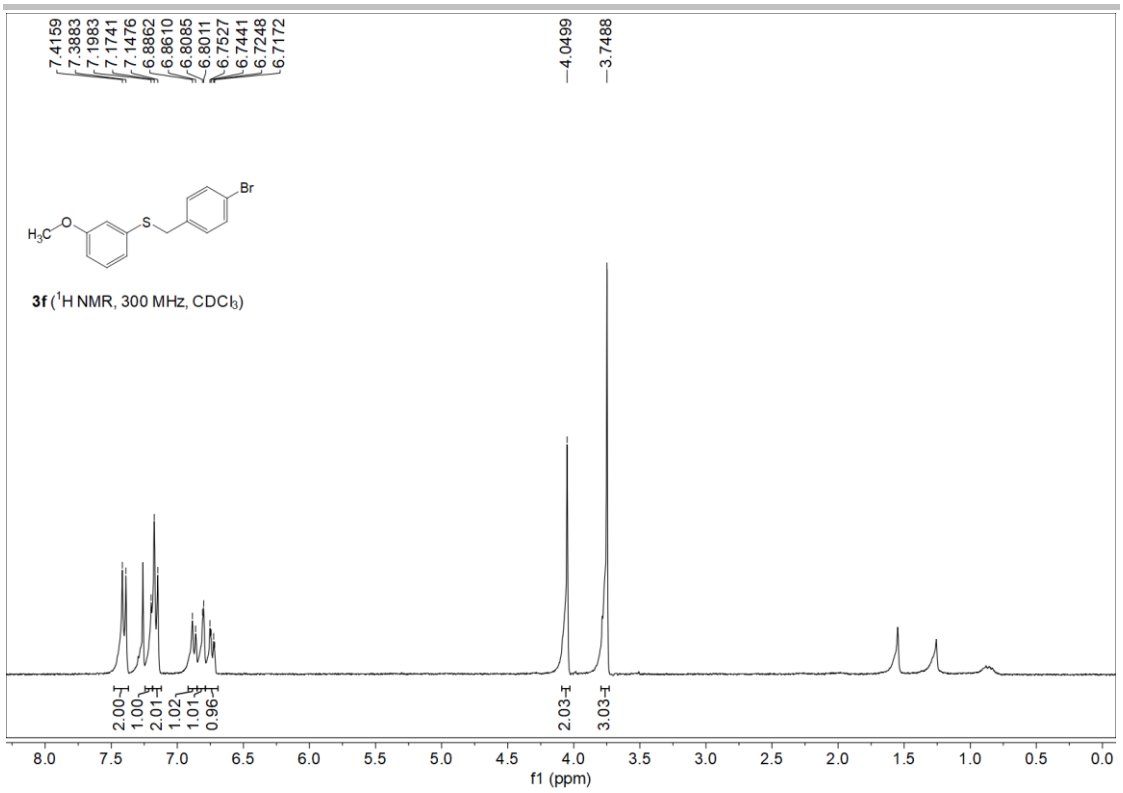
Br
S
3e (13C NMR, 101 MHz, CDCl3)
f1 (ppm)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6.7248
6.7172
4.0499
3.7488
Br
H3C
O
S
3f (1H NMR, 300 MHz, CDCl3)
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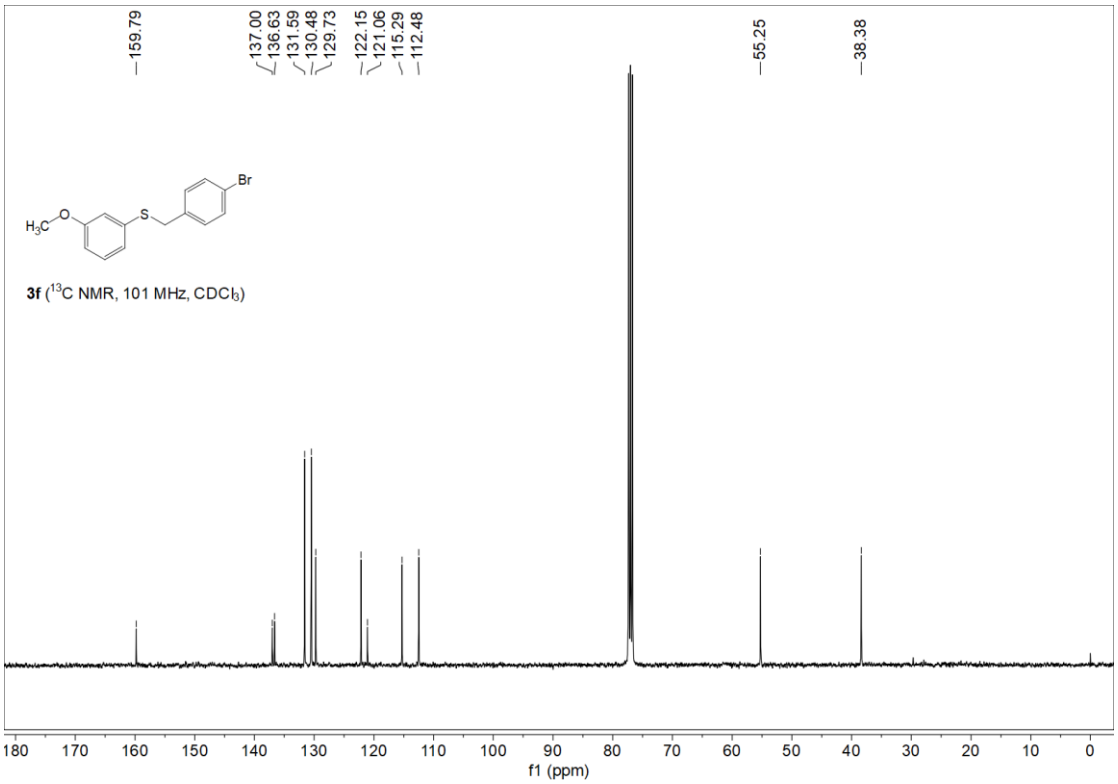
1.01
0.96
2.03
3.03
f1 (ppm)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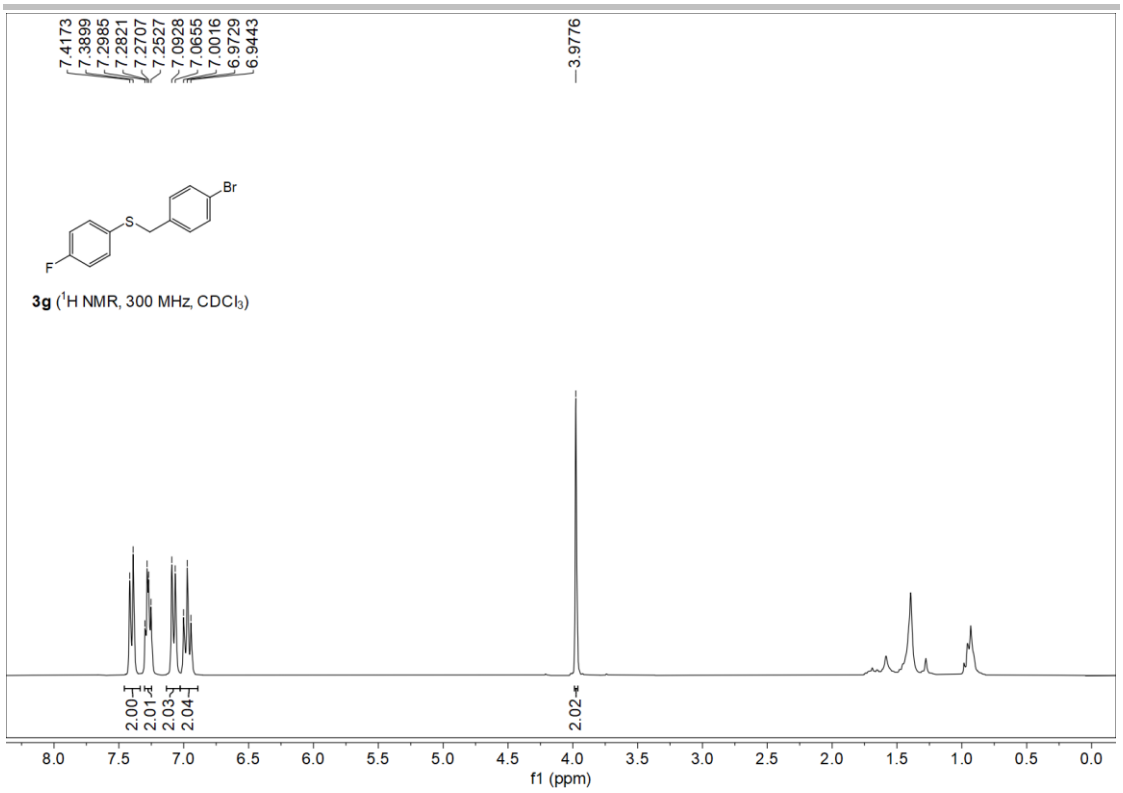
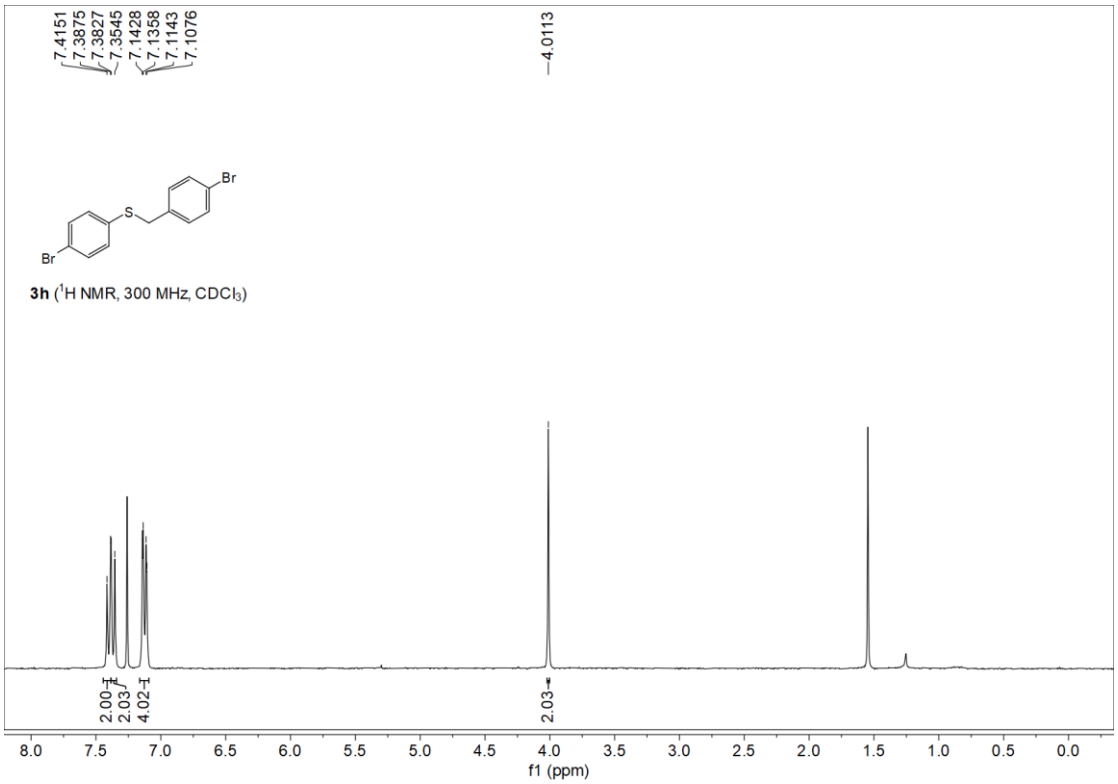
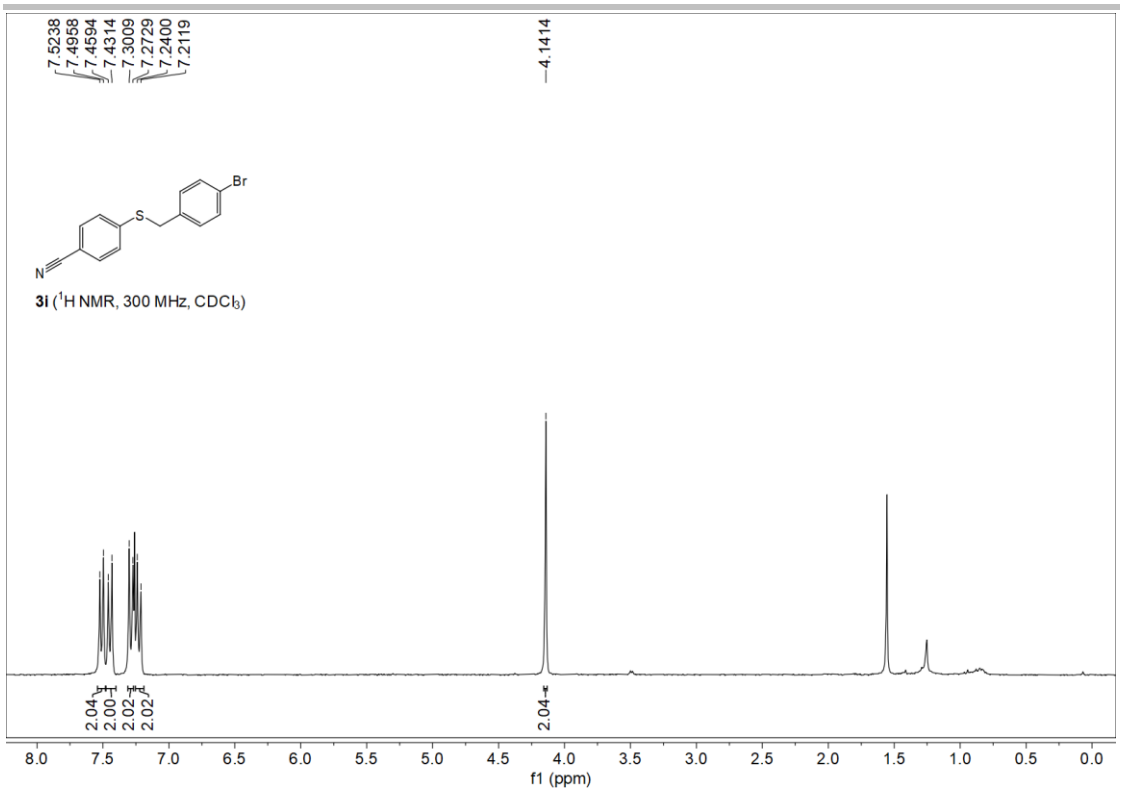
S
3f (13C NMR, 101 MHz, CDCl3)
f1 (ppm)



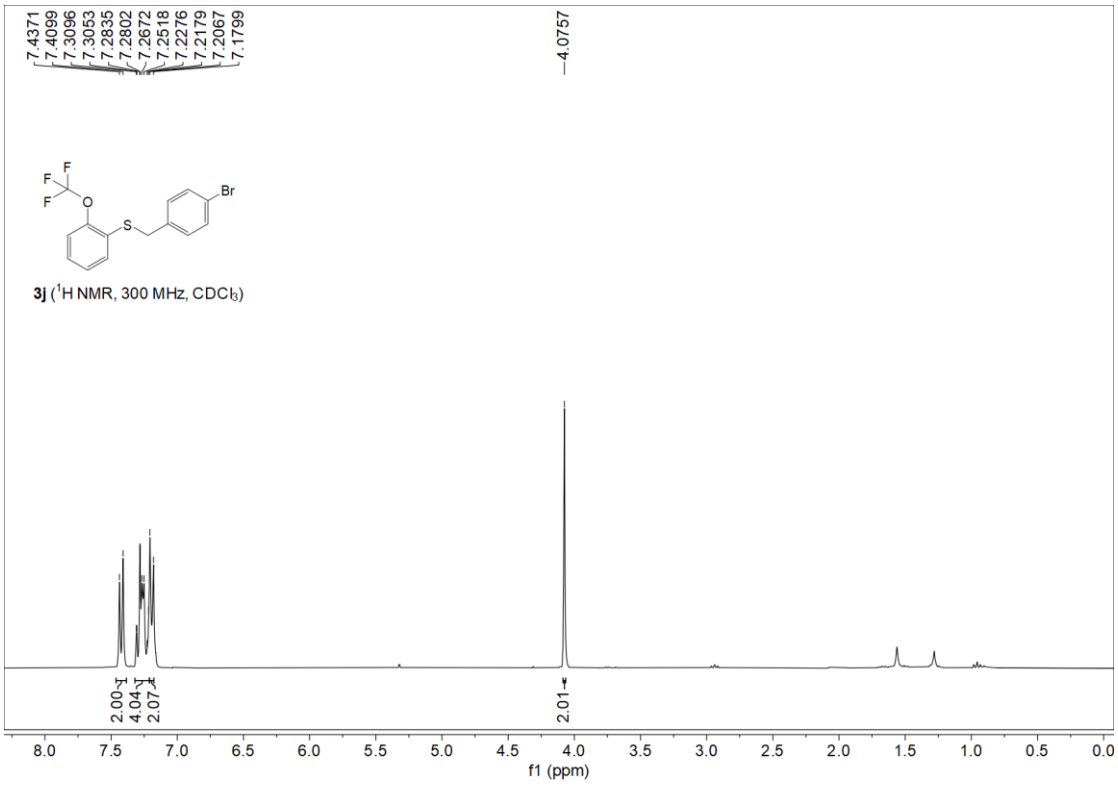
3g (^{1}H NMR, 300 MHz, $CDCl_3$)



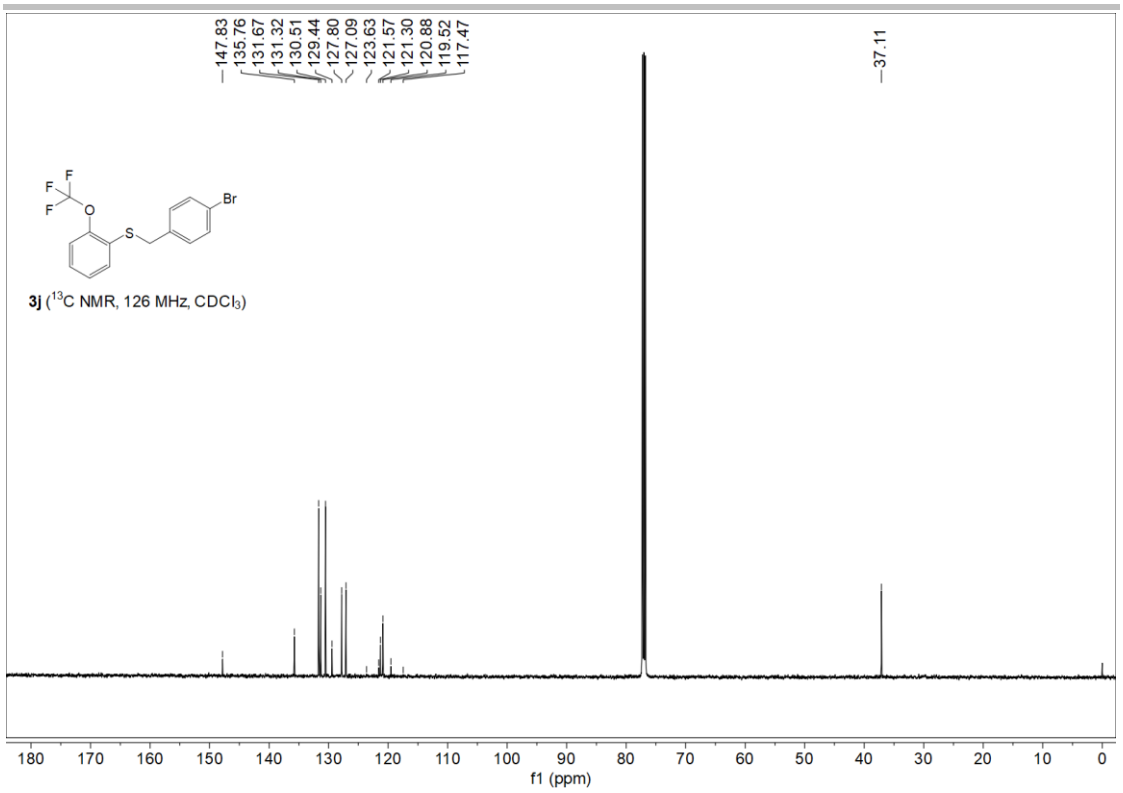
3h (^{1}H NMR, 300 MHz, $CDCl_3$)

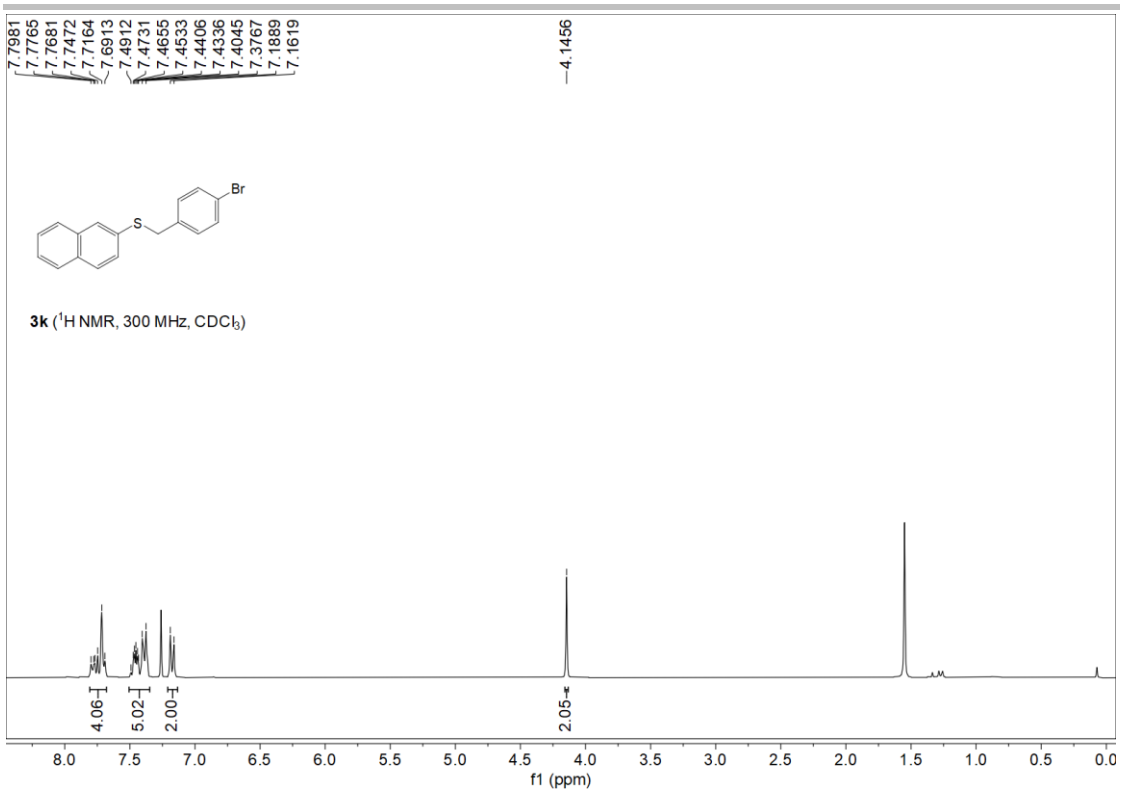


3i (^{1}H NMR, 300 MHz, $CDCl_3$)

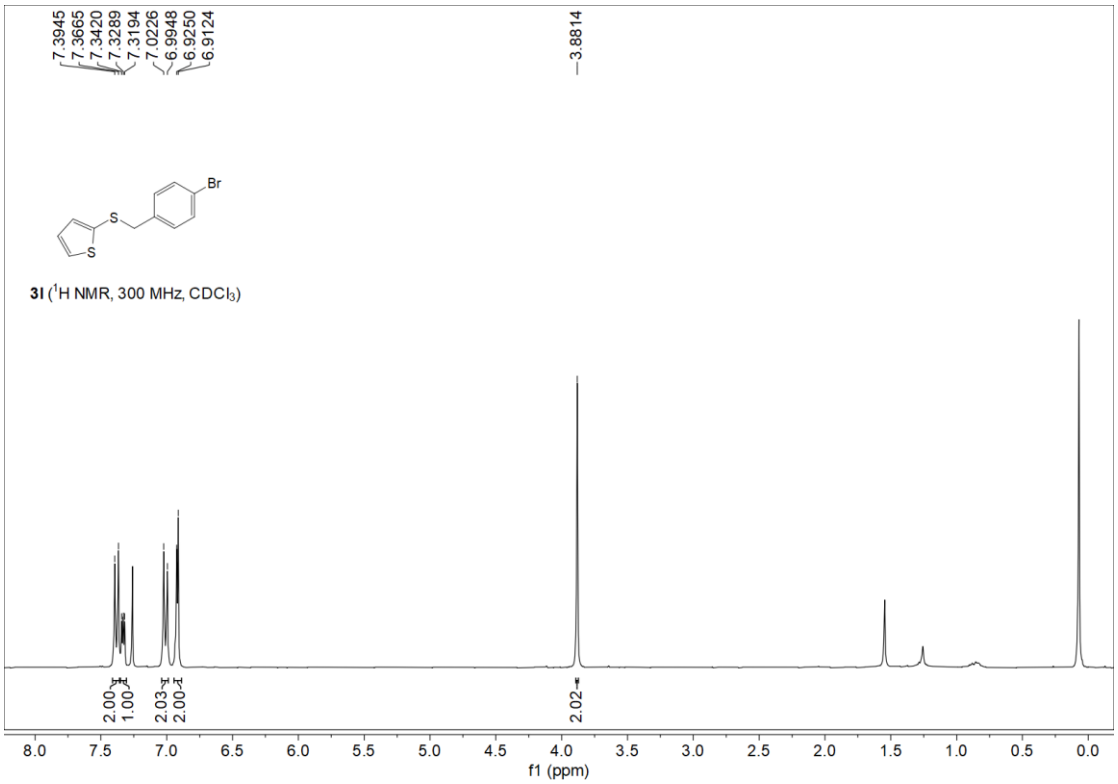


3j (^{1}H NMR, 300 MHz, $CDCl_3$)

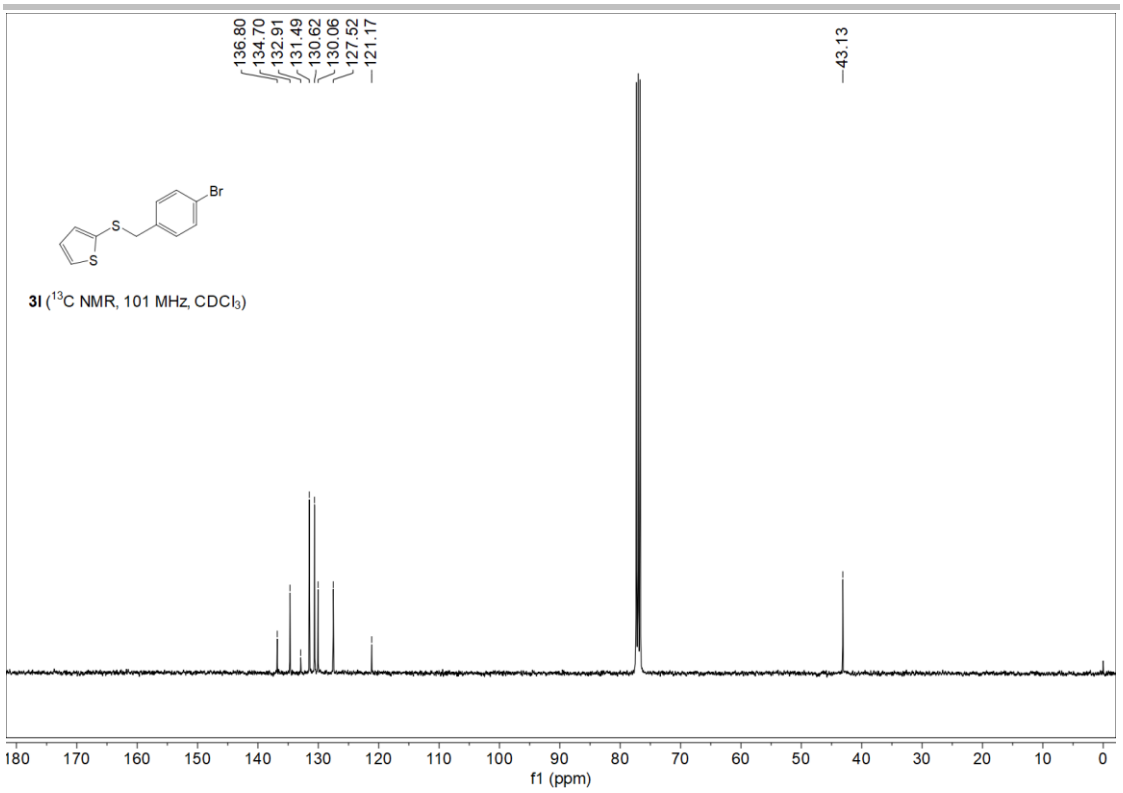

147.83
135.76
131.67
131.32
130.51
129.44
127.80
127.09
123.63
121.57
121.30
120.88
119.52
117.47
37.11
F
F
F
O
S
Br
3j (13C NMR, 126 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

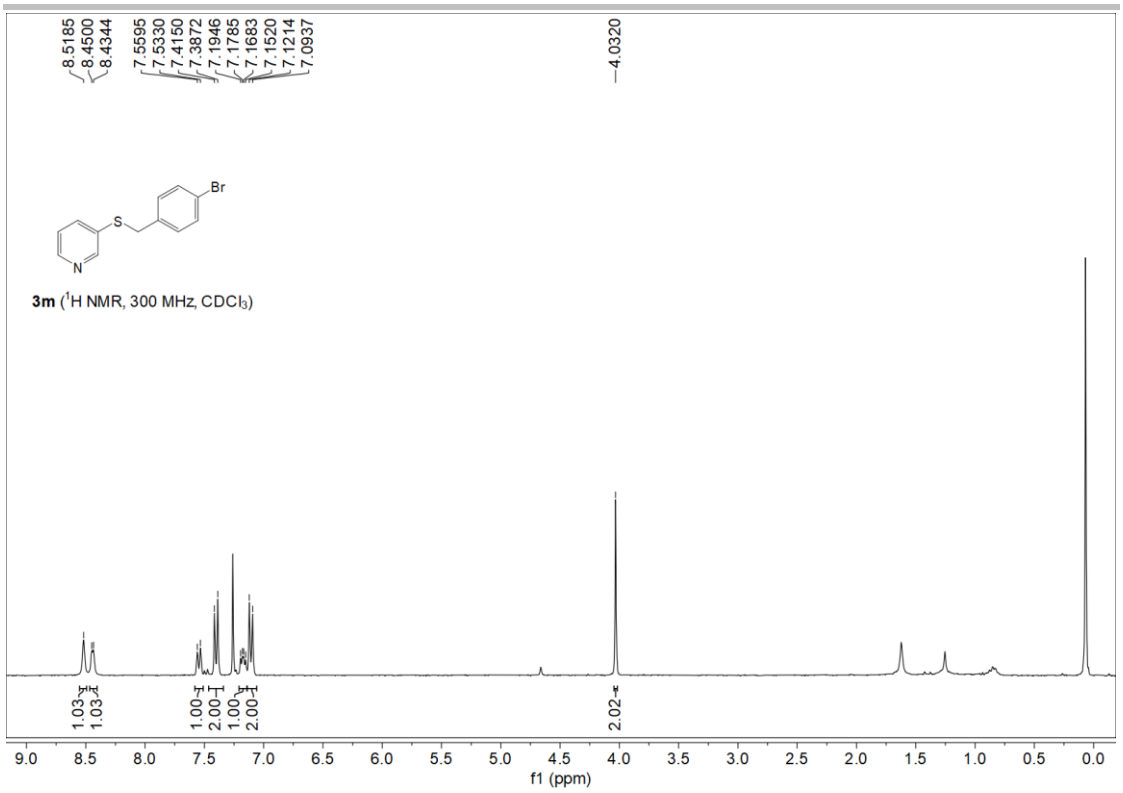


3k (^{1}H NMR, 300 MHz, $CDCl_3$)

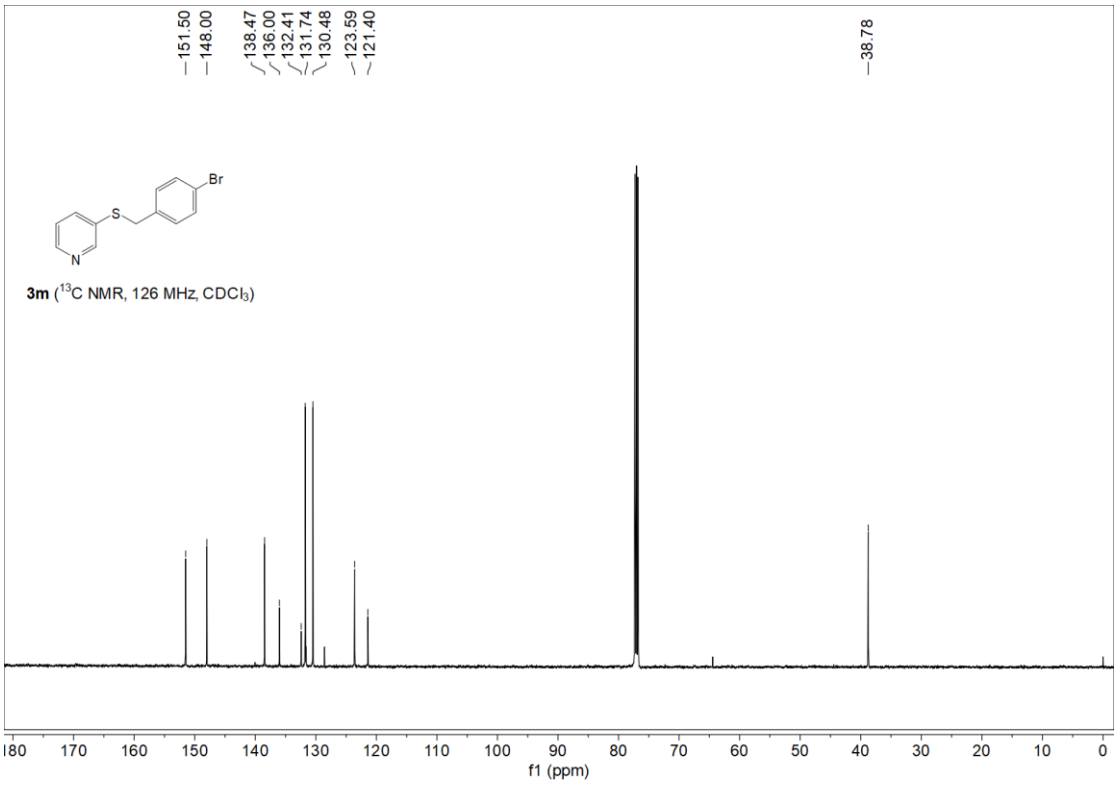


3l (^{1}H NMR, 300 MHz, $CDCl_3$)

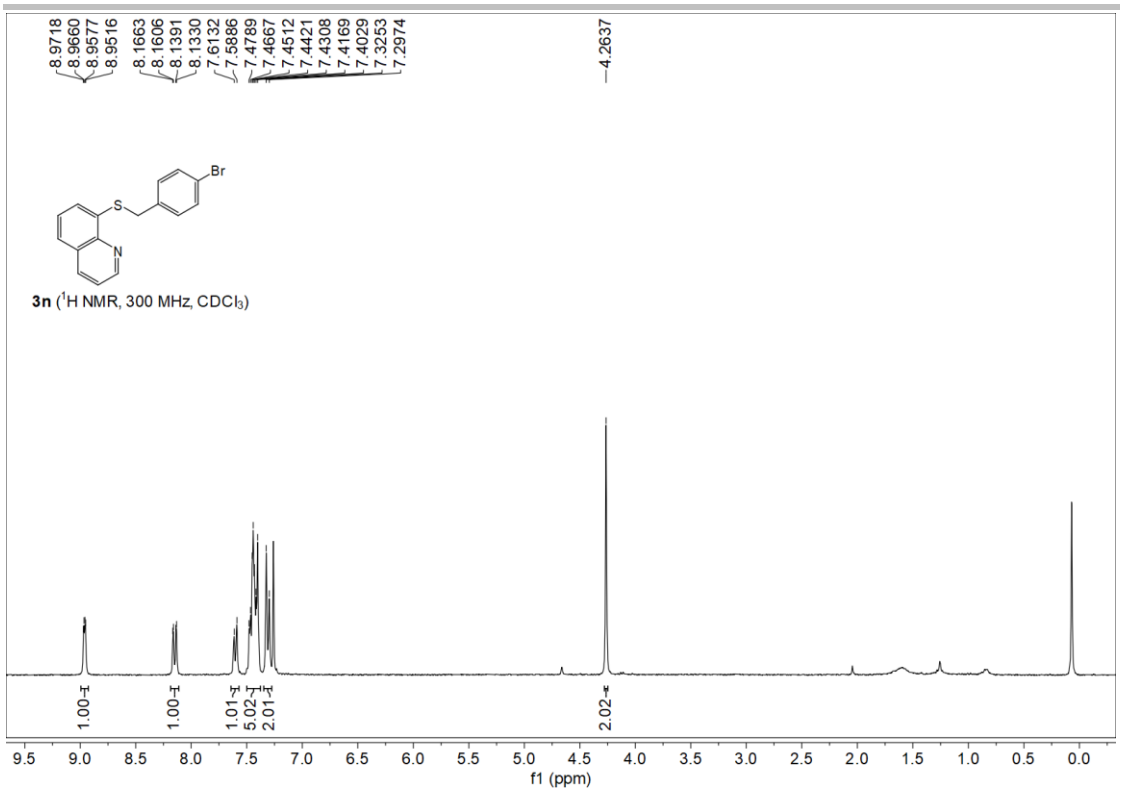

136.80
134.70
132.91
131.49
130.62
130.06
127.52
121.17
43.13
Br
S
S
3l (13C NMR, 101 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



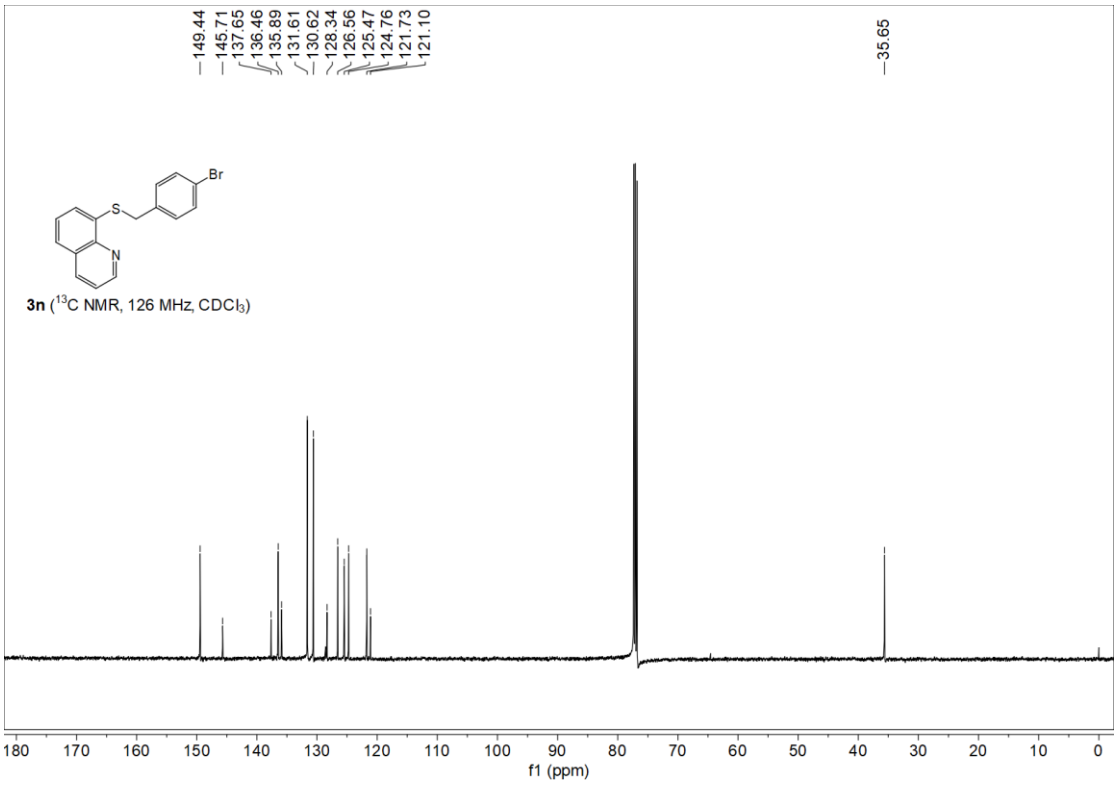
3m (^{1}H NMR, 300 MHz, $CDCl_3$)



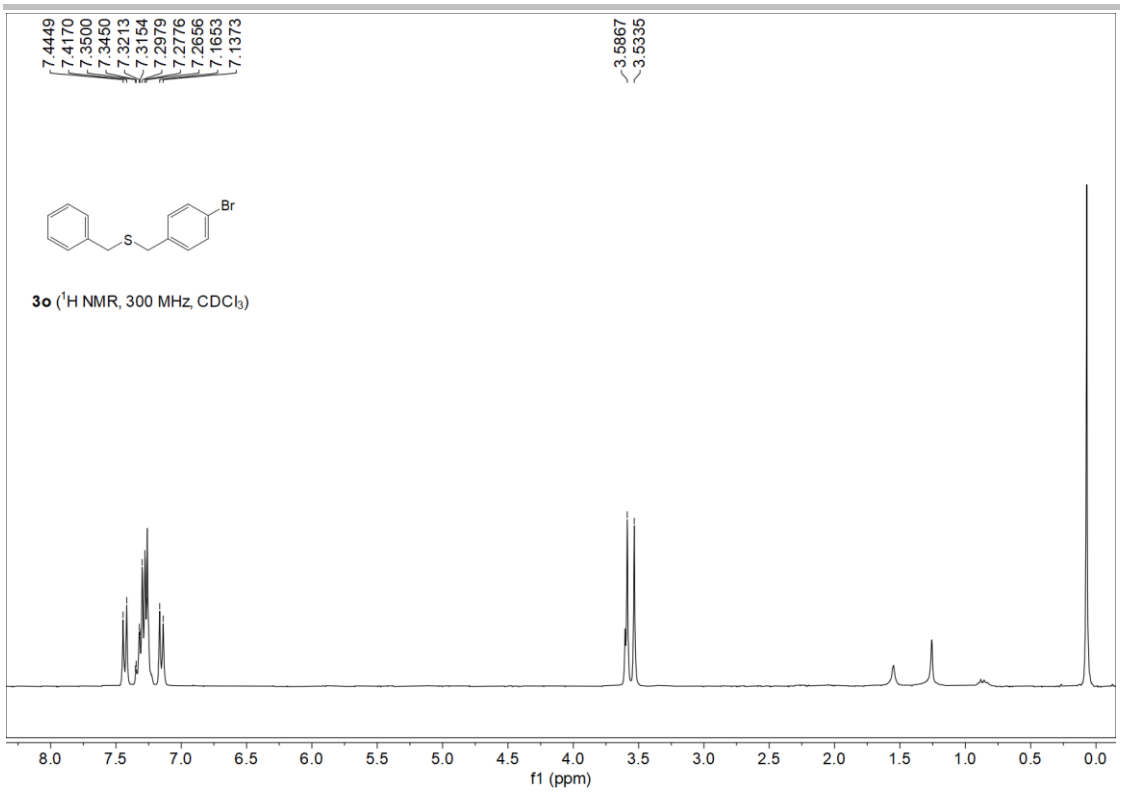
3m (^{13}C NMR, 126 MHz, $CDCl_3$)

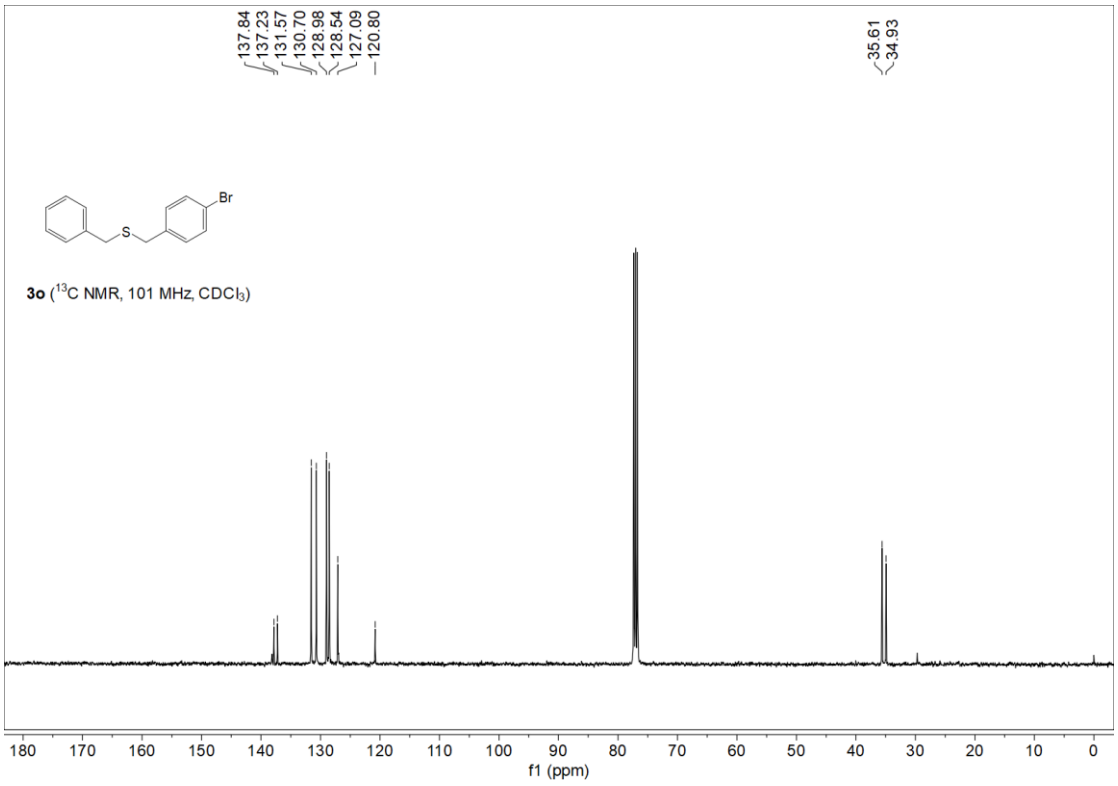


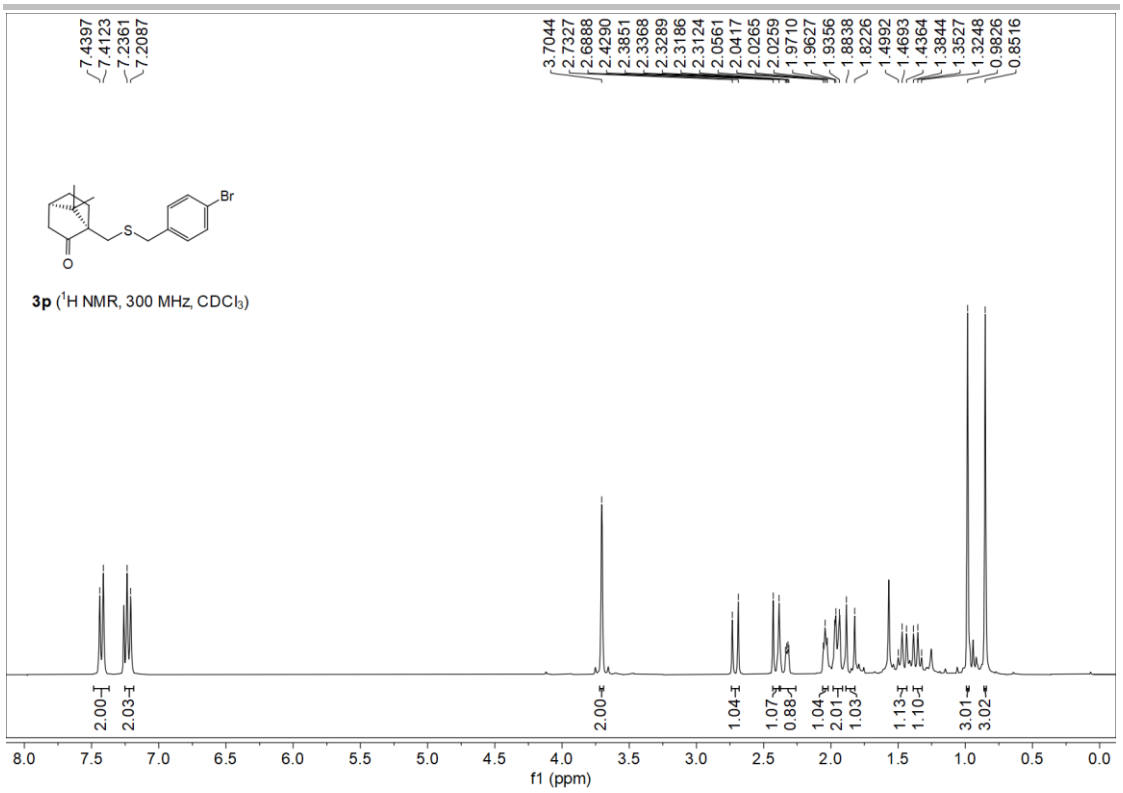
3n (^{1}H NMR, 300 MHz, $CDCl_3$)

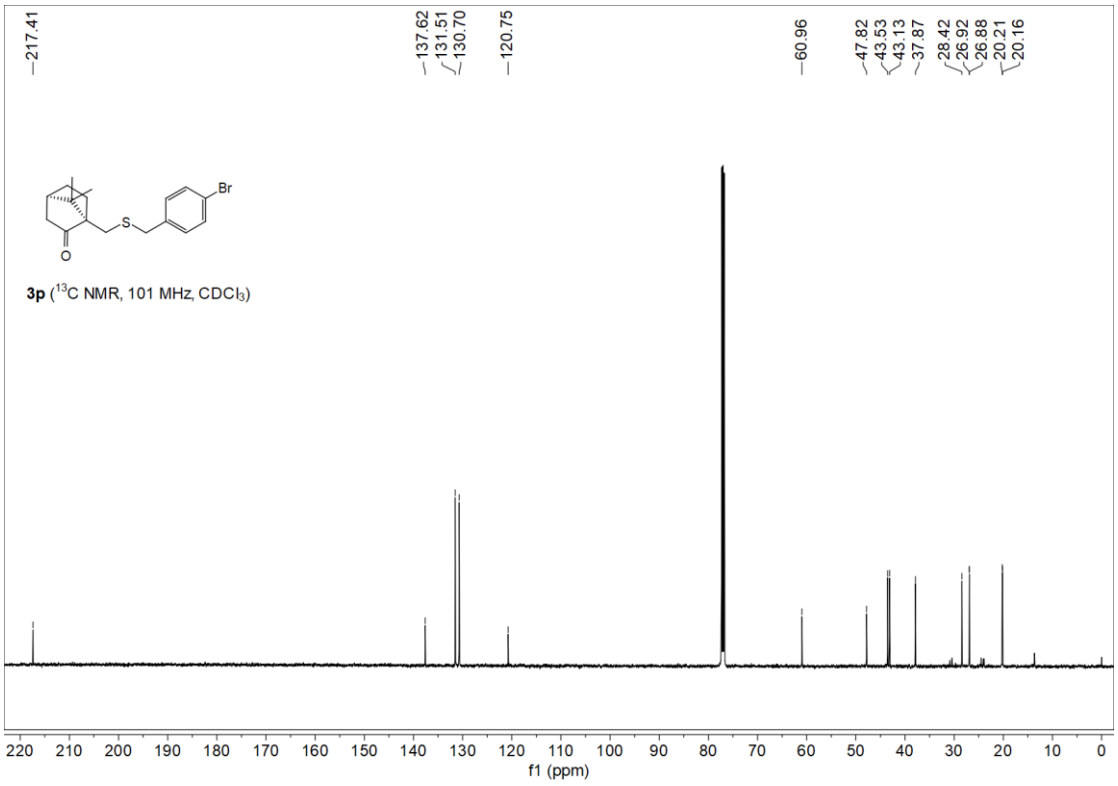


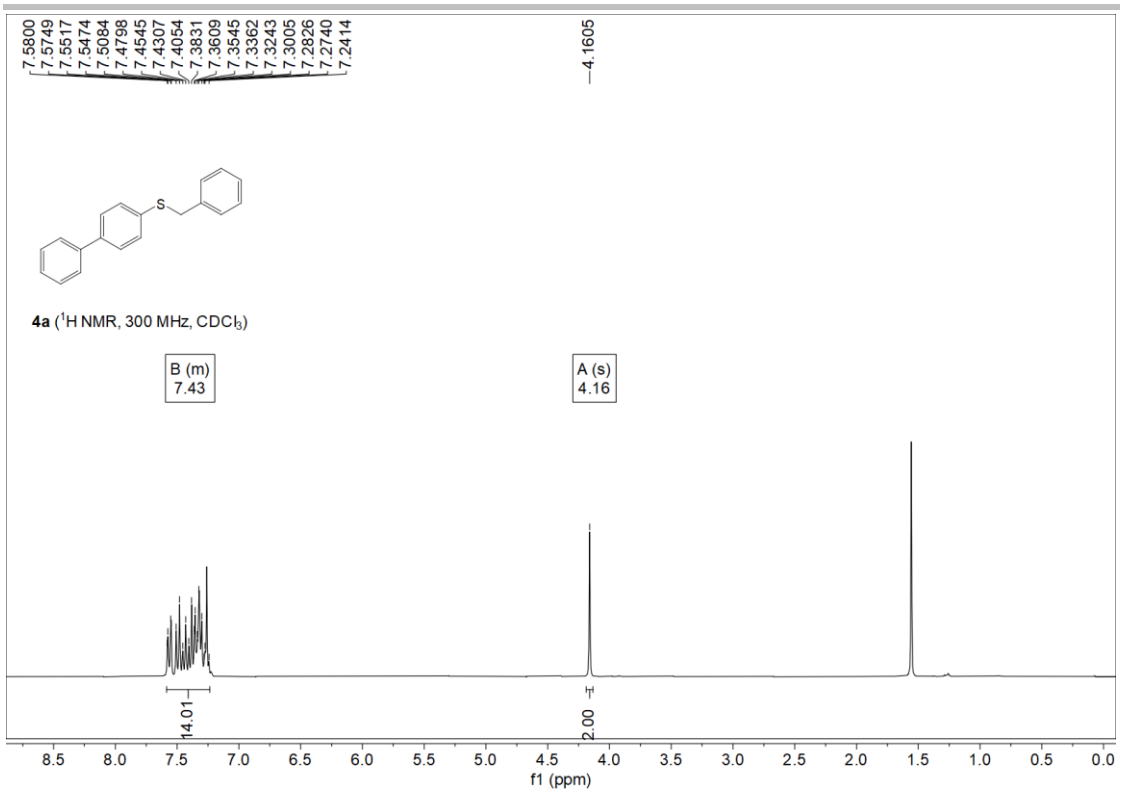
3n (^{13}C NMR, 126 MHz, $CDCl_3$)


7.4449
7.4170
7.3500
7.3450
7.3213
7.3154
7.2979
7.2776
7.2656
7.1653
7.1373
3.5867
3.5335
Br
S
3o (1H NMR, 300 MHz, CDCl3)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

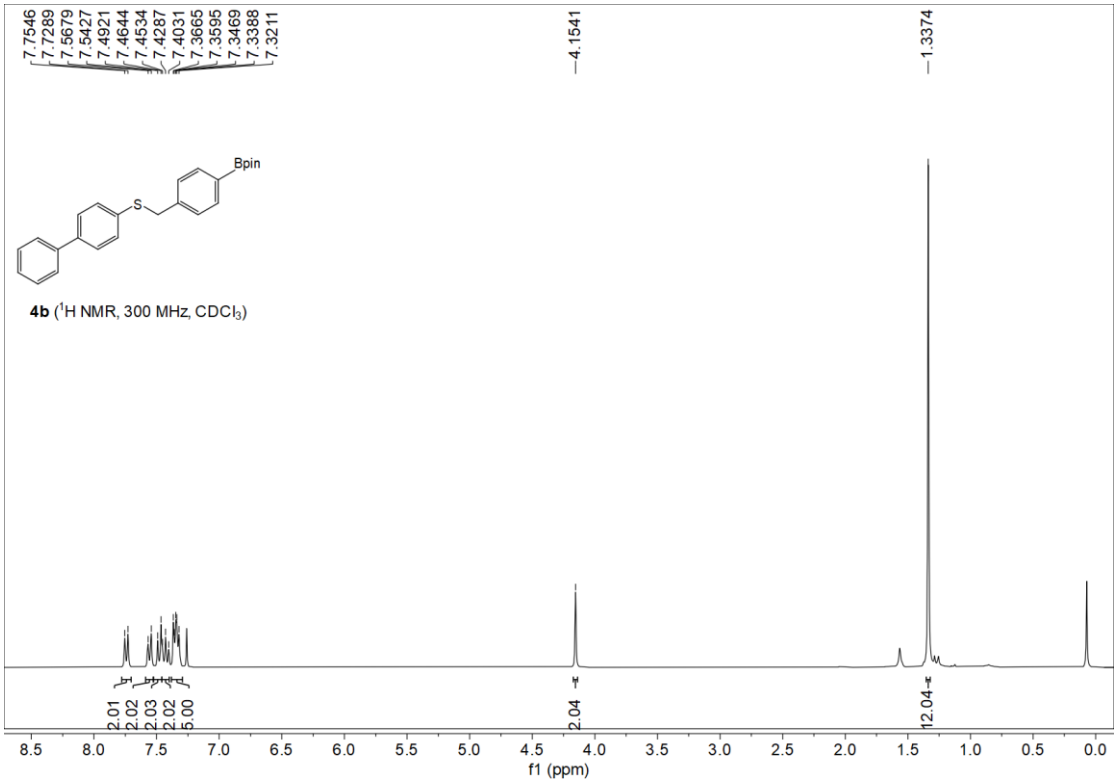

137.84
137.23
131.57
130.70
128.98
128.54
127.09
120.80
35.61
34.93
Br
S
3o (13C NMR, 101 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.4397
7.4123
7.2361
7.2087
3.7044
2.7327
2.6888
2.4290
2.3851
2.3368
2.3289
2.3186
2.3124
2.0561
2.0417
2.0265
2.0259
1.9710
1.9627
1.9356
1.8838
1.8226
1.4992
1.4693
1.4364
1.3844
1.3527
1.3248
0.9826
0.8516
Br
S
O
3p (1H NMR, 300 MHz, CDCl3)
2.00
2.03
2.00
1.04
1.07
0.88
1.04
2.01
1.03
1.13
1.10
3.01
3.02
f1 (ppm)

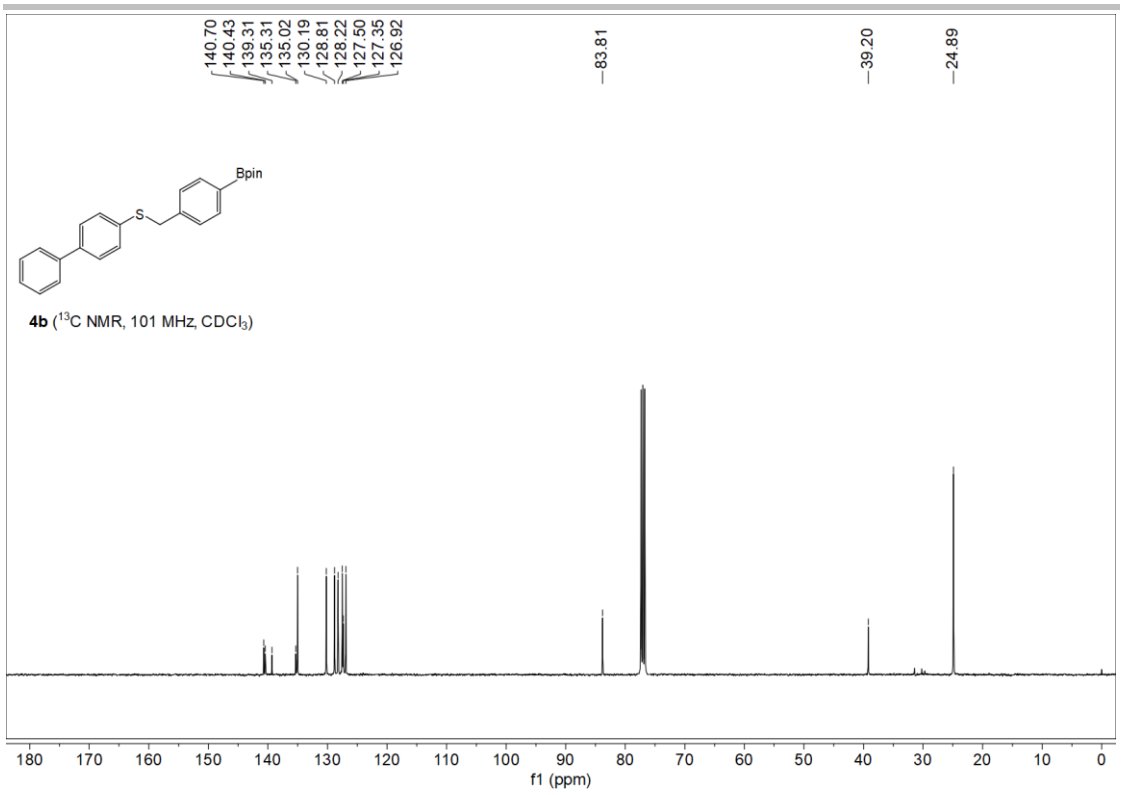

217.41
137.62
131.51
130.70
120.75
60.96
47.82
43.53
43.13
37.87
28.42
26.92
26.88
20.21
20.16
Br
S
O
3p (13C NMR, 101 MHz, CDCl3)
f1 (ppm)

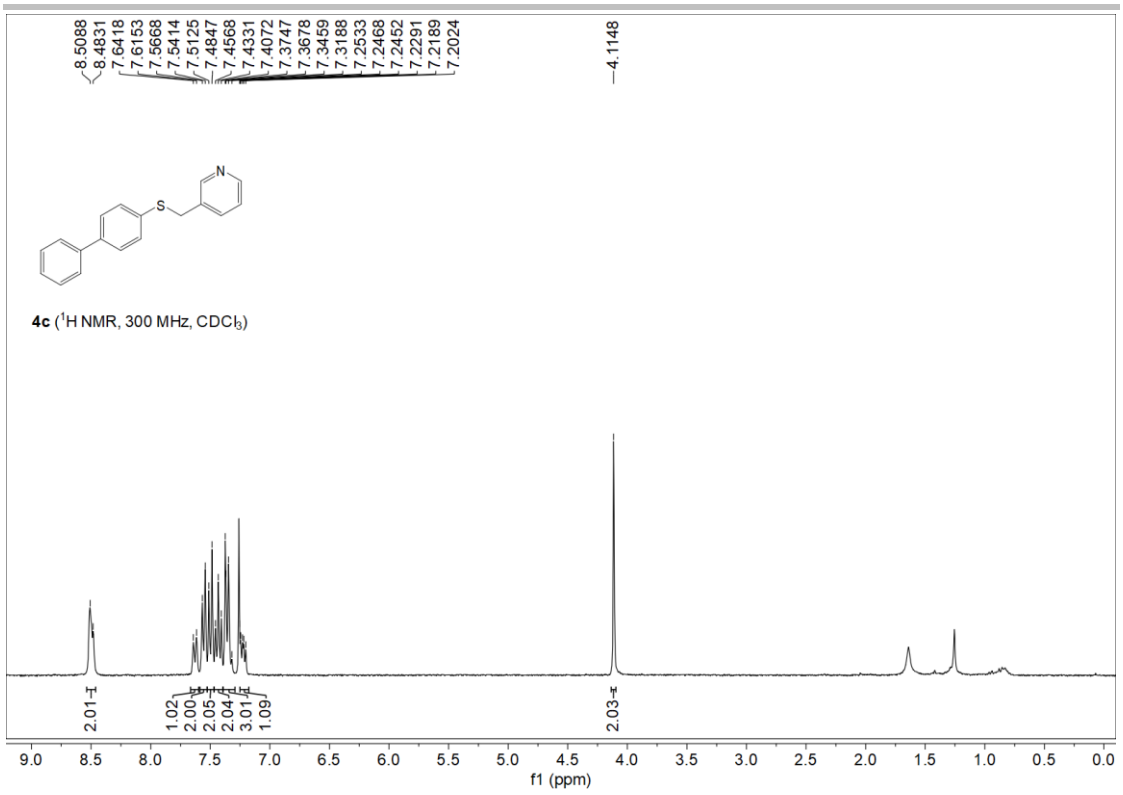


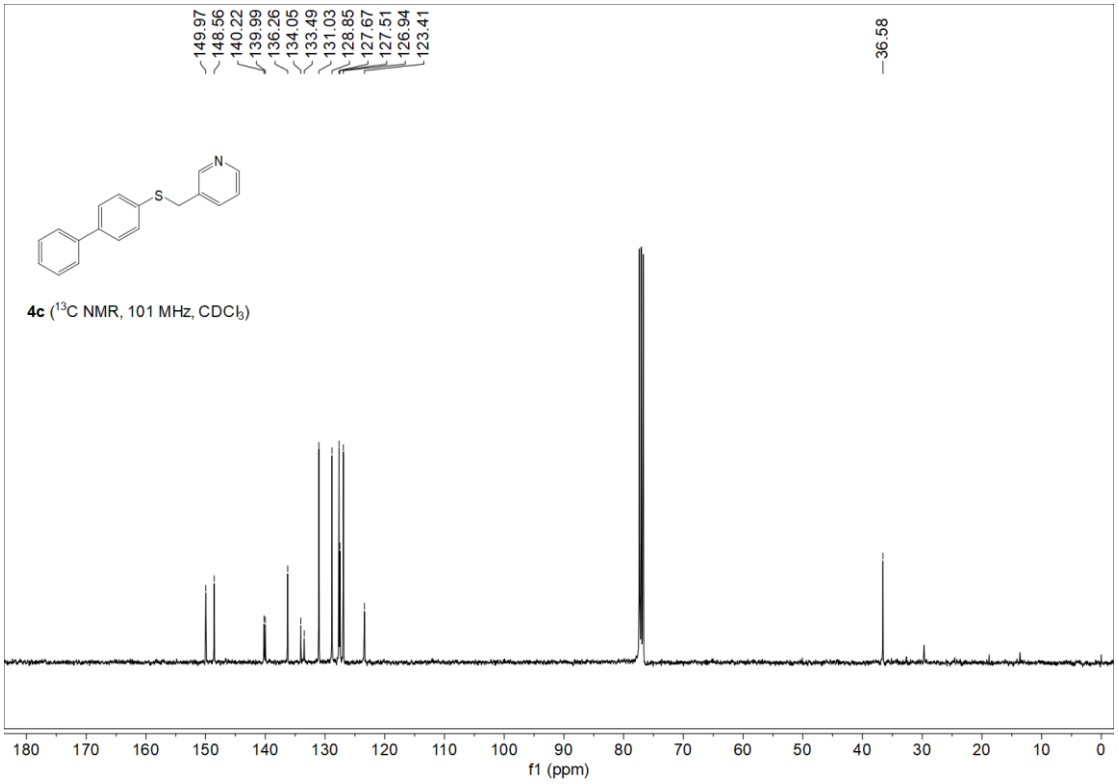
4a (^{1}H NMR, 300 MHz, $CDCl_3$)

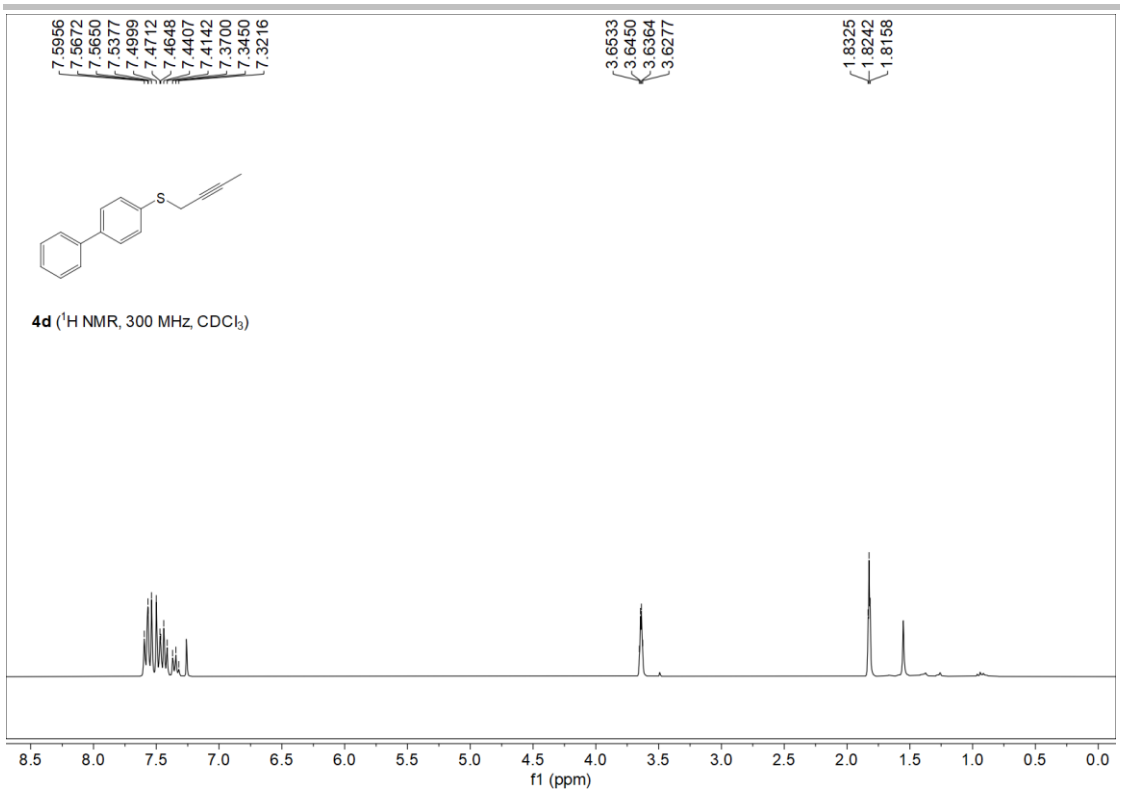


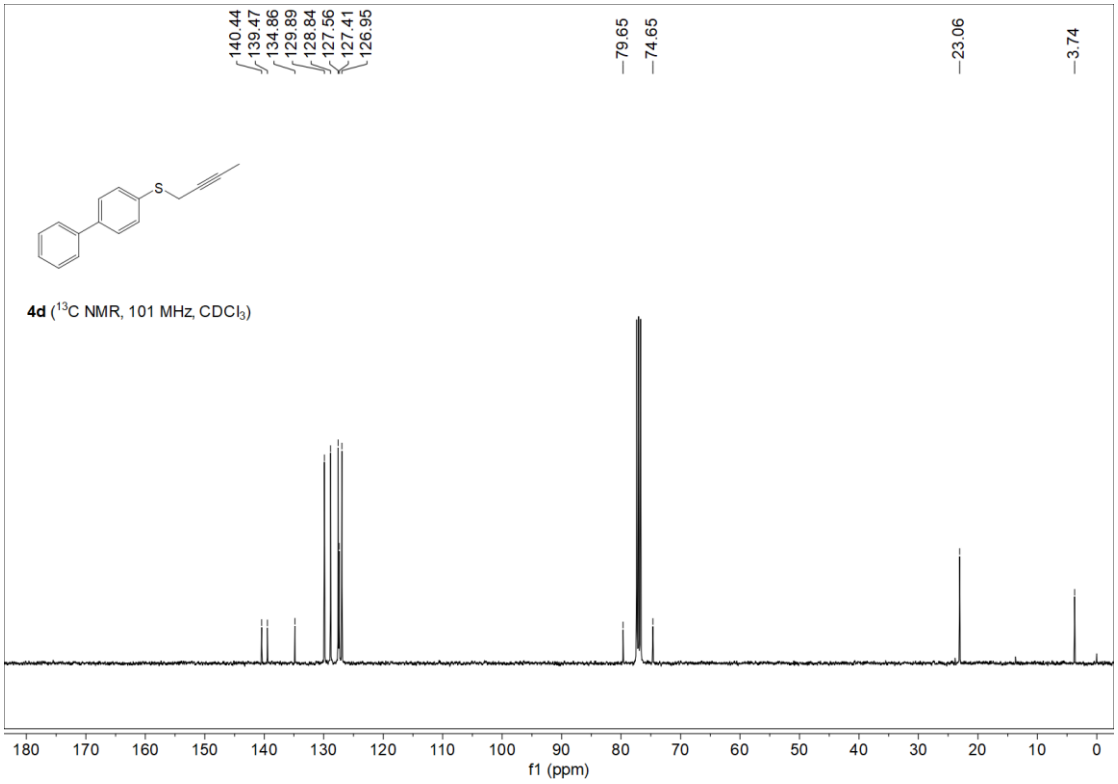
4b (^{1}H NMR, 300 MHz, $CDCl_3$)

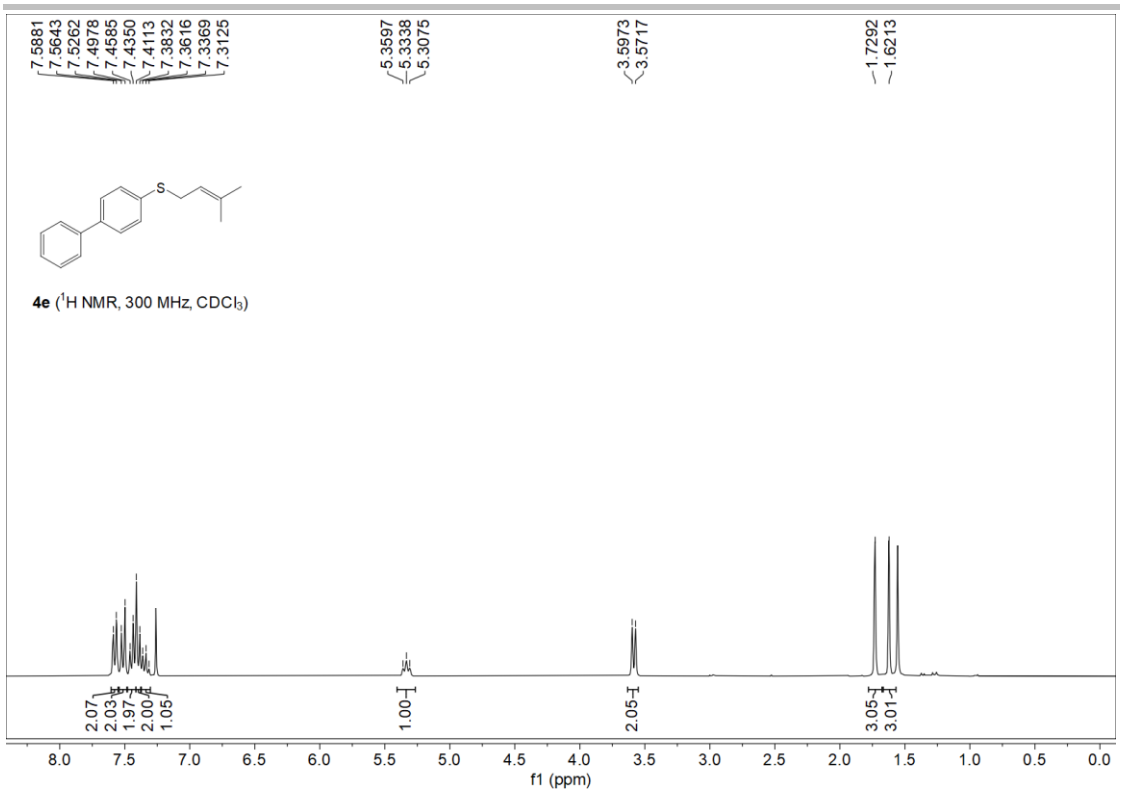

140.70
140.43
139.31
135.31
135.02
130.19
128.81
128.22
127.50
127.35
126.92
83.81
39.20
24.89
Bpin
S
4b (13C NMR, 101 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.5088
8.4831
7.6418
7.6153
7.5668
7.5414
7.5125
7.4847
7.4568
7.4331
7.4072
7.3747
7.3678
7.3459
7.3188
7.2533
7.2468
7.2452
7.2291
7.2189
7.2024
4.1148
N
S
4c (1H NMR, 300 MHz, CDCl3)
2.01
1.02
2.00
2.05
2.04
3.01
1.09
2.03
f1 (ppm)

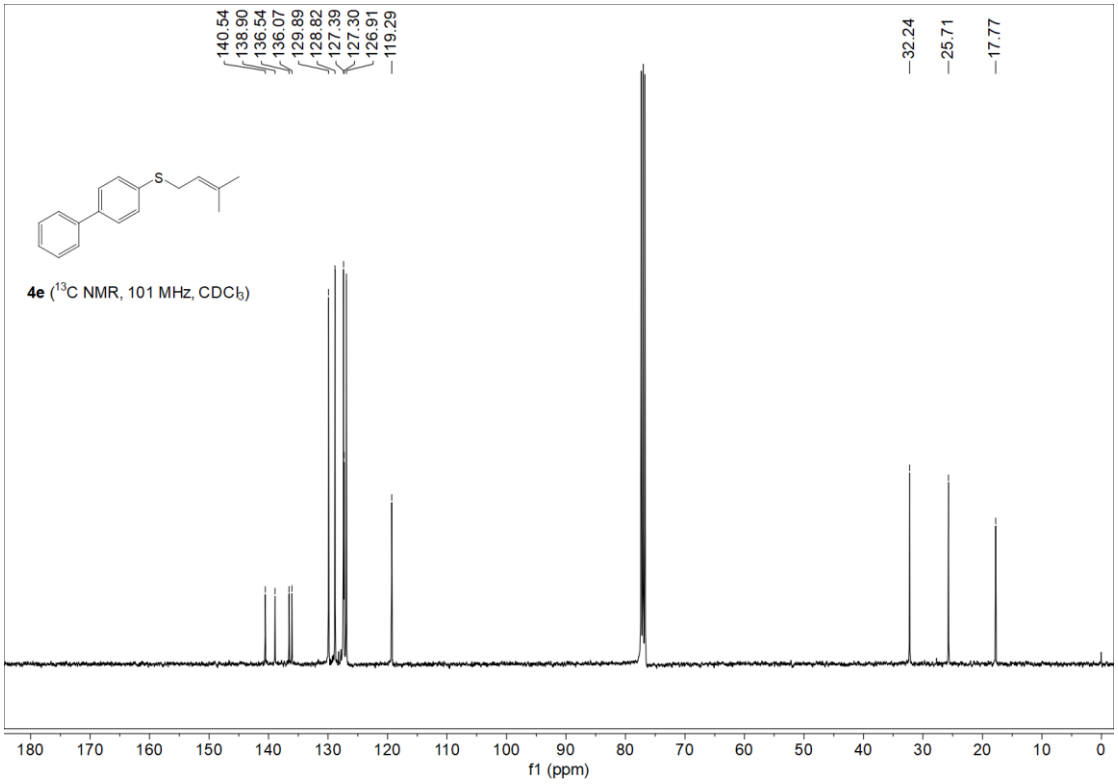

149.97
148.56
140.22
139.99
136.26
134.05
133.49
131.03
128.85
127.67
127.51
126.94
123.41
36.58
N
S
4c (13C NMR, 101 MHz, CDCl3)
f1 (ppm)


7.5956
7.5672
7.5650
7.5377
7.4999
7.4712
7.4648
7.4407
7.4142
7.3700
7.3450
7.3216
3.6533
3.6450
3.6364
3.6277
1.8325
1.8242
1.8158
S
4d (1H NMR, 300 MHz, CDCl3)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

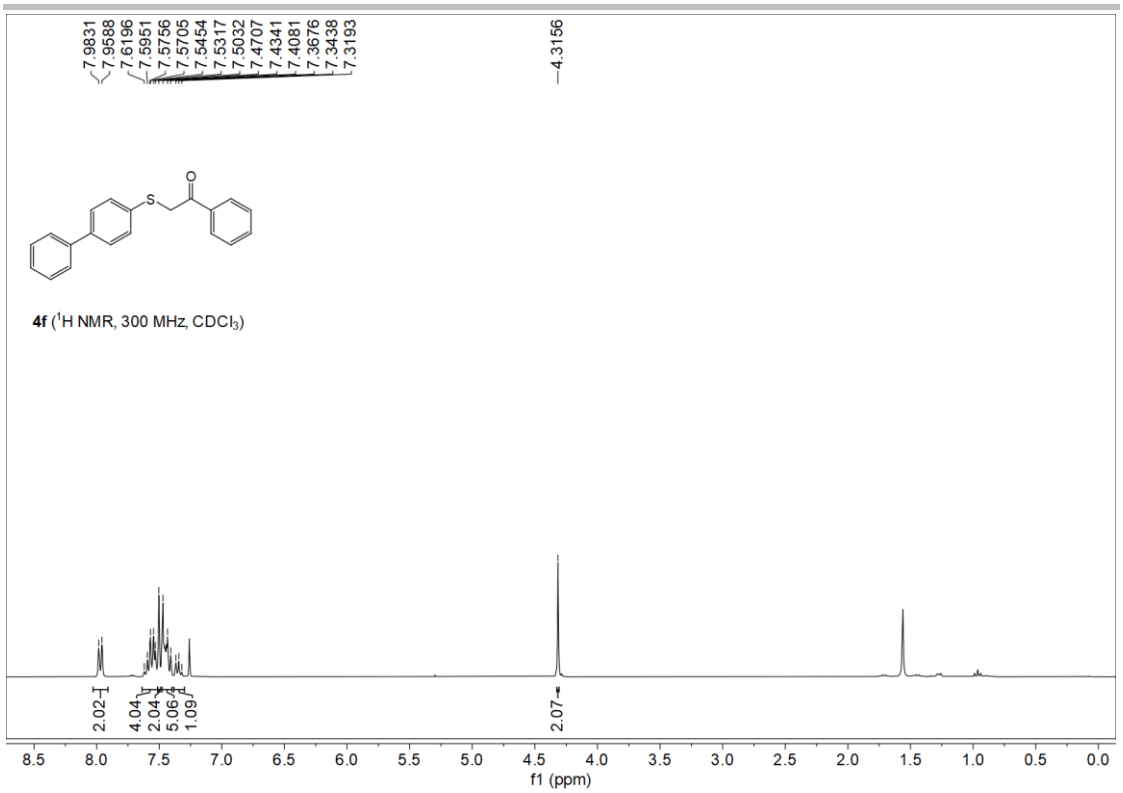

140.44
139.47
134.86
129.89
128.84
127.56
127.41
126.95
79.65
74.65
23.06
3.74
S
4d (13C NMR, 101 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



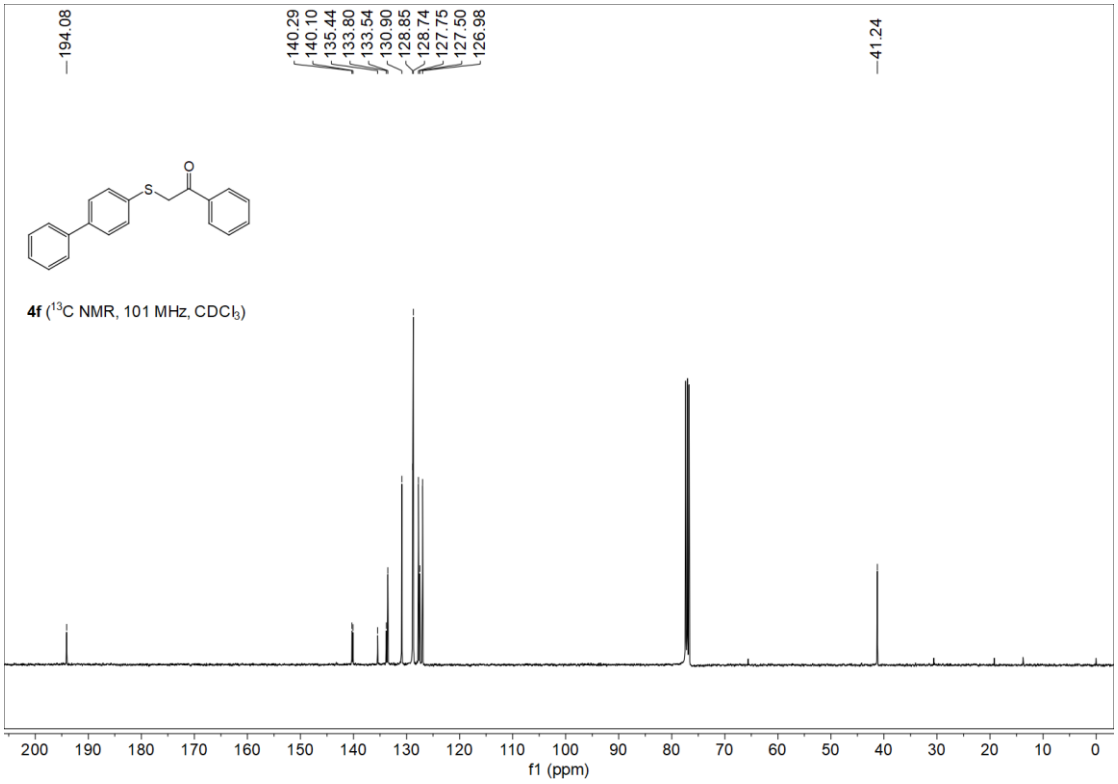
4e (^{1}H NMR, 300 MHz, $CDCl_3$)



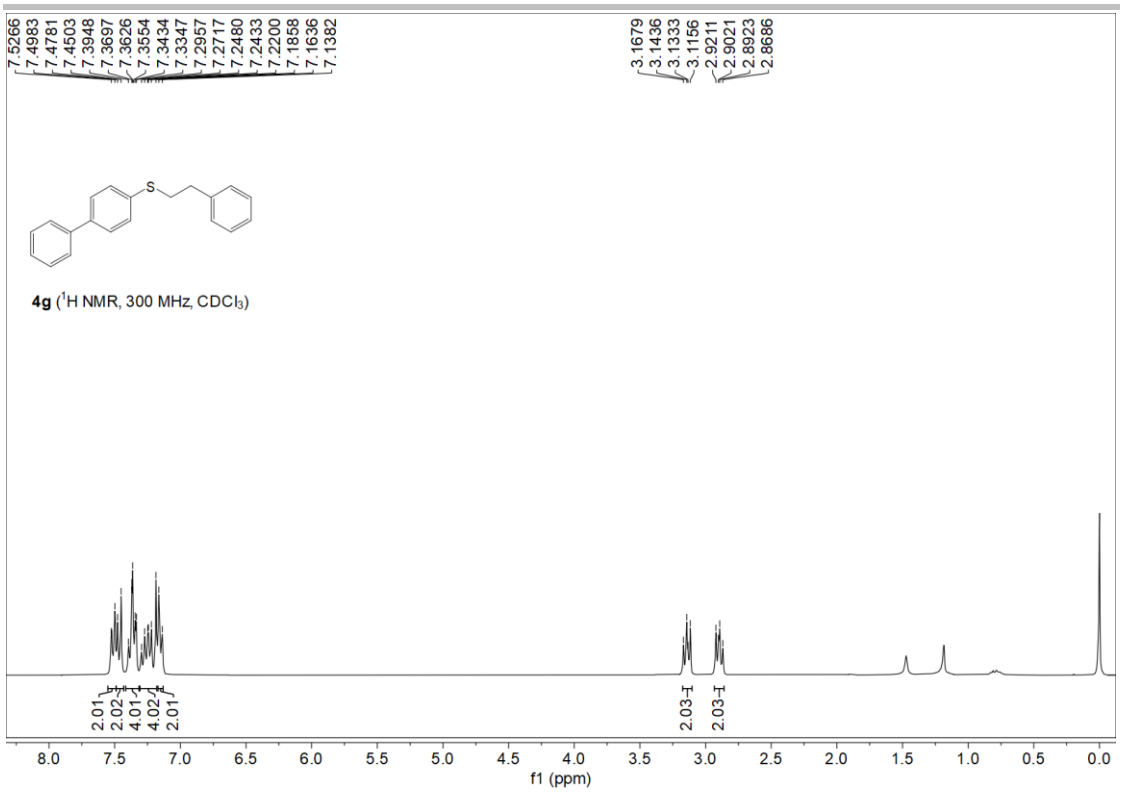
4e (^{13}C NMR, 101 MHz, $CDCl_3$)

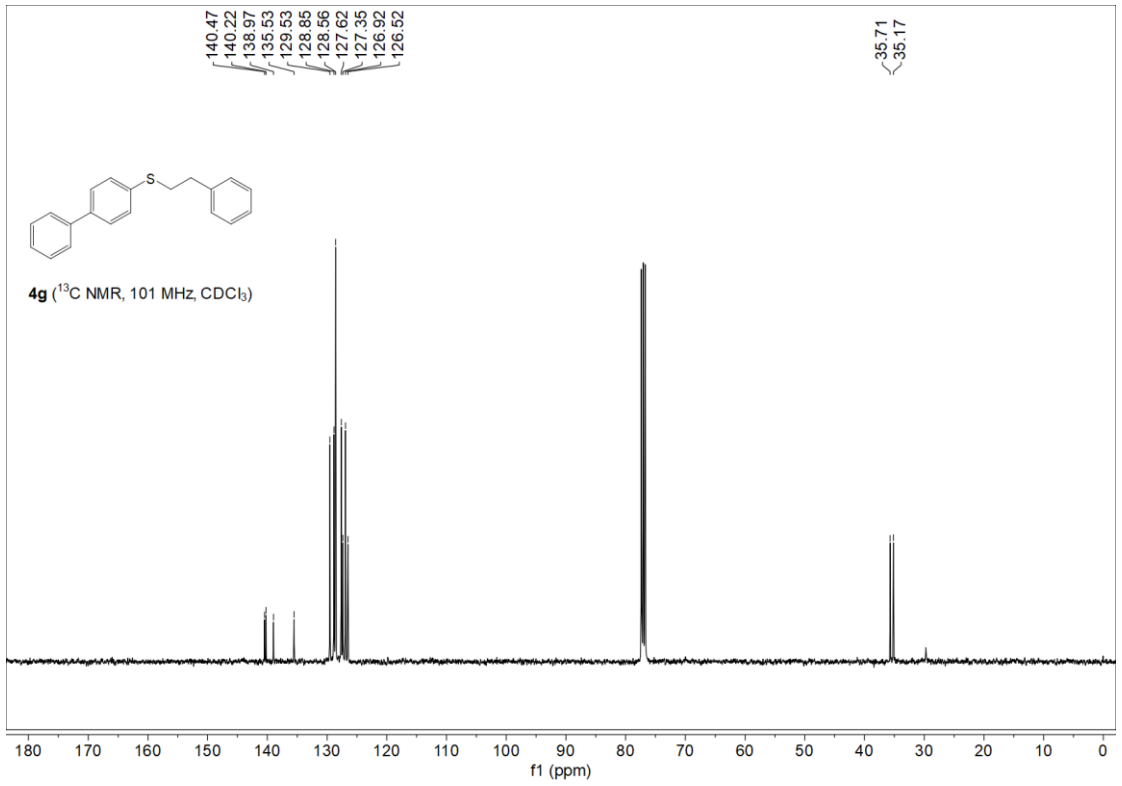


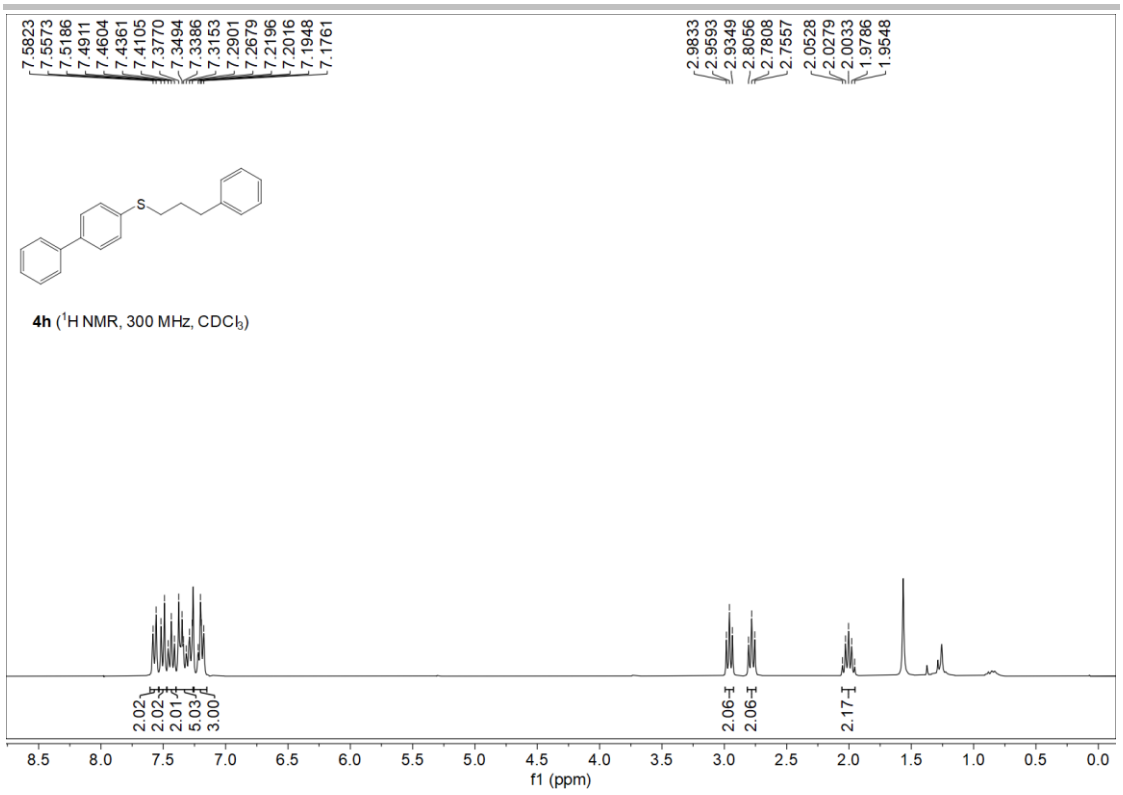
4f (^{1}H NMR, 300 MHz, $CDCl_3$)

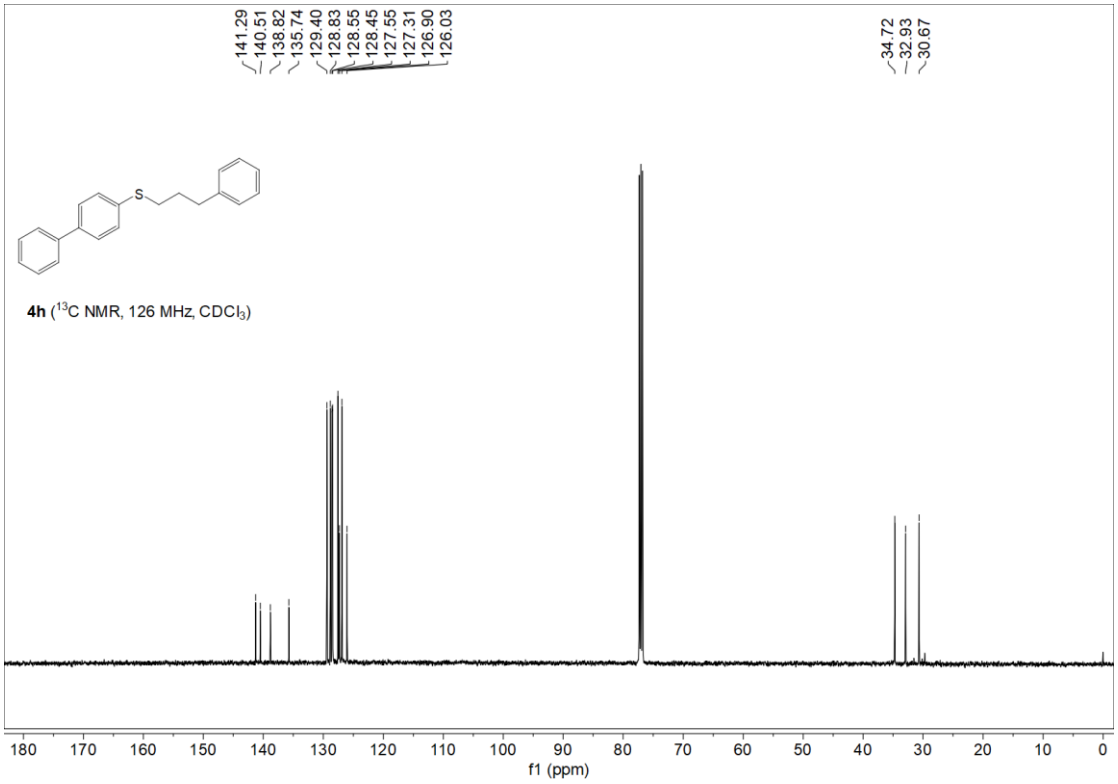


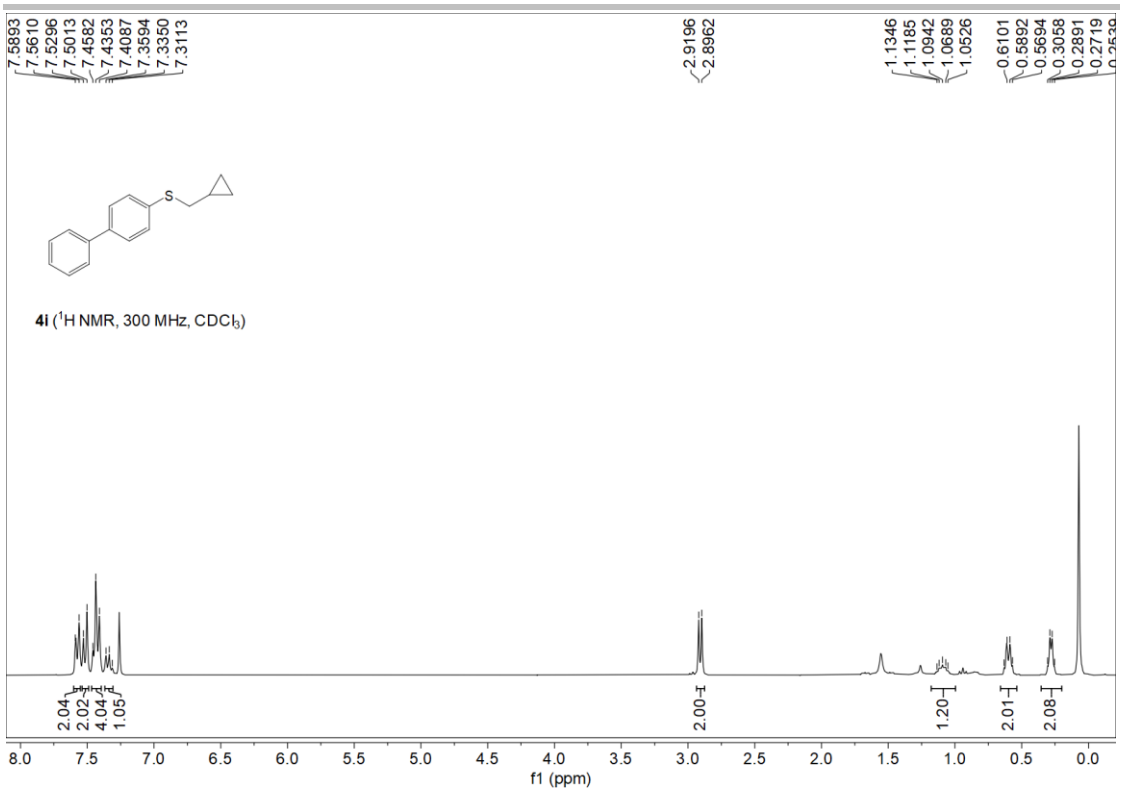
4f (^{13}C NMR, 101 MHz, $CDCl_3$)

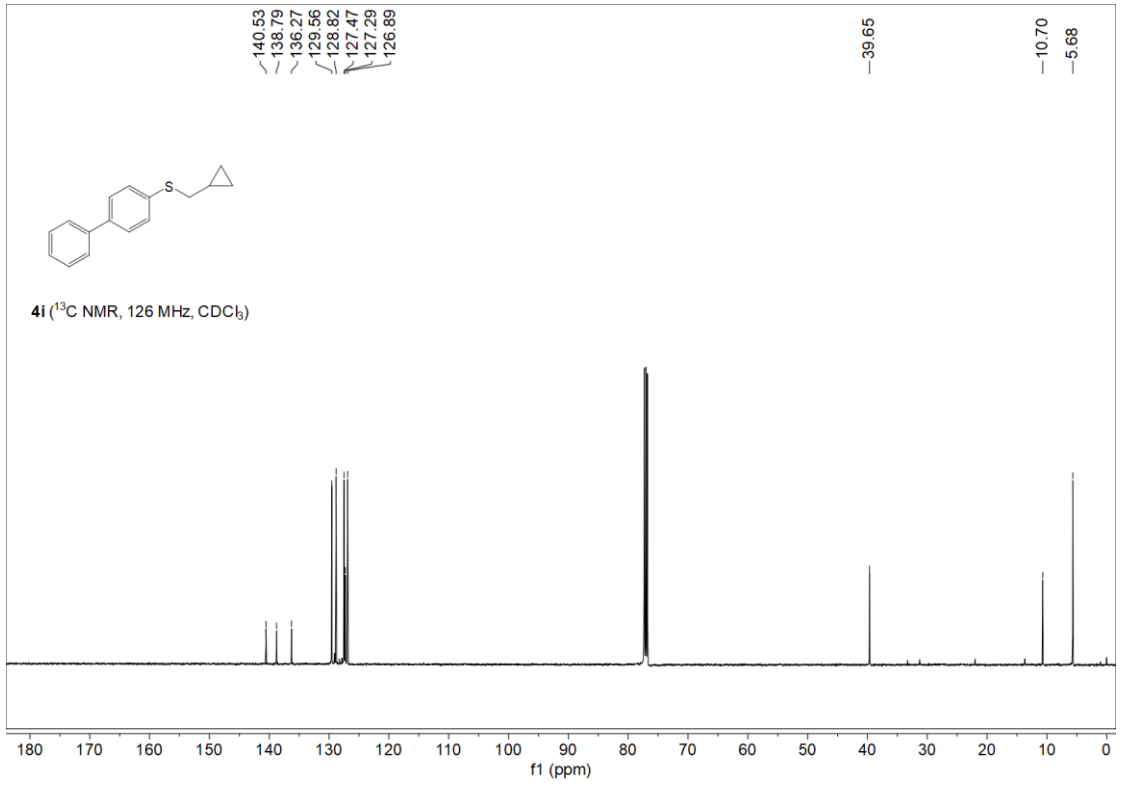

7.5266
7.4983
7.4781
7.4503
7.3948
7.3697
7.3626
7.3554
7.3434
7.3347
7.2957
7.2717
7.2480
7.2433
7.2200
7.1858
7.1636
7.1382
3.1679
3.1436
3.1333
3.1156
2.9211
2.9021
2.8923
2.8686
S
4g (1H NMR, 300 MHz, CDCl3)
2.01
2.02
4.01
4.02
2.01
2.03
2.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

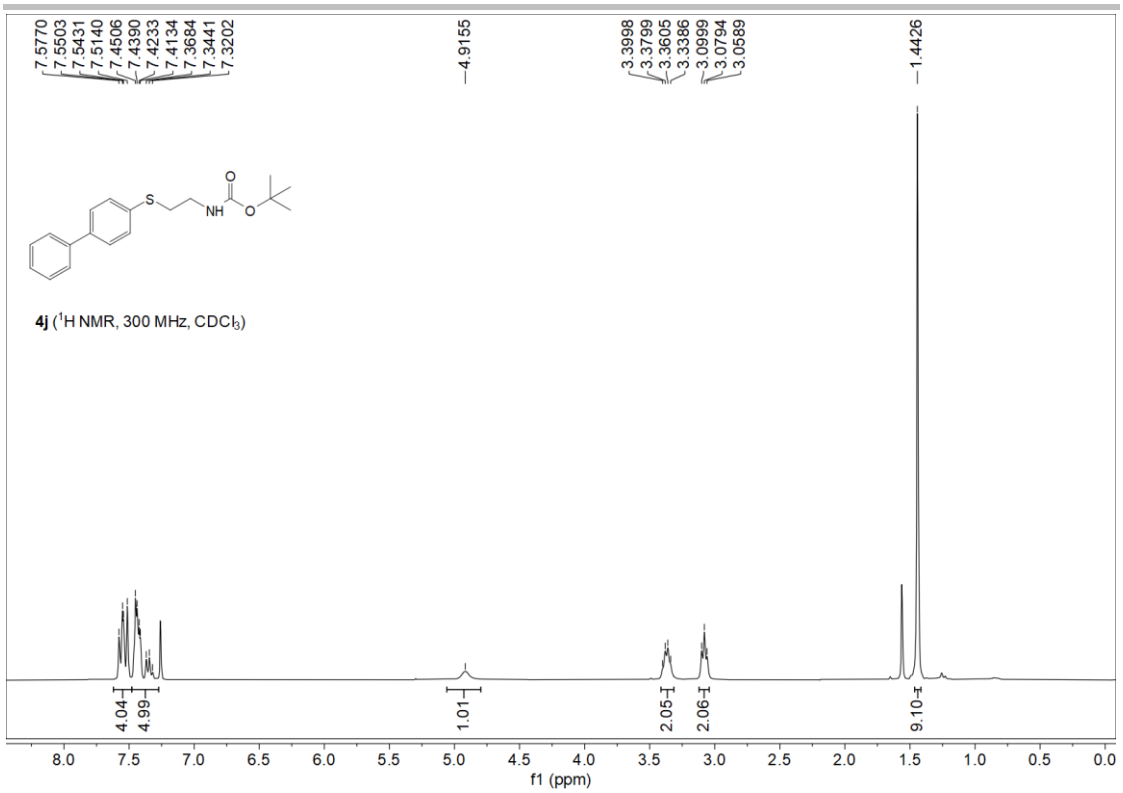

140.47
140.22
138.97
135.53
129.53
128.85
128.56
127.62
127.35
126.92
126.52
35.71
35.17
S
4g (13C NMR, 101 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.5823
7.5573
7.5186
7.4911
7.4604
7.4361
7.4105
7.3770
7.3494
7.3386
7.3153
7.2901
7.2679
7.2196
7.2016
7.1948
7.1761
2.9833
2.9593
2.9349
2.8056
2.7808
2.7557
2.0528
2.0279
2.0033
1.9786
1.9548
S
4h (1H NMR, 300 MHz, CDCl3)
2.02
2.02
2.01
5.03
3.00
2.06
2.06
2.17
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

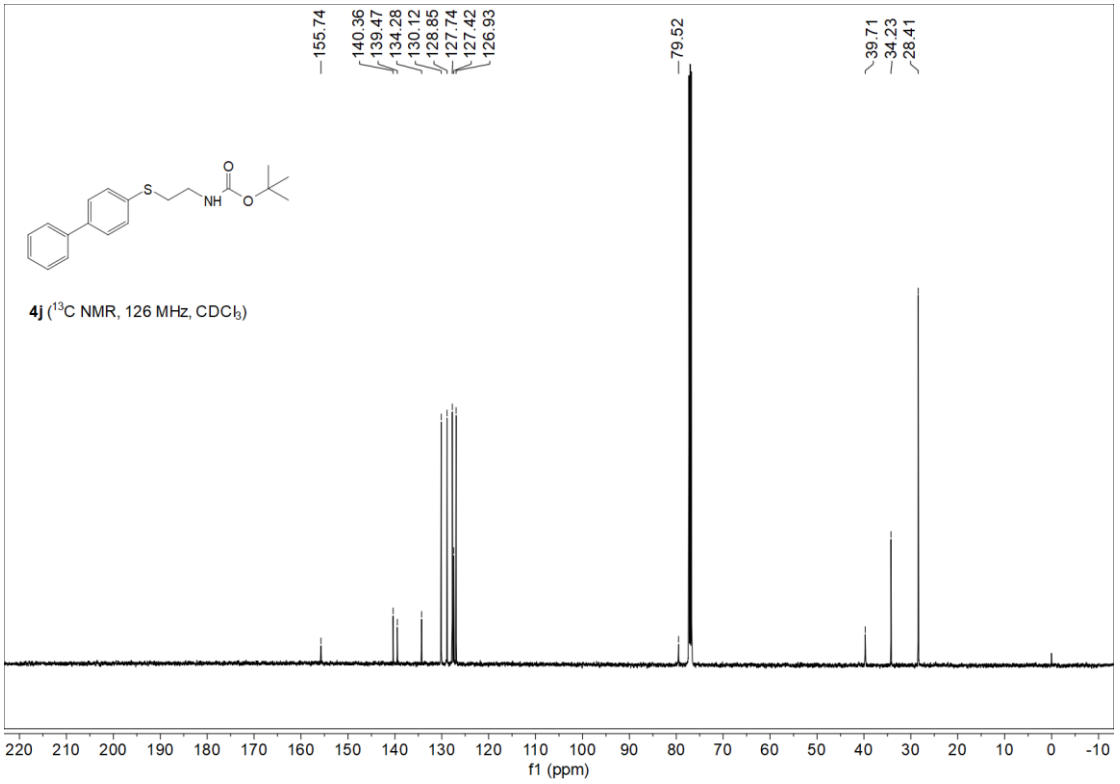

141.29
140.51
138.82
135.74
129.40
128.83
128.55
128.45
127.55
127.31
126.90
126.03
34.72
32.93
30.67
S
4h (13C NMR, 126 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.5893
7.5610
7.5296
7.5013
7.4582
7.4353
7.4087
7.3594
7.3350
7.3113
2.9196
2.8962
1.1346
1.1185
1.0942
1.0689
1.0526
0.6101
0.5892
0.5694
0.3058
0.2891
0.2719
S
4i (1H NMR, 300 MHz, CDCl3)
2.04
2.02
4.04
1.05
2.00
1.20
2.01
2.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

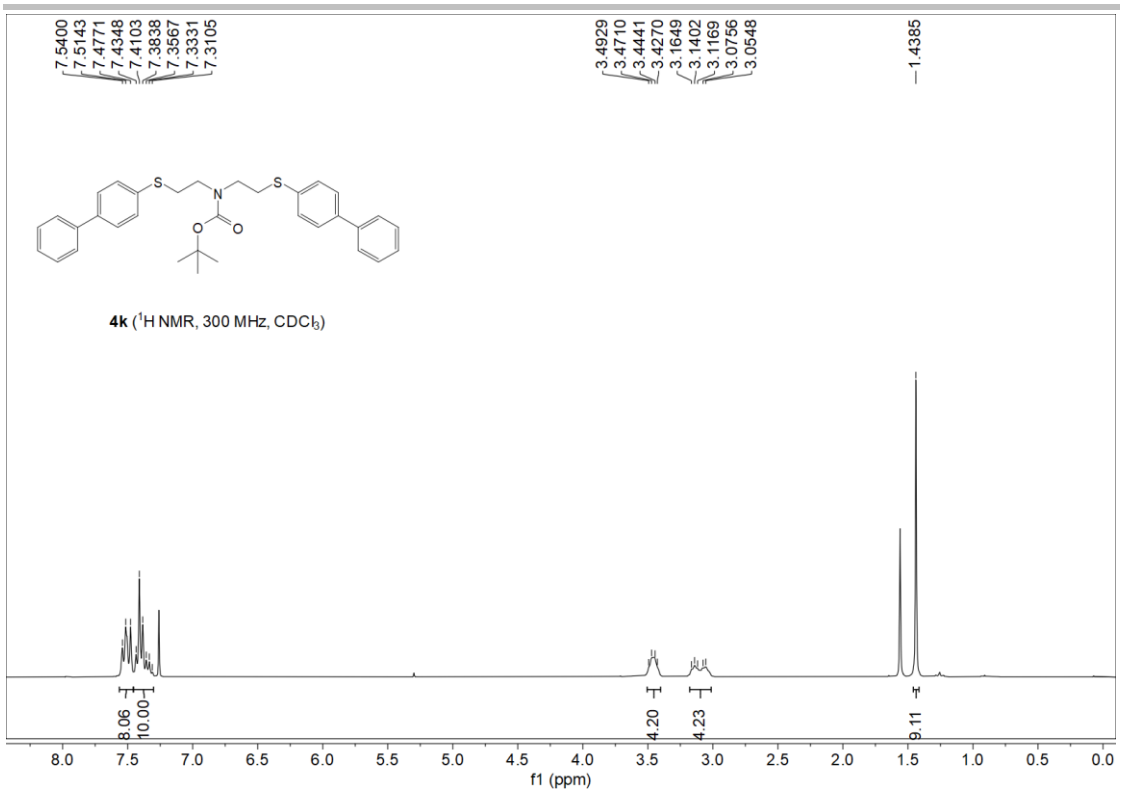

140.53
138.79
136.27
129.56
128.82
127.47
127.29
126.89
39.65
10.70
5.68
S
4i (13C NMR, 126 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



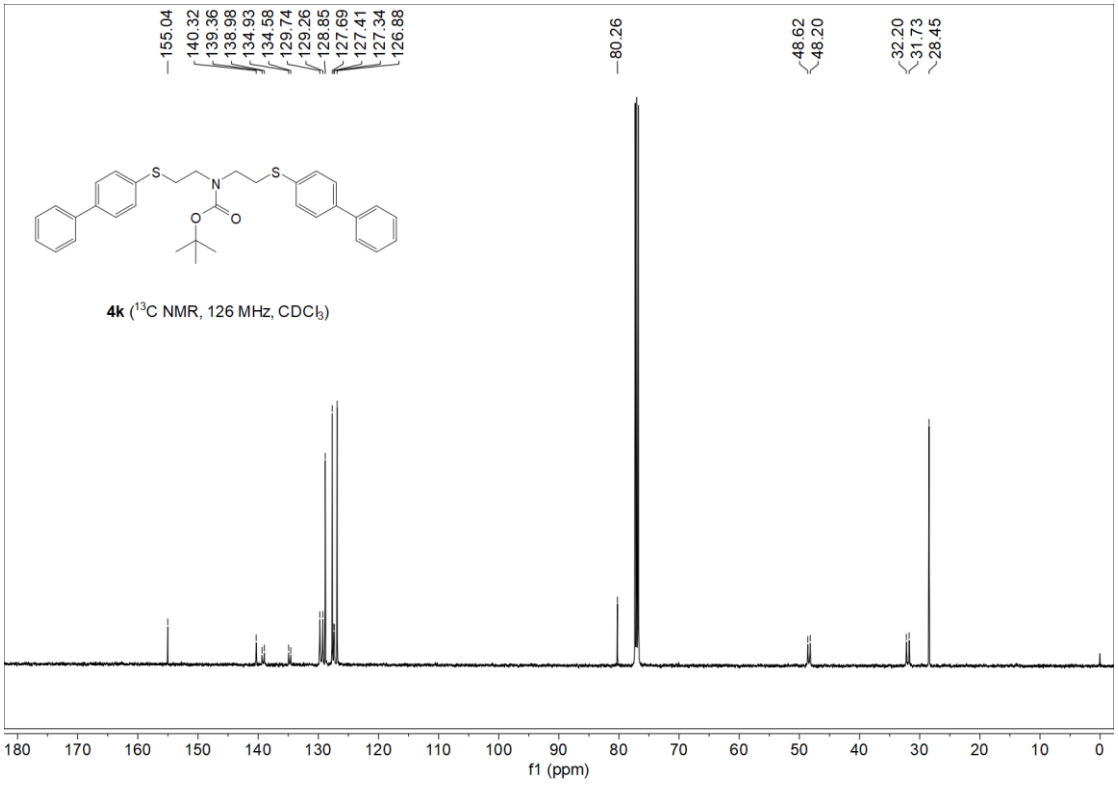
4j (^{1}H NMR, 300 MHz, $CDCl_3$)



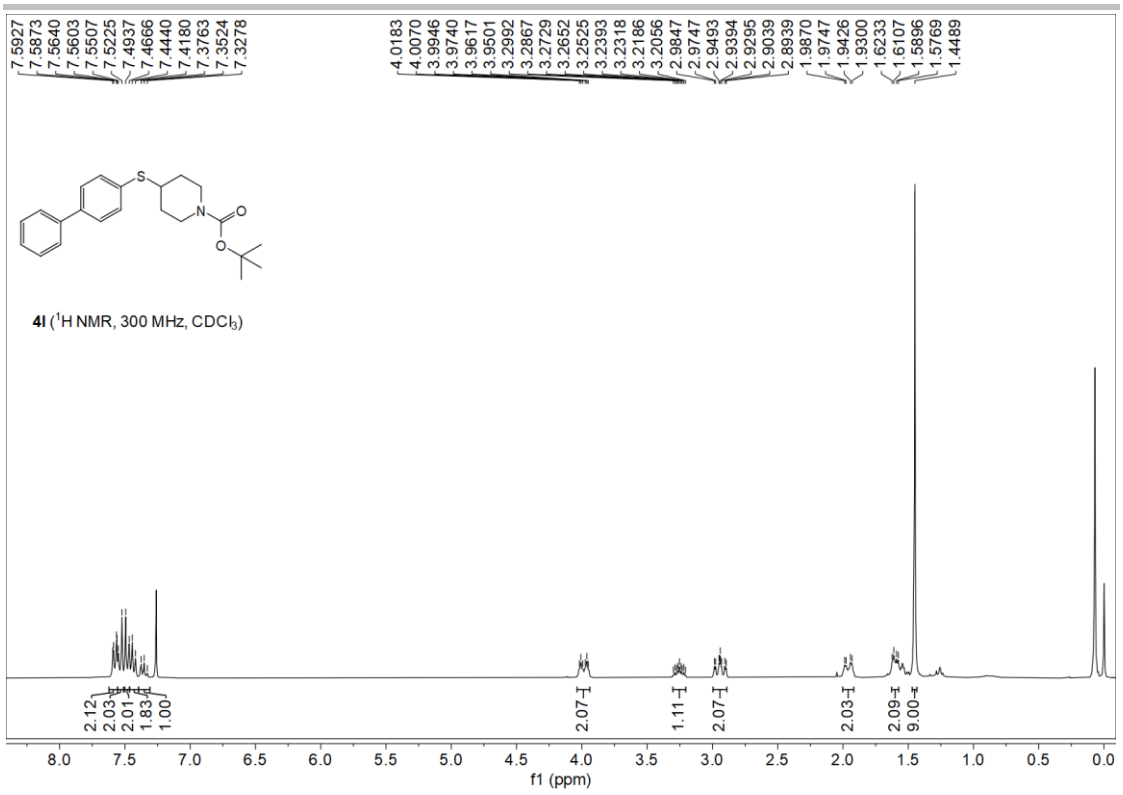
4j (^{13}C NMR, 126 MHz, $CDCl_3$)

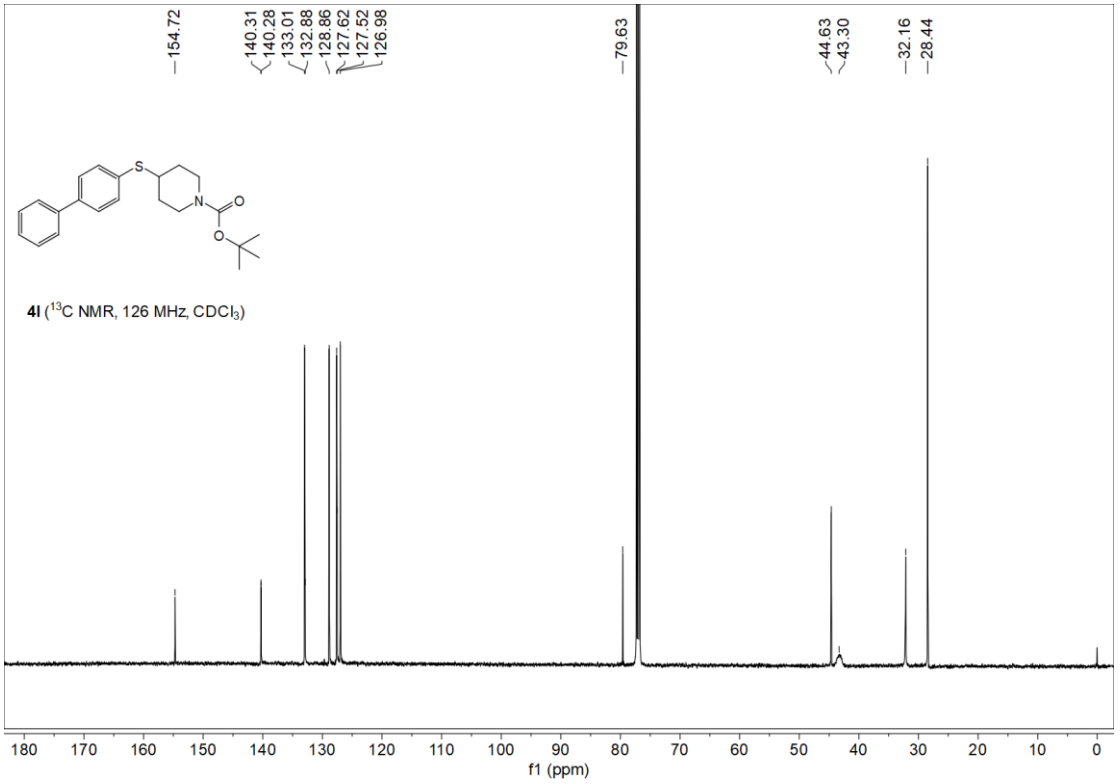


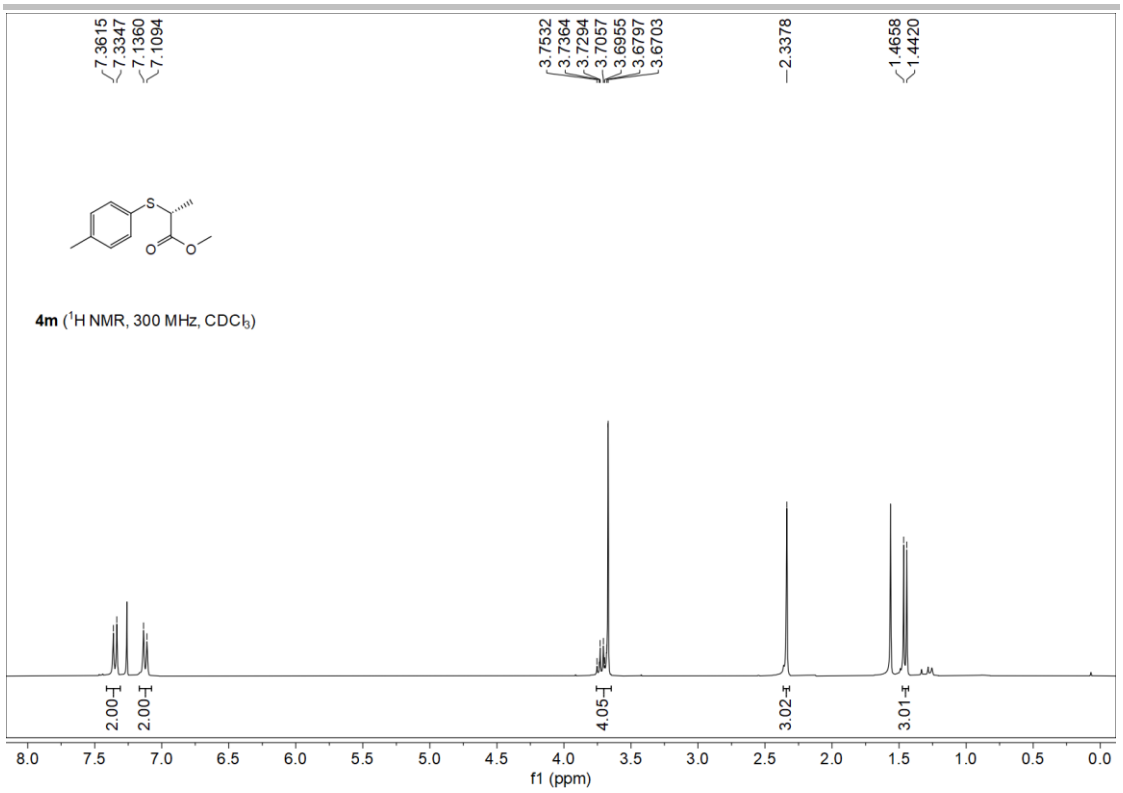
4k (^{1}H NMR, 300 MHz, $CDCl_3$)



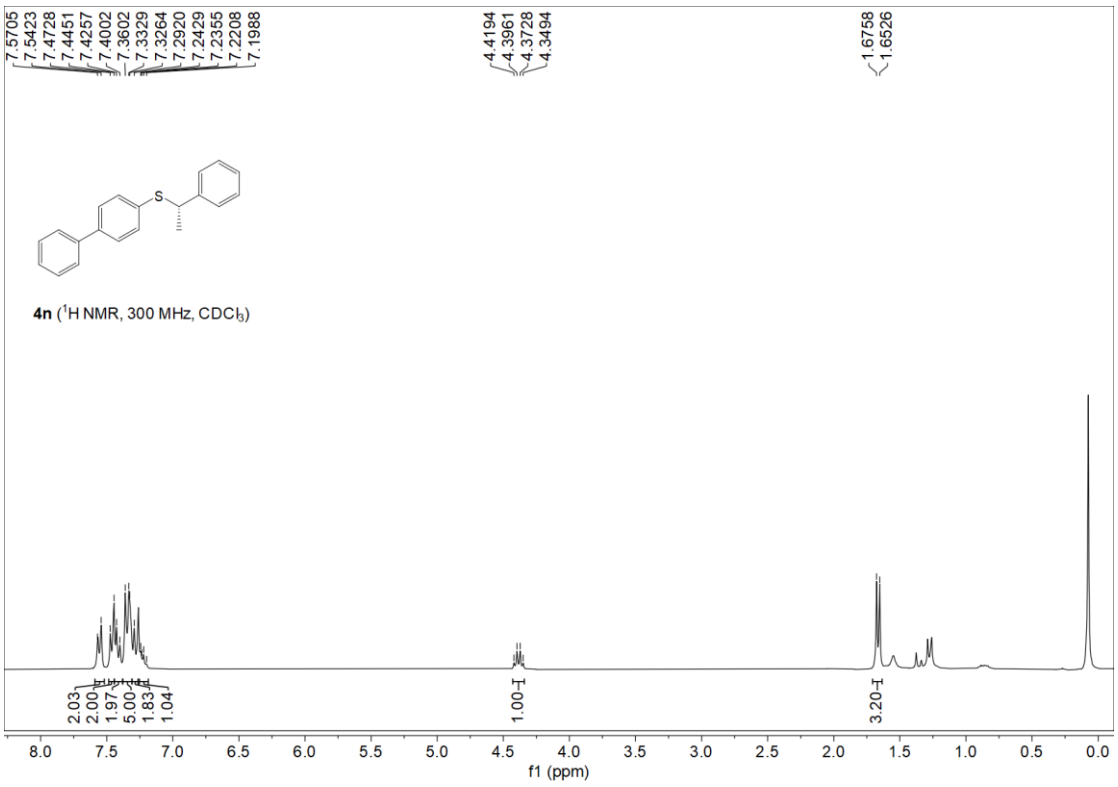
4k (^{13}C NMR, 126 MHz, $CDCl_3$)


7.5927
7.5873
7.5640
7.5603
7.5507
7.5225
7.4937
7.4666
7.4440
7.4180
7.3763
7.3524
7.3278
4.0183
4.0070
3.9946
3.9740
3.9617
3.9501
3.2992
3.2867
3.2729
3.2652
3.2525
3.2393
3.2318
3.2186
3.2056
2.9847
2.9747
2.9493
2.9394
2.9295
2.9039
2.8939
1.9870
1.9747
1.9426
1.9300
1.6233
1.6107
1.5896
1.5769
1.4489
S
N
O
O
4l (1H NMR, 300 MHz, CDCl3)
2.12
2.03
2.01
1.83
1.00
2.07
1.11
2.07
2.03
2.09
9.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

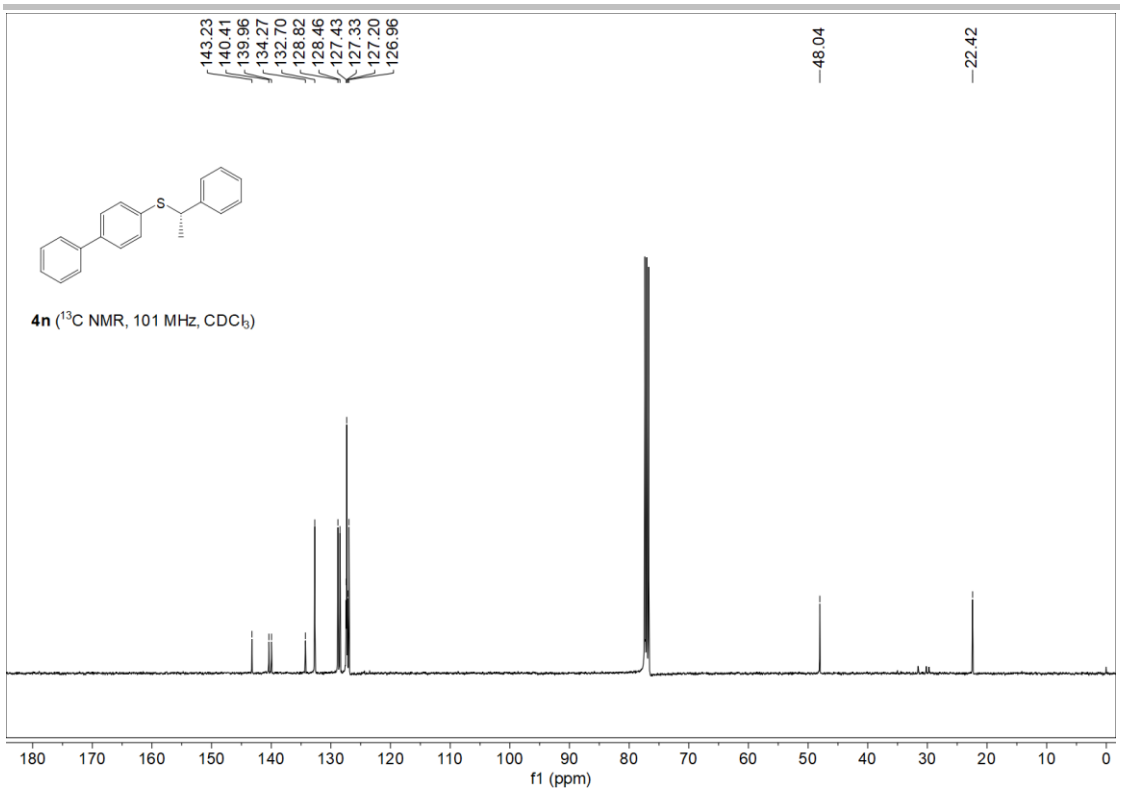

154.72
140.31
140.28
133.01
132.88
128.86
127.62
127.52
126.98
79.63
44.63
43.30
32.16
28.44
S
N
O
O
4l (13C NMR, 126 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

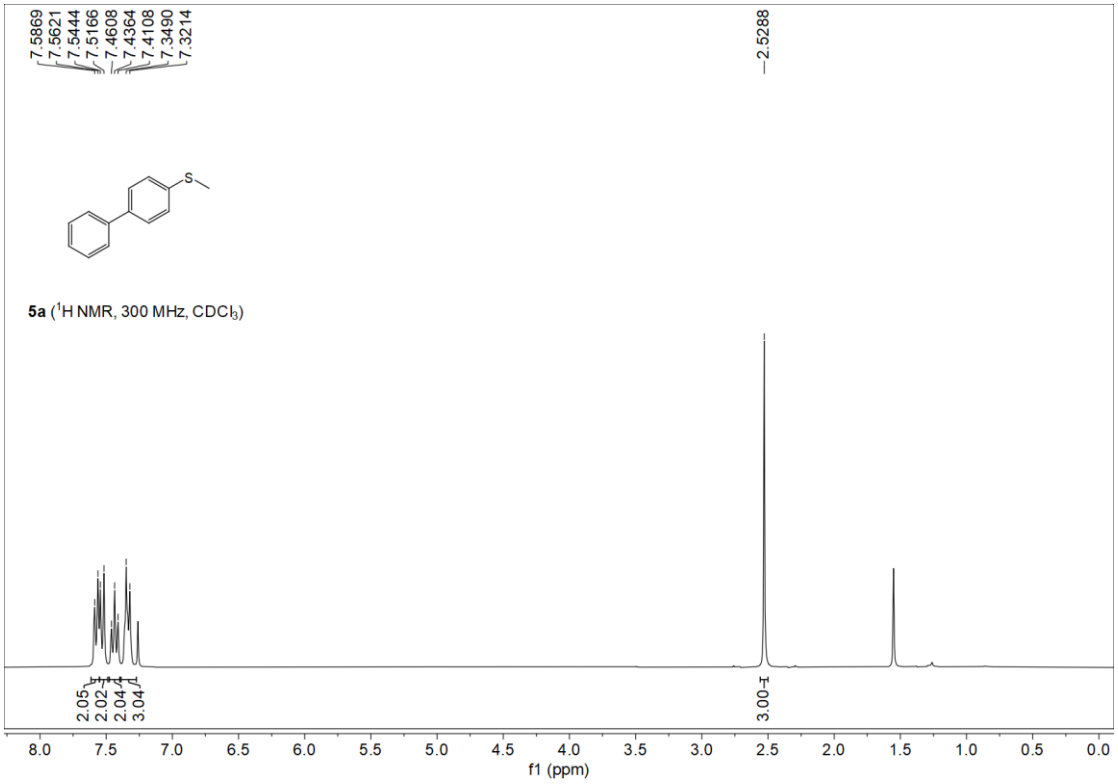


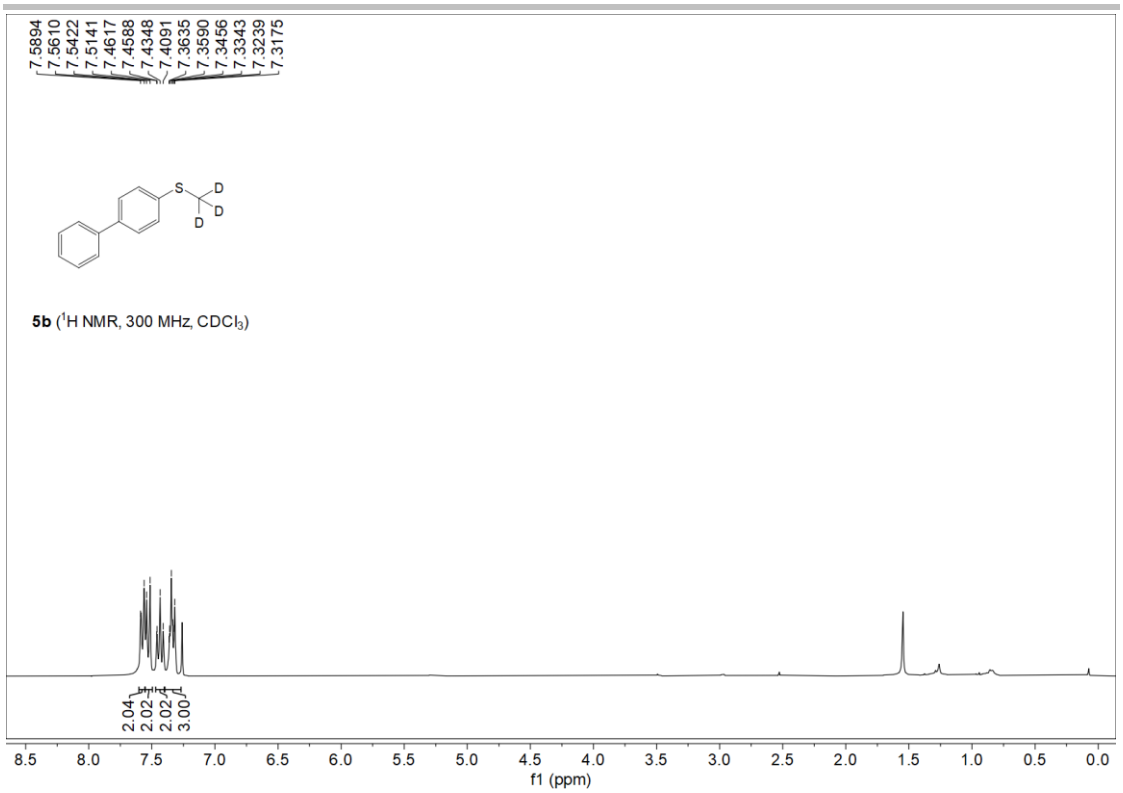
4m (^{1}H NMR, 300 MHz, $CDCl_3$)



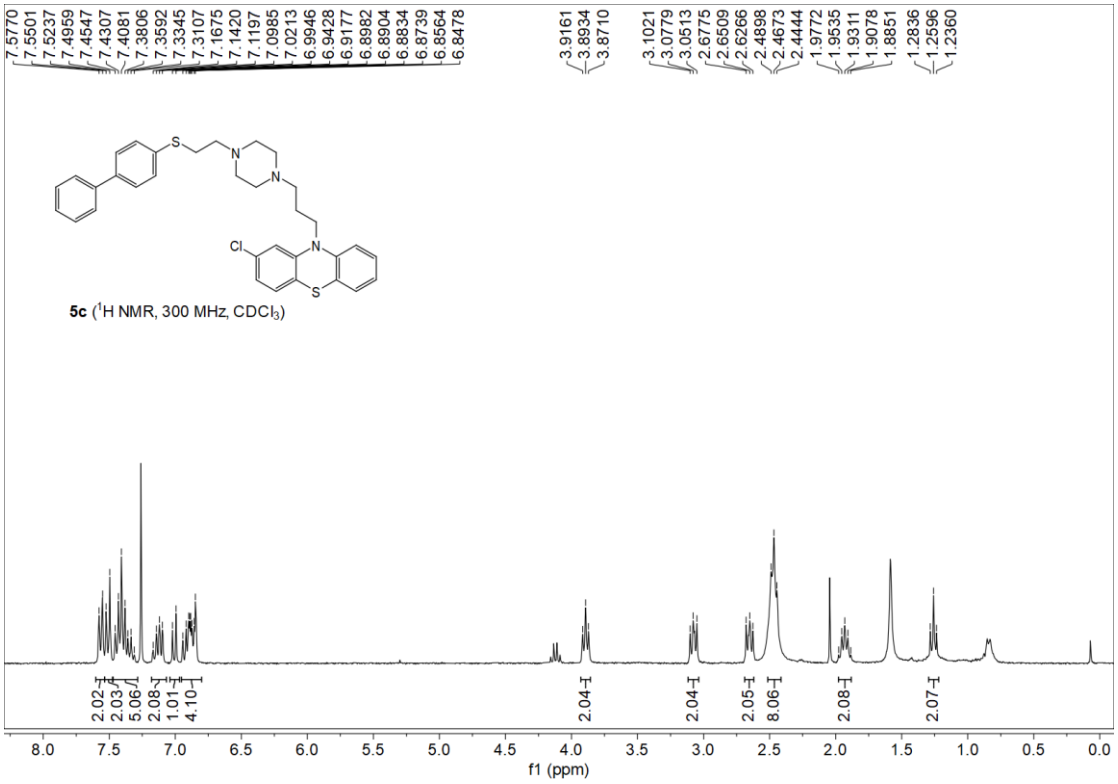
4n (^{1}H NMR, 300 MHz, $CDCl_3$)


143.23
140.41
139.96
134.27
132.70
128.82
128.46
127.43
127.33
127.20
126.96
48.04
22.42
S
4n (13C NMR, 101 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

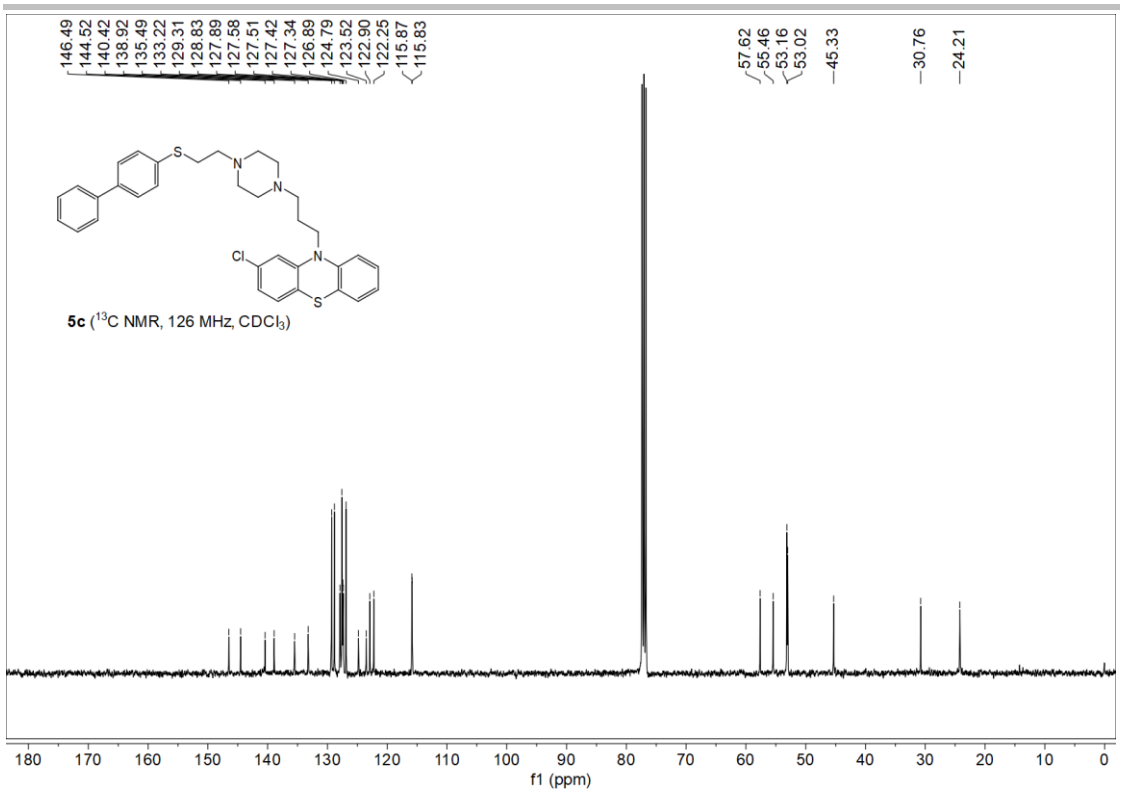

7.5869
7.5621
7.5444
7.5166
7.4608
7.4364
7.4108
7.3490
7.3214
2.5288
S
5a (1H NMR, 300 MHz, CDCl3)
2.05
2.02
2.04
3.04
3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

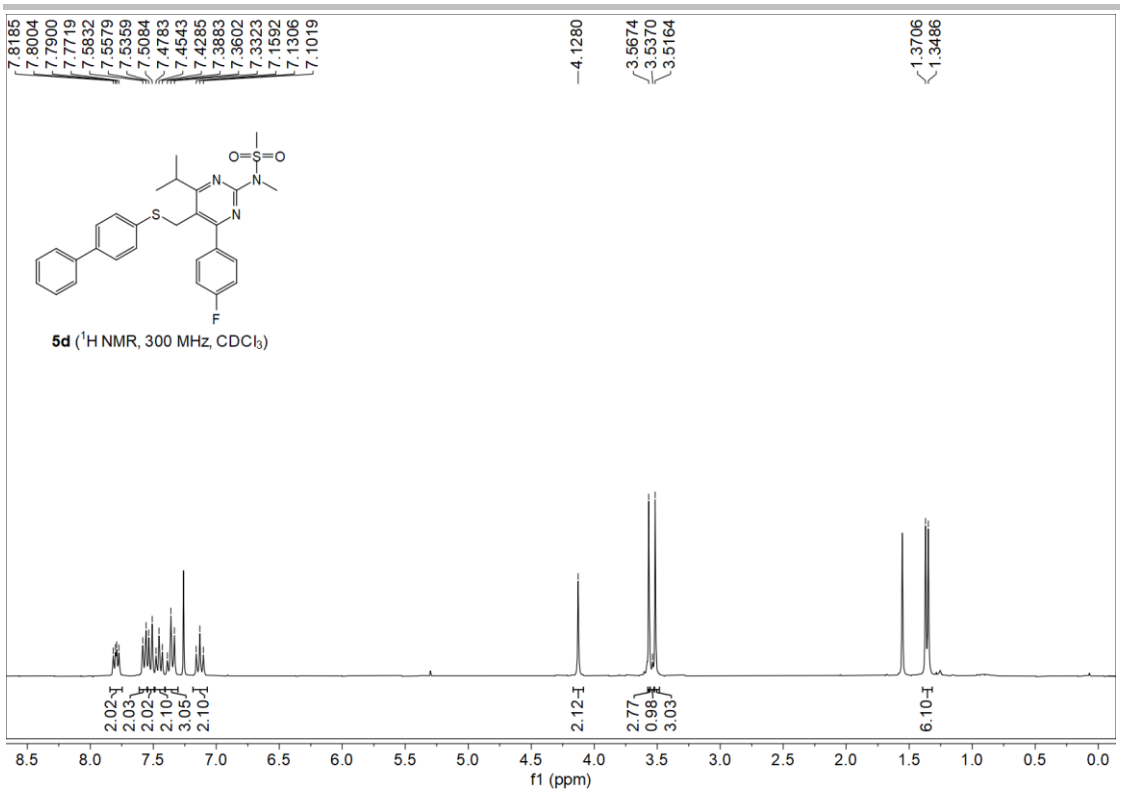


5b (^{1}H NMR, 300 MHz, $CDCl_3$)

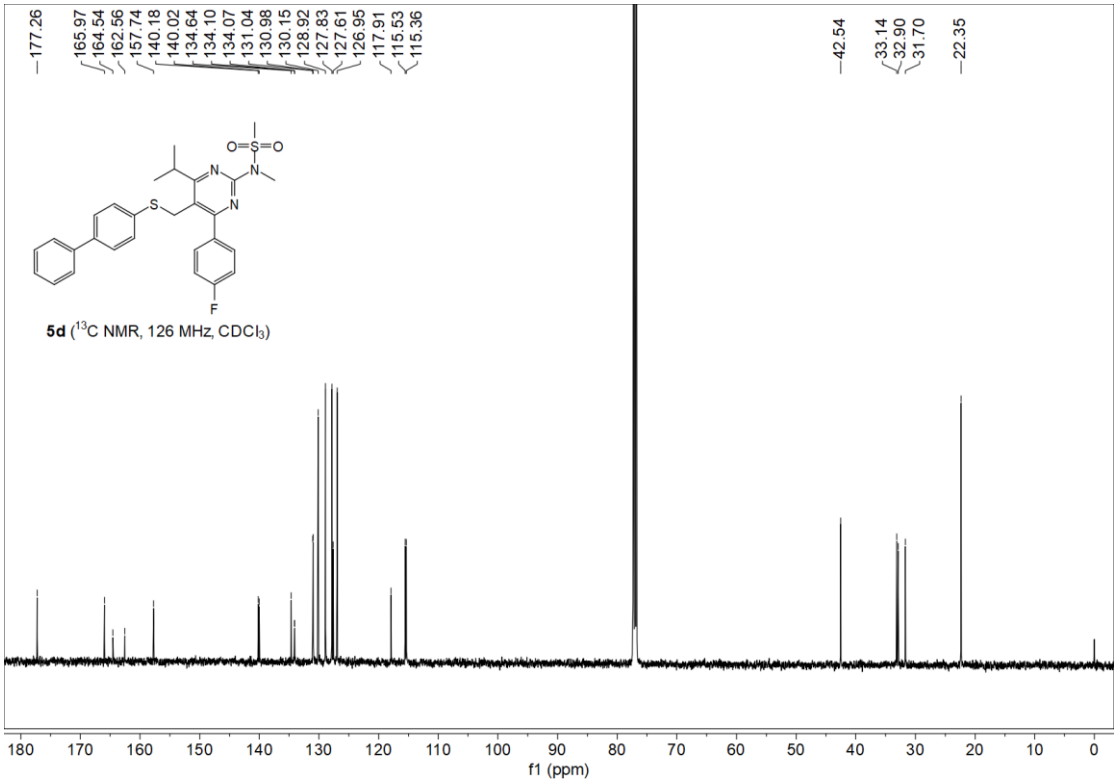


5c (^{1}H NMR, 300 MHz, $CDCl_3$)

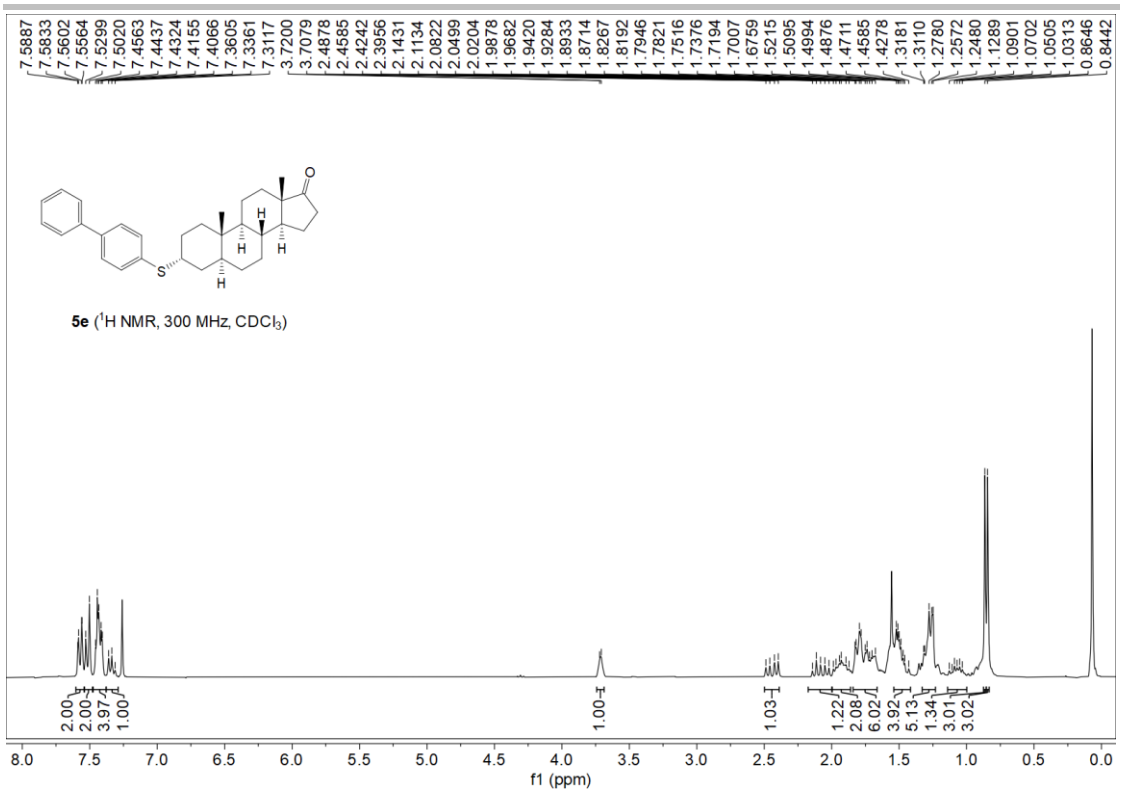

146.49
144.52
140.42
138.92
135.49
133.22
129.31
128.83
127.89
127.58
127.51
127.42
127.34
126.89
124.79
123.52
122.90
122.25
115.87
115.83
57.62
55.46
53.16
53.02
45.33
30.76
24.21
S
N
N
Cl
N
S
5c (13C NMR, 126 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

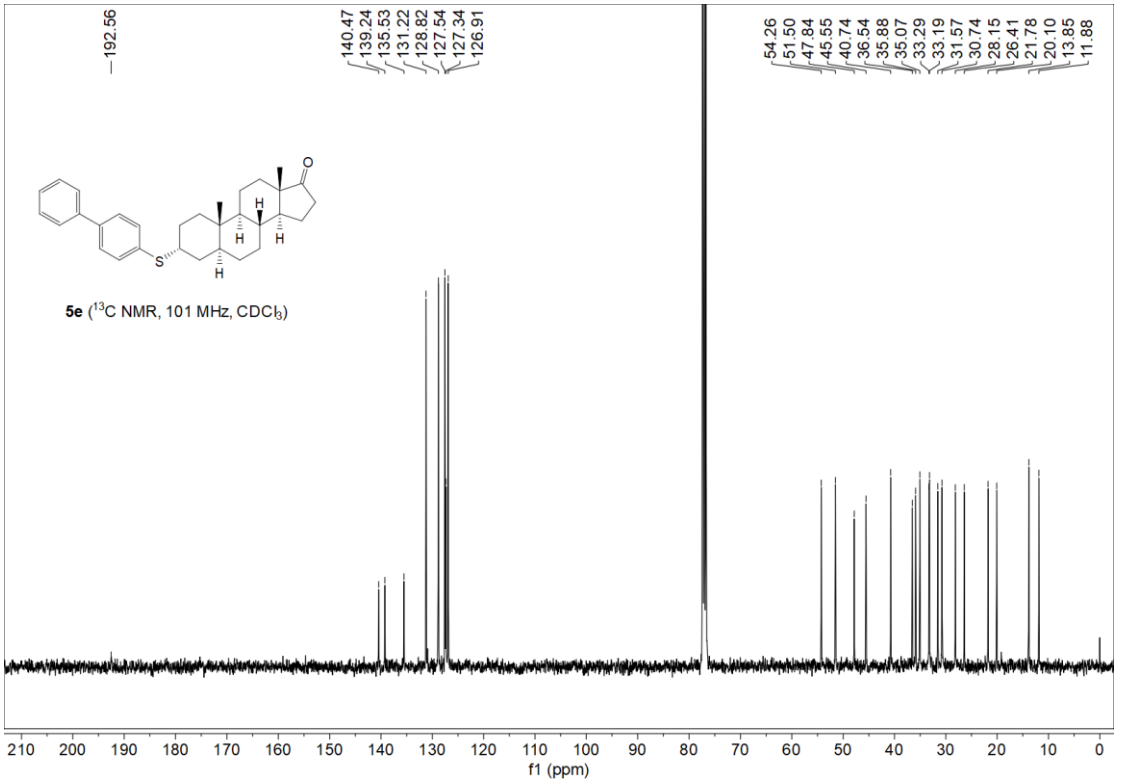


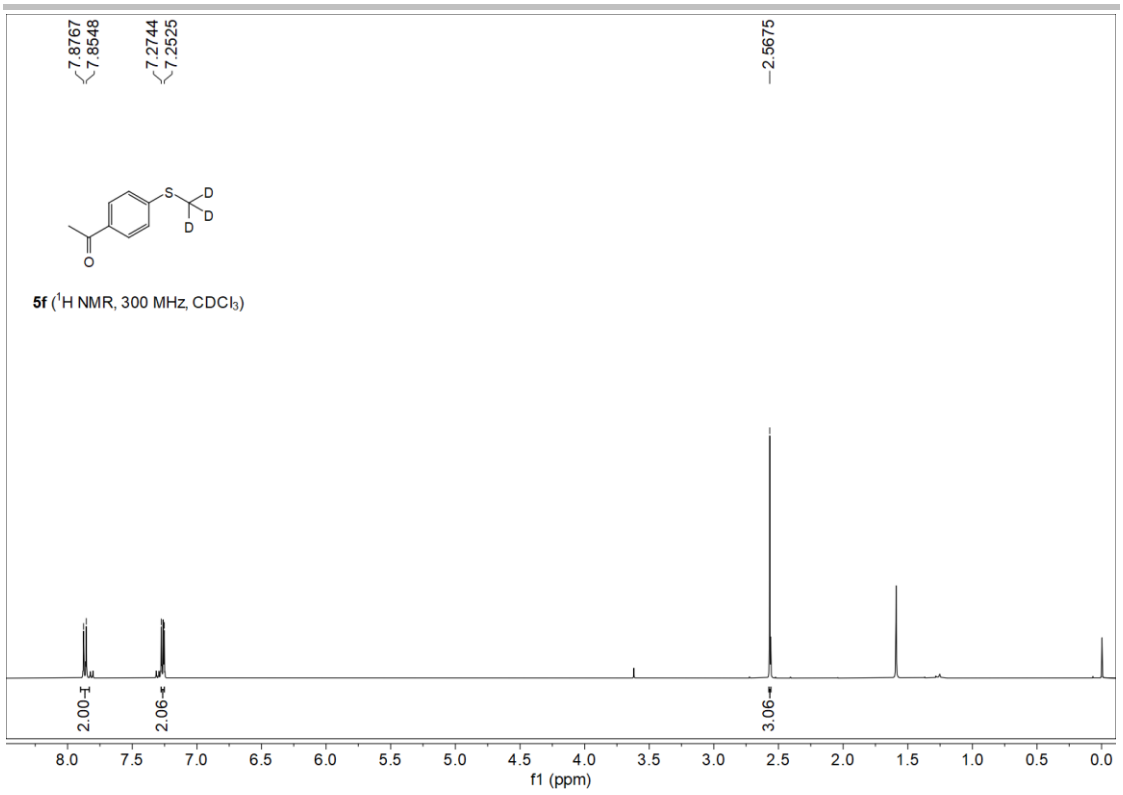
5d (^{1}H NMR, 300 MHz, $CDCl_3$)



5d (^{13}C NMR, 126 MHz, $CDCl_3$)


7.5887
7.5833
7.5602
7.5564
7.5299
7.5020
7.4563
7.4437
7.4324
7.4155
7.4066
7.3605
7.3361
7.3117
3.7200
3.7079
2.4878
2.4585
2.4242
2.3956
2.1431
2.1134
2.0822
2.0499
2.0204
1.9878
1.9682
1.9420
1.9284
1.8933
1.8714
1.8267
1.8192
1.7946
1.7821
1.7516
1.7376
1.7194
1.7007
1.6759
1.5215
1.5095
1.4994
1.4876
1.4711
1.4585
1.4278
1.3181
1.3110
1.2780
1.2572
1.2480
1.1289
1.0901
1.0702
1.0505
1.0313
0.8646
0.8442
O
H
H
H
S
H
5e (1H NMR, 300 MHz, CDCl3)
2.00
2.00
3.97
1.00
1.00
1.03
1.22
2.08
6.02
3.92
5.13
1.34
3.01
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


192.56
140.47
139.24
135.53
131.22
128.82
127.54
127.34
126.91
54.26
51.50
47.84
45.55
40.74
36.54
35.88
35.07
33.29
33.19
31.57
30.74
28.15
26.41
21.78
20.10
13.85
11.88
O
H
H
H
S
H
5e (13C NMR, 101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.8767
7.8548
7.2744
7.2525
2.5675
S
D
D
D
O
5f (1H NMR, 300 MHz, CDCl3)
2.00
2.06
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5. References

1 F. Li, D. Wang, H. Chen, Z. He, L. Zhou and Q. Zeng, *Chem. Commun.* 2020, **56**, 13029.

2 H. Sharghi, I. Ghaderi and M. M. Doroodmand, *Appl. Organomet. Chem.* 2017, **31**, e3869.

3 B. Wang, Y. Liu, C. Lin, Y. Xu, Z. Liu and Y. Zhang, *Org. Lett.* 2014, **16**, 4574.

4 A. K. Jaiswal, P. K.Prasad and R. D.Young, *Chem-Eur. J.* 2019, **25**, 6290.

5 M. A. M. Capozzi, G. Terraneo, G. Cavallo and C. Cardellicchio, *Tetrahedron* 2015, **71**, 4810.

6 M. Xuan, C. Lu and B.-L. Lin, *Chinese Chem. Lett.* 2020, **31**, 4810.

7 X. Yang, L. Wang and C. Li, U.S. Patent 9642839.

8 J. Ham, I. Yang and H. Kang, *J. Org. Chem.* 2004, **69**, 3236.

9 T. Cellnik and A. R. Healy, *J. Org. Chem.* 2022, **87**, 6454.

10 C. Zhang, N.-N. Ma, Z.-L. Yu, C. Shen, X. Zhou, X.-Q. Chu, W. Rao and Z.-L. Shen, *Org. Chem. Front.* 2021, **8**, 4865.

11 X. Xiao, Y.-Q. Huang, H.-Y. Tian, J. Bai, F.Cheng, X. Wang; M.-L. Ke and F.-E. Chen, *Chem. Commun.* 2022, **58**, 3015.

12 Y. Wang and H. Li, CN109265380A.

13 T. Bach and C. Körber, *J. Org. Chem.* 2000, **65**, 2358.

14 B. Ernst, R. Oehrlein, D. Belluš, J. Gonda, R. Jeschke and Udo. Nubbemeyeret, *Helv. Chim. Acta.* 1997, **80**, 876.