Electronic Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

2-(Aryl-Sulfonyl)Oxetanes as Designer 3-Dimensional Fragments for Fragment Screening: Synthesis and Strategies for Functionalisation

Kate F. Morgan,[a] Ian A. Hollingsworth[b] and James A. Bull*[a]

[a] *Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK.*
Tel: +44 (02)0 7594 5811. E-mail: j.bull@imperial.ac.uk.

[b] *AstraZeneca Mereside, Alderley Park, Cheshire, SK10 4TG, UK.*

General Experimental Conditions

All non-aqueous reactions were run under an inert atmosphere (argon or nitrogen) with flame-dried or oven-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns or obtained from commercial suppliers and used without further purification (THF, CH_2Cl_2, toluene, DMF).

Flash column chromatography was performed using 230-400 mesh silica, 70-290 mesh basic alumina modified to activity IV or ISCO Flash Silica cartridges with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), or aqueous potassium permanganate stain.

Infrared spectra (FTIR) were recorded in reciprocal centimeters (cm^{-1}).

Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm) or using chloroform with 1% tetramethylsilane as the internal standard. Data is reported as follows: chemical shift [integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm) or using chloroform with 1% tetramethylsilane as the internal standard.

Assignments of ^1H and ^{13}C spectra were made by the analysis of δ/J values and COSY, HSQC and HMBC experiments as appropriate.

Melting points are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary.

Compound Handling/Purification/Storage:

All synthetic intermediates were stored under argon at –20 ºC for short periods. Oxetanes **1a-d** were bench stable; oxetane **1a** was stored at rt for 3 months without degradation.

Where required for purification, the activity of basic alumina was altered by the addition of water to commercial basic alumina (activity I) and evenly distributed (activity IV: 10% w/w water).[1]

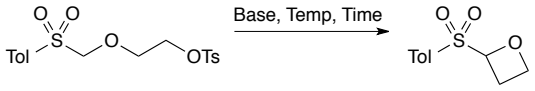
Preparation of a 0.61M solution of LiHMDS.

A solution of HMDS (0.14 ml, 0.67 mmol) in THF (0.48 mL) was cooled to –78 ºC for 5 min then *n*BuLi (0.38 mL, 0.61 mmol, 1.6 M in hexane) was added dropwise. Solution stirred at –78 ºC for 30 min then warmed to 0 ºC for 30 min prior to use.

Optimisation of Oxetane Formation

Initial investigations treated sulfone **4a** (0.52 mmol) with base (2 equiv.) in THF at 0 ºC for 1 h then warmed to rt for 1 h (Table S1, entries 1-7). Amine bases were generally successful in promoting cyclisation, with LiHMDS the most effective, especially when freshly prepared (entries 7 and 8).

Table S1: Selected optimisation: intramolecular cyclisation of sulfone **4a** to oxetane **1a**.



4a **1a**

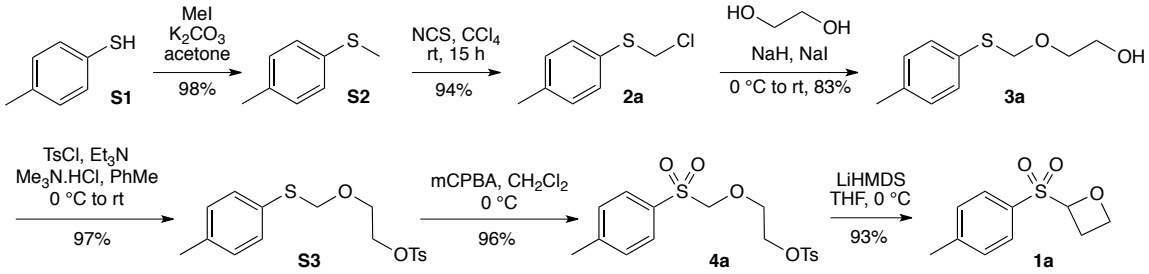
entry	base	equiv. base	concn [M]	order of addition[a]	yield (%)[b]
1	NaH	2	0.025	A	0
2	LDA[c]	2	0.025	A	12
3	LiTMP[c]	2	0.025	A	32
4	*n*BuLi[d]	2	0.025	A	68
5	KHMDS	2	0.025	A	45
6	NaHMDS	2	0.025	A	33
7	LiHMDS	2	0.025	A	50
8	LiHMDS[c]	2	0.025	A	63
9	*n*BuLi[d]	2	0.025	B	52
10	LiHMDS[c]	2	0.025	B	89
11	LiHMDS[c]	1.2	0.025	B	97
12	LiHMDS[c]	1.2	0.05	B	81
13	LiHMDS[c]	1.2	0.0125	B	99
14	LiHMDS[c,e]	1.2	0.025	B	99
15	**LiHMDS[c,e]**	**1.1**	**0.025**	**B**	**99**
16	LiHMDS[c,e]	1.05	0.025	B	93

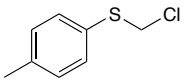
[a] Conditions A, addition of the substrate to a solution of the base; Conditions B, addition of the base to a solution of the substrate. [b] Yield determined by ^{1}H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard. [c] Base made immediately prior to use. [d] Reaction run at –78 ºC as opposed to 0 ºC. [e] Reaction time of 1h.

The order of addition of the base and substrate was examined next using LiHMDS and *n*BuLi as they were the two most effective bases under the original conditions adding a solution of tosyl sulfone **4a** to a solution of base in THF. Reversing the addition, base added to sulfone, resulted in a marked increase in yield using LiHMDS to 89% by ^{1}H NMR (entries 8 and 10). Under these conditions the amount of LiHMDS could be reduced to 1.2 equiv affording a further increase in yield (entry 11). The concentration of the reaction was next investigated, maintaining relatively dilute conditions to favour intramolecular cyclisation. Increasing the concentration from 0.025 M to 0.05 M gave a notable reduction in yield (entry 12). More dilute conditions (entry 13) gave a marginal increase in yield and 0.025 M was chosen as optimal. The reaction time could be reduced to 1 h at 0 ºC (entry 14). Further reduction of the amount of base to 1.1 equiv gave the optimal reaction conditions (entry 15) which afforded a quantitative conversion to the oxetane product; decreasing the equivalents further resulted in a decrease in yield (entry 16).

Under these conditions, the synthesis was scaled up to 6.5 mmol to give 1.2 g oxetane **1a** with a 93% isolated yield (Scheme 1).

Synthesis of 2-[(4-methylphenyl)sulfonyl]oxetane 1a

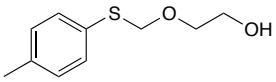




***p*-Methylphenyl chloromethyl sulfide (2a)**

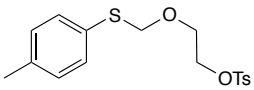
Potassium carbonate (122.2 g, 885 mmol) was added to a solution of 4-methyl benzene thiol **S1** (100 g, 805 mmol) in acetone (1 L) followed by MeI (52.6 mL, 845 mmol) and the reaction stirred at rt for 14 h. The reaction was filtered through celite and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with ether (150 mL) then the combined organics were washed with brine (100 mL), dried (Na_2SO_4) and solvent removed under reduced pressure to afford *p*-tolyl methyl sulfide **S2** (109.3 g, 98%) as a yellow liquid which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.11 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 2.48 (3 H, s, SCH_3), 2.33 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0 (Ar-C_q), 134.6 (Ar-C_q), 129.6 (2 × Ar-C), 127.22 (2 × Ar-C), 21.0 (Ar-CH_3), 16.5 (CH_3). The observed data (^{1}H) was consistent with that reported in the literature.[2]

N-Chlorosuccinimide (33.4 g, 250 mmol) was added portionwise to a solution of *p*-tolyl methyl sulfide **(S2)** (34.6 g, 228 mmol) in carbon tetrachloride (250 mL). The reaction was stirred at rt for 14.5 h then filtered through a short pad of silica, eluting with CCl_4 (30 mL) and the solvent removed under reduced pressure. Purification by vacuum distillation afforded chloromethyl sulfide **2a** (36.9 g, 94%) as an orange oil. b.p. = 98 ºC at 2.1 mbar (lit. b.p. = 88 ºC at 0.2 Torr).[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2 H, d, *J* = 8.5 Hz, 2 × Ph-H), 7.21 (2 H, d, *J* = 8.5 Hz, 2 × Ph-H), 4.95 (2 H, s, CH_2), 2.39 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (Ar-C_q), 131.6 (2 × Ar-C), 129.9 (2 × Ar-C), 129.4 (Ar-C_q), 51.9 (CH_2), 21.1 (CH_3). The observed data (^{1}H, ^{13}C) was consistent with that reported in the literature.[4]



***p*-Tolyl sulfanylmethoxy-ethanol (3a)**

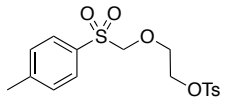
Sodium hydride (60% in mineral oil, 2.57 g, 64.2 mmol) was added to ethylene glycol (400 mL) at 0 ºC and stirred for 1 h 15 min. Sodium iodide (9.62 g, 64.2 mmol) was added followed by a solution of sulfide **2a** (10.04 g, 58.4 mmol) in ethylene glycol (5 mL). The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 4 h. H_2O (300 mL) was added and the product was extracted with ethyl acetate (10 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded alcohol **3a** (9.60 g, 83%) as a yellow oil. R_f = 0.34 (50% EtOAc/hexane). IR (film)/cm^{-1} 3449, 2926, 2872, 1734, 1493, 1461, 1373, 1250, 1052, 1017, 806, 734. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 7.13 (2 H, d, *J* = 8.1 Hz, 2 × Ar-H), 5.00 (2 H, s, SCH_2O), 3.78–3.72 (4 H, m, OCH_2CH_2), 2.34 (3 H, s, CH_3), 1.94 (1 H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (Ar-C_q), 131.5 (Ar-C_q), 131.1 (2 × Ar-C), 129.8 (2 × Ar-C), 77.0 (SCH_2O), 69.7 (OCH_2), 61.7 (OCH_2), 21.1 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{10}H_{14}NaO_2S^+$ $[M+Na]^+$: 221.0607; Found: 221.0607 $[M+Na]^+$.



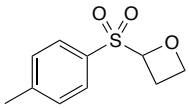
Toluene-4-sulfonic acid 2-*p* –tolylsulfanylmethoxy ethyl ester (S3)

Triethylamine (3.14 mL, 22.5 mmol) and trimethylamine hydrochloride (70 mg, 0.75 mmol) were added to a solution of sulfide **3a** (1.50 g, 7.5 mmol) in toluene (10 mL) at 0 ºC and stirred for 10 min. A suspension of 4-toluenesulfonyl chloride (2.86 g, 15 mmol) in toluene (10 mL) was added dropwise. The mixture was stirred at 0 ºC for 30 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 20 min. H_2O (100 mL) was added to the reaction and the product was extracted with EtOAc (4 × 50 mL). The

combined organic layers were washed with brine (50 mL) and H_2O (30 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded tosylate **S3** (2.50 g, 97%) as a yellow oil. R_f = 0.34 (40% EtOAc/hexane). IR (film)/cm^{-1} 2984, 2891, 1734, 1596,1499, 1362, 1237, 1175, 1095, 1011, 915, 807. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2 H, d, *J* = 8.2 Hz, 2 × Ts-H), 7.34–7.30 (4 H, m, 2 × Ts-H + 2 × Tol-H), 7.10 (2 H, d, *J* = 8.2 Hz, 2 × Tol-H), 4.90 (2 H, s, SCH_2O), 4.22–4.18 (2 H, m, $TsOCH_2$), 3.83–3.78 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, Ts-CH_3), 2.33 (3 H, s, Tol-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (Ts-C_q), 137.1 (Tol-C_q), 132.9 (Ts-C_q), 131.4 (Tol-C_q), 131.0 (2 × Ar-C), 129.8 (2 × Ar-C), 129.7 (2 × Ar-C), 127.9 (2 × Ar-C), 76.8 (SCH_2O), 68.7 (SCH_2OCH_2), 65.5 ($TsOCH_2$), 21.6 (Ts-CH_3), 21.0 (Tol-CH_3). HRMS (ESI) *m/z* Calculated for $C_{17}H_{24}NO_4S_2^+$ $[M+NH_4]^+$: 370.1141; Found: 370.1134 $[M+NH_4]^+$.

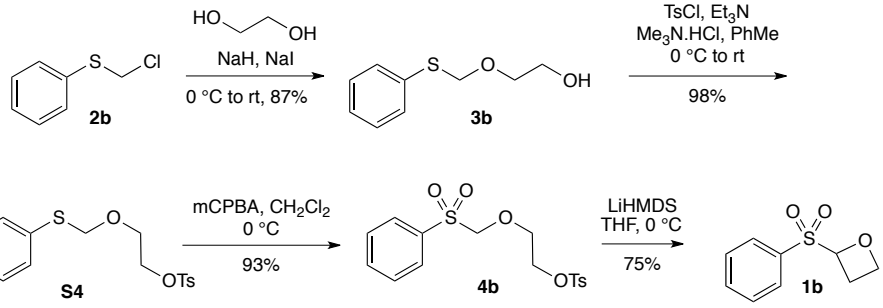


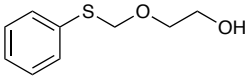
Toluene-4-sulfonic acid 2–toluene 4-sulfonylmethoxy ethyl ester (4a)
meta-Chloroperbenzoic acid (1.47 g 8.50 mmol) was added to a solution of sulfide **S3** (1.00 g, 2.84 mmol) in dichloromethane (15 mL) at 0 ºC and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with Na_2SO_3 (25 mL) and extracted with dichloromethane (6 × 20 mL). The combined organic layers were washed with 1 M NaOH (3 × 15 mL) and sat. aq. NH_4Cl (50 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **4a** (1.04 g, 96%) as a white solid; mp = 73–79 ºC. R_f = 0.65 (EtOAc). IR (film)/cm^{-1} 2992, 2926, 2885, 1599, 1461, 1350, 1327, 1300, 1170, 1130, 1080, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (4 H, m, 4 × Ar-H), 7.41–7.35 (4 H, m, 4 × Ar-H), 4.52 (2 H, s, SCH_2O), 4.19–4.15 (2 H, m, $TsOCH_2$), 4.12–4.08 (2 H, m, $TsOCH_2CH_2$), 2.49 (3 H, s, Ts-CH_3), 2.48 (3 H, s, Tol-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (Ar-C_q), 145.0 (Ar-C_q), 133.9 (Ar-C_q), 132.7 (Ar-C_q), 130.0 (2 × Ar-C), 129.9 (2 × Ar-C), 128.9 (2 × Ar-C), 127.9 (2 × Ar-C), 86.2 (SCH_2O), 70.6 ($TsOCH_2CH_2$), 68.5 ($TsOCH_2$), 21.7 (CH_3), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{17}H_{24}NO_6S_2^+$ $[M+NH_4]^+$: 402.1040; Found: 402.1040 $[M+NH_4]^+$.



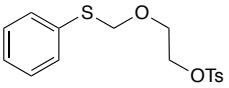
2-[(4-Methylphenyl)sulfonyl] oxetane (1a)
A solution of LiHMDS (0.61 M in THF, 11.7 mL, 7.16 mmol) was added dropwise to a solution of sulfone **4a** (2.50 g, 6.51 mmol) in THF (250 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (200 mL) and extracted with $CHCl_3$ (8 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **1a** (1.28 g, 93%) as a white solid; mp = 106–108 ºC. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 2977, 2901, 1596, 1447, 1406, 1310, 1147, 1089, 1030, 984, 909, 816, 717. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.4, 5.6 Hz, OC*H*S), 4.80–4.74 (1 H, m, OCH*H*), 4.67–4.61 (1 H, m, OC*H*H), 3.17–3.05 (2 H, m, OCH_2CH_2), 2.47 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (Ar-C_q), 132.2 (Ar-C_q), 129.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (O*C*HS), 71.3 (OCH_2), 22.4 (OCH_2CH_2), 21.7 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{10}H_{13}O_3S^+$ $[M+H]^+$: 213.0580; Found: 213.0580 $[M+H]^+$.

Synthesis of 2-[(phenyl)sulfonyl]oxetane 1b

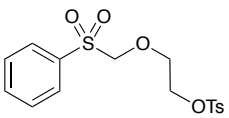




2-((Phenylthio)methoxy)ethanol (3b)
Sodium hydride (60% in mineral oil, 0.70 g, 17.6 mmol) was added to ethylene glycol (100 mL) at 0 ºC and stirred for 1 h 15 min. Sodium iodide (2.60 g, 17.3 mmol) was added followed by sulfide **2b** (2.50 g, 15.7 mmol). The resulting solution was stirred at 0 ºC for 1 h then warmed to rt for 5 h. H_2O (100 mL) was added and the product was extracted with ethyl acetate (6 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/heptane) afforded alcohol **3b** (2.54 g, 87%) as a colourless oil. R_f = 0.42 (50%, EtOAc/heptane). IR (film)/cm^{-1} 3402, 2927, 1583, 1480, 1438, 1370, 1304, 1102, 1053, 887, 823, 690, 673. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (2 H, m, 2 × Ar-H), 7.33–7.27 (2 H, m, 2 × Ar-H), 7.23 (1 H, tt, *J* = 7.3, 1.4 Hz), 5.03 (2 H, s, SCH_2O), 3.74–3.69 (4 H, m, OCH_2CH_2), 2.32 (1 H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (Ar-C_q), 130.4 (2 × Ar-C), 129.0 (2 × Ar-C), 126.9 (Ar-C), 76.4 (SCH_2O), 69.9 (OCH_2), 61.6 (OCH_2). HRMS (EI) *m/z* Calculated for $C_9H_{12}O_2S^+$ $[M]^+$: 184.0553; Found: 184.0550 $[M]^+$.

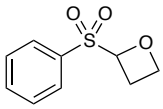


2-((Phenylthio)methoxy)ethyl 4-methylbenzenesulfonate (S4)
Triethylamine (5.54 mL, 39.7 mmol) and trimethylamine hydrochloride (127 mg, 1.32 mmol) were added to a solution of sulfide **3b** (2.44 g, 13.2 mmol) in toluene (20 mL) at 0 ºC and stirred for 20 min. A suspension of 4-toluenesulfonyl chloride (5.05 g, 26.5 mmol) in toluene (15 mL) was added dropwise. The mixture was stirred at 0 ºC for 35 min then allowed to warm to rt slowly over 40 min and stirred for a further 1 h 30 min. H_2O (150 mL) was added to the reaction and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/heptane) afforded tosylate **S4** (4.40 g, 98%) as a colourless oil. R_f = 0.49 (40% EtOAc/heptane). IR (film)/cm^{-1} 2972, 2903, 1593, 1566, 1468, 1443, 1389, 1314, 1270, 1231, 1185, 1064, 1029, 938, 908, 859, 829, 737, 722, 697, 677. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.43–7.39 (2 H, m, 2 × Ph-H), 7.30 (2 H, d, *J* = 8.3 Hz, 2 ×Ts-H), 7.29–7.19 (3 H, m, 3 × Ph-H), 4.93 (2 H, s, SCH_2O), 4.21–4.18 (2 H, m,$TsOCH_2$), 3.81–3.79 (2 H, m, CH_2OCH_2), 2.43 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (Ts-C_q), 135.3 (Ph-C_q), 133.0 (Ts-C_q), 130.3 (2 × Ar-C), 129.8 (2 × Ar-C), 128.9 (2 × Ar-C), 127.9 (2 × Ar-C), 126.9 (Ar-C), 76.3 (SCH_2O), 68.7 (SCH_2OCH_2), 65.7 ($TsOCH_2$), 21.6 (CH_3). HRMS (CI) *m/z* Calculated for $C_{16}H_{22}NO_4S_2^+$ $[M+NH_4]^+$: 356.0990; Found: 356.0997 $[M+NH_4]^+$.



2-((Phenylthio)methoxy)ethyl 4-methylbenzenesulfonate (4b)
meta-Chloroperbenzoic acid (8.34 g, 37.2 mmol) was added to a solution of sulfide **S4** (4.20 g, 12.4 mmol) in dichloromethane (65 mL) at 0 ºC and the mixture stirred at 0 ºC for 4 h. The reaction was quenched with Na_2SO_3 (60 mL) and extracted with dichloromethane (5 × 30 mL). The combined organic layers were washed with 2 M NaOH (3 × 30 mL) and sat. aq. NH_4Cl (60 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/heptane) afforded sulfone **4b** (4.27 g, 93%) as a white solid, mp = 82–83 ºC. R_f = 0.19 (40% EtOAc/heptane). IR (film)/cm^{-1} 3071, 1594, 1493, 1445, 1419, 1323, 1296, 1251, 1149, 1127, 1080, 1016, 927, 939, 893, 818, 803, 705. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.90 (2 H, m,

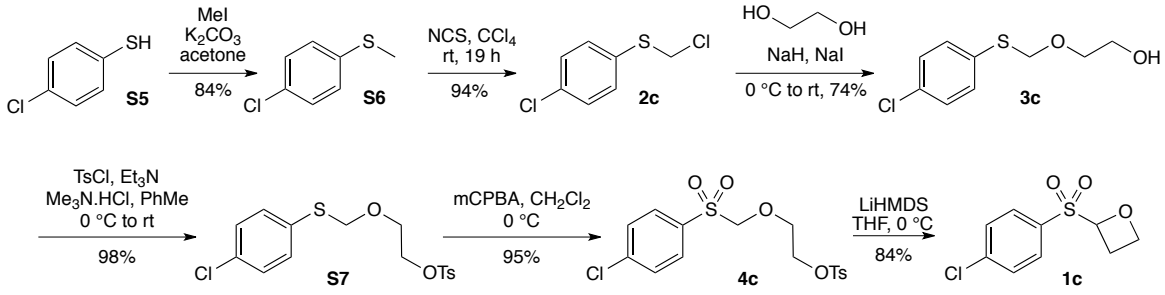
2 × Ts-H), 7.77 (2 H, dt, *J* = 8.3, 2.1 Hz, 2 × Ph-H), 7.70 (1 H, tt, *J* = 7.4, 1.3 Hz, Ph-H), 7.61–7.56 (2 H, m, 2 × Ph-H), 7.35–7.31 (2 H, m, 2 × Ts-H), 4.52 (2 H, s, SCH_2O), 4.18–4.15 (2 H, m,$TsOCH_2$), 4.10–4.08 (2 H, m, CH_2OCH_2). 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ar-C_q), 137.0 (Ar-C_q), 134.2 (Ph-C), 132.8 (Ar-C_q), 129.9 (2 × Ar-C), 129.3 (2 × Ar-C), 128.8 (2 × Ar-C), 127.9 (2 × Ar-C), 86.2 (SCH_2O), 70.7 (SCH_2OCH_2), 68.4 ($TsOCH_2$), 21.6 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{18}O_6S_2Na^+$ $[M+Na]^+$: 393.0442; Found: 393.0451 $[M+Na]^+$.

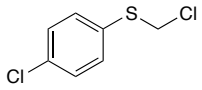


2-(Phenylsulfonyl)oxetane (1b)

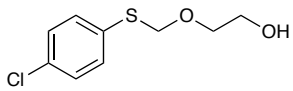
A solution of LiHMDS (0.61 M in THF, 12.2 mL, 7.4 mmol) was added dropwise to a solution of sulfone **4b** (2.50 g, 6.75 mmol) in THF (240 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (150 mL) and extracted with CH_2Cl_2 (5 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/heptane) afforded oxetane **1b** (1.01 g, 75%) as a white solid, mp = 87–88 ºC. R_f = 0.23 (40% EtOAc/heptane). IR (film)/cm^{-1} 2996, 2980, 2908, 1583, 1478, 1445, 1301, 1288, 1266, 1144, 1084, 1026, 977, 901, 762, 730. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.97 (2 H, m, 2 × Ar-H), 7.70 (1 H, tt, *J* = 7.5, 1.4 Hz, Ar-H), 7.62–7.56 (2 H, m, 2 × Ar-H), 5.39 (1 H, dd, *J* = 7.1, 6.0 Hz, OC*H*S), 4.81–4.76 (1 H, m, OCH*H*), 4.67–4.62 (1 H, m, OC*H*H), 3.16–3.07 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5 (Ar-C_q), 134.2 (Ar-C), 129.5 (2 × Ar-C), 129.2 (2 × Ar-C), 94.1 (O*C*HS), 71.4 (OCH_2), 22.4 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_9H_{11}O_3S^+$ $[M+H]^+$: 199.0423; Found: 199.0423 $[M+H]^+$.

Synthesis of 2-[(4-chlorophenyl)sulfonyl] oxetane 1c

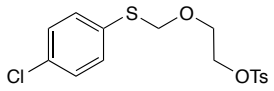




Chloromethyl 4-chlorophenyl sulfide (2c)
Potassium carbonate (109.7 g, 795 mmol) was added to a solution of 4-chloro benzene thiol **S5** (95 g, 722 mmol) in acetone (1.1 L) followed by MeI (50.5 mL, 811 mmol) and the reaction stirred at rt for 4 h. The reaction was filtered through celite and the solvent removed under reduced pressure. The crude material was dissolved in diethyl ether (300 mL) and washed with 5% NaOH (3 × 150 mL). The combined aqueous layers were extracted with ether (2 × 100 mL) then the combined organics were washed with brine (100 mL), dried (Na_2SO_4) and solvent removed under reduced pressure to afford 4-chlorophenyl methyl sulfide **S6** (96.5 g, 84%) as a yellow liquid which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2 H, m, 2 × Ar-H), 7.20 (2 H, m, 2 × Ar-H), 2.49 (3 H, s, SCH_3).
N-Chlorosuccinimide (9.26 g, 69 mmol) was added portionwise to a solution of 4-chloro phenyl methyl sulfide **S6** (10 g, 63 mmol) in carbon tetrachloride (65 mL). The reaction was stirred at rt for 19 h then filtered through a short pad of silica, eluting with CCl_4 (30 mL), and the solvent removed under reduced pressure to afforded chloromethyl 4-chlorophenyl sulfide **2c** (11.5 g, 94%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 7.36 (2 H, d, *J* = 8.9 Hz, 2 × Ar-H), 4.94 (2 H, s, SCH_2Cl). The observed data (^{1}H) was consistent with that reported in the literature.[5]

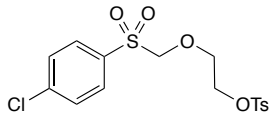


2-(((4-Chlorophenyl)thio)methoxy)ethanol (3c)
Sodium hydride (60% in mineral oil, 1.56 g, 38.9 mmol) was added to ethylene glycol (200 mL) at 0 ºC and stirred for 30 min. Sodium iodide (5.83 g, 38.9 mmol) was added followed by chloromethyl 4-chlorophenyl sulfide **2c** (6.26 g, 32.4 mmol) using DMF (5 mL) to aid transfer. The resulting solution was stirred at 0 ºC for 3 h then warmed to rt for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (200 mL) and the mixture extracted with EtOAc (4 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded alcohol **3c** (5.27 g, 74%) as a colourless oil. R_f = 0.31 (50% EtOAc/hexane). IR (film)/cm^{-1} 3388, 2934, 2872, 1481, 1392, 1313, 1095, 1059, 1013, 816, 683. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.36 (2 H, m, 2 × Ar-H), 7.31–7.23 (2 H, m, 2 × Ar-H), 5.01 (2 H, s, SCH_2O), 3.80–3.69 (4 H, m, OCH_2CH_2), 2.08 (1 H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9 (Ar-C_q), 133.0 (Ar-C_q), 131.6 (2 × Ar-C), 129.1 (2 × Ar-C), 76.4 (SCH_2O), 69.8 (OCH_2), 61.5 (OCH_2). HRMS (ESI) *m/z* Calculated for $C_9H_{11}ClNaO_2S^+$ $[M+Na]^+$: 241.0060; Found: 241.0060 $[M+Na]^+$.



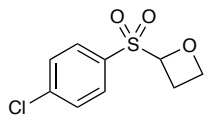
2-(((4-Chlorophenyl)thio)methoxy)ethyl 4-methylbenzenesulfonate (S7)
Triethylamine (6.19 mL, 44.4 mmol) and trimethylamine hydrochloride (141 mg, 1.48 mmol) were added to a solution of alcohol **3c** (3.24 g, 14.8 mmol) in toluene (40 mL) at 0 ºC and stirred for 20 min. 4-Toluenesulfonyl chloride (5.65 g, 29.6 mmol) was added portionwise. The mixture was stirred at 0 ºC for 30 min then at rt for 2h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (200 mL) and the mixture extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. NH_4Cl (100 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded tosylate **S7** (5.39 g, 98%) as a colourless oil. R_f = 0.24 (20% EtOAc/hexane). IR (film)/cm^{-1} 2920, 1601,1482, 1358, 1180, 1095, 1093, 1017, 922, 820, 776, 668, 559. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d,

J = 8.3 Hz, 2 × Ts-H), 7.38–7.31 (4 H, m, 2 × Ts-H + 2 × Ar-H), 7.26–7.20 (2 H, m, 2 × Ar-H), 4.92 (2 H, s, SCH_2O), 4.23–4.19 (2 H, m, $TsOCH_2$), 3.84–3.80 (2 H, m, CH_2OCH_2), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ts-C_q), 133.7 (Ar-C_q), 133.0 (Ts-C_q), 132.8 (Ar-C_q), 131.7 (2 × Ar-C), 129.8 (2 × Ar-C), 129.0 (2 × Ar-C), 127.9 (2 × Ar-C), 76.3 (SCH_2O), 68.6 (SCH_2OCH_2), 65.6 ($TsOCH_2$), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{21}ClNO_4S_2^+$ $[M+NH_4]^+$: 390.0595; Found: 390.0595 $[M+NH_4]^+$.



2-(((4-Chlorophenyl)sulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (4c)

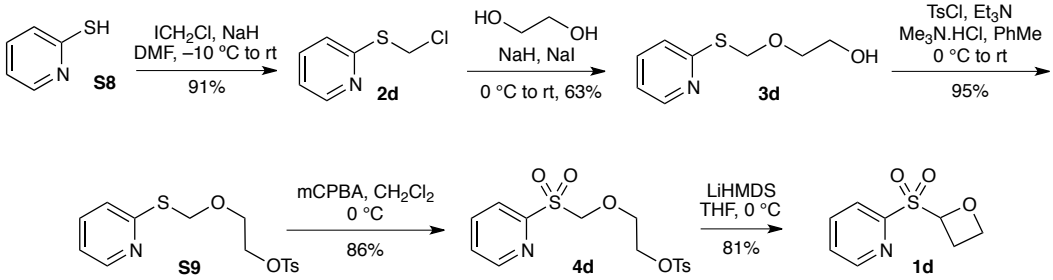
meta-Chloroperbenzoic acid (7.5 g 43.5 mmol) was added to a solution of sulfide **S7** (5.39g, 14.5 mmol) in dichloromethane (75 mL) at 0 ºC and the mixture stirred at 0 ºC for 5 h. The reaction was quenched with Na_2SO_3 (125 mL) and extracted with dichloromethane (6 × 35 mL). The combined organic layers were washed with 1 M NaOH (3 × 25 mL) and sat. aq. NH_4Cl (100 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/hexane) afforded sulfone **4c** (5.58 g, 95%) as a white solid, mp = 87–88 ºC. R_f = 0.19 (40% EtOAc/hexane). IR (film)/cm^{-1} 3130, 2952, 2892, 1578, 1495, 1474, 1423, 1397, 1357, 1323, 1291, 1135, 1108, 1040, 1017, 948, 804, 728, 701, 686. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2 H, d, *J* = 9.0 Hz, 2 × Ts-H), 7.77 (2 H, d, *J* = 7.8 Hz, 2 × Ar-H), 7.54 (2 H, d, *J* = 9.0 Hz, 2 × Ts-H), 7.35 (2 H, d, *J* = 7.8 Hz, 2 × Ar-H), 4.53 (2 H, s, SCH_2), 4.18–4.10 (4 H, m, 2 × CH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ts-C_q), 141.1 (Ar-C_q), 135.2 (Ts-C_q), 132.6 (Ar-C_q), 130.4 (2 × Ar-C), 129.9 (2 × Ar-C), 129.6 (2 × Ar-C), 127.9 (2 × Ar-C), 86.0 (SCH_2O), 70.6 ($TsOCH_2CH_2$), 68.4 ($TsOCH_2$), 21.7 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{16}H_{17}ClNaO_6S_2^+$ $[M+Na]^+$: 427.0047 Found: 427.0044 $[M+Na]^+$.

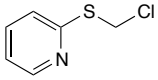


2-((4-Chlorophenyl)sulfonyl)oxetane (1c)

A solution of LiHMDS (0.61 M in THF, 4.45 mL, 2.72 mmol) was added dropwise to a solution of sulfone **4c** (0.99 g, 2.47 mmol) in THF (100 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (100 mL) and extracted with $CHCl_3$ (8 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/hexane) afforded oxetane **1c** (0.48 g, 84%) as a white solid, mp = 91–93 ºC. R_f = 0.36 (40% EtOAc/hexane). IR (film)/cm^{-1} 3092, 2977, 2927, 1654, 1581, 1474, 1393, 1312, 1273, 1144, 1087, 1010, 976, 940, 897, 843, 712. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.56 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 7.6, 5.4 Hz, OC*H*S), 4.83–4.77 (1 H, m, OCH*H*), 4.66 (1 H, dt, *J* = 8.6, 6.1 Hz, OC*H*H), 3.18–3.05 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (Ar-C_q), 133.7 (Ar-C_q), 130.9 (2 × Ar-C), 129.5 (2 × Ar-C), 94.0 (O*C*HS), 71.5 (OCH_2), 22.2 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_9H_{10}ClO_3S^+$ $[M+H]^+$: 233.0034 Found: 233.0034 $[M+H]^+$.

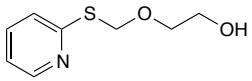
Synthesis of 2-(Oxetan-2-ylsulfonyl)pyridine 1d





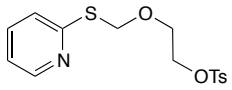
2-((Chloromethly)thio)pyridine (2d)

Sodium hydride (60% in mineral oil, 0.79 g, 19.8 mmol) was added to a solution of 2-mercaptopyridine **S8** (2.0 g, 18.0 mmol) in DMF (50 mL) at –5 ºC and stirred for 10 min. A solution of chloroiodomethane (1.96 mL, 27 mmol) in DMF (7 mL) was added in one portion and stirred for 1 h 45 min at rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted with EtOAc (30 mL) then extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give an orange oil. The crude product consisting of a 9:1 mixture of 2-((chloromethly)thio)pyridine **2d** and bis(pyridine-2-ylthio)methane (2.6 g, 91%, 9:1) was used without further purification. R_f = 0.80 (40% EtOAc/heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56–8.54 (1 H, m, Py-H), 7.58 (1 H, ddd, *J* = 8.0, 7.4, 1.9 Hz, Py-H), 7.27 (1 H, dt, *J* = 8.0, 1.0 Hz, Py-H), 7.11 (1 H, ddd, *J* = 7.4, 4.9, 1.0 Hz, Py-H), 5.38 (2 H, s, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (Py-C_q), 149.9 (Py-C), 136.6 (Py-C), 122.9 (Py-C), 120.8 (Py-C), 45.3 (SCH_2Cl). The observed data (^{1}H) was consistent with that reported in the literature.[6]



2-((Pyridine-2-ylthio)methoxy)ethanol (3d)

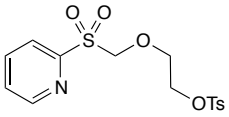
Sodium hydride (60% in mineral oil, 0.55 g, 13.78 mmol) was added to ethylene glycol (120 mL) at 0 ºC and stirred for 55 min. Sodium iodide (2.06 g, 13.78 mmol) was added followed by 2-((chloromethly)thio)pyridine **2d** (2.0 g, 12.53 mmol) using ethylene glycol (1 mL) to aid transfer. The resulting solution was stirred at 0 ºC for 25 min then warmed to rt for 19 h 20 min. The reaction was quenched by the addition of water (150 mL) and the mixture extracted with EtOAc (10 × 35 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–80% EtOAc/heptane) afforded alcohol **3d** (1.46 g, 63%) as a colourless oil. R_f = 0.59 (80% EtOAc/heptane). IR (film)/cm^{-1} 3344, 2925, 1656, 1577, 1454, 1416, 1281, 1102, 1060, 908, 824, 758, 721, 678. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46–8.44 (1 H, m, Py-H), 7.52 (1 H, ddd, *J* = 8.0, 7.2, 1.9 Hz, Py-H), 7.29 (1 H, dt, *J* = 8.0, 1.0 Hz, Py-H), 7.04 (1 H, ddd, *J* = 7.3, 5.0, 1.0 Hz, Py-H), 5.38 (2 H, s, SCH_2O), 3.77–3.72 (4 H, m, OCH_2CH_2), 2.95 (1 H, br, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (Py-C_q), 149.5 (Py-C), 136.5 (Py-C), 123.2 (Py-C), 120.4 (Py-C), 71.9 (SCH_2O), 70.5 (OCH_2CH_2), 61.6 (OCH_2CH_2). HRMS (ESI) *m/z* Calculated for $C_8H_{12}NO_2S^+$ $[M+H]^+$: 186.0583 Found: 186.0582 $[M+H]^+$.



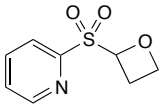
2-((Pyridin-2-ylthio)methoxy)ethyl 4-methylbenzenesulfonate (S9)

Triethylamine (4.06 mL, 29.2 mmol) and trimethylamine hydrochloride (93 mg, 0.97 mmol) were added to a solution of alcohol **3d** (0.90 g, 4.86 mmol) in toluene (30 mL) at 0 ºC and stirred for 30 min. A solution of 4-toluenesulfonyl chloride (3.71 g, 19.4 mmol) in toluene (10 mL) was added and the mixture was stirred at 0 ºC for 35 min then at rt for 2 h 35 min. The reaction was quenched by the addition of water (50 mL) and the mixture extracted with EtOAc (7 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–40% EtOAc/heptane) afforded tosylate **S9** (1.57 g, 95%) as a colourless oil. R_f = 0.36 (40% EtOAc/heptane). IR (film)/cm^{-1} 307, 2924, 1610, 1533, 1494, 1453, 1419, 1353, 1281, 1216, 1172, 1119, 1032, 1009, 916, 816, 767, 680. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43–8.41 (1 H, m, Py-H), 7.76 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.50 (1 H, ddd, *J* = 8.0, 7.4, 1.9 Hz, Py-H), 7.31 (2 H, d, *J* = 8.3 Hz, 2 × Ts-H), 7.24 (1 H, dt, *J* = 8.0, 1.0 Hz, Py-H), 7.02 (1 H,

ddd, *J* = 7.4, 4.9, 1.0 Hz, Py-H), 5.32 (2 H, s, SCH_2O), 4.18–4.16 (2 H, m, OCH_2CH_2), 3.79–3.76 (2 H, m, OCH_2CH_2), 2.42 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (Py-C_q), 149.4 (Py-C), 144.7 (Ts-C_q), 136.4 (Py-C), 133.0 (Ts-C_q), 129.7 (2 × Ts-C), 127.8 (2 × Ts-C), 122.8 (Py-C), 120.3 (Py-C), 71.8 (SCH_2O), 68.7 (OCH_2CH_2), 66.2 (OCH_2CH_2), 21.5 (CH_3). HRMS (NSI) *m/z* Calculated for $C_{15}H_{18}NO_4S_2^+$ $[M+H]^+$: 340.0672 Found: 340.0674 $[M+H]^+$.



2-((Pyridin-2-ylsulfonyl)methoxy)ethyl 4-methylbenzenesulfonate (4d)
meta-Chloroperbenzoic acid (3.05 g 12.4 mmol) was added to a solution of sulfide **S9** (1.40 g, 4.12 mmol) in dichloromethane (25 mL) at 0 ºC and the mixture stirred at 0 ºC for 2 h then at rt for a further 2.5 h. The reaction was quenched with Na_2SO_3 (20 mL) and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with 2 M NaOH (3 × 10 mL) and sat. aq. NH_4Cl (20 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (50% EtOAc/heptane) afforded sulfone **4d** (1.31 g, 86%) as a white solid, mp = 95–97 ºC. R_f = 0.46 (40% EtOAc/heptane). IR (film)/cm^{-1} 3069, 1598, 1454, 1431, 1358, 1323, 1238, 1173, 1127, 1104, 1032, 990, 926, 836, 824, 808, 736, 663. ^1H NMR (400 MHz, $CDCl_3$) δ 8.79–8.77 (1 H, m, Py-H), 8.11 (1 H, dt, *J* = 7.8, 1.0 Hz, Py-H), 8.00 (1 H, td, *J* = 7.8, 1.7 Hz, Py-H), 7.73 (2 H, d, *J* = 8.3 Hz, 2 × Tol-H), 7.59 (1 H, ddd, *J* = 7.8, 4.7, 1.3, Py-H), 7.33 (2 H, d, *J* = 8.3 Hz, Tol-H), 4.87 (2 H, s, SCH_2O), 4.10–4.08 (2 H, m, OCH_2CH_2OTs), 4.05–4.03 (2 H, m, OCH_2CH_2OTs), 2.45 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (Py-C_q), 150.4 (Py-C), 145.0 (Ts-C_q), 138.2 (Py-C), 132.7 (Ts-C_q), 129.8 (2 × Ts-C), 127.8 (2 × Ts-C), 127.6 (Py-C), 123.8 (Py-C), 82.9 (SCH_2O), 70.5 (OCH_2CH_2OTs), 68.4 (OCH_2CH_2OTs), 21.6 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{15}H_{18}NO_6S_2^+$ $[M+H]^+$: 372.0570 Found: 372.0576 $[M+H]^+$.



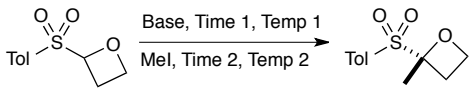
2-(Oxetan-2-ylsulfonyl)pyridine (1d)
A solution of LiHMDS (0.61 M in THF, 4.08 mL, 2.49 mmol) was added dropwise to a solution of sulfone **4d** (0.56 g, 1.52 mmol) in THF (70 mL) at 0 ºC and stirred for 1 h. Reaction quenched with sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (40% EtOAc/heptane) afforded oxetane **1d** (0.25 g, 81%) as a white solid, mp = 64–65 ºC. R_f = 0.16 (40% EtOAc/heptane). IR (film)/cm^{-1} 3101, 3051, 2974, 2904, 1580, 1426, 1415, 1311, 1272, 1230, 1161, 1108, 1040, 1024, 991, 906, 792, 734, 682. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77–8.75 (1 H, m, Py-H), 8.17 (1 H, dt, *J* = 7.8, 1.0 Hz, Py-H), 7.97 (1 H, td, *J* = 7.8, 1.8 Hz, Py-H), 7.56 (1 H, ddd, *J* = 7.7, 4.7, 1.2, Py-H), 5.96 (1 H, dd, *J* = 8.0, 5.2 Hz, OC*H*S), 4.93–4.87 (1 H, m, OCH*H*), 4.71–4.66 (1 H, m, OC*H*H), 3.31–3.15 (2 H, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (Py-C_q), 150.4 (Py-C), 138.0 (Py-C), 127.6 (Py-C), 124.3 (Py-C), 91.9 (O*C*HS), 72.0 (OCH_2), 21.9 (OCH_2CH_2). HRMS (ESI) *m/z* Calculated for $C_8H_{10}NO_3S^+$ $[M+H]^+$: 200.0386; Found: 200.0389 $[M+H]^+$.

Optimisation of Deprotonation of 1a for Reaction with Electrophiles

With LiHMDS (Conditions A, Table 1)

Under the initial conditions oxetane **1a** was treated with various bases at T1 for time 1 prior to the addition of MeI to form oxetane **5**. The reaction was then warmed to T2 over time 2. Entries 1-4 in table S2 show that under these conditions LiHMDS was the best base affording a yield of 76%. Warming to 0 ºC was required; quenching the reaction at –78 ºC afforded a much lower yield (entry 5). Increasing the deprotonation time to 30 min did increase the yield to 84% (entry 6). The equivalents of LiHMDS employed were also investigated however it was found that increasing the equivalents to 1.3 and 1.5 did not affect the reaction yield. The addition of the substrate in THF to a solution of the base was favourable over the addition of the base to the substrate (entries 6 and 7). Finally we investigated the addition of MeI immediately after the addition of base. Pleasingly this increased the yield of the reaction with MeI to 90% (entry 8), and provided our optimised set of conditions A.

Table S2: Selected optimisation: deprotonation of oxetane **1a** to form oxetanes **5**.



1a **5**

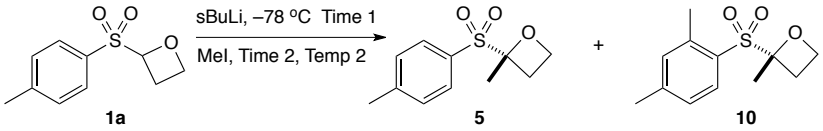
entry[a]	base	order of addition[b]	temperature 1 (T1, ºC)	temperature 2 (T2 ºC)	time 1 (min)	time 2 (min)	Yield[c]
1	LDA	B	–78	–78 to 0	15	45	62
2	*n*BuLi	B	–78	–78 to 0	15	45	49
3	*s*BuLi	B	–78	–78 to 0	15	45	20
4	LiHMDS	B	–78	–78 to 0	15	45	76
5	LiHMDS	B	–78	–78	15	45	22
6	LiHMDS	B	–78	–78 to 0	30	45	84
7	LiHMDS	A	–78	–78 to 0	30	45	61
8	**LiHMDS**	**B**	**–78**	**–78 to 0**	**90**		**90**

[a] Conditions: oxetane **1a** (0.24 mmol), base (1.1 equiv), at temp 1 for time 1; MeI (2 equiv) added then warmed to temp 2 for time 2. [b] Order of addition. A: addition of the base to a solution of the substrate; B: addition of the substrate to a solution of the base. [c] Yield determined by ^{1}H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard.

With *n*BuLi (Conditions B, Table 1)

During the course of this work, Capriati and co-workers reported the deprotonation of 2-phenyl-oxetane with *s*BuLi.[7] Consequently *s*BuLi was further examined to deprotonate the sulfonyl oxetane. A summary of the results is shown in Table S3.

Table S3: Selected optimisation: deprotonation of oxetane **1a** to form oxetanes **5**.



entry[a]	base	equiv. base	time 1 (min)	time 2 (min)	Temperature 2 (°C)	Yield[b] **5**	**1a**	**10**
1	*s*BuLi	1.1	5	25	–78	71	27	1
2	*s*BuLi	1.2	5	25	–78	77	4	3
3	*s*BuLi	1.4	5	25	–78	83	6	3
4	*s*BuLi	1.4	10	25	–78	84	4	12
5	*s*BuLi	1.1	10	25	–78	80	6	4
6	*s*BuLi	1.4	5	25	–78 to rt	68	0	20
7	*s*BuLi	1.4	35		–78	74	3	18
8	*n*BuLI	1.2	5	25	–78	64	21	0
9	***n*BuLi**	**1.3**	**5**	**25**	**–78**	**86**	**7**	**5**
10	*n*BuLi	1.4	5	25	–78	85	3	10

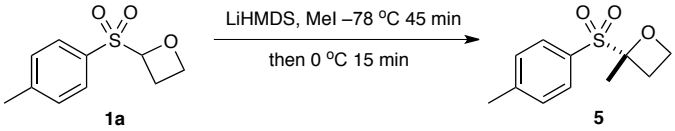
[a] Conditions: base added to oxetane **1a** (0.24 mmol), at –78 °C for time 1; MeI (2 equiv) added then warmed to temp 2 for time 2. [b] Yield determined by ^{1}H NMR with respect to 1,3,5 trimethoxybenzene as an internal standard.

The initial conditions employed 1.1 equivalents of *s*BuLi followed by the addition of 2 equivalents of MeI after 5 min. (table S3, entry 1). Two products were obtained, the desired methylated oxetane **5** but also 1% of the double methylated oxetane **10**, along with remaining **1a.** Increasing the equivalents of *s*BuLi employed from 1.1 to 1.2 and 1.4 increased the yield of the desired product however unreacted starting material and double methylated oxetane were also observed (table S3, entries 2 and 3). This implies that the second methylation occurs before all **1a** is consumed. Increasing the deprotonation time (time 1) afforded an increase in formation of oxetane **10** (entry 4). Using 1.1 equiv base with the longer deprotonation did reduce the formation of **10** but decreased the yield of the desired oxetane **5** as well (entry 5). Warming the reaction to rt immediately after addition of MeI significantly increased the amount of oxetane **10** formed and decreased the yield of oxetane **5**, however for the first time no unreacted starting material was observed (entry 6). The addition of MeI immediately after the addition of *s*BuLi was investigated (entry 7) but this was not an improvement on previous reaction conditions.

As a result we further investigated the use of *n*BuLi (entries 9-10), which displayed reduced formation of **10**. The optimal yield of oxetane **5** was achieved using 1.3 equiv *n*BuLi which limited the amounts of starting material and double methylated product whilst improving the yield of desired product to 86% (entry 9). This provided the second set of optimised conditions (conditions B).

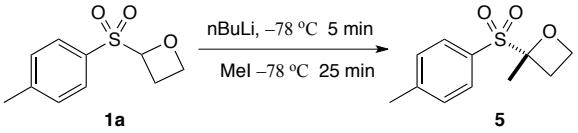
Synthesis of 2,2-disubstituted oxetanes 5-9 from oxetane 1a

General Procedure A (Table S2, entry 9; Conditions B Table 2)

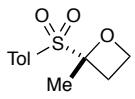


A solution of oxetane **1a** (50 mg, 0.24 mmol) in THF (1 mL) was added dropwise to a solution of LiHMDS (1 M in THF, 0.25 mL, 0.25 mmol) in THF (0.95 mL) at –78 ºC. The electrophile (for MeI: 0.03 mL, 0.47 mmol) was then added immediately and the reaction was stirred at –78 ºC for 1 h, before being warmed to 0 ºC in an ice bath for 15 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **5.**

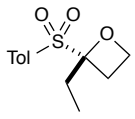
General Procedure B (Table S3, entry 8; Conditions B Table 2)



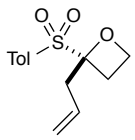
*n*BuLi (1.60 M in hexane, 0.18 mL, 0.28 mmol) was added dropwise to a solution of oxetane **1a** (50 mg, 0.22 mmol) in THF (1.2 mL) at –78 ºC and stirred at –78 ºC for 5 min. The electrophile (for MeI: 0.03 mL, 0.47 mmol) was added and the reaction stirred at –78 ºC for 25 min. The reaction was quenched by the addition of sat. aq. NH_4Cl (6 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) or by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **5.**



2-Methyl-2-[(4-methylphenyl)sulfonyl]oxetane (5)
Prepared according to the General Procedure A described above using methyl iodide (0.03 mL, 0.47 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **5** (51 mg, 93%) as a yellow solid. R_f = 0.27 (20% EtOAc/hexane). IR (film)/cm^{-1} 3064, 2978, 2906, 1602, 1444, 1375, 1287, 1141, 1113, 1075, 973, 941, 864, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 4.56–4.51 (1 H, m, OCH*H*), 4.45 (1 H, dt, *J* = 8.5, 5.4 Hz, OC*H*H), 3.25 (1 H, ddd, *J* = 12.4, 8.5, 5.4 Hz, OCH_2CH*H*), 2.76 (1 H, m, OCH_2C*H*H), 2.45 (3 H, s, Ar-CH_3), 1.64 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1 (Ar-C_q), 130.9 (Ar-C_q), 130.3 (2 × Ar-C), 129.6 (2 × Ar-C), 100.3 (C_q), 67.3 (OCH_2), 28.6 (OCH_2CH_2), 22.1 (CH_3), 21.7 (Ar-CH_3). HRMS (APCI) *m/z* Calculated for $C_{11}H_{15}O_3S^+$ $[M+H]^+$: 227.0736; Found: 227.0736 $[M+H]^+$.

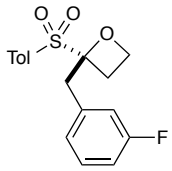


2-Ethyl-2-[(4-methylphenyl)sulfonyl]oxetane (6)
Prepared according to the General Procedure A described above using ethyl iodide (0.04 mL, 0.46 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **6** (47 mg, 85%) as a white solid. R_f = 0.44 (40% EtOAc/hexane). IR (film)/cm^{-1} 2971, 2899, 1596, 1460, 1309, 1299. 1288, 1237,1113, 1076, 1035, 967, 952, 931, 853, 813, 707. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.37 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 4.55–4.50 (1 H, m, OCH*H*),, 4.38 (1 H, dt, *J* = 8.7, 5.6 Hz, OC*H*H), 3.16–3.09 (1 H, m, OCH_2CH*H*), 2.91–2.84 (1 H, m , OCH_2C*H*H), 2.45 (3 H, s, Ar-CH_3), 2.00–1.91 (1 H, m, CCH*H*CH_3), 1.76–1.65 (1H, m, CC*H*HCH_3), 1.17 (3 H, t, *J* = 7.6 Hz, CCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (Ar-C_q), 131.5 (Ar-C_q), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 103.5 (C_q), 67.8 (OCH_2), 26.2 (CCH_2CH_3), 24.1 (OCH_2CH_2), 21.6 (Ar-CH_3), 7.1 (CH_3). HRMS (ESI) *m/z* Calculated for $C_{12}H_{17}O_3S^+$ $[M+H]^+$: 241.0893; Found: 241.0894 $[M+H]^+$.



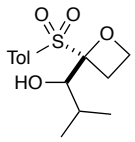
2-Allyl-2-tosyloxetane (7)

Prepared according to the General Procedure A described above using allyl bromide (0.04 mL, 0.48 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **7** (54 mg, 91%) as an orange solid. R_f = 0.28 (20% EtOAc/hexane)**.** IR (film)/cm^{-1} 2970, 2899, 1641, 1597, 1403, 1300, 1288, 1235, 1156, 1106 1070, 944, 857, 814, 710. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.2 Hz, 2 × Ar-H), 6.08–5.89 (1 H, m, C*H*=), 5.33–5.24 (2 H, m, =C*H*$_2$), 4.46 (1 H, ddd, *J* = 8.6, 7.5, 5,5 Hz, OC*H*H), 4.32 (1 H, ddd, *J* = 8.9, 5.7, 5,5 Hz, OCH*H*), 3.06 (1 H, ddd, *J* = 12.7, 8.6, 5.7 Hz, OCH$_2$C*H*H), 2.87 (1 H, ddd, *J* = 12.7, 8.9, 7.5 Hz, OCH$_2$CH*H*), 2.61 (1 H, dd, *J* = 14.6, 8.8 Hz, C*H*HCH=CH$_2$), 2.47–2.41 (4 H, m, CH$_3$ + CH*H*CH=CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (Ar-C$_q$), 131.0 (Ar-C$_q$), 130.4 (2 × Ar-C), 130.1 (*C*H=), 129.6 (2 × Ar-C), 121.0 (=*C*H$_2$), 101.9 (C$_q$), 67.7 (OCH$_2$), 37.5 (*C*H$_2$CH=CH$_2$), 24.3 (OCH$_2$*C*H$_2$), 21.7 (CH$_3$). HRMS (ESI) *m/z* Calculated for $C_{13}H_{17}O_3S^+$ [M+H]$^+$: 253.0893; Found: 253.0899 [M+H]$^+$.



2-(3-Fluorobenzyl)-2-tosyloxetane (8)

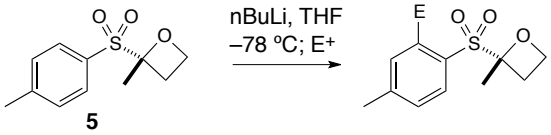
Prepared according to the General Procedure B described above using 3-fluorobenzyl bromide (0.06 mL, 0.48 mmol). Purification by flash chromatography on basic alumina (activity IV) (10–50% EtOAc/hexane) afforded oxetane **8** (68 mg, 90%) as a white solid. R_f = 0.26 (40% EtOAc/hexane). IR (film)/cm^{-1} 2970, 2899, 2255, 1616, 1590, 1487, 1449, 1301, 1255, 1155, 1104, 952, 941, 906, 861, 725, 703. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.40 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.33-7.27 (1 H, m, Ar-H), 7.09–6.98 (3 H, m, 3 × Ar-H), 4.28–4.23 (1 H, m, OC*H*H), 3.83 (1 H, dt, *J* = 9.0, 5.5 Hz, OCH*H*), 3.14 (1 H, d, *J* = 14.3 Hz, CC*H*H), 3.04–2.97 (1 H, m, OCH$_2$C*H*H), 2.93 (1 H, d, *J* = 14.3 Hz, CCH*H*), 2.54–2.47 (1 H, m, OCH$_2$CH*H*) 2.48 (3 H, s, CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 245.0 Hz, Ar-C$_q$), 145.3 (Ar-C$_q$), 136.7 (d, $J_{C\text{-}F}$ = 7.0 Hz, Ar-C$_q$), 131.1 (Ar-C$_q$), 130.4 (2 × Tol-C), 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz, Ar-C), 129.7 (2 × Tol-C), 126.3 (d $J_{C\text{-}F}$ = 2.6 Hz, Ar-C), 117.4 (d, $J_{C\text{-}F}$ = 21.3 Hz, Ar-C), 114.3 (d, $J_{C\text{-}F}$ = 21.3 Hz, Ar-C) 102.1 (C$_q$), 67.5 (OCH$_2$), 38.1 (C*C*H$_2$C), 24.2 (OCH$_2$*C*H$_2$), 21.7 (CH$_3$). HRMS (ESI) *m/z* Calculated for $C_{17}H_{18}FO_3S^+$ [M+H]$^+$: 321.0955; Found: 321.0978 [M+H]$^+$.



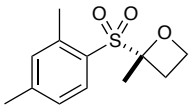
2-Methyl-1-(2-tosyloxetan-2-yl)propan-1-ol (9)

Prepared according to the General Procedure B using isobutyraldehyde (0.04 mL, 0.48 mmol). Purification by filtration through a pad of basic alumina (activity IV) eluting with Et_2O (15 mL) afforded oxetane **9** (57 mg, 86%, dr 1: 0.9). R_f = 0.28 (20% EtOAc/hexane)**.** IR (film)/cm^{-1} 3504, 2966, 2905, 1596, 1493, 1448, 1365, 1311, 1299, 1287, 1154, 1134, 1067, 935, 815, 713. **Major** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 4.30 (1 H, dt, *J* = 9.0, 5.7 Hz, OCH*H*), 4.14–4.03 (1 H, m, OC*H*H), 3.72–3.67 (1 H, m, HOC*H*), 3.24 (1 H, dt, *J* = 12.4, 8.6, OCH$_2$CH*H*), 2.92–2.85 (1 H, m, OCH$_2$C*H*H), 2.48 (3 H, s, Ar-CH$_3$), 2.42–2.36 (1 H, m, (CH$_3$)$_2$C*H*), 1.02 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$), 0.97 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (C$_q$), 132.6 (C$_q$), 130.4 (2 × Ar-C), 129.5 (2 × Ar-C), 104.5 (C$_q$), 74.4 (HO*C*H), 69.0 (OCH$_2$), 29.0 (CH$_3$)$_2$*C*H, 23.9 (OCH$_2$*C*H$_2$), 21.7 (Ar-CH$_3$), 20.8 (CH$_3$), 15.5 (CH$_3$). **Minor** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 7.39 (2 H, d, *J* = 8.0 Hz, 2 × Ar-H), 4.50–4.38 (2 H, m, OCH$_2$), 3.72–3.68 (1 H, m, HOC*H*), 3.19–2.98 (3 H, m, OCH$_2$C*H*$_2$ + (CH$_3$)$_2$C*H*), 2.48 (3 H, s, Ar-CH$_3$), 1.03 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$), 0.94 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4 (C$_q$), 132.6 (C$_q$), 130.5 (2 × Ar-C), 129.5 (2 × Ar-C), 103.7 (C$_q$), 74.4 (HO*C*H), 68.7 (OCH$_2$), 29.8 (CH$_3$)$_2$*C*H, 23.8 (OCH$_2$*C*H$_2$), 21.7 (Ar-CH$_3$), 20.9 (CH$_3$), 17.5 (CH$_3$). HRMS (ESI) *m/z* Calculated for $C_{14}H_{21}O_4S^+$ [M+H]$^+$: 285.1161; Found: 285.1179 [M+H]$^+$.

Preparation of Oxetane 10 by Directed *ortho*-Metallation



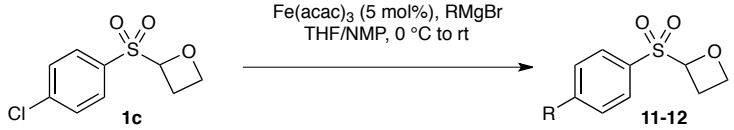
5



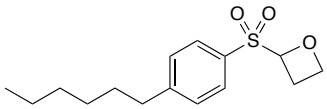
2-((2,4-Dimethylphenyl)sulfonyl)-2-methyloxetane (10)

*n*BuLi (1.60 M in hexane, 0.16 mL, 0.26 mmol) was added dropwise to a solution of oxetane **5** (50.0 mg, 0.22 mmol) in THF (1.2 mL) at –78 ºC and stirred at –78 ºC for 30 min. MeI (0.027 mL, 0.44 mmol) was added and the reaction stirred at –78 ºC for 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (6 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography on basic alumina (activity IV) (25% Et_2O/hexane) afforded oxetane **10** as a colourless oil. R_f = 0.28 (20% EtOAc/hextane). IR (film)/cm^{-1} 2974, 2931, 2900, 1602, 1567, 1440, 1373, 1294, 1212, 1174, 1107, 1050, 973, 948, 865, 744, 675. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1 H, d, *J* = 8.7 Hz, Ar-H), 7.19–7.14 (2 H, m, 2 × Ar-H), 4.57–4.50 (1 H, m, OCH*H*), 4.49–4.43 (1 H, m, OC*H*H), 3.31–3.22, (1 H, m, OCH_2CH*H*), 2.78 (1 H, dt, *J* = 12.6, 8.4 Hz, OCH_2C*H*H), 2.73 (3 H, s, Ar-CH_3), 2.39 (3 H, s, Ar-CH_3), 1.65 (3 H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (Ar-C_q), 141.3 (Ar-C_q), 133.6 (Ar-C), 132.6 (Ar-C), 129.6 (Ar-C_q) 126.8 (Ar-C), 101.6 (C_q), 67.3 (OCH_2), 29.0 (OCH_2CH_2), 22.1 (CH_3), 21.4 (Ar-CH_3), 21.3 (Ar-CH_3). HRMS (ESI) *m/z* Calculated for $C_{12}H_{17}O_3S^+$ $[M+H]^+$: 241.0893; Found: 241.0927 $[M+H]^+$.

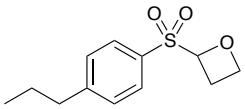
Preparation of Oxetanes 11–12 by Fe-Catalysed Cross-Coupling of Oxetane 1c with Grignard Reagents



Conditions reported by Fürstner were employed.[8]

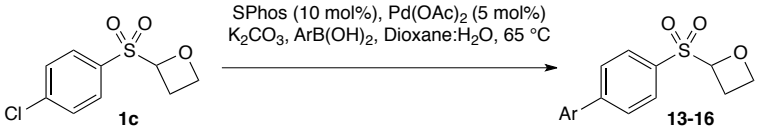


2-((4-Hexylphenyl)sulfonyl)oxetane (11)
*n*Hexylmagnesium bromide (0.16 mL, 0.25 mmol) was added dropwise to a solution of oxetane **1c** (48 mg, 0.21 mmol) and $Fe(acac)_3$ (3.6 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with 1M HCl (10 mL) then extracted with Et_2O (5 × 7 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–20% EtOAc/heptane) afforded oxetane **11** (41 mg, 70%) as a colourless oil. R_f = 0.18 (20% EtOAc/heptane). IR (film)/cm^{-1} 2928, 2858, 2257, 1596, 1465, 1408, 1309, 1232, 1148, 1089, 1029, 984, 908, 816, 727. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 5.37 (1 H, dd, *J* = 6.7, 6.2 Hz, OC*H*S), 4.80–4.75 (1 H, m, OCH*H*), 4.66–4.61 (1 H, m, OC*H*H), 3.13–3.08 (2 H, m, OCH_2CH_2), 2.70 (2 H, t, *J* = 7.6 Hz, Ar-CH_2CH_2), 1.64 (2 H, qn, *J* = 7.6 Hz, Ar-CH_2CH_2), 1.36–1.28 (6 H, m, 3 × CH_2), 0.89 (3 H, t, *J* = 6.9 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C_q), 132.5 (C_q), 129.5 (2 × Ar-C), 129.2 (2 × Ar-C), 94.1 (O*C*HS), 71.3 (O*C*H_2), 36.0 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{15}H_{26}NO_3S^+$ $[M+NH_4]^+$: 300.1628; Found: 300.1627 $[M+NH_4]^+$.

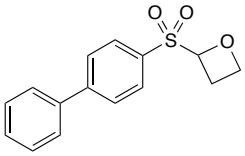


2-((4-Hexylphenyl)sulfonyl)oxetane (12)
*n*Propylmagnesium chloride (1 M in MeTHF, 0.25 mL, 0.25 mmol) was added dropwise to a solution of oxetane **1c** (50 mg, 0.21 mmol) and $Fe(acac)_3$ (4 mg, 0.01 mmol) in THF/NMP (9:1, 2 mL). The reaction was stirred at rt for 15 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with 1M HCl (10 mL) then extracted with Et_2O (5 × 7 mL). Combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **12** (37 mg, 71%) as a colourless oil. R_f = 0.19 (20% EtOAc/hexane). IR (film)/cm^1 2962, 2932, 2872, 1596, 1444, 1408, 1307, 1274, 1232, 1184, 1146, 1090, 1065, 1029, 939, 910, 843, 804, 768, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 7.38 (2 H, d, *J* = 8.3 Hz, 2 × Ar-H), 5.38 (1 H, dd, *J* = 6.9, 6.0 Hz, OC*H*S), 4.81–4.75 (1 H, m, OCH*H*), 4.67–4.62 (1 H, m, OC*H*H), 3.16–3.07 (2 H, m, OCH_2CH_2), 2.69 (2 H, t, *J* = 7.4 Hz, Ar-CH_2CH_2), 1.68 (2 H, tq, *J* = 7.5, 7.4 Hz, Ar-CH_2CH_2), 0.96 (3 H, t, *J* = 7.4 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (C_q), 133.3 (C_q), 129.5 (2 × Ar-C), 129.3 (2 × Ar-C), 94.0 (O*C*HS), 71.4 (O*C*H_2), 38.0 (CH_2), 24.1 (CH_2), 22.4 (OCH_2CH_2), 13.7 (CH_3). HRMS (APCI) *m/z* Calculated for $C_{12}H_{20}NO_3S^+$ $[M+NH_4]^+$: 258.1158; Found: 258.1158 $[M+NH_4]^+$.

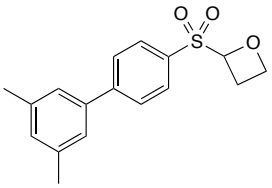
Preparation of Oxetanes 13–16 by Suzuki Cross-Coupling of Oxetane 1c



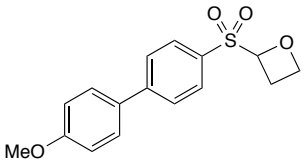
Conditions related to those reported by Buchwald were employed, using the S-Phos ligand.[9]



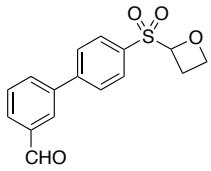
2-([1,1'-Biphenyl]-4-ylsulfonyl)oxetane (13)
Phenylboronic acid (38 mg, 0.31 mmol) and oxetane **1c** (54 mg, 0.23 mmol) were added to $Pd(OAc)_2$ (3 mg, 0.012 mmol), S-Phos (9 mg, 0.023 mmol) and K_2CO_3 (64 mg, 0.46 mmol) and the reaction vessel was placed under N_2. The mixture was dissolved in dioxane:water (4:1, 2.5 mL) and heated to 65 ºC for 3 h 30 min. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (0–100% EtOAc/heptane) afforded oxetane **13** (55 mg, 86%) as a white solid. R_f = 0.39 (40% EtOAc/heptane). IR (film)/cm^{-1} 3066, 2980, 2909, 1592, 1563, 1479, 1446, 1396, 1302, 1144, 1091, 900, 838, 762, 720, 657. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.79 (2 H, d, *J* = 8.7 Hz, 2 × Ar-H), 7.64–7.59 (2 H, m, 2 × Ar-H), 7.52–7.42 (3 H, m, 3 × Ar-H), 5.43 (1 H, dd, *J* = 7.0, 6.5 Hz, OC*H*S), 4.86–4.81 (1 H, m, OCH*H*), 4.70–4.65 (1 H, m, OC*H*H), 3.18–3.12 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (C_q), 139.2 (C_q), 133.9 (C_q), 130.0 (2 × Ar-C), 129.1 (2 × Ar-C), 128.7 (Ar-C), 127.8 (2 × Ar-C), 127.4 (2 × Ar-C), 94.1 (O*C*HS), 71.4 (OCH_2), 22.4 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_{15}H_{18}NO_3S^+$ $[M+NH_4]^+$: 292.1002; Found 292.1001 $[M+NH_4]^+$.



2-([3',5'-Dimethylbiphenyl]-4-ylsulfonyl)oxetane (14)
3,5-Dimethylbenzeneboronic acid (60 mg, 0.42 mmol) and oxetane **1c** (75 mg, 0.32 mmol) were added to $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K_2CO_3 (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65 ºC for 5 h. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (30% EtOAc/hexane) afforded oxetane **14** as a colourless oil (83 mg, 86%). R_f = 0.53 (40% EtOAc/hexane). IR (film)/cm^{-1} 2972, 2903, 1593, 1443, 1389, 1314, 1270, 1231, 1185 1064, 1029, 982, 908, 829, 737, 722, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 7.77 (2 H, d, *J* = 8.4 Hz, 2 × Ar-H), 7.23 (2 H, s, 2 × Ar-H), 7.09 (1 H, s, Ar-H), 5.43 (1 H, dd, *J* = 7.4, 6.0 Hz, OC*H*S), 4.84–4.77 (1 H, m, OCH*H*), 4.70–4.63 (1 H, m, OC*H*H), 3.19–3.08 (2 H, m, OCH_2CH_2), 2.40 (6 H, s, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5 (C_q), 139.0 (C_q), 138.6 (2 × C_q), 133.4 (C_q), 130.3 (Ar-C), 129.8 (2 × Ar-C), 127.7 (2 × Ar-C), 125.2 (2 × Ar-C), 94.0 (O*C*HS), 71.4 (OCH_2), 22.4 (OCH_2CH_2), 21.3 (2 × CH_3). HRMS (EI) *m/z* Calculated for $C_{17}H_{18}O_3S^+$ $[M]^+$: 302.0971; Found 302.0973 $[M]^+$.



2-([4'-Methoxybiphenyl]-4-ylsulfonyl)oxetane (15)
4-Methoxyphenylboronic acid (64 mg, 0.42 mmol) and oxetane **1c** (75 mg, 0.32 mmol) were added to $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K_2CO_3 (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65 ºC for 5 h 30 min. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **15** as a white solid (92 mg, 95%). R_f = 0.34 (40% EtOAc/hexane). IR (film)/cm^{-1} 2980, 2909, 2839, 1603, 1591, 1523, 1457, 1425, 1396, 1294, 1136, 1091, 1063, 1012, 982, 936, 907, 849, 819, 751, 712, 682. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.75 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.58 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 7.02 (2 H, d, *J* = 8.6 Hz, 2 × Ar-H), 5.42 (1 H, dd, *J* = 7.0, 6.4 Hz, OC*H*S), 4.85–4.79 (1 H, m, OCH*H*), 4.70–4.64 (1 H, m, OC*H*H), 3.88 (3 H, s, CH_3), 3.19–3.09 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C_q), 146.8 (C_q), 133.0 (C_q), 131.4 (C_q), 130.0 (2 × Ar-C), 128.6 (2 × Ar-C), 127.2 (2 × Ar-C), 114.5 (2 × Ar-C), 94.1 (O*C*HS), 71.4 (OCH_2), 55.4 (CH_3), 22.4 (OCH_2CH_2). HRMS (EI) *m/z* Calculated for $C_{16}H_{16}O_4S^+$ $[M]^+$: 304.0769; Found 304.0744 $[M]^+$.



2-([1,1'-Biphenyl]-3-carboxaldehyde-4-ylsulfonyl)oxetane (16)
3-Formylphenylboronic acid (60 mg, 0.42 mmol) and oxetane **1c** (75 mg, 0.32 mmol) were added to $Pd(OAc)_2$ (4 mg, 0.016 mmol), S-Phos (12 mg, 0.032 mmol) and K_2CO_3 (88 mg, 0.64 mmol) and the reaction vessel was placed under Ar. The mixture was dissolved in dioxane:water (4:1, 3.1 mL) and heated to 65 ºC for 20 h. The crude mixture was filtered through celite and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded oxetane **16** as a colourless oil (57 mg, 59%). R_f = 0.13 (40% EtOAc/hexane). IR (film)/cm^{-1} 2973, 2902, 2827, 1694, 1595, 1585, 1442, 1398, 1380, 1314, 1232, 1180, 1090, 1064, 1028, 937, 868, 843, 769, 761, 660. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (1 H, s, C*H*O), 8.13–8.11 (1 H, m, Ar-H), 8.06 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.93 (1 H, dt, *J* = 7.5, 1.4 Hz, Ar-H), 7.87 (1 H, dt, *J* = 7.7, 1.4 Hz, Ar-H), 7.81 (2 H, d, *J* = 8.5 Hz, 2 × Ar-H), 7.67 (1 H, t, *J* = 7.7 Hz, Ar-H), 5.43 (1 H, dd, *J* = 7.2, 5.5 Hz, OC*H*S), 4.85–4.79 (1 H, m, OCH*H*), 4.70–4.64 (1 H, m, OC*H*H), 3.21–3.07 (2 H, m, OCH_2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (C=O), 145.6 (C_q), 140.0 (C_q), 137.0 (C_q), 134.5 (C_q), 133.1 (Ar-C), 130.1 (2 × Ar-C), 130.0 (Ar-C), 129.8 (Ar-C), 128.1 (Ar-C), 127.8 (2 × Ar-C), 94.0 (O*C*HS), 71.5 (OCH_2), 22.3 (OCH_2CH_2). HRMS (APCI) *m/z* Calculated for $C_{16}H_{18}NO_4S^+$ $[M+NH_4]^+$: 320.0951; Found 320.0951 $[M+NH_4]^+$.

Calculated fragment-like and lead-like properties of oxetanes 1a-d, 5-9 and 10-16

The scope of oxetanes prepared were analysed against parameters used to indicate desirable molecular properties, with particular reference to the Astex 'rule of 3' for fragments, and lead-likeness criteria recently proposed by Churcher and co-workers.

Criteria as defined by Congreve *et al.* for fragments.[10]

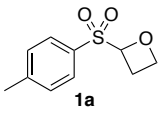
- cLogP < 3[11]
- Three or fewer H-bond donors (HBD)
- Three or fewer H-bond acceptors (HBA)
- MW < 300 daltons

Secondary criteria include: Number of rotatable bonds (NROT) ≤3; Polar surface area (PSA) ≤60. Köster *et al* recently proposed six or fewer HBA to be a more appropriate guideline.[12]

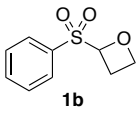
Criteria as defined by Churcher *et al.* for lead-like compound:[13]

- 14 ≤ heavy atoms ≤ 26 (200 ≤ Molecular weight (MW) ≤ 300 Da)
- -1 ≤ cLogP ≤ 3
- more 3D shape/sp^3 content favoured

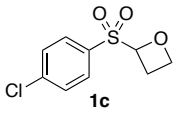
Compounds 1a-d



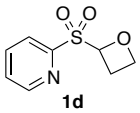
1a
MW = 212
cLogP = 0.26±0.4
HAC = 14
HBD/A = 0/3
TPSA = 43.4
NROT = 2



1b
MW = 198
cLogP = –0.2 ±0.4
HAC = 13
HBD/A = 0/3
TPSA = 43.4
NROT = 2



1c
MW = 232
cLogP = 0.35±0.5
HAC = 14
HBD/A = 0/3
TPSA = 43.4
NROT = 2

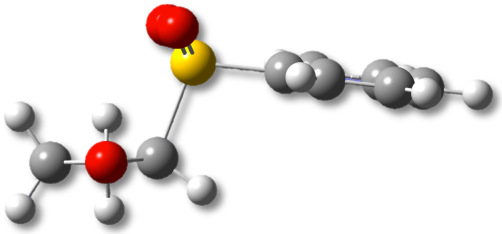


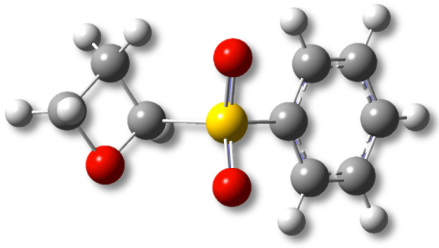
1d
MW = 199
cLogP = –1.28±0.4
HAC = 13
HBD/A = 0/4
TPSA = 56.3
NROT = 2

MW = molecular weight
cLogP = calculated log of partition coeficient (lipophilicity)
HAC = heavy atom count
HBD/A = hydrogen bond donors/acceptors
TPSA = topological polar surface area
NROT = number of rotatable bonds

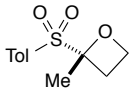
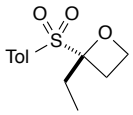
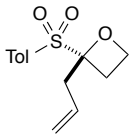
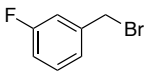
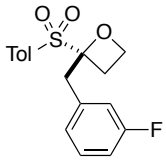
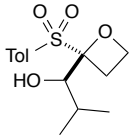
These compounds conform well to the fragment guidelines.

To illustrate the 3-dimensional shape of the oxetane fragments we calculated the minimum energy structure of **1a** using Gaussian 09 (GaussView 5),[14] up to the B3LYP/3-21G level of theory with default solvation (water; scrf = pcm).

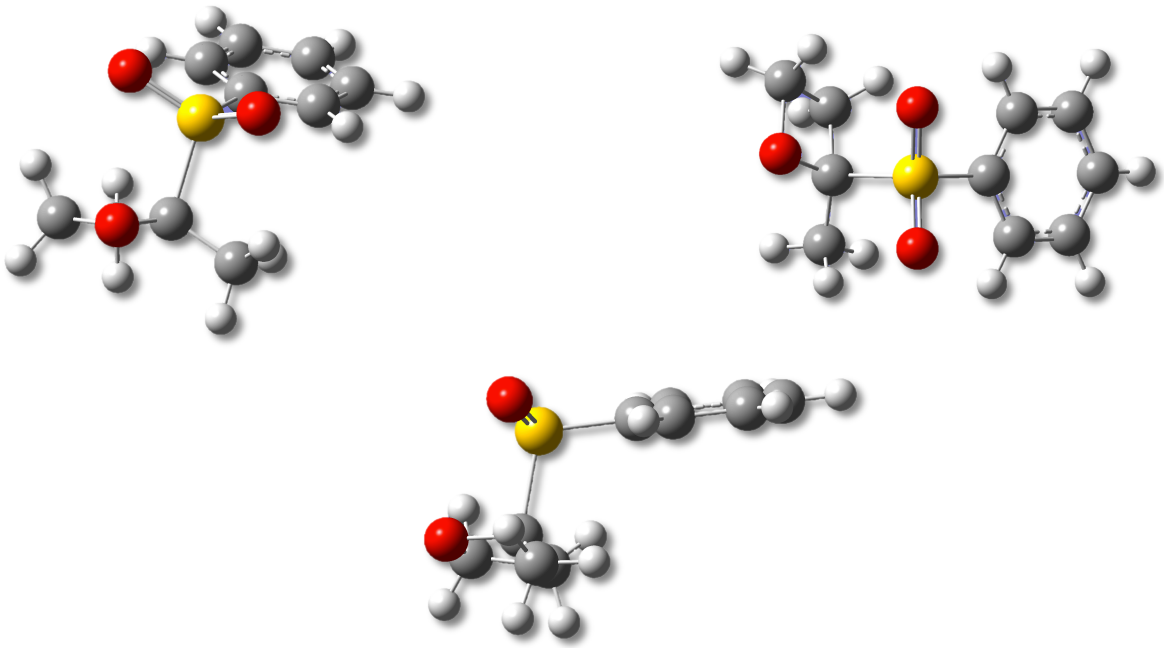




Oxetanes **5-9**

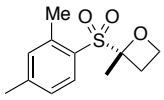
Entry	Electrophile (E^+)	Conditions [a]	Oxetane		Yield (%)	*Calculated molecular properties*
1 2	MeI MeI	A B		**5**	93% 71%	*MW = 226* *clogP = 0.80 ± 0.4* *HAC = 15* *HBD/A =0/3*
3	EtI	A		**6**	85%	*MW = 240* *clogP = 1.33 ± 0.4* *HAC = 16* *HBD/A = 0/3*
4	allyl bromide	A		**7**	91%	*MW = 252* *clogP = 1.64 ± 0.4* *HAC = 17* *HBD/A = 0/3*
5		B		**8**	90%	*MW = 320* *clogP = 2.62 ± 0.5* *HAC = 22* *HBD/A = 0/4*
6		B		**9**	86% [b]	*MW = 284* *clogP = 1.59 ± 0.5* *HAC = 19* *HBD/A = 1/4*

DFT calculation of minimum energy structure of oxetane **5** (B3LYP/3-21G, water);[14]



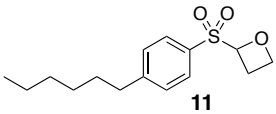
Oxetanes **10-16**

The physicochemical properties of these compounds conform well to lead-like guidelines.



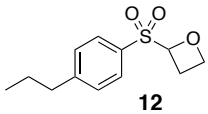
MW = 240
cLogP = 1.26 ±0.4
HAC = 16
HBD/A = 0/3

10



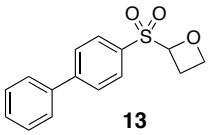
MW = 282
cLogP = 2.92 ±0.4
HAC = 19
HBD/A = 0/3

11



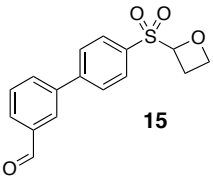
MW = 240
cLogP = 1.32 ±0.4
HAC = 16
HBD/A = 0/3

12



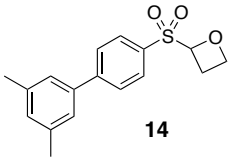
MW = 274
cLogP = 1.99 ±0.4
HAC = 19
HBD/A = 0/3

13



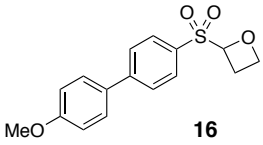
MW = 302
cLogP = 0.87 ±0.5
HAC = 21
HBD/A = 0/4

15



MW = 302
cLogP = 2.37 ±0.4
HAC = 21
HBD/A = 0/3

14

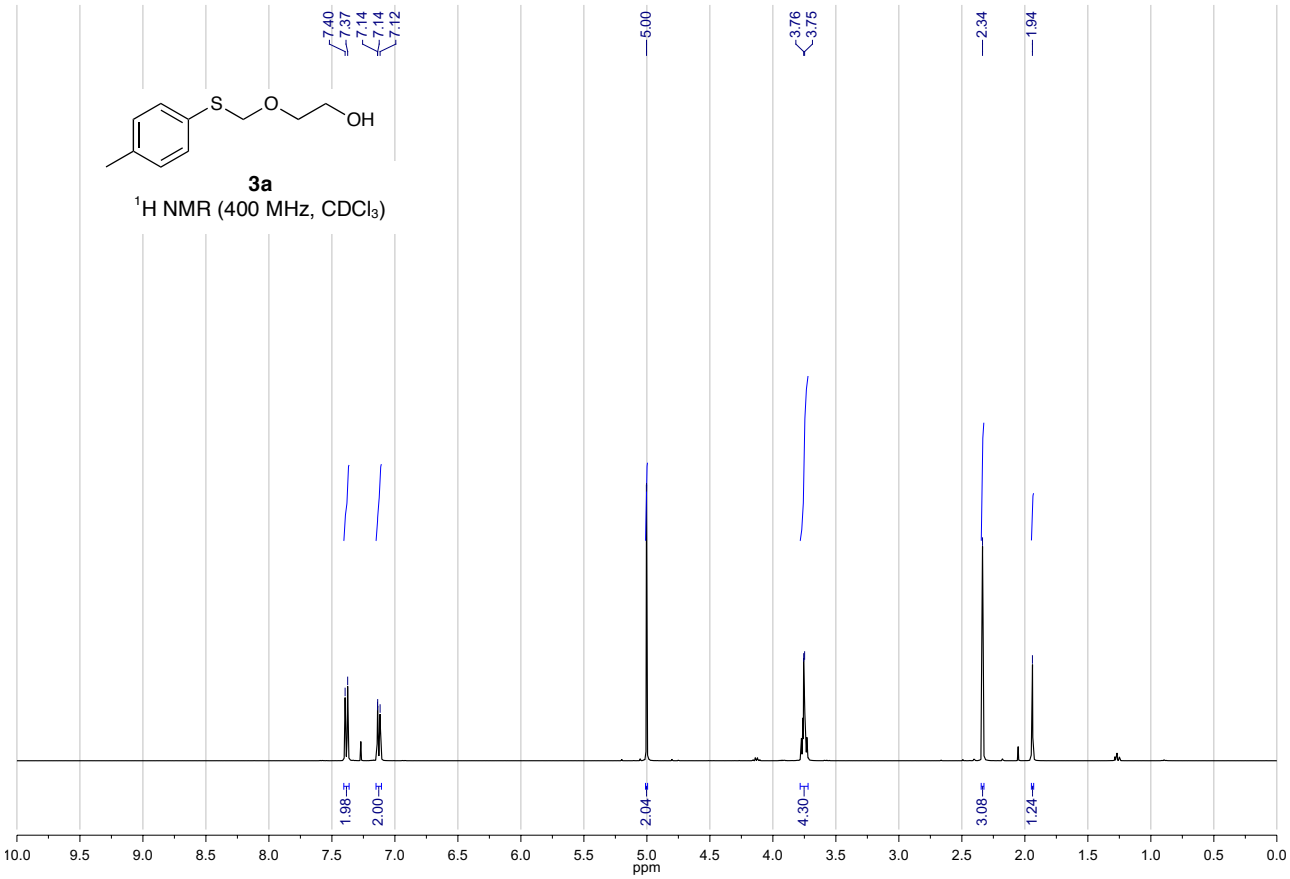


MW = 304
cLogP = 1.26 ±0.4
HAC = 21
HBD/A = 0/4

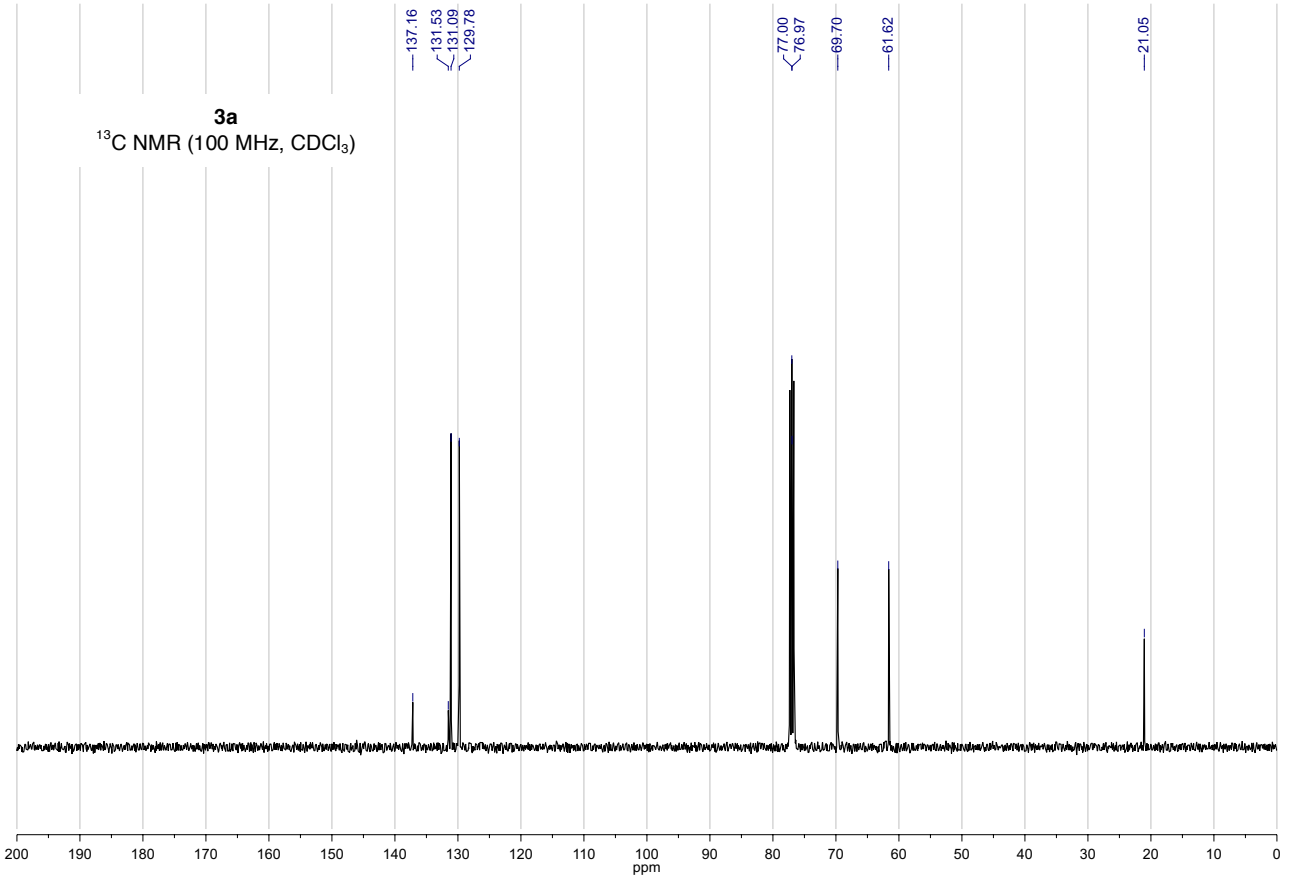
16

Electronic Supplementary Material (ESI) for Chemical Communications

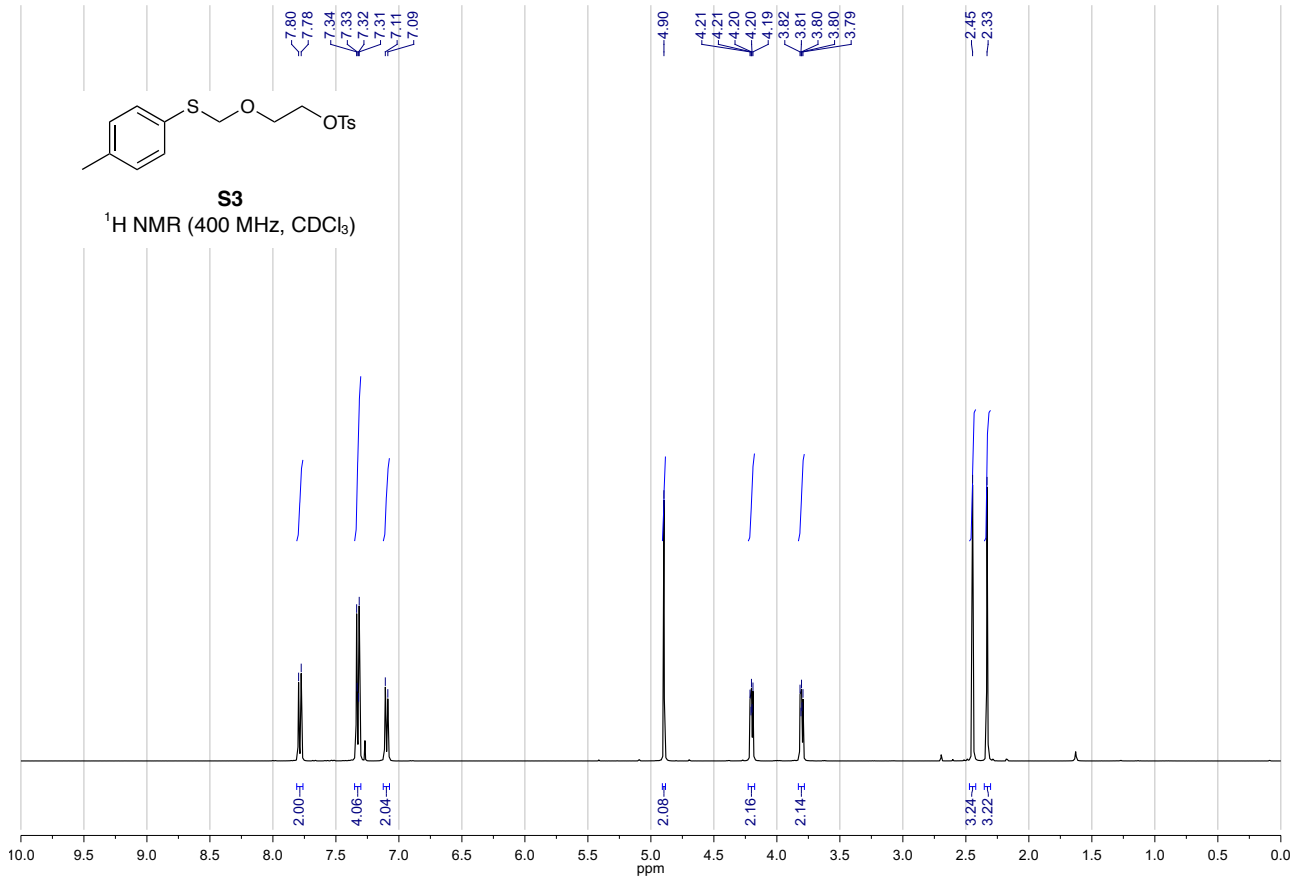
^{1}H and ^{13}C NMR spectra of selected compounds



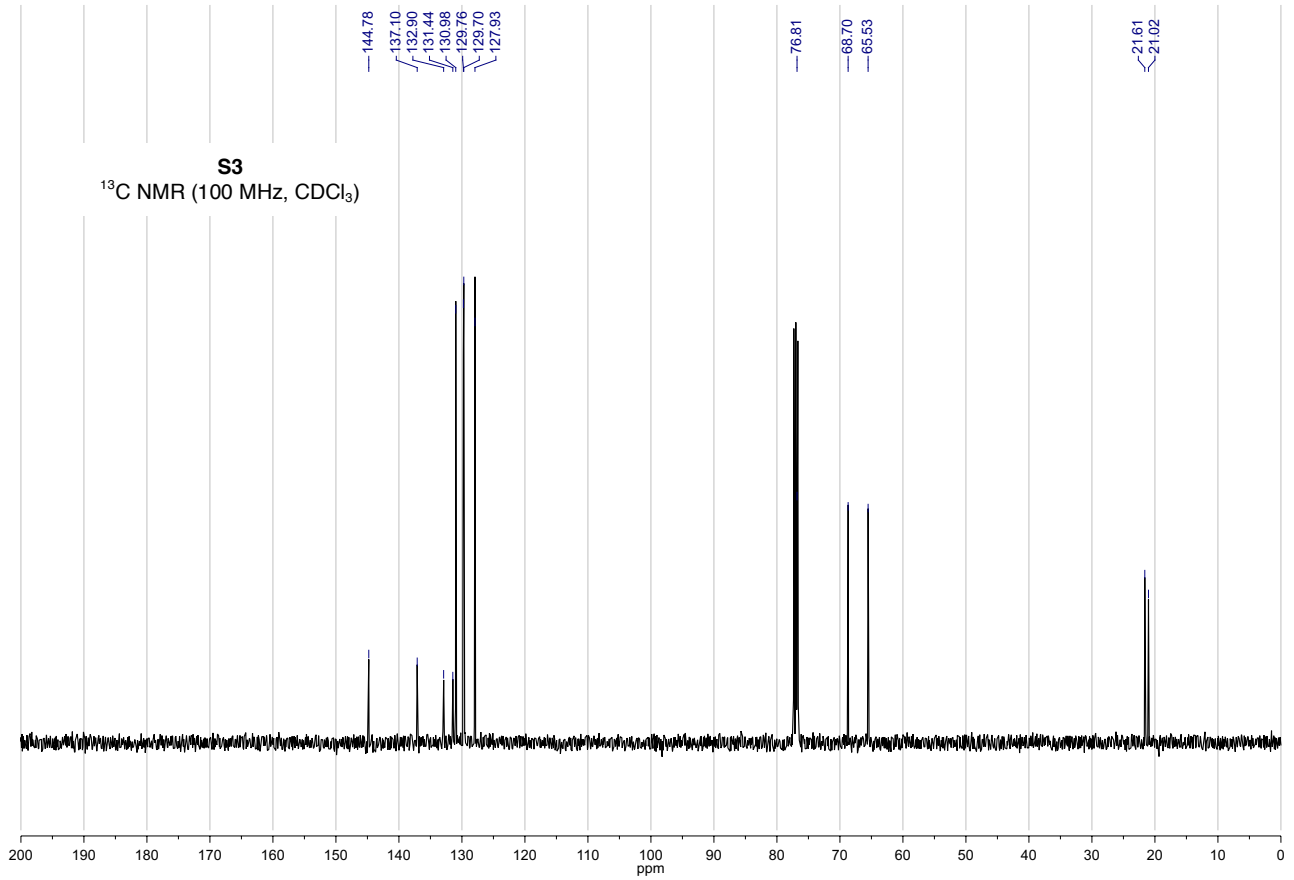
3a
^{1}H NMR (400 MHz, $CDCl_3$)



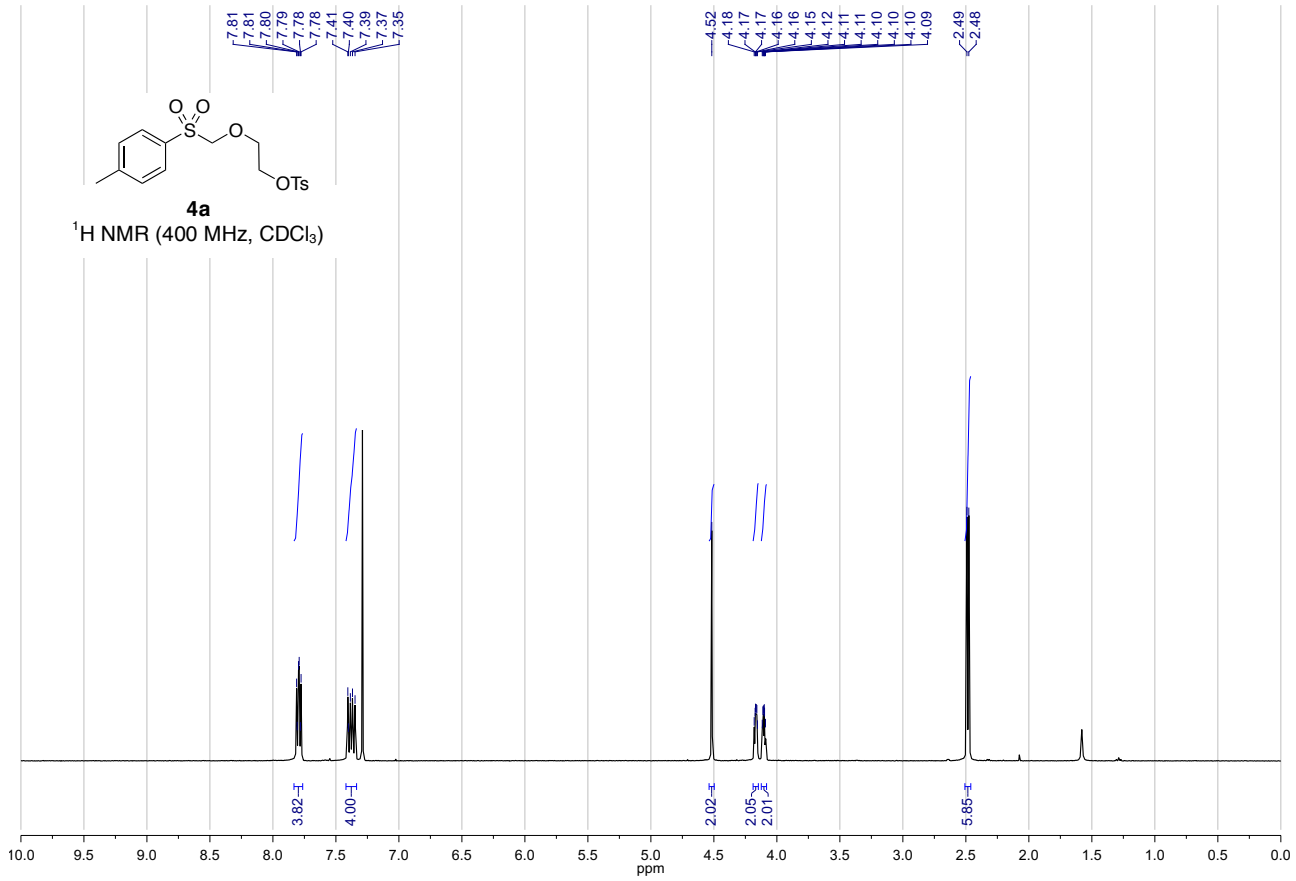
3a
^{13}C NMR (100 MHz, $CDCl_3$)

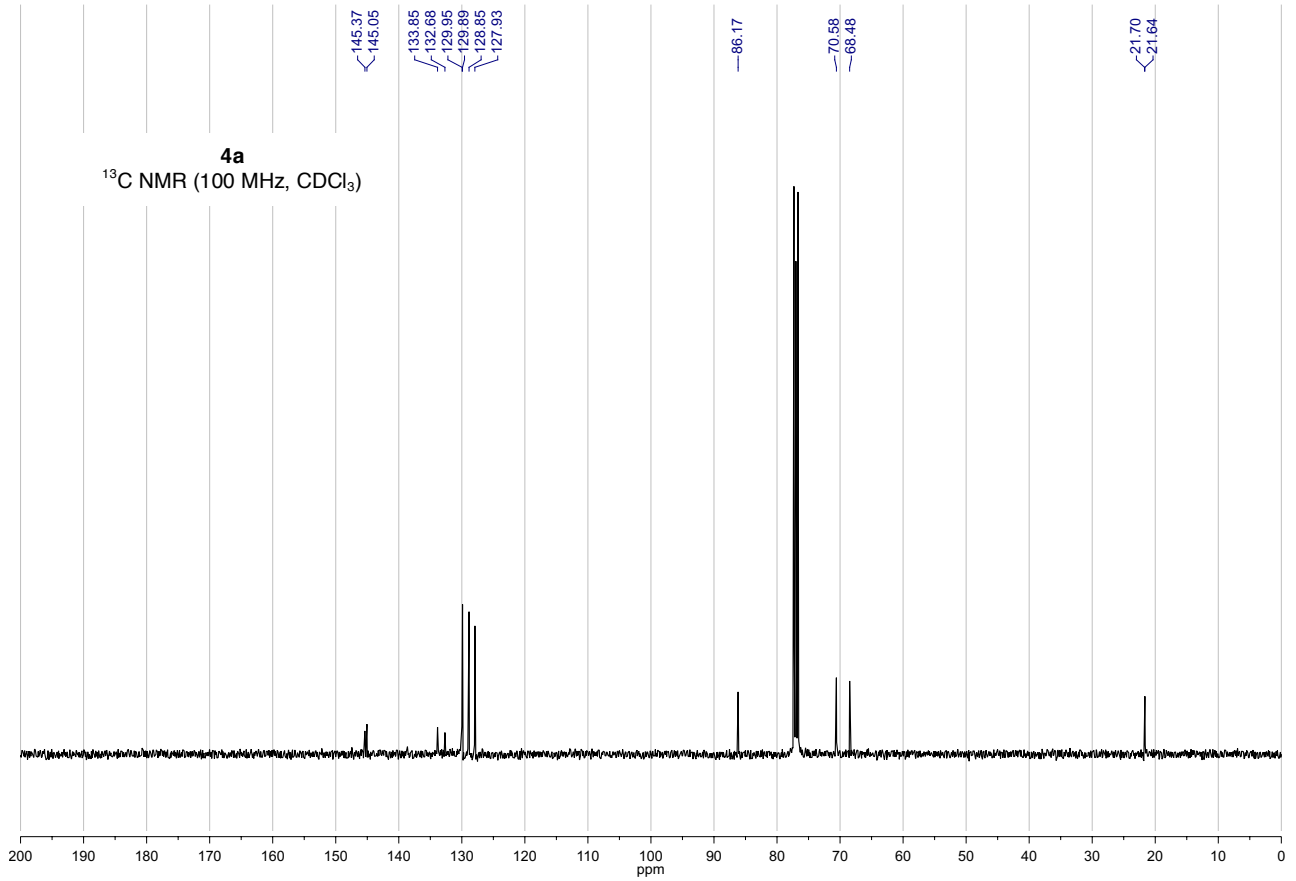


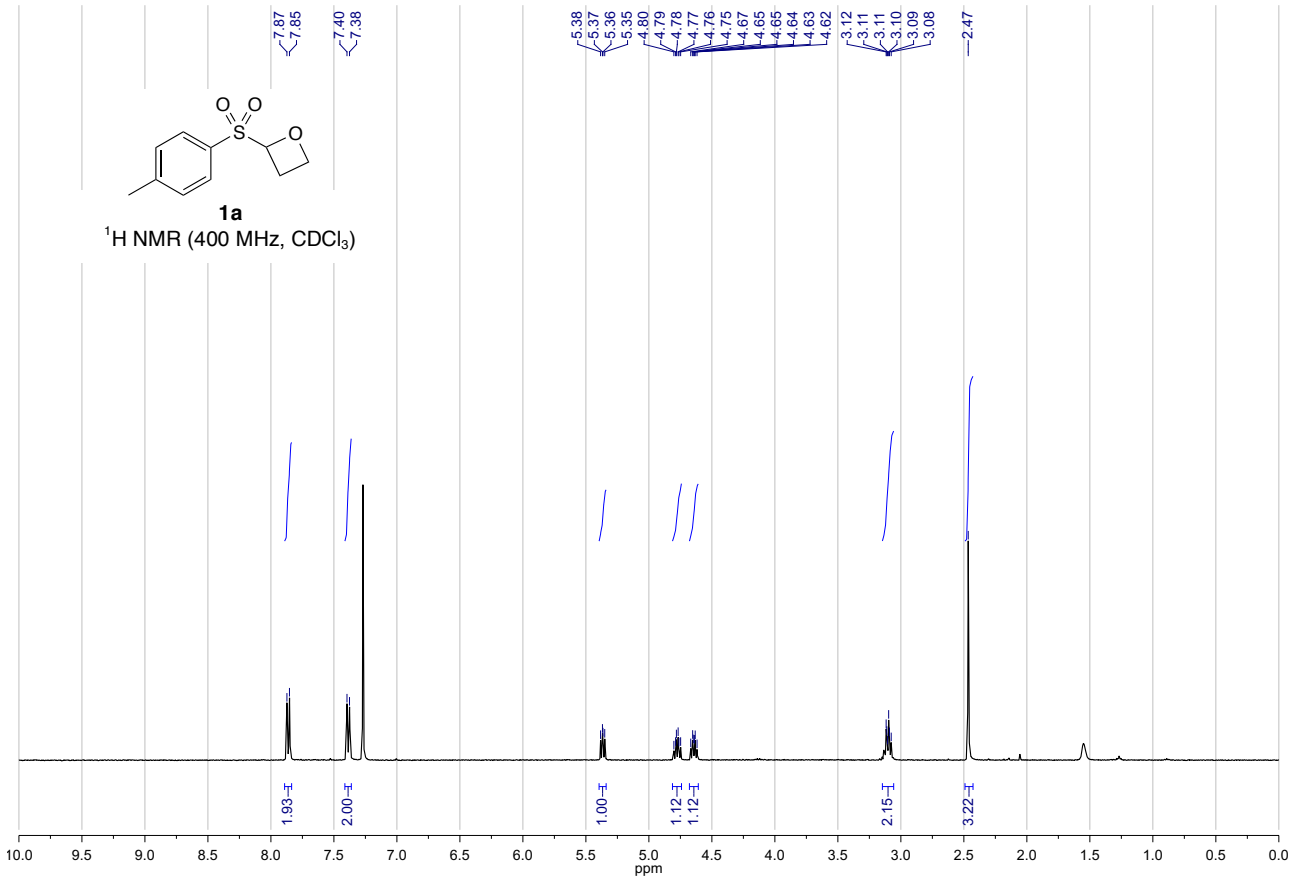
S3
^{1}H NMR (400 MHz, $CDCl_3$)



S3
^{13}C NMR (100 MHz, $CDCl_3$)

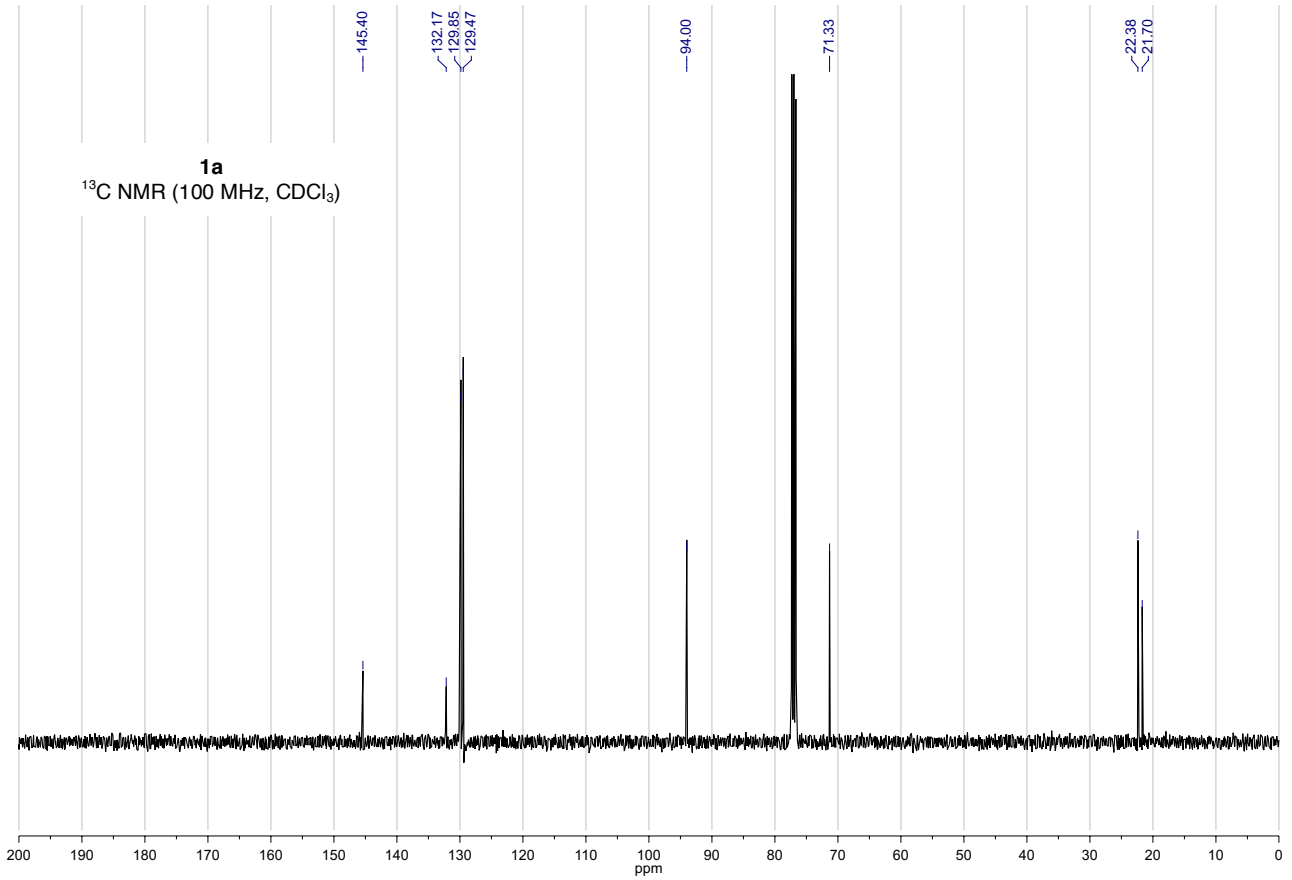

7.81
7.81
7.80
7.79
7.78
7.78
7.41
7.40
7.39
7.37
7.35
4.52
4.18
4.17
4.17
4.16
4.16
4.15
4.12
4.11
4.11
4.10
4.10
4.10
4.09
2.49
2.48
O
O
S
O
OTs
4a
1H NMR (400 MHz, CDCl3)
3.82
4.00
2.02
2.05
2.01
5.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


145.37
145.05
133.85
132.68
129.95
129.89
128.85
127.93
86.17
70.58
68.48
21.70
21.64
4a
13C NMR (100 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



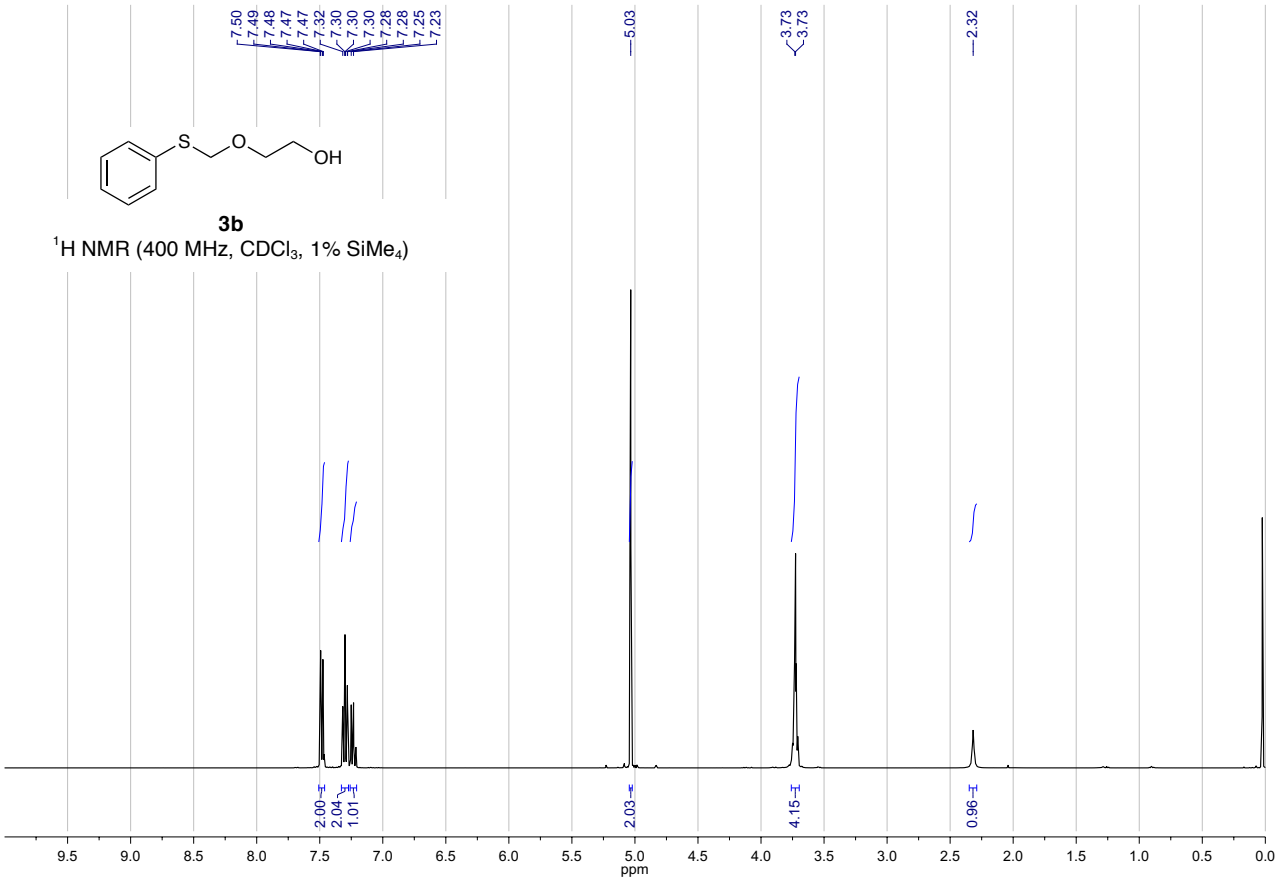
1a

^{1}H NMR (400 MHz, $CDCl_3$)



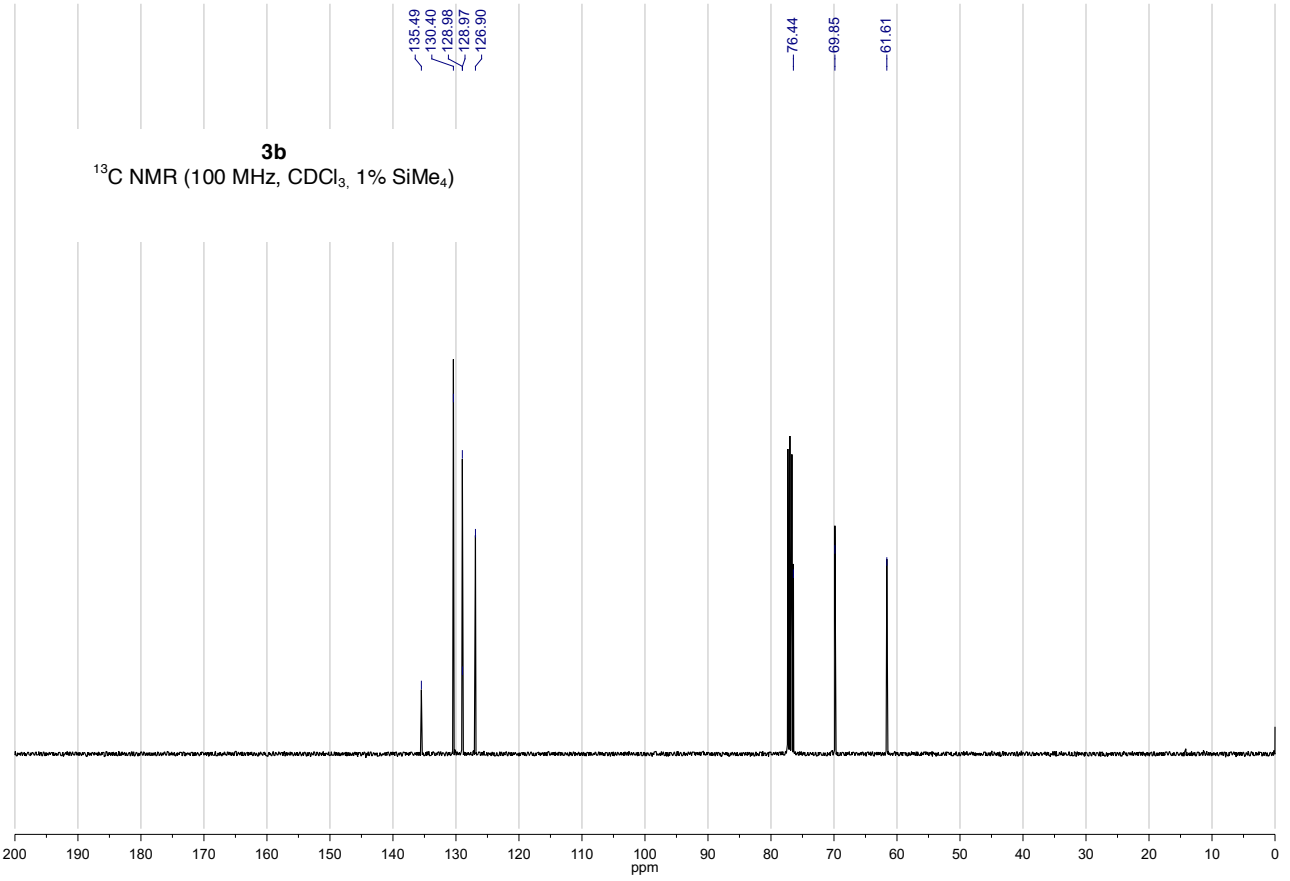
1a

^{13}C NMR (100 MHz, $CDCl_3$)



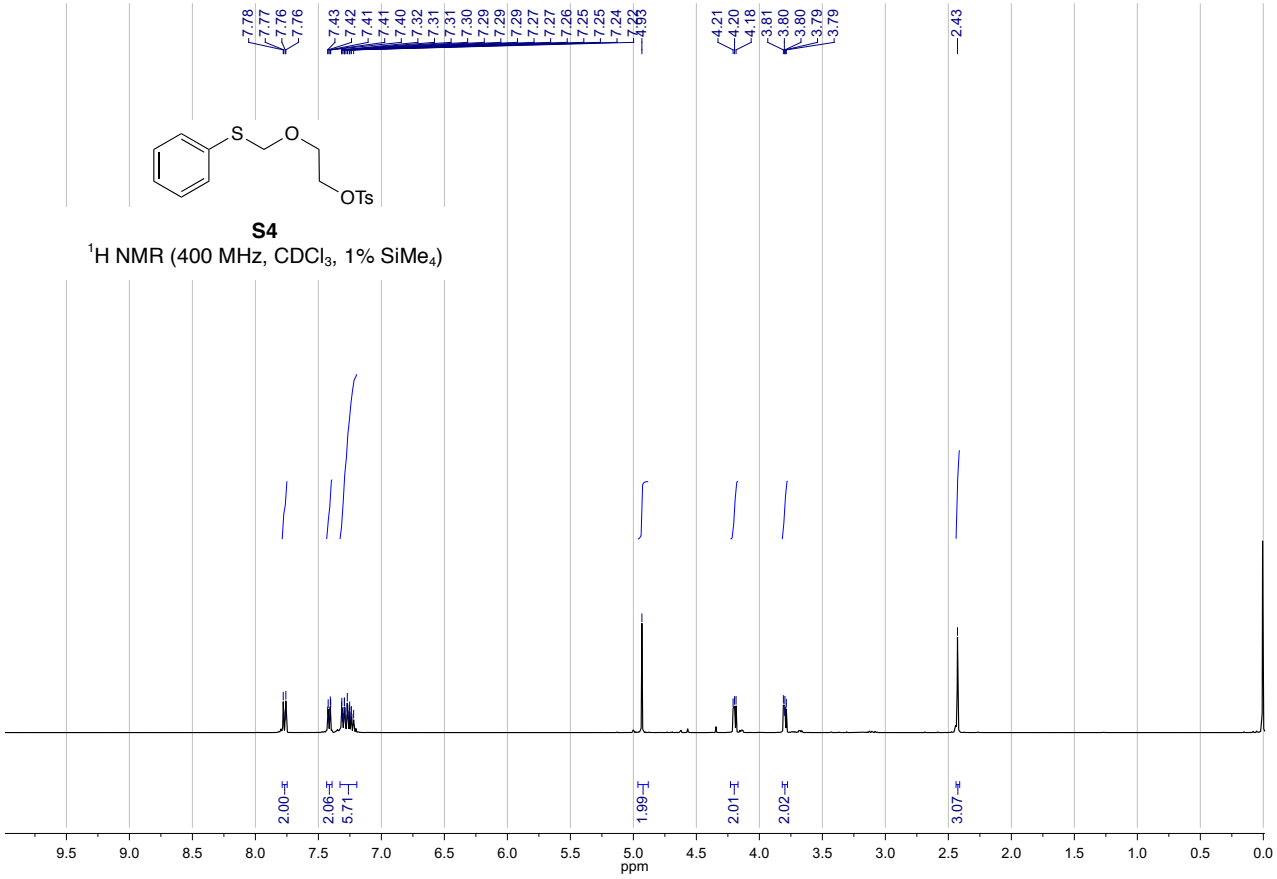
3b

^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)



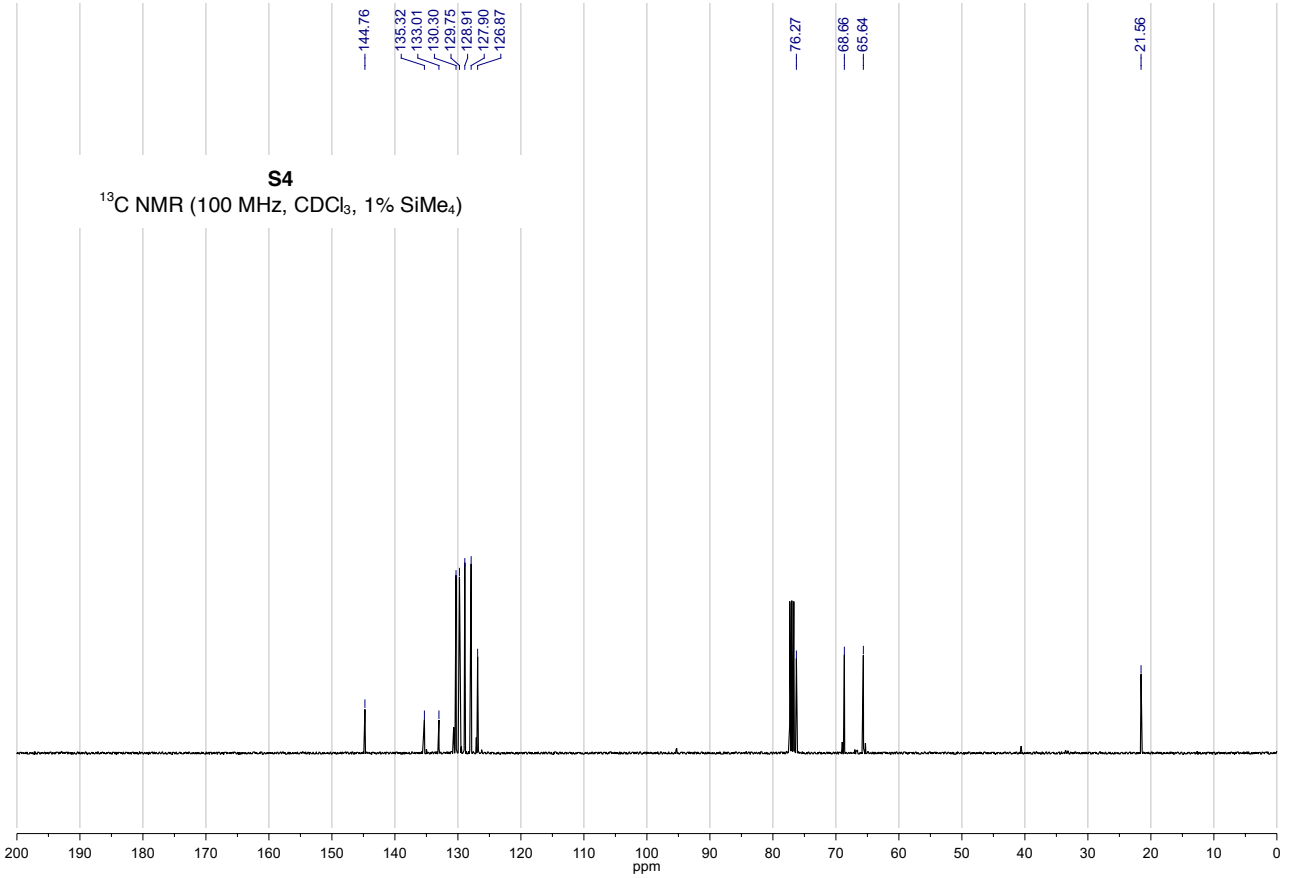
3b

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)



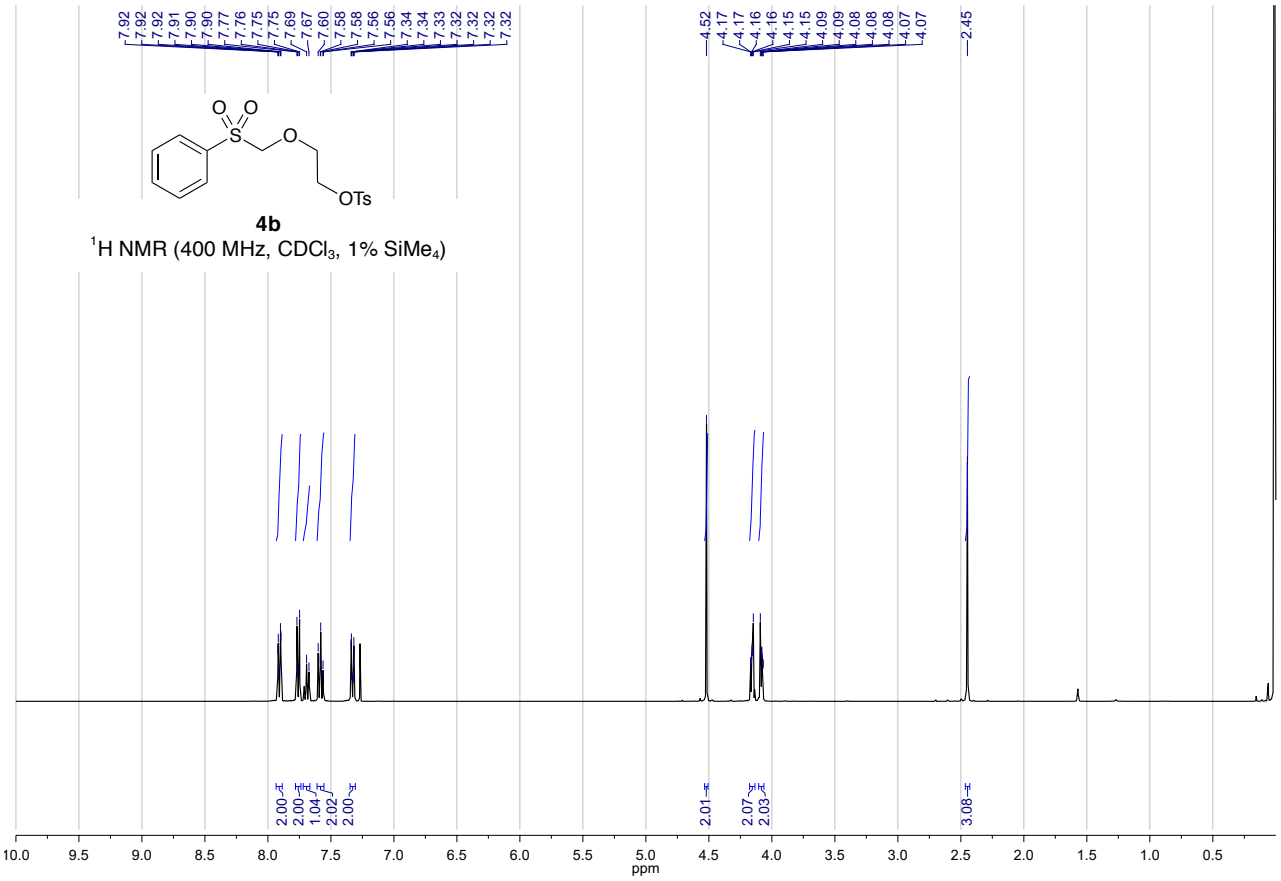
S4

^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)



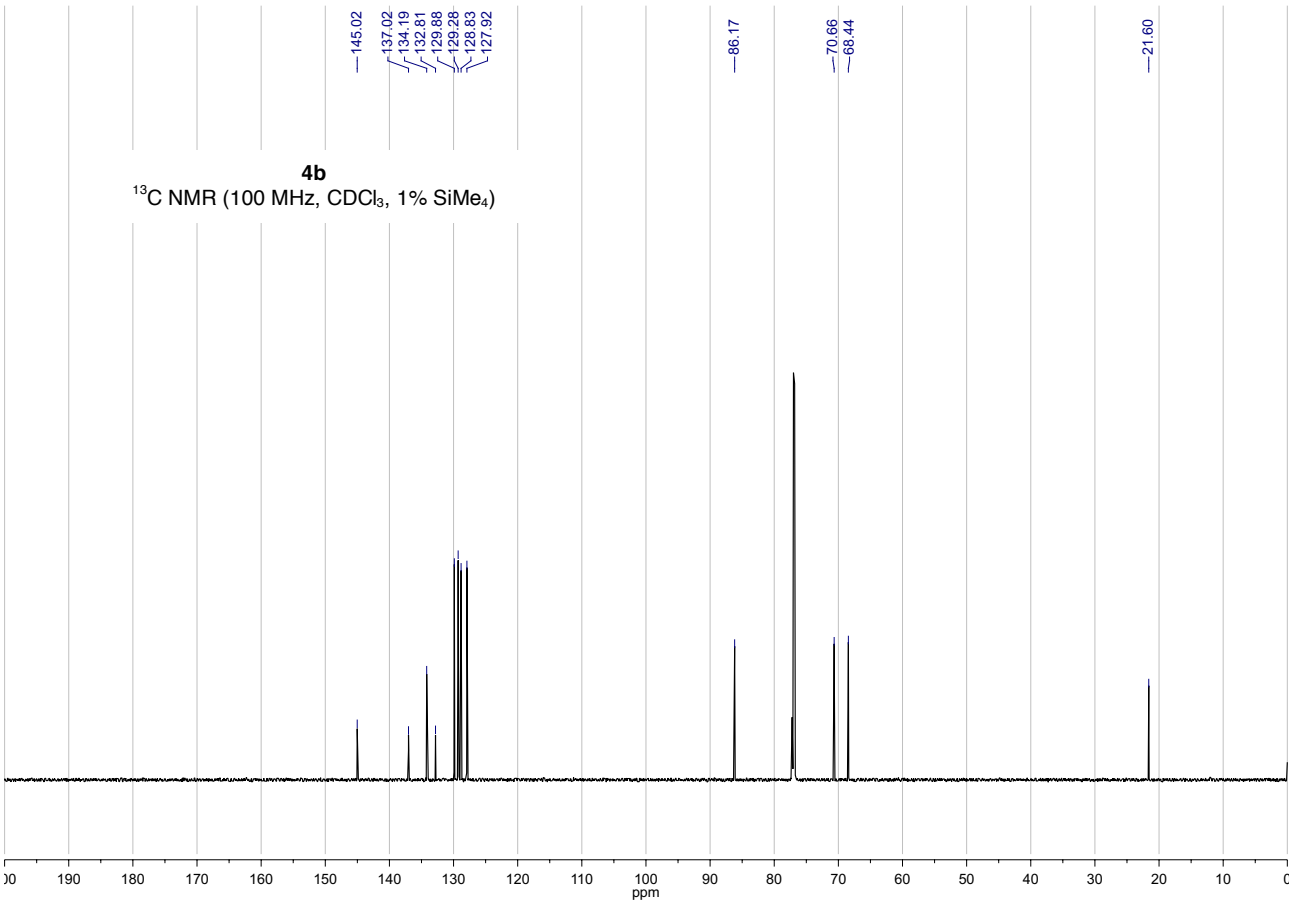
S4

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)



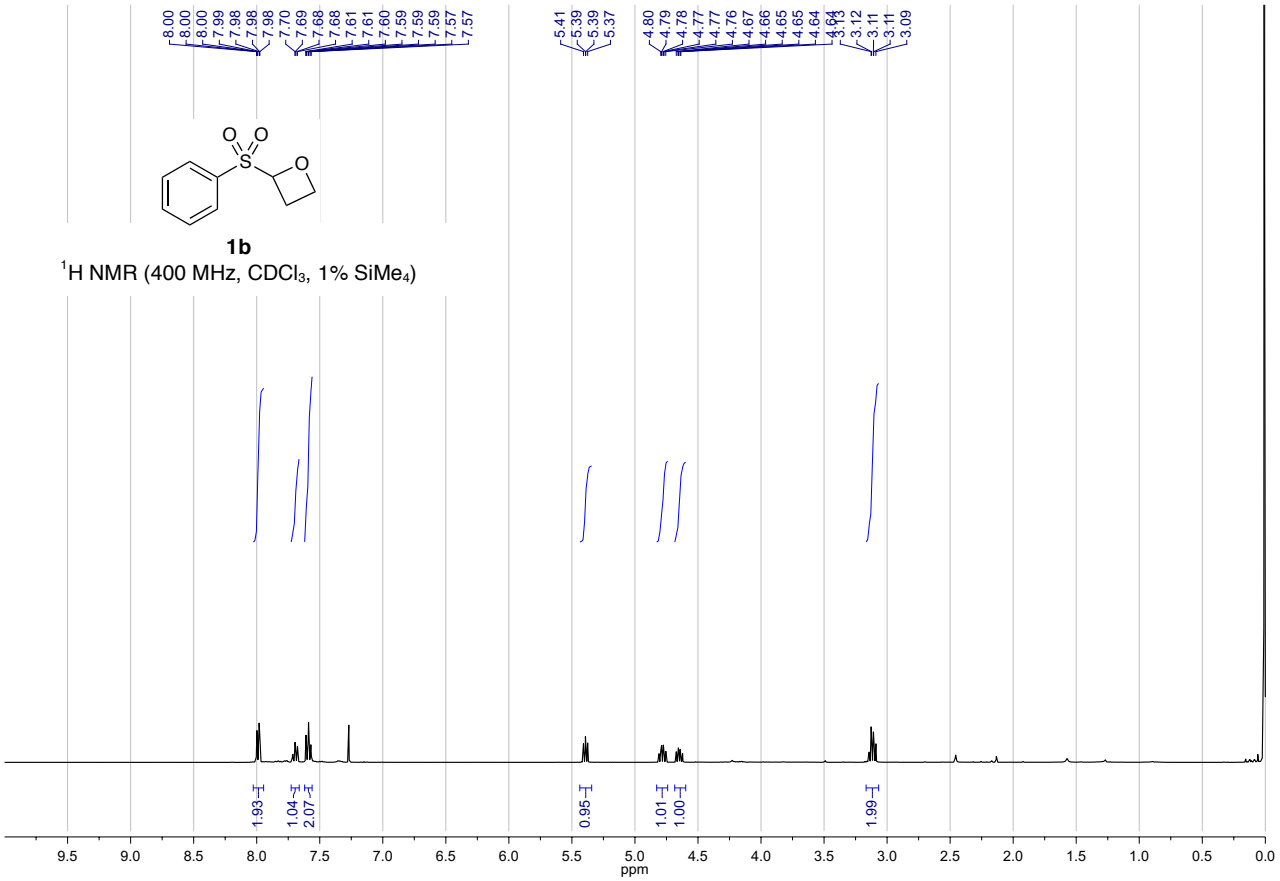
4b

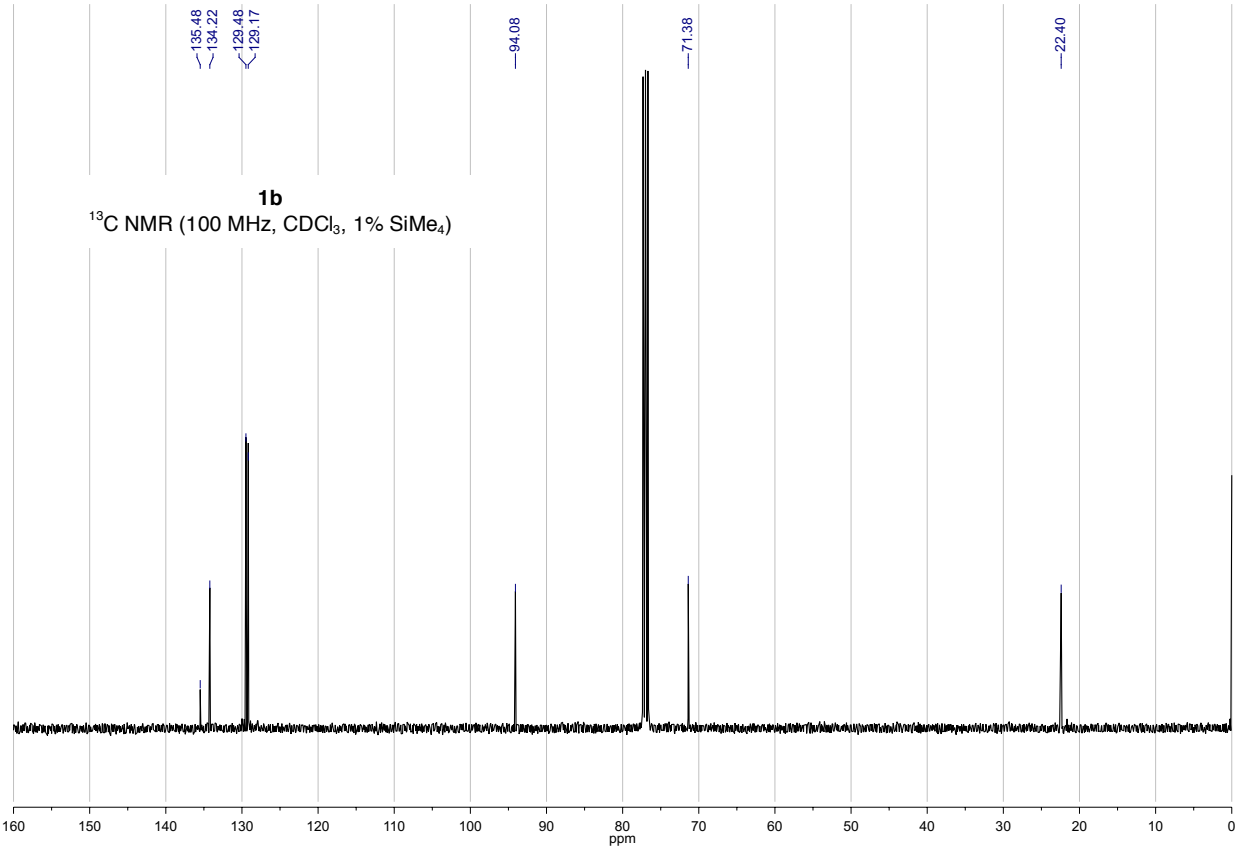
^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)

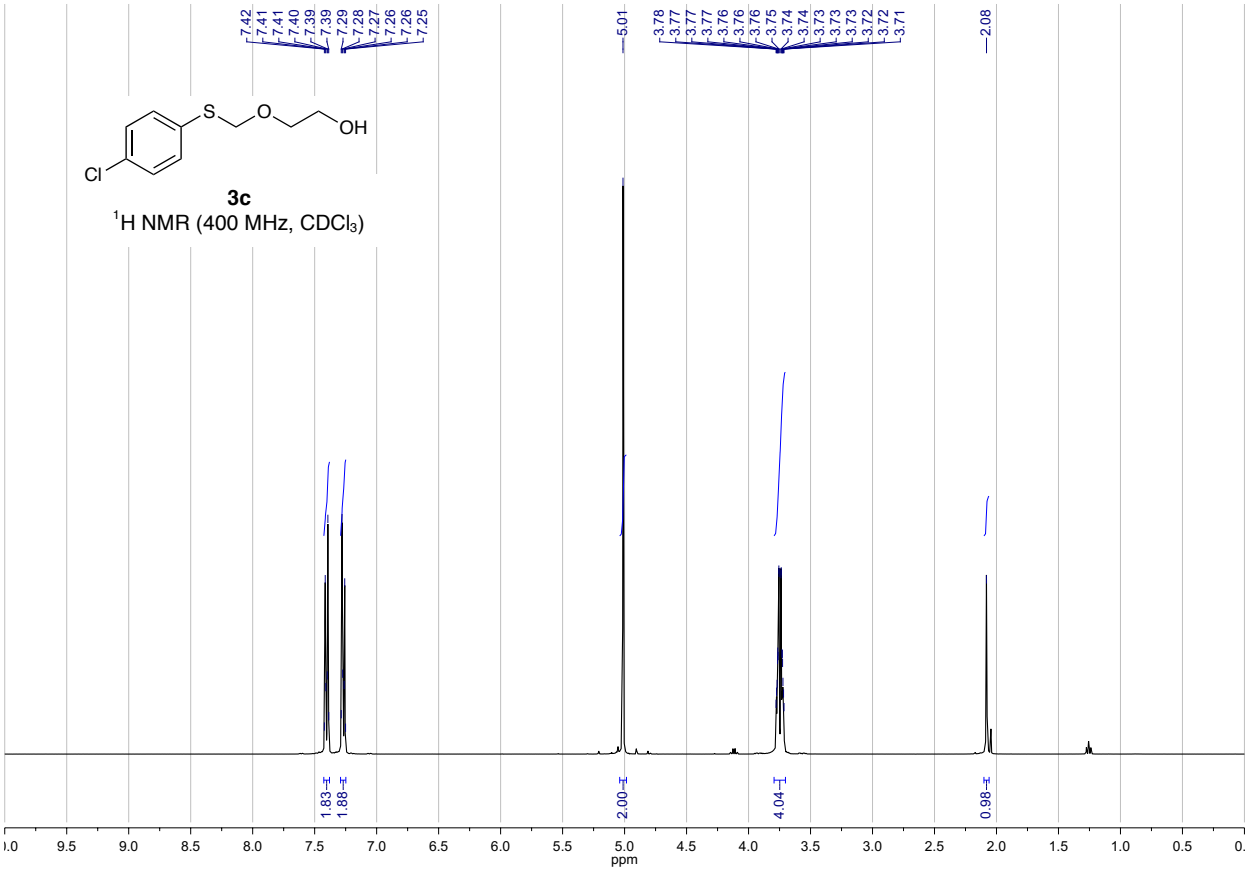


4b

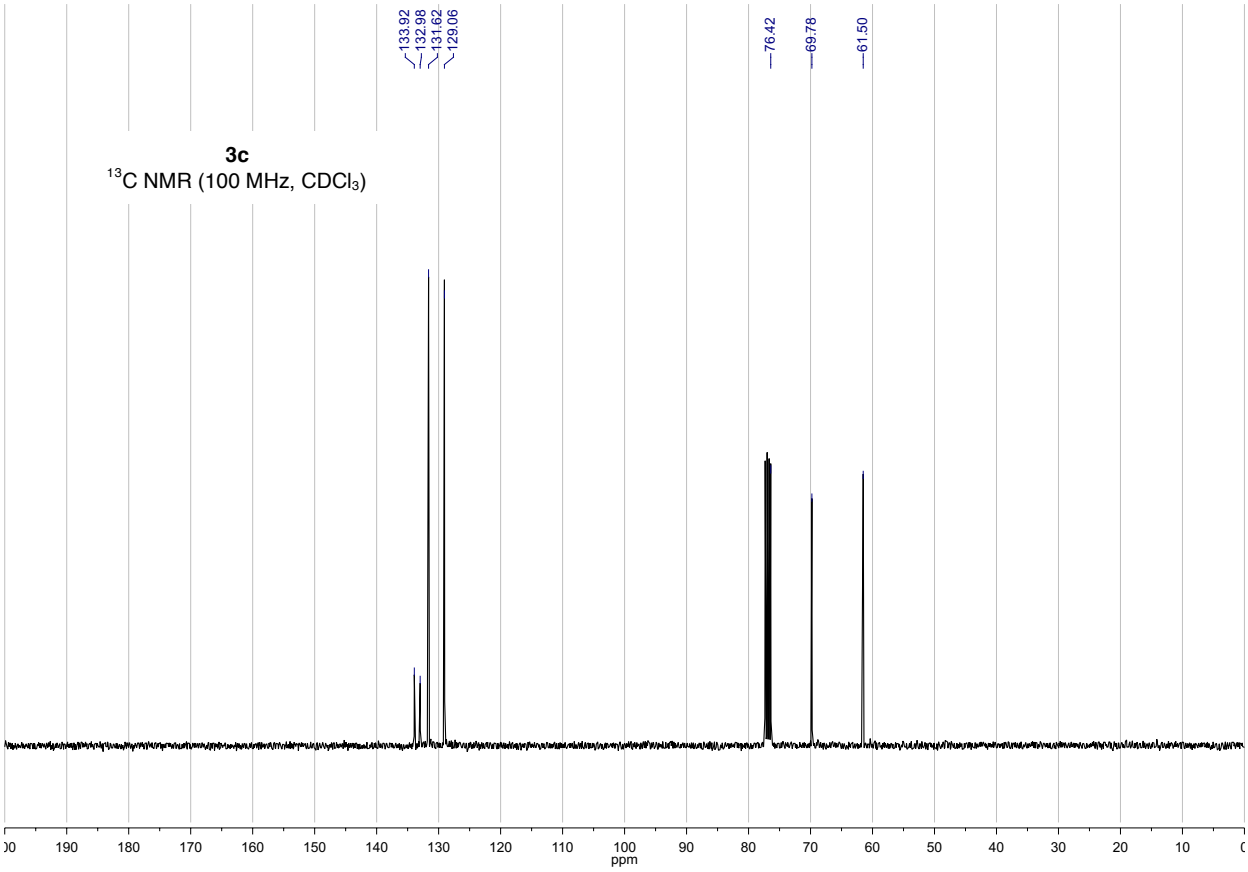
^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)


8.00
8.00
8.00
7.99
7.98
7.98
7.98
7.70
7.69
7.68
7.68
7.61
7.61
7.60
7.59
7.59
7.59
7.57
7.57
7.57
5.41
5.39
5.39
5.37
4.80
4.79
4.78
4.77
4.77
4.76
4.67
4.66
4.65
4.65
4.64
4.64
3.13
3.12
3.11
3.11
3.09
O
O
S
O
1b
1H NMR (400 MHz, CDCl3, 1% SiMe4)
1.93
1.04
2.07
0.95
1.01
1.00
1.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

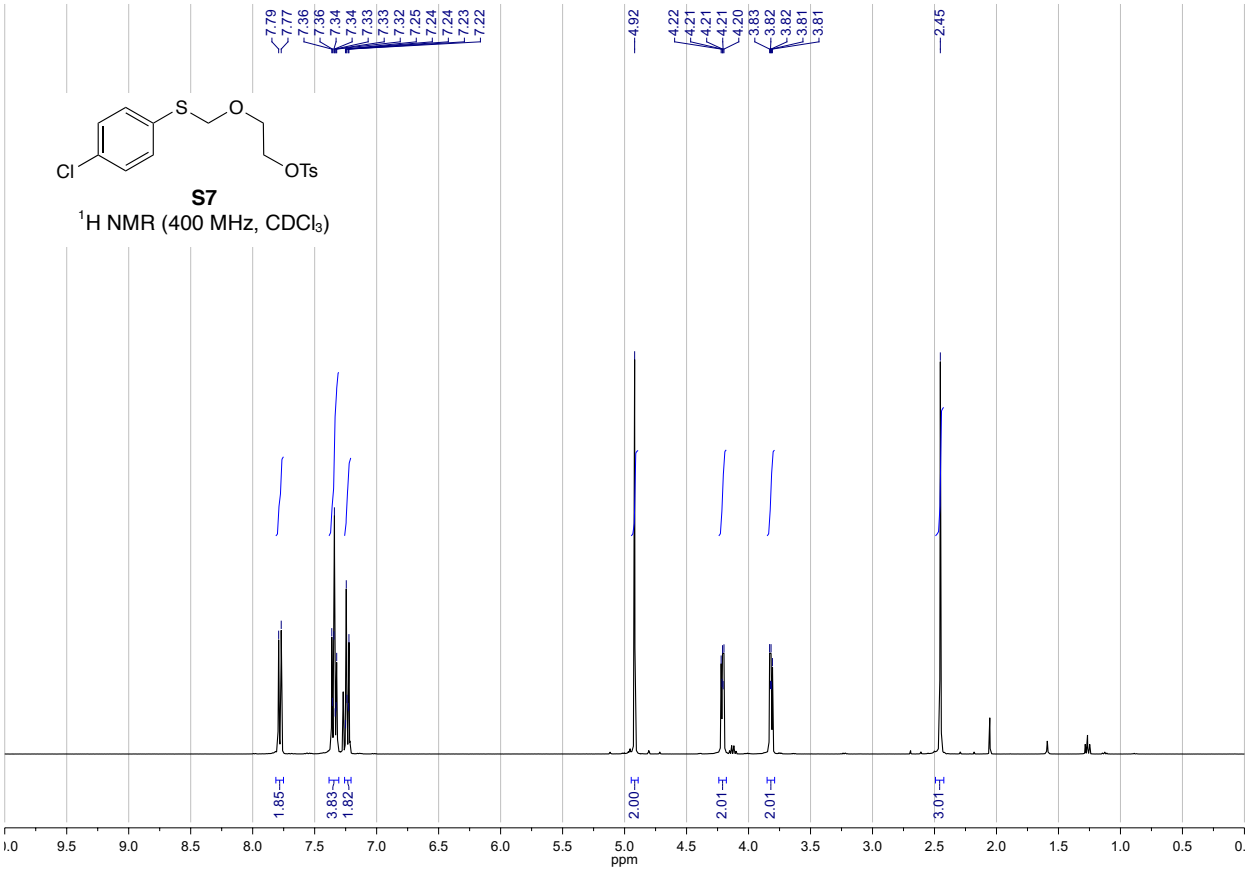

135.48
134.22
129.48
129.17
94.08
71.38
22.40
1b
13C NMR (100 MHz, CDCl3, 1% SiMe4)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

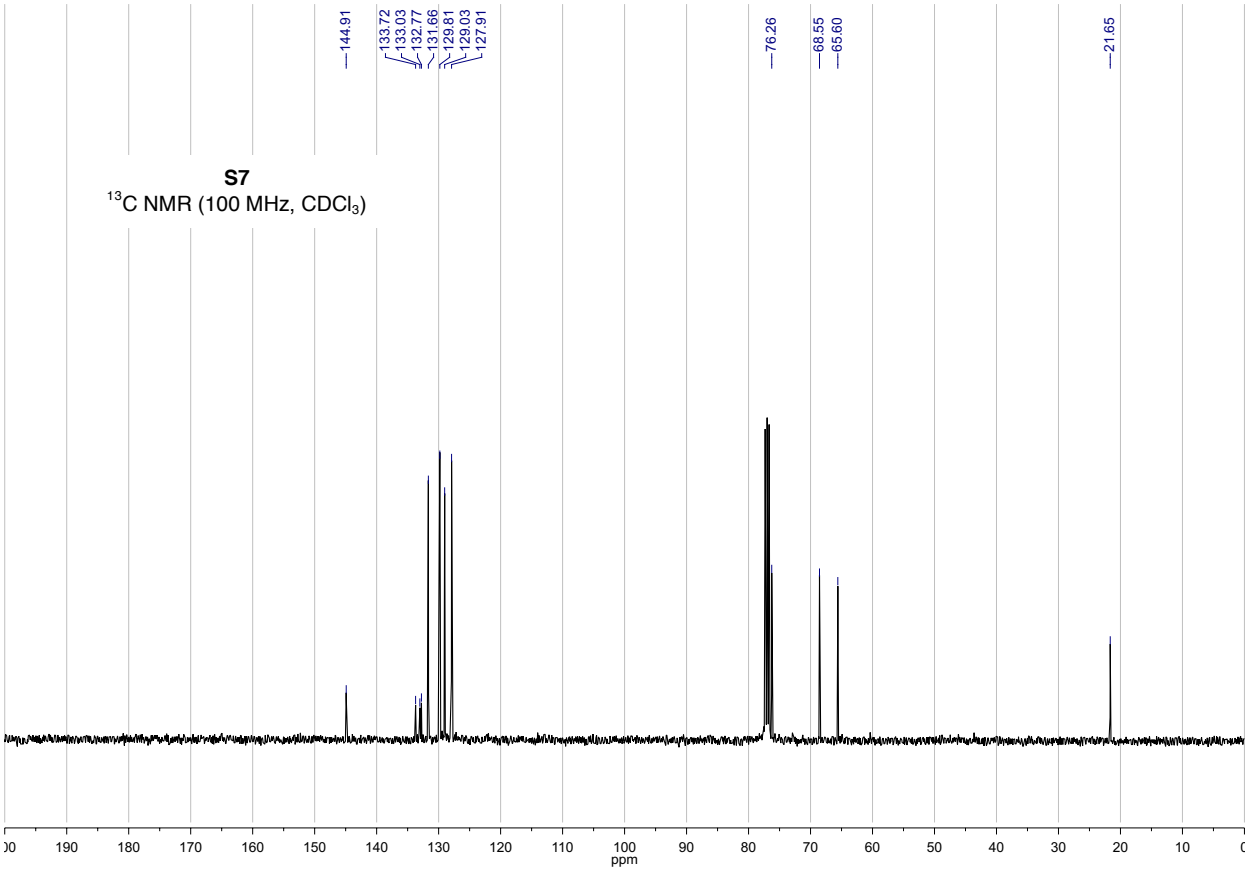


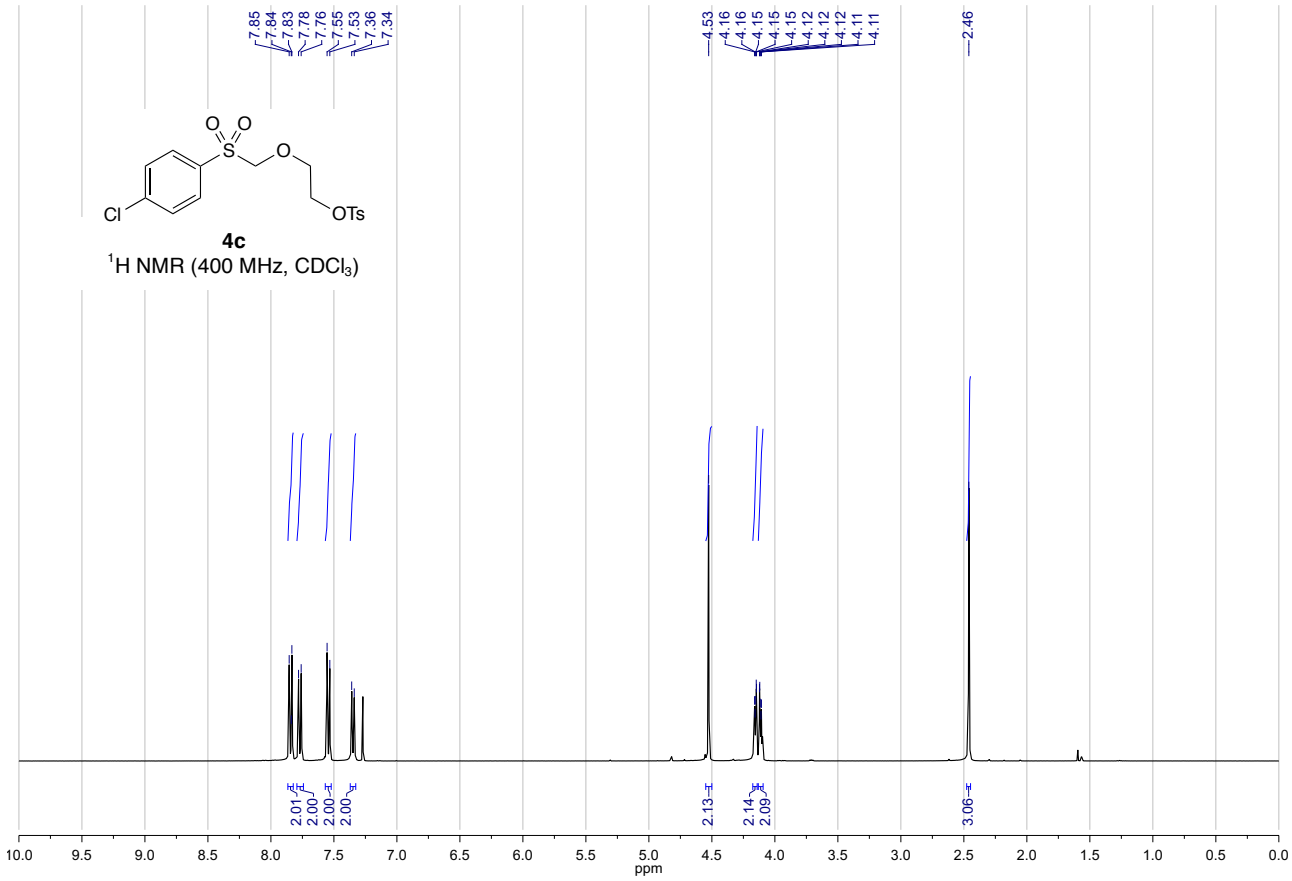
3c
^{1}H NMR (400 MHz, $CDCl_3$)



3c
^{13}C NMR (100 MHz, $CDCl_3$)

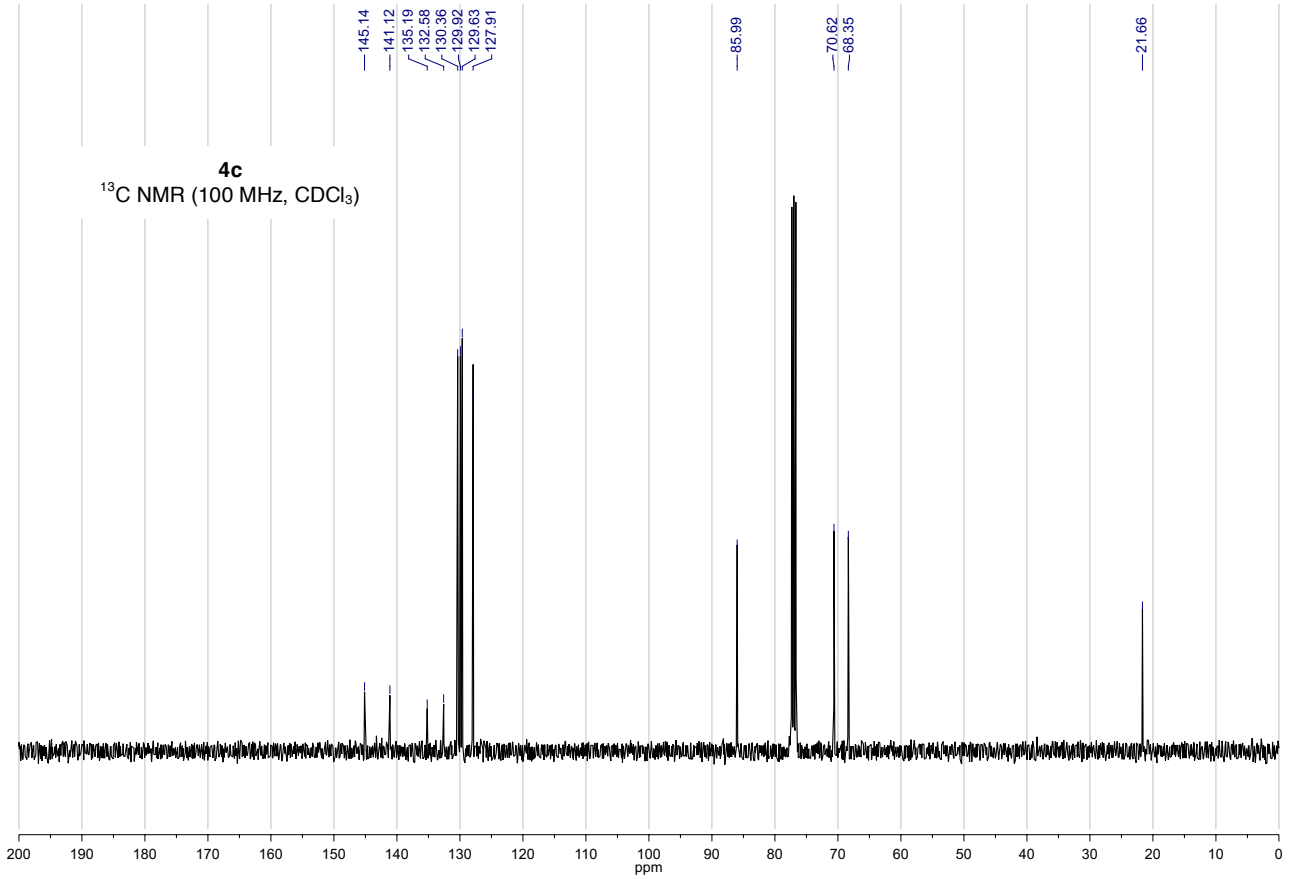

7.79
7.77
7.36
7.36
7.34
7.34
7.33
7.33
7.32
7.25
7.24
7.24
7.23
7.22
4.92
4.22
4.21
4.21
4.21
4.20
3.83
3.82
3.82
3.81
3.81
2.45
S
O
Cl
OTs
S7
^{1}H NMR (400 MHz, CDCl$_3$)
1.85
3.83
1.82
2.00
2.01
2.01
3.01
ppm


144.91
133.72
133.03
132.77
131.66
129.81
129.03
127.91
76.26
68.55
65.60
21.65
S7
^{13}C NMR (100 MHz, CDCl$_3$)
ppm



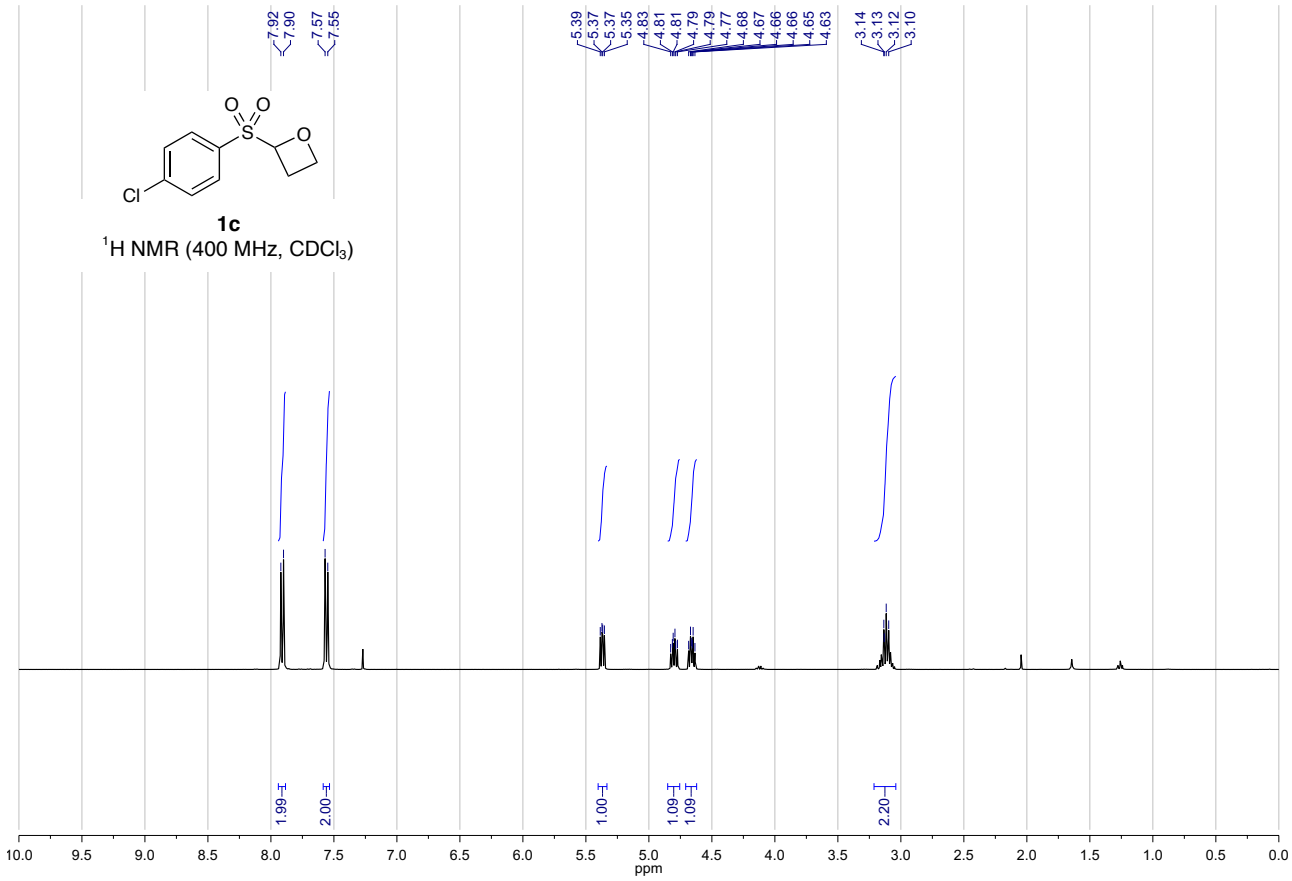
4c

^{1}H NMR (400 MHz, $CDCl_3$)

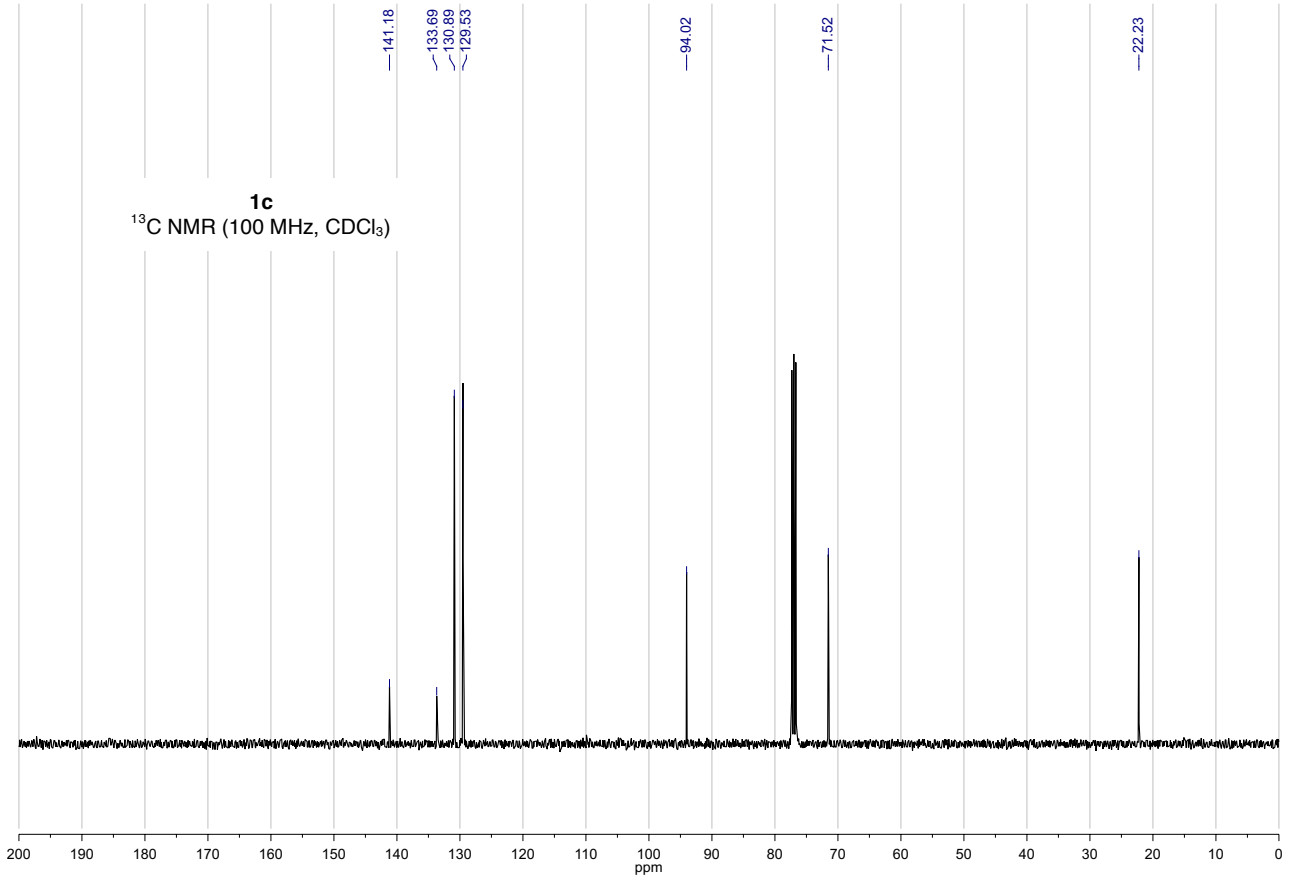


4c

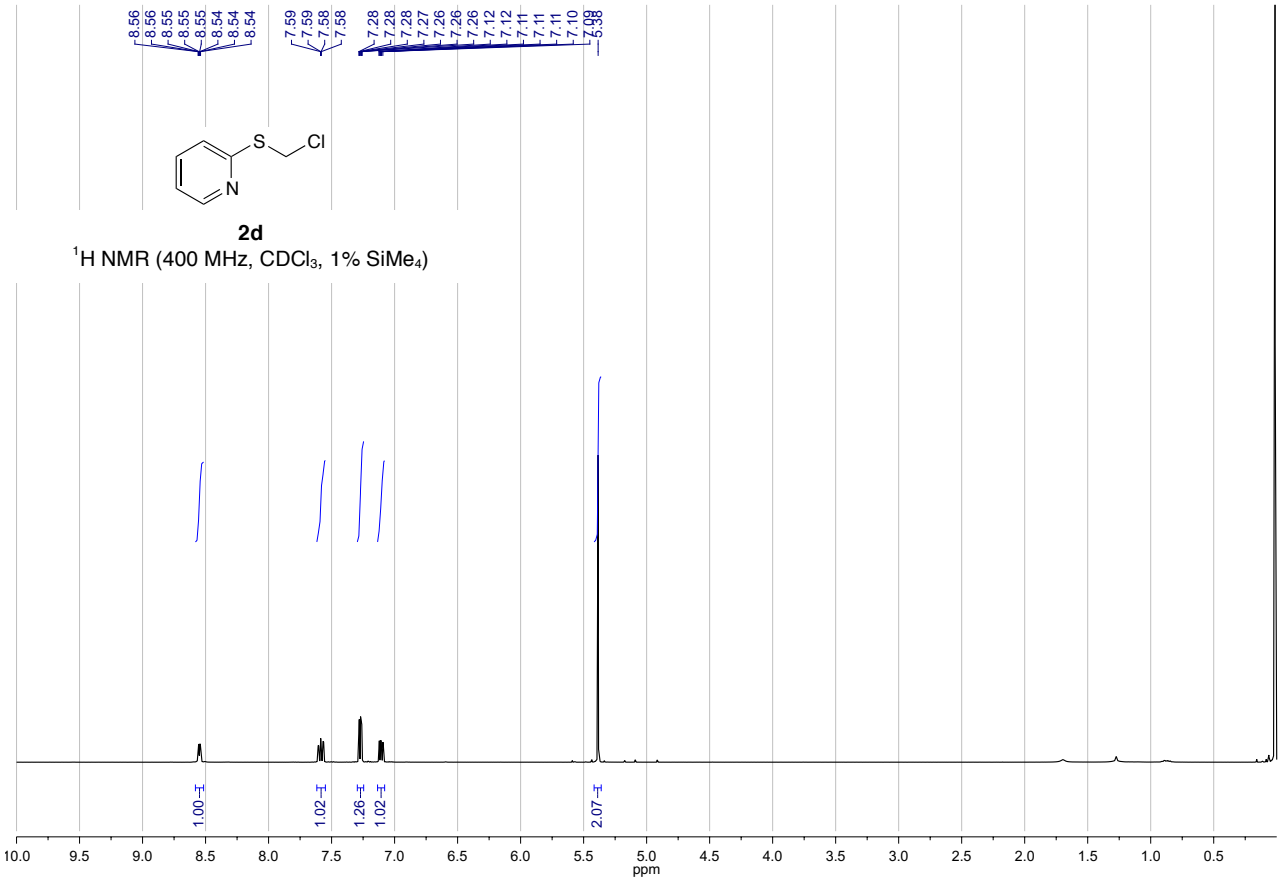
^{13}C NMR (100 MHz, $CDCl_3$)



1c
^{1}H NMR (400 MHz, $CDCl_3$)

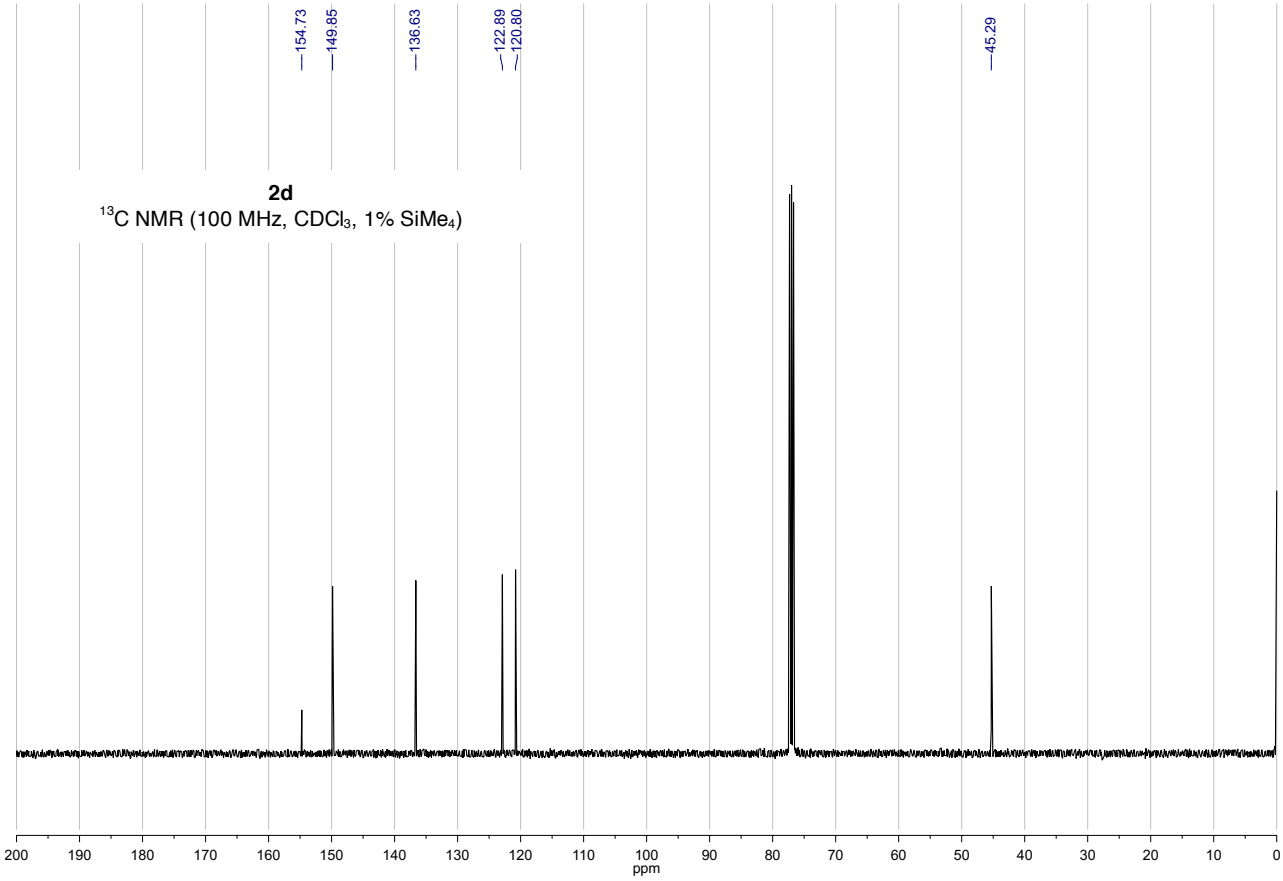


1c
^{13}C NMR (100 MHz, $CDCl_3$)



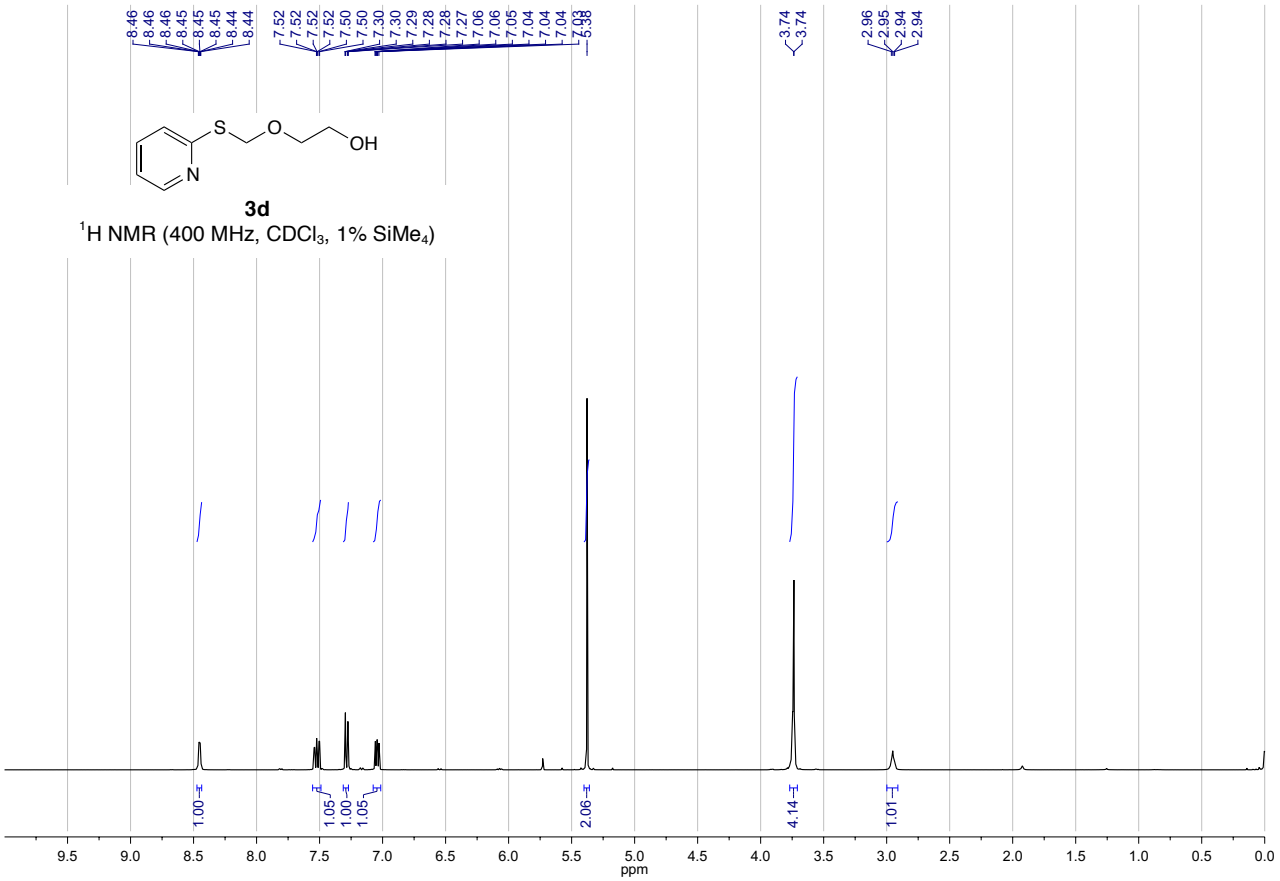
2d

^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)



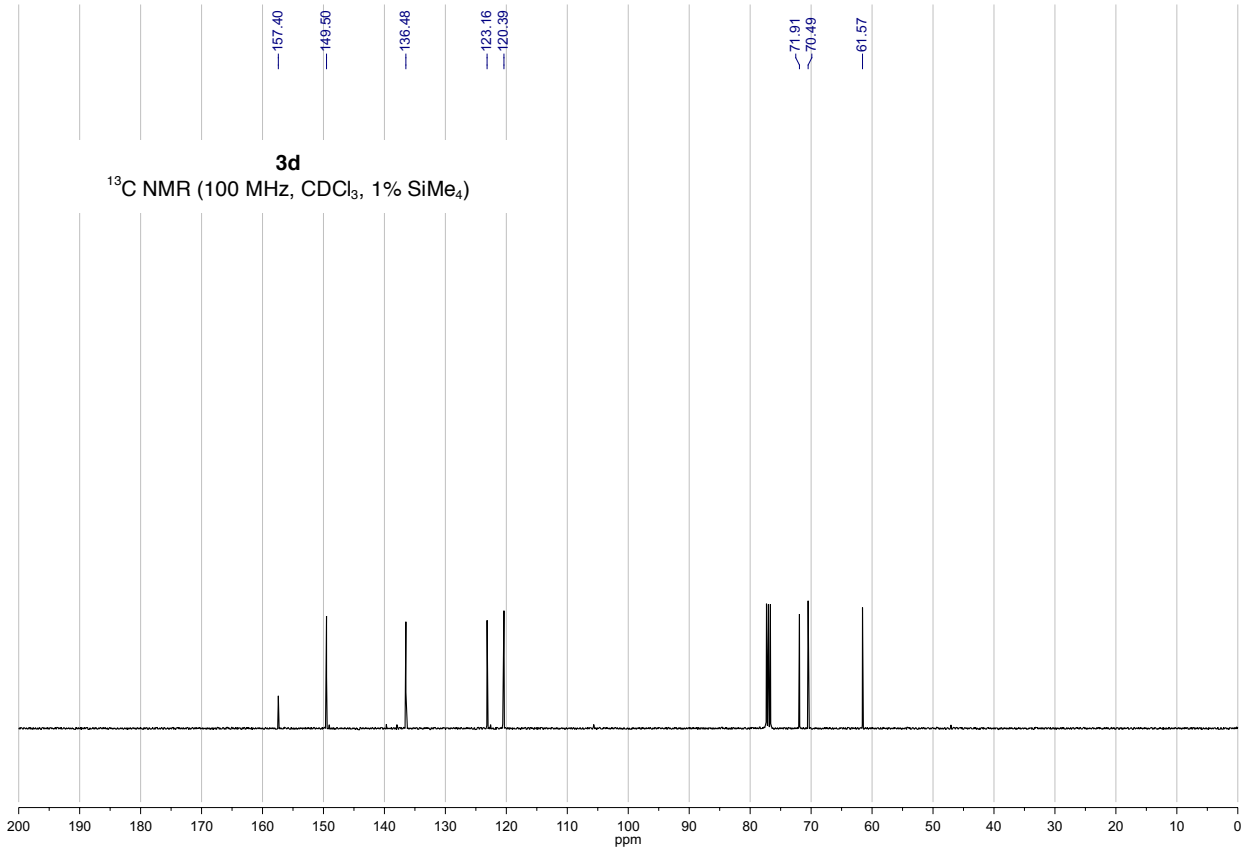
2d

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)



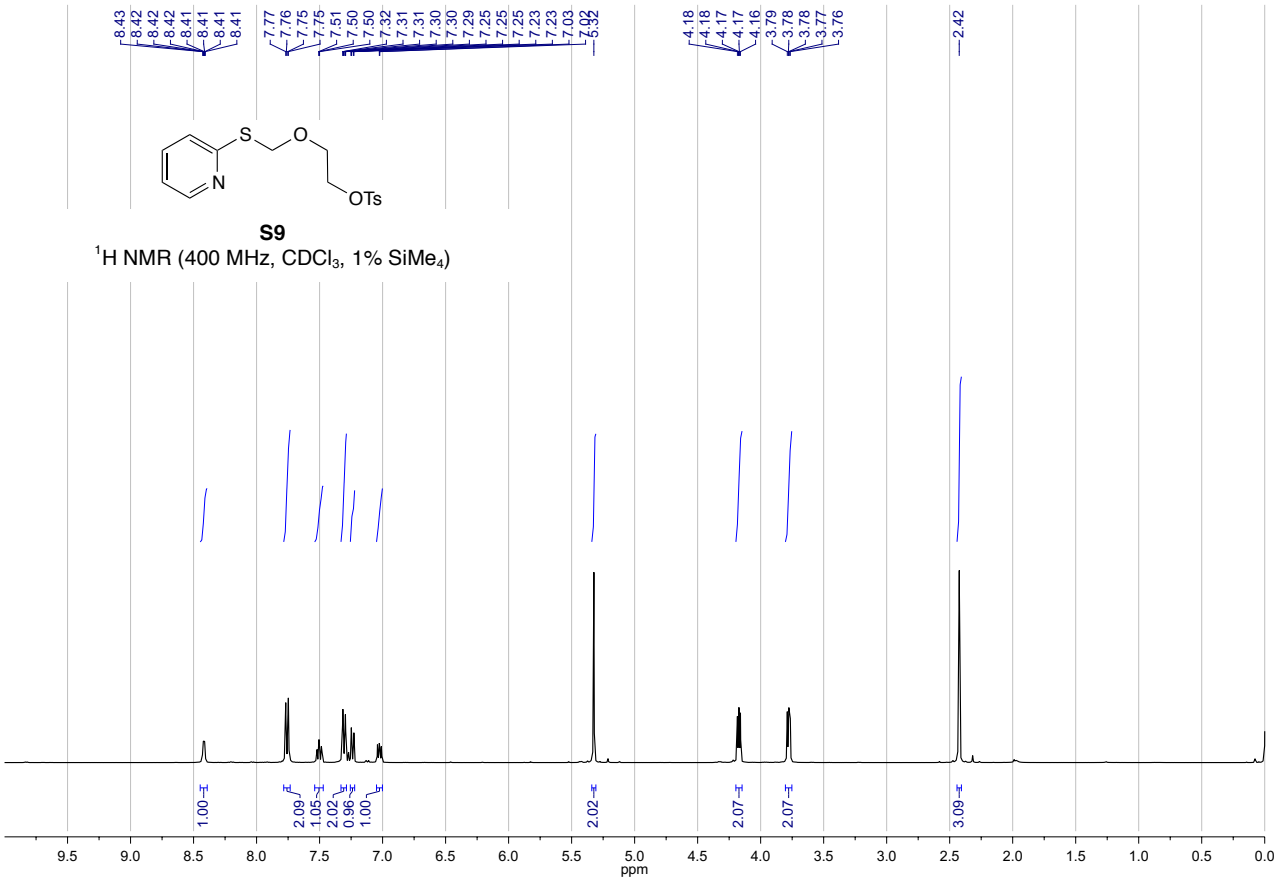
3d

^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)



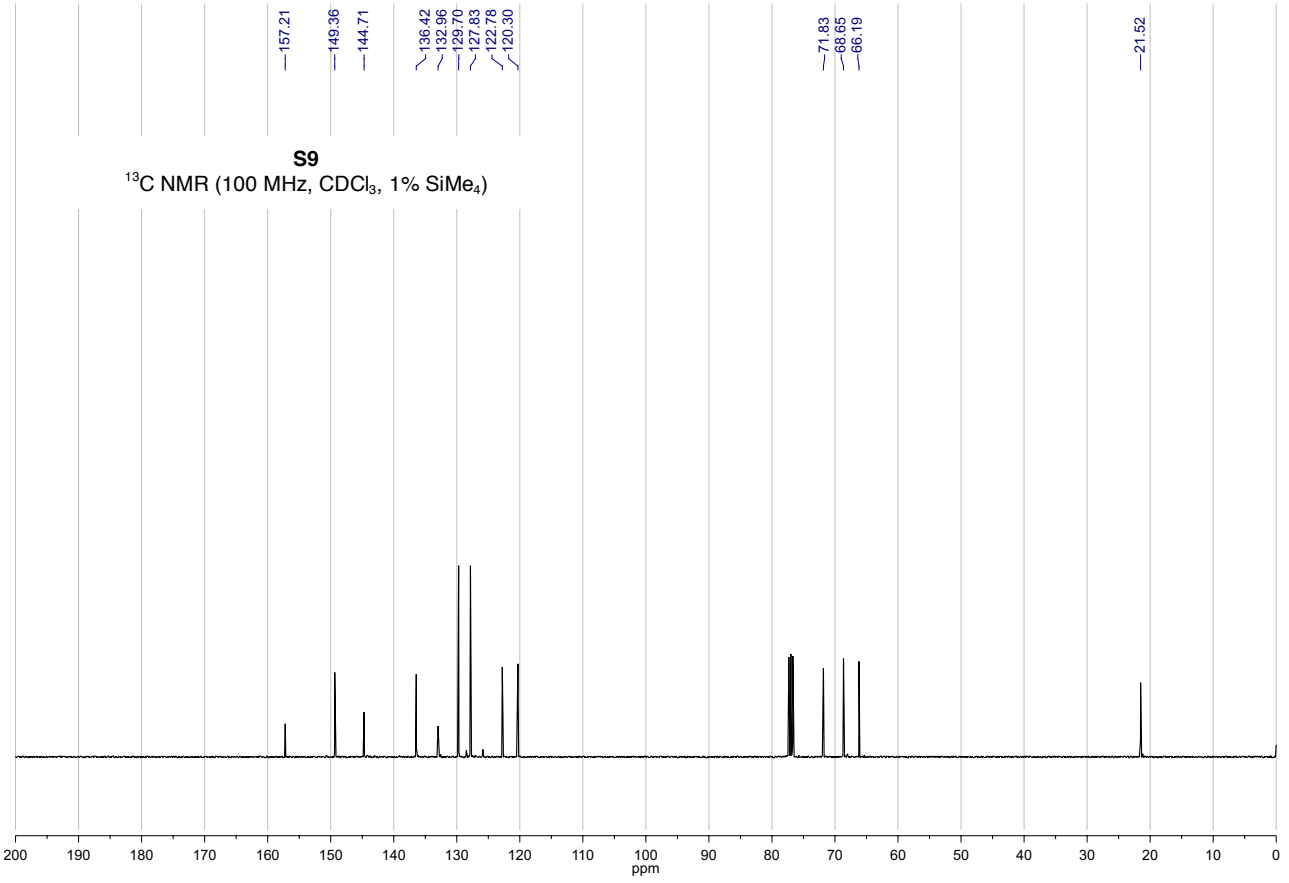
3d

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)



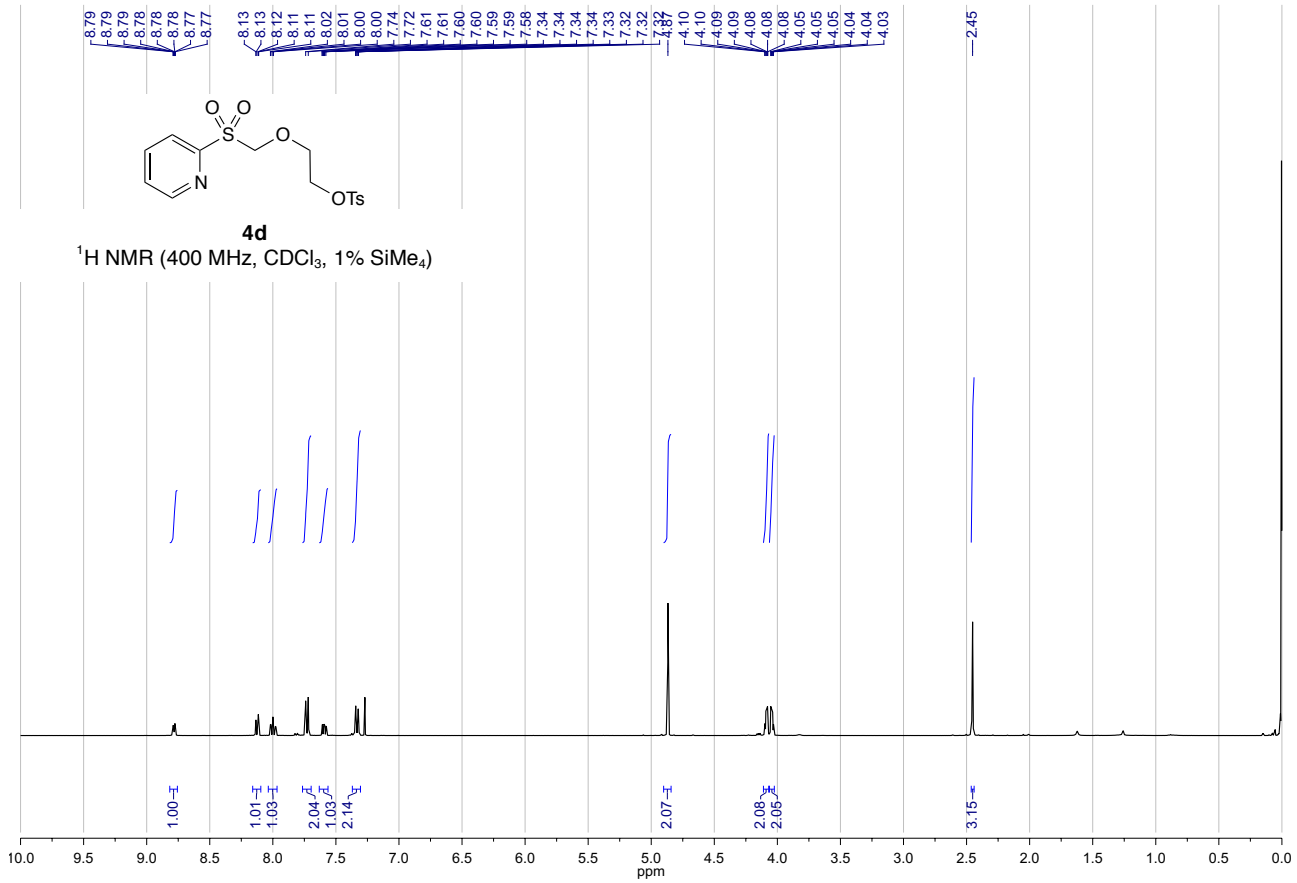
S9

^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)



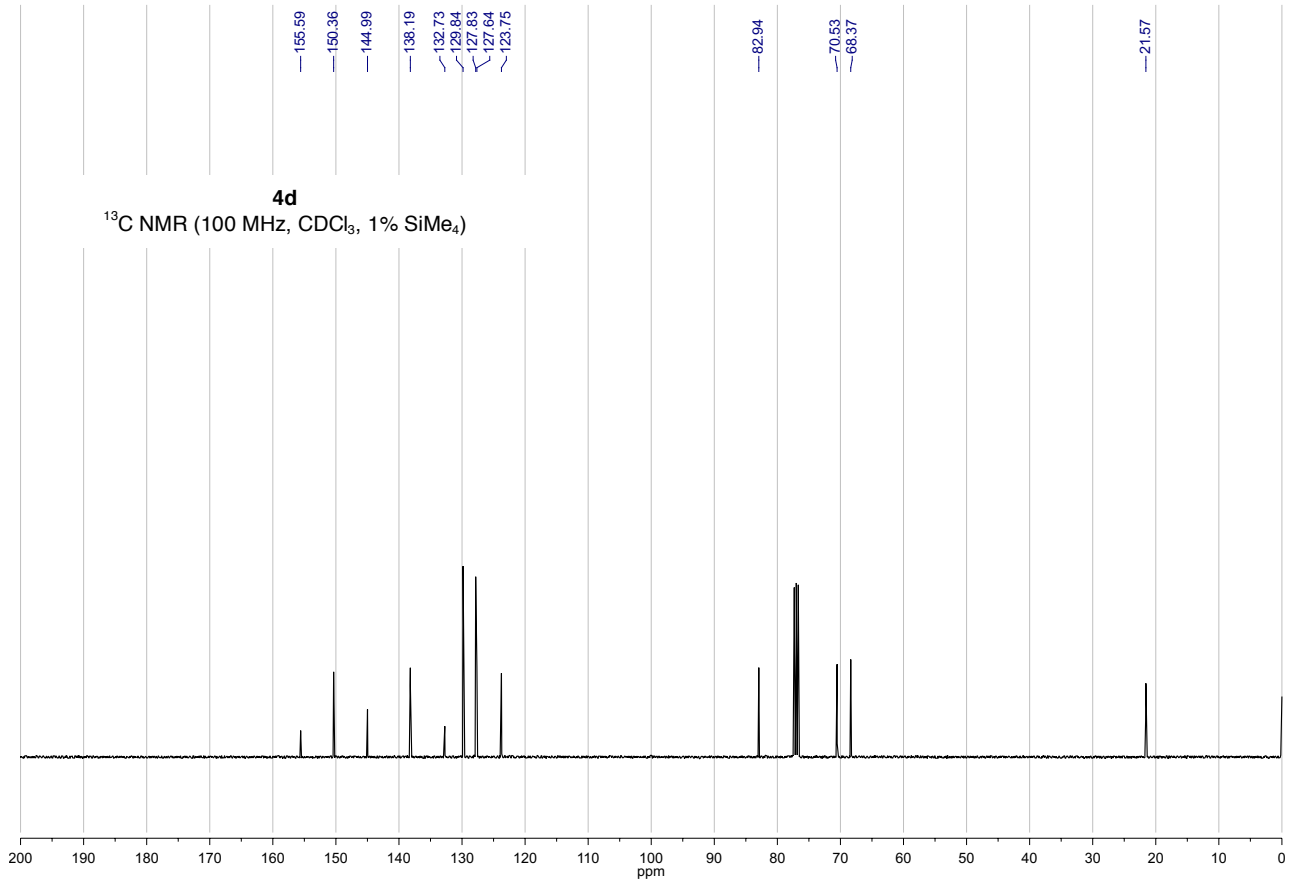
S9

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)



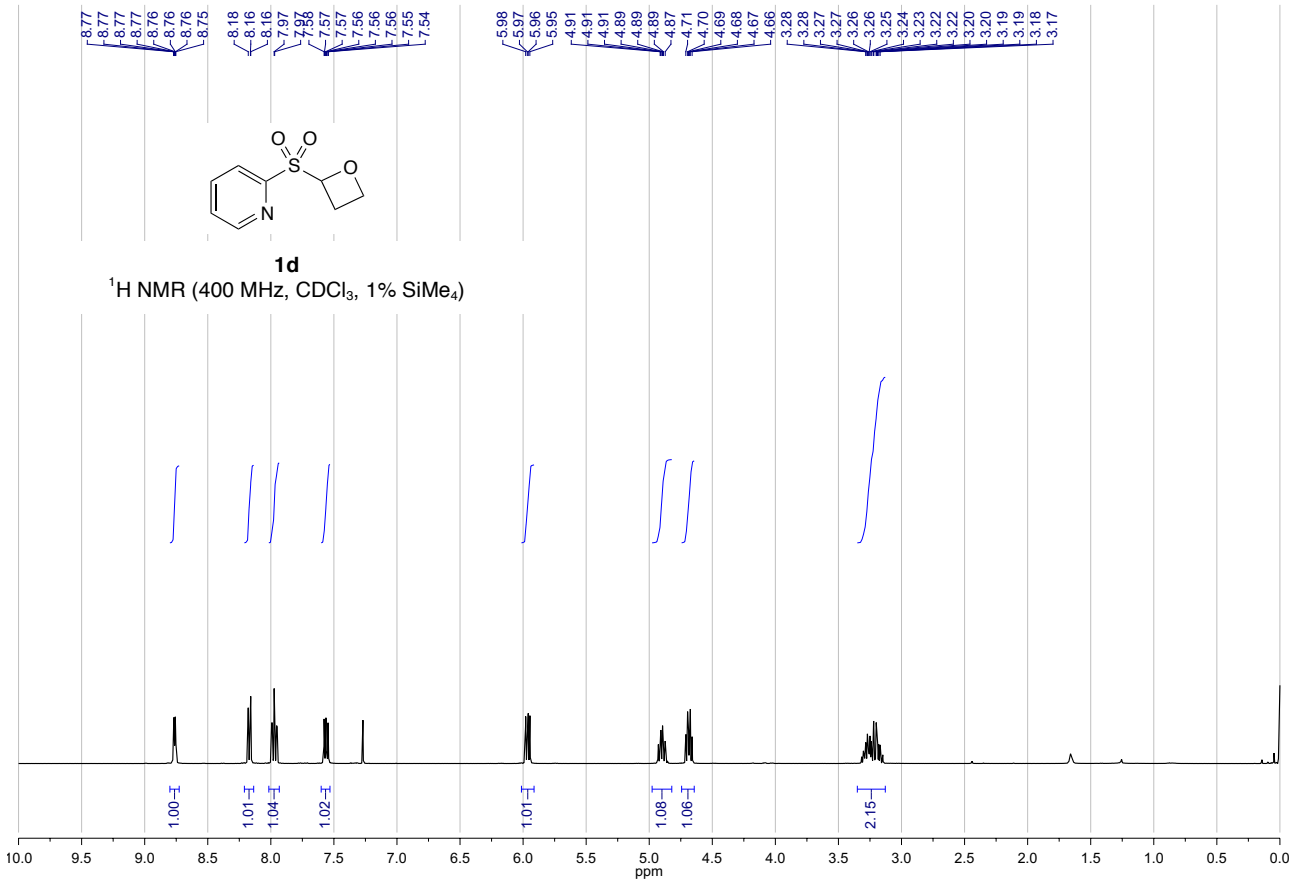
4d

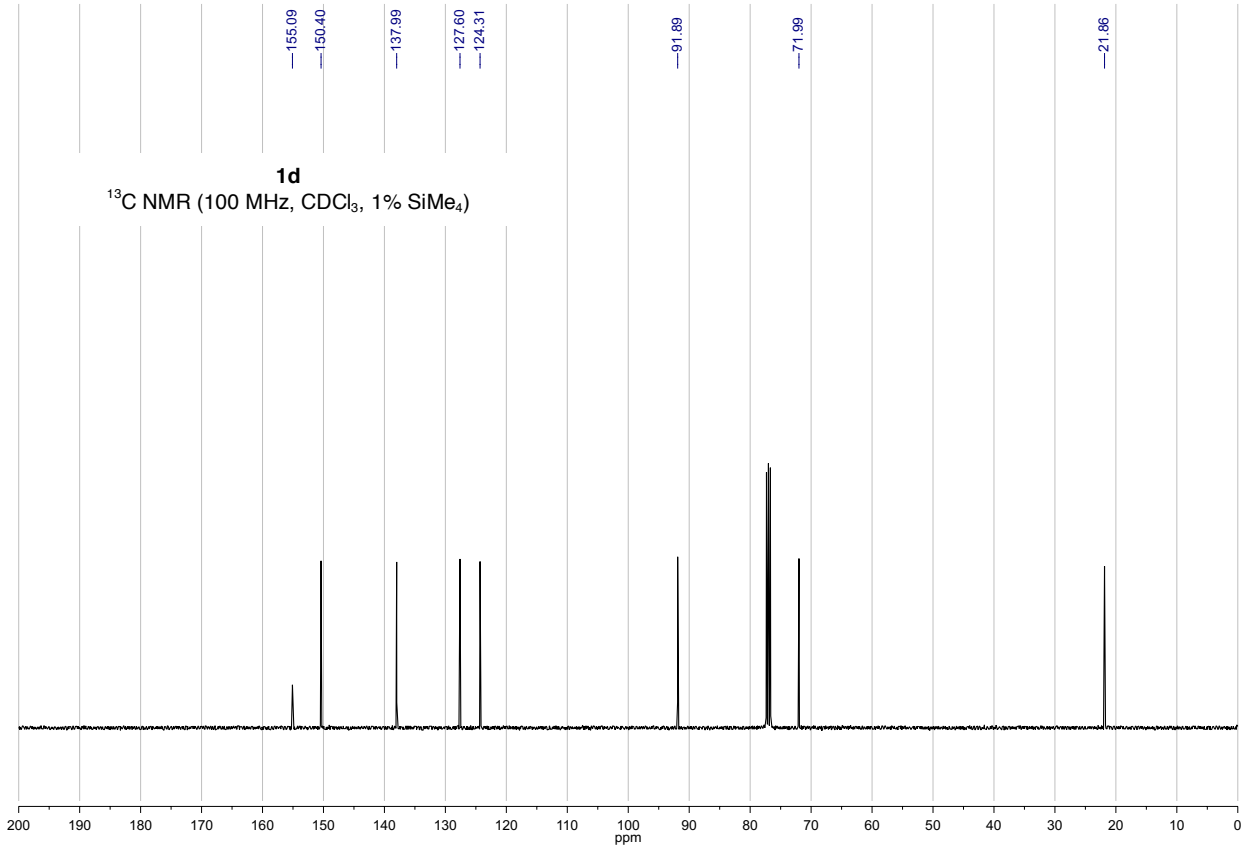
^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)

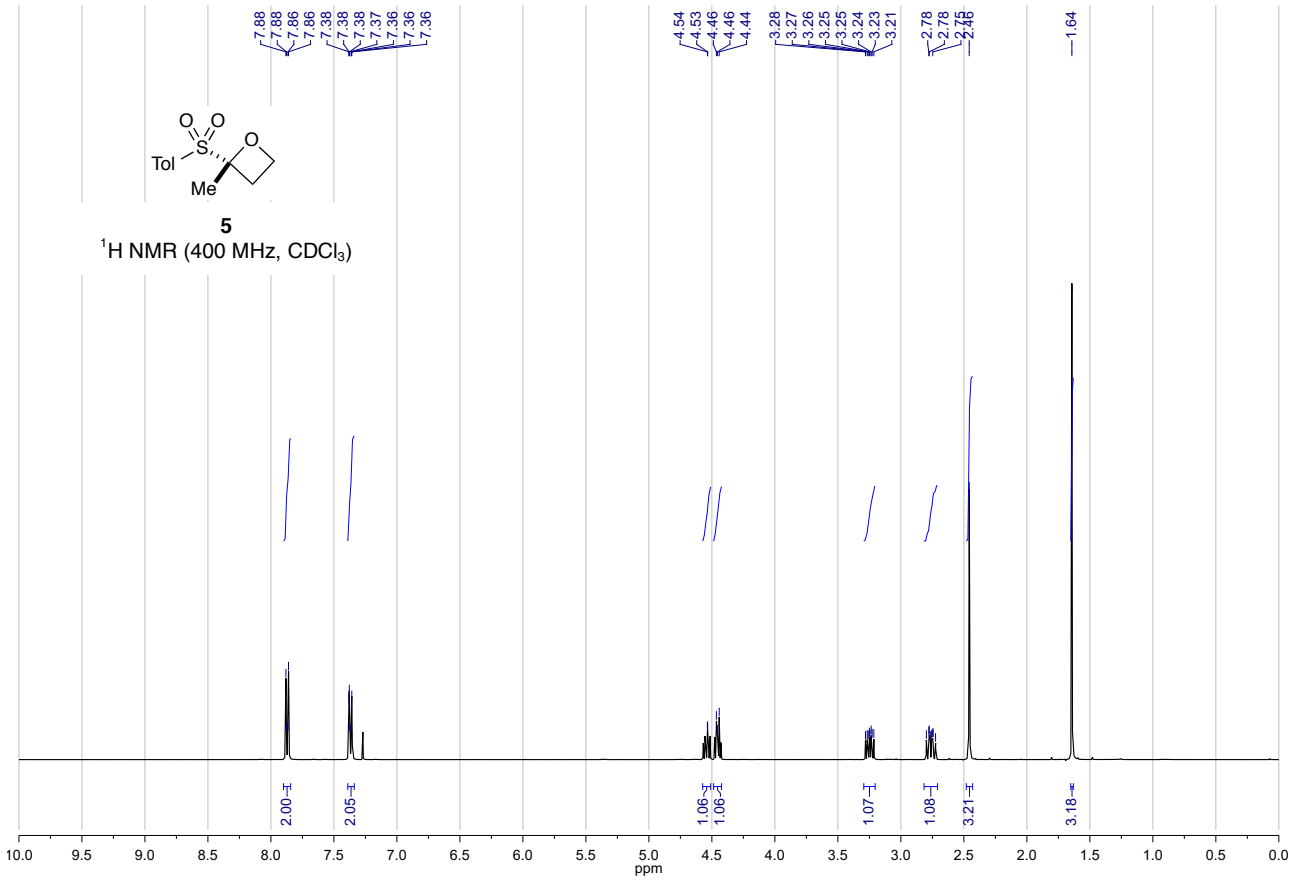


4d

^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)

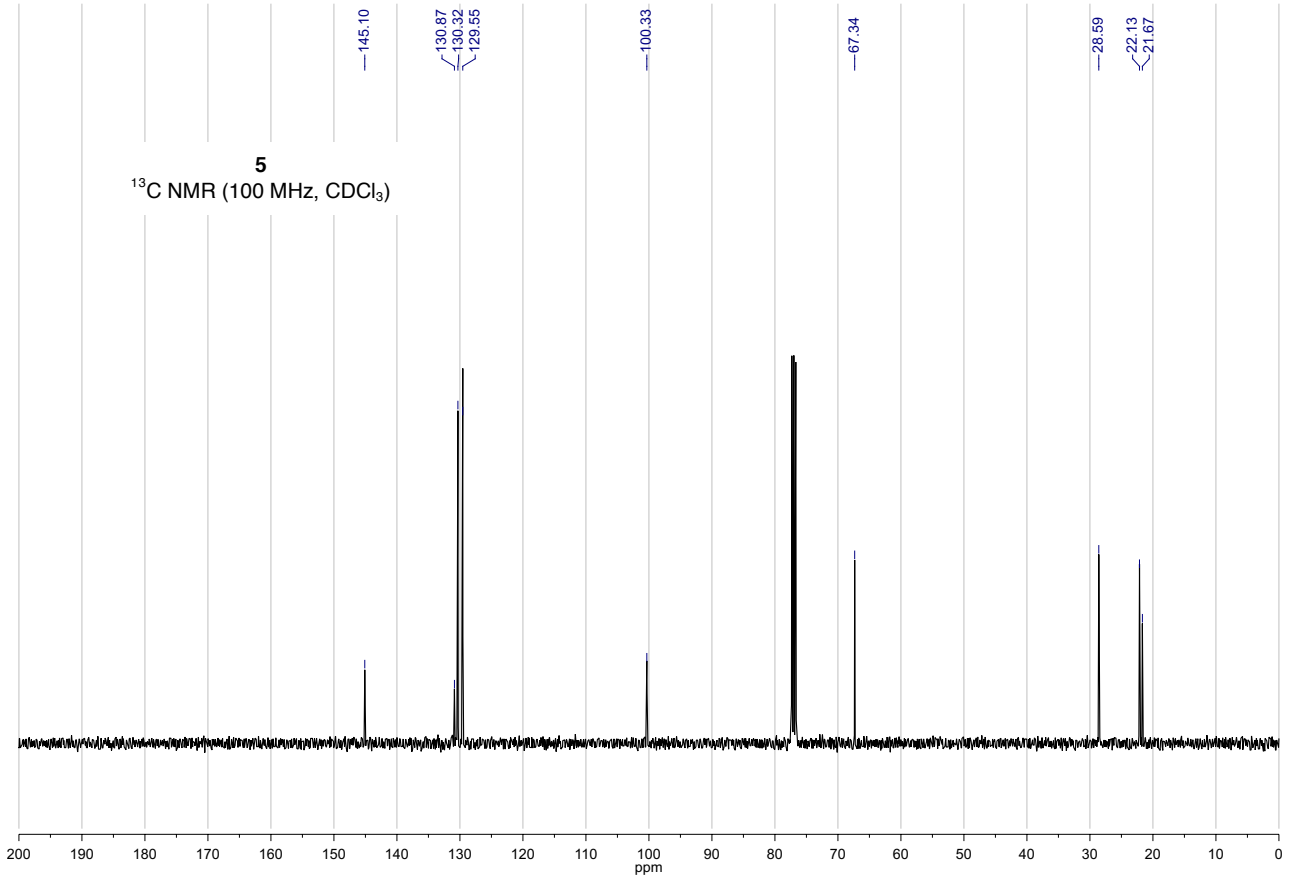

8.77 8.77 8.77 8.77 8.76 8.76 8.76 8.75
8.18 8.16 8.16 7.97 7.97 7.58 7.57 7.57 7.56 7.56 7.56 7.55 7.54
5.98 5.97 5.96 5.95
4.91 4.91 4.89 4.89 4.89 4.89 4.87 4.71 4.70 4.69 4.68 4.67 4.66
3.28 3.28 3.27 3.27 3.26 3.26 3.25 3.24 3.23 3.22 3.22 3.20 3.20 3.19 3.19 3.18 3.17
O
O
S
O
N
1d
^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)
1.00
1.01
1.04
1.02
1.01
1.08
1.06
2.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


155.09
150.40
137.99
127.60
124.31
91.89
71.99
21.86
1d
^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



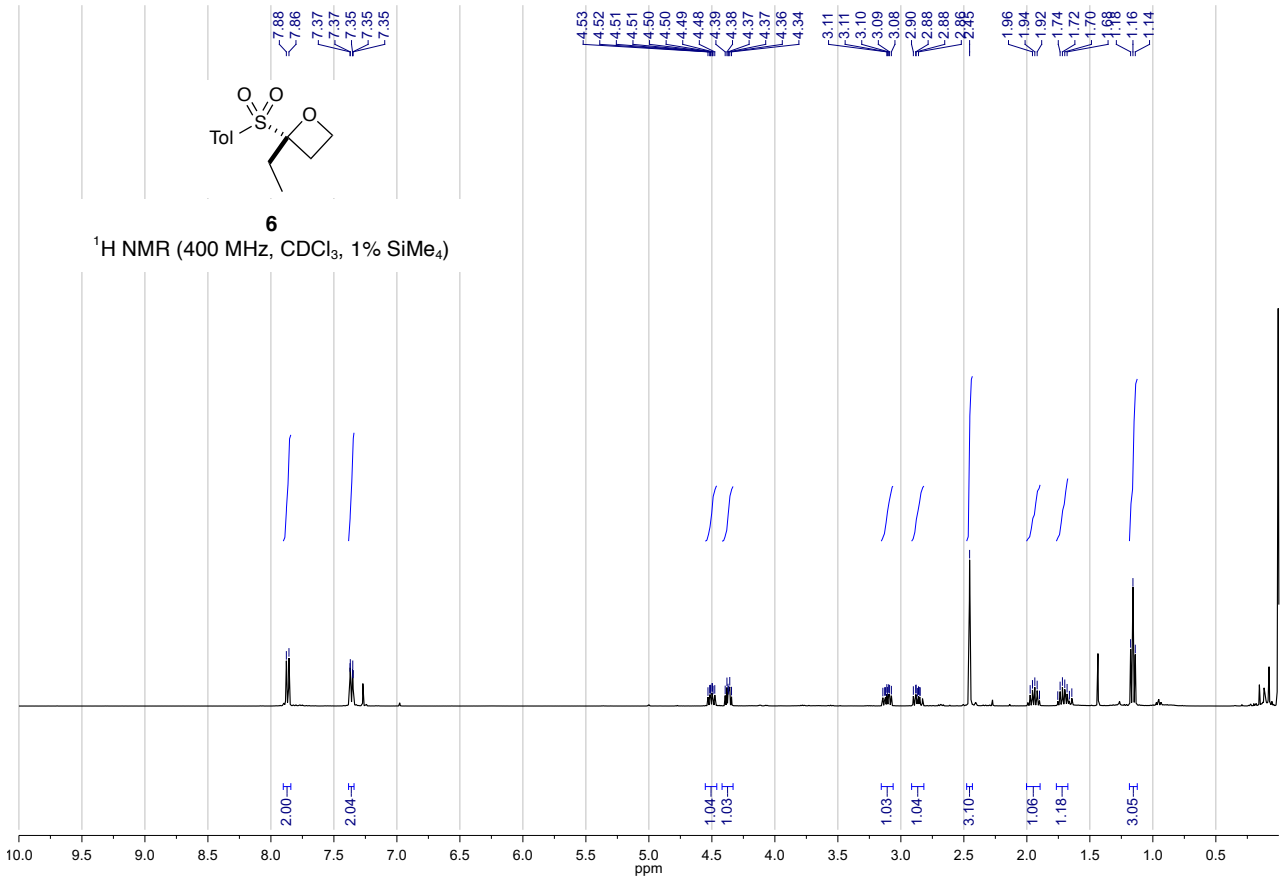
5

^{1}H NMR (400 MHz, $CDCl_3$)



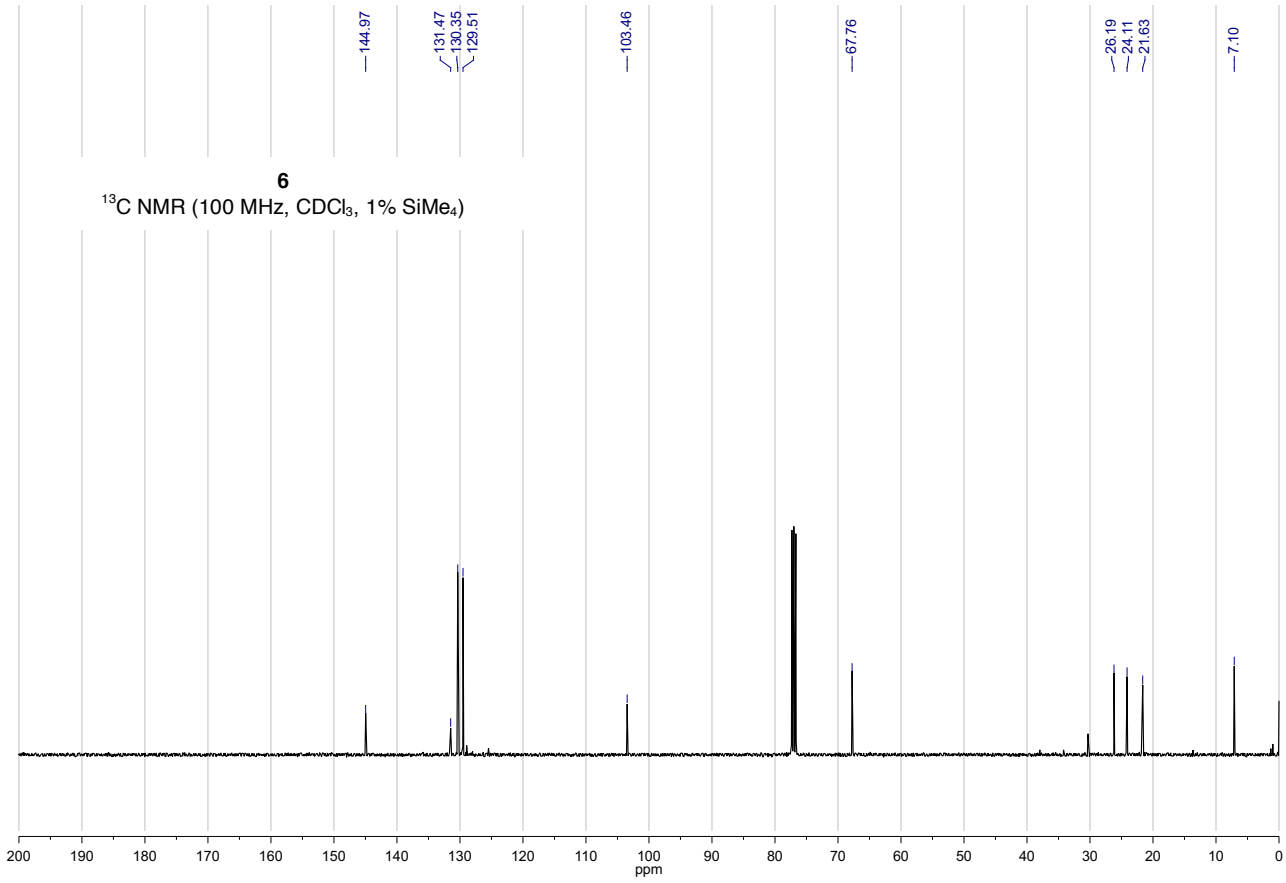
5

^{13}C NMR (100 MHz, $CDCl_3$)



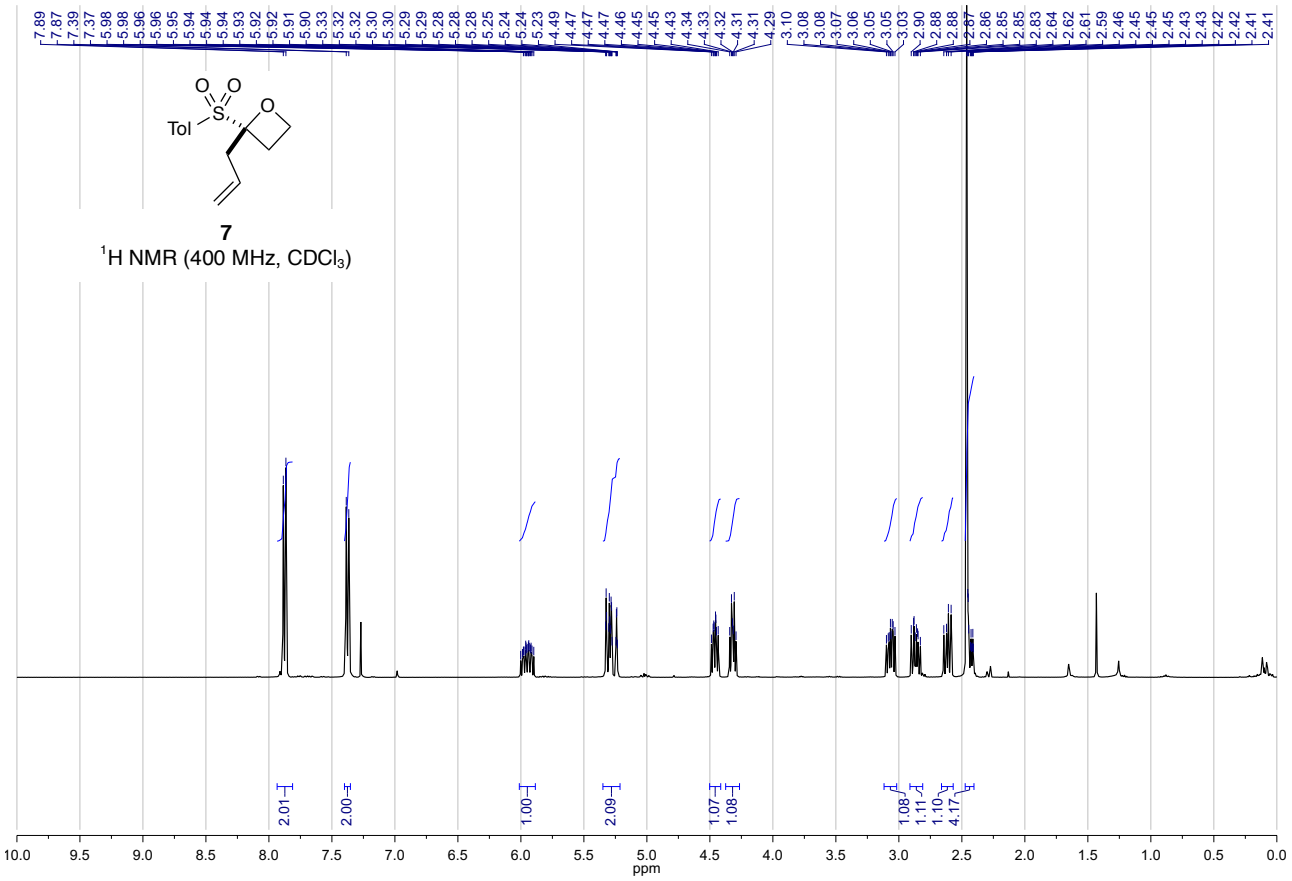
6

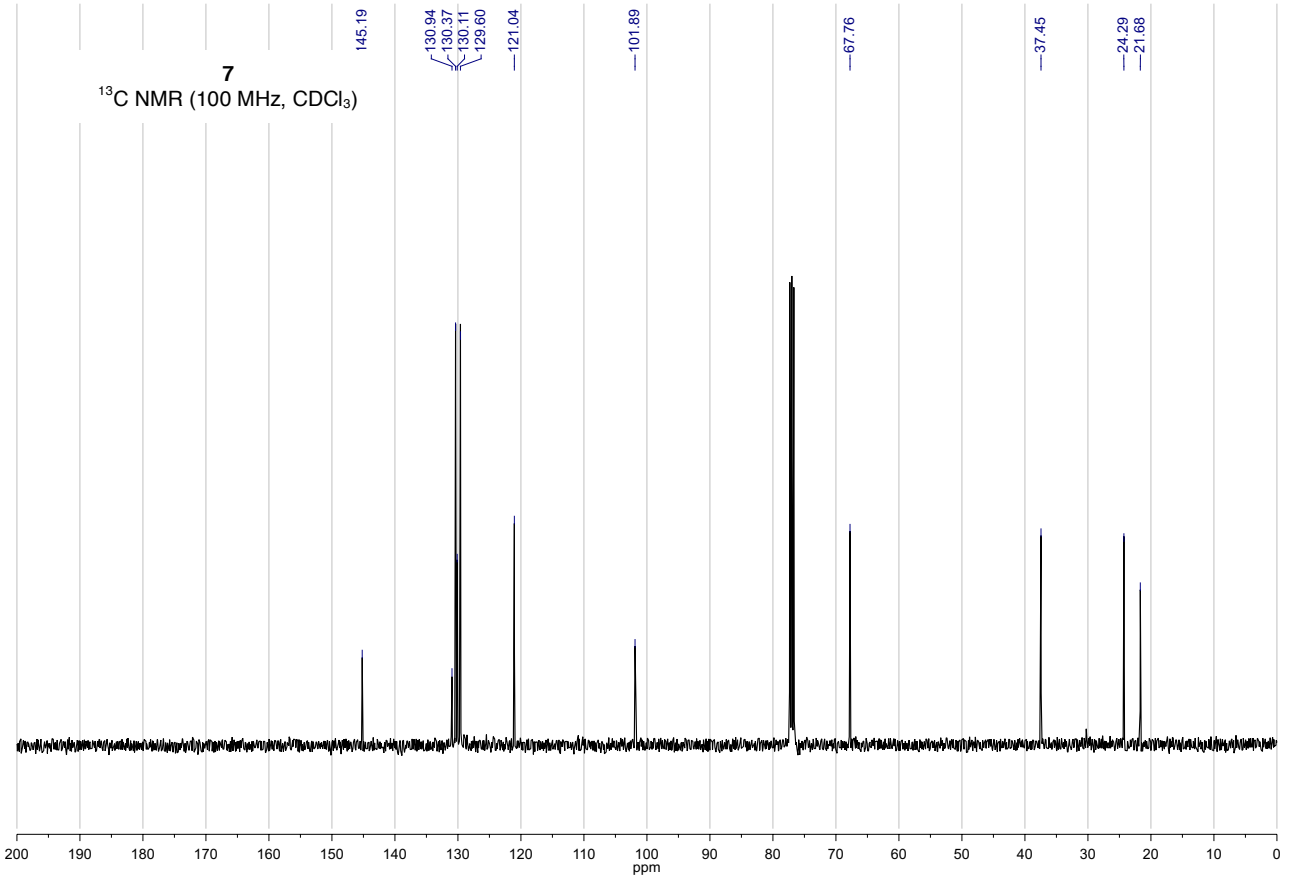
^{1}H NMR (400 MHz, $CDCl_3$, 1% $SiMe_4$)

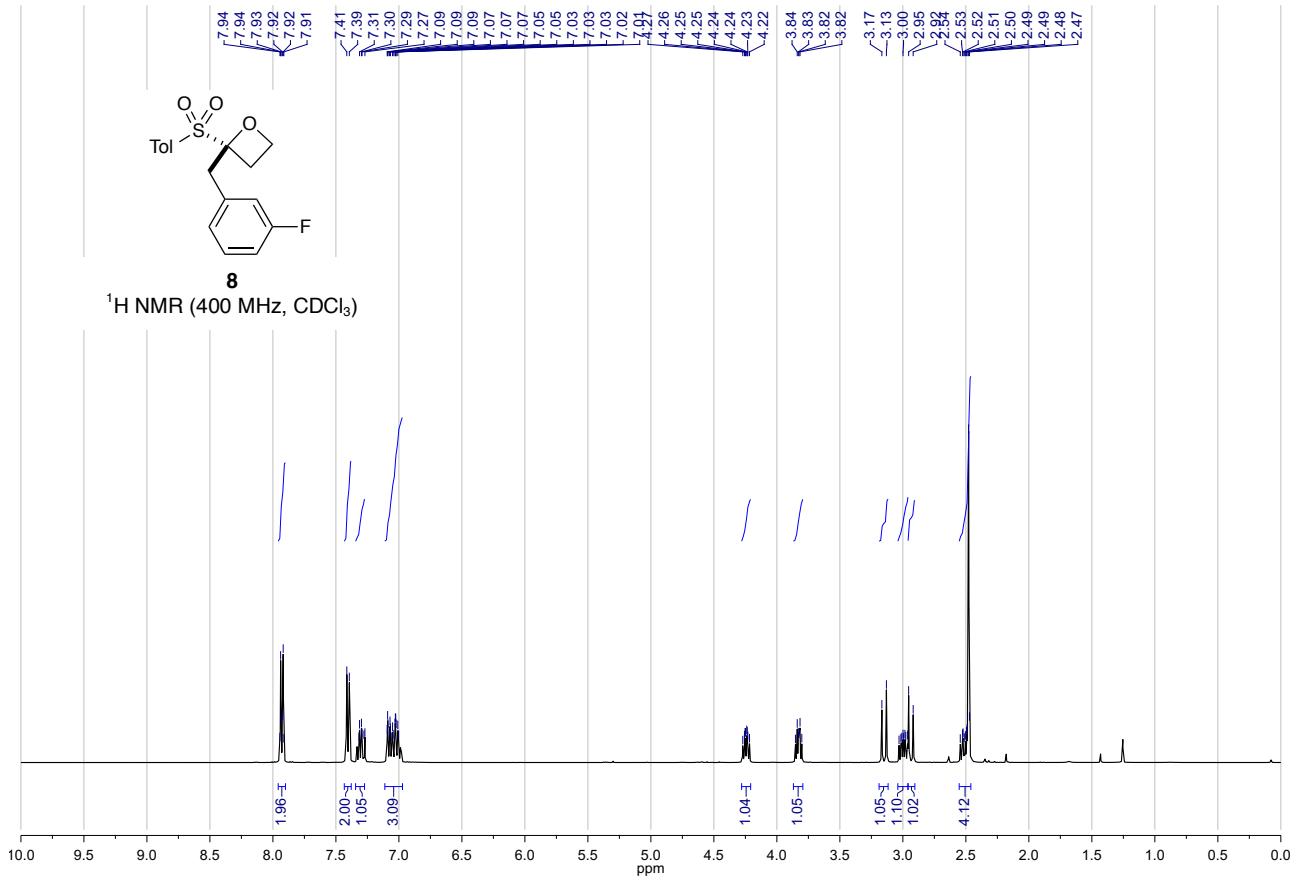


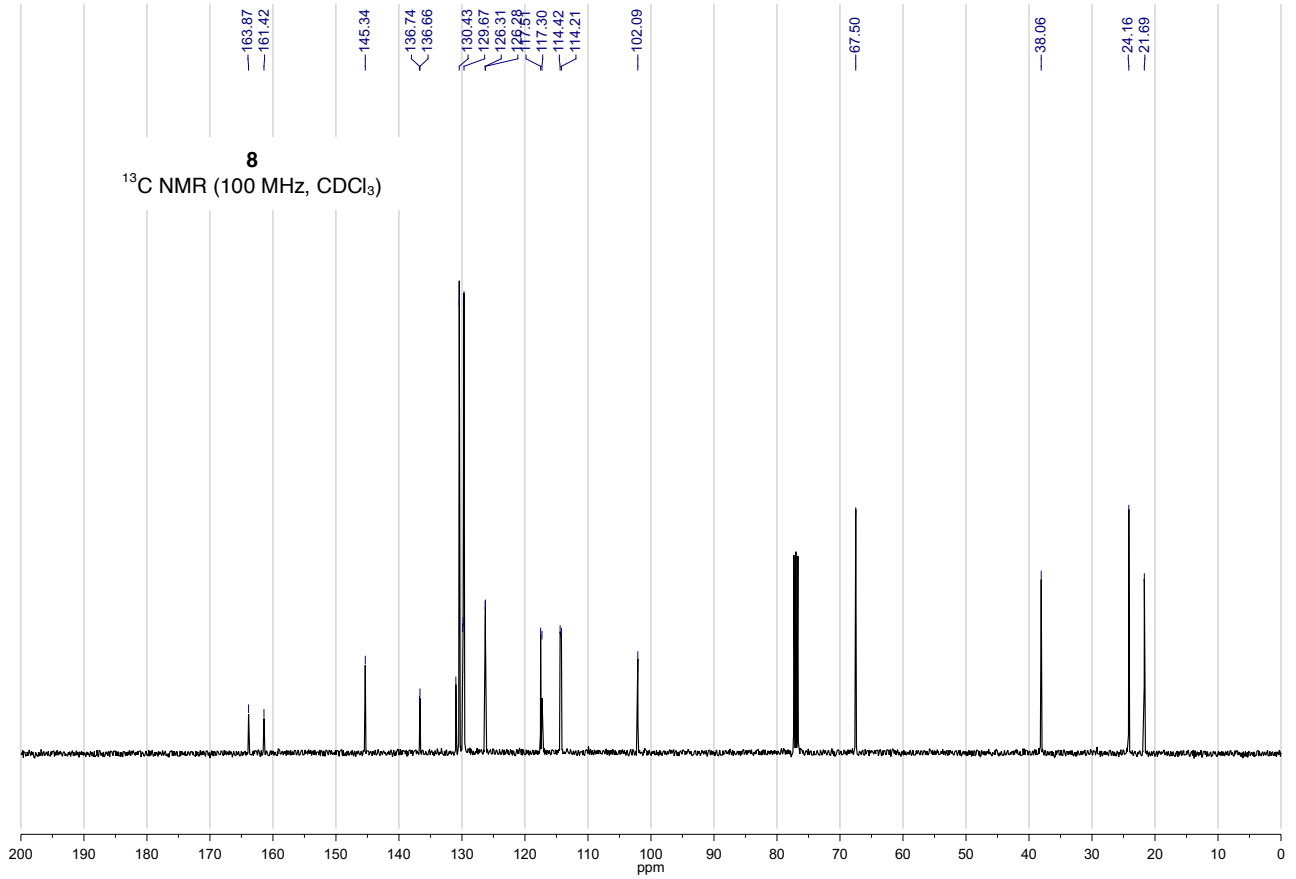
6

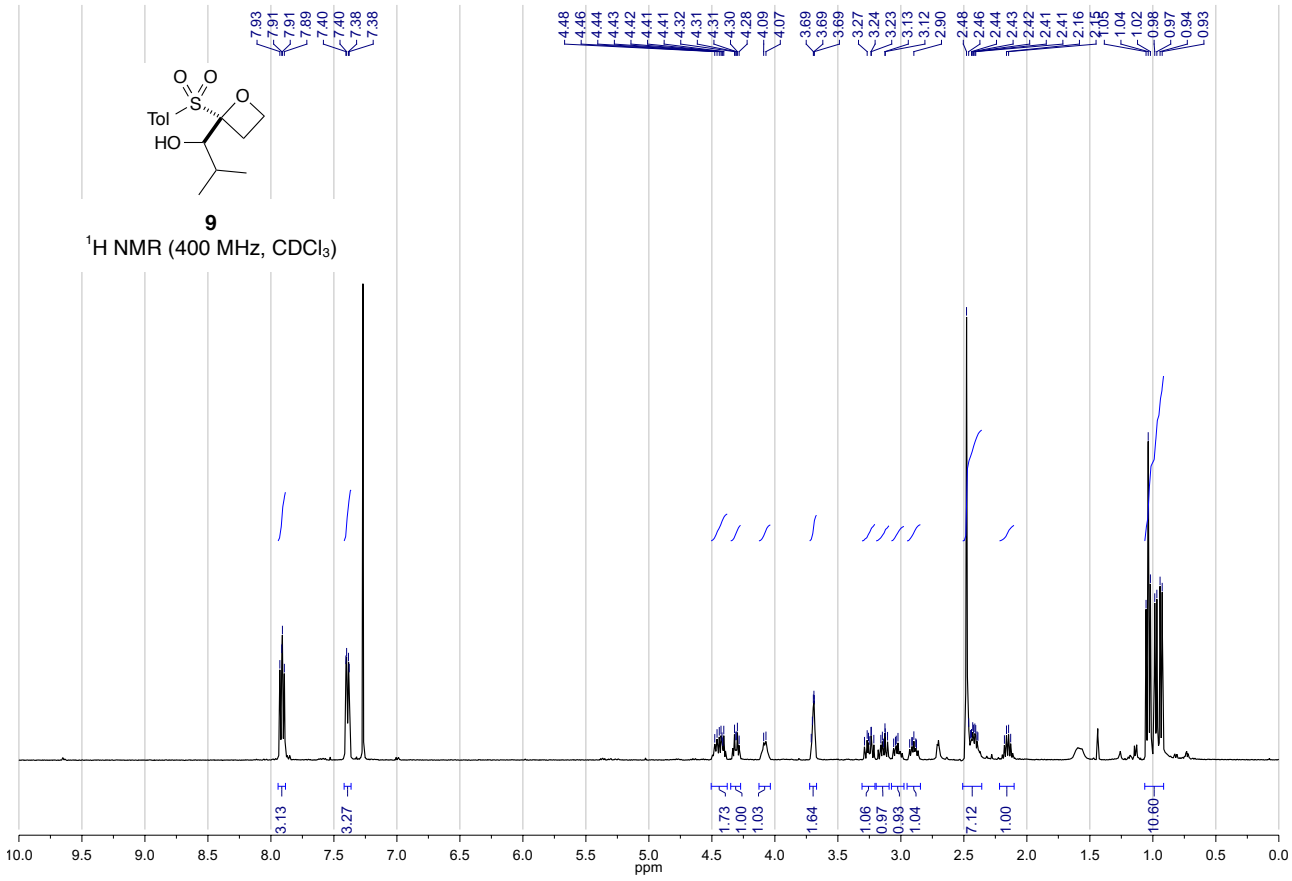
^{13}C NMR (100 MHz, $CDCl_3$, 1% $SiMe_4$)

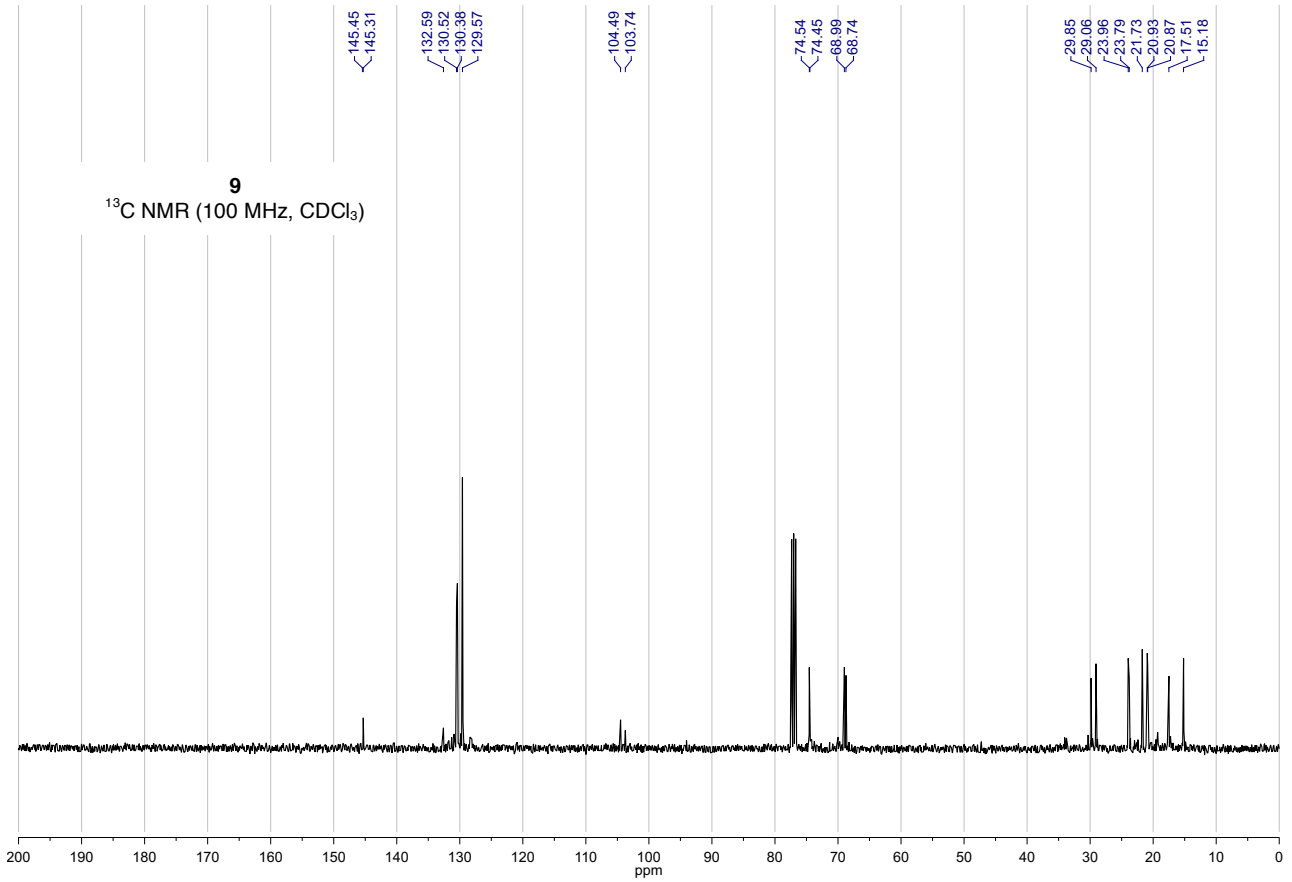

Tol
7
^{1}H NMR (400 MHz, CDCl$_3$)
2.01
2.00
1.00
2.09
1.07
1.08
1.08
1.11
1.10
4.17
ppm

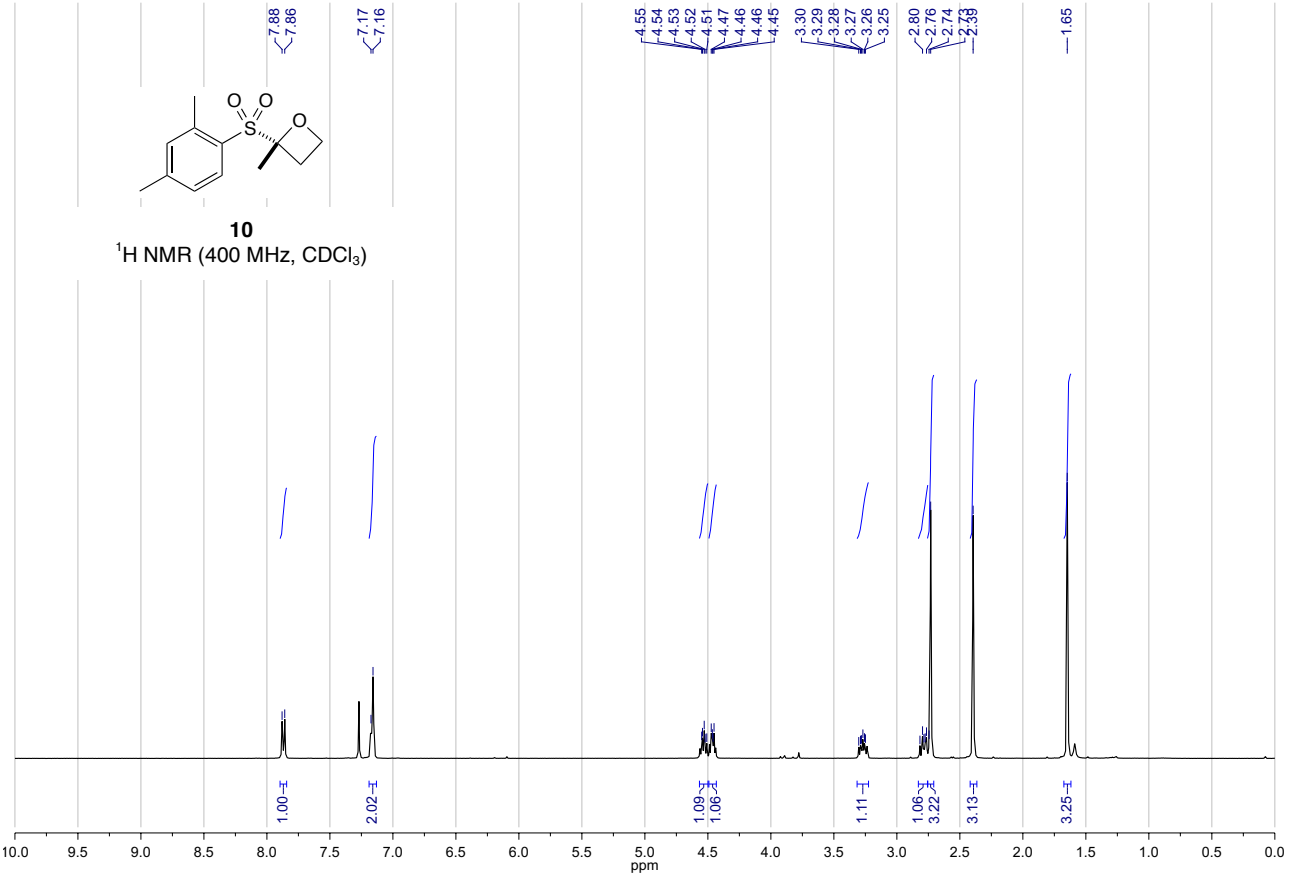

7
^{13}C NMR (100 MHz, CDCl$_3$)
145.19
130.94
130.37
130.11
129.60
121.04
101.89
67.76
37.45
24.29
21.68
ppm


7.94
7.94
7.93
7.92
7.92
7.91
7.41
7.39
7.31
7.30
7.29
7.27
7.09
7.09
7.09
7.07
7.07
7.07
7.05
7.05
7.03
7.03
7.02
7.01
4.27
4.26
4.25
4.25
4.24
4.24
4.23
4.22
3.84
3.83
3.82
3.82
3.17
3.13
3.00
2.95
2.53
2.52
2.51
2.50
2.49
2.48
2.47
O
O
S
O
Tol
F
8
^{1}H NMR (400 MHz, CDCl$_3$)
1.96
2.00
1.05
3.09
1.04
1.05
1.05
1.10
1.02
4.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

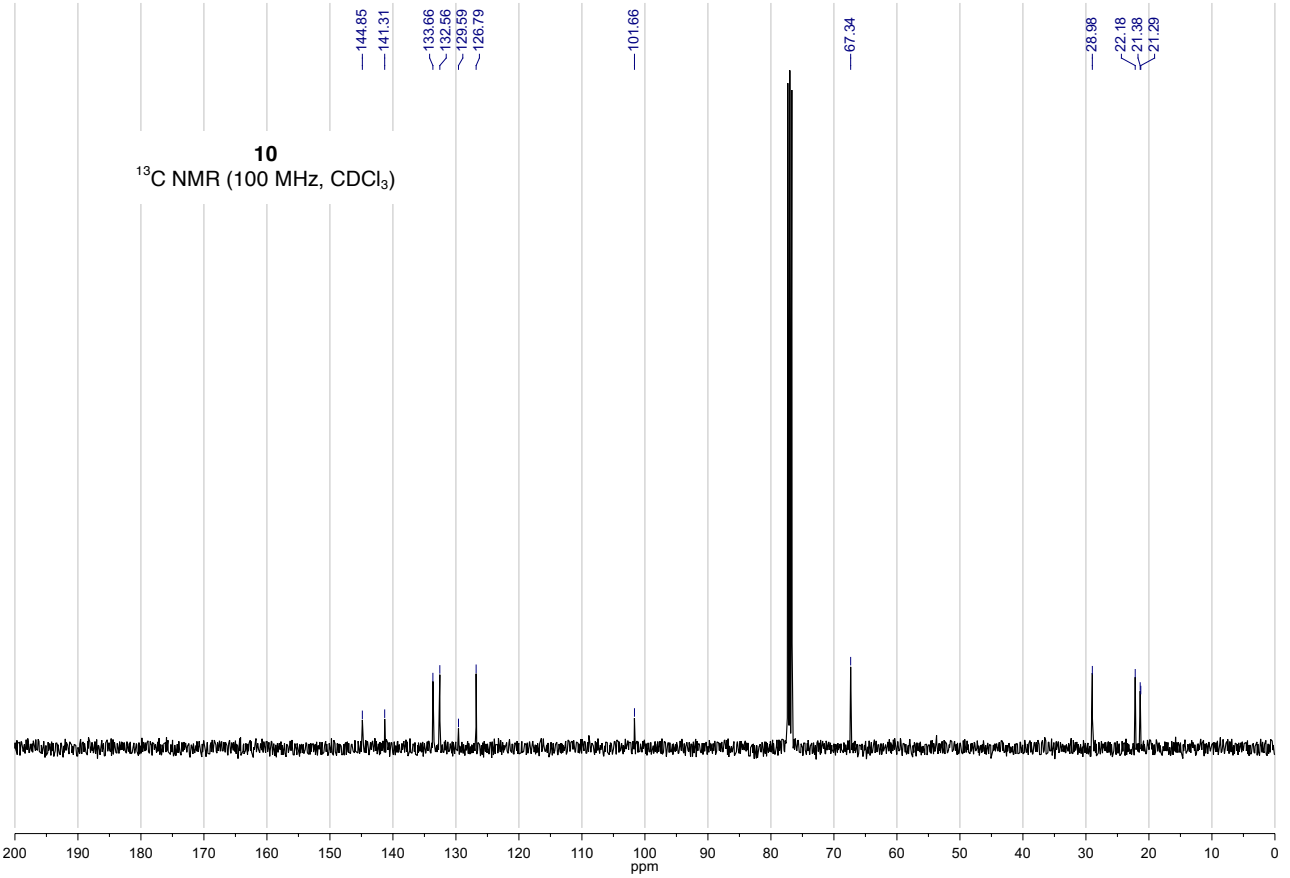

163.87
161.42
145.34
136.74
136.66
130.43
129.67
126.31
117.30
114.42
114.21
102.09
67.50
38.06
24.16
21.69
8
^{13}C NMR (100 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.93
7.91
7.91
7.89
7.40
7.40
7.38
7.38
4.48
4.46
4.44
4.43
4.42
4.41
4.41
4.32
4.31
4.31
4.30
4.28
4.09
4.07
3.69
3.69
3.69
3.27
3.24
3.23
3.13
3.12
2.90
2.48
2.46
2.44
2.43
2.42
2.41
2.41
2.16
2.15
1.05
1.04
1.02
0.98
0.97
0.94
0.93
O
O
S
O
Tol
HO
9
^{1}H NMR (400 MHz, $CDCl_3$)
3.13
3.27
1.73
1.00
1.03
1.64
1.06
0.97
0.93
1.04
7.12
1.00
10.60
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

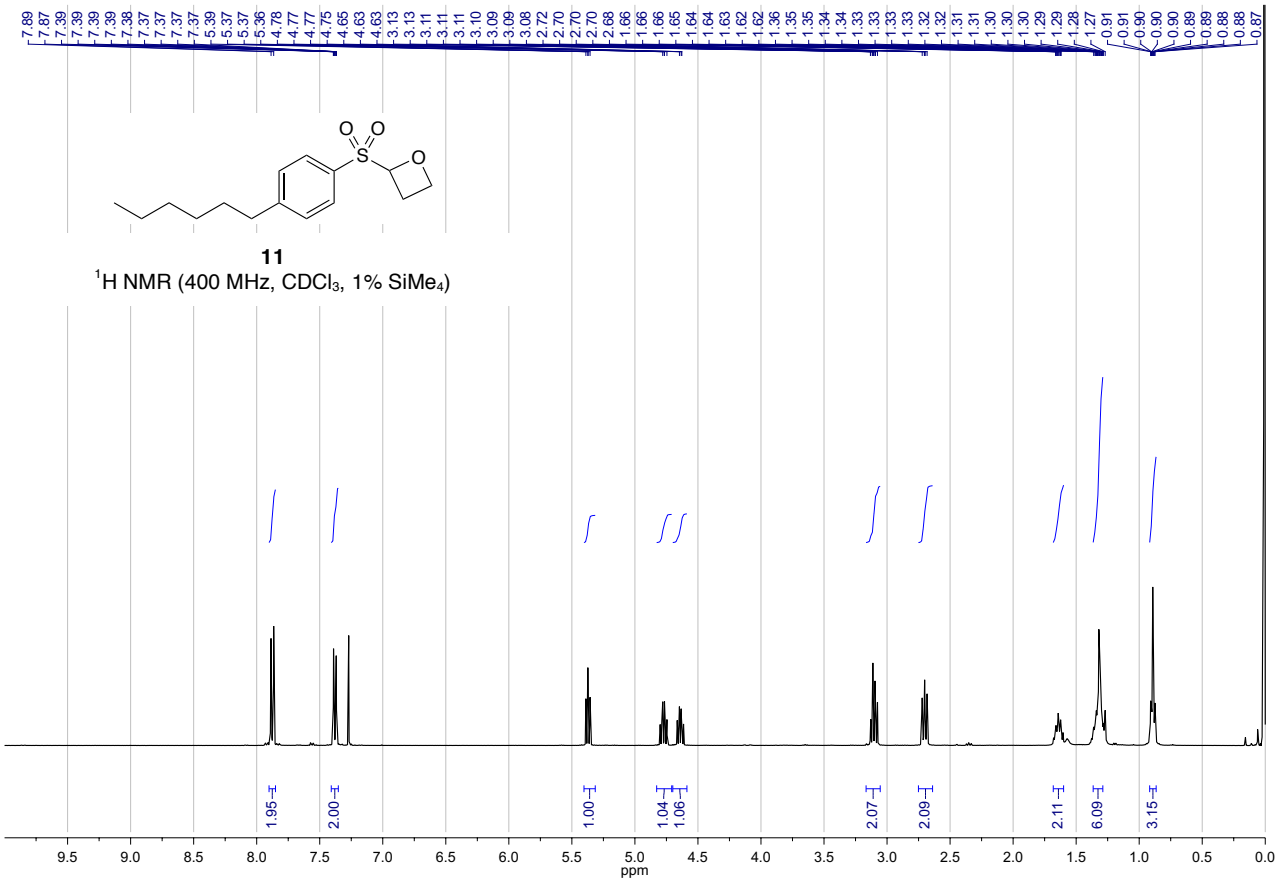

145.45
145.31
132.59
130.52
130.38
129.57
104.49
103.74
74.54
74.45
68.99
68.74
29.85
29.06
23.96
23.79
21.73
20.93
20.87
17.51
15.18
9
^{13}C NMR (100 MHz, $CDCl_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

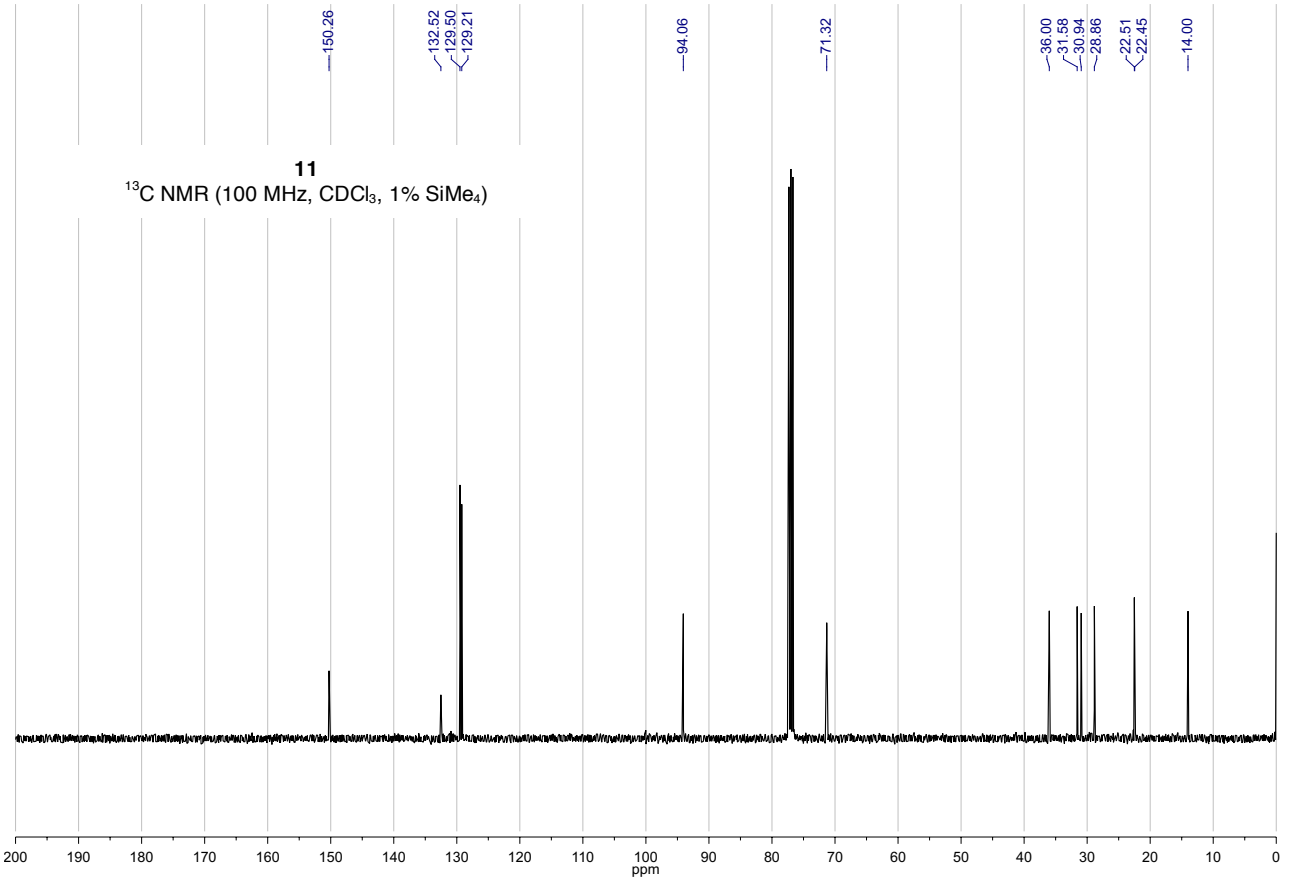


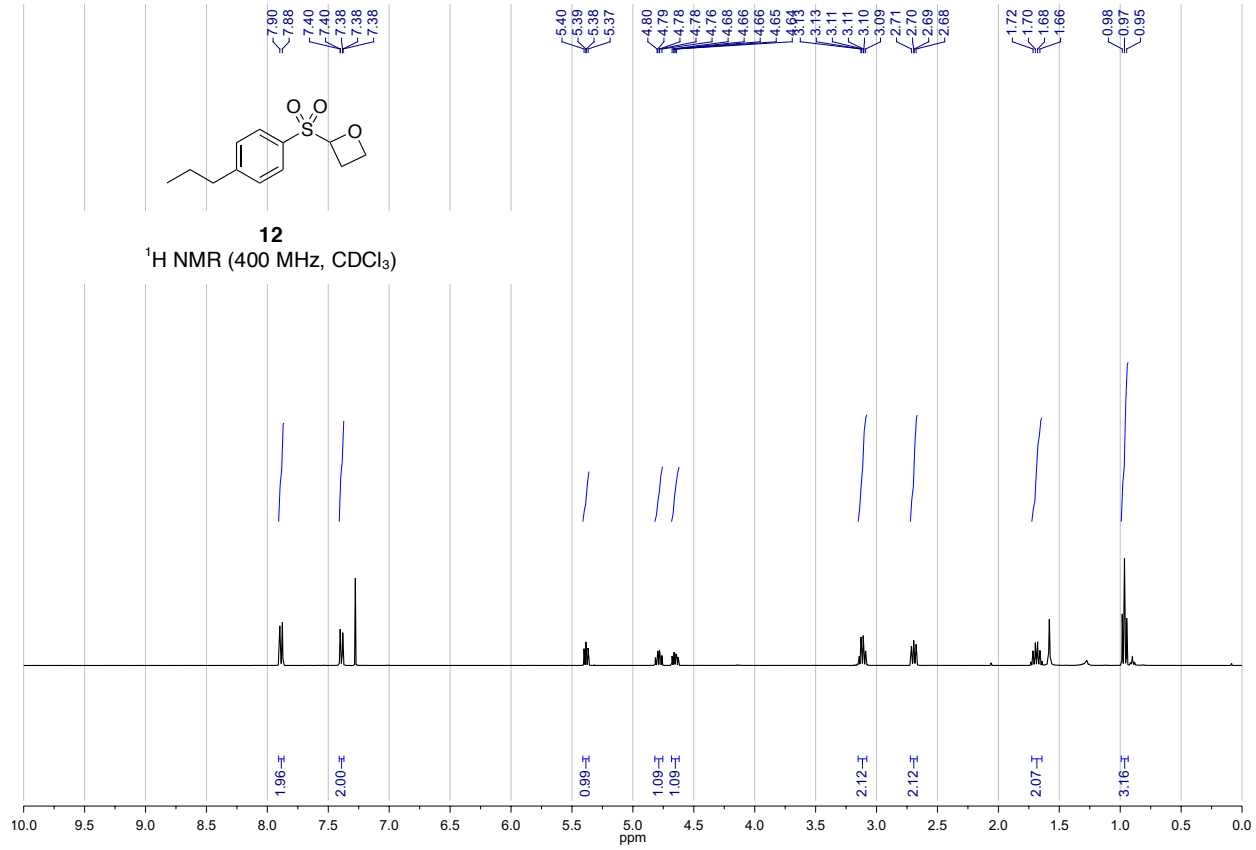
10
^{1}H NMR (400 MHz, $CDCl_3$)



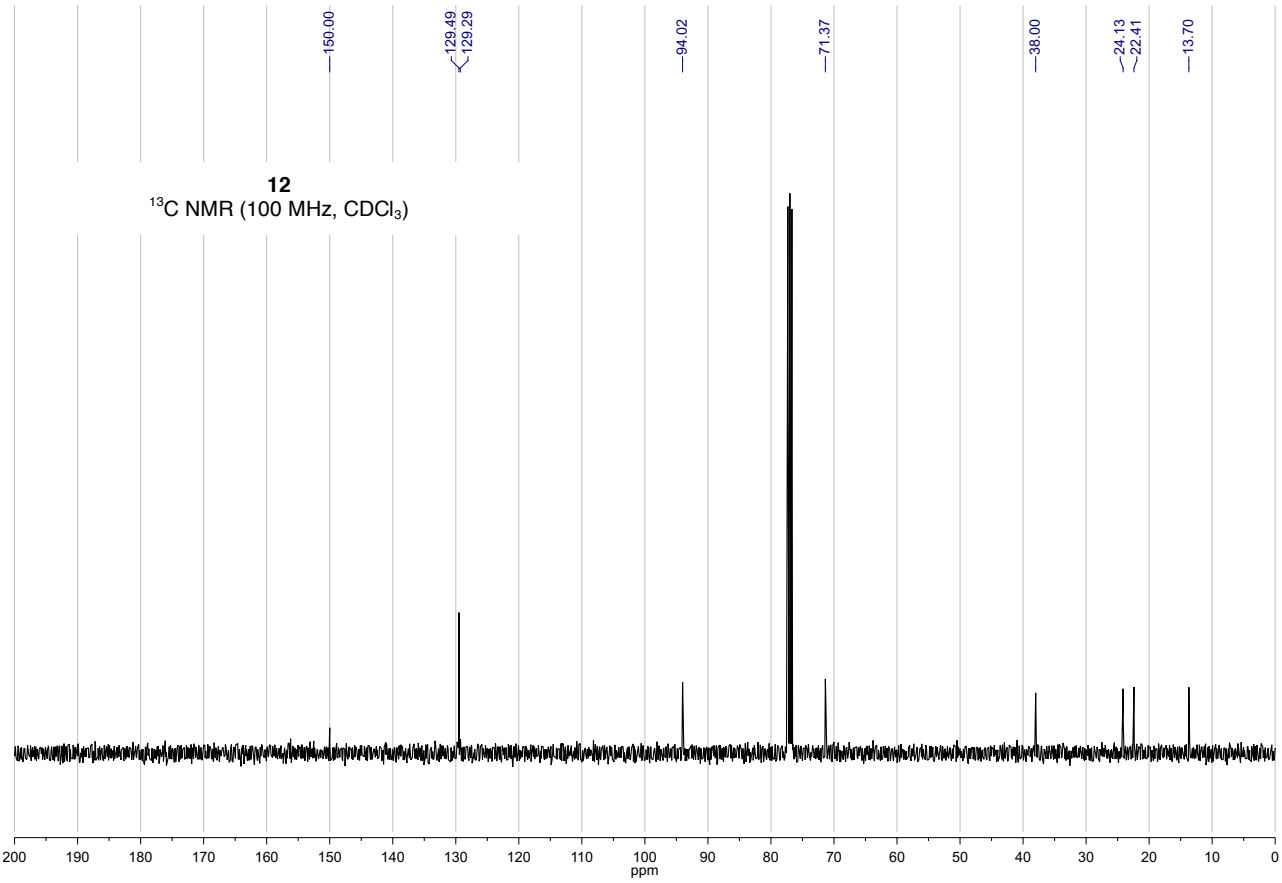
10
^{13}C NMR (100 MHz, $CDCl_3$)


11
^{1}H NMR (400 MHz, CDCl$_3$, 1% SiMe$_4$)
ppm

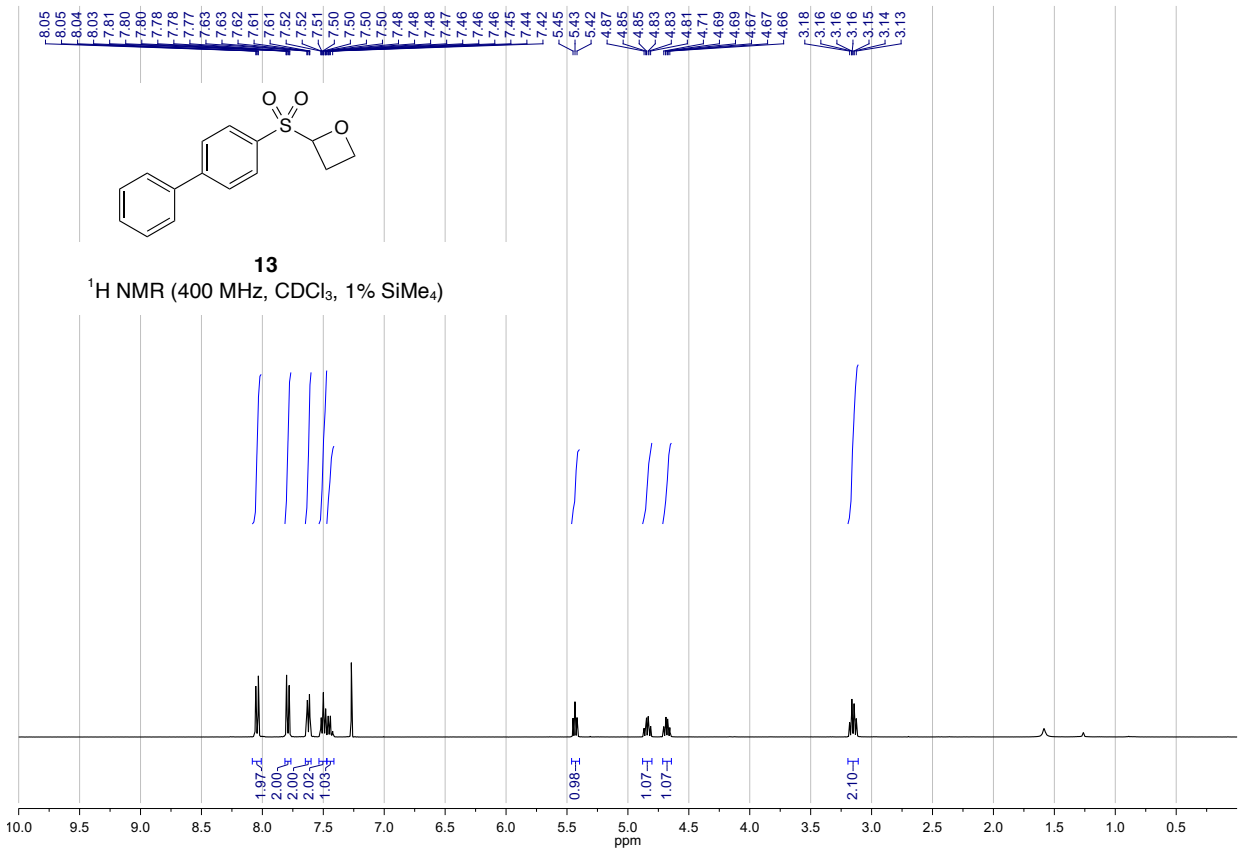

11
^{13}C NMR (100 MHz, CDCl$_3$, 1% SiMe$_4$)
ppm

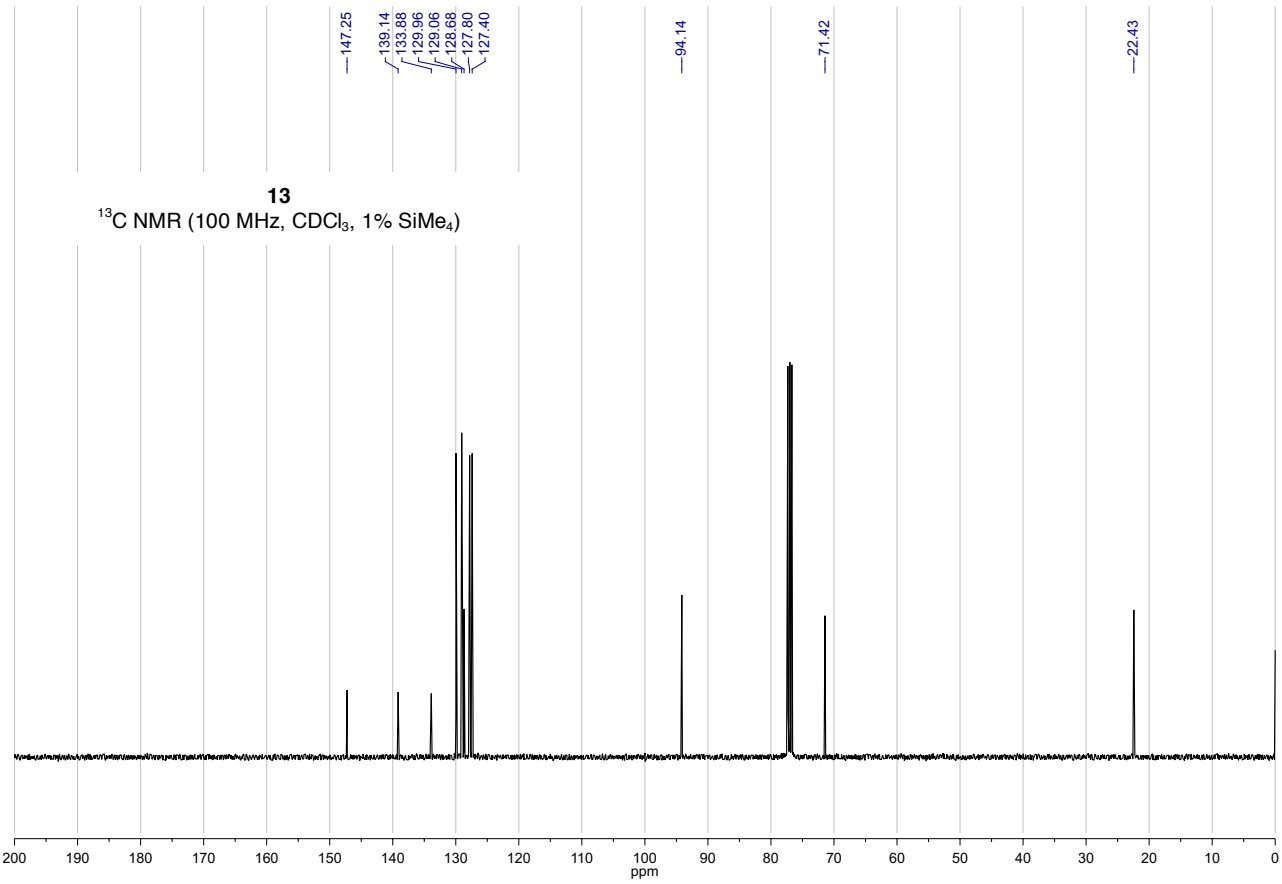


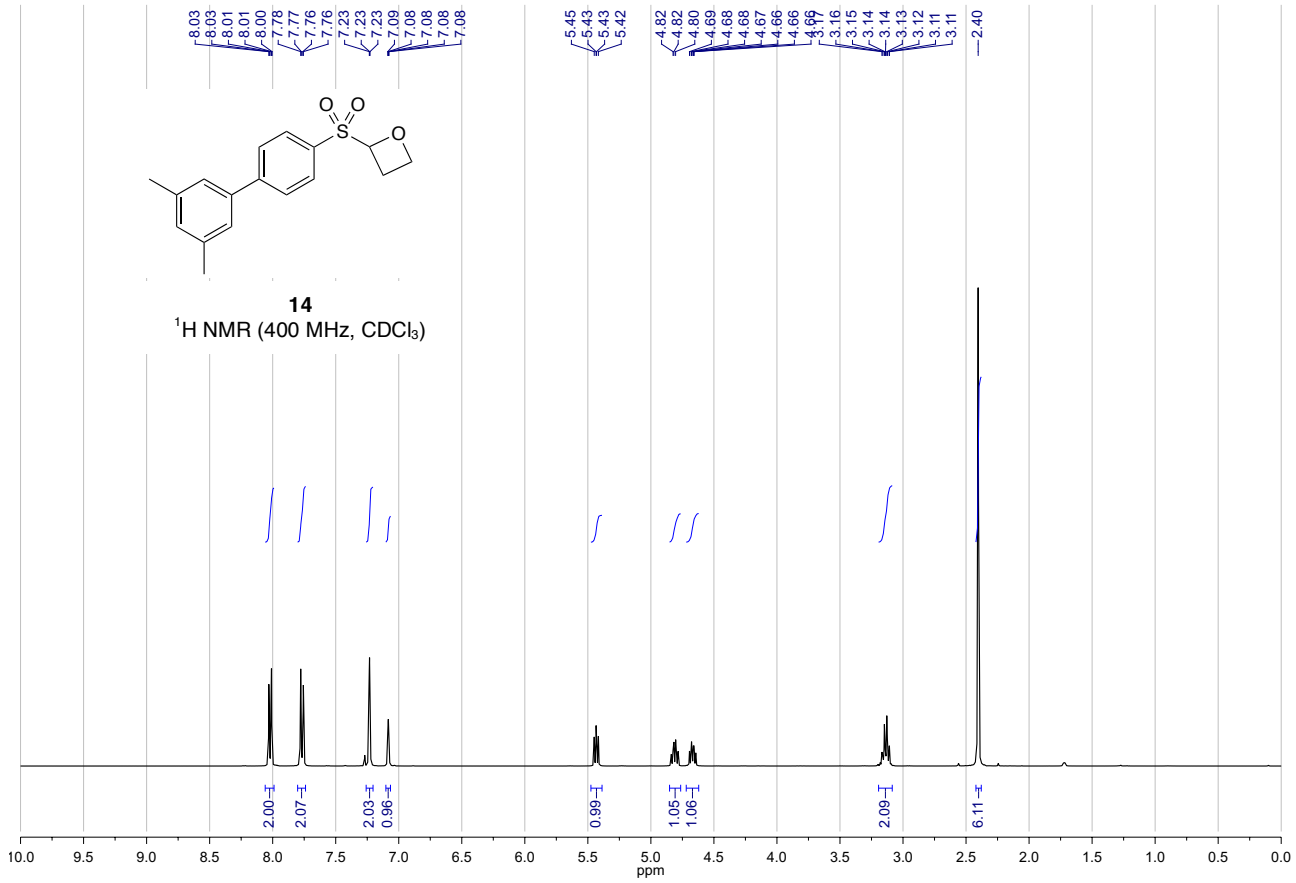
12
^{1}H NMR (400 MHz, $CDCl_3$)

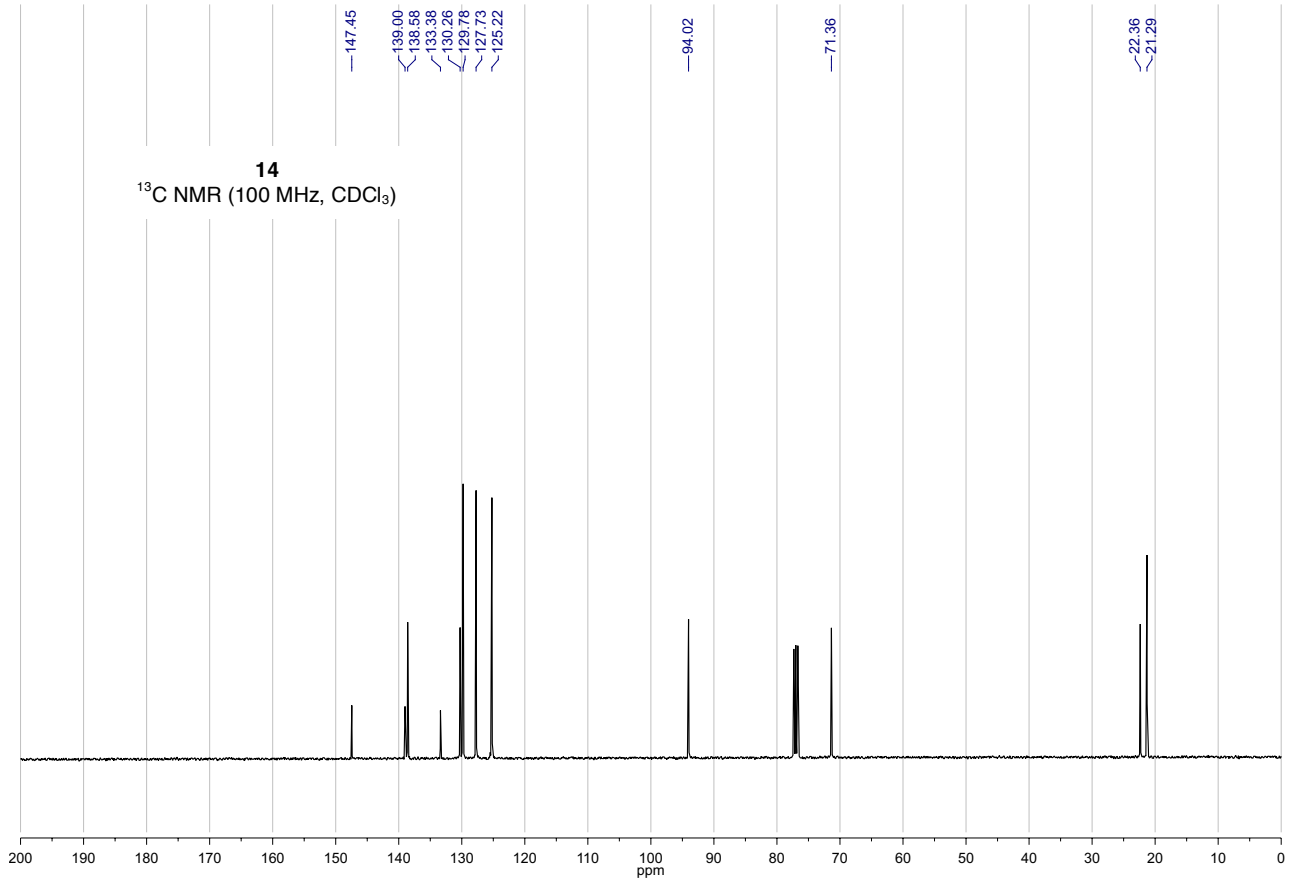


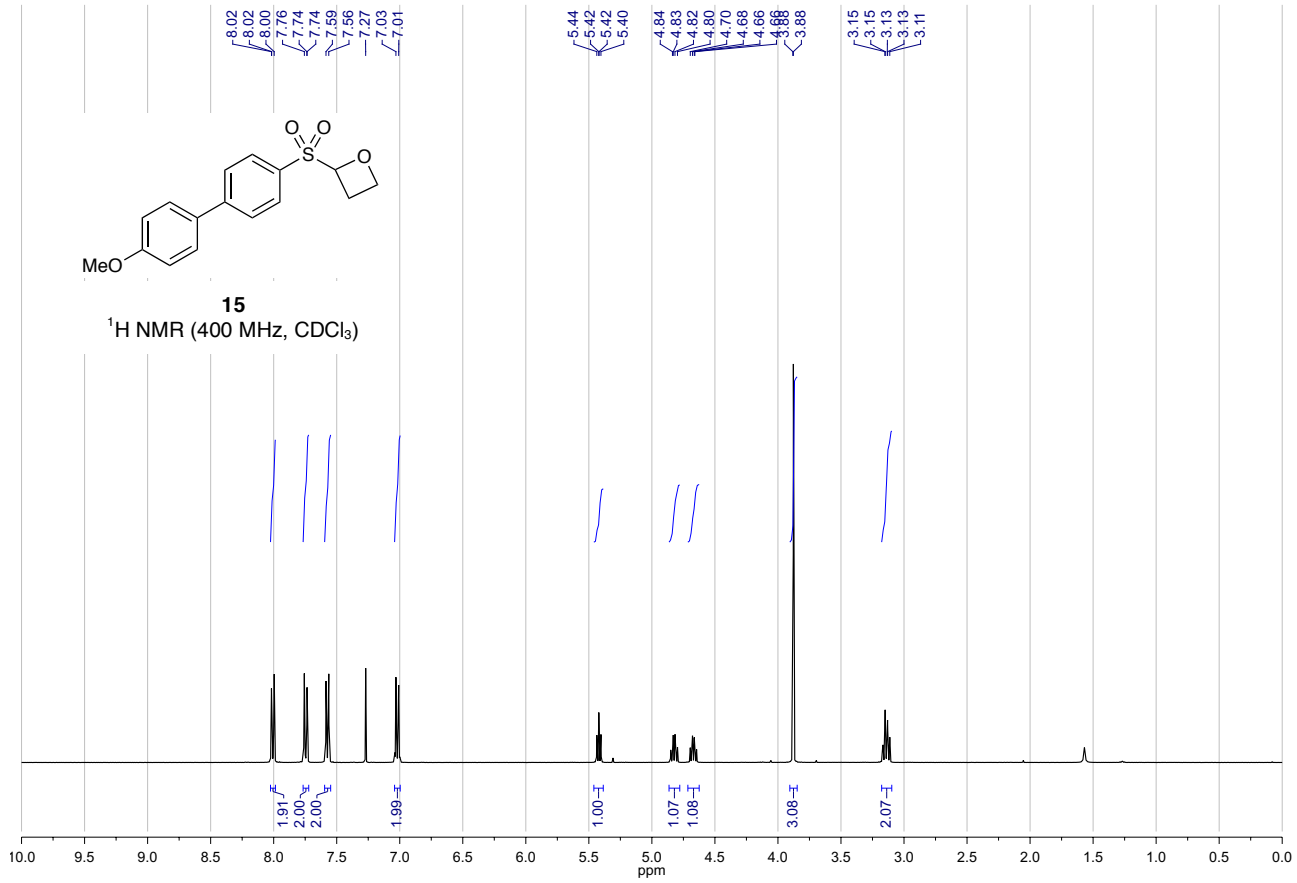
12
^{13}C NMR (100 MHz, $CDCl_3$)


8.05
8.05
8.04
8.03
7.81
7.80
7.80
7.78
7.78
7.77
7.63
7.63
7.62
7.61
7.61
7.52
7.52
7.51
7.50
7.50
7.50
7.50
7.48
7.48
7.48
7.47
7.46
7.46
7.46
7.45
7.44
7.42
5.45
5.43
5.42
4.87
4.85
4.85
4.83
4.83
4.81
4.71
4.69
4.69
4.67
4.67
4.66
3.18
3.16
3.16
3.16
3.15
3.14
3.13
O
O
S
O
13
1H NMR (400 MHz, CDCl3, 1% SiMe4)
1.97
2.00
2.00
2.02
1.03
0.98
1.07
1.07
2.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

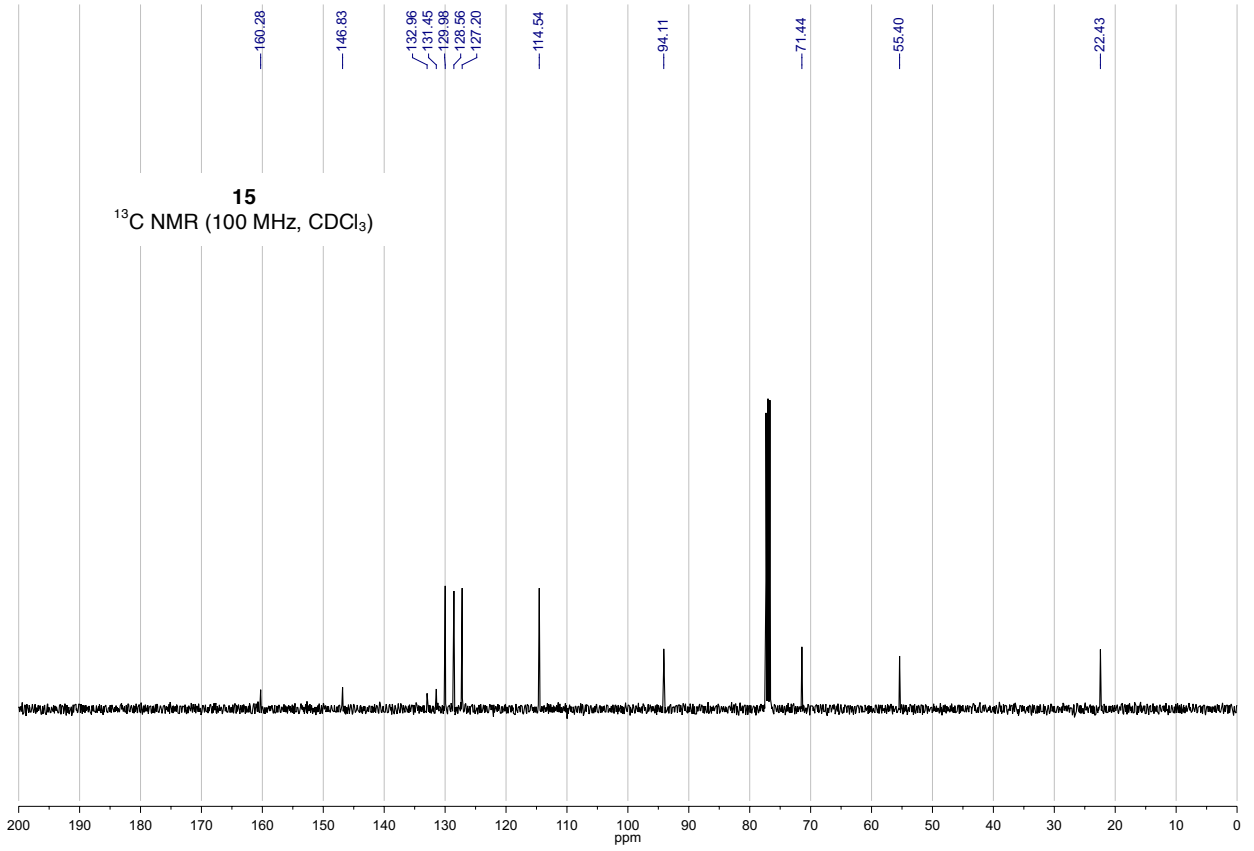

147.25
139.14
133.88
129.96
129.06
128.68
127.80
127.40
94.14
71.42
22.43
13
13C NMR (100 MHz, CDCl3, 1% SiMe4)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.03
8.03
8.01
8.01
8.00
7.78
7.77
7.76
7.76
7.23
7.23
7.23
7.09
7.08
7.08
7.08
7.08
5.45
5.43
5.43
5.42
4.82
4.82
4.80
4.69
4.68
4.68
4.67
4.66
4.66
4.66
3.17
3.16
3.15
3.14
3.14
3.13
3.12
3.11
3.11
2.40
O
O
S
O
14
1H NMR (400 MHz, CDCl3)
2.00
2.07
2.03
0.96
0.99
1.05
1.06
2.09
6.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

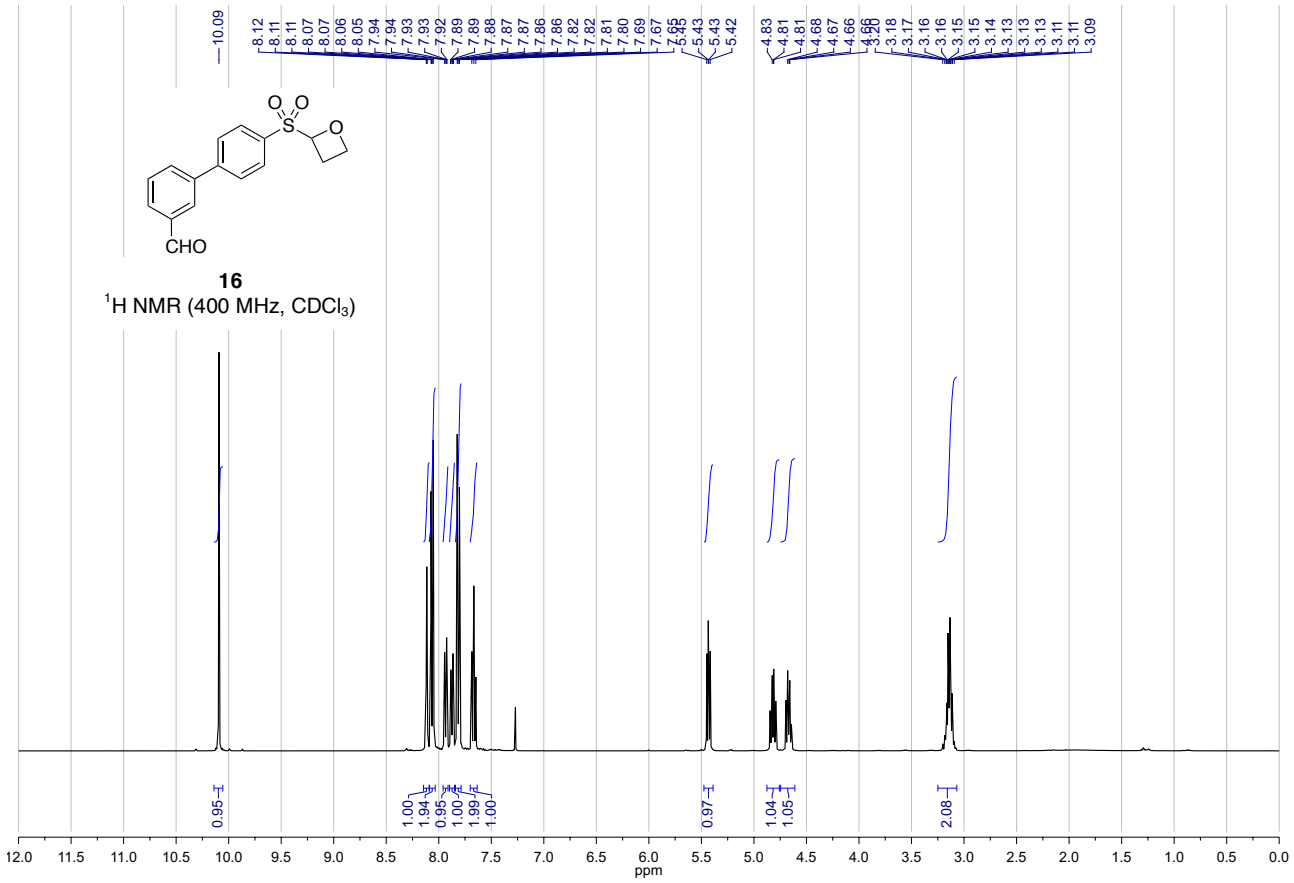

147.45
139.00
138.58
133.38
130.26
129.78
127.73
125.22
94.02
71.36
22.36
21.29
14
13C NMR (100 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

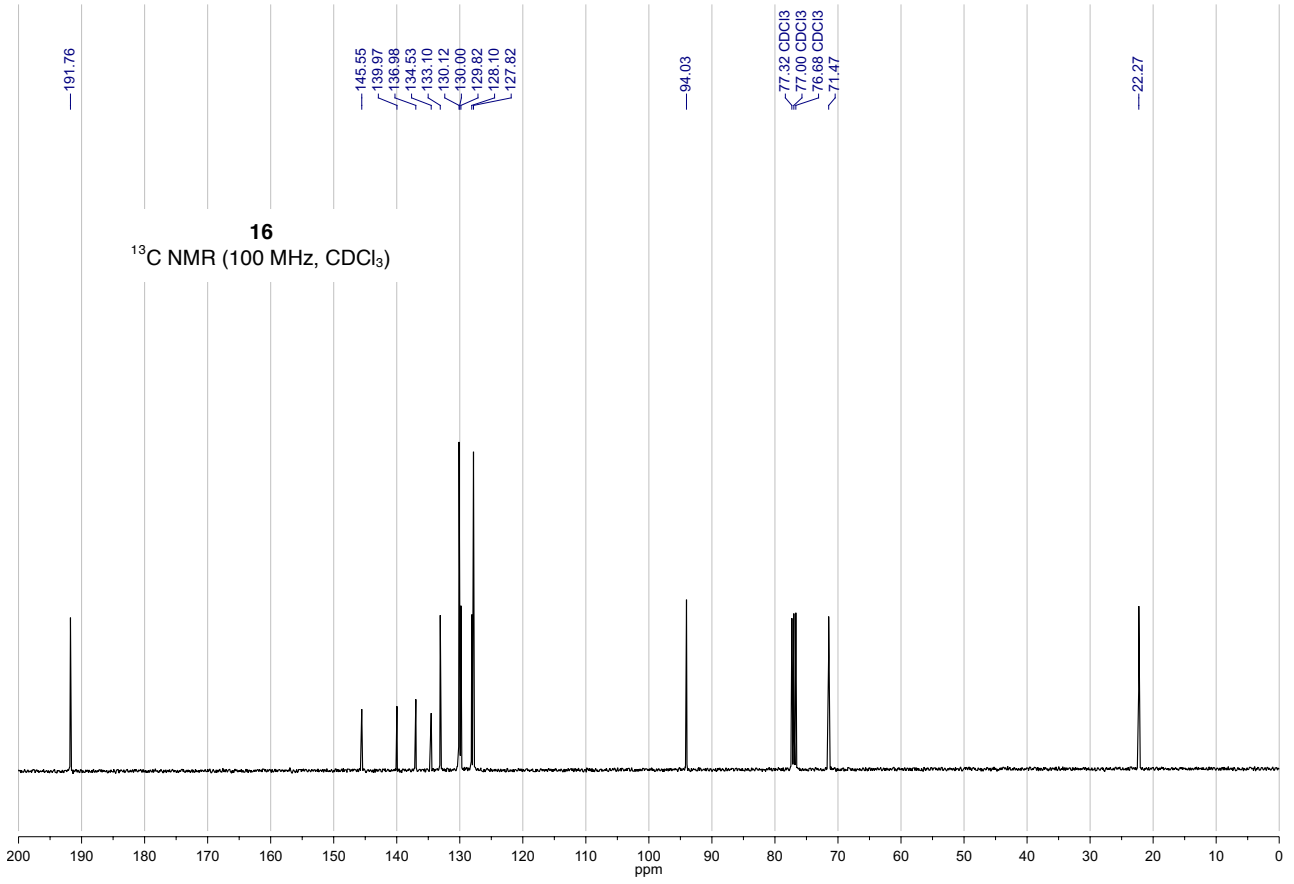


15
^{1}H NMR (400 MHz, $CDCl_3$)



15
^{13}C NMR (100 MHz, $CDCl_3$)


10.09
8.12
8.11
8.11
8.07
8.07
8.06
8.05
7.94
7.94
7.93
7.93
7.92
7.89
7.89
7.88
7.87
7.87
7.86
7.86
7.82
7.82
7.81
7.80
7.69
7.67
7.65
5.45
5.43
5.43
5.42
4.83
4.81
4.81
4.68
4.67
4.66
3.18
3.17
3.16
3.16
3.15
3.15
3.14
3.13
3.13
3.13
3.11
3.11
3.09
O
O
S
O
CHO
16
^{1}H NMR (400 MHz, CDCl$_3$)
0.95
1.00
1.94
0.95
1.00
1.99
1.00
0.97
1.04
1.05
2.08
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


191.76
145.55
139.97
136.98
134.53
133.10
130.12
130.00
129.82
128.10
127.82
94.03
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
71.47
22.27
16
^{13}C NMR (100 MHz, CDCl$_3$)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

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