Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of Oxetane and Azetidine Ethers as Ester Isosteres by Brønsted Acid Catalysed Alkylation of Alcohols with 3-Aryl-oxetanols and 3-Aryl-azetidinols

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General Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques, unless specified. Anhydrous solvents were obtained by filtration through drying columns (toluene, $CHCl_3$, CH_2Cl_2, DMF) or used as supplied (MeCN, DCE). Reactions that required thermal activation were heated using a water bath (for temperatures up to 25 °C) or a silicone oil bath (for temperatures >25 °C). rt refers to the room temperature in the laboratory (ca. 22 °C). Flash column chromatography was performed using 230–400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution, phosphomolybdic acid solution, *para*-anisaldehyde solution or ninhydrin solution in ethanol. 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). Only significantly strong and clearly assignable signals diagnostic for major functional groups are reported.

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 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 ($CHCl_3$: d = 7.27 ppm, DMSO: d = 2.50 ppm). Data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, 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). *J* values are reported in Hz. ^{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.

Melting points were recorded using an Optimelt MPA100 apparatus and are uncorrected. High resolution mass spectrometry (HRMS) analyses were performed through the Imperial College or EPSRC mass spectrometry service. HRMS analyses at Imperial College were performed using an electrospray ion source (ESI), nanospray ionisation (NSI), electron impact ionisation (EI) or atmospheric pressure chemical ionisation (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 or negative ion mode. 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 vaporised. HRMS analyses at the EPSRC UK National Mass Spectrometry Facility (NMSF) were performed using a nano-electrospray ion source (NSI), chemical ionisation (CI) or atmospheric pressure chemical ionisation (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 vaporised. The software used was either MassLynx 4.1 or Bruker Daltonics DataAnalysis 4.0. Please note: MassLynx 4.1 software, used at the Imperial College mass spectrometry service, 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]. Note that some oxetane ethers ionise with fragmention of the the substrate to form the oxetane carbocation. Consequently, $[M-OR]^+$ are found instead of $[M+H]^+$.

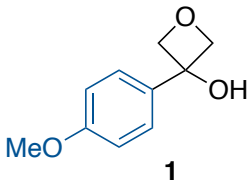
HPLC analyses were carried out on an Agilent 1260 Infinity Series system, employing Daicel Chiracel columns.

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

- Trifluoromethanesulfonimide (Tf_2NH) was purchased from Fluorochem (CAS: 82113-65-3, product code: 093934), stored under argon in the fridge (+4 °C) and used without further purification.
- 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] An average of three titrations was taken.

Further experimental data for novel compounds presented in this manuscript can be found at the Imperial College London Research Data Repository. DOI: 10.14469/hpc/12507 (https://data.hpc.imperial.ac.uk/resolve/?doi=12507).

Structures of Oxetan-3-ols and Azetidin-3-ols[2,3,4]



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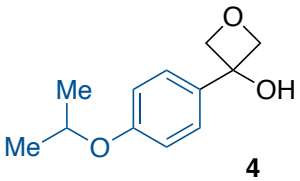

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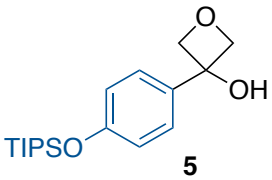

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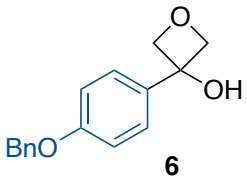

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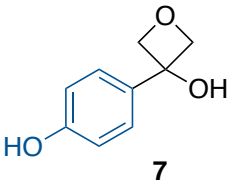

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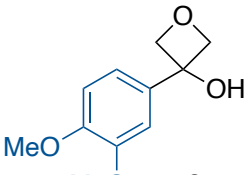

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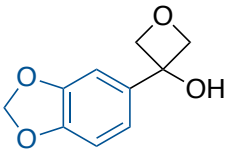

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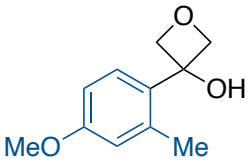

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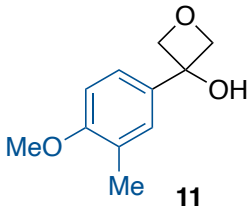

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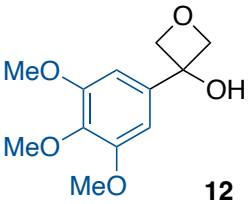

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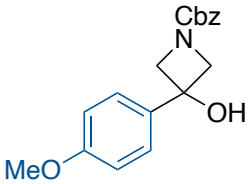

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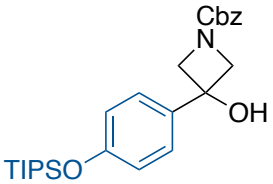

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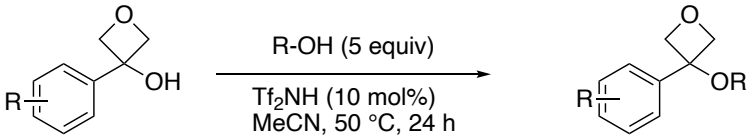
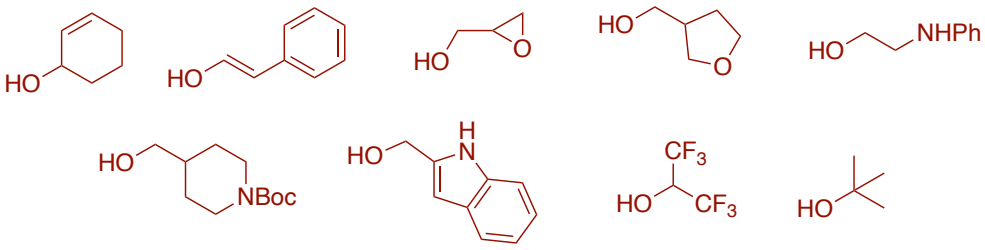
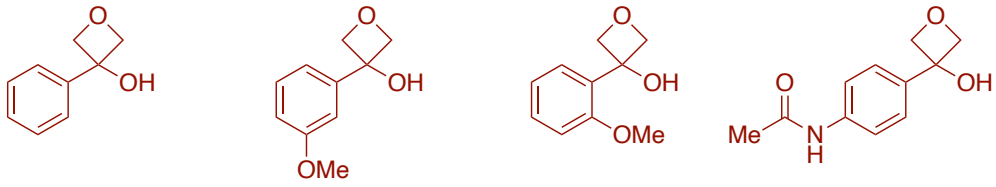
Unsuccessful substrates



Unsuccessful alcohol



Unsuccessful oxetane derivatives



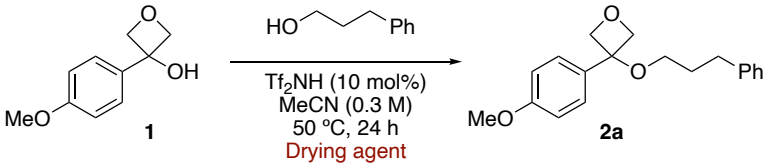
The above substrates were unsuccessful. Unsaturated alcohols (cyclic and acyclic) gave various side reactions. Acid labile groups and protecting groups reacted under the conditions. Tertiary butanol gave recovered starting material. More electron-poor oxetan-3-ols such as 3-phenyl oxetan-3-ol were unreactive, as well as the *ortho* and *meta* methoxy-phenyl oxetanol. The 4-acetamide oxetanol was also unsuccesful.

Effect of using drying agents

Attempts to remove water from the reaction mixture to aid the proposed equilibrium did not increase the yields. Drying agents such as Na_2SO_4, $MgSO_4$, and molecular sieves 4 Å had minimal effect (Table S1).

Attempts to run the reaction in toluene at 50 °C and under a Dean–Stark set-up at reflux were also unsuccessful (up to 27% yield).

Table S1: Removal of water from the reaction by drying agents.



Entry	Drying agent	Yield 2a (%)[a]
1	none	73
2	Na_2SO_4	71
3	$MgSO_4$	75
4	Molecular sieves 4Å	54

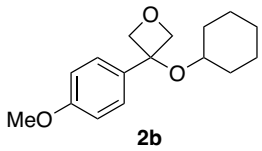
[a] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Stability of oxetane ether 2b to stationary phases

To investigate whether the oxetane ethers decomposed during chromatography due to the acidity of silica and to determine the optimal stationary phase, a stability test to different stationary phases was undertaken.[5] According to the literature procedure,[5] the stability test involved stirring oxetane ether **2b** with the stationary phases in the column eluent and examination of the recovered material (Table S2).

As a control, stirring the isolated product in 10% EtOAc/pentane for 60 min gave full recovery of ether **2b** (Table S2, entry 1). Silica gel gave a significant reduction in product recovery (entry 2), whilst silica gel treated with Et_3N (entry 3) slightly increased recovery. Significant losses were also observed with neutral alumina, basic alumina (Act I), and florisil (entries 4, 5 and 7). Pleasingly, basic alumina (Act IV) gave full recovery of oxetane ether **2b** (entry 6).

Table S2: Stability test **2b** to stationary phases.



2b

Entry	Stationary phase	Yield (%)[a]
1	none	quant
2	Silica gel	49
3	Silica gel + Et_3N	62
4	Neutral alumina	54
5	Basic alumina (Act I)	69
6	Basic alumina (Act IV)	quant
7	Florisil	82

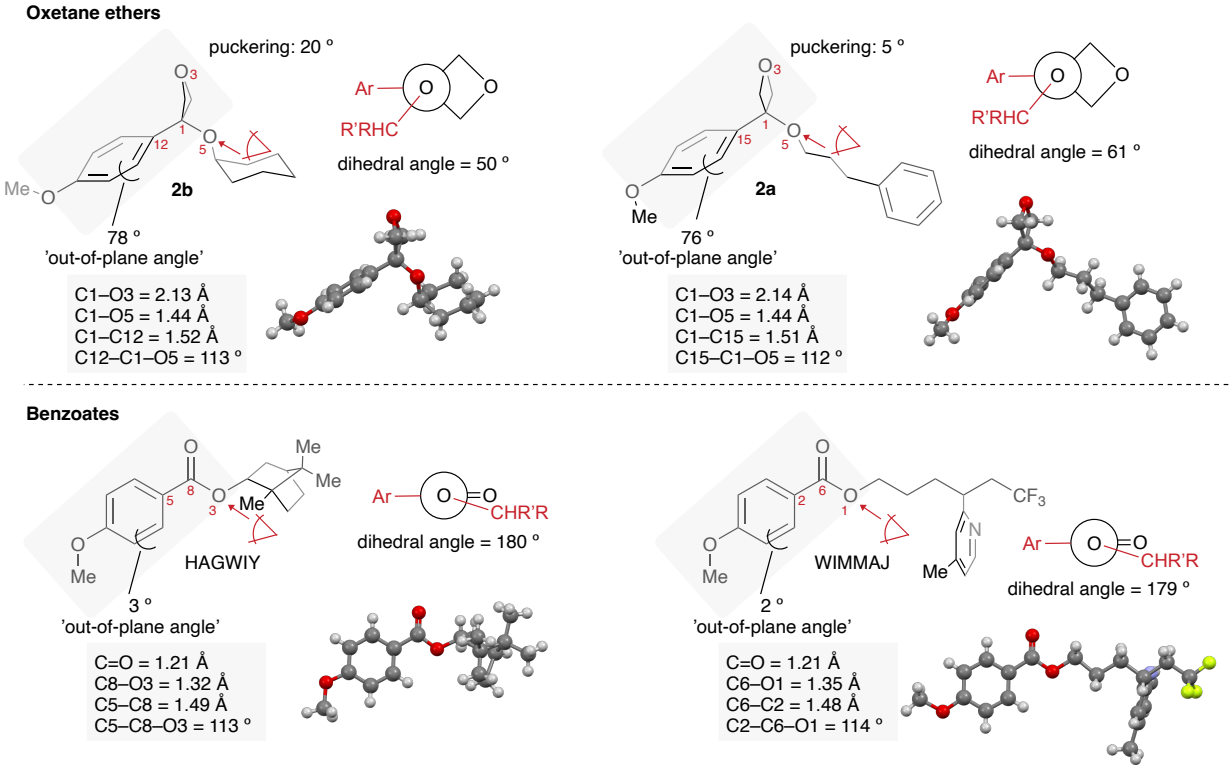
[a] Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Using basic alumina (Act IV) as a stationary phase for chromatography with oxetane ether **2b** gave a significant increase in isolated yield. However, there was no difference for ether **2a**. Consequently, silica gel was used primarily, but basic alumina (Act IV) was investigated where considered necessary.

Comparison of X-ray structures between oxetane ethers and esters.

The conformation of oxetane ethers **2a** and **2b**, determined by x-ray crystallography, differs to that of related esters. Disruption of the π–carbonyl–p_O conjugated system by the oxetane structure confers oxetane ethers with a dramatically increased 3-dimensionality, with the aryl ring twisted ca. 80° out of the O3–C1–C_{Ar} plane (C_{Ar} = C15 in **2a** and C12 in **2b**). In benzoates on the contrary, the aryl ring is only ca. 3° out of plane to maximise π-conjugation and resulting in a preferred flat conformation. As observed in our previous analysis on 3-aryl-3-alkyl-oxetanes,[6] the increased steric requirement of the oxetane ring provokes a switch in conformational preference of the ethereal substituent which lies on the aryl side in oxetane ethers in a *quasi*-staggered conformation, but on the carbonyl side in benzoate structures.

It is noteworthy that the oxetanyl puckering angle in ether **2b** (20°) is much larger than in **2a** (5°). The reason for this difference is not immediately obvious but it could be due to packing effects: **2b** shows close contacts at ca. 2.5 Å between O3 and 3 C–H bonds, whilst **2a** only shows one such contact. Further, the change in hybridisation of C1 (sp^2 in esters, sp^3 in oxetane ethers) lengthens the C_{Ar}–C1 and C1–O5 bonds in oxetane ethers compared to analogous benzoates. However, the acute internal angles imposed by the oxetane ring widen the C_{Ar}–C1–O5 angle in oxetane ethers to a comparable degree as in benzoates. It is also interesting that the ethereal substituent in **2b** is in the axial position of the cyclohexane. Presumably, the oxetane's CH_2 clash sterically with the axial cyclohexane protons in the equatorial conformation.



The X-ray crystal structure of 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)oxetane (2a)

Crystal data for **2a**: $C_{19}H_{22}O_3$, M = 298.36, triclinic, P-1 (no. 2), a = 8.3025(12), b = 9.7428(13), c = 10.8769(13) Å, α = 71.098(12), β = 81.271(11), γ = 71.101(12)°, V = 786.4(2) Å^3, Z = 2, D_c = 1.260 g cm^{-3}, μ(Cu-Kα) = 0.670 mm^{-1}, T = 173 K, colourless shards, Agilent Xcalibur PX Ultra A diffractometer; 2953 independent measured reflections (R_{int} = 0.0437), F^2 refinement,[7,8,9] R_1(obs) = 0.0500, wR_2(all) = 0.1385, 1892 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, completeness to θ_{full}(67.7°) = 97.6%], 201 parameters. CCDC 2250896.

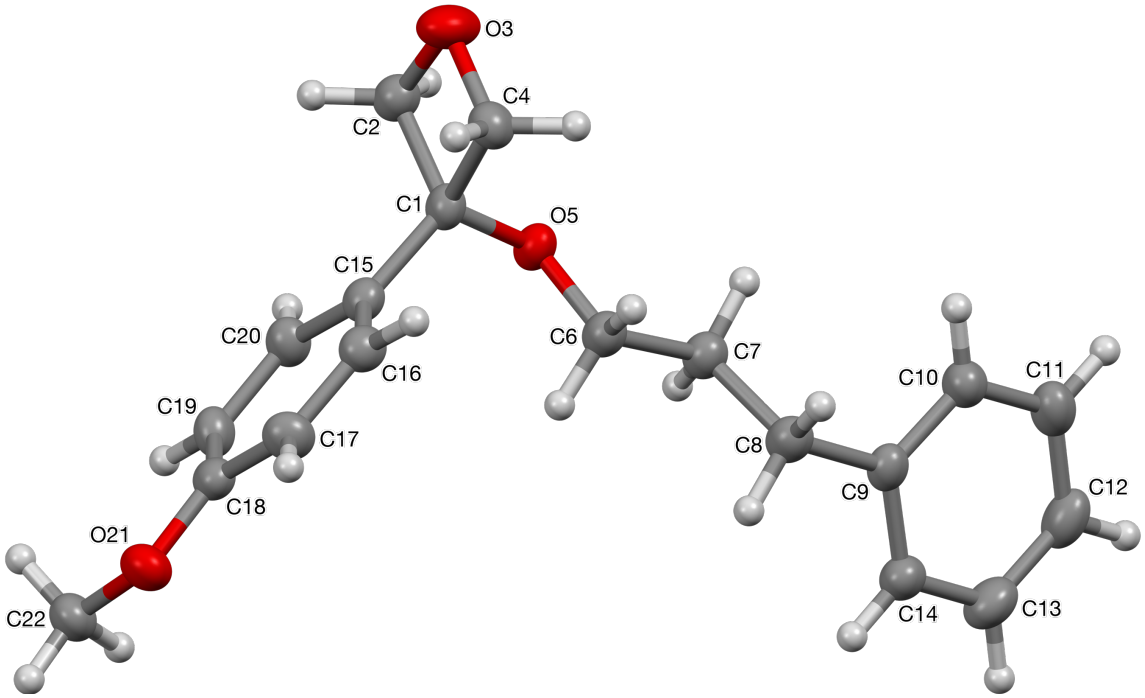


Fig. S1 The crystal structure of oxetane ether **2a** (50% probability ellipsoids).

The X-ray crystal structure of 3-(cyclohexyloxy)-3-(4-methoxyphenyl)oxetane (2b)

Crystal data for **2b**: $C_{16}H_{22}O_3$, M = 262.33, monoclinic, $P2_1/c$ (no. 14), a = 10.7892(5), b = 17.3283(6), c = 8.0868(3) Å, β = 110.601(4)°, V = 1415.23(10) Å^3, Z = 4, D_c = 1.231 g cm^{-3}, μ(Mo-Kα) = 0.083 mm^{-1}, T = 173 K, colourless tablets, Agilent Xcalibur 3 E diffractometer; 3171 independent measured reflections (R_{int} = 0.0457), F^2 refinement,[7,8,9] R_1(obs) = 0.0429, wR_2(all) = 0.1030, 2479 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, completeness to θ_{full}(25.2°) = 99.9%], 174 parameters. CCDC 2250897.

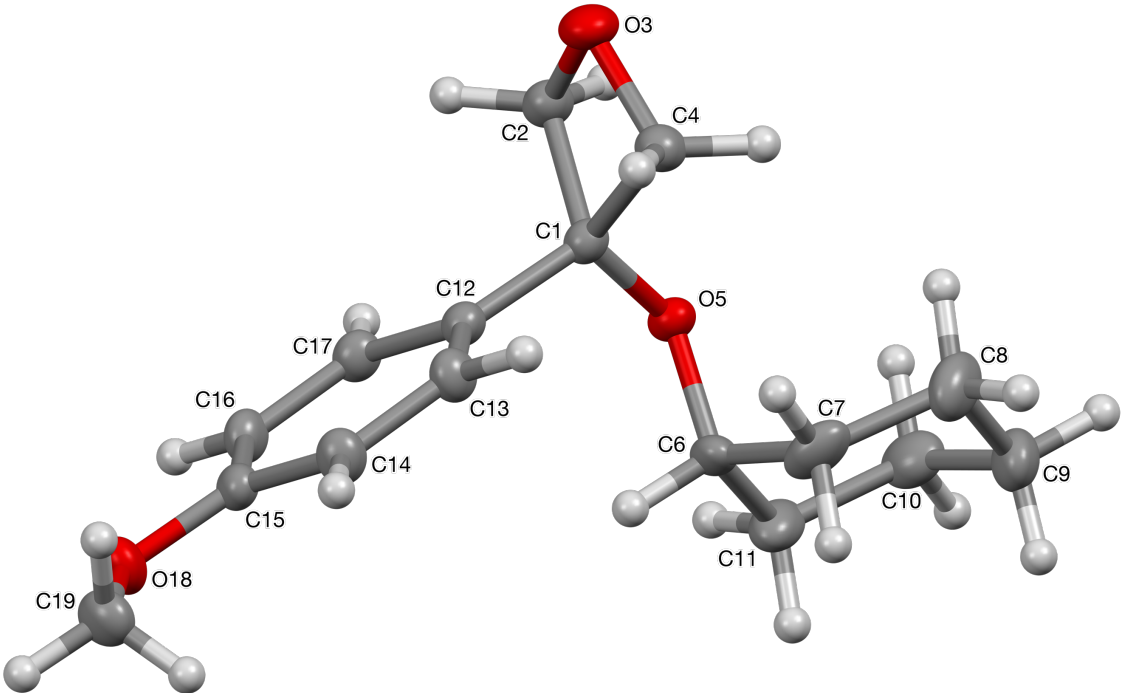


Fig. S2 The crystal structure of oxetane ether **2b** (50% probability ellipsoids).

Chemical and thermal stability of oxetane ethers vs esters

Temperature stability

50 mM stock solutions of oxetane ether **2a** and the ester pair **30** were prepared in MeOH using 1 mL volumetric flasks. A 33 mM stock solution of 1,3,5-trimethoxybenzene in MeOH was prepared as an internal standard. 100 μL solution of oxetane ether or ester pair was mixed with 100 μL of standard solution in vials with a magnetic stirrer and then evaporated the solvent *in vacuo*. Toluene-d8 or dimethylsulfoxide-d6 were added for each substrate and the solution was heated to 80 °C for 1 h and 24 h. 2 mL sat. aq. $NaHCO_3$ were added and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo* using a rotary evaporator. The recovery was determined by ^1H NMR spectroscopy with 20 s delay.

Acid-base stability

50 mM stock solutions of oxetane ether **2a** and the ester pair **30** were prepared in MeOH using 1 mL volumetric flasks and a 33 mM stock solution of 1,3,5-trimethoxybenzene in $CDCl_3$ as an internal standard. 100 μL solution of oxetane ether or ester pair was added to the test tube followed by 1 mL of 1 M aq. HCl or 1 M aq. NaOH. For the basic conditions, the tube was stirred at rt for 1 h and 24 h. The tube under the acid conditions was stirred at 37 °C for 1 h and 24 h. The reaction was quenched by adding 2 mL sat. $NaHCO_3$ and extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo* using a rotary evaporator. 100 μL of the internal standard solution were added and the recovery was determined by ^1H NMR spectroscopy with 20 s delay.

Chemical stability

NaI

Oxetane ether **2a** (29.8 mg, 0.1 mmol, 1.0 equiv) or the ester pair **30** (27.0 mg, 0.1 mmol, 1.0 equiv) was added to a flamed-dried vial, followed by acetone (0.5 mL). NaI (149.9 mg, 1.0 mmol, 10 equiv) was added and the reaction mixture was stirred at 50 °C for 1 h. sat. aq. $NaHCO_3$ was added (5 mL) and the aqueous phase 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 rotary evaporator. Recovery was determined by ^1H NMR spectroscopy with 20 s delay using 1,3,5-trimethoxybenzene as an internal standard.

$LiBH_4$

Oxetane ether **2a** (29.8 mg, 0.1 mmol, 1.0 equiv) or the ester pair **30** (27.0 mg, 0.1 mmol, 1.0 equiv) was added to a flamed-dried vial, followed by THF (0.33 mL). $LiBH_4$ (10.9 mg, 0.5 mmol, 5.0 equiv) was added and the reaction mixture was stirred at 65 °C for 1 h. Distilled water was added (5 mL) and the aqueous phase 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 rotary evaporator. Recovery was determined by ^1H NMR spectroscopy with 20 s delay using 1,3,5-trimethoxybenzene as an internal standard.

Thiol

Oxetane ether **2a** (29.8 mg, 0.1 mmol, 1.0 equiv) or the ester pair **30** (27.0 mg, 0.1 mmol, 1.0 equiv) was added to the flamed-dried vial, followed by a DMF/H_2O mixture (1:1; 1 mL). L-Cysteine methyl ester hydrochloride (17.2 mg, 0.1 mmol, 1.0 eqiuv) and K_2CO_3 (13.8 mg, 0.1 mmol, 1.0 equiv) were added and the reaction mixture was stirred at rt for 12 h. Distilled water was added (5 mL) and the aqueous phase 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 rotary evaporator. Recovery was determined by ^1H NMR spectroscopy with 20 s delay using 1,3,5-trimethoxybenzene as an internal standard.

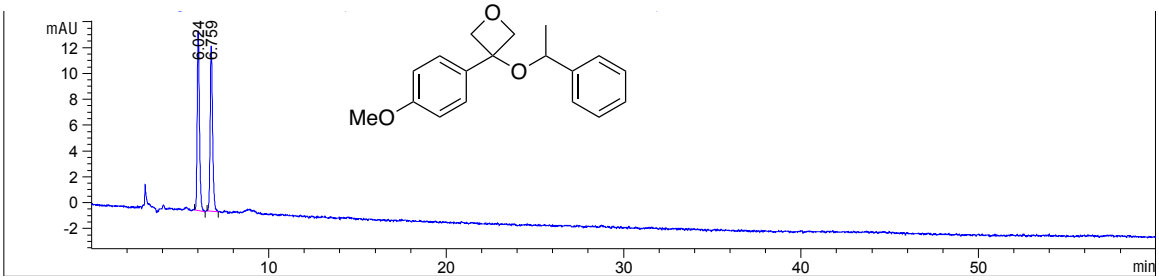
Enantiomerically enriched substrate: 2n

Example **2n** was run using enantiopure (*S*)-1-phenylethanol.

The minimum iPrOH (~1.0 mL) was added to the corresponding samples (~1 mg) until completely dissolved. The solution was filtered and analysed by HPLC.

3-(4-Methoxyphenyl)-3-(1-phenylethoxy)oxetane (racemic)

Conditions: Chiralpak IA 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL min^{-1}, 30 ° C. UV detection wavelength: 280 nm.



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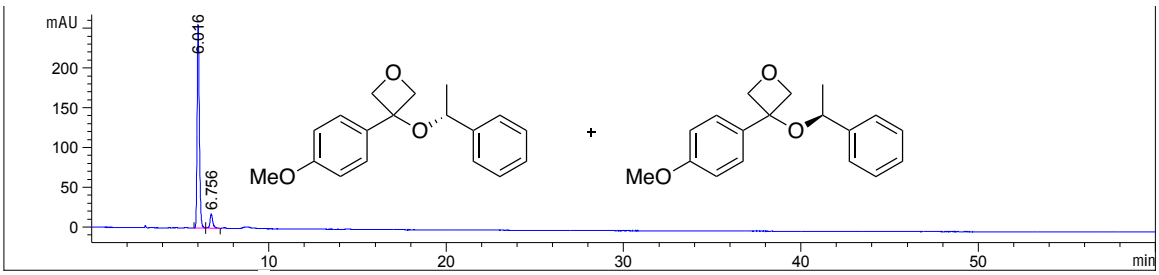
2	6.759	BB	0.1457	122.28416	12.77127	50.4237

(S)-3-(4-Methoxyphenyl)-3-(1-phenylethoxy)oxetane (2n)

Conditions: Chiralpak IA 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL min^{-1}, 30 ° C. UV detection wavelength: 280 nm.



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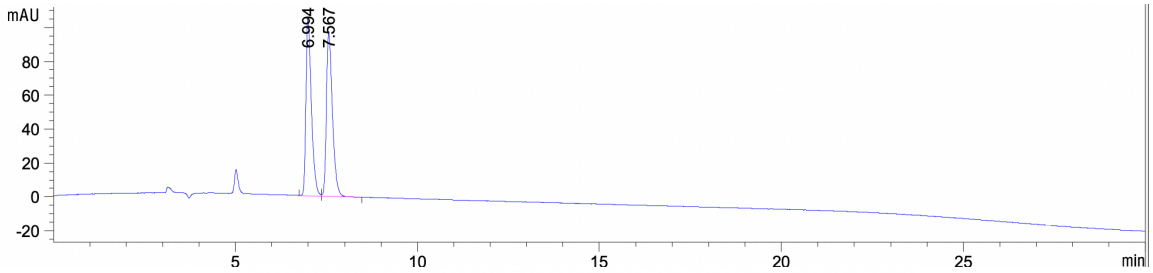
1	6.016	BV	0.1301	2198.21460	256.13397	91.8468
2	6.756	VB	0.1627	195.13329	17.97109	8.1532

92:8 *er*

Starting alcohol 1-phenylethanol (racemic)

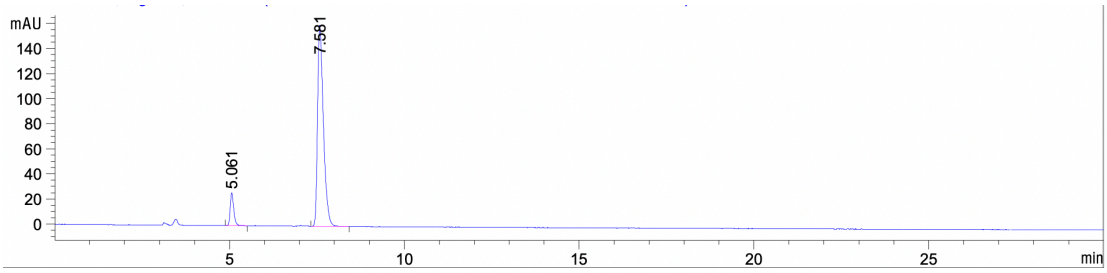
Conditions: Chiralpak IB 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL min^{-1}, 30 °C. UV detection wavelength: 254 nm.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.994	BV	0.1607	1106.83911	105.24891	49.8603
2	7.567	VB	0.1771	1113.04065	96.14695	50.1397

(*S*)-1-Phenylethanol

Conditions: Chiralpak IB 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL min^{-1}, 30 °C. UV detection wavelength: 254 nm.



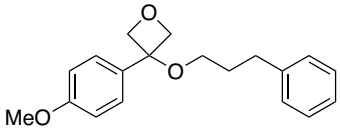
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.061	BB	0.1059	183.06377	26.07525	8.8753
2	7.581	BB	0.1787	1879.55273	160.42082	91.1247

>99:1 er

Experimental Procedures and Characterisation Data

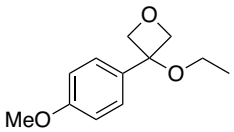
Synthesis of oxetane ethers

3-(4-Methoxyphenyl)-3-(3-phenylpropoxy)oxetane (2a)



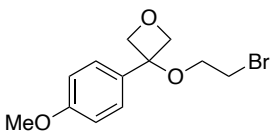
3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)oxetane **2a** (48.7 mg, 65%) as white solid. R_f = 0.31 (15% EtOAc/pentane); mp = 66–68 °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-H), 7.29–7.25 (m, 2 H, 2 × Ar-H), 7.20–7.16 (m, 3 H, 3 × Ar-H), 6.96–6.93 (m, 2 H, 2 × Ar-H), 4.91 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.83 (d, *J* = 6.4 Hz, 2 H, CH*H*-O-CH*H*), 3.84 (s, 3 H, OCH_3), 3.16 (t, *J* = 6.4 Hz, 2 H OCH_2CH_2), 2.71 (t, *J* = 7.6 Hz, 2 H, $PhCH_2$), 1.93–1.86 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 141.8 (Ph-C_qCH_2), 132.3 (Ar-C_qC_q), 128.4 (2 × Ar-C), 128.3 (2 × Ar-C), 127.2 (2 × Ar-C), 125.8 (Ph-C), 114.0 (2 × Ar-C), 81.3 (CH_2-O-CH_2), 80.0 (C_q-O), 62.9 (O-CH_2CH_2), 55.3 (OCH_3), 32.3 (O-CH_2CH_2), 31.4 ($PhCH_2$). The characterisation data (R_f, mp, IR, ^{1}H, ^{13}C) were in accordance with that reported previously.[10]
On a 6.0 mmol scale (**1**), the ether product (**2a**) was obtained in 1.04 g (61%).

3-Ethoxy-3-(4-methoxyphenyl)oxetane (2c)



Anhydrous ethanol (0.073 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-ethoxy-3-(4-methoxyphenyl)oxetane **2c** (28.7 mg, 55%) as a colourless oil. R_f = 0.23 (20% EtOAc/pentane); IR (film)/cm^{-1} 2948, 2873, 2837, 1610, 1581, 1511, 1459, 1302, 1244, 1175, 1134, 1067, 1028, 980, 830, 809, 638, 555, 527; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-H), 6.94 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-H), 4.91 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.82 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 3 H, OCH_3), 3.20 (q, *J* = 7.0 Hz, 2 H, O-CH_2CH_3), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 132.3 (Ar-C_q), 127.2 (2 × Ar-C), 114.0 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 79.9 (C_q-O), 59.4 (O-CH_2CH_2), 55.3 (OCH_3), 15.5 (CH_3); FTMS (APCI) *m/z* Calculated for $C_{10}H_{11}O_2^+$ [M-$OC_{2\,H5}$]$^+$: 163.0754; Found: 163.0756.

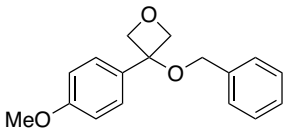
3-(2-Bromoethoxy)-3-(4-methoxyphenyl)oxetane (2d)



2-Bromoethanol (0.089 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(2-bromoethoxy)-3-(4-methoxyphenyl)oxetane **2d** (32.1 mg, 45%) as a colourless oil. R_f = 0.27 (10% EtOAc/pentane); IR (film)/cm^{-1} 2950, 2873, 2836, 1610, 1581, 1512, 1459, 1417, 1303, 1276, 1245, 1174, 1130, 1089, 1026, 979, 895, 830, 809, 616, 555,527, 424; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-H), 6.94 (d, *J* = 8.3 Hz, 2 H, 2 × Ar-H), 4.93 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.86 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 3 H, OCH_3), 3.52–3.35 (m, 4 H, CH_2-CH_2-Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (Ar-C_qOMe), 131.8 (Ar-C_q), 127.8 (2 × Ar-C), 114.6 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 80.9 (C_q-O), 64.7 (O-

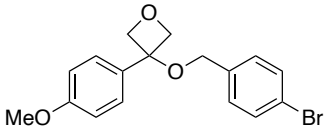
CH_2CH_2), 55.8 (OCH_3), 30.9 (CH_2-Br); FTMS (APCI) *m/z* Calculated for $C_{10}H_{11}O_2^+$ [M-OC_2H_4Br]$^+$: 163.0754; Found: 163.0755.

3-(Benzyloxy)-3-(4-methoxyphenyl)oxetane (2e)



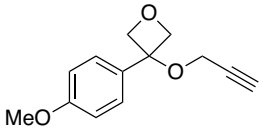
Benzyl alcohol (0.13 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(benzyloxy)-3-(4-methoxyphenyl)oxetanene **2e** (37.2 mg, 55%) as a white solid. R_f = 0.48 (20% EtOAc/pentane); mp = 67–70 °C; IR (film)/cm^{-1} 2961, 2935, 2869, 1607, 1578, 1511, 1450, 1377, 1243, 1176, 1122, 1020, 978, 876, 836, 814, 748, 695, 643, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 7.41–7.26 (m, 5 H, 5 × Ar-H), 7.00 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 5.02 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.91 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 4.25 (s, 2 H, CH_2-Ar), 3.88 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-C_qOMe), 138.1 (Ar-C_q), 132.0 (Ar-C_q), 128.6 (2 × Ar-C), 127.8 (Ph-C), 127.7 (2 × Ar-C), 127.5 (2 × Ar-C), 114.3 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 80.6 (C_q-O), 66.3 (Ph-CH_2), 55.5 (OCH_3); FTMS (+p NSI) *m/z* Calculated for $C_{17}H_{18}O_3Na$ [M+Na]$^{+.}$ 293.1148; Found: 293.1151.

3-((4-Bromobenzyl)oxy)-3-(4-methoxyphenyl)oxetane (2f)



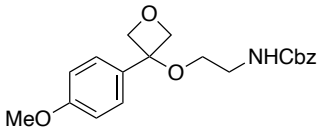
4-Bromobenzyl alcohol (233.8 mg, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-((4-bromobenzyl)oxy)-3-(4-methoxyphenyl)oxetane **2f** (54.1 mg, 62%) as a colourless oil. R_f = 0.27 (10% EtOAc/pentane); IR (film)/cm^{-1} 2948, 2872, 2835, 1609, 1581, 1511, 1485, 1460, 1406, 1344, 1374, 1302, 1280, 1245, 1173, 1129, 1067, 1029, 1009, 979, 884, 829, 801, 657, 611, 554, 474; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.39 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.20 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.97 (d, *J* = 8.3 Hz, 2 H, Ar-H), 4.96 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.89 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 4.17 (s, 2 H, CH_2-Ar), 3.84 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (Ar-C_qOMe), 137.1 (Ar-C_q), 131.7 (Ar-C_q), 131.7 (2 × Ar-C), 129.3 (2 × Ar-C), 127.5 (Ar-C_q), 121.7 (2 × Ar-C), 114.3 (2 × Ar-C), 81.3 (CH_2-O-CH_2), 80.8 (C_q-O), 65.6 (Ar-CH_2), 55.5 (OCH_3); FTMS (APCI) *m/z* Calculated for $C_{10}H_{11}O_2^+$ [M-OC_7H_6Br]$^+$: 163.0754; Found: 163.0754.

3-(4-Methoxyphenyl)-3-(prop-2-yn-1-yloxy)oxetane (2g)



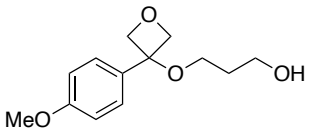
Propargyl alcohol (0.07 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-methoxyphenyl)-3-(prop-2-yn-1-yloxy)oxetane **2g** (36.9 mg, 68%) as a white solid. R_f = 0.31 (15% EtOAc/pentane); mp = 110–112 °C; IR (film)/cm^{-1} 3261 (alkyne C-H), 2948, 2876, 1611, 1578, 1511, 1453, 1307, 1245, 1128, 1065, 1030, 975, 940, 855, 818, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 6.95 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 5.04 (d, *J* = 7.4 Hz, 2 H, C*H*H-O-C*H*H), 4.87 (d, *J* = 7.4 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 3 H, OCH_3), 3.83 (d, *J* = 2.4 Hz, 2 H, O-CH_2C_q), 2.41 (t, *J* = 2.4 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (Ar-C_qOMe), 130.5 (Ar-C_q), 127.8 (2 × Ar-C), 114.2 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 80.9 (C_q-O), 79.9 (C_q-alkyne), 74.4 (CH), 55.3 (OCH_3), 52.5 (OCH_2C_q); FTMS (APCI) *m/z* Calculated for $C_{10}H_{11}O_2^+$ [M-OC_3H_3]$^+$: 163.0754; Found: 163.0761.

Benzyl (2-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)ethyl)carbamate (2h)



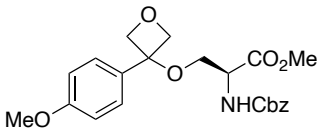
Benzyl (2-hydroxyethyl)carbamate (244.0 mg, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (20–50% EtOAc/pentane afforded impure benzyl (2-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)ethyl)carbamate **2h** as a colorless gum (45.0 mg). Repurification by flash column chromatography (10% Et2O/CH2Cl2) to obtain benzyl (2-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)ethyl)carbamate **2h** as a colorless gum (37.9 mg, 42%). R_f = 0.20 (10% Et_2O/CH_2Cl_2) IR (film)/cm^{-1} 3332 (NH), 2944, 2872, 1714 (C=O), 1610, 1511, 1246, 1176, 1127, 979, 832, 698, 557; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5 H, Ar-H), 7.27 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 6.92 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 5.24–5.17 (br s, 1 H, NH), 5.10 (s, 2 H, Ph-CH_2), 4.84 (s, 4 H, CH_2-O-CH_2), 3.82 (s, 3 H, OCH_3), 3.36 (t, *J* = 5.2 Hz, 2 H, CH_2), 3.21 (t, *J* = 5.2 Hz, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 156.4 (O=C_q), 136.5 (Ar-C_q), 131.4 (Ar-C_q), 128.6 (2 × Ar-C), 128.2 (Ph-C), 128.1(2 × Ar-C), 127.3 (2 × Ar-C), 114.1 (2 × Ar-C), 81.0 (CH_2-O-CH_2), 80.3 (C_q-O), 66.8 (O-CH_2-Ph), 62.9 (O-CH_2CH_2), 55.3 (O-CH_3), 41.1 (NH-CH_2); HRMS (ES-ToF) *m/z* Calculated for $C_{20}H_{23}NO_5Na$ [M+Na]: 380.1474; Found: 380.1479.

3-((3-(4-Methoxyphenyl)oxetan-3-yl)oxy)propan-1-ol (2i)



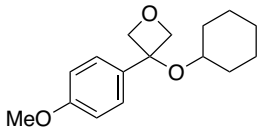
Propane-1,3-diol (0.09 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (30% EtOAc/pentane) afforded 3-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)propan-1-ol **2i** (22.9 mg, 38%) as a colourless oil. R_f = 0.32 (50% EtOAc/pentane); IR (film)/cm^{-1} 3431 (OH), 2934, 2874, 1610, 1512, 1461, 1303, 1244, 1168, 1056, 1027, 976, 831, 554; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 6.94 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 4.90 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 3 H), 3.81–3.72 (m, 2 H, O-CH_2CH_2), 3.31 (t, *J* = 5.8 Hz, 2 H, CH_2-OH), 2.03 (s, 1H, OH), 1.82 (tt, *J* = 5.8, 5.8 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 131.7 (Ar-C_q), 127.3 (2 × Ar-H), 114.1 (2 × Ar-H), 81.1 (CH_2-O-CH_2), 80.3 (C_q-O), 62.3 (O-CH_2CH_2), 61.3 (CH_2-OH), 55.3 (OCH_3), 32.3 (OCH_2CH_2); FTMS (APCI) *m/z* Calculated for $C_{13}H_{17}O_3^+$ $[M–OH]^+$: 221.1172; Found: 211.1174.

Methyl *N*-((benzyloxy)carbonyl)-*O*-(3-(4-methoxyphenyl)oxetan-3-yl)-*D*-serinate (2j)



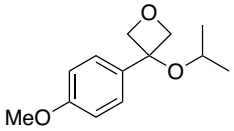
N-Cbz-L-serine methyl ester (316.5 mg, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (1:1:1 Et2O/CH_2Cl_2/hexane) afforded Methyl *N*-((benzyloxy)carbonyl)-*O*-(3-(4-methoxyphenyl)oxetan-3-yl)-*D*-serinate oxetane **2j** (41.8 mg, 44%) as a colourless gum. $[\alpha]_D^{21}$ = +3.39 (*c* 1.00, acetone), R_f = 0.66 (50% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 3425 (NH), 2952, 2918, 1722 (C=O), 1611, 1514, 1342, 1302, 1248, 1210, 1177, 1029, 982, 835, 699, 552; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5H, 5 × Ar-H), 7.22 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 6.91 (d, *J* = 8.6 Hz, 2H, 2 × Ar-H), 5.67 (d, *J* = 8.7 Hz, 1H, NH), 5.12 (s, 2H, O-CH_2), 4.84–4.78 (m, 4H, CHH-O-CHH), 4.47 (dt, *J* = 8.8, 3.1 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.58 (dd, *J* = 9.2, 2.9 Hz, 1H, OCH*H*), 3.40 (dd, *J* = 9.3, 3.1 Hz, 1H, OC*H*H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O), 159.5 (Ar-C_qOMe), 156.0 (C=O), 136.2 (Ar-C_q), 130.8 (Ar-C_q), 128.6 (2 × Ar-C), 128.3 (Ar-C), 128.1 (2 × Ar-C), 127.3 (2 × Ar-C), 114.2 (2 × Ar-C), 80.9 (CH_2-O), 80.5 (CH_2-O), 80.4 (C_q-O), 67.1 (OCH_2), 63.9 (OCHH), 55.3 (CH), 54.2 (OCH_3), 52.7 (OCH_3); HRMS (ES-ToF) *m/z* Calculated for $C_{22}H_{26}NO_7$ $[M+H]^+$: 416.1709; Found: 416.1719.

3-(Cyclohexyloxy)-3-(4-methoxyphenyl)oxetane (2b)



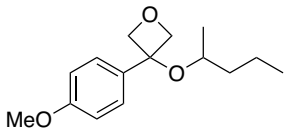
Cyclohexanol (0.132 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography using Basic alumina (Act IV) (100% pentane) afforded 3-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)propan-1-ol (32.1 mg, 49%) as a pale yellow solid. R_f = 0.23 (pentane/CH_2Cl_2/Et_2O 8:1:1); 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 7.35 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 6.93 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 4.94 (d, *J* = 7.0 Hz, 2 H, CH*H*-O-CH*H*), 4.85 (d, *J* = 7.0 Hz, 2 H, C*H*H-O-C*H*H), 3.84 (s, 3 H, OCH_3), 3.15 (tt, *J* = 9.8, 4.0 Hz, 1H, CH), 1.71–1.60 (m, 2 H, 2 × CH*H*), 1.60–1.51 (m, 3 H, 3 × CH*H*), 1.50–1.42 (m, 1H, CH*H*), 1.33–1.18 (m, 2 H, 2 × CH*H*), 1.18–1.01 (m, 3 H, 3 × CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 133.6 (Ar-C_q), 127.9 (2 × Ar-C), 114.2 (2 × Ar-C), 82.9 (CH_2-O-CH_2), 79.5 (C_q-O), 73.3 (CH), 55.6 (OCH_3), 34.0 (2 × CH_2), 25.8 (CH_2), 24.6 (2 × CH_2). The characterisation data (R_f, mp, IR, ^{1}H, ^{13}C) were in accordance with that reported previously.[10]

3-Isopropoxy-3-(4-methoxyphenyl)oxetane (2k)



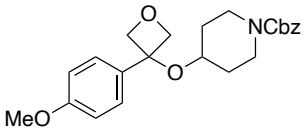
Isopropanol (0.096 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (8:1:1 pentane/CH_2Cl_2/Et_2O) afforded 3-isopropoxy-3-(4-methoxyphenyl)oxetane **2k** (45.8 mg, 82%) as a colourless oil. R_f = 0.31 (15% EtOAc/pentane); IR (film)/cm^{-1} 2948, 2873, 2837, 1610, 1581, 1511, 1459, 1390,1342, 1301, 1244, 1175, 1134, 1067, 1028, 980, 911, 830, 809, 568, 528; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 6.94 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 4.93 (d, *J* = 6.5 Hz, C*H*H-O-C*H*H), 4.87 (d, *J* = 6.5 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 3 H), 3.48 (hept, *J* = 6.1 Hz, O-CH), 1.00 (d, *J* = 6.1 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (Ar-C_qOMe), 133.5 (Ar-C_q), 128.2 (2 × Ar-C), 114.4 (2 × Ar-C), 82.9 (CH_2-O-CH_2), 79.7 (C_q-O), 67.4 (OCH), 55.8 (OCH_3), 23.9 (2 × CH_3); HRMS (ES-ToF) *m/z* Calculated for $C_{10}H_{11}O_2^+$[M-OC_3H_7]$^+$: 163.0754; Found: 163.0744.

3-(4-Methoxyphenyl)-3-(pentan-2-yloxy)oxetane (2l)



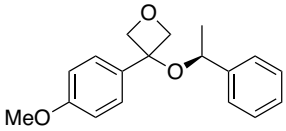
2-Pentanol (0.14 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-methoxyphenyl)-3-(pentan-2-yloxy)oxetane **2l** (22.5 mg, 36%) as a colourless oil. R_f = 0.56 (20% EtOAc/pentane); IR (film)/cm^{-1} 2957, 2933, 2872, 1511, 1513, 1461, 1246, 1177, 1115, 1031, 982, 832, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 6.93 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 5.01–4.89 (m, 3H, 3 × O-C*H*H), 4.82 (d, *J* = 6.3 Hz, 1H, O-CH*H*), 3.83 (s, 3H, OCH_3), 3.33 (hept, *J* = 6.1 Hz, 1H, OCH), 1.47 – 1.17 (m, 4H, CH_2C$H_2$$CH_3$), 0.89 (d, *J* = 6.1 Hz, 3H, CH-CH_3), 0.82 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (Ar-C_qOMe), 133.1 (Ar-C_q), 127.8 (2 × Ar-C), 113.8 (2 × Ar-C), 82.8 (CH_2-O-CH_2), 82.3 (CH_2-O-CH_2), 79.1 (C_q-O), 70.2 (OCH), 55.3 (OCH_3), 39.8 (CH_2), 21.00 (CH_2), 18.7 (CH_3), 14.1 (CH_3); HRMS (ES-ToF) *m/z* Calculated for $C_{15}H_{27}NO_3Na$ [M+NH_4+Na]$^+$: 292.1889; Found: 292.1882.

Benzyl 4-((3-(4-methoxyphenyl)oxetan-3-yl)oxy)piperidine-1-carboxylate (2m)



Benzyl 4-hydroxypiperidine-1-carboxylate (0.19 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (pentane/CH_2Cl_2/Et_2O 4:4:2) afforded 3-isopropoxy-3-(4-methoxyphenyl)oxetane **2m** (36.4 mg, 37%) as a yellow gum. R_f = 0.41 (20% Et_2O/CH_2Cl_2); IR (film)/cm^{-1} 2951, 2873, 1697 (C=O), 1611, 1583, 1514, 1431, 1363, 1308, 1273, 1247, 1228, 1179, 1136, 1068, 1028, 981, 876, 834, 809, 764, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 7 H, 7 × Ar-H), 6.93 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 5.10 (s, 2 H, O-CH_2-Ph), 4.91 (d, *J* = 6.5 Hz, 2 H, C*H*H-O-C*H*H), 4.88 (d, *J* = 6.5 Hz, 2 H, CH*H*-O-CH*H*), 3.83 (s, 5 H, OCH_3 and $CH_{eq}NCH_{eq}$), 3.37 (tt, *J* = 8.0, 3.9 Hz, 1 H, CH), 3.02 (ddd, *J* = 13.2, 9.2, 3.6 Hz, 2 H, $CH_{ax}NCH_{ax}$), 1.62–1.33 (br m, 4 H, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_qOMe), 155.2 (C_q=O), 136.8 (Ph-$C_q$$CH_2$O), 132.6 (Ar-$C_q$$C_q$), 128.4 (2 × Ar-C), 127.9 (Ph-C), 127.8 (2 × Ar-C), 127.6 (2 × Ar-C), 114.0 (2 × Ar-C), 82.1 (CH_2OCH_2), 79.6 (C_q), 69.8 (CH), 67.0 (OCH_2Ph), 55.3 (OCH_3), 41.4 (CH_2NCH_2), 32.4 (2 × CH_2; this peak is broader and smaller than expected due to chemical exchange); HRMS (ES-ToF) *m/z* Calculated for $C_{23\ H28}NO_5$ [M+H]: 398.1967; Found: 398.1961.

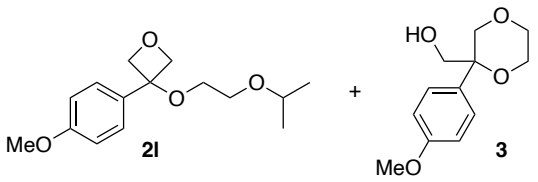
(*S*)-3-(4-Methoxyphenyl)-3-(1-phenylethoxy)oxetane (2n)



(*S*)-1-Phenylethan-1-ol (0.15 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxyphenyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography using Basic alumina (Act IV) (5% EtOAc/pentane) afforded (*S*)-3-(4-methoxyphenyl)-3-(1-phenylethoxy)oxetane **2n** (21.7 mg, 31%, 92:8 *er*) as a colorless oil. R_f = 0.47 (20% EtOAc/pentane). IR (film)/cm^{-1} 2952, 2926, 2871, 1610, 1513, 1454, 1249, 1176, 1031, 832, 701, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 7.36–7.21 (m, 5H, 5 × Ar-H), 6.98 (d, *J* = 8.8 Hz, 2H, 2 × Ar-H), 5.01 (d, *J* = 6.2 Hz, 1H, CH*H*-O-CHH), 4.72–4.63 (m, 2H, 2 × C*H*H-O-CHH), 4.54 (d, *J* = 6.2 Hz, 1H, CHH-O-C*H*H), 4.34 (q, *J* = 6.5 Hz, 1H, OCH), 3.88 (s, 3H, OCH_3), 1.37 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 144.2 (Ar-C_q), 132.8 (Ar-C_q), 128.4 (2 × Ar-C), 127.7 (2 × Ar-C), 127.5 (Ar-C), 126.3 (2 × Ar-C), 113.9 (2 × Ar-C), 83.6 (CH_2-O), 80.2 (CH_2-O), 80.0 (C_q-O), 72.9 (OCH), 55.3 (OCH_3), 24.5 (CH_3); HRMS (ES-ToF) *m/z* Calculated for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491; Found: 285.1483.

HPLC Conditions: Chiralpak IA column, 90:10 *n*-hexane:*i*PrOH, flow rate: 1 mL min^{-1}, 35 °C, UV detection wavelength: 280 nm. Retention times: 6 & 7 min.

3-(Isopropoxymethoxy)-3-(4-methoxyphenyl)oxetane (2o)

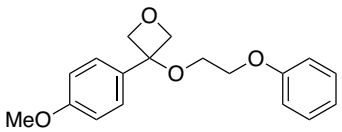


Isopropoxy ethanol (0.144 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxy phonyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (20% EtOAc/pentane) afforded 3-(2-isopropoxyethoxy)-3-(4-methoxyphenyl)oxetane **2o** (14.6 mg, 22%) as a colourless oil, followed by (2-phenyl-1,4-dioxan-2-yl)methanol **3** (14.8 mg, 33%) as a colourless oil.

3-(2-Isopropoxyethoxy)-3-(4-methoxyphenyl)oxetane **2o**: R_f = 0.27 (20% EtOAc/pentane); IR (film)/cm^{-1} 2968, 2872, 1611, 1513, 1462, 1247, 1177, 1129, 1091, 1031, 982, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 6.93 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 4.95 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.81 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.82 (s, 3 H, O-CH_3), 3.61 (hept, *J* = 6.1 Hz, 1H, CH), 3.55 (t, *J* = 5.5 Hz, 2 H, O-C$H_2$$CH_2$), 3.30 (d, *J* = 5.5 Hz, 2 H, O-CH_2CH_2), 1.16 (d, *J* = 6.1 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 132.1 (Ar-C_q), 127.4 (2 × Ar-C), 114.0 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 80.1 (C_q-O), 72.0 (O-CH), 67.2 (O-$CH_2$$CH_2$), 64.0 (O-$CH_2$$CH_2$), 55.3 (O-$CH_3$) , 22.1 (2 × CH_3); HRMS (ES ToF) *m/z* Calculated for $C_{15}H_{26}NO_4^+$ $[M+NH_4]^+$: 284.1856; Found: 284.1844; also: *m/z* Calculated for $C_{10}H_{11}O_2^+$ [M-$O_2C_5H_{11}$]: 163.0754; Found: 163.0767

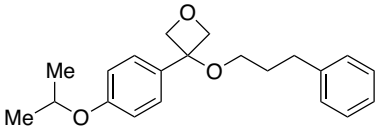
(2-Phenyl-1,4-dioxan-2-yl)methanol **3**: R_f = 0.20 (20% EtOAc/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H, 2 × Ar-H), 6.97–6.93 (m, 2 H, 2 × Ar-H), 4.27 (d, *J* = 12.3 Hz, 1 H, C_qC*H*HOCH$_2$), 3.99 (d, *J* = 12.3 Hz, 1 H, C_qCH*H*OCH$_2$), 3.82 (s, 3 H, OCH_3), 3.76–3.59 (m, 6 H, 3 × OCH_2), 1.88 (br s, 1 H, OH), The characterisation data (^{1}H) were in accordance with that reported previously.[2]

3-(4-Methoxyphenyl)-3-(2-phenoxyethoxy)oxetane (2p)



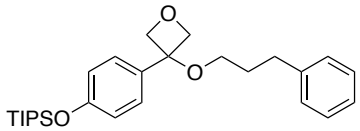
Phenoxy ethanol (0.156 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 4-methoxy phonyloxetanol **1** (45.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (20% EtOAc/pentane) afforded 3-(4-methoxyphenyl)-3-(2-phenoxyethoxy)oxetane **2p** (39.8 mg, 53%) as a colourless oil. R_f = 0.27 (20% EtOAc/pentane); IR (film)/cm^{-1} 2952, 2877, 1600, 1512, 1491, 1461, 1298, 1244, 1174, 1058, 1031, 974, 917, 755, 690, 561; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2 H, 2 × Ar-H), 7.33–7.24 (m, 2 H, 2 × Ar-H), 7.00–6.93 (m, 3 H, 3 × Ar-H), 6.91 (d, *J* = 7.6 Hz, 2 H, 2 × Ar-H), 4.97 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.86 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 4.10 (t, *J* = 5,1 Hz, 2 H, O-C$H_2$$CH_2$), 3.84 (s, 3 H, O-$CH_3$), 3.53 (t, *J* = 5.1 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 158.7 (Ph-C_q), 131.7 (Ar-C_q), 129.5 (2 × Ar-C), 127.4 (2 × Ar-C), 121.0 (Ph-C), 114.6 (2 × Ar-C), 114.1 (2 × Ar-C), 81.3 (CH_2-O-CH_2), 80.4 (C_q-O), 67.1 (O-$CH_2$$CH_2$), 62.9 (O-$CH_2$$CH_2$), 55.4 (O-$CH_3$); HRMS (ES ToF) *m/z* Calculated for $C_{18}H_{24}NO_4$ $[M+NH_4]$: 318.1705; Found: 318.1709; also: *m/z* Calculated for $C_{10}H_{11}O_2$ [M-$O_2C_5H_{11}$]: 163.0759; Found: 163.0762.

3-(4-Isopropoxyphenyl)-3-(3-phenylpropoxy)oxetane (13a)



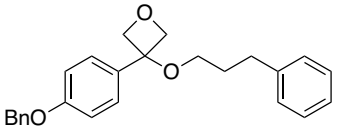
3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(4-isopropoxyphenyl)oxetan-3-ol **4** (52.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-isopropoxyphenyl)-3-(3-phenylpropoxy)oxetane **13a** (56.3 mg, 69%) as colourless oil. R_f = 0.43 (20% EtOAc/pentane); IR (film)/cm^{-1} 3026, 2940, 2974, 2871, 1607, 1579, 1508, 1452, 1379, 1296, 1241, 1175, 1107, 1074, 1034, 981, 951, 831, 745, 698, 662, 534, 487; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 4H, 4 × Ar-H), 7.18 (d, *J* = 7.5 Hz, 3 H, 3 × Ar-H), 6.92 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-H), 4.91 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.84 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 4.58 (hept, *J* = 6.0 Hz, 1 H, OCH), 3.17 (t, *J* = 6.3 Hz, 2 H, OCH_2CH$_2$), 2.71 (t, *J* = 7.7 Hz, 2 H, Ph-CH$_2$), 1.90 (tt, *J* = 7.7, 6.3 Hz, 2 H, Ph-CH$_2$CH_2), 1.37 (d, *J* = 6.0 Hz, 6 H, 2 × CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (Ar-C_qOCH), 141.9 (Ar-C$_q$), 132.0 (Ar-C$_q$), 128.6 (2 × Ar-C), 128.4 (2 × Ar-C), 127.4 (2 × Ar-C), 125.9 (Ph-C), 115.8 (2 × Ar-C), 81.5 (CH$_2$-O-CH$_2$), 80.1 (C$_q$-O), 70.0 (O-CH), 62.9 (O-CH_2CH$_2$), 32.4 (Ph-CH$_2$), 31.6 (OCH$_2$CH_2), 22.2 (2 × CH$_3$); HRMS (ES ToF) *m/z* Calculated for $C_{23}H_{30}NO_3$ [M+H+MeCN]: 368.2226; Found: 368.2226.

Triisopropyl(4-(3-(3-phenylpropoxy)oxetan-3-yl)phenoxy)silane (14a)



3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(4-((triisopropylsilyl)oxy)phenyl)oxetan-3-ol **5** (80.3 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded triisopropyl(4-(3-(3-phenylpropoxy)oxetan-3-yl)phenoxy)silane **14a** (33.3 mg, 30%) as a pale yellow oil. R_f = 0.60 (15% EtOAc/pentane); IR (film)/cm^{-1} 2942, 2890, 2865, 1605. 1509, 1459, 1261, 1170. 1132, 1072, 985, 910, 881, 837, 741, 683, 656, 561, 490, 458; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 4 H, 4 × Ar-H), 7.22–7.16 (m, 3 H, 3 ×Ar-H), 6.92 (d, *J* = 8.5 Hz, 2 H, 2 × Ar-H), 4.92 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.17 (t, *J* = 6.2 Hz, 2 H, O-CH_2CH$_2$), 2.72 (t, *J* = 7.8 Hz, 2 H, Ph-CH$_2$), 1.90 (tt, *J* = 7.8, 6.2 Hz, 2 H, CH$_2$-CH_2-CH$_2$), 1.30 (q, *J* = 7.3 Hz, 3 H, 3 ×Si-CH), 1.13 (d, *J* = 7.3 Hz, 18 H, 3 × Si-C(CH$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (Ar-C$_q$), 141.8 (Ar-C$_q$), 132.5 (Ar-C$_q$), 128.4 (2 × Ar-C), 128.3 (2 × Ar-C), 127.2 (2 × Ar-C), 125.8 (Ph-C), 119.9 (2 × Ar-C), 81.4 (CH$_2$-O-CH$_2$), 80.1 (Ar-C$_q$-O), 62.9 (O-CH_2CH$_2$), 32.3 (Ph-CH$_2$), 31.4 (O-CH$_2$CH_2), 17.9 (6 × CH$_3$), 12.7 (3 × Si-C); HRMS (ES ToF) *m/z* Calculated for $C_{29}H_{44}NO_3Si$ [M+H+MeCN]: 482.3090; Found: 482.3090.

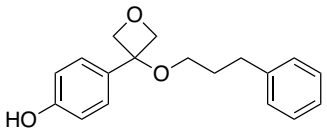
3-(4-(Benzyloxy)phenyl)-3-(3-phenylpropoxy)oxetane (15a)



3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(4-(benzyloxy)phenyl)oxetan-3-ol **6** (64.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-(benzyloxy)phenyl)-3-(3-phenylpropoxy)oxetane **15a** (46.5 mg, 50%) as a pale yellow solid. R_f = 0.44 (20% EtOAc/pentane); mp = 76–78 °C; IR (film)/cm^{-1} 3025, 2984, 2873, 1606, 1513, 1452, 1382, 1240, 1175, 1145, 1081, 1005, 968, 881, 838, 694, 672, 526, 501, 441; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.40 (m, 4 H, 4 × Ar-H), 7.40–7.33 (m, 3 H, 3 × Ar-H), 7.32–7.28 (m, 2 H, 3 × Ar-H), 7.25–7.17 (m, 3 H, 3 × Ar-H), 7.08–7.00 (m, 2 H, 2 × Ar-H), 5.12 (s, 2 H, Ph-CH$_2$-O), 4.93 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.19 (t, *J* = 6.3 Hz, 2 H, O-CH_2CH$_2$), 2.73 (t, *J* = 7.4 Hz, 2 H, Ph-CH_2CH$_2$), 1.92 (tt, *J* = 7.4, 6.3 Hz, 2 H, O-CH$_2$CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (Ar-C_qOBn), 141.6 (Ar-C$_q$), 136.7 (Ar-C$_q$), 132.3 (Ar-C$_q$), 128.5 (2 × Ar-C), 128.3 (2 × Ar-C), 128.1 (2 × Ar-C), 127.9 (2 × Ar-C), 127.3 (Ph-C), 127.1 (2 × Ar-C), 125.6 (Ph-C),

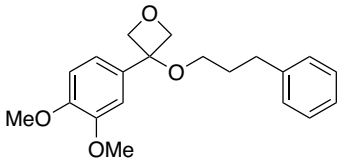
114.7 (2 × Ar-C), 81.1 (CH_2-O-CH_2), 79.7 (C_q-O), 70.0 (Ph-CH_2-O), 62.7 (O-*C*$H_2$$CH_2$), 32.1 (Ph-C*H*$_2$$CH_2$), 31.2 (O-$CH_2$*C*$H_2$); FTMS (APCI) *m/z* Calculated for $C_{16}H_{15}O_2^+$ [M-OC_9H_{11}]$^+$: 239.1067; Found: 239.1066.

4-(3-(3-Phenylpropoxy)oxetan-3-yl)phenol (16a)



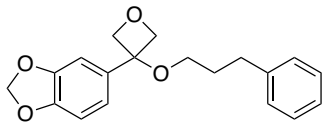
3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(4-hydroxyphenyl)oxetan-3-ol **7** (41.5 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. 10 mL CH_2Cl_2 was added and the organic solution was extracted with NaOH (1 M, 3 × 10 mL). This step separated phenol **16a** (basic aq. phase) from excess 3-phenyl-1-propanol (organic phase), which were challenging to separate by flash column chromatography. The combined aqueous layers were neutralised with aq. HCl (1 M). After neutralisation, the aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (50% EtOAC/pentane) afforded 4-(3-(3-phenylpropoxy)oxetan-3-yl)phenol **16a** (36.2 mg, 51%) as a white solid. R_f = 0.54 (40% EtOAc/pentane); mp = 89–93 °C; IR (film)/cm^{-1} 3298 (br, OH), 3023, 2943, 2880, 2857, 1591, 1514, 1447, 1262, 1215, 1170, 1130, 1069, 964, 745, 696, 552; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 4H, 4 × Ar-H), 7.23–7.16 (m, 3 H, 3 × Ar-H), 6.88 (d, *J* = 8.6 Hz, 2 H, 2 × Ar-H), 5.86 (s, 1H, OH), 4.96 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.89 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.18 (t, *J* = 6.2 Hz, 2 H, O-C*H*$_2$$CH_2$), 2.72 (t, *J* = 6.4 Hz, 2 H, Ph-CH_2), 1.91 (tt, *J* = 6.4, 6.2 Hz, 2 H, O-CH_2C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (Ar-*C*$_q$OH), 141.7 (Ar-C_q), 131.9 (Ar-C_q), 128.5 (2 × Ar-C), 128.4 (2 × Ar-C), 127.5 (2 × Ar-C), 125.9(Ph-C), 115.5 (2 × Ar-C), 81.5 (CH_2-O-CH_2), 79.9 (C_q-O), 62.9 (O-*C*$H_2$$CH_2$), 32.3 (Ph-$CH_2$), 31.4 (O-$CH_2$*C*$H_2$); FTMS (APCI) *m/z* Calculated for $C_{18}H_{19}O_2^+$ [M-OH]$^+$: 267.1380; Found: 267.1382.

3-(3,4-Dimethoxyphenyl)-3-(3-phenylpropoxy)oxetane (17a)



3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(3,4-dimethoxyphenyl)oxetan-3-ol **8** (52.6 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (25% EtOAc/pentane) afforded 3-(3,4-dimethoxyphenyl)-3-(3-phenylpropoxy)oxetane **17a** (25.4 mg, 31%) as a white solid. R_f = 0.58 (40% EtOAc/pentane); mp = 63–66°C; IR (film)/cm^{-1} 2942, 2871, 1602, 1485, 1435, 1250, 1226, 1176, 1031, 980, 932, 809, 732, 698, 510; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H, 2 × Ar-H), 7.22–7.18 (m, 3 H, 3 × Ar-H), 7.01 (dd, *J* = 8.2, 2.1 Hz, 1H, Ar-H), 6.95–6.88 (m, 2 H, 2 × Ar-H), 4.92 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.19 (t, *J* = 6.3 Hz, 2 H, OC*H*$_2$$CH_2$), 2.74 (t, *J* = 6.7 Hz, 2 H, Ph-CH_2), 1.93 (tt, *J* = 6.7, 6.3 Hz, 2 H, O-CH_2C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (Ar-*C*$_q$OMe), 148.7 (Ar-*C*$_q$OMe), 141.7 (Ar-C_q), 132.7 (Ar-C_q), 128.4 (2 × Ph-C), 128.4 (2 × Ph-C), 125.9 (Ar-C), 118.4 (Ar-C), 110.8 (Ar-C), 108.9 (Ar-C), 81.2 (CH_2-O-CH_2), 80.1 (C_q-O), 63.0 (O*C*$H_2$$CH_2$), 56.0 (2 × OCH_3), 32.4 (Ph-CH_2), 31.5 (O-CH_2*C*H_2); FTMS (APCI) *m/z* Calculated for $C_{11}H_{13}O_3^+$[M-OC_9H_{11}]$^+$: 193.0859; Found: 193.0861.

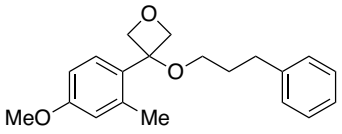
5-(3-(3-Phenylpropoxy)oxetan-3-yl)benzo[*d*][1,3]dioxol (18a)



3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(benzo[*d*][1,3]dioxol-5-yl)oxetan-3-ol **9** (48.5 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 5-(3-(3-phenylpropoxy)oxetan-3-yl)benzo[*d*][1,3]dioxole **18a** (45.6 mg, 58%) as colourless oil. R_f = 0.43 (20% EtOAc/pentane); IR (film)/cm^{-1} 2942, 2871, 1603, 1485, 1435, 1250, 1226, 1175, 1135, 1031, 980, 933, 859, 808, 698, 632, 512; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, 2 × Ar-H), 7.22–7.18 (m, 3 H, 3 × Ar-H), 6.94–6.82 (m, 3 H, 3 × Ar-H), 6.01 (s, 2 H,

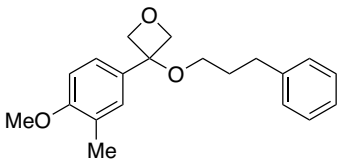
O-CH_2-O), 4.89 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.81 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 3.18 (t, *J* = 6.3 Hz, 2 H, O-C$H_2$$CH_2$), 2.73 (dd, *J* = 6.4 Hz, 2 H, Ph-CH_2), 1.90 (tt, *J* = 6.4, 6.3 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (Ar-C_qOCH), 147.3 (Ar-C_qOCH), 141.8 (Ar-C_q), 134.2 (Ar-C_q), 128.5 (2 × Ph-C), 128.4 (2 × Ph-C), 125.9 (Ar-C), 119.4 (Ar-C), 108.1 (Ar-C), 106.5 (Ar-C), 100.2 (O-CH_2-O), 81.2 (CH_2OCH_2), 80.1 (C_q-O), 62.9 (OCH_2CH_2), 32.3 (Ph-CH_2), 31.4 (O-$CH_2$$CH_2$); FTMS (APCI) *m/z* Calculated for $C_{19}H_{19}O_4^-$[M-H]$^-$: 311.1289; Found: 311.1289.

3-(4-Methoxy-2-methylphenyl)-3-(3-phenylpropoxy)oxetane (19a)



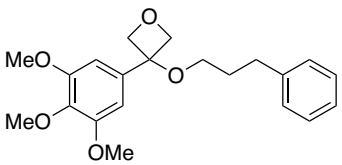
3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(4-methoxy-2-methylphenyl)oxetan-3-ol **10** (48.6 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-methoxy-2-methylphenyl)-3-(3-phenylpropoxy)oxetane **19a** (37.1 mg, 48%) as colourless oil. R_f = 0.49 (20% EtOAc/pentane); IR (film)/cm^{-1} 3024, 2939, 2867, 1607, 1575, 1499, 1452, 1303, 1268, 1245, 1183, 1165, 1128, 1055, 1028, 986, 945, 852, 810, 698, 633, 595, 491, 458; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m,, 2 H, 2 × Ar-H), 7.24–7.11 (m, 3 H, 3 × Ar-H), 7.06 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.78 (d, *J* = 2.7 Hz, 1H, Ar-H), 6.72 (dd, *J* = 8.4, 2.7 Hz, 1H, Ar-H), 5.10 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.91 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 3.84 (s, 3 H, OCH_3), 3.08 (t, *J* = 6.1 Hz, 2 H, OCH_2CH_2), 2.67 (t, *J* = 7.8 Hz, 2 H, Ph-CH_2), 2.24 (s, 3 H, CH_3), 1.84 (tt, *J* = 7.8, 6.1 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 142.0 (Ar-C_q), 138.8 (Ar-C_q), 129.2 (Ar-C_q), 128.6 (Ar-C), 128.4 (2 × Ph-C), 128.3 (2 × Ph-C), 125.8 (Ar-C), 117.3 (Ar-C), 109.8 (Ar-C), 81.5 (CH_2-O-CH_2), 80.8 (C_q-O), 62.5 (O-CH_2CH_2), 55.2 (OCH_3), 32.4 (Ph-CH_2), 31.6 (O-$CH_2$$CH_2$), 19.5 ($CH_3$); FTMS (APCI) *m/z* Calculated for $C_{11}H_{13}O_2^+$ [M-OC_9H_{11}]$^+$: 177.0910; Found: 177.0910.

3-(4-Methoxy-3-methylphenyl)-3-(3-phenylpropoxy)oxetane (20a)



3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(43-(4-methoxy-3-methylphenyl)oxetan-3-ol **11** (48.6 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-(4-methoxy-3-methylphenyl)-3-(3-phenylpropoxy)oxetane **20a** (40.3 mg, 52%) as colourless oil. R_f = 0.56 (20% EtOAc/pentane); IR (film)/cm^{-1} 3024, 2944, 2870, 1607, 1501, 1453, 1302, 1246, 1176, 1134, 1081, 1031, 981, 946, 887, 853, 811, 747, 698, 603, 503, 442; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2 H, 2 × Ar-H), 7.23–7.13 (m, 5H, 5 × Ar-H), 6.84 (d, *J* = 8.2 Hz, 1H, Ar-H), 4.91 (d, *J* = 6.5 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.5 Hz, 2 H, CH*H*-O-CH*H*), 3.86 (s, 3 H, OCH_3), 3.16 (t, *J* = 6.2 Hz, 2 H, OCH_2CH_2), 2.72 (t, *J* = 7.7 Hz, 2 H, Ph-CH_2), 2.26 (s, 3 H, CH_3), 1.90 (tt, *J* = 7.7, 6.2 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (Ar-C_qOMe), 141.9 (Ar-C_q), 131.7 (Ar-C_q), 128.5 (2 × Ph-C), 128.4 (2 × Ph-C), 128.3 (Ar-C_q), 127.0 (Ar-C), 125.8 (Ar-C), 124.5 (Ar-C), 109.7 (Ar-C), 81.4 (CH_2-O-CH_2), 80.0 (C_q-O), 62.8 (O-CH_2CH_2), 55.4 (OCH_3), 32.3 (Ph-CH_2), 31.5 (O-$CH_2$$CH_2$), 16.5 ($CH_3$); FTMS (APCI) *m/z* Calculated for $C_{11}H_{13}O_2^+$ [M-OC_9H_{11}]$^+$: 177.0910; Found: 177.0912.

3-(3-Phenylpropoxy)-3-(3,4,5-trimethoxyphenyl)oxetane (21a)

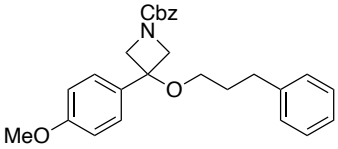


3-Phenyl-1-propanol (0.17 mL, 1.25 mmol, 5.0 equiv) was added to the solution of bis(trifluoromethanesulfonyl)amine (7.0 mg, 0.025 mmol, 0.1 equiv) in anhydrous acetonitrile (0.85 mL, 0.3 M) and then 3-(3,4,5-trimethoxyphenyl)oxetan-3-ol **12** (60.1 mg, 0.25 mmol, 1.0 equiv) was added and the reaction mixture stirred for 24 h at 50 °C. Sat. aq. $NaHCO_3$ (10 mL) was added to quench the reaction, then the aqueous mixture 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 rotary evaporator. Purification by preparative thin-layer chromatography (2:1:7 CH_2Cl_2/Et_2O/pentane) afforded 3-(3-phenylpropoxy)-3-(3,4,5-trimethoxyphenyl)oxetane **21a**

(20.4 mg, 23%) as a colourless oil. R_f = 0.40 (40% EtOAc/pentane); IR (film)/cm^{-1} 2937, 2871, 1586, 1505, 1453, 1411, 1331, 1171, 1123, 1033, 1006, 980, 846, 743, 698, 653, 491; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 2 H, 2 × Ar-H), 7.23–7.19 (m, 3 H, 3 × Ar-H), 6.68 (s, 2 H, 2 × Ar-H), 4.93 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.82 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.90 (s, 9H, 3 × OCH_3), 3.23 (t, *J* = 6.3 Hz, 2 H, O-C$H_2$$CH_2$), 2.76 (t, *J* = 7.5 Hz, 2 H, Ph-CH_2), 1.96 (tt, *J* = 7.5, 6.3 Hz, 2 H, O-CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (2 × Ar-C_qOMe), 141.7 (Ar-C_qOMe), 137.6 (Ar-C_q), 136.0 (Ar-C_q), 128.5 (2 × Ph-C), 128.4 (2 × Ph-C), 125.9 (Ph-C), 102.9 (2 × Ar-C), 81.2 (CH_2-O-CH_2), 80.3 (C_q-O), 63.2 (O-CH_2-CH_2), 60.9 (OCH_3), 56.2 (OCH_3), 32.3 (O-CH_2-CH_2), 31.5 (CH_3).

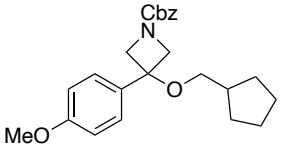
Synthesis of azetidine ethers

Benzyl 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate (24a)



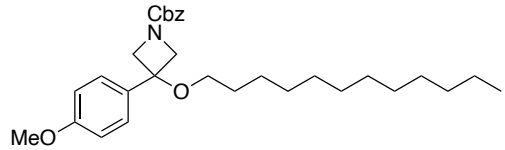
Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and 3-phenylpropanol (0.34 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL, 0.5 M). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (6:3:1 to 5:3:2 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate **24a** (171 mg, 80%) as a colourless oil. R_f = 0.42 (50% Et_2O/hexane); IR (film)/cm^{-1} 2930, 1707 (C=O), 1606, 1507, 1412, 1349, 1244, 1101, 1022, 698; ^1H NMR (400 MHz, $CDCl_3$) d 7.37–7.24 (m, 9H, Ar-H), 7.19–7.13 (m, 3 H, Ar-H), 6.93–6.89 (m, 2 H, Ar-H), 5.13 (s, 2 H, O-CH_2-Ph), 4.24 (br, s, 4H, CH_2-N-CH_2), 3.83 (s, 3 H, OCH_3), 3.11 (t, *J* = 6.2 Hz, 2 H, O-C*H*$_2$$CH_2$), 2.68–2.64 (m, 2 H, CH_2C*H*$_2$-Ph), 1.88–1.81 (m, 2 H, O-CH_2C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-*C*$_q$-OCH_3), 156.7 (C=O), 141.7 (Ph-*C*$_q$-CH_2-CH_2), 136.6 (Ar-*C*$_q$-C_q), 132.1 (Ph-*C*$_q$-CH_2-O), 128.5 (2 × Ar-C), 128.4 (2 × Ar-C), 128.3 (2 × Ar-C), 128.1 (Ph-C), 128.0 (2 × Ar-C), 127.4 (2 × Ar-C), 125.8 (Ph-C), 113.9 (2 × Ar-C), 76.1 (C_q-O), 66.8 (O-CH_2-Ph), 62.8 (O-*C*H$_2$$CH_2$), 60.7 (br, NCH_2), 59.4 (br, NCH_2), 55.3 (OCH_3), 32.2 (CH_2*C*H_2-Ph), 31.3 (O-CH_2*C*H_2); HRMS (ES-ToF) *m/z* Calculated for $C_{27}H_{30}NO_4$ [M+H]: 432.2175; Found: 432.2177.

Benzyl 3-(cyclopentylmethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24c)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and cyclopentanemethanol (0.27 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (6:3:1 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(cyclopentylmethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24c** as a colourless gum (166 mg, 84%). R_f = 0.54 (50% Et_2O/hexane); IR (film)/cm^{-1} 2951, 1711 (C=O), 1611, 1515, 1416, 1354, 1247, 1177, 1102, 1031, 831, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7 H, 7 × Ar-H), 6.94–6.90 (m, 2 H, 2 × Ar-H), 5.13 (s, 2 H, CH_2-Ph), 4.24 (br, s, 4 H, CH_2NCH_2), 3.83 (s, 3 H, OCH_3), 2.96 (d, *J* = 6.9 Hz, 2 H, O-C*H*$_2$CH), 2.08 (hept, *J* = 7.4 Hz, 1 H, O-CH_2*CH*), 1.75–1.67 (m, 2 H, CH_2), 1.57–1.47 (m, 4 H, 2 × CH_2), 1.20–1.12 (m, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-*C*$_q$OMe), 156.7 (C=O), 136.6 (Ar-*C*$_q$-C_q), 132.3 (Ph-C_q), 128.5 (2 × Ar-C), 128.01 (Ph-C), 127.94 (2 × Ar-C), 127.4 (2 × Ar-C), 113.9 (2 × Ar-C), 75.9 (C_q-O), 68.2 (O-*C*H_2-CH), 66.8 (O-CH_2-Ph), 60.8 (br, NCH_2), 59.3 (br, NCH_2), 55.3 (OCH_3), 39.5 (CH), 29.6 (2 × CH_2), 25.3 (2 × CH_2); HRMS (ES-ToF) *m/z* calculated for $C_{24}H_{30}NO_4$ [M+H]: 396.2175; Found: 396.2171.

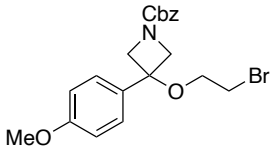
Benzyl 3-(dodecyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24d)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and 1-dodecanol (466 mg, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (7:2.25:0.75 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(dodecyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24d** as a colourless oil (209 mg, 84%). R_f = 0.60 (50% Et_2O/hexane); IR (film)/cm^{-1} 2925, 2849, 1714 (C=O), 1607, 1515, 1418, 1249, 1170, 1105, 1355, 831; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7 H, 7 × Ar-H), 6.94–6.90 (m, 2 H, 2 × Ar-H), 5.12 (s, 2 H, O-CH_2-Ph), 4.24 (br, s, 4 H, CH_2NCH_2), 3.83 (s, 3 H, OCH_3), 3.08 (t, *J* = 6.6 Hz, 2 H, O-C*H*$_2$$CH_2$), 1.52 (tt, *J* = 6.6, 6.6 Hz, 2 H, O-CH_2*CH*$_2$), 1.32–1.22 (m, 18 H, 9 × CH_2), 0.90–0.87 (m, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-*C*$_q$OMe), 156.7 (C=O), 136.6 (Ph-C_q), 132.3 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-C), 128.01

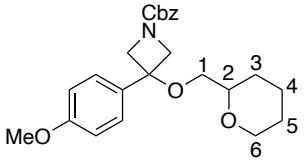
(Ph-C), 127.95 (2 × Ar-C), 127.3 (2 × Ar-C), 113.9 (2 × Ar-C), 75.9 (C_q-O), 66.8 (O-CH_2-Ph), 63.9 (O-*C*H_2-CH_2), 60.9 (br, NCH_2), 59.4 (br, NCH_2), 55.3 (OCH_3), 31.9 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.62 (CH_2), 29.58 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ES-ToF) *m/z* calculated for $C_{30}H_{44}NO_4$ [M+H]: 482.3270; Found: 482.3268.

Benzyl 3-(2-bromoethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24e)



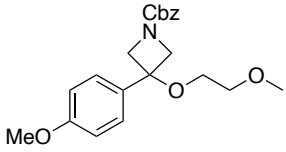
Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and 2-bromoethanol (0.18 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (40–70% Et_2O/pentane) afforded benzyl 3-(2-bromoethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24e** as a colourless oil (101 mg, 48%). R_f = 0.49 (50% Et_2O/hexane); IR (film)/cm^{-1} 2954, 2880, 2839, 1709 (C=O), 1611, 1583, 1515, 1420, 1356, 1309, 1249, 1105, 1177, 1144, 1028, 832, 764, 698, 610, 571; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 7 H, 7 × Ar-H), 6.86–6.82 (m, 2 H, 2 × Ar-H), 5.04 (s, 2 H, O-CH_2-Ph), 4.19 (br, s, 4 H, CH_2NCH_2), 3.74 (s, 3 H, OCH_3), 3.33–3.27 (m, 4 H, 2 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-C_qOMe), 156.6 (C=O), 136.5 (Ph-C_q), 131.2 (Ar-C_q-C_q), 128.5 (2 × Ar-C), 128.1 (Ph-C), 128.0 (2 × Ar-C), 127.5 (2 × Ar-C), 114.1 (2 × Ar-C), 76.6 (C_q-O), 66.8 (O-CH_2-Ph), 64.2 (O-*C*H_2CH_2), 60.6 (br, NCH_2), 59.3 (br, NCH_2), 55.3 (OCH_3), 30.3 (CH_2-Br); HRMS (ES-ToF) *m/z* calculated for $C_{20}H_{23}NO_4{}^{79}Br$ [M+H]:420.0810; Found: 420.0802.

Benzyl 3-(4-methoxyphenyl)-3-((tetrahydro-2 H-pyran-2-yl)methoxy)azetidine-1-carboxylate (24f)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and (tetrahydro-2 H-pyran-2-yl)methanol (0.28 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (7:2.25:0.75 to 6:3:1 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(4-methoxyphenyl)-3-((tetrahydro-2 H-pyran-2-yl)methoxy)azetidine-1-carboxylate **24f** as a colourless gum (90 mg, 44%). R_f = 0.23 (50% Et_2O/hexane); IR (film)/cm^{-1} 2931, 2856, 1712 (C=O), 1620, 1579, 1515, 1355, 1253, 1171, 1095, 1051, 831, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 7 H, 7 × Ar-H), 6.93–6.90 (m, 2 H, 2 × Ar-H), 5.12 (s, 2 H, CH_2-Ph), 4.31–4.25 (m, 4 H, CH_2NCH_2), 4.02–3.99 (m, 1 H, $CH_{(6)}$), 3.82 (s, 3 H, OCH_3), 3.47–3.41 (m, 2 H, $CH_{(6)}$, $CH_{(2)}$), 3.12 (dd, *J* = 9.9, 6.3 Hz, 1 H, $CH_{(1)}$), 3.03 (dd, *J* = 9.9, 3.9 Hz, 1 H, $CH_{(1)}$), 1.85–1.81 (m, 1 H, $CH_{(4)}$), 1.59–1.42 (m, 4 H, $CH_{(4)}$, $CH_{2(5)}$, $CH_{(3)}$), 1.29–1.20 (m, 1 H, $CH_{(3)}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_q-OMe), 156.6 (C=O), 136.6 (Ar-C_q-C_q), 131.8 (Ph-C_q), 128.4 (2 × Ar-C), 128.00 (Ph-C), 127.96 (2 × Ar-C), 127.5 (2 × Ar-C), 114.0 (2 × Ar-C), 76.5 ($CH_{(2)}$), 76.2 (C_q-O), 68.5 ($CH_{2(6)}$), 67.8 ($CH_{2(1)}$), 66.7 (O-CH_2-Ph), 60.8 (br, NCH_2), 59.5 (br, NCH_2), 55.3 (OCH_3), 28.31 ($CH_{2(3)}$), 25.8 ($CH_{2(5)}$), 23.0 ($CH_{2(4)}$); HRMS (ES-ToF) *m/z* calculated for $C_{24}H_{30}NO_5$ [M+H]:412.2124; Found: 412.2126.

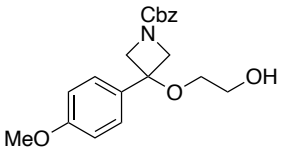
Benzyl 3-(2-methoxyethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24g)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and 2-methoxyethanol (0.20 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (40–60% Et_2O/pentane) afforded benzyl 3-(2-methoxyethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24g** as a colourless oil (97 mg, 52%). R_f = 0.17 (50% Et_2O/hexane); IR (film)/cm^{-1} 2921, 2877, 1709 (C=O), 1611, 1579, 1519, 1452, 1420, 1353, 1252, 1175, 1104, 1016, 832, 708, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 7 H, 7 × Ar-H), 6.94–6.90 (m, 2 H, 2 × Ar-H), 5.12 (s, 2 H, O-CH_2-Ph), 4.31–4.26 (m, 4 H, CH_2NCH_2), 3.83 (s, 3 H, OCH_3), 3.50–3.48 (m, 2 H, C*H*$_2$-OCH_3), 3.36 (s, 3 H, CH_2-OC*H*$_3$), 3.28–3.26 (m, 2 H, C*H*$_2CH_2$-OCH_3);

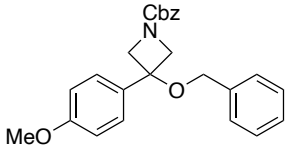
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (Ar-C_qOMe), 156.6 (C=O), 136.5 (Ph-C_q), 131.7 (Ar-C_q-C_q), 128.4 (2 × Ar-C), 128.01 (Ph-C), 127.96 (2 × Ar-C), 127.5 (2 × Ar-C), 114.0 (2 × Ar-C), 76.3 (C_q-O), 71.6 (CH_2-OCH_3), 66.8 (O-CH_2-Ph), 63.3 (CH_2CH_2-OCH_3), 60.8 (br, NCH_2), 59.4 (br, NCH_2), 59.1 (CH_2-OCH_3), 55.3 (Ar-OCH_3); HRMS (ES-ToF) *m/z* calculated for $C_{21}H_{26}NO_5$ [M+H]:372.1811; Found: 372.1815.

Benzyl 3-(2-hydroxyethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24h)



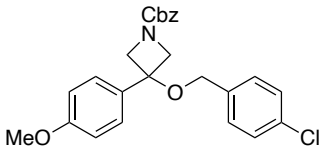
Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and ethylene glycol (0.14 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (7:2.25:0.75 to 6:3:1 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(2-hydroxyethoxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24h** as a white solid (141 mg, 79%). R_f = 0.59 (50% Et_2O/hexane); mp = 88–91 °C; IR (film)/cm^{-1} 3332 (OH), 2944, 2872, 2834, 1714 (C=O), 1610, 1511, 1455, 1246, 1176, 1027, 979, 832, 698, 447; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 7 H, 7 × Ar-H), 6.93 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-H), 5.13 (s, 2 H, O-CH_2-Ph), 4.28 (d, *J* = 4.6 Hz, 4 H, CH_2-N-CH_2), 3.83 (s, 3 H, OCH_3), 3.69 (t, *J* = 5.2 Hz, 2 H,), 3.24 (t, *J* = 5.2 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 156.6 (C=O), 136.4 (Ar-C_q), 131.4 (Ar-C_q), 128.4 (2 × Ar-C), 128.0 (Ph-C), 128.0 (2 × Ar-C), 127.4 (2 × Ar-C), 114.0 (2 × Ar-C), 76.3 (C_q-O), 66.8 (O-CH_2-Ph), 65.1 (OCH_3), 60.4 (br, NCH_2), 59.4 (br, NCH_2), 61.7 (OCH_2), 55.3 (OCH_2); HRMS (ES-ToF) *m/z* calculated for $C_{20}H_{23}NO_5Na$ $[M+Na]^+$: 380.1474; Found: 380.1479.

Benzyl 3-(benzyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24i)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and benzyl alcohol (0.26 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (6:3:1 pentane/CH_2Cl_2/Et_2O) afforded a mixture of benzyl 3-(benzyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24i** and benzyl alcohol, that after a repurification by flash column chromatography (6:3:1 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-(benzyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24i** as a white solid (127 mg, 63%). R_f = 0.38 (50% Et_2O/hexane); mp = 74–76 °C; IR (film)/cm^{-1} 2957, 1715 (C=O),1610, 1582, 1516, 1455, 1420, 1360, 1246, 1179, 1106, 1039, 833, 743, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 12 H, 12 × Ar-H), 6.98–6.95 (m, 2 H, 2 × Ar-H), 5.13 (s, 2 H, O-CH_2-Ph), 4.34 (br, s, 4 H, CH_2NCH_2), 4.18 (s, 2 H, O-CH_2), 3.85 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar-C_qOMe), 156.6 (C=O), 137.6 (Ph-C_q), 136.5 (Ph-C_q), 131.7 (Ar-C_q-C_q), 128.5 (2 × Ar-C), 128.4 (2 × Ar-C), 128.04 (Ph-C), 127.97 (2 × Ar-C), 127.7 (Ph-C), 127.6 (2 × Ar-C), 127.5 (2 × Ar-C), 114.1 (2 × Ar-C), 76.6 (C_q-O), 66.8 (O-CH_2-Ph), 66.2 (O-CH_2-Ph), 60.8 (br, NCH_2), 59.3 (br, NCH_2), 55.3 (OCH_3); HRMS (ES-ToF) *m/z* calculated for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1862; Found: 404.1856.

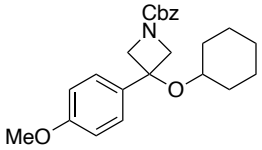
Benzyl 3-((4-chlorobenzyl)oxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24j)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and 4-chlorobenzyl alcohol (356 mg, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.0 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* *vacuo* using a rotary evaporator. Purification by flash column chromatography (7:2.25:0.75 to 6:3:1 pentane/CH_2Cl_2/Et_2O) afforded benzyl 3-((4-chlorobenzyl)oxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24j** as a colourless gum (144 mg, 66%). R_f = 0.59 (50% Et_2O/hexane); IR (film)/cm^{-1} 2953, 2881, 1709 (C=O), 1612, 1579, 1515, 1417, 1355, 1249, 1171, 1103, 808, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 9 H, 9 × Ar-H), 7.22–7.19 (m, 2 H, 2

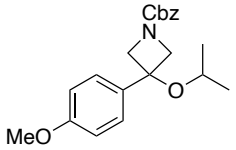
× Ar-H), 6.98–6.94 (m, 2 H, 2 × Ar-H), 5.13 (s, 2 H, O-CH_2-Ph), 4.33 (br, s, 4 H, CH_2NCH_2), 4.14 (s, 2 H, O-CH_2-Ph), 3.85 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-C_qOMe), 156.6 (C=O), 136.5 (Ar-C_q-CH_2), 136.1 (Ar-C_q-CH_2), 133.4 (Ar-C_q-Cl), 131.4 (Ar-C_q-C_q), 128.8 (2 × Ar-C), 128.54 (2 × Ar-C), 128.47 (2 × Ar-C), 128.07 (Ph-C), 127.99 (2 × Ar-C), 127.5 (2 × Ar-C), 114.1 (2 × Ar-C), 76.8 (C_q-O), 66.9 (O-CH_2-Ph), 65.4 (O-CH_2-Ph), 60.8 (br, NCH_2), 59.3 (br, NCH_2), 55.3 (OCH_3); HRMS (ES-ToF) *m/z* calculated for $C_{25}H_{25}NO_4{}^{35}Cl$ $[M+H]^+$:438.1472; Found: 438.1454.

Benzyl 3-(cyclohexyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate (24b)



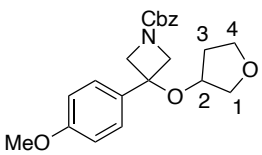
Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and cyclohexanol (0.26 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.66 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (30–50% Et_2O/hexane) afforded benzyl 3-(cyclohexyloxy)-3-(4-methoxyphenyl)azetidine-1-carboxylate **24b** as a colourless gum (92 mg, 47%). R_f = 0.50 (50% Et_2O/hexane); IR (film)/cm^{-1} 2932, 2855, 1707 (C=O), 1611, 1583, 1514, 1449, 1413, 1353, 1304, 1245, 1176, 1113, 1101, 1069, 1026, 965, 924, 866, 831, 765, 733, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7 H, 7 × Ar-H), 6.93–6.89 (m, 2 H, 2 × Ar-H), 5.11 (s, 2 H, O-CH_2-Ph), 4.31–4.25 (m, 4 H, CH_2NCH_2), 3.84 (s, 3 H, OCH_3), 3.11 (tt, $J_{ax,ax}$ = 9.7 Hz, $J_{ax,eq}$ = 4.0 Hz, 1 H, CH), 1.64–1.52 (m, 4 H, 4 × C*H*H), 1.47–1.45 (m, 2 H, CH_2), 1.26–1.18 (m, 2 H, CH_2), 1.13–1.05 (m, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_qOMe), 156.6 (C=O), 136.6 (Ph-C_q), 133.2 (Ar-C_q-C_q), 128.4 (2 × Ar-C), 128.00 (Ph-C), 127.95 (2 × Ar-C), 127.8 (2 × Ar-C), 113.8 (2 × Ar-C), 75.5 (C_q-O), 73.3 (O-CH), 66.7 (O-CH_2-Ph), 61.8 (br, NCH_2), 60.5 (br, NCH_2), 55.3 (OCH_3), 33.7 (2 × CH_2), 25.4 (CH_2), 24.3 (2 × CH_2); FTMS (+ p NSI) *m/z* calculated for $C_{24}H_{30}NO_4{}^+$ $[M+H]^+$: 396.2169; Found: 396.2169.

Benzyl 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate (24k)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and isopropanol (0.19 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.66 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (30% Et_2O/pentane) afforded benzyl 3-(4-methoxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate **24k** as a white solid (101 mg, 57%). R_f = 0.21 (30% Et_2O/pentane); mp = 68–72 °C; IR (film)/cm^{-1} 2968, 1705 (C=O), 1610, 1512, 1412, 1352, 1304, 1246, 1175, 1097, 1026, 961, 831, 759, 697, 568; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.5 Hz, 4H, 4 × Ar-H), 7.33–7.27 (m, 3 H, Ar-H), 6.95–6.87 (m, 2 H, Ar-H), 5.10 (s, 2 H, O-CH_2), 4.41–4.22 (m, 4H, CH_2-N-CH_2), 3.82 (s, 3 H, OCH_3), 3.46 (hept, *J* = 6.2 Hz, 1H, OCH), 0.97 (d, *J* = 6.2 Hz, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (Ar-C_q-OCH_3), 156.5 (C=O), 136.5 (Ar-C_q), 132.8 (Ar-C_q), 128.4 (2 × Ar-C), 128.0 (Ph-C), 127.9 (2 × Ar-C), 127.8 (2 × Ar-C), 113.8 (2 × Ar-C), 75.5 (Ar-C_q-O), 67.2 (OCH), 66.7 (OCH_2), 61.7 (br, NCH_2), 60.5 (br, NCH_2), 55.2 (OCH_3), 23.5 (2 × CH_3); HRMS (ES-ToF) *m/z* calculated for $C_{21}H_{26}NO_4$ $[M+H]^+$:356.1862; Found: 356.1877.

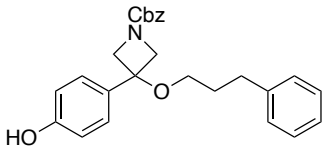
Benzyl 3-(4-methoxyphenyl)-3-((tetrahydrofuran-3-yl)oxy)azetidine-1-carboxylate (24l)



Benzyl 3-hydroxy-3-(4-methoxyphenyl)azetidine-1-carboxylate **22** (157 mg, 0.50 mmol, 1.0 equiv) and methyl (S)-3-hydroxytetrahydrofuran (0.20 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.66 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by reversed phase flash column chromatography (0–10% CH_3CN/H_2O) afforded benzyl 3-(4-methoxyphenyl)-3-((tetrahydrofuran-3-yl)oxy)azetidine-1-carboxylate **24l** as a white solid (94 mg, 49%). R_f = 0.22 (50% Et_2O/hexane); mp = 58–60 °C; IR (film)/cm^{-1} 2963, 2851, 1714 (C=O), 1638, 1617, 1513, 1412, 1380, 1355, 1247, 1175, 1132, 1103, 823, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 5 H, 5 × Ar-H), 7.20–7.16 (m, 2 H, 2 × Ar-H), 6.86–

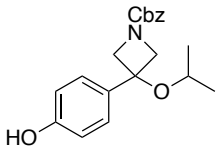
6.82 (m, 2 H, 2 × Ar-H), 5.03 (s, 2 H, O-CH_2-Ph), 4.27–4.23 (m, 2 H, C*H*HNC*H*H), 4.17 (dd, *J* = 8.9, 5.5 Hz, 2 H, CH*H*NCH*H*), 3.86 (ddd, *J* = 9.0, 5.2, 2.8 Hz, 1 H, $CH_{(2)}$), 3.80–3.73 (s, 4 H, C*H*$H_{(4)}$ + OCH_3), 3.60 (td, *J* = 8.2, 5.3 Hz, 1 H, CH*H*$_{(4)}$), 3.43 (br, s, 1 H, C*H*$H_{(1)}$), 3.34 (br, s, 1 H, CH*H*$_{(1)}$), 1.75–1.63 (m, 2 H, $CH_{2(3)}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (Ar-*C*$_q$OMe), 156.5 (C=O), 136.5 (Ph-C_q), 132.3 (Ar-*C*$_q$-C_q), 128.5 (2 × Ar-C), 128.1 (Ph-C), 128.0 (2 × Ar-C), 127.8 (2 × Ar-C), 114.1 (2 × Ar-C), 76.4 (C_q-O), 74.6 ($CH_{(2)}$), 73.2 ($CH_{2(1)}$), 66.9 ($CH_{2(4)}$), 66.8 (O-CH_2-Ph), 61.4 (br, NCH_2), 60.1 (br, NCH_2), 55.3 (OCH_3), 33.7 ($CH_{2(3)}$); HRMS (ES-ToF) *m/z* calculated for $C_{22}H_{26}NO_5$ $[M+H]^+$: 384.1811; Found: 384.1802.

Benzyl 3-(4-hydroxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate (25a)



Benzyl 3-hydroxy-3-(4-((triisopropylsilyl)oxy)phenyl)azetidine-1-carboxylate **23** (228 mg, 0.50 mmol, 1.0 equiv) and 3-phenyl-1-propanol (0.34 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine (14.0 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.66 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using rotary evaporator. Purification by flash column chromatography (20–30% Et_2O/pentane) afforded benzyl 3-(4-hydroxyphenyl)-3-(3-phenylpropoxy)azetidine-1-carboxylate **25a** as a colourless oil (166.2 mg, 80%). R_f = 0.11 (40% Et_2O/pentane); IR (film)/cm^{-1} 3350 (OH), 3027, 2946, 1676 (C=O), 1612, 1515, 1428, 1355, 1266, 1170, 1103, 1063, 907, 834, 727, 695, 517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H, Ar-H), 7.29–7.22 (m, 2 H, 2 × Ar-H), 7.21–7.10 (m, 5H, 5 × Ar-H), 6.94 (s, 1H, OH), 6.88–6.82 (m, 2 H, 2 × Ar-H), 5.17 (s, 2 H, O-CH_2-Ph), 4.26 (s, 4H, 2 × CH*H*NCH*H*), 3.10 (t, *J* = 6.2 Hz, 2 H, OC*H*$_2$$CH_2$), 2.72–2.58 (m, 2 H, Ph-CH_2), 1.85 (tt, *J* = 8.7, 6.2 Hz, 2 H, O-CH_2C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (Ar-C_qOH), 156.1 (C=O), 141.6 (Ar-C_q), 136.2 (Ar-C_q), 131.3 (Ar-C_q), 128.5 (2 × Ar-C), 128.4 (2 × Ar-C), 128.3 (2 × Ar-C), 128.2 (Ph-C), 128.0 (2 × Ar-C), 127.6(2 × Ar-C), 125.8 (Ph-C), 115.5 (2 × Ar-C), 76.0 (C_q-O), 67.1 (O-CH_2-Ph), 62.8 (O-*C*$H_2$$CH_2$), 60.4 ($NCH_2$), 59.6 ($NCH_2$), 32.2 (Ph-$CH_2$), 31.2 (O-$CH_2$*C*$H_2$); HRMS (ES-ToF) *m/z* calculated for $C_{26}H_{28}NO_4$ [M+H]: 418.2018; Found: 418.2010.

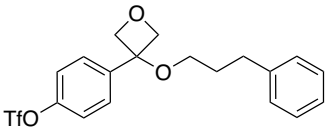
Benzyl 3-(4-hydroxyphenyl)-3-isopropoxyazetidine-1-carboxylate (25l)



Benzyl 3-hydroxy-3-(4-((triisopropylsilyl)oxy)phenNyl)azetidine-1-carboxylate **23** (228 mg, 0.50 mmol, 1.0 equiv) and isopropanol (0.19 mL, 2.50 mmol, 5.0 equiv) were added to a solution of bis(trifluoromethanesulfonyl)amine(14 mg, 0.05 mmol, 0.1 equiv) in anhydrous CH_3CN (1.66 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* using rotary evaporator. Purification by flash column chromatography (40% Et_2O/pentane) afforded benzyl 3-(4-hydroxyphenyl)-3-isopropoxyazetidine-1-carboxylate **25l** as a colourless oil (76.1 mg, 45%). R_f = 0.11 (40% Et_2O/pentane); IR (film)/cm^{-1} 3470 (OH), 3030, 2970, 1676 (C=O), 1613, 1515, 1428, 1355, 1265, 1171, 1146, 1098, 1027, 959, 909, 834, 729, 696, 520; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 5H, Ar-H), 7.17 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.83 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.12 (s, 2 H, O-CH_2), 4.33 (br, 2 H, C*H*H-N-C*H*H), 4.26 (d, *J* = 9.1 Hz, 2 H, CH*H*-N-CH*H*), 3.44 (hept, *J* = 6.1 Hz, 1H, O-CH), 0.95 (d, *J* = 6.2 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (Ar-C_qOH), 156.3 (C=O), 136.3 (Ar-C_q), 132.0 (Ar-C_q), 128.6 (2 × Ar-C), 128.2 (Ph-C), 128.1 (2 × Ar-C), 128.0 (2 × Ar-C) 115.5 (2 × Ar-C), 75.6 (C_q-O), 62.0 (NCH_2), 58.5 (NCH_2), 67.3 (O-CH_2), 67.2 (O-CH), 23.5 (2 × CH_3); HRMS (ES-ToF) *m/z* calculated for $C_{20}H_{24}NO_4$ [M+H]:342.1705; Found: 342.1693.

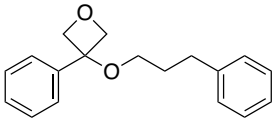
Synthesis of electron-poor oxetane ethers by reaction of triflate 26a

4-(3-(3-Phenylpropoxy)oxetan-3-yl)phenyl trifluoromethanesulfonate (26a)



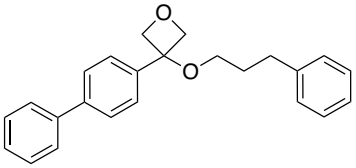
Triffic anhydride (0.09 mL, 0.275 mmol, 1.1 equiv) was slowly added to a solution of 4-(3-(3-phenylpropoxy)oxetan-3-yl)phenol **16a** (142.2 mg, 0.25 mmol, 1.0 equiv) and pyridine (0.081 mL, 0.5 mmol, 2 equiv) in anhydrous CH_2Cl_2 (1.0 mL, 0.25 M) at 0 °C. The reaction mixture was warmed up to 25 °C and stirred for 3 h at this temperature. sat. aq. $NaHCO_3$ (10 mL) was added to the reaction mixture and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 4-(3-(3-phenylpropoxy)oxetan-3-yl)phenyl trifluoromethanesulfonate **26a** (141.6 mg, 26%) as colourless liquid. R_f = 0.51 (20% EtOAc/pentane); IR (film)/cm^{-1} 2949, 2877, 1499, 1424 (S=O), 1249, 1212, 1140, 985, 888, 843,747, 700, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2 H, 2 × Ar-H), 7.35–7.27 (m, 4 H, 4 × Ar-H), 7.24–7.12 (m, 3 H, 3 × Ar-H), 4.95 (d, *J* = 6.9 Hz, 2 H, C*H*H-O-C*H*H), 4.74 (d, *J* = 6.9 Hz, 2 H, CH*H*-O-CH*H*), 3.23 (t, *J* = 6.2 Hz, 2 H, OC*H*$_2$CH$_2$), 2.76 (t, *J* = 7.4 Hz, 2 H, Ph-CH$_2$), 1.97 (tt, *J* = 7.4, 6.2 Hz, 2 H, O-CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (Ar-C$_q$), 141.9 (Ar-C$_q$), 141.6 (Ar-C$_q$), 128.9 (4 × Ar-C), 128.1 (2 × Ar-C), 126.4 (Ph-C), 122.1 (2 × Ar-C), 81.5 (CH$_2$-O-CH$_2$), 80.0 (C$_q$-O), 63.7 (O-*C*H$_2$CH$_2$), 32.6 (Ph-CH$_2$), 31.7 (O-CH$_2$*C*H$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.80; HRMS (ES-ToF) *m/z* Calculated for $C_{19}H_{18}O_5SF_3^-$ [M–H]$^-$: 415.0833; Found: 415.0827.

3-Phenyl-3-(3-phenylpropoxy)oxetane (27a)



Triethylamine (83.6 µL, 0.6 mmol, 3.0 equiv) and formic acid (15.0 µL, 0.4 mmol, 2.0 equiv) were added sequentially to a solution of triflate oxetane ether **26a** (83.3 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 equiv) and 1,1'-bis(diphenylphosphino)ferrocene (dppf; 5.6 mg, 0.01 mmol, 0.05 equiv) in DMF (2.0 mL, 0.5 M). The reaction mixture was stirred at 60 °C for 2 h and then sat. aq. NaCl (15 mL) was added followed by Et_2O (15 mL). The layers were separated and the aqueous portion was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* using a rotary evaporator. Purification by flash column chromatography (10% Et_2O /pentane) afforded 3-phenyl-3-(3-phenylpropoxy)oxetane **27a** (29.5 mg, 55%) as a colourless oil. R_f = 0.51 (15% EtOAc/pentane); IR (film)/cm^{-1} 3026, 2943, 2871, 1601, 1494, 1450, 1274, 1175, 1135, 1075, 1031, 752, 691, 491; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.38 (m, 4H, Ph-H), 7.38–7.31 (m, 1H, Ph-H), 7.31–7.23 (m, 2 H, Ph-H), 7.22–7.13 (m, 3 H, Ph-H), 4.93 (d, *J* = 6.7 Hz, 2 H, C*H*H-O-C*H*H), 4.85 (d, *J* = 6.7 Hz, 2 H, CH*H*-O-CH*H*), 3.19 (t, *J* = 6.2 Hz, 2 H, O-C*H*$_2$CH$_2$), 2.72 (t, *J* = 6.7 Hz, 2 H, Ph-CH$_2$), 1.91 (tt, *J* = 6.7, 6.2 Hz, 2 H, O-CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (Ph-C$_q$), 140.2 (Ph-C$_q$), 128.6 (2 × Ph-C), 128.4 (2 × Ph-C), 128.3(2 × Ph-C), 127.9 (Ph-C), 125.8 (2 × Ph-C), 125.8 (Ph-C), 81.2 (CH$_2$-O-CH$_2$), 80.1 (C$_q$-O), 63.0 (O*C*H$_2$CH$_2$), 32.2 (Ph-CH$_2$), 31.4 (O-CH$_2$*C*H$_2$); FTMS (APCI) *m/z* Calculated for $C_{18}H_{19}O_2$ [M–H]: 267.1385; Found: 267.1386.

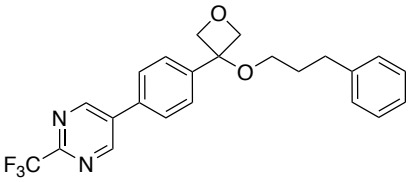
3-([1,1'-Biphenyl]-4-yl)-3-(3-phenylpropoxy)oxetane (28a)



4-(3-(3-Phenylpropoxy)oxetan-3-yl)phenyl trifluoromethanesulfonate **26a** (83.3 mg, 0.20 mmol, 1.0 equiv) and phenylboronic acid pinacol ester (61.2 mg, 0.30 mmol, 1.5 equiv) were added sequentially to a solution of palladium(II) acetate (2.2 mg, 0.01 mmol, 0.05 equiv), SPhos (8.2 mg, 0.02 mmol, 0.1 equiv), and K_3PO_4 (84.9 mg, 0.40 mmol, 2.0 equiv) in a dioxane/H_2O mixture (4:1; 2.0 mL, 0.1 M). After stirring the reaction mixture at 65 °C for 24 h, it was allowed to cool to rt and filtered through celite, eluting further with Et_2O (30 mL). The crude reaction mixture was concentrated *in vacuo* using a rotary evaporator and purification by flash column chromatography (10% EtOAc/pentane) afforded 5-(4-(3-(3-phenylpropoxy)oxetan-3-yl)phenyl)-2-(trifluoromethyl)pyrimidine **28a** (68.1 mg, 99%) as colourless oil; R_f = 0.57 (20% EtOAc/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (m, 4H, Ar-H), 7.52 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.47 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.38 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.32–7.24 (m, 2 H, Ar-H), 7.22–7.13 (m, 3 H, Ar-H), 4.97 (d, *J* = 6.6 Hz, 2 H, C*H*H-O-C*H*H), 4.88 (d, *J* = 6.6 Hz, 2 H, CH*H*-O-CH*H*), 3.24 (t, *J* = 6.2 Hz, 2 H, O-C*H*$_2$CH$_2$), 2.75 (t, *J* = 7.7 Hz, 2 H, Ph-CH$_2$), 1.95 (tt, *J* = 7.7, 6.2 Hz, 2 H, O-CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (Ar-C$_q$), 140.8 (Ar-C$_q$), 140.5 (Ar-C$_q$), 139.2 (Ar-C$_q$), 128.8 (2 × Ar-C), 128.4 (2 × Ar-C), 128.3 (2 × Ar-C), 127.5 (Ar-C), 127.4 (2 × Ar-C), 127.1 (2 × Ar-C), 126.3 (2 × Ar-C), 125.8 (Ph-C), 81.2 (CH$_2$-O-CH$_2$), 80.0

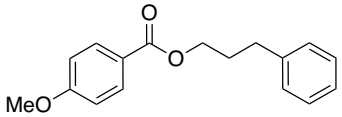
(C_q-O), 63.0 (O-*C*H_2CH$_2$), 32.2 (Ph-CH$_2$), 31.4 (O-CH$_2$*C*H$_2$); FTMS (APCI) *m/z* Calculated for $C_{18}H_{19}O_2^+$ [M–C_6H_5]$^+$: 267.1380; Found: 267.1390.

5-(4-(3-(3-Phenylpropoxy)oxetan-3-yl)phenyl)-2-(trifluoromethyl)pyrimidine (29a)



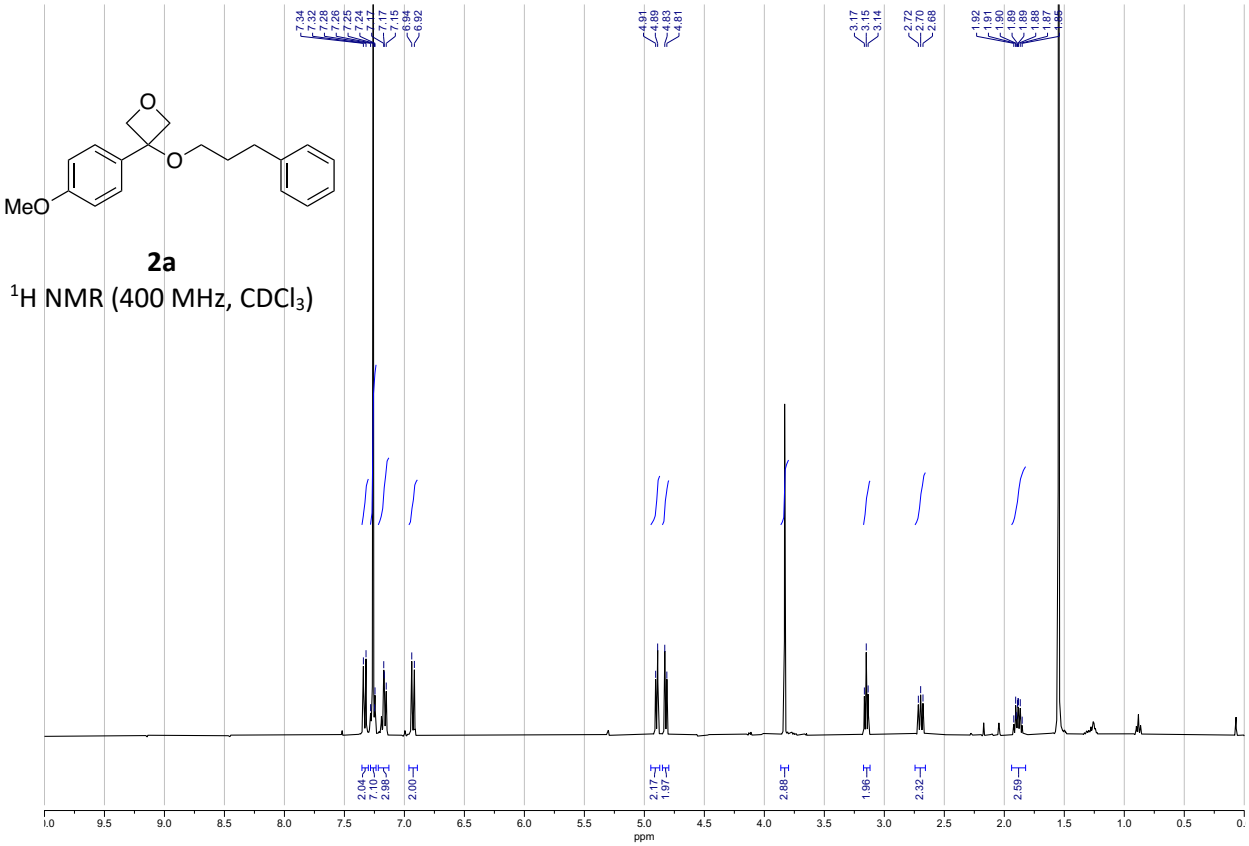
4-(3-(3-Phenylpropoxy)oxetan-3-yl)phenyl trifluoromethanesulfonate **26a** (83.3 mg, 0.20 mmol, 1.0 equiv) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyrimidine (82.2 mg, 0.30 mmol, 1.5 equiv) were added sequentially to a solution of palladium(II) acetate (2.2 mg, 0.01 mmol, 0.05 equiv), SPhos (8.2 mg, 0.02 mmol, 0.1 equiv), and K_3PO_4 (84.9 mg, 0.40 mmol, 2.0 equiv) in a dioxane/H_2O mixture (4:1; 2.0 mL, 0.1 M). After stirring the reaction mixture at 65 °C for 24 h, it was allowed to cool to rt and filtered through celite, eluting further with Et_2O (30 mL). The crude reaction mixture was concentrated *in vacuo* using a rotary evaporator and purification by flash column chromatography (20% EtOAc/pentane) afforded 5-(4-(3-(3-phenylpropoxy)oxetan-3-yl)phenyl)-2-(trifluoromethyl)pyrimidine **29a** (67.2 mg, 83%) as a yellow solid. R_f = 0.24 (20% EtOAc/pentane); mp = 91–94 °C; IR (film)/cm^{-1} 2945, 2922, 2874, 1353, 1194, 1146, 1119, 982, 837, 747, 699, 576; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 2 H, 2 × N-Ar-H), 7.67 (m, 4H, Ar-H), 7.33–7.24 (m, 2 H, Ar-H), 7.23–7.14 (m, 3 H, Ar-H), 4.99 (d, *J* = 7.1 Hz, 2 H, C*H*H-O-C*H*H), 4.82 (d, *J* = 7.1 Hz, 2 H, CH*H*-O-CH*H*), 3.25 (t, *J* = 6.2 Hz, 2 H, O-C*H*$_2$CH$_2$), 2.76 (t, *J* = 7.4 Hz, 2 H, Ph-CH$_2$), 1.97 (tt, *J* = 7.4,6.2 Hz, 2 H, O-CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (2 × N-CH), 155.5 (q, *J* = 36.5 Hz, CF_3-*C*), 142.5 (Ar-C_q), 141.5 (Ar-C_q), 135.7 (Ar-C_q), 132.5 (Ar-C_q), 128.5 (2 × Ar-C), 128.4 (2 × Ar-C), 127.7 (2 × Ar-C), 127.1 (2 × Ar-C), 126.0 (1 × Ph-C), 120.0 (q, *J* = 275.3 Hz, CF_3), 81.1 (CH$_2$-O-CH$_2$), 79.8 (Ar-C_q-O), 63.3 (O-*C*H$_2$CH$_2$), 32.2 (Ph-CH$_2$), 31.3 (O-CH$_2$*C*H$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –70.04; HRMS (ES-ToF) *m/z* Calculated for $C_{25}H_{25}N_3O_2F_3$ [M+H+MeCN]: 456.1899; Found: 456.1922.

3-Phenylpropyl 4-methoxybenzoate (30)



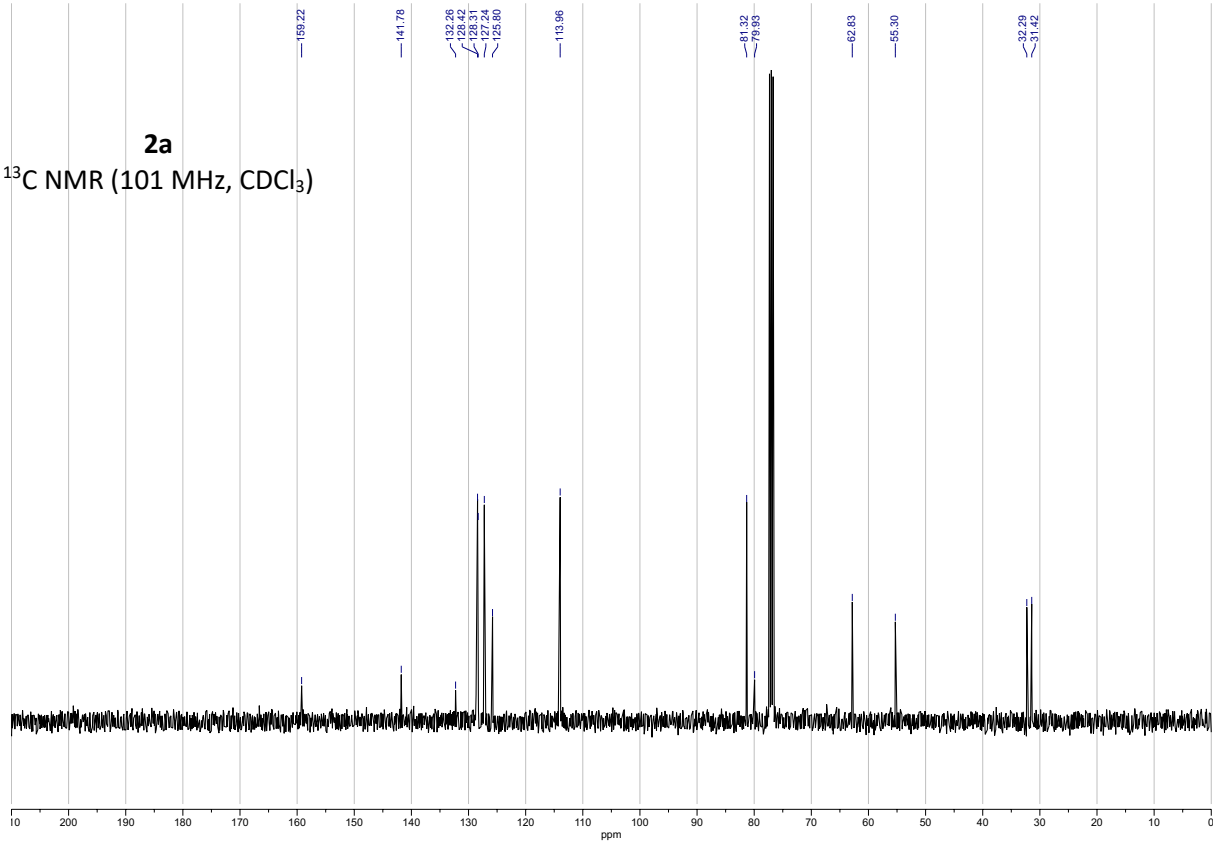
4-Methoxybenzoic acid (152.1 mg, 1.0 mmol, 1.0 equiv) was added to a solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC.HCl; 288.0 mg, 1.5 mmol, 1.5 equiv) and DMAP (24.0 mg, 0.2 mmol, 0.2 equiv) in anhydrous CH_2Cl_2 (2.0 mL, 0.5 M) at rt, followed by 3-phenyl-1-propanol (0.150 mL, 1.1 mmol, 1.1 equiv). The reaction was stirred at rt for 24 h. Distilled water (20 mL) was added to quench the reaction, then the aqueous phase 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 rotary evaporator. Purification by flash column chromatography (10% EtOAc/pentane) afforded 3-phenylpropyl 4-methoxybenzoate 30 (114 mg, 70%) as a colourless oil; R_f = 0.37 (10% EtOAc/pentane); IR (film)/cm^{-1} 2954, 1710 (C=O), 1605, 1511, 1456, 1316, 1275, 1254, 1167, 1105, 1029, 848, 771, 698, 613; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-H), 7.33–7.26 (m, 2 H, 2 × Ar-H), 7.25–7.14 (m, 3 H, 3 × Ar-H), 6.92 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-H), 4.31 (t, *J* = 6.5 Hz, 2 H, OCH$_2$), 3.87 (s, 3 H, OCH$_3$), 2.79 (t, *J* = 7.4 Hz, 2 H, Ph-CH$_2$), 2.09 (tt, *J* = 7.4, 6.5 Hz, 2 H, O-CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O), 163.3 (Ar-C_q), 141.3 (Ar-C_q), 131.6 (2 × Ar-C), 128.5 (4 × Ar-C), 126.0 (Ph-C), 122.8 (Ar-C_q), 113.6 (2 × Ar-C), 64.0 (O-CH$_2$), 55.5 (O-CH$_3$), 32.4 (Ph-CH$_2$), 30.4 (O-CH$_2$*C*H$_2$); HRMS (ES-ToF) *m/z* Calculated for $C_{17}H_{19}O_3$ [M+H]: 271.1334; Found: 271.1318.

^{1}H and ^{13}C NMR Spectra of Selected Compounds



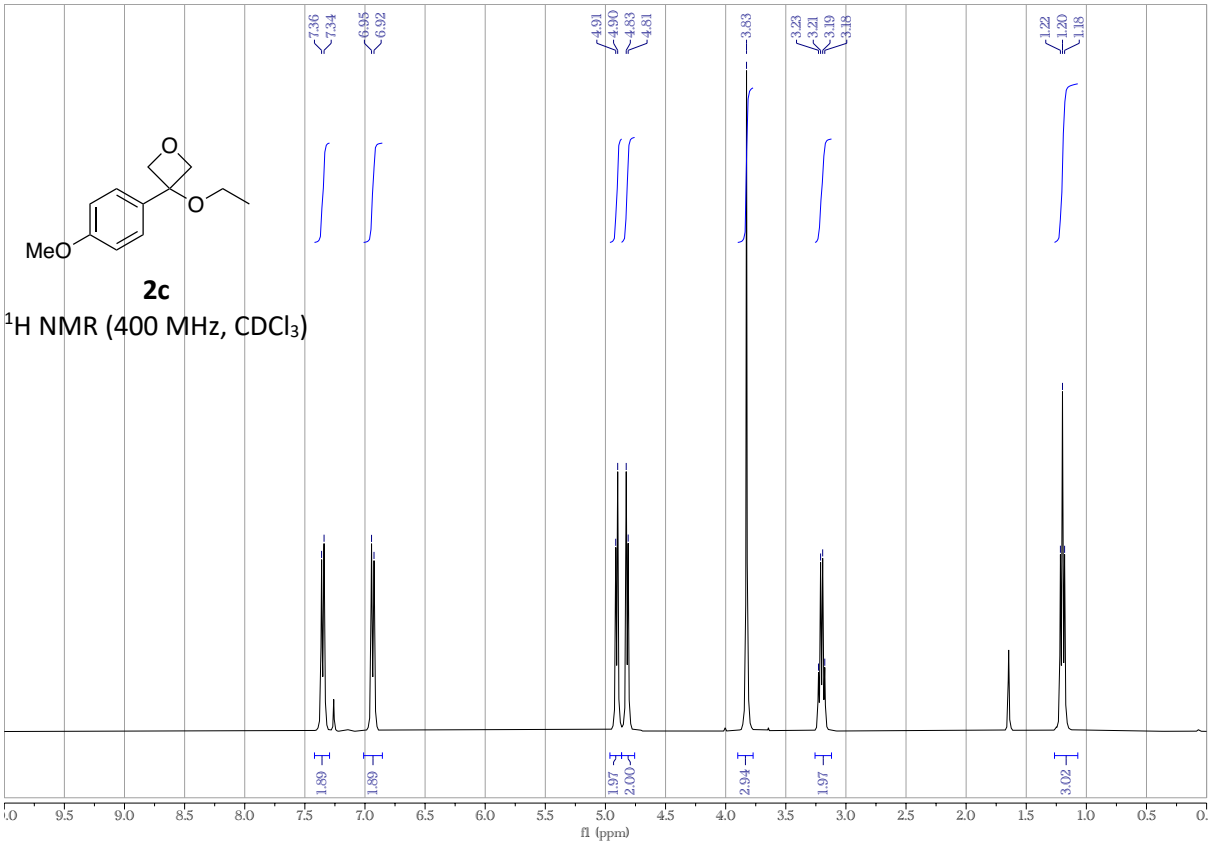
2a

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



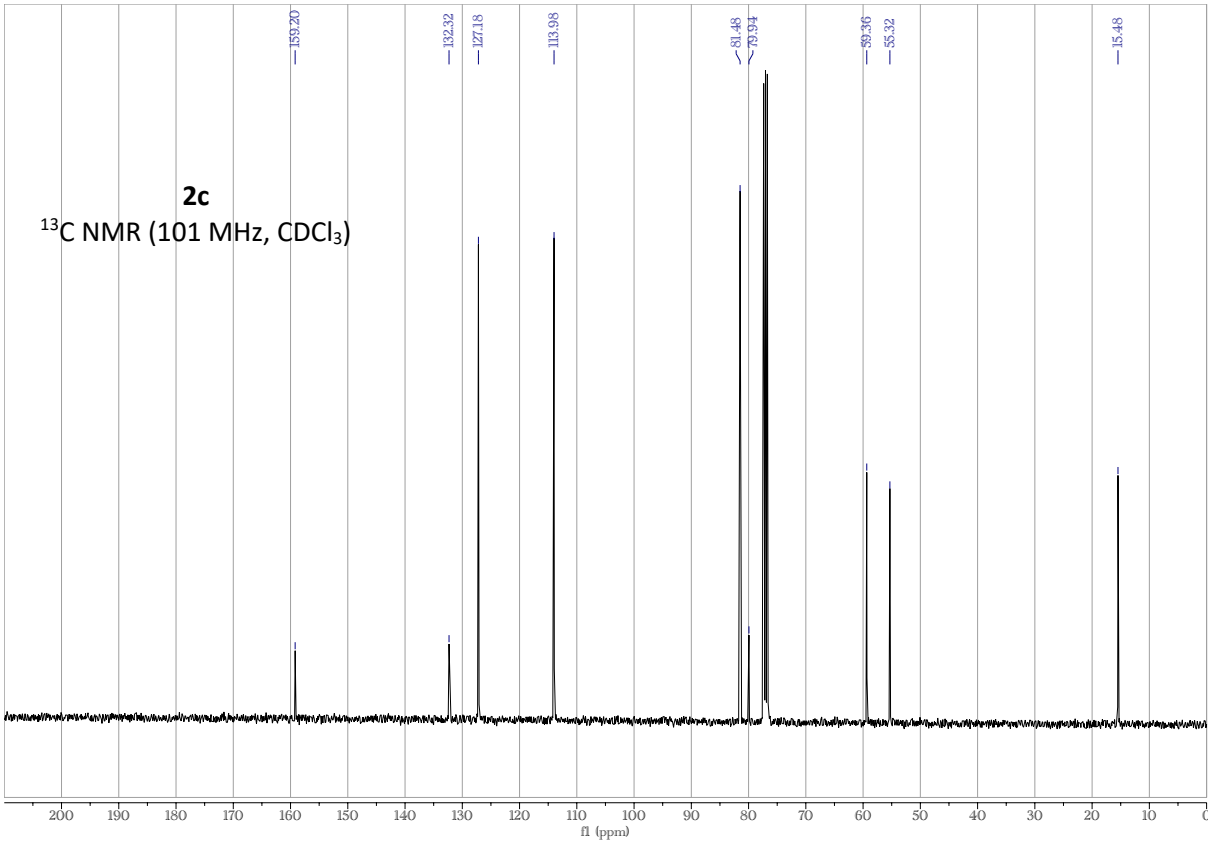
2a

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



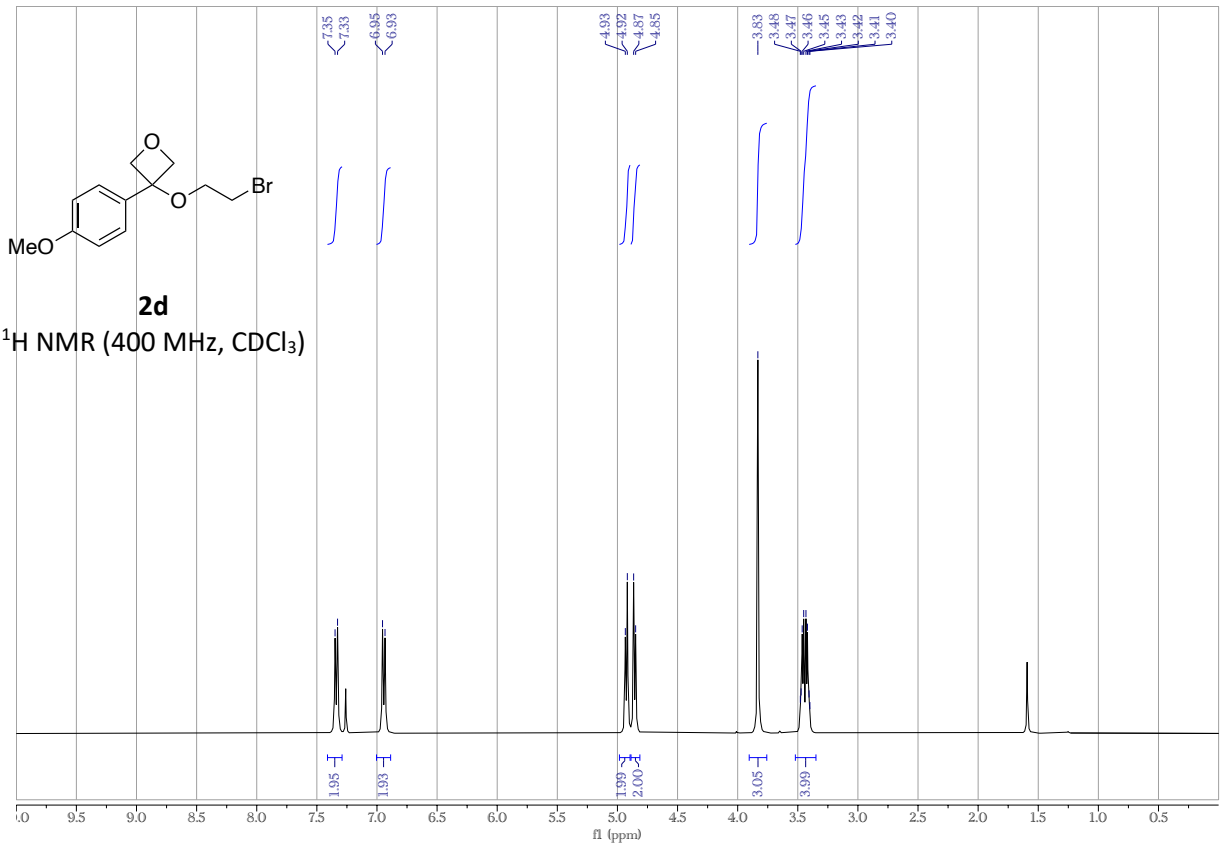
2c

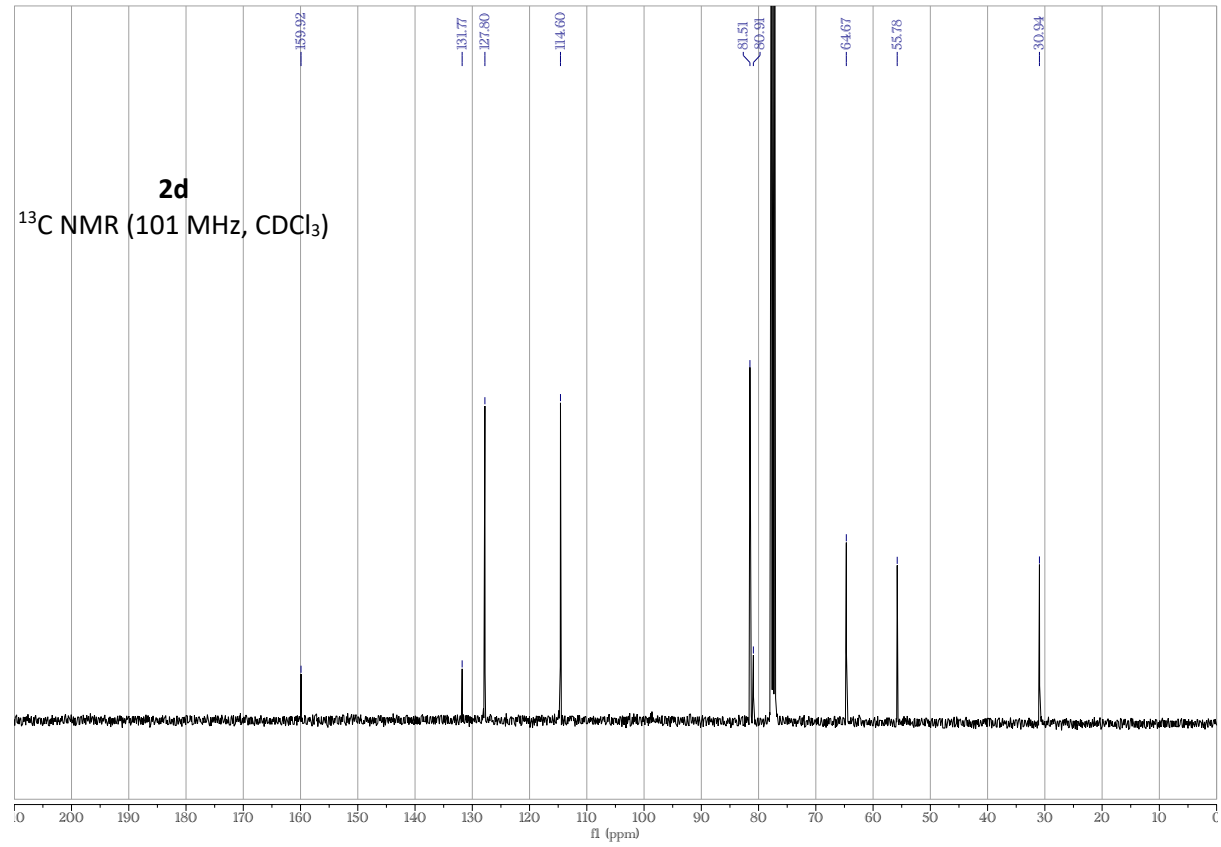
^{1}H NMR (400 MHz, $CDCl_3$)

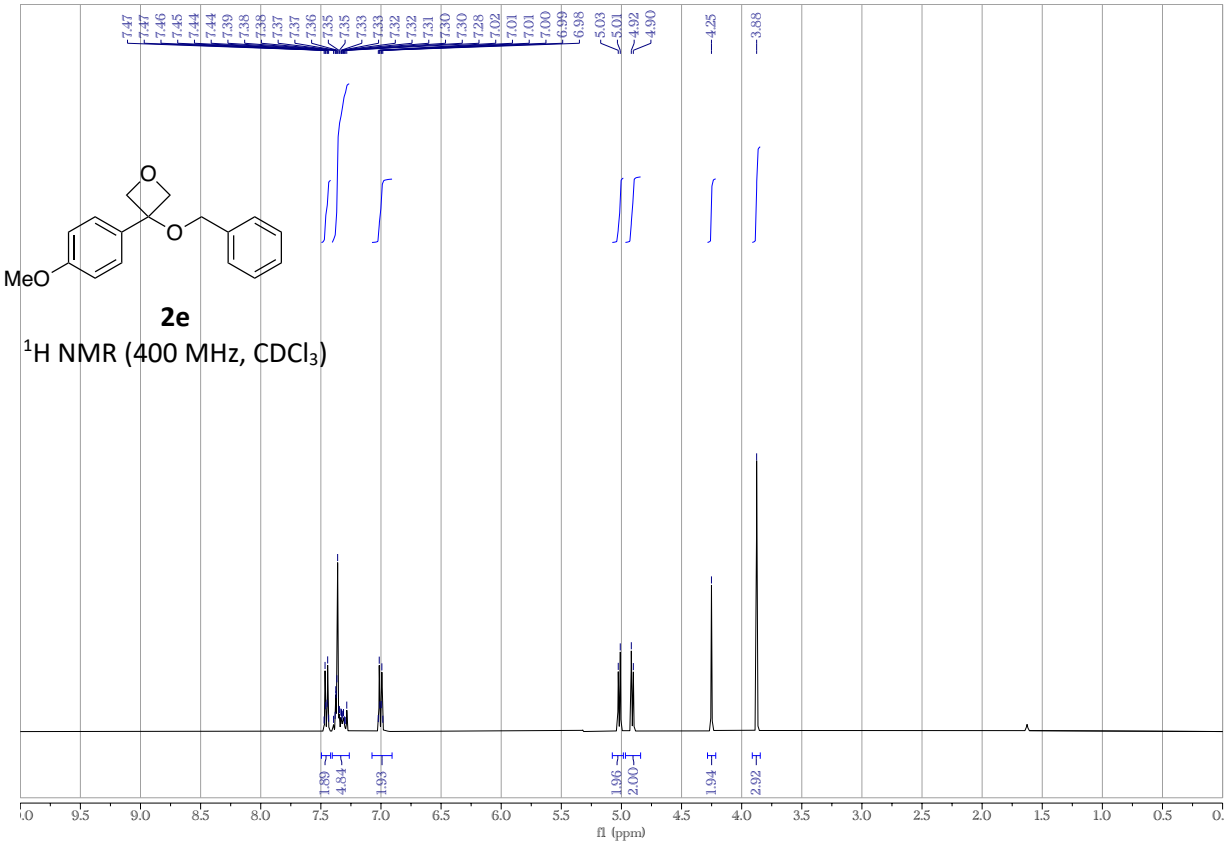


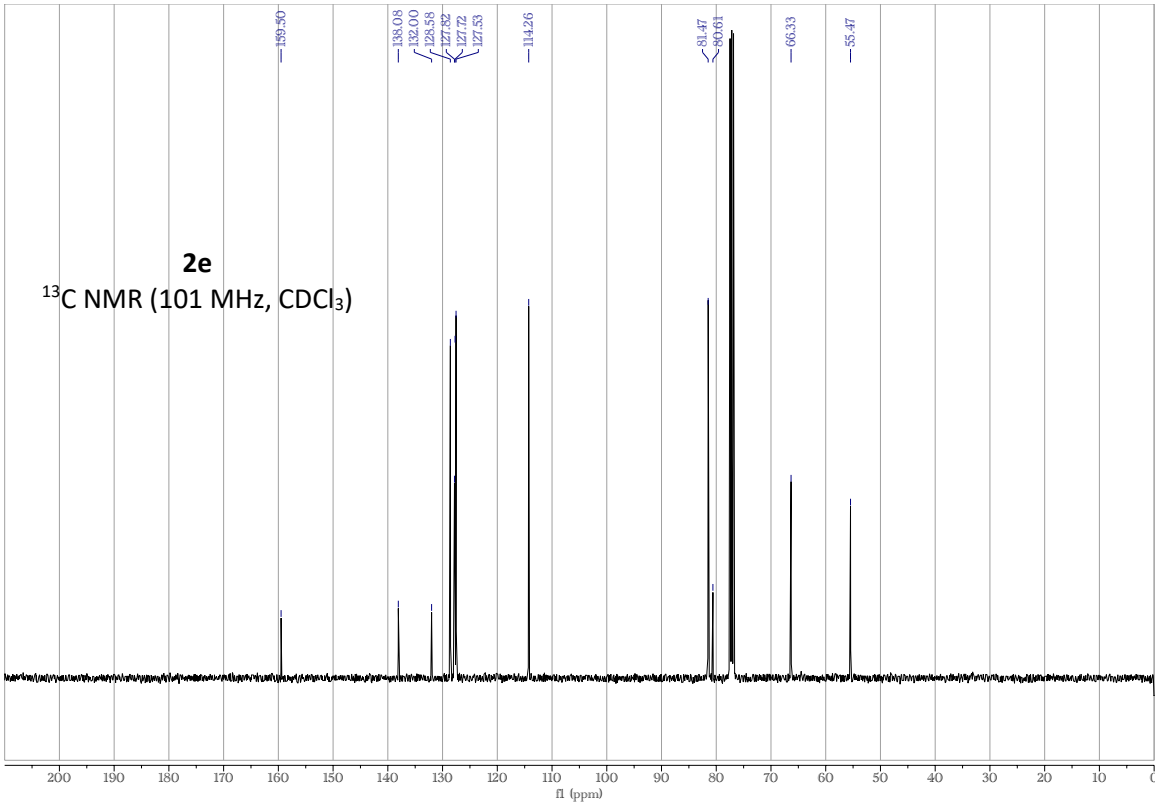
2c

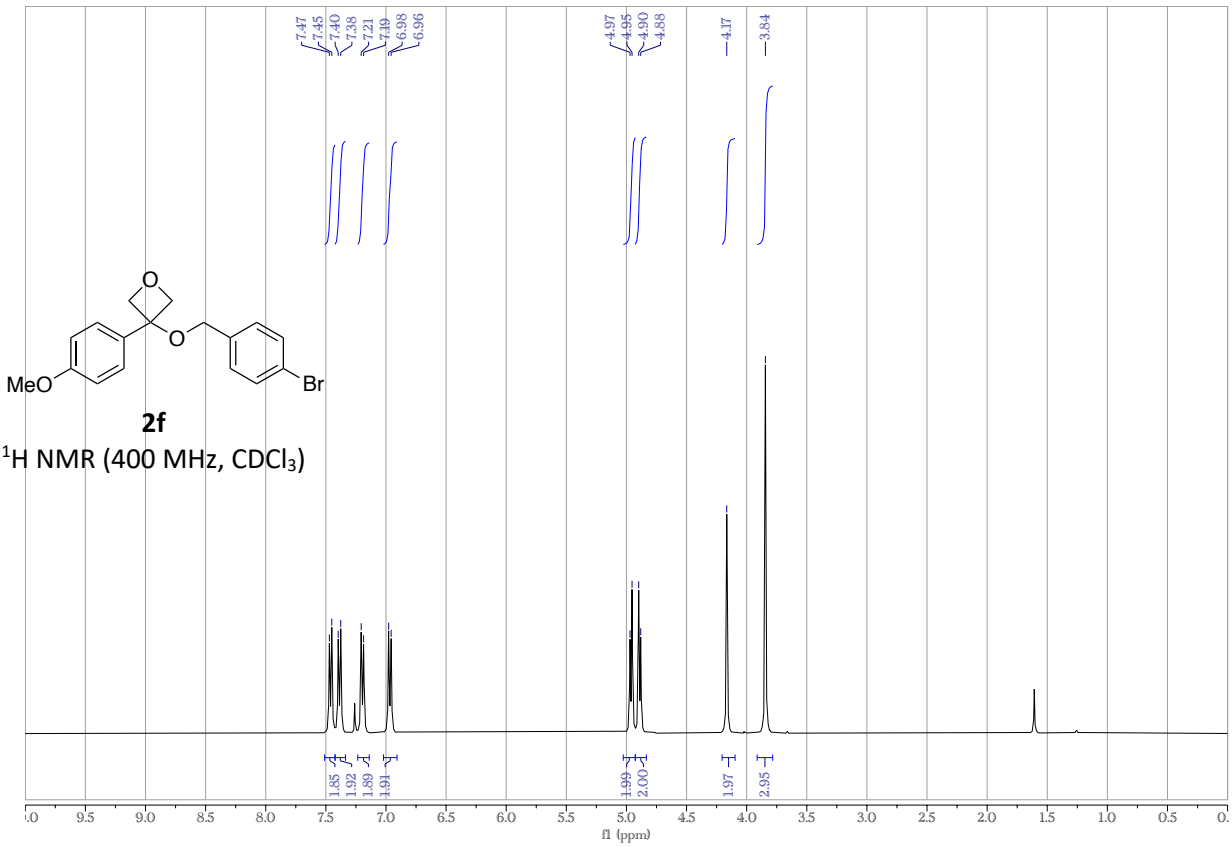
^{13}C NMR (101 MHz, $CDCl_3$)


MeO
O
O
Br
2d
^{1}H NMR (400 MHz, CDCl$_3$)
7.35
7.33
6.95
6.93
4.93
4.92
4.87
4.85
3.83
3.48
3.47
3.46
3.45
3.43
3.42
3.41
3.40
1.95
1.93
1.99
2.00
3.05
3.99
f1 (ppm)


2d
^{13}C NMR (101 MHz, CDCl$_3$)
159.92
131.77
127.80
114.60
81.51
80.91
64.67
55.78
30.94
f1 (ppm)

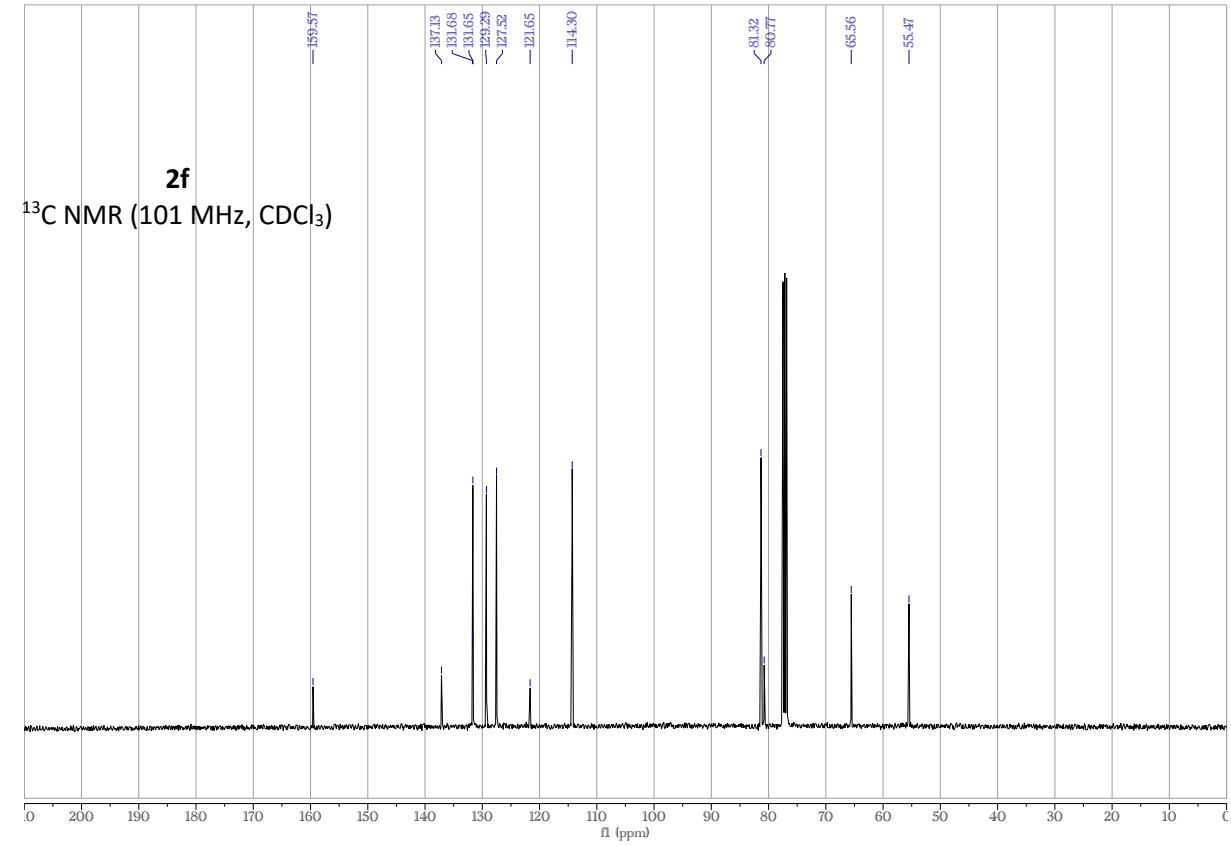

MeO
O
O
2e
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


2e
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)



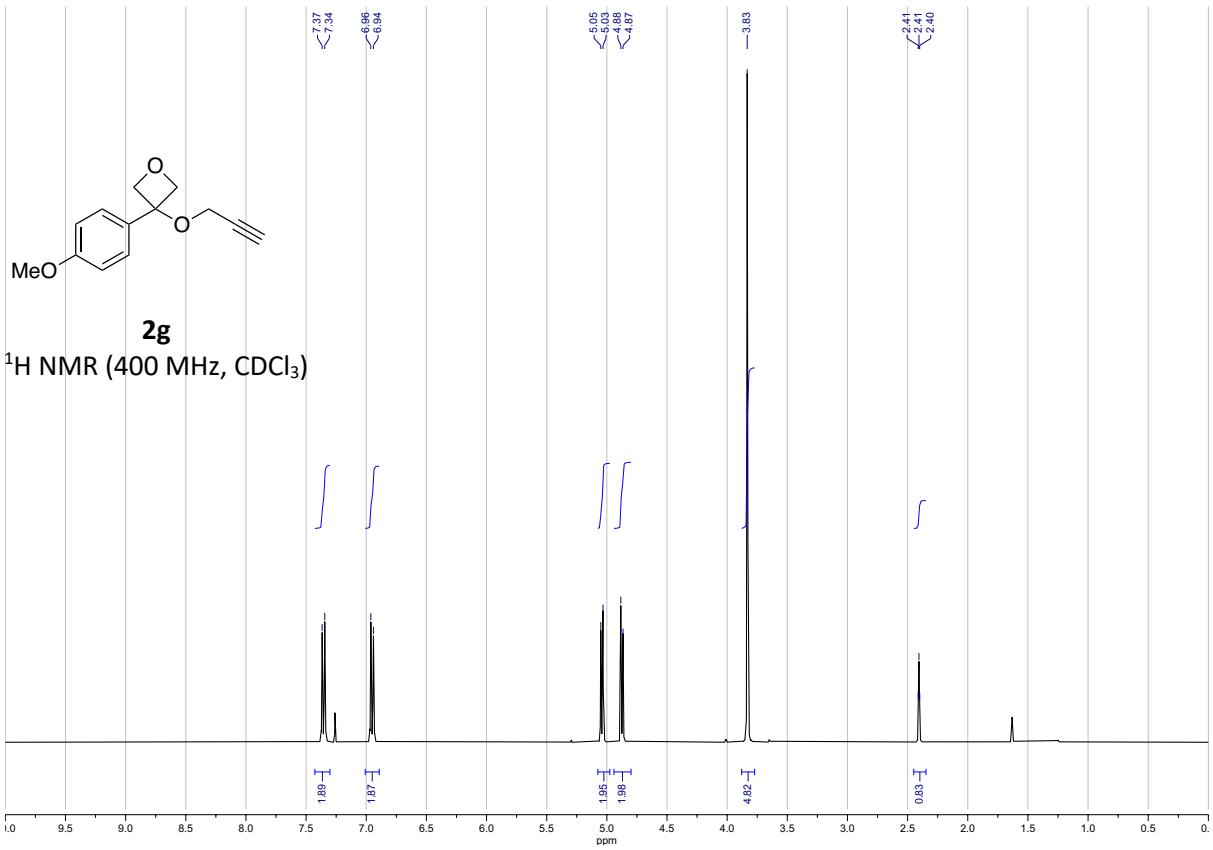
2f

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



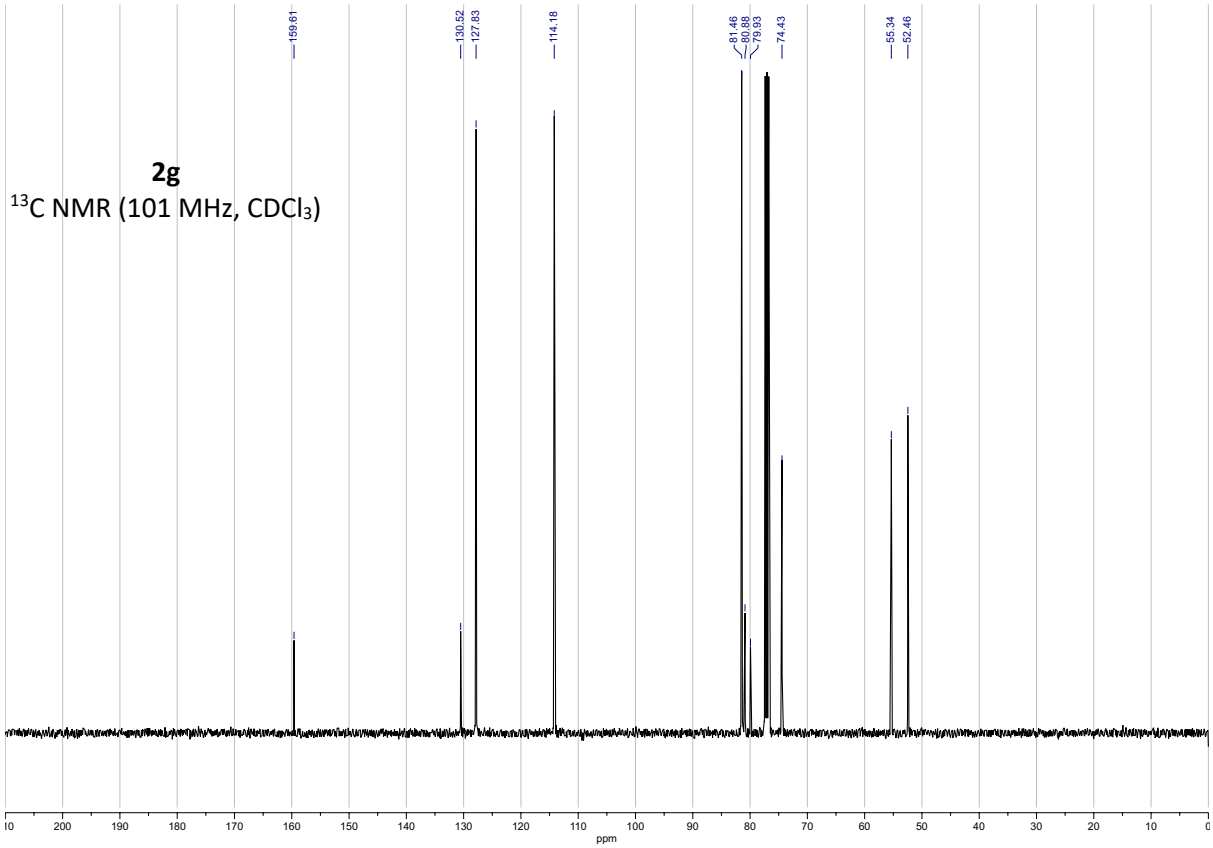
2f

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



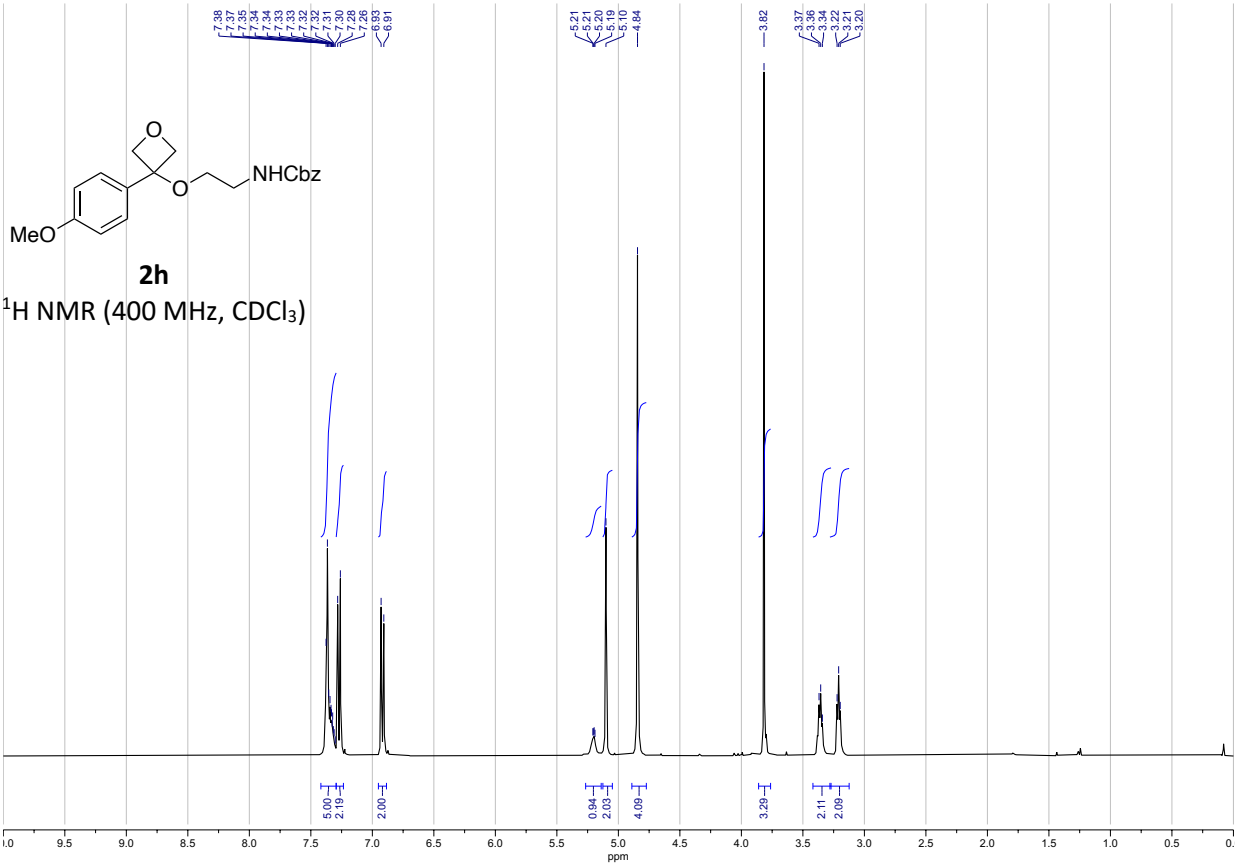
2g

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



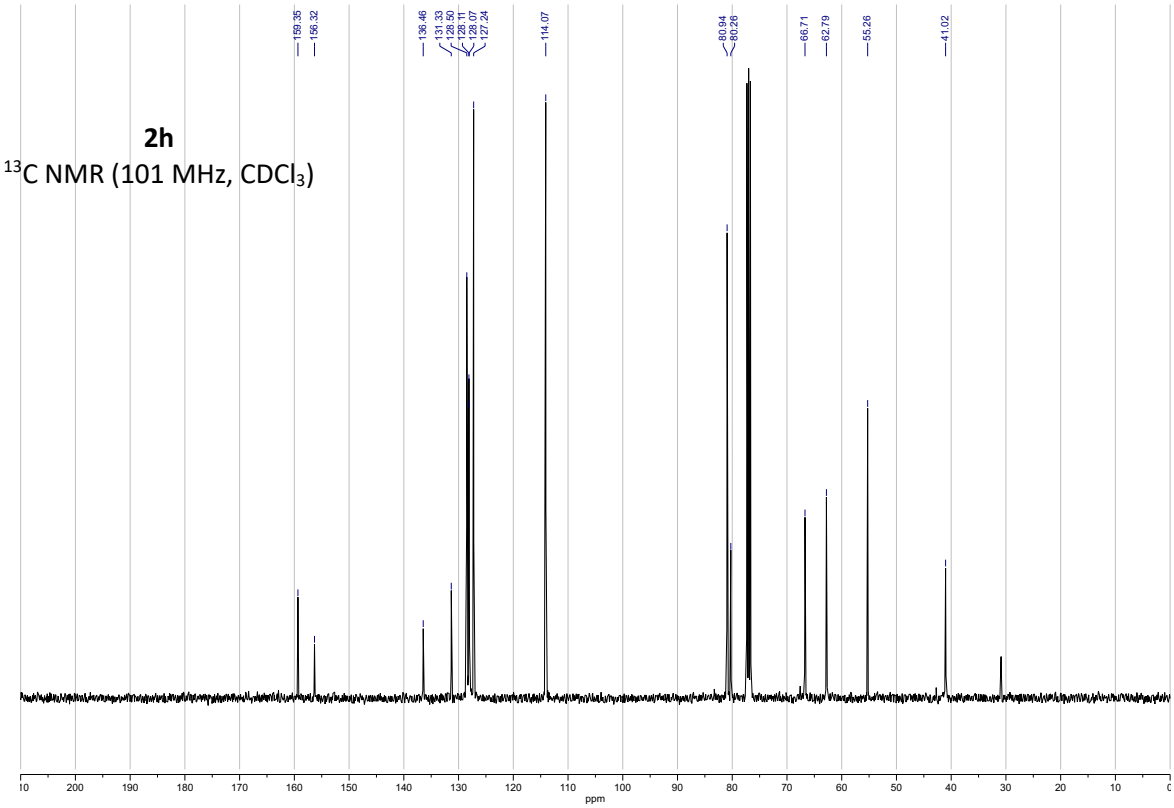
2g

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



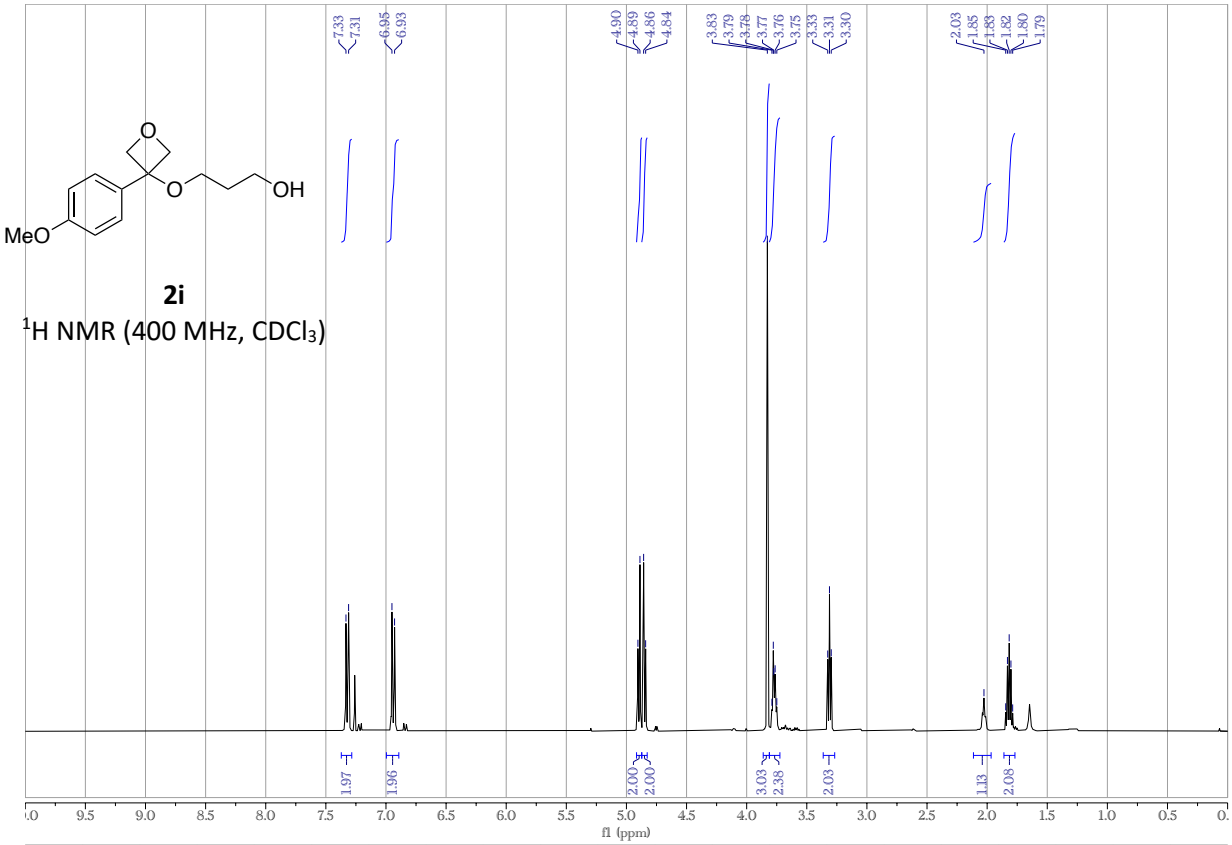
2h

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



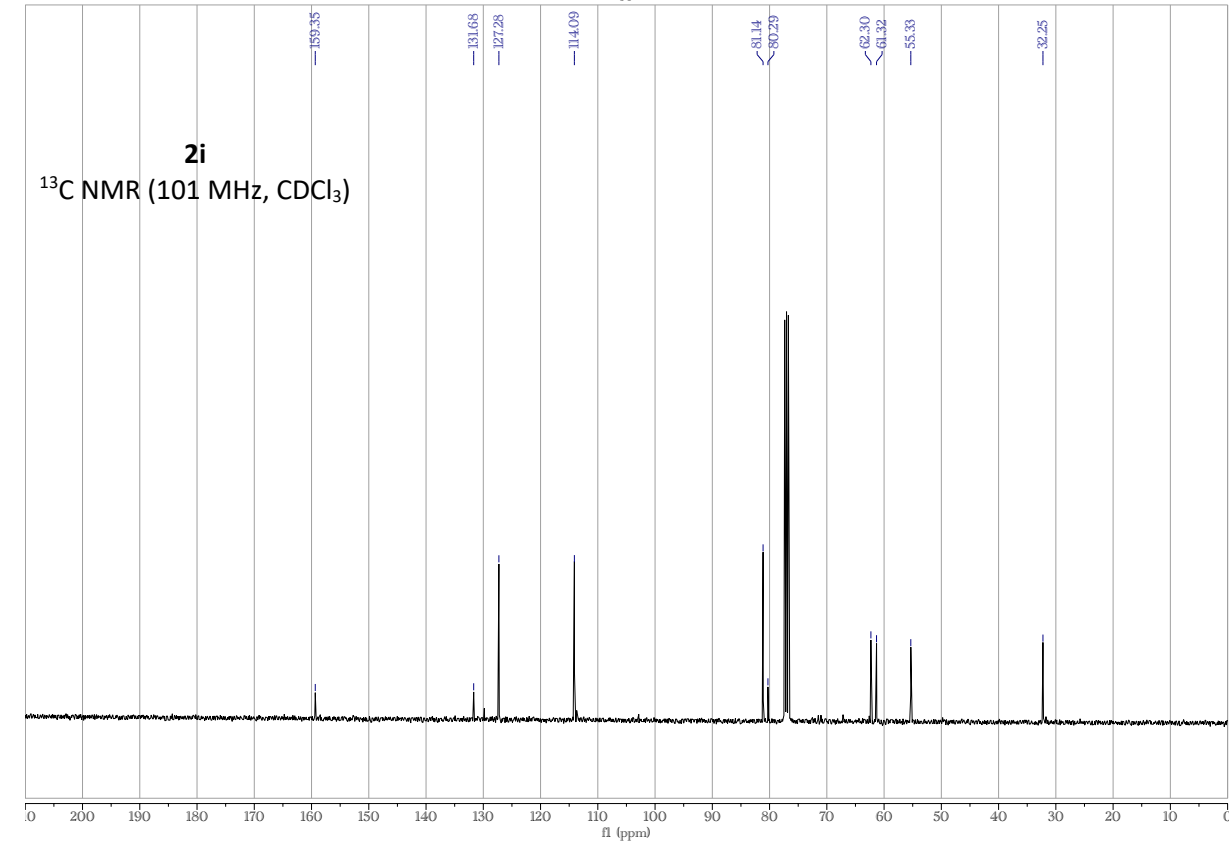
2h

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



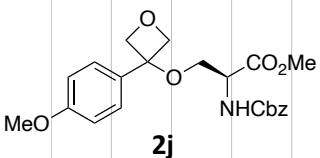
2i

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



2i

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

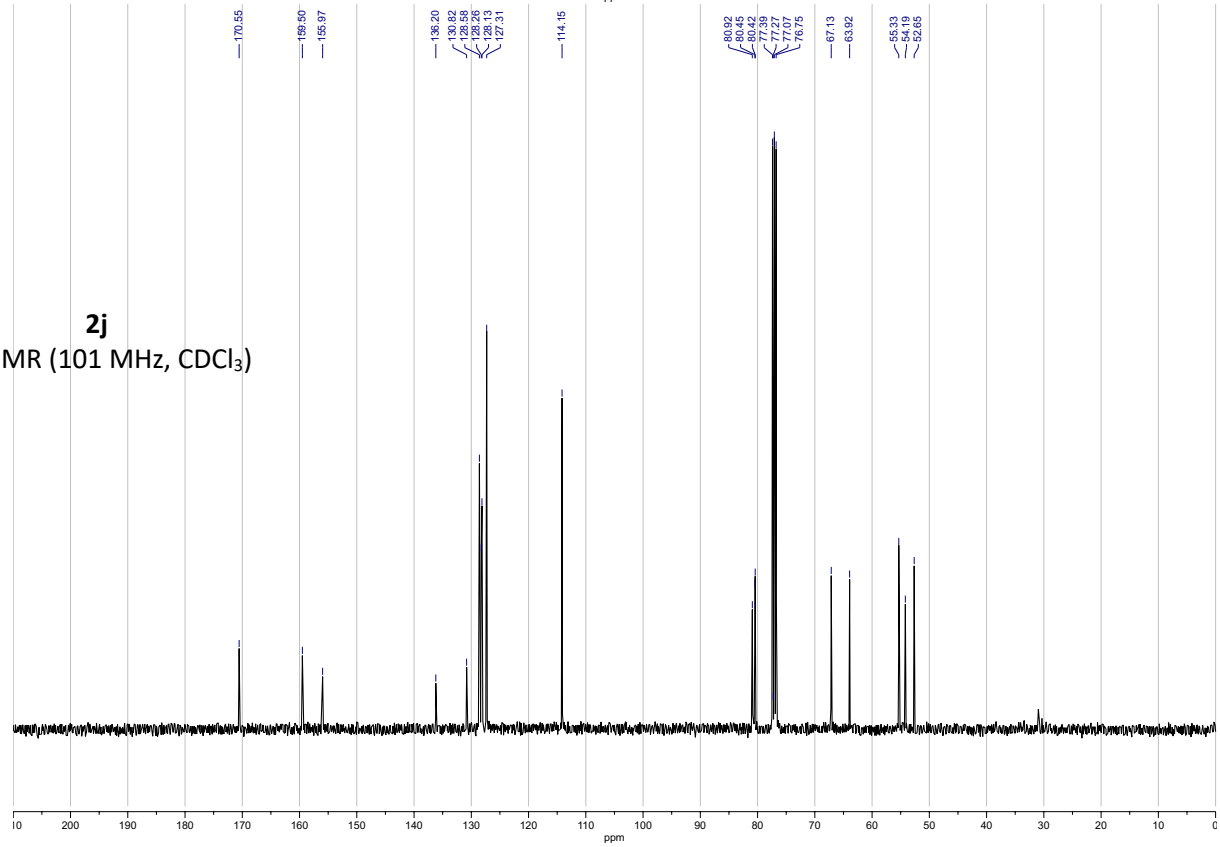


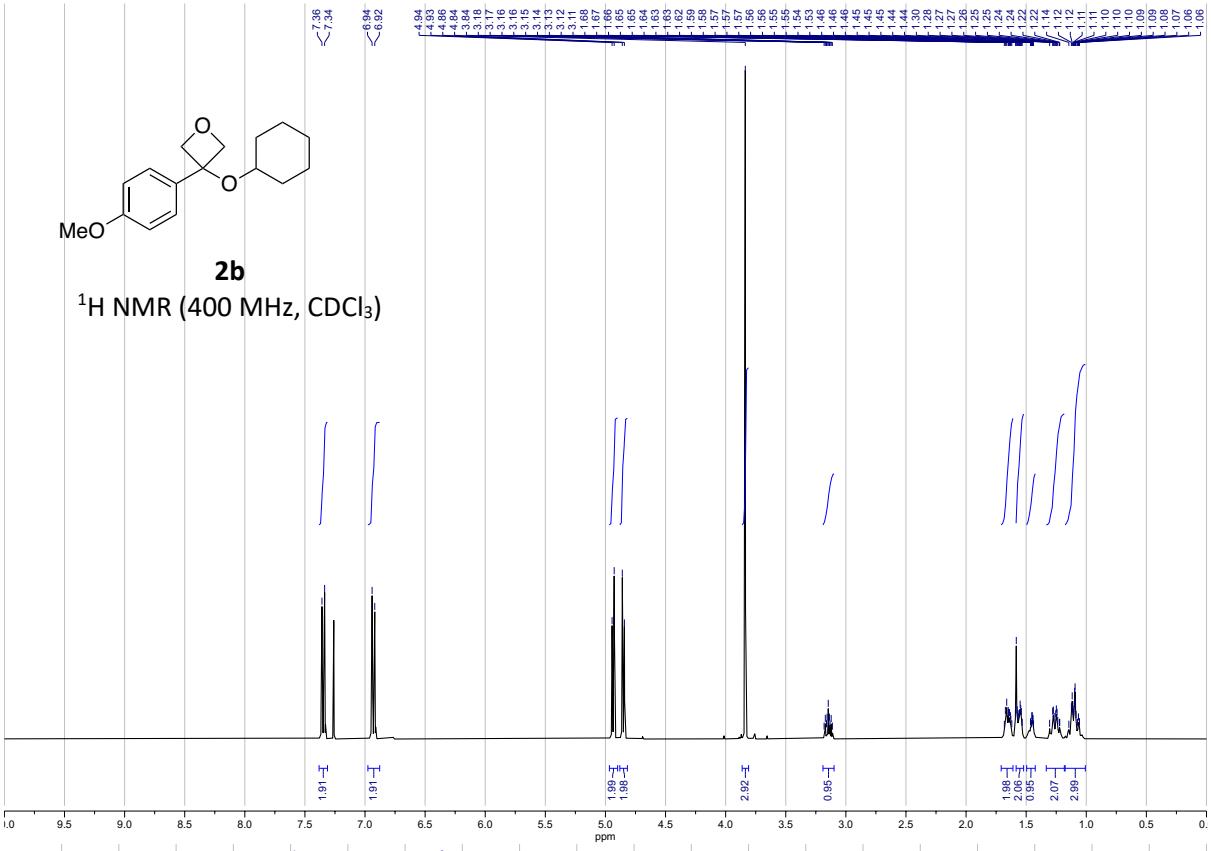
2j

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

2j

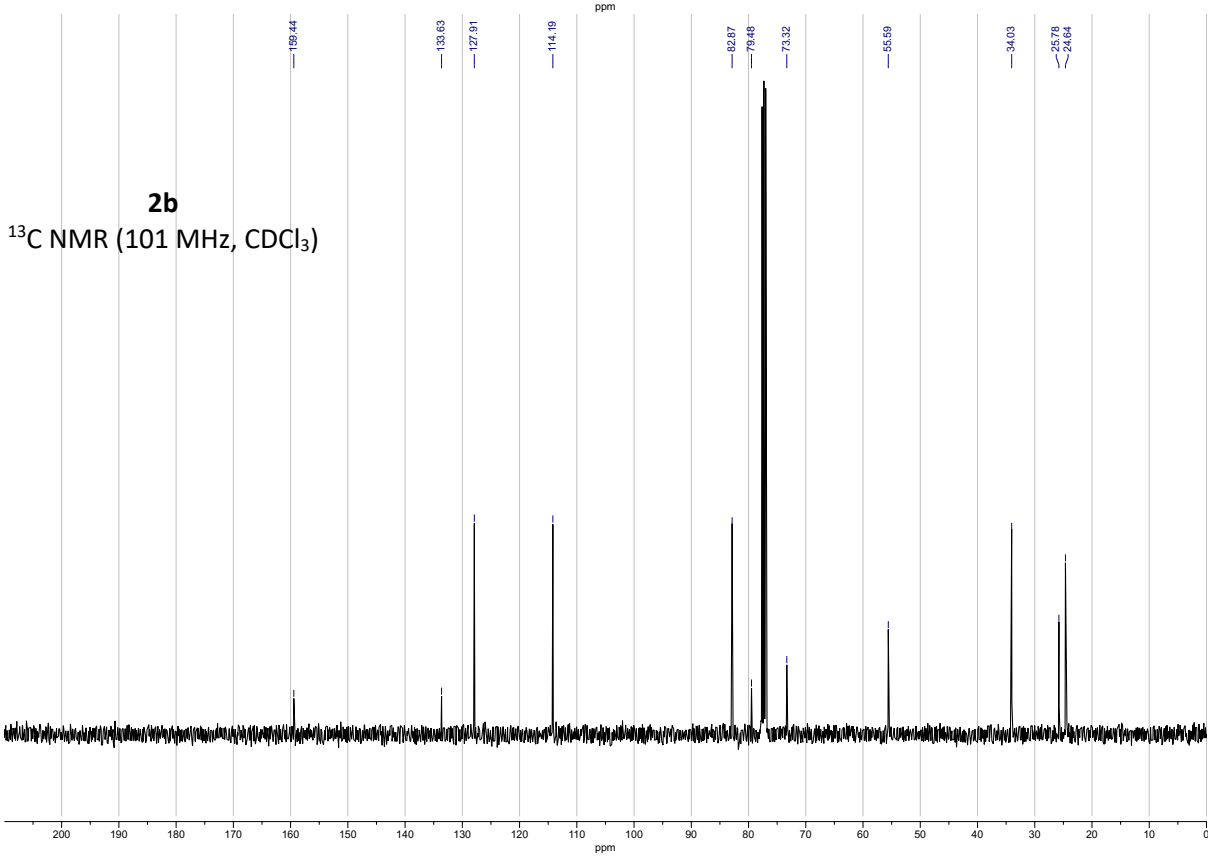
^{13}C NMR (101 MHz, $CDCl_3$)





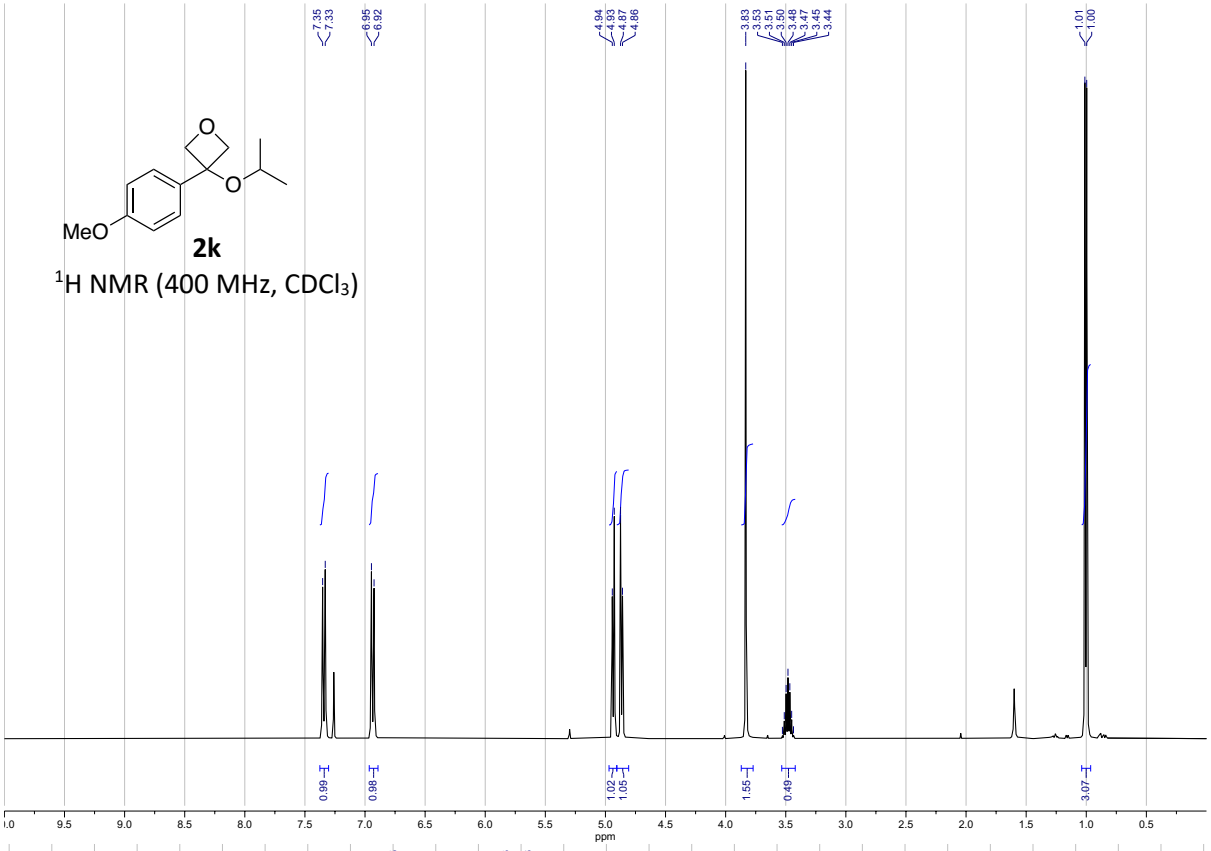
2b

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



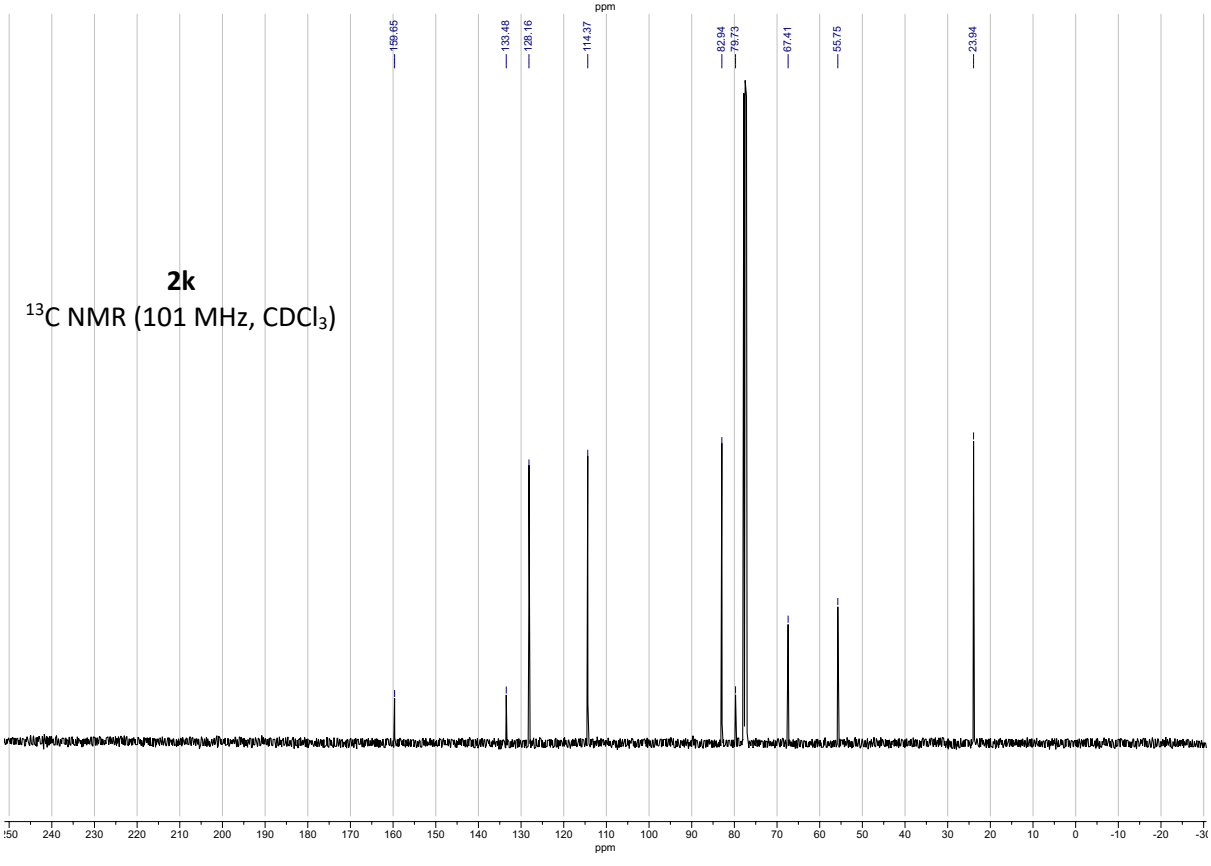
2b

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



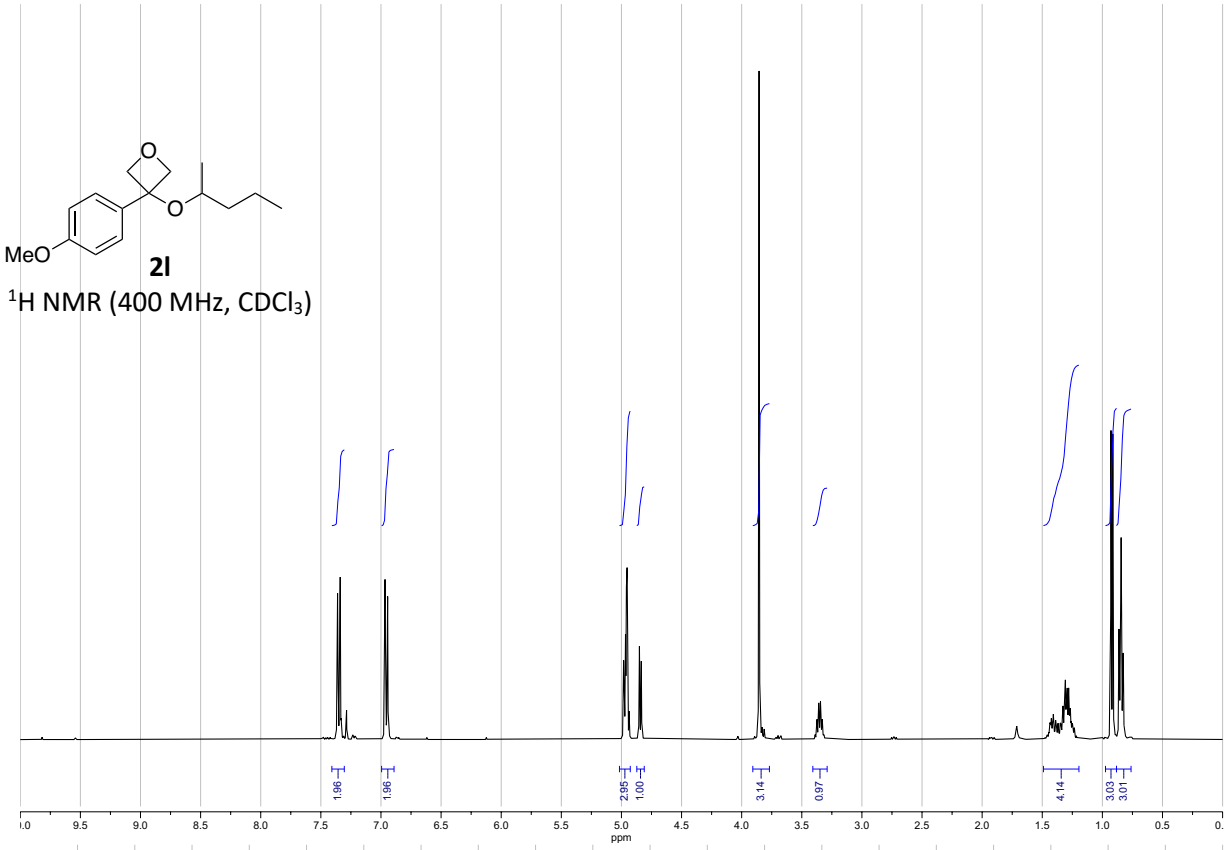
2k

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



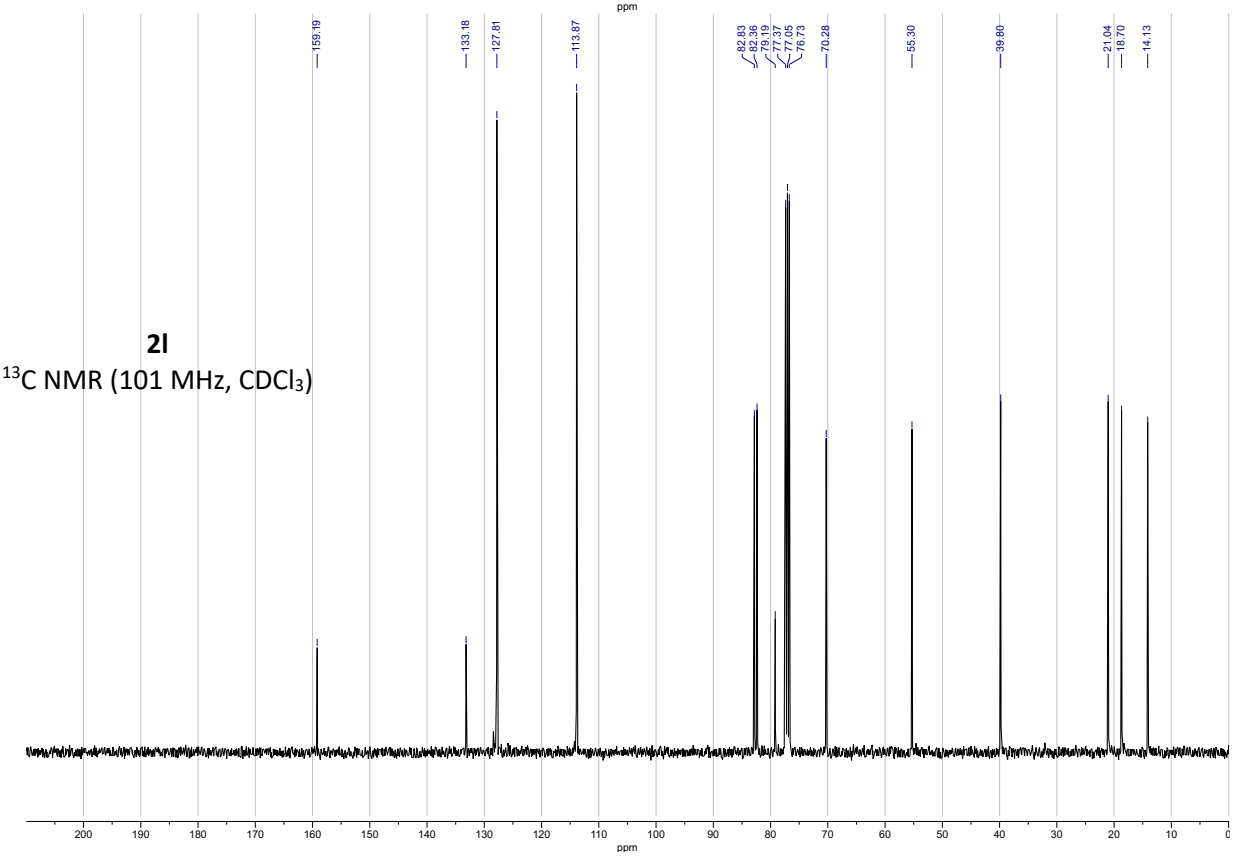
2k

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



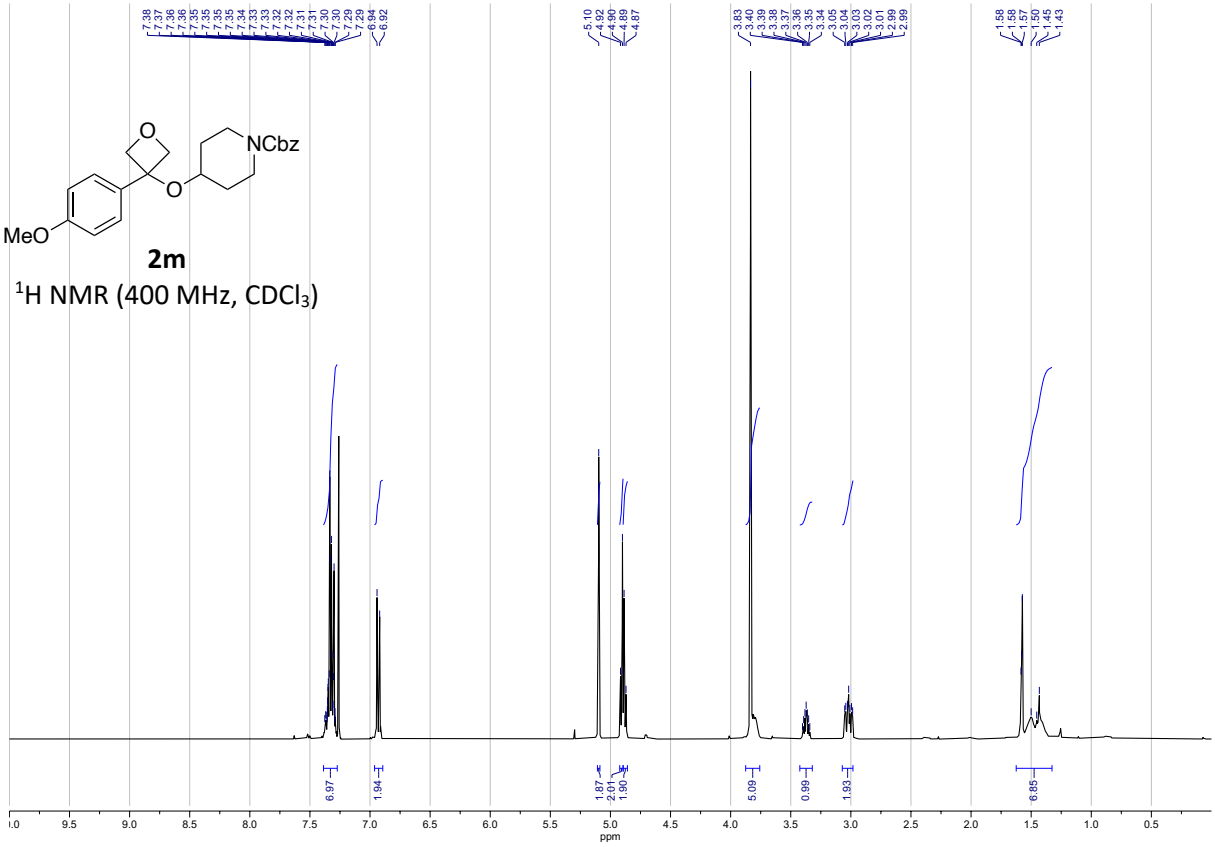
2l

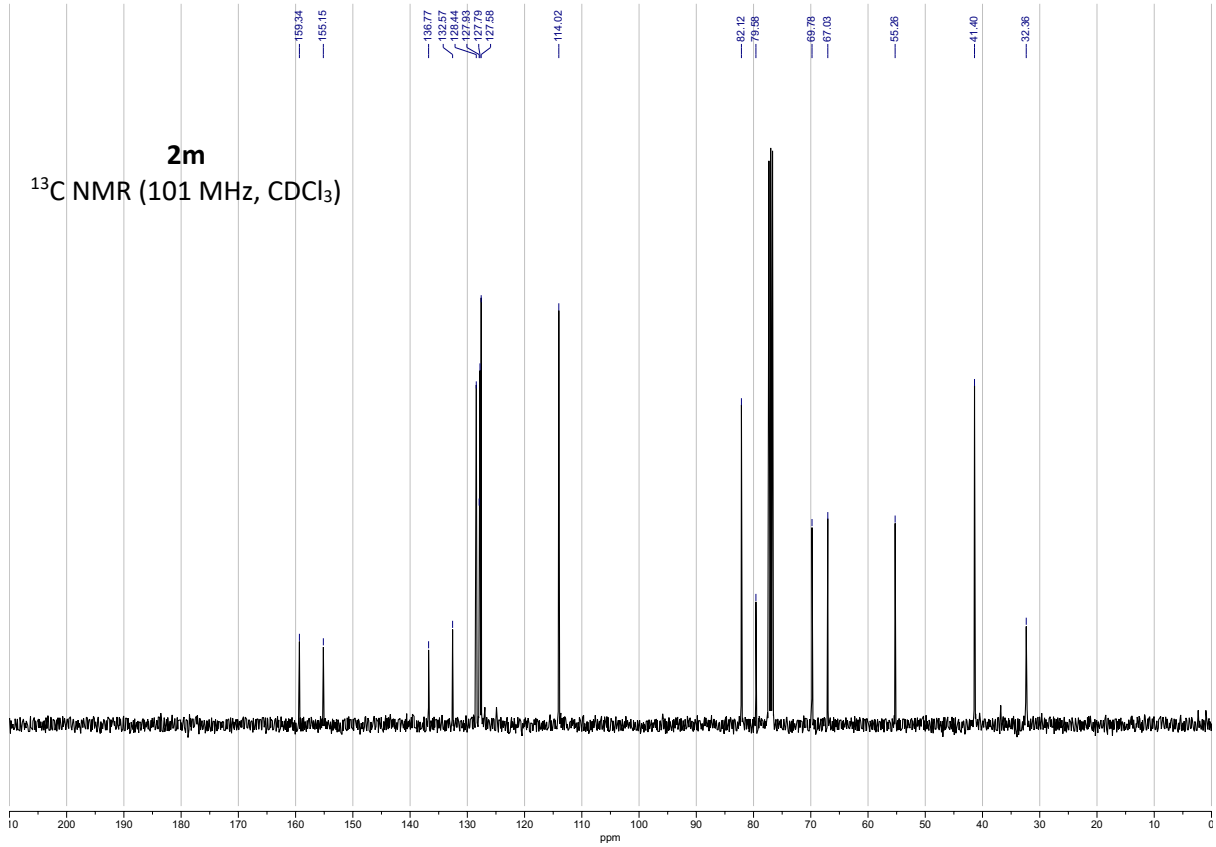
^{1}H NMR (400 MHz, $CDCl_3$)

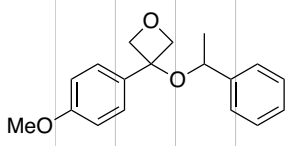


2l

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


NCbz
O
O
MeO
2m
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


2m
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

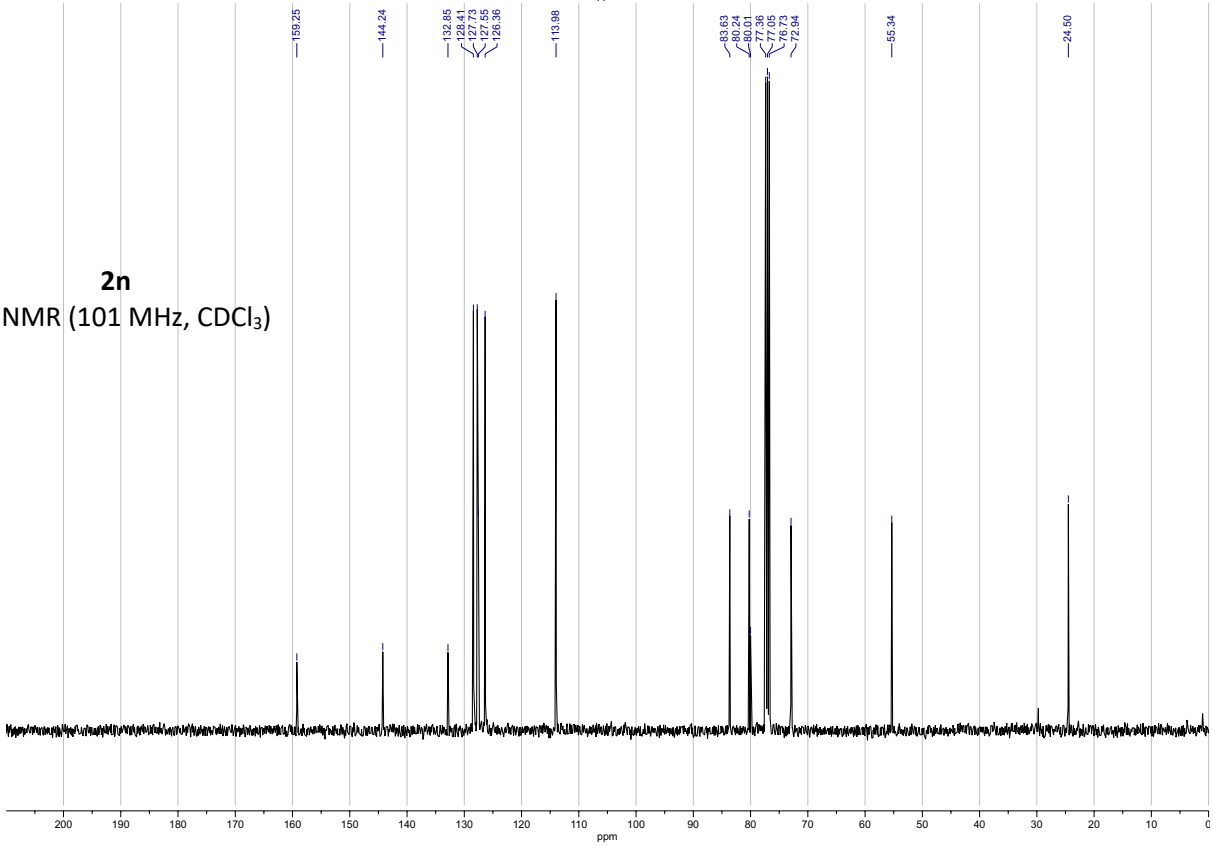


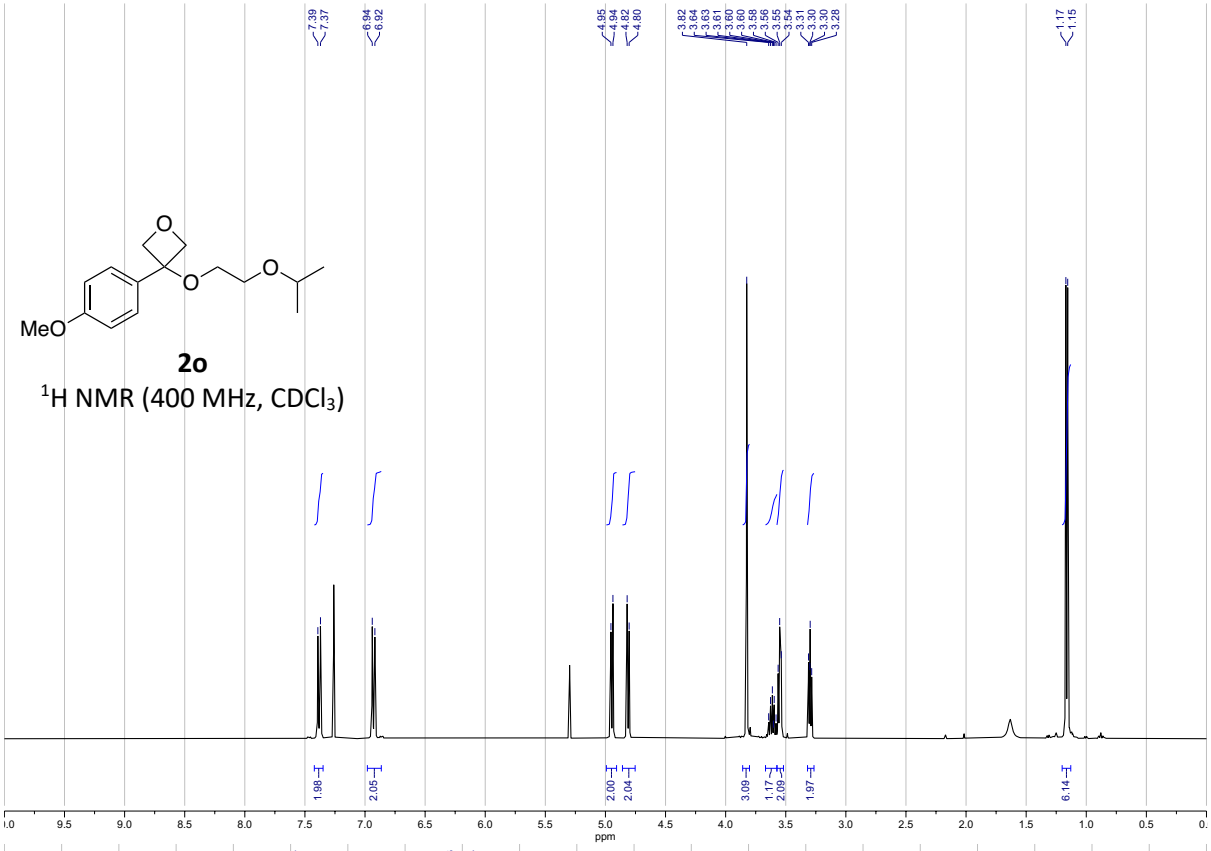
2n

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

2n

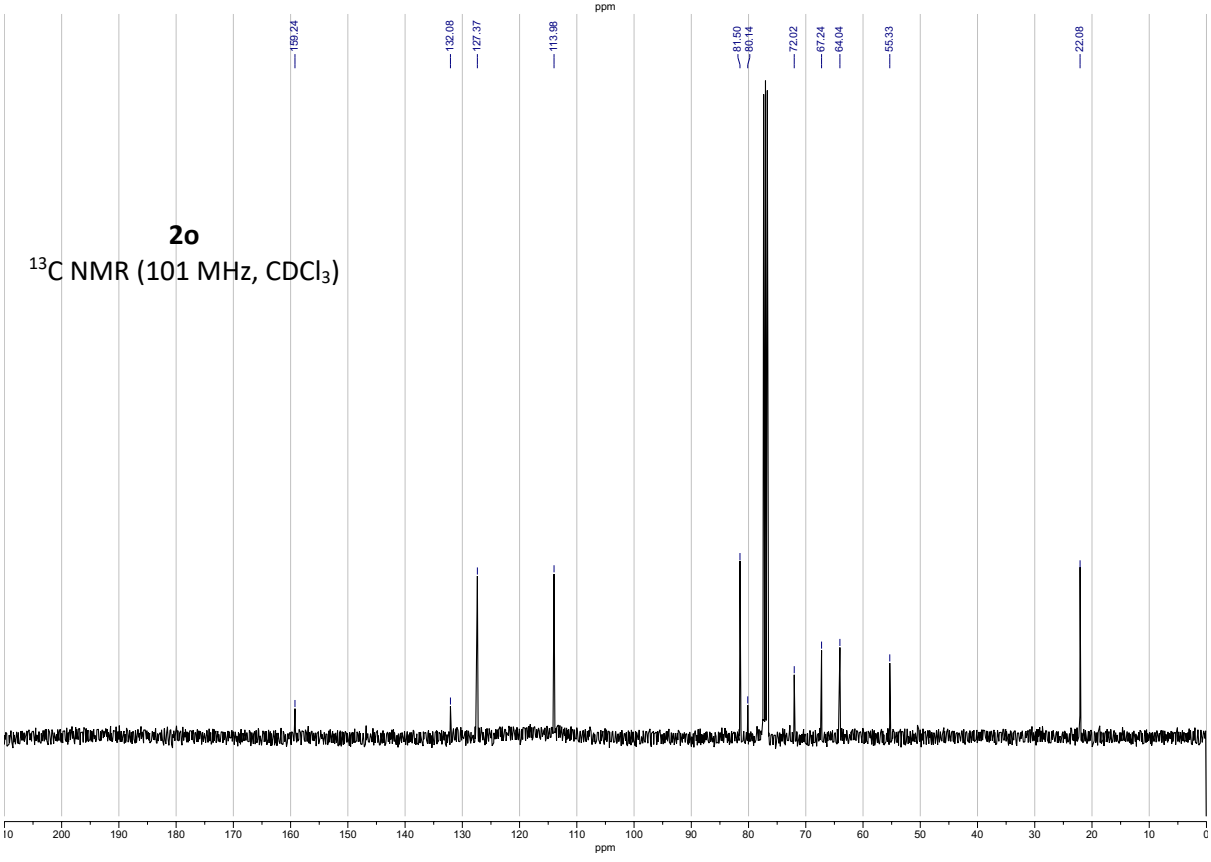
^{13}C NMR (101 MHz, $CDCl_3$)





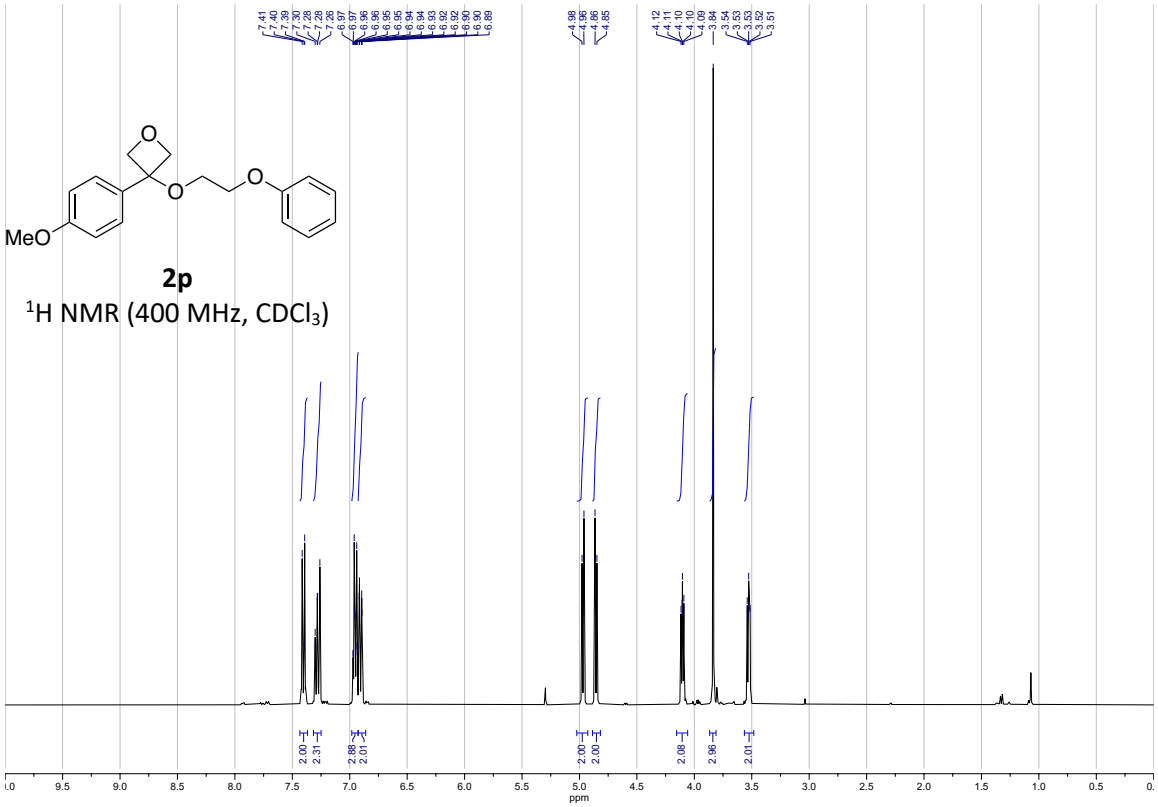
2o

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



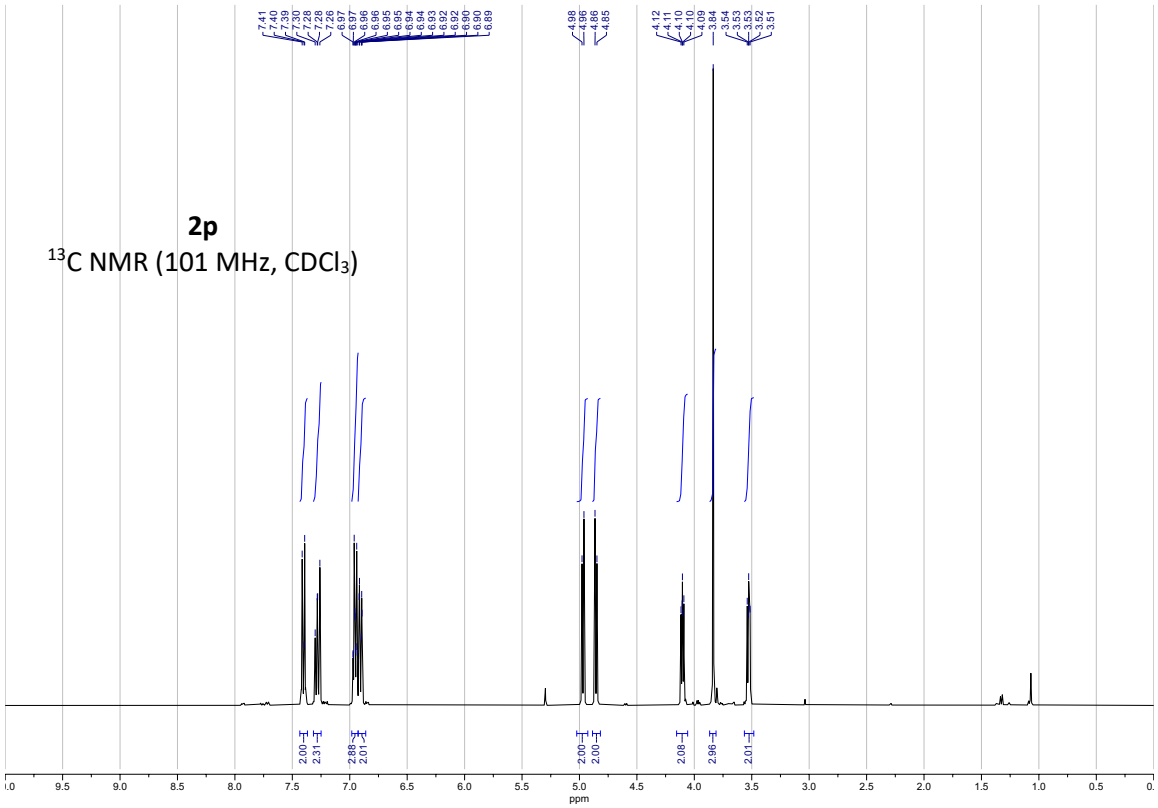
2o

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



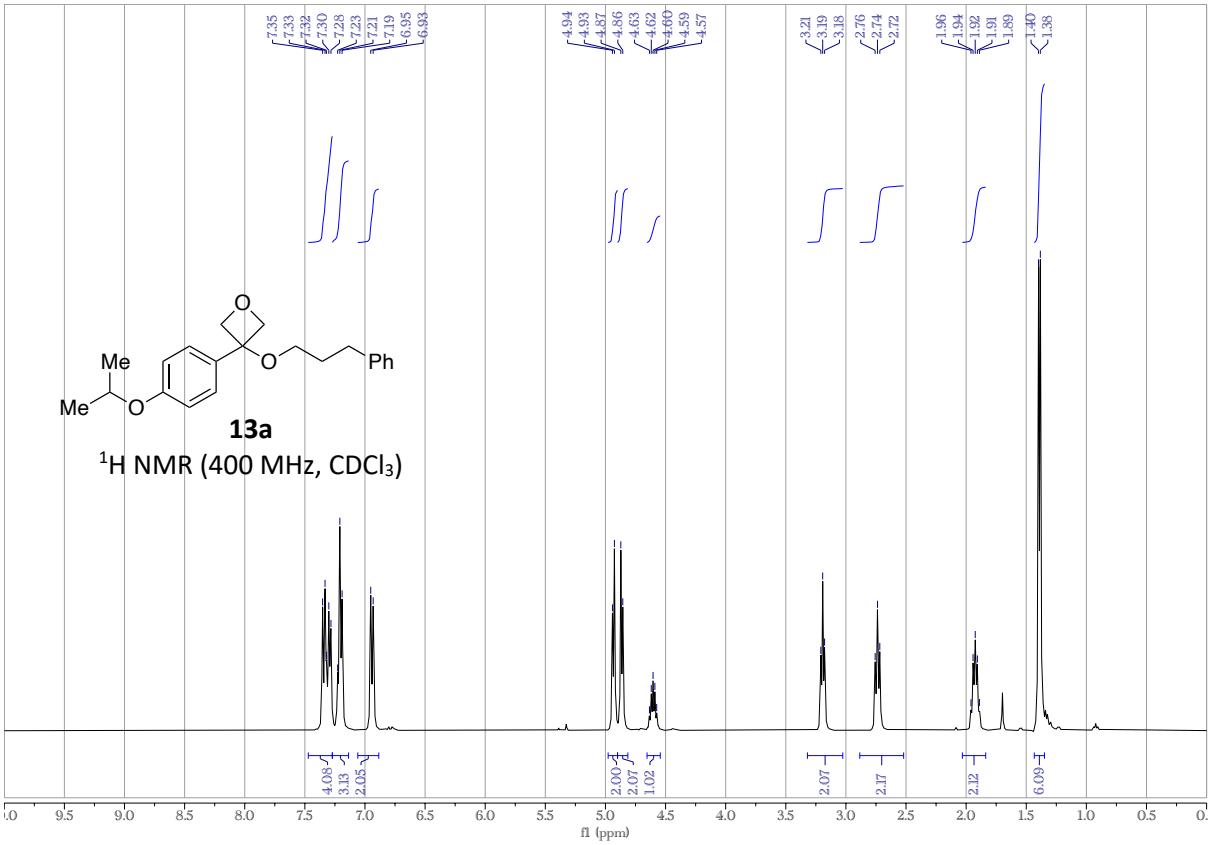
2p

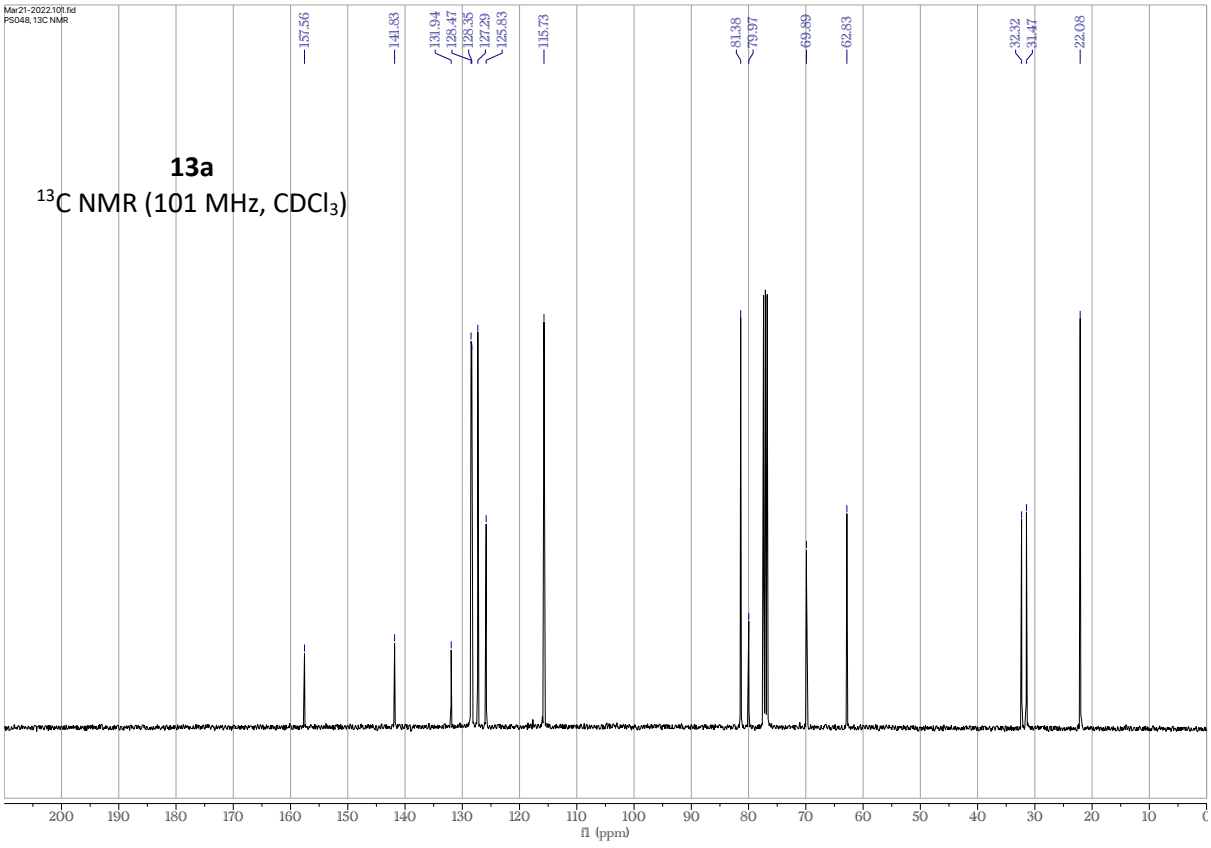
^{1}H NMR (400 MHz, $CDCl_3$)

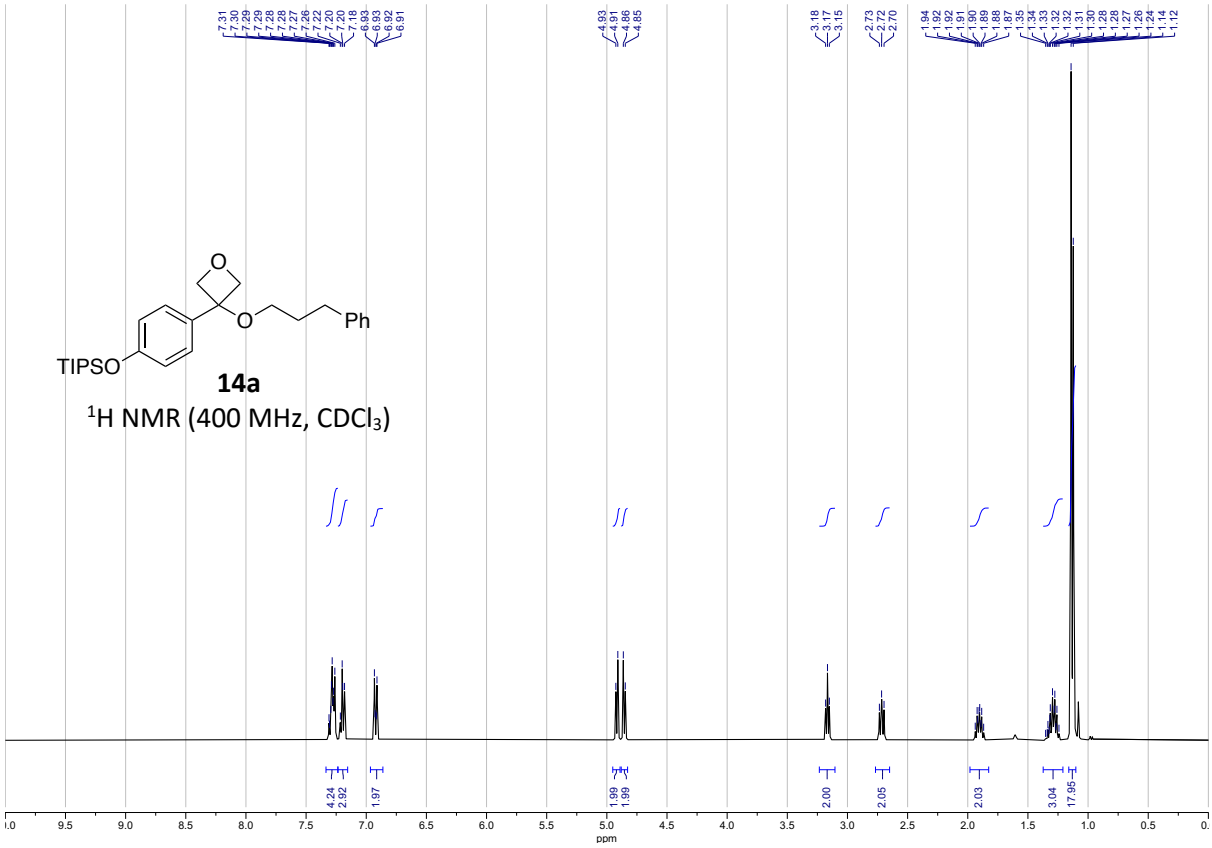


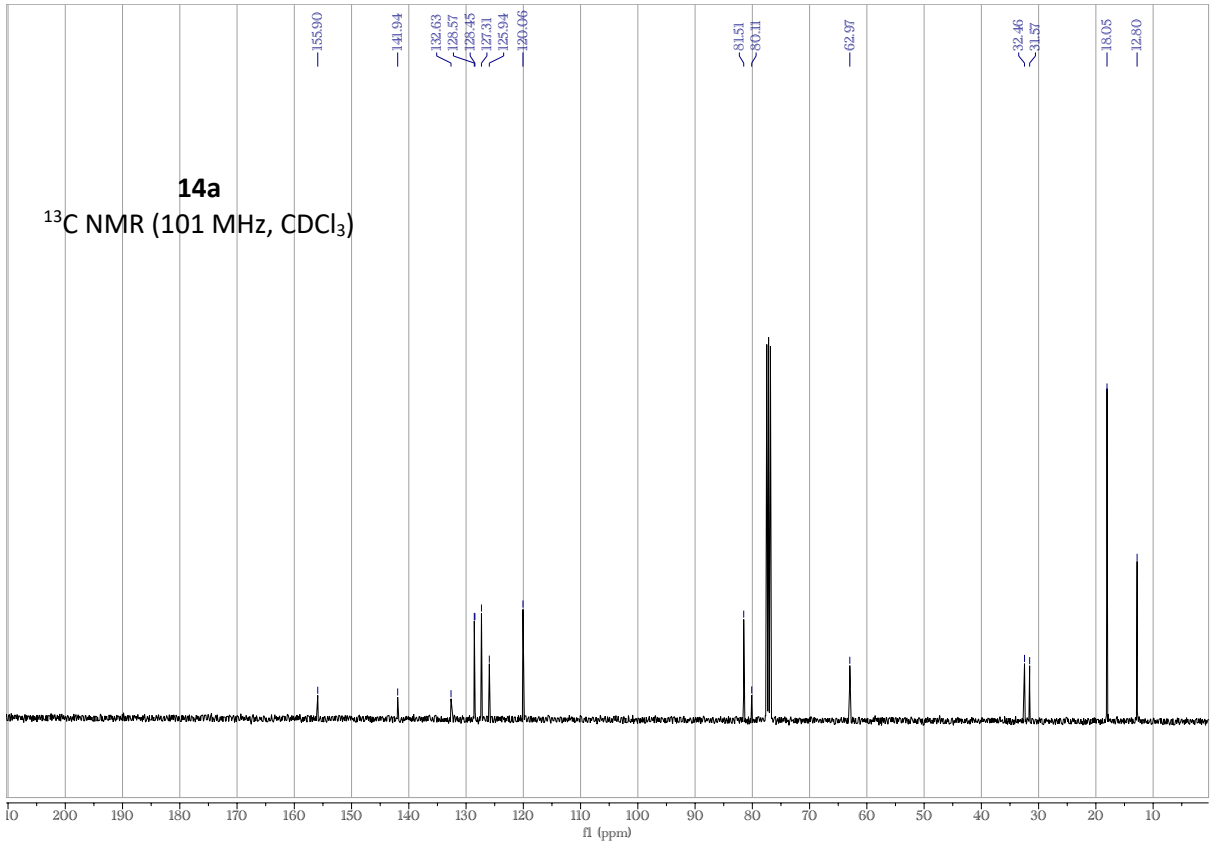
2p

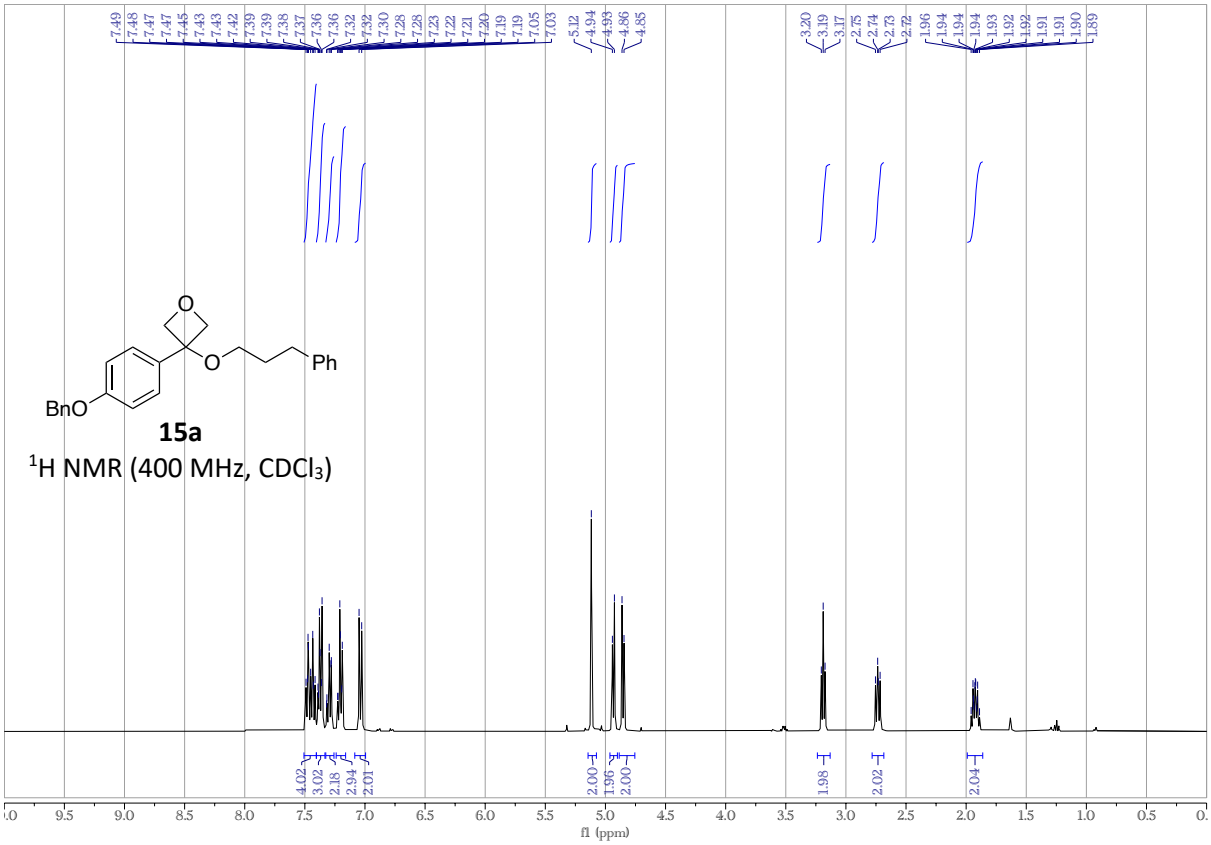
^{13}C NMR (101 MHz, $CDCl_3$)

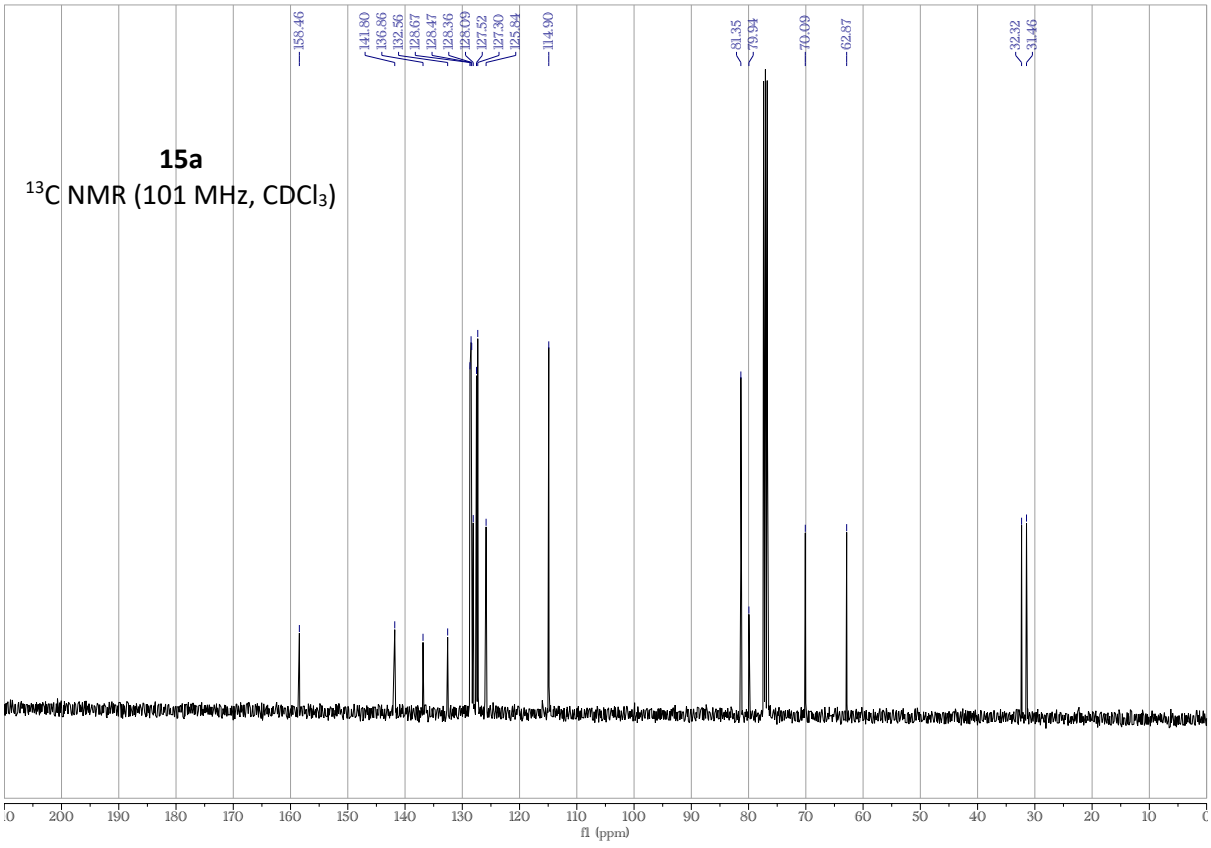

Me
Me
O
O
O
Ph
13a
^{1}H NMR (400 MHz, $CDCl_3$)
fl (ppm)

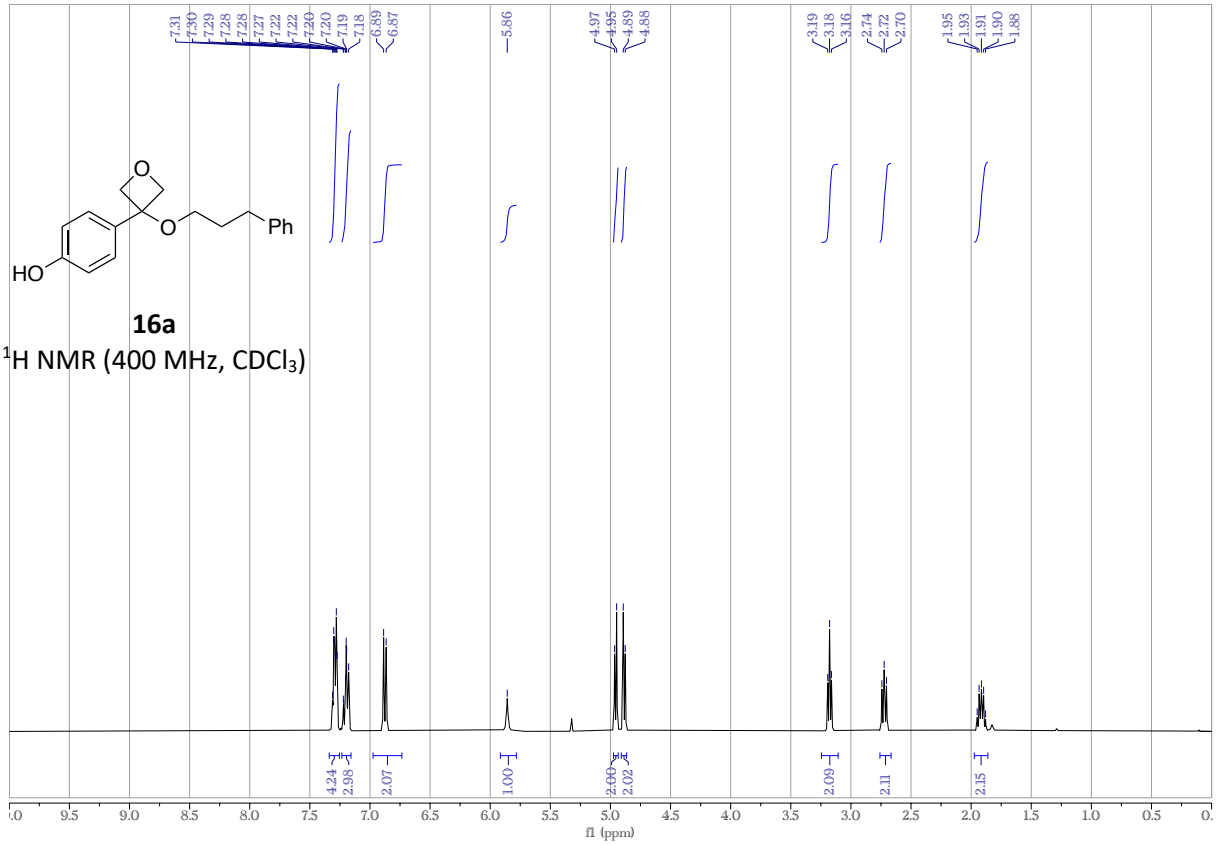

13a
^{13}C NMR (101 MHz, $CDCl_3$)
fl (ppm)

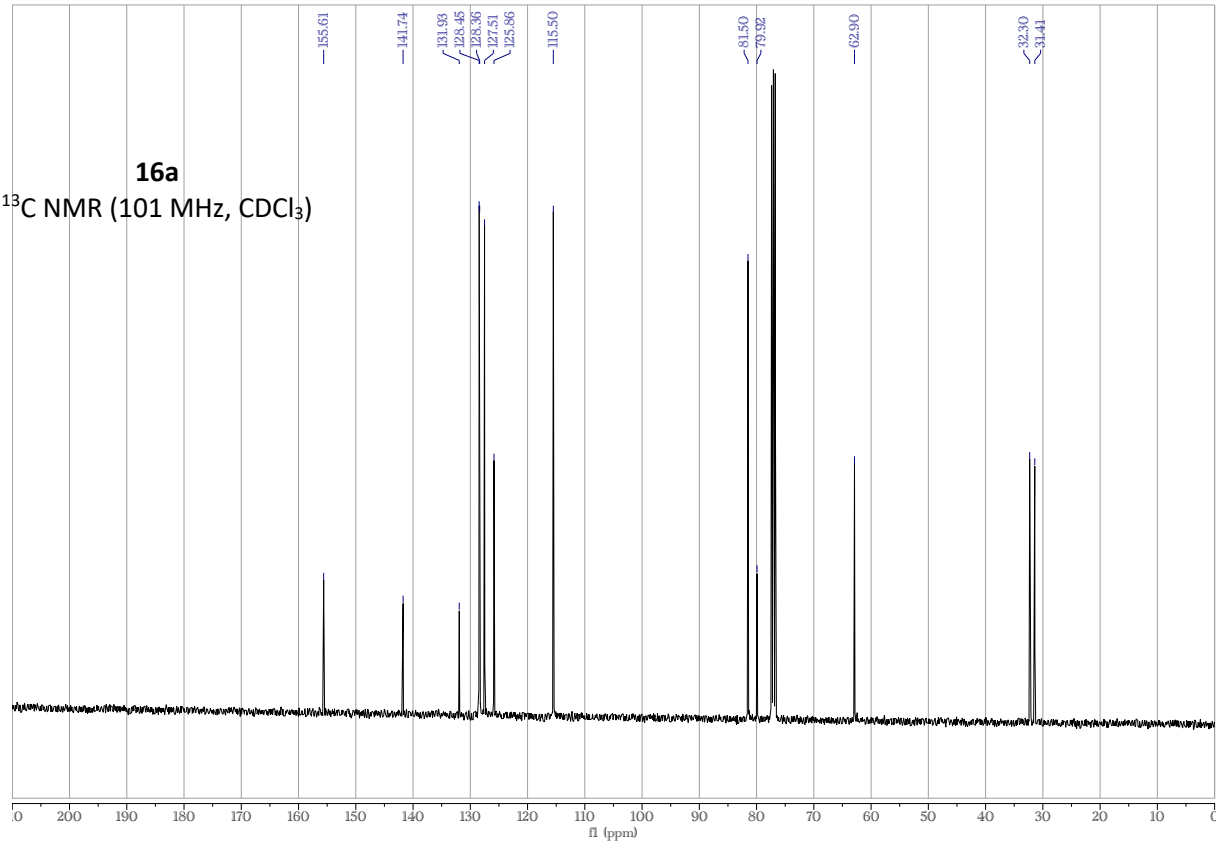

TIPSO
O
O
Ph
14a
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

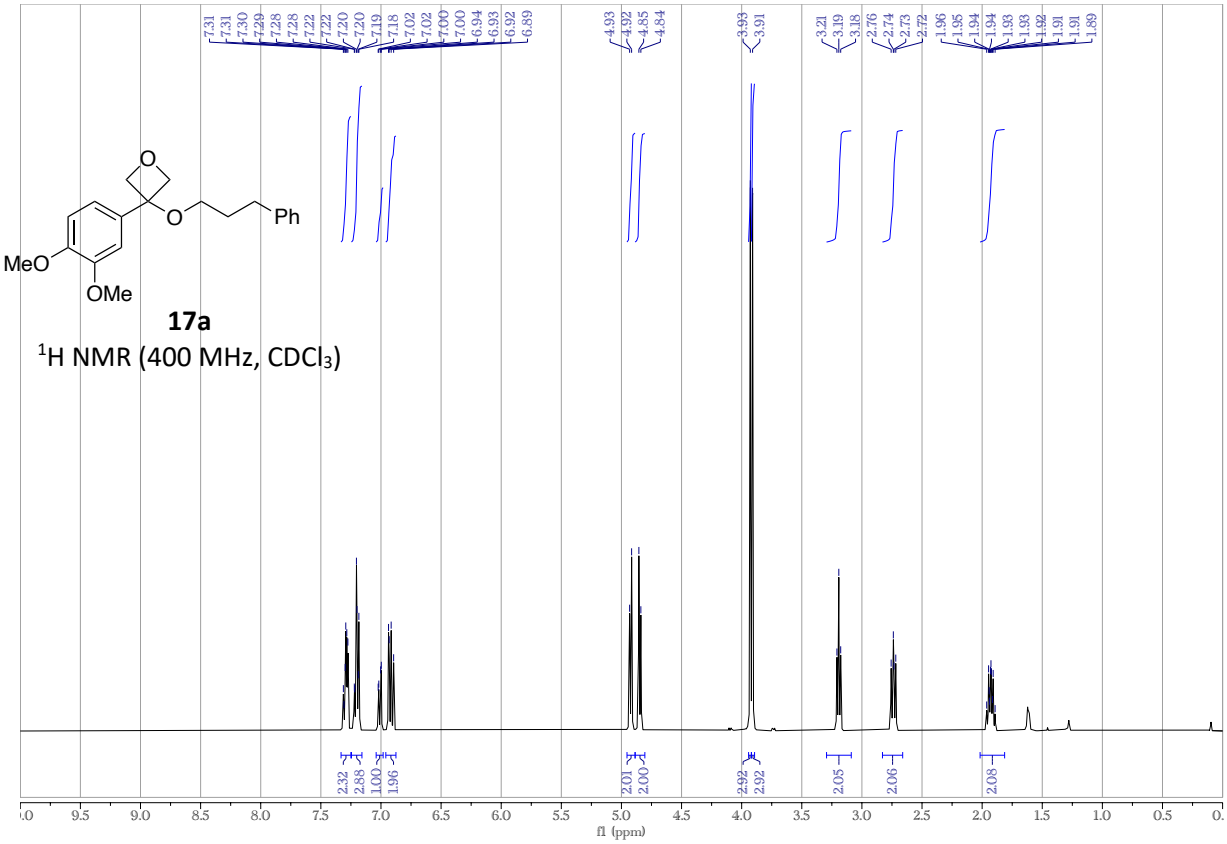

14a
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)

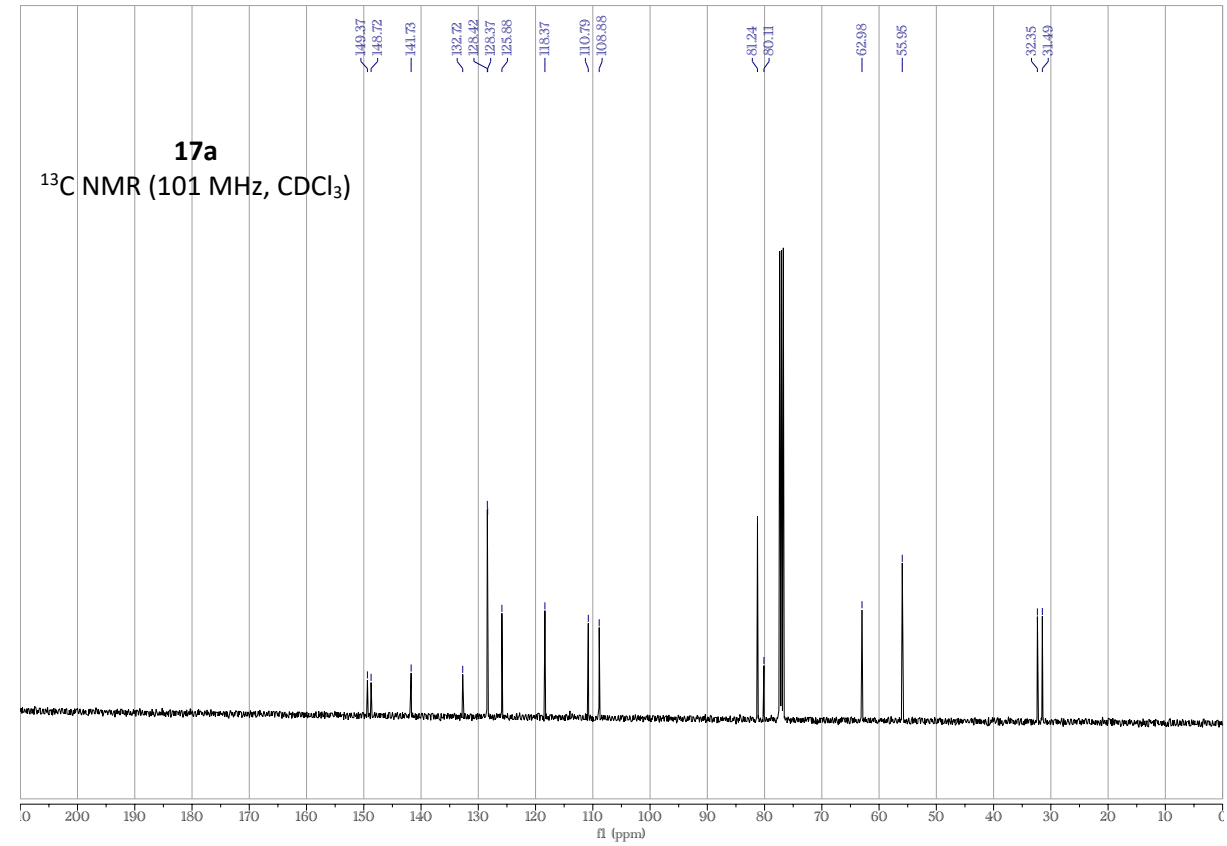

O
O
Ph
BnO
15a
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

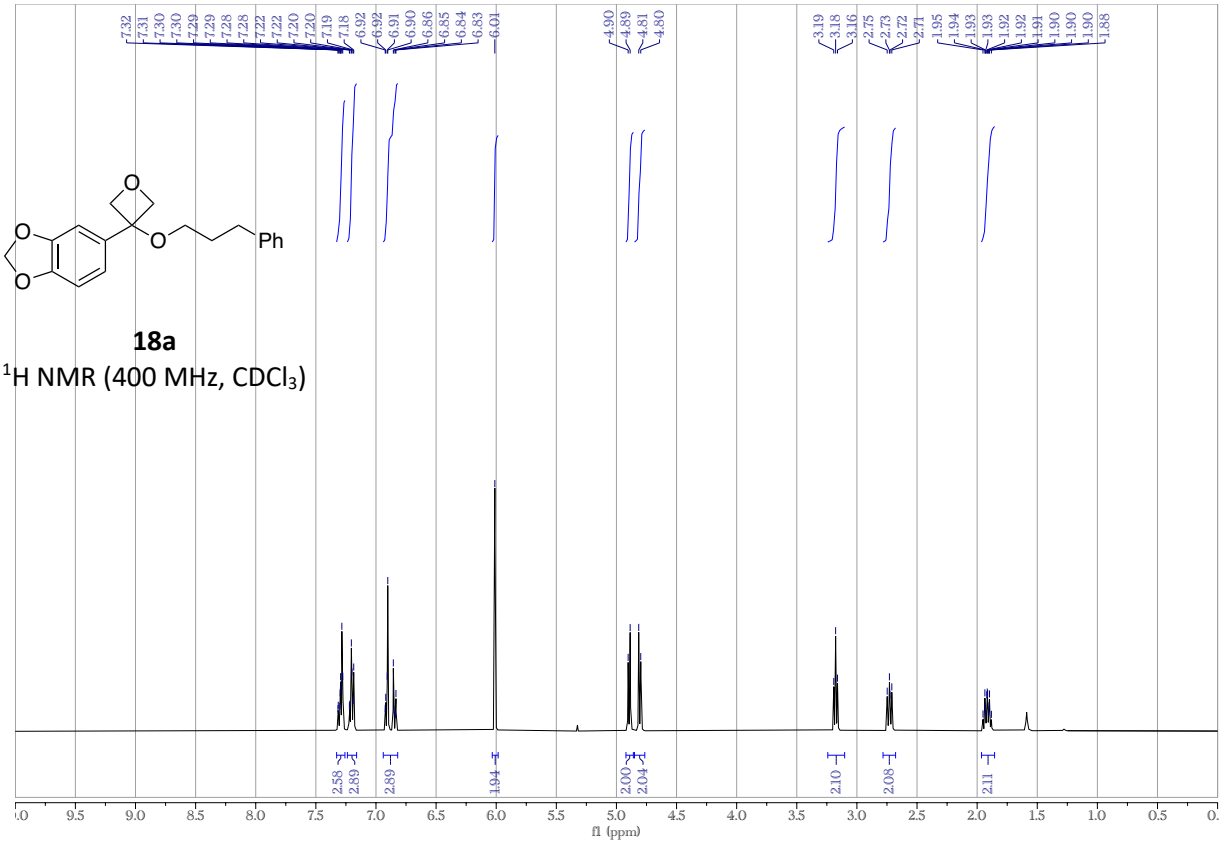

15a
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)


HO
O
O
Ph
16a
1H NMR (400 MHz, CDCl3)
f1 (ppm)


16a
13C NMR (101 MHz, CDCl3)
155.61
141.74
131.93
128.45
128.36
127.51
125.86
115.50
81.50
79.92
62.90
32.30
31.41
f1 (ppm)

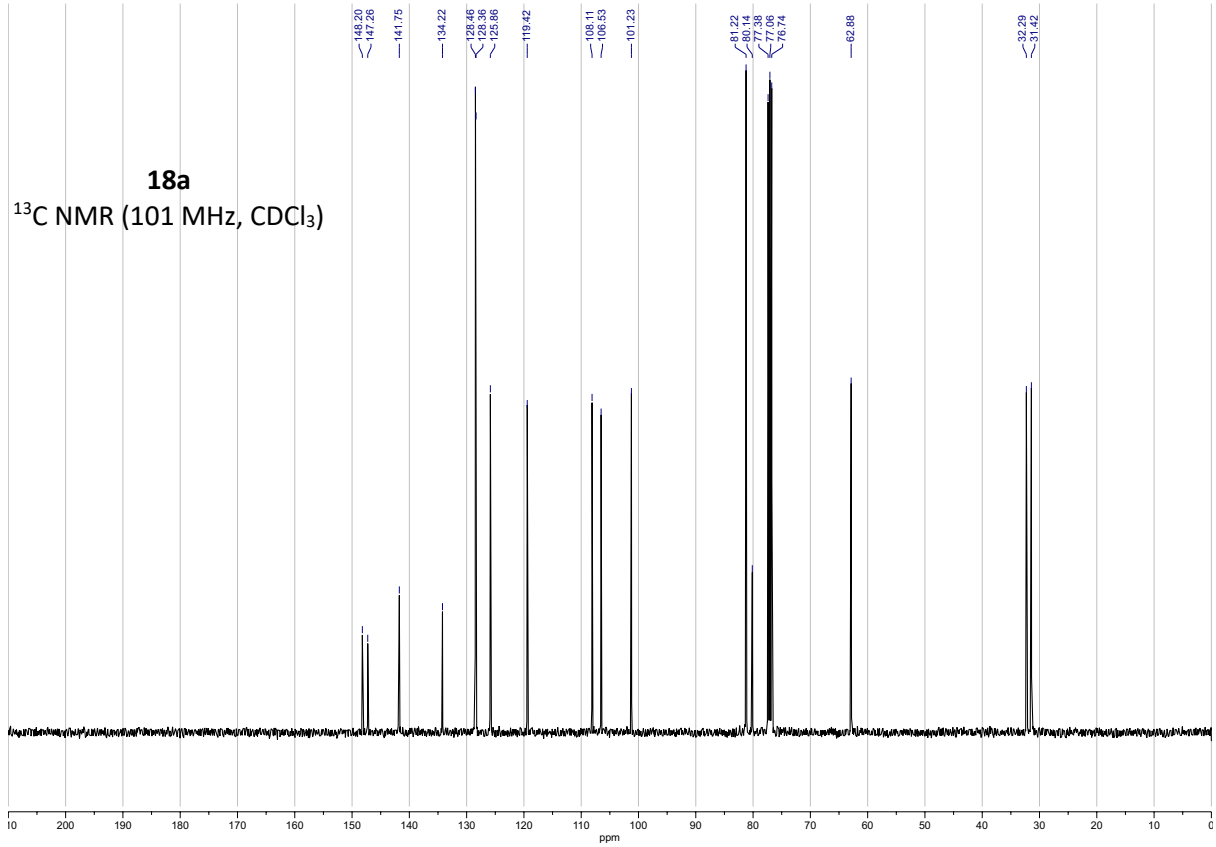

MeO
OMe
O
O
Ph
17a
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)


17a
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)



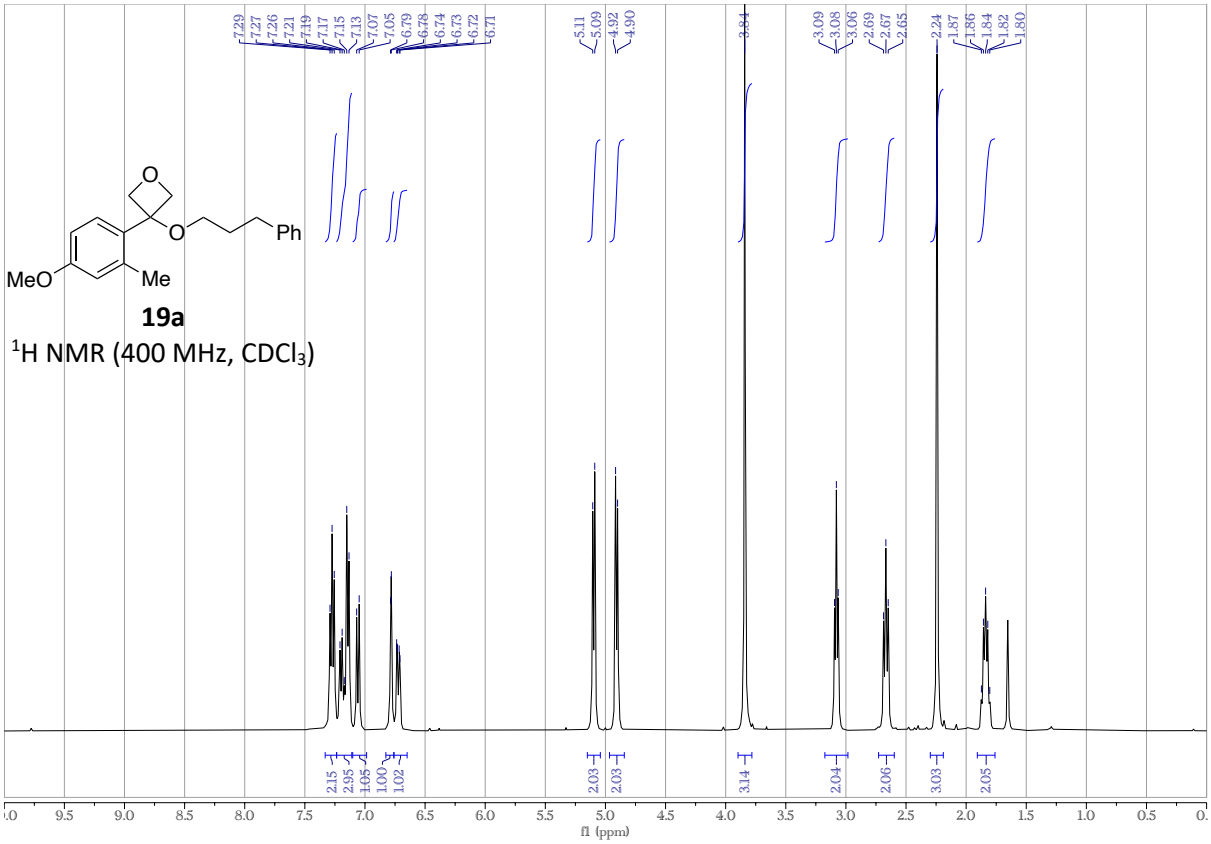
18a

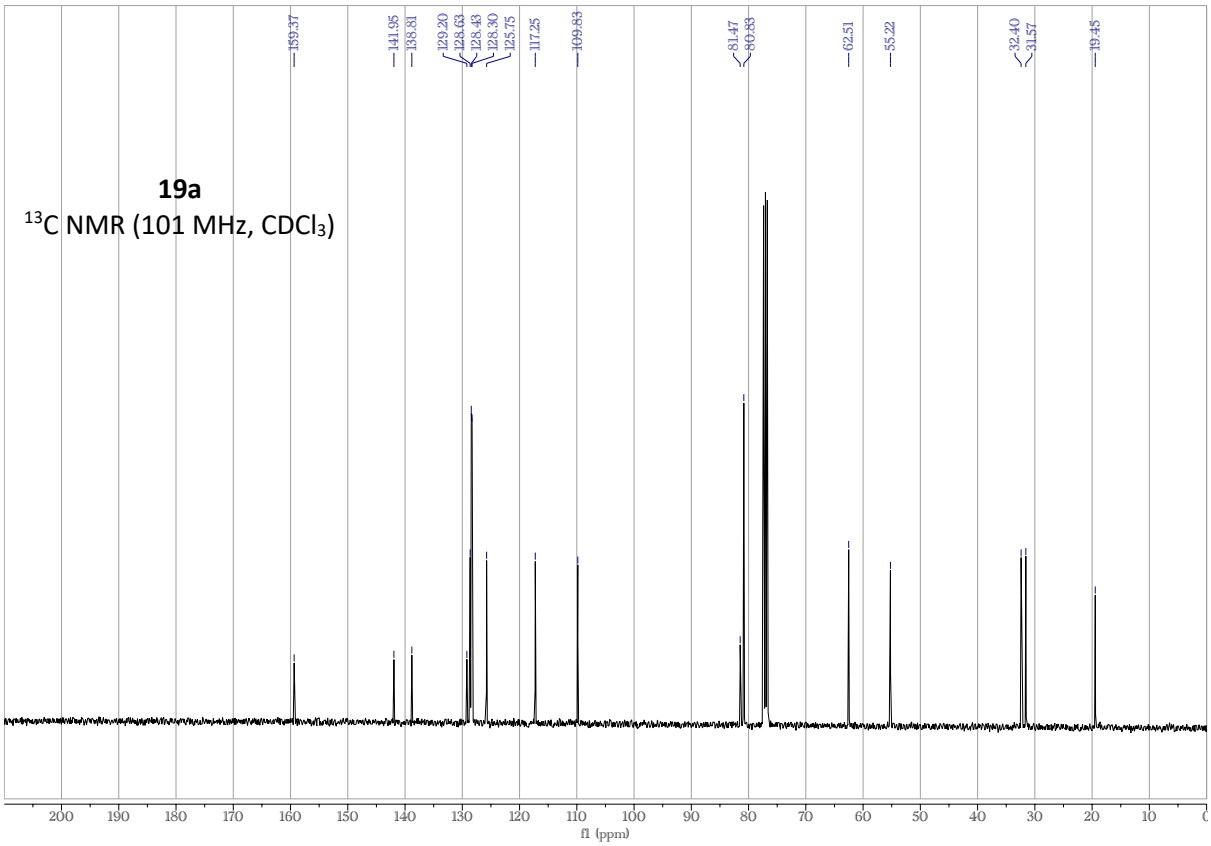
^{1}H NMR (400 MHz, $CDCl_3$)

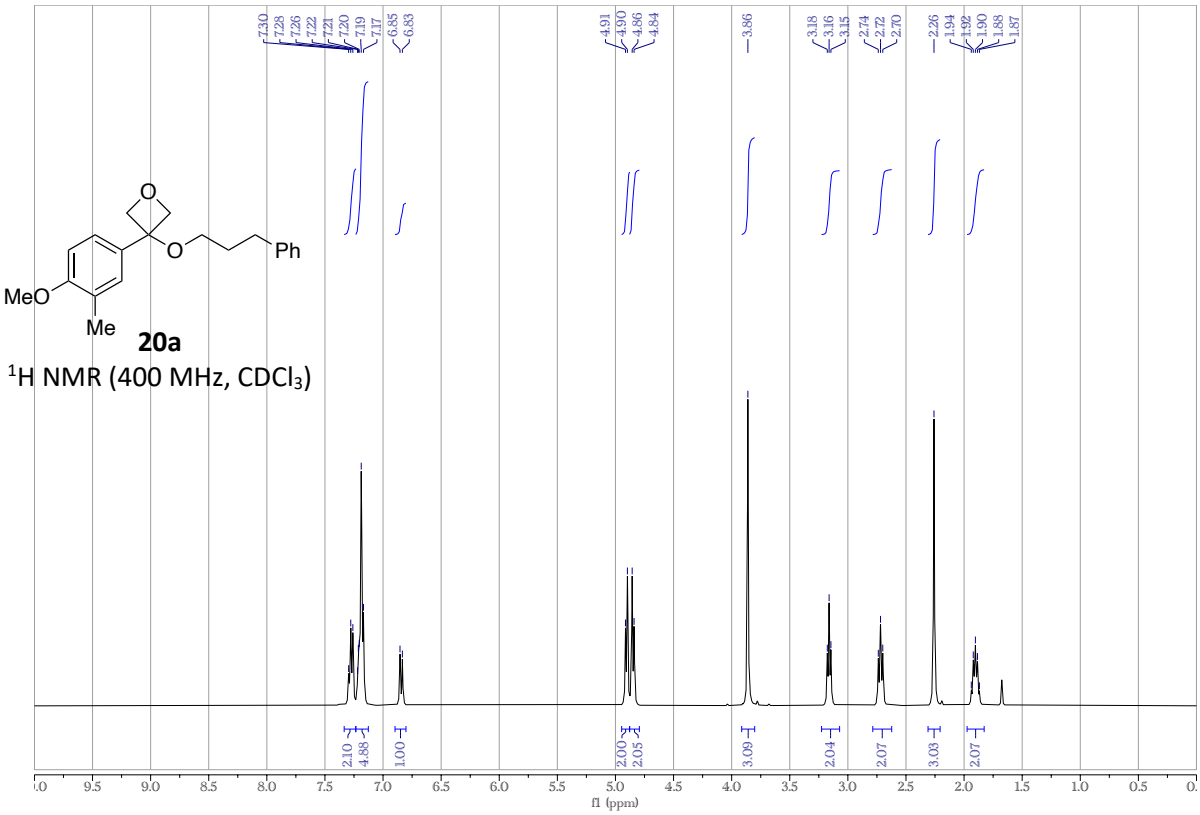


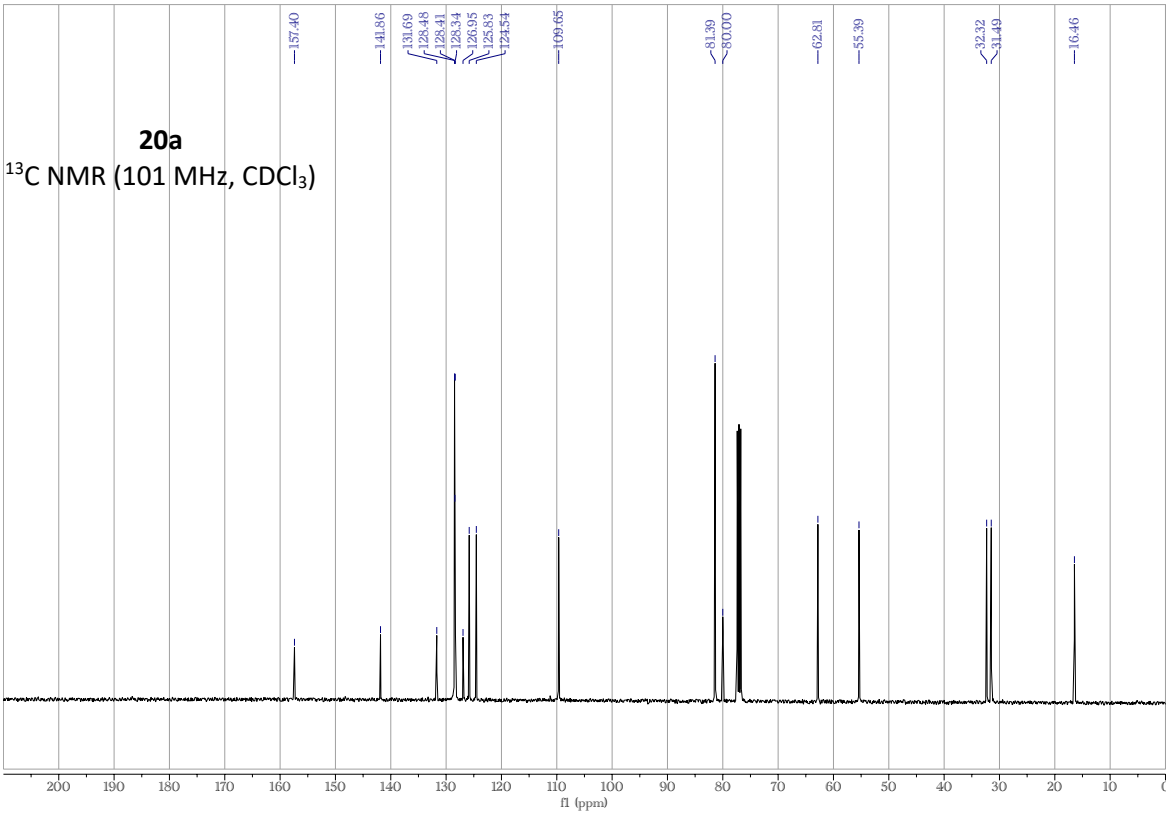
18a

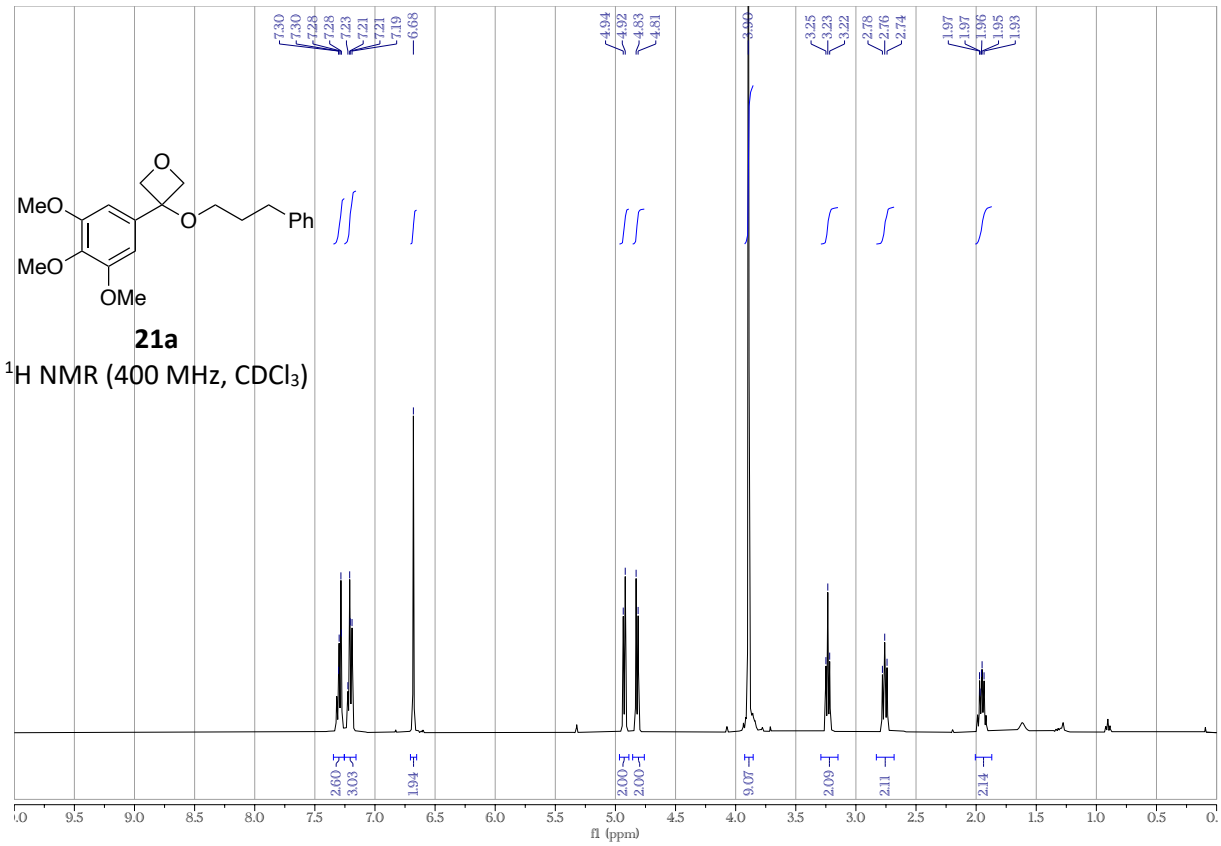
^{13}C NMR (101 MHz, $CDCl_3$)

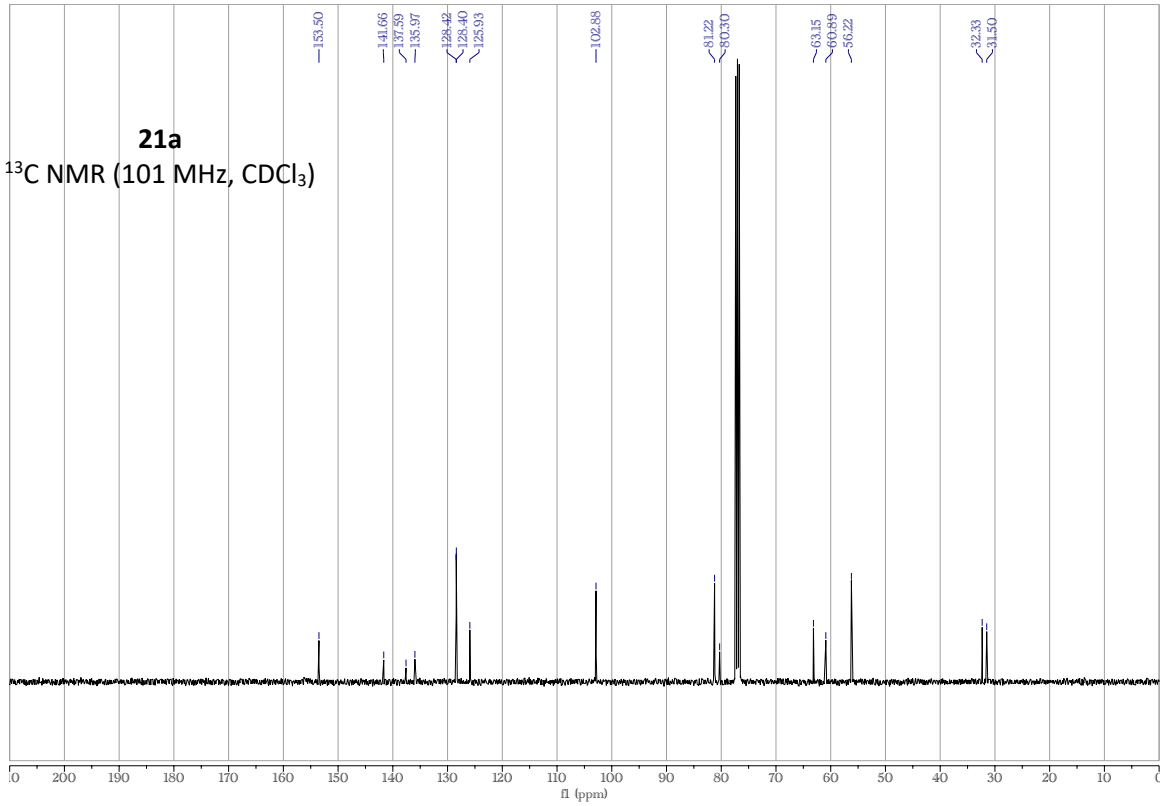

MeO
Me
O
O
Ph
19a
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)

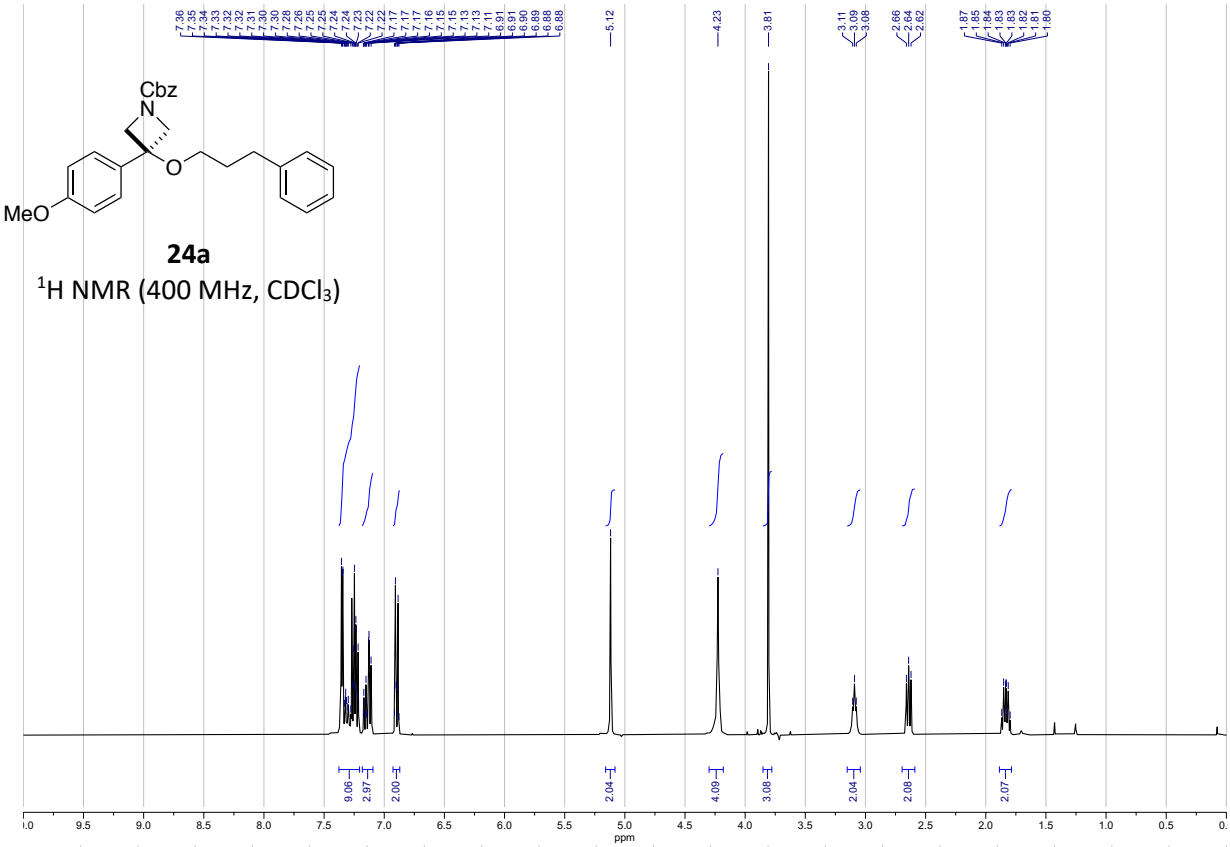

19a
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

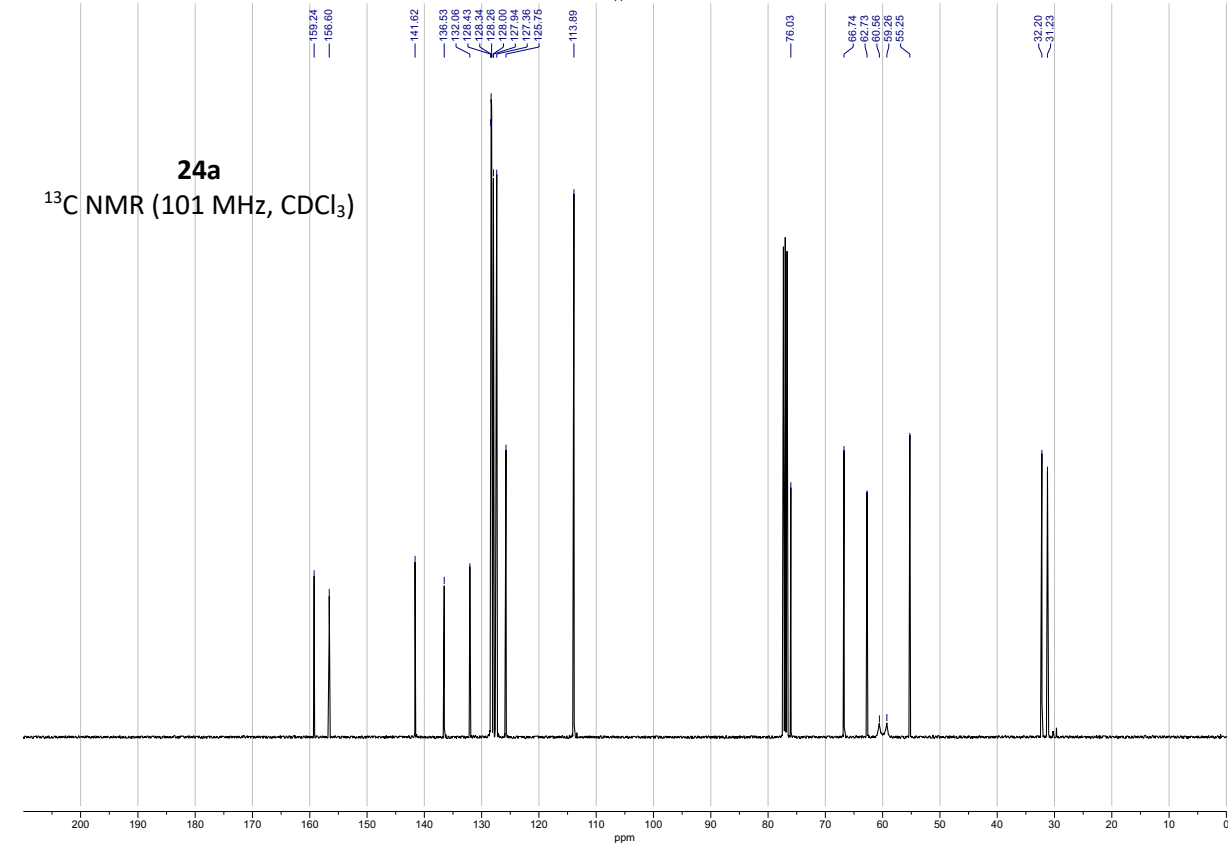

MeO
Me
O
O
Ph
20a
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)

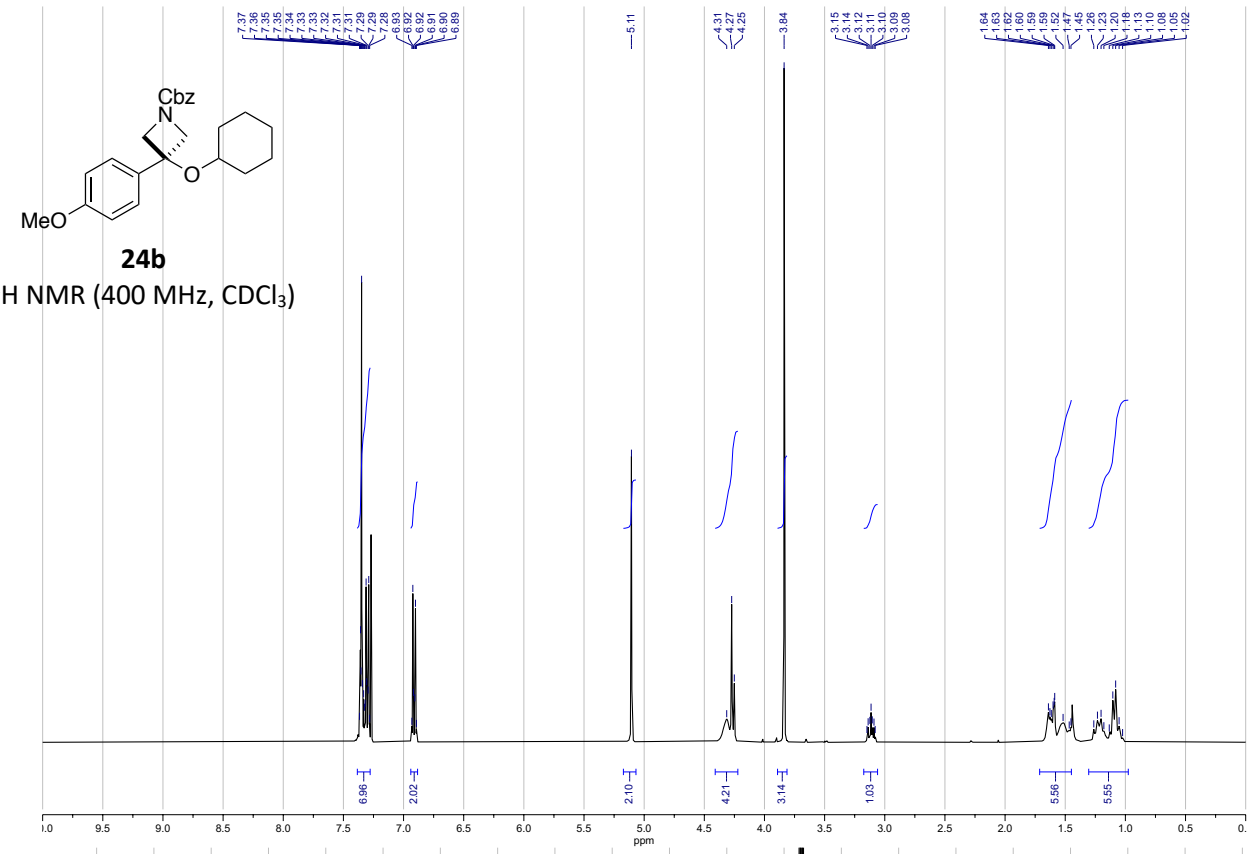

20a
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)


MeO
MeO
OMe
O
O
Ph
21a
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)


21a
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)

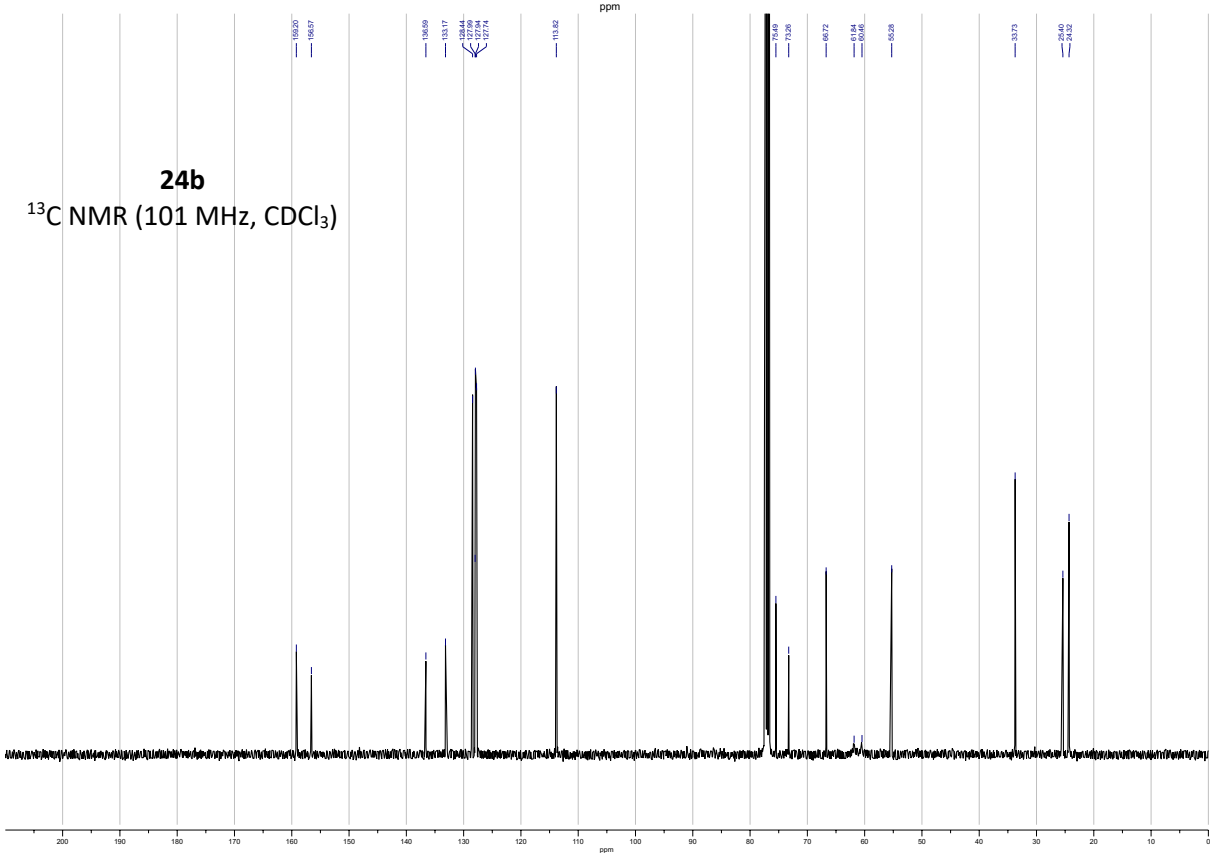

Cbz
N
O
MeO
24a
1H NMR (400 MHz, CDCl3)
ppm


24a
13C NMR (101 MHz, CDCl3)
ppm



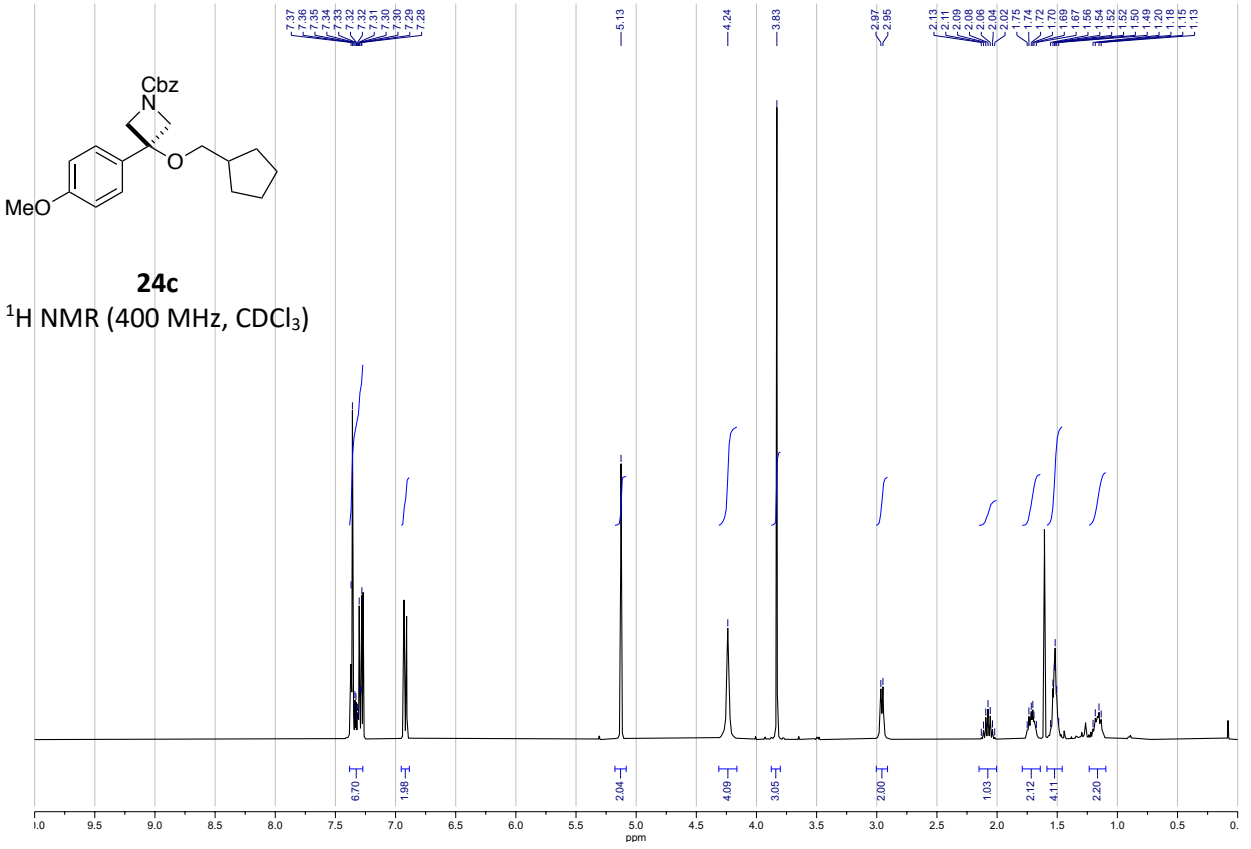
24b

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



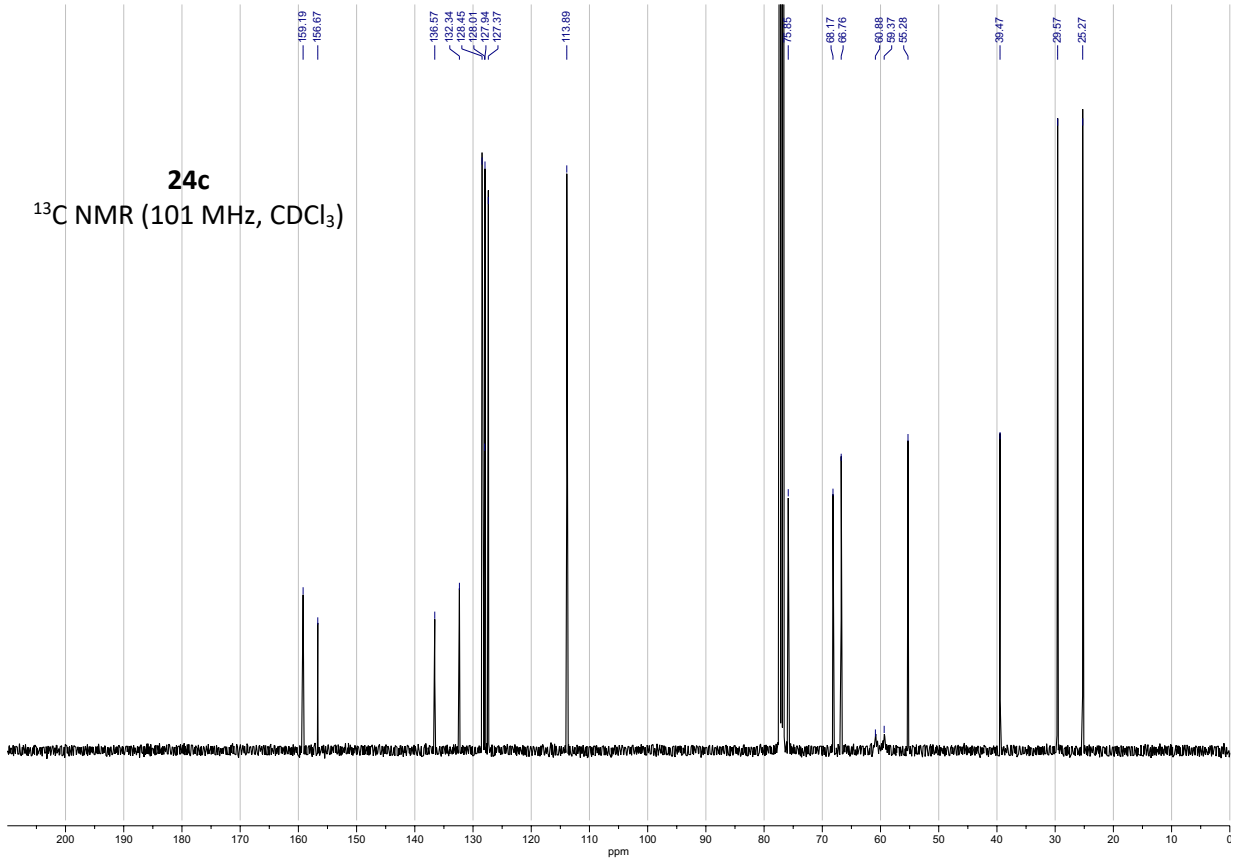
24b

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



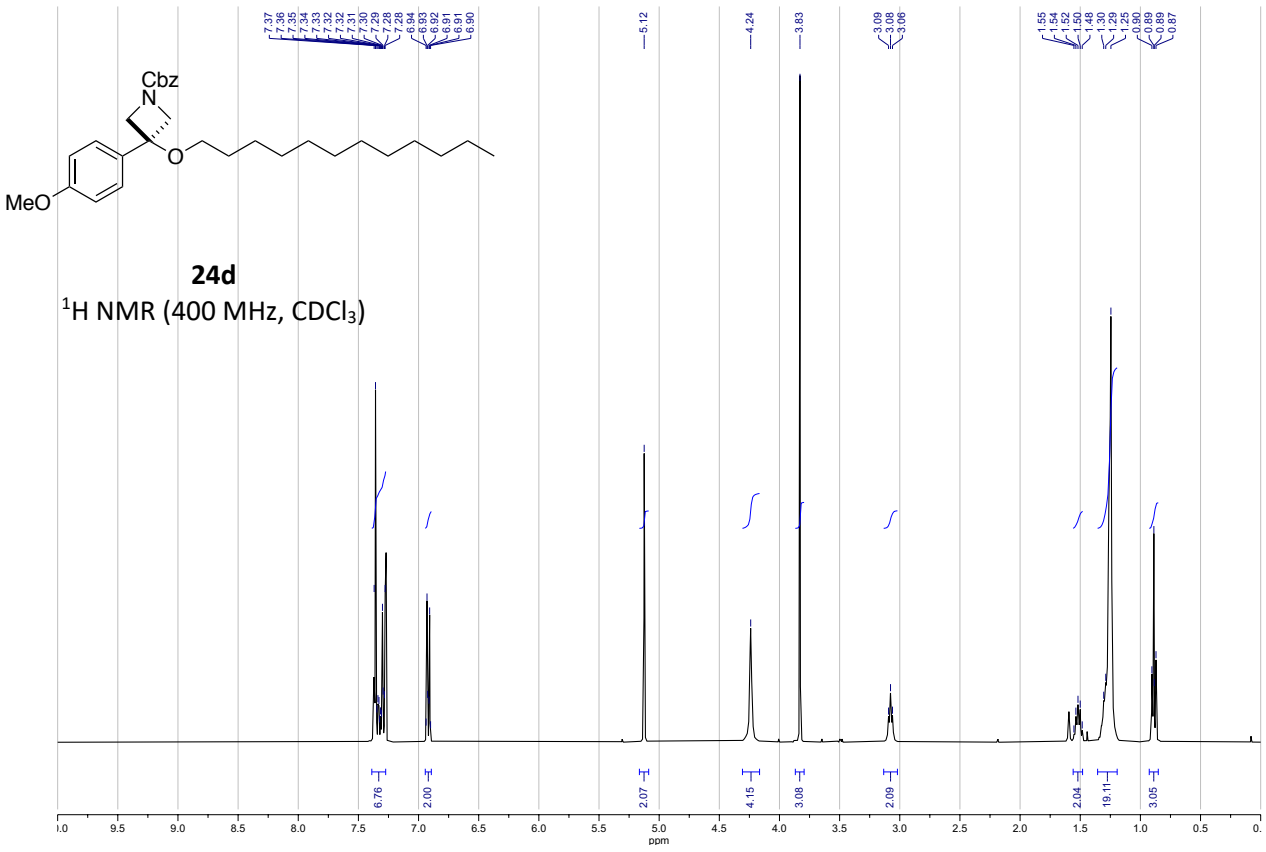
24c

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



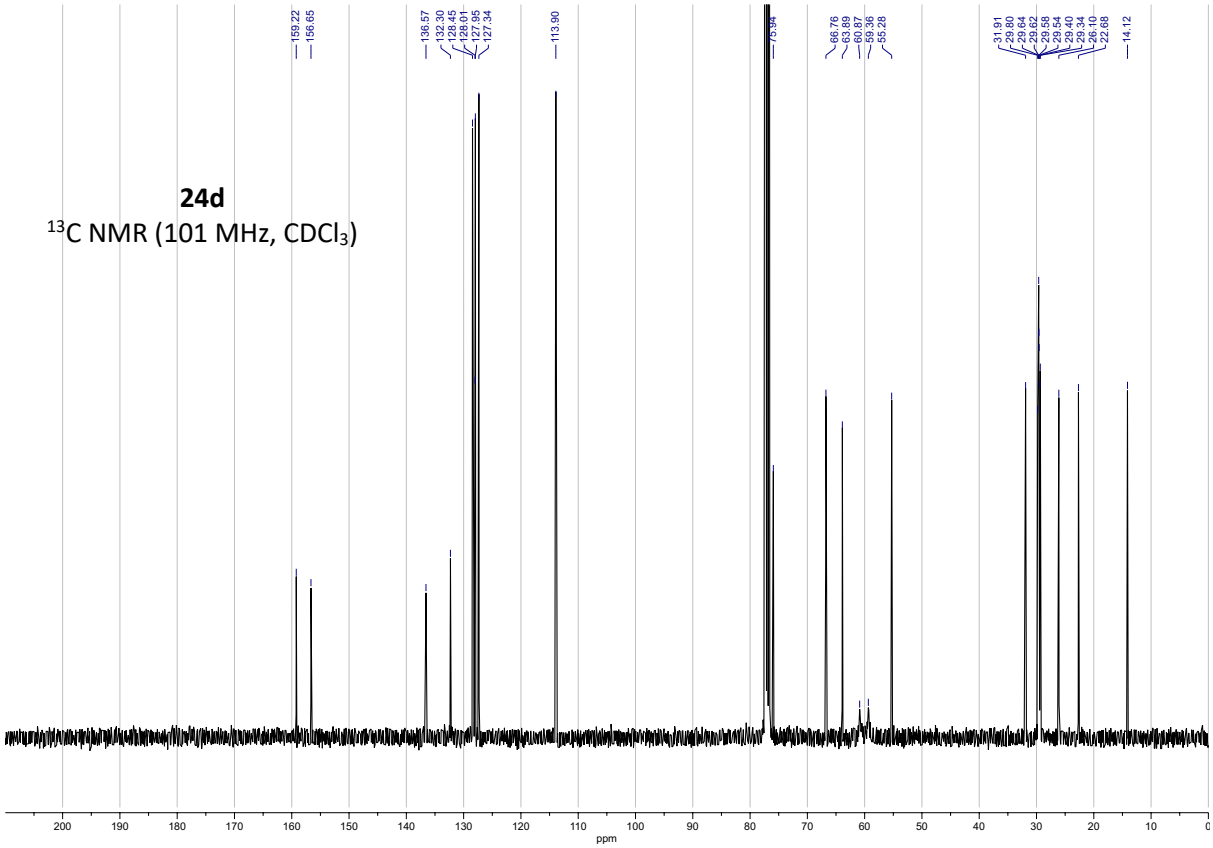
24c

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



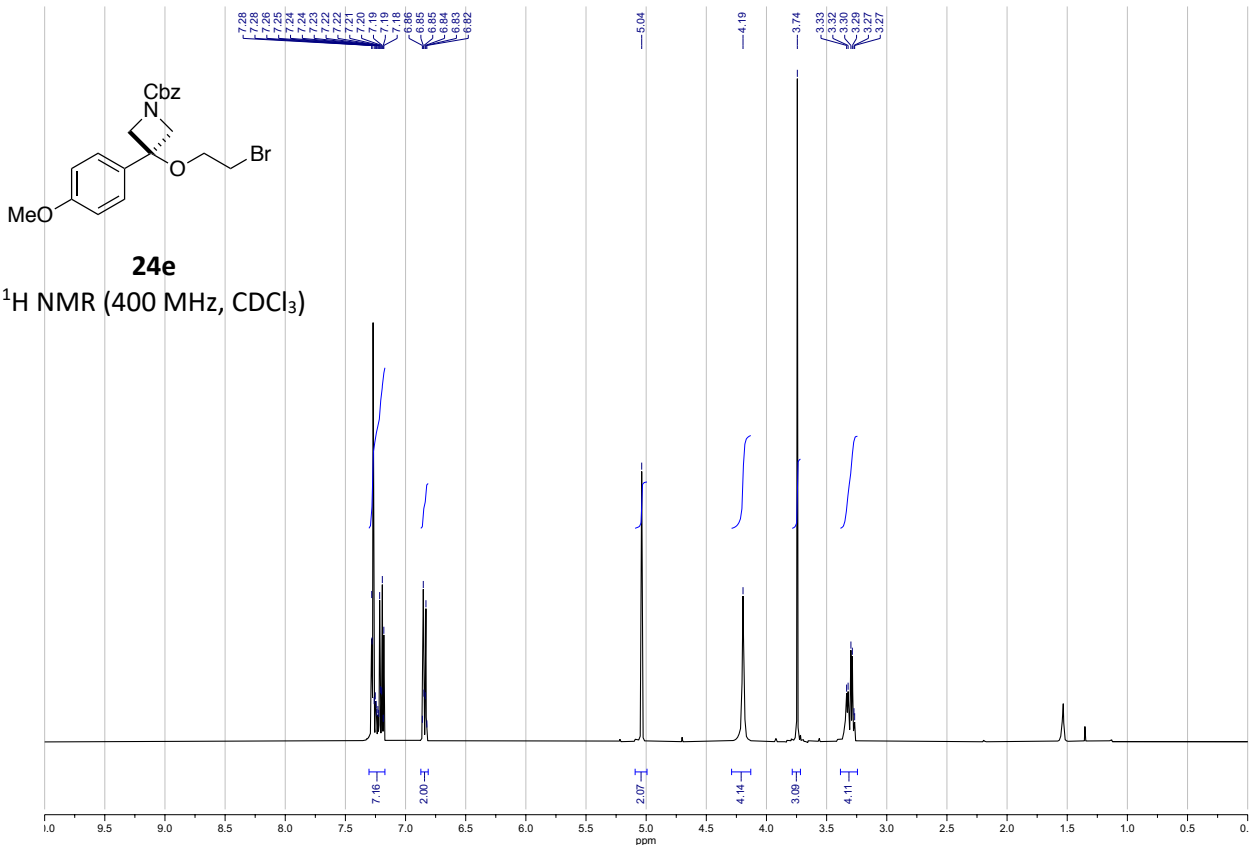
24d

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



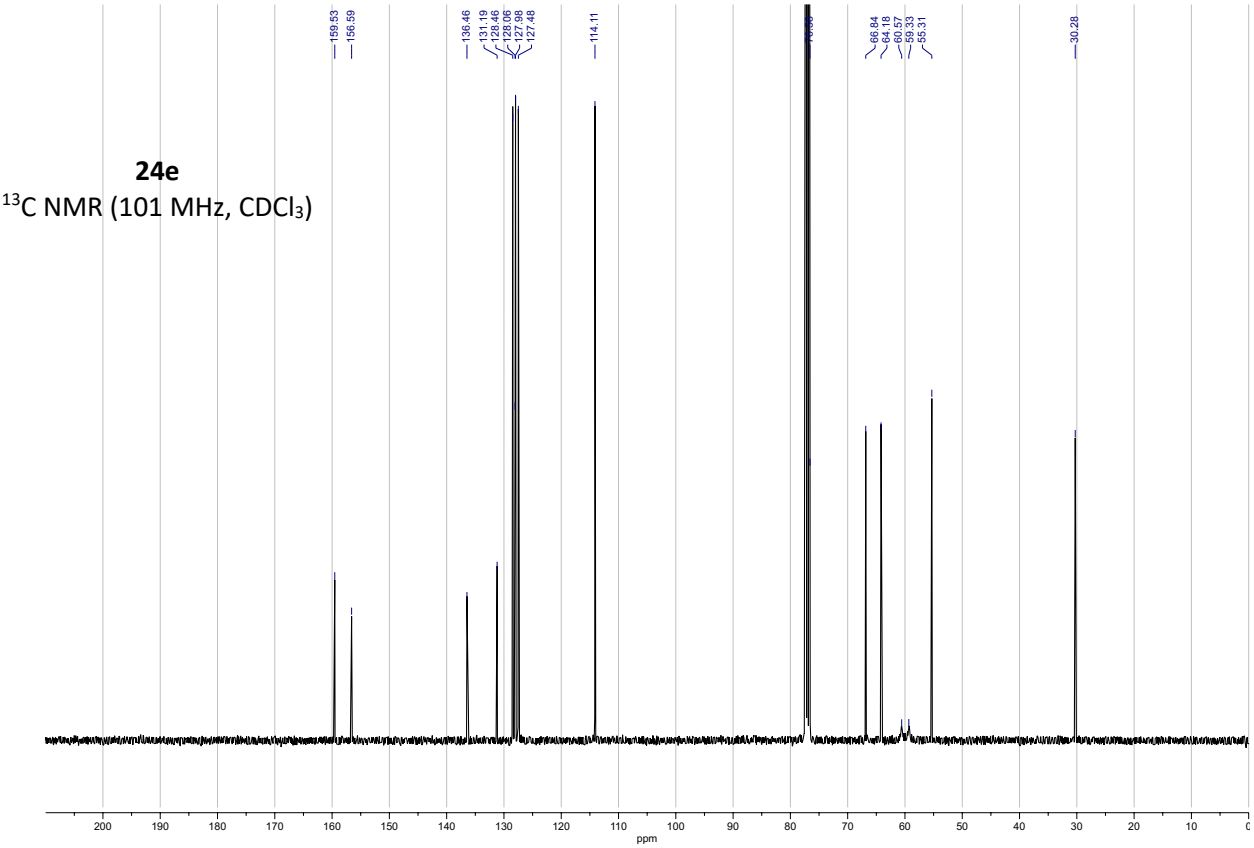
24d

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



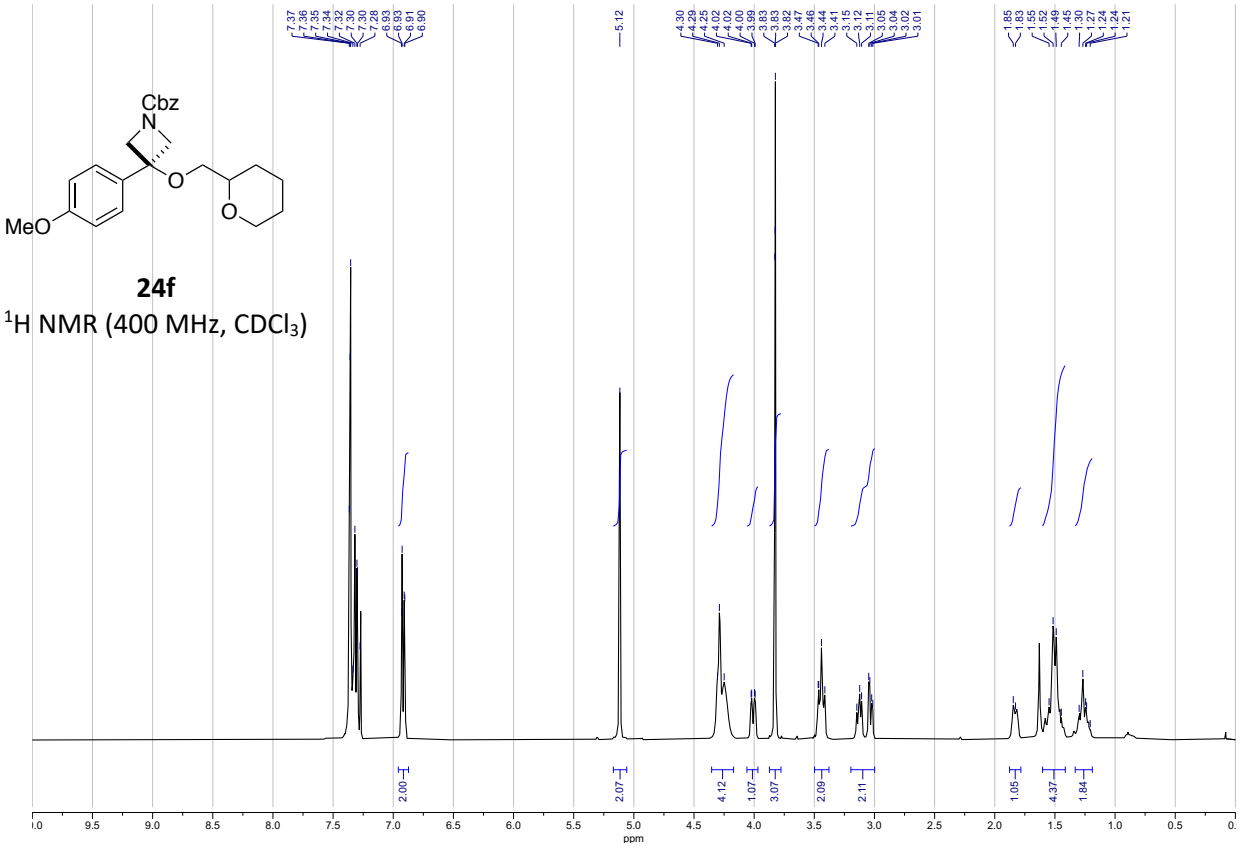
24e

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



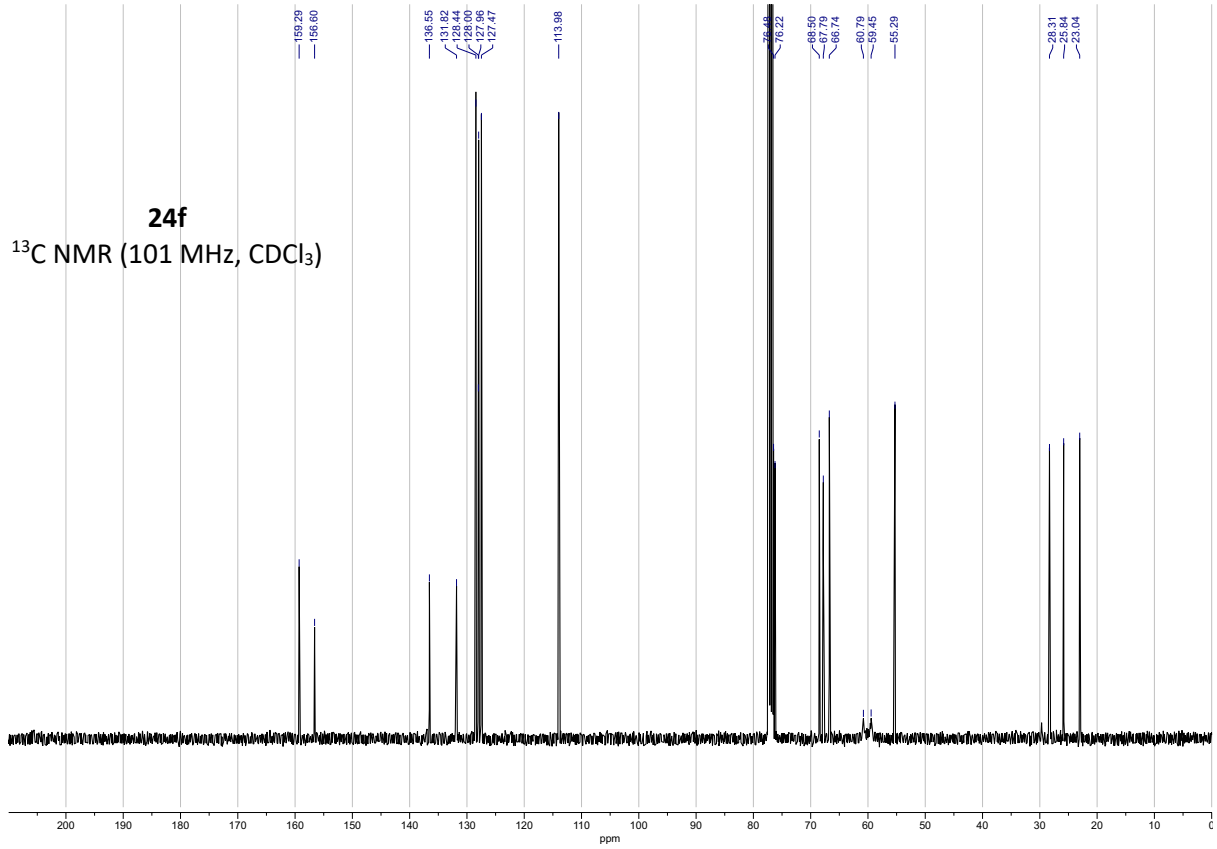
24e

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



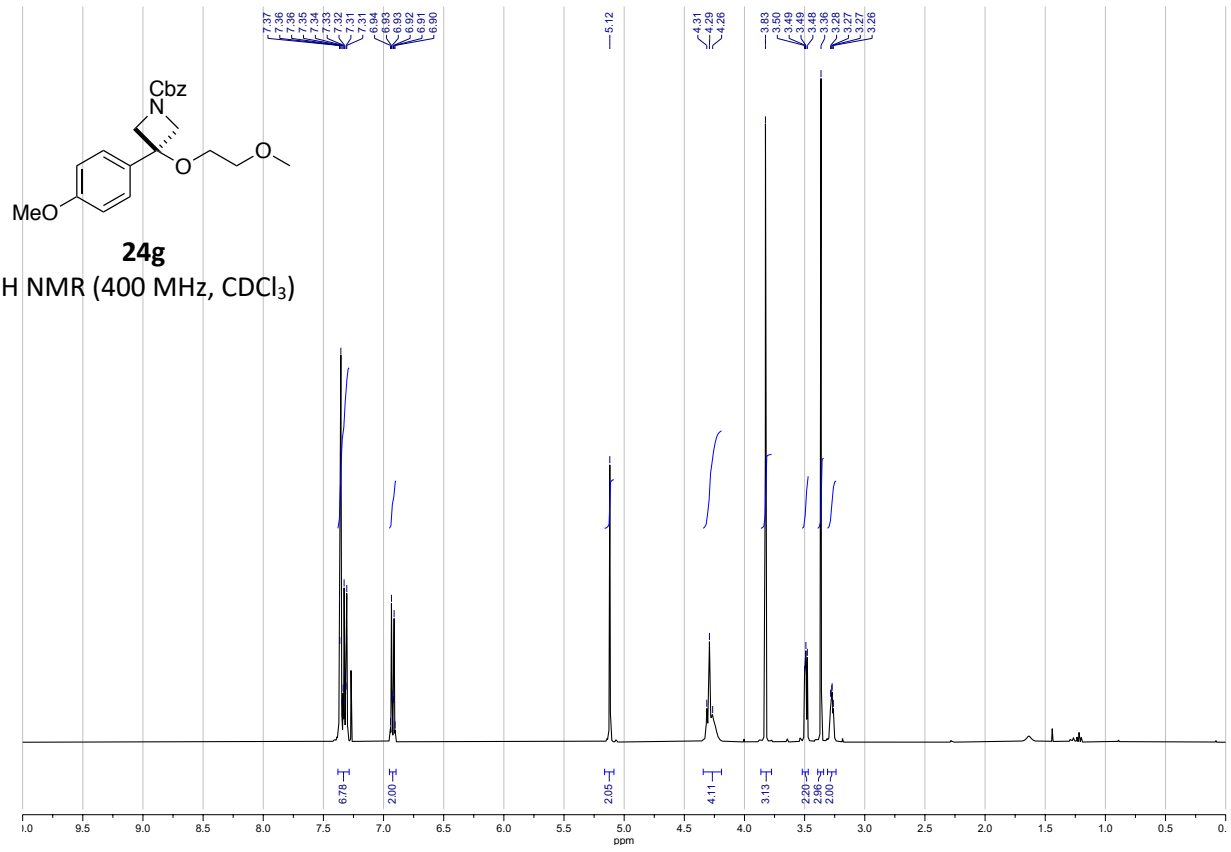
24f

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



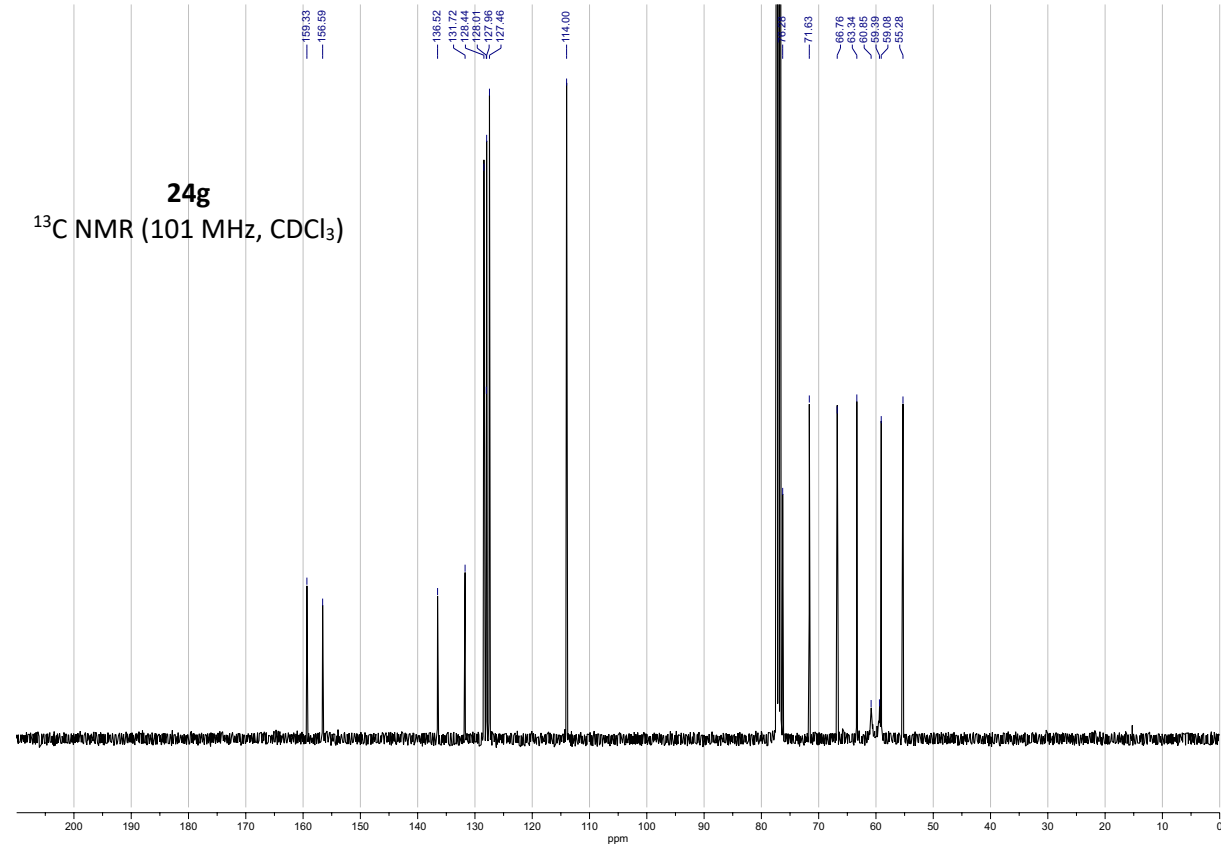
24f

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



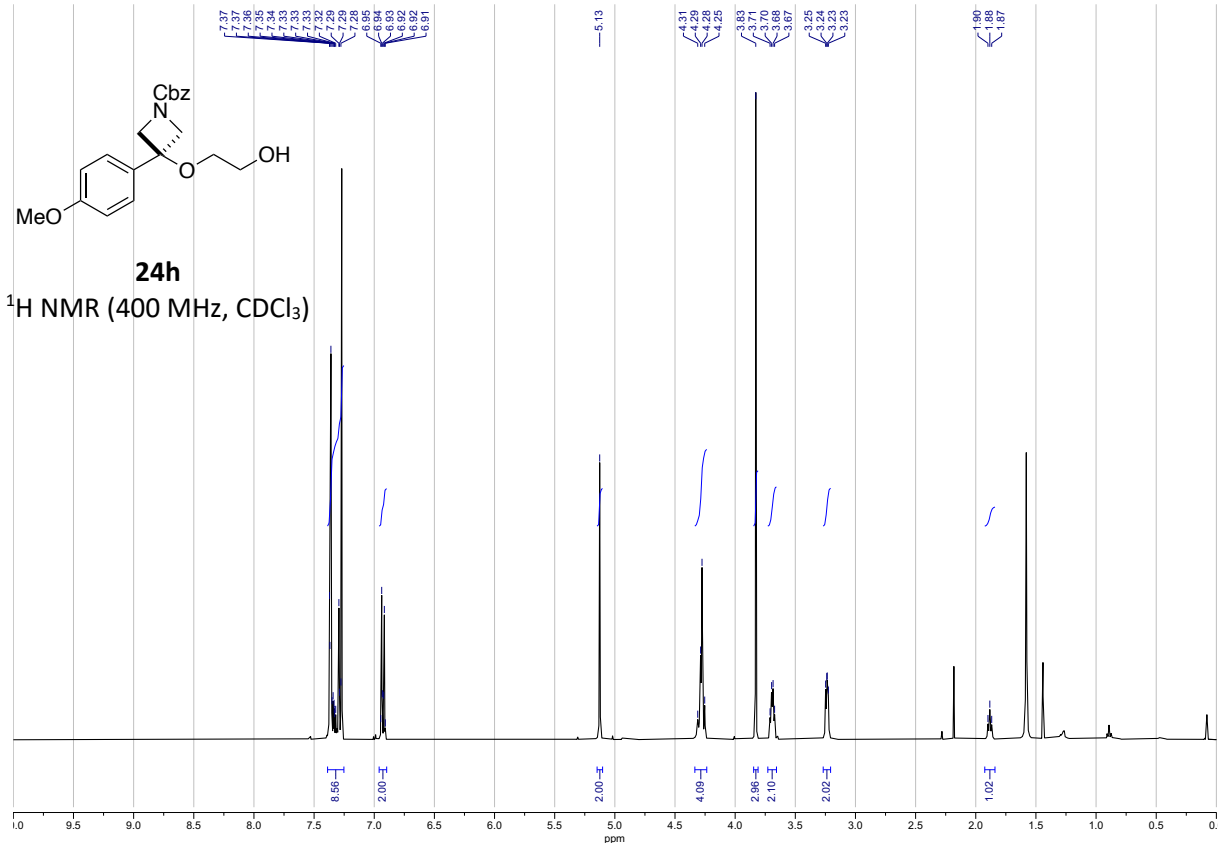
24g

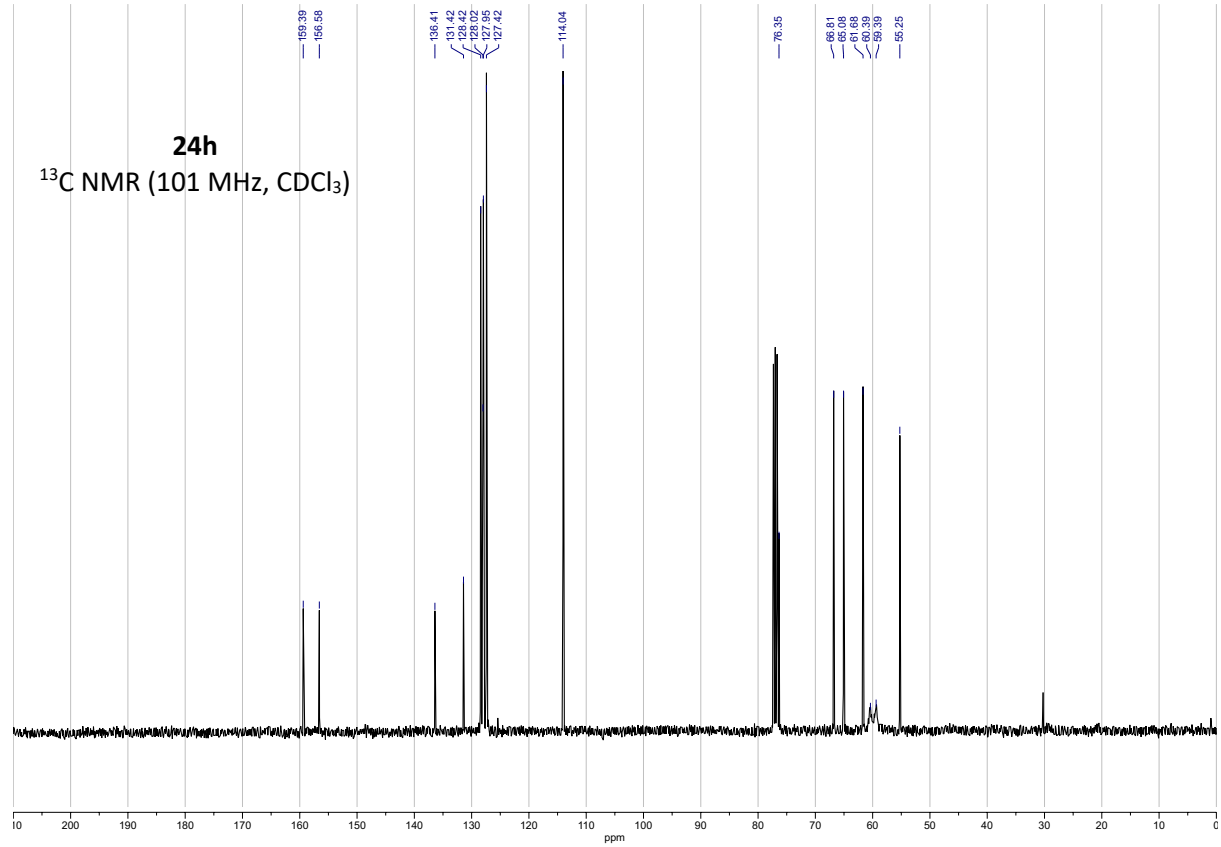
^{1}H NMR (400 MHz, $CDCl_3$)

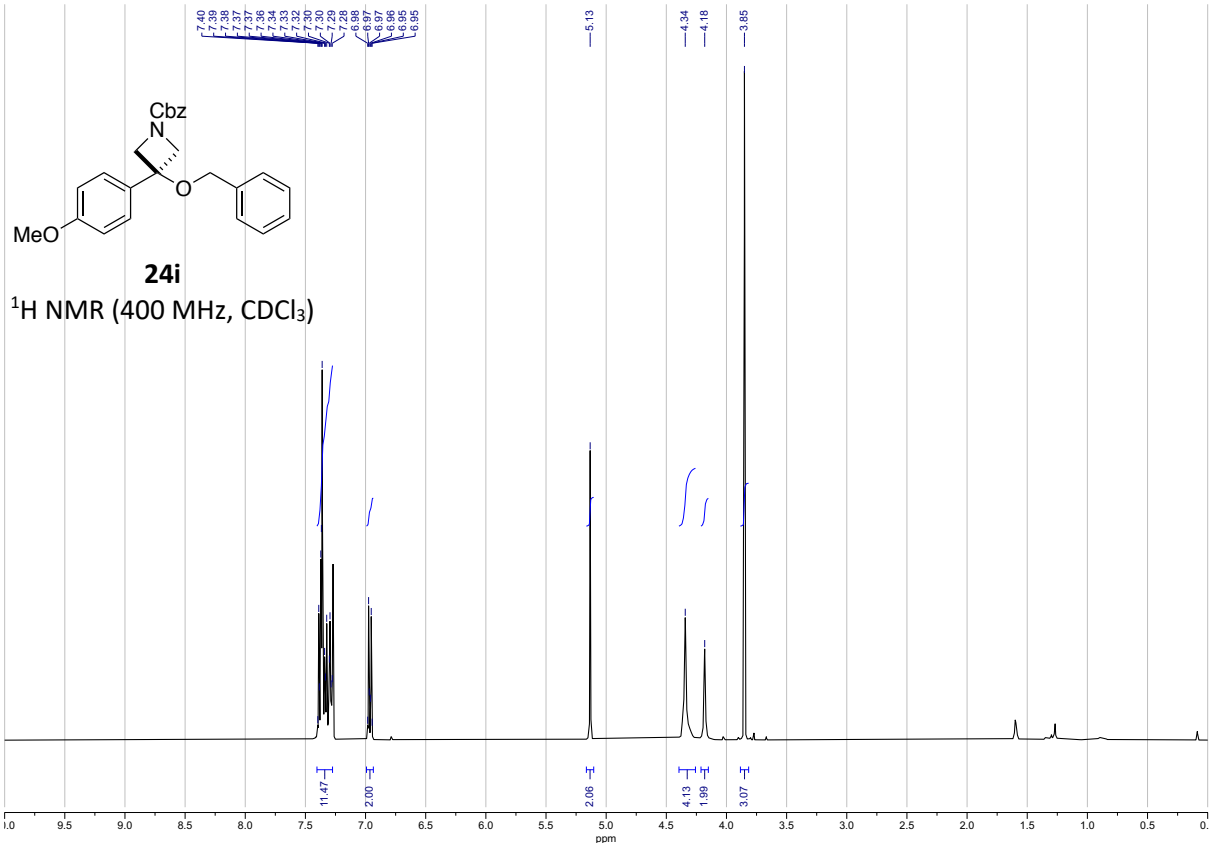


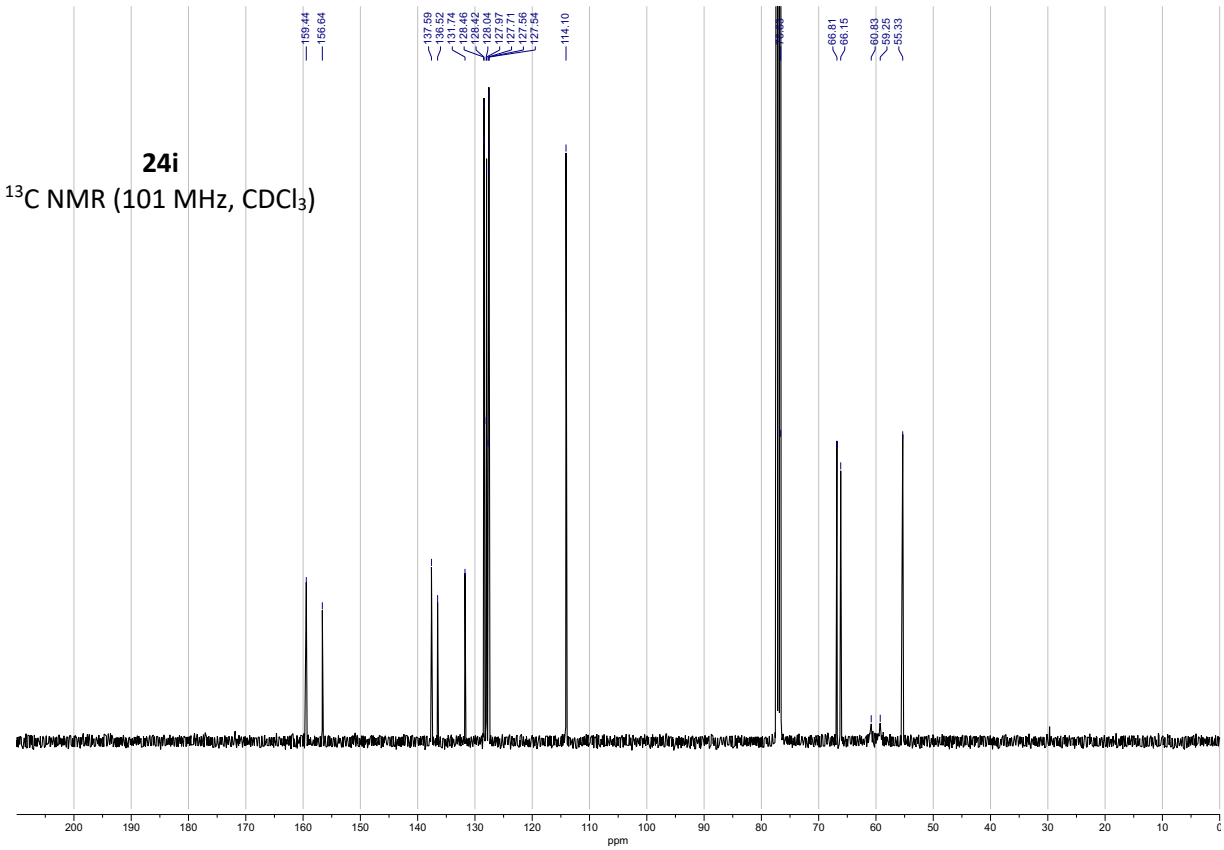
24g

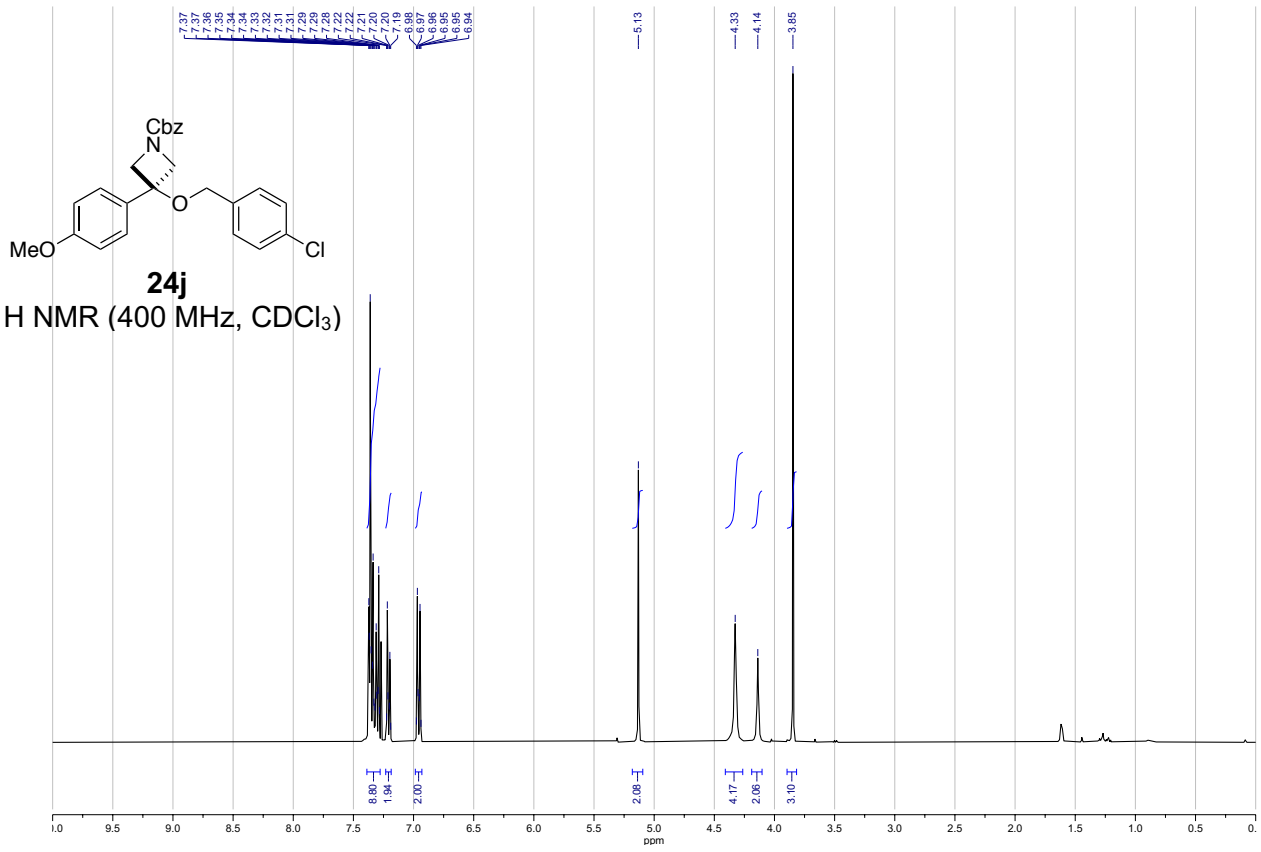
^{13}C NMR (101 MHz, $CDCl_3$)


Cbz
N
O
OH
MeO
24h
1H NMR (400 MHz, CDCl3)
ppm


24h
13C NMR (101 MHz, CDCl3)
ppm

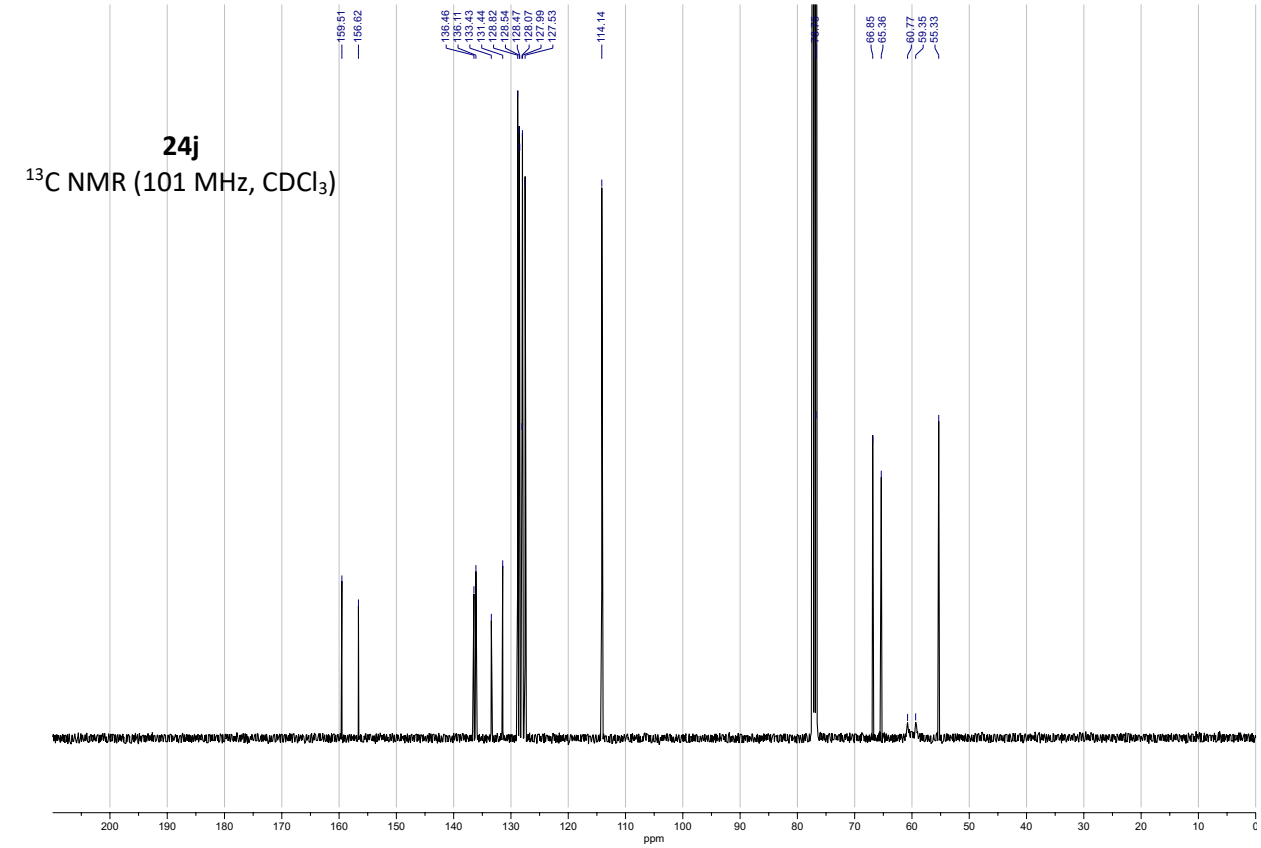

Cbz
N
O
MeO
24i
1H NMR (400 MHz, CDCl3)
7.40
7.39
7.38
7.37
7.37
7.36
7.34
7.33
7.32
7.30
7.30
7.29
7.28
6.98
6.97
6.97
6.96
6.95
6.95
5.13
4.34
4.18
3.85
11.47
2.00
2.06
4.13
1.99
3.07
ppm


24i
13C NMR (101 MHz, CDCl3)
159.44
156.64
137.59
136.52
131.74
128.46
128.42
128.04
127.97
127.71
127.56
127.54
114.10
66.81
66.15
60.83
59.25
55.33
ppm



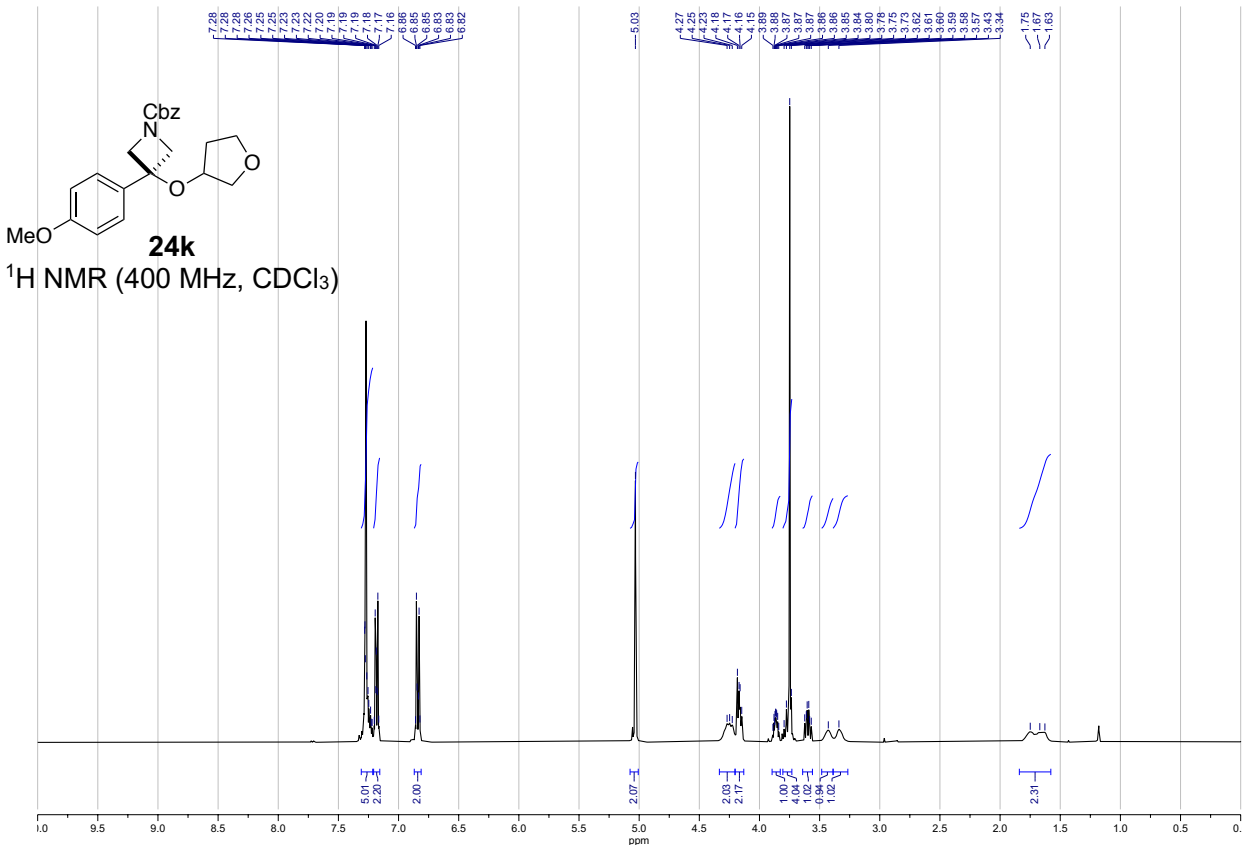
24j

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



24j

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

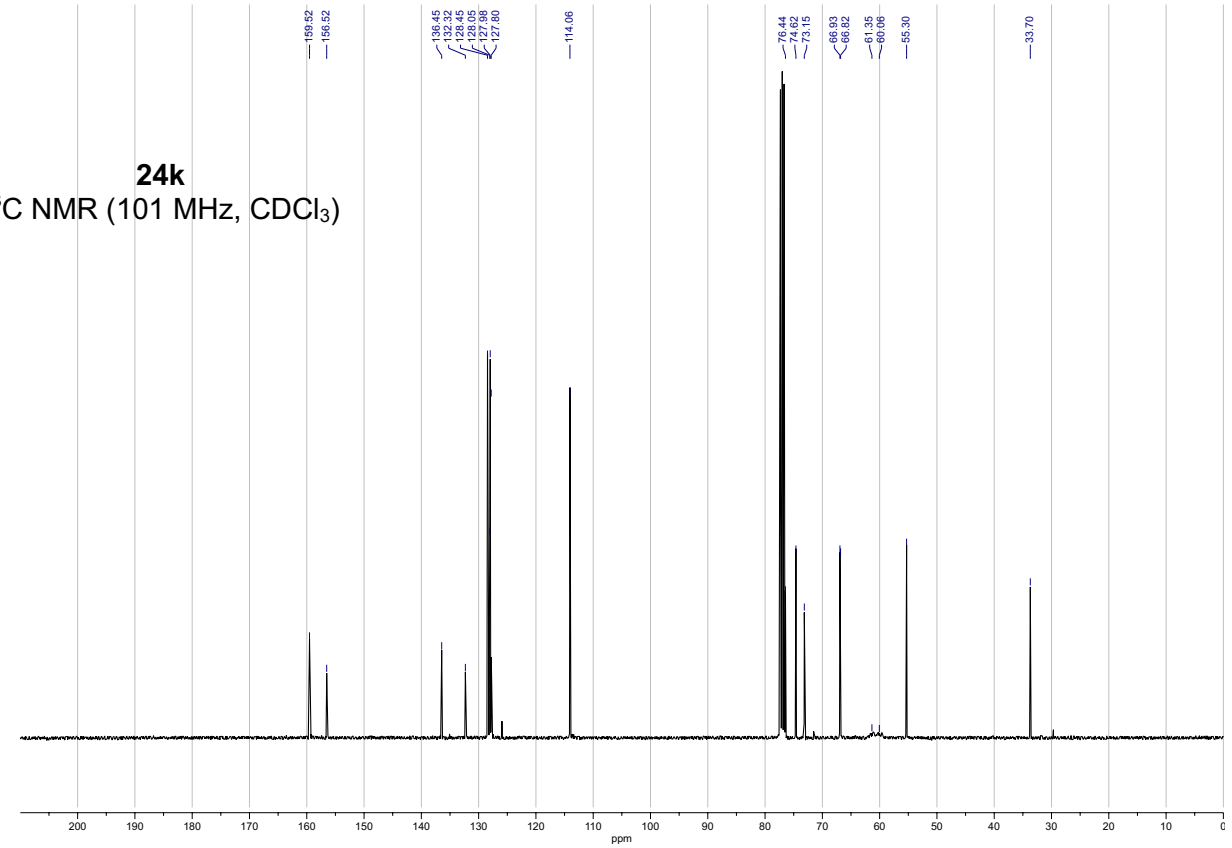


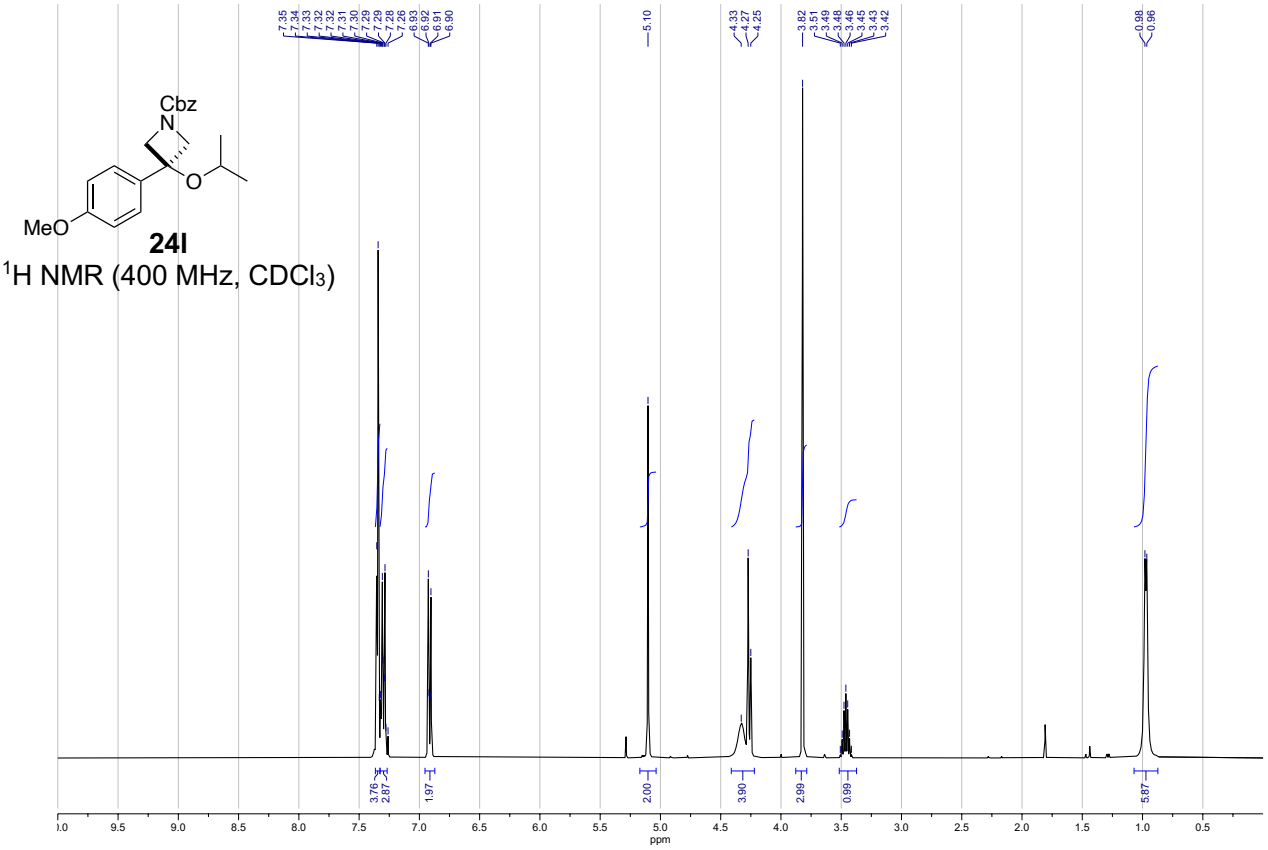
24k

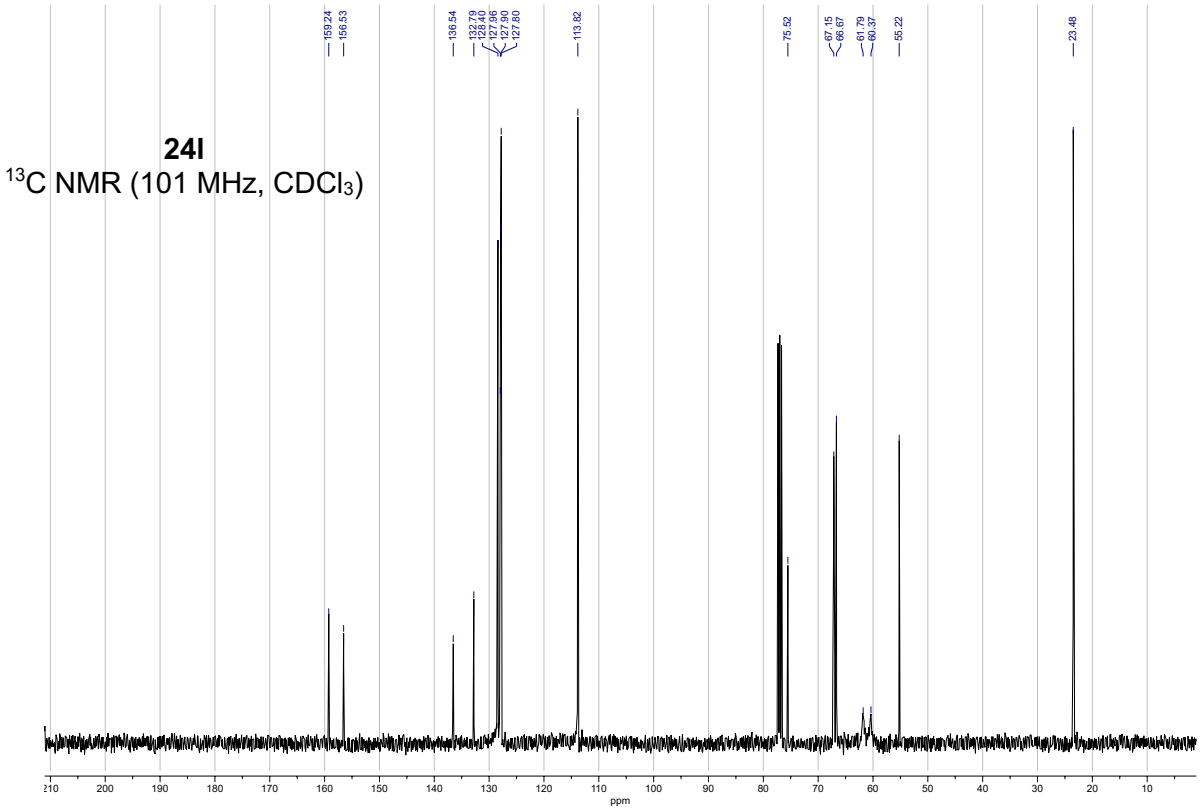
^{1}H NMR (400 MHz, $CDCl_3$)

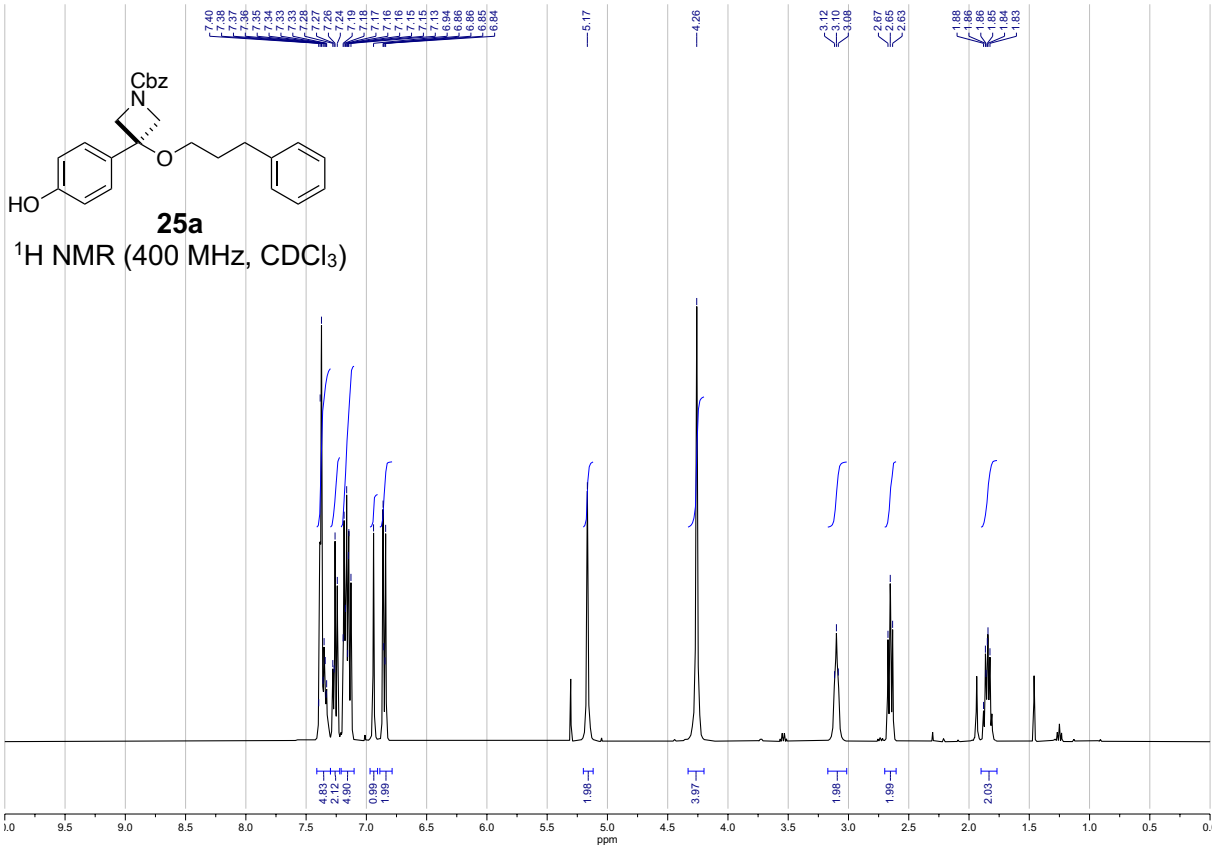
24k

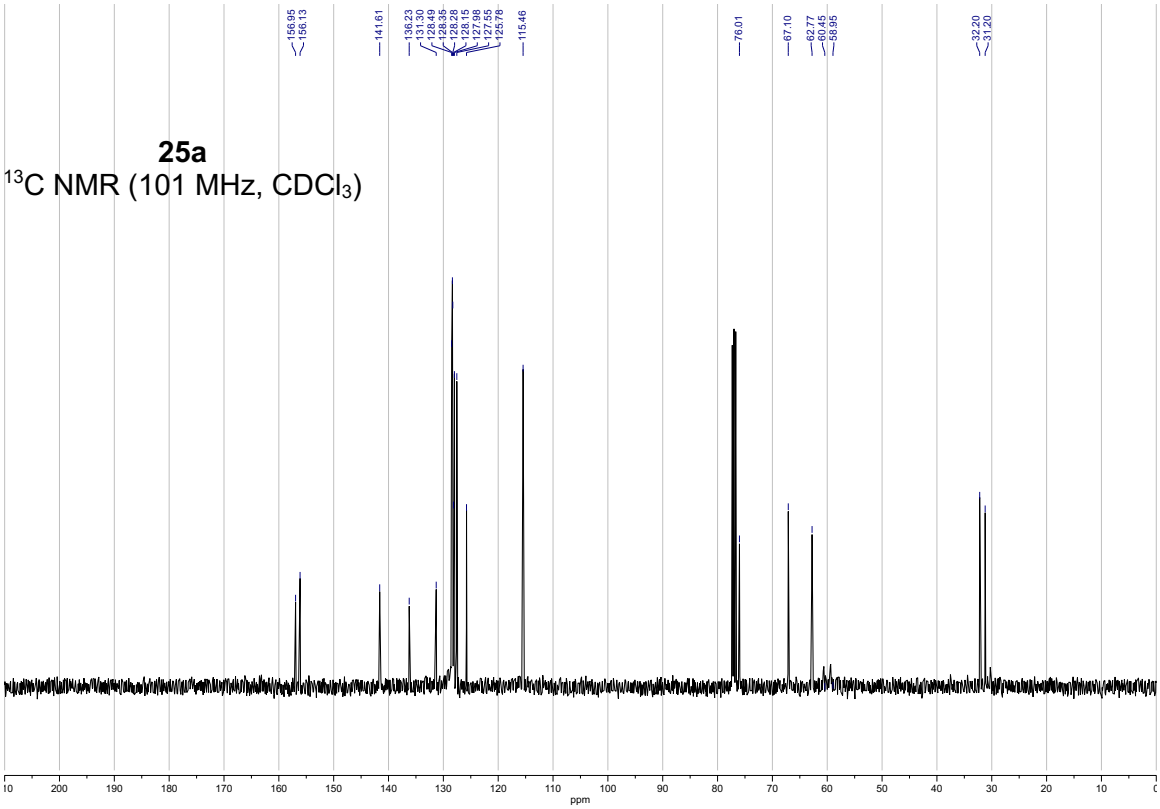
^{13}C NMR (101 MHz, $CDCl_3$)

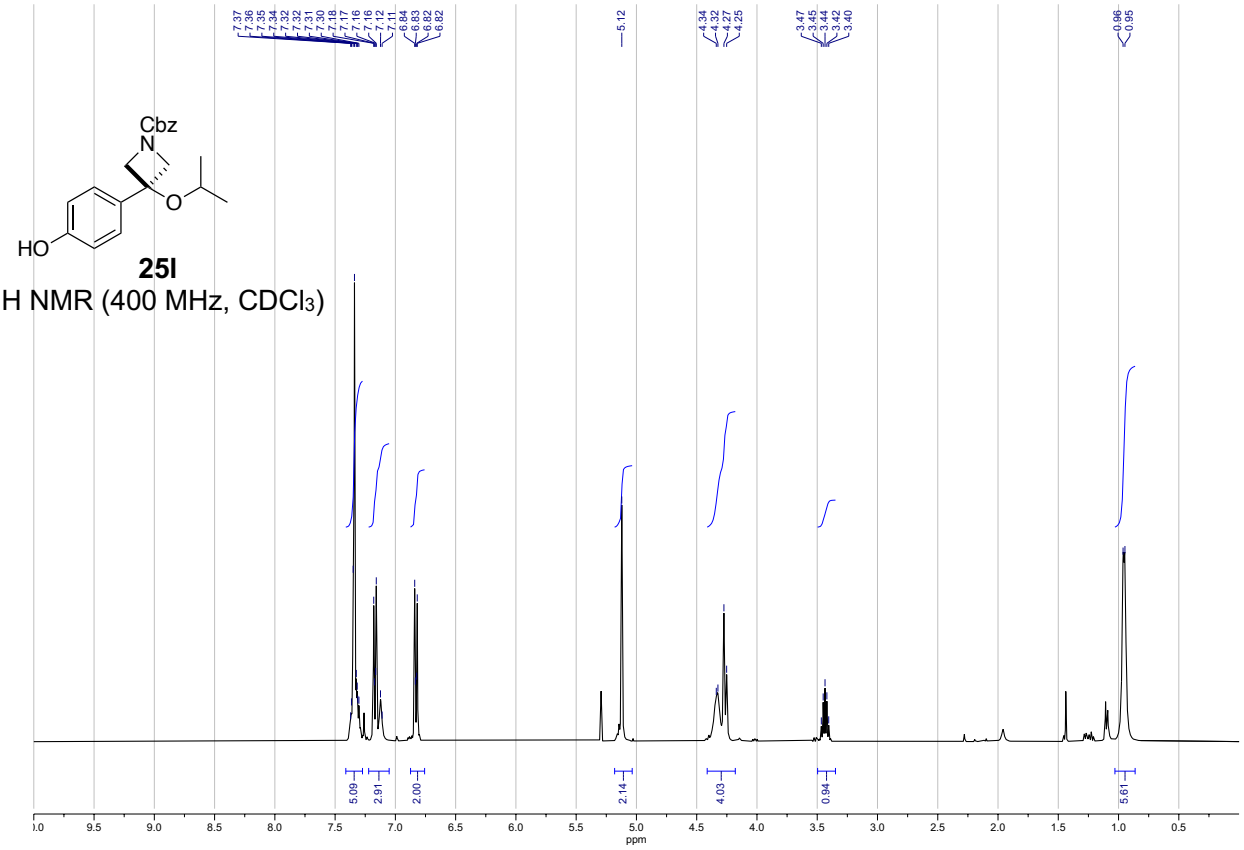


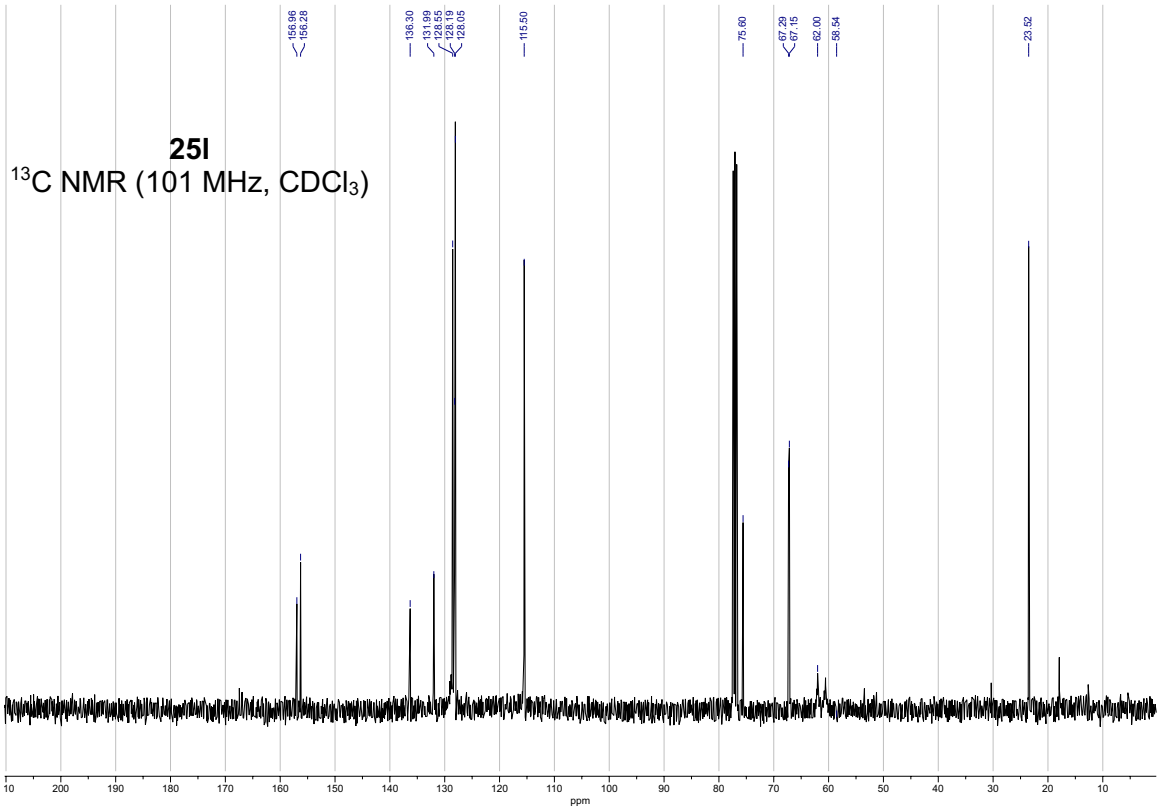

Cbz
N
O
MeO
24l
1H NMR (400 MHz, CDCl3)
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.26
6.93
6.92
6.91
6.90
5.10
4.33
4.27
4.25
3.82
3.51
3.49
3.48
3.46
3.45
3.43
3.42
0.98
0.96
3.76
2.87
1.97
2.00
3.90
2.99
0.99
5.87
ppm

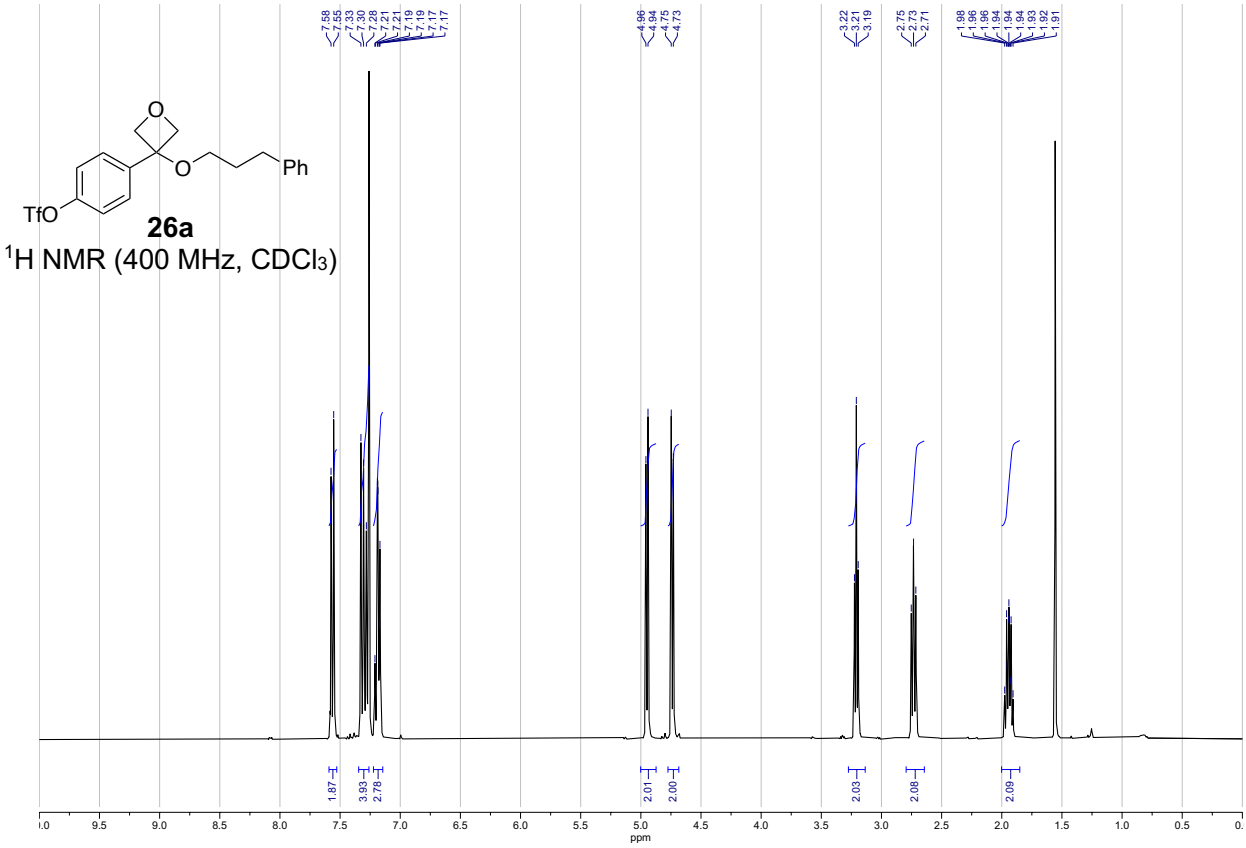

24l
13C NMR (101 MHz, CDCl3)
159.24
156.53
136.54
132.79
128.40
127.96
127.90
127.80
113.82
75.52
67.15
66.67
61.79
60.37
55.22
23.48
ppm

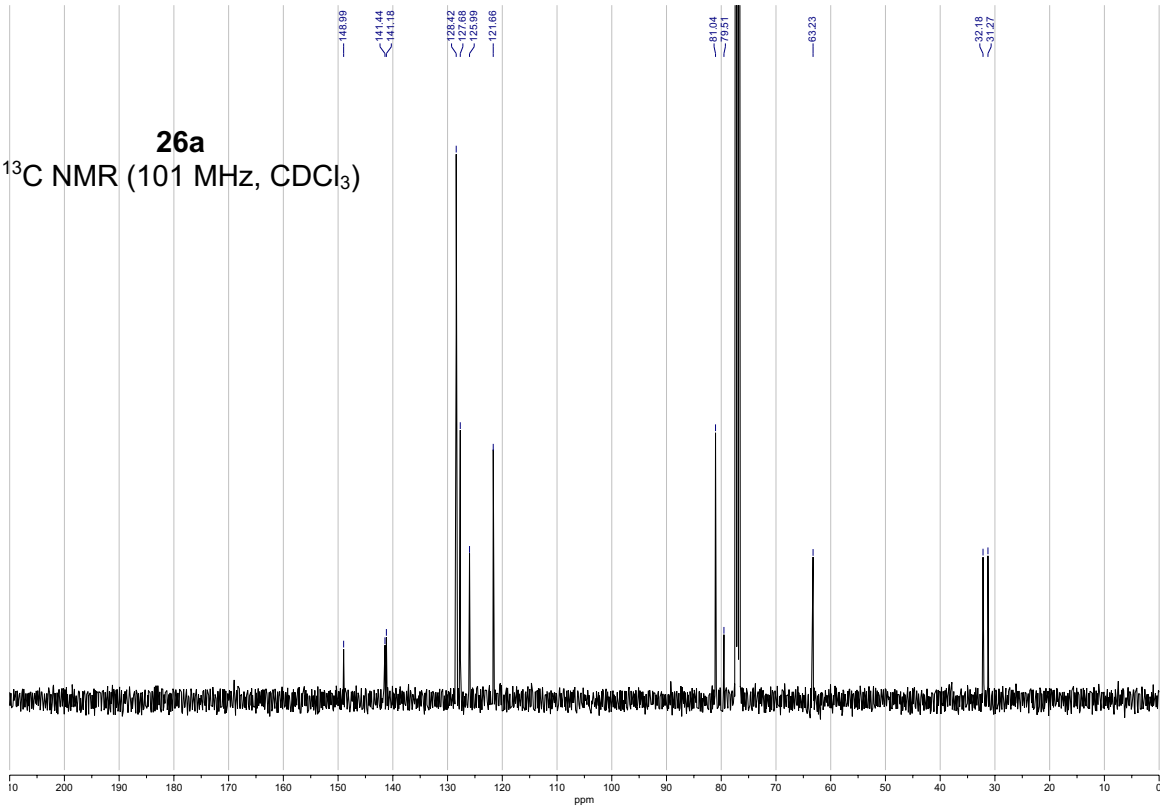

Cbz
N
O
HO
25a
^{1}H NMR (400 MHz, CDCl$_3$)
ppm

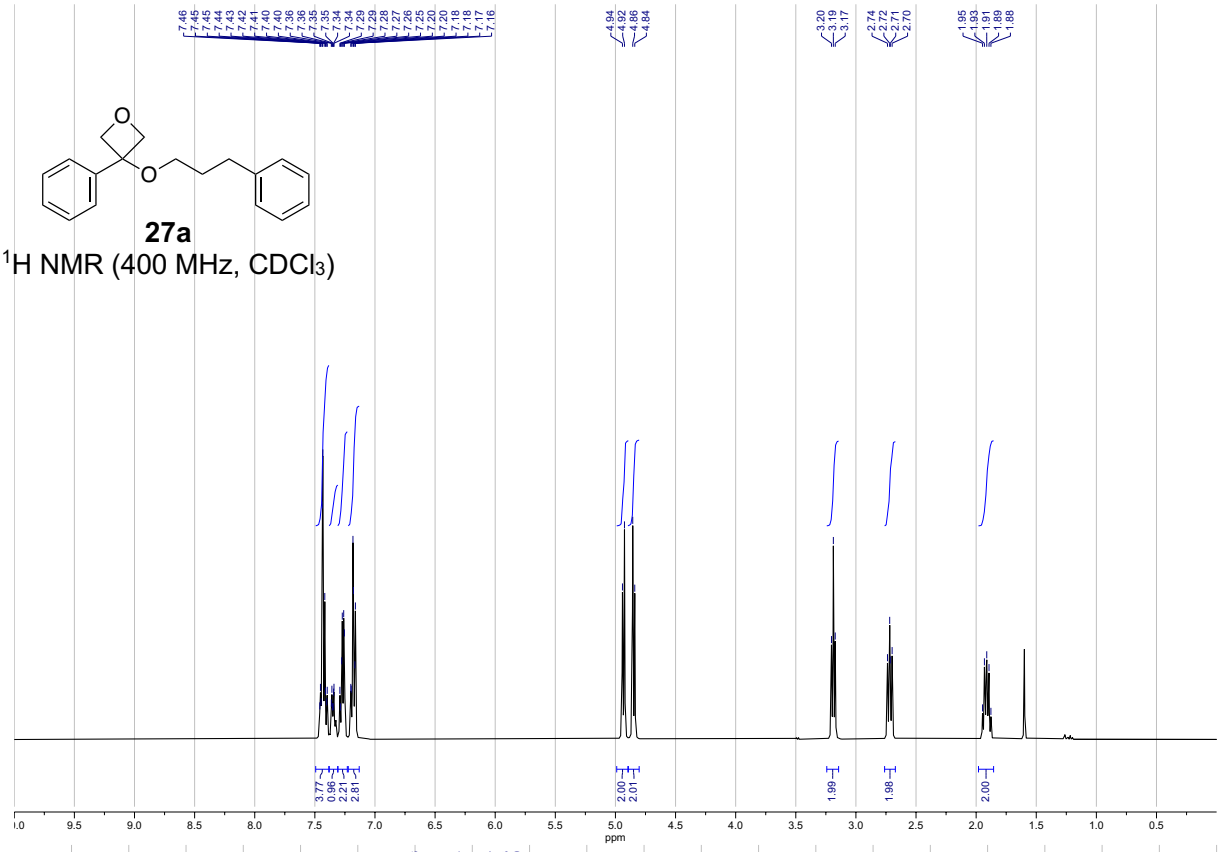

25a
^{13}C NMR (101 MHz, CDCl$_3$)
ppm


Cbz
N
O
HO
25l
1H NMR (400 MHz, CDCl3)
7.37
7.36
7.35
7.34
7.32
7.32
7.31
7.30
7.18
7.17
7.16
7.16
7.12
7.11
6.84
6.83
6.82
6.82
5.12
4.34
4.32
4.27
4.25
3.47
3.45
3.44
3.42
3.40
0.96
0.95
5.09
2.91
2.00
2.14
4.03
0.94
5.61
ppm


25l
13C NMR (101 MHz, CDCl3)
156.96
156.28
136.30
131.99
128.55
128.19
128.05
115.50
75.80
67.29
67.15
62.00
58.54
23.52
ppm

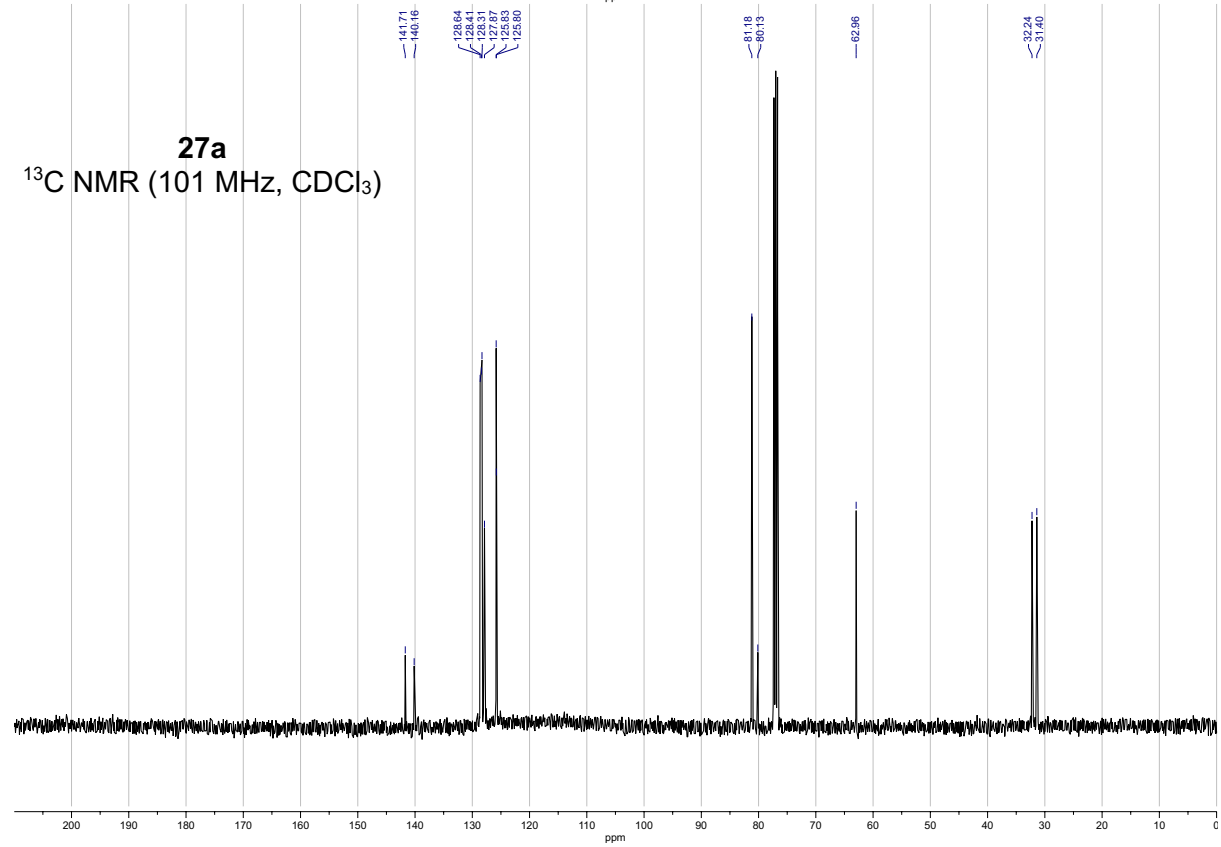

TfO
O
O
Ph
26a
^{1}H NMR (400 MHz, CDCl$_3$)
7.58
7.55
7.33
7.30
7.28
7.21
7.19
7.19
7.17
7.17
4.96
4.94
4.75
4.73
3.22
3.21
3.19
2.75
2.73
2.71
1.98
1.96
1.96
1.94
1.94
1.93
1.92
1.91
1.87
3.93
2.78
2.01
2.00
2.03
2.08
2.09
ppm


26a
^{13}C NMR (101 MHz, CDCl$_3$)
148.99
141.44
141.18
128.42
127.68
125.99
121.66
81.04
79.51
63.23
32.18
31.27
ppm



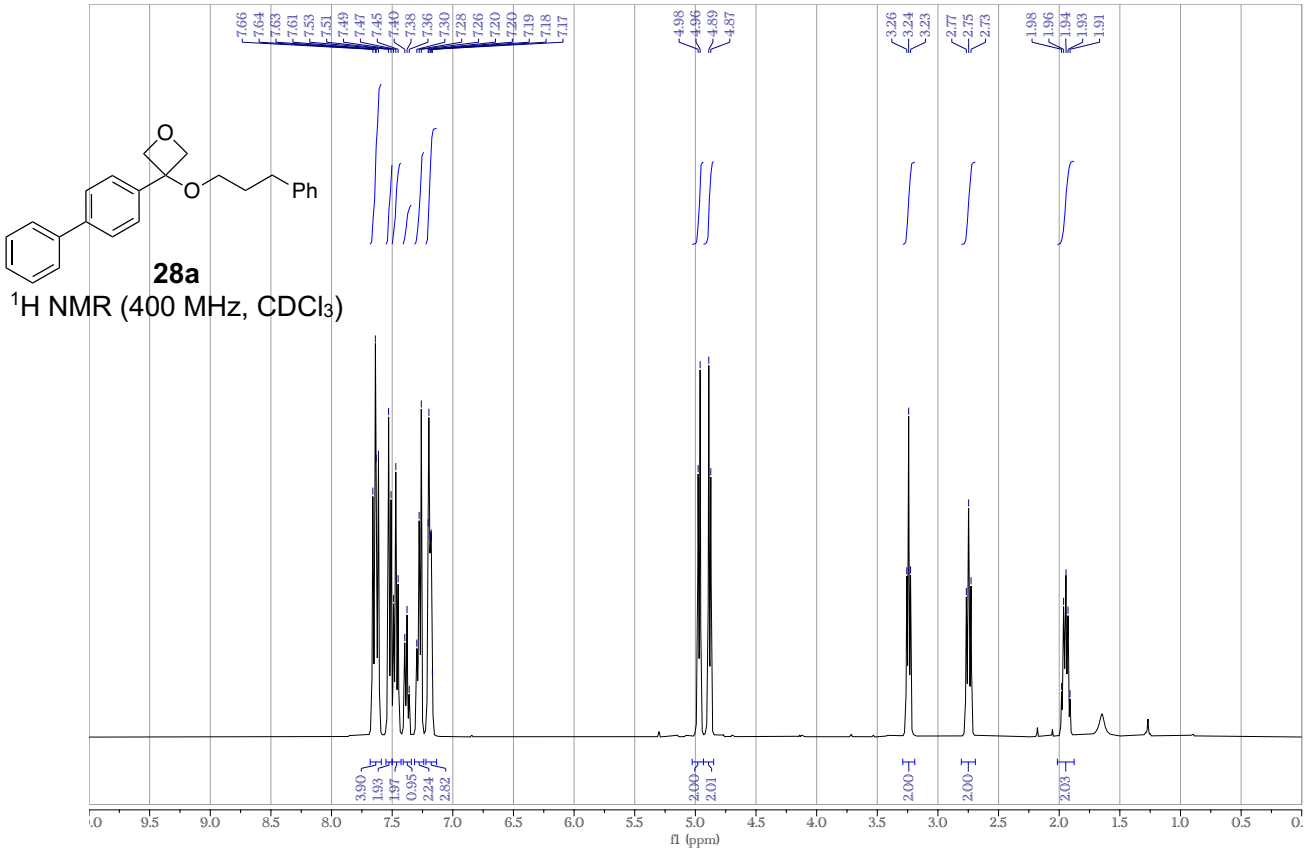
27a

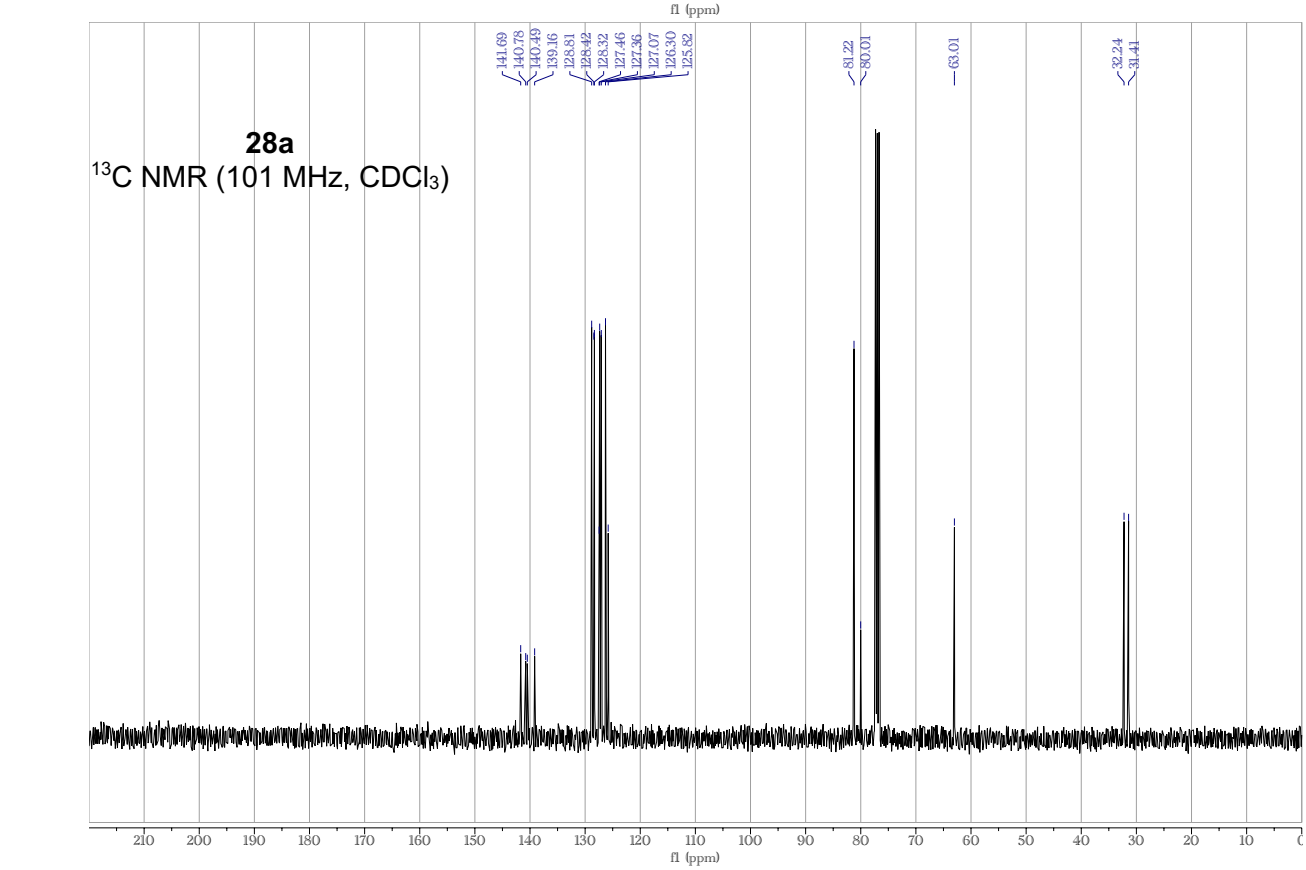
^{1}H NMR (400 MHz, $CDCl_3$)

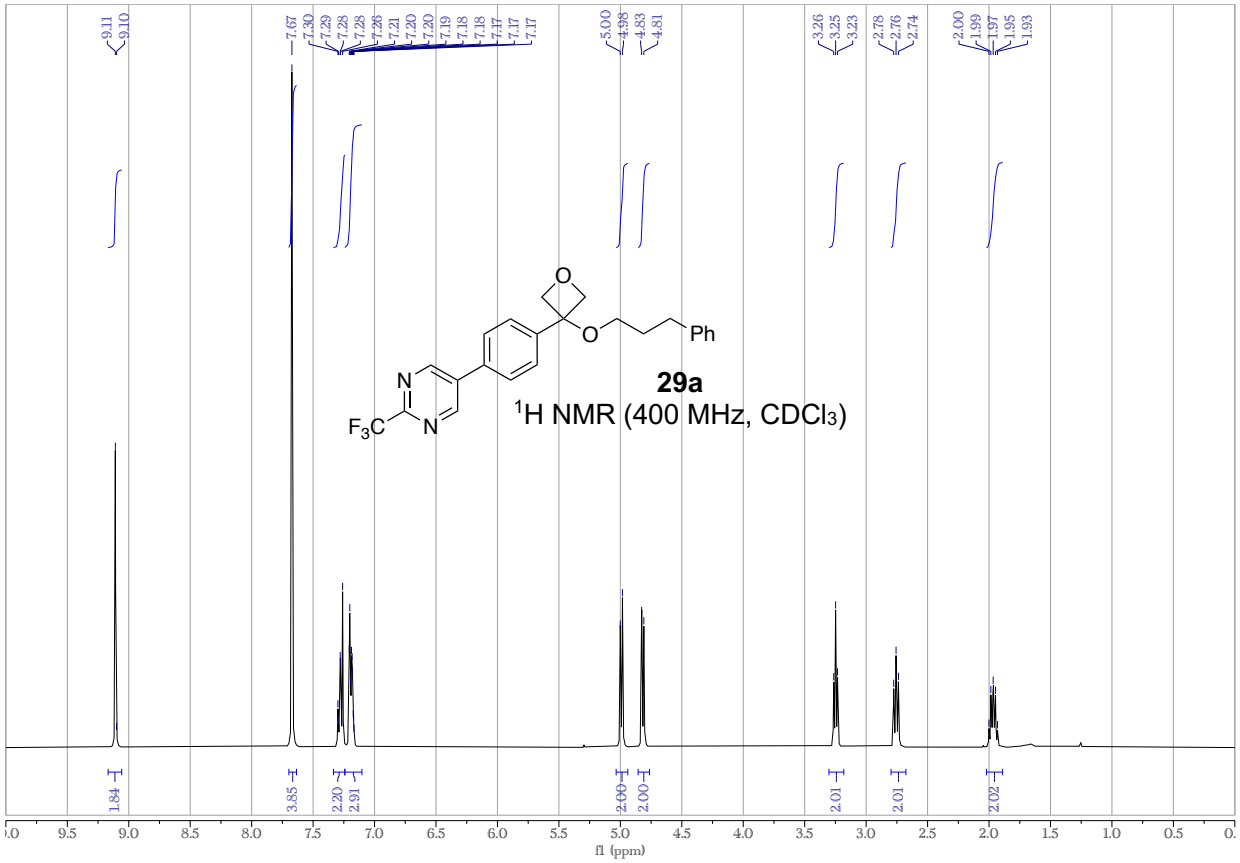


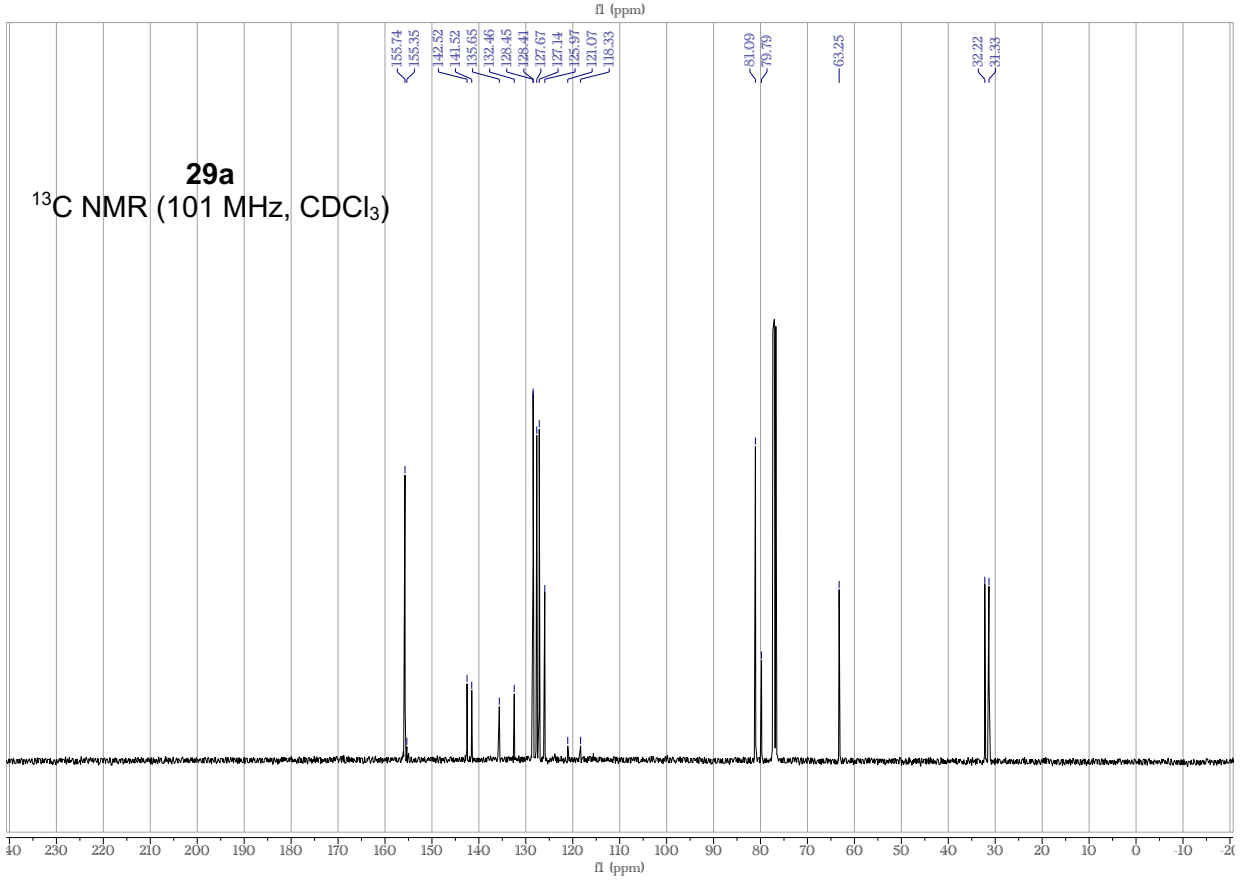
27a

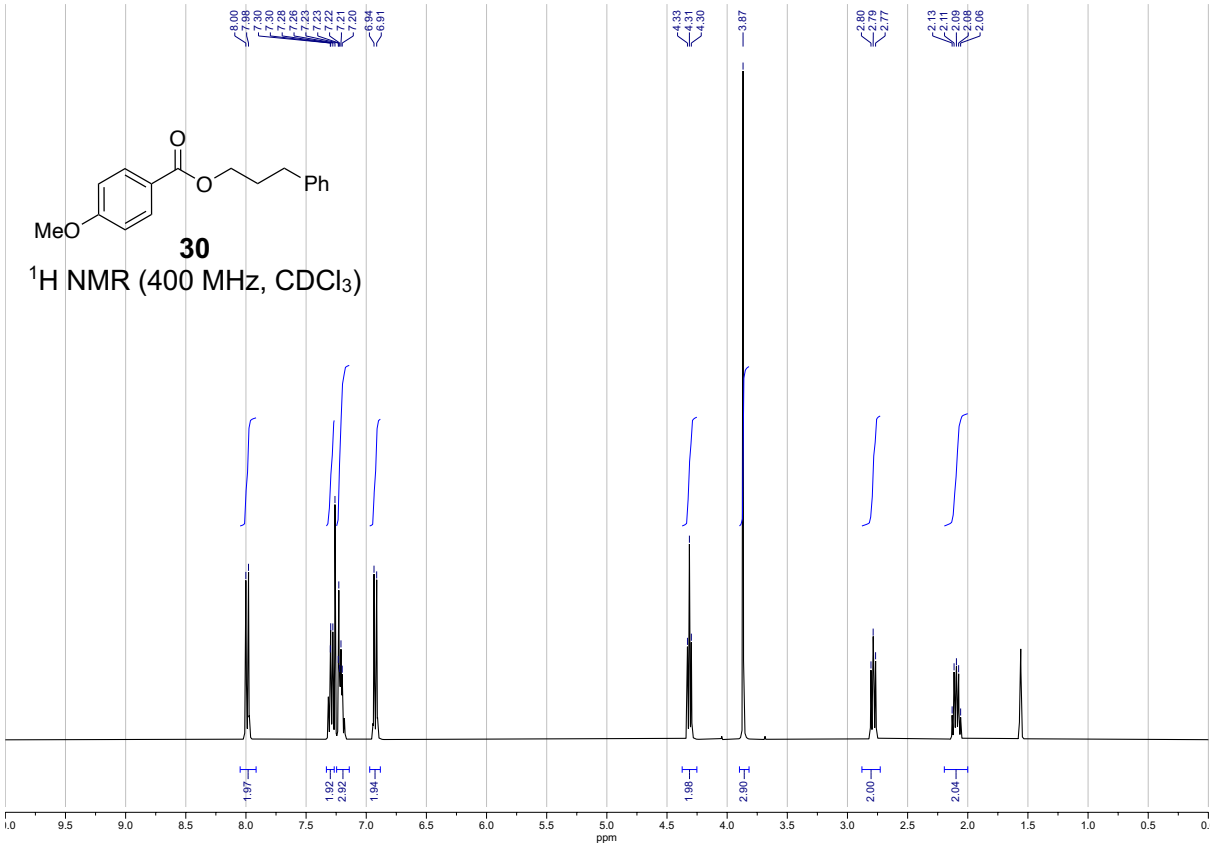
^{13}C NMR (101 MHz, $CDCl_3$)

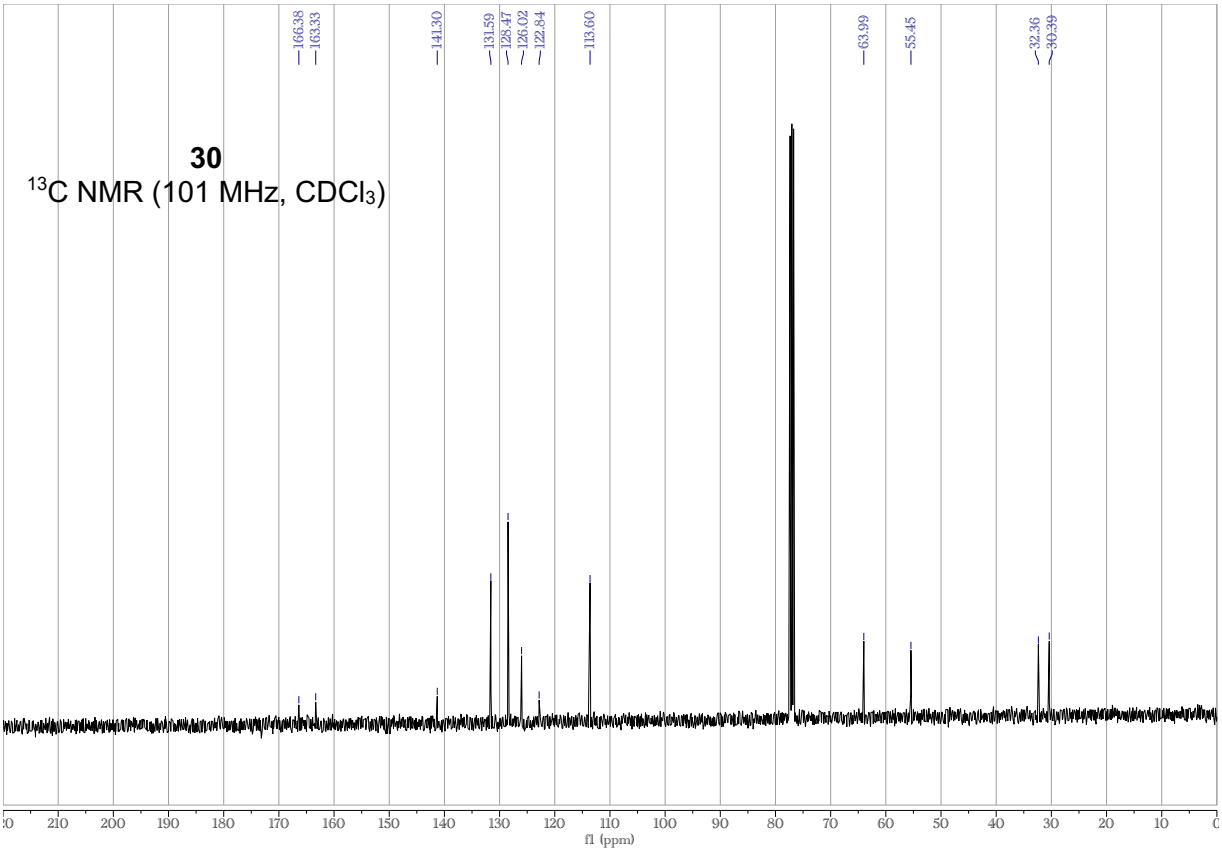

O
O
Ph
28a
^{1}H NMR (400 MHz, CDCl$_3$)
7.66
7.64
7.63
7.61
7.53
7.51
7.49
7.47
7.45
7.40
7.38
7.36
7.30
7.28
7.26
7.20
7.19
7.18
7.17
4.98
4.96
4.89
4.87
3.26
3.24
3.23
2.77
2.75
2.73
1.98
1.96
1.94
1.93
1.91
3.90
1.93
1.97
0.95
2.24
2.82
2.00
2.01
2.00
2.00
2.03
f1 (ppm)


28a
^{13}C NMR (101 MHz, CDCl$_3$)
141.69
140.78
140.49
139.16
128.81
128.42
128.32
127.46
127.36
127.07
126.30
125.82
81.22
80.01
63.01
32.24
31.41
f1 (ppm)


9.11
9.10
7.67
7.30
7.29
7.28
7.28
7.26
7.21
7.20
7.20
7.19
7.18
7.18
7.17
7.17
7.17
5.00
4.98
4.83
4.81
3.26
3.25
3.23
2.78
2.76
2.74
2.00
1.99
1.97
1.95
1.93
1.84
3.85
2.20
2.91
2.00
2.00
2.01
2.01
2.02
O
O
Ph
N
N
F3C
29a
1H NMR (400 MHz, CDCl3)
f1 (ppm)


155.74
155.35
142.52
141.52
135.65
132.46
128.45
128.41
127.67
127.14
125.97
121.07
118.33
81.09
79.79
63.25
32.22
31.33
29a
13C NMR (101 MHz, CDCl3)
f1 (ppm)


8.00
7.98
7.30
7.30
7.28
7.26
7.23
7.23
7.22
7.21
7.20
6.94
6.91
4.33
4.31
4.30
3.87
2.80
2.79
2.77
2.13
2.11
2.09
2.08
2.06
O
O
Ph
MeO
30
1H NMR (400 MHz, CDCl3)
1.97
1.92
2.92
1.94
1.98
2.90
2.00
2.04
ppm


166.38
163.33
141.30
131.59
128.47
126.02
122.84
113.60
63.99
55.45
32.36
30.39
30
13C NMR (101 MHz, CDCl3)
f1 (ppm)

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