nature portfolio

https://doi.org/10.1038/s41557-021-00856-2

Supplementary information

Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides

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SUPPORTING INFORMATION

Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides

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General Experimental Conditions

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware using standard techniques, unless otherwise specified. Anhydrous solvents were obtained by filtration through drying columns (CH_2Cl_2, THF) or used as supplied (MeCN, MeOH). Reactions in sealed tubes were run using Biotage microwave vials (2–5 mL) and aluminium caps with molded butyl septa.

Flash chromatography was performed using 230–400 mesh silica from Sigma Aldrich, 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) and stained with a ninhydrin, *p*-anisaldehyde or phosphomolybdic acid solution in ethanol, followed by heating.

Infrared spectra (ν_{max}, FTIR ATR) were obtained using an Agilent Technologies Cary 630 FTIR or a Perkin Elmer Spectrum 100 FTIR Spectrometer and recorded in reciprocal centimeters (cm^{-1}) (br = broad, w = weak, st = stretch, as = asymmetric, sy = symmetric).

Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. The frequency used to record the NMR spectra is given in each assignment and spectrum (^{1}H NMR at 400 or 500 MHz; ^{13}C NMR at 101 MHz or 126 MHz; ^{19}F NMR at 377 MHz). Chemical shifts for ^{1}H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CHCl_3$: δ = 7.27 ppm, DMSO: δ = 2.50 ppm, CH_3OD: δ = 3.31 ppm, H_2O: δ = 4.79 ppm, CH_3CN: δ = 1.97 ppm, $(CH_3)_2CO$: δ = 2.05 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet and br = broad], coupling constant (in Hz), integration of equivalent nuclei and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, $^{13}CD_3OD$: δ = 49.0 ppm, $(^{13}CD_3)_2CO$: δ = 29.8 ppm). *J* values are reported in Hz. Assignments of ^{1}H and ^{13}C spectra were based upon the analysis of δ and *J* values, as well as COSY, HMQC and HMBC experiments where appropriate. ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million (ppm). ^{19}F NMR spectra are indirectly referenced to $CFCl_3$ automatically by direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware.

For clarity NMR spectra are displayed as follows unless this would obscure signals: ^{1}H NMR spectra are displayed between 10.0 ppm and 0.0 ppm; ^{13}C NMR spectra are displayed between 210 ppm and 0 ppm; ^{19}F NMR spectra are displayed for the full sweep width as acquired.

Melting points were obtained using an Optimelt MPA100 melting point apparatus and are uncorrected.

High-resolution mass spectra (HRMS) were obtained through the Imperial College, EPSRC or Pfizer mass spectrometry service. HRMS analyses at Imperial College were performed using an electrospray ion source (ESI), electron ionization (EI) or atmospheric pressure chemical ionization (APCI) using an atmospheric solids analysis probe (ASAP). ESI was performed using a Waters LCT Premier (ES-ToF) equipped with an ESI source operated in positive ion mode. EI was performed using a Micromass Autospec Premier/Agilent HP6890 GC. APCI was performed using a Thermo Scientific Q-Extractive/Dionex Ultimate 3000 using an ASAP to insert samples into the APCI source operated in positive or negative mode. The sample was introduced at ambient temperature and the temperature increased until the sample vaporized. HRMS analyses at the EPSRC UK National Mass Spectrometry Facility (NMSF) were performed using a nano-electrospray ion source (NSI), chemical ionization (CI) or atmospheric pressure chemical ionization (APCI) using an atmospheric solids analysis probe (ASAP). NSI was performed using a Thermo Scientific LTQ Orbitrap XL operated in

positive or negative ion mode. CI was performed using a Finnigan MAT 95 XP operated in positive mode. APCI was performed using a Waters Xevo G2-S using an ASAP to insert samples into the APCI source operated in positive mode. The sample was introduced at ambient temperature and the temperature increased until the sample vaporized. HRMS analyses at Pfizer were performed using a Sciex 5600+ QToF operated in positive ion mode. The software used was either MassLynx 4.1 or Bruker Daltonics DataAnalysis 4.0. Please note: MassLynx 4.1 software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H]. In the cases where this software is used, we report the HRMS as [M+H].

Observed optical rotations (α') were measured at the indicated temperature (T °C) and converted to the corresponding specific rotations $[\alpha]_D^T$ in deg cm^2 g^{-1}, concentration (c) in g per 100 mL. HPLC analyses were carried out on an Agilent 1260 Infinity Series system, employing Daicel Chiracel columns.

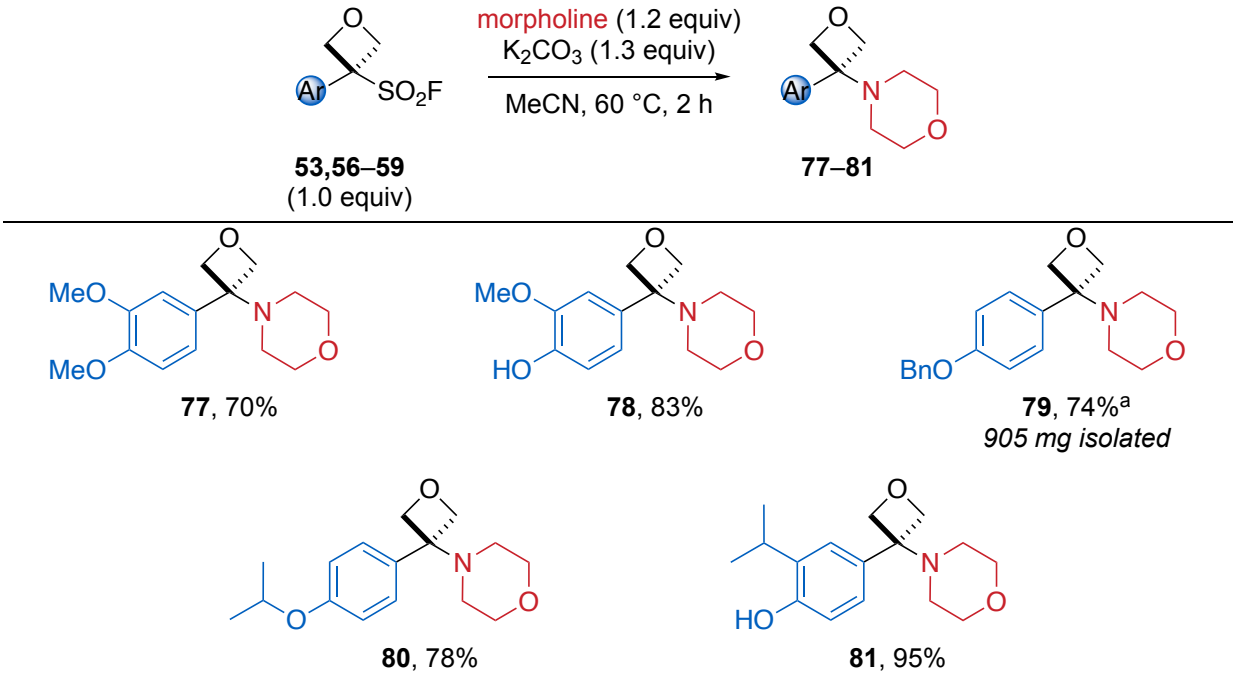
Reagents

Where the synthesis of a reagent is not stated, the reagent was commercially available. Commercial reagents were used as supplied or purified by standard techniques where necessary. All volatile amines were distilled over $MgSO_4$ or KOH pellets before use.

- Anhydrous potassium carbonate (≥98%; powder, –325 mesh, CAS: 584-08-7) was purchased from Sigma-Aldrich. In some cases K_2CO_3 was flame-dried as part of the reaction set-up.
- Bis(trifluoromethane)sulfonimide lithium salt (>99%, CAS: 90076-65-6) was purchased from Sigma-Aldrich and stored under an argon atmosphere in a desiccator.
- Sodium methoxide (pure, 5.4 M (30 wt %) solution in MeOH, CAS: 124-41-4, 67-56-1) was purchased from Acros Organics and stored under an argon atmosphere.
- The exact concentration of *n*-BuLi (1.6 M in hexanes, purchased from Sigma-Aldrich, CAS: 109-72-8) was determined by titration with salicylaldehyde phenylhydrazone as indicator before each reaction using a literature procedure.[1] The average of three titrations was taken.
- **O**xetane **S**ulfonyl **F**luorides are abbreviated as OSF.

Additional Scope of Morpholine Aminooxetanes

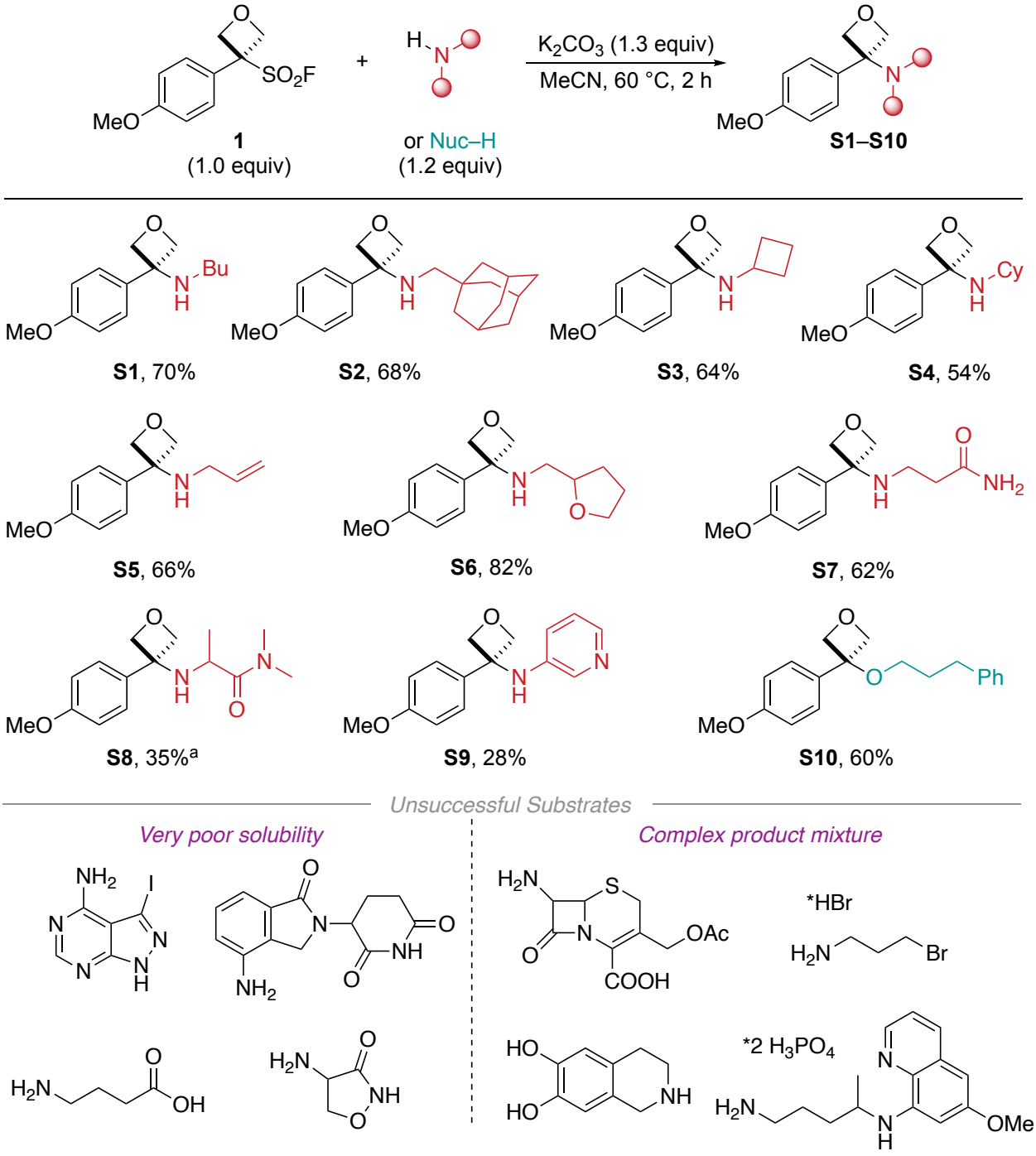
A series of morpholine aminooxetanes were synthesized from the prepared oxetane sulfonyl fluorides (**77**–**81**) in addition to the examples shown in Fig. 2 and 3. All the products were obtained in high yields (Scheme S1).



Scheme S1 Additional scope of morpholine amionoxetane amines with further oxetane sulfonyl fluorides. Reactions performed on a 0.2 mmol scale. [a]On 3.8 mmol scale.

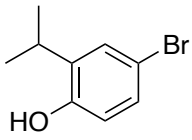
Additional Reaction Scope of Oxetane Products and Unsuccessful Substrates

Scheme S2 shows additional oxetane products that were prepared, in addition to those included in Table 1, and examples where the reaction did not yield the desired product.

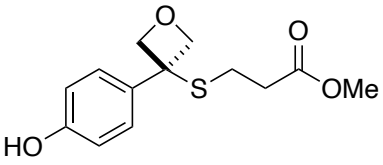


Scheme S2 Additional scope of oxetane products and unsuccessful amine coupling partners. [a]Amine used directly as the trifluoroacetate salt after Boc-deprotection with TFA and 2.6 equiv K_2CO_3 were added.

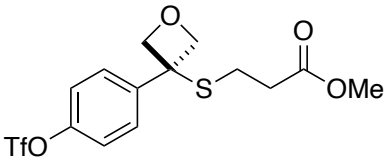
Structures of Additional Compounds in SI



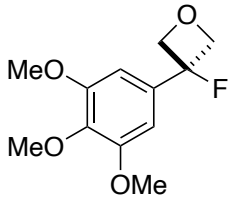
S11



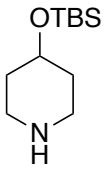
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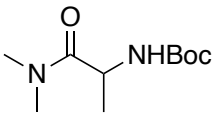
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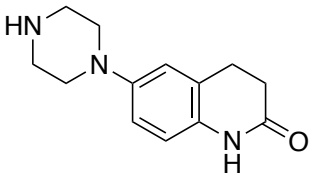
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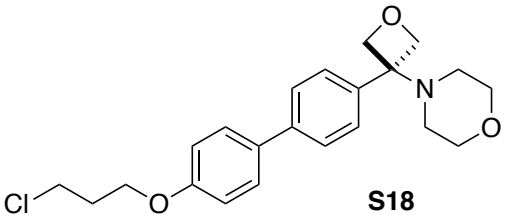
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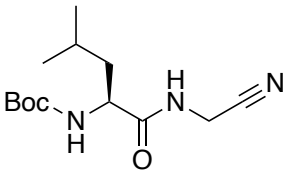
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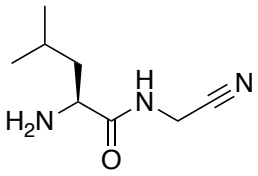
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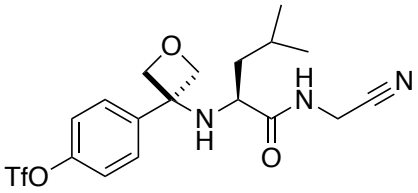
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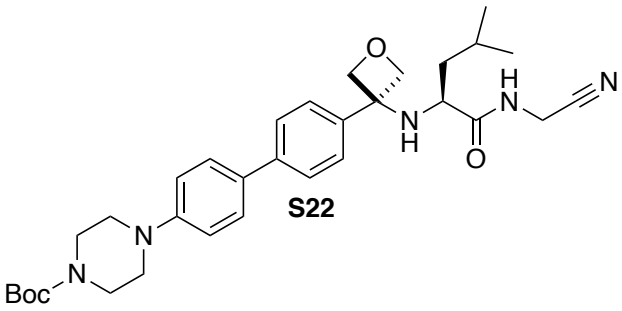
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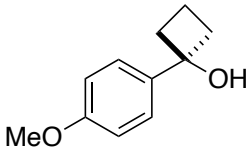
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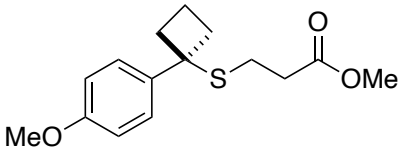
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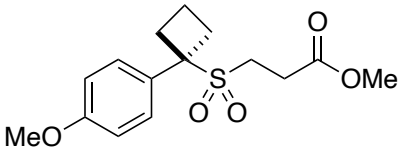
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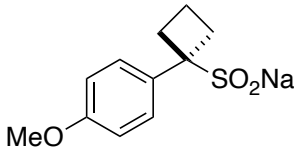
S23



S24

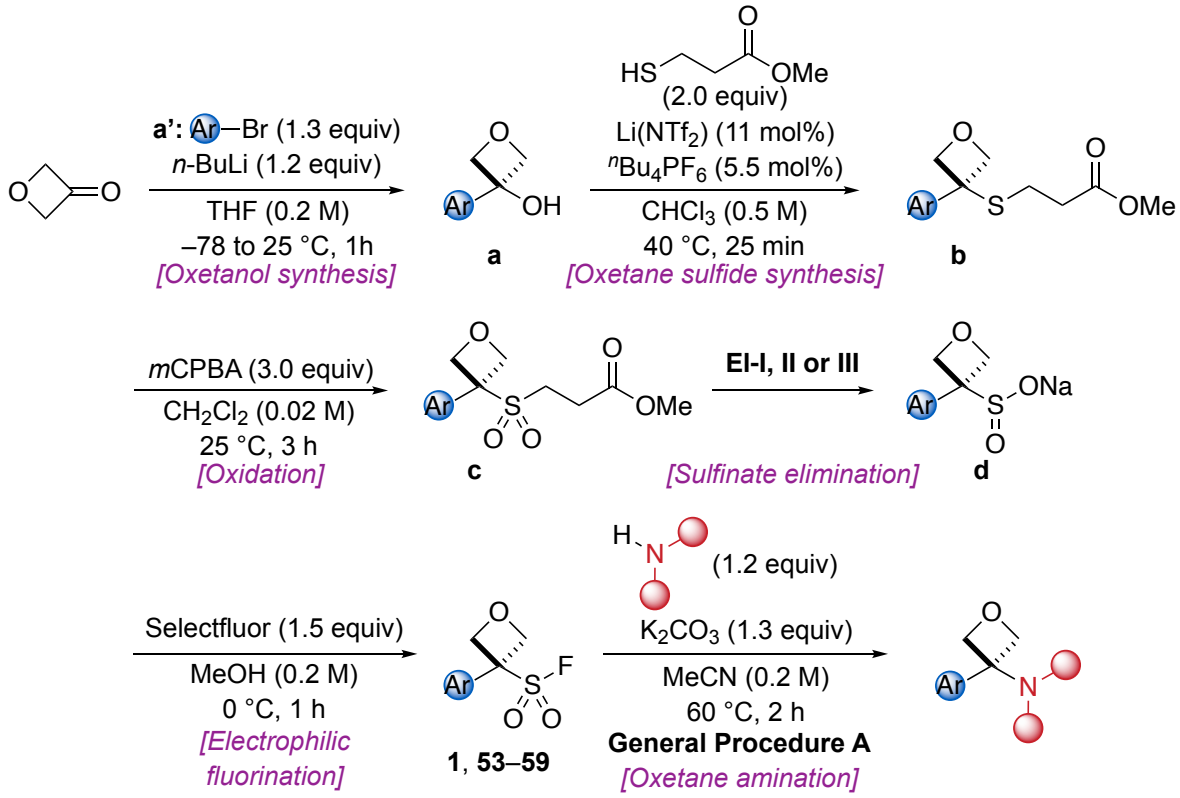


S25



S26

Optimization of the Synthesis of Oxetane Sulfonyl Fluorides and Aminooxetanes and Additional Considerations



EI-I	**EI-II**	**EI-III**
NaH (1.05 equiv) THF (0.2 M), 25 °C, 1 h	5 M NaOH in MeOH (1.05 equiv) CH_2Cl_2 (0.1 M), 0 °C, 15 min	5.4 M NaOMe in MeOH (1.0 equiv) THF (0.5 M), 25 °C, 20 min

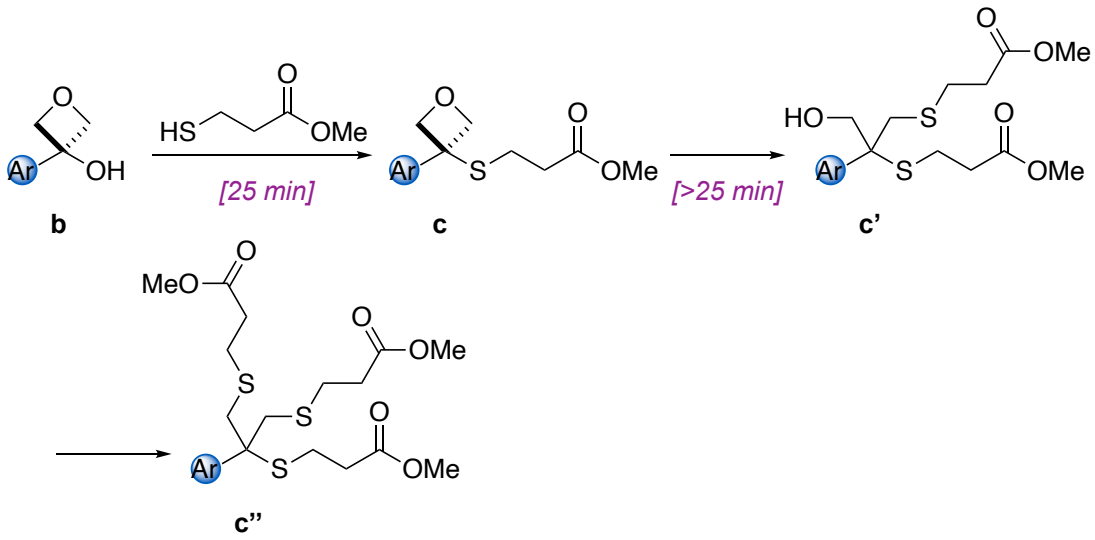
Scheme S3 General scheme for the reaction sequence from aryl bromides to oxetane amines.

Oxetane Sulfide Synthesis:[2]

In a typical procedure, the oxetanol was dissolved in non-anhydrous chloroform and methyl 3-mercaptopropionate (2.0 equiv) was added. Then, lithium bis(trifluoromethanesulfonimide) (0.11 equiv) and tetrabutylammonium hexafluorophosphate (0.055 equiv) were added sequentially to the solution. The reaction flask under argon was then placed into a preheated oil bath at 40 °C. There is a sharp change in color (most often from colorless to colorful) that indicates the beginning of the reaction. If there was no change in color after stirring for 15 min at 40 °C, the reaction was heated up at a rate of approximately 5 °C every 10 min until there was a change in color. The reaction can be monitored by TLC, but it is recommended to quench the reaction after exactly 25 min of the color change to maximize yield whilst minimizing formation of ring-opened products **c'** and **c''** (Scheme S4).

If there is no sharp change in color, the reaction has not started yet.

Initiation of the reaction was found to be key for this transformation. The following factors were found to be beneficial for the initiation: performing the reaction in round bottom flasks (instead of e.g. MW vials), using non-anhydrous chloroform, opening and closing the reaction mixture to air and/or stopping and restarting the stirring (whilst heating).



Scheme S4 Ring-opened side-products observed in the synthesis of oxetane sulfides.

Oxidation:

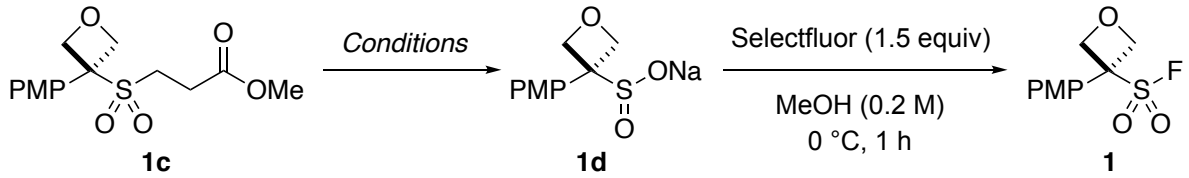
*m*CPBA was pre-washed before use. Procedure: a solution of commercial *m*CPBA (15 g, purity ≤77%, purchased from Sigma-Aldrich) in CH_2Cl_2 (300 mL) was washed with a phosphate buffer (pH = 7.5, 3 × 300 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to obtain pure *m*CPBA (free of benzoic acid and water). Special attention should be paid when handling pure *m*CPBA since it is shock-sensitive and potentially explosive. Do not heat on rotatory evaporators above 25 °C, do not scratch with a metal spatula when removing from round bottom flask (use for example a plastic spatula) and store at <4 °C.

The washing of *m*CPBA is not a requirement, but removes the need of a purification step after the reaction work-up.

Sulfinate Elimination:

3 Sets of conditions (**El-I, II and III**) were developed for the elimination of PMP-oxetane sulfone **1c** to sulfinate **1d**. The products were obtained in good yields for all three methods. With **El-II** and **El-III** the subsequent fluorination step was carried out in a telescoped process and the yield obtained after the two steps (Table S1).

Table S1 Elimination conditions for PMP oxetane sulfone **1c**.



1c **1d** **1**

	Conditions	Scale / mmol	Yield / % Elimination	Yield / % Fluorination
El-I	NaH (1.05 equiv) THF (0.2 M), 25 °C, 1 h	7.7	95	77
El-II	5 M NaOH in MeOH (1.05 equiv) CH_2Cl_2 (0.1 M), 0 °C, 15 min	3.8	61 (2 steps)	
El-III	5.4 M NaOMe in MeOH (1.0 equiv) THF (0.5 M), 25 °C, 20 min	4.0	54 (2 steps)	

Under all sets of conditions, sulfinate **1d** precipitates immediately upon formation and can be easily obtained after removal of solvent. For the more lipophilic examples (i.e. better soluble in organic solvents), the oxetane sulfinate was unstable in solution (see Fig. S1). Therefore, it was used directly for the fluorination step without analysis or characterization. All subsequent oxetane sulfonyl fluorides (except *p*-OBn-phenyl sulfonyl fluoride **57**) were synthesized in this manner.

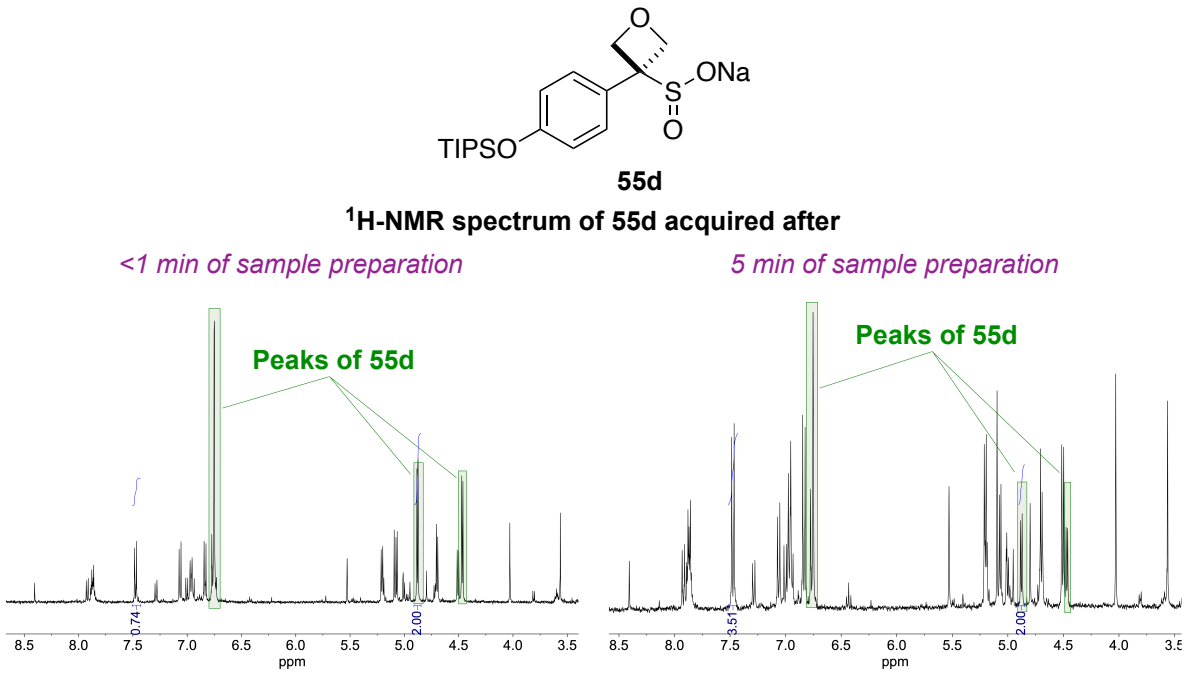


Fig. S1 ^{1}H NMR-Spectrum of **55d** in DMSO-d_6 from the same material acquired after different preparation times.

Further remarks:

Usually, oxetane sulfinate salts precipitate upon addition of base. For some lipophilic examples there was a color change of the reaction mixture instead of precipitation.

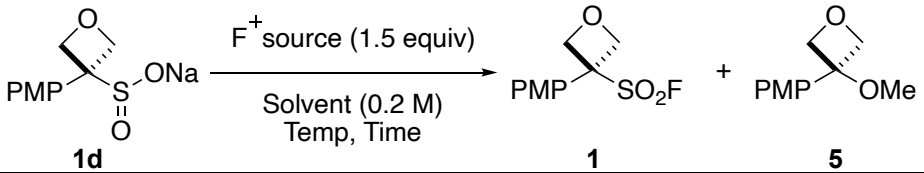
Special attention should be paid when concentrating the reaction mixture, since methyl acrylate (volatile and very toxic) is generated as a by-product. Only use rotatory evaporators in a ventilated space.

Electrophilic Fluorination:

Reaction Optimization (Table S2)

Selectfluor or *N*-fluorobenzenesulfonimide (NFSI) as electrophilic fluorine source proved successful for the fluorination of sulfinate salt **1d** (entries 1–2). Methanol was chosen as the optimal solvent (entries 2–4) and performing the reaction at 0 °C for 1 h showed the best result (entries 5–7).

Table S2 Optimization of the fluorination of sulfinate **1d**.



1d **1** **5**

Entry	F⁺ Source	Solvent	Temp / °C	Time / h	Yield / %[a]	
					1	**5**
1	NFSI	MeOH	25	2	70 (45)	17
2	Selectfluor	MeOH	25	2	68 (50)	16
3	Selectfluor	MeCN	25	2	60	NA
4	Selectfluor	*i*-PrOH	25	2	43	NA
5	Selectfluor	MeOH	0	2	90	0
6	Selectfluor	MeOH	0	1	89 (85)	0
7	Selectfluor	MeOH	0	0.5	84	0

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses.

Further remarks:

The sequence of addition of reaction components is important to achieve a good temperature control, especially for larger scale reactions (>1 mmol). The most reliable results were obtained by adding Selectfluor to precooled (0 °C) MeOH, stirring for 5 min and then adding the sulfinate salt.

For best results, especially for small-scale reactions (<1 mmol), remove as much sulfinate salt as possible from its reaction flask onto a weighing paper. Before adding the salt, rinse this flask with some of the ice-cold Selectfluor/MeOH solution (ca. 5 mL) to remove residual material on the walls of the flask. Then transfer this solution back to the reaction vessel for the fluorination step and add the remaining sulfinate from the weighing paper.

In general, oxetane sulfonyl fluorides are sensitive to temperature. Do not heat above 25 °C when concentrating *in vacuo* on rotatory evaporators.

Most oxetane sulfonyl fluorides are unstable on silica. Column chromatography should be performed in the shortest time possible (<15 min if possible) and using the shortest possible column. As a reference, a 3 mmol-scale reaction can be purified with 2.5 cm of silica in a column of 1.5 cm diameter.

One of the degradation products is the corresponding 3-fluorooxetane. For many examples this side product is volatile and can be removed with a high-vacuum pump. For other, heavier oxetanes, this

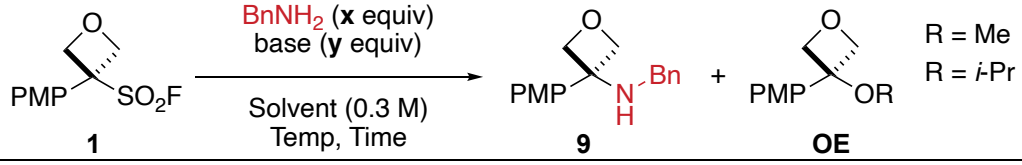
side product cannot be removed *in vacuo*, but it was shown that its presence does not affect the subsequent oxetane amination (see for example **56'**, page S81, **76**, page S138 and **78**, page S139).

Oxetane Amination:

Reaction Optimization (Table S3)

The equivalents of reaction components (entries 1–6) were investigated, as well as solvent (entries 7–11), concentration (entries 12–13), temperature (entries 14–16), base (entries 17–21) and time, leading to the optimal conditions (entry 22).

Table S3 Optimization of the oxetane amination with sulfonyl fluorides. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under argon and with an aqueous workup.



Entry	x	y	Solvent	Temp / °C	Time / h	Base	Yield / %[a]		
							9	OE	RSM
1	1.2	1.3	MeCN	60	1	NEt_3	68 (68)	NA	0
2	1	1.3	MeCN	60	1	NEt_3	55	NA	0
3	2	1.3	MeCN	60	1	NEt_3	48/62/74[b]	NA	0
4	1.2	2	MeCN	60	1	NEt_3	57	NA	0
5	1	1	MeCN	60	1	NEt_3	53	NA	0
6[c]	1	1.3	MeCN	60	1	NEt_3	67	NA	0
7	1.2	1.3	CH_2Cl_2	60	1	NEt_3	12	NA	88
8	1.2	1.3	1,4-dioxane	60	1	NEt_3	0	NA	98
9	1.2	1.3	MeOH	60	1	NEt_3	8	85	0
10	1.2	1.3	*i*-PrOH	60	1	NEt_3	19	28	41
11	31	1.3	$BnNH_2$	60	1	NEt_3	34	NA	17
12	1.2	1.3	MeCN (0.1 M)	60	1	NEt_3	68	NA	0
13	1.2	1.3	MeCN (1 M)	60	1	NEt_3	54	NA	0
14	1.2	1.3	MeCN	40	1	NEt_3	21	NA	76
15	1.2	1.3	MeCN	40	6	NEt_3	42	NA	12
16	1.2	1.3	MeCN	80	1	NEt_3	64	NA	0
17	1.2	1.3	MeCN	60	1	K_2CO_3	87	NA	9
18	1.2	1.3	MeCN	60	1	Cs_2CO_3	74	NA	8
19	1.2	1.3	MeCN	60	1	Na_2CO_3	72	NA	9
20	1.2	1.3	MeCN	60	1	Li_2CO_3	58	NA	6
21	1.2	1.3	MeCN	60	1	NaOAc	57	NA	4
22	**1.2**	**1.3**	**MeCN**	**60**	**2**	**K_2CO_3**	**(89)**	**NA**	**0**

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses. [b]The outcome of three independent reactions. [c]Using 1.2 equiv of OSF **1**. OE = Oxetane ether. RSM = Recovered starting material.

General Procedure A:

Anhydrous K_2CO_3 (36 mg, 0.26 mmol, 1.3 equiv), nucleophile (0.24 mmol, 1.2 equiv) and oxetane sulfonyl fluoride (0.20 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under air or inert gas (Ar or N_2). The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h and then either a Celite or aqueous workup was performed. Purification by flash column chromatography afforded the desired oxetane amine.

Celite Workup:

The reaction mixture was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was then removed *in vacuo* using a rotatory evaporator.

Aqueous Workup

The reaction mixture was left to cool to 25 °C and water (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator.

Further remarks:

When an ammonium salt was used instead of the free amine, 2.6 equiv K_2CO_3 (72 mg, 0.52 mmol) were added.

Residual water may lead to the formation of an oxetanol side product. Flame-drying K_2CO_3, using anhydrous solvent and distilling amines where possible reduced the amount of oxetanol formed. Oxetane fluoride is also observed as a side product, especially with slow-reacting amines such as *t*-butylamine. The low amounts and different polarity between these two side products and the desired oxetane amine allowed for a straight-forward purification in the majority of cases.

When using very volatile amines (e.g. diethylamine), it is beneficial to pre-weigh and add the sulfonyl fluoride into the vial directly after adding the amine and immediately sealing the vial to prevent any significant loss of amine due to evaporation.

In most cases, the atmosphere of the reaction does not affect the yield (see pages S26 and S35) and the reaction can be run both under air and inert gas.

Performing a Celite workup is beneficial when generating very polar products which are difficult to extract from the aqueous phase.

For very hindered amines (e.g. *t*-butylamine) it is beneficial to run the reaction under anhydrous conditions (inert atmosphere) and with 2.0 equivalents of amine (General Procedure B; see also Table S7):

General Procedure B:

Anhydrous K_2CO_3 (36 mg, 0.26 mmol, 1.3 equiv), amine (0.40 mmol, 2.0 equiv) and oxetane sulfonyl fluoride (0.20 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under Ar. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was then removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography afforded the desired oxetane amine.

Handling and Storage Considerations of Oxetane Sulfonyl Fluorides

Oxetane sulfonyl fluorides are remarkably stable at room temperature (25 °C), but very reactive at increased temperatures (60 °C). The stability of the sulfonyl fluoride is, however, somewhat substrate dependent. For example, PMP OSF **1** can be left at room temperature under air ('bench'-conditions) for prolonged periods of time (>6 months) without significant loss in purity (still >85% pure after 6 months). Contrastingly, OTIPS OSF **55** degraded completely from a white solid to a purple gum after 30 days on the bench. Oxetane sulfonyl fluorides turn from white to pink as a sign of degradation (Fig. S2). ^{1}H and ^{19}F NMR spectra of white and pink (111 days on the bench) **1** were identical. The 30-compound array (see page S35) used a 'pink' OSF **1** (6 months, >85% purity), which had no impact on the outcome of the reaction.

All the synthesized OSFs have been indefinitely stable (>6 months) in the freezer (–20 °C). PMP OSF **1** and OTIPS OSF **55** have remained stable in the freezer for >1 year.

Despite the relative bench-stability of oxetane sulfonyl fluorides and sulfinate salts, it is advised to store the bulk of synthesized material as the sulfone. Small batches of sulfonyl fluoride can be synthesized as required, through the 2-step elimination-fluorination protocol, in around 4 h in total from the oxetane sulfone (see for example **1**, page S69).

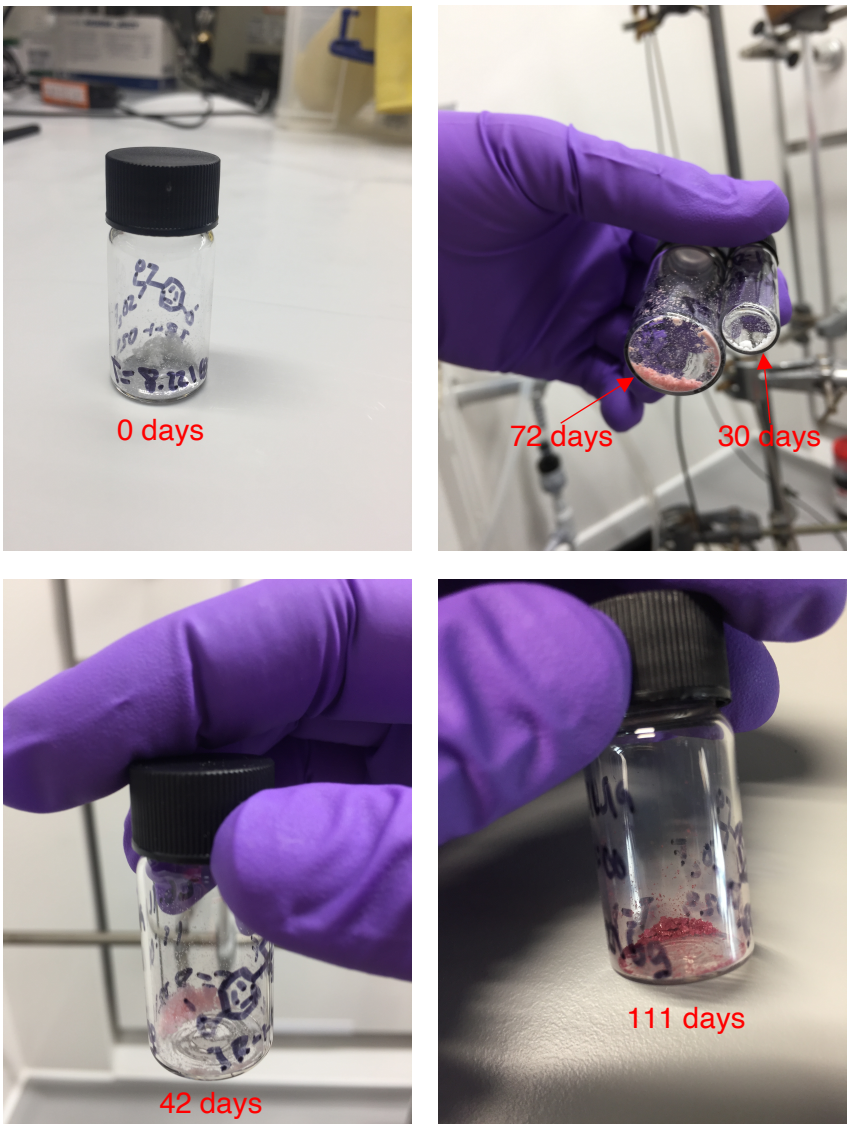


Fig. S2 Change in appearance of PMP OSF **1** with time.

Streamlined Synthesis of Oxetane Sulfonyl Fluoride 1 with Pictures, Tips and Tricks

To facilitate use of the protocol, the synthesis of OSF **1** was demonstrated in a streamlined manner. 1 gram of OSF **1** was obtained from oxetanol **1a** in 2 days (see Fig. S3). Useful details are provided below, alongside pictures and tips.

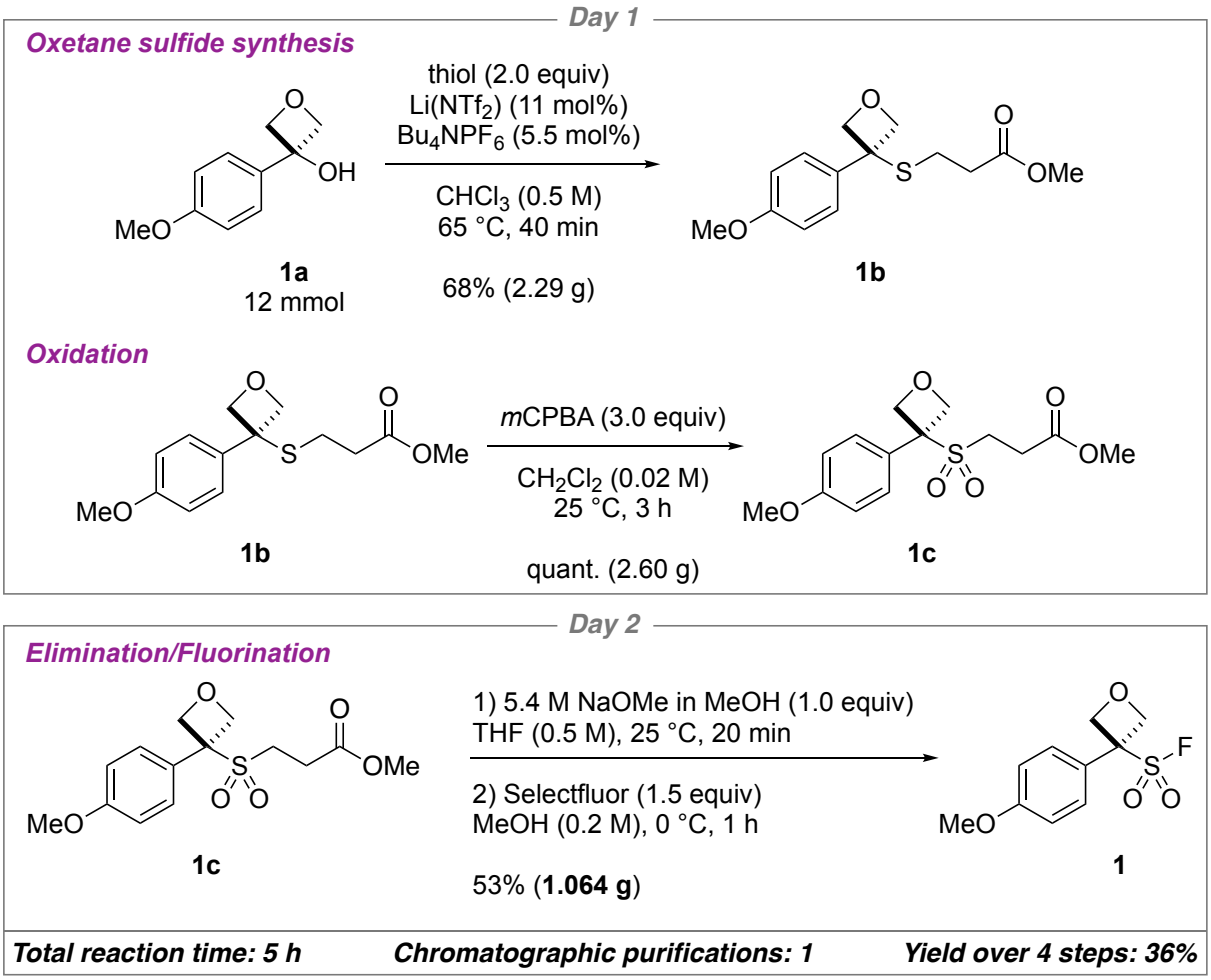
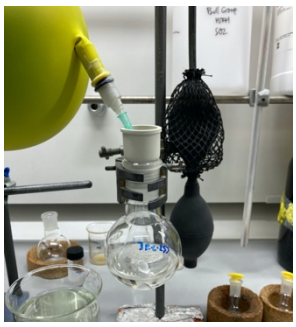


Fig. S3 Streamlined gram-synthesis of OSF **1**.

Oxetane sulfide synthesis:



A flame-dried 100 mL flask under Ar was charged sequentially with oxetanol **1a**, non-anhydrous $CHCl_3$, thiol, $Li(NTf_2)$ and Bu_4NPF_6. A colorless solution resulted. Excess thiol in the syringe was quenched with a dilute bleach bath (bleach:H_2O = 1:1). The syringe was left to stand in the bleach bath for 24 h before disposal.



The flask was inserted into a preheated oil bath at 65 °C. After 15 min of stirring, the reaction turned yellow and cloudy. Stopping and restarting the stirring helped trigger the color change. After 25 min of further stirring, the reaction was quenched with sat. aq. $NaHCO_3$ (25 mL).

Note: it was known from previous experience that this temperature was needed to trigger the start of the reaction. If it is a new substrate, it is recommended to start at 40 °C and warm the reaction mixture slowly until a color change is observed (see page S9 for further details).



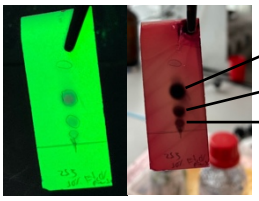


The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) (1). The combined organic layers were washed with aq. NaOH (1 M, 35 mL) (2). This step deprotonates unreacted thiol and brings the thiolate into the aqueous phase. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator (3).

Note: the phase separation during the wash with NaOH was very slow (2). 20 mL of brine were added to aid the separation.



TLC of crude reaction mixture (50% Et_2O/pentane) under UV (left) and with *p*-anisaldehyde (right)



1b

1b'' (ring-opened side product; see Scheme S4)

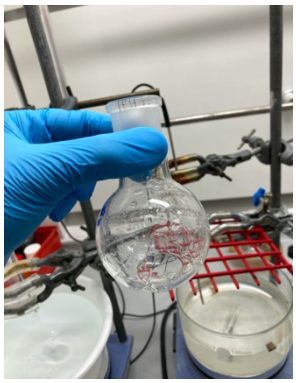
1a

Note: use a rotatory evaporator in a ventilated space. Minimal amounts of excess thiol (volatile and toxic) may still be present in the crude reaction mixture.





The crude mixture was purified by flash column chromatography (16 cm of silica in a column of 4 cm diameter; 300 mL 30% Et_2O/pentane, 300 mL 40% Et_2O/pentane, 1400 mL 50% Et_2O/pentane). Fractions 19–26 were collected. The product was concentrated *in vacuo* using a rotatory evaporator. Complete removal of solvent was achieved by drying on a rotatory evaporator (1 h at 40 °C, ca. 5 mbar) and then under high vacuum (30 min at 25 °C, ca. 1×10^{-3} mbar).



Oxetane sulfide **1b** was obtained as a colorless oil (2.29 g, 68%).

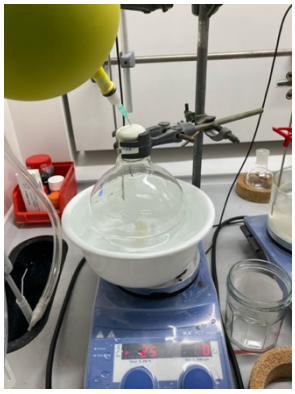
Note: on other occasions **1b** solidified to a white solid.



<u>Oxidation:</u>

A flame-dried 1 L flask under Ar was charged with oxetane sulfide **1b** and dissolved in anhydrous CH_2Cl_2.

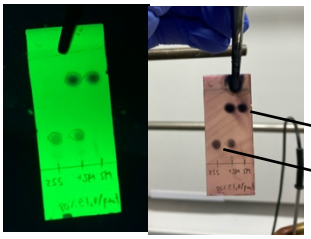




Washed *m*CPBA (see page S10 for further details) was added and the reaction mixture was stirred at 25 °C for 3 h.



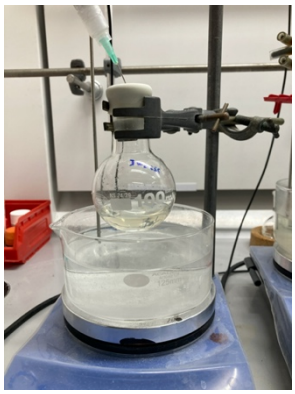
TLC of crude reaction mixture (80% Et_2O/ pentane) under UV (left) and with *p*-anisaldehyde (right)



Aq. KOH (3 M, 60 mL) was added and the phases were separated. This step brings the benzoic acid by-product into the aqueous phase (as the carboxylate). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator.

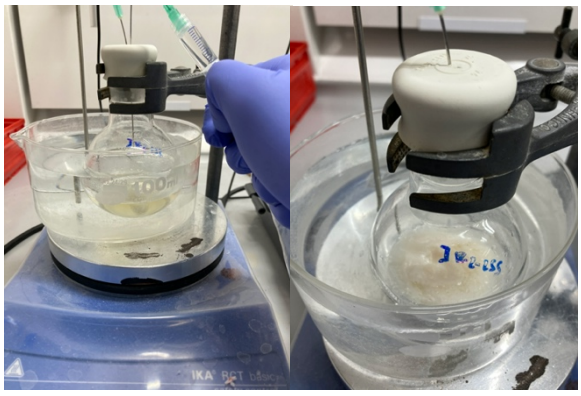


Complete removal of solvent was achieved by drying under high vacuum (overnight at 25 °C, ca. 1 × 10^{-3} mbar). Oxetane sulfone **1c** was obtained as a colorless oil which crystallized spontaneously to form white crystals (2.60 g, quant.).



Elimination:

The flask containing oxetane sulfone **1c** from the previous step was put under an atmosphere of Ar and charged with a stirring bar and anhydrous THF. The clear and pale-yellow reaction mixture was stirred at 25 °C.



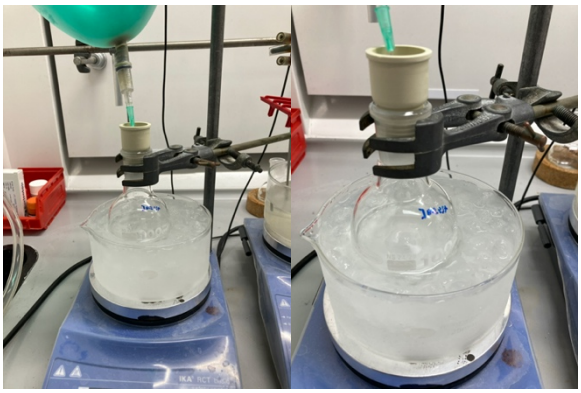
t = 0 min *t = 2 min*

Sodium methoxide (5.4 M in MeOH) was added dropwise to the reaction mixture, upon which it immediately turned yellow. After 2 min of the addition, sulfinate **1d** precipitated. The resulting slurry was stirred for further 18 min.

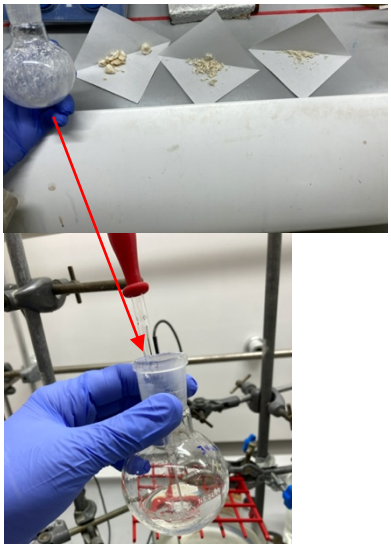


Concentration *in vacuo* using a rotatory evaporator yielded oxetane sulfinate **1d** as a pale-brown solid which was used directly for the next step.

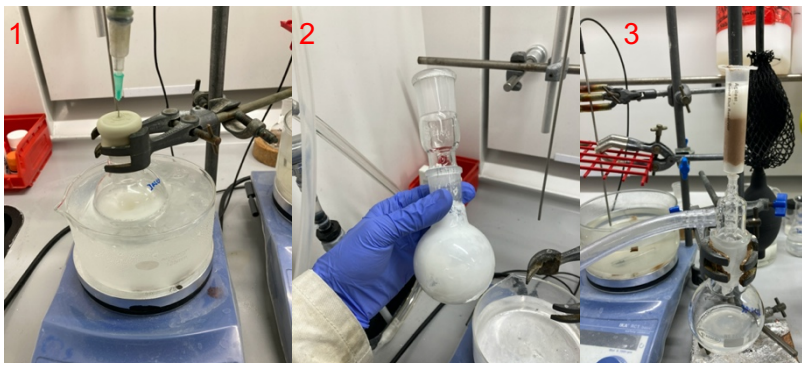
Fluorination (see page S13 for further details):



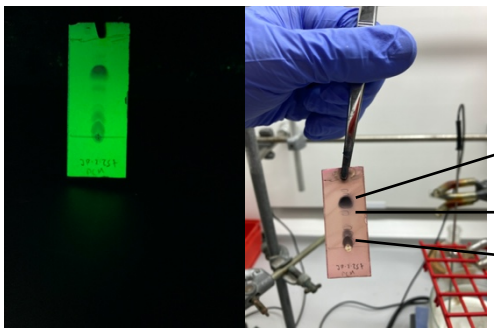
A flame-dried 100 mL flask under Ar was charged with anhydrous methanol and cooled to 0 °C. After stirring for 5 min at 0 °C, Selectfluor was added and stirred for further 5 min at 0 °C.



Oxetane sulfinate **1d** was transferred onto weighing paper using a spatula. The flask was rinsed with the ice-cold Selectfluor/methanol solution and transferred to the reaction vessel for the fluorination step. The remaining **1d** on the weighing paper was added portion wise.

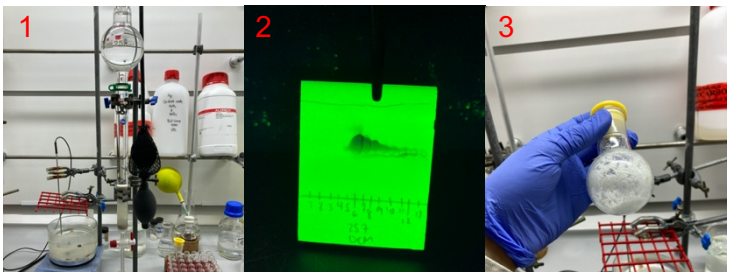


The heterogenous reaction mixture was stirred for 1 h at 0 °C (1), then concentrated *in vacuo* using a rotatory evaporator. The residue (2) was diluted with CH_2Cl_2 (30 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2 (3). The filtration through Celite removes insoluble Selectfluor salts.



TLC of crude reaction mixture (100% CH_2Cl_2) under UV (left) and with *p*-anisaldehyde (right).

Selectfluor by-products.



After concentration *in vacuo* using a rotatory evaporator, the crude mixture was filtered through a plug of silica (10 cm of silica in a column of 2 cm diameter; 80% CH_2Cl_2/pentane (1)). Fractions 5–13 were collected (2). The product was concentrated *in vacuo* using a rotatory evaporator. Complete removal of solvent was achieved by drying under high vacuum (overnight at 25 °C, ca. 1×10^{-3} mbar). Small amounts of oxetane fluoride **6**, which has a similar R_f to **1** and is volatile, is also removed under the reduced pressure. Oxetane sulfonyl fluoride **1** was obtained as a white solid (3) (1.064 g, 53% over 2 steps).

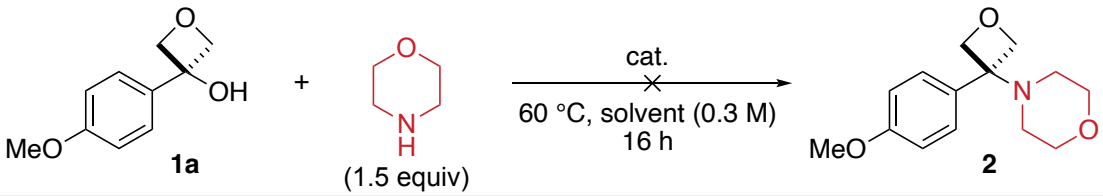
Attempts to Aminate Oxetanol 1a Directly

Attempts have been made in our group to prepare aryl aminooxetanes directly from oxetanols, akin to our previously reported Friedel–Crafts[3,4] and thiol alkylation works,[2] using Lewis acids.

For example, attempts were made to synthesize oxetane amine **2** directly from oxetanol **1a** and morpholine *via* the formation of an oxetane carbocation using lithium, calcium and iron catalysts. These Lewis acids were tested in combination with solvents (MeCN, toluene, $CHCl_3$) in which oxetane carbocations have also been previously generated. In addition, TfOH[5] and $Bi(OTf)_3$[6] were also tested as catalysts due to their previous success to dehydrate alcohol substrates.

Oxetane amine **2** was not observed in any of the combinations, and high amounts (79–100%) of the oxetanol starting material **1a** were recovered in all cases (Table S4). Presumably, and in line with the high degree of starting material recovery, the strongly coordinating amine nucleophile deactivates the acid catalyst and prevents the formation of an oxetane carbocation and thus, of oxetane amine.

Table S4 Unsuccessful direct amination of oxetanol **1a**.



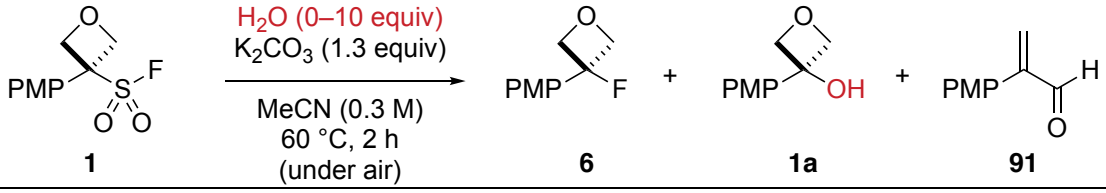
	Yield 1a (RSM) / %[a]				
	$Li(NTf_2)$ (11 mol%) NBu_4PF_6 (5.5 mol%)	$Ca(NTf_2)_2$ (5 mol%) NBu_4PF_6 (5 mol%)	$FeCl_3$ (7.5 mol%)	TfOH (10 mol%)	$Bi(OTf)_3$ (10 mol%)
MeCN	87	100	90	98	100
Toluene	91	100	79	98	96
$CHCl_3$	97	100	88	96	95

[a]Yields calculated by analysis of the ^1H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. RSM = recovered starting material.

Sensitivity of the Oxetane Amination towards Water

To assess the effect of water in the reaction, the reaction was performed with increasing amounts of water, which led to oxetanol **1a** in good yields, with an increase in yield using higher water concentrations (Table S5 and Fig. S4).

Table S5 Reaction of OSF **1** with increasing equivalents of water. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air, with flame-dried K_2CO_3 as part of the reaction set-up, without amine and with a Celite workup.



Entry	Equiv H_2O	Yield / %[a]			
		6	**1a**	**87**	**Total**
1	0[b]	78	6	1	85
2	0[c]	58	11	9	78
3	0	35	42	1	78
4	1	27	65	0	92
5	2	31	64	0	95
6	3	32	68	0	100
7	10	12	84	0	96

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. [b]In the absence of base. [c]Under Ar.

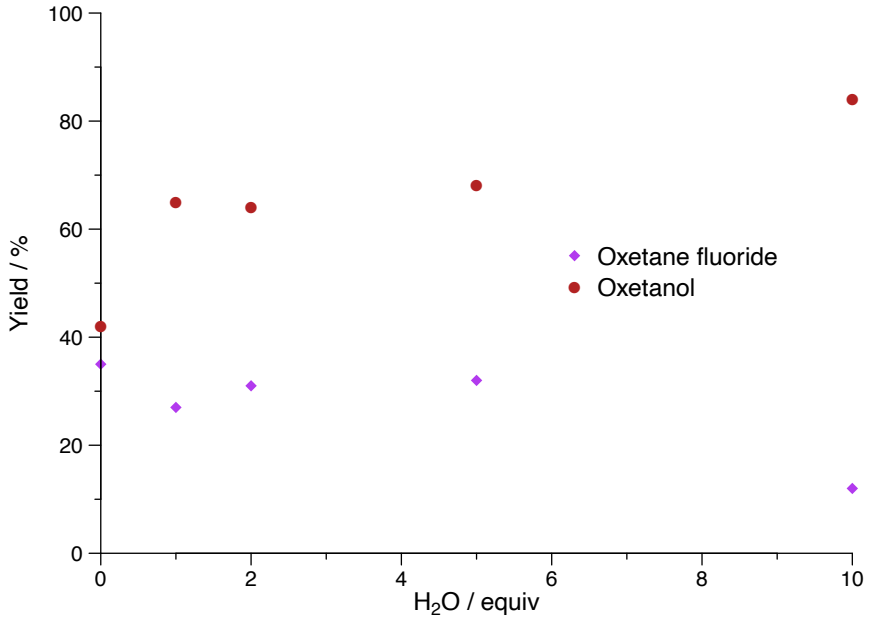
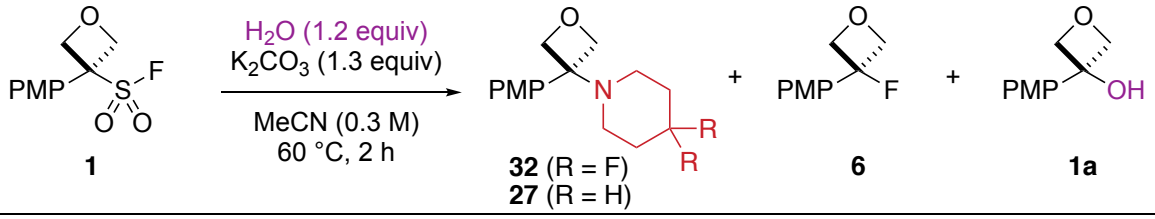


Fig. S4 Reactivity of OSF 1 with different equivalents of water. Graphical representation of entries 3–7 in Table S5.

However, in the presence of an amine nucleophile the reaction is insensitive towards moisture, which was shown in competition experiments between water and separately 4,4-difluoropiperidine and

piperidine (Table S6). In both cases the amine nucleophile outcompeted an attack by water and no decrease in yield of oxetane amine nor increase in yield of oxetanol **1a** was observed compared to the standard conditions (*cf* Table S11). Hence, most examples of the scope of the reaction were run under air to illustrate the facile nature of the reaction and suitability for wide application and use in array chemistry (also see Table S15).

Table S6 Competition experiments of OSF **1** with 4,4-difluoropiperidine, piperidine and water. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.

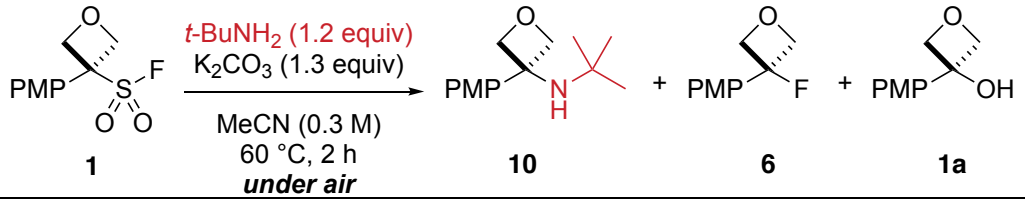


Entry	Change	Yield / %[a]			
		32/27	**6**	**1a**	**Total**
1	+ 4,4-difluoropiperidine (1.2 equiv)	87 (**32**)	5	1	93
2	+ piperidine (1.2 equiv)	67 (**27**)	11	8	86

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard.

However, significantly higher amounts of oxetanol **1a** were observed in the reaction with hindered amines such as *t*-BuNH$_2$. Hence, the amination of OSF **1** with *t*-BuNH$_2$ was investigated under anhydrous conditions and increased equivalents of nucleophile, which led to a remarkable increase in yield (Table S7).

Table S7 Reaction of OSF **1** with *t*-BuNH$_2$ under different conditions. Reactions were carried out on a 0.20 mmol scale using **General Conditions A** with a Celite workup.



Entry	Change	Yield / %[a]			
		10	**6**	**1a**	**Total**
1	none[b]	42 (40)	24	34	–
2	under Ar	71 (69)	8	8	87
3	under Ar + 1.5 equiv *t*-BuNH$_2$	85 (75)	5	3	93
4	under Ar + 2.0 equiv *t*-BuNH$_2$	85 (82)	8	1	94

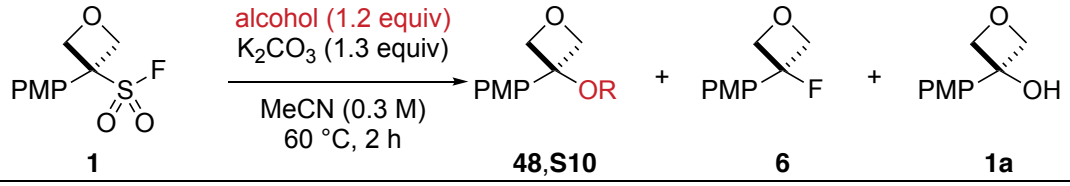
[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses. [b]In this entry, the *in situ* yields refer to the ratio of **10**:**6**:**1a** in the ^{1}H NMR spectrum of the crude mixture.

Reactivity of Oxetane Sulfonyl Fluorides

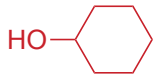
OSF **1** with Aliphatic Alcohols

Oxetane sulfonyl fluoride **1** also reacts efficiently with alcohol nucleophiles and oxetane ethers **48** and **S10** were obtained in good yields (Table S8).

Table S8 Reaction of OSF **1** with aliphatic alcohols. Reactions were carried out on a 0.20 mmol scale using **General Conditions A** under air and with a Celite workup.



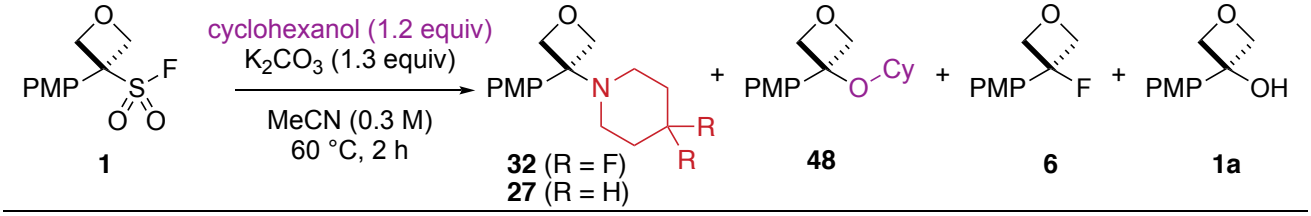
1 **48**,**S10** **6** **1a**

Entry	Alcohol	Oxetane ether	Yield / %[a] 6	1a	Total
1		**48**, 57 (50)	18	20	95
2		**S10**, 64 (60)	14	16	94

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses.

Remarkably, the defluorosulfonylation reaction is completely chemoselective for amines over alcohols, as was observed intramolecularly with aminoalcohols (**11**, **12**, **17**, **28**) and intermolecularly in competition experiments between cyclohexanol and 4,4-difluoropiperidine (electron-poor amine) and piperidine (electron-rich amine; Table S9).

Table S9 Competition experiments of OSF **1** with 4,4-difluoropiperidine, piperidine and cyclohexanol. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.



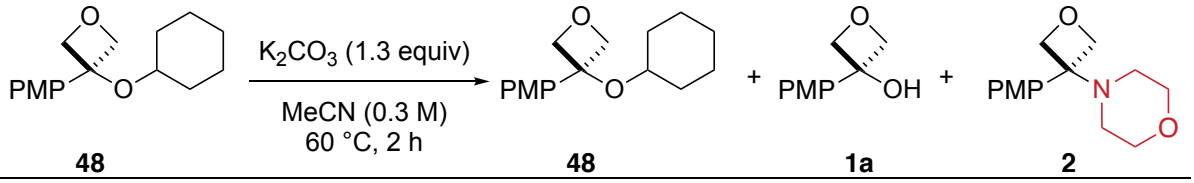
1 **32** (R = F) **27** (R = H) **48** **6** **1a**

Entry	Change	32/27	Yield / %[a] 48	6	1a	Total
1	+ 4,4-difluoropiperidine (1.2 equiv)	91 (**32**)	1	6	1	99
2	+ piperidine (1.2 equiv)	64 (**27**)	0	15	7	84

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard.

Since we have previously shown the ether bond formation in oxetane ethers to be reversible (shown for phenol ethers[7]), oxetane ether **48** was resubmitted to the reaction conditions in the presence and absence of an amine nucleophile to rule out degradation through either E_1 or E_2 elimination from the oxetane ether. In neither case was significant degradation of the oxetane ether (on average 85% recovery) observed (Table S10).

Table S10 Stability of oxetane ether **48** under the amination conditions. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.



48 **48** **1a** **2**

Entry	Change	Yield / %[a]		
		48 (RSM)	**1a**	**2**
1	none	84	0	NA
2	+ morpholine (1.2 equiv)	86	0	0

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. RSM = recovered starting material.

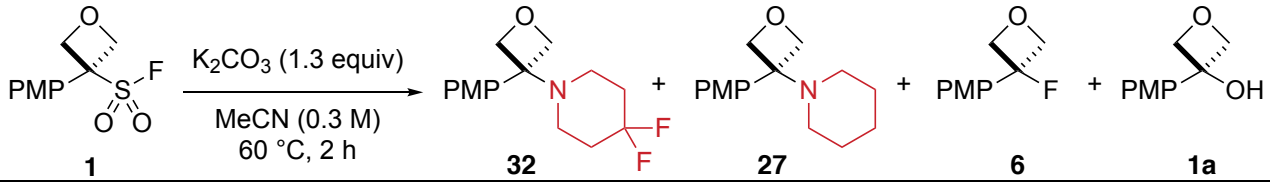
Competition Experiments with Piperidine Nucleophiles

The improved yields of electron-poor piperidines over their electron-richer counterparts prompted us to conduct competition experiments to investigate this inverse selectivity, since electron-rich nucleophiles usually react faster than electron-poor ones.

Competition experiments between 4,4-difluoropiperidine and unsubstituted piperidine were conducted and 4,4-difluoropiperidine was found to react much quicker with OSF **1** than piperidine (Table S11, entry 3). Furthermore, the total mass recovery with piperidine as nucleophile was significantly lower (entry 2). It is plausible that electron-rich piperidines (and electron-rich amines in general) lead to reduced yields due to their increased basicity which favors a degradative elimination pathway.

We speculate that the concentration of electron-rich amines is reduced due to protonation. A competition experiment in the absence of base gave a decrease in yield of the electron-rich piperidine, which is supportive of this hypothesis (9% increase/decrease in yield of **32**/**27** (entry 3 vs entry 4). Performing the reaction in the presence of Et_3N as base gave the same selectivity as K_2CO_3, indicating that neither potassium nor carbonate ions specifically influenced selectivity (entry 5).

Table S11 Competition experiments of OSF **1** with 4,4-difluoropiperidine and piperidine. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.



1 **32** **27** **6** **1a**

Entry	Change	Yield / %[a]				
		32	**27**	**6**	**1a**	**Total**
1	+ 4,4-difluoropiperidine (1.2 equiv)	90	NA	5	1	96
2	+ piperidine (1.2 equiv)	NA	64	11	8	83
3	+ both amines (1.2 equiv each)	50	29	8	2	89
4	Entry 3 + no base	59	20	13	12[b]	104
5	Entry 3 + NEt_3 as base	55	22	9	10[b]	96

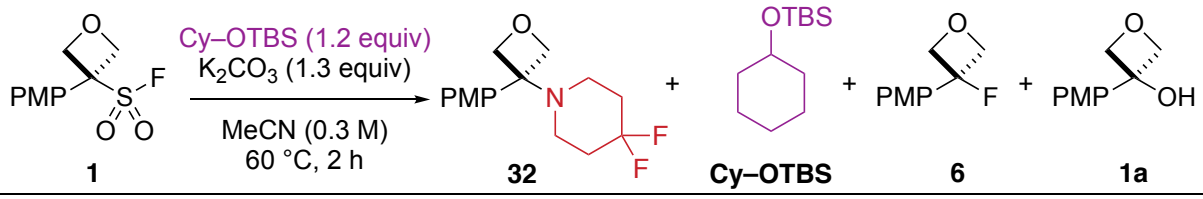
[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. [b]Approximate values, signals very obscured. NA = Not applicable.

Effect of OTBS in the Reaction

TBS-protected alcohols were tolerated in the reaction and no TBS-deprotection was observed for neither product (**29**) nor for unreacted starting material.

The impact of the OTBS group on the reaction was further assessed by subjecting OSF **1** to the reaction conditions in the presence/absence of 4,4-difluoropiperidine as nucleophile with equimolar amounts of TBS-protected cyclohexanol as additive (Table S12). In neither case was TBS-deprotection and/or formation of oxetane ether **48** observed and the oxetane amination with 4,4-difluoropiperidine remained unaffected by the TBS-alcohol.

Table S12 Effect of OTBS-protected cyclohexanol as additive. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.



1 **32** **Cy–OTBS** **6** **1a**

Entry	Change	Yield / %[a]			
		32	**Cy–OTBS**[b]	**6**	**1a**
1	none	NA	85	23	36
2	+ 4,4-difluoropiperidine (1.2 equiv)	88	69	4	1

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. [b]This compound is volatile and a significant amount may have been lost during solvent removal. NA = Not applicable.

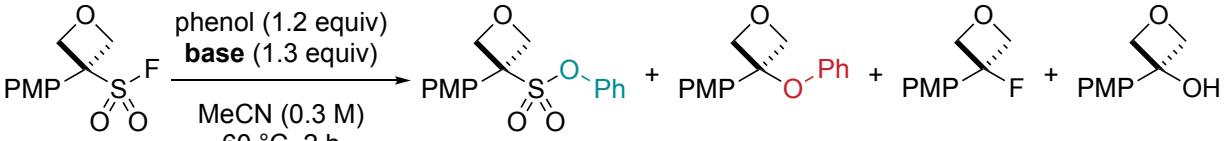
OSF **1** with Phenol and Effect of Base

The reaction of OSF **1** with phenol under the standard conditions (K_2CO_3; Table S13, entry 1) surprisingly yielded a mixture of SuFEx product **49** and defluorosulfonylation product **50**. A change to a soluble organic base (NEt_3) shifted the selectivity towards oxetane ether **50** (entry 2; in accordance with the observations made by *in situ* ^{1}H NMR, see Fig. S14). A change to a softer countercation of the carbonate base (Cs^+) led to selective formation of sulfonate ester **49** (entry 3) and the use of a weaker base ($KHCO_3$) unable to deprotonate phenol but able to trap fluoride ions yielded **50** in complete selectivity.

Pre-formation of sodium phenoxide with NaH gave SuFEx product **49** in very high yields and absolute selectivity (entry 5). Opposite selectivity was achieved with TMS-phenol, which is deprotected (hence activated) by the released fluoride ions *after* the defluorosulfonylation (entry 6). Interestingly, this reactivity contrasts previous reports which claimed silyl groups to be essential for the SuFEx reactivity of Si-protected phenols (Si–F bond formation "*the* main driving force"[8]).[9] In the absence of base a complex mixture was obtained (entry 7).

Presumably, the observed selectivities between sulfonate ester **49** and ether **50** arise from the phenol-phenoxide equilibrium and differences in reaction rates between the sulfur fluoride exchange and defluorosulfonylation: the rate of SuFEx between **1** and phenoxide is faster than defluorosulfonylation, but the rate of defluorosulfonylation is faster than SuFEx between **1** and phenol.

Table S13 Optimization of the oxetane amination with sulfonyl fluorides. Reactions were carried out on a 0.20 mmol scale using **General Conditions A** under argon and with a Celite workup.



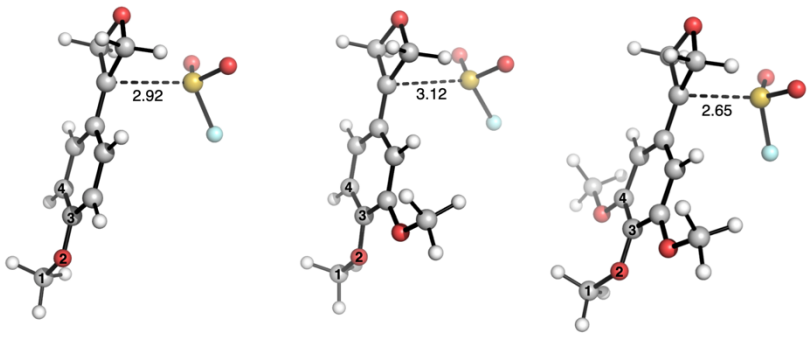
1 **49** **50** **6** **1a**

Entry	Base	Yield / %[a]				
		49	**50**	**6**	**1a**	**Total**
1	K_2CO_3	54 (41)	36 (30)	17	0	107
2	NEt_3	9 (8)	50 (49)	31	0	90
3	Cs_2CO_3	88 (76)	11 (10)	5	0	104
4	$KHCO_3$	0	49 (39)	53	0	102
5	NaH[b]	100 (83)	0	4	0	104
6	TMS-phenol (no base)	2	67 (62)	8	0	77
7	No base[c]	ND	ND (3)	ND	ND	ND

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard. Isolated yields in parentheses. [b]1.205 equiv NaH were used. NaH was added portionwise to a solution of phenol in MeCN at 0 °C. The reaction was warmed to 25 °C, OSF **1** was added and the reaction vial was sealed. The reaction mixture was warmed up to 60 °C and stirred at this temperature for 2 h. [c]The ^{1}H NMR spectrum of the crude mixture of the reaction was too complex to determine *in situ* yields. ND = Not determined.

Reaction Rates of OSF **1**, **53** and **54**

Trimethoxy sulfonyl fluoride **54** and dimethoxy sulfonyl fluoride **53** were found to react surprisingly slower (**54**) and faster (**53**) than sulfonyl fluoride **1** (see Fig.6 a iii and Fig. S11). Calculations corroborate this reactivity trend (Fig. S5), where the barriers to S_N1 ionization of **53** and **54** are lower and higher than **1**, respectively.



	TS-1	TS-53	TS-54
$\Delta G^{\ddagger}$ / kJ mol^{-1}	110.2	101.4	127.7
$q^{\ddagger}_{cation}$ / *e*	+0.81	+0.88	+0.68
$\angle_{123}$ / °	120.6	120.6	126.0
$\angle_{234}$ / °	123.6	115.2	126.4

Fig S5 Calculated S_N1 TSs for **1**, **53** and **54** at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP, ma-def2-TZVPP on F//SMD(MeCN)-PBE0-D3BJ/def2-SVP, ma-def2-SVP on F] level of theory. Partial charges (*e*) were calculated with the Hirshfeld method. Distances are shown in Å and angles in degrees.

We have rationalized these differences in rate below:

The methoxy substituent in the *para* position of **54**, which is responsible for the mesomeric stabilization of positive charge on oxetane, is sterically hindered by the two adjacent *meta*-methoxys and forced to adopt an orthogonal conformation to the aromatic ring; its lone pair p-orbital is thus unable to efficiently overlap with the π ring system. The additional energy required to overcome the unfavorable steric interactions to stabilize the forming carbocation results in an early transition state (TS) dominated by sterics (i.e. geometric distortion), whereby the formation of positive charge is not advanced at the transition state, so the contribution of the *p*-methoxy substituent towards the stabilization of the TS is lower than in the case of OSF **1** (Fig. S6).

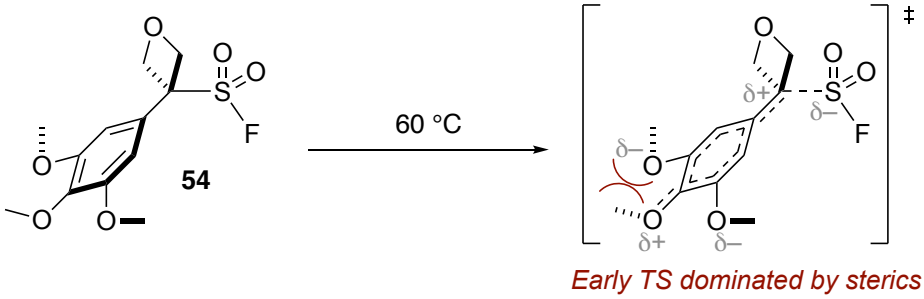


Fig. S6 Proposed early transition state (TS) of trimethoxy OSF **54** responsible for the slower rate observed.

Further evidence for the abovementioned hypothesis is provided by the crystal structures of OSF **1** and **54** (Fig. S7). The most striking difference is the conformation of the *p*-methoxy substituent, which in **1**, is coplanar with the aromatic ring, but in **54**, is orthogonal to the ring – as hypothesized above. Furthermore, the C–O–C bond angle of *p*-OMe in **1** is ca. 118 °, while in **54**, it is ca. 113 °. An angle of 118 ° suggests an orbital hybridization close to sp^2 (optimal bond angle 120 °), where one of the

oxygen lone pairs is localized in an (almost) pure p-orbital that overlaps efficiently with the aromatic π system. On the other hand, an angle of 113 ° corresponds to a hybridization closer to sp^3 (optimal bond angle 109.5 °) without any conjugation with the π system (π–p conjugations are more efficient than π–sp^3 ones).

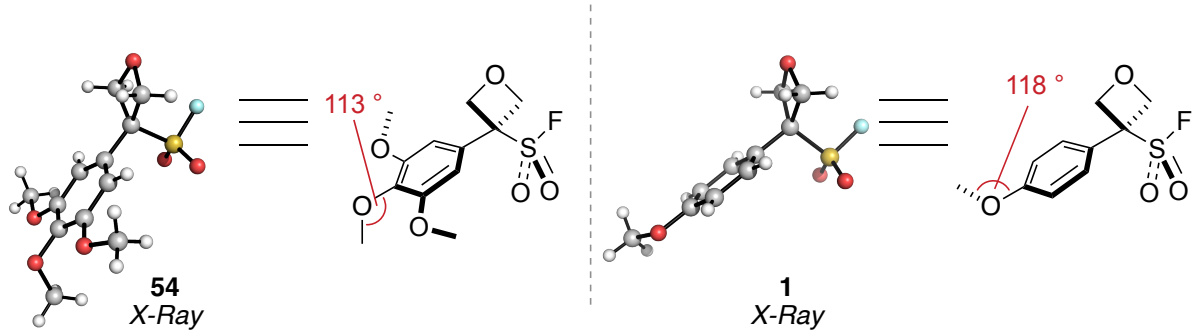


Fig. S7 Crystal structures of OSF **54** (left) and **1** (right) with the relevant C–O–C bond angle highlighted.

The enhanced reactivity of dimethoxy OSF **53** was unexpected since a methoxy group in the *meta*-position may be predicted to have a net electron withdrawing effect and thus, destabilize the oxetane carbocation ($\sigma^{+}_{(m-\mathrm{OMe})}$ = +0.05).[10] We speculate the following:

Once the *p*-OMe adapts a coplanar conformation to the aromatic ring, there is steric repulsion between the oxygen lone pairs. By increasing the donation of the *p*-OMe into the aromatic ring, the clashing sp^2 lone pair can 'contract' because there is less core repulsion on oxygen since electron density has been donated to the ring (Fig. S8 *Top*). Alternatively, the build-up of positive charge on the *para*-oxygen in the TS could be further stabilized by the adjacent sp^2 lone pair through an electrostatic interaction (Fig. S8 *Bottom*). In either case, the lone pair steric clash is reduced and the positive charge in the TS is better stabilized.

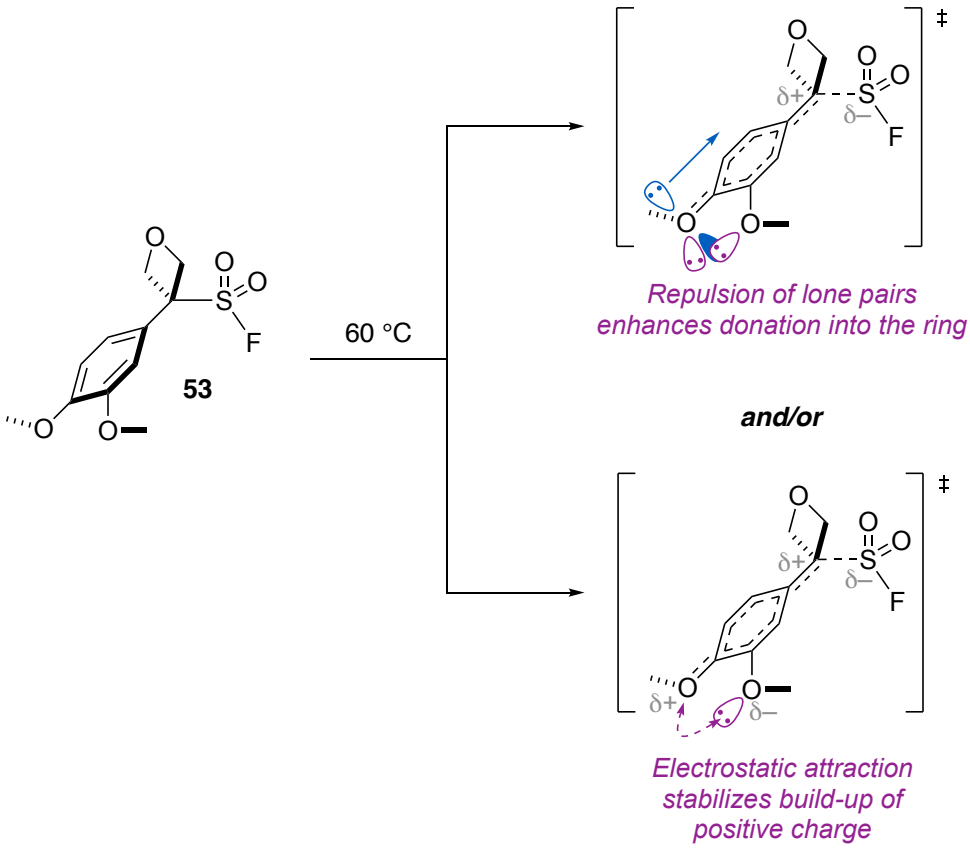
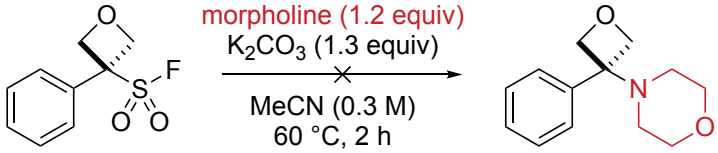


Fig. S8 Hypotheses towards the enhanced reactivity of OSF **53.**

Ph OSF **92** with Morpholine and Phenol

Electron-neutral phenyl OSF **92** did not react under the typical reaction conditions and starting material was recovered (Table S14, entry 1). Increased temperature did not improve reactivity and at 120 °C significant degradation of **92** was observed (entries 2–4). Using TMS–morpholine as nucleophile did not yield oxetane amine either (entry 5). Similar results were observed in the presence of additives which could activate the sulfonyl fluoride (entries 6–8).

Table S14 Reactivity of OSF **92** under different reaction conditions. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under air and with a Celite workup.

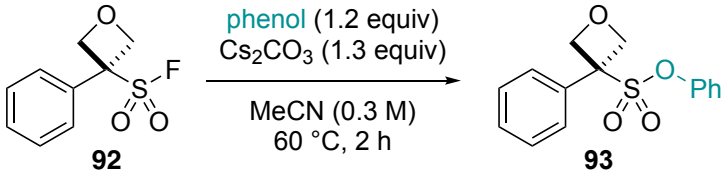


92

Entry	Change from Standard Conditions	RSM (92) / %[a]
1[b]	none	93
2	80 °C	76
3	100 °C	74
4	120 °C	34
5	TMS–morpholine, no K_2CO_3	65
6[c,d]	+ TMSCl (1.2 equiv) and 2.6 equiv. K_2CO_3	75
7[c]	+ 5% HOBt[11]	68
8[c]	+ $Ca(NTf_2)_2$ (1.1 equiv) and NEt_3 as base[12]	48

[a]Isolated yields. [b]0.2 mmol scale. [c]An aqueous workup was performed. [d]Under Ar. RSM = returned starting material.

On the other hand, and as observed with OSF **1** (see Table S13), Ph OSF **92** reacted smoothly with phenol as a nucleophile and Cs_2CO_3 as base in a SuFEx manner to give sulfonate ester **93** in nearly quantitative yield (Scheme S5).



92 **93**

98%

Scheme S5 Reaction of Ph OSF **92** with phenol.

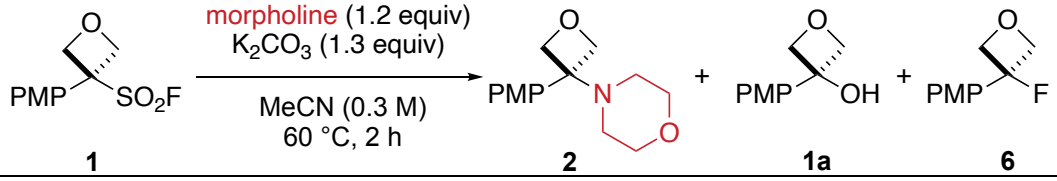
It is interesting that phenyl OSF **92**, which would generate a less stable carbocation than e.g. OSF **1** and is hence, less likely to defluorosulfonylate, did not show SuFEx reactivity with amines under any of the conditions described above either (Table S14). Steric hindrance in vicinity to the sulfur active center is believed to prevent S_N2-type attack by an amine nucleophile on the sulfonyl fluoride (see the crystal structures of OSF **1**, **54**, **56** and **92** on pages S193–S202). Phenoxides however,[13] which are much more nucleophilic than amines,[14] lead to a lower energetic barrier for the SuFEx pathway and yield the corresponding sulfonate ester SuFEx product.

Amine Array Screening

Optimization of Reaction Conditions for Compatibility with Array

The compatibility of the reaction with the typical conditions encountered in an array screening was assessed (Table S15). Pleasingly, the yield of oxetane amine was not affected severely under any of the deviations investigated (entries 1–5) and it was shown that there was no negative combination effect when several variations in conditions were applied simultaneously (entry 6). Notably, the reaction outcome was not affected by an air atmosphere, improving the accessibility and convenience of the reaction set-up.

Table S15 Sensitivity of the reaction towards air, high dilution and variable base loading. Reactions were carried out on a 0.10 mmol scale using **General Conditions A** under argon and with a Celite workup, with any deviations noted in the respective entry.



1 **2** **1a** **6**

Entry	Deviations from Standard	Yield / %[a]		
		2	**1a**	**6**
1	none	85	9	4
2	under air	93	4	3
3	0.07 M	82	11	6
4	3.0 equiv K_2CO_3	76	17	6
5	0.5 equiv K_2CO_3	57	21	19
6	under air, 0.07 M, 3.0 equiv K_2CO_3	92	3	2

[a]Yields calculated by analysis of the ^{1}H NMR spectrum of the crude mixture of the reaction using 1,3,5-trimethoxybenzene as internal standard.

With robust conditions in hand, an array of 30 diverse amines was tested (Scheme S6; See page S151–S178 for characterization by LCMS).

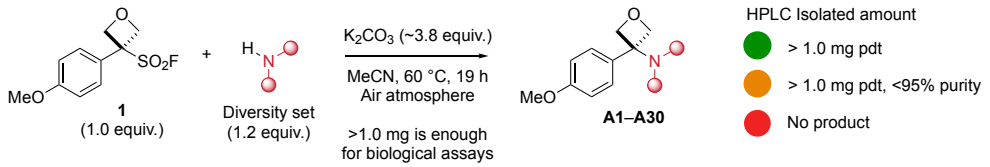
Set-up of Array and Complete Set of Amines Tested

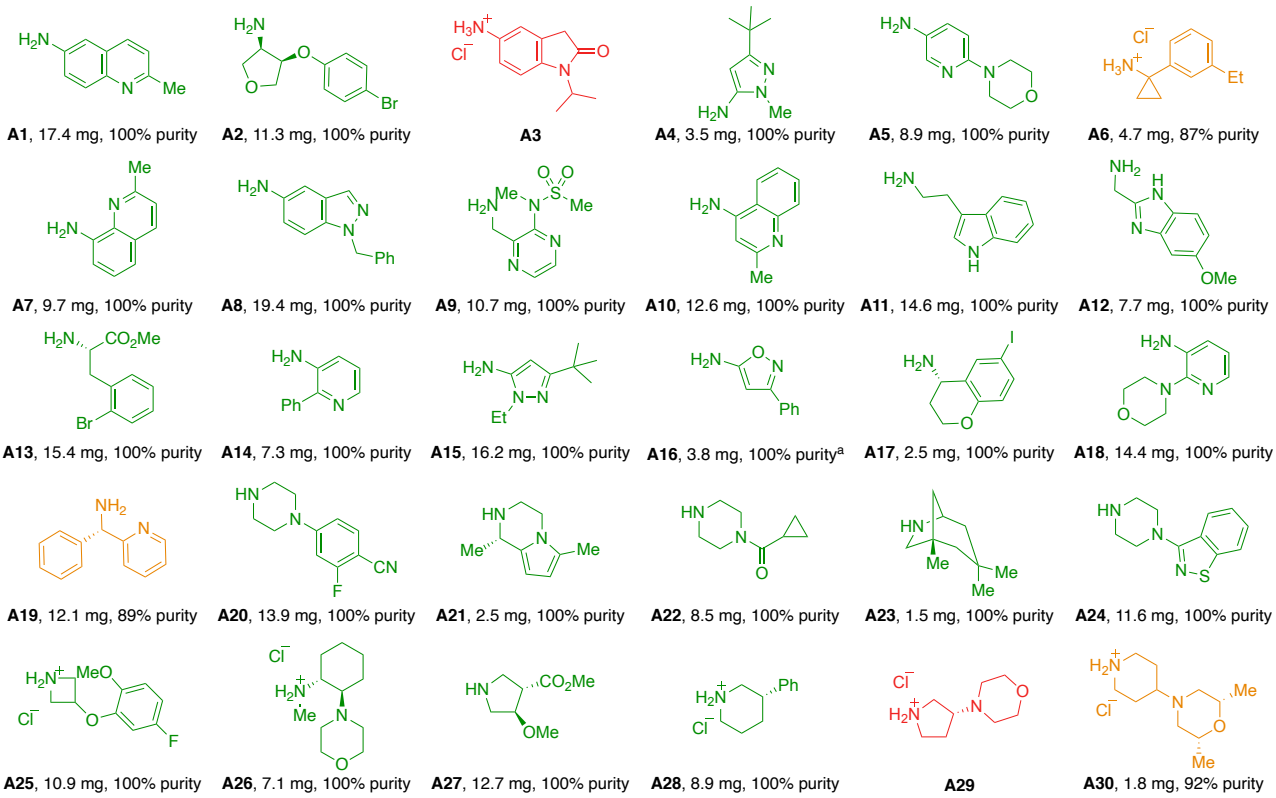
Stock solution: MeCN (0.2 M) was added to sulfonyl fluoride **1** (1.0 equiv per reaction, 25 mg, 0.10 mmol) in a round bottom flask under air.

A plate of 1-dram vials with septum caps under air were each charged with amine monomer (1.2 equiv. per reaction, 0.12 mmol) and a stirrer bar. Approximately 52 mg of K_2CO_3 (0.38 mmol) was added to each vial (not individually measured; one spatula tip ~52 mg). The stock solution of template (0.5 mL per reaction) was added by syringe to each vial containing amine/K_2CO_3, and the vials were transferred to a preheated block at 60 °C. The vials were stirred at 60 °C for 19 h.

The reactions were cooled to 23 °C and diluted with 1 mL EtOAc. The reaction mixtures were then filtered through a prepacked Na_2SO_4 plug into a 2-dram vial. The Na_2SO_4 plugs were rinsed with EtOAc (~1 mL) and the resulting solutions were concentrated by genevac to provide the crude mixtures. The resulting crude oxetanes were dissolved in 1 mL DMSO and submitted for high-throughput purification (column: Waters Sunfire C18 19x100, 5 µ; mobile phase A: 0.05% TFA in water (v/v); mobile phase B: 0.05% TFA in acetonitrile (v/v)). Purities were determined by ELSD detector on LCMS.

25 of the 30 amines tested were successful, yielding the oxetane amine product in more than 1.0 mg and over 90% purity, which is enough for a biological assay. It is worth noting that 4 of the 5 unsuccessful or lower purity examples used a hydrochloride salt, which can be a challenge due to the presence of competing chloride anion nucleophiles.





Scheme S6 Set of amines tested in the 30-compound array. The reactions were carried out on a 0.1 mmol scale as per described above. The colors indicate the amount and purity of oxetane amines obtained. [a]The purity of this compound is considered as 100% but consisted of two compounds (79.7% and 20.3%) with the same mass. This most likely resulted from the amino-isoxazole being a mixture of regioisomers which led to regioisomeric products.

Kinetic Experiments

The oxetane amination was monitored by *in situ* ^{1}H NMR to gain a better understanding of the reaction and its mechanism. Mesitylene was added to the reaction as an inert internal standard.

Quantitative Reaction Monitoring by ^{1}H NMR

General Procedure and Considerations: Mesitylene (ca. 13 mg, 0.1 mmol, 0.66 equiv) was added by syringe to a tared oven-dried vial, followed by triethylamine (27 μL, 0.195 mmol, 1.3 equiv; added by a Gilson micropipette), amine nucleophile (0.18 mmol, 1.2 equiv; added by a Gilson micropipette) and oxetane sulfonyl fluoride (0.15 mmol, 1.0 equiv). CD_3CN (0.5 mL, 0.5 M) was added to the vial by syringe and after solvation of all the contents in the vial, the mixture was transferred using a glass pipette to an oven-dried Young's NMR tube under Ar and the tube was sealed using the Young's valve. The sealed Young's NMR tube was inserted into a 400 MHz Bruker NMR machine with the probe pre-heated at 60 °C. The sample was locked to CD_3CN, shimmed and a spectrum was acquired every 30 s until all the starting material had been consumed (~2 h, except for OSF **54**, which is less reactive). The start of the reaction was taken as the time point when the sample was inserted into the pre-heated probe. The time point of the first measurement was taken as the time-interval between insertion of the sample into the probe and acquisition of the first spectrum. The ^{1}H NMR spectra were acquired with 8 number of scans (ns) and 1 s relaxation delay (d1) and processed using MestReNova (Version 12.0.4-22023). All the spectra of each reaction were superimposed and phase and baseline corrected using MestReNova. Then, the relevant signals for each species (Table S16) were integrated on the superimposed spectra. The absolute integral values were exported as a .txt file (Script: 1D Integral Series) and converted to the plotted concentrations by using the internal standard. For an example of the superimposed spectra of the standard reaction see Fig. S9. All statistical analyses and graphical representations were performed with the open-source statistical program 'R', version 3.2.2 (April 08, 2015 – "Fire Safety").[15]

Notes:

The exact amount of mesitylene added was measured by mass and it varied slightly between each experiment. The amounts of triethylamine and amine nucleophile added were measured by volume using a Gilson micropipette.

Triethylamine was used as base instead of K_2CO_3 to allow for a homogeneous reaction in the NMR tube. Optimization of the reaction had shown that using NEt_3 as base was successful and gave only a slightly lower yield, with increased formation of the oxetane fluoride (see Table S3 Entry 1 & 17).

*Trimethoxy OSF **54** needed ns = 16, d1 = 18 s to yield high-quality spectra. Thus, with this example, a spectrum was measured every 5 min.*

A broad signal (assigned as $\mathbf{H}Et_3N^+$) appeared on almost all reactions and was shifted downfield over the course of the reaction, presumably due to changes in its concentration (i.e. changes in the equilibrium between protonated and neutral species) and pH of the reaction mixture (see e.g. Fig. S9). This led in many cases to an overlap with the investigated signals during several minutes. These values were omitted from the analyses since they showed an artificial sharp increase (and later decrease) in concentration.

Similarly, the signals of morpholine and triethylamine (see Table S16 and Fig. S9) were also shifted downfield through the reaction. Accurate integration values were obtained by superimposing 10–20 spectra at a time and integrating the relevant signals over a small range.

Table S16 ^{1}H NMR signals analyzed to monitor the reaction.

Species	Chemical shift / ppm	Multiplicity	*J* / Hz	No. of Hs	Assignment
OSFs					
1	5.27	dd	8.5, 1.9	2	C*H*HOC*H*H
53	5.30	dd	8.5, 1.9	2	C*H*HOC*H*H
54	6.66	s	–	2	2 × Ar-CH
Oxetane amines					
2	4.81	d	0.9	4	$CH_2O_{(oxetane)}CH_2$
77	4.84–4.80[a]	2 × d	6.2	2 × 2	$CH_2O_{(oxetane)}CH_2$
64	6.38	s	–	2	2 × Ar-CH
36	4.93–4.87[a]	2 × d	6.2	2 × 2	CH_2OCH_2
9	4.75	dd	6.1, 0.6	2	C*H*HOC*H*H
23	4.91–4.81[a]	2 × d	6.2	2 × 2	CH_2OCH_2
Other					
6	5.03	dd	7.9, 1.3	1	C*H*HOCH_2
49	5.46	d	7.9	2	C*H*HOC*H*H
50	5.04	d	7.6	2	C*H*HOC*H*H
morpholine	3.60–3.75[b]	m	–	4	CH_2OCH_2
NEt_3	1.05–1.25[c]	t	7.2	9	$N(CH_2C\mathit{H_3})_3$
mesitylene	2.28[d]	d	0.7	9	3 × CH_3

[a]This signal is composed of two adjacent doublets which were integrated together as 4 protons. [b]The approximate range over which the multiplet shifts throughout progression of the reaction, not the range of the multiplet. [c]The approximate range over which the triplet shifts throughout progression of the reaction. [d]For the reaction with OSF **54** as substrate, the mesitylene signal at 6.83 ppm (d, *J* = 0.7 Hz, 3 H, 3 × Ar-CH) was used.

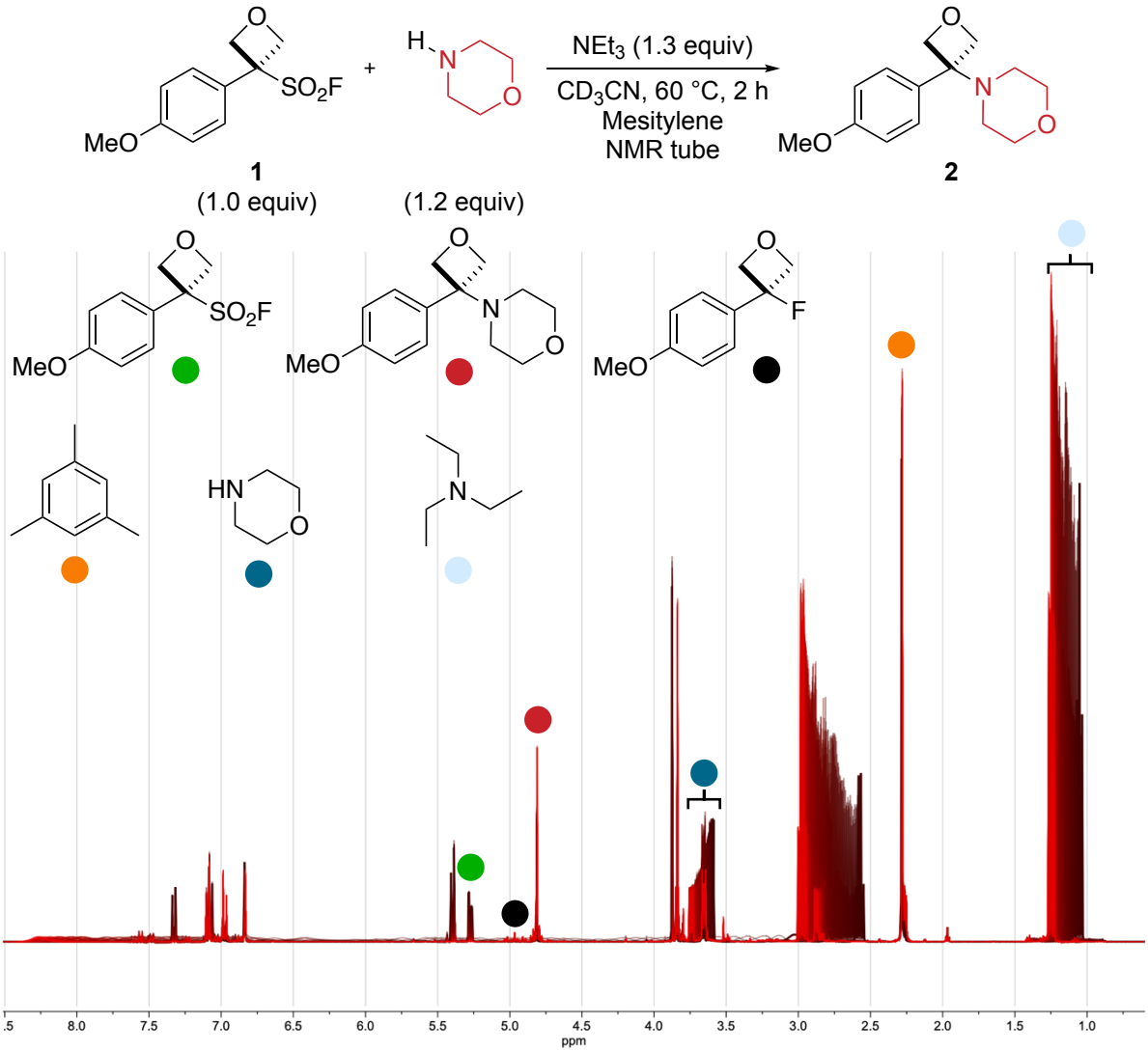


Fig. S9 Superimposed spectra for the standard reaction with morpholine. The color of the signals go with time from dark red to bright red. I.e., spectra measured at early time points appear as dark red (e.g. the signals for OSF **1**) and spectra measured at late stages of the reaction appear as bright red (e.g. the signals for oxetane amine **2**).

The monitoring of the standard reaction was performed three times to ensure reproducibility (Fig. S10). The graphs show that the consumption of starting material is highly reproducible and the traces of all three runs overlap almost perfectly. Product formation is, however, more variable. The exact reason for this is unknown, but probably there are small factors that lead to a slight preference of non-productive reaction pathways such as oxetane fluoride formation or elimination followed by degradation. Therefore, it was decided to perform all the following quantitative analyses by comparing the consumption of OSF. The reaction profile for the formation of product with morpholine was taken as the average of three runs (Fig. S12).

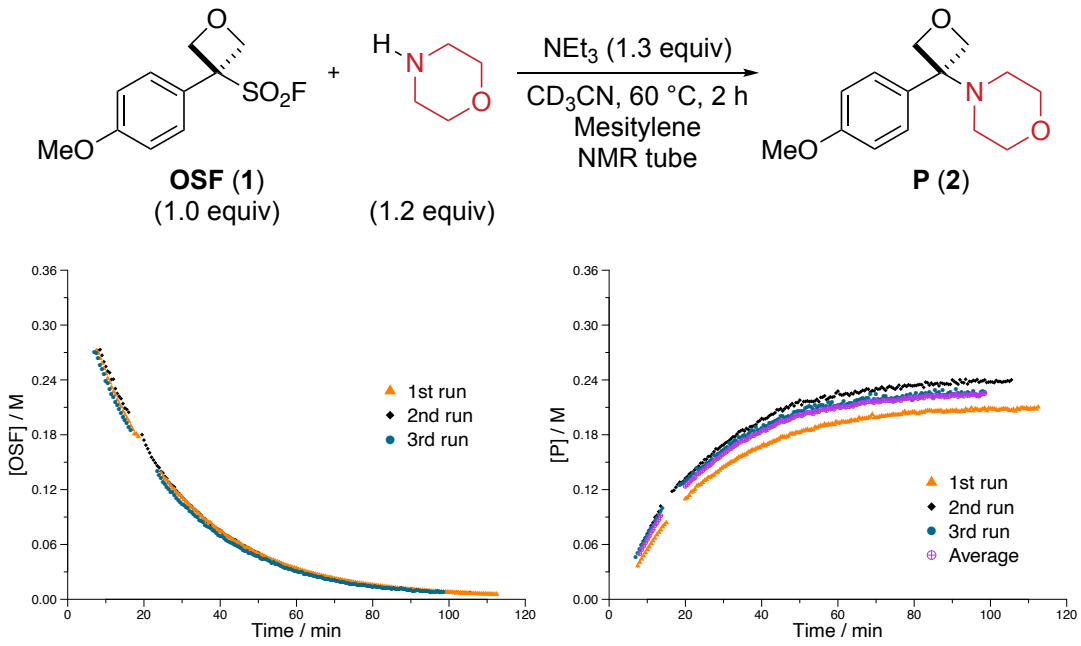


Fig. S10 Reaction monitoring of the standard oxetane amination by ^{1}H NMR. Consumption of starting material (OSF) is depicted on the left, while product (P) formation is shown on the right. The reaction profile for [OSF] consumption of the '1st run' was used for all further qualitative and quantitative analyses. An average of the reaction profiles for [P] formation of the three runs (purple line) was used for further illustrations.

Reaction Profile of OSF **1**, **53** and **54** with Morpholine

Next, the reaction of two further sulfonyl fluorides with morpholine was monitored (Fig. S11). The rate of reaction was observed to vary significantly with the structure of OSF. Trimethoxy OSF **54** reacts slower and dimethoxy OSF **53** faster than **1**. See pages S32–S33 for a rationalization of this behavior.

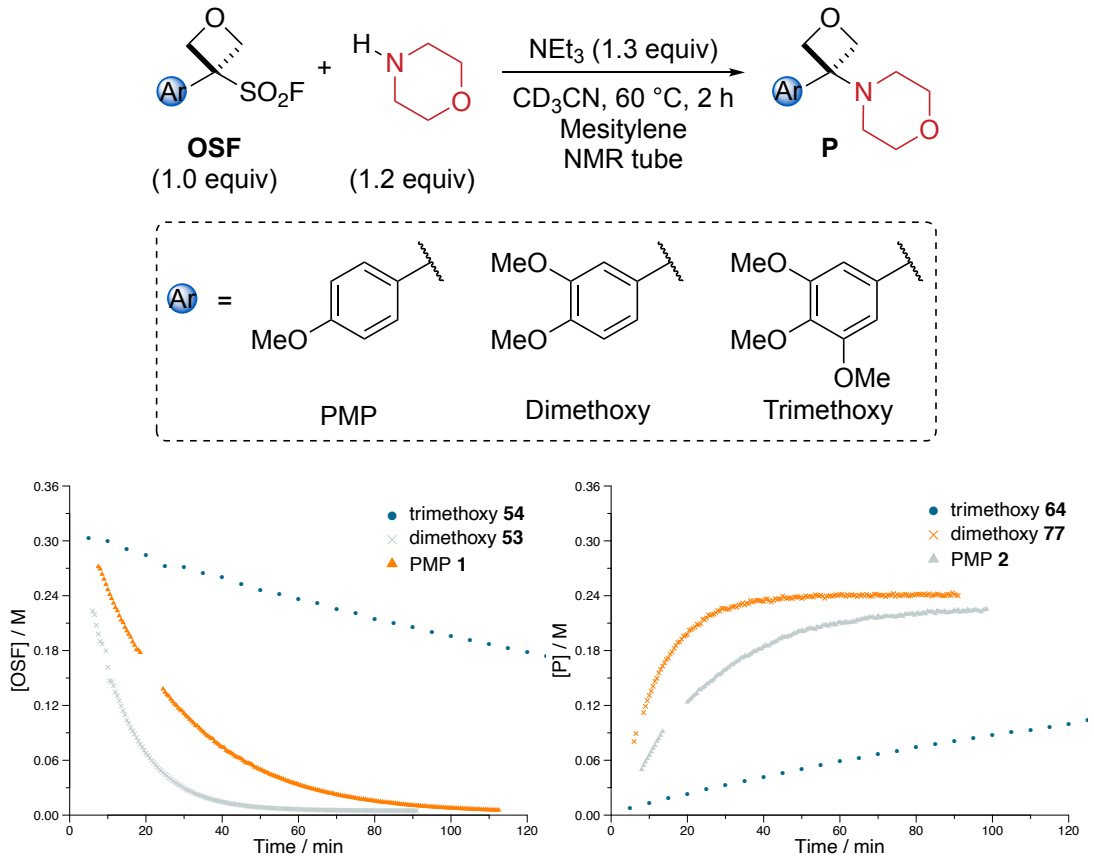
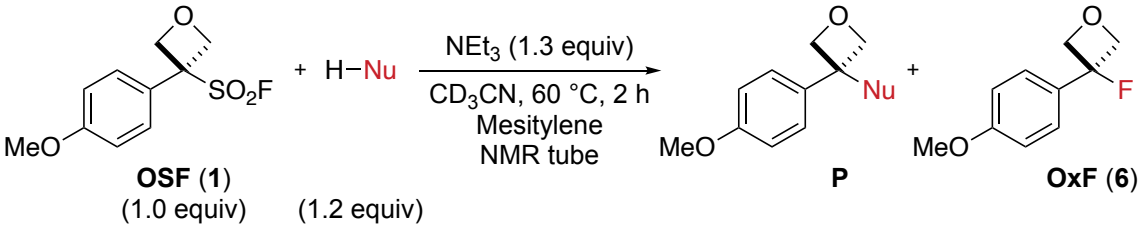


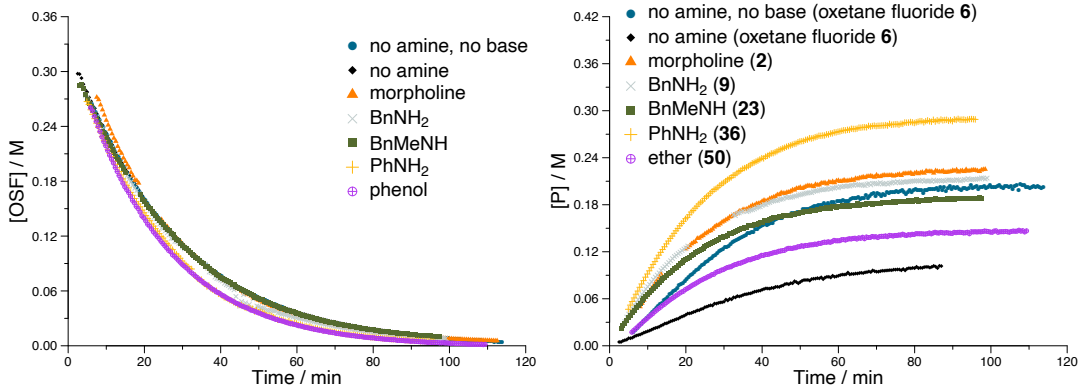
Fig. S11 Reaction monitoring of different OSFs by ^{1}H NMR. Consumption of starting material (OSF) is depicted on the left, while product (P) formation is shown on the right.

Reaction Profile of OSF **1** with Different Nucleophiles

Next, the reaction of PMP OSF **1** with different (or in the absence of) nucleophiles was monitored (Fig. S12). First, it can be seen graphically that the rate of starting material consumption is broadly the same under all the different conditions, but the rate of product formation varies greatly across nucleophiles, even taking into account the observed variability in the rate of product formation (see Fig. S10). This graphical comparison already suggests that OSFs react to an intermediate at a given rate independent of the reaction partner. This intermediate then reacts in a second step with the nucleophile to form the oxetane amine product, an oxetane fluoride, or undergoes degradation. The type of nucleophile *does* influence this second step.



*Consumption of OSF **1** (left) and product formation (right)*



*Formation of oxetane fluoride **6** with standard (left) and zoomed (right) y-axis*

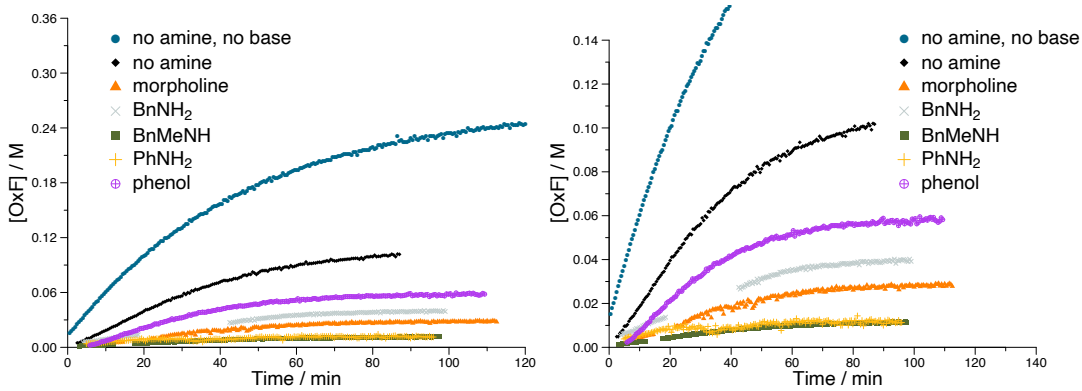


Fig. S12 Reaction monitoring of PMP OSF **1** with different nucleophiles by ^{1}H NMR. Consumption of starting material (OSF) is depicted on the top left, while product (P) formation is shown on the top right. Formation of oxetane fluoride **6** (OxF) is depicted on the bottom left and a zoom of this graph on the bottom right.

We therefore suggest that the reaction proceeds through the formation of an oxetane carbocation by an S_N1 process, which is only dependent on the concentration of OSF. The fate of the carbocation is then controlled by the nucleophile present in the reaction mixture. A noteworthy observation is that the difference in the amount of oxetane amine formed is not completely reflected in the difference of oxetane fluoride formation. This is seen very clearly by comparing the traces of [P] and [OxF] for aniline ($PhNH_2$, yellow line) with methylbenzylamine (BnMeNH, green line). This discrepancy suggests that there is an additional product being formed, which is neither identifiable nor

quantifiable by NMR spectroscopy. We presume this is an elimination product from the oxetane carbocation which forms an unstable oxete that decomposes into many degradation products (see Fig. 4d in the main manuscript for a full picture of the proposed mechanism). Aldehyde **91** was identified as one of such degradation products by ^{1}H NMR in the absence of amine (see Fig. S13). Additionally, the amount of oxetane fluoride formed (Fig. S12 *Bottom*) in the absence of amine (black line) is much lower than in the absence of amine *and* base (blue line). This suggests that basic conditions promote a degradative pathway, likely to be *via* elimination.

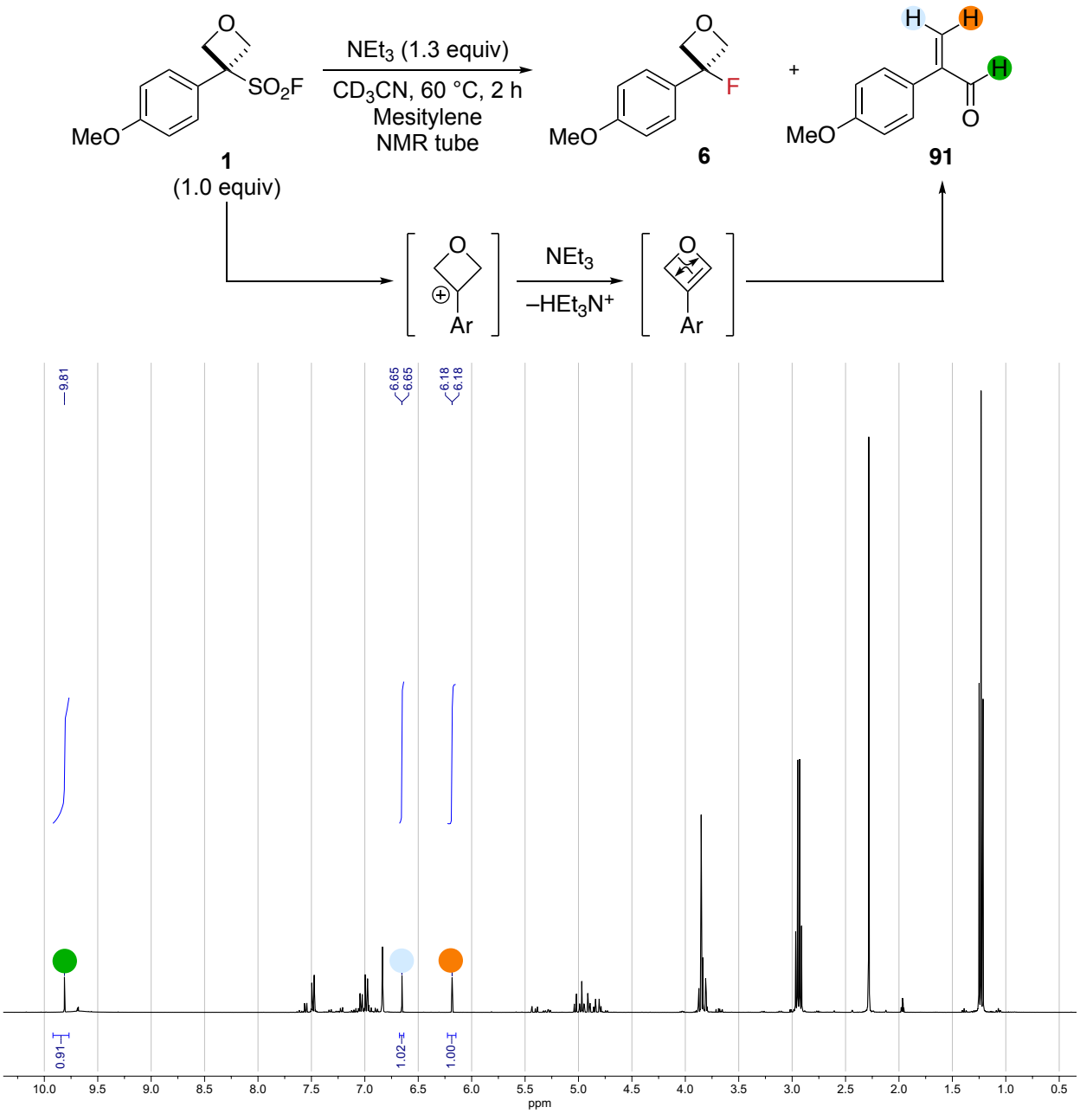


Fig. S13 Identification of aldehyde **91** in the ^{1}H NMR spectrum of the reaction mixture in the absence of amine. Notably, this species was not observed in the absence of amine and base, suggesting that the base plays an important role in its formation, likely *via* elimination to an oxetene followed by hetero electrocyclic ring-opening.

Reaction Profile of OSF **1** with Phenol

OSF **1** can react with phenol in a defluorosulfonylation or SuFEx manner to yield oxetane ether **50** or sulfonate ester **49**, respectively. The selectivity between the two pathways can be controlled by the choice of base (see Table S13). With triethylamine as base, mainly ether **50** was observed, both in-flask and in the NMR tube (Fig. S14). Interestingly, formation of sulfonate ester **49** occurs at the beginning of the reaction and stays constant after ca. 20 minutes (grey line). The decrease in total concentration (100% mass accountability ≙ 0.3 M) is a further indicative for a degradative pathway of OSF **1** (green line).

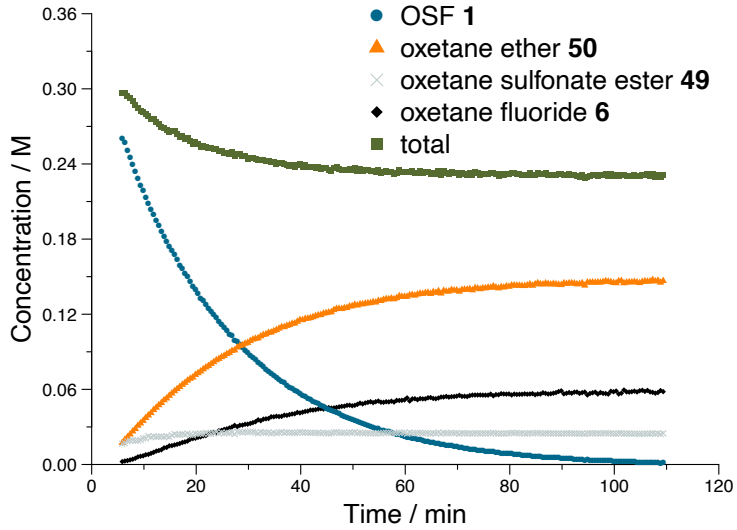
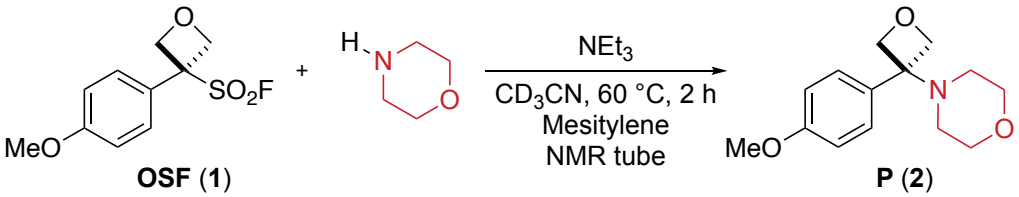


Fig. S14 Reaction monitoring of PMP OSF **1** with phenol by ^{1}H NMR.

Variable Time Normalization Analysis (VTNA)

The mechanism was further investigated by determining the reaction orders of each reactant. This was performed by using Variable Time Normalization Analysis (VTNA) developed by Burés and monitoring the amination of OSF **1** with morpholine by *in situ* ^{1}H NMR.[16] A series of 4 experiments were run, whereby the concentration of each reaction component was varied (Fig. S15).



Experiment	[OSF] / M	[morpholine] / M	[NEt_3] / M
standard	0.3	0.36	0.39
less amine	0.3	**0.3**	0.39
more OSF	**0.36**	0.36	0.39
more base	0.3	0.36	**0.468**
more amine	0.3	**0.45**	0.39

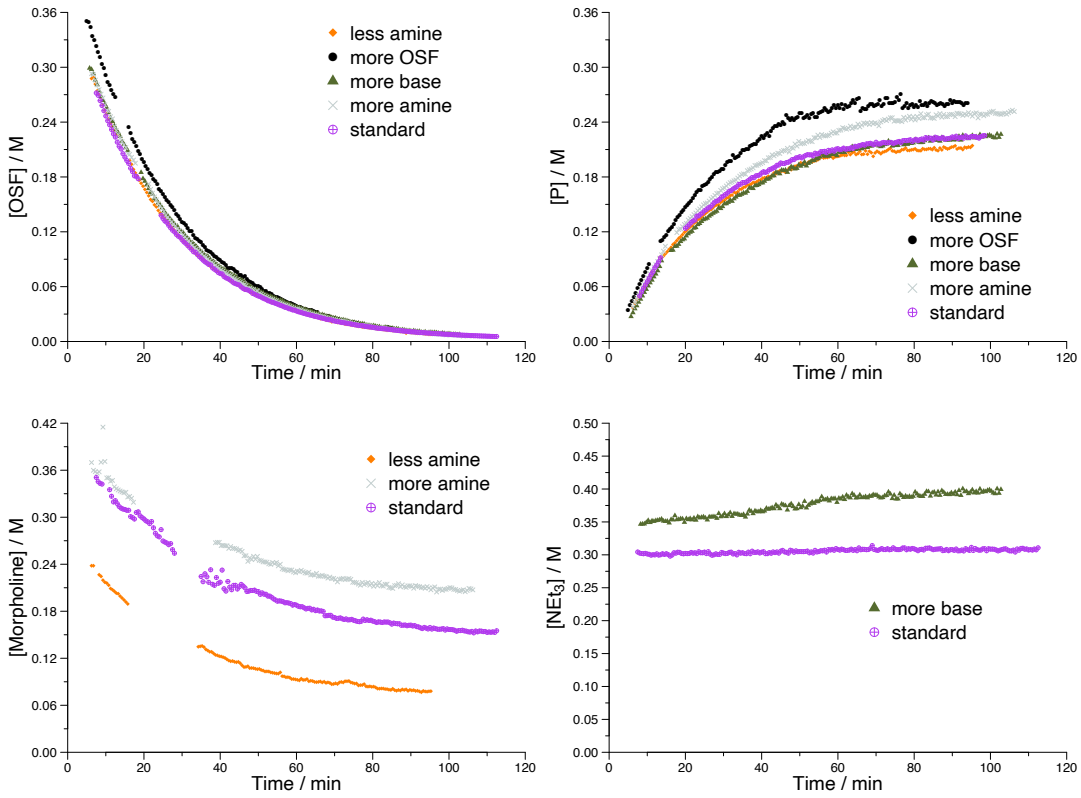


Fig. S15 Reaction monitoring of PMP OSF **1** with morpholine and varying reactant concentrations by ^{1}H NMR. *Top*: original traces of OSF consumption (left) and P formation (right) before applying mathematical manipulations. *Bottom*: concentration profiles of morpholine (left) and triethylamine (right) for the relevant reactions.

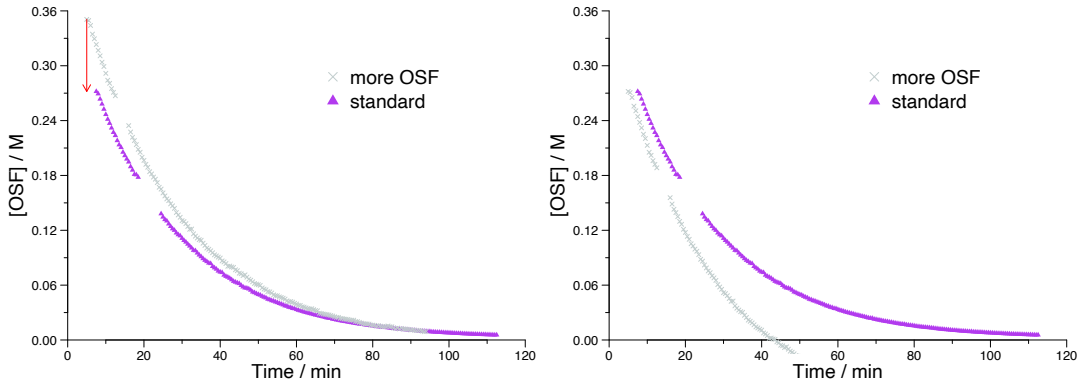
The data were manipulated mathematically to plot in the *x*-axis the sum of the concentration of the component to be analyzed (A,B,C…) to the power of its reaction order (α,β,γ…) and multiplied by the difference in time between the two measurements, as described by Burés[16]:

$$\sum_{i=1}^{n}\left(\frac{[\mathrm{A}]_i + [\mathrm{A}]_{i-1}}{2}\right)^{\alpha}(t_i - t_{i-1})\,.$$

These data are plotted for the standard conditions and for the different excess of the component being analyzed and several plots are generated with different reaction orders (e.g. –1, 0, 0.5, 1, 2). The overlays of the traces are compared for the graphs of the different reaction orders and the best overlay is indicative for the most likely reaction order for that component.

This analysis was first conducted to determine the order in OSF. Before performing the abovementioned mathematical manipulation, the trace of OSF consumption for 'more OSF' was shifted down artificially to match the first value of the 'standard' trace – as suggested by Burés.[17] This must be done to obtain an overlap of curves at the correct order, instead of parallel curves, which makes the visual assessment easier. Fig. S16 shows the result of the shift of the original trace (top two curves from left to right) and the subsequent VTNA analysis of different reaction orders (lower four graphs). The best curve overlap is obtained for a reaction order of one. Additionally, the obtained curve is linear, already suggesting that the rate of the reaction is only dependent on the concentration of OSF.

Artificial shift of 'more OSF' to match the starting value of the 'standard' reaction



VTNA analysis to determine the order in oxetane sulfonyl fluoride

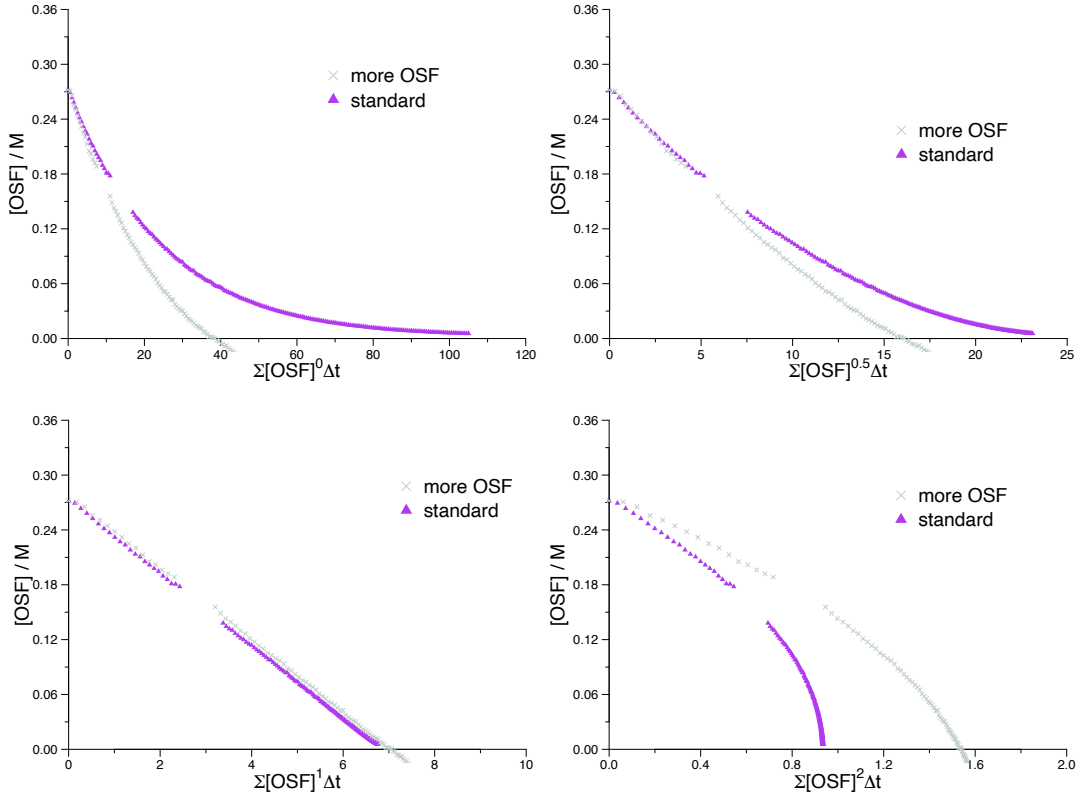


Fig. S16 VTNA analysis to determine the reaction order in OSF. *Top*: Artificial shift of the trace of 'more OSF' to match the first value of 'standard' (from left to right). *Middle* and *Bottom*: VTNA graphs using different reaction orders for OSF. A reaction order of 1 showed the best overlay.

The order in amine (Fig. S17) and base (Fig. S18) was determined to be zero following an analogous approach. While the best overlay for different orders in amine is clear, the situation is less unambiguous for the order in base. The difficulty arises from the fact that the concentration in base does not vary significantly throughout the reaction (see Fig. S15 *Bottom right*), which results in only a very subtle impact of the reaction order on the curve shape. Nevertheless, it can be seen that raising the reaction order worsens the overlay. The only two orders which show a very similar overlay are 0 and –0.5, but there is further evidence for a reaction order of 0 in base: 1) the curves are linear when only the order in OSF is set to 1 (Fig. S16). 2) The half-life of OSF is independent on its concentration (see e.g. Fig. S10), strongly suggesting it is a first-order reaction, ergo zero-order in base.

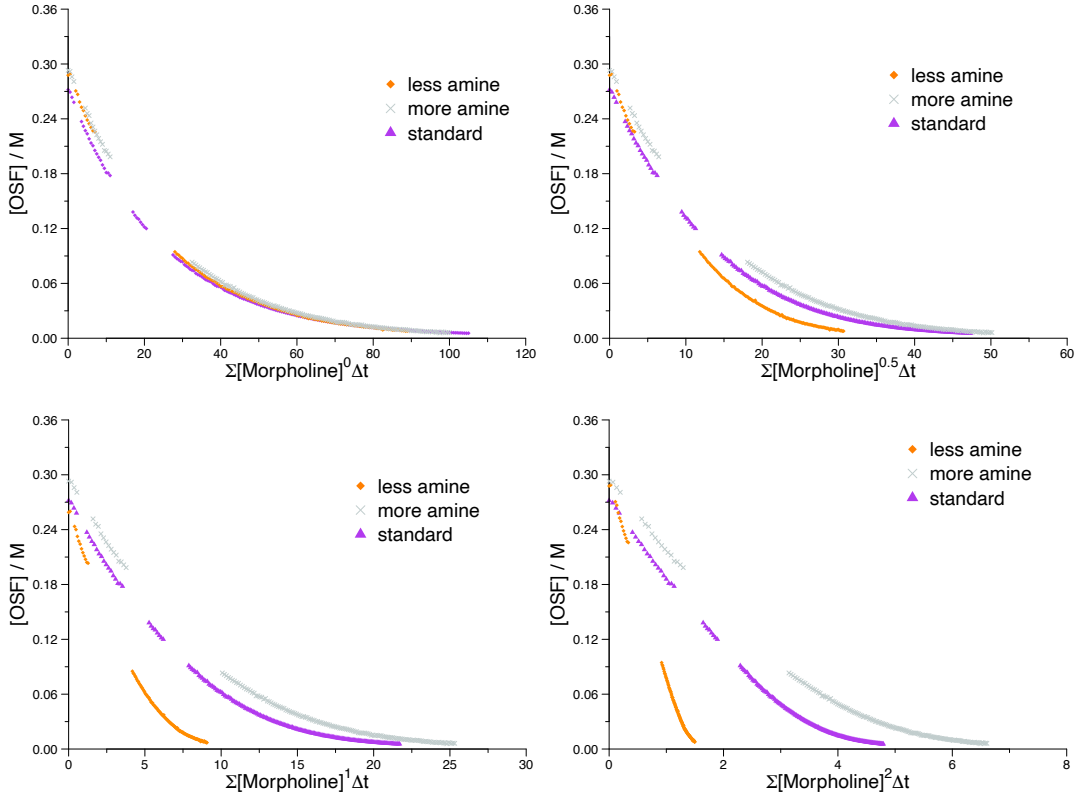


Fig. S17 VTNA analysis to determine reaction order in amine. A reaction order of 0 showed the best overlay.

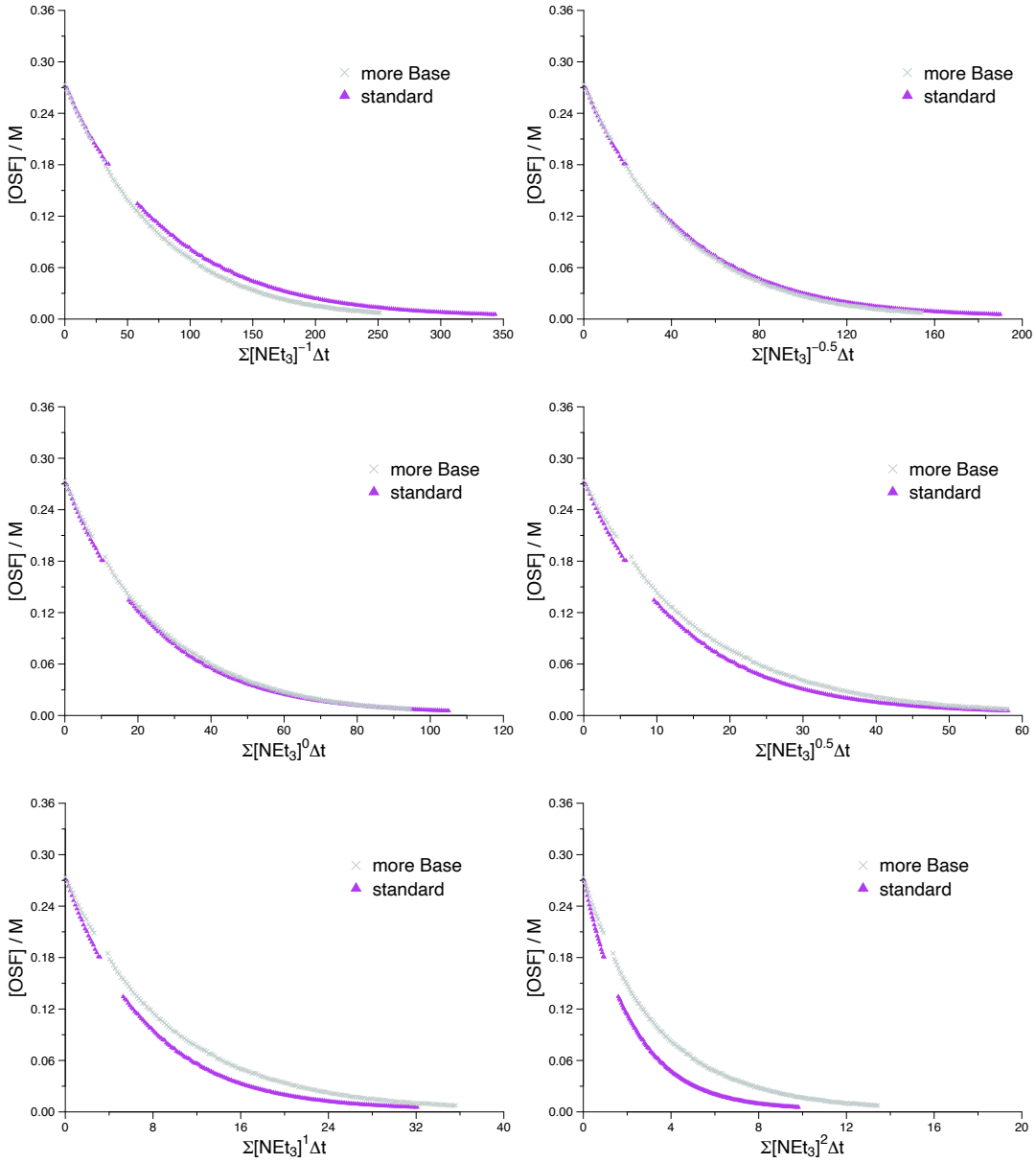


Fig. S18 VTNA analysis to determine reaction order in base. A reaction order of 0 gave the best overlay.

With the order of every reaction component in hand, the kinetic constant of the rate-determining step of the reaction (k_{Obs}) was determined by plotting the sum of all components to the power of their respective order times the difference in time, as described by Burés[16] (Fig. S19):

$$\sum_{i=1}^{n}\left(\frac{[\mathrm{OSF}]_i+[\mathrm{OSF}]_{i-1}}{2}\right)^1\left(\frac{[\mathrm{amine}]_i+[\mathrm{amine}]_{i-1}}{2}\right)^0\left(\frac{[\mathrm{NEt_3}]_i+[\mathrm{NEt_3}]_{i-1}}{2}\right)^0(t_i-t_{i-1})=$$

$$\sum_{i=1}^{n}\left(\frac{[\mathrm{OSF}]_i+[\mathrm{OSF}]_{i-1}}{2}\right)^1(t_i-t_{i-1})\,.$$

Since all components except OSF have a zero order, this term is identical to that plotted on the *x*-axis in Fig. S16 (order = 1). A linear regression was modelled on the curves with the (negative) slope equal to the kinetic constant of the reaction. The similar slope observed for all reaction profiles, reflected by the k_{Obs} values, is a good indication that the deduced overall rate law of the reaction (1st order in OSF) is correct. Note that the lines do not perfectly overlay because the first [OSF] value is somewhat variable due to differences in the time interval to acquire the first data point. The difference arises from unequal time requirements to lock and shim the NMR samples. A first order dependence

on [OSF] and zero order in all other components are in good accordance with an S_N1 mechanism and the formation of an oxetane carbocation.

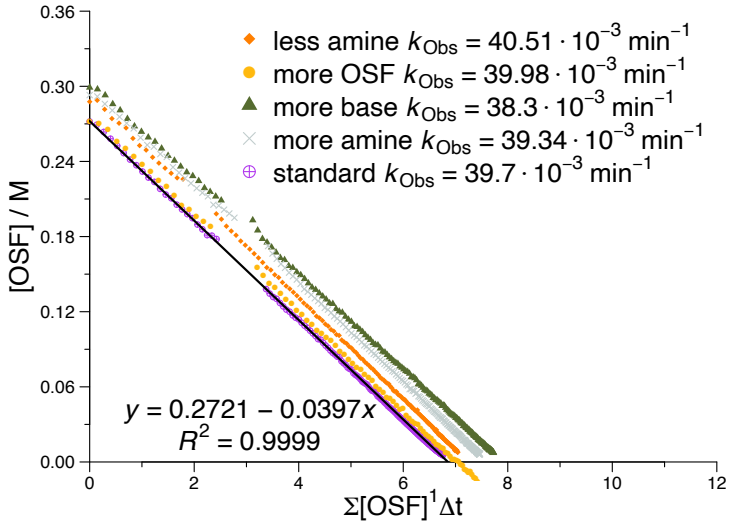


Fig. S19 VTNA analysis for the determination of k_{Obs}. Normalization of the time scale by the order in OSF leads to linearization of the reaction profiles with slope = $-k_{Obs}$. The equation and coefficient of determination R^2 are given for the line (black) modelled on the standard reaction profile (purple trace).

Arrhenius Plot and Determination of E_A and Half-Lives

Next, the reaction was monitored at variable temperatures (40 and 70 °C) to determine the activation energy of the rate-determining step (Fig. S20).

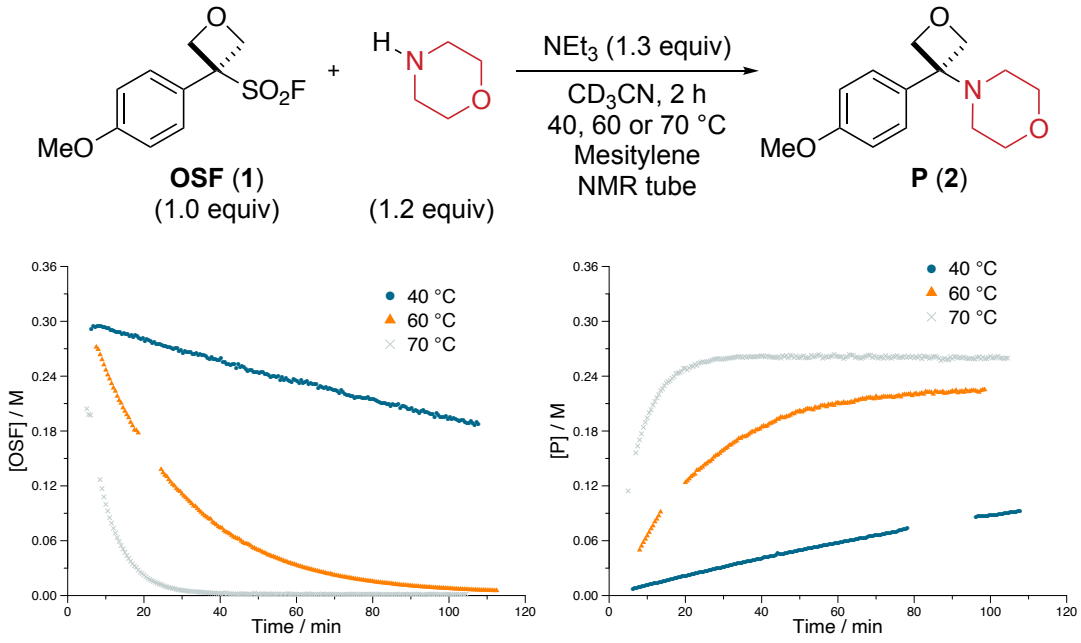


Fig. S20 Reaction profiles at different temperatures. Left [OSF] consumption and right [P] formation.

The same VTNA analysis as shown in Fig. S19 was applied to determine the kinetic constants at 40 and 70 °C. The errors of the kinetic constants represent the 95% confidence interval for each value, calculated from the standard deviation of the linear regression times the factor t_s.[1] An Arrhenius plot was then generated using the Arrhenius equation and the obtained kinetic constants (Fig. S21). A 'weighed' linear regression was then modelled on the data points since each value has its own standard deviation. In this way, values with a smaller error are given more significance in the regression. The standard deviation of the ln(*k*) values was calculated from the standard deviation of the original k_{Obs} values using the conventional Gaussian equation for error propagation:

$$s_z^2 = \left(\frac{\partial f}{\partial a}\right)^2 s_a^2 + \left(\frac{\partial f}{\partial b}\right)^2 s_b^2 + \left(\frac{\partial f}{\partial c}\right)^2 s_c^2 + \cdots,$$

whereby s_z^2 is the squared standard deviation of the new function *z* (*z* = *f*(*a*,*b*,*c*,…)) which depends on the values *a*,*b*,*c*,… and their squared standard deviations s_a^2, s_b^2, s_c^2 … The weighed linear regression was calculated using the following formulae[18]:

$$intercept\ a = \frac{\sum_{i=1}^{n}\frac{x_i^2}{s_i^2}\sum_{i=1}^{n}\frac{y_i}{s_i^2} - \sum_{i=1}^{n}\frac{x_i}{s_i^2}\sum_{i=1}^{n}\frac{x_i y_i}{s_i^2}}{\sum_{i=1}^{n}\frac{1}{s_i^2}\sum_{i=1}^{n}\frac{x_i^2}{s_i^2} - \left(\sum_{i=1}^{n}\frac{x_i}{s_i^2}\right)^2}$$

$$slope\ b = \frac{\sum_{i=1}^{n}\frac{1}{s_i^2}\sum_{i=1}^{n}\frac{x_i y_i}{s_i^2} - \sum_{i=1}^{n}\frac{x_i}{s_i^2}\sum_{i=1}^{n}\frac{y_i}{s_i^2}}{\sum_{i=1}^{n}\frac{1}{s_i^2}\sum_{i=1}^{n}\frac{x_i^2}{s_i^2} - \left(\sum_{i=1}^{n}\frac{x_i}{s_i^2}\right)^2}.$$

[1] t_s was determined using the degrees of freedom $\nu = n - 2$, whereby *n* is the number of data points of the reaction profile. 2 degrees of freedom are lost due to the linear regression because the intercept and slope also depend on the data points *n*.

The standard deviation of intercept and slope were calculated using the error propagation formula:

$$s_a^2 = \frac{\sum_{i=1}^{n} \frac{x_i^2}{s_i^2}}{\sum_{i=1}^{n} \frac{1}{s_i^2} \sum_{i=1}^{n} \frac{x_i^2}{s_i^2} - \left(\sum_{i=1}^{n} \frac{x_i}{s_i^2}\right)^2}$$

$$s_b^2 = \frac{\sum_{i=1}^{n} \frac{1}{s_i^2}}{\sum_{i=1}^{n} \frac{1}{s_i^2} \sum_{i=1}^{n} \frac{x_i^2}{s_i^2} - \left(\sum_{i=1}^{n} \frac{x_i}{s_i^2}\right)^2}.$$

And the correlation coefficient R^2:

$$R^2 = \left(\frac{\sum_{i=1}^{n} \frac{1}{s_i^2} \sum_{i=1}^{n} \frac{x_i y_i}{s_i^2} - \sum_{i=1}^{n} \frac{x_i}{s_i^2} \sum_{i=1}^{n} \frac{y_i}{s_i^2}}{\sqrt{\sum_{i=1}^{n} \frac{1}{s_i^2} \sum_{i=1}^{n} \frac{x_i^2}{s_i^2} - \left(\sum_{i=1}^{n} \frac{x_i}{s_i^2}\right)^2} \sqrt{\sum_{i=1}^{n} \frac{1}{s_i^2} \sum_{i=1}^{n} \frac{y_i^2}{s_i^2} - \left(\sum_{i=1}^{n} \frac{y_i}{s_i^2}\right)^2}} \right)^2.$$

The activation energy is then equal to the slope times the universal gas constant R, according to the Arrhenius equation. The error was calculated as described for the kinetic constants. The error of 1.6 kJ mol^{-1} is relatively high because the number of data points is very small (n = 3), which leads to only one degree of freedom. Nevertheless, an activation energy of ca. 97 kJ mol^{-1} is well in line with the observed reactivity.

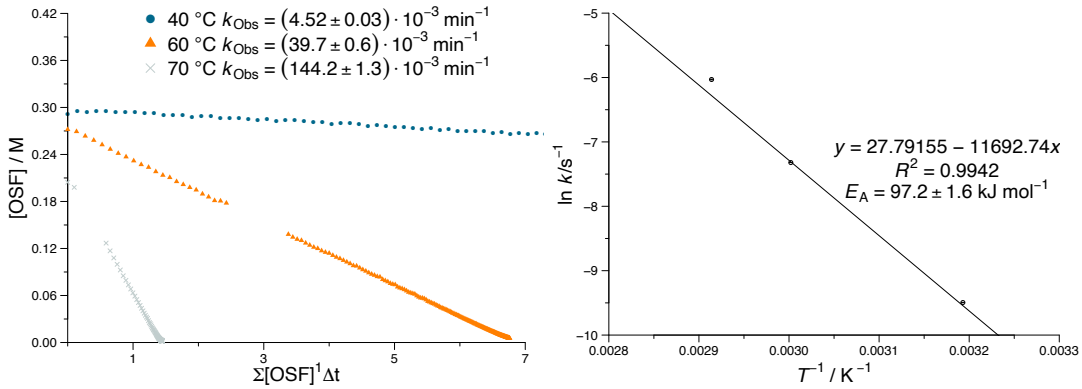


Fig. S21 Determination of the activation energy of the oxetane amination. Left: VTNA analysis at 40, 60 and 70 °C to calculate the kinetic constants. Right: Arrhenius plot to calculate the activation energy. ln refers to the natural logarithm. The equation and correlation coefficient R^2 are given for the modelled linear regression. The standard deviation of each ln(k) point is given as error bars, which are barely visible because the standard deviations are extremely small.

The half-life $t_{1/2}$ of OSF **1** at different temperatures was then calculated (see Table S17). The defluorosulfonylation of OSF **1** is a first order reaction and $t_{1/2}$ can be derived from the integrated rate law to:

$$t_{\frac{1}{2}} = \frac{\ln(2)}{k}.$$

Note that in a first-order reaction $t_{1/2}$ remains constant throughout the reaction progress. This can be clearly observed graphically (and numerically) in the reaction profiles of OSF **1** (see e.g. Fig. S10), further supporting the determined rate-law.

Table S17 Half-lives of OSF **1** at different temperatures. The depicted error corresponds to the 95% confidence interval with ν degrees of freedom ($\nu = n - 2$). For T = 40, 60 and 70 °C, n was taken as the number of data points in the NMR experiment. For T = 25 °C, n was taken as the number of data points used to determine $k_{(25\ °C)}$ from the Arrhenius equation (n = 3).

Temperature / °C	$\boldsymbol{k}$ **/ 10^{-3} min^{-1}**	$t_{1/2}$
70	144.2 ± 1.3	4.81 ± 0.04 min
60	39.7 ± 0.6	17.46 ± 0.03 min
40	4.52 ± 0.03	153.4 ± 0.9 min
25	0.011 ± 0.007[a]	(4 ± 3) × 10^{1} days

[a]k was calculated from the Arrhenius equation and the linear regression of the Arrhenius plot on Fig S21.

The large error of $t_{1/2}$ at 25 °C arises from the calculation of $k_{(25\ °C)}$ from the Arrhenius equation using the formula:

$$\ln(k) = \ln(A) - \frac{E_A}{R}\left(\frac{1}{T}\right),$$

which corresponds to the linear regression depicted on Fig. S21. Both A and E_A contain a relatively high error from the linear regression (due to the low number of data points; see above) which lead to a $k_{(25\ °C)}$ with an even larger error due to error propagation.

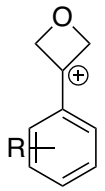
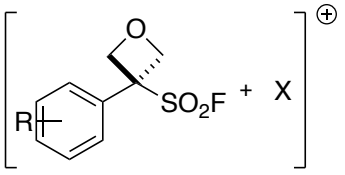
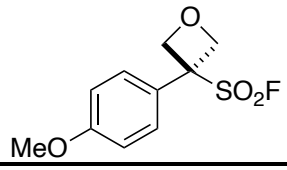
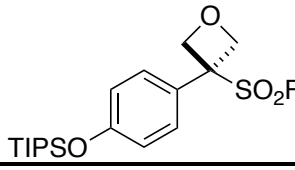
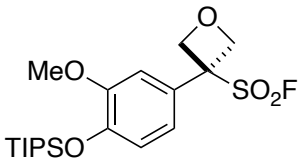
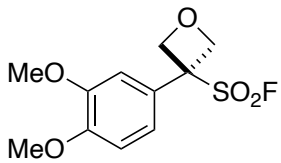
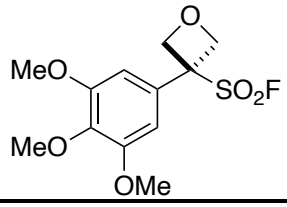
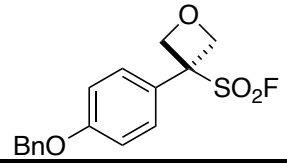
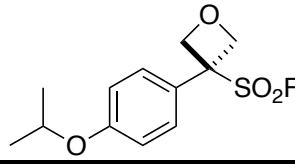
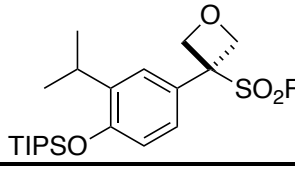
Nonetheless, a half-life of OSF **1** of 40 ± 30 days at room temperature (25 °C) is much higher than that at 60 °C (17.46 ± 0.03 min). This highlights the usefulness of OSF **1** as a reagent which is bench-stable, yet highly reactive at elevated temperatures.

Mass Spectrometry Analysis of Oxetane Sulfonyl Fluorides

The mass spectra of all synthesized oxetane sulfonyl fluorides were analyzed to investigate the generation of an oxetane carbocation formed in the ionization of the sulfonyl fluoride (Table S18). The oxetane carbocation was the peak of highest intensity (base peak) in all examples, and significant amounts of the molecular ion were only observed with trimethoxy OSF **54**, a less reactive OSF. The fact that the 3-aryloxetane carbocation is the base peak in every case is a strong indication that within these molecules, this is a particularly stable carbocation. Therefore, the loss of sulfur dioxide and fluoride is a probable degradation pathway, and thus, a pathway through which sulfonyl fluorides could react with nucleophiles.

Table S18 Detected ions by mass spectroscopy for all oxetane sulfonyl fluorides synthesized. APCI = Atmospheric pressure chemical ionization. CI = Chemical ionization. ESI = Electrospray ionization. All the ionization techniques used are "soft"-techniques, making the mass spectra comparable.

Ion detected **and** of highest intensity	Ion detected **but not** of highest intensity	Ion **not** detected

Detected Ions / **Sulfonyl Fluoride**[a]			**Ionization Technique**
			APCI
		$[M+NH_4]^+$ detected. 1% of base peak	CI
			APCI
			APCI
		$[M]^+$ detected. 35% of base peak	APCI
		$[M+NH_4]^+$ detected.[b]	CI
			ESI
			APCI

[a]The ion of Ph OSF **92** could not be detected by mass spectroscopy and was thus not included. [b]Only the peak of $[M+NH_4]^+$ was provided and not the the full mass spectrum. Therefore, no conclusion can be drawn with this substrate.

Computational Details

General Methods

Quantum mechanical calculations were run using ORCA (v. 4.1.1).[19] Optimizations and numerical frequency calculations of the planar and bicyclic forms of cations **[O$_H$]$^+$**, **[O$_{Ph}$]$^+$** and **[O$_{PMP}$]$^+$** were carried out at the SMD[20](MeCN)-RI-SCS-MP2[21]/def2-TZVP[22] level of theory (where RI denotes the use of the resolution of identity approximation), followed by single-point energy corrections at the SMD(MeCN)-DLPNO-CCSD(T)[23]/def2-TZVPP (TightPNO) level of theory. Transition state optimizations and sulfonyl fluoride/hydride exchange reaction calculations were carried out at the SMD(MeCN)-ωB97X-D3[24]/def2-SVP (ma-def2-SVP on fluoride) level of theory, followed by single point energy corrections at the SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO, ma-def2-TZVPP on fluoride) level of theory. To compare the stability of the cation of **1** with the corresponding benzyl and cyclobutyl cations, sulfonyl and hydride exchange reactions were calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO, ma-def2-TZVPP on fluoride)//ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. 'Tight' optimization criteria were used for all calculations where appropriate, corresponding to 10^{-8} Ha tolerance for the SCF, and 10^{-6} Ha for the optimization step. All calculations used Grid6/GridX6, corresponding to a Lebedev-590 angular grid, and a radical integral accuracy (IntAcc) of 5.34. The resolution of the identity approximation was employed through the RIJCOSX[25] keyword, using the appropriate auxiliary basis sets. Thermodynamic corrections were applied from the optimization level of theory, and the *otherm* code[26] was used to evaluate free energy differences at 298.15 and 333.15 K, employing Grimme's quasi-RRHO approximation[27] to obtain entropic corrections for a 1 M solution (ω_0 = 45 cm^{-1}, α = 4). Small imaginary frequencies were converted to their real counterparts for free energy calculations. Second order perturbation theory analysis of the NBO Fock matrix was carried out using NBO v7.0. Non-covalent interaction (NCI) isosurfaces were calculated using Multiwfn v3.6.[28]

Planar vs Bicyclic Oxetane Cations

The relative stability of the planar and bicyclic structure of aryl-substituted oxetane cations was evaluated using the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory. We have previously shown that this perturbative approach is able to provide accurate geometries in highly strained systems for which single-reference DFT methods may be less suitable.[29]

For both the unsubstituted and phenyl-substituted oxetane cations, two minima were found corresponding to planar and bicyclic geometries. For **[O$_H$]$^+$**, the bicyclic geometry was found to be ΔG (25 ºC) = 38.5 kJ mol^{-1} more stable than the planar form, reflecting the stabilization of the carbocation upon formation of a transannular C–O bond. Replacing the bridgehead hydrogen with a phenyl group reverses the order of stabilities, where the bicyclic form is ΔG (25 ºC) = 39.8 kJ mol^{-1} higher than the planar geometry. This is due primarily to the steric clash between the oxetane methylene group and the *ortho*-C–H bonds of the aryl group upon formation of the transannular C–O bond (Fig. S22). There is a clear difference in transannular C–O bond lengths between **[O$_H$]$^+$**and **[O$_{Ph}$]$^+$** bicyclic structures (Δr = 0.129 Å), suggesting that the steric clashes prevent the C–O bond from achieving its optimal length, therefore reducing the stabilization of the bicyclic cation in the substituted structure. Additionally, there is a loss of resonance stabilization of the carbocation upon distortion of the oxetane ring out of the plane of the arene ($\Delta E^{(2)}_{\pi(\text{planar})\rightarrow\pi(\text{bicyclic})}$ = –285 kJ mol^{-1}). Here, $E^{(2)}_{\pi}$ is defined as the total perturbation energy resulting from $\pi\longrightarrow\pi^*$ donation within the π-system of the arene, in addition to $\pi\longrightarrow$LV (i.e. $\pi\longrightarrow n^+$) donation from these π-bonds to the vacant orbital on the carbocation (see Table S19/S20).

To examine the effect of the *para*-MeO substituent on this equilibrium, we calculated the bicyclic and planar geometries for **[O$_{PMP}$]$^+$**. We found that the bicyclic geometry was not a minimum energy structure, and it smoothly converted back to the planar geometry upon geometry optimization. Constraining the transannular C–O bond length to that of **[O$_{Ph}$]$^+$** (1.673 Å) revealed the energy of the bicyclic geometry of **[O$_{PMP}$]$^+$** to be 59.4 kJ mol^{-1} higher than the planar geometry. In comparison, ΔE

for **[O$_{Ph}$]$^+$** is 34.8 kJ mol^{-1}, suggesting that the additional resonance stabilization from the *para*-MeO group is worth ~25 kJ mol^{-1}. This effect is confirmed by NBO perturbation theory analysis, where $\Delta E^{(2)}_{\pi(\text{planar})\rightarrow\pi(\text{bicyclic})}$ = –302 kJ mol^{-1} for **[O$_{PMP}$]$^+$** – a value that is 17 kJ mol^{-1} greater than that of **[O$_{Ph}$]$^+$**. The steric effect discussed above is still important for the instability of the bicyclic geometry of **[O$_{PMP}$]$^+$**: $r_{H\cdots H}$ = 2.285 Å, a value very similar to that of **[O$_{Ph}$]$^+$**, which shows significant aryl-oxetane steric clashing.

Considering the strong preference for the planar geometry in arene-substituted oxetane cations, which are well described by single-hybrid DFT, we decided to employ the more affordable ωB97X-D3/def2-SVP method for the subsequent mechanistic characterizations.

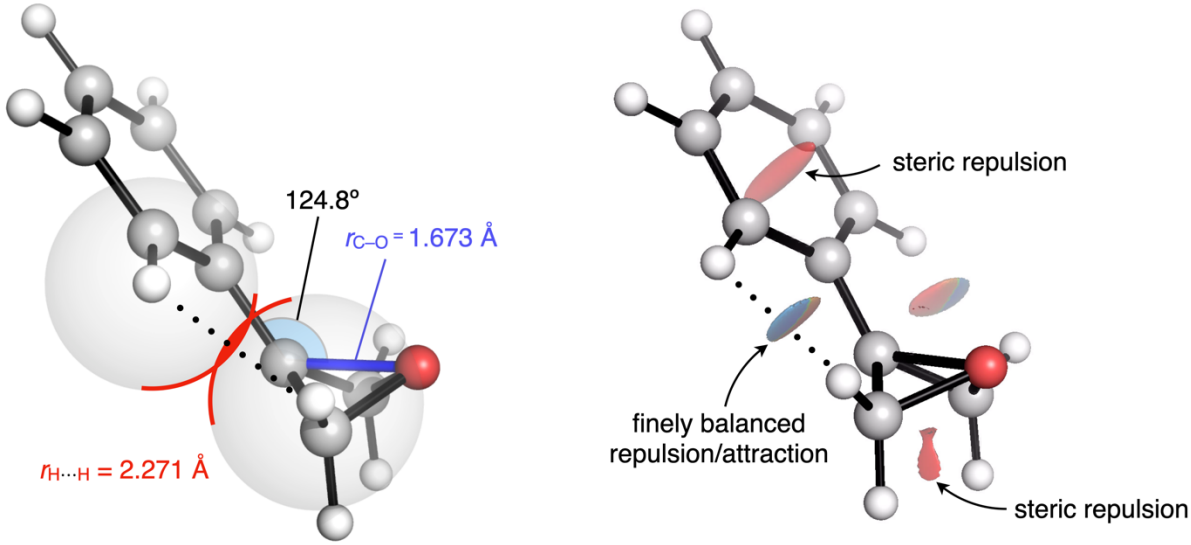


Fig. S22 Geometry of bicyclic phenyl-substituted form of the oxetane cation (**[O$_{Ph}$]$^+$**) showing overlapping van der Waal's spheres (left) and NCI isosurface (right, isovalue = 0.6 a.u.), calculated at the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory.

S_N1 Ionization of **1**

The transition state for the loss of SO_2F^- from sulfonyl fluoride **1** was obtained using an initial guess from a scan of the breaking C–S bond (Fig. S23). While the S–F bond also increases in length during this process, the SO_2F^- anion remains a single entity (characterized as a minimum energy structure), suggesting an overall stepwise process for the formation of the oxetane cation, SO_2 and fluoride from **1**. Attempts to locate a concerted TS using 2D scans in the TS-finding package *autodE*[30] were unsuccessful.

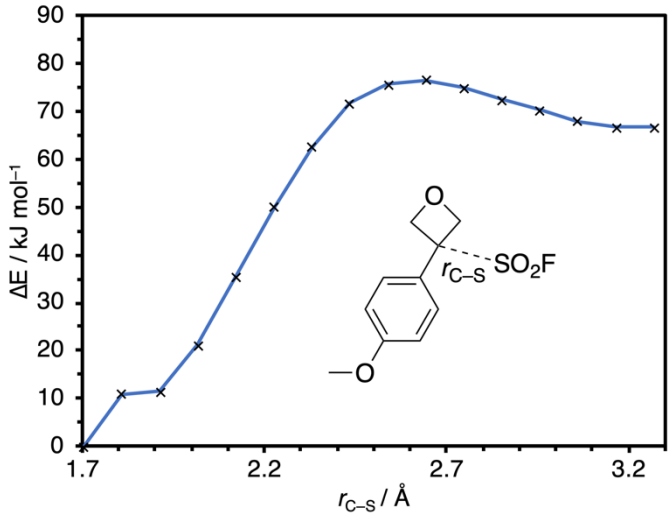


Fig. S23 Relaxed scan of the breaking C–S bond in **1**, calculated at the [SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory.

Sulfonyl and Hydride Exchange Reactions as a Measure of Oxetane Carbocation Stability

To assess the relative stabilities of the oxetane cation derived from **1** and the corresponding benzyl and cyclobutyl cations (**1-B** and **1-C** respectively), a series of exchange equilibria were set up with each cation / sulfonyl fluoride pair (Fig. S24 a). These equilibria suggest that formation of the oxetane cation is preferred over the benzyl cation by ΔG (25 ºC) = 24.8 kJ mol^{-1} (Fig. S24 a.1), but less favorable than formation of the cyclobutyl cation (ΔG (25 ºC) = +10.4 kJ mol^{-1}, Fig. S24 a.2).

It is important to note that these equilibria depend on the stability of both cation and sulfonyl fluoride species. To decouple these effects, hydride exchange equilibria were also set up for each system to remove the steric component of sulfonyl fluoride instability (Fig. S24 b). The similar values of ΔG between the oxetane (**1**) and benzyl (**1-B**) pairs for the sulfonyl fluoride and hydride exchanges (**a.1** and **b.1**) suggest that cation stability, rather than sterics, determines the position of the equilibrium between each cation / sulfonyl fluoride pair. In contrast, the equilibrium is shifted further towards the cyclobutyl cation for the hydride exchange reaction (**b.2**) than for the sulfonyl fluoride (**a.2**). This suggests that either SO_2F / oxetane steric repulsion is significantly stronger than SO_2F / cyclobutane repulsion, or that the C–S bond in **1-C** is stronger than in **1**; these effects oppose the overall bias for cyclobutyl cation formation in the equilibrium.

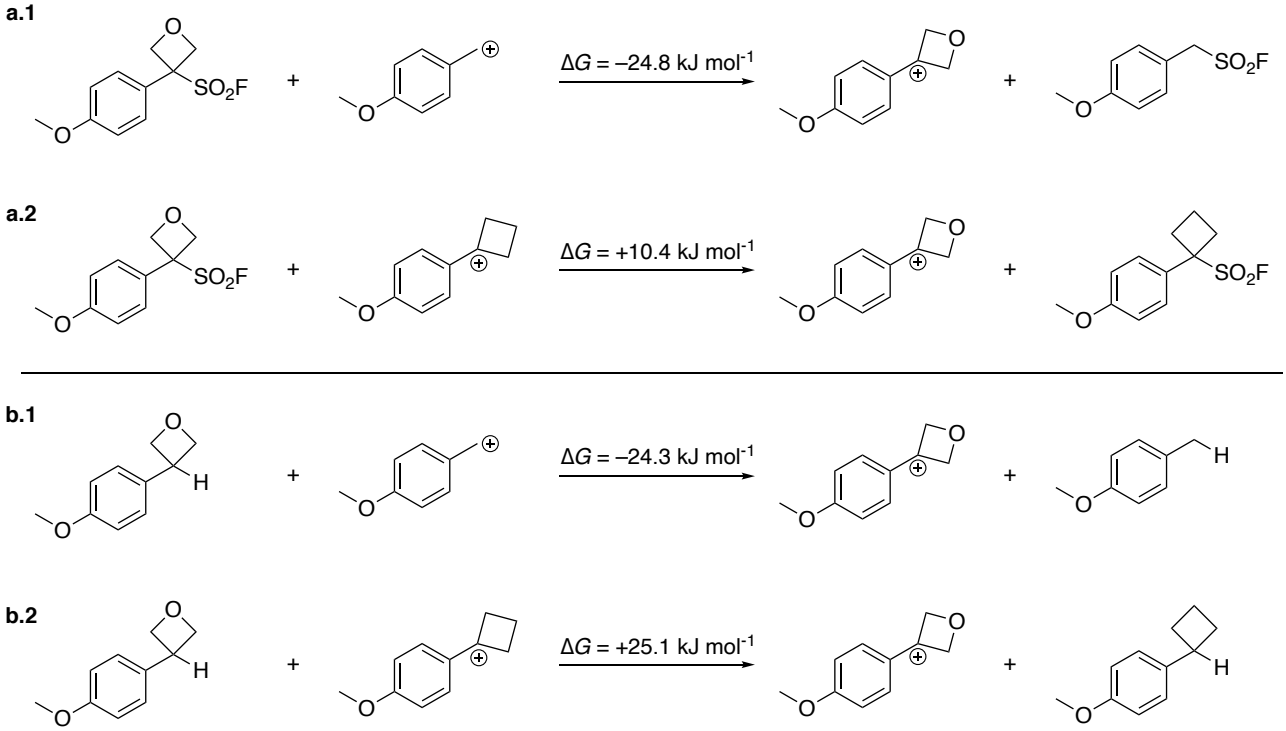
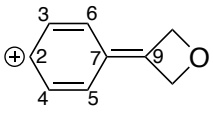


Fig. S24 Exchange equilibria for sulfonyl fluoride anion (**a.1** / **a.2**) and hydride (**b.1** / **b.2**) transfer between oxetane, benzyl and cyclobutyl cations, calculated at the [SMD(DLPNO)-CCSD(T)/def2-TZVPP (TightPNO, ma-def2-TZVPP on F)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on F)] level of theory.

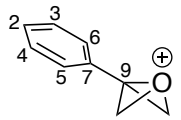
Calculated Thermodynamic and Electronic Data

Table S19 Second order perturbation theory analysis of the NBO Fock matrix for the π-delocalization energy ($E^{(2)}_{\pi}$) for planar **[O$_{Ph}$]$^+$**, calculated at the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory.



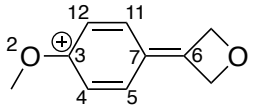
Donor	Acceptor	$E^{(2)}_{\pi}$ / kJ mol^{-1}
π(4,5)	LV(2)	585.2
π(3,6)	LV(2)	584.9
π(4,5)	π^*(7,9)	44.9
π(3,6)	π^*(7,9)	44.9
π(7,9)	π^*(3,6)	222.3
π(7,9)	π^*(4,5)	222.2
Sum		1704.4

Table S20 Second order perturbation theory analysis of the NBO Fock matrix for the π-delocalization energy ($E^{(2)}_{\pi}$) for bicyclic **[O$_{Ph}$]$^+$**, calculated at the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory.



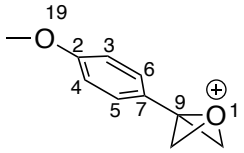
Donor	Acceptor	$E^{(2)}_{\pi}$ / kJ mol^{-1}
π(2,4)	π^*(3,6)	136.6
π(2,4)	π^*(5,7)	261.8
π(3,6)	π^*(2,4)	207.7
π(3,6)	π^*(5,7)	150.2
π(5,7)	π^*(2,4)	118.4
π(5,7)	π^*(3,6)	178.5
π(5,7)	LV(9)	366.1
Sum		1419.3

Table S21 Second order perturbation theory analysis of the NBO Fock matrix for the π-delocalization energy ($E^{(2)}_{\pi}$) for planar **[O$_{PMP}$]$^+$**, calculated at the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory.



Donor	Acceptor	$\Delta E^{(2)}_{\pi}$ / kJ mol^{-1}
LP(2)	LV(3)	571.9
π(4,5)	LV(3)	456.7
π(11,12)	LV(3)	511.0
π(4,5)	π^*(6,7)	43.1
π(11,12)	π^*(6,7)	46.0
π(6,7)	π^*(4,5)	195.9
π(6,7)	π^*(11,12)	177.4
Sum		2002.0

Table S22 Second order perturbation theory analysis of the NBO Fock matrix for the π-delocalization energy ($E^{(2)}_{\pi}$) for bicyclic **[O$_{PMP}$]$^+$**, calculated at the SMD(MeCN)-SCS-MP2/def2-TZVP level of theory.



Donor	Acceptor	$\Delta E^{(2)}_{\pi}$ / kJ mol^{-1}
LP(19)	π^*(2,4)	239.2
π(2,4)	π^*(3,6)	94.3
π(2,4)	π^*(5,7)	324.6
π(3,6)	π^*(2,4)	212.4
π(3,6)	π^*(5,7)	107.6
π(5,7)	π^*(2,4)	87.1
π(5,7)	π^*(3,6)	190.0
π(5,7)	LV(9)	444.9
Sum		1700.1

Solvent Effects on the Ionization of Sulfonyl Fluoride **1**

We explored the effect of solvent on the S_N1 activation barrier using computations, employing the SMD implicit solvent model for a range of solvent with dielectrics (ε_r) ranging from 2 to 47. As expected, more polar solvents stabilize the S_N1 TS (Fig. S25). TS energies relative to the MeCN solvent model were obtained at the [SMD(*solvent*)-ωB97X-D3/def2-SVP (ma-def2-SVP on F)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on F)] level of theory.

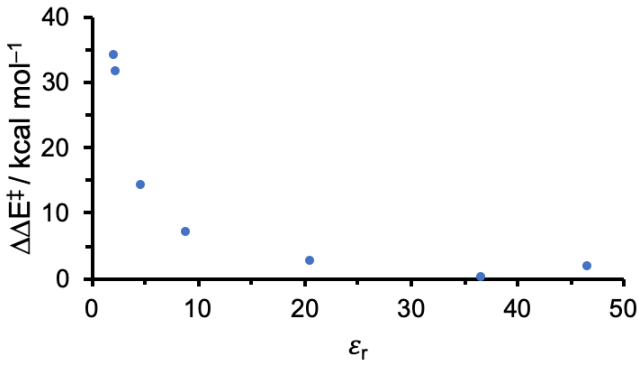


Fig. S25 Calculated relative S_N1 activation energies ($\Delta\Delta E^‡$ vs MeCN) as a function of the solvent dielectric (ε_r)

Table S23 Data for Fig. S25, with $\Delta E^‡$ in kJ mol^{-1}

Solvent	ε_r	$\Delta E^‡$	$\Delta\Delta E^‡$
MeCN	36.6	85.6	0.0
CH_2Cl_2	8.9	92.4	6.8
1,4-dioxane	2.3	119.5	33.9
PhMe	2.4	117.0	31.4
Acetone	20.7	88.1	2.5
$CHCl_3$	4.8	99.6	14.0
DMSO	46.7	87.2	1.6

Table S24 Energy differences (kJ mol^{-1}) between bicyclic and planar geometries of **[O$_H$]$^+$**, **[O$_{Ph}$]$^+$** and **[O$_{PMP}$]$^+$**, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-SCS-MP2/def2-TZVP] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	ΔE_{el}	**ΔZPE**	ΔH	$T\Delta$qh-S	Δqh-G	ΔE **DLPNO**	ΔG **DLPNO**
[O$_H$]$^+$_bicyclic	0.0	0.0	0.0	0.0	0.0	0.0	0.0
[O$_H$]$^+$_planar	65.4	-13.8	53.8	4.7	49.1	54.7	38.5
[O$_{Ph}$]$^+$_bicyclic	0.0	0.0	0.0	0.0	0.0	0.0	0.0
[O$_{Ph}$]$^+$_planar	-29.7	-3.1	-31.9	2.7	-34.6	-34.8	-39.7
[O$_{PMP}$]$^+$_bicyclic	0.0	-	-	-	-	0.0	-
[O$_{PMP}$]$^+$_planar	-57.3	-	-	-	-	-59.4	-

*ΔG DLPNO= ΔE DLPNO + (Δqh-G – ΔE_{el})

Table S25 Energy differences (kJ mol^{-1}) between stationary points for the S_N1 ionization of **1** at 25 ºC, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	ΔE_{el}	**ΔZPE**	ΔH **(298 K)**	$T\Delta$qh-S **(298 K)**	Δqh-G **(298 K)**	ΔE **DLPNO**	ΔG **DLPNO (298 K)**
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1_S_N1_TS	85.6	-10.8	77.1	9.5	70.7	126.0	111.1
1_ionic complex	54.9	-12.0	48.3	17.0	34.4	110.2	89.7
1_cation + SO_2F^-	100.2	-15.2	88.6	57.0	34.8	158.1	92.7

Table S26 Energy differences (kJ mol^{-1}) between stationary points for the S_N1 ionization of **1** at 60 ºC, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 333.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	**Δ*E*$_{el}$**	**ΔZPE**	**Δ*H* (333 K)**	***T*Δqh-*S* (333 K)**	**Δqh-*G* (333 K)**	**Δ*E* DLPNO**	**Δ*G* DLPNO (333 K)**
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1_S_N1_TS	85.6	-10.8	77.2	7.1	70.1	126.0	110.5
1_ionic complex	54.9	-12.0	48.7	15.7	33.0	110.2	88.3
1_cation + SO_2F^-	100.2	-15.2	88.6	59.9	28.7	158.1	86.6

Table S27 Energy differences (kJ mol^{-1}) for sulfonyl and hydride exchange reactions between **1**, **1-c** and **1-b**, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Reaction	**Δ*E*$_{el}$**	**ΔZPE**	**Δ*H***	***T*Δqh-*S***	**Δqh-*G***	**Δ*E* DLPNO**	**Δ*G* DLPNO**
1 + **1-C-cation ⟶ 1-cation + 1-C-SO_2F**	9.1	1.2	9.6	1.6	8.0	11.5	10.4
1-H + **1-C-cation ⟶ 1-cation + 1-C-H**	25.1	0.9	25.1	0.3	24.8	24.7	24.5
1 + **1-B-cation ⟶ 1-cation + 1-B-SO_2F**	-36.6	-1.9	-37.8	5.3	-43.1	-18.3	-24.8
1-H + **1-B-cation ⟶ 1-cation + 1-B-H**	-33.2	-5.3	-36.7	4.7	-41.4	-16.7	-24.9

Table S28 Absolute electronic energies and thermodynamic quantities (Ha) for the comparison of the bicyclic and planar geometries of **[O_H]$^+$**, **[O_{Ph}]$^+$** and **[O_{PMP}]$^+$** calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-SCS-MP2/def2-TZVP] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	E_{el}	ZPE	*H*	*T*qh-*S*	qh-*G*	*E* DLPNO	*G* DLPNO
[O_H]$^+$_bicyclic	-191.87914	0.07611	-191.79841	0.03006	-191.82847	-191.95378	-191.90311
[O_H]$^+$_planar	-191.85424	0.07086	-191.77792	0.03186	-191.80978	-191.93293	-191.88846
[O_{Ph}]$^+$_bicyclic	-422.41233	0.15681	-422.24646	0.04180	-422.28826	-422.58530	-422.46123
[O_{Ph}]$^+$_planar	-422.42363	0.15562	-422.25860	0.04282	-422.30142	-422.59856	-422.47635
[O_{PMP}]$^+$_bicyclic	-536.73738	-	-	-	-	-536.95036	-
[O_{PMP}]$^+$_planar	-536.75923	0.18956	-536.55784	0.04803	-536.60587	-536.97300	-536.81964

Table S29 Absolute electronic energies and thermodynamic quantities (Ha) for the S_N1 ionization of **1** at 25 ºC, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	E_{el}	ZPE	*H* (298 K)	*T*qh-*S* (298 K)	qh-*G* (298 K)	*E* DLPNO	*G* DLPNO (298 K)
1	-1185.60780	0.20526	-1185.38687	0.05355	-1185.44161	-1184.91644	-1184.75026
1_S_N1_TS	-1185.57521	0.20115	-1185.35752	0.05715	-1185.41467	-1184.86846	-1184.70792
1_cation	-537.35690	0.19042	-537.15467	0.04570	-537.20037	-536.97233	-536.81580
SO_2F^-	-648.21272	0.00905	-648.19844	0.02956	-648.22800	-647.88388	-647.89917
1_ionic complex	-1185.58688	0.20069	-1185.36849	0.06001	-1185.42850	-1184.87448	-1184.71609

Table S30 Absolute electronic energies and thermodynamic quantities (Ha) for the S_N1 ionization of **1** at 60 ºC, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 333.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	E_{el}	ZPE	H (333 K)	Tqh-S (333 K)	qh-G (333 K)	E DLPNO	G DLPNO (333 K)	$\tilde{\nu}_{imag}$ / cm^{-1}
1	-1185.60780	0.20526	-1185.38354	0.06449	-1185.44803	-1184.91644	-1184.75667	
1_S_N1_TS	-1185.57521	0.20115	-1185.35415	0.06718	-1185.42133	-1184.86846	-1184.71458	–161
1_cation	-537.35690	0.19042	-537.15218	0.05352	-537.20570	-536.97233	-536.82113	
SO_2F^-	-648.21272	0.00905	-648.19763	0.03377	-648.23140	-647.88388	-647.90256	
1_ionic complex	-1185.58688	0.20069	-1185.36498	0.07048	-1185.43546	-1184.87448	-1184.72306	

Table S31 Absolute electronic energies and thermodynamic quantities (Ha) for sulfonyl and hydride exchange reactions between **1**, **1-c** and **1-b**, calculated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP (TightPNO)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on fluoride)] level of theory. Free energies were evaluated at 298.15 K and 1 M concentration using a quasi-Harmonic (qh) approximation for the entropic contribution.

Name	E_{el}	ZPE	H	Tqh-S	qh-G	E DLPNO	G DLPNO
1	-1185.60783	0.20526	-1185.38687	0.05355	-1185.44041	-1184.91644	-1184.74903
1-H	-538.16134	0.20232	-537.94714	0.04582	-537.99296	-537.77641	-537.60803
1-cation	-537.35690	0.19042	-537.15467	0.04550	-537.20017	-536.97233	-536.81560
1-C-SO_2F	-1149.76349	0.22893	-1149.51865	0.05378	-1149.57242	-1149.04475	-1148.85368
1-C-H	-502.31090	0.22586	-502.07300	0.04556	-502.11856	-501.89967	-501.70732
1-C-cation	-501.51603	0.21364	-501.29011	0.04513	-501.33524	-501.10501	-500.92422
1-B-SO_2F	-1033.16145	0.16557	-1032.98275	0.04830	-1033.03105	-1032.55552	-1032.42512
1-B-H	-385.71369	0.16134	-385.54262	0.04033	-385.58296	-385.41491	-385.28419
1-B-cation	-384.89658	0.15145	-384.73617	0.03822	-384.77439	-384.60445	-384.48226

Table S32 Electronic energies (Ha) for the S_N1 TS as a function of SMD solvent, calculated at the [SMD(*solvent*)-ωB97X-D3/def2-SVP (ma-def2-SVP on F)//SMD(MeCN)-ωB97X-D3/def2-SVP (ma-def2-SVP on F)] level of theory.

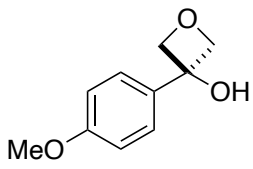
Solvent	**Name**	E_{el}
MeCN	**1**	-1185.60780
	1_S_N1_TS	-1185.57521
1,4-dioxane	**1**	-1185.60114
	1_S_N1_TS	-1185.55564
CH_2Cl_2	**1**	-1185.60754
	1_S_N1_TS	-1185.57235
MeOH	**1**	-1185.60641
	1_S_N1_TS	-1185.57766
i-PrOH	**1**	-1185.60729
	1_S_N1_TS	-1185.57655
PhMe	**1**	-1185.60386
	1_S_N1_TS	-1185.55931
Acetone	**1**	-1185.60939
	1_S_N1_TS	-1185.57584
$CHCl_3$	**1**	-1185.60532
	1_S_N1_TS	-1185.56740
DMSO	**1**	-1185.60724
	1_S_N1_TS	-1185.57405

Experimental Details and Characterization Data

Oxetane Sulfonyl Fluorides (1, 53–59, 92)

Sulfonyl Fluoride 1

3-(4-Methoxyphenyl)oxetan-3-ol (1a)



n-BuLi (1.59 M in hexanes, 98 mL, 155.8 mmol, 1.1 equiv) was added dropwise using a canula over 20 min to a solution of *p*-bromoanisole (21.3 mL, 170.0 mmol, 1.2 equiv) in anhydrous THF (650 mL, 0.22 M) at –78 °C in a 1 L 2-neck round bottom flask. After stirring for 1 h, oxetan-3-one (9.10 mL, 141.65 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 1 h of stirring at –78 °C, the reaction mixture was warmed up slowly to 25 °C, stirred for 2 h and quenched with distilled water (200 mL). The aqueous layer was extracted with diethylether (3 × 200 mL). The organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (45% EtOAc/hexane) afforded oxetanol **1a** as a white solid (23.03 g, 90%). R_f = 0.20 (45% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2 H, 2 × Ar-CH), 6.95–6.91 (m, 2 H, 2 × Ar-CH), 4.88 (d, *J* = 7.0 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 7.0 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.32 (br s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 134.5 (Ar-C_qC_q), 125.9 (2 × Ar-CH), 114.0 (2 × Ar-CH), 85.6 (CH_2OCH_2), 75.6 (C_q), 55.3 (OCH_3). The observed characterization data (R_f, ^{1}H, ^{13}C) were consistent with that previously reported in the group.[3]

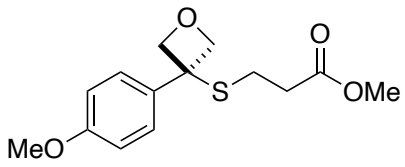
Notes:

The rate of the dropwise addition of n-BuLi *was controlled by employing a positive pressure on the bottle of n*-BuLi *with a balloon filled with argon.*

One 100 mL bottle of n-BuLi *was added to the reaction. 98 mL are an estimated volume based on losses during the preceding titration of n*-BuLi *and leftover liquid in the bottle and canula.*

Around 500 g of silica were used for flash column chromatography.

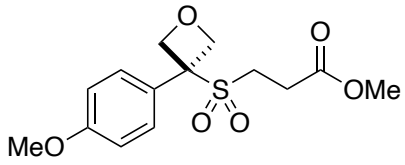
Methyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)thio)propanoate (1b)[2]



Lithium bis(trifluoromethanesulfonimide) (380 mg, 1.32 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (255.9 mg, 0.66 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **1a** (2.16 g, 12.0 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (2.6 mL, 24.0 mmol, 2.0 equiv) in non-anhydrous chloroform (25 mL, 0.5 M) in a 100 mL round bottom flask. The reaction flask was placed into a preheated oil bath at 40 °C. The reaction was stirred for 15 min and then heated up to 70 °C in 1 h. At 70 °C there was a change in color from colorless to yellow. From the moment of the color change, the reaction was stirred for further 25 min and quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were washed with aq. NaOH (1 M, 35 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50% Et_2O/pentane) afforded oxetane sulfide **1b** as a white solid (2.61 g, 77%). R_f = 0.26 (50% Et_2O/pentane); mp = 45–47 °C; IR (film)/cm^{-1} 2952, 2884, 1732 (C=O st), 1610, 1514, 1436, 1420, 1369, 1298, 1250, 1208, 1178, 1146, 1022, 980, 839, 819, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.12 (m, 2 H, 2 × Ar-CH), 6.92–6.89 (m, 2 H, 2 × Ar-CH), 5.19 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, Ar-$C_q$$OCH_3$), 3.68 (s, 3 H, CO_2CH_3), 2.67 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.42 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_q=O), 158.6 (Ar-C_qOMe), 134.2 (Ar-C_qC_q), 127.4 (2 × Ar-CH), 114.0 (2 × Ar-CH), 83.2 (CH_2OCH_2), 55.3 (Ar-C_qOCH_3), 52.2 (C_q), 51.8 (CO_2CH_3),

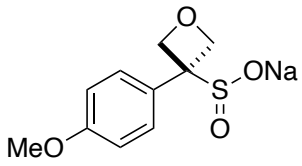
34.1 (CH_2CO_2Me), 25.2 (SCH_2); HRMS (APCI) *m/z* calcd for $C_{14}H_{22}NSO_4$ [M+NH_4]: 300.1270, found: 300.1266.

Methyl 3-((3-(4-methoxyphenyl)oxetan-3-yl)sulfonyl)propanoate (1c)



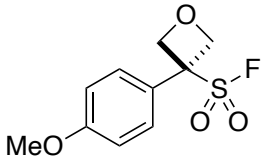
*m*CPBA (4.20 g, 24.3 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **1b** (2.29 g, 8.11 mmol, 1.0 equiv) in CH_2Cl_2 (400 mL, 0.02 M) in a 1000 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 50 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford sulfone **1c** as a white solid (2.60 g, quant.); R_f = 0.59 (75% EtOAc/hexane); mp = 79–82 °C; IR (film)/cm^{-1} 2939, 1741 (C=O st), 1512, 1309, 1302, 1269, 1248 (SO_2 st as), 1183, 1143, 1019, 987, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2 H, 2 × Ar-CH), 6.99–6.95 (m, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 7.2 Hz, 2 H, C*H*HOC*H*H), 5.12 (d, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, Ar-$C_q$$OCH_3$), 3.70 (s, 3 H, CO_2CH_3), 3.08 (dd, *J* = 8.2, 7.1 Hz, 2 H, SO_2CH_2), 2.71 (t, *J* = 8.2, 7.1 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_q=O), 160.3 (Ar-C_qOMe), 129.4 (2 × Ar-CH), 125.5 (Ar-C_qC_q), 114.5 (2 × Ar-CH), 76.3, (CH_2OCH_2), 68.3 (C_q), 55.4 (Ar-C_qOCH_3), 52.4 (CO_2CH_3), 43.2 (CH_2CO_2Me), 25.9 (SO_2CH_2); HRMS (APCI) *m/z* calcd for $C_{14}H_{19}SO_6$ [M+H]: 315.0902, found: 315.0898.

Sodium 3-(4-methoxyphenyl)oxetane-3-sulfinate (1d)



Prepared using elimination conditions **El-I**. Sulfone **1c** (2.43 g, 7.74 mmol, 1.0 equiv) was added to a solution of NaH (60% in mineral oil, 325 mg, 8.13 mmol, 1.05 equiv) in THF (45 mL, 0.17 M). The reaction mixture was stirred at 25 ºC for 1 h then quenched with anhydrous methanol (15 mL) and concentrated *in vacuo* using a rotatory evaporator to afford sulfinate salt **1d** as a white solid (1.95 g, 95%). R_f = 0.12 (20% MeOH/CH_2Cl_2); Melting point not determined, degradation observed at 250 ºC; IR (film)/cm^{-1} 2926, 2873, 1738, 1513, 1243, 1177, 1038, 989, 973, 928, 829, 661; ^{1}H NMR (400 MHz, D_2O) δ 7.07–7.02 (m, 4 H, 4 × Ar-CH), 5.12 (d, *J* = 7.2 Hz, C*H*HOC*H*H), 5.01 (d, *J* = 7.2 Hz, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, D_2O) δ 158.2 (Ar-C_qOMe), 128.7 (Ar-C_qC_q), 128.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 76.6 (CH_2OCH_2), 67.0 (C_q), 55.3 (OCH_3); HRMS (NSI) *m/z* calcd for $C_{10}H_{11}O_4S^-$ [M-Na]$^-$: 227.0384, found: 227.0385.

3-(4-Methoxyphenyl)oxetane-3-sulfonyl fluoride (1)



From sulfinate salt **1d**: Selectfluor (1.86 g, 5.30 mmol, 1.5 equiv) was added to anhydrous MeOH (17.5 mL, 0.2 M) at 0 ºC in a 50 mL round bottom flask, then stirred for 5 min. Sulfinate salt **1d** (876 mg, 3.50 mmol, 1.0 equiv) was added portionwise. The reaction mixture was stirred at 0 ºC for 1 h then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (30 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (100% CH_2Cl_2) afforded sulfonyl fluoride **1** as a white solid (644 mg, 77%). R_f = 0.47 (80% CH_2Cl_2/pentane); R_f = 0.60 (100% CH_2Cl_2); mp = 115–117 ºC, IR (film)/cm^{-1} 2969, 2903, 1738, 1615, 1517, 1393 (SO_2 st as), 1308, 1263, 1210 (SO_2 st sy), 1174, 1021, 997, 928; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.19 (m, 2 H, 2 × Ar-CH), 7.01–6.97 (m, 2 H, 2 × Ar-CH), 5.44 (d, *J* = 7.9 Hz, 2 H, C*H*HOC*H*H), 5.24 (dd, ^2J = 7.9 Hz, J_{HF} = 1.5 Hz, 2 H, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (Ar-C_qOMe), 129.5 (2 × Ar-CH), 123.3 (Ar-C_qC_q), 114.7 (2 × Ar-CH), 77.1 (CH_2OCH_2), 68.1 (d, $J_{C\text{-}F}$ = 14.4 Hz, C_q), 55.5 (OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.4, HRMS (APCI) *m/z* calcd for $C_{10}H_{11}O_2$ [M–SO_2F]: 163.0759, found: 163.0761.

Notes:

***1** was further characterized by X-ray crystallography (see Fig. S53–54).*

From Sulfone **1c:** Sulfonyl fluoride **1** was also synthesized in a telescope process from sulfone **1c** using the alternative elimination protocols **EI-II** and **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions.

EI-II: NaOH (5 M in MeOH, 0.8 mL, 4.00 mmol, 1.05 equiv) was added to a solution of sulfone (**1c**) (1.19 g, 3.80 mmol, 1.0 equiv) in CH_2Cl_2 (38 mL, 0.1 M) at 0 °C in a 50 mL round bottom flask. Oxetane sulfinate salt **1d** precipitated after 2 min of the start of of addition of base to form a white paste. The reaction mixture was stirred at 0 °C for 15 minutes then filtered and washed with ice cold hexane to afford oxetane sulfinate **1d** as a white solid, which was subjected directly to the next step without spectroscopical analysis. The fluorination step was carried out as described above. Purification by flash column chromatography through a very short column (90% CH_2Cl_2/pentane) afforded sulfonyl fluoride **1** as a white solid (574 mg, 61% over 2 steps).

EI-III: Sodium methoxide (5.4 M solution in MeOH, 1.5 mL, 8.11 mmol, 1.0 equiv) was added dropwise to a solution of oxetane sulfone **1c** (2.55 g, 8.11 mmol, 1.0 equiv) in anhydrous THF (16.2 mL, 0.5 M) in a 100 mL round bottom flask. Oxetane sulfinate salt **1d** precipitated after 2 min of the start of addition of base to form a light-yellow paste (Fig. S18). Sometimes, the precipitation occurred before all base had been added. The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfinate **1d** as a light-yellow solid, which was subjected directly to the next step without spectroscopical analysis. The fluorination step was carried out as described above. Purification by flash column chromatography through a very short column (80% CH_2Cl_2/pentane) afforded oxetane sulfonyl fluoride **1** as a white solid (1.064 g, 53% over 2 steps).

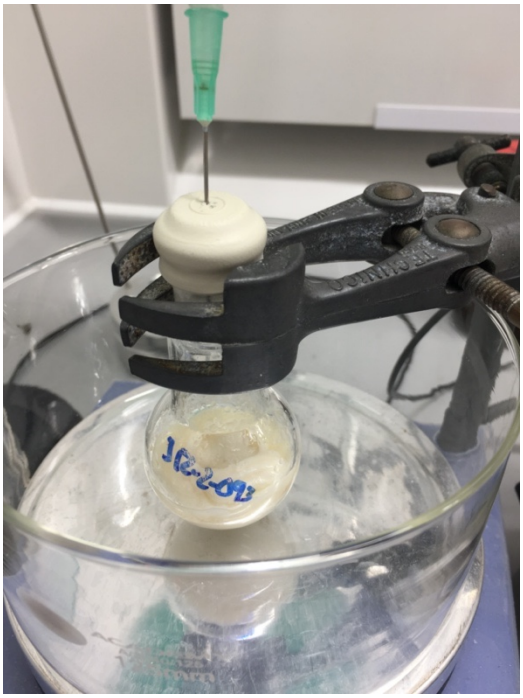
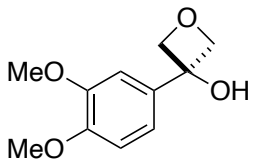


Fig. S26 Solidification of reaction mixture after addition of NaOMe in a 4.0 mmol scale reaction.

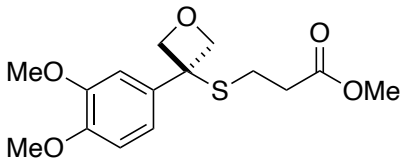
Sulfonyl Fluoride 53

3-(3,4-Dimethoxyphenyl)oxetan-3-ol (53a)



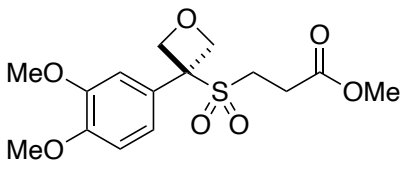
n-BuLi (1.60 M in hexanes, 7.5 mL, 12.0 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of 4-bromo-1,2-dimethoxybenzene (1.9 mL, 13.0 mmol, 1.3 equiv) in anhydrous THF (20 mL, 0.2 M) at –78 °C in a 100 mL round bottom flask. After stirring for 20 min, oxetan-3-one (0.64 mL, 10.0 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 5 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (50 mL). The aqueous layer was extracted with diethylether (3 × 50 mL). The organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetanol **53a** as a white solid (1.44 g, 69%). R_f = 0.15 (50% EtOAc/pentane); mp = 49–51 °C; IR (film)/cm^{-1} 3391 (br OH), 2952, 2873, 1591, 1517, 1461, 1416, 1259, 1140, 1025, 976, 857, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2 H, 2 × Ar-CH), 6.89 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 4.91 (d, *J* = 6.9 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 6.9 Hz, 2 H, CH*H*OCH*H*), 3.91 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 2.94 (br s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1 (Ar-C_qOMe), 148.6 (Ar-C_qOMe), 134.9 (Ar-C_qC_q), 116.7 (Ar-CH), 110.9 (Ar-CH), 107.9 (Ar-CH), 85.6 (CH_2OCH_2), 75.6 (C_q), 55.9 (2 × OCH_3); HRMS (APCI) *m/z* calcd for $C_{11}H_{13}O_3^+$ [M-OH]$^+$: 193.0859, found: 193.0858.

Methyl 3-((3-(3,4-dimethoxyphenyl)oxetan-3-yl)thio)propanoate (53b)



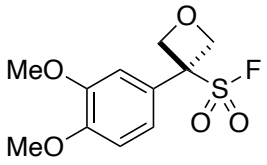
Lithium bis(trifluoromethanesulfonimide) (187 mg, 0.65 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (128 mg, 0.33 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **53a** (1.25 g, 5.95 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (1.3 mL, 12.0 mmol, 2.0 equiv) in non-anhydrous chloroform (12 mL, 0.5 M) in a 100 mL round bottom flask. The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (30% EtOAc/pentane) afforded oxetane sulfide **53b** as a colorless oil (1.79 g, 96%). R_f = 0.16 (30% EtOAc in pentane); IR (film)/cm^{-1} 2948, 2870, 2836, 1733 (C=O st), 1587, 1513, 1461, 1244, 1215, 1174, 1140, 1025, 984, 808, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.2 Hz, 1 H, Ar-C_qOMeAr-C*H*Ar-CH), 6.75 (dd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, 1 H, Ar-CHAr-C*H*Ar-C_qC_q), 6.71 (d, *J* = 2.2 Hz, 1 H, Ar-C_qOMeAr-CHAr-C_q), 5.18 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 3.88 (s, 3 H, Ar-C_qOCH_3), 3.87 (s, 3 H, Ar-C_qOCH_3), 3.66 (s, 3 H, CO_2CH_3), 2.65 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.40 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_q=O), 149.2 (Ar-C_qOMe), 148.2 (Ar-C_qOMe), 134.5 (Ar-C_qC_q), 118.5 (Ar-CH), 110.6 (Ar-CH), 109.5 (Ar-CH), 83.1 (CH_2OCH_2), 55.91 (Ar-C_qOCH_3), 55.86 (Ar-C_qOCH_3), 52.4 (C_q), 51.7 (CO_2CH_3), 34.0 (CH_2CO_2Me), 25.2 (SCH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_5SNa^+$ [M+Na]$^+$: 335.0924, found: 335.0923.

Methyl 3-((3-(3,4-dimethoxyphenyl)oxetan-3-yl)sulfonyl)propanoate (53c)



*m*CPBA (2.47 g, 14.3 mmol, 2.5 equiv) was added to a solution of oxetane sulfide **53b** (1.79 g, 5.73 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL, 0.03 M) in a 500 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then sat. aq. $NaHCO_3$ (60 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 75 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator Purification by flash column chromatography (60% EtOAc/pentane) afforded oxetane sulfone **53c** as a white solid (1.28 g, 65%). R_f = 0.17 (50% EtOAc in pentane); mp = 133–135 °C; IR (film)/cm^{-1} 3000, 2952, 2885, 1736 (C=O st), 1517, 1438, 1304, 1252, 1136, 1021, 883, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.4 Hz, 1 H, Ar-C_qOMeAr-C*H*Ar-CH), 6.86 (dd, ^3J = 8.3 Hz, ^4J = 2.2 Hz, 1 H, Ar-CHAr-C*H*Ar-C_qC_q), 6.78 (d, *J* = 2.2 Hz, 1 H, Ar-C_qOMeAr-CHAr-C_q), 5.40 (d, *J* = 7.2 Hz, 2 H, C*H*HOC*H*H), 5.14 (d, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.93 (s, 3 H, Ar-C_qOCH$_3$), 3.90 (s, 3 H, Ar-C_qOCH$_3$), 3.71 (s, 3 H, CO_2CH_3), 3.09 (dd, *J* = 8.2, 7.1 Hz, 2 H, SO_2CH_2), 2.72 (dd, *J* = 8.2, 7.1 Hz, 2 H, C*H*$_2$CO$_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_q=O), 149.9 (Ar-C_qOMe), 149.3 (Ar-C_qOMe), 125.8 (Ar-*C*$_q$C$_q$), 120.7 (Ar-CHAr-*C*HAr-C_qC_q), 111.1 (Ar-CH), 111.0 (Ar-CH), 76.2 (CH_2OCH_2), 68.5 (C_q), 56.1 (Ar-C_qOCH$_3$), 55.9 (Ar-C_qOCH$_3$), 52.4 (CO_2CH_3), 43.3 (*C*H$_2$CO$_2$Me), 25.9 (SO_2CH_2); HRMS (APCI) *m/z* calcd for $C_{15}H_{20}O_7S^{35}Cl^-$ [M+^{35}Cl]$^-$: 379.0624, found: 379.0623.

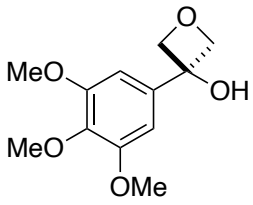
3-(3,4-Dimethoxyphenyl)oxetane-3-sulfonyl fluoride (53)



Sulfonyl fluoride **53** was synthesized in a telescope process from sulfone **53c** using the elimination protocol **EI-II** and submitting the sulfinate intermediate directly to the fluorination conditions. NaOH (5 M in MeOH, 315 μL, 1.58 mmol, 1.05 equiv) was added to a solution of sulfone **53c** (518 mg, 1.50 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL, 0.1 M) at 0 °C in a 25 mL round bottom flask. Oxetane sulfinate salt **53d** precipitated after 2 min of the start of addition of base to form a white paste. The reaction mixture was stirred at 0 °C for 15 minutes then filtered and washed with ice cold hexane to afford oxetane sulfinate **53d** as a white solid, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (795 mg, 2.24 mmol, 1.5 equiv) was added to anhydrous MeOH (7.5 mL, 0.2 M) at 0 ºC in a 50 mL round bottom flask, then stirred for 5 min. Sulfinate salt **53d** was added portionwise. The reaction mixture was stirred at 0 ºC for 1 h then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (30 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator*,* purification by flash column chromatography through a very short column (100% CH_2Cl_2) afforded sulfonyl fluoride **53** as a white solid (231 mg, 56%). R_f = 0.76 (100% CH_2Cl_2); mp = 110–112 °C; IR (film)/cm^{-1} 2963, 1520, 1398 (SO_2 st as), 1256, 1211, 1177, 1025, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.4 Hz, 1 H, Ar-C_qOMeAr-C*H*Ar-CH), 6.86 (dd, ^3J = 8.4 Hz, ^3J = 2.2 Hz, 1 H, Ar-CHAr-C*H*Ar-C_qC_q), 6.71 (d, *J* = 2.2 Hz, 1 H, Ar-C_qOMeAr-CHAr-C_q), 5.43 (d, J = 7.9 Hz, 2 H, C*H*HOC*H*H), 5.26 (dd, *J* = 7.9 Hz, J_{HF} = 1.5 Hz, 2 H, CH*H*OCH*H*), 3.93 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (Ar-C_qOMe), 149.5 (Ar-C_qOMe), 123.5 (Ar-*C*$_q$C$_q$), 121.2 (Ar-CHAr-*C*HAr-C_qC_q), 111.2 (Ar-CH), 110.8 (Ar-CH), 77.1 (CH_2OCH_2), 68.4 (d, $J_{C\text{-}F}$ = 14.6 Hz, C_q), 56.2 (OCH_3), 56.0 (OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.6; HRMS (APCI) *m/z* calcd for $C_{11}H_{13}O_3^+$ [M-SO_2F]$^+$: 193.0859, found: 193.0852.

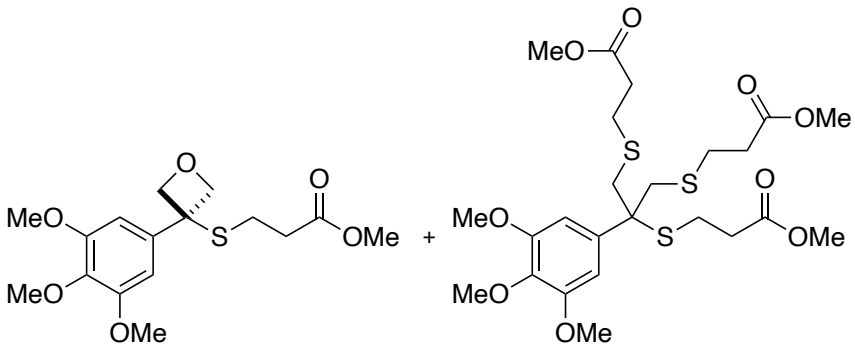
Sulfonyl Fluoride 54

3-(3,4,5-Trimethoxyphenyl)oxetan-3-ol (54a)[2]



n-BuLi (1.54 M in hexanes, 15.9 mL, 24.0 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of 5-bromo-1,2,3-trimethoxybenzene (6.42 g, 26.0 mmol, 1.3 equiv) in anhydrous THF (91 mL, 0.22 M) at –78 °C in a 250 mL round bottom flask. After stirring for 20 min, oxetan-3-one (1.28 mL, 20.0 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 5 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (60 mL). The aqueous layer was extracted with diethylether (3 × 60 mL). The organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (30–70% EtOAc/hexane) afforded oxetanol **54a** as a light-yellow solid (4.62 g, 96%). R_f = 0.16 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2 H, 2 × Ar-CH), 4.92 (s, 4 H, CH_2OCH_2), 3.91 (s, 6 H, 2 × OCH_3), 3.87 (s, 3 H, OCH_3), 2.57–2.53 (m, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (2 × Ar-C_qOMe), 138.3 (Ar-C_qOMe), 137.0 (Ar-C_qC_q), 101.6 (2 × Ar-CH), 85.7 (CH_2OCH_2), 75.3 (C_q), 60.7 (OCH_3), 56.0 (2 × OCH_3). The observed characterization data (R_f, ^{1}H, ^{13}C) were consistent with that previously reported in the group.[2]

Methyl 3-((3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)thio)propanoate (54b) and trimethyl 3,3',3''-((2-(3,4,5-trimethoxyphenyl)propane-1,2,3-triyl)tris(sulfanediyl))tripropionate (54b'')



54b **54b''**

Lithium bis(trifluoromethanesulfonimide) (607 mg, 2.11 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (407 mg, 1.05 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **54a** (4.61 g, 19.2 mmol, 1.0 equiv) and methyl 3-mercaptopro-pionate (4.15 mL, 38.4 mmol, 2.0 equiv) in non-anhydrous chloroform (38 mL, 0.5 M) in a 100 mL round bottom flask. The reaction flask was placed into a preheated oil bath at 40 °C. The reaction was stirred for 15 min and then heated up to 57 °C in 10 min. At 57 °C there was a change in color from light-yellow to dark purple (Fig. S19). From the moment of the color change, the reaction was stirred for further 25 min and quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were washed with aq. NaOH (1 M, 35 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (60–100% Et_2O/pentane) afforded oxetane sulfide **54b** as a light-yellow oil (1.34 g, 20%) followed by trisulfide **54b''** as a light-yellow oil (1.99 g, 18%).

Oxetane sulfide **54b**: R_f = 0.19 (60% Et_2O/pentane); IR (film)/cm^{-1} 2948, 1731 (C=O st), 1586, 1507, 1410, 1347, 1243, 1171, 1124, 1003, 977, 825, 770, 738, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 2 H, 2 × Ar-CH), 5.20 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.88 (s, 6 H, 2 × Ar-$C_q$$OCH_3$), 3.86 (s, 3 H, Ar-$C_q$$OCH_3$), 3.68 (s, 3 H, CO_2CH_3), 2.73 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.45 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_q=O), 153.3 (2 × Ar-C_qOMe), 137.8 (Ar-C_qOMe), 137.2 (Ar-C_qC_q), 103.6 (2 × Ar-CH), 83.0 (CH_2OCH_2), 60.9 (Ar-C_qOCH_3), 56.2 (2 × Ar-C_qOCH_3), 52.8 (C_q), 51.8 (CO_2CH_3), 34.0 (CH_2CO_2Me), 25.3 (SCH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_6SNa^+$ $[M+Na]^+$: 365.1029, found: 365.1032.

Trisulfide **54b''**: R_f = 0.12 (60% Et_2O/pentane); IR (film)/cm^{-1} 2948, 2866, 2255, 1737 (C=O st), 1603, 1513, 1465, 1413, 1357, 1275, 1245, 1178, 1141, 1036, 910, 816, 731, 686; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.78 (s, 2 H, 2 × Ar-CH), 3.89 (s, 6 H, 2 × Ar-$C_q$$OCH_3$), 3.85 (s, 3 H, Ar-$C_q$$OCH_3$), 3.68 (s, 6 H, 2 × CO_2CH_3), 3.64 (s, 3 H, CO_2CH_3), 3.38 (d, *J* = 12.7 Hz, 2 H, 2 × C_qC*H*HS), 3.33 (d, *J* = 12.7 Hz, 2 H, 2 × C_qCH*H*S), 2.73–2.69 (m, 4 H, 2 × SCH_2), 2.59–2.55 (m, 4 H, 2 × C*H*$_2CO_2$Me), 2.52–2.48 (m, 2 H, SCH_2), 2.41–2.37 (m, 2 H, C*H*$_2CO_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (2 × C_q=O), 172.0 (C_q=O), 152.8 (2 × Ar-C_qOMe), 137.4 (Ar-C_qOMe), 137.1 (Ar-*C*$_q$C$_q$), 105.2 (2 × Ar-CH), 60.9 (Ar-C_qO*C*H$_3$), 56.8 (C_q), 56.3 (2 × Ar-C_qO*C*H$_3$), 51.8 (3 × CO_2*C*H$_3$), 41.0 (2 × C_q*C*H$_2$S), 34.8 (2 × *C*H$_2CO_2$Me), 33.5 (*C*H$_2CO_2$Me), 28.5 (2 × S*C*H$_2$CH$_2$), 24.4 (S*C*H$_2$CH$_2$); HRMS (ESI) *m/z* calcd for $C_{24}H_{36}O_9S_3Na$ [M+Na]: 587.1419, found: 587.1417.

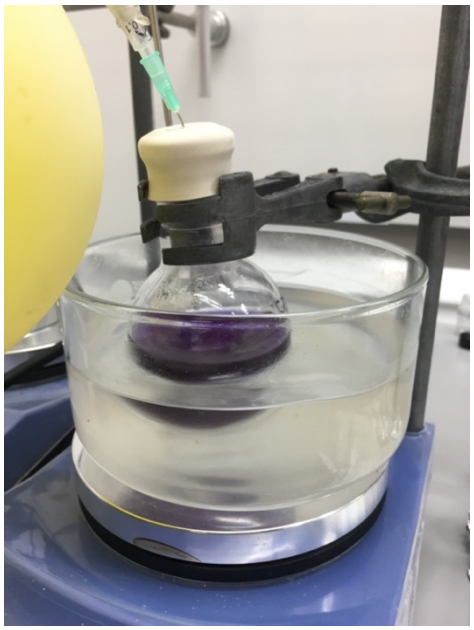
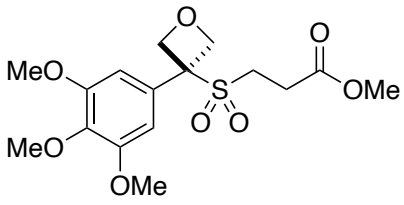


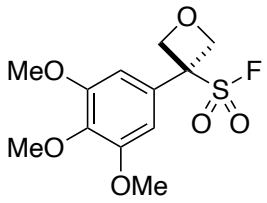
Fig. S27 Color change of reaction mixture to dark purple after heating up to 57 °C.

Methyl 3-((3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)sulfonyl)propanoate (54c)



*m*CPBA (2.03 g, 11.8 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **54b** (1.34 g, 3.90 mmol, 1.0 equiv) in CH_2Cl_2 (196 mL, 0.02 M) in a 500 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 110 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 55 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfone **54c** as a light-yellow solid (1.31 g, 89%). R_f = 0.27 (50% EtOAc/pentane); mp = 85–88 °C; IR (film)/cm^{-1} 2995, 2948, 2888, 2831, 1732 (C=O st), 1588, 1509, 1456, 1417, 1367, 1351, 1340, 1304 (SO_2 st as), 1267, 1257, 1200, 1183, 1088, 1059, 1034, 1001, 959, 917, 900, 837, 814, 779, 764, 744, 716, 673; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 2 H, 2 × Ar-CH), 5.38 (d, *J* = 7.3 Hz, 2 H, C*H*HOC*H*H), 5.14 (d, *J* = 7.3 Hz, 2 H, CH*H*OCH*H*), 3.881 (s, 3 H, Ar-$C_q$$OCH_3$), 3.876 (s, 6 H, 2 × Ar-$C_q$$OCH_3$), 3.71 (s, 3 H, CO_2CH_3) 3.15 (t, *J* = 7.5 Hz, 2 H, SO_2CH_2), 2.72 (t, *J* = 7.5 Hz, 2 H, C*H*$_2CO_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_q=O), 153.6 (2 × Ar-C_qOMe), 139.0 (Ar-C_qOMe), 129.0 (Ar-*C*$_q$C$_q$), 105.6 (2 × Ar-CH), 76.3 (CH_2OCH_2), 69.0 (C_q), 60.9 (Ar-C_qO*C*H$_3$), 56.4 (2 × Ar-C_qO*C*H$_3$), 52.4 (CO_2*C*H$_3$), 43.6 (*C*H$_2CO_2$Me), 26.1 (SO_2CH_2); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_8SNa$ [M+MeCN+Na]: 438.1199, found: 438.1195.

3-(3,4,5-Trimethoxyphenyl)oxetane-3-sulfonyl fluoride (54)



Sulfonyl fluoride **54** was synthesized in a telescope process from sulfone **54c** using the elimination protocol **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions. Sodium methoxide (5.4 M solution in MeOH, 0.28 mL, 1.50 mmol, 1.0 equiv) was added dropwise to a solution of oxetane sulfone **54c** (562 mg, 1.50 mmol, 1.0 equiv) in anhydrous THF (3.0 mL, 0.5 M) in a 10 mL round bottom flask. Oxetane sulfinate salt **54d** precipitated immediately after the start of addition of base to form a light-yellow paste (Fig. S20). The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfinate **54d**, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (797.1 mg, 2.25 mmol, 1.5 equiv) was added to anhydrous MeOH (7.5 mL, 0.2 M) at 0 °C in a 25 mL round bottom flask, then stirred for 5 min. Sulfinate salt **54d** was added portionwise. The reaction mixture was stirred for at 0 °C for 1 h, then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (15 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (100% CH_2Cl_2) afforded oxetane sulfonyl fluoride **54** as a white solid (348 mg, 76%). R_f = 0.14 (100% CH_2Cl_2); mp = 113 °C; IR (film)/cm^{-1} 2963, 2947, 2894, 2841, 1590, 1510, 1459, 1420, 1400 (SO_2 st as), 1351, 1338, 1249, 1208, 1177, 1130, 1002, 960, 913, 886, 837, 814, 789, 736, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 2 H, 2 × Ar-CH), 5.42 (d, *J* = 7.9 Hz, 2 H, C*H*HOC*H*H), 5.27 (dd, ^2J = 7.9 Hz, J_{HF} = 1.4 Hz, 2 H, CH*H*OCH*H*), 3.89 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 × OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (2 × Ar-C_qOMe), 139.6 (Ar-C_qOMe), 126.6 (Ar-C_qC_q), 105.6 (2 × Ar-CH), 77.0 (CH_2OCH_2), 68.7 (d, $^2J_{CF}$ = 14.8 Hz, C_q), 60.9 (OCH_3), 56.4 (2 × OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ 35.1; HRMS (APCI) *m/z* calcd for $C_{12}H_{15}FO_6S^{\bullet+}$ $[M]^{\bullet+}$: 306.0568, found: 306.0565.

Notes:

***54** was further characterized by X-ray crystallography (see Fig. S55–59).*

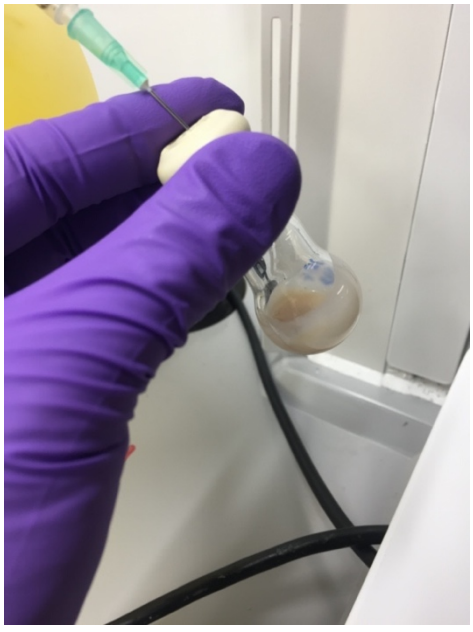
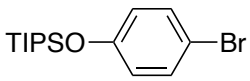


Fig. S28 Solidification of reaction mixture after addition of NaOMe. Picture was taken from a 0.5 mmol scale reaction.

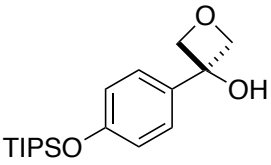
Sulfonyl Fluoride 55

(4-Bromophenoxy)triisopropylsilane (55a')[3]



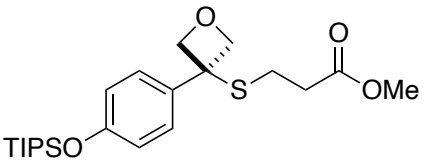
4-Bromophenol (10.38 g, 60.0 mmol, 1.0 equiv) was added portionwise to a solution of 1*H*-imidazole (10.21 g, 150.0 mmol, 2.5 equiv) in anhydrous CH_2Cl_2 (120 mL, 0.5 M) in a 500 mL round bottom flask at 0 °C. After stirring for 5 min, chlorotriisopropylsilane (15.4 mL, 72.0 mmol, 1.2 equiv) was added dropwise at 0 °C. The reaction mixture was warmed to 25 °C, and after stirring for 14 h at 25 °C, the reaction mixture was quenched with distilled water (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by filtration through a plug of silica (100% pentane) afforded aryl bromide **55a'** as a colorless oil (19.61 g, 99%). R_f = 0.68 (100% pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2 H, 2 × Ar-CH), 6.78–6.74 (m, 2 H, 2 × Ar-CH), 1.29–1.20 (m, 3 H, 3 × SiCH), 1.10 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (Ar-C_qOTIPS), 132.2 (2 × Ar-CH), 121.7 (2 × Ar-CH), 113.2 (Ar-C_qBr), 17.8 (6 × SiCH*C*H$_3$), 12.6 (3 × SiCH). The observed characterization data (R_f, ^{1}H, ^{13}C) were consistent with that previously reported in the group.[3]

3-(4-((Triisopropylsilyl)oxy)phenyl)oxetan-3-ol (55a)[3]



n-BuLi (1.60 M in hexanes, 27.5 mL, 44.0 mmol, 1.1 equiv) was added dropwise over 15 min to a solution of aryl bromide **55a'** (13.64 mL, 48.0 mmol, 1.2 equiv) in anhydrous THF (182 mL, 0.22 M) at –78 °C in a 500 mL round bottom flask. After stirring for 20 min, oxetan-3-one (2.56 mL, 40.0 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 15 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (90 mL). The aqueous layer was extracted with diethylether (3 × 90 mL). The organic layers were washed with brine (90 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (10–40% EtOAc/pentane) afforded oxetanol **55a** as a white solid (11.72 g, 91%). R_f = 0.20 (20% EtOAc/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 4.93 (d, 2 H, *J* = 6.9 Hz, C*H*HOC*H*H), 4.89 (d, 2 H, *J* = 6.9 Hz, CH*H*OCH*H*), 2.50 (s, 1 H, OH), 1.31–1.22 (m, 3 H, 3 × SiCH), 1.11 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Ar-C_qOTIPS), 134.7 (Ar-C_qC_q), 125.8 (2 × Ar-CH), 119.9 (2 × Ar-CH), 85.5 (CH_2OCH_2), 75.7 (C_q), 17.9 (6 × SiCH*C*H$_3$), 12.6 (3 × SiCH). The observed characterization data (R_f, ^{1}H, ^{13}C) were consistent with that previously reported in the group.[3]

Methyl 3-((3-(4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)thio)propanoate (55b)



Lithium bis(trifluoromethanesulfonimide) (429 mg, 1.50 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (291 mg, 0.75 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **55a** (4.39 g, 13.6 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (3.0 mL, 27.2 mmol, 2.0 equiv) in non-anhydrous chloroform (27 mL, 0.5 M) in a 100 mL round bottom flask. The reaction flask was placed into a preheated oil bath at 40 °C. The reaction was stirred for 15 min and then heated up to 60 °C in 1.25 h. At 60 °C there was a change in color from clear and colorless to yellow and cloudy (Fig. S21). From the moment of the color change, the reaction was stirred for further 35 min and quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were washed with aq. NaOH (1 M, 35 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (20% Et_2O/pentane) afforded oxetane sulfide **55b** as a colorless oil (4.13 g, 72%). R_f = 0.25 (20% Et_2O/pentane); IR (film)/cm^{-1} 2945, 2867, 1739 (C=O st), 1510, 1262, 987, 910, 883, 681; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.08–7.04 (m, 2 H, 2 × Ar-CH), 6.89–6.86 (m, 2 H, 2 × Ar-CH), 5.20 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.89 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 3.67 (s, 3 H, CO_2CH_3), 2.65 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.38 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me) 1.30–1.21 (m, 3 H, 3 × SiCH), 1.11 (d, *J* = 7.4 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C_q=O), 155.2 (Ar-C_qOTIPS), 134.5 (Ar-C_qC_q), 127.4 (2 × Ar-CH), 120.0 (2 × Ar-CH), 83.3 (CH_2OCH_2), 52.2 (C_q), 51.8 (CO_2CH_3), 34.1 (CH_2CO_2Me), 25.2 (SCH_2), 17.9 (6 × SiCHCH_3), 12.6 (3 × SiCH); HRMS (CI) *m/z* calcd for $C_{22}H_{40}NO_4SSi^+$ $[M+NH_4]^+$: 442.2442, found: 442.2452.

Reaction mixture before heating (T = 25 °C, t = 0 min)

Reaction mixture after heating to 60 °C

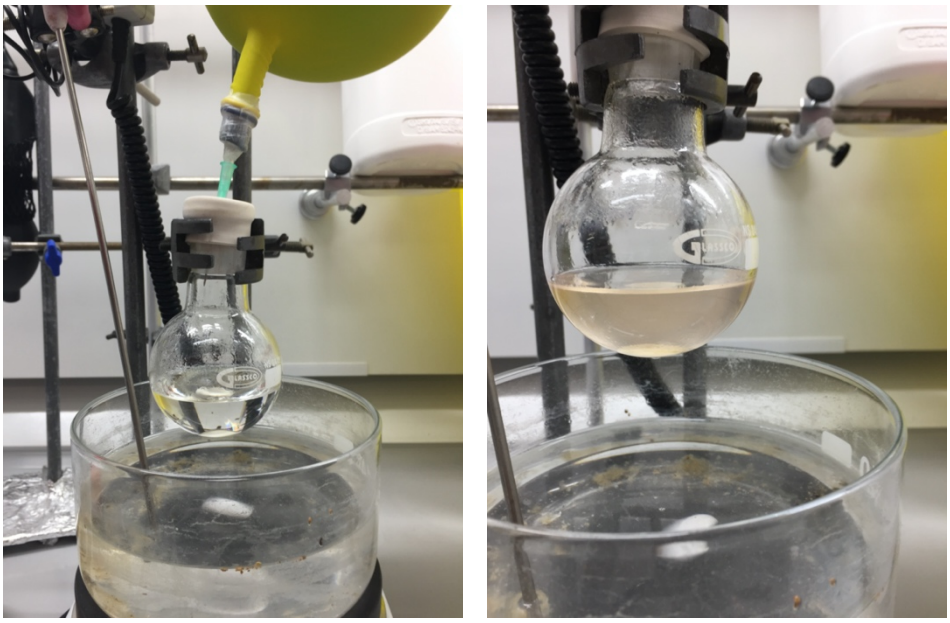
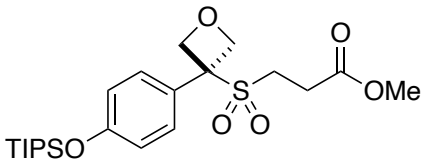


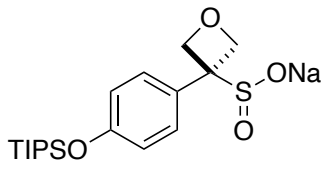
Fig. S29 Color change of reaction mixture from colorless and clear to yellow and cloudy after heating up to 60 °C.

Methyl 3-((3-(4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (55c)



*m*CPBA (3.73 g, 21.6 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **55b** (3.04 g, 7.15 mmol, 1.0 equiv) in CH_2Cl_2 (354 mL, 0.02 M) in a 1000 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 200 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfone **55c** as a white solid (3.17 g, 97%). R_f = 0.36 (30% EtOAc/pentane); IR (film)/cm^{-1} 2944, 2866, 1740 (C=O st), 1513, 1317, 1266, 1249 (SO_2 st as), 1179, 1137, 986, 913, 882, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.14 (m, 2 H, 2 × Ar-CH), 6.96–6.93 (m, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 7.2 Hz, 2H, C*H*HOC*H*H), 5.12 (d, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.70 (s, 3 H, CO_2CH_3), 3.06 (dd, *J* = 8.3 Hz, *J* = 7.0 Hz, 2 H, SO_2CH_2), 2.67 (dd, *J* = 8.3 Hz, *J* = 7.0 Hz, 2 H, CH_2CO_2Me), 1.32–1.23 (m, 3 H, 3 × SiCH), 1.11 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C_q=O), 157.1 (Ar-C_qOTIPS), 129.3 (2 × Ar-CH), 125.8 (Ar-C_qC_q), 120.4 (2 × Ar-CH), 76.3 (CH_2OCH_2), 68.3 (C_q), 52.4 (CO_2CH_3), 43.4 (CH_2CO_2Me), 25.0 (SO_2CH_2), 17.8 (6 × SiCHCH_3), 12.6 (3 × SiCH); HRMS (CI) *m/z* calcd for $C_{22}H_{40}NO_6SSi^+$ $[M+NH_4]^+$: 474.2340, found: 474.2343.

Sodium 3-(4-((triisopropylsilyl)oxy)phenyl)oxetane-3-sulfinate (55d)



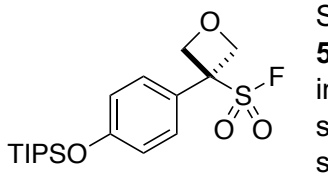
Prepared using elimination conditions **EI-I**. Sulfone **55c** (685 mg, 7.74 mmol, 1.0 equiv) was added to a solution of NaH (60% in mineral oil, 63.0 mg, 1.60 mmol, 1.05 equiv) in THF (8.8 mL, 0.17 M). The reaction mixture was stirred at 25 ºC for 1 h then quenched with anhydrous methanol (5 mL) and concentrated *in vacuo* using a rotatory evaporator to afford sulfinate salt **55d** as a white solid (545 mg, 93%). R_f = 0.20 (15% MeOH/CH_2Cl_2); Melting point not determined, degradation observed at 250 ºC; IR (film)/cm^{-1} 2944, 2867, 1509, 1260, 1034, 984, 971, 912, 882, 834, 740, 685; ^{1}H NMR (400 MHz, ($^{13}CD_3)_2SO$) δ 6.78–6.73 (m, 4 H, 4 × Ar-CH), 4.89 (d, *J* = 5.6 Hz, C*H*HOC*H*H), 4.47 (d, *J* = 5.6 Hz, CH*H*OCH*H*), 1.28–1.19 (m, 3 H, 3 × SiCH), 1.07 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, ($^{13}CD_3)_2SO$) δ 153.1 (Ar-C_qOTIPS), 127.5 (2 × Ar-CH), 124.1 (Ar-C_qC_q), 118.2 (2 × Ar-CH), 76.2 (CH_2OCH_2), 66.7 (C_q), 17.8 (6 × SiCH*C*H$_3$), 12.1 (3 × SiCH); HRMS (NSI) *m/z* calcd for $C_{18}H_{29}O_4SSi^-$ [M-Na]$^-$: 369.1561, found: 369.1561.

Notes:

*It was shown that sulfinate **55d** degrades in solution over time (see Fig. S1) and hence, sulfonyl fluoride **55** was prepared primarily by the telescoped process **EI-III**. This compound needs to be used directly for the fluorination step without analysis or characterisation since the more lipophilic oxetane sulfinate salts are unstable in solution.*

Signals from degradation products can also be seen in the ^{13}C NMR spectrum.

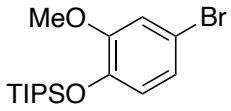
3-(4-((Triisopropylsilyl)oxy)phenyl)oxetane-3-sulfonyl fluoride (55)



Sulfonyl fluoride **55** was synthesized in a telescope process from sulfone **55c** using the elimination protocol **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions. Sodium methoxide (5.4 M solution in MeOH, 0.36 mL, 1.90 mmol, 1.0 equiv) was added dropwise to a solution of oxetane sulfone **55c** (884 mg, 1.90 mmol, 1.0 equiv) in anhydrous THF (3.9 mL, 0.5 M) in a 10 mL round bottom flask. Oxetane sulfinate salt **55d** did not precipitate after addition of base and there was no change in color. The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfinate **55d** as a light-yellow solid, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (1.031 g, 2.91 mmol, 1.5 equiv) was added to anhydrous MeOH (9.8 mL, 0.2 M) at 0 °C in a 25 mL round bottom flask, then stirred for 5 min. Sulfinate salt **55d** was added portionwise. The reaction mixture was stirred for at 0 °C for 1 h, then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (15 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column(80% CH_2Cl_2/pentane) afforded oxetane sulfonyl fluoride **55** as a white solid (478 mg, 63% over two steps). R_f = 0.71 (100% CH_2Cl_2); R_f = 0.60 (100% CH_2Cl_2); mp = 63–64 ºC, IR (film)/cm^{-1} 2948, 2868, 1607, 1510, 1270, 1268, 901, 881, 836, 795, 684, 653; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2 H, 2 × Ar-CH), 6.97–6.93 (m, 2 H, 2 × Ar-CH), 5.42 (d, *J* = 7.7 Hz, 2 H, C*H*HOC*H*H), 5.23 (dd, ^2J = 7.7 Hz, J_{HF} = 1.5 Hz, 2 H, CH*H*OCH*H*), 1.32–1.23 (m, 3 H, 3 × SiCH), 1.11 (d, *J* = 7.4 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (Ar-C_qOTIPS), 129.4 (2 × Ar-CH), 123.4 (Ar-C_qC_q), 120.4 (2 × Ar-CH), 77.1 (CH_2OCH_2), 68.1 (d, $J_{C\text{-}F}$ = 14.4 Hz, C_q), 17.9 (6 × SiCH*C*H$_3$), 12.7 (3 × SiCH); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.3, HRMS (CI) *m/z* calcd for $C_{18}H_{33}FNO_4SSi^+$ [M+NH_4]$^+$: 406.1878, found: 406.1875.

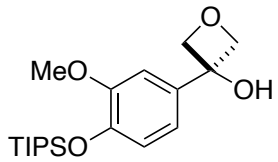
Sulfonyl Fluoride 56

(4-Bromo-2-methoxyphenoxy)triisopropylsilane (56a')



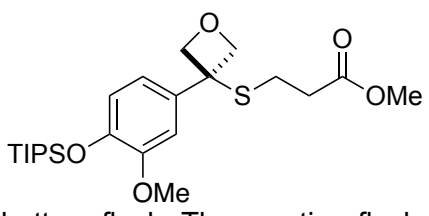
4-Bromo-2-methoxyphenol (6.09 g, 30.0 mmol, 1.0 equiv) was added dropwise to a solution of 1*H*-imidazole (5.106 g, 75.0 mmol, 2.5 equiv) in anhydrous CH_2Cl_2 (60 mL, 0.5 M) in a 250 mL round bottom flask at 0 °C. After stirring for 5 min, chlorotriisopropylsilane (7.7 mL, 36.0 mmol, 1.2 equiv) was added dropwise at 0 °C. The reaction mixture was warmed to 25 °C, stirred for 21 h and then quenched with distilled water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by filtration through a plug of silica (0–15% pentane) afforded a mixture of **56a'** with triisopropyl silanol which was purified by flash column chromatography (0–2% EtOAc/pentane) to afford TIPS-protected aryl bromide **56a'** as a colorless oil (10.42 g, 97%). R_f = 0.83 (10% EtOAc/pentane); IR (film)/cm^{-1} 2945, 2866, 1584, 1498, 1465, 1398, 1301, 1267, 1226, 1182, 1126, 1074, 1033, 910, 883, 835, 809, 734, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 2.4 Hz, 1H, Ar-C_qAr-CHCBr), 6.92 (dd, ^3J = 8.3 Hz, ^4J = 2.4 Hz, 1 H, Ar-CHAr-C*H*CBr), 6.74 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 3.80 (s, 3 H, OCH_3), 1.23 (hept, *J* = 7.3 Hz, 3 H, 3 × SiCH), 1.09 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (Ar-C_qOMe), 144.8 (Ar-C_q(OTIPS)), 123.4 (Ar-CH), 121.5 (Ar-CH), 115.4 (Ar-C_qAr-*C*HCBr), 113.0 (Ar-C_qBr), 55.6 (OCH_3), 17.8 (6 × SiCH*C*H$_3$), 12.8 (3 × SiCH). The observed characterization data (IR, ^{1}H, ^{13}C) were consistent with that previously reported.[31]

3-(3-Methoxy-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol (56a)



n-BuLi (1.51 M in hexanes, 17.7 mL, 26.8 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of aryl bromide **56a'** (10.42 g, 29.0 mmol, 1.3 equiv) in anhydrous THF (100 mL, 0.22 M) at –78 °C in a 250 mL round bottom flask. After stirring for 30 min, oxetan-3-one (1.43 mL, 22.3 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 30 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (65 mL). The aqueous layer was extracted with diethylether (3 × 65 mL). The organic layers were washed with brine (65 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50–60% Et_2O/pentane) afforded oxetanol **56a** as a colorless oil which crystallized in the freezer (7.26 g, 92%). R_f = 0.28 (60% Et_2O/pentane); mp = 60 °C; IR (film)/cm^{-1} 3392 (br OH), 2945, 2866, 1603, 1517, 1465, 1413, 1308, 1274, 1219, 1167, 1129, 1036, 969, 928, 883, 850, 712, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 2.2 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 7.00 (dd, ^3J = 8.3 Hz, ^4J = 2.2 Hz, 1 H, Ar-CH), 6.90 (d, ^3J = 8.3 Hz, 1 H, Ar-C_q(OTIPS)Ar-CH), 4.92 (d, *J* = 6.8 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 6.8 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 2.68 (br s, 1 H, OH), 1.32–1.30 (m, 3 H, 3 × SiCH), 1.10 (d, *J* = 7.4 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (Ar-C_qOMe), 145.3 (Ar-C_q(OTIPS)), 135.4 (Ar-$C_q$$C_q$), 120.3 (Ar-CH), 116.8 (Ar-CH), 108.7 (Ar-C_qAr-*C*HAr-C_q), 85.6 (CH_2OCH_2), 75.9 (C_q), 55.6 (OCH_3), 17.9 (6 × SiCH*C*H$_3$), 12.9 (3 × SiCH); HRMS (ESI) *m/z* calcd for $C_{19}H_{31}O_3Si$ [M–OH]: 335.2042, found: 335.2034.

Methyl 3-((3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)thio)propanoate (56b)



Lithium bis(trifluoromethanesulfonimide) (157.9 mg, 0.55 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (106.5 mg, 0.275 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **56a** (1.76 g, 5.0 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (1.08 mL, 10.0 mmol, 2.0 equiv) in non-anhydrous chloroform (10 mL, 0.5 M) in a 50 mL round bottom flask. The reaction flask was placed into a preheated oil bath at 40 °C. The reaction was stirred for 15 min and then heated up to 70 °C in 1 h. At 70 °C there was a change in color from clear

and colorless to dark orange (Fig. S22). From the moment of the color change, the reaction was stirred for further 25 min and quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with aq. NaOH (1 M, 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (30% Et_2O/pentane) afforded oxetane sulfide **56b** as a colorless oil which crystallized in the freezer to a white solid (1.36 g, 60%). R_f = 0.25 (30% Et_2O/pentane); mp = 49 °C; IR (film)/cm^{-1} 2945, 2866, 1737 (C=O st), 1513, 1465, 1308, 1275, 1249, 1215, 1133, 1036, 988, 913, 883, 813, 734, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.1 Hz, 1 H, (TIPSO)C_qAr-CH), 6.67 (d, *J* = 2.2 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 6.64 (dd, ^{3}*J* = 8.1 Hz, ^{4}*J* = 2.2 Hz, 1 H, Ar-CH), 5.20 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, Ar-$C_q$$OCH_3$), 3.66 (s, 3 H, CO_2CH_3), 2.64 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.36 (t, *J* = 7.4 Hz, 2 H, C*H*$_2CO_2$Me), 1.30–1.20 (m, 3 H, 3 × SiCH), 1.10 (d, *J* = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C_q=O), 151.1 (Ar-C_qOMe), 144.8 (Ar-C_q(OTIPS)), 135.1 (Ar-*C*$_q$$C_q$), 120.0 (Ar-CH), 118.6 (Ar-CH), 110.3 (Ar-C_qAr-*C*HAr-C_q), 83.3 (CH_2OCH_2), 55.5 (Ar-C_qO*C*H$_3$), 52.5 (Ar-C_q*C*$_q$), 51.8 (CO_2*C*H$_3$), 34.2 (*C*H$_2CO_2$Me), 25.2 (SCH_2), 17.9 (6 × SiCH*C*H$_3$), 12.8 (3 × SiCH); HRMS (APCI) *m/z* calcd for $C_{23}H_{38}O_5SSiNa^+$ $[M+Na]^+$: 477.2101, found: 477.2080; also found: *m/z* calcd for $C_{19}H_{31}O_3Si^+$ $[M–SCH_2CH_2CO_2Me]^+$: 335.2037, found: 335.2024.

Reaction mixture before heating (T = 25 °C, t = 0 min) *Reaction mixture after heating to 70 °C*

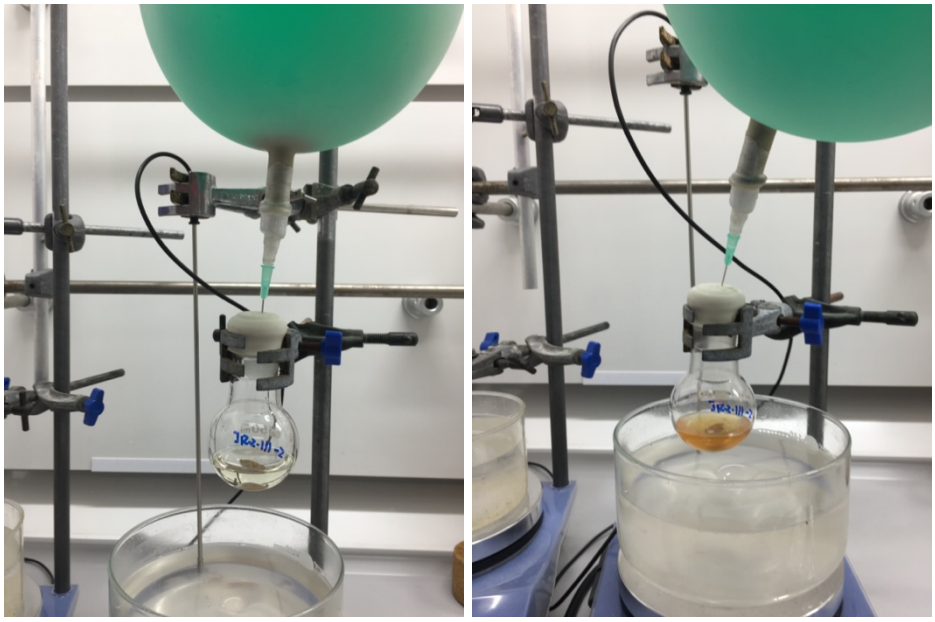
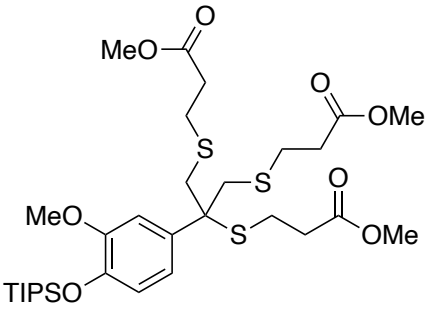


Fig. S30 Reaction mixture before and after heating. Start of reaction is marked by a sharp change in color. Here from clear and colorless to dark orange.

Notes:

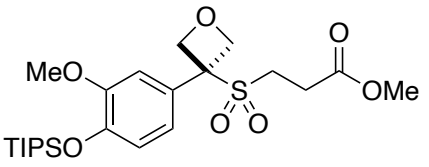
*On a 0.25 mmol scale, a trisulfide side product (**56b''**) was isolated in 11% yield (18.2 mg, colorless oil):*

Trimethyl 3,3',3''-((2-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)propane-1,2,3-triyl)tris(sulfanediyl))tripropionate (56b'')



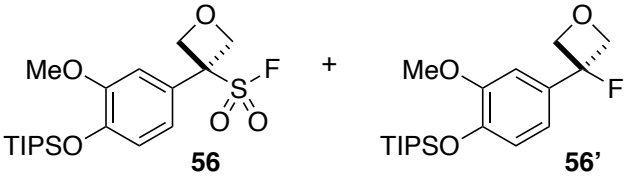
R_f = 0.11 (30% Et_2O/pentane); IR (film)/cm^{-1} 2948, 2866, 2255, 1737 (C=O st), 1603, 1513, 1465, 1413, 1357, 1275, 1245, 1178, 1141, 1036, 910, 816, 731, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 2.3 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 6.89 (dd, ^3J = 8.3 Hz, ^4J = 2.3 Hz, 1 H, Ar-CH), 6.81 (d, J = 8.3 Hz, 1 H, (TIPSO)C_qAr-CH), 3.83 (s, 3 H, Ar-$C_q$$OCH_3$), 3.69 (s, 6 H, 2 × CO_2CH_3), 3.62 (s, 3 H, CO_2CH_3), 3.39 (d, J = 12.8 Hz, 2 H, 2 × C_qC*H*HS), 3.33 (d, J = 12.8 Hz, 2 H, 2 × C_qCH*H*S), 2.71–2.66 (m, 4 H, 2 × SCH_2), 2.58–2.55 (m, 4 H, 2 × C*H*$_2CO_2$Me), 2.46–2.42 (m, 2 H, SCH_2), 2.35–2.31 (m, 2 H, C*H*$_2CO_2$Me), 1.30–1.19 (m, 3 H, 3 × SiCH), 1.08 (d, J = 7.4 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (2 × C_q=O), 172.0 (C_q=O), 150.9 (Ar-C_qOMe), 144.9 (Ar-C_q(OTIPS)), 134.6 (Ar-*C*$_q$C$_q$), 119.8 (Ar-CH), 119.7 (Ar-CH), 111.9 (Ar-C_qAr-*C*HAr-C_q), 56.4 (C_q), 55.6 (Ar-C_qO*C*H$_3$), 51.8 (2 × CO_2*C*H$_3$), 51.7 (CO_2*C*H$_3$), 40.8 (2 × C_q*C*H$_2$S), 34.8 (2 × *C*H$_2CO_2$Me), 33.7 (*C*H$_2CO_2$Me), 28.4 (2 × S*C*H$_2$CH$_2$), 24.4 (S*C*H$_2$CH$_2$), 17.8 (6 × SiCH*C*H$_3$), 12.8 (3 × SiCH); HRMS (APCI) *m/z* calcd for $C_{31}H_{52}O_8S_3Si^{35}Cl^-$ [M+^{35}Cl]$^-$: 711.2288, found: 711.2286.

Methyl 3-((3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (56c)



*m*CPBA (1.45 g, 8.4 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **56b** (1.27 g, 2.8 mmol, 1.0 equiv) in CH_2Cl_2 (140 mL, 0.02 M) in a 250 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 70 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfone **56c** as a white solid (1.36 g, quant.). R_f = 0.21 (50% Et_2O/pentane); mp = 153 °C; IR (film)/cm^{-1} 2945, 2866, 1741 (C=O st), 1603, 1512, 1465, 1364, 1312 (SO_2 st as), 1282 (SO_2 st sy), 1219, 1174, 1133, 1100, 1066, 1033, 917, 883, 813, 734, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93–6.90 (m, 1 H, (TIPSO)C_qAr-CH), 6.76–6.73 (m, 2 H, 2 × Ar-CH), 5.40 (d, J = 7.1 Hz, 2 H, C*H*HOC*H*H), 5.13 (d, J = 7.1 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, Ar-$C_q$$OCH_3$), 3.69 (s, 3 H, CO_2CH_3), 3.04 (t, J = 7.6 Hz, 2 H, SCH_2), 2.64 (t, J = 7.6 Hz, 2 H, C*H*$_2CO_2$Me), 1.31–1.21 (m, 3 H, 3 × SiCH), 1.10 (d, J = 7.3 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C_q=O), 151.3 (Ar-C_qOMe), 146.7 (Ar-C_q(OTIPS)), 126.4 (Ar-*C*$_q$C$_q$), 120.5 (Ar-CH), 120.4 (Ar-CH), 111.9 (Ar-C_qAr-*C*HAr-C_q), 76.3 (CH_2OCH_2), 68.6 (C_q), 55.7 (Ar-C_qO*C*H$_3$), 52.4 (CO_2*C*H$_3$), 43.6 (*C*H$_2CO_2$Me), 26.1 (SO_2CH_2), 17.8 (6 × SiCH*C*H$_3$), 12.8 (3 × SiCH); HRMS (ESI) *m/z* calcd for $C_{23}H_{42}NO_7SSi$ [M+NH_4]: 504.2451, found: 504.2437.

3-(3-Methoxy-4-((triisopropylsilyl)oxy)phenyl)oxetane-3-sulfonyl fluoride (56) and (4-(3-fluorooxetan-3-yl)-2-methoxyphenoxy)triisopropylsilane (56')



56 + **56'**

Sulfonyl fluoride **56** was synthesized in a telescope process from sulfone **56c** using the elimination protocol **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions. Sodium methoxide (5.4 M solution in MeOH, 0.22 mL, 1.20 mmol, 1.0 equiv) was added dropwise to a suspension of oxetane sulfone **56c** (583 mg, 1.20 mmol, 1.0 equiv) in anhydrous THF (2.4 mL, 0.5 M) in a 10 mL round bottom flask. The reaction mixture turns from colorless cloudy to dark orange and clear upon addition of base (Fig. S23). The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a

rotatory evaporator to afford oxetane sulfinate **56d** as a white solid, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (637.6 mg, 1.8 mmol, 1.5 equiv) was added to anhydrous MeOH (6.0 mL, 0.2 M) at 0 °C in a 25 mL round bottom flask, then stirred for 5 min. Sulfinate salt **56d** was added portionwise. The reaction mixture was stirred for at 0 °C for 1 h, then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (15 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (50% CH_2Cl_2/pentane) afforded a 95:5 mixture of oxetane sulfonyl fluoride **56** and oxetane fluoride **56'** as a white solid (337 mg, 66%). R_f = 0.31 (50% CH_2Cl_2/pentane); mp = 57-60 °C; IR (film)/cm^{-1} 2945, 2892, 2870, 1603, 1517, 1465, 1402 (SO_2 st as), 1320, 1282, 1260, 1208, 1182, 1133, 1070, 1036, 999, 917, 883, 824, 787, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.2 Hz, 1 H, (TIPSO)C$_q$Ar-CH), 6.73 (dd, ^3J = 8.2 Hz, ^4J = 2.3 Hz, 1 H, Ar-CH), 6.68 (d, *J* = 2.3 Hz, 1 H, Ar-C$_q$Ar-CHAr-C$_q$), 5.42 (d, *J* = 7.7 Hz, 2 H, C*H*HOC*H*H), 5.25 (dd, ^2J = 7.1 Hz, J_{HF} = 1.4 Hz, 2 H, CH*H*OCH*H*), 5.11 (dd, ^2J = 7.7 Hz, J_{HF} = 1.4 Hz, 0.05 H, C*H*HO, **56'**), 5.06 (dd, ^2J = 7.7 Hz, J_{HF} = 1.1 Hz, 0.05 H, C*H*HO, **56'**), 4.92 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 0.05 H, CH*H*O, **56'**), 4.87 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 0.05 H, CH*H*O, **56'**), 3.82 (s, 3 H, Ar-C$_q$OCH$_3$), 1.31–1.21 (m, 3.29 H, 3 × SiCH, **56** + **56'**), 1.10 (d, *J* = 7.4 Hz, 19.1 H, 6 × SiCHC*H*$_3$, **56** + **56'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (Ar-C$_q$OMe), 147.4 (Ar-C$_q$(OTIPS)), 123.8 (Ar-*C*$_q$C$_q$), 121.1 (Ar-CH), 120.5 (Ar-CH), 111.8 (Ar-C$_q$Ar-*C*HAr-C$_q$), 77.1 (CH_2OCH_2), 68.5 (d, $^2J_{CF}$ = 14.6 Hz, C$_q$), 55.7 (OCH_3), 17.8 (6 × SiCH*C*H$_3$), 12.9 (3 × SiCH); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.5 (**56**), –146.1 (**56'**); HRMS (APCI) *m/z* calcd for $C_{19}H_{31}O_3Si^+$ [M$_{\mathbf{54}}$–SO_2F or M$_{\mathbf{54'}}$–F]$^+$: 335.2037, found: 335.2037.

Notes:

*The R_f values of **56** and **56'** are very similar and attempts to further purify the obtained mixture by flash column chromatography led to significant loss in mass of sulfonyl fluoride **56** due to degradation on silica without improvement in purity. All following oxetane amination reactions were carried out successfully with this mixture showing that the presence of oxetane fluoride in the reaction mixture does not interfere with the oxetane amination.*

***56** was further characterized by X-ray crystallography (see Fig. S60–61).*

Reaction mixture before (left) and after (right) addition of base

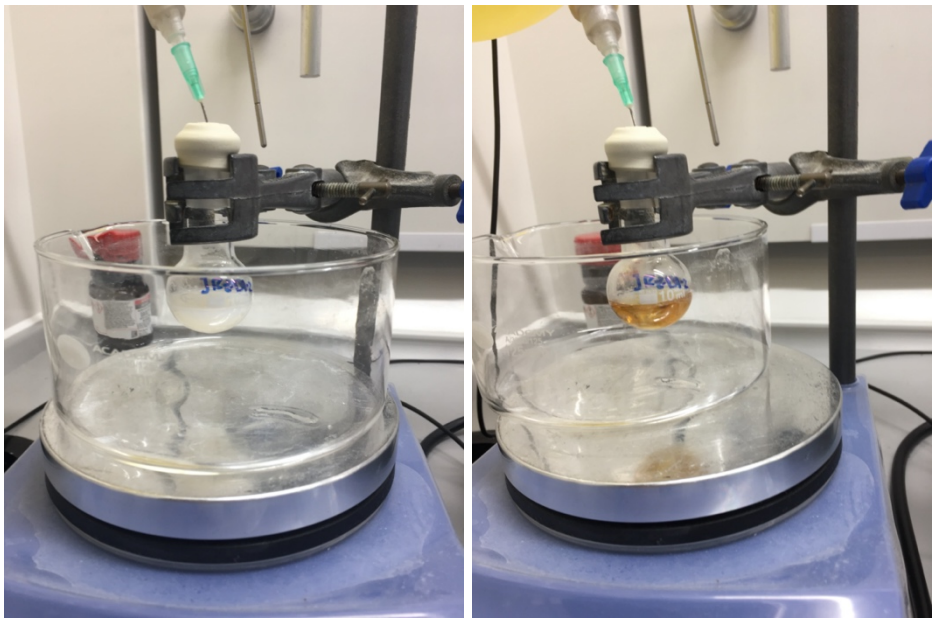
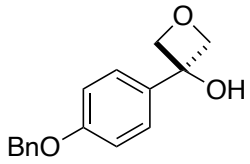


Fig. S31 Immediate change in appearance of reaction mixture after addition of base, including change in solubility properties.

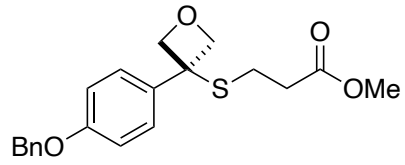
Sulfonyl Fluoride 57

3-(4-(Benzyloxy)phenyl)oxetan-3-ol (57a)[3]



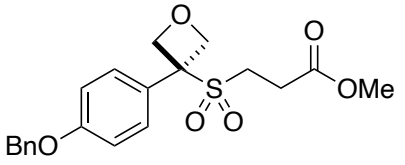
n-BuLi (2.40 M in hexanes, 10.0 mL, 24.0 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of 1-(benzyloxy)-4-bromobenzene (6.84 g, 26.0 mmol, 1.3 equiv) in anhydrous THF (90 mL, 0.22 M) at –78 °C in a 250 mL round bottom flask. After stirring for 30 min, oxetan-3-one (1.28 mL, 20.0 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After a further 45 min at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (80 mL). The aqueous layer was extracted with diethylether (3 × 100 mL). The organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetanol **57a** as a white solid (4.73 g, 92%). R_f = 0.24 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.32 (m, 7 H, 7 × Ar-CH), 7.05–7.01 (m, 2 H, 2 × Ar-CH), 5.10 (s, 2 H, Ph-CH_2), 4.93 (d, *J* = 6.9 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, *J* = 6.9 Hz, 2 H, CH*H*OCH*H*), 2.42 (br s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_qOBn), 136.8 (Ph-C_q), 134.7 (Ar-$C_q$$C_q$), 128.6 (2 × Ar-CH), 128.0 (Ar-CH), 127.4 (2 × Ar-CH), 125.9 (2 × Ar-CH), 115.0 (2 × Ar-CH), 85.5 (CH_2OCH_2), 75.7 (C_q), 70.1 (Ph-$C_q$$CH_2$). The observed characterization data (R_f, ^{1}H, ^{13}C) were consistent with that previously reported in the group.[3]

Methyl 3-((3-(4-(benzyloxy)phenyl)oxetan-3-yl)thio)propanoate (57b)



Lithium bis(trifluoromethanesulfonimide) (316 mg, 1.10 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (213 mg, 0.55 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **57a** (2.56 g, 10.0 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (2.2 mL, 20.1 mmol, 2.0 equiv) in non-anhydrous chloroform (20 mL, 0.5 M) in a 100 mL round bottom flask. The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (30% EtOAc/hexane) afforded oxetane sulfide **57b** as a white solid (2.63 g, 73%). R_f = 0.40 (35% EtOAc in hexane); IR (film)/cm^{-1} 2947, 2868, 1736 (C=O st), 1606, 1513, 1435, 1352, 1247, 1179, 1134, 1011, 983, 837, 823, 751, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.33 (m, 5 H, 5 × Ph-CH), 7.14 (d, *J* = 8.3 Hz, 2 H, 2 × Ar$_{(p\text{-OBn})}$-CH), 6.98 (d, *J* = 8.3 Hz, 2 H, 2 × Ar$_{(p\text{-OBn})}$-CH), 5.19 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 5.08 (s, 2 H, $PhCH_2$), 4.90 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.68 (s, 3 H, CO_2CH_3), 2.68 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.43 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_q=O), 157.8 (Ar-C_qOBn), 136.7 (Ph-$C_q$$CH_2$), 134.5 (Ar-$C_q$$C_q$), 128.6 (2 × Ph-CH), 128.0 (Ph-CH), 127.5 (2 × Ar$_{(p\text{-OBn})}$-CH), 127.4 (2 × Ph-CH), 114.9 (2 × Ar$_{(p\text{-OBn})}$-CH), 83.1 (CH_2OCH_2), 70.0 (Ph-$C_q$$CH_2$), 52.1 ($C_q$), 51.8 ($CO_2CH_3$), 34.0 ($CH_2CO_2Me$), 25.1 ($SCH_2$); HRMS (NSI) *m/z* calcd for $C_{20}H_{22}SO_4Na^+$ $[M+Na]^+$: 381.1131, found: 381.1136.

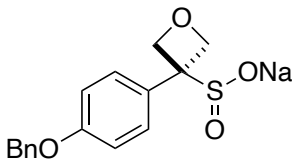
Methyl 3-((3-(4-(benzyloxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (57c)



*m*CPBA (3.37 g, 19.5 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **57b** (2.33 g, 6.50 mmol, 1.0 equiv) in CH_2Cl_2 (325 mL, 0.02 M) in a 1000 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 200 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (75% EtOAc/hexane) afforded oxetane sulfone **57c** as a white solid (2.31 g, 91%). R_f = 0.54 (75% EtOAc/hexane); mp = 129–131 °C; IR (film)/cm^{-1} 2953, 1744 (C=O st), 1516, 1435, 1306, 1271, 1248 (SO_2 st as), 1190, 1134, 1095, 1011, 998, 934, 841, 824, 740, 693; ^{1}H NMR

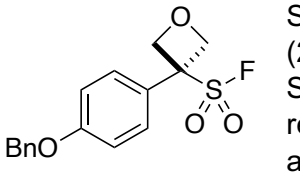
(400 MHz, $CDCl_3$) δ 7.45–7.34 (m, 5 H, 5 × Ph-CH), 7.25–7.21 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 7.07–7.03 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 5.40 (d, *J* = 7.2 Hz, 2 H, C*H*HOC*H*H), 5.13 (d, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 5.10 (s, 2 H, $PhCH_2$), 3.71 (s, 3 H, CO_2CH_3), 3.09 (dd, *J* = 8.2, 7.1 Hz, 2 H, SO_2CH_2), 2.72 (dd, *J* = 8.2, 7.1 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_q=O), 159.5 (Ar-C_qOBn), 136.3 (Ph-C_qCH_2), 129.5 (2 × $Ar_{(p\text{-}OBn)}$-CH), 128.7 (2 × Ph-CH), 128.2 (Ph-CH), 127.5 (2 × Ph-CH), 125.8 (Ar-C_qC_q), 115.4 (2 × $Ar_{(p\text{-}OBn)}$-CH), 76.3 (CH_2OCH_2), 70.2 (Ph-C_qCH_2), 68.3 (C_q), 52.4 (CO_2CH_3), 43.2 (CH_2CO_2Me), 25.9 (SO_2CH_2); HRMS (NSI) *m/z* calcd for $C_{20}H_{26}NO_6S^+$ $[M+NH_4]^+$: 408.1475, found: 408.1479.

Sodium 3-(4-(benzyloxy)phenyl)oxetane-3-sulfinate (57d)



Prepared using elimination conditions **EI-I**. Sulfone **57c** (2.15 g, 5.50 mmol, 1.0 equiv) was added to a solution of NaH (60% in mineral oil, 231 mg, 5.80 mmol, 1.05 equiv) in THF (35 mL, 0.16 M). The reaction mixture was stirred at 25 ºC for 1 h then quenched with anhydrous methanol (15 mL) and concentrated *in vacuo* using a rotatory evaporator to afford sulfinate salt **57d** as a white solid (1.80 g, 100%). R_f = 0.15 (15% MeOH/CH_2Cl_2); melting point not determined, degradation observed at 250 ºC; IR (film)/cm^{-1} 3617, 3312, 2889, 1511, 1250, 1029, 960, 753; ^1H NMR (400 MHz, D_2O) δ 7.52–7.38 (m, 5 H, 5 × Ph-CH), 7.10–7.06 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 7.01–6.97 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 5.17 (s, 2 H, $PhCH_2$), 5.09 (d, *J* = 7.1 Hz, C*H*HOC*H*H), 4.97 (d, *J* = 7.1 Hz, CH*H*OCH*H*); ^{13}C NMR (101 MHz, D_2O) δ 157.1 (Ar-C_qOBn), 136.5 (Ph-C_qCH_2), 129.1 (Ar-C_qC_q), 128.8 (2 × Ph-CH), 128.5 (2 × $A_{(p\text{-}OBn)}$r-CH), 128.4 (Ph-CH), 128.1 (2 × Ph-CH), 115.0 (2 × $Ar_{(p\text{-}OBn)}$-CH), 76.6 (CH_2OCH_2), 70.3 (Ph-C_qCH_2), 67.0 (C_q); HRMS (NSI) *m/z* calcd for $C_{16}H_{15}O_4S^-$ $[M-Na]^-$: 303.0697, found: 303.0701.

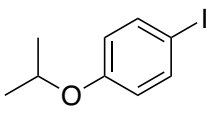
3-(4-(Benzyloxy)phenyl)oxetane-3-sulfonyl fluoride (57)



Selectfluor (2.13 g, 6.00 mmol, 1.5 equiv) was added to anhydrous MeOH (20.0 mL, 0.2 M) at 0 ºC in a 50 mL round bottom flask, then stirred for 5 min. Sulfinate salt **57d** (1.31 g, 4.00 mmol, 1.0 equiv) was added portionwise. The reaction mixture was stirred at 0 ºC for 1 h then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (30 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (100% CH_2Cl_2) afforded sulfonyl fluoride **57** as a white solid (854 mg, 66%). R_f = 0.46 (100% CH_2Cl_2); mp = 112–114 ºC; IR (film)/cm^{-1} 2895, 2361, 1513, 1397 (SO_2 st as), 1249, 1211, 1185, 1007, 1000, 830, 781, 755, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.34 (m, 5 H, 5 × Ph-CH), 7.23–7.19 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 7.09–7.05 (m, 2 H, 2 × $Ar_{(p\text{-}OBn)}$-CH), 5.43 (d, *J* = 7.6 Hz, C*H*HOC*H*H), 5.23 (dd, *J* = 7.6, 1.5 Hz, CH*H*OCH*H*), 5.11 (s, 2 H, $PhCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ160.0 (Ar-C_qOBn), 136.2 (Ph-C_qCH_2), 129.6 (2 × $Ar_{(p\text{-}OBn)}$-CH), 128.7 (2 × Ph-CH), 128.2 (Ph-CH), 127.4 (2 × Ph-CH), 123.5 (Ar-C_qC_q), 115.5 (2 × $Ar_{(p\text{-}OBn)}$-CH), 77.1 (CH_2OCH_2), 70.2 (Ph-C_qCH_2), 68.1 (d, $J_{C\text{-}F}$ = 14.5 Hz, C_q); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.4; HRMS (CI) *m/z* calcd for $C_{16}H_{19}FNO_4S^+$ $[M+NH_4]^+$: 340.1013, found: 340.1019.

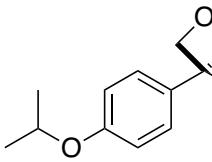
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1-Iodo-4-(propan-2-yloxy)benzene (58a')



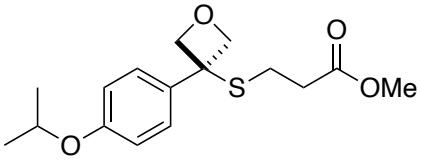
Using conditions developed by Larrosa,[32] I_2 (20.3 g, 80.0 mmol, 4.0 equiv), anhydrous K_3PO_4 (4.25 g, 20.0 mmol, 1.0 equiv) and 4-isopropoxybenzoic acid (3.60 g, 20.0 mmol, 1.0 equiv) were dissolved in acetonitrile (100 mL, 0.2 M) at 25 °C and stirred at 100°C for a further 18 h. The reaction mixture was allowed to cool to 25 °C and quenched first with 10% aq. $Na_2S_2O_3$ (200 mL) and then with sat. aq. $NaHCO_3$ (100 mL). The acetonitrile/water mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash chromatography (1% EtOAc/pentane) afforded **58a'** as a colorless oil (4.91 g, 94%). R_f = 0.25 (1% EtOAc/pentane); IR(film)/cm^{-1} 2974, 2930, 1580, 1480, 1278, 1237, 1178, 950, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2 H, 2 × Ar-CH), 6.69–6.65 (m, 2 H, 2 × Ar-CH), 4.51 (hept, *J* = 6.0 Hz, 1 H, CH), 1.33 (d, *J* = 6.0 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (Ar-C_qO*i*-Pr), 138.2 (2 × Ar-CH), 118.2 (2 × Ar-CH), 82.3 (Ar-C_qI), 70.0 (CH), 21.9 (2 × CH_3). The observed characterization data (IR, ^{1}H, ^{13}C) were consistent with that previously reported.[33]

3-(4-Isopropoxyphenyl)oxetan-3-ol (58a)



n-BuLi (1.51 M in hexanes, 2.7 mL, 4.08 mmol, 1.1 equiv) was added dropwise over 5 min to a solution of aryl iodide **58a'** (1.16 g, 4.43 mmol, 1.2 equiv) in anhydrous THF (17 mL, 0.2 M) at –78 °C in a 50 mL round bottom flask. After stirring for 30 min, oxetan-3-one (0.24 mL, 3.74 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 30 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (20 mL). The aqueous layer was extracted with diethylether (4 × 20 mL). The organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash chromatography (40% EtOAc/pentane) afforded oxetanol **58a** as a white solid (490 mg, 63%). R_f = 0.29 (40% EtOAc/pentane); mp = 64–65 °C; IR (film)/cm^{-1} 3340 (br OH), 2974, 2904, 1610, 1513, 1435, 1371, 1237, 1174, 1118, 958, 876, 824; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2 H, 2 × Ar-CH), 6.95–6.91 (m, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 7.0 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, *J* = 7.0 Hz, 2 H, CH*H*OCH*H*), 4.58 (hept, *J* = 6.0 Hz, 1 H, CH), 2.43 (s, 1 H, OH), 1.36 (d, *J* = 6.0 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (Ar-C_qO*i*-Pr), 134.2 (Ar-C_qC_q), 125.9 (2 × Ar-CH), 115.8 (2 × Ar-CH), 85.5 (CH_2OCH_2), 75.7 (C_q), 69.9 (CH), 22.0 (2 × CH_3); HRMS (APCI) *m/z* calcd for $C_{12}H_{15}O_2^+$ [M-OH]$^+$: 191.1067, found: 191.1067.

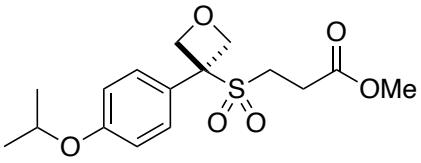
Methyl 3-((3-(4-isopropoxyphenyl)oxetan-3-yl)thio)propanoate (58b)



Lithium bis(trifluoromethanesulfonimide) (126 mg, 0.44 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (77.5 mg, 0.20 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **58a** (833 mg, 4.00 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (0.89 mL, 8.22 mmol, 2.1 equiv) in non-anhydrous chloroform (8 mL, 0.5 M) in a 25 mL round bottom flask. The reaction mixture was stirred at 50 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash chromatography (20% EtOAc/pentane) afforded sulfide **58b** as a white solid (1.12 g, 90%). R_f = 0.27 (20 % EtOAc/pentane); mp = 49–50 °C ; IR (film)/cm^{-1} 2974, 2937, 2870, 1729 (C=O st), 1606, 1513, 1438, 1353, 1284, 1248, 1166, 987, 954, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2 H, 2 × Ar-CH), 6.90–6.86 (m, 2 H, 2 × Ar-CH), 5.19 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.89 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 4.56 (hept, *J* = 6.1 Hz, 1 H, CH), 3.67 (s, 3 H, OCH_3), 2.68 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.42 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me), 1.35 (d, *J* = 6.1 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ

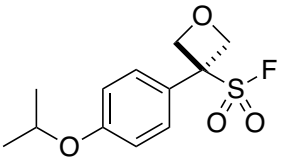
172.1 (C_q=O), 157.0 (Ar-C_qO*i*-Pr), 134.0 (Ar-C_qC_q), 127.5 (2 × Ar-CH), 115.8 (2 × Ar-CH), 83.2 (CH_2OCH_2), 70.0 (CH), 52.2 (C_q), 51.8 (CO_2CH_3), 34.1 (CH_2CO_2Me), 25.2 (SCH_2), 22.0 ($CH(CH_3)_2$); HRMS (APCI) *m/z* calcd for $C_{16}H_{23}O_4S^+$ $[M+H]^+$: 311.1312, found: 311.1324.

Methyl 3-((3-(4-isopropoxyphenyl)oxetan-3-yl)sulfonyl) propanoate (58c)



*m*CPBA (888 mg, 5.14 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **58b** (532 mg, 1.71 mmol, 1.0 equiv) in CH_2Cl_2 (86 mL, 0.02 M) in a 250 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 50 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford sulfone **58c** as a white solid (575 mg, 98%); R_f = 0.24 (40 % EtOAc/hexane); mp = 123–126 °C; IR (film)/cm^{-1} 2962, 1738 (C=O st), 1608, 1511, 1438, 1372, 1306 (SO_2 st as), 1254, 1187 (SO_2 st sy), 1096, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.18 (m, 2 H, 2 × Ar-CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 5.40 (d, *J* = 7.3 Hz, 2 H, C*H*HOC*H*H), 5.12 (d, *J* = 7.3 Hz, 2 H, CH*H*OCH*H*), 4.59 (hept, *J* = 6.1 Hz, 1 H, CH), 3.71 (s, 3 H, OCH_3), 3.09 (t, *J* = 7.7 Hz, 2 H, SCH_2), 2.71 (t, *J* = 7.7 Hz, 2 H, CH_2CO_2Me), 1.36 (d, *J* = 6.1 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_q=O), 158.7 (Ar-C_qO*i*-Pr), 129.4 (2 × Ar-CH), 125.0 (Ar-C_qCq), 116.0 (2 × Ar-CH), 76.3 (CH_2OCH_2), 70.0 (CH), 68.2 (Cq), 52.4 (CO_2CH_3), 43.2 (CH_2CO_2Me), 25.8 (SCH_2), 21.9 ($CH(CH_3)_2$); HRMS (ESI) *m/z* calcd for $C_{18}H_{25}NO_6SNa$ [M+MeCN+Na]: 406.1300, found: 406.1298.

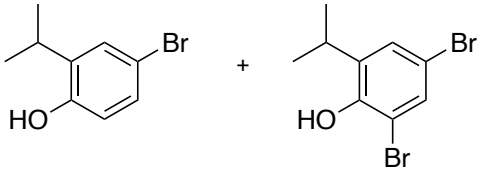
3-(4-Isopropoxyphenyl)oxetane-3-sulfonyl fluoride (58)



Sulfonyl fluoride **58** was synthesized in a telescope process from sulfone **58c** using the elimination protocol **EI-II** and submitting the sulfinate intermediate directly to the fluorination conditions. NaOH (5 M in MeOH, 252 μL, 1.26 mmol, 1.05 equiv) was added to a solution of sulfone **58c** (412 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL, 0.08 M) at 0 °C in a 25 mL round bottom flask. Oxetane sulfinate salt **58d** crushed out after 2 min of the start of addition of base to form a white paste. The reaction mixture was stirred at 0 °C for 15 minutes then filtered and washed with ice cold hexane to afford oxetane sulfinate **58d** as a white solid, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (795 mg, 2.24 mmol, 1.9 equiv) was added to anhydrous MeOH (7.5 mL, 0.16 M) at 0 ºC in a 50 mL round bottom flask, then stirred for 5 min. Sulfinate salt **58d** was added portionwise. The reaction mixture was stirred at 0 ºC for 1 h then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (30 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (100% CH_2Cl_2) afforded sulfonyl fluoride **58** as a white solid (226 mg, 68%). R_f = 0.20 (30% CH_2Cl_2/hexane); mp = 51–55 °C; IR (film)/cm^{-1} 2978, 2892, 1610, 1513, 1402 (SO_2 st as), 1297, 1252, 1215, 1189, 1111, 999, 954, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2 H, 2 × Ar-CH), 6.97–6.94 (m, 2 H, 2 × Ar-CH), 5.43 (d, *J* = 7.9 Hz, 2 H, C*H*HOC*H*H), 5.23 (dd, *J* = 7.9 Hz, J_{HF} = 1.5 Hz, 2 H, C*H*HOC*H*H), 4.60 (hept, *J* = 6.1 Hz, 1 H, CH), 1.37 (d, *J* = 6.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qO*i*-Pr), 129.5 (2 × Ar-CH), 122.7 (Ar-C_qC_q), 116.1 (2 × Ar-CH), 77.1 (CH_2OCH_2), 70.1 (CH), 68.1 (d, $J_{C\text{-}F}$ = 14.0 Hz, C_q), 21.9 (2 × CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.3; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_2^+$ $[M–SO_2F]^+$: 191.1067, found: 191.1069.

Sulfonyl Fluoride 59

4-Bromo-2-isopropylphenol (S11) and 2,4-dibromo-6-isopropylphenol (S11')[34]



S11 **S11'**

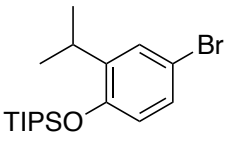
N-Bromosuccinimide (6.85 g, 38.5 mmol, 1.1 equiv) was added slowly and in portions to a solution of 2-isopropylphenol (4.7 mL, 34.9 mmol, 1.0 equiv) in anhydrous MeCN (50 mL, 0.7 M) in a 100 mL round bottom flask at 0 °C. After stirring for 5 h at 25 °C, the reaction mixture was concentrated *in vacuo* using a rotatory evaporator. Hexane was added to the residue and the formed suspension was filtered to remove any insoluble impurities. The filtrate was washed with distilled water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by automated column chromatography afforded dibromophenol **S11'** as a light-yellow liquid (235 mg, 2%) followed by bromophenol **S11** as an orange liquid (6.05 g, 81%).

Column Conditions: Column Type: Biotage® Sfär HC 100 g. Flow rate: 120 mL/min. 1 column volume (CV) 2% EtOAc/pentane, 12 CV 2–30% EtOAc/pentane, 3 CV 30–100% EtOAc/pentane, 3 CV 0–100% MeOH/EtOAc, 2 CV 100% MeOH. Fractions 1–43: mixture of **S11'** + 2-bromo-6-isopropylphenol, fractions 44–79: **S11'**, fractions 94–143: **S11**.

Dibromophenol **S11'**: R_f = 0.55 (10% EtOAc/pentane); IR (film)/cm^{-1} 3507 (br OH), 3079, 2963, 2870, 1565, 1439, 1402, 1320, 1264, 1226, 1159, 958, 906, 854, 783, 738, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 2.3 Hz, 1 H, CBrAr-CHCBr), 7.25 (J = 2.3 Hz, 1 H, Ar-C_qAr-CHCBr), 5.57 (s, 1 H, OH), 3.29 (hept, J = 6.9 Hz, 1 H, CH), 1.23 (d, J = 6.9 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (Ar-C_qOH), 138.0 (Ar-C_qCH), 131.0 (C_qAr-*C*HCBr), 129.1 (CBrAr-*C*HCBr), 112.6 (CHAr-C_qBrCH), 110.9 (Ar-C_qBrCOH), 28.1 (CH), 22.2 (2 × CH_3). The observed characterization data (^{1}H, ^{13}C) were consistent with that previously reported.[35]

Bromophenol **S11**: R_f = 0.18 (10% EtOAc/pentane); IR (film)/cm^{-1} 3548 (br OH), 2967, 2870, 1603, 1491, 1413, 1320, 1267, 1200, 1170, 1096, 880, 809, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 2.4 Hz, 1 H, Ar-C_qAr-CHCBr), 7.17 (dd, ^3J = 8.5 Hz, ^4J = 2.4 Hz, 1 H, Ar-CHAr-C*H*CBr), 6.64 (d, ^3J = 8.5 Hz, 1 H, Ar-C_qOHAr-C*H*), 4.75 (s, 1 H, OH), 3.18 (hept, J = 6.9 Hz, 1 H, CH), 1.26 (d, J = 6.9 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (Ar-C_qOH), 136.8 (Ar-C_qCH), 129.4 (Ar-CH), 129.3 (Ar-CH), 116.9 (Ar-CHAr-*C*HCBr), 113.2 (Ar-C_qBr), 27.1 (CH), 22.4 (2 × CH_3). The observed characterization data (^{1}H, ^{13}C) were consistent with that previously reported.[36]

(4-Bromo-2-isopropylphenoxy)triisopropylsilane (59a')



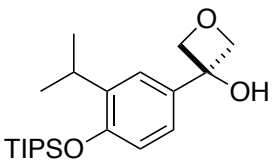
4-Bromo-2-isopropylphenol **S11** (6.04 g, 28.1 mmol, 1.0 equiv) was added dropwise to a solution of 1*H*-imidazole (4.78 g, 70.2 mmol, 2.5 equiv) in anhydrous CH_2Cl_2 (56 mL, 0.5 M) in a 250 mL round bottom flask at 0 °C. After stirring for 5 min, chlorotriisopropylsilane (7.21 mL, 33.7 mmol, 1.2 equiv) was added dropwise at 0 °C. The reaction mixture was warmed to 25 °C, stirred for 30 h and then additional chlorotriisopropylsilane (1.2 mL, 5.61 mmol, 0.2 equiv) and 1*H*-imidazole (764.7 mg, 11.2 mmol, 0.4 equiv) were added. After stirring for additional 20 h (50 h in total) at 25 °C, the reaction mixture was quenched with distilled water (90 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by filtration through a plug of silica (100% pentane) afforded aryl bromide **59a'** as a white solid (9.50 g, 91%). R_f = 0.70 (100% pentane); mp = 55–59 °C; IR (film)/cm^{-1} 2945, 2870, 1484, 1402, 1338, 1275, 1189, 1100, 921, 883, 794, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 2.6 Hz, 1 H, Ar-C_qAr-CHCBr), 7.12 (dd, ^3J = 8.6 Hz, ^4J = 2.6 Hz, 1 H, Ar-CHAr-C*H*CBr), 6.65 (d, ^3J = 8.6 Hz, 1 H, Ar-C_q(OTIPS)Ar-CH), 3.33 (hept, J = 6.9 Hz, 1 H, Ar-C_qCH), 1.35–1.26 (m, 3 H, 3 × SiCH), 1.20 (d, J = 6.9 Hz, 6 H, 2 × Ar-C_qCHC*H*$_3$),

1.11 (d, J = 7.4 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3 (Ar-C_qOTIPS), 141.0 (Ar-C_qCH), 129.3 (Ar-CH), 128.9 (Ar-CH), 119.4 (Ar-CHAr-*C*HCBr), 113.1 (Ar-C_qBr), 26.9 (Ar-C_q*C*H), 22.6 (2 × Ar-C_qCH*C*H$_3$), 18.0 (6 × SiCH*C*H$_3$), 13.0 (3 × SiCH). The observed characterization data (^{1}H, ^{13}C) were consistent with that previously reported.[37]

Notes:

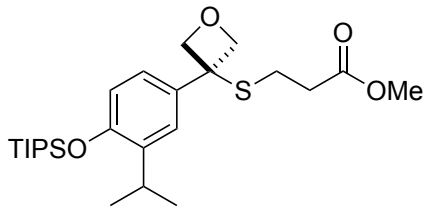
Starting material and product have the same R_f-value in different solvent systems and show the same color with different TLC-stains. Reaction monitoring by TLC suggested no consumption of starting material. Full consumption of starting material was confirmed by ^{1}H NMR of an aliquot.

3-(3-Isopropyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol (59a)



n-BuLi (1.41 M in hexanes, 16.7 mL, 23.5 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of aryl bromide **59a'** (9.48 g, 25.5 mmol, 1.3 equiv) in anhydrous THF (89 mL, 0.22 M) at –78 °C in a 250 mL round bottom flask. After stirring for 30 min, oxetan-3-one (1.26 mL, 19.7 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After further 30 min of stirring at –78 °C, the reaction mixture was warmed to 25 °C and quenched with distilled water (60 mL). The aqueous layer was extracted with diethylether (3 × 60 mL). The organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (10–20% EtOAc/pentane) afforded a mixture of oxetanol **59a** with ethyl acetate. Diethylether (10 mL) was added and the solvent was reduced under reduced pressure using a rotatory evaporator to afford oxetanol **59a** as a colorless oil which crystallized after several weeks in the freezer (6.51 g, 91%). R_f = 0.19 (15% EtOAc/pentane); mp = 51 °C; IR (film)/cm^{-1} 3392 (br OH), 2948, 2870, 1610, 1498, 1465, 1387, 1267, 1193, 1081, 973, 936, 834, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.5 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 7.21 (dd, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1 H, Ar-CH), 6.81 (d, J = 8.4 Hz, 1 H, (TIPSO)C_qAr-CH), 4.96 (d, J = 7.2 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, J = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.40 (hept, J = 6.9 Hz, 1 H, Ar-C_qCH), 2.35 (br s, 1 H, OH), 1.40–1.32 (m, 3 H, 3 × SiCH), 1.23 (d, J = 6.9 Hz, 6 H, 2 × Ar-C_qCHCH_3), 1.13 (d, J = 7.4 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (Ar-C_qOTIPS), 138.8 (Ar-$C_q$$C_q$), 134.3 (Ar-$C_q$CH), 122.6 (Ar-CH), 122.5 (Ar-CH), 117.7 (Ar-C_q(OTIPS)Ar-*C*H), 85.5 (CH_2OCH_2), 76.0 (Ar-$C_q$$C_q$), 26.9 (Ar-$C_q$*C*H), 22.8 (2 × Ar-$C_q$CH*C*H$_3$), 18.1 (6 × SiCH*C*H$_3$), 13.1 (3 × SiCH); HRMS (ESI) *m/z* calcd for $C_{21}H_{35}O_2Si$ [M–OH]: 347.2406, found: 347.2397.

Methyl 3-((3-(3-isopropyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)thio)propanoate (59b)



Lithium bis(trifluoromethanesulfonimide) (158.0 mg, 0.55 mmol, 0.11 equiv) and tetrabutylammonium hexafluorophosphate (106.8 mg, 0.276 mmol, 0.055 equiv) were added sequentially to a solution of oxetanol **59a** (1.82 g, 5.0 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (1.08 mL, 10.0 mmol, 2.0 equiv) in non-anhydrous chloroform (10 mL, 0.5 M) in a 50 mL round bottom flask. The reaction flask was placed into a preheated oil bath at 40 °C. The reaction was stirred for 15 min and then heated up to 70 °C in 1 h. At 70 °C there was a change in color from clear and colorless to light-pink and cloudy (Fig. S24). From the moment of the color change, the reaction was stirred for further 25 min and quenched with sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with aq. NaOH (1 M, 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (5% acetone/pentane) afforded oxetane sulfide **59b** as a white solid (1.77 g, 76%). R_f = 0.19 (5% acetone/pentane); mp = 53 °C; IR (film)/cm^{-1} 2948, 2870, 1737 (C=O st), 1607, 1495, 1461, 1342, 1275, 1189, 1081, 988, 910, 820, 790, 731, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 2.5 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 6.85 (dd,

^{3}J = 8.3 Hz, ^{4}J = 2.5 Hz, 1 H, Ar-CH), 6.75 (d, J = 8.3 Hz, 1 H, (TIPSO)C_qAr-CH), 5.21 (d, J = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.90 (d, J = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.65 (s, 3 H, OCH_3), 3.37 (hept, J = 6.9 Hz, 1 H, Ar-C_qCH), 2.67 (t, J = 7.4 Hz, 2 H, SCH_2), 2.32 (t, J = 7.4 Hz, 2 H, CH_2CO_2Me), 1.38–1.27 (m, 3 H, 3 × SiCH), 1.20 (d, J = 6.9 Hz, 6 H, 2 × Ar-C_qCHCH_3), 1.12 (d, J = 7.4 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C_q=O), 152.3 (Ar-C_qOTIPS), 138.8 (Ar-C_q), 134.1 (Ar-C_q), 124.1 (Ar-*C*HAr-C_qAr-*C*H), 117.7 (Ar-CH), 83.4 (CH_2OCH_2), 52.5 (C_q), 51.7 (OCH_3), 34.2 (CH_2CO_2Me), 26.7 (Ar-C_q*C*H), 25.2 (SCH_2), 22.7 (2 × Ar-C_qCH*C*H_3), 18.1 (6 × SiCH*C*H_3), 13.0 (3 × SiCH); HRMS (APCI) *m/z* calcd for $C_{25}H_{42}O_4SSiNa^+$ $[M+H]^+$: 489.2465, found: 489.2446.

Reaction mixture before heating (T = 25 °C, t = 0 min) *Reaction mixture after heating to 70 °C*

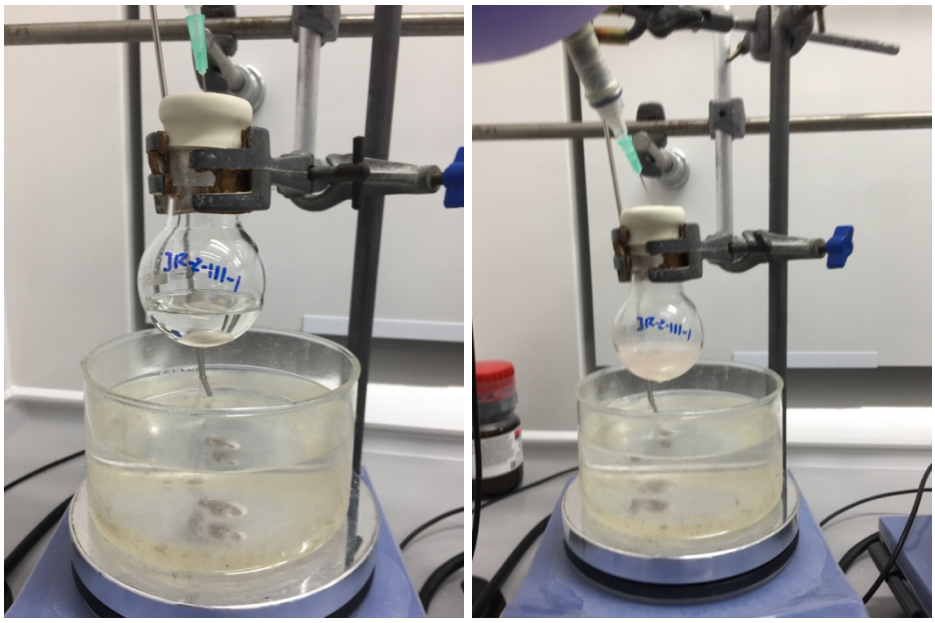
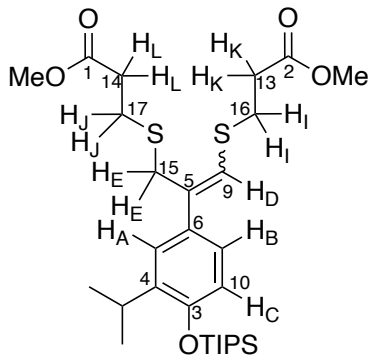


Fig. S32 Reaction mixture before and after heating. Start of reaction is marked by a sharp change in color. Here from clear and colorless to cloudy and light-pink.

Notes:

*On a 0.25 mmol scale, an alkene side product (**59b'''**) was isolated in 8% yield (11.0 mg, colorless oil):*

Dimethyl 3,3'-((2-(3-isopropyl-4-((triisopropylsilyl)oxy)phenyl)prop-1-ene-1,3-diyl)bis-(sulfanediyl))dipropionate (59b''')



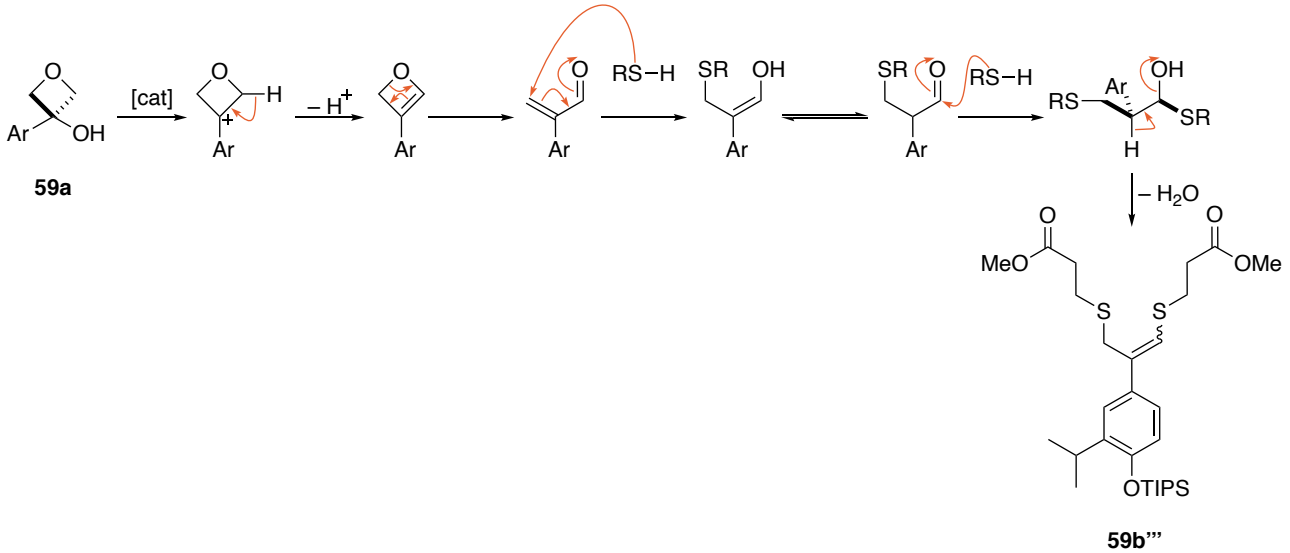
R_f = 0.13 (5% acetone/pentane); IR (film)/cm^{-1} 2948, 2866, 1737 (C=O st), 1603, 1495, 1461, 1439, 1357, 1271, 1077, 1018, 984, 932, 887, 813, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 2.5 Hz, 1 H, H_A), 7.07 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.5 Hz, 1 H, H_B), 6.72 (d, J = 8.4 Hz, 1 H, H_C), 6.30 (s, 1 H, H_D), 3.73 (s, 2 H, H_E), 3.70 (s, 3 H,CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.36 (hept, J = 6.9 Hz, 1 H, Ar-C_qCH), 3.04 (t, J = 7.3 Hz, 2 H, H_I), 2.80–2.76 (m, 2 H, H_J), 2.70 (t, J = 7.3 Hz, 2 H, H_K), 2.65–2.62 (m, 2 H, H_L), 1.36–1.29 (m, 3 H, 3 × SiCH), 1.22 (d, J = 6.9 Hz, 6 H, 2 × Ar-C_qCHCH_3), 1.12 (d, J = 7.4 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C1), 172.1 (C2), 152.8 (C3), 138.4 (C4), 136.6 (C5), 132.3 (C6), 123.61 (Ar-CH), 123.57 (Ar-CH), 117.6 (C10), 51.9 (OCH_3), 51.7 (OCH_3), 35.3 (C13), 34.8 (C14), 32.5 (C15), 29.4 (C16), 26.9 (C17), 26.8 (Ar-C_q*C*H),

22.8 (2 × Ar-C_qCH*C*H$_3$), 18.1 (6 × SiCH*C*H$_3$), 13.1 (3 × SiCH). HRMS (ESI) *m/z* calcd for $C_{29}H_{48}O_5S_2SiNa^+$ [M+H]$^+$: 591.2605, found: 591.2593.

Notes:

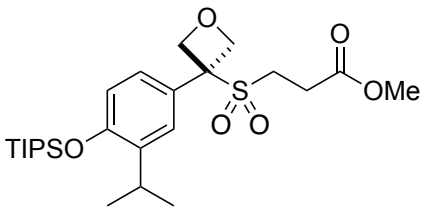
C9 is under the signals at 123.61 & 123.57 ppm. This was confirmed by HSQC and HMBC correlation spectra.

The unexpected alkene side product was potentially formed through a series of eliminations and nucleophilic additions (Scheme S7).



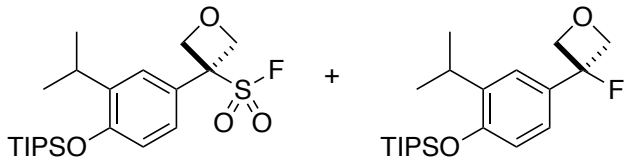
Scheme S7 Proposed mechanism for the formation of alkene **59b'''**.

Methyl 3-((3-(3-isopropyl-4-((triisopropylsilyl)oxy)phenyl)oxetan-3-yl)sulfonyl)propanoate (59c)



*m*CPBA (1.52 g, 8.8 mmol, 2.9 equiv) was added to a solution of oxetane sulfide **59b** (1.40 g, 3.0 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL, 0.02 M) in a 250 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 70 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfone **59c** as a white solid (1.50 g, quant.). R_f = 0.43 (50% Et_2O/pentane); mp = 125 °C; IR (film)/cm^{-1} 2948, 2866, 1741 (C=O st), 1607, 1495, 1461, 1309 (SO_2 st as), 1275, 1178, 1133, 1100, 999, 921, 887, 828, 794, 731, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.5 Hz, 1 H, Ar-C_qAr-CHAr-C_q), 6.96 (dd, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1 H, Ar-CH), 6.82 (d, *J* = 8.4 Hz, 1 H, (TIPSO)C_qAr-CH), 5.41 (d, *J* = 7.1 Hz, 2 H, C*H*HOC*H*H), 5.13 (d, *J* = 7.1 Hz, 2 H, CH*H*OCH*H*), 3.67 (s, 3 H, OCH_3), 3.39 (hept, *J* = 6.9 Hz, 1 H, Ar-C_qCH), 3.05 (t, *J* = 7.7 Hz, 2 H, SO_2CH_2), 2.58 (t, *J* = 7.7 Hz, 2 H, CH_2CO_2Me), 1.39–1.28 (m, 3 H, 3 × SiCH), 1.20 (d, *J* = 6.9 Hz, 6 H, 2 × Ar-C_qCHCH_3), 1.13 (d, *J* = 7.5 Hz, 18 H, 6 × SiCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C_q=O), 154.1 (Ar-C_qOTIPS), 139.6 (Ar-C_q), 126.2 (Ar-CH), 126.0 (Ar-CH), 125.4 (Ar-C_q), 118.2 (Ar-CH), 76.4 (CH_2OCH_2), 68.5 (C_q), 52.3 (OCH_3), 43.6 (CH_2CO_2Me), 26.7 (Ar-C_qCH), 26.2 (SO_2CH_2), 22.7 (2 × Ar-C_qCH*C*H$_3$), 18.0 (6 × SiCH*C*H$_3$), 13.0 (3 × SiCH); HRMS (ESI) *m/z* calcd for $C_{25}H_{46}NO_6SSi$ [M+NH_4]: 516.2815, found: 516.2812.

3-(3-Isopropyl-4-((triisopropylsilyl)oxy)phenyl)oxetane-3-sulfonyl fluoride (59) and (4-(3-fluorooxetan-3-yl)-2-isopropylphenoxy)triisopropylsilane (59')



59 **59'**

Sulfonyl fluoride **59** was synthesized in a telescope process from sulfone **59c** using the elimination protocol **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions. Sodium methoxide (5.4 M solution in MeOH, 0.28 mL, 1.50 mmol, 1.0 equiv) was added dropwise to a solution of oxetane sulfone **59c** (748 mg, 1.50 mmol, 1.0 equiv) in anhydrous THF (3.0 mL, 0.5 M) in a 10 mL round bottom flask. The reaction mixture turns from colorless to yellow upon addition of base (Fig. S25). The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfinate **59d** as a light-yellow solid, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (797.2 mg, 2.25 mmol, 1.5 equiv) was added to anhydrous MeOH (7.5 mL, 0.2 M) at 0 °C in a 25 mL round bottom flask, then stirred for 5 min. Sulfinate salt **59d** was added portionwise. The reaction mixture was stirred for at 0 °C for 1 h, then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (15 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (60% CH_2Cl_2/pentane) afforded a 9:1 mixture of oxetane sulfonyl fluoride **59** and oxetane fluoride **59'** as a colorless gum (461 mg, 72%). Repurification of the mixture by flash column chromatography (3% Et_2O/pentane) afforded oxetane fluoride **59'** as a colorless gum (38.8 mg, 7%) followed by oxetane sulfonyl fluoride **59** as a colorless gum which crystallized in the freezer to a white solid (342 mg, 53%).

Oxetane fluoride **59'**: R_f = 0.37 (3% EtOAc/pentane); IR (film)/cm^{-1} 2945, 2870, 1610, 1498, 1465, 1346, 1308, 1271, 1192, 1081, 984, 932, 883, 820, 768, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 2.4 Hz 1 H, Ar-C_qAr-CHAr-C_q), 7.19 (ddd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, $^5J_{HF}$ = 0.9 Hz, 1 H, Ar-CH), 6.82 (dd, ^3J = 8.4 Hz, J = 0.9 Hz, 1 H, (TIPSO)C_qAr-CH), 5.11 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 1 H, C*H*HO), 5.06 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 1 H, C*H*HO), 4.95 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 1 H, CH*H*O), 4.90 (dd, ^2J = 7.7 Hz, J_{HF} = 1.2 Hz, 1 H, CH*H*O), 3.41 (hept, J = 6.9 Hz, 1 H, Ar-C_qCH), 1.38–1.29 (m, 3 H, 3 × SiCH), 1.23 (d, J = 6.9 Hz, 6 H, 2 × Ar-C_qCHC*H*$_3$), 1.13 (d, J = 7.5 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (Ar-C_qOTIPS), 138.9 (Ar-*C*$_q$CH), 130.1 (d, $^2J_{CF}$ = 23.7 Hz, Ar-*C*$_q$C$_q$), 122.3 (d, $^3J_{CF}$ = 8.8 Hz, Ar-CH), 122.2 (d, $^3J_{CF}$ = 8.6 Hz, Ar-CH), 95.7 (d, $^1J_{CF}$ = 205.4 Hz, C_q) 83.1 (d, $^2J_{CF}$ = 26.0 Hz, CH_2OCH_2), 26.8 (Ar-C_q*C*H), 22.7 (2 × Ar-C_qCH*C*H$_3$), 18.1 (6 × SiCH*C*H$_3$), 13.1 (3 × SiCH); ^{19}F NMR (377 MHz, $CDCl_3$) δ 34.2; HRMS (APCI) *m/z* calcd for $C_{21}H_{35}O_2Si^+$ [M–F]$^+$: 347.2401, found: 347.2403.

Oxetane sulfonyl fluoride **59**: R_f = 0.23 (3% EtOAc/pentane); mp = 57-64 °C; IR (film)/cm^{-1} 2948, 2892, 2870, 1607, 1495, 1465, 1402 (SO_2 st as), 1342, 1279, 1215 (SO_2 st sy), 1193, 1111, 1003, 925, 887, 824, 783, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 2.5 Hz 1 H, Ar-C_qAr-CHAr-C_q), 6.94 (dd, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1 H, Ar-CH), 6.83 (d, J = 8.4 Hz, 1 H, (TIPSO)C_qAr-CH), 5.43 (d, J = 7.6 Hz, 2 H, C*H*HOC*H*H), 5.24 (dd, ^2J = 7.6 Hz, J_{HF} = 1.4 Hz, 2 H, CH*H*OCH*H*), 3.38 (hept, J = 7.0 Hz, 1 H, Ar-C_qCH), 1.38–1.29 (m, 3 H, 3 × SiCH), 1.21 (d, J = 7.0 Hz, 6 H, 2 × Ar-C_qCHC*H*$_3$), 1.13 (d, J = 7.4 Hz, 18 H, 6 × SiCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (Ar-C_qOTIPS), 139.7 (Ar-C_q), 126.3 (Ar-CH), 126.1 (Ar-CH), 123.1 (Ar-C_q), 118.1 (Ar-CH), 77.3 (CH_2OCH_2), 68.4 (d, $^2J_{CF}$ = 14.2 Hz, C_q), 26.8 (Ar-C_q*C*H), 22.6 (2 × Ar-C_qCH*C*H$_3$), 18.0 (6 × SiCH*C*H$_3$), 13.0 (3 × SiCH); ^{19}F NMR (377 MHz, $CDCl_3$) δ –145.0; HRMS (APCI) *m/z* calcd for $C_{21}H_{35}O_2Si^+$ [M–SO_2F]$^+$: 347.2401, found: 347.2401.

Reaction mixture before (left) and after (right) addition of base

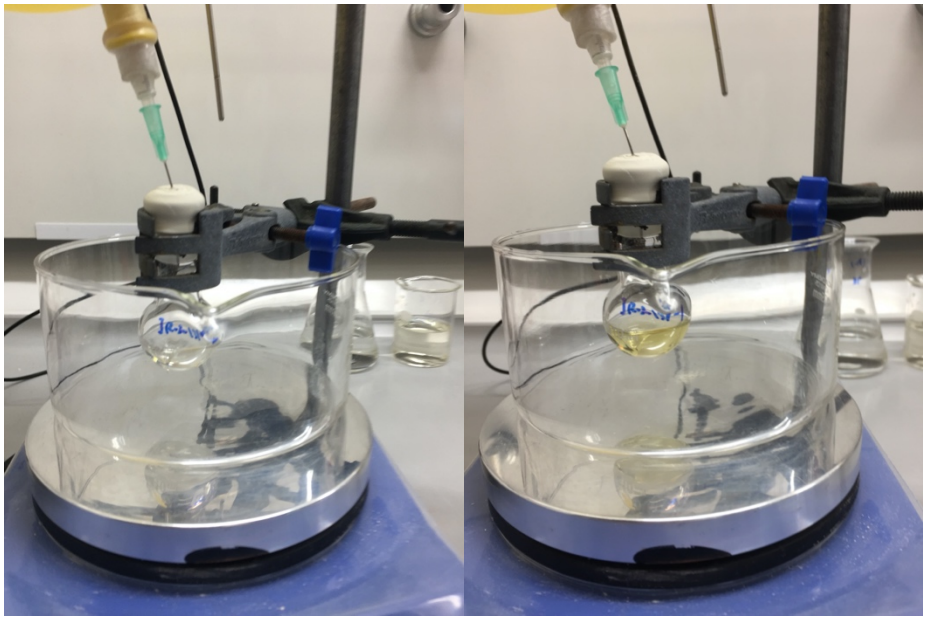
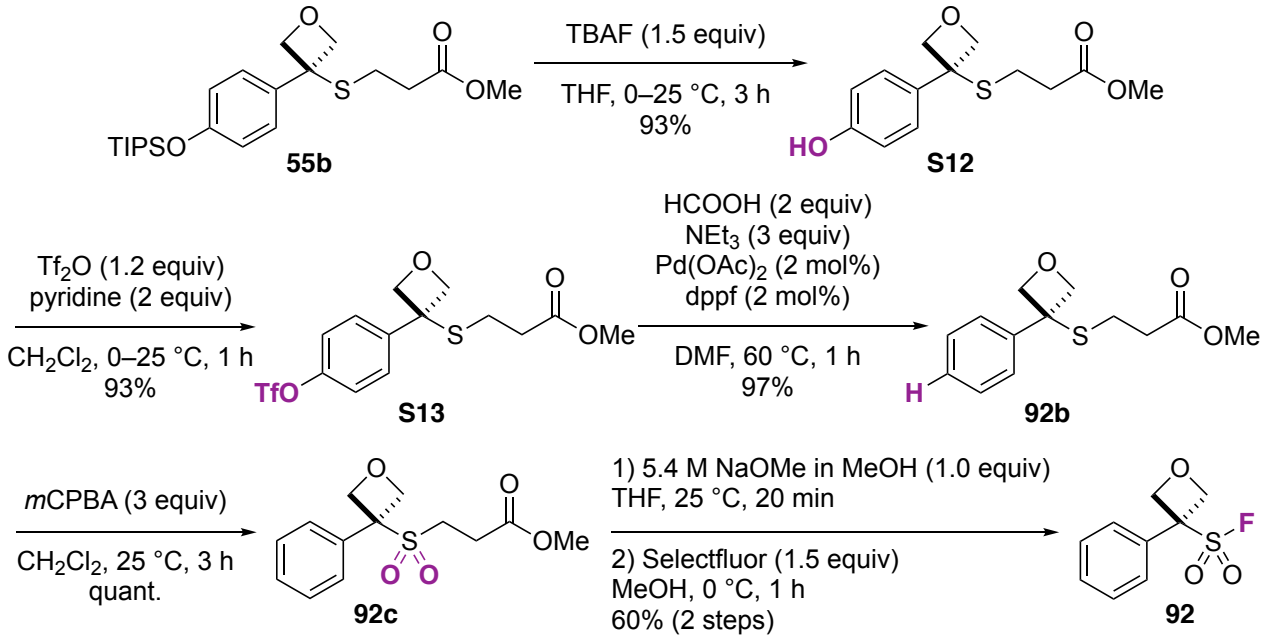


Fig. S33 Immediate change in appearance of reaction mixture after addition of base.

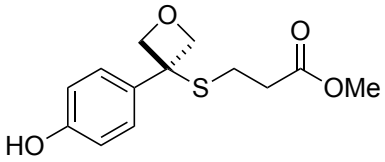
Sulfonyl Fluoride 92

Phenyl oxetane sulfide **92b** was synthesized from OTIPS oxetane sulfide intermediate **55b** in a short sequence in a very high overall yield of 84% over three steps (Scheme S8). **55b** was first TIPS deprotected using TBAF (**S12**), then triflated with triflic anhydride (**S13**) and finally deoxygenated using Pd-catalyzed conditions developed by Ortar (**92b**).[38] Synthesis of phenyl OSF **92** was achieved through the usual sequence (also see Scheme S3).



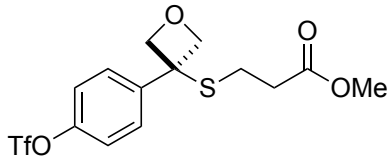
Scheme S8 Synthesis of phenyl-oxetane sulfonyl fluoride **92** from OTIPS oxetane sulfide **55b**.

Methyl 3-((3-(4-hydroxyphenyl)oxetan-3-yl)thio)propanoate (S12)



TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol, 1.5 equiv) was added dropwise to a solution of OTIPS oxetane sulfide **55b** (854 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (6.7 mL, 0.3 M) at 0 °C in a 50 mL round bottom flask. The reaction mixture was warmed to 25 °C and stirred for further 3 h. The reaction was then quenched with sat. aq. NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash chromatography (60–75% EtOAc/pentane) afforded phenol oxetanol sulfide **S12** as colorless crystals (497 mg, 93%). R_f = 0.30 (70% EtOAc/pentane); mp = 79 °C; IR (film)/cm^{-1} 3305 (br OH), 3018, 2947, 2871, 1730 (C=O st), 1610, 1591, 1512, 1435, 1358, 1218, 1173, 1111, 1039, 1013, 976, 923, 833, 732, 703, 579, 541; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.04 (m, 2 H, 2 × Ar-CH), 6.83–6.79 (m, 2 H, 2 × Ar-CH), 5.20 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.68 (s, 3 H, CH_3), 2.67 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.43 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C_q=O), 155.1 (Ar-C_qOH), 133.9 (Ar-C_qC_q), 127.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 83.3 (CH_2OCH_2), 52.1 (C_q), 52.0 (CO_2CH_3), 34.0 (CH_2CO_2Me), 25.1 (SCH_2); HRMS (APCI) *m/z* calcd for $C_{13}H_{15}SO_4^-$ $[M–H]^-$: 267.0697; found: 267.0694.

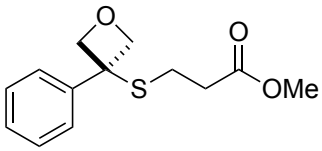
Methyl 3-((3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)oxetan-3-yl)thio)propanoate (S13)



Pyridine (0.25 mL, 3.12 mmol, 2.0 equiv) and triflic anhydride (0.32 mL, 1.87 mmol, 1.2 equiv) were added sequentially to a solution of phenol oxetane sulfide **S12** (418 mg, 1.56 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (20 mL, 0.08 M) at 0 °C in a 50 mL round bottom flask. The reaction mixture was warmed to 25 °C and

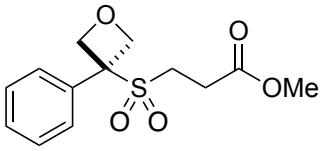
stirred for 1 h. The reaction was then quenched with distilled water (45 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50% Et_2O/pentane) afforded oxetane triflate **S13** as a colorless gum which solidified in the freezer (578 mg, 93%). R_f = 0.26 (50% Et_2O/pentane); mp = 35–38 °C; IR (film)/cm^{-1} 2952, 2878, 1737 (C=O st), 1506, 1424, 1208, 1141, 984, 887, 760, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4 H, 4 × Ar-CH), 5.18 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.93 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 3.69 (s, 3 H, CH_3), 2.69 (t, *J* = 7.3 Hz, 2 H, SCH_2), 2.45 (t, *J* = 7.3 Hz, 2 H, CH_2CO$_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C_q=O), 148.4 (Ar-C_qOTf), 143.0 (Ar-C_qC_q), 128.3 (2 × Ar-CH), 121.6 (2 × Ar-CH), 118.7 (q, J_{CF} = 321.1 Hz, CF_3) 82.6 (CH_2OCH_2), 51.9 (CO_2CH_3), 51.8 (C_q), 33.8 (CH_2CO$_2$Me), 25.0 (SCH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (APCI) *m/z* calcd for $C_{14}H_{16}F_3S_2O_6^+$ $[M+H]^+$: 401.0335; found: 401.0337.

Methyl 3-((3-phenyloxetan-3-yl)thio)propanoate (92b)[38]



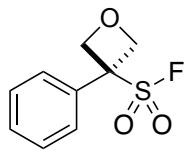
Triethyl amine (0.50 mL, 3.6 mmol, 3.0 equiv) and formic acid (90.6 μL, 2.4 mmol, 2.0 equiv) were added sequentially to a solution of oxetane triflate **S13** (480.5 mg, 1.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol, 0.02 equiv) and (ferrocene-1,1′-diyl) bis(diphenylphosphane) (dppf; 13.3 mg, 0.024 mmol, 0.02 equiv) in anhydrous DMF (12 mL, 0.1 M) in a 50 mL round bottom flask. The reaction mixture was warmed to 60 °C and stirred for 1 h. The reaction was cooled down to 25 °C, then brine was added (50 mL). The aqueous layer was extracted with EtOAc (4 × 50 mL). The organic layers were combined, washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50% Et_2O/pentane) afforded phenyl oxetane **92b** as a colorless gum (294 mg, 97%). R_f = 0.44 (50% Et_2O/pentane); IR (film)/cm^{-1} 2951, 2873, 1737 (C=O st), 1599, 1497, 1437, 1358, 1244, 1088, 986, 932, 835, 763, 529; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2 H, 2 × Ph-CH), 7.31–7.28 (m, 1 H, Ph-CH), 7.21–7.18 (m, 2 H, 2 × Ph-CH), 5.24 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.92 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.67 (s, 3 H, CH_3), 2.67 (t, *J* = 7.4 Hz, 2 H, SCH_2), 2.40 (t, *J* = 7.4 Hz, 2 H, CH_2CO$_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C_q=O), 142.2 (Ph-C_qC_q), 128.6 (2 × Ph-CH), 127.3 (Ph-CH), 126.2 (2 × Ph-CH), 82.9 (CH_2OCH_2), 52.4 (C_q), 51.8 (OCH_3), 33.9 (CH_2CO$_2$Me), 25.1 (SCH_2); HRMS (APCI) *m/z* calcd for $C_{13}H_{17}SO_3^+$ $[M+H]^+$: 253.0893; found: 253.0893.

Methyl 3-((3-phenyloxetan-3-yl)sulfonyl)propanoate (92c)



*m*CPBA (683 mg, 3.96 mmol, 3.0 equiv) was added to a solution of oxetane sulfide **92b** (333 mg, 1.32 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (70 mL, 0.02 M) in a 250 mL round bottom flask. The reaction mixture was stirred at 25 °C for 3 h then aq. KOH (3 M, 30 mL) was added and the phases were separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford sulfone **92c** as a white solid (376 mg, quant.). R_f = 0.27 (60% Et_2O/pentane); mp = 120 °C; IR (film)/cm^{-1} 2949, 2883, 1735 (C=O st), 1494, 1438, 1364, 1307 (SO_2 st as), 1279, 1251,1220, 1178, 1135 (SO_2 st sy), 1097, 1055, 1022, 996, 933, 831, 778, 702, 565, 533, 474; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 3 H, 3 × Ph-CH), 7.33–7.30 (m, 2 H, 2 × Ph-CH), 5.43 (d, *J* = 7.3 Hz, 2 H, C*H*HOC*H*H), 5.17 (d, *J* = 7.3 Hz, 2 H, CH*H*OCH*H*), 3.70 (s, 3 H, CH_3), 3.09 (t, *J* = 7.6 Hz, 2 H, SO_2CH_2), 2.70 (t, *J* = 7.6 Hz, 2 H, CH_2CO$_2$Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C_q=O), 133.8 (Ph-C_qC_q), 129.4 (Ph-CH), 129.1 (2 × Ph-CH), 128.1 (2 × Ph-CH), 76.3 (CH_2OCH_2), 68.7 (C_q), 52.4 (OCH_3), 43.3 (CH_2CO$_2$Me), 25.8 (SO_2CH_2); HRMS (APCI) *m/z* calcd for $C_{13}H_{17}SO_5^+$ $[M+H]^+$: 285.0791; found: 285.0798.

3-Phenyloxetane-3-sulfonyl fluoride (92)



Sulfonyl fluoride **92** was synthesized in a telescope process from sulfone **92c** using the elimination protocol **EI-III** and submitting the sulfinate intermediate directly to the fluorination conditions. Sodium methoxide (5.4 M solution in MeOH, 0.13 mL, 0.7 mmol, 1.0 equiv) was added dropwise to a suspension of oxetane sulfone **92c** (200 mg, 0.7 mmol, 1.0 equiv) in anhydrous THF (1.4 mL, 0.5 M) in a 10 mL round bottom flask. Oxetane sulfinate salt **92d** crushes immediately after addition of base to form a white paste (Fig. S34). The reaction mixture was stirred at 25 °C for 20 min, then concentrated *in vacuo* using a rotatory evaporator to afford oxetane sulfinate **92d**, which was subjected directly to the next step without spectroscopical analysis. For the fluorination step, Selectfluor (372 mg, 1.06 mmol, 1.5 equiv) was added to anhydrous MeOH (3.6 mL, 0.2 M) at 0 °C in a 25 mL round bottom flask, then stirred for 5 min. Sulfinate salt **92d** was added portionwise. The reaction mixture was stirred at 0 °C for 1 h, then concentrated *in vacuo* using a rotatory evaporator. The residue was diluted with CH_2Cl_2 (10 mL) and filtered through a plug of Celite, eluting with further CH_2Cl_2. After concentration *in vacuo* using a rotatory evaporator, purification by flash column chromatography through a very short column (80% CH_2Cl_2/pentane) afforded oxetane sulfonyl fluoride **92** as white crystals (91.1 mg, 60%). R_f = 0.52 (80% CH_2Cl_2/pentane); mp = 67 °C; IR (film)/cm^{-1} 2967, 2990, 1491, 1400 (SO_2 st as), 1215 (SO_2 st sy), 999, 932, 790, 567, 540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 3 H, 3 × Ph-CH), 7.32–7.28 (m, 2 H, 2 × Ph-CH), 5.46 (d, *J* = 8.0 Hz, 2 H, C*H*HOC*H*H), 5.29 (d, ^2J = 8.0 Hz, J_{HF} = 1.6 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7 (Ph-C_qC_q), 130.1 (Ph-CH), 129.2 (2 × Ph-CH), 128.1 (2 × Ph-CH), 77.0 (CH_2OCH_2), 68.3 (d, $^2J_{CF}$ = 15.0 Hz, C_q); ^{19}F NMR (377 MHz, $CDCl_3$) δ 35.1; HRMS (EI) *m/z* calcd for $C_9H_9FSO_3^{\cdot+}$ $[M–e]^{\cdot+}$: 216.0251; found: 216.0287 (error: 17 ppm). Also found: $C_9H_9O^+$ $[M–SO_2F]^+$: 133.0648; found: 133.0635 (error: 10 ppm).

Notes:

***92** did not ionize very well and a tractable ion could only be found using a hard ionization technique (EI) and a relatively high error (10 or 17 ppm). Further evidence for the structure of **92** was provided by X-ray crystallography (see Fig. S62–63).*

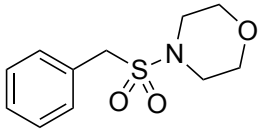
*t = 0: suspension of **92c** in THF* *t = ~ 2 min: after addtion of NaOMe*



Fig. S34 Solidification of reaction mixture after addition of NaOMe.

Sulfonamide **4** from PMSF

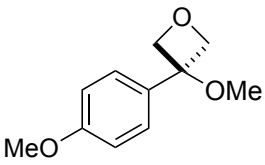
4-(Benzylsulfonyl)morpholine (4)



Triethylamine (36 μL, 0.26 mmol, 1.3 equiv) was added to a solution of phenyl methane sulfonyl fluoride (PMSF) (36 mg, 0.20 mmol, 1.0 equiv) and morpholine (21 μL, 0.24 mmol, 1.2 equiv) in acetonitrile (0.7 mL, 0.3 M). The reaction mixture was stirred at 60 ºC for 1 h then water (10 mL) was added, followed by CH_2Cl_2 (3 × 10 mL) and the layers separated. The organic extracts were combined, dried over Na_2SO_4 and filtered. Concentration *in vacuo* using a rotatory evaporator afforded sulfonamide **4** as a white solid (45 mg, 93%). R_f = 0.41 (50% EtOAc/hexane); mp = 173–175 ºC [Lit; 174–176 ºC (ethanol)][39], IR (film)/cm^{-1} 2857, 1451, 1345 (S=O), 1318, 1258, 1152 (S=O st), 1111, 1068, 944 923, 785, 746, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 5 H, 5 × Ph-CH), 4.24 (s, 2 H, $PhCH_2$), 3.63 (t, *J* = 4.6 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 3.11 (t, *J* = 4.6 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.7 (2 × Ph-CH), 128.89 (Ph-CH), 128.85 (2 × Ph-CH), 128.5 (Ar-$C_q$$CH_2$), 66.7 ($CH_2OCH_2$), 56.7 ($PhCH_2$), 46.1 ($CH_2NCH_2$). The observed characterization data (mp[39], ^{1}H, ^{13}C) were consistent with that previously reported.[40]

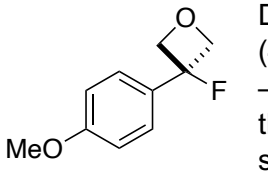
Oxetane Ether **5** and Oxetane Fluorides (**6**, **S14**)

3-Methoxy-3-(4-methoxyphenyl)oxetane (5)



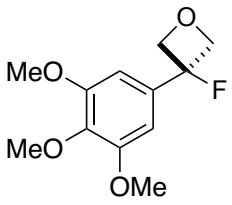
Oxetanol **1a** (90 mg, 0.5 mmol) was added to NaH (60% in mineral oil, 22 mg, 0.55 mmol) in DMF (2 mL) at 0 ºC and the reaction mixture stirred at 0 ºC for 1 h. MeI (93 μL, 1.5 mmol) was added and the reaction mixture stirred for a further 15 h at 25 ºC. Water (10 mL) was added and the aqueous phase extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (40% Et_2O/pentane) afforded oxetane ether **5** as a white solid (86 mg, 88%). R_f = 0.39 (40% Et_2O/pentane); mp = 42–44 ºC, IR (film)/cm^{-1} 2954, 2880, 1512, 1249, 1181, 1172, 1042, 1027, 973, 828, 819, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2 H, 2 × Ar-CH), 6.97–6.93 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 6.8 Hz, C*H*HOC*H*H), 4.84 (d, *J* = 6.8 Hz, CH*H*OCH*H*), 3.84 (s, 3 H, $ArOCH_3$), 3.10 (C_qOCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_qOMe), 131.5 (Ar-$C_q$$C_q$), 127.3 (2 × Ar-CH), 114.0 (2 × Ar-CH), 80.9 (CH_2OCH_2), 80.6 (C_q), 55.3 ($ArOCH_3$), 51.5 (C_qOCH_3); HRMS (APCI) *m/z* calcd for $C_{10}H_{11}O_2^+$ [M-OCH_3]$^+$: 163.0754, found: 163.0757.

3-Fluoro-3-(4-methoxyphenyl)oxetane (6)



DAST (40 μL, 0.3 mmol) was added dropwise to a solution of oxetanol **1a** (45 mg, 0.25 mmol) in CH_2Cl_2 (3.8 mL) at –78 °C. The reaction was stirred at –78 °C for 30 min then warmed to 0 °C using an ice bath. After 10 min at 0 °C the reaction was quenched with aq. NaOH (1 M, 10 mL) and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (15% Et_2O/pentane) afforded oxetane fluoride **6** as a clear oil (46 mg, 64%). R_f = 0.5 (15% Et_2O/pentane); IR (film)/cm^{-1} 3949, 2879, 1615, 1517, 1304, 1249, 1180, 1029, 978, 875, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2 H, 2 × Ar-CH), 6.99–6.95 (m, 2 H, 2 × Ar-CH), 5.10 (ddd, *J* = 21.5, 7.7, 1.2 Hz, 2 H, C*H*HOC*H*H), 4.89 (ddd, *J* = 21.5, 7.7, 1.2 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (Ar-C_qOMe), 130.3 (d, $J_{C\text{-}F}$ = 24.0 Hz, Ar-$C_q$$C_q$), 125.5 (d, $J_{C\text{-}F}$ = 8.1 Hz, 2 × Ar-CH), 114.0 (2 × Ar-CH), 95.2 (d, $J_{C\text{-}F}$ = 206.1 Hz, C_q), 83.0 (d, $J_{C\text{-}F}$ = 25.7 Hz, CH_2OCH_2), 55.3 (OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –145.9; HRMS (APCI) *m/z* calcd for $C_{10}H_{11}O_2^+$ [M-F]$^+$: 163.0754, found: 163.0756.

3-Fluoro-3-(3,4,5-trimethoxyphenyl)oxetane (S14)



A reaction tube was charged with sulfonyl fluoride **54** (30.6 mg, 0.1 mmol, 1.0 equiv), the reaction vessel was sealed and anhydrous acetonitrile (0.33 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 13 h, it was left to cool to 25 °C and the solvent was removed *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (5% Et_2O/CH_2Cl_2) afforded oxetane fluoride **S14** as a pink solid (3.0 mg, 12%). R_f = 0.63 (10% Et_2O/CH_2Cl_2); mp = 129 °C; IR (film)/cm^{-1} 2945, 2878, 2844, 1592, 1513, 1461, 1357, 1230, 1170, 1126, 1006, 980, 932, 854, 798, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 2 H, 2 × Ar-CH), 5.11 (ddd, J_{HF} = 21.2 Hz, J = 7.5, 1.2 Hz, 2 H, C*H*HOC*H*H), 4.88 (ddd, J_{HF} = 20.9 Hz, J = 7.5, 1.2 Hz, 2 H, CH*H*OCH*H*), 3.91 (s, 6 H, 2 × OCH_3), 3.87 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (2 × Ar-C_qOMe), 138.0 (Ar-C_qOMe), 101.1 (d, $^3J_{CF}$ = 9.2 Hz, 2 × Ar-CH), 95.1 (weak, d, $^1J_{CF}$ = 208.4 Hz, C_q), 83.2 (d, $^2J_{CF}$ = 25.5 Hz, CH_2OCH_2), 60.9 (OCH_3), 56.2 (2 × OCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –148.5; HRMS (APCI) *m/z* calcd for $C_{12}H_{16}FO_4^+$ $[M+H]^+$: 243.1027, found: 324.1025.

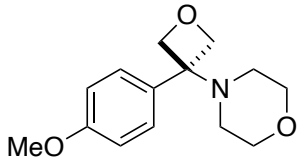
Notes:

*Due to the low quantity of **S14** isolated, the Ar-C_qOMe (para), and Ar-$\mathbf{C}_q C_q$ signals are not visible in the ^{13}C NMR spectrum. Ar-C_qOMe (para) was identified and assigned with HMBC correlation peaks. There were no HMBC correlation peaks with Ar-$\mathbf{C}_q C_q$.*

Oxetane Products

Secondary, Tertiary and Aromatic Oxetane Amines (**2**, **7**–**45**)

4-((3-(4-Methoxyphenyl)oxetan-3-yl)sulfonyl)morpholine (2)

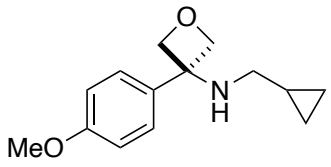


Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and morpholine (21 μL). Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane amine **2** as a white solid (43 mg, 86%). R_f = 0.21 (80% EtOAc/hexane); mp = 97–99 ºC, IR (film)/cm^{-1} 2950, 2855, 1610, 1513, 1453, 1296, 1246, 1179, 1114, 1029, 988, 929; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.96 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 5.9 Hz, C*H*HOC*H*H), 4.87 (d, *J* = 5.9 Hz, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 3.74 (t, *J* = 4.6 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.31 (t, *J* = 4.6 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 129.4 (Ar-C_qC_q), 128.4 (2 × Ar-CH), 113.3 (2 × Ar-CH), 79.3 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.4 (C_q), 55.3 (OCH_3), 46.4 (CH_2NCH_2); HRMS (APCI) *m/z* calcd for $C_{14}H_{19}NO_3^+$ [M+H]$^+$: 250.1443, found: 250.1438.

Notes:

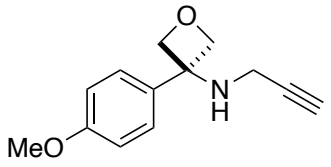
2 was also synthesized using 1.2 equiv of TMS-morpholine and in the absence of base (0.1 mmol scale, 20.0 mg, 80%).

***N*-(Cyclopropylmethyl)-3-(4-methoxyphenyl)oxetan-3-amine (7)**



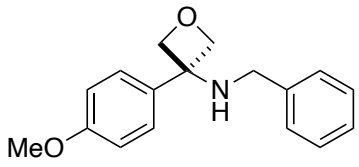
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and cyclopropylmethanamine (21 μL). Purification by flash column chromatography (35% EtOAc/pentane) afforded oxetane amine **7** as a colorless oil (37 mg, 79%). R_f = 0.17 (35% EtOAc in pentane); IR (film)/cm^{-1} 3075, 3000, 2948, 2836, 1610, 1513, 1461, 1304, 1244, 1177, 1028, 984, 831. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.72 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 2.22 (d, *J* = 6.9 Hz, 2 H, NCH_2), 2.01 (s, 1 H, NH), 0.94–0.84 (m, 1 H, NCH_2CH), 0.49–0.44 (m, 2 H, NCH_2CHCH_2), 0.07–0.03 (m, 2 H, NCH_2CHCH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 134.2 (Ar-C_qC_q), 127.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 82.8 (CH_2OCH_2), 62.8 (C_q), 55.2 (OCH_3), 48.7 (NCH_2), 11.4 (NCH_2CH), 3.5 (2 × NCH_2CHCH_2). HRMS (ESI) *m/z* calcd for $C_{14}H_{20}NO_2$ [M+H]: 234.1494, found: 234.1499.

3-(4-Methoxyphenyl)-N-(prop-2-yn-1-yl)oxetan-3-amine (8)



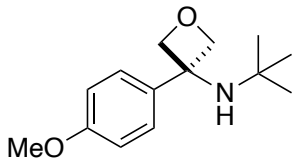
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and prop-2-yn-1-amine (15 μL). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **8** as a white solid (40 mg, 92%). R_f = 0.29 (50% EtOAc in pentane); mp = 113–115 °C; IR (film)/cm^{-1} 3280, 3257, 2944, 2877, 2806, 1613, 1517, 1308, 1248, 1177, 969, 823, 782. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 2 H, 2 × Ar-CH), 6.96–6.90 (m, 2 H, 2 × Ar-CH), 5.00–4.98 (m, 2 H, C*H*HOC*H*H), 4.89–4.86 (m, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 3.14 (d, *J* = 2.5 Hz, 2 H, NCH_2), 2.20 (t, *J* = 2.5 Hz, 1 H, C≡CH), 2.17 (s, 1 H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (Ar-C_qOMe), 132.9 (Ar-C_qC_q), 127.8 (2 × Ar-CH), 113.9 (2 × Ar-CH), 83.2 (CH_2OCH_2), 82.5 (*C*≡CH), 71.6 (C≡*C*H), 63.3 (C_q), 55.2 (OCH_3), 33.0 (NCH_2). HRMS (ESI) *m/z* calcd for $C_{13}H_{16}NO_2$ [M+H]: 218.1181, found: 218.1183.

_N_-Benzyl-3-(4-methoxyphenyl)oxetan-3-amine (9)



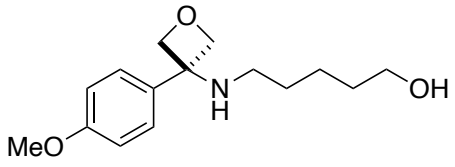
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and benzylamine (26 μL). Purification by flash column chromatography (40% EtOAc/hexane) afforded oxetane amine **9** as a white solid (48 mg, 89%). R_f = 0.29 (40% EtOAc/hexane); mp = 53–55 ºC, IR (film)/cm^{-1} 2949, 2869, 2836, 1610, 1513, 1454, 1245, 1177, 1027, 980, 829, 733, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 7.36–7.30 (m, 4 H, 4 × Ph-CH), 7.29–7.23 (m, 1 H, Ph-CH), 6.99–6.94 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 4.97 (d, J = 6.4 Hz, C*H*HOC*H*H), 4.77 (d, J = 6.4 Hz, CH*H*OCH*H*), 3.85 (s, 3 H, OCH_3), 3.56 (s, 2 H, CH_2Ph), 2.05 (br. s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 140.1 (Ph-C_q), 134.1 (Ar-$C_q$$C_q$), 128.4 (2 × Ph-CH), 128.1 (2 × Ph-CH), 127.4 (2 × $Ar_{(PMP)}$-CH), 127.1 (Ph-CH), 113.9 (2 × $Ar_{(PMP)}$-CH), 82.7 (CH_2OCH_2), 63.2 (C_q), 55.3 (OCH_3), 47.9 (CH_2Ph); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}NO_2$ [M+H]: 270.1494, found: 270.1495.

_N_-(*tert*-Butyl)-3-(4-methoxyphenyl)oxetan-3-amine (10)



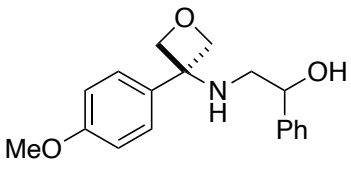
Prepared according to **General Procedure B** and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2-methylpropan-2-amine (42 μL). Purification by flash-column chromatography (0–35% Et_2O/CH_2Cl_2) afforded oxetane amine **10** as a white solid (38.6 mg, 82%). R_f = 0.08 (10–100% Et_2O/CH_2Cl_2); mp = 51 °C; IR (film)/cm^{-1} 3317 (weak, NH), 2960, 2870, 1614, 1584, 1513, 1461, 1361, 1308, 1245, 1178, 1115, 1036, 984, 910, 835, 809, 734, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.97 (d, J = 6.7 Hz, 2 H, C*H*HOC*H*H), 4.75 (d, J = 6.7 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 1.87 (br s, 1 H, NH), 0.85 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 135.9 (Ar-$C_q$$C_q$), 128.5 (2 × Ar-CH), 113.5 (2 × Ar-CH), 85.8 (CH_2OCH_2), 62.4 (Ar-$C_q$$C_q$), 55.2 ($OCH_3$), 51.9 ($HNC_q$), 31.2 (3 × CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NO_2$ [M+H]: 236.1651; found: 236.1643.

5-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)pentan-1-ol (11)



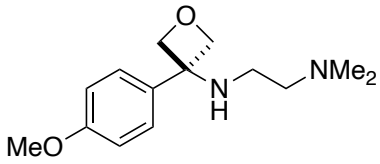
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 5-aminopentan-1-ol (25 mg). Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded oxetane amine **11** as a colorless oil (28 mg, 53%). R_f = 0.15 (2% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3384, 2933, 2862, 1610, 1513, 1461, 1300, 1245, 1177, 1029, 980, 831. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 4.94 (d, J = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.73 (d, J = 6.4 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.61 (t, J = 6.5 Hz, 2 H, CH_2NH), 2.39 (t, J = 7.0 Hz, 2 H, CH_2OH), 2.03 (br s, 2 H, NH + OH), 1.57–1.46 (m, 4 H, 2 × CH_2), 1.42–1.34 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 134.1 (Ar-$C_q$$C_q$), 127.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 82.4 (CH_2OCH_2), 63.0 (C_q), 62.5 (CH_2OH), 55.2 (OCH_3), 43.3 (CH_2NH), 32.4 (CH_2), 30.0 (CH_2), 23.4 (CH_2). HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NO_3$ [M+H]: 266.1756, found: 266.1749.

2-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)-1-phenylethan-1-ol (12)



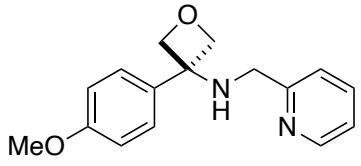
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2-amino-1-phenylethanol (33 mg). Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded oxetane amine **12** as a colorless oil (30 mg, 50%). R_f = 0.26 (2% MeOH/CH_2Cl_2); IRIR (film)/cm^{-1} 3340 (OH), 2937, 2870, 1696, 1610, 1513, 1454, 1245, 1025, 977, 831, 760, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H, 5 × $Ar_{(Ph)}$-CH), 7.28–7.19 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.95–6.88 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 4.99 (d, *J* = 6.3 Hz, 1 H, C*H*HOCH_2), 4.94 (d, *J* = 6.4 Hz, 1 H, CH_2OC*H*H), 4.75–4.71 (m, 2 H, CH*H*OCH*H*), 4.62 (dd, *J* = 8.5, 3.6 Hz, 1 H, CH), 3.82 (s, 3 H, OCH_3), 2.73 (dd, *J* = 12.0, 3.6 Hz, 1 H, NHC*H*H), 2.59 (dd, *J* = 12.0, 8.6 Hz, 1 H, NHCH*H*), 2.46 (br s, 2 H, NH + OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 142.1 (Ar-C_qCH), 134.1 (Ar-C_qC_q), 128.4 (2 × $Ar_{(Ph)}$-CH), 127.7 ($Ar_{(Ph)}$-CH), 127.2 (2 × $Ar_{(PMP)}$-CH), 125.7 (2 × $Ar_{(Ph)}$-CH), 114.0 (2 × $Ar_{(PMP)}$-CH), 82.3 (*C*H_2OCH_2), 82.0 (CH_2O*C*H_2), 72.6 (CH), 62.8 (C_q), 55.3 (OCH_3), 51.0 ($NHCH_2$); HRMS (ESI) *m/z* calculated for $C_{18}H_{22}NO_3$ [M+H]: 300.1600, found 300.1602.

***N*-(3-(4-Methoxyphenyl)oxetan-3-yl)-*N'*,N'-dimethylethane-1,2-diamine (13)**



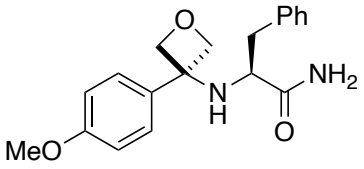
Anhydrous K_2CO_3 (359 mg, 2.6 mmol, 1.3 equiv), *N*,*N*-dimethylethylenediamine (0.26 mL, 2.4 mmol, 1.2 equiv) and sulfonyl fluoride **1** (493 mg, 2.0 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under Ar. The reaction vessel was sealed and anhydrous acetonitrile (7.0 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C and water (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (90:8:2, CH_2Cl_2: MeOH: Et_3N) afforded oxetane amine **13** as a yellow gum (201 mg, 40%). R_f = 0.41 (90:8:2, CH_2Cl_2: MeOH: Et_3N); IR (film)/cm^{-1} 3287 (br NH), 2945, 2864, 2820, 2771, 1611, 1514, 1458, 1243, 1178, 1029, 980, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, 2 × Ar-CH), 6.95–6.88 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.74 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 2.43–2.33 (m, 5 H, N*HCH*$_2$C*H*$_2$), 2.17 (s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 134.5 (Ar-C_qC_q), 127.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 82.7 (CH_2OCH_2), 62.7 (C_q), 59.1 (2 × NCH_3), 55.3 (OCH_3), 45.3 ($NHCH_2$), 40.7 ($NHCH_2CH_2$); HRMS (NSI) *m/z* calcd for $C_{14}H_{23}N_2O_2^+$ $[M+H]^+$: 251.1754, found: 251.1754.

3-(4-Methoxyphenyl)-*N*-(pyridin-2-ylmethyl)oxetan-3-amine (14)



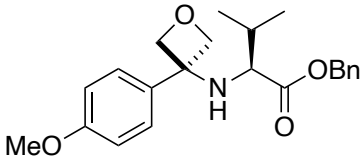
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2-picolinamine (25 μL). Purification by flash column chromatography (3% MeOH/CH_2Cl_2) afforded oxetane amine **14** as an orange oil (43 mg, 80%). R_f = 0.17 (3% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3299 (NH), 2946, 2869, 1610, 1592, 1513, 1463, 1433, 1301, 1244, 1178, 1028, 980, 831, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1 H, $Ar_{(py)}$-CH), 7.60 (td, *J* = 7.6, 1.8 Hz, 1 H, $Ar_{(py)}$-CH), 7.41–7.36 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 7.21 (d, *J* = 7.8 Hz, 1 H, $Ar_{(py)}$-CH), 7.15 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1 H, $Ar_{(py)}$-CH), 6.96–6.91 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 4.96 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.80 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.70 (s, 2 H, CH_2Py), 2.70 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 ($Ar_{(py)}$-C_q), 158.7 (Ar-C_qOMe), 149.2 ($Ar_{(py)}$-CH), 136.4 ($Ar_{(py)}$-CH), 134.2 (Ar-C_qC_q), 127.4 (2 × $Ar_{(PMP)}$-CH), 122.3 ($Ar_{(py)}$-CH), 122.0 ($Ar_{(py)}$-CH), 113.9 (2 × $Ar_{(PMP)}$-CH), 82.6 (CH_2OCH_2), 63.1 (C_q), 55.2 (OCH_3) 49.1 (CH_2Py); HRMS (ESI) *m/z* calculated for $C_{16}H_{19}N_2O_2$ [M+H]: 271.1447, found 271.1460.

(*S*)-2-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)-3-phenylpropanamide (15)



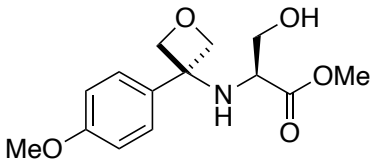
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and L-phenylalaninamide (39 mg). Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded amine **15** as an off-white paste (48 mg, 74%). $[\alpha]_D^{21}$ –26.0 (c 1.46, $CHCl_3$); R_f = 0.26 (2% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3429 (CONH), 3314 (NH), 3191 (CONH), 2952, 2873, 1670 (C=O st), 1610, 1513, 1454, 1245, 1178, 1029, 977, 831, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 3 H, 3 × $Ar_{(Ph)}$-CH), 7.16–7.11 (m, 2 H, 2 × $Ar_{(Ph)}$-CH), 7.00–6.95 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.88 (br d, *J* = 4.7 Hz, CON*H*H), 6.86–6.81 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 5.25 (br s, 1 H, CONH*H*), 4.85–4.79 (m, 2 H, C*H*HOC*H*H), 4.53 (d, *J* = 6.5 Hz, 1 H, CH*H*OCH$_2$), 4.29 (d, *J* = 6.3 Hz, 1 H, CHHOCH*H*), 3.82 (s, 3 H, OCH_3), 3.34 (dd, *J* = 9.0, 4.5 Hz, 1 H, CH), 3.06 (dd, *J* = 13.8, 4.5 Hz, 1 H, C*H*HPh), 2.75 (dd, *J* = 13.8, 9.0 Hz, 1 H, CH*H*Ph), 2.27 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2 (C_q=O), 158.8 (Ar-C_qOMe), 136.9 (Ar-C_qCH$_2$), 134.0 (Ar-C_qC_q), 129.2 (2 × $Ar_{(Ph)}$-CH), 128.8 (2 × $Ar_{(Ph)}$-CH), 127.2 (2 × $Ar_{(PMP)}$-CH), 127.1 ($Ar_{(Ph)}$-CH), 114.0 (2 × $Ar_{(PMP)}$-CH), 82.1 (*C*H$_2$OCH$_2$), 81.2 (CH$_2$O*C*H$_2$), 62.9 (Ar-C_qC_q), 59.0 (CH), 55.2 (OCH_3), 39.9 (*C*H$_2$Ph); HRMS (ESI) *m/z* calculated for $C_{19}H_{23}N_2O_3$ [M+H]: 327.1709, found 327.1721.

Benzyl (3-(4-methoxyphenyl)oxetan-3-yl)-L-valinate (16)



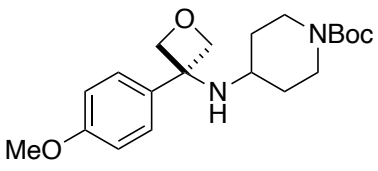
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and L-valine benzyl ester hydrochloride (59 mg). Purification by flash column chromatography (20% EtOAc/hexane) afforded amine **16** (52 mg, 90%) as a colorless oil. $[\alpha]_D^{21}$ –19.9 (*c* 1.51, $CHCl_3$). R_f = 0.20 (20% EtOAc/hexane); IR (film)/cm^{-1} 2958, 2873, 1727 (C=O st), 1611, 1515, 1456, 1244, 1177, 1144, 1029, 981, 831, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H, $Ar_{(Ph)}$-CH), 7.19–7.14 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.91–6.83 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 4.99 (s, 2 H, OCH$_2$Ph), 4.90 (d, *J* = 6.4 Hz, 1 H, C*H*HOCH$_2$), 4.81 (d, *J* = 6.4 Hz, 1 H, CH$_2$OC*H*H), 4.71–4.65 (m, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3), 2.90 (d, *J* = 6.1 Hz, 1 H, NHC*H*), 2.38 (br s, 1 H, NH), 1.84 (o, *J* = 6.7 Hz, 1 H, CH), 0.87 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.84 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (C_q=O), 158.7 (Ar-C_qOMe), 135.5 (Ar-C_qCH$_2$), 134.4 (Ar-C_qC_q), 128.52 (2 × $Ar_{(PMP)}$-CH), 128.49 (2 × $Ar_{(Ph)}$-CH), 128.4 ($Ar_{(Ph)}$-CH), 127.9 (2 × $Ar_{(Ph)}$-CH), 113.7 (2 × $Ar_{(PMP)}$-CH), 83.4 (*C*H$_2$OCH$_2$), 81.9 (CH$_2$O*C*H$_2$), 66.5 (O*C*H$_2$Ph), 62.8 (Ar-C_qC_q), 61.8 (CH), 55.2 (OCH_3), 32.0 (CH), 19.2 (CH*C*H$_3$), 18.2 (CH*C*H$_3$); HRMS (ESI) *m/z* calculated for $C_{22}H_{28}NO_4$ [M+H]: 370.2018, found 370.2029.

Methyl (3-(4-methoxyphenyl)oxetan-3-yl)-*L*-serinate (17)



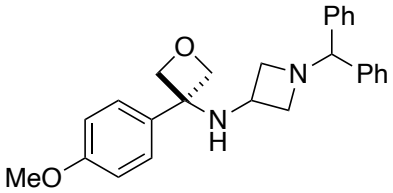
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *L*-serine methyl ester hydrochloride (37.7 mg). Purification by flash-column chromatography (0–5% MeOH/CH_2Cl_2) afforded oxetane amine **17** as a light-yellow oil (42.6 mg, 76%). $[a]_D^{16}$ –26.3 (c 1.1, $CHCl_3$); R_f = 0.17 (5% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3429 (br OH and NH), 2952, 2878, 1733 (C=O st), 1610, 1517, 1461, 1334, 1297, 1249, 1178, 1029, 980, 910, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.17 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 5.05 (d, *J* = 6.5 Hz, 1 H, C*H*HOCH$_2$), 4.92 (d, *J* = 6.5 Hz, 1 H, CH$_2$OC*H*H), 4.75 (d, *J* = 6.5 Hz, 1 H, CH*H*OCH$_2$), 4.72 (d, *J* = 6.5 Hz, 1 H, CH$_2$OCH*H*), 3.82 (s, 3 H, Ar-OCH_3), 3.64 (s, 3 H, CO_2CH_3), 3.50 (d, *J* = 5.4 Hz, 2 H, C*H*$_2$OH), 3.36 (t, *J* = 5.5 Hz, 1 H, CH), 2.67 (br s, 2 H, NH + OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C_q=O), 159.0 (Ar-C_qOMe), 133.9 (Ar-C_qC_q), 127.6 (2 × Ar-CH), 114.1 (2 × Ar-CH), 82.9 (CH$_2$O*C*H$_2$), 81.9 (*C*H$_2$OCH$_2$), 63.3 (CH$_2$OH), 62.7 (Ar-C_qC_q), 57.8 (CH), 55.3 (Ar-OCH_3), 52.4 (CO_2*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{20}NO_5$ [M+H]: 282.1341, found: 282.1345.

tert-Butyl 4-((3-(4-methoxyphenyl)oxetan-3-yl)amino)piperidine-1-carboxylate (18)



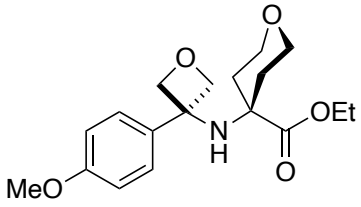
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4-amino-1-Boc-piperidine (48 mg). Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded oxetane amine **18** as a white solid (59 mg, 81%). R_f = 0.21 (2% MeOH/CH_2Cl_2); mp = 161–165 °C; IR (film)/cm^{-1} 3276 (NH), 2941, 2878, 1677, 1517, 1472, 1428, 1364, 1282, 1245, 1174, 1025, 976, 943, 869, 842; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, 2 × Ar-CH), 6.95–6.89 (m, 2 H, 2 × Ar-CH), 4.96 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 4.70 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 3.93 (br s, 2 H, (C*H*H)$_2$NBoc), 3.83 (s, 3 H, OCH_3), 2.57 (br t, *J* = 12.6 Hz, 2 H, (CH*H*)$_2$NBoc), 2.36 (tt, *J* = 10.6, 4.0 Hz, 1 H, CH), 1.76 (s, 1 H, NH), 1.57–1.45 (br m, 2 H, CH(C*H*H)$_2$), 1.43 (s, 9 H, 3 × CH_3), 1.26–1.12 (br m, 2 H, CH(CH*H*)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 154.6 (C_q=O), 134.5 (Ar-*C*$_q$C$_q$), 127.5 (2 × Ar-CH), 113.9 (2 × Ar-CH), 84.1 (CH_2OCH_2), 79.4 (*C*(CH$_3$)$_3$), 62.5 (Ar-C$_q$*C*$_q$), 55.2 (OCH_3), 50.9 (CH), 42.6 (br m, 2 × *C*H$_2$NBoc), 33.9 (2 × CH*C*H$_2$), 28.4 (3 × CH_3); HRMS (ESI) *m/z* calculated for $C_{20}H_{31}N_2O_4$ [M+H]: 363.2284, found 363.2294.

1-Benzhydryl-_N_-(3-(4-methoxyphenyl)oxetan-3-yl)azetidin-3-amine (19)



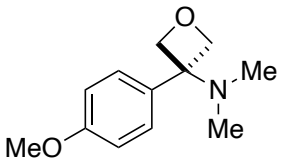
Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 1-benzhydrylazetidin-3-amine (57 mg). Purification by flash column chromatography (50% to 60% EtOAc/pentane) afforded oxetane amine **19** as a white solid (57 mg, 71%). R_f = 0.23 (50% EtOAc/pentane); mp = 100–102 °C; IR (film)/cm^{-1} 3269 (NH), 2941, 2870, 1614, 1517, 1454, 1252, 1200, 973, 831, 746, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 4 H, 4 × Ar-CH), 7.30–7.22 (m, 4 H, 4 × Ar-CH), 7.22–7.15 (m, 4 H, 4 × Ar-CH), 6.93–6.84 (m, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.65 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 4.26 (s, 1 H, C*H*Ph$_2$), 3.81 (s, 3 H, OCH_3), 3.48–3.34 (m, 3 H, NHC*H* + N(C*H*H)$_2$CH), 2.66–2.58 (m, 2 H, N(CH*H*)$_2$CH), 2.06 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 142.1 (2 × Ar-C_q), 134.4 (Ar-C_q), 128.4 (4 × Ar-CH), 127.3 (4 × Ar-CH), 127.2 (2 × Ar-CH), 127.1 (2 × Ar-CH), 113.9 (2 × Ar-CH), 82.9 (CH_2OCH_2), 78.4 (*C*HPh$_2$), 63.2 (CH_2NCH_2), 62.8 (C_q), 55.3 (OCH_3), 44.6 (NHCH); HRMS (ESI) *m/z* calculated for $C_{26}H_{29}N_2O_2$ [M+H]: 401.2229, found 401.2233.

Ethyl 4-((3-(4-methoxyphenyl)oxetan-3-yl)amino)tetrahydro-2H-pyran-4-carboxylate (20)



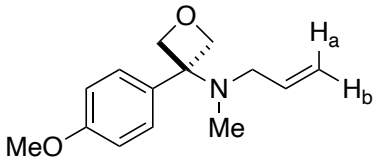
Prepared according to **General Procedure B** using oxetane sulfonyl fluoride **1** (49.2 mg) and ethyl 4-aminotetrahydro-2H-pyran-4-carboxylate (69.3 mg). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **20** as a colorless oil (30.1 mg, 45%). R_f = 0.15 (50% EtOAc/pentane); IR (film)/cm^{-1} 3314 (NH), 2956, 2870, 1722, (C=O st), 1610, 1513, 1461, 1245, 1179, 1137, 1103, 1029, 984, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H, 2 × Ar-CH), 6.93–6.85 (m, 2 H, 2 × Ar-CH), 4.91 (d, *J* = 6.5 Hz, 2 H, C*H*HO$_{(oxetane)}$C*H*H), 4.76 (d, *J* = 6.5 Hz, 2 H, CH*H*O$_{(oxetane)}$CH*H*), 3.97 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 3.82 (s, 3 H, OCH_3), 3.76 (ddt, *J* = 15.4, 6.0, 3.0 Hz, 2 H, C*H*HO$_{(THP)}$C*H*H), 3.36 (ddt, *J* = 11.6, 8.5, 3.8 Hz, 2 H, CH*H*O$_{(THP)}$CH*H*), 2.28 (br s, 1 H, NH), 1.86–1.76 (m, 2 H, O$_{(THP)}$(CH$_2$C*H*H)$_2$), 1.47 (ddd, *J* = 13.0, 8.5, 3.8 Hz, 2 H, O$_{(THP)}$(CH$_2$CH*H*)$_2$), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1 (C_q=O), 158.8 (Ar-C_qOMe), 134.9 (Ar-*C*$_q$C$_q$), 128.5 (2 × Ar-CH), 113.5 (2 × Ar-CH), 84.0 ($CH_2O_{(oxetane)}CH_2$), 64.0 ($CH_2O_{(THP)}CH_2$), 61.9 (Ar-C$_q$*C*$_q$), 61.0 (O*C*H$_2$CH$_3$), 58.6 (NH*C*$_q$CO$_2$Et), 55.2 (OCH_3), 35.1 (O$_{(THP)}$CH$_2$*C*H$_2$), 14.0 (OCH$_2$*C*H$_3$); HRMS (ESI) *m/z* calculated for $C_{18}H_{26}NO_5$ [M+H]: 336.1811, found 336.1814.

3-(4-Methoxyphenyl)-N,N-dimethyloxetan-3-amine (21)



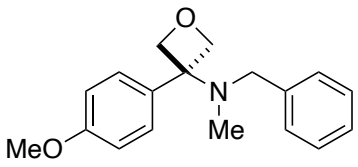
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and dimethylamine·HCl (45 mg). Purification by flash column chromatography (4% MeOH/CH_2Cl_2) afforded oxetane amine **21** as a white solid (30 mg, 72%). R_f = 0.20 (100% EtOAc); mp = 79–81 °C; IR (film)/cm^{-1} 2941, 2870, 2825, 2781, 1610, 1513, 1454, 1297, 1182, 1118, 1029, 988, 931, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.98 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 4.89 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.05 (s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 128.6 (2 × Ar-CH), 128.5 (Ar-C_qC_q), 113.0 (2 × Ar-CH), 80.0 (CH_2OCH_2), 66.5 (C_q), 55.2 (OCH_3), 38.2 (2 × NCH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NO_2$ [M+H]: 208.1343, found: 208.1338.

***N*-Allyl-3-(4-methoxyphenyl)-*N*-methyloxetan-3-amine (22)**



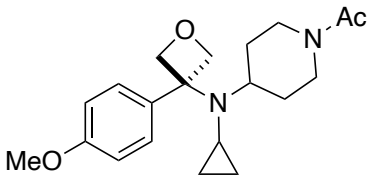
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *N*-methylprop-2-en-1-amine (17.1 mg). Purification by flash column chromatography (8–12% acetone/pentane) afforded oxetane amine **22** as a white solid (28.0 mg, 60%). R_f = 0.12 (10% acetone/pentane); mp = 59–61 °C; IR (film)/cm^{-1} 3027, 2941, 2870, 2781, 1610 (C=C st), 1577, 1513, 1446, 1413, 1349, 1297, 1249, 1178, 1118, 1062, 1021, 988, 932, 813, 779, 731, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–7.03 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 5.85 (ddt, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.4 Hz, ^3J = 6.4 Hz, 1 H, *H*C=CH_2), 5.14–5.11 (br m, 1 H, H_a), 5.10–5.09 (br m, 1 H, H_b), 4.90 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 2.71 (br d, *J* = 6.4 Hz, 2 H, CH_2N), 2.01 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 136.1 (H*C*=CH_2), 129.3 (Ar-C_qC_q), 128.5 (2 × Ar-CH), 117.4 (HC=*C*H_2), 113.1 (2 × Ar-CH), 80.5 (CH_2OCH_2), 66.6 (C_q), 55.3 (OCH_3), 54.3 (CH_2N), 34.8 (NCH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{20}NO_2$ [M+H]: 234.1494, found: 234.1497.

***N*-Benzyl-3-(4-methoxyphenyl)-N-methyloxetan-3-amine (23)**



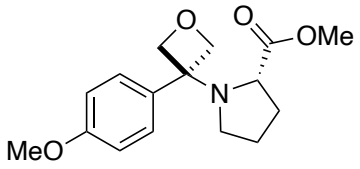
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *N*-methyl-1-phenylmethanamine (31 μL). Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetane amine **23** as a white solid (37 mg, 65%). R_f = 0.19 (40% Et_2O/hexane); mp = 113–114 °C; IR (film)/cm^{-1} 2944,2874, 2837, 2792, 1610, 1514, 1454, 1297, 1245, 1178, 1111, 1029, 988, 931, 827, 738, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4 H, 4 × Ar-CH), 7.28–7.23 (m, 1 H, Ar-CH), 7.14–7.11 (m, 2 H, 2 × Ar-CH), 6.99–6.95 (m, 2 H, 2 × Ar-CH), 4.97 (s, 4 H, CH_2OCH_2), 3.87 (s, 3 H, NCH_3), 3.22 (s, 2 H, NCH_2), 1.92 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 139.1 (Ar-C_q), 129.8 (Ar-C_q), 128.7 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.1 (Ar-CH), 113.3 (2 × Ar-CH), 80.7 (CH_2OCH_2), 66.8 (C_q), 55.3 (NCH_2), 55.2 (OCH_3), 34.6 (NCH_3); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_2$ [M+H]: 284.1651, found: 284.1647.

1-(4-(Cyclopropyl(3-(4-methoxyphenyl)oxetan-3-yl)amino)piperidin-1-yl)ethan-1-one (24)



Prepared according to **General Procedure A** under N_2 with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 1-(4-(cyclopropylamino)piperidin-1-yl)ethan-1-one (43.7 mg). Purification by flash chromatography (40% acetone/hexane) afforded oxetane amine **24** as a white solid (26.4 mg, 38%). R_f = 0.24 (40% acetone/hexane); mp = 154–156 °C; IR (film)/cm^{-1} 3004, 2952, 2870, 1640 (C=O st), 1513, 1449, 1244, 1181, 1028, 987, 831, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.29 (m, 2 H, 2 × Ar-CH), 7.08–6.83 (m, 2 H, 2 × Ar-CH), 5.13–4.99 (m, 2 H, C*H*HOC*H*H), 4.80 (d, *J* = 5.7 Hz, 1 H, CH*H*OCH$_2$), 4.78 (d, *J* = 5.7 Hz, 1 H, CH$_2$OCH*H*) , 4.56 (ddt, *J* = 13.3, 4.4, 2.4 Hz, 1 H, C*H*HNCH$_2$), 3.83 (s, 3 H, OCH$_3$), 3.70 (ddt, *J* = 13.6, 4.2, 2.4 Hz, 1 H, CH$_2$NC*H*H), 2.86 (td, *J* = 13.2, 2.1 Hz, 1 H, CH*H*NCH$_2$), 2.52 (tt, *J* = 11.8, 3.6 Hz, 1 H, C$_{(piperidine)}$H), 2.33 (ddt, *J* = 13.3, 4.4, 2.4 Hz, 1 H, CH$_2$NCH*H*), 2.03 (s, 3 H, C(O)CH$_3$), 1.72–1.65 (m, 1 H, C$_{(cyclopropyl)}$H), 1.61–1.48 (m, 2 H, 2 × C*H*HC$_{(piperidine)}$H), 1.34 (d, *J* = 12.6 Hz, 2 H, 2 × CH*H*C$_{(piperidine)}$H), 0.59–0.47 (m, 4 H, 2 × C$_{(cyclopropyl)}$H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C$_q$=O), 158.7 (Ar-C$_q$OMe), 133.9 (Ar-*C*$_q$C$_q$), 127.9 (2 × Ar-CH), 113.4 (2 × Ar-CH), 81.1 (*C*H$_2$OCH$_2$), 81.0 (CH$_2$O*C*H$_2$), 68.1 (C$_q$), 57.4 (C$_{(piperidine)}$H), 55.2 (OCH$_3$), 46.5 (*C*H$_2$NCH$_2$), 41.6 (CH$_2$N*C*H$_2$), 32.3 (*C*H$_2$C$_{(piperidine)}$HCH$_2$), 31.5 (CH$_2$C$_{(piperidine)}$H*C*H$_2$), 27.3 (C$_{(cyclopropyl)}$H), 21.4 (C(O)*C*H$_3$), 6.4 (2 × C$_{(cyclopropyl)}$H$_2$); HRMS (ESI) *m/z* calcd for $C_{20}H_{29}N_2O_3^+$ [M+H]$^+$: 345.2178, found: 345.2183.

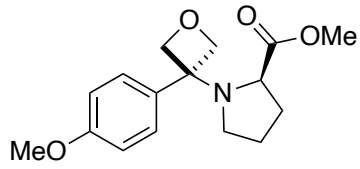
Methyl (3-(4-methoxyphenyl)oxetan-3-yl)-L-prolinate ((–)-25)



Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and L-proline methyl ester hydrochloride (40 mg). Purification by flash column chromatography (10% Et_2O/CH_2Cl_2) afforded oxetane amine (–)-**25** as a colorless oil (42 mg, 72%, 100% *ee*). $[\alpha]_D^{21}$ – 37.9 (*c* 1.16, $CHCl_3$). R_f = 0.22 (10% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2950, 2876, 1730 (C=O st), 1611, 1513, 1460, 1245, 1177, 1160, 1029, 984, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 2 H, 2 × Ar-CH), 6.93–6.86 (m, 2 H, 2 × Ar-CH), 5.05–4.95 (m, 3 H, C*H*$_2$OC*H*H), 4.86 (d, *J* = 6.4 Hz, CH$_2$OCH*H*), 3.82 (s, 3 H, Ar-OCH$_3$), 3.58 (s, 3 H, CO$_2$CH$_3$), 3.55–3.49 (m, 1 H, CH), 3.22–3.15 (m, 1 H, NC*H*H), 2.84–2.86 (m, 1 H, NCH*H*), 2.03–1.88 (m, 3 H, NCHC*H*$_2$ + NCH$_2$C*H*H), 1.83–1.72 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C$_q$=O), 158.7 (Ar-C$_q$OMe), 133.8 (Ar-*C*$_q$C$_q$), 128.4 (2 × Ar-CH), 113.6 (2 × Ar-CH), 80.6 (*C*H$_2$OCH$_2$), 79.3 (CH$_2$O*C*H$_2$), 65.5 (Ar-C$_q$*C*$_q$), 60.2 (CH), 55.2 (Ar-OCH$_3$), 51.7 (CO$_2$*C*H$_3$), 48.2 (NCH$_2$), 30.7 (NCH*C*H$_2$), 24.0 (NCH$_2$*C*H$_2$); HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO_4$ [M+H]: 292.1549, found 292.1560.

HPLC Conditions: Chiralpak IF 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 13.9 min (*R* enantiomer), 15.9 min (*S* enantiomer).

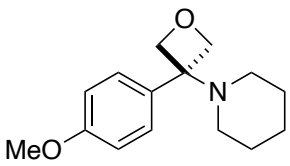
Methyl (3-(4-methoxyphenyl)oxetan-3-yl)-D-prolinate ((+)-26)



Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and D-proline methyl ester hydrochloride (40 mg). Purification by flash column chromatography (10% Et_2O/CH_2Cl_2) afforded oxetane amine (+)-**26** as a colorless oil (40 mg, 69%, 99.3% *ee*). $[\alpha]_D^{23}$ + 30.7 (*c* 1.30, $CHCl_3$). Characterization data identical to that reported for enantiomeric oxetane amine (–)-**25**.

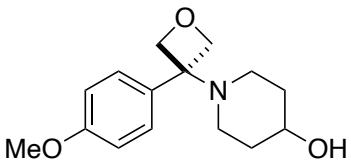
HPLC Conditions: Chiralpak IF 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 13.9 min (*R* enantiomer), 15.9 min (*S* enantiomer).

1-(3-(4-Methoxyphenyl)oxetan-3-yl)piperidine (27)



Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and piperidine (24 μL). Purification by flash column chromatography (40% EtOAc/pentane) afforded oxetane amine **27** as a colorless oil (27.2 mg, 55%). R_f = 0.18 (40% EtOAc/pentane); IR (film)/cm^{-1} 2934, 1610, 1512, 1454, 1297, 1245, 1178, 1115, 1030, 989, 923, 833, 811; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.95 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, 2 × Ar-CH), 4.90–4.84 (m, 4 H, CH_2OCH_2), 3.83 (s, 3 H, OCH_3), 2.16 (br s, 4 H, CH_2NCH_2), 1.60 (p, *J* = 5.7 Hz, 4 H, 2 × NCH_2CH_2), 1.37–1.24 (br m, 2 H, $NCH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_qOMe), 129.5 (Ar-C_qC_q), 128.6 (2 × Ar-CH), 112.9 (2 × Ar-CH), 80.5 (CH_2OCH_2), 66.6 (C_q), 55.2 (OCH_3), 47.1 (CH_2NCH_2), 26.1 (2 × NCH_2CH_2), 24.3 ($NCH_2CH_2CH_2$); HRMS (ESI) *m/z* calculated for $C_{15}H_{22}NO_2$ [M+H]: 248.1651, found 248.1658.

1-(3-(4-Methoxyphenyl)oxetan-3-yl)piperidin-4-ol (28)

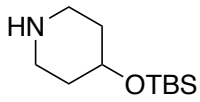


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and piperidin-4-ol (24.4 mg). Purification by flash column chromatography (1–5% MeOH/CH_2Cl_2) afforded oxetane amine **28** as a white solid (26.3 mg, 50%). R_f = 0.28 (10% MeOH/ CH_2Cl_2); mp = 126 °C; IR (film)/cm^{-1} 3399 (br OH), 2941, 2837, 1610, 1513, 1465, 1368, 1297, 1245, 1179, 1145, 1118, 1081, 1029, 992, 929, 924, 835, 760, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.96 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.89 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 3.52–3.49 (br m, 1 H, CH), 2.60–2.58 (br m, 2 H, $CH_{eq}HNCH_{eq}H$), 1.94–1.84 (br m, 4 H, $CH_{ax}NCH_{ax}$ + $CH_{eq}HCHCH_{eq}H$), 1.66–1.43 (m, 3 H, $CH_{ax}CHCH_{ax}$ + OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 129.1 (Ar-C_qC_q), 128.4 (2 × Ar-CH), 113.1 (2 × Ar-CH), 80.4 (CH_2OCH_2), 67.8 (br and weak, CH), 66.2 (C_q), 55.3 (OCH_3), 43.7 (CH_2NCH_2), 34.6 (CH_2CHCH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_3$ [M+H]: 264.1600, found: 264.1600.

Notes:

The multiplet in the ^{1}H NMR spectrum at 1.66–1.43 ppm is a mixture of a broad singlet (1.66–1.43, OH) and a dddd (1.62, ^2J = 13.4 Hz, $^3J_{ax,ax}$ = 10.3 Hz, $^3J_{ax,ax}$ = 9.4 Hz, $^3J_{ax,eq}$ = 4.2 Hz, $CH\mathbf{H}_{ax}CHCH\mathbf{H}_{ax}$).

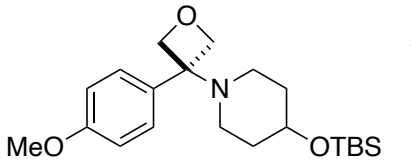
4-((*tert*-Butyldimethylsilyl)oxy)piperidine (S15)[41]



Pyridine (0.4 mL, 4.9 mmol, 1.2 equiv) was added dropwise to a solution of piperidin-4-ol (404.7 mg, 4 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (4 mL, 1 M) in a 25 mL round bottom flask at 0 °C. After stirring for 5 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.01 mL, 4.4 mmol, 1.1 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h and then quenched with ice-cold (0 °C) distilled water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (3–15% MeOH/CH_2Cl_2) afforded a mixture of the free piperidine **S15** with its triflate salt as a light-yellow solid (938.4 mg; presence of salt detected by ^{13}C and ^{19}F NMR). This mixture was dissolved in CH_2Cl_2 (30 mL) and washed with a saturated aqueous sodium bicarbonate solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to again afford a mixture of the free piperidine and triflate salt. This residue was dissolved in CH_2Cl_2 (30 mL) and washed with aq. NaOH (1 M, 3 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to afford piperidine **S15** as a light-yellow oil (470.4 mg, 55%). R_f = 0.24 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 2930, 2885, 2855,

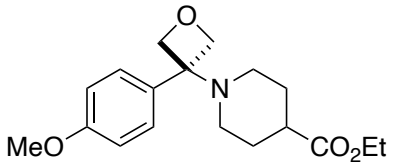
1468, 1361, 1316, 1252, 1103, 1051, 1178, 1003, 910, 835, 775, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (tt, $^{3}J_{ax,ax}$ = 8.8 Hz, $^{3}J_{ax,eq}$ = 3.9 Hz, 1 H, CH), 3.07 (ddd, ^{2}J = 12.7 Hz, $^{3}J_{eq,eq}$ and $^{3}J_{eq,ax}$ = 3.9 Hz, 2 H, CH_{eq}HNCH_{eq}H), 2.61 (ddd, ^{2}J = 12.7 Hz, $^{3}J_{ax,ax}$ = 9.6 Hz, $^{3}J_{ax,eq}$ = 3.1 Hz, 2 H, CHH_{ax}NCHH_{ax}), 1.80–1.74 (br m, 2 H, CH_{eq}HCHCH_{eq}H), 1.55 (br s, 1 H, NH) 1.43 (dddd, ^{2}J = 13.0 Hz, $^{3}J_{ax,ax}$ = 9.6 Hz, $^{3}J_{ax,ax}$ = 8.8 Hz, $^{3}J_{ax,eq}$ = 3.9 Hz, 2 H, CHH_{ax}CHCHH_{ax}), 0.90 (s, 9 H, 3 × $SiCCH_3$), 0.06 (s, 6 H, 2 × $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 68.5 (CH), 44.0 (CH_2NCH_2), 36.3 (CH_2CHCH_2), 25.8 (3 × SiC_qCH_3), 18.0 ($SiC_q(CH_3)_3$), -4.7 (2 × $SiCH_3$). The observed characterization data (^{1}H, ^{13}C) were consistent with that previously reported.[42]

4-((*tert*-Butyldimethylsilyl)oxy)-1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidine (29)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and OTBS-piperidine **S15** (51.7 mg). Purification by flash column chromatography (5–10% acetone/pentane) afforded oxetane amine **29** as a colorless oil (45.3 mg, 60%). R_f = 0.16 (10% acetone/pentane); IR (film)/cm^{-1} 2945, 2855, 1610, 1513, 1469, 1409, 1375, 1297, 1249, 1178, 1103, 1051, 992, 924, 869, 835, 775, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.98 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.88 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 3.51–3.47 (br m, 1 H, CH), 2.56–2.53 (br m, 2 H, CH_{eq}HNCH_{eq}H), 1.84 (br dd, ^{2}J and $^{3}J_{ax,ax}$ = 9.3 Hz, 2 H, CHH_{ax}NCHH_{ax}), 1.80–1.73 (br m, 2 H, CH_{eq}HCHCH_{eq}H) 1.60 (dddd, ^{2}J = 12.7 Hz, $^{3}J_{ax,ax}$ = 9.3 Hz, $^{3}J_{ax,ax}$ = 9.2 Hz, $^{3}J_{ax,eq}$ = 3.6 Hz, 2 H, CHH_{ax}CHCHH_{ax}), 0.80 (s, 9 H, 3 × $SiCCH_3$), –0.03 (s, (^{29}Si satellites: d, $^{2}J_{HSi}$ = 6.1 Hz), 6 H, 2 × $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 129.4 (Ar-C_qC_q), 128.5 (2 × Ar-CH), 113.0 (2 × Ar-CH), 80.4 (CH_2OCH_2), 68.2 (br and weak, CHOTBS), 66.3 (Ar-C_qC_q), 55.3 (OCH_3), 43.6 (CH_2NCH_2), 35.0 (CH_2CHCH_2), 25.8 (3 × SiC_qCH_3), 18.0 ($SiC_q(CH_3)_3$), –4.7 (2 × $SiCH_3$); HRMS (ESI) *m/z* calcd for $C_{21}H_{36}NO_3Si$ [M+H]: 378.2464, found: 378.2468.

Ethyl 1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidine-4-carboxylate (30)

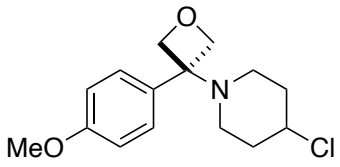


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and ethyl piperidine-4-carboxylate (38.5 mg). Purification by flash column chromatography (30–35% EtOAc/pentane) afforded oxetane amine **30** as white crystals (47.1 mg, 74%). R_f = 0.09 (30% EtOAc/pentane); mp = 80 °C; IR (film)/cm^{-1} 2952, 2874, 2810, 1718 (C=O st), 1610, 1510, 1443, 1368, 1297, 1245, 1204, 1178, 1118, 1059, 1021, 988, 928, 816, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.96 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.88 (d, *J* = 5.8 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 5.8 Hz, 2 H, CH*H*OCH*H*), 4.09 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.83 (s, 3 H, OCH_3), 2.73 (br d, ^{2}J = 10.7 Hz, 2 H, CH_{eq}HNCH_{eq}H), 2.12–2.04 (m, 1 H, CH), 1.91–1.87 (m, 2 H, CH_{eq}HCHCH_{eq}H), 1.84–1.78 (m, 2 H, CHH_{ax}CHCHH_{ax}), 1.76–1.67 (m, 2 H, CHH_{ax}NCHH_{ax}), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (C_q=O), 158.6 (Ar-C_qOMe), 129.1 (Ar-C_qC_q), 128.4 (2 × Ar-CH), 113.0 (2 × Ar-CH), 80.3 (CH_2OCH_2), 66.3 (Ar-C_qC_q), 60.2 (OCH_2CH_3), 55.3 (OCH_3), 45.7 (CH_2NCH_2), 41.0 (CH), 28.3 (CH_2CHCH_2), 14.1 (OCH_2CH_3); HRMS (APCI) *m/z* calcd for $C_{18}H_{26}NO_4^+$ $[M+H]^+$: 320.1856, found: 320.1861.

Notes:

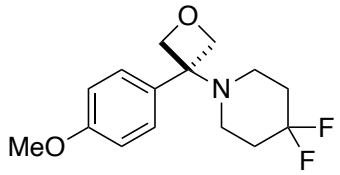
***30** was further characterized by X-ray crystallography (see Fig. S36–37).*

4-Chloro-1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidine (31)



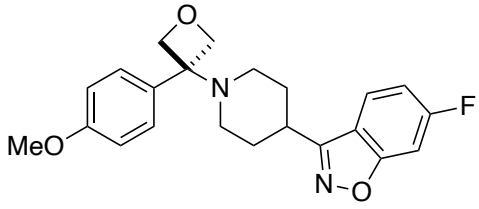
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4-chloropiperidine (29.0 mg). Purification by flash column chromatography (2–3% MeOH/CH_2Cl_2) afforded oxetane amine **31** as a pale-yellow solid (43.7 mg, 78%). R_f = 0.33 (3% MeOH/ CH_2Cl_2); mp = 91–92 °C; IR (film)/cm^{-1} 2941, 2870, 2833, 2761, 1674, 1607, 1510, 1450, 1383, 1342, 1297, 1245, 1179, 1144, 1025, 988, 929, 869, 842, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.96 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 4.89 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.84 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.97–3.73 (br s, 1 H, CH), 3.83 (s, 3 H, OCH_3), 2.59 (br s, 2 H, CH_{eq}HNCH_{eq}H), 2.14–2.09 (br m, 2 H, CH_{eq}HCHCH_{eq}H), 1.97–1.90 (br m, 4 H, CHH_{ax}NCHH_{ax} + CHH_{ax}CHCHH_{ax}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 129.0 (Ar-C_qC_q), 128.3 (2 × Ar-CH), 113.1 (2 × Ar-CH), 80.2 (CH_2OCH_2), 66.2 (C_q), 57.1 (CH), 55.3 (OCH_3), 44.4 (br and weak, CH_2NCH_2), 35.8 (*C*H_2CH*C*H_2); HRMS (APCI) *m/z* calcd for $C_{15}H_{21}{}^{35}ClNO_2^+$ $[M+H]^+$: 282.1255, found: 282.1255.

4,4-Difluoro-1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidine (32)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4,4-difluoropiperidine (29.6 mg). Purification by flash column chromatography (0–10% Et_2O/CH_2Cl_2) afforded oxetane amine **32** as a white solid (46.2 mg, 82%). R_f = 0.32 (10% Et_2O/CH_2Cl_2); mp = 72–75 °C; IR (film)/cm^{-1} 2945, 2878, 2837, 1610, 1513, 1469, 1364, 1297, 1249, 1182, 1118, 1033, 995, 969, 910, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.96 (m, 2 H, 2 × Ar-CH), 6.92–6.89 (m, 2 H, 2 × Ar-CH), 4.92 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.84 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.33 (br t, ^3J = 5.6 Hz, 4 H, CH_2NCH_2), 2.03 (tt, $^3J_{HF}$ = 13.3 Hz, ^3J = 5.6 Hz, 4 H, $CH_2CF_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 128.9 (Ar-C_qC_q), 128.2 (2 × Ar-CH), 121.6 (t, $^1J_{CF}$ = 241.7 Hz, CF_2), 113.3 (2 × Ar-CH), 80.2 (CH_2OCH_2), 66.1 (Ar-C_qC_q), 55.3 (OCH_3), 43.0 (t, $^3J_{CF}$ = 5.6 Hz, CH_2NCH_2), 34.3 (t, $^2J_{CF}$ = 22.8 Hz, *C*H_2CF_2CH$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –97.5 (br); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO_2F_2$ $[M+H]$: 284.1462, found: 284.1463.

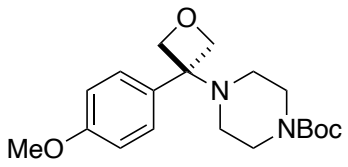
6-Fluoro-3-(1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidin-4-yl)benzo[*d*]isoxazole (33)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (53.2 mg). Purification by flash column chromatography (35–50% EtOAc/pentane) afforded oxetane amine **33** as a white solid (44.3 mg, 58%). R_f = 0.25 (50% EtOAc/pentane); mp = 166 °C; IR (film)/cm^{-1} 2945, 2876, 2810, 1614, 1513, 1446, 1349, 1297, 1245, 1178, 1122, 1066, 1028, 992, 958, 924, 839, 760, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, ^3J = 8.7 Hz, $^4J_{HF}$ = 5.1 Hz, 1 H, Ar-CFAr-CHAr-C*H*), 7.24 (ddd, $^3J_{HF}$ = 8.5 Hz, ^4J = 2.1 Hz, ^5J = 0.5 Hz, 1 H, Ar-CFAr-CH-Ar-C_q), 7.08–7.01 (m, 3 H, 2 × $Ar_{(PMP)}$-CH + Ar-CFAr-C*H*Ar-CH), 6.96–6.93 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 4.94 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3), 2.94–2.91 (br m, 2 H, CH_{eq}HNCH_{eq}H), 2.90–2.84 (m, 1 H, CH), 2.19–2.09 (m, 2 H, CHH_{ax}CHCHH_{ax}), 2.07–2.03 (br m, 2 H, CH_{eq}HCHCH_{eq}H), 1.87 (ddd, ^2J and $^3J_{ax,ax}$ = 11.4 Hz, $^3J_{ax,eq}$ = 2.4 Hz, 2 H, CHH_{ax}NCHH_{ax}); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0 (d, $^1J_{CF}$ = 250.5 Hz, Ar-CF), 163.8 (d, $^3J_{CF}$ = 13.3 Hz, OAr-C_qCH), 160.9 (C_q=N), 158.7 (Ar-C_qOMe), 129.0 ($Ar_{(PMP)}$-C_qC_q), 128.5 (2 × $Ar_{(PMP)}$-CH), 122.5 (d, $^3J_{CF}$ = 11.2 Hz, Ar-CFAr-CHAr-*C*H), 117.2 (OAr-C_qAr-C_q), 113.1 (2 × $Ar_{(PMP)}$-CH), 112.3 (d, $^2J_{CF}$ = 25.2 Hz, Ar-CFAr-*C*HAr-CH), 97.4 (d, $^2J_{CF}$ = 26.5 Hz, Ar-CFAr-*C*HAr-C_q), 80.3 (CH_2OCH_2), 66.4 (C_q), 55.3 (OCH_3), 46.3 (CH_2NCH_2), 34.5 (CH), 30.6 (*C*H_2CH*C*H_2);

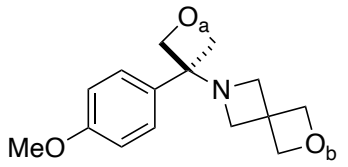
^{19}F NMR (377 MHz, $CDCl_3$) δ –109.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N_2O_3F$ [M+H]: 383.1771, found: 383.1775.

tert-Butyl 4-(3-(4-methoxyphenyl)oxetan-3-yl)piperazine-1-carboxylate (34)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *tert*-butyl piperazine-1-carboxylate (45 mg). Purification by flash column chromatography (50% EtOAc/hexane) afforded oxetane amine **34** as a white solid (48 mg, 69%). R_f = 0.11 (50% EtOAc/hexane); mp = 134–136 °C; IR (film)/cm^{-1} 2937, 2870, 1688, 1610, 1513, 1457, 1420, 1364, 1249, 1174, 1125, 1032, 991, 864, 835, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97–6.94 (m, 2 H, 2 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.45 (br t, *J* = 5.1 Hz, 4 H, $CH_2NBocCH_2$), 2.20 (br t, *J* = 5.1 Hz, 4 H, $CH_2N_{(oxetane)}CH_2$), 1.40 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 154.4 (C_q=O), 128.9 (Ar-C_qC_q), 128.4 (2 × Ar-CH), 113.2 (2 × Ar-CH), 79.8 (CH_2OCH_2), 79.6 ($C_q(CH_3)_3$), 66.2 (Ar-C_qC_q), 55.3 (OCH_3), 45.8 ($CH_2N_{(oxetane)}CH_2$), 44.0 (br and weak, $CH_2NBocCH_2$), 43.2 (br and weak, $CH_2NBocCH_2$), 28.3 (3 × CH_3); HRMS (ESI) *m/z* calcd for $C_{19}H_{29}N_2O_4$ [M+H]: 349.2127, found: 349.2140.

6-(3-(4-Methoxyphenyl)oxetan-3-yl)-2-oxa-6-azaspiro[3.3]heptane (35)

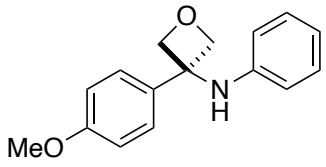


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2-oxa-6-azaspiro[3.3]heptane (24.0 mg). Purification by flash column chromatography (20–90% Et_2O/CH_2Cl_2, then 1–4% MeOH/Et_2O) afforded oxetane amine **35** as a white solid (33.8 mg, 65%). R_f = 0.10 (1% MeOH/Et_2O); mp = 87–89 °C; IR (film)/cm^{-1} 2945, 2866, 1610, 1513, 1461, 1342, 1301, 1249, 1179, 1143, 1103, 1033, 977, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.92–6.89 (m, 2 H, 2 × Ar-CH), 4.86–4.82 (m, 4 H, $CH_2O_aCH_2$), 4.77 (s, 4 H, $CH_2O_bCH_2$), 3.82 (s, 3 H, OCH_3), 3.51 (s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 132.6 (Ar-C_qC_q), 127.4 (2 × Ar-CH), 113.7 (2 × Ar-CH), 81.4 ($CH_2O_bCH_2$), 77.6 ($CH_2O_aCH_2$), 65.2 (Ar-C_qC_q), 57.2 (CH_2NCH_2), 55.2 (OCH_3), 37.7 (C_qCH_2N); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO_3$ [M+H]: 262.1443, found: 262.1437.

Notes:

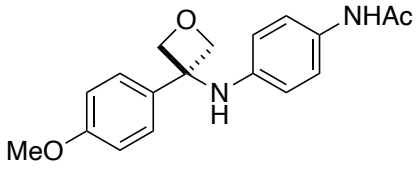
*The multiplet in the ^{1}H NMR spectrum at 4.86–4.82 ppm is likely to be two separate doublets (C**H**HO$_a$C**H**H and CH**H**O$_a$CH**H**) with J = 6.9 Hz.*

3-(4-Methoxyphenyl)-N-phenyloxetan-3-amine (36)



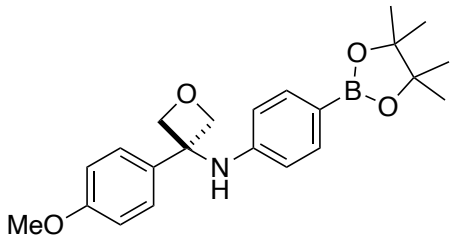
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and aniline (22 μL). Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetane amine **36** as a white solid (47 mg, 92%). R_f = 0.22 (40% Et_2O/hexane); mp = 169–170 °C; IR (film)/cm^{-1} 3347, 2952, 2873, 2837, 1603, 1506, 1301, 1245, 1178, 1029, 984, 831, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2 H, 2 × Ar-CH), 7.14–7.09 (m, 2 H, 2 × Ar-CH), 6.94–6.91 (m, 2 H, 2 × Ar-CH), 6.72 (tt, *J* = 7.3, 1.1 Hz, 1 H, Ar-CH), 6.32–6.29 (m, 2 H, 2 × Ar-CH), 4.98 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.89 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 4.62 (s, 1 H, NH), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 144.6 (Ar-C_qNH), 133.9 (Ar-C_qC_q), 129.1 (2 × Ar-CH), 126.6 (2 × Ar-CH), 118.0 (Ar-CH), 114.1 (2 × Ar-CH), 114.0 (2 × Ar-CH), 84.4 (CH_2OCH_2), 59.8 (C_q), 55.2 (OCH_3); HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_2$ [M+H]: 256.1338, found: 256.1328.

_N_-(4-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)phenyl) acetamide (37)



Prepared according to **General Procedure A** under N_2 with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *N*-(4-aminophenyl) acetamide (36 mL). Purification by flash chromatography (60% acetone/hexane) afforded oxetane amine **37** as a white solid (58.0 mg, 93%). R_f = 0.30 (60% acetone/hexane); mp = 100–103 °C; IR (film)/cm^{-1} 3295 (NH), 1654 (C=O st), 1606, 1513, 1300, 1244, 1177, 1028, 980, 820 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 2 H, 2 × Ar-CH), 7.19–7.15 (m, 2 H, 2 × Ar-CH), 7.13 (br s, 1 H, AcNH), 6.94–6.87 (m, 2 H, 2 × Ar-CH), 6.26–6.22 (m, 2 H, 2 × Ar-CH), 4.95 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 6.3 Hz, 2H, CH*H*OCH*H*), 4.61 (br s, 1 H, NH), 3.81 (s, 3 H, OCH_3), 2.10 (s, 3 H, $C(O)CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C_q=O), 158.8 (Ar-C_qOMe), 141.8 (Ar-C_qNH), 133.7 (Ar-C_qC_q), 128.6 (Ar-C_qNHAc), 126.6 (2 × Ar-CH) , 122.2 (2 × Ar-CH), 114.3 (2 × Ar-CH), 114.0 (2 × Ar-CH), 84.3 (CH_2OCH_2), 59.9 (Ar-C_qC_q), 55.3 (OCH_3), 24.2 (CH_3CO); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}N_2O_3$ [M+H]: 313.1552, found: 313.1558.

3-(4-Methoxyphenyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-amine (38)



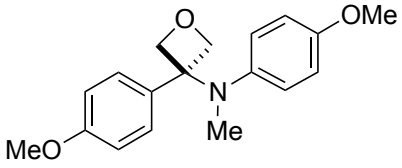
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (53 mg). Purification by flash column chromatography (40% Et_2O/hexane) afforded oxetane amine **38** as a white solid (58 mg, 76%). R_f = 0.15 (40% Et_2O/hexane); mp = 152–154 °C, IR (film)/cm^{-1} 3362, 2974, 2877, 1602, 1513, 1394, 1356, 1319, 1181, 1140, 1088, 987, 861, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.54 (m, 4 H, 4 × Ar-CH), 6.92–6.88 (m, 2 H, 2 × Ar-CH), 6.29–6.26 (m, 2 H, 2 × Ar-CH), 4.97 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.89 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 4.82 (s, 1 H, NH), 3.81 (s, 3 H, OCH_3), 1.31 (s, 12 H, 4 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (Ar-C_qOMe), 147.3 (Ar-C_qNH), 136.1 (2 × Ar-CH), 133.5 (Ar-C_qC_q), 126.6 (2 × Ar-CH), 114.0 (2 × Ar-CH), 113.2 (2 × Ar-CH), 84.3 (CH_2OCH_2), 83.2 (OC_qC_qO), 59.7 (Ar-C_qC_q), 55.2 (OCH_3), 24.8 (4 × CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{29}{}^{11}BNO_4$ [M+H]: 382.2190, found: 382.2197.

Notes:

The Ar-C_qBpin signal was not observed in the ^{13}C NMR spectrum.

***38** was further characterized by X-ray crystallography (see Fig. S38–39).*

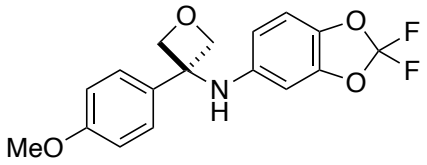
_N_,3-bis(4-Methoxyphenyl)-_N_-methyloxetan-3-amine (39)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4-methoxy-*N*-methylaniline (33.0 mg). Purification by flash column chromatography (5% acetone/pentane) afforded oxetane amine **39** with 20% of an unknown impurity as a light-yellow gum (55.9 mg). Repurification of the mixture by flash column chromatography (5–10% acetone/pentane) afforded oxetane fluoride **39** as a light-yellow gum (47.0 mg, 78%). R_f = 0.11 (10% acetone/pentane); IR (film)/cm^{-1} 2997, 2952, 2878, 2833, 2248, 1610, 1510, 1461, 1349, 1297, 1241, 1178, 1133, 1070, 1033, 992, 906, 816, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2 × Ar-CH), 6.94–6.90 (m, 2 × Ar-CH), 6.80–6.75 (m, 2 × Ar-CH), 6.29–7.25 (m, 2 × Ar-CH), 5.12 (d, *J* = 6.1 Hz, C*H*HOC*H*H), 4.70 (d, *J* = 6.1 Hz, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 2.99 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 ($Ar_{(PMP)}$-C_qOMe), 151.5 ($Ar_{(Aniline)}$-C_qOMe), 141.4 (Ar-C_qN), 134.1 (Ar-C_qC_q), 126.9 (2 × Ar-CH), 114.6 (2 × Ar-CH), 114.2 (2 × Ar-CH), 114.0 (2 × Ar-CH), 82.8

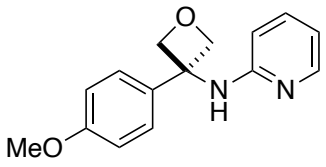
(CH_2OCH_2), 64.8 (C_q), 55.6 (OCH_3), 55.2 (OCH_3), 35.8 (NCH_3); HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_3$ [M+H]: 300.1600, found: 300.1589.

2,2-Difluoro-*N*-(3-(4-methoxyphenyl)oxetan-3-yl)benzo[d][1,3]dioxol-5-amine (40)



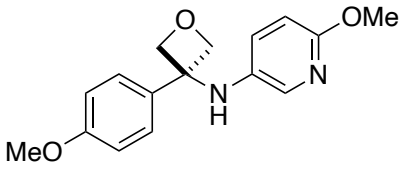
Prepared according to **General Procedure A** under N_2 with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2,2-difluorobenzo[d][1,3]dioxol-5-amine-methane (29.7 μL). Purification by flash chromatography (40% Et_2O/hexane) afforded oxetane amine **40** as a white solid (66 mg, 98%). R_f = 0.18 (40% Et_2O/hexane); mp = 116–118 °C; IR (film)/cm^{-1} 3324 (NH), 1610, 1498, 1360, 1244, 1140, 1025, 965, 935; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.51 (m, 2 H, 2 × Ar-CH), 6.97–6.91 (m, 2 H, 2 × Ar-CH), 6.78 (d, *J* = 8.6 Hz, 1 H, NHAr-C_qAr-CHAr-C*H*), 6.04 (d, *J* = 2.3 Hz, 1 H, NHAr-C_qAr-C*H*), 5.94 (dd, *J* = 8.6, 2.4 Hz, 1 H, NHAr-C_qAr-C*H*Ar-CH), 4.96 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 4.63 (br s, 1 H, NH), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_qOMe), 144.5 (Ar-$C_q$$OCF_2$), 141.6 (Ar-$C_q$NH), 136.3 (Ar-$C_q$$OCF_2$), 133.1 (Ar-$C_q$$C_q$), 131.6 (t, J_{C-F} = 254.0 Hz, CF_2), 126.6 (2 × Ar-CH), 114.2 (2 × Ar-CH), 109.8 (Ar-CH), 108.0 (Ar-CH), 96.6 (Ar-CH), 84.0 (CH_2OCH_2), 60.2 (Ar-$C_q$$C_q$), 55.3 ($OCH_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –50.33; HRMS (APCI) *m/z* calcd for $C_{17}H_{16}F_2NO_4^+$ $[M+H]^+$: 336.1042, found: 336.1052.

***N*-(3-(4-Methoxyphenyl)oxetan-3-yl)pyridin-2-amine (41)**



Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 2-aminopyridine (23 mg). Purification by flash column chromatography (basic alumina [activity IV], 30% EtOAc/pentane) afforded oxetane amine **41** as a white solid (16 mg, 59%). R_f = 0.18 (silica TLC plate, 40% EtOAc/pentane); mp = 154–156 °C; IR (film)/cm^{-1} 3314 (NH), 2956, 2870, 1722, 1610, 1513, 1461, 1245, 1179, 1137, 1103, 1029, 984, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H, NAr-CH), 7.62–7.53 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 7.32 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1 H, $Ar_{(Py)}$-CH), 6.95–6.88 (m, 2 H, 2 × Ar-CH), 6.60 (ddd, 7.1, 5.0, 0.7 Hz, 1 H, $Ar_{(Py)}$-CH), 5.91 (d, *J* = 8.4 Hz, 1 H, $Ar_{(Py)}$-CH), 5.71 (s, 1 H, NH), 5.02–4.94 (m, 4 H, CH_2OCH_2), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 156.5 (NHAr-C_q), 148.5 ($Ar_{(Py)}$-CH), 137.4 ($Ar_{(Py)}$-CH), 134.0 (Ar-$C_q$$C_q$), 126.4 (2 × $Ar_{(PMP)}$-CH), 114.0 (2 × $Ar_{(PMP)}$-CH), 113.6 ($Ar_{(Py)}$-CH), 107.2 (NHAr-C_qAr-*C*H), 84.1 (CH_2OCH_2), 68.9 (C_q), 55.2 (OCH_3); HRMS (ESI) *m/z* calculated for $C_{15}H_{17}N_2O_2$ [M+H]: 257.1290, found 257.1287.

6-Methoxy-*N*-(3-(4-methoxyphenyl)oxetan-3-yl)pyridin-3-amine (42)

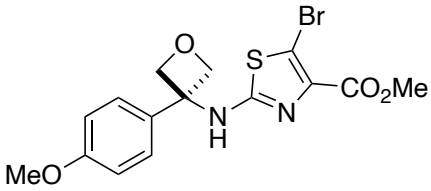


Prepared according to **General Procedure A** under N_2 with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 6-methoxypyridin-3-amine (29.8 mg). Purification by flash chromatography (20% Et_2O/CH_2Cl_2) afforded oxetane amine **42** as a pink solid (49.4 mg, 86%). R_f = 0.28 (20% Et_2O/CH_2Cl_2); mp = 74–76 °C; IR (film)/cm^{-1} 3280 (NH), 2948, 1610, 1490, 1375, 1300, 1185, 1028, 976, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.50 (m, 2 H, 2 × Ar-CH), 7.19 (d, *J* = 2.6 Hz, 1H, $Ar_{(Py)}$-CH), 6.97–6.88 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1 H, $Ar_{(Py)}$-CH), 6.56 (dd, *J* = 8.8, 0.4 Hz, 1 H, $Ar_{(Py)}$-CH), 4.98 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 4.32 (br s, 1 H, NH), 3.818 (s, 3 H, OCH_3), 3.817 (s, 3 H, OCH_3); δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (Ar-C_qOMe), 157.7 ($Ar_{(py)}$-C_qOMe), 135.4 (Ar-$C_q$$C_q$), 133.2 ($Ar_{(py)}$-CH), 131.8 (Ar-$C_q$-NH), 127.1 (2 × $Ar_{(PMP)}$-CH), 126.7 ($Ar_{(py)}$-CH), 114.2 (2 × $Ar_{(PMP)}$-CH), 110.9 ($Ar_{(py)}$-CH), 83.9 (CH_2OCH_2), 60.4 (C_q), 55.3 ($Ar_{(PMP)}$-OCH_3), 53.2 ($Ar_{(py)}$-OCH_3); HRMS (ESI) *m/z* calcd for $C_{16}H_{19}N_2O_3$ [M+H]: 287.1396, found: 287.1402.

Notes:

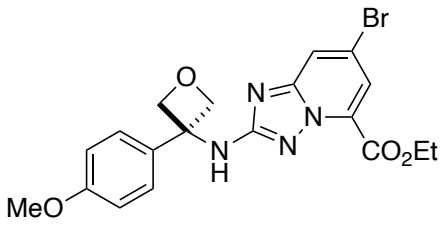
The singlets at 3.818 and 3.817 ppm were integrated together to 6 H.

Methyl 5-bromo-2-((3-(4-methoxyphenyl)oxetan-3-yl)amino)thiazole-4-carboxylate (43)



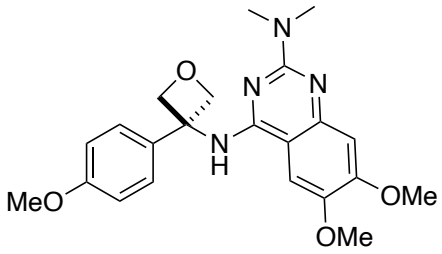
Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and methyl 2-amino-5-bromothiazole-4-carboxylate (57 mg). Purification by flash column chromatography (40% EtOAc/pentane) afforded oxetane amine **43** as an off-white solid (51 mg, 60%). R_f = 0.18 (40% EtOAc/pentane); mp = 124–126 °C; IR (film)/cm^{-1} 3172 (NH), 3079, 2952, 2874, 1722 (C=O st), 1573, 1510, 1439, 1245, 1211, 1179, 1025, 980, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2 H, 2 × Ar-CH), 7.30 (br s, 1 H, NH), 7.00–6.92 (m, 2 H, 2 × Ar-CH), 4.97 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.88 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C_q=O), 161.3 (NHAr-C_q), 159.7 (Ar-C_qOMe), 138.9 (Ar-$C_q$$CO_2$Me), 129.9 (Ar-$C_q$$C_q$), 127.4 (2 × Ar-CH), 114.5 (2 × Ar-CH), 105.4 (Ar-C_qBr), 82.5 (CH_2OCH_2), 61.3 (Ar-$C_q$$C_q$NH), 55.3 ($OCH_3$), 52.3 ($OCH_3$); HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N_2O_4S^{79}Br$ [M–H]: 396.9858, found 396.9863.

Ethyl 7-bromo-2-((3-(4-methoxyphenyl)oxetan-3-yl)amino)-[1,2,4]triazolo[1,5-a]pyridine-5-carboxylate (44)



Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and ethyl 2-amino-7-bromo-[1,2,4]triazolo[1,5-a]pyridine-5-carboxylate (68 mg). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **44** as an off-white solid (55 mg, 62%). R_f = 0.24 (50% EtOAc/pentane); mp = 61–64 °C; IR (film)/cm^{-1} 3276 (NH), 3079, 2956, 1737 (C=O st), 1558, 1513, 1465, 1297, 1245, 1156, 984, 828; ^{1}H NMR (400 MHz, $CDCl_3$, observed as a mixture of 2 rotamers) δ 7.69 and 7.68 (2 × d, *J* = 2.1 Hz, 1 H, Ar-CH), 7.58 and 7.57 (2 × d, *J* = 2.2 Hz, 1 H, Ar-CH), 7.57–7.51 (m, 2 H, 2 × Ar-CH), 6.91–6.83 (m, 2 H, 2 × Ar-CH), 5.85 (br s, 1 H, NH), 5.17 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 4.99 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 4.47 and 4.46 (2 × q, *J* = 7.1 Hz, 2 H, OCH_2CH$_3$), 3.79 and 3.78 (2 × s, 3 H, OCH_3), 1.41 and 1.40 (2 × t, *J* = 7.2 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C_q=O), 159.3 (NHAr-C_q), 158.8 (Ar-C_qOMe), 152.5 (NAr-C_qN), 134.6 (Ar-CqCO_2Et), 129.1 (Ar-C_qC_q), 126.5 (2 × Ar-CH), 121.4 (Ar-C_qBr), 119.4 (Ar-CH), 119.1 (Ar-Ch), 113.8 (2 × Ar-CH), 83.3 (CH_2OCH_2), 62.7 (C_q), 59.7 (OCH_2CH_3), 55.2 (OCH_3), 14.1 (OCH_2CH_3); HRMS (ESI) *m/z* calculated for $C_{19}H_{20}N_4O_4{}^{79}Br$ [M+H]: 447.0668, found 447.0675.

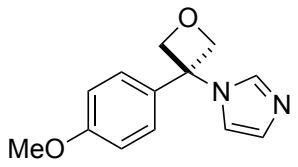
6,7-Dimethoxy-*N*^{4}-(3-(4-methoxyphenyl)oxetan-3-yl)-*N*^{2},*N*^{2}-dimethylquinazoline-2,4-diamine (45)



Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 6,7-dimethoxy-*N*^{2},*N*^{2}-dimethylquinazoline-2,4-diamine hydrochloride (68 mg). Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded oxetane amine **45** as a white solid (30 mg, 36%). R_f = 0.62 (10% MeOH/CH_2Cl_2); mp = 153–156 °C; IR (film)/cm^{-1} 3220 (NH), 2937, 1607, 1558, 1510, 1435, 1375, 1230, 1182, 1025, 977, 831; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, observed as a mixture of 2 tautomers) δ 11.89 (br s, 0.4 H, NH), 9.90 (br s, 0.6 H, NH), 7.99 (br s, 1 H, Ar-CH), 7.59–7.57 (m, 2 H, 2 × Ar-CH), 7.20 (br s, 1 H, Ar-CH), 6.99–6.87 (m, 2 H, 2 × Ar-CH), 5.17 (d, *J* = 6.7 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 3.91 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 2.97 (br s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 158.1 (Ar-C_qOMe), 156.9 (Ar-C_qNH), 154.6 (Ar-C_qOMe), 154.1 (br, Ar-$C_q(CH_3)_2$N), 145.9 (Ar-C_qOMe), 141.1 (br, Ar-C_q), 134.9 (Ar-C_q), 126.1 (2 × Ar-CH), 113.6 (2 × Ar-CH), 104.3 (Ar-CH), 102.1 (Ar-C_q), 101.8 (br, Ar-CH), 81.3 (CH_2OCH_2), 59.1 (C_q), 56.4 (OCH_3), 55.8 (OCH_3), 55.0 (OCH_3), 37.2 (2 × NCH_3); HRMS (ESI) *m/z* calculated for $C_{22}H_{27}N_4O_4$ [M+H]: 411.2032, found 411.2025.

Oxetane Products from Other Nucleophiles (**46**–**52**)

1-(3-(4-Methoxyphenyl)oxetan-3-yl)-1*H*-imidazole (46)

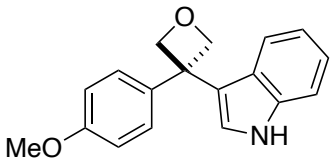


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and imidazole (16.3 mg). Purification by flash column chromatography (100% EtOAc/hexane) afforded oxetane-imidazole **46** as a colorless oil (23.9 mg, 52%). R_f = 0.21 (100% EtOAc); IR (film)/cm^{-1} 2960, 2884, 1613, 1515, 1492, 1463, 1301, 1250, 1184, 1076, 1027, 987, 905, 830, 730, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1 H, $Ar_{(imidazole)}$-CH), 7.18 (s, 1 H, $Ar_{(imidazole)}$-CH), 7.11–7.05 (m, 3 H, $Ar_{(imidazole)}$-CH + 2 × $Ar_{(p\text{-}OMe)}$-CH), 6.97–6.91 (m, 2 H, 2 × $Ar_{(p\text{-}OMe)}$-CH), 5.23 (s, 4 H, CH_2OCH_2), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (Ar-C_q-OMe), 136.2 ($Ar_{(imidazole)}$-CH), 131.9 (Ar-C_q-C_q), 130.0 ($Ar_{(imidazole)}$-CH), 126.9 (2 × $Ar_{(p\text{-}OMe)}$-CH), 117.6 ($Ar_{(imidazole)}$-CH), 114.4 (2 × $Ar_{(p\text{-}OMe)}$-CH), 83.5 (CH_2OCH_2), 63.1 (C_q), 55.4 (OCH_3); HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O_2^+$ $[M+H]^+$: 231.1134, found: 231.1138.

Notes:

***46** was assigned as the oxetane imidazole and not as the oxetane sulfonate imidazole based on the absence of the SO_2 stretches in the IR spectrum and the absence of sulfur-containing fragments in the mass spectrum.*

3-(3-(4-Methoxyphenyl)oxetan-3-yl)-1*H*-indole (47)



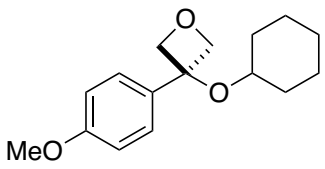
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 1*H*-indole (28.1 mg). Purification by flash-column chromatography (30–90% Et_2O/pentane) afforded diaryloxetane **47** as a white solid (47.5 mg, 85%). R_f = 0.54 (40% EtOAc/pentane); mp = 184 °C; IR (film)/cm^{-1} 3244 (br NH), 3050, 2987, 2946, 2873, 2829, 1608, 1510, 1456, 1428, 1339, 1299, 1246, 1183, 1152, 1115, 1027, 974, 933, 837, 743, 627, 582, 564; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1 H, NH), 7.69 (d, *J* = 8.0 Hz, $Ar_{(indole)}$-CH), 7.41 (d, *J* = 8.1 Hz, $Ar_{(indole)}$-CH), 7.29–7.22 (m, 3 H, 2 × $Ar_{(PMP)}$-CH + $Ar_{(indole)}$-CH), 7.12 (ddd, ^3J = 8.0, 7.0 Hz, ^4J = 1.0 Hz, $Ar_{(indole)}$-CH), 6.93–6.89 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.69 (d, *J* = 2.5 Hz, HNAr-C*H*), 5.41 (d, *J* = 5.6 Hz, 2 H, C*H*HOC*H*H), 5.30 (d, *J* = 5.6 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (Ar-C_qOMe), 137.6 ($Ar_{(PMP)}$-C_qC_q), 136.9 (NHAr-C_q), 127.6 (2 × $Ar_{(PMP)}$-CH), 125.7 (NHAr-C_qAr-C_q), 122.4 (NHAr-CH), 122.3 ($Ar_{(indole)}$-CH), 121.4 ($Ar_{(indole)}$-C_qC_q), 120.0 ($Ar_{(indole)}$-CH), 119.8 ($Ar_{(indole)}$-CH), 113.7 (2 × $Ar_{(PMP)}$-CH), 111.4 ($Ar_{(indole)}$-CH), 84.2 (CH_2OCH_2), 55.3 (OCH_3), 46.0 (C_q); HRMS (ESI) *m/z* calcd for $C_{18}H_{18}NO_2$ [M+H]: 280.1338; found: 280.1336.

Notes:

The indole ring was determined to be C-bound and not N or SO_2-bound (SuFEx) to the oxetane based on the following:

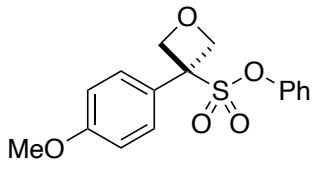
- *The diagnostic chemical shift of the oxetane quaternary carbon (46.0 ppm) lies in the range for diaryl oxetanes (46.0–51.0 ppm)[7] and way below the chemical shift that would be expected for oxetane amines or sulfone derivatives (60–69 ppm).*
- *The IR spectrum shows a broad N–H stretch.*
- *The C3-carbon of the indole ring (121.4 ppm) shows no HSQC correlations.*
- *The C3-carbon of the indole ring (121.4 ppm) shows HMBC correlations (through 3 bonds) to the oxetane CH_2 signals (5.41 and 5.30 ppm). These correlations would be very unlikely to happen were the indole N or SO_2-bound to the oxetane (through 5 and 4 bonds, respectively).*

3-(Cyclohexyloxy)-3-(4-methoxyphenyl)oxetane (48)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and cyclohexanol (25.4 μL). Purification by flash column chromatography (0–3%Et_2O/CH_2Cl_2) afforded oxetane ether **48** as a yellow gum that solidified in the freezer to a pale-yellow solid (26.4 mg, 50%). R_f = 0.14 (3%Et_2O/CH_2Cl_2); mp = 48 °C; IR (film)/cm^{-1} 2935, 2855, 1612, 1585, 1514, 1453, 1310, 1248, 1180, 1031, 979, 906, 832, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2 H, 2 × Ar-CH), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 4.95 (d, *J* = 7.0 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 7.0 Hz, 2 H, CH*H*OCH*H*), 3.85 (s, 3 H, OCH_3), 3.16 (tt, $J_{ax,ax}$ = 9.8 Hz, $J_{ax,eq}$ = 4.0 Hz, 1 H, CH), 1.69–1.63 (m, 2 H, 2 × CH_{eq}HCHO), 1.59–1.56 (m, 2 H, 2 × CH_{eq}HCH$_2$CHO), 1.50–1.44 (m, 1 H, CH_{eq}HCH$_2$CH$_2$CHO), 1.31–1.22 (m, 2 H, 2 × CHH_{ax}CHO), 1.16–1.05 (m, 3 H, 2 × CHH_{ax}CH$_2$CHO and CHH_{ax}CH$_2$CH$_2$CHO); ^{13}C NMR (101 MHz $CDCl_3$) δ 159.1 (Ar-C_qOMe), 133.3 (Ar-C_qC$_q$), 127.6 (2 × Ar-CH), 113.9 (2 × Ar-CH), 82.6 (CH_2OCH_2), 79.2 (C_q), 73.0 (CH), 55.3 (OCH_3), 33.7 (2 × CH_2), 25.5 (CH_2), 24.3 (2 × CH_2); HRMS (NSI) *m/z* calcd for $C_{16}H_{26}NO_3^+$ $[M+NH_4]^+$: 280.1907; found: 280.1912.

Phenyl 3-(4-methoxyphenyl)oxetane-3-sulfonate (49)



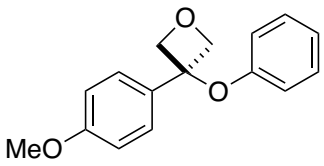
Using NaH: NaH (60 wt% dispersion in mineral oil, 9.6 mg, 0.241 mmol, 1.205 equiv) was added portionwise to a solution of phenol (22.6 mg, 0.24 mmol, 1.20 equiv) in anhydrous acetonitrile (0.66 mL) at 0 °C. The reaction was warmed to 25 °C, oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv) was added and the reaction vial was sealed. The reaction mixture was warmed up to 60 °C and after stirring the reaction mixture at this temperature for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (20–30% Et_2O/pentane) afforded oxetane sulfonate ester **49** as a white solid (53.1 mg, 83%). R_f = 0.29 (40% Et_2O/pentane); mp = 84–86 °C, IR (film)/cm^{-1} 2958, 2899, 1488, 1362 (SO_2 st as), 1250, 1200, 1178, 1142 (SO_2 st sy), 1021, 989, 862, 834, 760, 746, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 2 H, 2 × Ar-CH), 7.29–7.25 (m, 3 H, 3 × Ar-CH), 7.11–7.08 (m, 2 H, 2 × Ar-CH), 7.01–6.97 (m, 2 H, 2 × Ar-CH), 5.53 (d, *J* = 7.2 Hz, 2 H, C*H*HOC*H*H), 5.24 (d, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (Ar-C_qOMe), 149.1 (Ar-C_qOSO$_2$C$_q$), 129.8 (4 × Ar-CH), 127.0 (Ar-CH), 125.5 (Ar-C_qC$_q$), 121.8 (2 × Ar-CH), 114.2 (2 × Ar-CH), 77.4 (CH_2OCH_2), 67.9 (C_q), 55.4 (OCH_3); HRMS (APCI) *m/z* calcd for $C_{16}H_{15}O_3^-$ $[M–SO_2Ph–H]^-$: 255.1027, found: 255.1027. Also found: $C_{10}H_{11}O_5S^-$ $[M–Ph]^-$: 243.0333, found: 243.0332; $C_{10}H_{11}O_4S^-$ $[M–OPh]^-$: 227.0384, found: 227.0381.

Using Cs_2CO_3: A reaction tube was charged with oven-dried Cs_2CO_3 (84.7 mg, 0.26 mmol, 1.3 equiv), followed by phenol (22.6 mg, 0.24 mmol, 1.2 equiv) and oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (5–25% Et_2O/pentane) afforded oxetane ether **50** as a colorless gum (5.2 mg, 10%), followed by oxetane sulfonate ester **49** as a white solid (48.4 mg, 76%).

Notes:

*The structure of oxetane sulfonate ester **49** was confirmed by X-ray crystallography (see Fig. S40–44).*

3-(4-Methoxyphenyl)-3-phenoxyoxetane (50)



Using TMS-phenol: a reaction tube was charged with trimethyl(phenoxy)silane (43.4 mL, 0.24 mmol, 1.2 equiv) followed by oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv). The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (5–10% Et_2O/pentane) afforded oxetane ether **50** as a colorless gum (31.9 mg, 62%). R_f = 0.54 (10% EtOAc/pentane); IR (film)/cm^{-1} 2950, 2873, 2834 1585, 1511, 1487, 1458, 1335, 1299, 1280, 1247, 1232, 1176, 1143, 1110, 1072, 1029, 985, 960, 897, 831, 808, 753, 692, 599, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2 H, 2 × Ar-CH), 7.19–7.15 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 3 H, 2 × Ar-CH), 6.55–6.51 (m, 2 H, 2 × Ar-CH), 5.11 (d, *J* = 7.4 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 7.4 Hz, 2 H, CH*H*OCH*H*), 3.81 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_qOMe), 154.8 (Ar-C_qOC_q), 132.1 (Ar-$C_q$$C_q$), 129.4 (2 × Ar-CH), 126.0 (2 × Ar-CH), 121.0 (Ar-CH), 116.2 (2 × Ar-CH), 114.1 (2 × Ar-CH), 82.9 (CH_2OCH_2), 80.1 (C_q), 55.3 (OCH_3); HRMS (APCI) *m/z* calcd for $C_{10}H_{11}O_2^+$ [M–OPh]$^+$: 163.0754, found: 163.0751.

Using NEt_3 as base: a reaction tube was charged with NEt_3 (36.2 mL, 0.26 mmol, 1.3 equiv) followed by phenol (22.6 mg, 0.24 mmol, 1.2 equiv) and oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv). The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (5–25% Et_2O/pentane) afforded oxetane ether **50** as a colorless gum (24.9 mg, 49%) followed by oxetane sulfonate ester **49** as a white solid (5.4 mg, 8%).

Notes:

*On one occasion **50** crystallized to white crystals. mp = 71–73 °C.*

*The structure of oxetane ether **50** was confirmed by the diagnostic chemical shift of the oxetane quaternary carbon (80.1 ppm)[7] and by the synthesis of a genuine sample from oxetanol **1a** using previously developed Lewis acid catalyzed conditions (Fig. S35).[7] The structure of **50** was unambiguously confirmed by X-ray crystallography (see Fig. S49–52).*

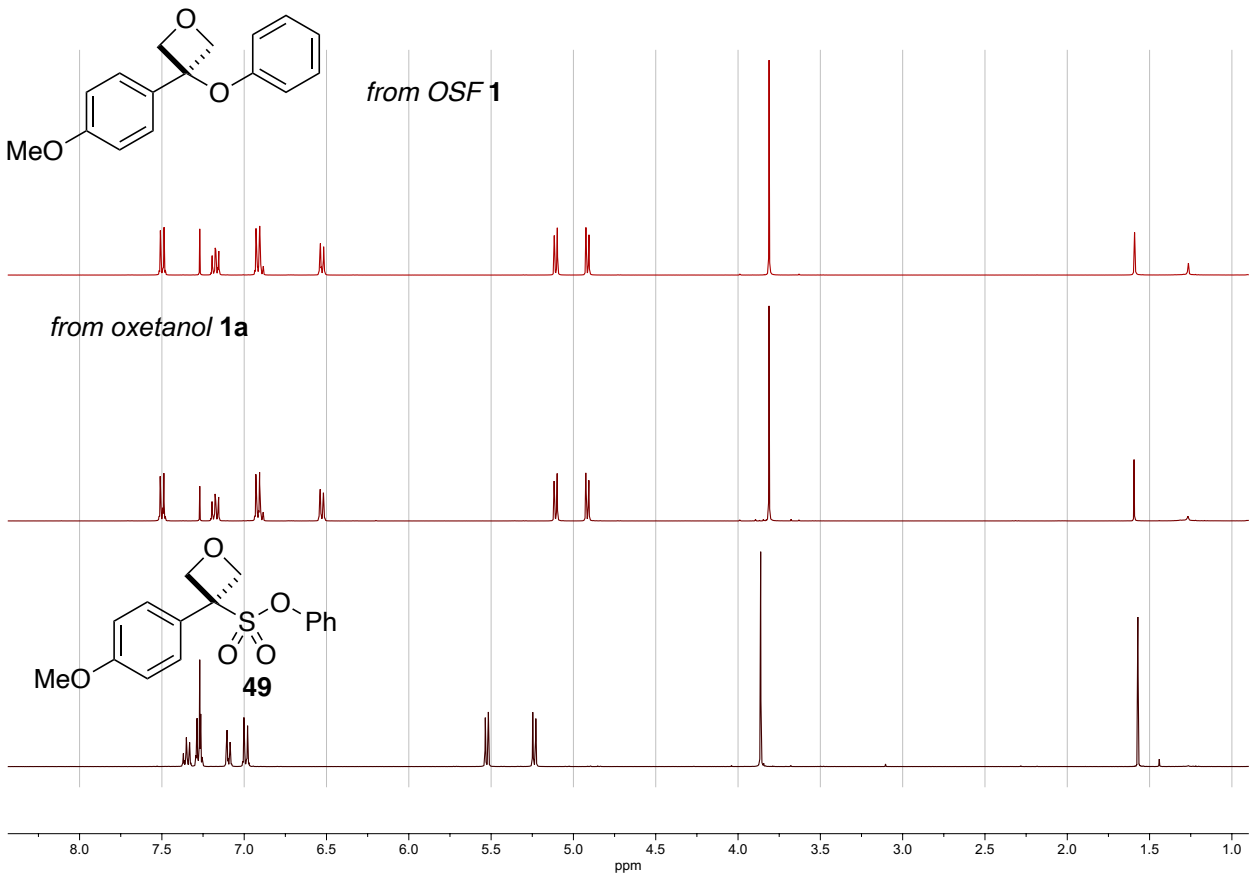
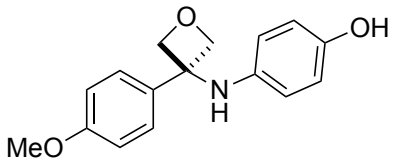


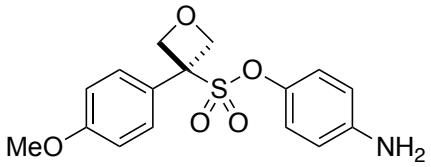
Fig. S35 Comparison of ^{1}H NMR spectra of oxetane ether **50** from OSF **1** (*Top*), from oxetanol **1a** (*Middle*) and of oxetane sulfonate ester **49** (*Bottom*).

4-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)phenol (51)



Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 4-aminophenol (26.2 mg). Purification by flash column chromatography (60% Et_2O/pentane) afforded oxetane amine **51** as a white solid (47 mg, 87%). R_f = 0.22 (60% Et_2O/pentane); mp = 154–156 ºC; IR (film)/cm^{-1} 3396 (NH), 3272 (br, OH), 2953, 2892, 1615, 1509, 1304, 1255, 1214, 1175, 1032, 944, 817; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.93–6.88 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.63–6.60 (m, 2 H, 2 × $Ar_{(p\text{-}OH)}$-CH), 6.22–6.20 (m, 2 H, 2 × $Ar_{(p\text{-}OH)}$-CH), 4.96 (d, *J* = 6.3 Hz, C*H*HOC*H*H), 4.85 (d, *J* = 6.3 Hz, CH*H*OCH*H*), 4.45 (br s, 2 H, NH + OH), 3.82 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qOMe), 148.1 (Ar-C_qOH), 138.6 (Ar-C_qNH), 134.1 (Ar-$C_q$$C_q$), 126.8 (2 × $Ar_{(PMP)}$-CH), 116.1 (2 × $Ar_{(p\text{-}OH)}$-CH), 115.7 (2 × $Ar_{(p\text{-}OH)}$-CH), 114.0 (2 × $Ar_{(PMP)}$-CH), 84.3 (CH_2OCH_2), 60.3 (C_q), 55.3 (OCH_3); HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_3$ [M+H]: 272.1287, found: 272.1284.

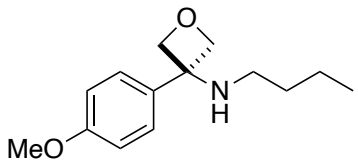
4-Aminophenyl 3-(4-methoxyphenyl)oxetane-3-sulfonate (52)



A reaction tube was charged with oven-dried Cs_2CO_3 (84.7 mg, 0.26 mmol, 1.3 equiv), followed by 4-aminophenol (26.2 mg, 0.24 mmol, 1.2 equiv) and oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C and water (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (70% EtOAc/hexane) afforded sulfonate ester **52** as a cream solid (55 mg, 82%). R_f = 0.47 (70% EtOAc/hexane); mp = 146–148 ºC, IR (film)/cm^{-1} 3485 (NH_2), 3387 (NH_2), 2973, 1516, 1506, 1339 (SO_2 st as), 1263, 1199, 1146 (SO_2 st sy), 1022, 1000, 866, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 7.00–6.96 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 6.89–6.85 (m, 2 H, 2 × $Ar_{(aniline)}$-CH), 6.61–6.56 (m, 2 H, 2 × $Ar_{(aniline)}$-CH), 5.51 (d, *J* = 7.2 Hz, C*H*HOC*H*H), 5.21 (d, *J* = 7.2 Hz, CH*H*OCH*H*), 3.86 (s, 3 H, OCH_3), 3.69 (br s, 2 H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2 (Ar-C_q-OMe), 145.4 (Ar-$C_q$$OSO_2$), 140.8 (Ar-$C_q$$NH_2$), 129.8 (2 × $Ar_{(PMP)}$-CH), 125.8 (Ar-$C_q$$C_q$), 122.7 (2 × $Ar_{(aniline)}$-CH), 115.5 (2 × $Ar_{(aniline)}$-CH), 114.2 (2 × $Ar_{(PMP)}$-CH), 77.4 (CH_2OCH_2), 67.5 (C_q), 55.4 (OCH_3); HRMS (ESI) *m/z* calcd for $C_{16}H_{18}NO_5S^+$ $[M+H]^+$: 336.0900, found: 336.0897. Also found: $C_{16}H_{18}NO_3^+$ $[M–SO_2+H]^+$: 272.1287, found: 272.1286.

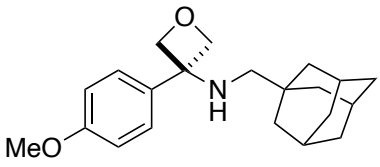
Additional Oxetane Products (**S1**–**S10**)

_N_-Butyl-3-(4-methoxyphenyl)oxetan-3-amine (S1)



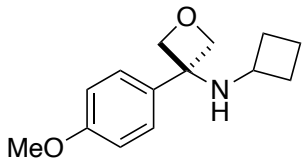
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and *n*-butylamine (24 μL). Purification by flash column chromatography (35% EtOAc/pentane) afforded oxetane amine **S1** as a colorless oil (33 mg, 70%). R_f = 0.21 (35% EtOAc in pentane); IR (film)/cm^{-1} 2952, 2870, 1610, 1513, 1461, 1244, 1177, 1032, 984, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H, 2 × Ar-CH), 6.94–6.89 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*HO), 4.73 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.38 (t, *J* = 7.1 Hz, 2 H, NCH_2), 1.77 (s, 1 H, NH), 1.48–1.42 (m, 2 H, NCH_2CH_2), 1.38–1.27 (m, 2 H, $N(CH_2)_2CH_2$), 0.88 (t, *J* = 7.3 Hz, 3 H, $N(CH_2)_3CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 134.6 (Ar-C_qC_q), 127.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 82.7 (CH_2OCH_2), 63.0 (C_q), 55.2 (OCH_3), 43.1 (NCH_2), 32.6 (NCH_2CH_2), 20.4 ($N(CH_2)_2CH_2$), 13.9 ($N(CH_2)_3CH_3$). HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NO_2$ [M+H]: 236.1651, found: 236.1651.

_N_-(((3_r_,5_r_,7_r_)-Adamantan-1-yl)methyl)-3-(4-methoxyphenyl)oxetan-3-amine (S2)



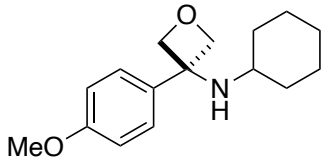
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 1-adamantanemethylamine (43 μL). Purification by flash column chromatography (10% EtOAc/hexane) afforded oxetane amine **S2** as a colorless oil (45 mg, 68%). R_f = 0.18 (10% EtOAc/hexane); IR (film)/cm^{-1} 2897, 2845, 1611, 1513, 1452, 1302, 1244, 1175, 1110, 1030, 981, 829, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 2 H, 2 × Ar-CH), 6.94–6.89 (m, 2 H, 2 × Ar-CH), 4.89 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.71 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.04 (s, 2 H, $NHCH_2$), 2.00–1.94 (br m, 3 H, 3 × CH), 1.76–1.60 (br m, 7 H, 3 × CH_2, NH), 1.51 (br d, *J* = 2.9 Hz, 6 H, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (Ar-C_qOMe), 134.8 (Ar-C_qC_q), 127.3 (2 × Ar-CH), 113.7 (2 × Ar-CH), 82.7 (CH_2OCH_2), 62.7 (NHC_q), 55.6 ($NHCH_2$), 55.2 (OCH_3), 40.7 (3 × CH_2), 37.2 (3 × CH_2), 33.0 (Ad-C_q), 28.4 (3 × CH); HRMS (ESI) *m/z* calculated for $C_{21}H_{30}NO_2$ [M+H]. 328.2277, found 328.2283.

_N_-Cyclobutyl-3-(4-methoxyphenyl)oxetan-3-amine (S3)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and cyclobutanamine (21 μL). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **S3** as a colorless oil (30 mg, 64%). R_f = 0.18 (40% EtOAc in pentane); IR (film)/cm^{-1} 2952, 2870, 1610, 1513, 1461, 1300, 1244, 1177, 1028, 980, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2 H, 2 × Ar-CH), 6.95–6.90 (m, 2 H 2 × Ar-CH), 4.94 (dd, *J* = 6.2, 0.6 Hz, 2 H, C*H*HOC*H*H), 4.74 (dd, *J* = 6.2, 0.6 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.16–3.08 (m, 1 H, CH), 2.09–2.02 (m, 2 H, $NCH(CHH)_2$), 1.96 (br s, 1 H, NH), 1.74–1.45 (m, 4 H, $NCH(CH_2)_2CH_2$ + $NCH(CHH)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 135.0 (Ar-C_qC_q), 127.3 (2 × Ar-CH), 113.8 (2 × Ar-CH), 83.3 (CH_2OCH_2), 62.7 (C_q), 55.2 (OCH_3), 49.8 (CH), 33.3 ($NCH(CH_2)_2$), 15.2 ($NCH(CH_2)_2CH_2$). HRMS (ESI) *m/z* calcd for $C_{14}H_{20}NO_2$ [M+H]: 234.1494, found: 234.1495.

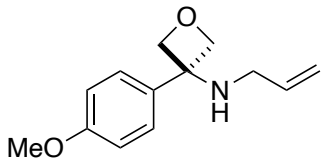
_N_-Cyclohexyl-3-(4-methoxyphenyl)oxetan-3-amine (S4)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and cyclohexanamine (27 μL). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **S4** as a colorless oil

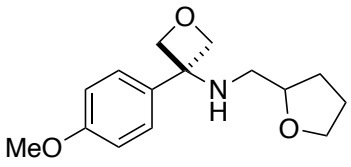
(28 mg, 54%). R_f = 0.26 (50% EtOAc in pentane); IR (film)/cm^{-1} 2926, 2851, 1610, 1513, 1449, 1244, 1177, 1032, 980, 831. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 4.95 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.73 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 2.24–2.18 (m, 1 H, CH), 1.85 (br s, 1 H, NH), 1.63–1.51 (m, 5 H, 5 × C*H*H), 1.10–0.98 (m, 5 H, 5 × CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 135.1 (Ar-C_qC_q), 127.5 (2 × Ar-CH), 113.8 (2 × Ar-CH), 84.4 (CH_2OCH_2), 62.6 (C_q), 55.3 (OCH_3), 52.6 (CH), 35.1 (2 × NCHCH_2), 25.8 (NCH$(CH_2)_2CH_2$), 25.2 (2 × NCHCH_2CH_2). HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_2$ [M+H]: 262.1807, found: 262.1810.

_N_-Allyl-3-(4-methoxyphenyl)oxetan-3-amine (S5)



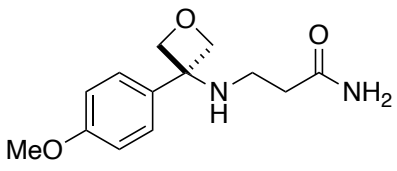
Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and prop-2-en-1-amine (18 μL). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **S5** as a colorless oil (29 mg, 66%). R_f = 0.31 (50% EtOAc in pentane); IR (film)/cm^{-1} 2948, 2870, 2836, 1610, 1513, 1461, 1300, 1244, 1177, 1028, 984, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 5.89 (ddt, *J* = 17.2, 10.2, 5.9 Hz, 1 H, NCH_2CHCH_2), 5.18 (dq, *J* = 17.2, 1.6 Hz, 1 H, NCH_2CHCHH), 5.08 (dq, *J* = 10.2, 1.4 Hz, 1 H, NCH_2CHCHH), 4.95 (d, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.75 (d, *J* = 6.3 Hz, 2 H, CH*H*OCH*H*), 3.83 (s, 3 H, OCH_3), 3.03 (dt, *J* = 5.9, 1.5 Hz, 2 H, NCH_2), 1.91 (s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qOMe), 136.5 (2 × Ar-CH), 134.1 (Ar-C_qC_q), 127.3 (NCH_2CHCH_2), 116.0 (2 × Ar-CH), 113.8 (NCH_2CHCH_2), 82.7 (CH_2OCH_2), 63.0 (C_q), 55.2 (OCH_3), 46.4 (NCH_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO_2$ [M+H]: 220.1338, found: 220.1344.

3-(4-Methoxyphenyl)-_N_-((tetrahydrofuran-2-yl)methyl)oxetan-3-amine (S6)



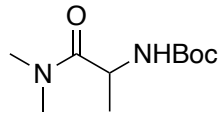
Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and tetrahydrofurfurylamine (25 μL). Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane amine **S6** as a colorless oil (43 mg, 82%). R_f = 0.23 (80% EtOAc/hexane); IRIR (film)/cm^{-1} 2946, 2868, 1611, 1513, 1461, 1303, 1244, 1178, 1056, 1028, 980, 829, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2 H, 2 ×Ar-CH), 6.94–6.88 (m, 2 H, 2 ×Ar-CH), 4.95 (d, *J* = 6.3 Hz, 1 H, C*H*HOCH_2), 4.89 (d, *J* = 6.3 Hz, 1 H, CH_2OC*H*H), 4.78–4.72 (m, 2 H, CH*H*OCH*H*), 3.93 (qd, *J* = 7.1, 3.9 Hz, 1 H, OCH), 3.87–3.79 (m, 4 H, $O_{(THF)}$C*H*H + OCH_3), 3.74 (dt, *J* = 8.3, 6.8 Hz, 1 H, $O_{(THF)}$CH*H*), 2.51–2.36 (m, 2 H, NHC*H*$_2$), 2.15 (br s, 1 H, NH), 1.97–1.81 (m, 3 H, OCHC*H*H + OCH_2CH_2), 1.57–1.46 (m, 1 H, OCHCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (Ar-C_qOMe), 134.4 (Ar-C_qC_q), 127.4 (2 × Ar-CH), 113.8 (2 × Ar-CH), 82.8 (CH_2OCH_2), 82.5 (CH_2OCH_2), 78.4 (OCH), 67.9 ($O_{(THF)}CH_2$), 62.7 (C_q), 55.2 (OCH_3), 47.8 ($NHCH_2$), 29.1 ($OCHCH_2$), 25.7 (OCH_2CH_2); HRMS (ESI) *m/z* calculated for $C_{15}H_{22}NO_3$ [M+H]: 264.1600, found 264.1601.

3-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)propanamide (S7)



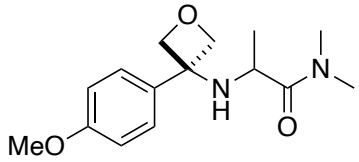
Prepared according to **General Procedure A** under Ar with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 3-aminopropanamide hydrochloride (30 mg). Purification by flash column chromatography (8% MeOH/CH_2Cl_2) afforded oxetane amine **S7** as a white solid (31 mg, 62%). R_f = 0.26 (10% MeOH/CH_2Cl_2); mp = 118–120 °C; IR (film)/cm^{-1} 3362 (CONH), 3273 (NH), 3168 (CONH), 2960, 2878, 1655 (C=O st), 1614, 1521, 1431, 1312, 1252, 1204, 1179, 1029, 973, 816, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2 H, 2 × Ar-CH), 6.94–6.88 (m, 2 H, Ar-CH), 6.75 (br s, 1 H, CON*H*H), 5.75 (br s, 1 H, CONH*H*), 4.95 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.73 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 3.82 (s, 3 H, OCH_3), 3.65 (t, *J* = 5.9 Hz, 2 H, NHC*H*$_2$), 2.34 (t, *J* = 5.9 Hz, 2 H, C*H*$_2$CO), 2.22 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C_q=O), 158.8 (Ar-C_qOMe), 133.7 (Ar-C_qC_q), 127.2 (2 × Ar-CH), 114.0 (2 × Ar-CH), 81.9 (CH_2OCH_2), 63.0 (Ar-C_qC_q), 55.3 (OCH_3) 39.1 ($NHCH_2$), 35.8 (*C*H_2CO); HRMS (ESI) *m/z* calculated for $C_{13}H_{19}N_2O_3$ [M+H]: 251.1396, found 251.1406.

***tert*-Butyl(1-(dimethylamino)-1-oxopropan-2-yl)-l2-azanecarboxylate (S16)**



N,*N*-Diisopropylethylamine (0.84 mL, 4.8 mmol, 1.2 equiv) was added dropwise to a solution of dimethylamine hydrochloride (391.5 mg, 4.8 mmol, 1.2 equiv) and DMAP (97.8 mg, 0.8 mmol, 0.2 equiv) in CH_2Cl_2 (80 mL, 0.05 M). The reaction mixture was stirred at 25 °C for 10 min. *N*-(tert-Butoxycarbonyl)-L-alanine (755.4 mg, 4.0 mmol, 1.0 equiv) followed by EDC hydrochloride (920.2 mg, 4.8 mmol, 1.2 equiv) were added to the reaction mixture and stirred at 25 °C for a further 16 h and then quenched with aq. HCl (1M, 30 mL). The layers were separated and the aqueous portion extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with aq. NaOH (1M, 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* using a rotatory evaporator. Purification by flash chromatography (5% MeOH/CH_2Cl_2) afforded **S16** as a colorless oil (756 mg, 87%). R_f = 0.22 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (br d, *J* = 6.9 Hz, 1 H, NH), 4.63 (td, *J* = 6.9, 6.9 Hz, 1 H, CH), 3.07 (s, 3 H, NCH_3), 2.97 (s, 3 H, NCH_3), 1.44 (s, 9 H, 3 × C_qCH_3), 1.30 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C=O$_{(amide)}$), 155.1 (C=O$_{(carbonate)}$), 79.4 (C_q), 46.2 (CH), 36.9 (NCH_3), 35.7 (NCH_3), 28.3 ((*C*H_3)$_3C_q$), 19.0 (*C*H_3CH). The observed characterization data (^{1}H, ^{13}C) were consistent with that previously reported.[43]

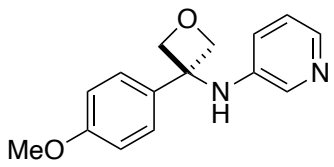
2-((3-(4-Methoxyphenyl)oxetan-3-yl)amino)-*N*,*N*-dimethylpropanamide (S8)



Trifluoroacetic acid (2.7 mL, 35 mmol, 10 equiv) was added dropwise to a solution of *tert*-butyl(1-(dimethylamino)-1-oxopropan-2-yl)-l2-azanecarboxylate **S16** (756.2 mg, 3.5 mmol, 1.0 equiv) in CH_2Cl_2 (17.5 mL, 0.2 M) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, warmed to 25 °C and stirred for a further 2.5 h. Concentration *in vacuo* using a rotatory evaporator afforded 1-(dimethylamino)-1-oxopropan-2-aminium trifluoroacetate (809.5 mg) of which a portion was used in the next step without further purification. Anhydrous K_2CO_3 (77.4 mg, 0.56 mmol, 2.8 equiv), 1-(dimethylamino)-1-oxopropan-2-aminium trifluoroacetate (58.1 mg, 0.25 mmol, 1.25 equiv) and sulfonyl fluoride **1** (49.2 mg, 0.20 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under N_2. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C, EtOAc (5 mL) was added and the mixture filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was then removed *in vacuo* using a rotatory evaporator. Purification by flash chromatography (50% acetone/hexane) afforded oxetane amine **S8** as a colorless oil (19.7 mg, 35%). R_f = 0.20 (50% acetone/hexane); IR (film)/cm^{-1} 3298 (NH), 2937, 2870, 1640 (C=O st), 1513, 1461, 1392, 1244, 1177, 1118, 976, 834, 715; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, 2 × Ar-CH), 6.94–6.90 (m, 2 H, 2 × Ar-CH), 4.93 (d,

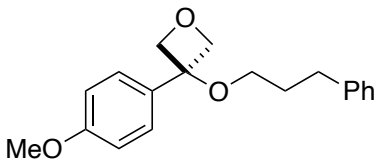
J = 6.4 Hz, 1 H, C*H*HOCH$_2$), 4.84 (d, *J* = 6.6 Hz, 1 H, CH*H*OCH$_2$), 4.82 (d, *J* = 6.6 Hz, 1 H, CH$_2$OCH*H*), 4.72 (d, *J* = 6.4 Hz, 1 H, CH$_2$OC*H*H), 3.83 (s, 3 H, OCH$_3$), 3.42 (q, *J* = 6.9 Hz, 1 H, CH), 2.88 (s, 3 H, NCH$_3$), 2.74 (s, 3 H, NCH$_3$), 1.75 (br s, 1 H, NH), 1.13 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.7 (C$_q$=O), 158.7 (Ar-C$_q$OMe), 134.6 (Ar-*C*$_q$C$_q$), 127.7 (2 × Ar-CH), 113.8 (2 × Ar-CH), 84.0 (*C*H$_2$OCH$_2$), 82.6 (CH$_2$O*C*H$_2$), 62.8 (Ar-C$_q$*C*$_q$), 55.3 (OCH$_3$), 48.5 (*C*HCH$_3$), 36.5 (NCH$_3$), 35.8 (NCH$_3$), 20.2 (CH$_3$); HRMS (ESI) *m/z* calcd for C$_{15}$H$_{23}$N$_2$O$_3^+$ [M+H]$^+$: 279.1703, found: 279.1710.

_N_-(3-(4-Methoxyphenyl)oxetan-3-yl)pyridin-3-amine (S9)



Prepared according to **General Procedure A** under Ar with an aqueous workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 3-aminopyridine (23 mg). Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane amine **S9** (14 mg, 28%) as a pale-yellow solid. R$_f$ = 0.13 (80% EtOAc/hexane); mp = 121–123 ºC; IR (film)/cm^{-1} 3222 (NH), 3032, 2949, 2877, 1578, 1513, 1479, 1309, 1274, 1248, 1176, 1023, 987, 832, 816, 795, 705; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (dd, *J* = 4.8, 1.3 Hz, 1 H, Ar$_{(Py)}$-CH), 7.88 (d, *J* = 2.9 Hz, 1 H, Ar$_{(Py)}$-CH), 7.56–7.51 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 6.98 (dd, *J* = 8.3, 4.8 Hz, 1 H, Ar$_{(Py)}$-CH), 6.94–6.90 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 6.46 (ddd, *J* = 8.3, 2.9, 1.3 Hz, 1 H, Ar$_{(Py)}$-CH), 4.99 (d, *J* = 6.4 Hz, C*H*HOC*H*H), 4.87 (d, *J* = 6.4 Hz, CH*H*OCH*H*), 4.79 (br s, 1 H, NH), 3.81 (s, 3 H, OCH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.1 (Ar-C$_q$OMe), 140.9 (Ar-C$_q$NH), 139.4 (Ar$_{(Py)}$-CH), 137.1 (Ar$_{(Py)}$-CH), 132.7 (Ar-*C*$_q$C$_q$), 126.5 (2 × Ar$_{(PMP)}$-CH), 123.5 (Ar$_{(Py)}$-CH), 119.9 (Ar$_{(Py)}$-CH), 114.3 (2 × Ar$_{(PMP)}$-CH), 83.9 (CH$_2$OCH$_2$), 59.9 (C$_q$), 55.3 (OCH$_3$); HRMS (ESI) *m/z* calcd for C$_{15}$H$_{17}$N$_2$O$_2^+$ [M+H]$^+$: 257.1290, found: 257.1283.

3-(4-Methoxyphenyl)-3-(3-phenylpropoxy)oxetane (S10)

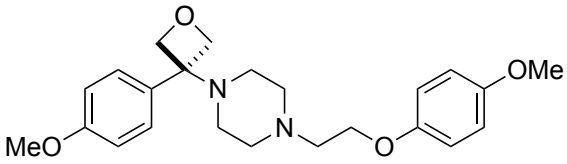


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 3-phenylpropanol (32.7 μL). Purification by flash column chromatography (10% EtOAc/pentane) afforded oxetane ether **S10** as a colorless gum that solidified in the freezer to a white solid (35.8 mg, 60%). R$_f$ = 0.14 (15% EtOAc/pentane); mp = 60–62 °C; IR (film)/cm^{-1} 2943, 2873, 1612, 1514, 1455, 1305, 1249, 1178, 1031, 983, 910, 832, 732, 701; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.32 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 7.30–7.25 (m, 2 H, 2 × Ar$_{(Ph)}$-CH), 7.21–7.20 (m, 3 H, 3 × Ar$_{(Ph)}$-CH), 6.96–6.92 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 4.91 (d, *J* = 6.6 Hz, 2 H, C*H*HOC*H*H), 4.83 (d, *J* = 6.6 Hz, 2 H, CH*H*OCH*H*), 3.84 (s, 3 H, OCH$_3$), 3.16 (t, *J* = 6.3 Hz, 2 H, OCH$_2$), 2.71 (t, *J* = 7.6 Hz, 2 H, PhCH$_2$), 1.93–1.86 (m, 2 H, CH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (101 MHz CDCl$_3$) δ 159.2 (Ar-C$_q$OMe), 141.8 (Ar-*C*$_q$CH$_2$), 132.3 (Ar-*C*$_q$C$_q$), 128.4 (2 × Ar-CH), 128.3 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.8 (Ar-CH), 114.0 (2 × Ar-CH), 81.3 (CH$_2$OCH$_2$), 79.9 (C$_q$), 62.8 (OCH$_2$), 55.3 (OCH$_3$), 32.3 (CH$_2$*C*H$_2$CH$_2$), 31.4 (PhCH$_2$); HRMS (ESI) *m/z* calcd for C$_{19}$H$_{23}$O$_3$ [M+H]: 299.1647; found: 299.1655.

Oxetane Analogues of Benzamide-Containing Drugs (**60–76**)

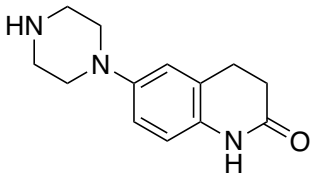
1-(2-(4-Methoxyphenoxy)ethyl)-4-(3-(4-methoxyphenyl)oxetan-3-yl)piperazine (60)

Analogue of D3 dopamine receptor agonist (C=O)[44]



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **1** (49.2 mg) and 1-(2-(4-methoxyphenoxy) ethyl)piperazine (56.7 mg). Purification by flash column chromatography (20–50% Et_2O/CH_2Cl_2) afforded oxetane amine **60** as a light-yellow gum (53.5 mg, 67%). R_f = 0.13 (20% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 3001, 2945, 2878, 2833, 1610, 1510, 1461, 1353, 1297, 1230, 1178, 1122, 1036, 910, 828, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–6.95 (m, 2 H, 2 × Ar-CH), 6.90–6.87 (m, 2 H, 2 × Ar-CH), 6.81 (s, 4 H, 4 × Ar-CH), 4.90 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 4.01 (t, *J* = 5.8 Hz, 2 H, OCH_2CH_2), 3.81 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.78 (t, *J* = 5.8 Hz, 2 H, OCH_2CH_2), 2.67 (br s, 4 H, CH_2NCH_2), 2.35 (br s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (Ar-C_qO), 153.8 (Ar-C_qO), 152.8 (Ar-C_qO), 129.2 (Ar-C_qC_q), 128.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 114.5 (2 × Ar-CH), 113.2 (2 × Ar-CH), 79.8 (CH_2OCH_2), 66.3 (OCH_2CH_2), 66.2 (C_q), 57.2 (OCH_2CH_2), 55.7 (OCH_3), 55.3 (OCH_3), 53.7 (CH_2NCH_2), 45.5 (CH_2NCH_2); HRMS (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_4^+$ $[M+H]^+$: 399.2278, found: 399.2273.

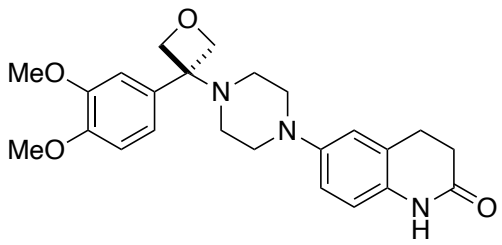
6-(Piperazin-1-yl)-3,4-dihydroquinolin-2(1*H*)-one (S17)



Piperazine (1.03 g, 12.0 mmol, 6.0 equiv), 6-bromo-3,4-dihydroquinolin-2(1H)-one (452 mg, 2.0 mmol, 1.0 equiv), $Pd_2(dba)_3$ (37 mg, 0.04 mmol, 2 mol%), DavePhos (20 mg, 0.05 mmol, 2.4 mol%) were added to a flame-dried microwave vial and sealed. The vial was evacuated and refilled with N_2 (3 ×). 1 M LiHMDS in THF (4.4 mL, 4.4 mmol, 2.2 equiv) was added and the mixture heated to 65 °C for 72 h. The reaction mixture was left to cool to room temperature and 1 M HCl (1 mL) was added and stirred for 5 min followed by sat. aq. $NaHCO_3$ (3 mL). The aqueous mixture was then extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* using a rotatory evaporator. Purification by automated column chromatography on a Biotage system (SiO_2, 100% MeOH) afforded amine **S17** as a white solid (105 mg, 23%). R_f = 0.11 (100% MeOH); mp = 226–228 °C; IR (film)/cm^{-1} 3254, 2795, 1666, 1505, 1371, 1233, 1189, 946, 846; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1 H, NH), 6.78–6.75 (m, 2 H, 2 × Ar-CH), 6.66 (dd, *J* = 7.9, 1.0 Hz, 1 H, Ar-CH), 3.06 (ttd, *J* = 8.2, 4.2, 1.6 Hz, 8 H, 4 × NCH_2), 2.96–2.92 (m, 2 H, Ar-C_qCH_2), 2.64–2.60 (m, 2 H, $COCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C_q=O), 148.1 (Ar-C_q), 130.3 (Ar-C_q), 124.5 (Ar-C_q), 116.5 (Ar-CH), 115.9 (Ar-CH), 115.5 (Ar-CH), 51.2 (2 × $HNCH_2$), 46.2 (2 × Ar-C_qNCH_2), 30.8 ($COCH_2$), 25.9 (Ar-C_qCH_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{18}N_3O$ [M+H]: 232.1450, found: 232.1443. The observed characterization data (^{1}H, ^{13}C, IR) were consistent with that previously reported.[45]

6-(4-(3-(3,4-Dimethoxyphenyl)oxetan-3-yl)piperazin-1-yl)-3,4-dihydroquinolin-2(1*H*)-one (61)

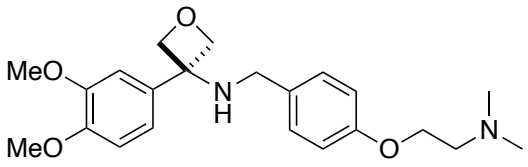
Analogue of Vesnarinone (C=O)[46]



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **53** (55 mg) and 6-(piperazin-1-yl)-3,4-dihydroquinolin-2(1*H*)-one **S17** (56 mg). Purification by flash column chromatography (20% acetone in pentane) afforded oxetane amine **61** as a white solid (42 mg, 50%). R_f = 0.24 (20% acetone in pentane); mp = 216–217 °C; IR (film)/cm^{-1} 3205, 2940, 2832, 1669, 1509, 1453, 1248, 1144, 1029, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.19 (m, 1 H, NH), 6.88 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.71–6.65 (m, 4 H, 4 × Ar-CH), 6.59 (d, *J* = 2.1 Hz, 1 H, Ar-CH), 4.94 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.895 (s, 3 H, OCH_3), 3.887 (s, 3 H, OCH_3), 3.15 (t, *J* = 4.9 Hz, 4 H, 2 × NCH_2), 2.90 (dd, *J* = 8.5, 6.4 Hz, 2H, Ar-$C_q$$CH_2$), 2.60 (dd, *J* = 8.5, 6.5 Hz, 2 H, $COCH_2$), 2.49 (t, *J* = 4.9 Hz, 4 H, 2 × NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C_q=O), 148.6 (Ar-C_q), 148.4 (Ar-C_q), 147.5 (Ar-C_q), 130.4 (Ar-C_q), 130.0 (Ar-C_q), 124.5 (Ar-C_q), 119.8 (Ar-CH), 116.5 (Ar-CH), 115.9 (Ar-CH), 115.6 (Ar-CH), 110.7 (Ar-CH), 110.5 (Ar-CH), 79.4 (CH_2OCH_2), 66.6 (Ar-$C_q$$C_q$), 56.1 ($OCH_3$), 55.9 ($OCH_3$), 50.3 (2 × C_qNCH_2), 46.0 (2 × Ar-C_qNCH_2), 30.7 (COCH_2), 25.8 (Ar-$C_q$$CH_2$); HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_3O_4$ [M+H]: 424.2236, found: 424.2241.

3-(3,4-Dimethoxyphenyl)-*N*-(4-(2-(dimethylamino)ethoxy)benzyl)oxetan-3-amine (62)

Analogue of Itopride (C=O)[47]



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **53** (55.3 mg) and 2-(4-(aminomethyl)phenoxy)-*N*,*N*-dimethylethan-1-amine (47.0 mg). Purification by flash column chromatography (2–15% MeOH/CH_2Cl_2) afforded oxetane amine **62** as a light-yellow solid (37.5 mg, 49%). R_f = 0.12 (10% MeOH/CH_2Cl_2); mp = 93–96 °C; IR (film)/cm^{-1} 2941, 2870, 2825, 2773,1685, 1610, 1513, 1461, 1409, 1334, 1297, 1249, 1170, 1029, 984, 913, 813, 764, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.18 (m, 2 H, 2 × Ar-CH), 7.04–7.01 (m, 2 H, Ar-C_qOMeAr-CHAr-C_qAr-CH), 6.90 (d, *J* = 8.6 Hz, 1 H, Ar-C_qOMeC*H*CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 6.4 Hz, 2 H, C*H*HOC*H*H), 4.73 (d, *J* = 6.4 Hz, 2 H, CH*H*OCH*H*), 4.08 (t, *J* = 5.7 Hz, 2 H, OC$H_2$$CH_2$), 3.91 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.47 (s, 2 H, NCH_2Ar-C_q), 2.78 (t, *J* = 5.7 Hz, 2 H, OCH_2CH_2), 2.38 (s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (Ar-C_qO), 149.2 (Ar-C_qO), 148.2 (Ar-C_qO), 134.5 (Ar-$C_q$$C_q$), 132.3 (Ar-$C_q$$C_q$), 129.2 (2 × Ar-CH), 118.5 (Ar-CH), 114.5 (2 × Ar-CH), 110.8 (Ar-CH), 109.3 (Ar-CH), 82.7 (CH_2OCH_2), 65.7 (OCH_2CH_2), 63.4 (C_q), 58.1 (OCH_2CH_2), 55.91 (OCH_3), 55.87 (OCH_3), 47.3 (NCH_2Ar-C_q), 45.7 (2 × NCH_3); HRMS (APCI) *m/z* calcd for $C_{22}H_{31}N_2O_4^+$ [M+H]$^+$: 387.2278, found: 387.2276.

Notes:

The multiplet at 7.04–7.01 is composed of a dd and a singlet. The ^3J is obscured by the singlet, but the ^4J equals to 2.1 Hz.

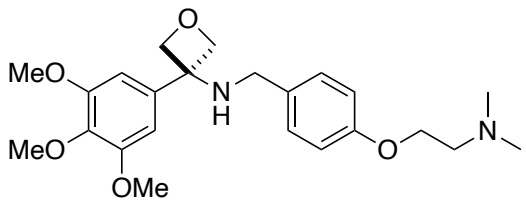
The doublet at 6.90 (1 H) and the multiplet at 6.88–6.85 (2 H) ppm were integrated together to 3 H.

The singlets at 3.91 (3 H) and 3.90 (3 H) ppm were integrated together to 6 H.

There is a very broad singlet under the triplet at 2.78 ppm which was assigned to NH + H_2O.

_N_-(4-(2-(Dimethylamino)ethoxy)benzyl)-3-(3,4,5-trimethoxyphenyl)oxetan-3-amine (63)

Analogue of Trimethobenzamide (C=O)[48]



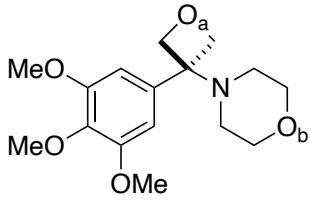
Prepared according to **General Procedure A** under air with a Celite workup for 13 h and using oxetane sulfonyl fluoride **54** (61.6 mg) and 2-(4-(aminomethyl)phenoxy)-*N*,*N*-dimethylethan-1-amine (47.0 mg). Purification by flash column chromatography (5–10% MeOH/CH_2Cl_2) afforded oxetane amine **63** as a colorless oil (26.5 mg, 32%). R_f = 0.21 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 2941, 2870, 2825, 2773, 1588, 1510, 1461, 1413, 1334, 1297, 1238, 1175, 1126, 1036, 828, 775, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.20 (m, 2 H, 2 × Ar-CH), 6.89–6.85 (m, 2 H, 2 × Ar-CH), 6.72 (s, 2 H, 2 × Ar-CH), 4.93 (d, *J* = 6.5 Hz, 2 H, C*H*HOC*H*H), 4.73 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 4.08 (t, *J* = 5.6 Hz, 2 H, OCH_2CH$_2$), 3.89 (s, 6 H, 2 × OCH_3), 3.87 (s, 3 H, OCH_3), 3.50 (s, 2 H, NCH_2Ph), 2.78 (t, *J* = 5.6 Hz, 2 H, OCH_2CH_2), 2.59 (br s, 1 H, NH), 2.38 (s, 6 H, 2 × NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (Ar-C_qOCH$_2$), 153.3 (2 × Ar-C_qOMe), 137.7 (Ar-C_qOMe), 137.0 (Ar-C_qC_q), 132.2 (Ar-C_qCH$_2$), 129.2 (2 × Ar-CHC$_q$CH$_2$), 114.5 (2 × Ar-CHC$_q$OCH$_2$), 103.3 (2 × Ar-CHC$_q$C$_q$), 82.7 (CH_2OCH_2), 65.7 (OCH_2CH_2), 63.7 (Ar-C_qC_q), 60.8 (OCH_3), 58.1 (OCH_2CH_2), 56.2 (2 × OCH_3), 47.3 (NCH_2Ph), 45.7 (2 × NCH_3); HRMS (ESI) *m/z* calcd for $C_{23}H_{33}N_2O_5$ [M+H]: 417.2389, found: 417.2389.

Notes:

The product was somewhat unstable on silica. Column chromatography should be performed in the shortest time possible (<30 min) and using the shortest possible column. A benzaldehyde side product which was not present in the crude reaction mixture, was observed in some of the collected fractions after the purification. The aldehyde is formed presumably due to oxidation at the non-oxetanyl aminobenzylic position.

4-(3-(3,4,5-Trimethoxyphenyl)oxetan-3-yl)morpholine (64)

Analogue of Trimetozine (C=O)[49] and Trithiozine (C=S)[50]



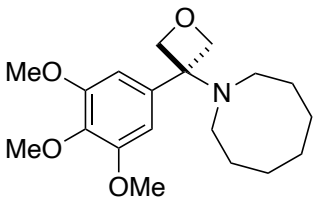
Prepared according to **General Procedure A** under air with a Celite workup for 13 h and using oxetane sulfonyl fluoride **54** (61.3 mg) and morpholine (21 μL). Purification by flash column chromatography (100% EtOAc) afforded oxetane amine **64** as a white solid (55.6 mg, 90%). R_f = 0.14 (100% EtOAc); mp = 164–170 °C; IR (film)/cm^{-1} 2952, 2878, 2833, 1589, 1510, 1453, 1417, 1331, 1290, 1245, 1185, 1126, 992, 954, 913, 813, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 2 H, 2 × Ar-CH), 4.89 (br s, 4 H, $CH_2O_aCH_2$), 3.87 (s, 9 H, 3 × OCH_3), 3.76 (br s, 4 H, $CH_2O_bCH_2$), 2.41 (br s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (2 × Ar-C_qOMe), 137.5 (weak, Ar-C_qOMe), 133.4 (weak, Ar-C_qC_q), 104.7 (2 × Ar-CH), 78.7 (br, $CH_2O_aCH_2$), 67.1 (br, $CH_2O_bCH_2$ and Ar-C_qC_q), 60.9 (OCH_3), 56.3 (2 × OCH_3), 46.5 (CH_2NCH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_5$ [M+H]: 310.1654, found: 310.1655.

Notes:

*^{13}C NMR signal at 67.1 ppm: $CH_2O_bCH_2$ was assigned by analogy to other morpholine-containing oxetanes. Ar-C_q**C**$_q$ was assigned by an HMBC correlation spectrum. The signal is also broad and contains a shoulder.*

1-(3-(3,4,5-Trimethoxyphenyl)oxetan-3-yl)azocane (65)

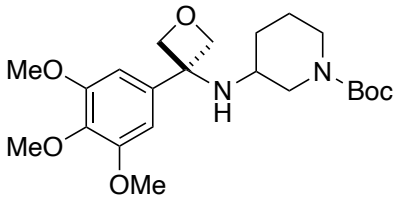
Analogue of Trocimine (C=O)[51]



Prepared according to **General Procedure A** under air with a Celite workup for 13 h and using oxetane sulfonyl fluoride **54** (61.3 mg) and azocane (31 μL). Purification by automated column chromatography afforded oxetane amine **65** as a colorless gum with unknown impurities (45.1 mg). Repurification by flash column chromatography (40% Et_2O/pentane) afforded oxetane amine **65** as a colorless gum (30.8 mg, 46%). R_f = 0.38 (40% Et_2O/pentane); IR (film)/cm^{-1} 2919, 1584, 1510, 1454, 1413, 1327, 1245, 1170, 1126, 987, 958, 869, 835, 772, 739, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 2 H, 2 × Ar-CH), 4.88 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.84 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.87 (s, 6 H, 2 × OCH_3), 3.86 (s, 3 H, OCH_3), 2.50 (t, *J* = 5.9 Hz, 4 H, CH_2NCH_2), 1.73–1.58 (m, 10 H, 5 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (2 × Ar-C_qOMe), 137.4 (Ar-C_qOMe), 136.9 (Ar-C_q), 104.1 (2 × Ar-CH), 80.8 (CH_2OCH_2), 68.0 (C_q), 60.9 (OCH_3), 56.2 (2 × OCH_3), 49.0 (CH_2NCH_2), 28.8 (2 × CH_2), 28.4 (CH_2), 25.3 (2 × CH_2); HRMS (ESI) *m/z* calcd for $C_{19}H_{30}NO_4$ [M+H]: 336.2175, found: 336.2175.

Automated column conditions: Column Type: Biotage® Sfär HC 10 g. Flow rate: 40 mL/min. 14 column volumes (CV) 0–4% MeOH/CH_2Cl_2, 2 CV 4–100% MeOH/CH_2Cl_2. Fractions 5–21: impure oxetane amine **65**.

***tert*-Butyl 3-((3-(3,4,5-trimethoxyphenyl)oxetan-3-yl)amino)piperidine-1-carboxylate (66)**



Prepared according to **General Procedure A** under air with a Celite workup for 13 h and using oxetane sulfonyl fluoride **54** (61.3 mg) and *tert*-butyl 3-aminopiperidine-1-carboxylate (48.3 mg). Purification by flash column chromatography (25% acetone/pentane) afforded oxetane amine **66** as a yellow gum (62.8 mg, 74%). R_f = 0.24 (30% acetone/pentane); IR (film)/cm^{-1} 2937, 2864, 1685 (C=O st), 1588, 1510, 1465, 1416, 1364, 1241, 1126, 1007, 980, 924, 857, 768, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (br s, 2 H, 2 × Ar-CH), 5.08 (br s, 1 H, C*H*HO), 4.93 (d, *J* = 6.3 Hz, 1 H, C*H*HO), 4.74 (br s, 2 H, 2 × C*H*HO), 3.89 (s, 6 H, 2 × OCH_3), 3.86 (s, 3 H, OCH_3), 2.79 (ddd, $^3J_{ax,ax}$ = 13.5, 10.6 Hz, $^3J_{ax,eq}$ = 3.1 Hz, CH), 2.59 (br s, 1 H, C*H*HN), 2.38 (br s, 1 H, C*H*HN), 1.97–1.50 (br m, 5 H, 5 × C*H*H), 1.46–1.24 (br m, 10 H, 3 × C_qCH_3 + C*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (C_q=O), 153.3 (2 × Ar-C_qOMe), 137.2 (weak, Ar-C_qOMe), 103.6 (2 × Ar-CH), 83.7 (br and weak, CH_2OCH_2), 79.5 ($C_q(CH_3)_3$), 63.2 (Ar-C_qC_q), 60.8 (OCH_3), 56.2 (2 × OCH_3), 49.9 (NCH_2CH), 43.8 (br and weak, CH), 32.5 (br and weak, CH_2), 28.3 (3 × C_qCH_3), 23.8 (CH_2); HRMS (APCI) *m/z* calcd for $C_{22}H_{35}N_2O_6^+$ $[M+H]^+$: 423.2490, found: 423.2480.

Notes:

The singlet for the tert-butyl group is located at 1.40 ppm under the broad multiplet between 1.46–1.24.

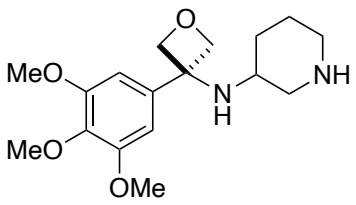
Most signals in the ^{1}H and ^{13}C NMR spectra are broadened and/or weak due to chemical exchange between conformers caused by N and ring-inversion and carbamate rotation.

*The weak ^{13}C signals were assigned by HSQC and HMBC correlation spectra. The Ar**C**$_q$C$_q$ and one CH_2 signal were not found neither in the ^{13}C NMR spectrum nor 2D correlation spectra. There seems to be a weak HMBC correlation between $C_{(oxetane)}H_2$'s and a very weak and broad peak at 138.0 ppm which could be the Ar**C**$_q$C$_q$ signal (see spectra). This is in agreement with the observed chemical shift of **67**.*

*The identity of **67** was confirmed by HRMS and the assignment of its Boc-deprotected derivative **67**.*

_N_-(3-(3,4,5-Trimethoxyphenyl)oxetan-3-yl)piperidin-3-amine (67)

Analogue of Troxipide (C=O)[52]

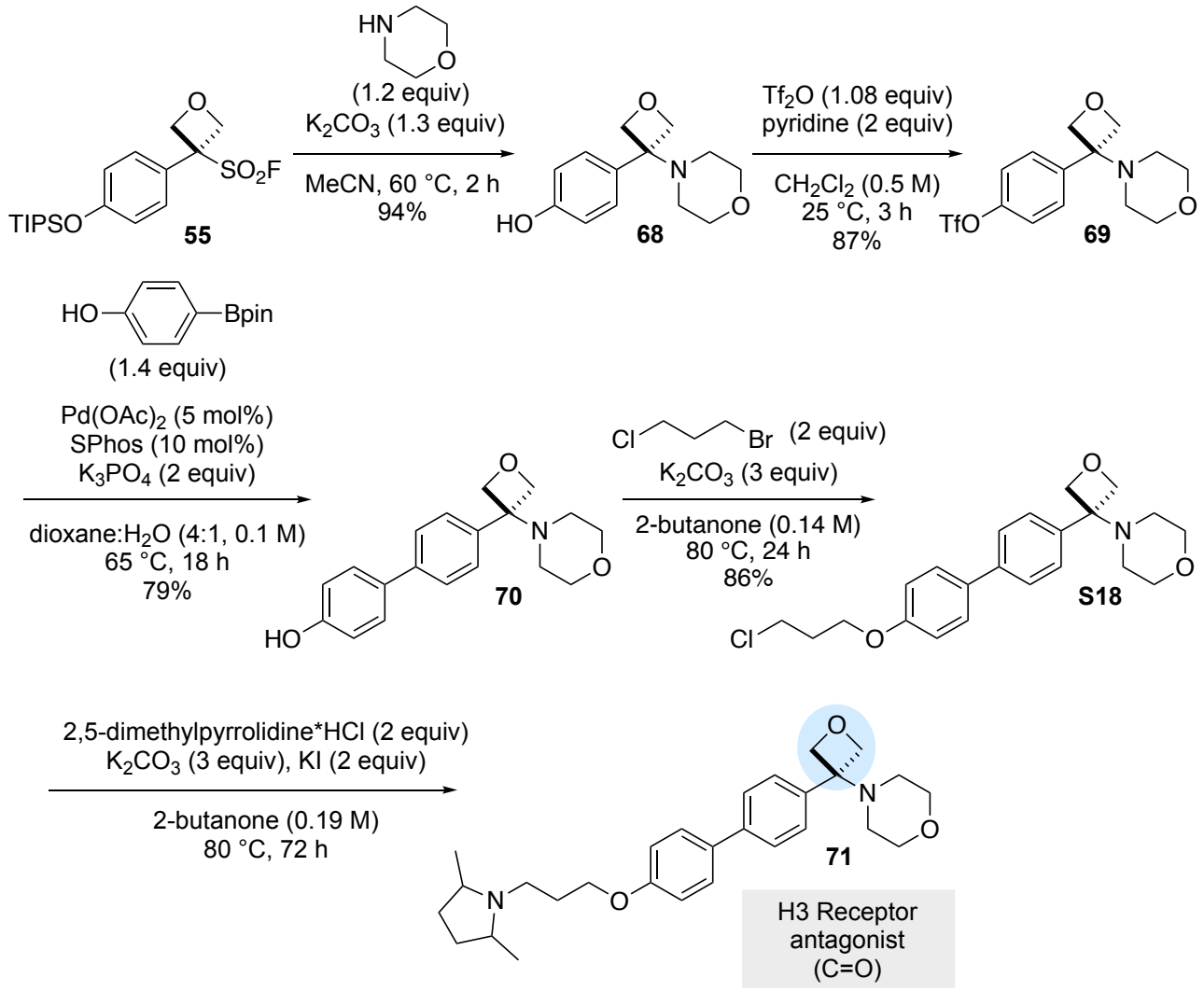


Trifluoroacetic acid (0.11 mL, 1.44 mmol, 10 equiv) was added dropwise to a solution of oxetane amine **66** (62.6 mg, 0.148 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.74 mL, 0.2 M) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was warmed to 25 °C and stirred for further 16 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with EtOAc (6 × 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to yield oxetane di-amine **67** as a light-yellow gum (32.7 mg). Brine (5 mL) and aq. NaOH (1 M, 2 mL) were added to the aqueous phase and it was reextracted with EtOAc (2 × 10 mL), CH_2Cl_2 (2 × 10 mL) and a mixture of $CHCl_3$:isopropanol (3:1, 2 × 10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator to yield further oxetane di-amine **67** as a light-yellow gum (15.0 mg). A total of 47.7 mg (quant.) were obtained. R_f = 0.17 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 2945, 2870, 1677, 1592, 1510, 1465, 1416, 1334, 1241, 1200, 1126, 1006, 910, 835, 768, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2 H, 2 × Ar-CH), 4.99 (d, *J* = 6.3 Hz, 1 H, C*H*HOCHH), 4.90 (d, *J* = 6.3 Hz, 1 H, CHHOC*H*H), 4.69 (d, *J* = 6.3 Hz, 1 H, CH*H*OCHH), 4.68 (d, *J* = 6.3 Hz, 1 H, CHHOCH*H*), 3.87 (s, 6 H, 2 × OCH_3), 3.85 (s, 3 H, OCH_3), 3.25 (br s, 2 H, 2 × NH), 2.92–2.87 (m, 1 H, NC*H*HCH_2), 2.76 (dd, ^2J = 11.8 Hz, $^3J_{eq,ax}$ = 3.8 Hz, 1 H, NCH_{eq}HCH), 2.64–2.53 (m, 2 H, CH + NCH*H*CH_2), 2.34 (dd, ^2J = 11.8 Hz, $^3J_{ax,ax}$ = 8.7 Hz, NCHH_{ax}CH), 1.76–1.69 (m, 2 H, CHC*H*HC*H*H), 1.53–1.42 (m, 1 H, $CHCH_2$CH*H*), 1.31–1.21 (m, 1 H, CHCH*H*CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (2 × Ar-C_qOMe), 138.3 (Ar-C_qC_q), 137.2 (Ar-C_qOMe), 103.5 (2 × Ar-CH), 83.9 (CH_2OCH_2), 83.1 (CH_2OCH_2), 63.4 (C_q), 60.9 (OCH_3), 56.2 (2 × OCH_3), 52.4 (NCH_2CH), 49.7 (CH), 45.4 (NCH_2CH_2), 32.5 ($CHCH_2$), 23.7 ($CHCH_2CH_2$); HRMS (APCI) *m/z* calcd for $C_{17}H_{27}N_2O_4^+$ $[M+H]^+$: 323.1965, found: 323.1965.

Notes:

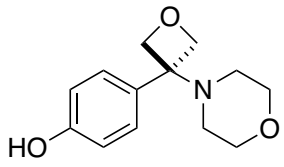
The two doublets at 4.69 (1 H) and 4.68 (1 H) ppm were integrated together to 2 H.

Synthesis of an Oxetane Analogue of an H3 Receptor Agonist (**68**–**71**, **S18**)



Scheme S9 Short reaction sequence for the synthesis of drug analogue **71** from OTIPS OSF **55**.

4-(3-Morpholinooxetan-3-yl)phenol (68)

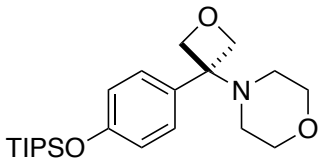


Anhydrous K_2CO_3 (438 mg, 3.2 mmol, 1.3 equiv), morpholine (0.26 mL, 2.9 mmol, 1.2 equiv) and sulfonyl fluoride **55** (950 mg, 2.4 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under Ar. The reaction vessel was sealed and anhydrous acetonitrile (8.0 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C and water (40 mL) and CH_2Cl_2 (40 mL) were added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (80–100% EtOAc/hexane) afforded oxetane amine **68** as a white solid (574 mg, 94%). R_f = 0.21 (80% EtOAc/hexane); mp = 172–174 °C; IR (film)/cm^{-1} 3282 (br OH), 2938, 2866, 1612, 1518, 1263, 1224, 1115, 1104, 1062, 982, 928, 912, 841; ^{1}H NMR (400 MHz, $(CD_3)CO$) δ 8.40 (s, 1 H, OH), 7.02–7.00 (m, 2 H, 2 × Ar-CH), 6.88–6.85 (m, 2 H, 2 × Ar-CH), 4.80–4.73 (m, 4 H, CH_2OCH_2), 3.61 (t, *J* = 4.6 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.24 (s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $(CD_3)CO$) δ 157.3 (Ar-C_qOH), 129.6 (2 × Ar-CH), 129.1 (Ar-C_qC_q), 115.2 (2 × Ar-CH), 81.1 (CH_2OCH_2), 67.6 ($CH_2CH_2OCH_2CH_2$), 66.8 (C_q), 47.2 (CH_2NCH_2); HRMS (NSI) *m/z* calcd for $C_{13}H_{18}NO_3^+$ $[M+H]^+$: 236.1281, found: 236.1283.

Alternatively, oxetane amine **68** can be synthesized through the benzyl deprotection of oxetane amine **79**: palladium on carbon (10% w/w, 72 mg) was added to a solution of oxetane amine **79** (716 mg, 2.2 mmol) in ethanol (17.5 mL). The reaction mixture was stirred under an atmosphere of hydrogen at 25 °C for 1 h. The reaction mixture was filtered through Celite, washed through with ethanol and then concentrated *in vacuo* using a rotatory evaporator to afford oxetane amine **68** as a white solid (465 mg, 90%).

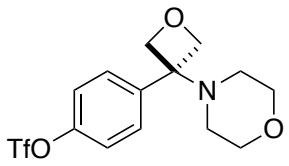
If TMS-morpholine was used as nucleophile, TIPS-protected morpholine-oxetane **72** was obtained:

4-(3-(4-((Triisopropylsilyl)oxy)phenyl)oxetan-3-yl)morpholine (72)



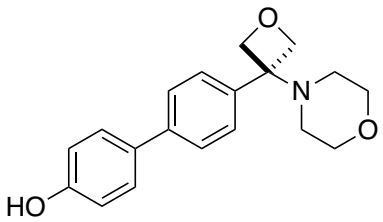
TMS-morpholine (0.4 mmol, 2.0 equiv) and sulfonyl fluoride **55** (78 mg, 0.20 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under Ar. The reaction vessel was sealed and anhydrous acetonitrile (0.7 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C and water (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane amine **72** as a white solid (58 mg, 73%). R_f = 0.39 (80% EtOAc/hexane); mp = 87–89 °C; IR (film)/cm^{-1} 2938, 2863, 1509, 1236, 1177, 1121, 1112, 1009, 986, 924, 914, 810, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 4 H, 4 × Ar-CH), 4.90 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.74 (t, *J* = 4.5 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.29 (t, *J* = 4.5 Hz, 4 H, CH_2NCH_2), 1.31–1.22 (m, 3 H, 3 × C*H*$(CH_3)_2$), 1.11 (d, *J* = 7.3 Hz, 18 H, 6 × CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (Ar-C_qOTIPS), 129.4 (Ar-*C*$_q$C$_q$), 128.3 (2 × Ar-CH), 119.2 (2 × Ar-CH), 79.4 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.3 (C_q), 46.4 (CH_2NCH_2) 17.9 (3 × CH(*C*$H_3)_2$), 12.6 (3 × *C*H$(CH_3)_2$); HRMS (CI) *m/z* calcd for $C_{22}H_{38}NO_3Si^+$ $[M+H]^+$: 392.2615, found: 392.2614.

4-(3-Morpholinooxetan-3-yl)phenyl trifluoromethanesulfonate (69)



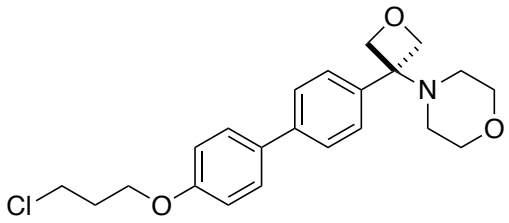
Pyridine (0.21 mL, 2.6 mmol, 2.0 equiv) then triflic anhydride (0.24 mL, 1.4 mmol, 1.08 equiv) were added to a solution of oxetane amine **68** (306 mg, 1.3 mmol, 1.0 equiv) in CH_2Cl_2 (2.6 mL, 0.5 M). The reaction mixture was stirred at 25 °C for 3 h then sat. aq. $NaHCO_3$ (20 mL) was added followed by CH_2Cl_2 (15 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane triflate **69** as a yellow gum (417 mg, 87%). R_f = 0.39 (80% EtOAc/hexane); IR (film)/cm^{-1} 2951, 2858, 1501, 1421, 1205, 1136, 1115, 883, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2 H, 2 × Ar-CH), 7.20–7.16 (m, 2 H, 2 × Ar-CH), 4.91 (d, *J* = 6.2 Hz, 2 H, C*H*HOC*H*H), 4.85 (d, *J* = 6.2 Hz, 2 H, CH*H*OCH*H*), 3.73 (t, *J* = 4.5 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.31 (t, *J* = 4.5 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (Ar-C_qOTf), 138.2 (Ar-*C*$_q$C$_q$), 128.9 (2 × Ar-CH), 121.0 (2 × Ar-CH), 118.7 (q, J_{CF} = 320.9 Hz, CF_3), 78.5 (CH_2OCH_2), 66.8 ($CH_2CH_2OCH_2CH_2$), 66.5 (C_q), 46.4 (CH_2NCH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (NSI) *m/z* calcd for $C_{14}H_{17}NO_5SF_3^+$ $[M+H]^+$: 368.0774, found: 368.0775.

4'-(3-Morpholinooxetan-3-yl)-[1,1'-biphenyl]-4-ol (70)



Triflate **69** (184 mg, 0.5 mmol, 1.0 equiv), 4-hydroxyphenylboronic acid pinacol ester (147 mg, 0.7 mmol, 1.4 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%), SPhos (20.5 mg, 0.05 mmol, 10 mol%) and K_3PO_4 (213 mg, 1.0 mmol, 2 equiv) were added to a reaction vial. The reaction vial was evacuated and then refilled with N_2 (3 ×). Dioxane/water (4:1, 5.0 mL, 0.1 M) was added by syringe. The reaction mixture was stirred at 65 °C for 18 h then cooled to 25 °C. Diethylether (15 mL) was added and the crude mixture was filtered through Celite and then concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (80% EtOAc/hexane) afforded biaryl **70** as a white solid (122 mg, 79%). R_f = 0.19 (80% EtOAc/hexane); mp = 194–196 °C; IR (film)/cm^{-1} 3287 (br OH), 2823, 1497, 1268, 1172, 1107, 968, 929, 806, 723, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2 H, 2 × Ar-CH), 7.48–7.46 (m, 2 H, 2 × Ar-CH), 7.11–7.09 (m, 2 H, 2 × Ar-CH), 6.92–6.90 (m, 2 H, 2 × Ar-CH), 5.09 (s, 1 H, OH), 4.97 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 4.93 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*), 3.77 (t, *J* = 4.5 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.38 (t, *J* = 4.5 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (Ar-C_qOH), 140.0 (Ar$_{(phenol)}$-C_qC_q), 135.3 (Ar-C_qAr-$C_{q(phenol)}$), 133.1 (Ar-$C_qC_{q(oxetane)}$), 128.3 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 115.7 (2 × Ar-CH), 79.2 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.7 (C_q), 46.4 (CH_2NCH_2); HRMS (NSI) *m/z* calcd for $C_{19}H_{22}NO_4S^+$ $[M+H]^+$: 360.1264, found: 360.1262.

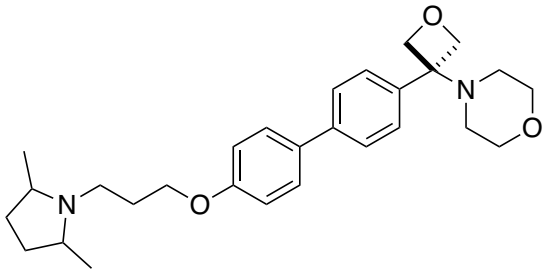
4-(3-(4'-(3-Chloropropoxy)-[1,1'-biphenyl]-4-yl)oxetan-3-yl)morpholine (S18)



1-Bromo-3-chloropropane (20 µL, 0.2 mmol, 2.0 equiv) was added to a solution of biaryl **70** (31 mg, 0.1 mmol, 1.0 equiv) and K_2CO_3 (42 mg, 0.3 mmol, 3.0 equiv) in 2-butanone (0.7 mL, 0.14 M). The reaction mixture was stirred at 80 °C for 24 h then cooled to 25 °C. Water (10 mL) and CH_2Cl_2 (10 mL) were added and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (4 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (60% EtOAc/hexane) afforded chloro-oxetane **S18** as a white solid (33 mg, 86%). R_f = 0.22 (60% EtOAc/hexane); mp = 108–111 °C; IR (film)/cm^{-1} 2946, 2867, 1740, 1513, 1270, 1139, 911, 883; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (m, 4 H, 4 × Ar-CH), 7.12–7.08 (m, 2 H, 2 × Ar-CH), 7.03–6.99 (m, 2 H, 2 × Ar-CH), 4.97 (d, *J* = 6.1 Hz, 2 H, C*H*HOC*H*H), 4.92 (d, *J* = 6.1 Hz, 2 H, CH*H*OCH*H*), 4.18 (t, *J* = 6.1 Hz, 2 H, Ar-OCH_2), 3.80–3.75 (m, 6 H, $CH_2CH_2OCH_2CH_2$ + CH_2Cl), 2.37 (br t, *J* = 4.5 Hz, 4 H, CH_2NCH_2), 2.28 (p, *J* = 6.1 Hz, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (Ar-C_qO), 139.9 (Ar-C_qC_q), 135.4 (Ar-$C_qC_{q(oxetane)}$), 133.2 (Ar-C_qC_q), 128.1 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 114.8 (2 × Ar-CH), 79.2 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.6 (C_q), 64.3 (Ar-OCH_2), 46.4 (CH_2NCH_2), 41.5 (CH_2Cl), 32.2 ($CH_2CH_2CH_2$); HRMS (CI) *m/z* calcd for $C_{22}H_{27}NO_3{}^{35}Cl^+$ $[M+H]^+$: 388.1674, found: 388.1674.

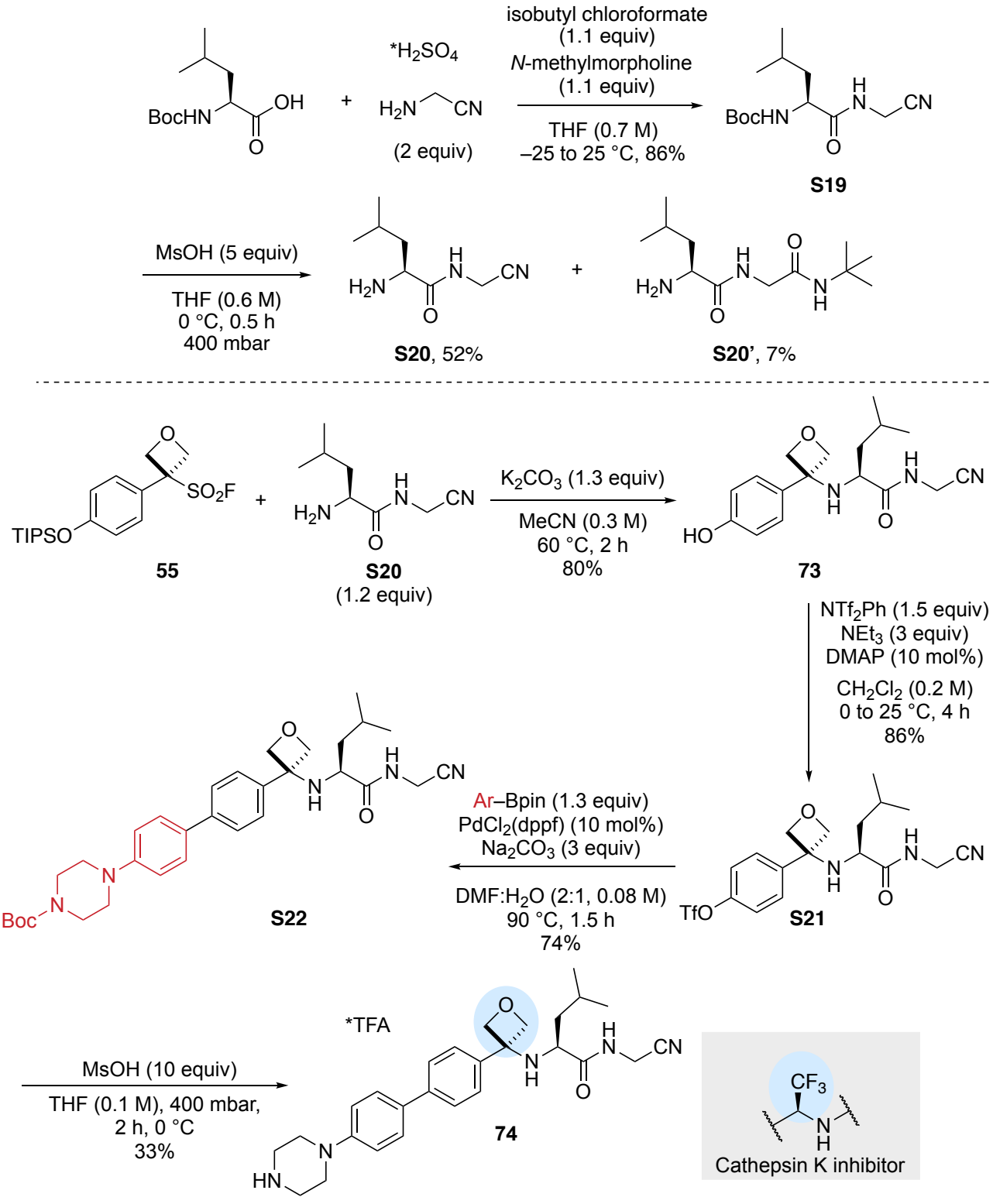
4-(3-(4'-(3-(2,5-Dimethylpyrrolidin-1-yl)propoxy)-[1,1'-biphenyl]-4-yl)oxetan-3-yl) morpholine (71)

Analogue of an H3 Receptor Antagonist (C=O)[53]



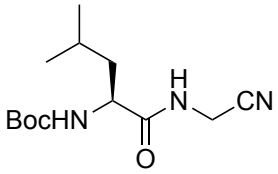
2,5-Dimethylpyrrolidine (20.3 mg, 0.15 mmol, 2.0 equiv) was added to a solution of chloro-oxetane **S18** (29.1 mg, 0.075 mmol, 1.0 equiv), K_2CO_3 (31.1 mg, 0.225 mmol, 3 equiv), potassium iodide (24.9 mg, 0.15 mmol, 2.0 equiv) in 2-butanone (0.4 mL, 0.19 M). The reaction mixture was stirred at 80 °C for 72 h then cooled to 25 °C, and water (10 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (2% Et_3N/EtOAc) afforded oxetane diamine **71** as a white solid (14.8 mg, 44%). R_f = 0.21 (2% Et_3N/EtOAc); mp = 89–91 °C; IR (film)/cm^{-1} 2956, 2870, 1739, 1608, 1498, 1247, 1186, 1115, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.51 (m, 4 H, 4 × Ar-CH), 7.10–7.08 (m, 2 H, 2 × Ar-CH), 7.00–6.98 (m, 2 H, 2 × Ar-CH), 4.96 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.91 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 4.06 (t, *J* = 6.1 Hz, 2 H, Ar-OCH_2), 3.76 (t, *J* = 4.5 Hz, 4 H $CH_2CH_2OCH_2CH_2$), 2.79 (t, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2N$), 2.64 (br q, *J* = 6.0 Hz, 2 H, 2 × C*H*CH_3), 2.37 (br t, *J* = 4.5 Hz, 4 H, CH_2NCH_2), 2.00–1.96 (m, 2 H, $CH_2CH_2CH_2$), 1.85–1.80 (m, 2 H, CHC*H*HC*H*HCH), 1.41–1.37 (m, 2 H, CHCH*H*CH*H*CH), 1.14 (d, *J* = 6.0 Hz, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (Ar-C_qO), 140.0 (Ar-C_qAr-C_q), 135.4 (Ar-$C_q$$C_{q(oxetane)}$), 132.2 (Ar-$C_q$Ar-$C_q$), 128.0 (2 × Ar-CH), 127.6 (2 × Ar-CH), 126.2 (2 × Ar-CH), 114.8 (2 × Ar-CH), 79.2 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.7 (C_q), 66.5 (Ar-OCH_2), 60.4 (2 × *C*HCH_3), 48.1 ($CH_2CH_2CH_2N$), 46.4 (CH_2NCH_2), 31.4 ($CHCH_2CH_2CH$), 27.4 ($CH_2CH_2CH_2$), 20.9 (2 × CH_3); HRMS (NSI) *m/z* calcd for $C_{28}H_{39}N_2O_3^+$ $[M+H]^+$: 451.2955, found: 451.2943.

Synthesis of an Oxetane Analogue of a Cathepsin K Inhibitor (**73**,**74**, **S19**–**S22**)



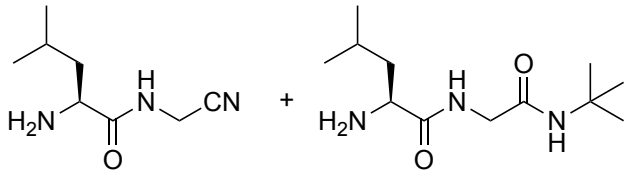
Scheme S10 Short reaction sequence for the synthesis of drug analogue **74** from OTIPS OSF **55**

tert-Butyl (_S_)-(1-((cyanomethyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (S19)



Prepared in a 5.0 mmol scale from *N*-Boc-leucine using a literature procedure.[54] Concentration *in vacuo* using a rotatory evaporator afforded nitrile-Boc-leucine **S19** as white solid (1.16 g, 86%). $[\alpha]_D^{21}$ –32.0 (c 1, $CDCl_3$) (Lit.: $[\alpha]_D^{20}$ –23.4 (c 2.11, MeOH));[55] R_f = 0.42 (10% MeOH/CH_2Cl_2); mp = 103–110 °C (Lit.: mp = 114–116 °C);[55] IR (film)/cm^{-1} 3302 (br NH), 2960, 2874, 2255 (weak, C≡N st), 1670 (C=O st), 1521, 1368, 1249, 1163, 1126, 1047, 913, 872, 783, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1 H, NH), 5.36–5.10 (br m, 1 H, NH), 4.20 (br s, 1 H, NCH), 4.15 (d, *J* = 5.7 Hz, 2 H, CH_2CN), 1.69–1.54 (m, 3 H, NCHC*H*$_2$C*H*), 1.45 (s, 9 H, 3 × C_qCH_3), 0.95 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$), 0.92 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C_q=O$_{(amide)}$), 156.2 (C_q=O$_{(carbamate)}$), 116.0 (C≡N), 80.6 (*C*$_q$(CH$_3$)$_3$), 52.7 (NBocCH), 40.8 (*C*H$_2$CH), 28.3 (3 × C_q(*C*H$_3$)), 27.3 (*C*H$_2$CN), 24.6 (*C*H(CH$_3$)$_2$), 22.9 (CH*C*H$_3$), 21.8 (CH*C*H$_3$). The observed characterization data (mp, [α]$_D$, ^{1}H, ^{13}C) were consistent with that previously reported.[55]

(_S_)-2-Amino-_N_-(cyanomethyl)-4-methylpentanamide (S20) and (_S_)-2-amino-_N_-(2-(_tert_-butylamino)-2-oxoethyl)-4-methylpentanamide (S20')[56]



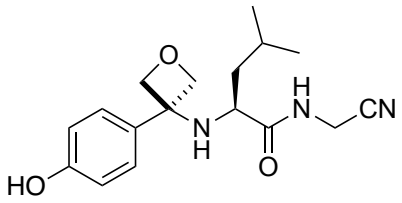
S20 **S20'**

Methane sulfonic acid (1.42 mL, 21.9 mmol, 5.0 equiv) was added dropwise to a solution of nitrile-Boc-leucine **S19** in anhydrous THF (8.8 mL, 0.5 M) at 0 °C under a flow of N_2. Then, a light vacuum (~400 mbar) was applied to the reaction using a water jet pump while keeping the flow of N_2. After stirring the reaction for further 30 min at 0 °C, THF was removed *in vacuo* using a rotatory evaporator. Aq. NaOH (1 M) was added to the residue until a pH of ~10 was reached and the resulting aqueous solution was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (0–10% MeOH/MeCN) afforded nitrile-leucine **S20** as a yellow gum (384.3 mg, 52%), followed by *tert*-butyl leucine **S20'** as a white solid (79.2 mg, 7%).

S20: $[\alpha]_D^{20}$ +14.0 (c 1, MeOH) (Lit.: $[\alpha]_D^{18}$ +4.5 (c 1.569, H_2O));[57] R_f = 0.29 (10% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3314 (br NH), 2956, 2870, 2255 (weak, C≡N st), 1659 (C=O st), 1506, 1413, 1342, 1256, 1141, 1115, 1029, 962, 902, 824; ^{1}H NMR (400 MHz, CD_3OD) δ 4.17 (d, *J* = 2.7 Hz, 2 H, CH_2CN), 3.38 (dd, *J* = 8.2, 6.1 Hz, 1 H, NCH), 1.70 (dh, *J* = 13.1, 6.6 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.54 (ddd, *J* = 13.6, 7.8, 6.1 Hz, 1 H, C*H*HCH), 1.41 (ddd, *J* = 13.6, 8.2, 6.4 Hz, 1 H, CH*H*CH), 0.96 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 0.94 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 178.5 (C_q=O), 117.6 (C≡N), 54.3 (NCH), 45.4 (*C*H$_2$CH), 27.9 (*C*H$_2$CN), 25.7 (*C*H(CH$_3$)$_2$), 23.4 (CH*C*H$_3$), 22.4 (CH*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_8H_{16}N_3O$ [M+H]: 170.1293, found: 170.1290. The observed characterization data (mp, [α]$_D$, ^{1}H, ^{13}C) were consistent with that previously reported.[54,57]

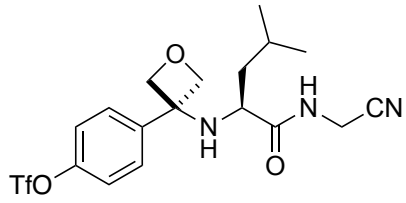
S20': $[\alpha]_D^{20}$ +8.0 (c 1, MeOH); R_f = 0.09 (10% MeOH/CH_2Cl_2); mp = 164–167 °C; IR (film)/cm^{-1} 3325 (br NH), 3086, 2960, 2870, 2475, 2400, 1640 (C=O st), 1517, 1435, 1390, 1327, 1275, 1226, 1074, 1044, 999, 928, 891, 828, 790, 697; ^{1}H NMR (400 MHz, CD_3OD) δ 3.77 (d, *J* = 3.7 Hz, 2 H, NCH_2), 3.37 (dd, *J* = 8.3, 6.1 Hz, 1 H, NCH), 1.78–1.67 (m, 1 H, C*H*(CH$_3$)$_2$), 1.55 (ddd, *J* = 13.6, 7.9, 6.1 Hz, 1 H, C*H*HCH), 1.39 (ddd, *J* = 13.6, 8.3, 6.4 Hz, 1 H, CH*H*CH), 1.33 (s, 9 H, 3 × C_qCH_3), 0.96 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 0.94 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 178.2 (C_q=O), 170.4 (C_q=O), 54.4 (NCH), 52.1 (*C*$_q$(CH$_3$)$_3$), 45.1 (*C*H$_2$CH), 43.7 (NCH_2), 28.9 (3 × C_qCH_3), 25.8 (*C*H(CH$_3$)$_2$), 23.4 (CH*C*H$_3$), 22.4 (CH*C*H$_3$); HRMS (APCI) *m/z* calcd for $C_{12}H_{26}N_3O_2^+$ [M+H]$^+$: 244.2020, found: 244.2018.

(*S*)-*N*-(Cyanomethyl)-2-((3-(4-hydroxyphenyl)oxetan-3-yl)amino)-4-methylpentanamide (73)



A reaction tube was charged with K_2CO_3 (103.3 mg, 0.748 mmol, 1.3 equiv), flame-dried, and allowed to cool under air. Amine **S29** (116.9 mg, 0.691 mmol, 1.2 equiv) and sulfonyl fluoride **55** (223.5 mg, 0.575 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and anhydrous acetonitrile (1.9 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (20–30% MeCN/CH_2Cl_2) afforded oxetane amine **73** as a colorless, solid foam (146.2 mg, 80%). $[a]_D^{20}$ –32.0 (c 1, MeOH); R_f = 0.21 (30% MeCN/CH_2Cl_2); mp = 65–70 °C; IR (film)/cm^{-1} 3317 (br OH/NH), 2956, 2870, 2468, 1655 (C=O st), 1614, 1517, 1469, 1342, 1264, 1234, 1174, 1115, 1036, 977, 902, 835, 686; ^{1}H NMR (400 MHz, CD_3OD) δ 7.17–7.14 (m, 2 H, 2 × Ar-CH), 6.81–6.78 (m, 2 H, 2 × Ar-CH), 4.94 (d, *J* = 6.4 Hz, 1 H, C*H*HOCH$_2$), 4.84 (d, *J* = 6.0 Hz, 1 H, CH$_2$OC*H*H), 4.76 (d, *J* = 6.4 Hz, 1 H, CH*H*OCH$_2$), 4.73 (d, *J* = 6.0 Hz, 1 H, CH$_2$OCH*H*), 3.96 (d, *J* = 2.8 Hz, 2 H, CH$_2$CN), 2.92 (dd, *J* = 8.6, 5.6 Hz, 1 H, NCH), 1.71–1.58 (m, 1 H, C*H*(CH$_3$)$_2$), 1.38 (ddd, *J* = 13.7, 8.6, 5.7 Hz, 1 H, C*H*HCH), 1.28 (ddd, *J* = 13.7, 8.3, 5.6 Hz, 1 H, CH*H*CH), 0.85 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 0.72 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, CD_3OD) 178.9 (C$_q$=O), 157.9 (Ar-C$_q$OH), 134.0 (Ar-*C*$_q$C$_q$), 129.3 (2 × Ar-CH), 117.3 (C≡N), 116.3 (2 × Ar-CH), 85.0 (*C*H$_2$OCH$_2$), 83.2 (CH$_2$O*C*H$_2$), 64.1 (Ar-C$_q$*C*$_q$), 57.1 (NCH), 44.8 (*C*H$_2$CH), 27.8 (*C*H$_2$CN), 25.6 (*C*H(CH$_3$)$_2$), 23.4 (CH*C*H$_3$), 22.3 (CH*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N_3O_3$ [M+H]: 318.1818, found: 318.1806.

(*S*)-4-(3-((1-((Cyanomethyl)amino)-4-methyl-1-oxopentan-2-yl)amino)oxetan-3-yl)phenyl trifluoromethanesulfonate (S21)

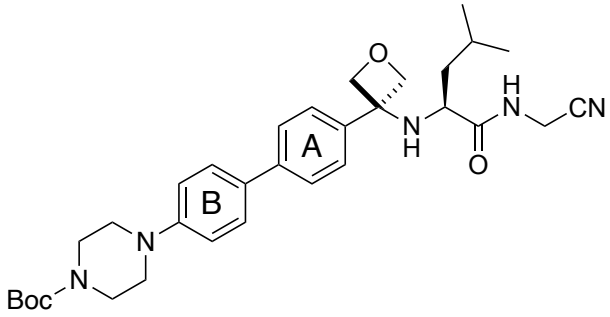


Triethylamine (0.15 mL, 1.07 mmol, 3 equiv), 4-dimethylaminopyridine (DMAP, 4.3 mg, 0.0355 mmol, 0.1 equiv) and *N*,*N*-bis(Trifluoromethylsulfonyl)aniline (NTf$_2$Ph, 190.3 mg, 0.53 mmol, 1.5 equiv) were added sequentially to a solution of phenol oxetane amine **73** (112.7 mg, 0.355 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.8 mL, 0.2 M) at 0 °C. After stirring for 5 min at 0 °C, the ice bath was removed and the reaction mixture was stirred for further 4 h at 25 °C. Then, the reaction mixture was concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (10% Et$_2$O/CH_2Cl_2) afforded triflate **S21** as colorless crystals (137.1 mg, 86%). $[a]_D^{20}$ –42.0 (c 1, $CDCl_3$); R_f = 0.23 (25% acetone/pentane); mp = 116 °C; IR (film)/cm^{-1} 3321 (br NH), 3038, 2956, 2878, 2363 (weak, , C≡N st), 1670 (C=O st), 1599, 1506, 1424, 1346, 1215, 1141, 1018, 984, 947, 891, 846, 783, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 4 H, 4 × Ar-CH), 7.16 (br app. t, *J* = 6.0 Hz, 1 H, N*H*CH$_2$), 4.98 (app. t, *J* = 6.3 Hz, 2 H, C*H*HOC*H*H), 4.70 (d, *J* = 7.0 Hz, 1 H, CH*H*OCH$_2$), 4.68 (d, *J* = 7.0 Hz, 1 H, CH$_2$OCH*H*), 4.03 (dd, *J* = 17.5, 6.1 Hz, 1 H, C*H*HCN), 3.82 (dd, *J* = 17.5, 5.7 Hz, 1 H, CH*H*CN), 3.14 (dd, *J* = 8.9, 4.8 Hz, 1 H, NCH), 2.33 (br s, 1 H, N*H*CH), 1.64–1.54 (m, 1 H, C*H*(CH$_3$)$_2$), 1.49 (ddd, *J* = 13.5, 8.6, 4.8 Hz, 1 H, C*H*HCH), 1.44–1.36 (m, 1 H, CH*H*CH), 0.90 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$), 0.77 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) 174.7 (C$_q$=O), 148.9 (Ar-C$_q$OTf), 142.0 (Ar-*C*$_q$C$_q$), 128.4 (2 × Ar-CH), 122.1 (2 × Ar-CH), 118.7 (q, J_{CF} = 320.8 Hz, CF_3), 115.7 (C≡N), 81.5 (CH$_2$O*C*H$_2$), 81.0 (*C*H$_2$OCH$_2$), 63.4 (Ar-C$_q$*C*$_q$), 56.4 (NCH), 43.8 (*C*H$_2$CH), 26.9 (*C*H$_2$CN), 24.7 (*C*H(CH$_3$)$_2$), 23.1 (CH*C*H$_3$), 21.8 (CH*C*H$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –72.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_3O_5SF_3$ [M+H]: 450.1311, found: 450.1306.

Notes:

The reaction should be monitored by TLC and stopped as soon as all starting material has been consumed. A lower yield was observed when the reaction was stirred for 13 h.

tert-Butyl (*S*)-4-(4'-(3-((1-((cyanomethyl)amino)-4-methyl-1-oxopentan-2-yl)amino)oxetan-3-yl)-[1,1'-biphenyl]-4-yl)piperazine-1-carboxylate (S22)



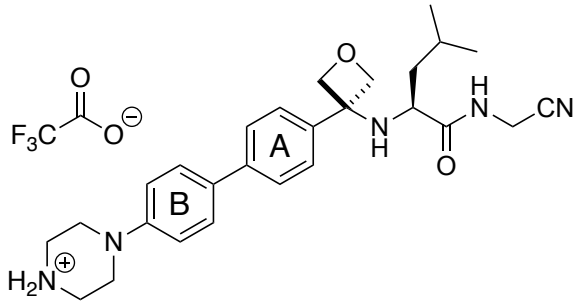
A reaction tube was charged sequentially with triflate **S21** (89.1 mg, 0.198 mmol, 1.0 equiv), *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (100.1 mg, 0.258 mmol, 1.3 equiv), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2$(dppf), 7.2 mg, 0.0099 mmol, 0.05 equiv) and sodium carbonate (63.0 mg, 0.594 mmol, 3.0 equiv). The reaction vessel was sealed and evacuated and refilled with argon (× 3). In a separate flask, anhydrous DMF was sparged with argon for 15 min. The same procedure was performed with distilled water. Sparged DMF (1.65 mL, DMF:H_2O = 2:1, 0.08 M) and sparged water (0.83 mL) were added to the reaction mixture by syringe. After stirring the reaction mixture at 90 ºC for 1.5 h, it was left to cool to 25 °C and EtOAc (10 mL) and water (10 mL) were added. The phases were separated and the aqueous phase was extracted with EtOAc (6 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (15–25% acetone/pentane) afforded biaryl oxetane **S22** as a white solid (82.5 mg, 74%). $[a]_D^{21}$ –46.0 (c 1, $CDCl_3$); R_f = 0.27 (25% acetone/pentane); mp = 176–180 °C; IR (film)/cm^{-1} 3314 (br NH), 2960, 2870, 2822, 2095 (weak, , C≡N st), 1689 (C=O st), 1607, 1528, 1502, 1457, 1424, 1234, 1167, 1126, 1085, 1051, 999, 917, 820, 772, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br d, *J* = 8.2 Hz, 2 H, 2 × $Ar_{(A)}$-CH), 7.52 (br d, *J* = 8.7 Hz, 2 H, 2 × $Ar_{(B)}$-CH), 7.30 (br app. t, *J* = 5.5 Hz, 1 H, N*H*CH_2), 7.20 (br d, *J* = 8.2 Hz, 2 H, 2 × $Ar_{(A)}$-CH), 7.02 (br d, *J* = 8.2 Hz, 2 H, 2 × $Ar_{(B)}$-CH), 5.08 (d, *J* = 6.4 Hz, 1 H, C*H*HOCH_2), 5.05 (d, *J* = 6.7 Hz, 1 H, CH_2OC*H*H), 4.69 (app. t, *J* = 7.2 Hz, 2 H, CH*H*OCH*H*), 3.98 (dd, *J* = 17.5, 6.2 Hz, 1 H, C*H*HCN), 3.67 (dd, *J* = 17.5, 5.5 Hz, 1 H, CH*H*CN), 3.62 (br app. t, *J* = 4.7 Hz, 4 H, CH_2N-ArCH_2), 3.24–3.20 (m, 5 H, NCH + CH_2NBocCH_2), 2.34 (br s, N*H*CH), 1.70–1.60 (m, 1 H, C*H*(CH_3)$_2$), 1.56–1.48 (m, 1 H, C*H*HCH), 1.50 (s, 9 H, 3 × $C_q$$CH_3$), 1.41 (ddd, *J* = 14.0, 9.0, 5.4 Hz, 1 H, CH*H*CH), 0.92 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$), 0.81 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) 174.7 (br and weak, C_q=$O_{(amide)}$), 154.7 (C_q=$O_{(carbamate)}$), 150.5 (br and weak, Ar-C_qN) 140.5 ($Ar_{(A)}$-*C*$_q$Ar-C_q), 139.2 (br and weak, Ar-*C*$_q$$C_q$), 131.8 (br and weak, $Ar_{(B)}$-*C*$_q$Ar-C_q), 127.8 (2 × $Ar_{(B)}$-CH), 126.9 (2 × $Ar_{(A)}$-CH), 126.7 (2 × $Ar_{(A)}$-CH), 116.8 (br and weak, 2 × $Ar_{(B)}$-CH), 115.7 (C≡N), 81.5 (CH_2O*C*H_2), 81.4 (*C*H_2OCH_2), 80.0 (*C*q(CH_3)$_3$), 63.7 (Ar-C_q*C*$_q$), 56.5 (NCH), 49.3 (br and weak, CH_2NBocCH_2), 43.6 (*C*H_2CH), 43.1 (br and weak, CH_2N-ArCH_2), 28.4 (3 × C_q*C*H_3), 26.9 (*C*H_2CN), 24.7 (*C*H(CH_3)$_2$), 23.1 (CH*C*H_3), 21.8 (CH*C*H_3); HRMS (ESI) *m/z* calcd for $C_{32}H_{44}N_5O_4$ [M+H]: 562.3393, found: 562.3406.

Notes:

In the ^{1}H NMR spectrum, the dd at 3.67 ppm and the br app. t at 3.62 ppm were integrated together to 5 H. Also, the m at 1.56–1.48 ppm and the s at 1.50 ppm were integrated together to 10 H.

Some signals in the ^{13}C NMR spectrum appear very weak and broad due to chemical exchange caused by the presence of conformers. The signals were identified and assigned with HSQC and HMBC correlation spectra (see spectra).

(*S*)-*N*-(Cyanomethyl)-4-methyl-2-((3-(4'-(piperazin-1-yl)-[1,1'-biphenyl]-4-yl)oxetan-3-yl)amino)pentanamide 2,2,2-trifluoroacetic acid salt (74)



Methane sulfonic acid (72 μL, 1.11 mmol, 10.0 equiv) was added dropwise to a solution of biaryl oxetane **S22** in anhydrous THF (1.1 mL, 0.1 M) at 0 °C under a flow of N_2. Then, a light vacuum (~400 mbar) was applied to the reaction using a water jet pump while keeping the flow of N_2. After stirring the reaction for further 30 min at 0 °C, THF was removed *in vacuo* using a rotatory evaporator. Aq. NaOH (1 M) was added to the residue until a pH of ~10 was reached and the resulting aqueous solution was extracted with EtOAc (6 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (20:1:79 MeOH:NEt_3:MeCN) afforded impure oxetane amine **74** as a light-yellow gum (29.3 mg). Repurification by automated column chromatography afforded impure oxetane amine **74** as a colorless gum (23.8 mg). Repurification by automated reversed-phase column chromatography afforded oxetane amine **74** as TFA salt as a colorless gum (21.0 mg, 33%). $[a]_D^{21}$ –8.0 (c 0.5, MeOH); R_f = 0.31 (20% MeOH/CH_2Cl_2); IR (film)/cm^{-1} 3347 (br NH), 3060, 2363 (weak, C≡N st), 2028, 1670 (C=O st), 1610, 1532, 1506, 1461, 1200, 1137, 928, 820, 723; ^{1}H NMR (400 MHz, CD_3OD) δ 7.79–7.76 (m 2 H, 2 × $Ar_{(A)}$-CH), 7.67–7.63 (m 2 H, 2 × $Ar_{(B)}$-CH), 7.53–7.49 (m 2 H, 2 × $Ar_{(A)}$-CH), 7.16–7.12 (m 2 H, 2 × $Ar_{(B)}$-CH), 5.23 (d, *J* = 8.0 Hz, 1 H, C*H*HOCH_2), 5.14–5.08 (m, 3 H, CH*H*OC*H*$_2$), 4.00 (d, *J* = 8.3, Hz, 2 H, CH_2CN), 3.51–3.48 (m, 4 H, CH_2N-ArCH_2), 3.41–3.36 (m, 5 H, NCH + C*H*$_2$NHC*H*$_2$), 1.74–1.54 (m, 3 H, C*H*$(CH_3)_2$ + C*H*$_2$CH), 0.88 (d, *J* = 6.2 Hz, 3 H, CHC*H*$_3$), 0.85 (d, *J* = 6.2 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (101 MHz, CD_3OD) 170.6 (C_q=O), 151.5 (Ar-C_qN) 143.6 ($Ar_{(A)}$-*C*$_q$Ar-C_q), 134.1 (Ar-*C*$_q$C$_q$), 133.2 ($Ar_{(B)}$-*C*$_q$Ar-C_q), 129.5 (2 × $Ar_{(A)}$-CH), 128.9 (2 × $Ar_{(B)}$-CH), 128.3 (2 × $Ar_{(A)}$-CH), 118.1 (2 × $Ar_{(B)}$-CH), 116.8 (C≡N), 80.6 (CH_2OCH_2), 79.8 (*C*H_2OCH_2), 65.6 (Ar-C_q*C*$_q$), 58.0 (NCH), 47.5 (CH_2N-ArCH_2), 44.7 (CH_2NHCH_2), 42.0 (*C*H_2CH), 28.0 (*C*H_2CN), 25.5 (*C*H$(CH_3)_2$), 22.9 (CH*C*H$_3$), 22.4 (CH*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_5O_2$ [M–$C_2F_3O_2$]: 462.2869, found: 462.2859.

Automated column conditions: Column Type: Biotage® Sfär HC 5 g. Flow rate: 18 mL/min. 1 column volumes (CV) 10% MeOH/CH_2Cl_2, 10 CV 10–40% MeOH/CH_2Cl_2, 15 CV 40% MeOH/CH_2Cl_2. Fractions 8–26: impure oxetane amine **74**.

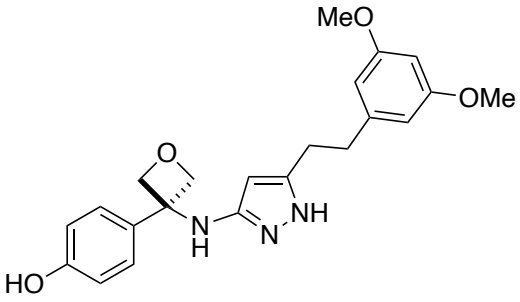
Automated reversed-phase column conditions: Column Type: Biotage® Sfär C18 D Duo 6 g. Flow rate: 6 mL/min. Modifier: 0.1% 2,2,2-trifluoroacetic acid. 8 column volumes (CV) 0–50% MeCN/H_2O, 5 CV 50–100% MeCN/H_2O, 5 CV 100% MeCN/H_2O. Fractions 9–11: oxetane amine **74**. Fractions 12–14: impure oxetane amine **74** (not collected).

Notes:

There is no visual difference between fractions 9–14 by TLC (normal phase). The fractions were separated on the basis of the UV trace measured by the Biotage instrument.

Synthesis of an Oxetane Analogue of the core structure of FGFR Inhibitor AZD4547 (**75**)

4-(3-((5-(3,5-Dimethoxyphenethyl)-1*H*-pyrazol-3-yl)amino)oxetan-3-yl)phenol (75)



Prepared according to **General Procedure A** using oxetane sulfonyl fluoride **55** (77.6 mg) and 5-(3,5-dimethoxyphenethyl)-1*H*-pyrazol-3-amine (59.4 mg). Purification by flash column chromatography (2–5% MeOH/CH_2Cl_2) afforded oxetane amine **75** as a white solid (71.4 mg, 90%). R_f = 0.25 (10% MeOH/CH_2Cl_2); mp = 192 °C; IR (film)/cm^{-1} 3224 (br OH), 2997, 2956, 2885, 2833, 2673, 2479, 2378, 2184, 2113, 1987, 1908, 1610, 1588, 1551, 1510, 1476, 1458, 1372, 1316, 1260, 1200, 1159, 1107, 1066, 1018, 932, 876, 835, 746, 719, 682; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.18 (br s, 1 H, $N_{(pyrazole)}H$), 9.25 (br s, 1 H, OH), 7.33–7.31 (m, 2 H, 2 × Ar-CH), 6.70–6.68 (m, 2 H, 2 × Ar-CH), 6.34 (d, *J* = 2.3 Hz, 2 H, 2 × Ar-CH), 6.30 (t, *J* = 2.3 Hz, 2 H, Ar-CH), 6.16 (br s, 1 H, $N_{(amine)}H$), 5.03 (br s, 1 H, $C_{(pyrazole)}H$), 4.78 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.65 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.69 (s, 6 H, 2 × OCH_3), 2.76–2.69 (m, 2 H, $C_{(pyrazole)}CH_2$), 2.67–2.60 (m, 2 H, $C_{(pyrazole)}CH_2CH_2$); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 160.3 (2 × Ar-C_qOMe), 155.8 (Ar-C_qOH), 153.9 (weak, $C_{q(pyrazole)}CH_2$), 143.5 (Ar-C_qCH_2), 142.3 (weak, $C_{q(pyrazole)}NH$), 134.6 (weak, Ar-C_qC_q), 126.7 (2 × $Ar_{(phenol)}$-CH), 114.6 (Ar-*C*HAr-C_qOHAr-*C*H), 106.2 (2 × $Ar_{(di\text{-}OMe)}$-CH), 97.8 (Ar-CH), 90.1 (weak, $C_{(pyrazole)}H$), 82.5 (CH_2OCH_2), 59.5 (Ar-C_qC_q), 55.0 (2 × OCH_3), 34.8 ($C_{(pyrazole)}CH_2CH_2$), 26.9 ($C_{(pyrazole)}CH_2CH_2$); HRMS (APCI) *m/z* calcd for $C_{22}H_{26}N_3O_4^+$ $[M+H]^+$: 396.1918, found: 396.1913.

Notes:

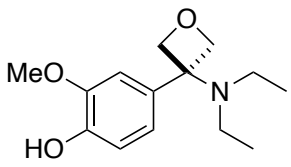
The OH and NH signals are of broad and of lower intensity due to chemical exchange.

In this example, both the H_2O (3.35 ppm) and HDO (3.32 ppm) peaks were visible in the ^{1}H NMR spectrum.

*Some peaks (Ar-C_qOH, Ar-**C**HAr-C_qOHAr-**C**H and Ar-C_q**C_q**) in the ^{13}C NMR spectrum appear as two signals and some peaks (**$C_{q(pyrazole)}CH_2$**, $C_{q(pyrazole)}NH$, Ar-**C_q**C_q and $C_{(pyrazole)}H$) are very broad and weak due to chemical exchange caused by an equilibrium between pyrazole tautomers. In the former case, the chemical shift is given as the average of both signals.*

4-(3-(Diethylamino)oxetan-3-yl)-2-methoxyphenol (76)

Analogue of Ethamivan (C=O)[58]



A reaction tube was charged with K_2CO_3 (18.0 mg, 0.13 mmol, 1.3 equiv), flame-dried, and allowed to cool under air. Diethylamine (12.4 μL) and oxetane sulfonyl fluoride **56** (41.9 mg, 0.10 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and acetonitrile (0.33 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (80% Et_2O/pentane) afforded oxetane amine **76** as a colorless gum (20.1 mg, 80%). R_f = 0.18 (80% Et_2O/pentane); IR (film)/cm^{-1} 3291 (br OH), 2967, 2874, 2837, 1599, 1513, 1461, 1420, 1375, 1271, 1219, 1126, 1074, 1033, 984, 921, 883, 787, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.2 Hz, 1 H, HOC_qAr-C*H*), 6.80 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1 H, Ar-CH), 6.77 (br s, 1 H, Ar-C_qAr-CHAr-C_q), 5.70 (br s, 1 H, OH), 4.92 (d, *J* = 5.9 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 5.9 Hz, 2 H, CH*H*OCH*H*), 3.90 (s, 3 H, OCH_3), 2.40 (q, *J* = 7.2 Hz, 4 H, 2 × NCH_2), 1.06 (t, *J* = 7.2 Hz, 6 H, 2 × $NCH_2C\mathit{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (Ar-C_qOMe), 144.7 (Ar-C_qOH), 132.7 (Ar-C_qC_q), 120.1 (Ar-CH), 113.7 (Ar-C_qOHAr-*C*H), 109.7 (Ar-C_qOMeAr-*C*H), 81.5 (CH_2OCH_2), 67.4 (C_q), 56.0 (OCH_3), 43.6 (2 × NCH_2), 15.4 (2 × CH_2CH_3); HRMS (APCI) *m/z* calcd for $C_{14}H_{20}NO_3^-$ $[M–H]^-$: 250.1449, found: 266.1446.

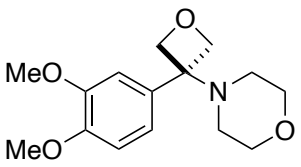
Notes:

***76** was also obtained in 87% yield (21.8 mg) using 3 equivalents of diethylamine.*

*A 95:5 mixture of oxetane sulfonyl fluoride **56** and oxetane fluoride **56'** was used.*

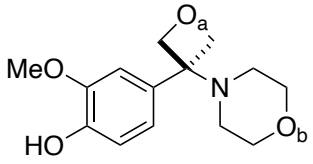
Additional Morpholine Aminooxetanes (**77**–**81**)

4-(3-(3,4-Dimethoxyphenyl)oxetan-3-yl)morpholine (77)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **53** (55 mg) and morpholine (21 μL). Purification by flash column chromatography (70% EtOAc/pentane) afforded oxetane amine **77** as a white solid (39 mg, 70%). R_f = 0.21 (70% EtOAc in pentane); mp = 135–137 °C; IR (film)/cm^{-1} 2948, 2832, 1587, 1513, 1453, 1252, 1170, 1114, 1025, 939, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 8.2 Hz, 1 H, Ar-CH), 6.63 (dd, *J* = 8.2, 2.1 Hz, 1 H, Ar-CH), 6.55 (d, *J* = 2.1 Hz, 1 H, Ar-CH), 4.89 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.89 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.73 (t, *J* = 4.6 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.35 (br t, *J* = 4.6 Hz, 4 H, $N(CH_2)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5 (Ar-C_qOMe), 148.3 (Ar-C_qOMe), 130.1 (Ar-C_qC_q), 119.7 (Ar-CH), 110.5 (Ar-CH), 110.4 (Ar-CH), 79.0 (CH_2OCH_2), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.7 (C_q), 56.0 (OCH_3), 55.9 (OCH_3), 46.4 (CH_2NCH_2); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_4$ [M+H]: 280.1549, found: 280.1553.

2-Methoxy-4-(3-morpholinooxetan-3-yl)phenol (78)

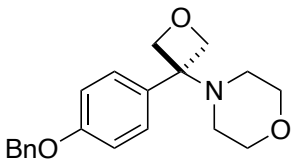


Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **56** (83.7 mg) and morpholine (20.8 μL). Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded oxetane amine **78** as a white solid (44.0 mg, 83%). R_f = 0.14 (5% MeOH/CH_2Cl_2); mp = 135 °C; IR (film)/cm^{-1} 3306 (br OH), 2952, 2878, 1599, 1517, 1454, 1375, 1275, 1215, 1115, 1066, 1029, 988, 939, 854, 816, 731, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.1 Hz, 1 H, HOC_qAr-C*H*), 6.58 (dd, ^3J = 8.1 Hz, ^4J = 1.9 Hz, 1 H, Ar-CH), 6.54 (br s, 1 H, Ar-C_qAr-CHAr-C_q), 5.72 (br s, 1 H, OH), 4.91–4.87 (br m, 4 H, $CH_2O_aCH_2$),3.90 (s, 3 H, OCH_3), 3.75 (br t, *J* = 4.6 Hz, 4 H, $CH_2O_bCH_2$), 2.36 (br s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (Ar-C_qOMe), 145.0 (Ar-C_qOH), 129.5 (Ar-C_qC_q), 120.4 (Ar-CH), 113.8 (Ar-C_qOHAr-*C*H), 109.8 (Ar-C_qOMeAr-*C*H), 79.1 ($CH_2O_aCH_2$), 67.1 ($CH_2O_bCH_2$), 66.8 (C_q), 56.0 (OCH_3), 46.4 (CH_2NCH_2); HRMS (APCI) *m/z* calcd for $C_{14}H_{20}NO_4^+$ $[M+H]^+$: 266.1387, found: 266.1389.

Notes:

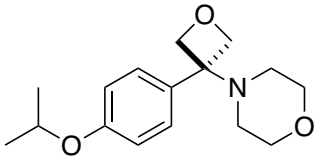
*A 95:5 mixture of oxetane sulfonyl fluoride **56** and oxetane fluoride **56'** was used.*

4-(3-(4-(Benzyloxy)phenyl)oxetan-3-yl)morpholine (79)



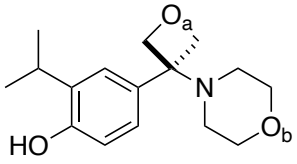
Anhydrous K_2CO_3 (674 mg, 4.9 mmol, 1.3 equiv), morpholine (0.39 mL, 4.5 mmol, 1.2 equiv) and sulfonyl fluoride **57** (1.21 g, 3.8 mmol, 1.0 equiv) were added sequentially to a flame-dried reaction tube under Ar. The reaction vessel was sealed and anhydrous acetonitrile (12.5 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool to 25 °C and water (50 mL) was added. The layers were separated, and the aqueous portion extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (80% EtOAc/hexane) afforded oxetane amine **79** as a white solid (905 mg, 74%). R_f = 0.41 (80% EtOAc/hexane); mp = 154–156 ºC, IR (film)/cm^{-1} 2938, 2863, 1509, 1236, 1177, 1121, 1112, 1009, 986, 924, 914, 810, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.33 (m, 5 H, 5 × Ph-CH), 7.01–6.96 (m, 4 H, 4 × Ar-CH), 5.09 (s, 2 H, $PhCH_2$), 4.90 (d, *J* = 6.0 Hz, C*H*HOC*H*H), 4.87 (d, *J* = 6.0 Hz, CH*H*OCH*H*), 3.74 (t, *J* = 4.5 Hz, 4 H, $CH_2CH_2OCH_2CH_2$), 2.32 (t, *J* = 4.5 Hz, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (Ar-C_qOBn), 136.8 (Ph-$C_q$$CH_2$), 129.6 (Ar-$C_q$$C_q$), 128.6 (2 × Ph-CH), 128.4 (2 × Ar-CH), 128.0 (Ph-CH), 127.4 (2 × Ar-CH), 114.2 (2 × Ar-CH), 79.3 (CH_2OCH_2), 70.1 ($PhCH_2$), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.4 (C_q), 46.3 (CH_2NCH_2); HRMS (ESI) *m/z* calcd for $C_{20}H_{24}NO_3$ [M+H]: 326.1756, found: 326.1750.

4-(3-(4-Isopropoxyphenyl)oxetan-3-yl)morpholine (80)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **58** (55 mg) and morpholine (21 μL). Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetane amine **80** as a white solid (43 mg, 78%). R_f = 0.20 (50% EtOAc in pentane); mp = 102–104 °C; IR (film)/cm^{-1} 2972, 2854, 2821, 1607, 1509, 1291, 1243, 1183, 1113, 954, 939, 934; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97–6.93 (m, 2 H, 2 × Ar-CH), 6.90–6.87 (m, 2 H, 2 × Ar-CH), 4.90 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.86 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 4.56 (hept, *J* = 6.1 Hz, 1 H, CH), 3.75–3.73 (m, 4 H, $CH_2CH_2OCH_2CH_2$), 2.33–2.32 (br m, 4 H, $N(CH_2)_2$), 1.36 (d, *J* = 6.1 Hz, 6 H, $(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (Ar-C_qOMe), 129.0 (Ar-$C_q$$C_q$), 128.4 (2 × Ar-CH), 115.0 (2 × Ar-CH), 79.3 (CH_2OCH_2), 69.9 ($CH(CH_3)_2$), 67.1 ($CH_2CH_2OCH_2CH_2$), 66.3 (C_q), 46.3 (CH_2NCH_2), 22.0 (2 × CH_3); HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_3$ [M+H]: 278.1756, found: 278.1746.

2-Isopropyl-4-(3-morpholinooxetan-3-yl)phenol (81)



Prepared according to **General Procedure A** under air with a Celite workup and using oxetane sulfonyl fluoride **59** (86.1 mg) and morpholine (20.8 μL). Purification by flash column chromatography (80–100% Et_2O/pentane) afforded oxetane amine **81** as a white solid (52.5 mg, 95%). R_f = 0.14 (80% Et_2O/pentane); mp = 172-175 °C; IR (film)/cm^{-1} 3299 (br OH), 3027, 2960, 2870, 2740, 1610, 1506, 1454, 1424, 1342, 1267, 1193, 1111, 1066, 980, 939, 910, 857, 813, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1 H, Ar-CH), 6.70 (app. d, *J* = 1.3 Hz, 2 H, 2 × Ar-CH), 5.89 (br s, 1 H, OH), 4.93 (d, *J* = 6.0 Hz, 2 H, C*H*HO_aC*H*H), 4.89 (d, *J* = 6.0 Hz, 2 H, CH*H*O_aCH*H*), 3.76 (br t, *J* = 4.6 Hz, 4 H, $CH_2O_bCH_2$), 3.24 (hept, *J* = 6.9 Hz, 1 H, Ar-C_qCH), 2.30 (br t, *J* = 4.6 Hz, 4 H, CH_2NCH_2), 1.24 (d, *J* = 6.9 Hz, 6 H, 2 × Ar-C_qCHC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4 (Ar-C_qOH), 134.1 (Ar-C_q), 128.7 (Ar-C_q), 125.5 (Ar-CH), 125.3 (Ar-CH), 114.5 (Ar-CH), 79.6 ($CH_2O_aCH_2$), 67.1 ($CH_2O_bCH_2$), 66.5 (C_q), 46.2 (CH_2NCH_2), 26.9 (Ar-C_q*C*H), 22.5 (2 × Ar-C_qCH*C*H$_3$); HRMS (APCI) *m/z* calcd for $C_{16}H_{24}NO_3^+$ $[M+H]^+$: 278.1751, found: 278.1753.

Late-Stage Functionalization of Complex Nucleophiles (**82**–**90**)

For late-stage functionalization reactions, the nucleophiles was used as limiting reagent and the oxetane sulfonyl fluoride in slight excess (1.2 equiv). See General Procedure C.

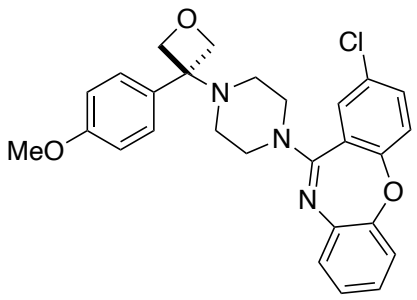
General Procedure C:

Anhydrous K_2CO_3 (18.0 mg, 0.13 mmol, 1.3 equiv), nucleophile (0.1 mmol, 1.0 equiv) and oxetane sulfonyl fluoride (0.12 mmol, 1.2 equiv) were added sequentially to a flame-dried reaction tube under air or N_2. The reaction vessel was sealed and acetonitrile (0.33 mL, 0.3 M) was added by syringe. The reaction mixture was stirred at 60 ºC for 2 h, left to cool down to 25 °C and EtOAc (5 mL) was added. The resulting mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL), then the solvent was removed *in vacuo* using a rotatory evaporator. Purification by flash column chromatography afforded the desired oxetane amine.

Further remarks:

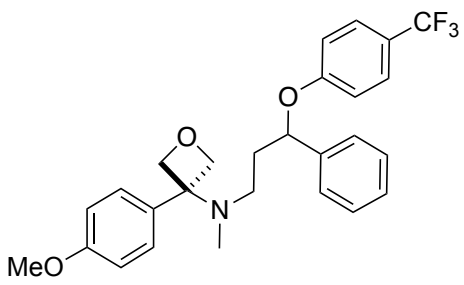
When an ammonium salt was used instead of the free amine, 2.6 equiv K_2CO_3 (36.0 mg, 0.26 mmol) were added.

2-Chloro-11-(4-(3-(4-methoxyphenyl)oxetan-3-yl)piperazin-1-yl)dibenzo[b,f][1,4]oxazepine (82)



Prepared according to **General Procedure C** under N_2 using oxetane sulfonyl fluoride **1** (29.6 mg) and amoxapine (31.4 mg). Purification by flash chromatography (25% acetone/pentane) afforded oxetane amine **82** as a colorless paste (27.8 mg, 58%). R_f = 0.50 (25% acetone/pentane); IR (film)/cm^{-1} 2940, 2836, 1587, 1558, 1513, 1468, 1244, 1177, 1103, 1028, 909, 827, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.6, 2.6 Hz, 1 H, $Ar_{(amoxapine)}$-CH), 7.18–6.93 (m, 10 H, 4 × Ar-CH + 6 × $Ar_{(amoxapine)}$-CH), 4.94 (d, *J* = 6.0 Hz, 2 H, C*H*HOC*H*H), 4.92 (d, *J* = 6.0 Hz, 2 H, CH*H*OCH*H*), 3.85 (s, 3 H, OCH_3), 3.58 (br s, 4 H, CH_2NCH_2), 2.40 (br s, 4 H, CH_2NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C_q=N), 158.8 (Ar-C_qO), 158.6 (Ar-C_qO), 151.7 (Ar-C_qO), 140.1 ($Ar_{(amoxapine)}$-C_q), 132.4 ($Ar_{(amoxapine)}$-CH), 130.1 ($Ar_{(amoxapine)}$-C_q), 129.2 ($Ar_{(PMP)}$-C_qC_q), 128.9 ($Ar_{(amoxapine)}$-CH), 128.4 (2 × $Ar_{(PMP)}$-CH), 127.0 ($Ar_{(amoxapine)}$-CH), 125.7 ($Ar_{(amoxapine)}$-CH), 124.8 ($Ar_{(amoxapine)}$-C_qCl), 124.4 ($Ar_{(amoxapine)}$-CH), 122.6 ($Ar_{(amoxapine)}$-CH), 120.0 ($Ar_{(amoxapine)}$-CH), 113.4 (2 × $Ar_{(PMP)}$-CH), 79.7 (CH_2OCH_2), 66.3 (C_q), 55.3 (OCH_3), 47.4 (br, CH_2NCH_2), 46.0 (CH_2NCH_2); HRMS (ESI) *m/z* calcd for $C_{27}H_{27}N_3O_3{}^{35}Cl^+$ $[M+H]^+$: 476.1741, found: 476.1747.

3-(4-Methoxyphenyl)-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)oxetan-3-amine (83)



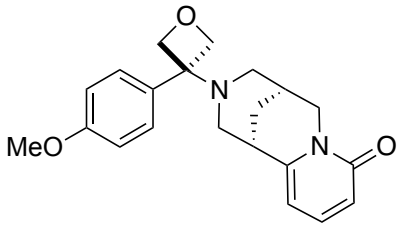
Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **1** (29.6 mg) and fluoxetine (31.0 mg). Purification by flash column chromatography (10% acetone/pentane) afforded oxetane amine **83** as a colorless gum (29.7 mg, 63%). R_f = 0.30 (15% acetone/pentane); IR (film)/cm^{-1} 3306 (br OH), 2952, 2878, 1599, 1517, 1454, 1375, 1275, 1215, 1115, 1066, 1029, 988, 939, 854, 816, 731, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.6 Hz, 2 H, 2 × Ar$_{(CF_3)}$-CH), 7.38–7.33 (m, 4 H, 4 × Ar$_{(Ph)}$-CH), 7.30–7.25 (m, 1 H, Ar$_{(Ph)}$-CH), 7.02 (d, J = 8.7 Hz, 2 H, 2 × Ar$_{(PMP)}$-CH), 6.94 (d, J = 8.6 Hz, 2 H, 2 × Ar$_{(CF_3)}$-CH), 6.89 (d, J = 8.7 Hz, 2 H, 2 × Ar$_{(PMP)}$-CH), 5.43 (dd, J = 8.4, 4.1 Hz, 1 H, CH), 4.85–4.83 (m, 3 H, C*H*$_2$OC*H*H), 4.72 (br d, J = 5.8 Hz, 1 H, CH$_2$OCH*H*), 3.82 (s, 3 H, OCH_3), 2.53–2.46 (m, 1 H, NC*H*HCHH), 2.19–2.11 (m, 2 H, NCH*H*C*H*H), 2.09 (s, 3 H, NCH_3), 2.03–1.92 (m, 1 H, NCHHCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (Ar-*C*$_q$OCH), 158.6 (Ar-C$_q$OMe), 141.1 (Ar-*C*$_q$CH), 129.4 (Ar-*C*$_q$C$_q$), 128.8 (2 × Ar$_{(PMP)}$-CH), 128.5 (2 × Ar$_{(Ph)}$-CH), 127.8 (Ar-CH), 126.8 (q, $^3J_{CF}$ = 3.9 Hz, 2 × Ar$_{(CF_3)}$-CH), 125.9 (2 × Ar$_{(Ph)}$-CH), 124.3 (q, J_{CF} = 271.1 Hz, CF_3), 122.8 (q, J_{CF} = 32.8 Hz, Ar-*C*$_q$CF$_3$), 115.8 (2 × Ar$_{(CF_3)}$-CH), 113.2 (2 × Ar$_{(PMP)}$-CH), 80.4 (*C*H$_2$OCH$_2$), 80.1 (CH$_2$O*C*H$_2$), 77.6 (CH), 67.0 (C$_q$N), 55.2 (OCH_3), 46.8 (N*C*H$_2$), 36.6 (NCH$_2$*C*H$_2$), 34.7 (NCH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –61.5; HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_3F_3$ [M+H]: 472.2100, found: 472.2098.

Notes:

The free-amine form of fluoxetine was acquired by pre-washing a solution of the commercially-available hydrochloride salt (100 mg in 20 mL CH_2Cl_2) with 1 M aq. NaOH (3 × 15 mL), drying over Na_2SO_4, filtering and concentrating in vacuo using a rotatory evaporator. Hydrochloride salts can normally be used in the reaction but lead to a lower yield due to formation of an oxetane chloride as a side product.

Only the two central peaks of the quartet ^{13}C signals at 124.3 and 122.8 ppm were observed due to the low intensity of these quaternary signals. The two outer peaks of the quartet at 126.8 ppm are seen as shoulders of the central peaks.

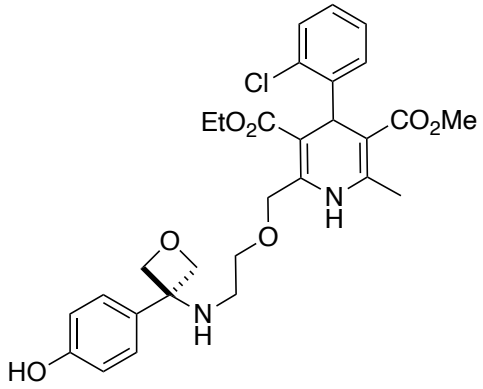
(1*R*,5*S*)-3-(3-(4-Methoxyphenyl)oxetan-3-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (84)



Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **1** (29.7 mg) and cytisine (19.2 mg). Purification by flash column chromatography (0–4% MeOH/EtOAc) afforded oxetane amine **84** as a colorless gum (27.1 mg, 77%) which solidified to a pale-yellow solid. $[a]_D^{21}$ –110.0 (c 1, $CDCl_3$); R_f = 0.19 (2% MeOH/EtOAc); mp = 175–180 °C; IR (film)/cm^{-1} 2941, 2870, 2810, 1651 (C=O st), 1610, 1547, 1469, 1357, 1297, 1249, 1178, 1144, 1115, 1059, 1029, 988, 947, 917, 831, 798, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 9.0, 6.8 Hz, 1 H, C*H*CHC$_q$=O), 6.96–6.92 (m, 2 H, 2 × Ar-CH), 6.90–6.85 (m, 2 H, 2 × Ar-CH), 6.50 (dd, ^3J = 9.0 Hz, ^4J = 1.4 Hz, 1 H, CHC$_q$=O), 5.97 (dd, ^3J = 6.8 Hz, ^4J = 1.4 Hz, 1 H, C*H*CHCHC$_q$=O), 4.76 (d, J = 5.9 Hz, 1 H, C*H*HOCH$_2$), 4.70 (d, J = 5.9 Hz, 1 H, CH*H*OCH$_2$), 4.68 (d, J = 5.8 Hz, 1 H, CH$_2$OC*H*H), 4.44 (d, J = 5.8 Hz, 1 H, CH$_2$OCH*H*), 4.07 (d, J = 15.3 Hz, 1 H, C*H*HNC$_q$=O), 3.95 (dd, ^2J = 15.3 Hz, ^3J = 6.6 Hz, 1 H, CH*H*NC$_q$=O), 3.81 (s, 3 H, OCH_3), 2.92 (br s, 1 H, CHC$_q$N), 2.82 (br d, J = 10.9 Hz, 1 H, NC*H*HCHCH$_2$NC$_q$=O), 2.71 (br d, J = 10.5 Hz, 1 H, NC*H*HCHC$_q$), 2.42 (br s, 1 H, C*H*CH$_2$NC$_q$=O), 2.08–2.02 (m, 2 H, CH*H*NCH*H*), 1.83 (br d, J = 12.8 Hz, 1 H, C$_{(bridge)}$*H*H), 1.60 (br d, J = 12.8 Hz, 1 H, C$_{(bridge)}$H*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (C$_q$=O), 158.7 (Ar-C$_q$OMe), 151.2 (*C*$_q$NC$_q$=O), 138.6 (*C*HCHC$_q$=O), 129.3 (Ar-*C*$_q$C$_q$), 128.1

(2 × Ar-CH), 116.8 (*C*HC_q=O), 113.2 (2 × Ar-CH), 104.5 (*C*HCHCHC_q=O), 79.7 (*C*H_2OCH_2), 79.4 (CH_2OCH_2), 65.5 (Ar-C_qC_q), 55.2 (OCH_3), 53.7 (N*C*H_2CHC_q), 52.9 (N*C*$H_2CHCH_2NC_q$=O), 49.8 (*C*H_2NC_q=O), 35.1 (*C*HC_qN), 27.6 (*C*HCH_2NC_q=O), 25.6 ($C_{(bridge)}H_2$); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O_3$ [M+H]: 353.1865, found: 353.1877.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-((3-(4-hydroxyphenyl)oxetan-3-yl)amino)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (85)



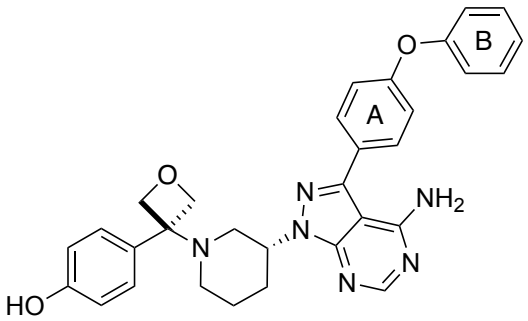
Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **55** (46.6 mg) and amlodipine besylate (56.7 mg). Purification by flash column chromatography (80% EtOAc/pentane) afforded oxetane amine **85** as a colorless gum (55.9 mg, quant.). R_f = 0.30 (80% EtOAc/pentane); IR (film)/cm^{-1} 3317 (br OH), 2948, 2870, 1681 (C=O st), 1610, 1517, 1476, 1431, 1368, 1279, 1208, 1096, 1033, 980, 910, 835, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1 H, CHAr-C_qAr-CH), 7.31 (br s, 1 H, C_qNHC_q), 7.24 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1 H, ClAr-C_qAr-CH), 7.22–7.18 (m, 2 H, 2 × $Ar_{(phenol)}$-CH), 7.14 (ddd, ^3J = 7.8, 7.5 Hz, ^4J = 1.3 Hz, 1 H, CHAr-C_qAr-CHAr-C*H*), 7.05 (ddd, ^3J = 7.9, 7.5 Hz, ^4J = 1.7 Hz, 1 H, ClAr-C_qAr-CHAr-C*H*), 6.84–6.80 (m, 2 H, 2 × $Ar_{(phenol)}$-CH), 5.41 (s, 1 H, CH), 4.99 (dd, ^2J = 6.5 Hz, *J* = 1.6 Hz, 2 H, C*H*HOC*H*H), 4.76 (d, *J* = 16.3 Hz, 1 H, OC*H*HC_qNHC_q), 4.75 (d, *J* = 6.5 Hz, 2 H, CH*H*OCH*H*), 4.65 (d, *J* = 16.3 Hz, 1 H, OCH*H*C_qNHC_q), 4.05 (qd, ^3J = 7.1 Hz, *J* = 2.6 Hz, 2 H, OC*H*$_2CH_3$), 3.63 (s, 3 H, OCH_3), 3.59 (br t, *J* = 5.2 Hz, 2 H, OC*H*$_2CH_2$), 2.70 (t, *J* = 5.2 Hz, 2 H, OCH_2CH_2), 2.33 (s, 3 H, C_qCH_3), 1.18 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (*C*O_2Me), 167.2 (*C*O_2Et), 155.4 (Ar-C_qOH), 145.6 (Ar-*C*$_q$CH), 145.4 ($OCH_2C_qNHC_q$), 144.1 (*C*$_qCH_3$), 133.4 (Ar-*C*$_qC_q$), 132.3 (Ar-C_qCl), 131.5 (CHAr-C_qAr-*C*H), 129.3 (ClAr-C_qAr-*C*H), 127.5 (2 × $Ar_{(phenol)}$-CH), 127.4 (ClAr-C_qAr-CHAr-*C*H), 126.8 (CHAr-C_qAr-CHAr-*C*H), 115.6 (2 × $Ar_{(phenol)}$-CH), 103.9 (*C*$_qCO_2$Me), 101.5 (*C*$_qCO_2$Et), 82.3 (CH_2OCH_2), 71.2 (O*C*H_2CH_2), 67.8 (O*C*$H_2C_qNHC_q$), 63.1 (Ar-C_q*C*$_q$), 59.9 (O*C*H_2CH_3), 50.9 (O*C*H_3), 42.8 (OCH_2CH_2), 37.2 (Ar-C_q*C*H), 19.5 (C_q*C*H_3), 14.2 (OCH_2CH_3); HRMS (APCI) *m/z* calcd for $C_{29}H_{34}{}^{35}ClN_2O_7^+$ $[M+H]^+$: 557.2049, found: 557.2047.

Notes:

The doublets at 4.76 (1 H) and 4.75 (2 H) ppm were integrated together to 3 H.

The OH and NH signals (+ H_2O) are probably a very broad peak between 2.79 and 1.46 ppm.

(*R*)-4-(3-(3-(4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)oxetan-3-yl)phenol (86)



Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **55** (46.6 mg) and ibrutinib N-1 (38.6 mg). Purification by flash column chromatography (0–10% MeOH/EtOAc) afforded oxetane amine **86** as a white solid (18.9 mg, 35%). $[\alpha]_D^{21}$ +30.0 (c 1, MeOH); R_f = 0.18 (100% EtOAc); mp = 152–156 °C; IR (film)/cm^{-1} 3481, 3321 (br OH and NH_2), 3191, 2945, 2878, 2818, 1618, 1521, 1487, 1372, 1312, 1238, 1200, 1141, 1107, 1051, 984, 947, 872, 805, 757, 727, 693; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (br s, 1 H, NAr-CHN), 7.60–7.58 (m, 2 H, 2 × $Ar_{(A)}$-CH), 7.39–7.35 (m, 2 H, 2 × $Ar_{(B)}$-CH), 7.16 (tt, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1 H, $Ar_{(B)}$-CH), 7.13–7.10 (m, 2 H, 2 × $Ar_{(A)}$-CH), 7.07–7.04 (m, 2 H, 2 × $Ar_{(B)}$-CH), 6.91 (br d, J = 8.5 Hz, 2 H, 2 × $Ar_{(phenol)}$-CH), 6.79 (br d, J = 8.5 Hz, 2 H, 2 × $Ar_{(phenol)}$-CH), 5.80 (br s, 3 H, OH and NH_2), 5.06 (dddd, $^3J_{ax,ax}$ = 10.5, 10.5 Hz, $^3J_{ax,eq}$ = 4.2, 4.2 Hz, 1 H, CH), 4.94 (d, J = 5.9 Hz, 1 H, C*H*HOCHH), 4.90 (d, J = 5.9 Hz, 1 H, CHHOC*H*H), 4.88 (d, J = 5.9 Hz,1 H, CHHOCH*H*), 4.83 (d, J = 5.9 Hz, 1 H, CH*H*OCHH), 3.02 (dd, ^2J = 10.5 Hz, $^3J_{eq,ax}$ = 4.2 Hz, 1 H, NC*H*$_{eq}$HCH), 2.80–2.73 (m, 1 H, NC*H*HCH$_2$), 2.31 (dd, ^2J = 10.5 Hz, $^3J_{ax,ax}$ = 10.5 Hz, 1 H, NCH*H*$_{ax}$CH), 2.06–1.98 (m, 2 H, NCH$_2$C*H*$_2$), 1.87–1.81 (m, 3 H, NCH*H*CH$_2$C*H*$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5 ($Ar_{(A)}$-*C*$_q$OAr$_{(B)}$-C$_q$), 157.6 (br and weak, $Ar_{(het)}$-C), 156.3 ($Ar_{(A)}$-C$_q$OAr$_{(B)}$-*C*$_q$), 155.4 (Ar-C$_q$OH), 154.9 (br and weak, $Ar_{(het)}$-C), 153.7 ($Ar_{(het)}$-C), 143.8 (Ar-*C*$_q$Ar$_{(A)}$-C$_q$), 129.9 (2 × $Ar_{(A)}$-CH and 2 × $Ar_{(B)}$-CH), 128.9 ($Ar_{(phenol)}$-*C*$_q$C$_q$), 128.5 (2 × $Ar_{(phenol)}$-CH), 127.6 (Ar-C$_q$Ar$_{(A)}$-*C*$_q$), 124.0 ($Ar_{(B)}$-CH), 119.5 (2 × $Ar_{(B)}$-CH), 119.1 (2 × $Ar_{(A)}$-CH), 114.9 (2 × $Ar_{(phenol)}$-CH), 98.6 (very weak, H$_2$NAr-C$_q$Ar-*C*$_q$), 80.4 (*C*H$_2$OCH$_2$), 80.1 (CH$_2$O*C*H$_2$), 66.3 (C$_q$), 54.5 (CH), 51.1 (N*C*H$_2$CH), 45.9 (N*C*H$_2$CH$_2$), 29.6 (CH*C*H$_2$CH$_2$), 24.6 (NCH$_2$*C*H$_2$); HRMS (ESI) *m/z* calcd for $C_{31}H_{31}N_6O_3$ [M+H]: 535.2458, found: 535.2451.

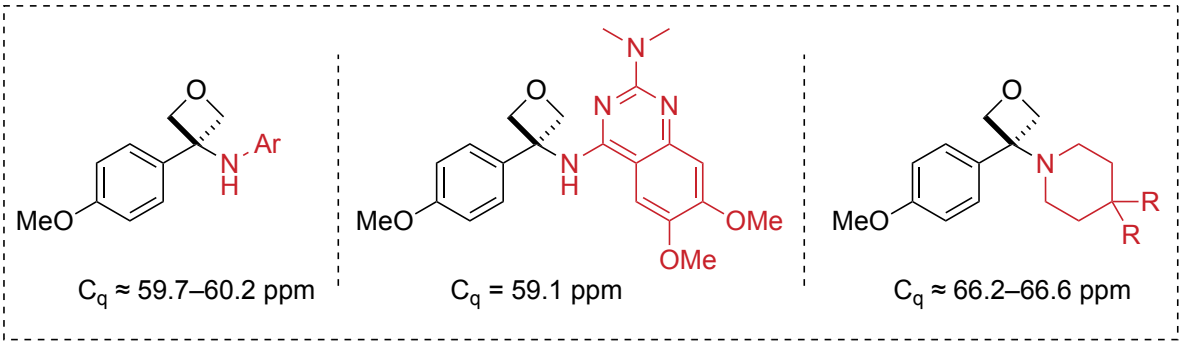
Notes

Due to chemical exchange, the OH and NH_2 signals appear as one very broad peak with a lower integration (~2.5 H).

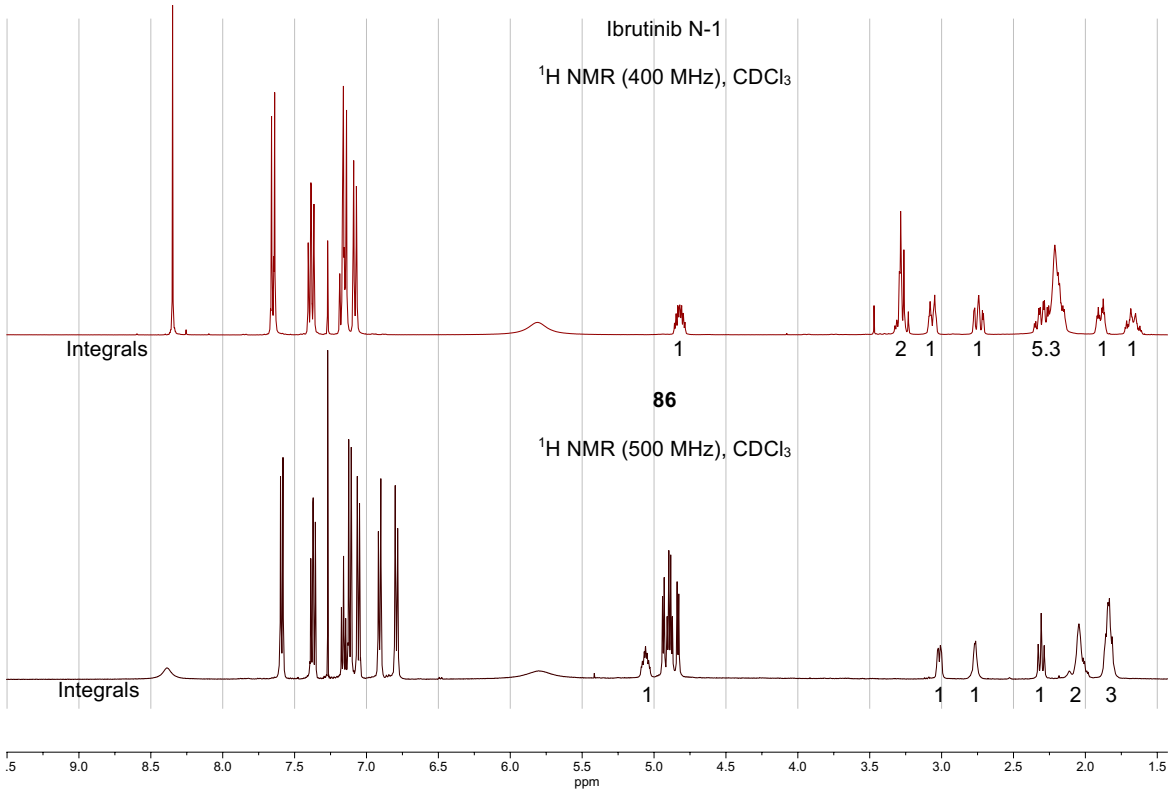
The ^{13}C NMR signal at 98.6 ppm is very weak due to chemical exchange, presumably caused by tautomerism of the pyrazolopyrimidine. A stronger signal could not be obtained even at a very high NMR sample concentration and number of scans (12'288). The identity of this signal is supported by the presence of a signal at 98.4 ppm in the measured spectrum of ibrutinib N-1 (see spectra).

*The reaction of ibrutinib N-1 with OSF **55** through the piperidine (as per the suggested structure of **86**) and not through the heteroaromatic amine is proposed based on the observed analytical data:*

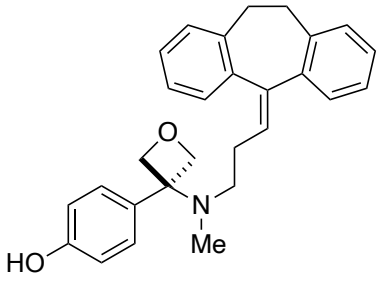
- *The chemical shift of the oxetane C$_q$ (66.3 ppm) is in line with the observed chemical shift of other oxetane-piperidines and is significantly different from the chemical shift of (hetero)aromatic aminooxetanes.*



- *The piperidine region of the ^{1}H NMR spectrum of **86** is very different from that of ibrutinib N-1 (see stacked spectra below), suggesting that this part of the molecule has undergone significant change, ergo reacted with the oxetane.*



4-(3-((3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)(methyl)amino)oxetan-3-yl)phenol (87)



Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **55** (46.7 mg) and nortriptyline (26.4 mg). Purification by flash column chromatography (35–45% EtOAc/pentane) afforded oxetane amine **87** as a colorless gum (29.6 mg, 72%). R_f = 0.33 (45% EtOAc/pentane); IR (film)/cm^{-1} 3273 (br OH), 3060, 3019, 2945, 2878, 2796, 2248, 1730, 1610, 1513, 1484, 1443, 1364, 1234, 1174, 1115, 1059, 1036, 977, 910, 835, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.28 (m, 1 H, Ar-CH), 7.22–7.20 (m, 2 H, 2 × Ar-CH), 7.18–7.11 (m, 4 H, 4 × Ar-CH), 6.91 (d, *J* = 8.6 Hz, 2 × Ar$_{(phenol)}$-CH), 6.91 (d, *J* = 8.6 Hz, 2 × Ar$_{(phenol)}$-CH), 5.87 (t, *J* = 7.3 Hz, 1 H, HC=C), 4.87 (br s, 4 H, CH_2OCH_2), 3.42–3.30 (m, 2 H, Ar-C$_q$C*H*HCHHAr-C$_q$ and Ar-C$_q$CHHC*H*HAr-C$_q$), 3.01–2.91 (m, 1 H, Ar-C$_q$CH*H*CHHAr-C$_q$), 2.79 (br s, 1 H, Ar-C$_q$CHHCH*H*Ar-C$_q$), 2.30 (td, *J* = 7.3, 7.3 Hz, 2 H, NCH_2CH_2), 2.14 (t, *J* = 7.3 Hz, 2 H, NCH_2CH_2), 1.93 (s, 3 H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (Ar-C$_q$-OH), 143.9 (HC=C$_q$), 141.1 (Ar-C$_q$), 140.0 (Ar-C$_q$), 139.3 (Ar-C$_q$), 137.0 (Ar-C$_q$), 130.0 (Ar-CH), 128.8 (HC=C$_q$), 128.6 (2 × Ar$_{(phenol)}$-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 126.0 (Ar-CH), 125.7 (Ar-CH), 114.7 (2 × Ar$_{(phenol)}$-CH), 80.7 (CH_2OCH_2), 66.7 (Ar-C$_q$C$_q$), 50.8 (NCH_2), 34.8 (NCH_3), 33.7 (Ar-C$_q$$CH_2$), 32.0 (Ar-C$_q$$CH_2$), 27.8 ($NCH_2CH_2$); HRMS (ESI) *m/z* calcd for $C_{28}H_{30}NO_2$ [M+H]: 412.2277, found: 412.2274.

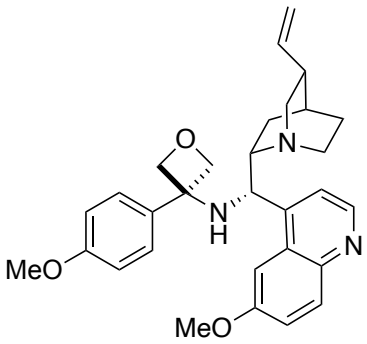
Notes:

The free-amine form of nortriptyline was acquired by pre-washing a solution of the commercially available hydrochloride salt (100 mg in 20 mL CH_2Cl_2) with 1 M aq. NaOH (3 × 15 mL), drying over Na_2SO_4, filtering and concentrating in vacuo using a rotatory evaporator.

Hydrochloride salts can normally be used in the reaction but lead to a lower yield due to formation of an oxetane chloride as a side product.

*The Ar-**C**$_q$C$_q$ signal is under the signals at 128.8 & 128.6 ppm and is probably the observed shoulder at 128.7 ppm. This was confirmed by an HMBC correlation spectrum.*

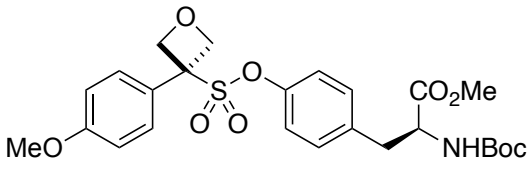
3-(4-Methoxyphenyl)-*N*-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)oxetan-3-amine (88)



Anhydrous K_2CO_3 (128.0 mg, 0.93 mmol, 3.0 equiv), (*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methanamine (100.0 mg, 0.31 mmol, 1.0 equiv) and oxetane sulfonyl fluoride **1** (91.4 mg, 0.37 mmol, 1.2 equiv) were added sequentially to a flame-dried reaction tube under air. The reaction vessel was sealed, acetonitrile (3.09 mL, 0.1 M) was added by syringe and the reaction mixture was stirred at 60 ºC for 16 h. The reaction mixture was left to cool to 25 °C and then filtered through a plug of Celite, eluting with further MeCN (5 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by preparative HPLC (20–50% Et_2O/CH_2Cl_2) afforded oxetane amine **88** as an oil (18.0 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.5 Hz, 1 H, Ar-CH), 8.76 (br s, 1 H, Ar-CH), 8.10 (d, *J* = 9.2 Hz, 1 H, Ar-CH), 7.78 (br s, 1 H, Ar-CH), 7.73 (d, *J* = 4.5 Hz, 1 H, Ar-CH), 7.47 (dd, *J* = 9.2, 2.5 Hz, 1 H, Ar-CH), 7.33 (br s, 1 H, Ar-CH), 7.01 (br d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 5.85 (ddd, $^3J_{trans}$ = 17.1 Hz, $^3J_{cis}$ = 10.4 Hz, ^3J = 7.2 Hz, 1 H, H_2C=C*H*), 5.29 (d, $^3J_{trans}$ = 17.1 Hz, 1 H, *H*HC=CH), 5.19 (d, $^3J_{cis}$ = 10.4 Hz, 1 H, H*H*C=CH), 4.67 (d, *J* = 10.4 Hz, 1 H, NHCH), 4.61 (br s, 2 H, C*H*HOC*H*H), 4.30–4.24 (m, 2 H, CH*H*OCH*H*), 3.99 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.60 (d, *J* = 12.4 Hz, 1 H, NCH), 3.37–3.34 (m, 3 H, 3 × NCH), 2.86 (br s, 1 H, NCH), 1.97–1.88 (m, 3 H, 3 × CH), 1.68 (br s, 1 H, CH), 1.35 (t, *J* = 7.3 Hz, 1 H, CH), 0.91–0.80 (m, 1 H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (Ar-C_q), 159.4 (Ar-C_qOMe), 158.6 (Ar-C_qOMe), 148.3 (Ar-CH), 144.9 (Ar-C_q), 141.0 (H*C*=CH_2), 136.9 (Ar-C_q), 132.5 (2 × Ar-CH), 132.1 (Ar-CH), 127.9 (Ar-CH), 127.5 (br, Ar-C_q), 121.4 (Ar-CH), 119.6 (Ar-CH), 118.1 (Ar-CH), 114.8 (HC=*C*H_2), 100.8 (Ar-CH), 70.1 (*C*H_2OCH_2), 65.3 (CH_2O*C*H_2), 63.8 (C_q), 62.5 (NCH), 60.0 (NCH), 55.7 (OCH_3), 55.3 (OCH_3), 51.7 (NCH), 50.3 (NCH), 38.0 (*C*HCH=CH_2), 26.0 (CH), 25.7 (CH_2), 25.1 (CH_2); HRMS (QToF) *m/z* calcd for $C_{30}H_{36}N_3O_3^+$ $[M+H]^+$: 486.2751, found: 486.2757.

Preparative HPLC: Column: Princeton Methane Sulfonamide 250 mm × 10 mm × 5 μm. Isocratic A: 70% CO_2, B: 30% ethanol + 0.2% ammonia (7 N in methanol). Flow rate: 15 mL/min.

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(((3-(4-methoxyphenyl)oxetan-3-yl)sulfonyl)oxy)phenyl) propanoate (89)



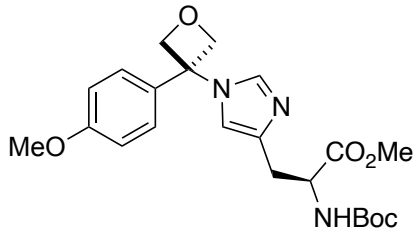
A reaction tube was charged with oven-dried Cs_2CO_3 (84.7 mg, 0.26 mmol, 1.3 equiv), followed by methyl (*tert*-butoxycarbonyl)-*L*-tyrosinate (Boc-Tyr-OMe; 70.9 mg, 0.24 mmol, 1.2 equiv) and oxetane sulfonyl fluoride **1** (49.2 mg, 0.2 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (25% acetone/pentane) afforded oxetane sulfonate ester **89** as a white solid (81.3 mg, 80%). $[a]_D^{21}$ +30.0 (c 1, $CDCl_3$); R_f = 0.42 (30% acetone/pentane); mp = 114 °C; IR (film)/cm^{-1} 3376 (br NH), 2971, 2889, 2839, 1742 (C=O st), 1710 (C=O st), 1609, 1581, 1510, 1441, 1389, 1358 (SO_2 st as), 1301, 1252, 1201, 1165 (SO_2 st sy), 1146, 1105, 1055, 1022, 998, 932, 867, 837, 785, 732, 688, 643, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2 H, 2 × $Ar_{(PMP)}$-CH), 7.11–7.09 (m, 2 H, 2 × $Ar_{(Tyr)}$-CH), 7.03–6.96 (m, 4 H, 2 × $Ar_{(PMP)}$-CH + 2 × $Ar_{(Tyr)}$-CH), 5.50 (d, *J* = 7.4 Hz,

2 H, C*H*HOC*H*H), 5.22 (d, *J* = 7.4 Hz, 2 H, CH*H*OCH*H*), 4.99 (d, *J* = 8.2 Hz, 1 H, NH), 4.56 (br dd, *J* = 6.2 , 5.8 Hz, 1 H, CH), 3.86 (s, 3 H, Ar-C_qOCH_3), 3.70 (s, 3 H, CO_2CH_3), 3.11 (dd, *J* = 13.9, 5.8 Hz, 1 H, Ar-C_qC*H*H), 3.01 (dd, *J* = 13.9, 6.2 Hz, 1 H, Ar-C_qCH*H*), 1.42 (s, 9 H, 3 × C_qCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (CO_2Me), 160.3 (Ar-C_qOMe), 155.0 (NHCO_2*t*-Bu), 148.0 (Ar-*C*$_q$OSO_2C$_q$), 135.2 (Ar-*C*$_q$CH_2), 130.6 (2 × Ar$_{(Tyr)}$-CH), 129.8 (2 × Ar$_{(PMP)}$-CH), 125.4 (Ar-*C*$_q$C$_q$), 121.8 (2 × Ar$_{(Tyr)}$-CH), 114.2 (2 × Ar$_{(PMP)}$-CH), 80.1 (*C*$_q$(CH_3)$_3$), 77.3 (CH_2OCH_2), 67.8 (Ar-C_q*C*$_q$), 55.4 (Ar-C_qO*C*H_3), 54.2 (CH), 52.3 (CO_2*C*H_3), 37.7 (Ar-C_q*C*H_2), 28.2 (3 × C_q*C*H_3); HRMS (ESI) *m/z* calcd for $C_{25}H_{31}NO_9NaS$ [M+Na]: 544.1617, found: 544.1596.

Notes:

*The structure of **89** was confirmed by X-ray crystallography (see Fig. S45–46).*

Methyl *N*^{a}-(*tert*-butoxycarbonyl)-*N*^{t}-(3-(4-methoxyphenyl)oxetan-3-yl)-*L*-histidinate (90)



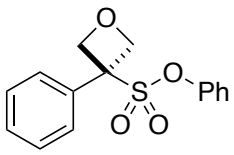
Prepared according to **General Procedure C** under air using oxetane sulfonyl fluoride **1** (29.7 mg) and methyl (*tert*-butoxycarbonyl)-*L*-histidinate (Boc-His-OMe; 26.9 mg). Purification by flash column chromatography (50–80% EtOAc/pentane) afforded oxetane imidazole **90** as a colorless gum (15.1 mg, 35%). $[\alpha]_D^{21}$ +14.0 (c 1, $CDCl_3$); R_f = 0.10 (80% EtOAc/pentane); IR (film)/cm^{-1} 3357 (br NH), 2969, 2837, 1743 (C=O st), 1708 (C=O st), 1611, 1580, 1513, 1490, 1458, 1437, 1388, 1364, 1299, 1251, 1166, 1093, 1053, 1026, 990, 925, 832, 757, 732, 648, 575, 552; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (br s, 1 H, Ar$_{(imidazole)}$-CH), 7.08–7.04 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 6.96–6.93 (m, 2 H, 2 × Ar$_{(PMP)}$-CH), 6.90 (br s, 1 H, Ar$_{(imidazole)}$-CH), 5.91 (d, *J* = 8.3 Hz, 1 H, NH), 5.22 (dd, *J* = 6.8, 1.9 Hz, 2 H, C*H*HOC*H*H), 5.17 (dd, *J* = 10.5, 6.8 Hz, 2 H, CH*H*OCH*H*), 4.60–4.56 (m, 1 H, CH), 3.84 (s, 3 H, Ar-C_qOCH_3), 3.70 (s, 3 H, CO_2CH_3), 3.17–3.04 (m, 2 H, Ar-C_qCH_2), 1.43 (s, 9 H, 3 × C_qCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (CO_2Me), 159.9 (Ar-C_qOMe), 155.6 (NHCO_2*t*-Bu), 137.8 (Ar-*C*$_q$CH_2), 135.6 (Ar$_{(imidazole)}$-CH), 131.1 (Ar-*C*$_q$C$_q$), 127.0 (2 × Ar$_{(PMP)}$-CH), 115.4 (Ar$_{(imidazole)}$-CH), 114.5 (2 × Ar$_{(PMP)}$-CH), 83.2 (CH_2OCH_2), 79.7 (*C*$_q$(CH_3)$_3$), 63.5 (Ar-C_q*C*$_q$), 55.4 (Ar-C_qO*C*H_3), 53.4 (CH), 52.3 (CO_2*C*H_3), 30.1 (Ar-C_q*C*H_2), 28.3 (3 × C_q*C*H_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{30}N_3O_6$ [M+H]: 432.2135, found: 432.2120.

Notes:

***90** was assigned as the oxetane imidazole and not as the oxetane sulfonate imidazole based on the absence of the SO_2 stretches in the IR spectrum and the absence of sulfur-containing fragments in the mass spectrum. The regiochemistry of the imidazole ring was assigned based on the assumption that the sterically less hindered site would react faster.*

Phenyl Oxetane Sulfonate Ester (**93**)

Phenyl 3-phenyloxetane-3-sulfonate (93)



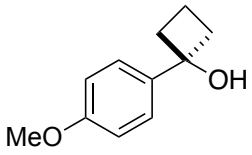
A reaction tube was charged with oven-dried Cs_2CO_3 (49.6 mg, 0.152 mmol, 1.3 equiv), followed by phenol (13.3 mg, 0.141 mmol, 1.2 equiv) and oxetane sulfonyl fluoride **92** (25.2 mg, 0.117 mmol, 1.0 equiv) were added sequentially. The reaction vessel was sealed and anhydrous acetonitrile (0.39 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography (15% Et_2O/pentane) afforded oxetane sulfonate ester **93** as colorless crystals (33.3 mg, 98%). R_f = 0.17 (15% Et_2O/pentane); mp = 96 °C, IR (film)/cm^{-1} 3059, 2954, 2885, 1584, 1484, 1454, 1352 (SO_2 st as), 1285, 1197, 1167, 1141 (SO_2 st sy), 1107, 1087, 1023, 996, 934, 910, 861, 772, 720, 680, 666, 603, 545, 481; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.45 (m, 3 H, 3 × Ph-CH), 7.38–7.32 (m, 4 H, 4 × Ph-CH), 7.29–7.25 (m, 1 H, Ph-CH), 7.07–7.03 (m, 2 H, 2 × Ph-CH), 5.56 (d, *J* = 7.7 Hz, 2 H, C*H*HOC*H*H), 5.29 (d, *J* = 7.7 Hz, 2 H, CH*H*OCH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (Ph-C_qOSO$_2$C$_q$), 133.8 (Ph-C_qC$_q$), 129.8 (2 × Ph-CH), 129.4 (Ph-CH), 128.8 (2 × Ph-CH), 128.5 (2 × Ph-CH), 127.1 (Ph-CH), 121.7 (2 × Ph-CH), 77.3 (CH_2OCH_2), 68.2 (C_q).

Notes:

***93** did not ionize very well and a tractable mass ion was not found. Further evidence for the structure of **93** was provided by X-ray crystallography (see Fig. S47–48).*

Towards the Synthesis of a Cyclobutane Sulfonyl Fluoride

1-(4-Methoxyphenyl)cyclobutan-1-ol (S23)[4]

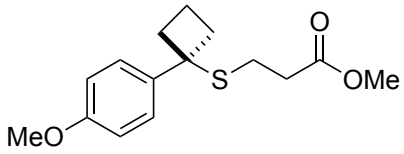


n-BuLi (2.3 M in hexanes, 5.22 mL, 12 mmol, 1.2 equiv) was added dropwise over 5 min to a solution of *p*-bromoanisole (1.6 mL, 13 mmol, 1.3 equiv) in THF (50 mL, 0.2 M) at –78 °C. The reaction mixture was stirred at –78 °C for a further 20 min and cyclobutanone (0.75 mL, 10 mmol, 1.0 equiv) was added dropwise to the reaction mixture. Following a further 5 min at –78 °C, the reaction mixture was warmed to 25 °C then quenched with water (50 mL). The layers were separated and the aqueous portion extracted with diethylether (3 × 50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (35% Et_2O/pentane) afforded cyclobutanol **S23** as a white solid (1.49 g, 84%). R_f = 0.20 (35% Et_2O/pentane); mp = 66–68 °C; IR (film)/cm^{-1} 3397 (br. OH), 2938, 2836, 1611, 1563, 1512, 1464, 1442, 1426, 1299, 1243, 1177, 1132, 1108, 1068, 1029, 962, 957, 908, 828, 792, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 3.82 (s, 3 H, OCH_3), 2.58–2.51 (m, 2 H, C_qCH_2), 2.40–2.32 (m, 2 H, C_qCH_2), 2.13 (br s, 1 H, OH), 2.03–1.93 (m, 1 H, CH_2CHHCH_2), 1.70–1.59 (m, 1 H, CH_2CHHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (2 × Ar-C_qOMe), 138.4 (Ar-C_qC_q), 126.3 (2 × Ar-CH), 113.7 (2 × Ar-CH), 76.6 (C_q), 55.2 (OCH_3), 36.8 (2 × C_qCH_2), 12.8 ($C_qCH_2CH_2$). The observed characterization data (IR, ^{1}H) were consistent with that previously reported.[59]

Notes:

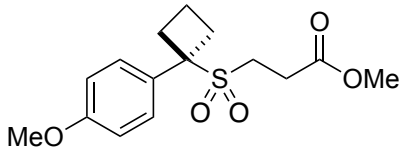
*The same batch of cyclobutanol **S23** reported in ref. 4 was used for the synthesis of cyclobutane sulfide **S24**.*

Methyl 3-((1-(4-methoxyphenyl)cyclobutyl)thio)propanoate (S24)



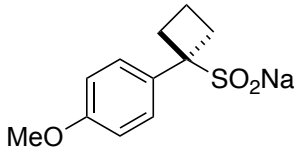
Lithium bis(trifluoromethanesulfonimide) (158 mg, 0.55 mmol, 11 mol%) and tetrabutylammonium hexafluorophosphate (107 mg, 0.275 mmol, 5.5 mol%) were added to a solution of cyclobutanol **S23** (891 mg, 5.0 mmol, 1.0 equiv) and methyl 3-mercaptopropionate (1.11 mL, 10.0 mmol, 2.0 equiv) in chloroform (10 mL, 0.5 M). The reaction mixture was stirred at 40 °C for 25 min then quenched with sat. aq. $NaHCO_3$ (40 mL). Dichloromethane (40 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (10% Et_2O/pentane) afforded cyclobutane sulfide **S24** as a white solid (321 mg, 23%). R_f = 0.15 (10% Et_2O/pentane); mp = 69–71 °C; IR (film)/cm^{-1} 2985, 2956, 1736 (C=O st), 1509, 1249, 1236, 1211, 1176, 1153, 1038, 833, 813; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.16 (m, 2 H, 2 × Ar-CH), 6.88–6.84 (m, 2 H, 2 × Ar-CH), 3.81 (s, 3 H, Ar-OCH_3), 3.64 (s, 3 H, CO_2CH_3), 2.67–2.59 (m, 2 H, C_qCH_2), 2.49 (t, J = 7.4 Hz, 2 H, SCH_2), 2.43–2.34 (m, 3 H, C_qCH_2 + CH_2CHHCH_2), 2.30 (t, J = 7.4 Hz, 2 H, CH_2CO_2Me), 1.92–1.83 (m, 1 H, CH_2CHHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C_q=O), 157.9 (Ar-C_qOMe), 139.3 (Ar-C_qC_q), 127.0 (2 × Ar-CH), 113.5 (2 × Ar-CH), 83.2 (CH_2OCH_2), 55.3 (Ar-OCH_3), 52.9 (C_q), 51.6 (CO_2CH_3), 35.2 (2 × CH_2), 34.1 (CH_2CO_2Me), 24.9 (SCH_2), 16.6 ($CH_2CH_2CH_2$); HRMS (APCI) *m/z* calcd for $C_{15}H_{19}SO_3^-$ [M–H]$^-$: 279.1055, found: 279.1056.

Methyl 3-((1-(4-methoxyphenyl)cyclobutyl)sulfonyl)propanoate (S25)



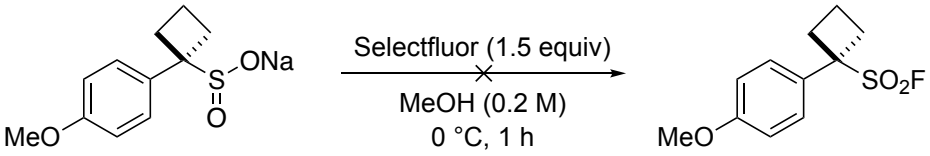
*m*CPBA (518 mg, 3.0 mmol, 3.0 equiv) was added to a solution of cyclobutane **S24** (280 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL, 0.02 M). The reaction mixture was stirred at 25 ºC for 3 h then aq. KOH (3 m, 40 mL) was added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL), the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotatory evaporator. Purification by flash column chromatography (50% EtOAc/hexane) afforded sulfone **S25** as a white solid (301 mg, 96%). R_f = 0.15 (10% Et_2O/pentane); mp = 67–71 °C; IR (film)/cm^{-1} 2946, 1735 (C=O st), 1516, 1287, 1250, 1131, 1093, 1018, 840, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.35 (m, 2 H, 2 × Ar-CH), 6.94–6.92 (m, 2 H, 2 × Ar-CH), 3.83 (s, 3 H, Ar-OCH_3), 3.67 (s, 3 H, CO_2CH_3), 3.18–3.10 (m, 2 H, C_qCH_2), 2.90 (t, *J* = 7.6 Hz, 2 H, SCH_2), 2.68–2.59 (m, 4 H, C_qCH_2 + CH_2CO_2Me), 2.33–2.22 (m, 1 H, CH_2CHHCH_2), 2.05–1.96 (m, 1 H, CH_2CHHCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C_q=O), 159.7 (Ar-C_qOMe), 129.6 (2 × Ar-CH), 129.0 (Ar-C_qC_q), 114.0 (2 × Ar-CH), 67.8 (C_q), 55.3 (Ar-OCH_3), 52.2 (CO_2CH_3), 41.7 (SO_2CH_2), 29.3 (2 × CH_2), 25.7 (CH_2CO_2Me), 15.8 ($CH_2CH_2CH_2$); HRMS (APCI) *m/z* calcd for $C_{15}H_{21}SO_5^+$ $[M+H]^+$: 313.1110, found: 313.1107.

Sodium 1-(4-methoxyphenyl)cyclobutane-1-sulfinate (S26)



Sulfone **S25** (250 mg, 0.8 mmol, 1.0 equiv) was added to a solution of NaH (60% in mineral oil, 34 mg, 0.84 mmol, 1.05 equiv) in THF (5 mL, 0.16 M). The reaction mixture was stirred at 25 ºC for 1 h then quenched with anhydrous methanol (5 mL) and concentrated *in vacuo* to afford sulfinate salt **S26** (176 mg, 89%). R_f = 0.13 (20% MeOH/CH_2Cl_2); mp = 214–216 °C; IR (film)/cm^{-1} 3271, 2954, 1610,1510, 1458, 1442, 1299, 1249, 980, 953, 829; ^{1}H NMR (400 MHz, D_2O) δ 7.08–7.04 (m, 2 H, 2 × Ar-CH), 6.93–6.89 (m, 2 H, 2 × Ar-CH), 3.74 (s, 3 H, OCH_3), 2.56–2.48 (m, 2 H, C_qCH_2), 2.28–2.21 (m, 2 H, C_qCH_2), 1.92–1.74 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, D_2O) δ 157.5 (Ar-C_qOMe), 133.9 (Ar-C_qC_q), 128.9 (2 × Ar-CH), 113.5 (2 × Ar-CH), 67.7 (C_q), 55.3 (OCH_3), 27.0 (2 × CH_2), 15.1 ($CH_2CH_2CH_2$); HRMS (NSI) *m/z* calcd for $C_{11}H_{14}SO_3Na^+$ $[M+H]^+$: 249.0556, found: 249.0558.

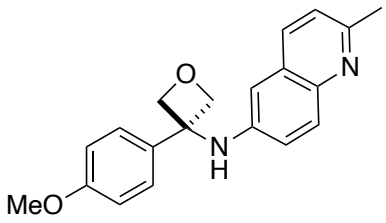
The PMP-cyclobutane sulfonyl fluoride could not be synthesized, presumably, and in line with our calculations (see page S59), due to its instability at room temperature (Scheme S11).



S26

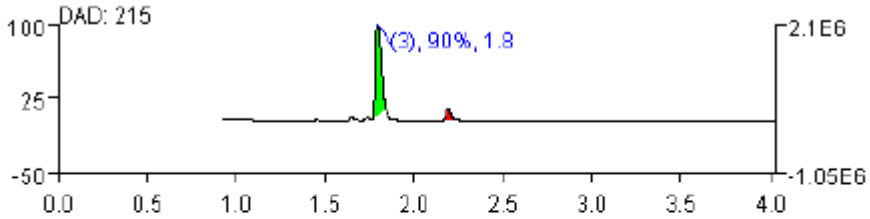
Scheme S11 Unsuccessful synthesis of PMP cyclobutane sulfonyl fluoride.

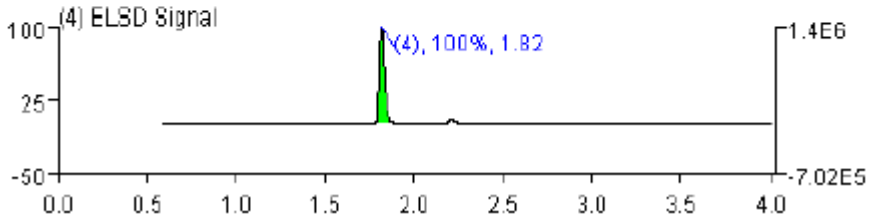
Oxetane Amine Data from Library Synthesis

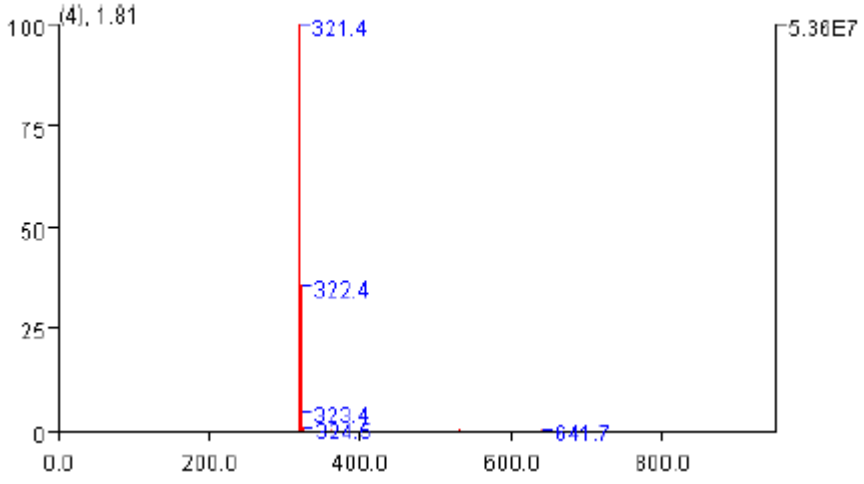


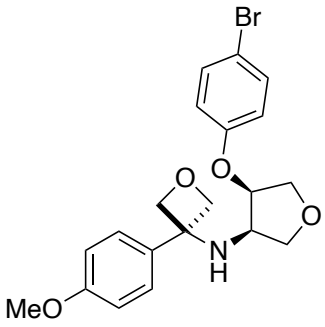
A1

17.4 mg product obtained. LC-MS data – Ret. time 1.8: MS ES+ *m/z* 321 ($[M+H]^+$).



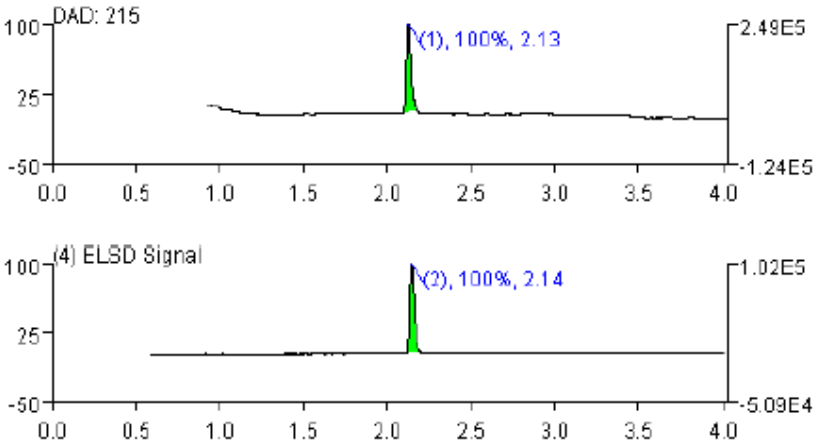


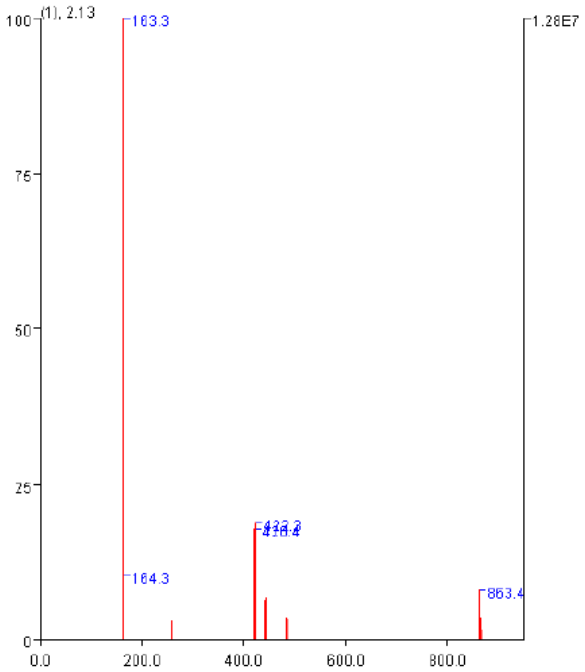


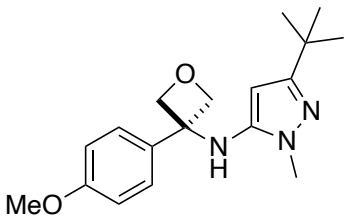


A2

11.3 mg product obtained. LC-MS data – Ret. time 2.1: MS ES+ *m/z* 420 ([M+H]$^+$).

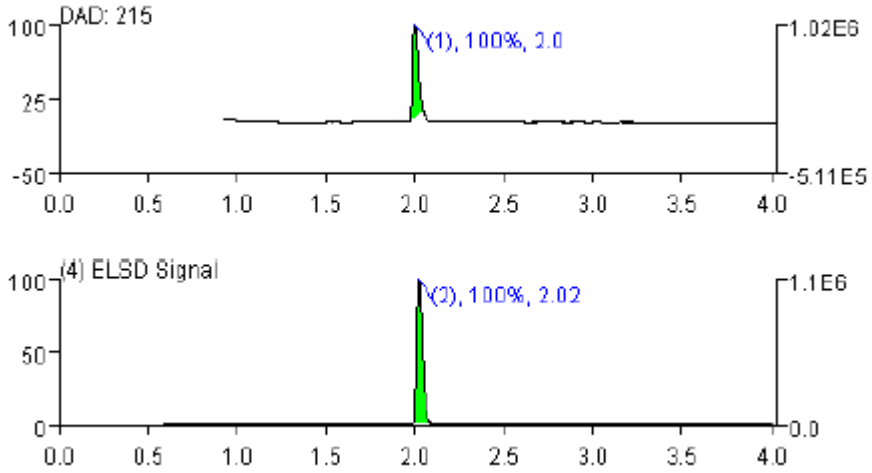


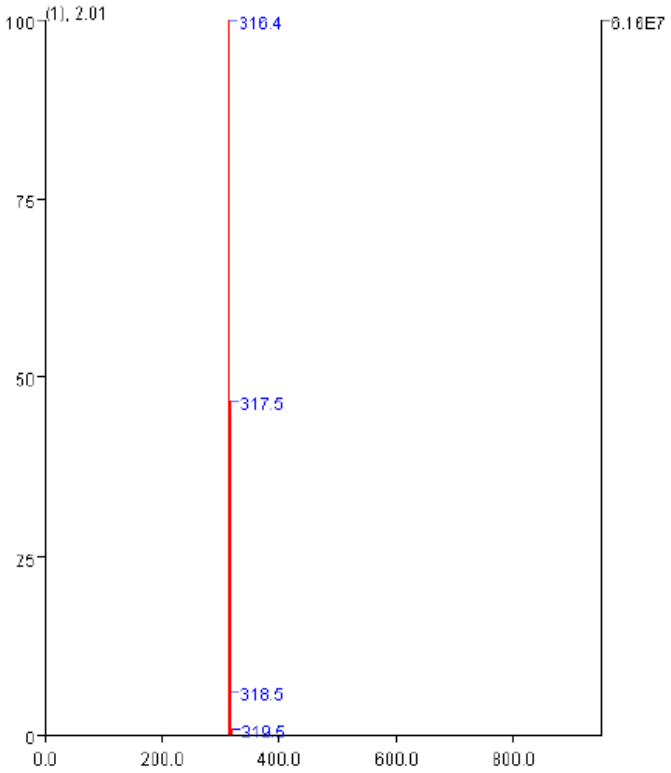


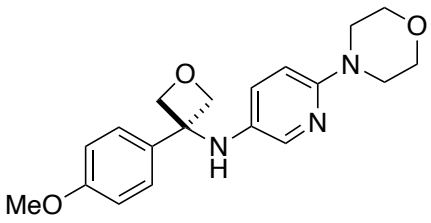


A4

3.5 mg product obtained. LC-MS data – Ret. time 2.0: MS ES+ *m/z* 316 ([M+H]$^+$).

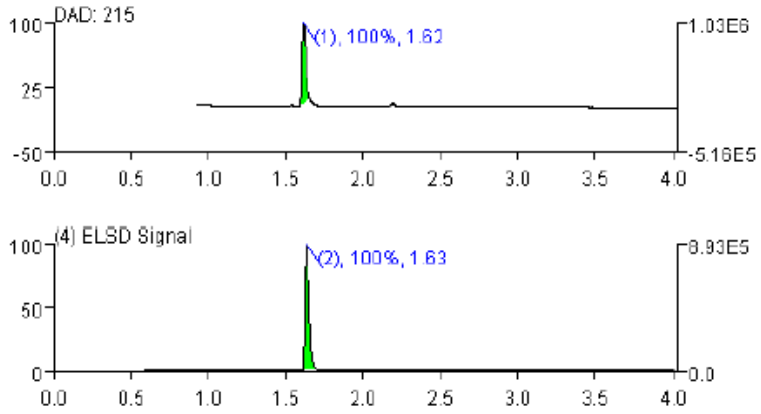


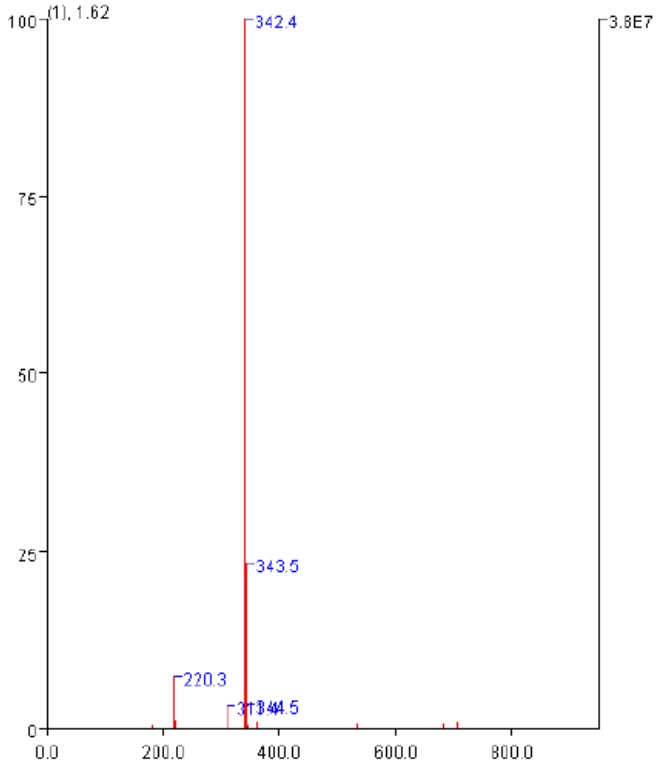


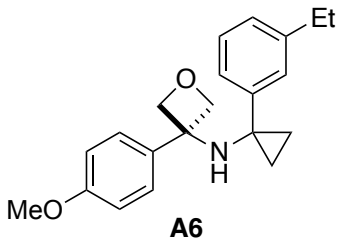


A5

8.9 mg product obtained. LC-MS data – Ret. time 1.6: MS ES+ *m/z* 342 ($[M+H]^+$).

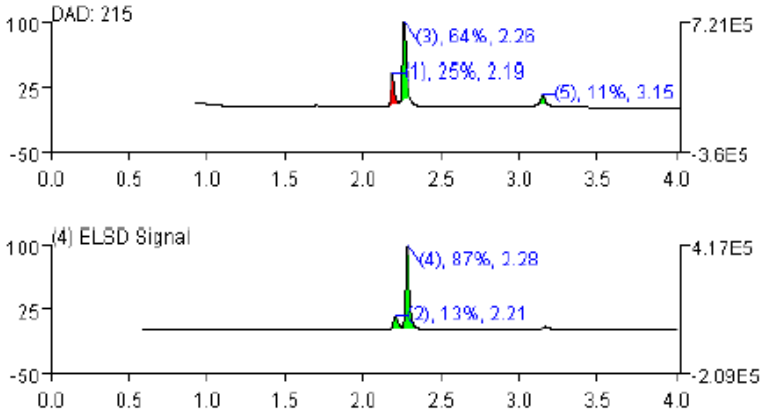


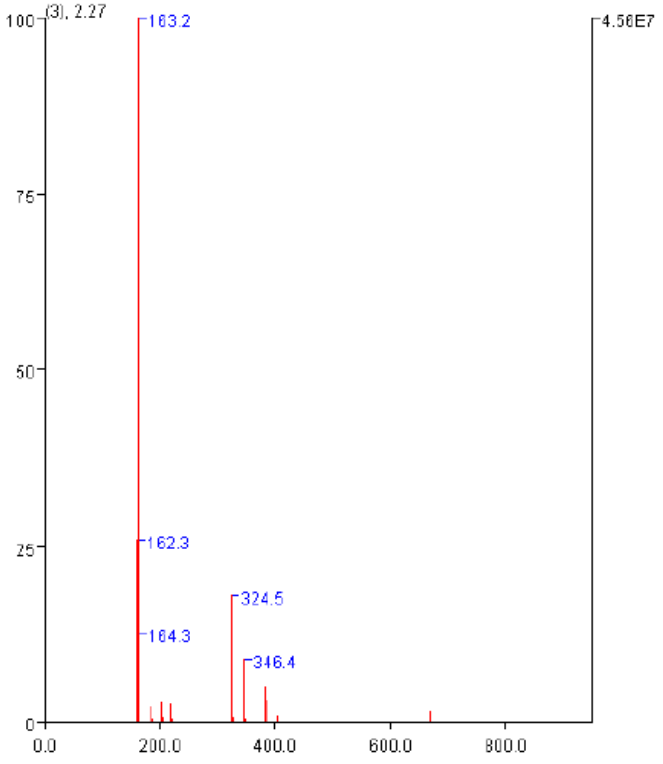


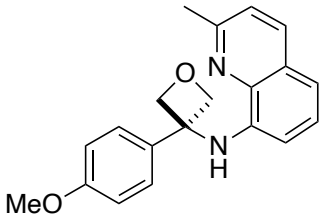


A6

4.7 mg product obtained. LC-MS data – Ret. time 2.2: MS ES+ *m/z* 324 ([M+H]$^+$).

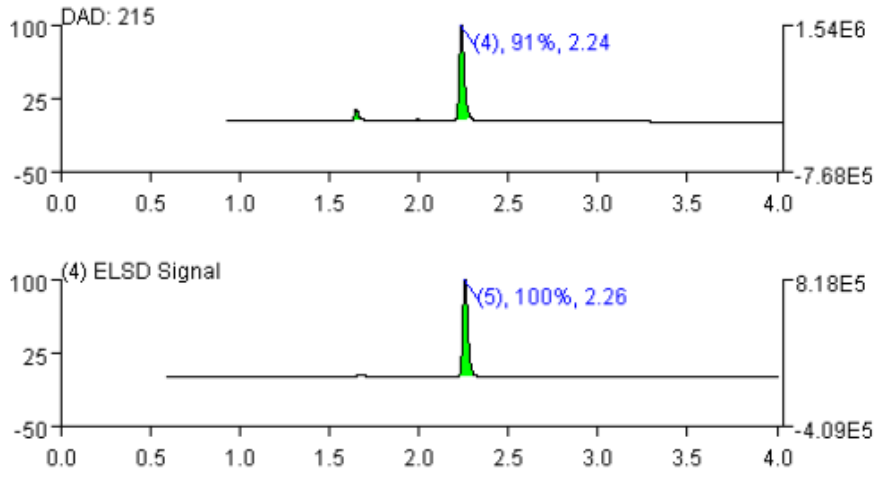


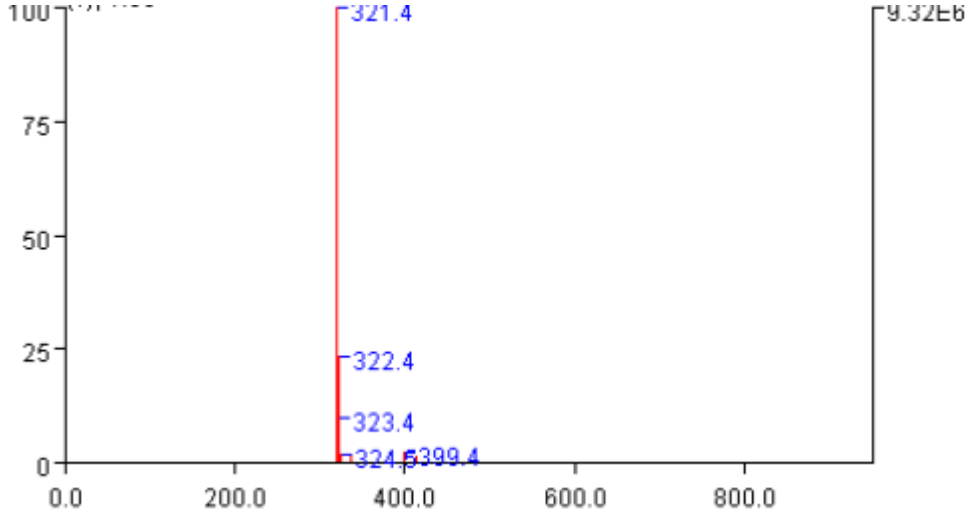


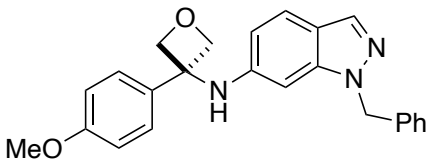


A7

9.7 mg product obtained. LC-MS data – Ret. time 2.2: MS ES+ *m/z* 321 ($[M+H]^+$).

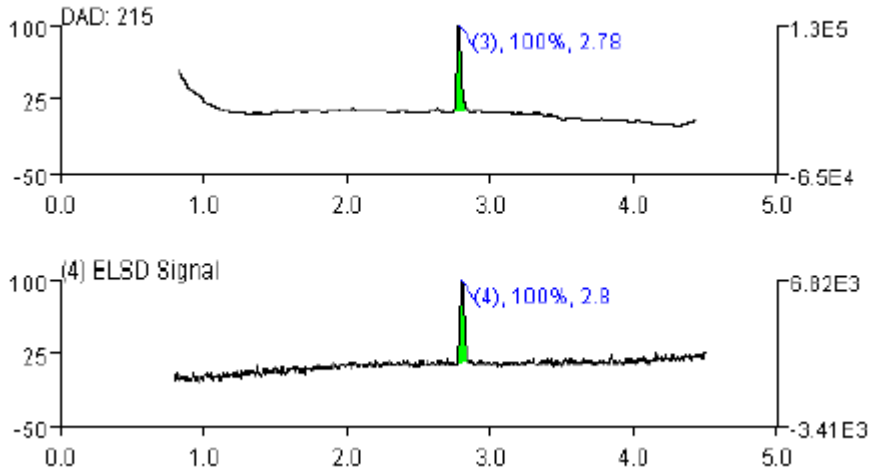


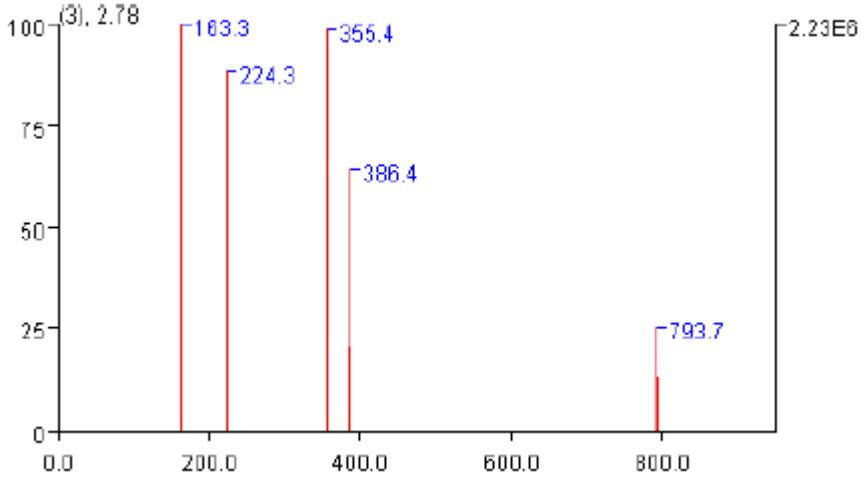


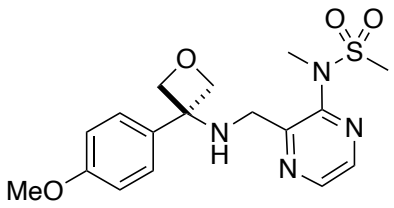


A8

19.4 mg product obtained. LC-MS data – Ret. time 2.8: MS ES+ *m/z* 386 ([M+H]$^+$).

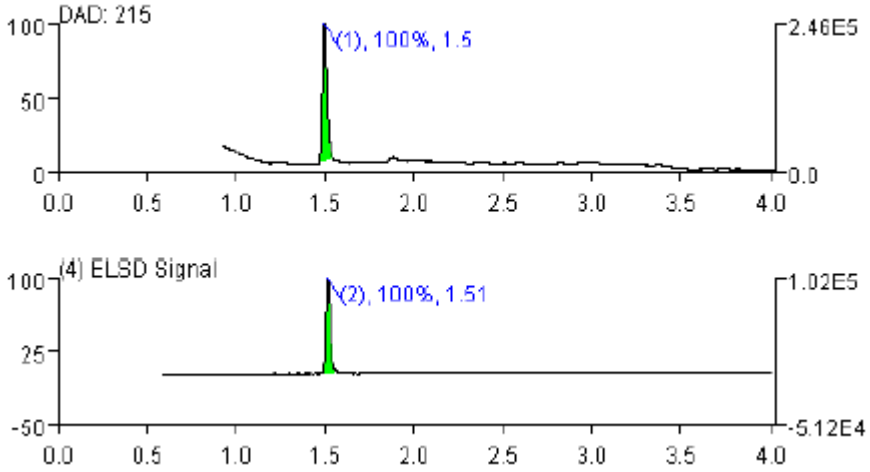


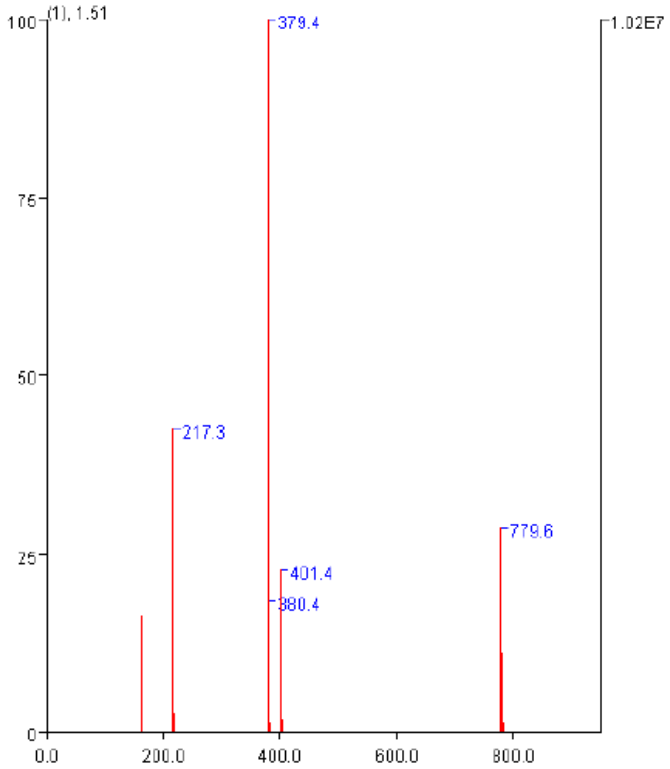


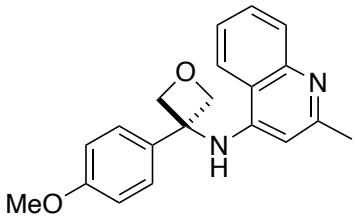


A9

10.7 mg product obtained. LC-MS data – Ret. time 1.5: MS ES+ *m/z* 379 ([M+H]$^+$).

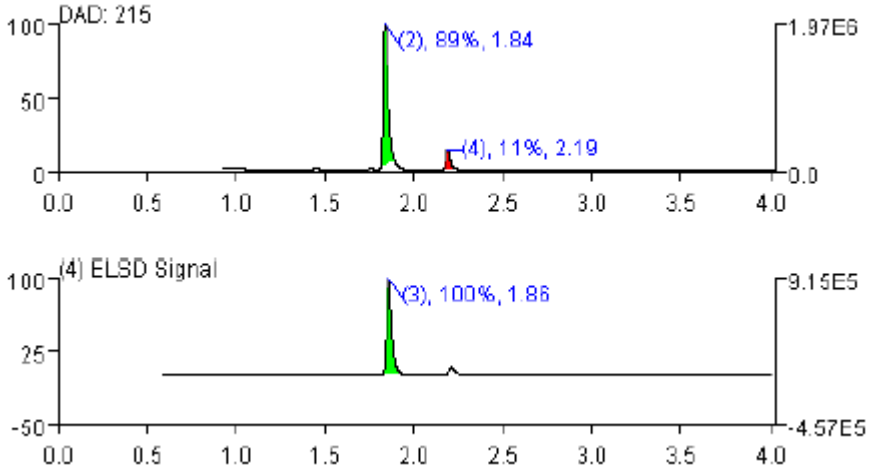


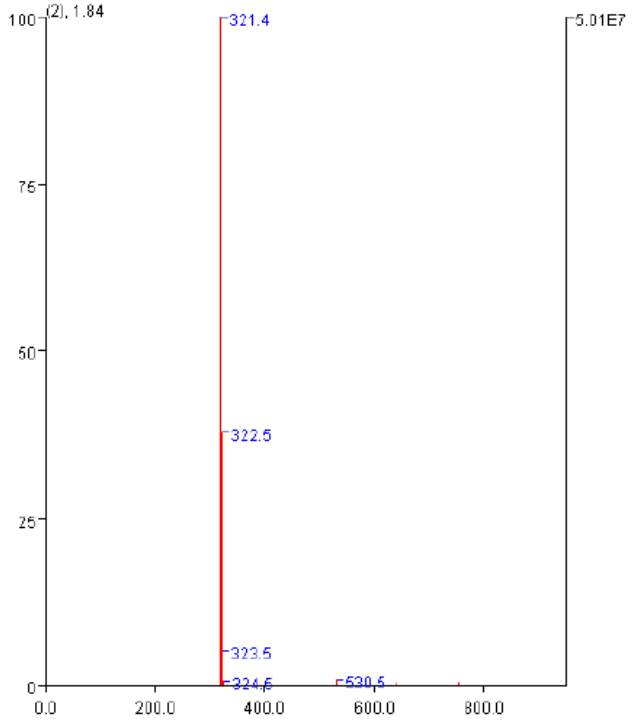


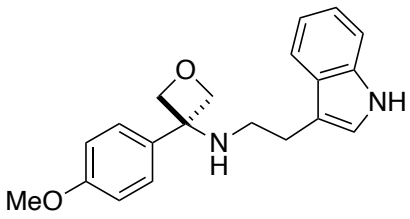


A10

12.6 mg product obtained. LC-MS data – Ret. time 1.8: MS ES+ *m/z* 321 ($[M+H]^+$).

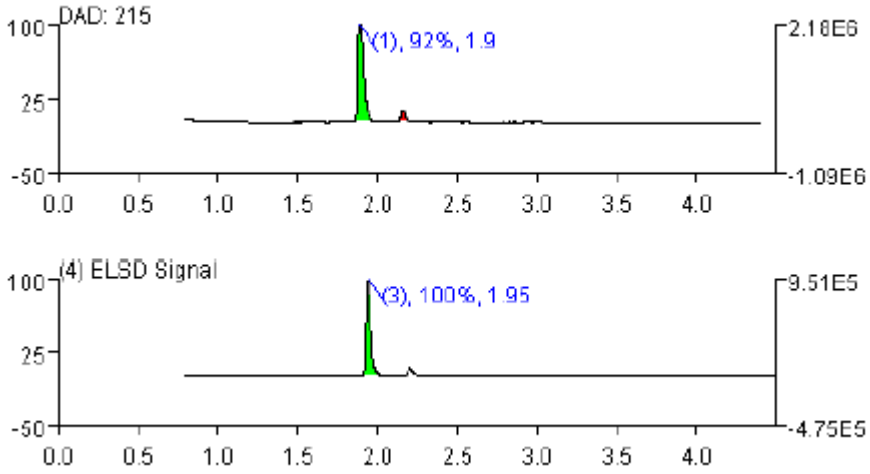


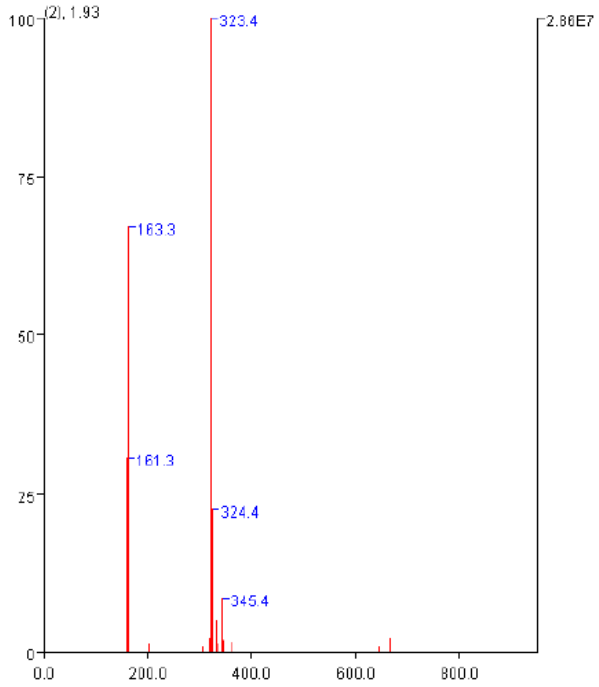


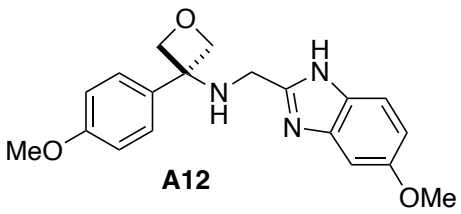


A11

14.6 mg product obtained. LC-MS data – Ret. time 1.9: MS ES+ *m/z* 323 ([M+H]$^+$).

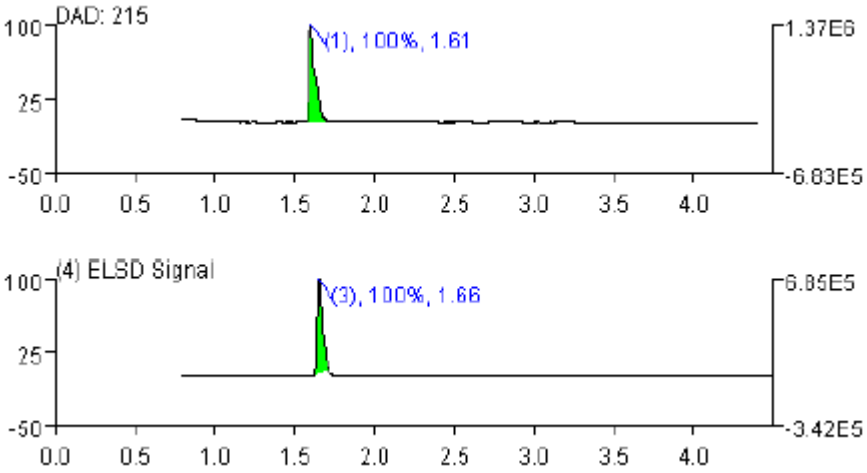


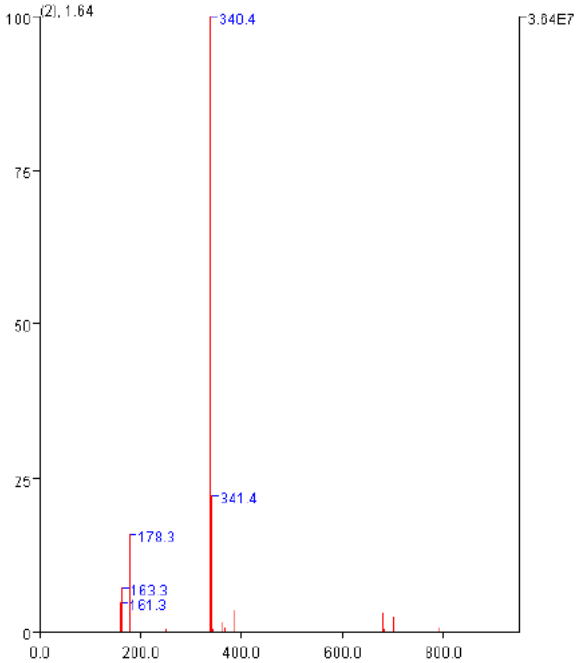


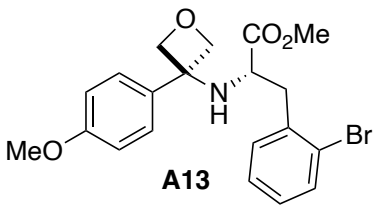


A12

7.7 mg product obtained. LC-MS data – Ret. time 1.6: MS ES+ *m/z* 340 ([M+H]$^+$).

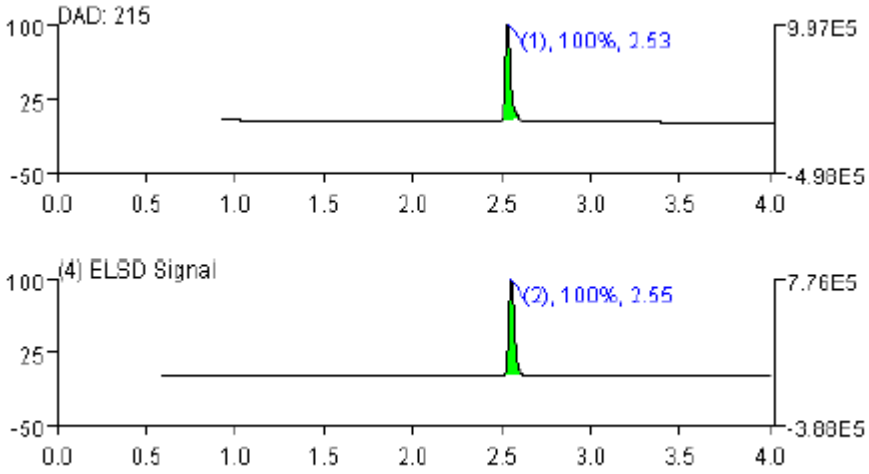


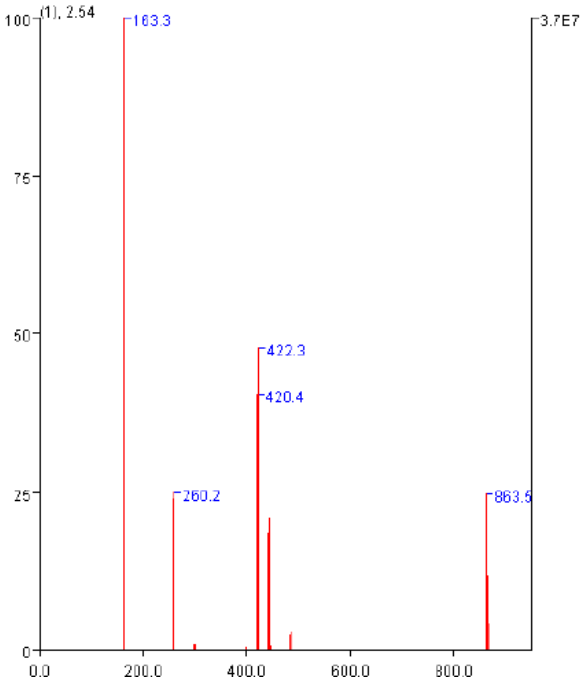


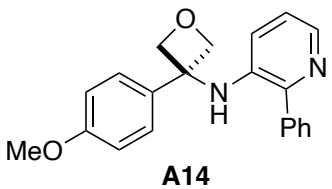


A13

15.4 mg product obtained. LC-MS data – Ret. time 2.5: MS ES+ *m/z* 420 ($[M+H]^+$).

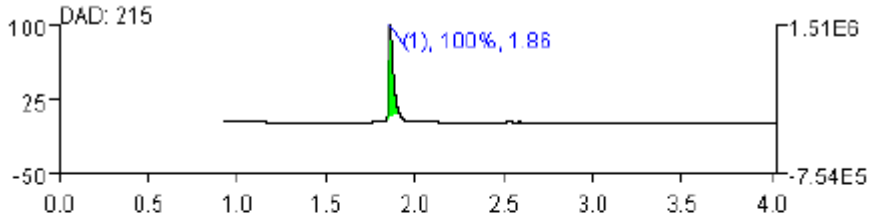


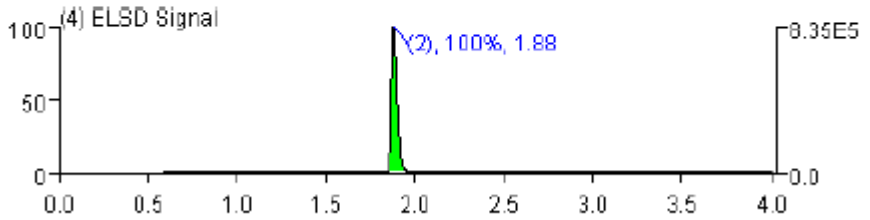


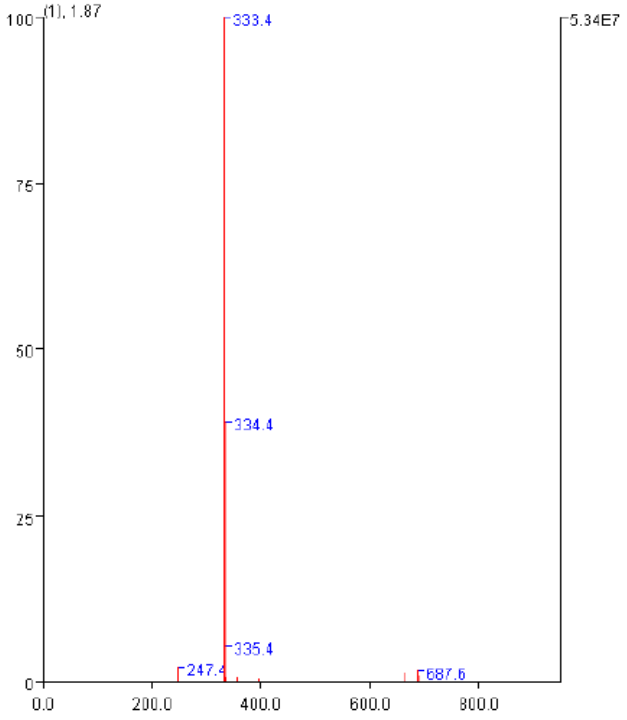


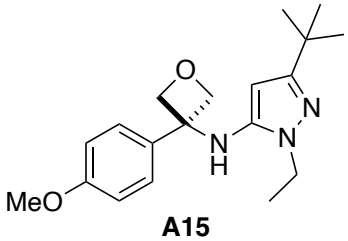
A14

7.3 mg product obtained. LC-MS data – Ret. time 1.9: MS ES+ *m/z* 333 ($[M+H]^+$).



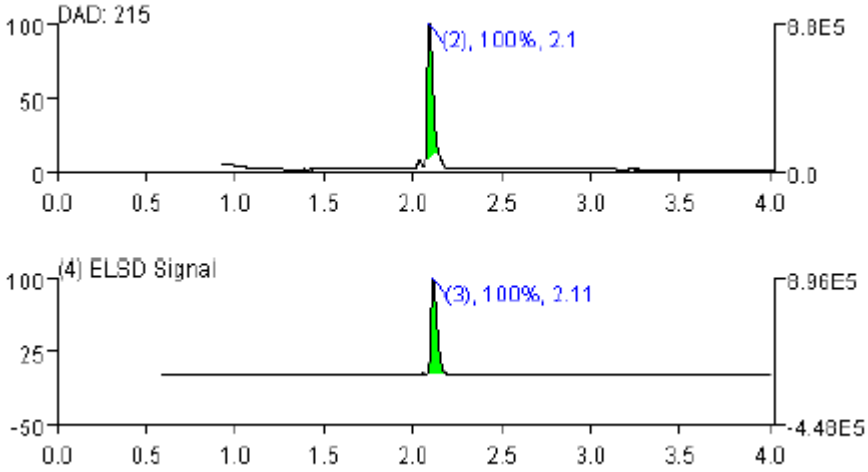


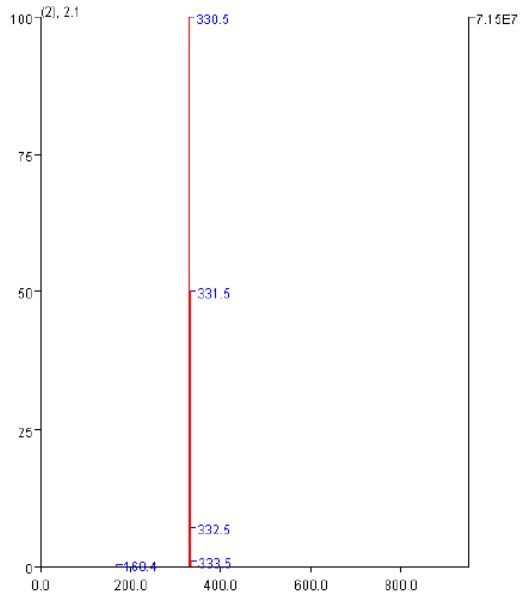


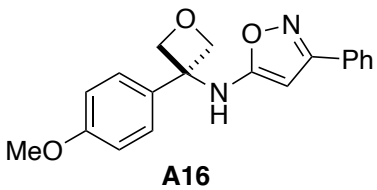


A15

16.2 mg product obtained. LC-MS data – Ret. Time 2.1: MS ES+ *m/z* 330 ($[M+H]^+$).

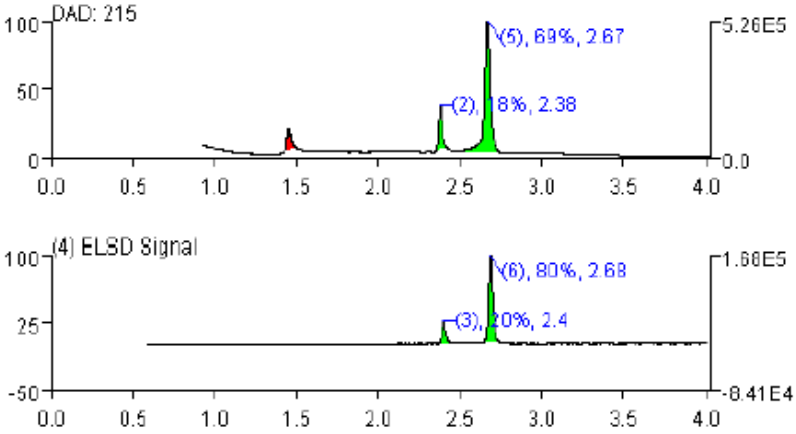


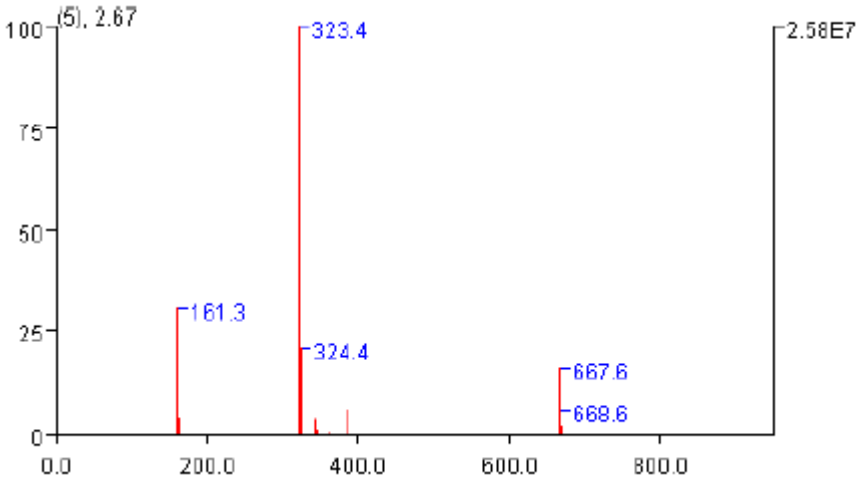


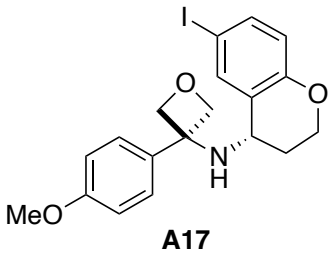


A16

3.8 mg product obtained. LC-MS data – Ret. Time 2.7: MS ES+ *m/z* 323 ([M+H]$^+$).

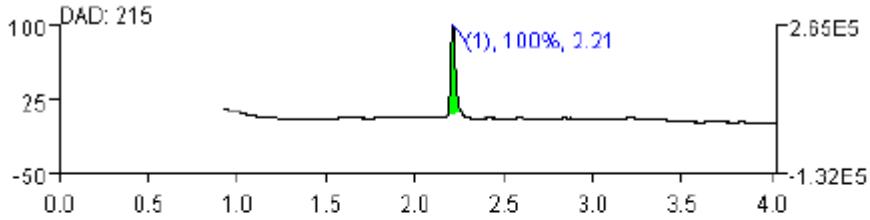


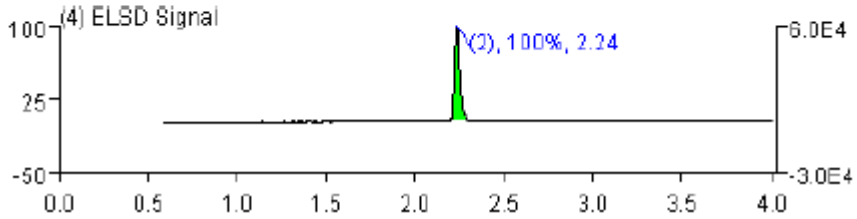


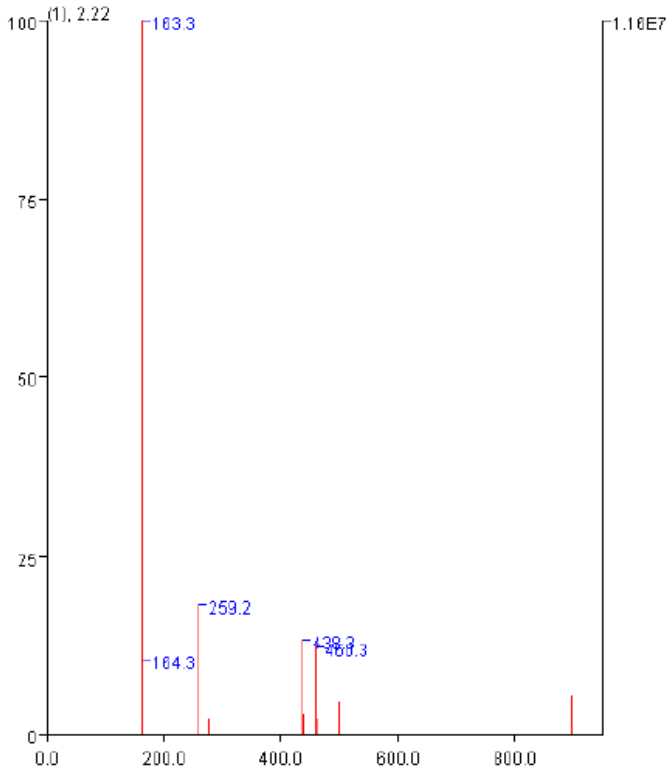


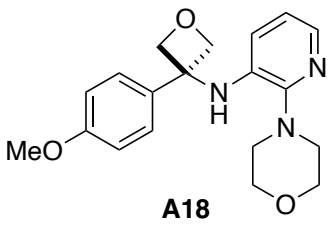
A17

2.5 mg product obtained. LC-MS data – Ret. Time 2.2: MS ES+ *m/z* 438 ($[M+H]^+$).



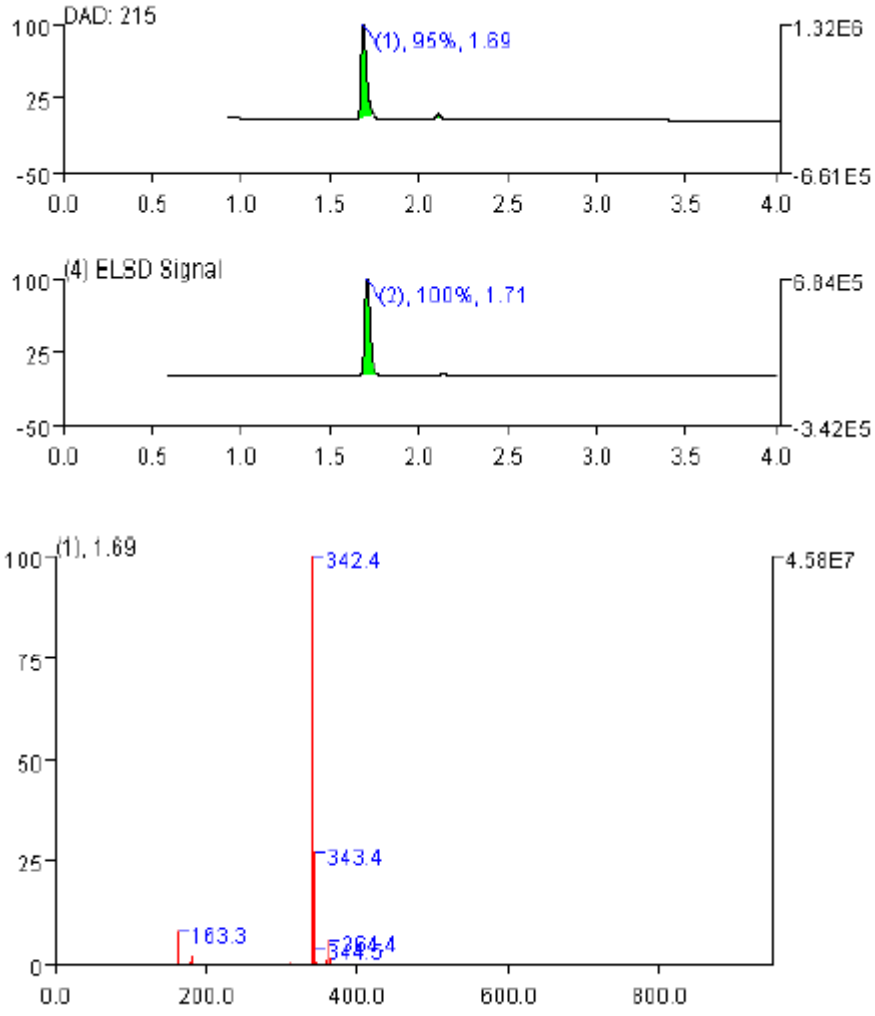


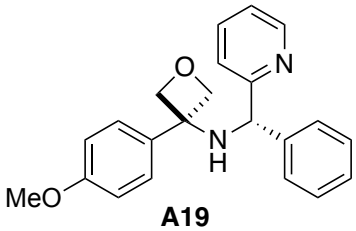




A18

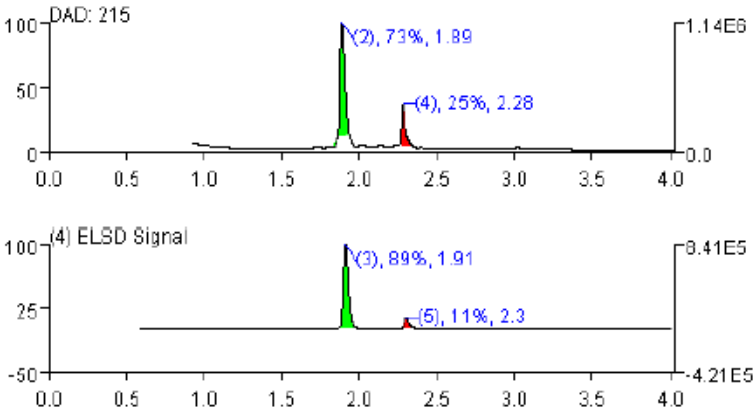
14.4 mg product obtained. LC-MS data – Ret. time 1.7: MS ES+ *m/z* 342 ($[M+H]^+$).

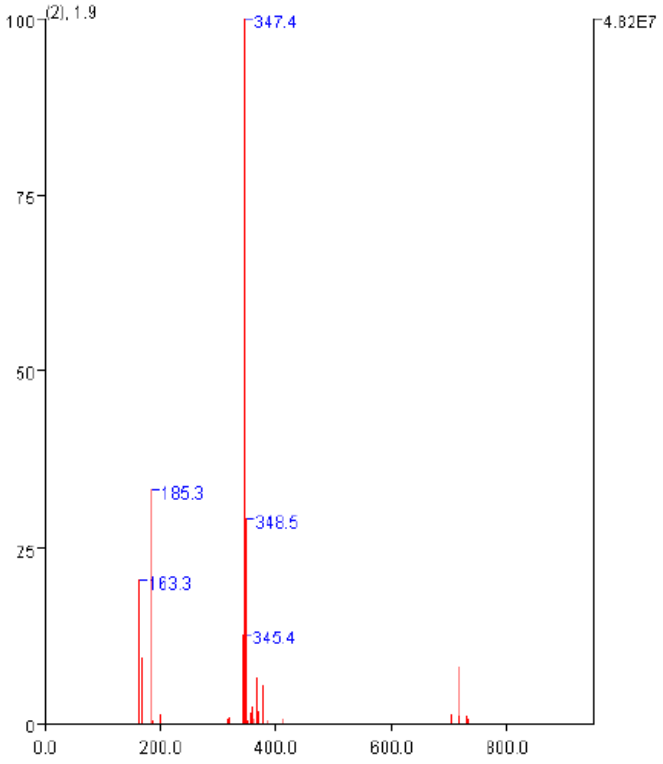


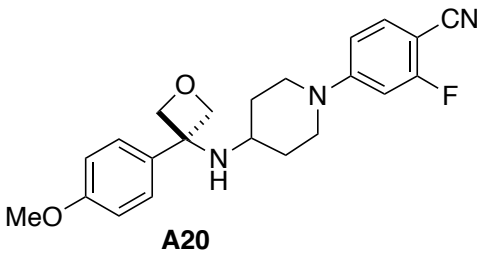


A19

12.1 mg product obtained. LC-MS data – Ret. time 1.9: MS ES+ *m/z* 347 ([M+H]$^+$).

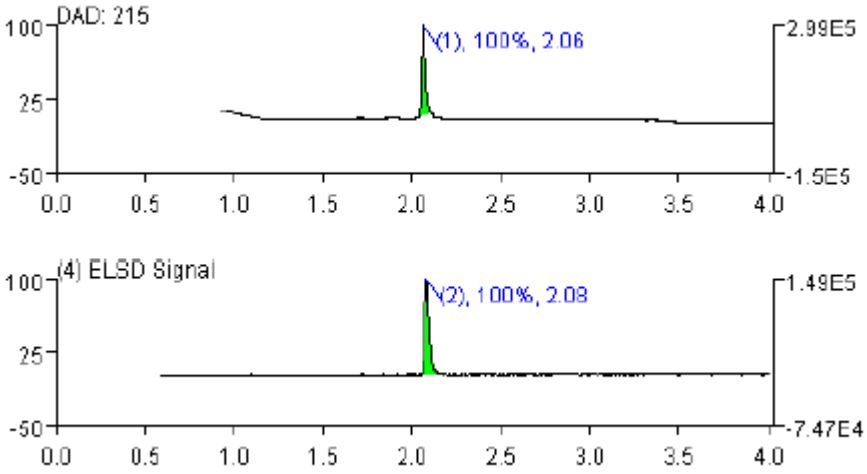


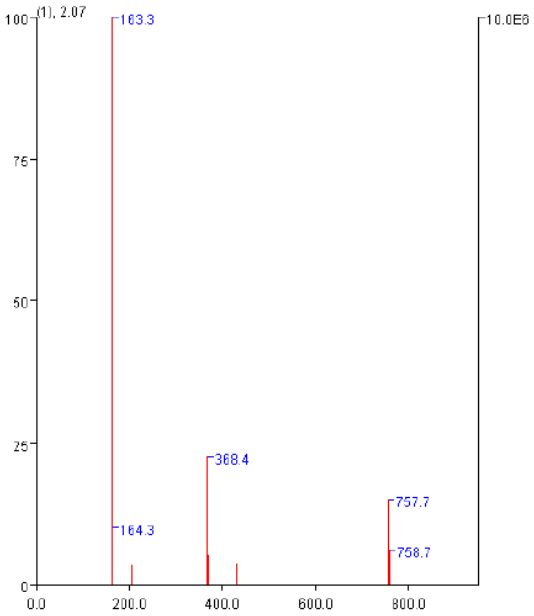


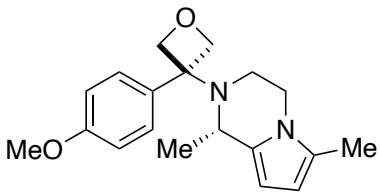


A20

13.9 mg product obtained. LC-MS data – Ret. time 2.1: MS ES+ *m/z* 368 ([M+H]$^+$).

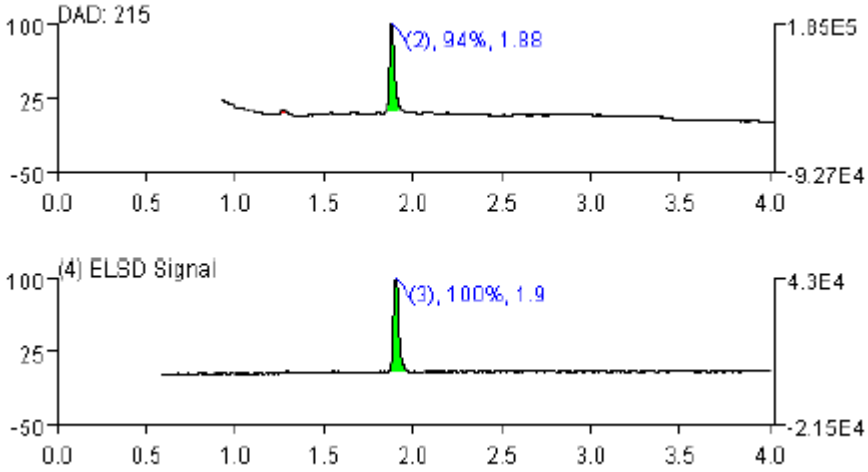


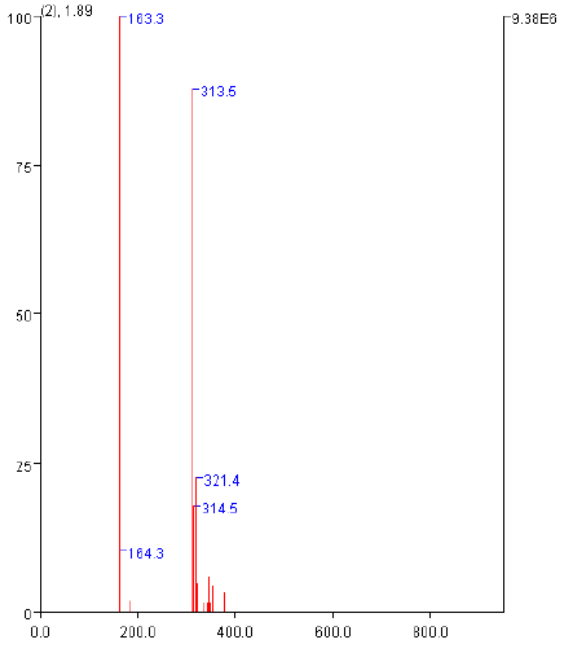


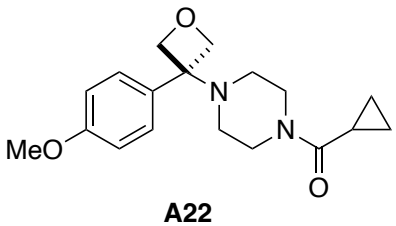


A21

2.5 mg product obtained. LC-MS data – Ret. time 1.9: MS ES+ *m/z* 313 ([M+H]$^+$).

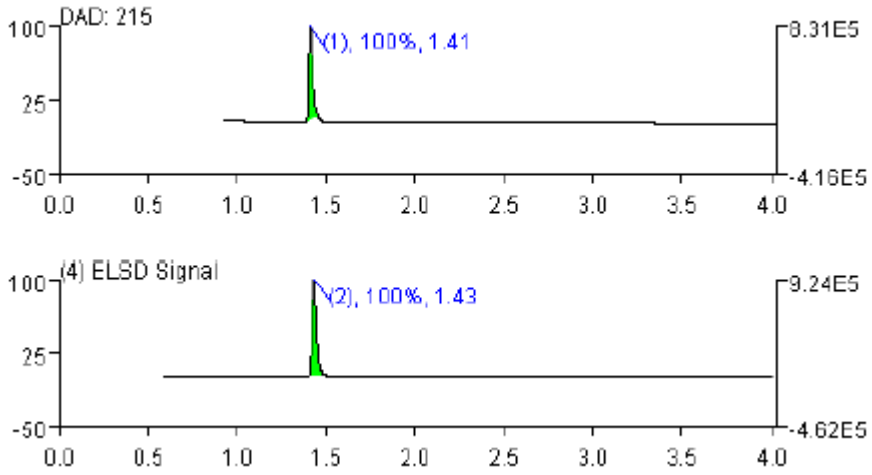


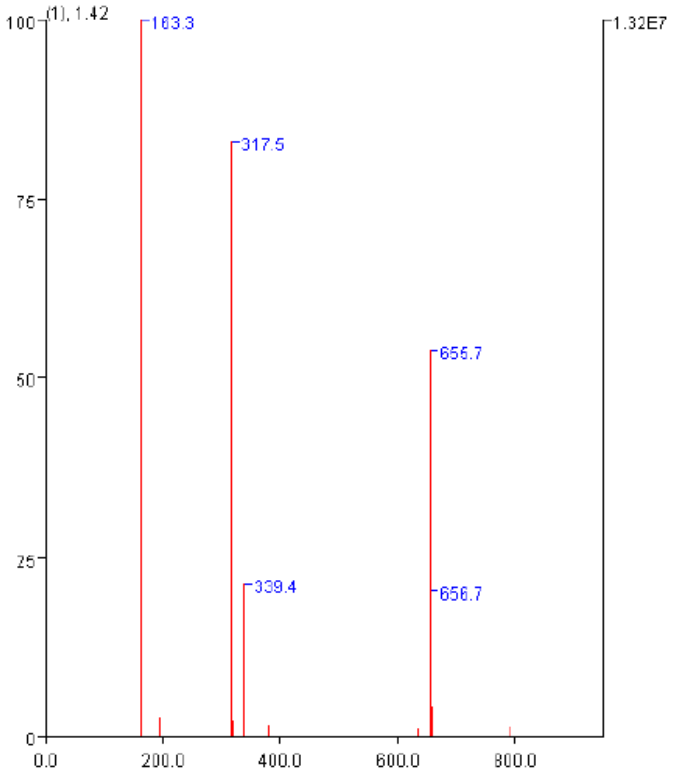


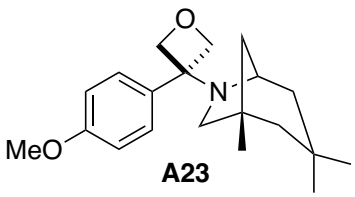


A22

8.5 mg product obtained. LC-MS data – Ret. time 1.4: MS ES+ *m/z* 317 ([M+H]$^+$).

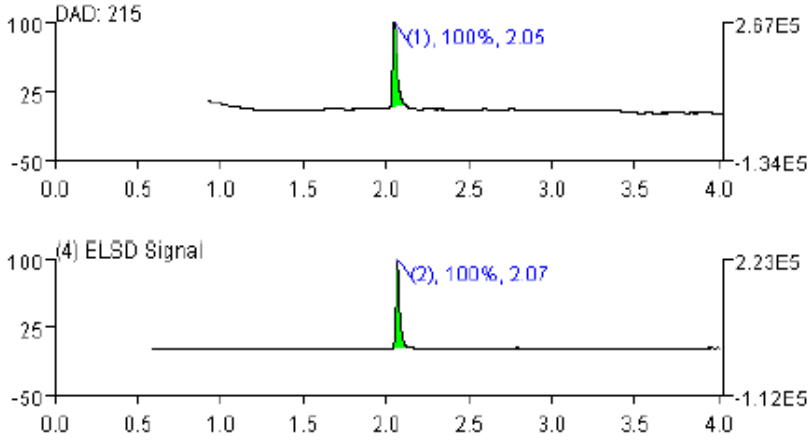


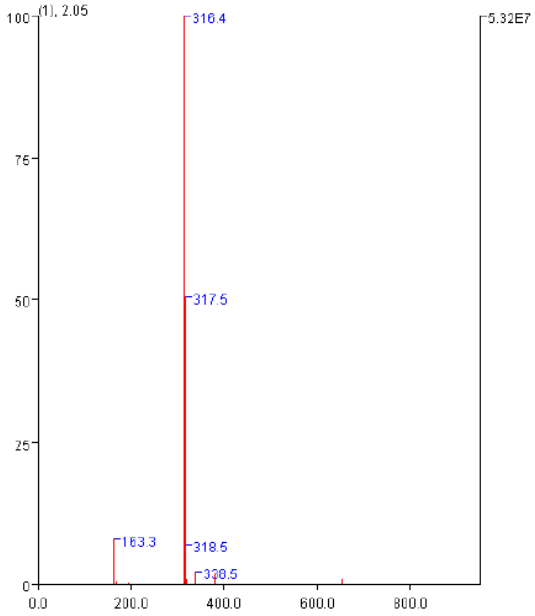


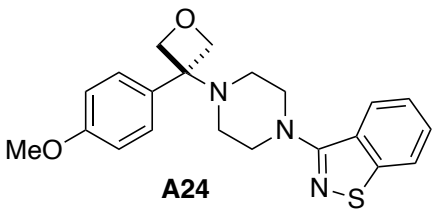


A23

1.5 mg product obtained. LC-MS data – Ret. time 2.1: MS ES+ *m/z* 316 ($[M+H]^+$).

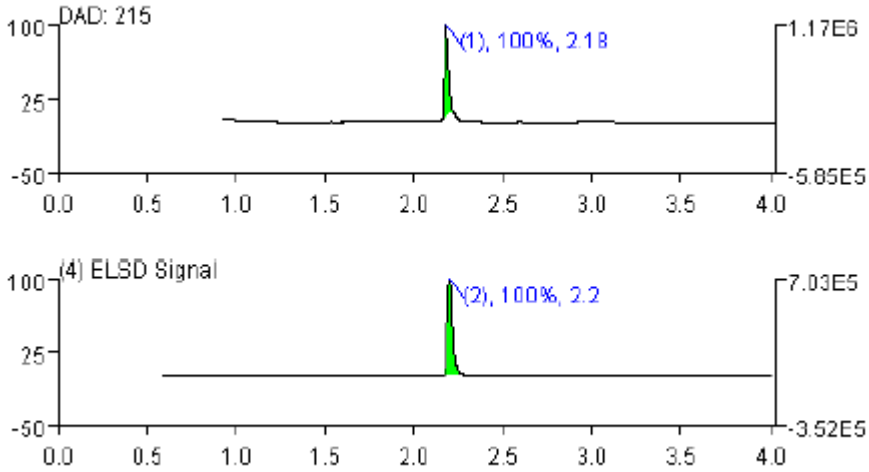


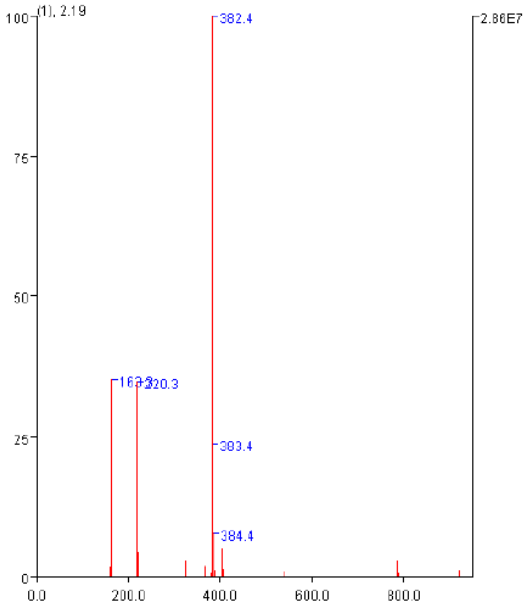


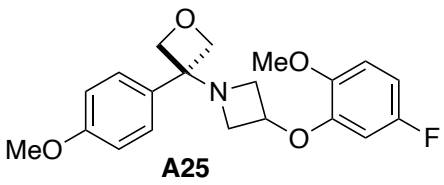


A24

11.6 mg product obtained. LC-MS data – Ret. time 2.2: MS ES+ *m/z* 382 ($[M+H]^+$).

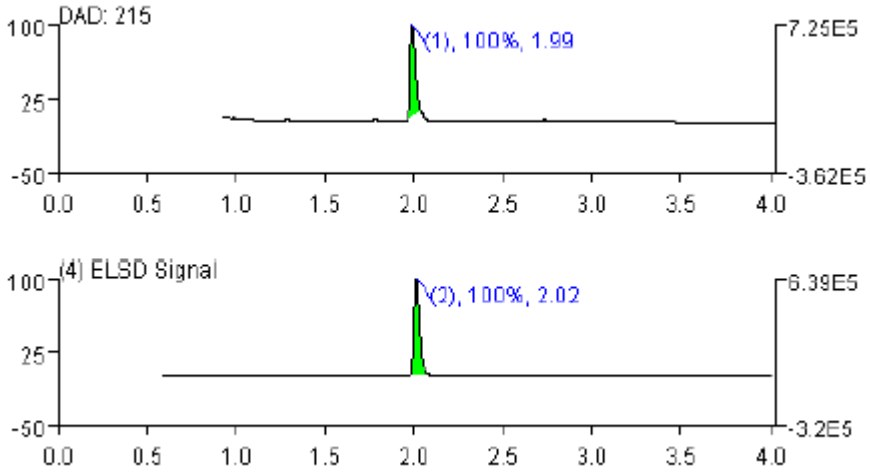


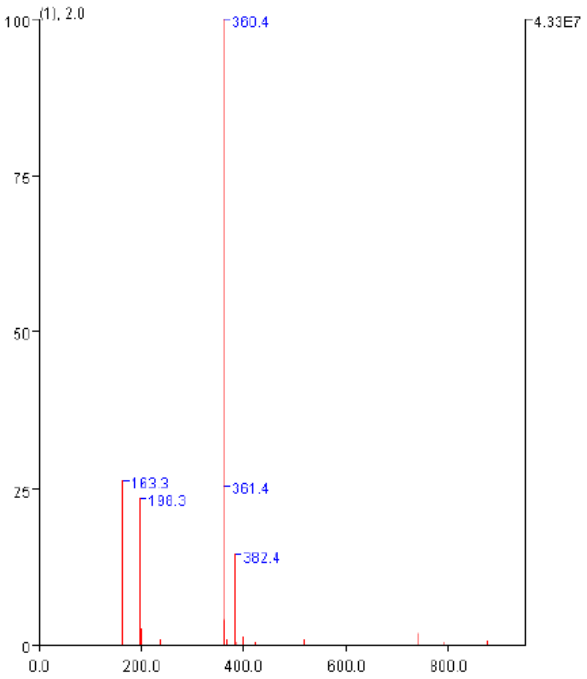


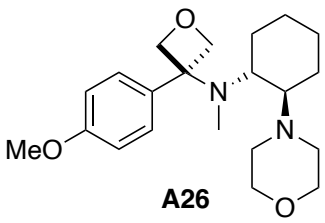


A25

10.9 mg product obtained. LC-MS data – Ret. time 2.0: MS ES+ *m/z* 360 ($[M+H]^+$).

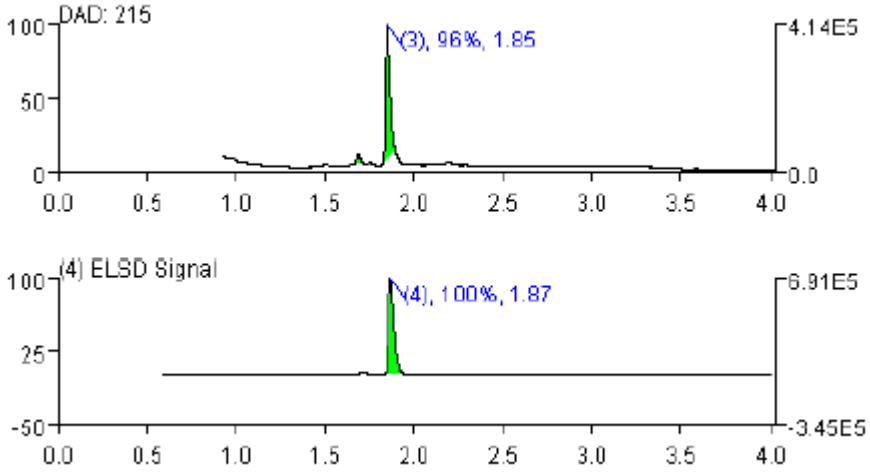


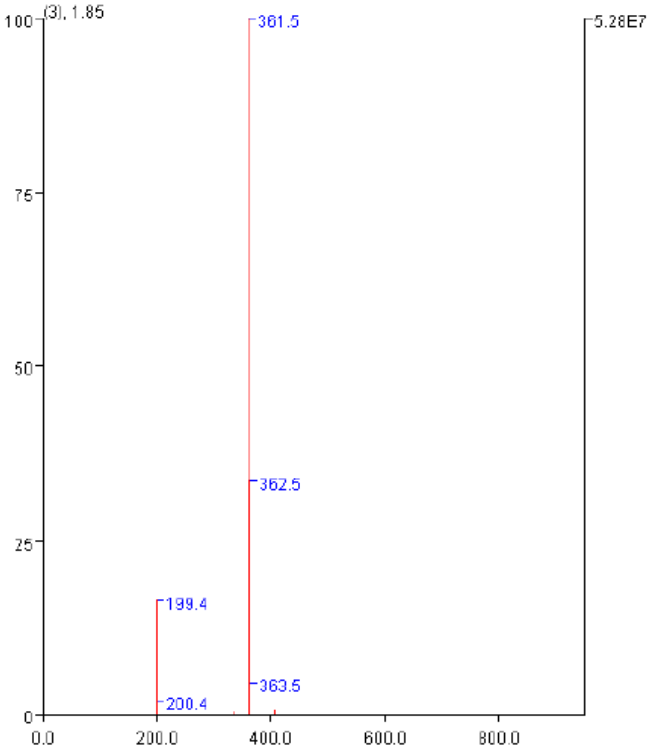


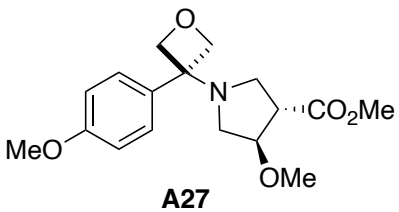


A26

7.1 mg product obtained. LC-MS data – Ret. time 1.7: MS ES+ *m/z* 361 ($[M+H]^+$).

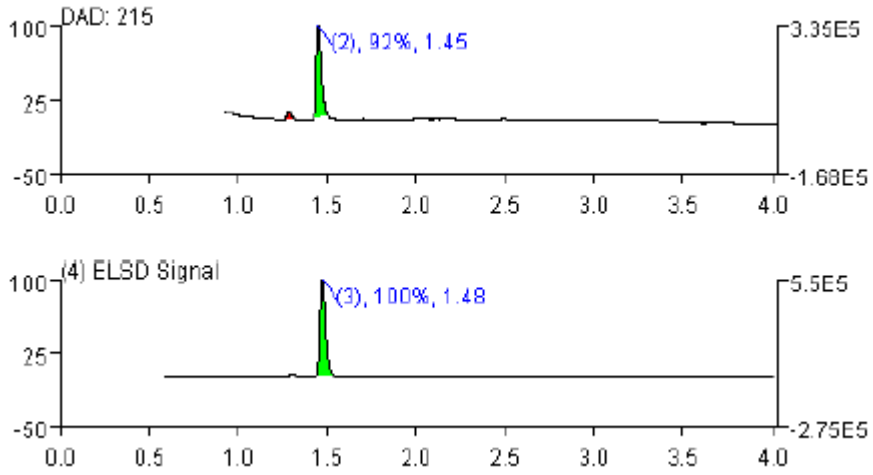


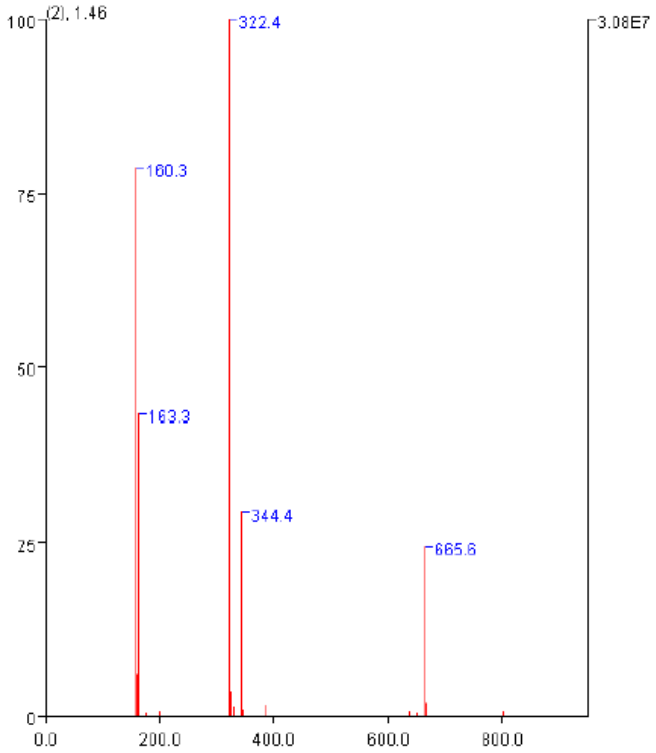


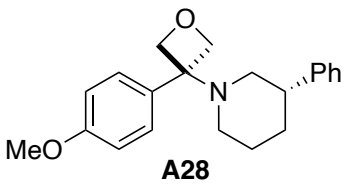


A27

12.7 mg product obtained. LC-MS data – Ret. time 1.5: MS ES+ *m/z* 322 ([M+H]$^+$).

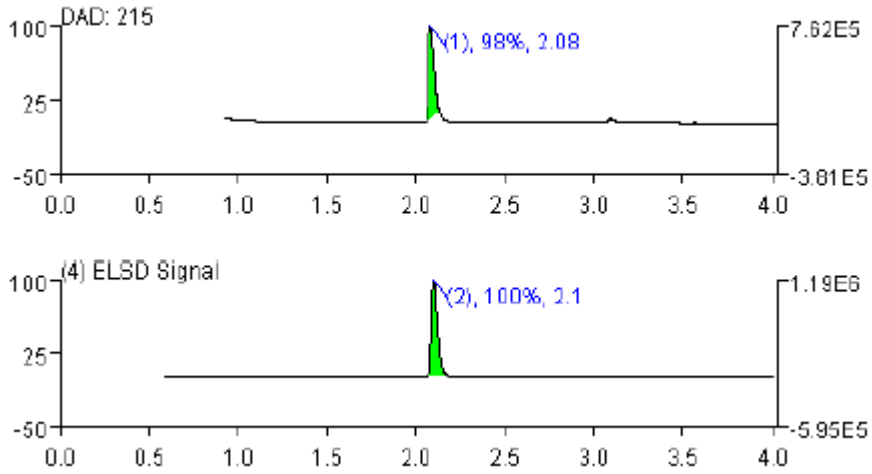


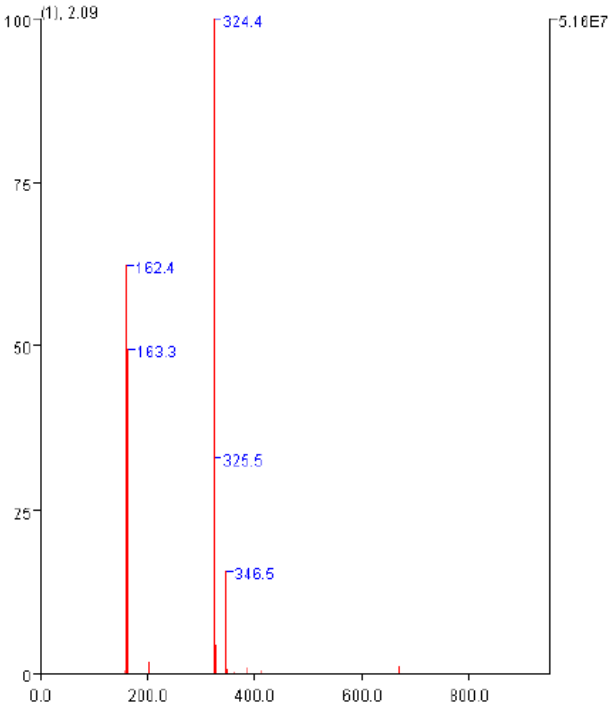


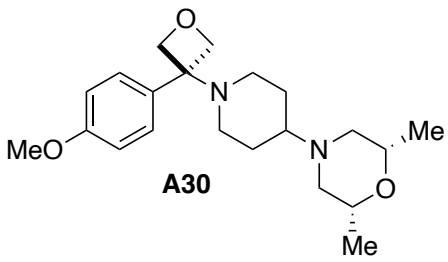


A28

8.9 mg product obtained. LC-MS data – Ret. time 2.1: MS ES+ *m/z* 324 ([M+H]$^+$).

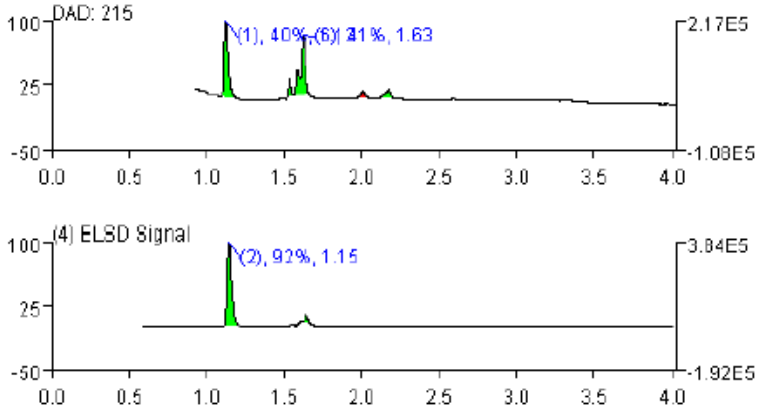


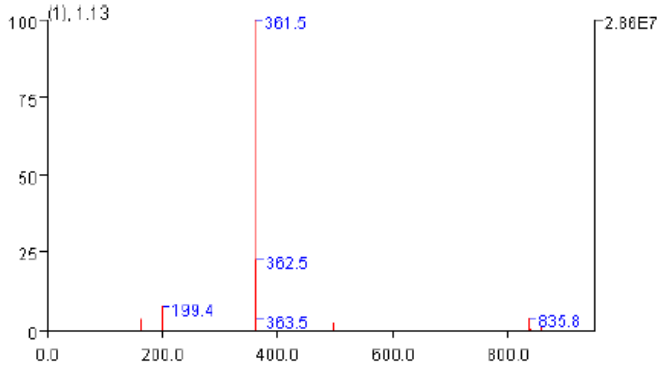


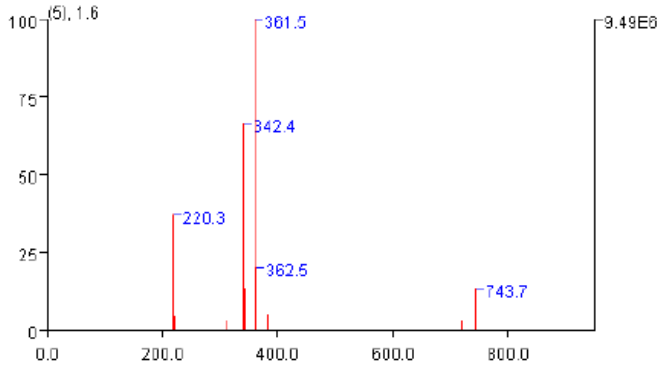


A30

1.8 mg product obtained. LC-MS data – Ret. time 1.1: MS ES+ *m/z* 361 ($[M+H]^+$).



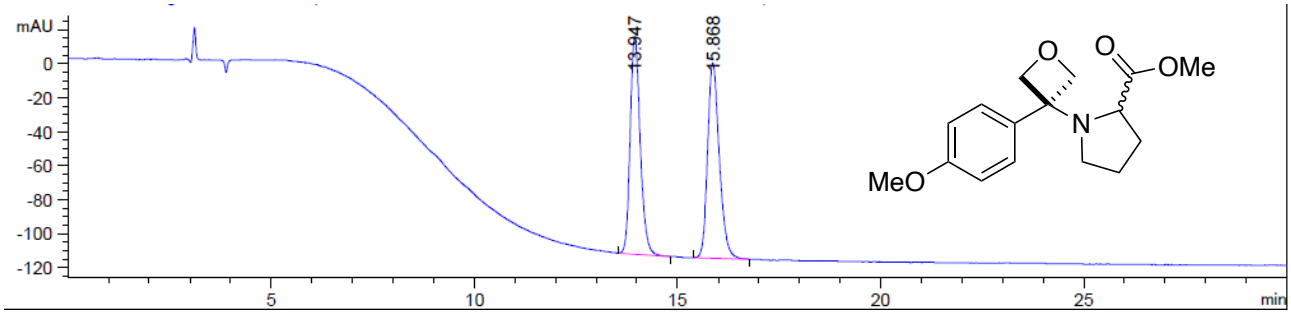




HPLC Traces of Enantioenriched Oxetane Amines 25 and 26

Scalemic Mixture of Enantioenriched Oxetane Amines (–)-25 and (+)-26

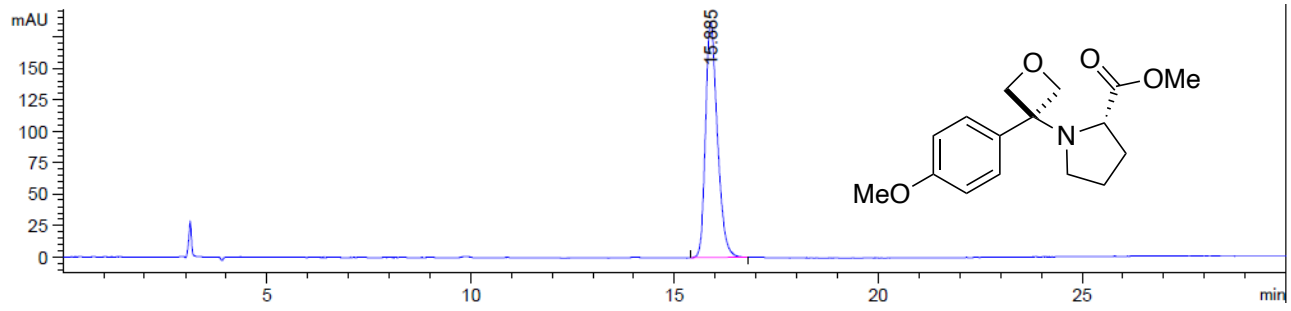
Conditions: Chiralpak IF 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.947	BB	0.2603	2195.84229	127.89033	48.8584
2	15.868	BB	0.3034	2298.45459	114.86771	51.1416
Totals :				4494.29688	242.75803	

Methyl (3-(4-methoxyphenyl)oxetan-3-yl)-L-prolinate ((–)-25)

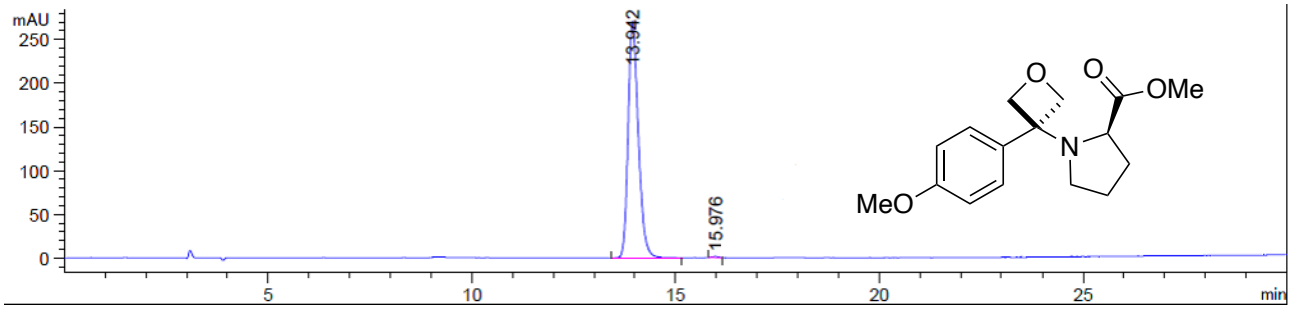


Signal 3: DAD1 C, Sig=210,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.885	BB	0.3099	3794.60352	187.62798	100.0000
Totals :				3794.60352	187.62798	

***ee* = 100%**

Methyl (3-(4-methoxyphenyl)oxetan-3-yl)-D-prolinate ((+)-26)



Signal 3: DAD1 C, Sig=210,10 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.942	BB	0.2680	4726.60742	270.36615	99.6277
2	15.976	MM	0.2318	17.66191	1.26966	0.3723
Totals :				4744.26933	271.63581	

***ee* = 99.3%**

X-Ray Crystallography Details

Oxetane Amines

Structural Analysis

X-Ray crystallography provides a means to assess the structural changes induced by replacing a benzamide group with an aryloxetane amine. See Fig. S37 and S39 for a summary of the pertinent bond lengths and angles in **30** and **38**. The following properties are worthy of note:

1. The C_q–O through-space distance in oxetanes (2.15–2.17 Å) is significantly longer than the typical distance of the benzamide C=O double bond (1.23 Å).
2. The C–N distance (1.46–1.47 Å) is also longer than that of amides (1.35 Å), since the amide C–N bond has partial double bond character and is thus, shorter.
3. The puckering angle is very small. Other polysubstituted oxetanes (e.g. 16 ° for EDO),[60] have a higher puckering angle to reduce gauche interactions between the substituents.
4. Importantly, the oxetane substituents are positioned almost orthogonal to the O–C_q–C_q plane (O–C_q–N plane respectively) to reduce steric repulsions. This is in contrast to what is typically observed in benzamides, where the aromatic group is almost on the same plane of the C=O bond as to increase π-conjugation. Likewise, the benzamide-nitrogen is more planar and aligned with the C=O plane. Consequently, aryloxetane amines are overall less planar than their benzamide analogues.

X-Ray crystal structure of ethyl 1-(3-(4-methoxyphenyl)oxetan-3-yl)piperidine-4-carboxylate (30)

Crystals suitable for X-ray analysis were grown by slow evaporation from $CDCl_3$ at 25 °C.

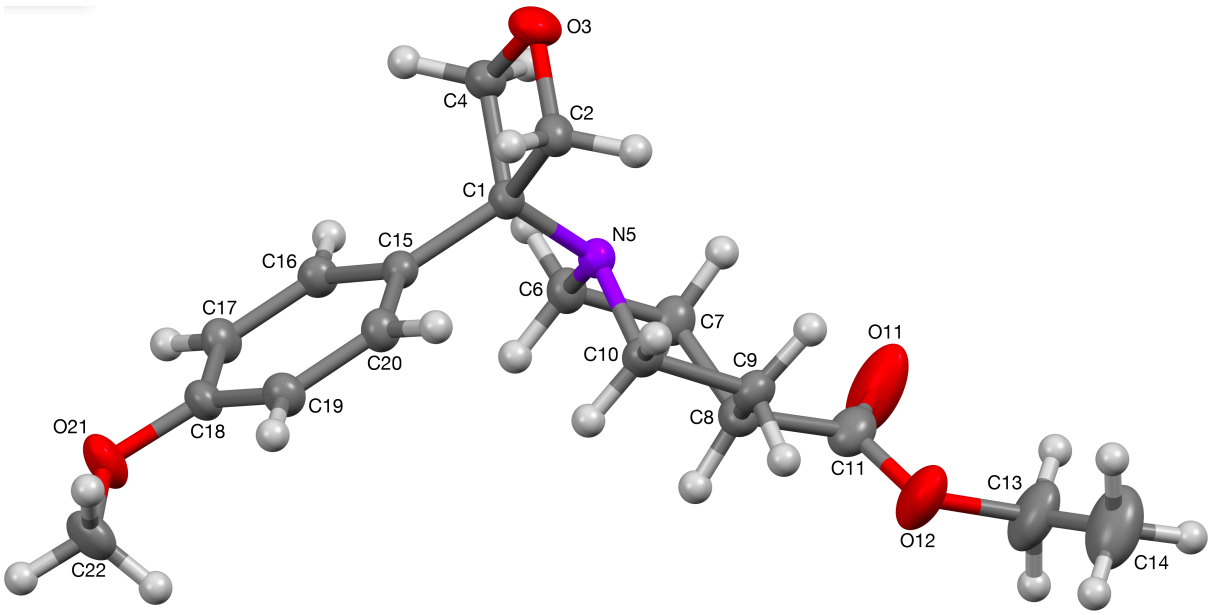
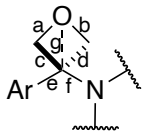


Fig. S36 X-Ray crystal structure of **30** (50% probability ellipsoids).

Crystal data for **30**: $C_{18}H_{25}NO_4$, M = 319.39, monoclinic, $P2_1/n$ (no. 14), a = 10.6757(4), b = 15.9885(5), c = 11.0058(4) Å, β = 115.784(5)°, V = 1691.52(12) Å^3, Z = 4, D_c = 1.254 g cm^{-3}, μ(Mo-Kα) = 0.088 mm^{-1}, T = 173 K, colorless blocks, Agilent Xcalibur 3 E diffractometer; 3792 independent measured reflections (R_{int} = 0.0286), F^2 refinement,[X1,X2] R_1(obs) = 0.0485, wR_2(all) = 0.1237 ($R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 3007 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], completeness to θ_{full}(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 211 parameters. CCDC 2049639.

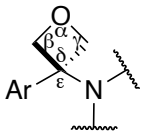
Most relevant bond lengths and angles:

Bond lengths



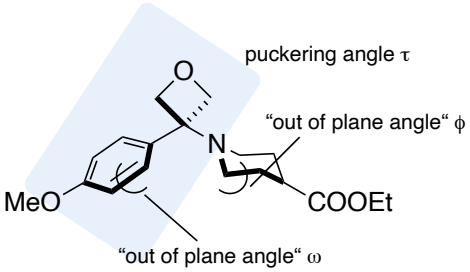
a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.45 Å
c = C(1)–C(2) = 1.54 Å
d = C(1)–C(4) = 1.54 Å
e = C(1)–C(15) = 1.52 Å
f = C(1)–N(5) = 1.47 Å
g[a] = C(1)–O(3) = 2.15 Å

Bond angles



α = C(2)–O(3)–C(4) = 91.5 °
β = O(3)–C(2)–C(1) = 92.1 °
γ = O(3)–C(4)–C(1) = 92.0 °
δ = C(2)–C(1)–C(4) = 84.3 °
ε = C(15)–C(1)–N(5) = 114.9 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 2.3 °
ω = O(3)–C(1)–C(15)–C(20) = 86.2 °
ϕ = O(3)–C(1)–N(5)–C(10) = 62.3 °

Fig. S37 Most relevant bond lengths and angles in the crystal structure of **30**. [a]g is the through-space distance between C(1) and O(3), not a bond length. This distance can be directly compared to the C=O bond length of amides.

X-Ray crystal structure of 3-(4-methoxyphenyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-amine (38)

Crystals suitable for X-ray analysis were grown by slow evaporation from Et_2O at 25 °C.

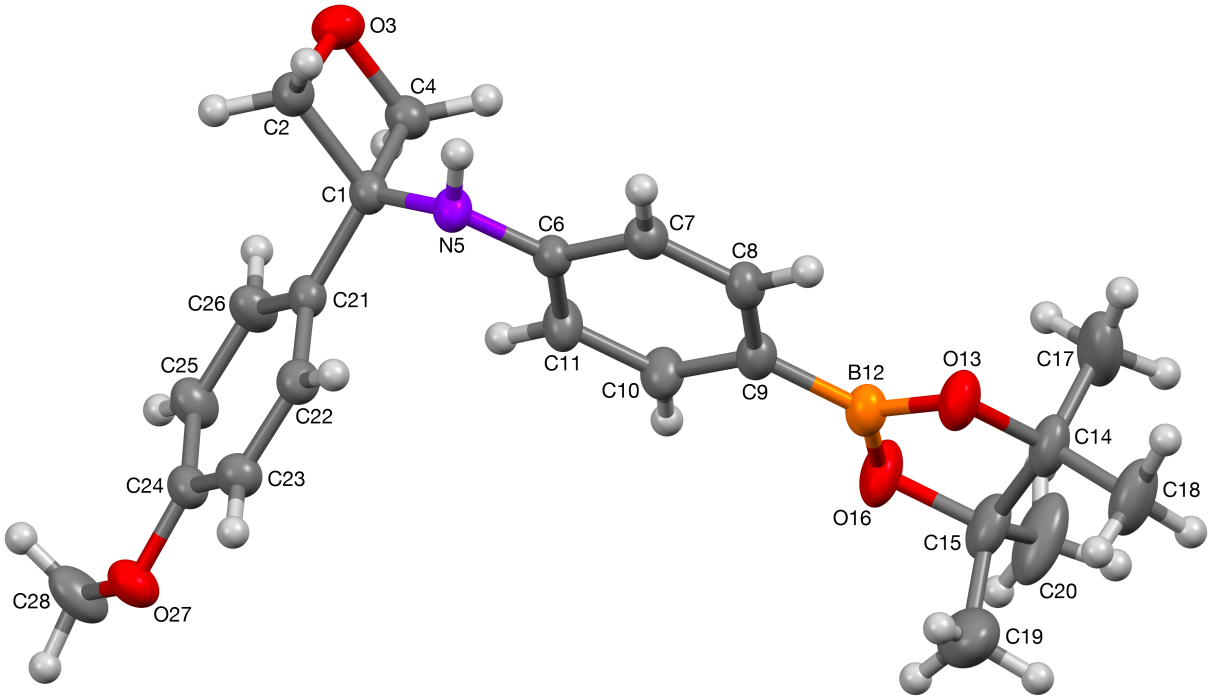


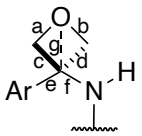
Fig. S38 X-Ray crystal structure of **38** (50% probability ellipsoids).

Crystal data for **38**: $C_{22}H_{28}BNO_4$, M = 381.26, monoclinic, $P2_1/c$ (no. 14), a = 9.1846(3), b = 14.9971(5), c = 15.9699(4) Å, β = 106.604(3)°, V = 2108.02(12) Å^3, Z = 4, D_c = 1.201 g cm^{-3}, μ(Cu-Kα) = 0.650 mm^{-1}, T = 173 K, colorless blocky needles, Agilent Xcalibur PX Ultra A diffractometer; 4185 independent measured reflections (R_{int} = 0.0503), F^2 refinement,[X1,X2] R_1(obs) = 0.0456, wR_2(all) = 0.1231 (R_1 = Σ||F_o| – |F_c||/Σ|F_o|; wR_2 = {Σ[w(F_o^2 – F_c^2)^2] / Σ[w(F_o^2)^2]}$^{1/2}$; w^{-1} = σ^2(F_o^2) + (aP)^2 + bP), 3218 independent observed absorption-corrected reflections [|F_o| > 4σ(|F_o|), completeness to θ$_{full}$(67.7°) = 100% {completeness to 0.84 Å resolution}], 263 parameters. CCDC 2049640.

The N5–H hydrogen atom in the structure of **38** was located from a ΔF map and refined freely subject to an N–H distance constraint of 0.90 Å.

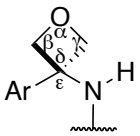
Most relevant bond lengths and angles:

Bond lengths



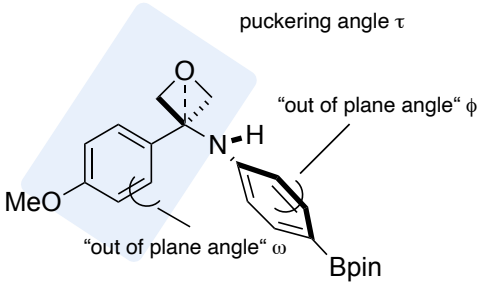
a = C(2)–O(3) = 1.45 Å
b = C(4)–O(3) = 1.46 Å
c = C(1)–C(2) = 1.55 Å
d = C(1)–C(4) = 1.56 Å
e = C(1)–C(21) = 1.52 Å
f = C(1)–N(5) = 1.46 Å
g[a] = C(1)–O(3) = 2.17 Å

Bond angles



α = C(2)–O(3)–C(4) = 91.3 °
β = O(3)–C(2)–C(1) = 92.7 °
γ = O(3)–C(4)–C(1) = 91.9 °
δ = C(2)–C(1)–C(4) = 84.0 °
ε = C(21)–C(1)–N(5) = 112.6 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 4.6 °
ω = O(3)–C(1)–C(21)–C(22) = 31.1 °
ϕ = O(3)–C(1)–N(5)–C(6) = 74.3 °

Fig. S39 Most relevant bond lengths and angles in the crystal structure of **38**. [a]g is the through-space distance between C(1) and O(3), not a bond length. This distance can be directly compared to the C=O bond length of amides.

Oxetane Sulfonate Esters

X-Ray crystal structure of phenyl 3-(4-methoxyphenyl)oxetane-3-sulfonate (49)

Crystals suitable for X-ray analysis were grown by slow evaporation from $CDCl_3$ at 25 °C.

The structure of **49** was found to contain four crystallographically independent molecules (**49-A**, **49-B**, **49-C**, and **49-D**) in the asymmetric unit, with rotated methoxy motif.

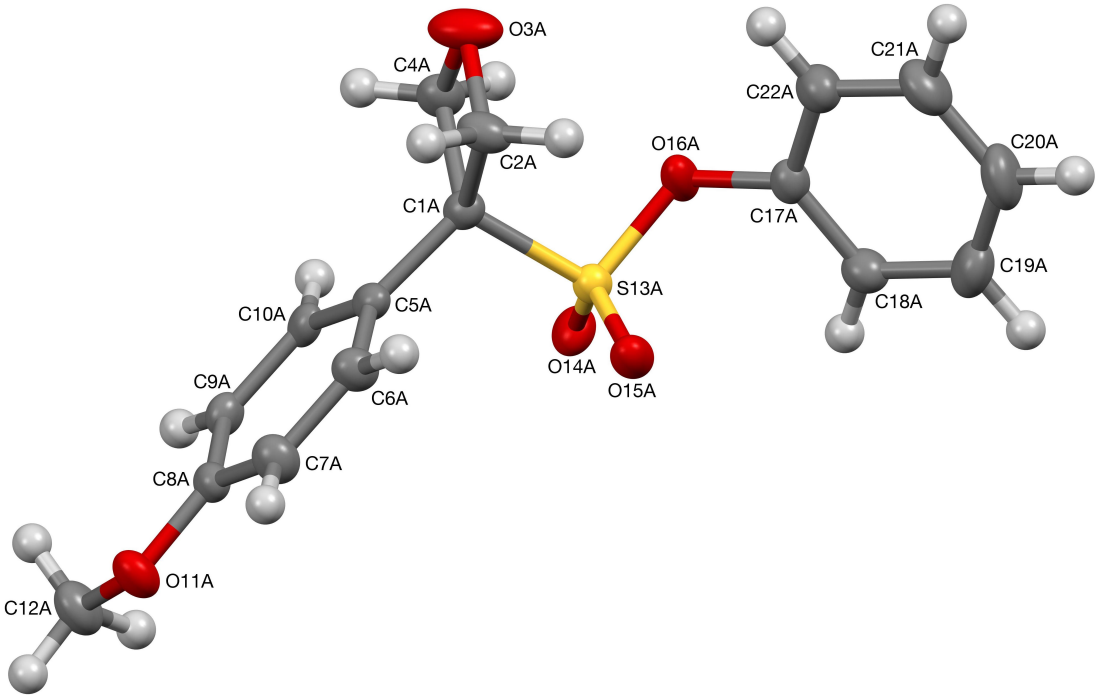


Fig. S40 The structure of **49-A**, one of the four independent molecules present in the crystal of **49** (50% probability ellipsoids).

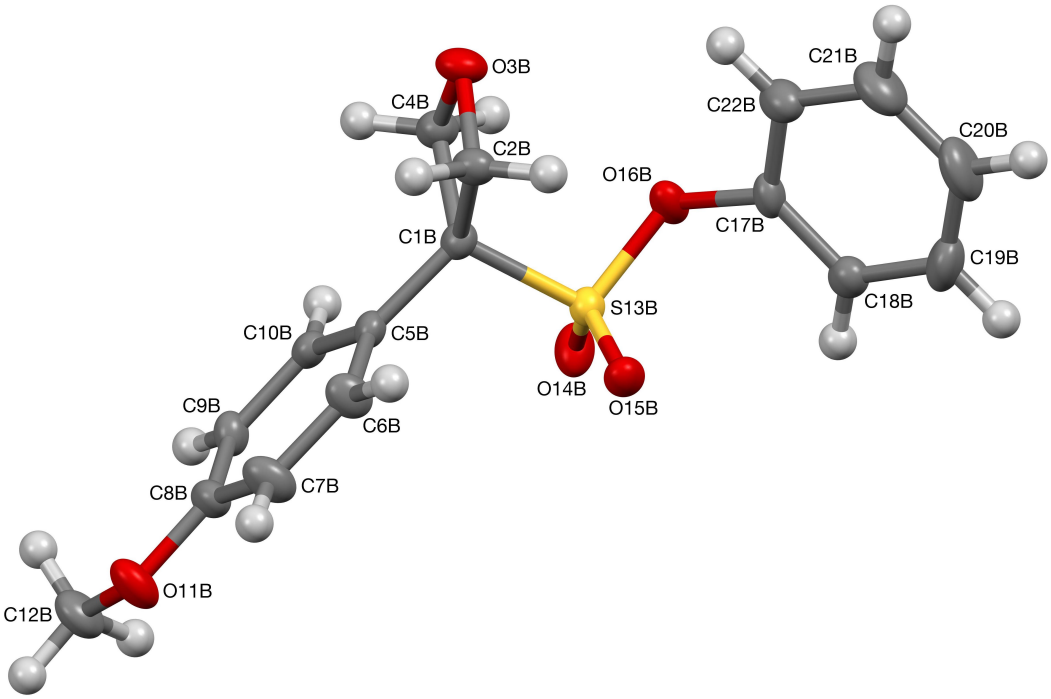


Fig. S41 The structure of **49-B**, one of the four independent molecules present in the crystal of **49** (50% probability ellipsoids).

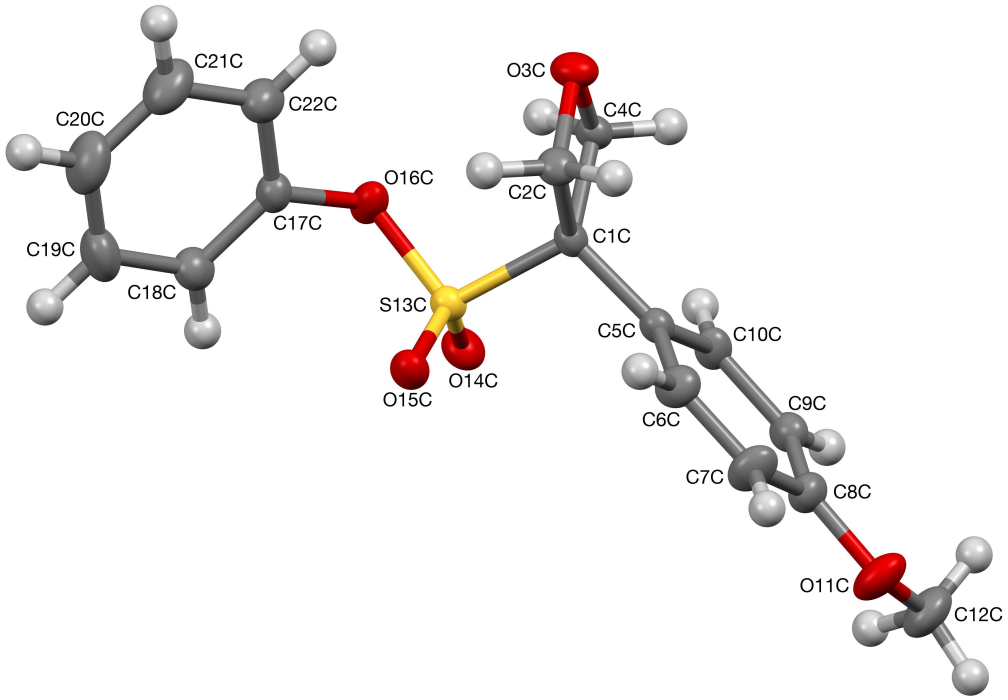


Fig. S42 The structure of **49-C**, one of the four independent molecules present in the crystal of **49** (50% probability ellipsoids).

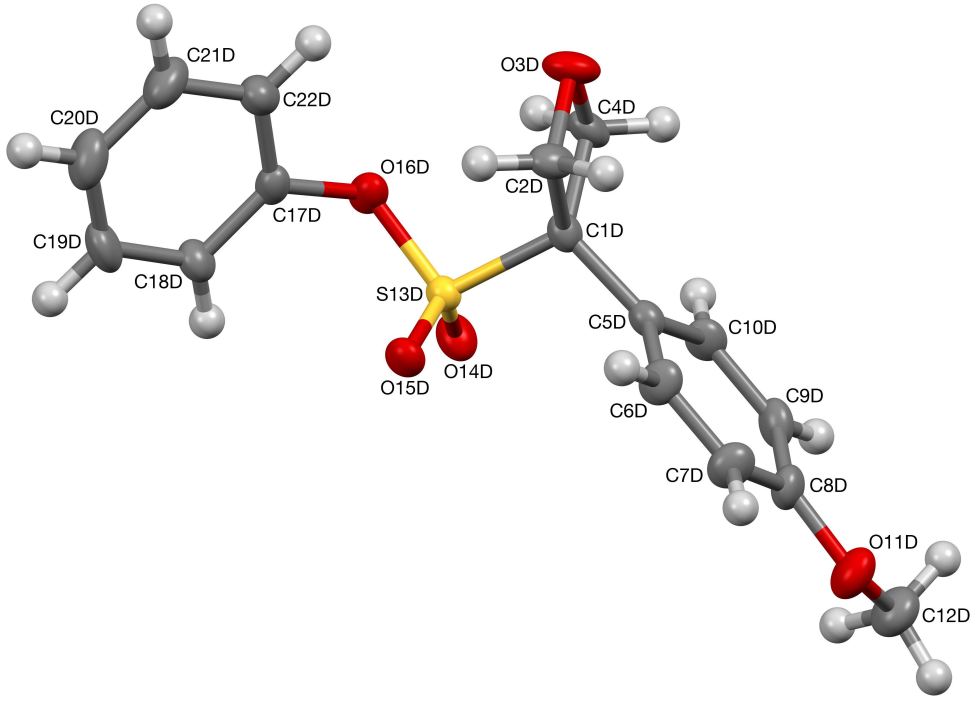


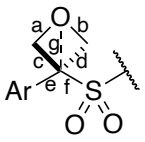
Fig. S43 The structure of **49-D**, one of the four independent molecules present in the crystal of **49** (50% probability ellipsoids).

Crystal data for **49**: $C_{16}H_{16}O_5S$, M = 320.35, monoclinic, $P2_1$ (no. 4), a = 11.4381(3), b = 18.9180(5), c = 13.7930(4) Å, β = 90.393(3)°, V = 2984.53(14) Å^3, Z = 8 [4 independent molecules], D_c = 1.426 g cm^{-3}, μ(Mo-Kα) = 0.238 mm^{-1}, T = 173 K, colorless tablets, Agilent Xcalibur 3 E diffractometer; 10361 independent measured reflections (R_{int} = 0.0236), F^2 refinement,[X1,X2] R_1(obs) = 0.0414, wR_2(all) = 0.0926 (R_1 = Σ||F_o| – |F_c||/Σ|F_o|; wR_2 = {Σ[w(F_o^2 – F_c^2)^2] / Σ[w(F_o^2)^2]}$^{1/2}$; w^{-1} = σ^2(F_o^2) + (aP)^2 + bP), 8500 independent observed absorption-corrected reflections [|F_o| > 4σ(|F_o|), completeness to θ$_{full}$(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 798 parameters. CCDC 2094792.

The absolute structure of **49** was determined by use of the Flack parameter [*x* = –0.04(4)].

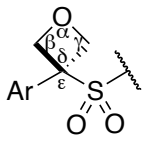
Most relevant bond lengths and angles:

Bond lengths



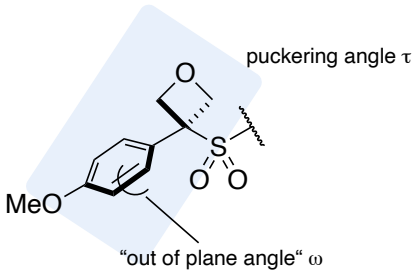
a = C(2)–O(3) = 1.45 Å
b = C(4)–O(3) = 1.45 Å
c = C(1)–C(2) = 1.55 Å
d = C(1)–C(4) = 1.54 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–S(13) = 1.80 Å
g[a] = C(1)–O(3) = 2.14 Å

Bond angles



α = C(2)–O(3)–C(4) = 92.5 °
β = O(3)–C(2)–C(1) = 90.9 °
γ = O(3)–C(4)–C(1) = 91.2 °
δ = C(2)–C(1)–C(4) = 85.4 °
ε = C(5)–C(1)–S(13) = 106.0 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 4.0 °
ω = O(3)–C(1)–C(5)–C(10) = 88.8 °

Fig. S44 Most relevant bond lengths and angles in the crystal structure of **49**. All values are the average of the four crystallographically independent molecules (**49-A**, **49-B**, **49-C**, and **49-D**) in the asymmetric unit. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

X-Ray crystal structure of methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(((3-(4-methoxyphenyl)oxetan-3-yl)sulfonyl)oxy)phenyl)propanoate (89)

Crystals suitable for X-ray analysis were grown by slow evaporation from acetone at 25 °C.

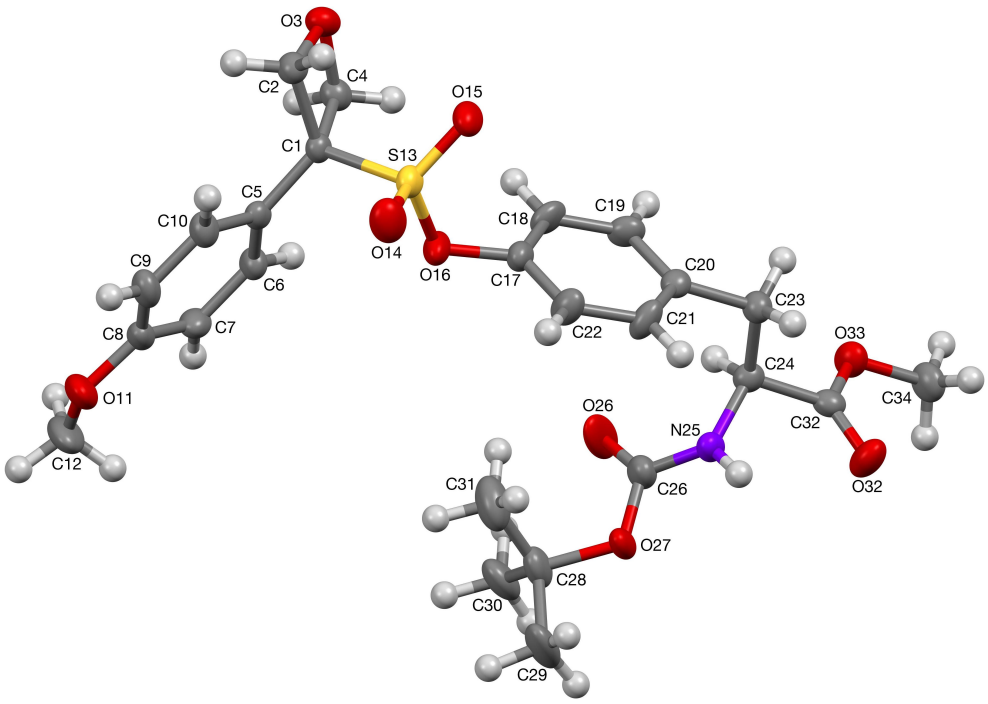


Fig. S45 X-Ray crystal structure of **89** (50% probability ellipsoids).

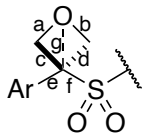
Crystal data for **89**: $C_{25}H_{31}NO_9S$, M = 521.57, monoclinic, $P2_1$ (no. 4), a = 11.8400(7), b = 5.9755(3), c = 18.9619(9) Å, β = 107.631(6)°, V = 1278.53(12) Å^3, Z = 2, D_c = 1.355 g cm^{-3}, μ(Mo-Kα) = 0.180 mm^{-1}, T = 173 K, colorless needles, Agilent Xcalibur 3 E diffractometer; 3877 independent measured reflections (R_{int} = 0.0179), F^2 refinement,[X1,X2] R_1(obs) = 0.0380, wR_2(all) = 0.0860 (R_1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 3353 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], completeness to θ_{full}(25.2°) = 98.5% {completeness to 0.84 Å resolution}], 361 parameters. CCDC 2094795.

The C26-based CO_2tBu (Boc) group in the structure of **89** was found to be disordered. Two orientations were identified of *ca*. 55 and 45% occupancy, their geometries were optimised, the thermal parameters of adjacent atoms were restrained to be similar, and only the non-hydrogen atoms of the major occupancy orientation were refined anisotropically (those of the minor occupancy orientation were refined isotropically). The N25–H hydrogen atom in the structure of **89** was located from a ΔF map and refined freely subject to an N–H distance constraint of 0.90 Å.

The structure of **89** was expected to be enantiomerically pure with a known chiral center, so Friedel opposites were not deliberately collected as part of the diffraction experiment. Despite this, the Flack parameter calculated using the data that was collected was still clear enough to determine the absolute structure [x = 0.06(6)]. This observation accounts for the B-level alert observed on compound **89**.

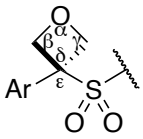
Most relevant bond lengths and angles:

Bond lengths



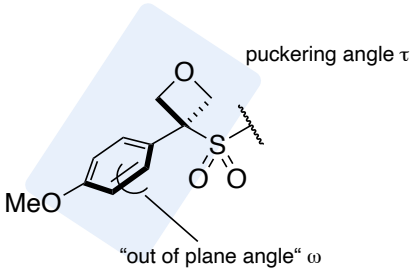
a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.45 Å
c = C(1)–C(2) = 1.55 Å
d = C(1)–C(4) = 1.54 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–S(13) = 1.80 Å
g[a] = C(1)–O(3) = 2.14 Å

Bond angles



α = C(2)–O(3)–C(4) = 91.4 °
β = O(3)–C(2)–C(1) = 91.2 °
γ = O(3)–C(4)–C(1) = 91.7 °
δ = C(2)–C(1)–C(4) = 84.4 °
ε = C(5)–C(1)–S(13) = 111.6 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 12.2 °
ω = O(3)–C(1)–C(5)–C(6) = 88.0 °

Fig. S46 Most relevant bond lengths and angles in the crystal structure of **89**. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

X-Ray crystal structure of phenyl 3-phenyloxetane-3-sulfonate (93)

Crystals suitable for X-ray analysis were grown by slow evaporation from acetone at 25 °C.

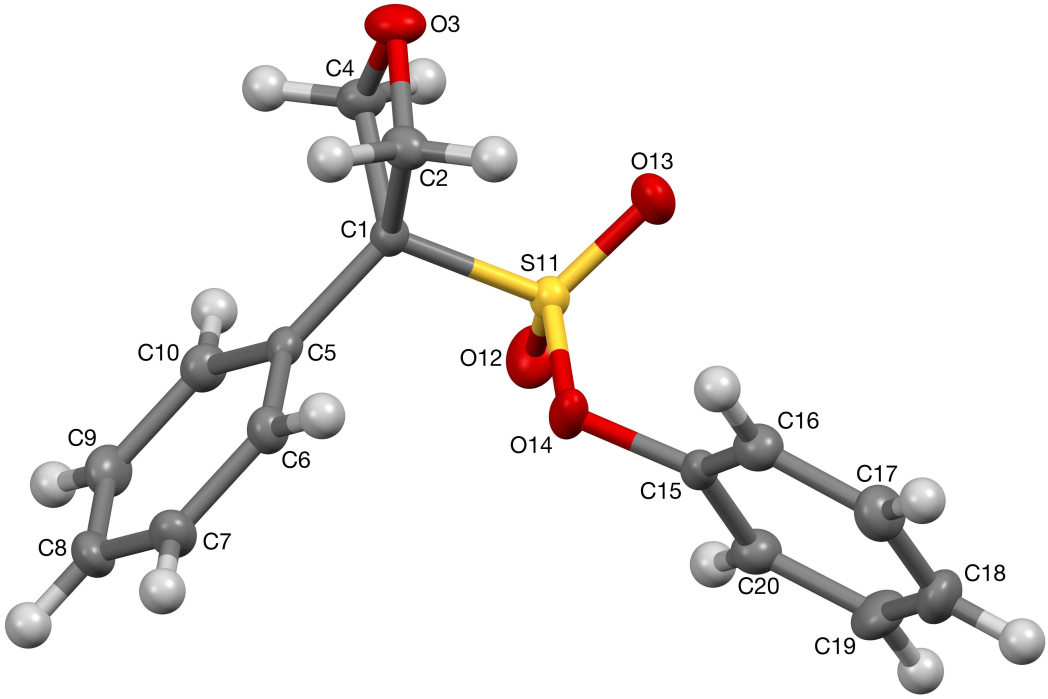
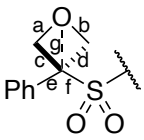


Fig. S47 X-Ray crystal structure of **93** (50% probability ellipsoids).

Crystal data for **93**: $C_{15}H_{14}O_4S$, M = 290.32, monoclinic, $P2_1/n$ (no. 14), a = 14.3671(3), b = 5.83868(13), c = 16.5636(4) Å, β = 105.604(3)°, V = 1338.22(6) Å^3, Z = 4, D_c = 1.441 g cm^{-3}, μ(Mo-Kα) = 0.252 mm^{-1}, T = 173 K, colorless blocks, Agilent Xcalibur 3 E diffractometer; 2989 independent measured reflections (R_{int} = 0.0265), F^2 refinement,[X1,X2] R_1(obs) = 0.0320, wR_2(all) = 0.0825 ($R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 2644 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], completeness to θ_{full}(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 182 parameters. CCDC 2094796.

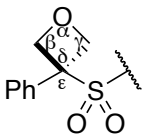
Most relevant bond lengths and angles:

Bond lengths



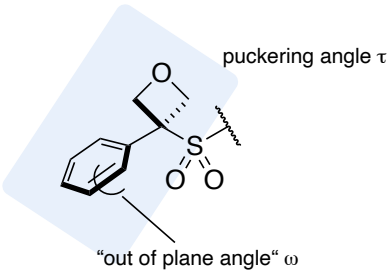
a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.45 Å
c = C(1)–C(2) = 1.54 Å
d = C(1)–C(4) = 1.55 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–S(11) = 1.79 Å
g[a] = C(1)–O(3) = 2.14 Å

Bond angles



α = C(2)–O(3)–C(4) = 92.0 °
β = O(3)–C(2)–C(1) = 91.2 °
γ = O(3)–C(4)–C(1) = 91.3 °
δ = C(2)–C(1)–C(4) = 84.6 °
ε = C(5)–C(1)–S(11) = 110.8 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 10.2 °
ω = O(3)–C(1)–C(5)–C(10) = 86.9 °

Fig. S48 Most relevant bond lengths and angles in the crystal structure of **93**. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

Oxetane Ether 50

X-Ray crystal structure of 3-(4-methoxyphenyl)-3-phenoxyoxetane (50)

Crystals suitable for X-ray analysis were grown by slow evaporation from acetone at 25 °C.

The structure of **50** was found to contain three crystallographically independent molecules (**50-A**, **50-B**, and **50-C**) in the asymmetric unit, with rotated methoxy motif.

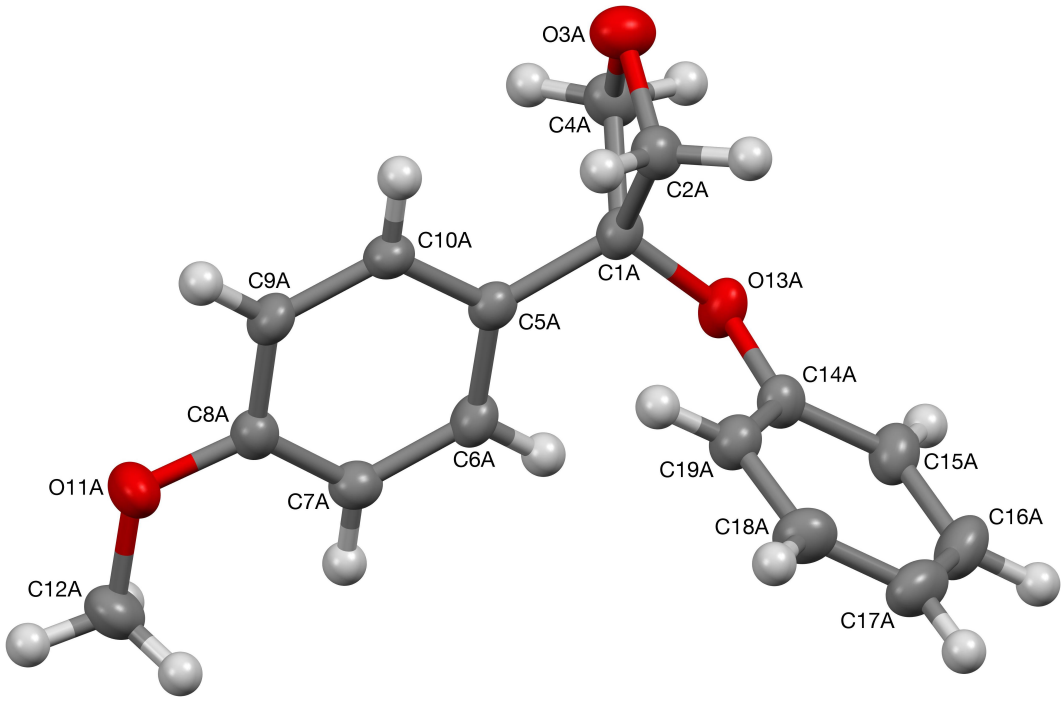


Fig. S49 The structure of **50-A**, one of the three independent molecules present in the crystal of **50** (50% probability ellipsoids).

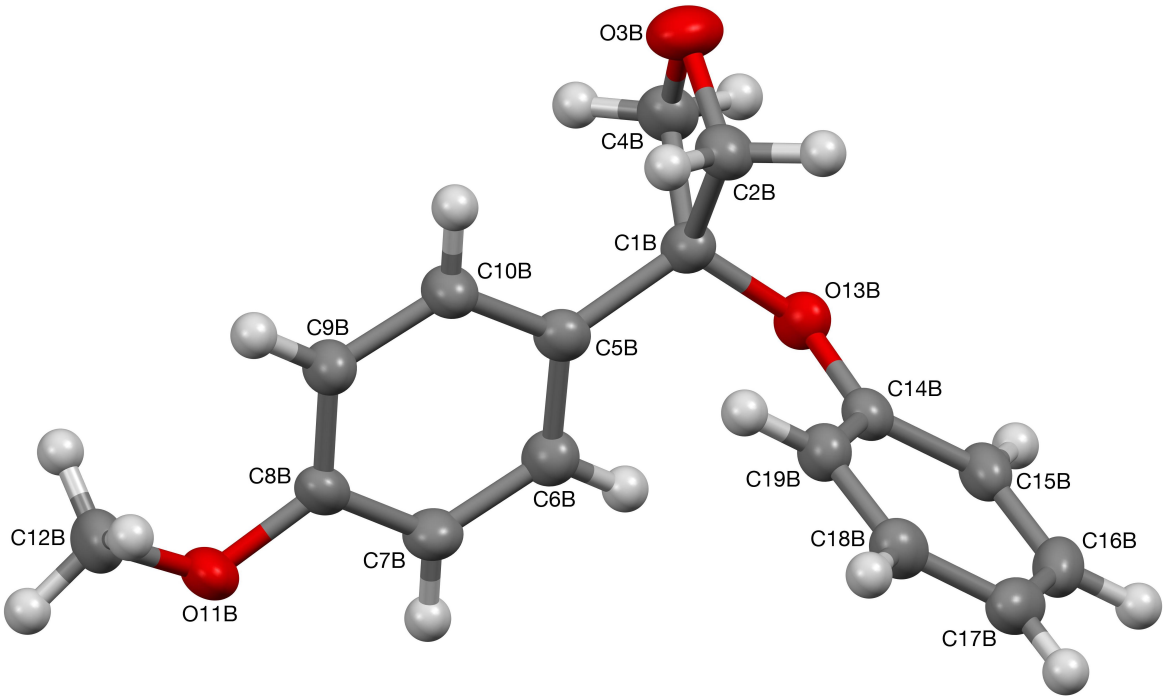


Fig. S50 The structure of **50-B**, one of the three independent molecules present in the crystal of **50** (50% probability ellipsoids).

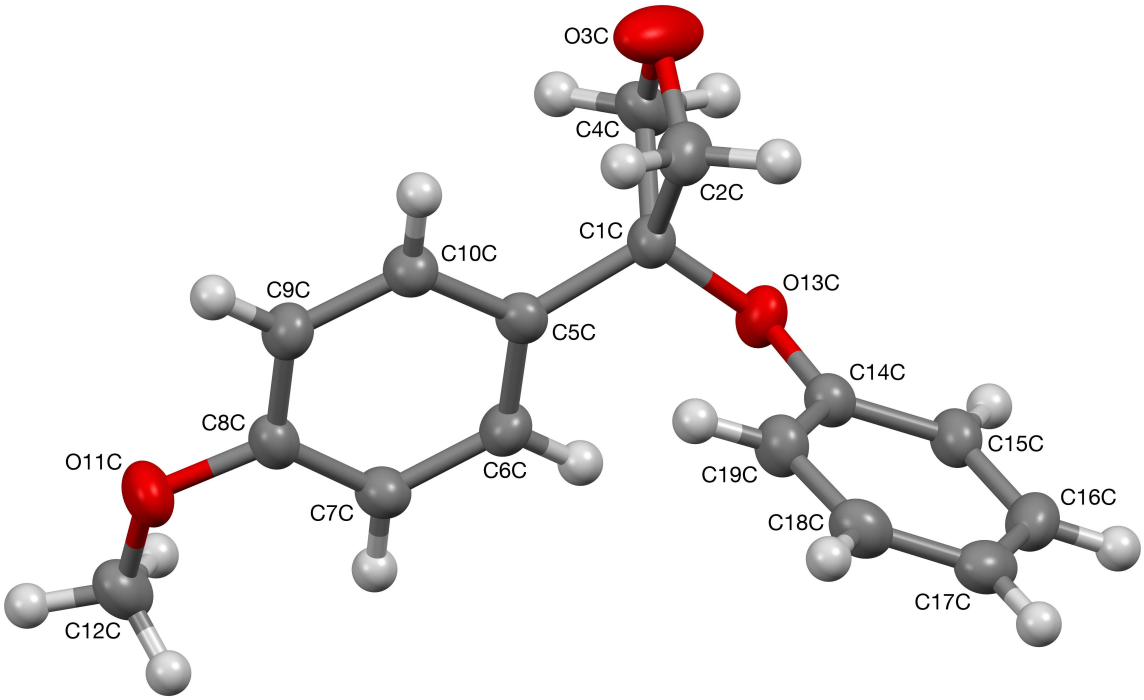
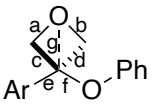


Fig. S51 The structure of **50-C**, one of the three independent molecules present in the crystal of **50** (50% probability ellipsoids).

Crystal data for **50**: $C_{16}H_{16}O_3$, M = 256.29, monoclinic, $P2_1/c$ (no. 14), a = 17.7895(6), b = 5.67825(19), c = 39.7922(13) Å, β = 100.936(3)°, V = 3946.5(2) Å^3, Z = 12 [3 independent molecules], D_c = 1.294 g cm^{-3}, μ(Cu-Kα) = 0.718 mm^{-1}, T = 173 K, colorless needles, Agilent Xcalibur 3 PX Ultra A diffractometer; 7536 independent measured reflections (R_{int} = 0.0394), F^2 refinement,[X1,X2] R_1(obs) = 0.0486, wR_2(all) = 0.1314 ($R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 4957 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], completeness to θ_{full}(25.2°) = 98.5% {completeness to 0.84 Å resolution}], 518 parameters. CCDC 2094793.

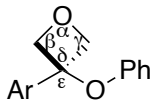
Most relevant bond lengths and angles:

Bond lengths



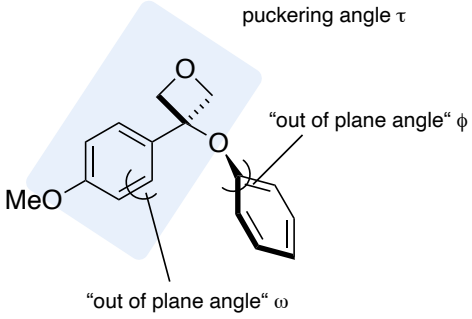
a = C(2)–O(3) = 1.45 Å
b = C(4)–O(3) = 1.44 Å
c = C(1)–C(2) = 1.54 Å
d = C(1)–C(4) = 1.54 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–O(13) = 1.43 Å
g[a] = C(1)–O(3) = 2.14 Å

Bond angles



α = C(2)–O(3)–C(4) = 91.5 °
β = O(3)–C(2)–C(1) = 91.4 °
γ = O(3)–C(4)–C(1) = 91.3 °
δ = C(2)–C(1)–C(4) = 84.5 °
ε = C(5)–C(1)–O(13) = 112.9 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 11.8 °
ω = O(3)–C(1)–C(5)–C(10) = 18.8 °
ϕ = O(3)–C(1)–O(13)–C(14) = 71.6 °

Fig. S52 Most relevant bond lengths and angles in the crystal structure of **50**. All values are the average of the three crystallographically independent molecules (**50-A**, **50-B** and **50-C**) in the asymmetric unit. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

Oxetane Sulfonyl Fluorides

Structural Analysis

The relative stability of sulfonyl fluorides is further highlighted by the acquirement crystal structures. The following properties are worthy of note:

1. The conformation of the *p*-methoxy substituent in trimethoxy OSF **54** differs significantly from that observed in the crystal structure of OSF **1** (see pages S32–S33 for details).
2. The sulfur center is significantly congested in the crystal structures of all sulfonyl fluorides, which could provide an explanation for the inability of oxetane sulfonyl fluorides to undergo sulfur fluoride exchange with amine nucleophiles.

X-Ray crystal structure of 3-(4-methoxyphenyl)oxetane-3-sulfonyl fluoride (1)

Crystals suitable for X-ray analysis were grown by slow evaporation from acetone at 25 °C.

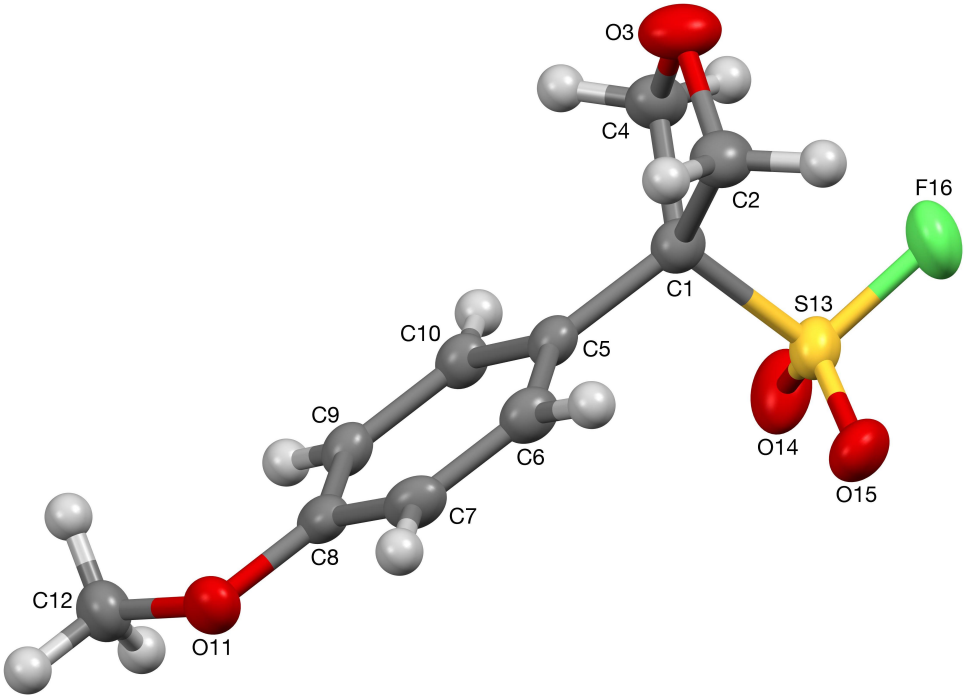
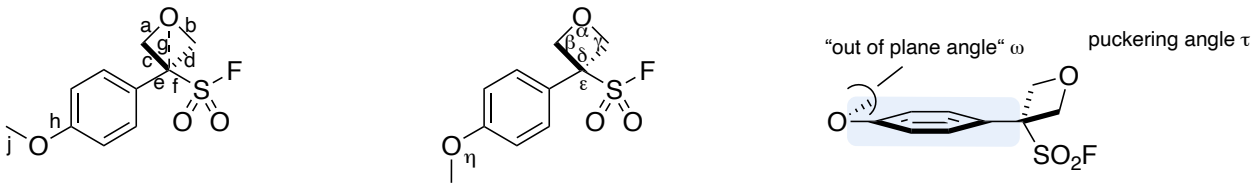


Fig. S53 X-Ray crystal structure of **1** (50% probability ellipsoids).

Crystal data for **1**: $C_{10}H_{11}FO_4S$, M = 246.25, orthorhombic, *Pbca* (no. 61), a = 9.78831(19), b = 7.45856(15), c = 28.6249(5) Å, V = 2089.81(7) Å^3, Z = 8, D_c = 1.565 g cm^{-3}, μ(Cu-Kα) = 2.906 mm^{-1}, T = 173 K, colorless platy shards, Agilent Xcalibur PX Ultra A diffractometer; 2095 independent measured reflections (R_{int} = 0.0524), F^2 refinement,[X1,X2] R_1(obs) = 0.0356, wR_2(all) = 0.0951 (R_1 = Σ||F_o| – |F_c||/Σ|F_o|; wR_2 = {Σ[w(F_o^2 – F_c^2)^2] / Σ[w(F_o^2)^2]}$^{1/2}$; w^{-1} = σ^2(F_o^2) + (aP)^2 + bP), 1771 independent observed absorption-corrected reflections [|F_o| > 4σ(|F_o|), completeness to θ_{full}(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 146 parameters. CCDC 2094791.

Most relevant bond lengths and angles:

Bond lengths ***Bond angles*** ***Torsion angles***



a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.44 Å
c = C(1)–C(2) = 1.55 Å
d = C(1)–C(4) = 1.55 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–S(13) = 1.78 Å
g[a] = C(1)–O(3) = 2.13 Å
h = C(8)–O(11) = 1.367 Å
j = C(12)–O(11) = 1.43 Å

α = C(2)–O(3)–C(4) = 92.8 °
β = O(3)–C(2)–C(1) = 90.7 °
γ = O(3)–C(4)–C(1) = 90.7 °
δ = C(2)–C(1)–C(4) = 84.7 °
ε = C(5)–C(1)–S(13) = 106.7 °
η = C(12)–O(11)–C(8) = 117.9 °

τ = O(3)–C(2)–C(4)–C(1) = 10.7 °
ω = C(12)–O(11)–C(8)–C(9) = 8.4 °

Fig. S54 Most relevant bond lengths and angles in the crystal structure of **1**. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

X-Ray crystal structure of 3-(3,4,5-trimethoxyphenyl)oxetane-3-sulfonyl fluoride (54)

Crystals suitable for X-ray analysis were grown by slow evaporation from $CDCl_3$ at 25 °C.

The structure of **54** was found to contain four crystallographically independent molecules (**54-A**, **54-B**, **54-C**, and **54-D**) in the asymmetric unit, with rotated sulfonyl fluoride motif.

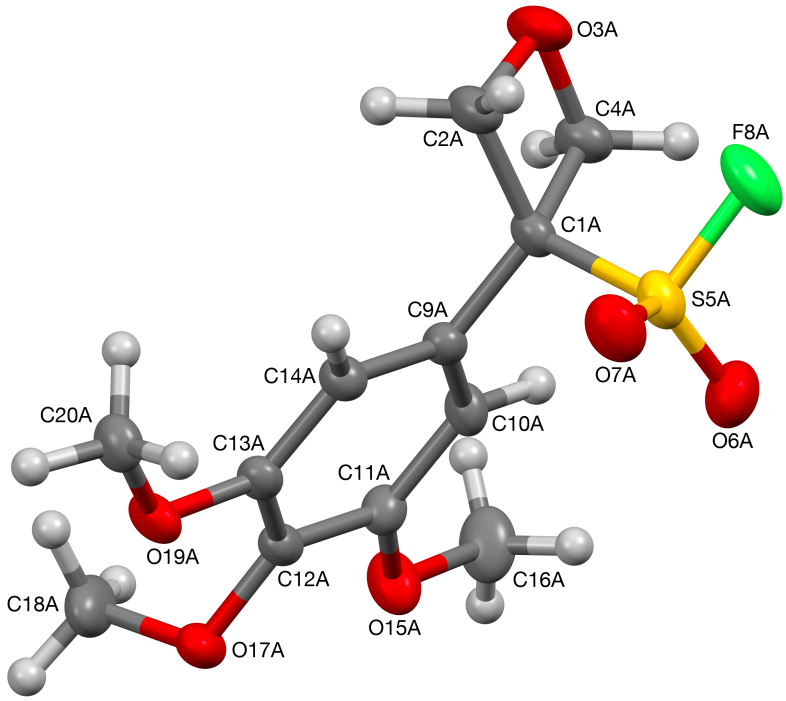


Fig. S55 The structure of **54-A**, one of the four independent molecules present in the crystal of **54** (50% probability ellipsoids).

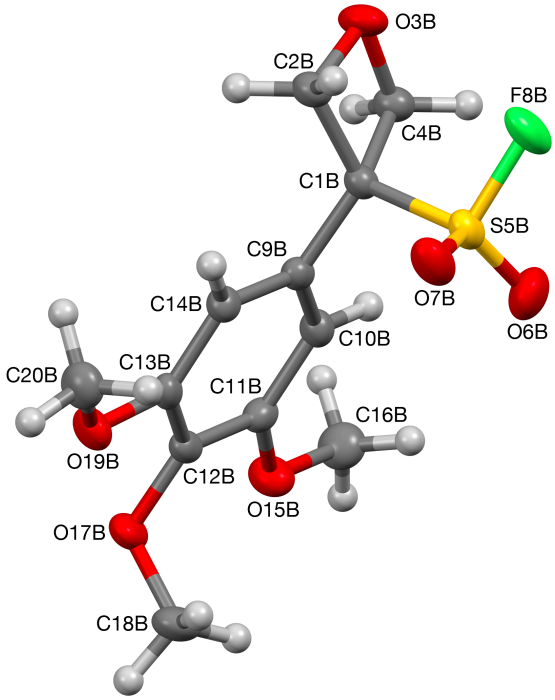


Fig. S56 The structure of **54-B**, one of the four independent molecules present in the crystal of **54** (50% probability ellipsoids).

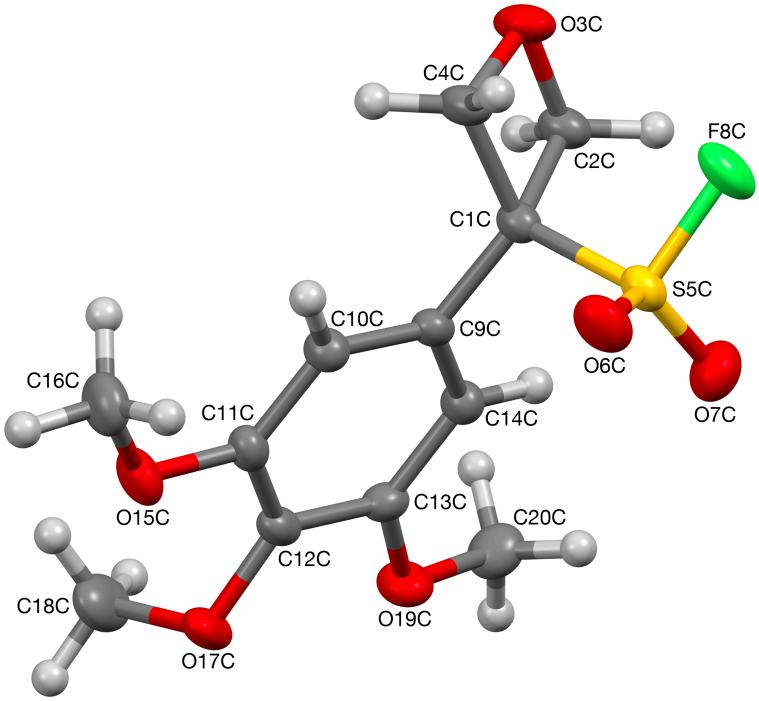


Fig. S57 The structure of **54-C**, one of the four independent molecules present in the crystal of **54** (50% probability ellipsoids).

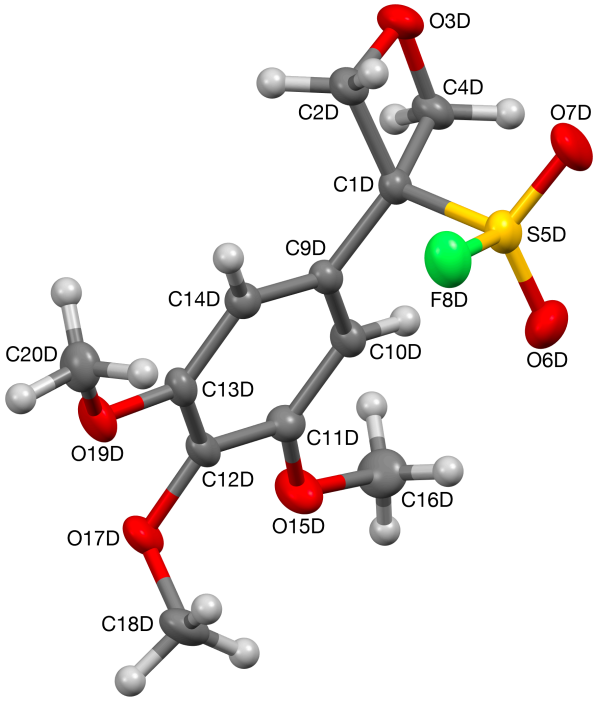
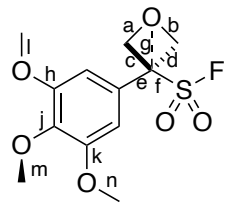


Fig. S58 The structure of **54-D**, one of the four independent molecules present in the crystal of **54** (50% probability ellipsoids).

Crystal data for **54**: $C_{12}H_{15}FO_6S$, M = 306.30, monoclinic, $P2_1/n$ (no. 14), a = 10.5165(3), b = 14.3316(3), c = 36.4326(9) Å, β = 97.233(2)°, V = 5447.4(2) Å^3, Z = 16 [4 independent molecules], D_c = 1.494 g cm^{-3}, μ(Mo-Kα) = 0.272 mm^{-1}, T = 173 K, colorless blocky needles, Agilent Xcalibur 3 E diffractometer; 11525 independent measured reflections (R_{int} = 0.0311), F^2 refinement,[X1,X2] R_1(obs) = 0.0423, wR_2(all) = 0.1047 (R_1 = Σ||F_o| – |F_c||/Σ|F_o|; wR_2 = {Σ[w(F_o^2 – F_c^2)^2] / Σ[w(F_o^2)^2]}$^{1/2}$; w^{-1} = σ^2(F_o^2) + (aP)^2 + bP), 8860 independent observed absorption-corrected reflections [|F_o| > 4σ(|F_o|), completeness to θ$_{full}$(25.2°) = 99.7% {completeness to 0.84 Å resolution}], 734 parameters. CCDC 2049754.

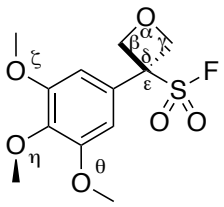
Most relevant bond lengths and angles:

Bond lengths



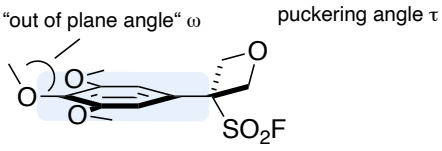
a = C(2)–O(3) = 1.45 Å
b = C(4)–O(3) = 1.44 Å
c = C(1)–C(2) = 1.55 Å
d = C(1)–C(4) = 1.55 Å
e = C(1)–C(9) = 1.51 Å
f = C(1)–S(5) = 1.79 Å
g[a] = C(1)–O(3) = 2.14 Å
h = C(13)–O(19) = 1.362 Å
j = C(12)–O(17) = 1.374 Å
k = C(11)–O(15) = 1.365 Å
l = O(19)–C(20) = 1.42 Å
m = O(17)–C(18) = 1.43 Å
n = O(15)–C(16) = 1.42 Å

Bond angles



α = C(2)–O(3)–C(4) = 92.0 °
β = O(3)–C(2)–C(1) = 91.1 °
γ = O(3)–C(4)–C(1) = 91.3 °
δ = C(2)–C(1)–C(4) = 84.3 °
ε = C(9)–C(1)–S(5) = 107.5 °
ζ = C(13)–O(19)–C(20) = 117.6 °
η = C(12)–O(17)–C(18) = 112.8 °
θ = C(11)–O(15)–C(16) = 118.2 °

Torsion angles



τ = O(3)–C(2)–C(4)–C(1) = 11.4 °
ω = C(18)–O(17)–C(12)–C(13) = 86.8 °

Fig. S59 Most relevant bond lengths and angles in the crystal structure of **54**. All values are the average of the four crystallographically independent molecules (**54-A**, **54-B**, **54-C**, and **54-D**) in the asymmetric unit. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

X-Ray crystal structure of 3-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)oxetane-3-sulfonyl fluoride (56)

Crystals suitable for X-ray analysis were grown by slow evaporation from CH_2Cl_2 at 25 °C.

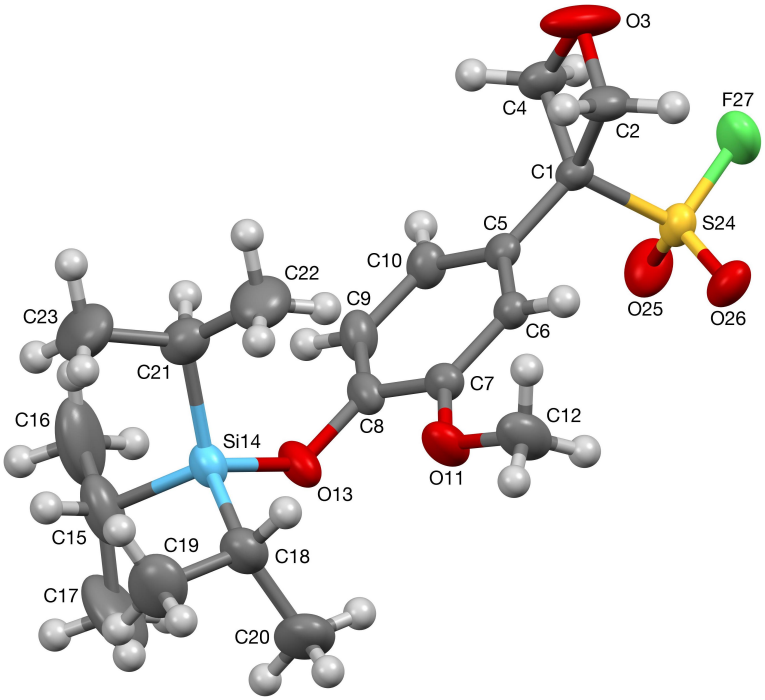


Fig. S60 X-Ray crystal structure of **56** (50% probability ellipsoids).

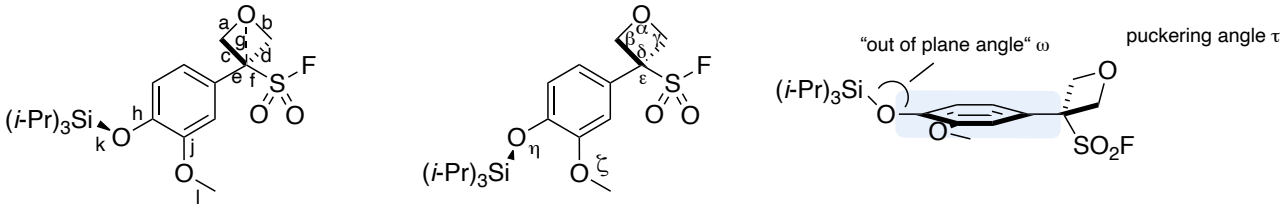
Crystal data for **56**: $C_{19}H_{31}FO_4SSi$, M = 418.59, orthorhombic, *Pbca* (no. 61), a = 10.1479(4), b = 12.1911(5), c = 35.6650(15) Å, V = 4412.3(3) Å^3, Z = 8, D_c = 1.260 g cm^{-3}, μ(Mo-Kα) = 0.235 mm^{-1}, T = 173 K, colorless needles, Agilent Xcalibur 3 E diffractometer; 4921 independent measured reflections (R_{int} = 0.0500), F^2 refinement,[X1,X2] R_1(obs) = 0.0582, wR_2(all) = 0.1373 (R_1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 3559 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, completeness to θ_{full}(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 282 parameters. CCDC 2094794.

The Si14-based Si(*i*-Pr)$_3$ unit in the structure of **56** was found to be disordered. Two orientations for the three *i*-Pr units were identified of *ca*. 83 and 17% occupancy, their geometries were optimised, the thermal parameters of adjacent atoms were restrained to be similar, and only the non-hydrogen atoms of the major occupancy orientation were refined anisotropically (those of the minor occupancy orientation were refined isotropically).

A slight lengthening of the S24–O25 bond in the structure of **56**, slight shortening of the S–F bond and noticeable Hirshfeld differences for the S24–O25 bond suggest that there may be some oxygen/fluorine positional disorder in this structure. The thermal parameters of the atoms involved are all quite small, however, and modelling this disorder does not lead to substantive overall improvements in the structure, so the ordered model was preferred. This observation accounts for the B-level alert observed on compound **56**.

Most relevant bond lengths and angles:

Bond lengths ***Bond angles*** ***Torsion angles***



a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.43 Å
c = C(1)–C(2) = 1.54 Å
d = C(1)–C(4) = 1.55 Å
e = C(1)–C(5) = 1.50 Å
f = C(1)–S(24) = 1.79 Å
g[a] = C(1)–O(3) = 2.13 Å
h = C(8)–O(13) = 1.37 Å
j = C(7)–O(11) = 1.36 Å
k = Si(14)–O(13) = 1.67 Å
l = C(12)–O(11) = 1.43 Å

α = C(2)–O(3)–C(4) = 92.8 °
β = O(3)–C(2)–C(1) = 90.9 °
γ = O(3)–C(4)–C(1) = 91.3 °
δ = C(2)–C(1)–C(4) = 84.5 °
ε = C(5)–C(1)–S(24) = 106.7 °
η = Si(14)–O(13)–C(8) = 129.5 °
ζ = C(12)–O(11)–C(7) = 117.7 °

τ = O(3)–C(2)–C(4)–C(1) = 7.4 °
ω = Si(14)–O(13)–C(8)–C(9) =77.4 °

Fig. S61 Most relevant bond lengths and angles in the crystal structure of **56**. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

X-Ray crystal structure of 3-phenyloxetane-3-sulfonyl fluoride (92)

Crystals suitable for X-ray analysis were grown by slow evaporation from acetone at 25 °C.

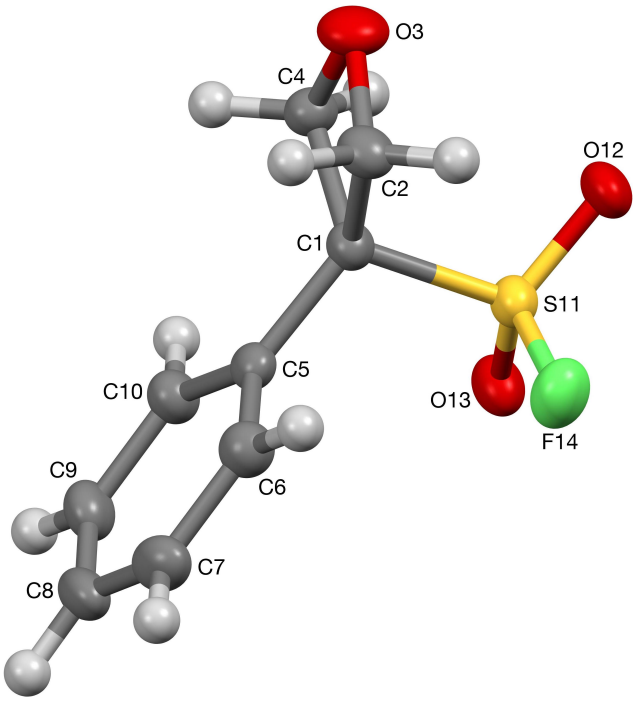


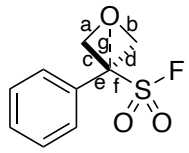
Fig. S62 X-Ray crystal structure of **92** (50% probability ellipsoids).

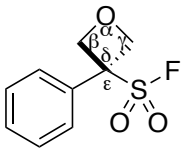
Crystal data for **92**: $C_9H_9FO_3S$, M = 216.22, monoclinic, $P2_1/n$ (no. 14), a = 11.1386(6), b = 7.7611(3), c = 11.4102(5) Å, β = 110.797(5)°, V = 922.12(8) Å^3, Z = 4, D_c = 1.557 g cm^{-3}, μ(Mo-Kα) = 0.343 mm^{-1}, T = 173 K, colorless blocks, Agilent Xcalibur 3 E diffractometer; 2104 independent measured reflections (R_{int} = 0.0441), F^2 refinement,[X1,X2] R_1(obs) = 0.0453, wR_2(all) = 0.1177 (R_1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$), 1639 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], completeness to θ_{full}(25.2°) = 99.9% {completeness to 0.84 Å resolution}], 127 parameters. CCDC 2094871.

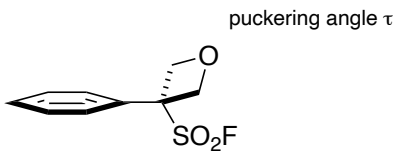
A slight shortening of the S–F bond in the structure of **92** and noticeable Hirshfeld differences for the S11–O13 bond suggest that there may be some oxygen/fluorine positional disorder in this structure. The thermal parameters of the atoms involved are all quite small, however, and modelling this disorder does not lead to substantive overall improvements in the structure, so the ordered model was preferred. This observation accounts for the B-level alert observed on compound **92**.

Most relevant bond lengths and angles:

Bond lengths ***Bond angles*** ***Torsion angles***







a = C(2)–O(3) = 1.44 Å
b = C(4)–O(3) = 1.45 Å
c = C(1)–C(2) = 1.54 Å
d = C(1)–C(4) = 1.54 Å
e = C(1)–C(5) = 1.51 Å
f = C(1)–S(11) = 1.78 Å
g[a] = C(1)–O(3) = 2.14 Å

α = C(2)–O(3)–C(4) = 91.5 °
β = O(3)–C(2)–C(1) = 91.1 °
γ = O(3)–C(4)–C(1) = 91.4 °
δ = C(2)–C(1)–C(4) = 84.1 °
ε = C(5)–C(1)–S(11) = 109.5 °

τ = O(3)–C(2)–C(4)–C(1) = 14.5 °

Fig. S63 Most relevant bond lengths and angles in the crystal structure of **92**. [a]g is the through-space distance between C(1) and O(3) and not a bond length.

References

[X1] SHELXTL v5.1, Bruker AXS, Madison, WI, 1998.

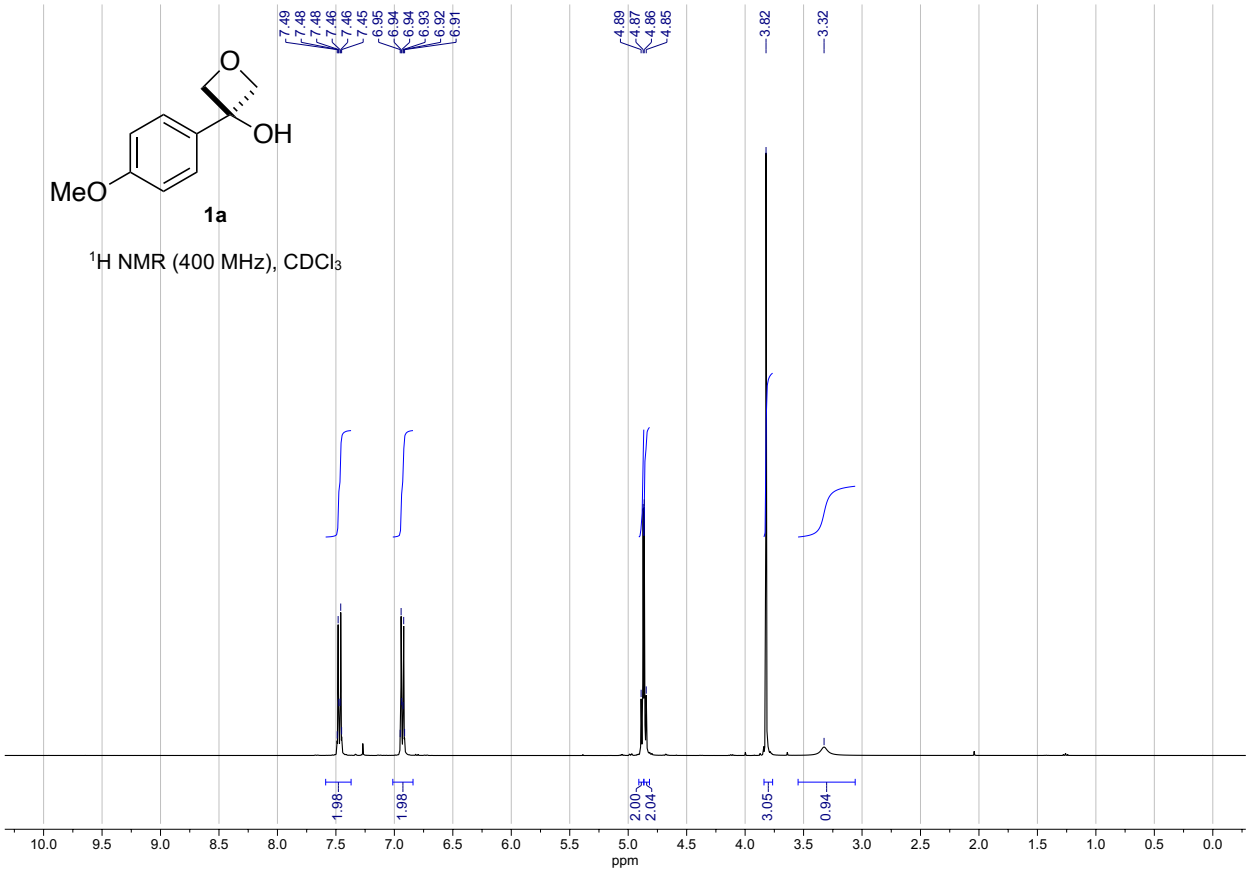
[X2] SHELX-2013, G.M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3-8.

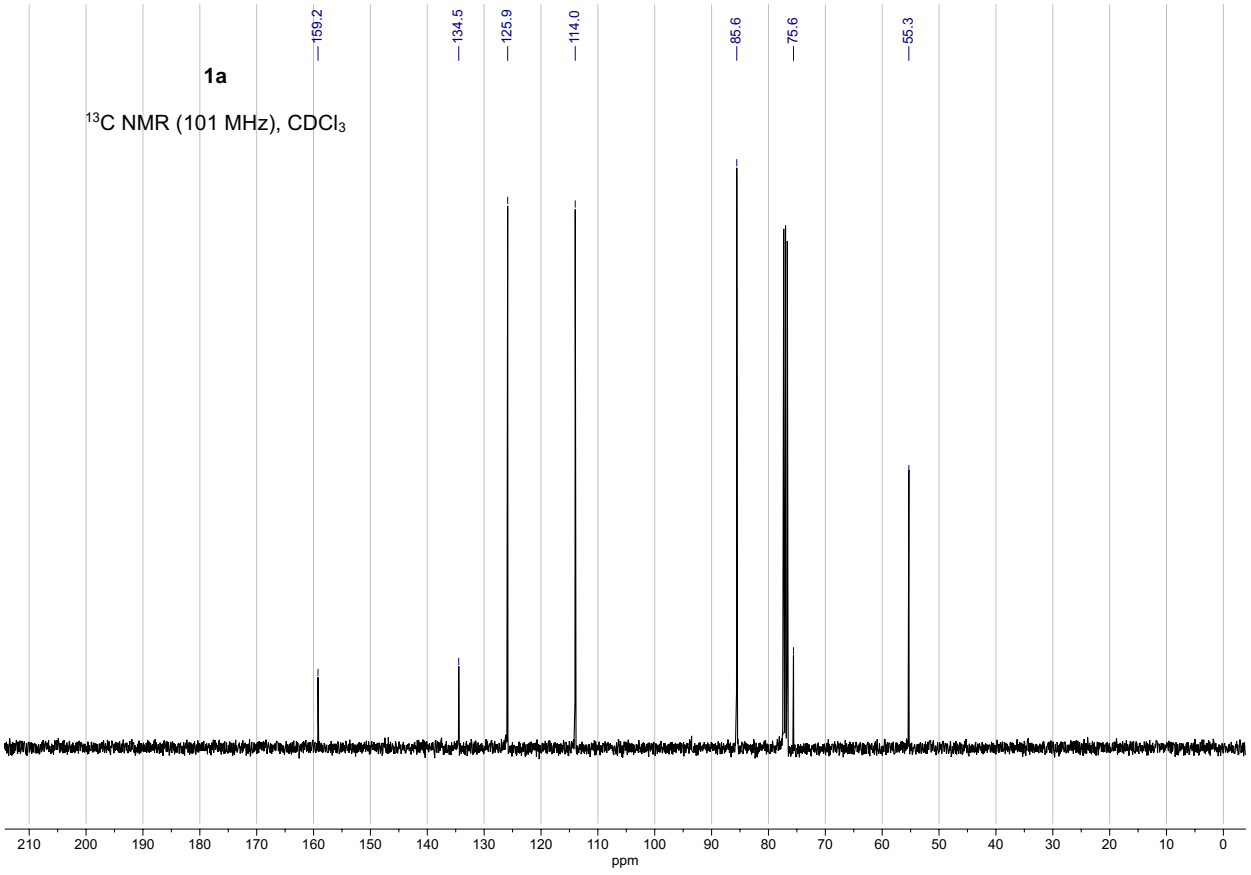
References

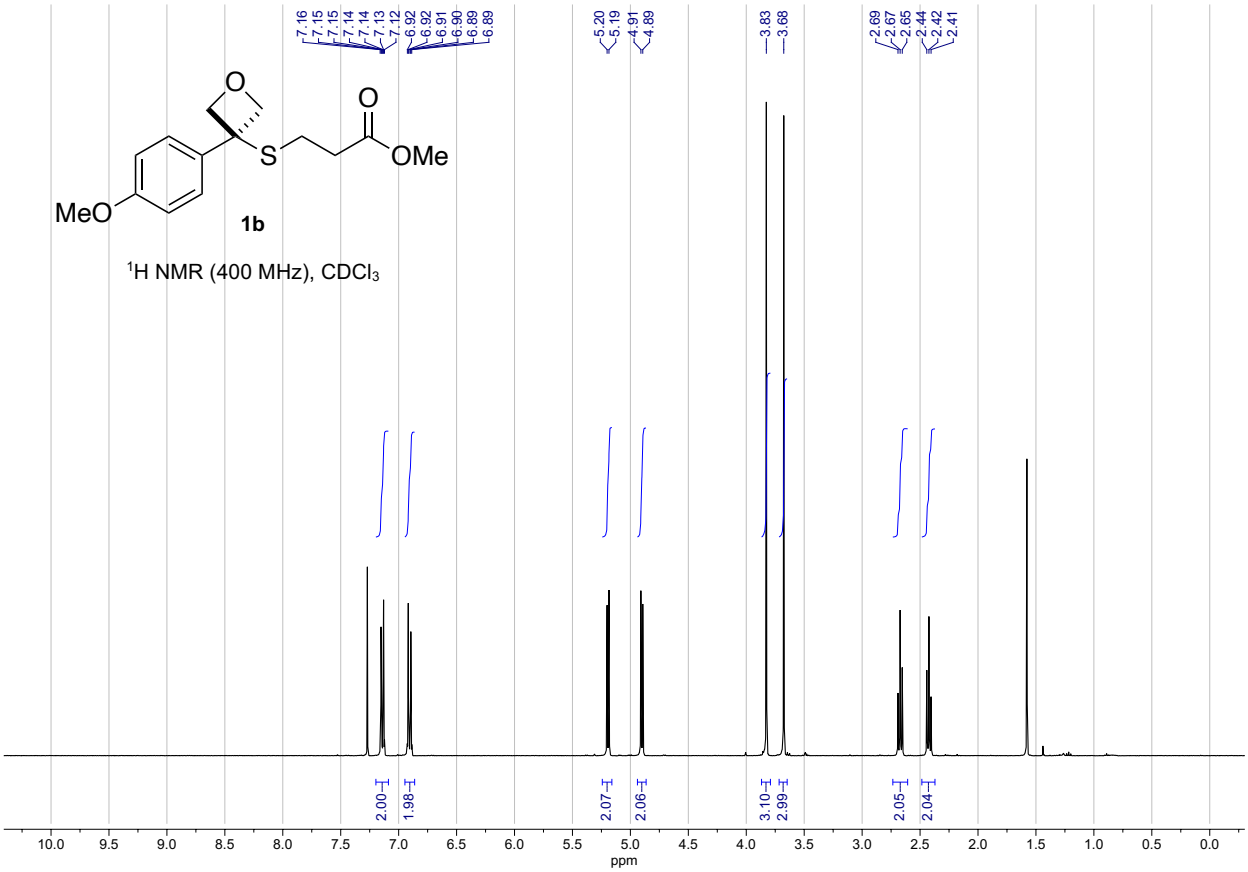
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^{1}H, ^{13}C and ^{19}F NMR Spectra for Selected Compounds

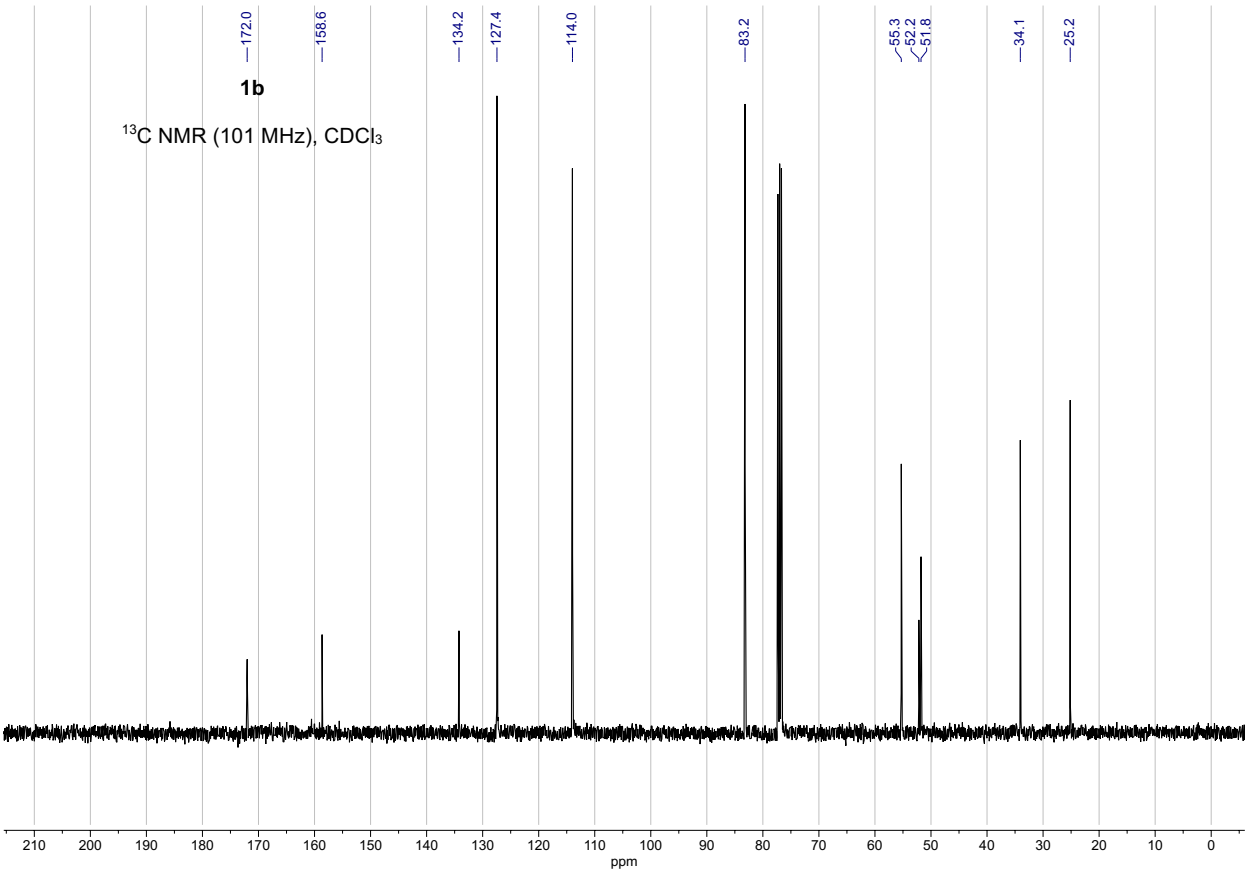

7.49
7.48
7.48
7.46
7.46
7.45
6.95
6.94
6.94
6.93
6.92
6.91
4.89
4.87
4.86
4.85
3.82
3.32
O
OH
MeO
1a
^{1}H NMR (400 MHz), CDCl$_3$
1.98
1.98
2.00
2.04
3.05
0.94
ppm


159.2
134.5
125.9
114.0
85.6
75.6
55.3
1a
^{13}C NMR (101 MHz), CDCl$_3$
ppm



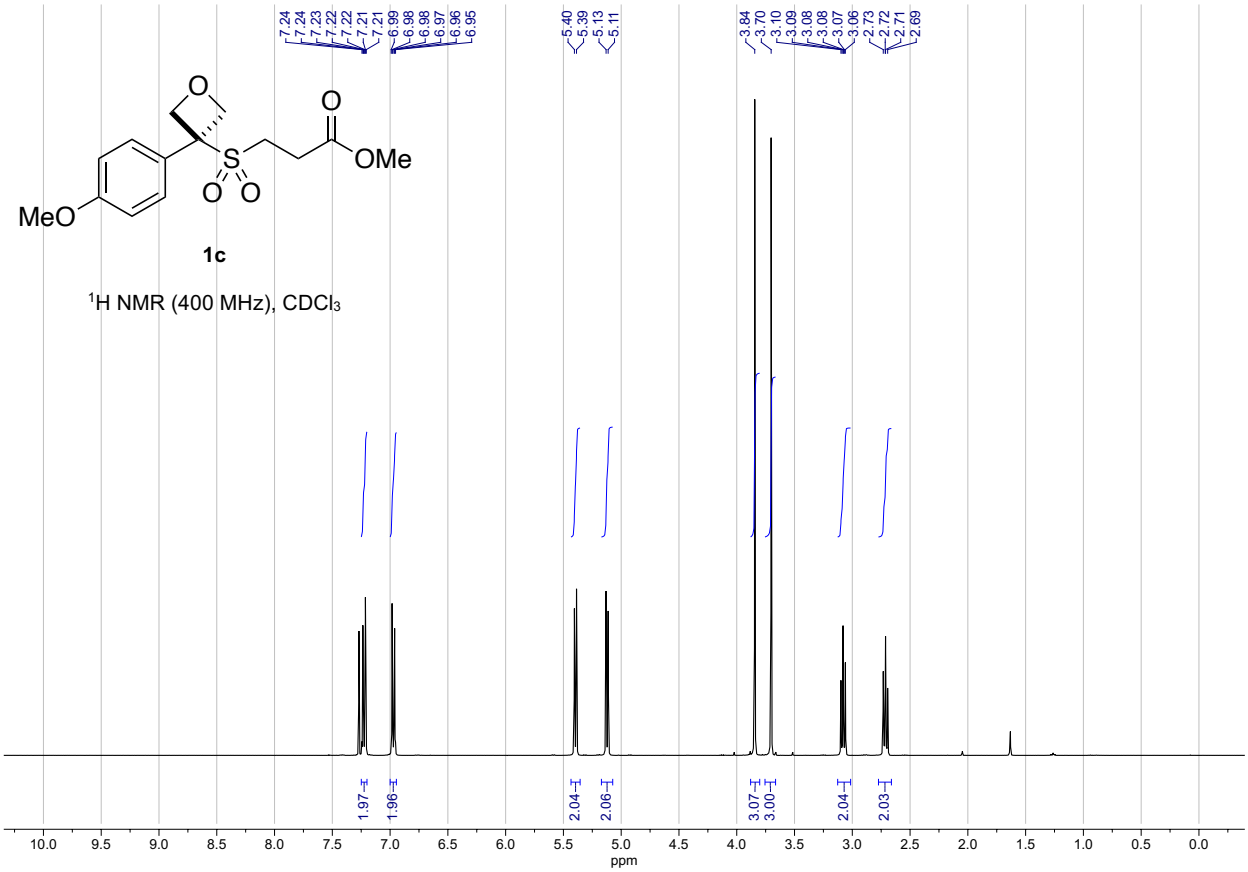
1b

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



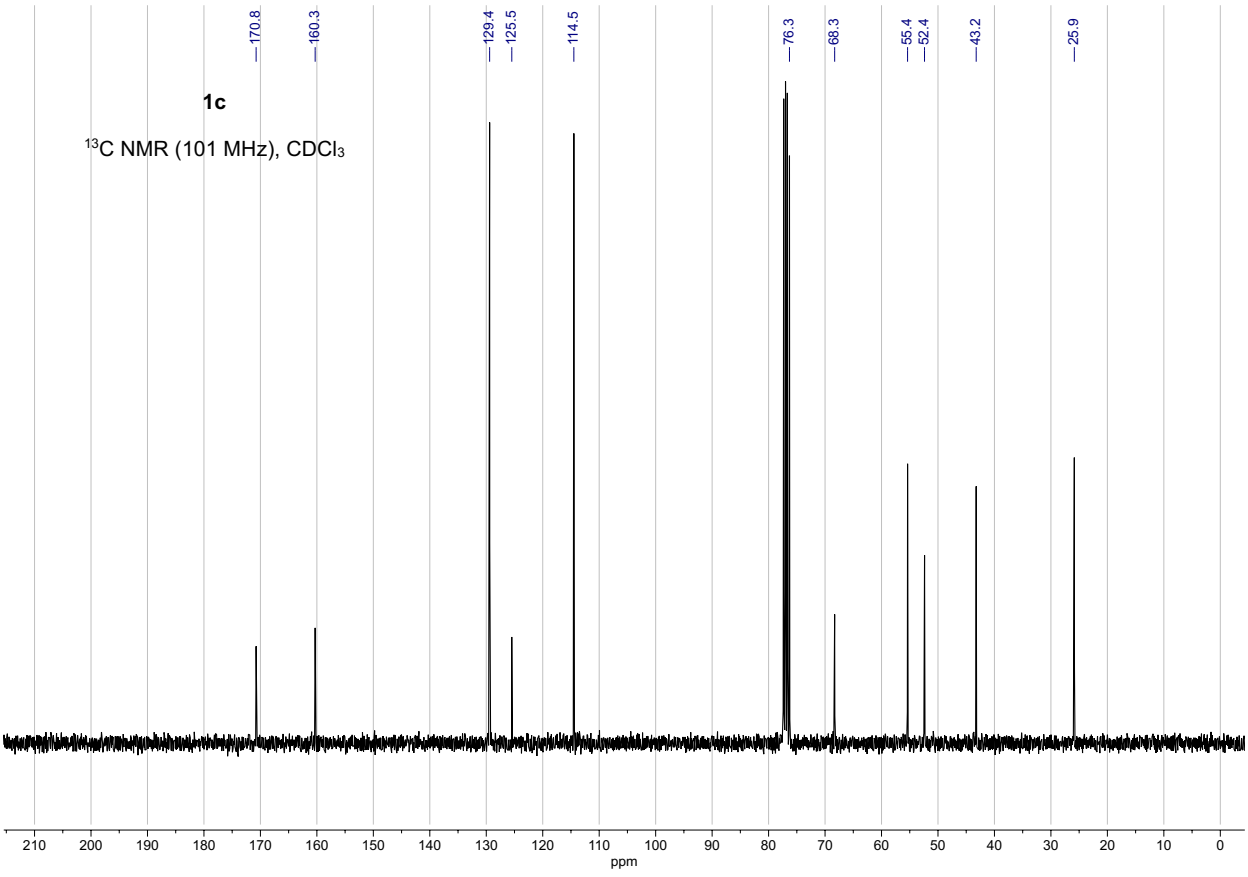
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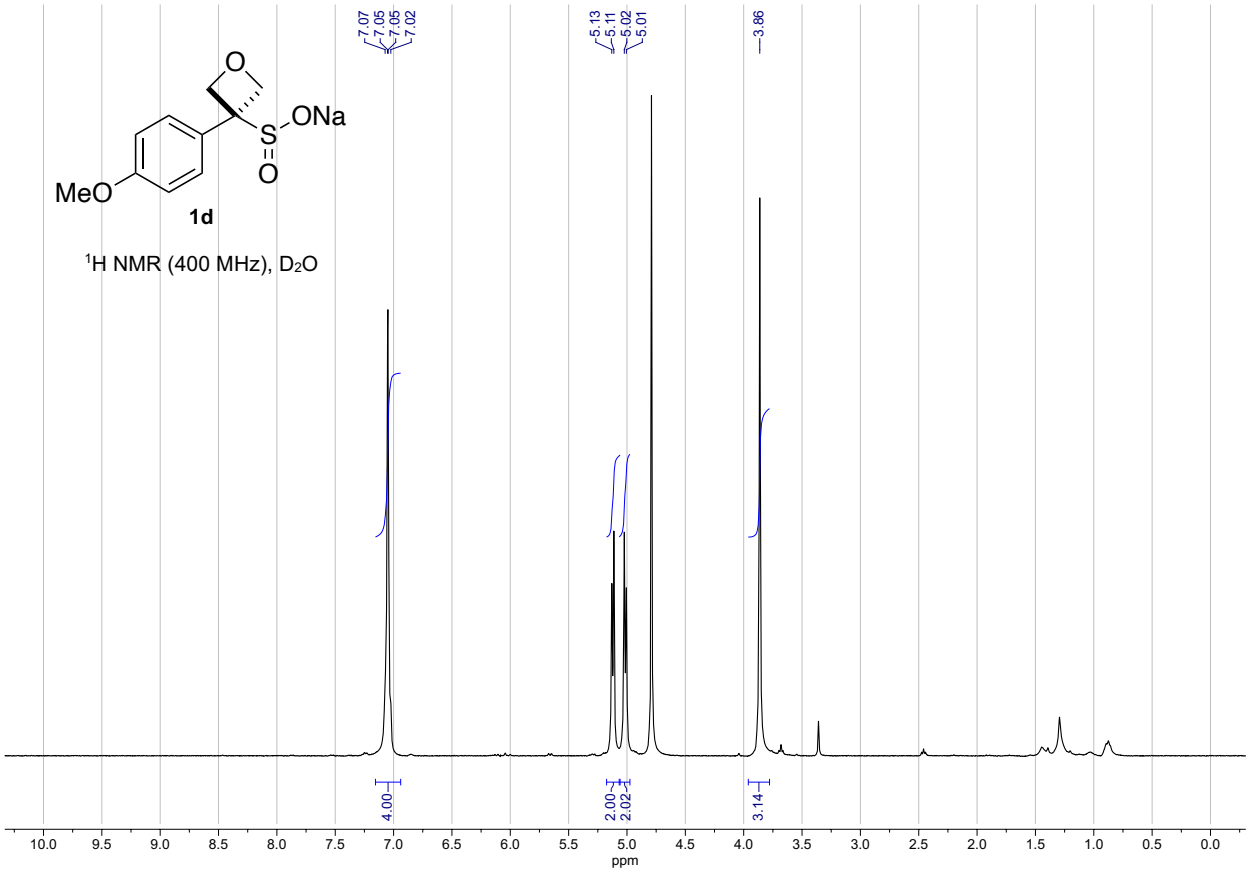
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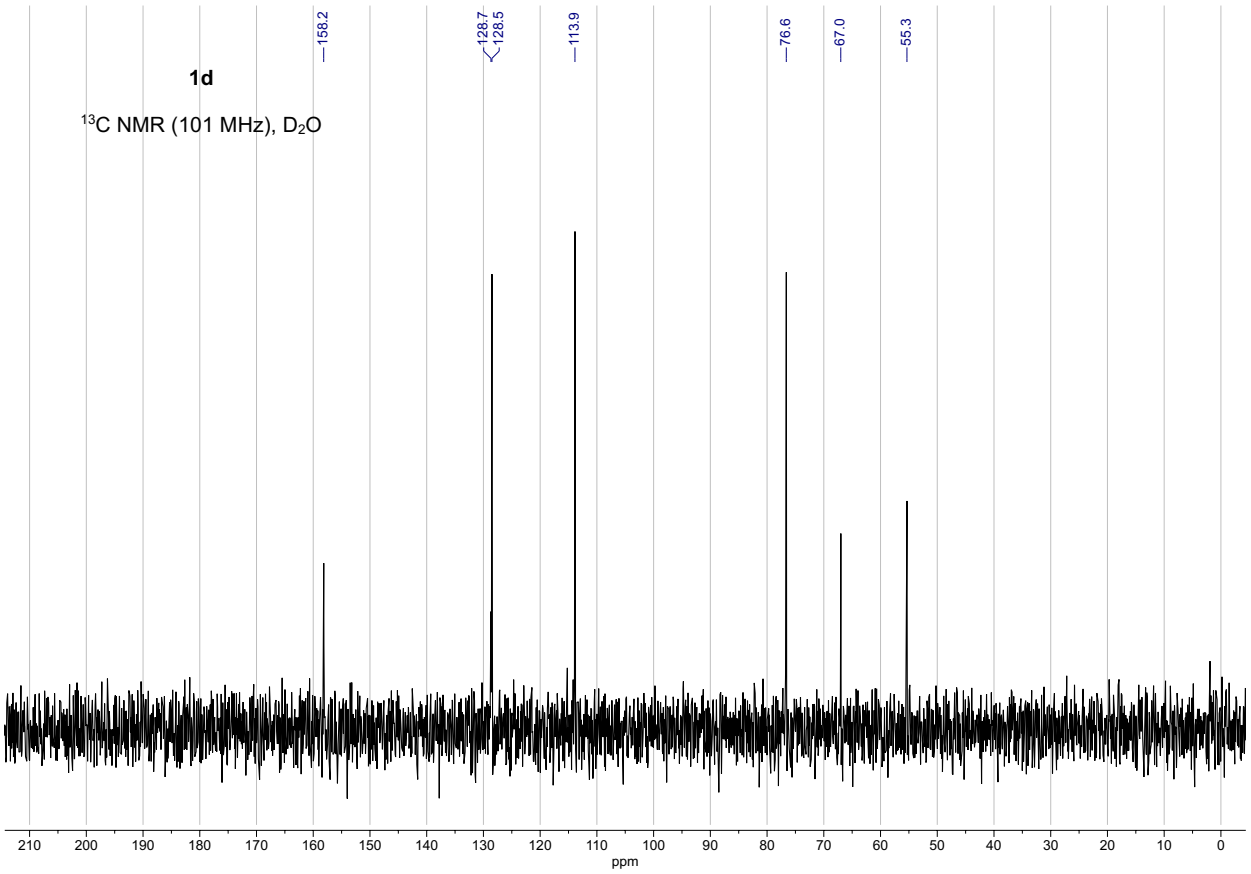
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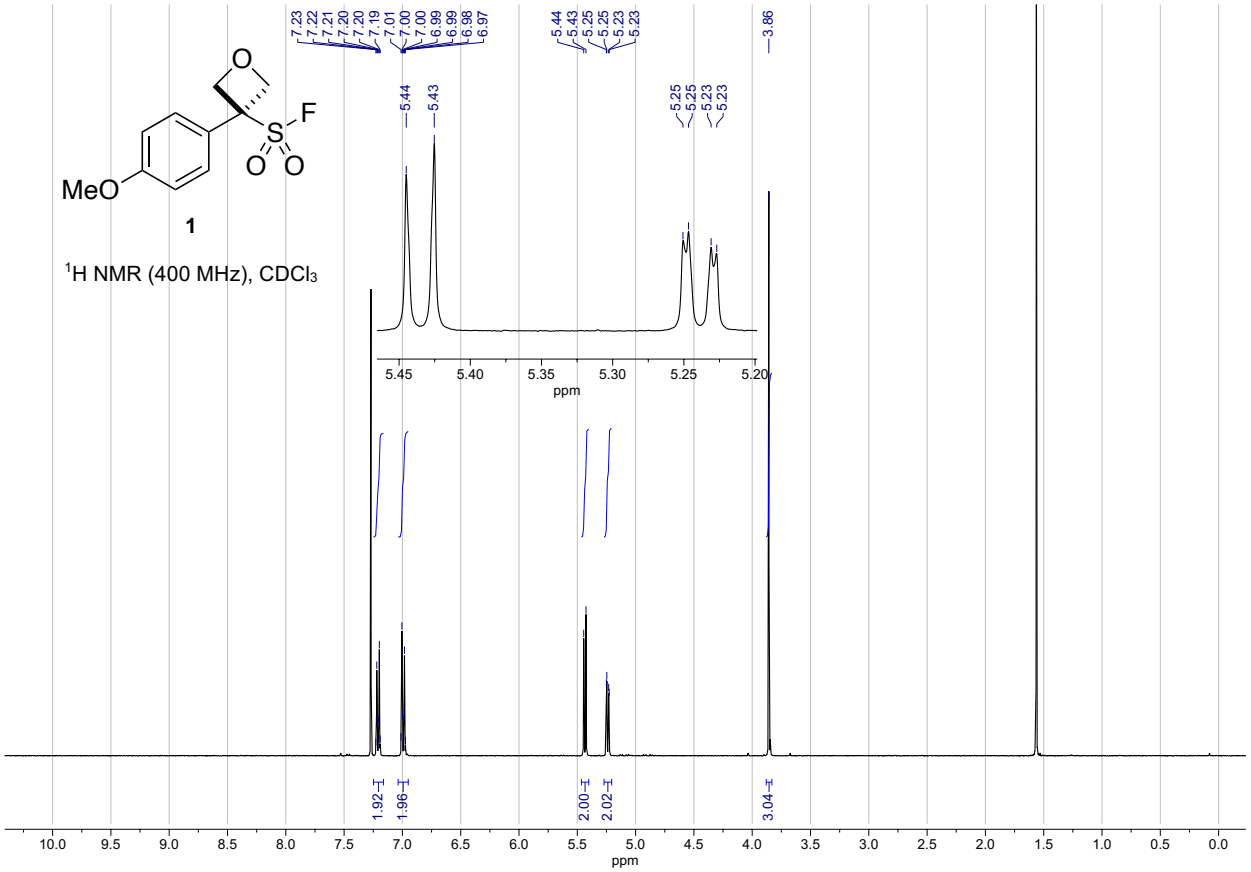
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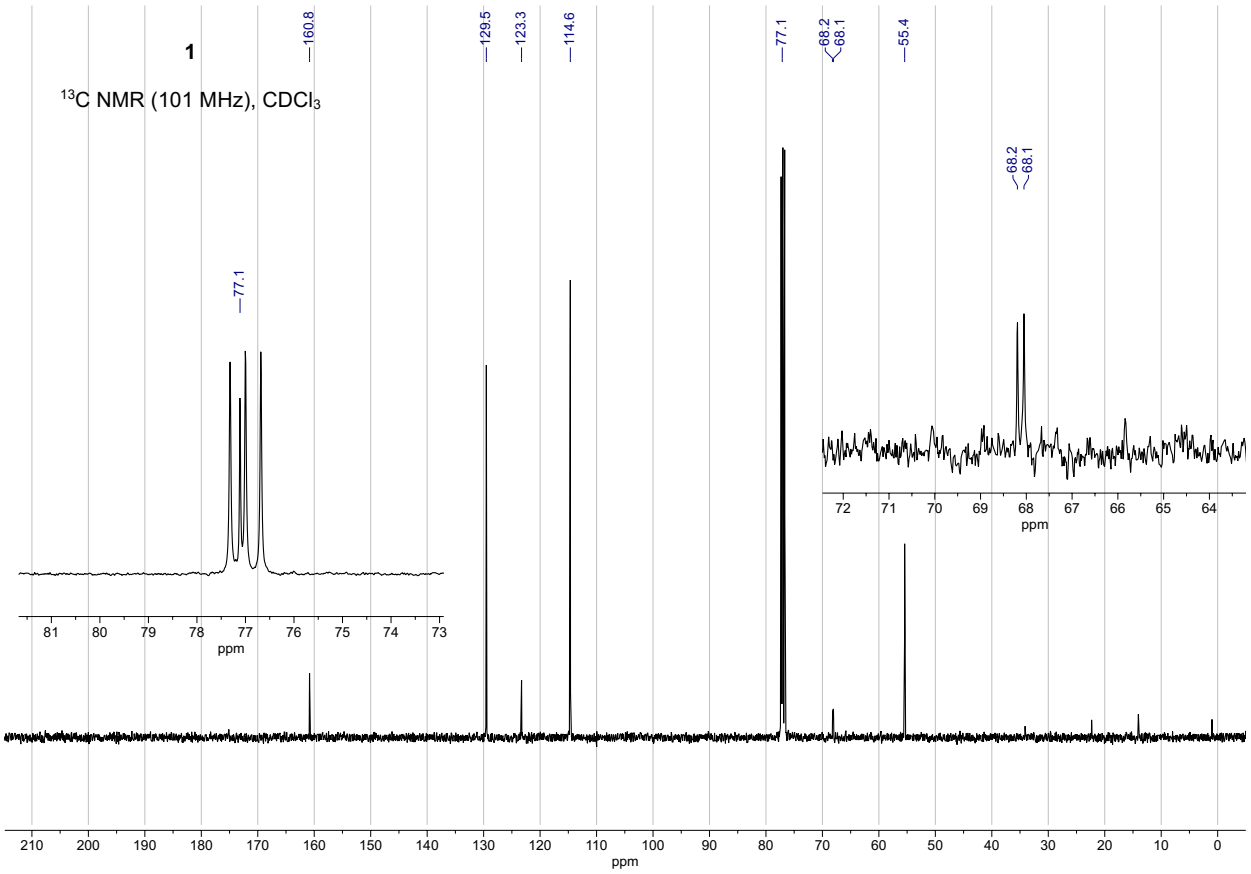
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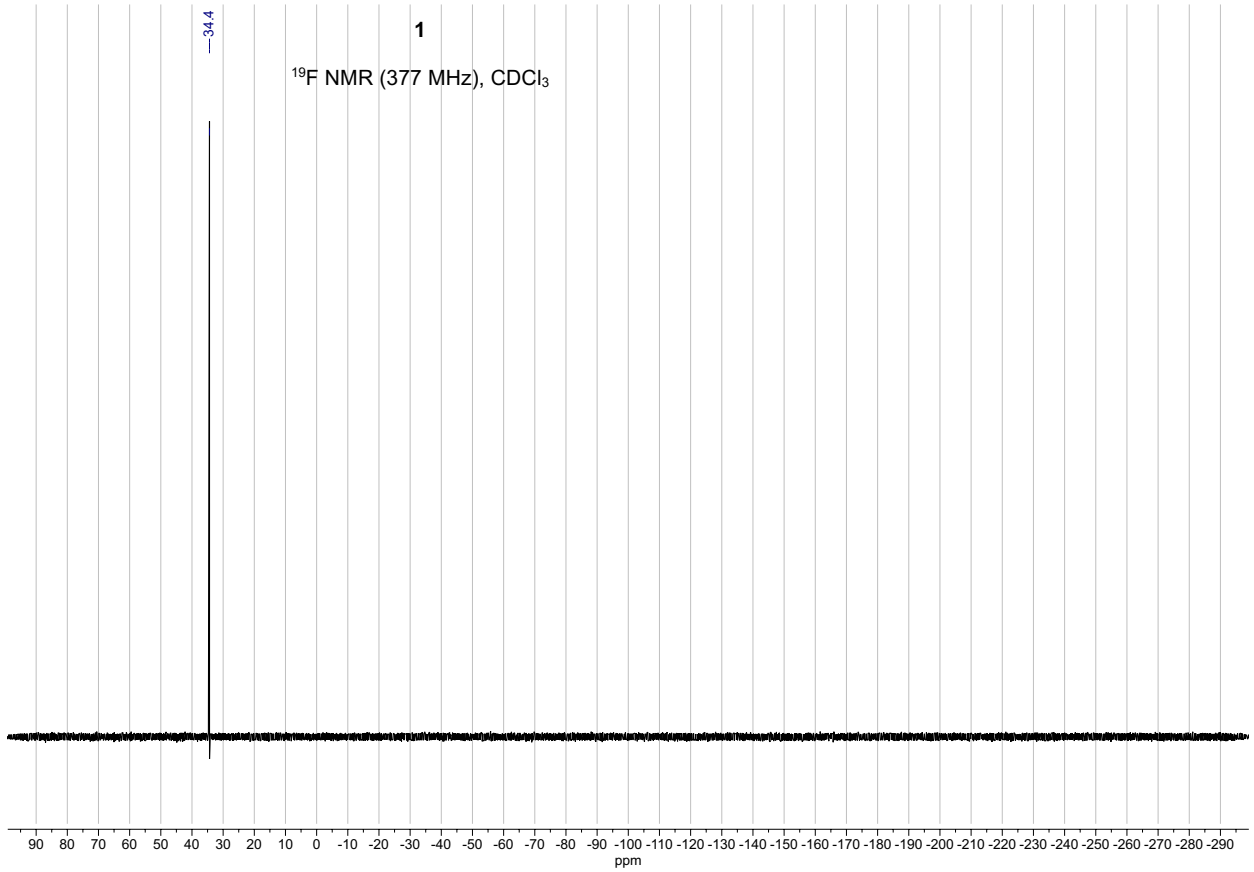


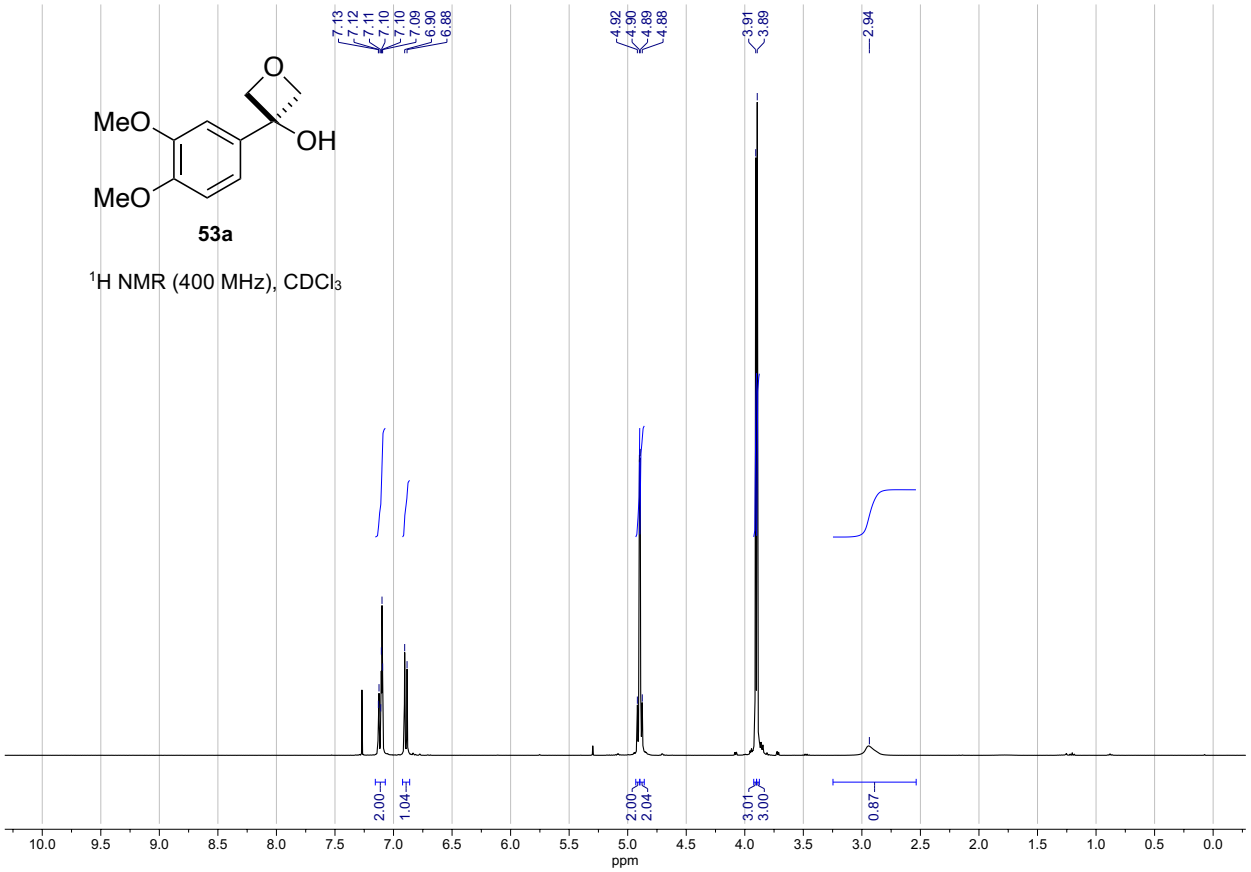
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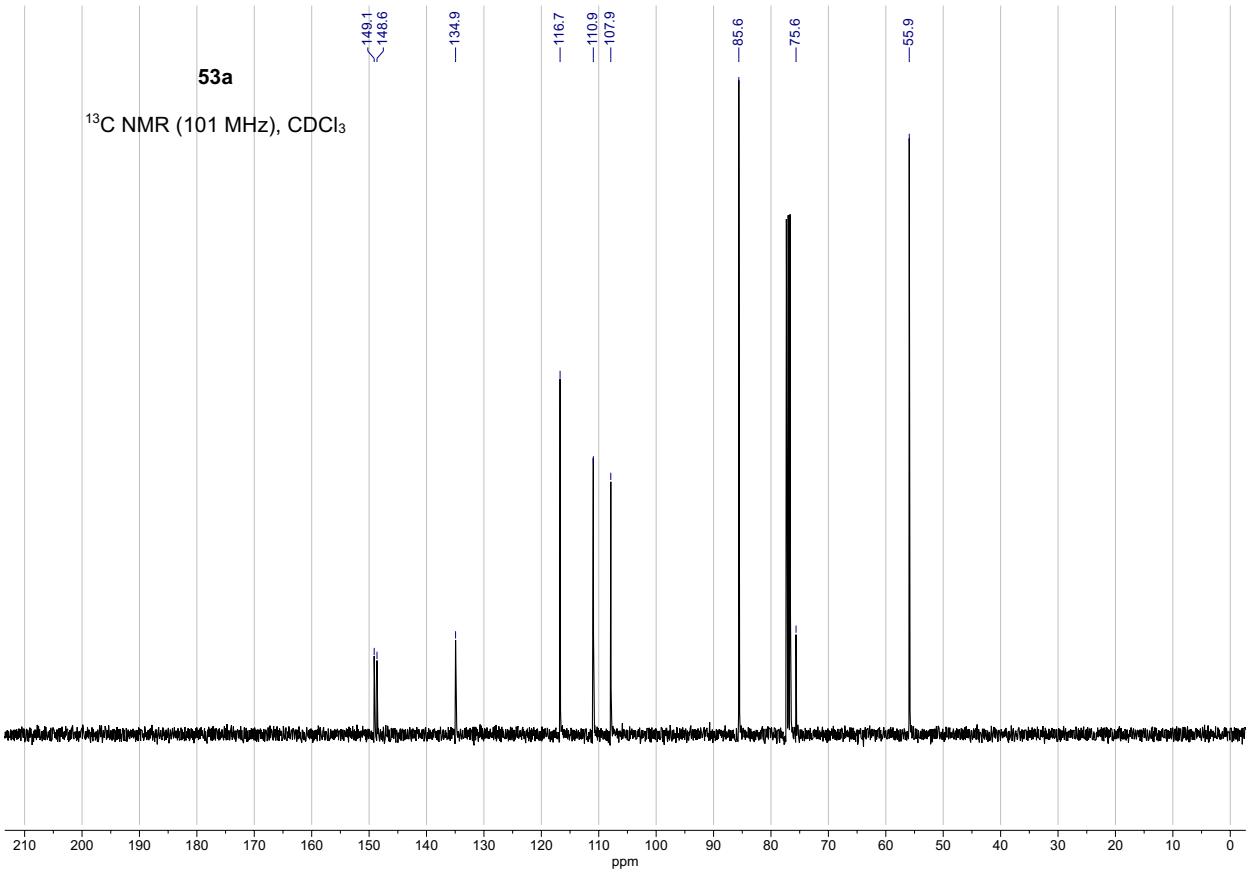
^{13}C NMR (101 MHz), D_2O

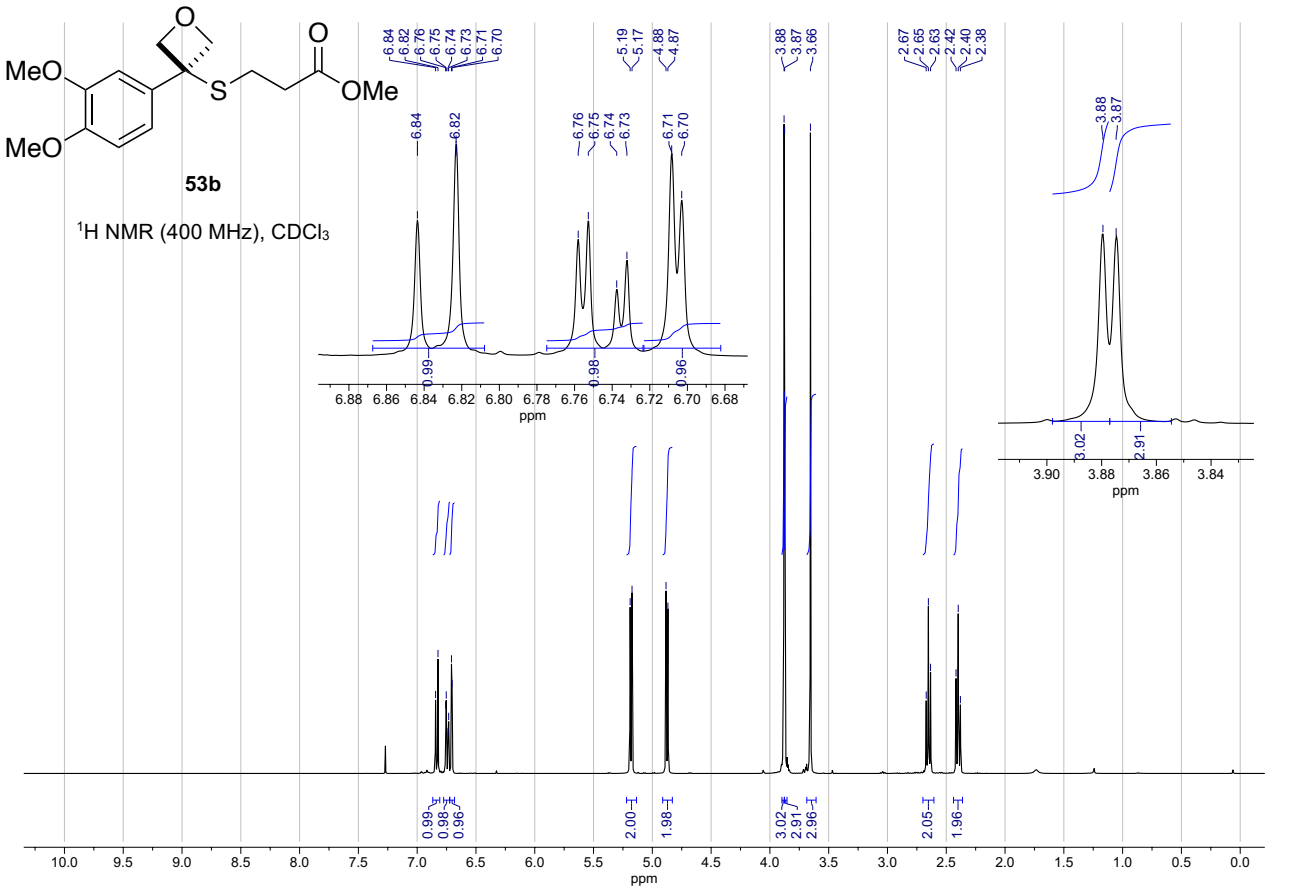

MeO
F
O
O
O
S
1
^{1}H NMR (400 MHz), CDCl$_3$
7.23
7.22
7.21
7.20
7.20
7.19
7.01
7.00
7.00
6.99
6.99
6.98
6.97
5.44
5.43
5.25
5.25
5.23
5.23
3.86
1.92
1.96
2.00
2.02
3.04
ppm

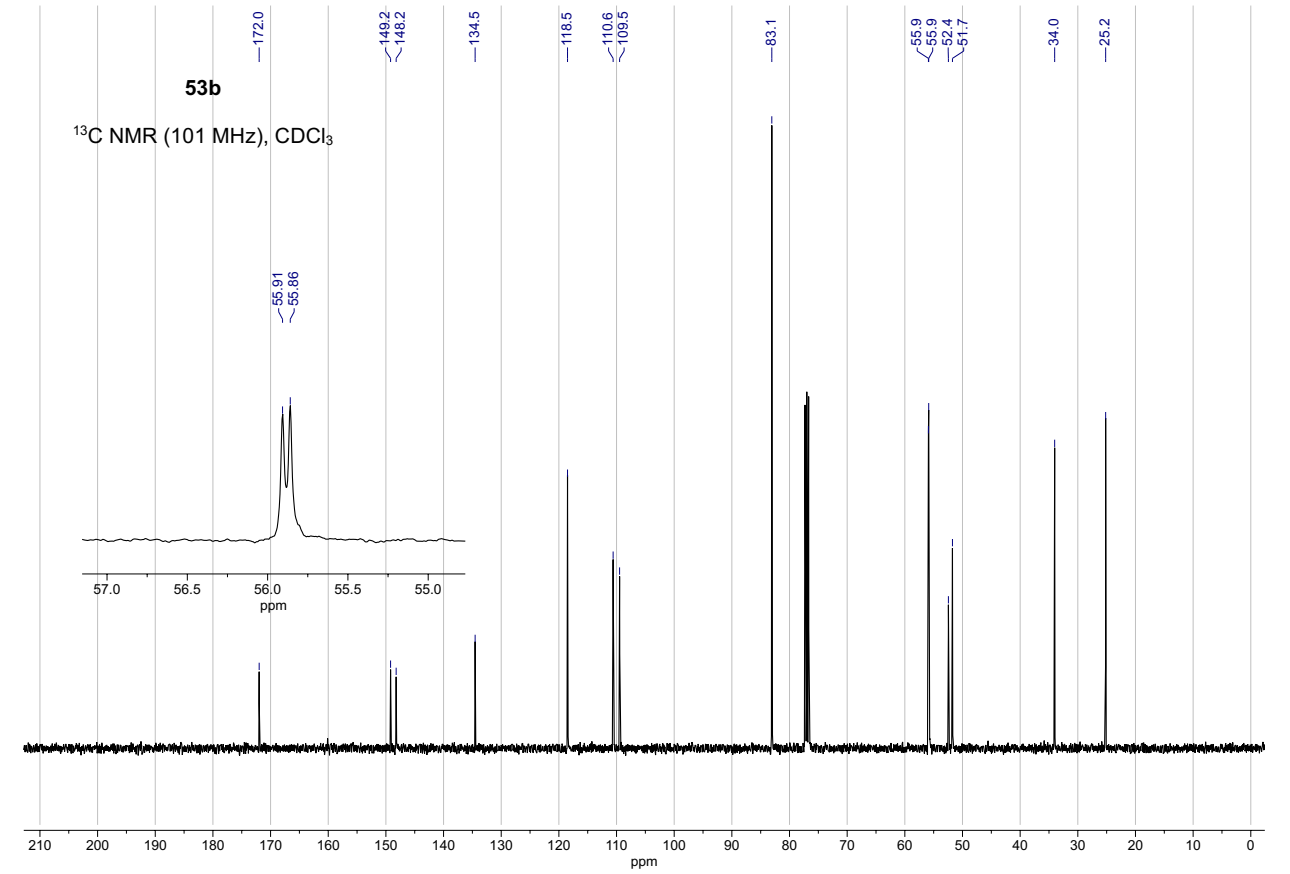

1
^{13}C NMR (101 MHz), CDCl$_3$
160.8
129.5
123.3
114.6
77.1
68.2
68.1
55.4
ppm

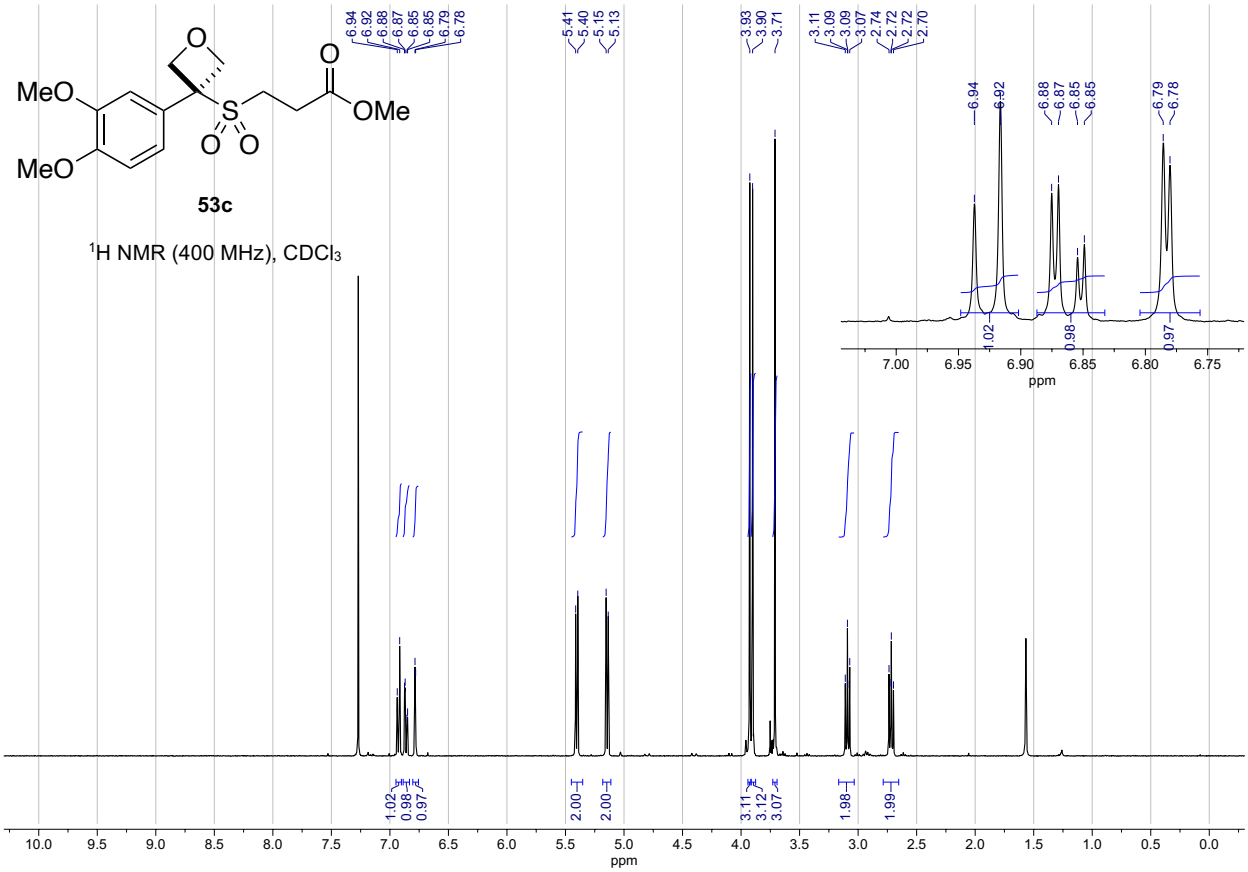

34.4
1
^{19}F NMR (377 MHz), $CDCl_3$
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

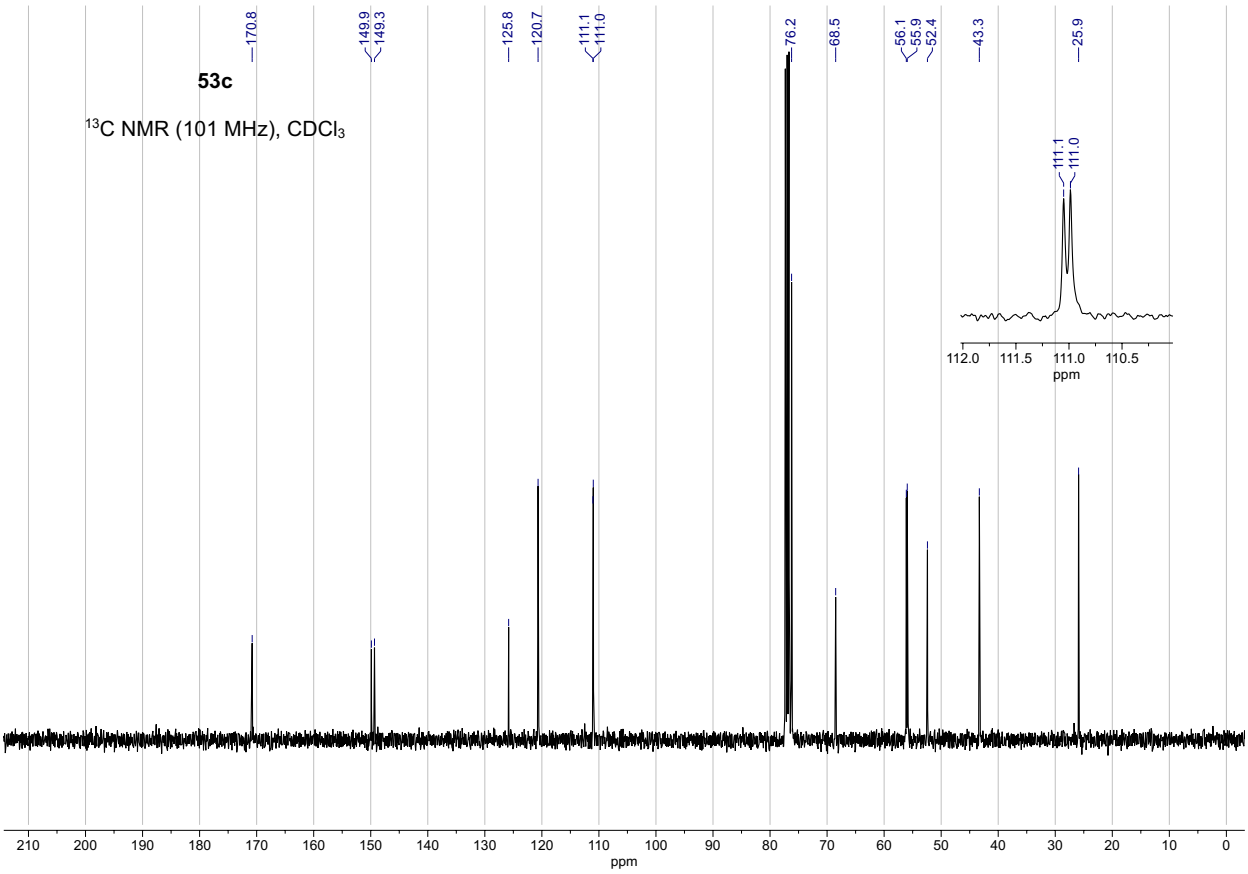

MeO
MeO
OH
O
53a
^{1}H NMR (400 MHz), CDCl$_3$
7.13
7.12
7.11
7.10
7.10
7.09
6.90
6.88
4.92
4.90
4.89
4.88
3.91
3.89
2.94
2.00
1.04
2.00
2.04
3.01
3.00
0.87
ppm

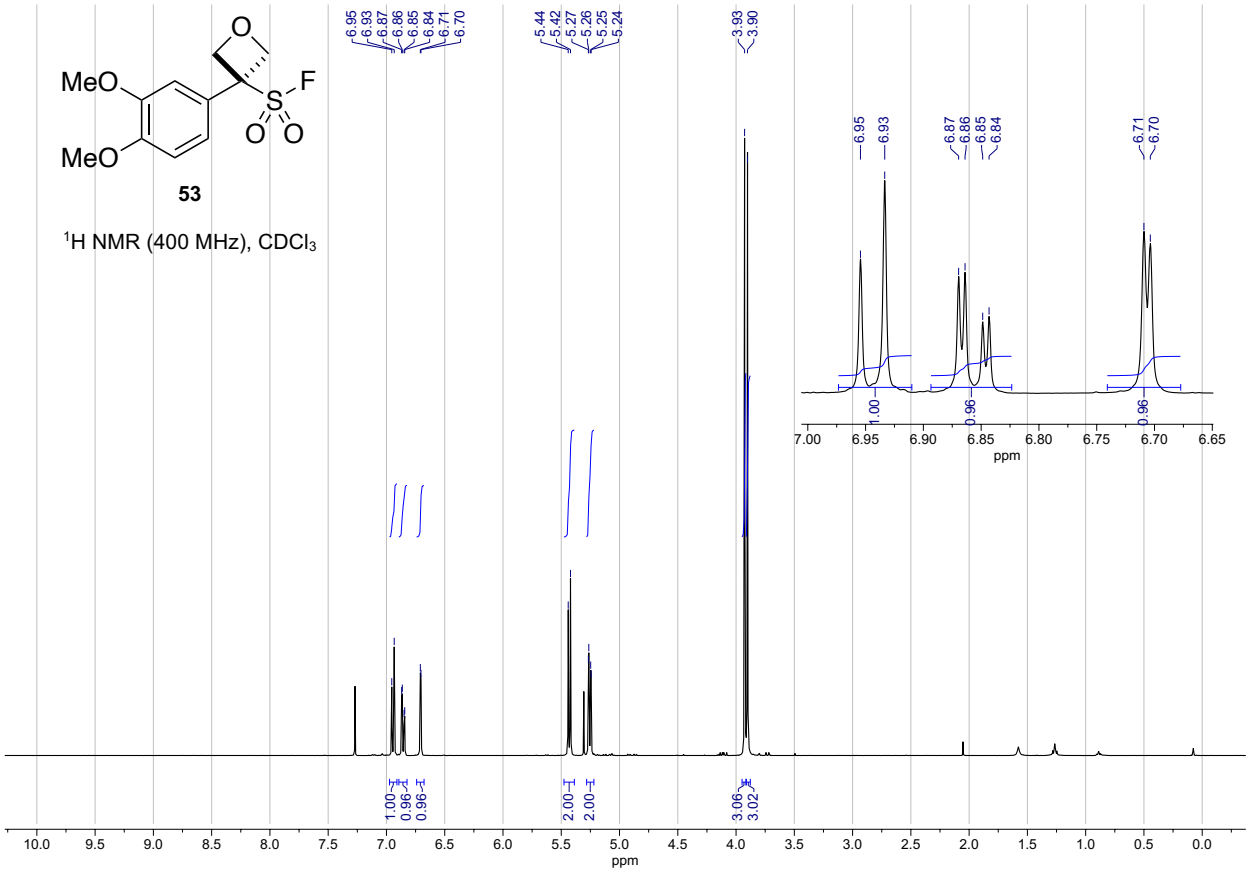

53a
^{13}C NMR (101 MHz), CDCl$_3$
149.1
148.6
134.9
116.7
110.9
107.9
85.6
75.6
55.9
ppm

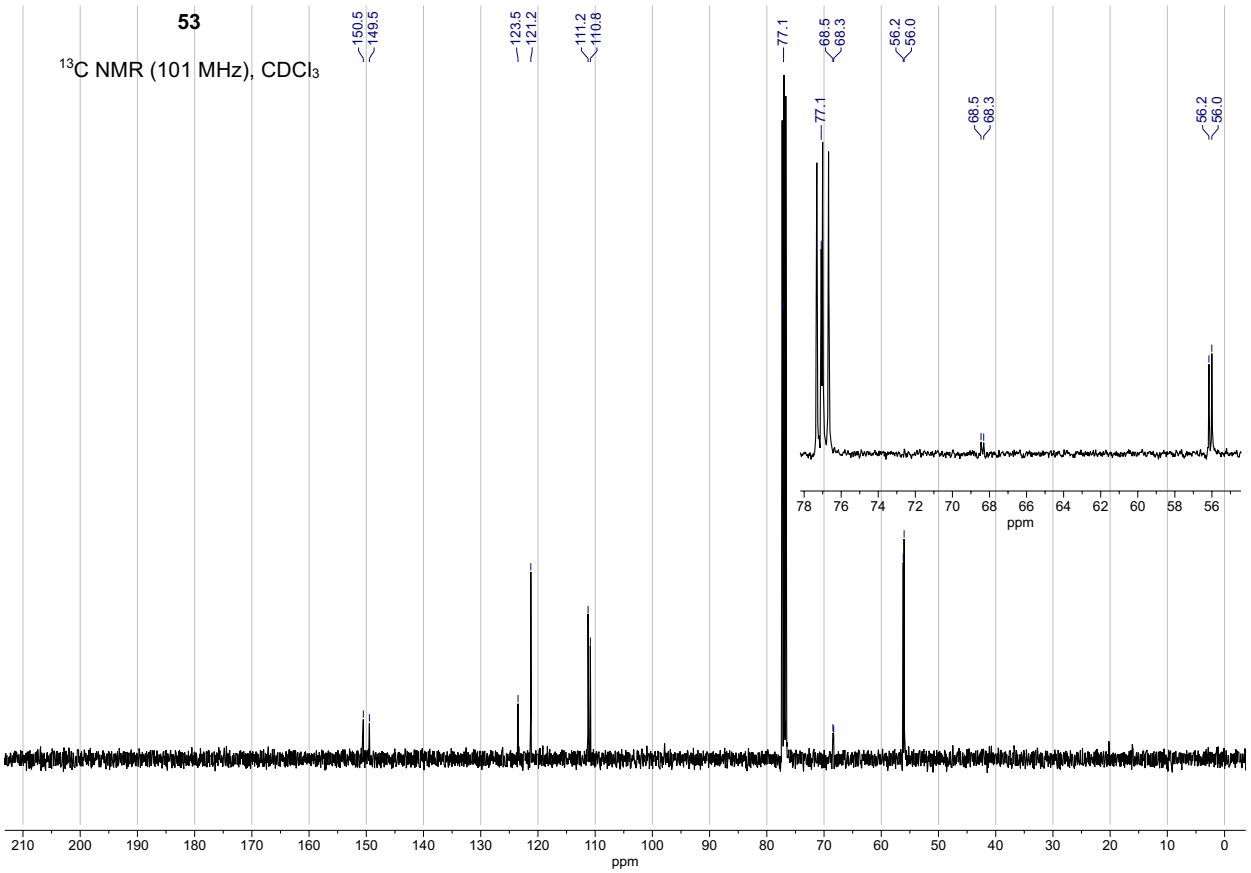

MeO
MeO
O
S
O
OMe
53b
^{1}H NMR (400 MHz), CDCl$_3$
6.84 6.82 6.76 6.75 6.74 6.73 6.71 6.70
5.19 5.17 4.88 4.87
3.88 3.87 3.66
2.67 2.65 2.63 2.42 2.40 2.38
0.99 0.98 0.96 2.00 1.98 3.02 2.91 2.96 2.05 1.96
ppm


53b
^{13}C NMR (101 MHz), CDCl$_3$
172.0
149.2 148.2
134.5
118.5
110.6 109.5
83.1
55.9 55.9 52.4 51.7
34.0
25.2
55.91 55.86
ppm


MeO
MeO
O
S
O
O
O
OMe
53c
^{1}H NMR (400 MHz), CDCl$_3$
6.94
6.92
6.88
6.87
6.85
6.85
6.79
6.78
5.41
5.40
5.15
5.13
3.93
3.90
3.71
3.11
3.09
3.09
3.07
2.74
2.72
2.72
2.70
1.02
0.98
0.97
2.00
2.00
3.11
3.12
3.07
1.98
1.99
ppm

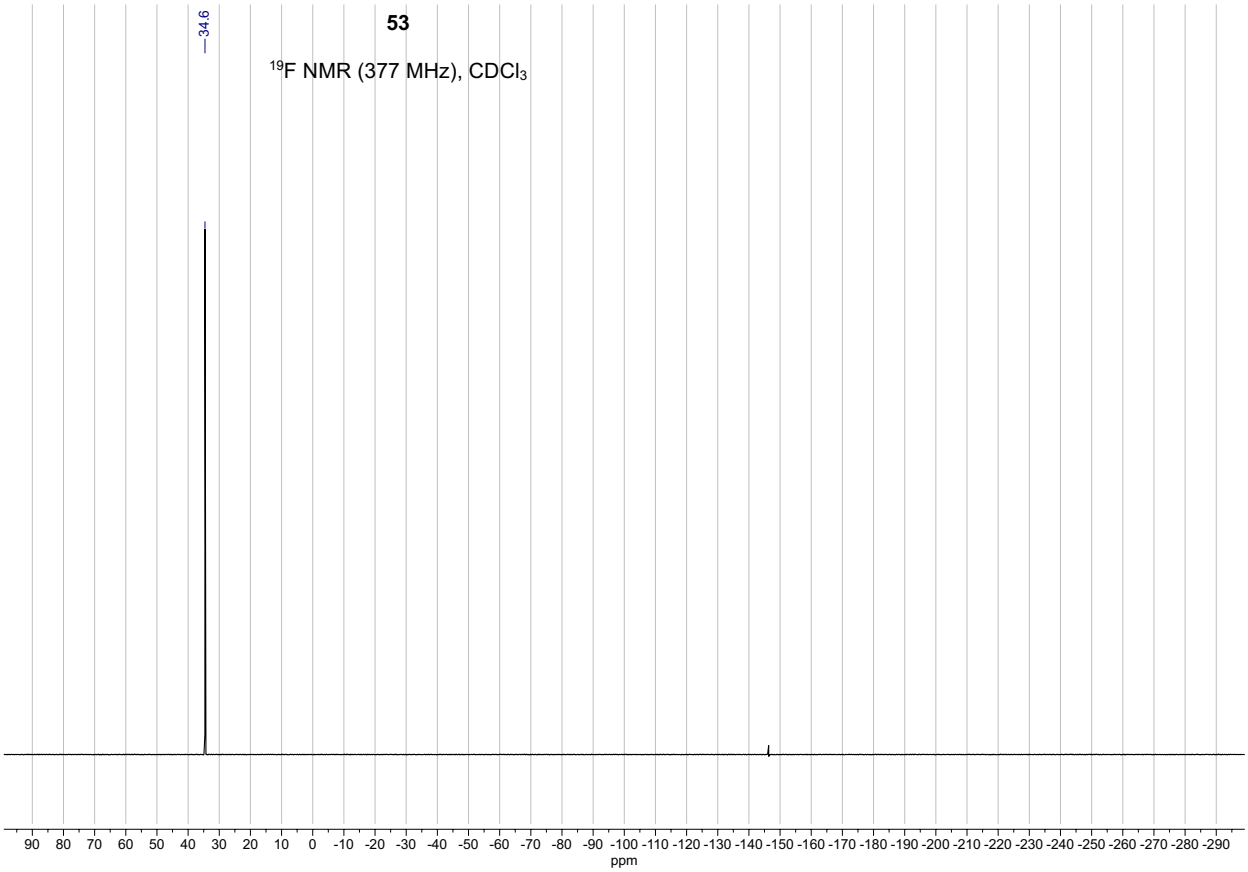

53c
^{13}C NMR (101 MHz), CDCl$_3$
170.8
149.9
149.3
125.8
120.7
111.1
111.0
76.2
68.5
56.1
55.9
52.4
43.3
25.9
ppm

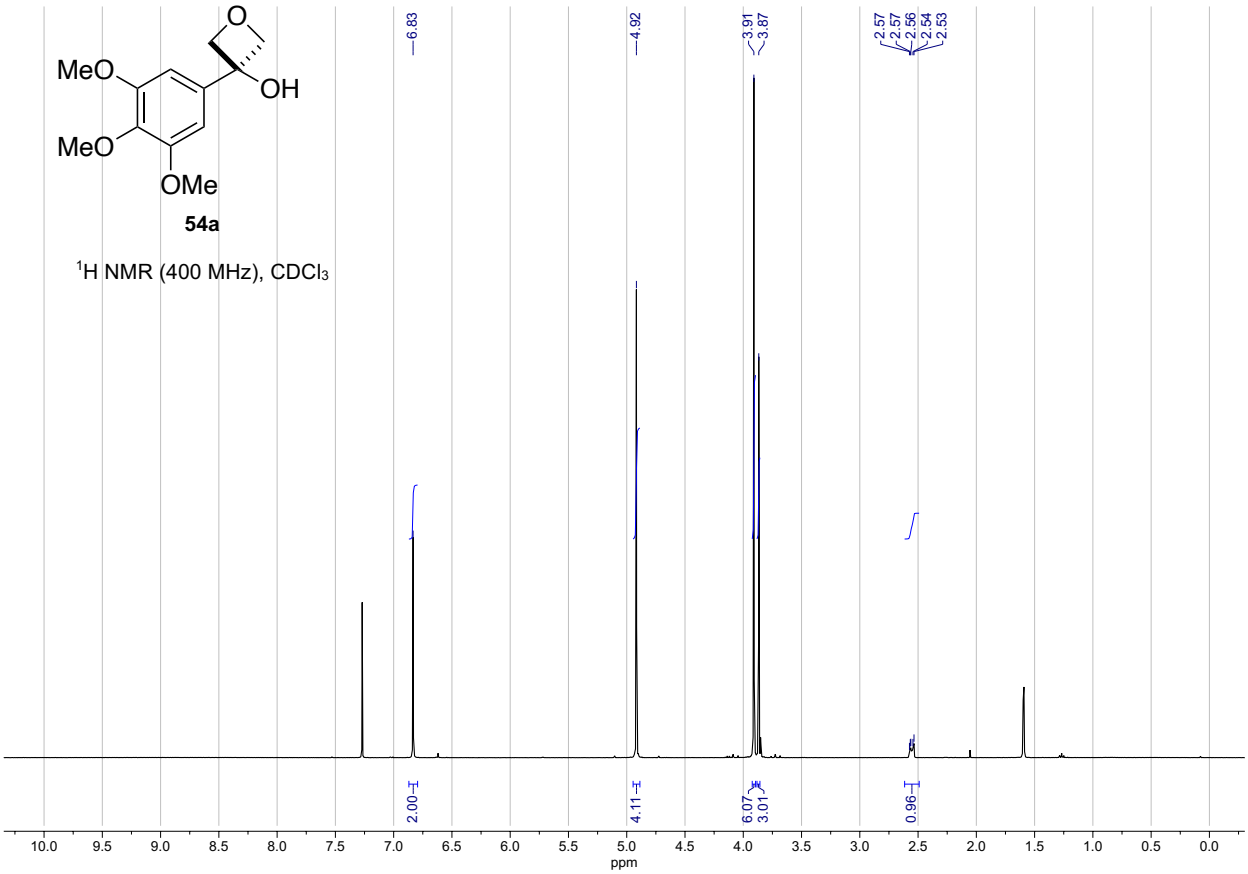

MeO
MeO
O
S
F
O
O
53
^{1}H NMR (400 MHz), CDCl$_3$
6.95
6.93
6.87
6.86
6.85
6.84
6.71
6.70
5.44
5.42
5.27
5.26
5.25
5.24
3.93
3.90
1.00
0.96
0.96
2.00
2.00
3.06
3.02
ppm


53
^{13}C NMR (101 MHz), CDCl$_3$
150.5
149.5
123.5
121.2
111.2
110.8
77.1
68.5
68.3
56.2
56.0
ppm

53

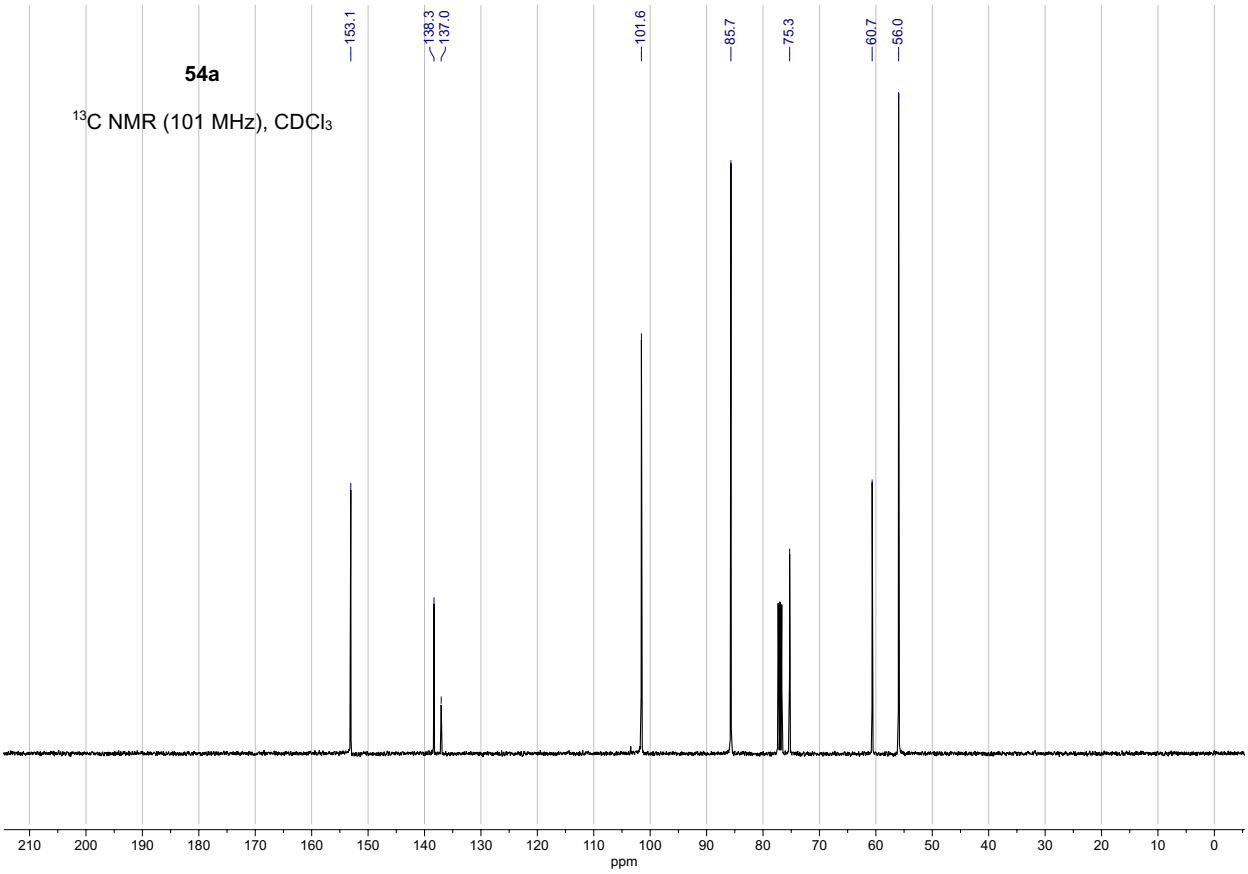
^{19}F NMR (377 MHz), $CDCl_3$





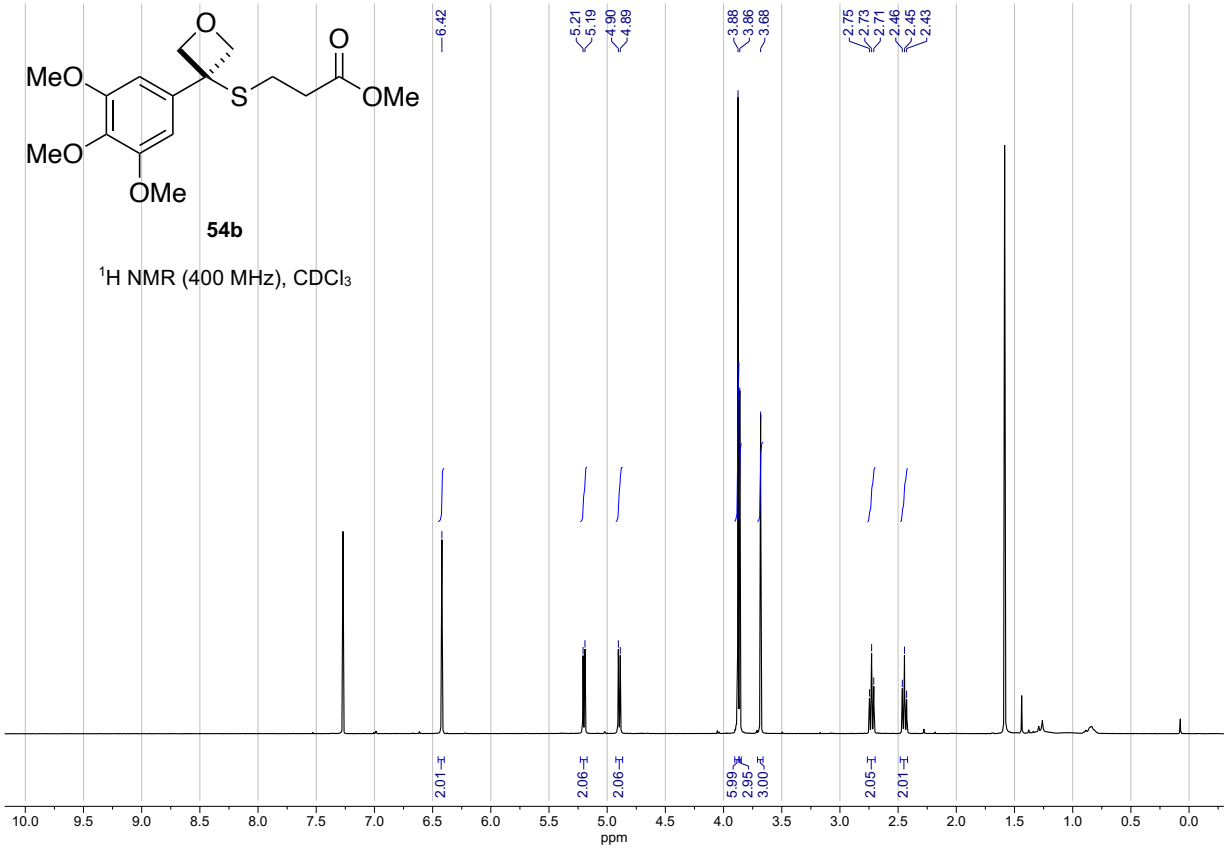
54a

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



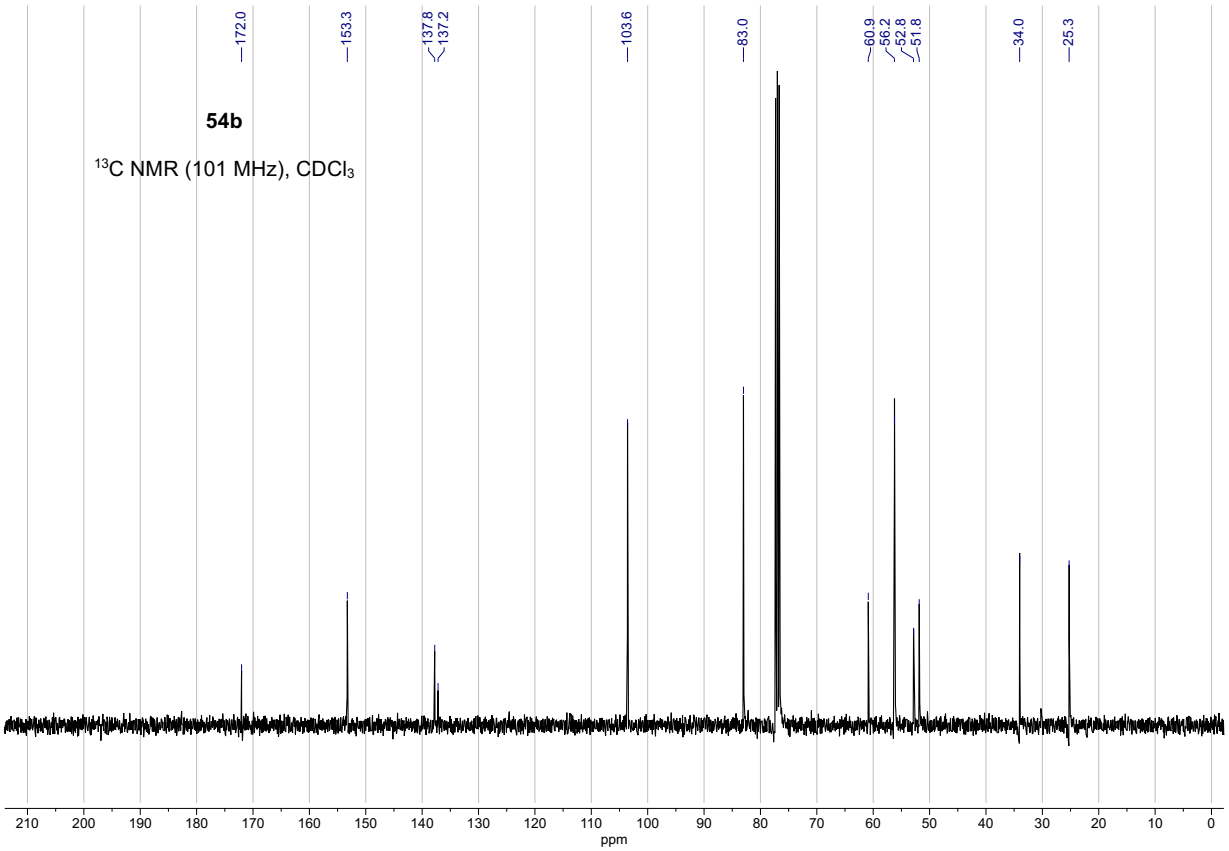
54a

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



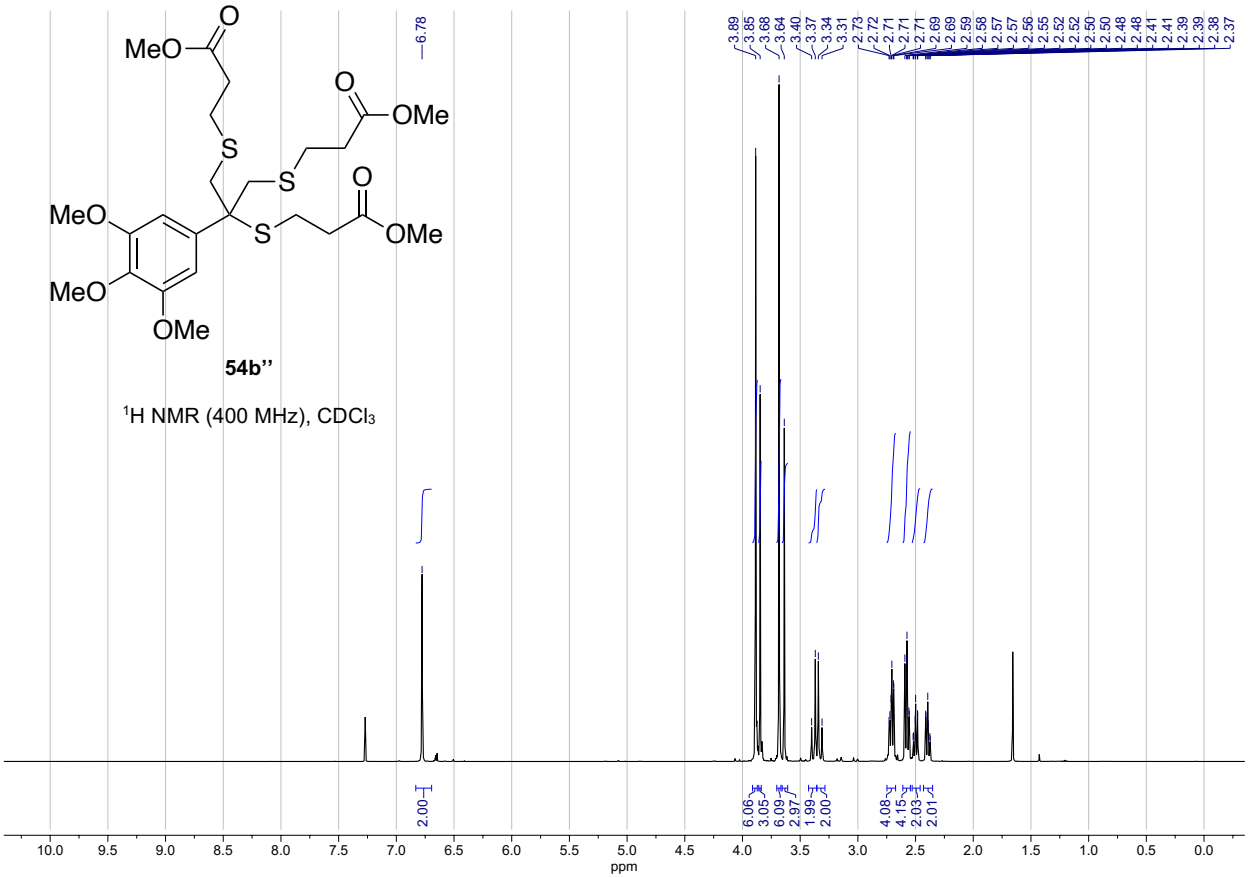
54b

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



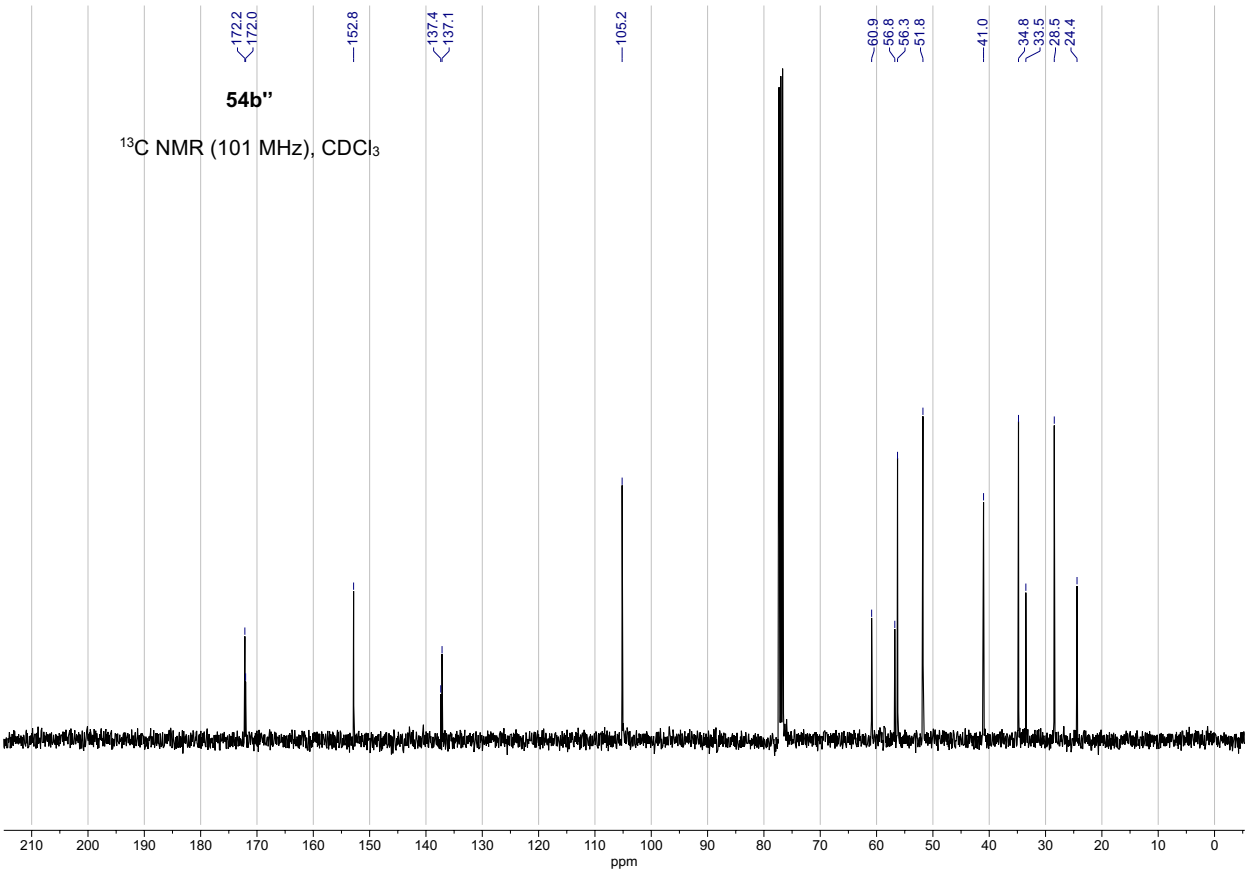
54b

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



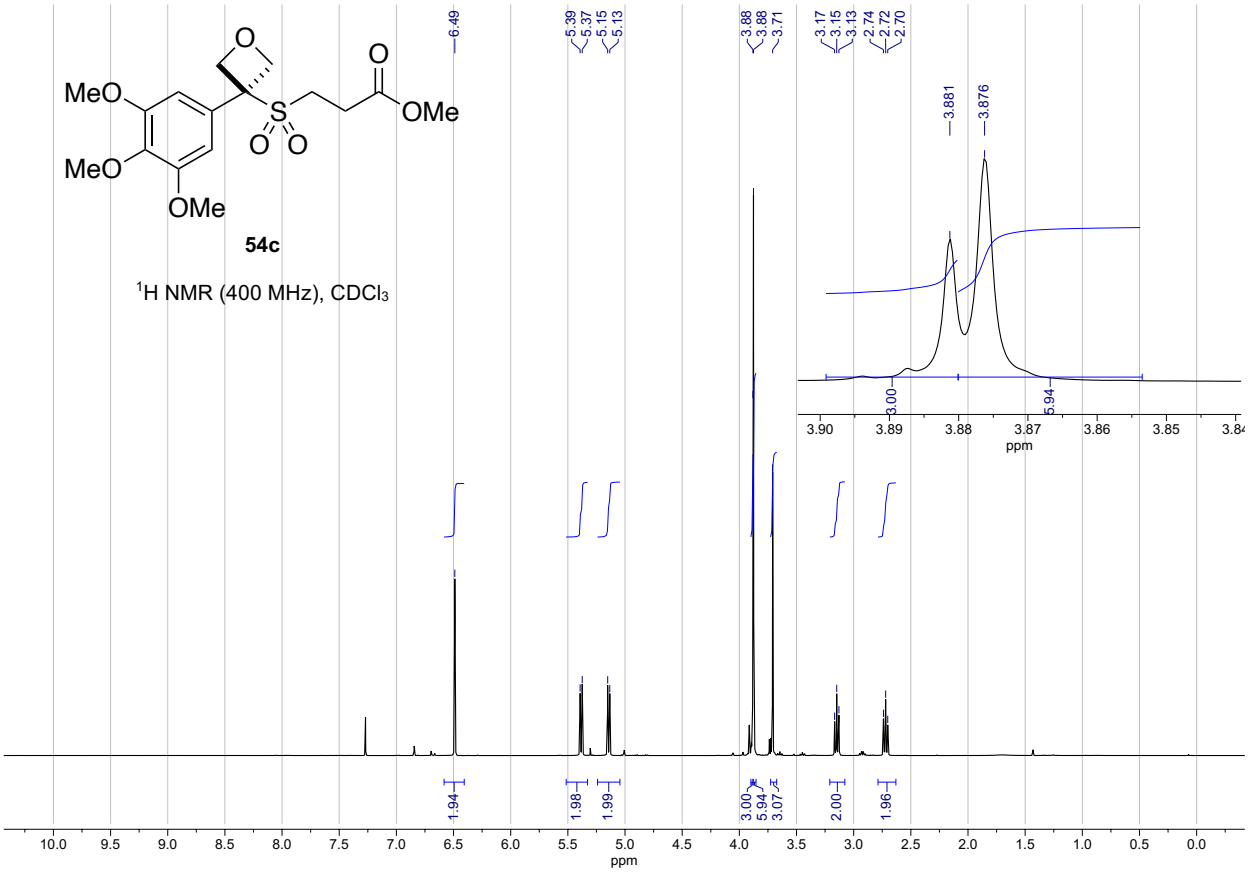
54b''

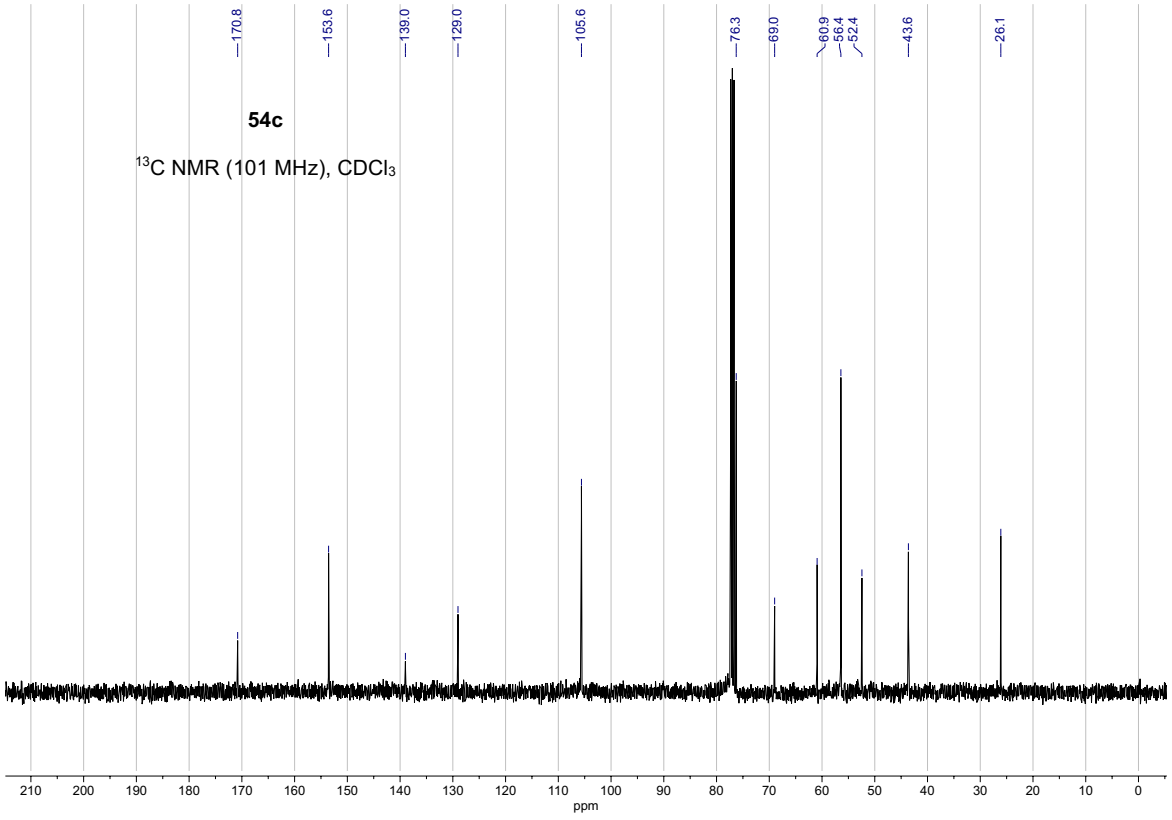
^{1}H NMR (400 MHz), $CDCl_3$

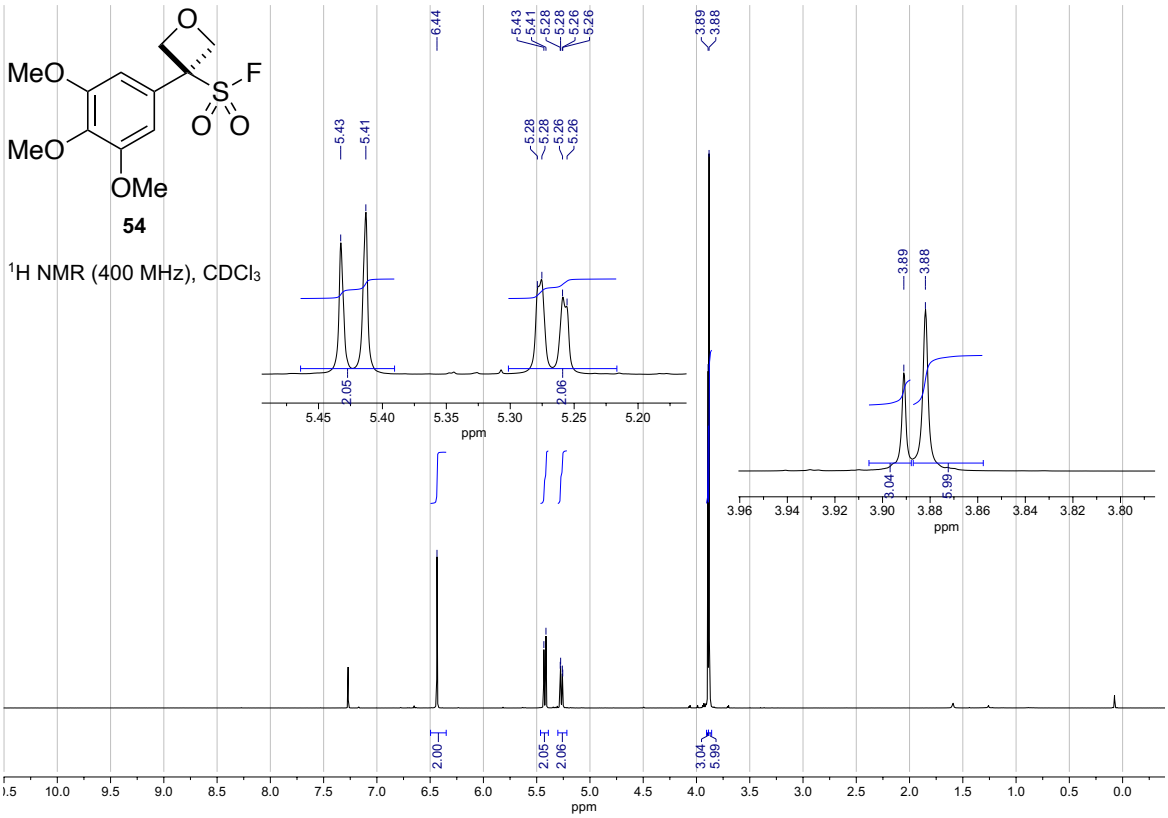


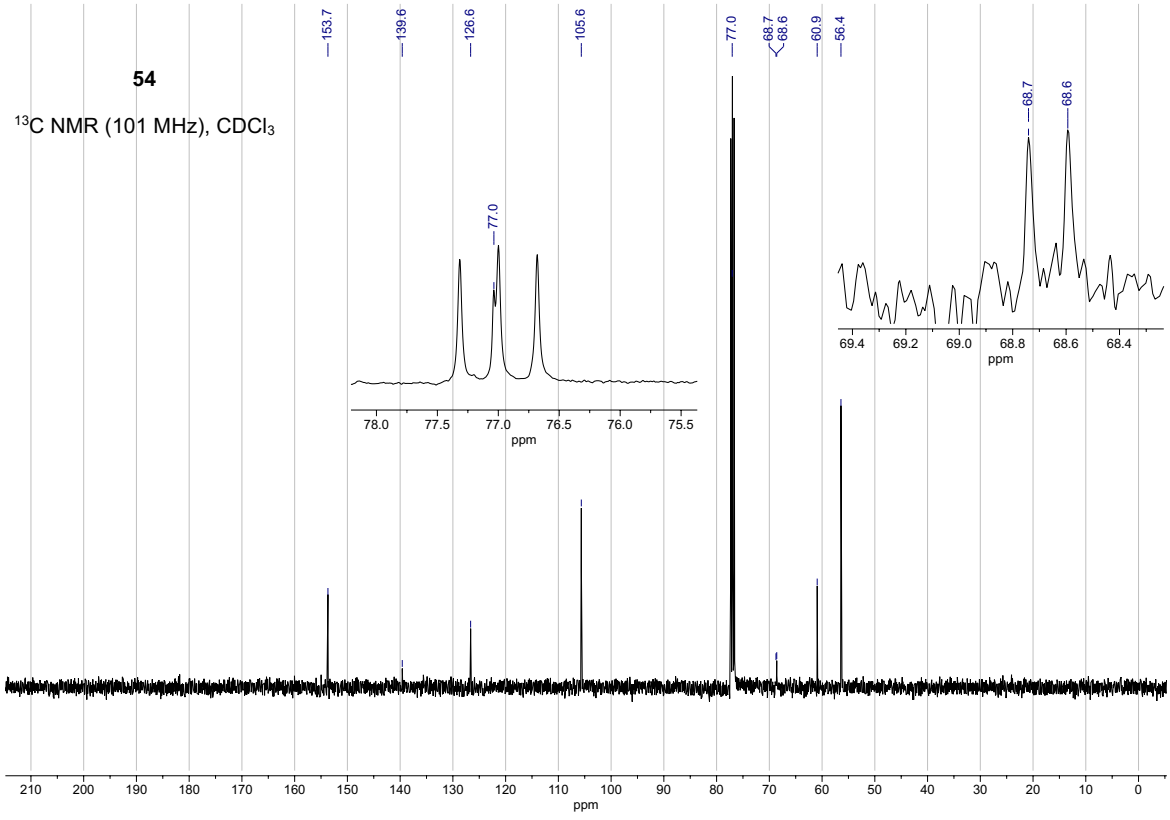
54b''

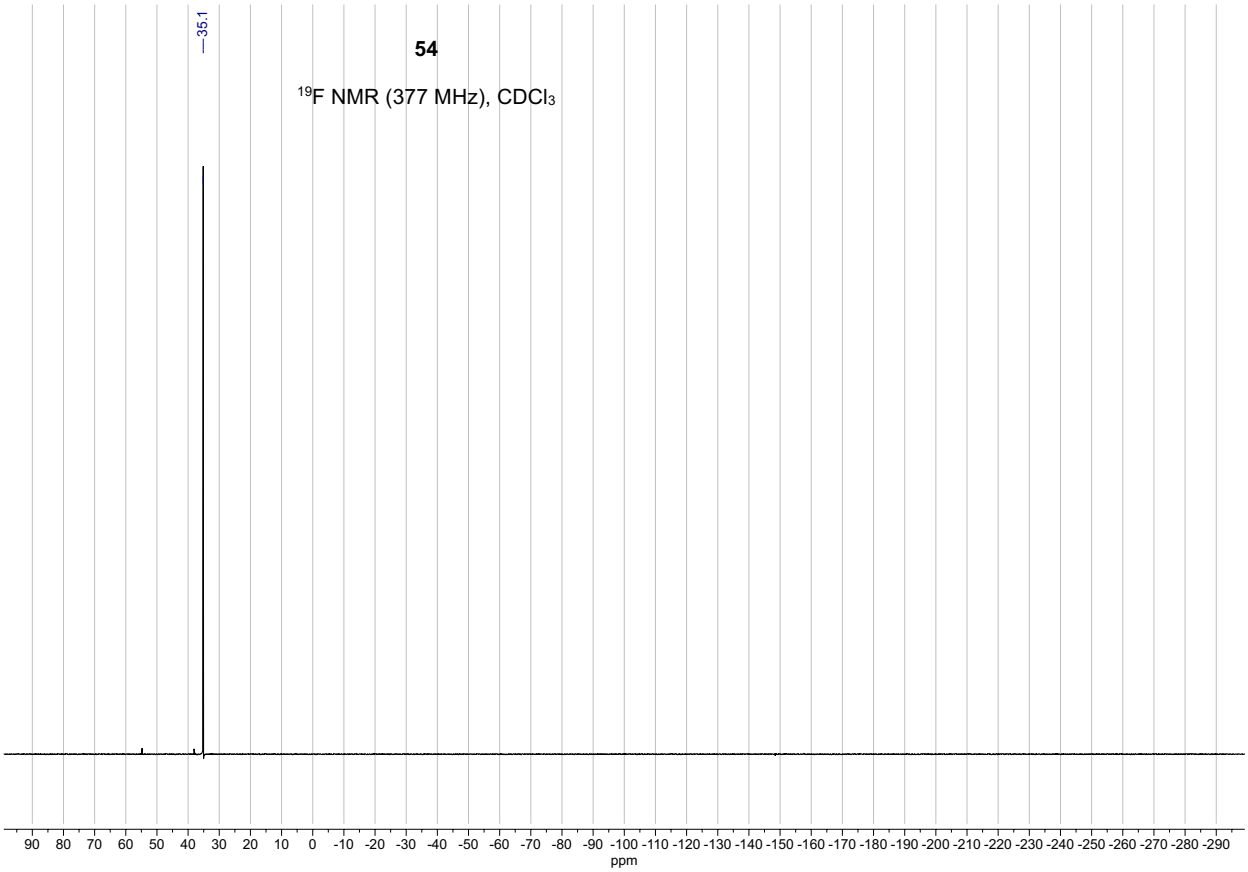
^{13}C NMR (101 MHz), $CDCl_3$

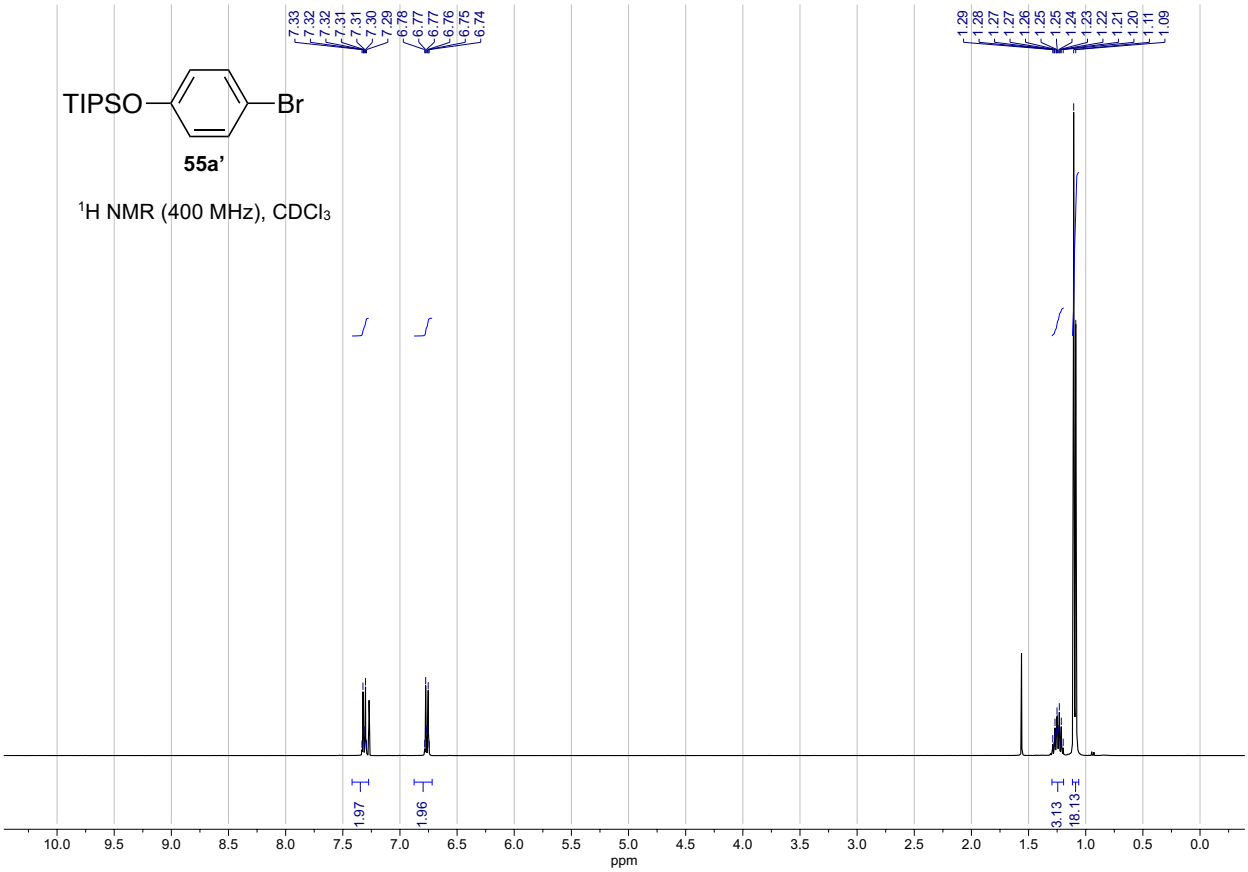

MeO
MeO
OMe
O
O
S
O
O
O
OMe
54c
^{1}H NMR (400 MHz), CDCl$_3$
6.49
5.39
5.37
5.15
5.13
3.88
3.88
3.71
3.17
3.15
3.13
2.74
2.72
2.70
3.881
3.876
3.00
5.94
1.94
1.98
1.99
3.00
5.94
3.07
2.00
1.96
ppm

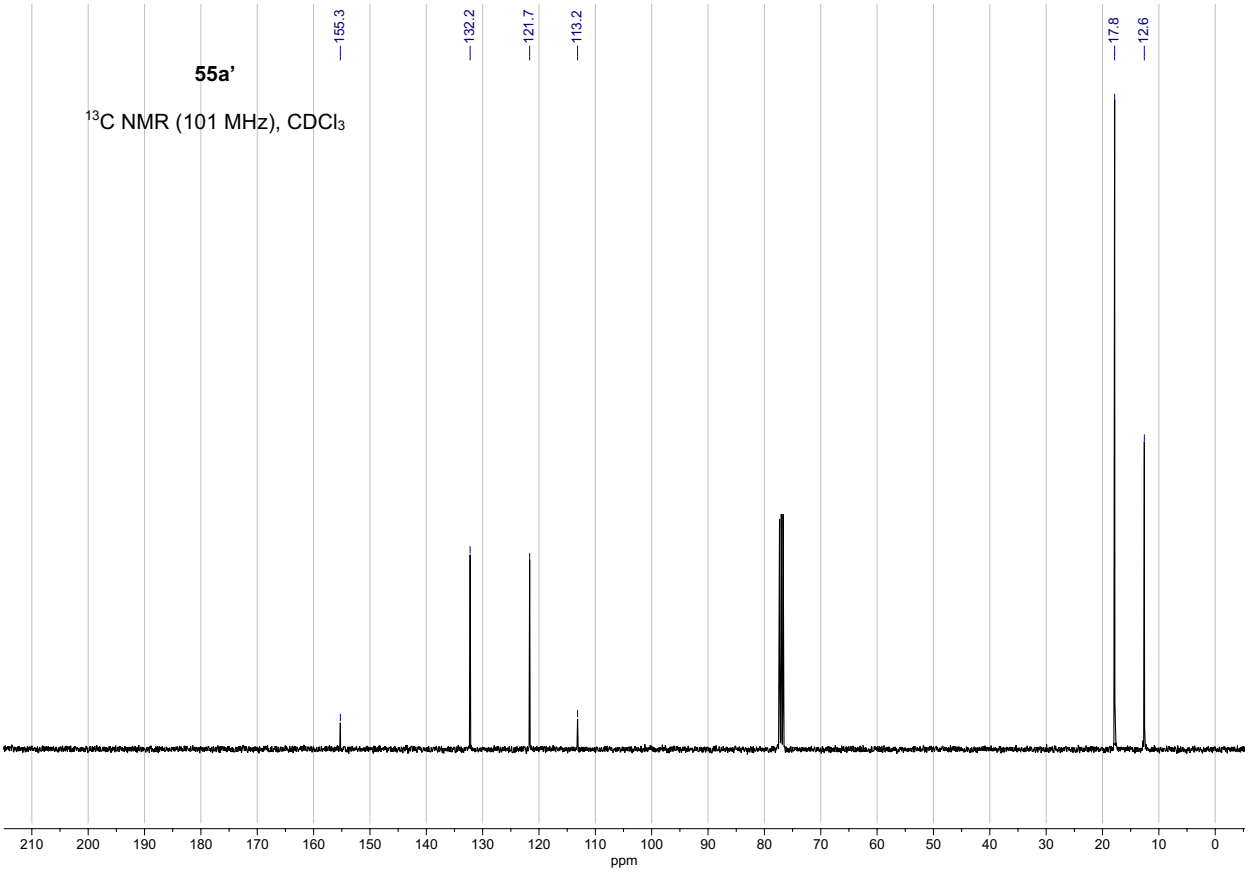

54c
^{13}C NMR (101 MHz), CDCl$_3$
170.8
153.6
139.0
129.0
105.6
76.3
69.0
60.9
56.4
52.4
43.6
26.1
ppm

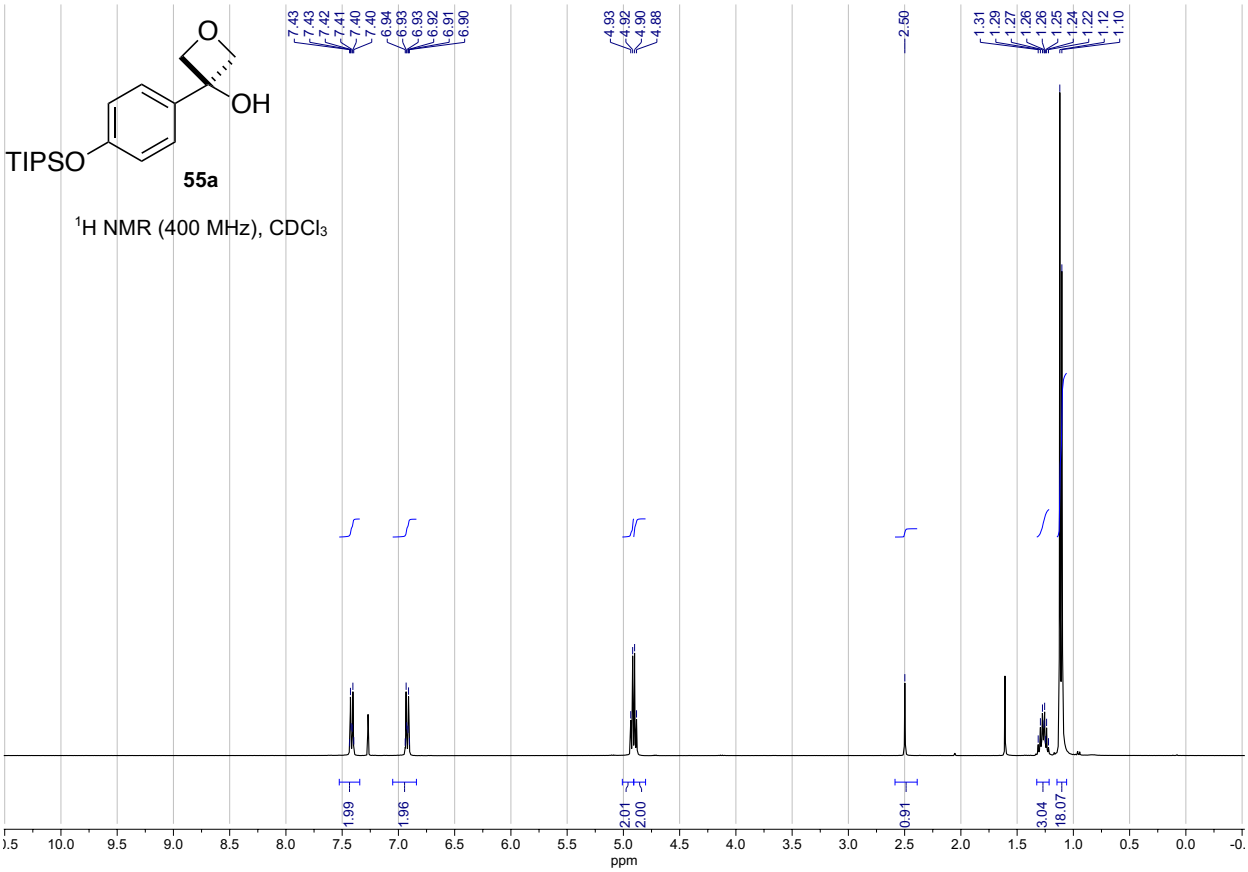

MeO
MeO
OMe
O
S
F
O
O
54
^{1}H NMR (400 MHz), CDCl$_3$
6.44
5.43
5.41
5.28
5.28
5.26
5.26
3.89
3.88
2.05
2.06
3.04
5.99
2.00
2.05
2.06
3.04
5.99
ppm

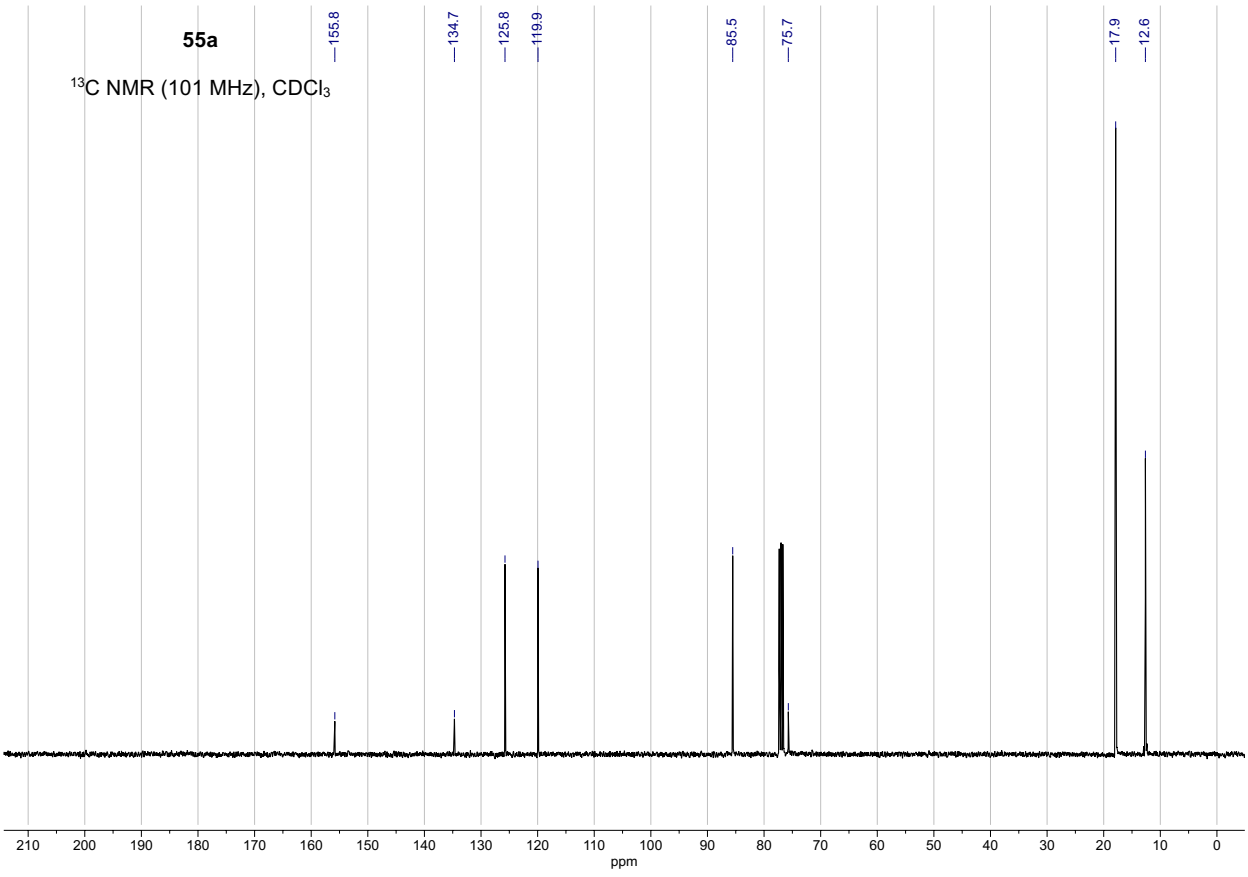

54
^{13}C NMR (101 MHz), CDCl$_3$
153.7
139.6
126.6
105.6
77.0
68.7
68.6
60.9
56.4
ppm

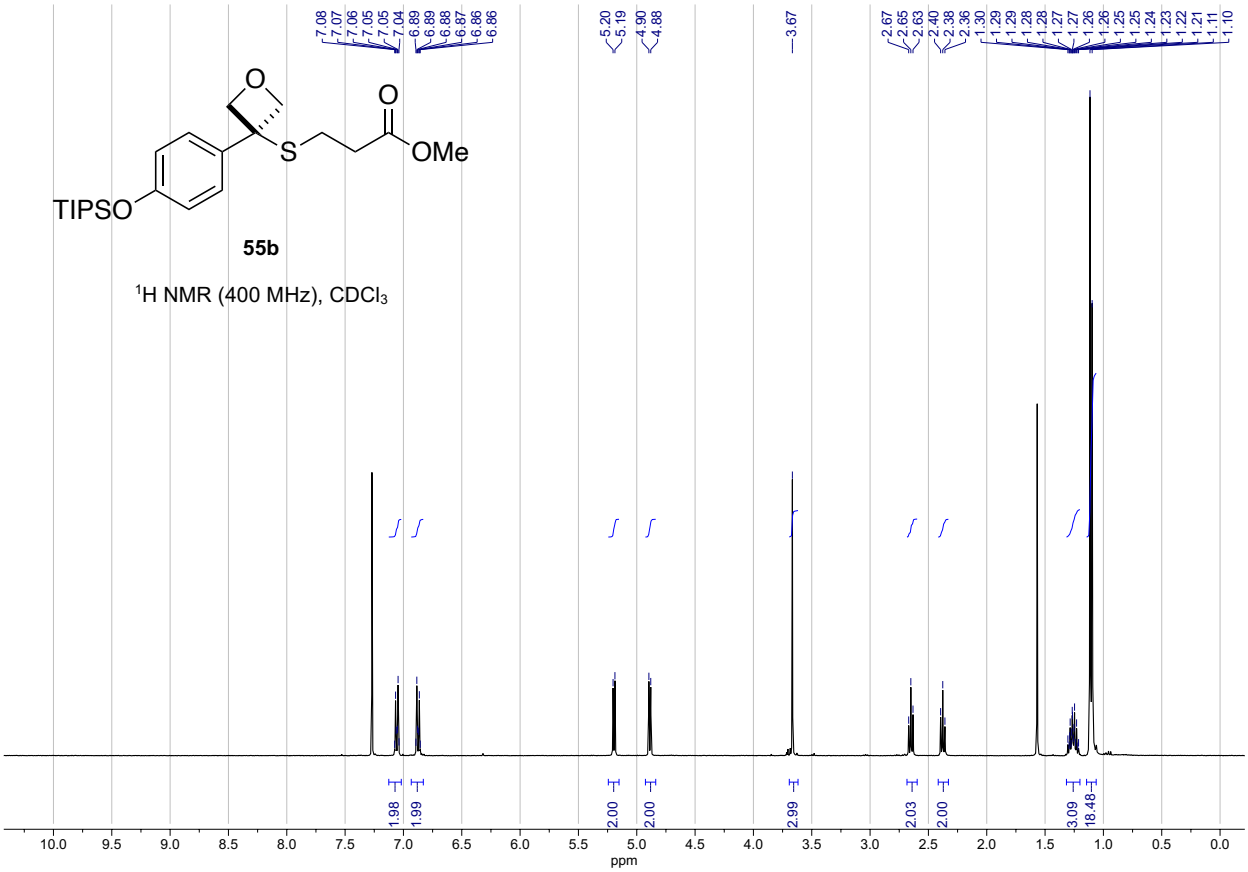

35.1
54
^{19}F NMR (377 MHz), $CDCl_3$
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

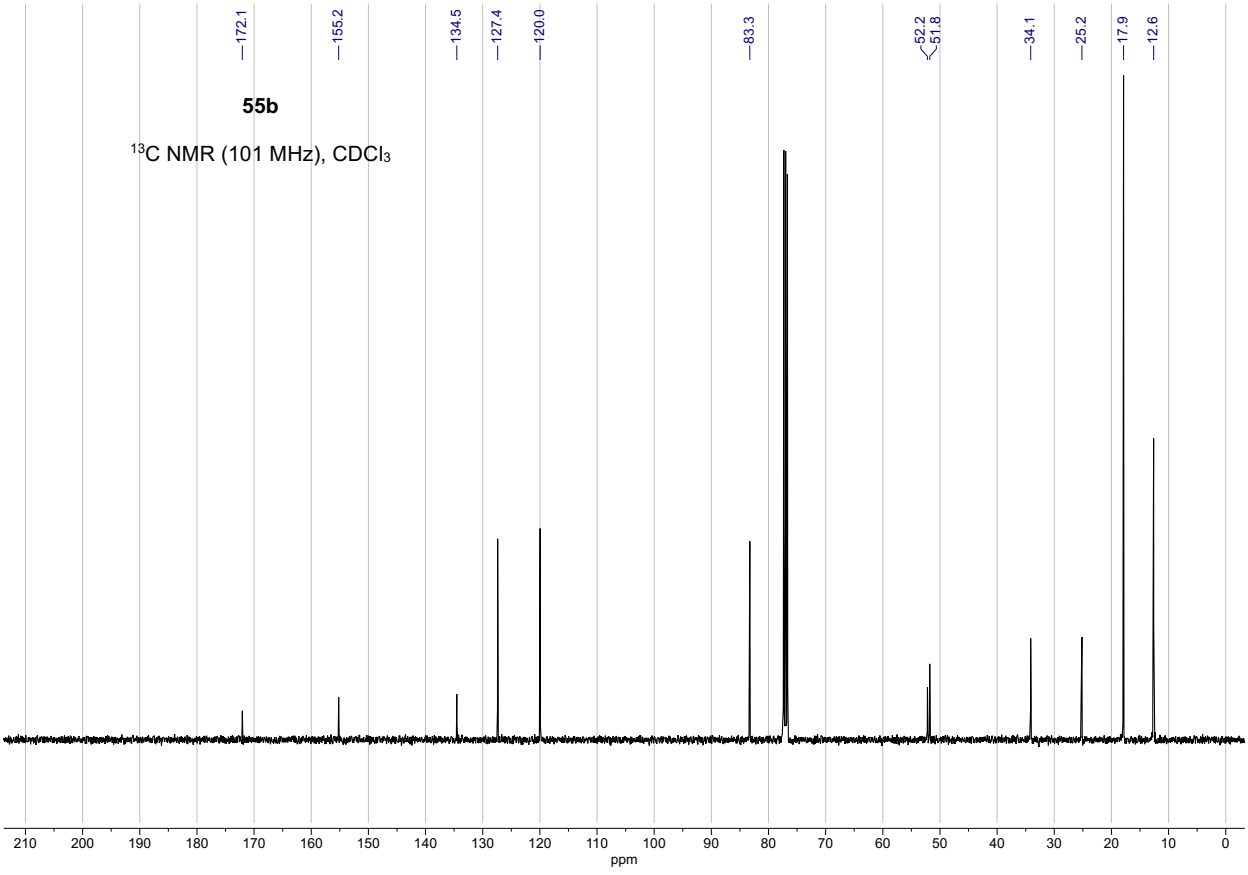

TIPSO
Br
55a'
^{1}H NMR (400 MHz), CDCl$_3$
7.33
7.32
7.32
7.31
7.31
7.30
7.29
6.78
6.77
6.77
6.76
6.75
6.74
1.29
1.28
1.27
1.27
1.26
1.25
1.25
1.24
1.23
1.22
1.21
1.20
1.11
1.09
1.97
1.96
3.13
18.13
ppm

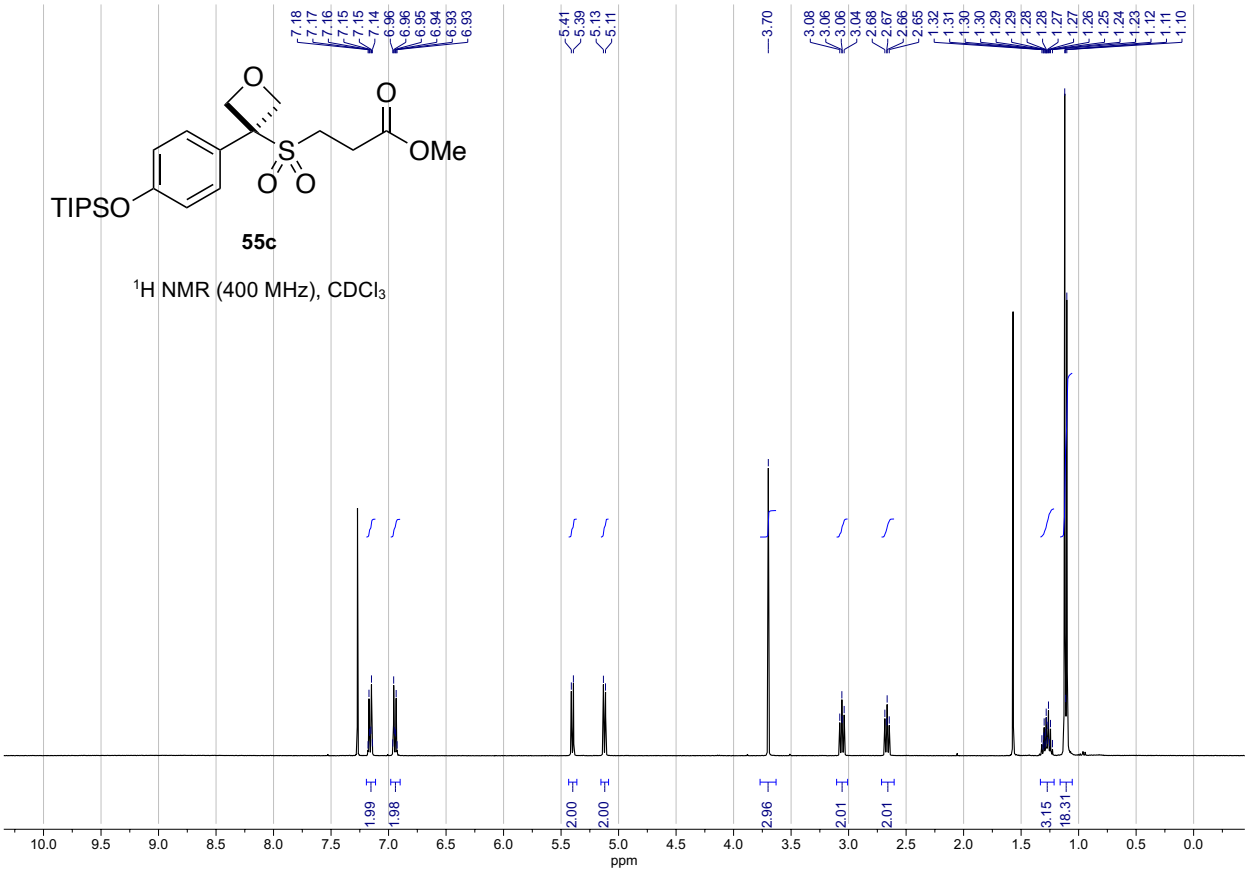

55a'
^{13}C NMR (101 MHz), CDCl$_3$
155.3
132.2
121.7
113.2
17.8
12.6
ppm

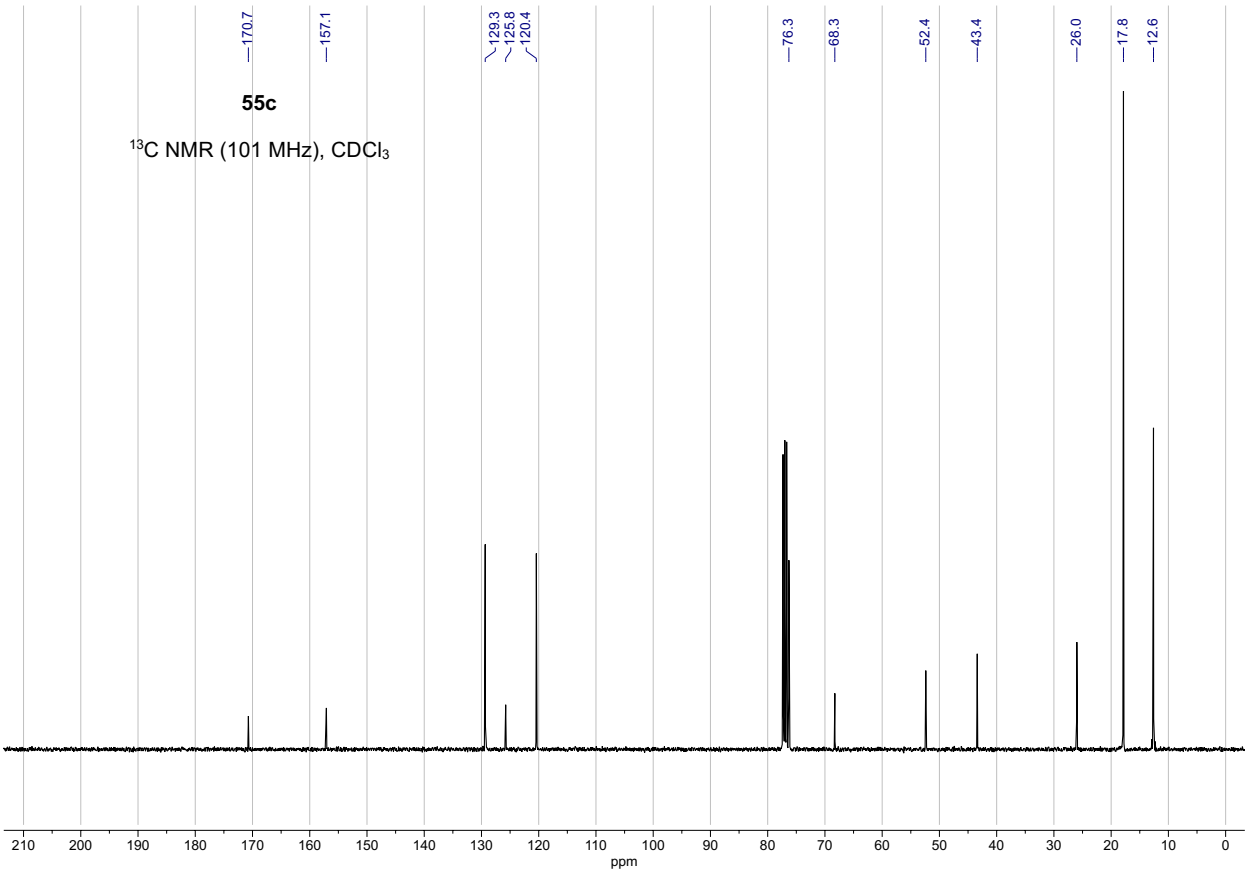

TIPSO
OH
O
55a
^{1}H NMR (400 MHz), CDCl$_3$
7.43
7.43
7.42
7.41
7.40
7.40
6.94
6.93
6.93
6.92
6.91
6.90
4.93
4.92
4.90
4.88
2.50
1.31
1.29
1.27
1.26
1.26
1.25
1.24
1.22
1.12
1.10
1.99
1.96
2.01
2.00
0.91
3.04
18.07
ppm

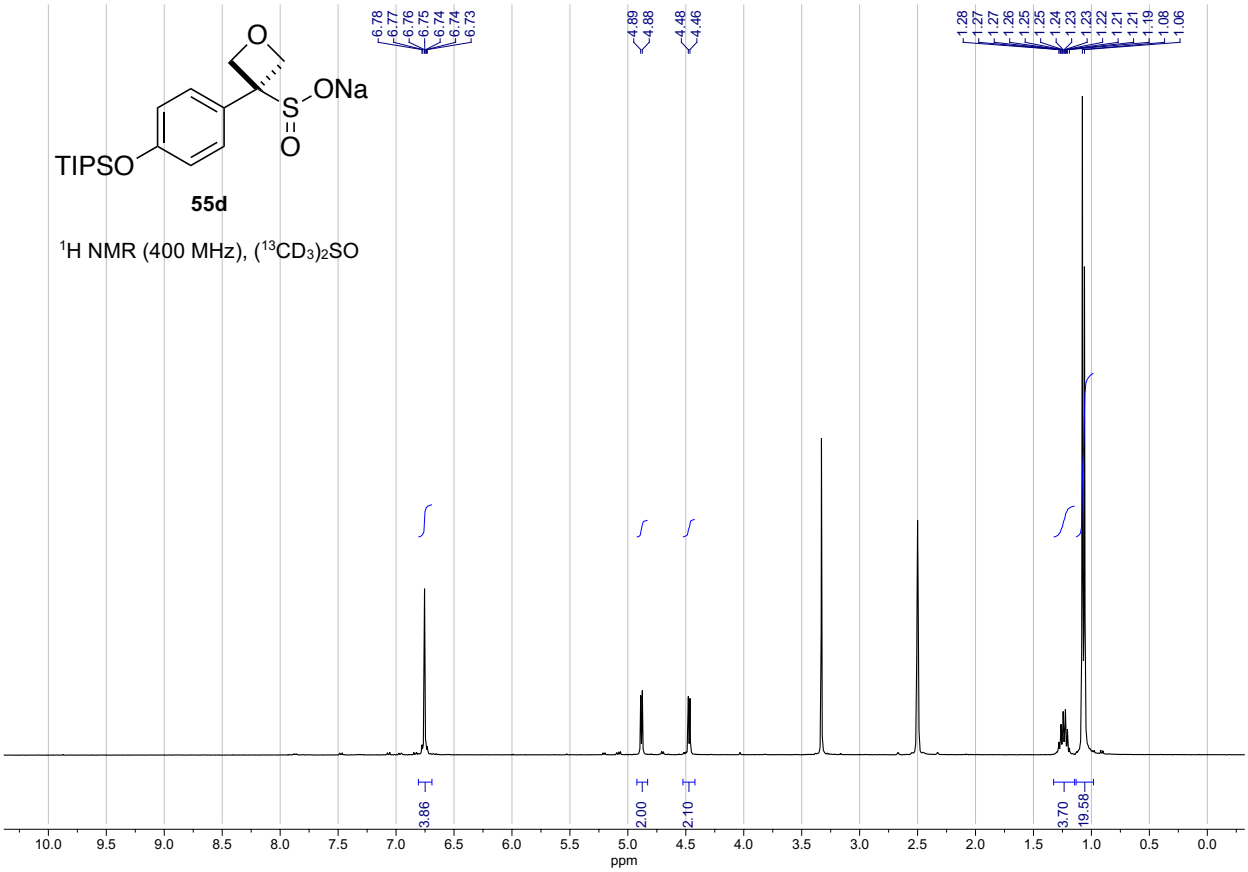

55a
^{13}C NMR (101 MHz), CDCl$_3$
155.8
134.7
125.8
119.9
85.5
75.7
17.9
12.6
ppm

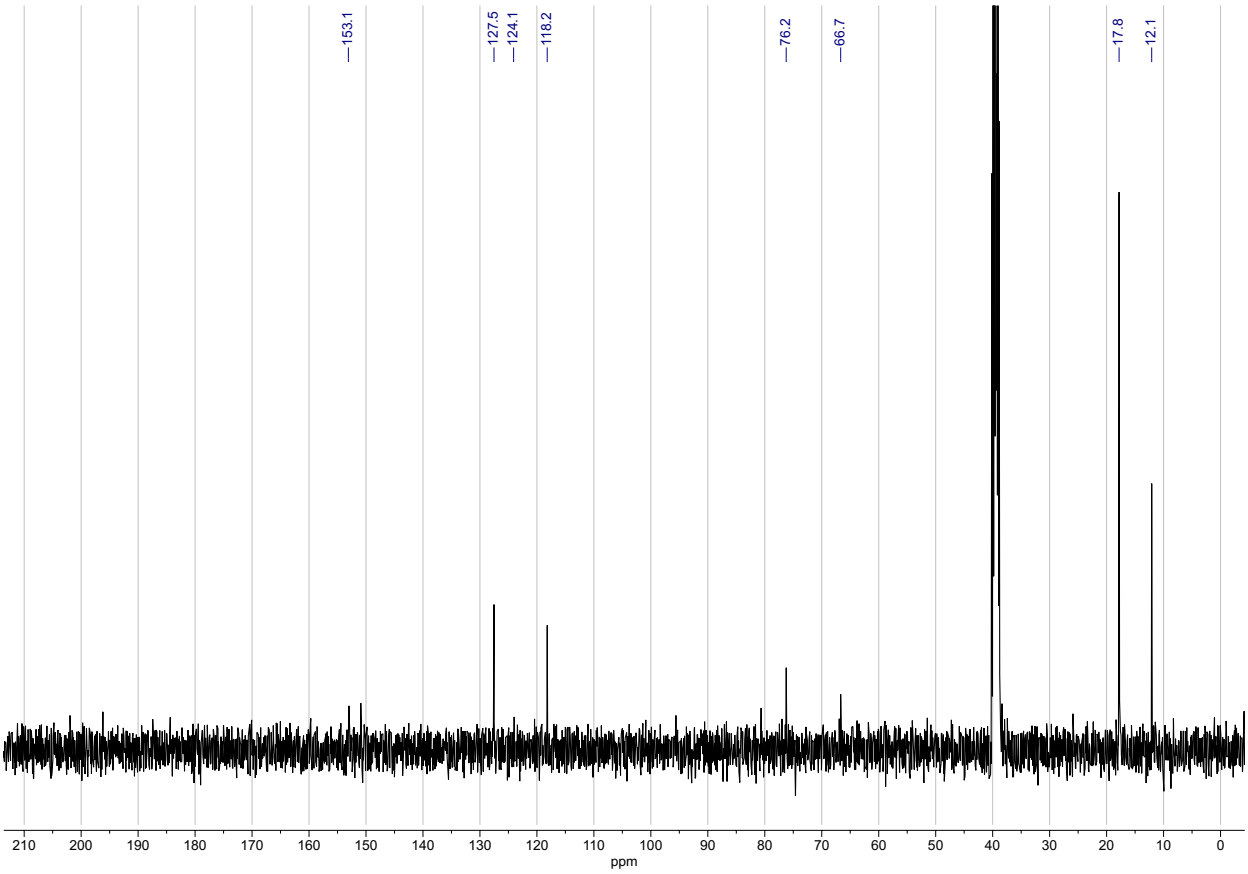

TIPSO
O
S
O
OMe
55b
^{1}H NMR (400 MHz), CDCl$_3$
ppm

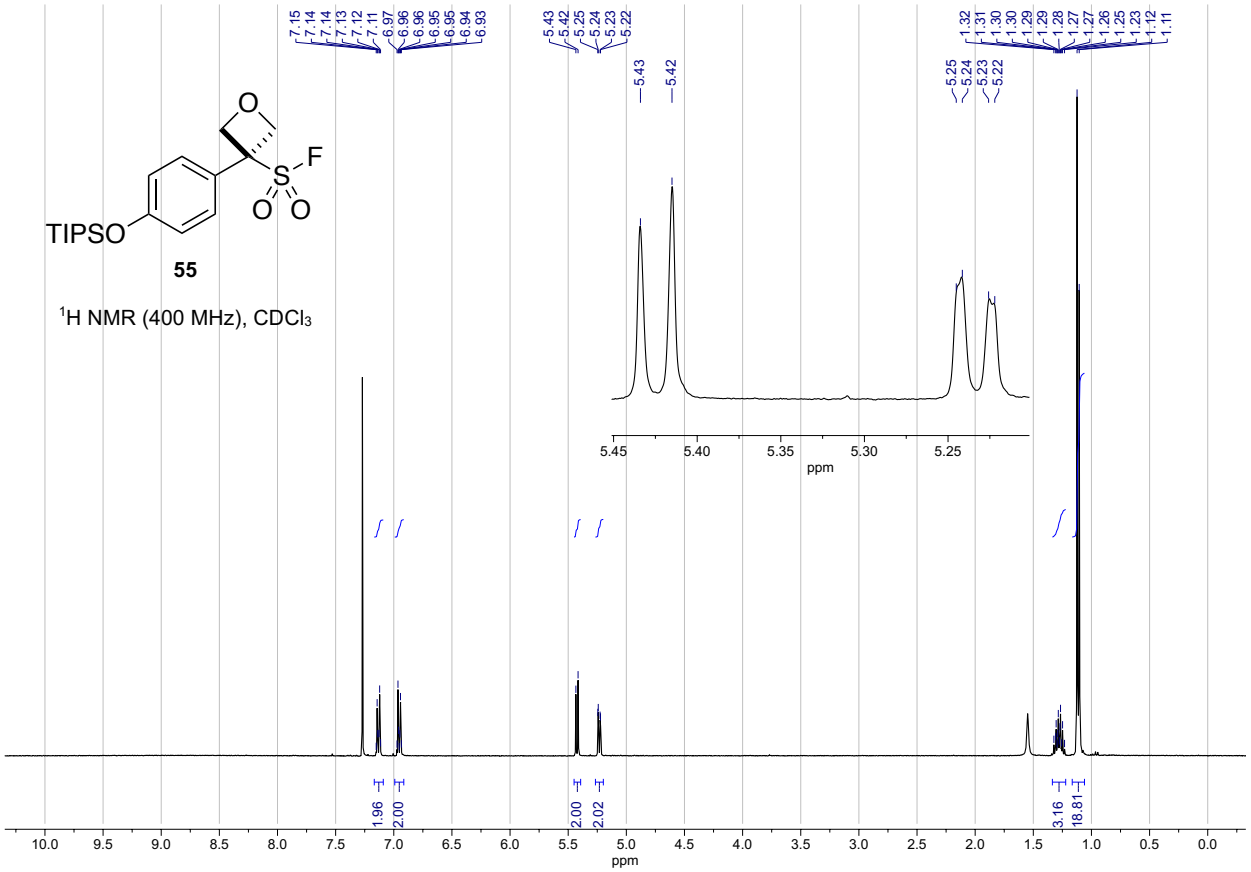

55b
^{13}C NMR (101 MHz), CDCl$_3$
ppm

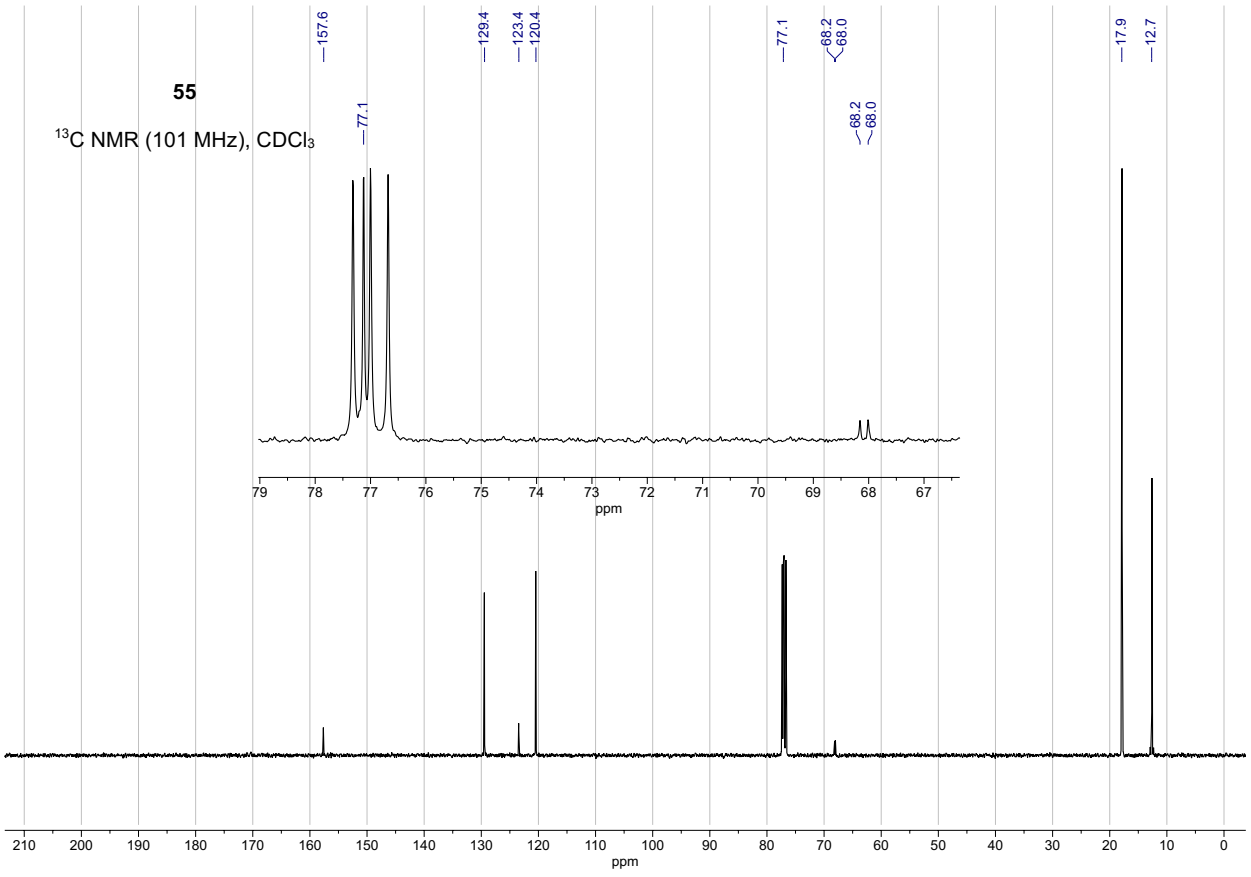

TIPSO
O
S
O
O
O
OMe
55c
^{1}H NMR (400 MHz), $CDCl_3$
7.18 7.17 7.16 7.15 7.15 7.14 6.96 6.96 6.95 6.94 6.93 6.93
5.41 5.39 5.13 5.11
3.70
3.08 3.06 3.06 3.04 2.68 2.67 2.66 2.65 1.32 1.31 1.30 1.29 1.29 1.28 1.28 1.27 1.27 1.26 1.25 1.24 1.23 1.12 1.11 1.10
1.99 1.98 2.00 2.00 2.96 2.01 2.01 3.15 18.31
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


55c
^{13}C NMR (101 MHz), $CDCl_3$
170.7
157.1
129.3
125.8
120.4
76.3
68.3
52.4
43.4
26.0
17.8
12.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


TIPSO
O
S
ONa
O
55d
^{1}H NMR (400 MHz), ($^{13}CD_3$)$_2$SO
6.78
6.77
6.76
6.75
6.74
6.74
6.73
4.89
4.88
4.48
4.46
1.28
1.27
1.27
1.26
1.25
1.25
1.24
1.23
1.23
1.22
1.21
1.21
1.19
1.08
1.06
3.86
2.00
2.10
3.70
19.58
ppm

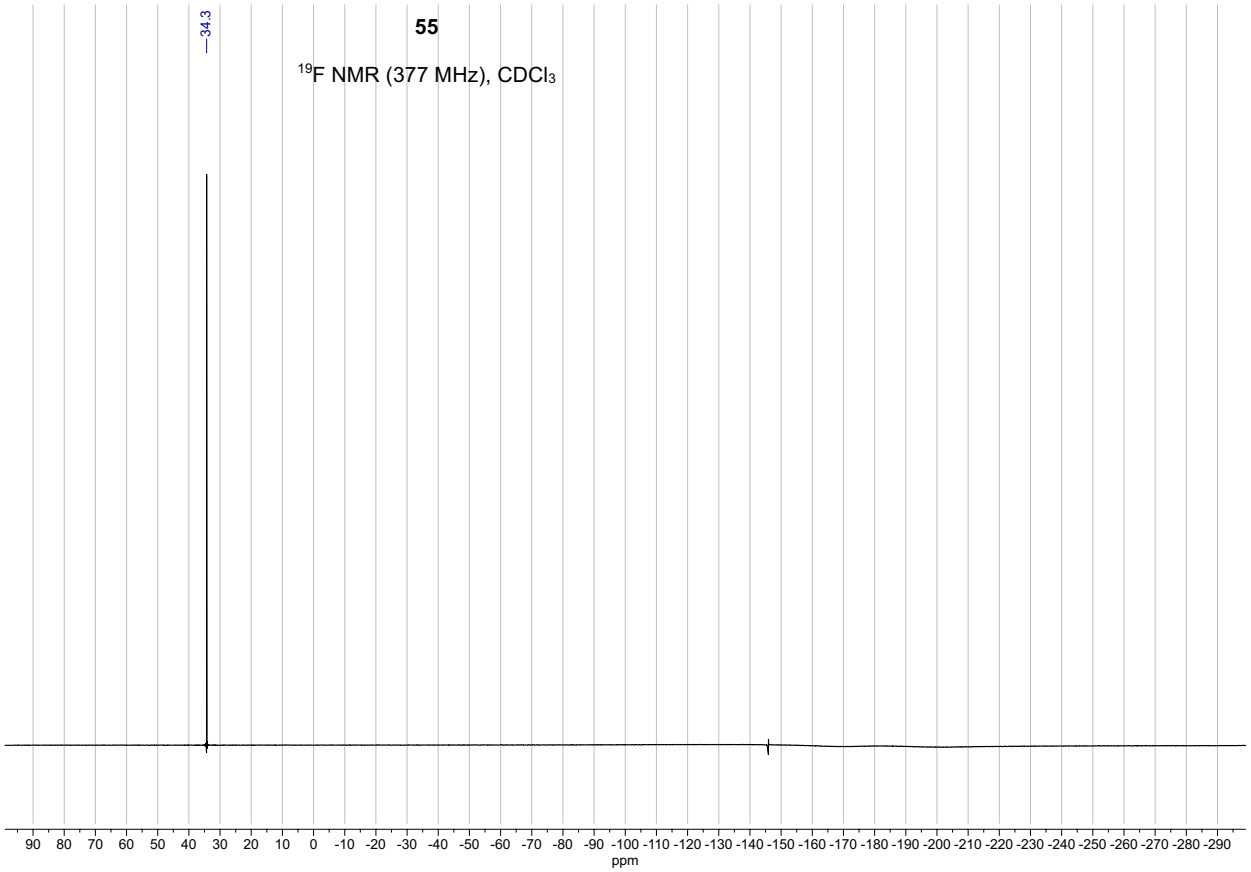

153.1
127.5
124.1
118.2
76.2
66.7
17.8
12.1
ppm

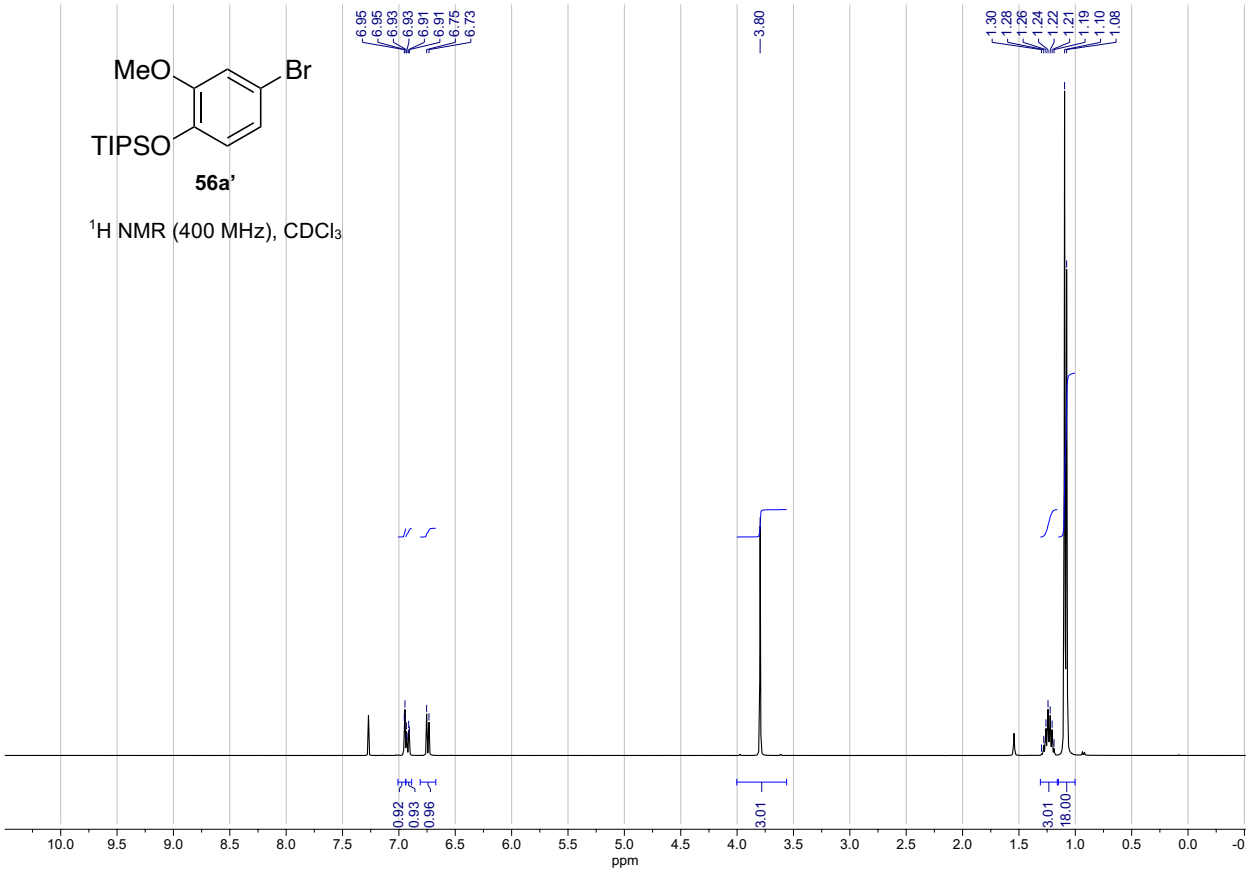

TIPSO
O
S
F
O
O
55
^{1}H NMR (400 MHz), $CDCl_3$
7.15
7.14
7.14
7.13
7.12
7.11
6.97
6.96
6.96
6.95
6.95
6.94
6.93
5.43
5.42
5.25
5.24
5.23
5.22
1.32
1.31
1.30
1.30
1.29
1.29
1.28
1.27
1.27
1.26
1.25
1.23
1.12
1.11
1.96
2.00
2.00
2.02
3.16
18.81
ppm

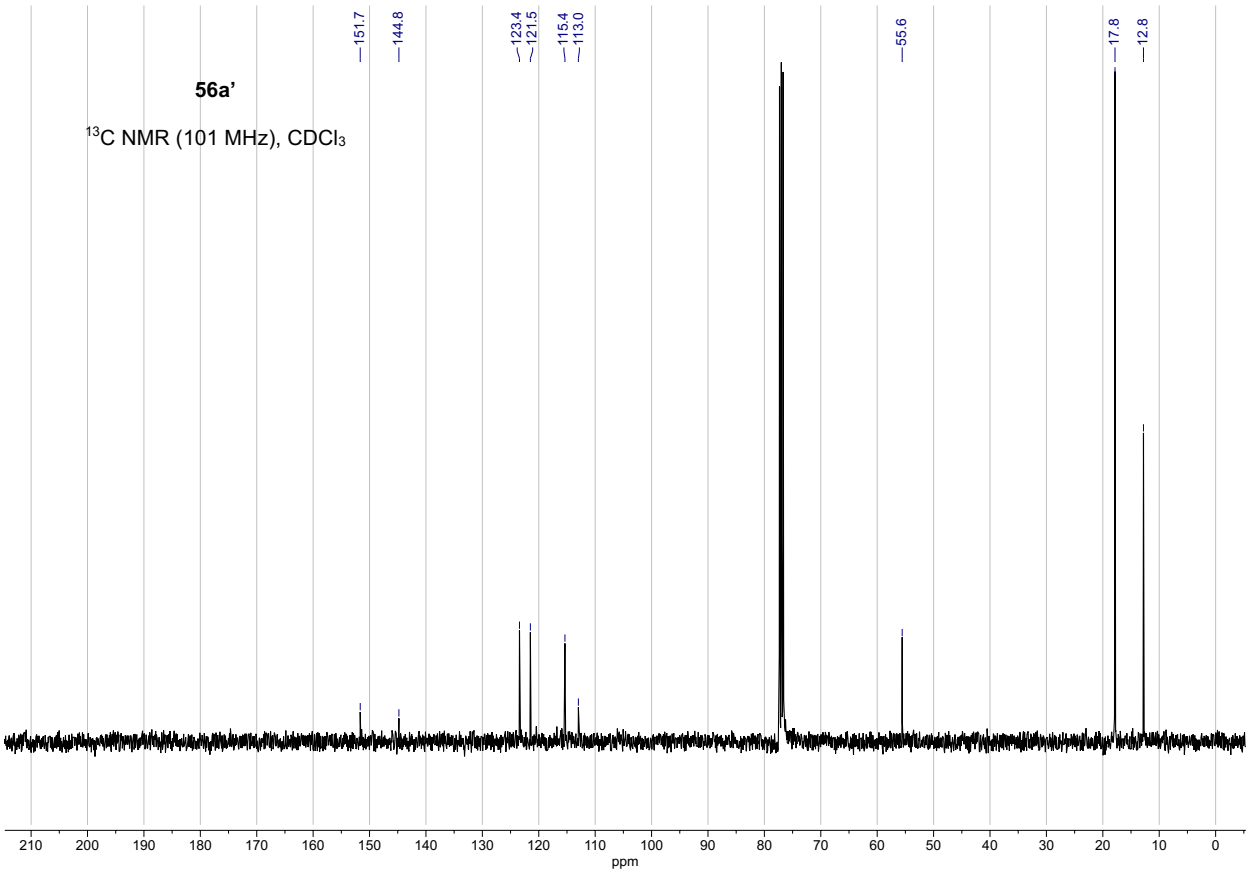

55
^{13}C NMR (101 MHz), $CDCl_3$
157.6
129.4
123.4
120.4
77.1
68.2
68.0
17.9
12.7
ppm

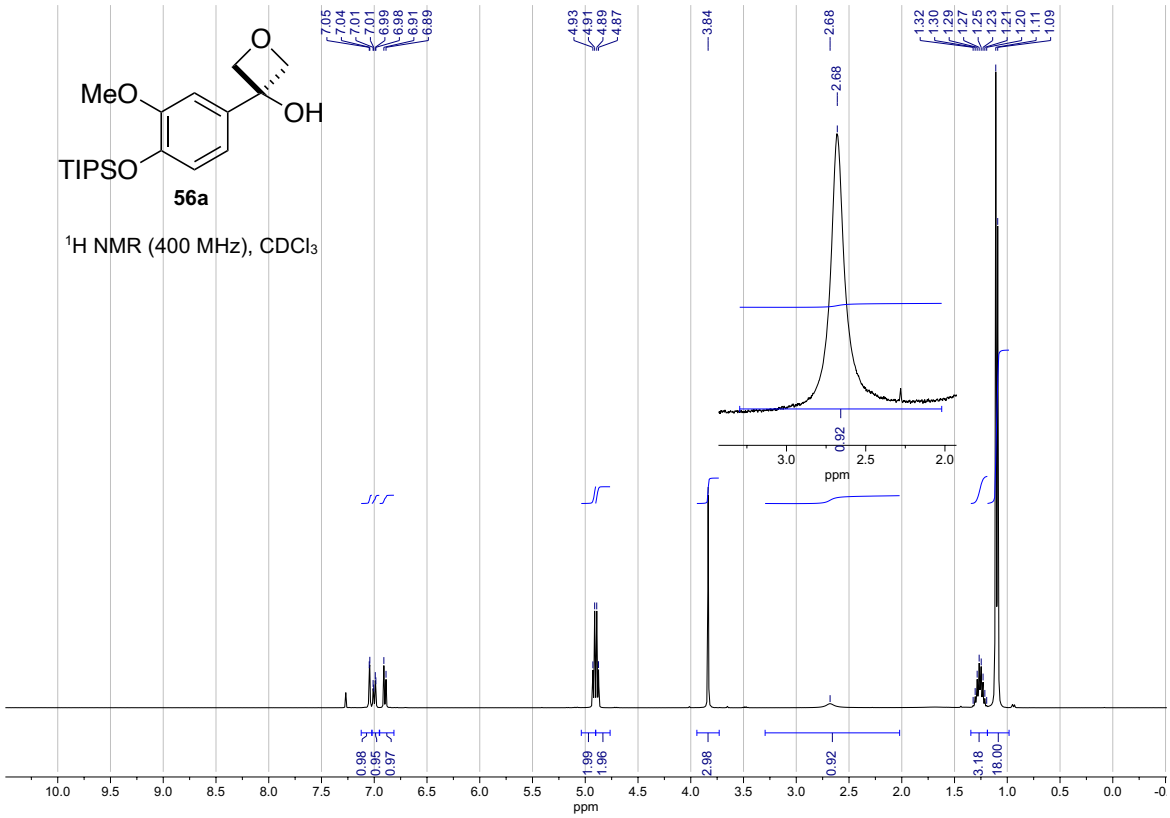
55

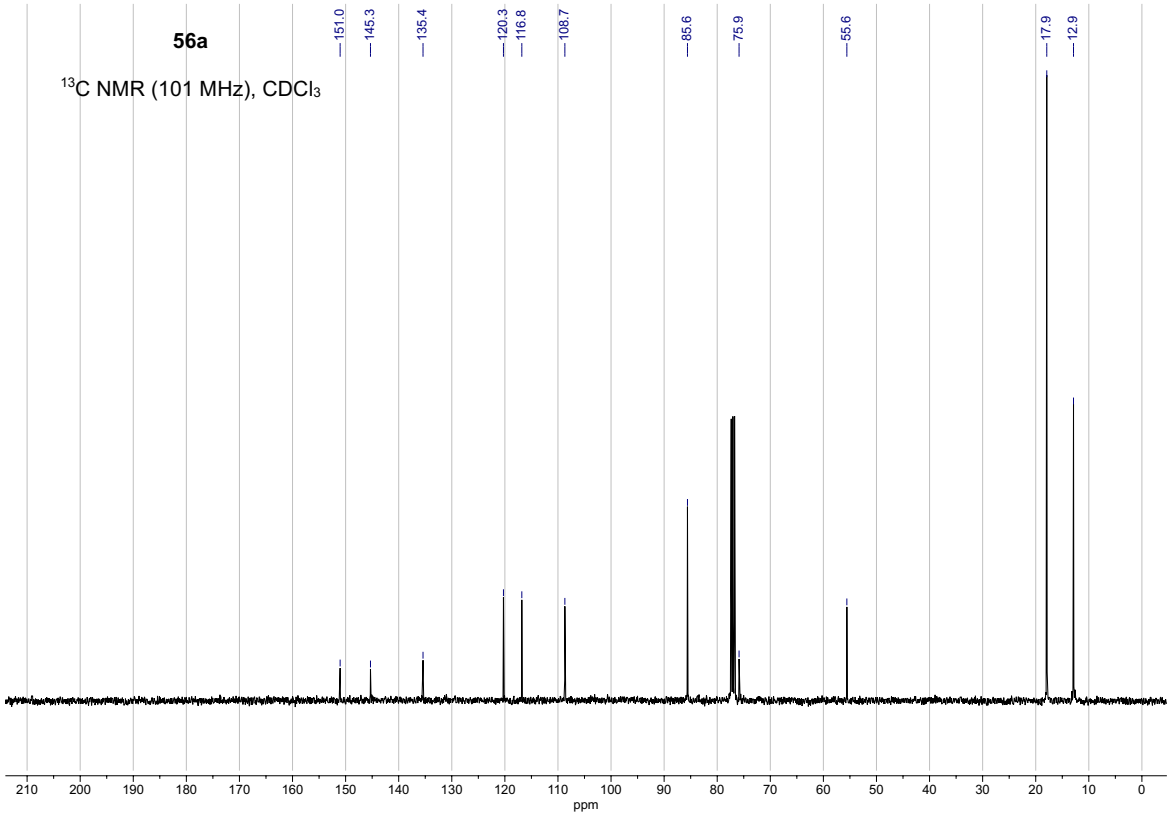
^{19}F NMR (377 MHz), $CDCl_3$

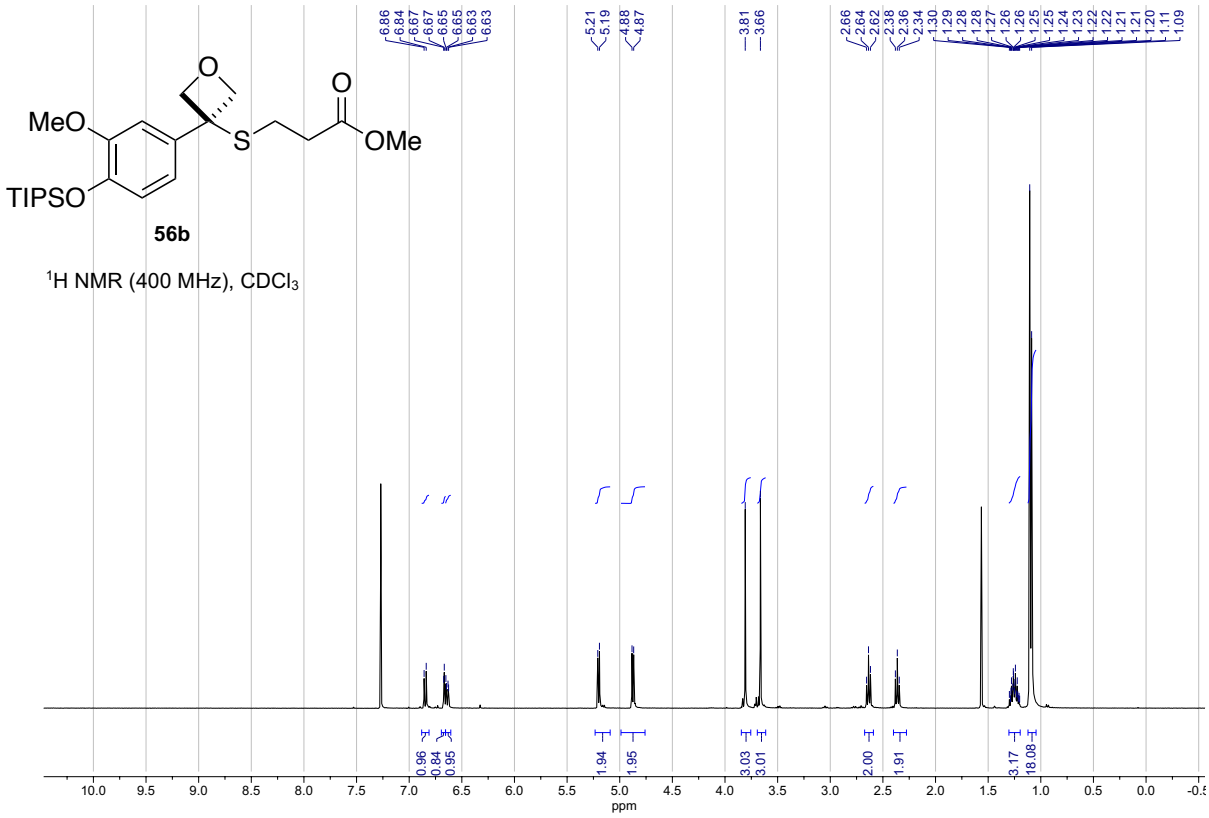



MeO
Br
TIPSO
56a'
^{1}H NMR (400 MHz), CDCl$_3$
6.95
6.95
6.93
6.93
6.91
6.91
6.75
6.73
3.80
1.30
1.28
1.26
1.24
1.22
1.21
1.19
1.10
1.08
0.92
0.93
0.96
3.01
3.01
18.00
ppm


56a'
^{13}C NMR (101 MHz), CDCl$_3$
151.7
144.8
123.4
121.5
115.4
113.0
55.6
17.8
12.8
ppm

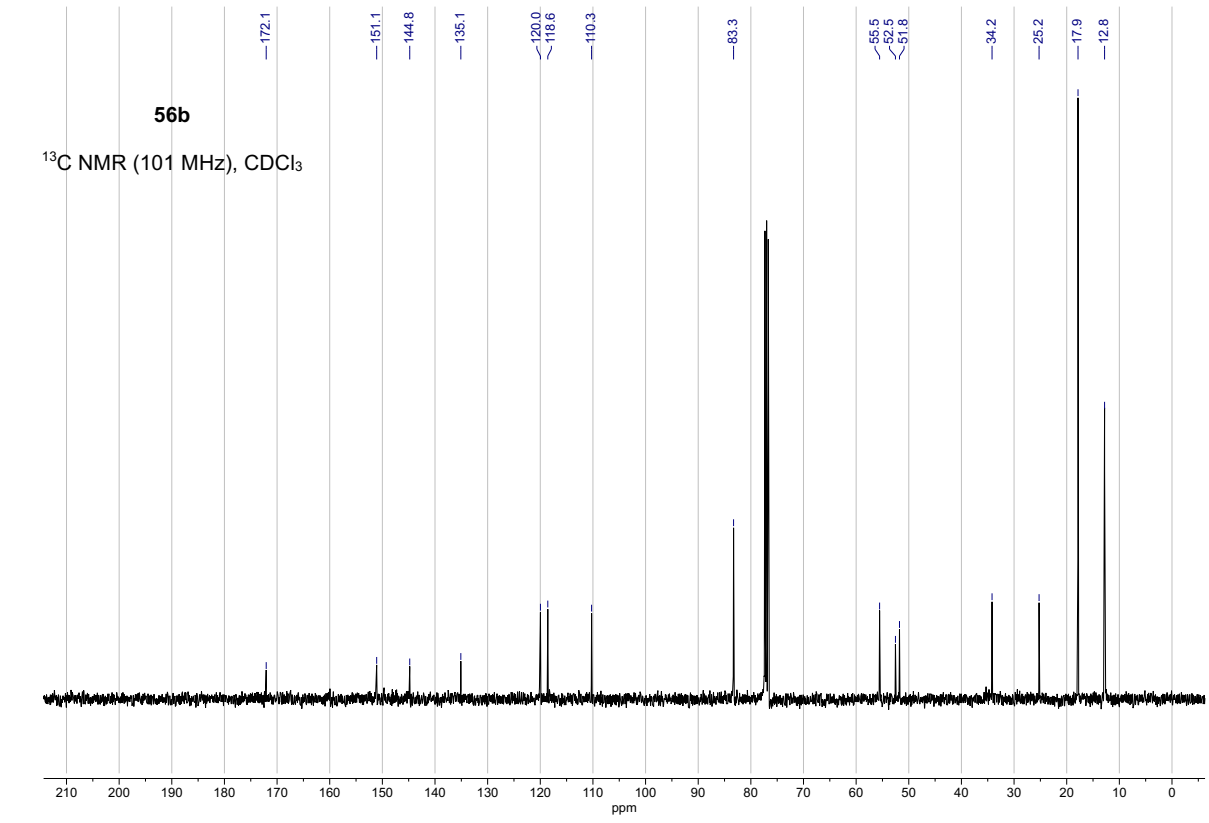

MeO
TIPSO
O
OH
56a
^{1}H NMR (400 MHz), CDCl$_3$
7.05
7.04
7.01
7.01
6.99
6.98
6.91
6.89
4.93
4.91
4.89
4.87
3.84
2.68
2.68
1.32
1.30
1.29
1.27
1.25
1.23
1.21
1.20
1.11
1.09
0.92
ppm
0.98
0.95
0.97
1.99
1.96
2.98
0.92
3.18
18.00
ppm


56a
^{13}C NMR (101 MHz), CDCl$_3$
151.0
145.3
135.4
120.3
116.8
108.7
85.6
75.9
55.6
17.9
12.9
ppm



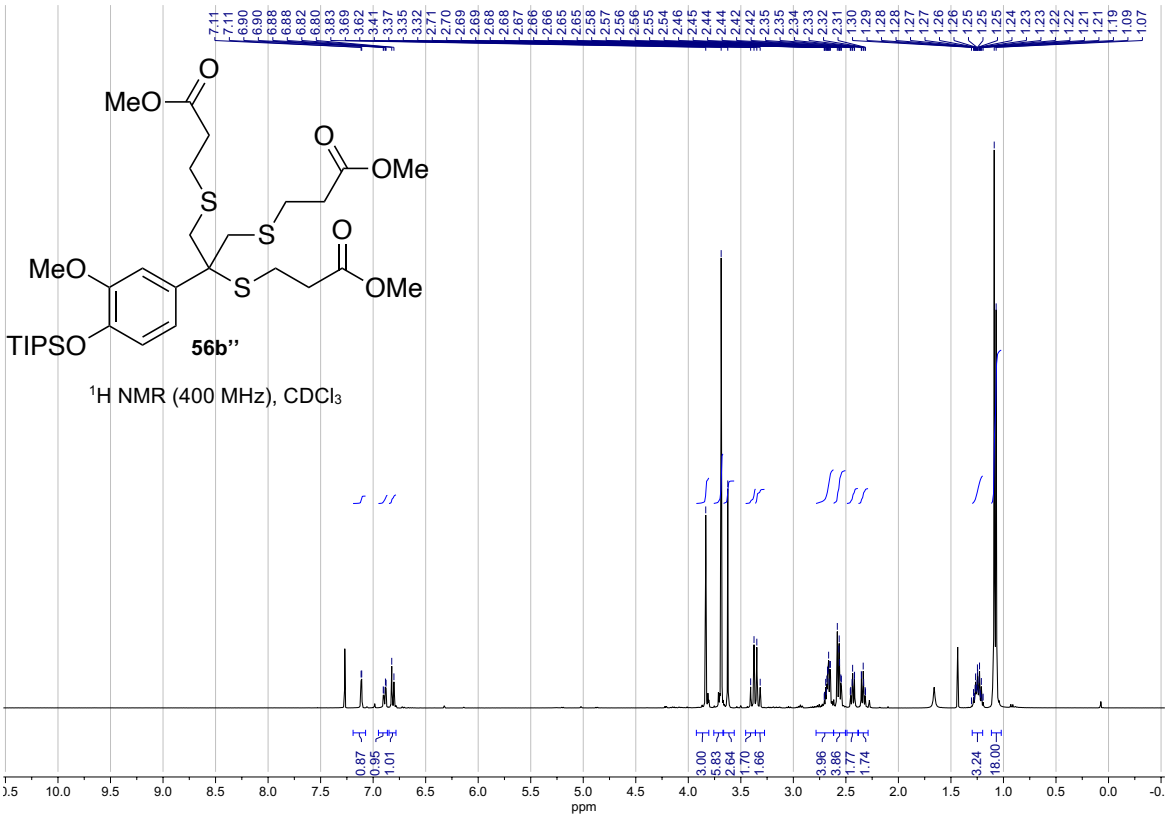
56b

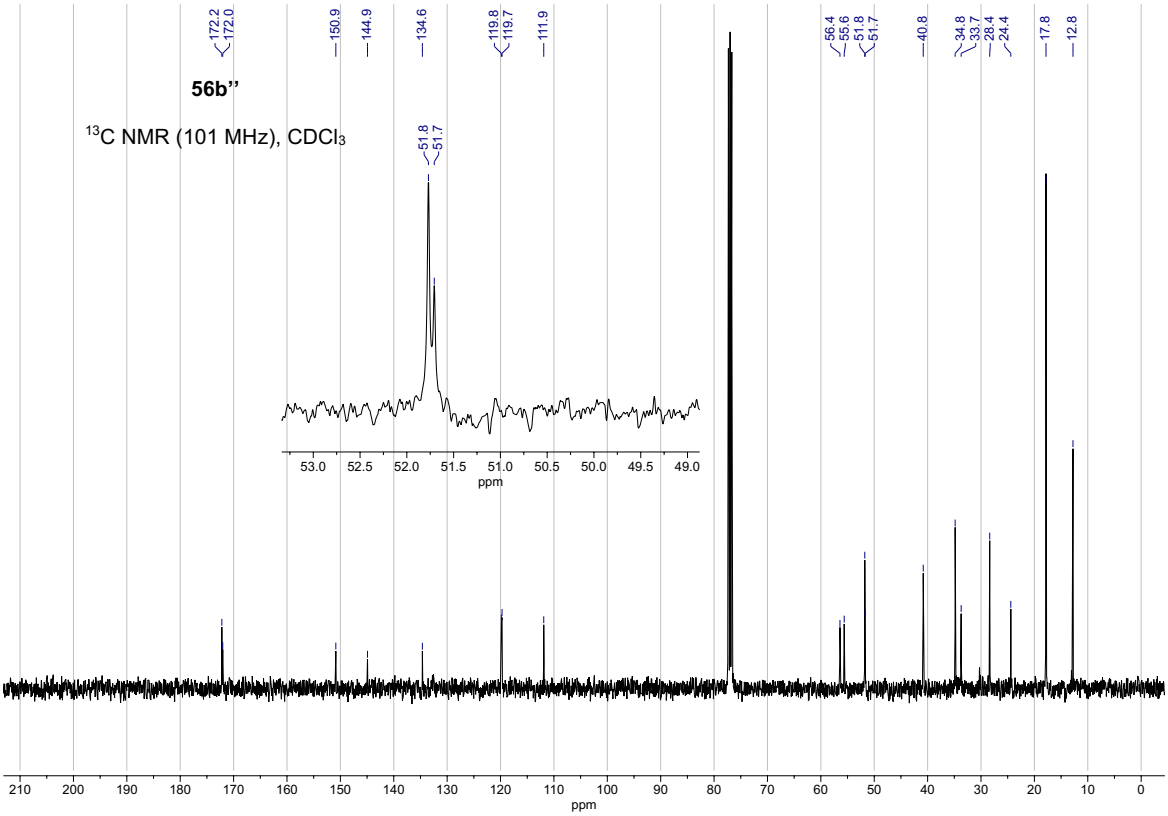
^{1}H NMR (400 MHz), $CDCl_3$

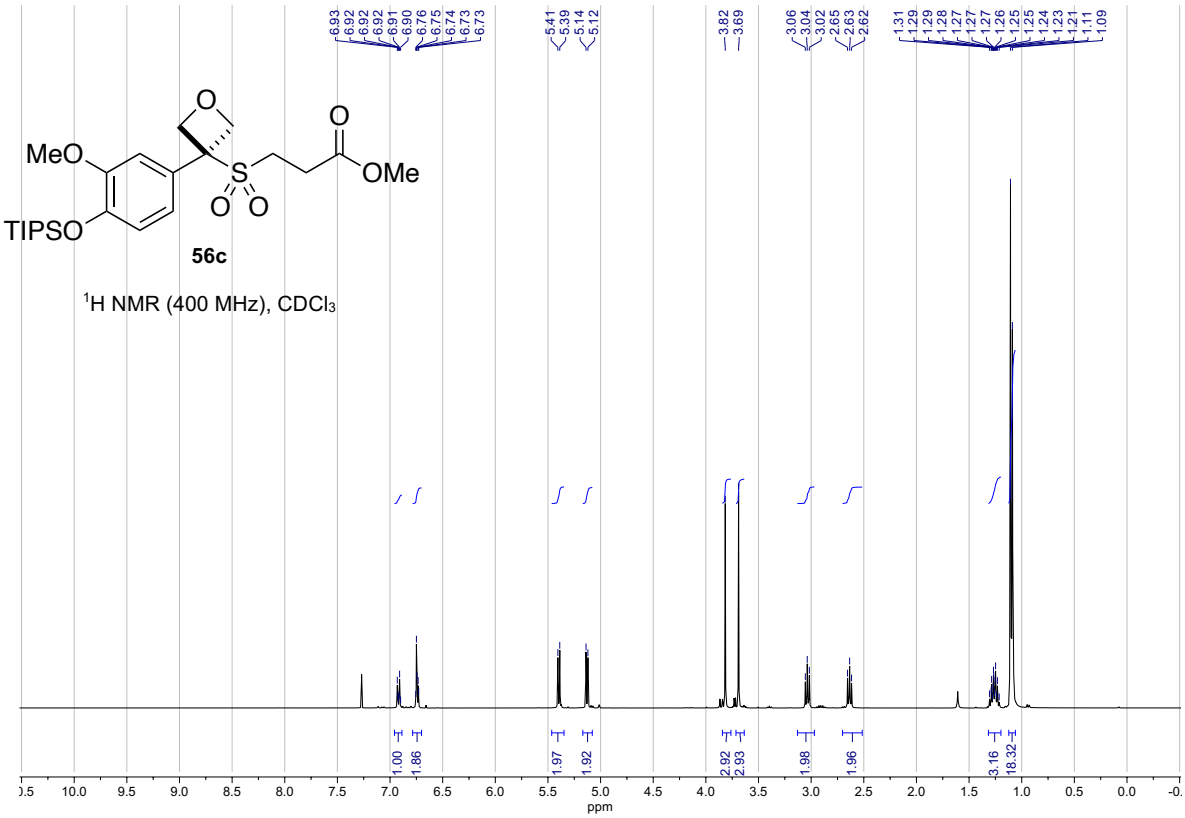


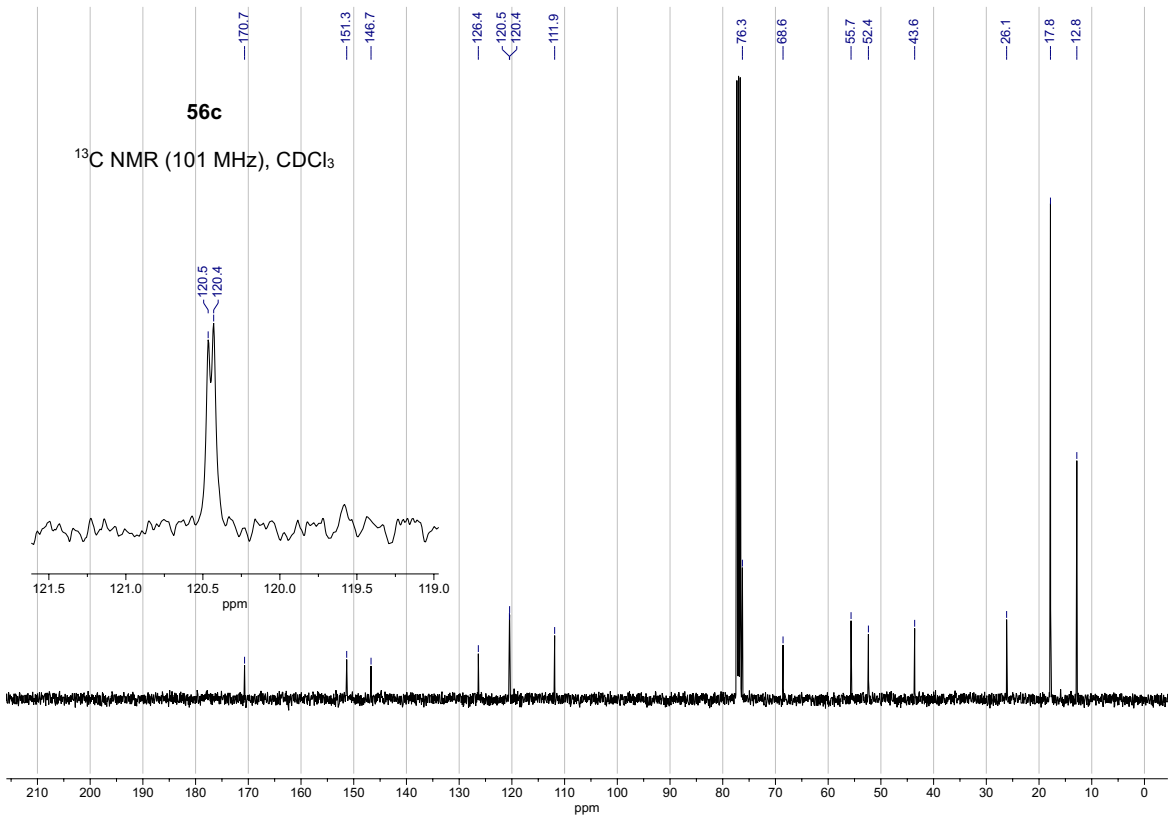
56b

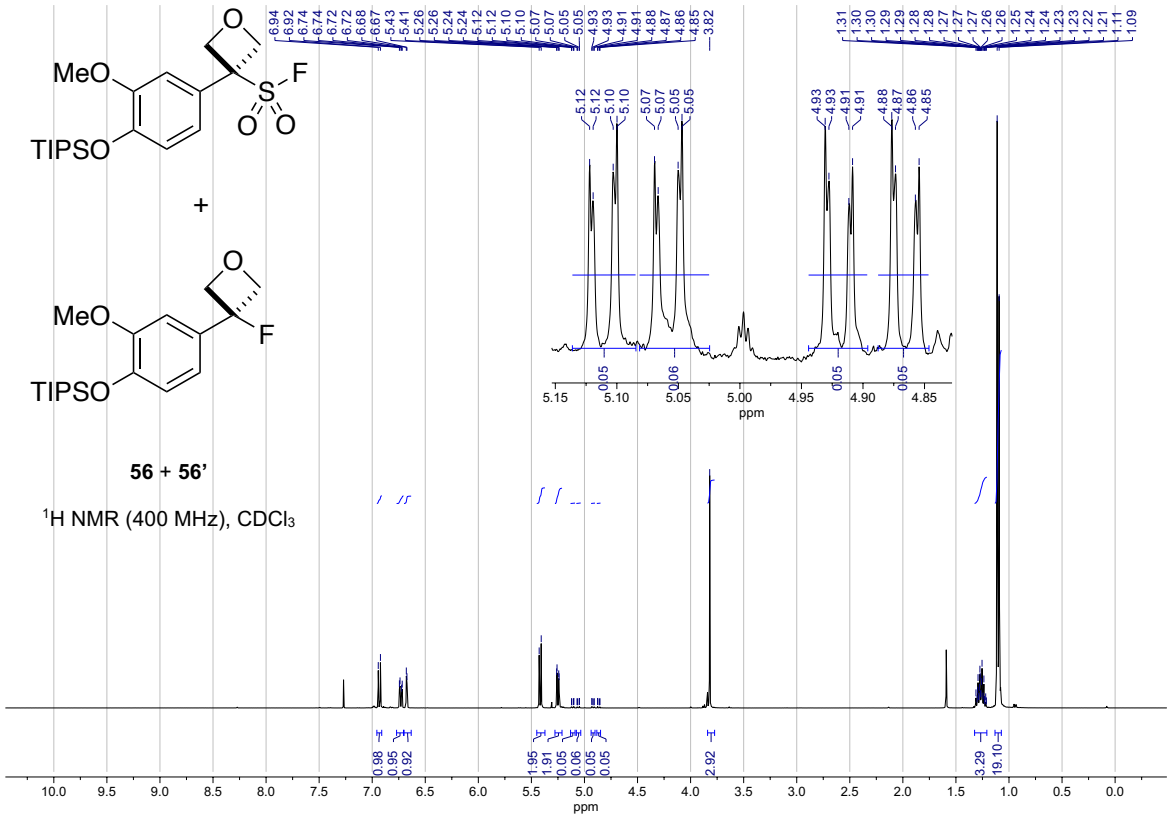
^{13}C NMR (101 MHz), $CDCl_3$

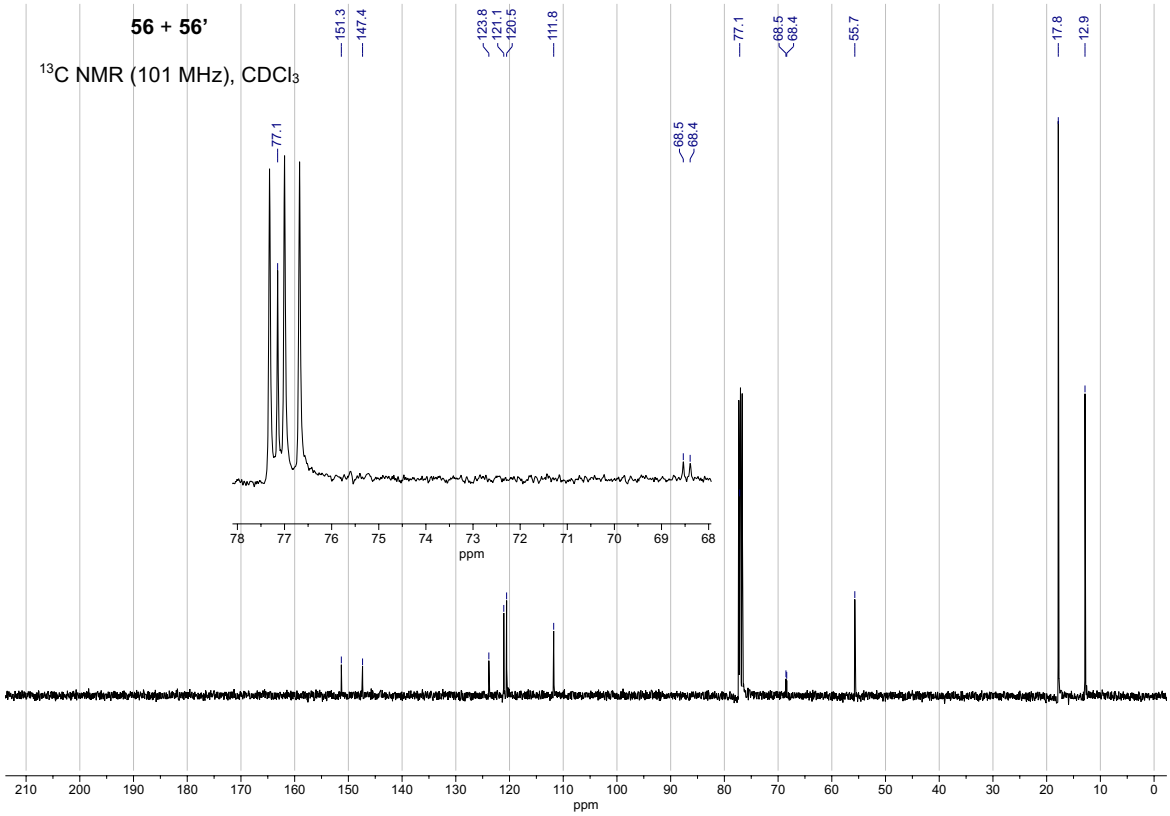

MeO
O
S
O
OMe
S
O
MeO
S
OMe
TIPSO
56b''
^{1}H NMR (400 MHz), $CDCl_3$
ppm

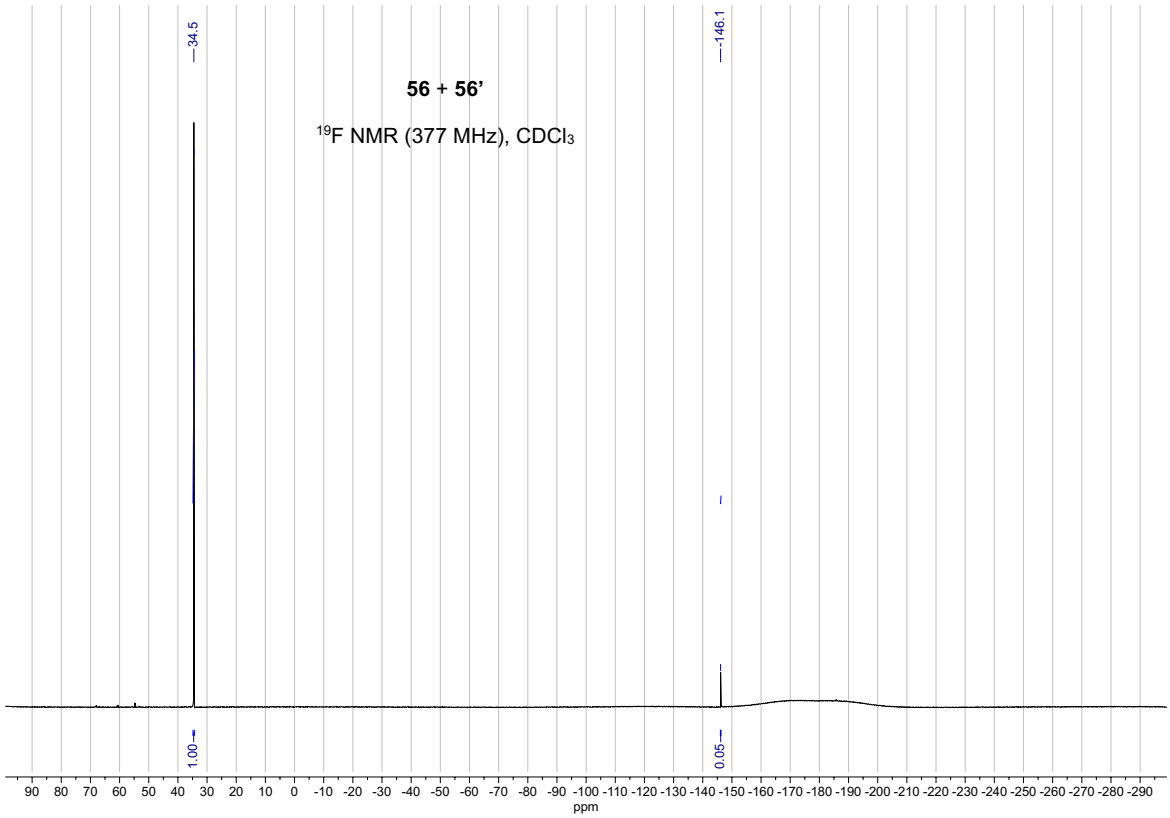

56b''
^{13}C NMR (101 MHz), $CDCl_3$
ppm

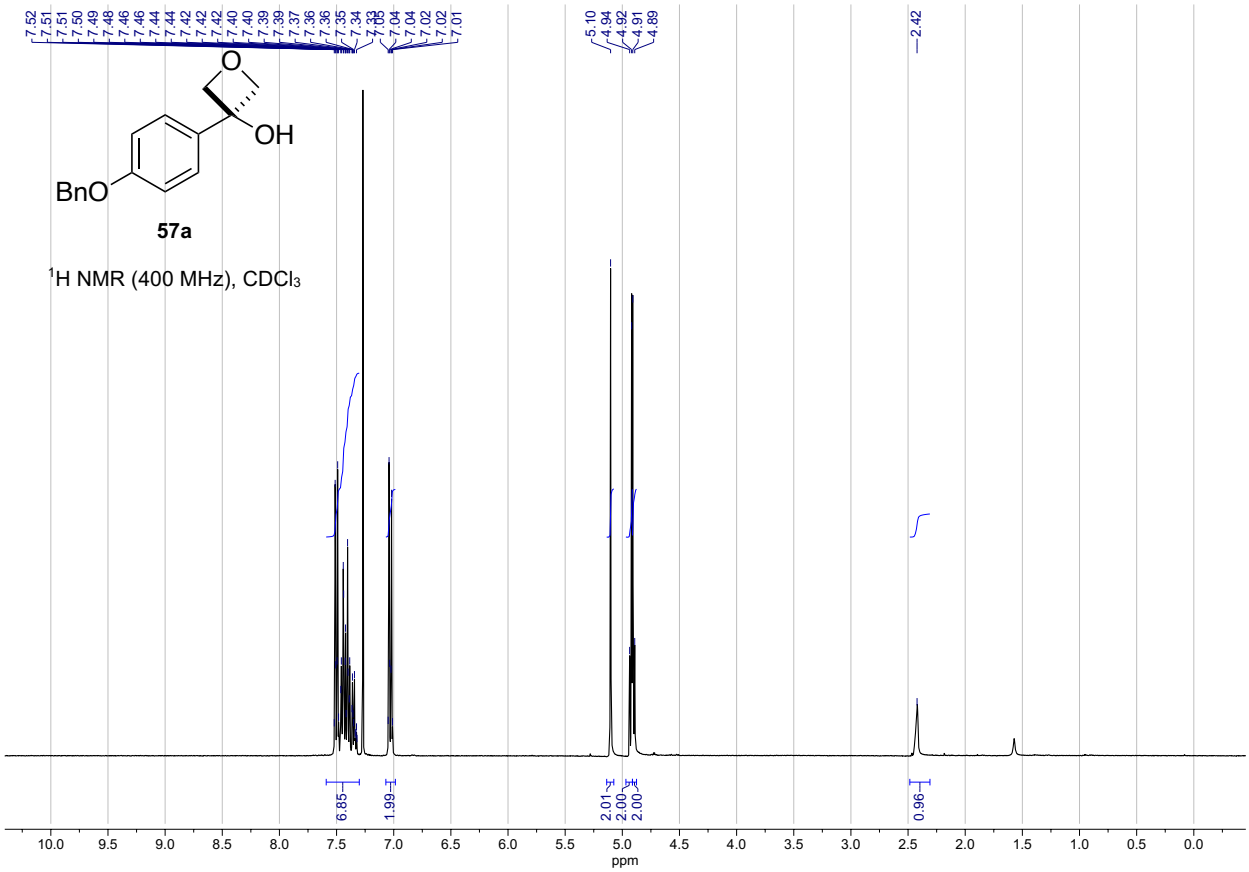

MeO
TIPSO
O
S
O
O
O
OMe
56c
^{1}H NMR (400 MHz), CDCl$_3$
ppm

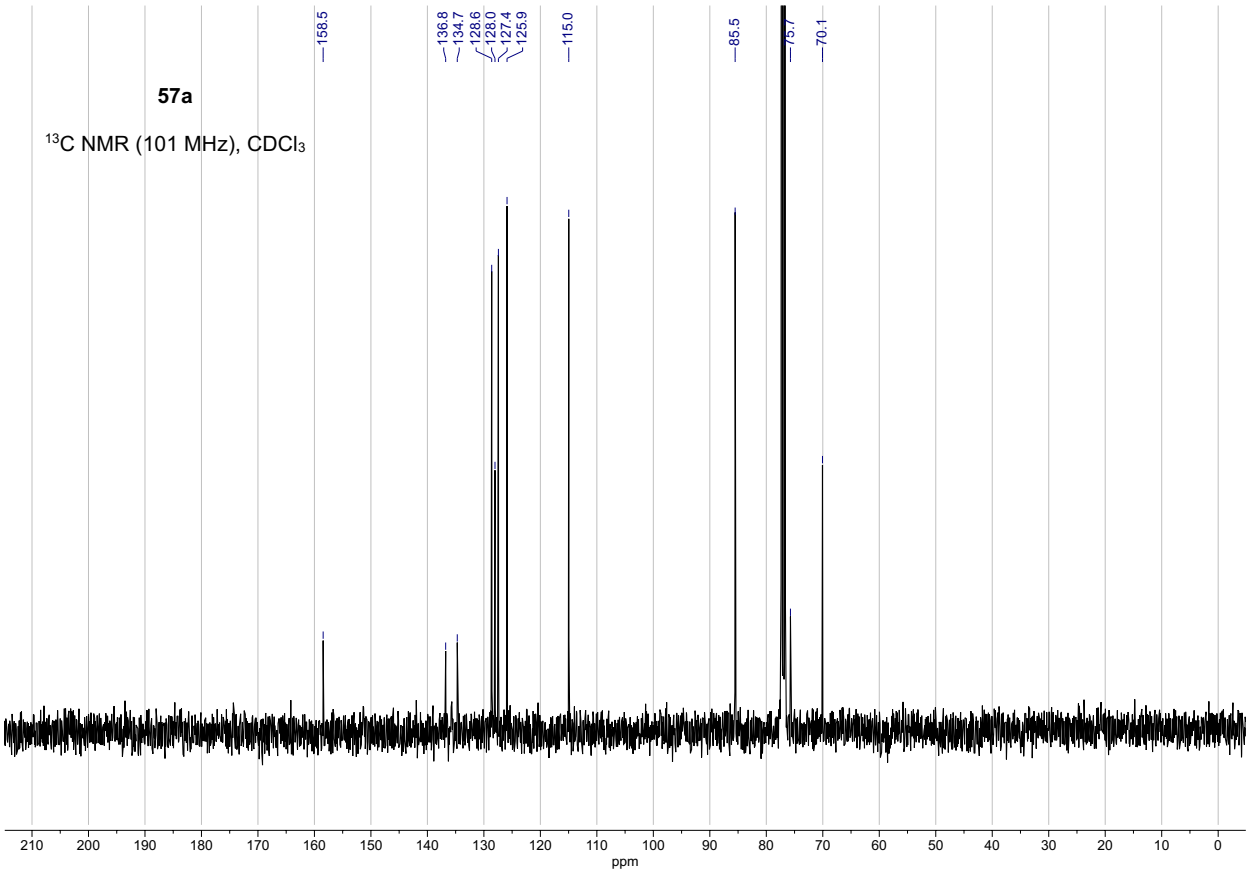

56c
^{13}C NMR (101 MHz), CDCl$_3$
ppm

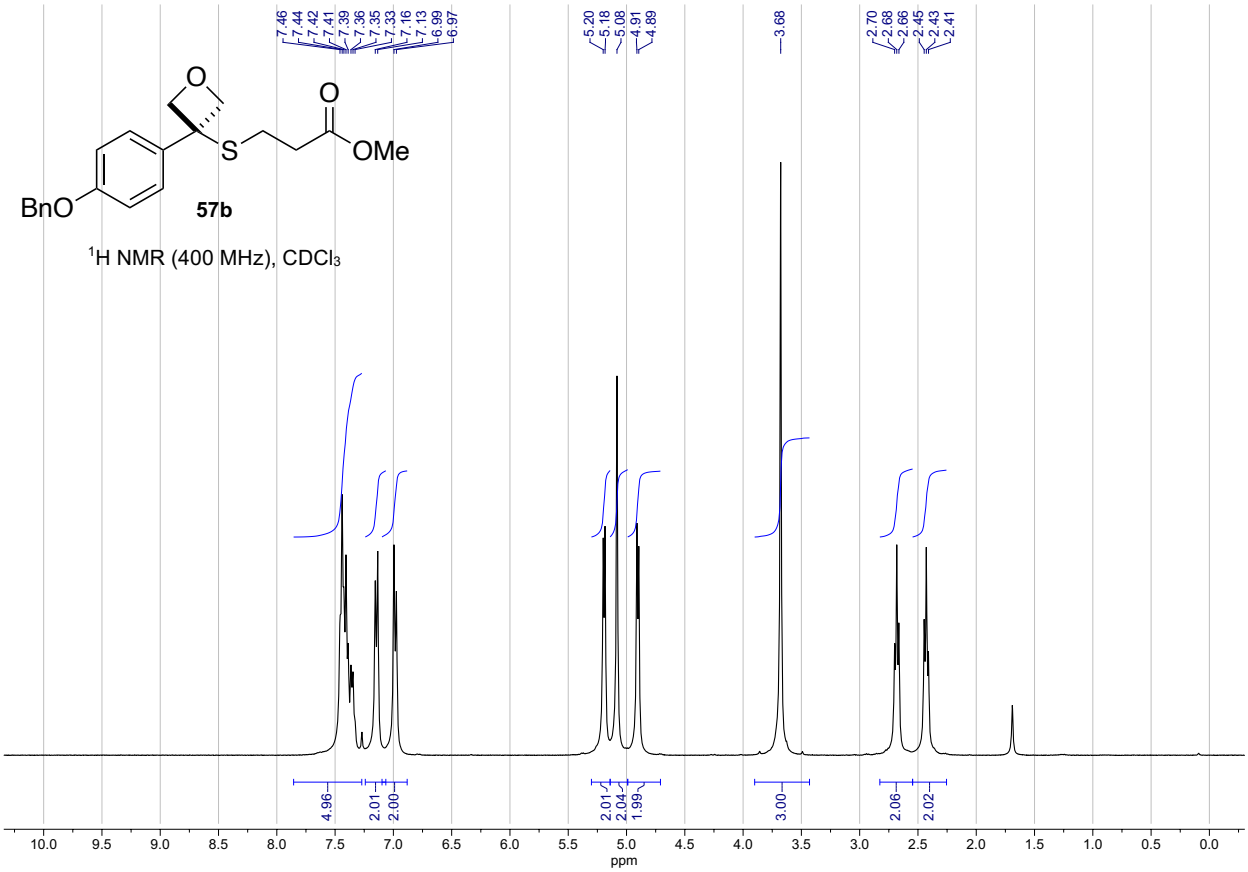

MeO
TIPSO
F
O
S
O
O
+
MeO
TIPSO
F
O
56 + 56'
^{1}H NMR (400 MHz), CDCl$_3$
ppm

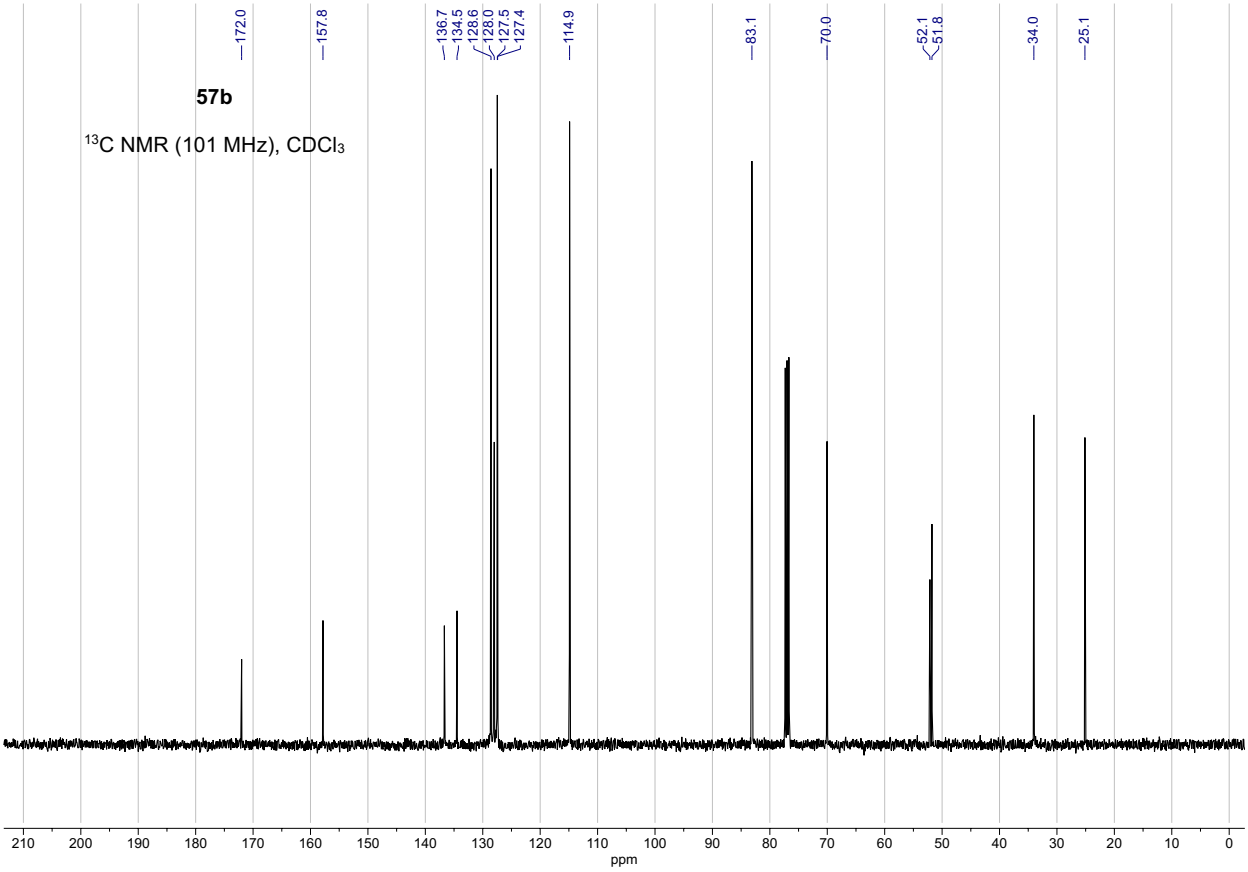

56 + 56'
^{13}C NMR (101 MHz), CDCl$_3$
151.3
147.4
123.8
121.1
120.5
111.8
77.1
68.5
68.4
55.7
17.8
12.9
ppm

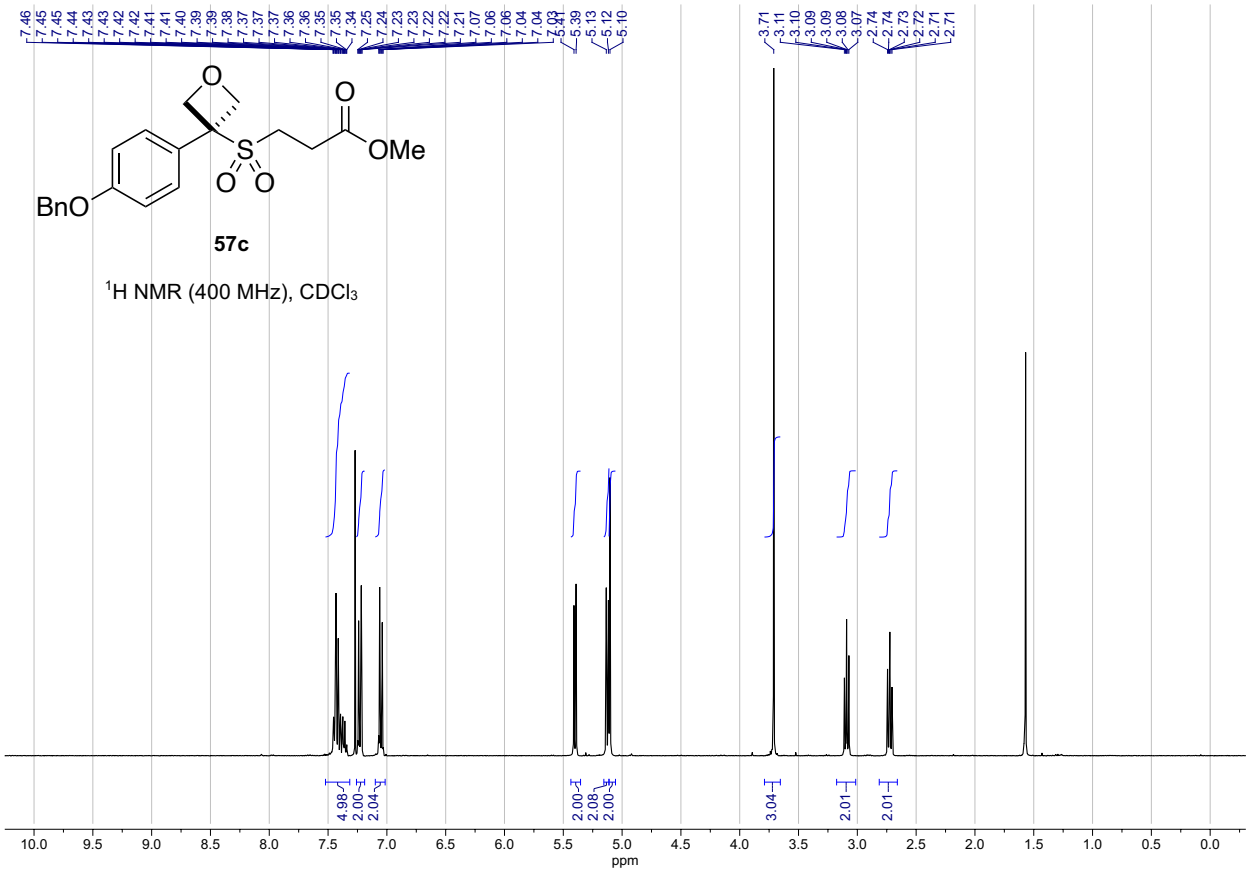

-34.5
-146.1
56 + 56'
^{19}F NMR (377 MHz), $CDCl_3$
1.00
0.05
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

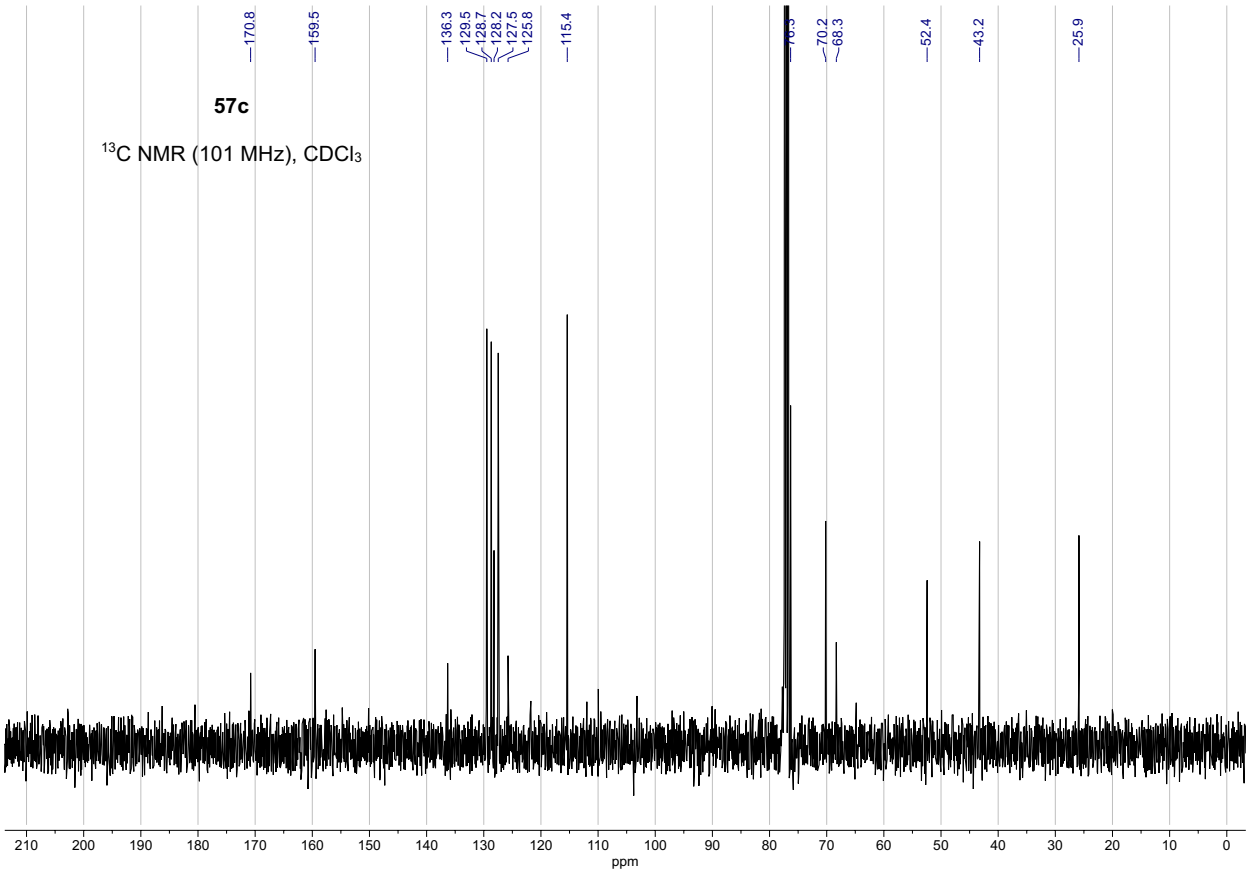

7.52
7.51
7.51
7.50
7.49
7.48
7.46
7.46
7.44
7.44
7.42
7.42
7.42
7.40
7.40
7.39
7.39
7.37
7.36
7.36
7.35
7.34
7.33
7.05
7.04
7.04
7.02
7.02
7.01
5.10
4.94
4.92
4.91
4.89
2.42
O
OH
BnO
57a
^{1}H NMR (400 MHz), CDCl$_3$
6.85
1.99
2.01
2.00
2.00
0.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

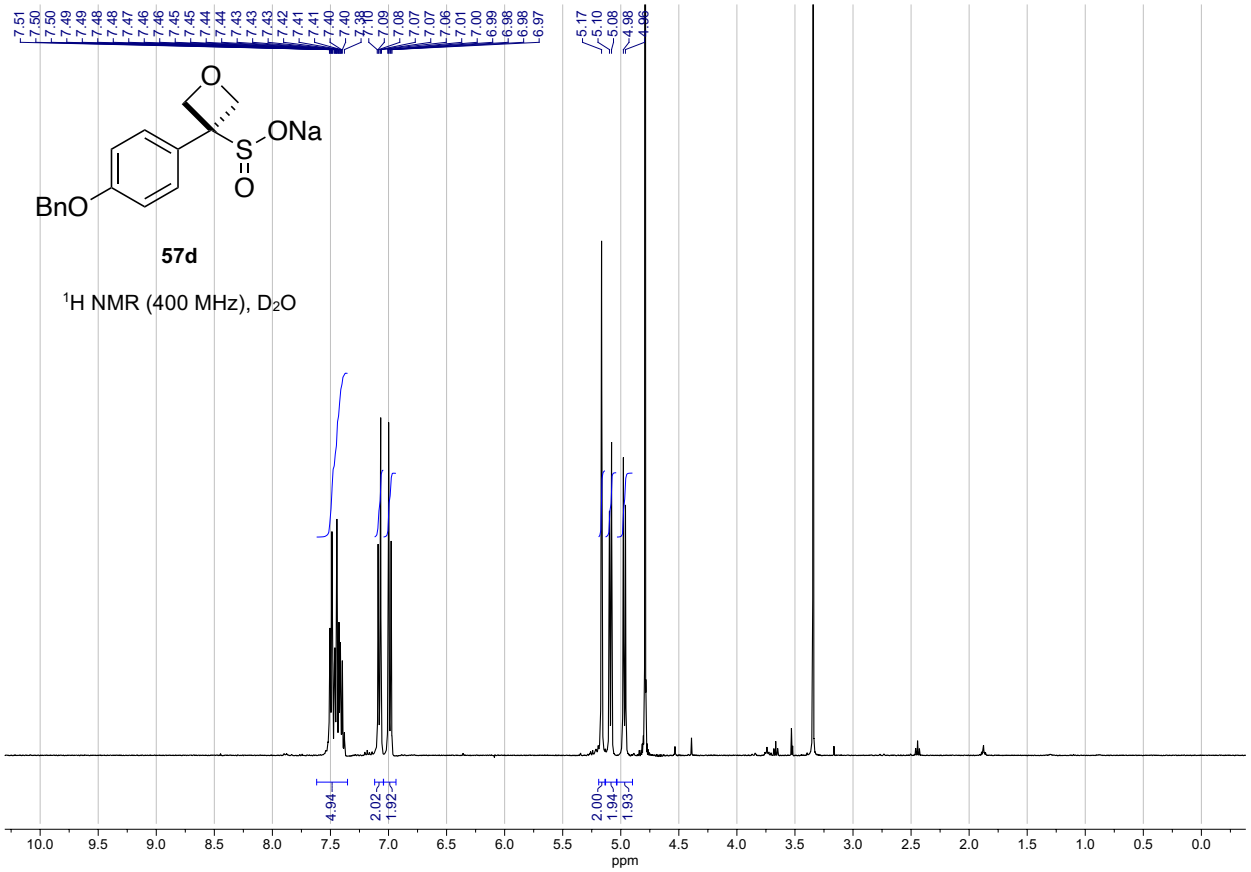

158.5
136.8
134.7
128.6
128.0
127.4
125.9
115.0
85.5
75.7
70.1
57a
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

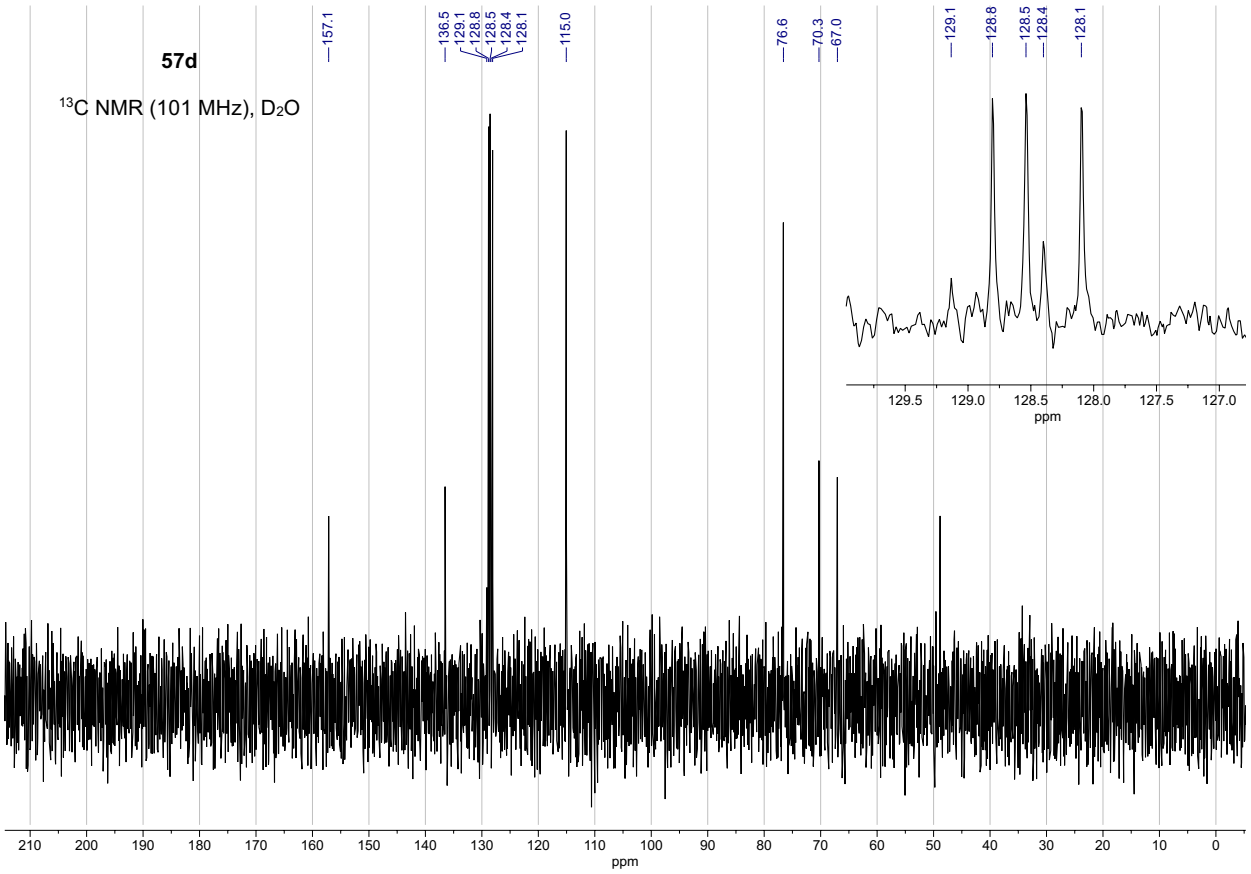

7.46
7.44
7.42
7.41
7.39
7.36
7.35
7.33
7.16
7.13
6.99
6.97
5.20
5.18
5.08
4.91
4.89
3.68
2.70
2.68
2.66
2.45
2.43
2.41
O
O
S
OMe
BnO
57b
^{1}H NMR (400 MHz), CDCl$_3$
4.96
2.01
2.00
2.01
2.04
1.99
3.00
2.06
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

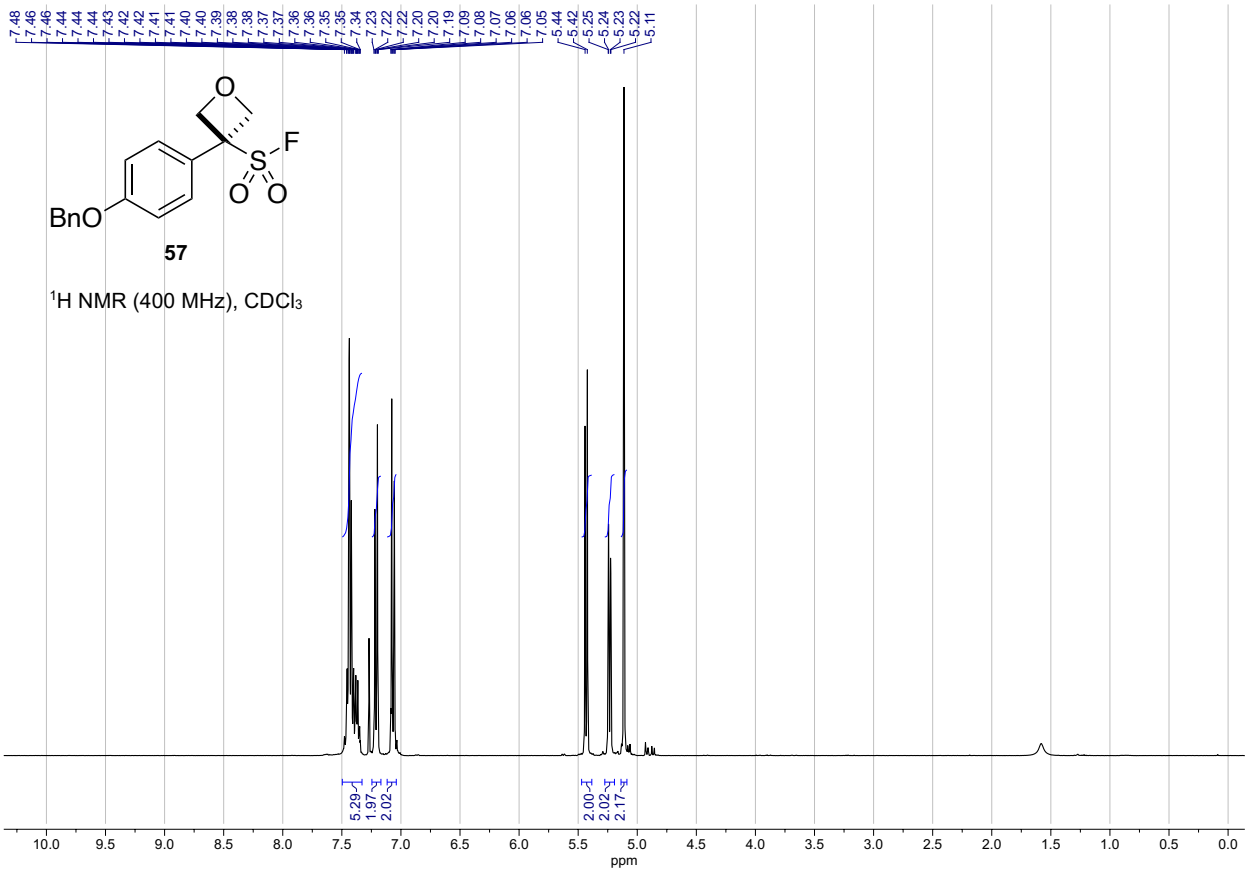

172.0
157.8
136.7
134.5
128.6
128.0
127.5
127.4
114.9
83.1
70.0
52.1
51.8
34.0
25.1
57b
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

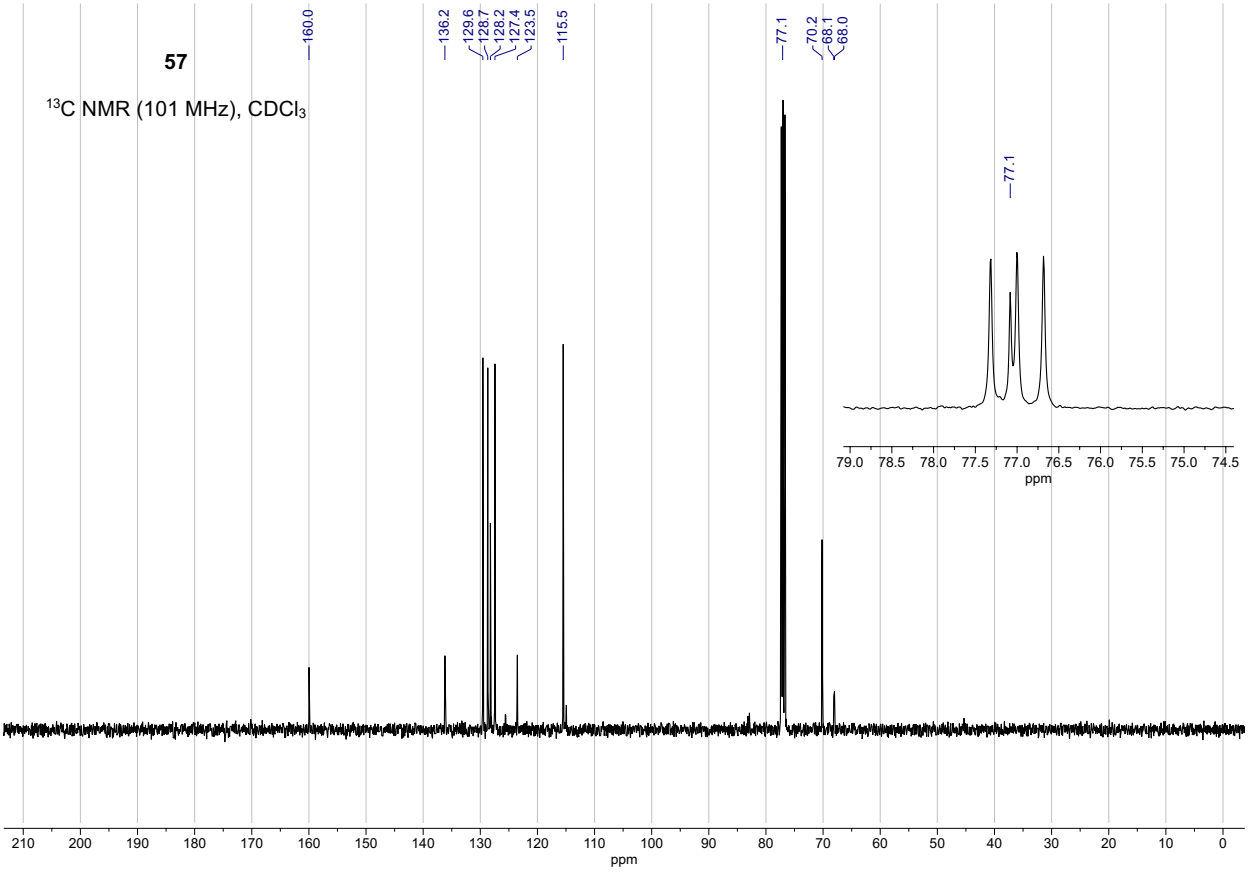

BnO
O
S
O
O
O
OMe
57c
^{1}H NMR (400 MHz), $CDCl_3$
ppm

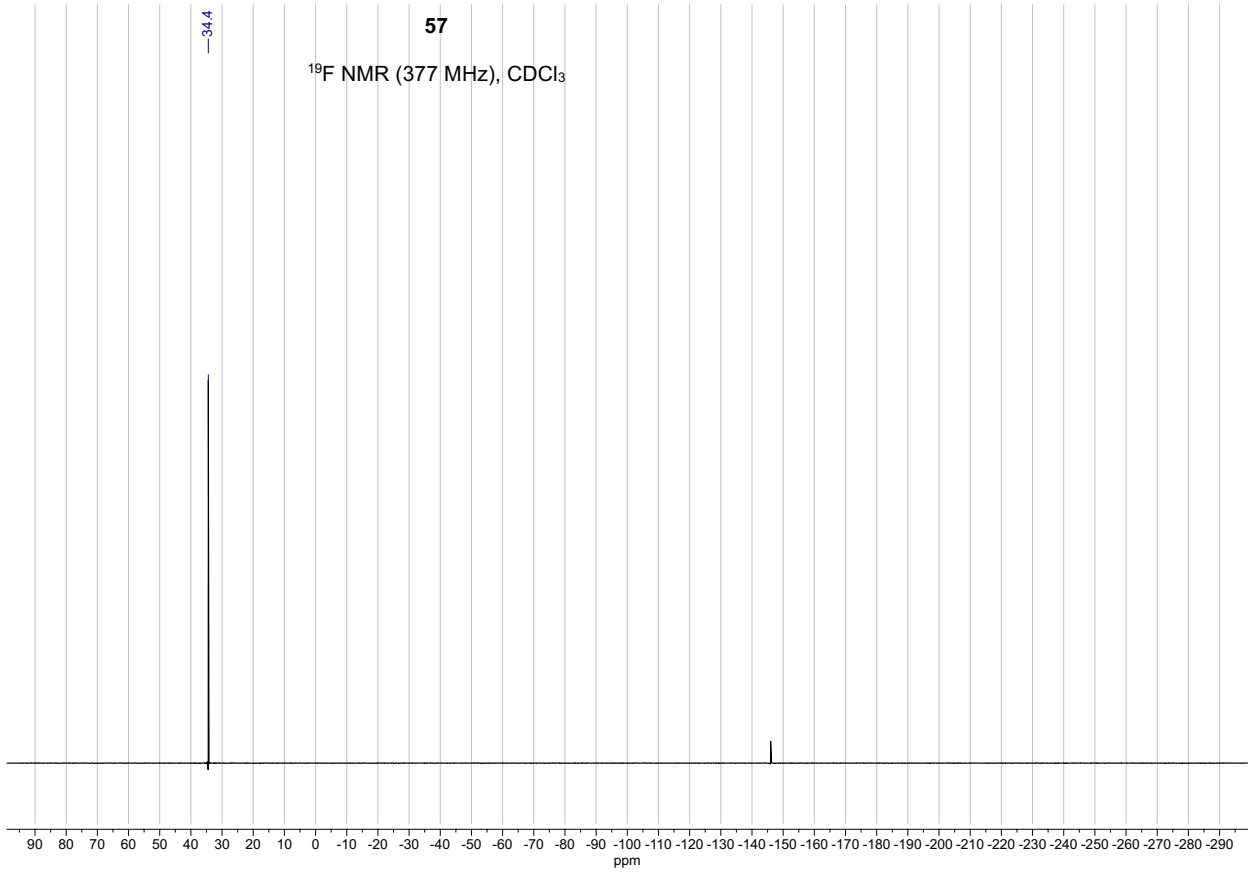

57c
^{13}C NMR (101 MHz), $CDCl_3$
ppm

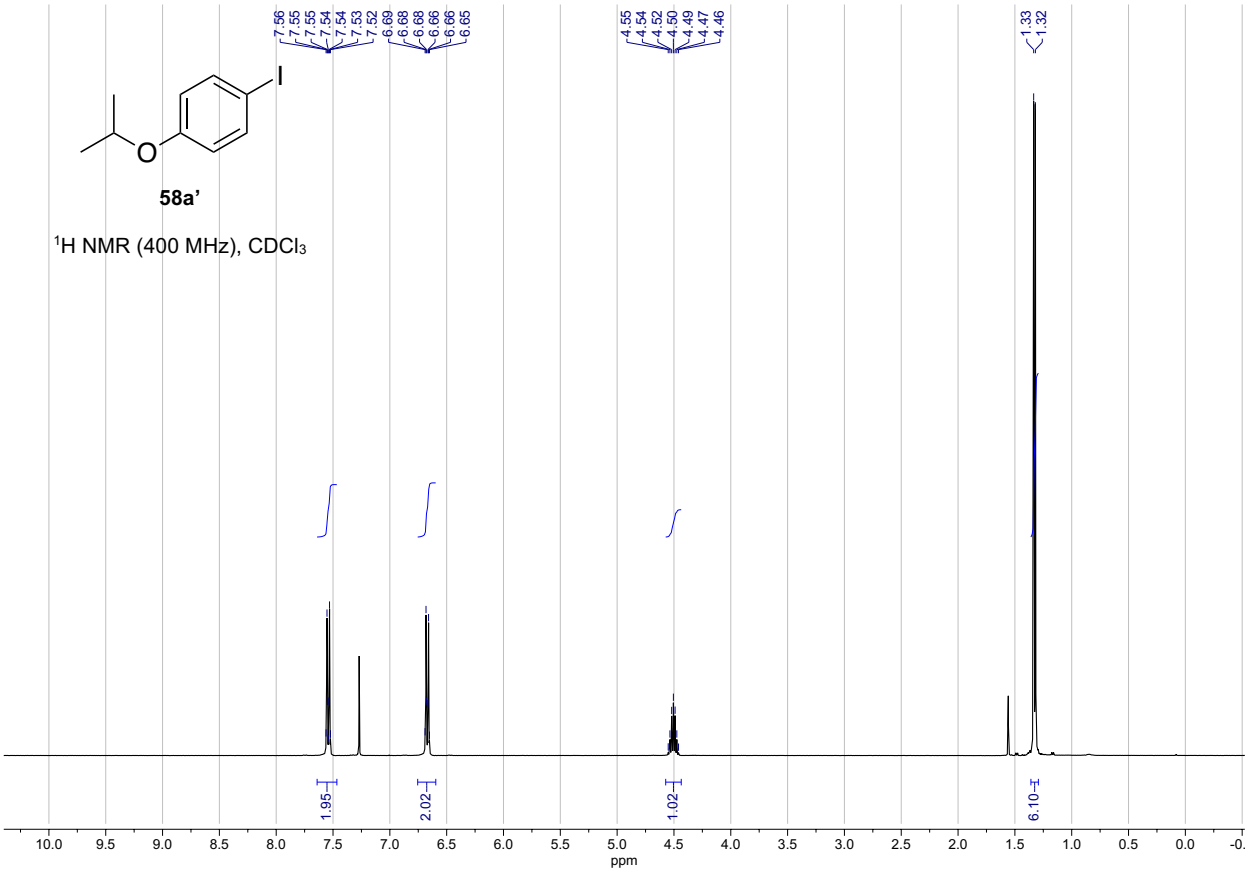

7.51 7.50 7.50 7.49 7.49 7.48 7.48 7.47 7.46 7.46 7.45 7.45 7.44 7.44 7.43 7.43 7.43 7.42 7.41 7.41 7.40 7.40 7.38 7.10 7.09 7.08 7.07 7.07 7.06 7.01 7.00 6.99 6.98 6.98 6.97
5.17 5.10 5.08 4.98 4.96
O
ONa
S
O
BnO
57d
^{1}H NMR (400 MHz), D_2O
4.94 2.02 1.92
2.00 1.94 1.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 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

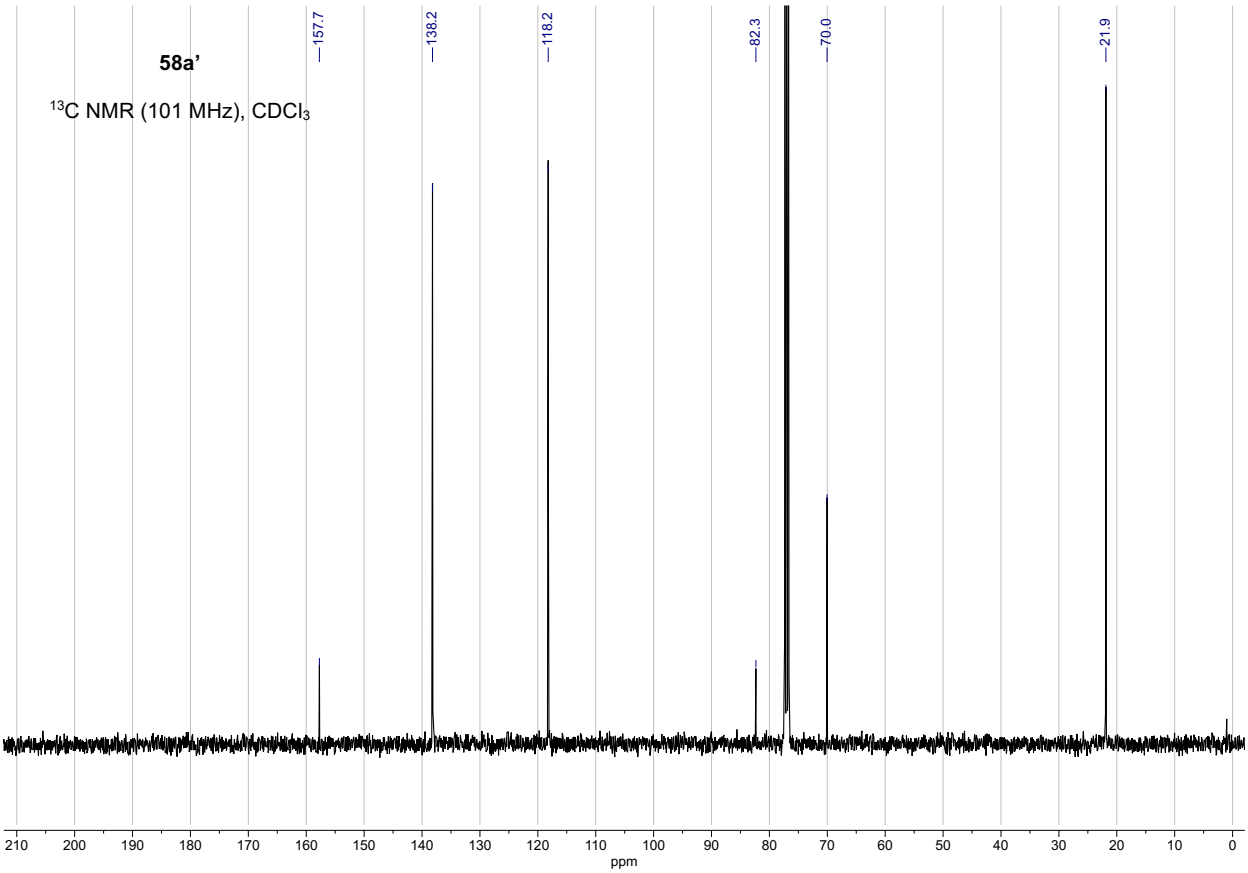

57d
^{13}C NMR (101 MHz), D_2O
157.1
136.5 129.1 128.8 128.5 128.4 128.1
115.0
76.6
70.3
67.0
129.1
128.8
128.5
128.4
128.1
129.5 129.0 128.5 128.0 127.5 127.0
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

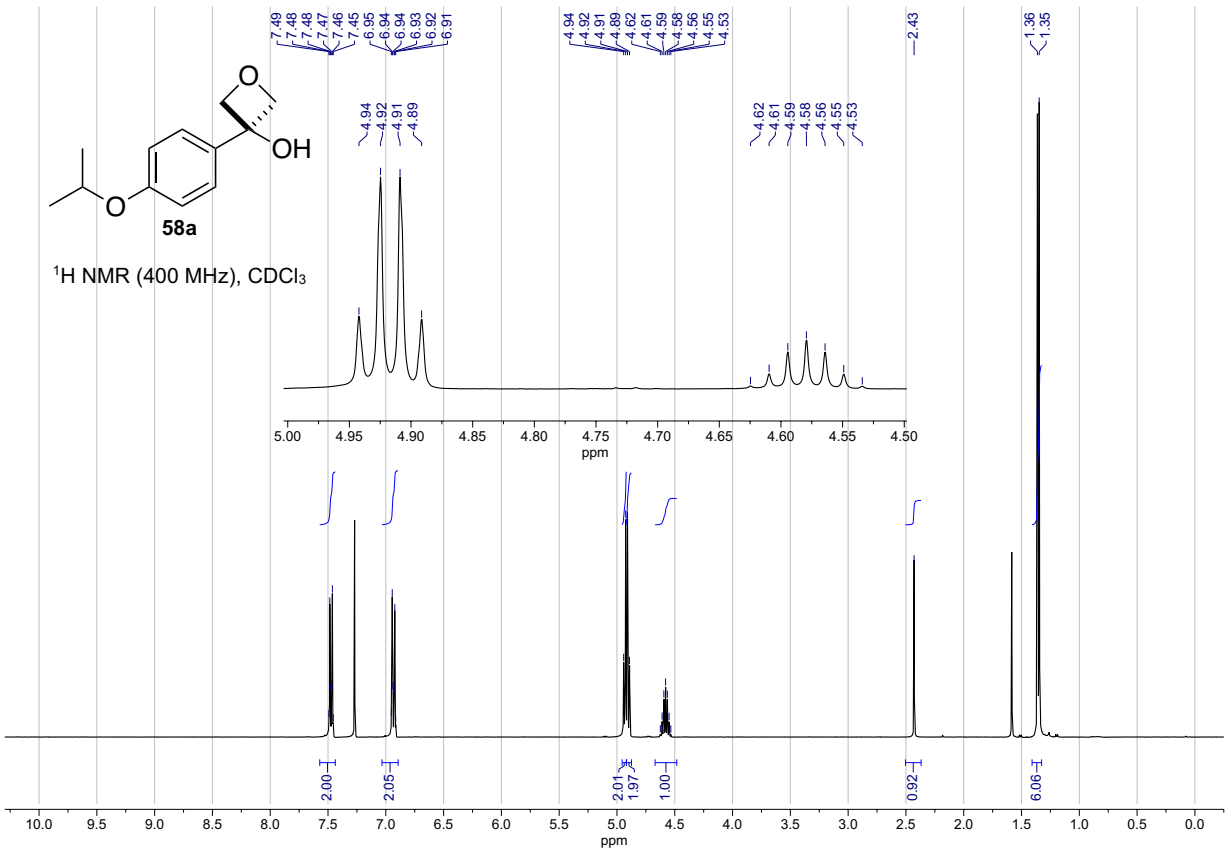

7.48 7.46 7.46 7.44 7.44 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.23 7.22 7.22 7.20 7.20 7.19 7.09 7.08 7.07 7.06 7.06 7.05 5.44 5.42 5.25 5.24 5.23 5.22 5.11
O
S
F
O
O
BnO
57
1H NMR (400 MHz), CDCl3
5.29
1.97
2.02
2.00
2.02
2.17
10.0 9.5 9.0 8.5 8.0 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

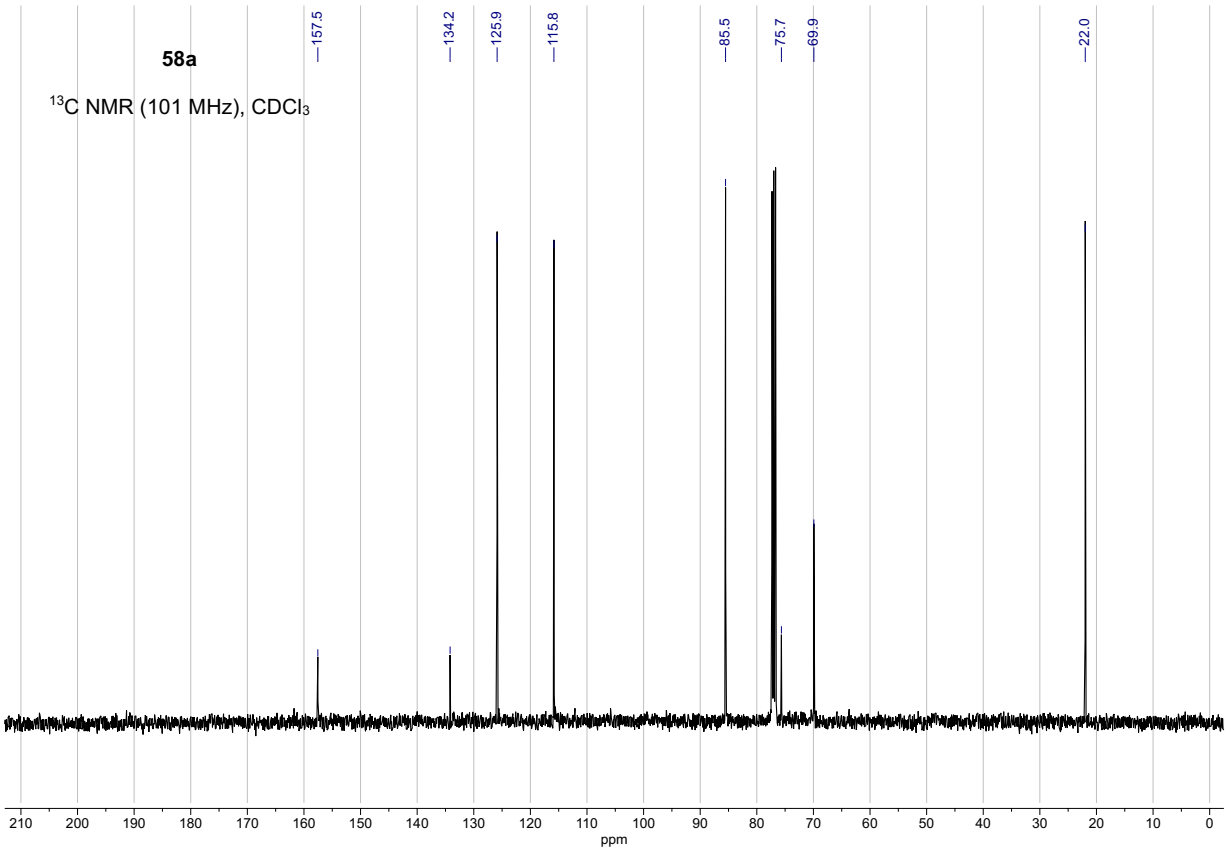

57
13C NMR (101 MHz), CDCl3
160.0
136.2
129.6
128.7
128.2
127.4
123.5
115.5
77.1
70.2
68.1
68.0
77.1
79.0 78.5 78.0 77.5 77.0 76.5 76.0 75.5 75.0 74.5
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

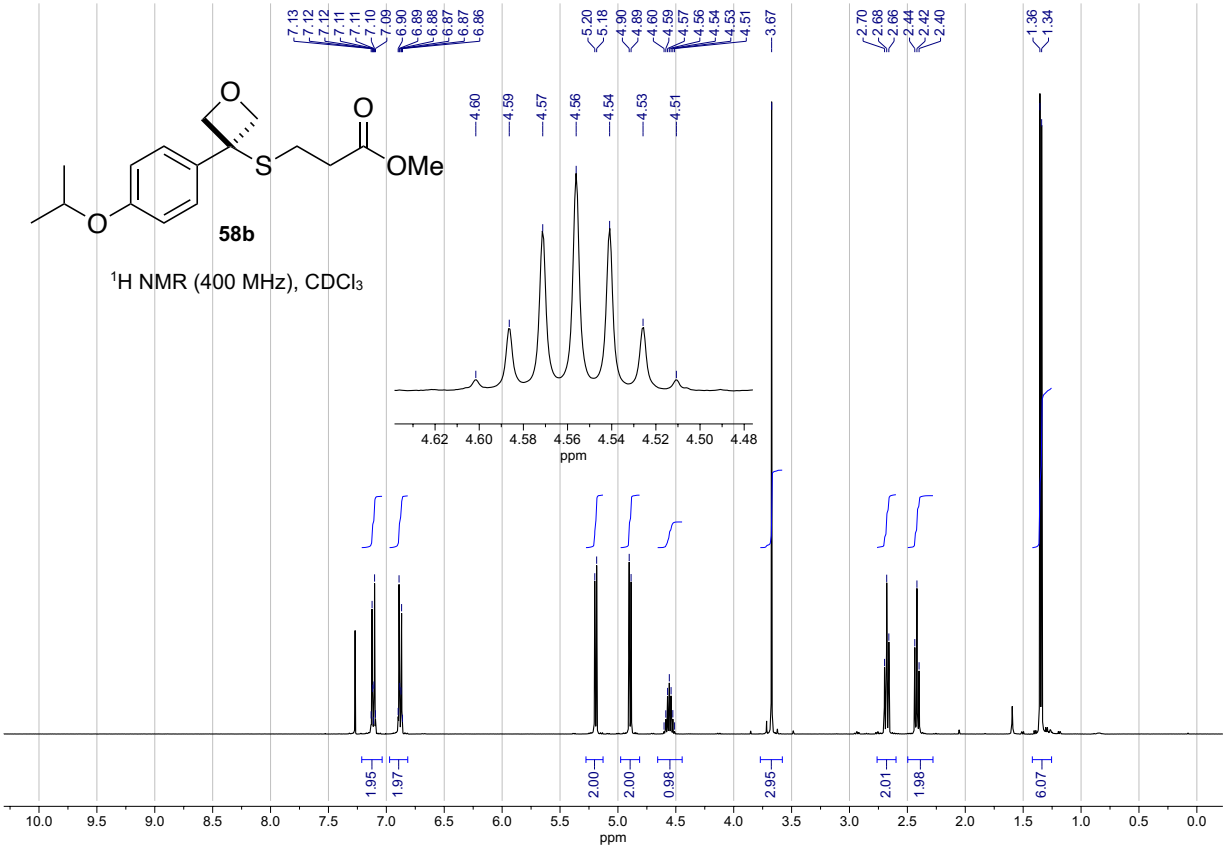

34.4
57
^{19}F NMR (377 MHz), $CDCl_3$
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

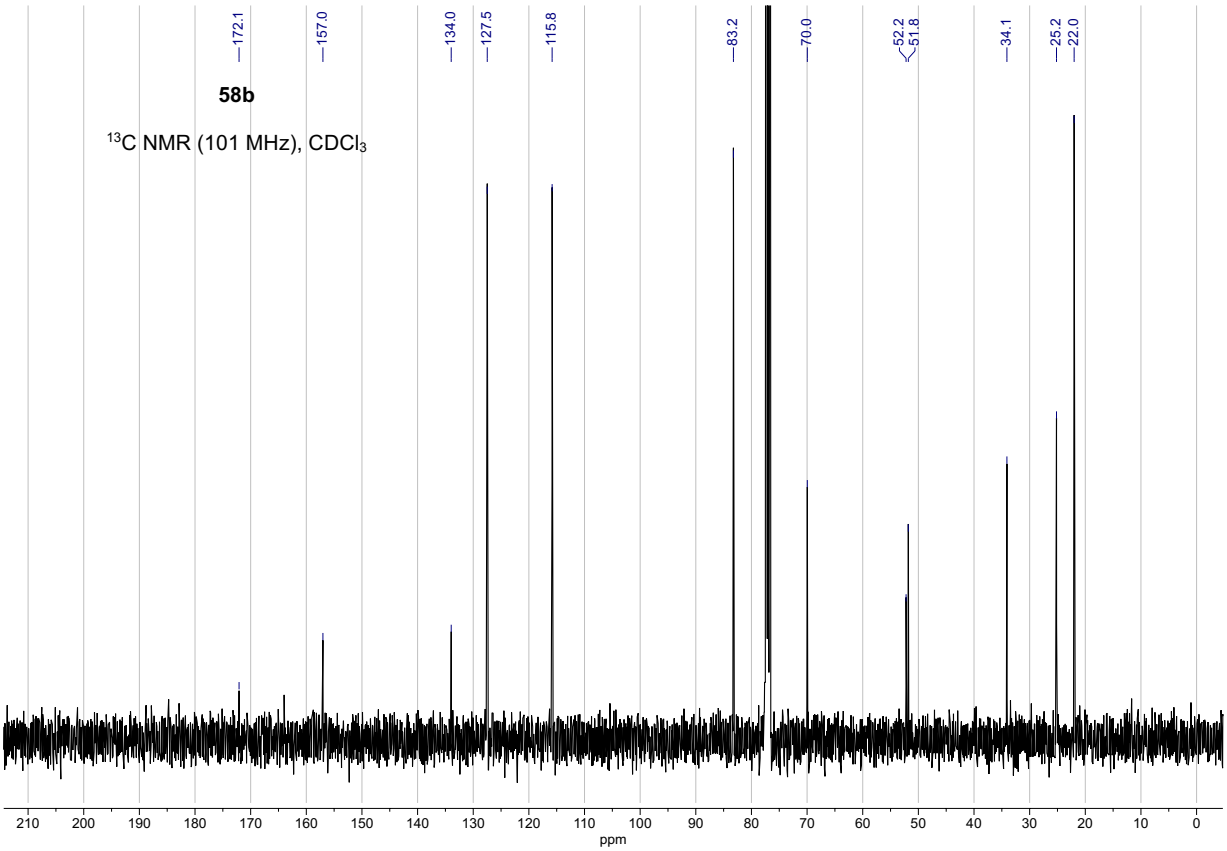

7.56
7.55
7.55
7.54
7.54
7.53
7.52
6.69
6.68
6.68
6.66
6.66
6.65
4.55
4.54
4.52
4.50
4.49
4.47
4.46
1.33
1.32
I
O
58a'
^{1}H NMR (400 MHz), $CDCl_3$
1.95
2.02
1.02
6.10
ppm

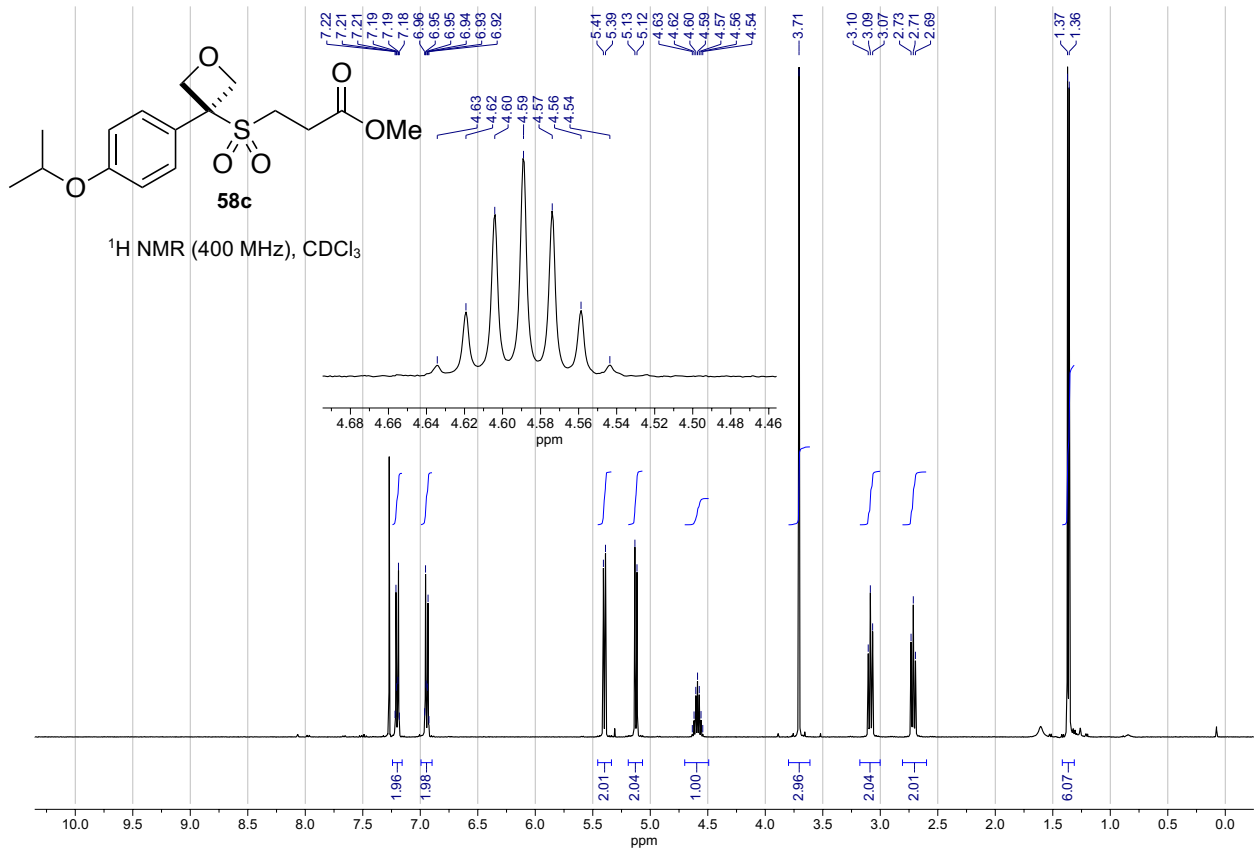

58a'
^{13}C NMR (101 MHz), $CDCl_3$
157.7
138.2
118.2
82.3
70.0
21.9
ppm

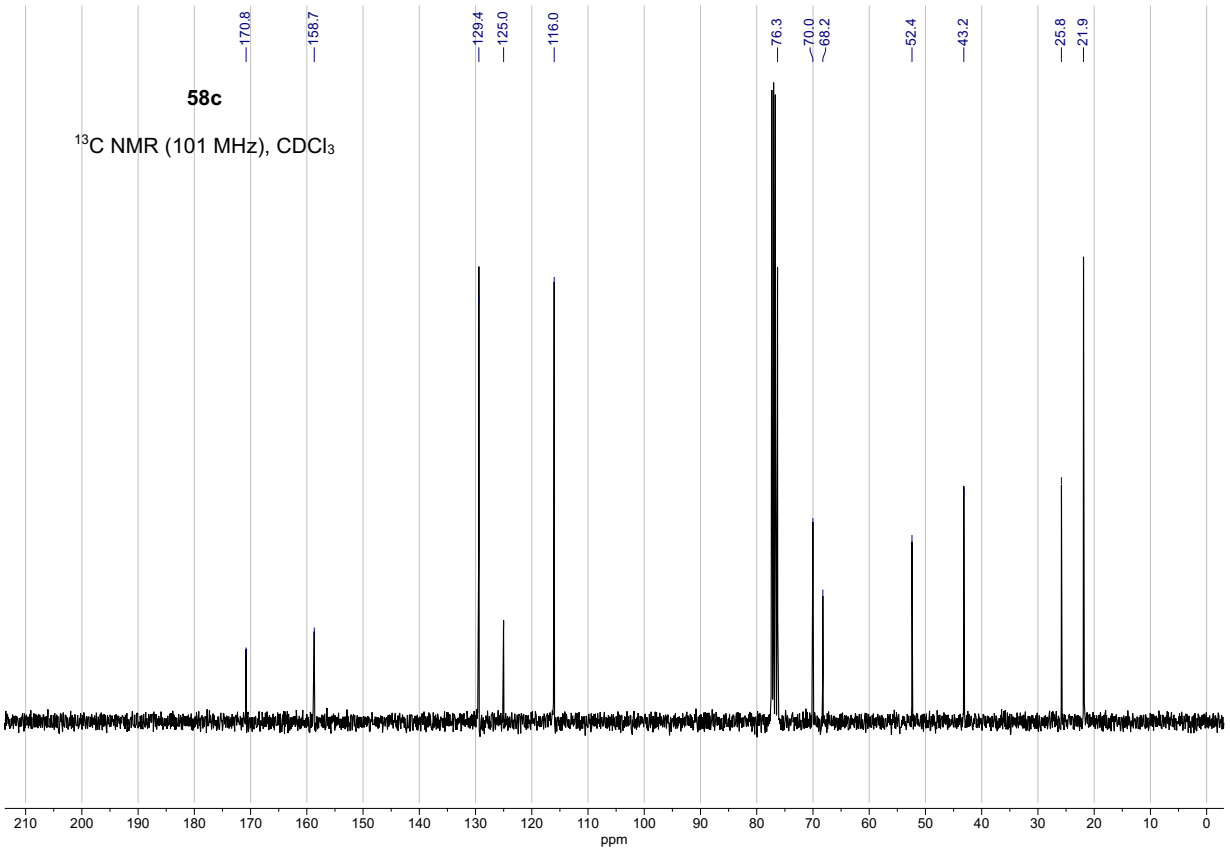

58a
^{1}H NMR (400 MHz), CDCl$_3$
ppm

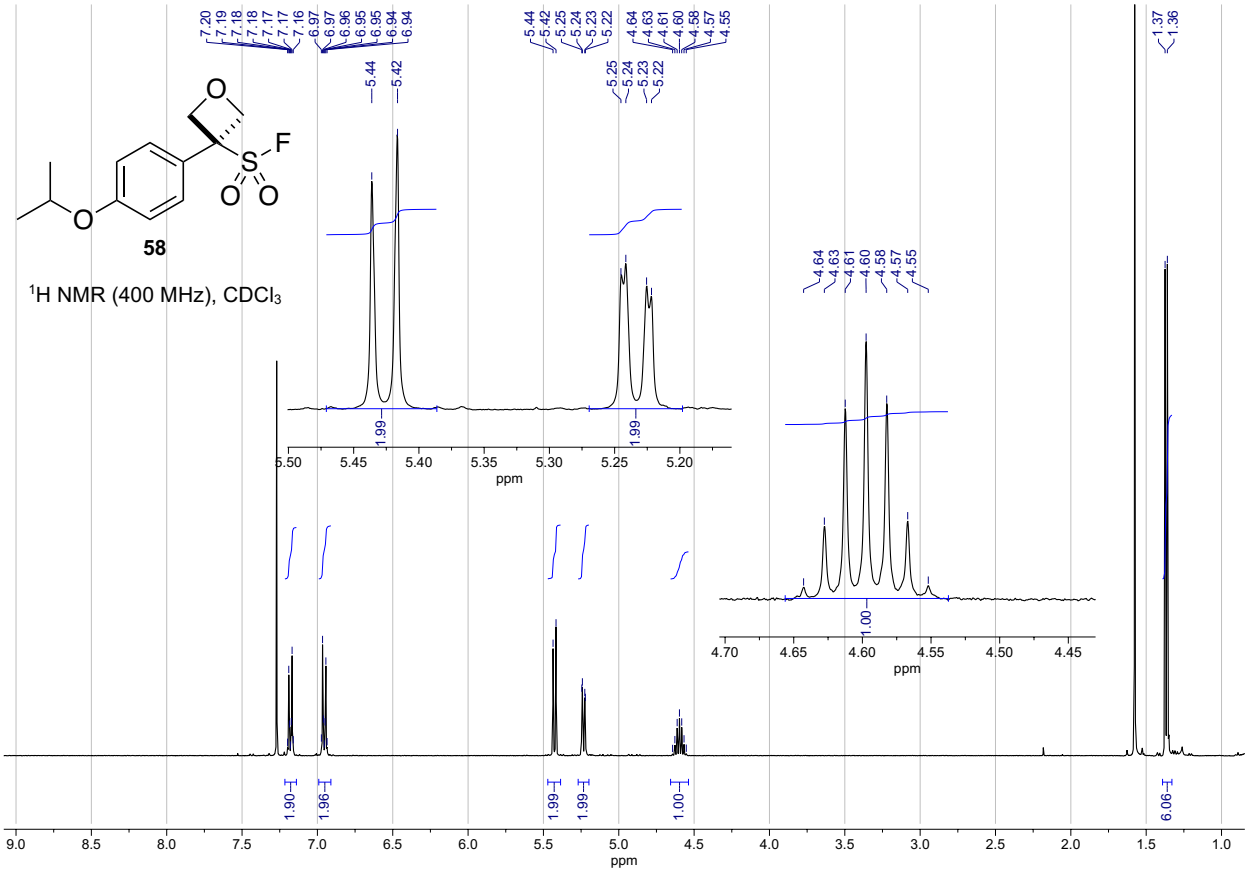

58a
^{13}C NMR (101 MHz), CDCl$_3$
ppm

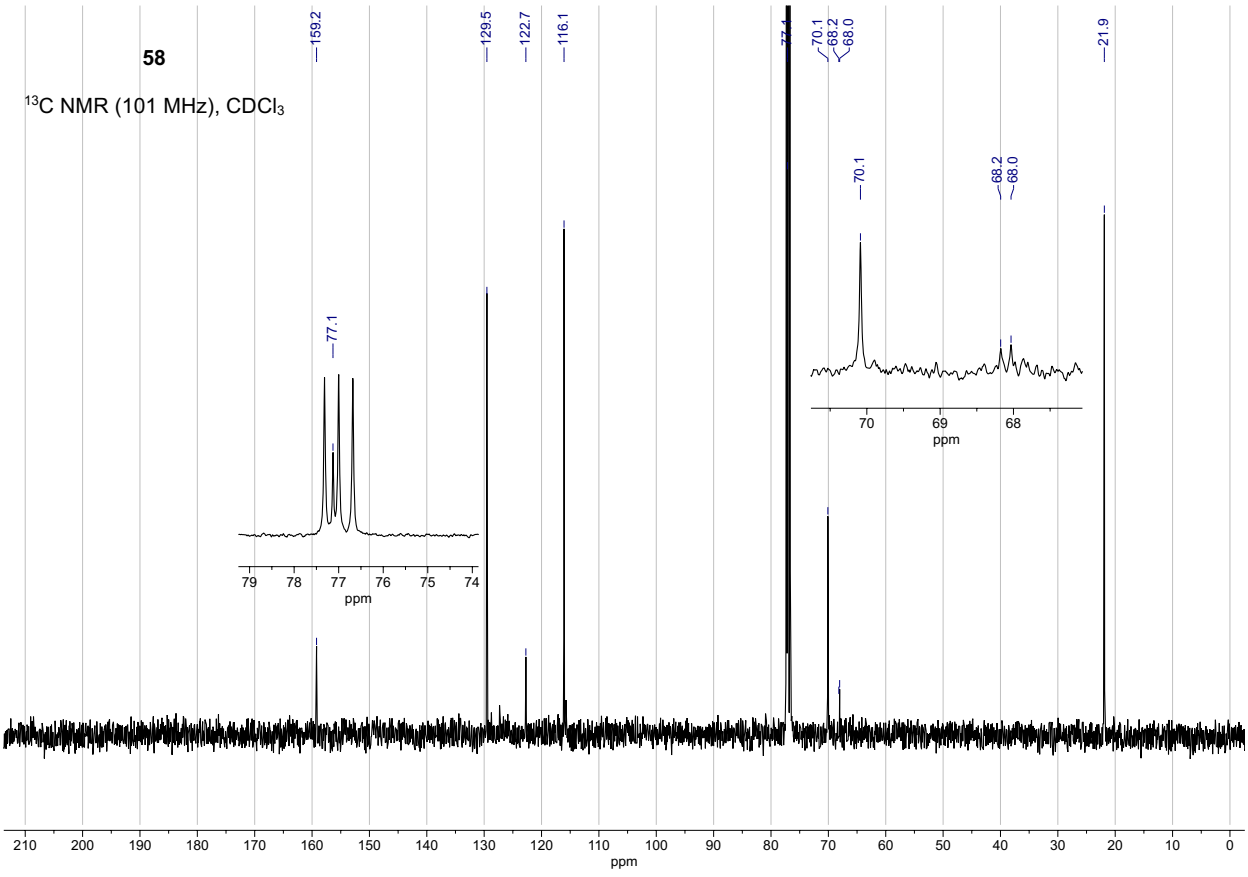

58b
^{1}H NMR (400 MHz), CDCl$_3$
ppm

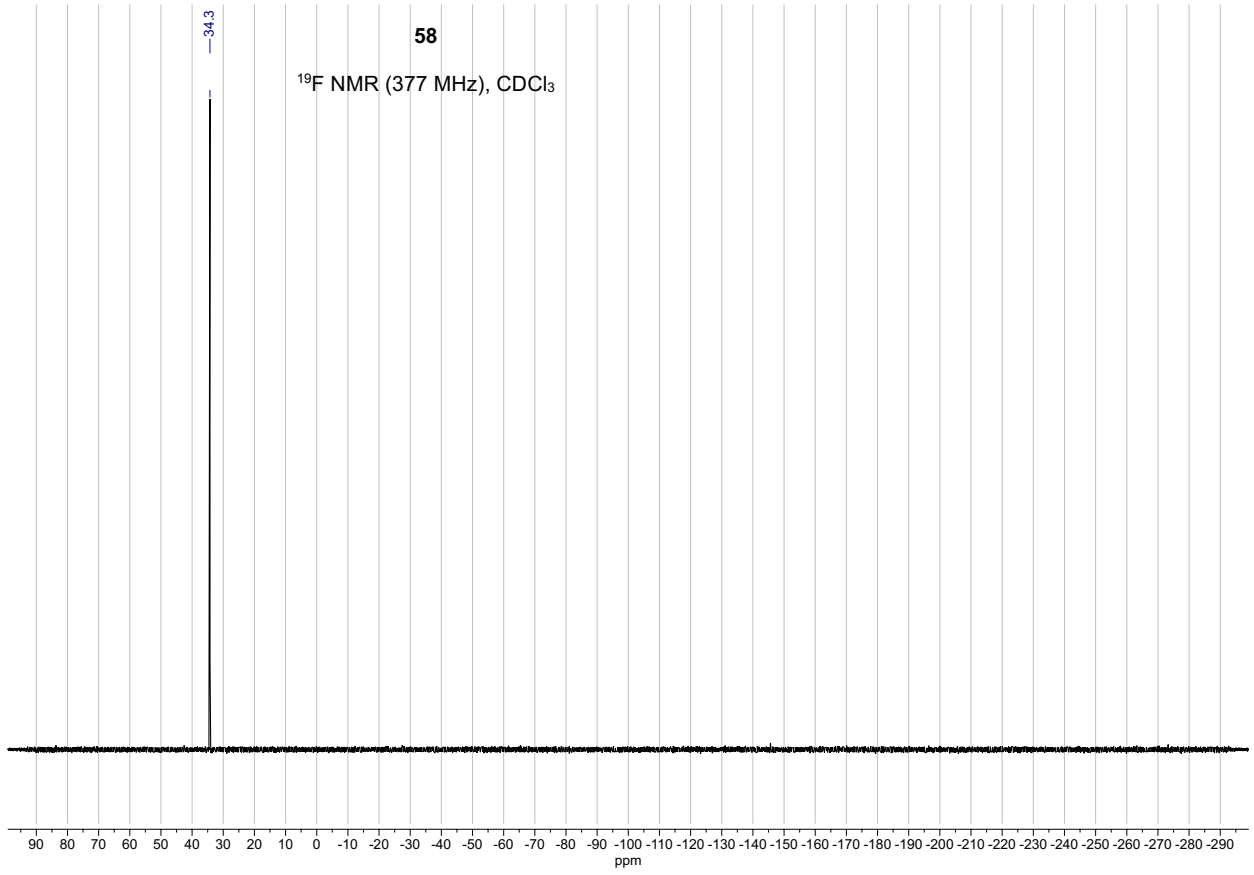

58b
^{13}C NMR (101 MHz), CDCl$_3$
ppm

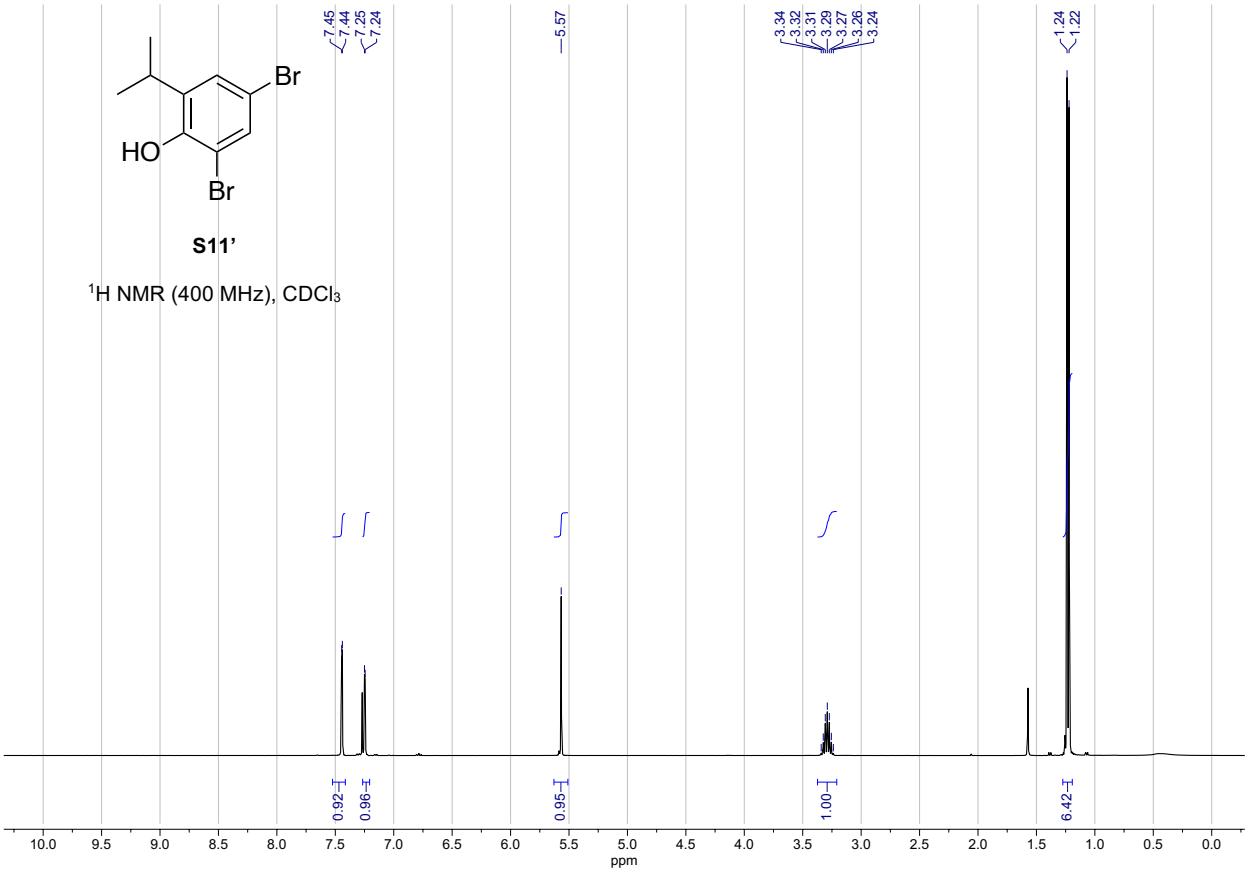

58c
^{1}H NMR (400 MHz), CDCl$_3$
ppm


58c
^{13}C NMR (101 MHz), CDCl$_3$
ppm


58
^{1}H NMR (400 MHz), $CDCl_3$
ppm

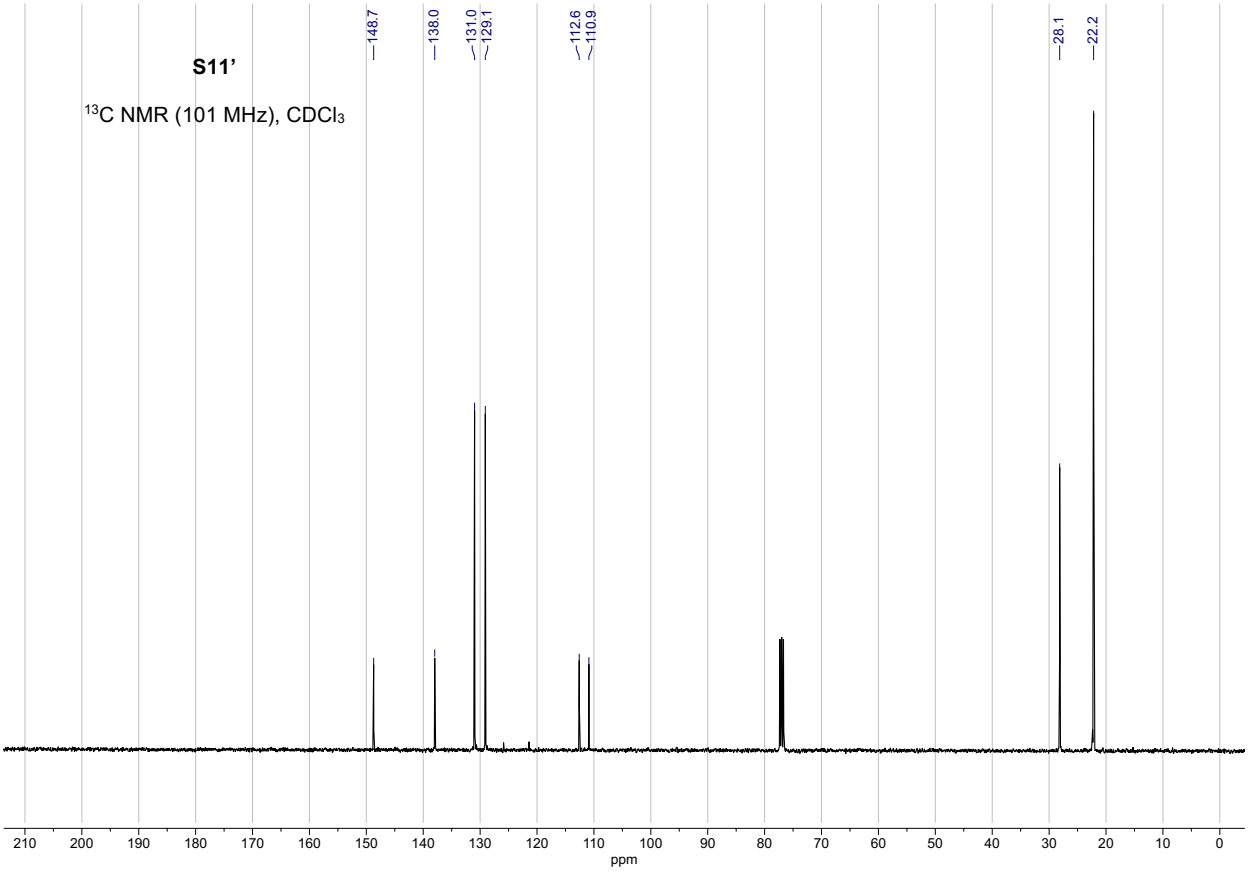

58
^{13}C NMR (101 MHz), $CDCl_3$
ppm


34.3
58
^{19}F NMR (377 MHz), $CDCl_3$
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm



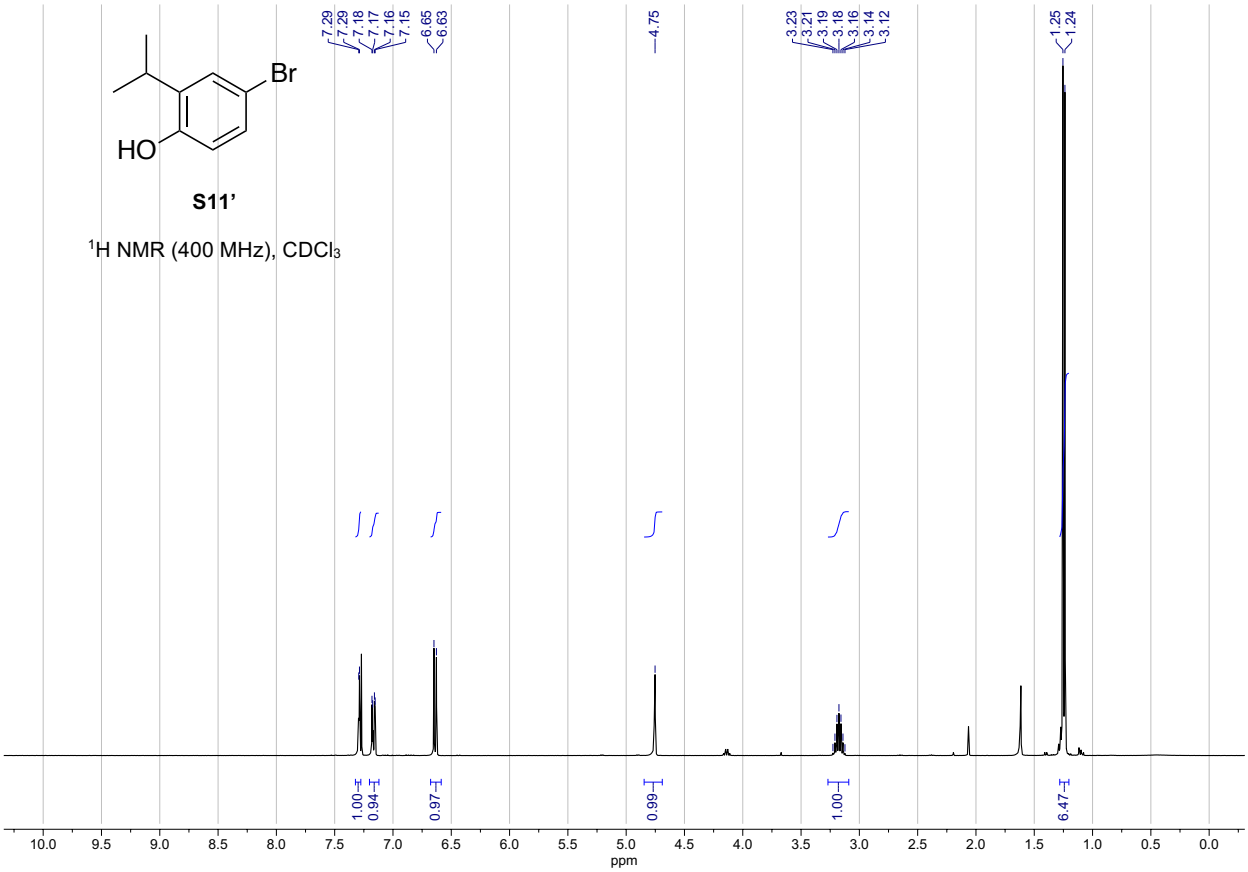
S11'

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



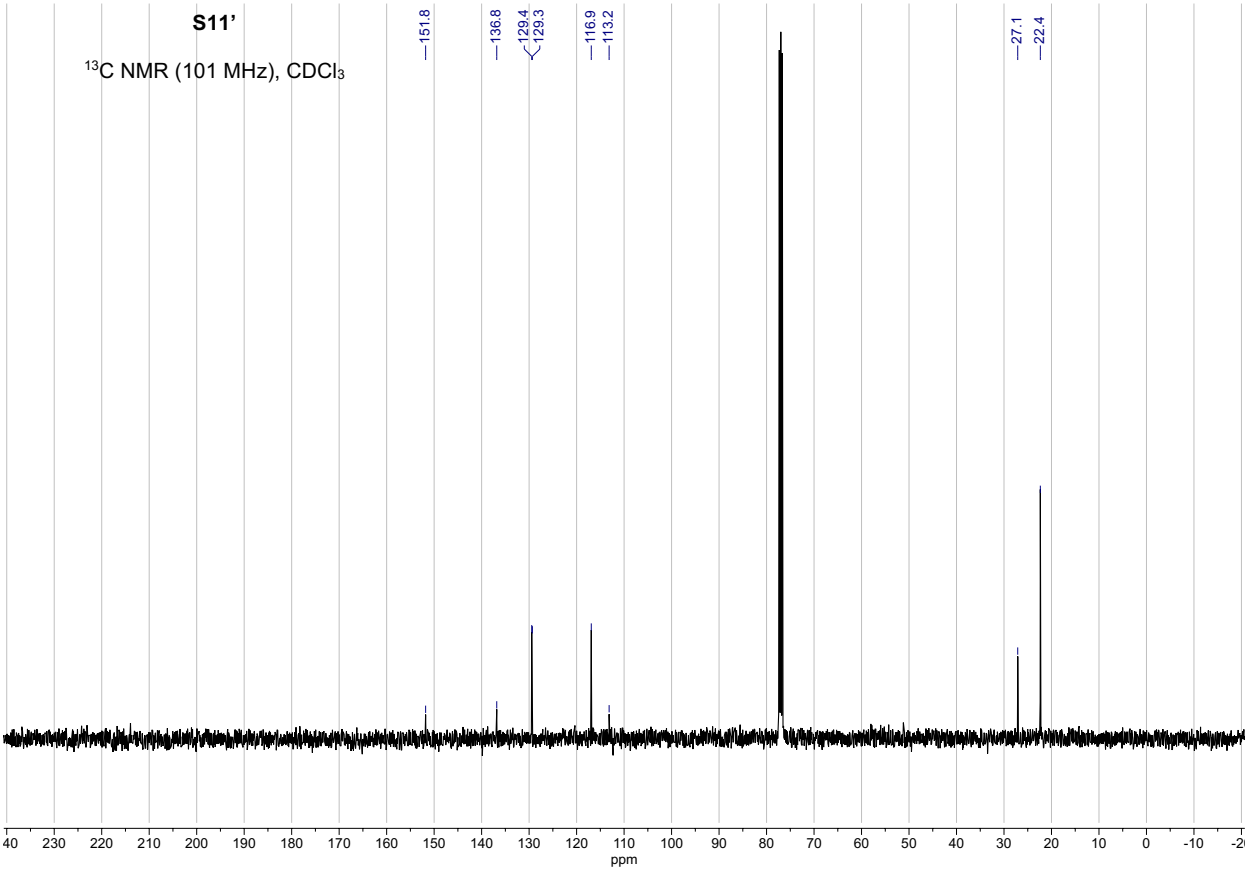
S11'

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



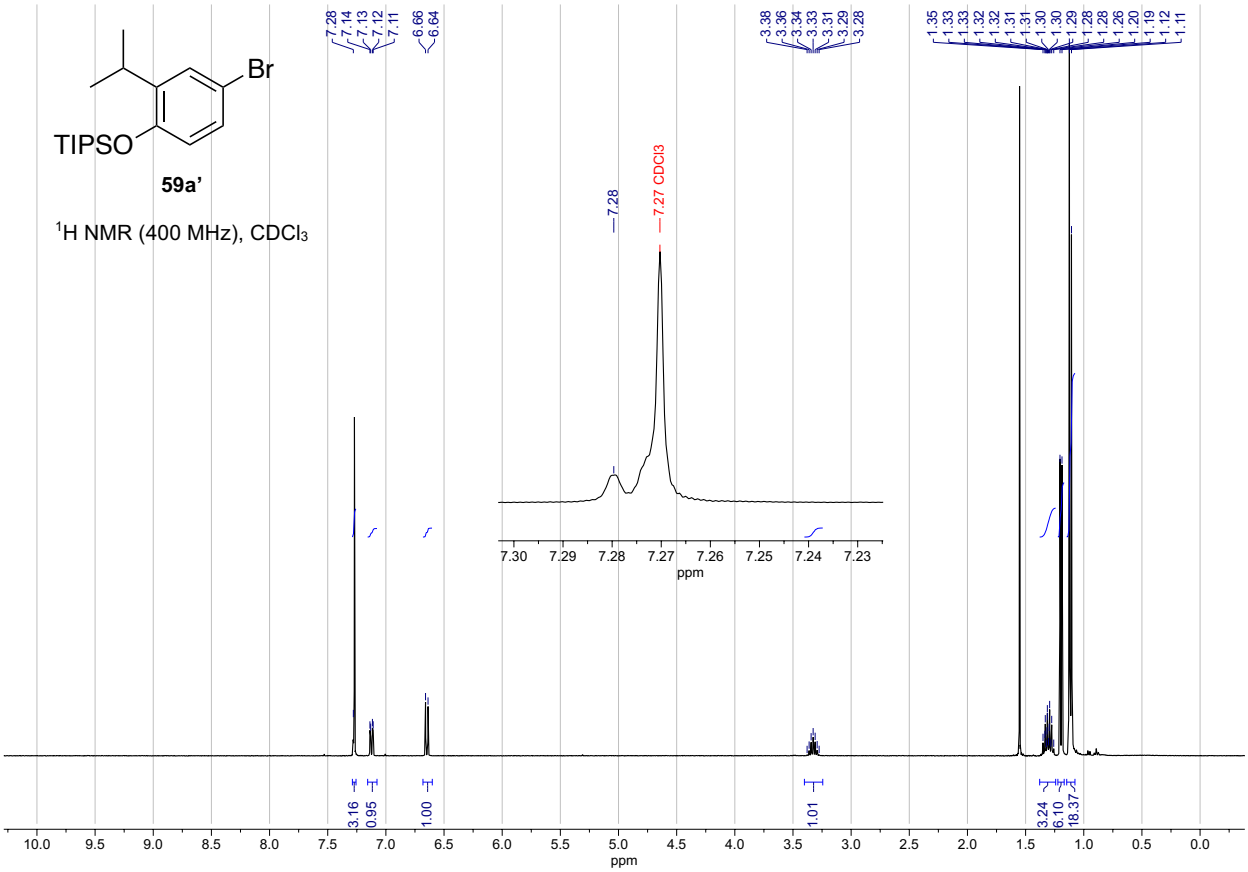
S11'

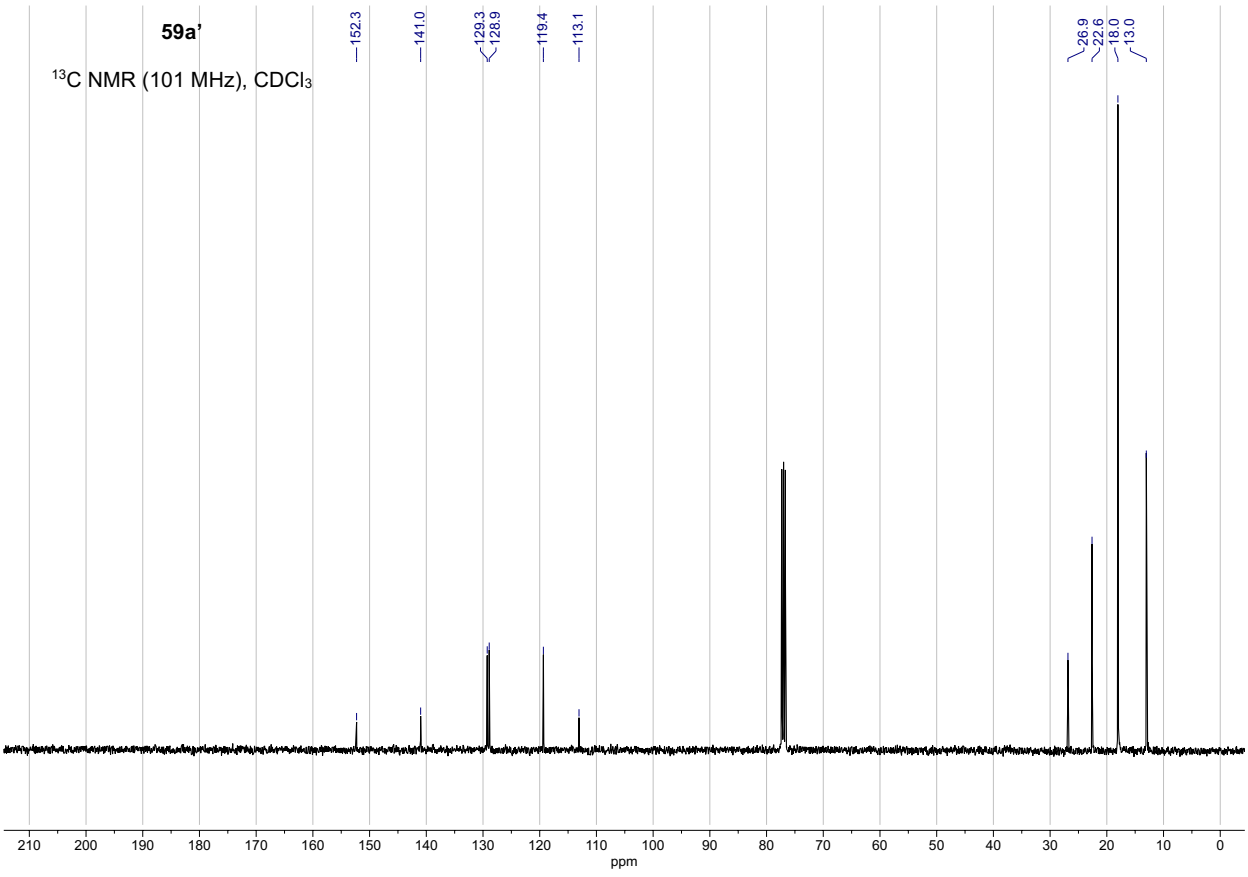
^{1}H NMR (400 MHz), $CDCl_3$

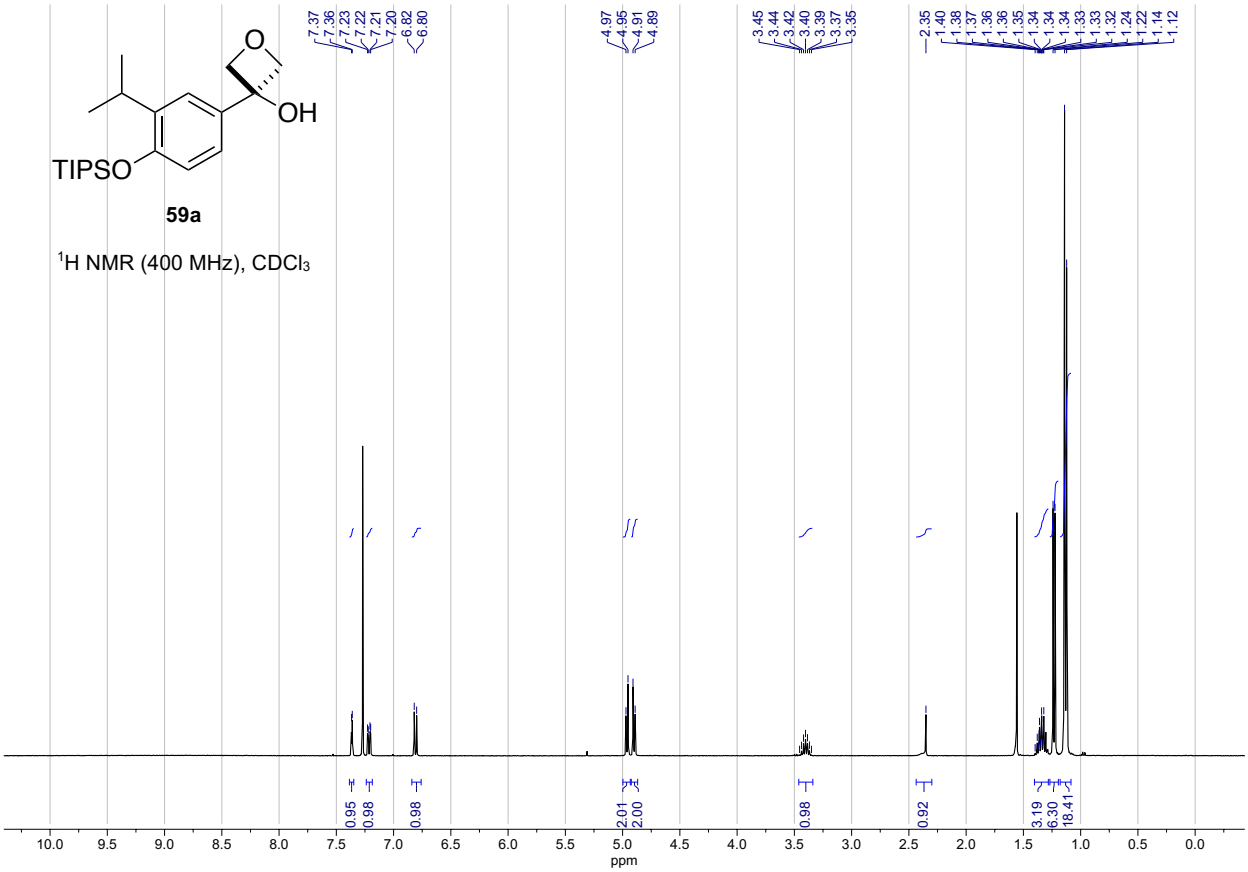


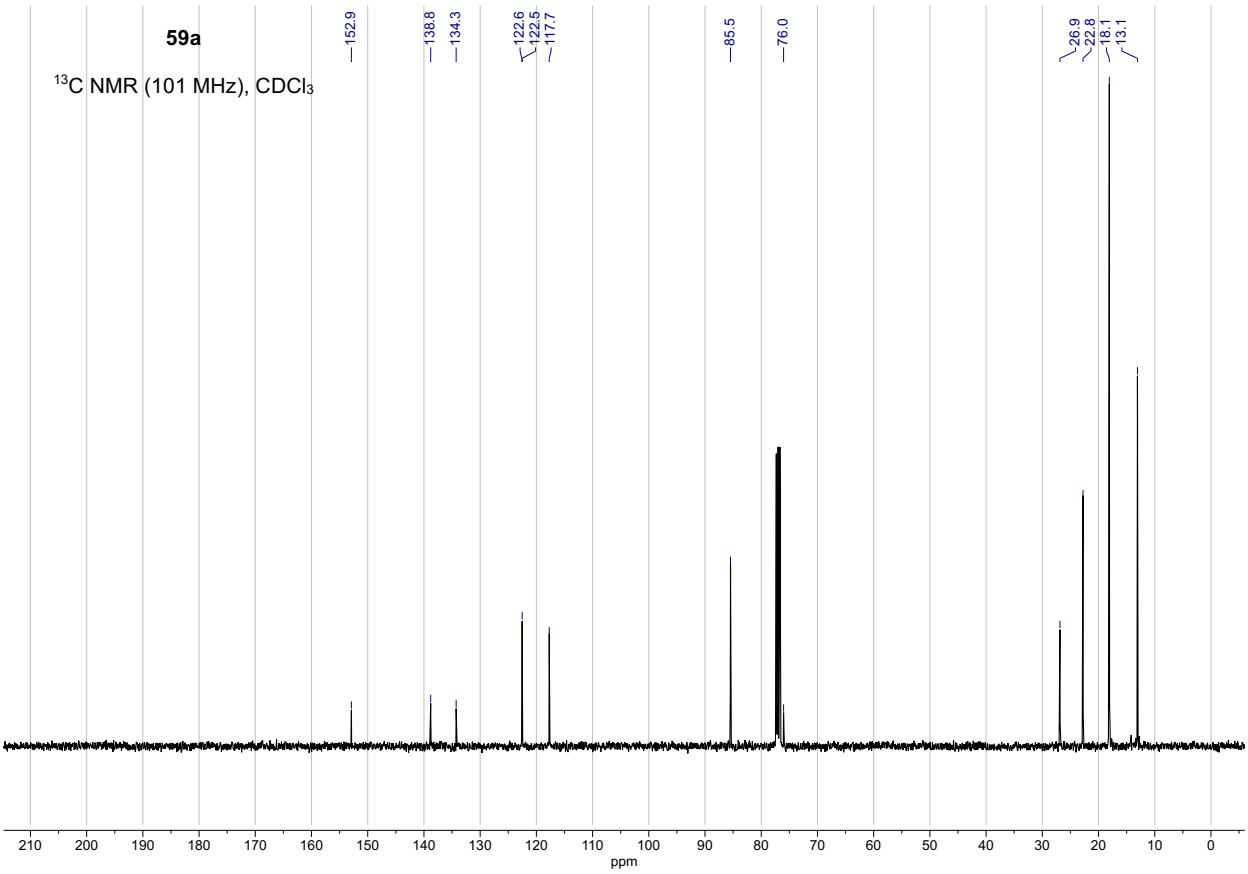
S11'

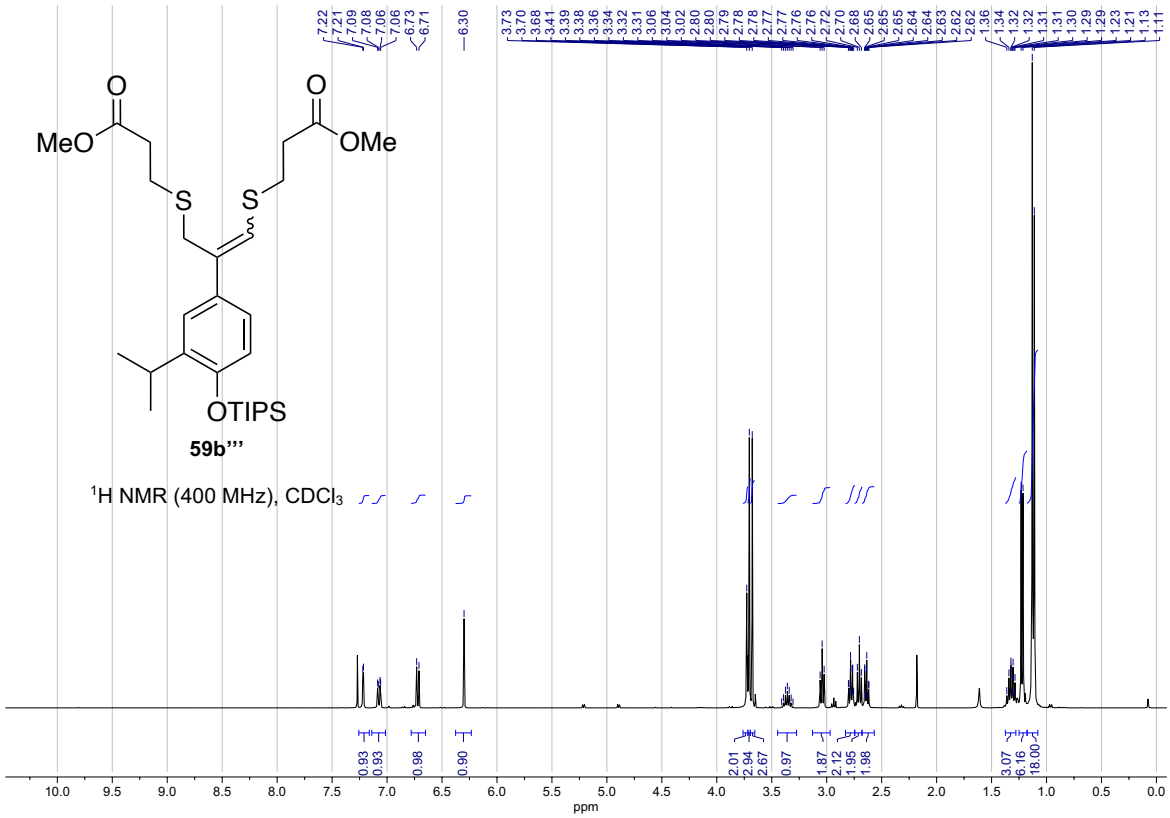
^{13}C NMR (101 MHz), $CDCl_3$

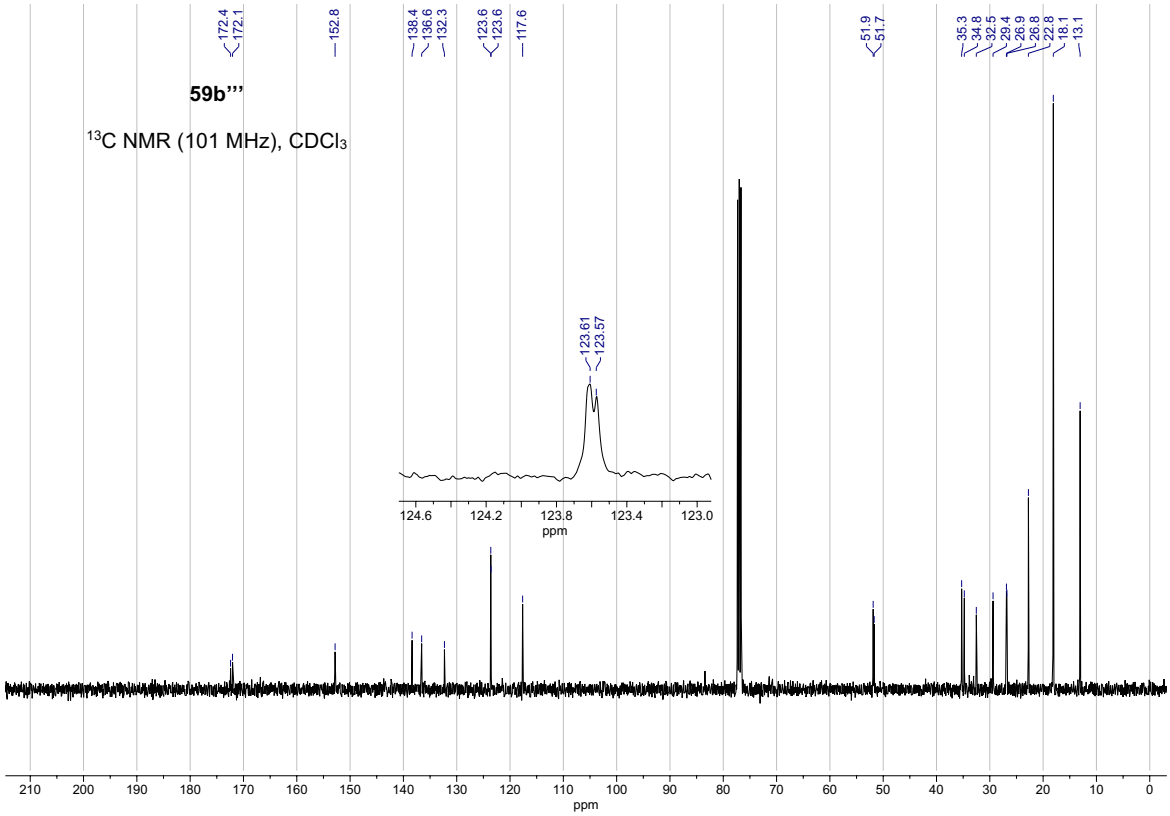

Br
TIPSO
59a'
^{1}H NMR (400 MHz), CDCl$_3$
7.28
7.27 CDCl3
ppm

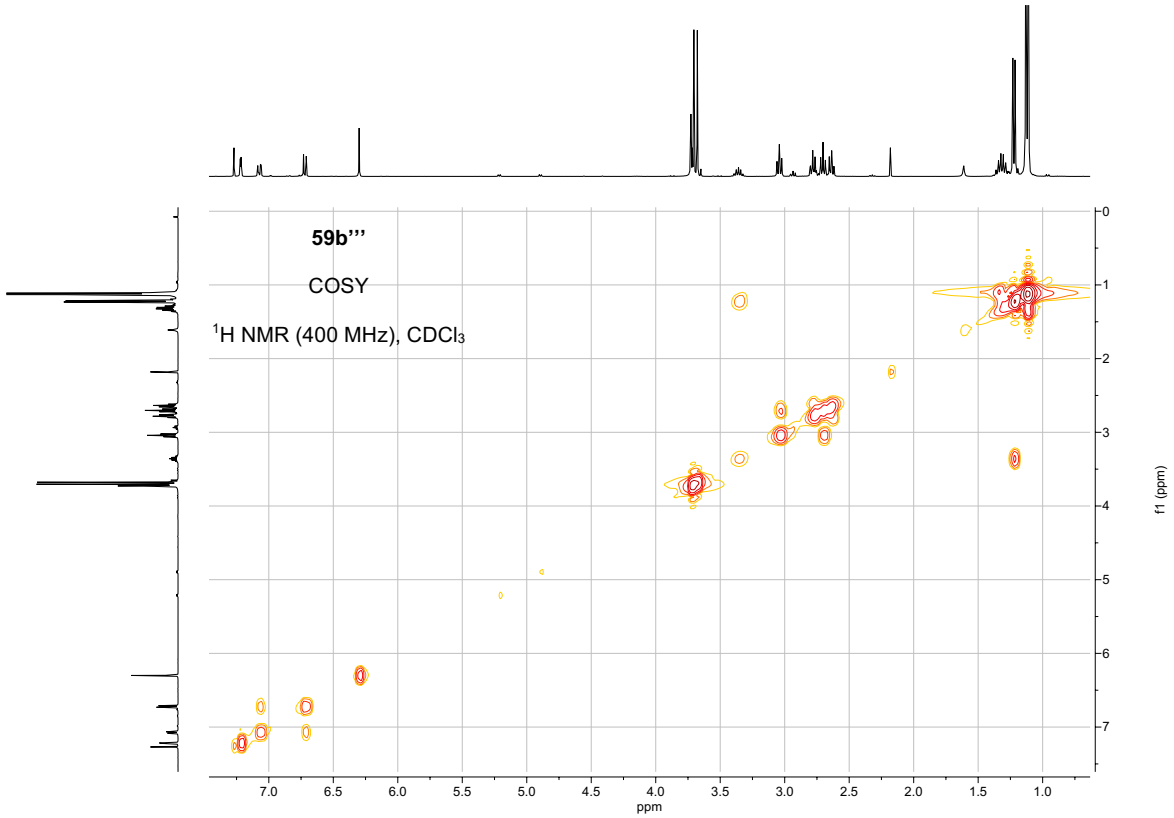

59a'
^{13}C NMR (101 MHz), CDCl$_3$
152.3
141.0
129.3
128.9
119.4
113.1
26.9
22.6
18.0
13.0
ppm

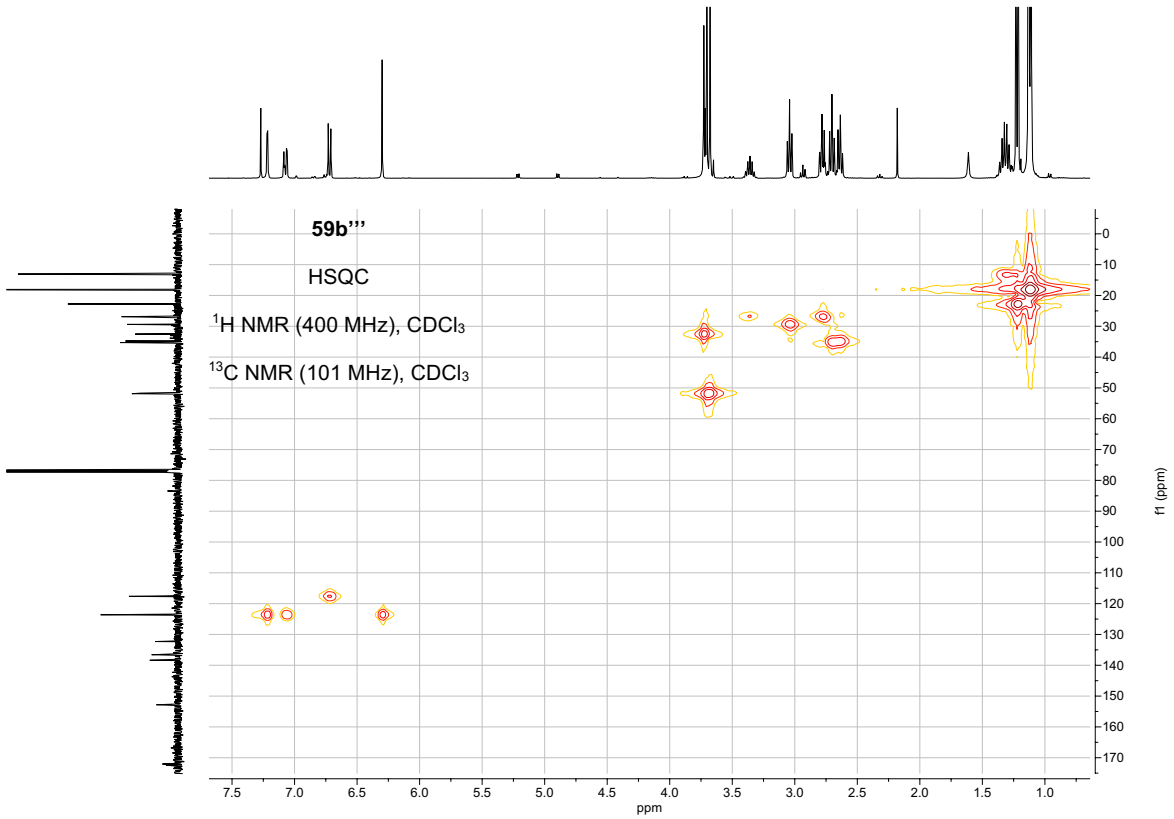

TIPSO
O
OH
59a
^{1}H NMR (400 MHz), CDCl$_3$
7.37
7.36
7.23
7.22
7.21
7.20
6.82
6.80
4.97
4.95
4.91
4.89
3.45
3.44
3.42
3.40
3.39
3.37
3.35
2.35
1.40
1.38
1.37
1.36
1.36
1.35
1.34
1.34
1.34
1.33
1.32
1.24
1.22
1.14
1.12
0.95
0.98
0.98
2.01
2.00
0.98
0.92
3.19
6.30
18.41
ppm


59a
^{13}C NMR (101 MHz), CDCl$_3$
152.9
138.8
134.3
122.6
122.5
117.7
85.5
76.0
26.9
22.8
18.1
13.1
ppm


MeO
O
O
OMe
S
S
OTIPS
59b'''
^{1}H NMR (400 MHz), CDCl$_3$
ppm


59b'''
^{13}C NMR (101 MHz), CDCl$_3$
123.61
123.57
ppm


59b'''
COSY
^{1}H NMR (400 MHz), CDCl$_3$
ppm
f1 (ppm)

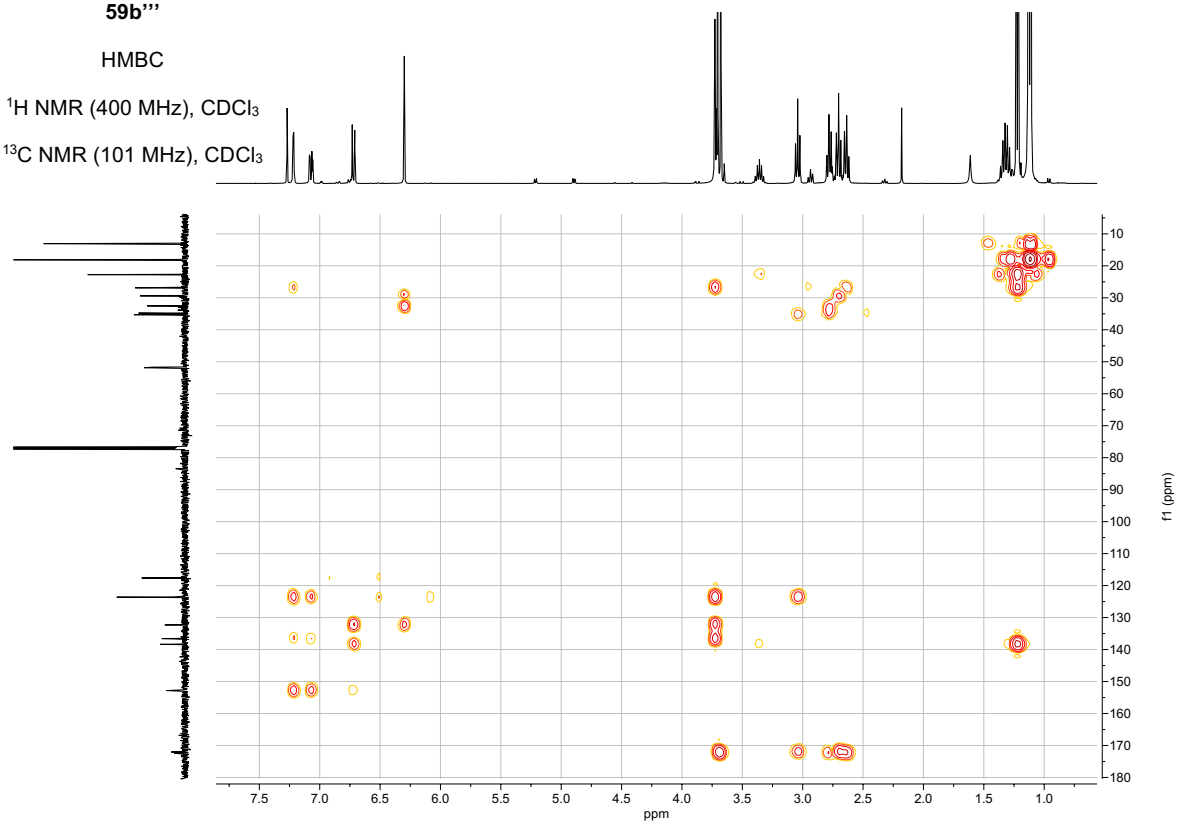

59b'''
HSQC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
ppm
f1 (ppm)

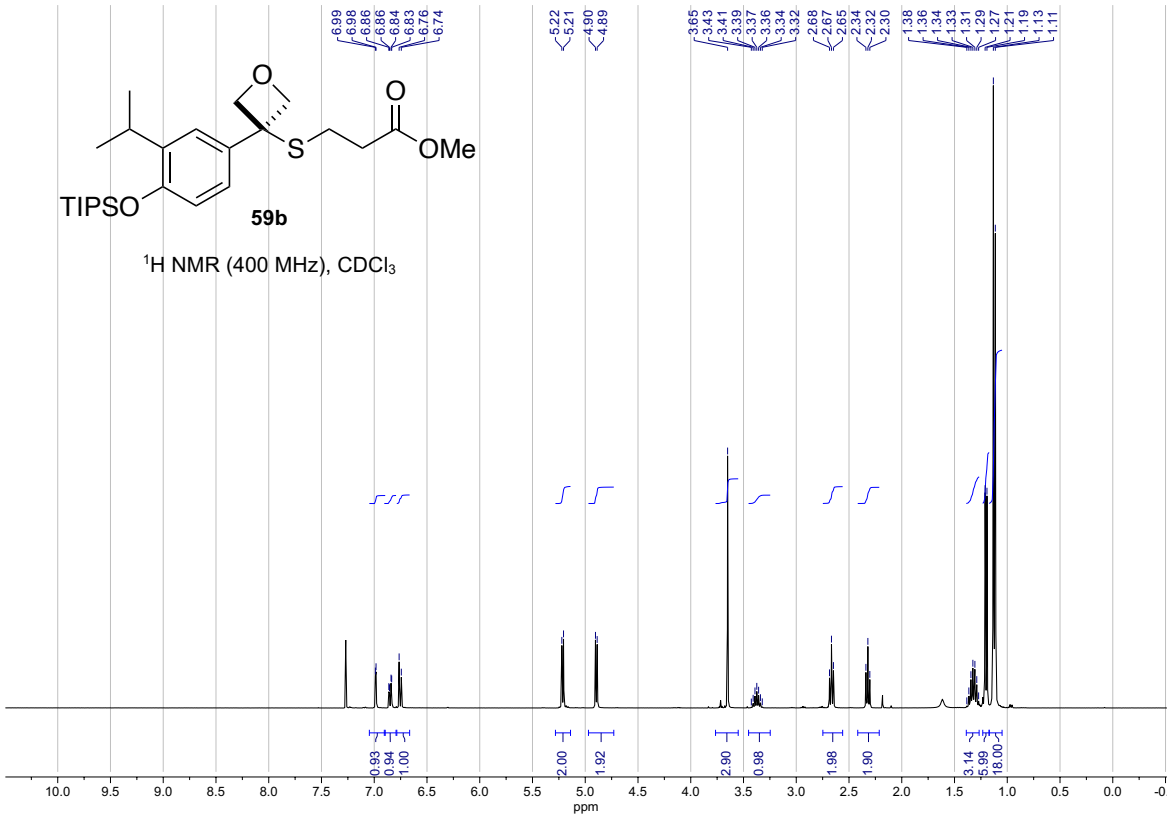
59b'''

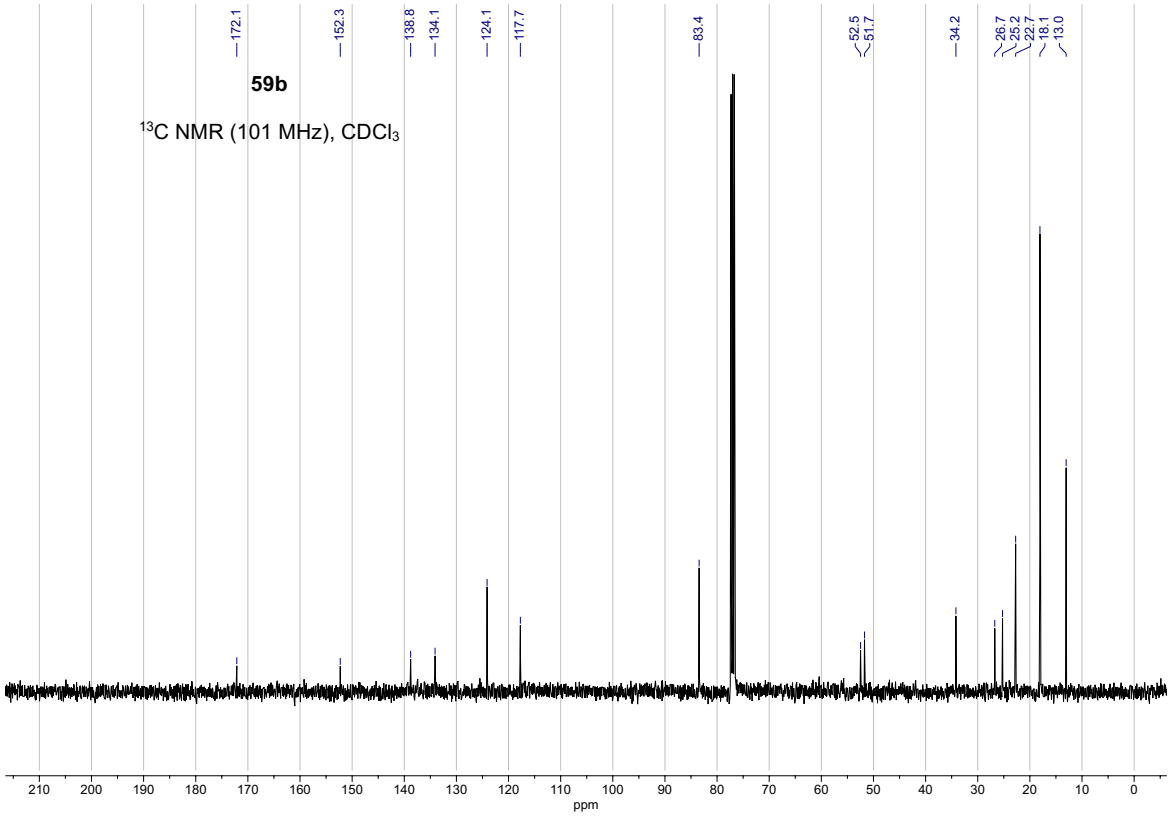
HMBC

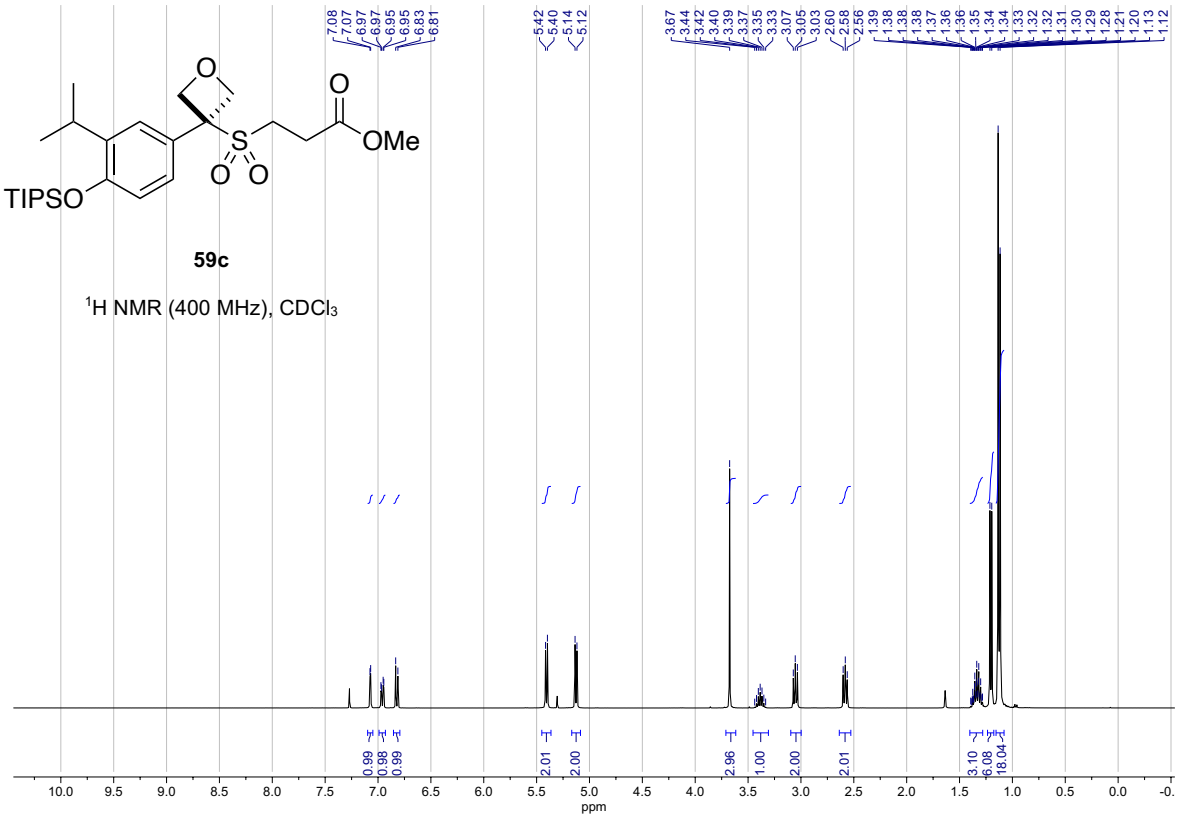
^{1}H NMR (400 MHz), $CDCl_3$

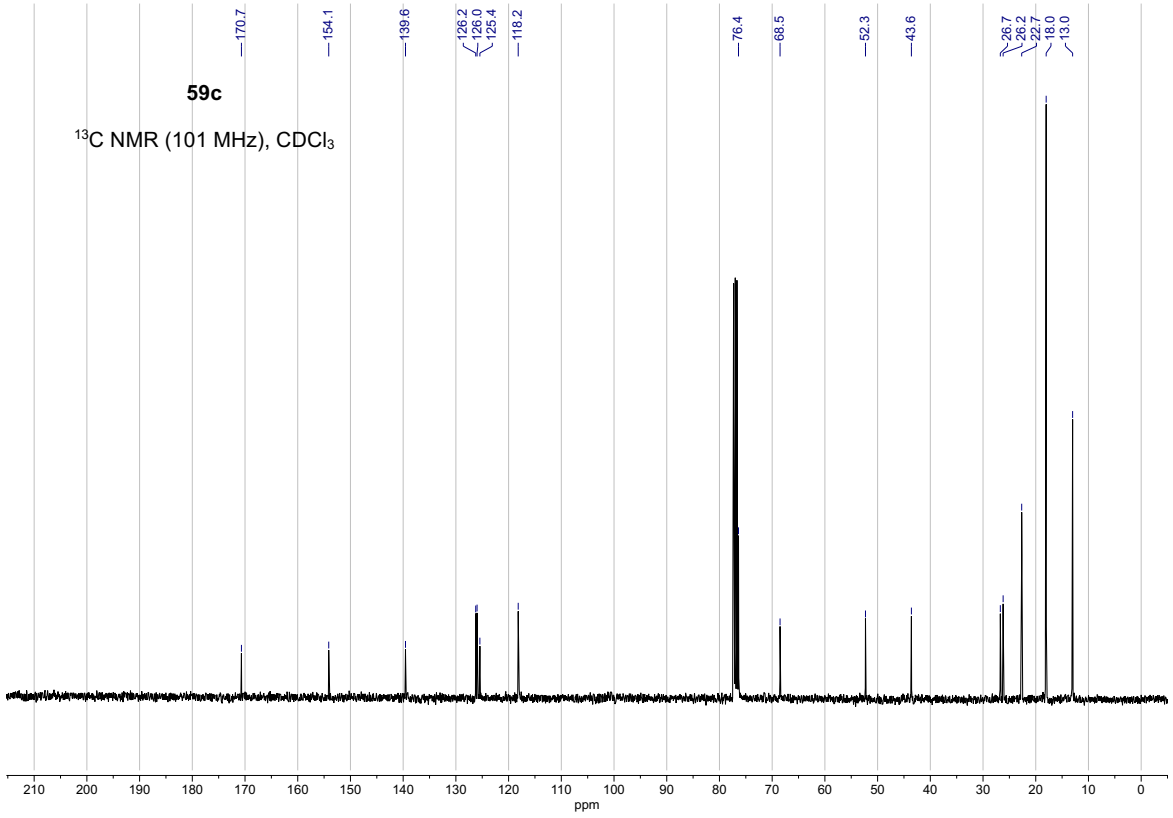
^{13}C NMR (101 MHz), $CDCl_3$

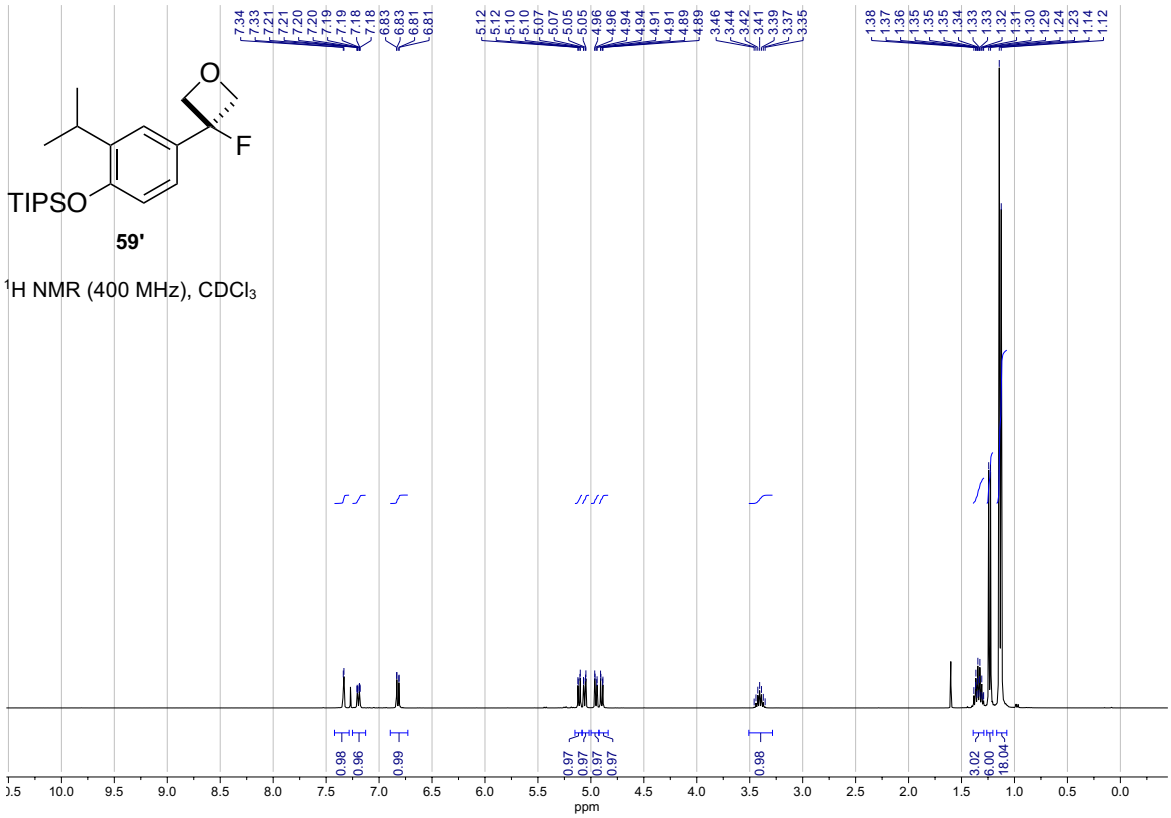


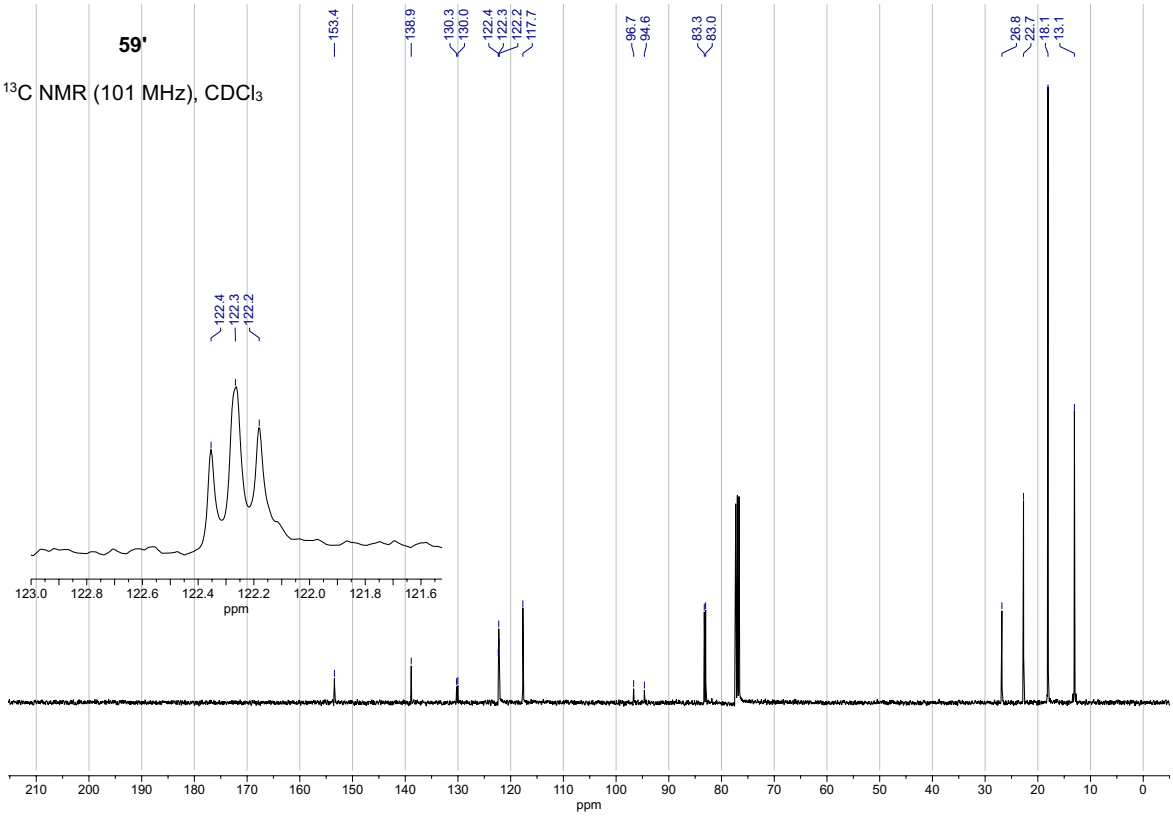

TIPSO
O
S
O
OMe
59b
^{1}H NMR (400 MHz), $CDCl_3$
ppm

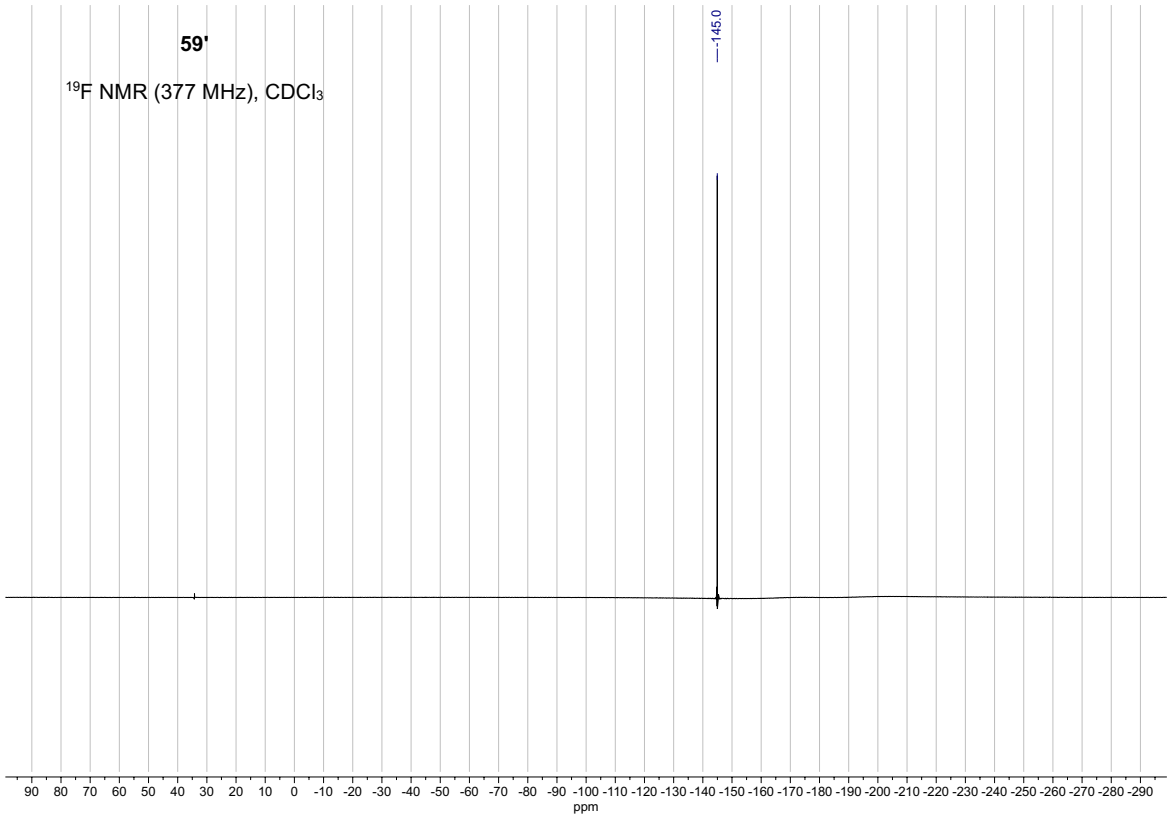

59b
^{13}C NMR (101 MHz), $CDCl_3$
ppm


TIPSO
O
S
O
O
O
OMe
59c
^{1}H NMR (400 MHz), $CDCl_3$
ppm


59c
^{13}C NMR (101 MHz), $CDCl_3$
ppm

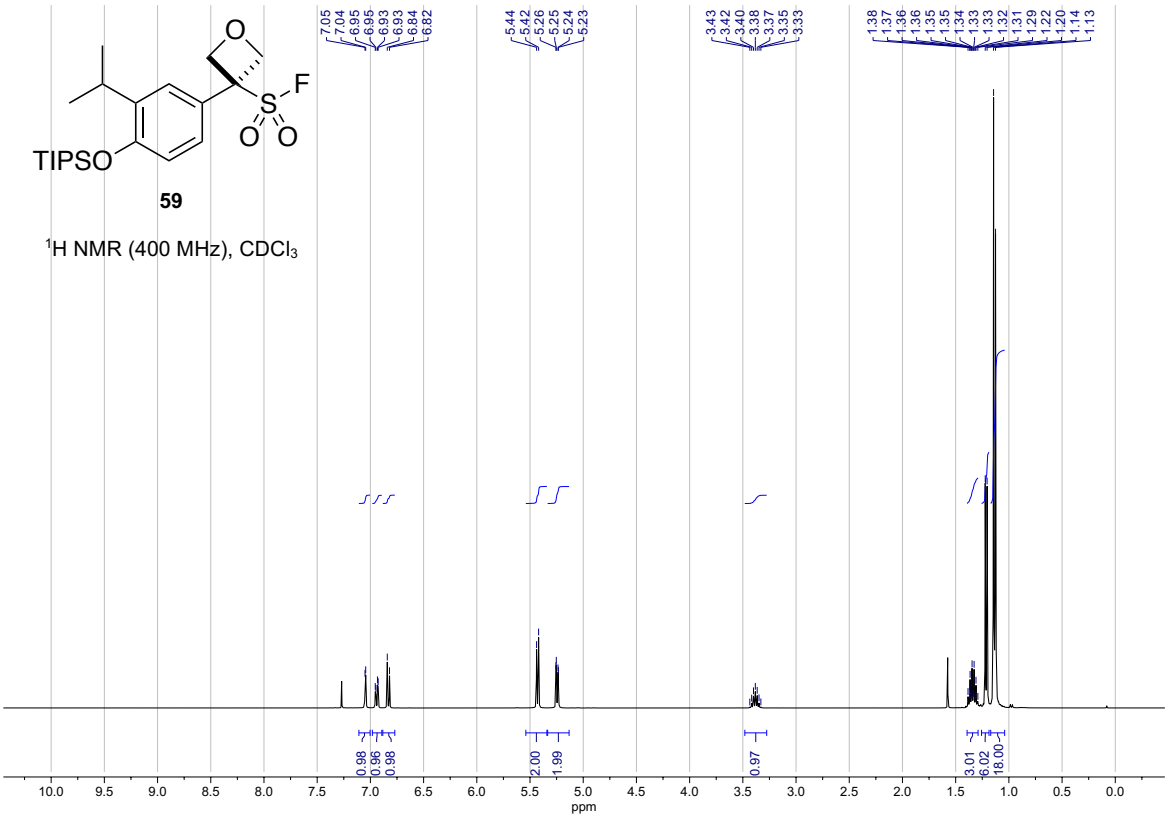

TIPSO
F
O
59'
^{1}H NMR (400 MHz), $CDCl_3$
ppm


59'
^{13}C NMR (101 MHz), $CDCl_3$
153.4
138.9
130.3
130.0
122.4
122.3
122.2
117.7
96.7
94.6
83.3
83.0
26.8
22.7
18.1
13.1
ppm


59'
^{19}F NMR (377 MHz), $CDCl_3$
-145.0
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

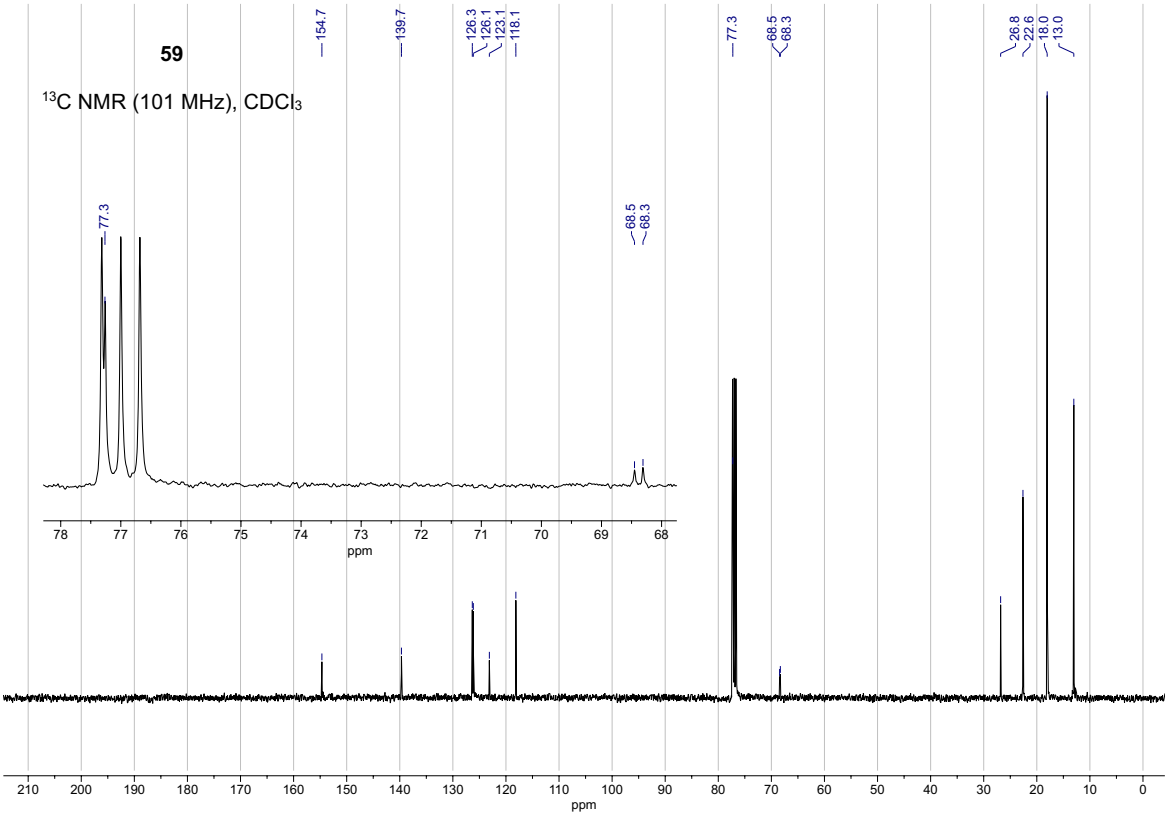
59

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



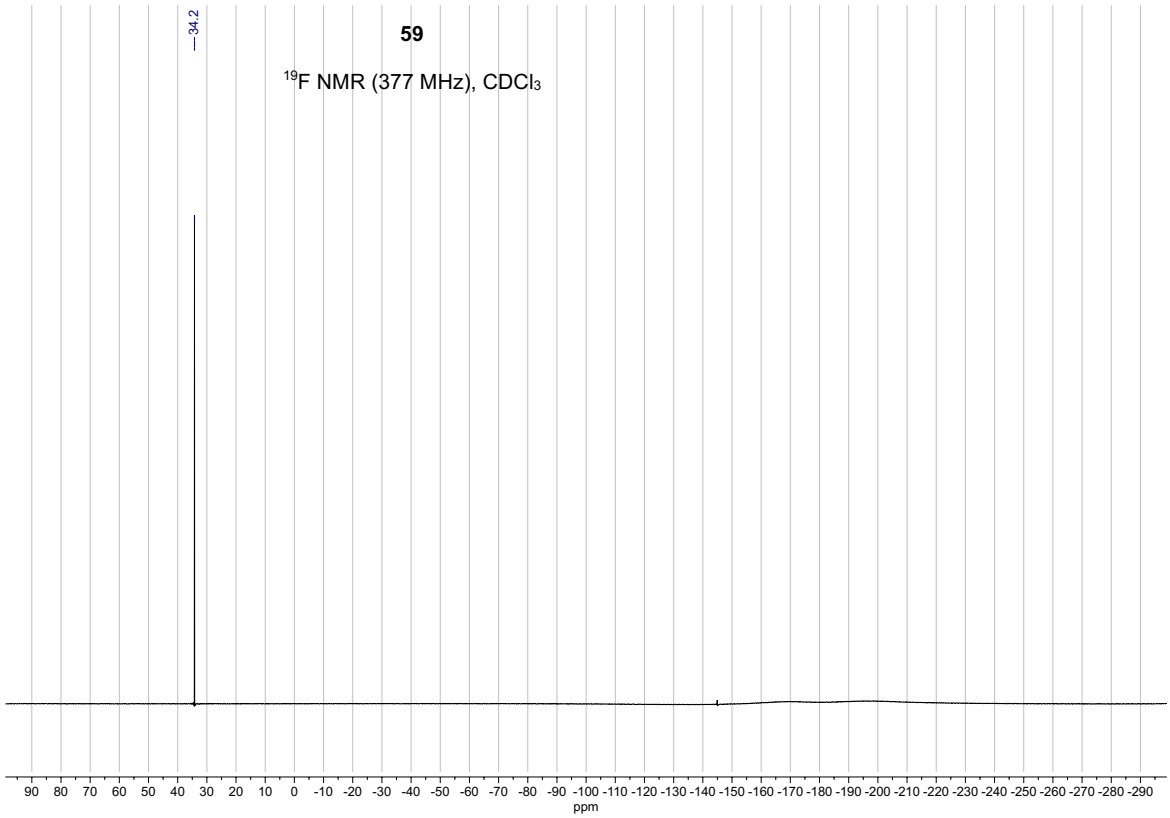
59

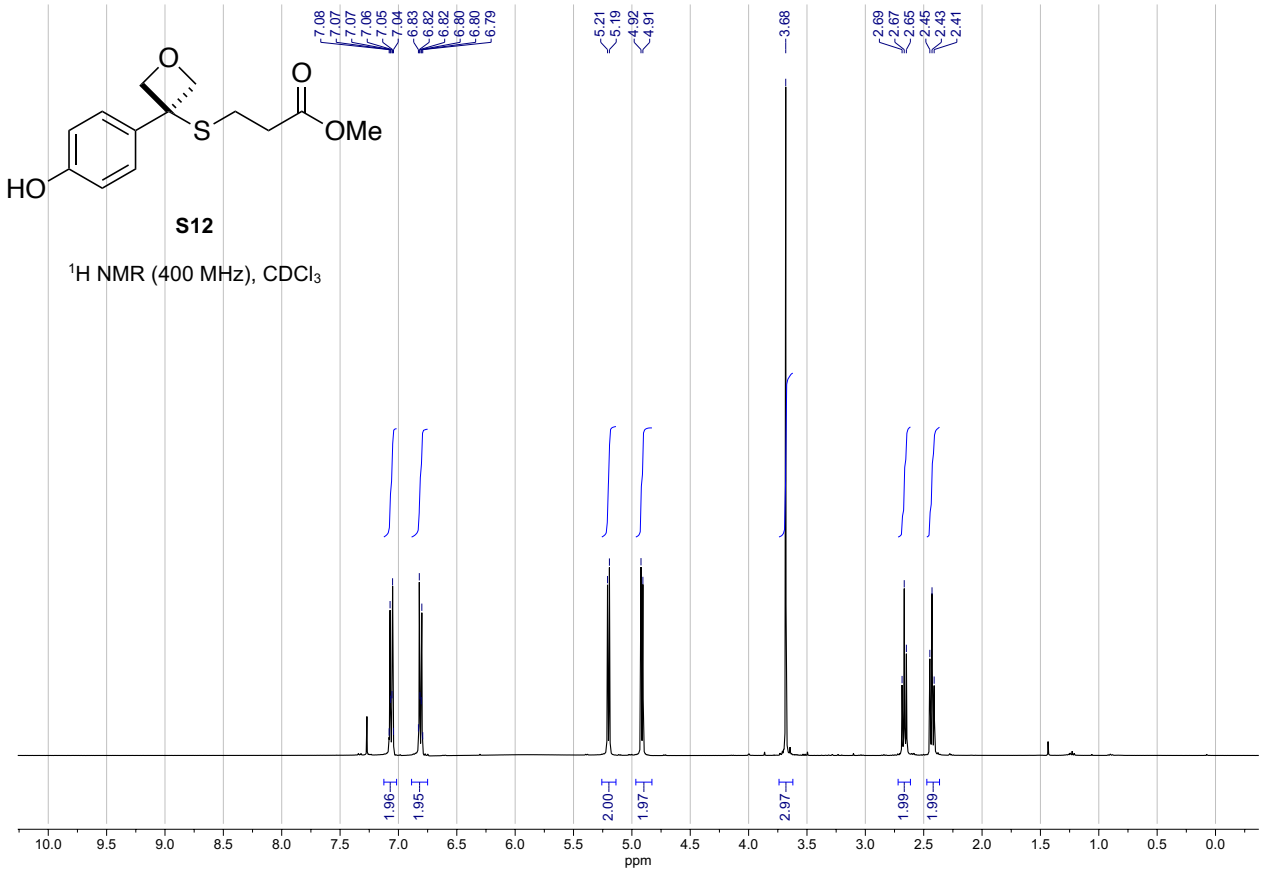
^{13}C NMR (101 MHz), $CDCl_3$



59

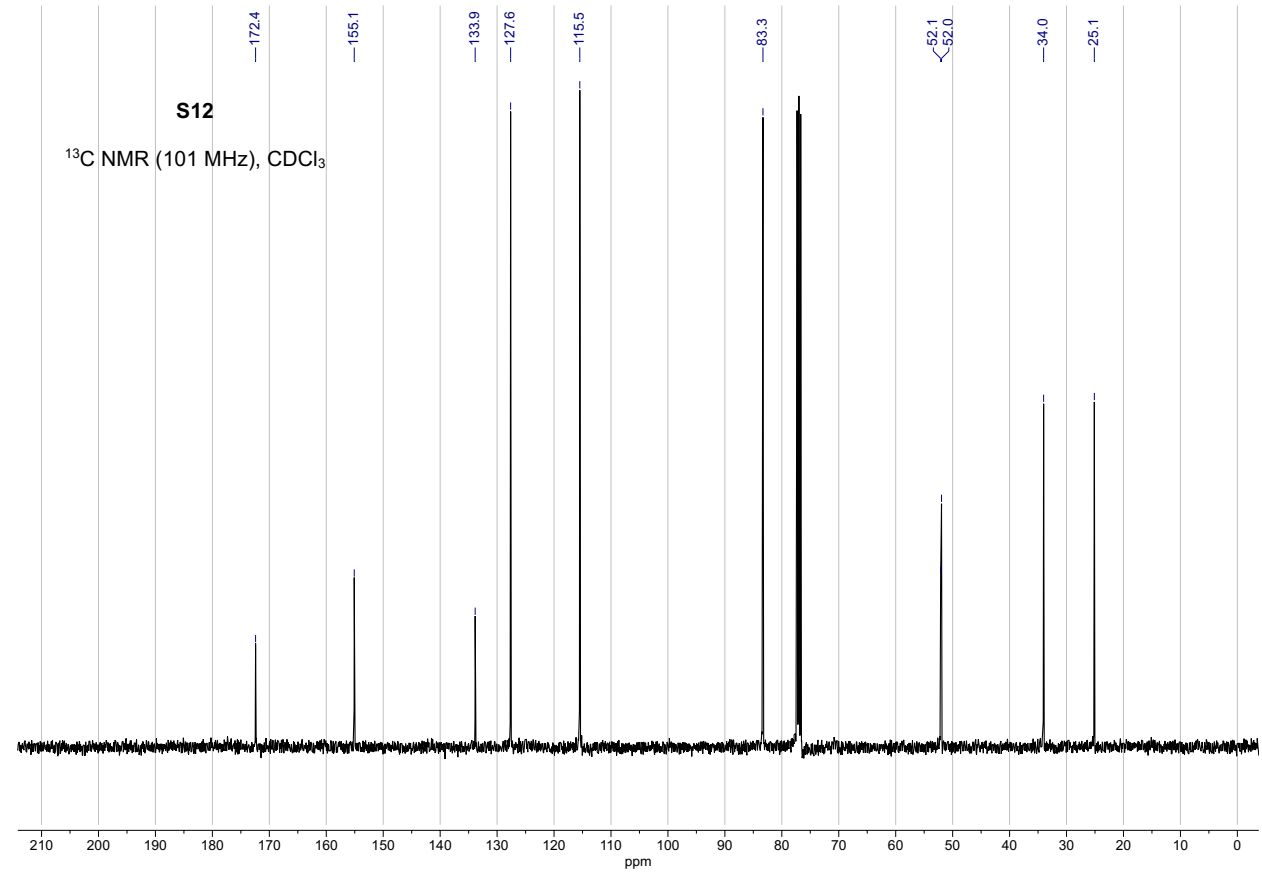
^{19}F NMR (377 MHz), $CDCl_3$





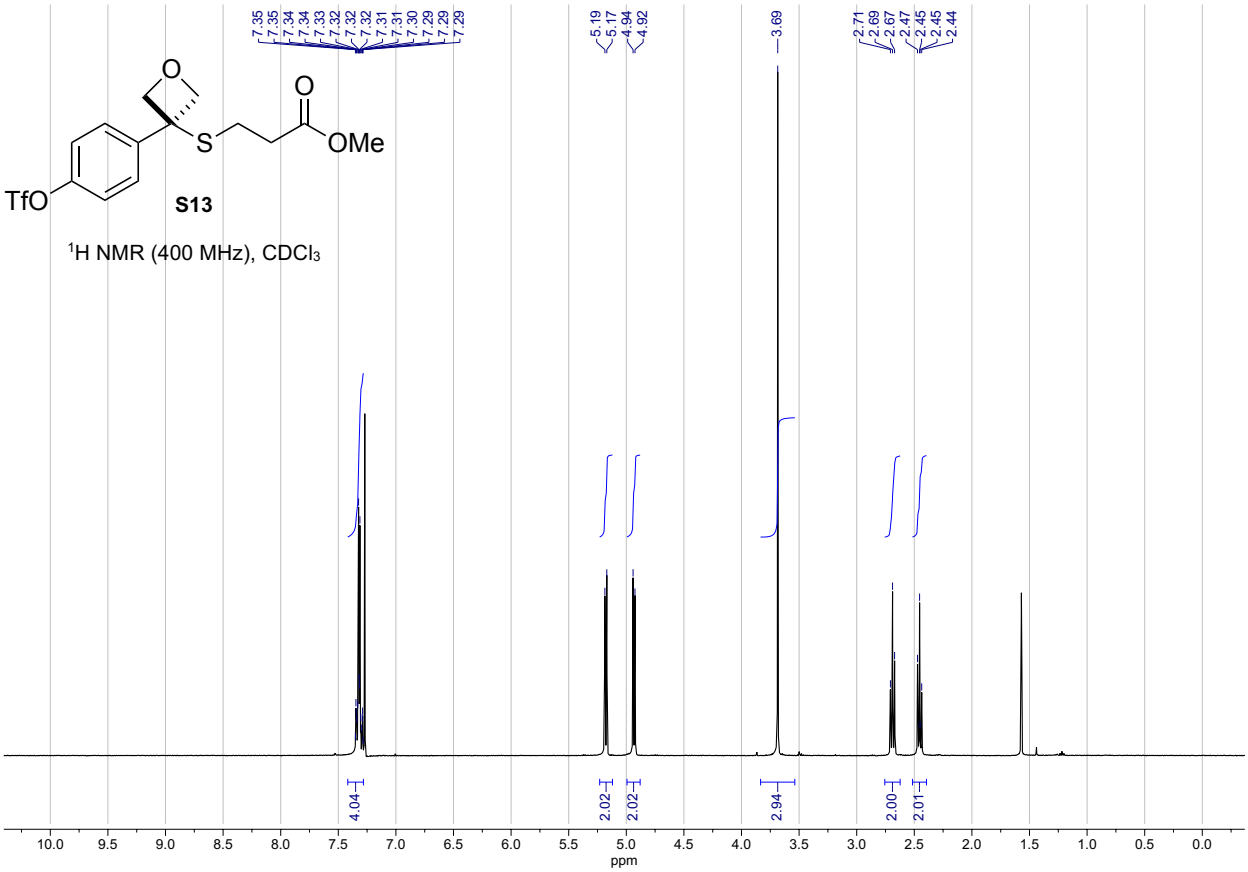
S12

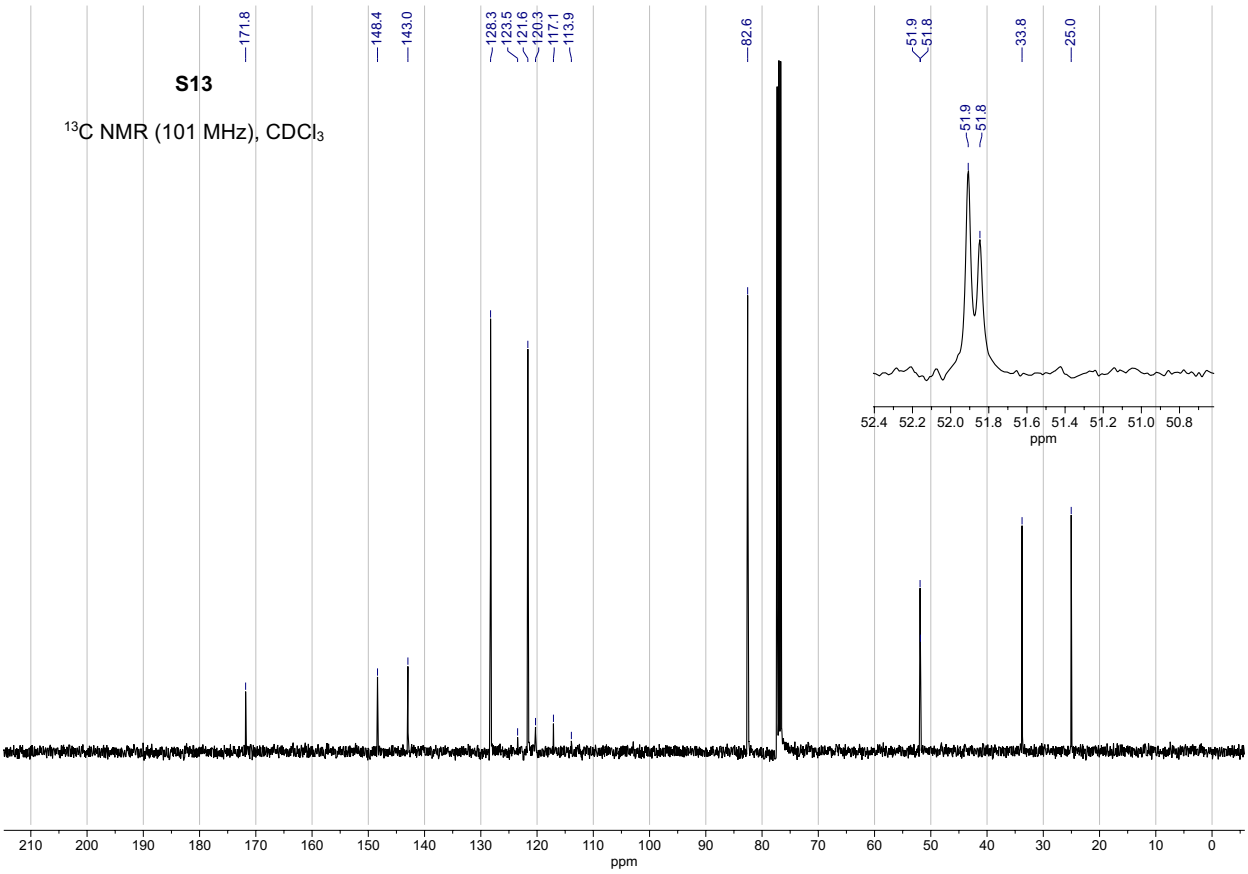
^{1}H NMR (400 MHz), $CDCl_3$

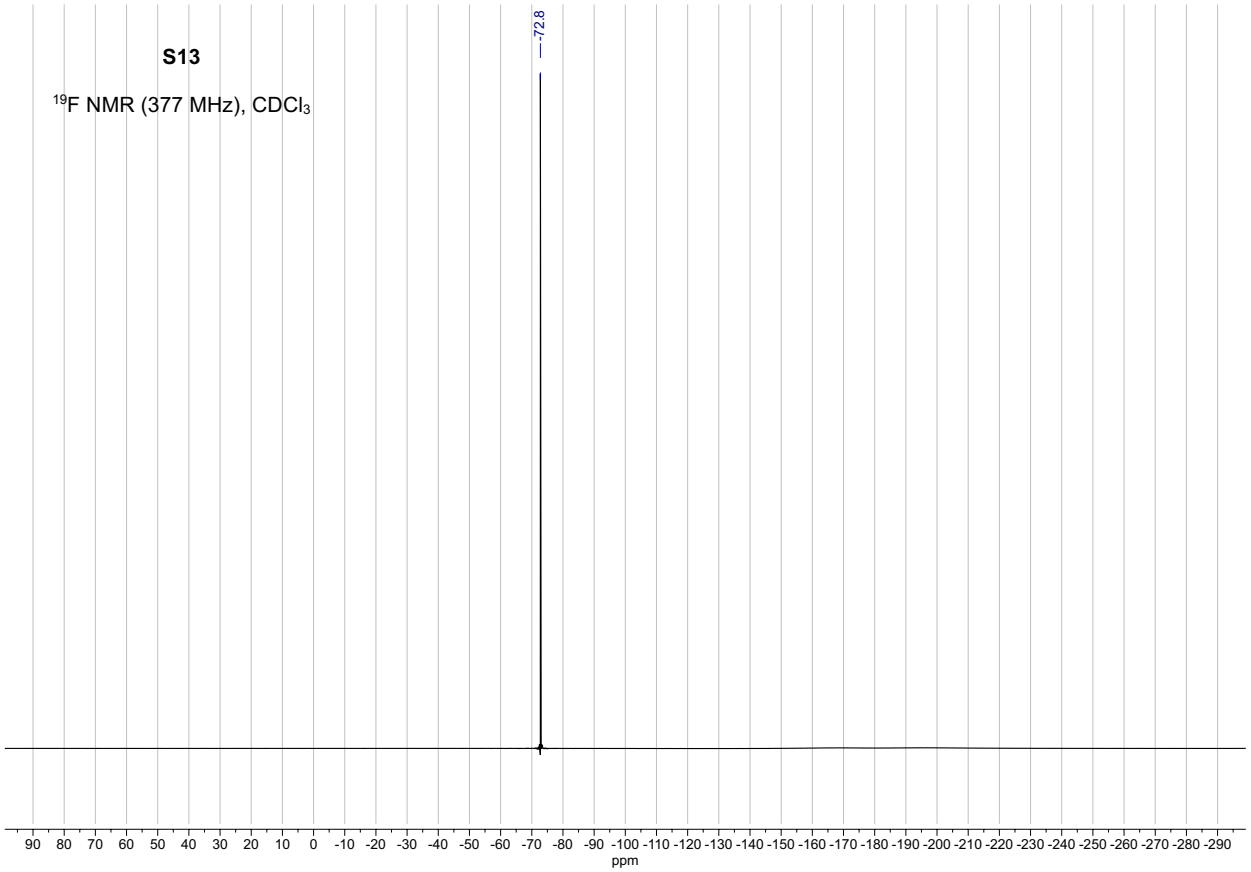


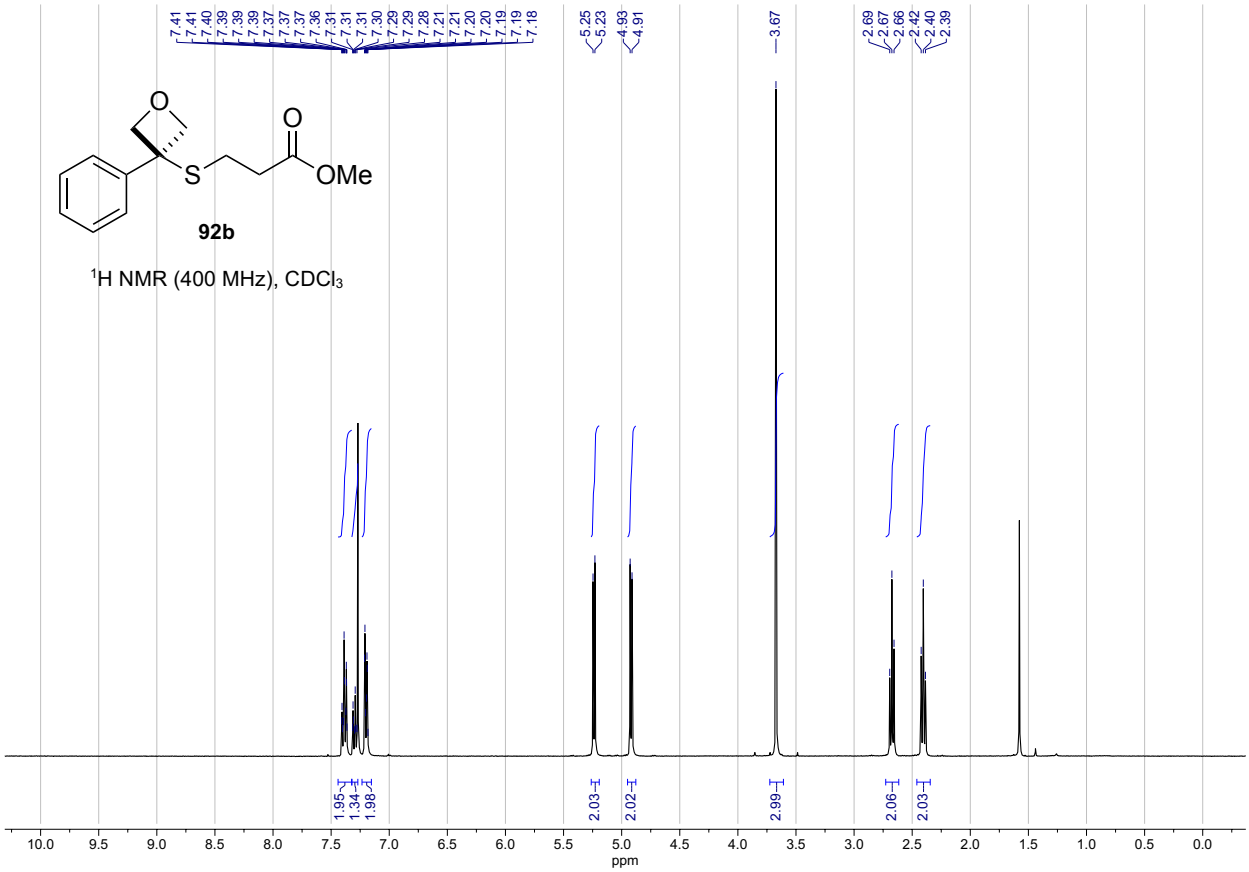
S12

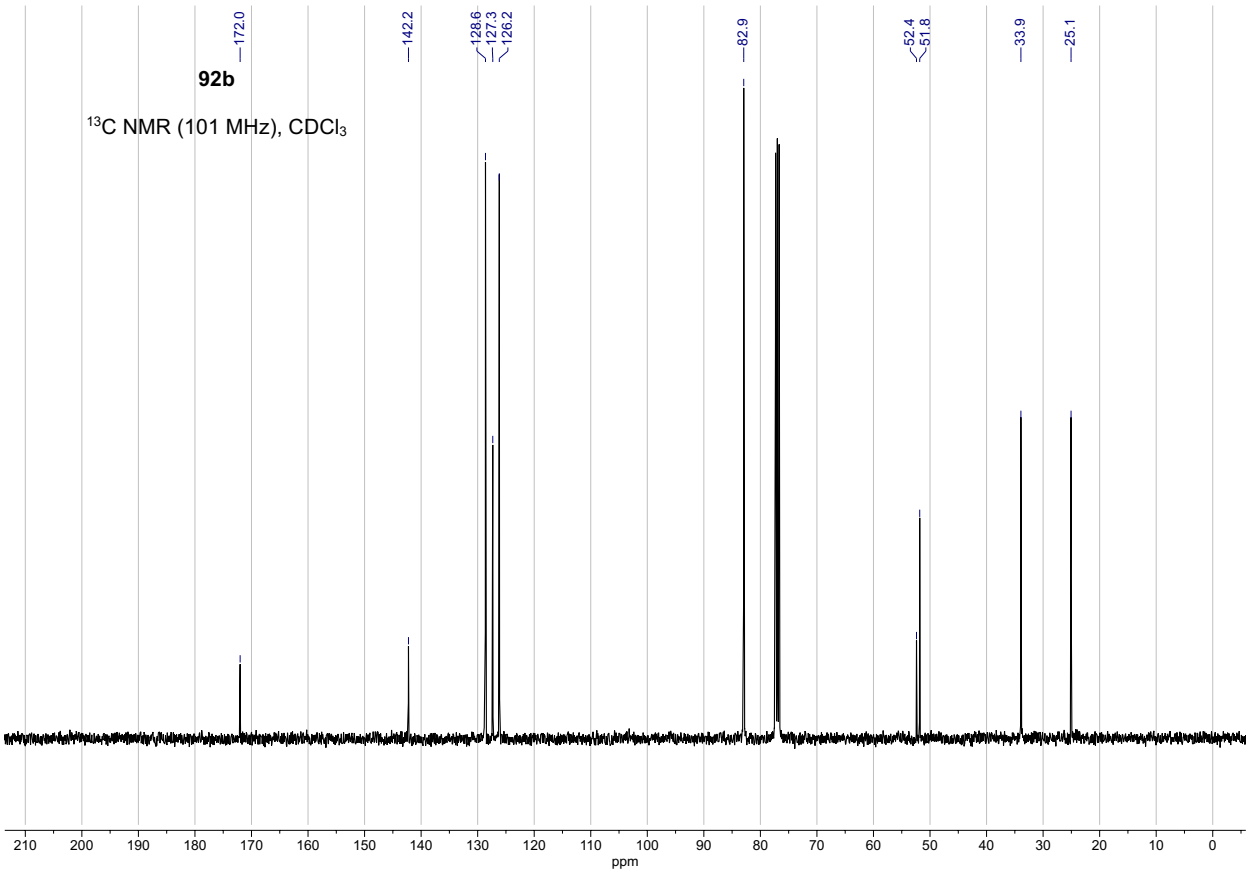
^{13}C NMR (101 MHz), $CDCl_3$

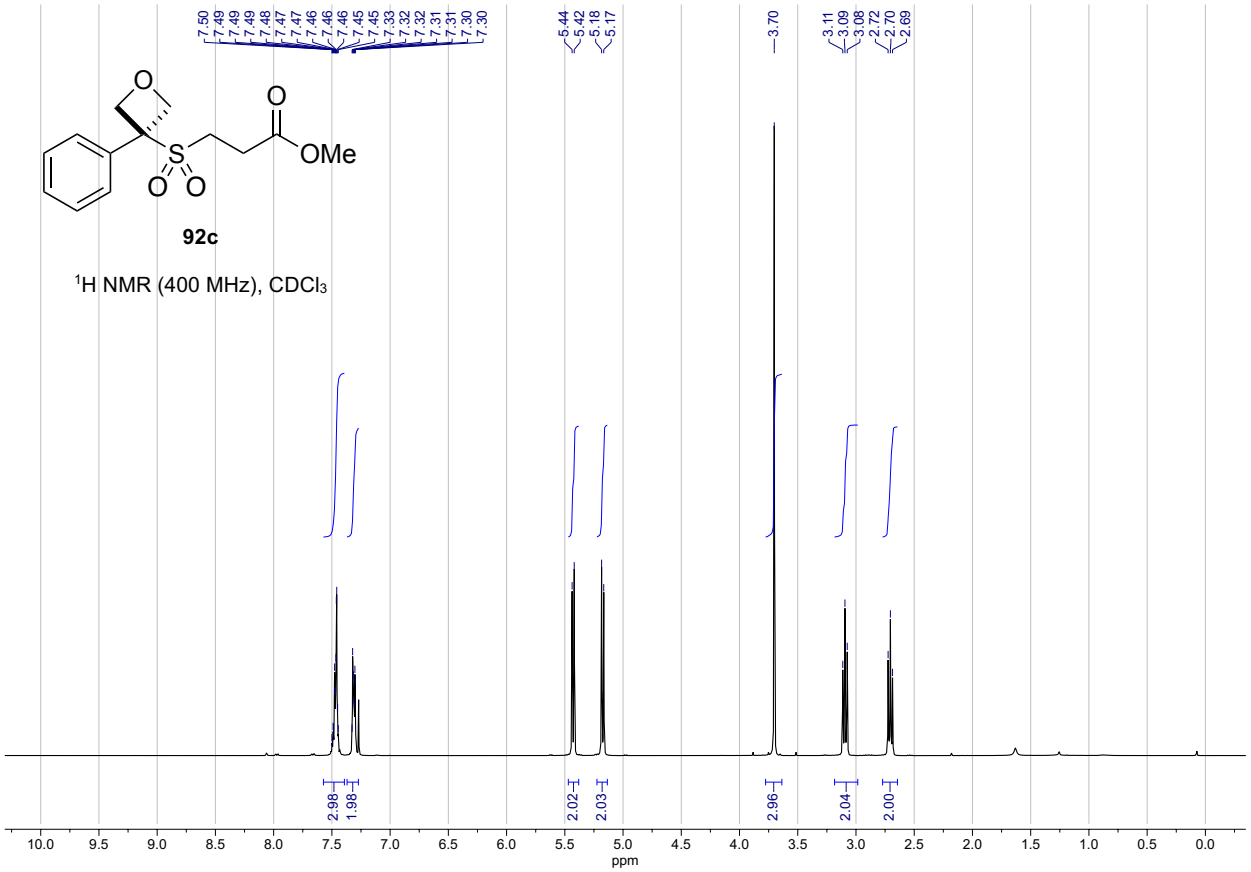

TfO
O
S
O
OMe
S13
^{1}H NMR (400 MHz), CDCl$_3$
7.35 7.35 7.34 7.34 7.33 7.32 7.32 7.32 7.31 7.31 7.30 7.29 7.29 7.29
5.19 5.17 4.94 4.92
3.69
2.71 2.69 2.67 2.47 2.45 2.45 2.44
4.04 2.02 2.02 2.94 2.00 2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

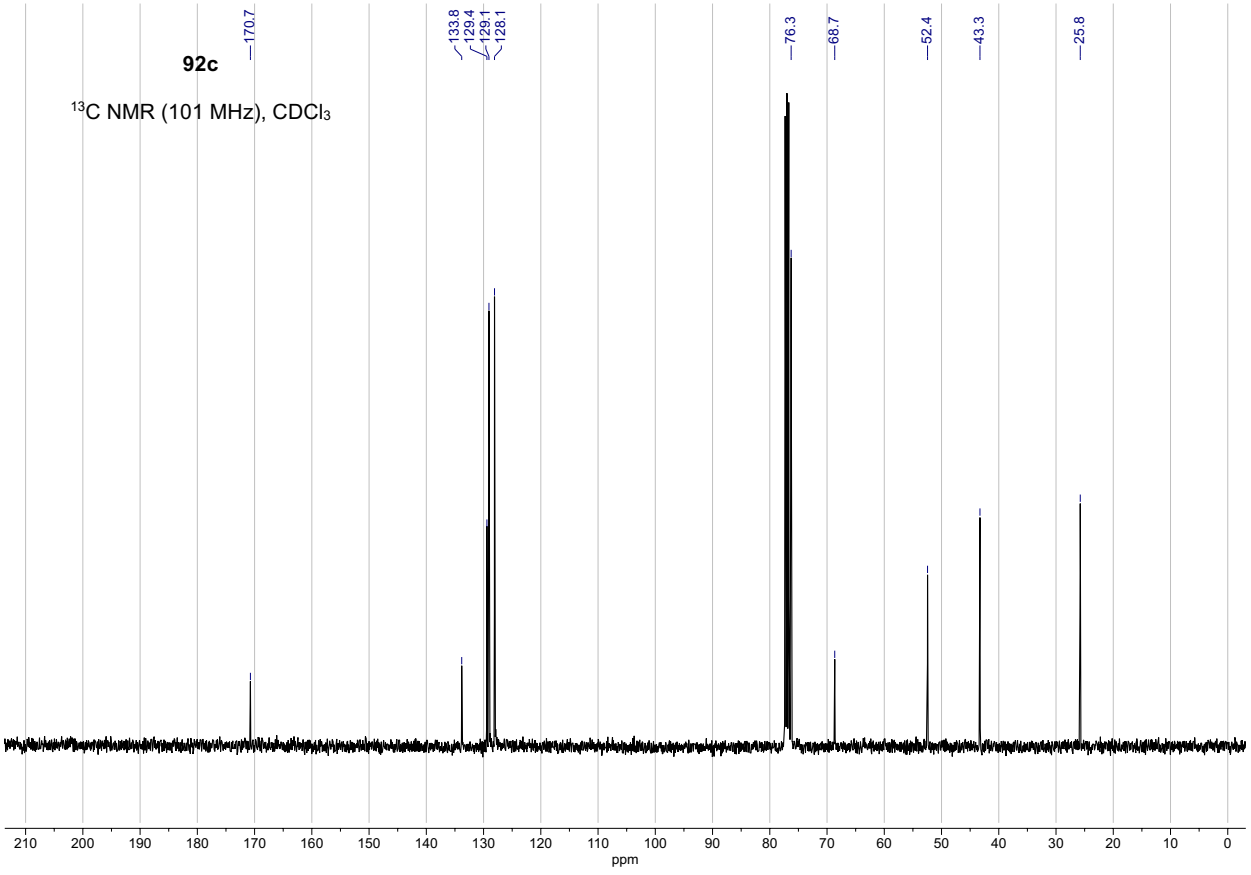

S13
^{13}C NMR (101 MHz), CDCl$_3$
171.8
148.4
143.0
128.3
123.5
121.6
120.3
117.1
113.9
82.6
51.9
51.8
33.8
25.0
52.4 52.2 52.0 51.8 51.6 51.4 51.2 51.0 50.8
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

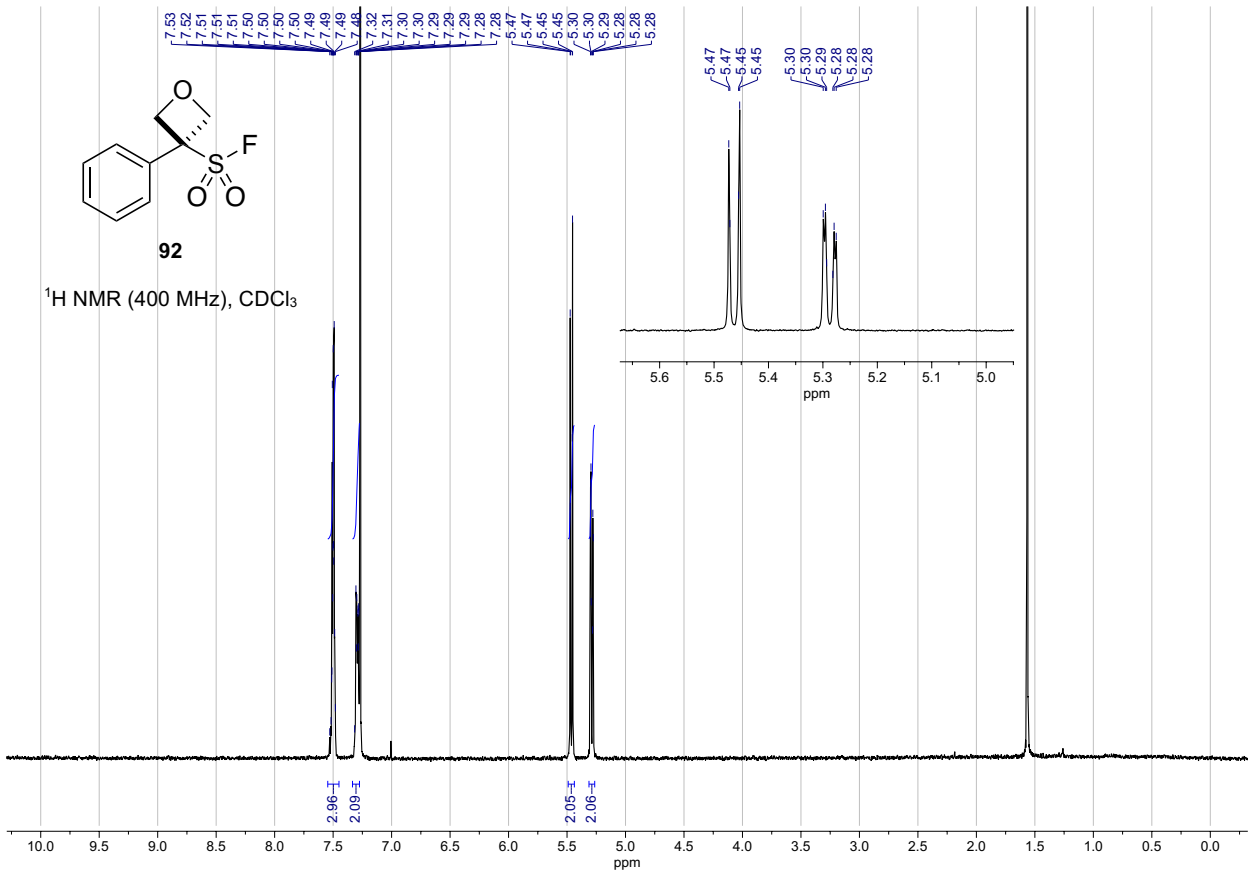

S13
^{19}F NMR (377 MHz), $CDCl_3$
-72.8
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

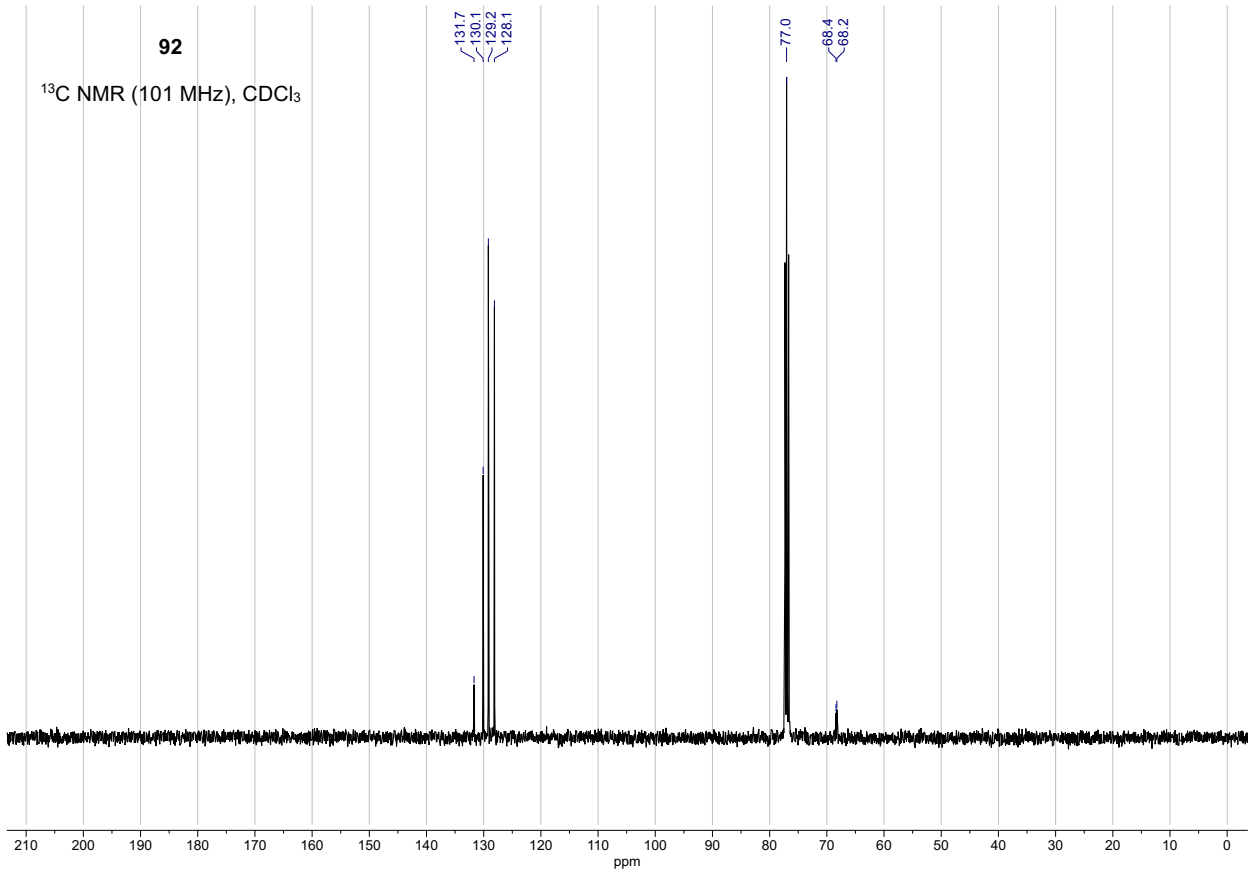

7.41
7.41
7.40
7.39
7.39
7.39
7.37
7.37
7.37
7.36
7.31
7.31
7.31
7.30
7.29
7.29
7.28
7.21
7.21
7.20
7.20
7.19
7.19
7.18
5.25
5.23
4.93
4.91
3.67
2.69
2.67
2.66
2.42
2.40
2.39
O
O
S
OMe
92b
1H NMR (400 MHz), CDCl3
1.95
1.34
1.98
2.03
2.02
2.99
2.06
2.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


172.0
142.2
128.6
127.3
126.2
82.9
52.4
51.8
33.9
25.1
92b
13C NMR (101 MHz), CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.50
7.49
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.46
7.45
7.45
7.33
7.32
7.32
7.31
7.31
7.30
7.30
5.44
5.42
5.18
5.17
3.70
3.11
3.09
3.08
2.72
2.70
2.69
O
O
S
O
O
OMe
92c
^{1}H NMR (400 MHz), $CDCl_3$
2.98
1.98
2.02
2.03
2.96
2.04
2.00
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

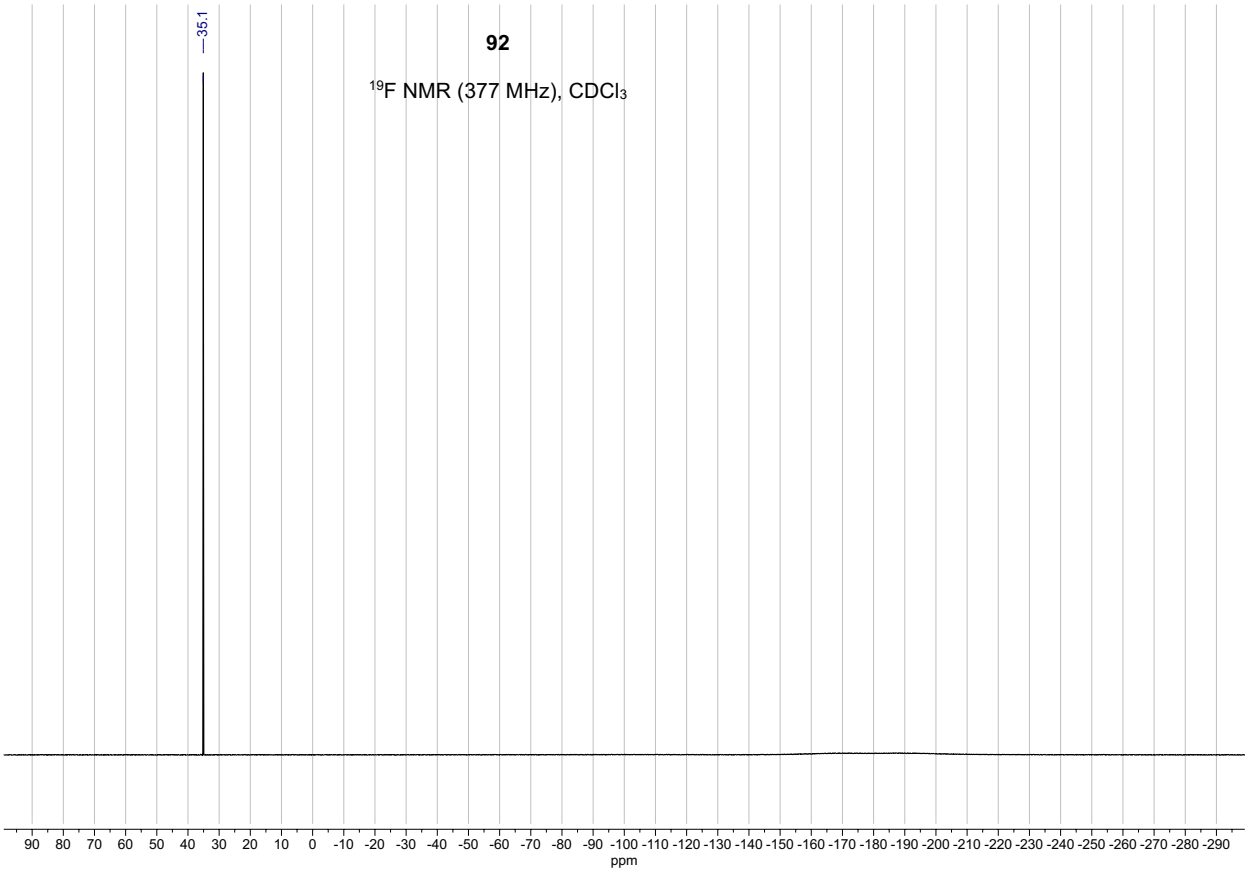

92c
^{13}C NMR (101 MHz), $CDCl_3$
170.7
133.8
129.4
129.1
128.1
76.3
68.7
52.4
43.3
25.8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

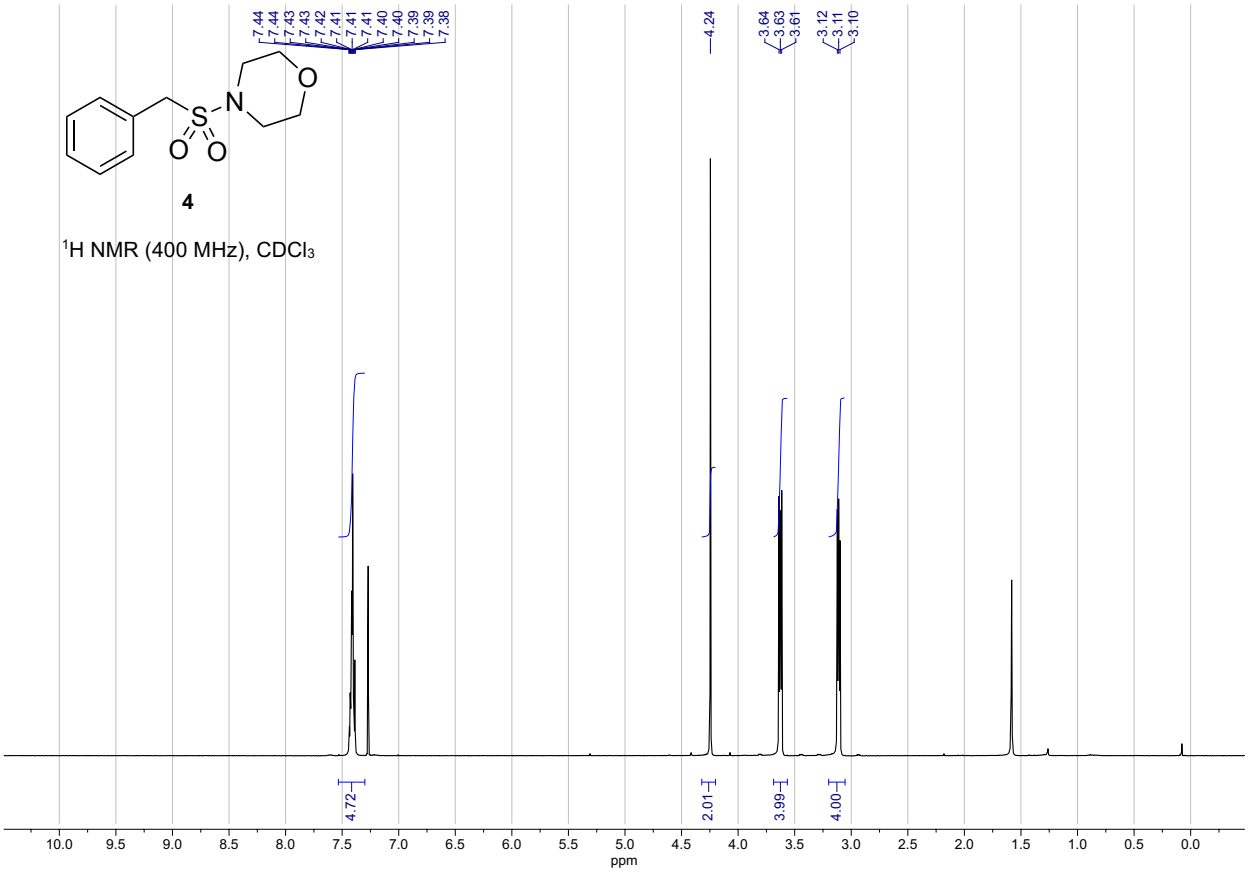

92
^{1}H NMR (400 MHz), CDCl$_3$
ppm

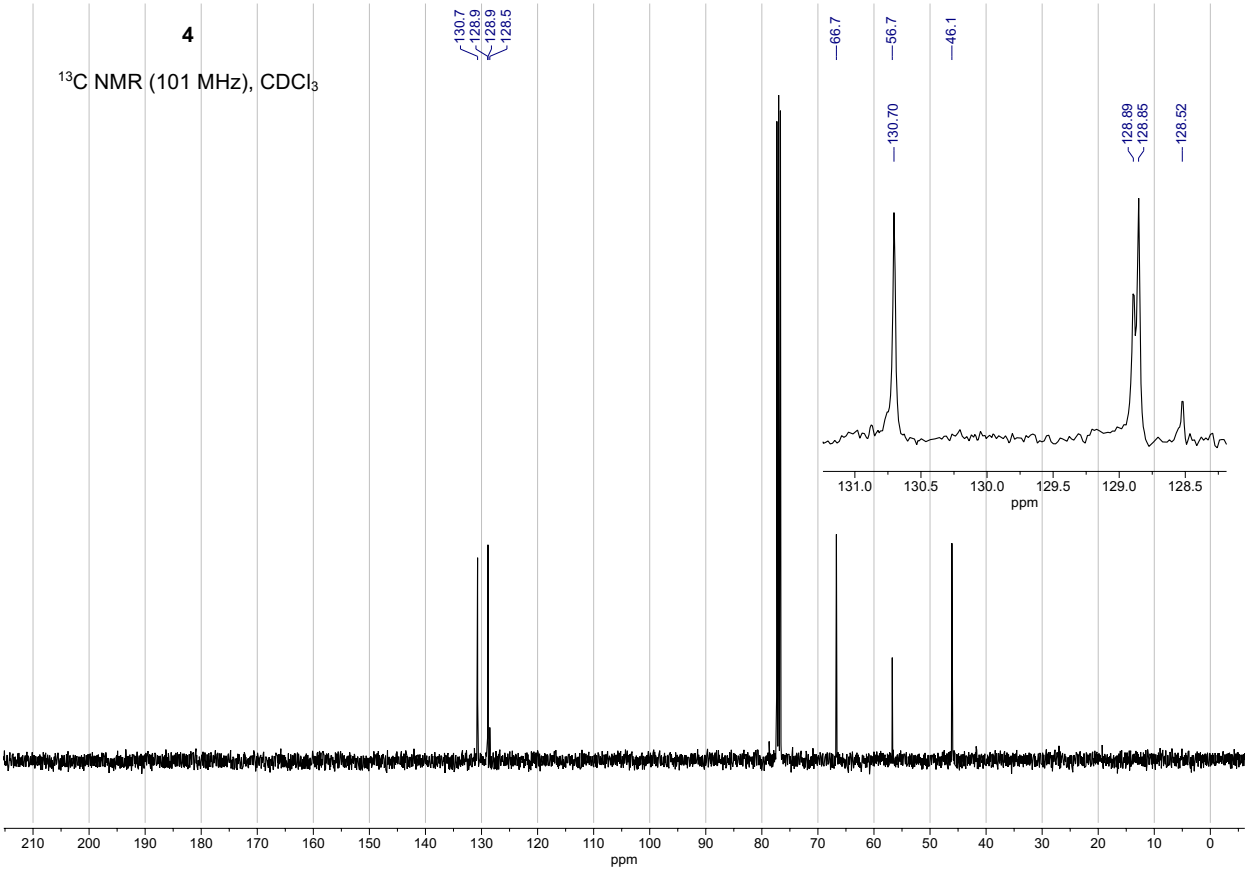

92
^{13}C NMR (101 MHz), CDCl$_3$
ppm

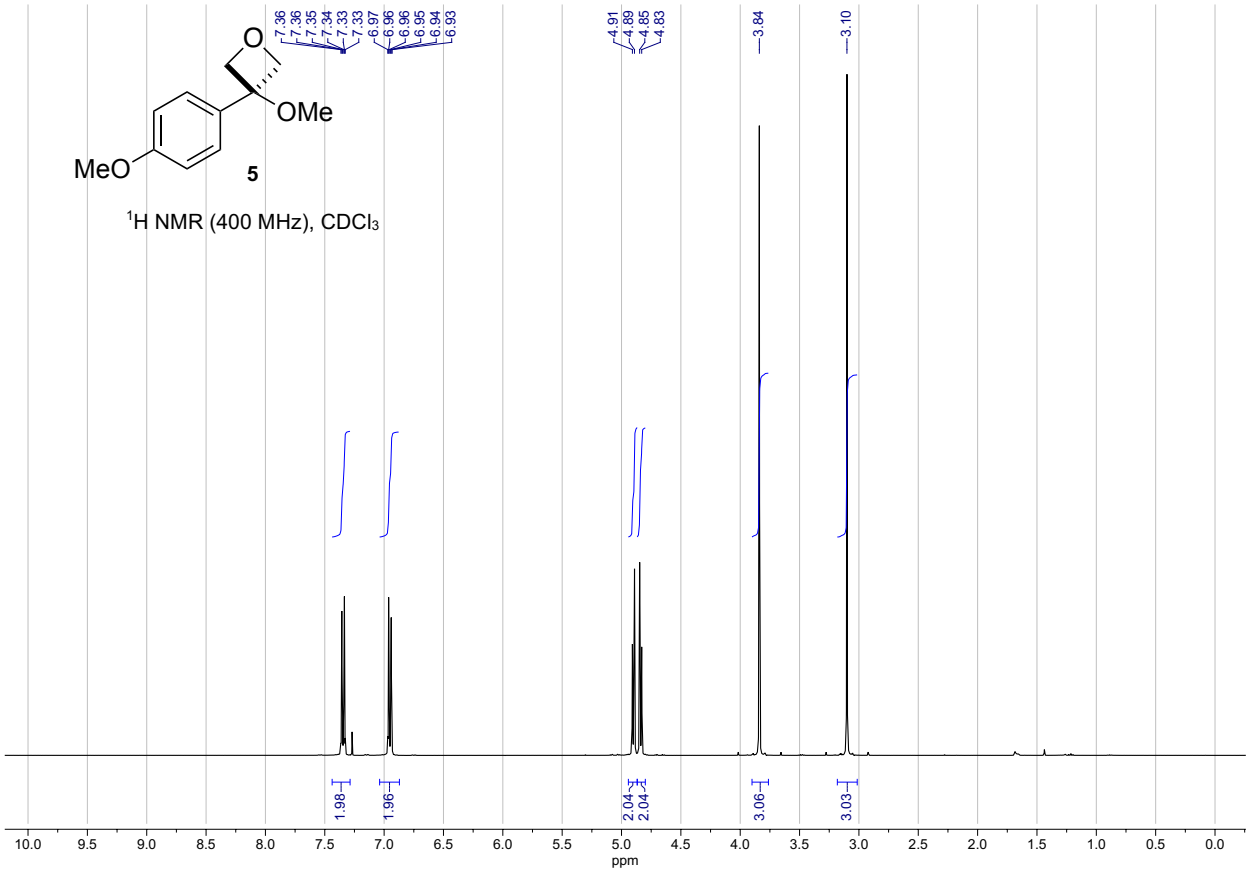
92

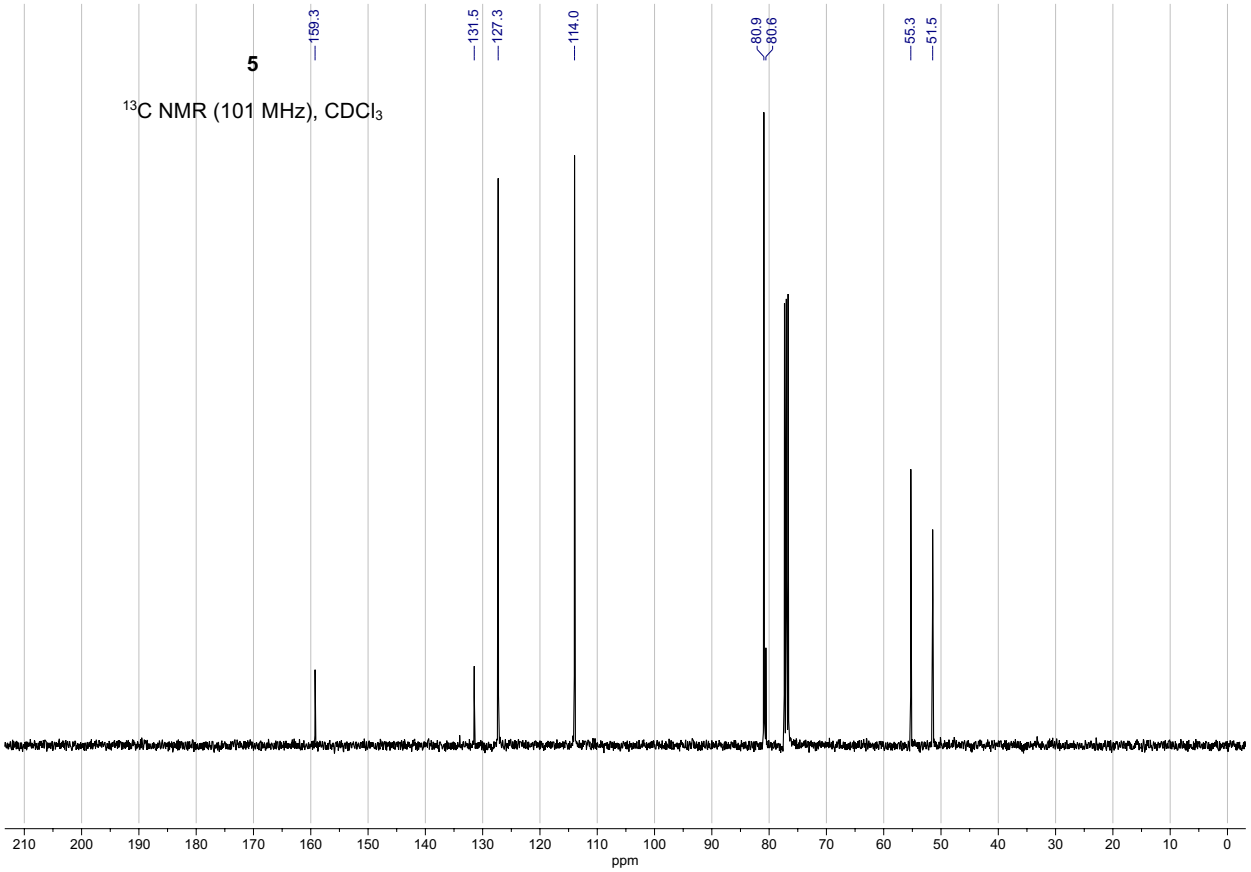
^{19}F NMR (377 MHz), $CDCl_3$

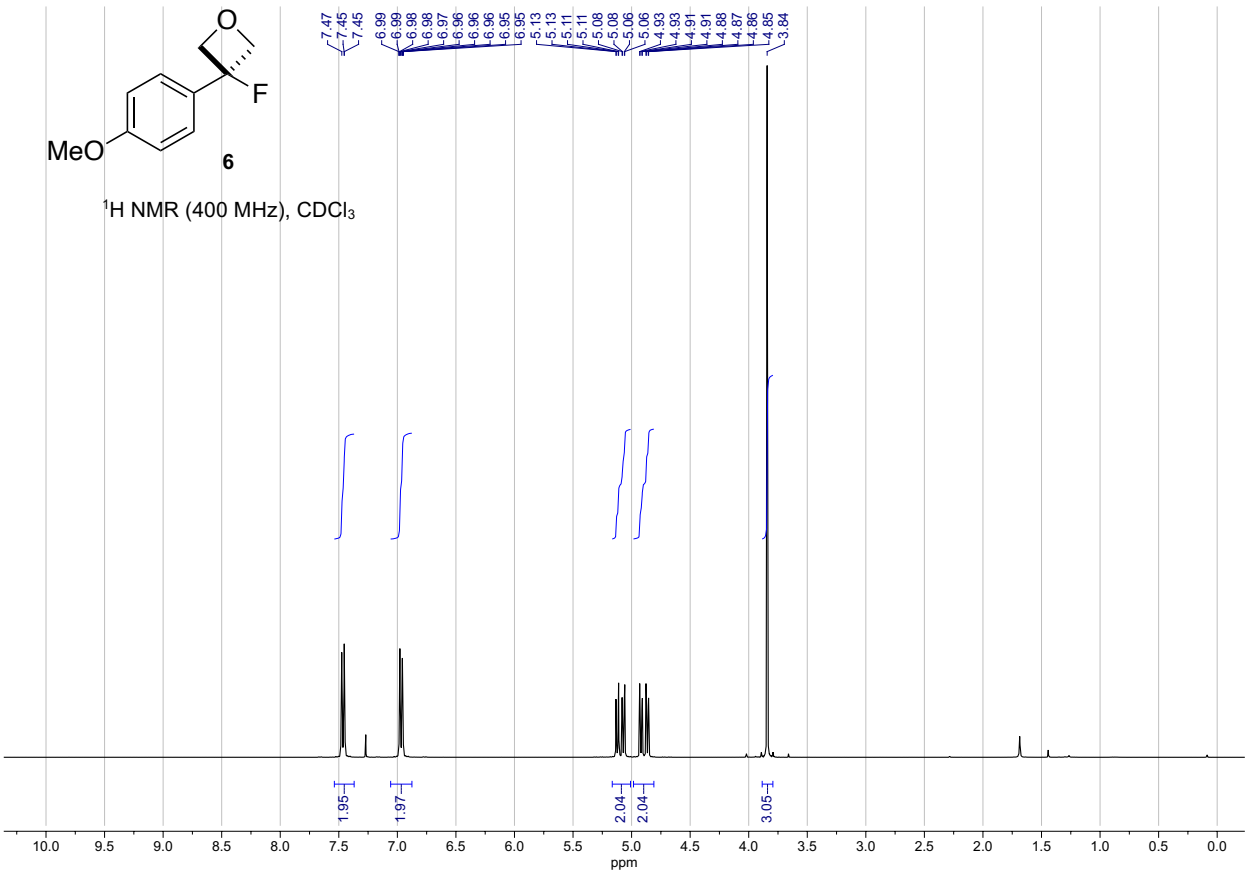


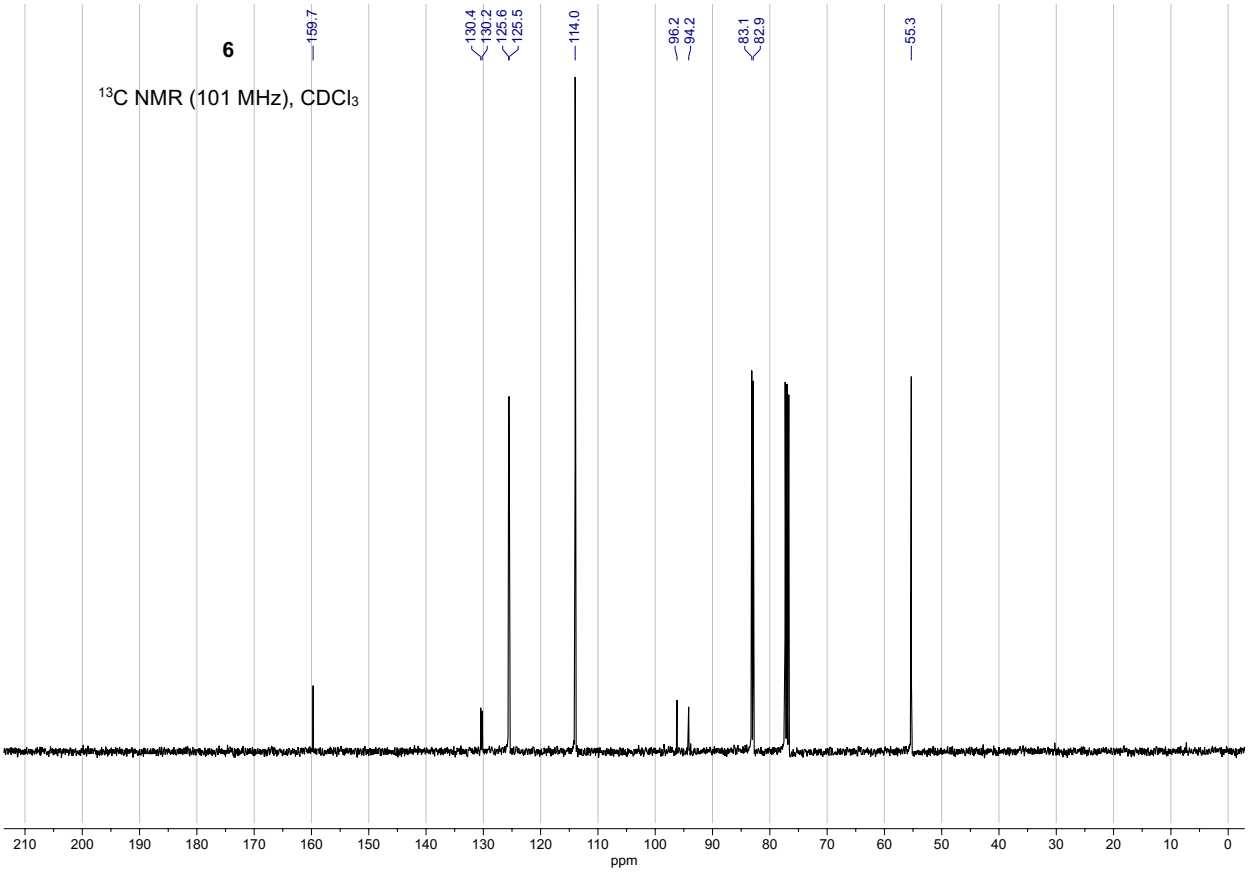

7.44
7.44
7.43
7.43
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.39
7.38
4.24
3.64
3.63
3.61
3.12
3.11
3.10
O
N
S
O
O
4
^{1}H NMR (400 MHz), CDCl$_3$
4.72
2.01
3.99
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

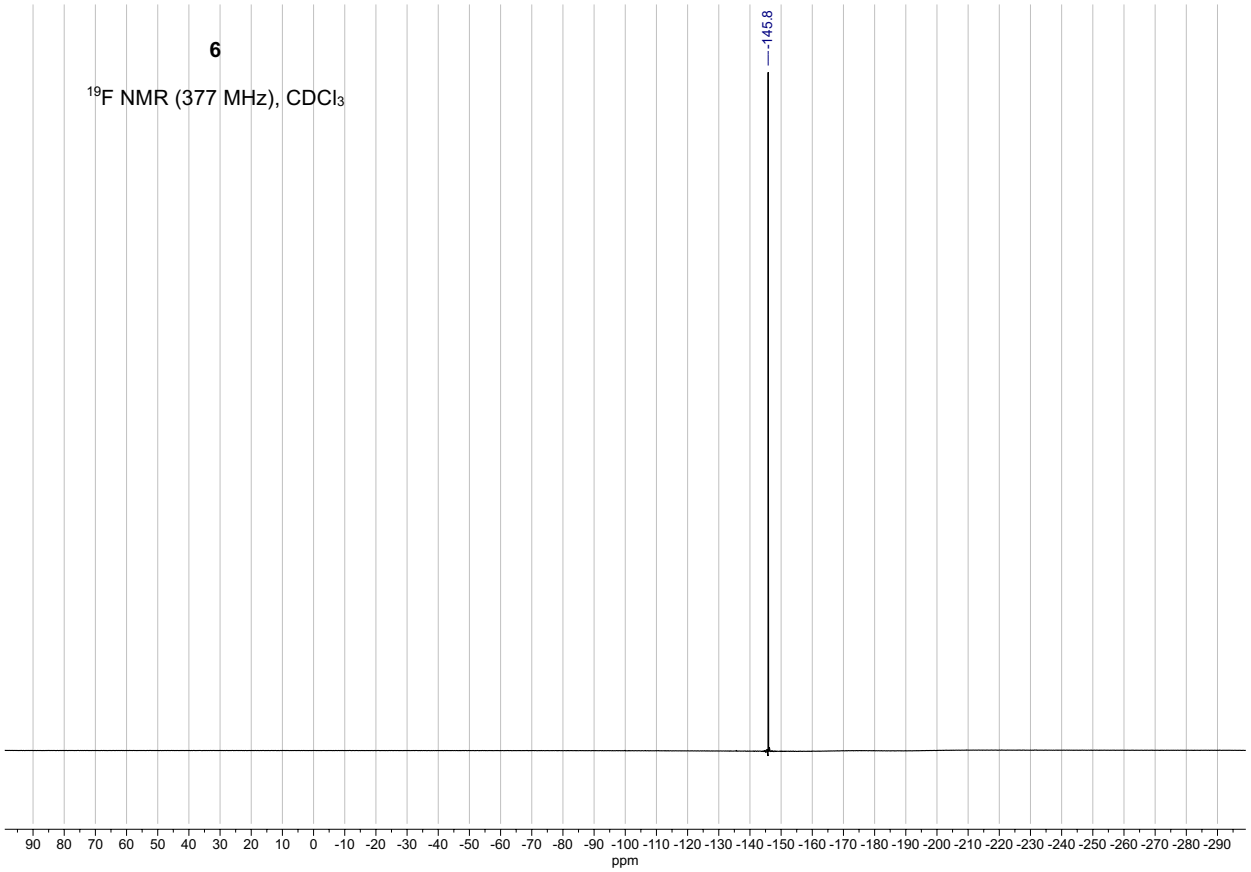

4
^{13}C NMR (101 MHz), CDCl$_3$
130.7
128.9
128.9
128.5
66.7
56.7
46.1
130.70
128.89
128.85
128.52
131.0
130.5
130.0
129.5
129.0
128.5
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

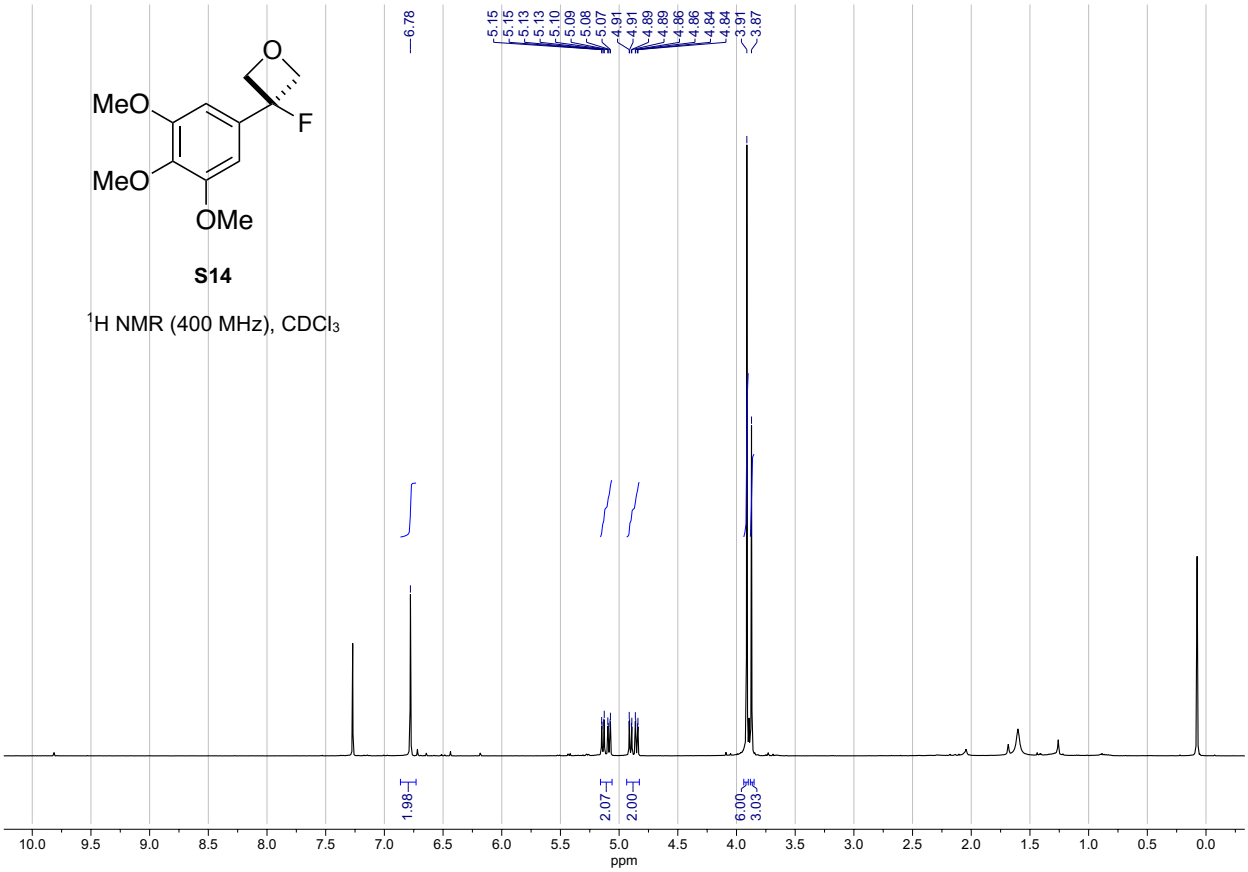

7.36
7.36
7.35
7.34
7.33
7.33
6.97
6.96
6.96
6.95
6.94
6.93
4.91
4.89
4.85
4.83
3.84
3.10
O
OMe
MeO
5
1H NMR (400 MHz), CDCl3
1.98
1.96
2.04
2.04
3.06
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

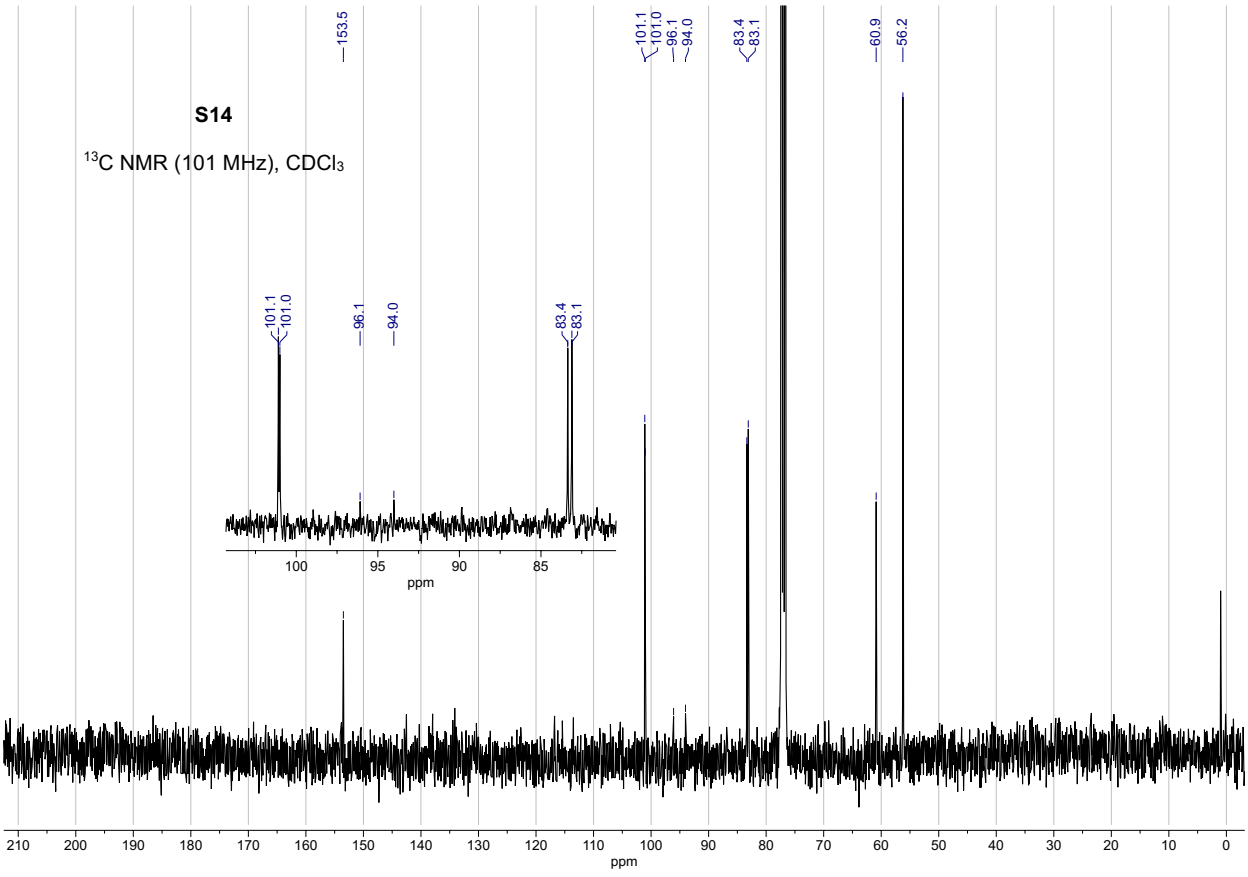

159.3
131.5
127.3
114.0
80.9
80.6
55.3
51.5
5
13C NMR (101 MHz), CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

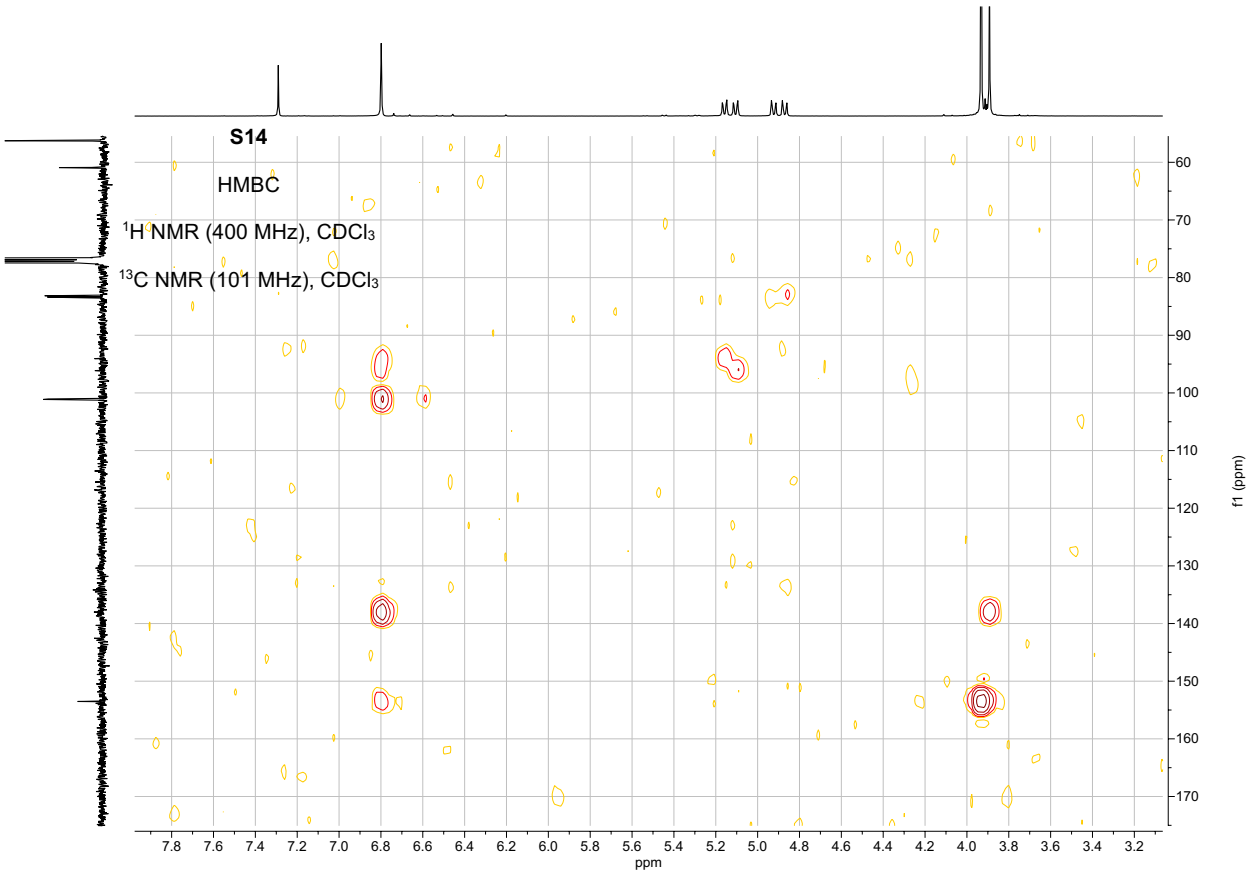

MeO
F
O
6
^{1}H NMR (400 MHz), CDCl$_3$
7.47
7.45
7.45
6.99
6.99
6.98
6.98
6.97
6.96
6.96
6.96
6.95
6.95
5.13
5.13
5.11
5.11
5.08
5.08
5.06
5.06
4.93
4.93
4.91
4.91
4.88
4.87
4.86
4.85
3.04
1.95
1.97
2.04
2.04
3.05
ppm

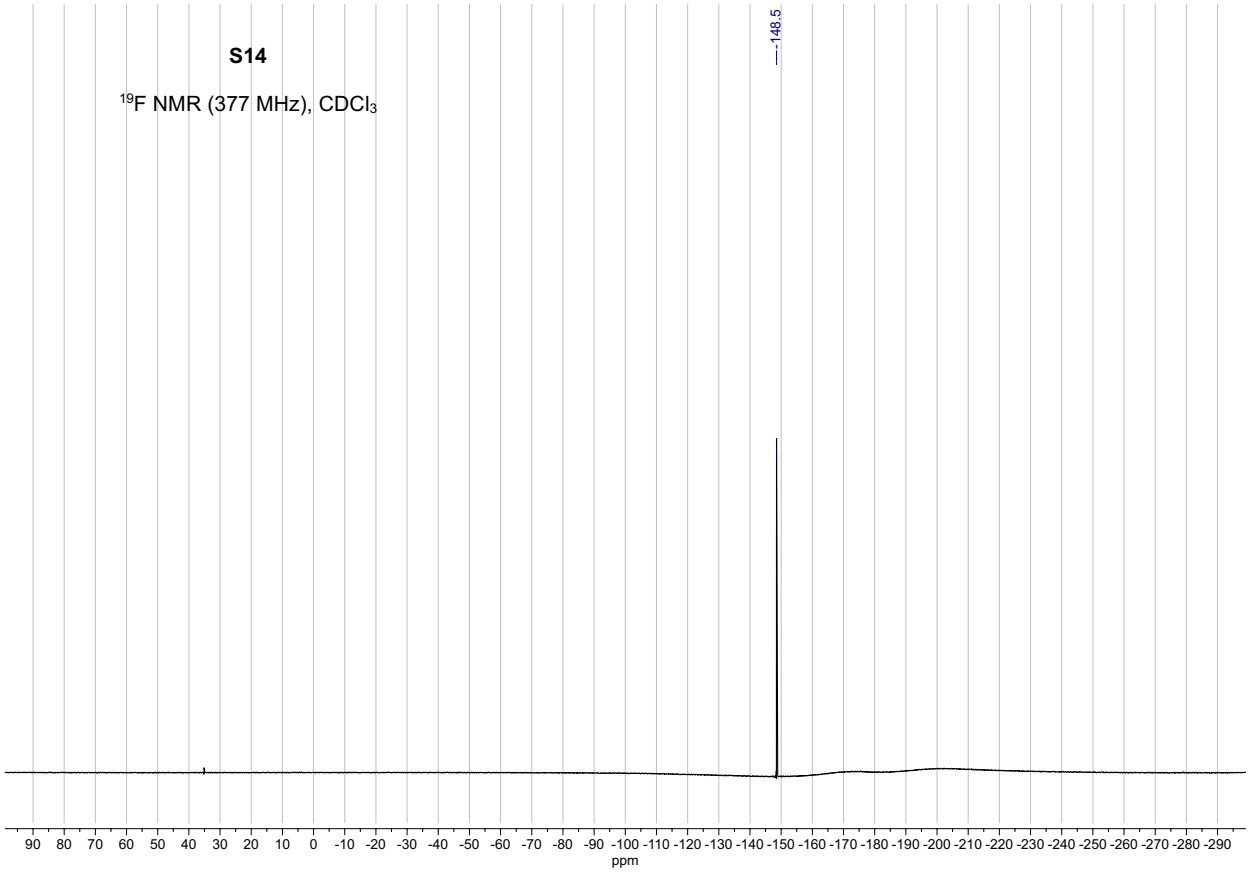

6
^{13}C NMR (101 MHz), CDCl$_3$
159.7
130.4
130.2
125.6
125.5
114.0
96.2
94.2
83.1
82.9
55.3
ppm

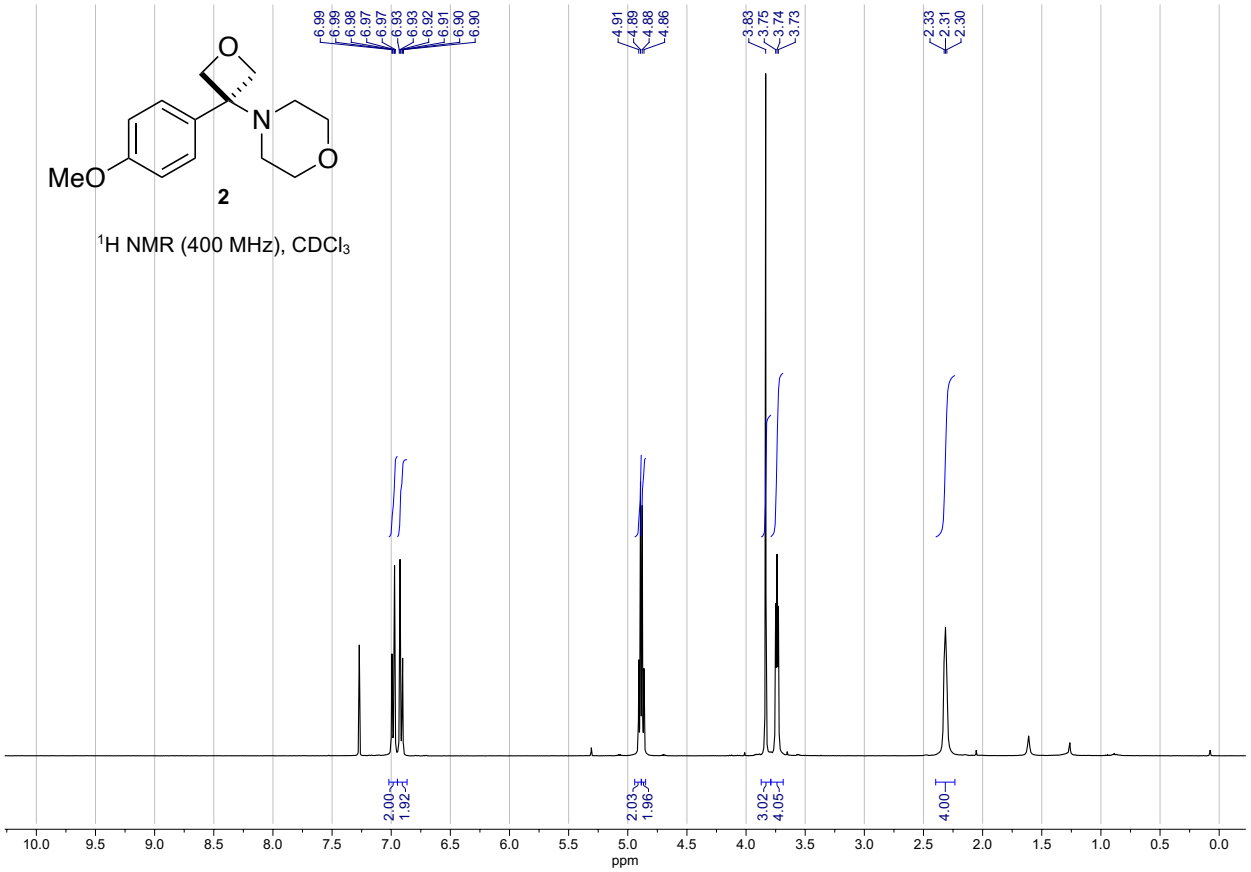

6
^{19}F NMR (377 MHz), $CDCl_3$
-145.8
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

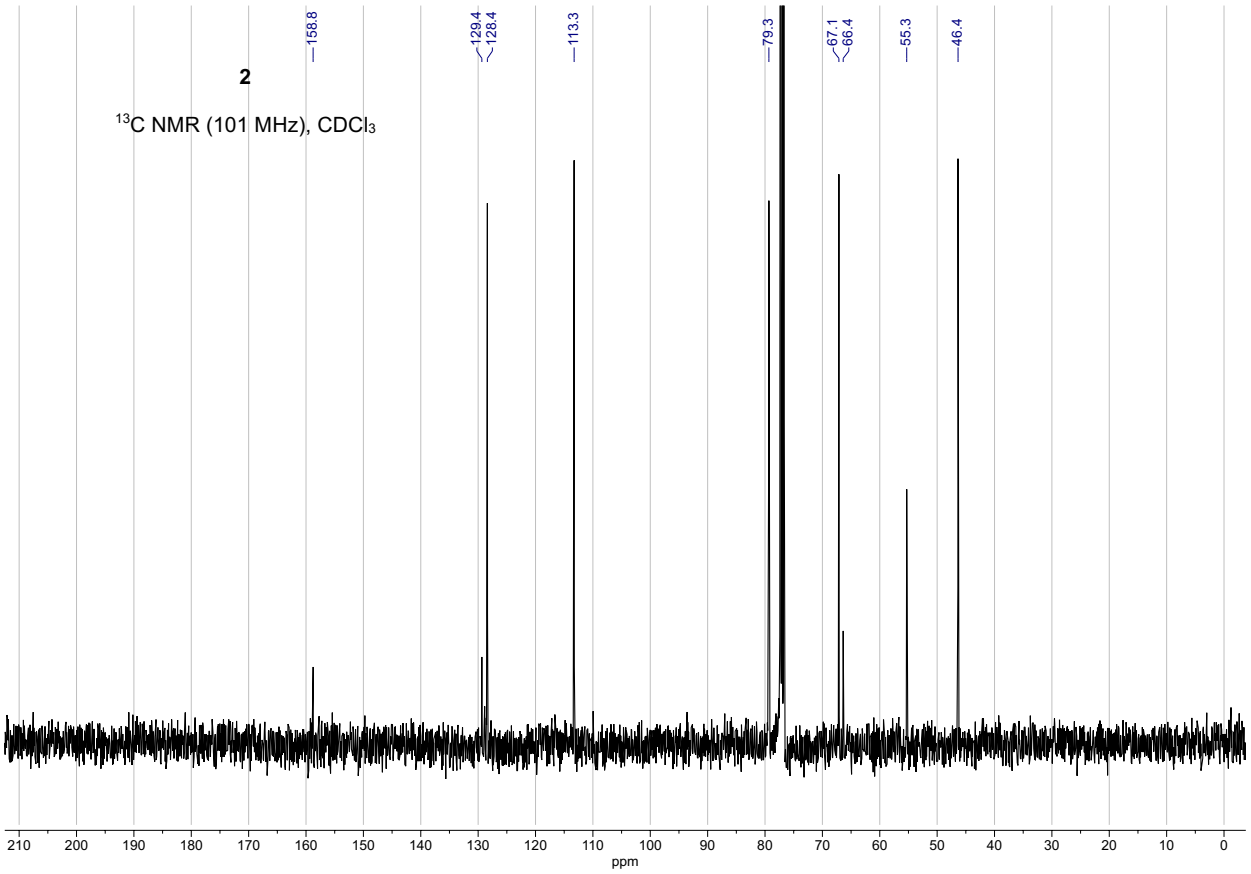

MeO
MeO
OMe
O
F
S14
^{1}H NMR (400 MHz), CDCl$_3$
6.78
5.15
5.15
5.13
5.13
5.10
5.09
5.08
5.07
4.91
4.91
4.89
4.89
4.86
4.86
4.84
4.84
3.91
3.87
1.98
2.07
2.00
6.00
3.03
ppm

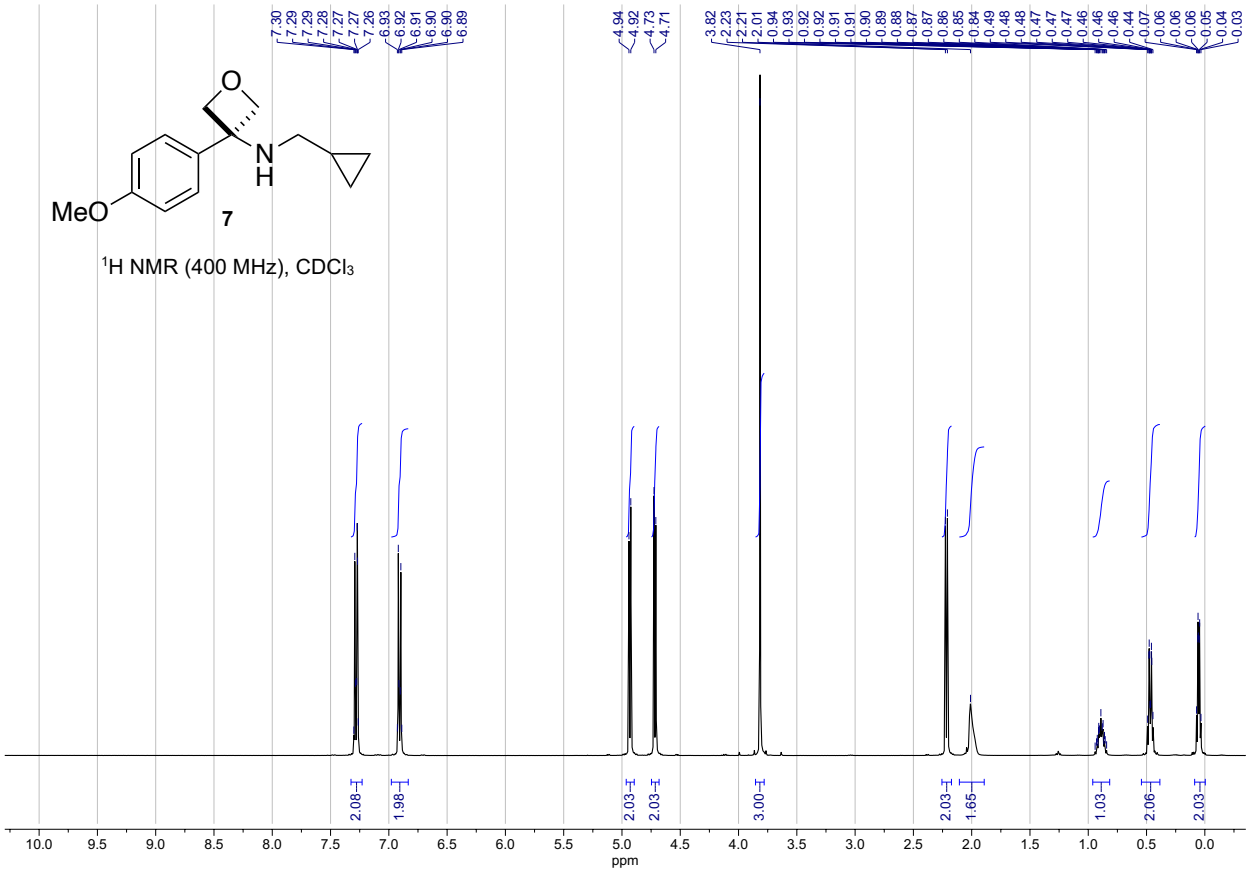

S14
^{13}C NMR (101 MHz), CDCl$_3$
153.5
101.1
101.0
96.1
94.0
83.4
83.1
60.9
56.2
ppm

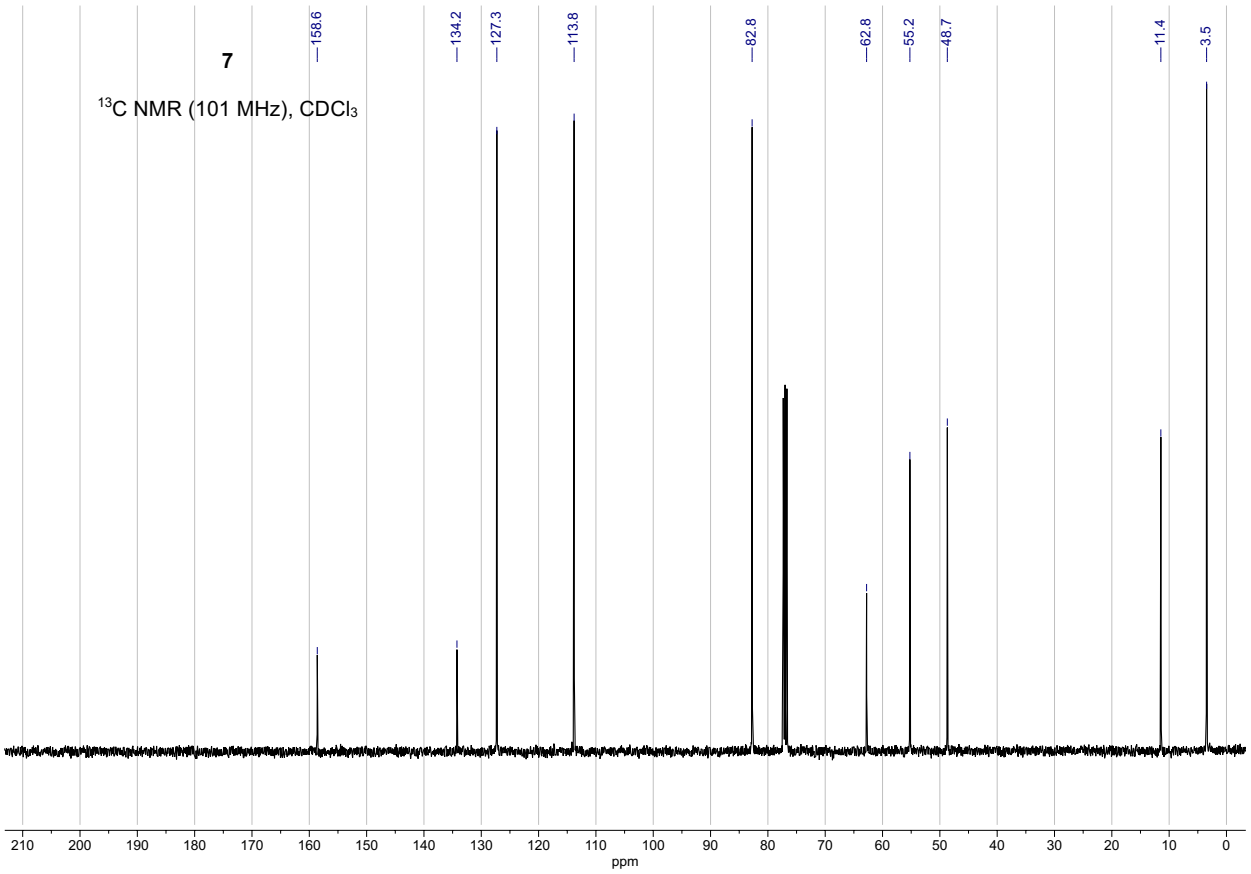

S14
HMBC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
f1 (ppm)
ppm

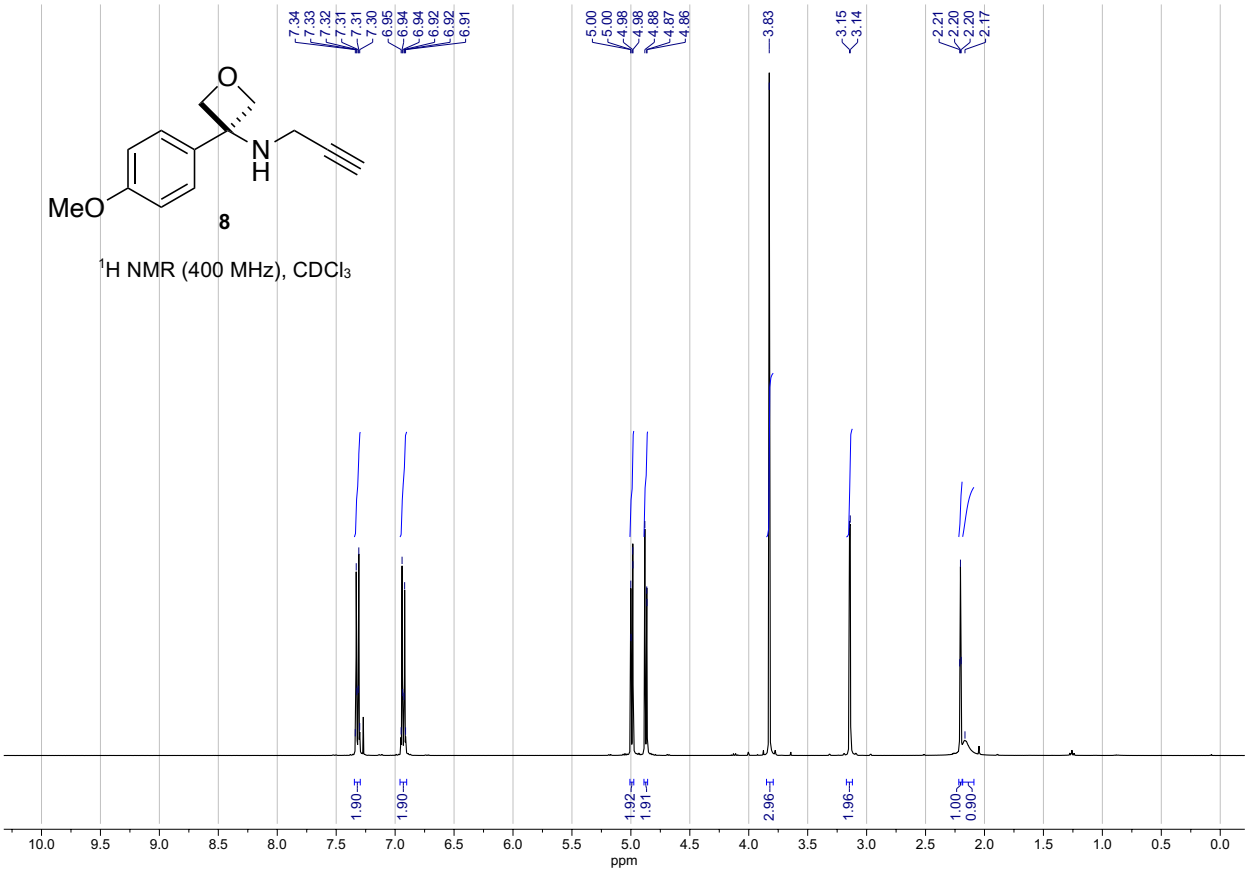

S14
^{19}F NMR (377 MHz), CDCl$_3$
-148.5
ppm

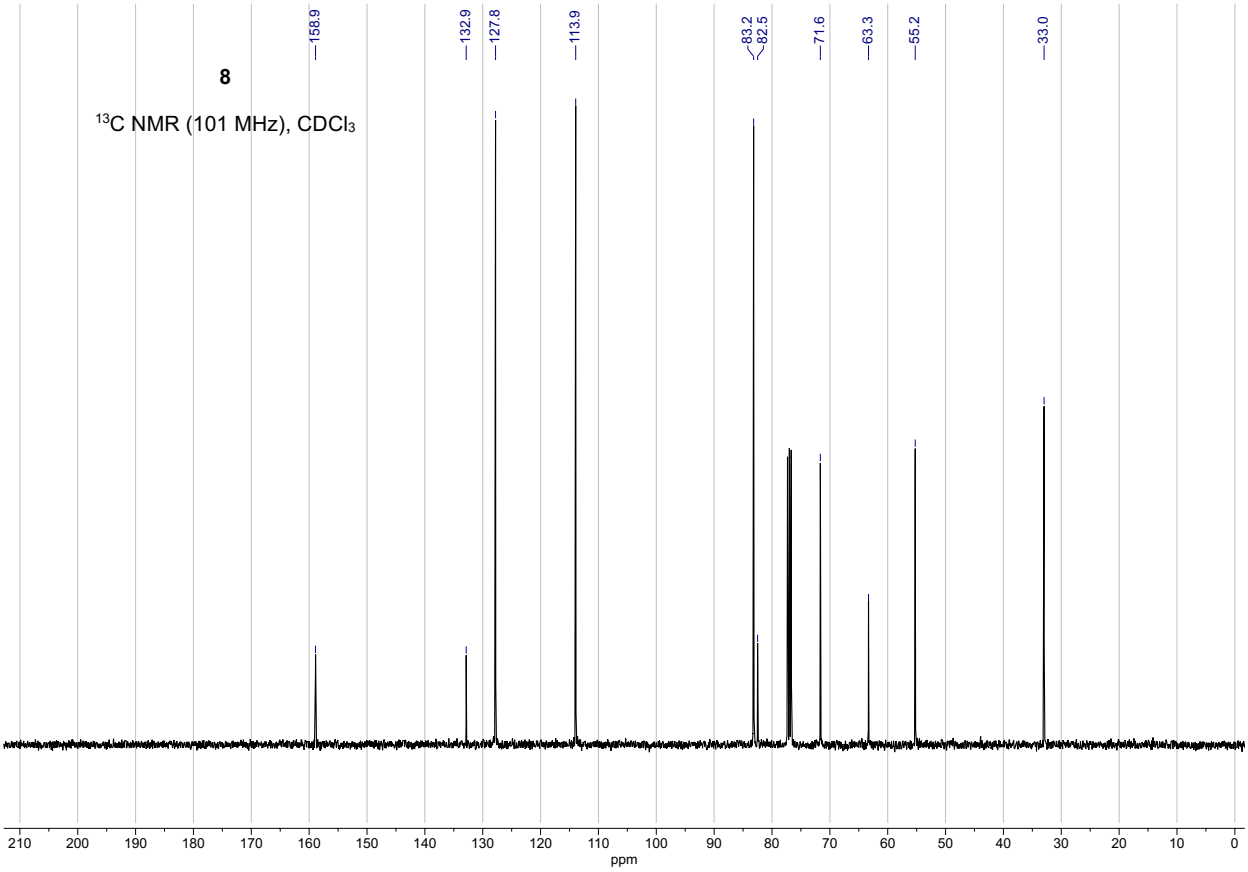

6.99
6.99
6.98
6.97
6.97
6.93
6.93
6.92
6.91
6.90
6.90
4.91
4.89
4.88
4.86
3.83
3.75
3.74
3.73
2.33
2.31
2.30
O
N
O
MeO
2
^{1}H NMR (400 MHz), CDCl$_3$
2.00
1.92
2.03
1.96
3.02
4.05
4.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

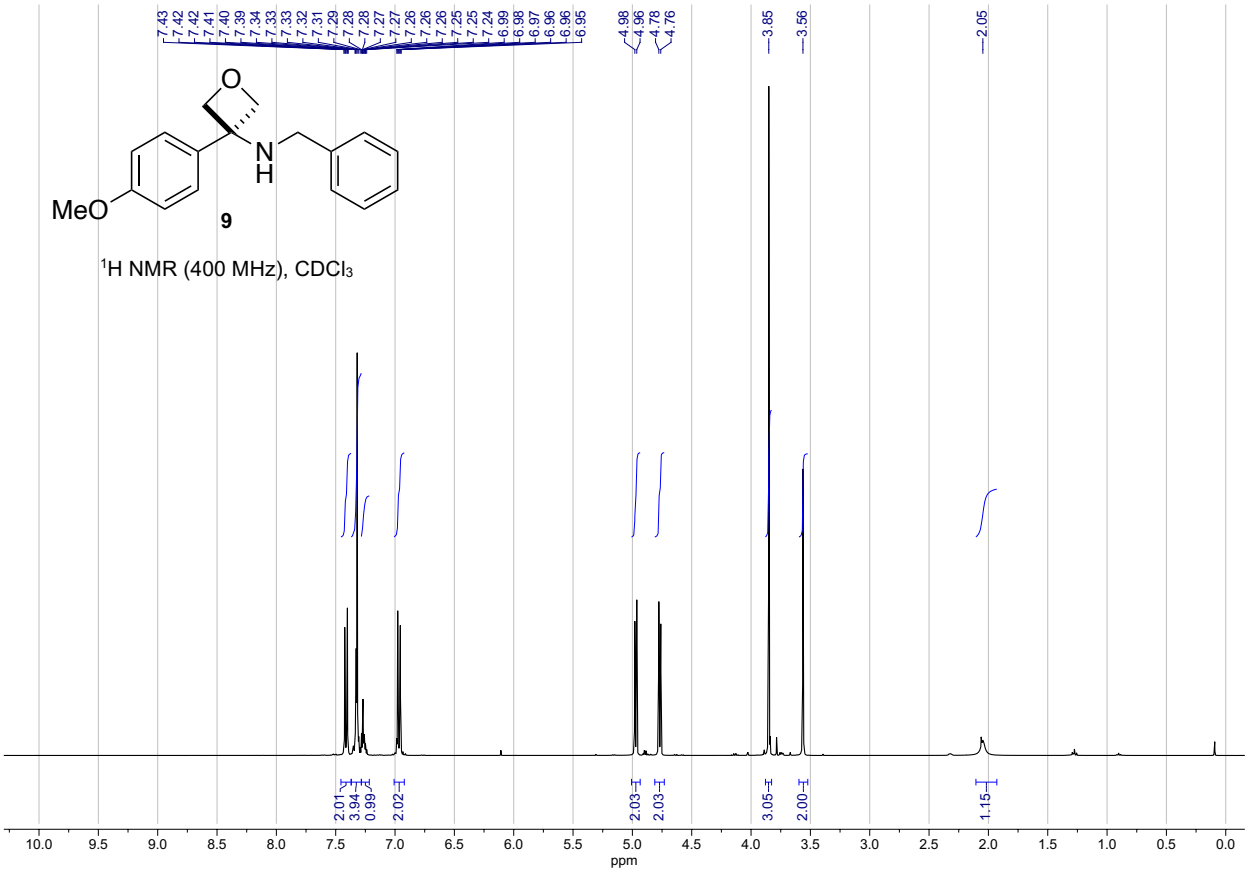

158.8
129.4
128.4
113.3
79.3
67.1
66.4
55.3
46.4
2
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

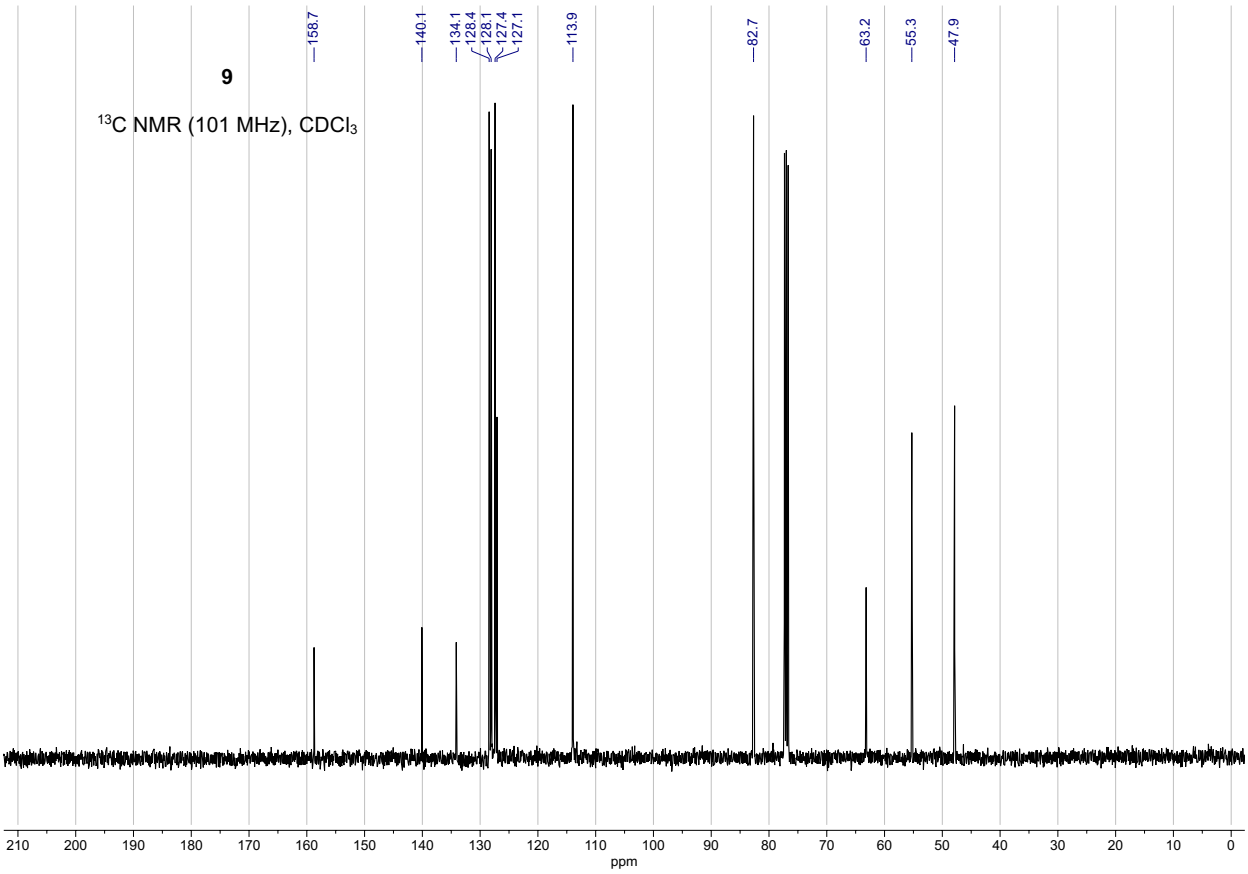

7.30
7.29
7.29
7.28
7.27
7.27
7.26
6.93
6.92
6.91
6.90
6.90
6.89
4.94
4.92
4.73
4.71
3.82
2.23
2.21
2.01
0.94
0.93
0.92
0.92
0.91
0.91
0.90
0.89
0.88
0.87
0.87
0.86
0.85
0.84
0.49
0.48
0.48
0.47
0.47
0.47
0.46
0.46
0.46
0.44
0.07
0.06
0.06
0.06
0.05
0.04
0.03
O
N
H
MeO
7
^{1}H NMR (400 MHz), CDCl$_3$
2.08
1.98
2.03
2.03
3.00
2.03
1.65
1.03
2.06
2.03
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

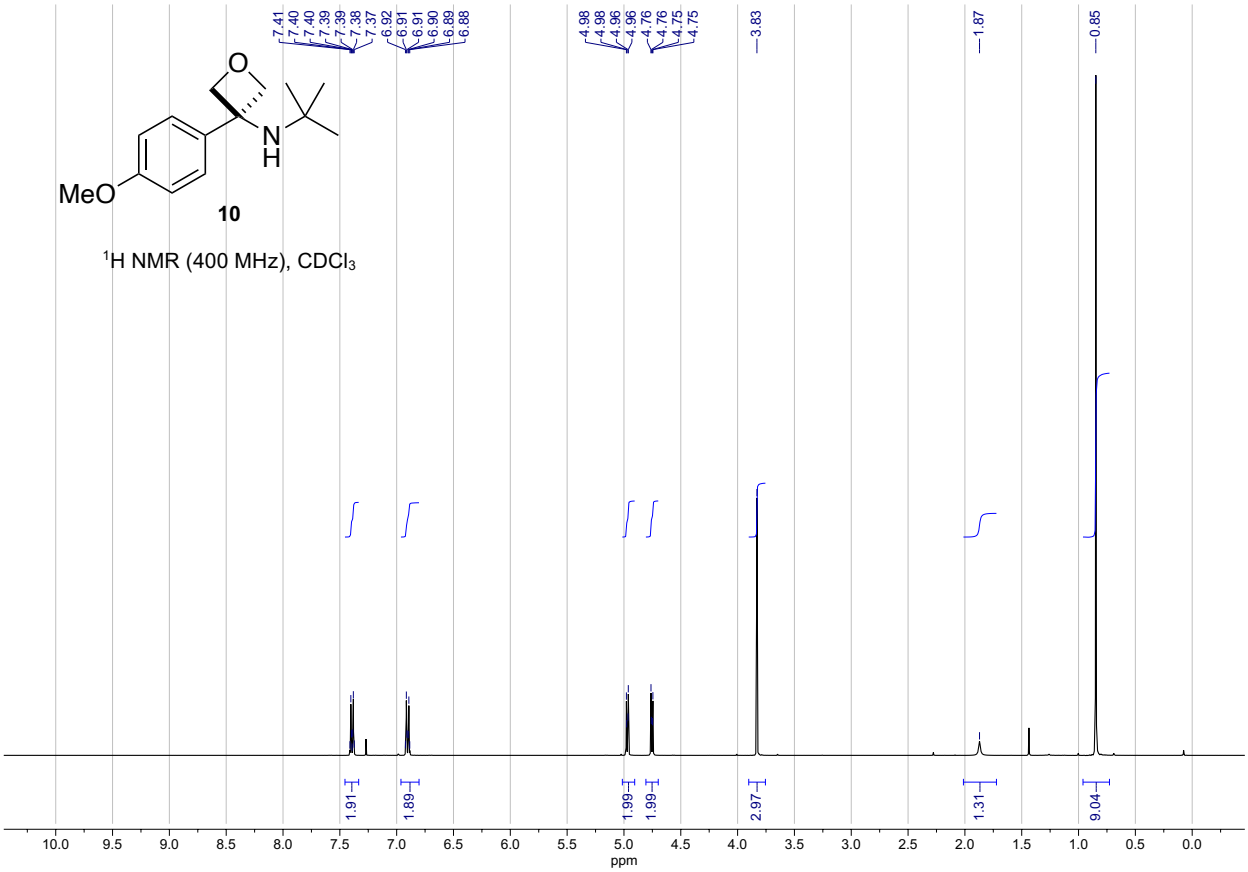

7
^{13}C NMR (101 MHz), CDCl$_3$
158.6
134.2
127.3
113.8
82.8
62.8
55.2
48.7
11.4
3.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


7.34
7.33
7.32
7.31
7.31
7.30
6.95
6.94
6.94
6.92
6.92
6.91
5.00
5.00
4.98
4.98
4.88
4.87
4.86
3.83
3.15
3.14
2.21
2.20
2.20
2.17
O
N
H
MeO
8
^{1}H NMR (400 MHz), CDCl$_3$
1.90
1.90
1.92
1.91
2.96
1.96
1.00
0.90
ppm


158.9
132.9
127.8
113.9
83.2
82.5
71.6
63.3
55.2
33.0
8
^{13}C NMR (101 MHz), CDCl$_3$
ppm

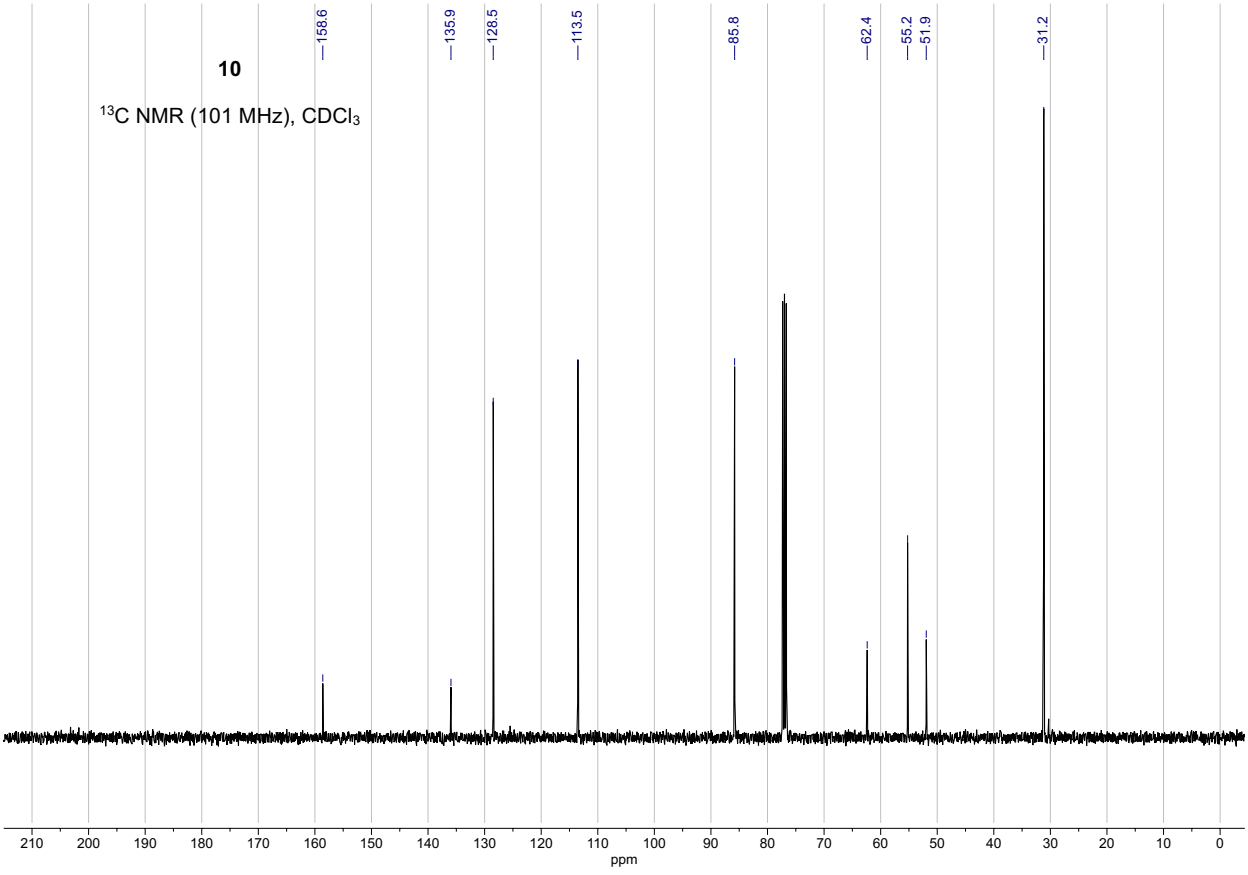

7.43 7.42 7.42 7.41 7.40 7.39 7.34 7.33 7.32 7.31 7.29 7.28 7.28 7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.24 6.99 6.98 6.97 6.96 6.96 6.95
4.98 4.96 4.78 4.76
3.85
3.56
2.05
O
N
H
MeO
9
^{1}H NMR (400 MHz), CDCl$_3$
2.01 3.94 0.99 2.02 2.03 2.03 3.05 2.00 1.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


158.7
140.1
134.1
128.4
128.1
127.4
127.1
113.9
82.7
63.2
55.3
47.9
9
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



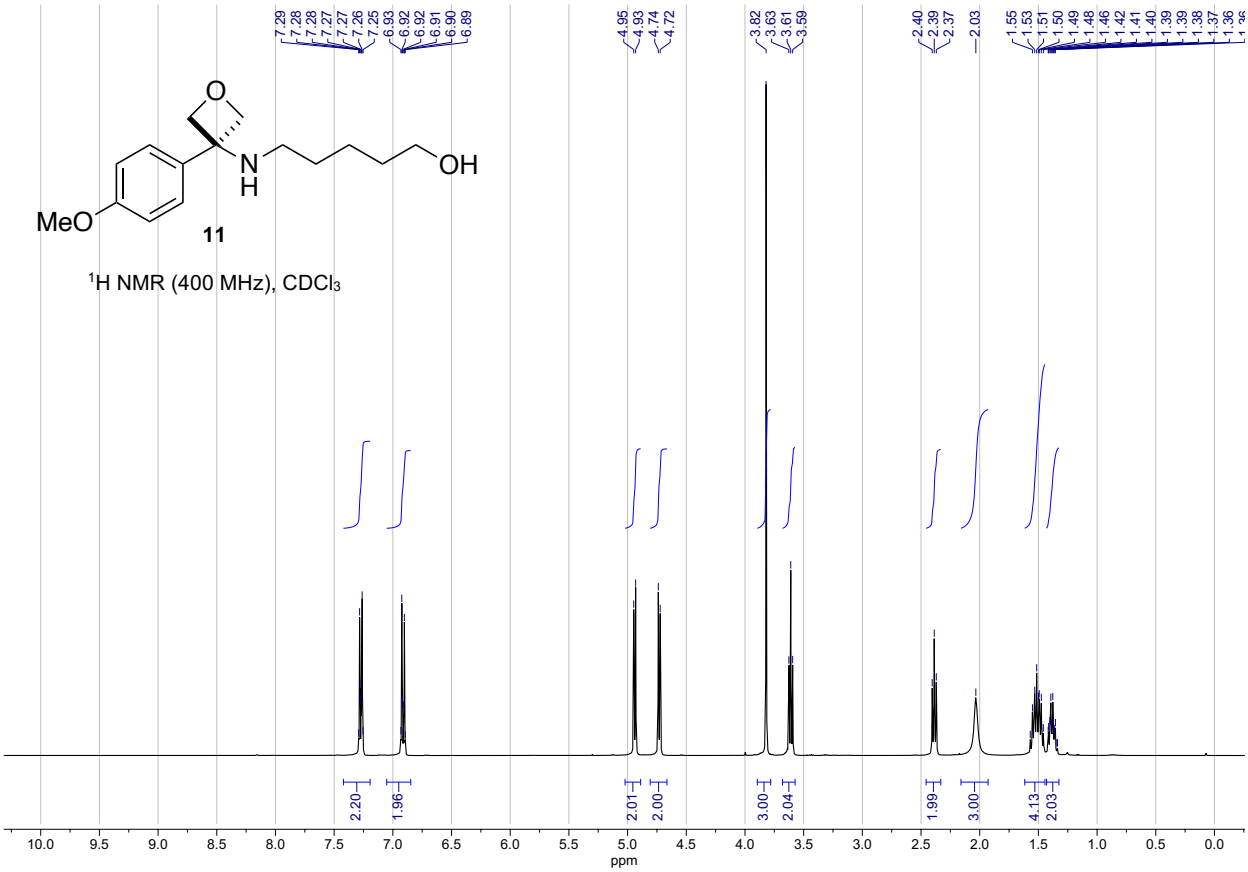
10

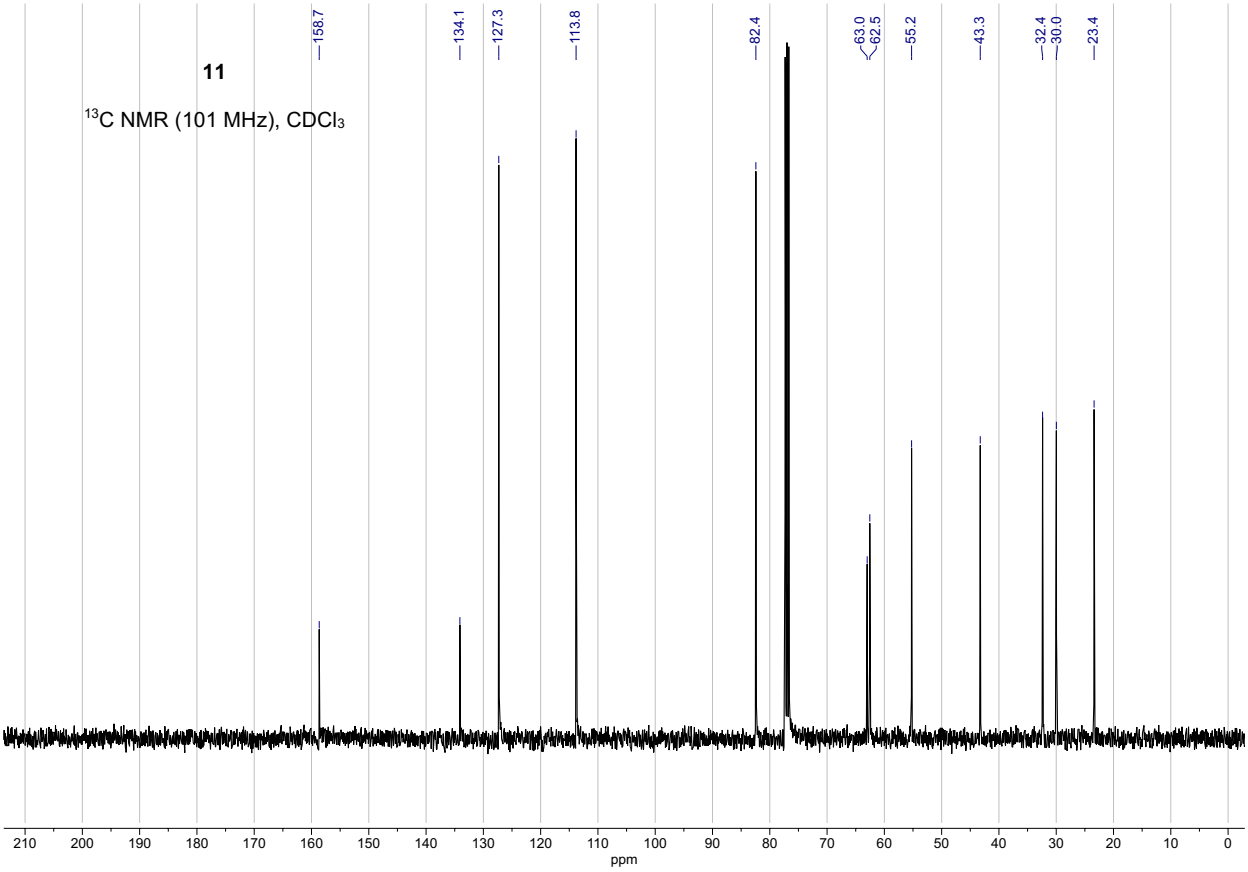
^{1}H NMR (400 MHz), $CDCl_3$

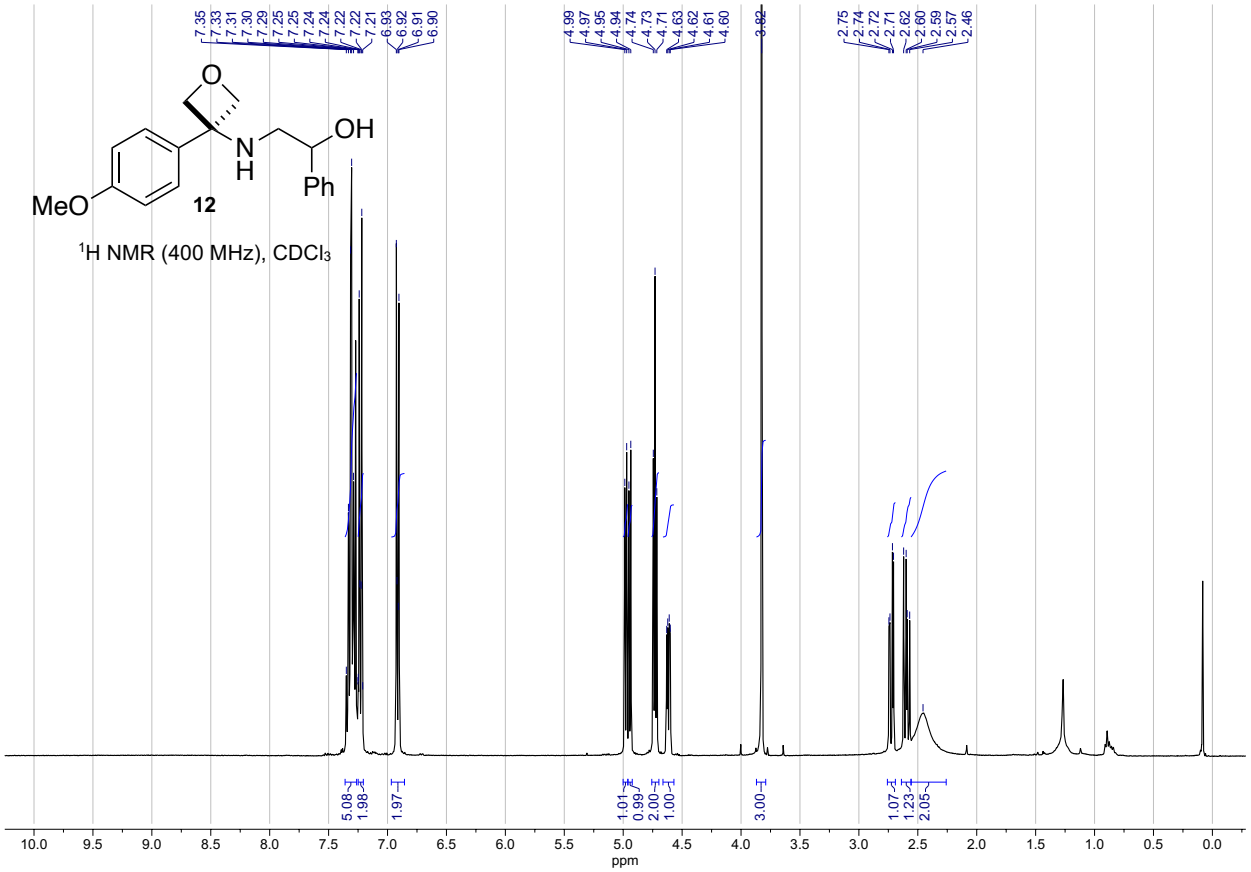


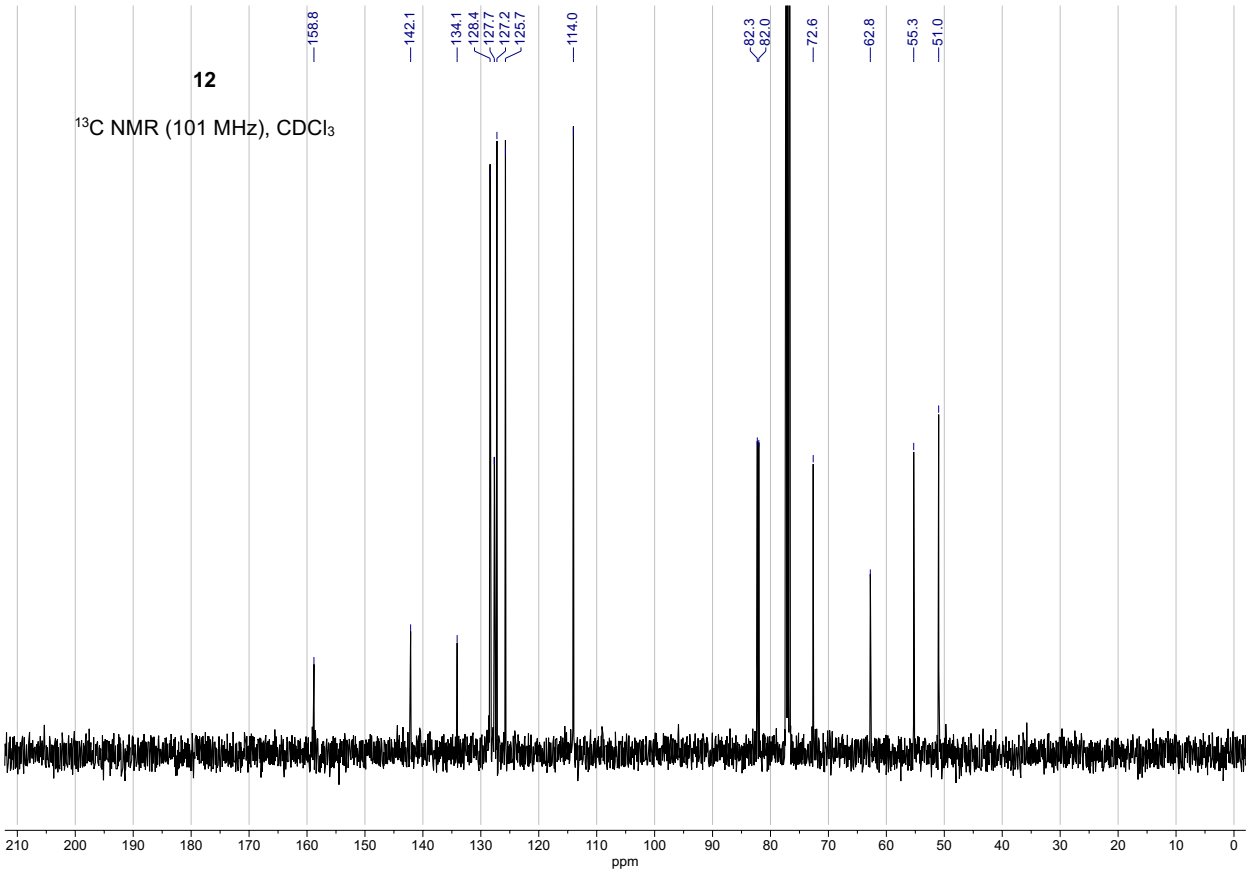
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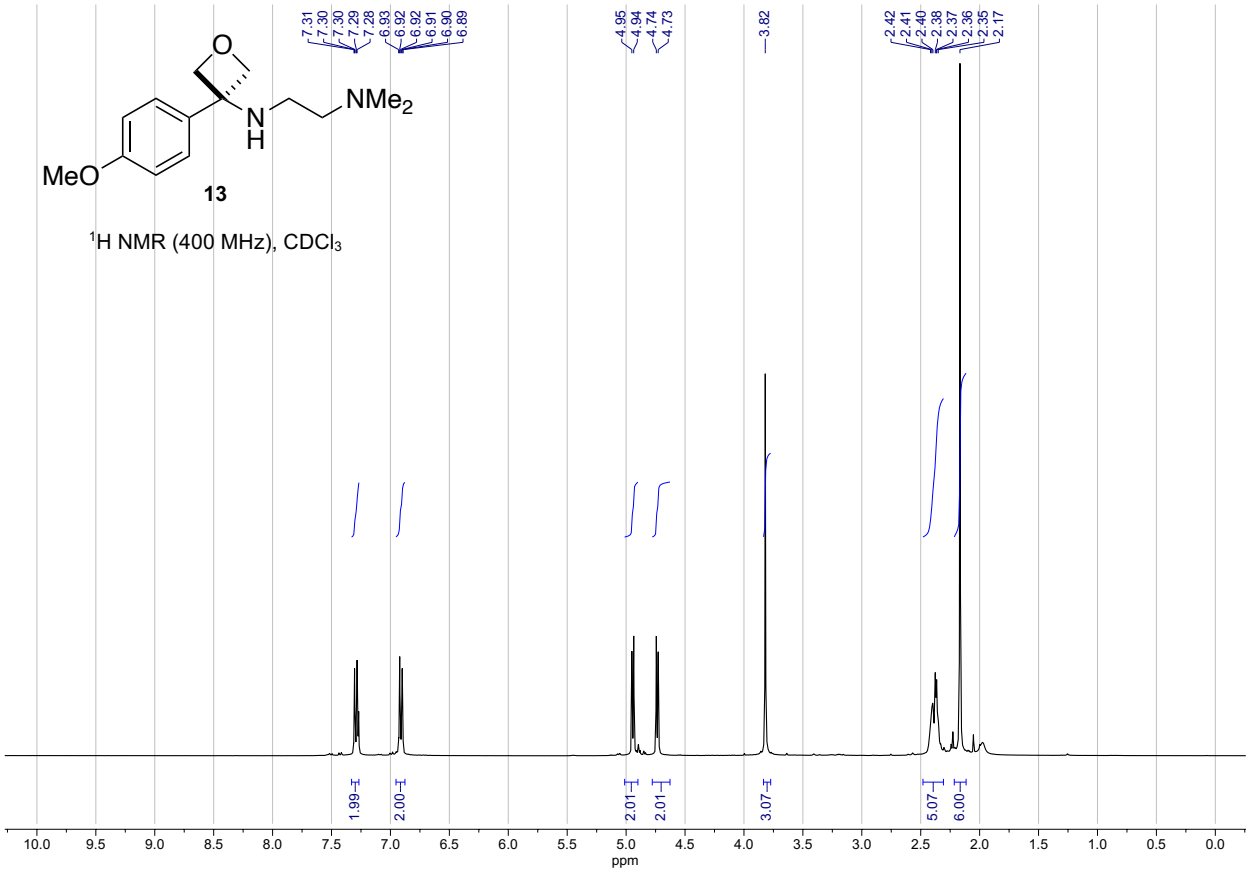
^{13}C NMR (101 MHz), $CDCl_3$

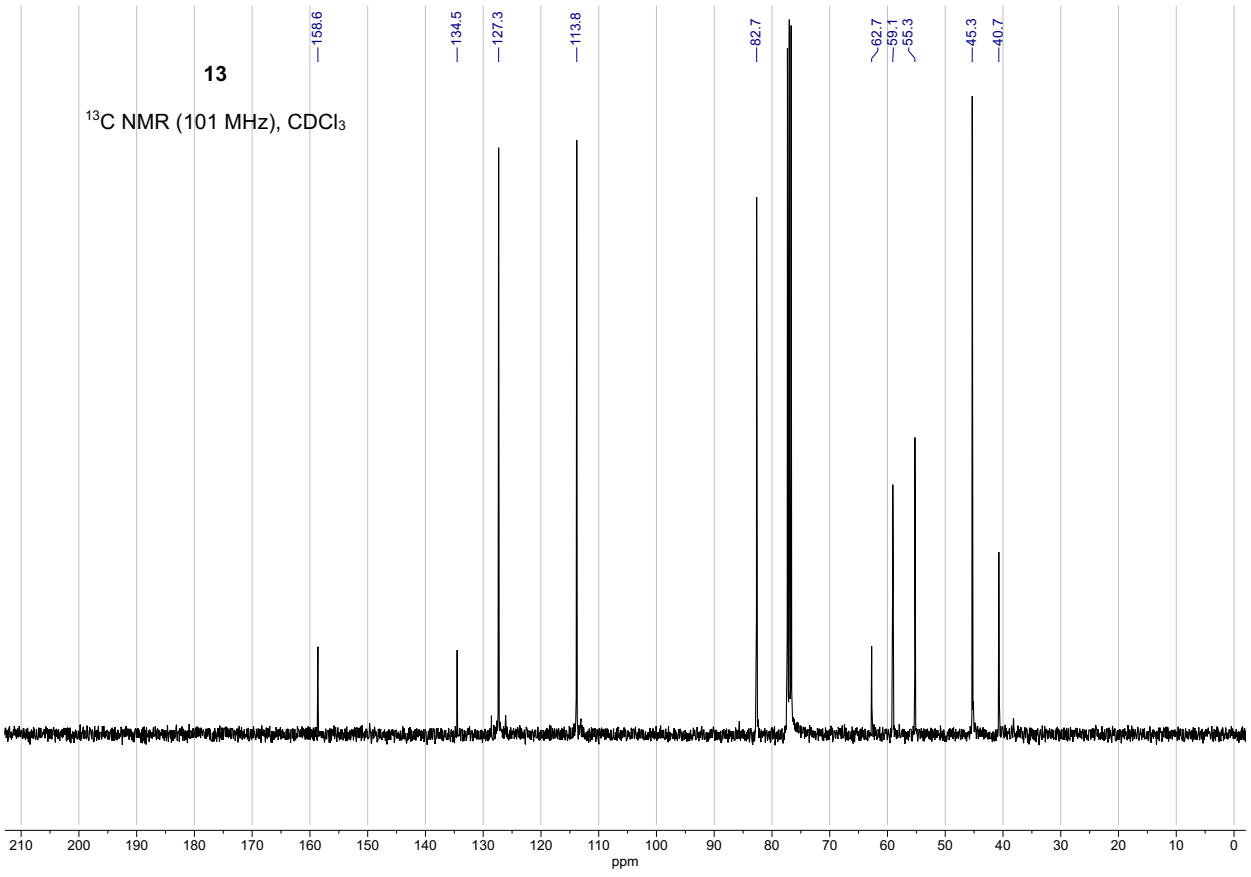

MeO
O
N
H
OH
11
^{1}H NMR (400 MHz), CDCl$_3$
ppm

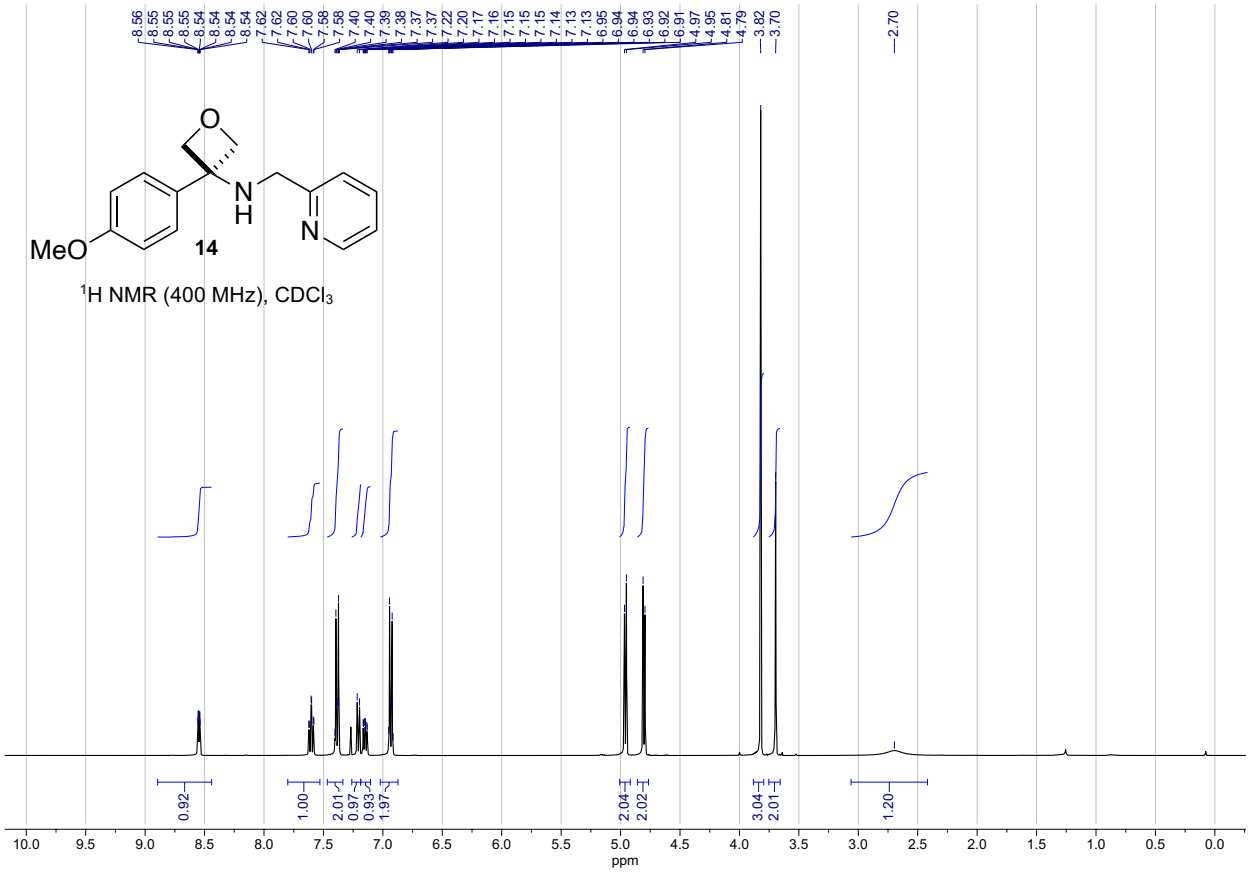

11
^{13}C NMR (101 MHz), CDCl$_3$
ppm

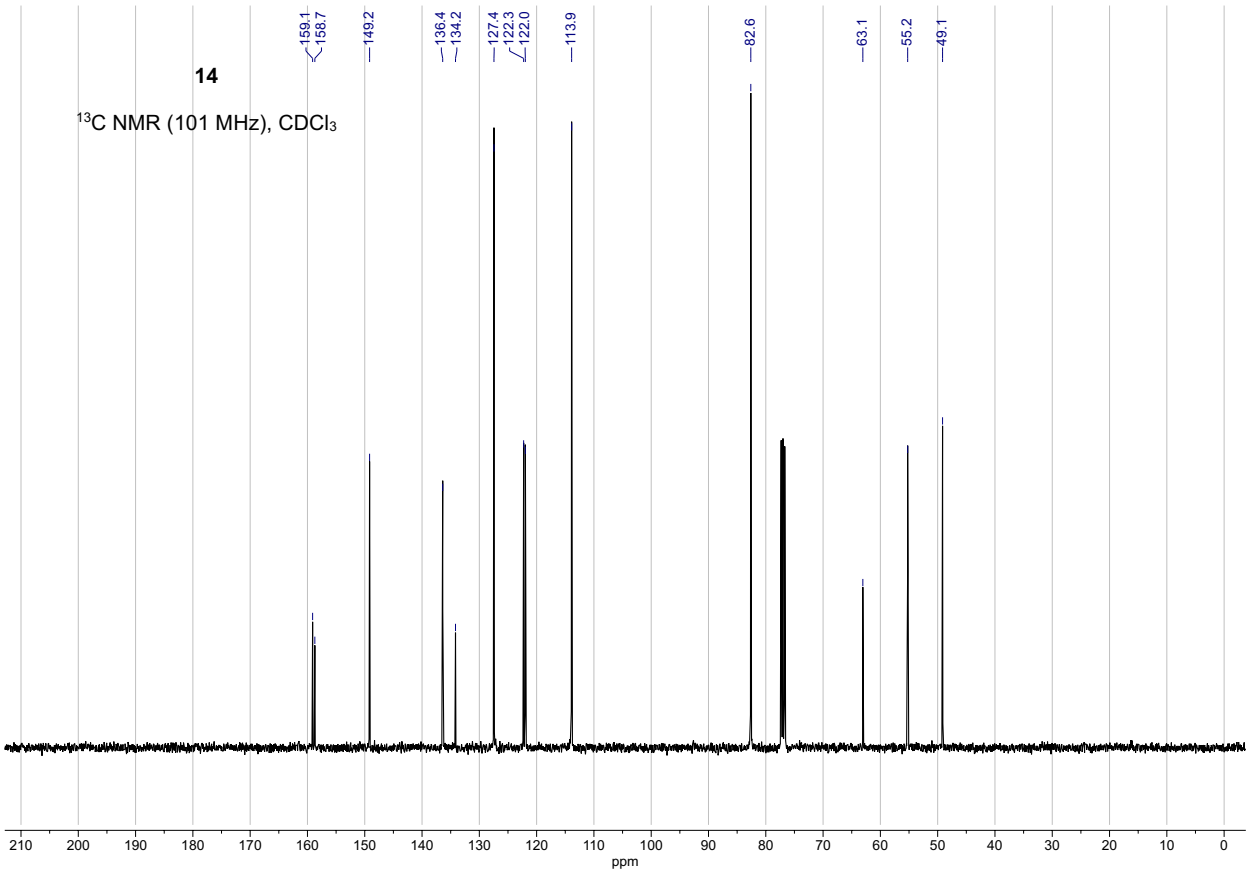

MeO
O
N
H
OH
Ph
12
^{1}H NMR (400 MHz), CDCl$_3$
ppm

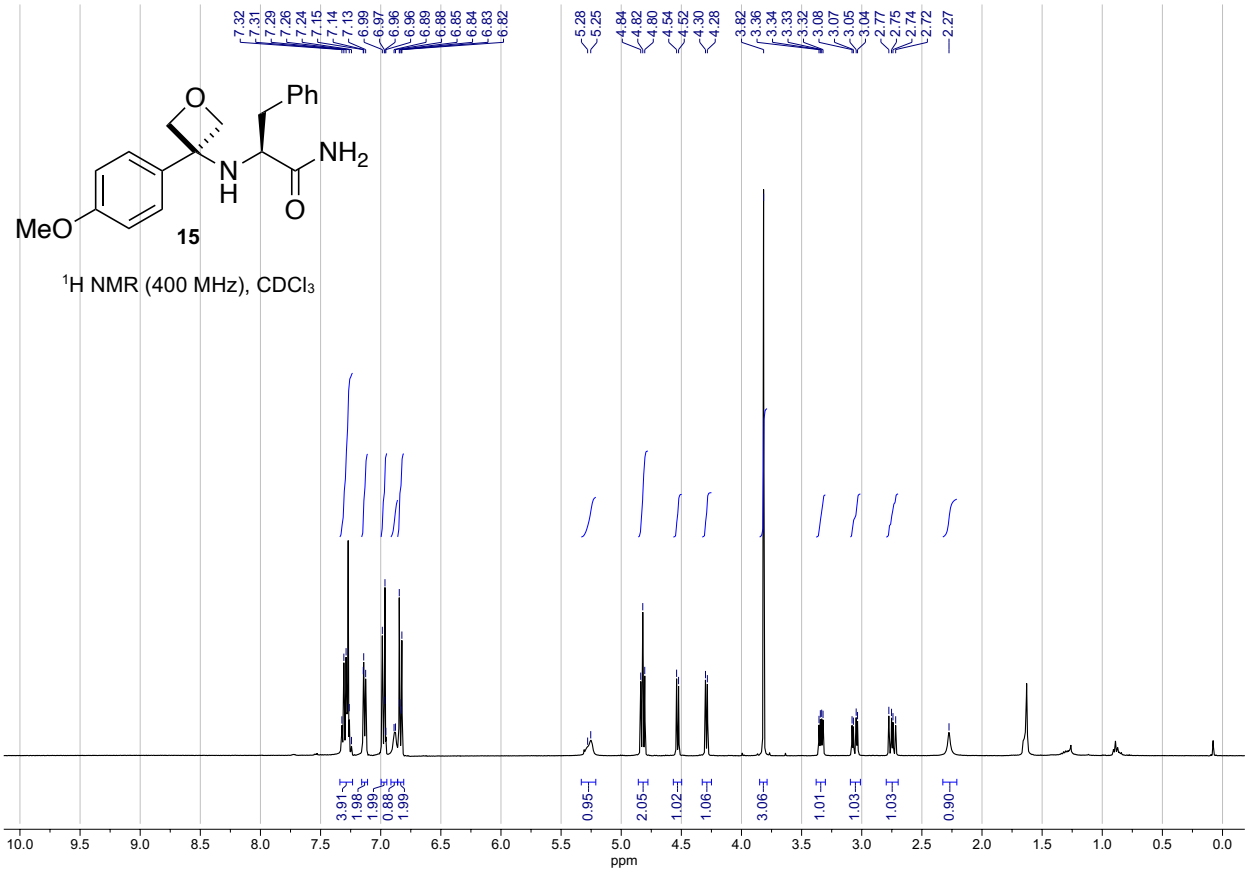

12
^{13}C NMR (101 MHz), CDCl$_3$
ppm

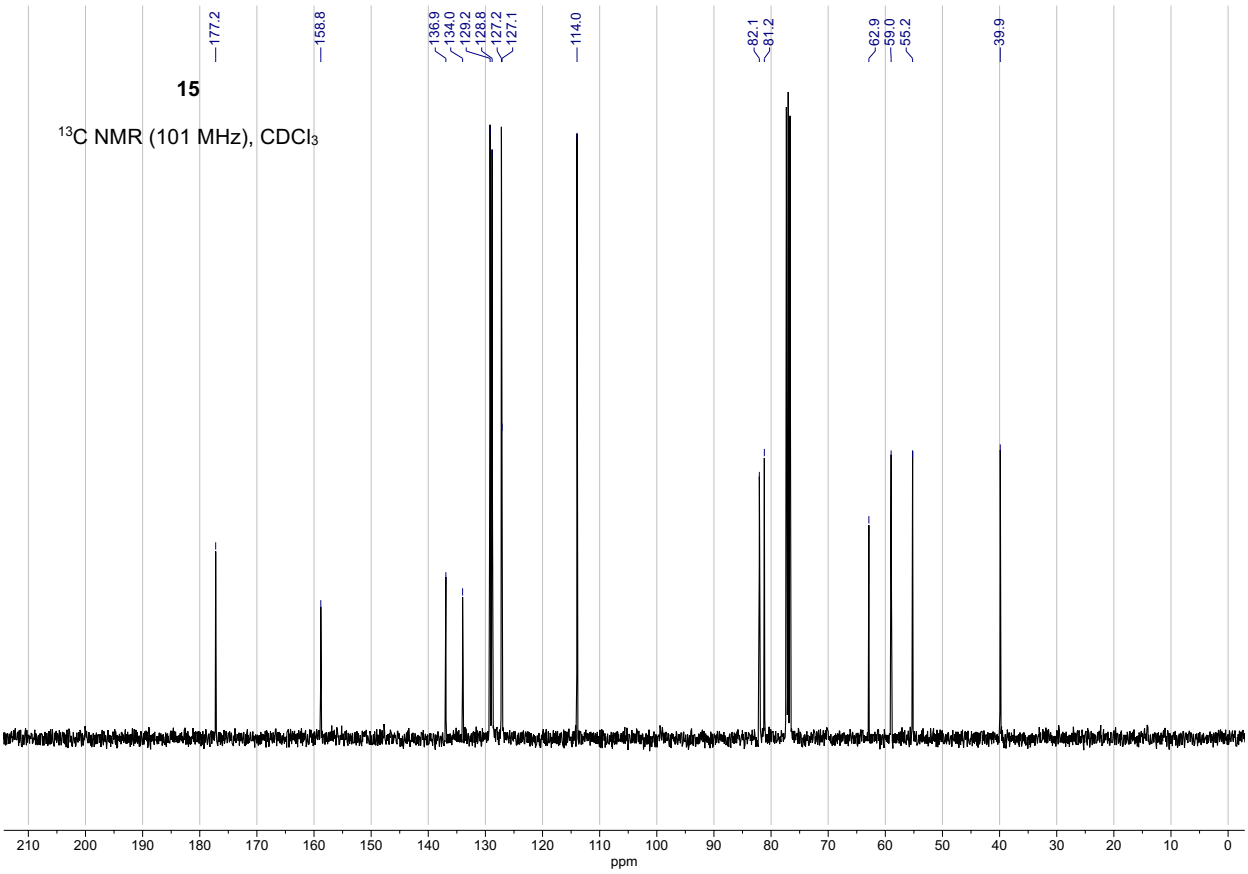

MeO
O
N
H
NMe2
13
1H NMR (400 MHz), CDCl3
7.31
7.30
7.30
7.29
7.28
6.93
6.92
6.92
6.91
6.90
6.89
4.95
4.94
4.74
4.73
3.82
2.42
2.41
2.40
2.38
2.37
2.36
2.35
2.17
1.99
2.00
2.01
2.01
3.07
5.07
6.00
ppm

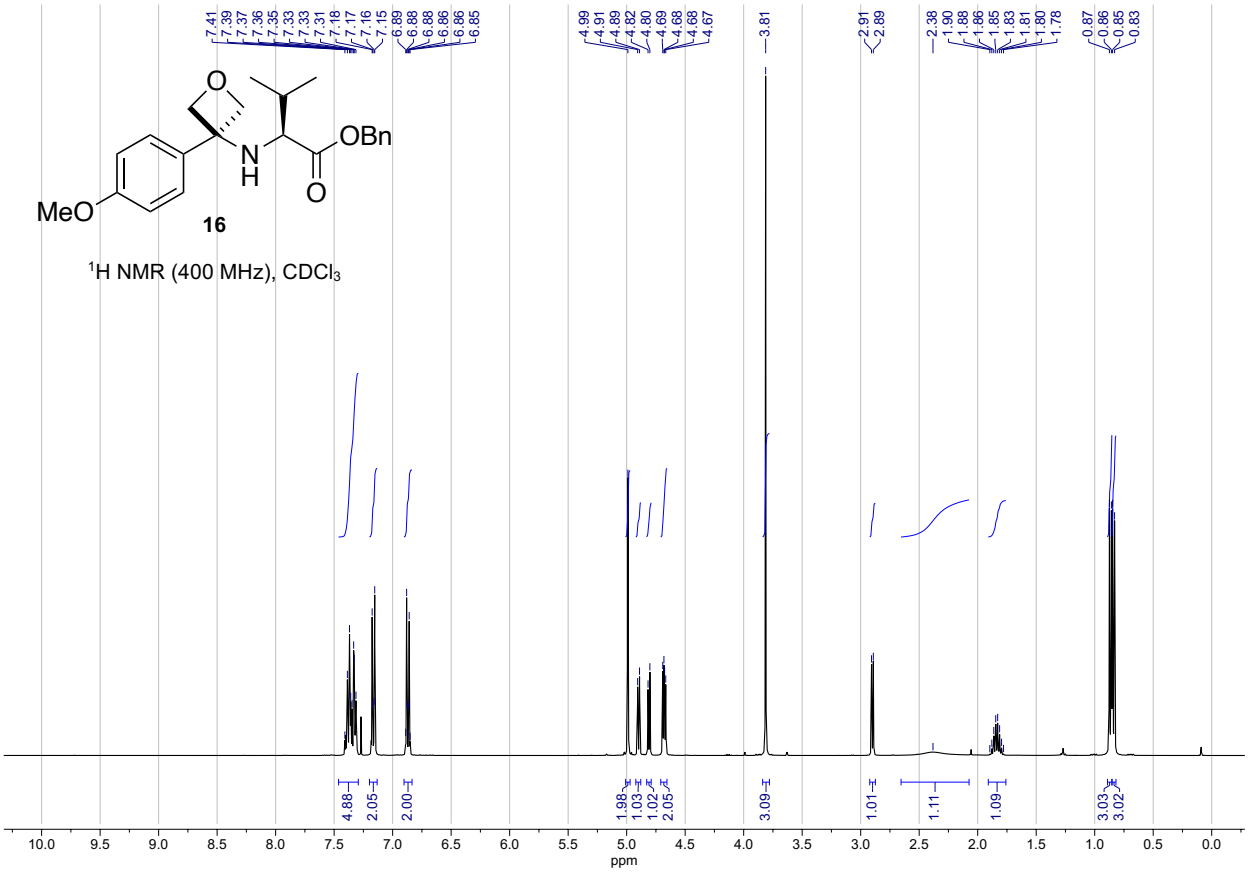

13
13C NMR (101 MHz), CDCl3
158.6
134.5
127.3
113.8
82.7
62.7
59.1
55.3
45.3
40.7
ppm

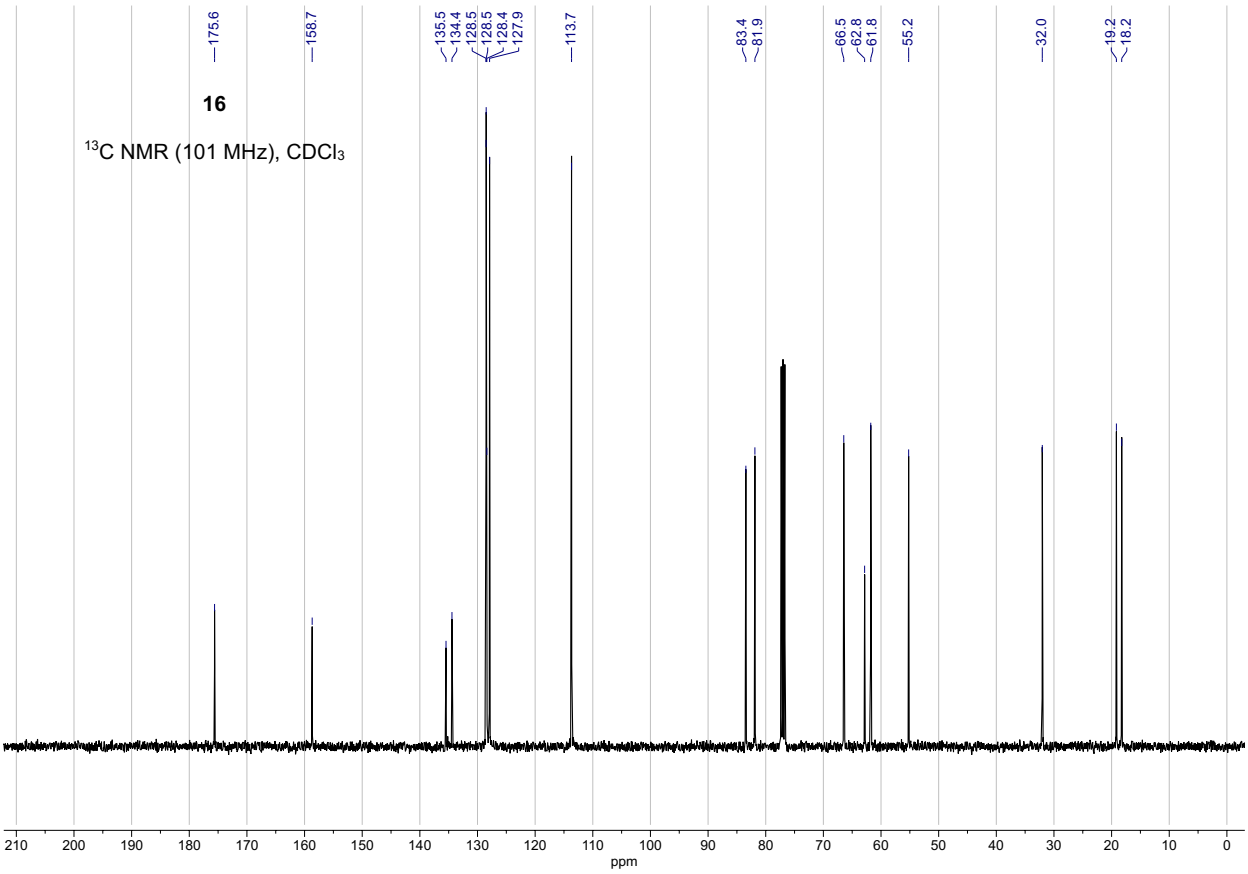

8.56 8.55 8.55 8.54 8.54 8.54 8.54 7.62 7.62 7.60 7.60 7.58 7.40 7.40 7.39 7.38 7.37 7.37 7.22 7.20 7.17 7.16 7.15 7.15 7.15 7.14 7.13 7.13 6.95 6.94 6.94 6.93 6.92 6.91 4.97 4.95 4.81 4.79 3.82 3.70 2.70
O
N
H
N
MeO
14
^{1}H NMR (400 MHz), CDCl$_3$
0.92 1.00 2.01 0.97 0.93 1.97 2.04 2.02 3.04 2.01 1.20
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

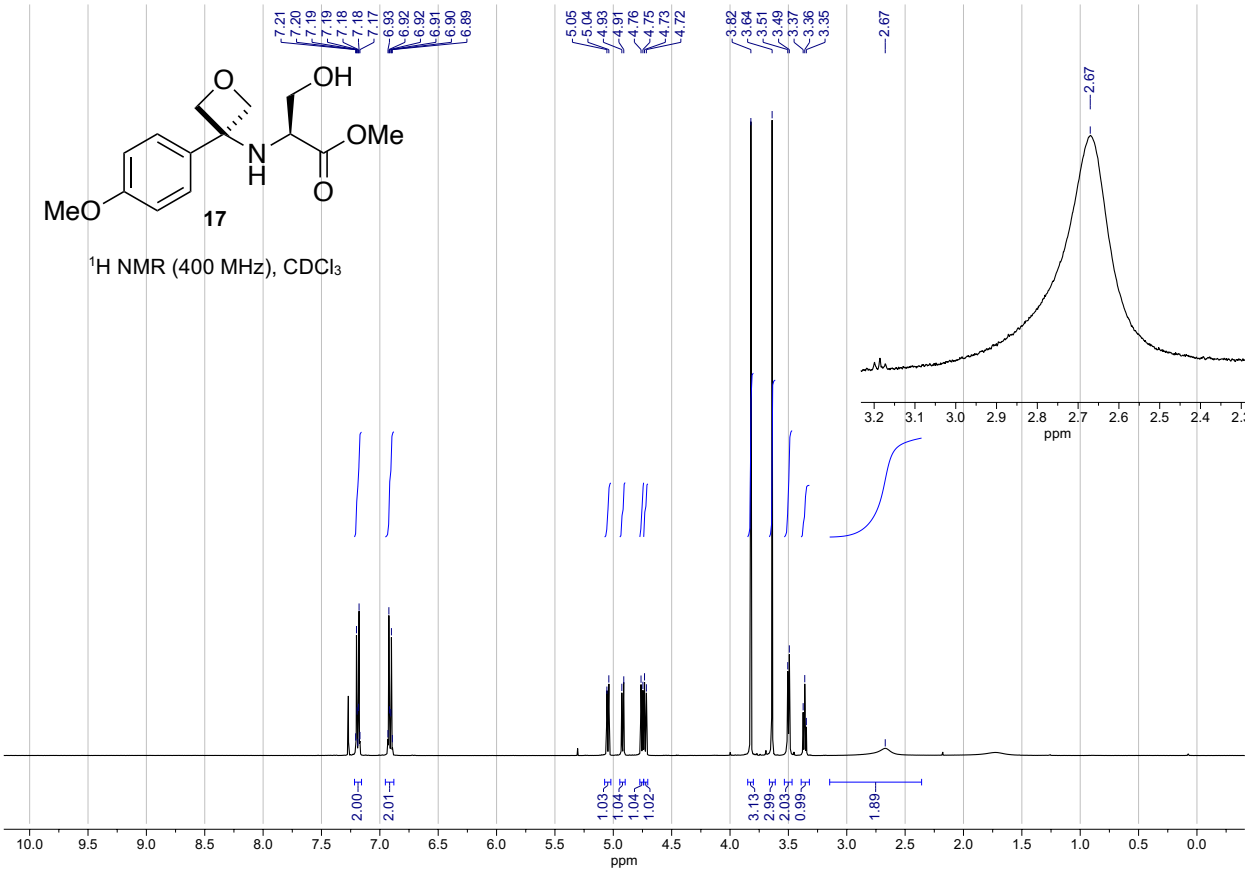

159.1 158.7 149.2 136.4 134.2 127.4 122.3 122.0 113.9 82.6 63.1 55.2 49.1
14
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

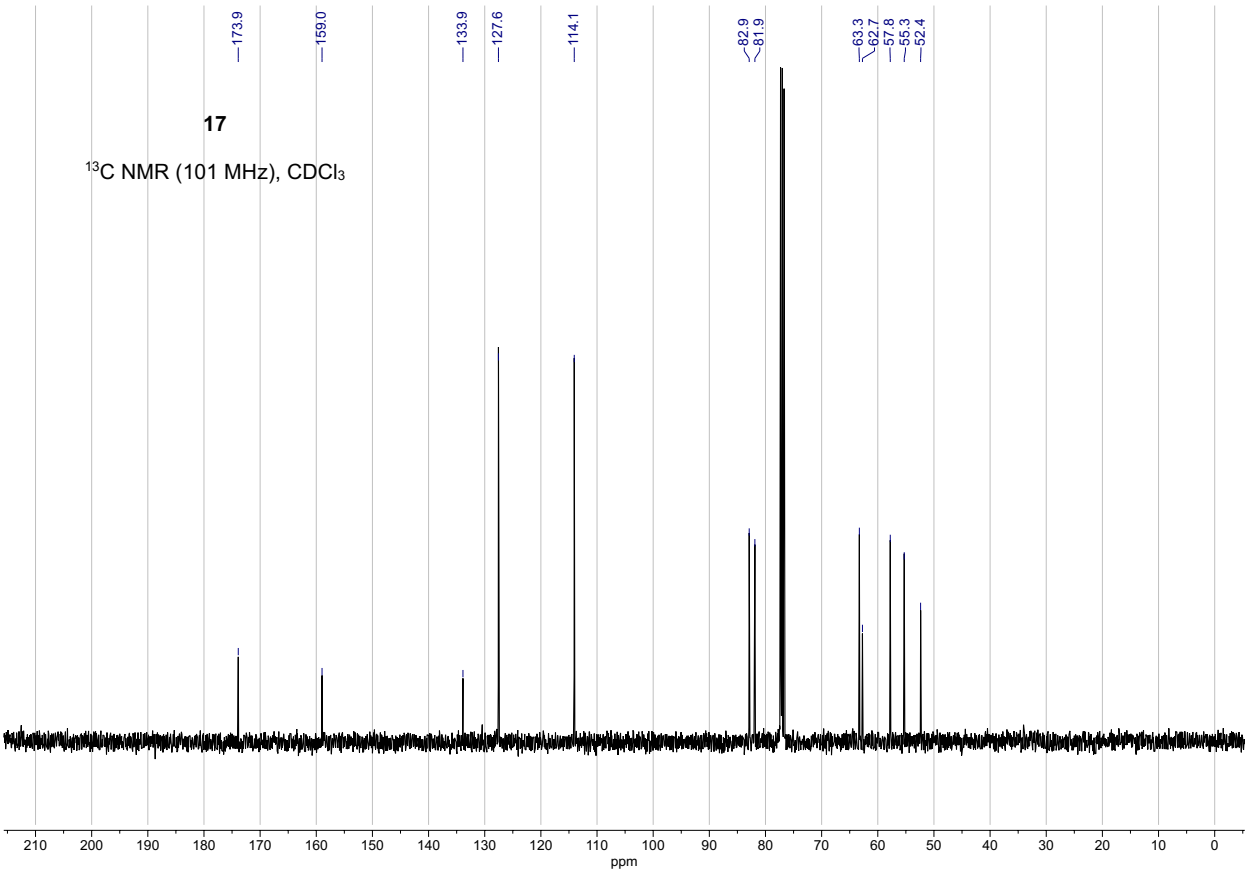

7.32
7.31
7.29
7.26
7.24
7.15
7.14
7.13
6.99
6.97
6.96
6.96
6.89
6.88
6.85
6.84
6.83
6.82
5.28
5.25
4.84
4.82
4.80
4.54
4.52
4.30
4.28
3.82
3.36
3.34
3.33
3.32
3.08
3.07
3.05
3.04
2.77
2.75
2.74
2.72
2.27
O
Ph
NH2
N
H
O
MeO
15
1H NMR (400 MHz), CDCl3
3.91
1.98
1.99
0.88
1.99
0.95
2.05
1.02
1.06
3.06
1.01
1.03
1.03
0.90
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

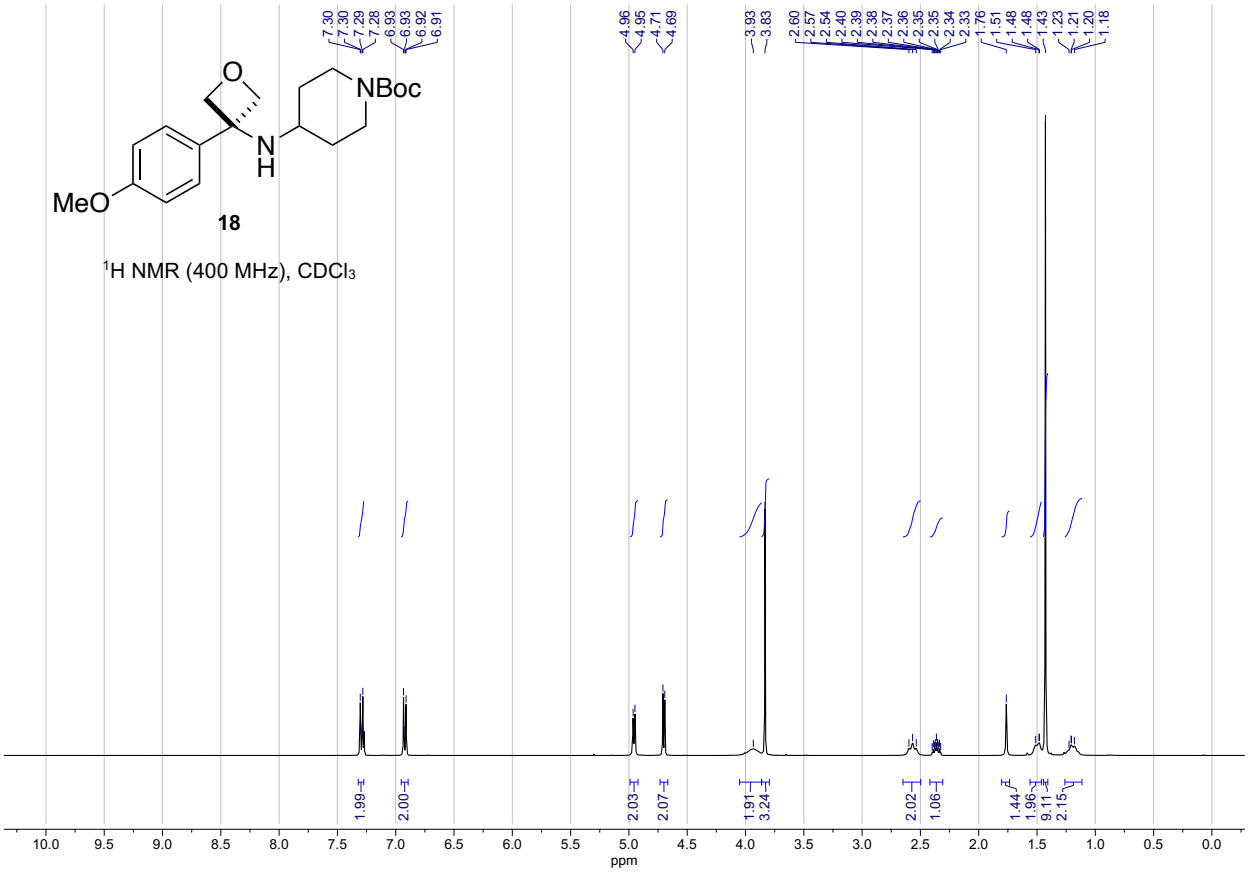

177.2
158.8
136.9
134.0
129.2
128.8
127.2
127.1
114.0
82.1
81.2
62.9
59.0
55.2
39.9
15
13C NMR (101 MHz), CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

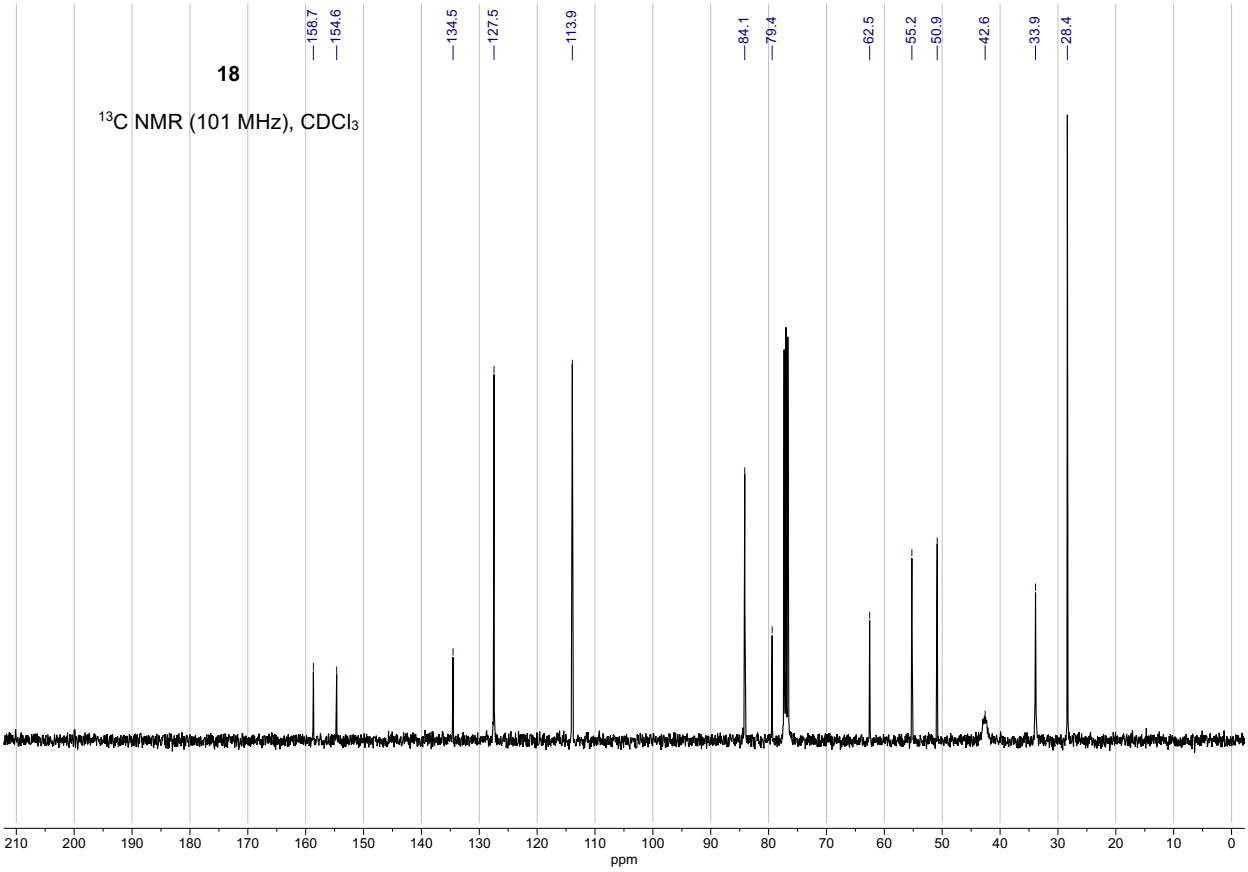

7.41
7.39
7.37
7.36
7.35
7.33
7.33
7.31
7.18
7.17
7.16
7.15
6.89
6.88
6.88
6.86
6.86
6.85
4.99
4.91
4.89
4.82
4.80
4.69
4.68
4.68
4.67
3.81
2.91
2.89
2.38
1.90
1.88
1.86
1.85
1.83
1.81
1.80
1.78
0.87
0.86
0.85
0.83
O
N
H
O
OBn
MeO
16
^{1}H NMR (400 MHz), $CDCl_3$
4.88
2.05
2.00
1.98
1.03
1.02
2.05
3.09
1.01
1.11
1.09
3.03
3.02
ppm

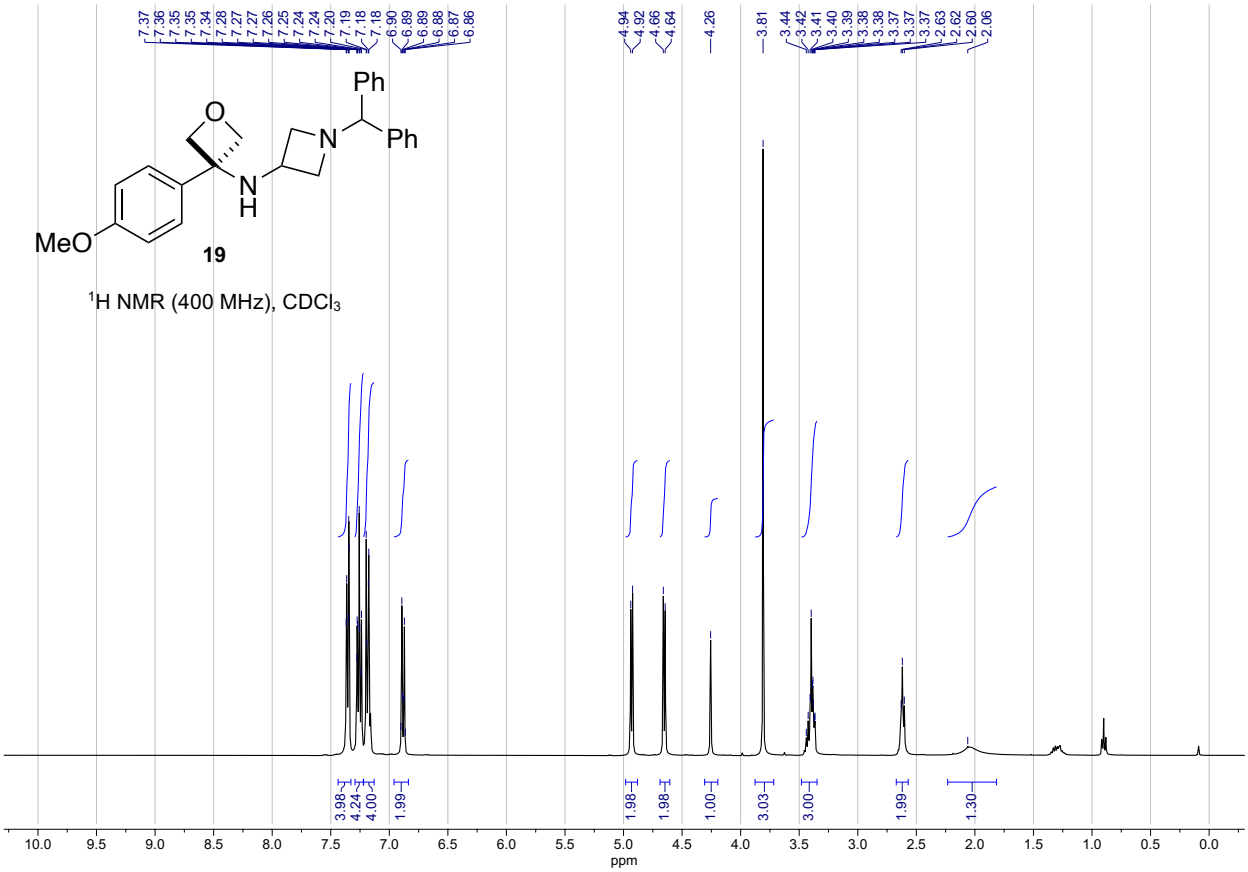

175.6
158.7
135.5
134.4
128.5
128.5
128.4
127.9
113.7
83.4
81.9
66.5
62.8
61.8
55.2
32.0
19.2
18.2
16
^{13}C NMR (101 MHz), $CDCl_3$
ppm

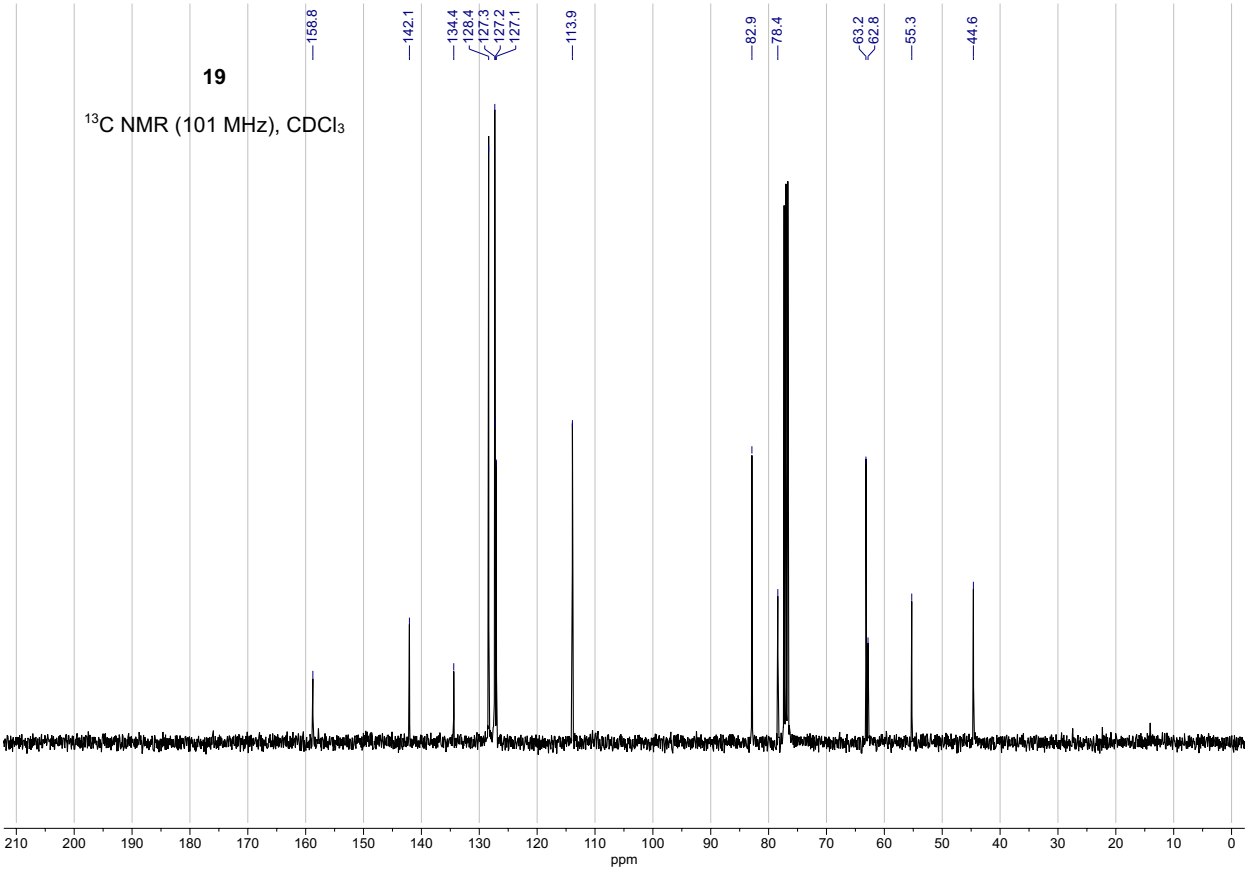

7.21
7.20
7.19
7.19
7.18
7.18
7.17
6.93
6.92
6.92
6.91
6.90
6.89
5.05
5.04
4.93
4.91
4.76
4.75
4.73
4.72
3.82
3.64
3.51
3.49
3.37
3.36
3.35
2.67
2.67
O
OH
N
H
OMe
O
MeO
17
^{1}H NMR (400 MHz), CDCl$_3$
2.00
2.01
1.03
1.04
1.04
1.02
3.13
2.99
2.03
0.99
1.89
ppm

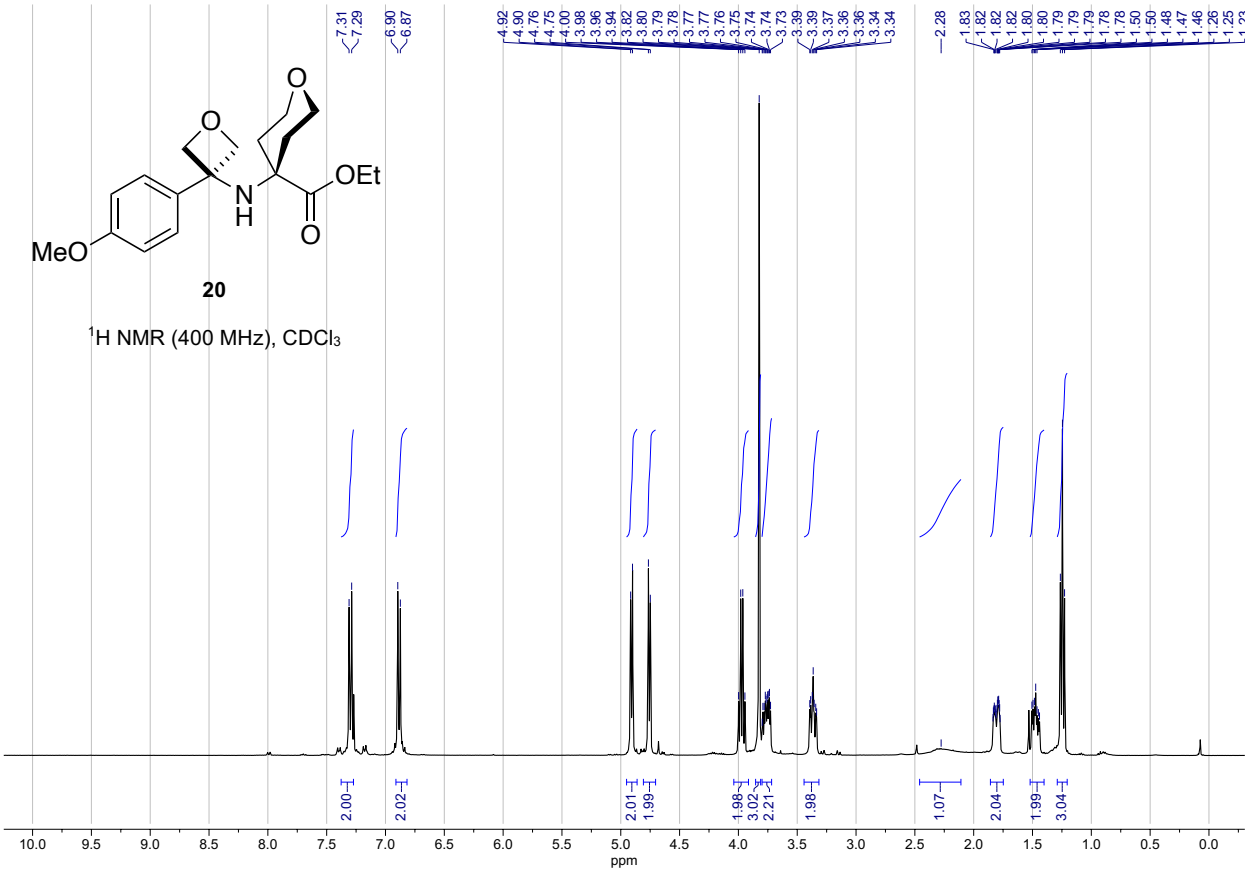

173.9
159.0
133.9
127.6
114.1
82.9
81.9
63.3
62.7
57.8
55.3
52.4
17
^{13}C NMR (101 MHz), CDCl$_3$
ppm

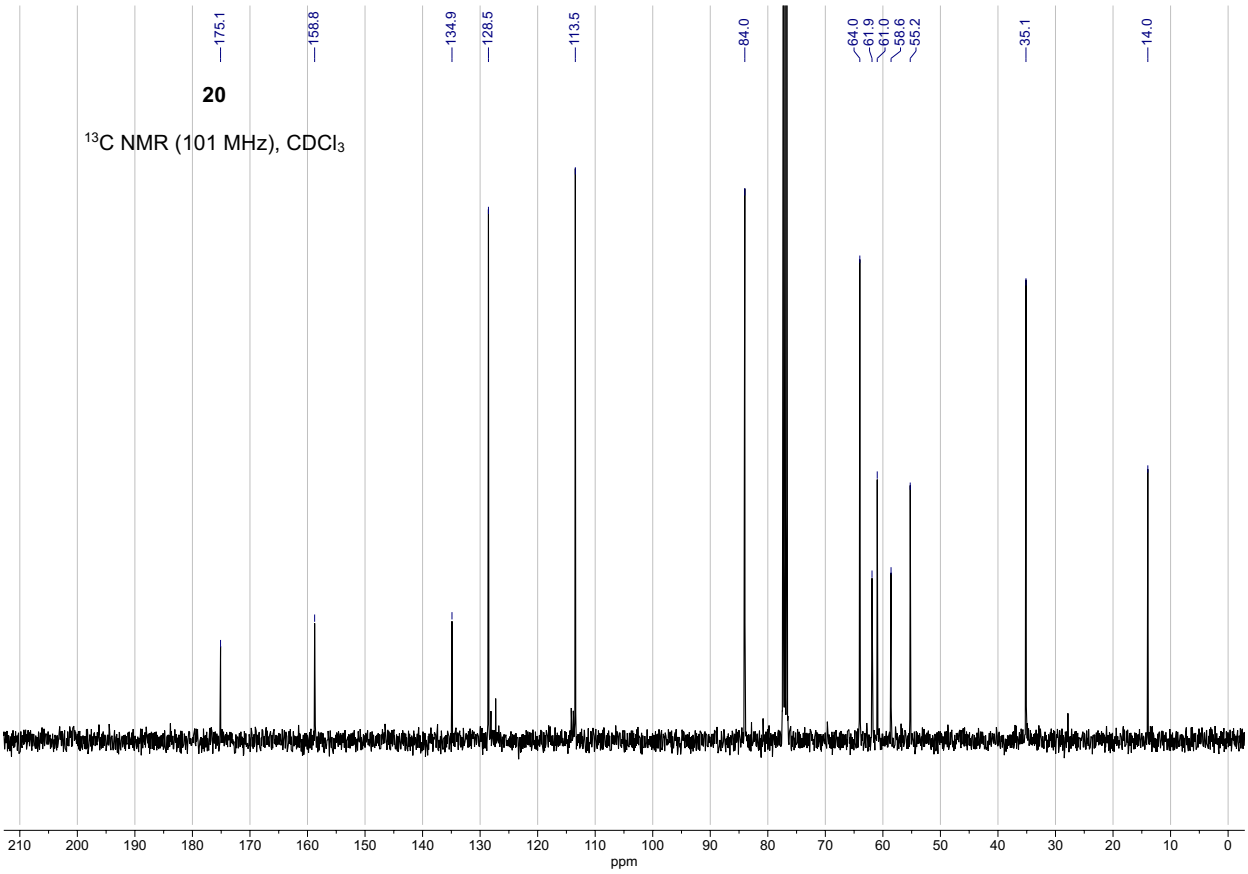

7.30
7.30
7.29
7.28
6.93
6.93
6.92
6.91
4.96
4.95
4.71
4.69
3.93
3.83
2.60
2.57
2.54
2.40
2.39
2.38
2.37
2.36
2.35
2.35
2.34
2.33
1.76
1.51
1.48
1.48
1.43
1.23
1.21
1.20
1.18
O
NBoc
N
H
MeO
18
^{1}H NMR (400 MHz), $CDCl_3$
1.99
2.00
2.03
2.07
1.91
3.24
2.02
1.06
1.44
1.96
9.11
2.15
10.0 9.5 9.0 8.5 8.0 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

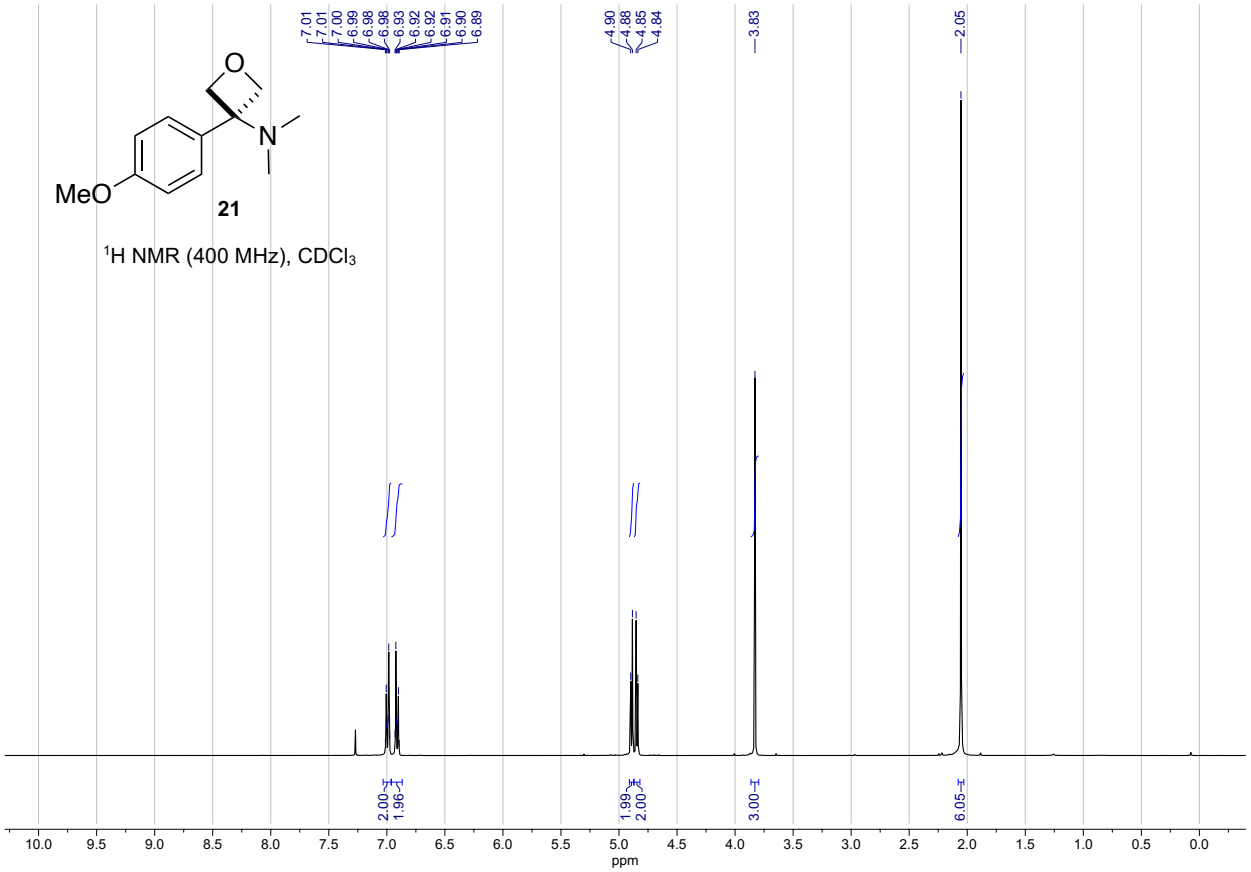

158.7
154.6
134.5
127.5
113.9
84.1
79.4
62.5
55.2
50.9
42.6
33.9
28.4
18
^{13}C NMR (101 MHz), $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

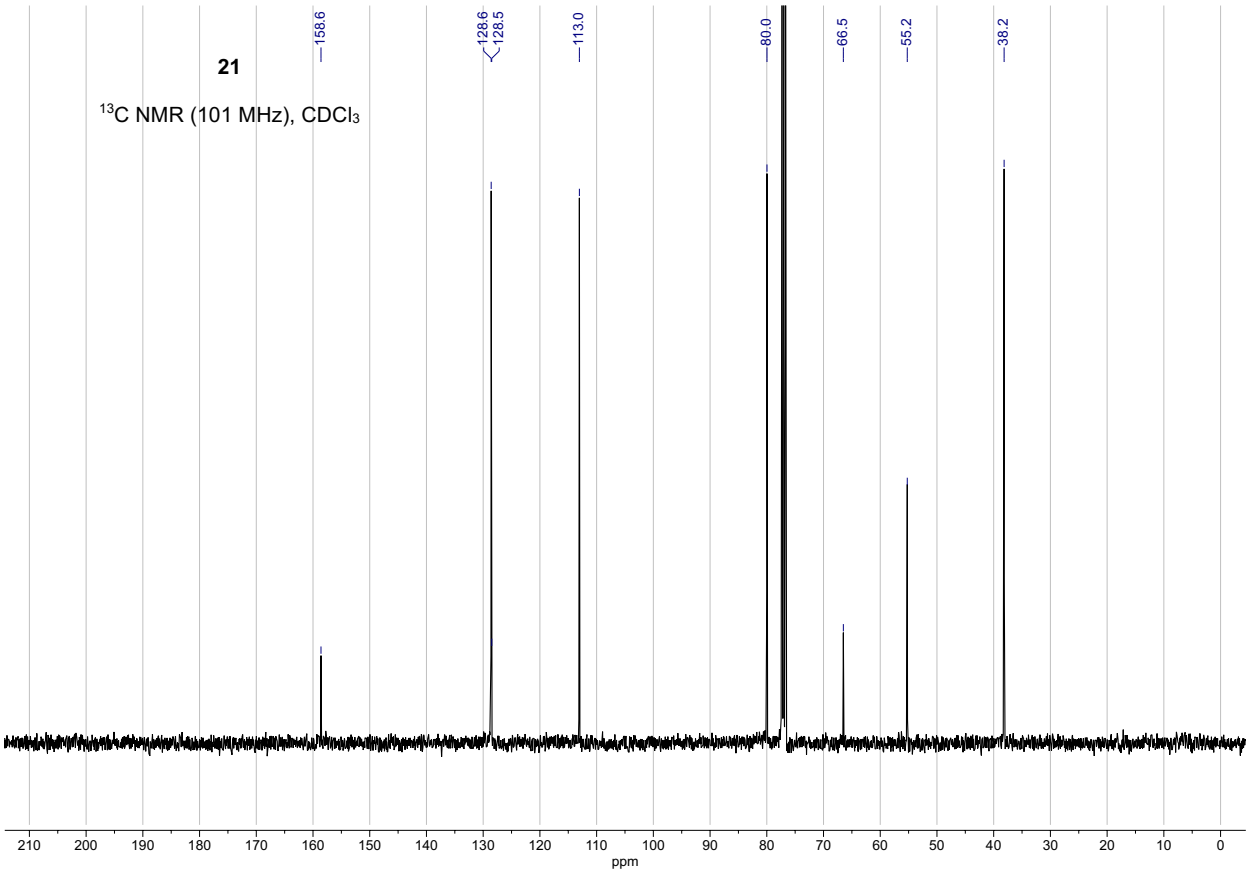

7.37
7.36
7.35
7.35
7.34
7.28
7.27
7.27
7.26
7.25
7.24
7.24
7.20
7.19
7.18
7.18
6.90
6.89
6.89
6.88
6.87
6.86
4.94
4.92
4.66
4.64
4.26
3.81
3.44
3.42
3.41
3.40
3.39
3.38
3.38
3.37
3.37
3.37
2.63
2.62
2.60
2.06
Ph
Ph
N
O
N
H
MeO
19
^{1}H NMR (400 MHz), CDCl$_3$
3.98
4.24
4.00
1.99
1.98
1.98
1.00
3.03
3.00
1.99
1.30
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

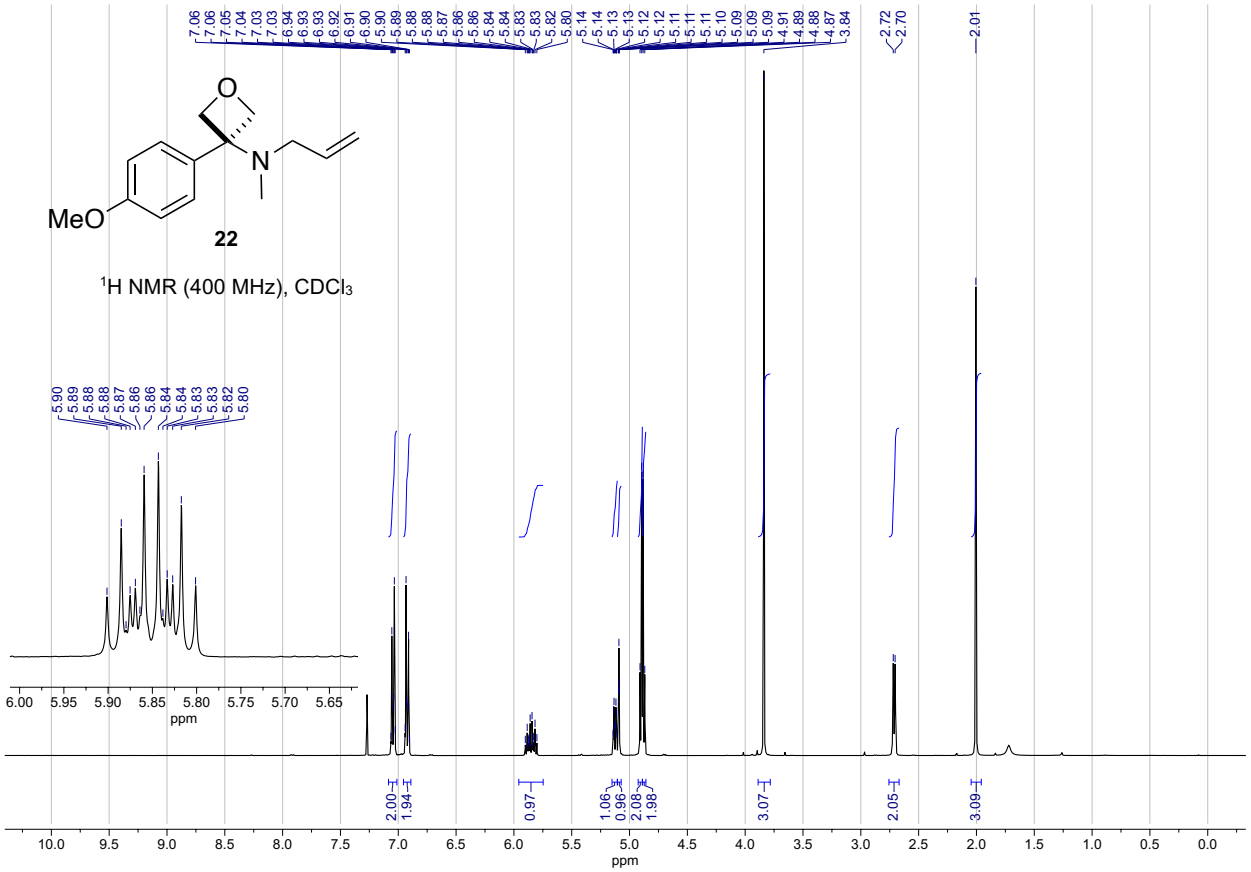

158.8
142.1
134.4
128.4
127.3
127.2
127.1
113.9
82.9
78.4
63.2
62.8
55.3
44.6
19
^{13}C NMR (101 MHz), CDCl$_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

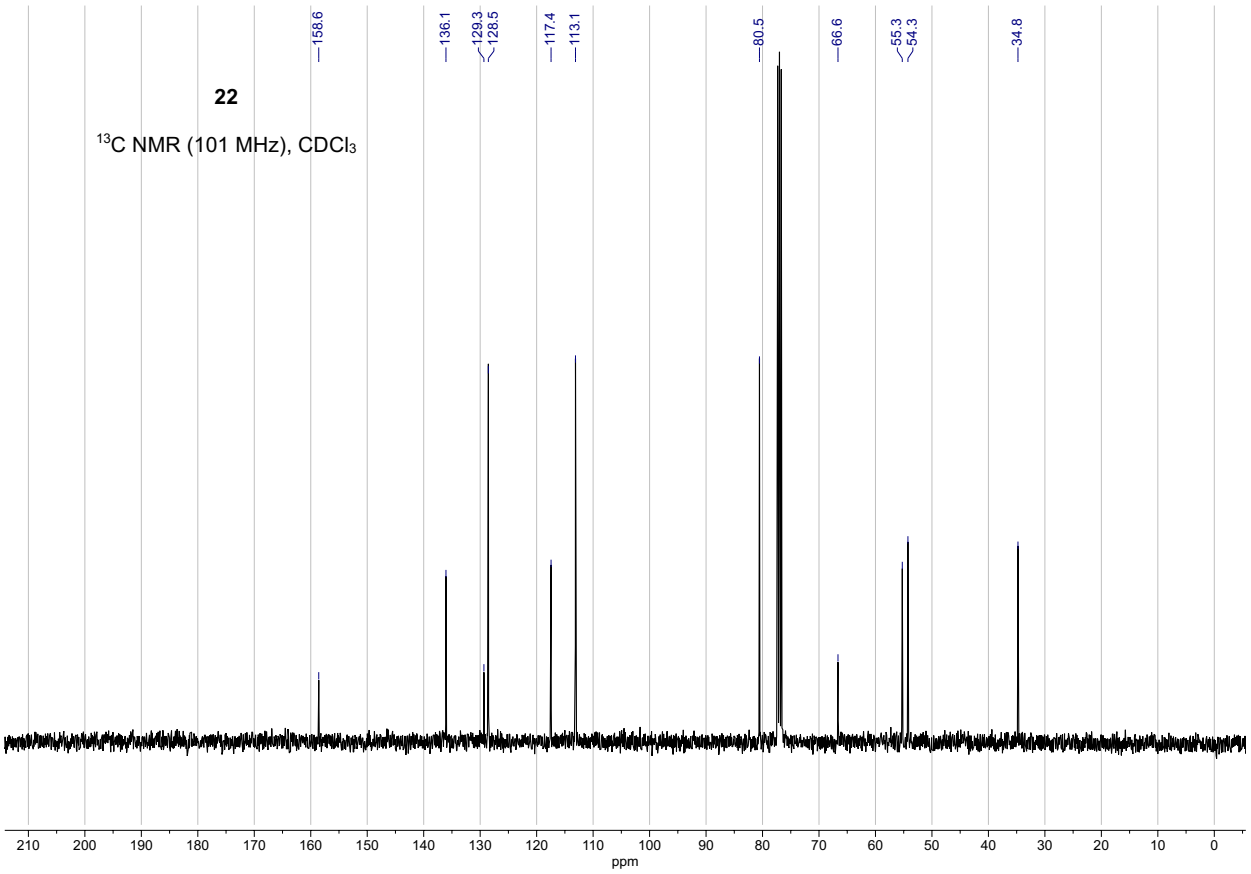

MeO
O
N
H
O
OEt
O
20
^{1}H NMR (400 MHz), CDCl$_3$
ppm

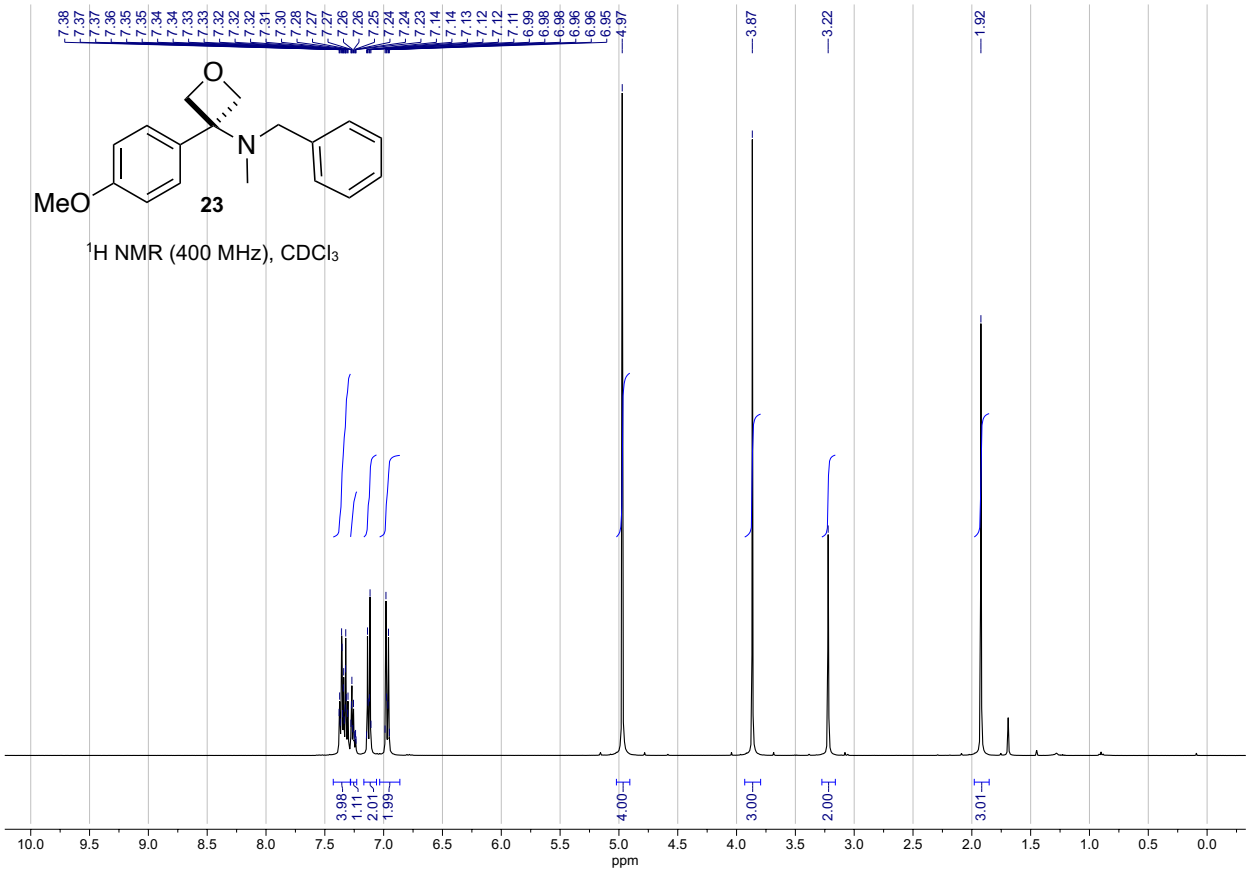

20
^{13}C NMR (101 MHz), CDCl$_3$
ppm

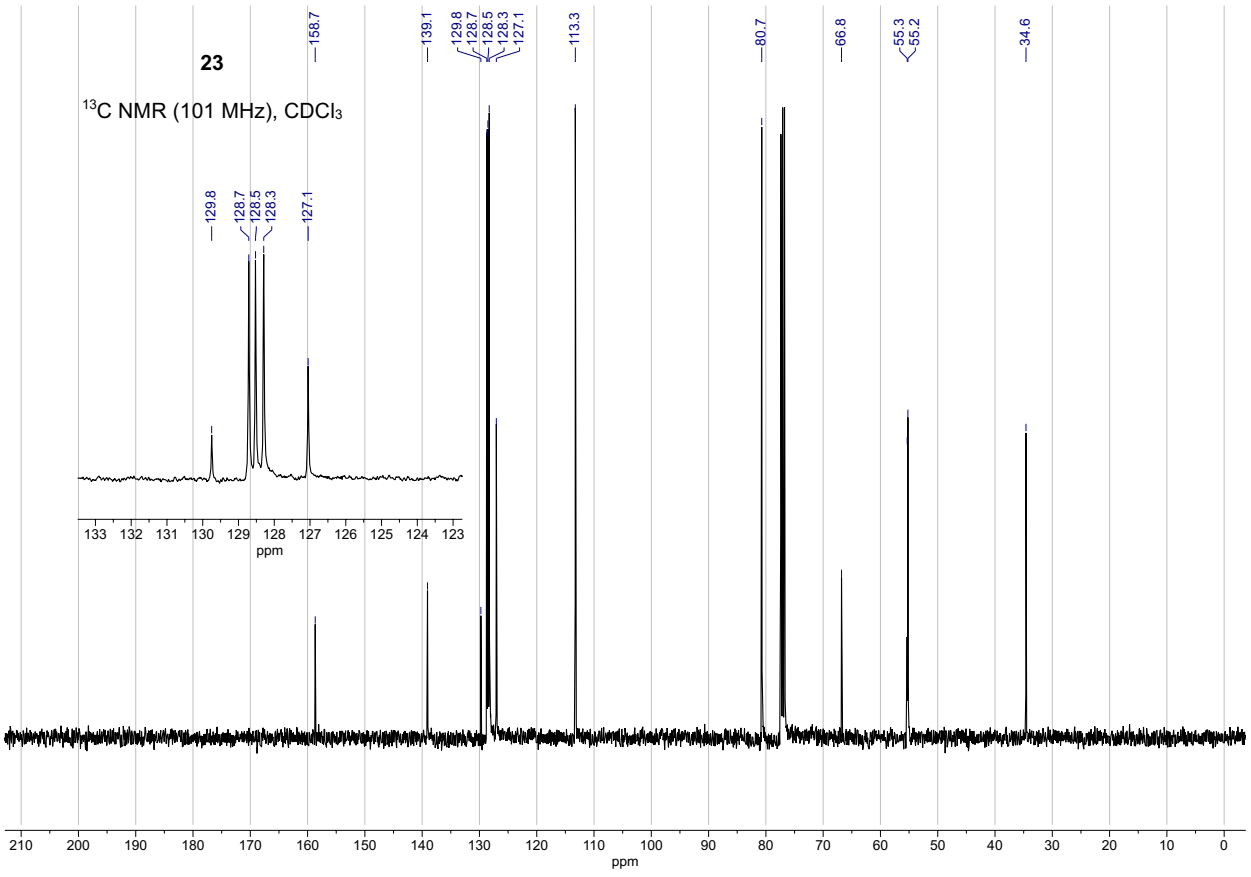

7.01
7.01
7.00
6.99
6.98
6.98
6.93
6.92
6.92
6.91
6.90
6.89
4.90
4.88
4.85
4.84
3.83
2.05
O
N
MeO
21
^{1}H NMR (400 MHz), $CDCl_3$
2.00
1.96
1.99
2.00
3.00
6.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

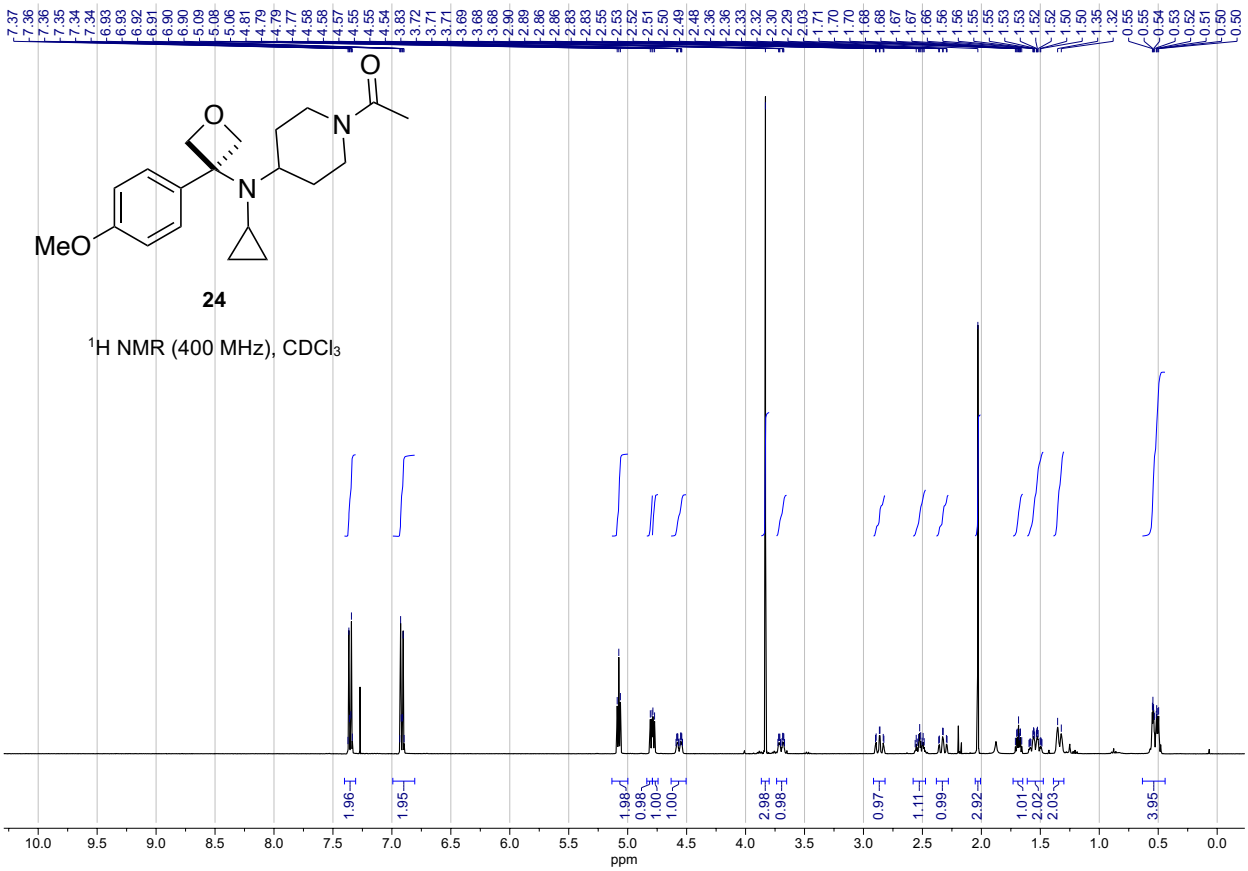

158.6
128.6
128.5
113.0
80.0
66.5
55.2
38.2
21
^{13}C NMR (101 MHz), $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

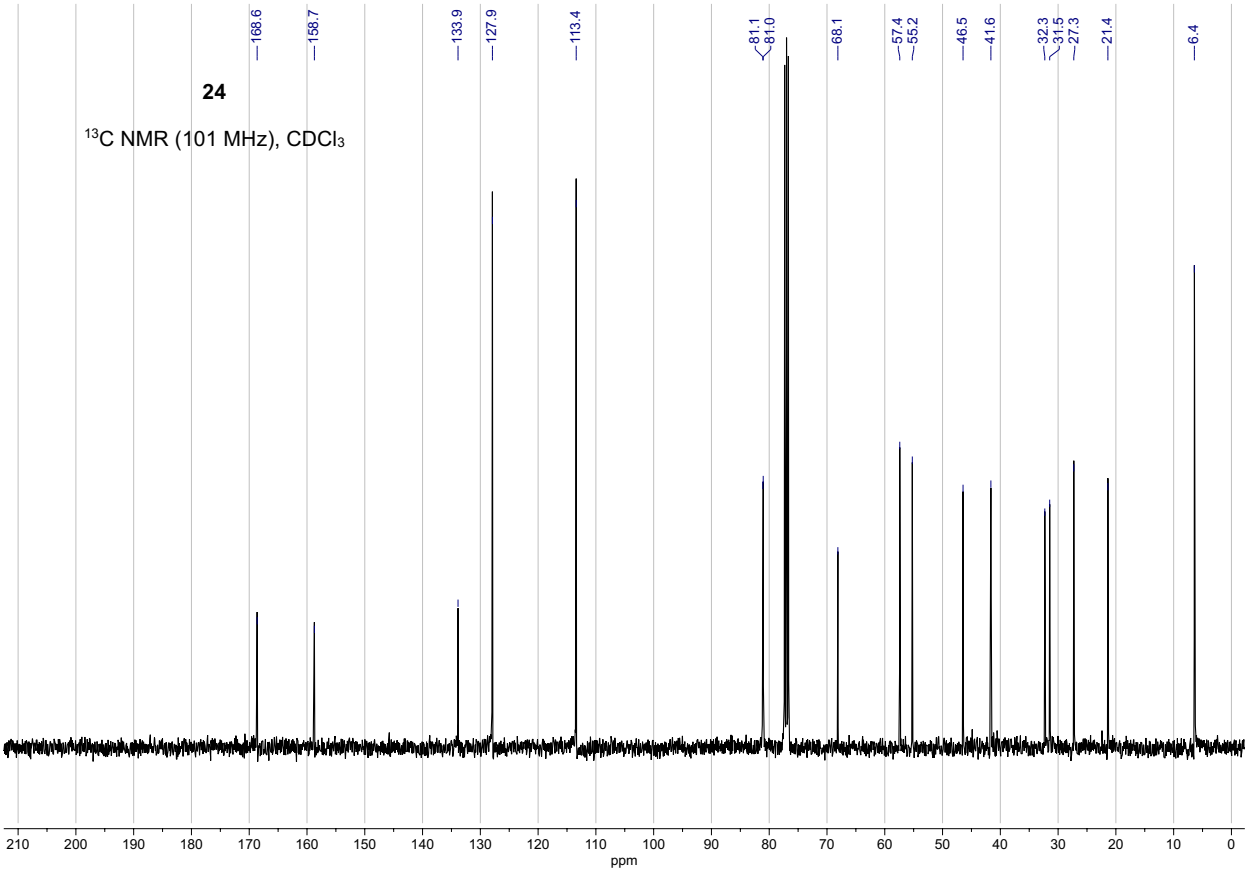

MeO
O
N
22
^{1}H NMR (400 MHz), CDCl$_3$
ppm

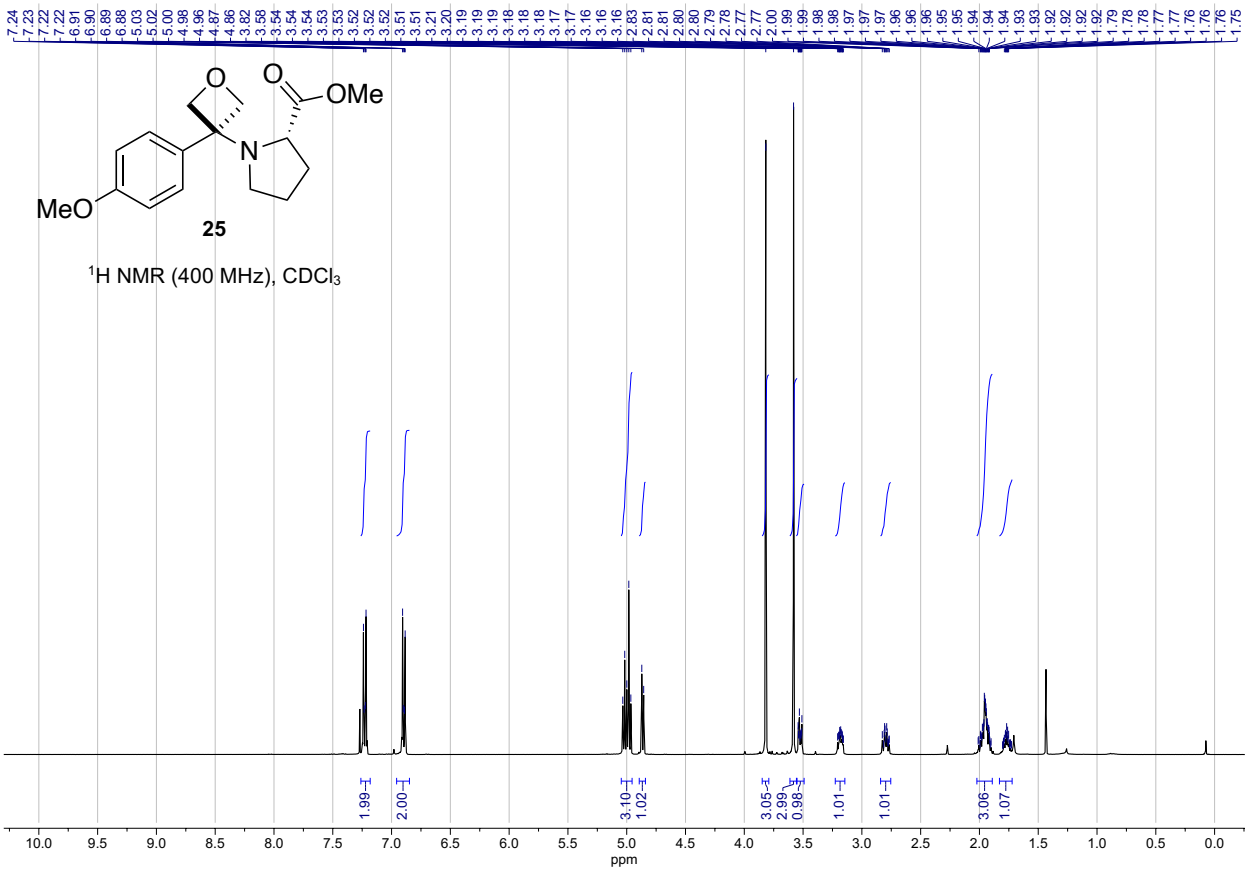

22
^{13}C NMR (101 MHz), CDCl$_3$
158.6
136.1
129.3
128.5
117.4
113.1
80.5
66.6
55.3
54.3
34.8
ppm

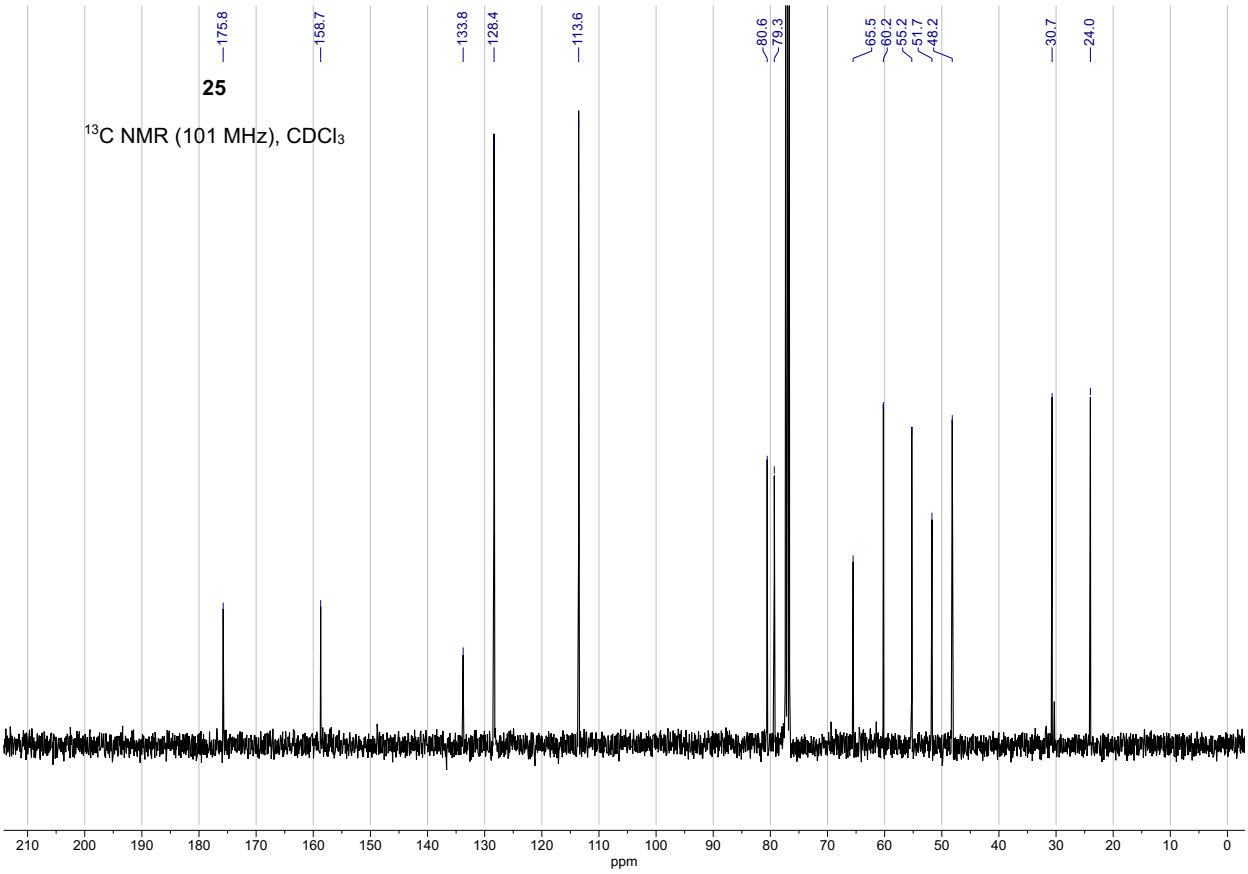

MeO
N
O
23
^{1}H NMR (400 MHz), CDCl$_3$
ppm

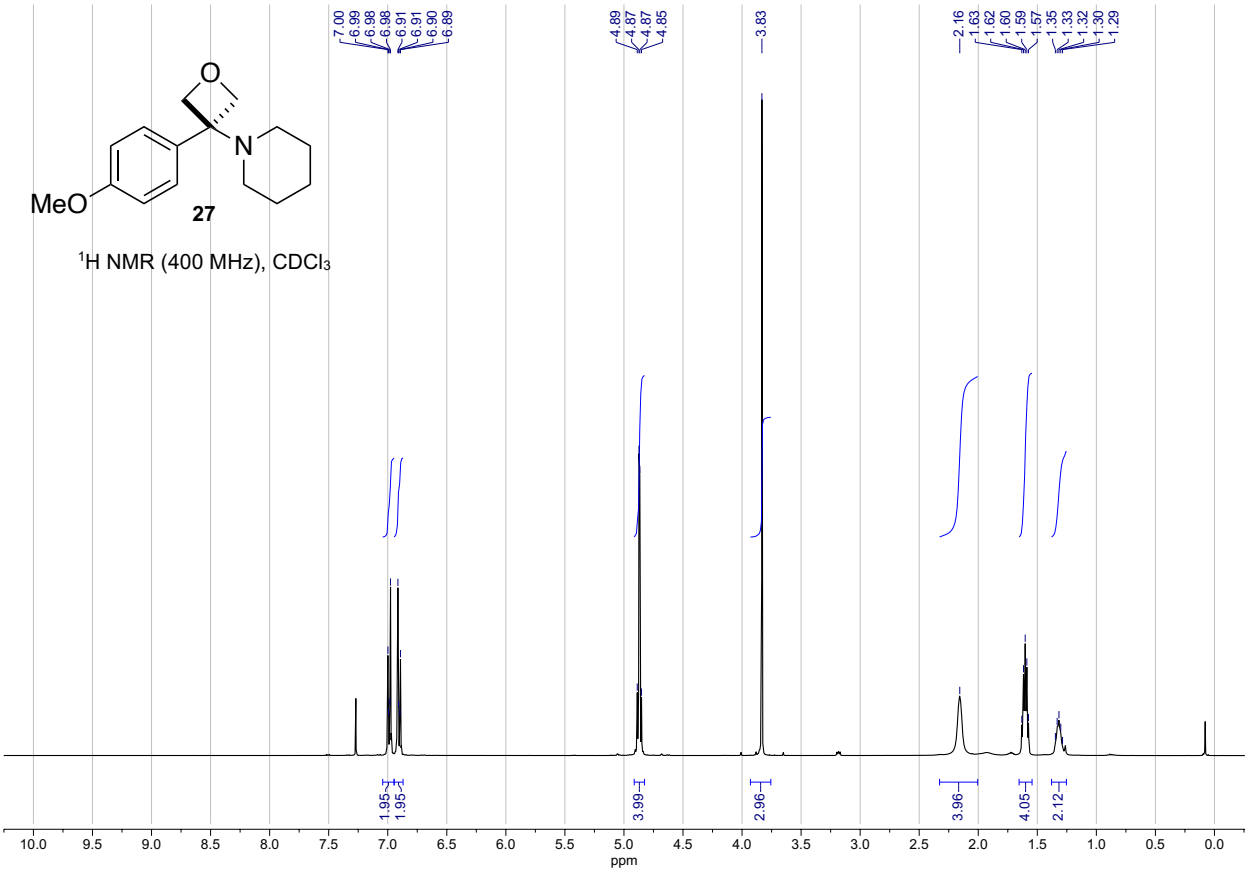

23
^{13}C NMR (101 MHz), CDCl$_3$
ppm

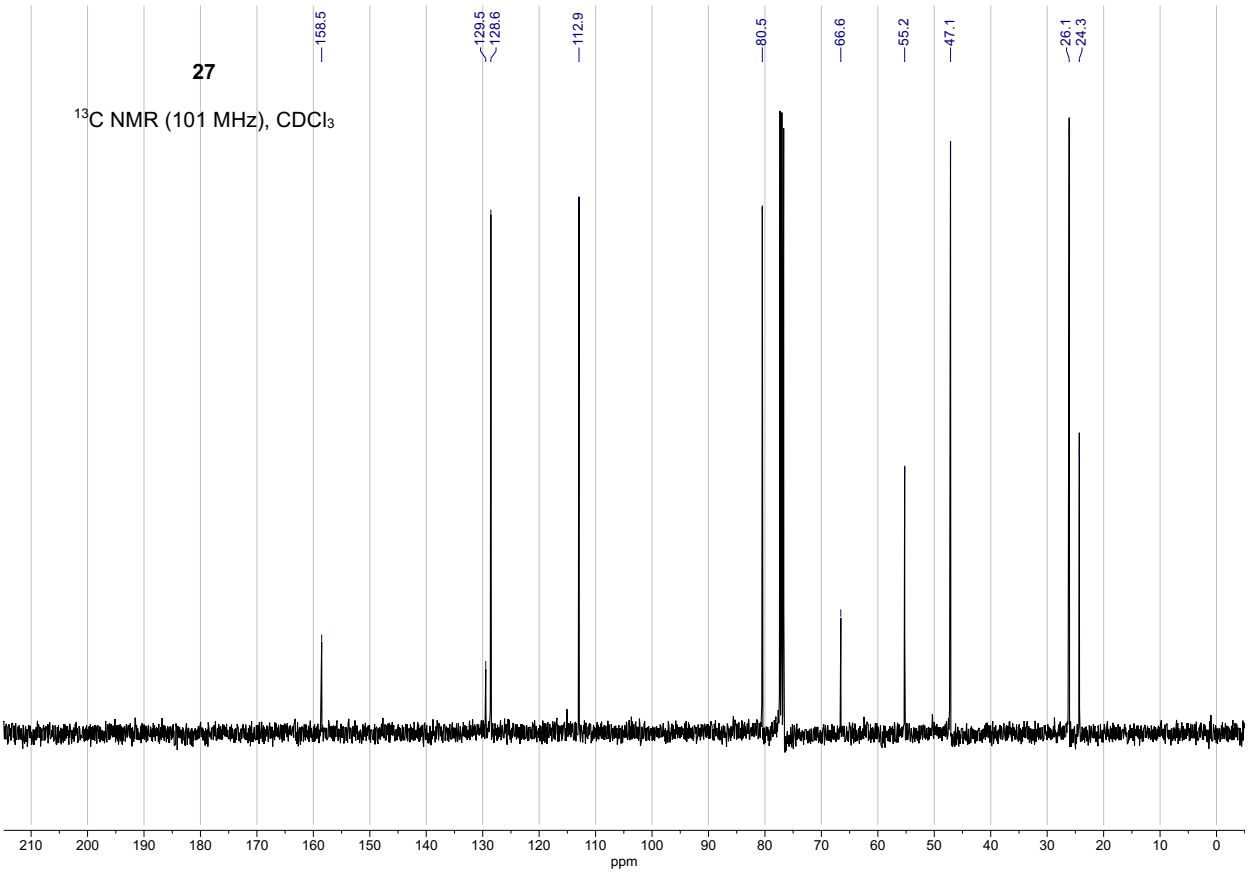

MeO
O
N
O
N
24
^{1}H NMR (400 MHz), CDCl$_3$
ppm

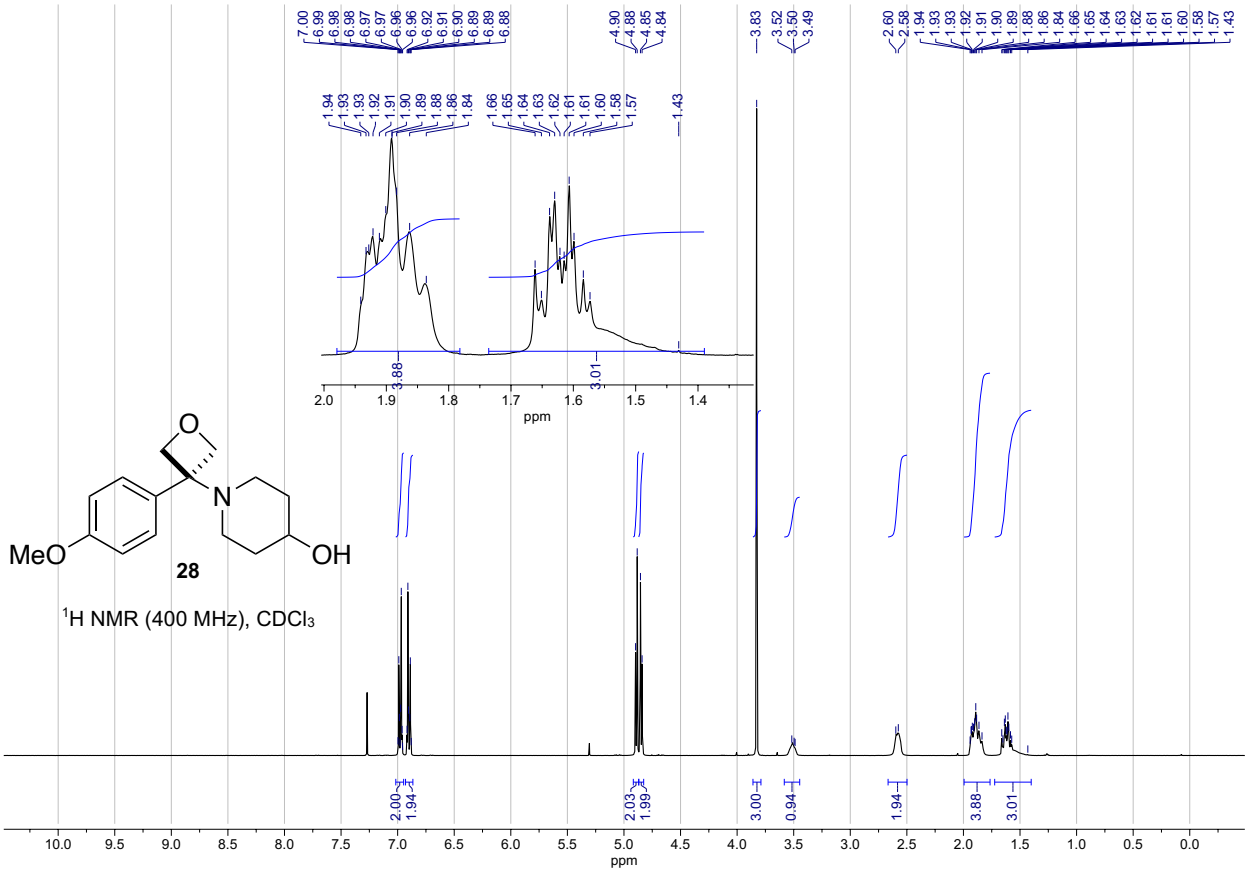

24
^{13}C NMR (101 MHz), CDCl$_3$
168.6
158.7
133.9
127.9
113.4
81.1
81.0
68.1
57.4
55.2
46.5
41.6
32.3
31.5
27.3
21.4
6.4
ppm

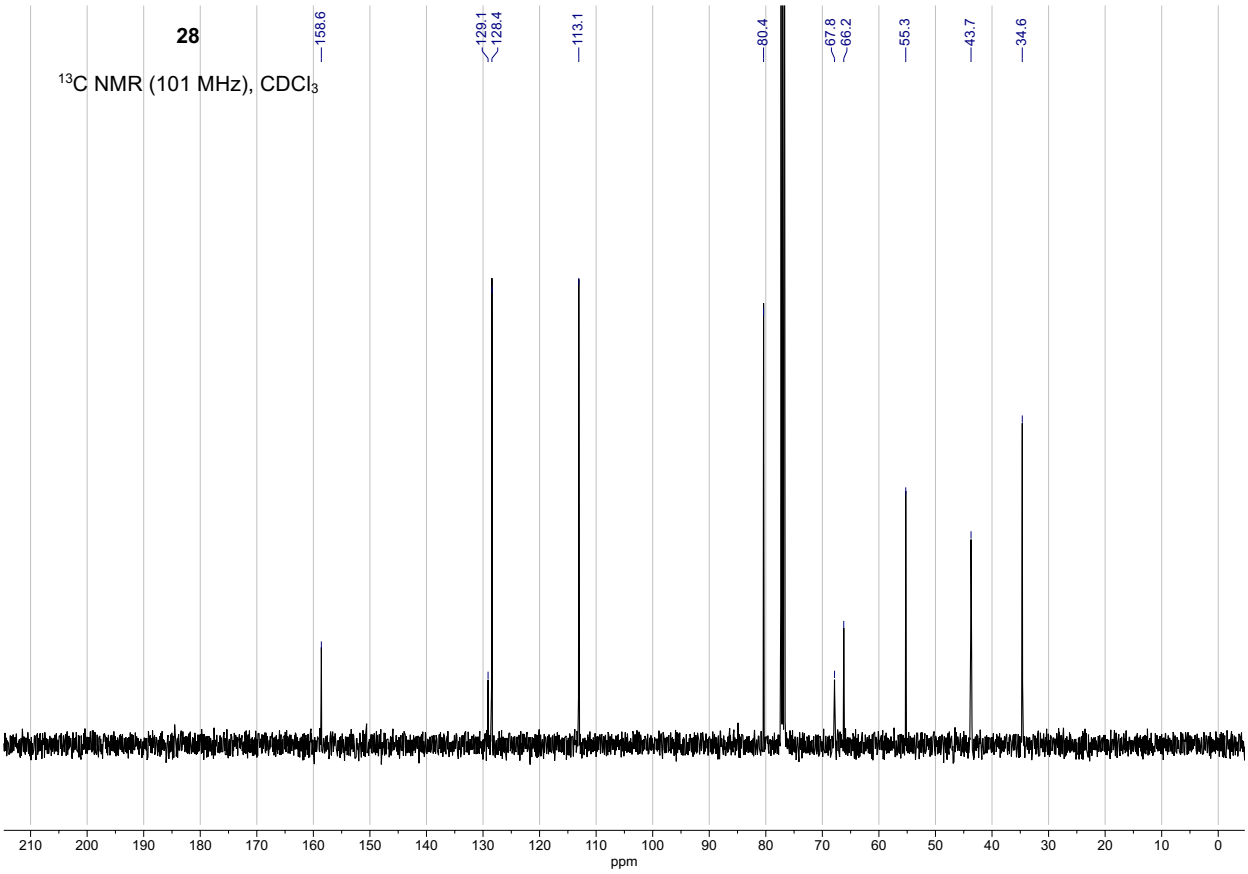

MeO
O
O
OMe
N
25
^{1}H NMR (400 MHz), CDCl$_3$
ppm

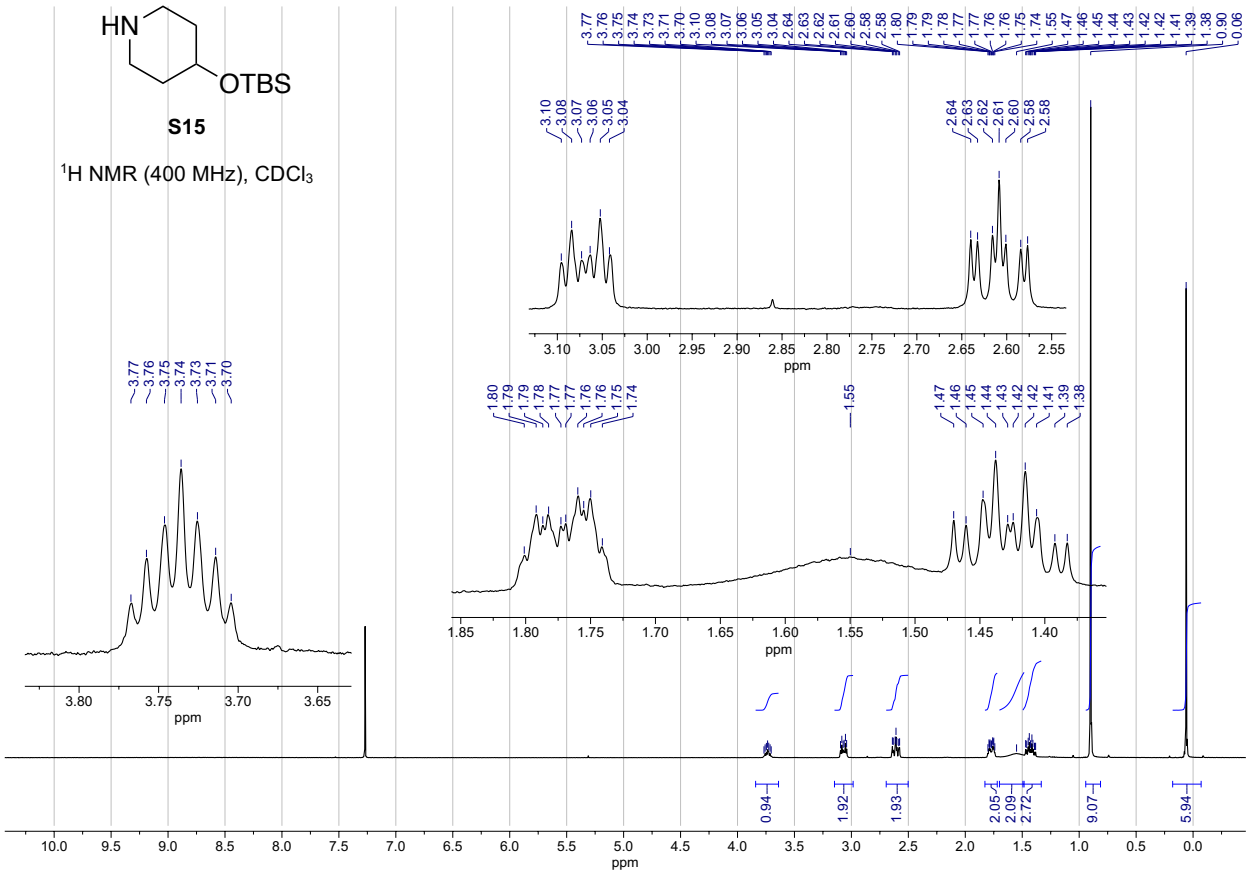

175.8
158.7
133.8
128.4
113.6
80.6
79.3
65.5
60.2
55.2
51.7
48.2
30.7
24.0
25
^{13}C NMR (101 MHz), CDCl$_3$
ppm

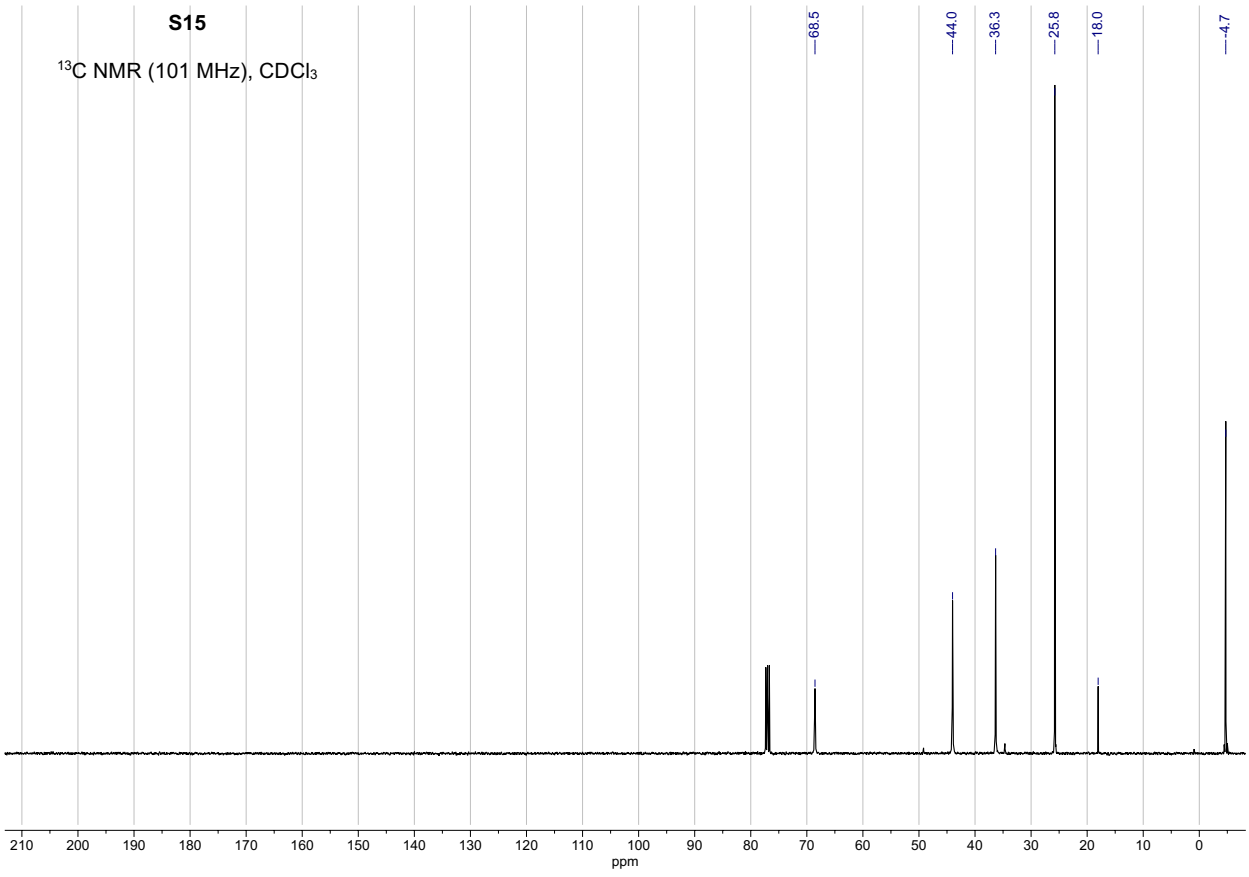

MeO
O
N
27
^{1}H NMR (400 MHz), CDCl$_3$
7.00
6.99
6.98
6.98
6.91
6.91
6.90
6.89
4.89
4.87
4.87
4.85
3.83
2.16
1.63
1.62
1.60
1.59
1.57
1.35
1.33
1.32
1.30
1.29
1.95
1.95
3.99
2.96
3.96
4.05
2.12
ppm

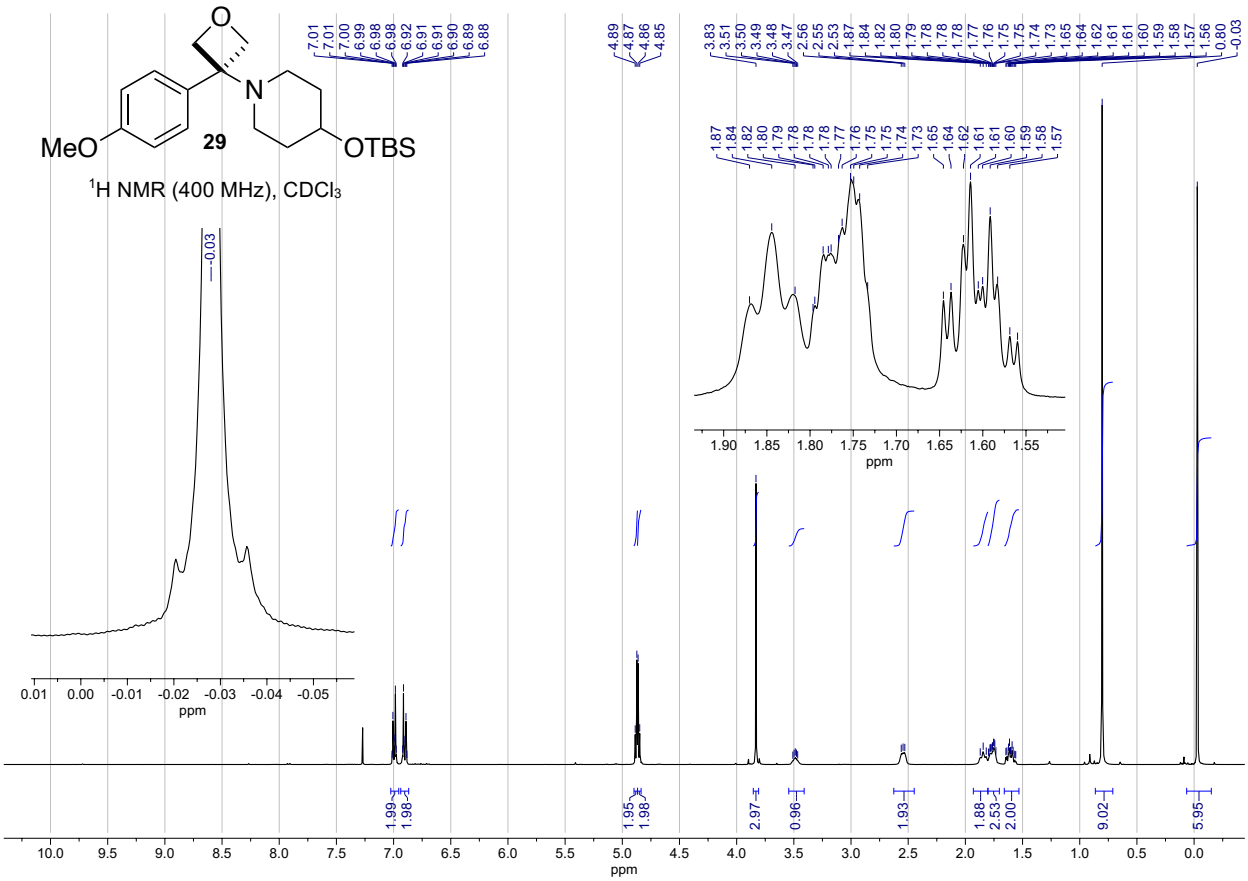

27
^{13}C NMR (101 MHz), CDCl$_3$
158.5
129.5
128.6
112.9
80.5
66.6
55.2
47.1
26.1
24.3
ppm

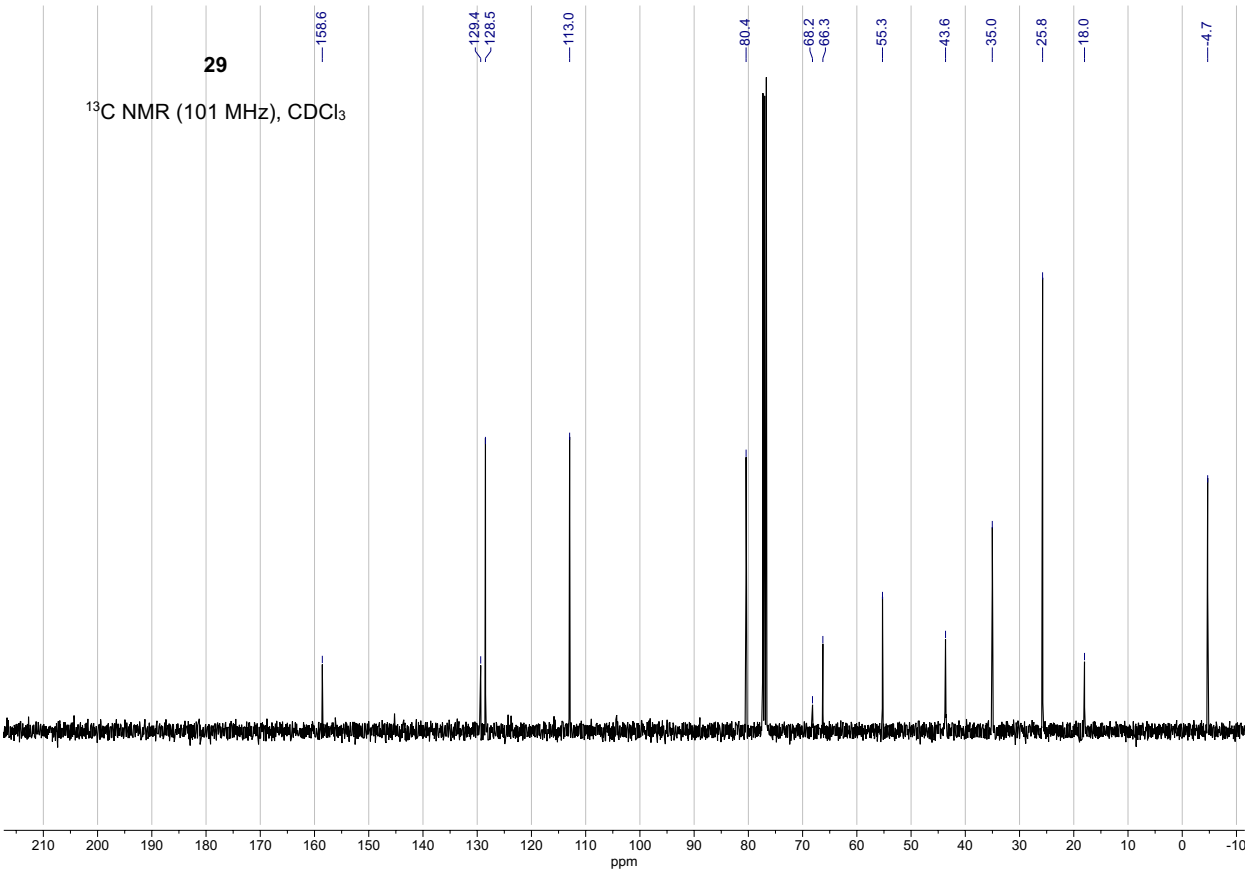

MeO
OH
O
N
28
^{1}H NMR (400 MHz), CDCl$_3$
ppm

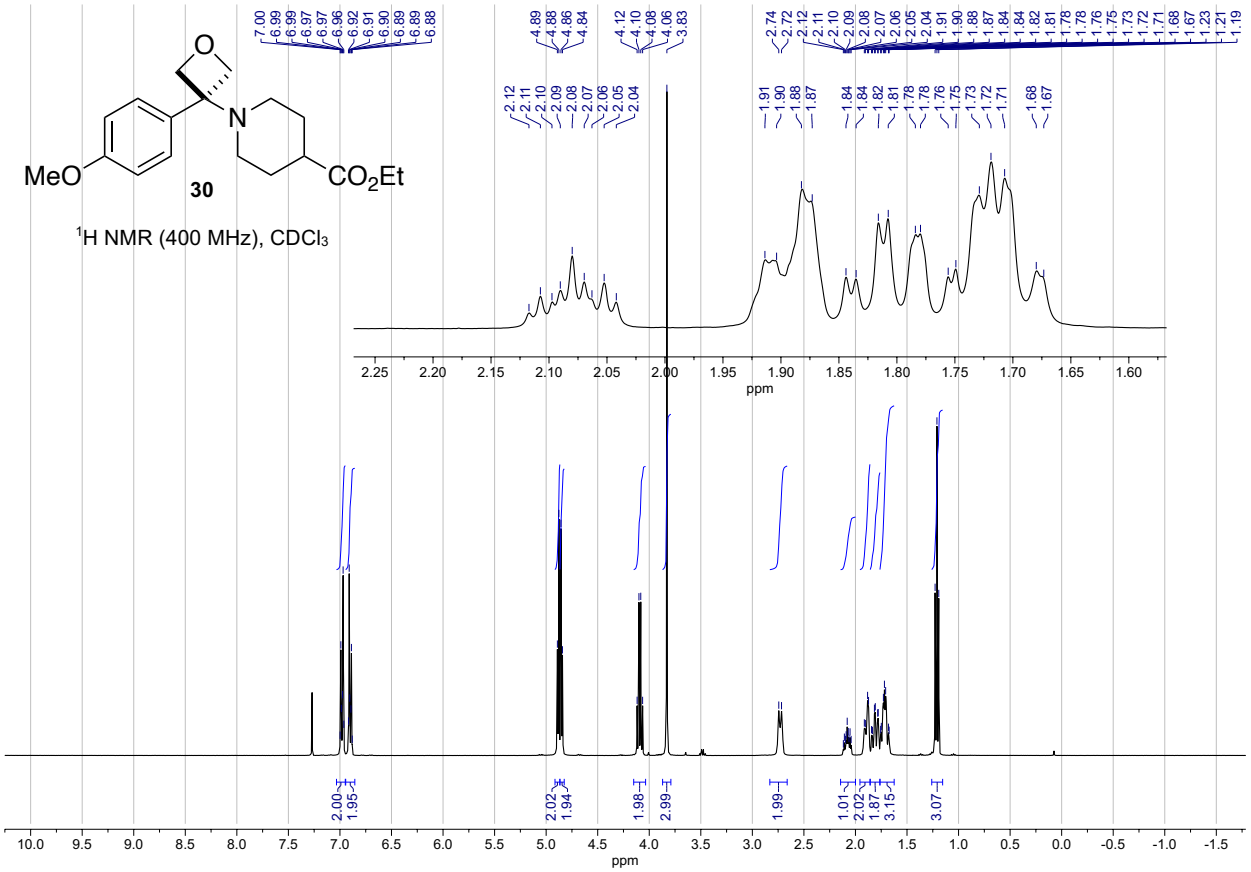

28
^{13}C NMR (101 MHz), CDCl$_3$
158.6
129.1
128.4
113.1
80.4
67.8
66.2
55.3
43.7
34.6
ppm

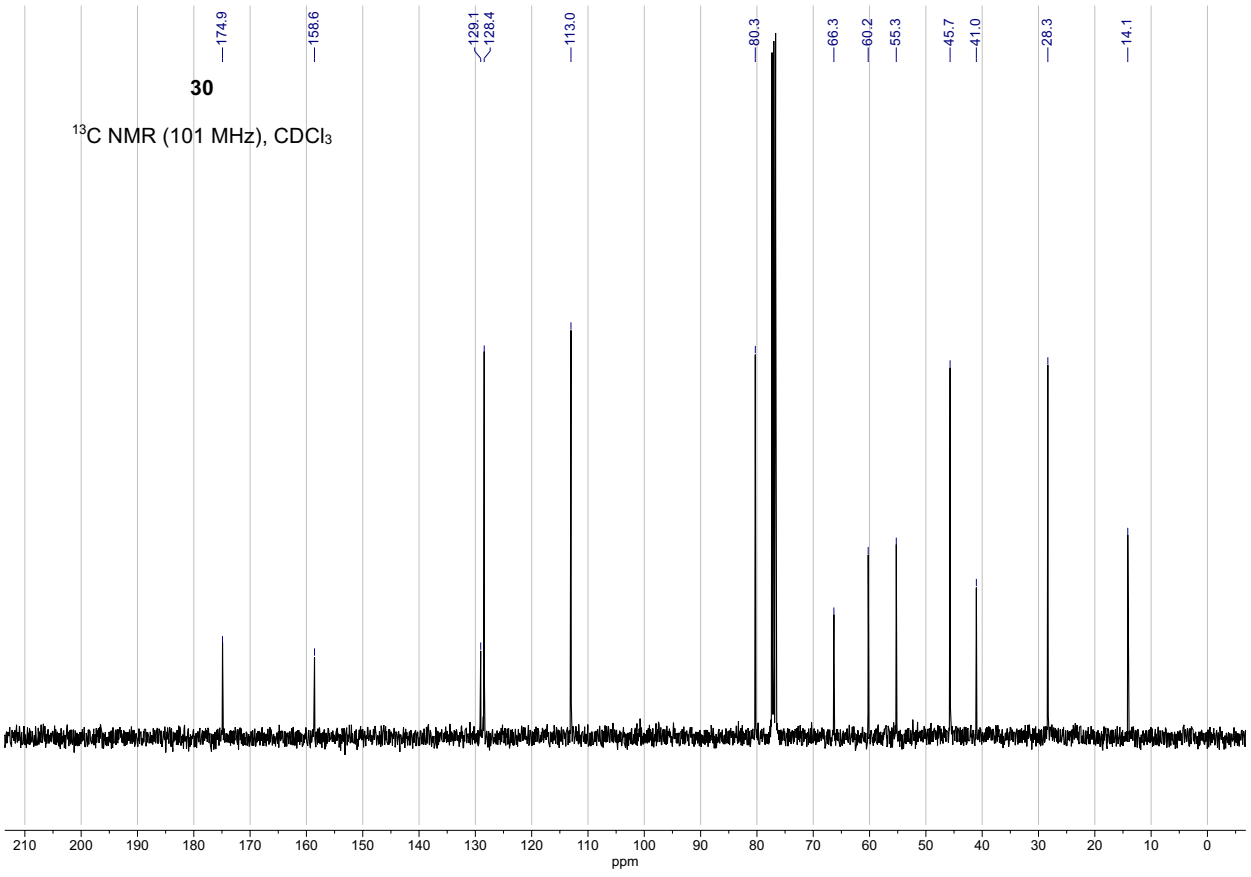

HN
OTBS
S15
1H NMR (400 MHz), CDCl3
ppm

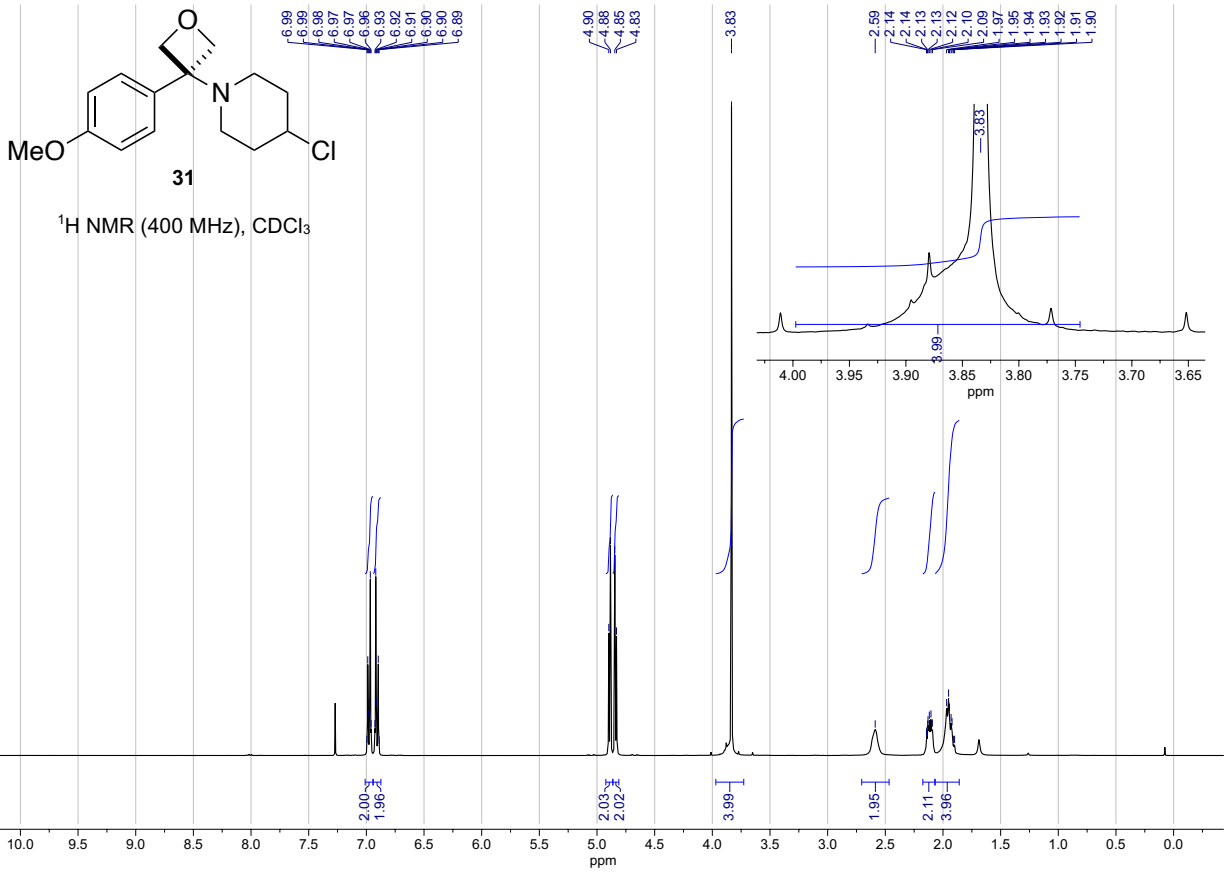

S15
13C NMR (101 MHz), CDCl3
68.5
44.0
36.3
25.8
18.0
-4.7
ppm

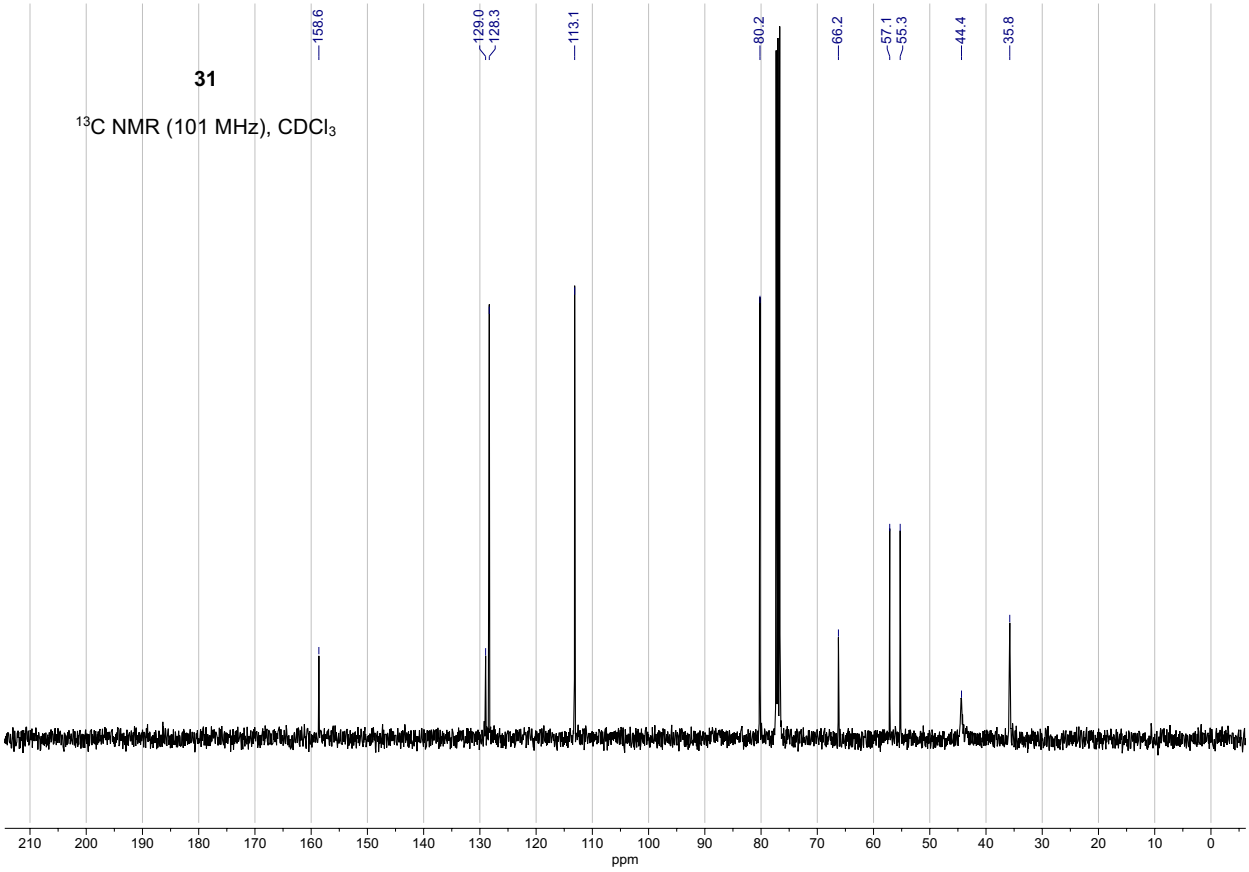

MeO
29
OTBS
^{1}H NMR (400 MHz), CDCl$_3$
ppm

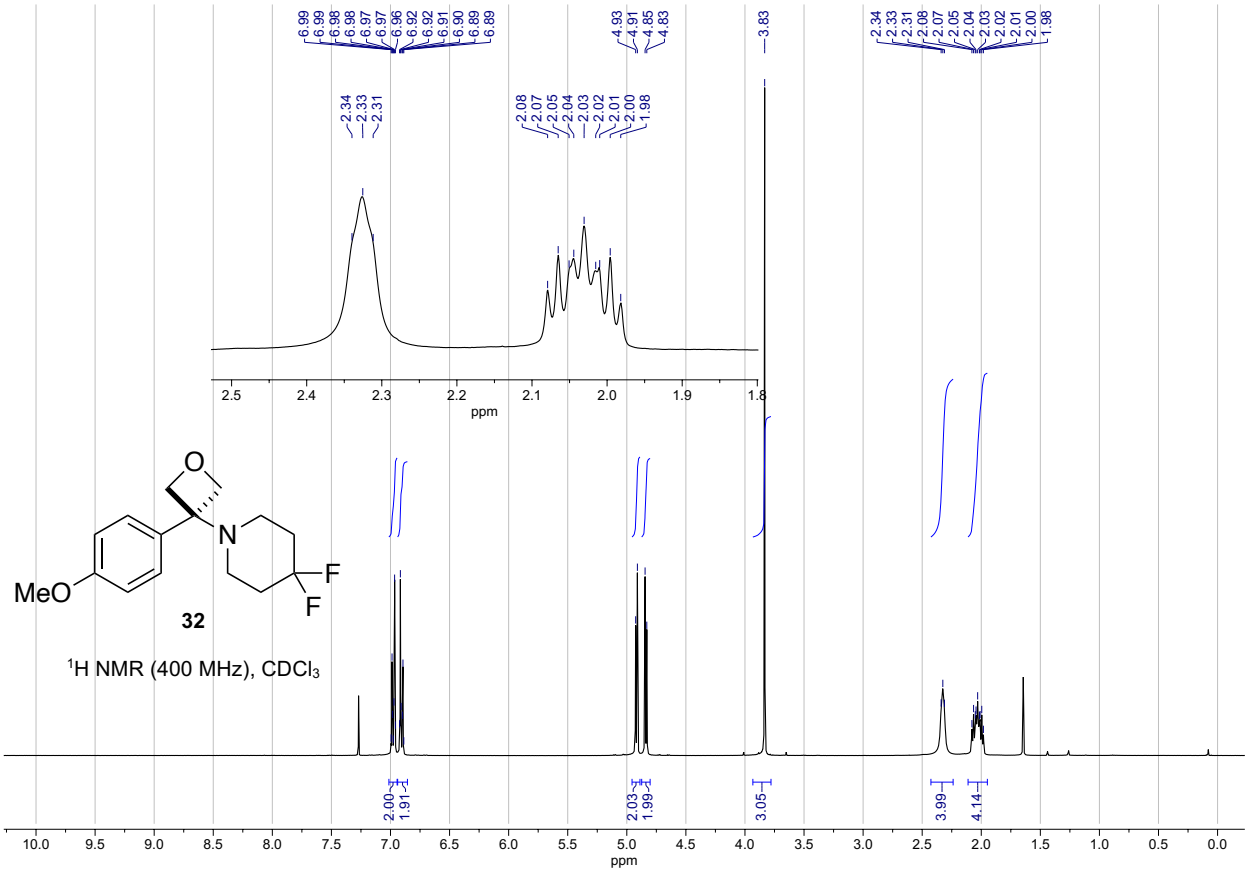

29
^{13}C NMR (101 MHz), CDCl$_3$
ppm

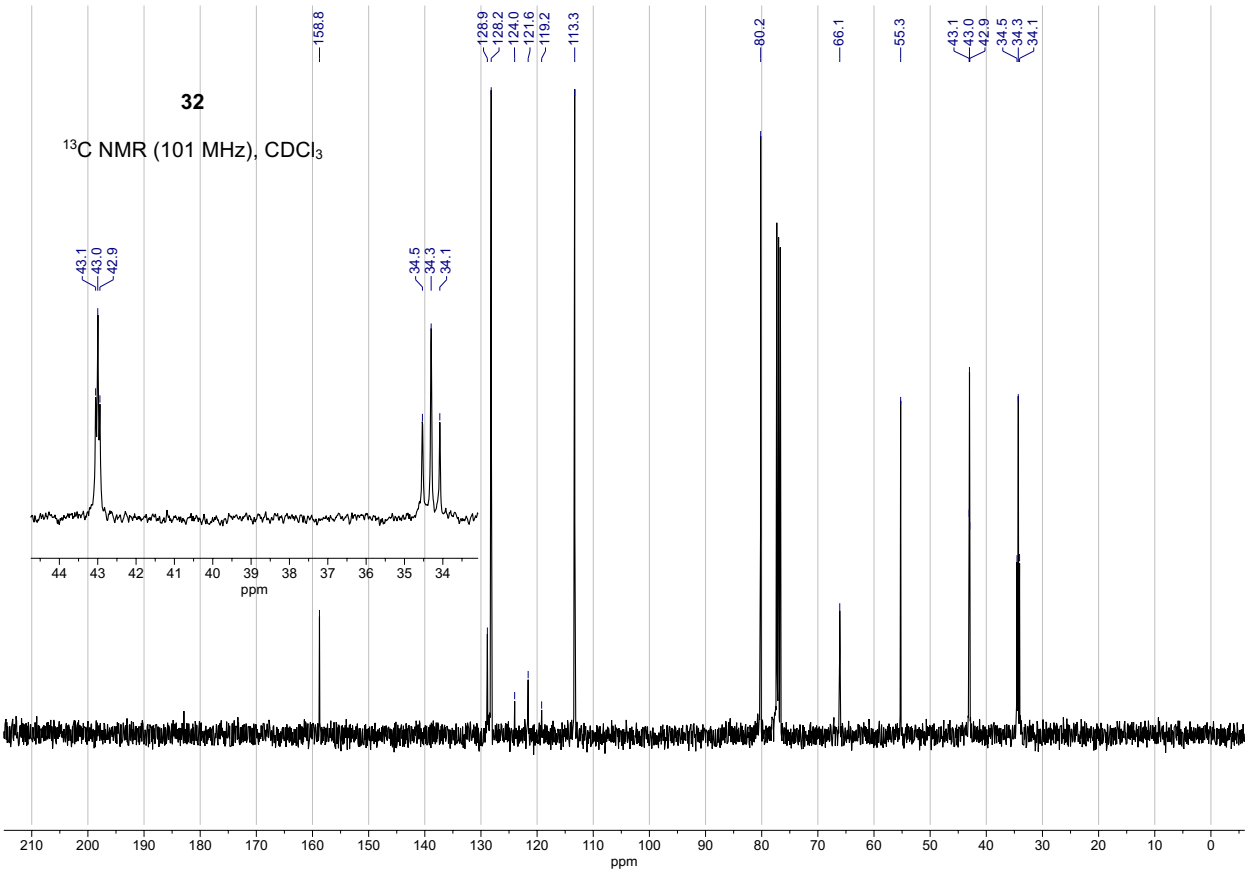

MeO
CO2Et
30
1H NMR (400 MHz), CDCl3
ppm

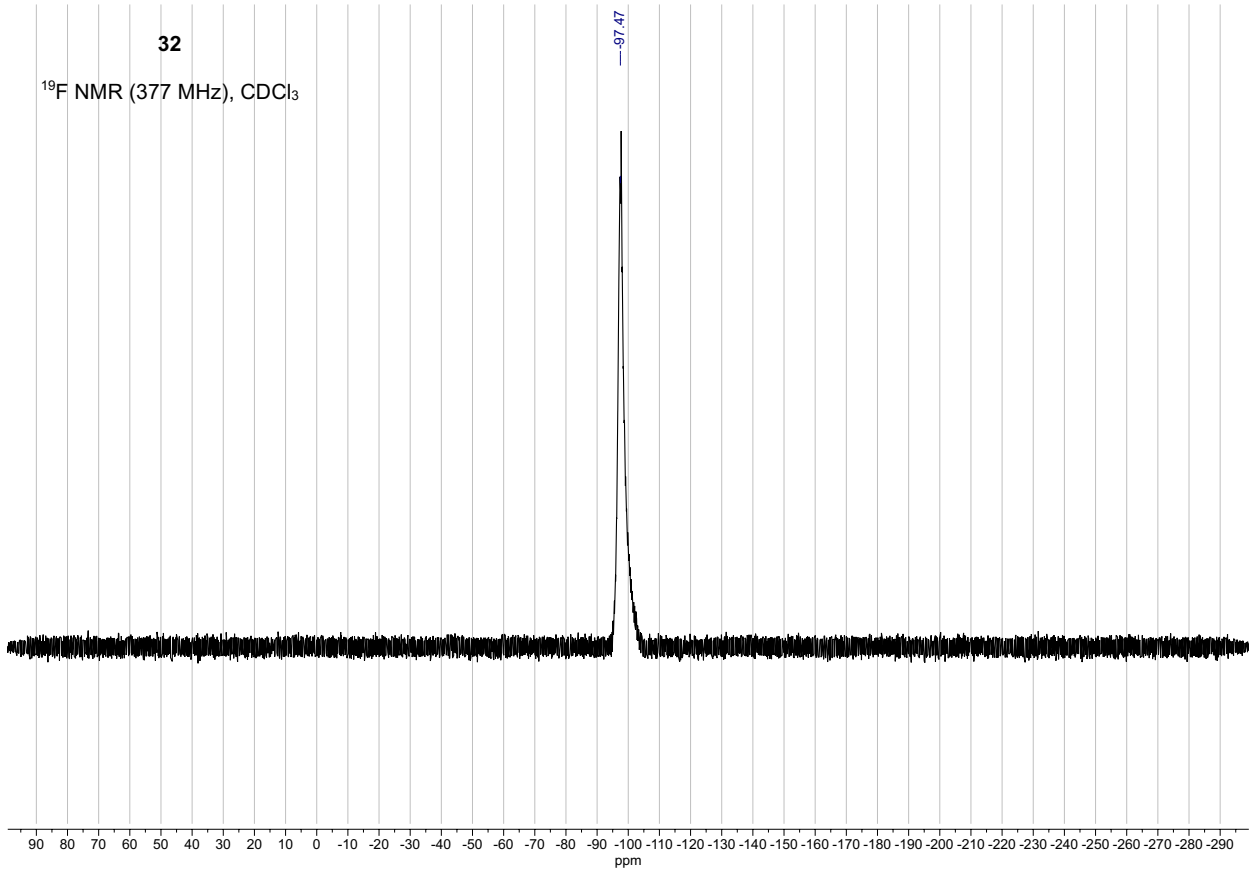

30
13C NMR (101 MHz), CDCl3
ppm

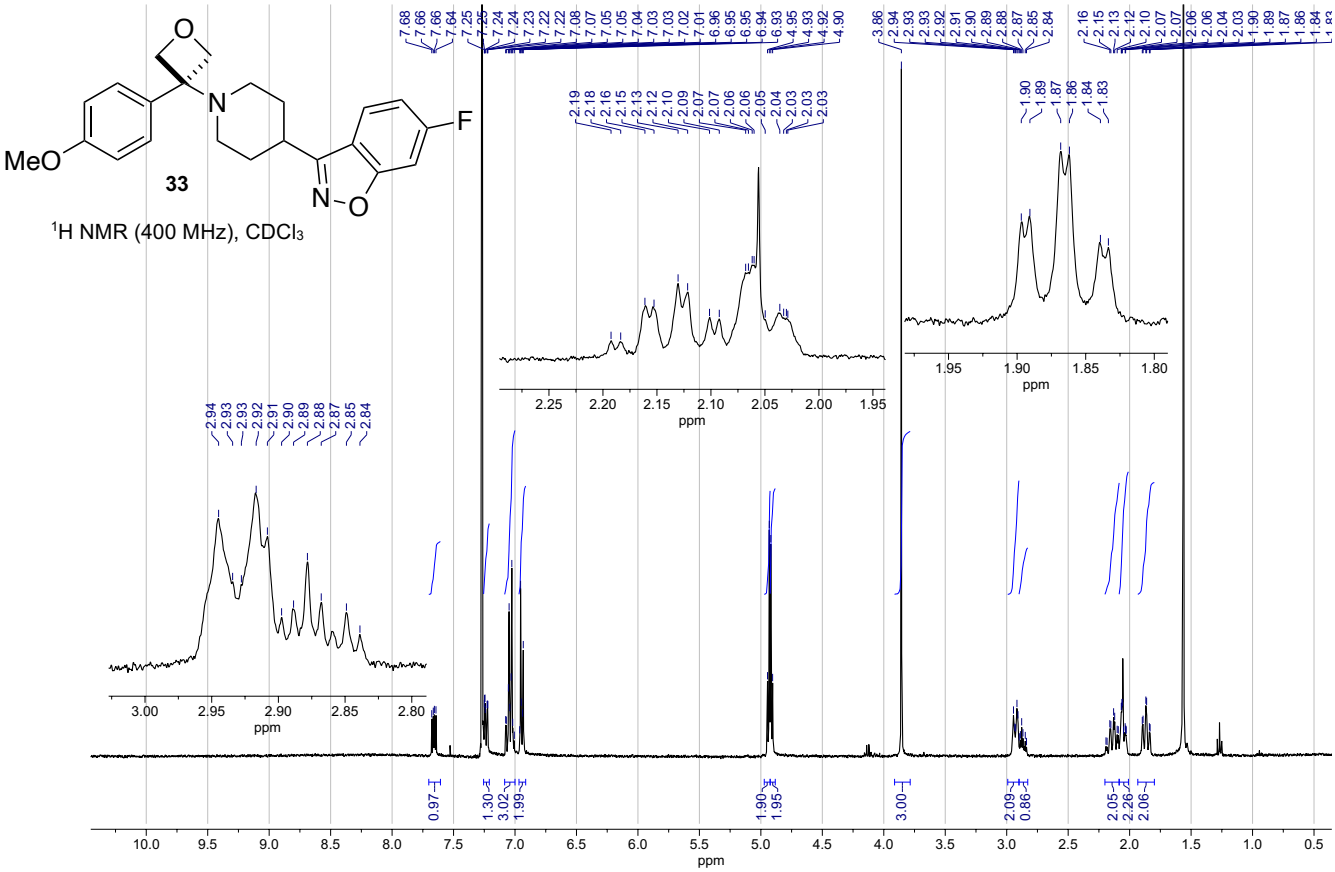

MeO
Cl
O
N
31
^{1}H NMR (400 MHz), CDCl$_3$
6.99
6.99
6.98
6.97
6.97
6.96
6.93
6.92
6.91
6.90
6.90
6.89
4.90
4.88
4.85
4.83
3.83
2.59
2.14
2.13
2.13
2.12
2.10
2.09
1.97
1.95
1.94
1.93
1.92
1.91
1.90
3.99
4.00
3.95
3.90
3.85
3.80
3.75
3.70
3.65
ppm
2.00
1.96
2.03
2.02
3.99
1.95
2.11
3.96
10.0
9.5
9.0
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

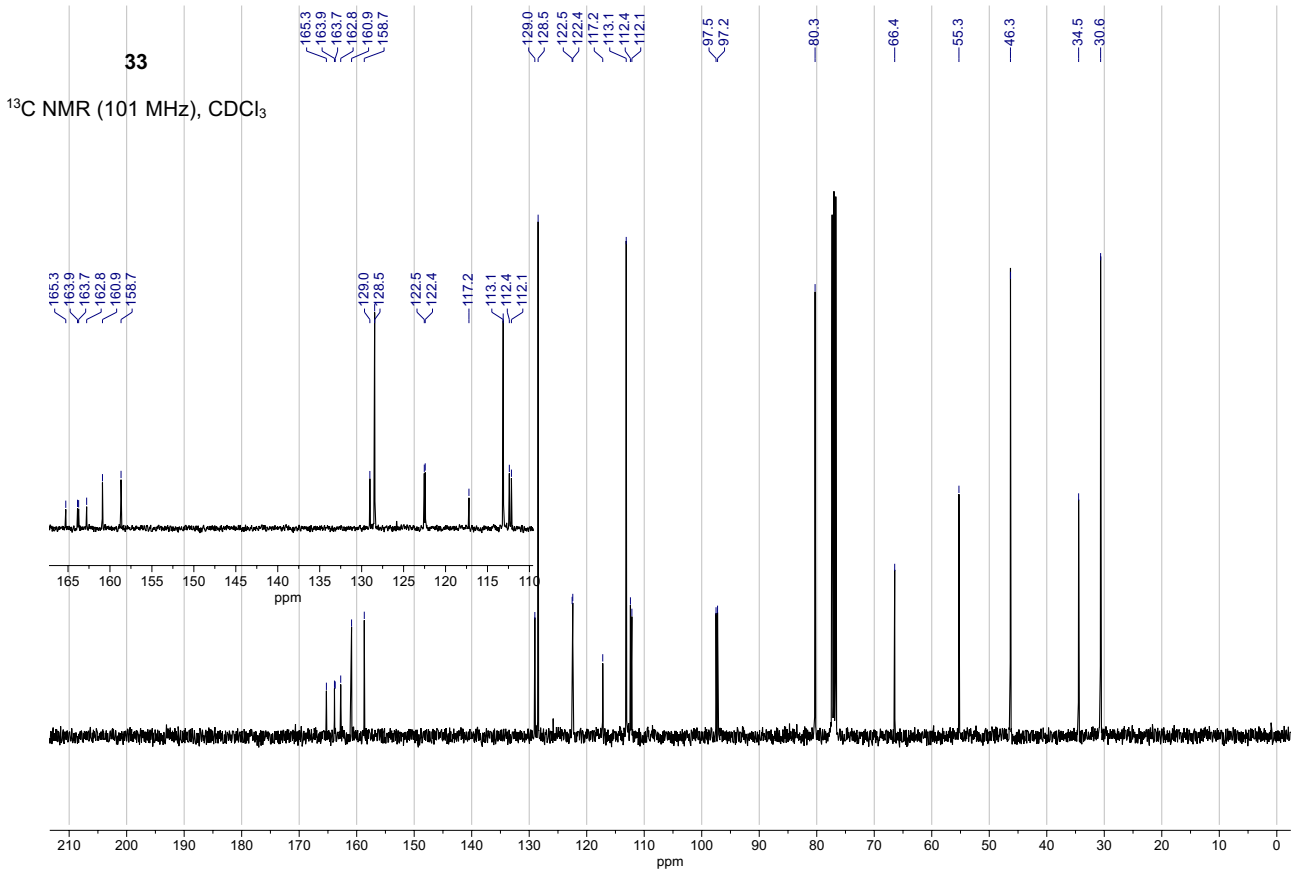

31
^{13}C NMR (101 MHz), CDCl$_3$
158.6
129.0
128.3
113.1
80.2
66.2
57.1
55.3
44.4
35.8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


MeO
O
N
F
F
32
^{1}H NMR (400 MHz), $CDCl_3$
ppm


32
^{13}C NMR (101 MHz), $CDCl_3$
ppm

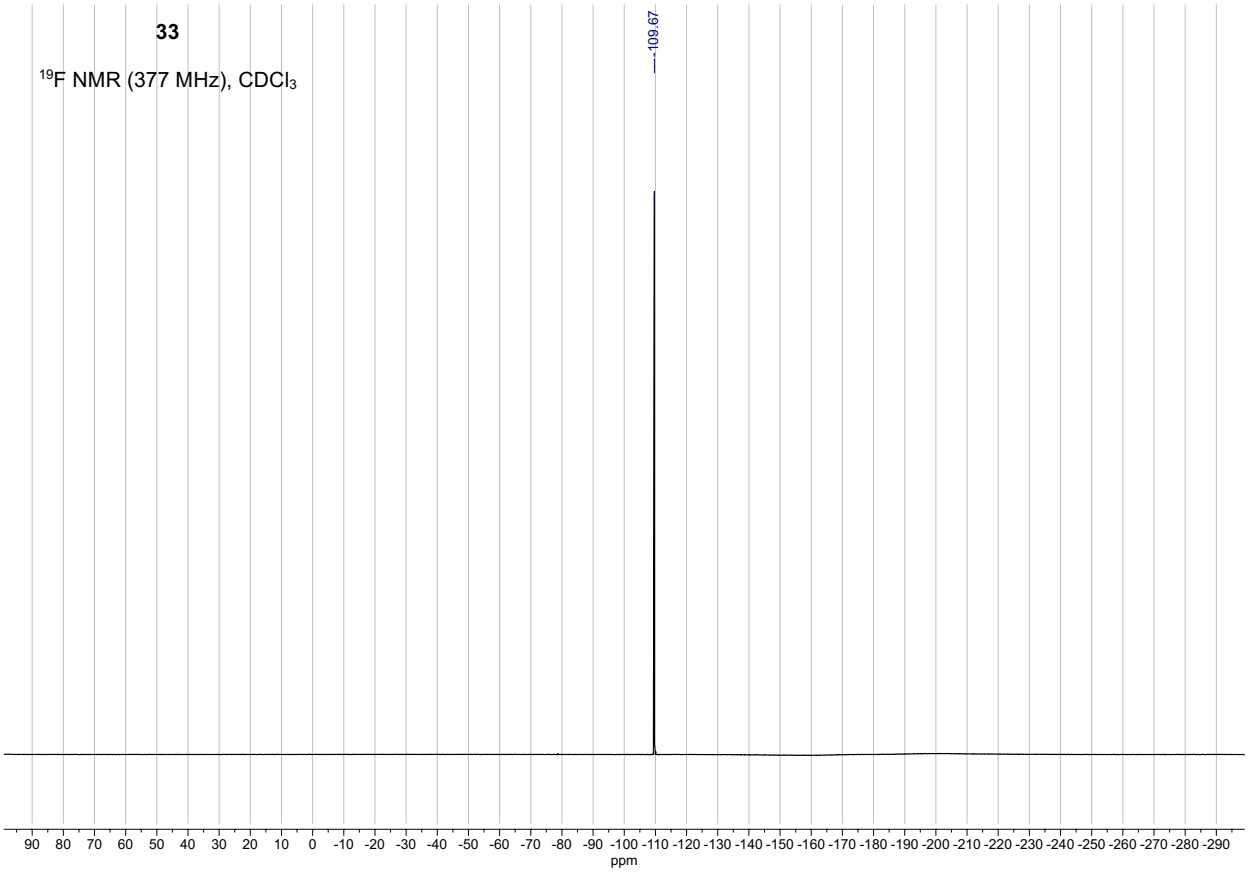

32
^{19}F NMR (377 MHz), $CDCl_3$
-97.47
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
ppm

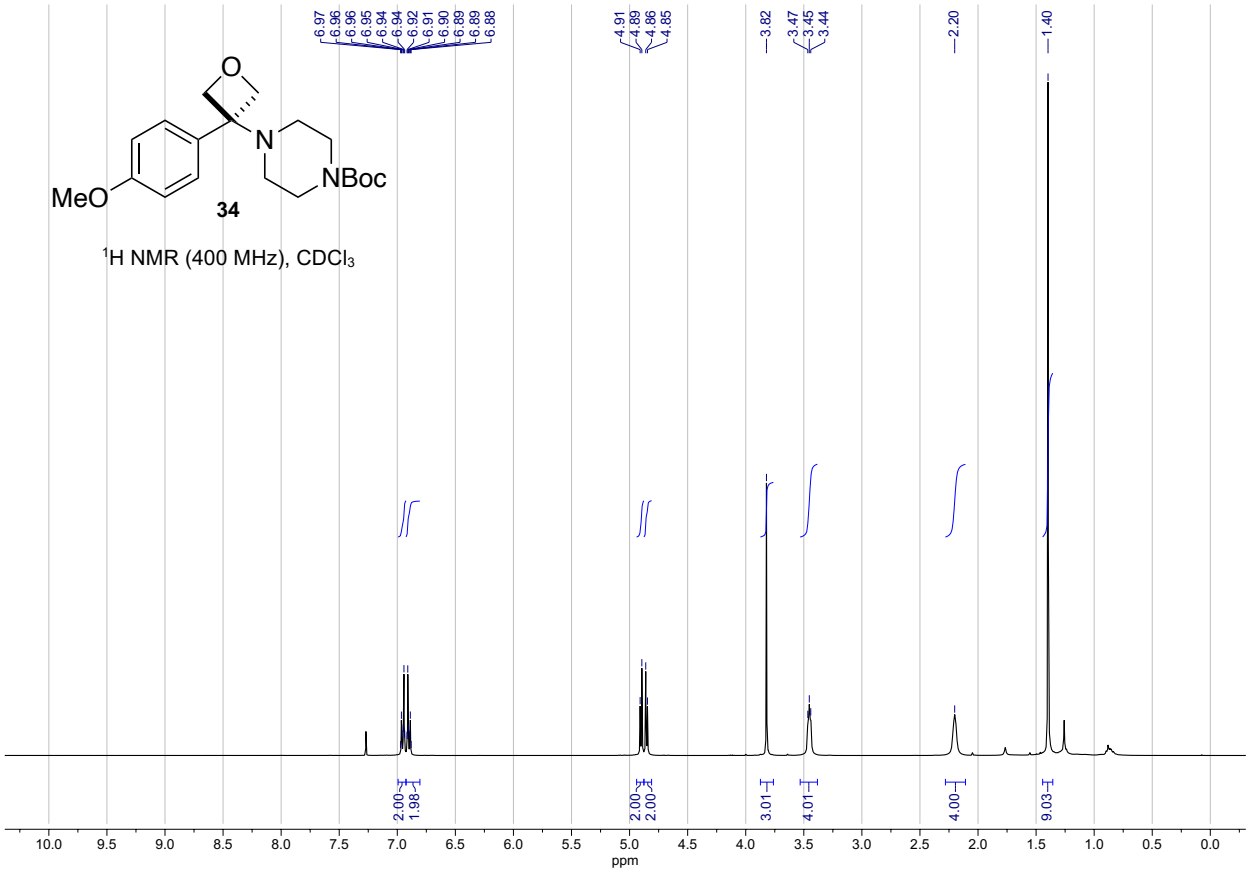

MeO
O
N
F
N
O
33
^{1}H NMR (400 MHz), $CDCl_3$
ppm

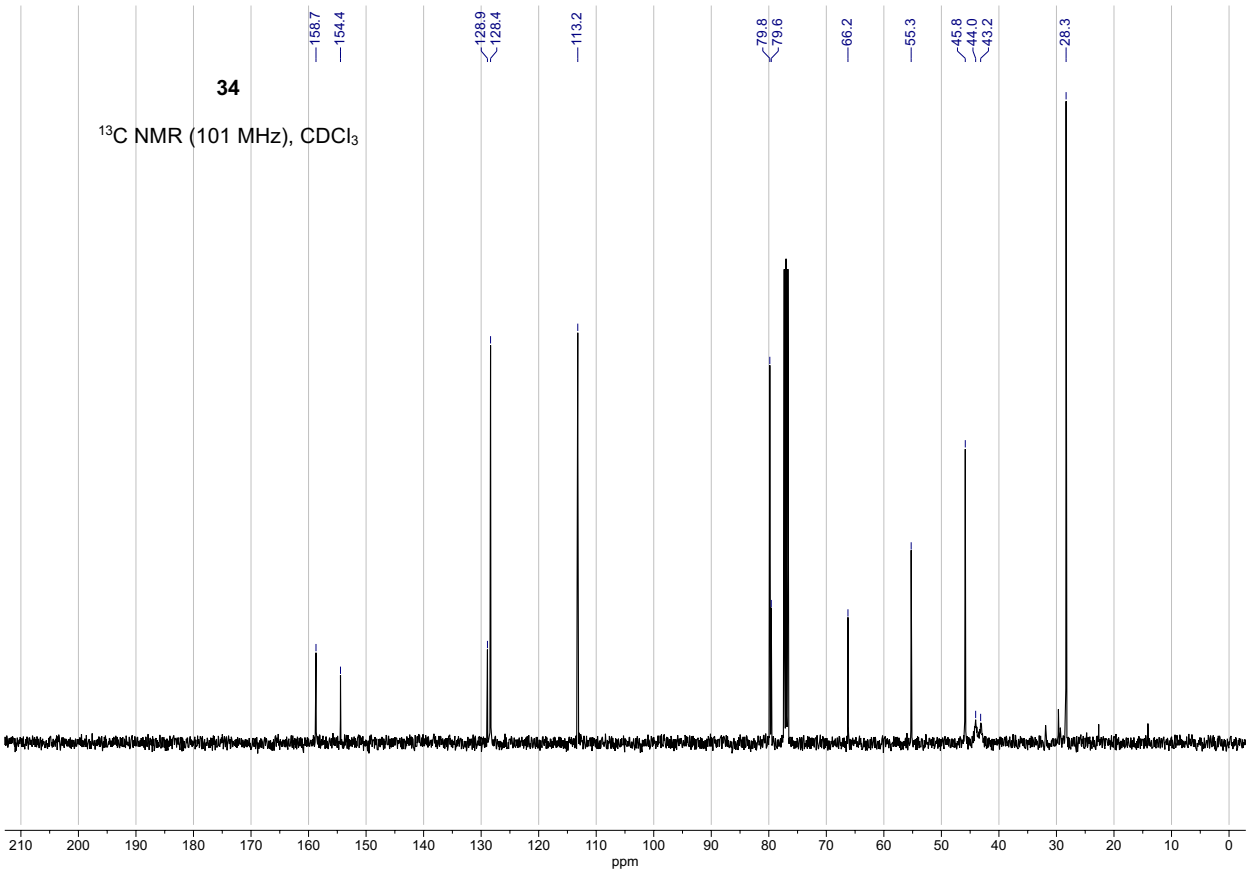

33
^{13}C NMR (101 MHz), $CDCl_3$
ppm

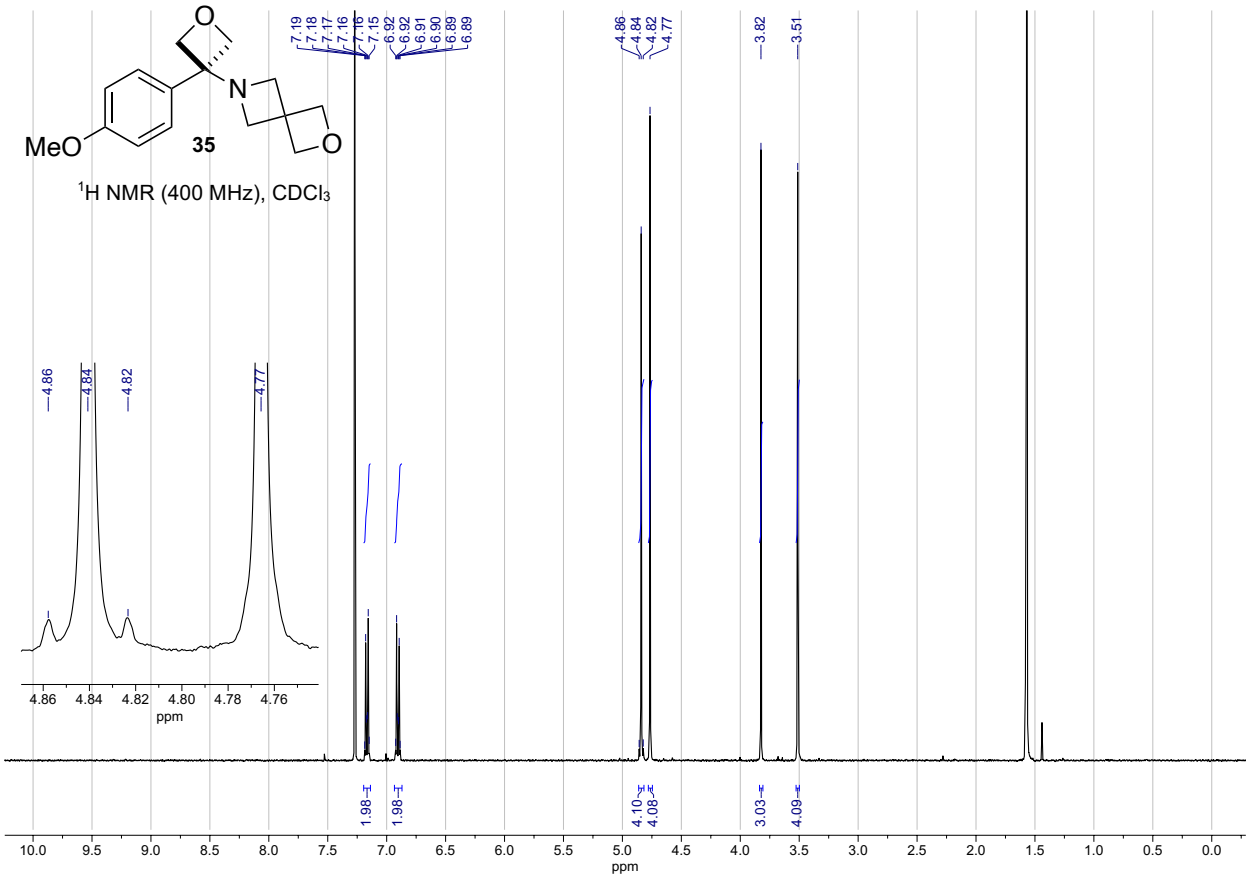
33

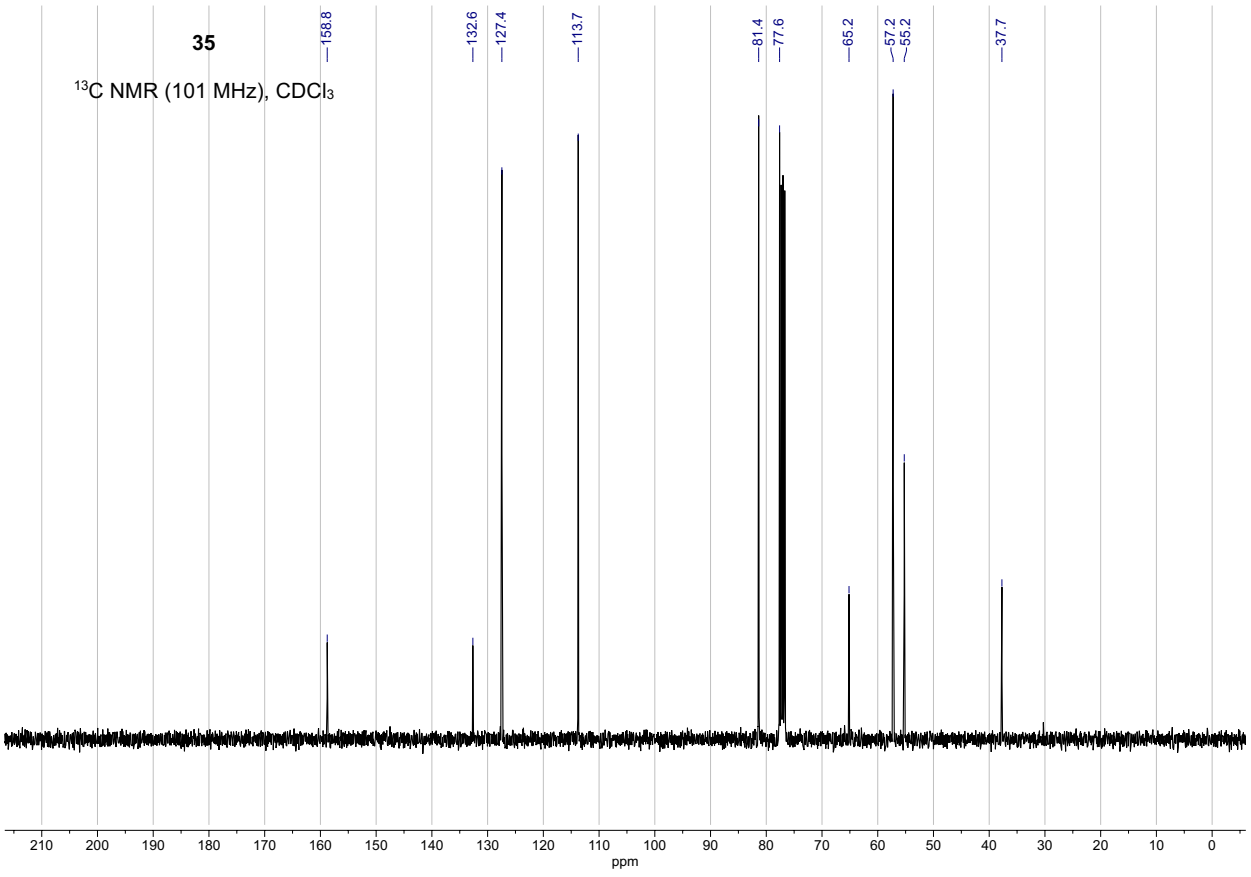
^{19}F NMR (377 MHz), $CDCl_3$

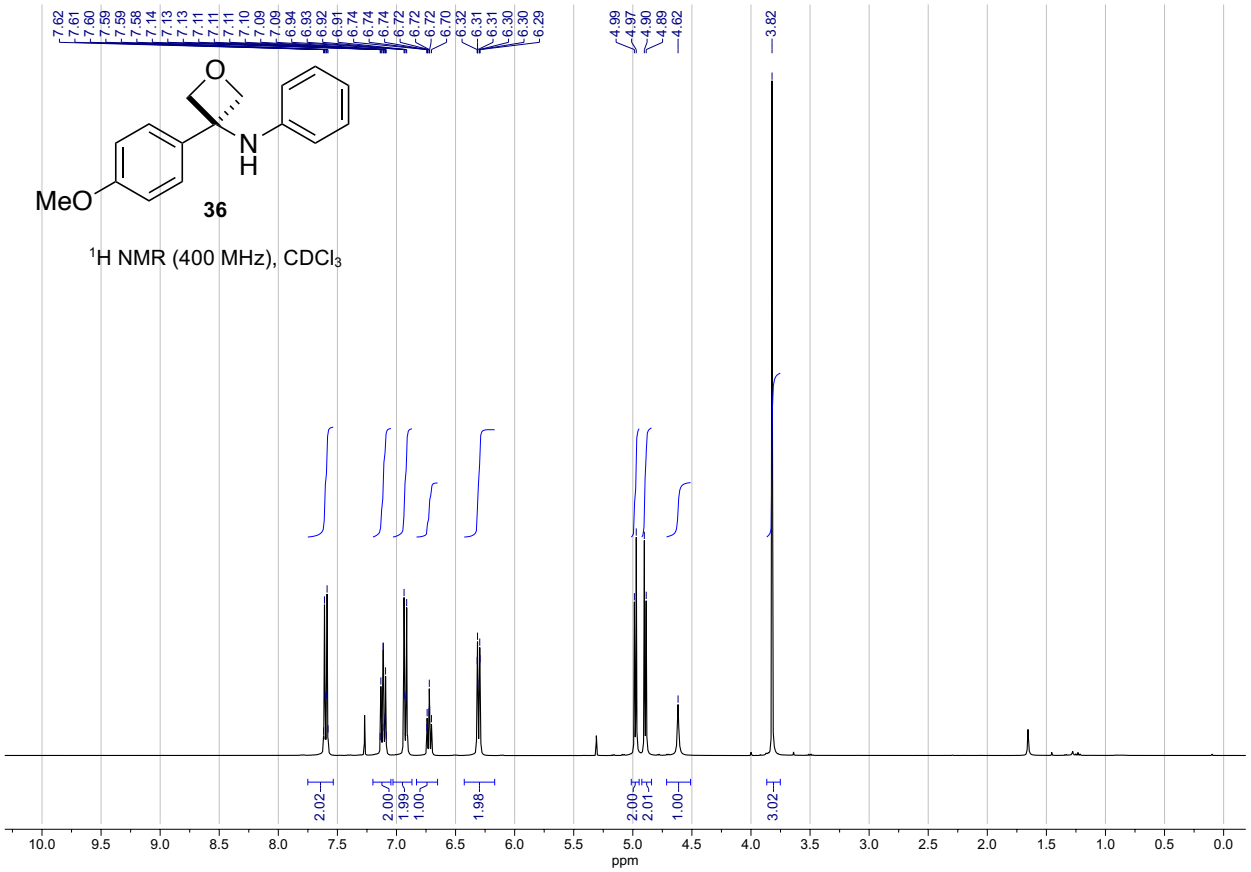


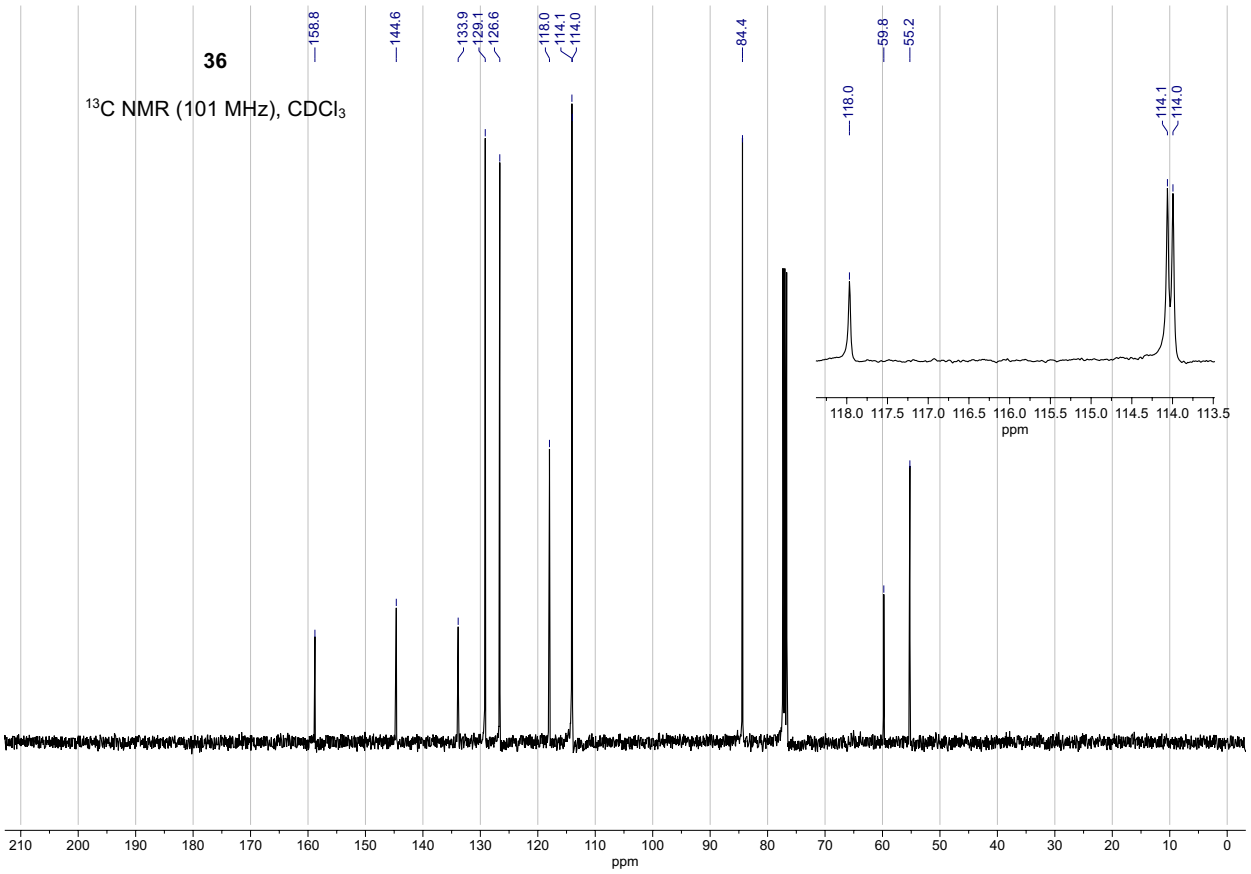

6.97
6.96
6.96
6.95
6.94
6.94
6.92
6.91
6.90
6.89
6.89
6.88
4.91
4.89
4.86
4.85
3.82
3.47
3.45
3.44
2.20
1.40
O
N
NBoc
MeO
34
^{1}H NMR (400 MHz), $CDCl_3$
2.00
1.98
2.00
2.00
3.01
4.01
4.00
9.03
ppm

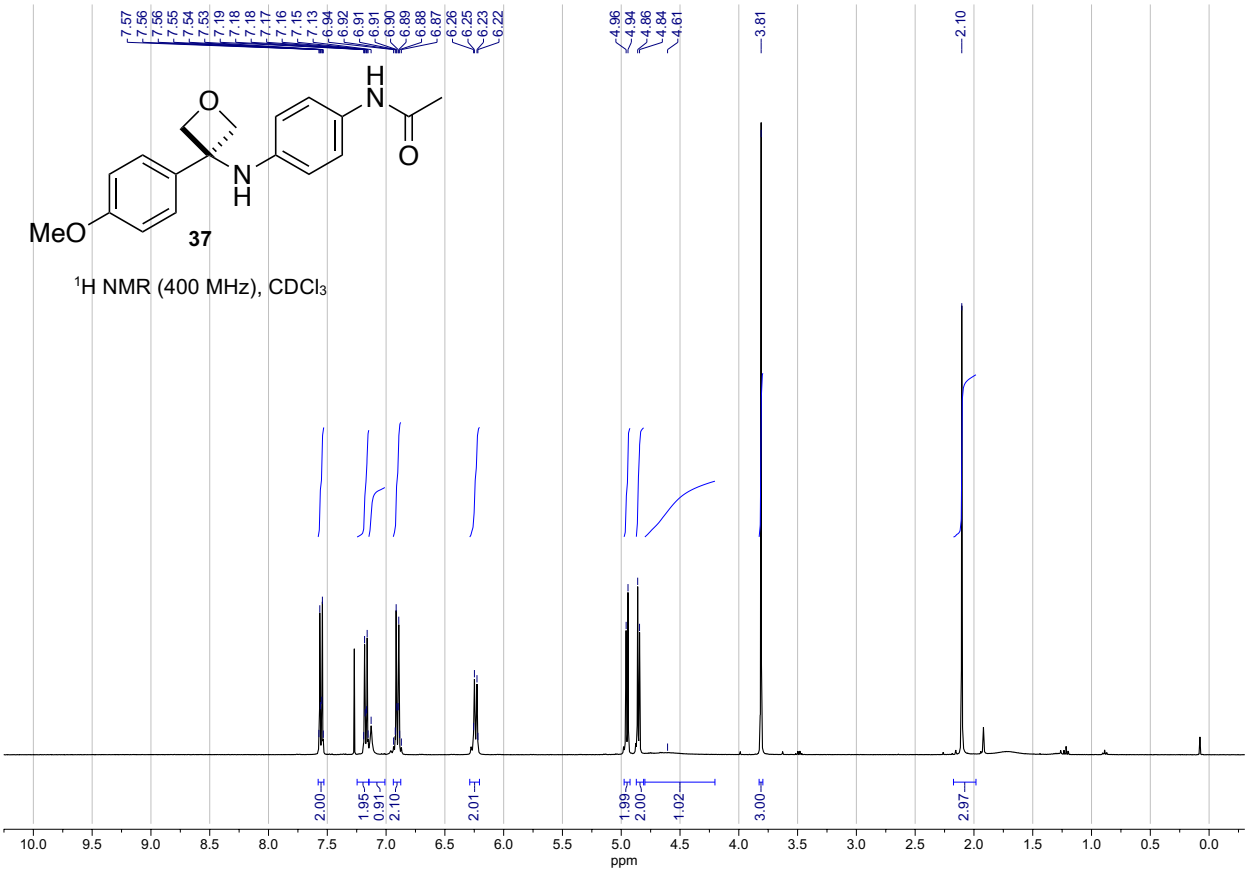

158.7
154.4
128.9
128.4
113.2
79.8
79.6
66.2
55.3
45.8
44.0
43.2
28.3
34
^{13}C NMR (101 MHz), $CDCl_3$
ppm

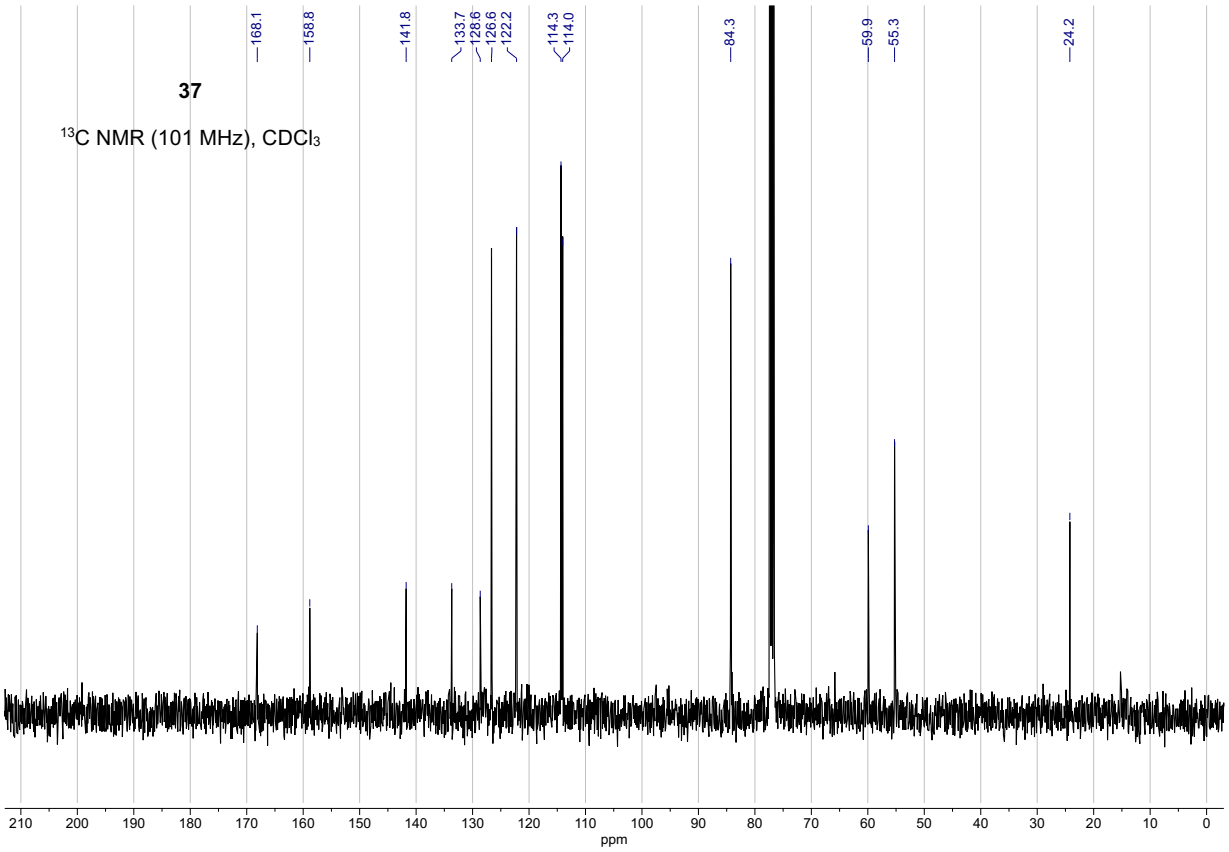

MeO
35
^{1}H NMR (400 MHz), CDCl$_3$
ppm

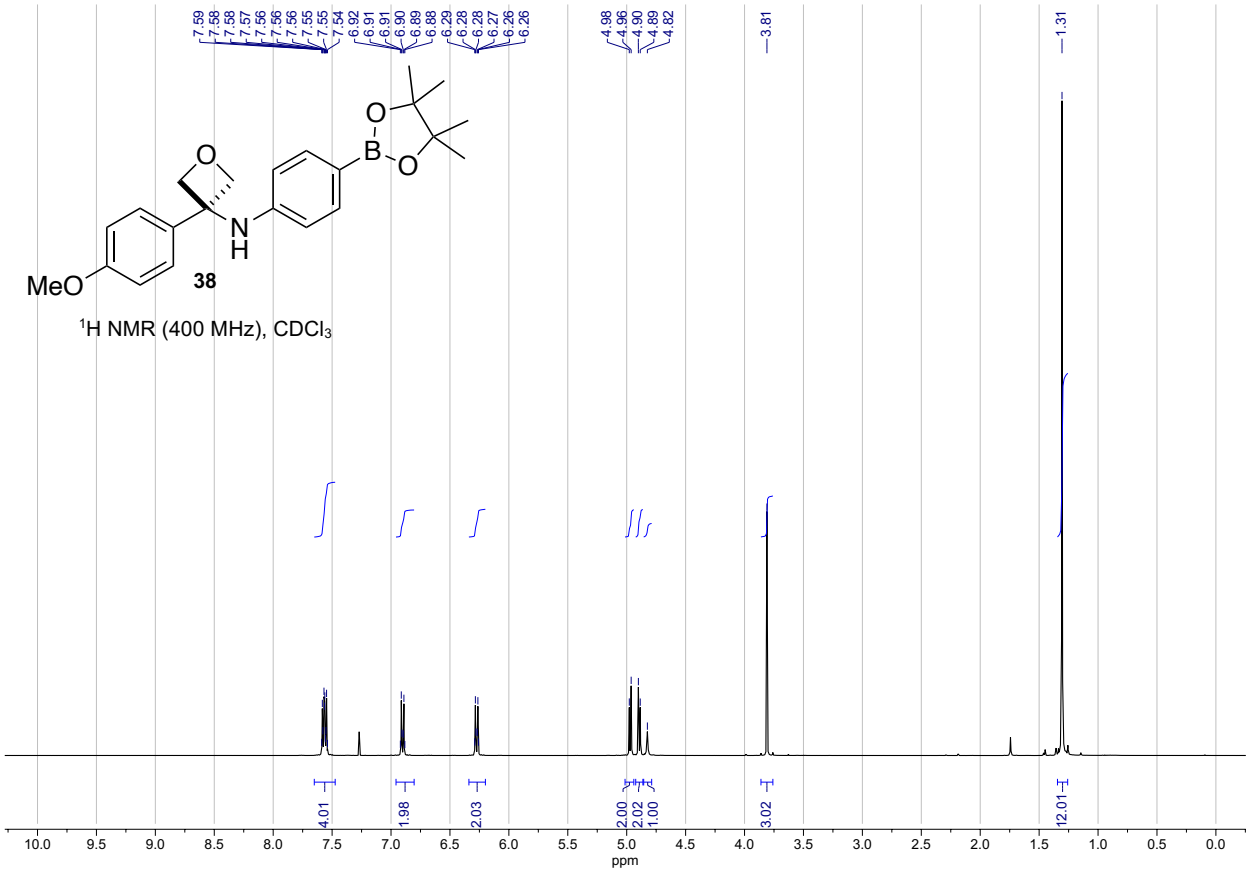

35
^{13}C NMR (101 MHz), CDCl$_3$
ppm

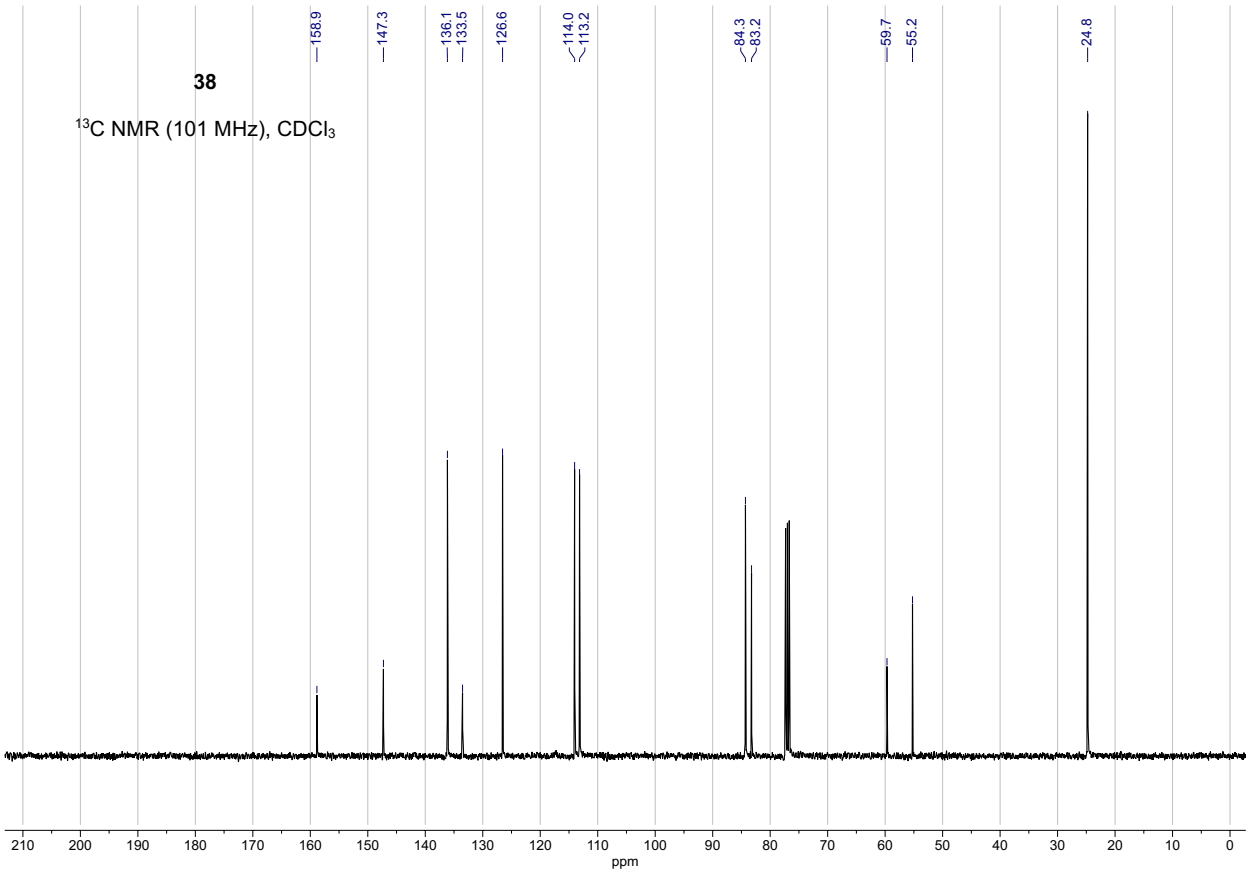

7.62
7.61
7.60
7.59
7.59
7.58
7.14
7.13
7.13
7.11
7.11
7.11
7.10
7.09
7.09
6.94
6.93
6.92
6.91
6.74
6.74
6.74
6.72
6.72
6.72
6.70
6.32
6.31
6.31
6.30
6.30
6.29
4.99
4.97
4.90
4.89
4.62
3.82
O
N
H
MeO
36
^{1}H NMR (400 MHz), CDCl$_3$
2.02
2.00
1.99
1.00
1.98
2.00
2.01
1.00
3.02
10.0 9.5 9.0 8.5 8.0 7.5 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

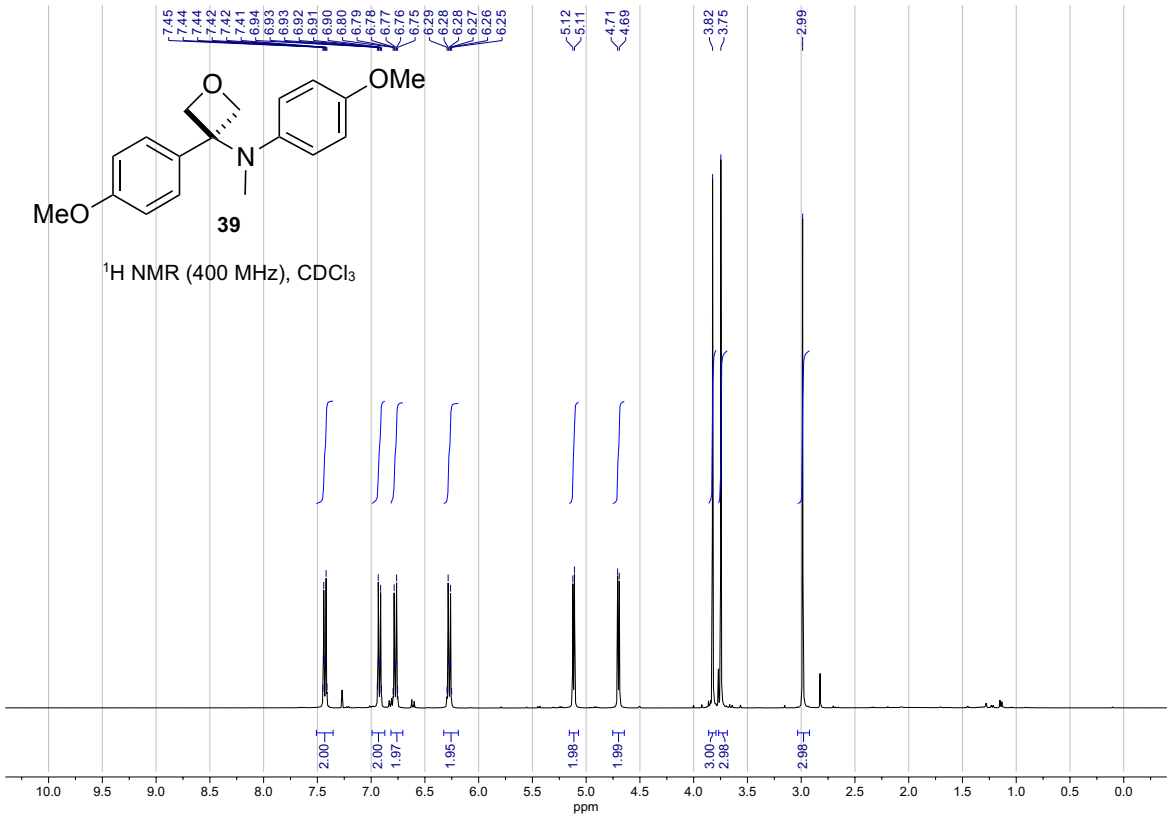

36
^{13}C NMR (101 MHz), CDCl$_3$
158.8
144.6
133.9
129.1
126.6
118.0
114.1
114.0
84.4
59.8
55.2
118.0
114.1
114.0
118.0 117.5 117.0 116.5 116.0 115.5 115.0 114.5 114.0 113.5
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

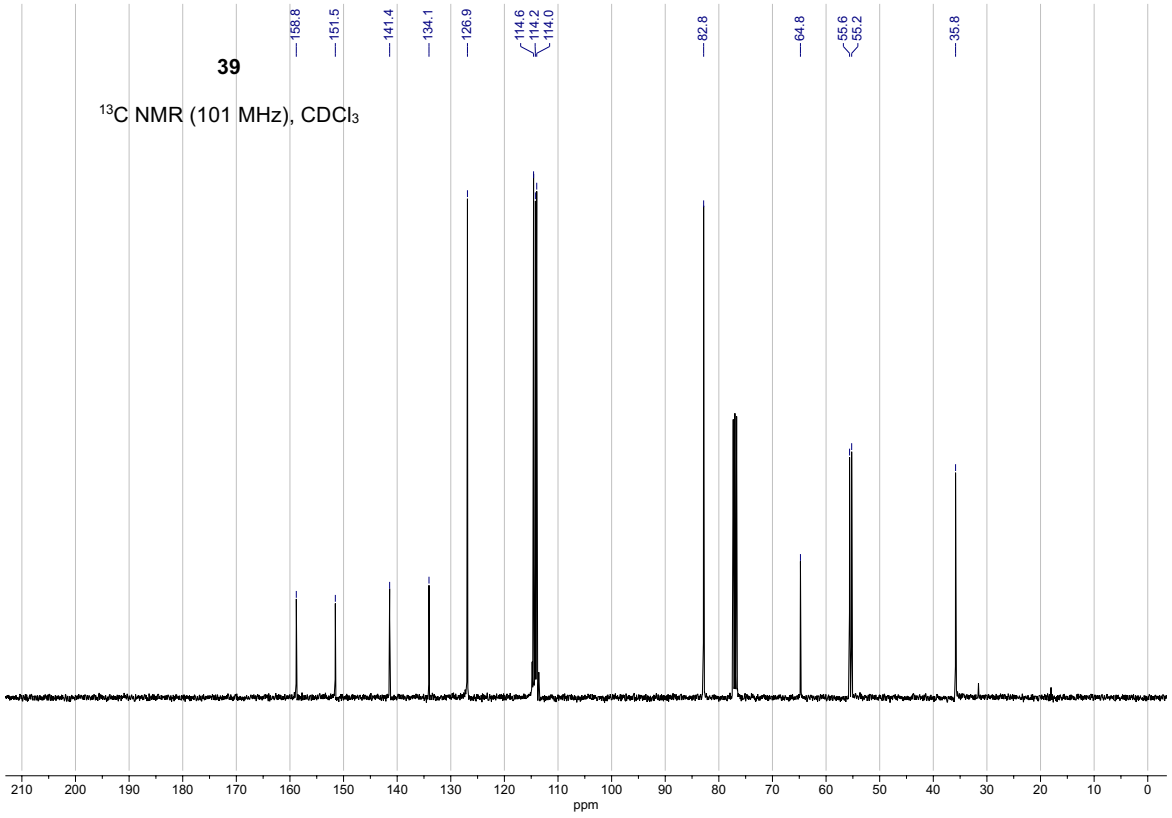

7.57
7.56
7.56
7.55
7.54
7.53
7.19
7.18
7.18
7.17
7.16
7.15
7.13
6.94
6.92
6.91
6.91
6.90
6.89
6.88
6.87
6.26
6.25
6.23
6.22
4.96
4.94
4.86
4.84
4.61
3.81
2.10
H
N
O
O
N
H
MeO
37
^{1}H NMR (400 MHz), $CDCl_3$
2.00
1.95
0.91
2.10
2.01
1.99
2.00
1.02
3.00
2.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

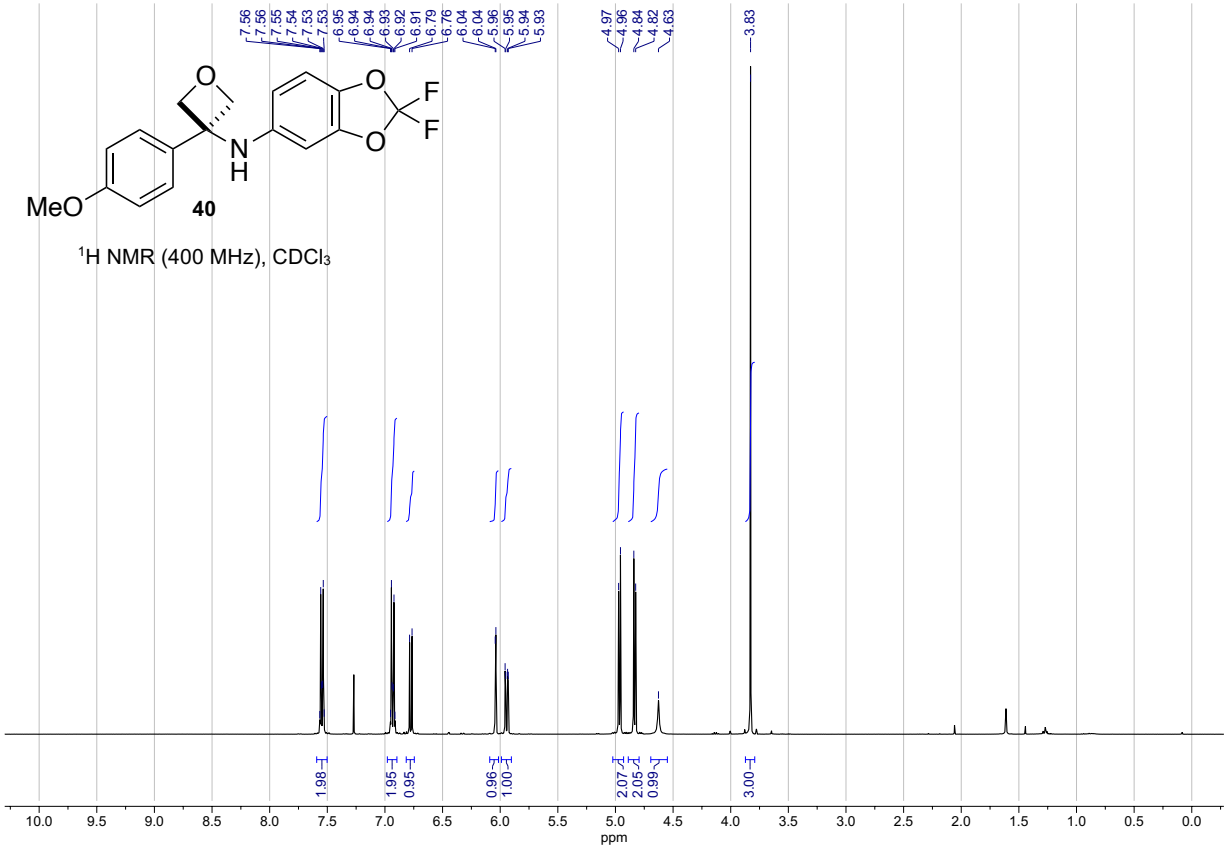

168.1
158.8
141.8
133.7
128.6
126.6
122.2
114.3
114.0
84.3
59.9
55.3
24.2
37
^{13}C NMR (101 MHz), $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

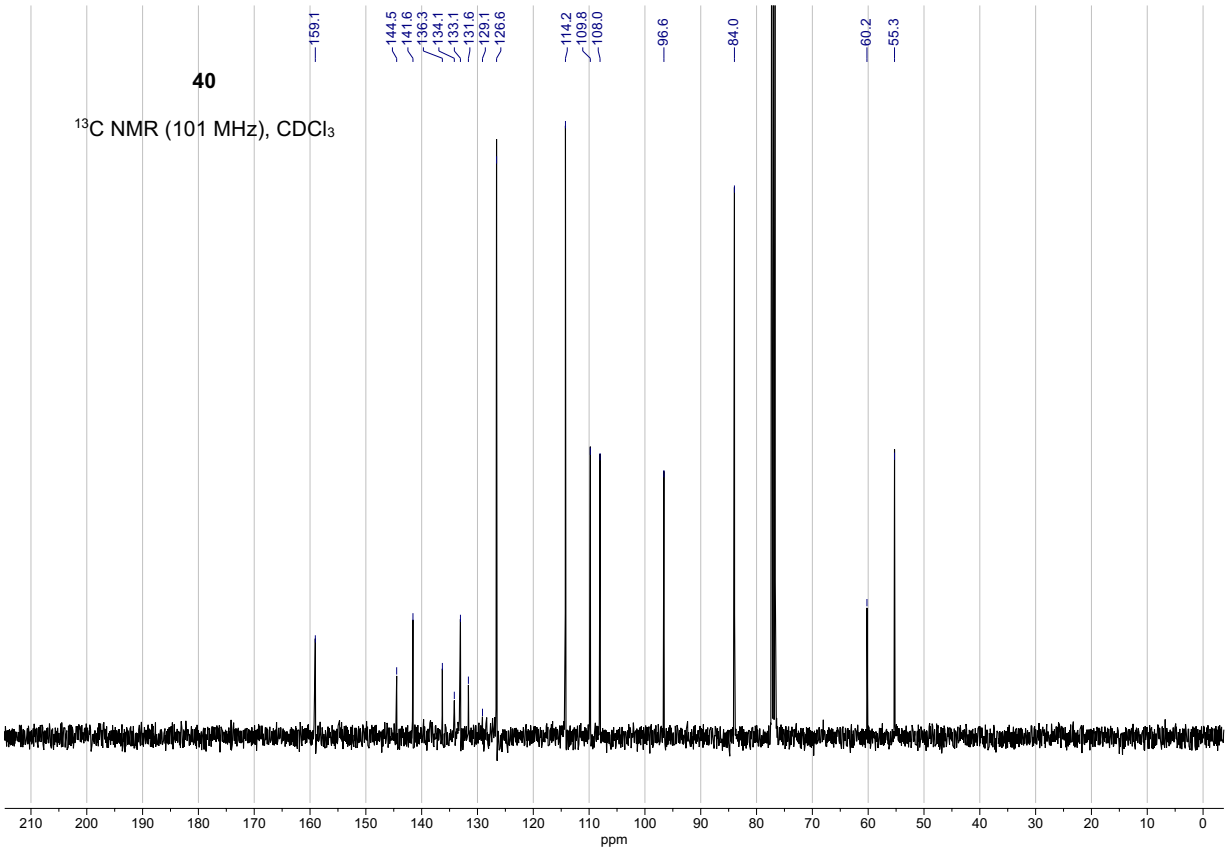

7.59
7.58
7.58
7.57
7.56
7.56
7.56
7.55
7.55
7.54
6.92
6.91
6.91
6.90
6.89
6.88
6.29
6.28
6.28
6.27
6.26
6.26
4.98
4.96
4.90
4.89
4.82
3.81
1.31
O
B
O
O
N
H
MeO
38
^{1}H NMR (400 MHz), $CDCl_3$
4.01
1.98
2.03
2.00
2.02
1.00
3.02
12.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

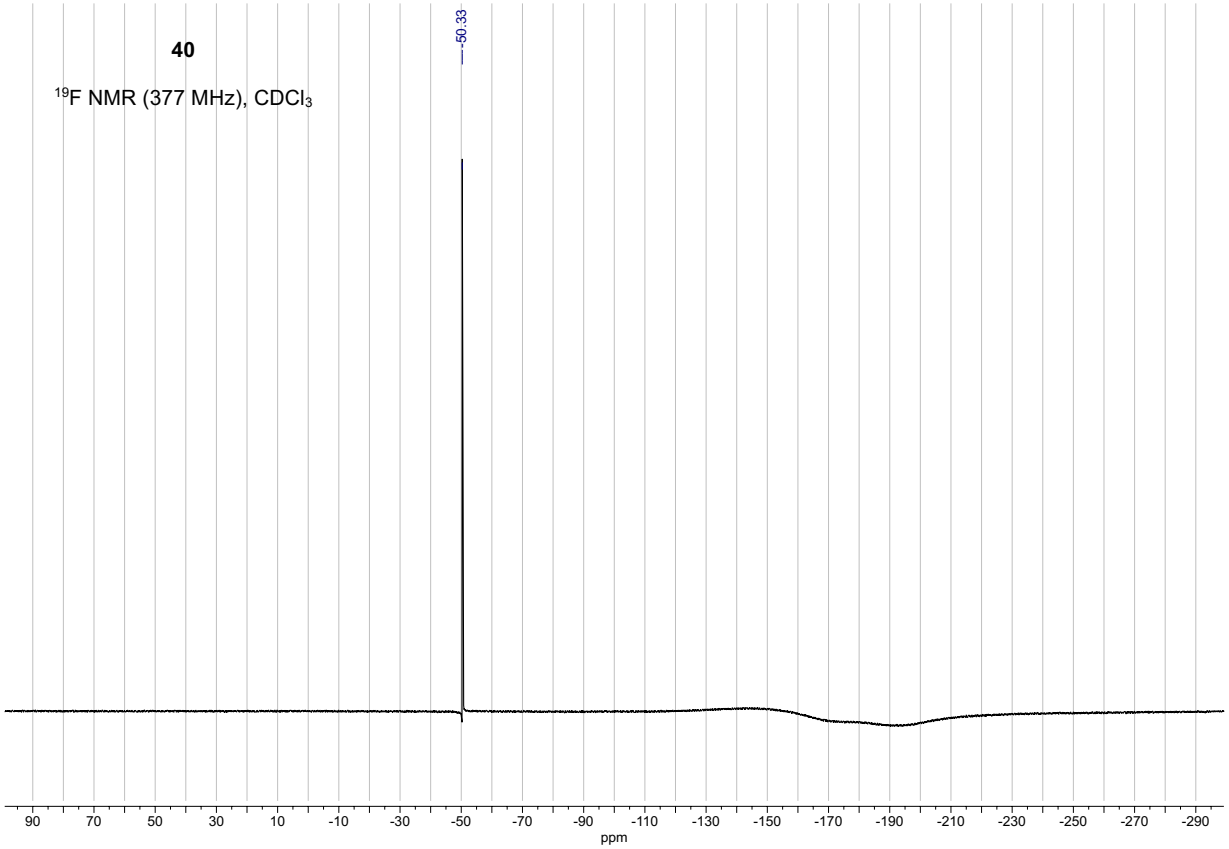

158.9
147.3
136.1
133.5
126.6
114.0
113.2
84.3
83.2
59.7
55.2
24.8
38
^{13}C NMR (101 MHz), $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

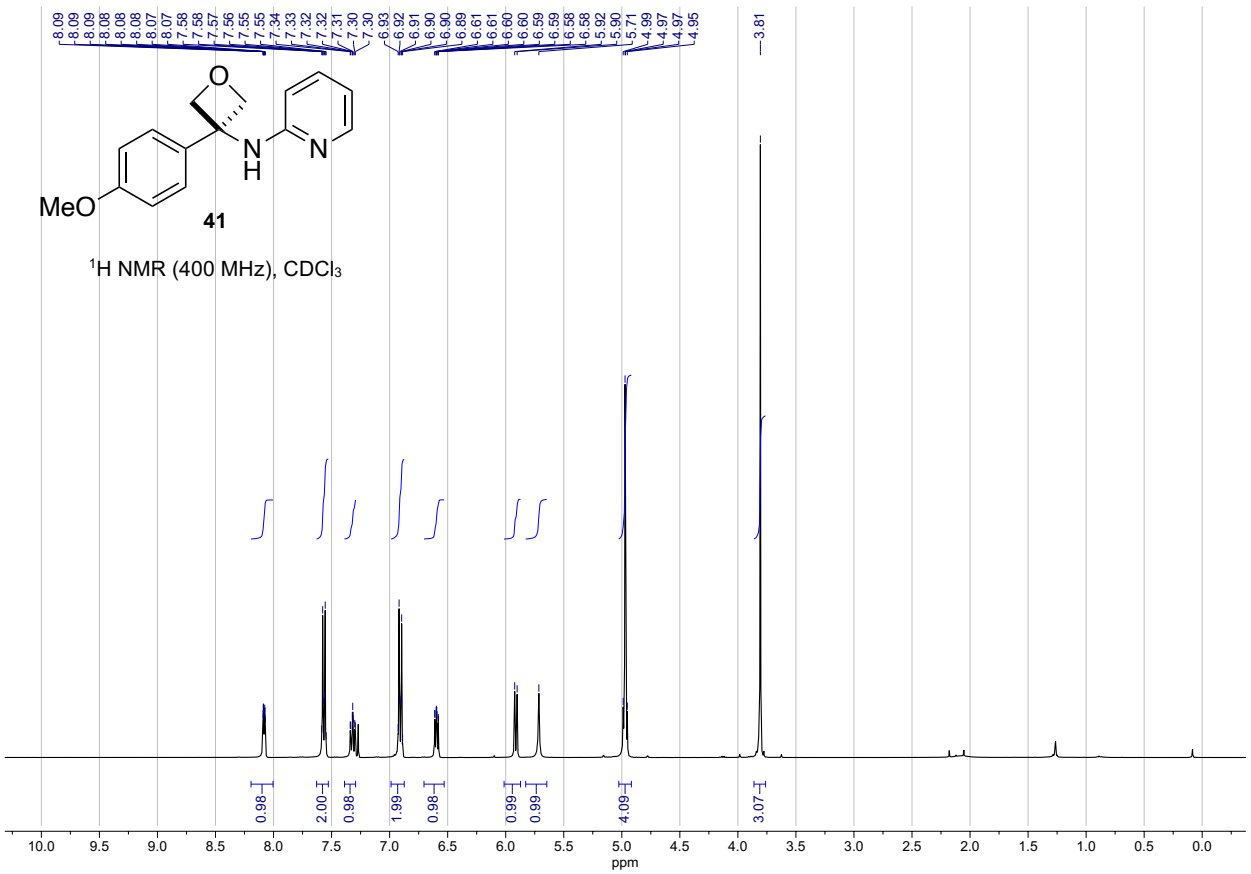

7.45
7.44
7.44
7.42
7.42
7.41
6.94
6.93
6.93
6.92
6.91
6.90
6.80
6.79
6.78
6.77
6.76
6.75
6.29
6.28
6.28
6.27
6.26
6.25
5.12
5.11
4.71
4.69
3.82
3.75
2.99
O
OMe
N
MeO
39
^{1}H NMR (400 MHz), CDCl$_3$
2.00
2.00
1.97
1.95
1.98
1.99
3.00
2.98
2.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

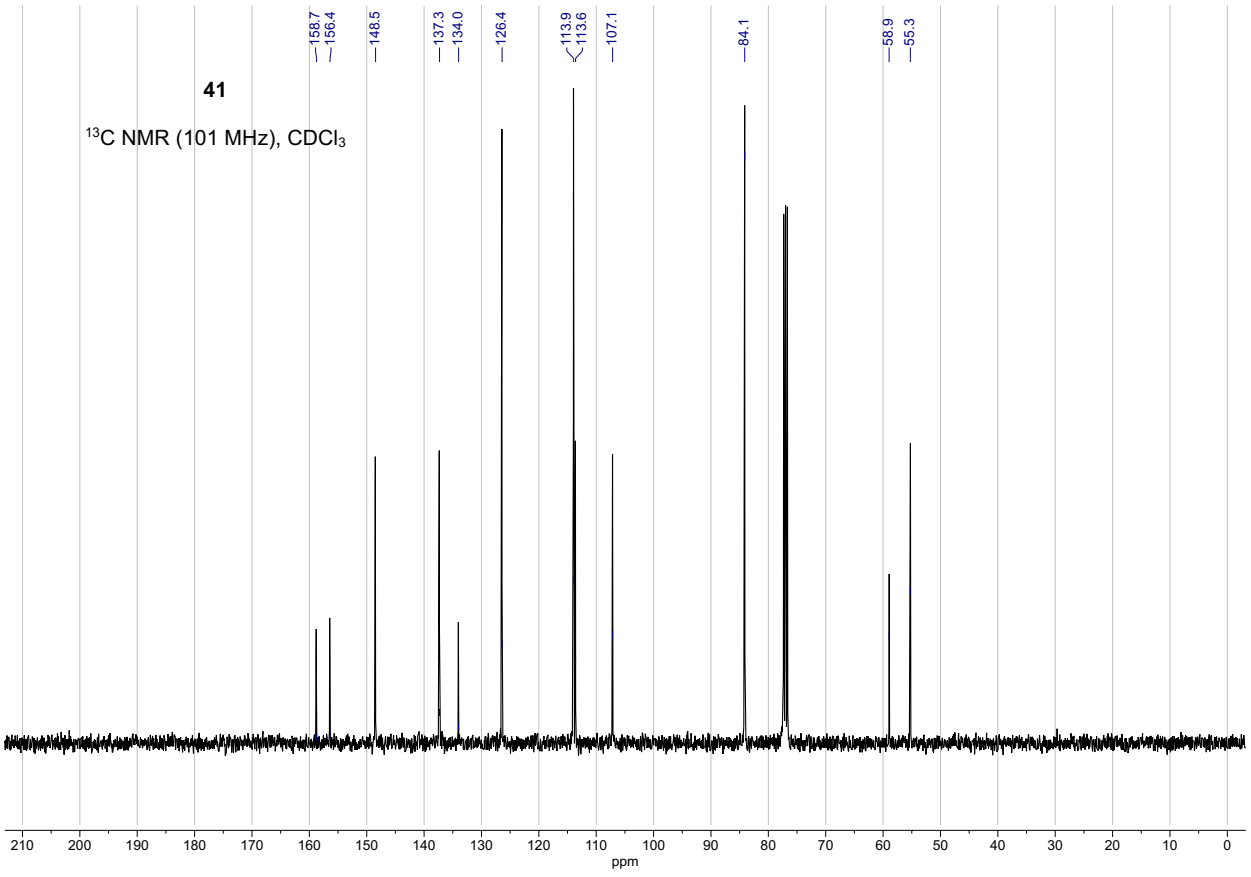

158.8
151.5
141.4
134.1
126.9
114.6
114.2
114.0
82.8
64.8
55.6
55.2
35.8
39
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

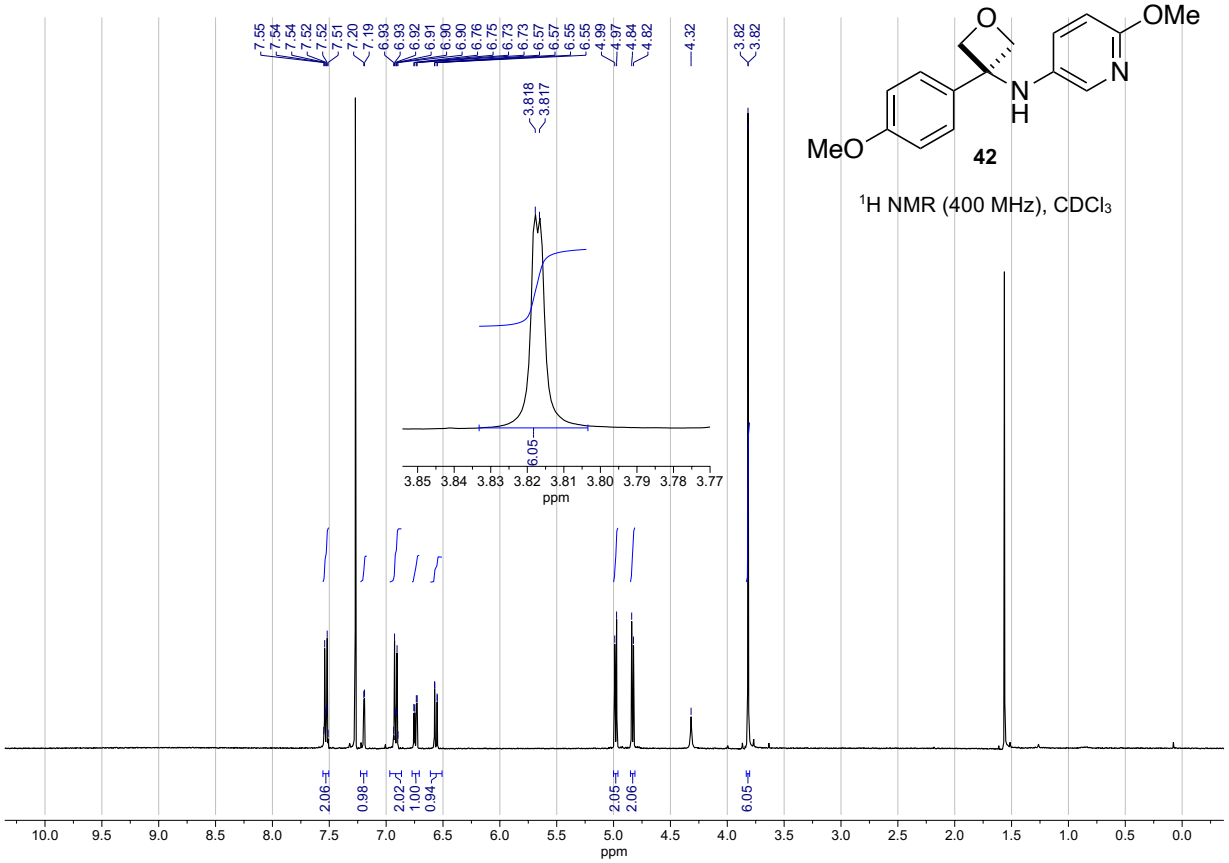

7.56
7.56
7.55
7.54
7.53
7.53
6.95
6.94
6.94
6.93
6.92
6.91
6.79
6.76
6.04
6.04
5.96
5.95
5.94
5.93
4.97
4.96
4.84
4.82
4.63
3.83
O
O
F
F
O
N
H
MeO
40
^{1}H NMR (400 MHz), CDCl$_3$
1.98
1.95
0.95
0.96
1.00
2.07
2.05
0.99
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

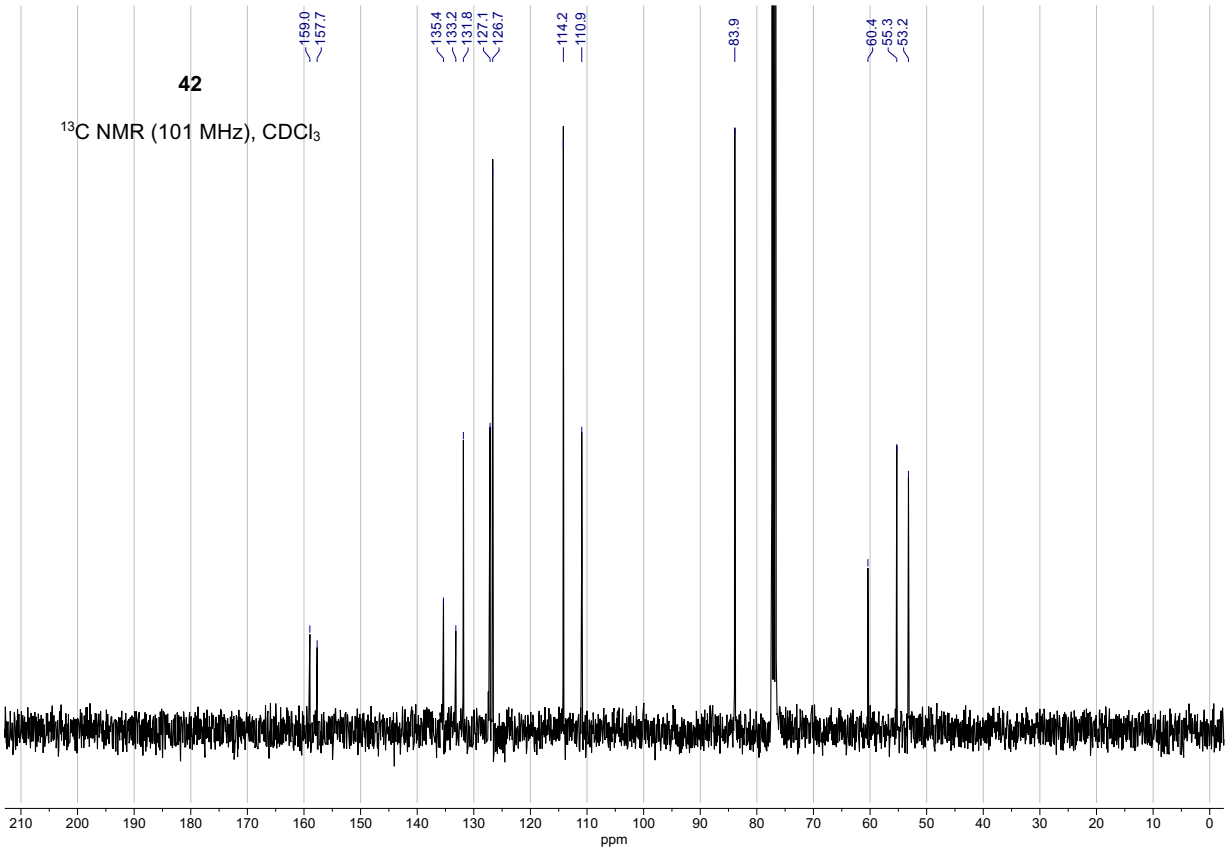

159.1
144.5
141.6
136.3
134.1
133.1
131.6
129.1
126.6
114.2
109.8
108.0
96.6
84.0
60.2
55.3
40
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

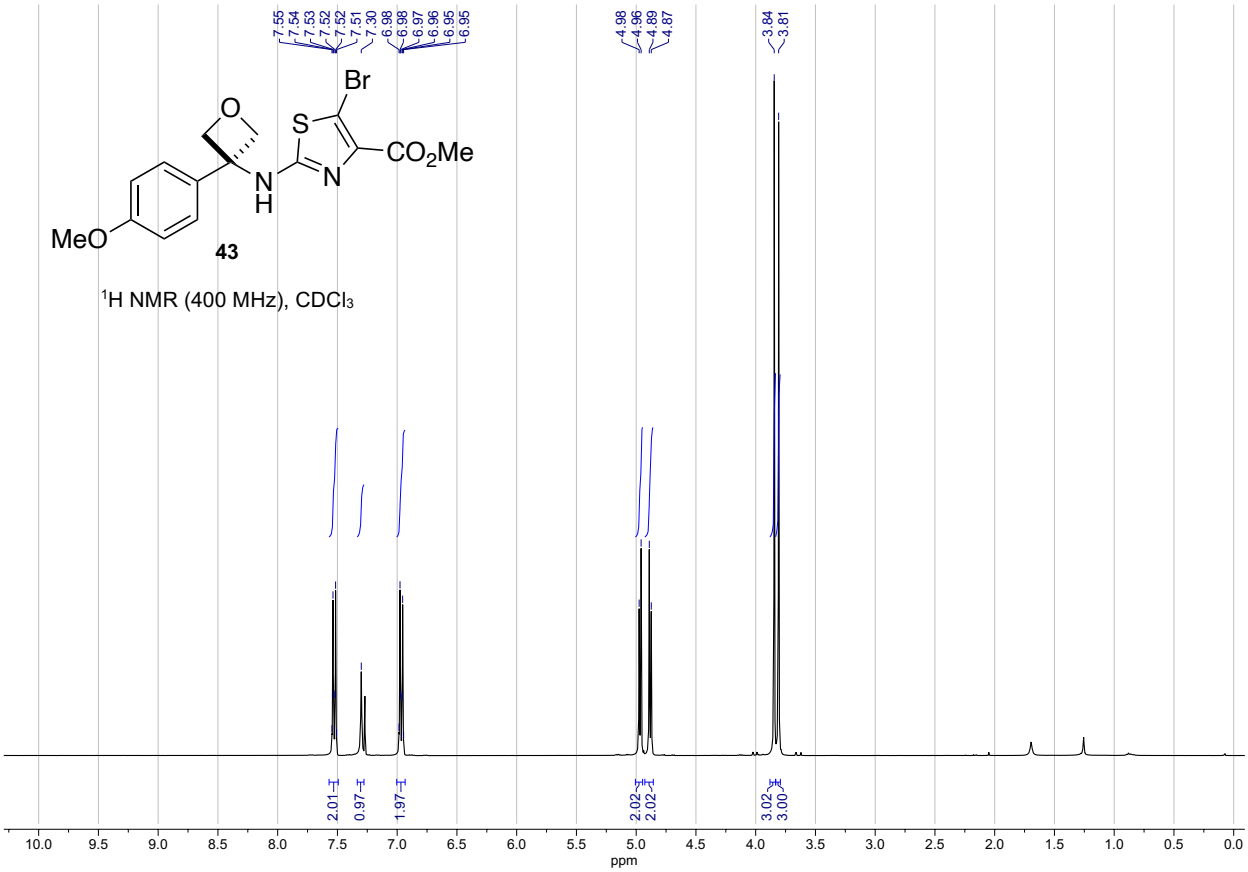

40
^{19}F NMR (377 MHz), $CDCl_3$
-50.33
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290
ppm

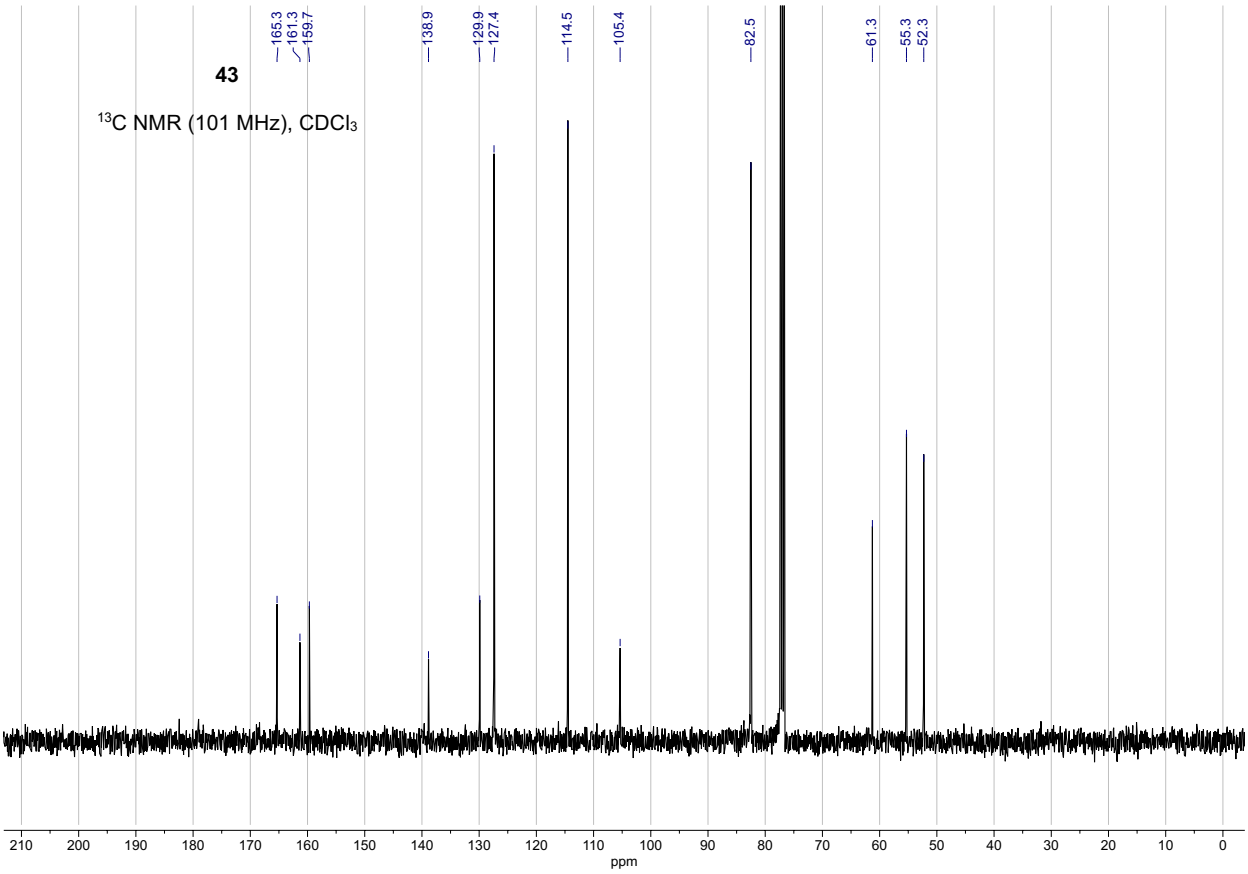

MeO
O
N
H
N
41
^{1}H NMR (400 MHz), CDCl$_3$
ppm

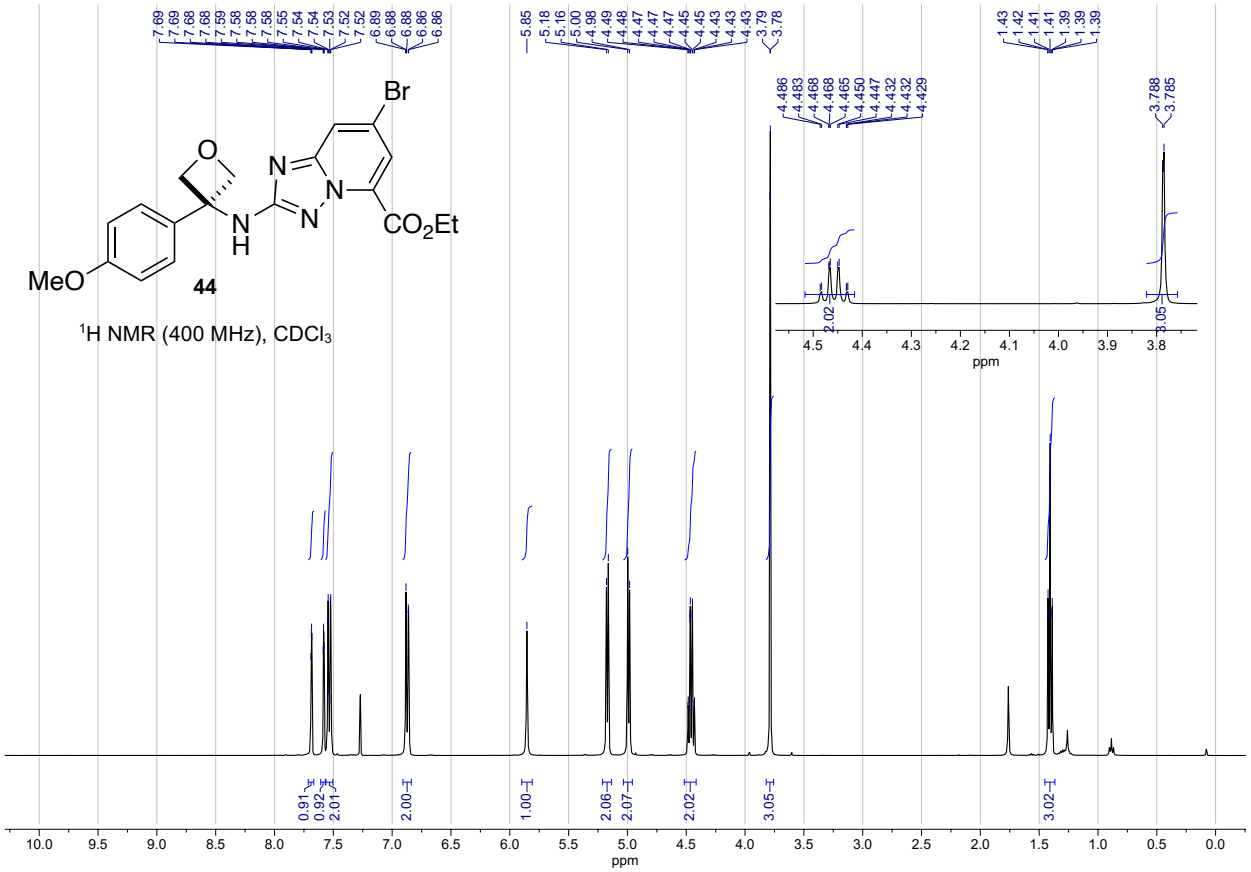

41
^{13}C NMR (101 MHz), CDCl$_3$
ppm

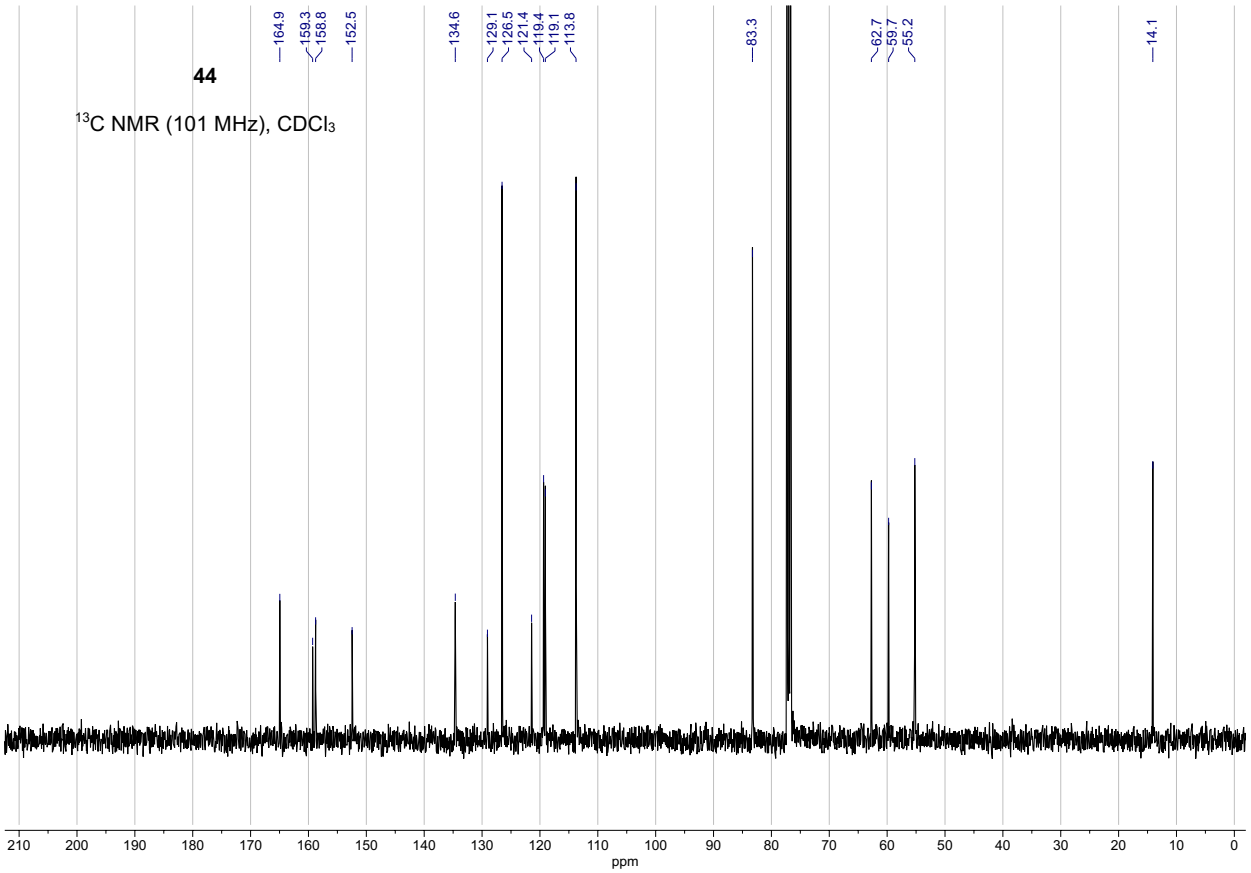

7.55
7.54
7.54
7.52
7.52
7.51
7.20
7.19
6.93
6.93
6.92
6.91
6.90
6.90
6.76
6.75
6.73
6.73
6.57
6.57
6.55
6.55
4.99
4.97
4.84
4.82
4.32
3.82
3.82
3.818
3.817
6.05
3.85 3.84 3.83 3.82 3.81 3.80 3.79 3.78 3.77
ppm
2.06
0.98
2.02
1.00
0.94
2.05
2.06
6.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
O
OMe
N
H
N
MeO
42
^{1}H NMR (400 MHz), $CDCl_3$

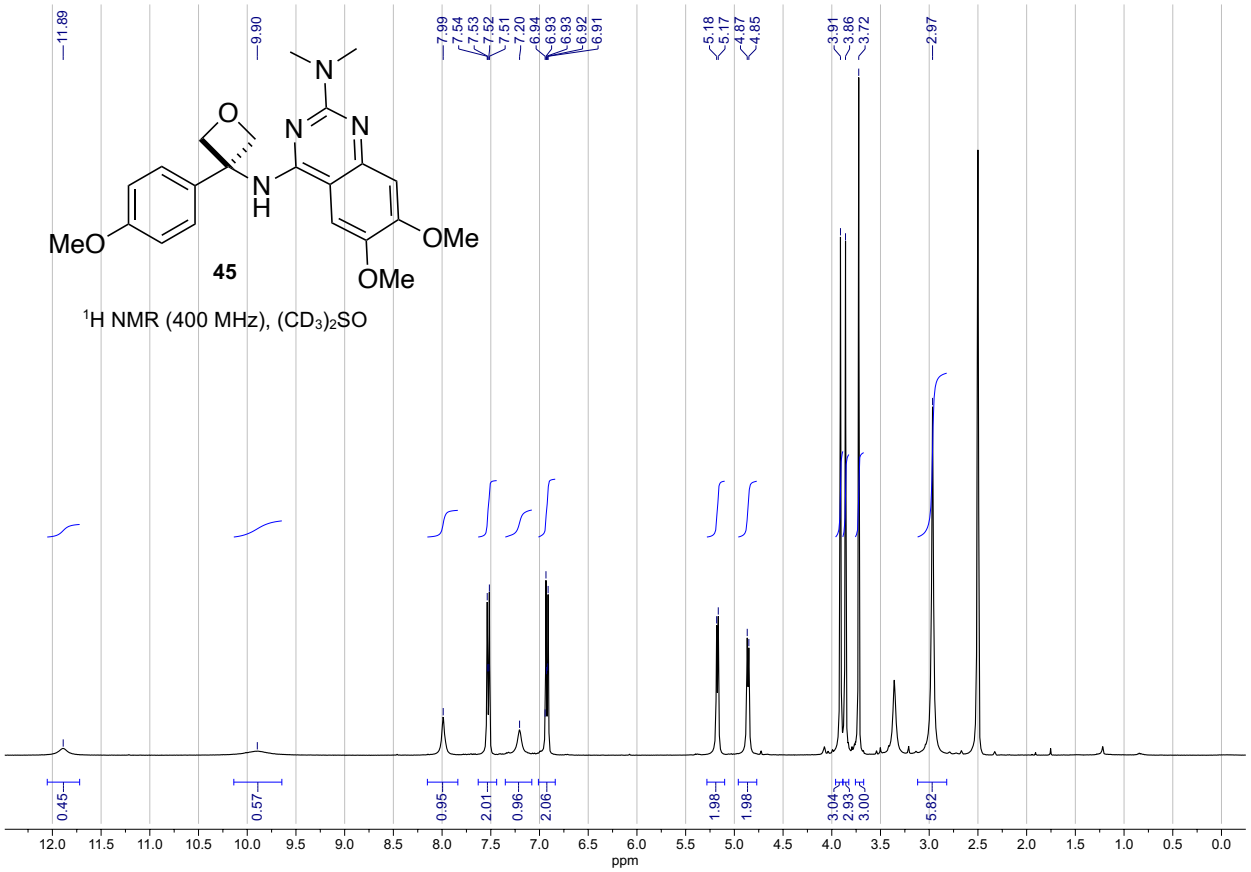

159.0
157.7
135.4
133.2
131.8
127.1
126.7
114.2
110.9
83.9
60.4
55.3
53.2
42
^{13}C NMR (101 MHz), $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

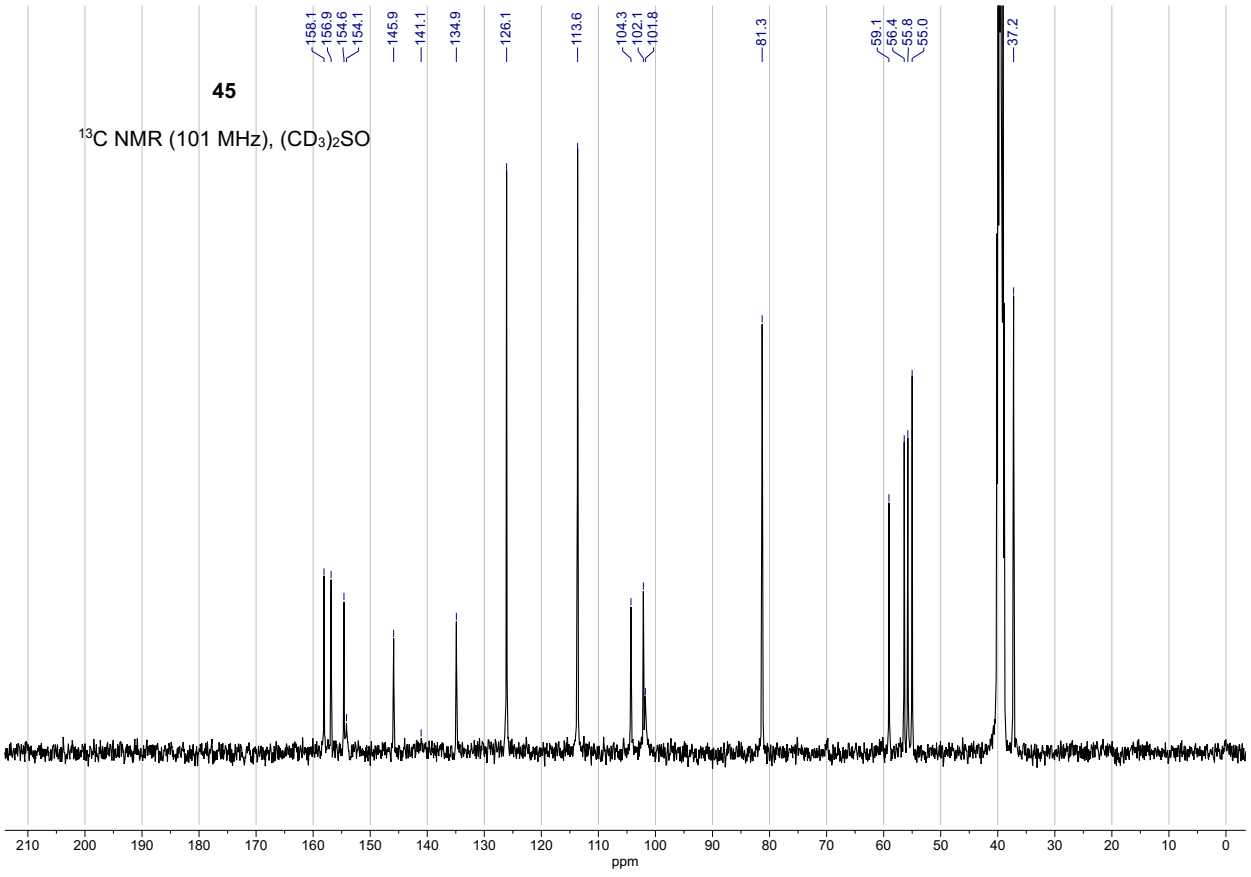

7.55
7.54
7.53
7.52
7.52
7.51
7.30
6.98
6.98
6.97
6.96
6.95
6.95
4.98
4.96
4.89
4.87
3.84
3.81
Br
O
S
CO2Me
N
N
H
MeO
43
1H NMR (400 MHz), CDCl3
2.01
0.97
1.97
2.02
2.02
3.02
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

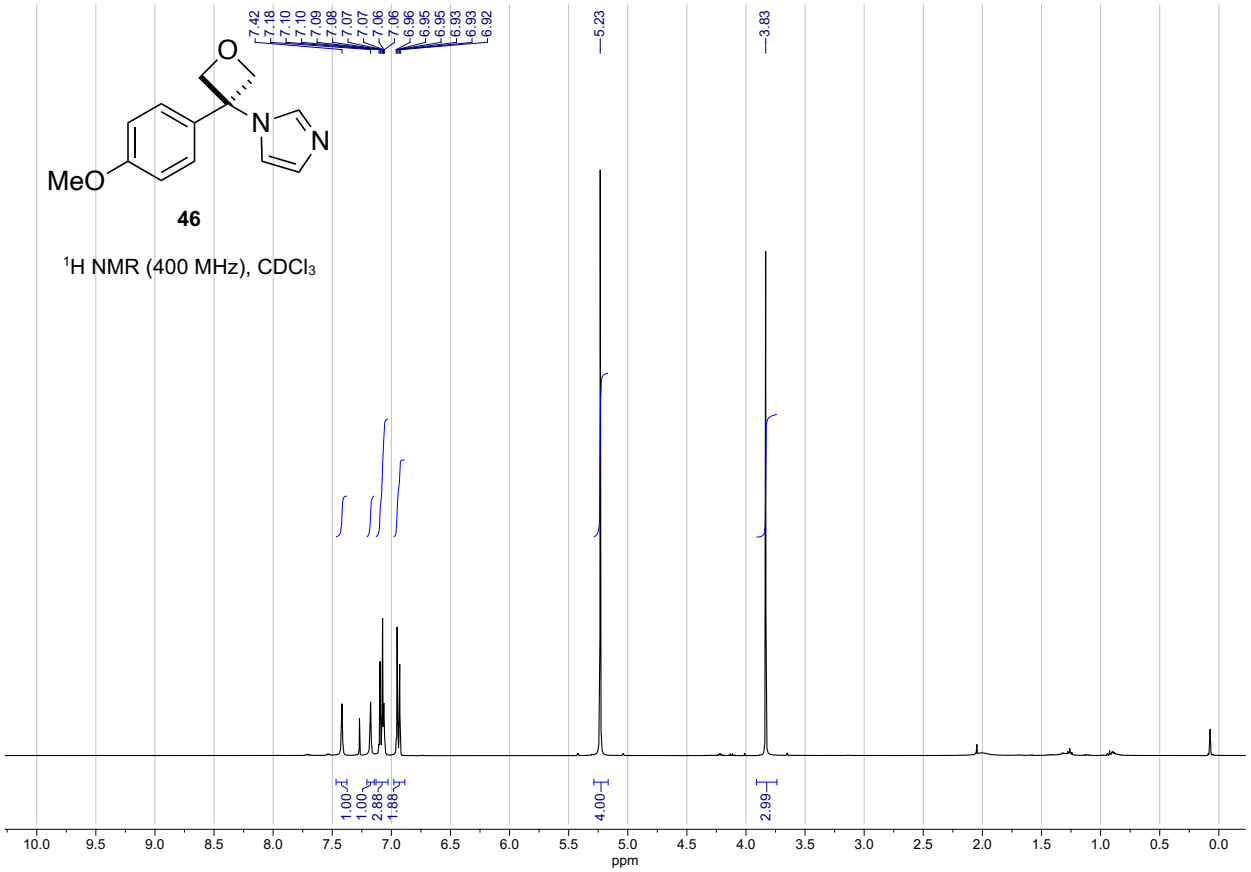

165.3
161.3
159.7
138.9
129.9
127.4
114.5
105.4
82.5
61.3
55.3
52.3
43
13C NMR (101 MHz), CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


Br
O
N
N
N
N
H
CO2Et
MeO
44
1H NMR (400 MHz), CDCl3
ppm


44
13C NMR (101 MHz), CDCl3
ppm

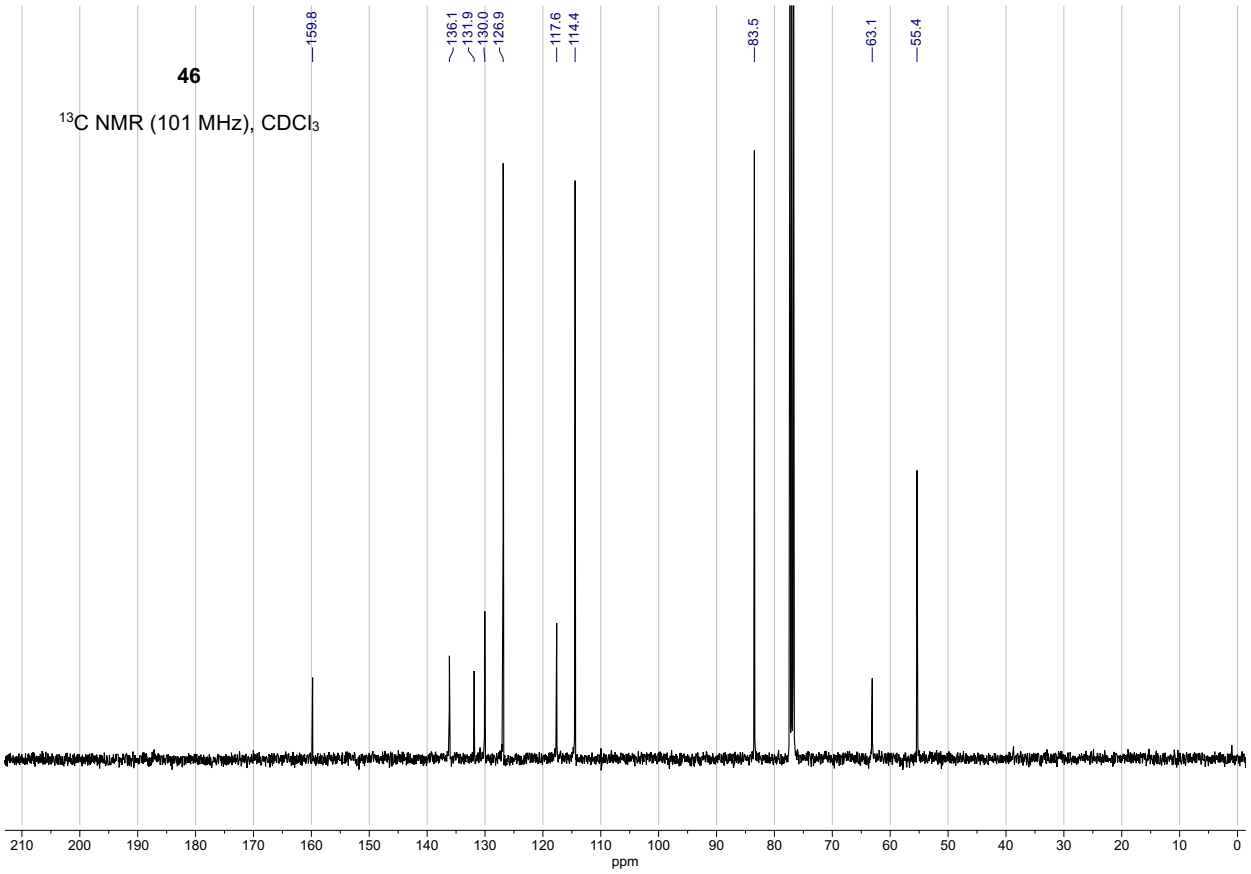

11.89
9.90
7.99
7.54
7.53
7.52
7.51
7.20
6.94
6.93
6.93
6.92
6.91
5.18
5.17
4.87
4.85
3.91
3.86
3.72
2.97
MeO
OMe
OMe
45
^{1}H NMR (400 MHz), $(CD_3)_2SO$
0.45
0.57
0.95
2.01
0.96
2.06
1.98
1.98
3.04
2.93
3.00
5.82
ppm


158.1
156.9
154.6
154.1
145.9
141.1
134.9
126.1
113.6
104.3
102.1
101.8
81.3
59.1
56.4
55.8
55.0
37.2
45
^{13}C NMR (101 MHz), $(CD_3)_2SO$
ppm



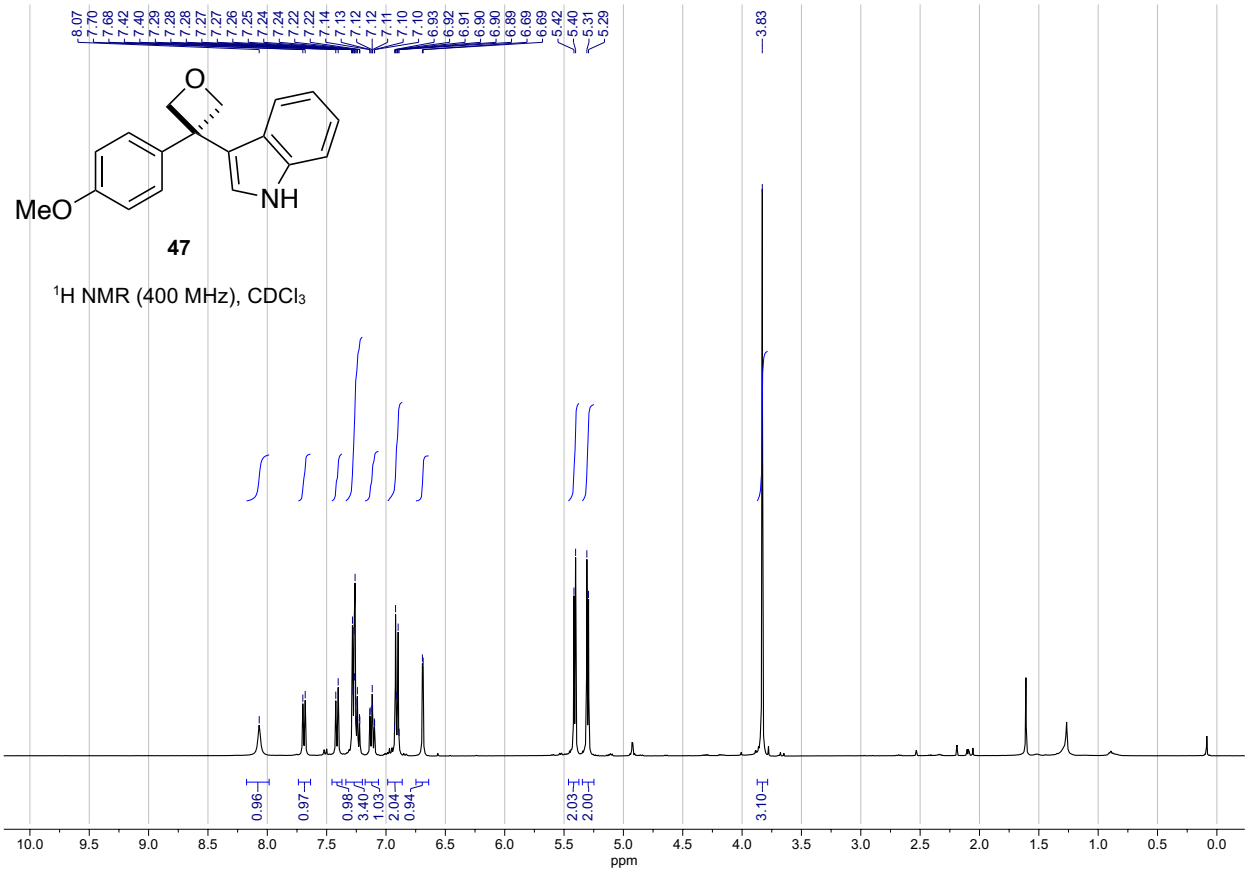
46

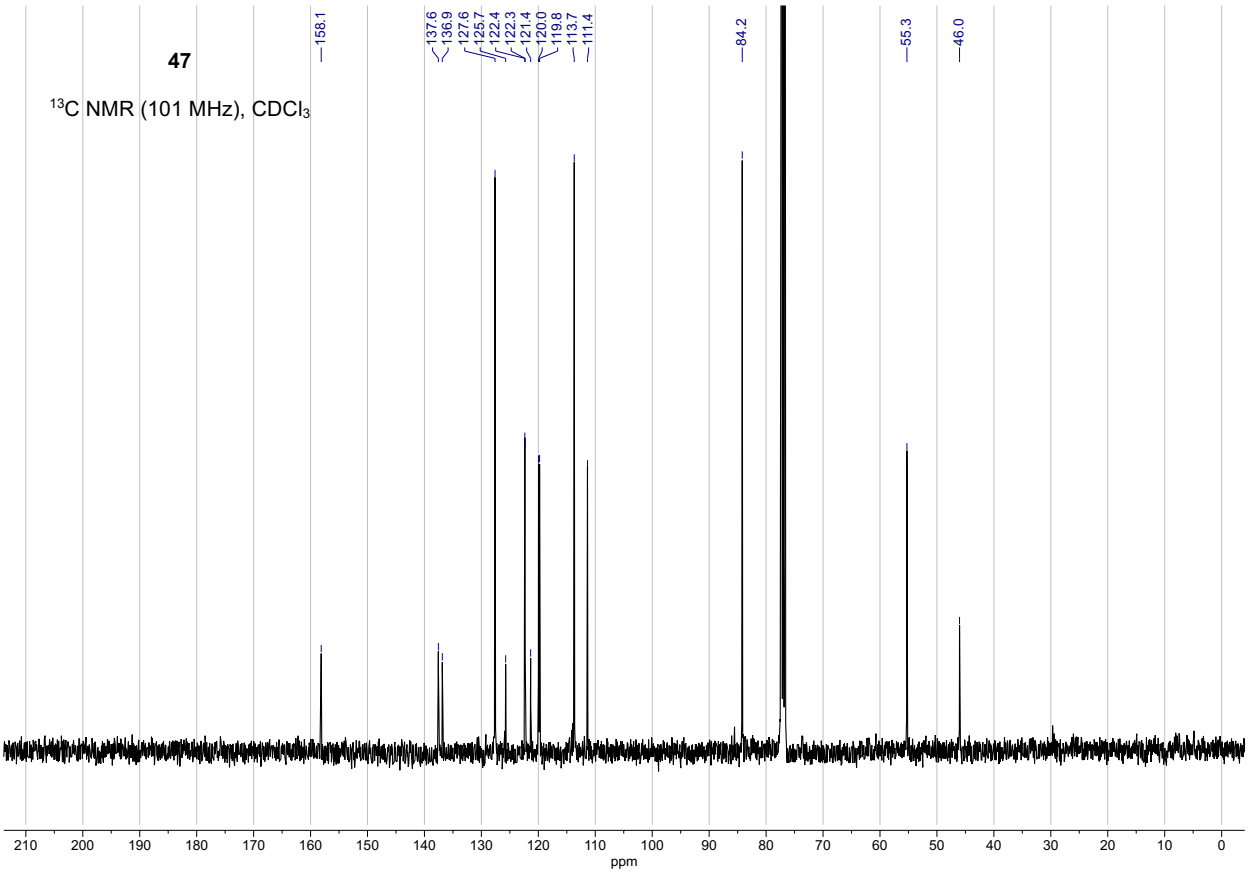
^{1}H NMR (400 MHz), $CDCl_3$

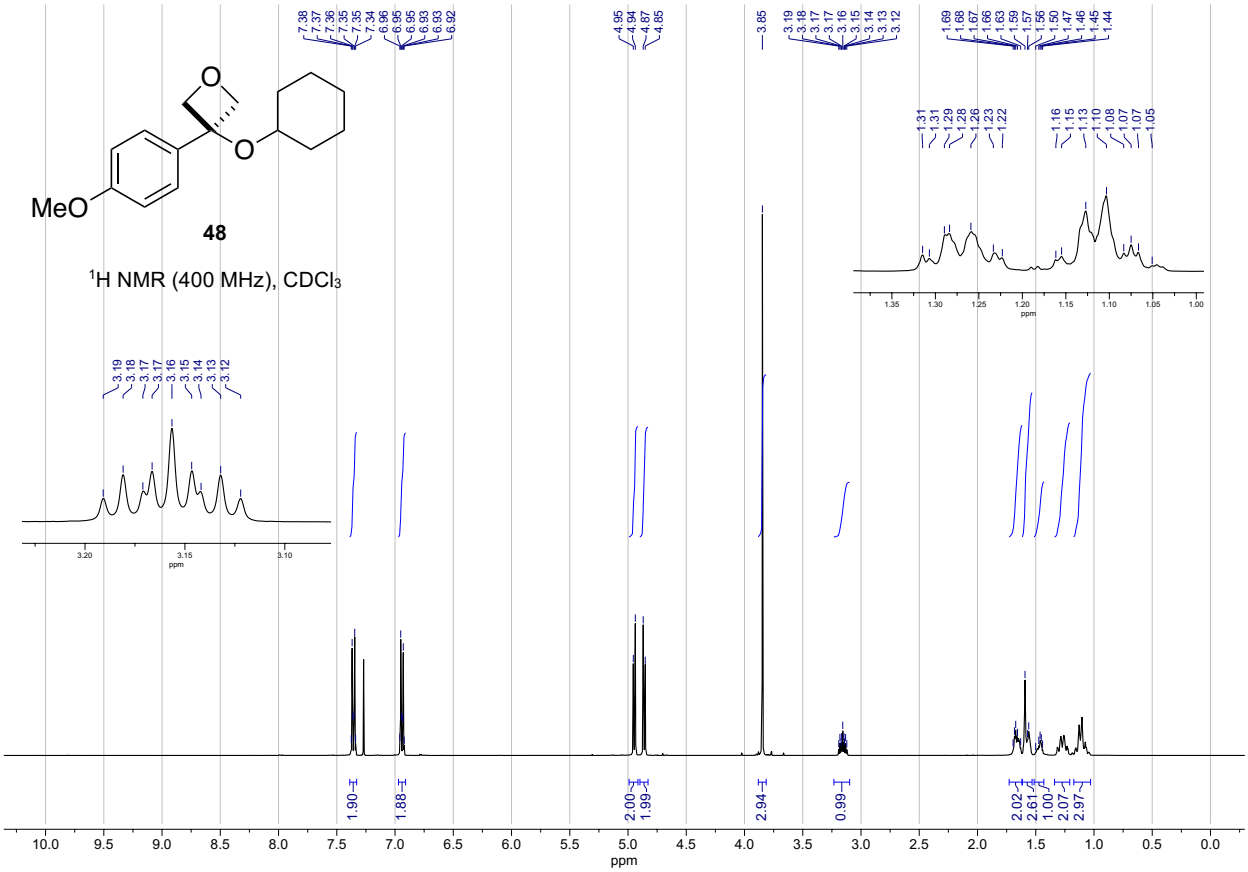


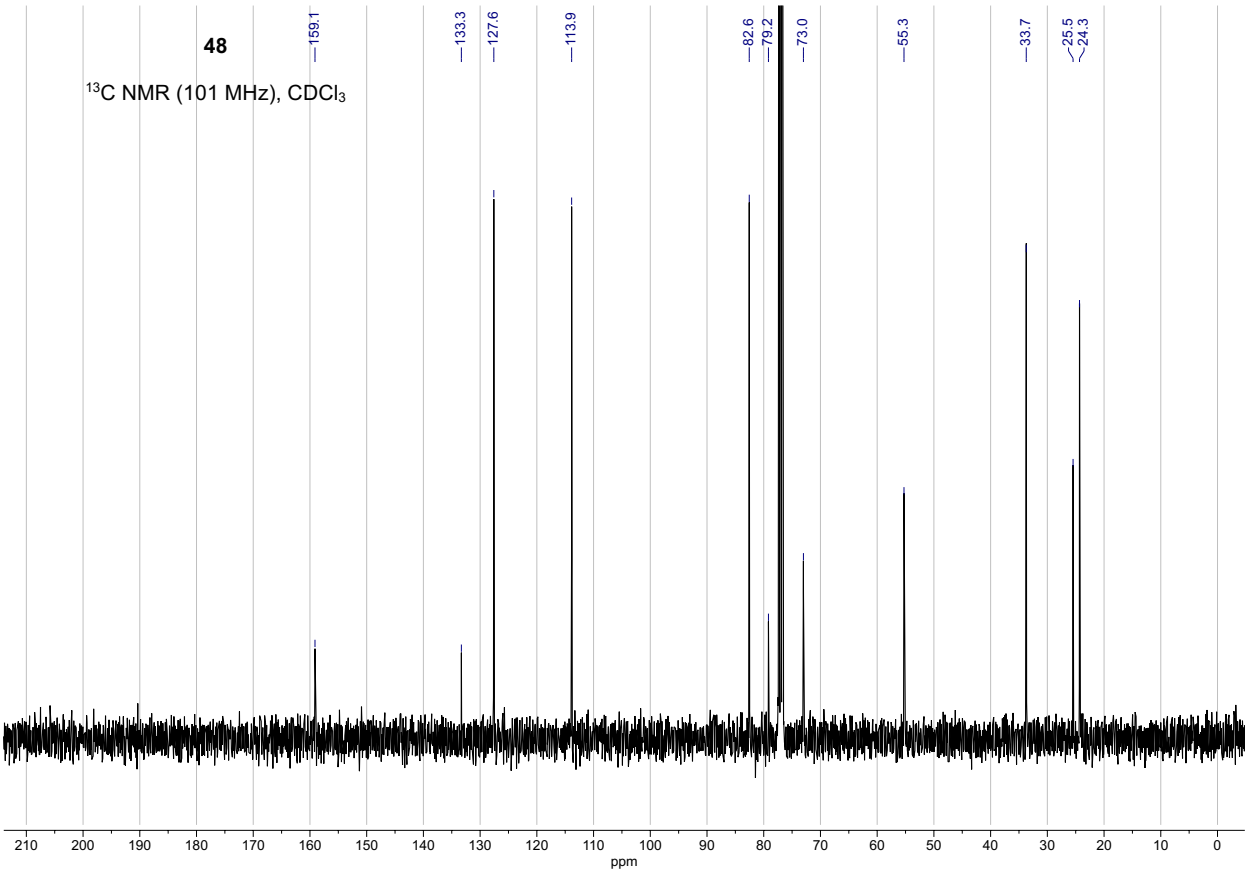
46

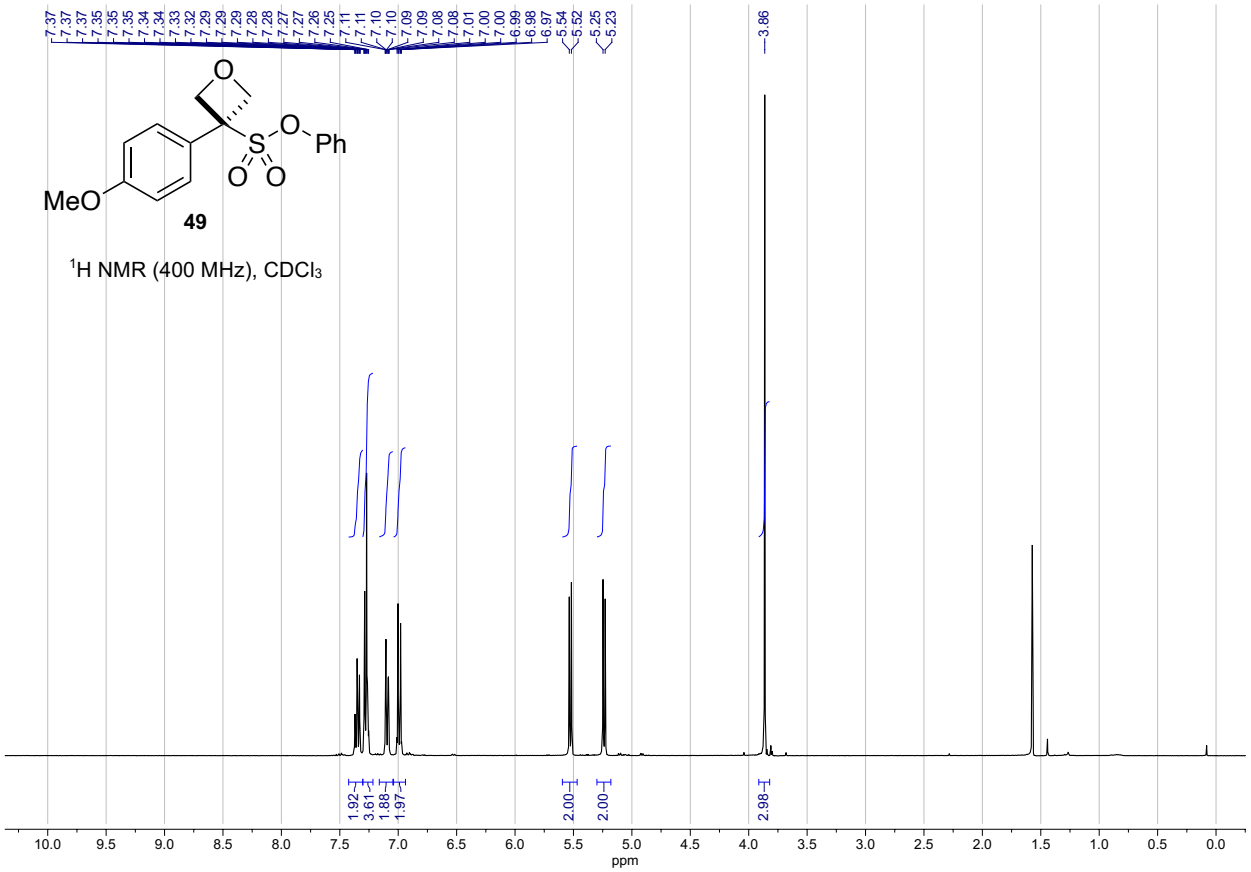
^{13}C NMR (101 MHz), $CDCl_3$

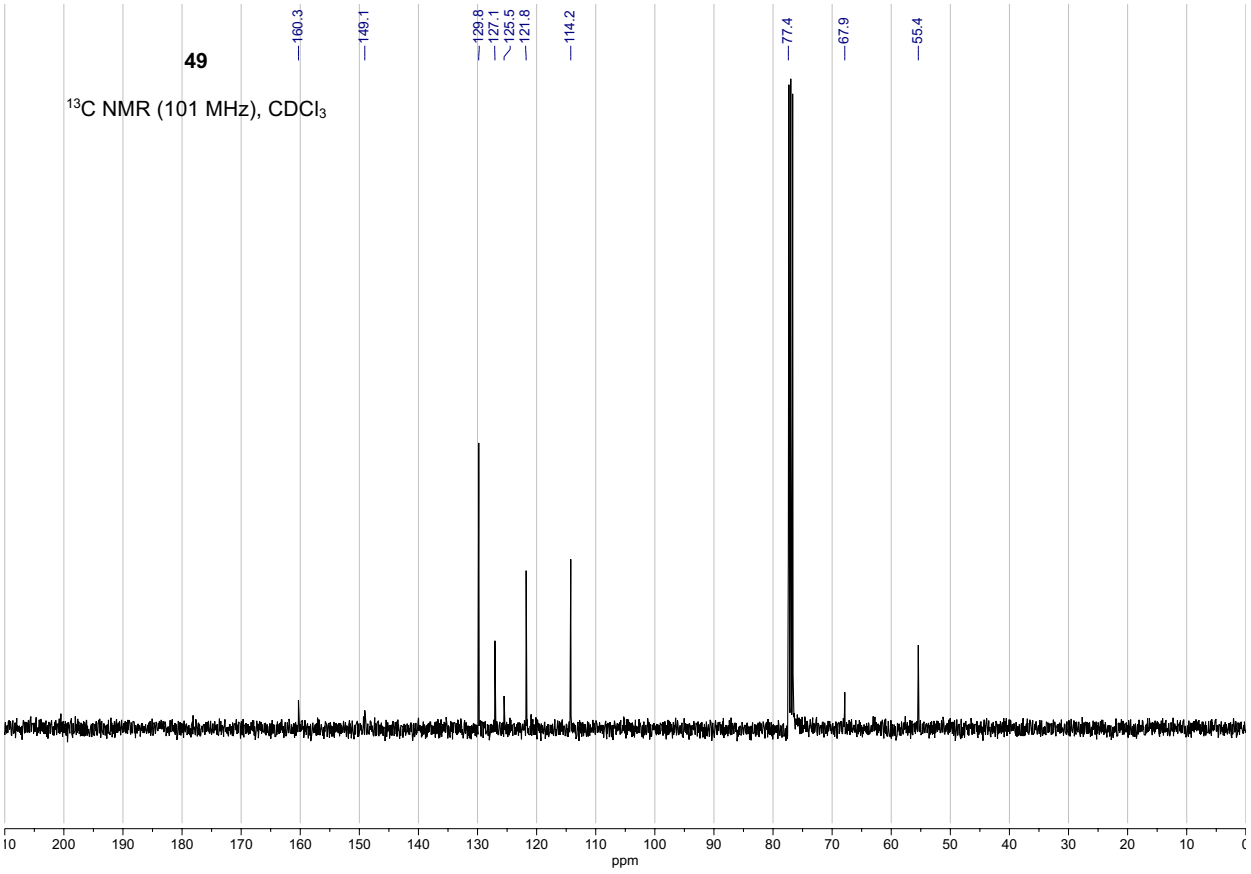

8.07
7.70
7.68
7.42
7.40
7.29
7.28
7.28
7.27
7.27
7.26
7.25
7.24
7.24
7.22
7.22
7.14
7.13
7.12
7.12
7.11
7.10
7.10
6.93
6.92
6.91
6.90
6.90
6.89
6.69
6.69
5.42
5.40
5.31
5.29
3.83
O
MeO
NH
47
^{1}H NMR (400 MHz), CDCl$_3$
0.96
0.97
0.98
3.40
1.03
2.04
0.94
2.03
2.00
3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 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 0.0
ppm

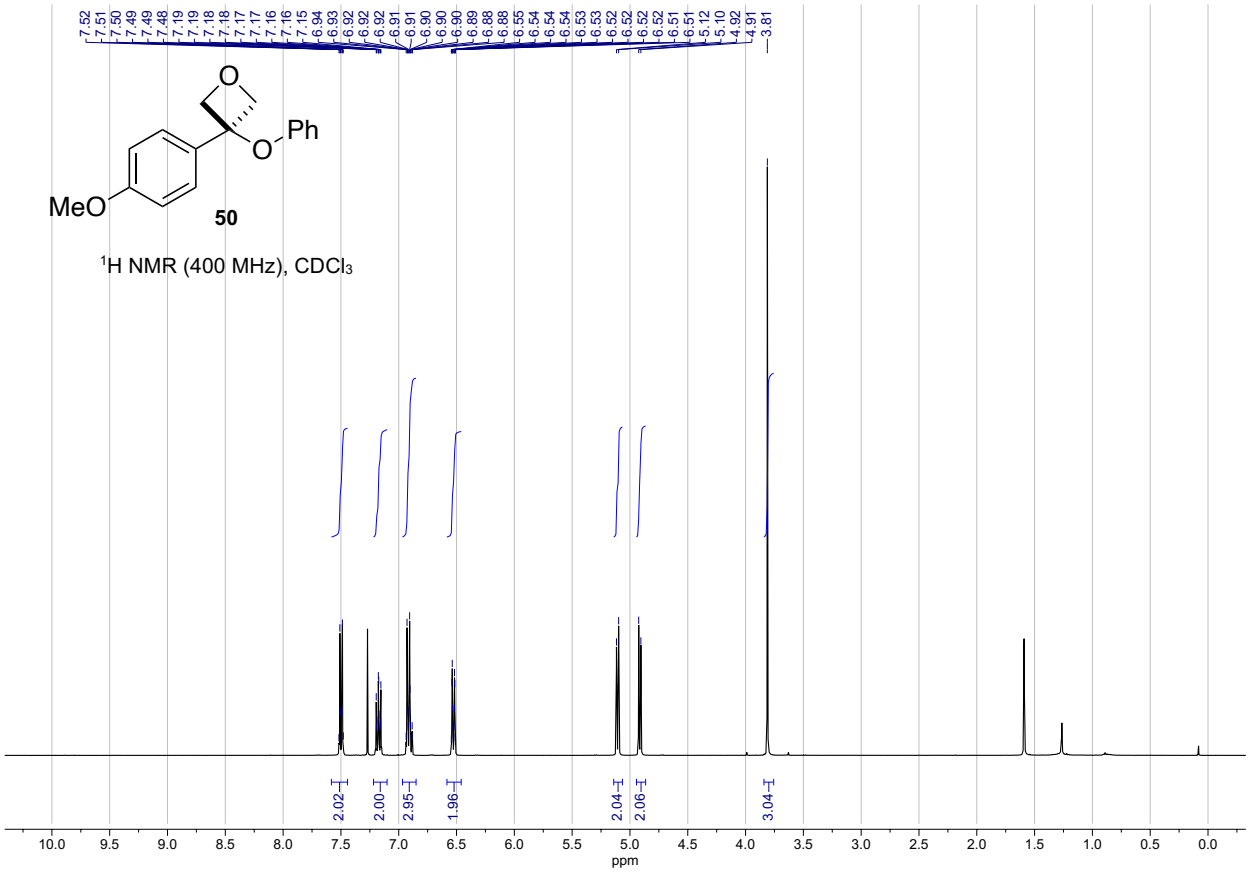

47
^{13}C NMR (101 MHz), CDCl$_3$
158.1
137.6
136.9
127.6
125.7
122.4
122.3
121.4
120.0
119.8
113.7
111.4
84.2
55.3
46.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

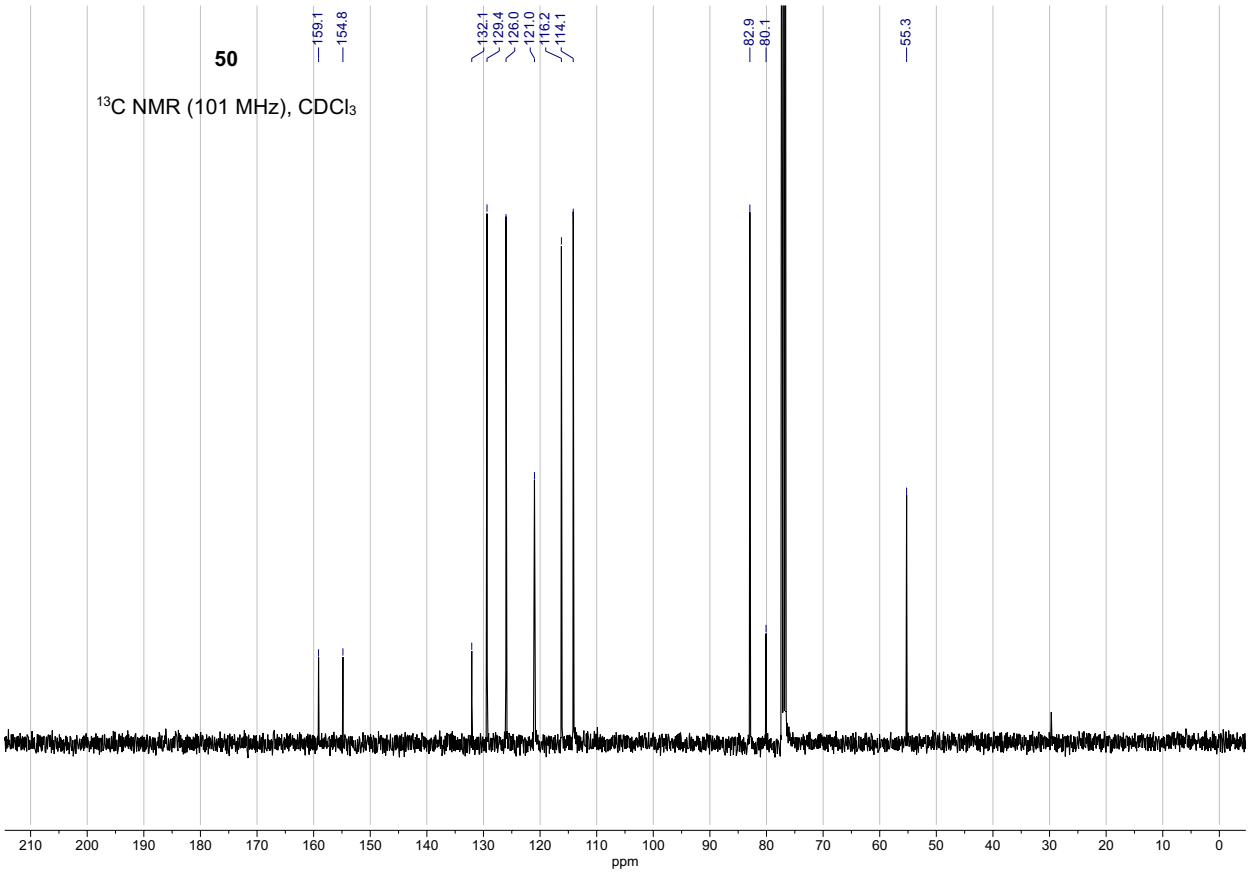

MeO
48
^{1}H NMR (400 MHz), CDCl$_3$
ppm

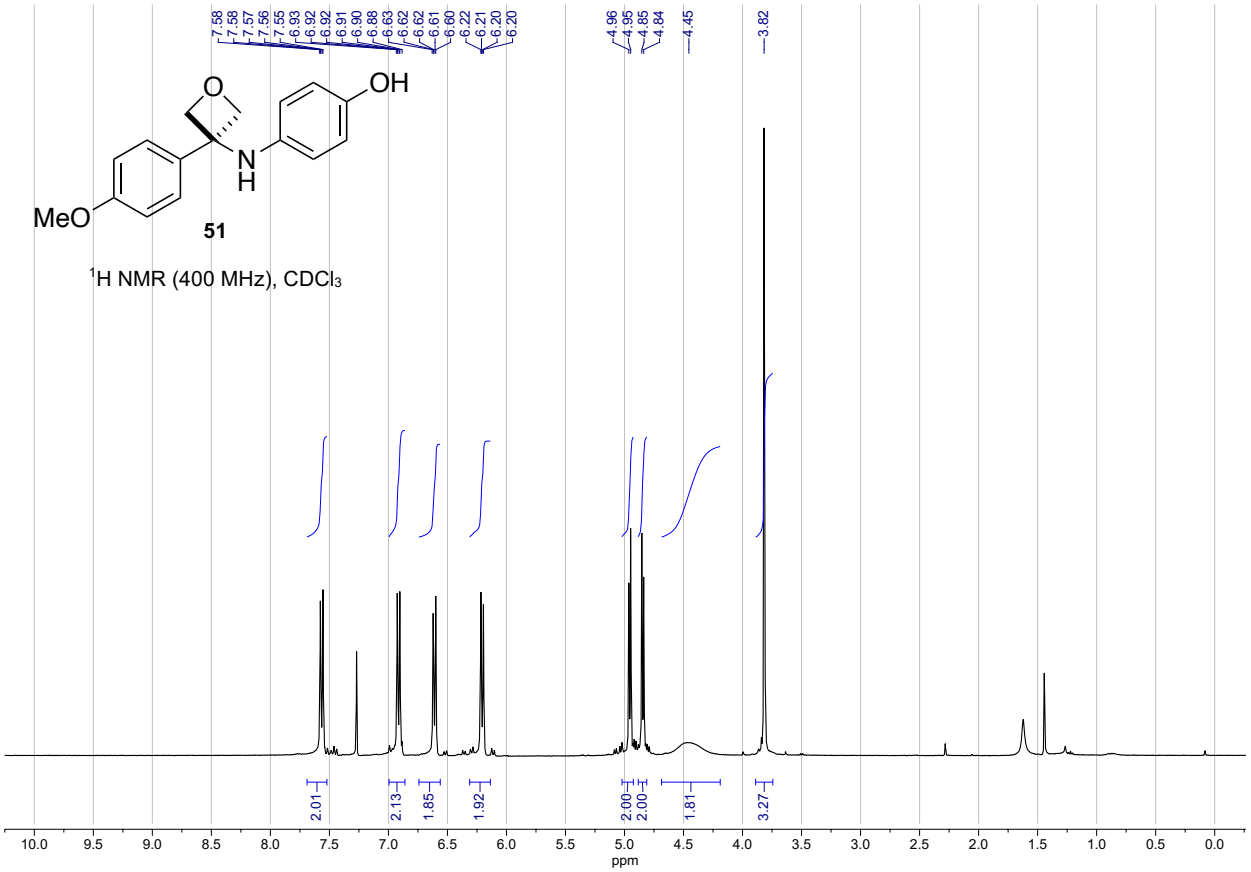

48
^{13}C NMR (101 MHz), CDCl$_3$
ppm

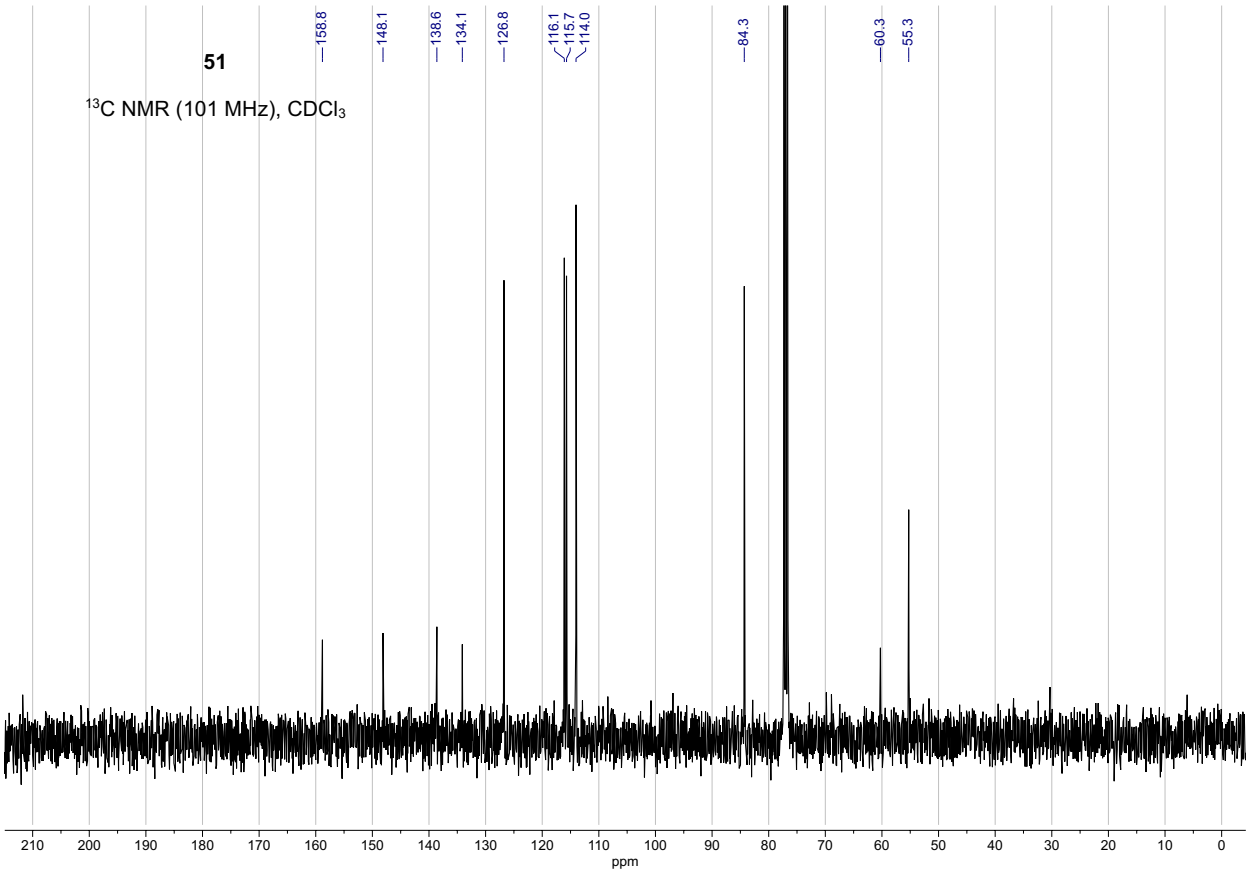

7.37
7.37
7.37
7.35
7.35
7.34
7.34
7.33
7.32
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.25
7.11
7.11
7.10
7.10
7.09
7.09
7.08
7.08
7.01
7.00
7.00
6.99
6.98
6.97
5.54
5.52
5.25
5.23
3.86
O
O
Ph
S
O
O
MeO
49
^{1}H NMR (400 MHz), $CDCl_3$
1.92
3.61
1.88
1.97
2.00
2.00
2.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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

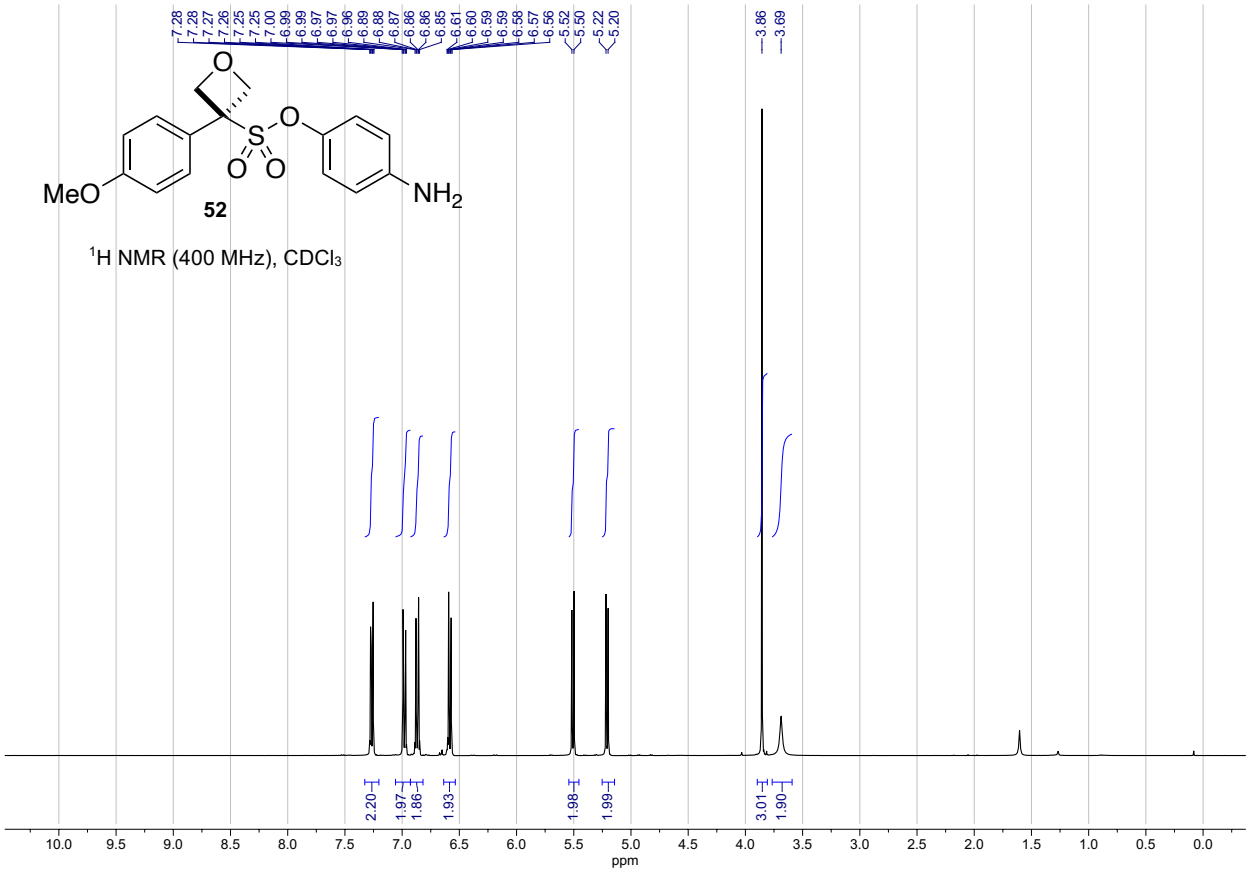

49
^{13}C NMR (101 MHz), $CDCl_3$
160.3
149.1
129.8
127.1
125.5
121.8
114.2
77.4
67.9
55.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

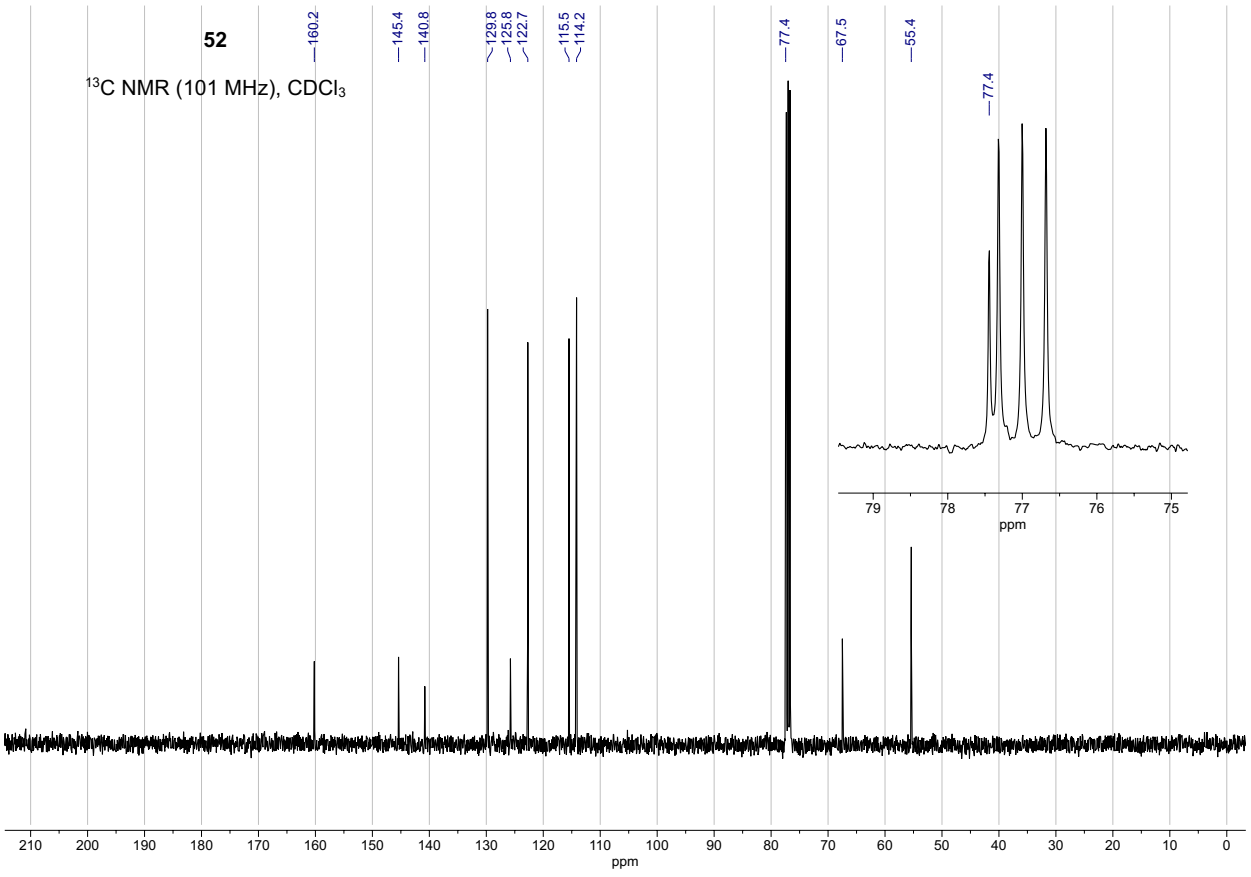

MeO
O
O
Ph
50
^{1}H NMR (400 MHz), CDCl$_3$
ppm

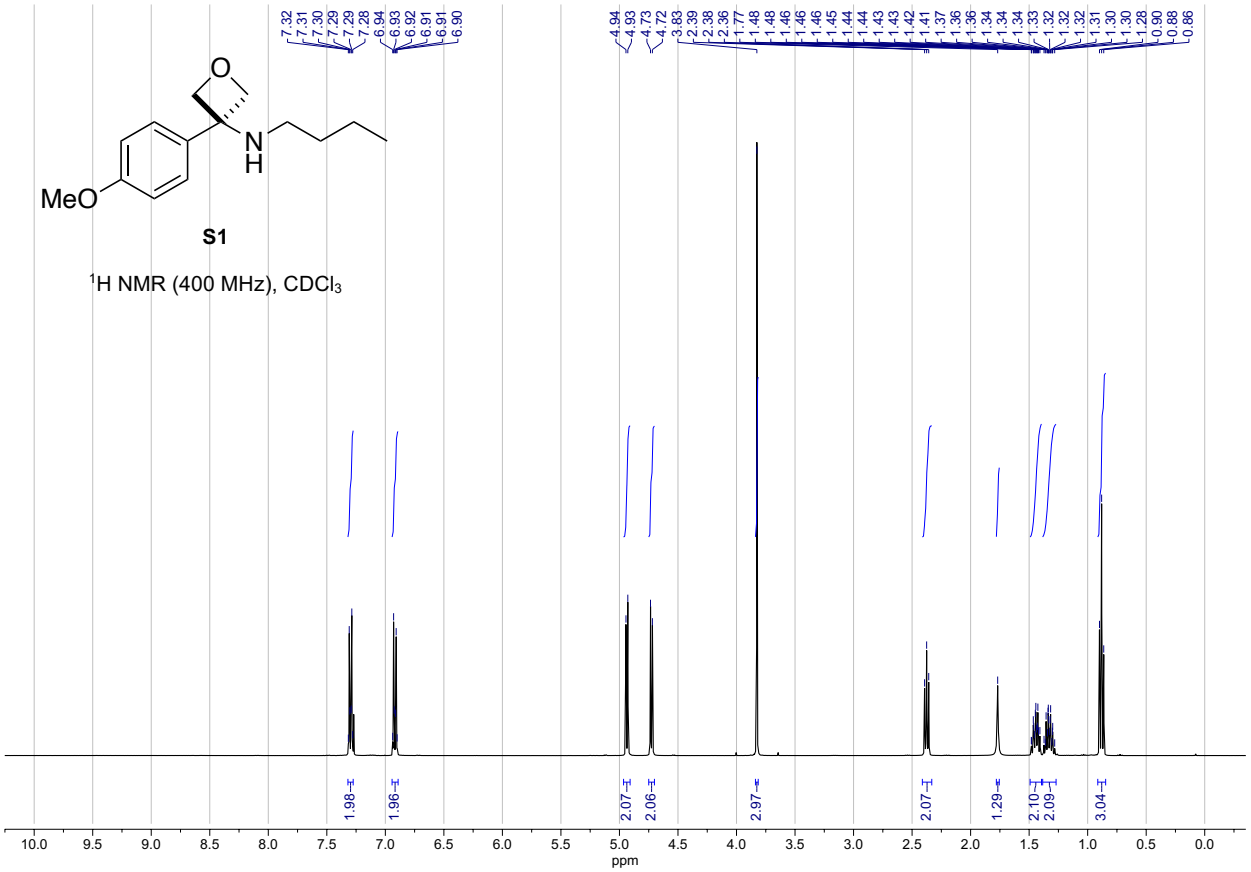

50
^{13}C NMR (101 MHz), CDCl$_3$
ppm

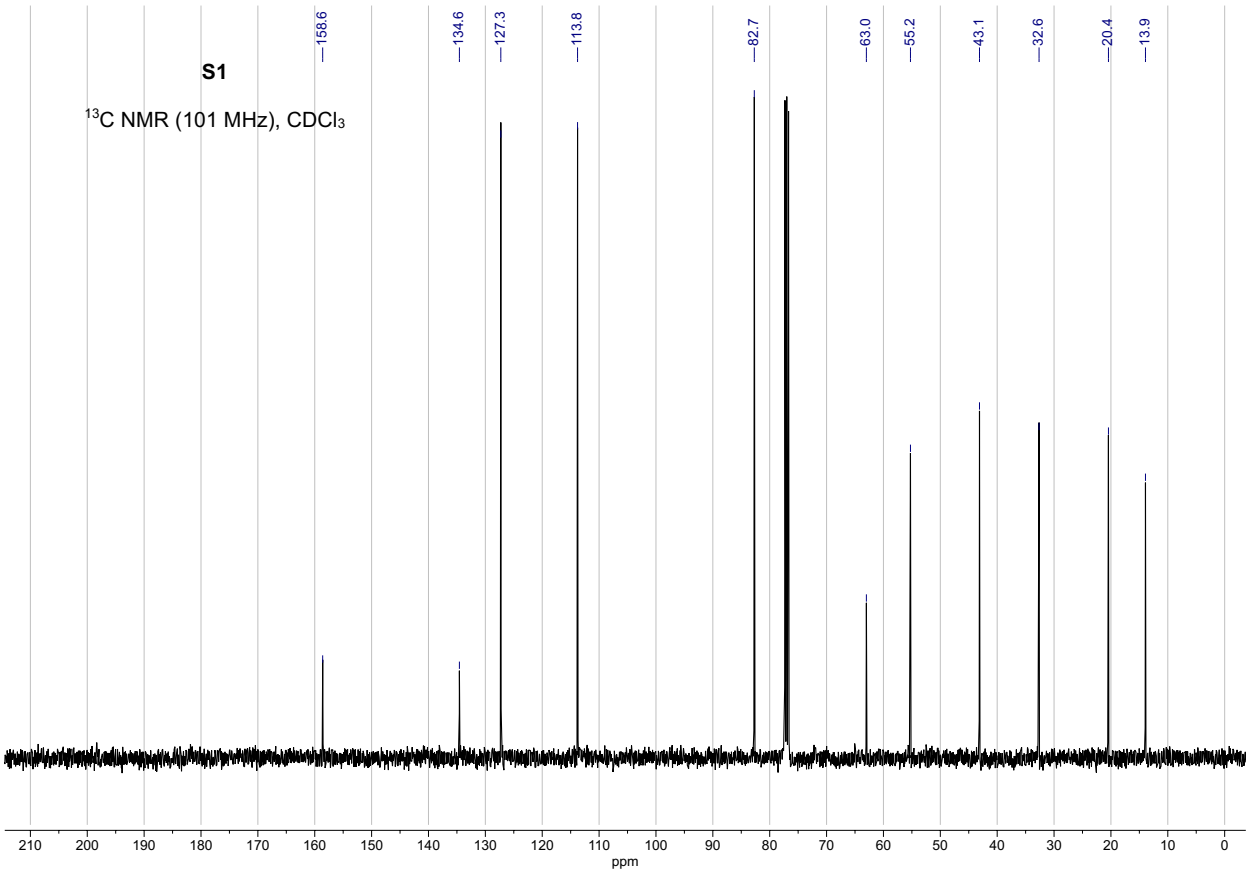

7.58
7.58
7.57
7.56
7.55
6.93
6.92
6.92
6.91
6.90
6.88
6.63
6.62
6.62
6.61
6.60
6.22
6.21
6.20
6.20
4.96
4.95
4.85
4.84
4.45
3.82
O
OH
N
H
MeO
51
^{1}H NMR (400 MHz), CDCl$_3$
2.01
2.13
1.85
1.92
2.00
2.00
1.81
3.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

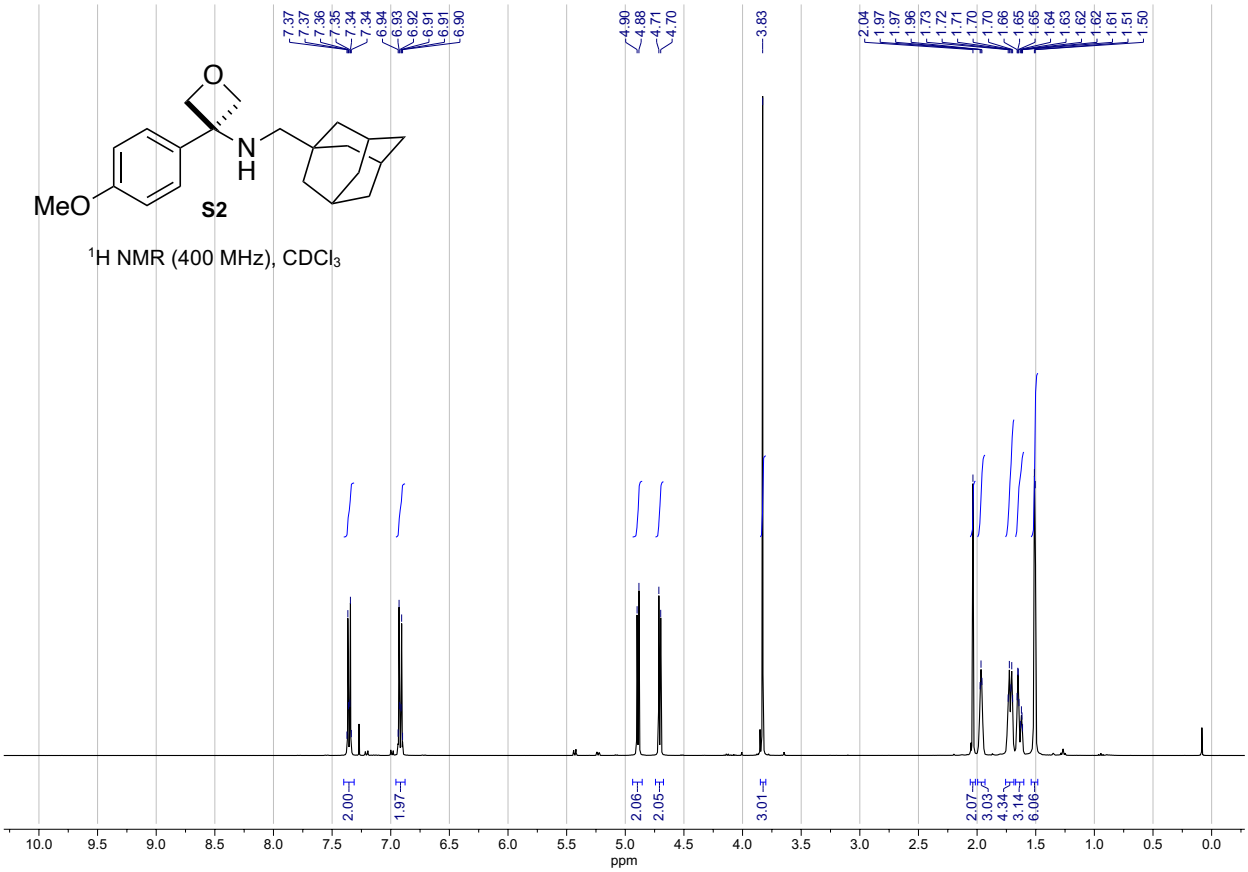

158.8
148.1
138.6
134.1
126.8
116.1
115.7
114.0
84.3
60.3
55.3
51
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

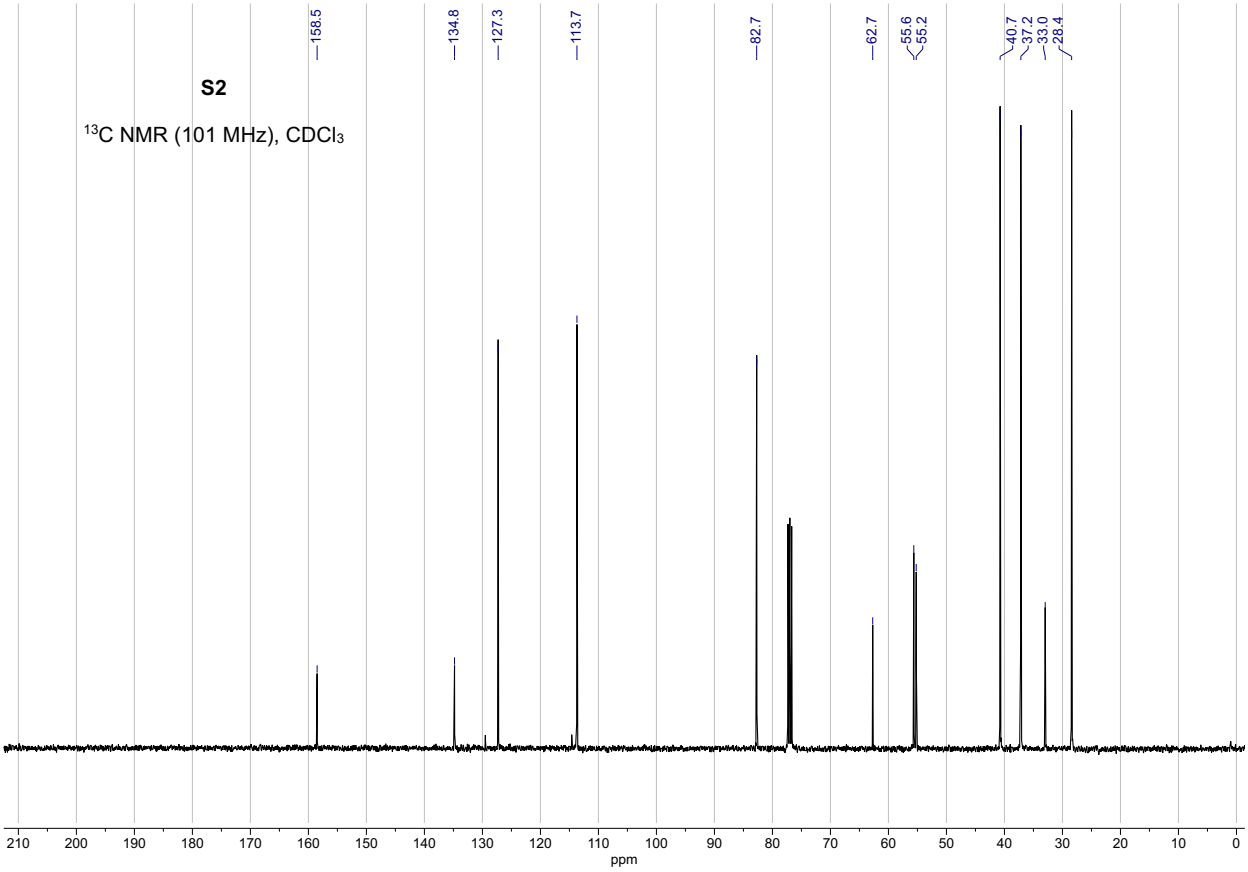

7.28
7.28
7.27
7.26
7.25
7.25
7.00
6.99
6.99
6.97
6.97
6.96
6.89
6.88
6.87
6.86
6.86
6.85
6.61
6.60
6.59
6.59
6.58
6.57
6.56
5.52
5.50
5.22
5.20
3.86
3.69
O
O
S
O
O
O
MeO
NH2
52
1H NMR (400 MHz), CDCl3
2.20
1.97
1.86
1.93
1.98
1.99
3.01
1.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

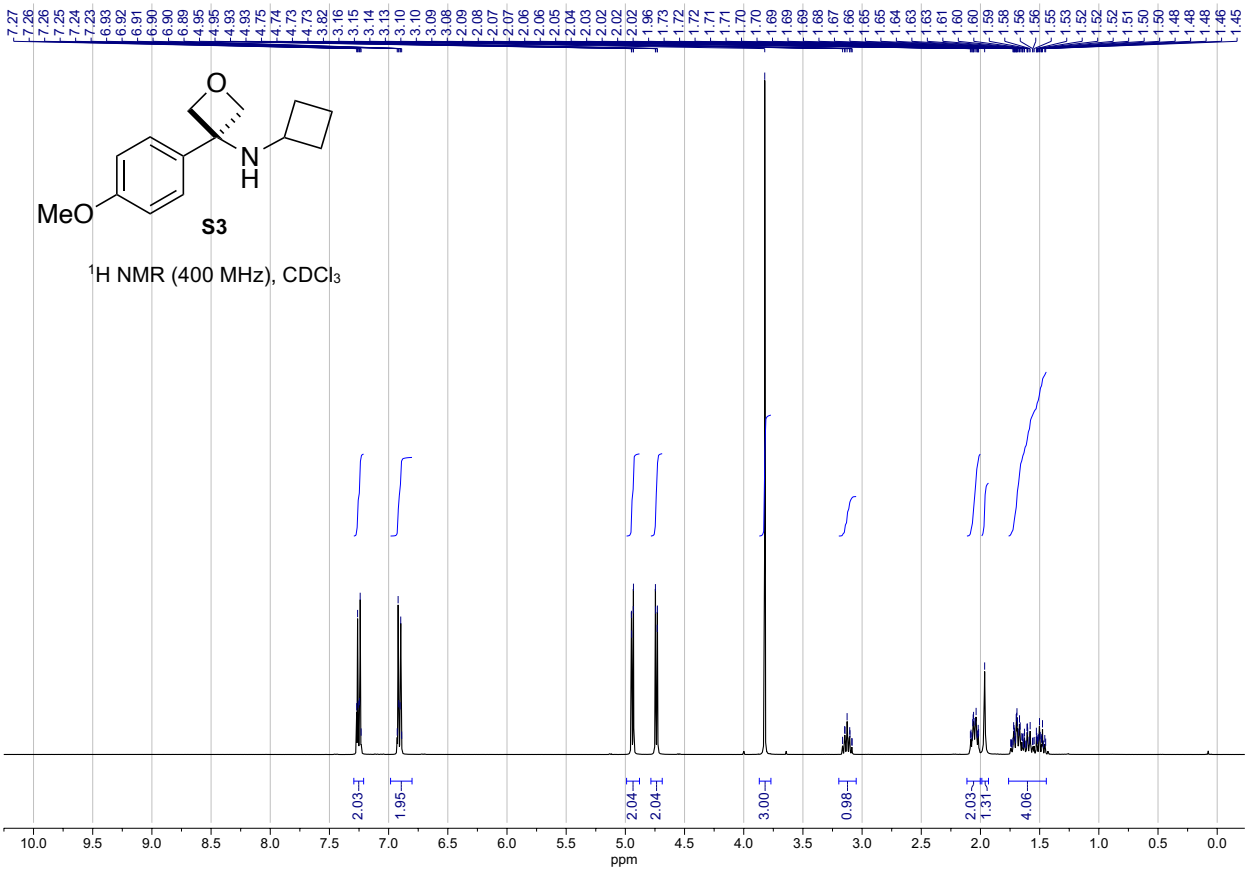

52
13C NMR (101 MHz), CDCl3
160.2
145.4
140.8
129.8
125.8
122.7
115.5
114.2
77.4
67.5
55.4
77.4
79 78 77 76 75
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

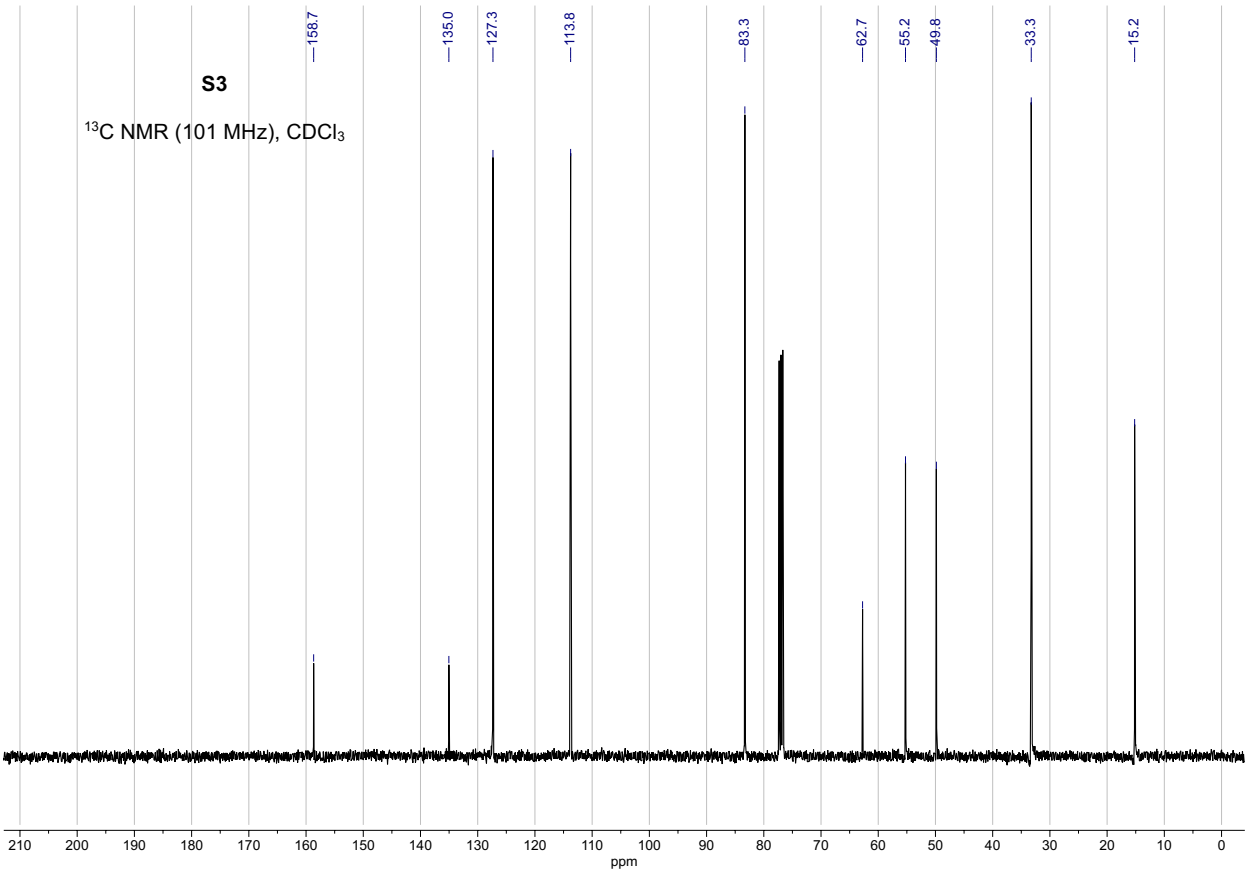

MeO
O
N
H
S1
^{1}H NMR (400 MHz), CDCl$_3$
7.32 7.31 7.30 7.29 7.29 7.28 6.94 6.93 6.92 6.91 6.91 6.90
4.94 4.93 4.73 4.72 3.83 2.39 2.38 2.36 1.77 1.48 1.48 1.46 1.46 1.46 1.45 1.44 1.44 1.43 1.43 1.42 1.41 1.37 1.36 1.36 1.34 1.34 1.34 1.33 1.32 1.32 1.32 1.31 1.30 1.30 1.28 0.90 0.88 0.86
1.98 1.96 2.07 2.06 2.97 2.07 1.29 2.10 2.09 3.04
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

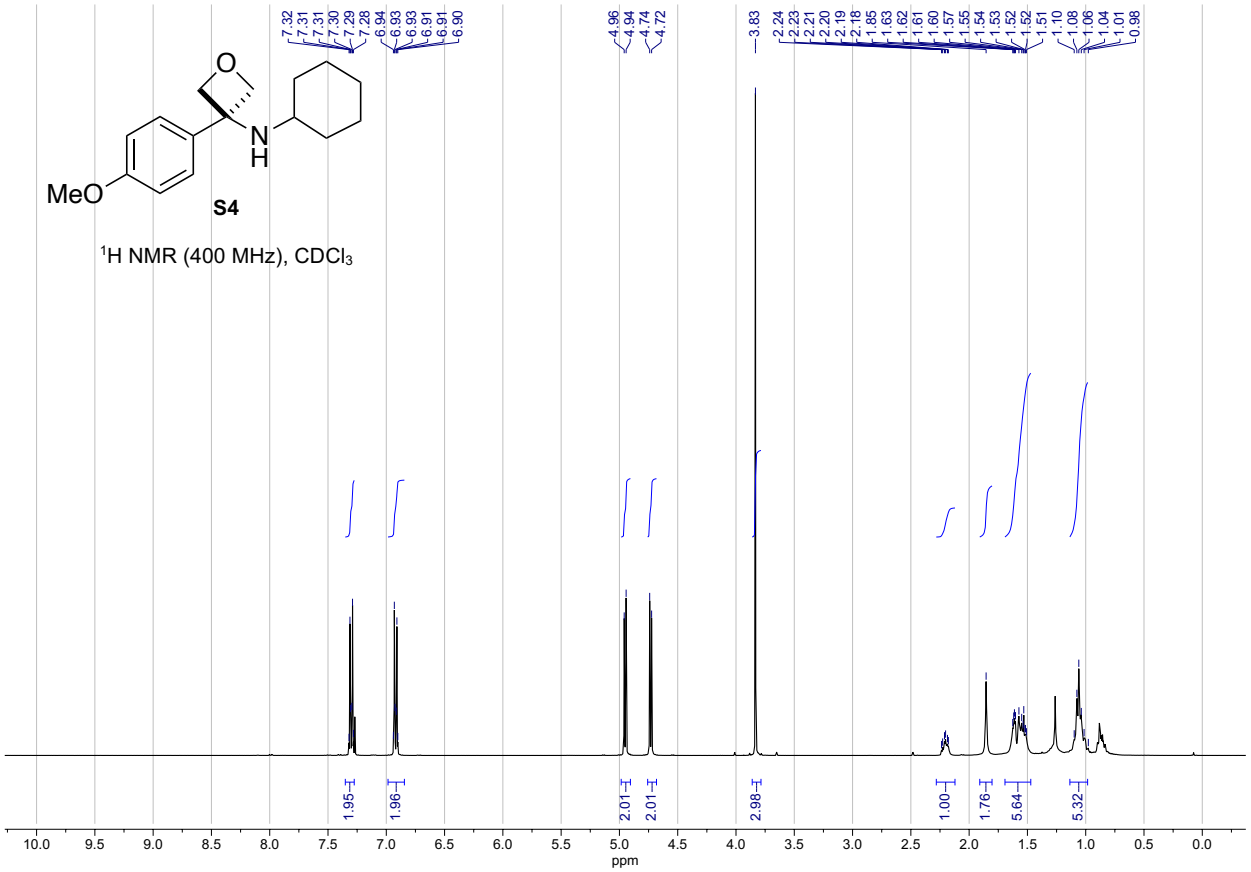

S1
^{13}C NMR (101 MHz), CDCl$_3$
158.6 134.6 127.3 113.8 82.7 63.0 55.2 43.1 32.6 20.4 13.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

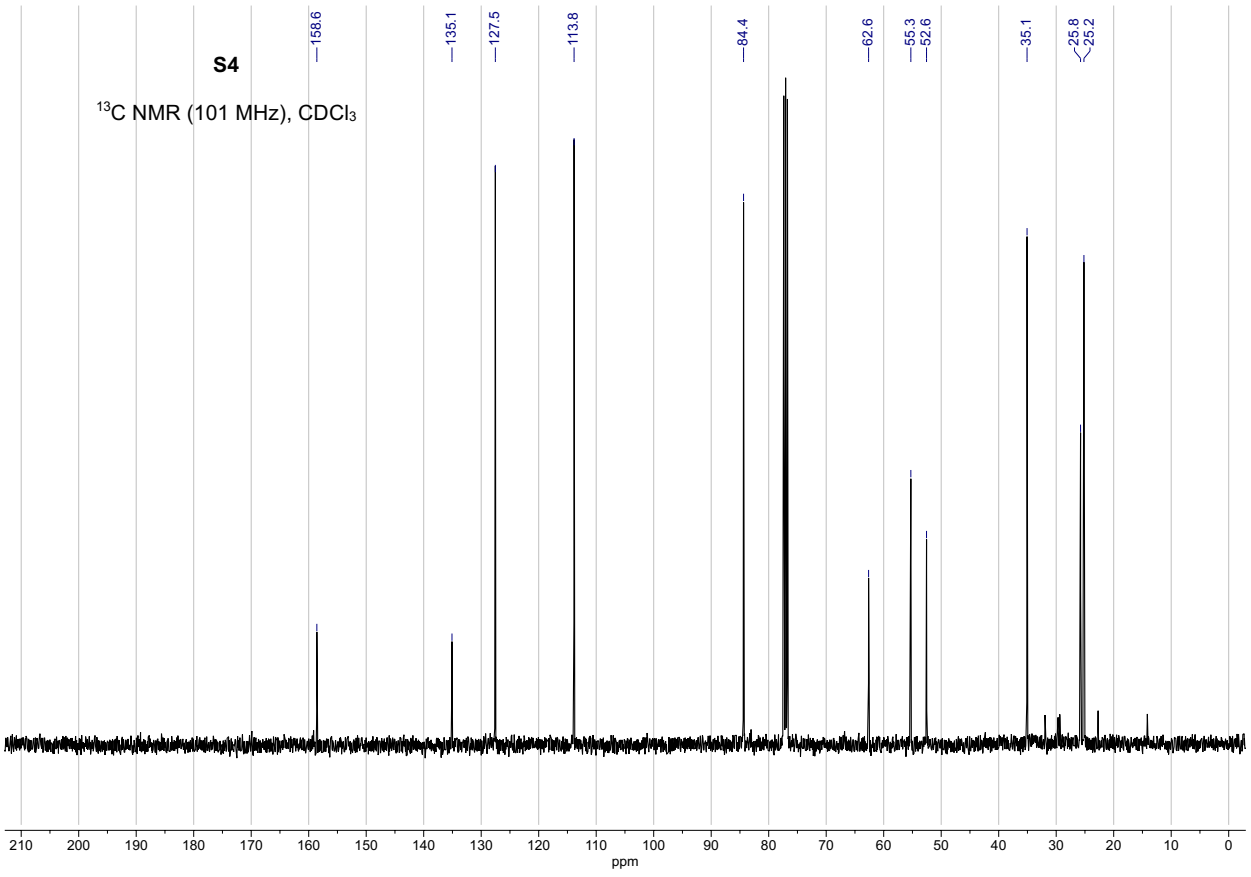

MeO
O
N
H
S2
^{1}H NMR (400 MHz), CDCl$_3$
7.37
7.37
7.36
7.35
7.34
7.34
6.94
6.93
6.92
6.91
6.91
6.90
4.90
4.88
4.71
4.70
3.83
2.04
1.97
1.97
1.96
1.73
1.72
1.71
1.71
1.70
1.70
1.66
1.65
1.65
1.64
1.63
1.62
1.62
1.61
1.51
1.50
2.00
1.97
2.06
2.05
3.01
2.07
3.03
4.34
3.14
6.06
ppm

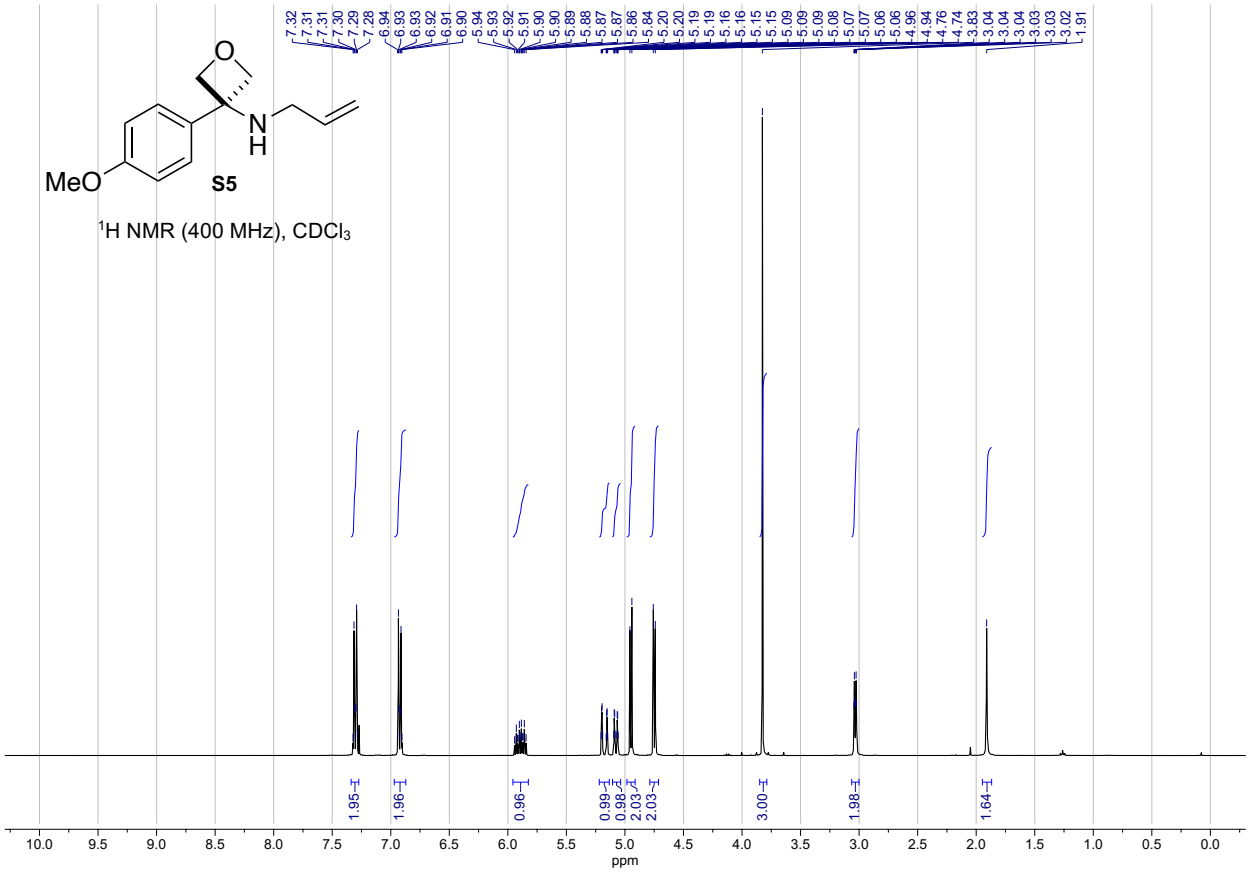

S2
^{13}C NMR (101 MHz), CDCl$_3$
158.5
134.8
127.3
113.7
82.7
62.7
55.6
55.2
40.7
37.2
33.0
28.4
ppm

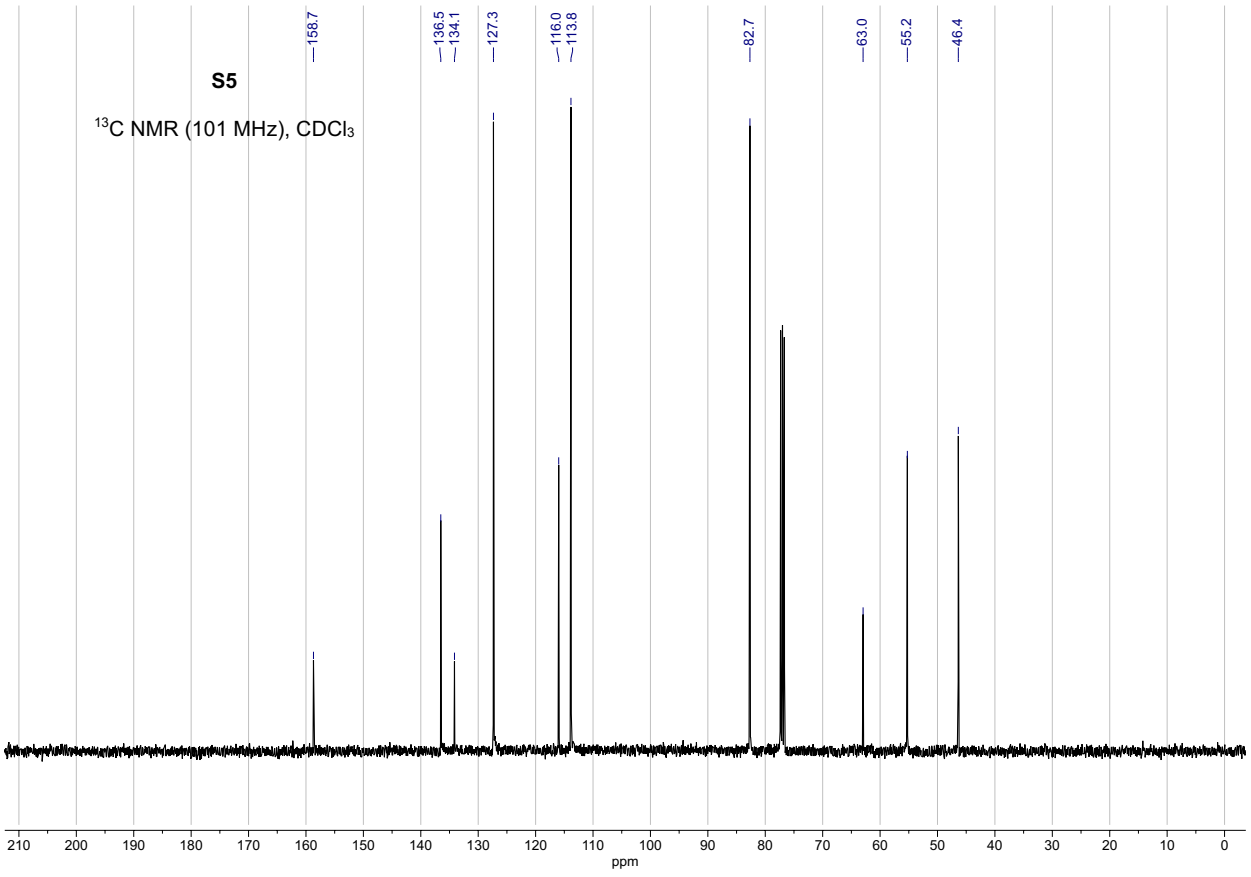

MeO
O
N
H
S3
^{1}H NMR (400 MHz), CDCl$_3$
ppm

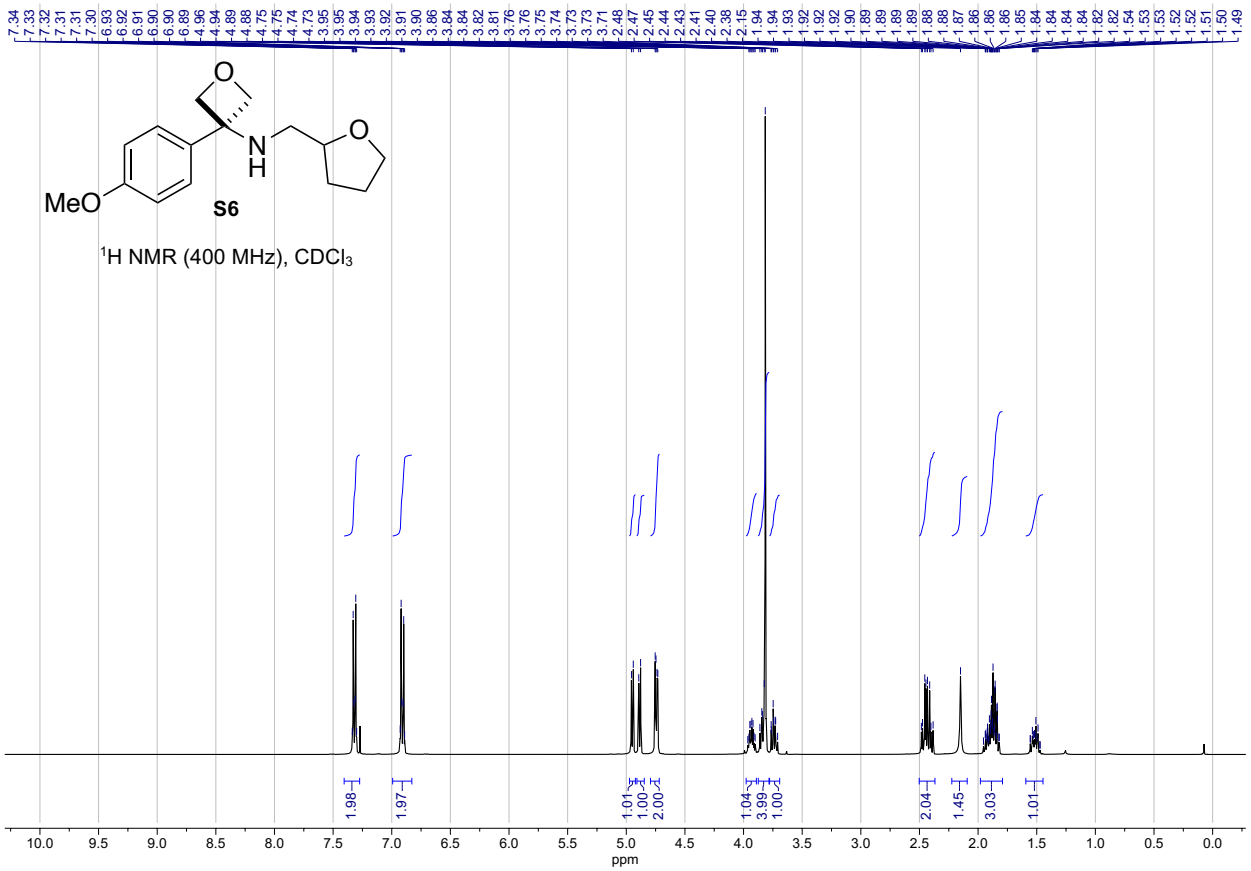

S3
^{13}C NMR (101 MHz), CDCl$_3$
158.7
135.0
127.3
113.8
83.3
62.7
55.2
49.8
33.3
15.2
ppm

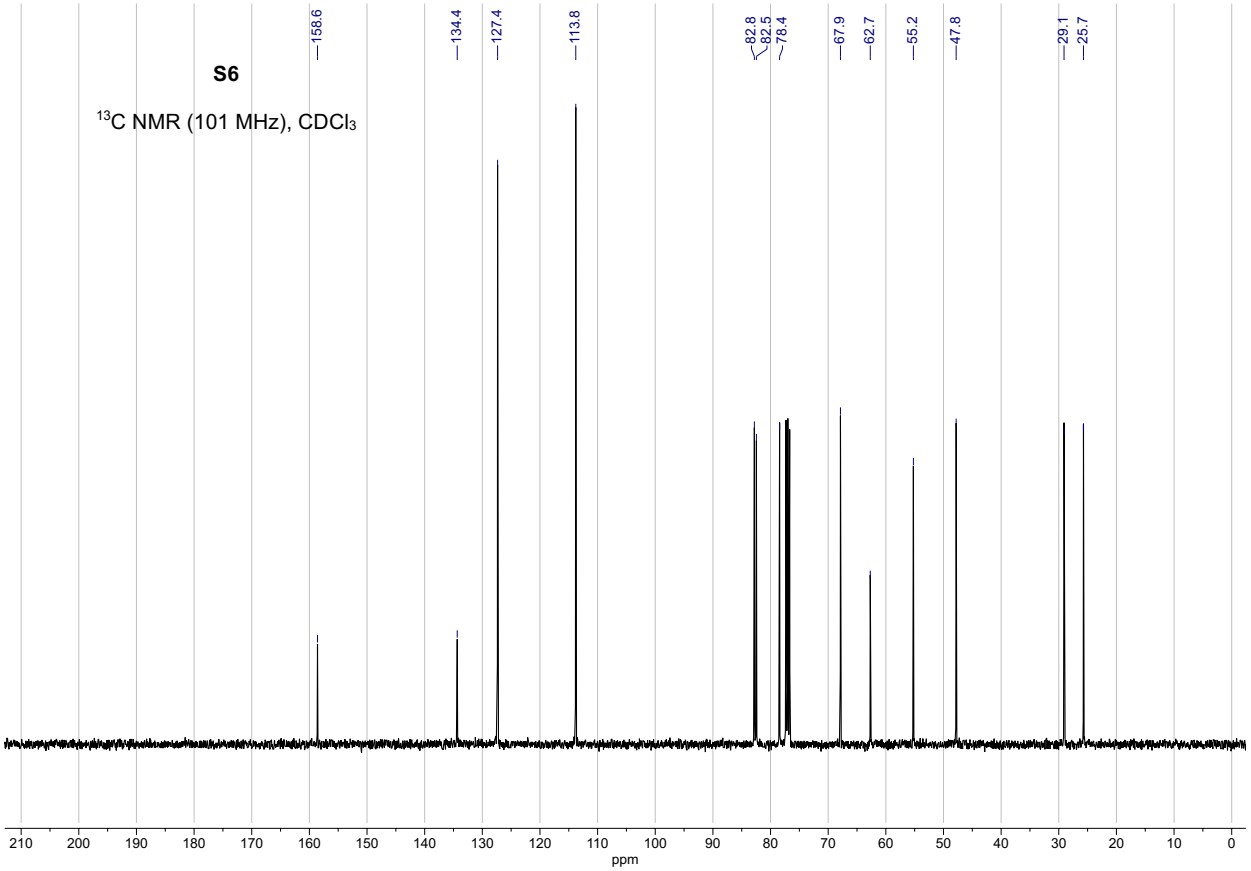

MeO
O
N
H
S4
^{1}H NMR (400 MHz), CDCl$_3$
7.32
7.31
7.31
7.30
7.29
7.28
6.94
6.93
6.93
6.91
6.91
6.90
4.96
4.94
4.74
4.72
3.83
2.24
2.23
2.21
2.20
2.19
2.18
1.85
1.63
1.62
1.61
1.60
1.57
1.55
1.54
1.53
1.52
1.52
1.51
1.10
1.08
1.06
1.04
1.01
0.98
1.95
1.96
2.01
2.01
2.98
1.00
1.76
5.64
5.32
ppm

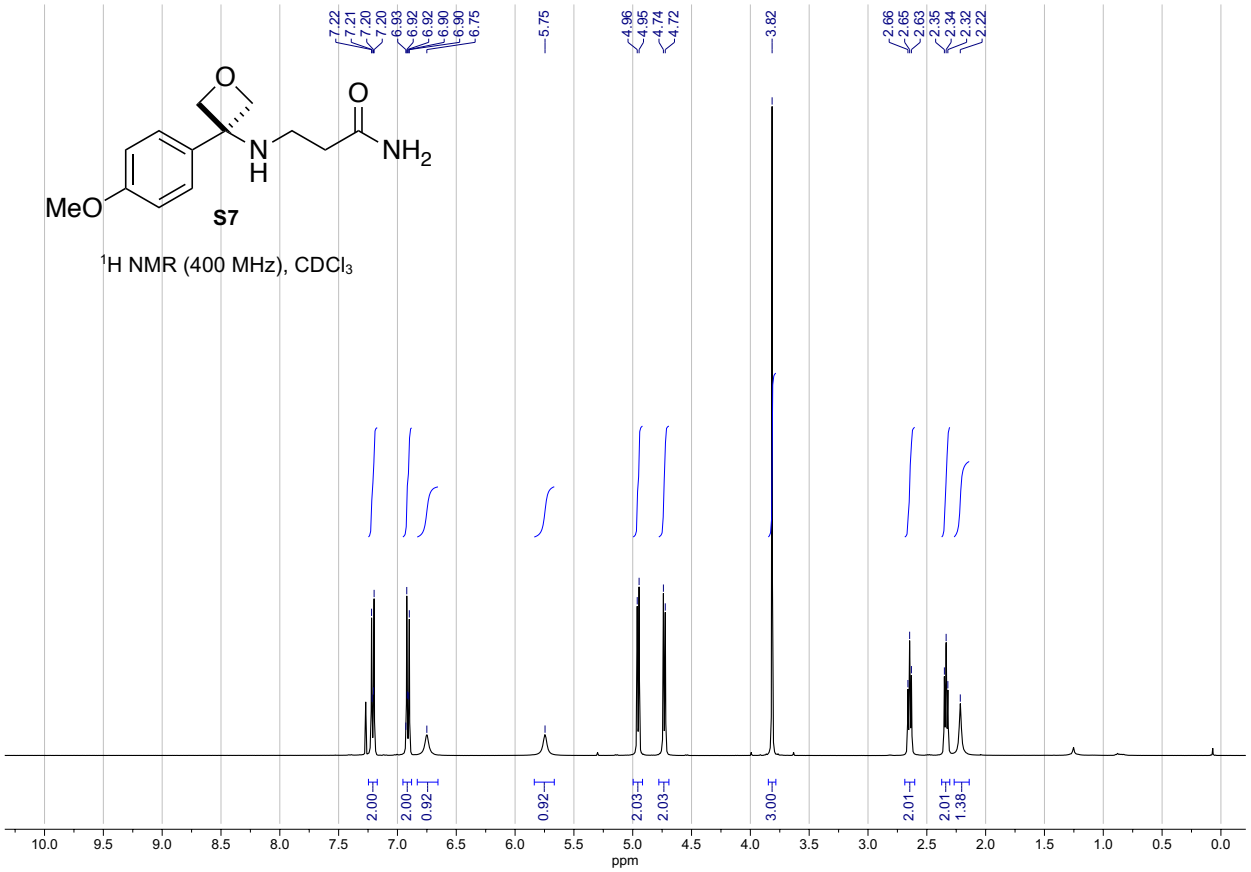

S4
^{13}C NMR (101 MHz), CDCl$_3$
158.6
135.1
127.5
113.8
84.4
62.6
55.3
52.6
35.1
25.8
25.2
ppm


MeO
O
N
H
S5
^{1}H NMR (400 MHz), CDCl$_3$
ppm


S5
^{13}C NMR (101 MHz), CDCl$_3$
168.7
136.5
134.1
127.3
116.0
113.8
82.7
63.0
55.2
46.4
ppm

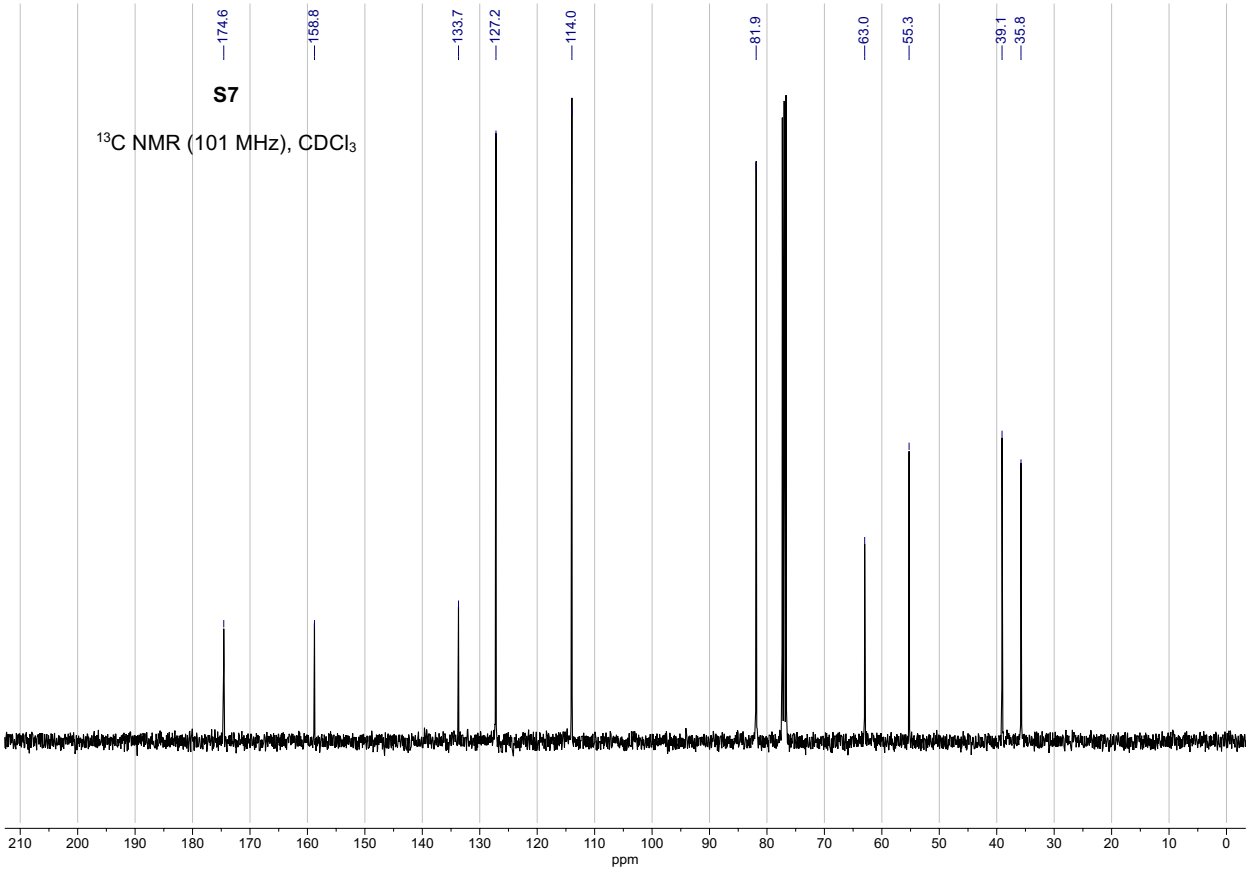

MeO
O
N
H
O
S6
^{1}H NMR (400 MHz), CDCl$_3$
ppm


S6
^{13}C NMR (101 MHz), CDCl$_3$
158.6
134.4
127.4
113.8
82.8
82.5
78.4
67.9
62.7
55.2
47.8
29.1
25.7
ppm



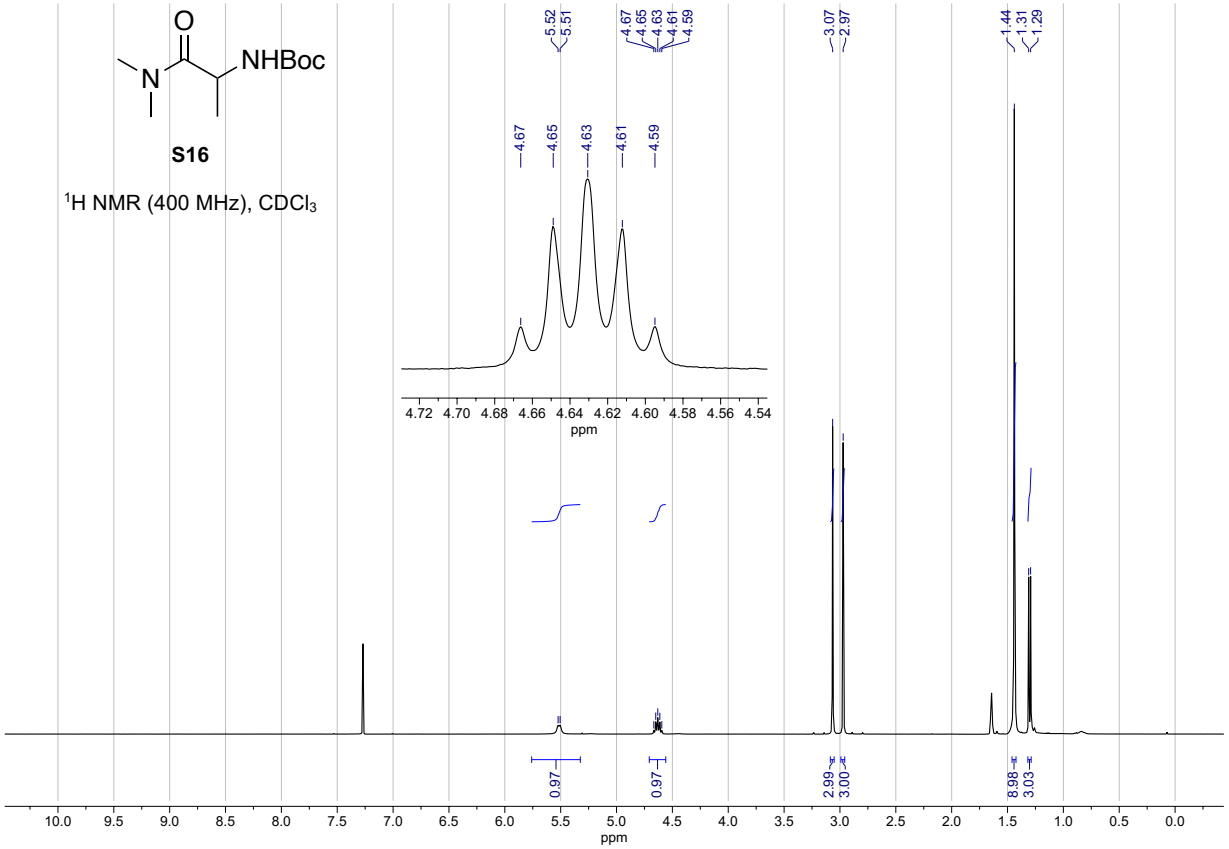
S7

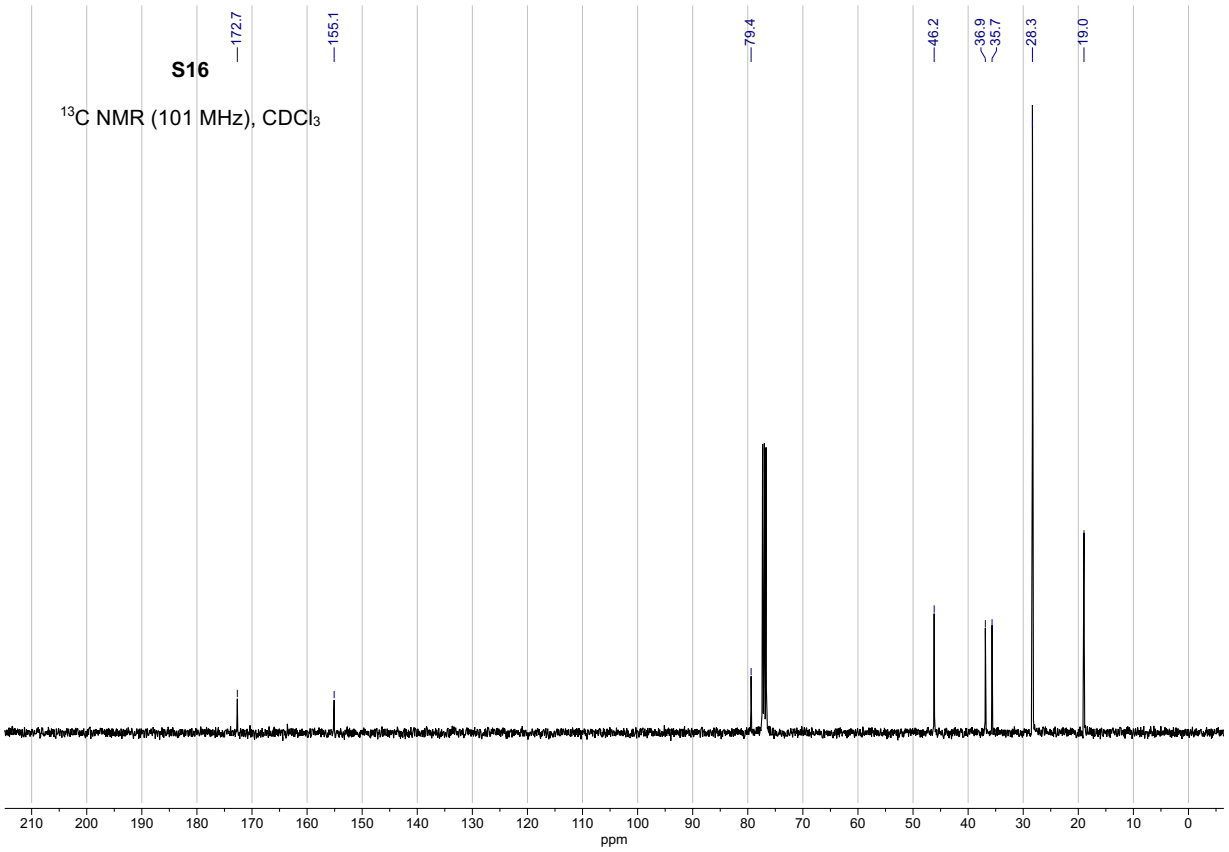
^{1}H NMR (400 MHz), $CDCl_3$

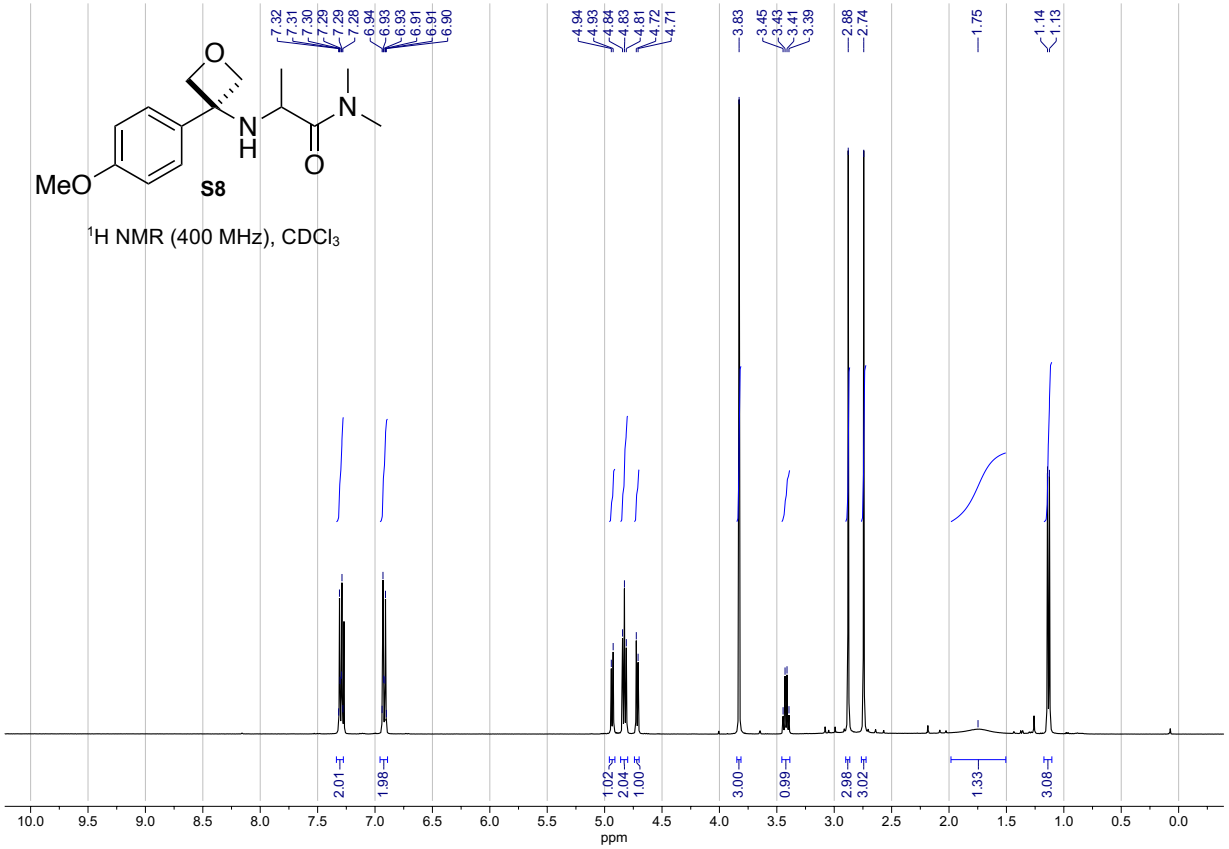


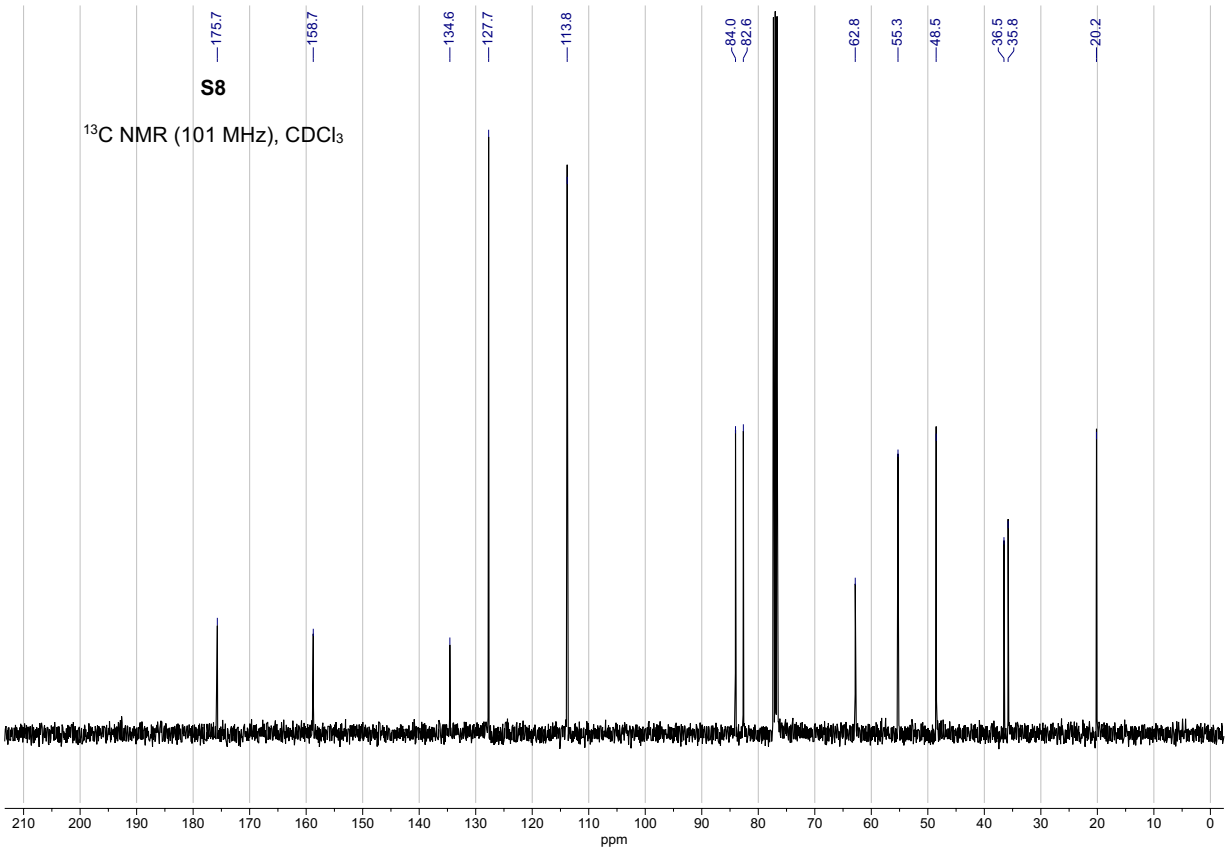
S7

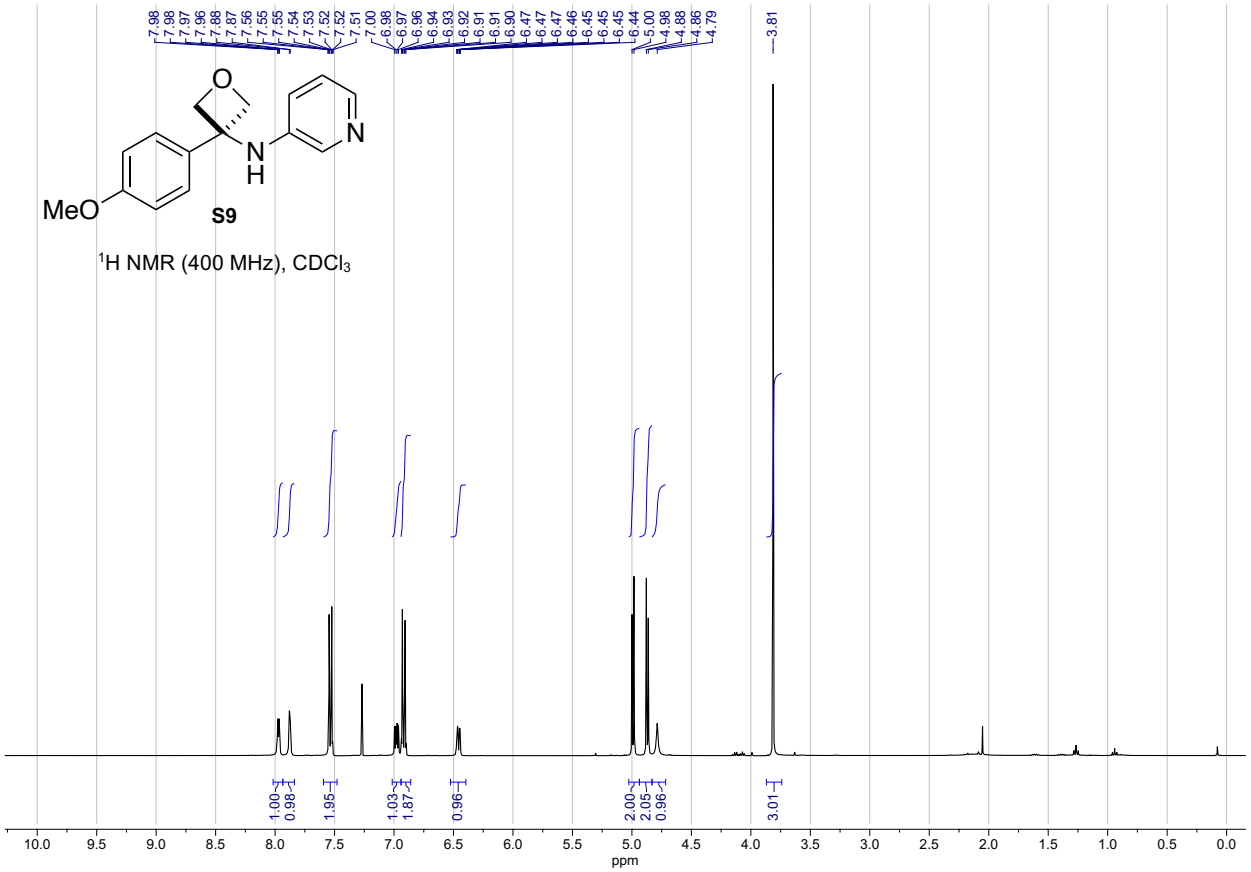
^{13}C NMR (101 MHz), $CDCl_3$

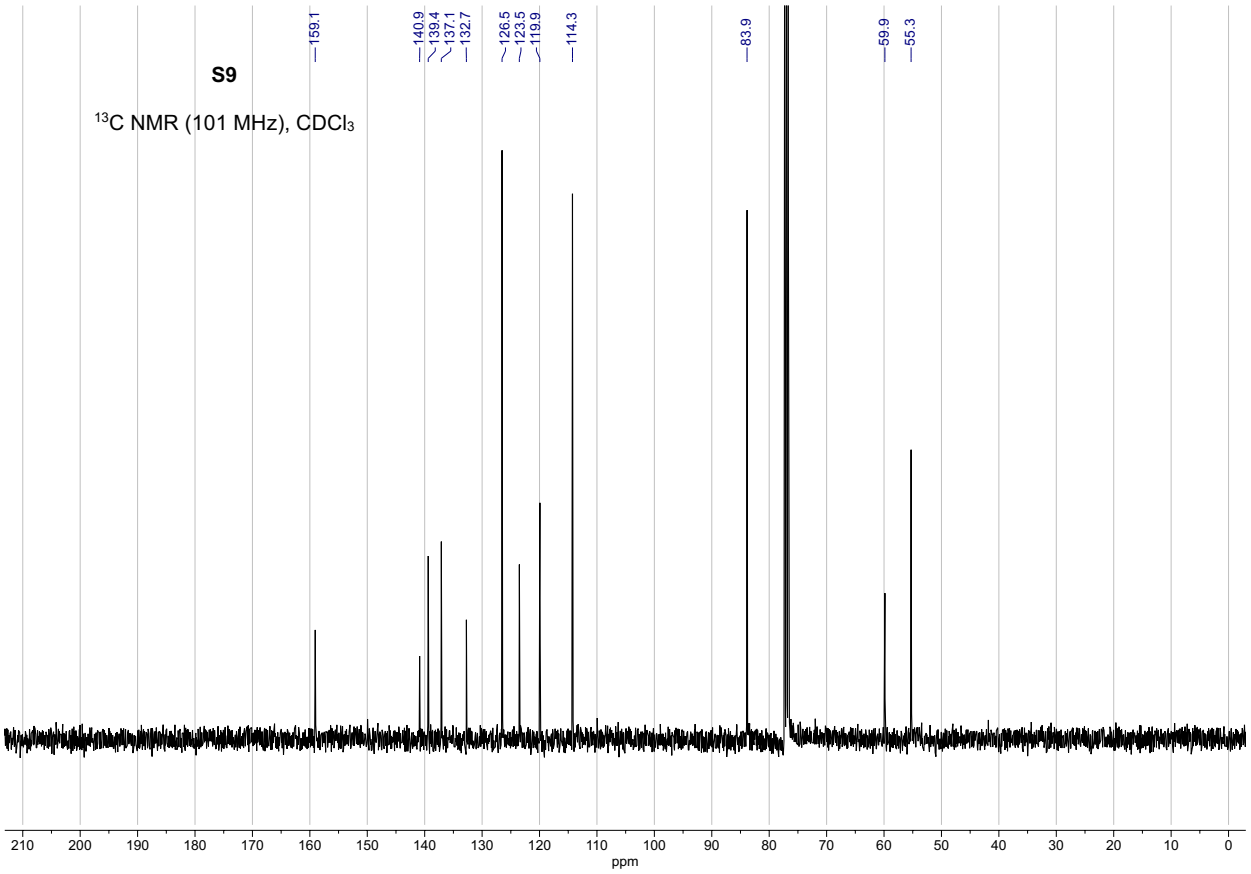

O
N
NHBoc
S16
^{1}H NMR (400 MHz), CDCl$_3$
5.52
5.51
4.67
4.65
4.63
4.61
4.59
3.07
2.97
1.44
1.31
1.29
4.72 4.70 4.68 4.66 4.64 4.62 4.60 4.58 4.56 4.54
ppm
0.97
0.97
2.99
3.00
8.98
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

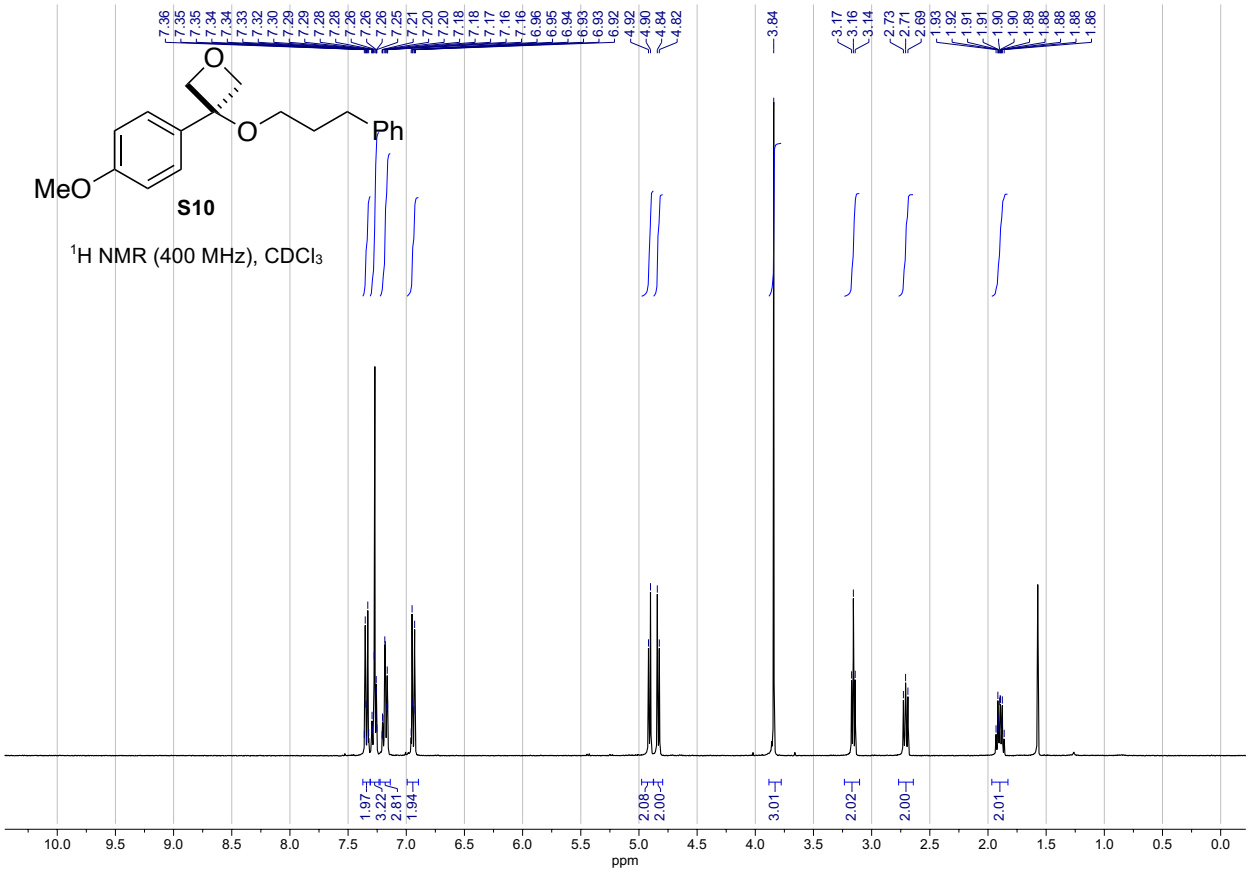

S16
^{13}C NMR (101 MHz), CDCl$_3$
172.7
155.1
79.4
46.2
36.9
35.7
28.3
19.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

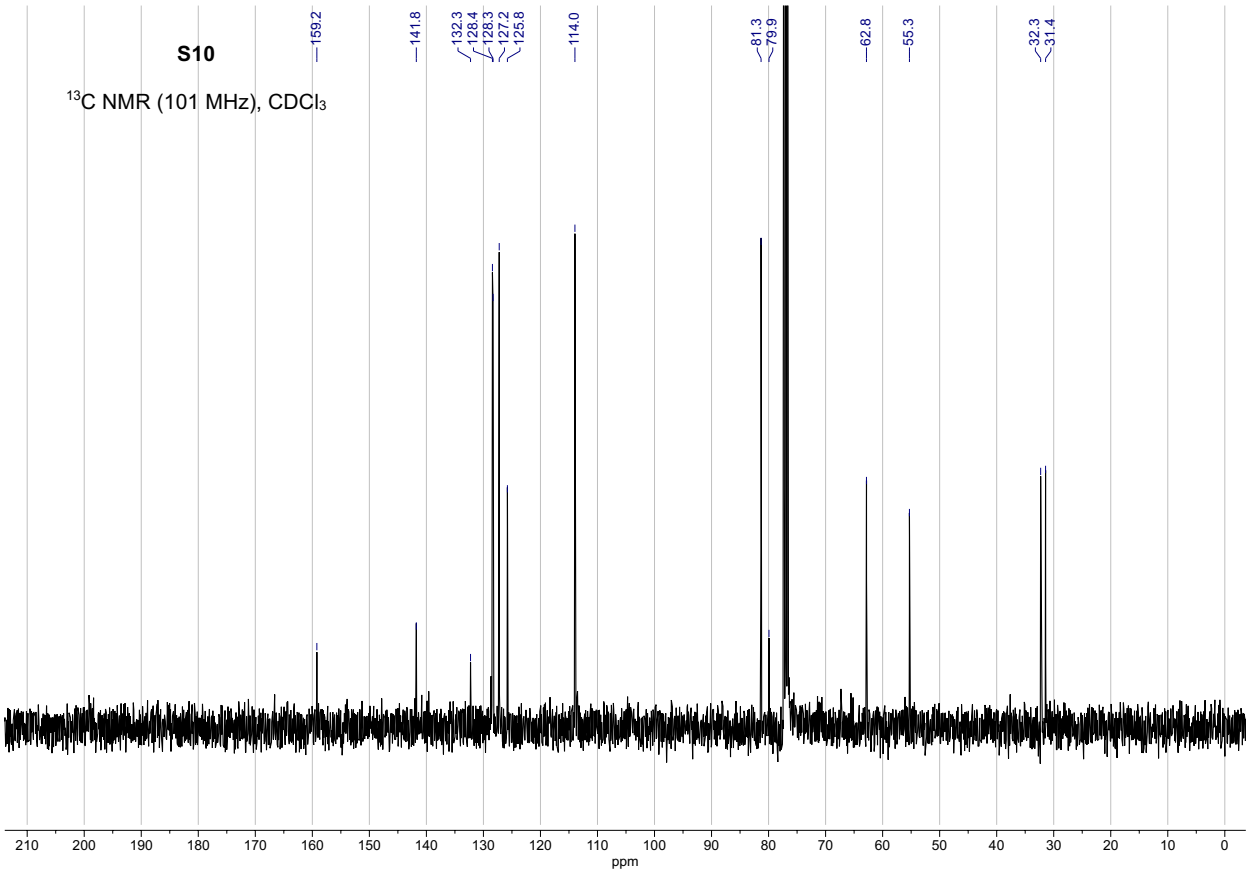

7.32
7.31
7.30
7.29
7.29
7.28
6.94
6.93
6.93
6.91
6.91
6.90
4.94
4.93
4.84
4.83
4.81
4.72
4.71
3.83
3.45
3.43
3.41
3.39
2.88
2.74
1.75
1.14
1.13
O
N
H
N
O
MeO
S8
^{1}H NMR (400 MHz), CDCl$_3$
2.01
1.98
1.02
2.04
1.00
3.00
0.99
2.98
3.02
1.33
3.08
ppm

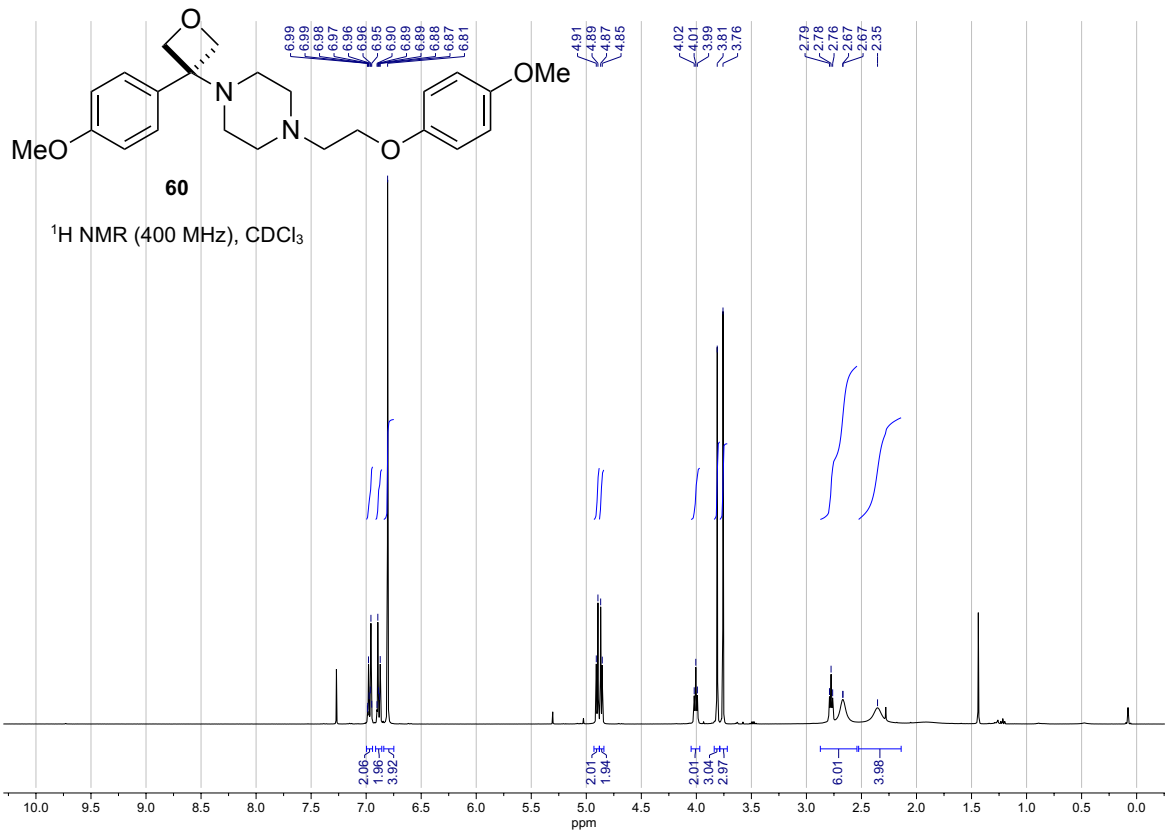

175.7
158.7
134.6
127.7
113.8
84.0
82.6
62.8
55.3
48.5
36.5
35.8
20.2
S8
^{13}C NMR (101 MHz), CDCl$_3$
ppm

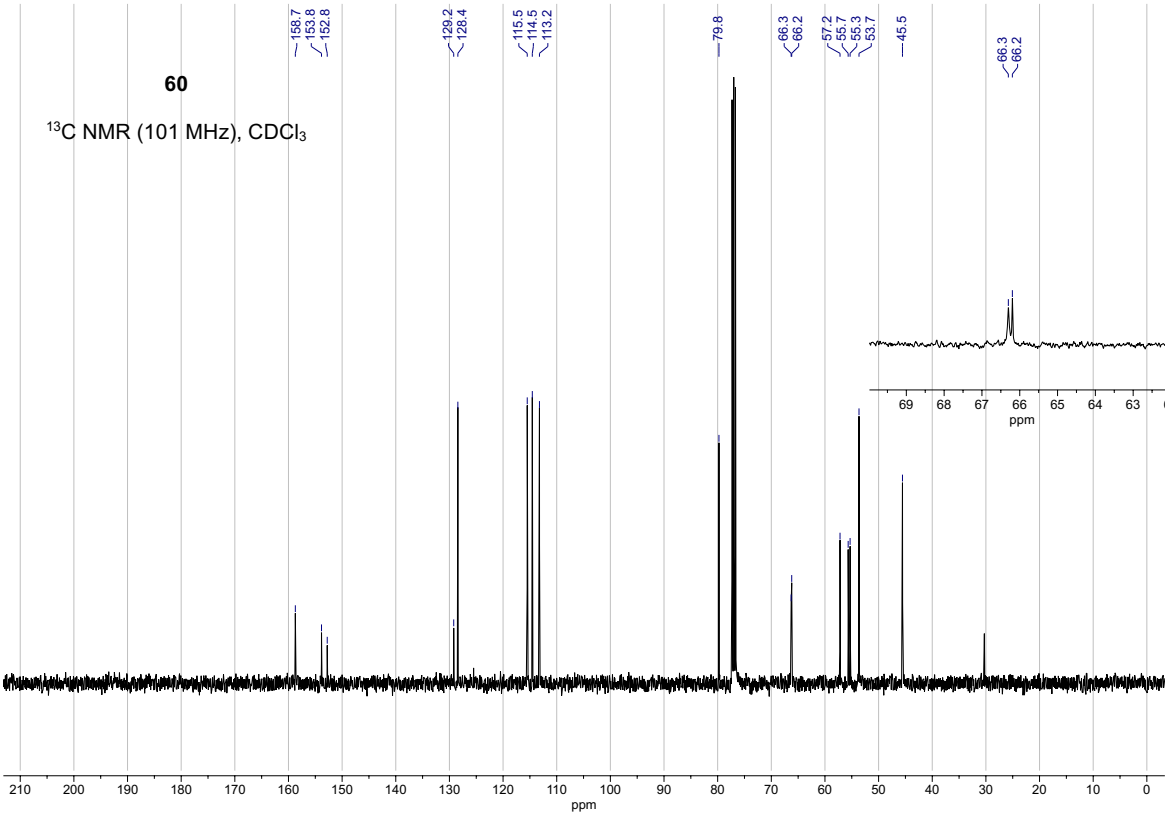

7.98
7.98
7.97
7.96
7.88
7.87
7.56
7.55
7.55
7.54
7.53
7.52
7.52
7.51
7.00
6.98
6.97
6.96
6.94
6.93
6.92
6.91
6.91
6.90
6.47
6.47
6.47
6.46
6.45
6.45
6.45
6.44
5.00
4.98
4.88
4.86
4.79
3.81
O
N
H
N
MeO
S9
^{1}H NMR (400 MHz), CDCl$_3$
1.00
0.98
1.95
1.03
1.87
0.96
2.00
2.05
0.96
3.01
10.0 9.5 9.0 8.5 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

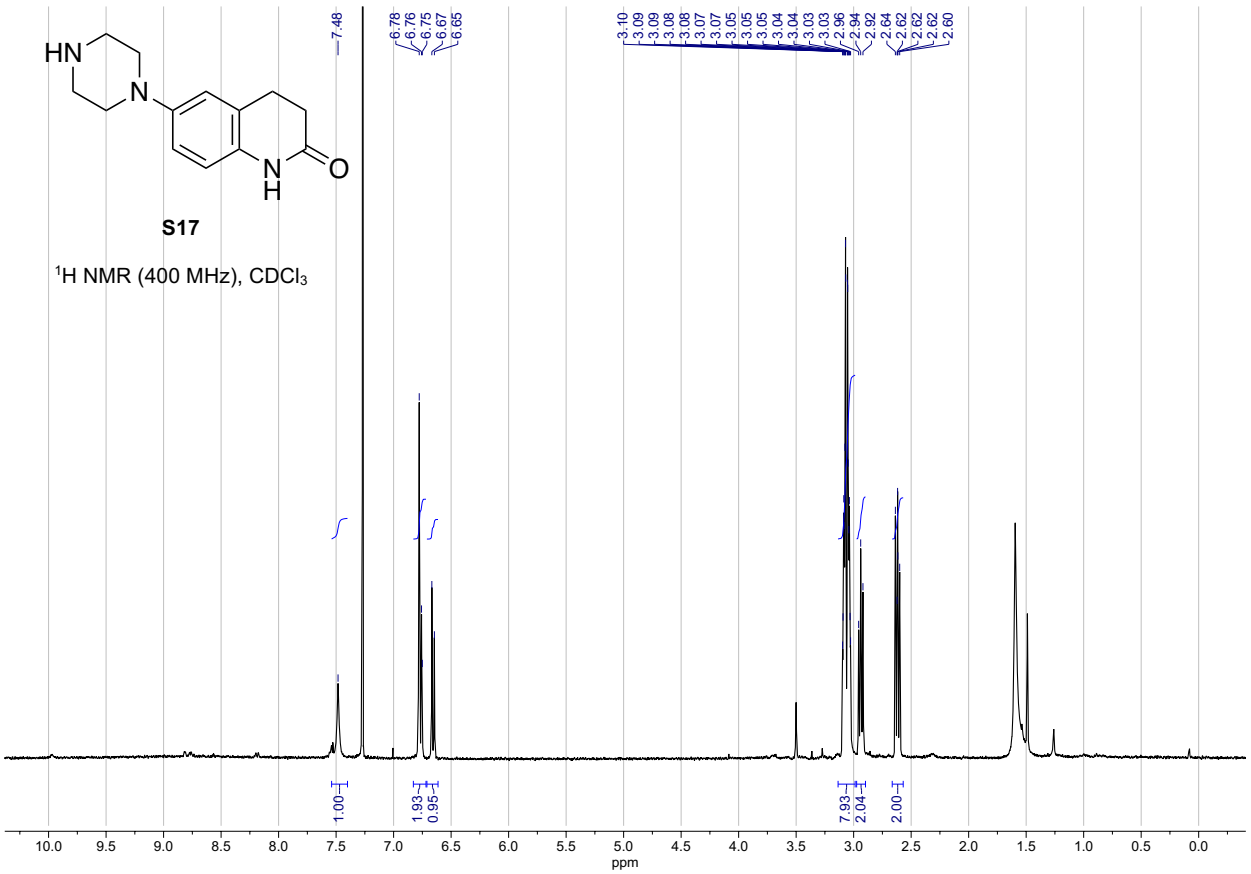

159.1
140.9
139.4
137.1
132.7
126.5
123.5
119.9
114.3
83.9
59.9
55.3
S9
^{13}C NMR (101 MHz), CDCl$_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

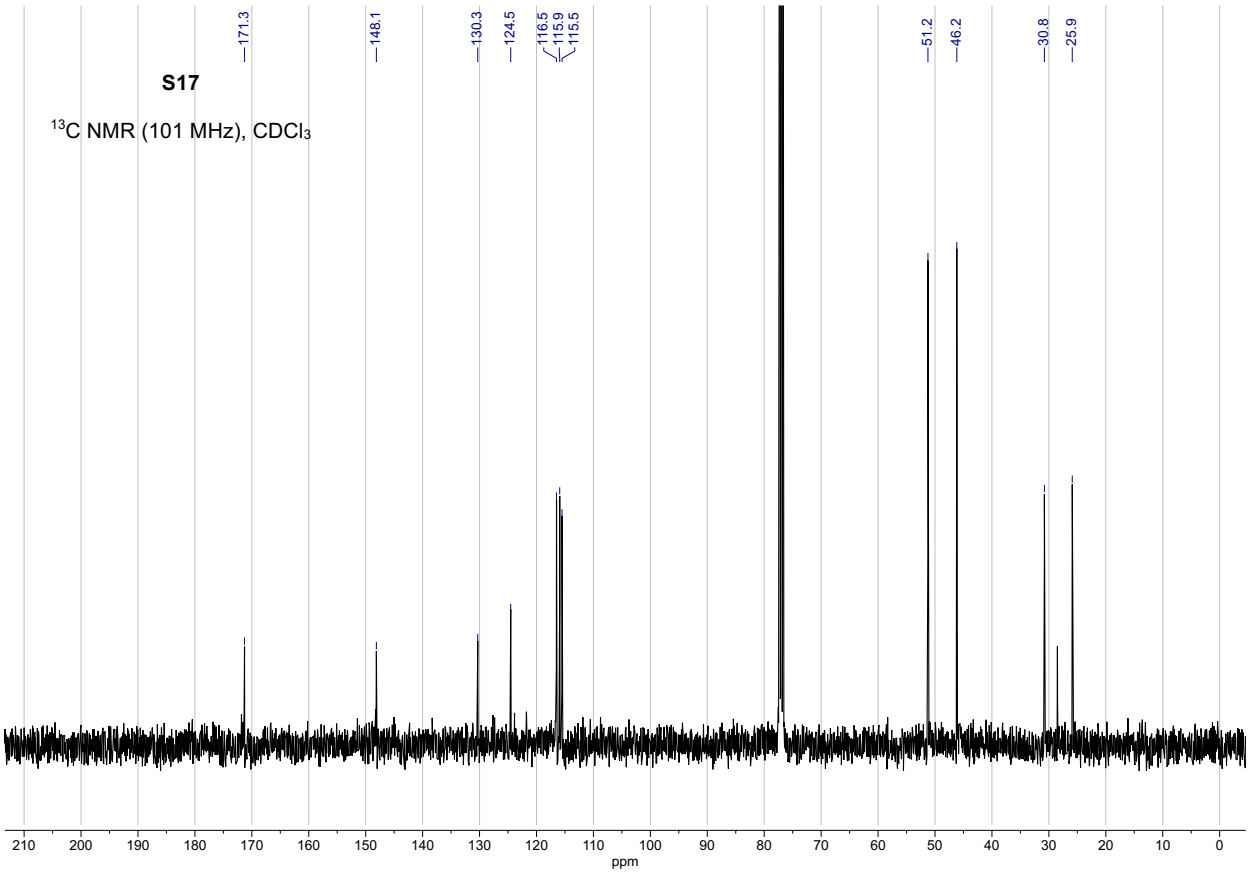

MeO
O
O
Ph
S10
^{1}H NMR (400 MHz), CDCl$_3$
ppm

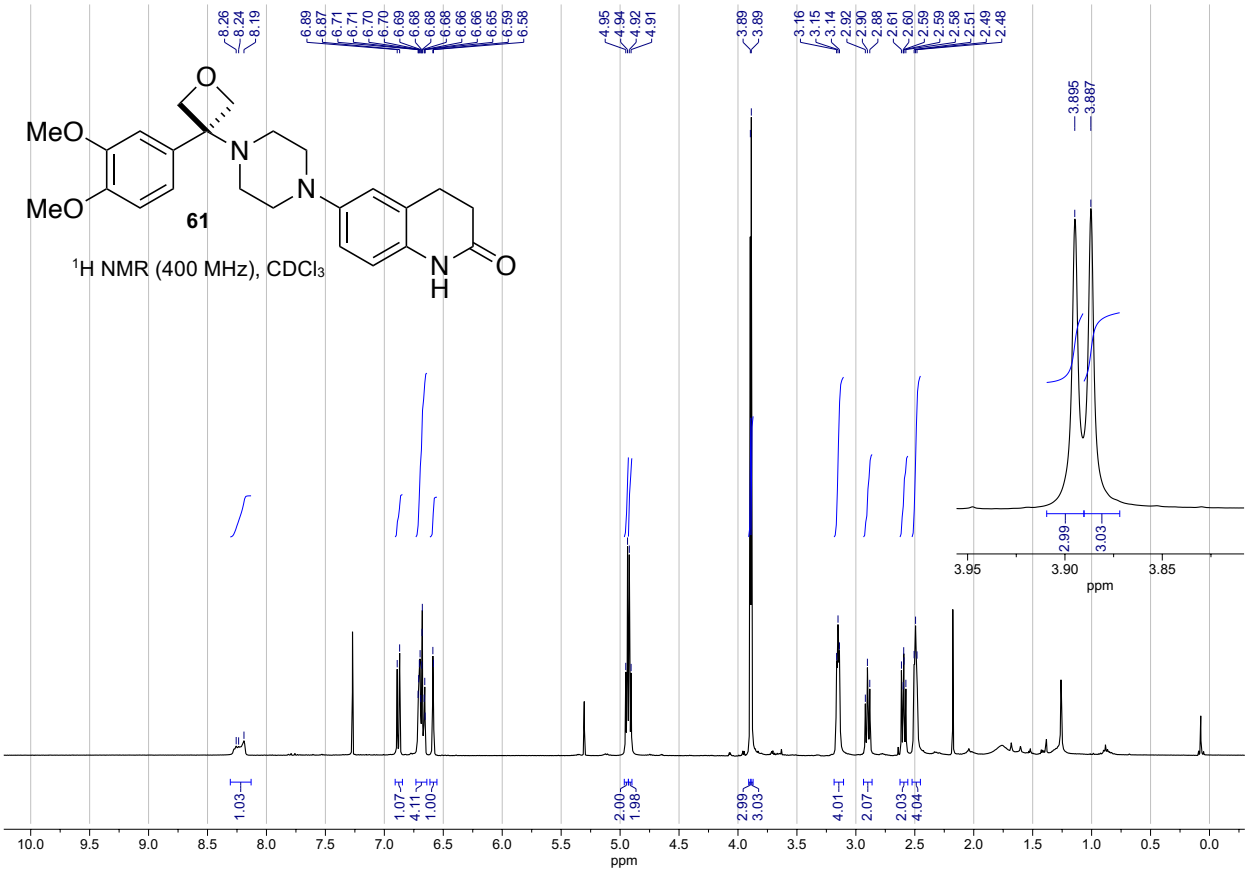

S10
^{13}C NMR (101 MHz), CDCl$_3$
ppm

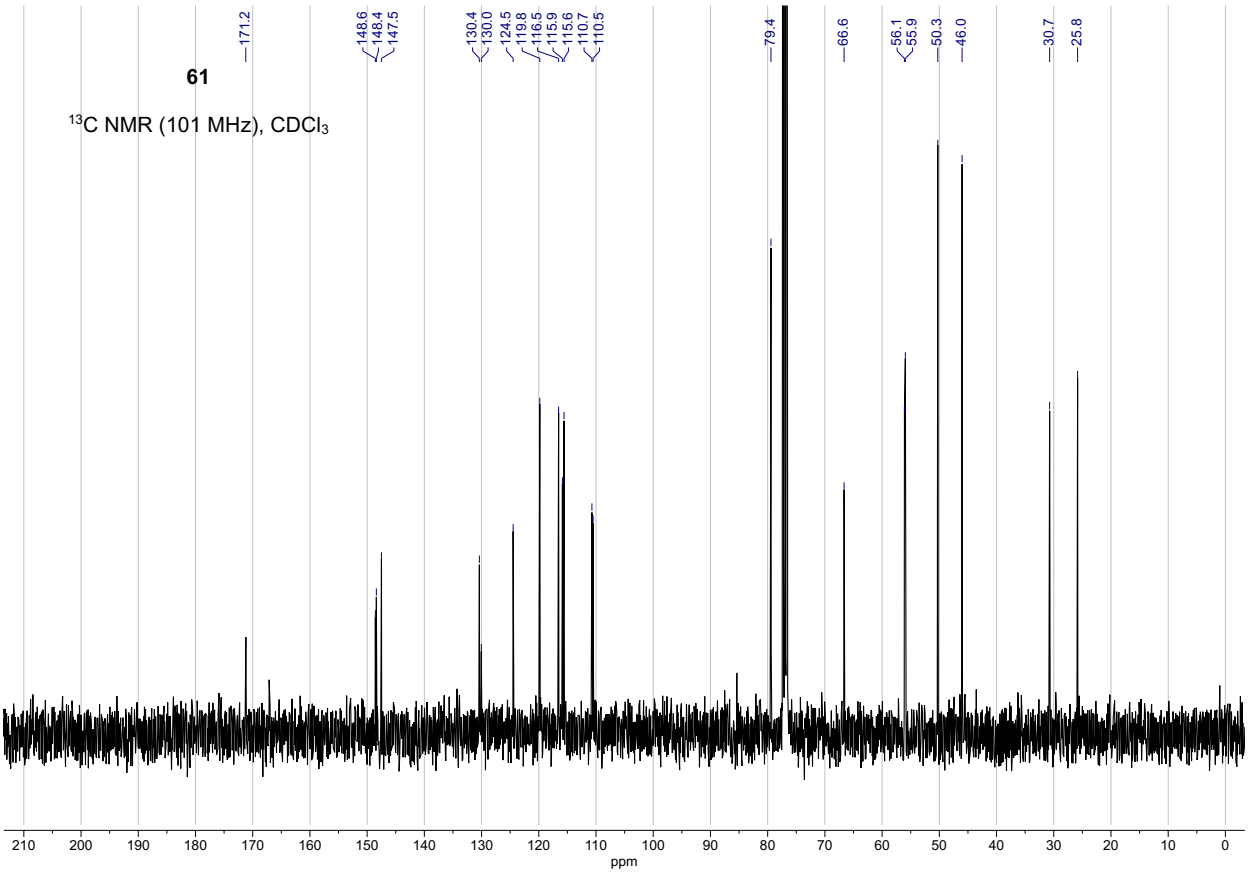

MeO
OMe
N
N
O
O
60
^{1}H NMR (400 MHz), $CDCl_3$
6.99
6.99
6.98
6.97
6.96
6.96
6.95
6.90
6.89
6.89
6.88
6.87
6.81
4.91
4.89
4.87
4.85
4.02
4.01
3.99
3.81
3.76
2.79
2.78
2.76
2.67
2.67
2.35
2.06
1.96
3.92
2.01
1.94
2.01
3.04
2.97
6.01
3.98
ppm

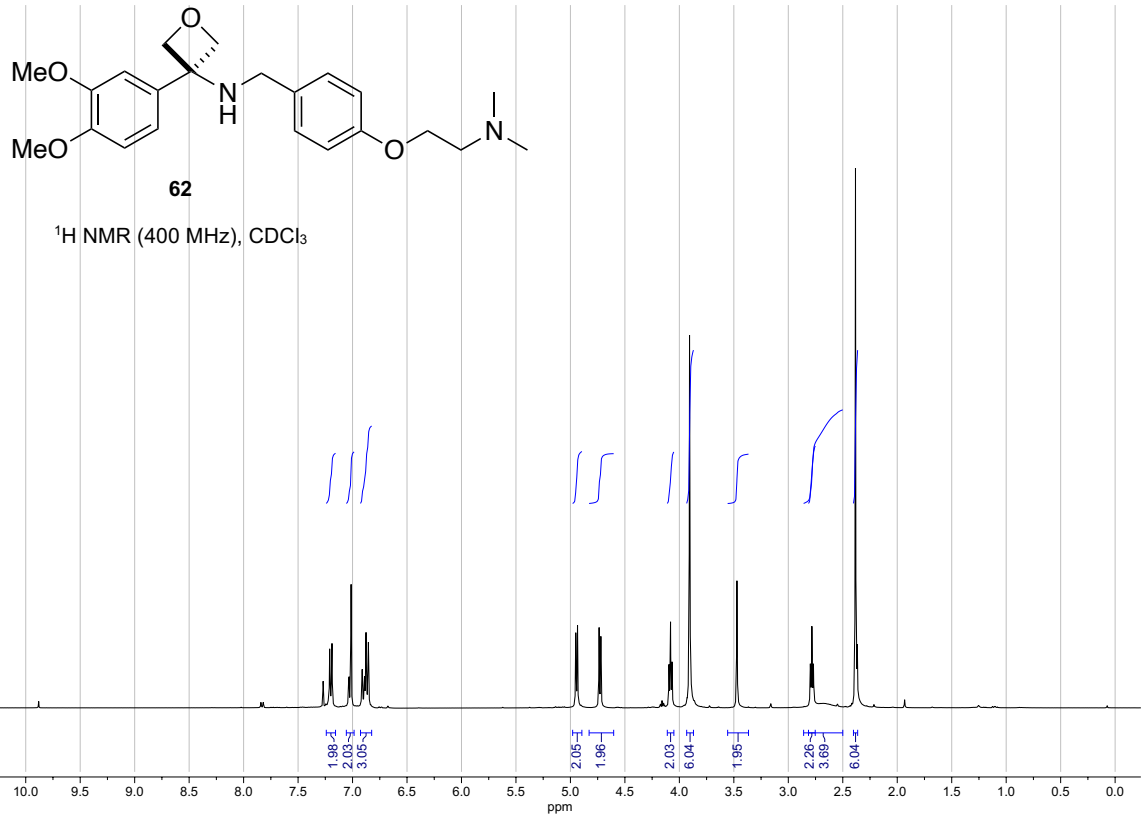

60
^{13}C NMR (101 MHz), $CDCl_3$
158.7
153.8
152.8
129.2
128.4
115.5
114.5
113.2
79.8
66.3
66.2
57.2
55.7
55.3
53.7
45.5
66.3
66.2
ppm
ppm

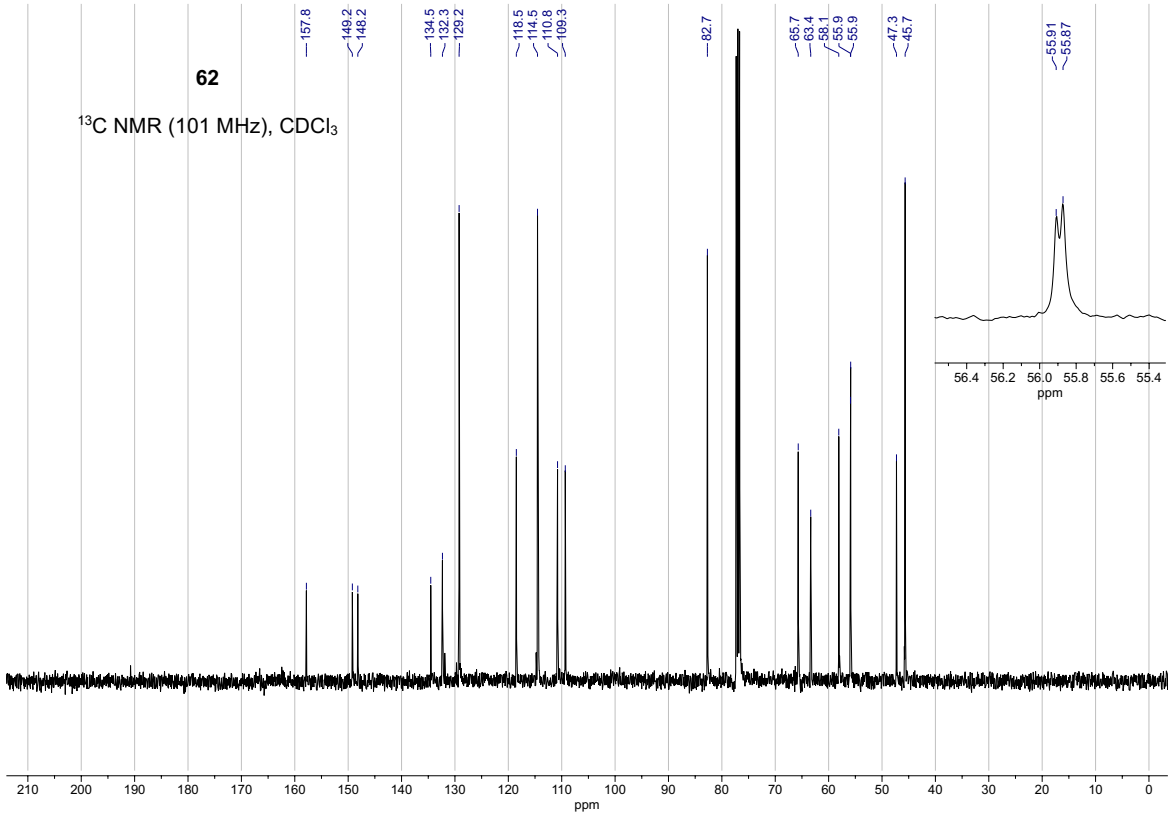

HN
N
N
H
O
S17
^{1}H NMR (400 MHz), $CDCl_3$
7.48
6.78
6.76
6.75
6.67
6.65
3.10
3.09
3.09
3.08
3.08
3.07
3.07
3.05
3.05
3.05
3.04
3.04
3.03
3.03
2.96
2.94
2.92
2.64
2.62
2.62
2.62
2.60
1.00
1.93
0.95
7.93
2.04
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

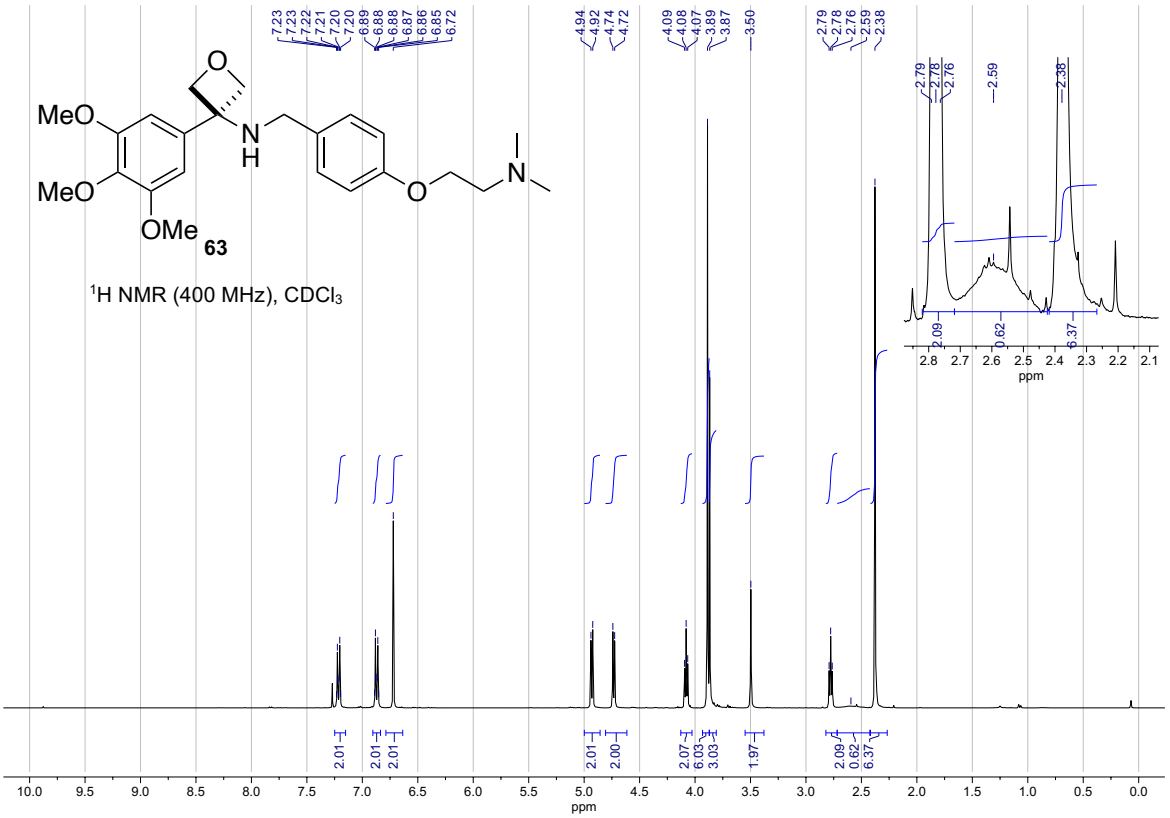

S17
^{13}C NMR (101 MHz), $CDCl_3$
171.3
148.1
130.3
124.5
116.5
115.9
115.5
51.2
46.2
30.8
25.9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

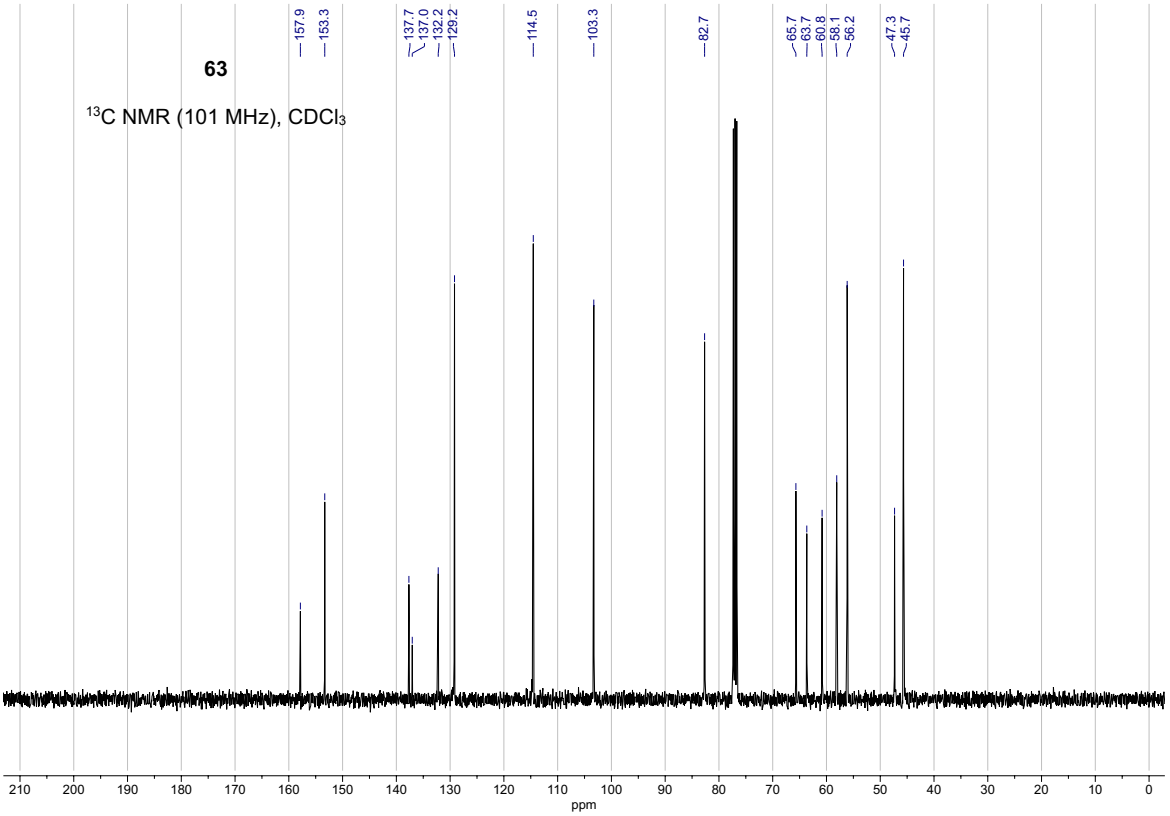

MeO
MeO
O
N
N
N
H
O
61
^{1}H NMR (400 MHz), CDCl$_3$
8.26
8.24
8.19
6.89
6.87
6.71
6.71
6.70
6.70
6.69
6.68
6.68
6.68
6.66
6.66
6.65
6.59
6.58
4.95
4.94
4.92
4.91
3.89
3.89
3.16
3.15
3.14
2.92
2.90
2.88
2.61
2.60
2.59
2.59
2.58
2.51
2.49
2.48
3.895
3.887
2.99
3.03
3.95
3.90
3.85
ppm
1.03
1.07
4.11
1.00
2.00
1.98
2.99
3.03
4.01
2.07
2.03
4.04
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

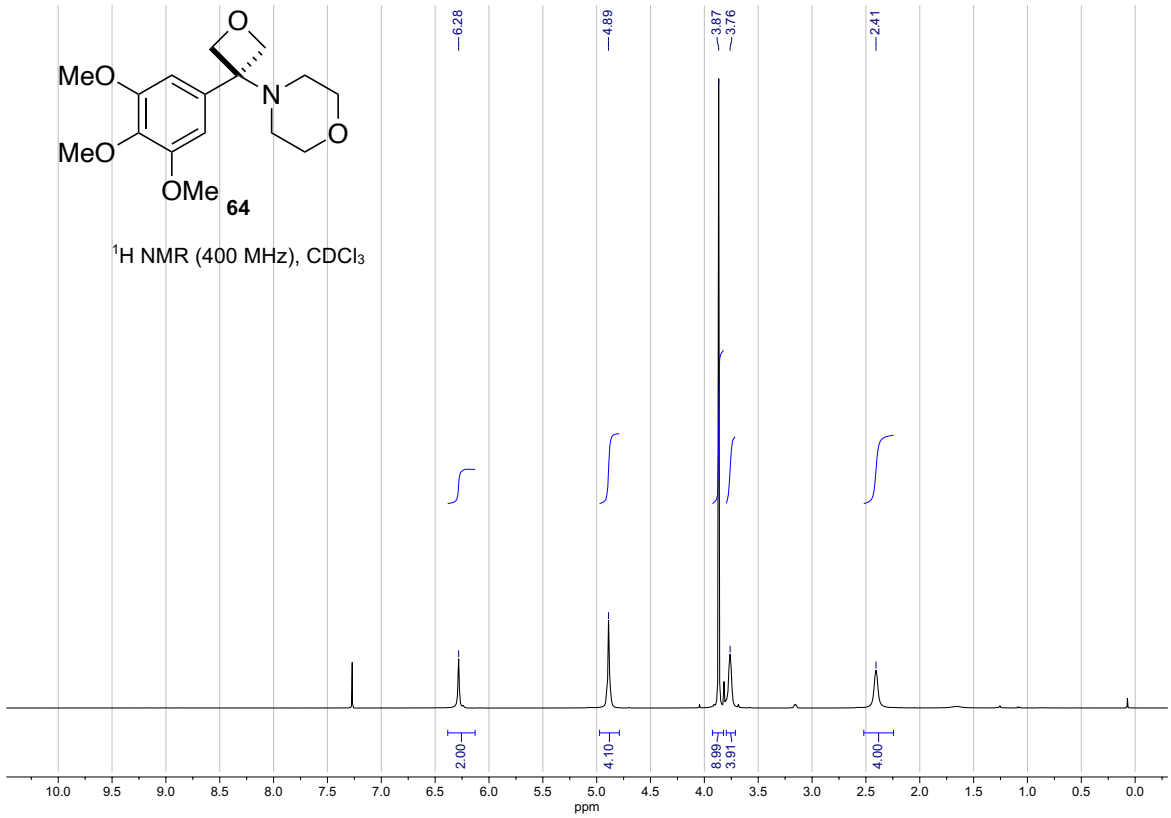

61
^{13}C NMR (101 MHz), CDCl$_3$
171.2
148.6
148.4
147.5
130.4
130.0
124.5
119.8
116.5
115.9
115.6
110.7
110.5
79.4
66.6
56.1
55.9
50.3
46.0
30.7
25.8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

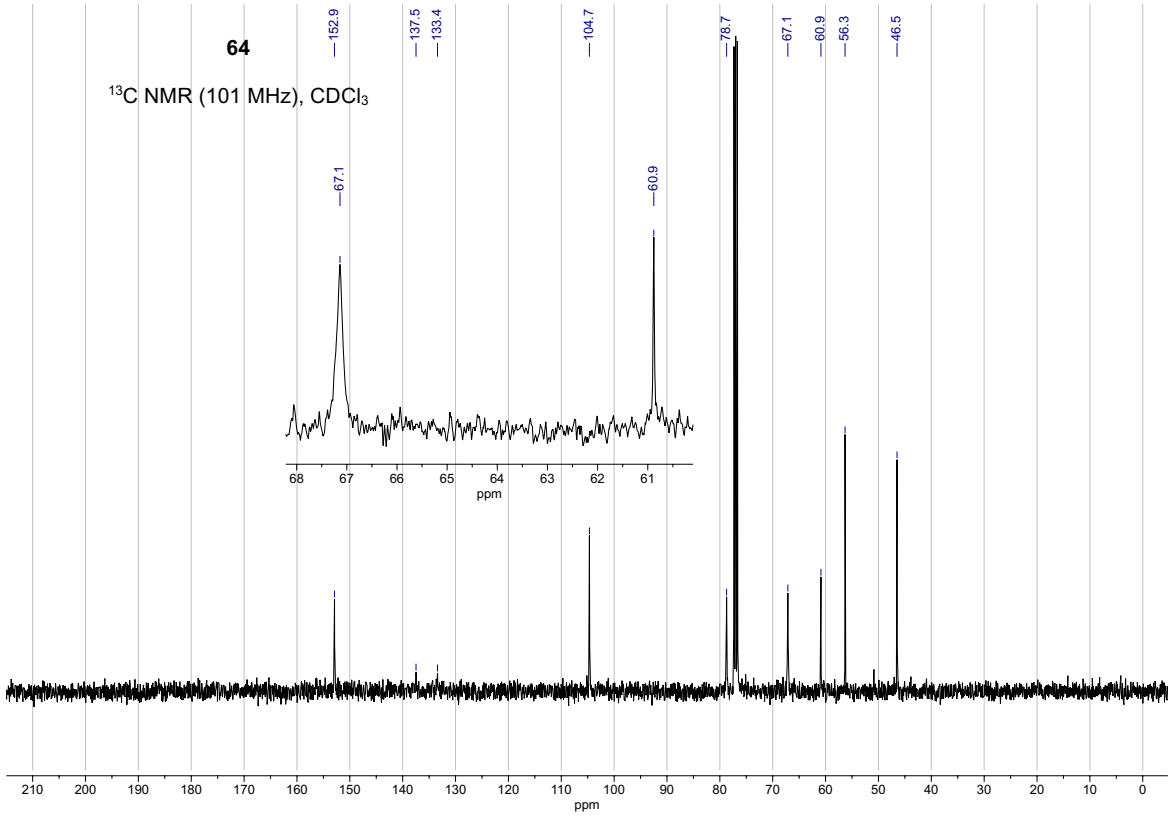

MeO
MeO
O
N
H
O
N
62
^{1}H NMR (400 MHz), CDCl$_3$
1.98
2.03
3.05
2.05
1.96
2.03
6.04
1.95
2.26
3.69
6.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


62
^{13}C NMR (101 MHz), CDCl$_3$
157.8
149.2
148.2
134.5
132.3
129.2
118.5
114.5
110.8
109.3
82.7
65.7
63.4
58.1
55.9
55.9
47.3
45.7
55.91
55.87
56.4 56.2 56.0 55.8 55.6 55.4
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


MeO
MeO
OMe
O
N
H
O
N
63
^{1}H NMR (400 MHz), CDCl$_3$
ppm


63
^{13}C NMR (101 MHz), CDCl$_3$
ppm


MeO
MeO
OMe
O
N
O
64
^{1}H NMR (400 MHz), CDCl$_3$
6.28
4.89
3.87
3.76
2.41
2.00
4.10
8.99
3.91
4.00
ppm

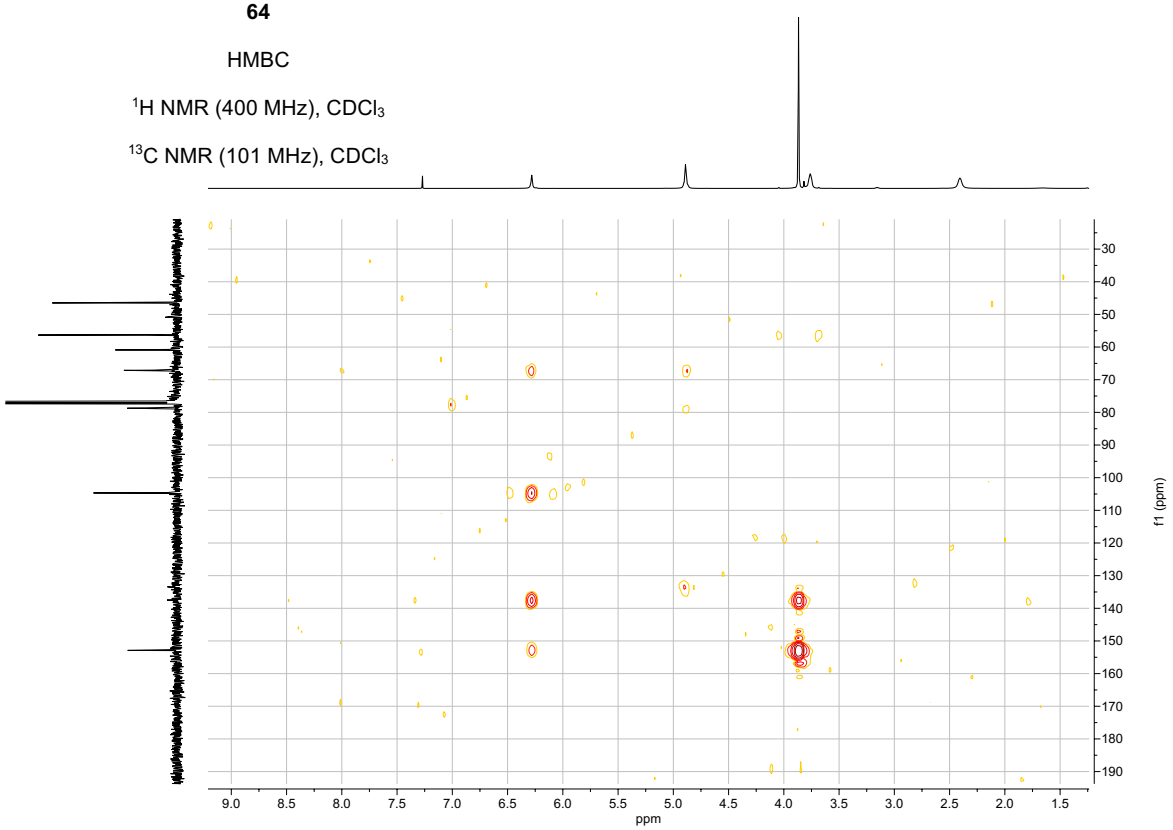

64
^{13}C NMR (101 MHz), CDCl$_3$
152.9
137.5
133.4
104.7
78.7
67.1
60.9
56.3
46.5
ppm

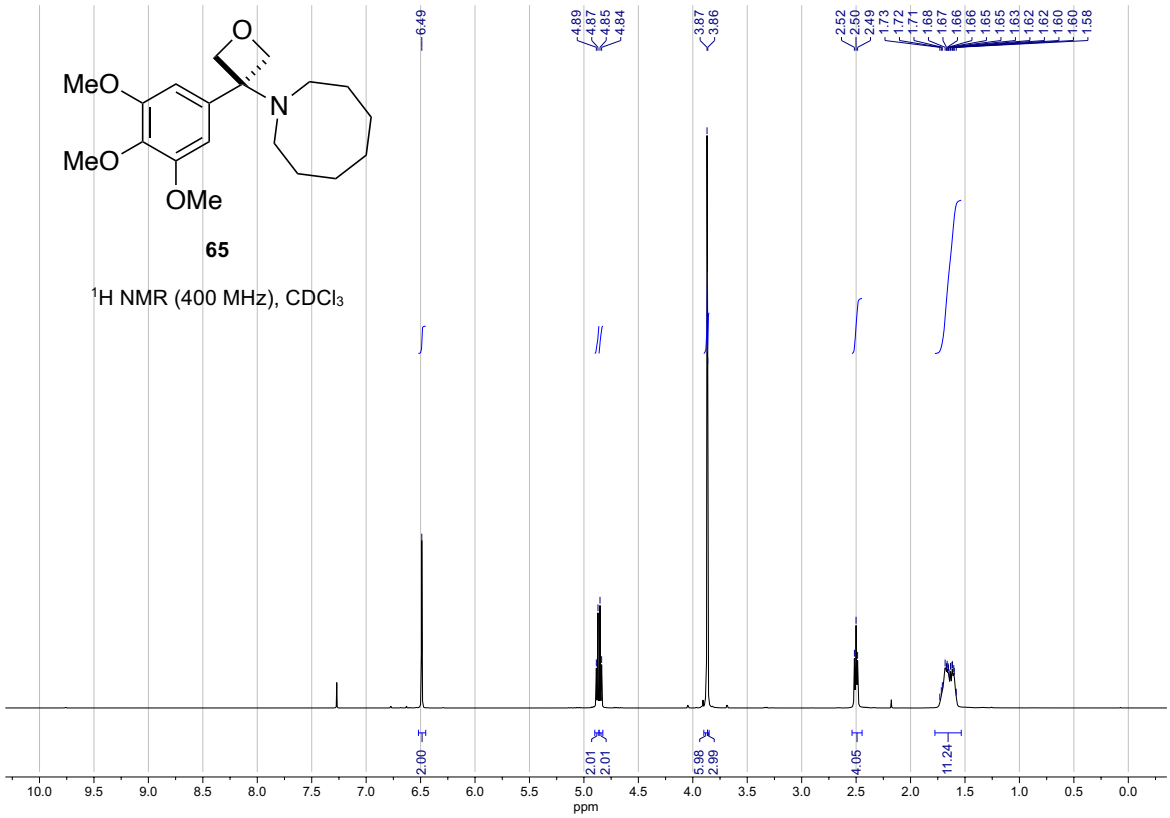
64

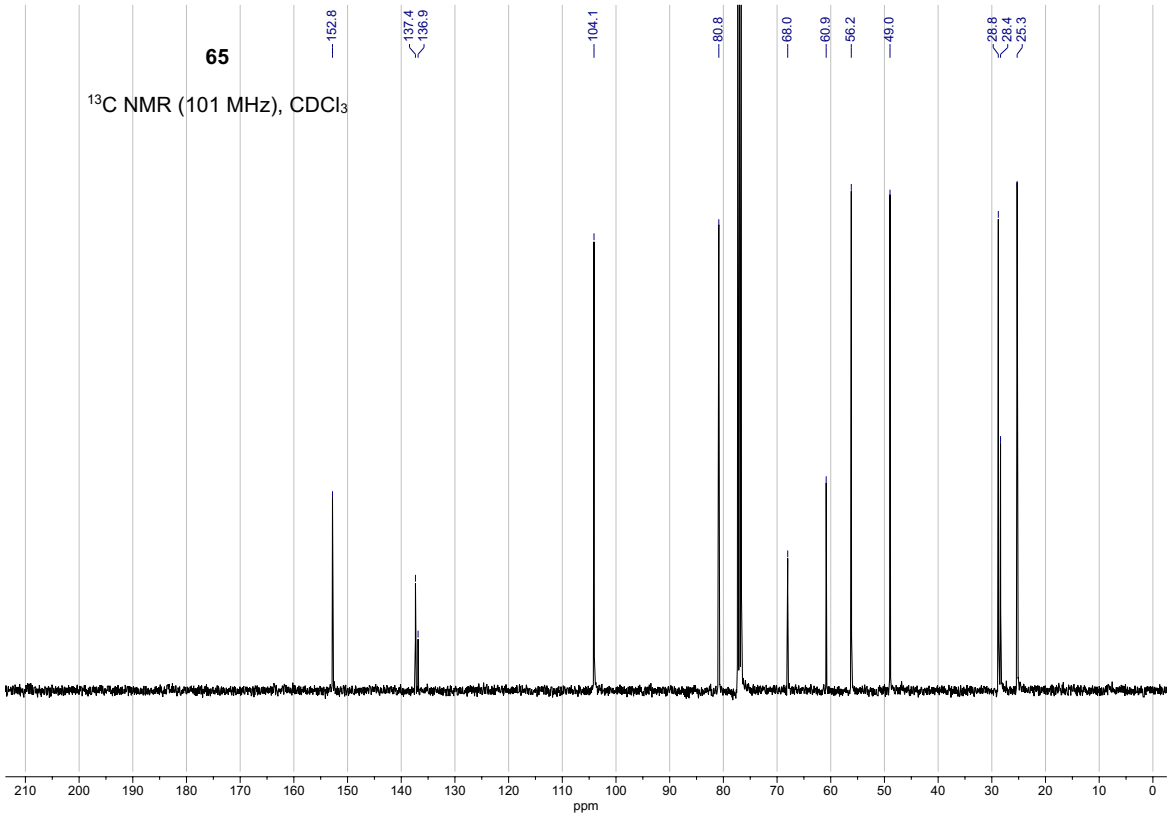
HMBC

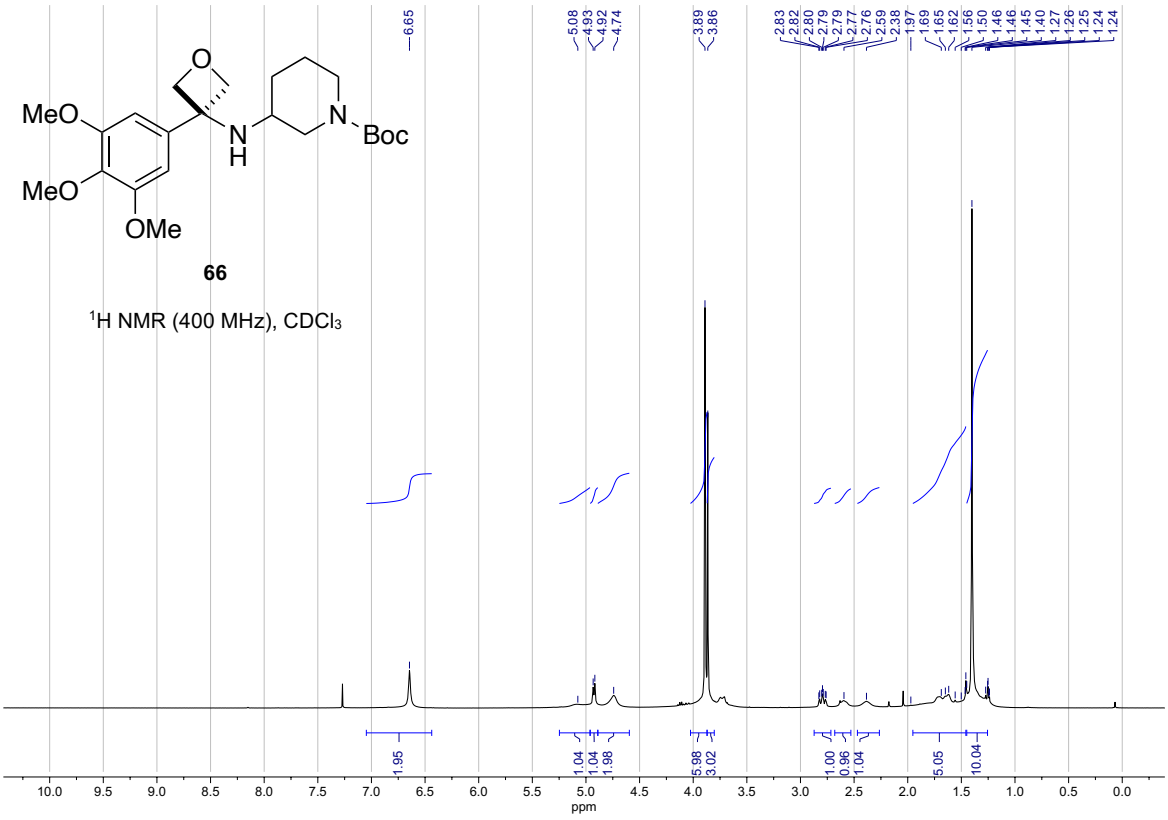
^{1}H NMR (400 MHz), $CDCl_3$

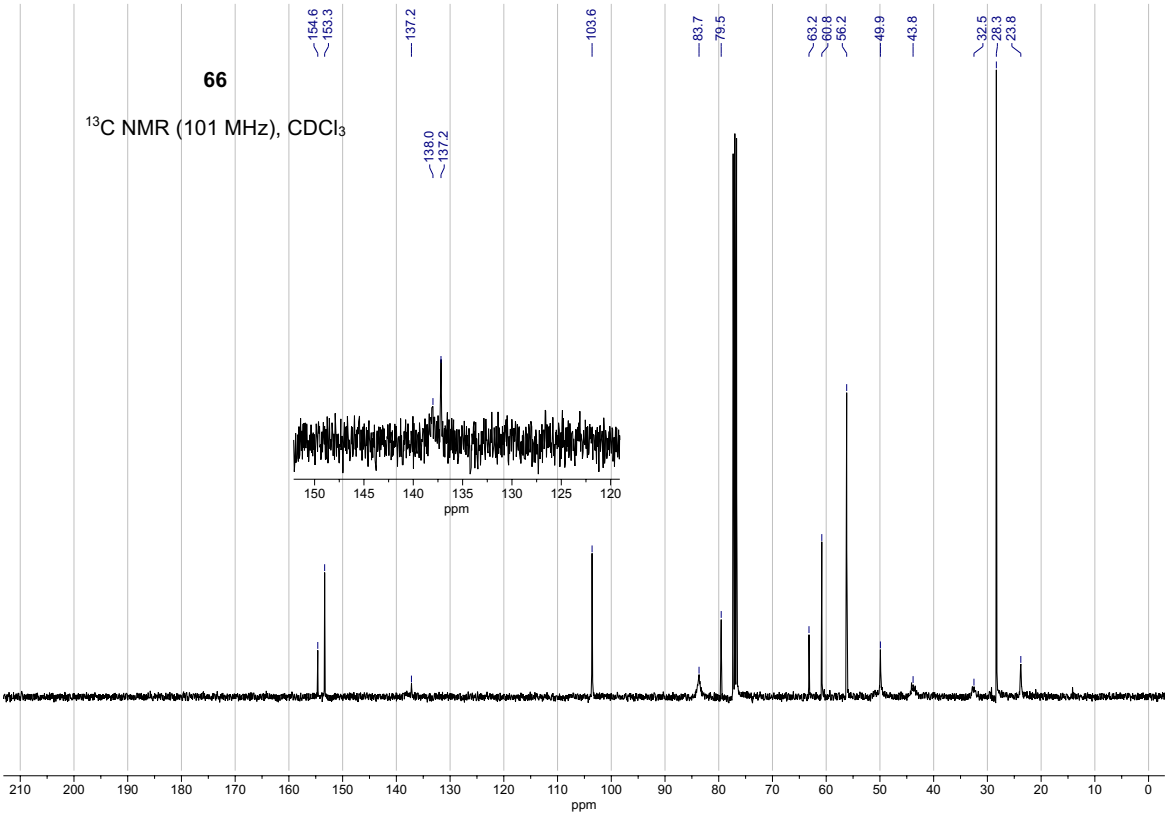
^{13}C NMR (101 MHz), $CDCl_3$

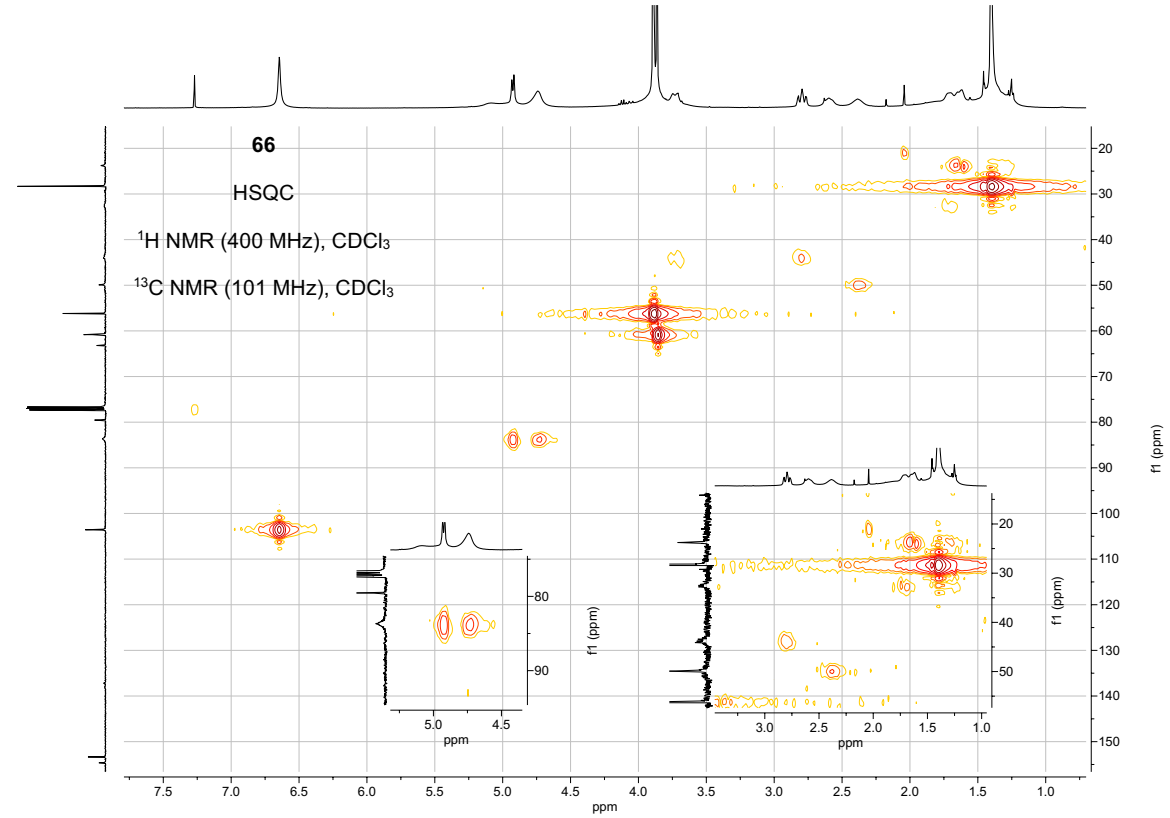


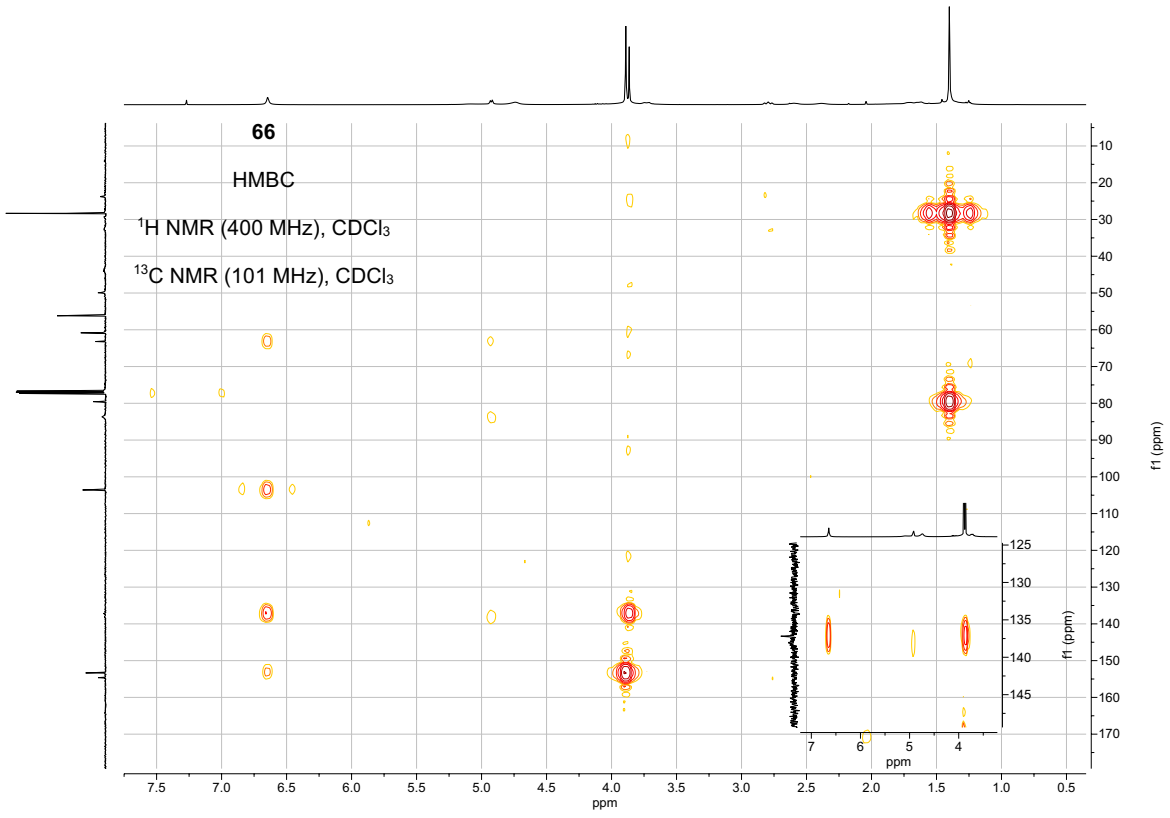

MeO
MeO
OMe
O
N
65
^{1}H NMR (400 MHz), CDCl$_3$
6.49
4.89
4.87
4.85
4.84
3.87
3.86
2.52
2.50
2.49
1.73
1.72
1.71
1.68
1.67
1.66
1.66
1.65
1.65
1.63
1.62
1.62
1.60
1.60
1.58
2.00
2.01
2.01
5.98
2.99
4.05
11.24
ppm

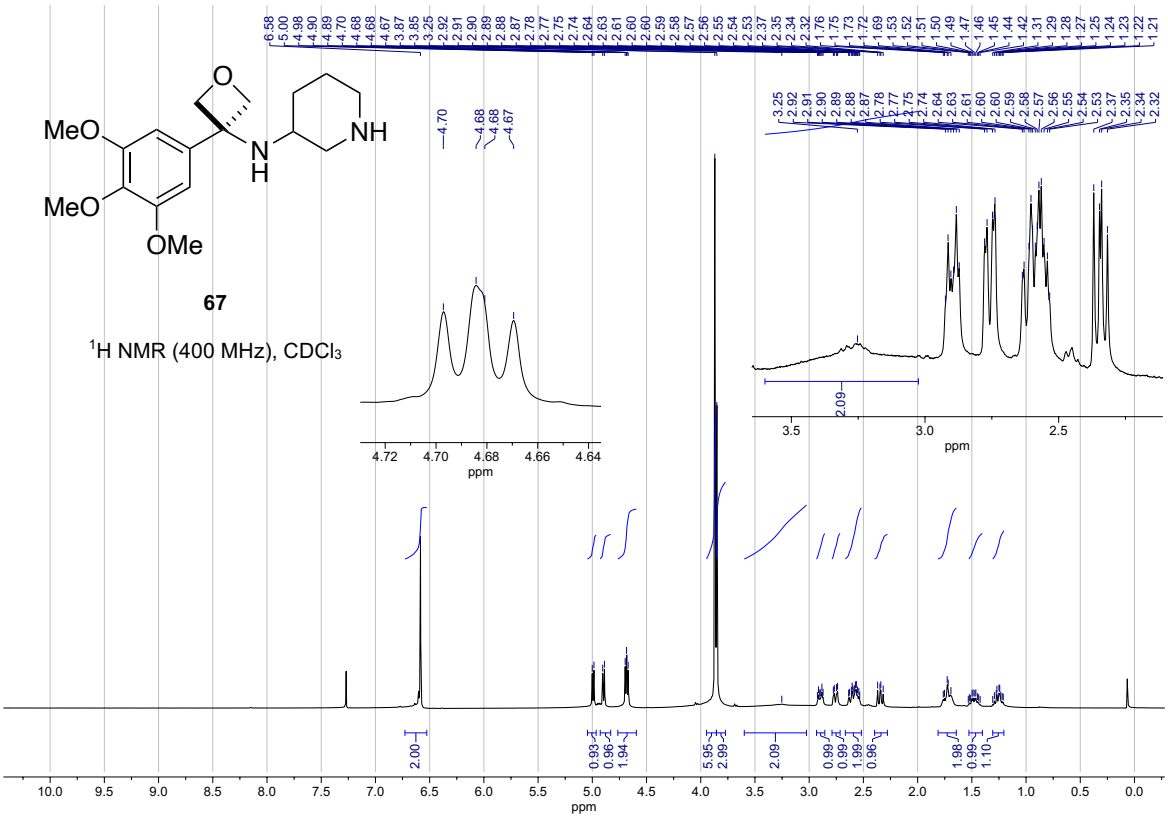

65
^{13}C NMR (101 MHz), CDCl$_3$
152.8
137.4
136.9
104.1
80.8
68.0
60.9
56.2
49.0
28.8
28.4
25.3
ppm

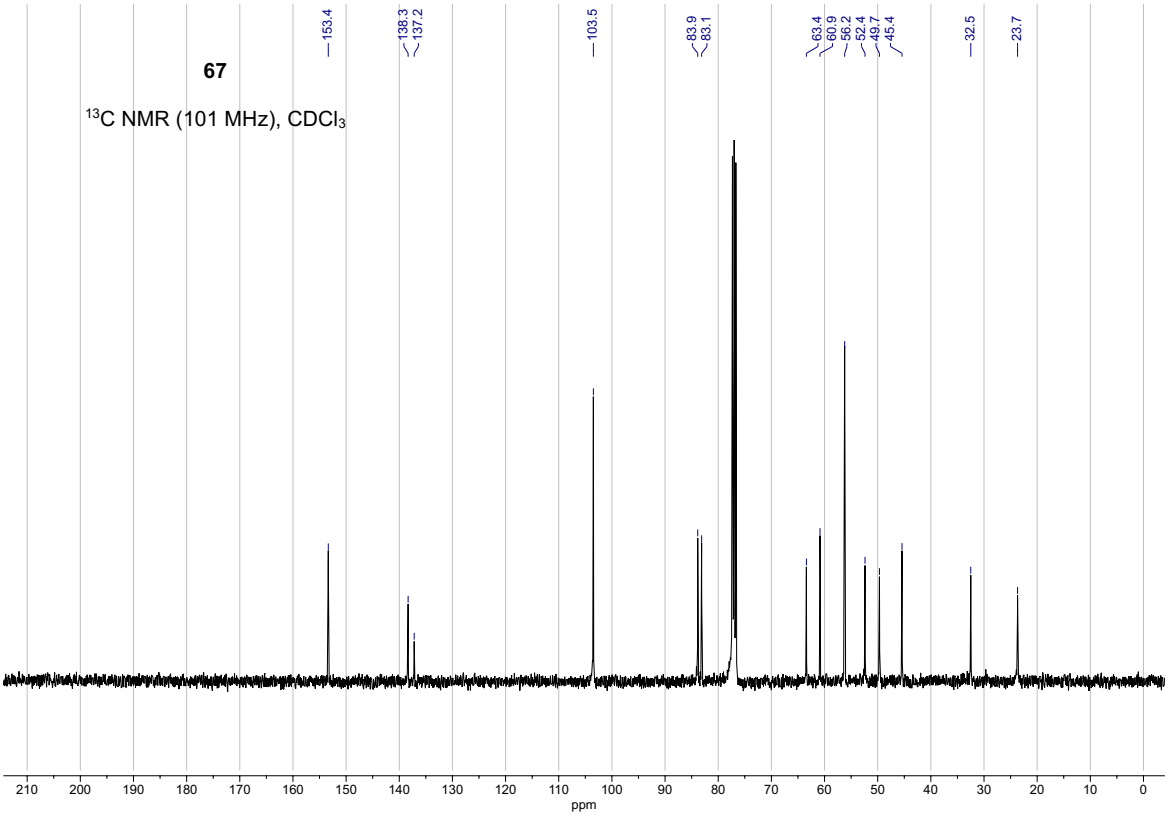

MeO
MeO
OMe
O
N
H
N
Boc
66
^{1}H NMR (400 MHz), CDCl$_3$
6.65
5.08
4.93
4.92
4.74
3.89
3.86
2.83
2.82
2.80
2.79
2.79
2.77
2.76
2.59
2.38
1.97
1.69
1.65
1.62
1.56
1.50
1.46
1.46
1.45
1.40
1.27
1.26
1.25
1.24
1.24
1.95
1.04
1.04
1.98
5.98
3.02
1.00
0.96
1.04
5.05
10.04
ppm

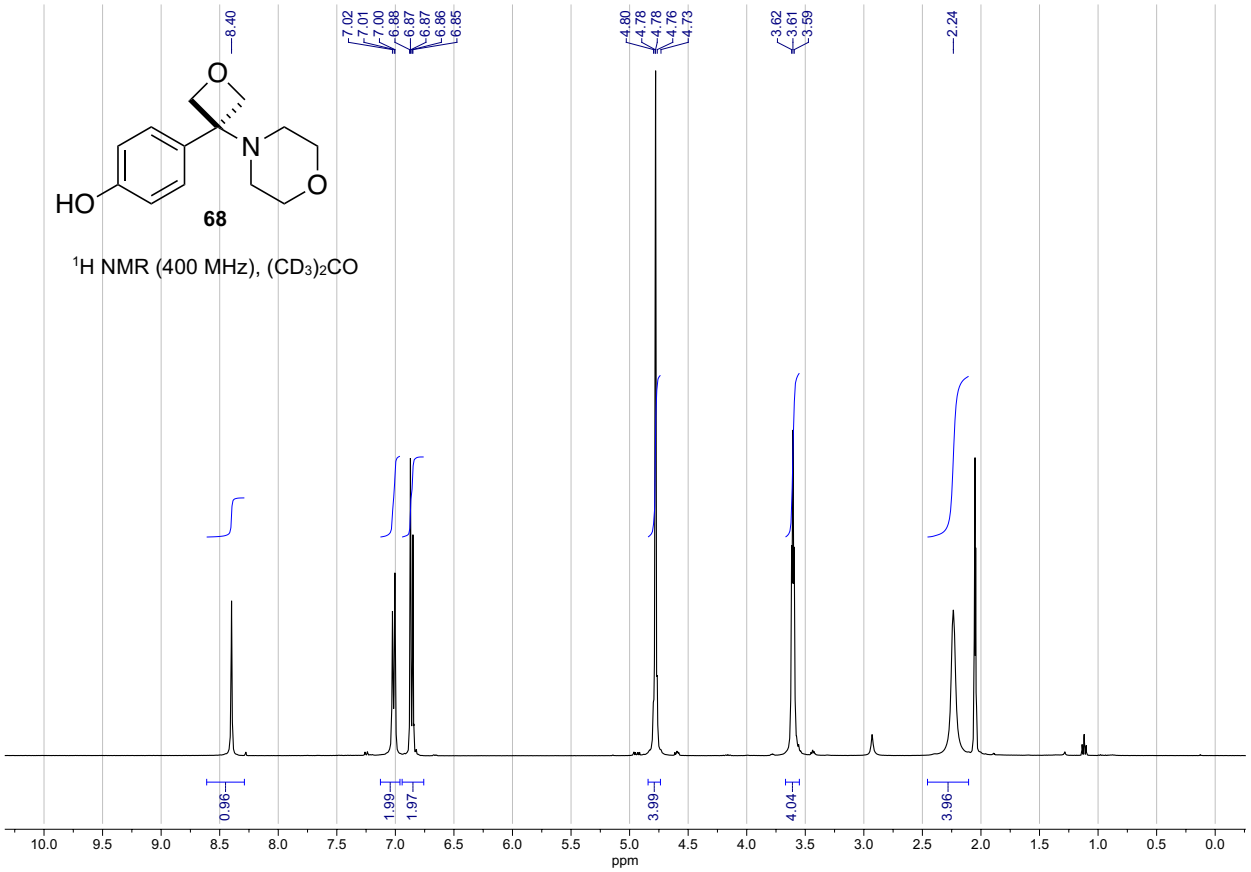

66
^{13}C NMR (101 MHz), CDCl$_3$
154.6
153.3
137.2
138.0
137.2
103.6
83.7
79.5
63.2
60.8
56.2
49.9
43.8
32.5
28.3
23.8
ppm

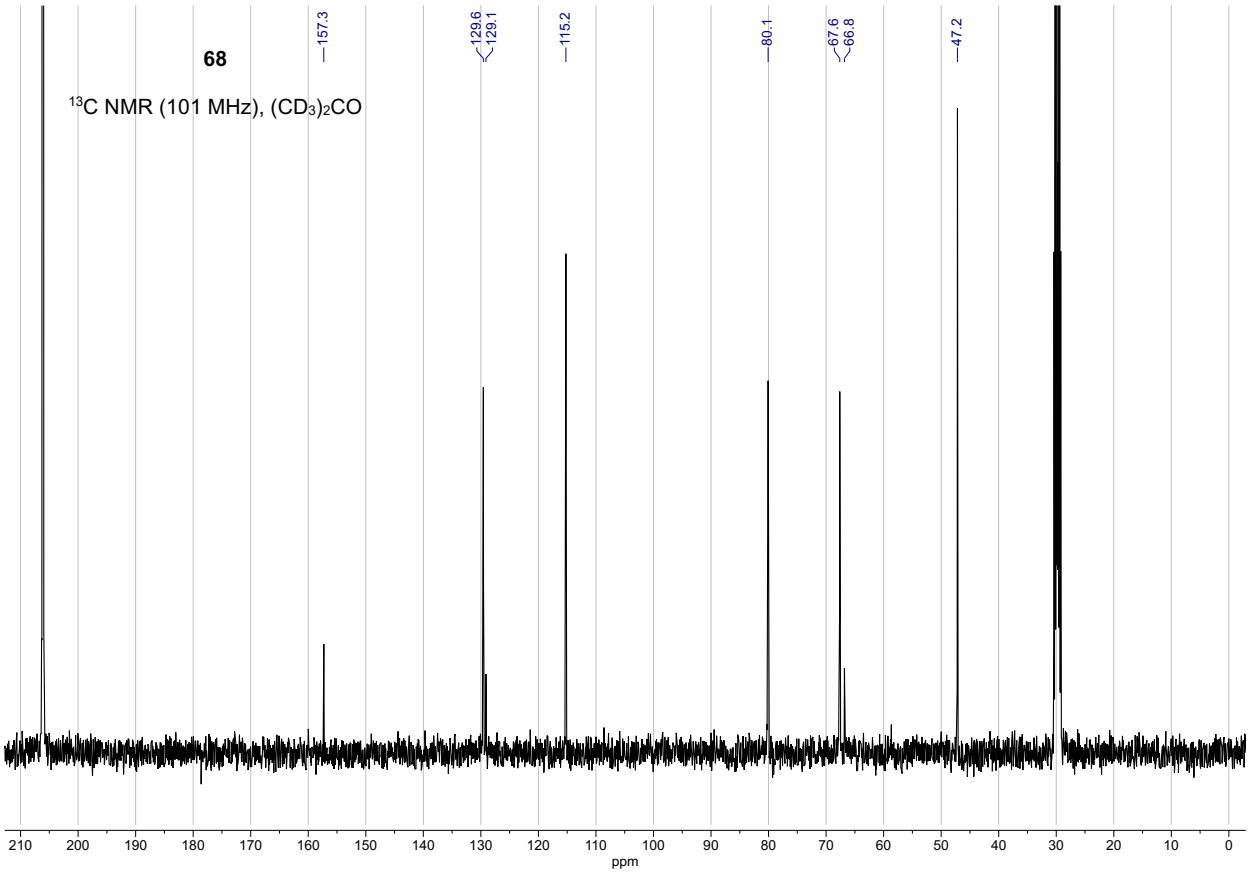

66
HSQC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
ppm
f1 (ppm)

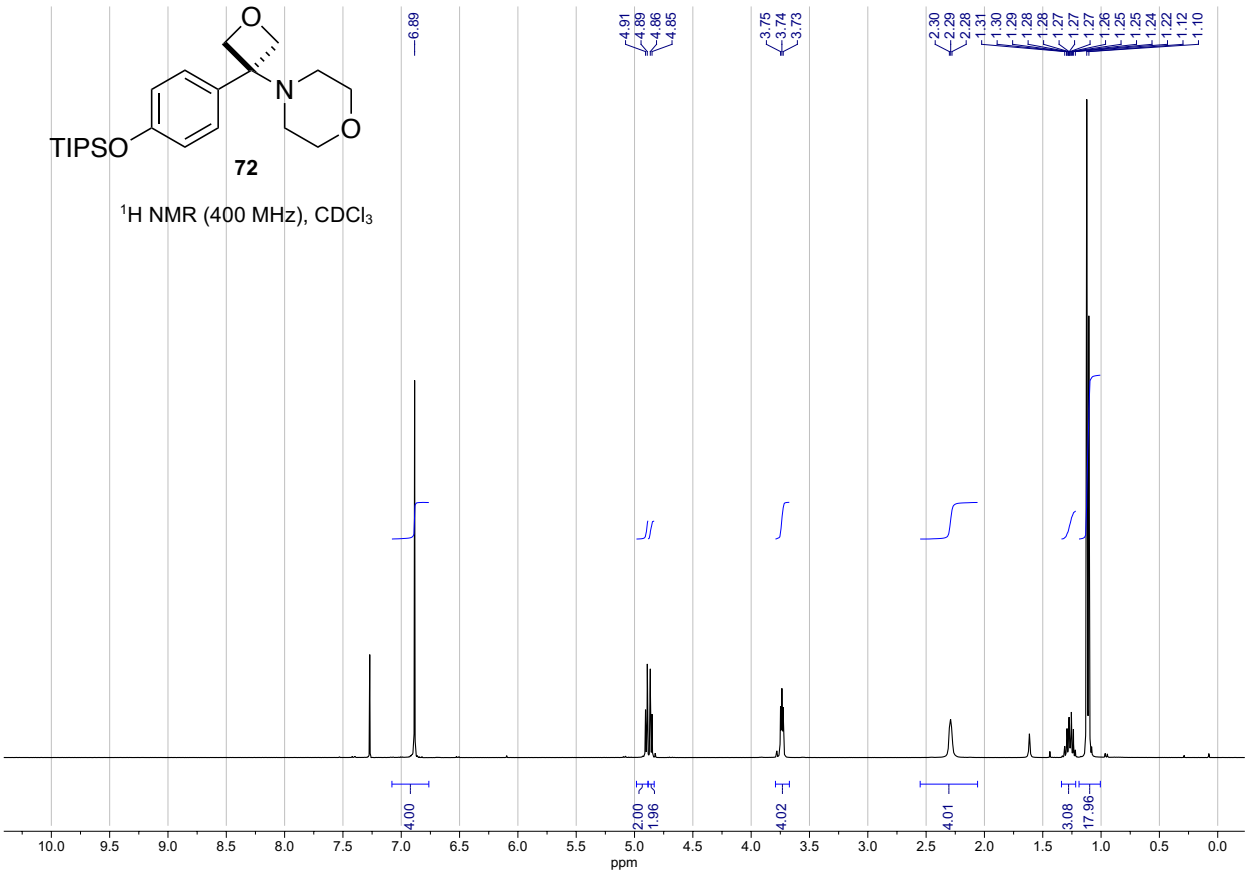

66
HMBC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
ppm
f1 (ppm)

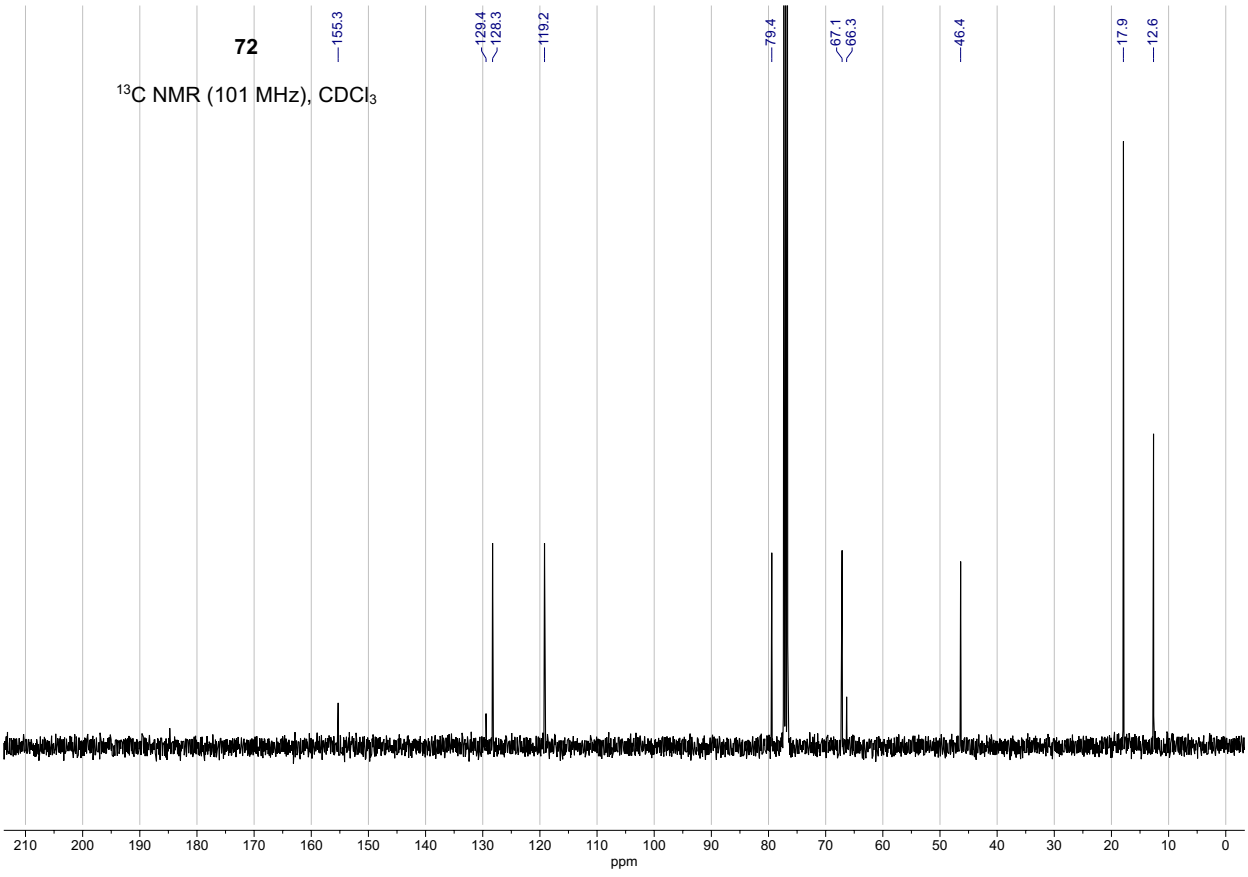

MeO
MeO
OMe
O
N
H
NH
67
^{1}H NMR (400 MHz), CDCl$_3$
ppm

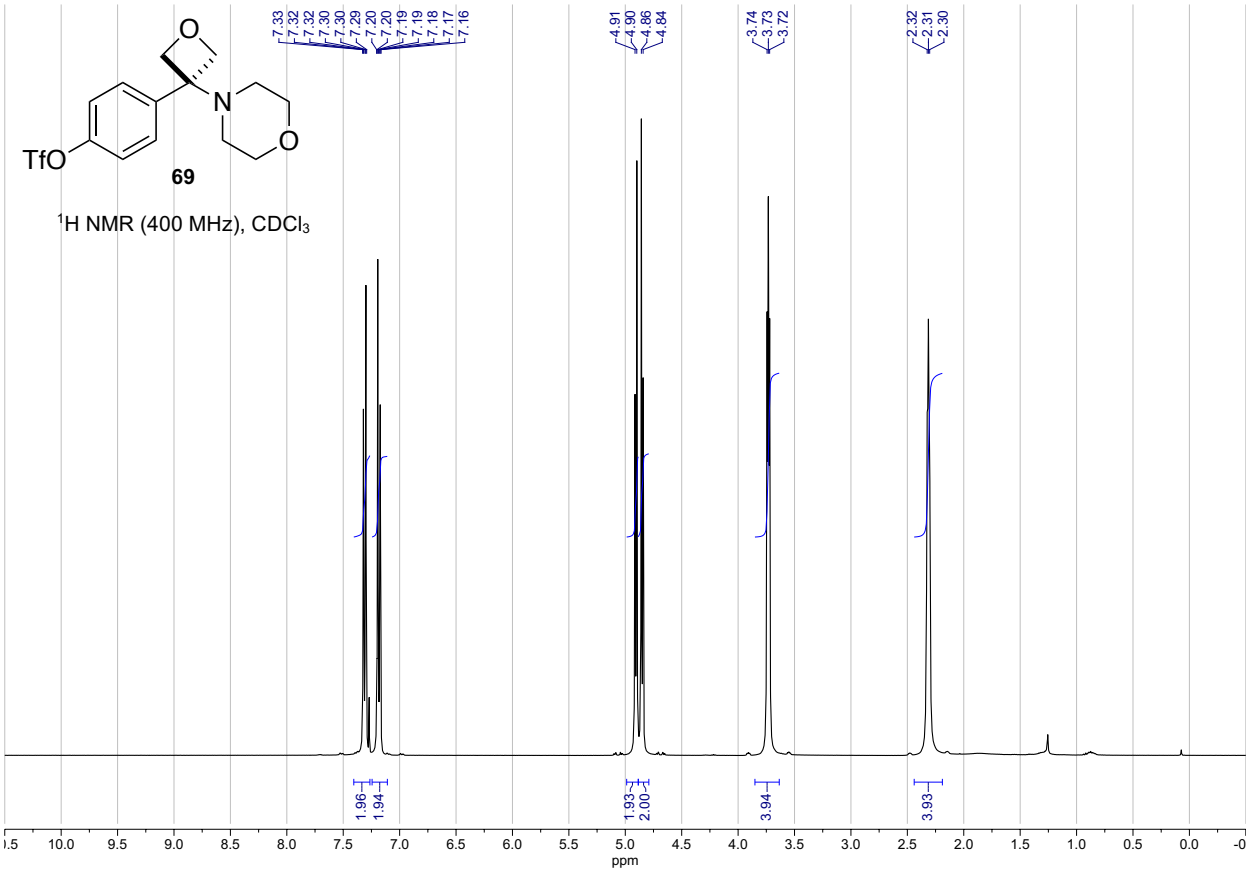

67
^{13}C NMR (101 MHz), CDCl$_3$
ppm

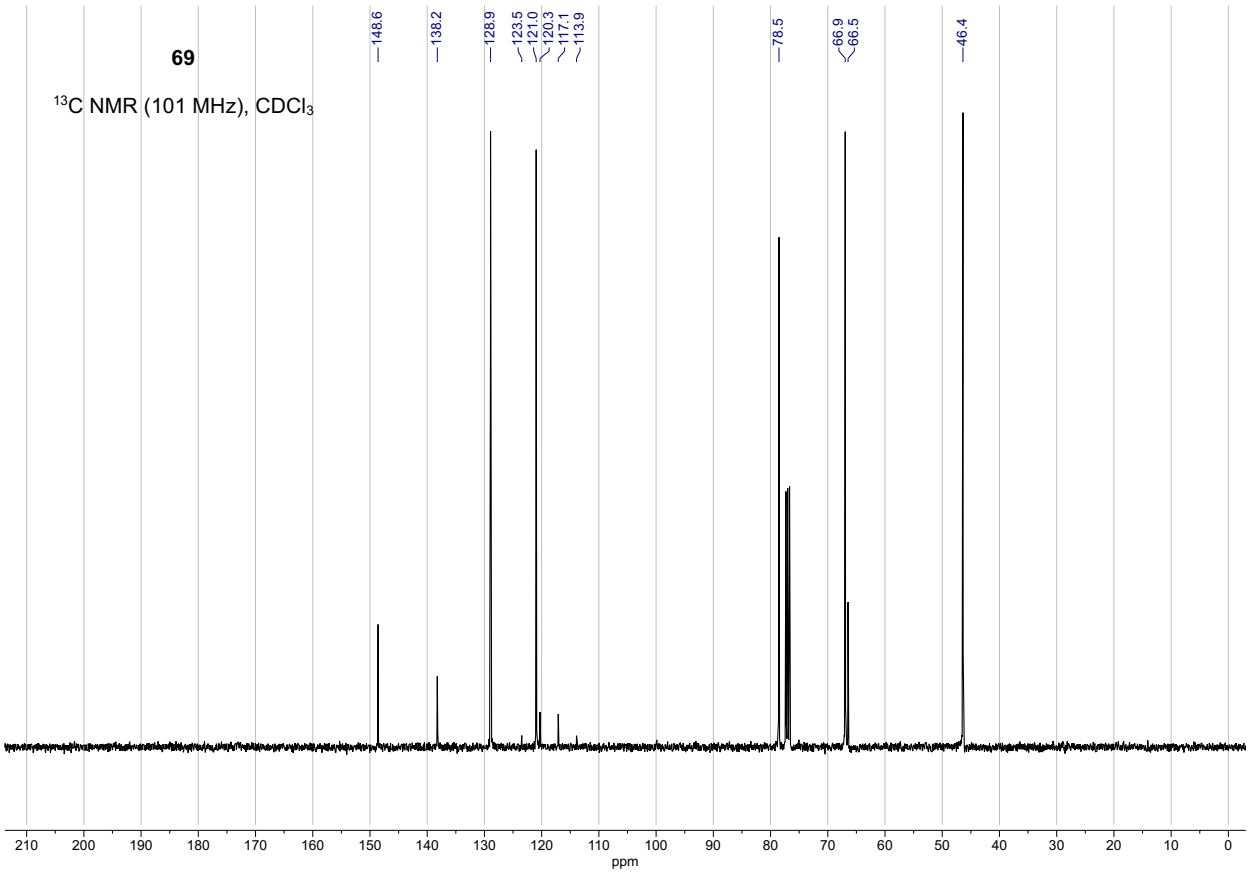

8.40
7.02
7.01
7.00
6.88
6.87
6.87
6.86
6.85
4.80
4.78
4.78
4.76
4.73
3.62
3.61
3.59
2.24
O
N
O
HO
68
^{1}H NMR (400 MHz), $(CD_3)_2CO$
0.96
1.99
1.97
3.99
4.04
3.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


68
^{13}C NMR (101 MHz), $(CD_3)_2CO$
157.3
129.6
129.1
115.2
80.1
67.6
66.8
47.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


TIPSO
O
N
O
72
^{1}H NMR (400 MHz), CDCl$_3$
6.89
4.91
4.89
4.86
4.85
3.75
3.74
3.73
2.30
2.29
2.28
1.31
1.30
1.29
1.28
1.28
1.27
1.27
1.27
1.26
1.25
1.25
1.24
1.22
1.12
1.10
4.00
2.00
1.96
4.02
4.01
3.08
17.96
ppm

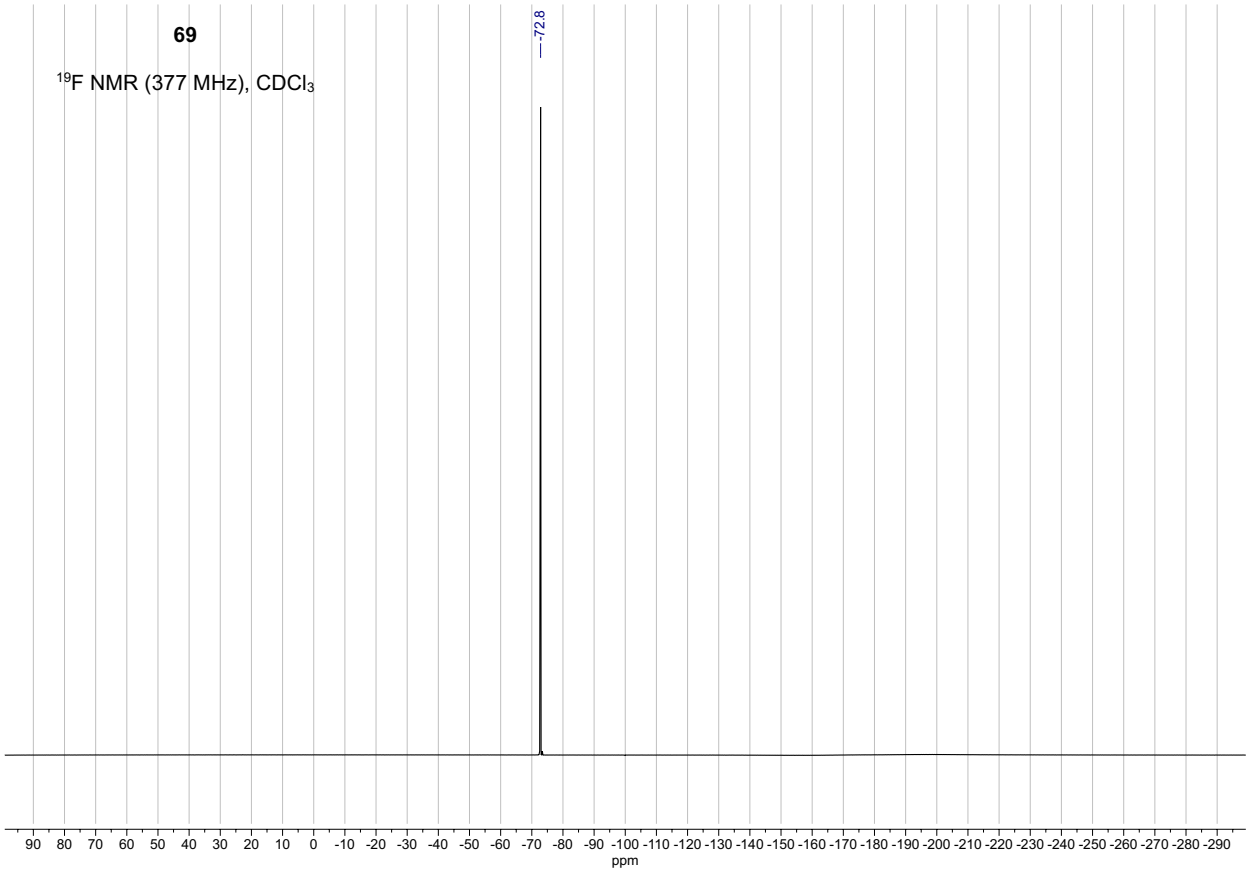

72
^{13}C NMR (101 MHz), CDCl$_3$
155.3
129.4
128.3
119.2
79.4
67.1
66.3
46.4
17.9
12.6
ppm

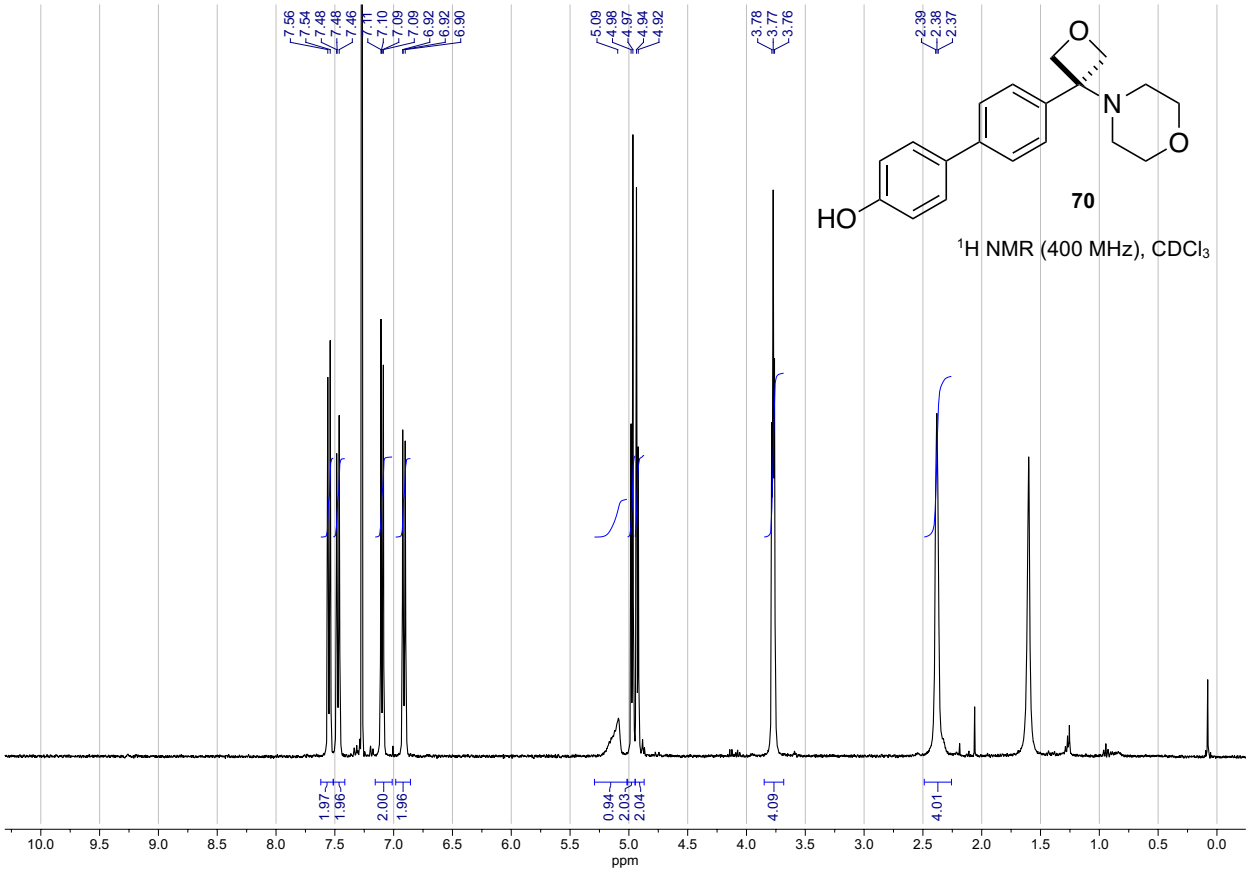

TfO
O
N
O
69
^{1}H NMR (400 MHz), CDCl$_3$
7.33
7.32
7.32
7.30
7.30
7.29
7.20
7.20
7.19
7.19
7.18
7.17
7.16
4.91
4.90
4.86
4.84
3.74
3.73
3.72
2.32
2.31
2.30
1.96
1.94
1.93
2.00
3.94
3.93
ppm

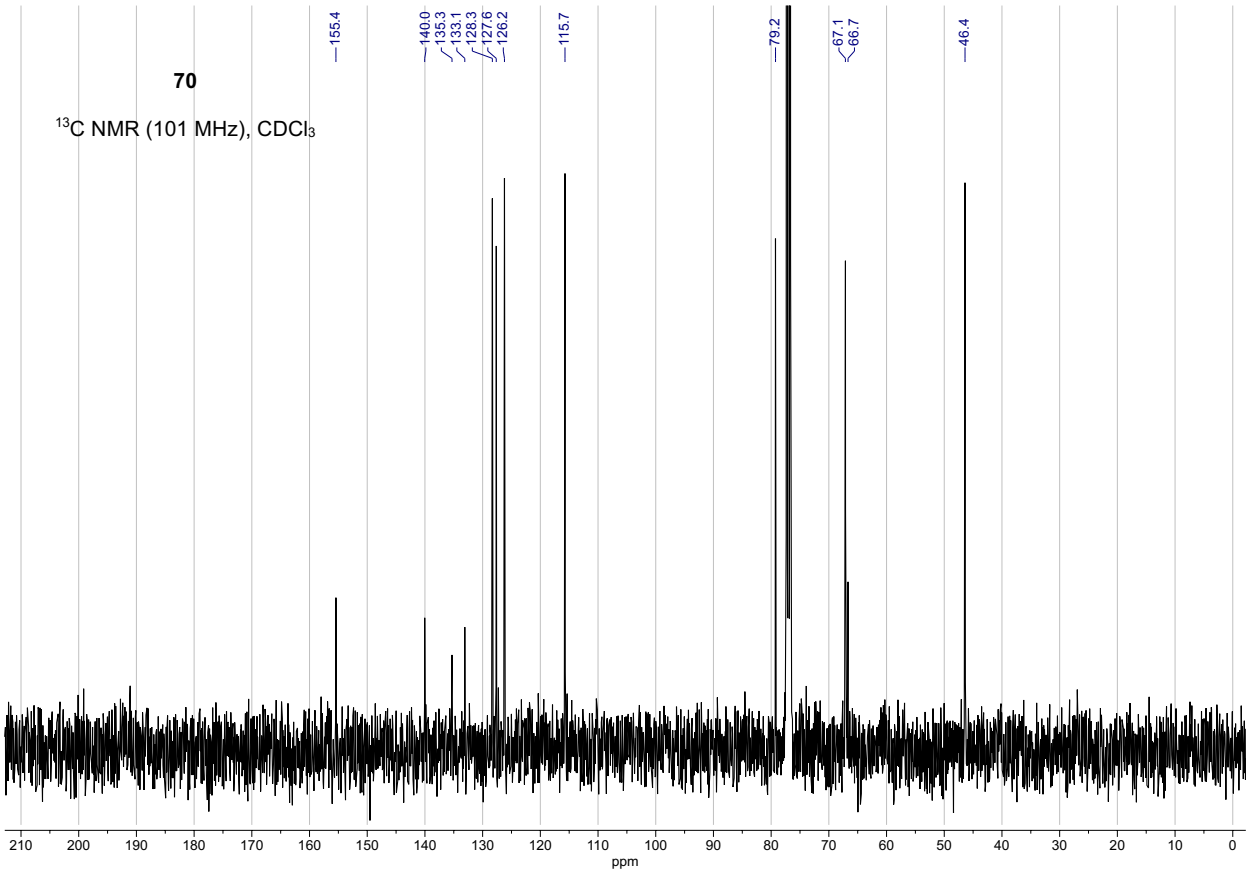

69
^{13}C NMR (101 MHz), CDCl$_3$
148.6
138.2
128.9
123.5
121.0
120.3
117.1
113.9
78.5
66.9
66.5
46.4
ppm

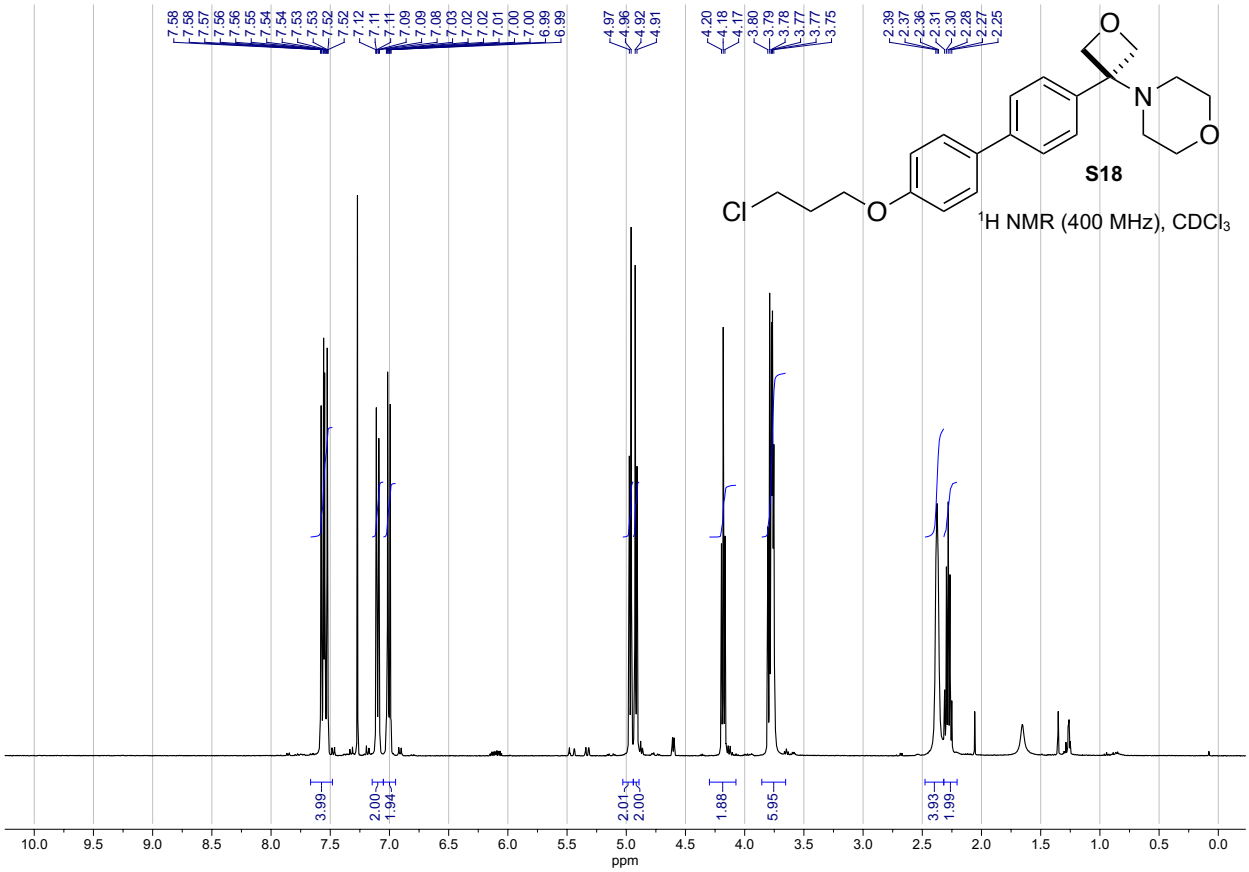
69

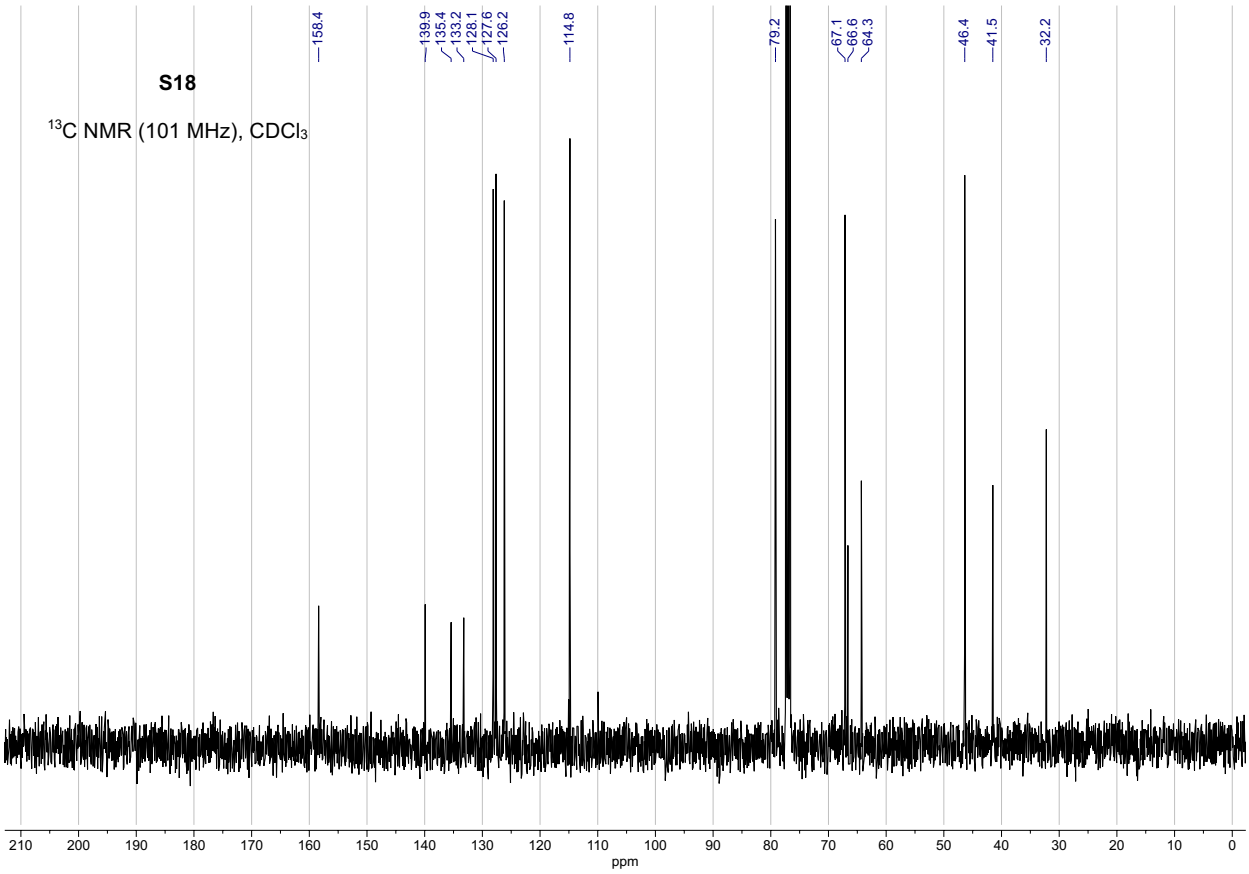
^{19}F NMR (377 MHz), $CDCl_3$

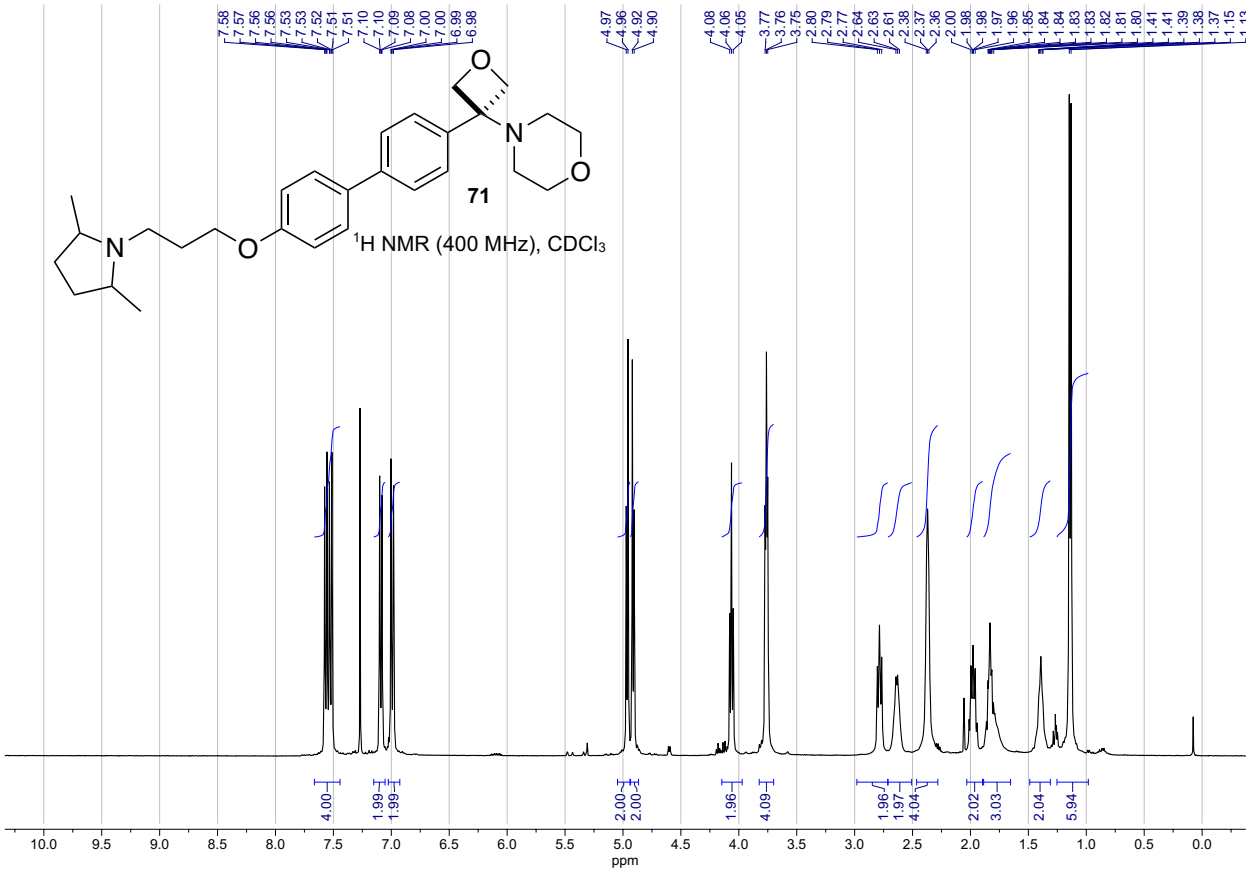


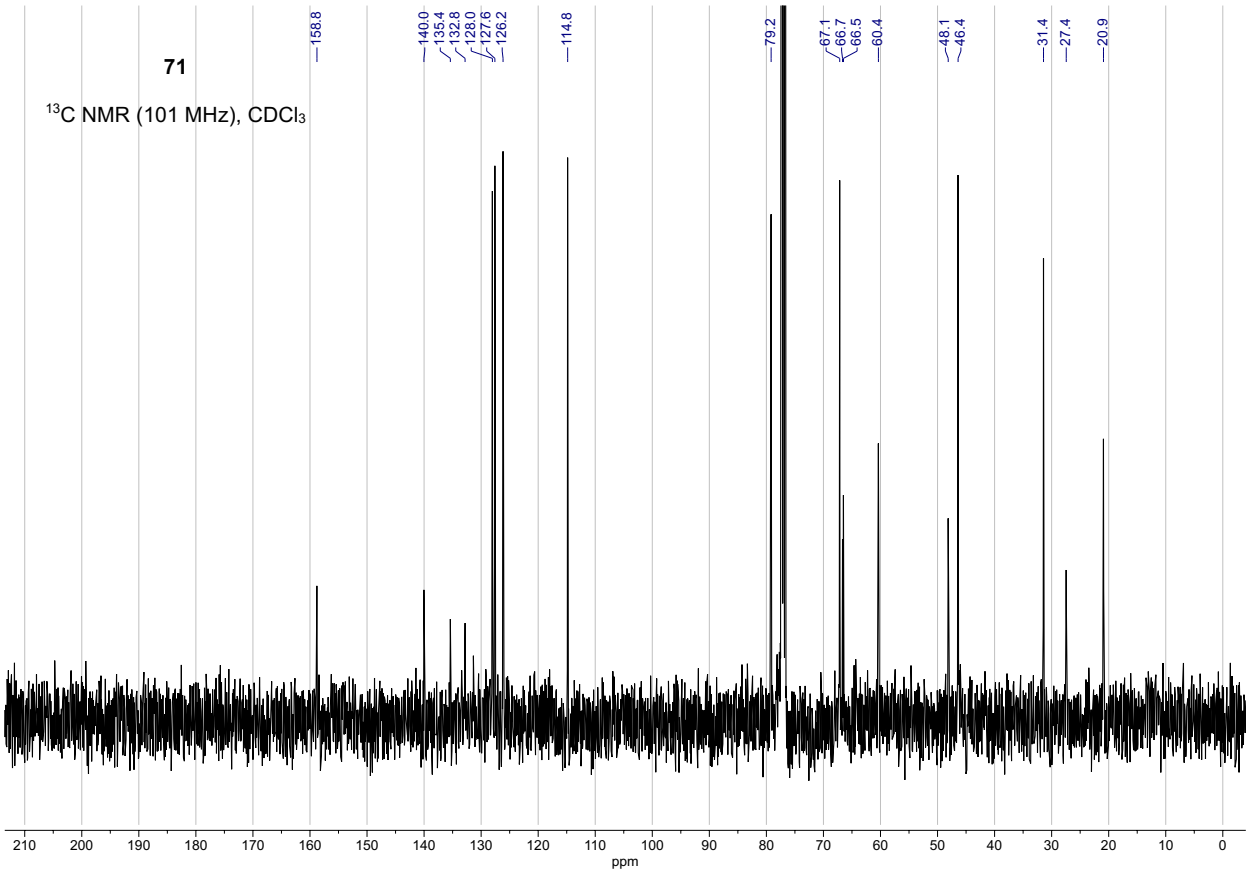

7.56
7.54
7.48
7.48
7.46
7.11
7.10
7.09
7.09
6.92
6.92
6.90
5.09
4.98
4.97
4.94
4.92
3.78
3.77
3.76
2.39
2.38
2.37
1.97
1.96
2.00
1.96
0.94
2.03
2.04
4.09
4.01
ppm
O
N
O
HO
70
^{1}H NMR (400 MHz), $CDCl_3$

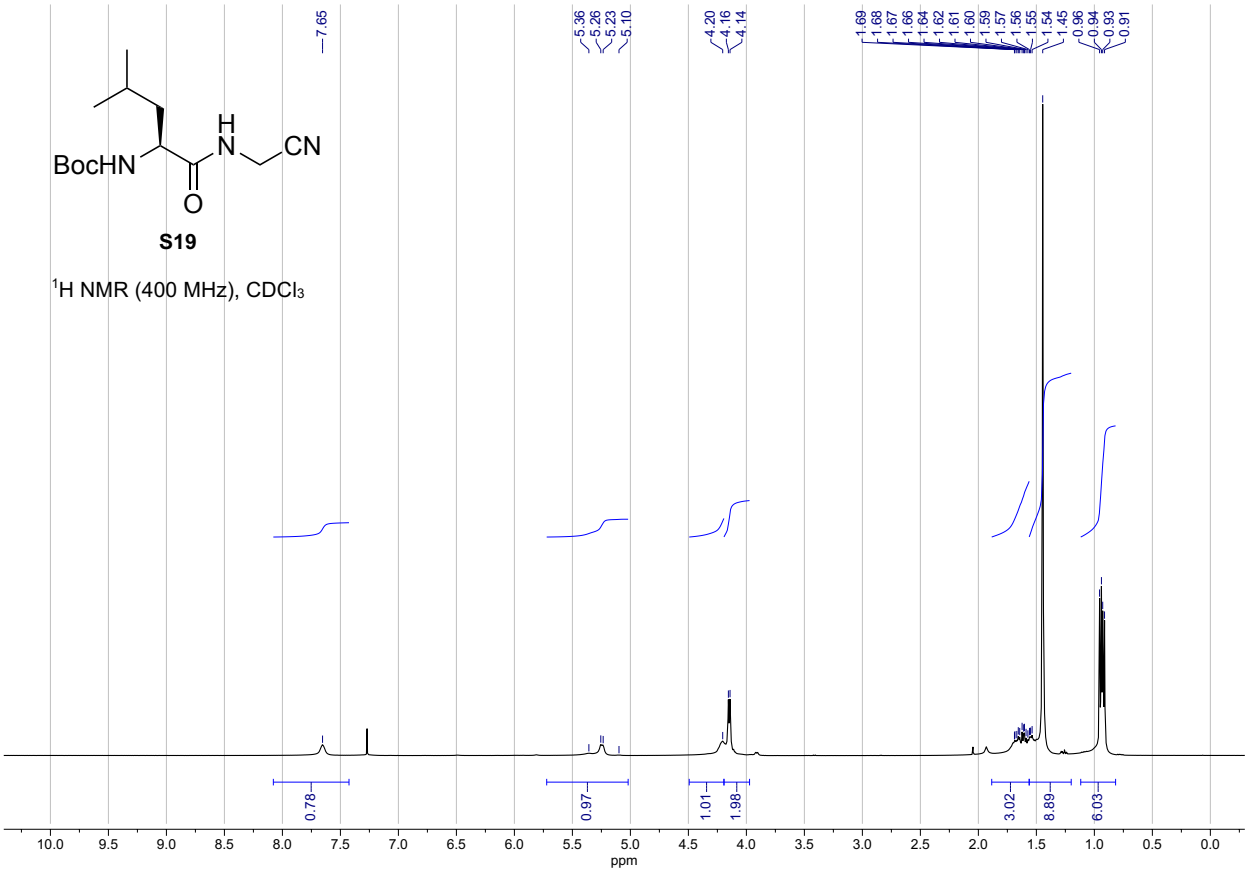

155.4
140.0
135.3
133.1
128.3
127.6
126.2
115.7
79.2
67.1
66.7
46.4
70
^{13}C NMR (101 MHz), $CDCl_3$
ppm

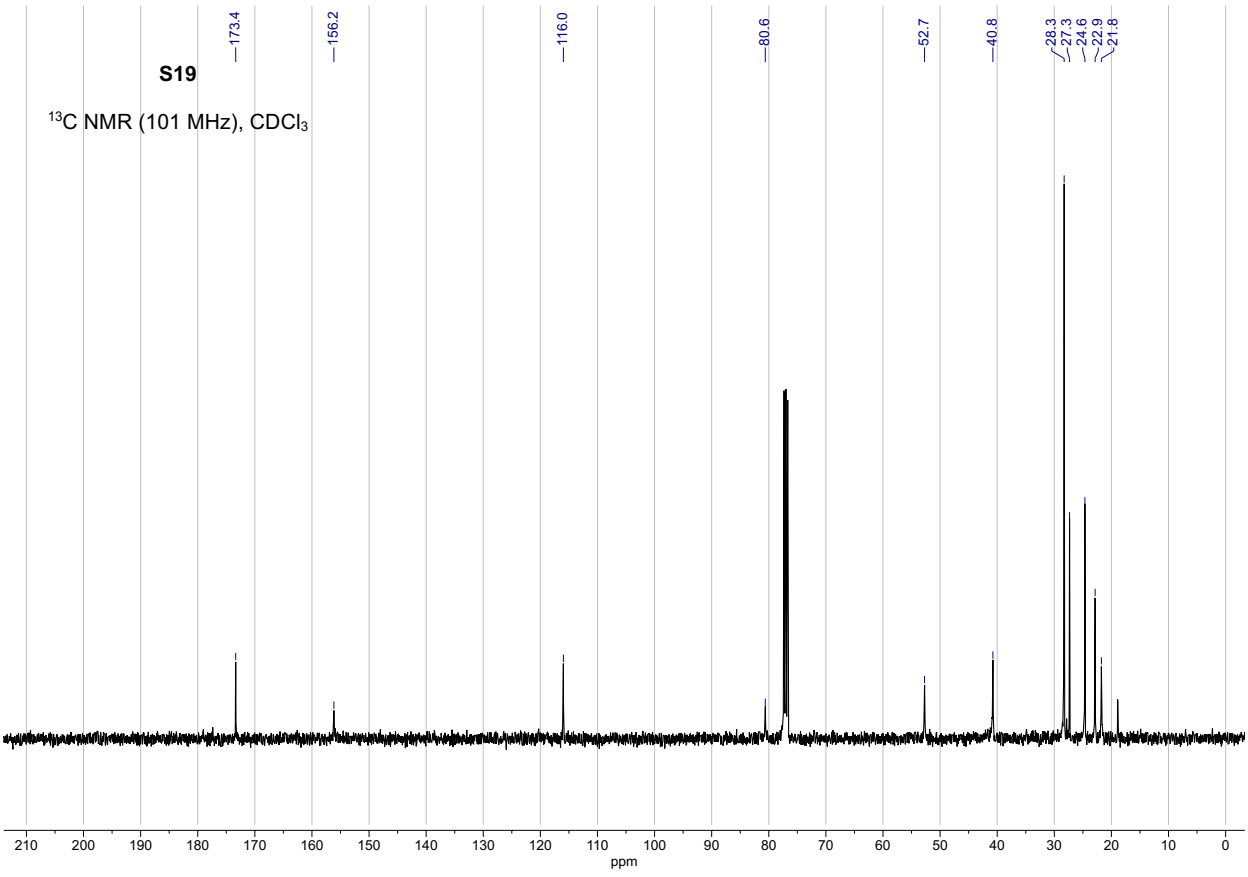

7.58
7.58
7.57
7.56
7.56
7.55
7.54
7.54
7.53
7.53
7.52
7.52
7.12
7.11
7.11
7.09
7.09
7.08
7.03
7.02
7.02
7.01
7.00
7.00
6.99
6.99
4.97
4.96
4.92
4.91
4.20
4.18
4.17
3.80
3.79
3.78
3.77
3.77
3.75
2.39
2.37
2.36
2.31
2.30
2.28
2.27
2.25
O
N
O
Cl
O
S18
^{1}H NMR (400 MHz), $CDCl_3$
3.99
2.00
1.94
2.01
2.00
1.88
5.95
3.93
1.99
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

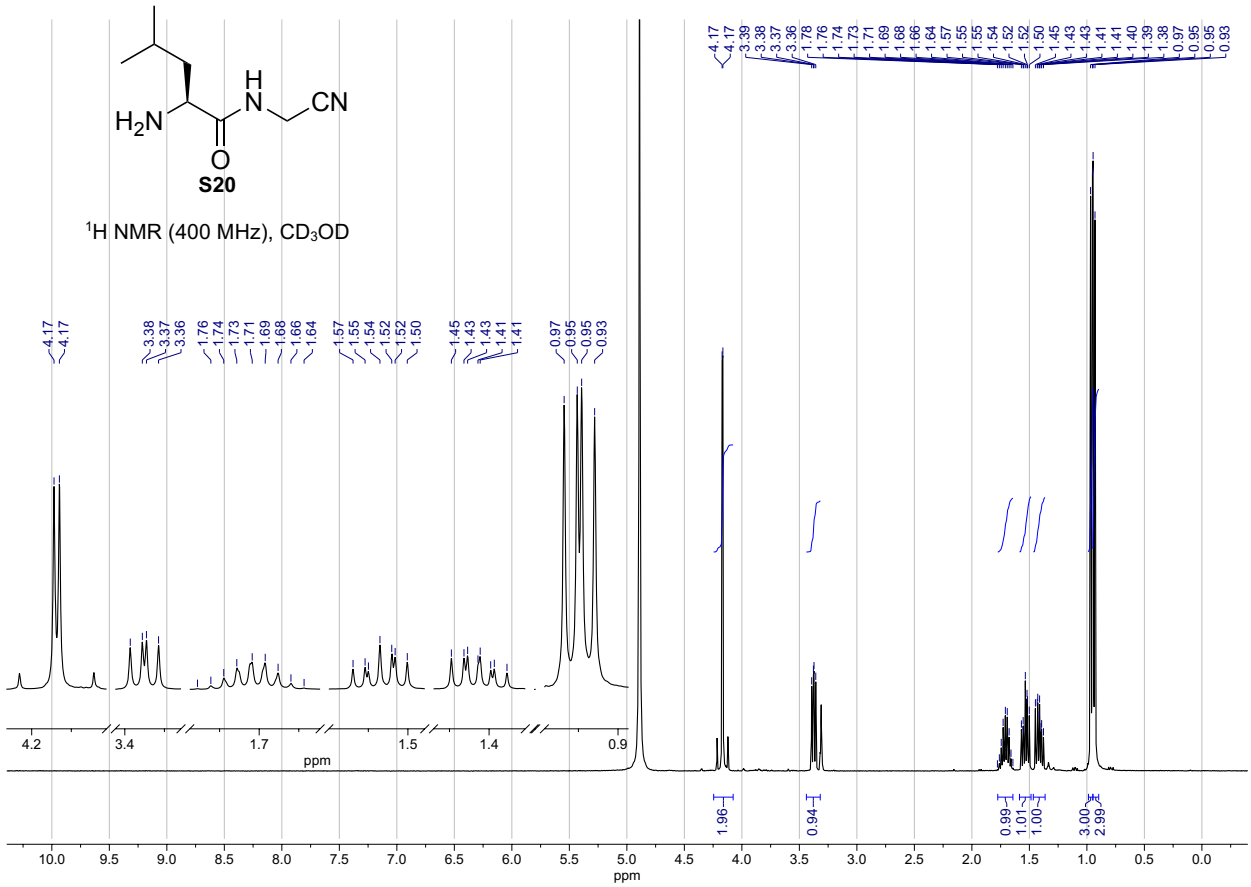

158.4
139.9
135.4
133.2
128.1
127.6
126.2
114.8
79.2
67.1
66.6
64.3
46.4
41.5
32.2
S18
^{13}C NMR (101 MHz), $CDCl_3$
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

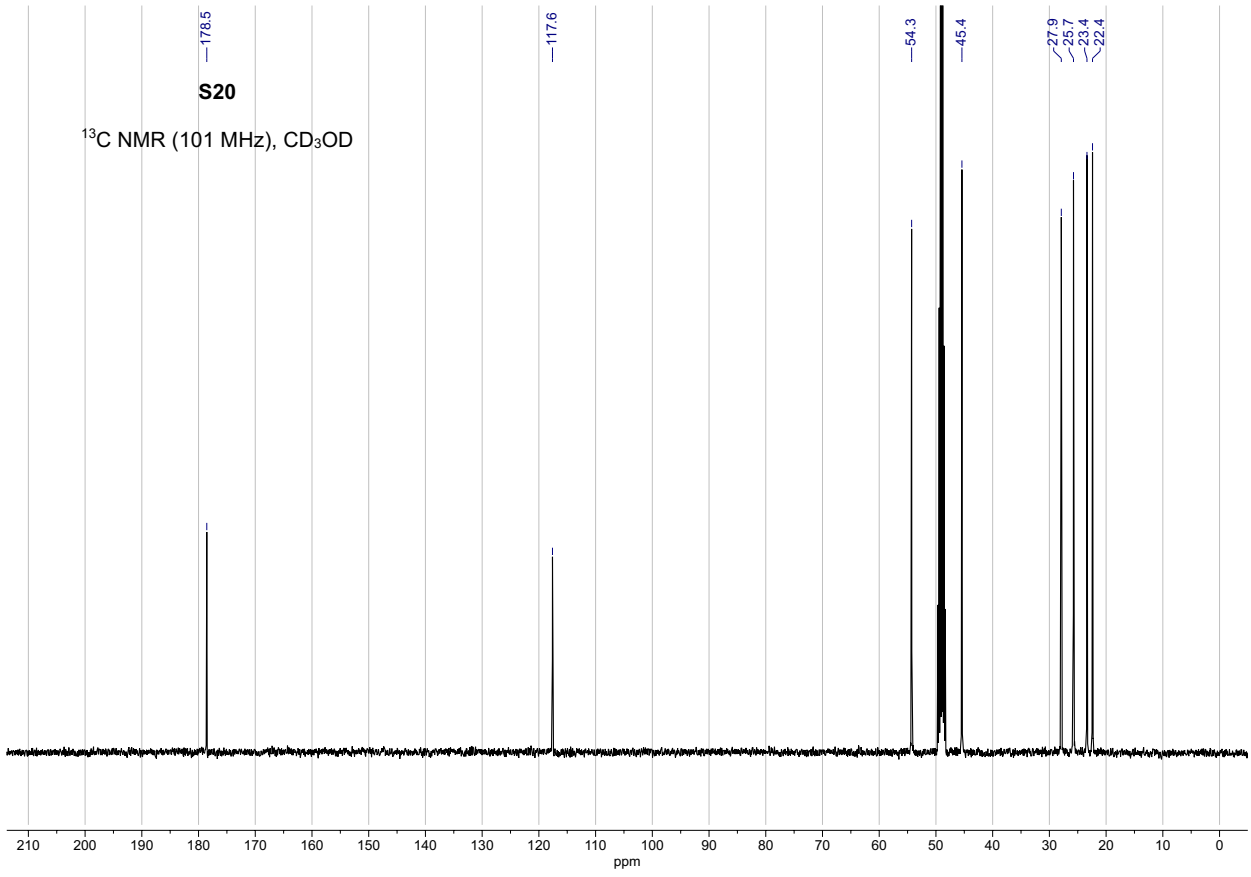

71
^{1}H NMR (400 MHz), CDCl$_3$
ppm


71
^{13}C NMR (101 MHz), CDCl$_3$
ppm


BocHN
H
N
CN
O
S19
^{1}H NMR (400 MHz), CDCl$_3$
7.65
5.36
5.26
5.23
5.10
4.20
4.16
4.14
1.69
1.68
1.67
1.66
1.64
1.62
1.61
1.60
1.59
1.57
1.56
1.55
1.54
1.45
0.96
0.94
0.93
0.91
0.78
0.97
1.01
1.98
3.02
8.89
6.03
ppm

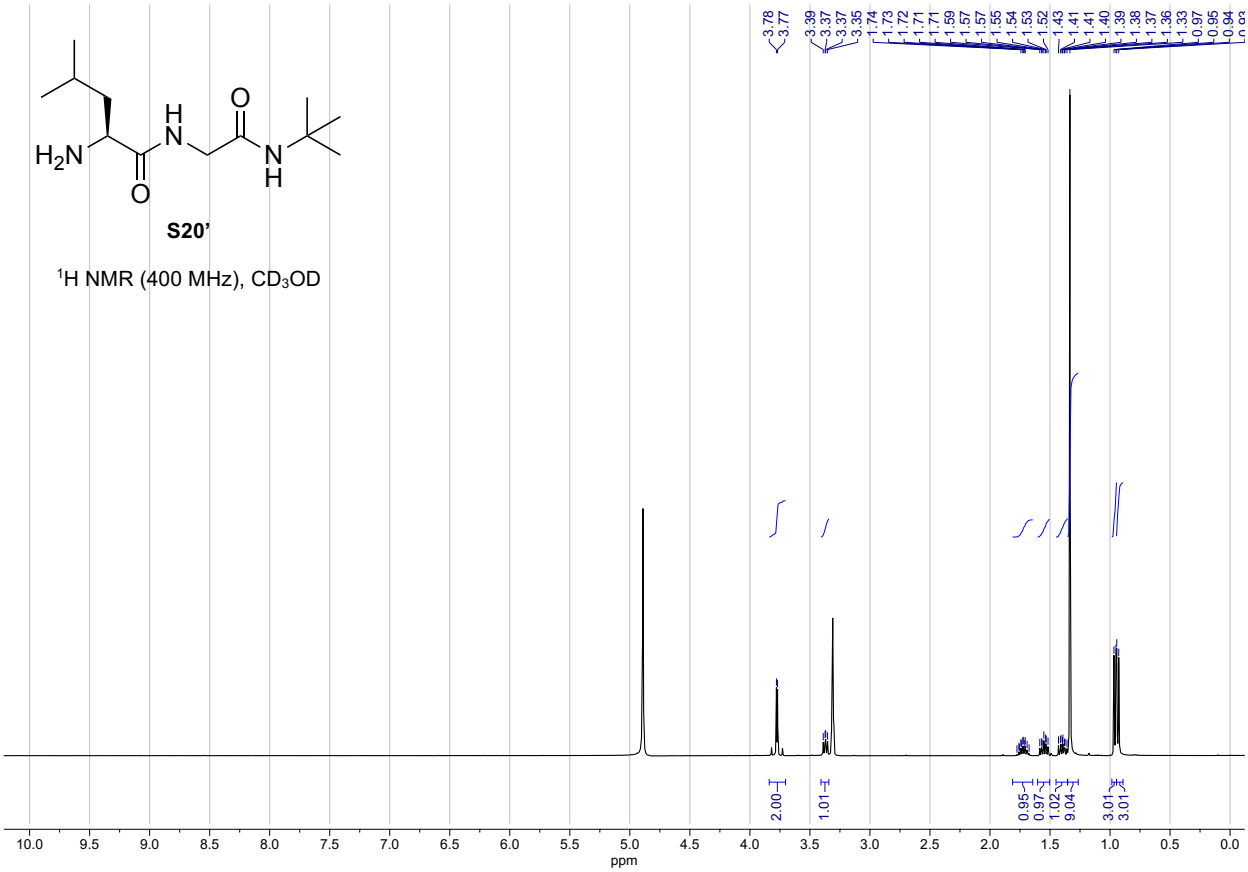

S19
^{13}C NMR (101 MHz), CDCl$_3$
173.4
156.2
116.0
80.6
52.7
40.8
28.3
27.3
24.6
22.9
21.8
ppm


S20
^{1}H NMR (400 MHz), CD$_3$OD
ppm


S20
^{13}C NMR (101 MHz), CD$_3$OD
178.5
117.6
54.3
45.4
27.9
25.7
23.4
22.4
ppm

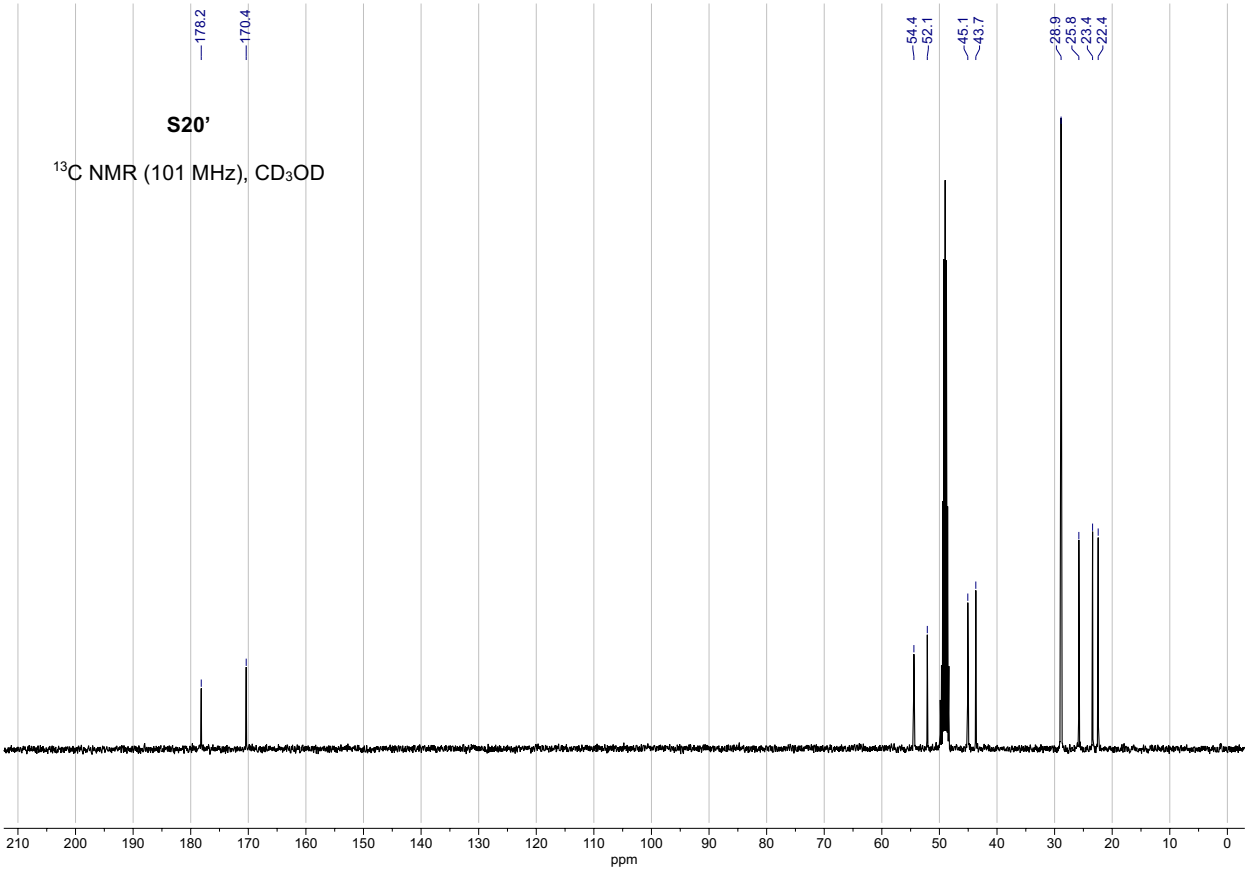
S20'

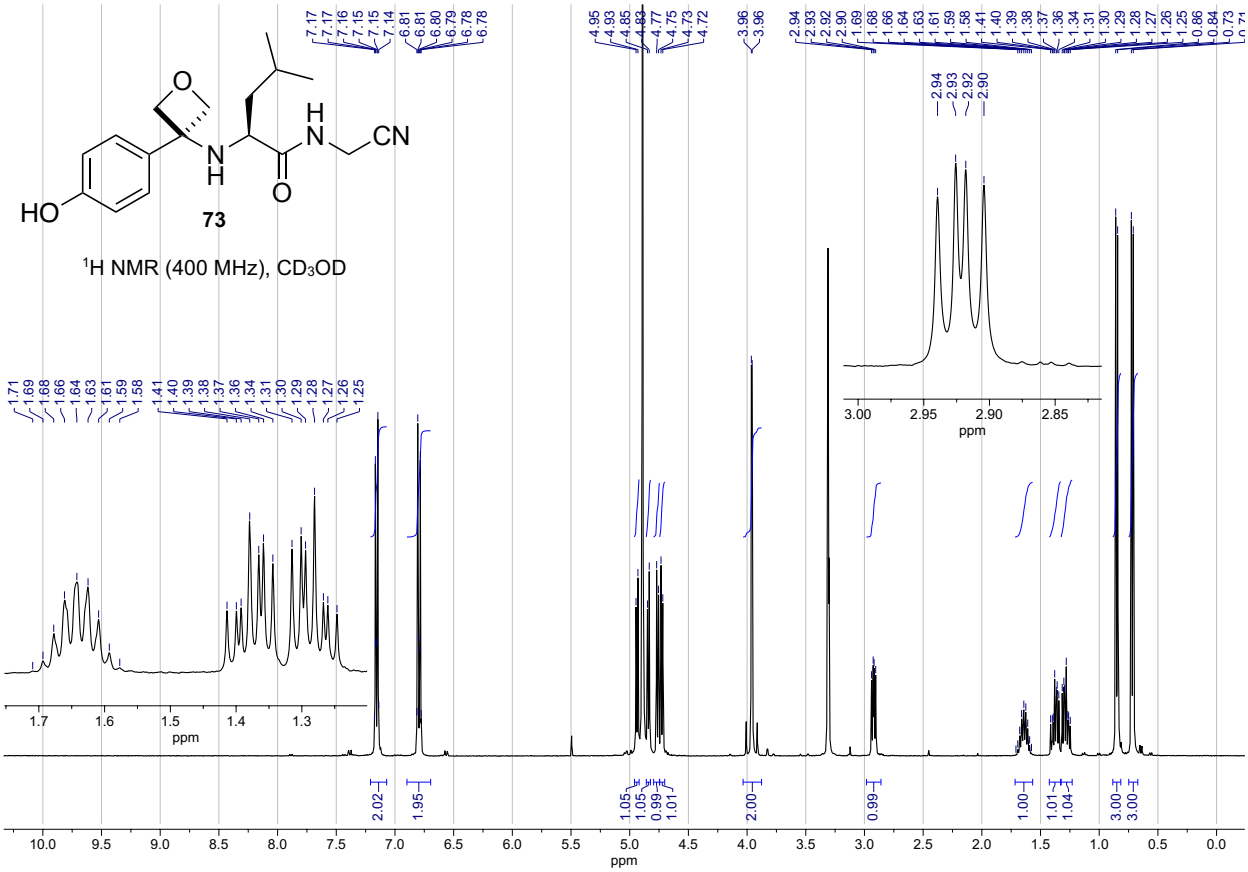
^{1}H NMR (400 MHz), CD_3OD

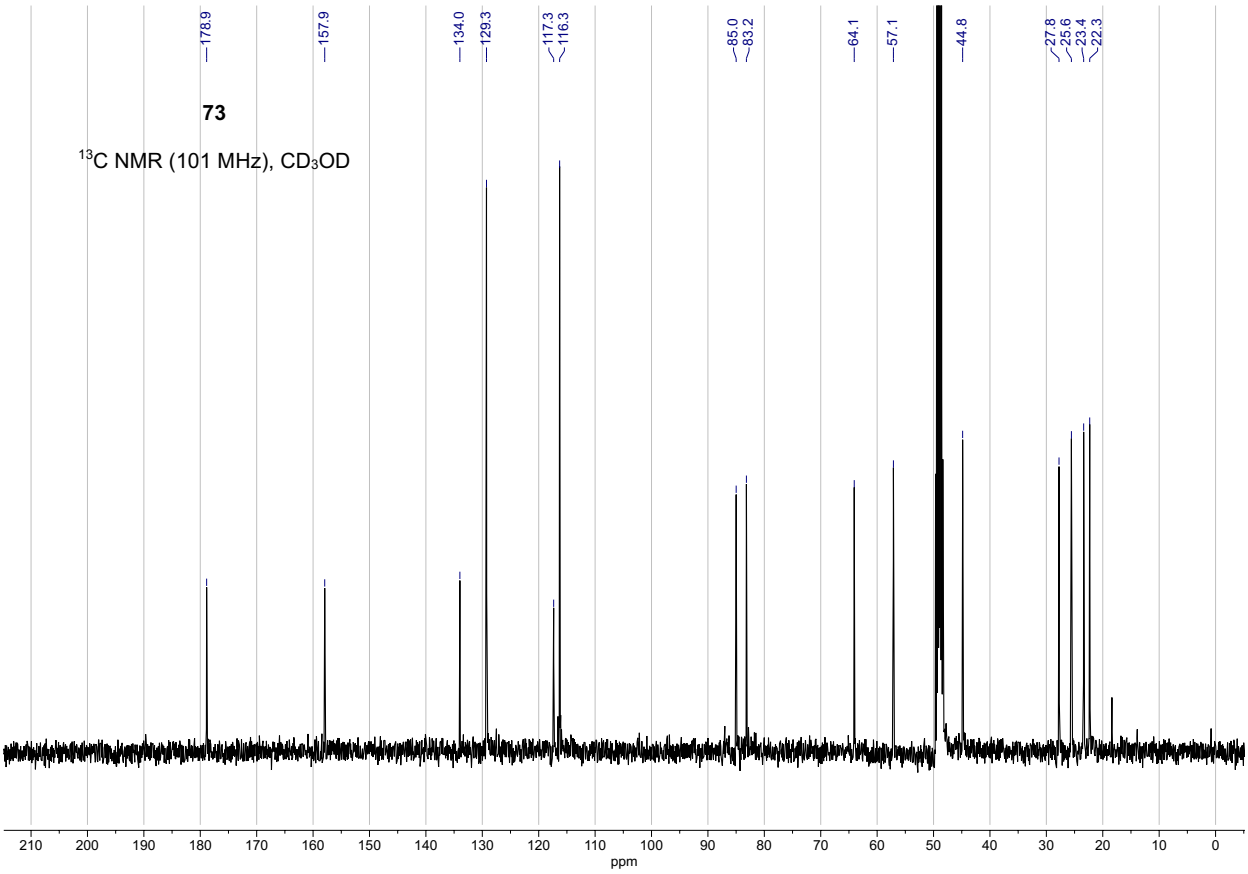


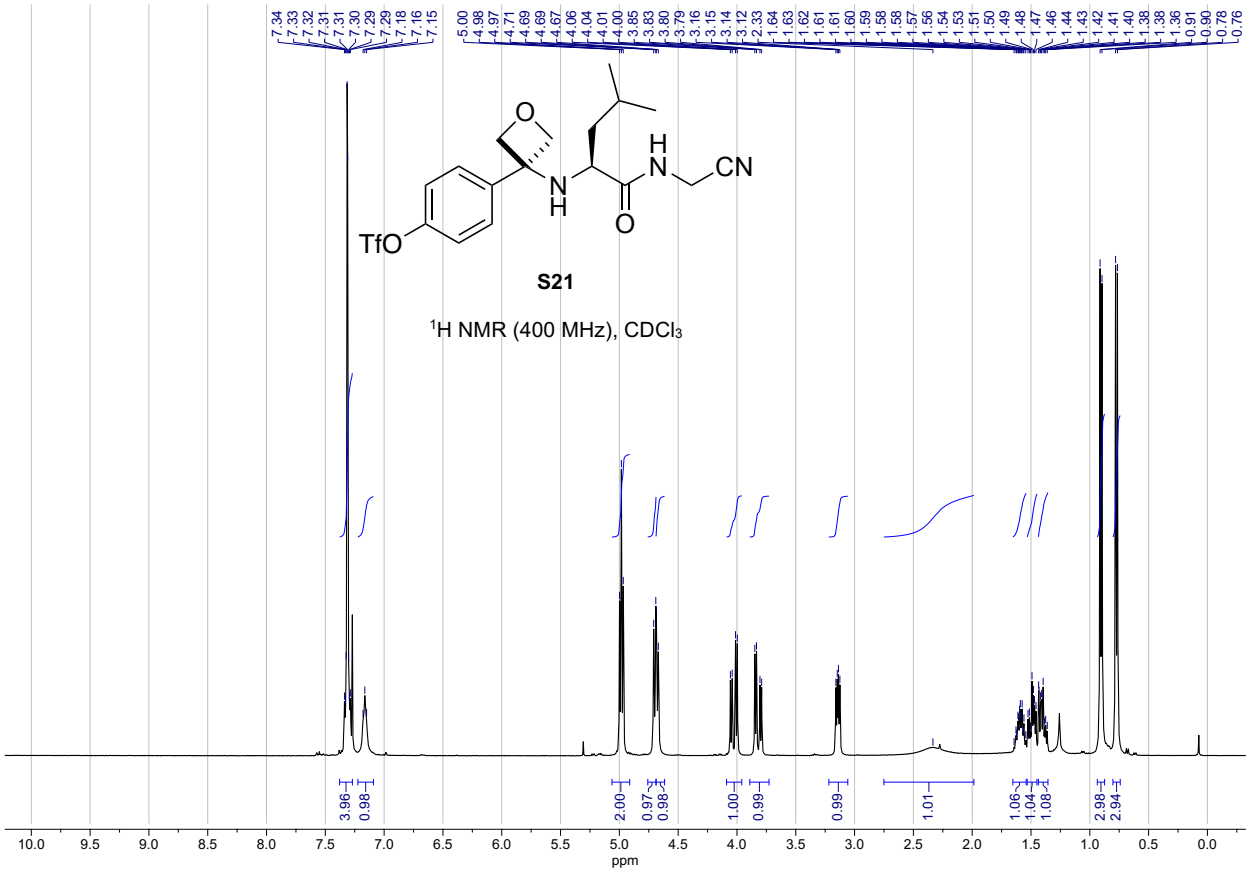
S20'

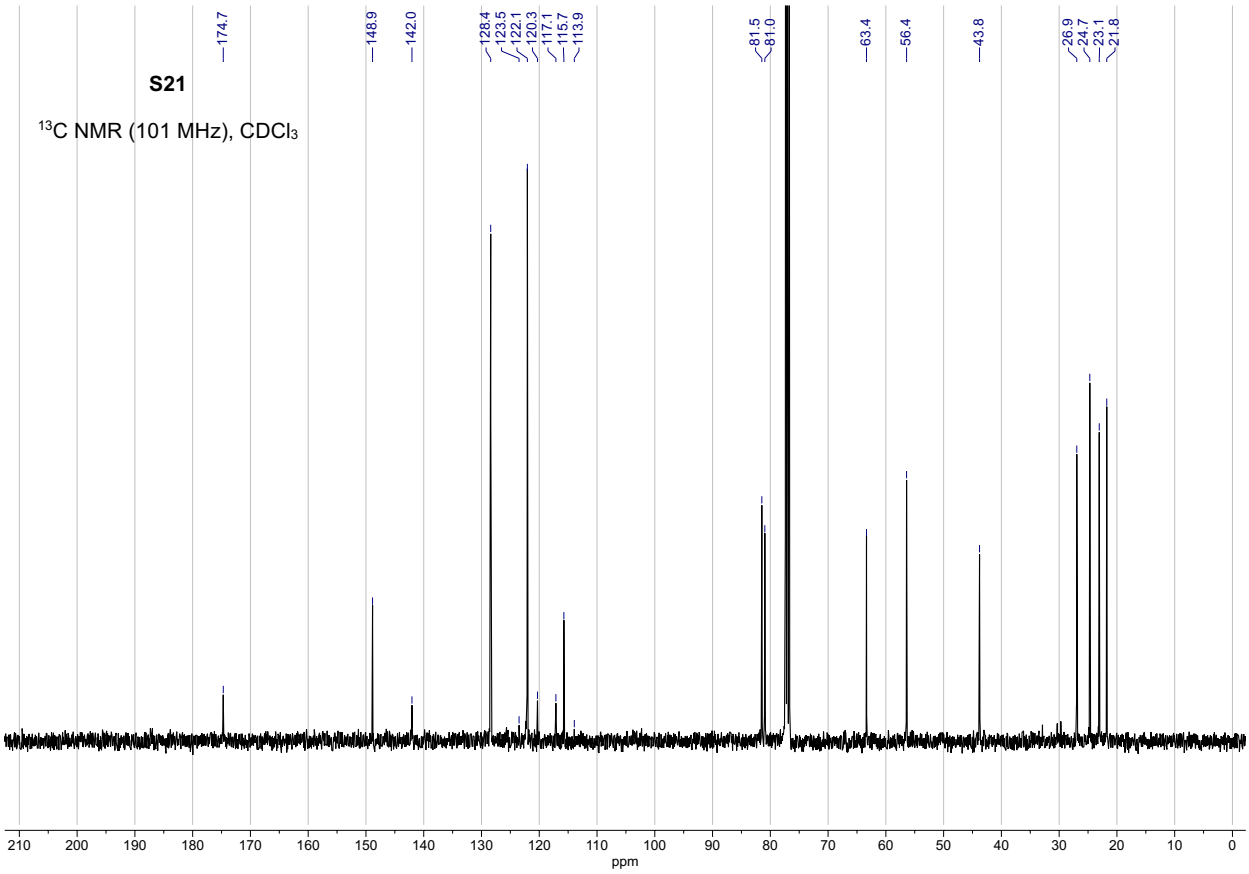
^{13}C NMR (101 MHz), CD_3OD




HO
O
N
H
H
N
O
CN
73
^{1}H NMR (400 MHz), CD_3OD
ppm

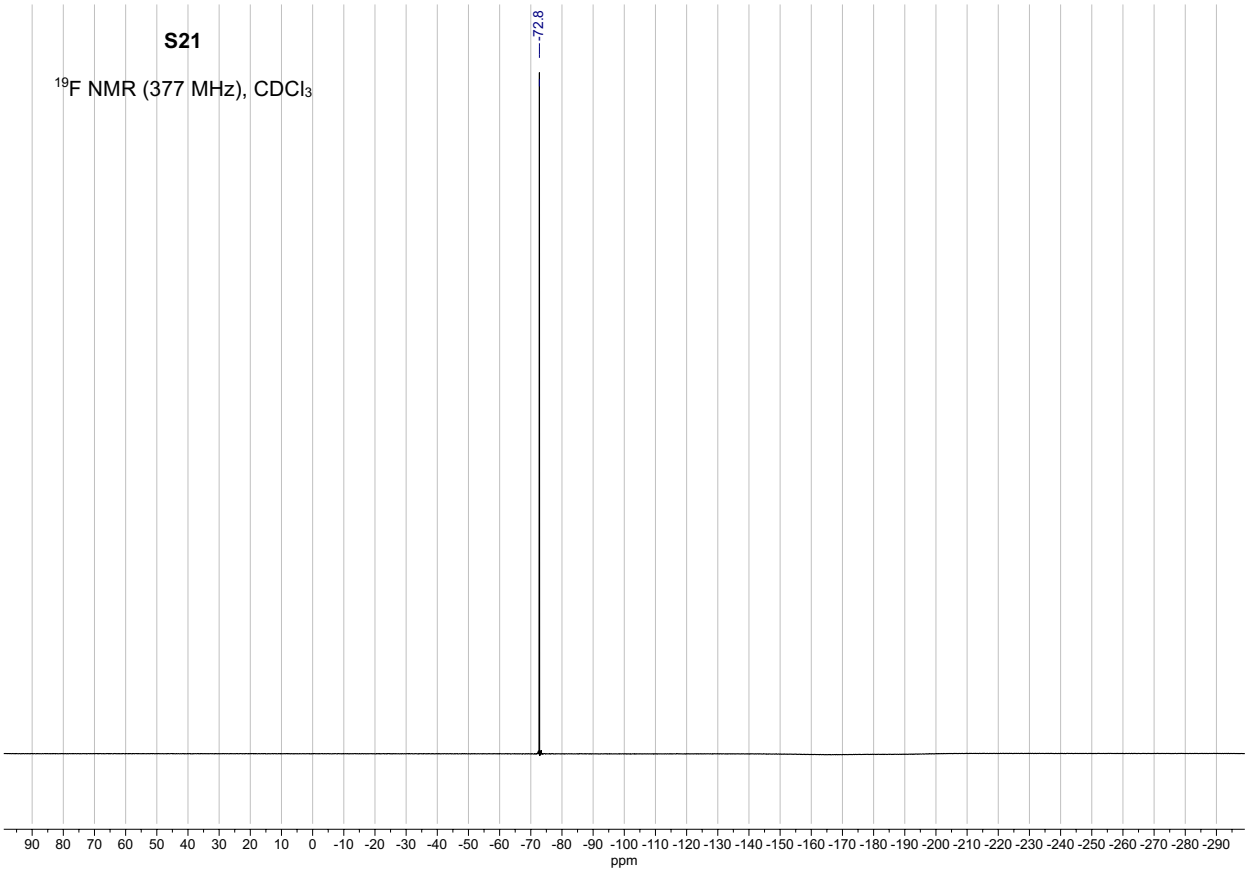

73
^{13}C NMR (101 MHz), CD_3OD
ppm

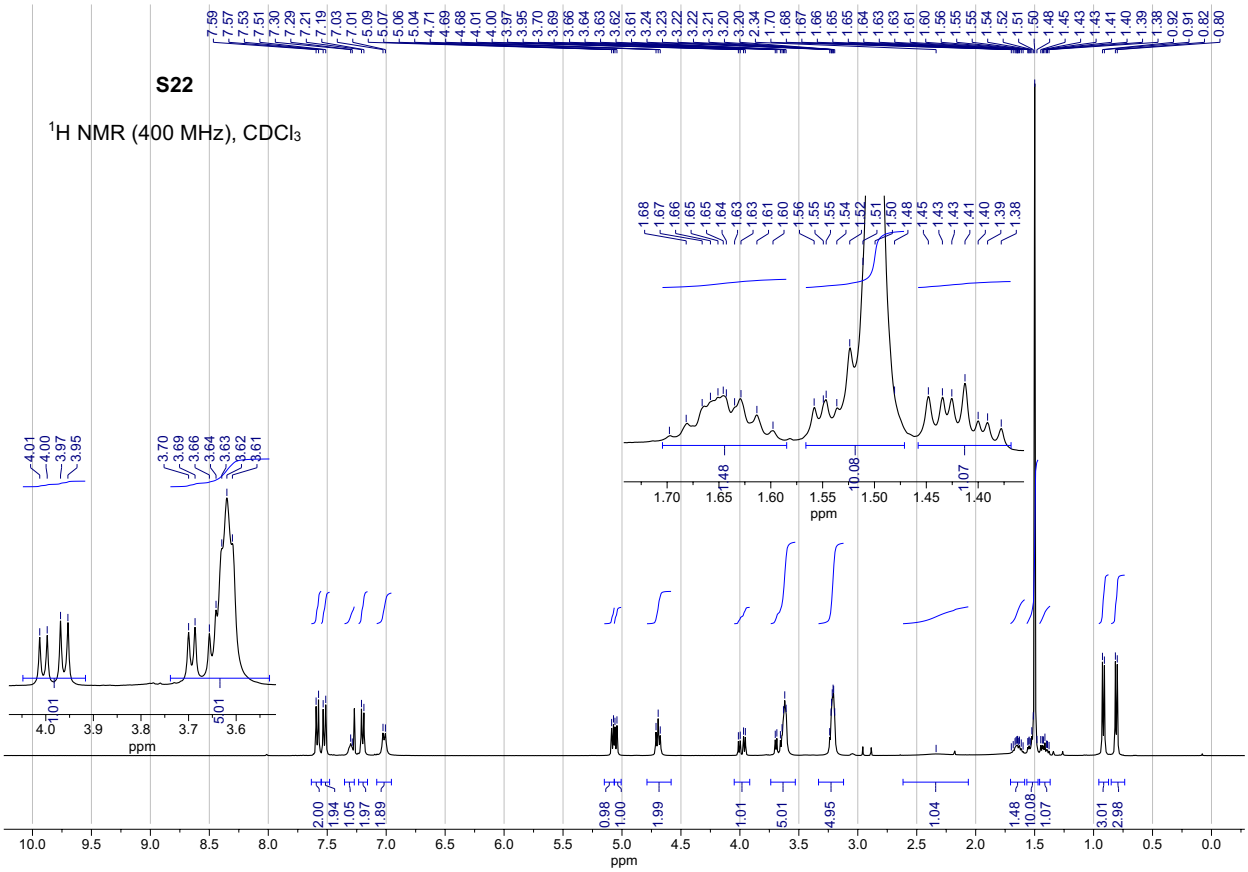

TfO
O
N
H
H
N
CN
O
S21
^{1}H NMR (400 MHz), CDCl$_3$
ppm

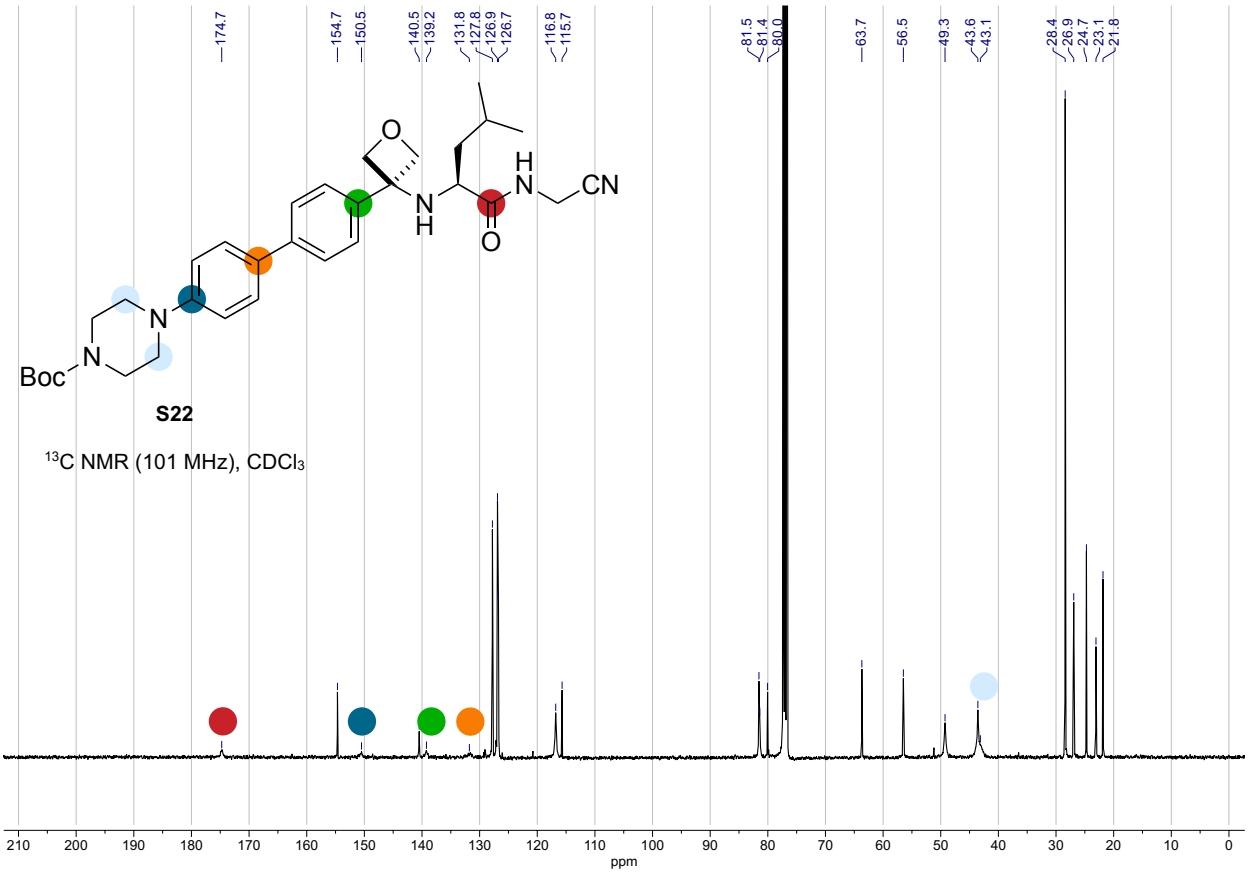

S21
^{13}C NMR (101 MHz), CDCl$_3$
ppm

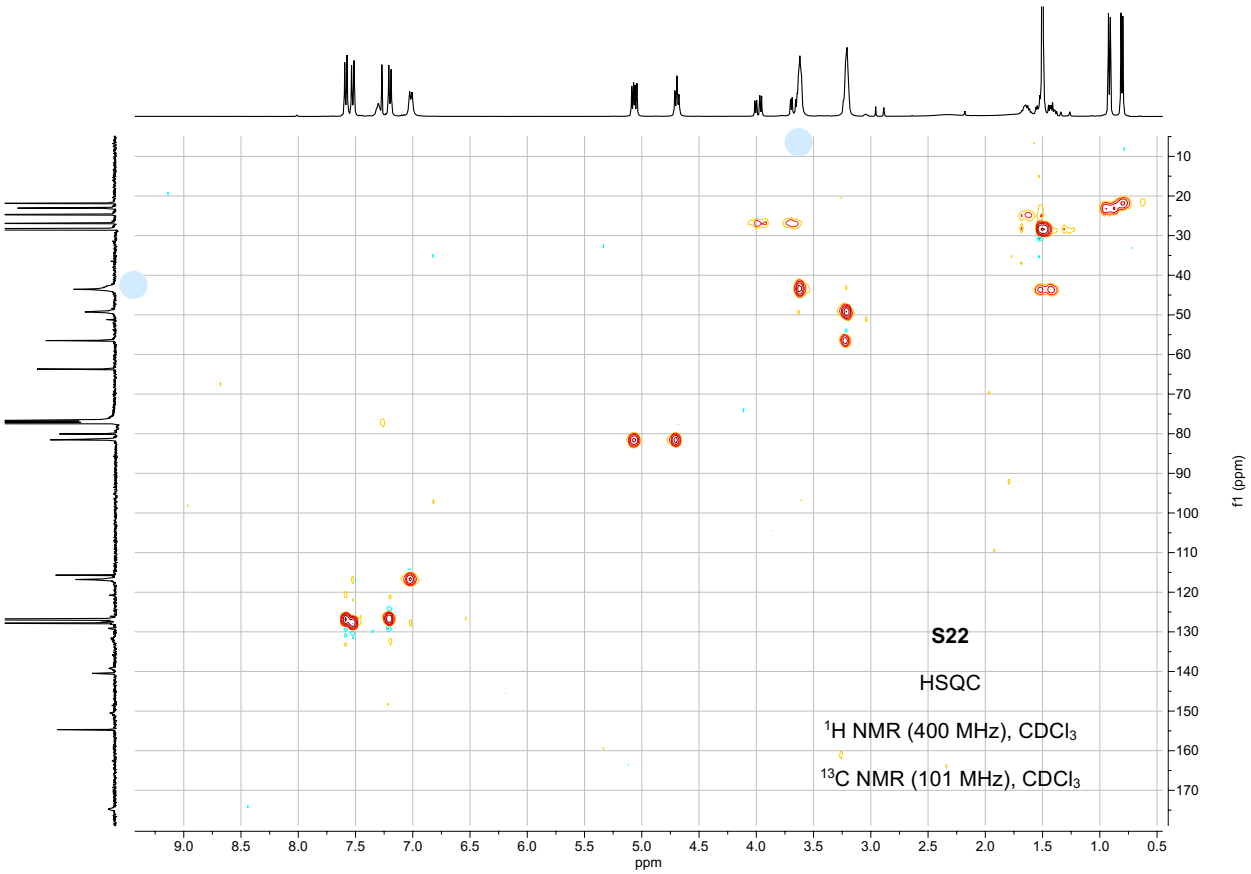
S21

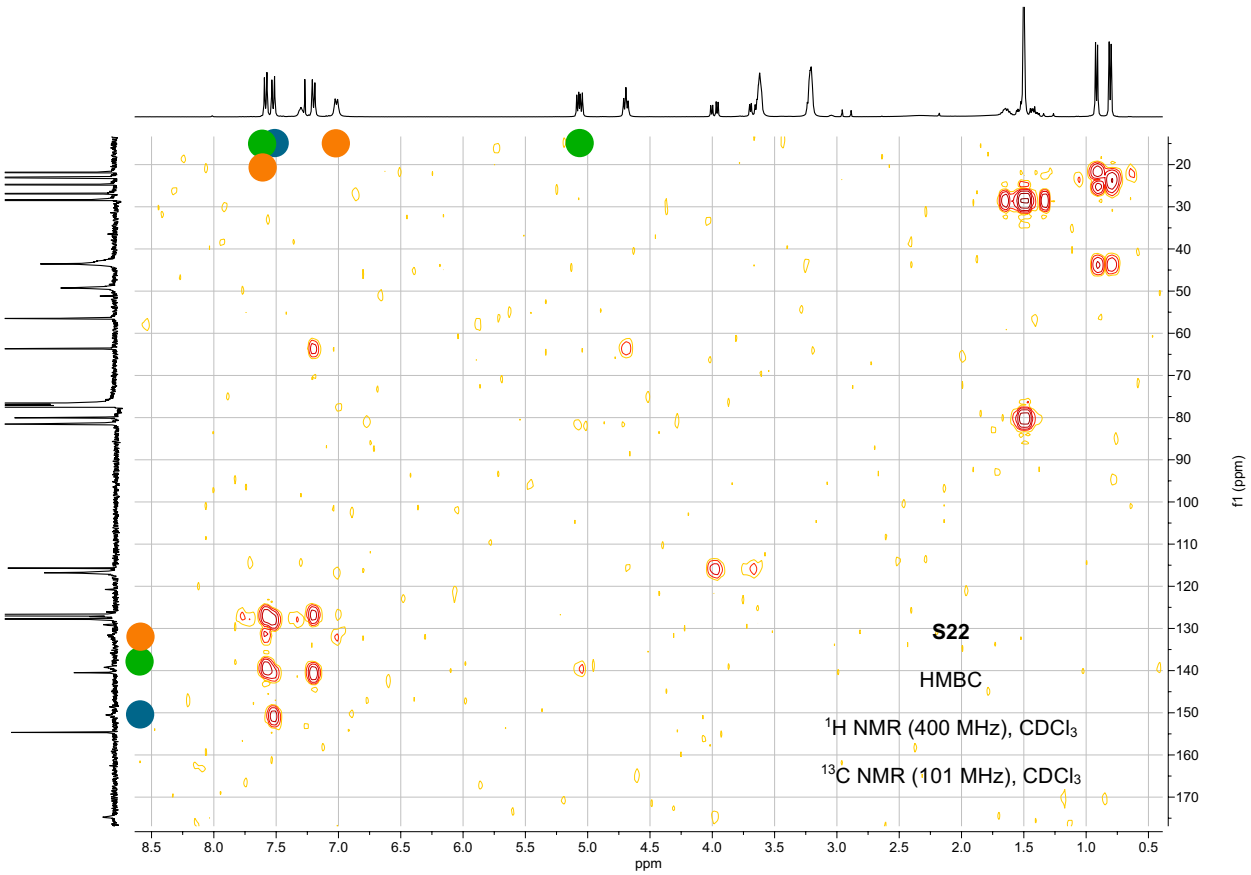
^{19}F NMR (377 MHz), $CDCl_3$

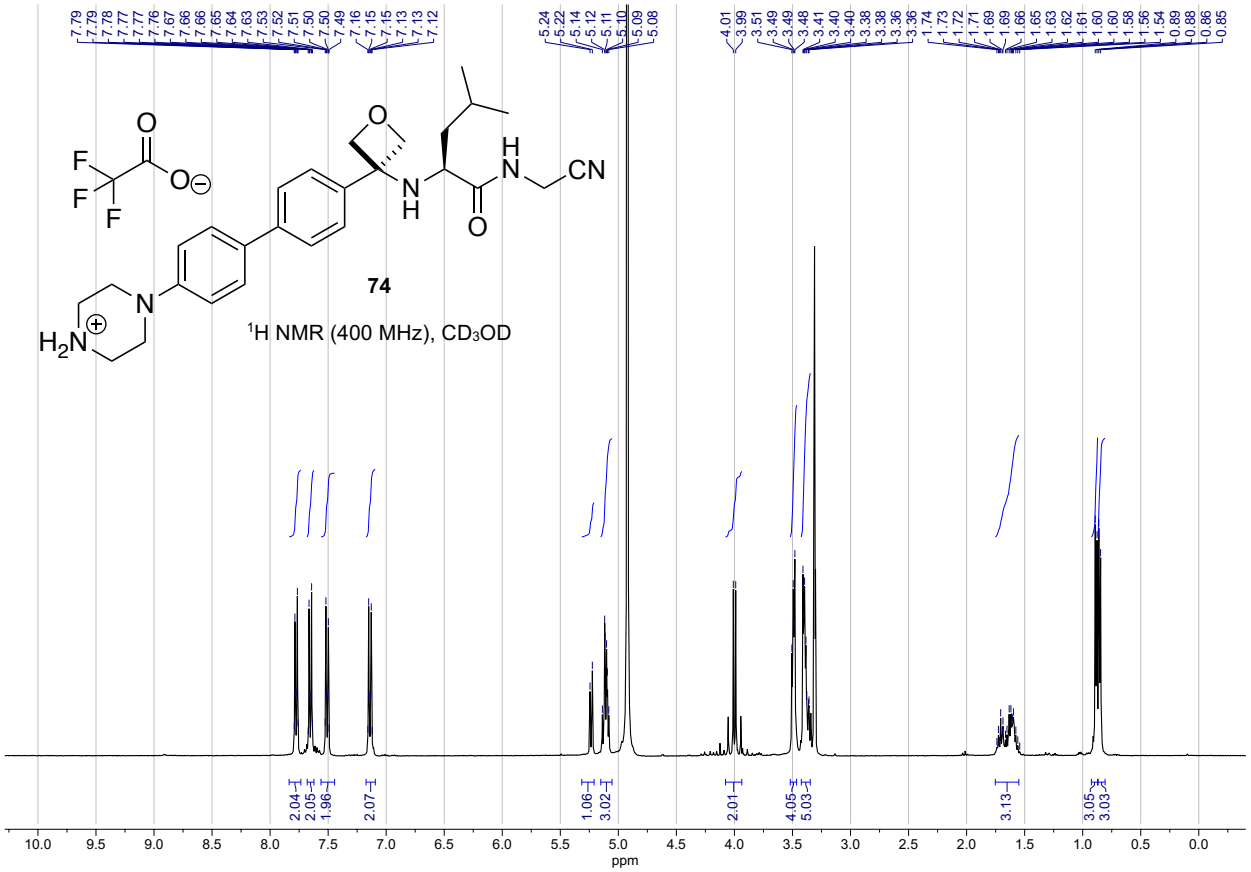


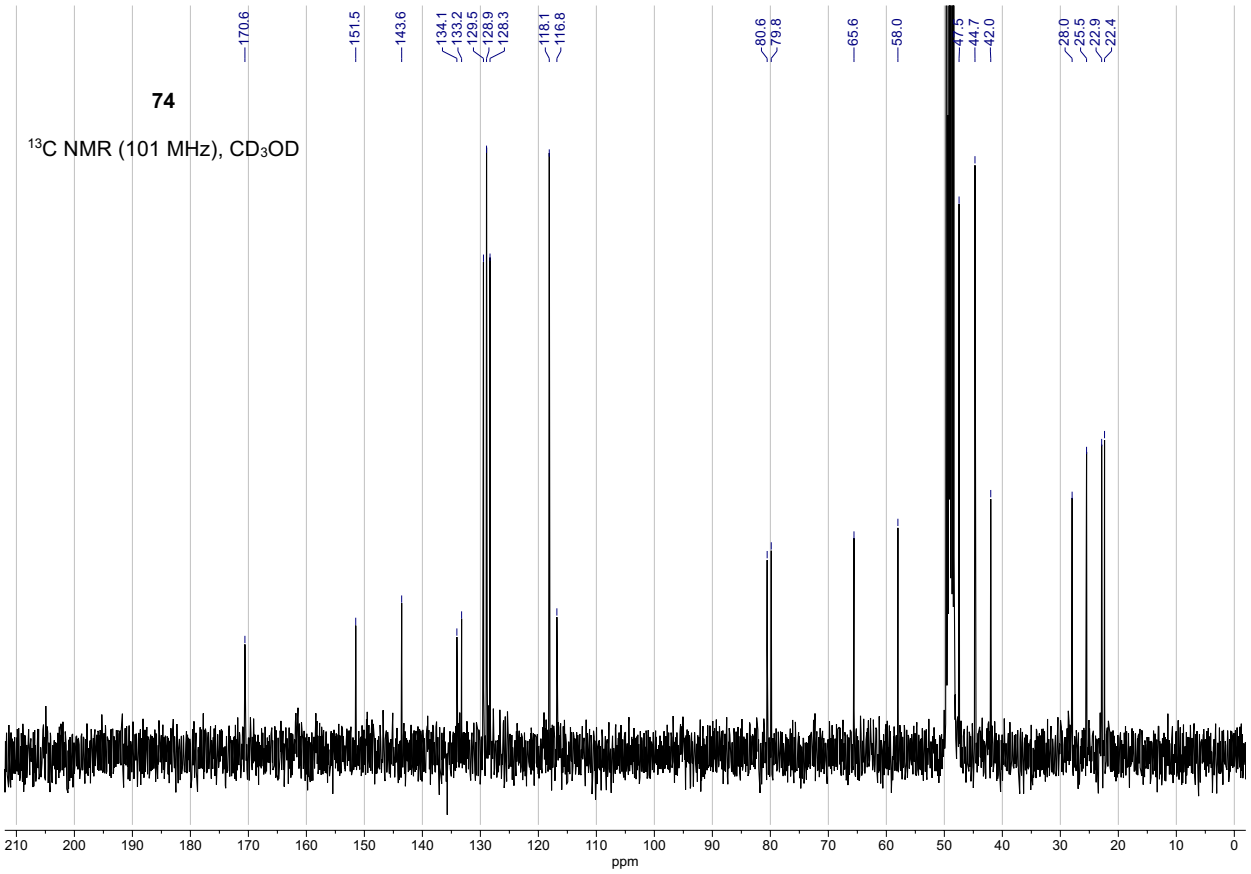

S22
^{1}H NMR (400 MHz), CDCl$_3$
ppm

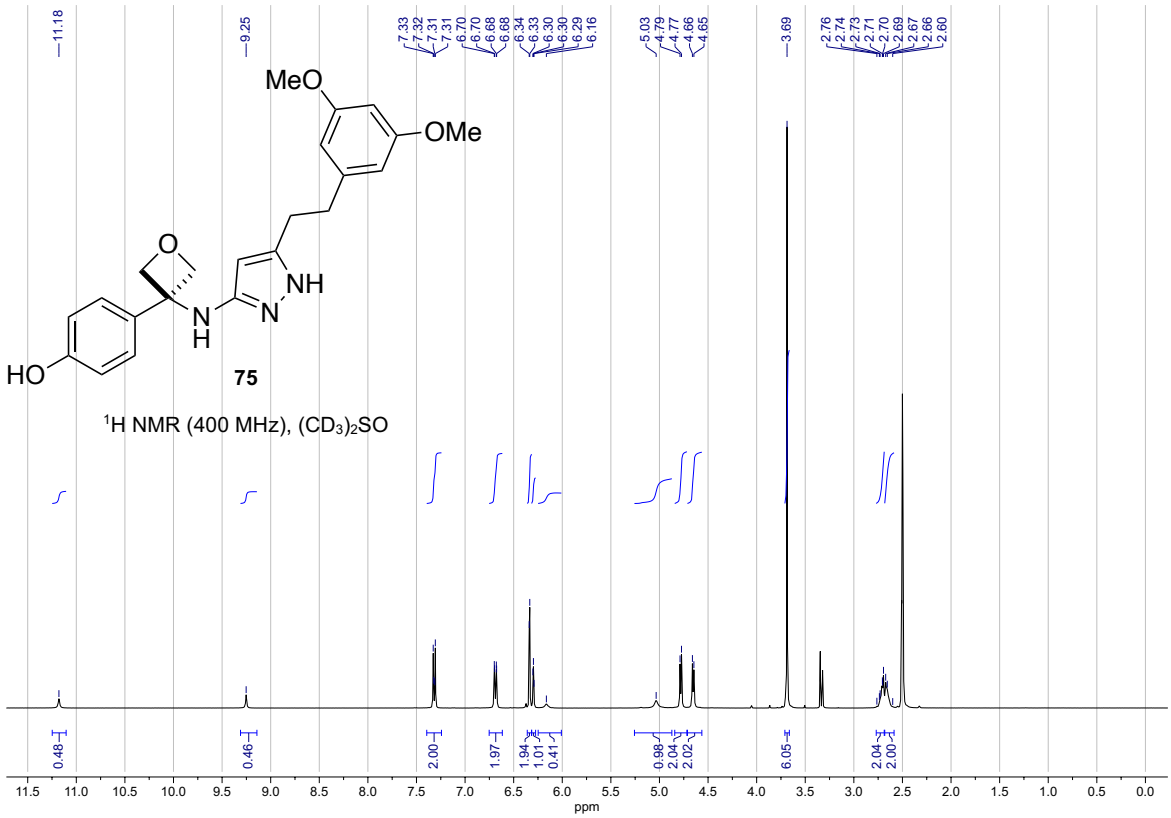

Boc
O
N
H
CN
S22
^{13}C NMR (101 MHz), CDCl$_3$
ppm

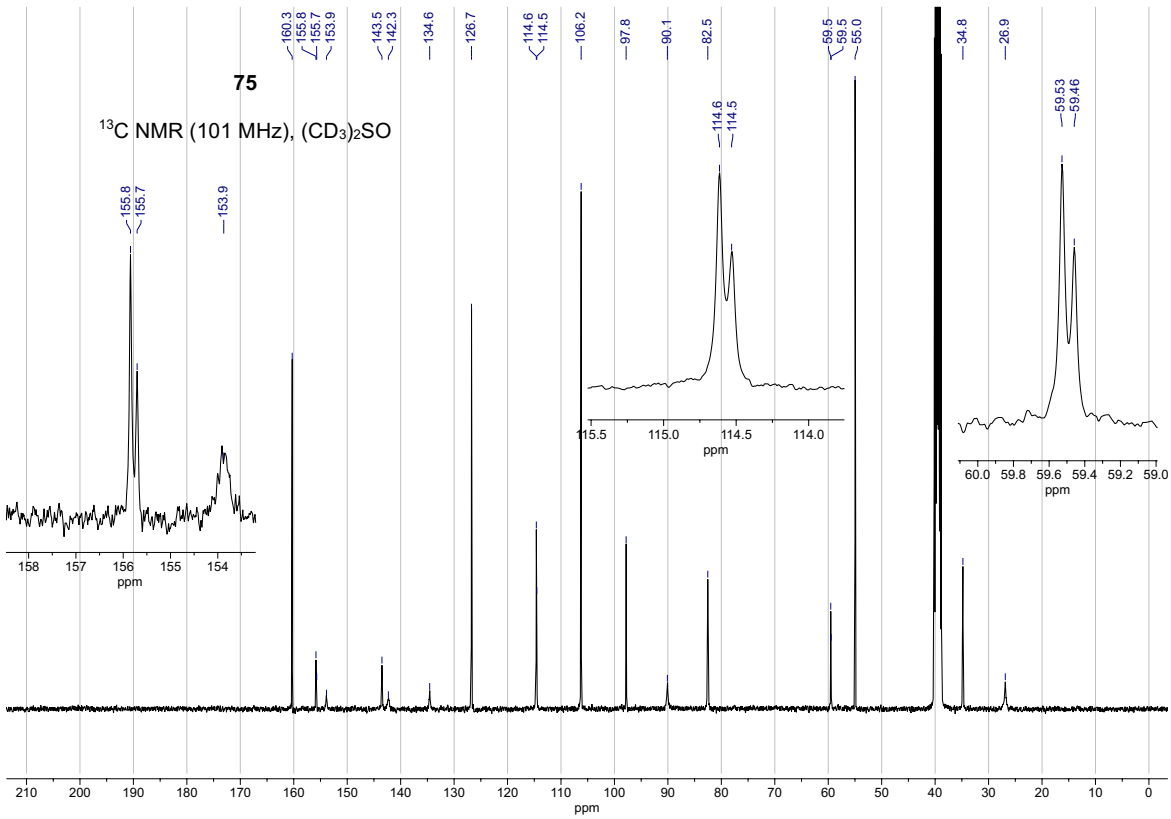

S22
HSQC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
ppm
f1 (ppm)

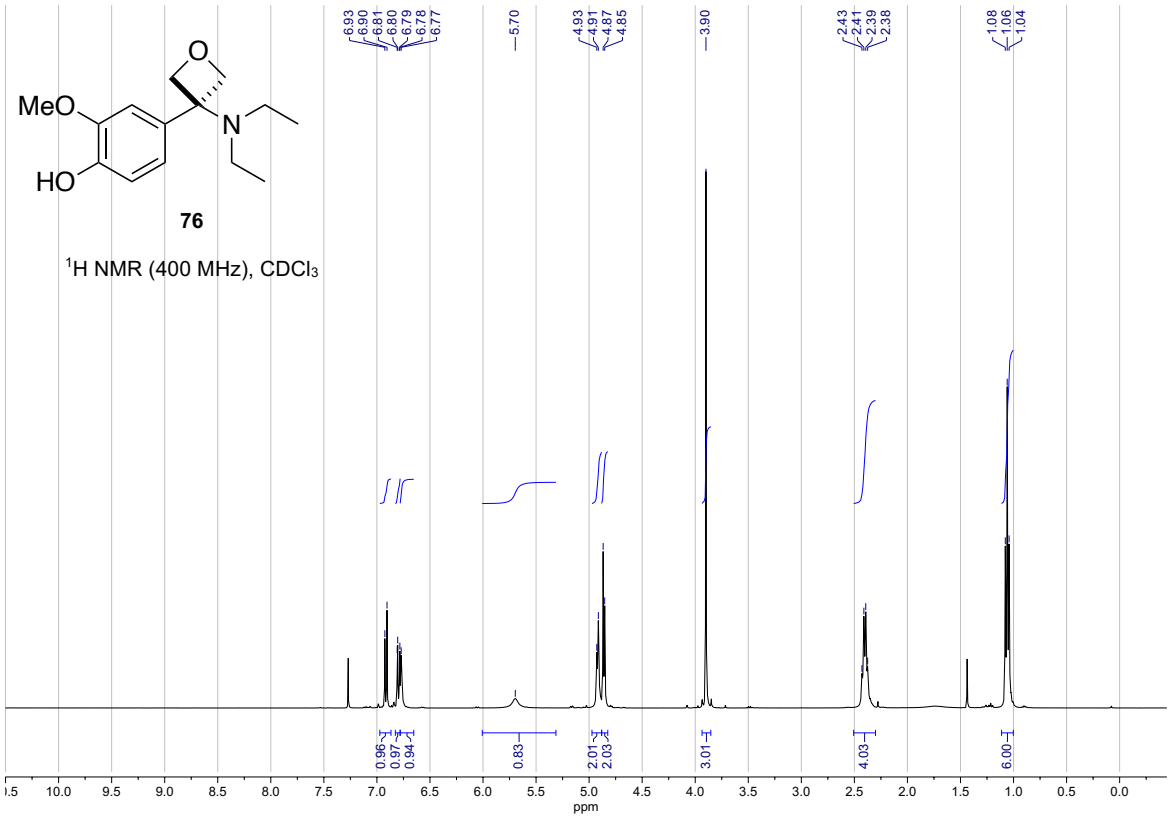

S22
HMBC
^{1}H NMR (400 MHz), CDCl$_3$
^{13}C NMR (101 MHz), CDCl$_3$
ppm
f1 (ppm)

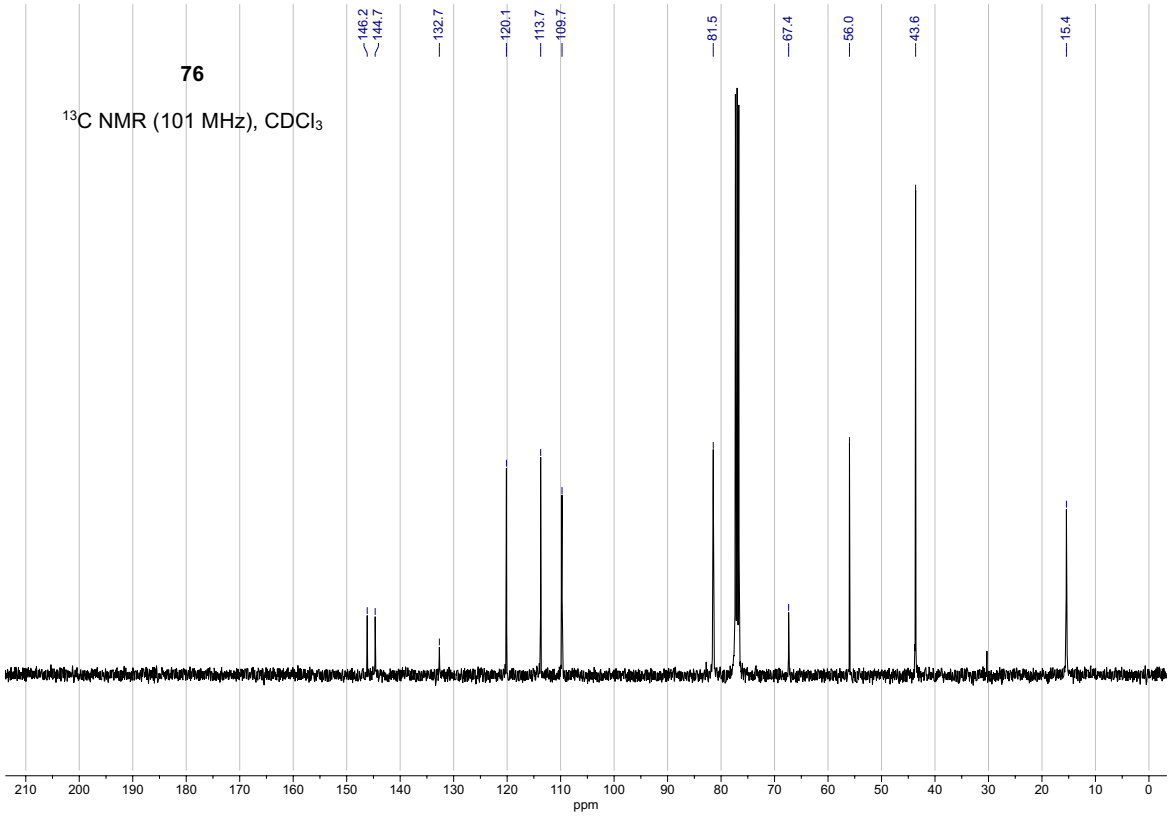

74
^{1}H NMR (400 MHz), CD_3OD
ppm

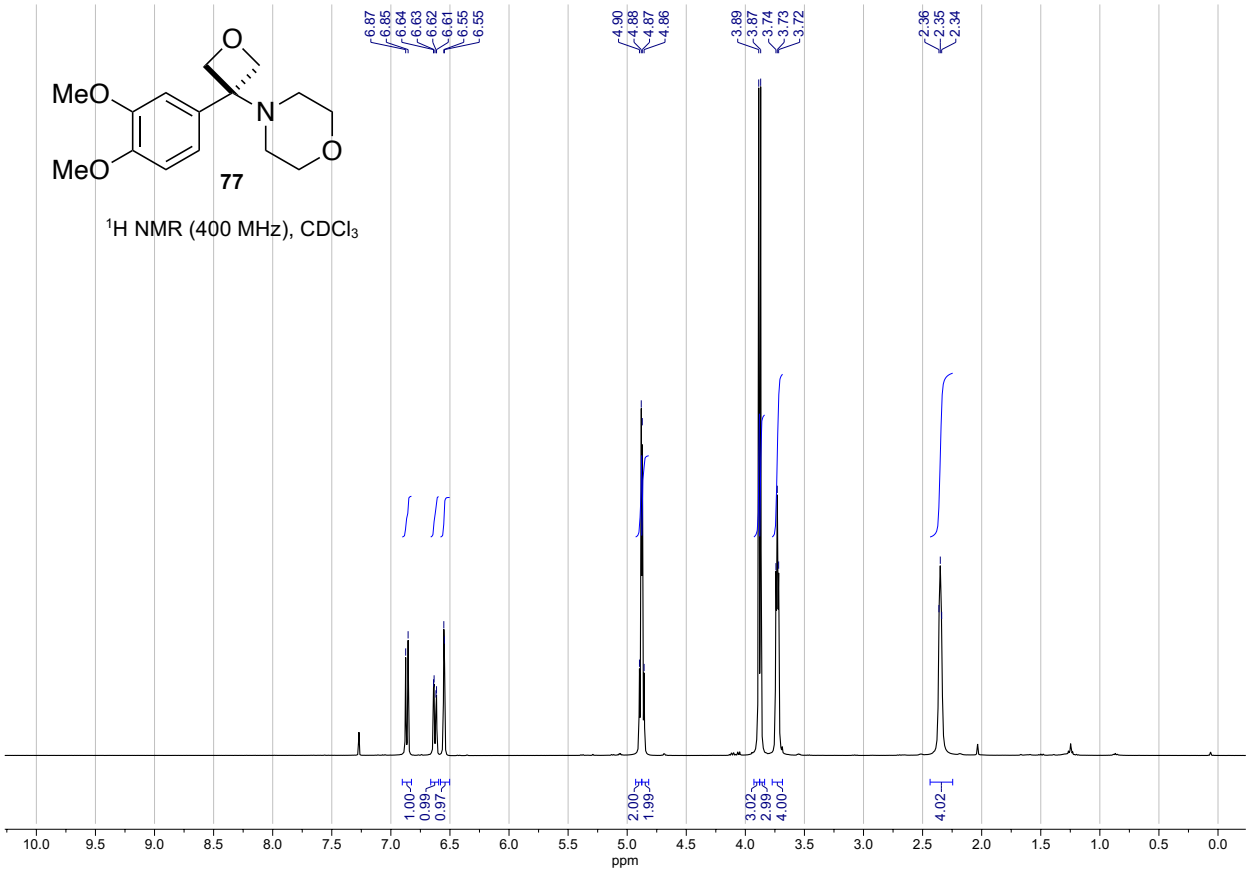

74
^{13}C NMR (101 MHz), CD_3OD
ppm

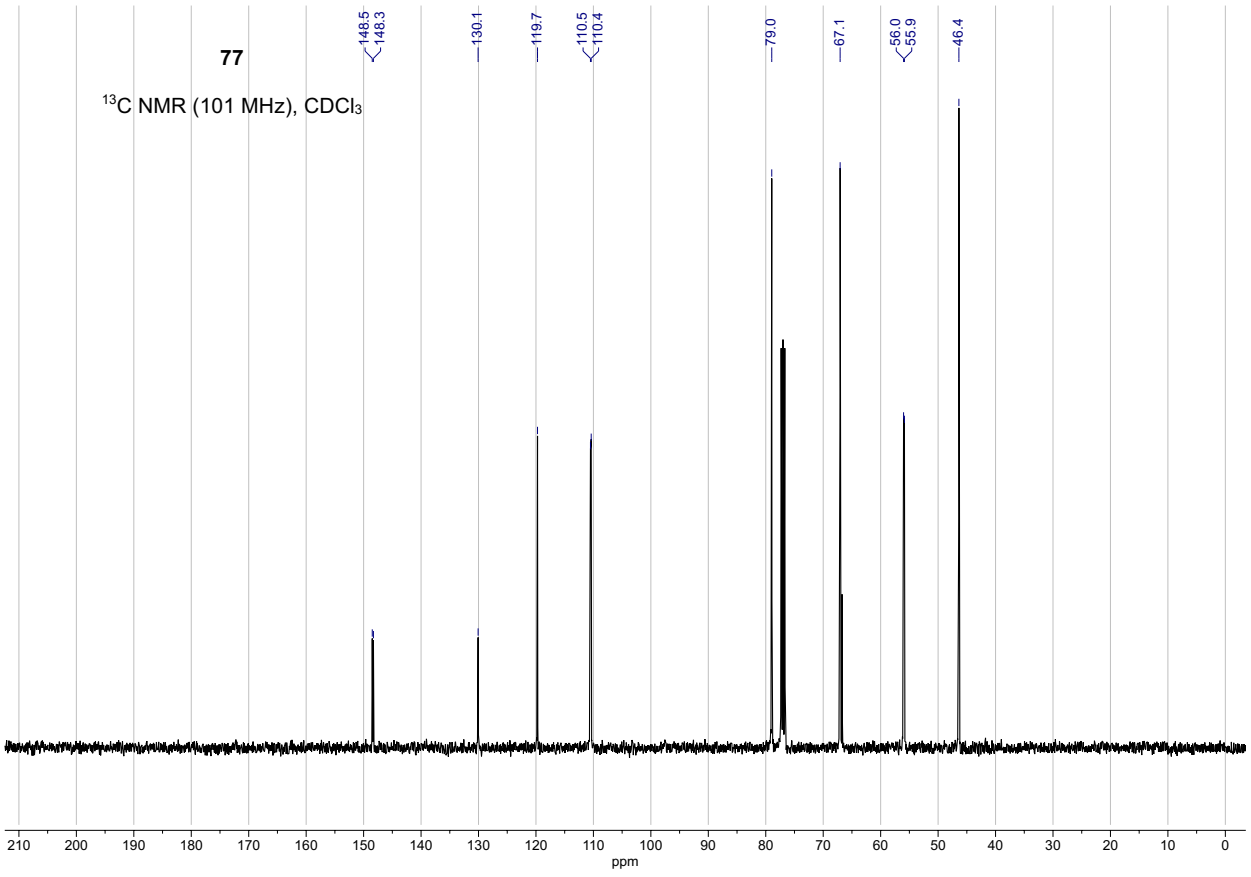

MeO
OMe
O
NH
N
N
H
HO
75
^{1}H NMR (400 MHz), $(CD_3)_2SO$
ppm

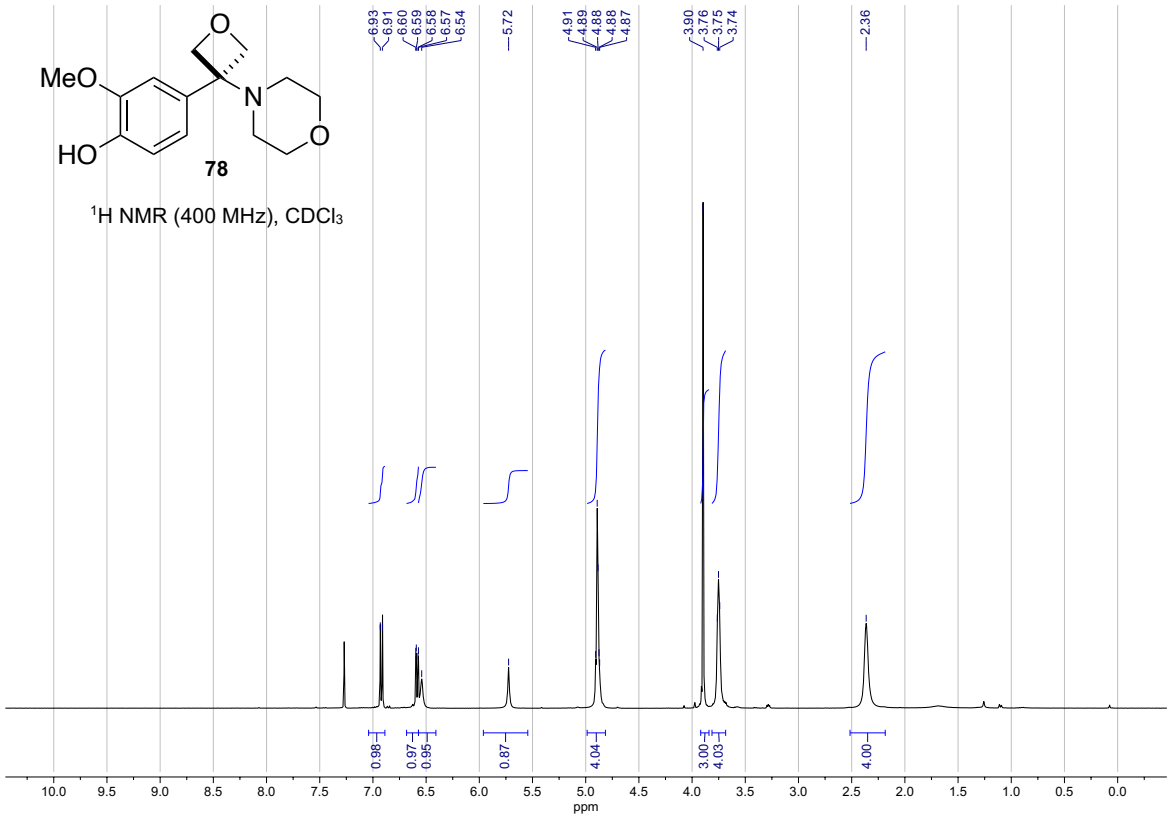

75
^{13}C NMR (101 MHz), $(CD_3)_2SO$
ppm

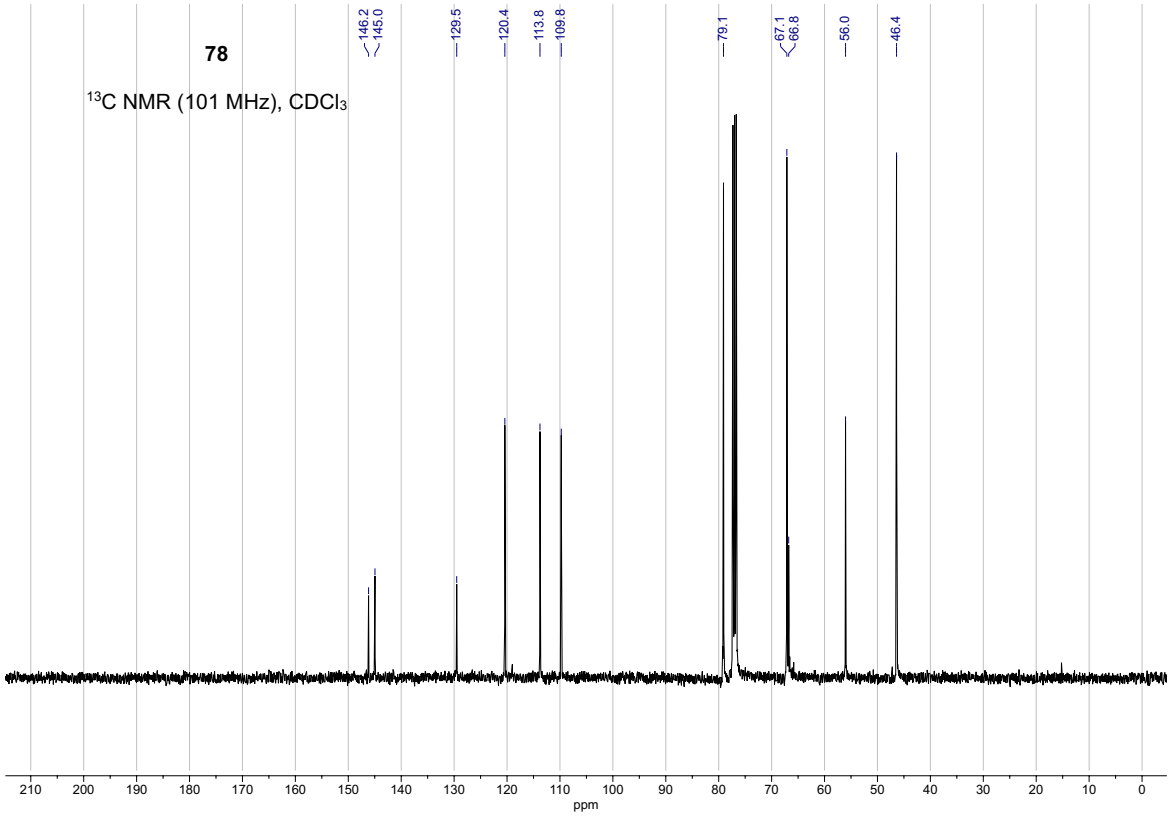

MeO
HO
O
N
76
^{1}H NMR (400 MHz), CDCl$_3$
6.93
6.90
6.81
6.80
6.79
6.78
6.77
5.70
4.93
4.91
4.87
4.85
3.90
2.43
2.41
2.39
2.38
1.08
1.06
1.04
0.96
0.97
0.94
0.83
2.01
2.03
3.01
4.03
6.00
ppm

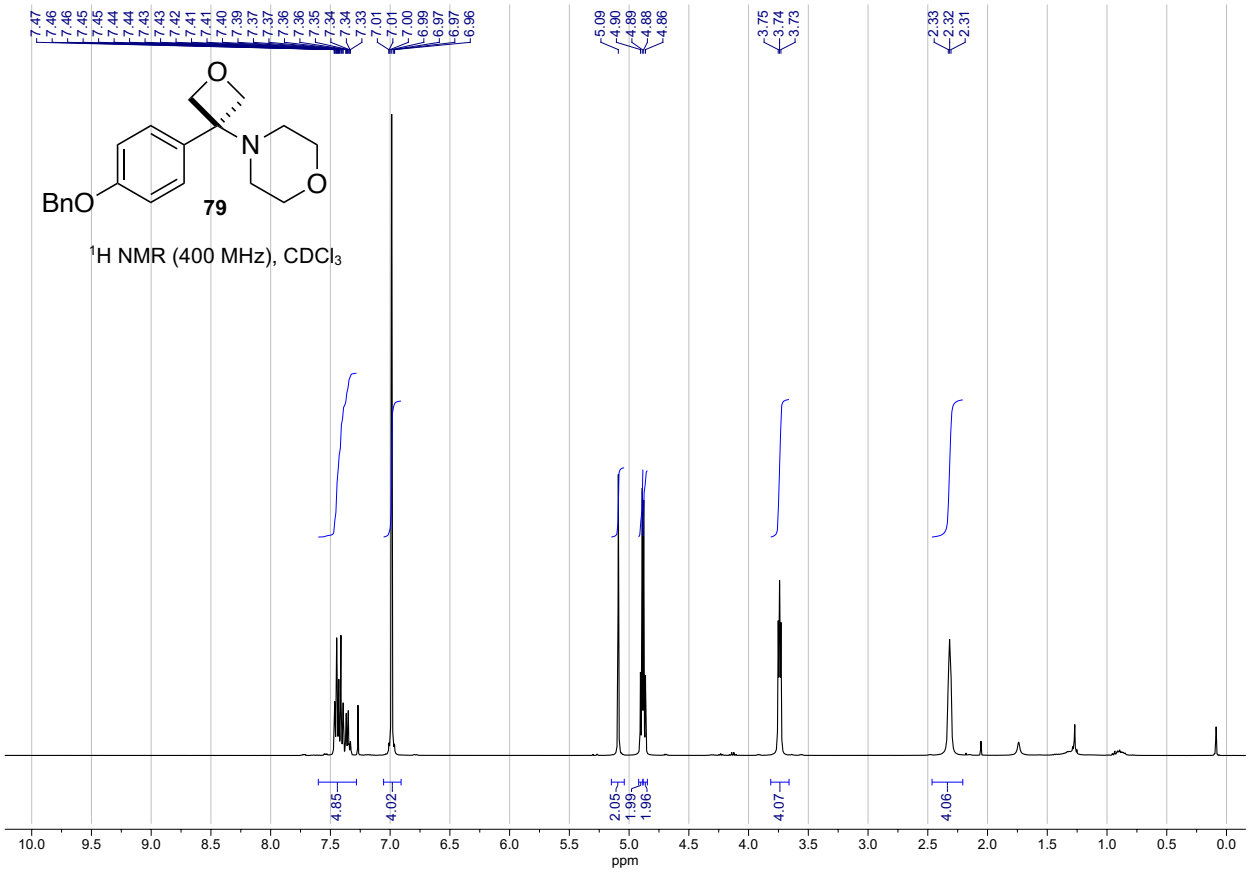

76
^{13}C NMR (101 MHz), CDCl$_3$
146.2
144.7
132.7
120.1
113.7
109.7
81.5
67.4
56.0
43.6
15.4
ppm

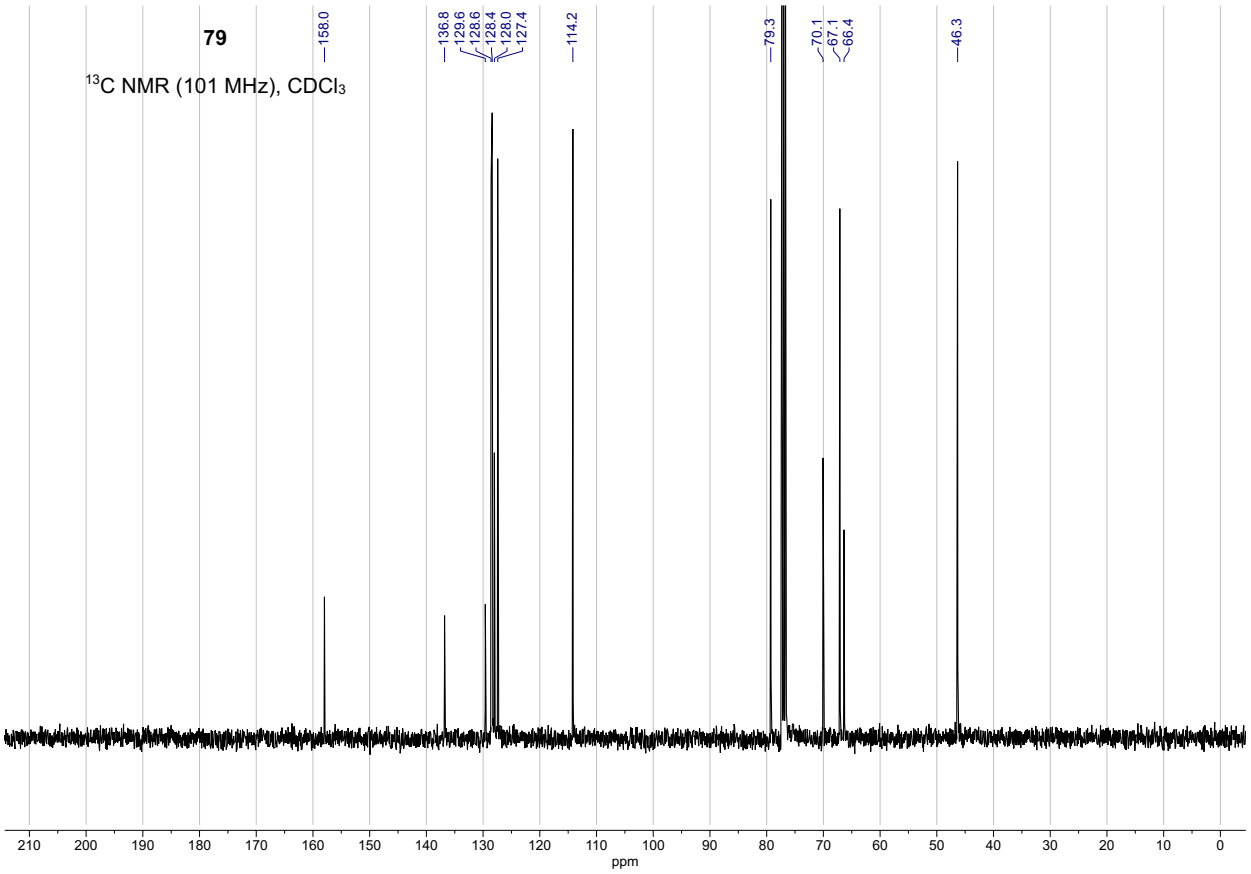

MeO
MeO
O
N
O
77
^{1}H NMR (400 MHz), $CDCl_3$
6.87
6.85
6.64
6.63
6.62
6.61
6.55
6.55
4.90
4.88
4.87
4.86
3.89
3.87
3.74
3.73
3.72
2.36
2.35
2.34
1.00
0.99
0.97
2.00
1.99
3.02
2.99
4.00
4.02
ppm

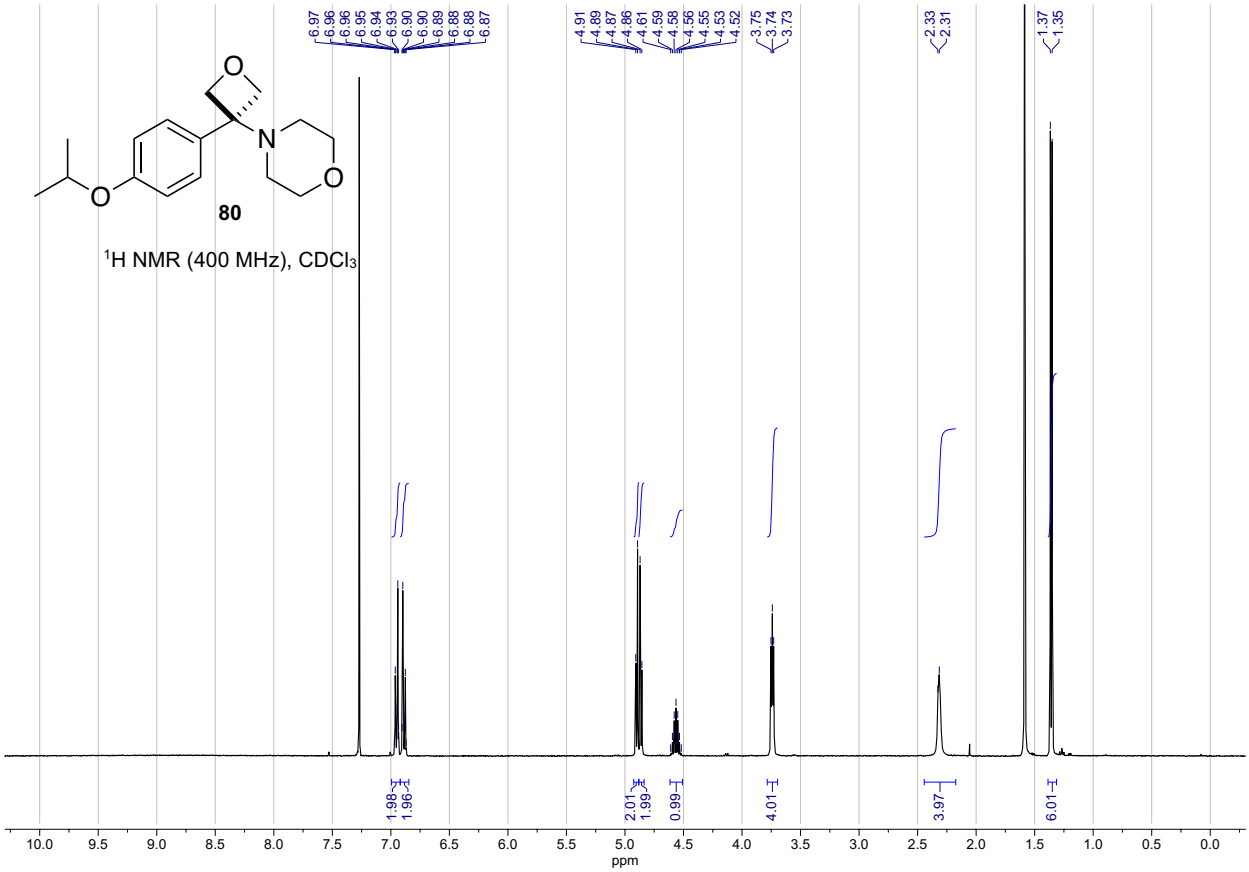

77
^{13}C NMR (101 MHz), $CDCl_3$
148.5
148.3
130.1
119.7
110.5
110.4
79.0
67.1
56.0
55.9
46.4
ppm

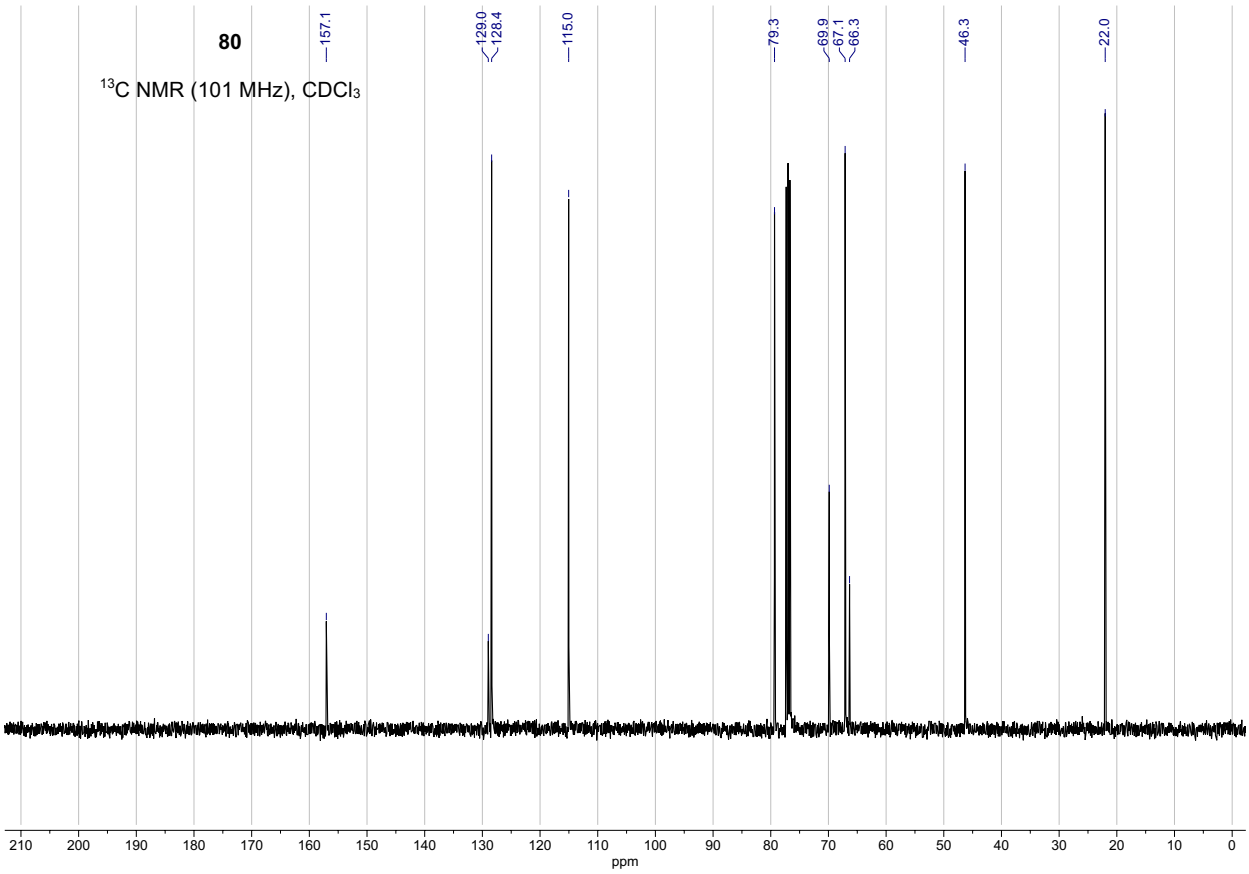

MeO
HO
O
N
O
78
^{1}H NMR (400 MHz), CDCl$_3$
6.93
6.91
6.60
6.59
6.58
6.57
6.54
5.72
4.91
4.89
4.88
4.88
4.87
3.90
3.76
3.75
3.74
2.36
0.98
0.97
0.95
0.87
4.04
3.00
4.03
4.00
ppm

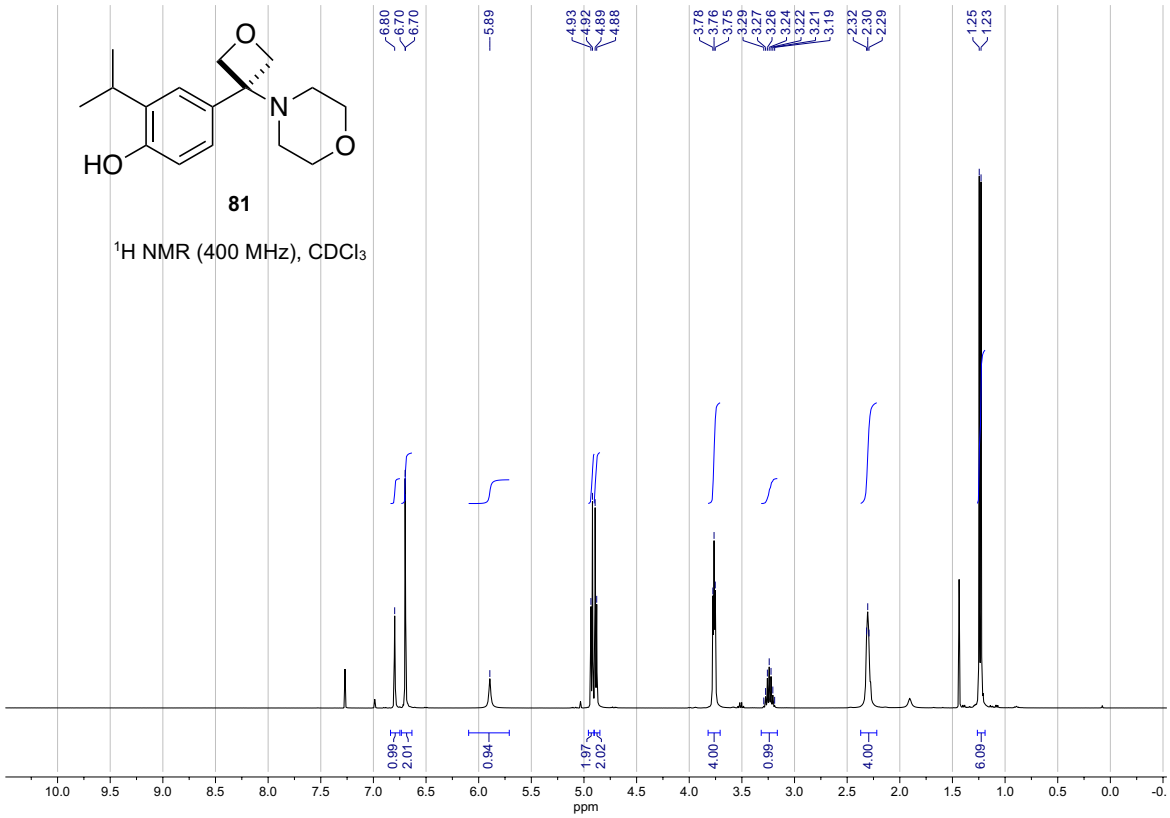

78
^{13}C NMR (101 MHz), CDCl$_3$
146.2
145.0
129.5
120.4
113.8
109.8
79.1
67.1
66.8
56.0
46.4
ppm


7.47 7.46 7.46 7.45 7.45 7.44 7.44 7.43 7.43 7.42 7.41 7.41 7.40 7.39 7.37 7.37 7.36 7.36 7.35 7.34 7.34 7.33 7.01 7.01 7.00 6.99 6.97 6.97 6.96
5.09 4.90 4.89 4.88 4.86
3.75 3.74 3.73
2.33 2.32 2.31
O
N
O
BnO
79
^{1}H NMR (400 MHz), $CDCl_3$
4.85 4.02 2.05 1.99 1.96 4.07 4.06
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


79
^{13}C NMR (101 MHz), $CDCl_3$
158.0
136.8 129.6 128.6 128.4 128.0 127.4
114.2
79.3
70.1 67.1 66.4
46.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

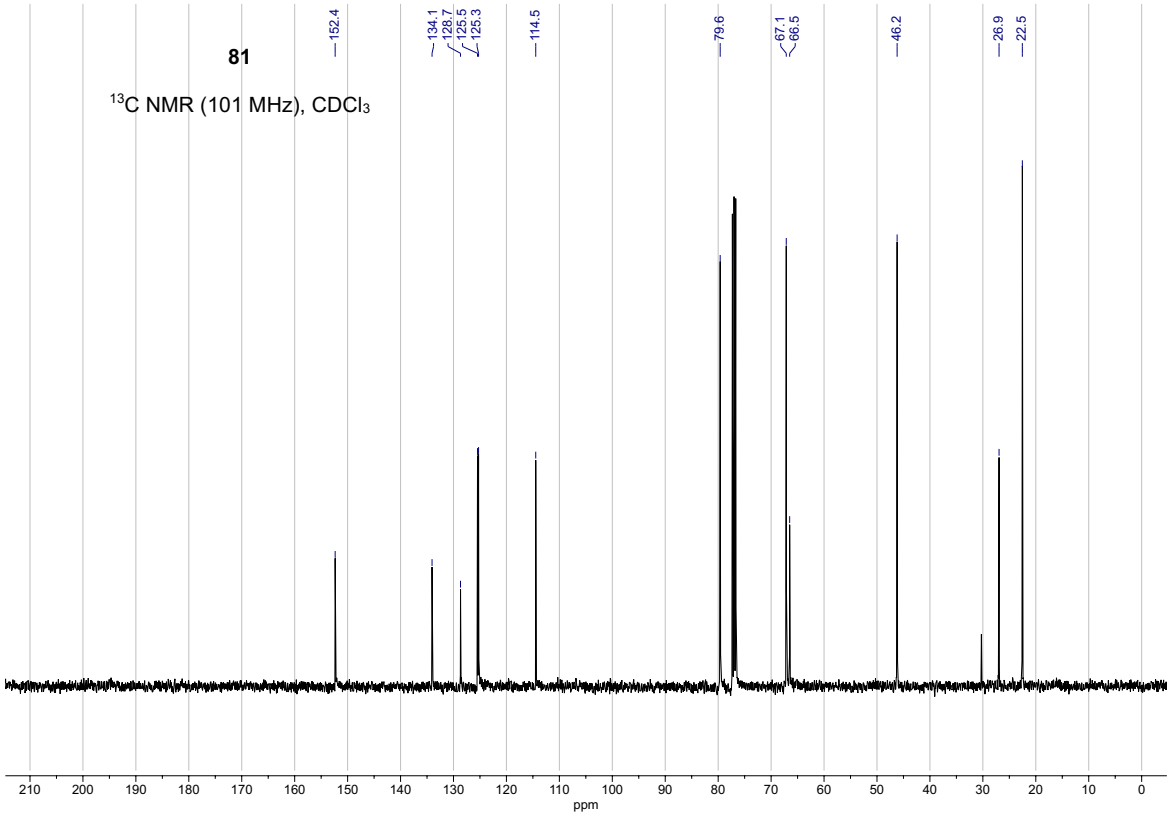

6.97
6.96
6.96
6.95
6.94
6.93
6.90
6.90
6.89
6.88
6.88
6.87
4.91
4.89
4.87
4.86
4.61
4.59
4.58
4.56
4.55
4.53
4.52
3.75
3.74
3.73
2.33
2.31
1.37
1.35
O
N
O
O
80
^{1}H NMR (400 MHz), CDCl$_3$
1.98
1.96
2.01
1.99
0.99
4.01
3.97
6.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


80
^{13}C NMR (101 MHz), CDCl$_3$
157.1
129.0
128.4
115.0
79.3
69.9
67.1
66.3
46.3
22.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



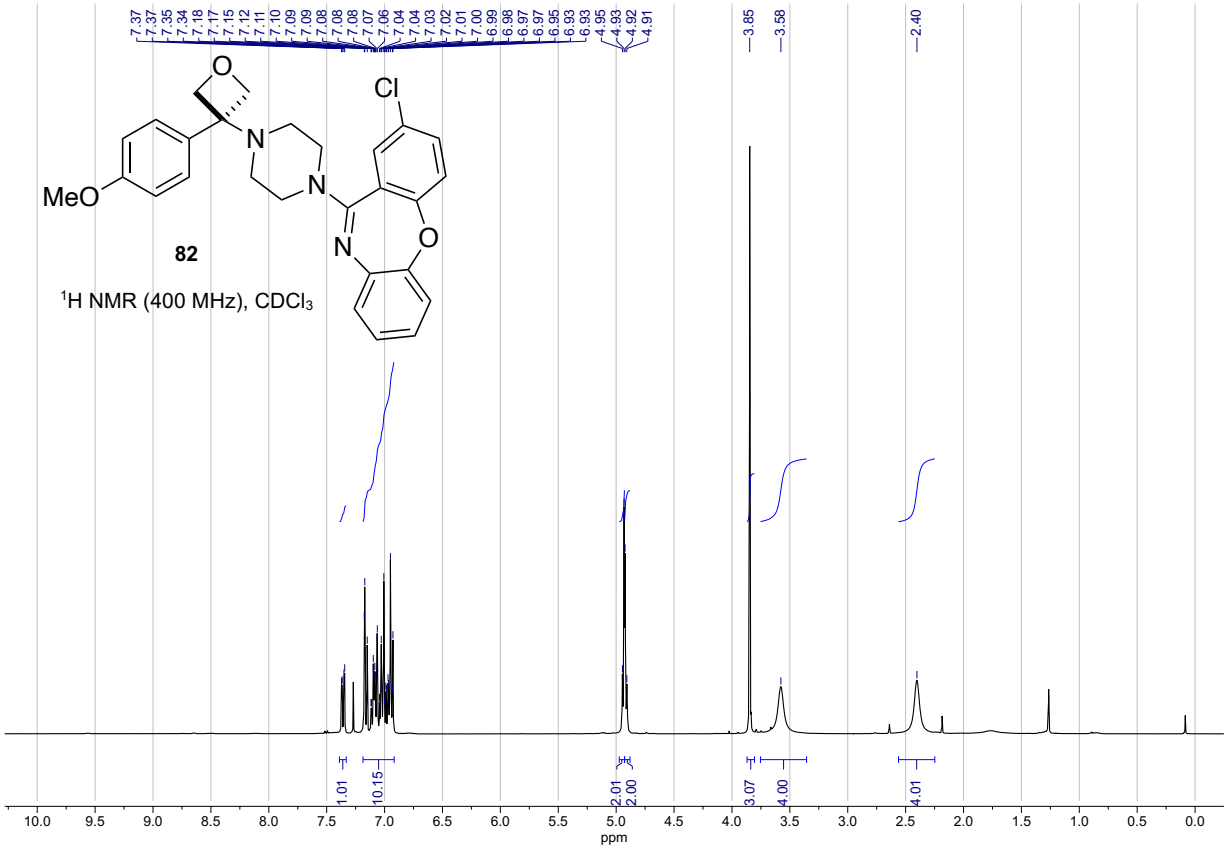
81

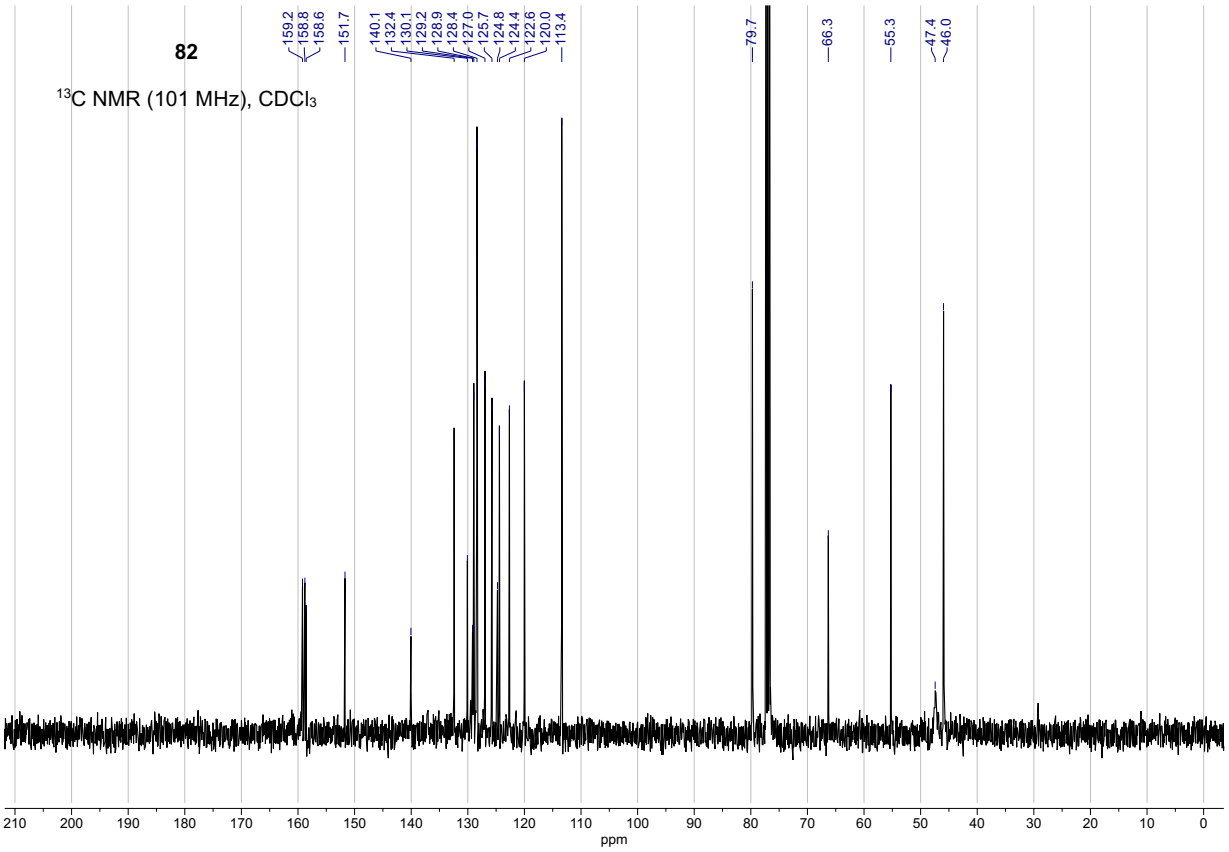
^{1}H NMR (400 MHz), $CDCl_3$

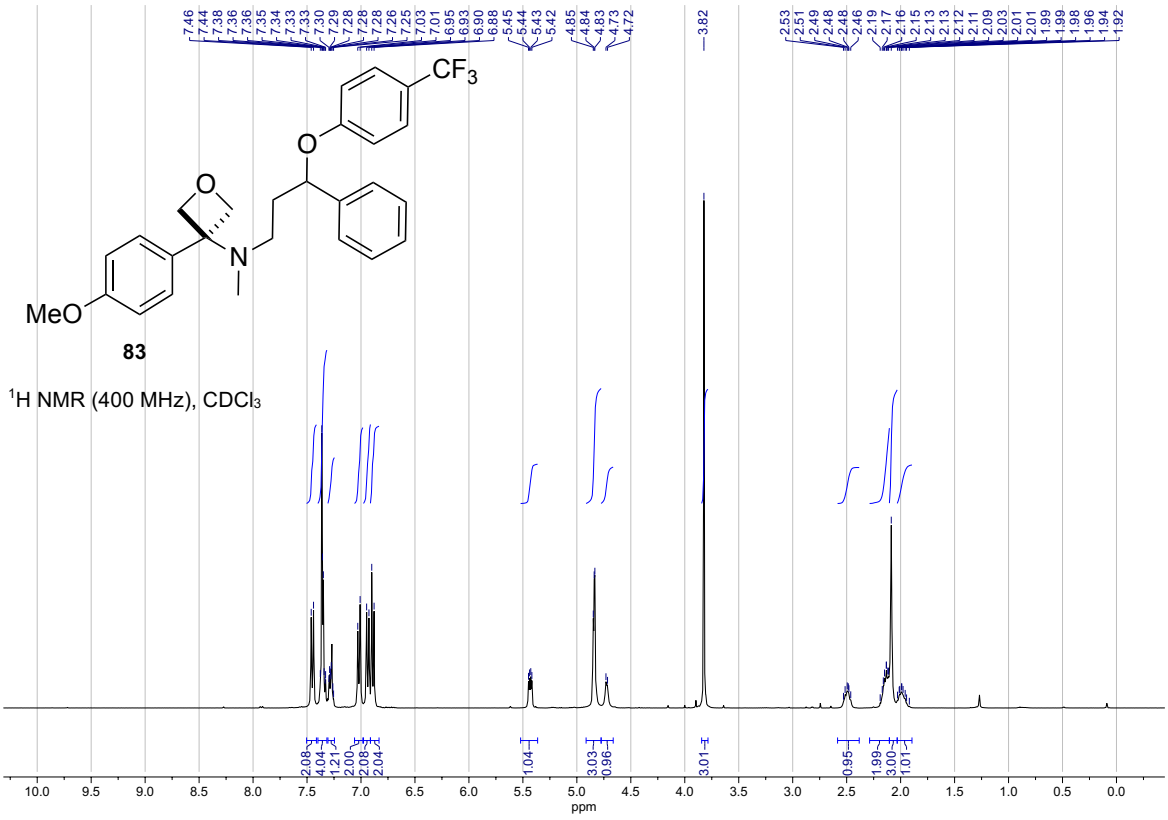


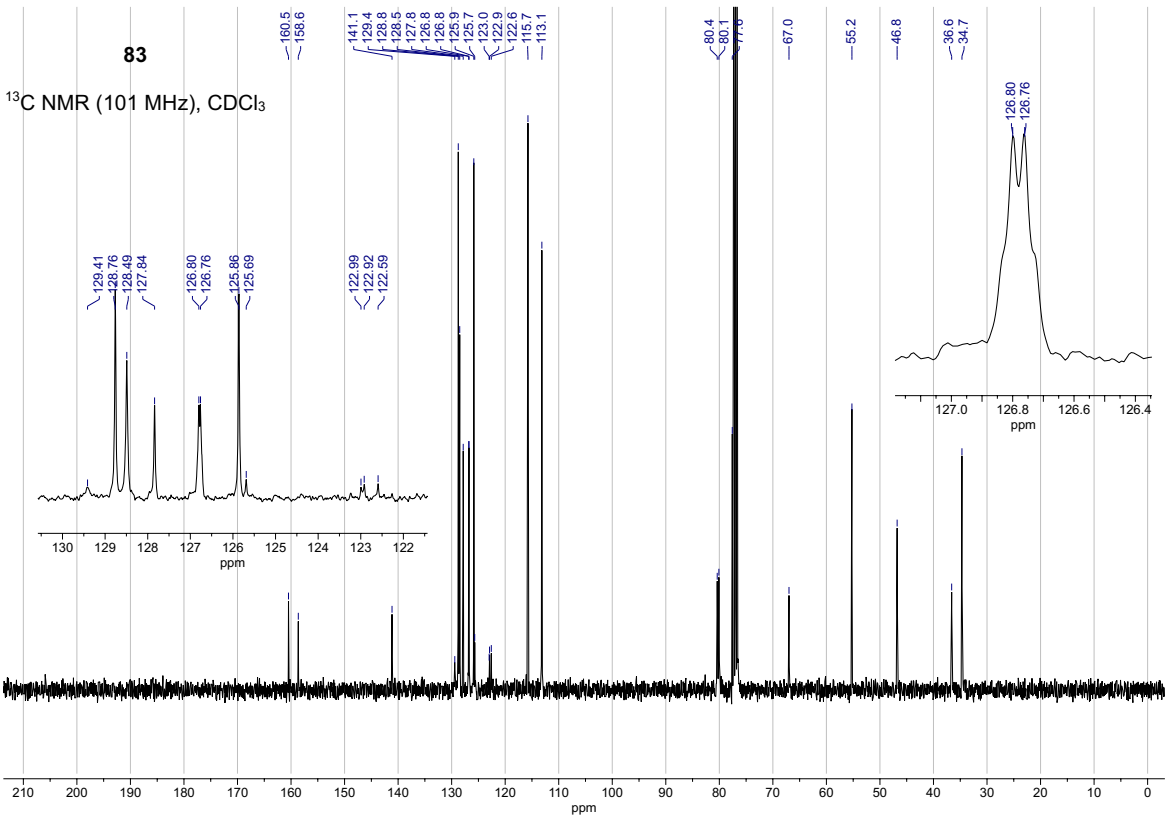
81

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


7.37
7.37
7.35
7.34
7.18
7.17
7.15
7.12
7.11
7.10
7.09
7.09
7.08
7.08
7.08
7.07
7.06
7.04
7.04
7.03
7.02
7.01
7.00
6.99
6.98
6.97
6.97
6.95
6.93
6.93
4.95
4.93
4.92
4.91
3.85
3.58
2.40
O
Cl
N
N
MeO
N
O
82
^{1}H NMR (400 MHz), CDCl$_3$
1.01
10.15
2.01
2.00
3.07
4.00
4.01
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

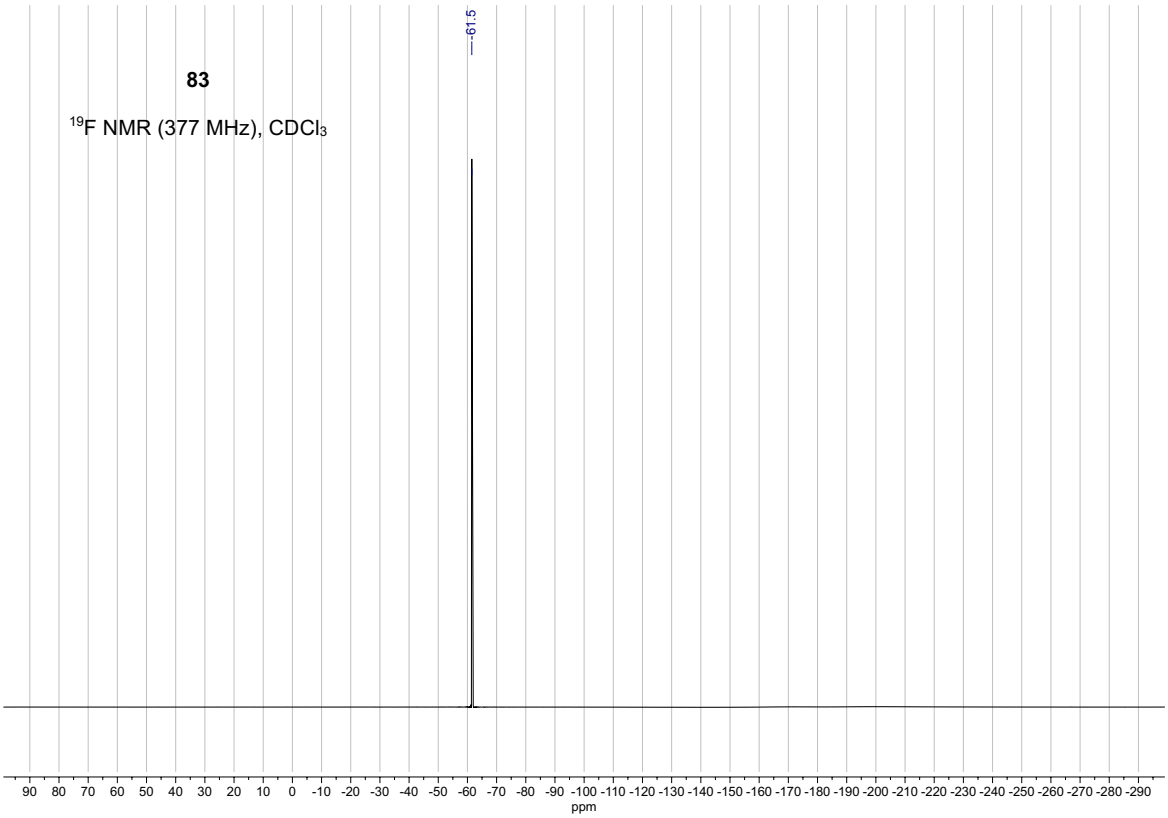

82
^{13}C NMR (101 MHz), CDCl$_3$
159.2
158.8
158.6
151.7
140.1
132.4
130.1
129.2
128.9
128.4
127.0
125.7
124.8
124.4
122.6
120.0
113.4
79.7
66.3
55.3
47.4
46.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

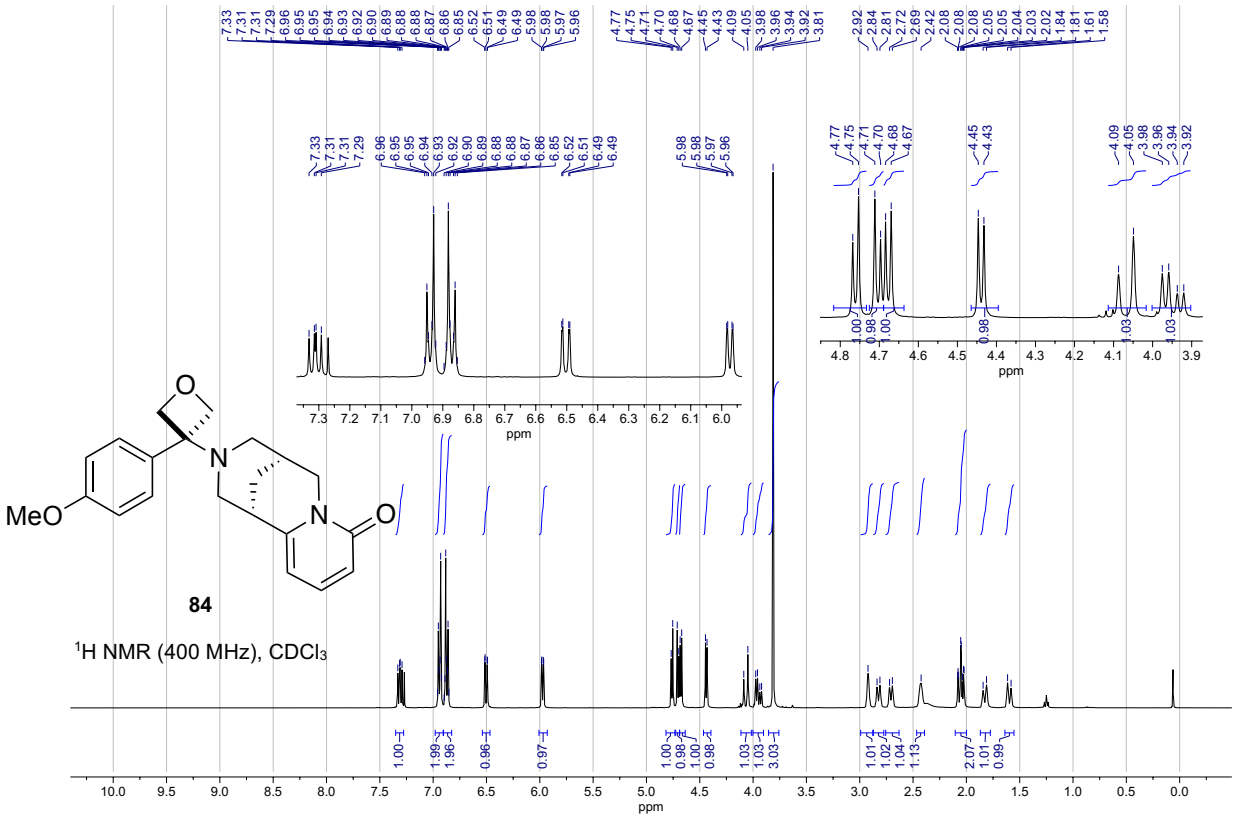

CF3
O
O
N
MeO
83
1H NMR (400 MHz), CDCl3
ppm

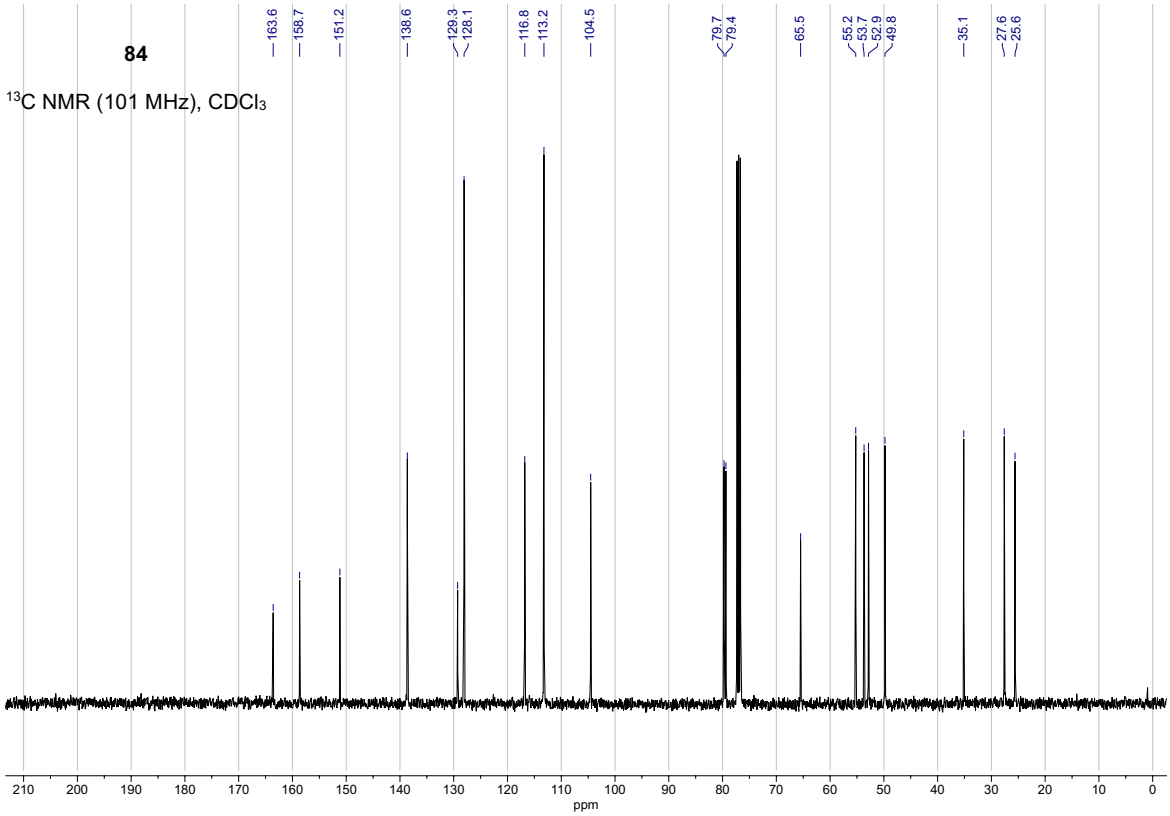

83
13C NMR (101 MHz), CDCl3
ppm

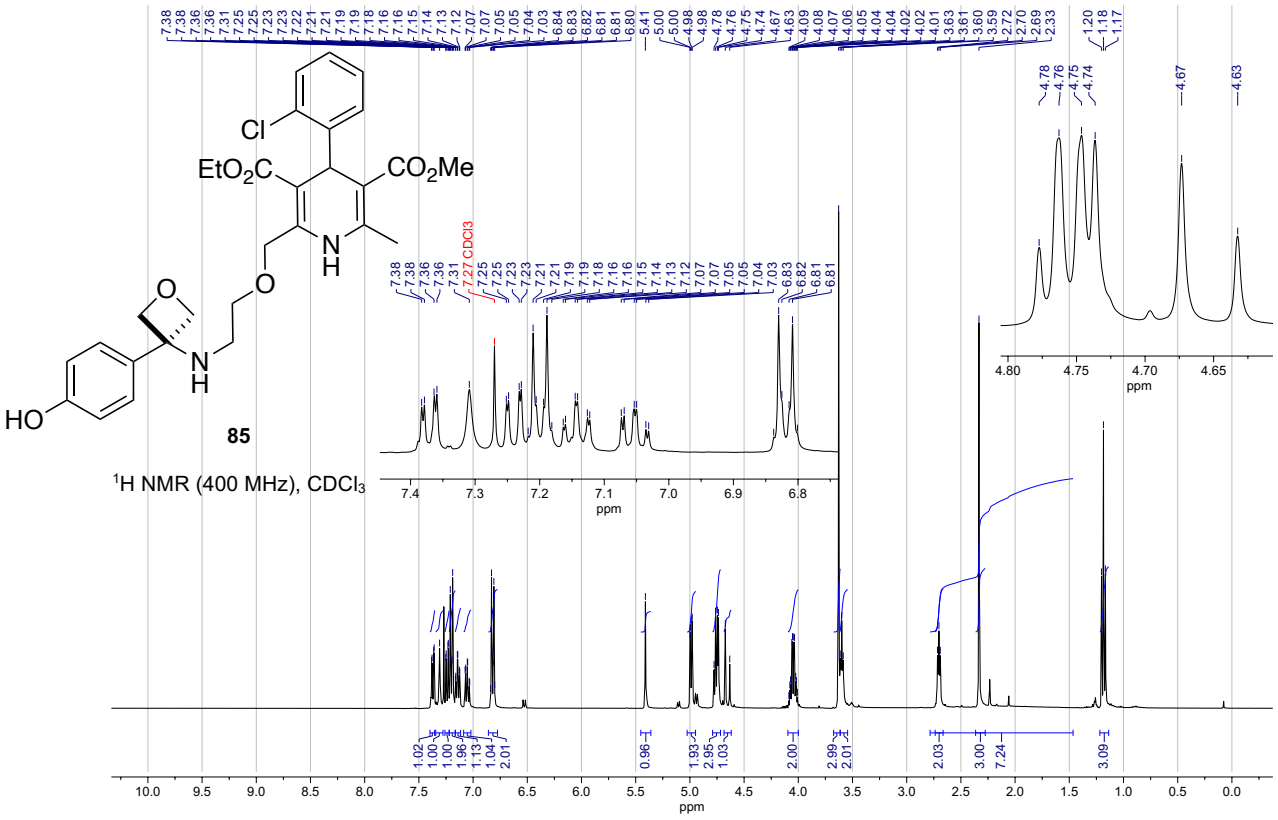
83

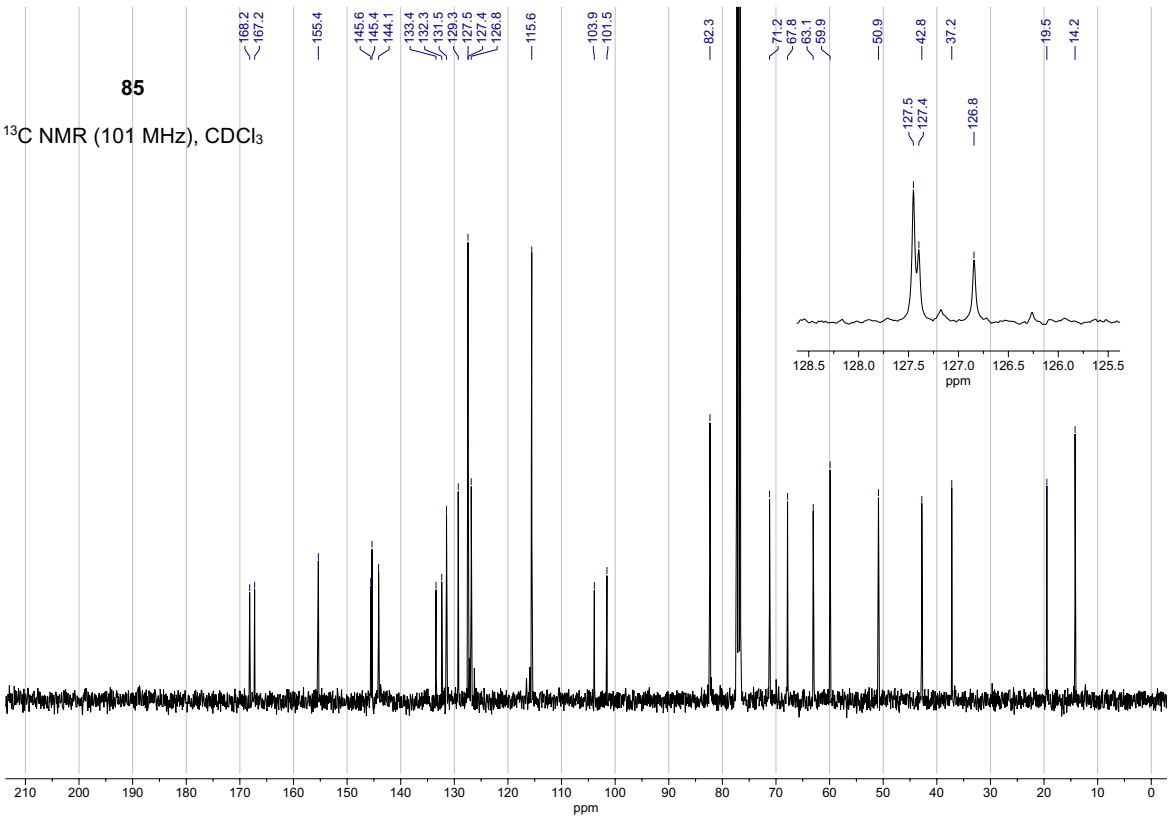
^{19}F NMR (377 MHz), $CDCl_3$

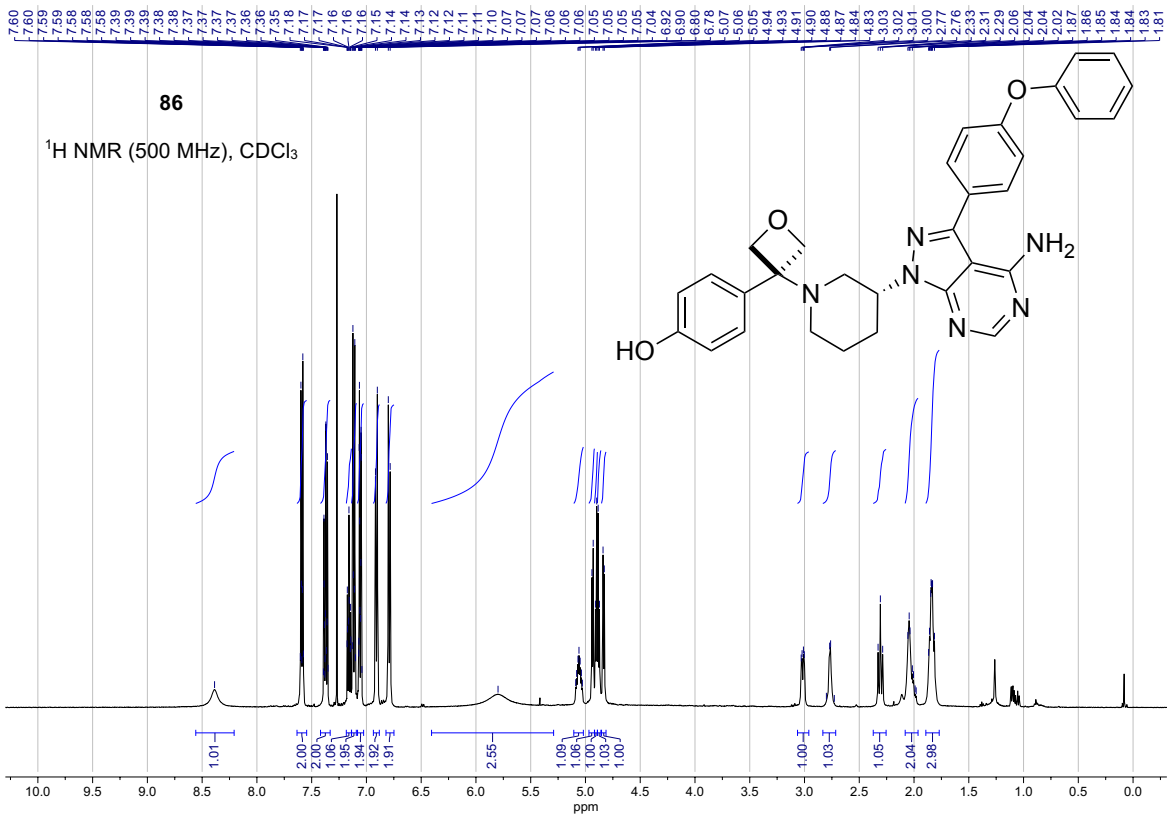


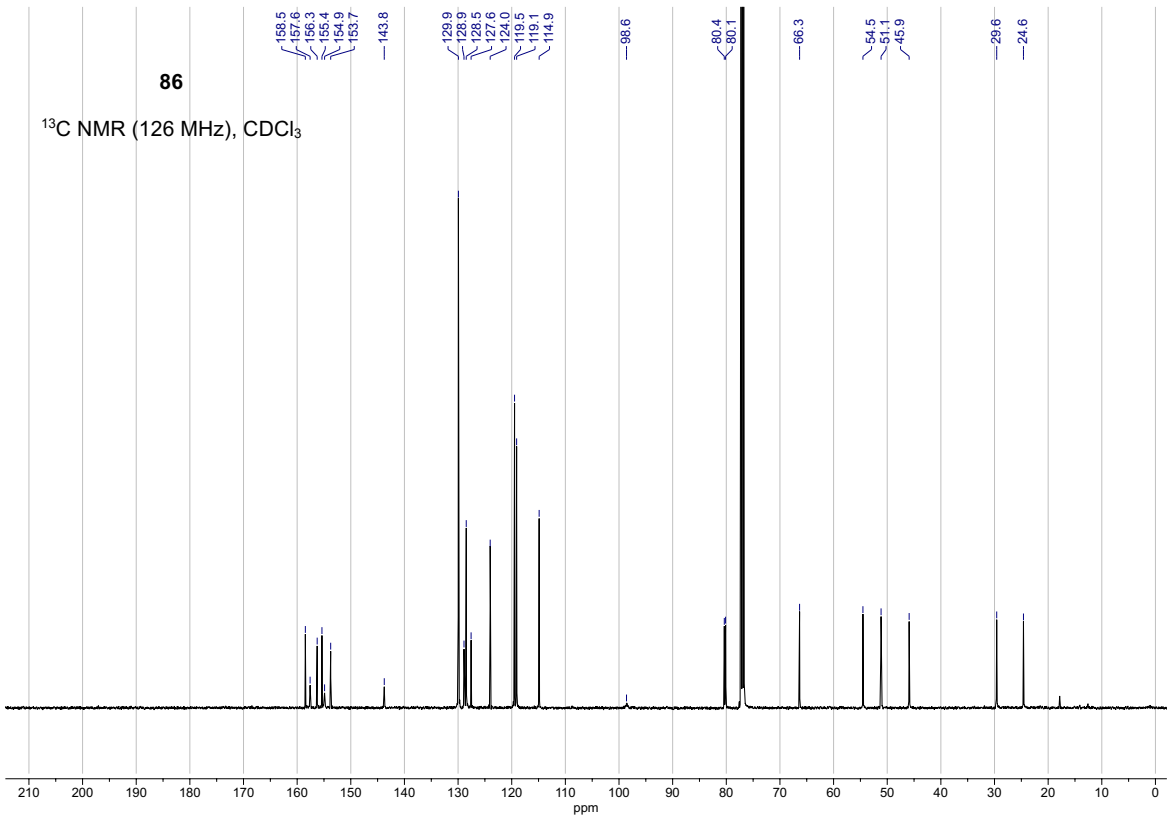

MeO
O
N
N
O
84
^{1}H NMR (400 MHz), CDCl$_3$
ppm

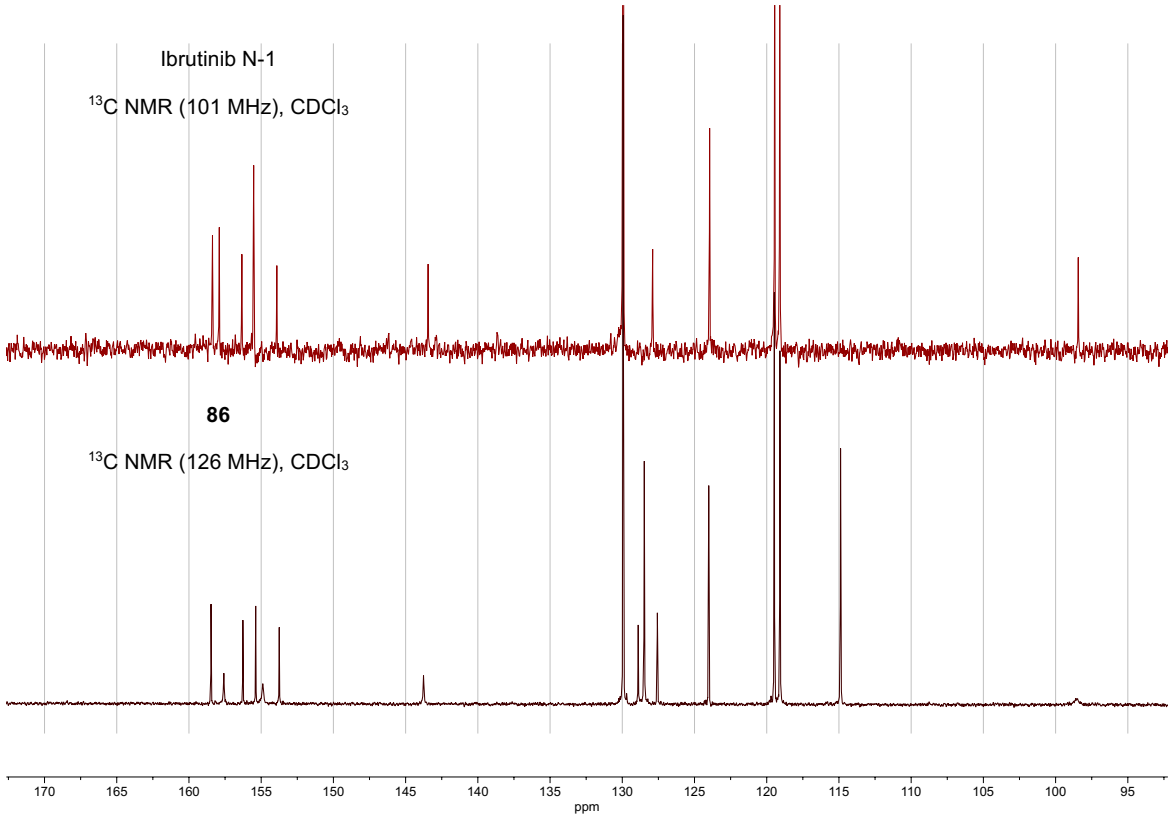

84
^{13}C NMR (101 MHz), CDCl$_3$
163.6
158.7
151.2
138.6
129.3
128.1
116.8
113.2
104.5
79.7
79.4
65.5
55.2
53.7
52.9
49.8
35.1
27.6
25.6
ppm

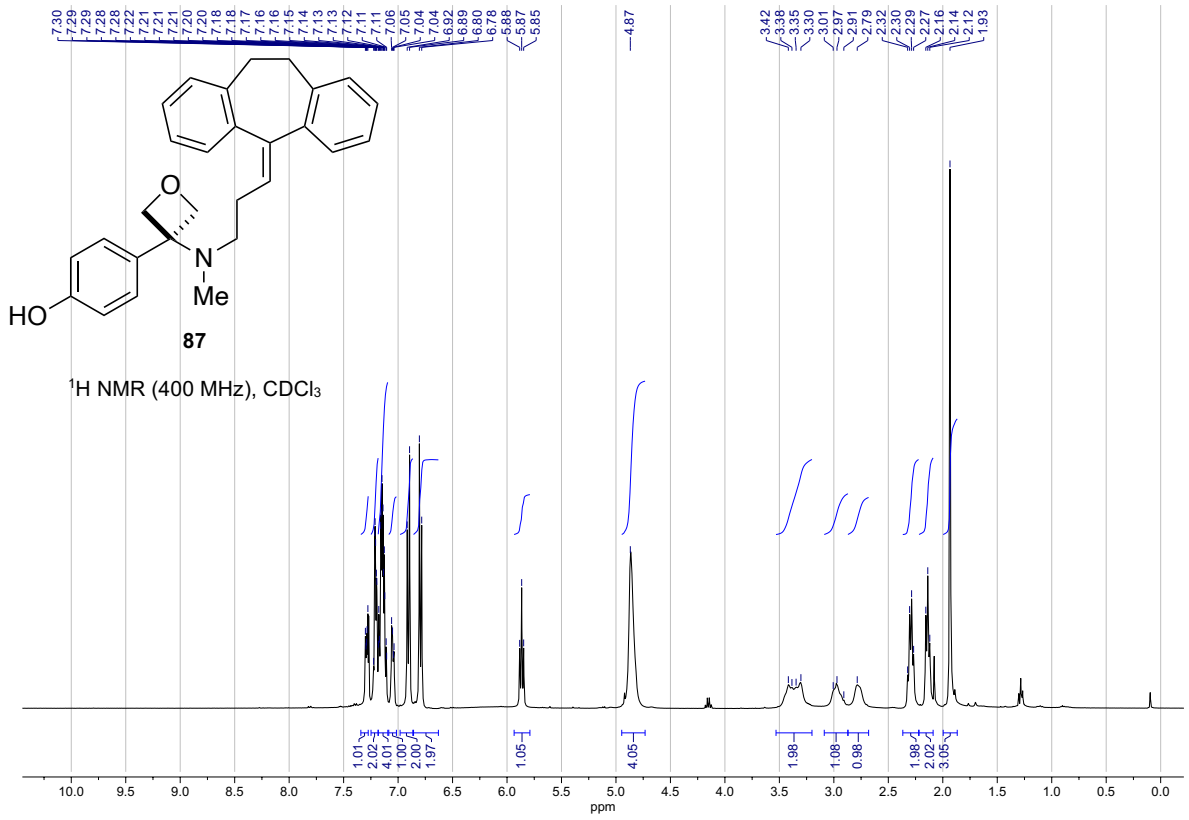

Cl
EtO2C
CO2Me
N
H
O
O
N
H
HO
85
1H NMR (400 MHz), CDCl3
ppm

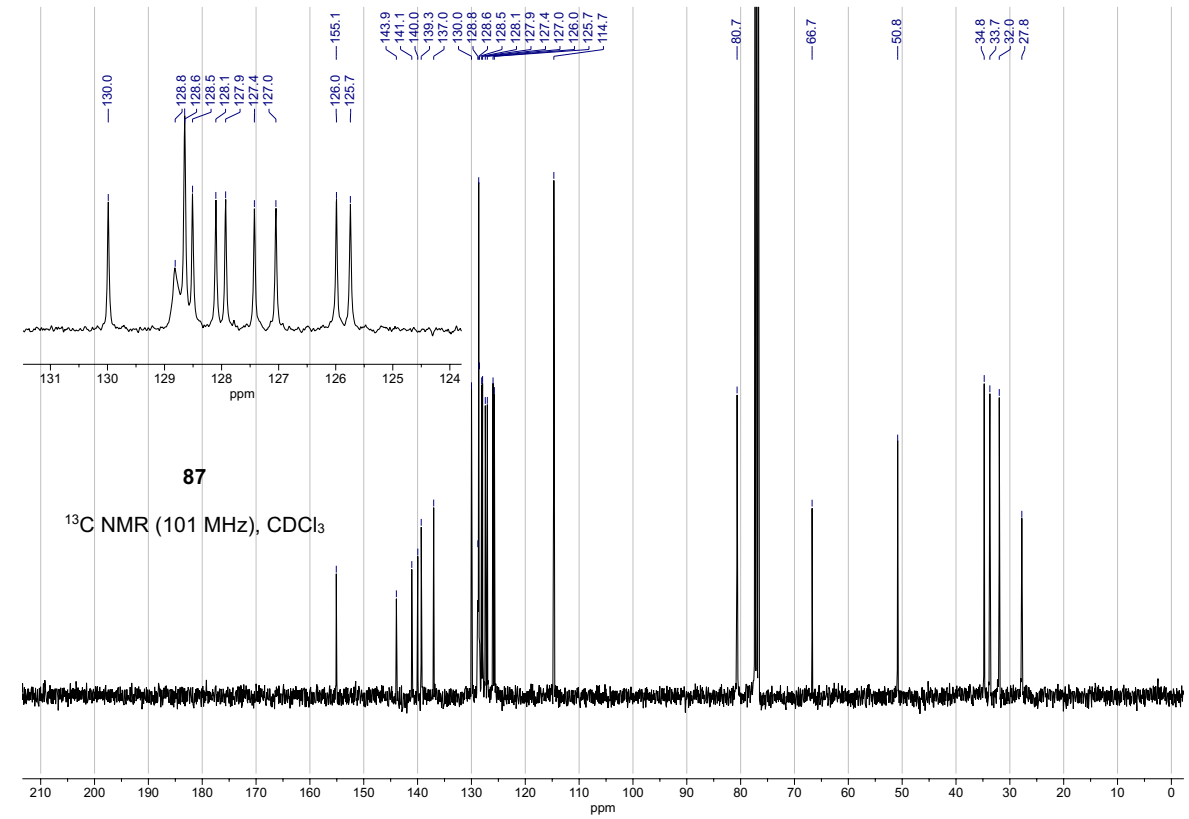

85
13C NMR (101 MHz), CDCl3
ppm

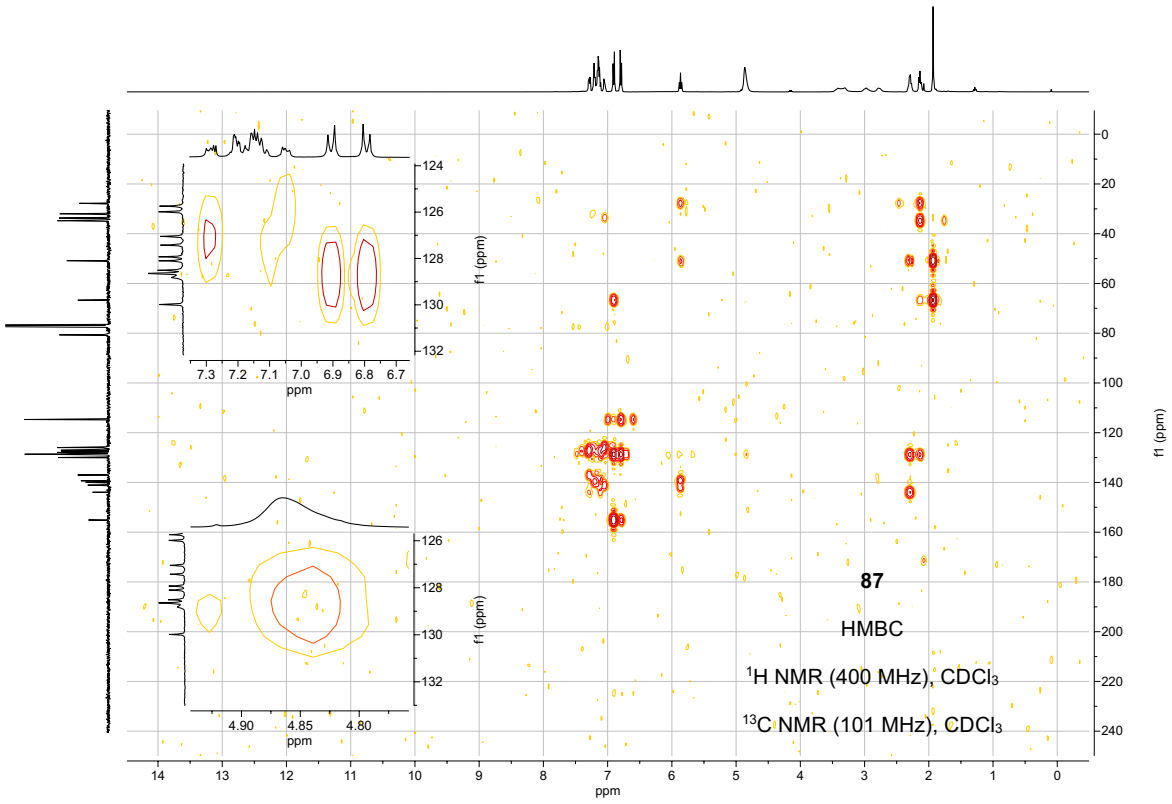

86
^{1}H NMR (500 MHz), CDCl$_3$
O
N
N
N
NH$_2$
N
N
HO
ppm

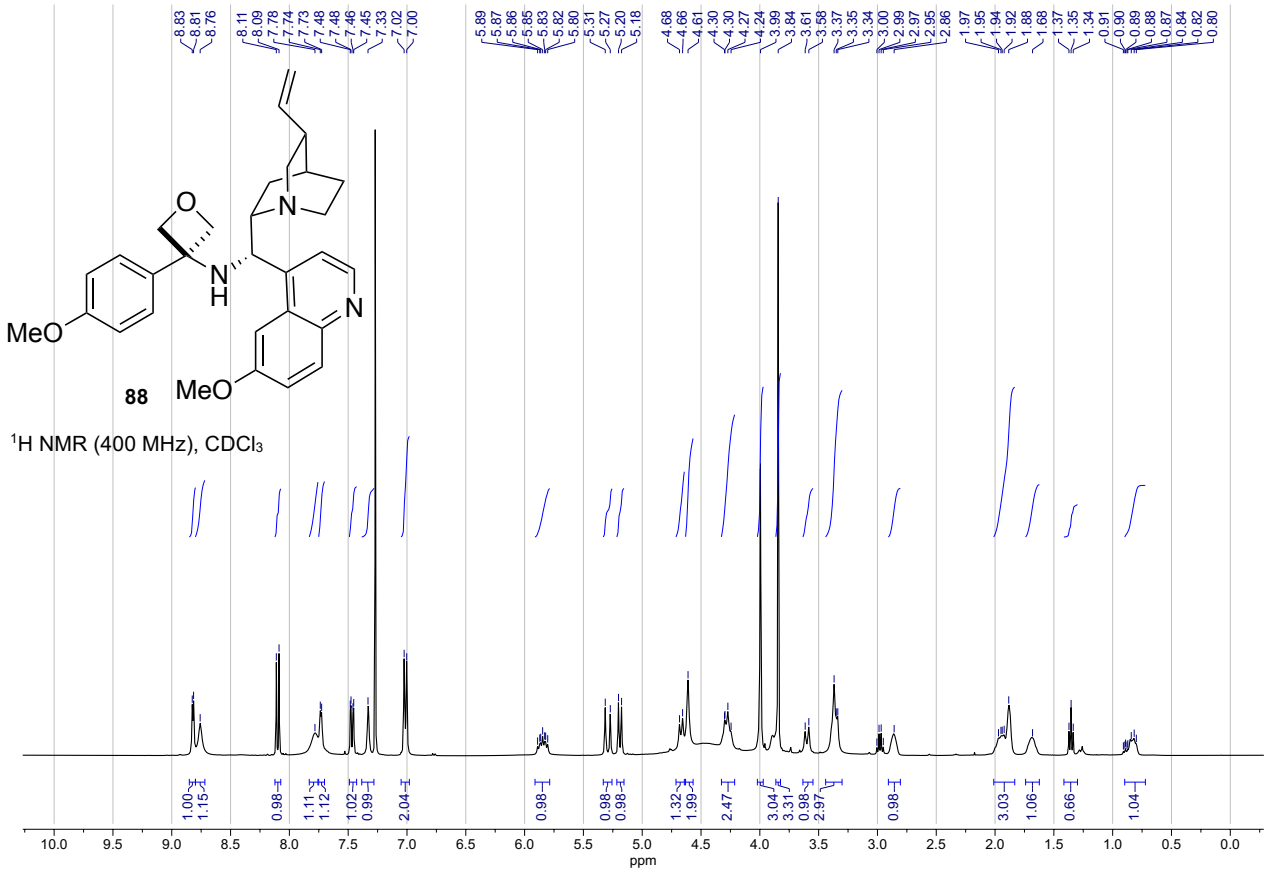

86
^{13}C NMR (126 MHz), CDCl$_3$
158.5
157.6
156.3
155.4
154.9
153.7
143.8
129.9
128.9
128.5
127.6
124.0
119.5
119.1
114.9
98.6
80.4
80.1
66.3
54.5
51.1
45.9
29.6
24.6
ppm

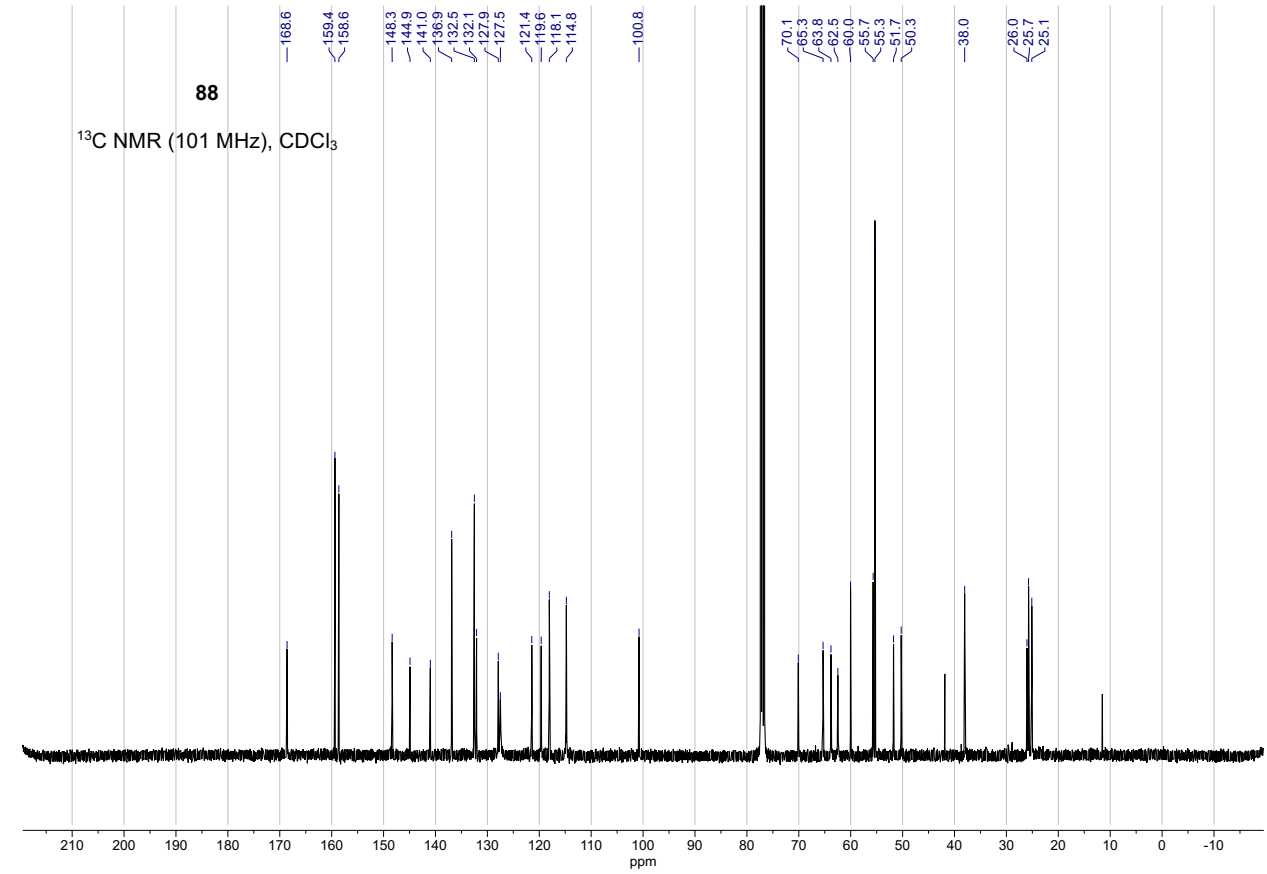

Ibrutinib N-1
^{13}C NMR (101 MHz), CDCl$_3$
86
^{13}C NMR (126 MHz), CDCl$_3$
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
ppm

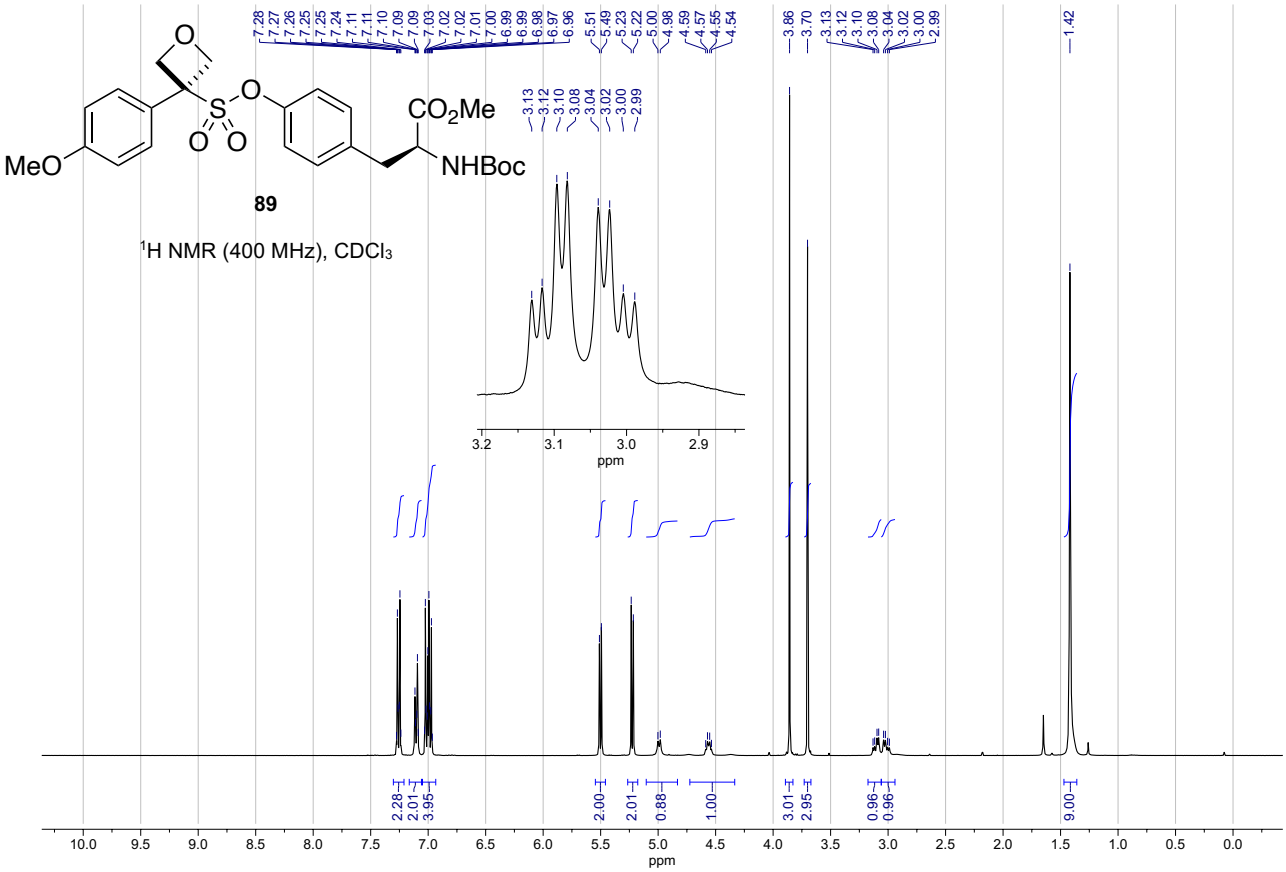

HO
N
Me
O
87
^{1}H NMR (400 MHz), CDCl$_3$
ppm

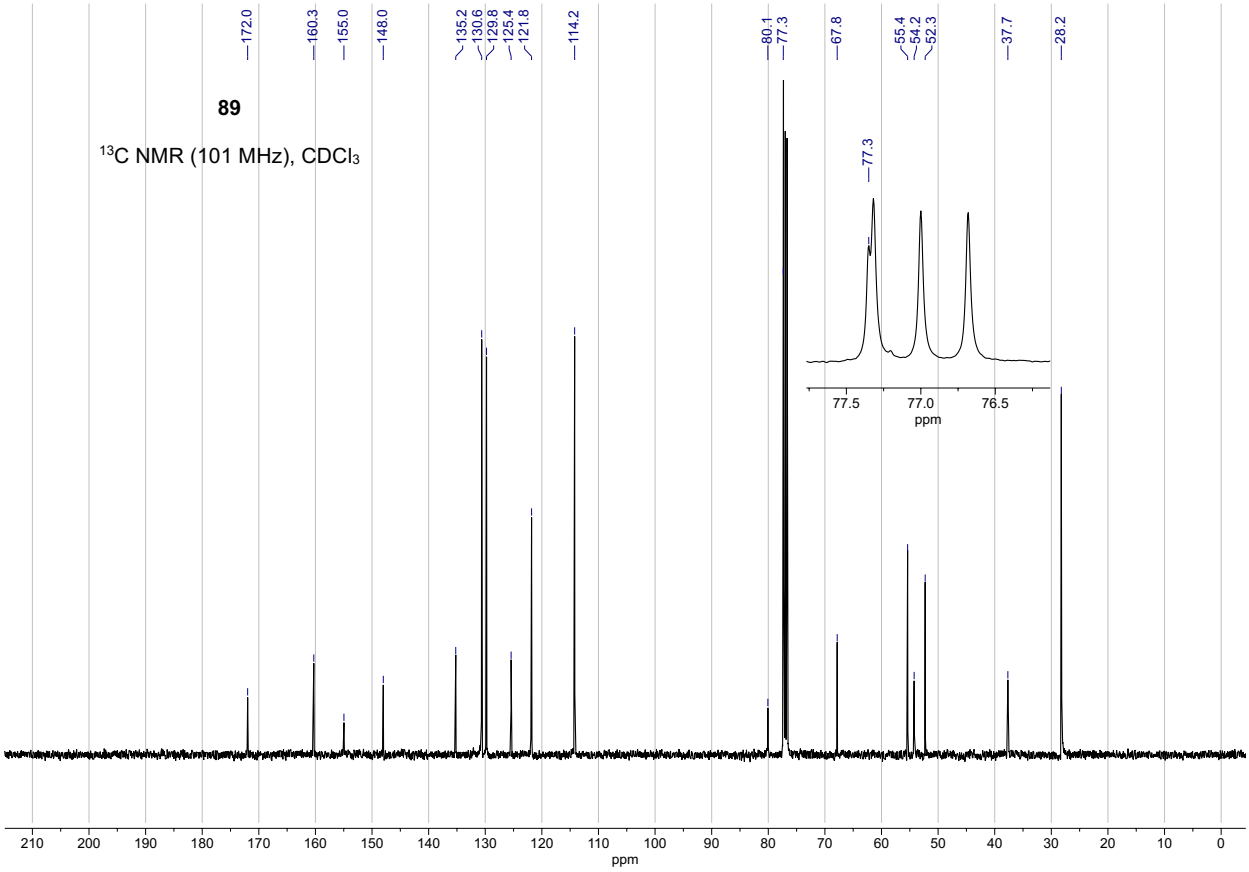

87
^{13}C NMR (101 MHz), CDCl$_3$
ppm

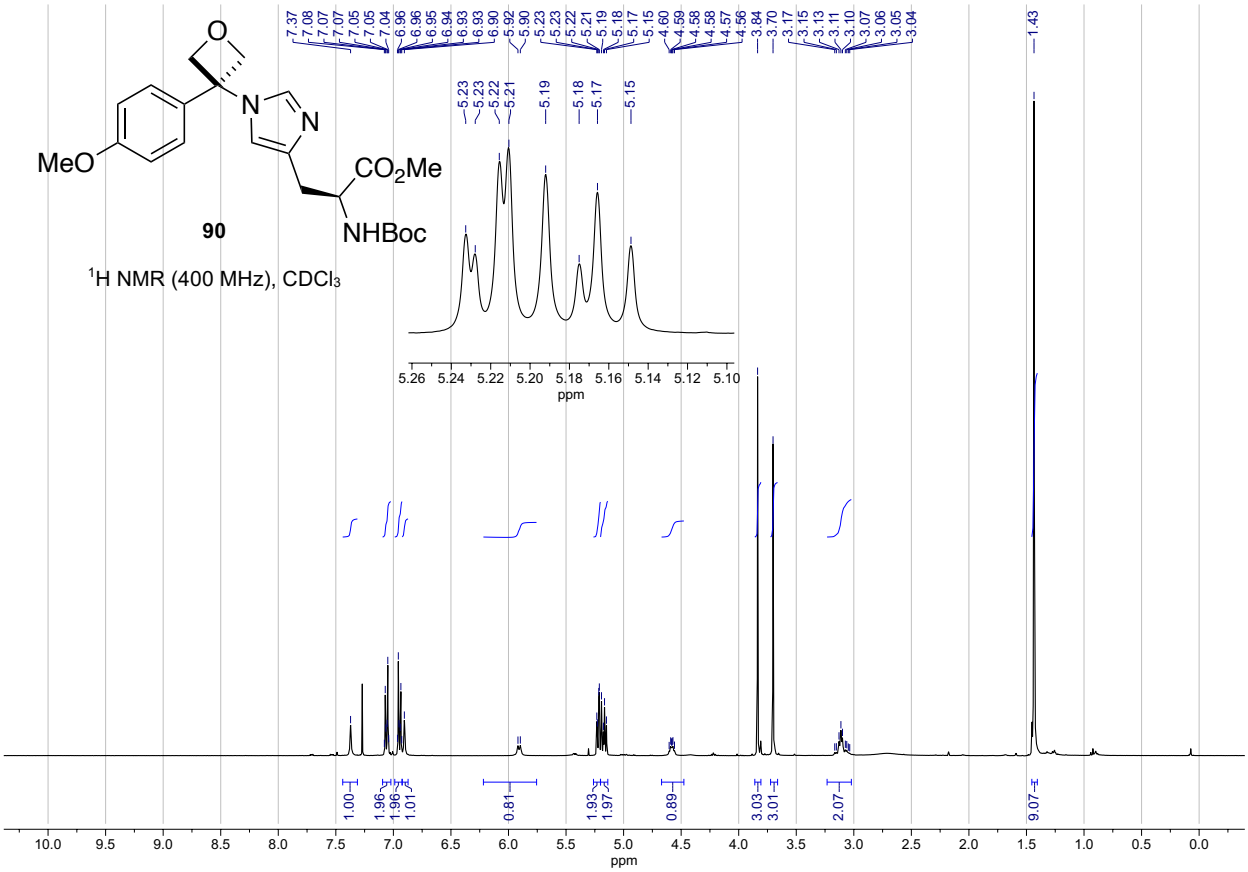

87
HMBC
^{1}H NMR (400 MHz), $CDCl_3$
^{13}C NMR (101 MHz), $CDCl_3$
ppm
f1 (ppm)

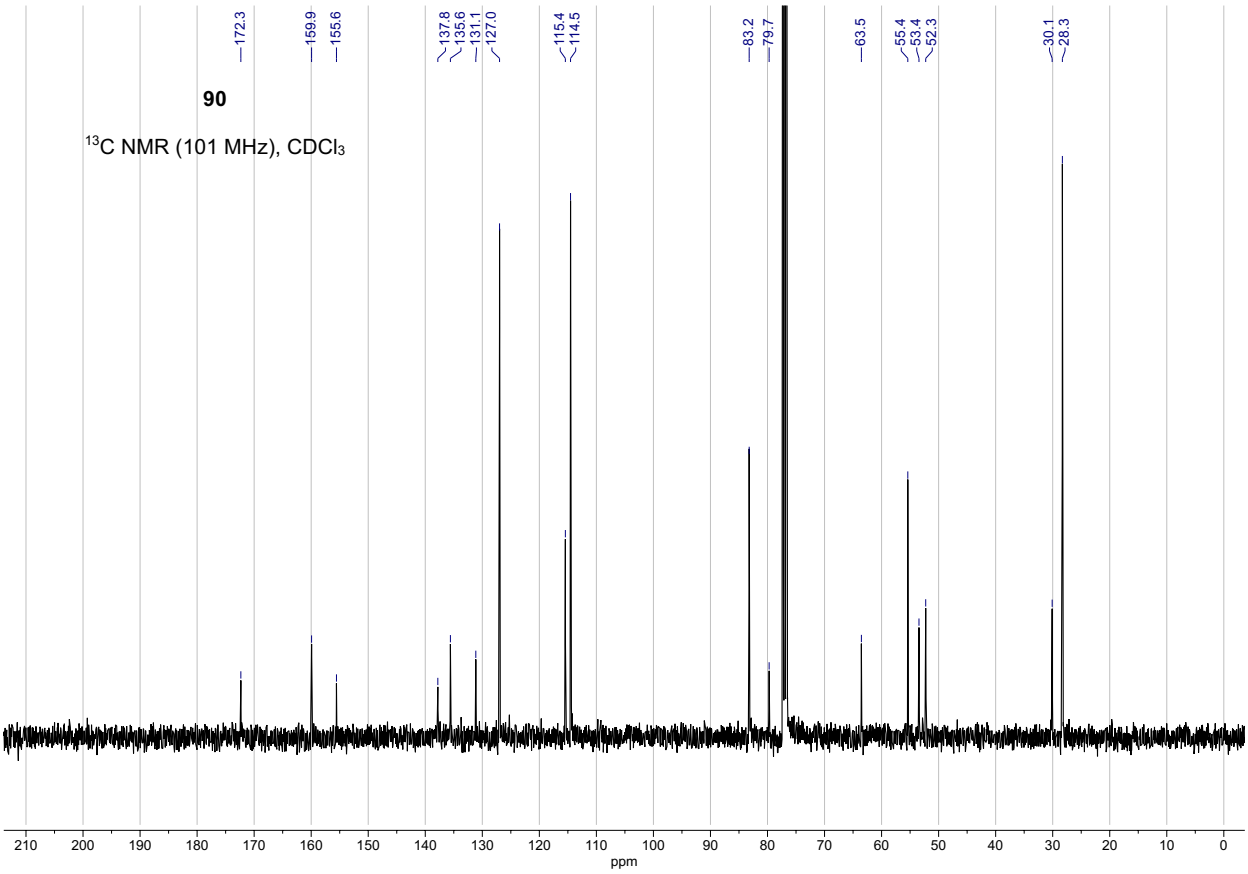

MeO
O
N
H
N
N
MeO
88
^{1}H NMR (400 MHz), CDCl$_3$
ppm

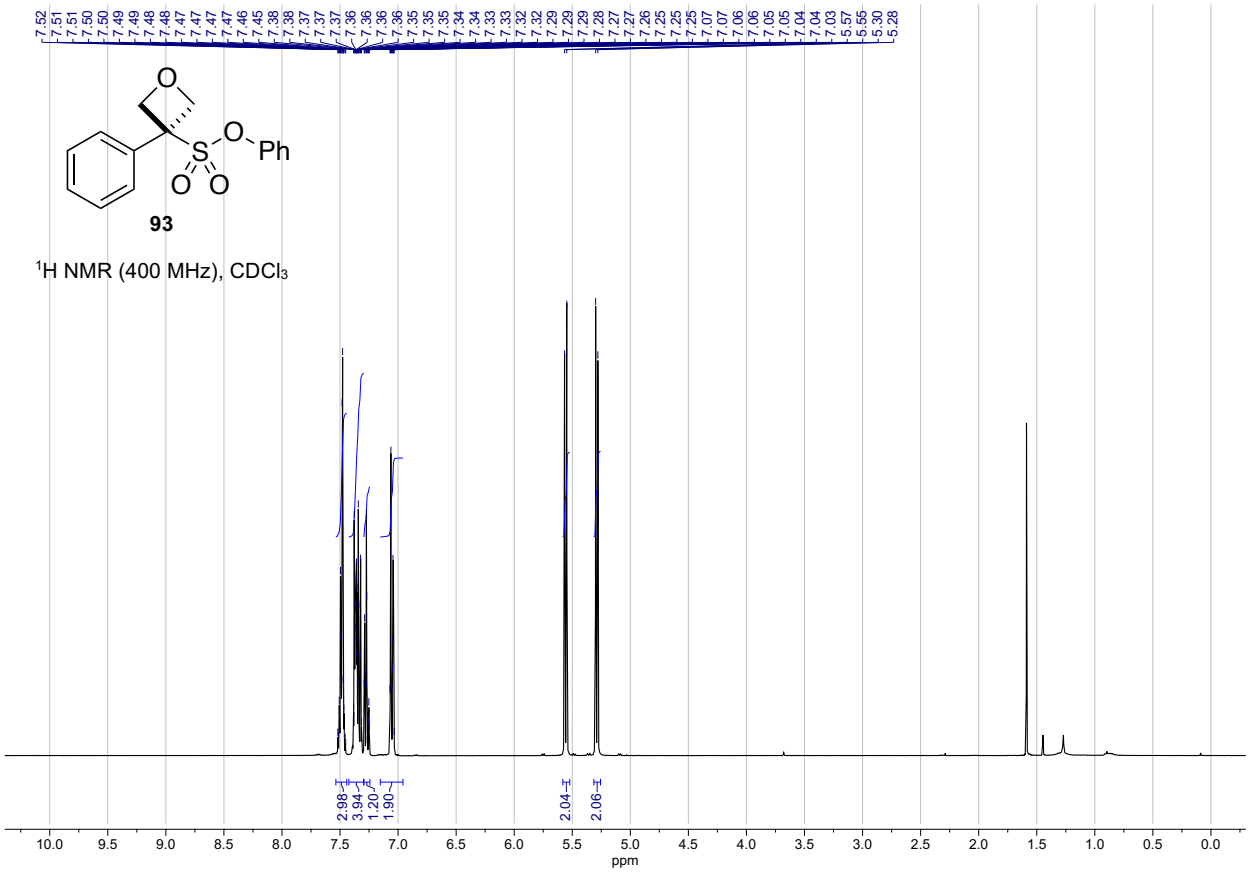

88
^{13}C NMR (101 MHz), CDCl$_3$
ppm

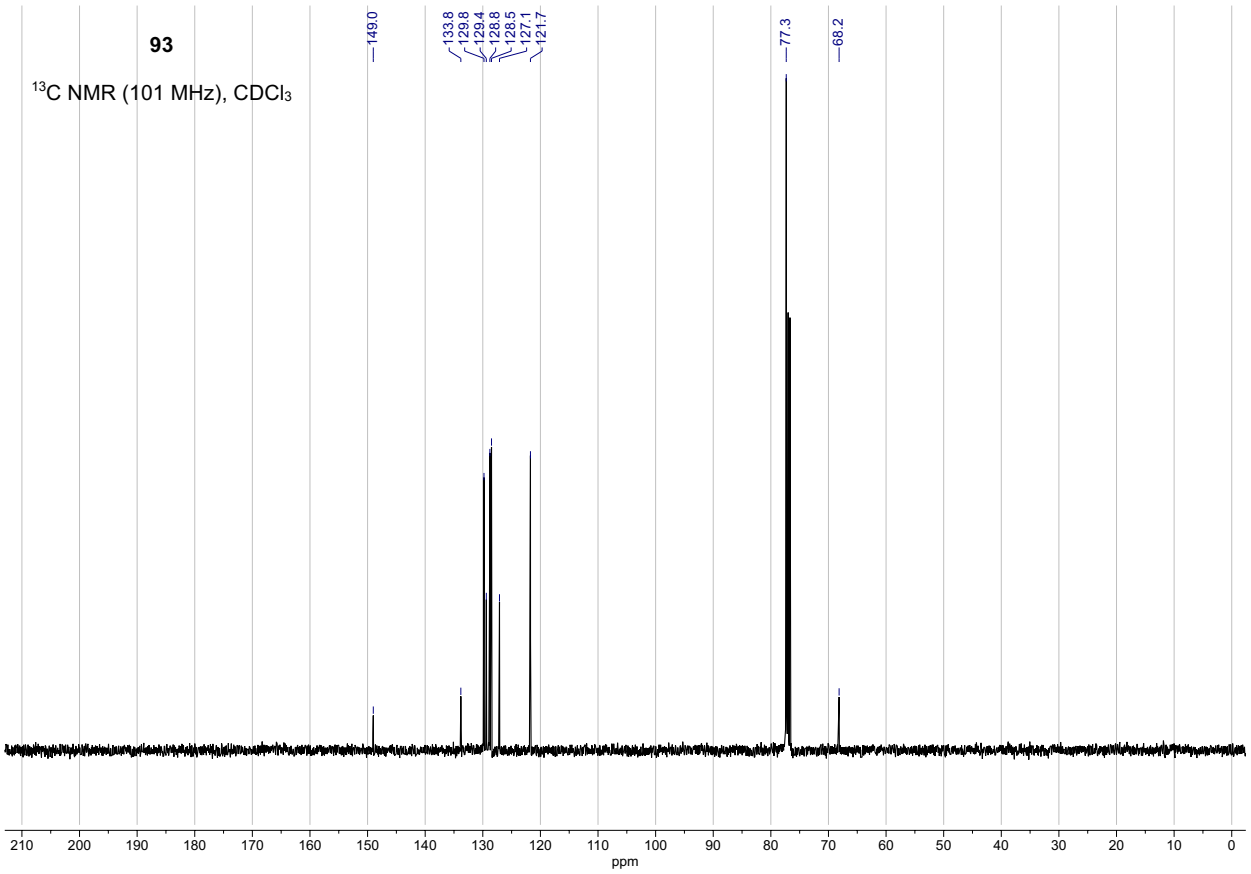

MeO
O
S
O
O
O
O
CO2Me
NHBoc
89
1H NMR (400 MHz), CDCl3
ppm

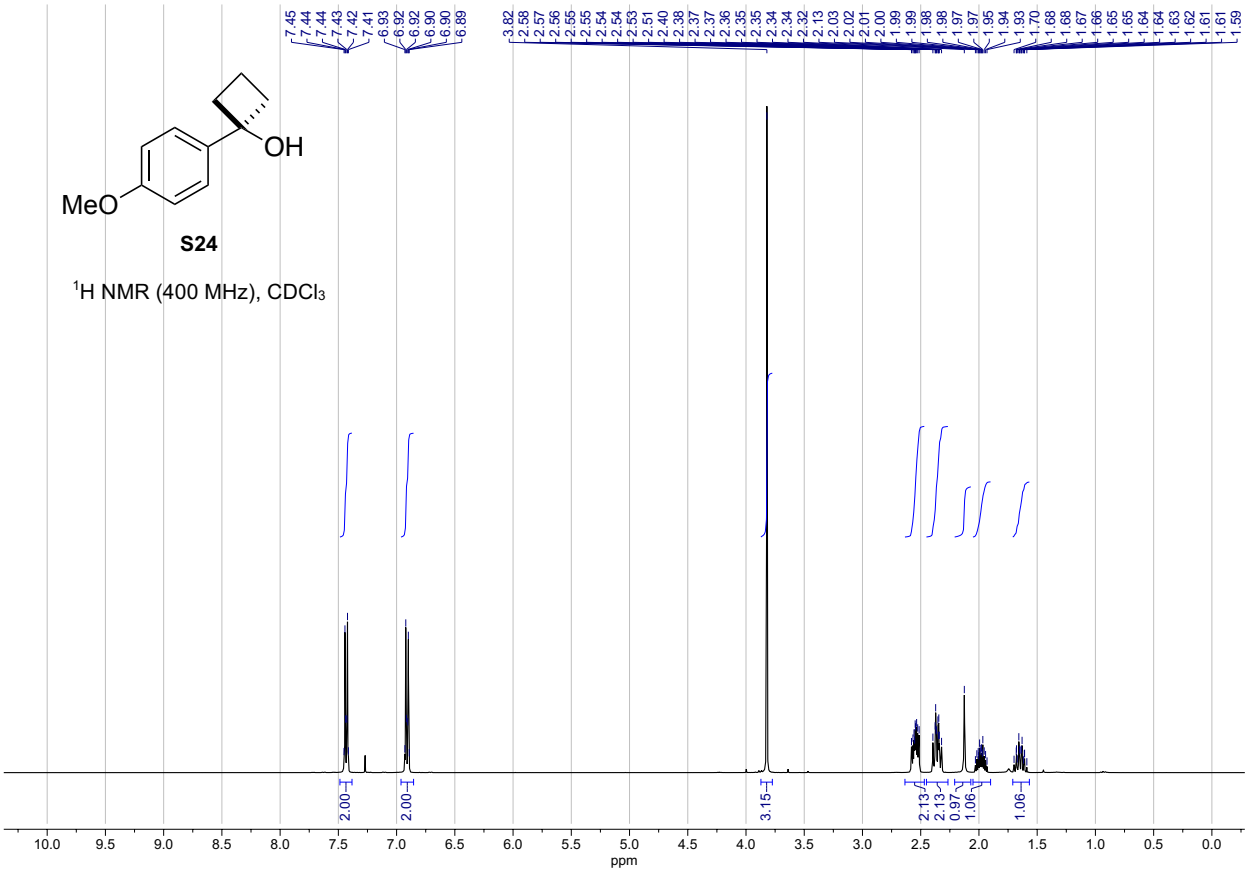

89
13C NMR (101 MHz), CDCl3
ppm

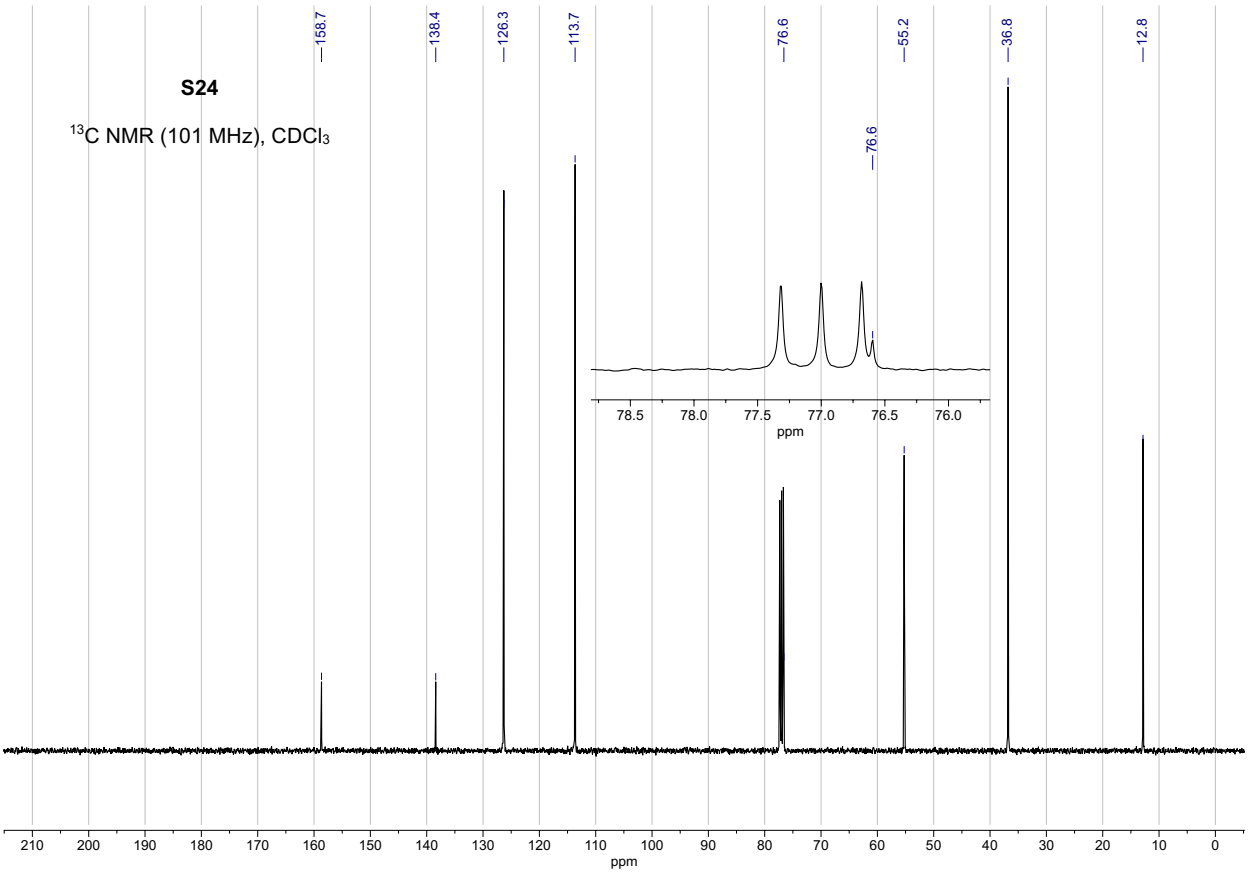

MeO
O
N
N
CO2Me
NHBoc
90
1H NMR (400 MHz), CDCl3
ppm

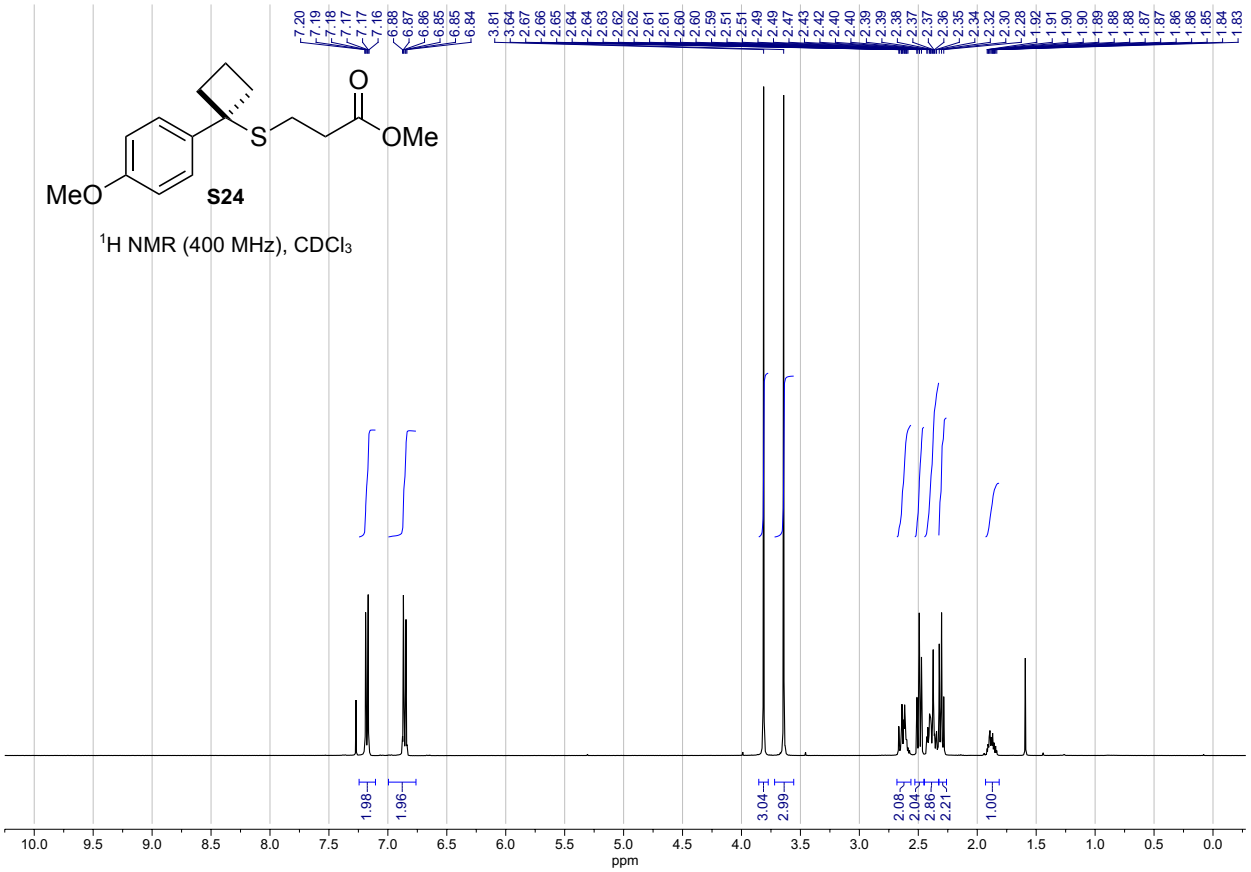

90
13C NMR (101 MHz), CDCl3
ppm

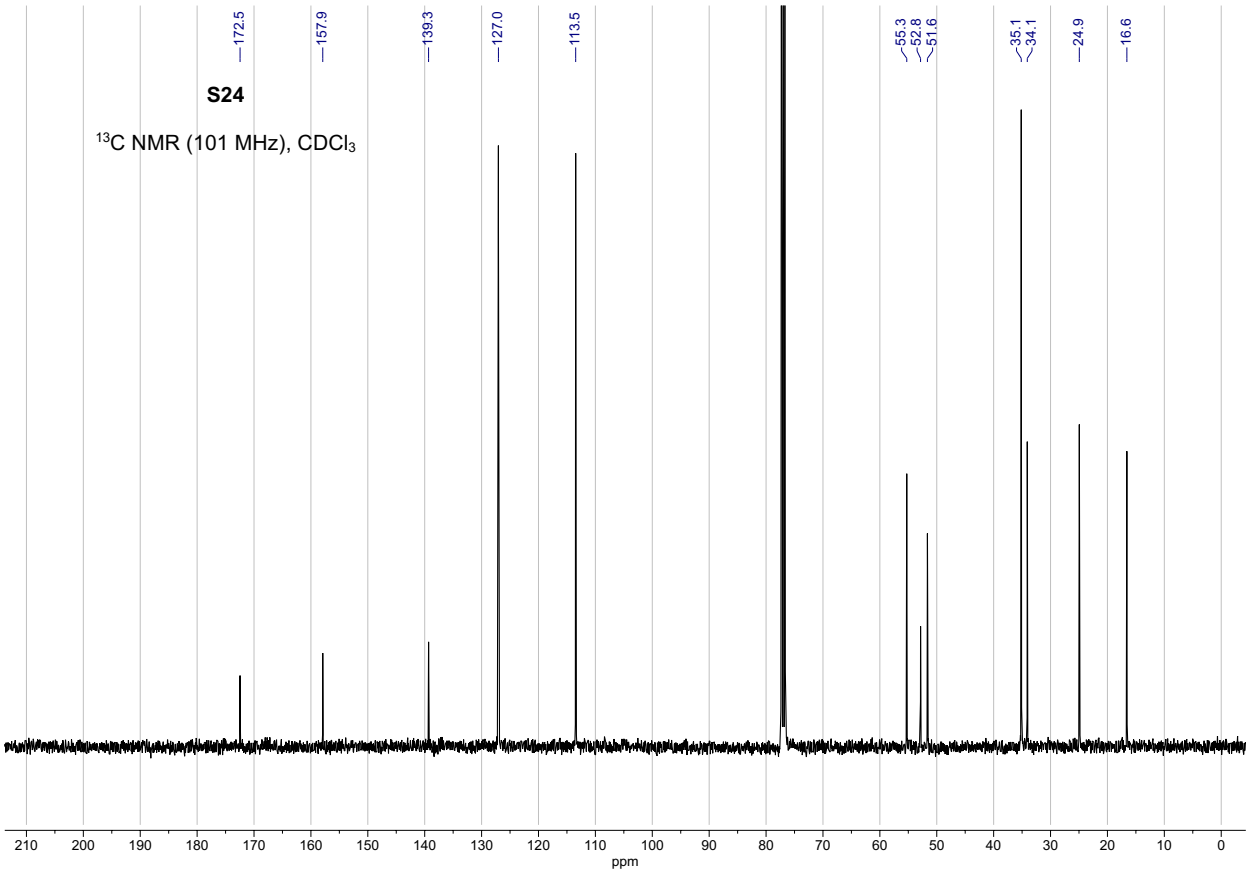

7.52 7.51 7.51 7.50 7.50 7.49 7.49 7.48 7.48 7.47 7.47 7.47 7.47 7.46 7.45 7.38 7.38 7.37 7.37 7.37 7.36 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.33 7.32 7.29 7.29 7.29 7.28 7.27 7.27 7.26 7.25 7.25 7.25 7.07 7.07 7.06 7.06 7.05 7.05 7.04 7.04 7.03 5.57 5.55 5.30 5.28
O
O
S
O
O
Ph
O
93
^{1}H NMR (400 MHz), $CDCl_3$
2.98
3.94
1.20
1.90
2.04
2.06
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

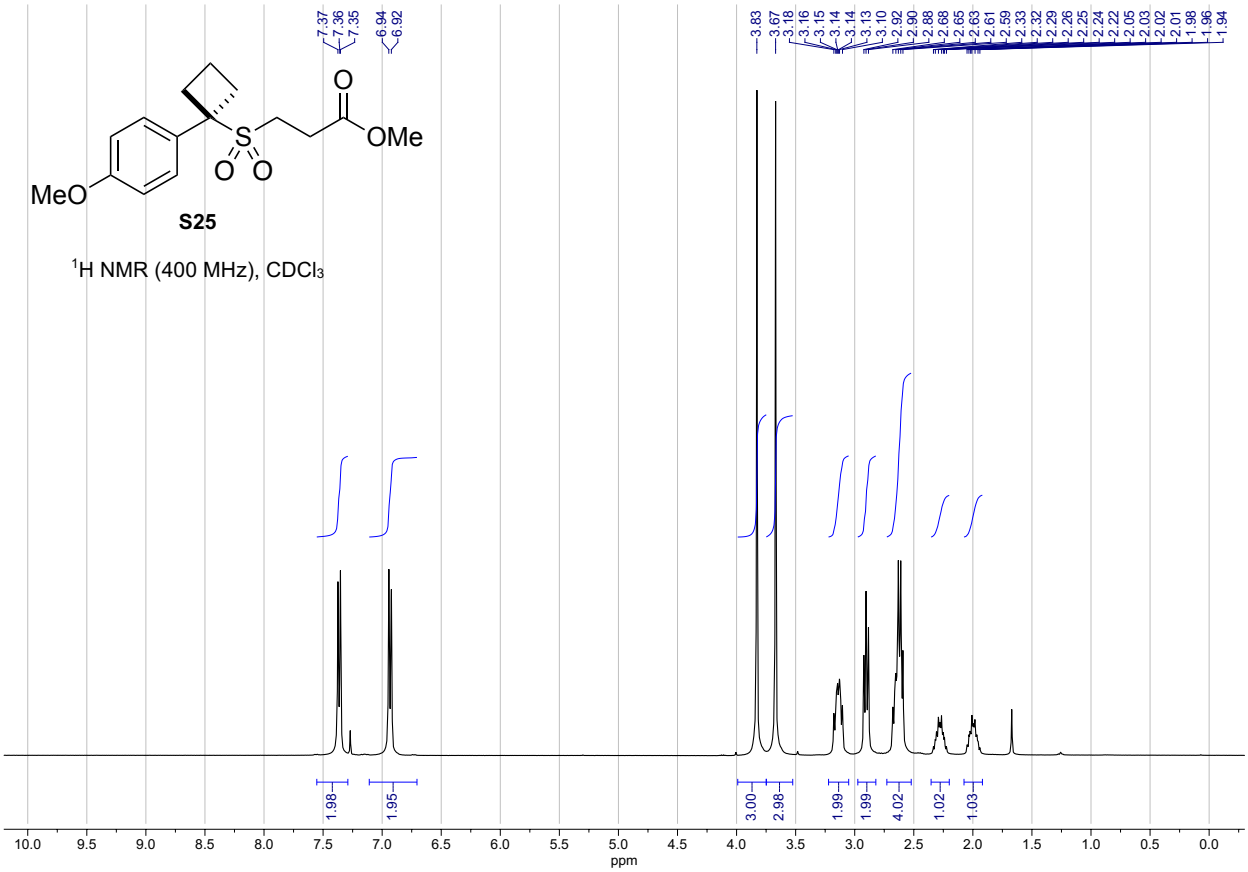

93
^{13}C NMR (101 MHz), $CDCl_3$
149.0
133.8
129.8
129.4
128.8
128.5
127.1
121.7
77.3
68.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

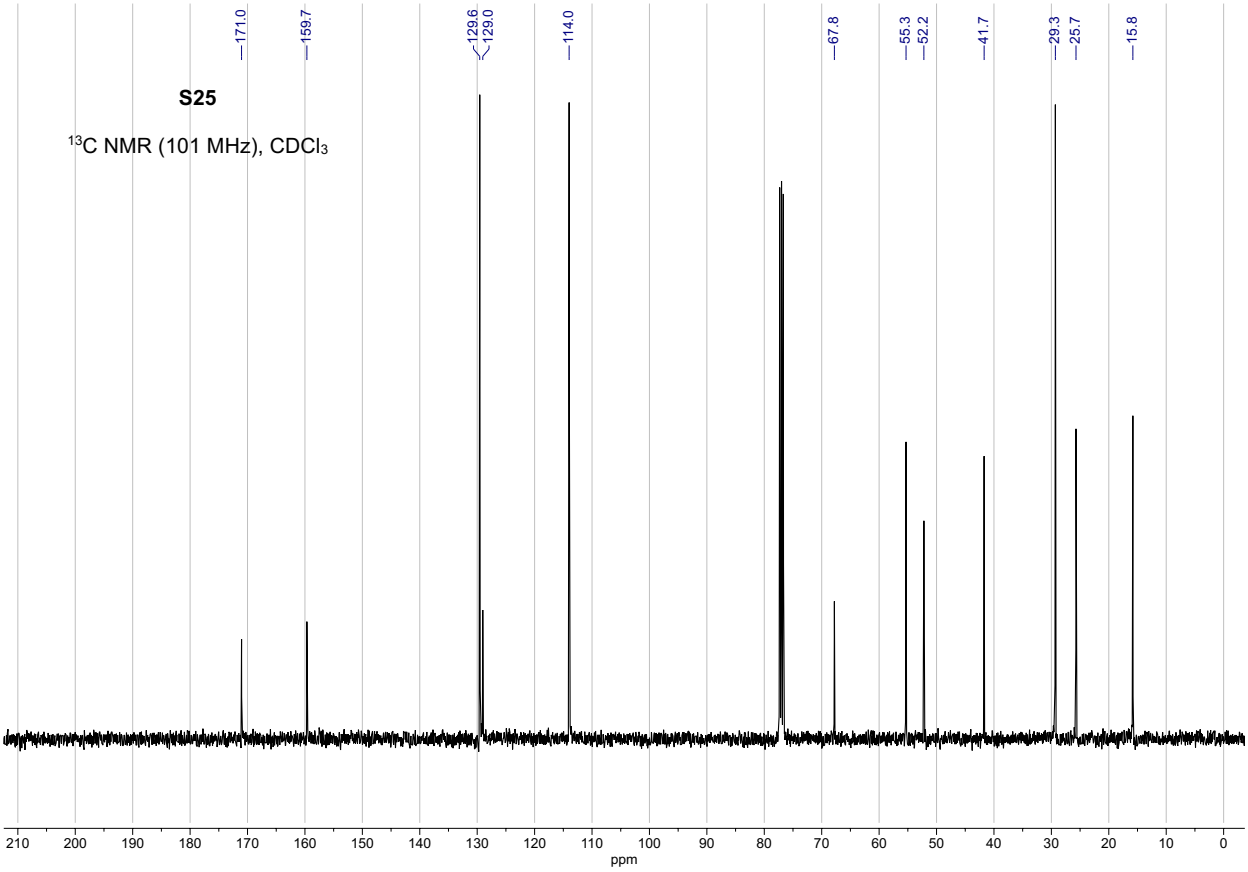

OH
MeO
S24
^{1}H NMR (400 MHz), CDCl$_3$
ppm

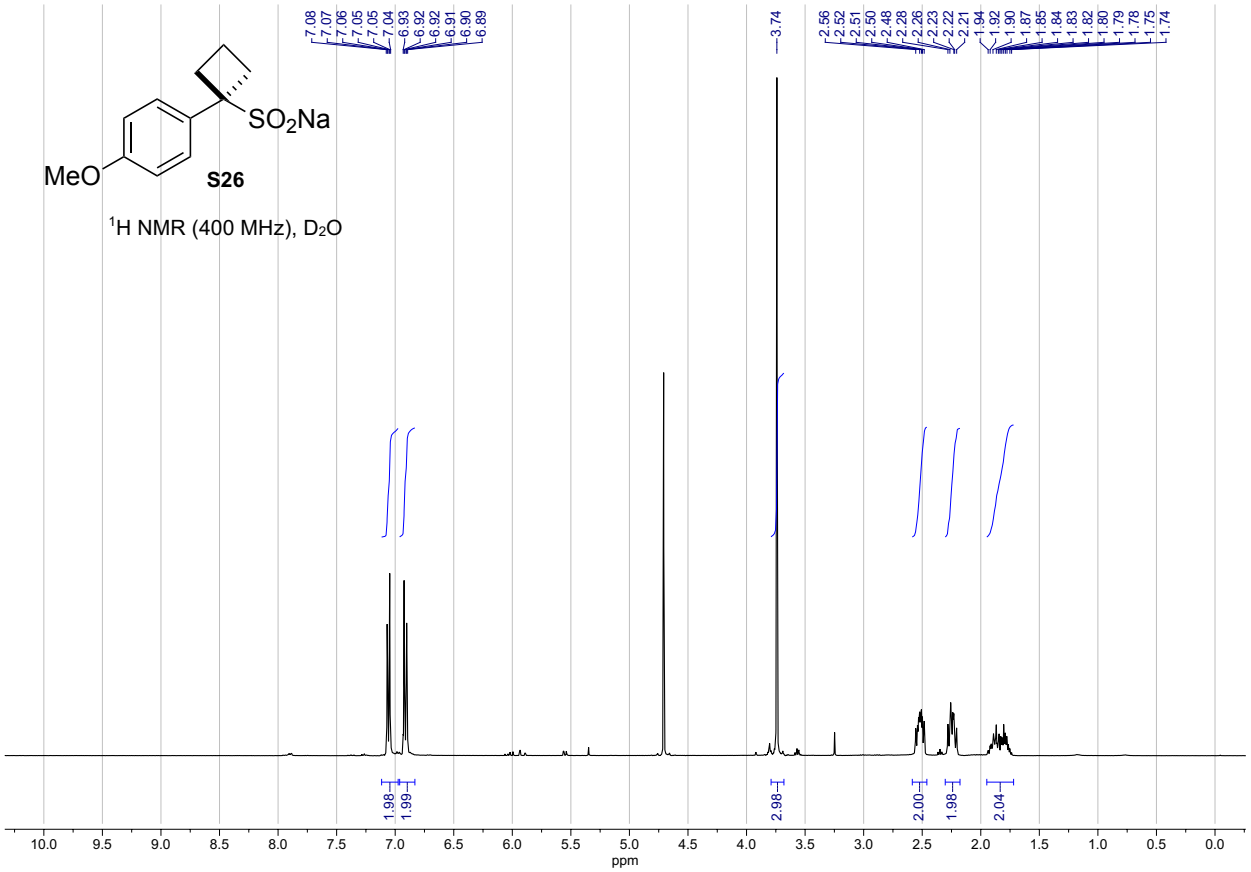

S24
^{13}C NMR (101 MHz), CDCl$_3$
158.7
138.4
126.3
113.7
76.6
55.2
36.8
12.8
ppm

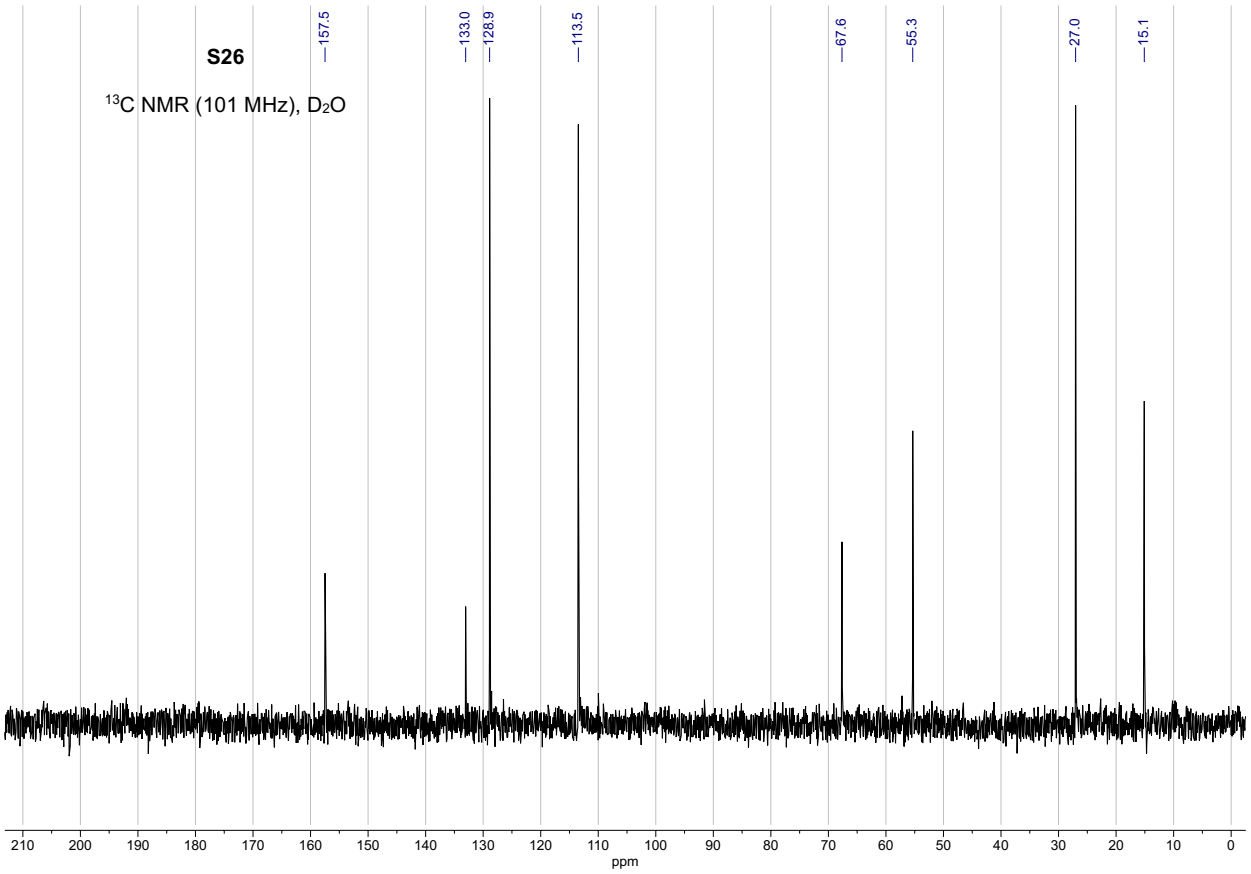

MeO
S
O
OMe
S24
^{1}H NMR (400 MHz), $CDCl_3$
ppm


S24
^{13}C NMR (101 MHz), $CDCl_3$
ppm


MeO
O
S
O
O
OMe
S25
^{1}H NMR (400 MHz), CDCl$_3$
7.37
7.36
7.35
6.94
6.92
3.83
3.67
3.18
3.16
3.15
3.14
3.13
3.10
2.92
2.90
2.88
2.68
2.65
2.63
2.61
2.59
2.33
2.32
2.29
2.26
2.25
2.24
2.22
2.05
2.03
2.02
2.01
1.98
1.96
1.94
1.98
1.95
3.00
2.98
1.99
1.99
4.02
1.02
1.03
ppm


S25
^{13}C NMR (101 MHz), CDCl$_3$
171.0
159.7
129.6
129.0
114.0
67.8
55.3
52.2
41.7
29.3
25.7
15.8
ppm


MeO
SO2Na
S26
1H NMR (400 MHz), D2O
7.08
7.07
7.06
7.05
7.05
7.04
6.93
6.92
6.92
6.91
6.90
6.89
3.74
2.56
2.52
2.51
2.50
2.48
2.28
2.26
2.23
2.22
2.21
1.94
1.92
1.90
1.87
1.85
1.84
1.83
1.82
1.80
1.79
1.78
1.75
1.74
1.98
1.99
2.98
2.00
1.98
2.04
ppm


S26
13C NMR (101 MHz), D2O
157.5
133.0
128.9
113.5
67.6
55.3
27.0
15.1
ppm