Electronic Supplementary Material (ESI) for ChemComm.

SUPPORTING INFORMATION

Synthesis of Diversely Functionalised 2,2-Disubstituted Oxetanes: Fragment Motifs in New Chemical Space

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Calculated Fragment-Like Properties of Selected Oxetanes

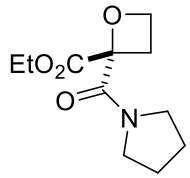
A selection of the oxetanes synthesized were analysed against parameters used to indicate desirable molecular properties, with particular reference to the Astex 'rule of 3' for fragments.

Criteria for fragments as defined by Congreve and co-workers:[1]

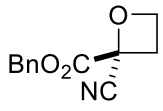
- M_w < 300 daltons
- cLogP < 3[2]
- H-bond donors (HBD) ≤ 3
- H-bond acceptors (HBA) ≤ 3

Klebe and co-workers proposed that HBA ≤ 6 is appropriate for fragments to allow for fragment growing/merging due to appropriate functional groups frequently display properties as hydrogen bond acceptors.[3]

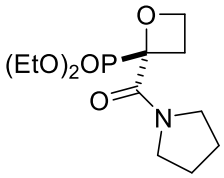
Selected Oxetanes



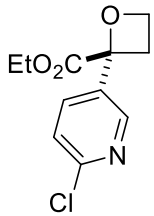
3a
M_w = 227
cLogP = 0.66 ± 0.53
HBD/HBA = 0/5



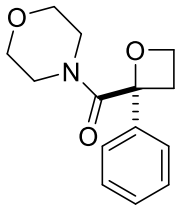
3e
M_w = 217
cLogP = 1.38 ± 0.42
HBD/HBA = 0/4



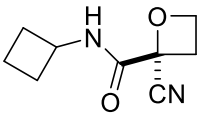
3g
M_w = 291
cLogP = –0.06 ± 0.53
HBD/HBA = 0/6



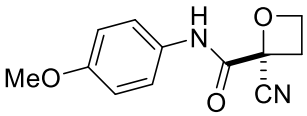
8f
M_w = 241
cLogP = 1.39 ± 0.44
HBD/HBA = 0/4



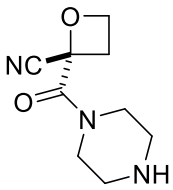
10
M_w = 247
cLogP = 1.30 ± 0.68
HBD/HBA = 0/4



12
M_w = 180
cLogP = –0.78 ± 0.48
HBD/HBA = 1/4



13
M_w = 232
cLogP = 0.44 ± 0.42
HBD/HBA = 1/5



14
M_w = 195
cLogP = –1.43 ± 0.58
HBD/HBA = 1/5

These oxetanes conform well to fragment guidelines.

General Experimental Considerations

All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware and anhydrous solvents using standard techniques.

Anhydrous solvents were obtained by filtration through drying columns (THF, DMF, CH_2Cl_2) or used as supplied (DMF, benzene).

Flash column chromatography was performed using 230-400 mesh silica or 50-200 μm Brockmann basic alumina (activity IV) with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate stain, PMA (phosphomolybdic acid), ninhydrin or vanillin.

Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on either 400 MHz or 500 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 7.27 ppm, DMSO: δ = 2.50 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, sep = septet, m = multiplet and br = broad), coupling constant in Hz, integration, assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm, $(^{13}CD_3)_2SO$: 39.5 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million referenced to the standard monofluorobenzene: −113.5 ppm. *J* values are reported in Hz. Assignments of $^1H/^{13}C$ spectra were made by the analysis of δ/J values, and COSY, DEPT-135, HSQC, and HMBC experiments as appropriate. Melting points are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary. 2-Substituted β-bromhydrins were prepared by reported procedures.[4]

Notes:

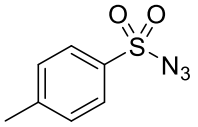
- *Although we have not experienced any problems in the handling of azides or diazo reagents, extreme care should be taken when manipulating them due to their potentially explosive nature.*
- *For all diazo compounds synthesized (apart from **1a** and **1i**), the resonance for the fully substituted C=N=N carbon in the ^{13}C NMR could not be seen due to quadrupole coupling to ^{14}N. The carbon resonance is not reported.*
- *Where diastereoisomers were separable by flash chromatography, attempts to determine their relative stereochemistry were conducted using NMR experiments (NOESY and selective NOE). However, this was not possible in all cases. Diastereomers that were not separable by flash chromatography have been characterized as mixtures.*
- *For β-bromohydrin **S9** (derived from N-Boc-2,5-dihydro-1H-pyrrole; pg S40), the carbon resonances in the ^{13}C NMR are doubled. This is due to the compound existing as rotamers at rt in $CDCl_3$ on the NMR timescale. The assignment of this compound has taken this into consideration.*

Preparation of a 0.61 M solution of LiHMDS

A solution of freshly distilled HMDS (0.31 ml, 1.47 mmol) in THF (1.06 mL) was cooled to –78 ºC for 5 min then *n*-butyllithium (1.6 M in hexanes, 0.84 mL, 1.34 mmol) was added dropwise. The solution was stirred at –78 ºC for 30 min then warmed to 0 ºC for 30 min prior to immediate use.

Synthesis of Diazo Transfer Reagents Sa–Sc

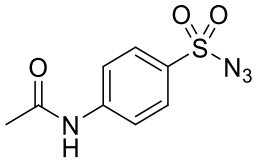
4-Toluenesulfonyl azide (Sa)[5]



Sodium azide (6.24 g, 96 mmol) in water (26 mL) was added in one portion to a stirring mixture of 4-toluenesulfonyl chloride (15.25 g, 80 mmol) in isopropyl alcohol (46 mL). The resulting mixture was stirred at 25 °C for 90 min. Water (300 mL) was added and the mixture stirred at 25 °C for 1 h. The aquous mixture was extracted with CH_2Cl_2 (4 x 100 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford azide **Sa** as a colorless oil (15.62 g, 99%); IR (film) / cm^{-1} 2126 (N=N=N), 1596, 1495, 1370, 1298, 1191, 1167, 1086, 814, 747, 703, 661, 592, 540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.83 (m, 2 H, 2 x Ts-H), 7.45–7.39 (m, 2 H, 2 x Ts-H), 2.50 (s, 3 H, Ts-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (Ts-C_q-SO_2), 135.6 (Ts-C_q-Me), 130.3 (2 x Ts-CH), 127.5 (2 x Ts-CH), 21.8 (Ts-CH_3).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[6,7]

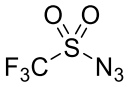
4-Acetamidobenzene-1-sulfonyl azide (*p*-ABSA, Sb)[8]



Acetylsulfanilyl chloride (1.17 g, 5.0 mmol) was added portionwise over 2 min to a stirring mixture of sodium azide (325 mg, 5.0 mmol) in acetone (117 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 48 h. The reaction mixture was then filtered and concentrated *in vacuo* to yield azide **Sb** as a light brown solid (1.19 g, 99%); mp = 107–109 °C; IR (film) / cm^{-1} 3259 (N-H), 3187, 3112, 2118 (N=N=N), 1672 (C=O), 1585, 1529, 1404, 1362, 1314, 1265, 1160, 1086, 1041, 1011, 838, 743, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.88 (m, 2 H, 2 x Ar-H), 7.80–7.73 (m, 2 H, 2 x Ar-H), 7.57 (br s, 1 H, NH), 2.25 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C=O), 143.8 (Ar-C_q-SO_2), 129.1 (2 x Ar-CH), 119.5 (2 x Ar-CH), 110.0 (Ar-C_q-NH), 24.9 (CH_3).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[9]

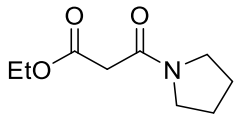
Trifluoromethanesulfonyl azide solution (Sc)[10]



Triflic anhydride (10 g, 5.96 mL, 35.4 mmol) in *n*-hexane (35 mL) was added dropwise to a stirring mixture of sodium azide (4.95 g, 76.2 mmol) and tetrabutylammonium hydrogen sulfate (241 mg, 0.71 mmol) in water (35 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min. The layers were separated and the aqueous mixture was extracted with *n*-hexane (35 mL). The organic extracts were combined, dried over sodium hydroxide pellets and decanted. The *n*-hexane solution of trifyl azide (0.47 M) was either used immediately or was stored at –15 °C for several weeks without significant decomposition. The concentration of the azide was estimated based on the total volume of the solution and assuming a quantitative conversion based on the amount of triflic anhydride used.

Synthesis of Activated Methylene Species S1–S8

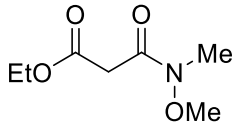
Ethyl 3-oxo-3-(pyrrolidin-1-yl)propanoate (S1)



Pyrrolidine (0.60 mL, 7.2 mmol) was added to a stirring mixture of ethyl potassium malonate (1.02 g, 6.0 mmol), EDC·HCl (1.36 g, 7.2 mmol) and HOBt hydrate (1.10 g, 8.2 mmol) in CH_2Cl_2 (25 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 70 h. A 1 M HCl solution (10 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (3% MeOH in CH_2Cl_2) afforded amide **S1** as a colorless oil (550 mg, 49%); R_f = 0.14 (5% MeOH in CH_2Cl_2); IR (film) / cm^{-1} 2978, 2877, 1734 (C=O ester), 1638 (C=O amide), 1433, 1367, 1307, 1251, 1151, 1031, 973, 943, 915, 863, 789, 666, 604, 568; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.47 (t, *J* = 6.9 Hz, 2 H, NCH_2), 3.42 (t, *J* = 6.8 Hz, 2 H, NCH_2), 3.36 (s, 2 H, CH_2), 1.99–1.90 (m, 2 H, NCH_2CH_2), 1.90–1.81 (m, 2 H, NCH_2CH_2), 1.26 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (C=O), 164.3 (C=O), 61.3 ($CO_2CH_2CH_3$), 47.1 (NCH_2), 45.8 (NCH_2), 42.4 (CH_2), 26.0 (NCH_2CH_2), 24.4 (NCH_2CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_9H_{16}NO_3^+$ $[M+H]^+$: 186.1130, Found: 186.1128.

Observed data (IR) was consistent with that previously reported.[11]

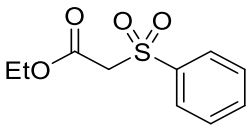
Ethyl 2-[methoxy(methyl)carbamoyl]acetate (S2)



N,N-Diisopropylethylamine (3.14 mL, 18.0 mmol) was added to a stirring mixture of ethyl potassium malonate (1.02 g, 6.0 mmol), *N,O*-dimethylhydroxylamine hydrochloride (703 mg, 7.2 mmol) and HATU (2.73 g, 7.2 mmol) in CH_2Cl_2 (30 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 68 h. A 1 M HCl solution (30 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded Weinreb amide **S2** as a colorless oil (852 mg, 81%); R_f = 0.26 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2984, 2944, 1736 (C=O ester), 1666 (C=O amide), 1465, 1445, 1416, 1385, 1369, 1323, 1252, 1153, 1123, 1031, 1005, 934, 857, 753, 706, 667, 566; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.66 (s, 3 H, OCH_3), 3.43 (s, 2 H, CH_2), 3.16 (s, 3 H, NCH_3), 1.22 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (CO_2 and CON), 61.2 (OCH_3), 61.1 ($CO_2CH_2CH_3$), 40.1 (CH_2), 32.0 (NCH_3), 13.9 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_7H_{14}NO_4^+$ $[M+H]^+$: 176.0923, Found: 176.0927.

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[12]

Ethyl 2-(benzenesulfonyl)acetate (S3)

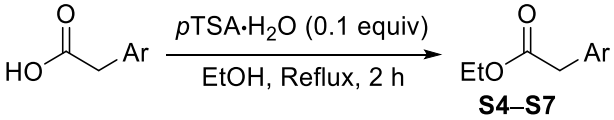


n-Butyllithium (1.62 M in hexanes, 7.78 mL, 12.6 mmol) was added dropwise to a stirring solution of methyl phenyl sulfone (936 mg, 6.0 mmol) in THF (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. Ethyl chloroformate (0.6 mL, 6.3 mmol) was then added and the resulting mixture was stirred at 0 °C for 90 min. Saturated aq. NH_4Cl (60 mL) was added. The layers were separated and the aqueous mixture was

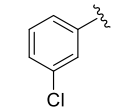
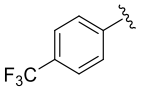
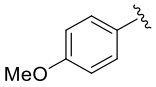
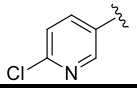
extracted with EtOAc (2 x 60 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc in hexanes) afforded ethyl 2-(benzenesulfonyl)acetate **S3** as a colorless oil (1.09 g, 80%); R_f = 0.26 (30% EtOAc in hexanes); IR (film) / cm^{-1} 2986, 2944, 1736 (C=O), 1586, 1478, 1448, 1397, 1368, 1324, 1310, 1275, 1148, 1083, 1024, 999, 910, 844, 810, 760, 741, 721, 686, 619, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.91 (m, 2 H, 2 x Ph-H), 7.74–7.67 (m, 1 H, Ph-H), 7.64–7.55 (m, 2 H, 2 x Ph-H), 4.14 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.12 (s, 2 H, CH_2), 1.19 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (CO_2), 138.7 (Ph-C_q), 134.3 (Ph-CH), 129.2 (2 x Ph-CH), 128.5 (2 x Ph-CH), 62.4 ($CO_2CH_2CH_3$), 61.0 (CH_2), 13.8 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[13]

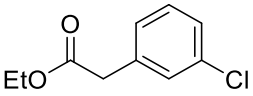
Synthesis of activated methylene species **S4–S7** from acid derivatives (**Table S1**).



S4–S7

Entry	Ar =	Yield (%)
1		99 (**S4**)
2		94 (**S5**)
3		99 (**S6**)
4		94 (**S7**)

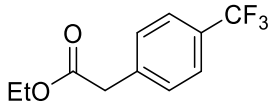
Ethyl 2-(3-chlorophenyl)acetate (S4)



A solution of 2-(3-chlorophenyl)acetic acid (1.02 g, 6.0 mmol) and *p*-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. $NaHCO_3$ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) concentrated *in vacuo* to afford ester **S4** as a colorless oil which was used without further purification (1.18 g, 99%); R_f = 0.33 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 1732 (C=O), 1599, 1575, 1477, 1433, 1368, 1335, 1249, 1218, 1155, 1094, 1079, 1029, 1000, 943, 893, 868, 850, 781, 763, 734, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.16 (m, 4 H, 4 x Ar-H), 4.18 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.60 (s, 2 H, CH_2), 1.28 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (CO_2), 136.0 (Ar-C_q-CH_2), 134.4 (Ar-C_q-Cl), 129.8 (Ar-CH), 129.5 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 61.1 ($CO_2CH_2CH_3$), 41.1 (CH_2), 14.2 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[14]

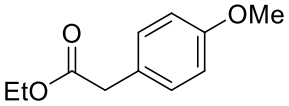
Ethyl 2-[4-(trifluoromethyl)phenyl]acetate (S5)



A solution of 2-[4-(trifluoromethyl)phenyl]acetic acid (1.22 g, 6.0 mmol) and *p*-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. $NaHCO_3$ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield ester **S5** as a colorless oil which was used without further purification (1.30 g, 94%); R_f = 0.63 (50% EtOAc/hexane); IR (film) / cm^{-1} 2990, 1720 (C=O), 1619, 1421, 1374, 1225, 1155, 1128, 1111, 1068, 1019, 886, 843, 823, 765, 741, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2 H, 2 x Ar-H), 7.42 (d, J = 8.0 Hz, 2 H, 2 x Ar-H), 4.18 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.68 (s, 2 H, CH_2), 1.27 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (CO_2), 138.2 (Ar-C_q-CH_2), 129.7 (2 x Ar-CH), 129.5 (q, $J_{C\text{-}F}$ = 33 Hz, Ar-C_q-CF_3), 125.8 (q, $J_{C\text{-}F}$ = 264 Hz, CF_3), 125.6 (q, $J_{C\text{-}F}$ = 4 Hz, 2 x Ar-CH), 61.2 ($CO_2CH_2CH_3$), 41.2 (CH_2), 14.2 ($CO_2CH_2CH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6.

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[15]

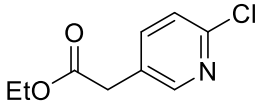
Ethyl 2-(4-methoxyphenyl)acetate (S6)



A solution of 2-(4-methoxyphenyl)acetic acid (1.00 g, 6.0 mmol) and *p*-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. $NaHCO_3$ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield ester **S6** as a colorless oil which was used without further purification (1.16 g, 99%); R_f = 0.27 (10% EtOAc/hexane); IR (film) / cm^{-1} 2982, 2837, 1730 (C=O), 1613, 1512, 1464, 1443, 1368, 1300, 1244, 1150, 1029, 946, 880, 820, 790, 765, 723, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2 H, 2 x Ar-H), 6.87 (d, J = 8.6 Hz, 2 H, 2 x Ar-H), 4.15 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.80 (s, 3 H, OCH_3), 3.56 (s, 2 H, CH_2), 1.26 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (CO_2), 158.7 (Ar-C_q-OCH_3), 130.3 (2 x Ar-CH), 126.3 (Ar-C_q-CH_2), 114.0 (2 x Ar-CH), 60.8 ($CO_2CH_2CH_3$), 55.3 (OCH_3), 40.6 (CH_2), 14.3 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[16]

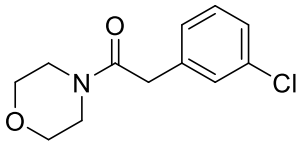
Ethyl 2-(6-chloropyridin-3-yl)acetate (S7)



A solution of 2-(6-chloropyridin-3-yl)acetic acid (1.03 g, 6.0 mmol) and *p*-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol) in ethanol (15 mL) was heated under reflux for 2 h. The solvent was then removed *in vacuo*. Saturated aq. $NaHCO_3$ (30 mL) was added and the product was extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to yield ester **S7** as a colorless oil which was used without further purification (1.30 g, 94%); R_f = 0.59 (50% EtOAc/hexane); IR (film) / cm^{-1} 2984, 1730 (C=O), 1589, 1567, 1460, 1385, 1368, 1334, 1262, 1230, 1160, 1140, 1102, 1023, 946, 879, 819, 752, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.5 Hz, 1 H, Ar-H), 7.60 (dd, J = 8.1, 2.5 Hz, 1 H, Ar-H), 7.27 (d, J = 8.1 Hz, 1 H, Ar-H), 4.14 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.58 (s, 2 H, CH_2), 1.23 (t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (C=O), 150.3 (Ar-C_q-Cl) 150.2 (Ar-CH), 139.7 (Ar-CH), 128.8 (Ar-C_q-CH_2), 124.1 (Ar-CH), 61.4 ($CO_2CH_2CH_3$), 37.6 (CH_2), 14.1 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[17]

2-(3-Chlorophenyl)-1-(morpholin-4-yl)ethan-1-one (S8)



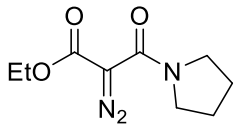
N,N-Diisopropylethylamine (3.14 mL, 18.0 mmol) was added to a stirring mixture of 2-(3-chlorophenyl)acetic acid (1.02 g, 6.0 mmol), HATU (2.74 g, 7.2 mmol) and morpholine (0.63 mL, 7.2 mmol) in CH_2Cl_2 (30 mL) at 25 °C. The reaction was stirred at 25 °C for 48 h. A 1 M HCl solution (30 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded amide **S8** as a colorless oil (1.26 g, 88%); R_f = 0.13 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2977, 2912, 2852, 1638 (C=O), 1575, 1475, 1436, 1413, 1364, 1319, 1271, 1231, 1190, 1116, 1079, 1036, 1019, 965, 944, 922, 902, 877, 850, 811, 768, 699, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.10 (m, 4 H, 4 x Ar-H), 3.72 (s, 2 H, CH_2), 3.69–3.65 (m, 4 H, 2 x OCH_2), 3.58–3.53 (m, 2 H, NCH_2), 3.49–3.41 (m, 2 H, NC'H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C=O), 136.8 (Ar-C_q-CH_2), 134.7 (Ar-C_q-Cl), 130.1 (Ar-CH), 128.9 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 66.9 (OCH_2), 66.6 (OC'H_2), 46.6 (NCH_2), 42.3 (NC'H_2), 40.3 (CH_2).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[18]

Synthesis of Disubstituted Diazos 1a–1i

Synthesis of disubstituted diazos **1a–1i** were adapted from procedures of Lee and co-worker (TsN_3),[19] or procedures of Charette and co-workers (TfN_3).[20,21]

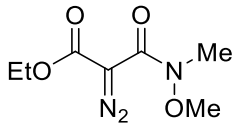
Ethyl 2-diazo-3-oxo-3-(pyrrolidin-1-yl)propanoate (1a)



Cesium carbonate (813 mg, 2.5 mmol) was added in one portion to a stirring solution of tosyl azide **Sa** (496 mg, 2.5 mmol) and amide **S1** (463 mg, 2.5 mmol) in THF (25 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 3 h 30 min. The reaction mixture was diluted with Et_2O (50 mL), and washed with 1 M aq. NaOH (2 x 10 mL) and brine (10 mL). The combined aqueous washes were then re-extracted with Et_2O (20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (30% to 40% EtOAc in pentane) afforded diazo amide **1a** as a yellow oil (515 mg, 93%); R_f = 0.34 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2977, 2881, 2118 (C=N=N out-of-phase),[22] 1707 (C=O ester), 1613 (C=O amide), 1407, 1368 (C=N=N in-phase),[22] 1343, 1283, 1231, 1168, 1096, 1032, 1015, 934, 906, 873, 857, 820, 753, 709, 585, 566, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.60–3.46 (m, 4 H, 2 x NCH_2), 1.96–1.83 (m, 4 H, 2 x NCH_2CH_2), 1.31 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (C=O), 159.5 (C=O), 66.7 (C_qN_2), 61.1 ($CO_2CH_2CH_3$), 48.3 (br, NCH_2), 47.3 (br, NCH_2), 25.9 (br, NCH_2CH_2), 24.3 (br, NCH_2CH_2), 14.3 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_9H_{14}N_3O_3^+$ $[M+H]^+$: 212.1035, Found: 212.1033.

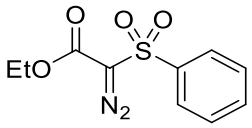
Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[23]

Ethyl 2-diazo-2-[methoxy(methyl)carbamoyl]acetate (1b)



Tosyl azide **Sa** (592 mg, 3.0 mmol) in THF (6 mL) was added dropwise to a stirring suspension of Weinreb amide **S2** (525 mg, 3.0 mmol) and cesium carbonate (981 mg, 3.0 mmol) in THF (24 mL). The resulting mixture was stirred at 25 °C for 2 h 30 min. The reaction mixture was filtered through celite, the precipitate washed with Et_2O (100 mL) and the filtrate concentrated *in vacuo*. Purification by flash chromatography (40% to 50% EtOAc in pentane) afforded diazo amide **1b** as a yellow oil (444 mg, 74%); R_f = 0.32 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 2940, 2120 (C=N=N out-of-phase), 1728 (C=O ester), 1650 (C=O amide), 1463, 1407, 1369 (C=N=N in-phase), 1282, 1248, 1171, 1137, 1106, 1053, 1014, 967, 889, 749, 705, 665, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.70 (s, 3 H, OCH_3), 3.21 (s, 3 H, NCH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (C=O), 161.1 (C=O), 61.5 ($CO_2CH_2CH_3$), 61.2 (OCH_3), 33.6 (NCH_3), 14.3 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_7H_{12}N_3O_4^+$ $[M+H]^+$: 202.0828, Found: 202.0823.

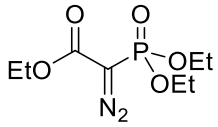
Ethyl 2-(benzenesulfonyl)-2-diazoacetate (1c)[19]



Tosyl azide **Sa** (787 mg, 4.0 mmol) in THF (8 mL) was added dropwise to a stirring suspension of ethyl 2-(benzenesulfonyl)acetate **S3** (911 mg, 4.0 mmol) and cesium carbonate (1.30 g, 4.0 mmol) in THF (32 mL). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through celite, the precipitate washed with Et_2O (100 mL) and the filtrate concentrated *in vacuo*. Purification by flash chromatography (20% to 30% EtOAc in hexanes) afforded diazo sulfone **1c** as an orange solid (746 mg, 73%); R_f = 0.47 (30% EtOAc in hexanes); mp = 49–52 °C; IR (film) / cm^{-1} 2986, 2124 (C=N=N out-of-phase), 1711 (C=O), 1584, 1477, 1448, 1393, 1370 (C=N=N in-phase), 1336, 1285, 1213, 1156, 1097, 1070, 1000, 909, 855, 804, 720, 684, 607, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.94 (m, 2 H, 2 x Ph-H), 7.65–7.59 (m, 1 H, Ph-H), 7.56–7.48 (m, 2 H, 2 x Ph-H), 4.17 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 1.19 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (CO_2), 141.3 (Ph-C_q), 133.9 (Ph-CH), 128.9 (2 x Ph-CH), 127.6 (2 x Ph-CH), 62.1 ($CO_2CH_2CH_3$), 13.9 ($CO_2CH_2CH_3$).

Observed data (mp, IR, ^{1}H, ^{13}C) was consistent with that previously reported.[13]

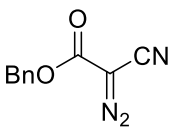
Ethyl 2-diazo-2-(diethoxyphosphoryl)acetate (1d)[19]



Tosyl azide **Sa** (1.18 g, 6.0 mmol) in THF (12 mL) was added dropwise to a stirring suspension of triethyl phosphonoacetate (1.19 mL, 6.0 mmol) and cesium carbonate (1.95 g, 6.0 mmol) in THF (48 mL). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered through celite, the precipitate washed with Et_2O (70 mL) and the filtrate concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded diazo phosphonate **1d** as a pale yellow oil (1.23 g, 82%); R_f = 0.23 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2985, 2125 (C=N=N out-of-phase), 1701 (C=O), 1478, 1446, 1392, 1368 (C=N=N in-phase), 1273 (P=O), 1165, 1095, 1013, 976, 859, 796, 744, 588, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30–4.09 (m, 6 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3), 1.36 (t, *J* = 7.1 Hz, 6 H, 2 x OCH_2CH_3), 1.29 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, $J_{C\text{-}P}$ = 12.1 Hz, CO_2), 63.6 (d, $J_{C\text{-}P}$ = 5.6 Hz, 2 x OCH_2CH_3), 61.7 ($CO_2CH_2CH_3$), 16.1 (d, $J_{C\text{-}P}$ = 6.9 Hz, 2 x OCH_2CH_3), 14.3 ($CO_2CH_2CH_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ 10.1.

Observed data (IR, ^{1}H, ^{13}C, ^{31}P) was consistent with that previously reported.[24]

Benzyl cyano(diazo)formate (1e)[20]

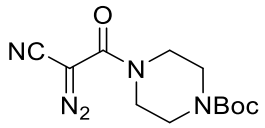


Pyridine (0.97 mL, 12.0 mmol) was added dropwise over 5 min to a stirring solution of benzyl cyanoacetate (0.92 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution **Sc** (0.47 M in *n*-hexane, 19.3 mL, 9.0 mmol) in CH_3CN (13 mL) at 0 °C. The resulting biphasic mixture was vigorously stirred at 25 °C for 15 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (90% $CHCl_3$ in hexanes to $CHCl_3$) afforded diazo nitrile **1e** as a yellow oil (610 mg, 51%); R_f = 0.23 ($CHCl_3$); IR (film) / cm^{-1} 3036, 2957, 2919, 2850, 2229 (C≡N), 2130 (C=N=N out-of-phase), 1712 (C=O), 1588, 1499, 1456, 1381 (C=N=N in-phase), 1317, 1292, 1265, 1243, 1121, 1030, 949, 909, 791, 735, 697, 602, 544; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 5 H, 5 x Ph-H), 5.31 (s, 2 H, CO_2CH_2Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (CO_2), 134.3 (Ph-Cq), 128.9 (Ph-CH), 128.7 (2 x Ph-CH), 128.5 (2 x Ph-CH), 107.1 (C≡N), 68.6 (CO_2CH_2Ph).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[20]

Reaction performed on a large scale (2 x 12.5 mmol of benzyl cyanoacetate) using the following modified work up procedure: After the reaction time, the reaction mixture was concentrated *in vacuo*, diluted with EtOAc (100 mL), washed with 1 M aq. NaOH (2 x 20 mL) and brine (20 mL). The combined aqueous washes were then re-extracted with EtOAc (2 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Combination of the 2 reactions afforded a combined isolated yield of diazo **1e** (2.19 g, 44%) after flash chromatography.

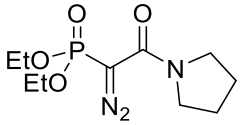
tert-Butyl 4-[cyano(diazo)carbonyl]piperazine-1-carboxylate (1f)



Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of cyanoacetic acid (427 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 1 h then at 25 °C for 1 h. The reaction mixture was concentrated *in vacuo*, CH_2Cl_2 (10 mL) was then added to the residue and again concentrated *in vacuo*. The reaction flask was re-purged with Ar, the residue dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. *N*-Boc-piperazine (1.40 g, 7.5 mmol) in CH_2Cl_2 (2 mL) was added, and the reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH_4Cl (10 mL) was added, the layers separated and the aqueous mixture extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford the α-cyano acetamide.

Triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution **Sc** (0.506 M, 11.9 mL, 6.0 mmol) were added to a solution of α-cyanoacetamide in CH_3CN (10 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated *in vacuo* and saturated aq. NH_4Cl (10 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (2% to 4% to 6% CH_3CN in CH_2Cl_2) afforded diazo **1f** as a yellow solid (523 mg, 37% over 2 steps); R_f = 0.15 (5% CH_3CN in CH_2Cl_2); mp = 92–95 °C; IR (film) / cm^{-1} 2978, 2932, 2216 (C≡N), 2118 (C=N=N out-of-phase), 1694 (C=O), 1634 (C=O), 1456, 1413, 1366 (C=N=N in-phase), 1288, 1242, 1164, 1211, 1011, 996, 887, 861, 770, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67–3.56 (m, 4 H, 2 x CH_2), 3.53–3.44 (m, 4 H, 2 x CH_2), 1.47 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (C=O amide), 154.3 (C=O carbamate), 109.5 (C≡N), 80.6 ($C_q(CH_3)_3$), 45.1 (2 x CH_2), 43.2 (br, 2 x CH_2), 28.3 (3 x CH_3); HRMS (FTMS +pNSI) *m/z* Calcd for $C_{12}H_{21}N_6O_3^+$ $[M+NH_4]^+$: 297.1670, Found: 297.1674.

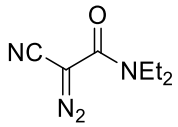
Diethyl [1-diazo-2-oxo-2-(pyrrolidin-1-yl)ethyl]phosphonate (1g)



Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of diethylphosphonoacetic acid (0.80 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 90 min then at 25 °C for 3 h. The reaction mixture was concentrated *in vacuo*, CH_2Cl_2 (10 mL) was then added to the residue and again concentrated *in vacuo*. The reaction flask was re-purged with Ar, the residue dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Pyrrolidine (1.00 mL, 12.0 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 90 min then 25 °C for 1 h. A 1 M HCl solution (10 mL) was then added. The layers were separated and the aqueous mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford the α-phosphono acetamide.

Cesium carbonate (1.90 g, 5.8 mmol) was added in one portion to a stirring solution of tosyl azide **Sa** (1.09 g, 5.5 mmol) and α-phosphono acetamide in THF (50 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 5 h 30 min. The reaction mixture was diluted with EtOAc (100 mL), and washed with 1 M aq. NaOH (2 x 15 mL) and brine (15 mL). The combined aqueous washes were then re-extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (2% MeOH in CH_2Cl_2) afforded diazo phosphonate **1g** as a yellow oil (1.27 g, 93% over 2 steps); R_f = 0.29 (5% MeOH in CH_2Cl_2); IR (film) / cm^{-1} 2980, 2877, 2120 (C=N=N out-of-phase), 1615 (C=O), 1444, 1389 (C=N=N in-phase), 1347, 1253 (P=O), 1193, 1162, 1097, 1011, 968, 873, 794, 758, 731, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33–4.06 (m, 4 H, 2 x OC*H*$_2$CH$_3$), 3.56–3.41 (m, 4 H, 2 x NCH$_2$), 1.89 (br s, 4 H, 2 x NCH$_2$C*H*$_2$), 1.35 (t, *J* = 7.1 Hz, 6 H, 2 x OCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (d, $J_{C\text{-}P}$ = 10.7 Hz, C=O), 63.5 (d, $J_{C\text{-}P}$ = 6.1 Hz, 2 x O*C*H$_2$CH$_3$), 47.4 (2 x NCH$_2$), 25.2 (br, 2 x NCH$_2$*C*H$_2$), 16.1 (d, $J_{C\text{-}P}$ = 6.9 Hz, 2 x OCH$_2$*C*H$_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.0; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{21}N_4O_4PNa^+$ $[M+CH_3CN+Na]^+$: 339.1198, Found: 339.1201.

(Diethylcarbamoyl)methanecarbonimidoyl cyanide (1h)[21]

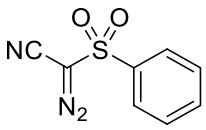


Oxalyl chloride (0.51 mL, 6.0 mmol) was added dropwise to a solution of cyanoacetic acid (425 mg, 5.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. DMF (6 drops) was added and the reaction mixture was stirred at 0 °C for 75 min then at 25 °C for 1 h. The reaction mixture was concentrated *in vacuo*, CH_2Cl_2 (10 mL) was then added to the residue and again concentrated *in vacuo*. The reaction flask was re-purged with Ar, the residue dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Diethylamine (1.0 mL, 10.0 mmol) was added dropwise over 3 min. The reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH_4Cl (10 mL) was added, the layers separated and the aqueous mixture extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford the α-cyano acetamide.

Triethylamine (0.84 mL, 6.0 mmol) and trifluoromethanesulfonyl azide solution **Sc** (0.506 M, 11.9 mL, 6.0 mmol) were added to a solution of the α-cyanoacetamide in CH_3CN (10 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated *in vacuo* and saturated aq. NH_4Cl (10 mL) added. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography ($CHCl_3$) afforded diazo **1h** as a dark yellow liquid (566 mg, 68% over 2 steps); R_f = 0.16 ($CHCl_3$); IR (film) / cm^{-1} 2980, 2940, 2215 (C≡N), 2134, 2113 (C=N=N), 1629 (C=O), 1480, 1459, 1425, 1385, 1363 (C=N=N), 1312, 1278, 1257, 1215, 1191, 1101, 893, 868, 789, 724, 668, 629; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (q, *J* = 7.1 Hz, 4 H, 2 x CH_2), 1.22 (t, *J* = 7.1 Hz, 6 H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (C=O), 110.1 (C≡N), 42.5 (2 x CH_2), 13.6 (br, 2 x CH_3).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[21]

(Benzenesulfonyl)methanecarbonimidoyl cyanide (1i)



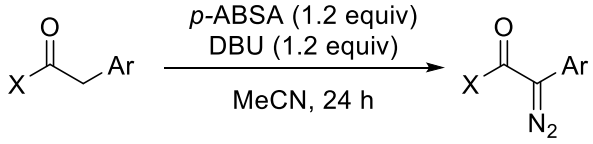
Pyridine (0.49 mL, 6.0 mmol) was added dropwise over 5 min to a stirring solution of (phenylsulfonyl)acetonitrile (543 mg, 3.0 mmol) and trifluoromethanesulfonyl azide solution **Sc** (0.47 M in *n*-hexane, 7.1 mL, 3.3 mmol) in CH_3CN (6 mL) at 0 °C. The resulting biphasic mixture was vigorously stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (50% to 75% $CHCl_3$ in toluene) afforded diazo nitrile **1i** as a yellow solid (118 mg, 19%); R_f = 0.33 (50% $CHCl_3$ in toluene); mp = 102–105 °C (decomp.) (lit.[25] mp = 103–108 °C (decomp.)); IR (film) / cm^{-1} 2936, 2256 (C≡N), 2127 (C=N=N out-of-phase), 1698, 1584, 1449, 1333 (C=N=N in-phase), 1158, 1068, 976, 907, 808, 726,

683, 648, 628, 588, 558; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.89 (m, 2 H, 2 x Ph-H), 7.80–7.73 (m, 1 H, Ph-H), 7.70–7.62 (m, 2 H, 2 x Ph-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (Ph-Cq), 135.0 (Ph-CH), 130.0 (2 x Ph-CH), 127.1 (2 x Ph-CH), 110.0 (C≡N), 105.7 (C_qN_2).

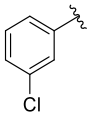
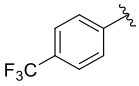
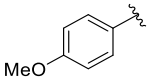
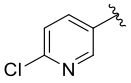
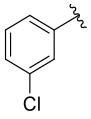
Observed data (mp, IR) was consistent with that previously reported.[25]

Synthesis of Disubstituted Aryl Diazos 6a–6g

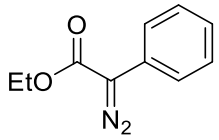
Synthesis of disubstituted aryl diazos **6a–6g** using *p*-ABSA, adapted from the procedure of Davies and co-workers (**Table S2**).[26]



6a–6g

Entry	X =	Ar =	Yield (%)
1	OEt		75 (**6a**)
2	O*i*Pr		52 (**6b**)
3	OEt		86 (**6c**)
4	OEt		86 (**6d**)
5	OEt		48 (**6e**)
6	OEt		83 (**6f**)
7			15 (**6g**)

Ethyl 2-diazo-2-phenylacetate (6a)

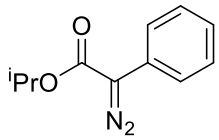


DBU (0.90 mL, 6.0 mmol) was added to a stirred solution of *p*-ABSA **Sb** (1.44 g, 6.0 mmol) and ethyl 2-phenylacetate (0.80 mL, 5.0 mmol) in CH_3CN (8.3 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (3% Et_2O in petroleum ether) afforded diazo **6a** as an orange oil (713 mg, 75%); R_f = 0.30 (5% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 2079 (C=N=N out-of-phase), 1699 (C=O), 1599, 1499, 1450, 1370 (C=N=N in-phase), 1337, 1242, 1149, 1095, 1048, 1028, 904, 753, 689, 666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.45 (m, 2 H, 2 x Ph-H), 7.42–7.33 (m, 2 H, 2 x Ph-H), 7.22–7.14 (m, 1 H, Ph-H), 4.34 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 1.35 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (CO_2), 128.9 (2 x Ph-CH), 125.7 (Ph-CH), 125.6 (Ph-C_q), 124.0 (2 x Ph-CH), 61.0 ($CO_2CH_2CH_3$), 14.5 ($CO_2CH_2CH_3$).

Reaction performed on a large scale (15 mmol ethyl 2-phenylacetate) afforded an isolated yield of diazo **6a** (1.83 g, 64%).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[27]

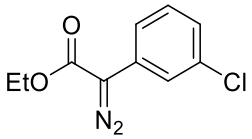
Propan-2-yl 2-diazo-2-phenylacetate (6b)



DBU (0.63 mL, 4.2 mmol) was added to a stirred solution of *p*-ABSA **Sb** (1.00 g, 4.2 mmol) and propan-2-yl 2-phenylacetate (0.62 mL, 3.5 mmol) in CH_3CN (35 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (3% Et_2O in petroleum ether) afforded diazo **6b** as a yellow oil (372 mg, 52%); R_f = 0.59 (3% Et_2O in petroleum ether); IR (film) / cm^{-1} 2982, 2935, 2077 (C=N=N out-of-phase), 1695 (C=O), 1599, 1363 (C=N=N in-phase), 1327, 1286, 1243, 1163, 1104, 1008, 996, 906, 753, 689, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.45 (m, 2 H, 2 x Ph-H), 7.43–7.34 (m, 2 H, 2 x Ph-H), 7.21–7.13 (m, 1 H, Ph-H), 5.22 (sep, *J* = 6.5 Hz, 1 H, $CO_2CH(CH_3)_2$), 1.33 (d, *J* = 6.5 Hz, 6 H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (CO_2), 128.9 (2 x Ph-CH), 125.8 (Ph-C_q), 125.7 (Ph-CH) 123.9 (2 x Ph-CH), 68.7 ($CO_2CH(CH_3)_2$), 22.1 (2 x CH_3).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[28]

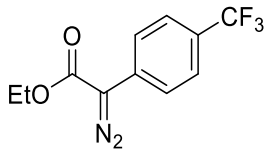
2-(3-Chlorophenyl)-2-diazoacetic acid (6c)



DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of *p*-ABSA **Sb** (865 mg, 3.6 mmol) and ester **S4** (596 mg, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (5% Et_2O in pentane) afforded diazo **6c** as a yellow solid (581 mg, 86%); R_f = 0.47 (5% diethylether in pentane); IR (film) / cm^{-1} 2991, 2907, 2089 (C=N=N out-of-phase), 1698 (C=O), 1592, 1559, 1479, 1446, 1425, 1391 (C=N=N in-phase), 1341, 1276, 1241, 1166, 1114, 1097, 1081, 1047, 993, 885, 865, 825, 776, 735, 679, 657; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1 H, Ar-H), 7.36–7.28 (m, 2 H, 2 x Ar-H), 7.17–7.12 (m, 1 H, Ar-H), 4.35 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 1.36 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (CO_2), 135.0 (Ar-C_q-CN_2), 130.0 (Ar-CH), 127.9 (Ar-C_q-Cl), 125.7 (Ar-CH), 123.7 (Ar-CH), 121.6 (Ar-CH), 61.2 ($CO_2CH_2CH_3$), 14.5 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[29]

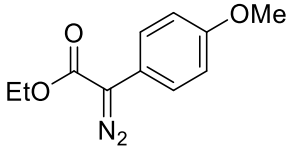
Ethyl 2-diazo-2-[4-(trifluoromethyl)phenyl]acetate (6d)



DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of *p*-ABSA **Sb** (865 mg, 3.6 mmol) and ester **S5** (697 mg, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (5% Et_2O in pentane) afforded diazo **6d** as a yellow solid (667 mg, 86%); R_f = 0.35 (5% Et_2O in pentane); IR (film) / cm^{-1} 2988, 2092 (C=N=N out-of-phase), 1691 (C=O), 1618, 1572, 1518, 1466, 1450, 1420, 1372 (C=N=N in-phase), 1320, 1297, 1241, 1198, 1153, 1112, 1069, 1040, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 4 H, 4 x Ar-H), 4.36 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 1.37 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (CO_2), 130.2 (Ar-C_q-CN_2), 127.5 (q, $J_{C\text{-}F}$ = 33 Hz, Ar-C_q-CF_3), 125.8 (q, $J_{C\text{-}F}$ = 4 Hz, 2 x Ar-CH), 124.1 (q, $J_{C\text{-}F}$ = 272 Hz, CF_3), 123.4 (2 x Ar-CH), 61.3 ($CO_2CH_2CH_3$), 14.4 ($CO_2CH_2CH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4.

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[30]

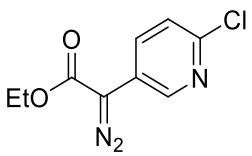
Ethyl 2-diazo-2-(4-methoxyphenyl)acetate (6e)



DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of *p*-ABSA **Sb** (865 mg, 3.6 mmol) and ester **S6** (583 mg, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (5% Et_2O in pentane) afforded diazo **6e** as a red solid (314 mg, 48%); R_f = 0.17 (5% Et_2O in pentane); IR (film) / cm^{-1} 2983, 2916, 2837, 2089 (C=N=N out-of-phase), 1692 (C=O), 1609, 1574, 1510, 1478, 1468, 1444, 1393, 1367 (C=N=N in-phase), 1343, 1318, 1295, 1252, 1238, 1189, 1162, 1049, 1031, 990, 828, 734, 639, 615, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.35 (m, 2 H, 2 x Ar-H), 7.00–6.91 (m, 2 H, 2 x Ar-H), 4.33 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.82 (s, 3 H, OCH_3), 1.34 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (CO_2), 158.0 (Ar-C_q-OCH_3), 125.9 (2 x Ar-CH), 117.0 (Ar-C_q-CN_2), 114.6 (2 x Ar-CH), 60.9 ($CO_2CH_2CH_3$), 55.3 (OCH_3), 14.5 ($CO_2CH_2CH_3$).

Observed data (IR, ^{1}H, ^{13}C) was consistent with that previously reported.[31]

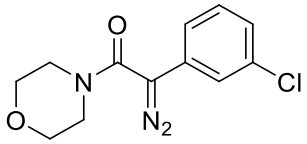
Ethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (6f)



DBU (0.53 mL, 3.6 mmol) was added to a stirred solution of *p*-ABSA **Sb** (865 mg, 3.6 mmol) and ester **S7** (599 mg, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50%

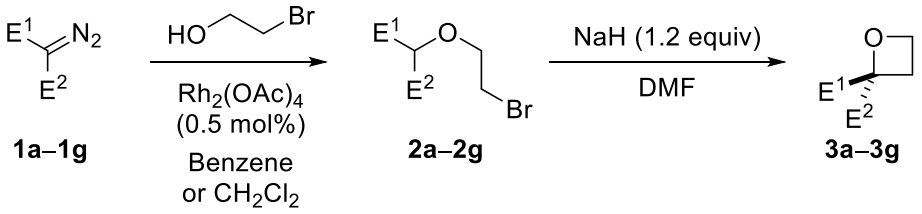
Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (10% Et_2O in pentane) afforded diazo **6f** as a yellow solid (564 mg, 83%); R_f = 0.18 (10% Et_2O in pentane); IR (film) / cm^{-1} 2981, 2089 (C=N=N out-of-phase), 1689 (C=O), 1579, 1549, 1471, 1399, 1383 (C=N=N in-phase), 1341, 1307, 1253, 1228, 1166, 1105, 1047, 1018, 988, 842, 832, 814, 741, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 2.7, 0.7 Hz, 1 H, Ar-H), 7.87 (dd, *J* = 8.5, 2.7 Hz, 1 H, Ar-H), 7.34 (dd, *J* = 8.5, 0.7 Hz, 1 H, Ar-H), 4.36 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 1.36 (t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3 (CO_2), 148.4 (Ar-C_q-Cl) 144.4 (Ar-CH), 133.8 (Ar-CH), 124.2 (Ar-CH), 122.0 (Ar-C_q-CN_2), 61.6 ($CO_2CH_2CH_3$), 14.4 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_9H_9N_3O_2Cl^+$ $[M+H]^+$: 226.0383, Found: 226.0390.

2-(3-Chlorophenyl)-2-diazo-1-(morpholin-4-yl)ethan-1-one (6g)

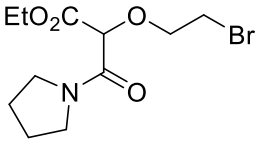


DBU (0.54 mL, 3.6 mmol) was added to a stirred solution of *p*-ABSA **Sb** (865 mg, 3.6 mmol) and amide **S8** (719 mg, 3.0 mmol) in CH_3CN (5.0 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was then taken up with 50% Et_2O in petroleum ether (50 mL), filtered and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc in hexanes) afforded diazo **6g** as a yellow oil (124 mg, 15%); R_f = 0.15 (25% EtOAc in hexanes); IR (film) / cm^{-1} 2968, 2856, 2059 (C=N=N out-of-phase), 1645, 1625 (C=O), 1591, 1563, 1481, 1456, 1424, 1362 (C=N=N in-phase), 1324, 1299, 1281, 1268, 1254, 1180, 1112, 1085, 1062, 1023, 993, 874, 867, 835, 782, 753, 727, 715, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.9 Hz, 1 H, Ar-H), 7.24 (t, *J* = 2.0 Hz, 1 H, Ar-H), 7.15 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1 H, Ar-H), 7.09 (ddd, *J* = 8.0, 1.8, 0.9 Hz, 1 H, Ar-H), 3.72–3.64 (m, 4 H, 2 x OCH_2), 3.50–3.45 (m, 4 H, 2 x NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C=O), 135.3 (Ar-C_q-CN_2), 130.4 (Ar-CH), 129.5 (Ar-C_q-Cl), 126.0 (Ar-CH), 124.1 (Ar-CH), 122.2 (Ar-CH), 66.6 (2 x OCH_2), 46.0 (2 x NCH_2); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{16}N_4O_2Cl^+$ $[M+CH_3CN+H]^+$: 307.0962, Found: 307.0956.

Synthesis of 2,2-Disubstituted Oxetanes 3a–3g

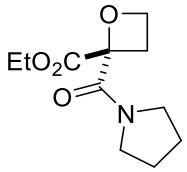


(±)-Ethyl 2-(2-bromoethoxy)-3-oxo-3-(pyrrolidin-1-yl)propanoate (2a)



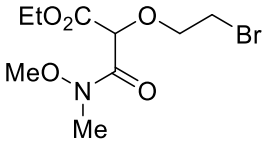
A mixture of diazo amide **1a** (442 mg, 2.1 mmol), 2-bromoethanol (249 mg, 2.0 mmol) and dirhodium(II) tetraacetate (4.4 mg, 0.010 mmol) in benzene (20 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide **2a** as a white solid (462 mg, 75%); R_f = 0.16 (50% EtOAc in hexanes); mp = 44–47 °C; IR (film) / cm^{-1} 2976, 2877, 1752 (C=O ester), 1645 (C=O amide), 1440, 1369, 1338, 1276, 1204, 1186, 1126, 1065, 1027, 915, 865, 715, 661, 603, 568, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 1 H, C*H*(CO_2Et)(CON)), 4.30 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.06–3.98 (m, 1 H, OC*H*H), 3.95–3.86 (m, 1 H, OCH*H*), 3.70–3.63 (m, 1 H, NC*H*H), 3.63–3.58 (m, 1 H, NCH*H*), 3.58–3.47 (m, 4 H, CH_2Br and NCH_2), 2.01–1.93 (m, 2 H, NCH_2CH_2),1.92–1.83 (m, 2 H, NCH_2CH_2) 1.31 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C=O), 163.6 (C=O), 80.0 (*C*H(CO_2Et)(CON)), 70.2 (OCH_2), 61.7 ($CO_2CH_2CH_3$), 46.4 (NCH_2), 46.3 (NCH_2), 29.9 (CH_2Br), 26.1 (NCH_2CH_2), 23.8 (NCH_2CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{19}BrNO_4^+$ $[M+H]^+$: 308.0497, Found: 308.0502.

(±)-Ethyl 2-(pyrrolidine-1-carbonyl)oxetane-2-carboxylate (3a)



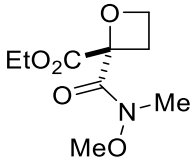
DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide **2a** (154 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded oxetane **3a** as a colorless oil (106 mg, 93%); R_f = 0.13 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2977, 2895, 1745 (C=O ester), 1647 (C=O amide), 1430, 1368, 1341, 1252, 1153, 1109, 1057, 1015, 971, 947, 859, 749, 721, 666, 558; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75–4.65 (m, 1 H OC*H*H), 4.58–4.49 (m, 1 H, OCH*H*), 4.31 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.69–3.43 (m, 4 H, NCH_2 and NC*H*H and C*H*H), 3.22–3.10 (m, 1 H, NCH*H*), 2.90–2.78 (m, 1 H, CH*H*), 1.98–1.75 (m, 4 H, 2 x NCH_2CH_2), 1.31 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O), 166.0 (C=O), 86.1 (C_q(CO_2Et)(CON)), 67.3 (OCH_2), 61.9 ($CO_2CH_2CH_3$), 46.6 (NCH_2), 45.7 (NCH_2), 29.0 (CH_2), 26.2 (NCH_2CH_2), 23.4 (NCH_2CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{18}NO_4^+$ $[M+H]^+$: 228.1236, Found: 228.1244.

(±)-Ethyl 2-(2-bromoethoxy)-2-[methoxy(methyl)carbamoyl]acetate (2b)



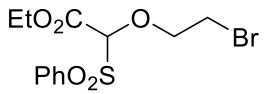
A mixture of diazo amide **1b** (220 mg, 1.1 mmol), 2-bromoethanol (125 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (4% to 5% MeOH in CH_2Cl_2) afforded bromide **2b** as a colorless oil (153 mg, 51%); R_f = 0.25 (5% MeOH in CH_2Cl_2); IR (film) / cm^{-1} 2979, 2942, 2874, 1755 (C=O ester), 1668 (C=O amide), 1445, 1424, 1388, 1370, 1332, 1277, 1181, 1122, 1025, 863, 804, 761, 708 656, 641, 588; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (s, 1 H, C*H*(CO_2Et)(CON)), 4.31–4.22 (m, 2 H, $CO_2CH_2CH_3$), 4.10–4.02 (m, 1 H, OC*H*H), 4.00–3.92 (m, 1 H, OCH*H*), 3.77 (s, 3 H, OCH_3), 3.55 (t, *J* = 6.3 Hz, 2 H, CH_2Br), 3.23 (s, 3 H, NCH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (C=O), 166.6 (C=O), 78.3 (*C*H(CO_2Et)(CON(Me)(OMe))), 71.0 (OCH_2), 61.9 (OCH_3), 61.7 ($CO_2CH_2CH_3$), 32.4 (NCH_3), 29.5 (CH_2Br), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_9H_{17}BrNO_5^+$ $[M+H]^+$: 298.0290, Found: 298.0289.

(±)-Ethyl 2-[methoxy(methyl)carbamoyl]oxetane-2-carboxylate (3b)



DMF (10 mL) was added to a flask containing sodium hydride (60% in mineral oil, 16 mg, 0.41 mmol) which had been cooled to 0 °C. Bromide **2b** (101 mg, 0.34 mmol) in DMF (3.6 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 1 h then 25 °C for 1 h. Saturated aq. NH_4Cl (14 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (30% to 40% EtOAc in hexanes) afforded oxetane **3b** as a colorless oil (71 mg, 96%); R_f = 0.38 (40% EtOAc in hexanes); IR (film) / cm^{-1} 2980, 2941, 2901, 1757 (C=O ester), 1670 (C=O amide), 1446, 1416, 1384, 1298, 1258, 1211, 1112, 1079, 1051, 992, 967, 947, 861, 752, 735, 700, 645; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78–4.69 (m, 1 H OC*H*H), 4.65–4.55 (m, 1 H, OCH*H*), 4.37–4.20 (m, 2 H, $CO_2CH_2CH_3$), 3.67 (s, 3 H, OCH_3), 3.51–3.42 (m, 1 H, C*H*H), 3.22 (s, 3 H, NCH_3), 2.81–2.71 (m, 1 H, CH*H*), 1.29 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (CO_2 and CON), 85.0 (C_q(CO_2Et)(CON)), 67.8 (OCH_2), 61.7 (OCH_3), 61.5 ($CO_2CH_2CH_3$), 32.8 (NCH_3), 27.7 (CH_2), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_9H_{16}NO_5^+$ $[M+H]^+$: 218.1028, Found: 218.1037.

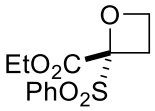
(±)-Ethyl 2-(benzenesulfonyl)-2-(2-bromoethoxy)acetate (2c)



A mixture of diazo sulfone **1c** (280 mg, 1.1 mmol), 2-bromoethanol (124 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.5 mg, 0.006 mmol) in benzene (10 mL) was heated at 80 °C for 90 min. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc in hexanes) afforded bromide **2c** as a white solid (323 mg, 92%); R_f = 0.15 (25% EtOAc in hexanes); mp = 47–50 °C; IR (film) / cm^{-1} 2982, 1745 (C=O), 1585, 1448, 1424, 1394, 1370, 1323, 1310, 1281, 1233, 1186, 1146, 1115, 1077, 1022, 1000, 859, 836, 760, 721,

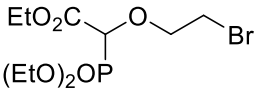
686, 631, 563; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.87 (m, 2 H, 2 x Ph-H), 7.74–7.67 (m, 1 H, Ph-H), 7.62–7.53 (m, 2 H, 2 x Ph-H), 5.01 (s, 1 H, C*H*(CO_2Et)(SO_2Ph)), 4.31 (dt, *J* = 11.1, 5.9 Hz, 1 H, OC*H*H), 4.21 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.07 (dt, *J* = 11.1, 6.2 Hz, 1 H, OCH*H*), 3.51–3.44 (m, 2 H, CH_2Br), 1.25 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (CO_2), 135.4 (Ph-C_q), 134.6 (Ph-CH), 129.8 (2 x Ph-CH), 129.0 (2 x Ph-CH), 94.3 (*C*H(CO_2Et)(SO_2Ph)), 73.4 (OCH_2), 62.8 ($CO_2CH_2CH_3$), 29.0 (CH_2Br), 13.9 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{18}BrNO_5SNa^+$ [M+CH_3CN+Na]$^+$: 413.9987, Found: 413.9986.

(±)-Ethyl 2-(benzenesulfonyl)oxetane-2-carboxylate (3c)



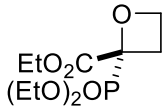
DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide **2c** (175 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (40% EtOAc in hexanes) afforded oxetane **3c** as a white solid (117 mg, 87%); R_f = 0.30 (40% EtOAc in hexanes); mp = 67–70 °C; IR (film) / cm^{-1} 2980, 2907, 1739 (C=O), 1584, 1477, 1448, 1392, 1369, 1310, 1283, 1233, 1156, 1144, 1115, 1084, 1063, 1013, 964, 931, 886, 855, 759, 723, 689, 584, 559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.88 (m, 2 H, 2 x Ph-H), 7.75–7.66 (m, 1 H, Ph-H), 7.62–7.51 (m, 2 H, 2 x Ph-H), 4.84–4.76 (m, 1 H OC*H*H), 4.57 (dt, *J* = 8.9, 5.5 Hz, 1 H, OCH*H*), 4.19 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.52–3.43 (m, 1 H, C*H*H), 3.32–3.22 (m, 1 H, CH*H*), 1.18 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (CO_2), 134.6 (Ph-CH), 134.1 (Ph-C_q), 130.2 (2 x Ph-CH), 128.8 (2 x Ph-CH), 98.7 (C_q(CO_2Et)(SO_2Ph)), 68.9 (OCH_2), 62.8 ($CO_2CH_2CH_3$), 26.5 (CH_2), 13.8 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{15}O_5S^+$ [M+H]$^+$: 271.0640, Found: 271.0633.

(±)-Ethyl 2-(2-bromoethoxy)-2-(diethoxyphosphoryl)acetate (2d)



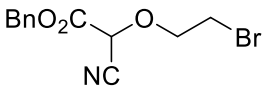
A mixture of diazo phosphonate **1d** (375 mg, 1.5 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide **2d** as a light yellow oil (267 mg, 77%); R_f = 0.21 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 2933, 1746 (C=O), 1445, 1392, 1254 (P=O), 1124, 1016, 974, 857, 794, 737, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (d, $J_{P\text{-}H}$ = 18.5 Hz, 1 H, C*H*(CO_2Et)($PO(OEt)_2$)), 4.35–4.16 (m, 6 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3), 4.04 (dt, *J* = 10.5, 6.0 Hz, 1 H, OC*H*H), 3.83 (dt, *J* = 10.5, 6.5 Hz, 1 H, OCH*H*), 3.58–3.46 (m, 2 H, CH_2Br), 1.41–1.29 (m, 9 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (CO_2), 76.9 (d, $J_{C\text{-}P}$ = 157.4 Hz, *C*H(CO_2Et)($PO(OEt)_2$)), 72.3 (d, $J_{C\text{-}P}$ = 12.5 Hz, O*C*H_2CH_2Br), 63.9 (d, $J_{C\text{-}P}$ = 6.3 Hz, O*C*H_2CH_3), 63.8 (d, $J_{C\text{-}P}$ = 6.3 Hz, O*C*H_2CH_3), 62.0 ($CO_2CH_2CH_3$), 29.3 (CH_2Br), 16.4 (d, $J_{C\text{-}P}$ = 6.1 Hz, 2 x OCH_2CH_3), 14.1 ($CO_2CH_2CH_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.4; HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{20}BrO_6PNa^+$ [M+Na]$^+$: 369.0079, Found: 369.0091.

(±)-Ethyl 2-(diethoxyphosphoryl)oxetane-2-carboxylate (3d)



DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Bromide **2d** (174 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% to 60% EtOAc in hexanes to EtOAc) afforded oxetane **3d** as a colorless oil (93 mg, 70%); R_f = 0.11 (60% EtOAc in hexanes); IR (film) / cm^{-1} 2982, 2905, 1733 (C=O), 1447, 1392, 1369, 1256 (P=O), 1195, 1163, 1100, 1010, 968, 941, 857, 794, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84–4.75 (m, 1 H, OC*H*H), 4.67–4.57 (m, 1 H, OCH*H*), 4.41–4.13 (m, 6 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3), 3.26–3.13 (m, 1 H, C*H*H), 3.12–2.97 (m, 1 H, CH*H*), 1.39–1.29 (m, 9 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (d, $J_{C\text{-}P}$ = 12.0 Hz, CO_2), 83.6 (d, $J_{C\text{-}P}$ = 159.0 Hz, $C_q(CO_2Et)(PO(OEt)_2)$, 69.2 (d, $J_{C\text{-}P}$ = 4.5 Hz, OCH_2), 64.2 (d, $J_{C\text{-}P}$ = 7.0 Hz, OCH_2CH_3), 63.8 (d, $J_{C\text{-}P}$ = 7.0 Hz, OCH_2CH_3), 62.0 ($CO_2CH_2CH_3$), 28.4 (d, $J_{C\text{-}P}$ = 3.5 Hz, CH_2), 16.44 (d, $J_{C\text{-}P}$ = 6.0 Hz, OCH_2CH_3), 16.41 (d, $J_{C\text{-}P}$ = 6.0 Hz, OCH_2CH_3), 14.1 ($CO_2CH_2CH_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{20}O_6P^+$ $[M+H]^+$: 267.0998, Found: 267.0989.

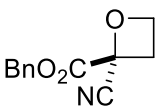
(±)-Benzyl 2-(2-bromoethoxy)-2-cyanoacetate (2e)



A mixture of diazo nitrile **1e** (221 mg, 1.1 mmol), 2-bromoethanol (125 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded bromide **2e** as a yellow oil (253 mg, 85%); R_f = 0.30 (20% EtOAc in hexanes); IR (film) / cm^{-1} 3036, 2931, 2877, 2251 (C≡N), 1760 (C=O), 1498, 1456, 1423, 1379, 1282, 1213, 1127, 988, 907, 826, 776, 749, 697, 601, 574; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 5 H, 5 x Ph-H), 5.33 (d, *J* = 12.2 Hz, 1 H, CO_2CHHPh), 5.29 (d, *J* = 12.2 Hz, 1 H, CO_2CHHPh), 4.99 (s, 1 H, $CH(CO_2Bn)(CN)$), 4.13–4.04 (m, 1 H, OC*H*H), 4.04–3.95 (m, 1 H, OCH*H*), 3.52 (t, *J* = 6.0 Hz, 2 H, CH_2Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (CO_2), 133.9 (Ph-C_q), 128.9 (Ph-CH), 128.7 (2 x Ph-CH), 128.4 (2 x Ph-CH), 113.1 (C≡N), 70.2 (OCH_2), 68.9 (CO_2CH_2Ph), 67.2 ($CH(CO_2Bn)(CN)$), 28.5 (CH_2Br); HRMS (CI) *m/z* Calcd for $C_{12}H_{16}BrN_2O_3^+$ $[M+NH_4]^+$: 315.0344, Found: 315.0357.

Reaction performed on a large scale (10 mmol 2-bromoethanol, 11 mmol diazo **1e**) afforded an isolated yield of bromide **2e** (2.79 g, 93%).

(±)-Benzyl 2-cyanooxetane-2-carboxylate (3e)

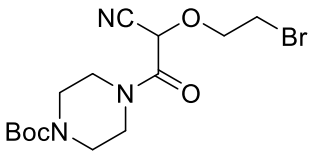


DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide **2e** (149 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (40% EtOAc in hexanes) afforded oxetane **3e** as a yellow oil which solidified upon storage at –20 °C (95 mg, 88%); R_f = 0.47 (40% EtOAc in hexanes); mp = 30–32 °C; IR (film) / cm^{-1} 3035, 2980, 2909,

2244 (C≡N), 1746 (C=O), 1498, 1456, 1379, 1268, 1195, 1161, 1105, 1029, 965, 938, 907, 738, 696, 601, 588; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.35 (m, 5 H, 5 x Ph-H), 5.36 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh), 5.32 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh) 4.90–4.82 (m, 1 H, OC*H*H), 4.81–4.73 (m, 1 H, OCH*H*), 3.32–3.22 (m, 1 H, C*H*H), 3.21–3.12 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (CO_2), 134.1 (Ph-C_q), 128.8 (Ph-CH), 128.7 (2 x Ph-CH), 128.3 (2 x Ph-CH), 116.3 (C≡N), 75.6 ($C_q(CO_2Bn)(CN)$), 69.4 (OCH_2), 68.8 (CO_2CH_2Ph), 31.5 (CH_2); HRMS (FTMS +pNSI) *m/z* Calcd for $C_{12}H_{11}NO_3Na^+$ $[M+Na]^+$: 240.0631, Found: 240.0631.

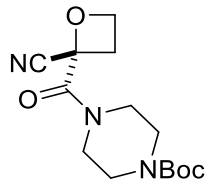
Reaction performed on a large scale (8 mmol bromide **2e**) afforded an isolated yield of oxetane **3e** (1.61 g, 93%).

(±)-*tert*-Butyl 4-[2-(2-bromoethoxy)-2-cyanoacetyl]piperazine-1-carboxylate (2f)



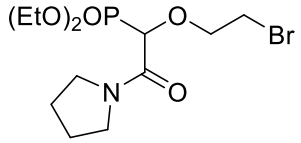
A mixture of diazo amide **1f** (336 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (2.3 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (3% to 4% to 6% CH_3CN in CH_2Cl_2) afforded bromide **2f** as a pale yellow viscous oil (252 mg, 67%); R_f = 0.11 (4% CH_3CN in CH_2Cl_2); IR (film) / cm^{-1} 2977, 2931, 2868, 2223 (C≡N), 1664 (C=O), 1460, 1419, 1366, 1286, 1254, 1235, 1167, 1126, 1050, 996, 864, 771, 577, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 1 H, (NC)CH(O)), 4.18–4.08 (m, 1 H, OC*H*H), 4.05–3.95 (m, 1 H, OCH*H*), 3.74–3.46 (m, 10 H, CH_2Br and 4 x CH_2), 1.50 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4 (C=O amide), 154.3 (C=O carbamate), 113.6 (C≡N), 80.6 ($C_q(CH_3)_3$), 70.4 (OCH_2), 70.1 (NC)*C*H(O)), 45.9 (2 x CH_2), 42.8 (2 x CH_2), 29.0 (CH_2Br), 28.3 (3 x CH_3); HRMS (FTMS +pNSI) *m/z* Calcd for $C_{14}H_{26}BrN_4O_4^+$ $[M+NH_4]^+$: 393.1132, Found: 393.1131.

(±)-*tert*-Butyl 4-(2-cyanooxetane-2-carbonyl)piperazine-1-carboxylate (3f)



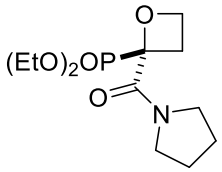
DMF (20 mL) was added to a flask containing sodium hydride (60% in mineral oil, 30 mg, 0.76 mmol) which had been cooled to 0 °C. Bromide **2f** (237 mg, 0.63 mmol) in DMF (5 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (25 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 25 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (70% Et_2O in hexanes) afforded oxetane **3f** as a white solid (161 mg, 87%); R_f = 0.22 (70% Et_2O in hexanes); mp = 76–79 °C; IR (film) / cm^{-1} 2978, 2908, 2254 (C≡N), 1693 (C=O), 1661 (C=O), 1416, 1366, 1287, 1247, 1234, 1162, 1139, 1119, 1018, 995, 940, 917, 864, 770, 728, 669, 647, 594, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (td, *J* = 8.1, 5.8 Hz, 1 H, OC*H*H), 4.54 (dt, *J* = 9.1, 5.8 Hz, 1 H, OCH*H*), 3.73–3.35 (m, 9 H, 4 x NCH_2 and C*H*H), 3.15–3.03 (m, 1 H, CH*H*), 1.46 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (C=O amide), 154.4 (C=O carbamate), 117.4 (C≡N), 80.4 ($C_q(CH_3)_3$), 76.0 (C_q(CN)(CON)), 68.4 (OCH_2), 45.7 (2 x NCH_2), 42.9 (2 x NCH_2), 30.3 (CH_2), 28.3 (3 x CH_3); HRMS (FTMS +pNSI) *m/z* Calcd for $C_{14}H_{25}N_4O_4^+$ $[M+NH_4]^+$: 313.1873, Found: 313.1870.

(±)-Diethyl [1-(2-bromoethoxy)-2-oxo-2-(pyrrolidin-1-yl)ethyl]phosphonate (2g)



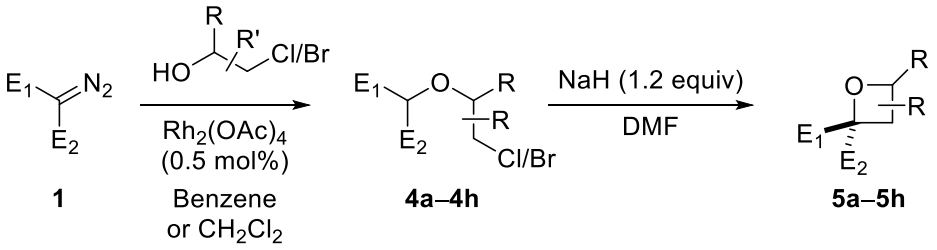
A mixture of diazo phosphonate **1g** (612 mg, 2.2 mmol), 2-bromoethanol (250 mg, 2.0 mmol) and dirhodium(II) tetraacetate (4.5 mg, 0.010 mmol) in benzene (20 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (4% MeOH in CH_2Cl_2) afforded bromide **2g** as a green oil (623 mg, 84%); R_f = 0.16 (4% MeOH in CH_2Cl_2); IR (film) / cm^{-1} 2979, 2878, 1642 (C=O), 1433, 1392, 1340, 1250 (P=O), 1163, 1112, 1018, 968, 867, 749, 664, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, $J_{P\text{-}H}$ = 16.8 Hz, 1 H, C*H*(CON)(PO(OEt)$_2$)), 4.27–4.16 (m, 4 H, 2 x OC*H*$_2$CH$_3$), 4.03–3.95 (m, 1 H, OC*H*H), 3.80–3.70 (m, 2 H, OCH*H* and NC*H*H), 3.69–3.61 (m, 1 H, NCH*H*), 3.58–3.43 (m, 4 H, CH_2Br and NCH_2), 2.00–1.89 (m, 2 H, NCH_2CH_2), 1.89–1.78 (m, 2 H, NCH_2CH_2) 1.41–1.26 (m, 6 H, 2 x OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8 (C=O), 77.7 (d, $J_{C\text{-}P}$ = 155.3 Hz, *C*H(CON)(PO(OEt)$_2$)), 71.7 (d, $J_{C\text{-}P}$ = 13.1 Hz, OCH_2CH_2Br), 63.8 (d, $J_{C\text{-}P}$ = 6.6 Hz, OCH_2CH_3), 63.6 (d, $J_{C\text{-}P}$ = 6.6 Hz, OCH_2CH_3), 46.7 (NCH_2), 46.6 (NCH_2), 29.7 (CH_2Br), 26.2 (NCH_2CH_2), 23.7 (NCH_2CH_2), 16.4 (d, $J_{C\text{-}P}$ = 6.1 Hz, 2 x OCH_2CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.8; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{24}BrNO_5P^+$ $[M+H]^+$: 372.0575, Found: 372.0579.

(±)-Diethyl [2-(pyrrolidine-1-carbonyl)oxetan-2-yl]phosphonate (3g)



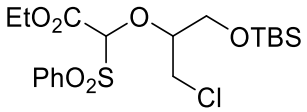
DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol) which had been cooled to 0 °C. Bromide **2g** (186 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (5 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (EtOAc to 5% MeOH in EtOAc) afforded oxetane **3g** as a yellow oil (105 mg, 72%); R_f = 0.10 (EtOAc); IR (film) / cm^{-1} 2976, 2895, 1629 (C=O), 1429, 1392, 1343, 1250 (P=O), 1163, 1098, 1020, 968, 944, 854, 791, 720, 756, 681, 573, 547; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74–4.64 (m, 1 H OC*H*H), 4.55–4.46 (m, 1 H, OCH*H*), 4.34–4.23 (m, 2 H, OC*H*$_2$CH$_3$), 4.23–4.12 (m, 2 H, OC*H*$_2$CH$_3$), 3.82–3.71 (m, 1 H, NC*H*H), 3.69–3.59 (m, 1 H, NCH*H*), 3.58–3.48 (m, 2 H, NCH_2), 3.29–3.04 (m, 2 H, CH_2), 1.94–1.72 (m, 4 H, 2 x NCH_2CH_2), 1.38 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.32 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (d, $J_{C\text{-}P}$ = 12.1 Hz, C=O), 85.3 (d, $J_{C\text{-}P}$ = 153.1 Hz, C_q(CON)(PO(OEt)$_2$)), 68.4 (d, $J_{C\text{-}P}$ = 4.1 Hz, OCH_2), 63.7 (d, $J_{C\text{-}P}$ = 6.7 Hz, OCH_2CH_3), 63.5 (d, $J_{C\text{-}P}$ = 6.7 Hz, OCH_2CH_3), 47.2 (NCH_2), 46.7 (NCH_2), 29.5 (d, $J_{C\text{-}P}$ = 3.4 Hz, CH_2), 26.5 (NCH_2CH_2), 23.3 (NCH_2CH_2), 16.5 (d, $J_{C\text{-}P}$ = 5.6 Hz, OCH_2CH_3), 16.4 (d, $J_{C\text{-}P}$ = 5.6 Hz, OCH_2CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.8; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{23}NO_5P^+$ $[M+H]^+$: 292.1314, Found: 292.1313.

Synthesis of Tri- and Tetrasubstituted Oxetanes 5a–5h



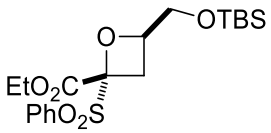
1 **4a–4h** **5a–5h**

(±)-Ethyl 2-(benzenesulfonyl)-2-({1-[(*tert*-butyldimethylsilyl)oxy]-3-chloropropan-2-yl}oxy)acetate (4a)



A mixture of diazo sulfone **1c** (279 mg, 1.1 mmol), (±)-1-[(*tert*-butyldimethylsilyl)oxy]-3-chloropropan-2-ol[4] (225 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 90 min. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded chloride **4a** as a mixture of diastereoisomers as a colorless oil (300 mg, 66%, d.r. 1.5:1.0); R_f = 0.35 (20% EtOAc in hexanes); IR (film) / cm^{-1} 2954, 2930, 2858, 1753 (C=O), 1586, 1472, 1448, 1371, 1326, 1311, 1254, 1228, 1186, 1149 1117, 1078, 1052, 1024, 939, 904, 835, 778, 758, 721, 686, 557, 522; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.87 (m, 2 H, 2 x Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.60–7.53 (m, 2 H, 2 x Ph-H), 5.39 (s, 1 H, C*H*(CO_2Et)(SO_2Ph)), 4.27–4.13 (m, 2 H, $CO_2CH_2CH_3$), 4.13–4.06 (m, 1 H, OC*H*(CH_2Cl)), 3.90–3.80 (m, 2 H, CH_2OTBS), 3.80–3.66 (m, 1 H, C*H*HCl), 3.66–3.55 (m, 1 H, CH*H*Cl), 1.236 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.86 (s, 9 H, C(CH_3)$_3$), 0.04 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu), 0.01 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (CO_2), 135.69 (Ph-C_q), 134.5 (Ph-CH), 129.7 (2 x Ph-CH), 128.91 (2 x Ph-CH), 94.2 (*C*H(CO_2Et)(SO_2Ph)), 83.5 (O*C*H(CH_2Cl)), 63.9 (CH_2OTBS), 62.56 ($CO_2CH_2CH_3$), 42.3 (CH_2Cl), 25.73 (C(*C*H_3)$_3$), 18.1 (*C*$_q$(CH_3)$_3$), 13.8 ($CO_2CH_2CH_3$), –5.7 (OSi(*C*H_3)$_2$(*t*Bu); **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.87 (m, 2 H, 2 x Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.60–7.53 (m, 2 H, 2 x Ph-H), 5.32 (s, 1 H, C*H*(CO_2Et)(SO_2Ph)), 4.27–4.13 (m, 2 H, $CO_2CH_2CH_3$), 4.06–3.98 (m, 1 H, OC*H*(CH_2Cl)), 3.80–3.66 (m, 2 H, C*H*HOTBS and C*H*HCl), 3.66–3.55 (m, 1 H, CH*H*OTBS and CH*H*Cl), 1.239 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.88 (s, 9 H, C(CH_3)$_3$), 0.07 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu), 0.06 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (CO_2), 135.66 (Ph-C_q), 134.5 (Ph-CH), 129.8 (2 x Ph-CH), 128.86 (2 x Ph-CH), 93.9 (*C*H(CO_2Et)(SO_2Ph)), 83.4 (O*C*H(CH_2Cl)), 62.66 (CH_2OTBS), 62.61 ($CO_2CH_2CH_3$), 44.1 (CH_2Cl), 25.70 (C(*C*H_3)$_3$), 18.1 (*C*$_q$(CH_3)$_3$), 13.9 ($CO_2CH_2CH_3$), –5.5 (OSi(*C*H_3)(C'H_3)(*t*Bu), –5.6 (OSi(CH_3)(*C*'H_3)(*t*Bu); HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{32}ClO_6SSi^+$ $[M+H]^+$: 451.1377, Found: 451.1389.

(±)-Ethyl 2-(benzenesulfonyl)-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}oxetane-2-carboxylate (5a)



MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.6 mmol) which had been cooled to 0 °C. Chloride **4a** (226 mg, 0.5 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash

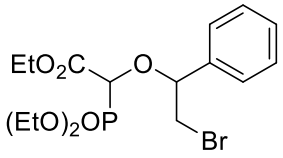
chromatography (20% EtOAc in hexanes) afforded major oxetane **5a** as a pale yellow oil (104 mg, 51%) followed by minor oxetane **5a'** as a pale yellow oil (86 mg, 41%) (total yield 92%, d.r. 55:45).

Major Product 5a: R_f = 0.33 (20% EtOAc in hexanes); IR (film) / cm^{-1} 2954, 2930, 2857, 1743 (C=O), 1585, 1472, 1448, 1390, 1369, 1323, 1311, 1284, 1254, 1229, 1138, 1108, 1089, 1068, 1020, 995, 834, 778, 758, 722, 687, 580, 567; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (m, 2 H, 2 x Ph-H), 7.71–7.65 (m, 1 H, Ph-H), 7.58–7.52 (m, 2 H, 2 x Ph-H), 4.95 (tt, *J* = 7.2, 2.3 Hz, 1 H, OC*H*(CH_2OTBS)), 4.14 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.83 (dd, *J* = 12.6, 2.3 Hz, 1 H, C*H*HOTBS), 3.57 (dd, *J* = 12.6, 2.3 Hz, 1 H, CH*H*OTBS), 3.38 (dd, *J* = 12.6, 7.5 Hz, 1 H, C*H*H), 3.31 (dd, *J* = 12.6, 6.9 Hz, 1 H, CH*H*), 1.14 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.86 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu)), 0.02 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (CO_2), 134.4 (Ph-CH), 134.3 (Ph-C_q), 130.2 (2 x Ph-CH), 128.8 (2 x Ph-CH), 95.9 ($C_q(CO_2Et)(SO_2Ph)$), 79.9 (OCH(CH_2OTBS)), 63.5 (CH_2OTBS), 62.4 ($CO_2CH_2CH_3$), 26.5 (CH_2), 25.7 ($C(CH_3)_3$), 18.2 ($C_q(CH_3)_3$), 13.7 ($CO_2CH_2CH_3$), –5.5 (OSi(CH_3)(C'H_3)(*t*Bu), –5.7 (OSi(CH_3)(C'H_3)(*t*Bu); HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{33}NO_6SSiNa^+$ $[M+CH_3CN+Na]^+$: 478.1696, Found: 478.1712.

Minor Product 5a': R_f = 0.24 (20% EtOAc in hexanes); IR (film) / cm^{-1} 2954, 2930, 2857, 1742 (C=O), 1585, 1472, 1448, 1390, 1368, 1324, 1275, 1258, 1154, 1099, 1082, 999, 835, 777, 758, 721, 686, 589, 561; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.87 (m, 2 H, 2 x Ph-H), 7.74–7.65 (m, 1 H, Ph-H), 7.60–7.51 (m, 2 H, 2 x Ph-H), 4.85–4.74 (m, 1 H, OC*H*(CH_2OTBS)), 4.19 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.10 (dd, *J* = 11.2, 6.6 Hz, 1 H, C*H*HOTBS), 3.86 (dd, *J* = 11.2, 5.6 Hz, 1 H, CH*H*OTBS), 3.27 (dd, *J* = 13.0, 6.7 Hz, 1 H, C*H*H), 3.17 (dd, *J* = 13.0, 7.6 Hz, 1 H, CH*H*), 1.17 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 0.91 (s, 9 H, $C(CH_3)_3$), 0.12 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu)), 0.11 (s, 3 H, OSi(CH_3)(C'H_3)(*t*Bu)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (CO_2), 134.5 (Ph-CH), 134.3 (Ph-C_q), 130.3 (2 x Ph-CH), 128.8 (2 x Ph-CH), 95.8 ($C_q(CO_2Et)(SO_2Ph)$), 79.2 (OCH(CH_2OTBS)), 65.4 (CH_2OTBS), 62.8 ($CO_2CH_2CH_3$), 28.7 (CH_2), 25.9 ($C(CH_3)_3$), 18.3 ($C_q(CH_3)_3$), 13.8 ($CO_2CH_2CH_3$), –5.27 (OSi(CH_3)(C'H_3)(*t*Bu), –5.33 (OSi(CH_3)(C'H_3)(*t*Bu); HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{33}NO_6SSiNa^+$ $[M+CH_3CN+Na]^+$: 478.1696, Found: 478.1707.

The relative stereochemistries for the major and minor isomers of oxetane **5a** were determined based on NOE studies (see page S119).

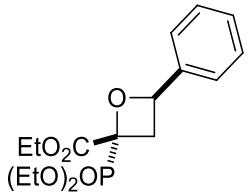
(±)-Ethyl 2-(2-bromo-1-phenylethoxy)-2-(diethoxyphosphoryl)acetate (4b)



A mixture of diazo phosphonate **1d** (500 mg, 2.0 mmol), (±)-2-bromo-1-phenylethan-1-ol[4] (268 mg, 1.3 mmol) and dirhodium(II) tetraacetate (3.0 mg, 0.007 mmol) in benzene (13 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded bromide **4b** as a mixture of diastereoisomers as a light yellow oil (361 mg, 64%, d.r. 1.2:1.0); R_f = 0.39 (60% EtOAc in hexanes); IR (film) / cm^{-1} 2982, 1748 (C=O), 1455, 1369, 1257 (P=O), 1162, 1104, 1018, 975, 755, 702; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5 H, 5 x Ph-H), 4.90 (dd, *J* = 7.5, 5.0 Hz, 1 H, OCH(Ph)), 4.39–4.14 (m, 6 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3), 4.12–4.02 (m, 1 H, C*H*(CO_2Et)(PO(OEt)$_2$)), 3.76–3.69 (m, 1 H, C*H*HBr), 3.59–3.47 (m, 1 H, CH*H*Br), 1.42–1.26 (m, 6 H, 2 x OCH_2CH_3), 1.16 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (CO_2), 137.4 (Ph-C_q), 129.1 (Ph-CH), 128.6 (2 x Ph-CH), 127.4 (2 x Ph-CH), 83.8 (d, J_{C-P} = 6.1 Hz, OCH(Ph)), 75.0 (d, J_{C-P} = 156.3 Hz, C*H*(CO_2Et)(PO(OEt)$_2$)), 63.9 (d, J_{C-P} = 6.6 Hz, O*C*H_2CH_3), 63.5 (d, J_{C-P} = 6.6 Hz, O*C*H_2CH_3), 61.6 ($CO_2CH_2CH_3$), 34.8 (CH_2Br), 16.3 (d, J_{C-P} = 6.6 Hz, 2 x OCH_2CH_3), 13.9 ($CO_2CH_2CH_3$); ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.3; **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5 H, 5 x Ph-H), 4.72–4.65 (m, 1 H, OCH(Ph)), 4.39–4.14 (m, 6 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3), 4.12–4.02 (m, 1 H, C*H*(CO_2Et)(PO(OEt)$_2$)), 3.76–3.69 (m, 1 H, C*H*HBr), 3.59–3.47 (m, 1 H, CH*H*Br), 1.42–1.26 (m, 9 H, $CO_2CH_2CH_3$ and 2 x OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (CO_2), 136.6 (Ph-C_q), 129.2 (Ph-CH),

128.8 (2 x Ph-CH), 127.4 (2 x Ph-CH), 81.9 (d, $J_{C\text{-}P}$ = 14.7 Hz, OCH(Ph)), 73.9 (d, $J_{C\text{-}P}$ = 157.9 Hz, *C*H(CO_2Et)(PO(OEt)$_2$)), 63.8 (d, $J_{C\text{-}P}$ = 6.8 Hz, O*C*$H_2$$CH_3$), 63.7 (d, $J_{C\text{-}P}$ = 6.8 Hz, O*C*$H_2$$CH_3$), 61.8 ($CO_2$*C*$H_2$$CH_3$), 35.1 ($CH_2$Br), 16.4 (d, $J_{C\text{-}P}$ = 6.8 Hz, 2 x OCH_2*C*H_3), 14.1 (CO_2CH_2*C*H_3); ^{31}P (162 MHz, $CDCl_3$) δ 13.4; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{25}BrO_6P^+$ $[M+H]^+$: 423.0572, Found: 423.0568.

(±)-Ethyl 2-(diethoxyphosphoryl)-4-phenyloxetane-2-carboxylate (5b)

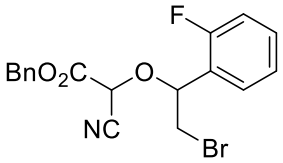


MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide **4b** (212 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 25 °C for 20 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (70% EtOAc in hexanes) afforded oxetane **5b** as a mixture of diastereoisomers as a colorless oil (122 mg, 71%, d.r. 54:46); R_f = 0.32 (70% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 2934, 2128, 1733 (C=O), 1446, 1392, 1368, 1255, 1163, 1100, 1013, 970, 941, 856, 793, 757, 699, 597, 562; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 1 H, Ph-H), 7.46–7.28 (m, 4 H, 4 x Ph-H), 5.85 (t, *J* = 7.5 Hz, 1 H, OCH(Ph)), 4.47–4.09 (m, 6 H, CO_2C*H*$_2$$CH_3$ and 2 x OC*H*$_2$$CH_3$), 3.59–3.38 (m, 1 H, C*H*H), 3.06–2.91 (m, 1 H, C*H*H), 1.43–1.27 (m, 9 H, CO_2CH_2C*H*$_3$ and 2 x OCH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (d, $J_{C\text{-}P}$ = 12.1 Hz, CO_2), 140.4 (Ph-C_q), 128.6 (2 x Ph-CH), 128.4 (Ph-CH), 125.8 (2 x Ph-CH), 79.8 (d, $J_{C\text{-}P}$ = 3.3 Hz, OCH(Ph)), 79.4 (d, $J_{C\text{-}P}$ = 159.7 Hz, *C*$_q$(CO_2Et)(PO(OEt)$_2$), 64.4 (d, $J_{C\text{-}P}$ = 6.6 Hz, O*C*$H_2$$CH_3$), 63.8 (d, $J_{C\text{-}P}$ = 6.6 Hz, O*C*$H_2$$CH_3$), 62.3 ($CO_2$*C*$H_2$$CH_3$), 36.9 (d, $J_{C\text{-}P}$ = 2.4 Hz, CH_2), 16.53 (d, $J_{C\text{-}P}$ = 5.2 Hz, OCH_2*C*H_3), 16.47 (d, $J_{C\text{-}P}$ = 5.2 Hz, OCH_2*C*H_3), 14.1 (CO_2CH_2*C*H_3); ^{31}P (162 MHz, $CDCl_3$) δ 16.3; **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.56 (m, 1 H, Ph-H), 7.46–7.28 (m, 4 H, 4 x Ph-H), 5.88 (t, *J* = 7.5 Hz, 1 H, OCH(Ph)), 4.47–4.09 (m, 6 H, CO_2C*H*$_2$$CH_3$ and 2 x OC*H*$_2$$CH_3$), 3.59–3.38 (m, 1 H, C*H*H), 3.29–3.17 (m, 1 H, C*H*H), 1.43–1.27 (m, 9 H, CO_2CH_2C*H*$_3$ and 2 x OCH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (d, $J_{C\text{-}P}$ = 12.1 Hz, CO_2), 141.1 (Ph-C_q), 128.6 (2 x Ph-CH), 128.5 (Ph-CH), 126.4 (2 x Ph-CH), 81.3 (d, $J_{C\text{-}P}$ = 8.9 Hz, OCH(Ph)), 80.2 (d, $J_{C\text{-}P}$ = 161.5 Hz, *C*$_q$(CO_2Et)(PO(OEt)$_2$), 64.0 (d, $J_{C\text{-}P}$ = 6.6 Hz, O*C*$H_2$$CH_3$), 63.7 (d, $J_{C\text{-}P}$ = 6.6 Hz, O*C*$H_2$$CH_3$), 62.0 ($CO_2$*C*$H_2$$CH_3$), 36.7 (d, $J_{C\text{-}P}$ = 4.4 Hz, CH_2), 16.36 (d, $J_{C\text{-}P}$ = 6.0 Hz, OCH_2*C*H_3), 16.34 (d, $J_{C\text{-}P}$ = 6.0 Hz, OCH_2*C*H_3), 14.1 (CO_2CH_2*C*H_3); ^{31}P (162 MHz, $CDCl_3$) δ 14.5; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{26}NO_6PNa^+$ $[M+CH_3CN+Na]^+$: 406.1395, Found: 406.1395.

The relative stereochemistries for the major and minor isomers of oxetane **5b** were assigned by analogy to that observed for oxetane **5a**.

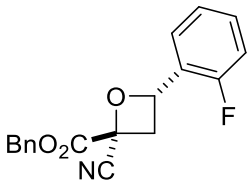
(±)-Benzyl 2-[2-bromo-1-(2-fluorophenyl)ethoxy]-2-cyanoacetate (4c)



A mixture of diazo nitrile **1e** (193 mg, 0.96 mmol), (±)-2-bromo-1-(2-fluorophenyl)ethan-1-ol[4] (191.4 mg, 0.87 mmol) and dirhodium(II) tetraacetate (1.9 mg, 0.0043 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (70% CH_2Cl_2 in hexanes) afforded bromide **4c** as a mixture of diastereoisomers as a yellow oil (277 mg, 81%, d.r. 1.4:1.0); R_f = 0.30 (70% CH_2Cl_2 in hexanes); IR (film) / cm^{-1} 3037, 2968, 2244 (C≡N), 1753 (C=O), 1616, 1587, 1489,

1456, 14420, 1378, 1277, 1216, 1111, 1016, 946, 908, 827, 759, 697, 663, 605, 528; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.44 (m, 1 H, Ar-H), 7.44–7.32 (m, 6 H, Ar-H and 5 x Ph-H), 7.29–7.16 (m, 1 H, Ar-H), 7.16–7.06 (m, 1 H, Ar-H), 5.34–5.20 (m, 3 H, OCH(Ar) and CO_2CH_2Ph), 4.75 (s, 1 H, C*H*(CO_2Bn)(CN)), 3.73–3.59 (m, 2 H, CH_2Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (CO_2), 160.5 (d, $J_{C\text{-}F}$ = 248 Hz, Ar-C_q-F), 133.87 (Ph-C_q), 131.2 (d, $J_{C\text{-}F}$ = 8 Hz, Ar-CH), 128.90 (Ph-CH), 128.7 (2 x Ph-CH), 128.4 (2 x Ph-CH), 127.9 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 124.9 (Ar-CH), 123.1 (d, $J_{C\text{-}F}$ = 13 Hz, Ar-*C*$_q$-CH(O)),115.9 (d, $J_{C\text{-}F}$ = 21 Hz, Ar-CH), 113.1 (C≡N), 76.0 (d, $J_{C\text{-}F}$ = 2 Hz, OCH(Ar)), 68.91 (CO_2*C*H_2Ph), 66.14 (*C*H(CO_2Bn)(CN)), 33.1 (CH_2Br); ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.6; **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.44 (m, 1 H, Ar-H), 7.44–7.32 (m, 6 H, Ar-H and 5 x Ph-H), 7.29–7.16 (m, 1 H, Ar-H), 7.16–7.06 (m, 1 H, Ar-H), 5.34–5.20 (m, 3 H, OCH(Ar) and CO_2CH_2Ph), 4.80 (s, 1 H, C*H*(CO_2Bn)(CN)), 3.73–3.59 (m, 2 H, CH_2Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (CO_2), 160.4 (d, $J_{C\text{-}F}$ = 248 Hz, Ar-C_q-F), 133.88 (Ph-C_q), 131.2 (d, $J_{C\text{-}F}$ = 8 Hz, Ar-CH), 128.92 (Ph-CH), 128.7 (2 x Ph-CH), 128.5 (2 x Ph-CH), 128.1 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 124.9 (Ar-CH), 123.4 (d, $J_{C\text{-}F}$ = 13 Hz, Ar-*C*$_q$-CH(O)),116.0 (d, $J_{C\text{-}F}$ = 21 Hz, Ar-CH), 113.2 (C≡N), 76.8 (d, $J_{C\text{-}F}$ = 2 Hz, OCH(Ar)), 68.93 (CO_2*C*H_2Ph), 66.06 (*C*H(CO_2Bn)(CN)), 33.3 (CH_2Br); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.0; HRMS (FTMS +pNSI) *m/z* Calcd for $C_{18}H_{19}BrFN_2O_3^+$ $[M+NH_4]^+$: 409.0558, Found: 409.0556.

(±)-Benzyl 2-cyano-4-(2-fluorophenyl)oxetane-2-carboxylate (5c)

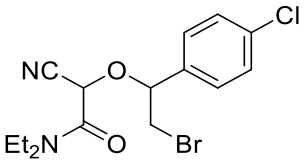


MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol) which had been cooled to 0 °C. Bromide **4c** (197 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane **5c** as a mixture of diastereoisomers as a pale yellow oil (126 mg, 80%, d.r. 70:30); R_f = 0.45 (20% EtOAc in hexanes); IR (film) / cm^{-1} 3037, 2964, 2220 (C≡N), 1746 (C=O), 1619, 1588, 1492, 1456, 1377, 1269, 1235, 1170, 1114, 1062, 1030, 967, 929, 817, 751, 696, 599; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.67 (m, 1 H, Ar-H), 7.48–7.35 (m, 6 H, Ar-H and 5 x Ph-H), 7.32–7.25 (m, 1 H, Ar-H), 7.12–6.99 (m, 1 H, Ar-H), 6.15 (t, *J* = 7.5 Hz, 1 H, OCH(Ar)), 5.42 (d, *J* = 12.1 Hz, 1 H, CO_2C*H*HPh), 5.39 (d, *J* = 12.1 Hz, 1 H, CO_2CH*H*Ph), 3.52 (dd, *J* = 12.1, 7.9 Hz, 1 H, C*H*H), 3.29 (dd, *J* = 12.1, 7.2 Hz, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2), 159.3 (d, $J_{C\text{-}F}$ = 248 Hz, Ar-C_q-F), 134.1 (Ph-C_q), 130.7 (d, $J_{C\text{-}F}$ = 8 Hz, Ar-CH), 129.0 (Ph-CH), 128.81 (2 x Ph-CH), 128.40 (2 x Ph-CH), 127.2 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 127.0 (d, $J_{C\text{-}F}$ = 13 Hz, Ar-*C*$_q$-CH(O)), 124.8 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 116.1 (C≡N), 115.5 (d, $J_{C\text{-}F}$ = 21 Hz, Ar-CH), 75.8 (d, $J_{C\text{-}F}$ = 4 Hz, OCH(Ar)), 72.60 (*C*$_q$(CO_2Bn)(CN)), 69.1 (CO_2*C*H_2Ph), 39.0 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.5; **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.67 (m, 1 H, Ar-H), 7.48–7.35 (m, 6 H, Ar-H and 5 x Ph-H), 7.21–7.13 (m, 1 H, Ar-H), 7.12–6.99 (m, 1 H, Ar-H), 6.28 (t, *J* = 7.7 Hz, 1 H, OCH(Ar)), 5.36 (d, *J* = 12.1 Hz, 1 H, CO_2C*H*HPh), 5.32 (d, *J* = 12.1 Hz, 1 H, CO_2CH*H*Ph), 3.57 (dd, *J* = 12.1, 7.6 Hz, 1 H, C*H*H), 3.24 (dd, *J* = 12.1, 7.8 Hz, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (CO_2), 159.1 (d, $J_{C\text{-}F}$ = 248 Hz, Ar-C_q-F), 134.0 (Ph-C_q), 130.6 (d, $J_{C\text{-}F}$ = 8 Hz, Ar-CH), 128.9 (Ph-CH), 128.75 (2 x Ph-CH), 128.44 (2 x Ph-CH), 127.7 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 126.8 (d, $J_{C\text{-}F}$ = 13 Hz, Ar-*C*$_q$-CH(O)), 124.6 (d, $J_{C\text{-}F}$ = 3 Hz, Ar-CH), 116.6 (C≡N), 115.2 (d, $J_{C\text{-}F}$ = 21 Hz, Ar-CH), 74.5 (d, $J_{C\text{-}F}$ = 4 Hz, OCH(Ar)), 72.58 (*C*$_q$(CO_2Bn)(CN)), 69.0 (CO_2*C*H_2Ph), 39.2 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.8; HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}FN_2O_3Na^+$ $[M+CH_3CN+Na]^+$: 375.1121, Found: 375.1116.

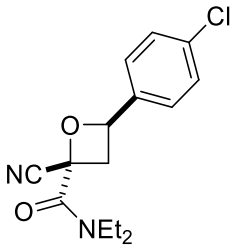
The relative stereochemistries for the major and minor isomers of oxetane **5c** were assigned by analogy to that observed for oxetane **5d**.

(±)-2-[2-Bromo-1-(4-chlorophenyl)ethoxy]-2-cyano-N,N-diethylacetamide (4d)



A mixture of diazo amide **1h** (199 mg, 1.2 mmol), (±)-2-bromo-1-(4-chlorophenyl)ethan-1-ol[4] (236 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (35% to 40% Et_2O in hexanes) afforded bromide **4d** as a mixture of diastereoisomers as a colorless oil (235 mg, 63%, d.r. 1.0:1.0); R_f = 0.61 and 0.50 (75% Et_2O in hexanes); IR (film) / cm^{-1} 2975, 2938, 2216 (C≡N), 1653 (C=O), 1598, 1491, 1463, 1383, 1363, 1312, 1252, 1215, 1145, 1088, 1015, 834, 729, 628, 552; **Diastereoisomer 1:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.37 (m, 2 H, 2 x Ar-H), 7.34–7.28 (m, 2 H, 2 x Ar-H), 4.92–4.86 (m, 2 H, OCH(Ar) and C*H*(CN)(CONEt$_2$)), 3.67–3.60 (m, 1 H, C*H*HBr), 3.59–3.36 (m, 5 H, CH*H*Br and 2 x NC*H*$_2$CH$_3$), 1.24 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$), 1.15 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (C=O), 135.9 (Ar-C_q-CH(O)), 135.0 (Ar-C_q-Cl), 129.5 (2 x Ar-CH), 128.5 (2 x Ar-CH), 114.3 (C≡N), 81.6 (OCH(Ar)), 68.0 (*C*H(CN)(CONEt$_2$), 42.2 (N*C*H$_2$CH$_3$), 40.9 (N*C*H$_2$CH$_3$), 33.7 (CH$_2$Br), 14.0 (NCH$_2$*C*H$_3$), 12.31 (NCH$_2$*C*H$_3$); **Diastereoisomer 2:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.37 (m, 2 H, 2 x Ar-H), 7.34–7.28 (m, 2 H, 2 x Ar-H), 4.78 (dd, *J* = 8.0, 4.6 Hz, 1 H, OCH(Ar)), 4.71 (s, 1 H, C*H*(CN)(CONEt$_2$)), 3.67–3.60 (m, 1 H, C*H*HBr), 3.59–3.36 (m, 4 H, 2 x NC*H*$_2$CH$_3$), 3.27 (dd, *J* = 13.7, 7.0 Hz, 1 H, CH*H*Br), 1.24 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$), 1.10 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (C=O), 135.6 (Ar-C_q-CH(O)), 134.1 (Ar-C_q-Cl), 129.3 (2 x Ar-CH), 128.4 (2 x Ar-CH), 113.9 (C≡N), 81.2 (OCH(Ar)), 68.1 (*C*H(CN)(CONEt$_2$), 41.9 (N*C*H$_2$CH$_3$), 40.8 (N*C*H$_2$CH$_3$), 34.2 (CH$_2$Br), 13.7 (NCH$_2$*C*H$_3$), 12.30 (NCH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{19}BrClN_2O_2^+$ $[M+H]^+$: 373.0318, Found: 373.0331.

(±)-4-(4-Chlorophenyl)-2-cyano-N,N-diethyloxetane-2-carboxamide (5d)



MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.63 mmol) which had been cooled to 0 °C. Bromide **4d** (193 mg, 0.52 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 8 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (40% Et_2O in hexanes) afforded minor oxetane **5d** as a white solid (33 mg, 22%) followed by major oxetane **5d'** as a white solid (96 mg, 64%) (total yield 86%, d.r. 74:26).

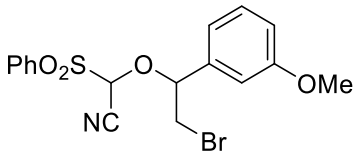
Minor Product 5d: R_f = 0.50 (50% Et_2O in hexanes); mp = 86–89 °C; IR (film) / cm^{-1} 2978, 2939, 2223 (C≡N), 1655 (C=O), 1599, 1494, 1448, 1383, 1369, 1283, 1218, 1190, 1155, 1091, 1016, 949, 868, 825, 734, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2 H, 2 x Ar-H), 7.31–7.25 (m, 2 H, 2 x Ar-H), 5.81 (t, *J* = 7.8 Hz, 1 H, OC*H*(Ar)), 3.61 (dd, *J* = 12.4, 8.0 Hz, 1 H, C*H*H), 3.51–3.37 (m, 5 H, CH*H* and 2 x NC*H*$_2$CH$_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$), 1.22 (t, *J* = 7.1 Hz, 3 H, NCH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (C=O), 138.1 (Ar-C_q-CH(O)), 135.1 (Ar-C_q-Cl), 129.0 (2 x Ar-CH), 127.7 (2 x Ar-CH), 118.0 (C≡N), 78.5 (OCH(Ar)), 72.7 (*C*$_q$(CN)(CONEt$_2$)), 42.0 (N*C*H$_2$CH$_3$), 40.9 (N*C*H$_2$CH$_3$), 38.9 (CH$_2$), 13.5

(NCH_2CH_3), 13.2 (NCH_2CH_3); HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{18}ClN_2O_2^+$ $[M+H]^+$: 293.1057, Found: 293.1067.

Major Product 5d': R_f = 0.28 (50% Et_2O in hexanes); mp = 89–91 °C; IR (film) / cm^{-1} 2978, 2938, 2221 (C≡N), 1654 (C=O), 1598, 1493, 1447, 1383, 1364, 1283, 1217, 1188, 1091, 1015, 951, 825, 739, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2 H, 2 x Ar-H), 7.45–7.39 (m, 2 H, 2 x Ar-H), 5.67–5.59 (m, 1 H, OC*H*(Ar)), 4.00 (dd, *J* = 12.3, 8.1 Hz, 1 H, C*H*H), 3.58–3.37 (m, 4 H, 2 x NCH_2CH_3), 3.09 (dd, *J* = 12.3, 6.8 Hz, 1 H, CH*H*), 1.28 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3), 1.23 (t, *J* = 7.1 Hz, 3 H, NCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (C=O), 138.5 (Ar-C_q-CH(O)), 135.0 (Ar-C_q-Cl), 129.1 (2 x Ar-CH), 127.3 (2 x Ar-CH), 117.7 (C≡N), 79.4 (OCH(Ar)), 72.7 (C_q(CN)($CONEt_2$), 42.1 (NCH_2CH_3), 40.9 (NCH_2CH_3), 38.8 (CH_2), 13.4 (NCH_2CH_3), 12.3 (NCH_2CH_3); HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{18}ClN_2O_2^+$ $[M+H]^+$: 293.1057, Found: 293.1050.

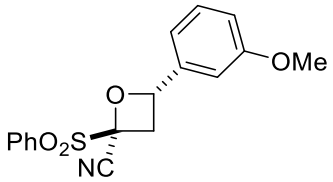
The relative stereochemistries for the major and minor isomers of oxetane **5d** were determined based on NOE studies (see page S119).

(±)-2-(Benzenesulfonyl)-2-[2-bromo-1-(3-methoxyphenyl)ethoxy]acetonitrile (4e)



A mixture of diazo nitrile **1i** (110 mg, 0.53 mmol), (±)-2-Bromo-1-(3-methoxyphenyl)ethan-1-ol[4] (112 mg, 0.48 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in CH_2Cl_2 (4.8 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (70% CH_2Cl_2 in hexanes) afforded bromide **4e** as a mixture of diastereoisomers as a yellow crystalline solid (158 mg, 80%, d.r. 1.4:1.0); R_f = 0.50 (70% CH_2Cl_2 in hexanes); mp = 100–104 °C; IR (film) / cm^{-1} 2964, 2838, 2236 (C≡N), 1601, 1586, 1489, 1449, 1436, 1332, 1314, 1287, 1259, 1212, 1145, 1099, 1074, 1041, 995, 909, 872, 791, 754, 725, 704, 684, 609, 587; **Major Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 1 H, Ph-H), 8.00–7.91 (m, 1 H, Ph-H), 7.86–7.75 (m, 1 H, Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.65–7.58 (m, 1 H, Ph-H), 7.41–7.29 (m, 1 H, Ar-H), 7.02–6.95 (m, 1 H, Ar-H), 6.94–6.89 (m, 1 H, Ar-H), 6.88–6.81 (m, 1 H, Ar-H), 5.36 (dd, *J* = 8.7, 3.8 Hz, 1 H, OCH(Ar)), 4.91 (s, 1 H, CH(SO_2Ph)(CN)), 3.83 (s, 3 H, OCH_3), 3.65–3.57 (m, 1 H, C*H*HBr), 3.55–3.48 (m, 1 H, CH*H*Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5 (Ar-C_q-OMe), 136.5 (Ar-C_q-CH(O)), 135.7 (Ph-CH), 133.3 (Ph-C_q), 130.9 (2 x Ph-CH), 130.8 (Ar-CH), 129.4 (2 x Ph-CH), 119.5 (Ar-CH), 116.2 (Ar-CH), 112.5 (Ar-CH), 112.0 (C≡N), 85.6 (OCH(Ar)), 80.8 (*C*H(SO_2Ph)(CN)), 55.3 (OCH_3), 33.6 (CH_2Br); **Minor Product:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21–8.16 (m, 1 H, Ph-H), 8.00–7.91 (m, 1 H, Ph-H), 7.86–7.75 (m, 1 H, Ph-H), 7.73–7.66 (m, 1 H, Ph-H), 7.65–7.58 (m, 1 H, Ph-H), 7.41–7.29 (m, 1 H, Ar-H), 7.02–6.95 (m, 1 H, Ar-H), 6.88–6.81 (m, 2 H, 2 x Ar-H), 5.05 (s, 1 H, CH(SO_2Ph)(CN)), 4.88 (dd, *J* = 8.4, 4.2 Hz, 1 H, OCH(Ar)), 3.84 (s, 3 H, OCH_3), 3.65–3.57 (m, 1 H, C*H*HBr), 3.55–3.48 (m, 1 H, CH*H*Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (Ar-C_q-OMe), 136.2 (Ar-C_q-CH(O)), 135.6 (Ph-CH), 133.1 (Ph-C_q), 130.7 (2 x Ph-CH), 130.4 (Ar-CH), 129.3 (2 x Ph-CH), 119.3 (Ar-CH), 115.8 (Ar-CH), 112.3 (Ar-CH), 111.7 (C≡N), 83.9 (OCH(Ar)), 81.3 (*C*H(SO_2Ph)(CN)), 55.4 (OCH_3), 34.0 (CH_2Br); HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{19}BrN_2O_4SNa^+$ $[M+CH_3CN+Na]^+$: 473.0147, Found: 473.0161.

(±)-2-(Benzenesulfonyl)-4-(3-methoxyphenyl)oxetane-2-carbonitrile (5e)

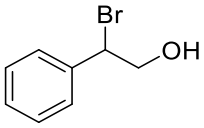


MAJOR

DMF (9 mL) was added to a flask containing sodium hydride (60% in mineral oil, 15 mg, 0.37 mmol) which had been cooled to 0 °C. Bromide **4e** (127 mg, 0.31 mmol) in DMF (3.4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (10 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 15 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane **5e** as a mixture of diastereoisomers a yellow oil (44 mg, 43%, d.r. 70:30); R_f = 0.44 (30% EtOAc in hexanes); IR (film) / cm^{-1} 2941, 2839, 2234 (C≡N), 1602, 1585, 1491, 1448, 1331, 1292, 1263, 1155, 1037, 967, 918, 850, 784, 753, 725, 684, 604, 568; **Major Product:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.13–8.09 (m, 2 H, 2 x Ph-H), 7.83–7.76 (m, 1 H, Ph-H), 7.70–7.61 (m, 2 H, 2 x Ph-H), 7.39–7.33 (m, 1 H, Ar-H), 7.04–7.00 (m, 1 H, Ar-H), 7.00–6.96 (m, 1 H, Ar-H), 6.96–6.91 (m, 1 H, Ar-H), 6.00 (t, *J* = 7.3 Hz, 1 H, OCH(Ar)), 3.94 (dd, *J* = 13.0, 7.6 Hz, 1 H, C*H*H), 3.83 (s, 3 H, OCH_3), 3.33 (dd, *J* = 13.0, 7.1 Hz, 1 H, CH*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1 (Ar-C_q-OMe), 140.1 (Ar-C_q-CH(O)), 135.7 (Ph-CH), 132.1 (Ph-C_q), 130.82 (2 x Ph-CH), 130.2 (Ar-CH), 129.47 (2 x Ph-CH), 118.0 (Ar-CH), 115.4 (Ar-CH), 114.2 (C≡N), 111.2 (Ar-CH), 86.8 (C_q(SO_2Ph)(CN)), 82.6 (OCH(Ar)), 55.3 (OCH_3), 36.4 (CH_2); **Minor Product:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.09–8.05 (m, 2 H, 2 x Ph-H), 7.83–7.76 (m, 1 H, Ph-H), 7.70–7.61 (m, 2 H, 2 x Ph-H), 7.39–7.33 (m, 1 H, Ar-H), 7.17–7.13 (m, 1 H, Ar-H), 7.00–6.96 (m, 1 H, Ar-H), 6.90–6.84 (m, 1 H, Ar-H), 5.91 (t, *J* = 7.6 Hz, 1 H, OCH(Ar)), 3.90 (s, 3 H, OCH_3), 3.86 (dd, *J* = 12.6, 8.1 Hz, 1 H, C*H*H), 3.48 (dd, *J* = 12.6, 7.1 Hz, 1 H, CH*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0 (Ar-C_q-OMe), 139.3 (Ar-C_q-CH(O)), 135.7 (Ph-CH), 132.0 (Ph-C_q), 130.80 (2 x Ph-CH), 129.8 (Ar-CH), 129.49 (2 x Ph-CH), 119.4 (Ar-CH), 116.1 (Ar-CH), 115.0 (C≡N), 112.2 (Ar-CH), 86.1 (C_q(SO_2Ph)(CN)), 81.0 (OCH(Ar)), 55.4 (OCH_3), 36.0 (CH_2); HRMS (EI^+) *m/z* Calcd for $C_{17}H_{17}NO_5S$ [M+H_2O]: 347.0822, Found: 347.0821.

The relative stereochemistries for the major and minor isomers of oxetane **5e** were assigned by analogy to that observed for oxetane **5d**.

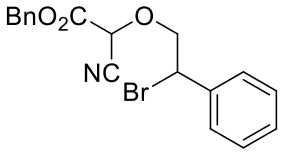
(±)-2-Bromo-2-phenylethan-1-ol (S9)[32]



Ammonium cerium(IV) nitrate (1.64 g, 3.0 mmol) was added portionwise to a stirring mixture of styrene oxide (1.14 mL, 10.0 mmol) and tetrabutylammonium bromide (9.67 g, 30.0 mmol) in CH_3CN (30 mL) at 25 °C. The reaction was stirred at 25 °C for 3 h. The reaction mixture was concentrated *in vacuo* and water (30 mL) was added to the residue. The aqueous mixture was extracted with Et_2O (3 x 60 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% to 30% Et_2O in pentane) afforded β-bromohydrin **S9** as a yellow crystalline solid oil (263 mg, 13%); R_f = 0.13 (20% Et_2O in pentane); mp = 35–37 °C (lit.[33] mp = 38 °C); IR (film) / cm^{-1} 3354 (br O-H), 3030, 2921, 1493, 1381, 1235, 1158, 1067, 1024, 840, 760, 696, 591; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2 H, 2 x Ph-H), 7.41–7.33 (m, 3 H, 3 x Ph-H), 5.08 (dd, *J* = 7.9, 5.6 Hz, 1 H, CH(Br)), 4.09 (ddd, *J* = 12.3, 7.9, 5.8 Hz, 1 H, C*H*H(OH)), 3.98 (ddd, *J* = 12.3, 8.1, 5.6 Hz, 1 H, CH*H*(OH)), 2.08 (dd, *J* = 8.1, 5.8 Hz, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (Ph-C_q), 129.0 (Ph-CH), 128.9 (2 x Ph-CH), 127.9 (2 x Ph-CH), 67.5 (CH_2OH), 57.0 (CH(Br)).

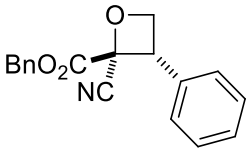
Observed data (mp, IR, ^1H, ^{13}C) was consistent with that previously reported.[33,34]

(±)-Benzyl 2-(2-bromo-2-phenylethoxy)-2-cyanoacetate (4f)



A mixture of diazo nitrile **1e** (221 mg, 1.1 mmol), β-bromohydrin **S9** (198 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc in hexanes) afforded bromide **4f** as a yellow oil (283 mg, 77%, d.r. 1.0:1.0); R_f = 0.18 (15% EtOAc in hexanes); IR (film) / cm^{-1} 3067, 3033, 2254 (C≡N), 1761 (C=O ester), 1496, 1455, 1379, 1280, 1203, 1128, 1003, 968, 907, 838, 728, 695, 648, 596; **Diastereoisomer 1:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.32 (m, 10 H, 10 x Ph-H), 5.35–5.25 (m, 2 H, CO_2CH_2Ph), 5.16–5.09 (m, 1 H, CH(Br)), 4.99 (s, 1 H, C*H*(CO_2Bn)(CN)), 4.31–4.17 (m, 2 H, OCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.67 (CO_2), 137.72 (Ph-C_q), 133.9 (Ph-C_q), 129.0 (Ph-CH), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.7 (2 x Ph-CH), 128.46 (2 x Ph-CH), 127.8 (2 x Ph-CH), 113.0 (C≡N), 73.9 (OCH_2), 68.9 (CO_2CH_2Ph), 67.2 (*C*H(CO_2Bn)(CN)), 49.9 (CH(Br)); **Diastereoisomer 2:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.32 (m, 10 H, 10 x Ph-H), 5.35–5.25 (m, 2 H, CO_2CH_2Ph), 5.16–5.09 (m, 1 H, CH(Br)), 4.91 (s, 1 H, C*H*(CO_2Bn)(CN)), 4.31–4.17 (m, 2 H, OCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.66 (CO_2), 137.65 (Ph-C_q), 133.9 (Ph-C_q), 129.0 (Ph-CH), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.7 (2 x Ph-CH), 128.45 (2 x Ph-CH), 127.7 (2 x Ph-CH), 113.0 (C≡N), 73.9 (OCH_2), 68.9 (CO_2CH_2Ph), 67.2 (*C*H(CO_2Bn)(CN)), 49.6 (CH(Br)); HRMS (CI) *m/z* Calcd for $C_{18}H_{20}BrN_2O_3^+$ $[M+NH_4]^+$: 391.0657, Found: 391.0660.

(±)-Benzyl 2-cyano-3-phenyloxetane-2-carboxylate (5f)



MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 25 mg, 0.61 mmol) which had been cooled to 0 °C. Bromide **4f** (188 mg, 0.50 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 7 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded minor oxetane **5f** as a colorless oil (49 mg, 33%) followed by major oxetane **5f'** as a colorless oil (62 mg, 42%) (total yield 75%, d.r. 56:44).

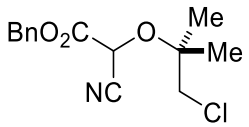
Minor Product 5f: R_f = 0.34 (20% EtOAc in hexanes); IR (film) / cm^{-1} 3066, 3036, 2972, 2907, 2242 (C≡N), 1761 (C=O ester), 1587, 1498, 1456, 1379, 1270, 1212, 1097, 1069, 1027, 945, 906, 851, 789, 733, 695, 599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 8 H, 8 x Ph-H), 7.10–6.95 (m, 2 H, 2 x Ph-H), 5.17–5.10 (m, 2 H, OCH_2), 4.93–4.85 (m, 2 H, CH(Ph) and CO_2CHHPh), 4.71 (d, *J* = 12.0 Hz, 1 H, CO_2CHHPh); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (CO_2), 133.6 (Ph-C_q), 132.6 (Ph-C_q), 129.1 (Ph-CH), 128.9 (2 x Ph-CH), 128.6 (Ph-CH), 128.5 (2 x Ph-CH), 128.4 (2 x Ph-CH), 128.0 (2 x Ph-CH), 116.5 (C≡N), 80.5 (C_q(CO_2Bn)(CN)), 73.8 (OCH_2), 68.5 (CO_2CH_2Ph), 50.2 (CH(Ph)); HRMS (CI) *m/z* Calcd for $C_{18}H_{19}N_2O_3^+$ $[M+NH_4]^+$: 311.1396, Found: 311.1403.

Major Product 5f': R_f = 0.27 (20% EtOAc in hexanes); IR (film) / cm^{-1} 3067, 3035, 2979, 2908, 2240 (C≡N), 1764 (C=O), 1499, 1456, 1378, 1265, 1225, 1108, 1086, 1064, 1033, 1003, 954, 904, 750, 696, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.28 (m, 10 H, 10 x Ph-H), 5.44 (d, *J* = 12.1 Hz, 1 H, CO_2CHHPh), 5.34 (d, *J* = 12.1 Hz, 1 H, CO_2CHHPh), 5.11 (dd, *J* = 7.6, 6.2 Hz, 1 H, OC*H*H), 5.02 (dd, *J* = 8.5, 6.2 Hz, 1 H, OCH*H*), 4.53 (t, *J* = 8.0 Hz, 1 H, CH(Ph)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (CO_2), 134.2 (Ph-C_q), 133.6 (Ph-C_q), 129.11 (Ph-CH), 129.06 (2 x Ph-CH), 129.0 (Ph-CH), 128.8 (2 x Ph-CH), 128.4 (2 x Ph-CH), 128.0

(2 x Ph-CH), 114.3 (C≡N), 82.1 (C_q(CO_2Bn)(CN)), 74.2 (OCH_2), 68.9 (CO_2CH_2Ph), 48.3 (CH(Ph)); HRMS (CI) *m/z* Calcd for $C_{18}H_{19}N_2O_3^+$ $[M+NH_4]^+$: 311.1396, Found: 311.1403.

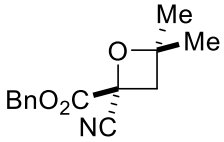
The relative stereochemistries for the major and minor isomers of oxetane **5f** were proposed based on NOE studies (see page S119).

(±)-Benzyl 2-[(1-chloro-2-methylpropan-2-yl)oxy]-2-cyanoacetate (4g)



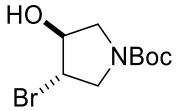
A mixture of diazo nitrile **1e** (221 mg, 1.1 mmol), 1-chloro-2-methyl-2-propanol (109 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded chloride **4g** as a pale yellow oil (114 mg, 40%); R_f = 0.13 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2982, 2258 (C≡N), 1751 (C=O), 1499, 1457, 1389, 1374, 1270, 1213, 1106, 1003, 900, 794, 736, 697, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5 H, 5 x Ph-H), 5.30 (s, 2 H, CO_2CH_2Ph), 5.01 (s, 1 H, C*H*(CO_2Bn)(CN)), 3.57 (d, *J* = 11.7 Hz, 1 H, C*H*HCl), 3.54 (d, *J* = 11.7 Hz, 1 H, CH*H*Cl), 1.43 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (CO_2), 134.2 (Ph-C_q), 128.9 (Ph-CH), 128.8 (2 x Ph-CH), 128.4 (2 x Ph-CH), 115.2 (C≡N), 79.7 (OC_q(CH_3)$_2$), 68.9 (CO_2CH_2Ph), 61.7 (*C*H(CO_2Bn)(CN)), 51.5 (CH_2Cl), 23.8 (CH_3), 23.2 (CH_3); HRMS (CI) *m/z* Calcd for $C_{14}H_{20}ClN_2O_3^+$ $[M+NH_4]^+$: 299.1152, Found: 299.1162.

(±)-Benzyl 2-cyano-4,4-dimethyloxetane-2-carboxylate (5g)



DMF (9 mL) was added to a flask containing sodium hydride (60% in mineral oil, 13 mg, 0.33 mmol) which had been cooled to 0 °C. Bromide **4g** (78 mg, 0.28 mmol) in DMF (3 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 6 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane **5g** as a yellow oil (37 mg, 54%); R_f = 0.31 (20% EtOAc in hexanes); IR (film) / cm^{-1} 2974, 2932, 2249 (C≡N), 1743 (C=O), 1499, 1456, 1375, 1281, 1166, 1150, 1079, 1048, 1012, 970, 909, 839, 779, 741, 696, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5 H, 5 x Ph-H), 5.32 (s, 2 H, CO_2CH_2Ph), 2.97 (s, 2 H, CH_2), 1.67 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (CO_2), 134.3 (Ph-C_q), 128.83 (Ph-CH), 128.75 (2 x Ph-CH), 128.3 (2 x Ph-CH), 117.4 (C≡N), 84.8 (C_q(CO_2Bn)(CN)), 69.4 (OC_q(CH_3)$_2$), 68.8 (CO_2CH_2Ph), 43.1 (CH_2), 29.3 (CH_3), 29.1 (CH_3); HRMS (CI) *m/z* Calcd for $C_{14}H_{19}N_2O_3^+$ $[M+NH_4]^+$: 263.1384, Found: 263.1390.

(±)-*trans*-*tert*-Butyl 3-bromo-4-hydroxypyrrolidine-1-carboxylate (S10)[35]

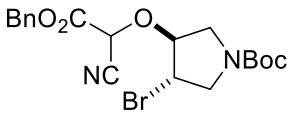


N-Bromosuccinimide (1.06 g, 6.0 mmol) was added portionwise to a stirring mixture of *N*-Boc-2,5-dihydro-1*H*-pyrrole (845 mg, 5.0 mmol) in DMSO (5 mL) and H_2O (0.75 mL) at 0 °C. The reaction was stirred at 25 °C for 17 h. Water (20 mL) was added. The aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (60 mL), dried (Na_2SO_4) and

concentrated *in vacuo*. Purification by flash chromatography (1% NEt_3, 30% EtOAc in hexanes to 1% NEt_3, 40% EtOAc in hexanes) afforded β-bromohydrin **S10** as a white crystalline solid (979 mg, 74%); R_f = 0.27 (40% EtOAc in hexanes); mp = 55–59 °C; IR (film) / cm^{-1} 3376 (br O-H), 2977, 2935, 1661 (C=O), 1478, 1416, 1367, 1281, 1255, 1158, 1116, 1083, 1001, 959, 930, 866, 769, 741, 642, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (br s, 1 H, C*H*(OH)), 4.19–4.14 (m, 1 H, CHBr), 4.14–4.05 (m, 1 H, OH), 4.01 (dd, *J* = 12.9, 4.9 Hz, 1 H, NC*H*H), 3.85–3.66 (m, 2 H, NCH*H* and NC'*H*H), 3.38 (dd, *J* = 11.9, 2.8 Hz, 1 H, NC'H*H*), 1.45 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 and 154.7 (C=O), 80.3 and 80.2 ($C_q(CH_3)_3$), 76.7 and 75.9 (CH(OH)), 53.0 and 52.4 (NCH_2), 51.4 and 51.1 ($NC'H_2$), 50.6 and 50.1 (CHBr), 28.4 (3 x CH_3).

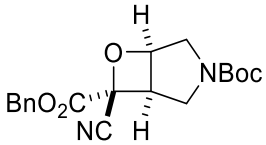
Observed data (IR, ^{1}H) was consistent with that previously reported.[36]

(±)-*trans*-*tert*-Butyl 3-[2-(benzyloxy)-1-cyano-2-oxoethoxy]-4-bromopyrrolidine-1-carboxylate (4h)



A mixture of diazo nitrile **1e** (223 mg, 1.1 mmol), β-bromohydrin **S10** (266 mg, 1.0 mmol) and dirhodium(II) tetraacetate (2.2 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (15% to 20% EtOAc in hexanes) afforded bromide **4h** as a viscous pale yellow oil (286 mg, 65%, d.r. 1.1:1.0); R_f = 0.70 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2977, 2886, 2245 (C≡N), 1764 (C=O ester), 1683 (C=O carbamate), 1456, 1404, 1367, 1213, 1160, 1107, 1002, 960, 869, 769, 749, 697, 652, 549; **Diastereoisomer 1:** ^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.44–7.30 (m, 5 H, 5 x Ph-H), 5.88 (s, 1 H, C*H*(CO_2Bn)(CN)), 5.33 (d, *J* = 12.8 Hz, 1 H, CO_2CHHPh), 5.29 (d, *J* = 12.8 Hz, 1 H, CO_2CH*H*Ph), 4.66–4.62 (m, 1 H, CHBr), 4.58–4.53 (m, 1 H, CH(O)), 3.89–3.82 (m, 1 H, NC*H*H), 3.82–3.75 (m, 1 H, NC'*H*H), 3.70–3.61 (m, 1 H, NCH*H*), 3.50–3.41 (m, 1 H, NC'H*H*), 1.428 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 163.0 (C=O ester), 153.2 (C=O carbamate), 134.4 (Ph-C_q), 128.1 (3 x Ph-CH), 127.7 (2 x Ph-CH), 114.3 (C≡N), 84.1 (br, CH(O)), 78.8 ($C_q(CH_3)_3$), 67.8 (CO_2CH_2Ph), 66.3 (*C*H(CO_2Bn)(CN)), 52.4 (NCH_2), 49.2 ($NC'H_2$), 47.5 (br, CHBr), 27.7 (3 x CH_3); **Diastereoisomer 2:** ^{1}H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.44–7.30 (m, 5 H, 5 x Ph-H), 5.87 (s, 1 H, C*H*(CO_2Bn)(CN)), 5.33 (d, *J* = 12.8 Hz, 1 H, CO_2CHHPh), 5.29 (d, *J* = 12.8 Hz, 1 H, CO_2CH*H*Ph), 4.62–4.59 (m, 1 H, CHBr), 4.58–4.53 (m, 1 H, CH(O)), 3.89–3.82 (m, 1 H, NC*H*H), 3.82–3.75 (m, 1 H, NC'*H*H), 3.70–3.61 (m, 1 H, NCH*H*), 3.50–3.41 (m, 1 H, NC'H*H*), 1.425 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 353 K) δ 163.0 (C=O ester), 153.1 (C=O carbamate), 134.3 (Ph-C_q), 128.1 (3 x Ph-CH), 127.6 (2 x Ph-CH), 114.2 (C≡N), 84.1 (br, CH(O)), 78.8 ($C_q(CH_3)_3$), 67.7 (CO_2CH_2Ph), 66.2 (*C*H(CO_2Bn)(CN)), 52.4 (NCH_2), 49.0 ($NC'H_2$), 47.5 (br, CHBr), 27.7 (3 x CH_3); HRMS (FTMS +pNSI) *m/z* Calcd for $C_{19}H_{27}BrN_3O_5^+$ $[M+NH_4]^+$: 456.1124, Found: 456.1129.

(±)-*cis*-7-Benzyl 3-*tert*-butyl 7-cyano-6-oxa-3-azabicyclo[3.2.0]heptane-3,7-dicarboxylate (5h)



MAJOR

DMF (16 mL) was added to a flask containing sodium hydride (60% in mineral oil, 24 mg, 0.61 mmol) which had been cooled to 0 °C. Bromide **4h** (223 mg, 0.51 mmol) in DMF (4 mL) was added dropwise to the stirred suspension of sodium hydride in DMF at 0 °C over 10 min. The reaction mixture was stirred at 25 °C for 16 h. Saturated aq. NH_4Cl (20 mL) was added. The aqueous mixture was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexanes) afforded minor oxetane **5h** as a white solid (22 mg, 12%) followed by major oxetane **5h'** as a white solid (151 mg, 83%) (total yield 95%, d.r. 83:17).

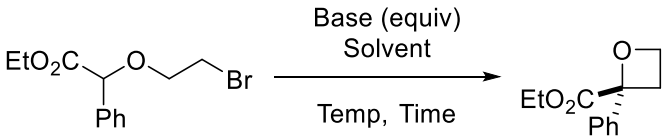
Minor Product 5h: R_f = 0.61 (60% EtOAc in hexanes); mp = 152–155 °C; IR (film) / cm^{-1} 2982, 2930, 2876, 2236 (C≡N), 1770 (C=O ester), 1696 (C=O carbamate), 1479, 1455, 1420, 1367, 1239, 1165, 1098, 1031, 1010, 876, 747, 698, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.34 (m, 5 H, 5 x Ph-H), 5.52 (dd, *J* = 5.8, 3.6 Hz, 1 H, OCH), 5.35 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh), 5.29 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh), 4.06 (t, *J* = 6.1 Hz, 1 H, CH), 3.86–3.76 (m, 2 H, NC*H*H and NC'*H*H), 3.21 (dd, *J* = 13.5, 6.6 Hz, 1 H, NCH*H*), 3.13 (dd, *J* = 13.7, 3.6 Hz, 1 H, NC'H*H*), 1.43 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8 (C=O ester), 153.0 (C=O carbamate), 134.1 (Ph-C_q), 128.1 (3 x Ph-CH), 127.6 (2 x Ph-CH), 116.4 (C≡N), 83.4 (OCH), 78.8 ($C_q(CH_3)_3$), 75.2 ($C_q(CO_2Bn)(CN)$), 67.9 (CO_2CH_2Ph), 51.5 (NC'H_2), 47.4 (CH), 45.4 (NCH_2), 27.7 (3 x CH_3); HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{25}N_3O_5Na^+$ $[M+CH_3CN+Na]^+$: 422.1692, Found: 422.1685.

Major Product 5h': R_f = 0.52 (60% EtOAc in hexanes); mp = 120–122 °C; IR (film) / cm^{-1} 2979, 2931, 2874, 2243 (C≡N), 1749 (C=O ester), 1696 (C=O carbamate), 1456, 1417, 1367, 1237, 1167, 1101, 1077, 1006, 875, 847, 785, 750, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.35 (m, 5 H, 5 x Ph-H), 5.38 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh), 5.37 (dd, *J* = 9.1, 5.7 Hz, 1 H, OCH), 5.33 (d, *J* = 12.3 Hz, 1 H, CO_2CHHPh), 4.11–4.06 (m, 1 H, NC*H*H), 3.82 (d, *J* = 13.7 Hz, 1 H, NC'*H*H), 3.76 (t, *J* = 6.0 Hz, 1 H, CH), 3.34 (dd, *J* = 13.1, 6.5 Hz, 1 H, NCH*H*), 3.12 (dd, *J* = 13.7, 3.4 Hz, NC'H*H*), 1.46 (s, 9 H, 3 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C=O ester), 153.2 (C=O carbamate), 134.4 (Ph-C_q), 128.1 (2 x Ph-CH), 128.0 (Ph-CH), 127.6 (2 x Ph-CH), 113.7 (C≡N), 84.6 (OCH), 78.8 ($C_q(CH_3)_3$), 77.6 ($C_q(CO_2Bn)(CN)$), 67.9 (CO_2CH_2Ph), 51.4 (NC'H_2), 47.0 (NCH_2), 45.3 (CH), 27.7 (3 x CH_3); HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{25}N_3O_5Na^+$ $[M+CH_3CN+Na]^+$: 422.1692, Found: 422.1699.

The relative stereochemistries for the major and minor isomers of oxetane **5h** were determined based on NOE studies (see page S119).

Optimisation of C–C Bond Forming Cyclisation using Aryl Bromide 7a

Selected optimization of reaction conditions (**Table S3**).



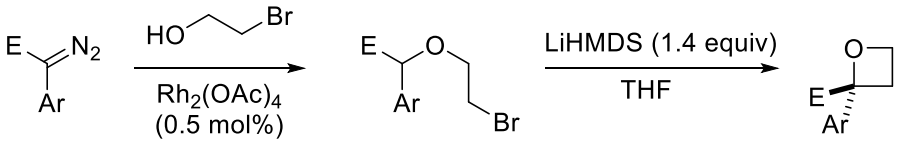
7a **8a**

Entry[a]	Solvent	Base (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	DMF	NaH (1.2)	1	25	75
2	DMF	NaH (1.2)	5	25	35
3	DMF	NaH (1.2)	1	0	88
4	DMF	NaH (1.2)	1 h 30 min	0	32–82
5	THF	LiHMDS (1.2)	1	0	95
6	THF	LiHMDS (1.3)	1	0	96
7	**THF**	**LiHMDS (1.4)**	**1**	**0**	**99 (93)**
8	THF	LiHMDS (1.5)	1	0	94
9	THF	LiHMDS (2.0)	1	0	(73)

[a]0.3 mmol bromide **7a**. [b]Yield determined by ^{1}H NMR with respect to an internal standard (1,3,5-trimethoxybenzene). Isolated yield in parentheses.

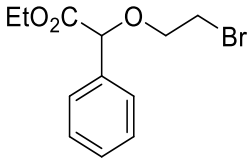
Initial studies were conducted using 1.2 equivalents of NaH and after 1 hour at 25 °C a 75% yield of desired product was observed (entry 1). Oxetane **8a** could not be separated from ether **7a**. An extended reaction time of 5 h led to a decrease in yield presumably due to degradation of product at this temperature (entry 2). Decreasing the temperature to 0 °C gave variable yields with up to 88% of oxetane **8a** (entries 3 and 4) with the mass balance accounted for by ether **7a**. Switching to LiHMDS led to an immediate increase in yield to 95% (entry 5) and increasing the number of equivalents of base to 1.4 led to the highest conversion (99% by ^{1}H NMR) with an isolated yield of 93% (entry 7).

Synthesis of Aryl 2,2-Disubstituted Oxetanes 8a–8g



6a–6g **7a–7g** **8a–8g**

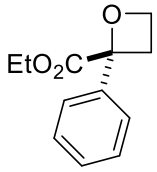
(±)-Ethyl 2-(2-bromoethoxy)-2-phenylacetate (7a)



A mixture of aryl diazo **6a** (550 mg, 2.9 mmol), 2-bromoethanol (137 μL, 1.9 mmol) and dirhodium(II) tetraacetate (2.1 mg, 0.005 mmol) in benzene (19 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide **7a** as a light yellow oil (478 mg, 86%); R_f = 0.34 (15% EtOAc in hexanes); IR (film) / cm^{-1} 2981, 1744 (C=O), 1495, 1454, 1392, 1369, 1272, 1205, 1177, 1105, 1024, 730, 696, 567; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.32 (m, 5 H, 5 x Ph-H), 4.96 (s, 1 H, C*H*(CO_2Et)(Ph)), 4.30–4.08 (m, 2 H, $CO_2CH_2CH_3$), 3.91 (ddd, *J* = 10.5, 7.0, 6.0 Hz, 1 H, OC*H*H), 3.78 (dt, *J* = 10.5, 6.5 Hz, 1 H, OCH*H*), 3.58–3.45 (m, 2 H, CH_2Br), 1.23 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (CO_2), 136.0 (Ph-C_q), 128.8 (Ph-CH), 128.7 (2 x Ph-CH), 127.3 (2 x Ph-CH), 81.3 (*C*H(CO_2Et)(Ph)), 69.5 (OCH_2), 61.4 ($CO_2CH_2CH_3$), 29.6 (CH_2Br), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{18}NNaBrO_3^+$ $[M+CH_3CN+Na]^+$: 350.0368, Found: 350.0378.

Reaction performed on a large scale (7.5 mmol 2-bromoethanol, 8.3 mmol diazo **6a**) afforded an isolated yield of bromide **7a** (1.73 g, 80%).

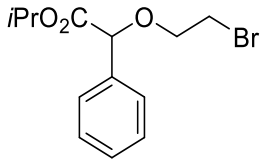
(±)-Ethyl 2-phenyloxetane-2-carboxylate (8a)



LiHMDS (0.61 M in THF, 115 μL, 0.70 mmol) was added dropwise to a stirring solution of bromide **7a** (144 mg, 0.5 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane **8a** as a colorless oil (95 mg, 93%); R_f = 0.24 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2980, 2893, 1728 (C=O), 1494, 1448, 1368, 1269, 1107, 1015, 968, 948, 857, 760, 731, 698, 623; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.47 (m, 2 H, 2 x Ph-H), 7.43–7.37 (m, 2 H, 2 x Ph-H), 7.36–7.28 (m, 1 H, Ph-H), 4.67 (ddd, *J* = 8.5, 6.5, 6.0 Hz, 1 H, OC*H*H), 4.57 (ddd, *J* = 8.5, 7.0, 6.0 Hz, 1 H, OCH*H*), 4.30–4.12 (m, 2 H, $CO_2CH_2CH_3$), 3.39 (ddd, *J* = 11.5, 8.5, 7.0 Hz, 1 H, C*H*H), 2.91 (ddd, *J* = 11.5, 8.5, 6.5 Hz, 1 H, CH*H*), 1.25 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (CO_2), 141.1 (Ph-C_q), 128.3 (2 x Ph-CH), 127.8 (Ph-CH), 124.3 (2 x Ph-CH), 86.2 (C_q(CO_2Et)(Ph)), 65.9 (OCH_2), 61.6 ($CO_2CH_2CH_3$), 33.2 (CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{17}NNaO_3^+$ $[M+CH_3CN+Na]^+$: 270.1106, Found: 270.1115.

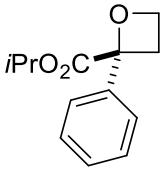
Reaction performed on a large scale (5 mmol bromide **7a**) afforded an isolated yield of oxetane **8a** (784 mg, 76%).

(±)-Propan-2-yl 2-(2-bromoethoxy)-2-phenylacetate (7b)



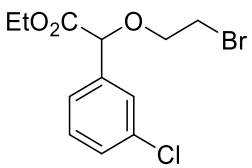
A mixture of aryl diazo **6b** (153 mg, 0.75 mmol), 2-bromoethanol (36 μL, 0.50 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (5 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide **7b** as a colorless oil (131 mg, 87%); R_f = 0.29 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2981, 1740 (C=O), 1454, 1375, 1275, 1208, 1177, 1101, 1015, 963, 920, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.31 (m, 5 H, 5 x Ph-H), 5.05 (sep, *J* = 6.5 Hz, 1 H, $CO_2CH(CH_3)_2$), 4.92 (s, 1 H, $CH(CO_2iPr)(Ph)$), 3.98 (ddd, *J* = 10.5, 7.0, 6.0 Hz, 1 H, OC*H*H), 3.76 (dt, *J* = 10.5, 7.0 Hz, 1 H, OCH*H*), 3.57–3.47 (m, 2 H, CH_2Br), 1.25 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.12 (d, *J* = 6.0 Hz, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (CO_2), 136.1 (Ph-C_q), 128.7 (Ph-CH), 128.6 (2 x Ph-CH), 127.2 (2 x Ph-CH), 81.3 ($CH(CO_2iPr)(Ph)$), 69.4 (OCH_2), 69.0 ($CO_2CH(CH_3)_2$), 29.7 (CH_2Br), 21.8 (CH_3), 21.5 (CH_3); HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{20}BrNNaO_3^+$ $[M+CH_3CN+Na]^+$: 364.0519, Found: 364.0527.

(±)-Propan-2-yl 2-phenyloxetane-2-carboxylate (8b)



LiHMDS (0.61 M in THF, 78 μL, 0.48 mmol) was added dropwise to a stirring solution of bromide **7b** (100 mg, 0.34 mmol) in THF (12.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane **8b** as a colorless oil (54 mg, 72%); R_f = 0.26 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2981, 2891, 1743 (C=O), 1724, 1449, 1375, 1277, 1182, 1145, 1099, 970, 950, 887, 828, 759, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.46 (m, 2 H, 2 x Ph-H), 7.44–7.35 (m, 2 H, 2 x Ph-H), 7.34–7.28 (m, 1 H, Ph-H), 5.07 (sep, *J* = 6.5 Hz, 1 H, $CO_2CH(CH_3)_2$), 4.66 (ddd, *J* = 8.5, 6.5, 6.0 Hz, 1 H, OC*H*H), 4.56 (ddd, *J* = 8.5, 7.0, 6.0 Hz, 1 H, OCH*H*), 3.35 (ddd, *J* = 11.5, 8.5, 7.0 Hz, 1 H, C*H*H), 2.90 (ddd, *J* = 11.5, 8.5, 6.5 Hz, 1 H, CH*H*), 1.22 (dd, *J* = 9.0, 6.0 Hz, 6 H, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (CO_2), 141.3 (Ph-C_q), 128.2 (2 x Ph-CH), 127.8 (Ph-CH), 124.3 (2 x Ph-CH), 86.2 ($C_q(CO_2iPr)(Ph)$), 69.1 ($CO_2CH(CH_3)_2$), 65.9 (OCH_2), 33.2 (CH_2), 21.5 (2 x CH_3); HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{19}NNaO_3^+$ $[M+CH_3CN+Na]^+$: 284.1263, Found: 284.1272.

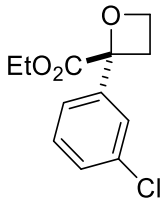
(±)-Ethyl 2-(2-bromoethoxy)-2-(3-chlorophenyl)acetate (7c)



A mixture of aryl diazo **6c** (270 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was

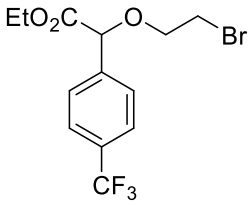
extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (7% EtOAc in hexanes) afforded bromide **7c** as a light yellow oil (222 mg, 69%); R_f = 0.13 (7% EtOAc in hexanes); IR (film) cm^{-1} 2982, 1745 (C=O), 1597, 1576, 1475, 1432, 1393, 1369, 1335, 1256, 1204, 1180, 1115, 1079, 1024, 910, 884, 769, 730, 681, 648, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 1 H, Ar-H), 7.38–7.28 (m, 3 H, 3 x Ar-H), 4.92 (s, 1 H, C*H*(CO_2Et)(Ar)), 4.29–4.11 (m, 2H, $CO_2CH_2CH_3$), 3.92 (td, *J* = 10.4, 6.3 Hz, 1 H, OC*H*H), 3.77 (td, *J* = 10.4, 6.3 Hz, 1 H, OCH*H*), 3.53 (td, *J* = 6.4, 2.0 Hz, 2 H, CH_2Br), 1.24 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (CO_2), 138.0 (Ar-C_q-CH), 134.6 (Ar-C_q-Cl), 129.9 (Ar-CH), 129.0 (Ar-CH), 127.3 (Ar-CH), 125.3 (Ar-CH), 80.5 (*C*H(CO_2Et)(Ar)), 69.7 (OCH_2), 61.6 ($CO_2CH_2CH_3$), 29.5 (CH_2Br), 14.1 ($CO_2CH_2CH_3$); HRMS (CI) *m/z* calcd for $C_{12}H_{15}O_3BrCl^+$ $[M+H]^+$: 320.9888, Found: 320.9893.

(±)-Ethyl 2-(3-chlorophenyl)oxetane-2-carboxylate (8c)



LiHMDS (0.61 M in THF, 115 μL, 0.70 mmol) was added dropwise to a stirring solution of bromide **7c** (161 mg, 0.5 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane **8c** as a colorless oil (116 mg, 97%); R_f = 0.12 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2980, 2895, 1730 (C=O), 1596, 1574, 1475, 1448, 1422, 1368, 1230, 1190, 1145, 1109, 1079, 1045, 1015, 969, 948, 857, 777, 697, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (m, 1 H, Ar-H), 7.40–7.28 (m, 3 H, 3 x Ar-H), 4.68 (ddd, *J* = 8.7, 6.6, 5.9 Hz, 1 H, OC*H*H), 4.57 (ddd, *J* = 8.7, 6.8, 5.9 Hz, 1 H, OCH*H*), 4.28–4.18 (m, 2 H, $CO_2CH_2CH_3$), 3.39 (ddd, *J* = 11.4, 8.7, 6.8 Hz, 1 H, C*H*H), 2.87 (ddd, *J* = 11.4, 8.7, 6.6 Hz, 1 H, CH*H*), 1.26 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (CO_2), 143.3 (Ar-C_q), 134.5 (Ar-C_q-Cl), 129.7 (Ar-CH), 128.1 (Ar-CH), 124.8 (Ar-CH), 122.6 (Ar-CH), 85.7 (C_q(CO_2Et)(Ar)), 66.1 (OCH_2), 61.9 ($CO_2CH_2CH_3$), 33.3 (CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{16}NO_3NaCl^+$ $[M+CH_3CN+Na]^+$: 304.0716, Found: 304.0716.

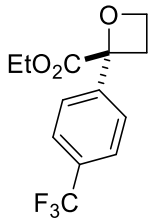
(±)-Ethyl 2-(2-bromoethoxy)-2-[4-(trifluoromethyl)phenyl]acetate (7d)



A mixture of aryl diazo **6d** (310 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide **7d** as a light yellow oil (227 mg, 64%); R_f = 0.20 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2983, 1747 (C=O), 1620, 1420, 1370, 1323, 1277, 1210, 1164, 1120, 1105, 1066, 1018, 841, 810, 789, 757, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.54 (m, 4 H, 4 x Ar-H), 5.02 (s, 1 H, C*H*(CO_2Et)(Ar)), 4.29–4.10 (m, 2 H, $CO_2CH_2CH_3$), 3.96 (td, *J* = 10.5, 6.0 Hz, 1 H, OC*H*H), 3.78 (td, *J* = 10.5, 6.5 Hz, 1 H, OCH*H*), 3.58–3.53 (m, 2 H, CH_2Br), 1.25 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (CO_2), 139.9 (Ar-C_q-CH), 130.9 (q, $J_{C\text{-}F}$ = 32 Hz, Ar-C_q-CF_3), 127.4 (2 x Ar-CH), 125.6 (q, $J_{C\text{-}F}$ = 4 Hz, 2 x Ar-CH), 124.0 (q, $J_{C\text{-}F}$ = 272 Hz, CF_3),

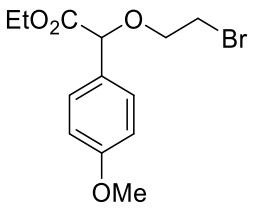
80.6 (*C*H(CO_2Et)(Ar)), 69.8 (OCH_2) 61.7 ($CO_2CH_2CH_3$), 29.6 (CH_2Br), 14.0 ($CO_2CH_2CH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{17}NO_3NaBrF_3^+$ [M+CH_3CN+Na]$^+$: 418.0242, Found: 418.0236.

(±)-Ethyl 2-[4-(trifluoromethyl)phenyl]oxetane-2-carboxylate (8d)



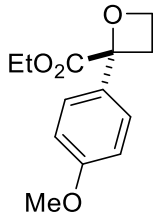
LiHMDS (0.61 M in THF, 115 μL, 0.70 mmol) was added dropwise to a stirring solution of bromide **7d** (178 mg, 0.5 mmol) in THF (18.9 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded oxetane **8d** as a colorless oil (105 mg, 77%); R_f = 0.17 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2982, 2900, 1732 (C=O), 1618, 1449, 1410, 1369, 1324, 1302, 1263, 1164, 1107, 1072, 1061, 1016, 969, 948, 845, 812, 757, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4 H, 4 x Ar-H), 4.69 (td, *J* = 8.7, 6.2 Hz, 1 H, OC*H*H), 4.57 (td, *J* = 8.4, 6.2 Hz, 1 H, OCH*H*), 4.26–4.18 (m, 2 H, $CO_2CH_2CH_3$), 3.42 (ddd, *J* = 11.5, 8.8, 6.7 Hz, 1 H, C*H*H), 2.88 (ddd, *J* = 11.5, 8.7, 6.7 Hz, 1 H, CH*H*), 1.25 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (CO_2), 145.2 (Ar-C_q), 130.2 (q, $J_{C\text{-}F}$ = 33 Hz, Ar-C_q-CF_3), 125.4 (q, $J_{C\text{-}F}$ = 4 Hz, 2 x Ar-CH), 124.9 (2 x Ar-CH), 124.0 (q, $J_{C\text{-}F}$ = 272 Hz, CF_3), 85.9 (C_q(CO_2Et)(Ar)), 66.2 (OCH_2) 62.0 ($CO_2CH_2CH_3$), 33.4 (CH_2), 14.0 ($CO_2CH_2CH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{16}NO_3NaF_3^+$ [M+CH_3CN+Na]$^+$: 338.0980, Found: 338.0988.

(±)-Ethyl 2-(2-bromoethoxy)-2-(4-methoxyphenyl)acetate (7e)



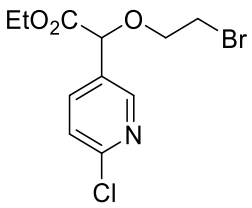
A mixture of aryl diazo **6e** (264 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide **7e** as a light yellow oil (274 mg, 86%); R_f = 0.20 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2980, 2905, 2838, 1743 (C=O), 1611, 1511, 1464, 1444, 1369, 1333, 1304, 1247, 1207, 1173, 1097, 1027, 911, 836, 795, 755, 731, 667, 573; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 2 H, 2 x Ar-H), 6.93–6.87 (m, 2 H, 2 x Ar-H), 4.90 (s, 1 H, C*H*(CO_2Et)(Ar)), 4.29–4.08 (m, 2 H, $CO_2CH_2CH_3$) 3.92–3.83 (m, 1 H, OC*H*H), 3.81 (s, 3 H, OCH_3), 3.74 (dt, *J* = 10.5, 6.7 Hz, 1 H, OCH*H*), 3.57–3.42 (m, 2 H, CH_2Br), 1.23 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (CO_2), 160.0 (Ar-C_q-OCH_3), 128.6 (2 x Ar-CH), 128.1 (Ar-C_q-CH), 114.0 (2 x Ar-CH), 80.8 (*C*H(CO_2Et)(Ar)), 69.2 (OCH_2), 61.3 ($CO_2CH_2CH_3$), 55.3 (OCH_3), 29.7 (CH_2Br), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{20}NNaO_4Br^+$ [M+CH_3CN+Na]$^+$: 380.0473, Found: 380.0491.

(±)-Ethyl 2-(4-methoxyphenyl)oxetane-2-carboxylate (8e)



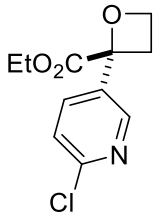
LiHMDS (0.61 M in THF, 92 μL, 0.56 mmol) was added dropwise to a stirring solution of bromide **7e** (90 mg, 0.28 mmol) in THF (10.5 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc in hexanes) afforded oxetane **8e** as a colorless oil (27 mg, 41%); R_f = 0.26 (25% EtOAc in hexanes); IR (film) / cm^{-1} 2976, 2894, 2839, 1728 (C=O), 1610, 1583, 1510, 1464, 1445, 1368, 1299, 1243, 1174, 1104, 1028, 968, 949, 856, 834, 804, 731, 634, 582; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2 H, 2 x Ar-H), 6.95–6.87 (m, 2 H, 2 x Ar-H), 4.65 (ddd, *J* = 8.7, 6.7, 5.8 Hz, 1 H, OC*H*H), 4.56 (ddd, *J* = 8.7, 6.8, 5.8 Hz, 1 H, OCH*H*), 4.29–4.13 (m, 2 H, $CO_2CH_2CH_3$), 3.82 (s, 3 H, OCH_3), 3.35 (ddd, *J* = 11.3, 8.7, 6.8 Hz, 1 H, C*H*H), 2.89 (ddd, *J* = 11.3, 8.7, 6.7 Hz, 1 H, CH*H*), 1.25 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (CO_2), 159.3 (Ar-C_q-OCH_3), 133.2 (Ar-C_q), 125.8 (2 x Ar-CH), 113.7 (2 x Ar-CH), 86.0 ($C_q(CO_2Et)(Ar)$), 65.9 (OCH_2), 61.5 ($CO_2CH_2CH_3$), 55.3 (OCH_3), 33.2 (CH_2), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{17}O_4^+$ $[M+H]^+$: 237.1127, Found: 237.1121.

(±)-Ethyl 2-(2-bromoethoxy)-2-(6-chloropyridin-3-yl)acetate (7f)



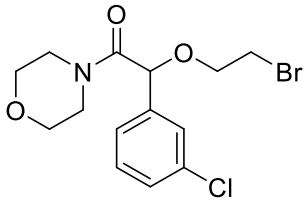
A mixture of aryl diazo **6f** (271 mg, 1.2 mmol), 2-bromoethanol (71 μL, 1.0 mmol) and dirhodium(II) tetraacetate (1.1 mg, 0.0025 mmol) in benzene (10 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded bromide **7f** as a light yellow oil (175 mg, 54%); R_f = 0.09 (10% EtOAc in hexanes); IR (film) / cm^{-1} 2982, 1745 (C=O), 1587, 1568, 1468, 1458, 1382, 1330, 1282, 1214, 1181, 1101, 1020, 927, 836, 774, 736, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.80 (dd, *J* = 8.3, 2.4 Hz, 1 H, Ar-H), 7.35 (d, *J* = 8.3 Hz, 1 H, Ar-H), 4.97 (s, 1 H, C*H*(CO_2Et)(Ar)), 4.34–4.11 (m, 2 H, $CO_2CH_2CH_3$), 4.01 (td, *J* = 10.5, 5.8 Hz, 1 H, OC*H*H), 3.76 (td, *J* = 10.5, 6.4 Hz, 1 H, OCH*H*), 3.52 (t , *J* = 6.2 Hz, 2 H, CH_2Br), 1.23 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (CO_2), 151.8 (Ar-C_q-Cl) 148.4 (Ar-CH), 137.3 (Ar-CH), 130.9 (Ar-C_q-CH), 124.3 (Ar-CH), 78.2 (*C*H(CO_2Et)(Ar)), 70.1 (OCH_2), 61.9 ($CO_2CH_2CH_3$), 29.5 (CH_2Br), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{14}NO_3ClBr^+$ $[M+H]^+$: 321.9846, Found: 321.9854.

(±)-Ethyl 2-(6-chloropyridin-3-yl)oxetane-2-carboxylate (8f)



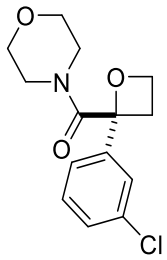
LiHMDS (0.61 M in THF, 78 μL, 0.48 mmol) was added dropwise to a stirred solution of bromide **7f** (110 mg, 0.34 mmol) in THF (12.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc in hexanes) afforded oxetane **8f** as a colorless oil (62 mg, 76%); R_f = 0.11 (20% EtOAc in hexanes); IR (film) / cm^{-1} 2981, 2899, 1731, 1586, 1564, 1455, 1366, 1245, 1104, 1054, 1015, 967, 947, 837, 753, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.5 Hz, 1 H, Ar-H), 7.78 (dd, *J* = 8.3, 2.5 Hz, 1 H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 1 H, Ar-H), 4.74–4.64 (m, 1 H, OC*H*H), 4.58 (ddd, *J* = 8.7, 6.8, 5.8 Hz, 1 H, OCH*H*) 4.29–4.16 (m, 2 H, $CO_2CH_2CH_3$), 3.38 (ddd, *J* = 11.5, 8.7, 6.7 Hz, 1 H, C*H*H), 2.87 (ddd, *J* = 11.5, 8.7, 6.7 Hz, 1 H, CH*H*), 1.25 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (CO_2), 151.1 (Ar-C_q-Cl) 146.4 (Ar-CH), 135.8 (Ar-C_q), 135.4 (Ar-CH), 123.8 (Ar-CH), 84.3 (C_q(CO_2Et)(Ar)), 66.5 (OCH_2) 62.1 ($CO_2CH_2CH_3$), 33.2 (CH_2), 13.9 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{13}NO_3Cl^+$ $[M+H]^+$: 242.0584, Found: 242.0592.

(±)-2-(2-Bromoethoxy)-2-(3-chlorophenyl)-1-(morpholin-4-yl)ethan-1-one (7g)



A mixture of aryl diazo **6g** (111 mg, 0.42 mmol), 2-bromoethanol (27 μL, 0.38 mmol) and dirhodium(II) tetraacetate (0.8 mg, 0.002 mmol) in benzene (3.8 mL) was heated at 80 °C for 1 h. The reaction mixture was allowed to cool to rt. Water (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (40% EtOAc in hexanes) afforded bromide **7g** as a light yellow oil (101 mg, 73%); R_f = 0.11 (40% EtOAc in hexanes); IR (film) / cm^{-1} 2965, 2900, 2856, 1640 (C=O), 1597, 1574, 1458, 1433, 1360, 1299, 1272, 1225, 1192, 1111, 1079, 1033, 1012, 964, 920, 884, 761, 720, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.41 (m, 1 H, Ar-CH), 7.37–7.29 (m, 3 H, 3 x Ar-CH), 5.21 (s, 1 H, C*H*(CON)(Ar)), 4.03–3.89 (m, 2 H, OCH_2CH_2Br), 3.72–3.29 (m, 10 H, CH_2Br and 2 x NCH_2 and 2 x OCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9 (C=O), 138.2 (Ar-C_q-CH), 134.8 (Ar-C_q-Cl), 130.0 (Ar-CH), 128.6 (Ar-CH), 126.1 (Ar-CH), 124.0 (Ar-CH), 82.7 (*C*H(CON)(Ar)), 70.3 (OCH_2CH_2Br), 66.8 (OCH_2), 66.5 (OC'H_2), 45.8 (NCH_2), 42.8 (NC'H_2), 30.2 (CH_2Br); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{18}NO_3ClBr^+$ $[M+H]^+$: 362.0159, Found: 362.0160.

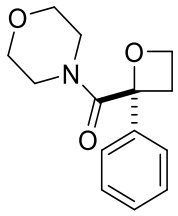
(±)-4-[2-(3-Chlorophenyl)oxetane-2-carbonyl]morpholine (8g)



LiHMDS (0.61 M in THF, 57 μL, 0.35 mmol) was added dropwise to a stirring solution of bromide **7g** (91 mg, 0.25 mmol) in THF (9.4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 0 °C for 1 h. Saturated aq. NH_4Cl (30 mL) was added. The aqueous mixture was extracted with EtOAc (6 x 30 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc in hexanes) afforded oxetane **8g** as a colorless oil (63 mg, 90%); R_f = 0.18 (30% EtOAc in hexanes); IR (film) / cm^{-1} 2966, 2894, 2855, 1638 (C=O), 1594, 1572, 1460, 1436, 1300, 1274, 1259, 1226, 1113, 1067, 1027, 970, 951, 858, 787, 752, 694, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.51 (m, 1 H, Ar-H), 7.40–7.28 (m, 3 H, Ar-H), 4.55 (dd, *J* = 8.4, 7.1 Hz, 2 H, OC*H*$_2$CH$_2$), 3.77–3.54 (m, 5 H, C*H*H and 2 x OCH_2), 3.54-3.34 (m, 2 H, NCH_2), 3.13 (ddd, *J* = 11.0, 6.3, 3.0 Hz, 1 H, N'C*H*H), 3.04 (ddd, *J* = 13.7, 6.5, 3.0 Hz, 1 H, N'CH*H*), 2.55 (dt, *J* = 11.5, 7.5 Hz, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O), 144.3 (Ar-C_q), 135.0 (Ar-C_q-Cl), 130.2 (Ar-CH), 128.0 (Ar-CH), 123.7 (Ar-CH), 121.5 (Ar-CH), 88.8 (*C*$_q$(CON)(Ar)), 66.7 (OCH_2), 66.4 (OC'H_2), 66.1 (O*C*H_2CH$_2$), 46.1 (NCH_2), 42.8 (N'CH_2), 34.4 (CH_2); HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{17}NO_3Cl^+$ $[M+H]^+$: 282.0897, Found: 282.0895.

Functionalisation of Oxetanes 8a, 3e and 3f

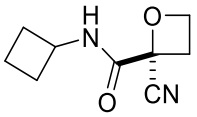
(±)-4-(2-Phenyloxetane-2-carbonyl)morpholine (10)



A microwave vial (2.0–5.0 mL volume) was charged with oxetane **8a** (103 mg, 0.50 mmol). The reaction vial was flushed with argon, sealed with a cap and then further flushed with argon. Anhydrous ethanol (2.4 mL) was added followed by 1 N aq. NaOH (0.55 mL, 0.55 mmol). The reaction mixture was stirred in an oil bath at 30 °C for 22 h. The reaction mixture was concentrated to afford (±)-2-phenyloxetane-2-carboxylate sodium salt **9** as a white solid which was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49–7.39 (m, 2 H, 2 x Ph-H), 7.25 (t, J = 7.6 Hz, 2 H, 2 x Ph-H), 7.15 (t, J = 7.3 Hz, 1 H, Ph-H), 4.29–4.14 (m, 2 H, OCH_2), 3.14–3.09 (m, 1 H, C*H*H), 2.54–2.51 (m, 1 H, CH*H*).

HATU (228 mg, 0.6 mmol) and morpholine (53 μL, 0.60 mmol) were added to a flask containing (±)-2-phenyloxetane-2-carboxylate sodium salt **9** (0.50 mmol) in DMF (2.5 mL). *N,N*-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 16 h. The reaction was concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexane) afforded oxetane **10** as a yellow oil (97 mg, 78% over 2 steps); R_f = 0.36 (50% EtOAc in hexanes); IR (film) / cm^{-1} 2968, 2892, 2855, 1692, 1639 (C=O), 1435, 1365, 1300, 1275, 1260, 1225, 1150, 1112, 1066, 1027, 968, 952, 910, 850, 758, 727, 700, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 2 H, 2 x Ph-H), 7.44–7.37 (m, 2 H, 2 x Ph-H), 7.36–7.29 (m, 1 H, Ph-H), 4.66–4.57 (dd, J = 8.4, 7.2 Hz, 2 H, OCH_2CH$_2$), 3.78–3.53 (m, 5 H, C*H*H and OCH_2 and NCH_2), 3.49–3.36 (m, 2 H, OC'*H*H and NC'*H*H), 3.14–2.98 (m, 2 H, OC'H*H* and N'CH*H*), 2.62–2.50 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C=O), 142.2 (Ph-C_q), 128.8 (2 x Ph-CH). 127.8 (Ph-CH), 123.3 (2 x Ph-CH), 89.3 (C_q(CON)(Ph)), 66.7 (OCH_2), 66.3 (OC'H_2), 66.1 (OCH_2CH_2), 46.1 (NC'H_2), 42.8 (NCH_2), 34.5 (CH_2); HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{20}N_2O_3Na^+$ [M+CH_3CN+Na]$^+$: 311.1372, Found: 311.1365.

(±)-2-cyano-N-cyclobutyloxetane-2-carboxamide (12)

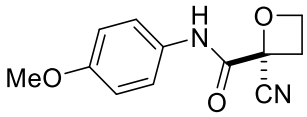


Lithium hydroxide monohydrate (23 mg, 0.54 mmol) in H_2O (2 mL) was added to a solution of oxetane **3e** (109 mg, 0.50 mmol) in THF (6 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated in vacuo affording (±)-2-cyanooxetane-2-carboxylate lithium salt **11** as a viscous yellow oil which was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.61–4.52 (m, 1 H, OC*H*H), 4.45–4.36 (m, 1 H, OCH*H*) 2.99–2.90 (m, 1 H, C*H*H), 2.89–2.79 (m, 1 H, CH*H*). Benzyl alcohol was removed overnight under high vacuum at rt.

HATU (209 mg, 0.55 mmol) and cyclobutylamine (64 μL, 0.75 mmol) were added to a flask containing (±)-2-cyanooxetane-2-carboxylate lithium salt **11** (0.50 mmol) in DMF (2.5 mL). *N,N*-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 18 h. The reaction was concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexane) afforded oxetane **12** as a white crystalline solid (27 mg, 30% over 2 steps); R_f = 0.22 (50% EtOAc in hexanes); mp = 126–130 °C; IR (film) / cm^{-1} 3303 (N-H), 2983, 2944, 2908, 2875, 2249 (C≡N), 1664 (C=O), 1524, 1482, 1454, 1275, 1246, 1215, 1196, 1170, 1147, 1121, 1033, 968, 937, 810, 777, 750, 716, 639; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (br s, 1 H, NH), 4.97–4.87 (m, 1 H, OC*H*H), 4.69–4.60 (m, 1 H, OCH*H*), 4.52–4.38 (m, 1 H, NHC*H*$(CH_2)_2$), 3.37–3.25 (m, 1 H, OCH_2C*H*H), 3.15–3.03 (m, 1 H, OCH_2CH*H*), 2.49–2.33 (m, 2 H,

2 x NHCH(C*H*H)), 2.08–1.92 (m, 2 H, 2 x NHCH(CH*H*)), 1.86–1.74 (m, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5 (C=O), 116.9 (C≡N), 76.2 (*C*$_q$(CONH)(CN)), 68.9 (OCH_2), 44.6 (NH*C*H(CH_2)$_2$), 32.2 (OCH_2*C*H_2), 30.9 (NHCH(*C*H_2)), 30.8 (NHCH(*C*'H_2)), 15.0 (CH_2); HRMS (CI) *m/z* calcd for $C_9H_{16}N_3O_2^+$ $[M+NH_4]^+$: 198.1243, Found: 198.1240.

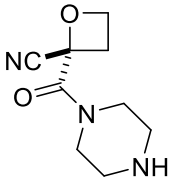
(±)-2-cyano-N-(4-methoxyphenyl)oxetane-2-carboxamide (13)



Lithium hydroxide monohydrate (23 mg, 0.54 mmol) in H_2O (2 mL) was added to a solution of oxetane **3e** (109 mg, 0.50 mmol) in THF (6 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated in vacuo affording (±)-2-cyanooxetane-2-carboxylate lithium salt **11** as a viscous yellow oil which was used without further purification. Benzyl alcohol was removed overnight under high vacuum at rt.

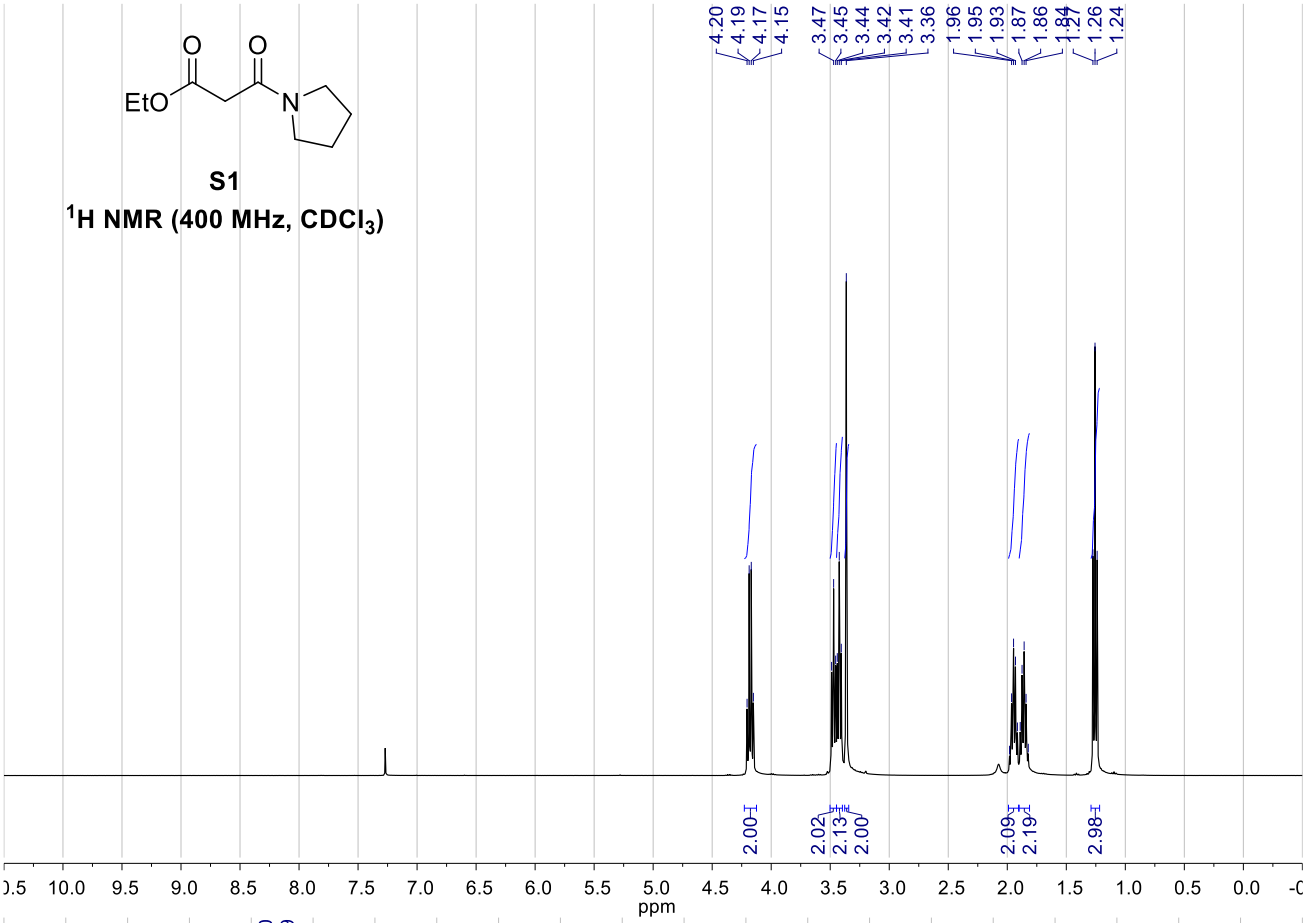
HATU (209 mg, 0.55 mmol) and *p*-anisidine (67 mg, 0.55 mmol) were added to a flask containing (±)-2-cyanooxetane-2-carboxylate lithium salt **11** (0.50 mmol) in DMF (2.5 mL). *N,N*-Diisopropylethylamine (0.26 mL, 1.50 mmol) was then added dropwise and the reaction mixture was stirred at 25 °C for 24 h. The reaction was concentrated *in vacuo*. Purification by flash chromatography on deactivated basic alumina (activity IV) (2% Et_2O in CH_2Cl_2) afforded oxetane **13** as a beige solid (41 mg, 35% over 2 steps); R_f = 0.27 (2% Et_2O in CH_2Cl_2); mp = 84–86 °C; IR (film) / cm^{-1} 3320 (N-H), 2972, 2909, 2839, 2253 (C≡N), 1681 (C=O), 1598, 1511, 1465, 1444, 1417, 1302, 1247, 1234, 1180, 1158, 1030, 935, 830, 810, 731, 672, 541; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (br s, 1 H, NH), 7.58–7.46 (m, 2 H, 2 x Ar-H), 6.96–6.86 (m, 2 H, 2 x Ar-H), 5.03–4.93 (m, 1 H, OC*H*H), 4.77–4.68 (m, 1 H, OCH*H*), 3.81 (s, 3 H, OCH_3), 3.44–3.33 (m, 1 H, C*H*H), 3.25–3.15 (m, 1 H, CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (C=O), 157.2 (Ar-*C*$_q$-OMe), 129.0 (Ar-C$_q$-NH), 121.5 (2 x Ar-CH), 116.7 (C≡N), 114.3 (2 x Ar-CH), 76.4 (*C*$_q$(CONH)(CN)), 69.1 (OCH_2), 55.5 (OCH_3), 32.4 (CH_2); HRMS (CI) *m/z* calcd for $C_{12}H_{16}N_3O_3^+$ $[M+NH_4]^+$: 250.1192, Found: 250.1199.

(±)-2-(Piperazine-1-carbonyl)oxetane-2-carbonitrile (14)



Trifluoroacetic acid (78 mL, 1.0 mmol) was added to a solution of oxetane **3f** (30 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min then 25 °C for 22 h. Toluene (5 mL) was added and the reaction mixture was concentrated *in vacuo*. Water (5 mL) was added to the residue followed by saturated aq. Na_2CO_3 (5 mL). The aqueous mixture was extracted with CH_2Cl_2 (5 x 5 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography on deactivated basic alumina (activity IV) (2% MeOH in CH_2Cl_2) afforded oxetane **14** as a colorless oil (16 mg, 79%); R_f = 0.36 (10% MeOH in CH_2Cl_2); IR (film) / cm^{-1} 3323 (br N-H), 2909, 2854, 2249 (C≡N), 1656 (C=O), 1444, 1322, 1269, 1162, 1141, 1122, 1023, 969, 941, 802, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87–4.79 (m, 1 H, OC*H*H), 4.60–4.52 (m, 1 H, OCH*H*), 3.71–3.59 (m, 3 H, OCNCH_2 and C*H*H), 3.57–3.47 (m, 2 H, OCNCH_2), 3.14–3.04 (m, 1 H, CH*H*), 3.00–2.84 (m, 4 H, 2 x HNCH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (C=O), 117.6 (C≡N), 76.1 (*C*$_q$(CN)(CON)), 68.4 (OCH_2), 47.2 (OCN*C*H_2), 45.8 (HNCH_2), 45.7 (HNCH_2), 44.2 (OCN*C*H_2), 30.5 (CH_2); HRMS (ESI-TOF) *m/z* Calcd for $C_{11}H_{17}N_4O_2^+$ $[M+CH_3CN+H]^+$: 237.1352, Found: 237.1359.

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


EtO
O
O
N
S1
^{1}H NMR (400 MHz, CDCl$_3$)
4.20
4.19
4.17
4.15
3.47
3.45
3.44
3.42
3.41
3.36
1.96
1.95
1.93
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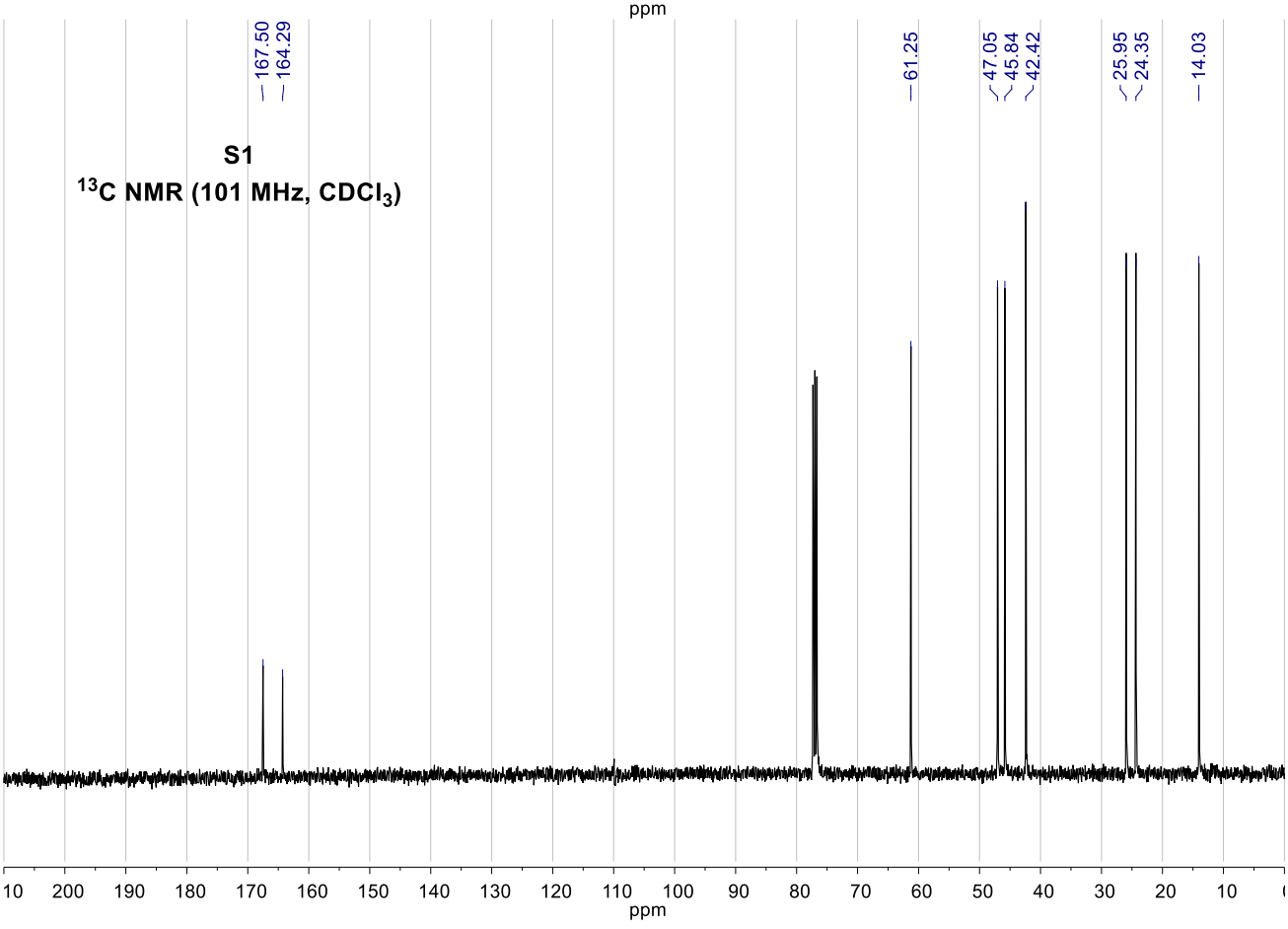
2.13
2.00
2.09
2.19
2.98
ppm


S1
^{13}C NMR (101 MHz, CDCl$_3$)
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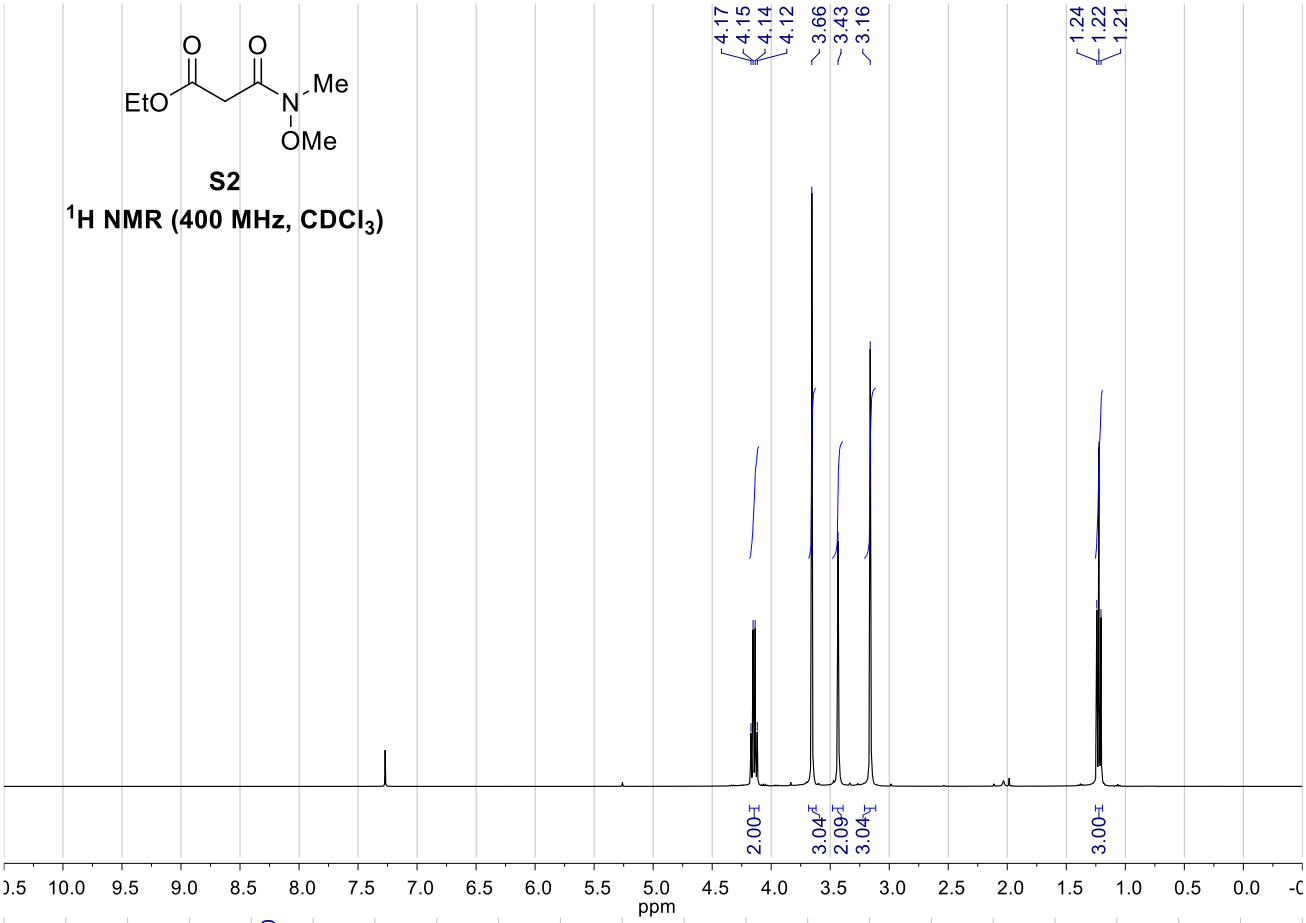
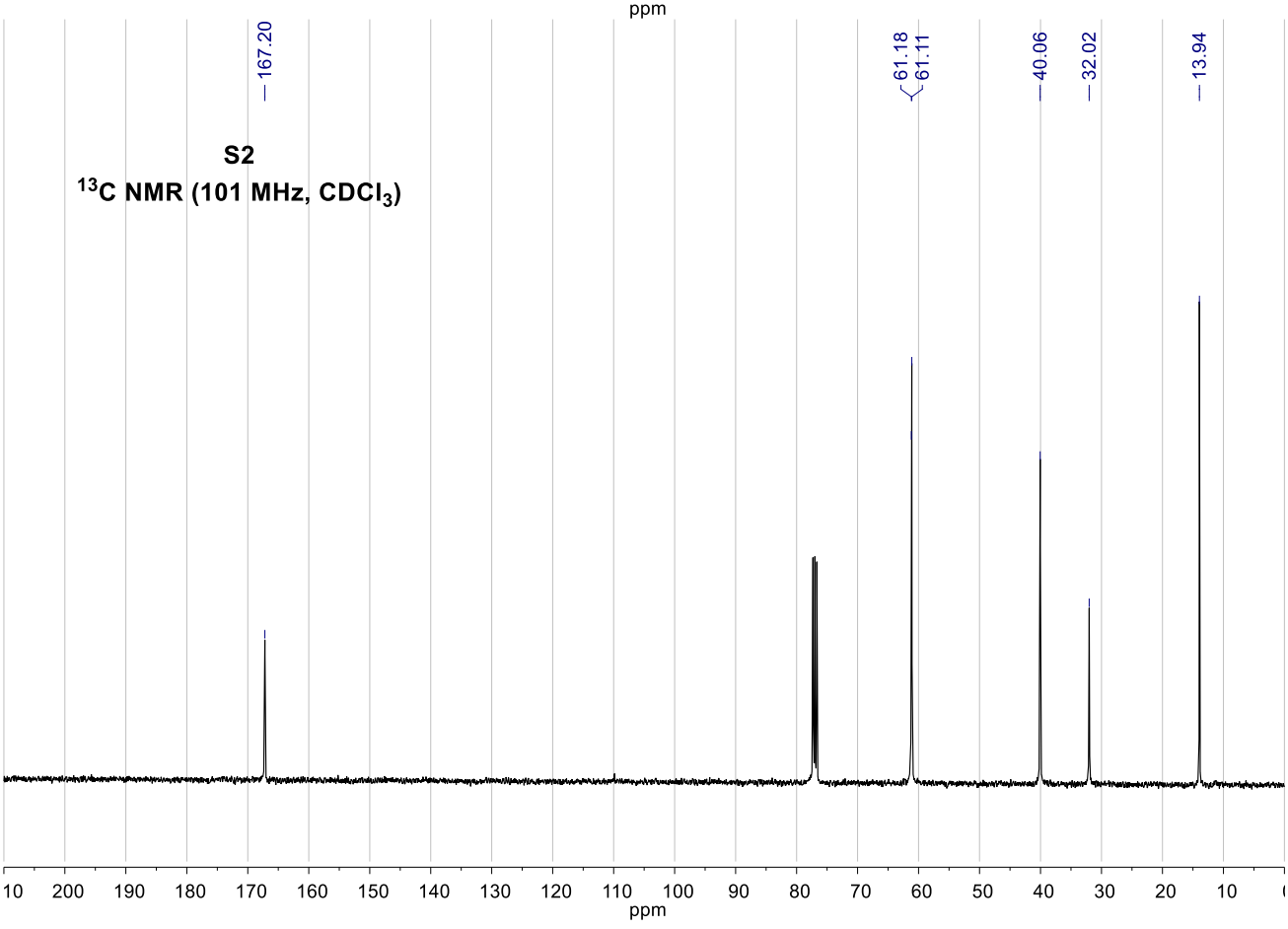
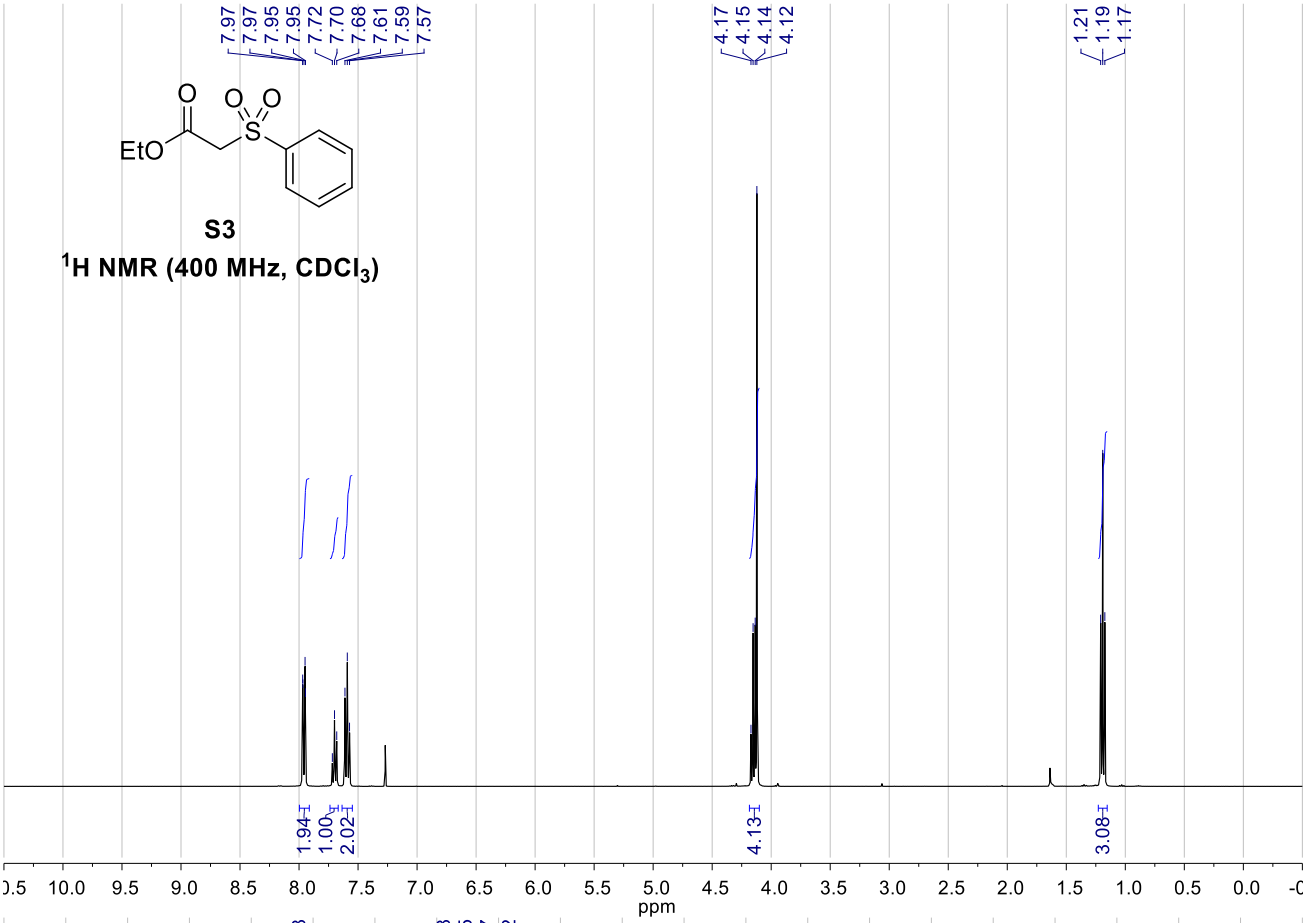
164.29
61.25
47.05
45.84
42.42
25.95
24.35
14.03
ppm

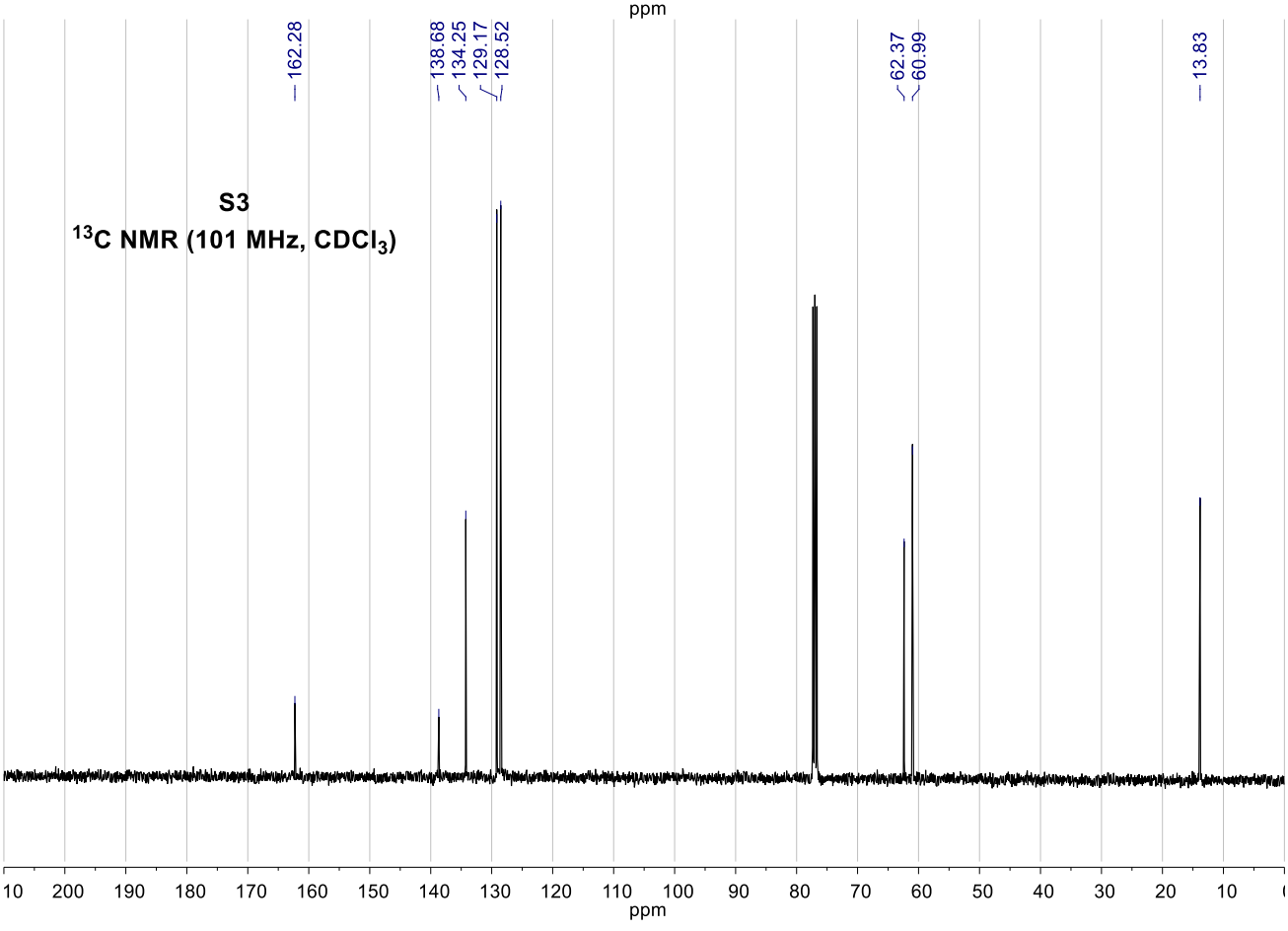

EtO
O
O
N
Me
OMe
S2
^{1}H NMR (400 MHz, CDCl$_3$)
4.17
4.15
4.14
4.12
3.66
3.43
3.16
1.24
1.22
1.21
2.00
3.04
2.09
3.04
3.00
ppm


S2
^{13}C NMR (101 MHz, CDCl$_3$)
167.20
61.18
61.11
40.06
32.02
13.94
ppm



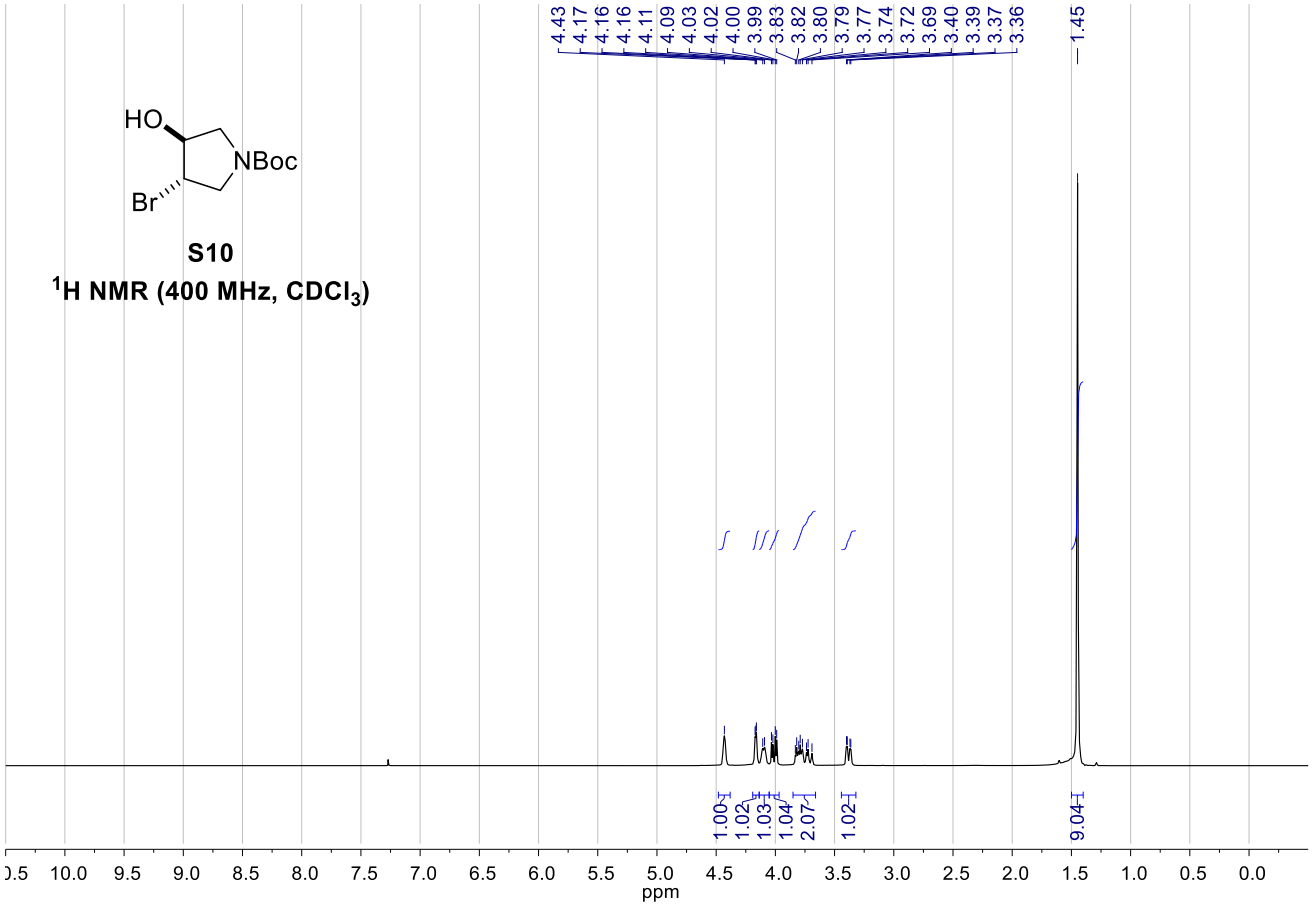
S3

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



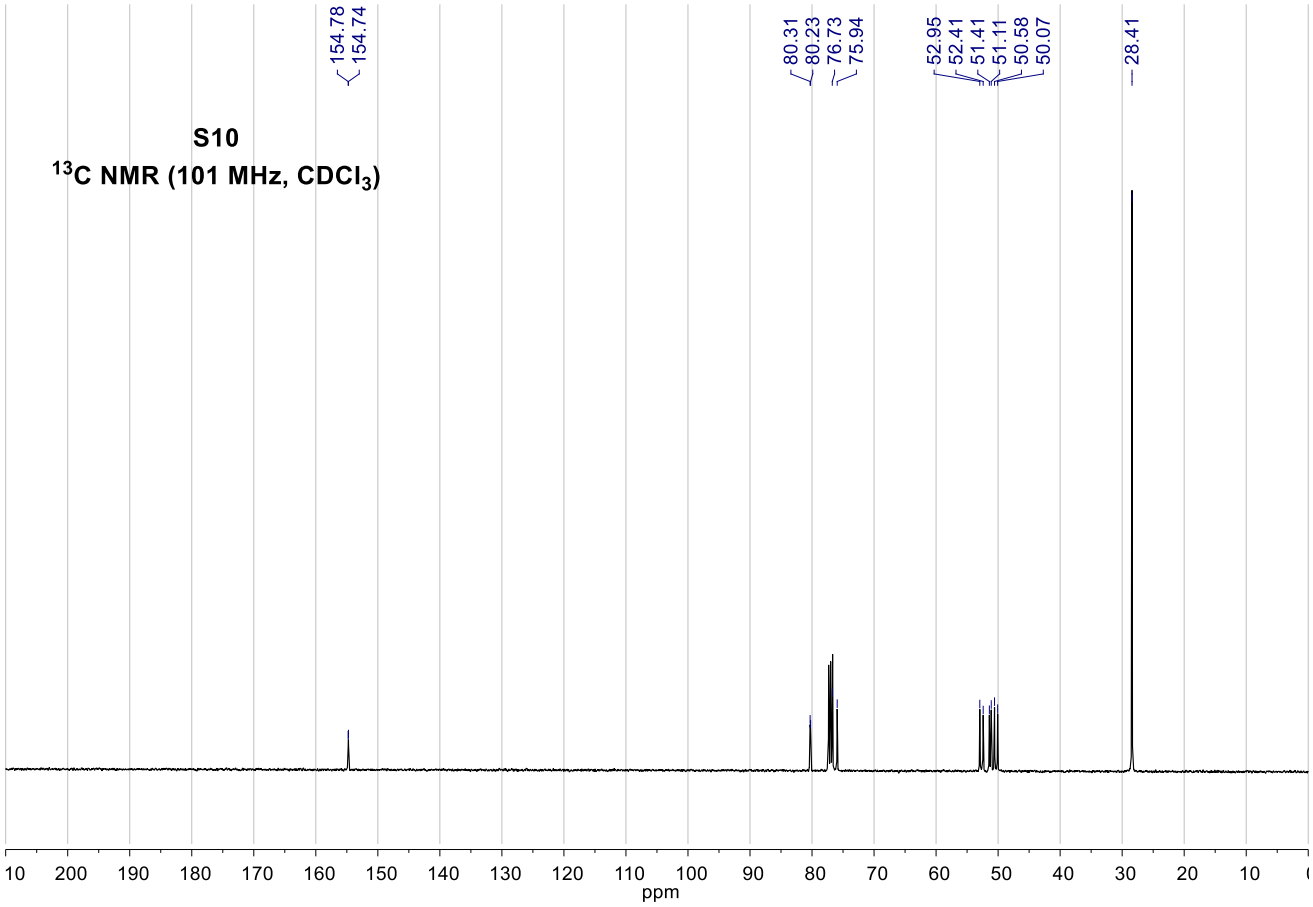
S3

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



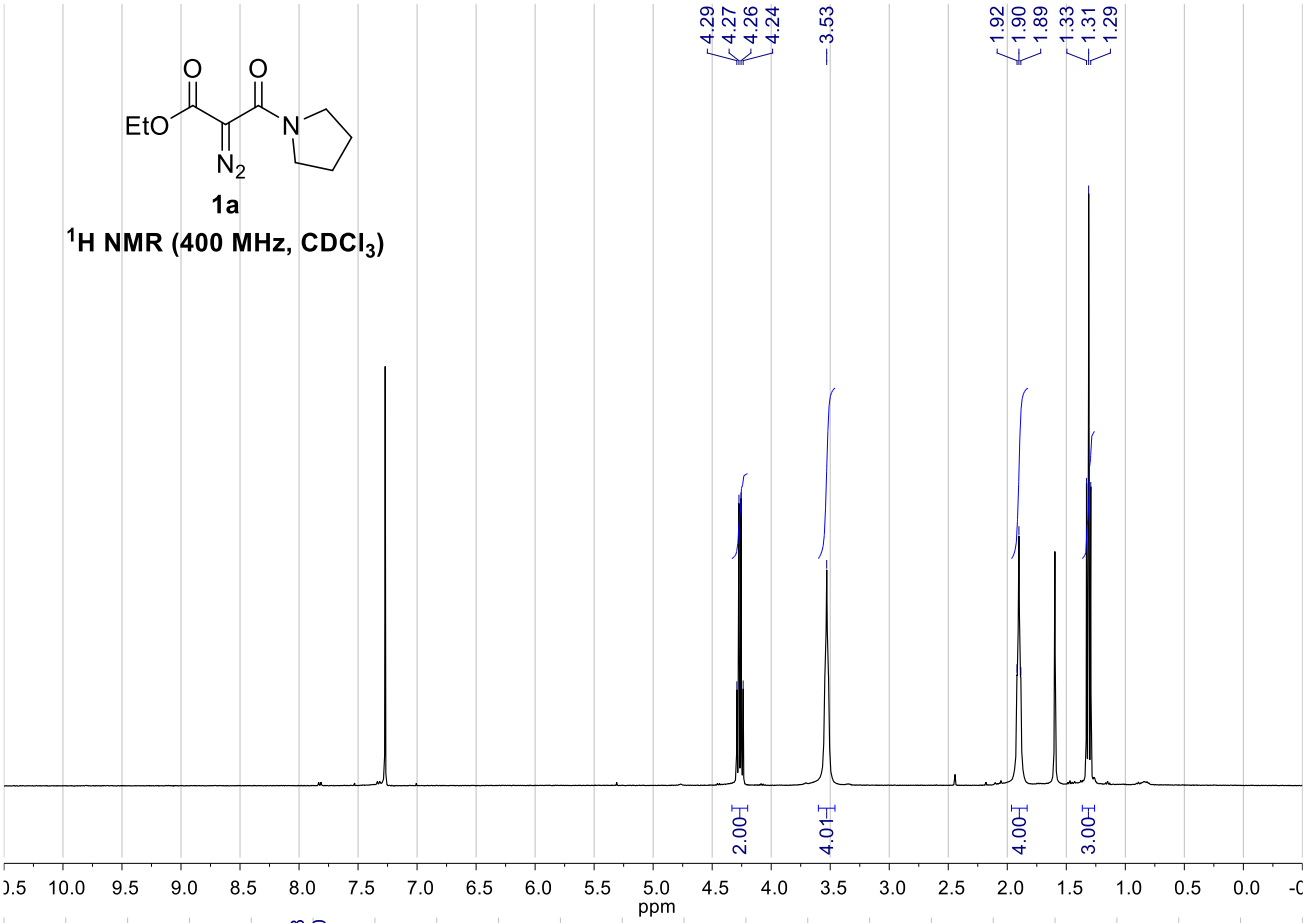
S10

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



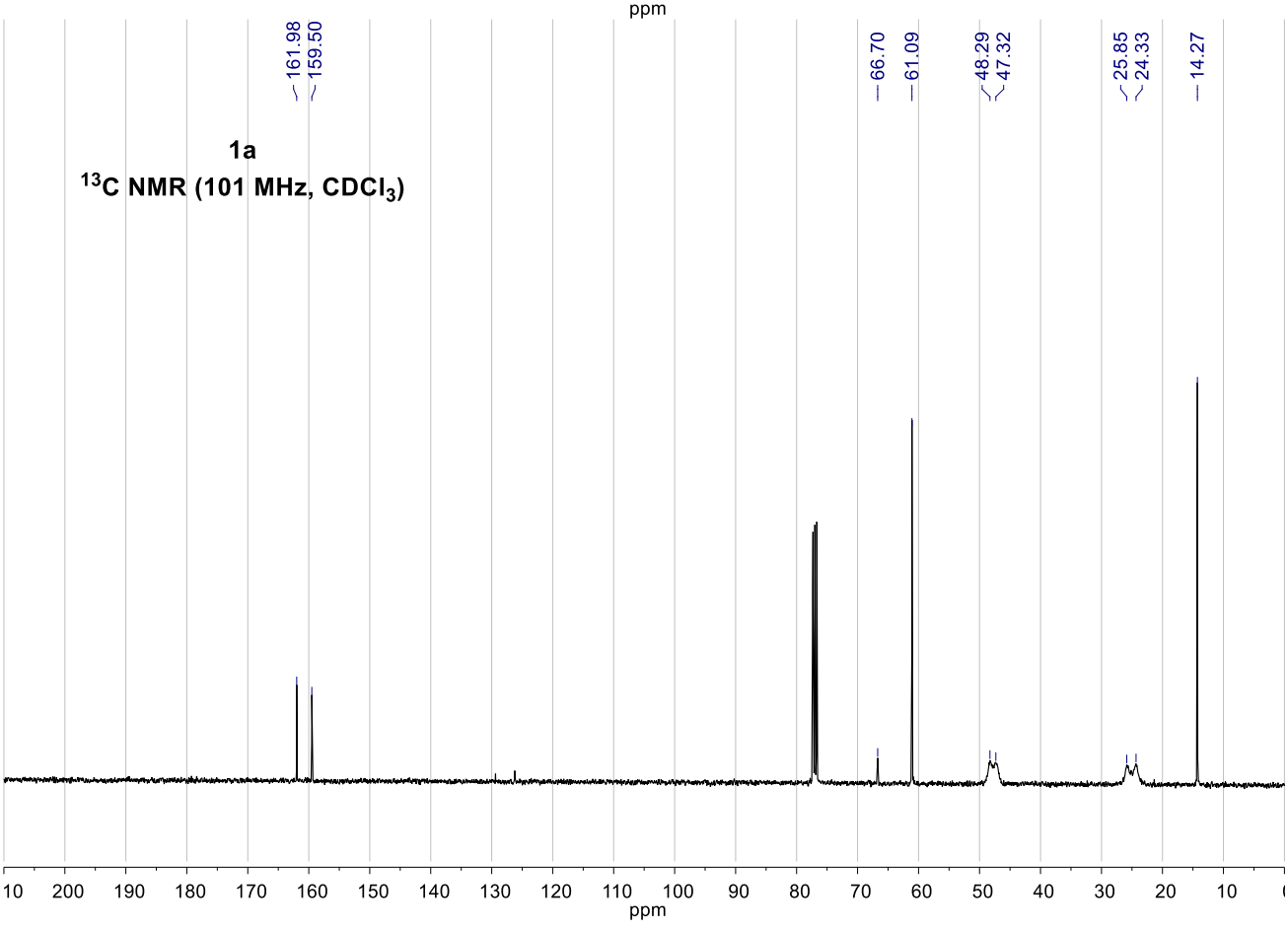
S10

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



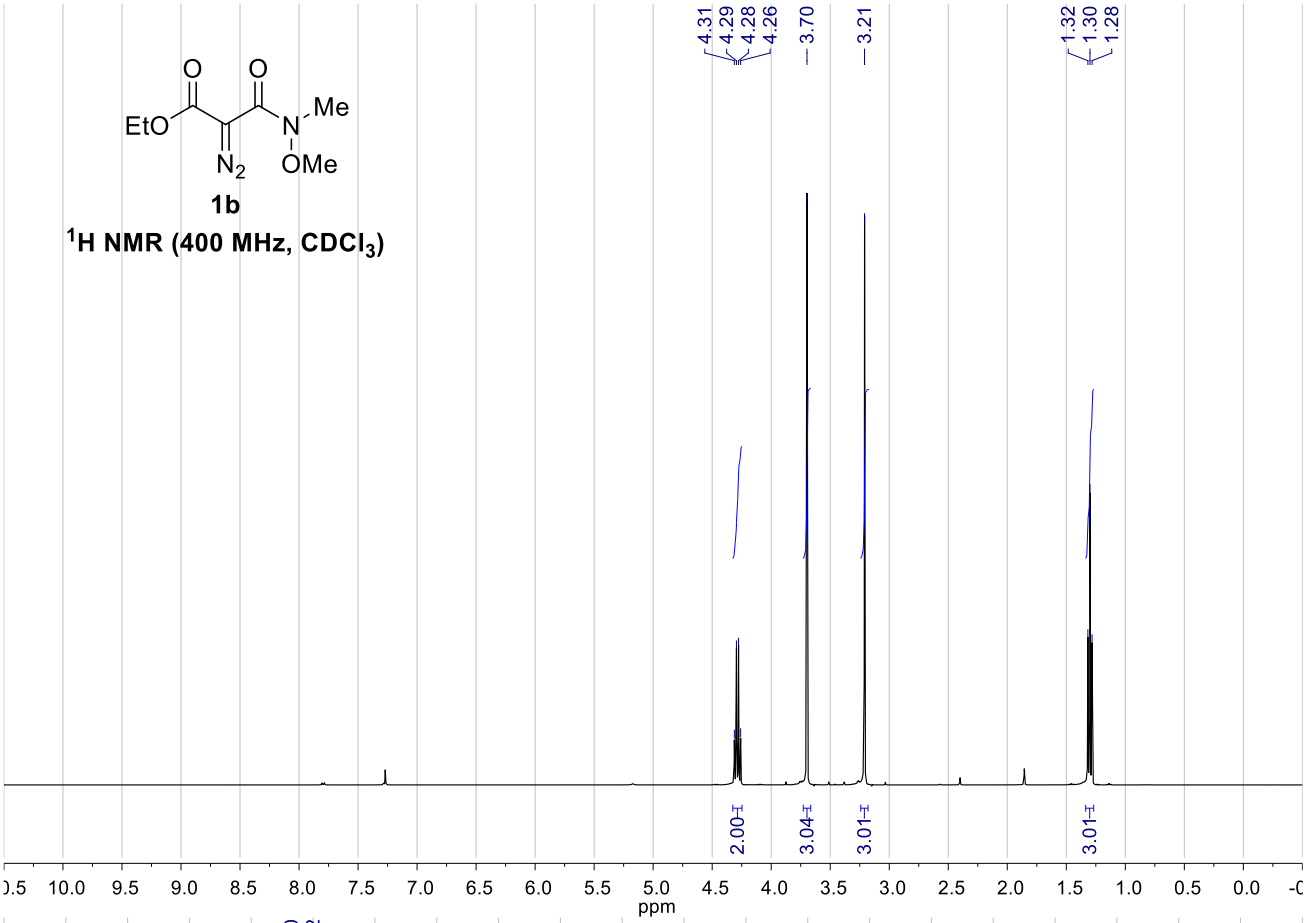
1a

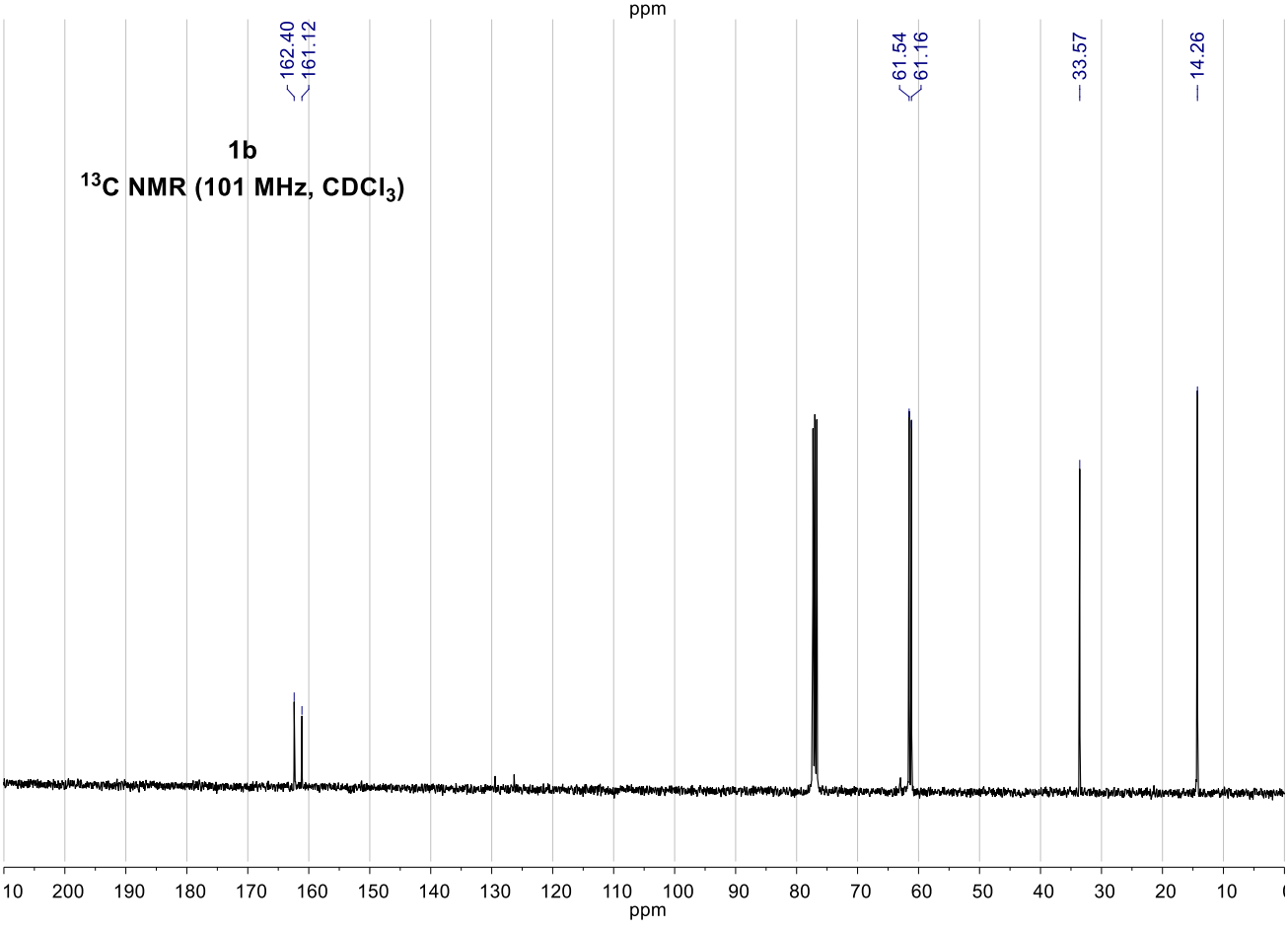
^{1}H NMR (400 MHz, $CDCl_3$)

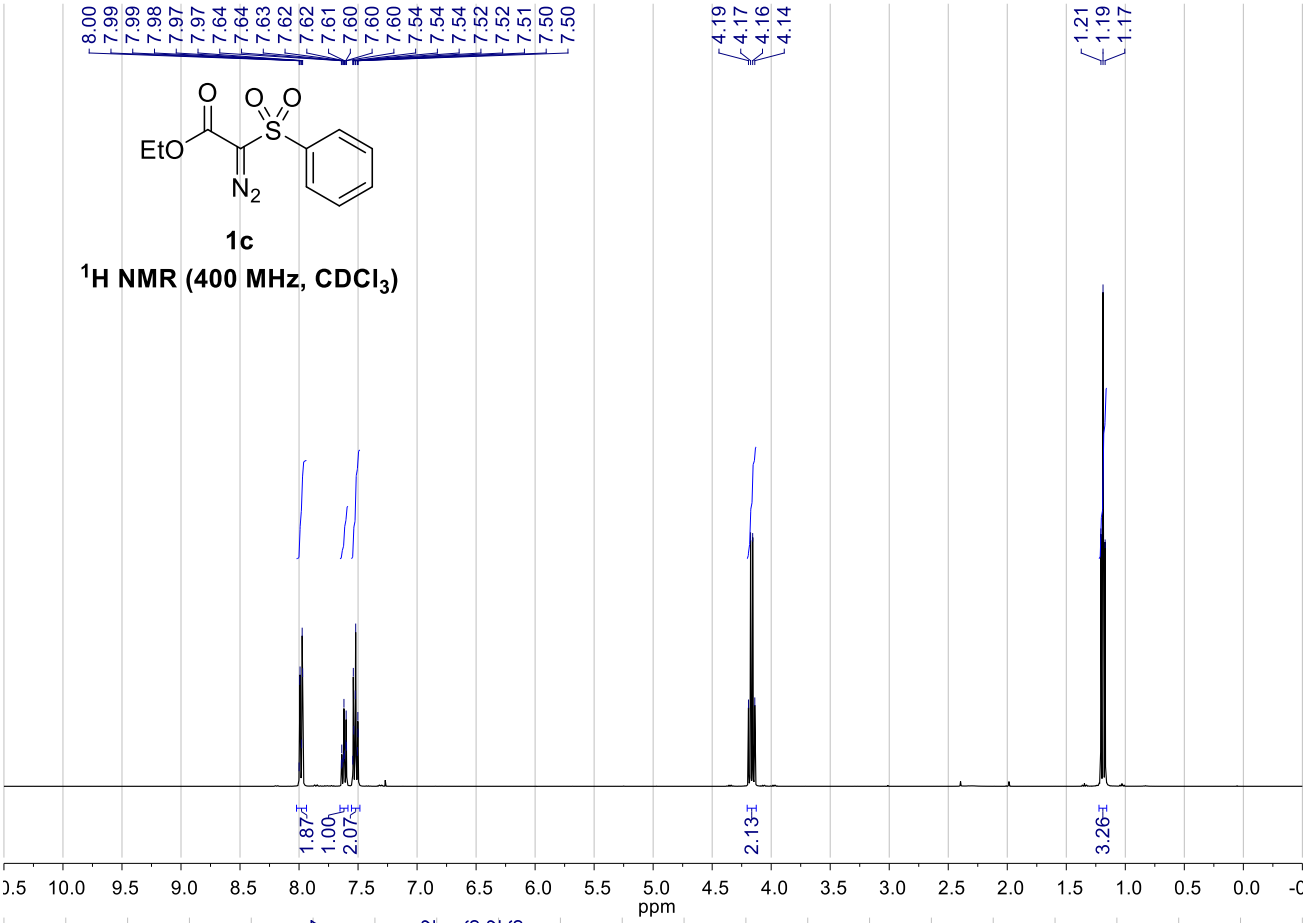


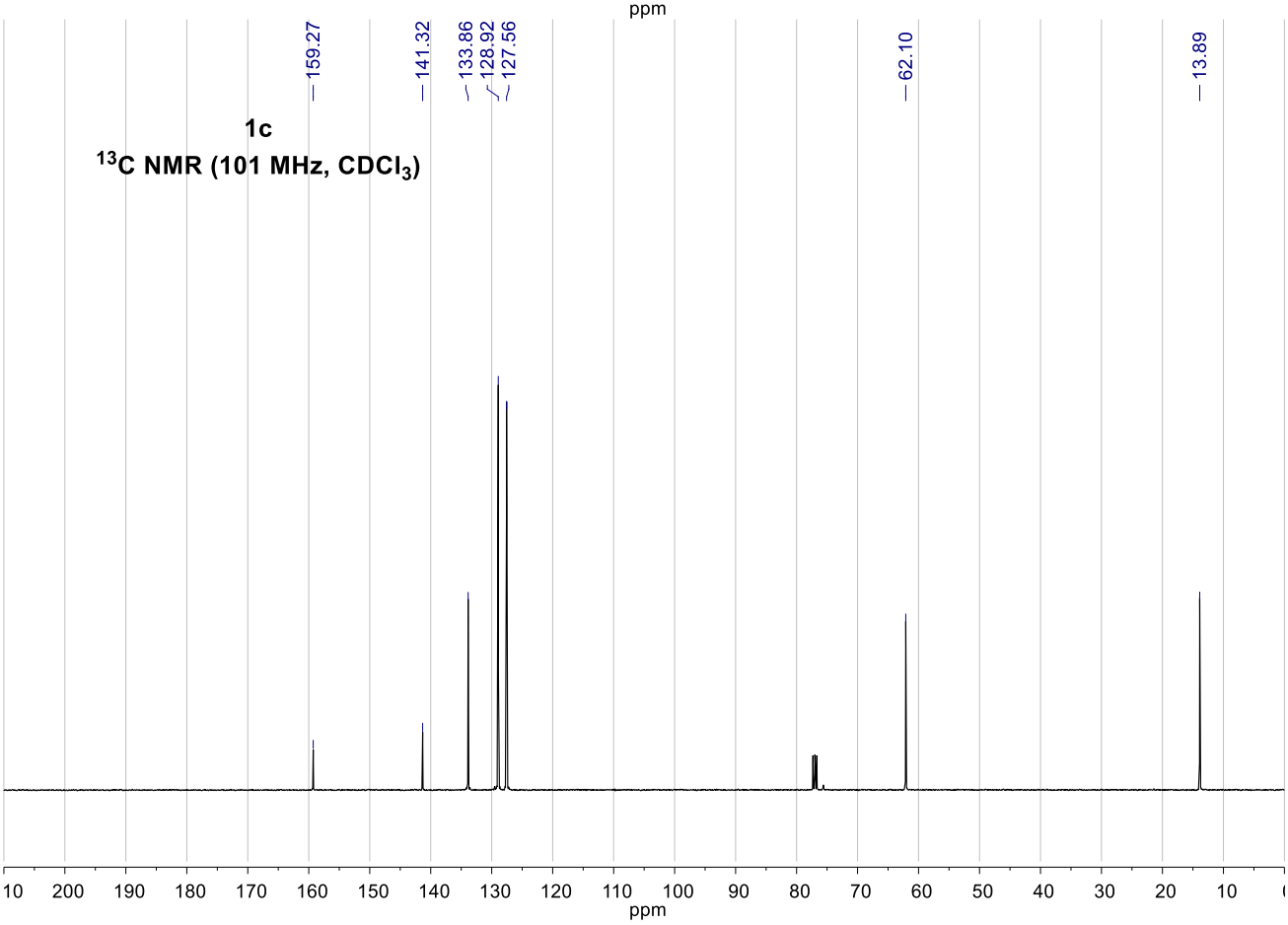
1a

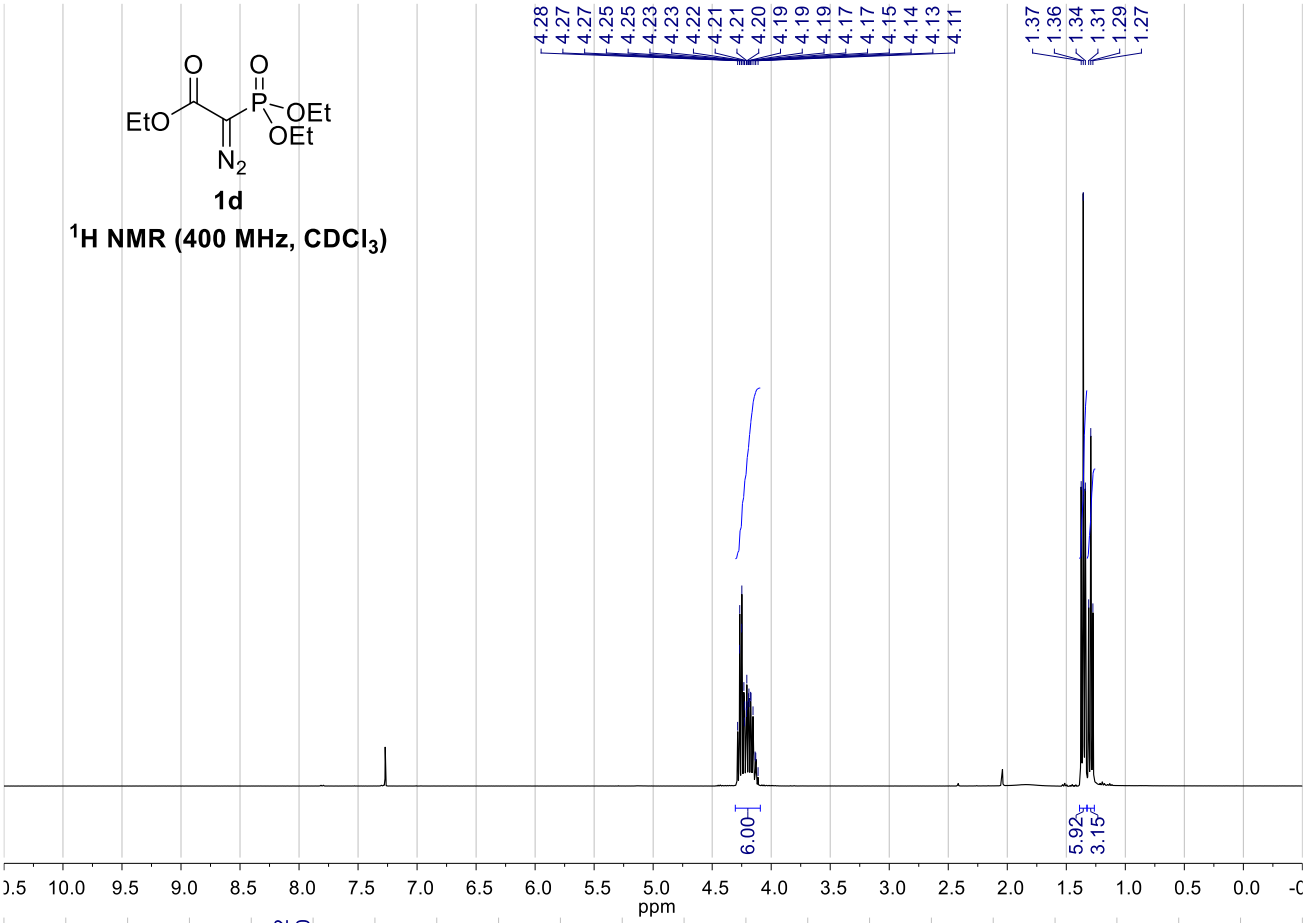
^{13}C NMR (101 MHz, $CDCl_3$)


EtO
O
O
N
Me
OMe
N2
1b
1H NMR (400 MHz, CDCl3)
4.31
4.29
4.28
4.26
3.70
3.21
1.32
1.30
1.28
2.00
3.04
3.01
3.01
ppm


1b
13C NMR (101 MHz, CDCl3)
162.40
161.12
61.54
61.16
33.57
14.26
ppm

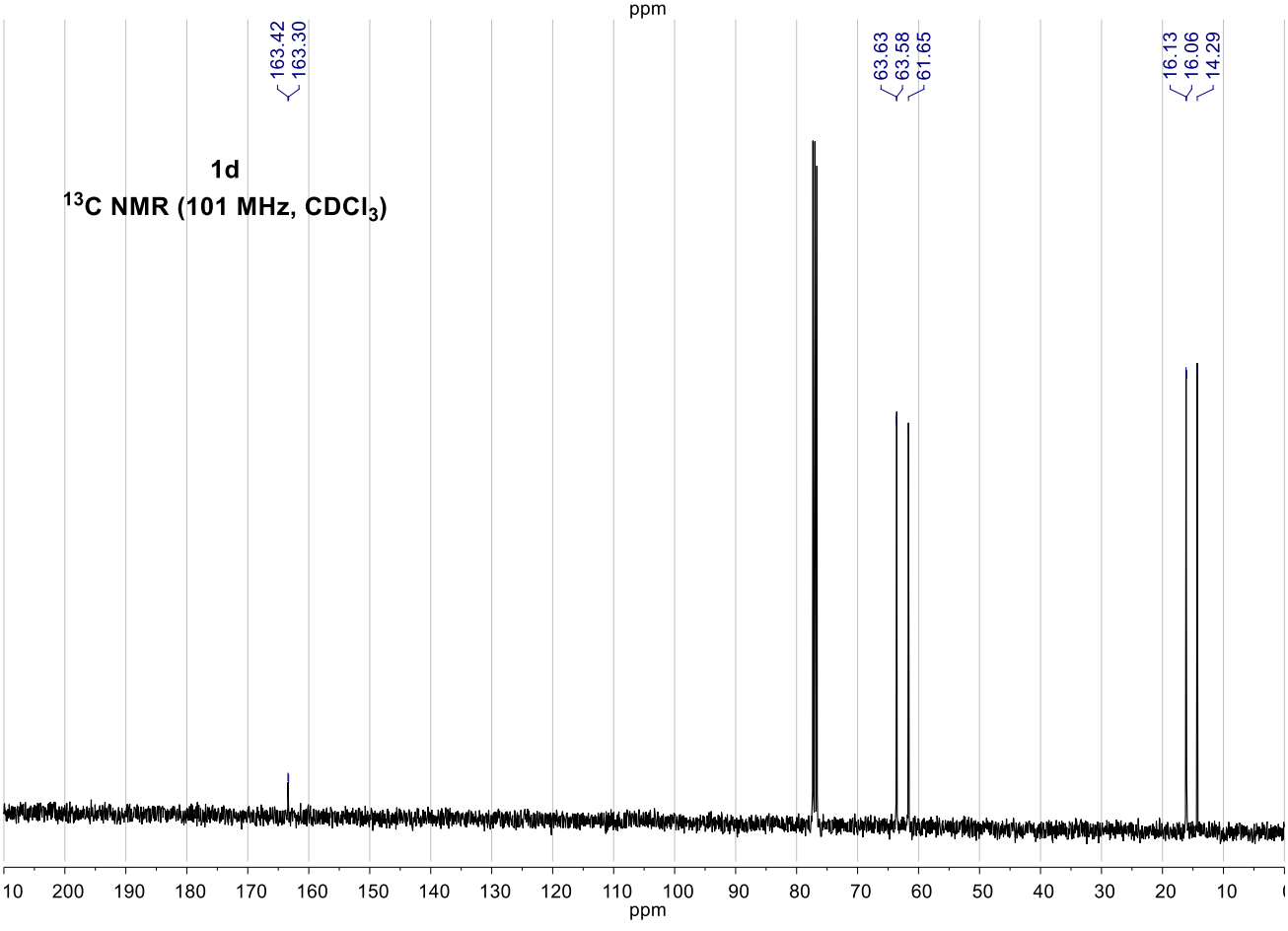

8.00
7.99
7.99
7.98
7.97
7.97
7.64
7.64
7.63
7.62
7.62
7.61
7.60
7.60
7.60
7.54
7.54
7.54
7.52
7.52
7.51
7.50
7.50
4.19
4.17
4.16
4.14
1.21
1.19
1.17
EtO
O
O
O
S
N2
1c
1H NMR (400 MHz, CDCl3)
1.87
1.00
2.07
2.13
3.26
ppm


159.27
141.32
133.86
128.92
127.56
62.10
13.89
1c
13C NMR (101 MHz, CDCl3)
ppm



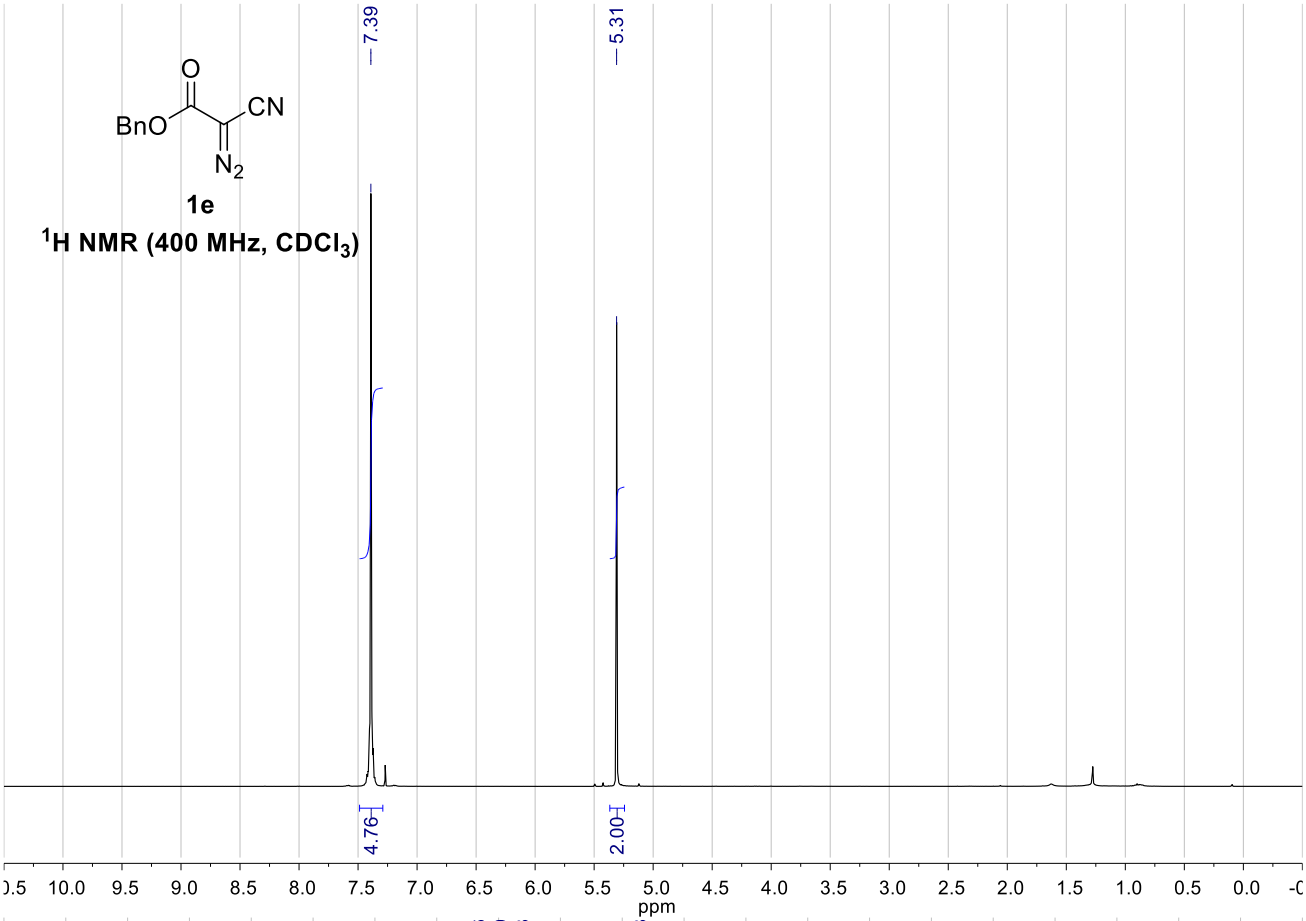
1d

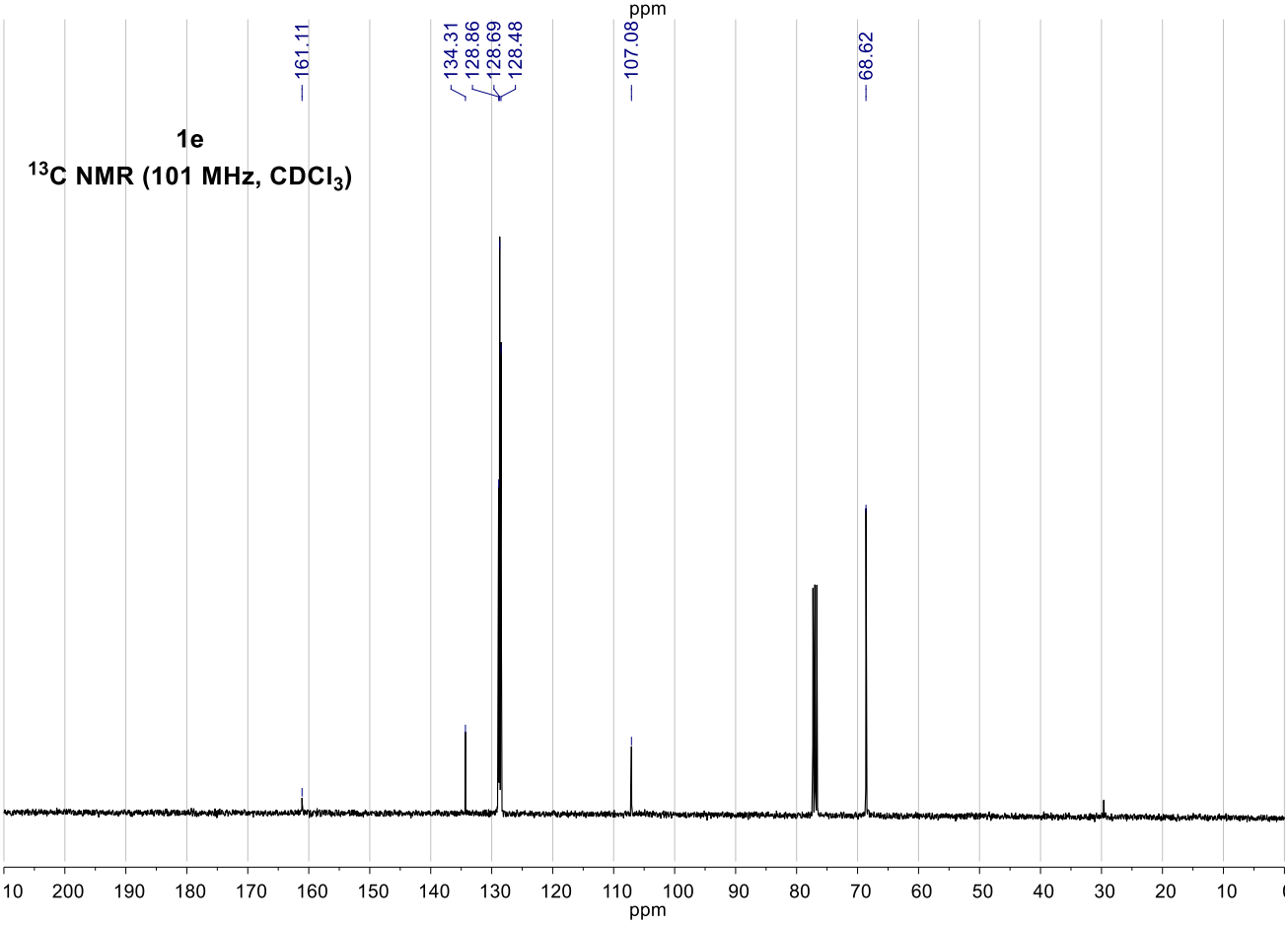
^{1}H NMR (400 MHz, $CDCl_3$)

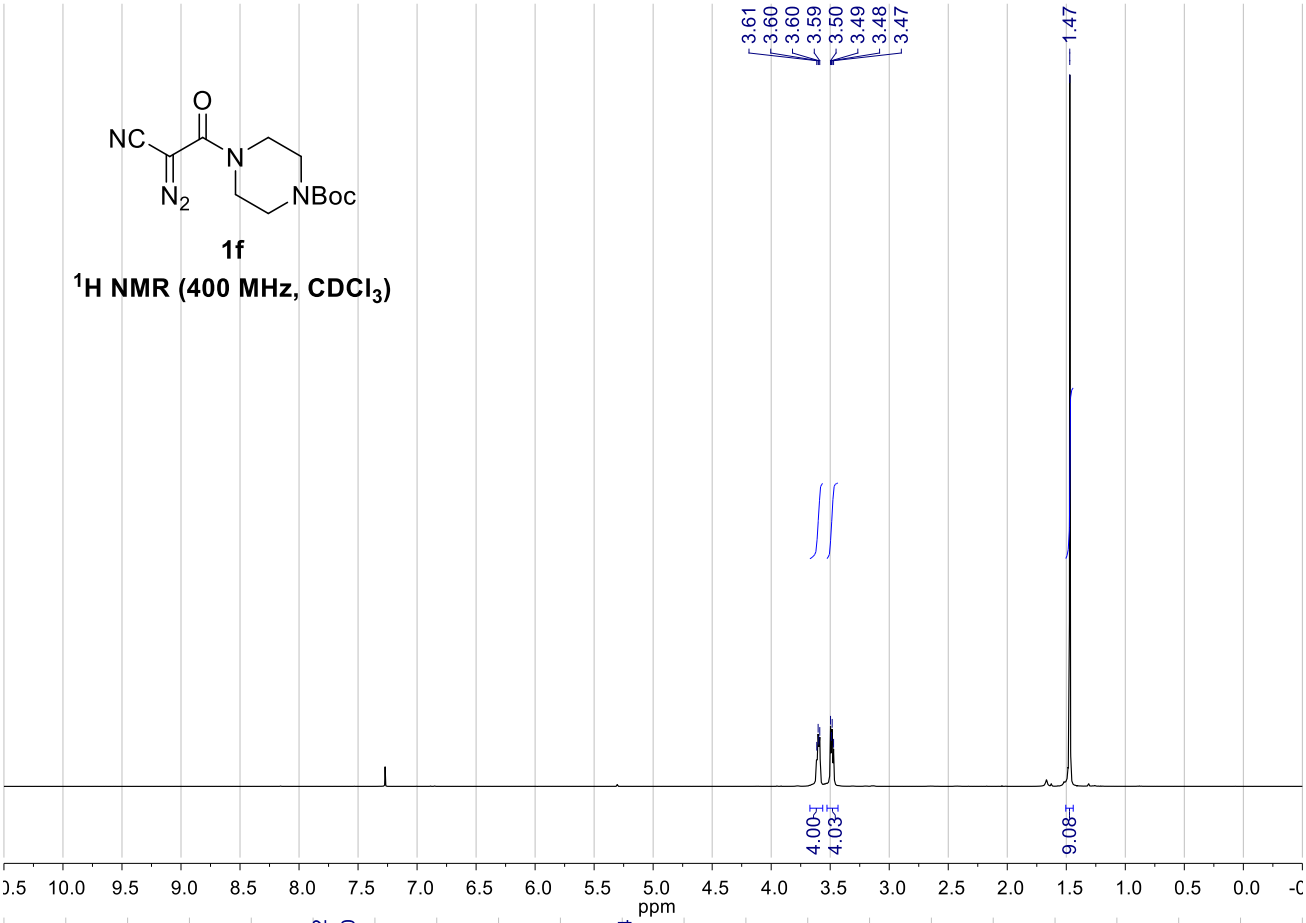


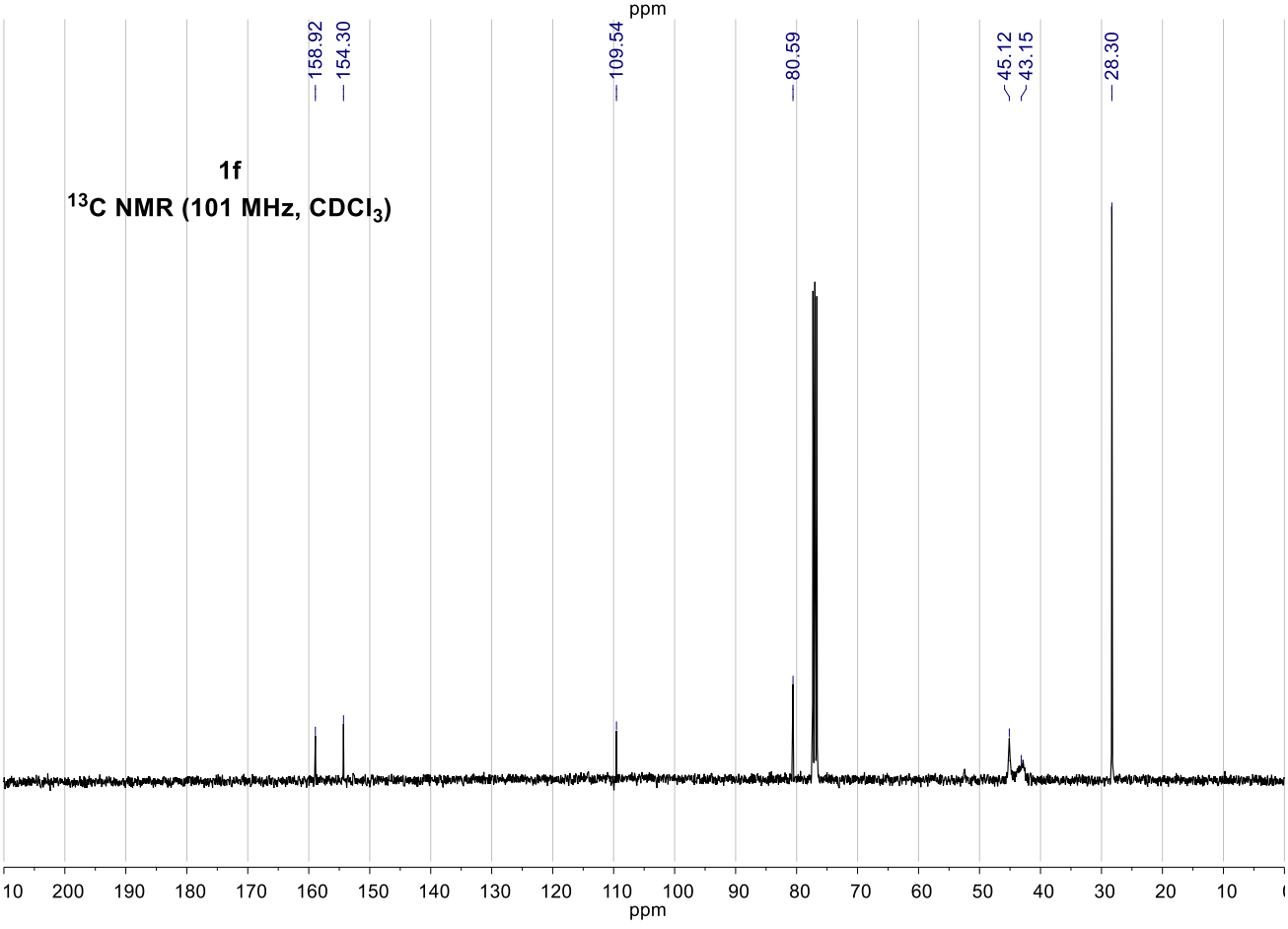
1d

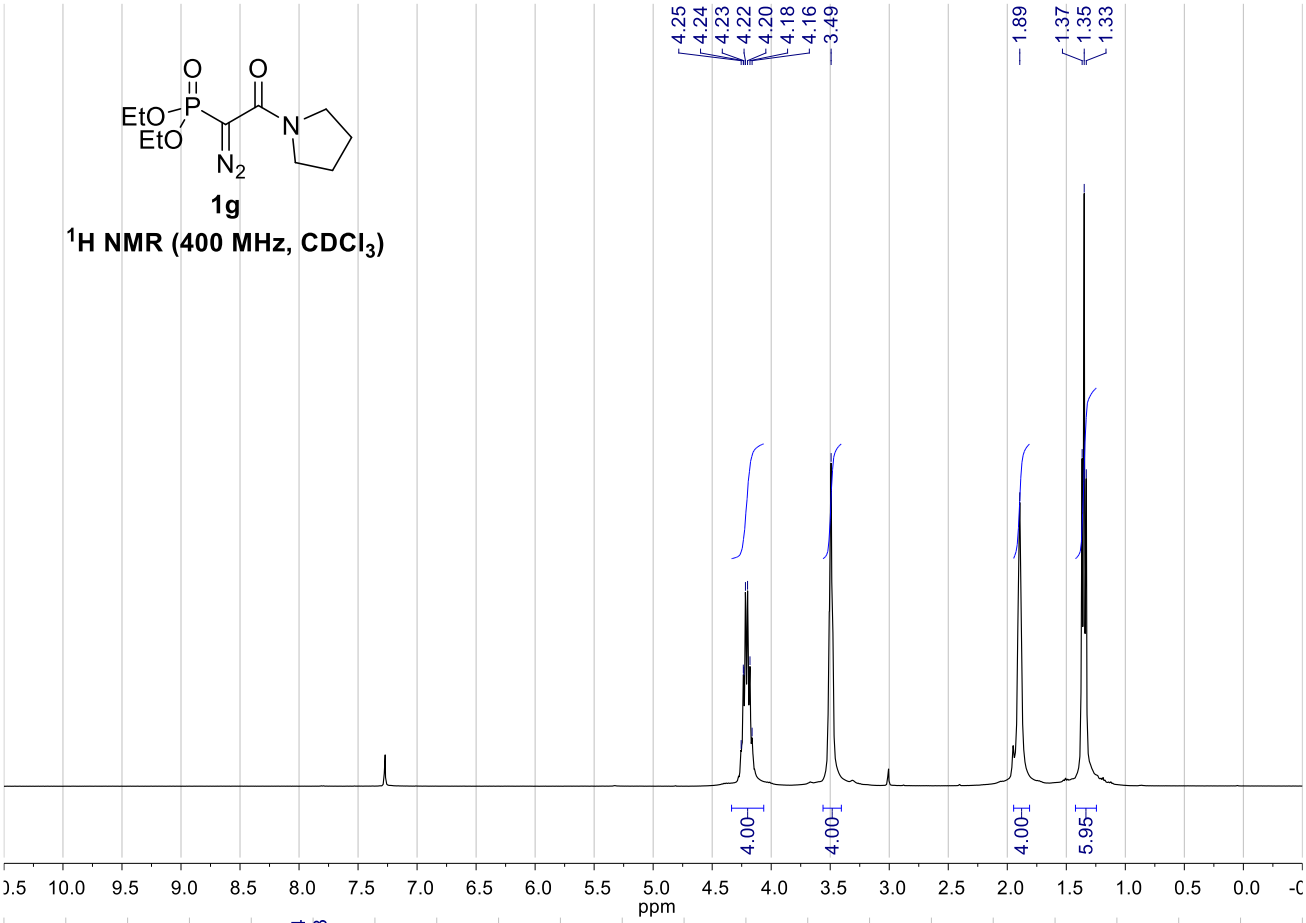
^{13}C NMR (101 MHz, $CDCl_3$)


7.39
5.31
BnO
CN
N2
1e
1H NMR (400 MHz, CDCl3)
4.76
2.00
ppm


161.11
134.31
128.86
128.69
128.48
107.08
68.62
1e
13C NMR (101 MHz, CDCl3)
ppm

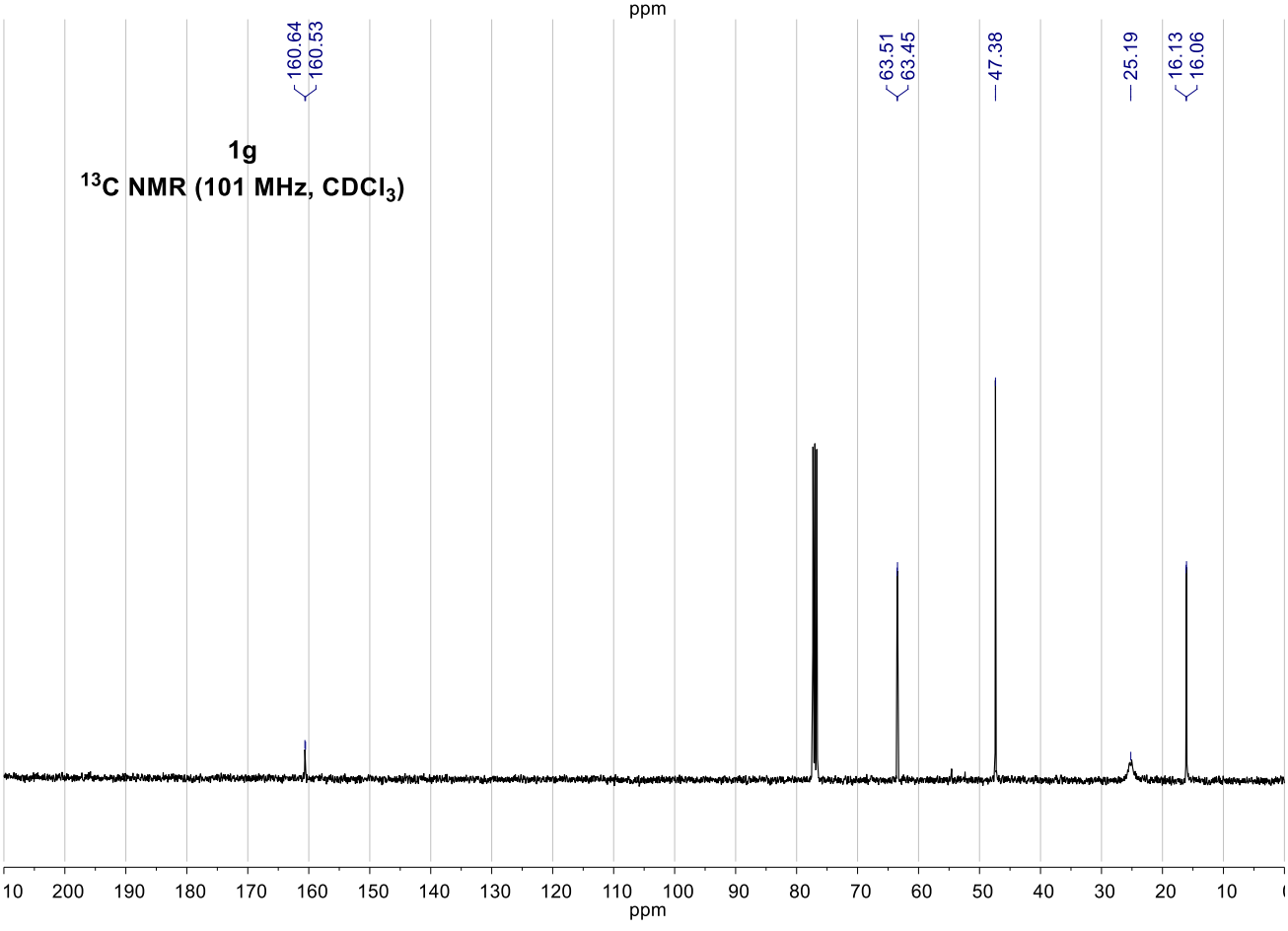

NC
O
N
N2
NBoc
1f
1H NMR (400 MHz, CDCl3)
3.61
3.60
3.60
3.59
3.50
3.49
3.48
3.47
1.47
4.00
4.03
9.08
ppm


1f
13C NMR (101 MHz, CDCl3)
158.92
154.30
109.54
80.59
45.12
43.15
28.30
ppm



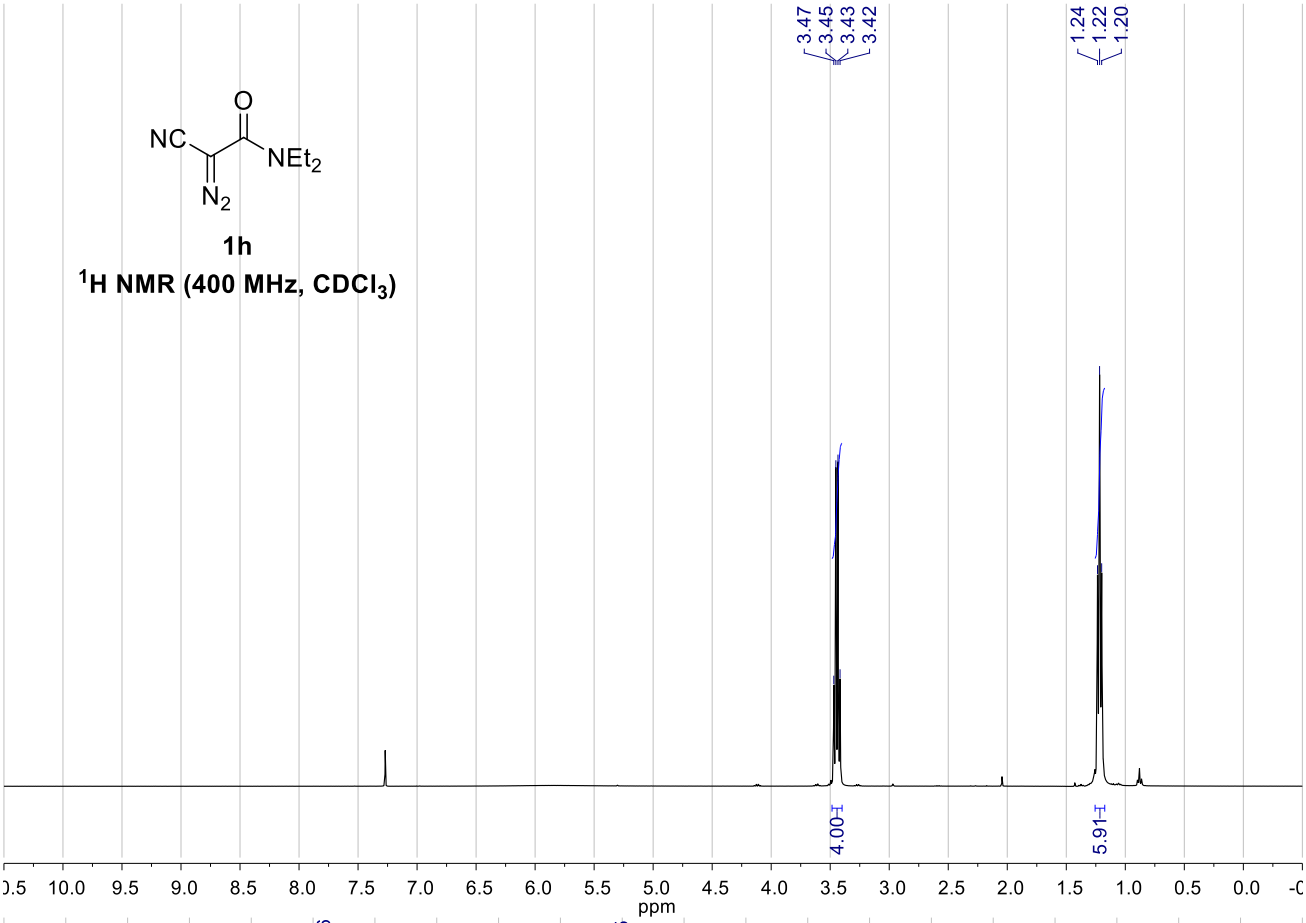
1g

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



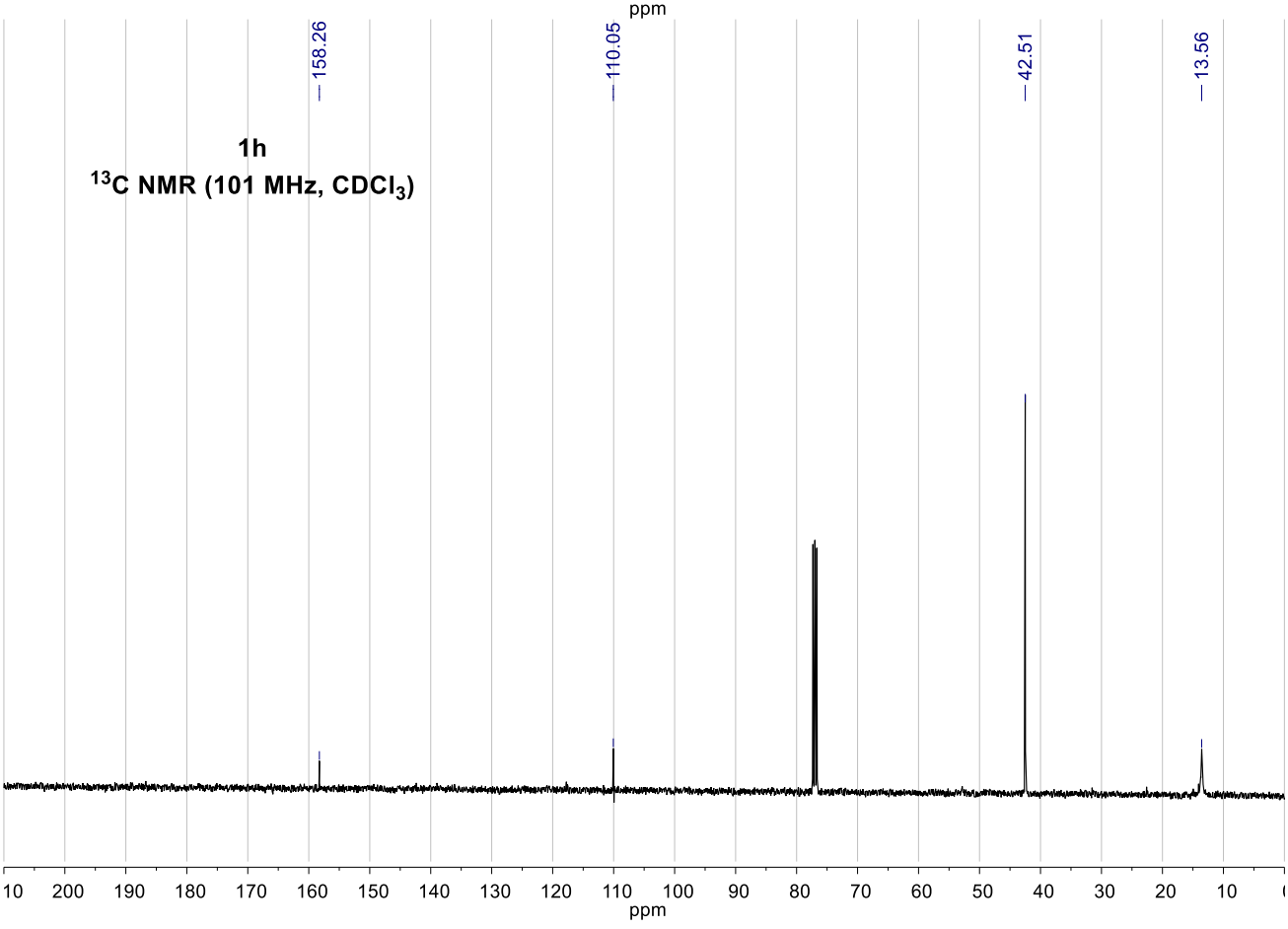
1g

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



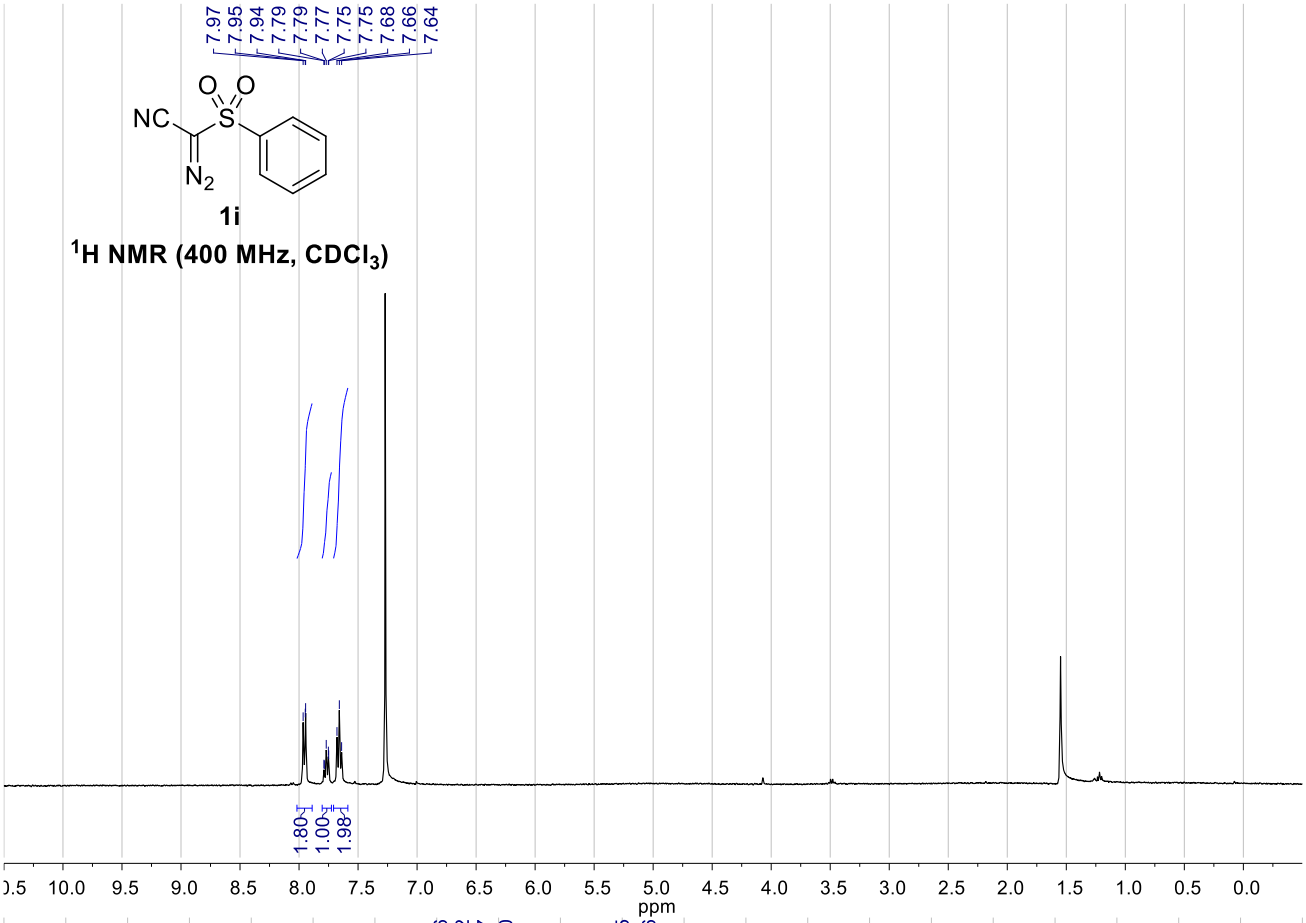
1h

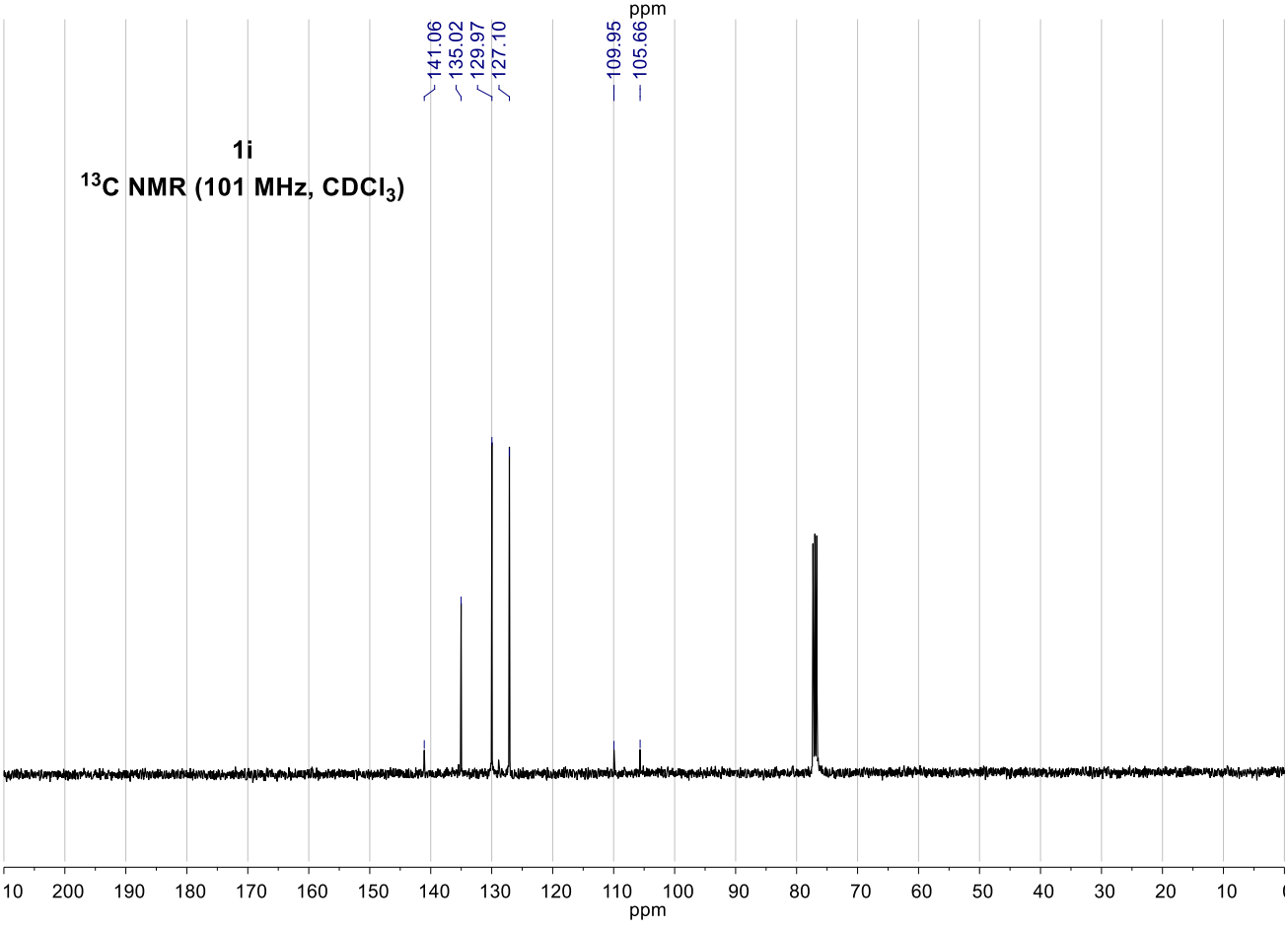
^{1}H NMR (400 MHz, $CDCl_3$)

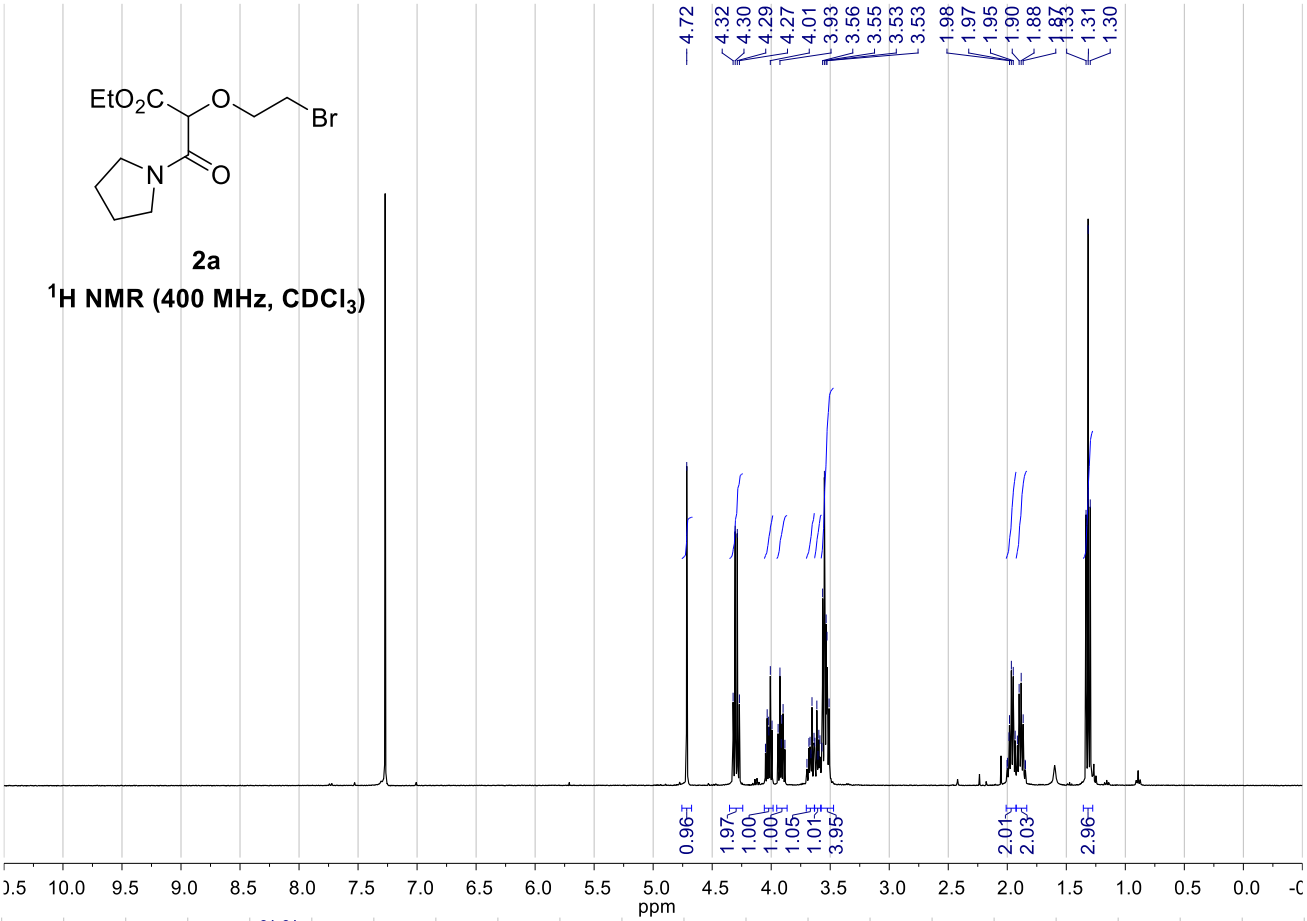


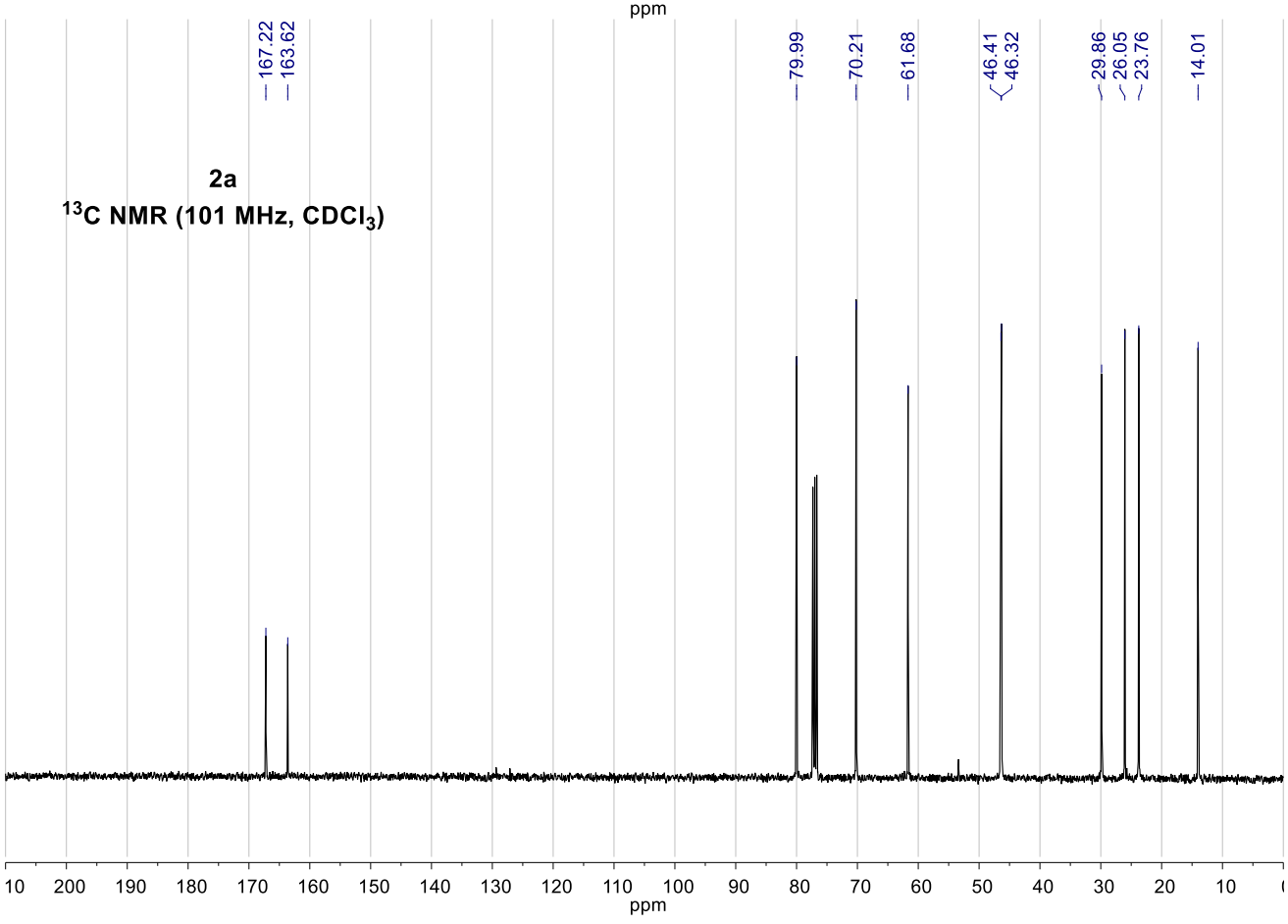
1h

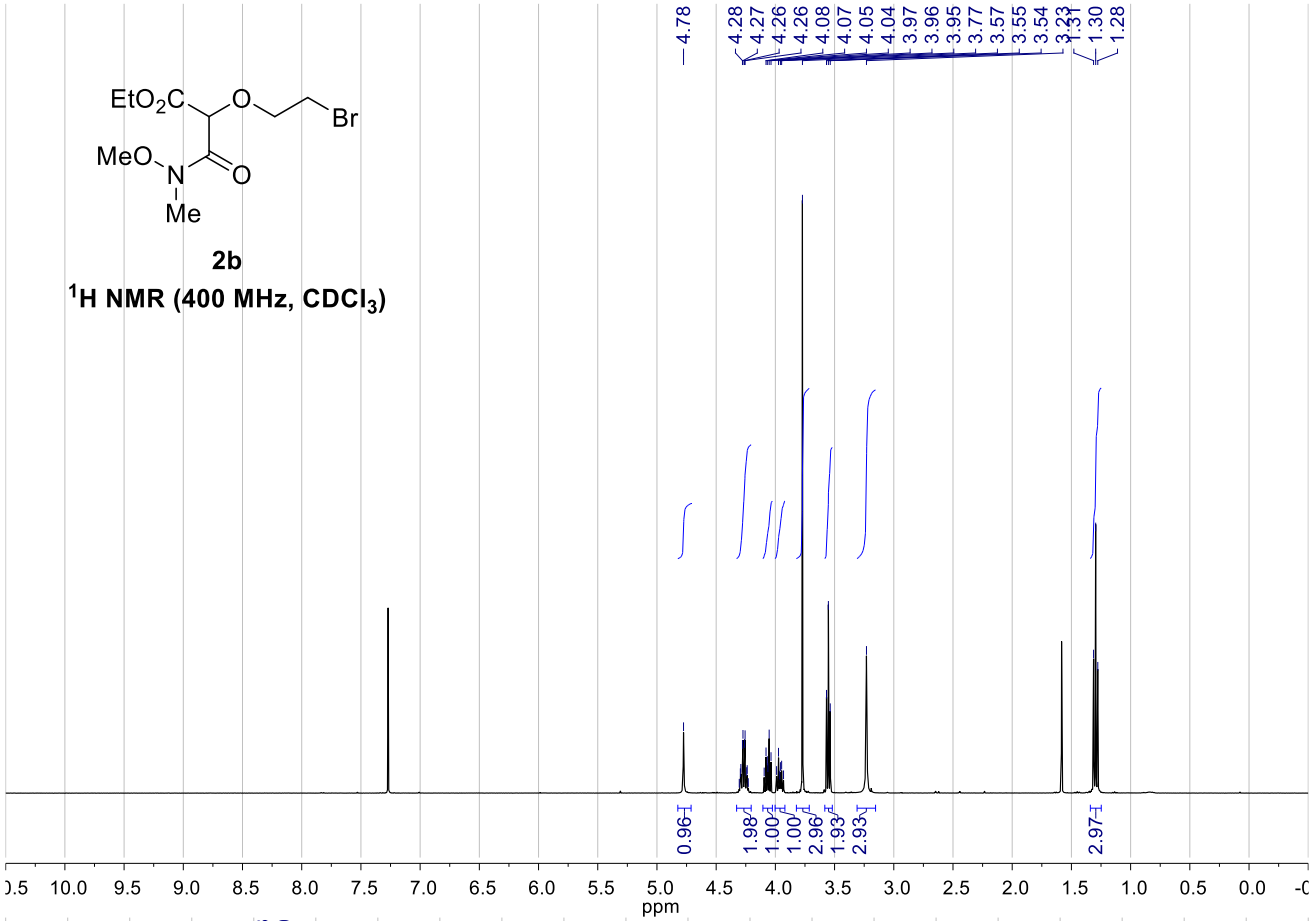
^{13}C NMR (101 MHz, $CDCl_3$)

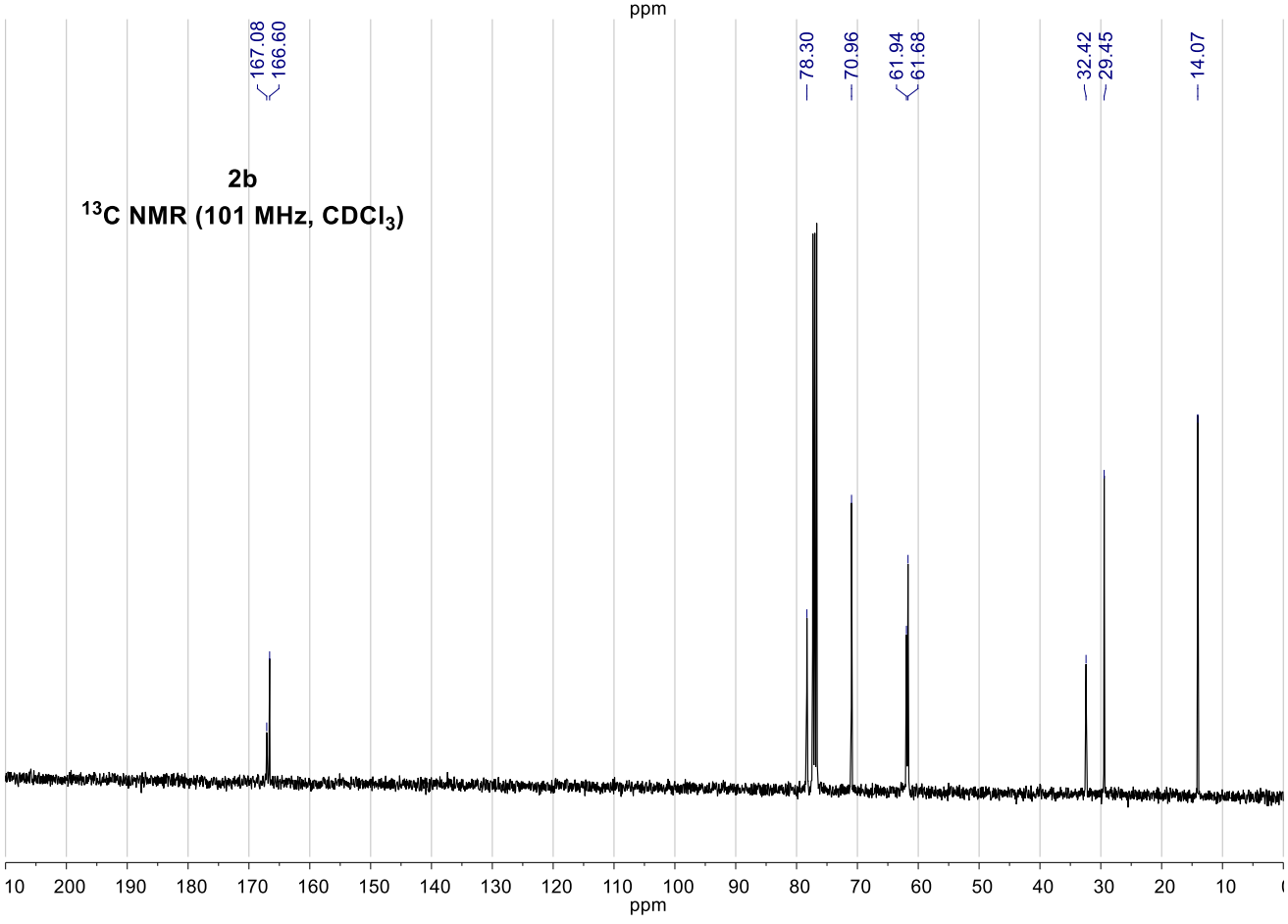

7.97
7.95
7.94
7.79
7.79
7.77
7.75
7.75
7.68
7.66
7.64
O
O
S
NC
N2
1i
1H NMR (400 MHz, CDCl3)
1.80
1.00
1.98
ppm

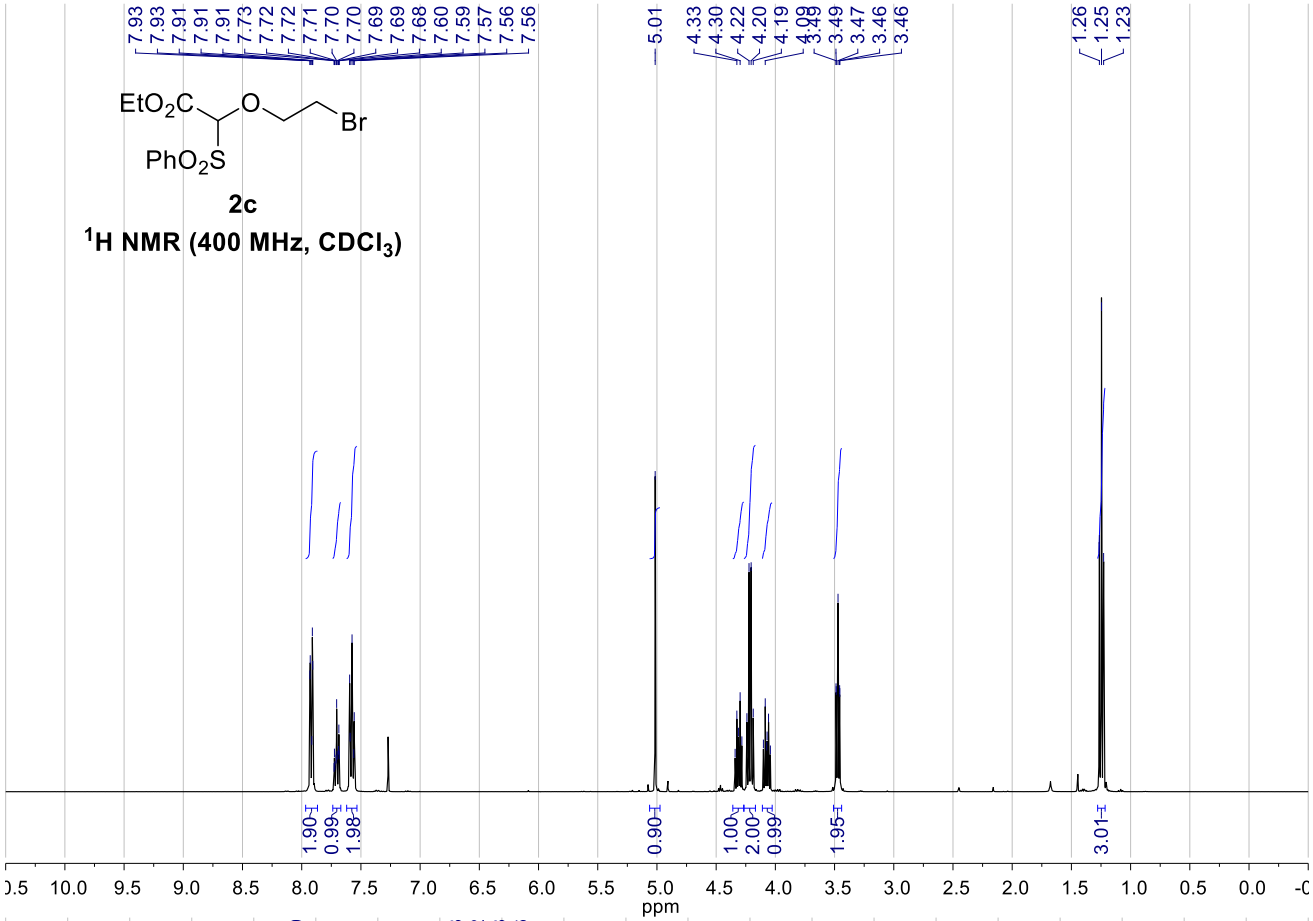

141.06
135.02
129.97
127.10
109.95
105.66
1i
13C NMR (101 MHz, CDCl3)
ppm

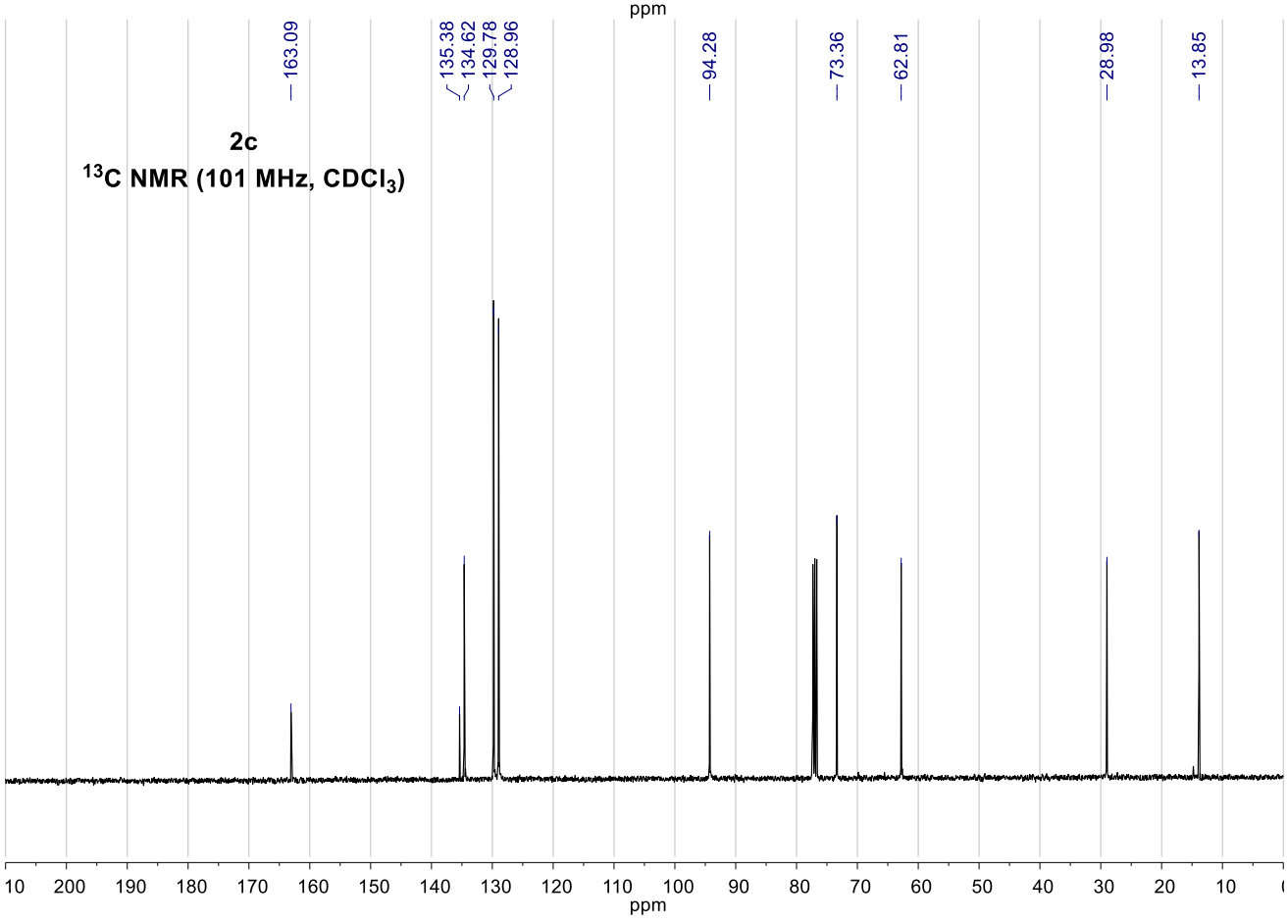

EtO2C
O
Br
N
O
2a
1H NMR (400 MHz, CDCl3)
4.72
4.32
4.30
4.29
4.27
4.01
3.93
3.56
3.55
3.53
3.53
1.98
1.97
1.95
1.90
1.88
1.31
1.30
0.96
1.97
1.00
1.00
1.05
1.01
3.95
2.01
2.03
2.96
ppm

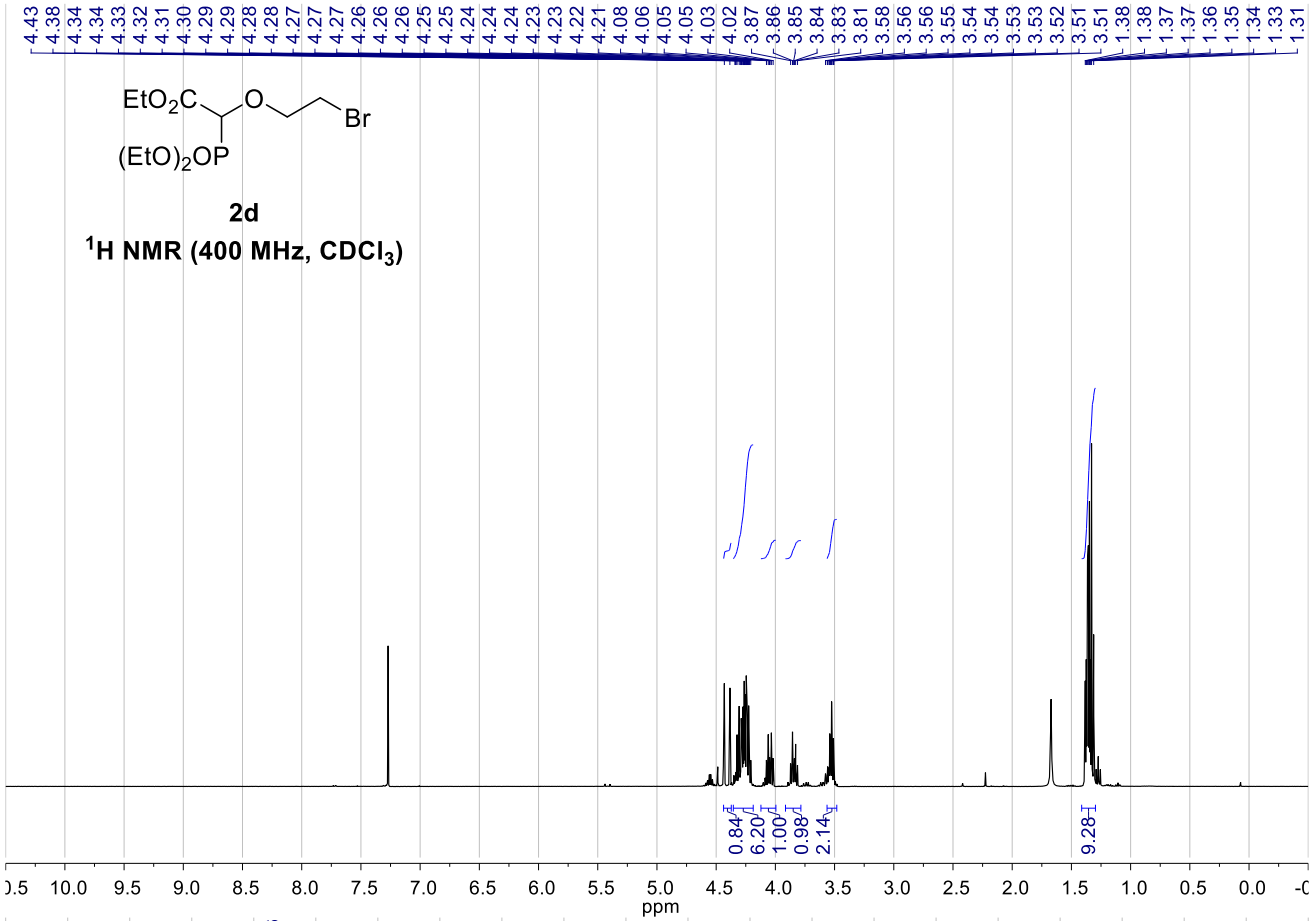

2a
13C NMR (101 MHz, CDCl3)
167.22
163.62
79.99
70.21
61.68
46.41
46.32
29.86
26.05
23.76
14.01
ppm

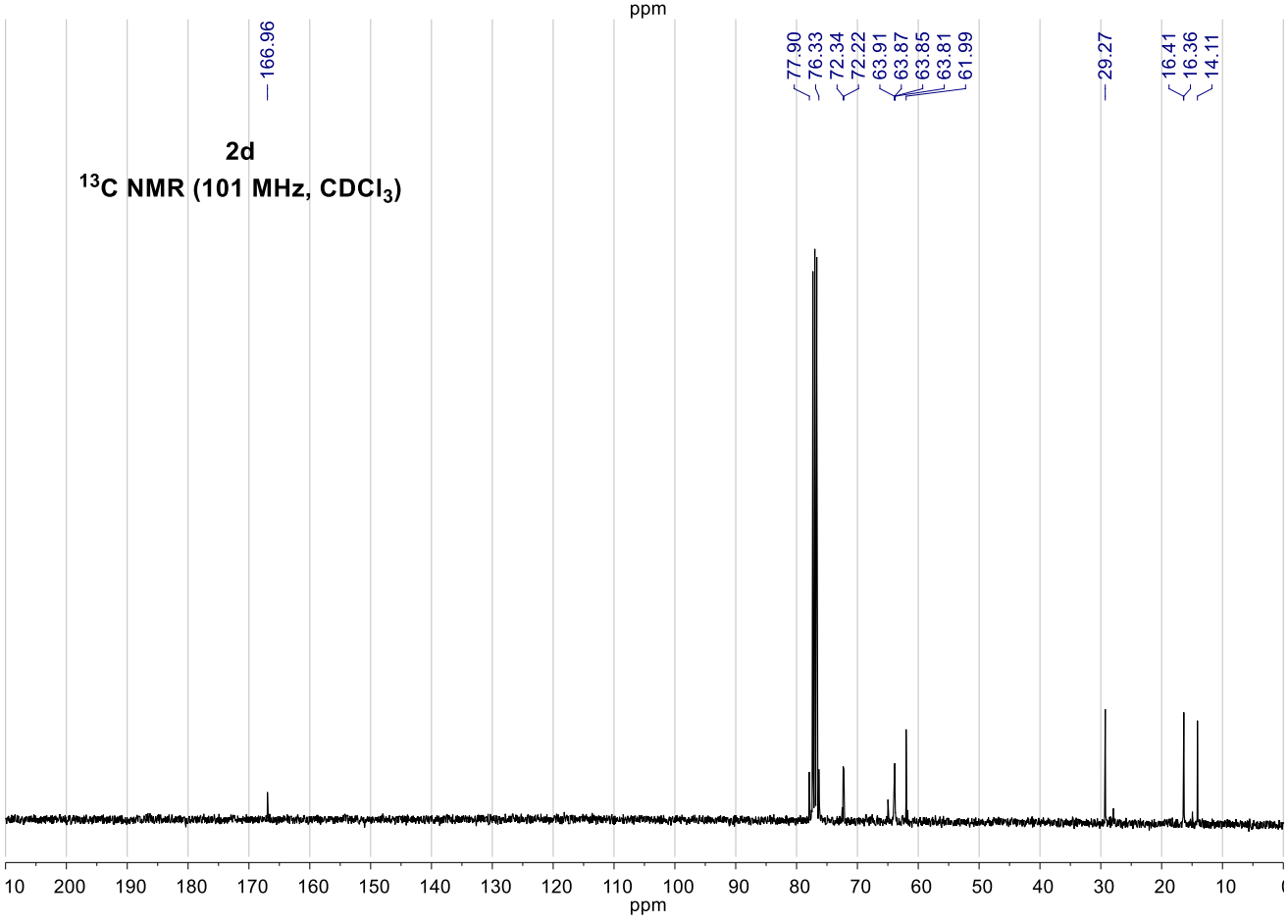

EtO2C
O
Br
MeO
N
O
Me
2b
1H NMR (400 MHz, CDCl3)
4.78
4.28
4.27
4.26
4.26
4.08
4.07
4.05
4.04
3.97
3.96
3.95
3.77
3.57
3.55
3.54
1.30
1.28
0.96
1.98
1.00
1.00
2.96
1.93
2.93
2.97
ppm

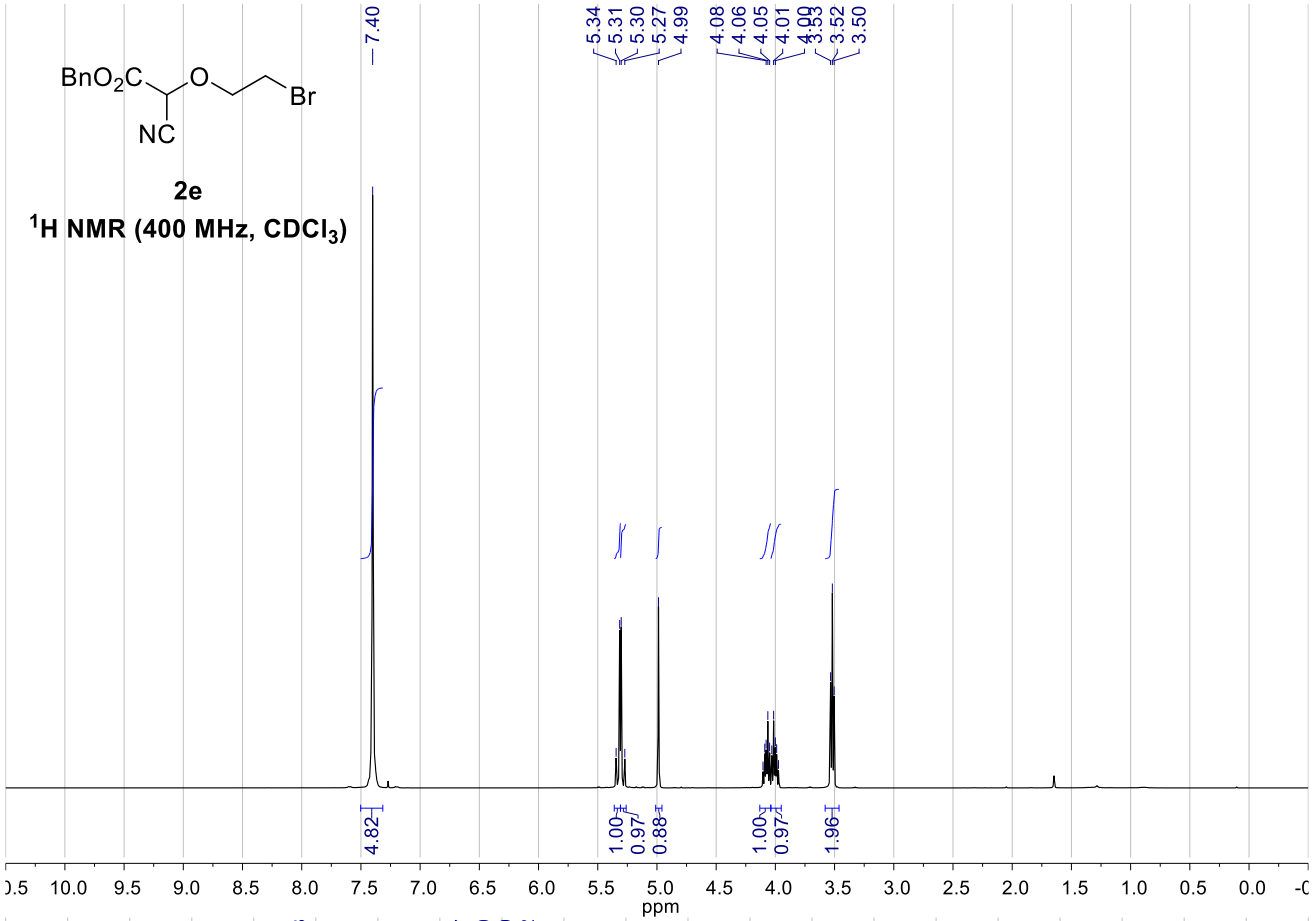

167.08
166.60
78.30
70.96
61.94
61.68
32.42
29.45
14.07
2b
13C NMR (101 MHz, CDCl3)
ppm

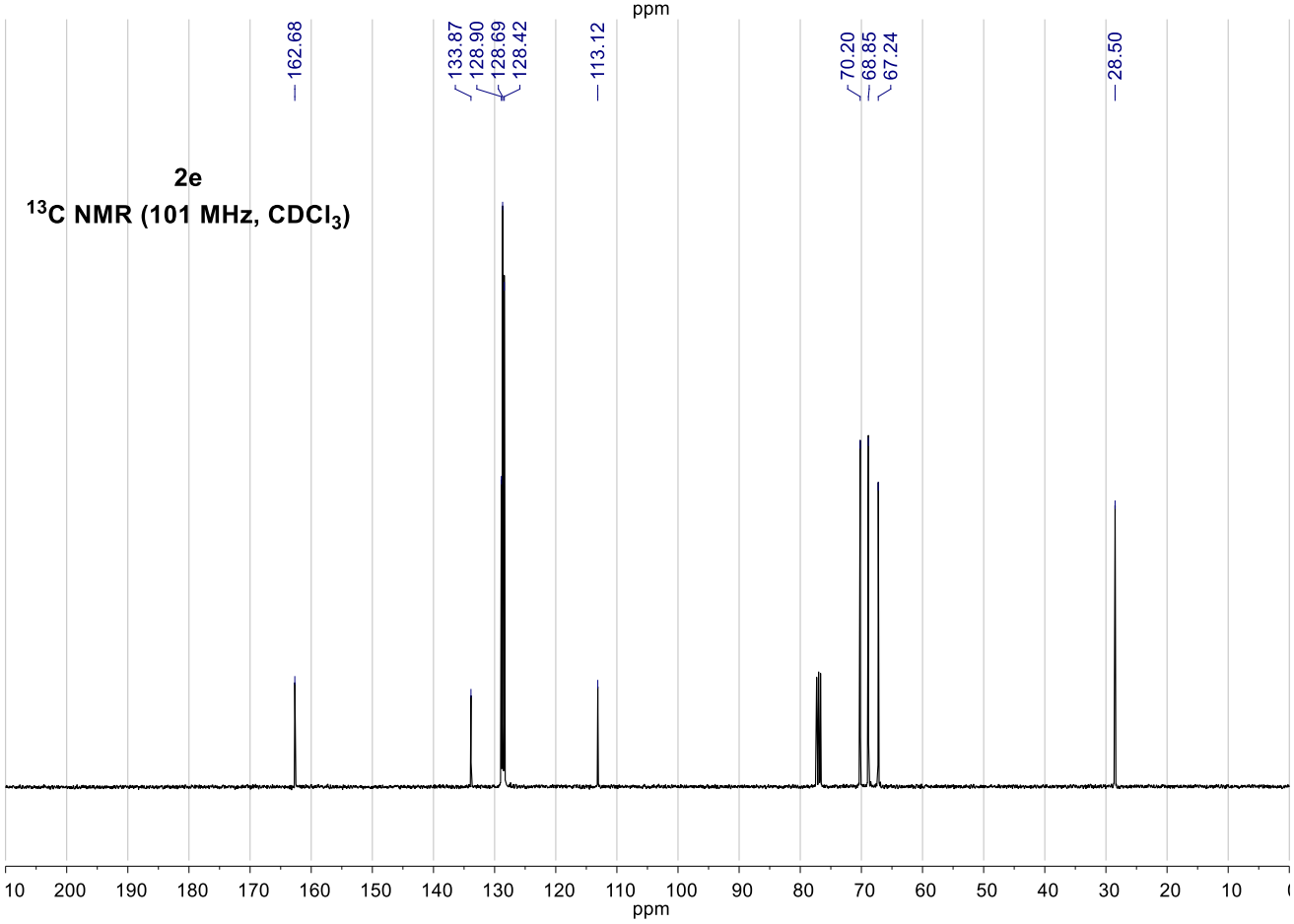

7.93
7.93
7.91
7.91
7.91
7.73
7.72
7.72
7.71
7.70
7.70
7.69
7.69
7.68
7.60
7.59
7.57
7.56
7.56
5.01
4.33
4.30
4.22
4.20
4.19
4.09
3.49
3.47
3.46
3.46
1.26
1.25
1.23
EtO2C
O
Br
PhO2S
2c
1H NMR (400 MHz, CDCl3)
1.90
0.99
1.98
0.90
1.00
2.00
0.99
1.95
3.01
ppm

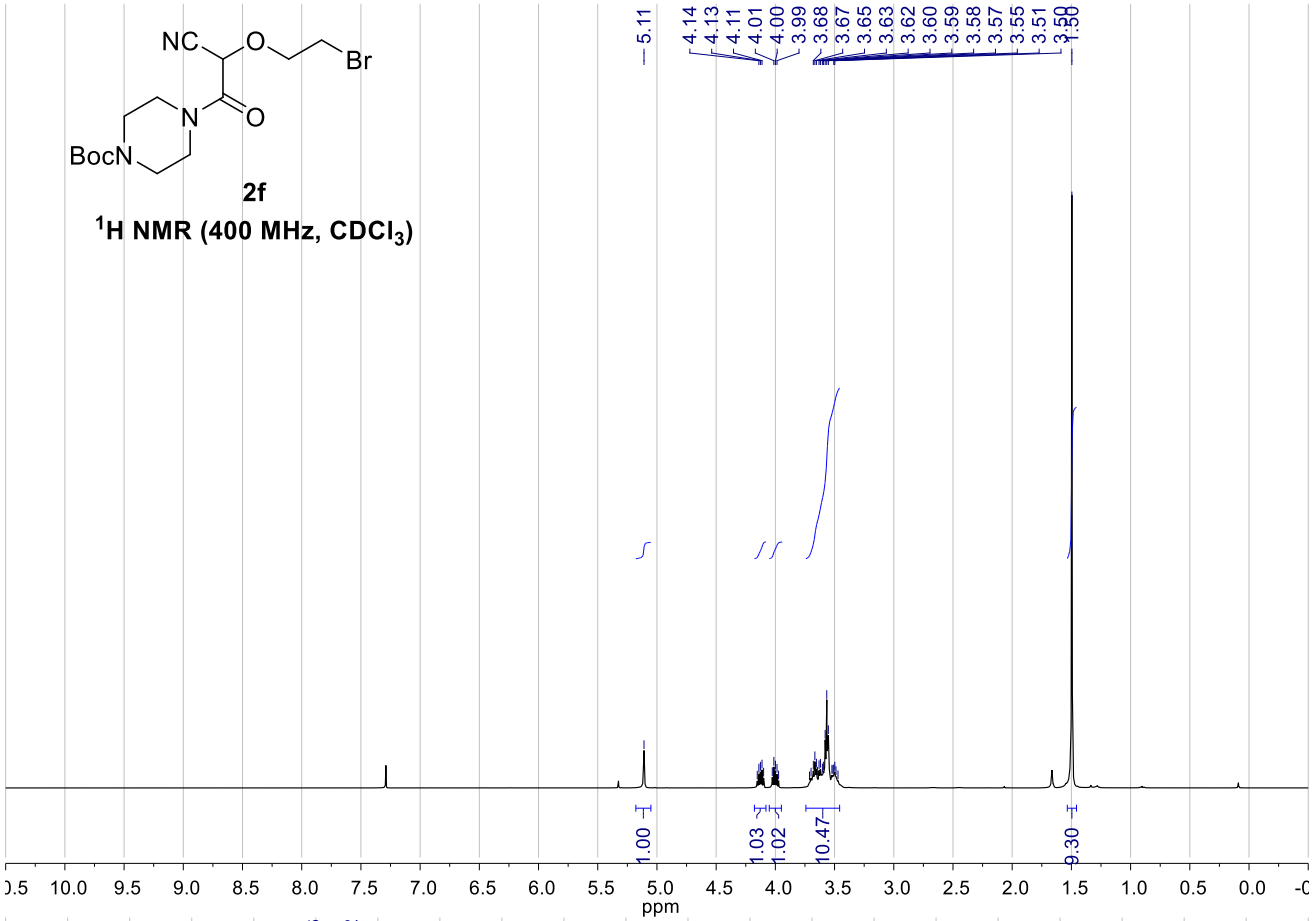

163.09
135.38
134.62
129.78
128.96
94.28
73.36
62.81
28.98
13.85
2c
13C NMR (101 MHz, CDCl3)
ppm

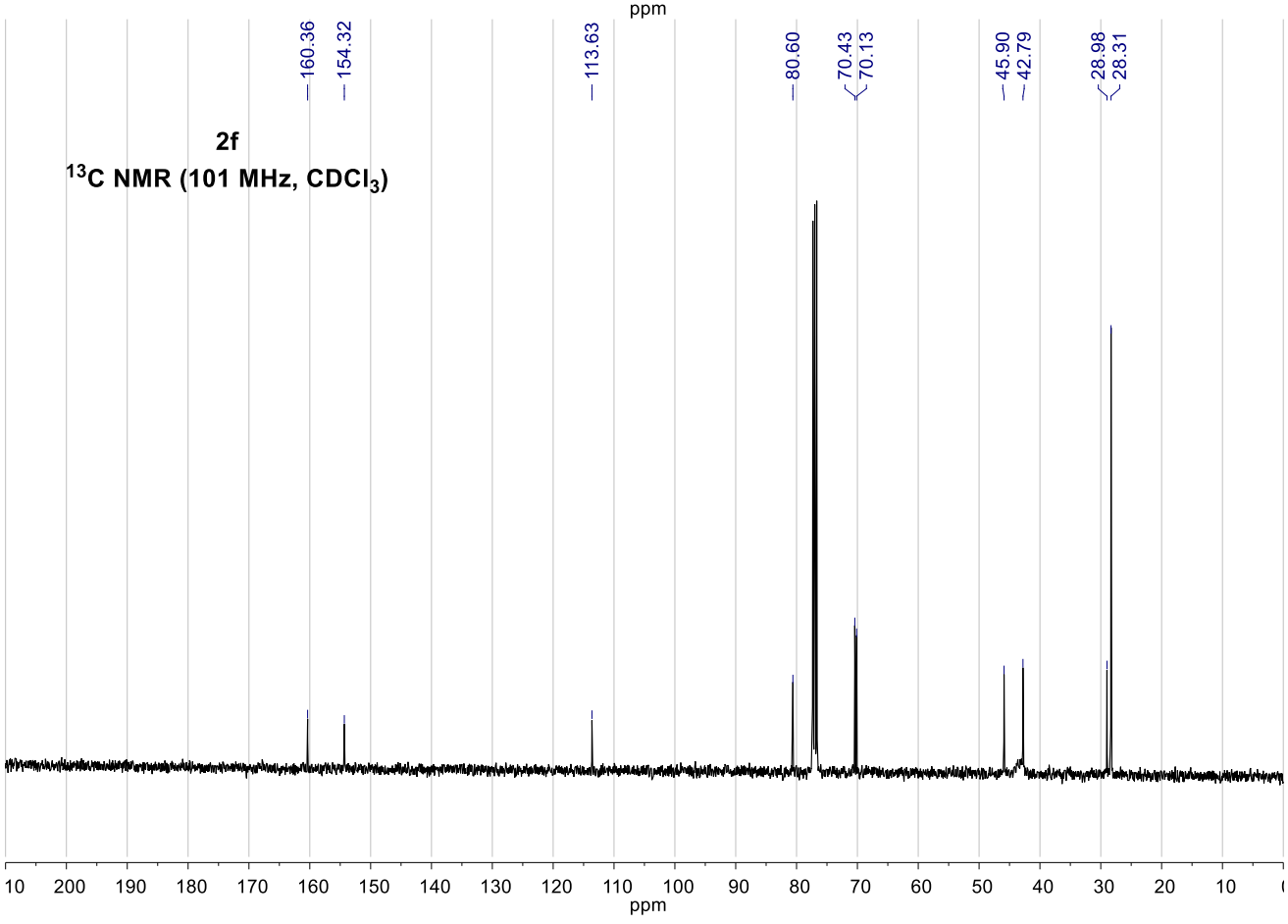

EtO2C
O
Br
(EtO)2OP
2d
1H NMR (400 MHz, CDCl3)
ppm

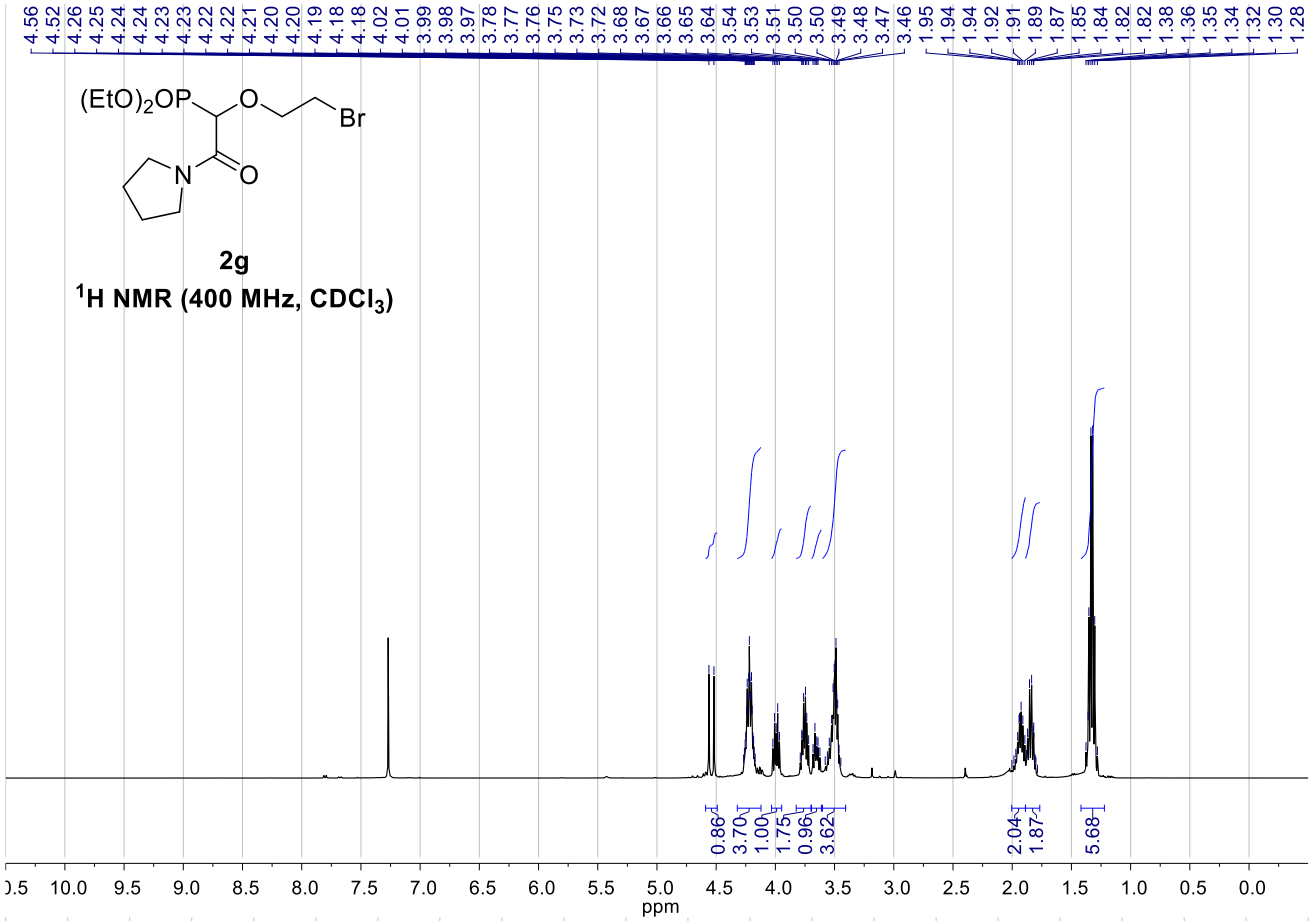

2d
13C NMR (101 MHz, CDCl3)
ppm

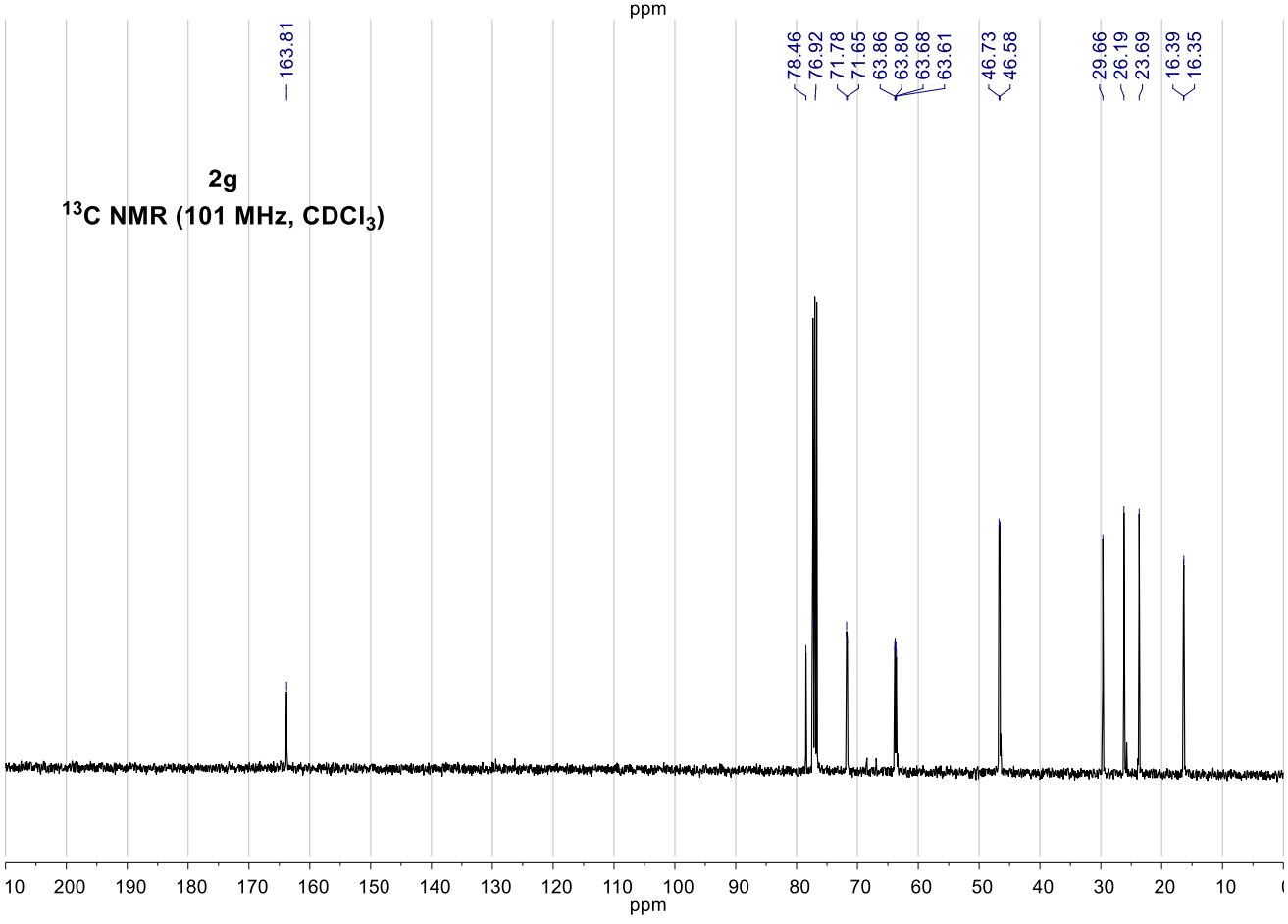

BnO2C
O
Br
NC
2e
1H NMR (400 MHz, CDCl3)
7.40
5.34
5.31
5.30
5.27
4.99
4.08
4.06
4.05
4.01
4.00
3.53
3.52
3.50
4.82
1.00
0.97
0.88
1.00
0.97
1.96
ppm

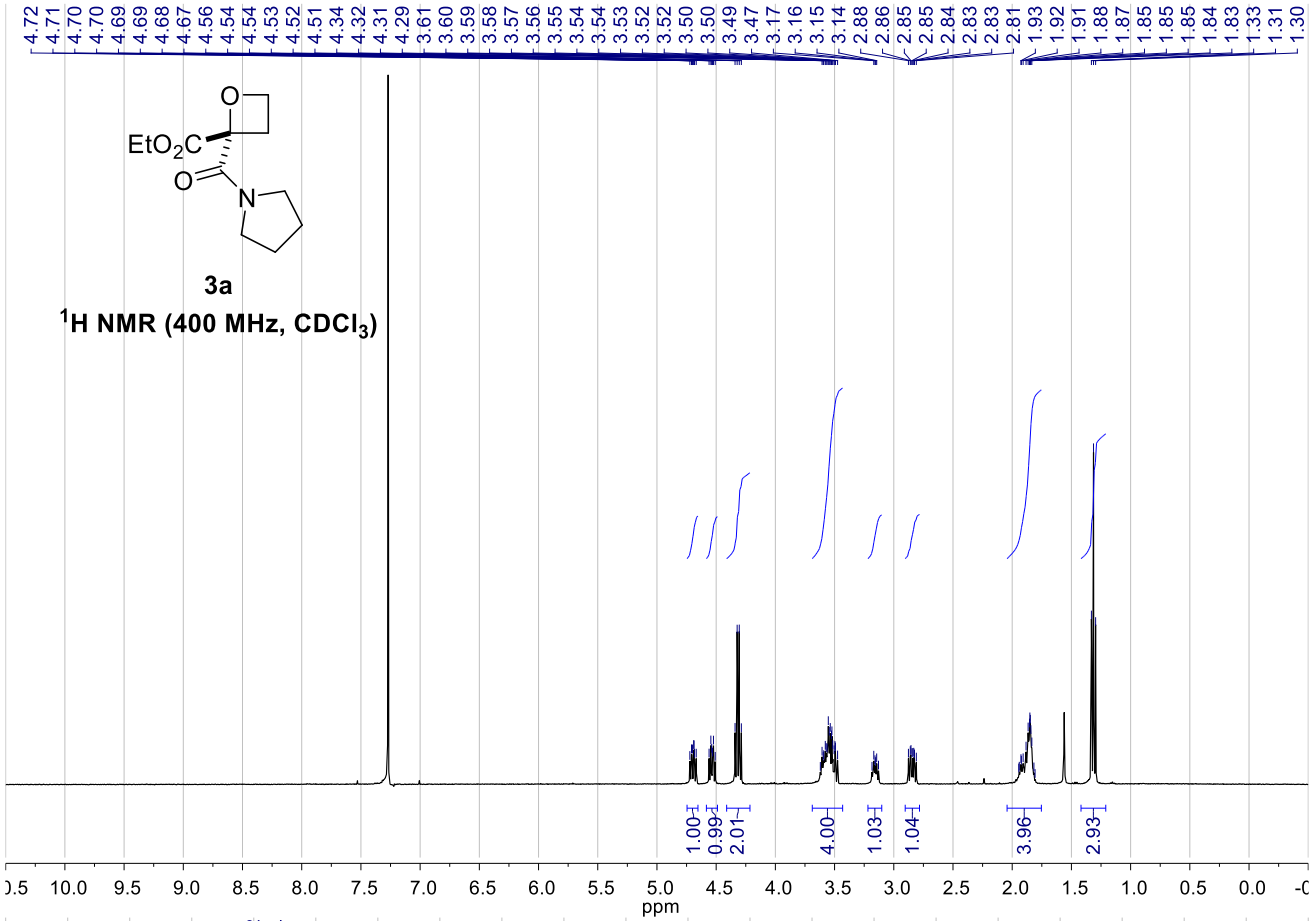

162.68
133.87
128.90
128.69
128.42
113.12
70.20
68.85
67.24
28.50
2e
13C NMR (101 MHz, CDCl3)
ppm

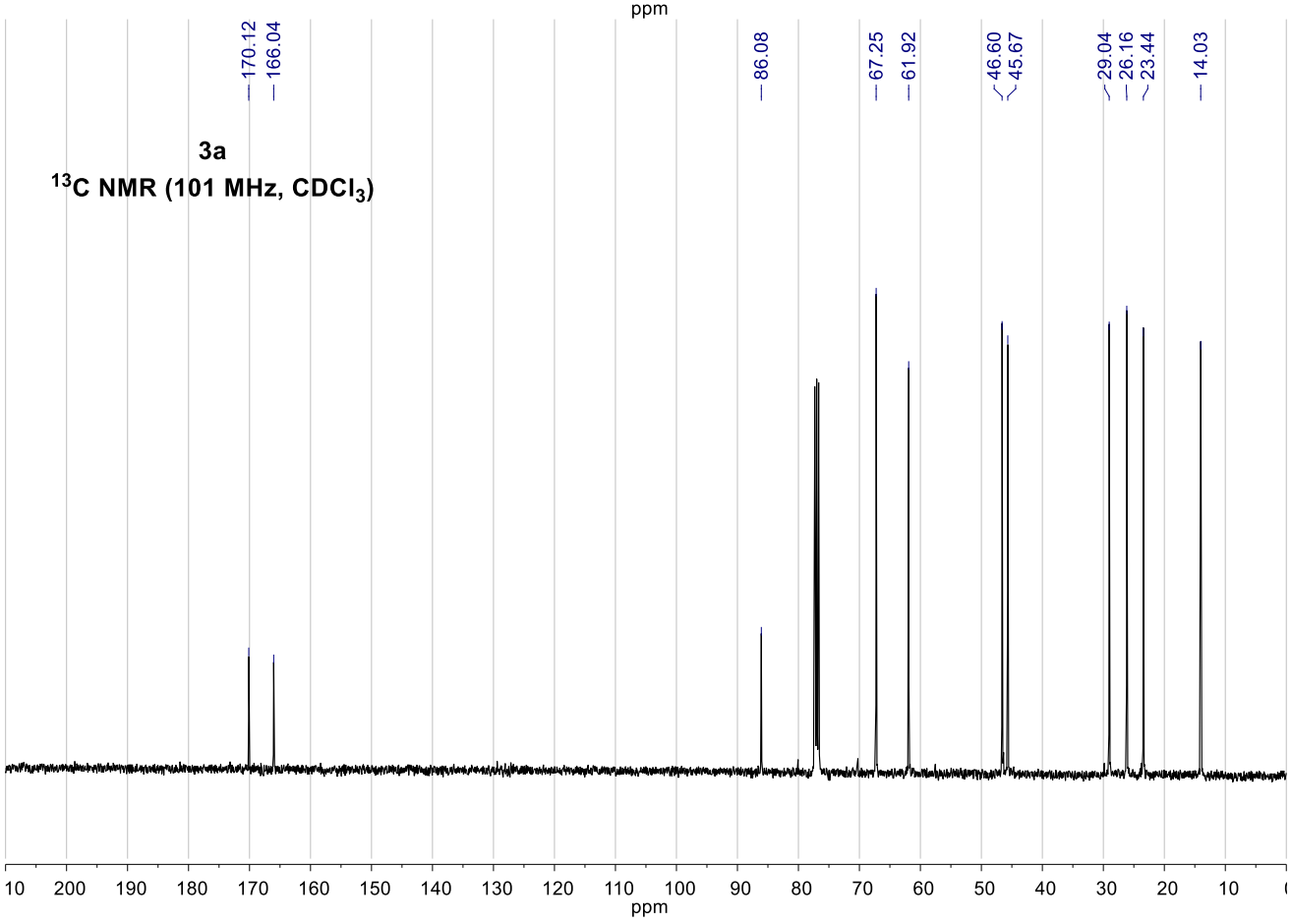

NC
O
Br
N
O
BocN
2f
^{1}H NMR (400 MHz, CDCl$_3$)
5.11
4.14
4.13
4.11
4.01
4.00
3.99
3.68
3.67
3.65
3.63
3.62
3.60
3.59
3.58
3.57
3.55
3.51
3.50
1.50
1.00
1.03
1.02
10.47
9.30
ppm

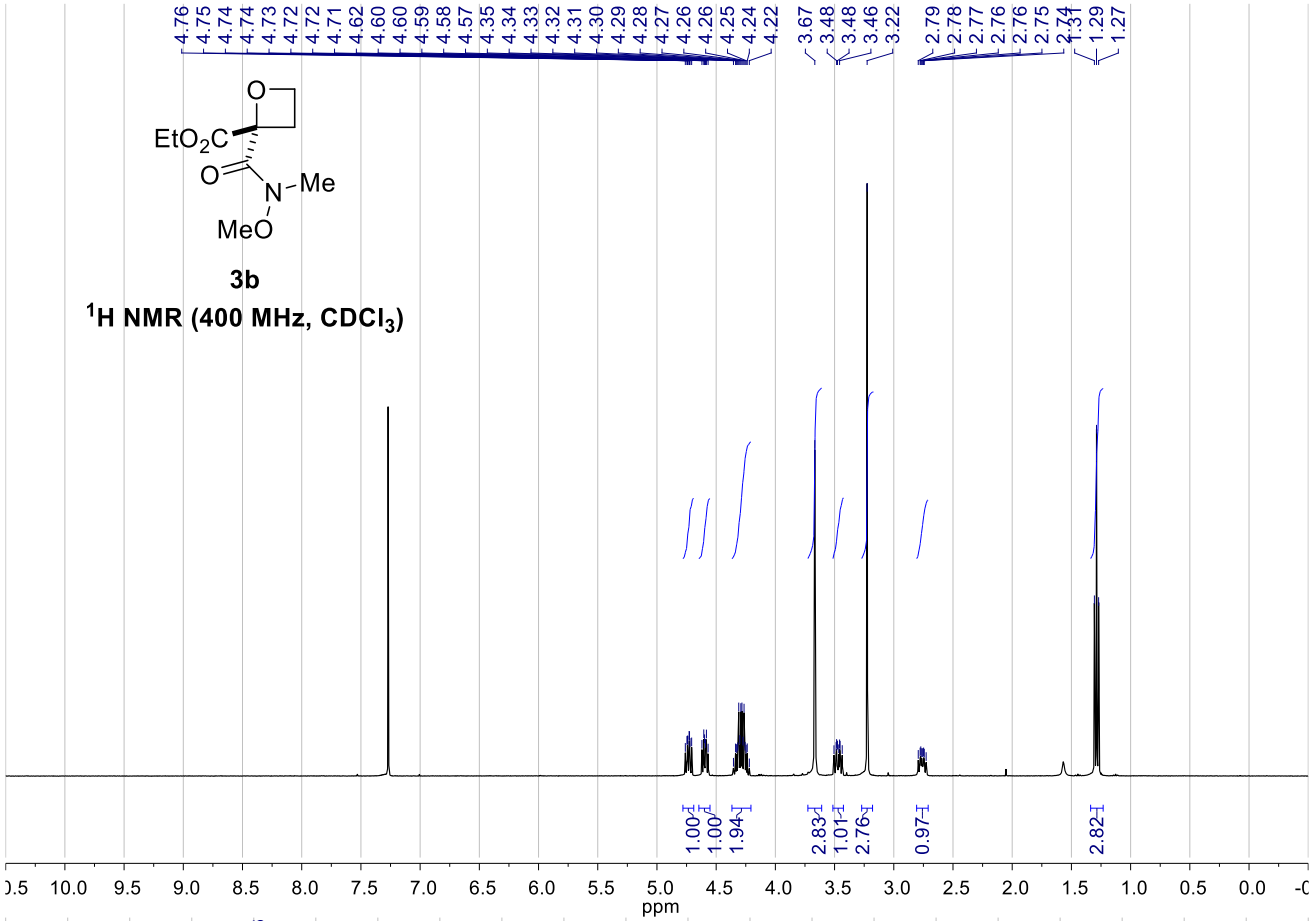

2f
^{13}C NMR (101 MHz, CDCl$_3$)
160.36
154.32
113.63
80.60
70.43
70.13
45.90
42.79
28.98
28.31
ppm

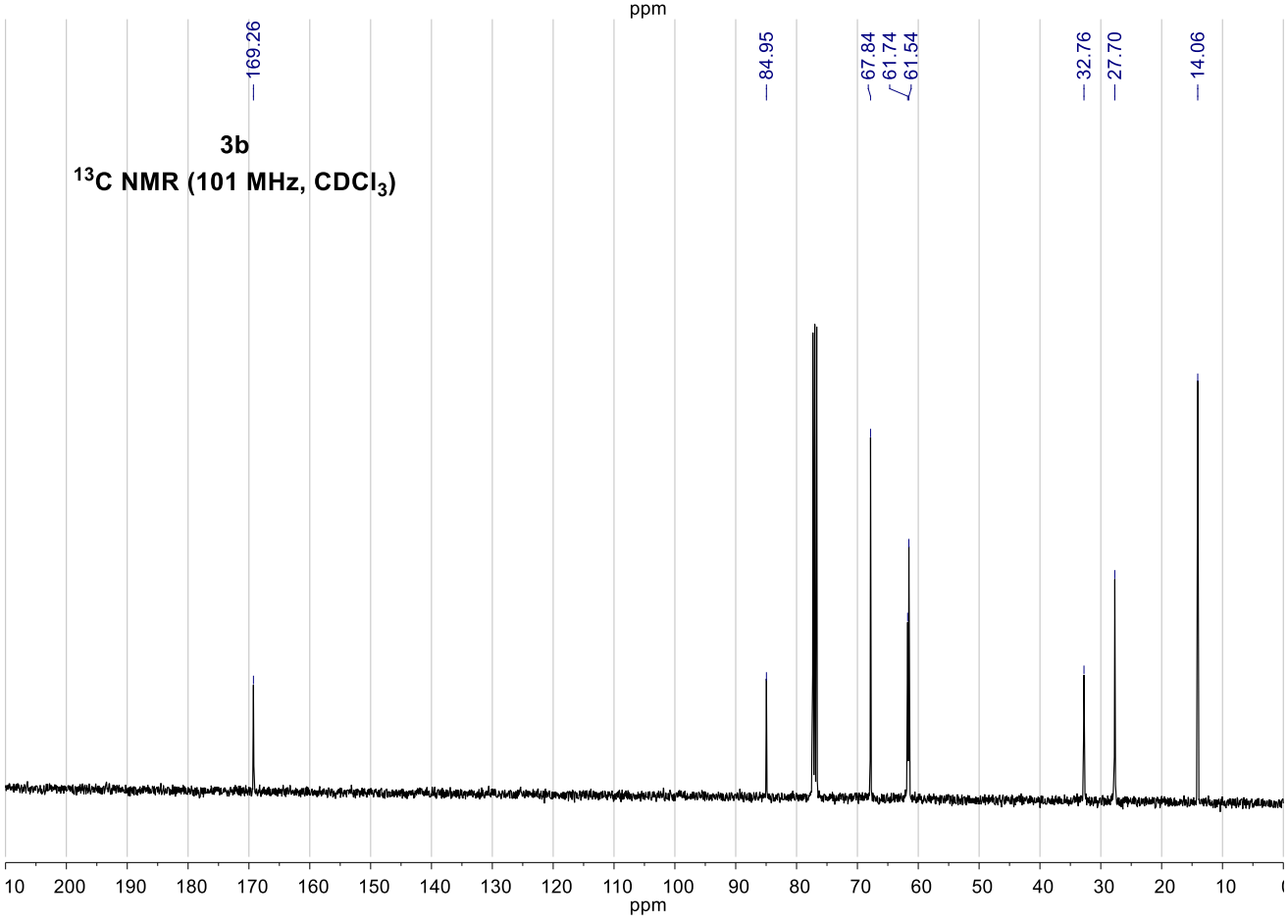

4.56 4.52 4.26 4.25 4.24 4.24 4.23 4.23 4.22 4.22 4.21 4.20 4.20 4.19 4.18 4.18 4.02 4.01 3.99 3.98 3.97 3.78 3.77 3.76 3.75 3.73 3.72 3.68 3.67 3.66 3.65 3.64 3.54 3.53 3.51 3.50 3.50 3.49 3.48 3.47 3.46 1.95 1.94 1.94 1.92 1.91 1.89 1.87 1.85 1.84 1.82 1.82 1.38 1.36 1.35 1.34 1.32 1.30 1.28
(EtO)2OP
O
Br
N
O
2g
1H NMR (400 MHz, CDCl3)
0.86 3.70 1.00 1.75 0.96 3.62 2.04 1.87 5.68
ppm

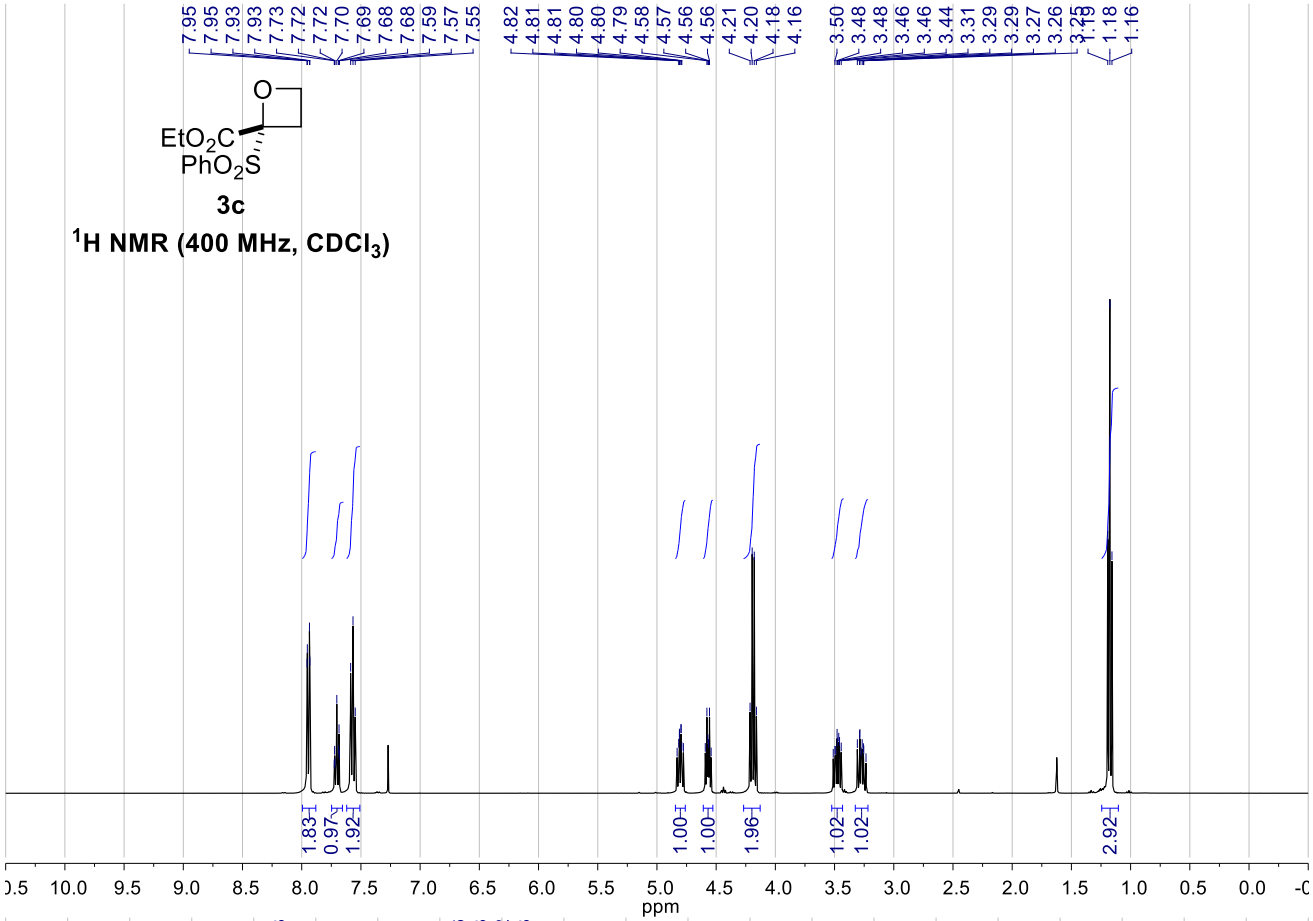

163.81
78.46 76.92 71.78 71.65 63.86 63.80 63.68 63.61 46.73 46.58 29.66 26.19 23.69 16.39 16.35
2g
13C NMR (101 MHz, CDCl3)
ppm

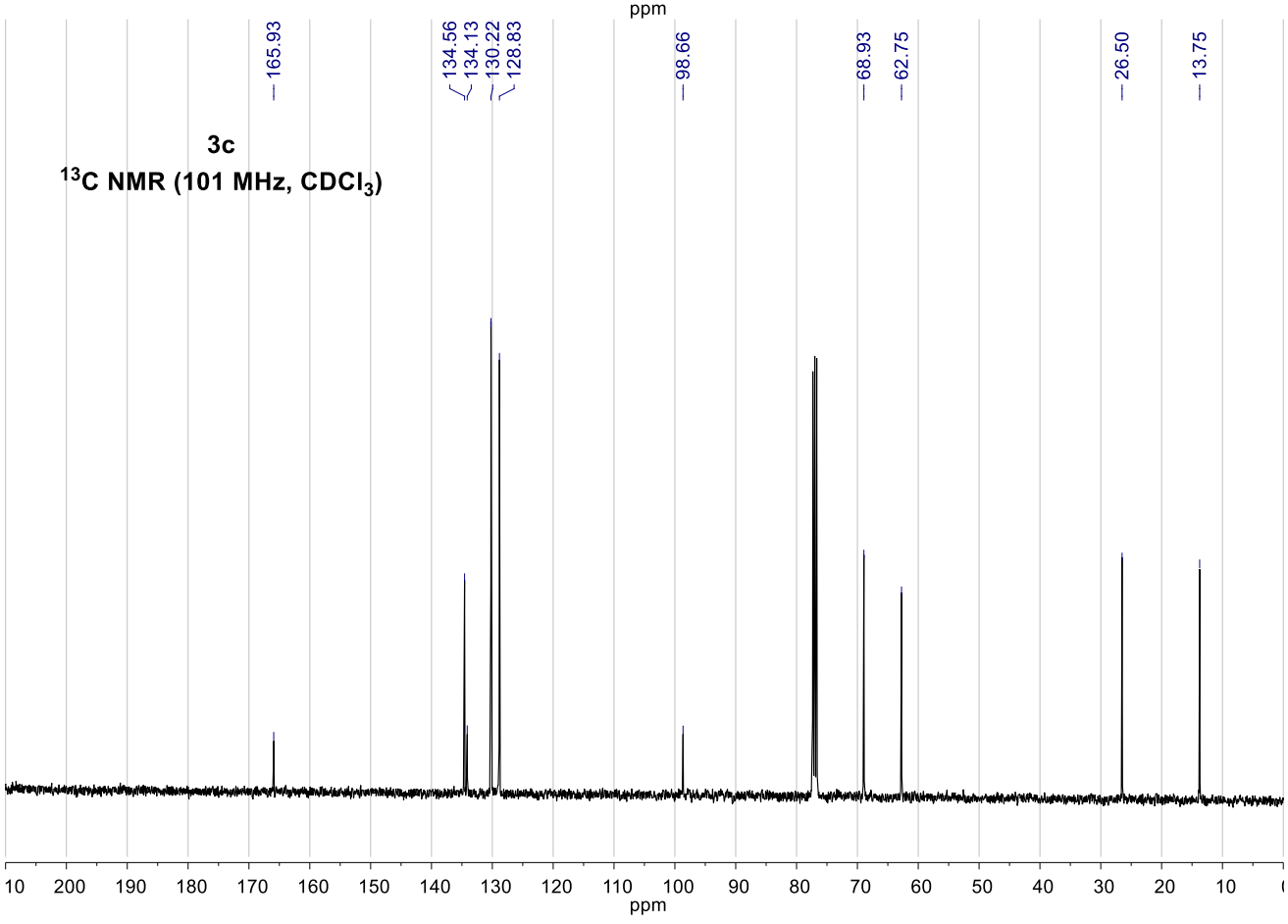

4.72 4.71 4.70 4.70 4.69 4.69 4.68 4.67 4.56 4.54 4.54 4.53 4.52 4.51 4.34 4.32 4.31 4.29 3.61 3.60 3.59 3.58 3.57 3.56 3.55 3.54 3.54 3.53 3.52 3.52 3.50 3.50 3.49 3.47 3.17 3.16 3.15 3.14 2.88 2.86 2.85 2.85 2.84 2.83 2.83 2.81 1.93 1.92 1.91 1.88 1.87 1.85 1.85 1.85 1.84 1.83 1.33 1.31 1.30
O
EtO2C
O
N
3a
1H NMR (400 MHz, CDCl3)
1.00 0.99 2.01 4.00 1.03 1.04 3.96 2.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

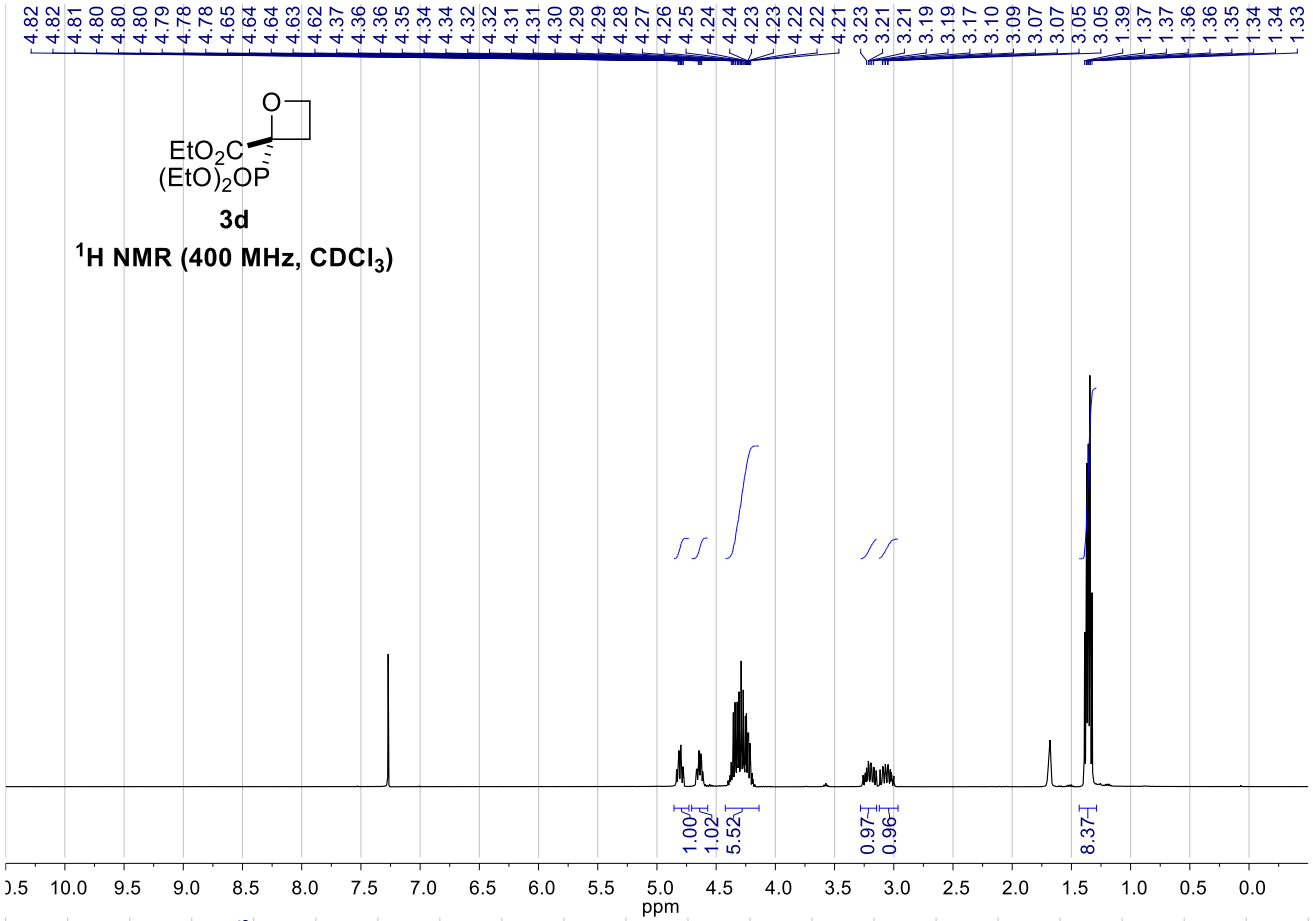

170.12
166.04
86.08
67.25
61.92
46.60
45.67
29.04
26.16
23.44
14.03
3a
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

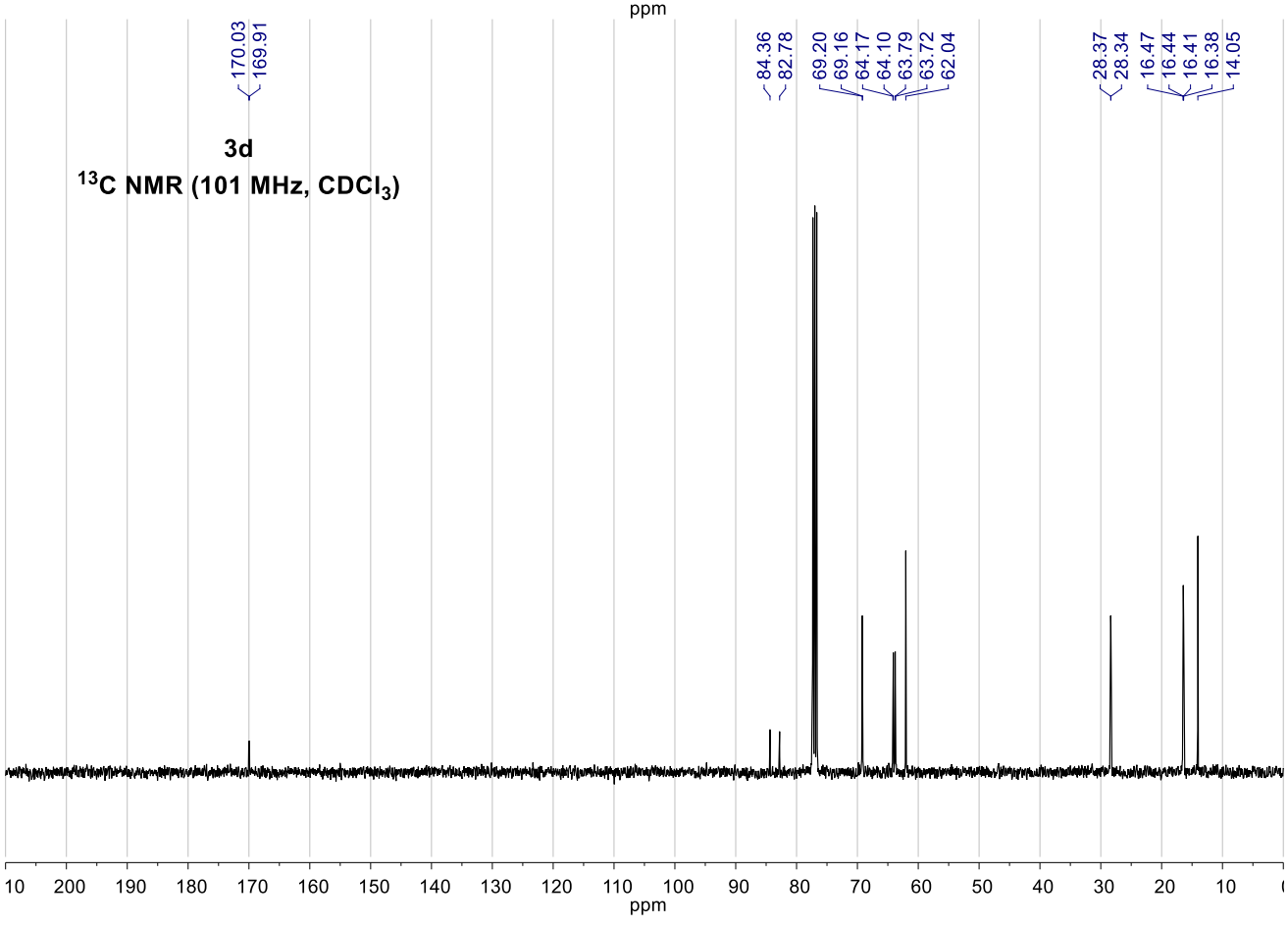

4.76 4.75 4.74 4.74 4.73 4.72 4.72 4.71 4.62 4.60 4.60 4.59 4.58 4.57 4.35 4.34 4.33 4.32 4.31 4.30 4.29 4.28 4.27 4.26 4.26 4.25 4.24 4.22
3.67 3.48 3.48 3.46 3.22
2.79 2.78 2.77 2.76 2.76 2.75 2.74 1.31 1.29 1.27
EtO2C
O
N
Me
MeO
3b
1H NMR (400 MHz, CDCl3)
1.00 1.00 1.94 2.83 1.01 2.76 0.97 2.82
ppm

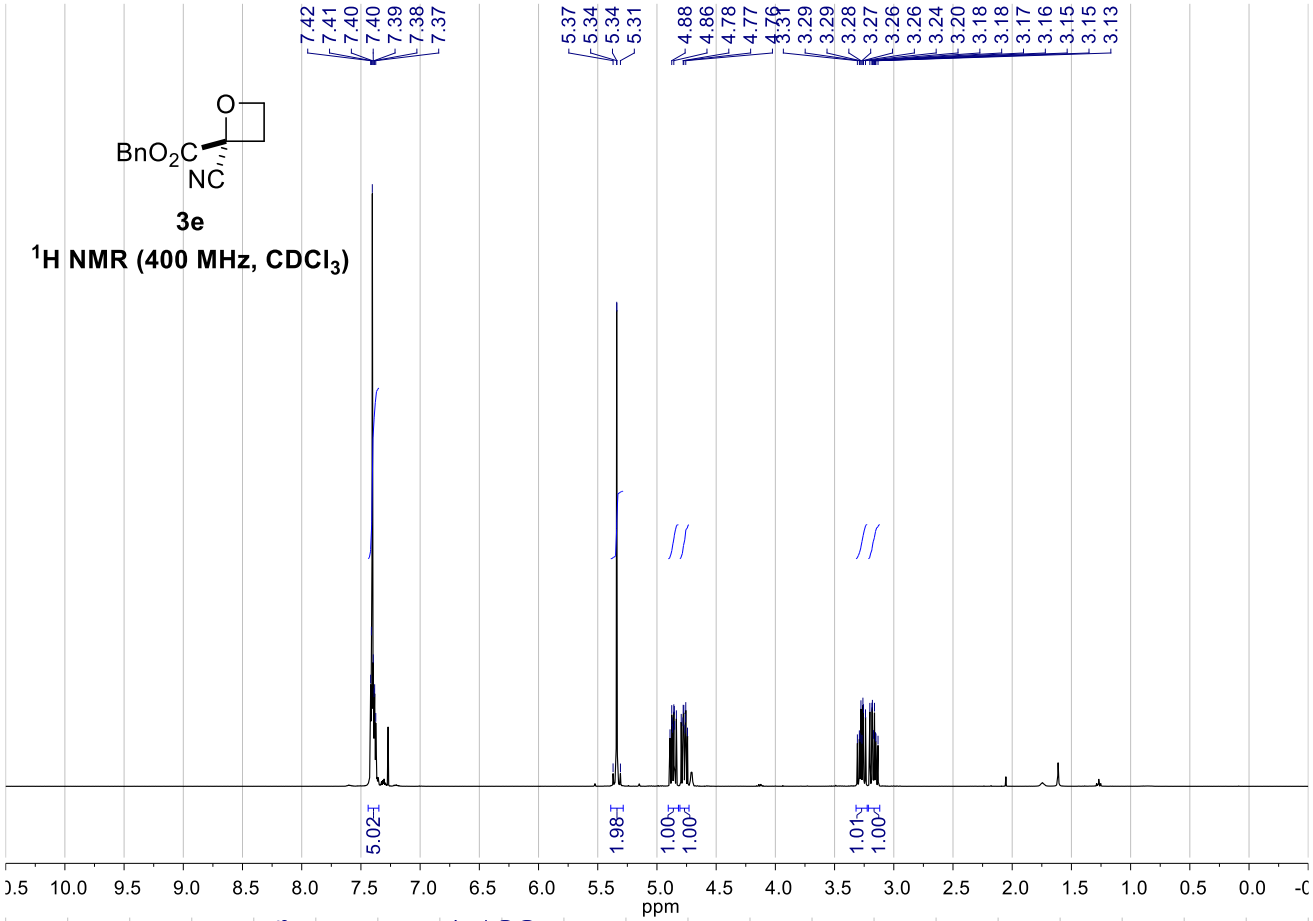

169.26
84.95
67.84
61.74
61.54
32.76
27.70
14.06
3b
13C NMR (101 MHz, CDCl3)
ppm

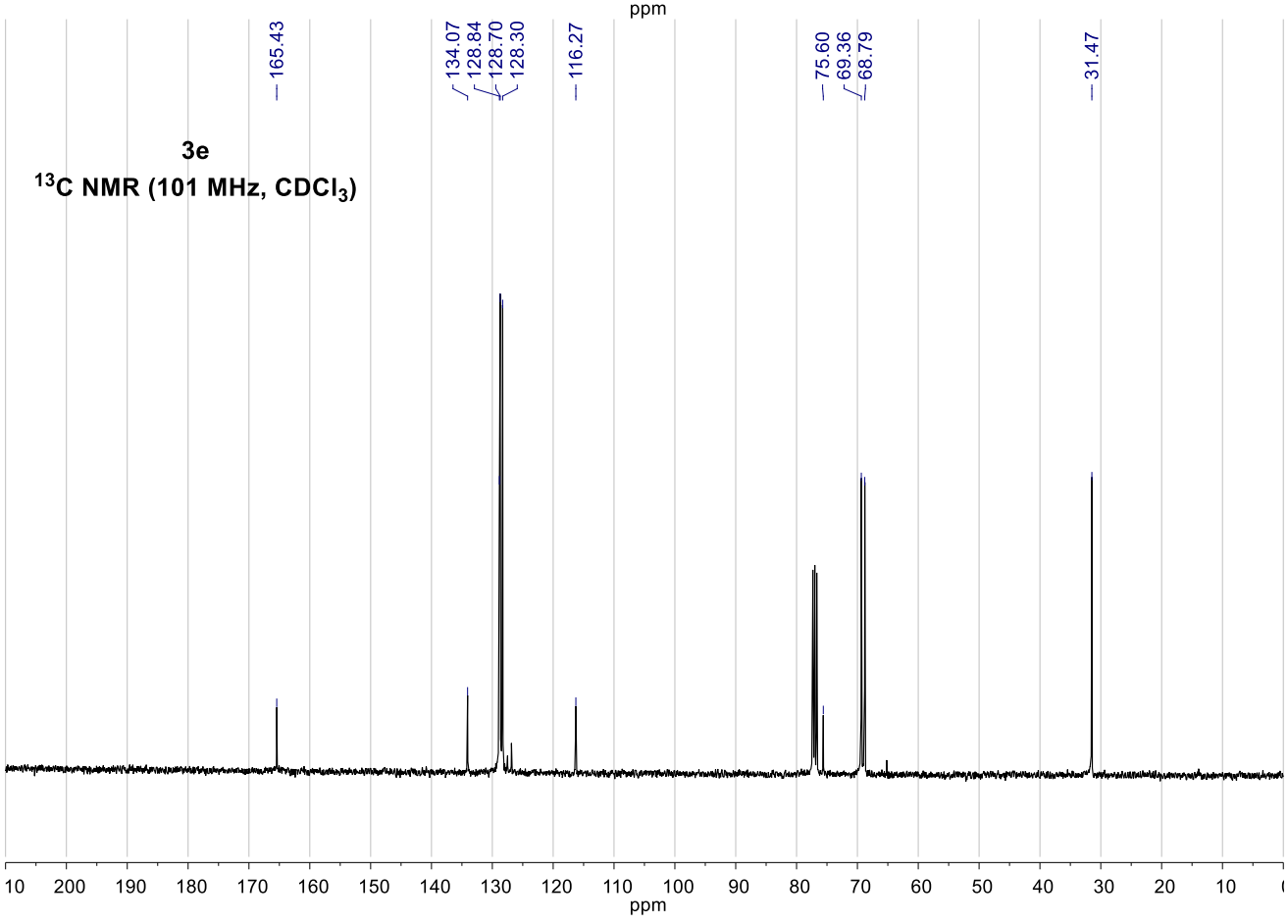

7.95 7.95 7.93 7.93 7.73 7.72 7.72 7.70 7.69 7.68 7.68 7.59 7.57 7.55
4.82 4.81 4.81 4.80 4.80 4.79 4.58 4.57 4.56 4.56
4.21 4.20 4.18 4.16
3.50 3.48 3.48 3.46 3.46 3.44 3.31 3.29 3.29 3.27 3.26 3.25 3.19
1.18 1.16
O
EtO2C
PhO2S
3c
1H NMR (400 MHz, CDCl3)
1.83 0.97 1.92 1.00 1.00 1.96 1.02 1.02 2.92
ppm

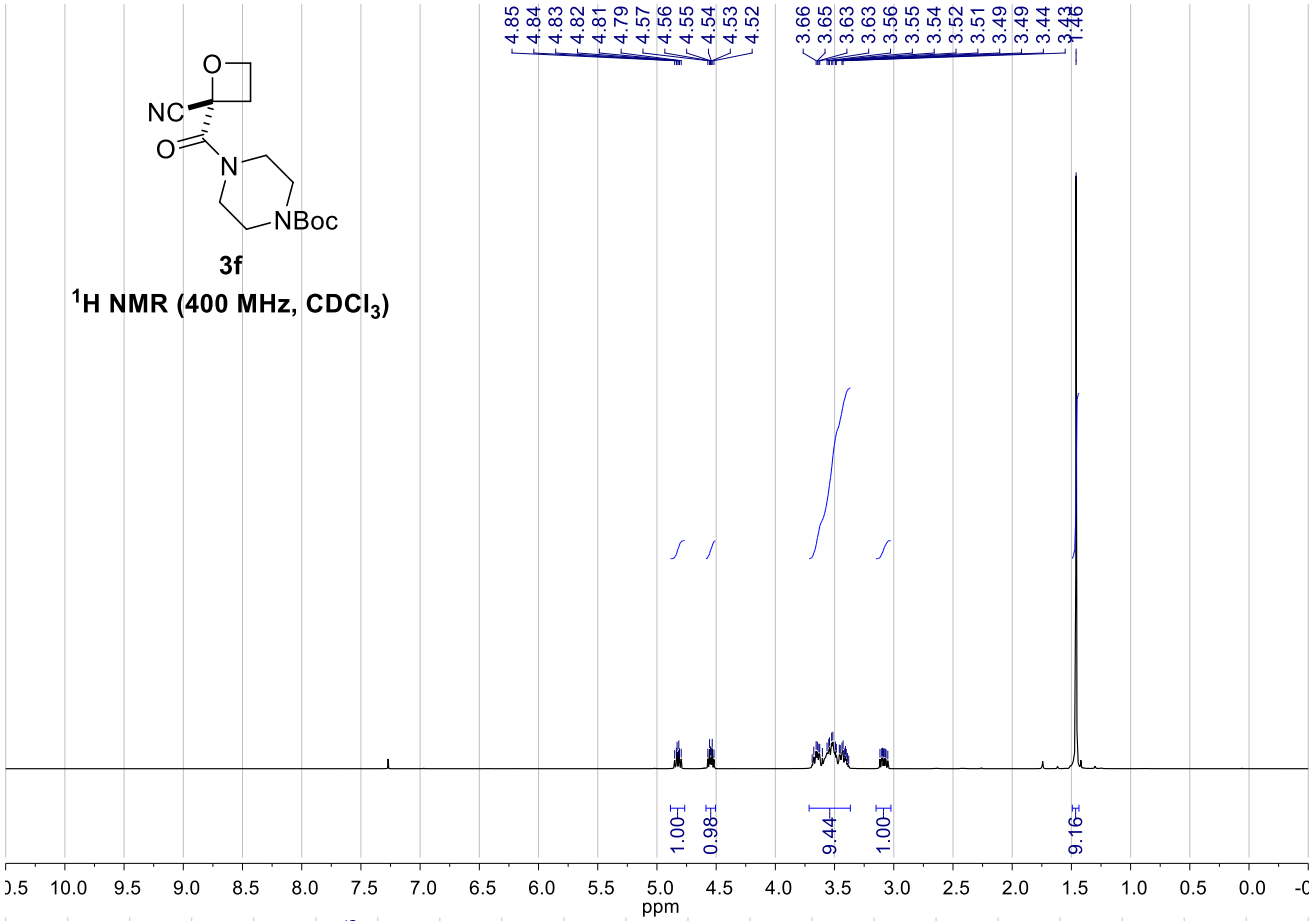

165.93
134.56 134.13 130.22 128.83
98.66
68.93 62.75
26.50
13.75
3c
13C NMR (101 MHz, CDCl3)
ppm


4.82 4.82 4.81 4.80 4.80 4.80 4.79 4.78 4.78 4.65 4.64 4.64 4.63 4.62 4.37 4.36 4.36 4.35 4.34 4.34 4.32 4.32 4.31 4.31 4.30 4.29 4.29 4.28 4.27 4.26 4.25 4.24 4.24 4.23 4.23 4.22 4.22 4.21 3.23 3.21 3.21 3.19 3.19 3.17 3.10 3.09 3.07 3.07 3.05 3.05 1.39 1.37 1.37 1.36 1.36 1.35 1.34 1.34 1.33
O
EtO2C
(EtO)2OP
3d
1H NMR (400 MHz, CDCl3)
1.00
1.02
5.52
0.97
0.96
8.37
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


170.03
169.91
84.36
82.78
69.20
69.16
64.17
64.10
63.79
63.72
62.04
28.37
28.34
16.47
16.44
16.41
16.38
14.05
3d
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

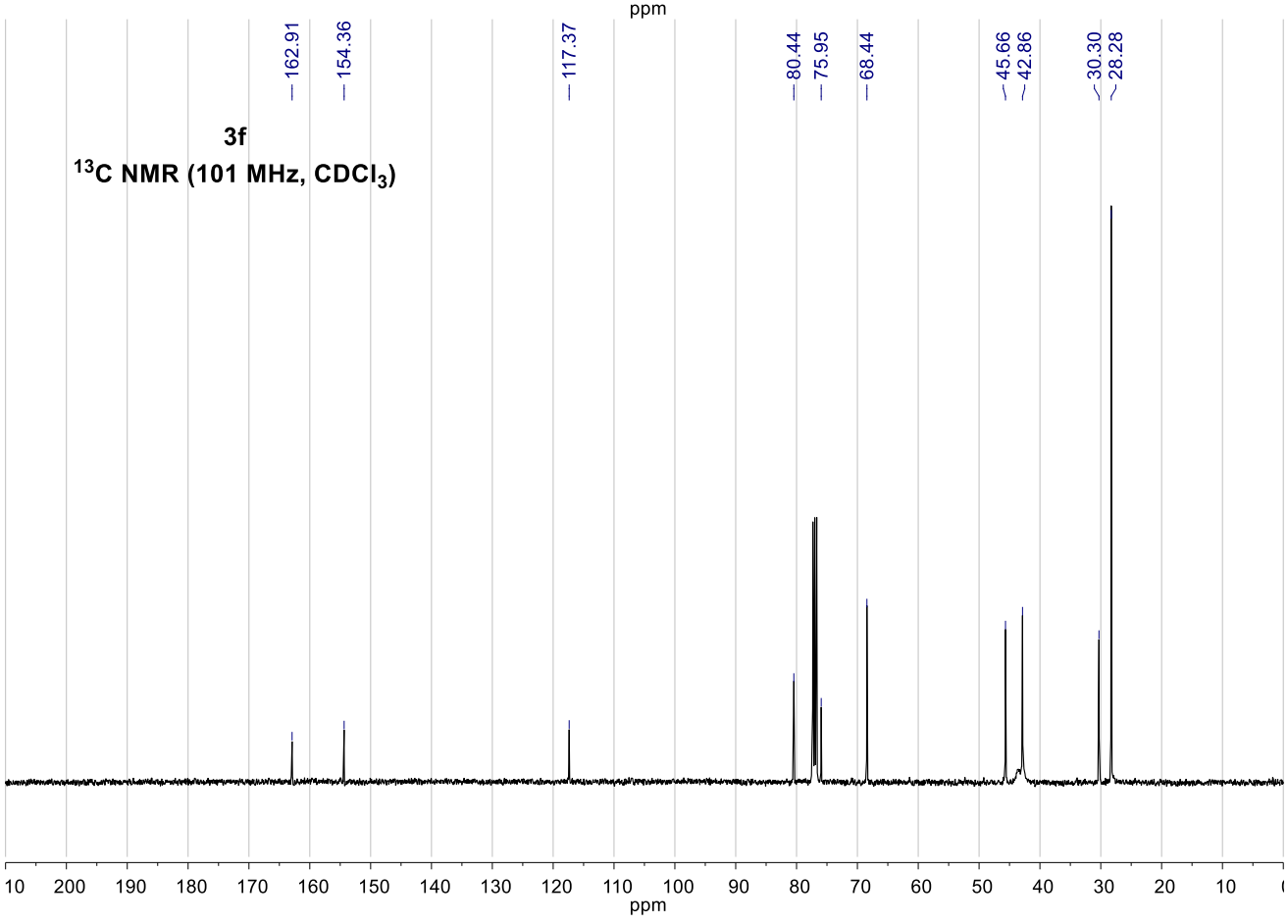

7.42
7.41
7.40
7.40
7.39
7.38
7.37
5.37
5.34
5.34
5.31
4.88
4.86
4.78
4.77
4.76
3.31
3.29
3.29
3.28
3.27
3.26
3.26
3.24
3.20
3.18
3.18
3.17
3.16
3.15
3.15
3.13
O
BnO2C
NC
3e
1H NMR (400 MHz, CDCl3)
5.02
1.98
1.00
1.00
1.01
1.00
ppm


165.43
134.07
128.84
128.70
128.30
116.27
75.60
69.36
68.79
31.47
3e
13C NMR (101 MHz, CDCl3)
ppm



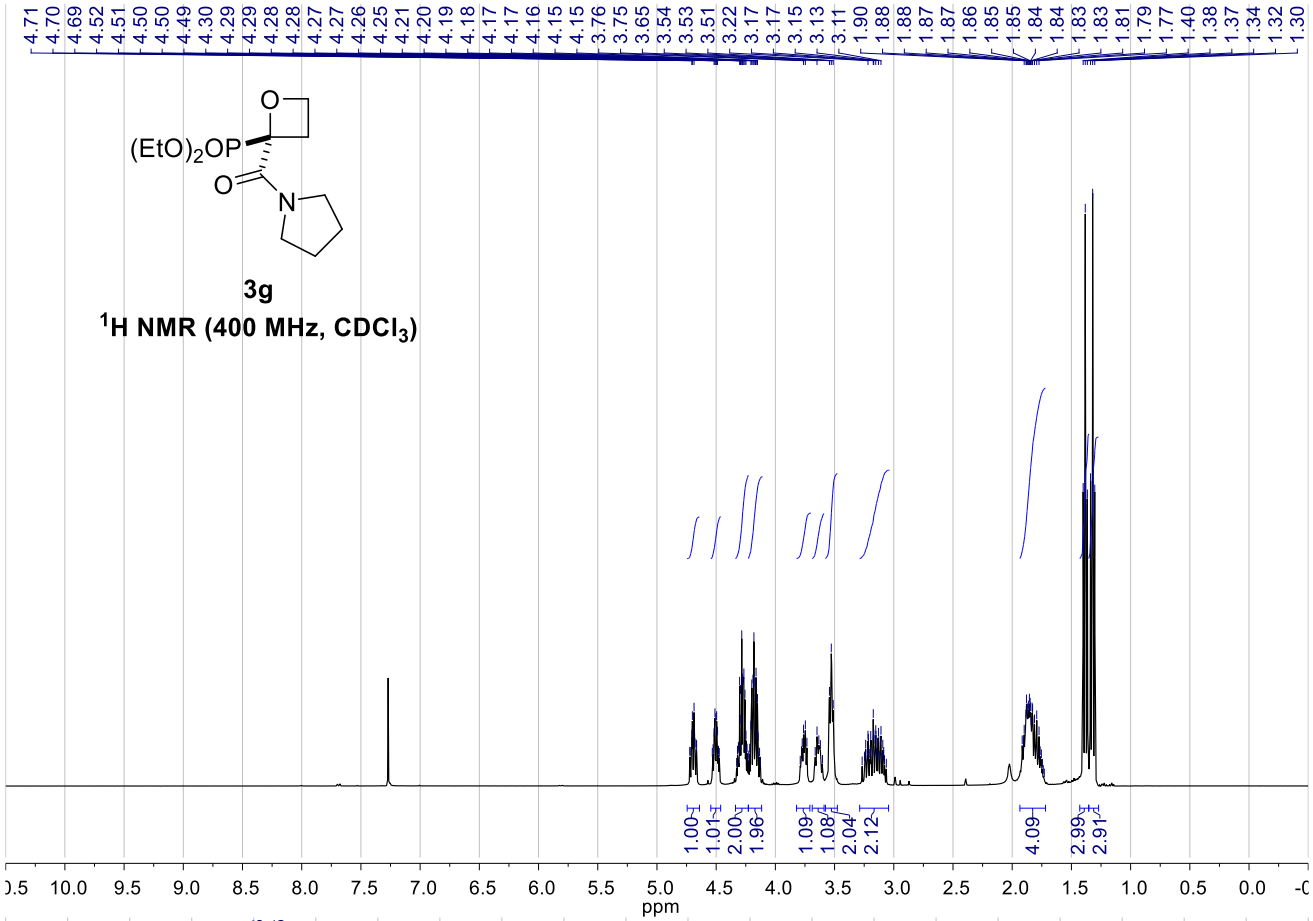
3f

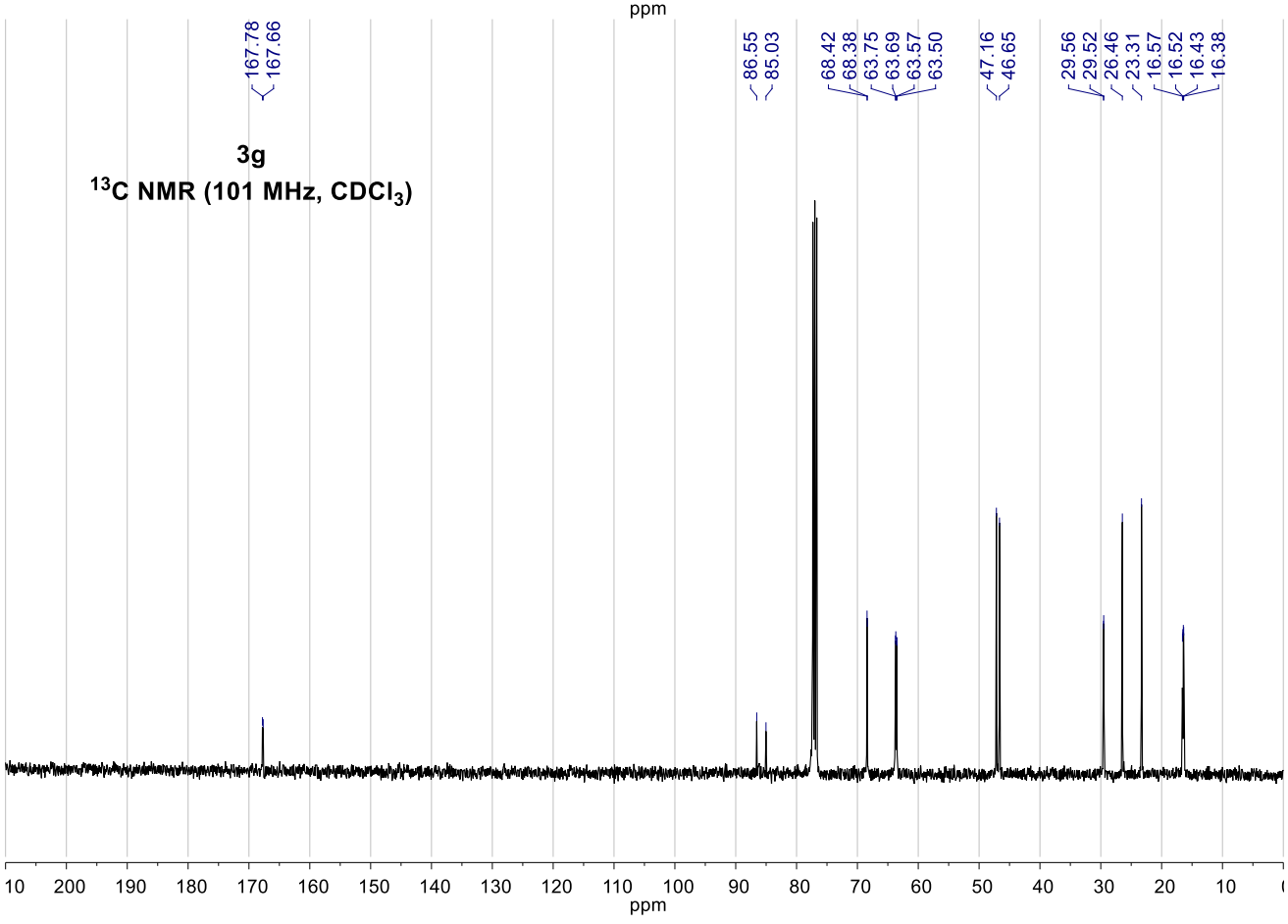
^{1}H NMR (400 MHz, $CDCl_3$)

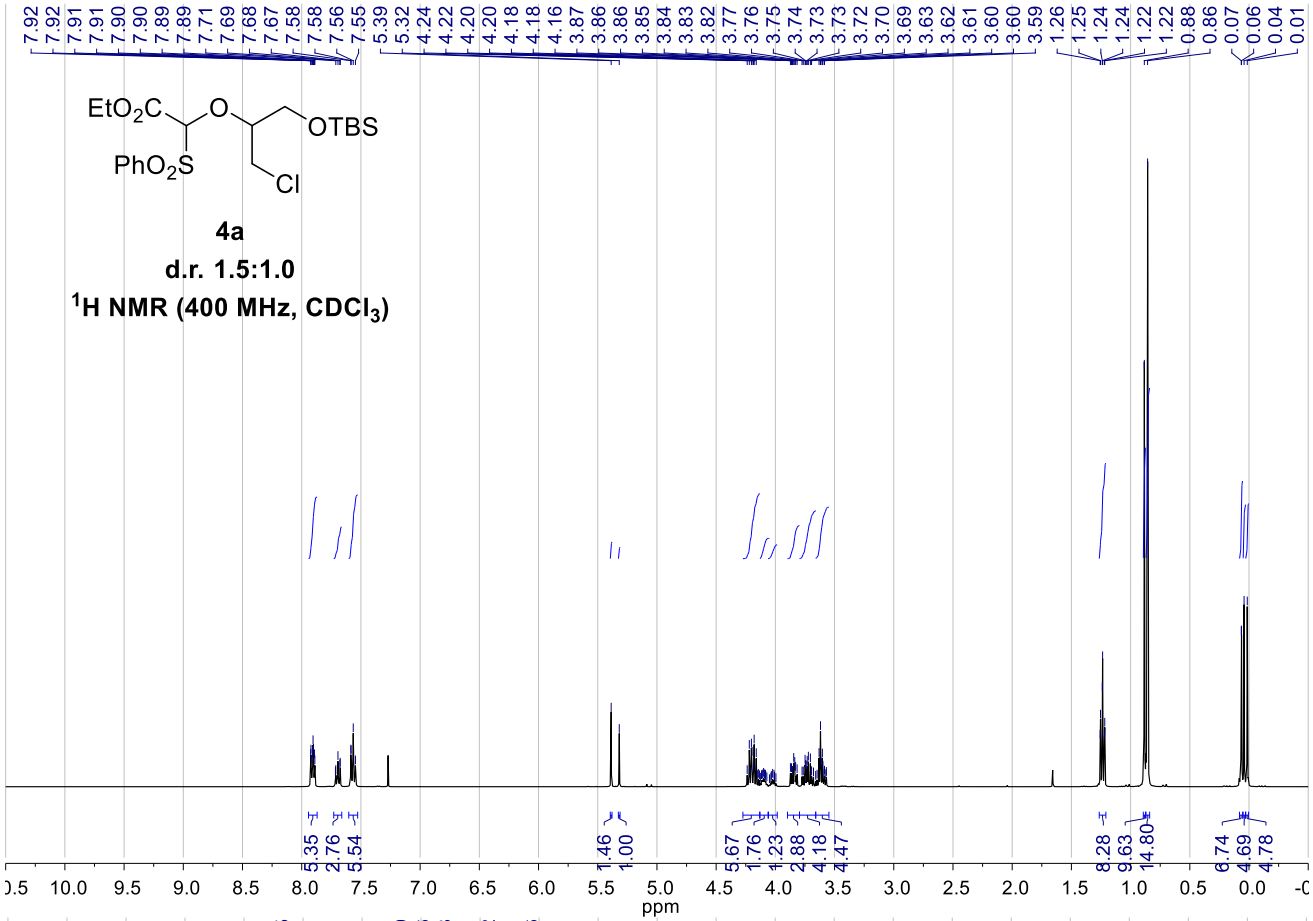


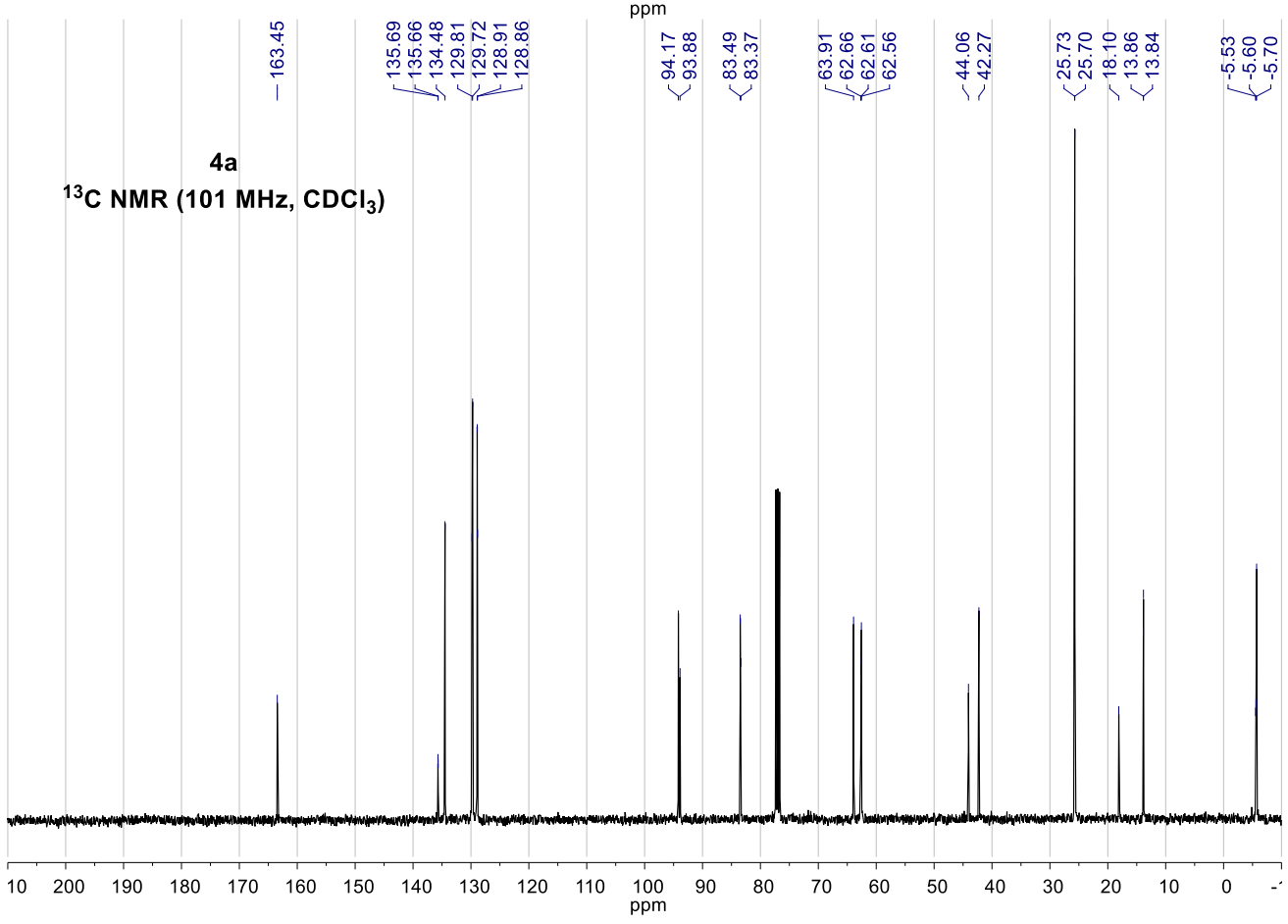
3f

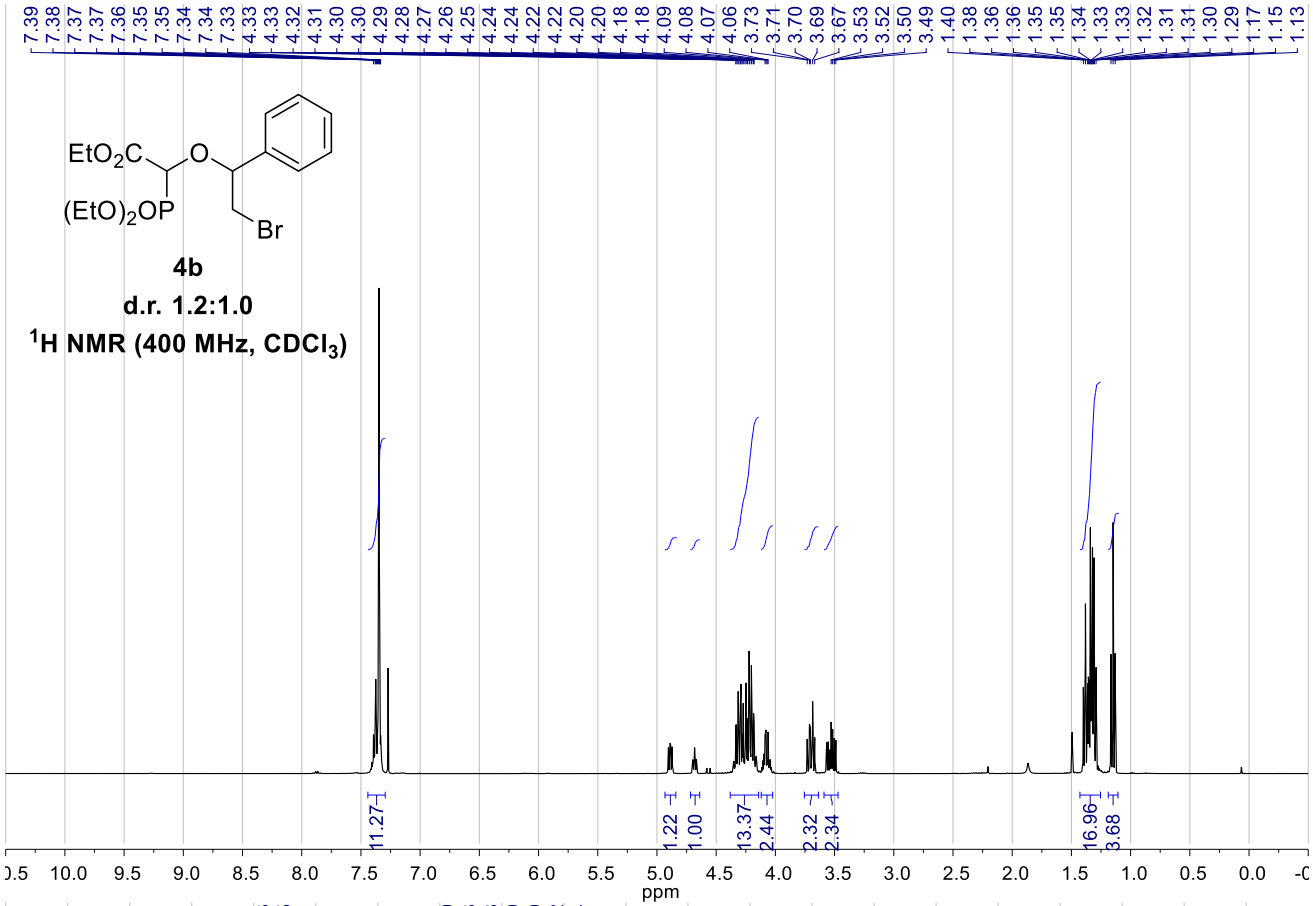
^{13}C NMR (101 MHz, $CDCl_3$)

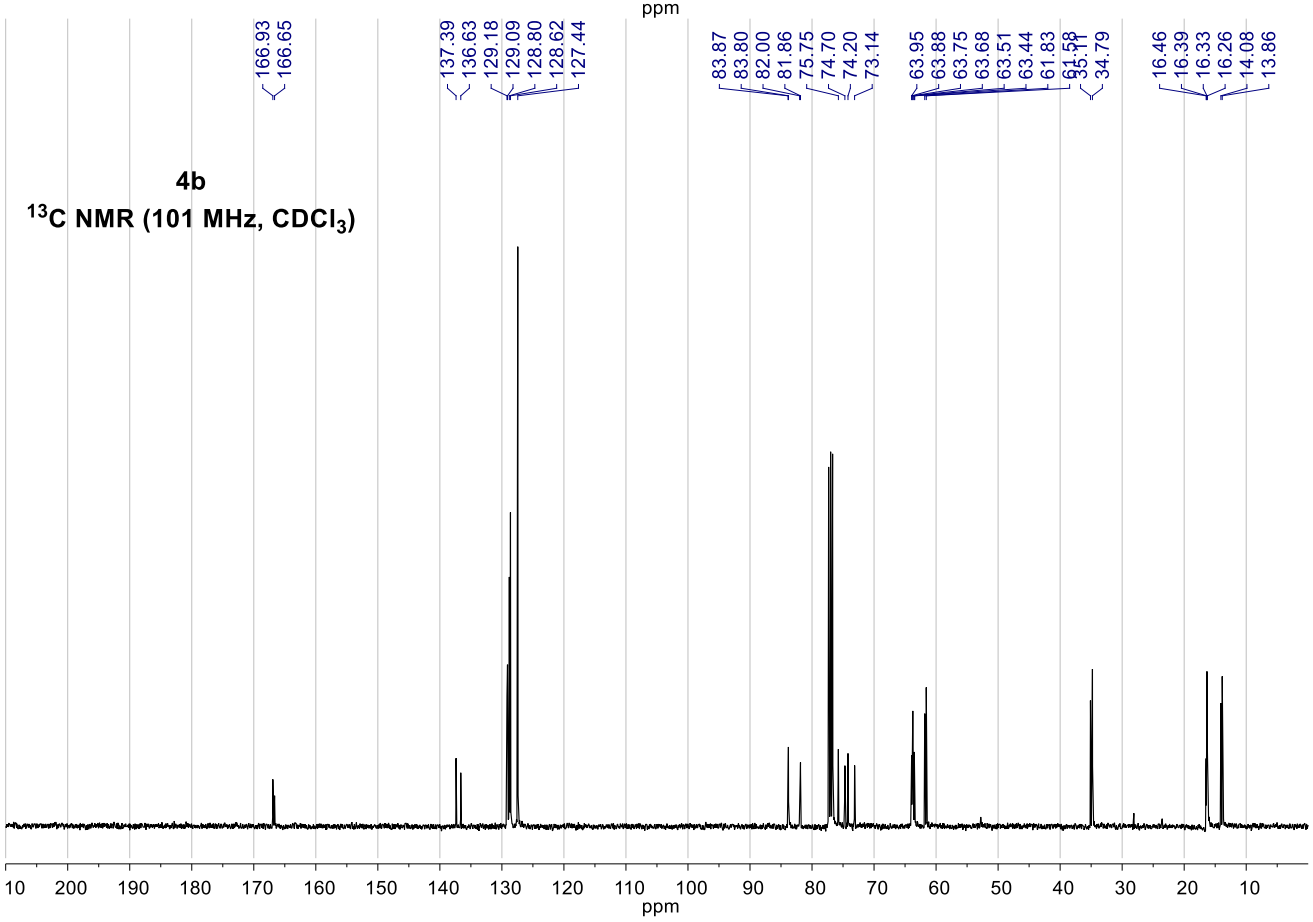

(EtO)2OP
O
O
N
3g
1H NMR (400 MHz, CDCl3)
ppm

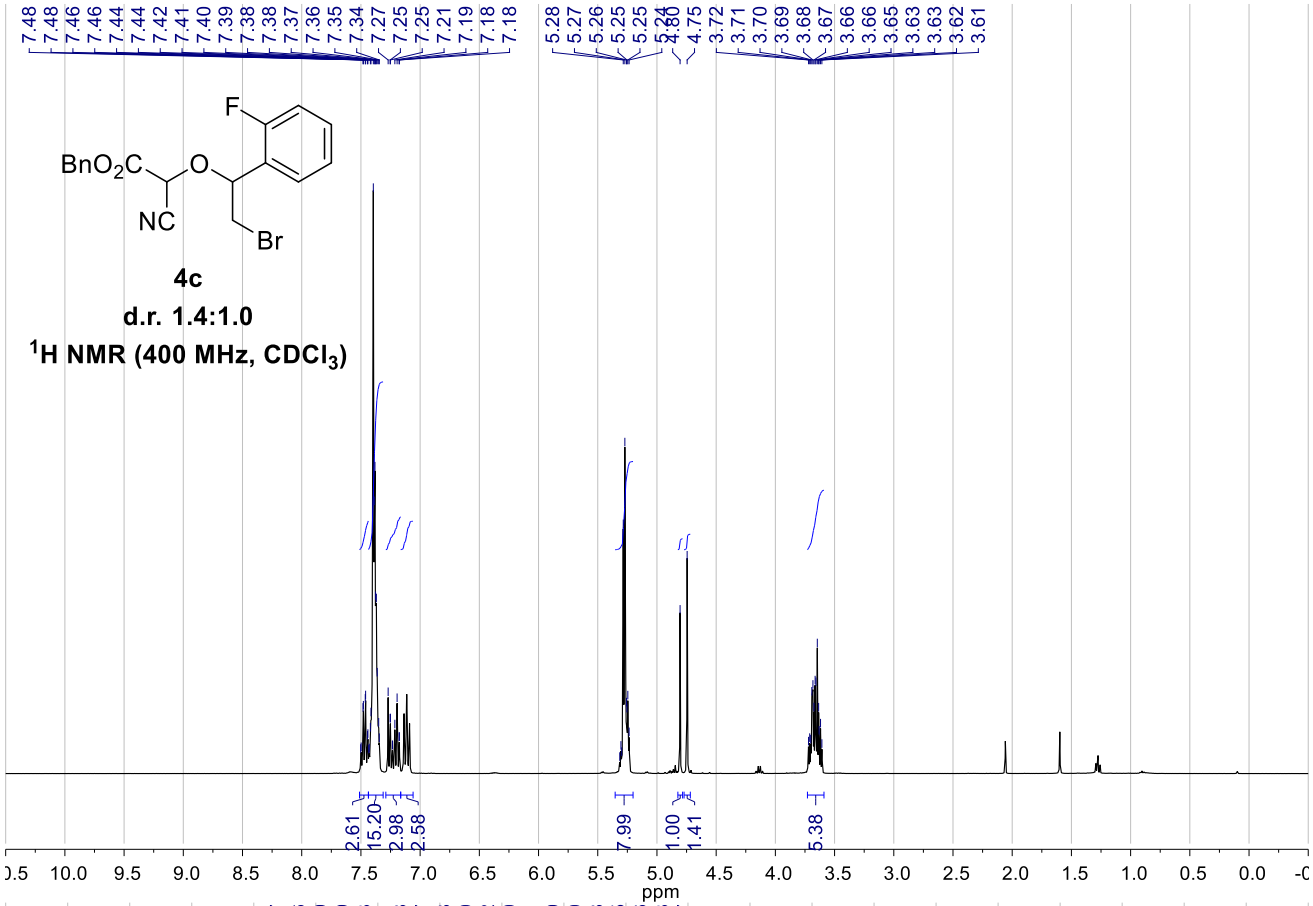

3g
13C NMR (101 MHz, CDCl3)
ppm

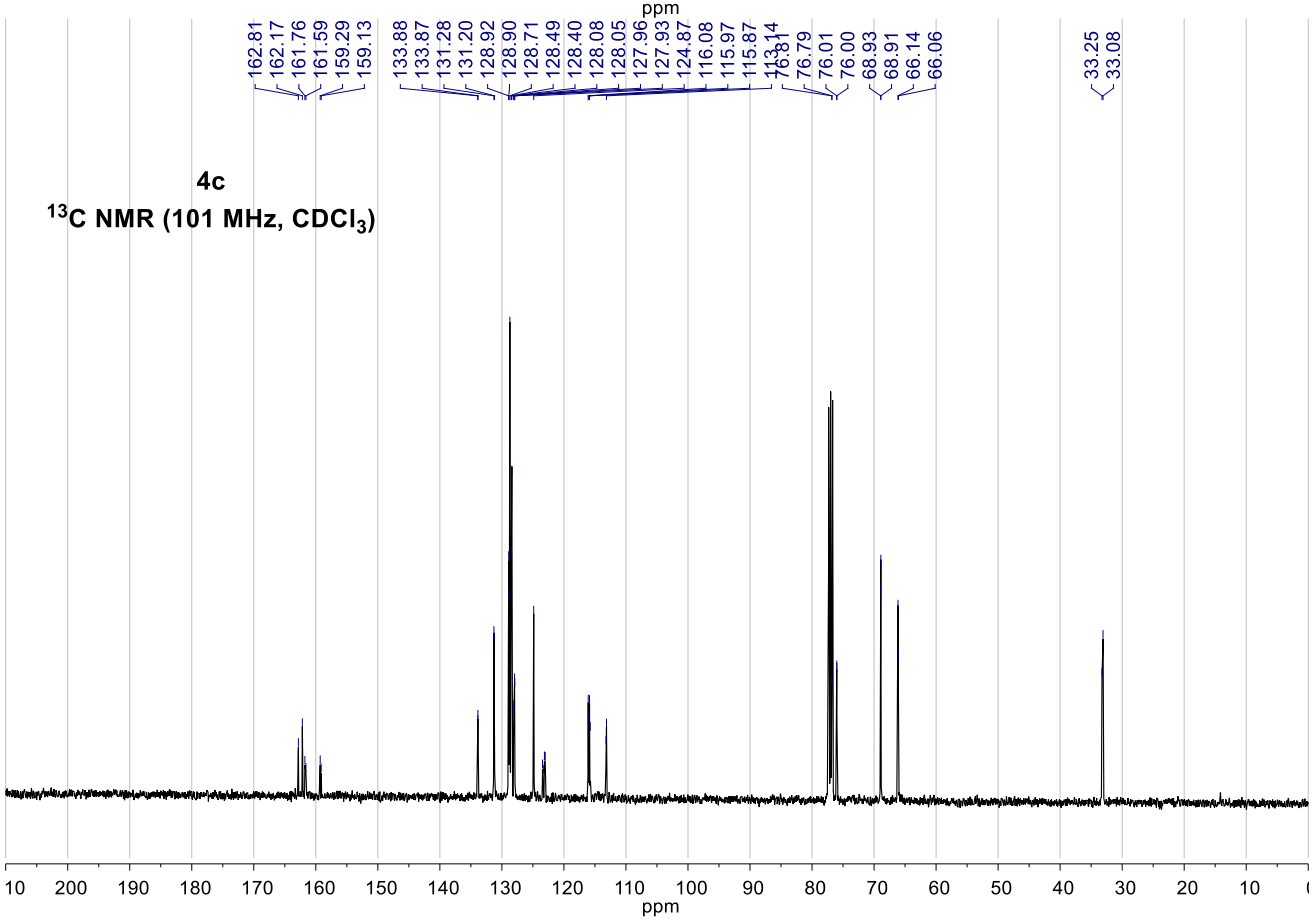

EtO2C
O
OTBS
PhO2S
Cl
4a
d.r. 1.5:1.0
1H NMR (400 MHz, CDCl3)
ppm

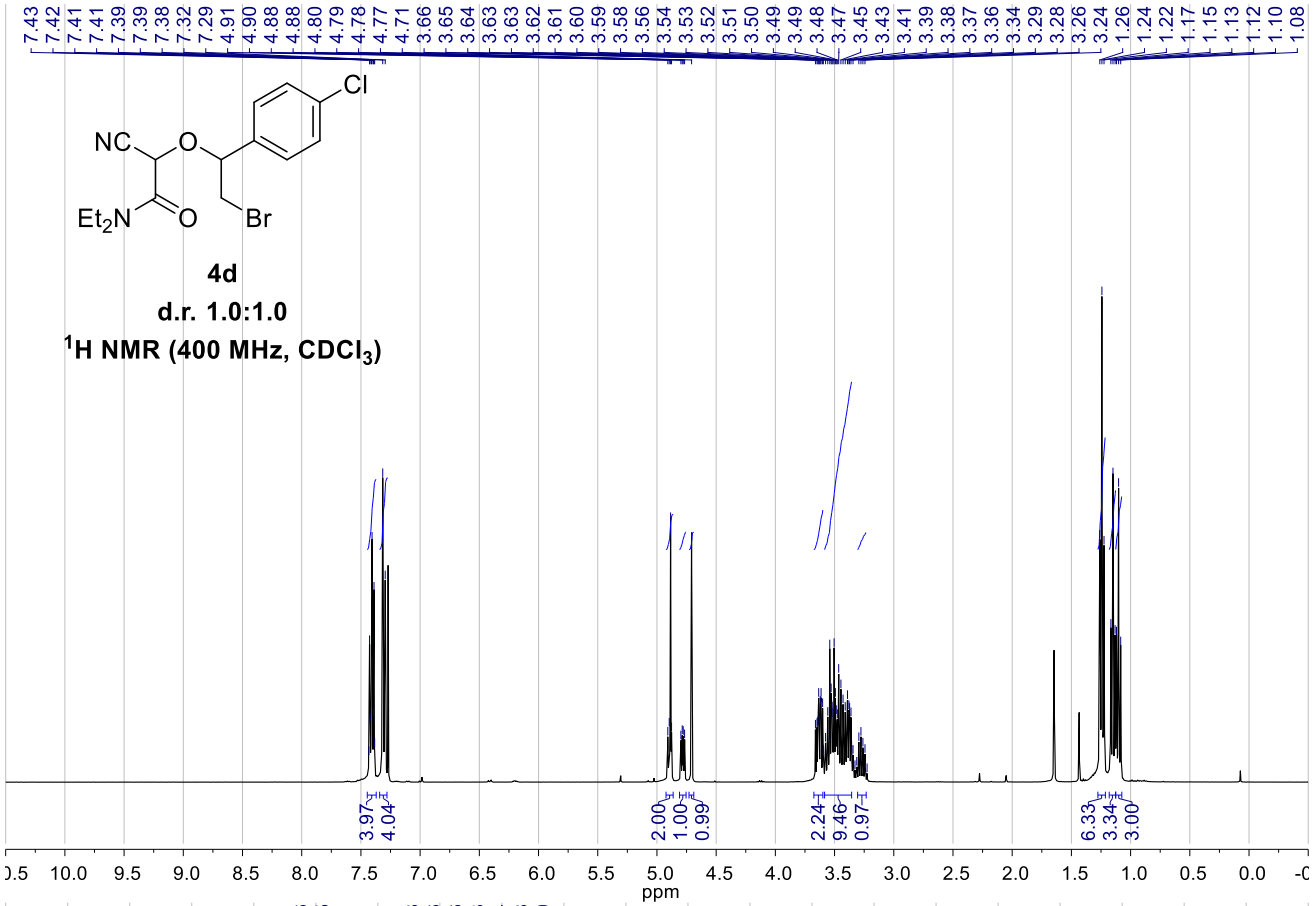

4a
13C NMR (101 MHz, CDCl3)
ppm

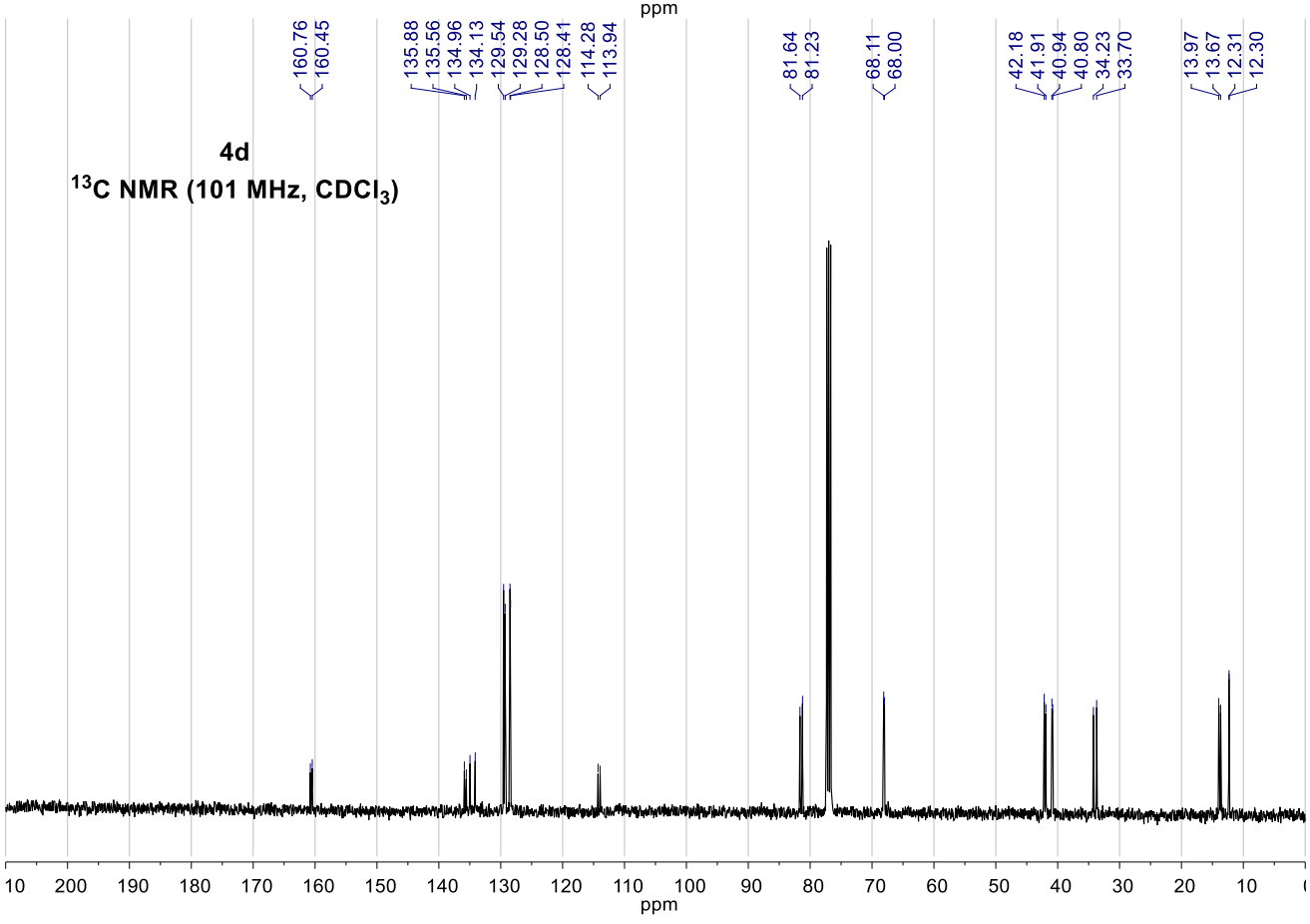

EtO2C
O
(EtO)2OP
Br
4b
d.r. 1.2:1.0
1H NMR (400 MHz, CDCl3)
ppm

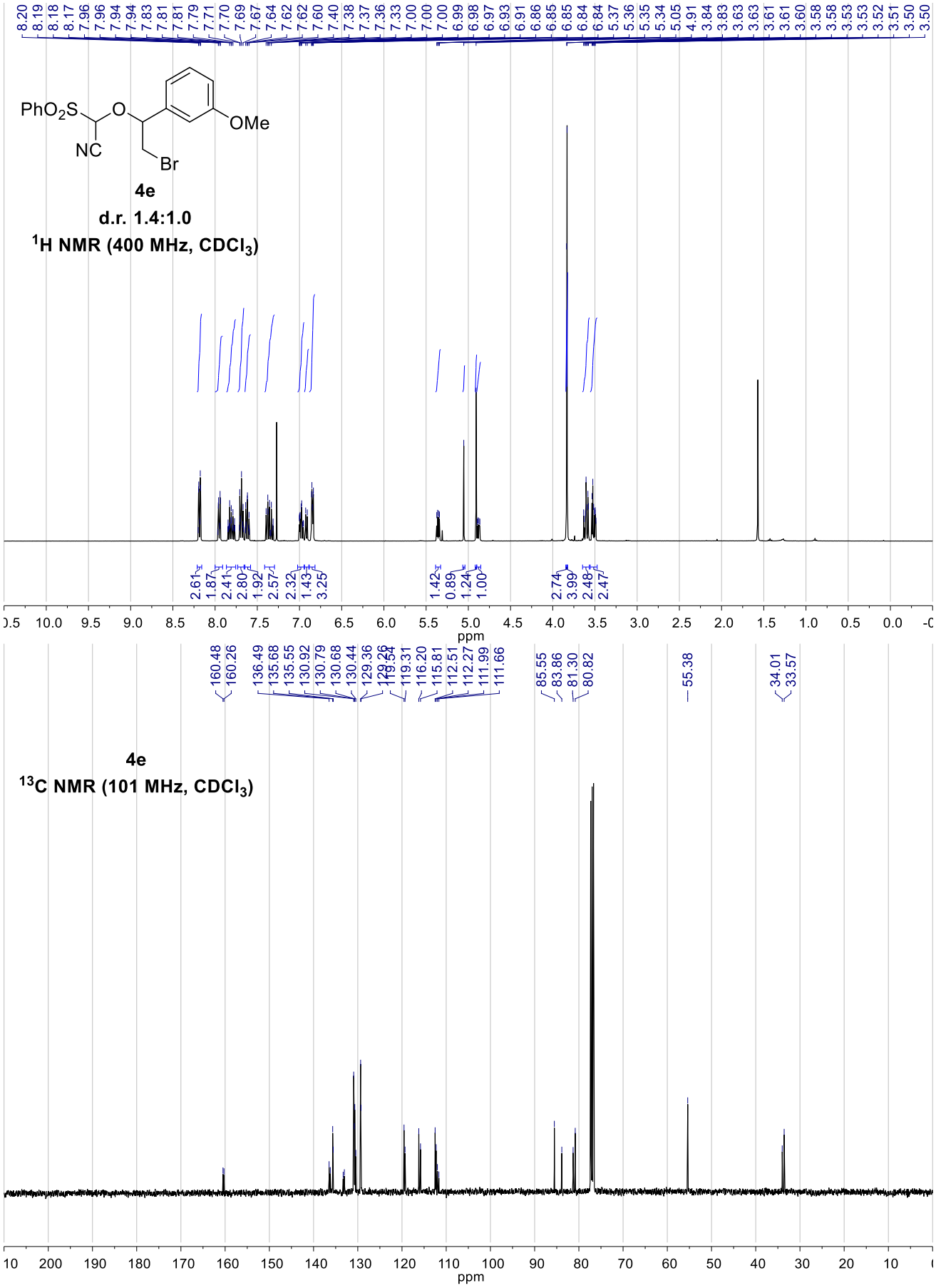

4b
13C NMR (101 MHz, CDCl3)
ppm

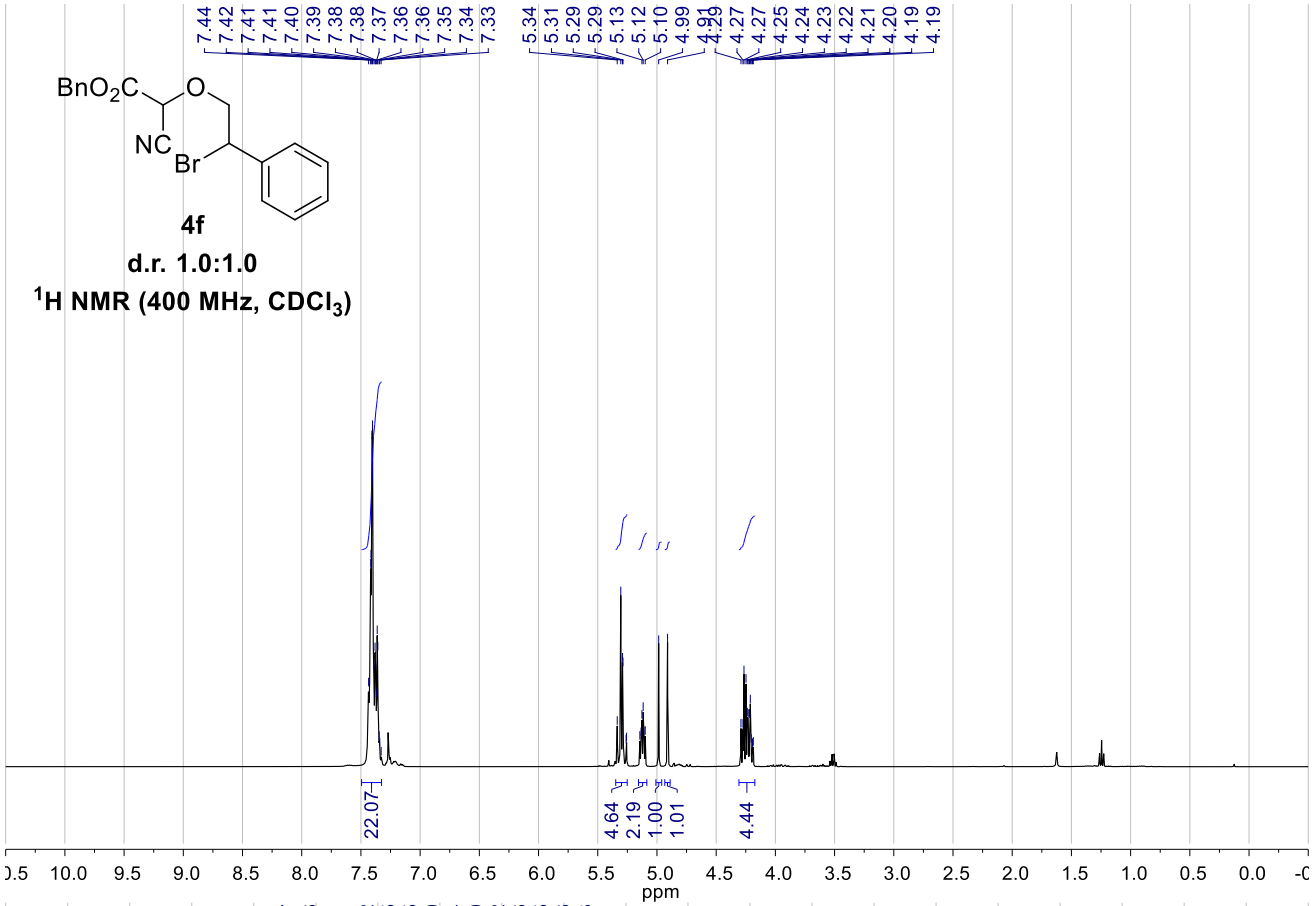

F
BnO2C
O
NC
Br
4c
d.r. 1.4:1.0
1H NMR (400 MHz, CDCl3)
ppm

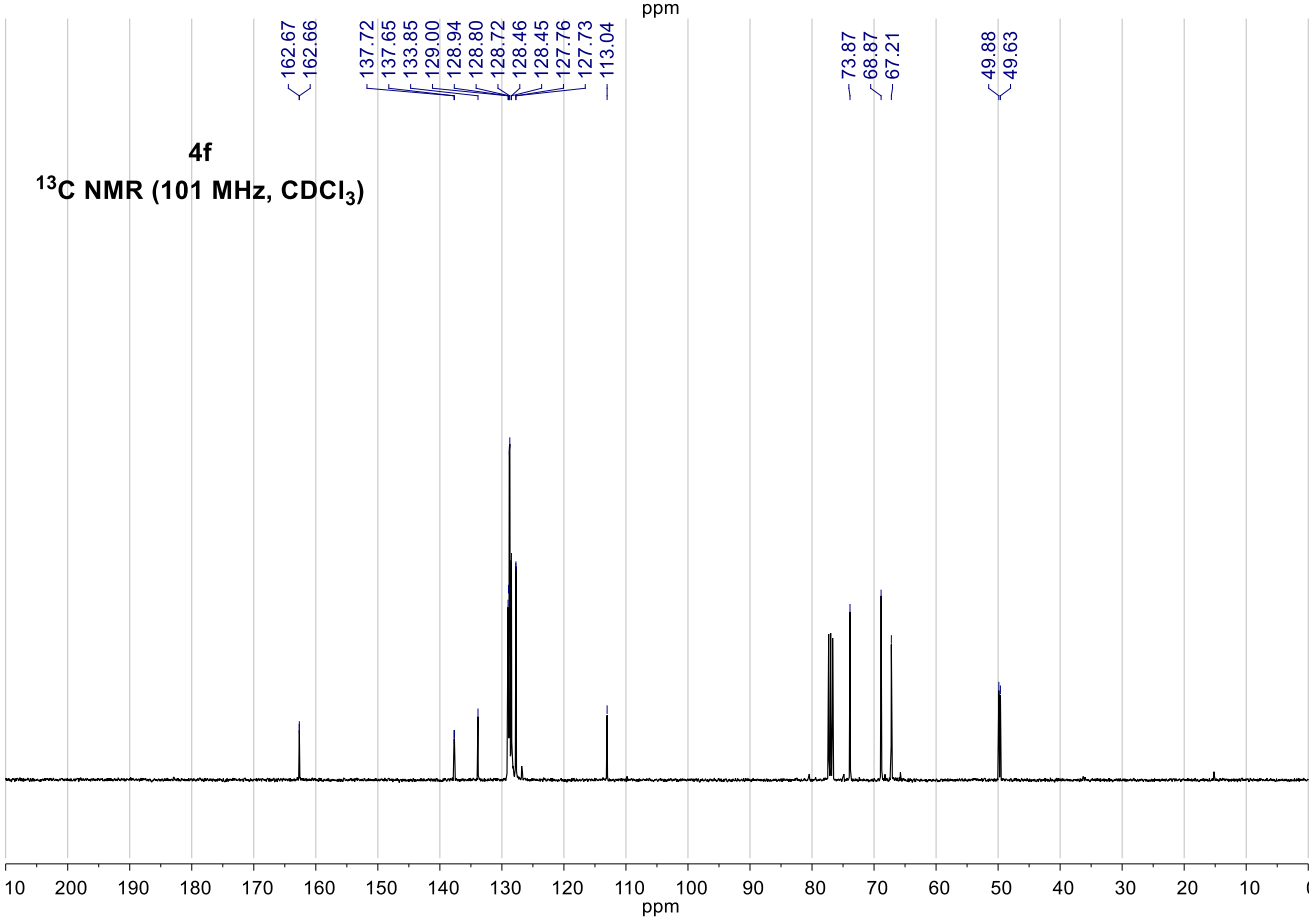

4c
13C NMR (101 MHz, CDCl3)
ppm

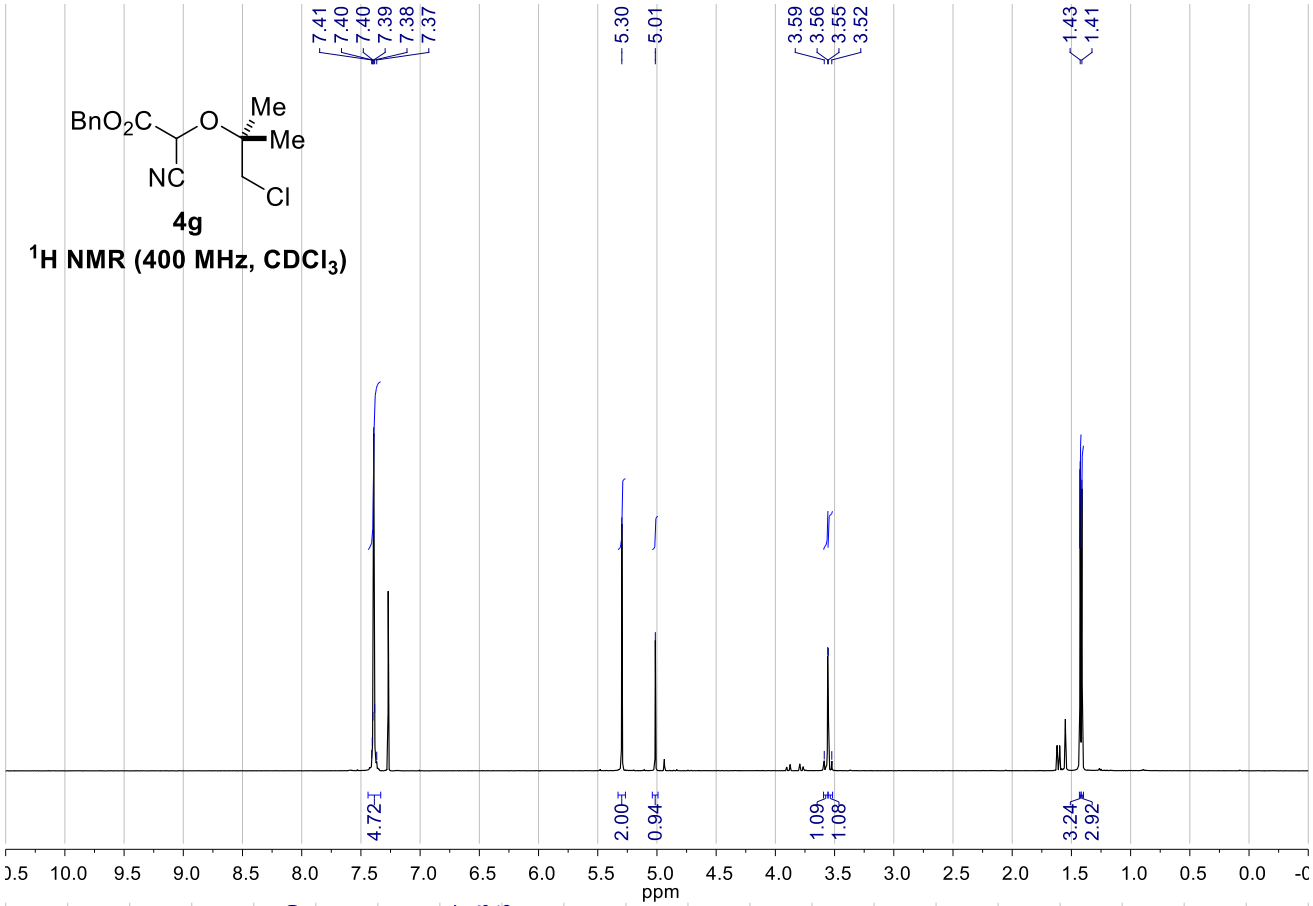

7.43 7.42 7.41 7.41 7.39 7.39 7.38 7.32 7.29 4.91 4.90 4.88 4.88 4.80 4.79 4.78 4.77 4.71 3.66 3.65 3.64 3.63 3.63 3.62 3.61 3.60 3.59 3.58 3.56 3.54 3.53 3.52 3.51 3.50 3.49 3.49 3.48 3.47 3.45 3.43 3.41 3.39 3.38 3.37 3.36 3.34 3.29 3.28 3.26 3.24 1.26 1.24 1.22 1.17 1.15 1.13 1.12 1.10 1.08
Cl
NC
O
Et2N
O
Br
4d
d.r. 1.0:1.0
1H NMR (400 MHz, CDCl3)
3.97 4.04 2.00 1.00 0.99 2.24 9.46 0.97 6.33 3.34 3.00
ppm

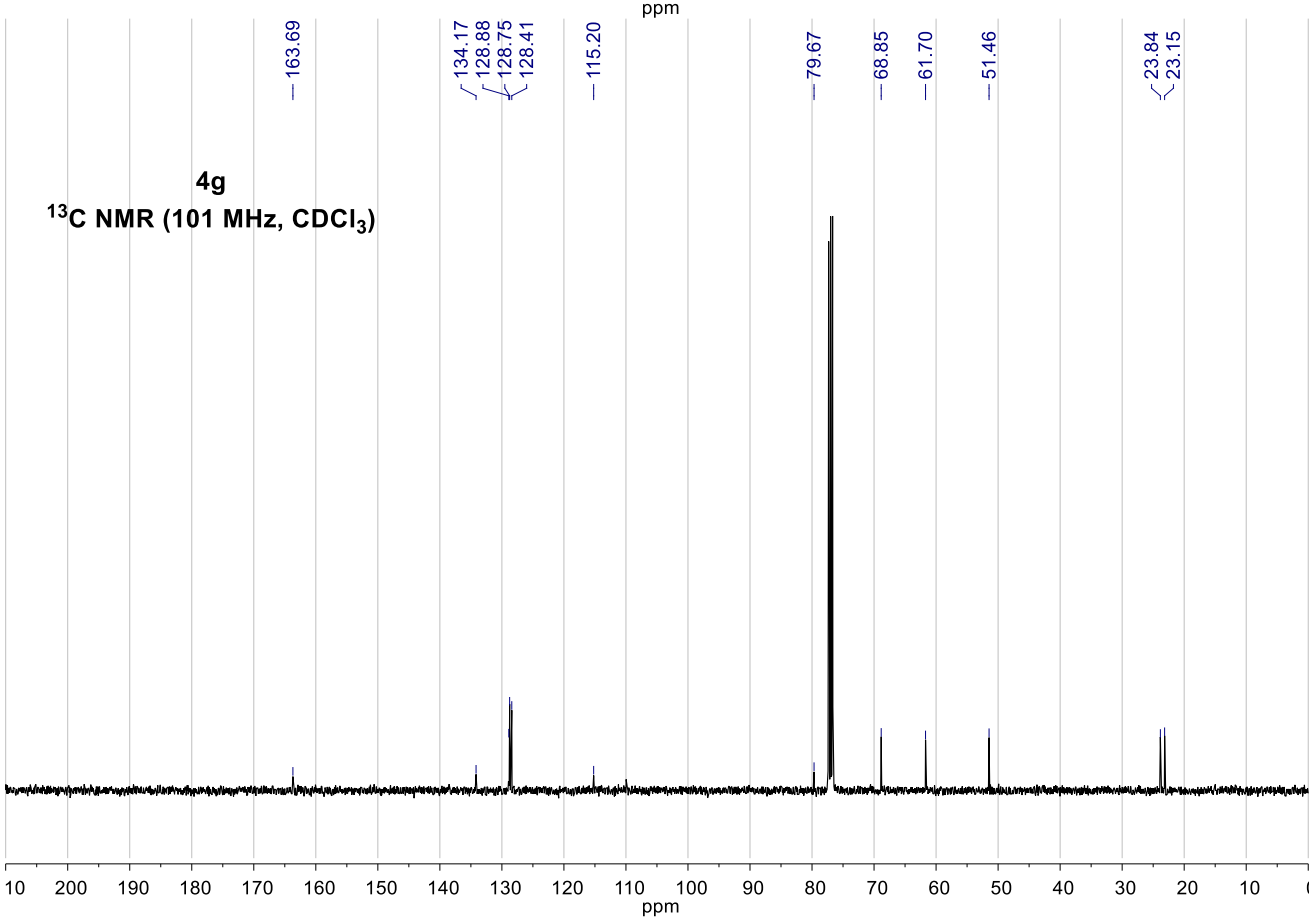

160.76 160.45 135.88 135.56 134.96 134.13 129.54 129.28 128.50 128.41 114.28 113.94 81.64 81.23 68.11 68.00 42.18 41.91 40.94 40.80 34.23 33.70 13.97 13.67 12.31 12.30
4d
13C NMR (101 MHz, CDCl3)
ppm

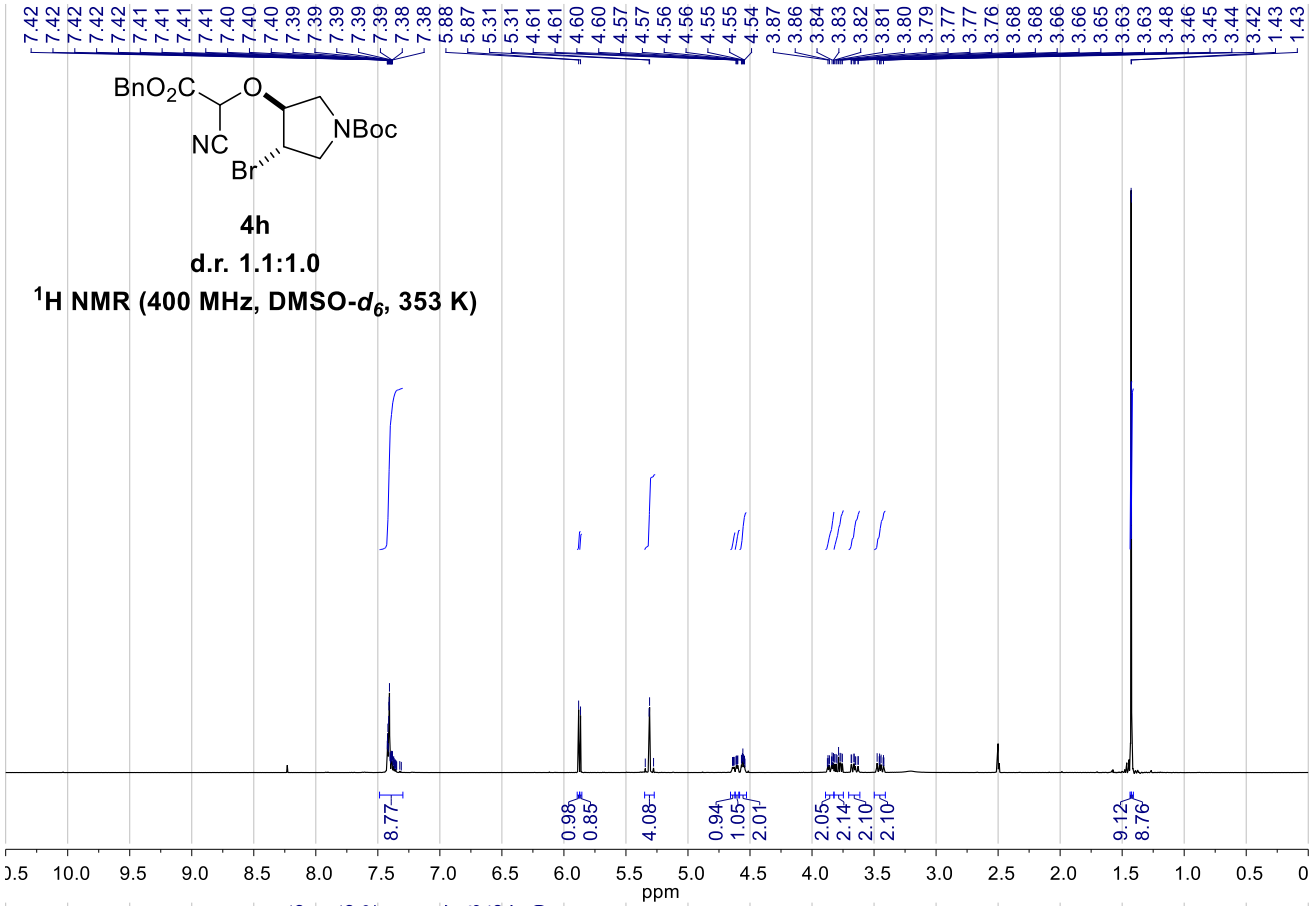

PhO2S
O
NC
OMe
Br
4e
d.r. 1.4:1.0
1H NMR (400 MHz, CDCl3)
ppm
4e
13C NMR (101 MHz, CDCl3)
ppm

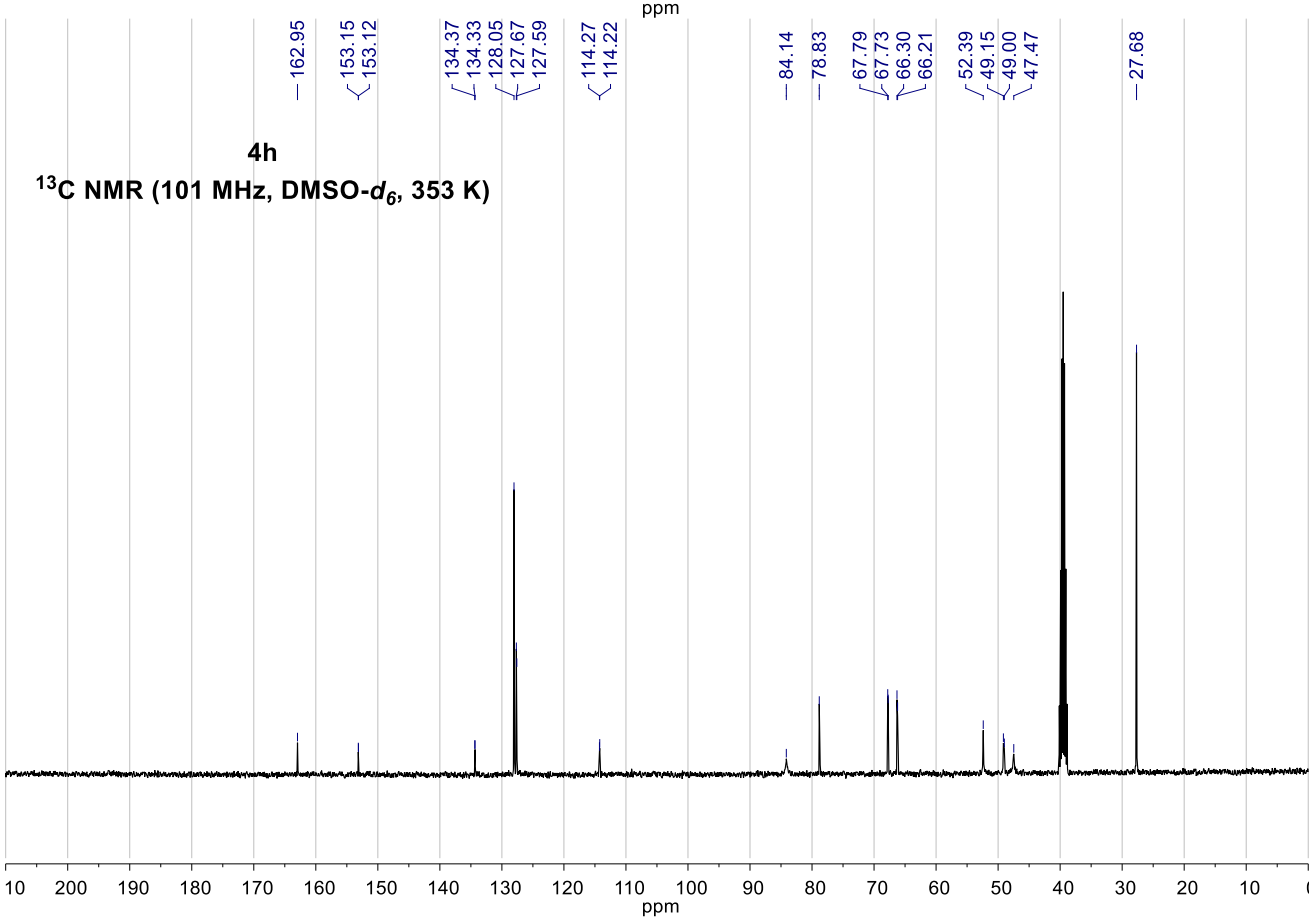

7.44 7.42 7.41 7.41 7.40 7.39 7.38 7.38 7.37 7.36 7.36 7.35 7.34 7.33
5.34 5.31 5.29 5.29 5.13 5.12 5.10 4.99 4.91 4.29 4.27 4.27 4.25 4.24 4.23 4.22 4.21 4.20 4.19 4.19
BnO2C
O
NC
Br
4f
d.r. 1.0:1.0
1H NMR (400 MHz, CDCl3)
22.07
4.64
2.19
1.00
1.01
4.44
ppm

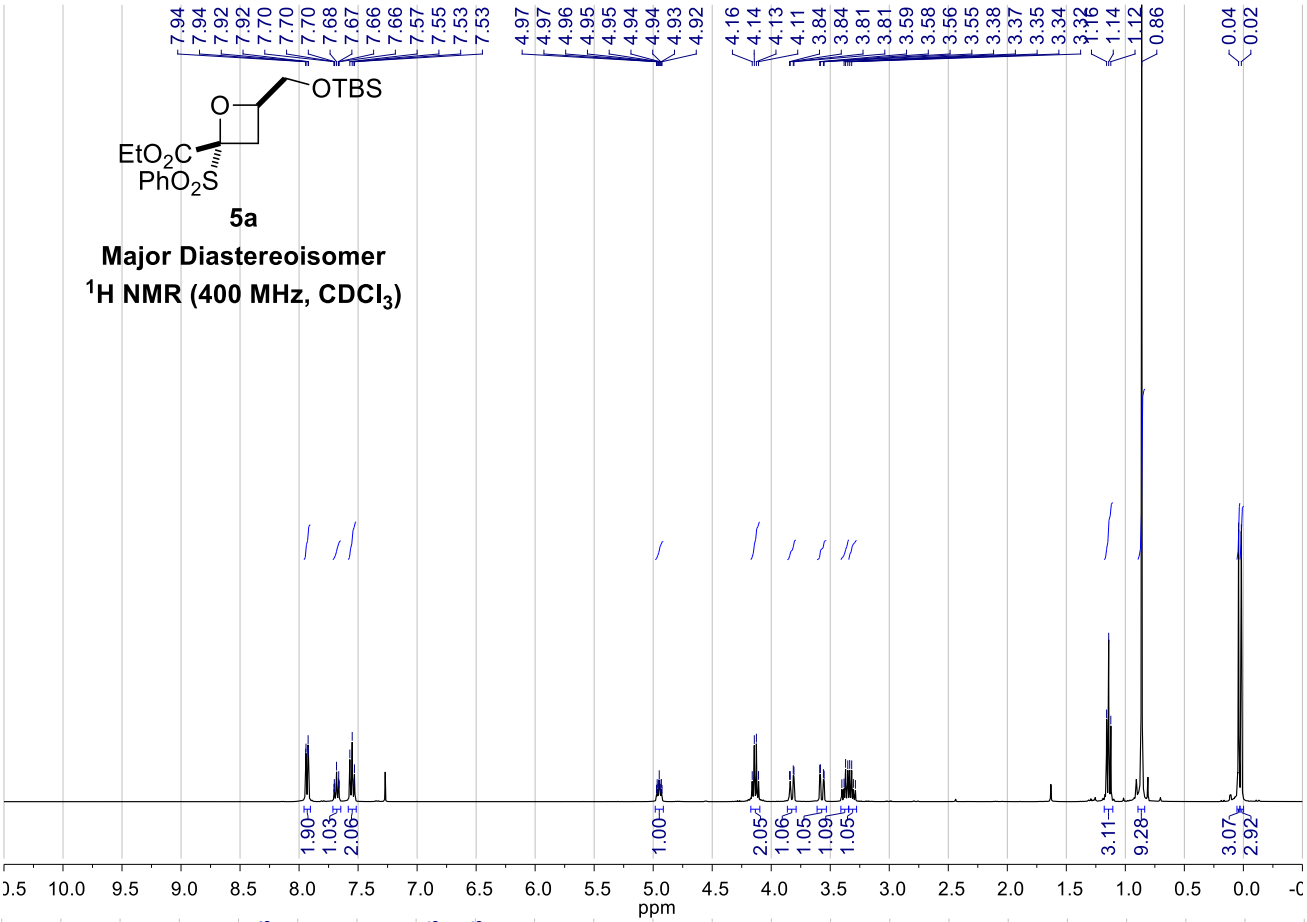

162.67 162.66
137.72 137.65 133.85 129.00 128.94 128.80 128.72 128.46 128.45 127.76 127.73
113.04
73.87 68.87 67.21
49.88 49.63
4f
13C NMR (101 MHz, CDCl3)
ppm

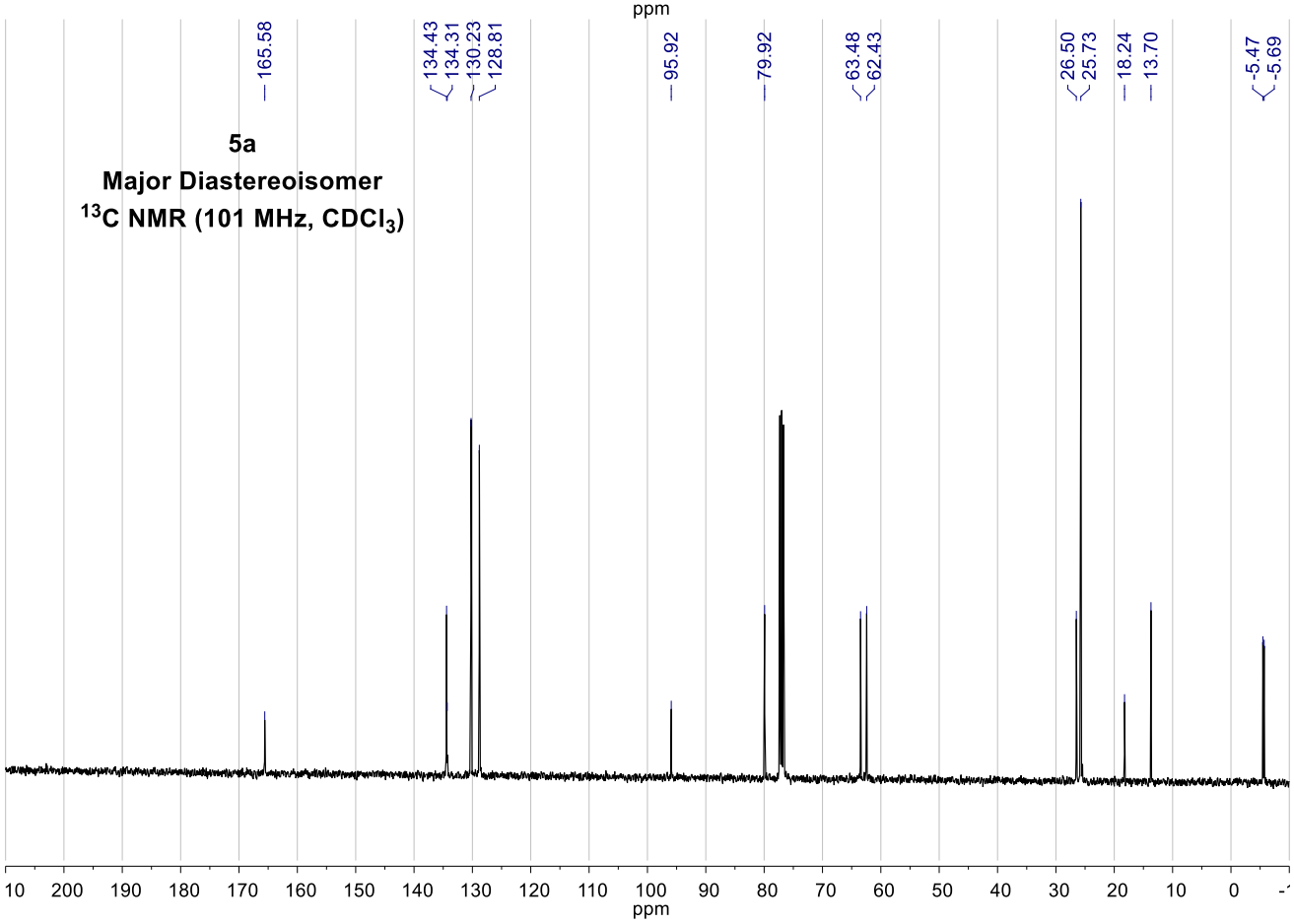

7.41
7.40
7.40
7.39
7.38
7.37
5.30
5.01
3.59
3.56
3.55
3.52
1.43
1.41
BnO2C
O
Me
Me
NC
Cl
4g
1H NMR (400 MHz, CDCl3)
4.72
2.00
0.94
1.09
1.08
3.24
2.92
ppm

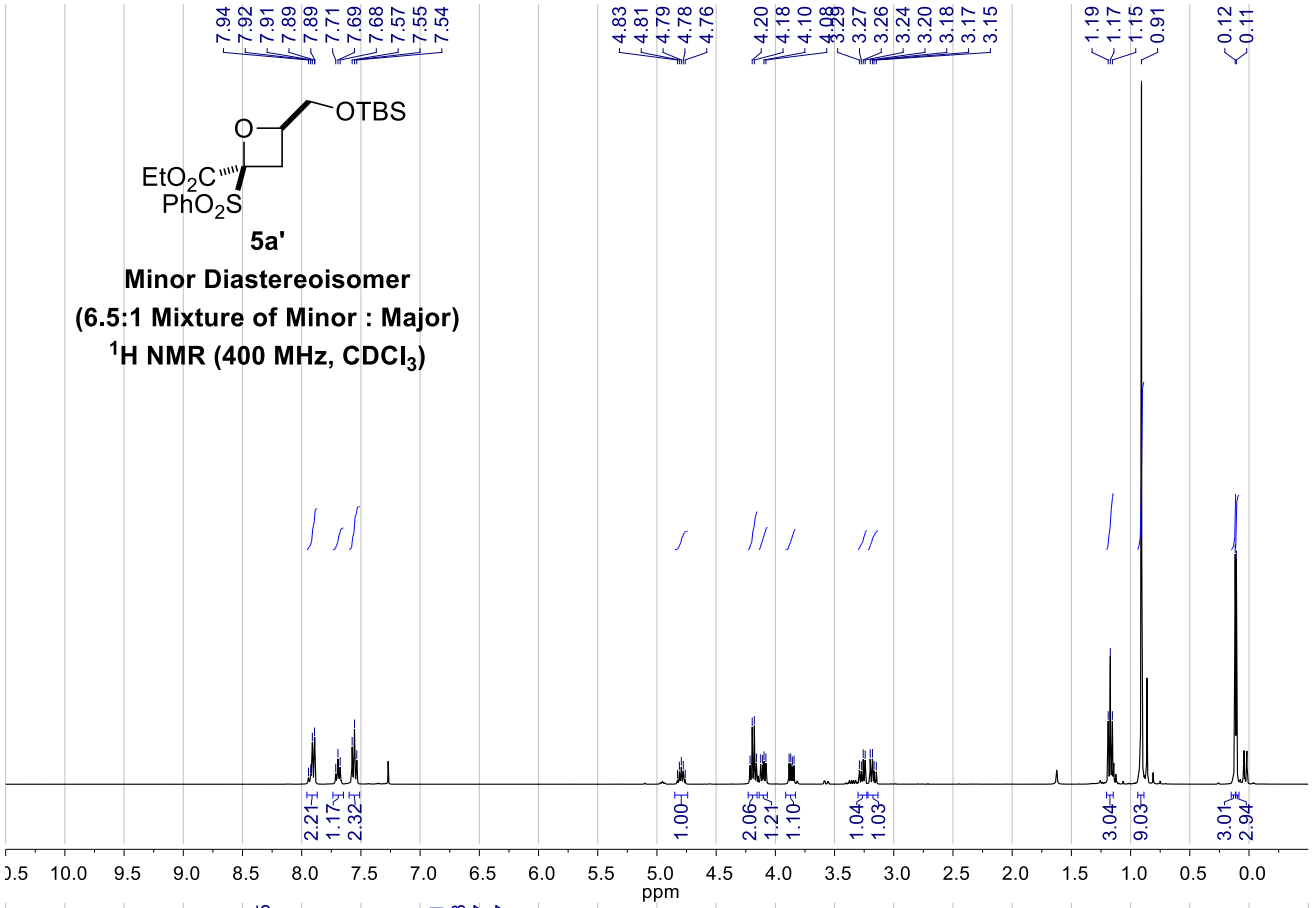

163.69
134.17
128.88
128.75
128.41
115.20
79.67
68.85
61.70
51.46
23.84
23.15
4g
13C NMR (101 MHz, CDCl3)
ppm

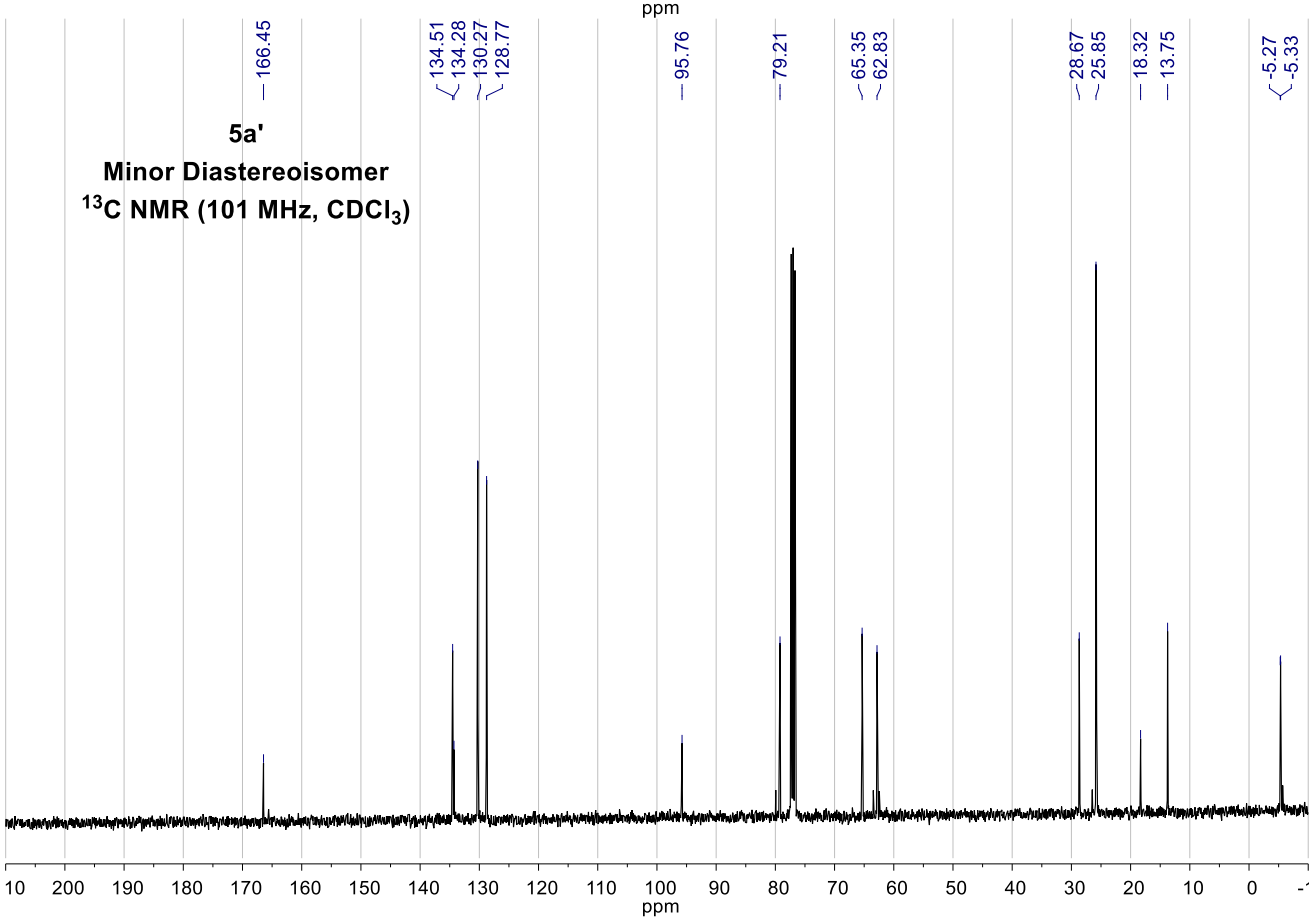

BnO2C
O
NC
NBoc
Br
4h
d.r. 1.1:1.0
1H NMR (400 MHz, DMSO-d6, 353 K)
ppm

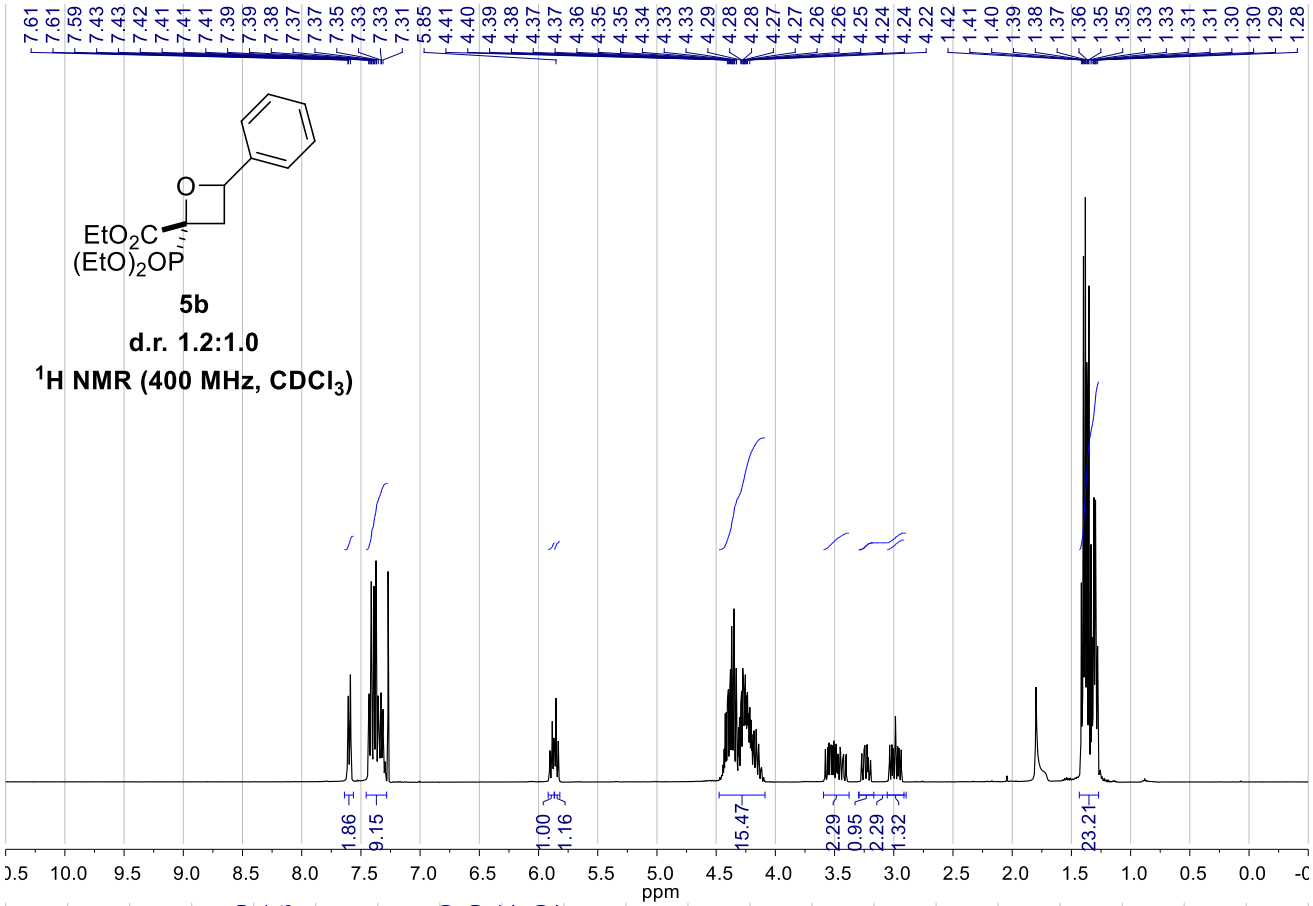

4h
13C NMR (101 MHz, DMSO-d6, 353 K)
ppm

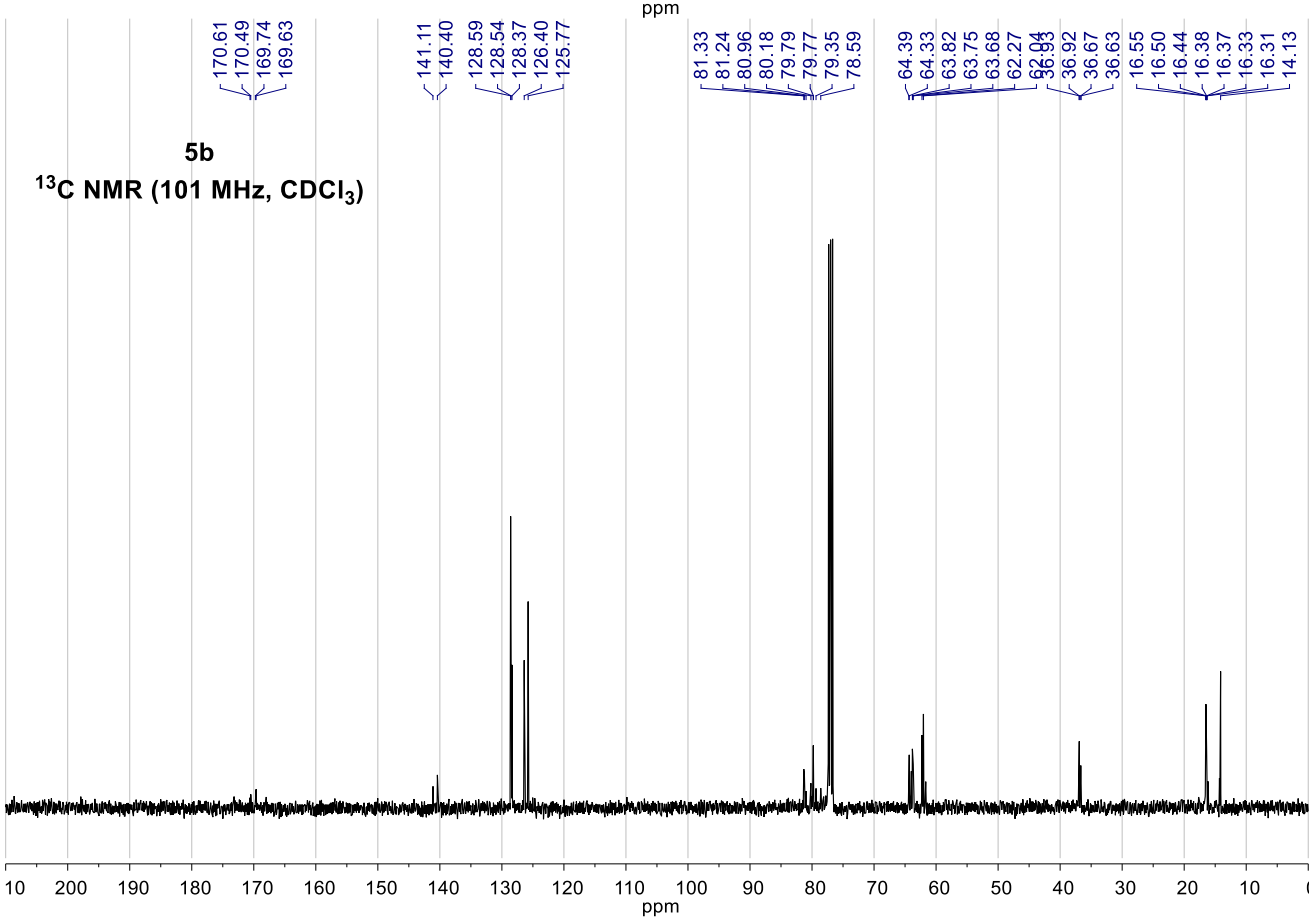

OTBS
O
EtO2C
PhO2S
5a
Major Diastereoisomer
1H NMR (400 MHz, CDCl3)
ppm

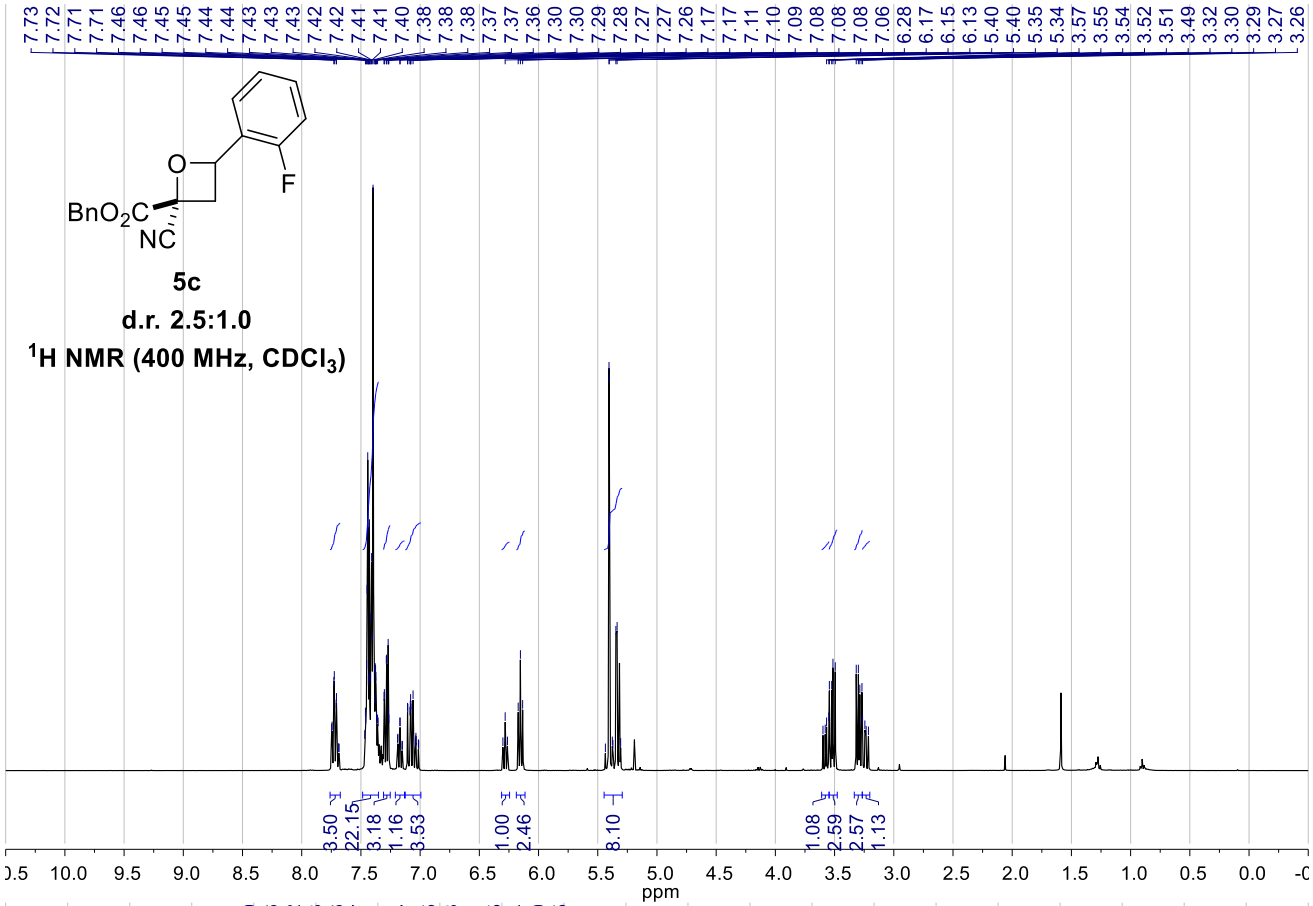

5a
Major Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm

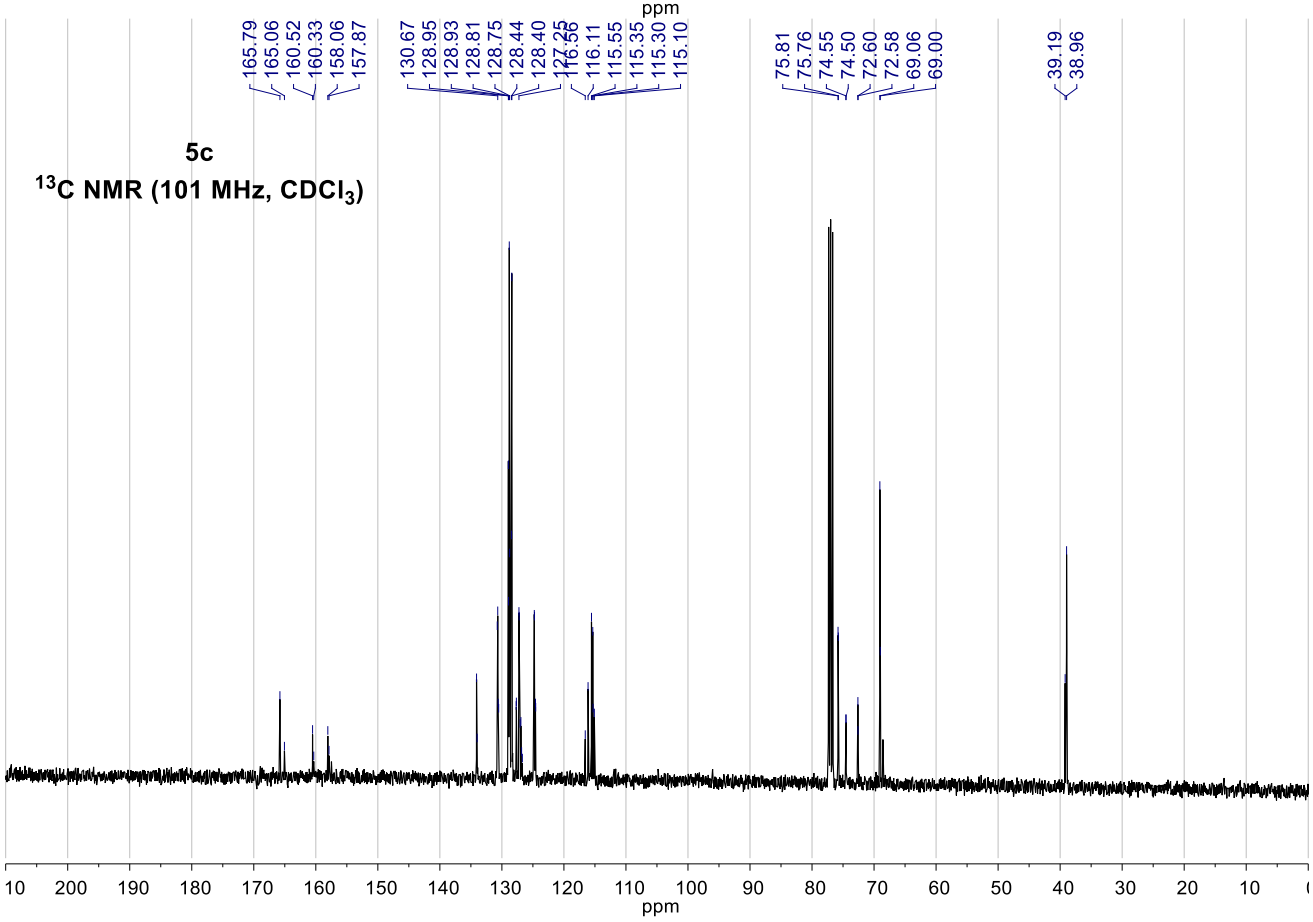

7.94
7.92
7.91
7.89
7.89
7.71
7.69
7.68
7.57
7.55
7.54
4.83
4.81
4.79
4.78
4.76
4.20
4.18
4.10
3.27
3.26
3.24
3.20
3.18
3.17
3.15
1.19
1.17
1.15
0.91
0.12
0.11
OTBS
O
EtO2C
PhO2S
5a'
Minor Diastereoisomer
(6.5:1 Mixture of Minor : Major)
1H NMR (400 MHz, CDCl3)
2.21
1.17
2.32
1.00
2.06
1.21
1.10
1.04
1.03
3.04
9.03
3.01
2.94
ppm

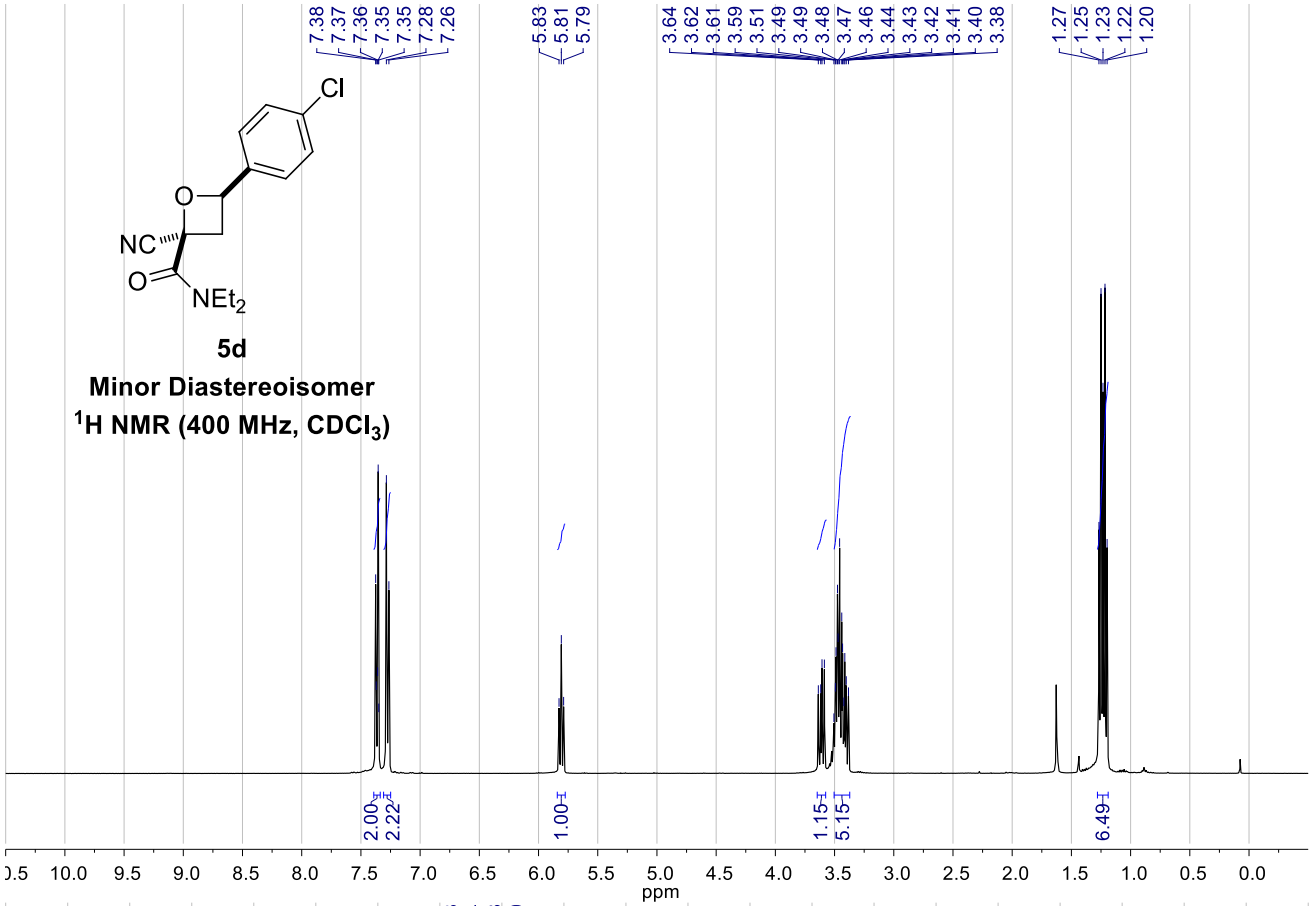

166.45
134.51
134.28
130.27
128.77
95.76
79.21
65.35
62.83
28.67
25.85
18.32
13.75
-5.27
-5.33
5a'
Minor Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm

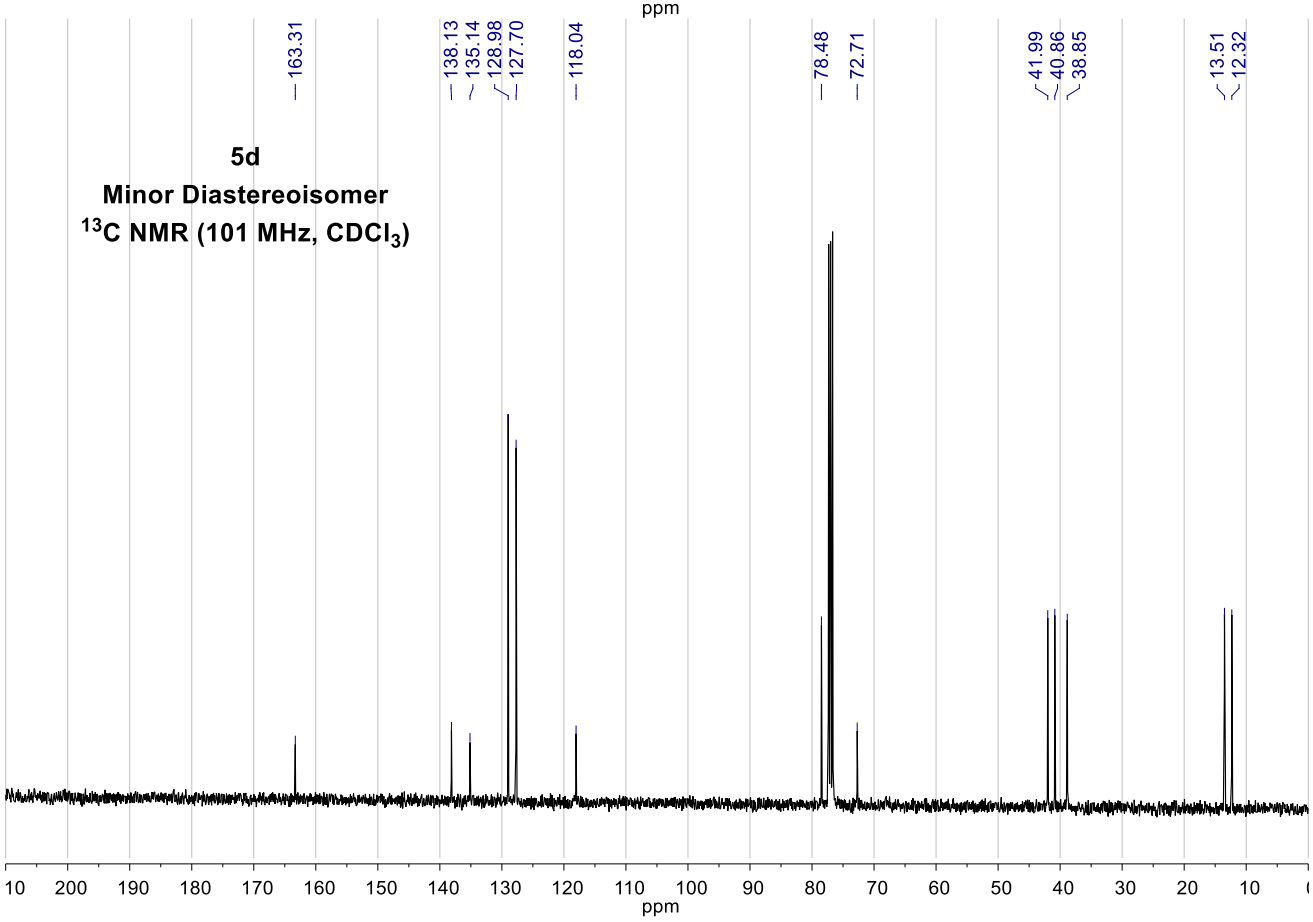

7.61 7.61 7.59 7.43 7.43 7.42 7.41 7.41 7.41 7.39 7.39 7.38 7.37 7.37 7.35 7.33 7.33 7.31
5.85 4.41 4.40 4.39 4.38 4.37 4.37 4.36 4.35 4.35 4.34 4.33 4.33 4.29 4.28 4.28 4.27 4.26 4.26 4.25 4.24 4.24 4.22
1.42 1.41 1.40 1.39 1.38 1.37 1.36 1.35 1.35 1.33 1.33 1.31 1.30 1.30 1.29 1.28
O
EtO2C
(EtO)2OP
5b
d.r. 1.2:1.0
1H NMR (400 MHz, CDCl3)
1.86 9.15 1.00 1.16 15.47 2.29 0.95 2.29 1.32 23.21
ppm

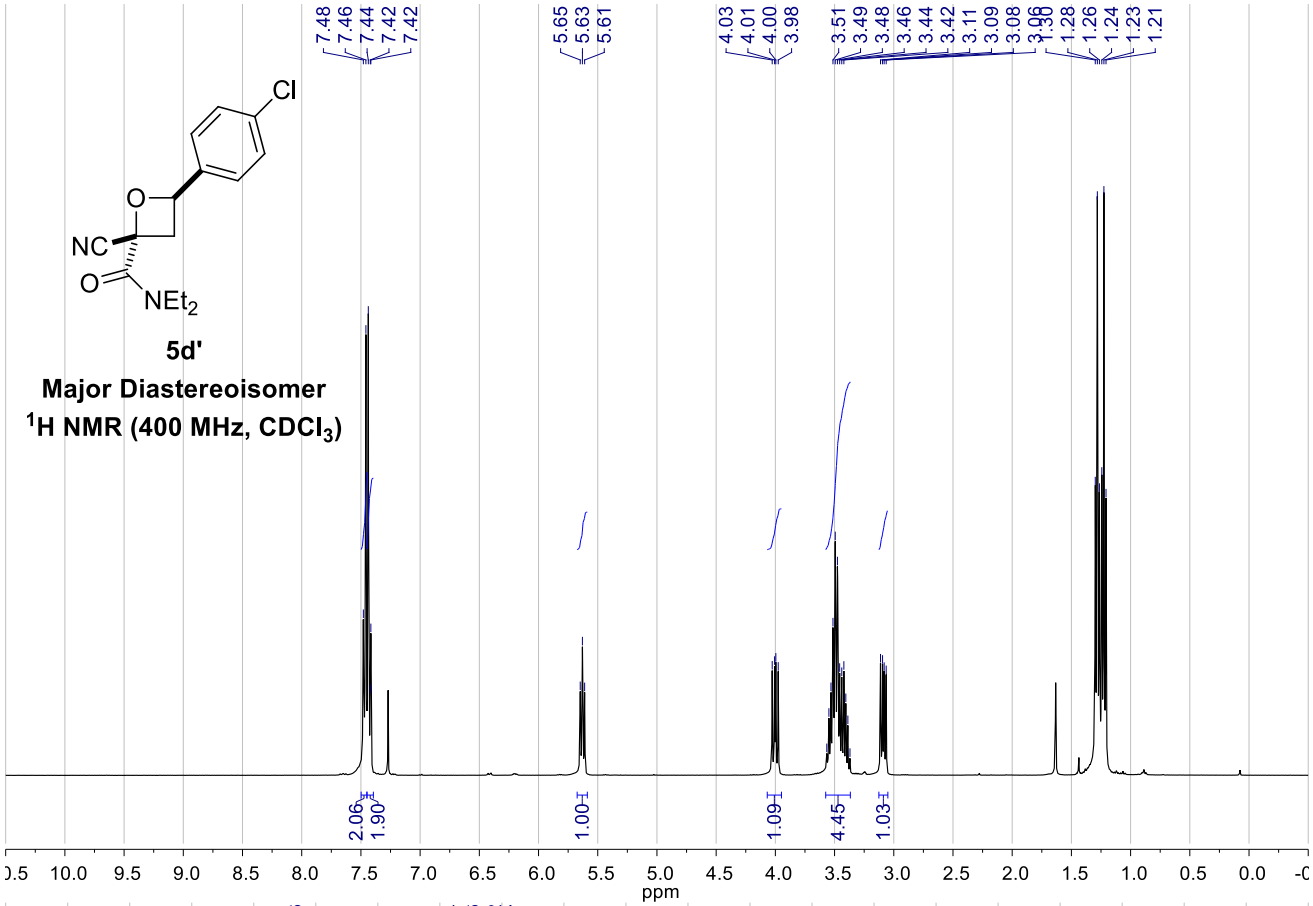

170.61 170.49 169.74 169.63
141.11 140.40 128.59 128.54 128.37 126.40 125.77
81.33 81.24 80.96 80.18 79.79 79.77 79.35 78.59
64.39 64.33 63.82 63.75 63.68 62.27 62.04 36.93 36.92 36.67 36.63
16.55 16.50 16.44 16.38 16.37 16.33 16.31 14.13
5b
13C NMR (101 MHz, CDCl3)
ppm

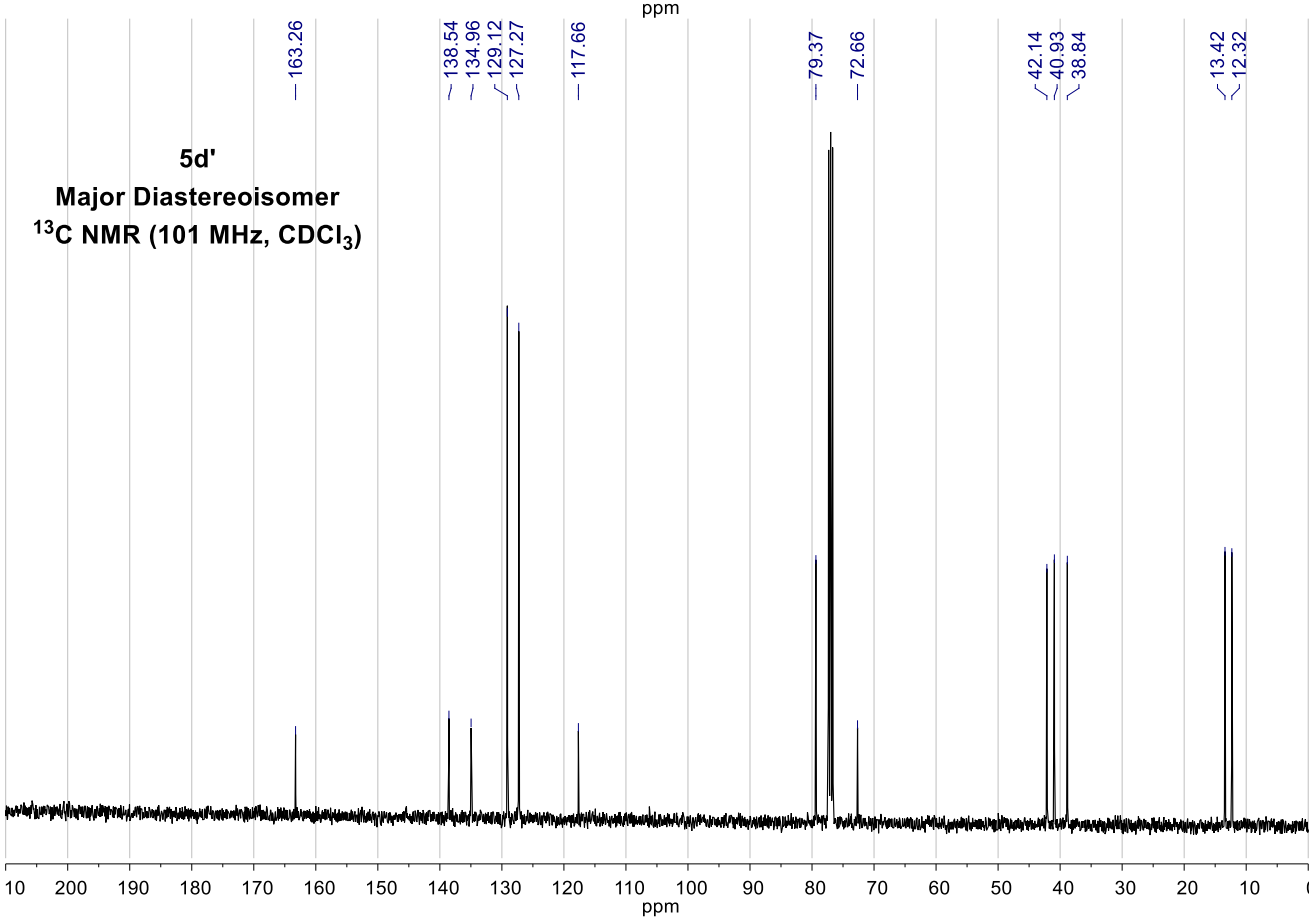

O
F
BnO2C
NC
5c
d.r. 2.5:1.0
1H NMR (400 MHz, CDCl3)
ppm


5c
13C NMR (101 MHz, CDCl3)
ppm


7.38
7.37
7.36
7.35
7.35
7.28
7.26
5.83
5.81
5.79
3.64
3.62
3.61
3.59
3.51
3.49
3.49
3.48
3.47
3.46
3.44
3.43
3.42
3.41
3.40
3.38
1.27
1.25
1.23
1.22
1.20
Cl
O
NC
O
NEt2
5d
Minor Diastereoisomer
1H NMR (400 MHz, CDCl3)
2.00
2.22
1.00
1.15
5.15
6.49
ppm


163.31
138.13
135.14
128.98
127.70
118.04
78.48
72.71
41.99
40.86
38.85
13.51
12.32
5d
Minor Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm


7.48
7.46
7.44
7.42
7.42
5.65
5.63
5.61
4.03
4.01
4.00
3.98
3.51
3.49
3.48
3.46
3.44
3.42
3.11
3.09
3.08
1.28
1.26
1.24
1.23
1.21
Cl
O
NC
O
NEt2
5d'
Major Diastereoisomer
1H NMR (400 MHz, CDCl3)
2.06
1.90
1.00
1.09
4.45
1.03
ppm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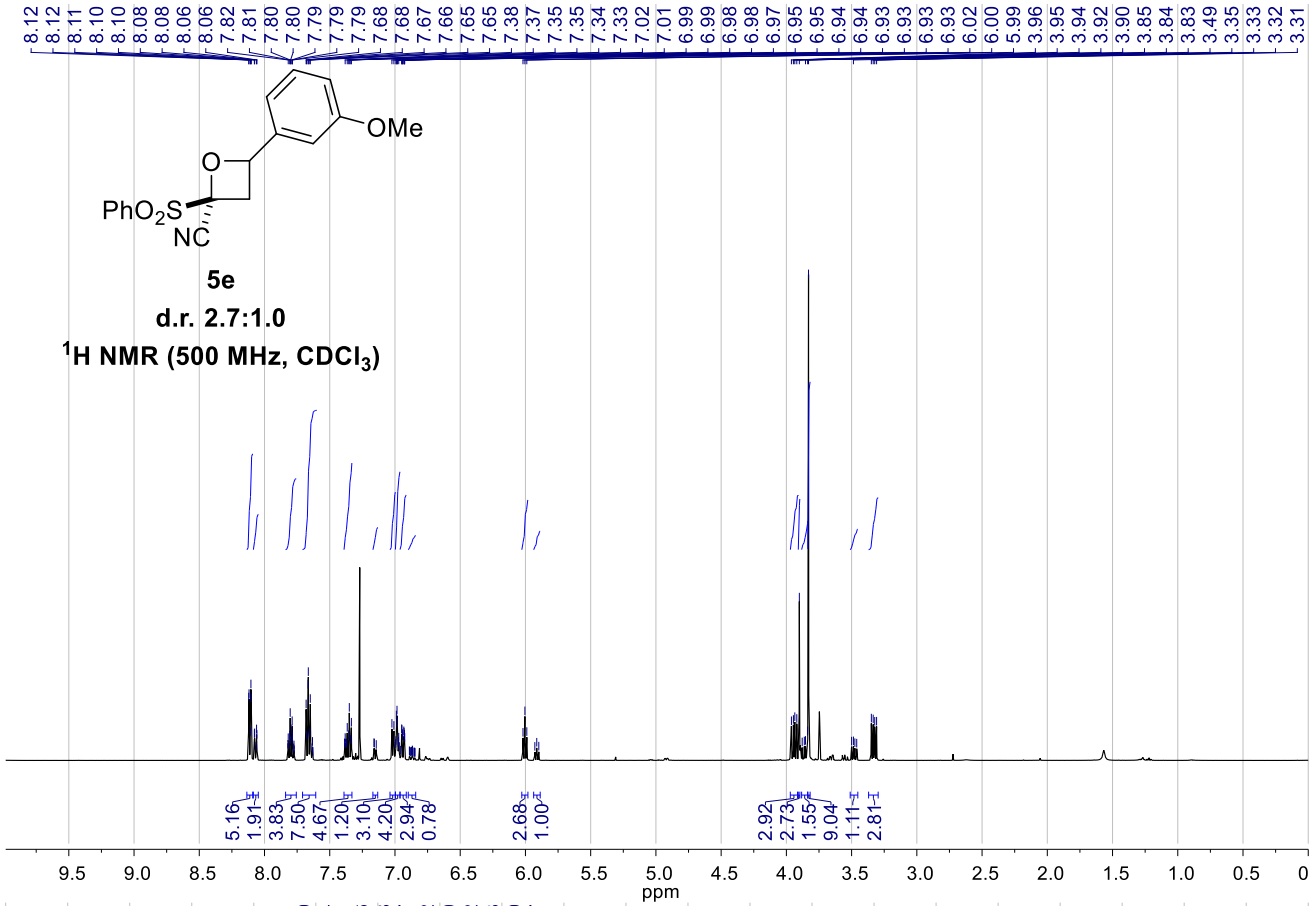
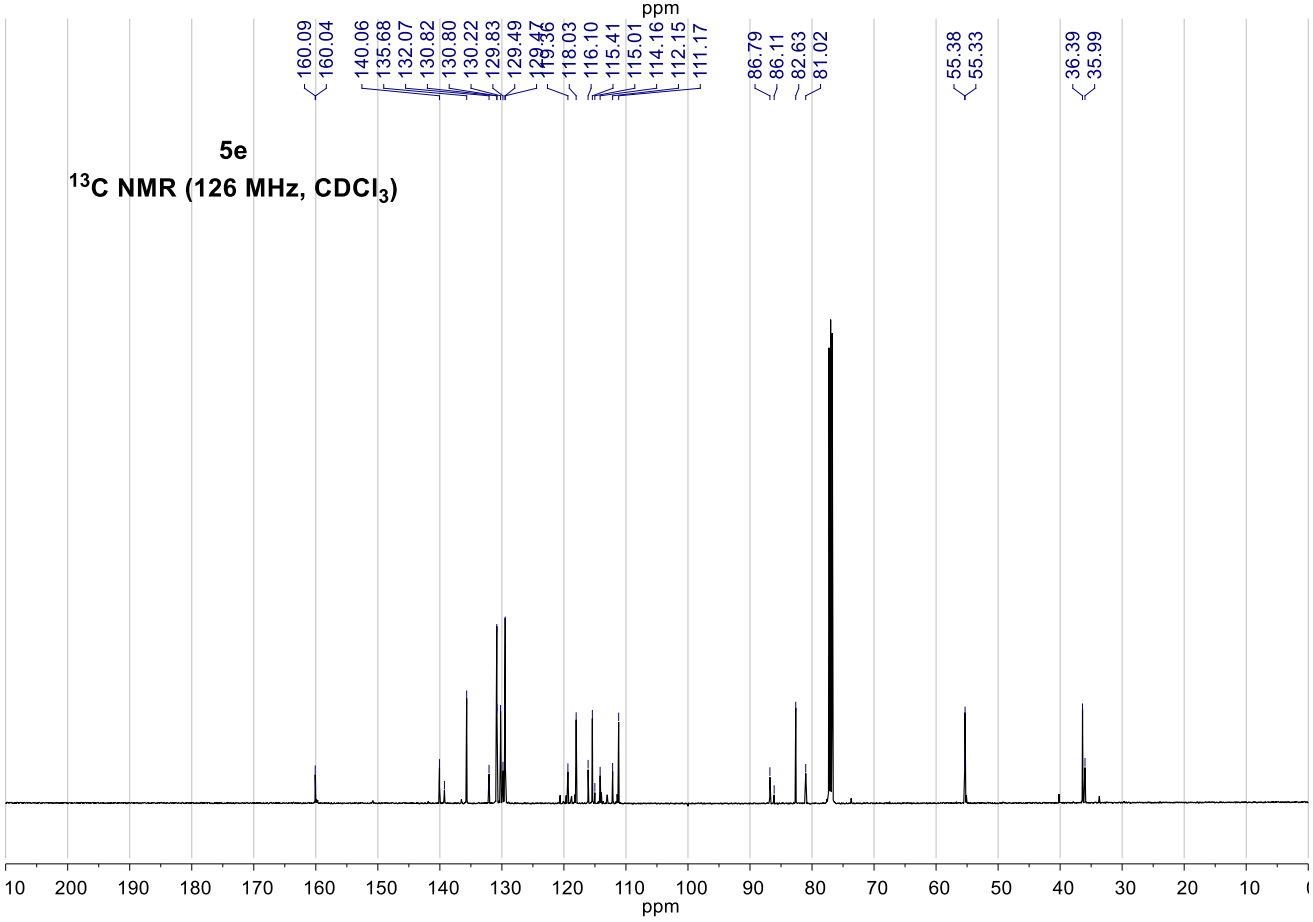
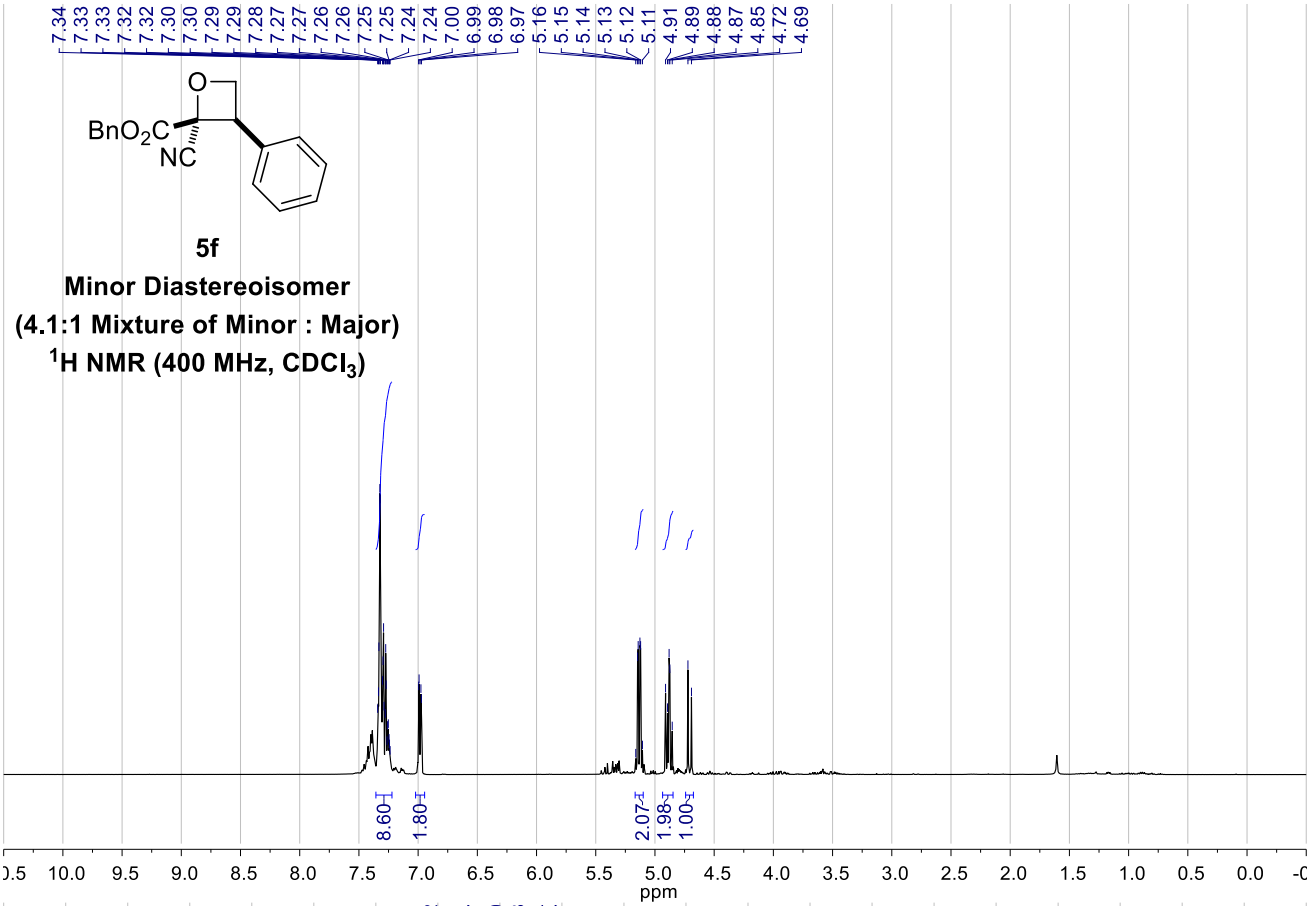
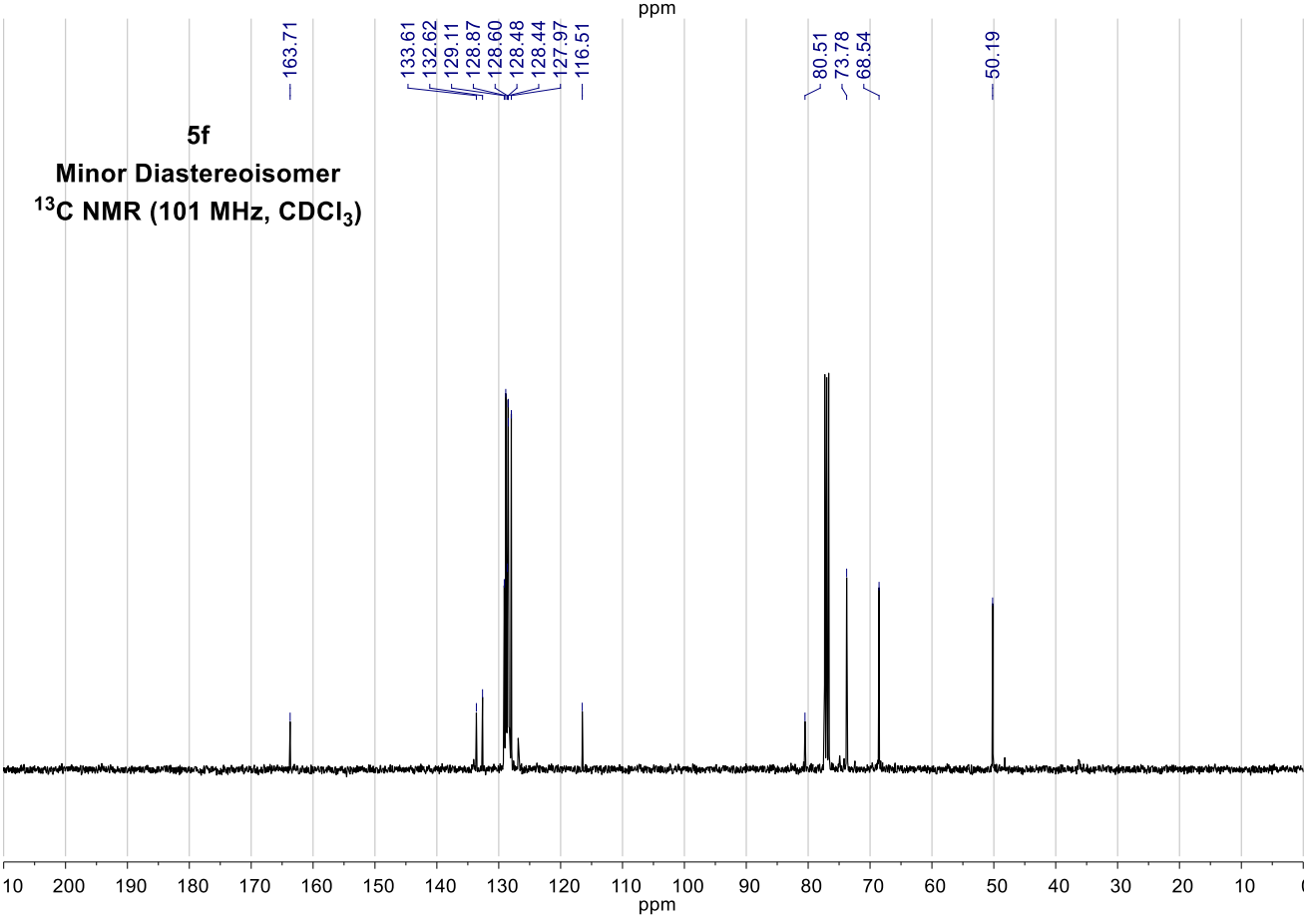
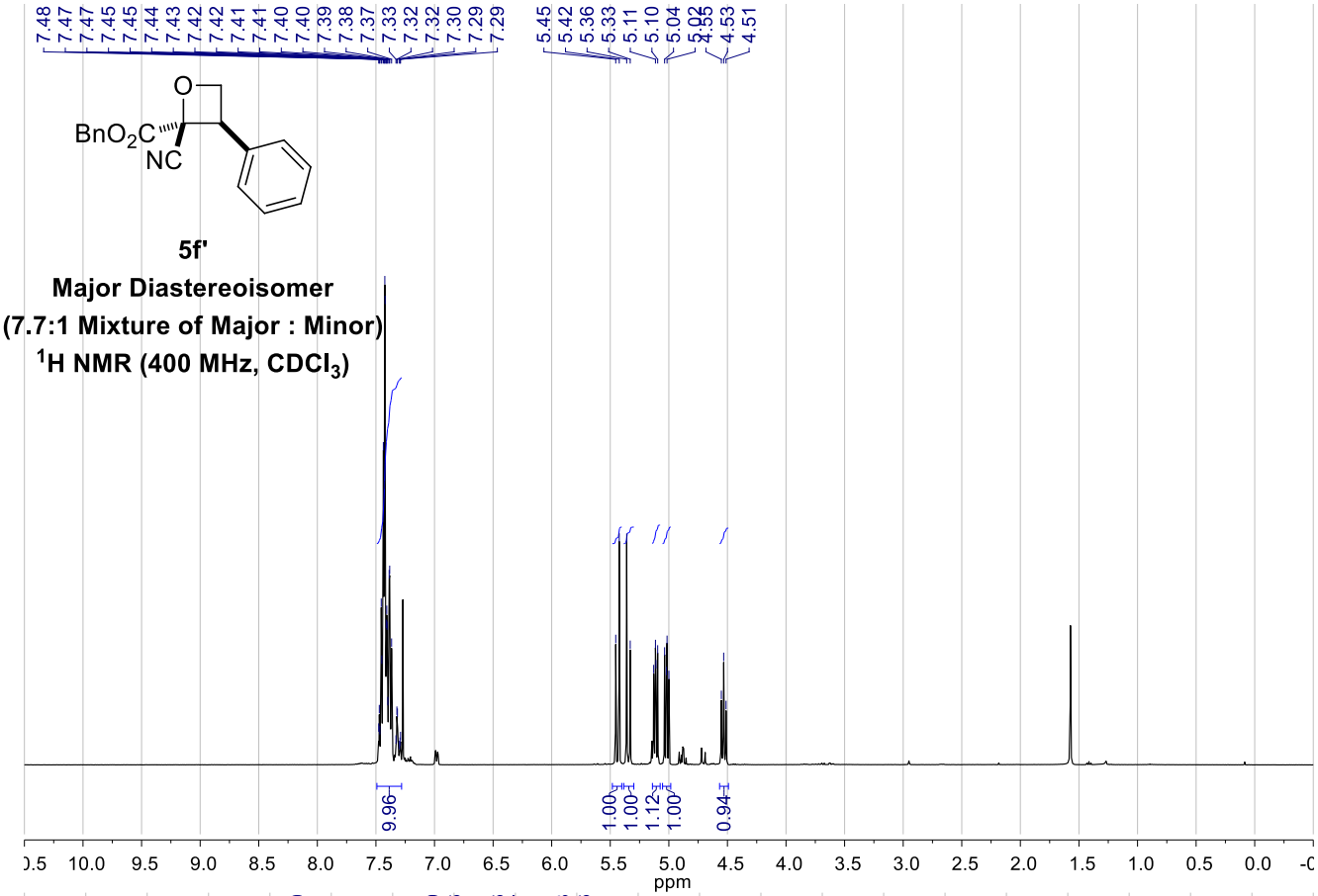
138.54
134.96
129.12
127.27
117.66
79.37
72.66
42.14
40.93
38.84
13.42
12.32
5d'
Major Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm

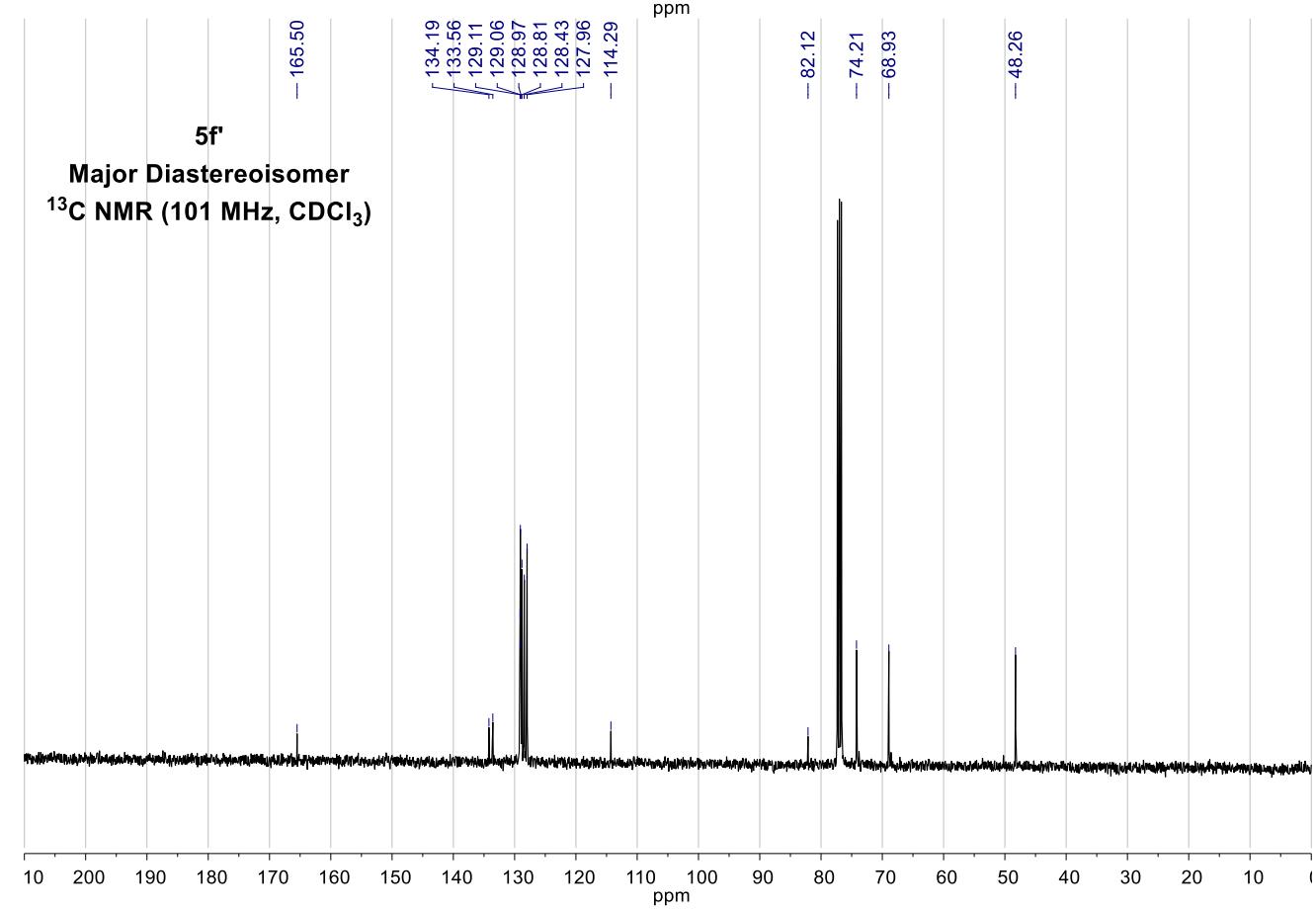

OMe
O
PhO2S
NC
5e
d.r. 2.7:1.0
1H NMR (500 MHz, CDCl3)
ppm

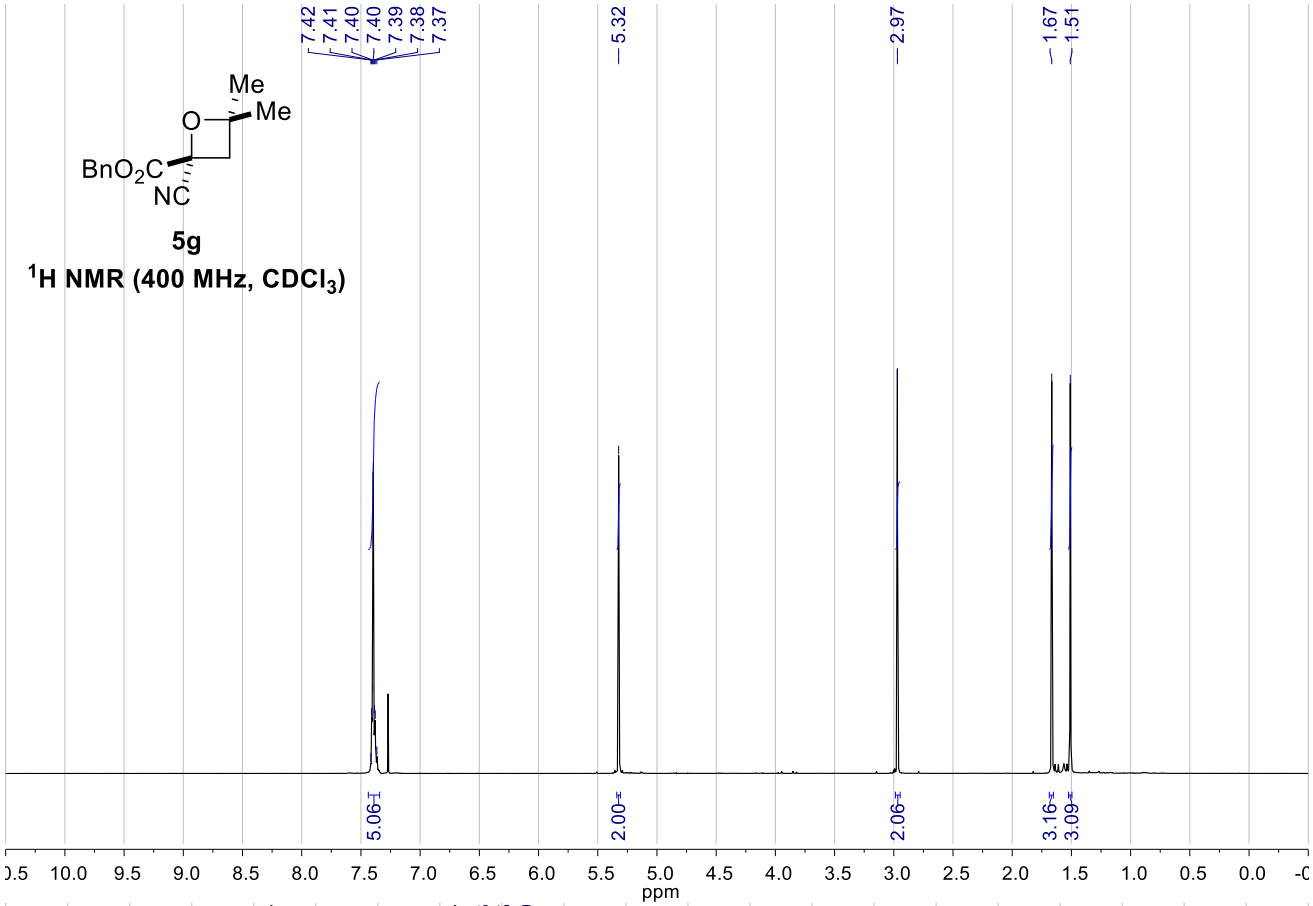

5e
13C NMR (126 MHz, CDCl3)
ppm

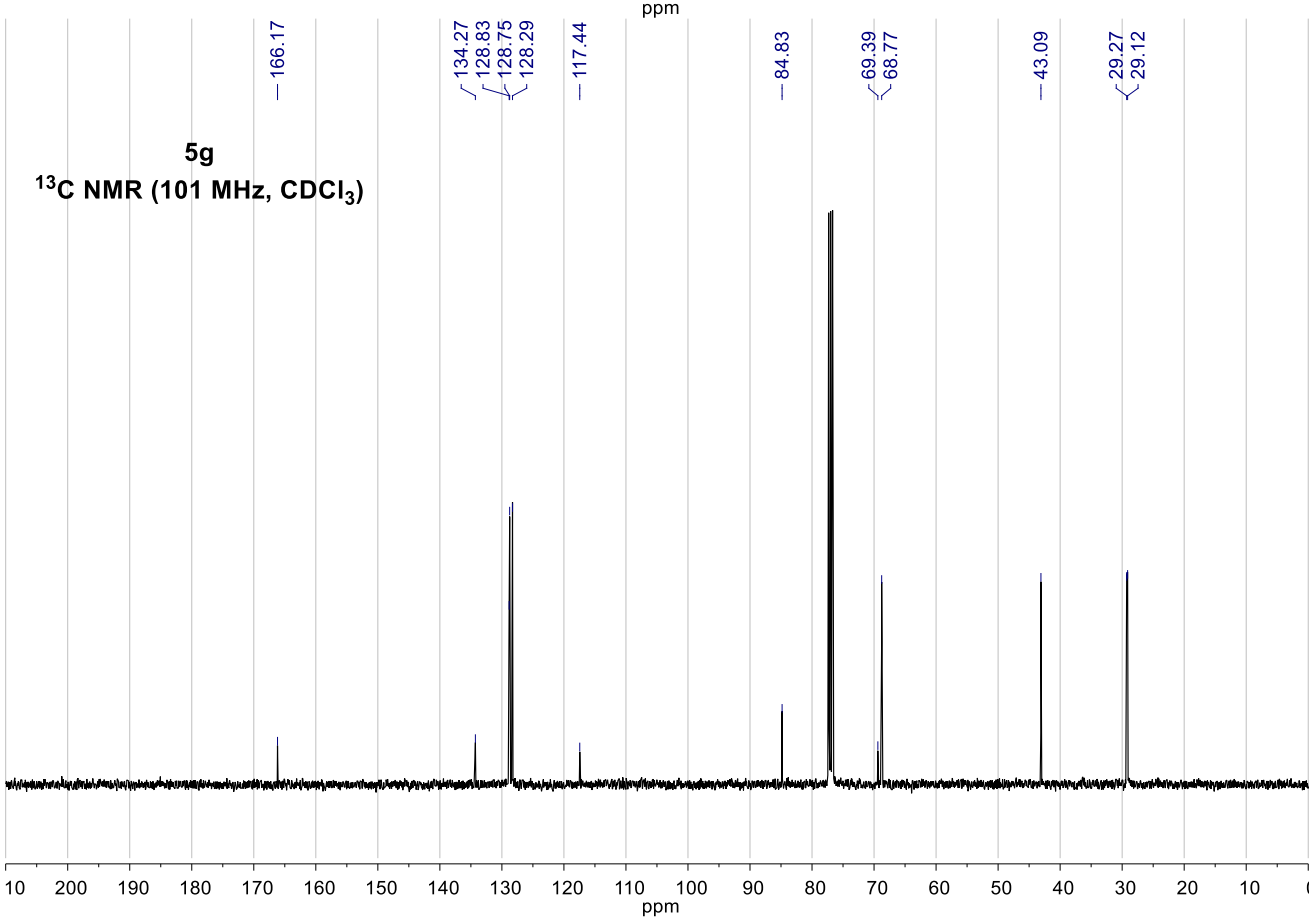

7.34
7.33
7.33
7.32
7.32
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
7.00
6.99
6.98
6.97
5.16
5.15
5.14
5.13
5.12
5.11
4.91
4.89
4.88
4.87
4.85
4.72
4.69
O
BnO2C
NC
5f
Minor Diastereoisomer
(4.1:1 Mixture of Minor : Major)
1H NMR (400 MHz, CDCl3)
8.60
1.80
2.07
1.98
1.00
ppm

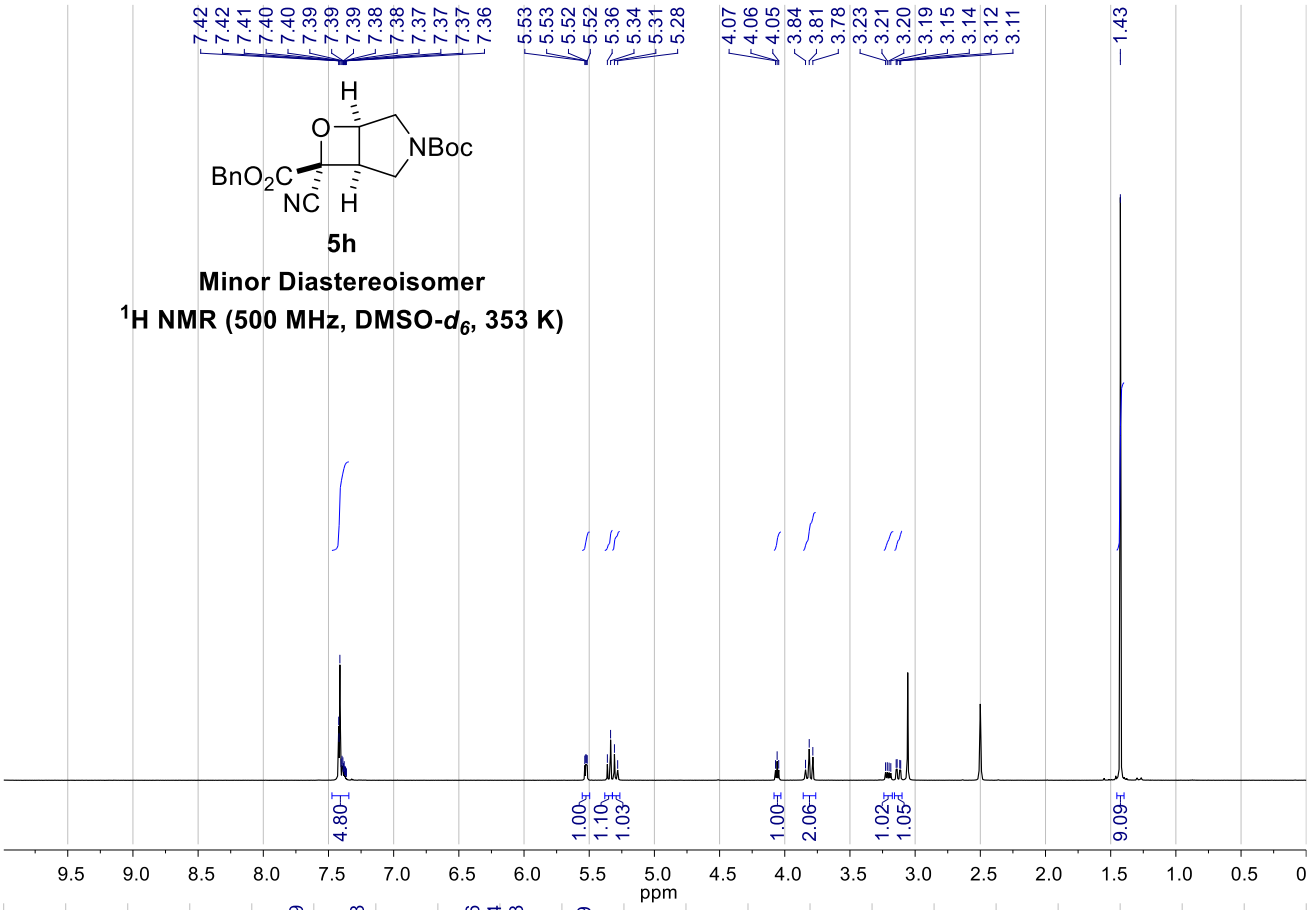

163.71
133.61
132.62
129.11
128.87
128.60
128.48
128.44
127.97
116.51
80.51
73.78
68.54
50.19
5f
Minor Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm

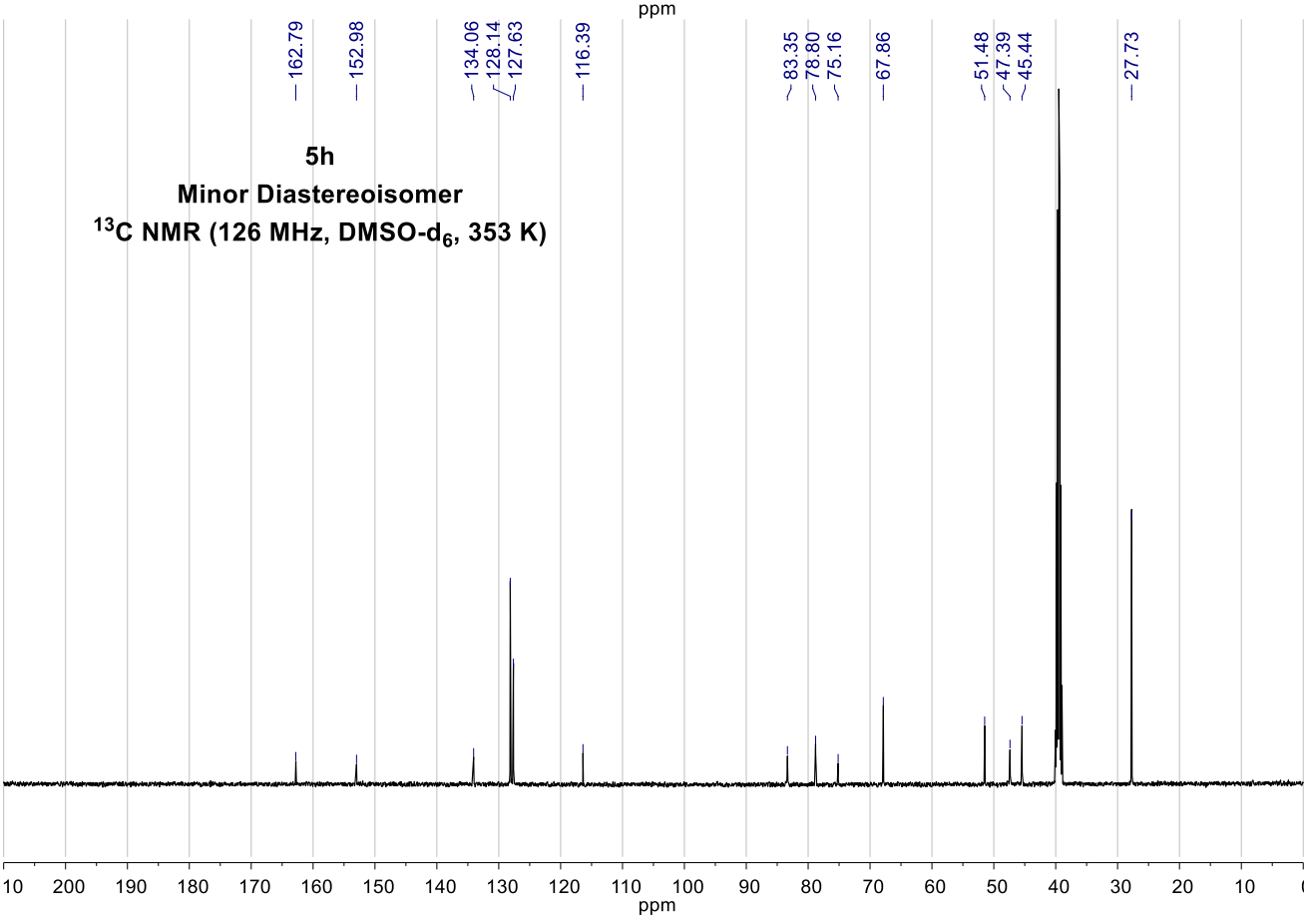

7.48
7.47
7.47
7.45
7.45
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.37
7.33
7.32
7.32
7.30
7.29
7.29
5.45
5.42
5.36
5.33
5.11
5.10
5.04
4.55
4.53
4.51
O
BnO2C
NC
5f'
Major Diastereoisomer
(7.7:1 Mixture of Major : Minor)
1H NMR (400 MHz, CDCl3)
9.96
1.00
1.00
1.12
1.00
0.94
ppm

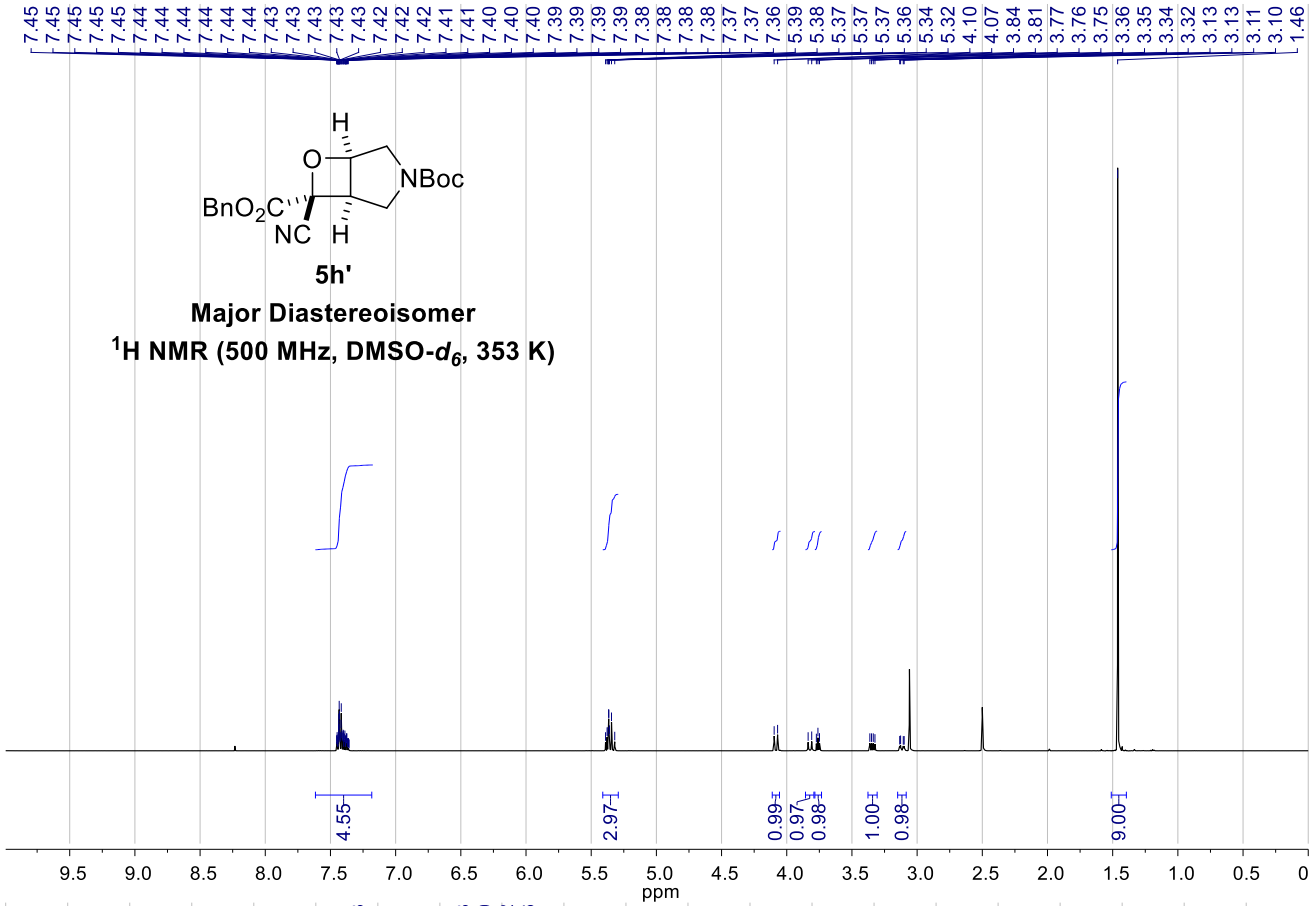

165.50
134.19
133.56
129.11
129.06
128.97
128.81
128.43
127.96
114.29
82.12
74.21
68.93
48.26
5f'
Major Diastereoisomer
13C NMR (101 MHz, CDCl3)
ppm

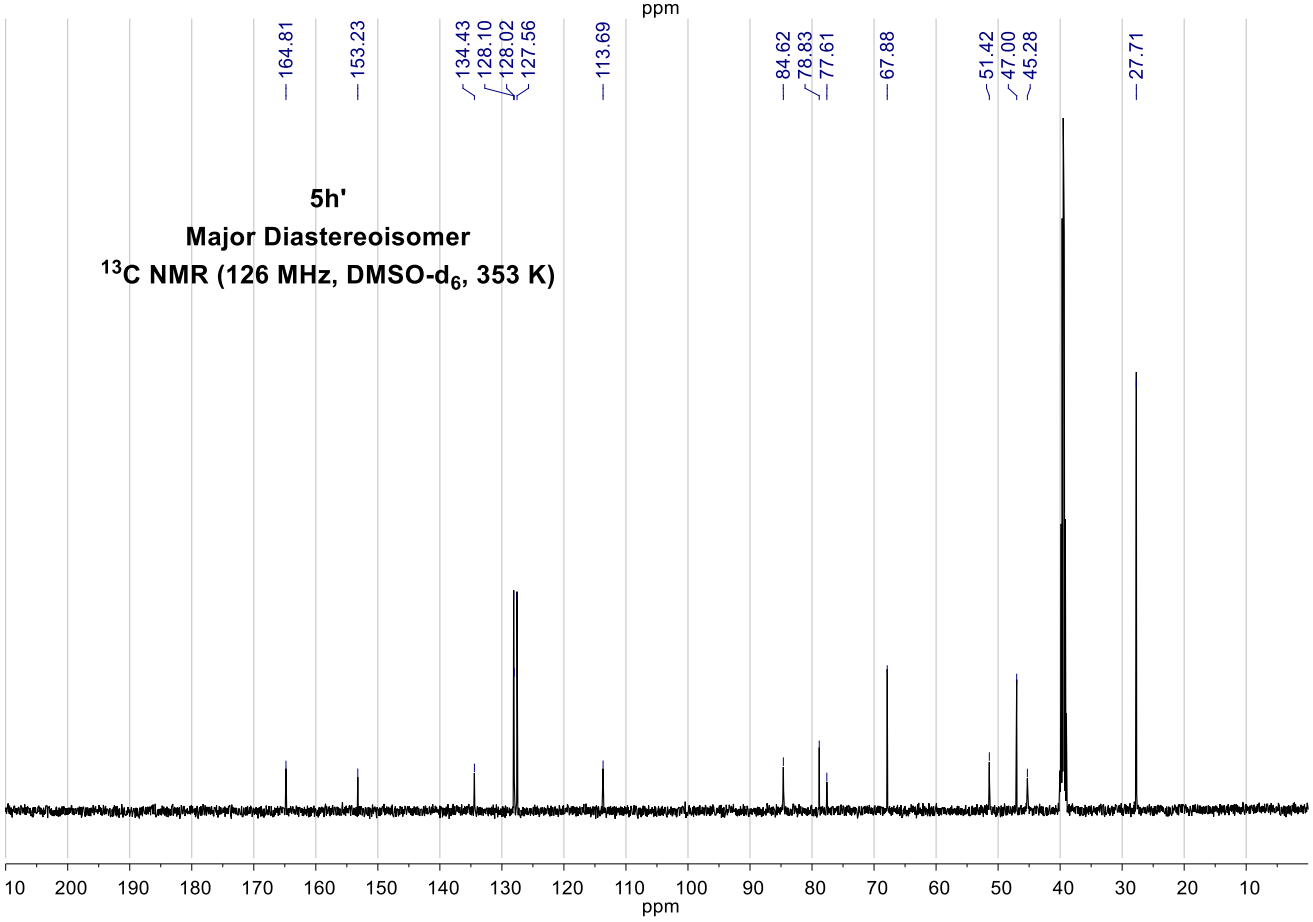

7.42
7.41
7.40
7.40
7.39
7.38
7.37
5.32
2.97
1.67
1.51
Me
Me
O
BnO2C
NC
5g
1H NMR (400 MHz, CDCl3)
5.06
2.00
2.06
3.16
3.09
ppm

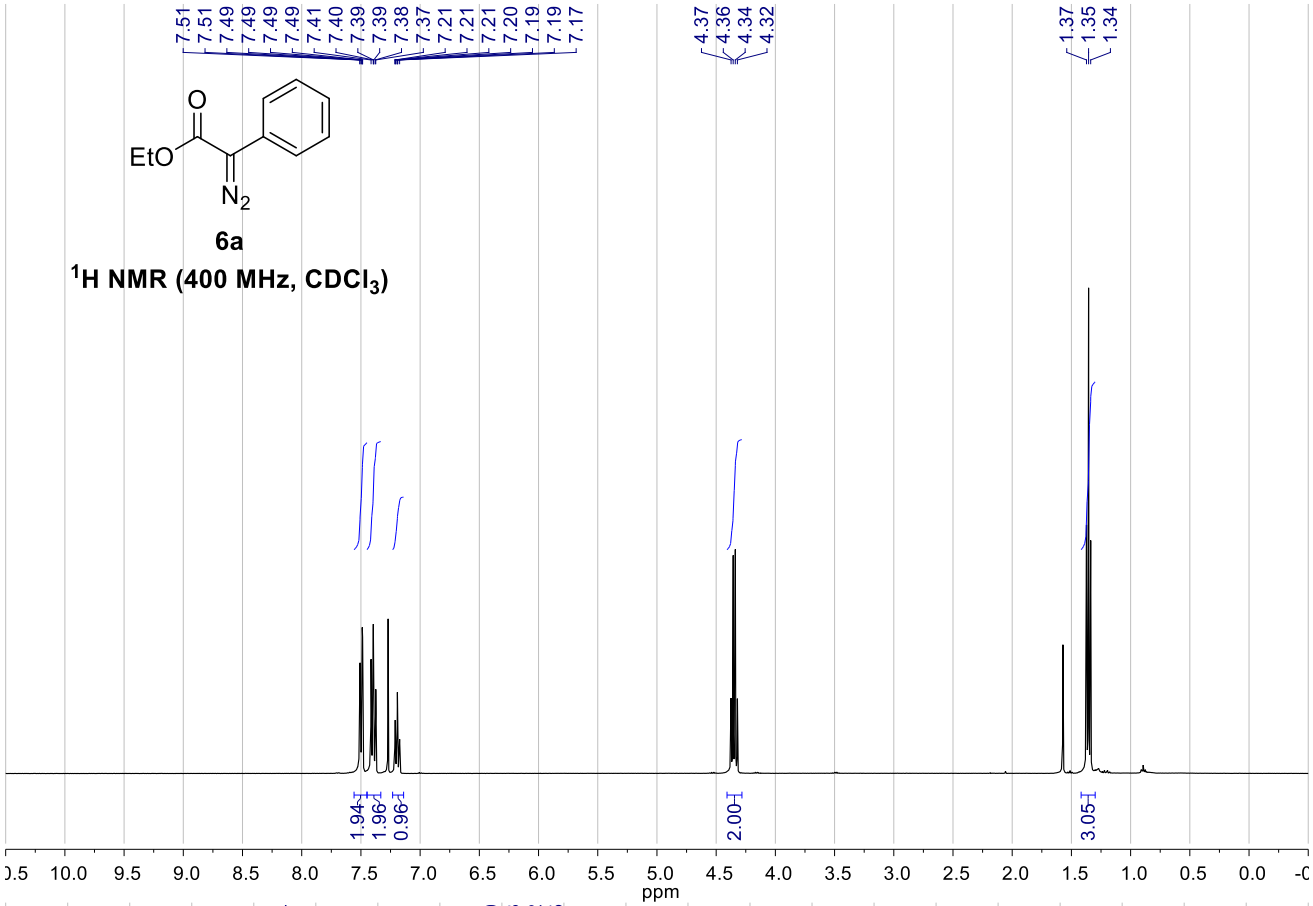

166.17
134.27
128.83
128.75
128.29
117.44
84.83
69.39
68.77
43.09
29.27
29.12
5g
13C NMR (101 MHz, CDCl3)
ppm

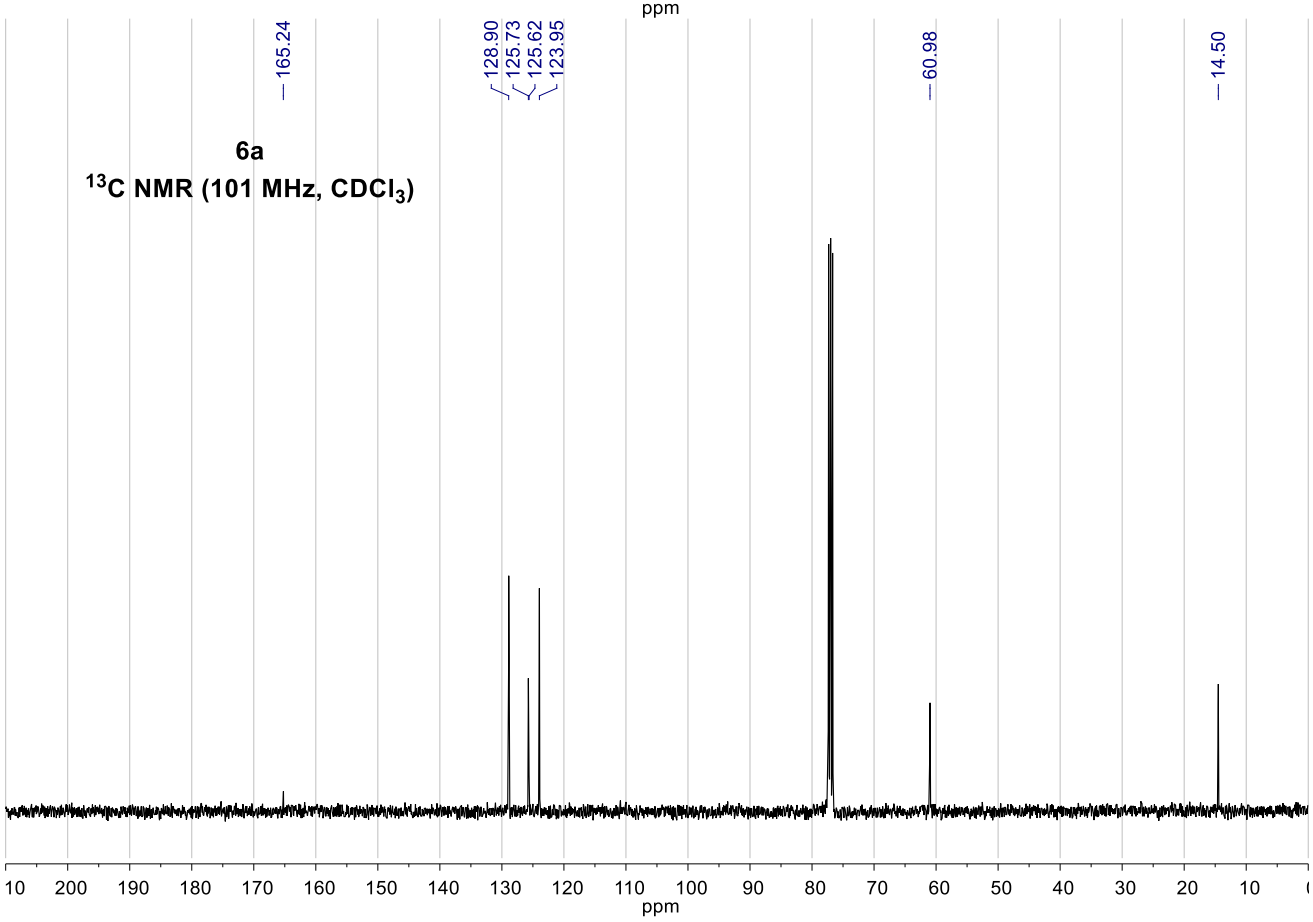

7.42 7.42 7.41 7.40 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.37 7.36
5.53 5.53 5.52 5.52 5.36 5.34 5.31 5.28
4.07 4.06 4.05 3.84 3.81 3.78
3.23 3.21 3.20 3.19 3.15 3.14 3.12 3.11
1.43
H
O
NBoc
BnO2C
NC
H
5h
Minor Diastereoisomer
1H NMR (500 MHz, DMSO-d6, 353 K)
4.80
1.00
1.10
1.03
1.00
2.06
1.02
1.05
9.09
ppm

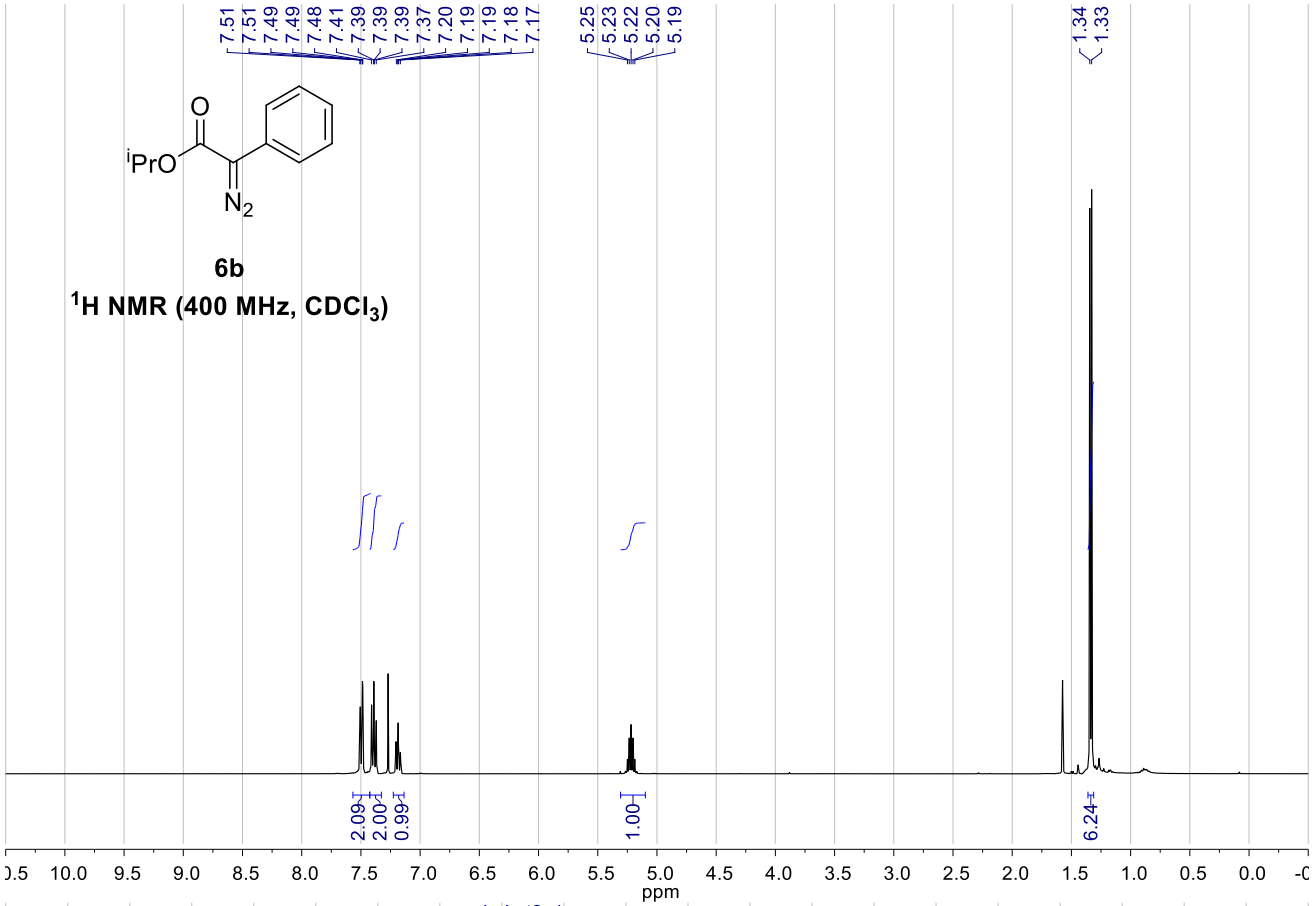

162.79
152.98
134.06
128.14
127.63
116.39
83.35
78.80
75.16
67.86
51.48
47.39
45.44
27.73
5h
Minor Diastereoisomer
13C NMR (126 MHz, DMSO-d6, 353 K)
ppm

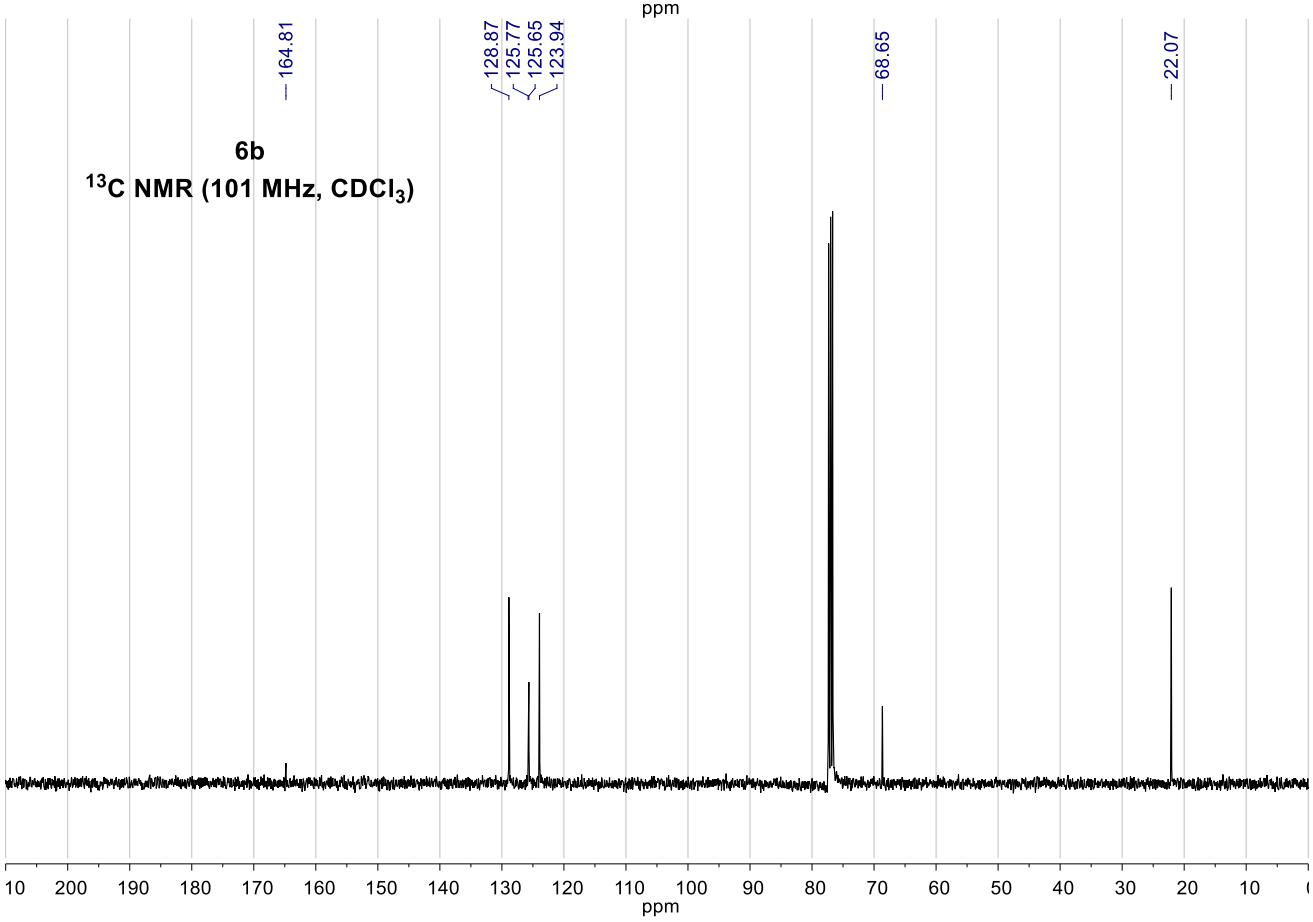

H
O
NBoc
BnO2C
NC
H
5h'
Major Diastereoisomer
1H NMR (500 MHz, DMSO-d6, 353 K)
4.55
2.97
0.99
0.97
0.98
1.00
0.98
9.00
ppm

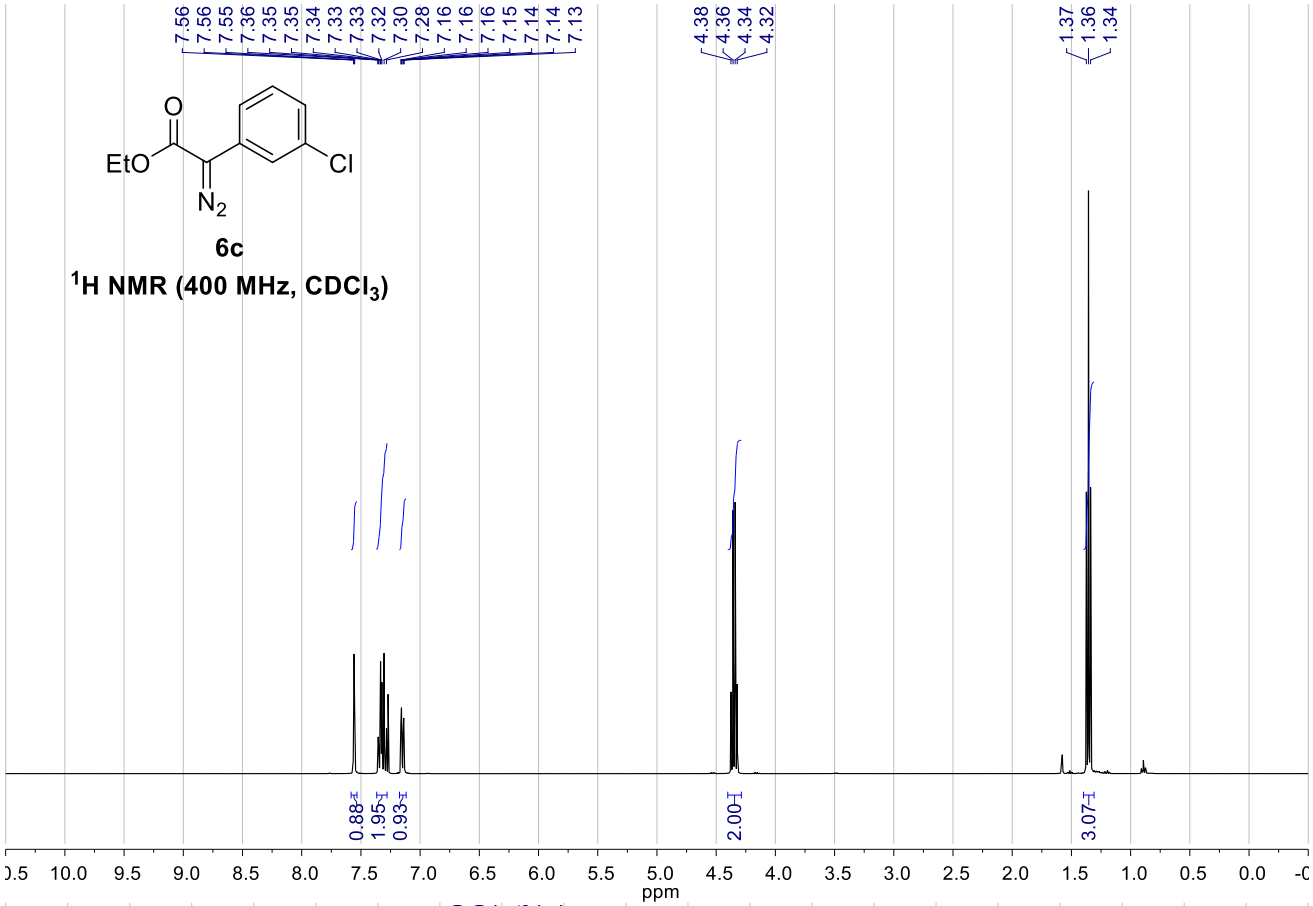

164.81
153.23
134.43
128.10
128.02
127.56
113.69
84.62
78.83
77.61
67.88
51.42
47.00
45.28
27.71
5h'
Major Diastereoisomer
13C NMR (126 MHz, DMSO-d6, 353 K)
ppm

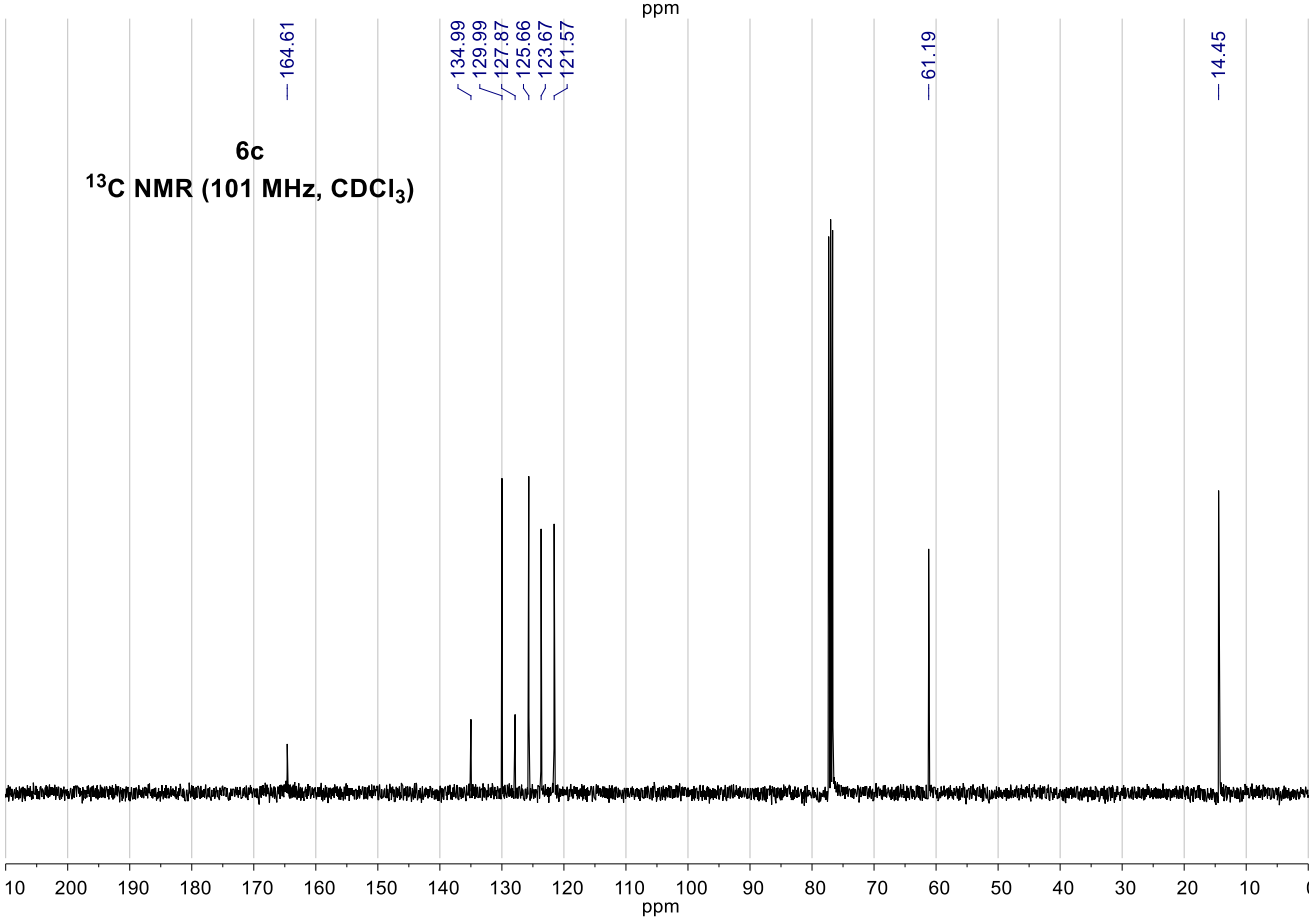

7.51
7.51
7.49
7.49
7.49
7.49
7.41
7.40
7.39
7.39
7.38
7.37
7.21
7.21
7.21
7.20
7.19
7.19
7.17
4.37
4.36
4.34
4.32
1.37
1.35
1.34
O
EtO
N2
6a
1H NMR (400 MHz, CDCl3)
1.94
1.96
0.96
2.00
3.05
ppm

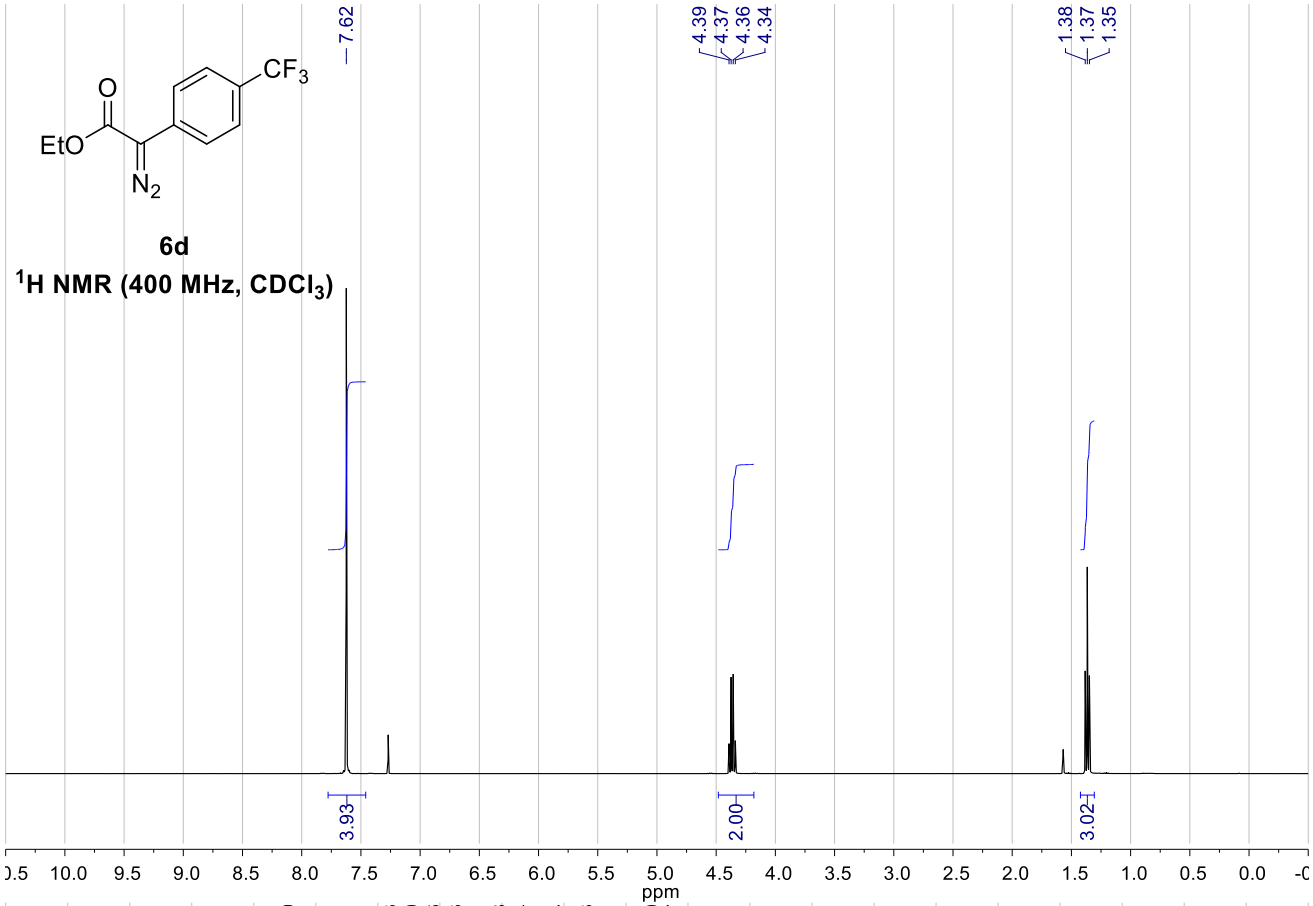

165.24
128.90
125.73
125.62
123.95
60.98
14.50
6a
13C NMR (101 MHz, CDCl3)
ppm


7.51
7.51
7.49
7.49
7.48
7.41
7.39
7.39
7.39
7.37
7.20
7.19
7.19
7.18
7.17
5.25
5.23
5.22
5.20
5.19
1.34
1.33
O
iPrO
N2
6b
1H NMR (400 MHz, CDCl3)
2.09
2.00
0.99
1.00
6.24
ppm


164.81
128.87
125.77
125.65
123.94
68.65
22.07
6b
13C NMR (101 MHz, CDCl3)
ppm

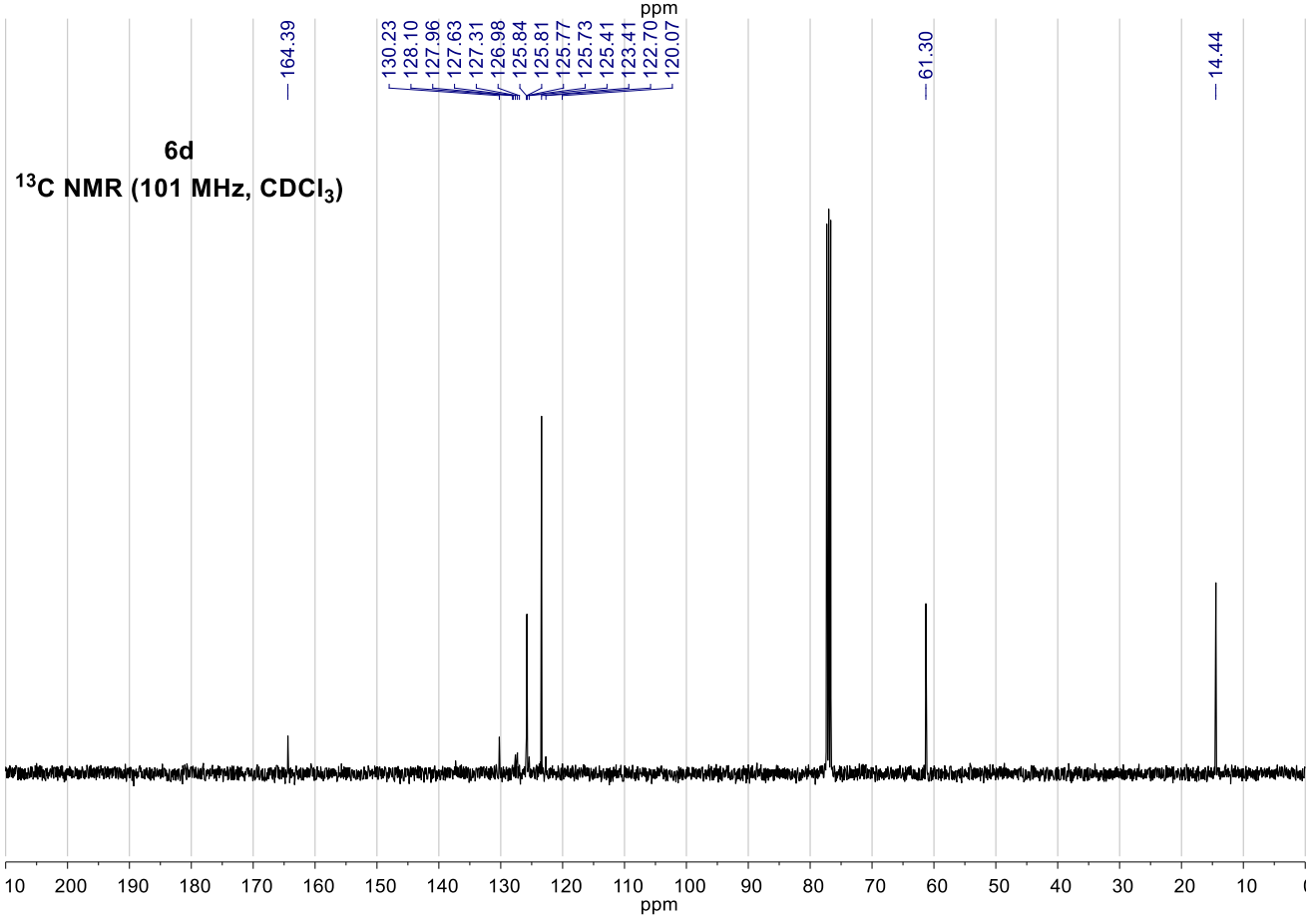

7.56
7.56
7.55
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.30
7.28
7.16
7.16
7.16
7.15
7.14
7.14
7.13
4.38
4.36
4.34
4.32
1.37
1.36
1.34
O
EtO
Cl
N2
6c
1H NMR (400 MHz, CDCl3)
0.88
1.95
0.93
2.00
3.07
ppm


164.61
134.99
129.99
127.87
125.66
123.67
121.57
61.19
14.45
6c
13C NMR (101 MHz, CDCl3)
ppm



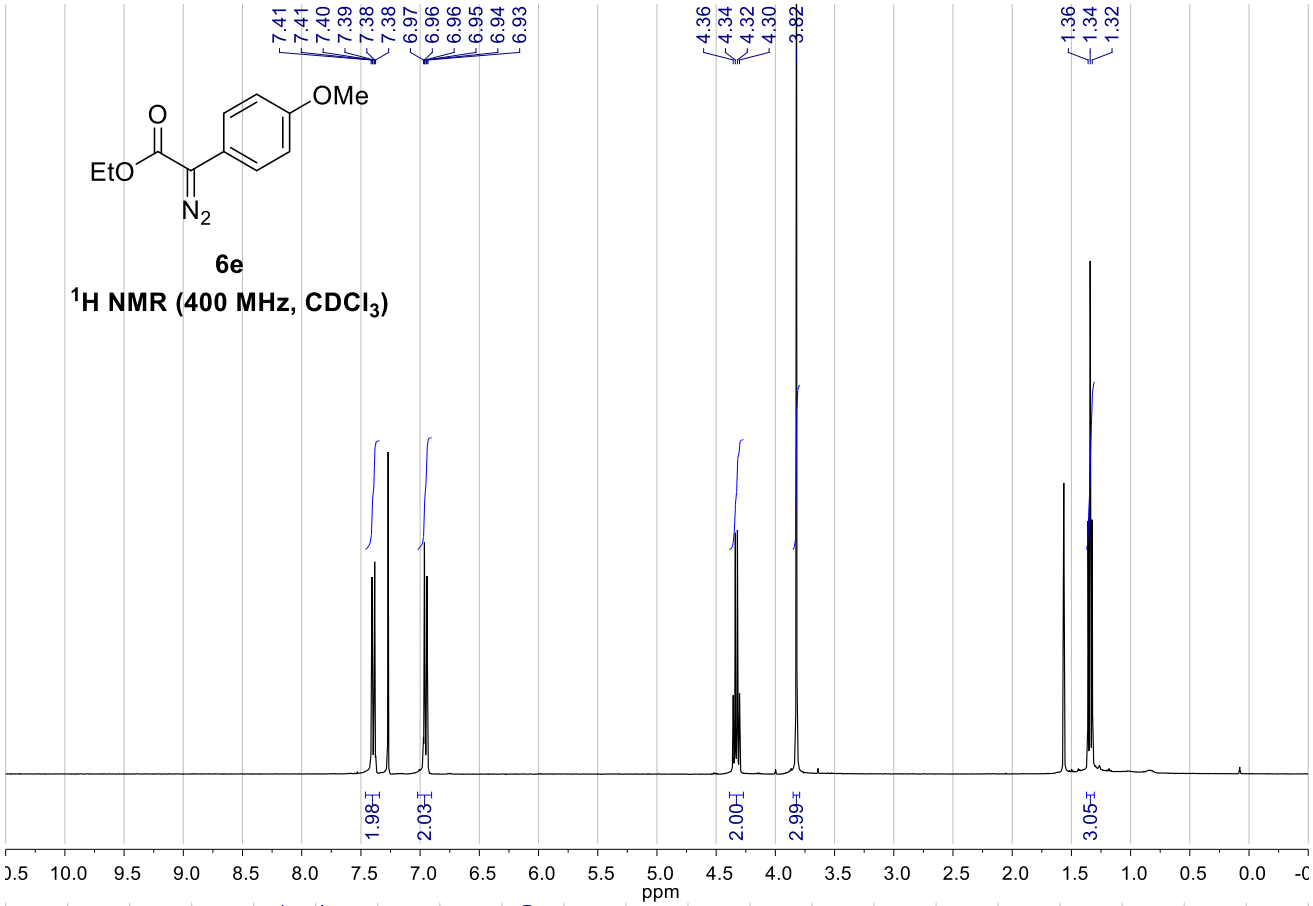
6d

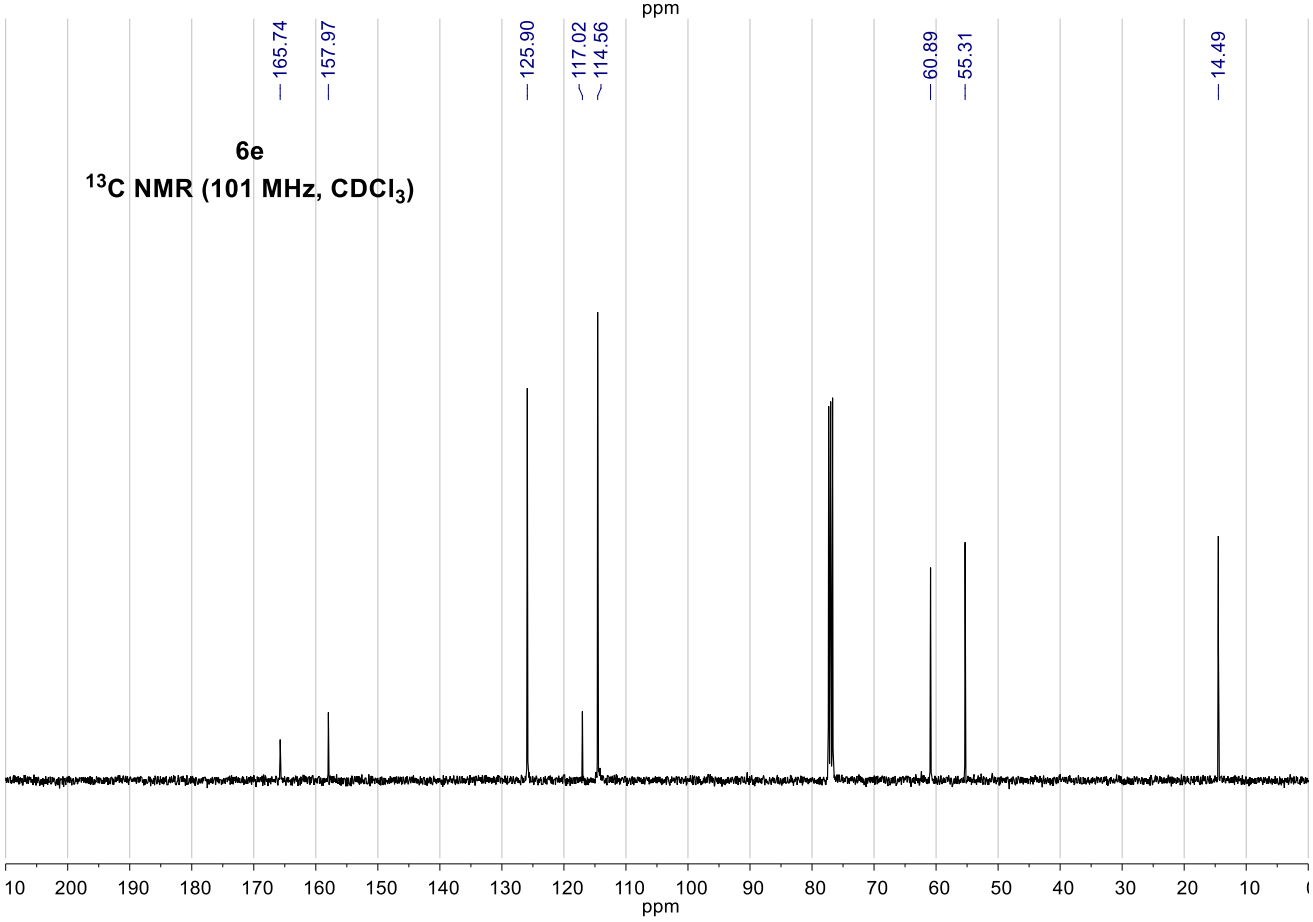
^{1}H NMR (400 MHz, $CDCl_3$)

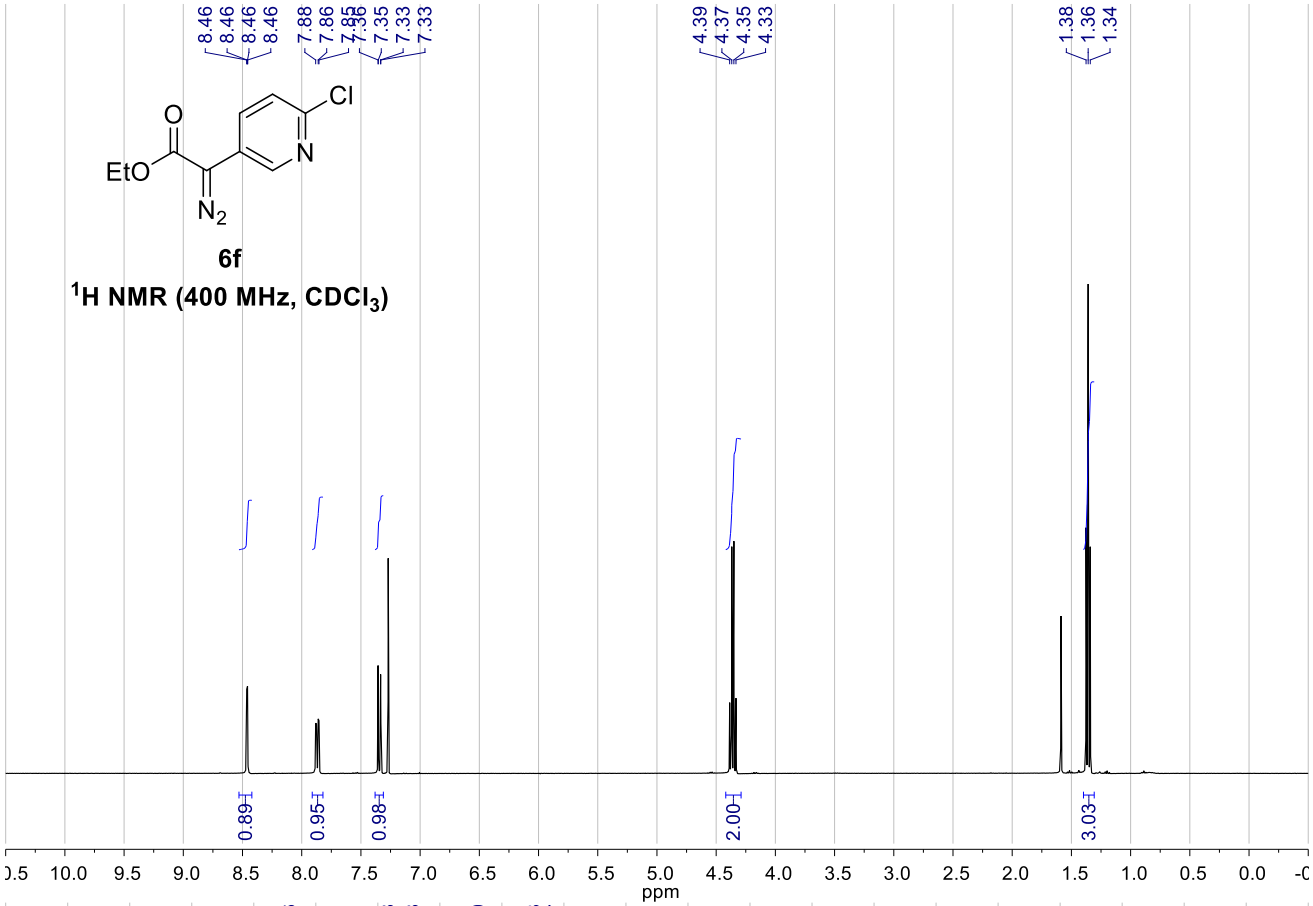


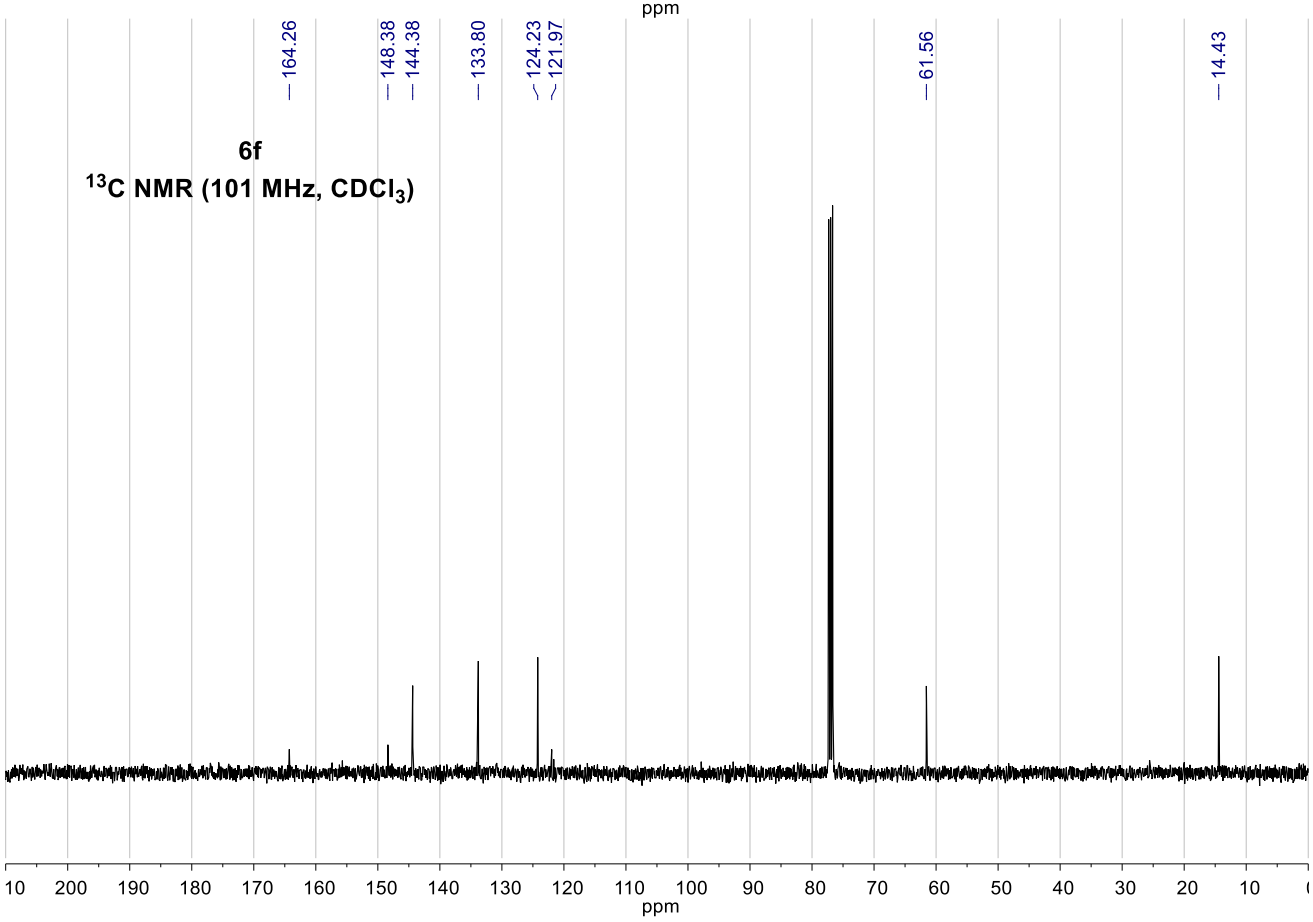
6d

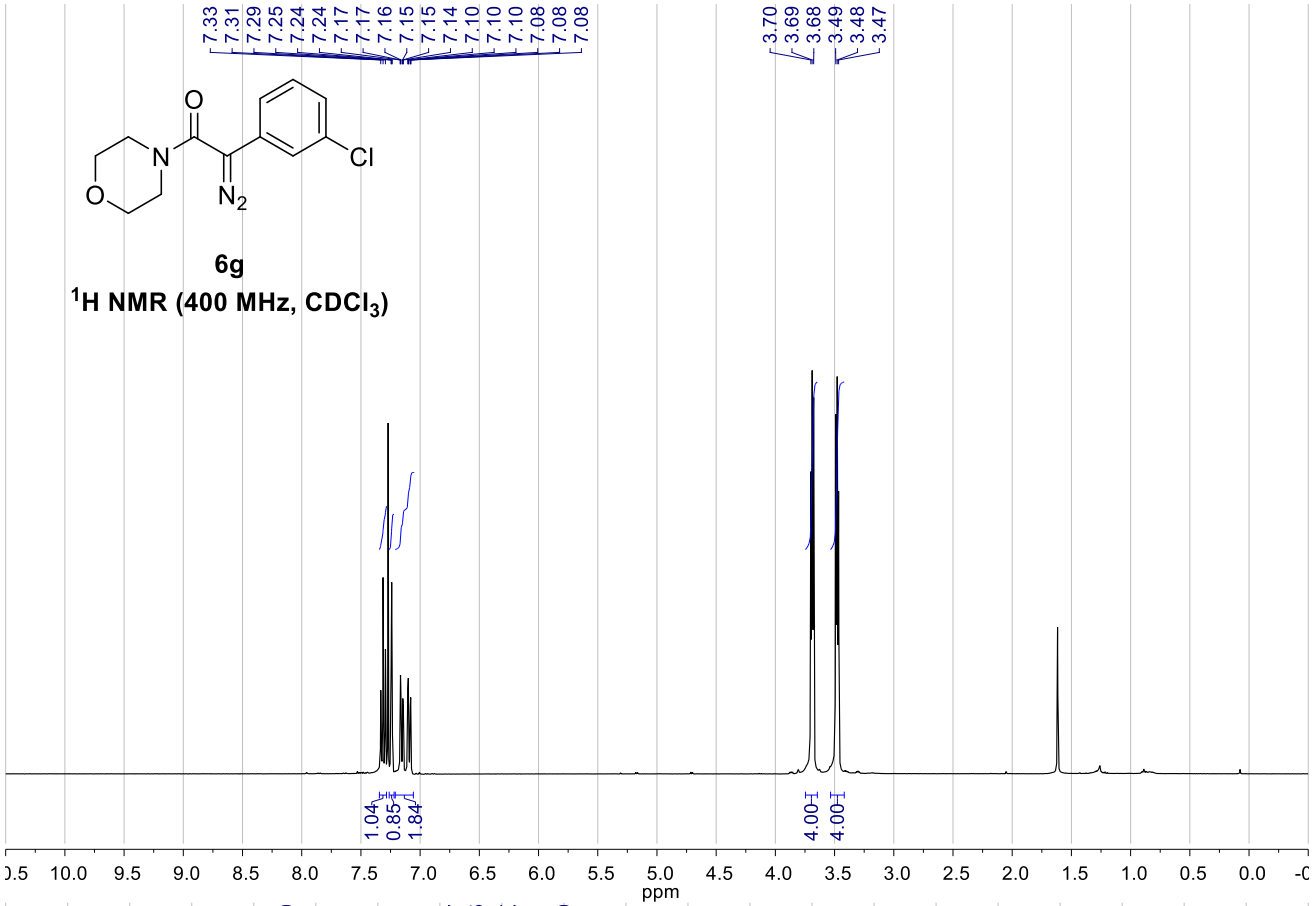
^{13}C NMR (101 MHz, $CDCl_3$)

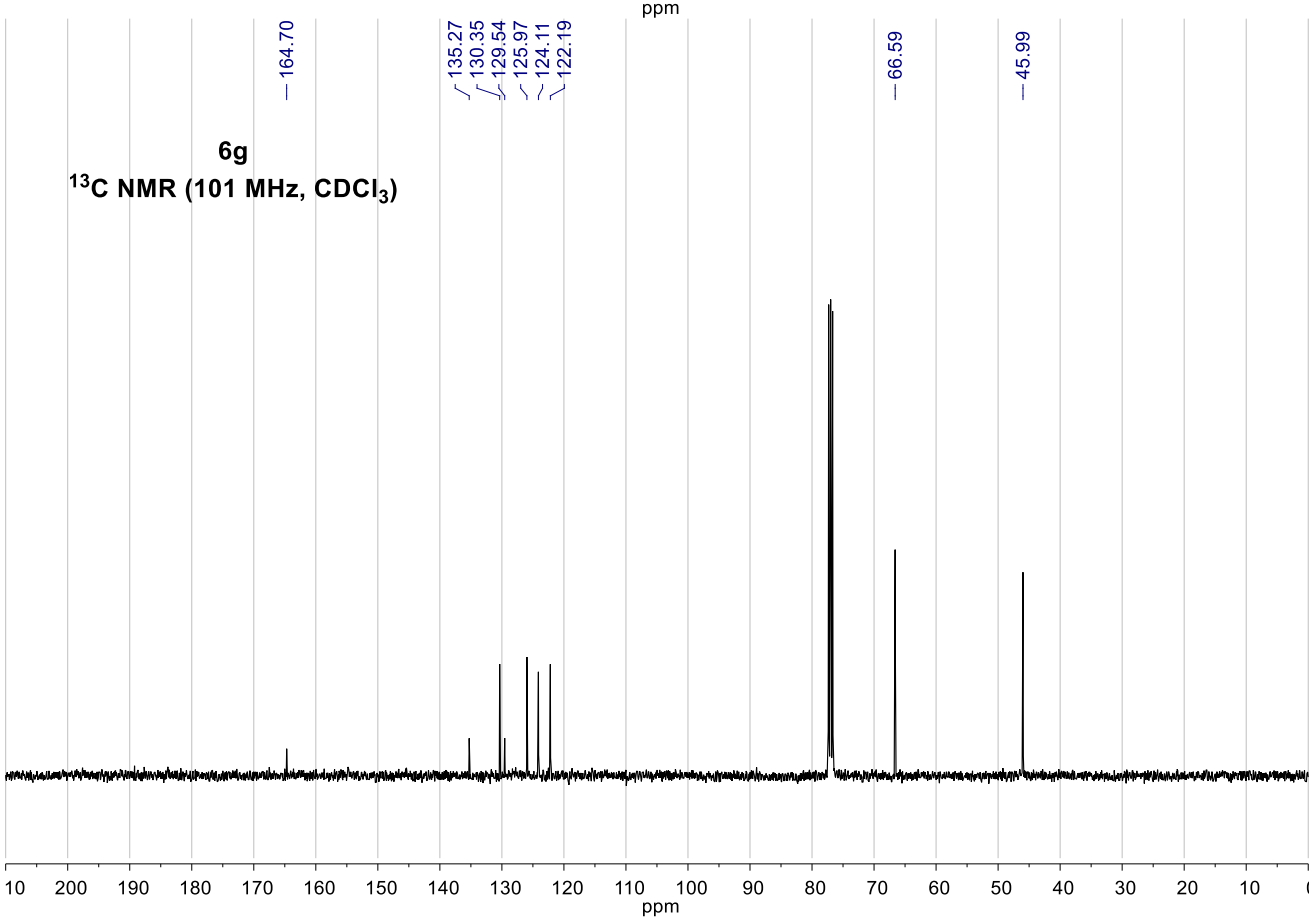

7.41
7.41
7.40
7.39
7.38
7.38
6.97
6.96
6.96
6.95
6.94
6.93
4.36
4.34
4.32
4.30
3.82
1.36
1.34
1.32
OMe
O
EtO
N2
6e
1H NMR (400 MHz, CDCl3)
1.98
2.03
2.00
2.99
3.05
ppm

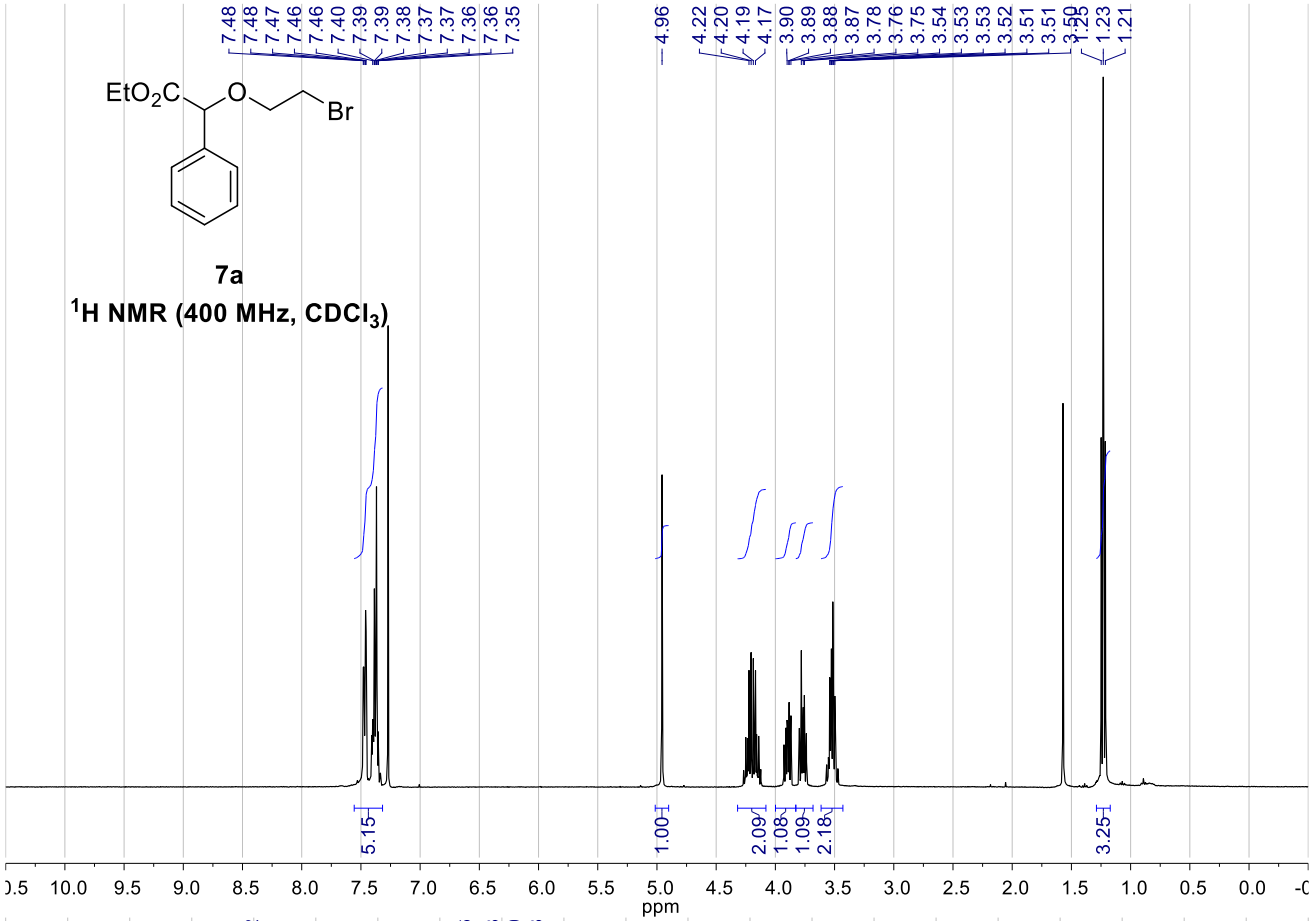

165.74
157.97
125.90
117.02
114.56
60.89
55.31
14.49
6e
13C NMR (101 MHz, CDCl3)
ppm

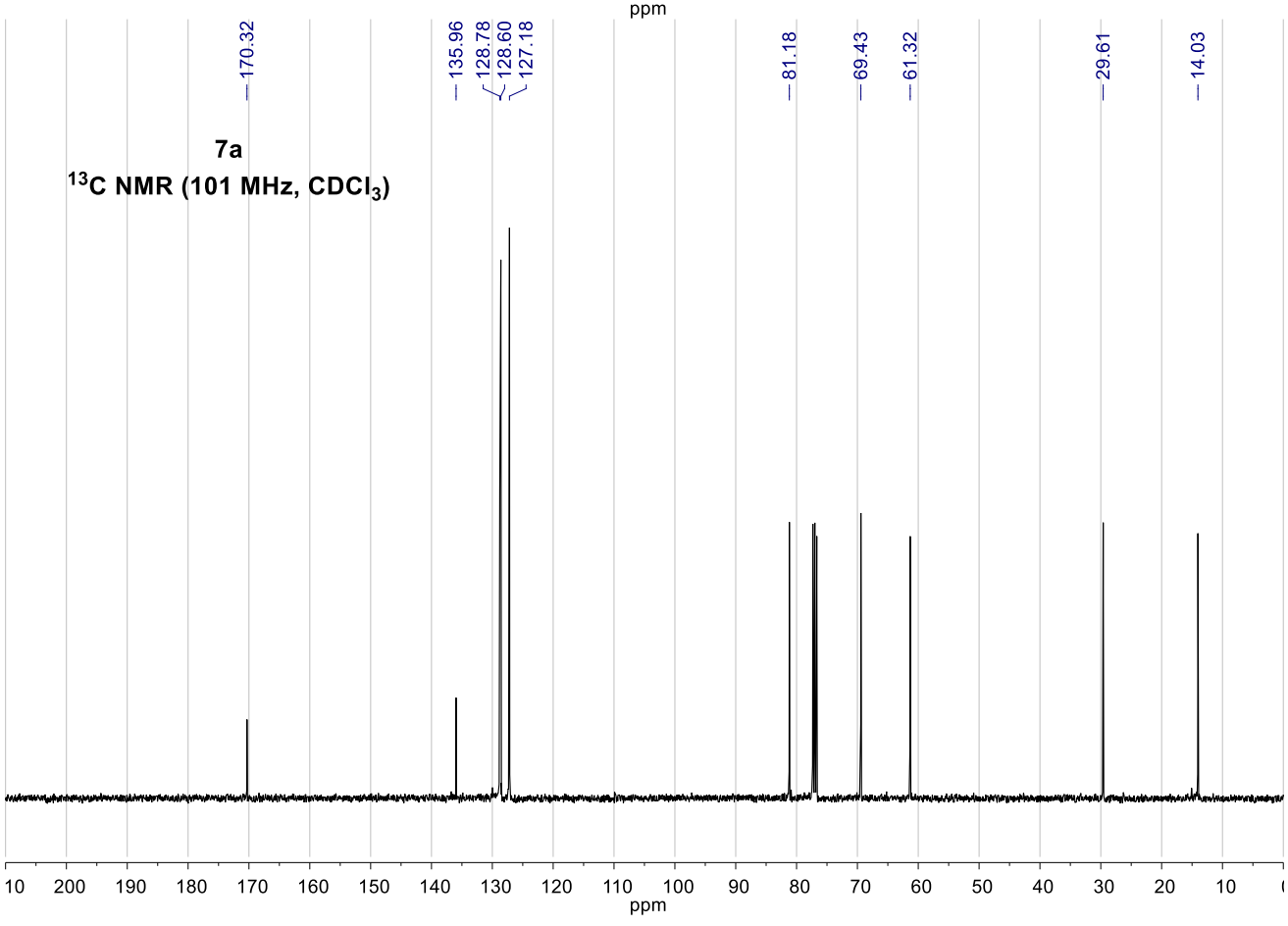

8.46
8.46
8.46
8.46
7.88
7.86
7.85
7.36
7.35
7.33
7.33
4.39
4.37
4.35
4.33
1.38
1.36
1.34
Cl
O
EtO
N
N2
6f
1H NMR (400 MHz, CDCl3)
0.89
0.95
0.98
2.00
3.03
ppm

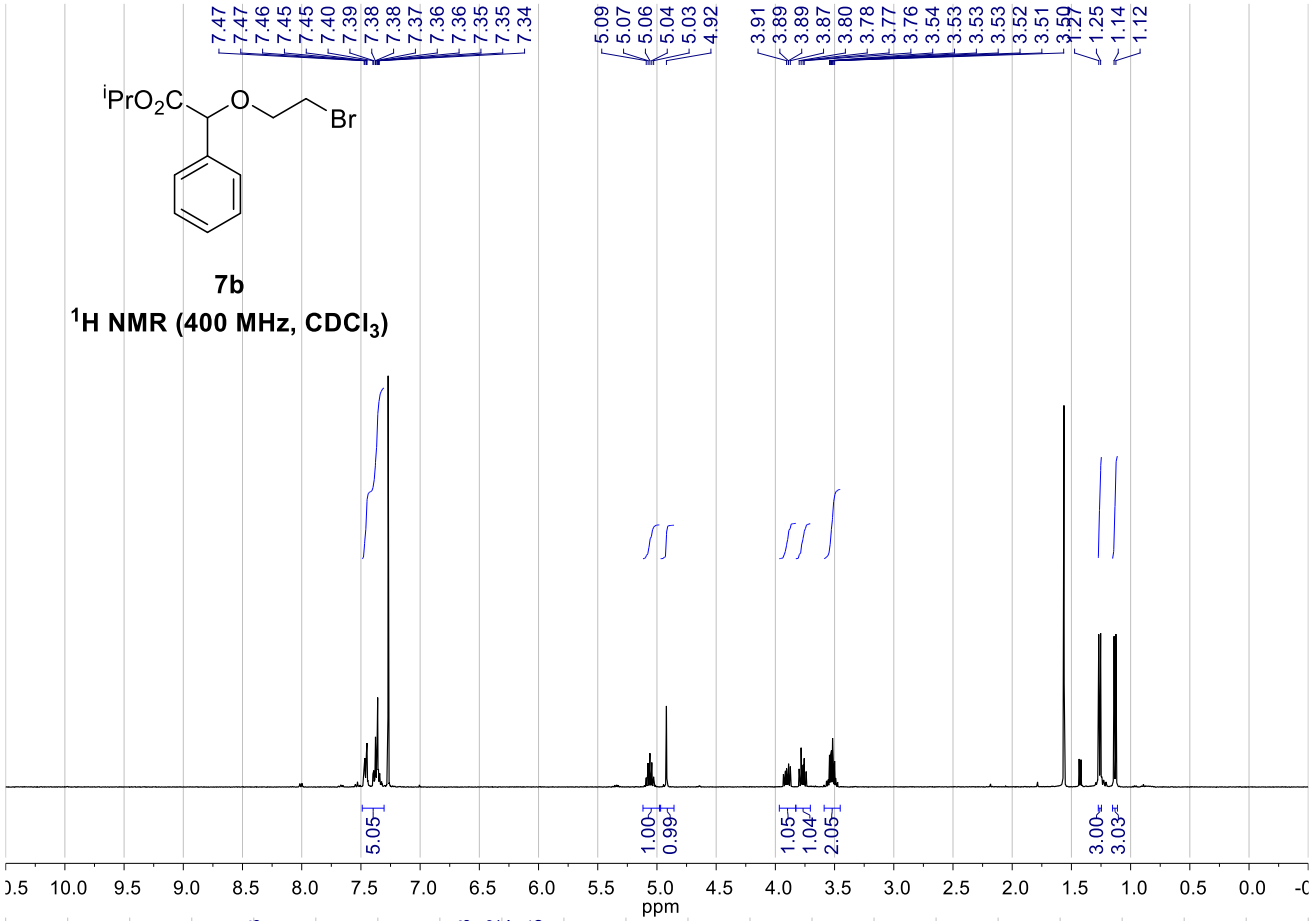

164.26
148.38
144.38
133.80
124.23
121.97
61.56
14.43
6f
13C NMR (101 MHz, CDCl3)
ppm

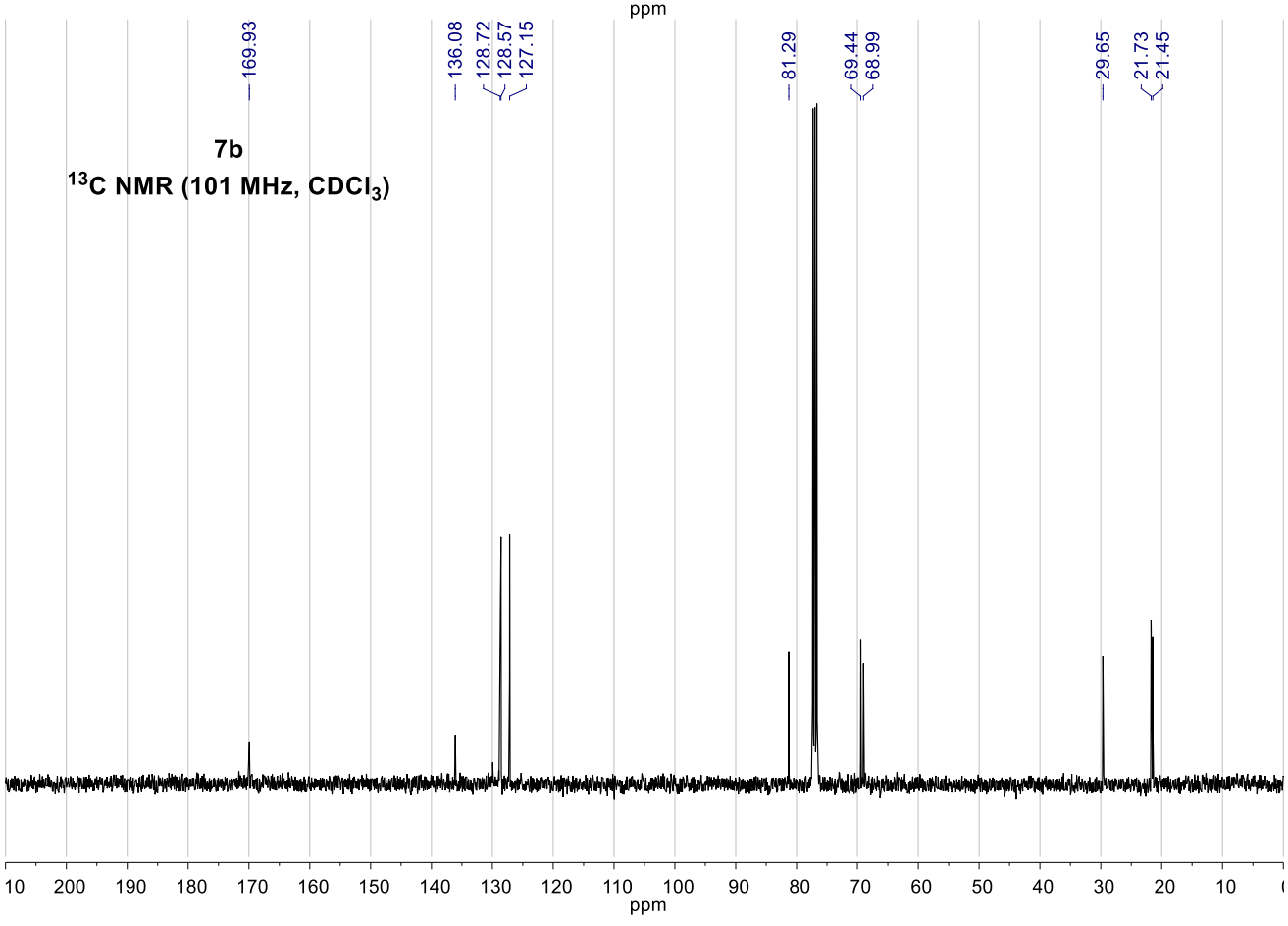

7.33
7.31
7.29
7.25
7.24
7.24
7.17
7.17
7.16
7.15
7.15
7.14
7.10
7.10
7.10
7.08
7.08
7.08
3.70
3.69
3.68
3.49
3.48
3.47
O
N
O
N2
Cl
6g
1H NMR (400 MHz, CDCl3)
1.04
0.85
1.84
4.00
4.00
ppm

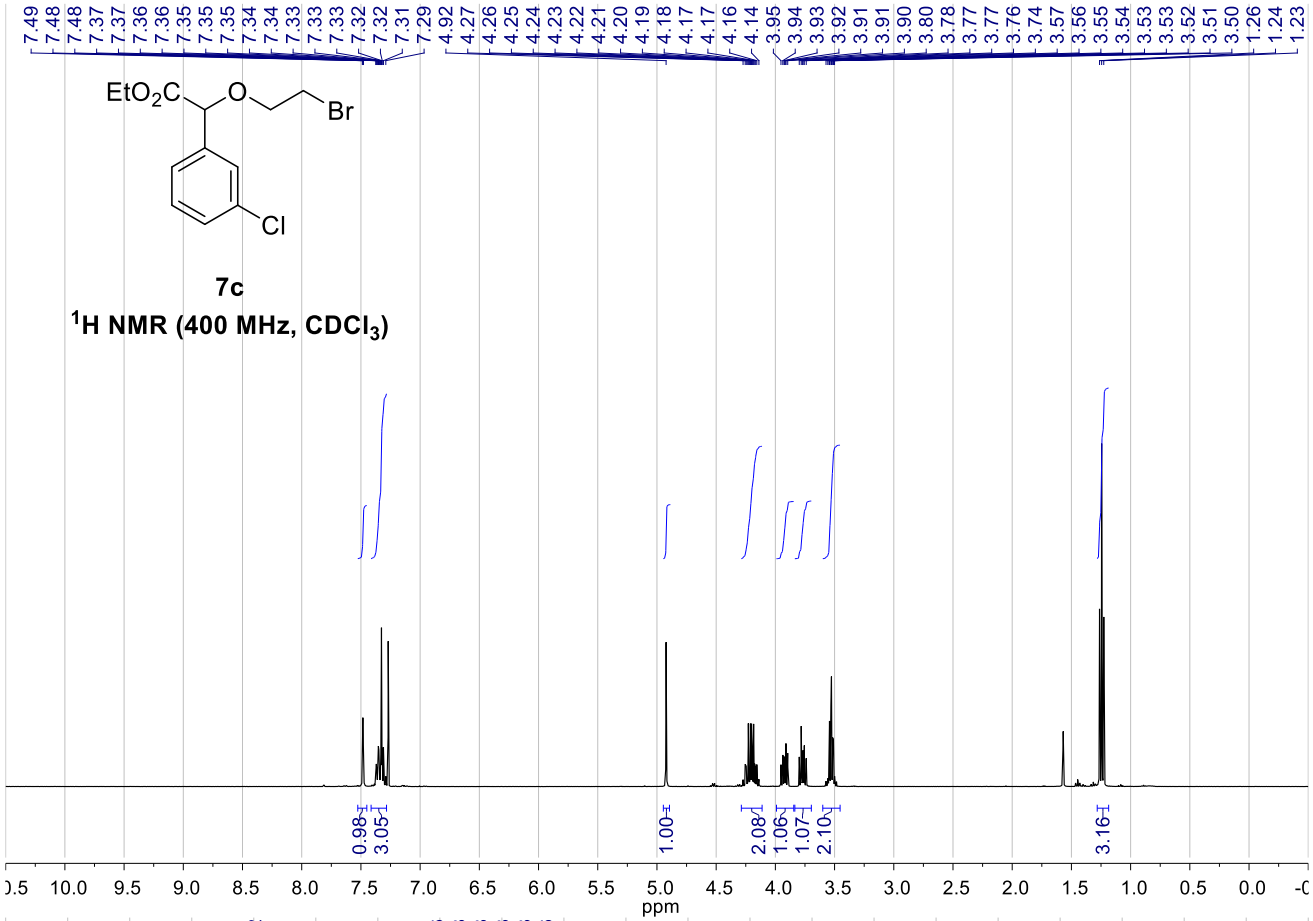

164.70
135.27
130.35
129.54
125.97
124.11
122.19
66.59
45.99
6g
13C NMR (101 MHz, CDCl3)
ppm

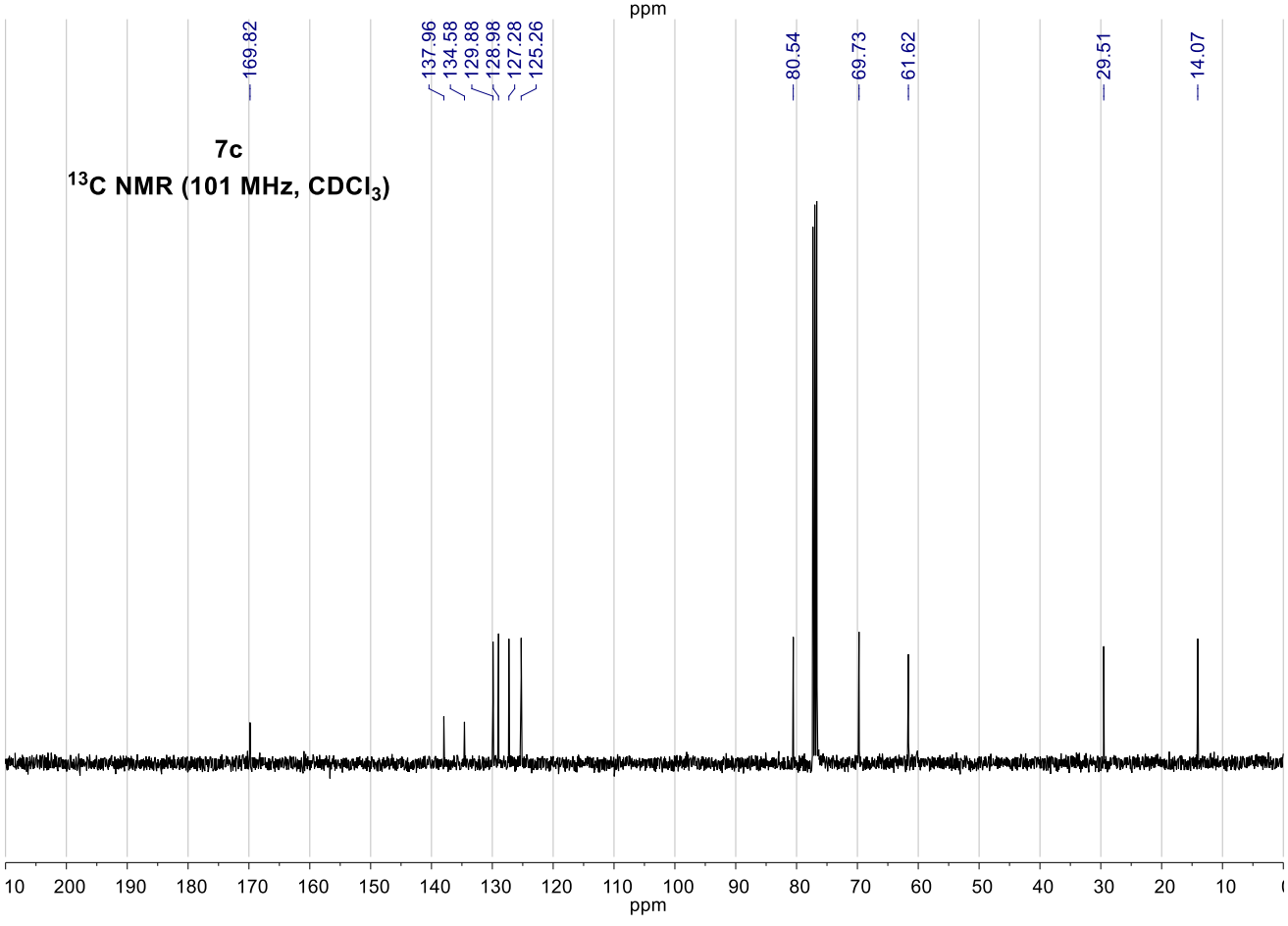

7.48
7.48
7.47
7.46
7.46
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
4.96
4.22
4.20
4.19
4.17
3.90
3.89
3.88
3.87
3.78
3.76
3.75
3.54
3.53
3.53
3.52
3.51
3.51
3.50
1.23
1.21
EtO2C
O
Br
7a
1H NMR (400 MHz, CDCl3)
5.15
1.00
2.09
1.08
1.09
2.18
3.25
ppm

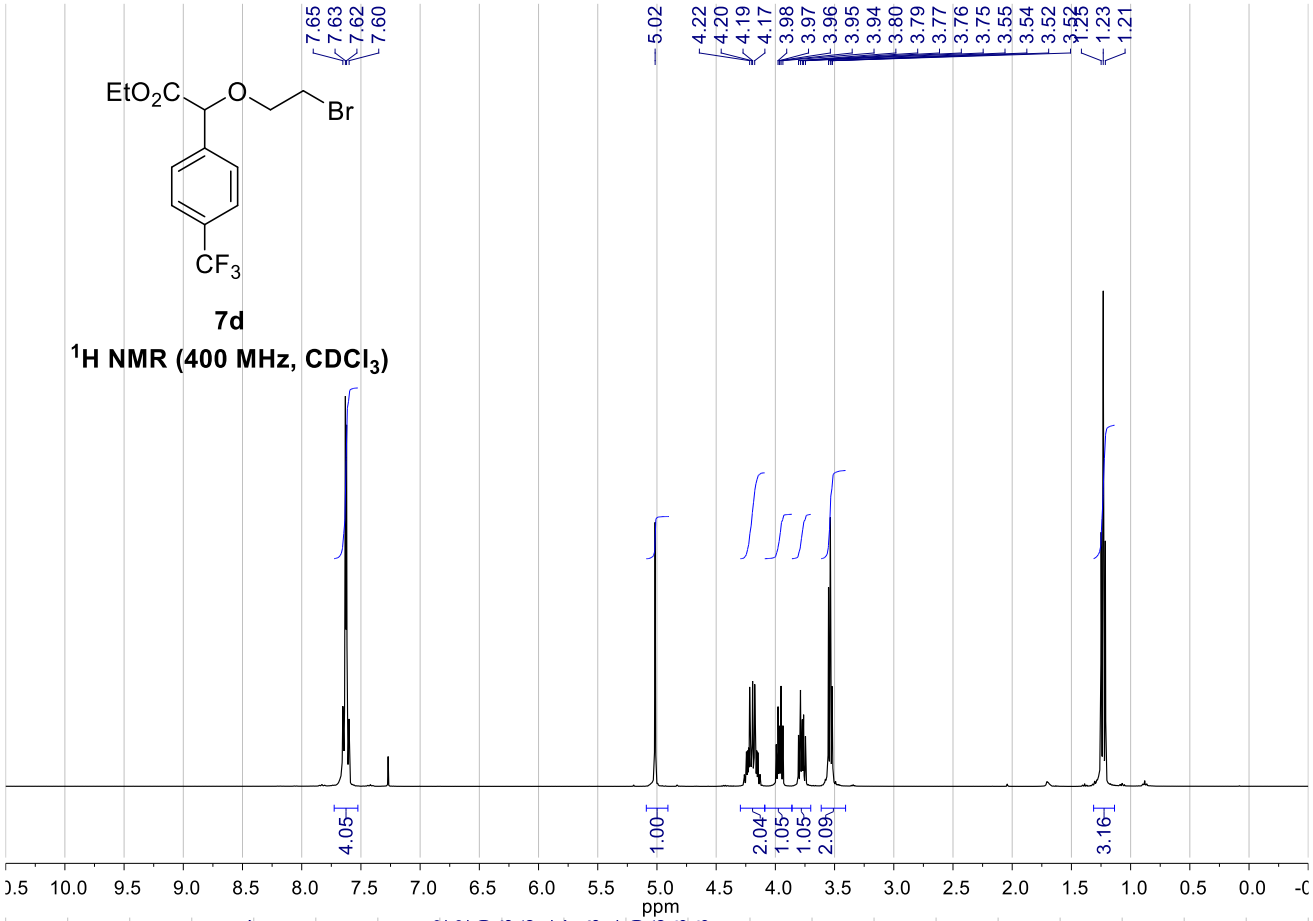

170.32
135.96
128.78
128.60
127.18
81.18
69.43
61.32
29.61
14.03
7a
13C NMR (101 MHz, CDCl3)
ppm

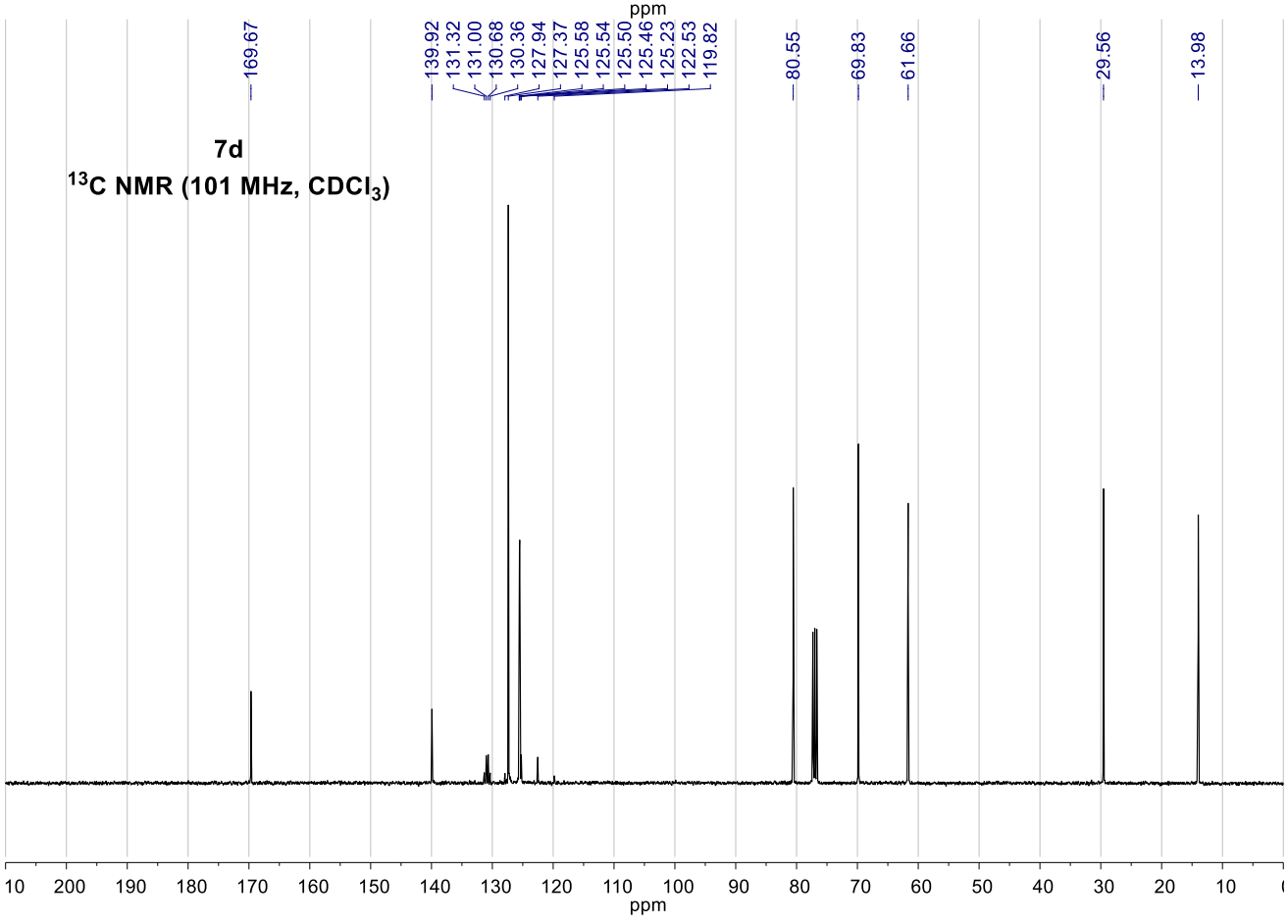

7.47
7.47
7.46
7.45
7.45
7.40
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
5.09
5.07
5.06
5.04
5.03
4.92
3.91
3.89
3.89
3.87
3.80
3.78
3.77
3.76
3.54
3.53
3.53
3.53
3.52
3.51
1.25
1.14
1.12
iPrO2C
O
Br
7b
1H NMR (400 MHz, CDCl3)
5.05
1.00
0.99
1.05
1.04
2.05
3.00
3.03
ppm

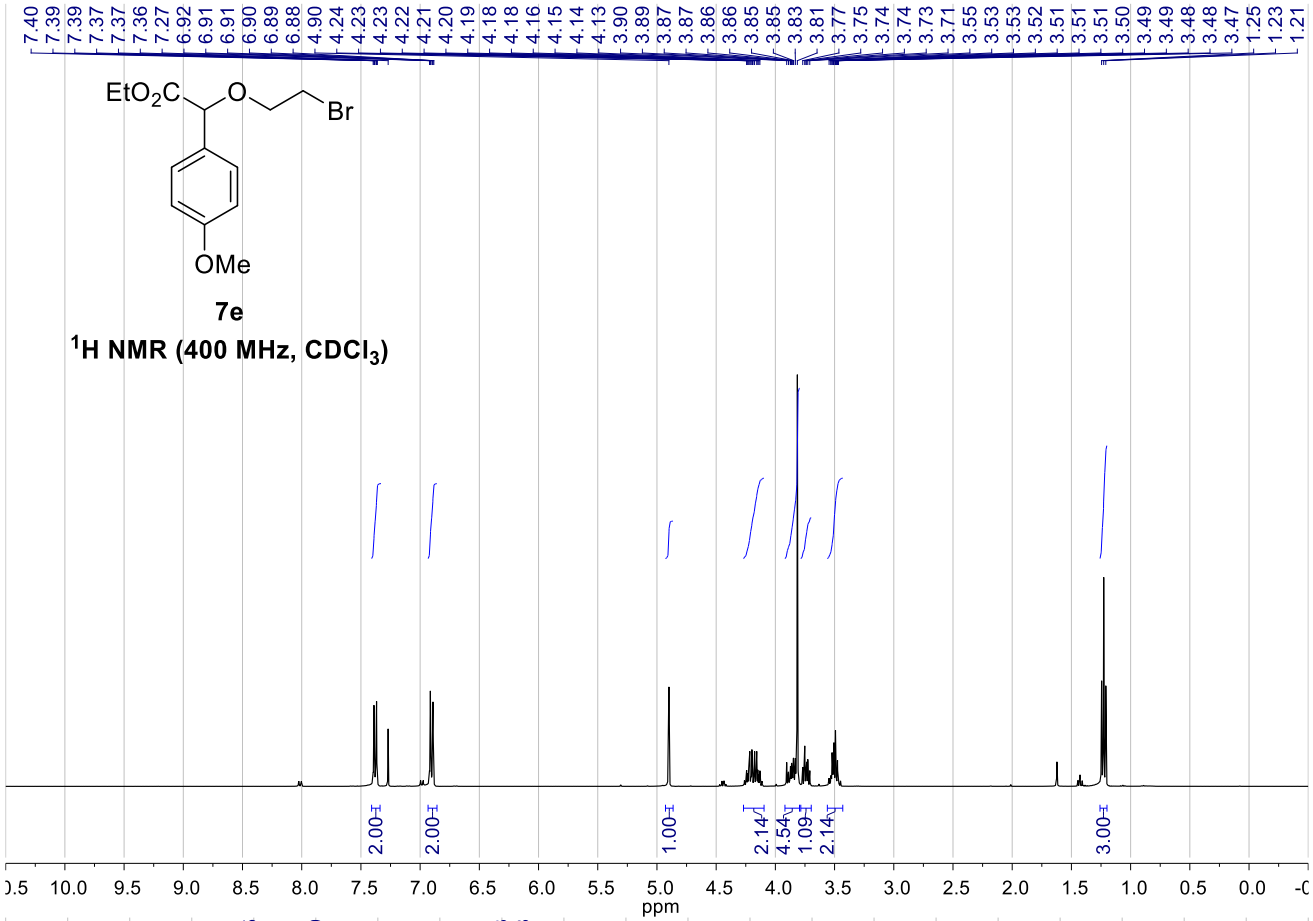

169.93
136.08
128.72
128.57
127.15
81.29
69.44
68.99
29.65
21.73
21.45
7b
13C NMR (101 MHz, CDCl3)
ppm

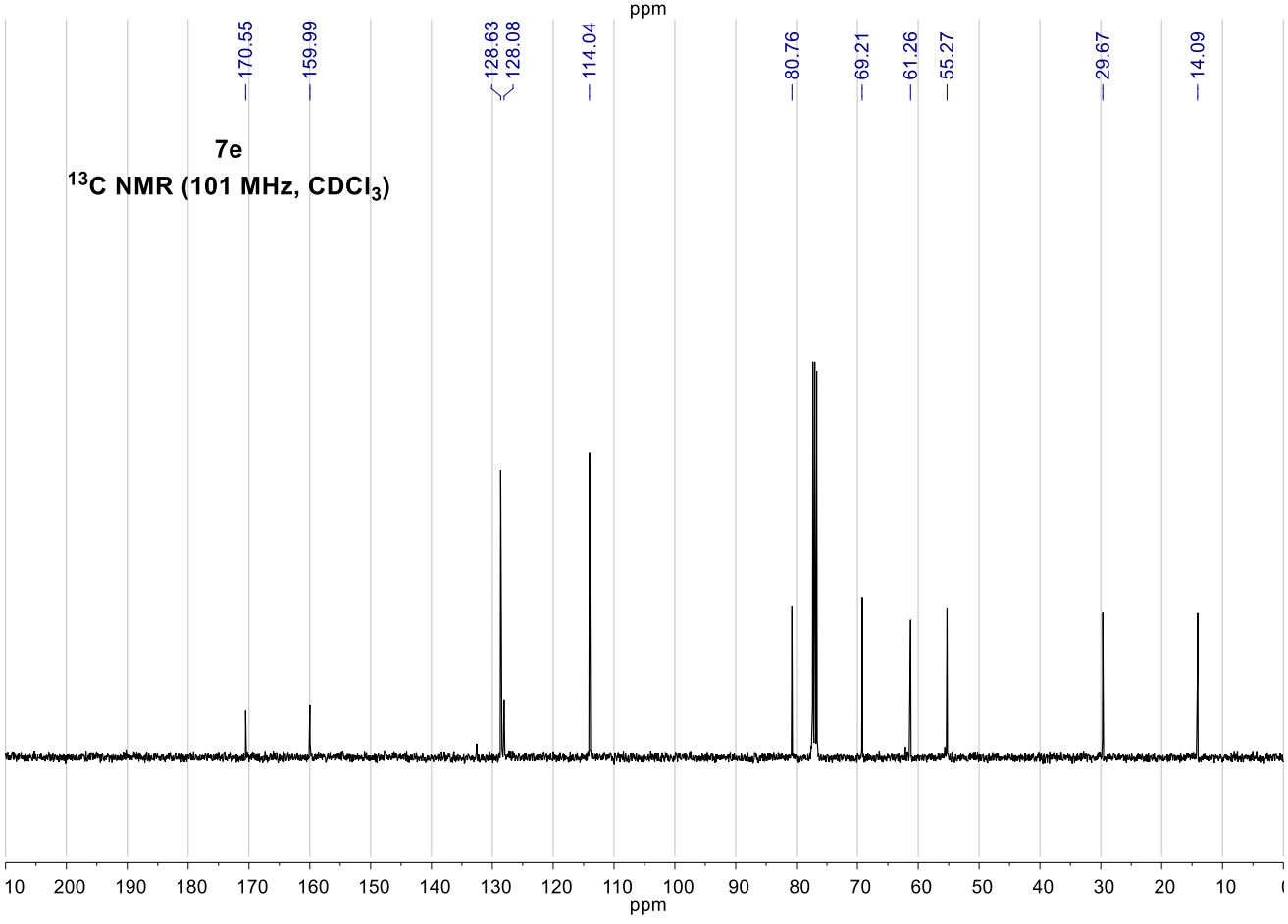

7.49 7.48 7.48 7.37 7.37 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.33 7.33 7.33 7.32 7.32 7.31 7.29
4.92 4.27 4.26 4.25 4.24 4.23 4.22 4.21 4.20 4.19 4.18 4.17 4.17 4.16 4.14 3.95 3.94 3.93 3.92 3.91 3.91 3.90 3.80 3.78 3.77 3.77 3.76 3.74 3.57 3.56 3.55 3.54 3.53 3.53 3.52 3.51 3.50 1.26 1.24 1.23
EtO2C
O
Br
Cl
7c
1H NMR (400 MHz, CDCl3)
0.98
3.05
1.00
2.08
1.06
1.07
2.10
3.16
ppm

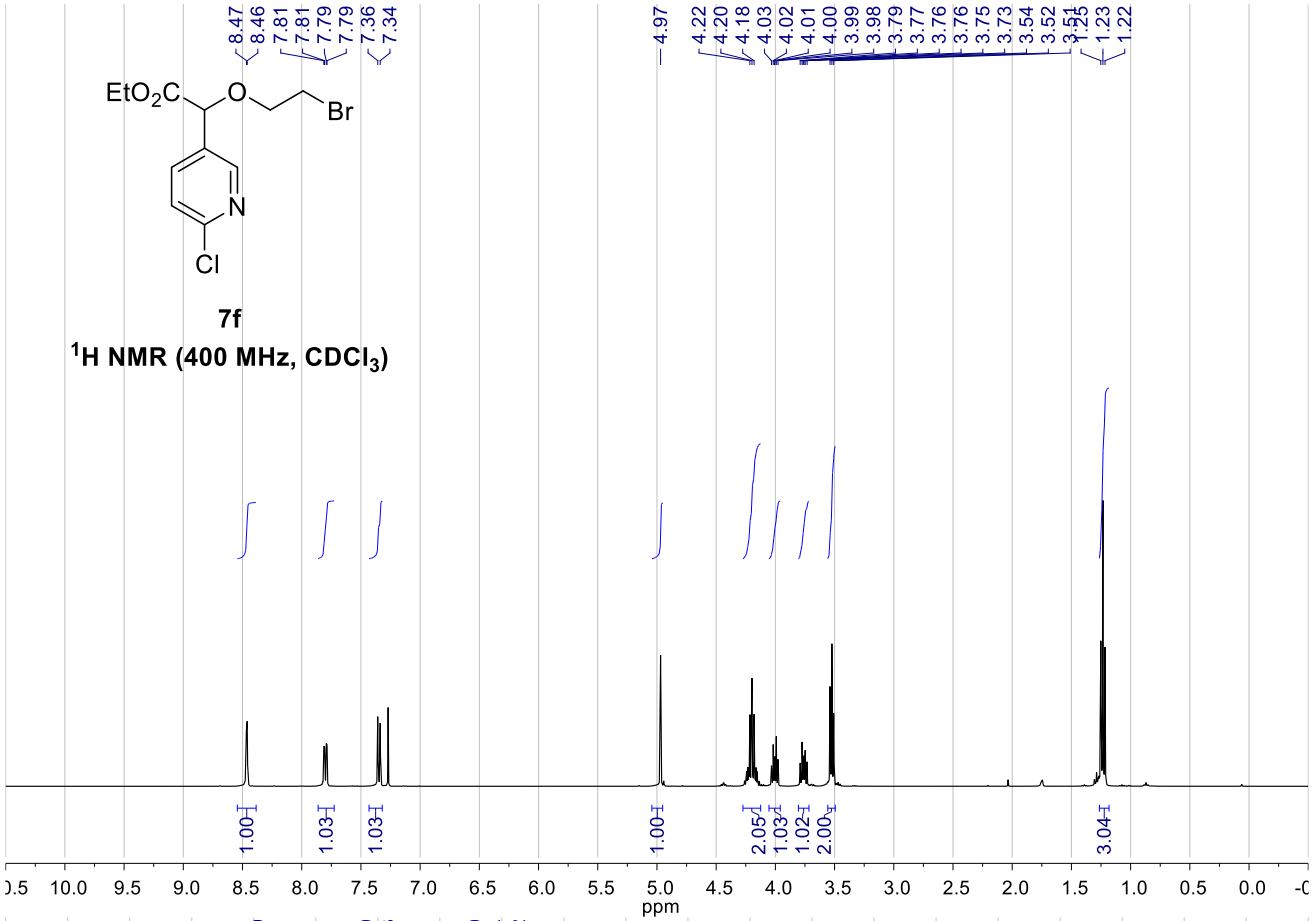

169.82
137.96
134.58
129.88
128.98
127.28
125.26
80.54
69.73
61.62
29.51
14.07
7c
13C NMR (101 MHz, CDCl3)
ppm

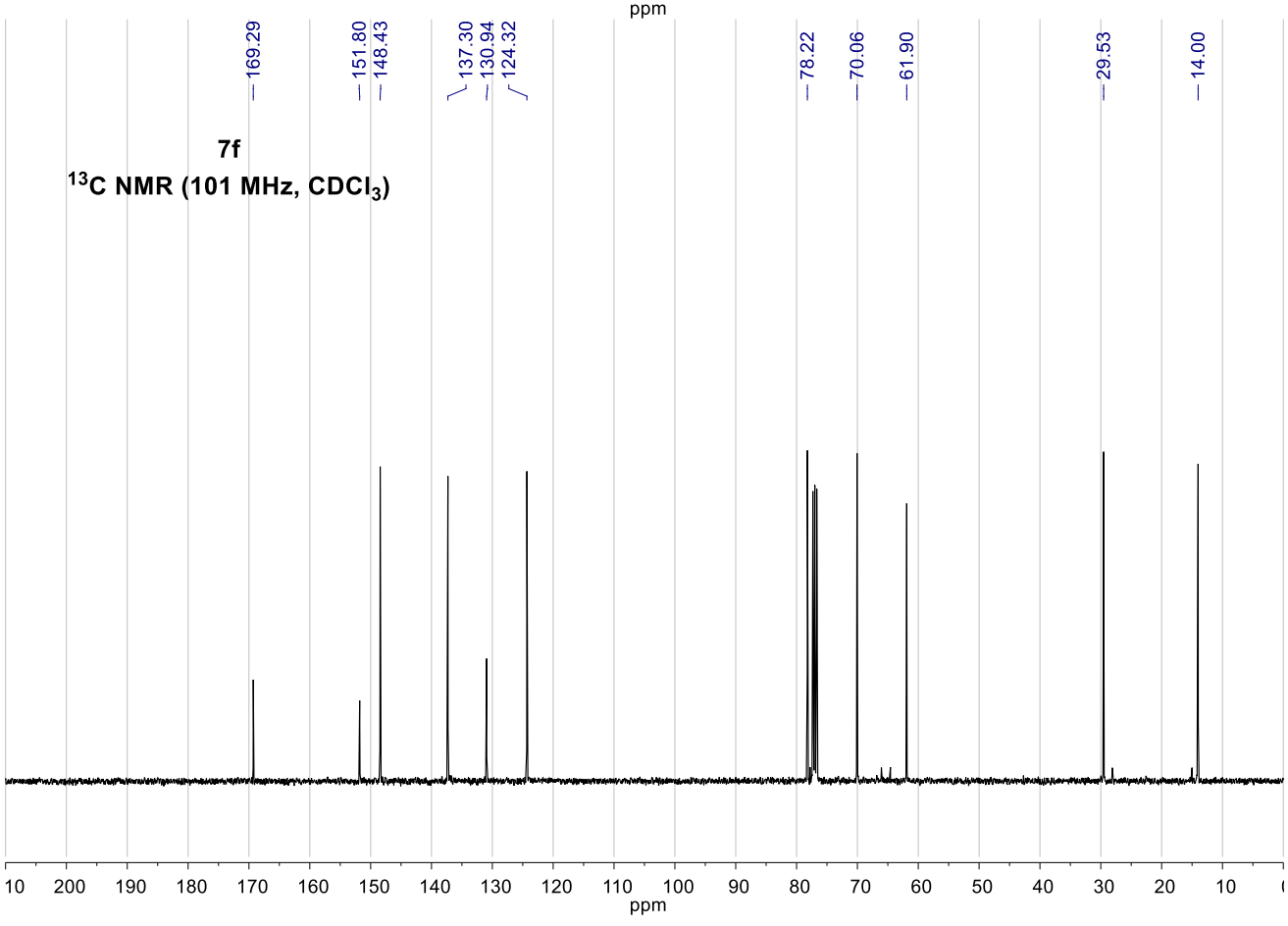

7.65
7.63
7.62
7.60
5.02
4.22
4.20
4.19
4.17
3.98
3.97
3.96
3.95
3.94
3.80
3.79
3.77
3.76
3.75
3.55
3.54
3.52
1.23
1.21
EtO2C
O
Br
CF3
7d
1H NMR (400 MHz, CDCl3)
4.05
1.00
2.04
1.05
1.05
2.09
3.16
ppm

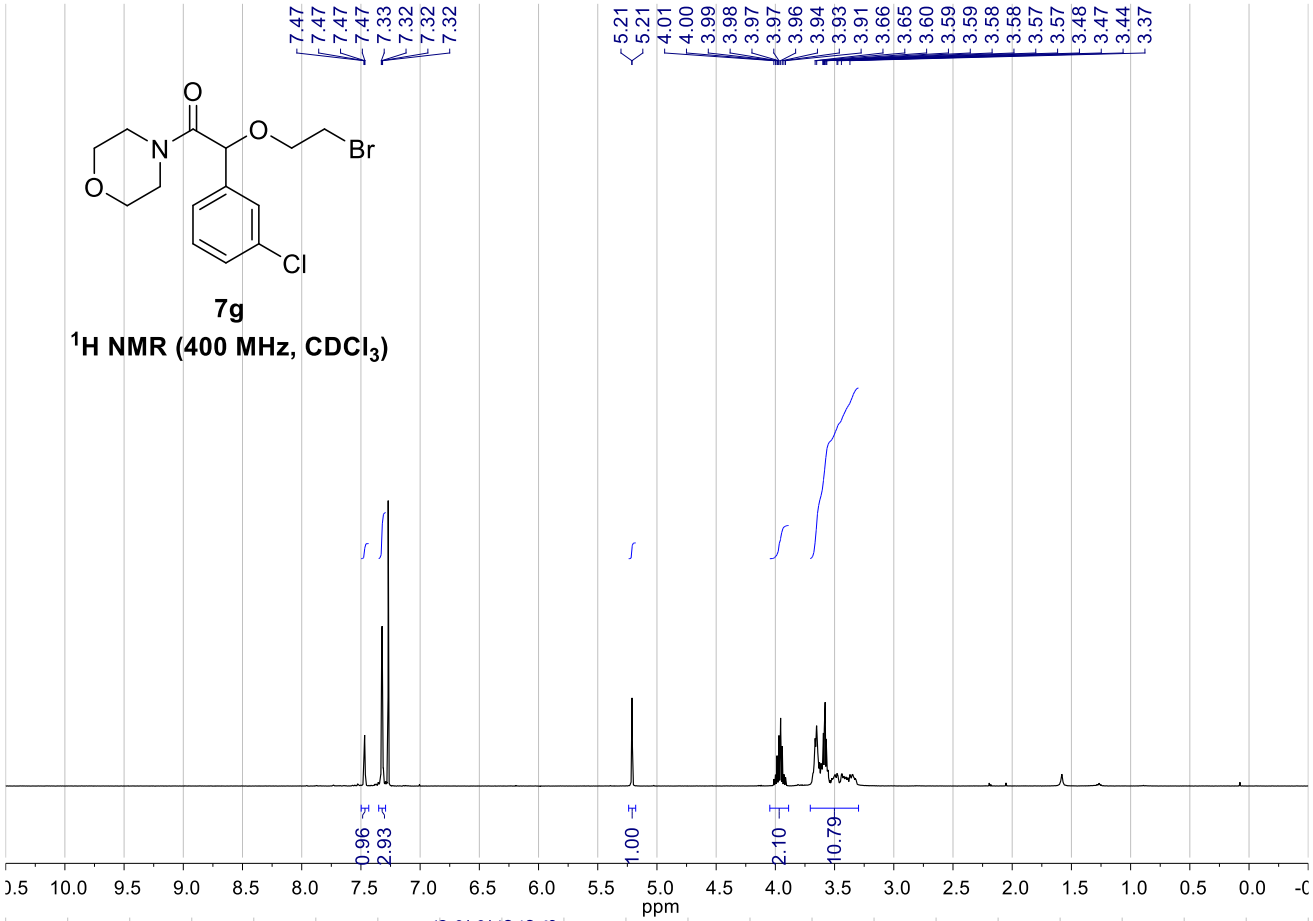

169.67
139.92
131.32
131.00
130.68
130.36
127.94
127.37
125.58
125.54
125.50
125.46
125.23
122.53
119.82
80.55
69.83
61.66
29.56
13.98
7d
13C NMR (101 MHz, CDCl3)
ppm

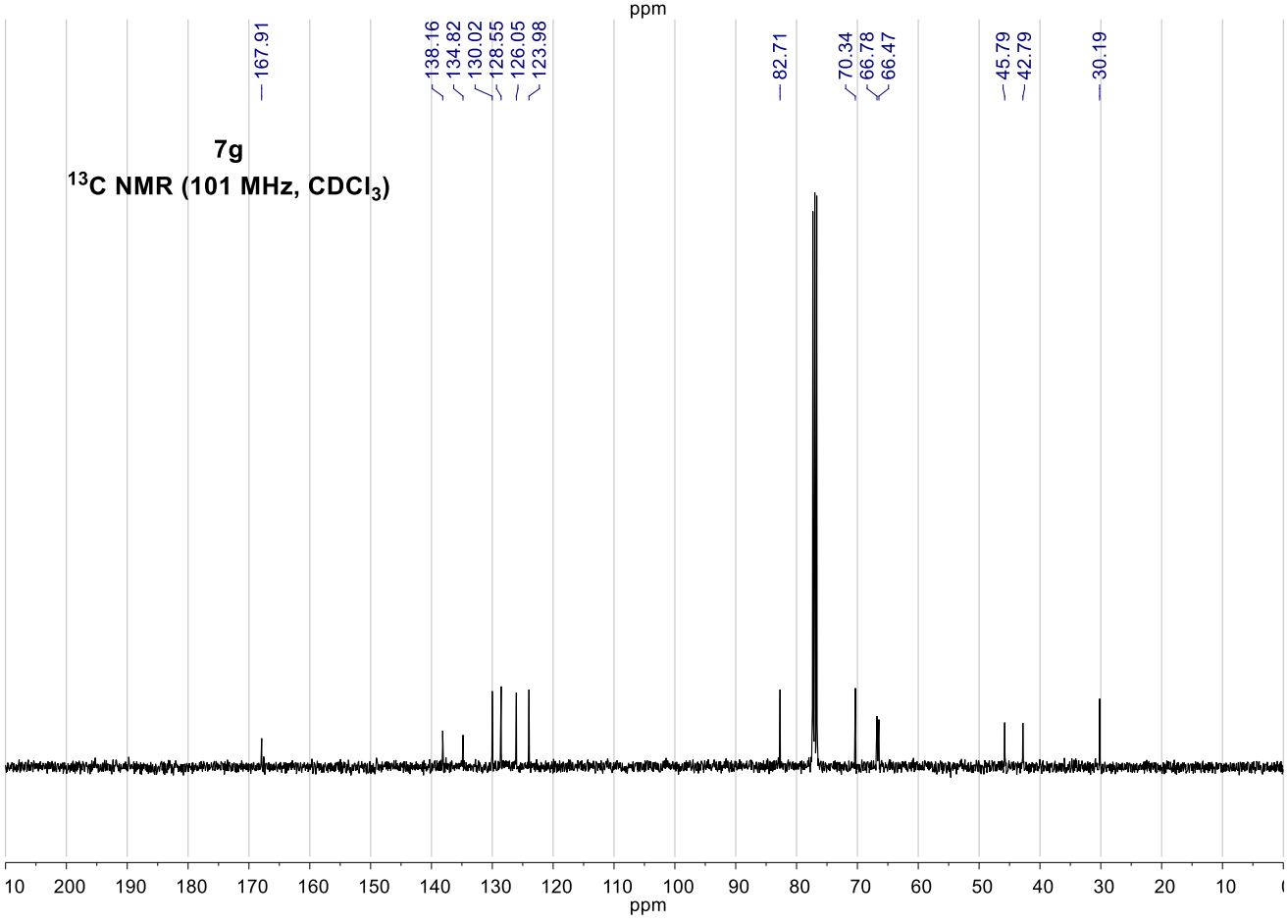

7.40 7.39 7.39 7.37 7.37 7.36 7.27 6.92 6.91 6.91 6.90 6.89 6.88 4.90 4.24 4.23 4.23 4.22 4.21 4.20 4.19 4.18 4.18 4.16 4.15 4.14 4.13 3.90 3.89 3.87 3.87 3.86 3.86 3.85 3.85 3.83 3.81 3.77 3.75 3.74 3.74 3.73 3.71 3.55 3.53 3.53 3.52 3.51 3.51 3.51 3.50 3.49 3.49 3.48 3.48 3.47 1.25 1.23 1.21
EtO2C
O
Br
OMe
7e
1H NMR (400 MHz, CDCl3)
2.00
2.00
1.00
2.14
4.54
1.09
2.14
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

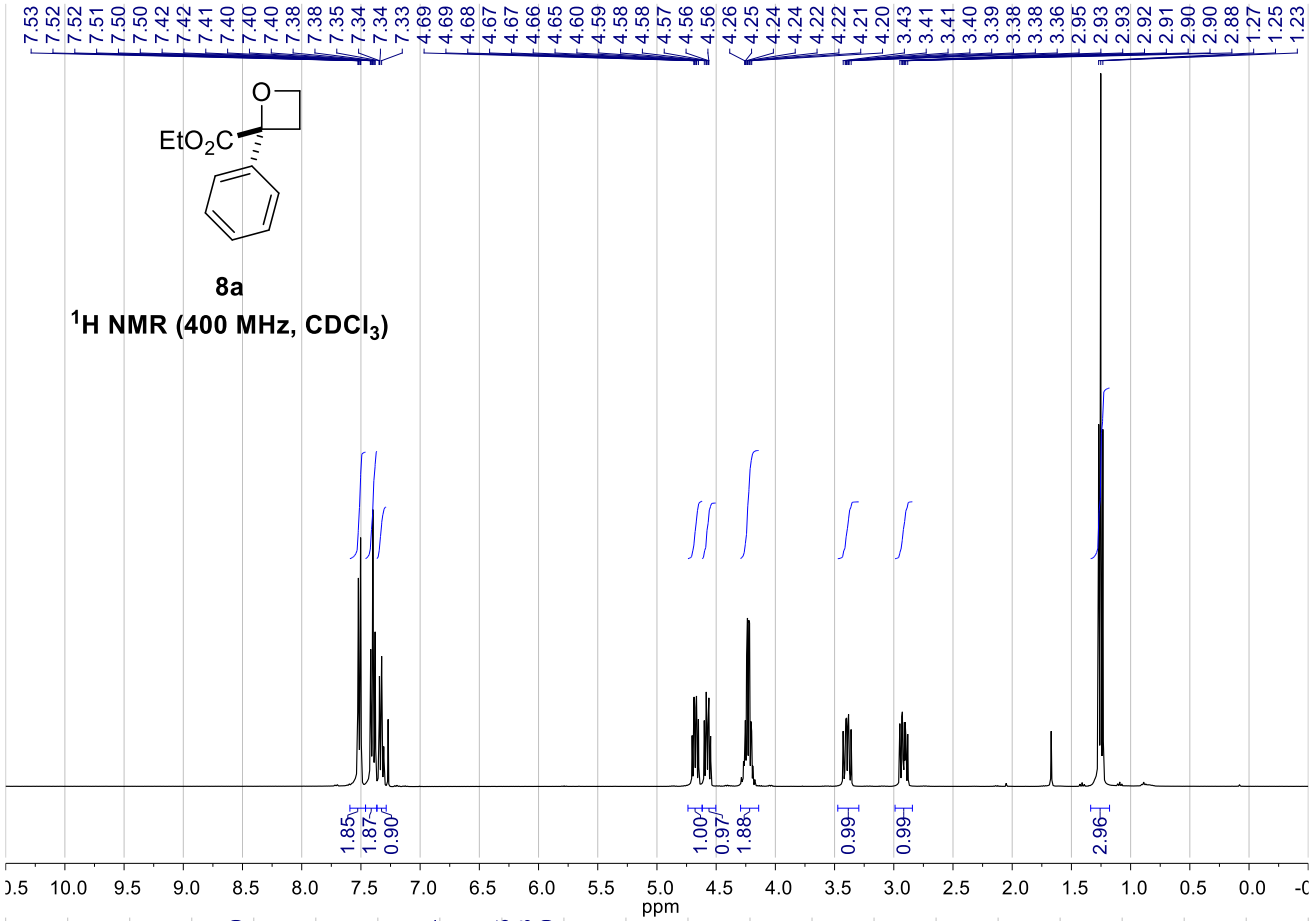

170.55
159.99
128.63
128.08
114.04
80.76
69.21
61.26
55.27
29.67
14.09
7e
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

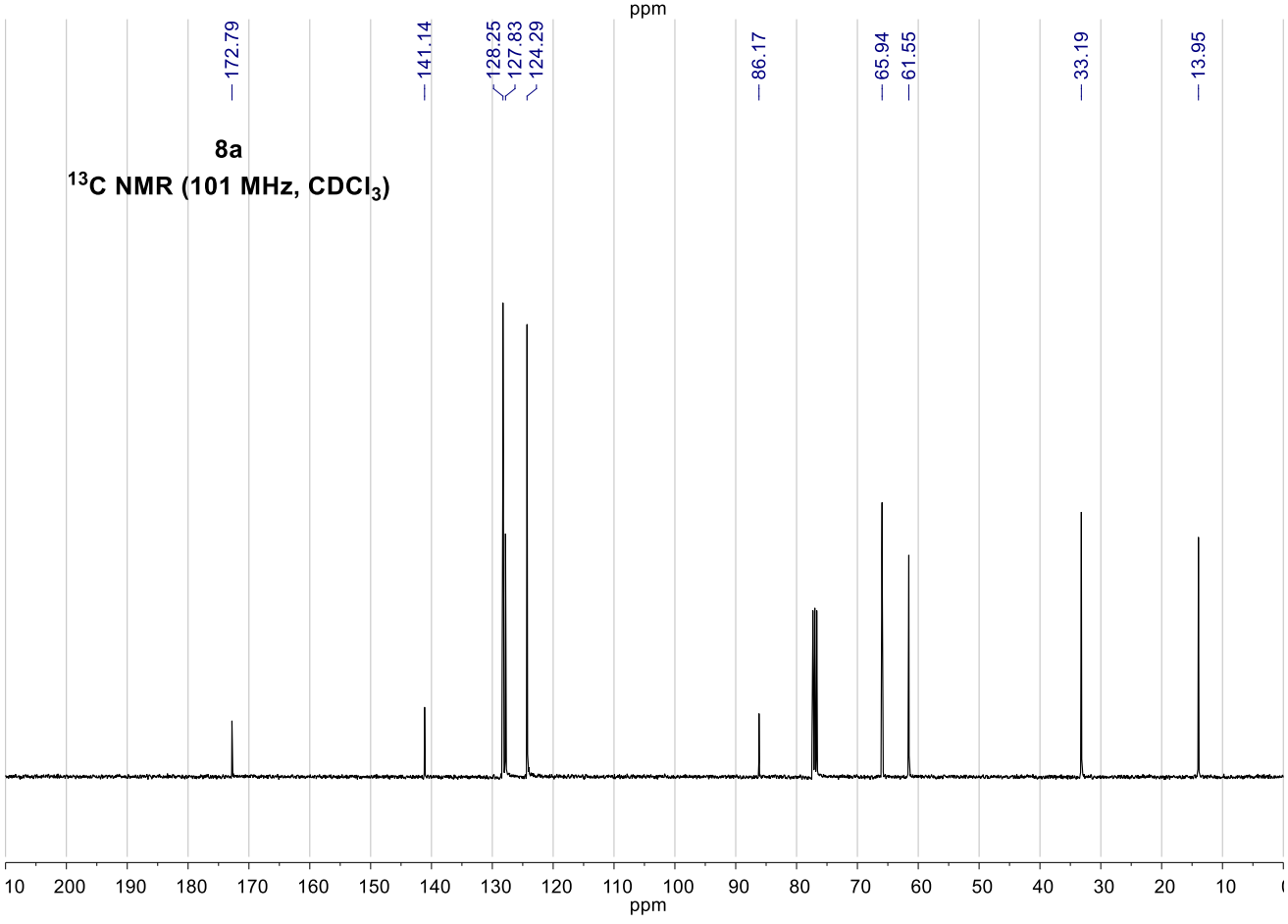

8.47
8.46
7.81
7.81
7.79
7.79
7.36
7.34
4.97
4.22
4.20
4.18
4.03
4.02
4.01
4.00
3.99
3.98
3.79
3.77
3.76
3.76
3.75
3.73
3.54
3.52
3.51
1.25
1.23
1.22
EtO2C
O
Br
N
Cl
7f
1H NMR (400 MHz, CDCl3)
1.00
1.03
1.03
1.00
2.05
1.03
1.02
2.00
3.04
ppm

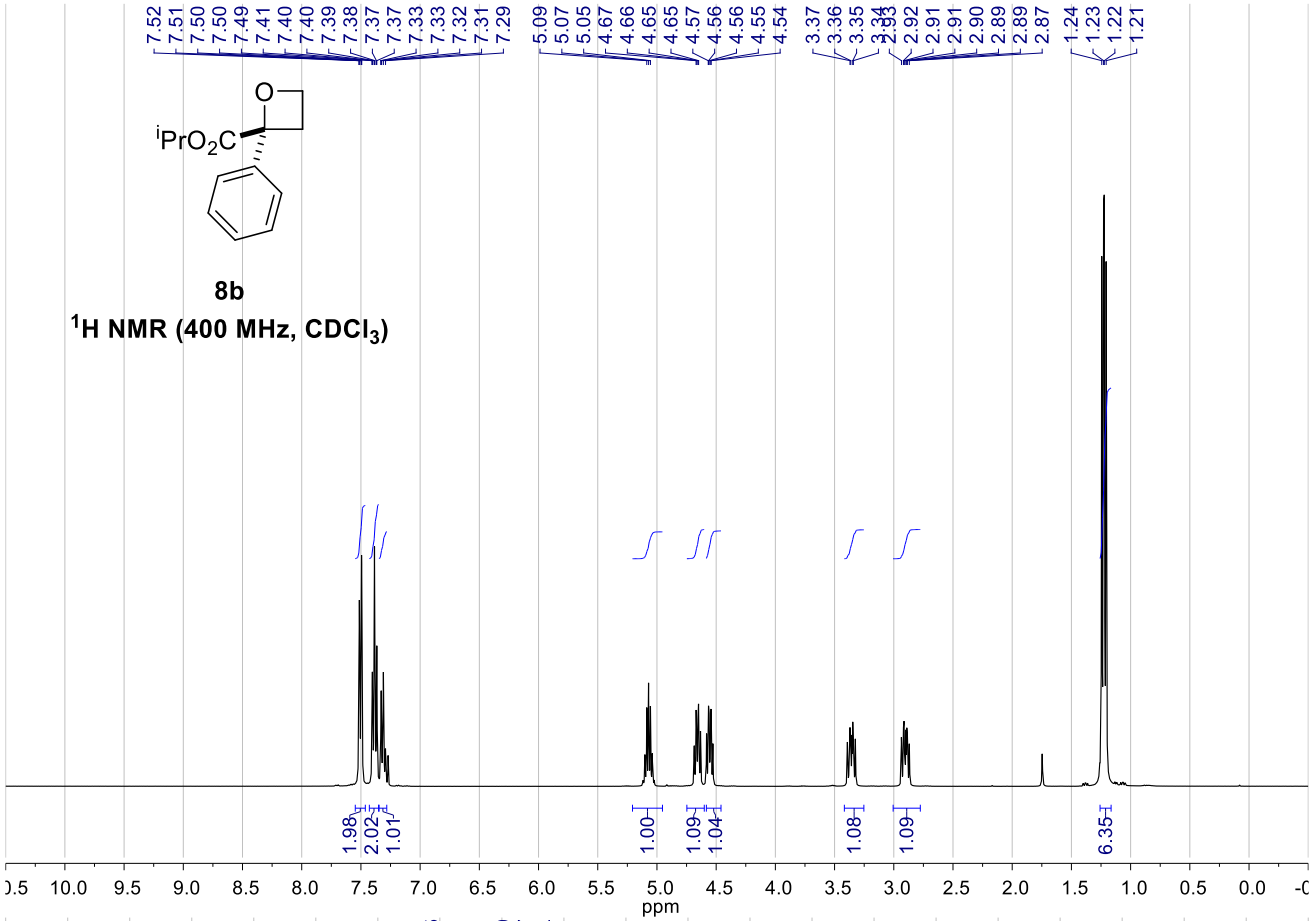

169.29
151.80
148.43
137.30
130.94
124.32
78.22
70.06
61.90
29.53
14.00
7f
13C NMR (101 MHz, CDCl3)
ppm

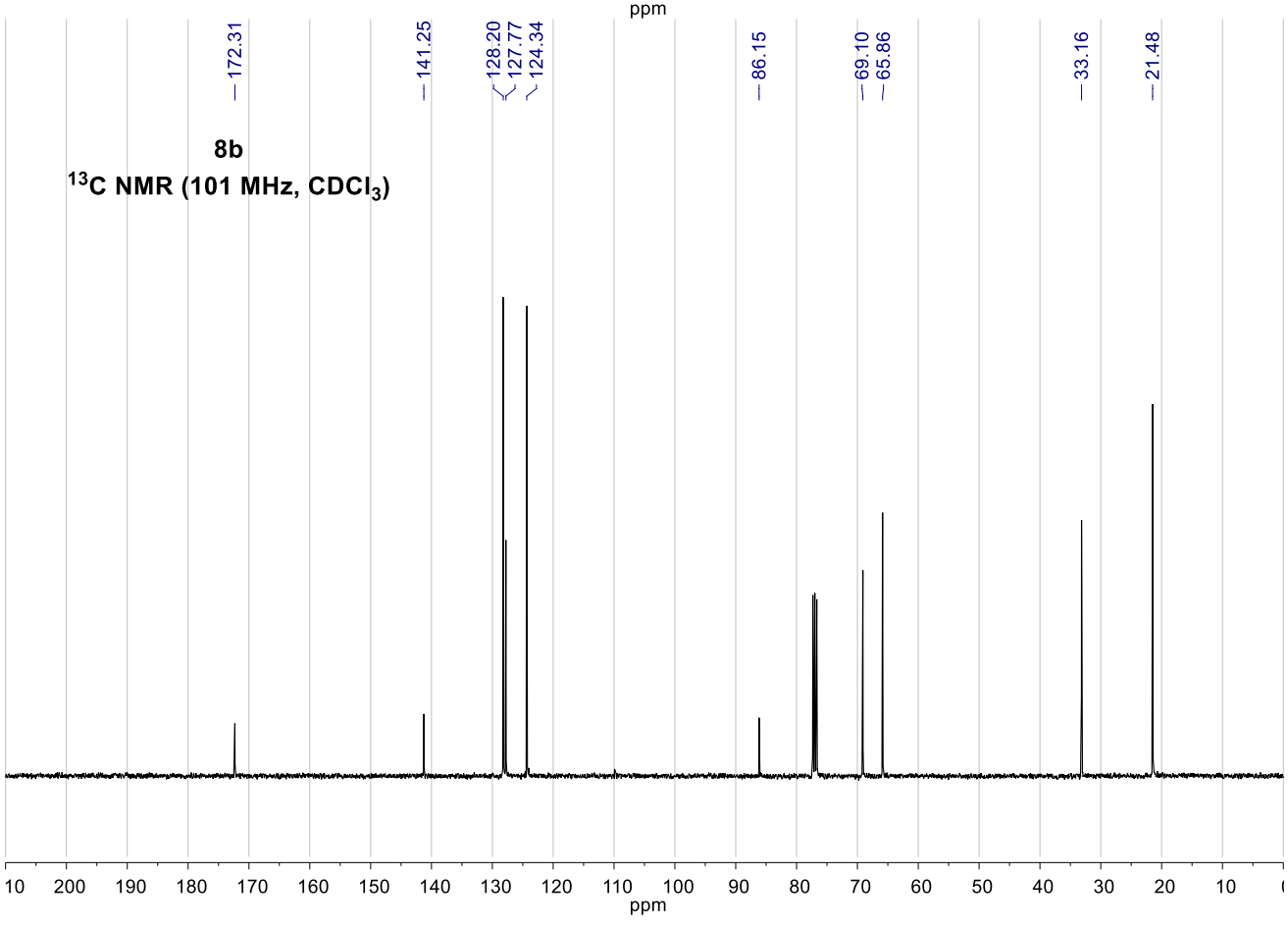

7.47
7.47
7.47
7.47
7.33
7.32
7.32
7.32
5.21
5.21
4.01
4.00
3.99
3.98
3.97
3.97
3.96
3.94
3.93
3.91
3.66
3.65
3.60
3.59
3.59
3.58
3.58
3.57
3.57
3.48
3.47
3.44
3.37
O
N
O
O
Br
Cl
7g
^{1}H NMR (400 MHz, CDCl$_3$)
0.96
2.93
1.00
2.10
10.79
ppm

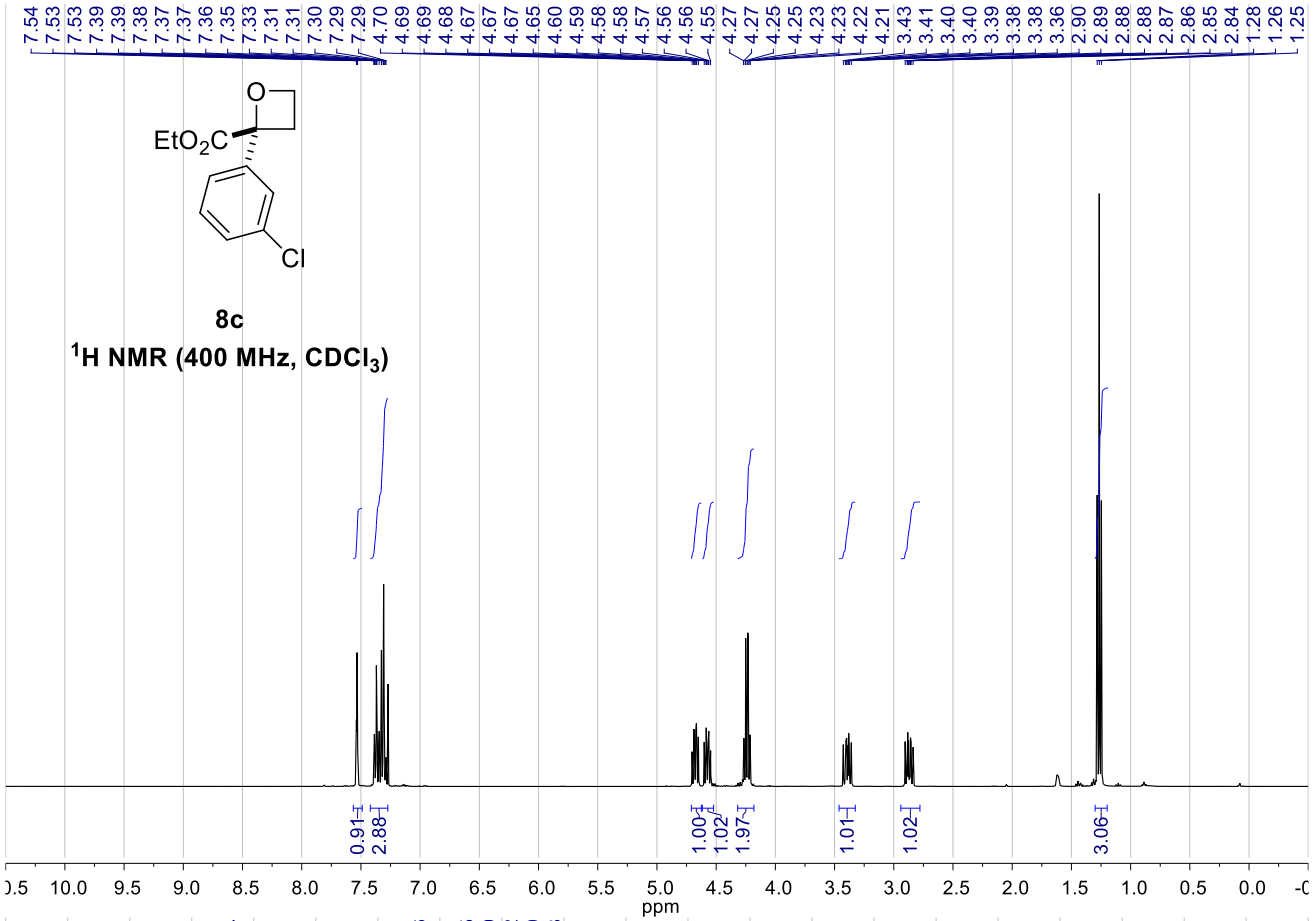

167.91
138.16
134.82
130.02
128.55
126.05
123.98
82.71
70.34
66.78
66.47
45.79
42.79
30.19
7g
^{13}C NMR (101 MHz, CDCl$_3$)
ppm

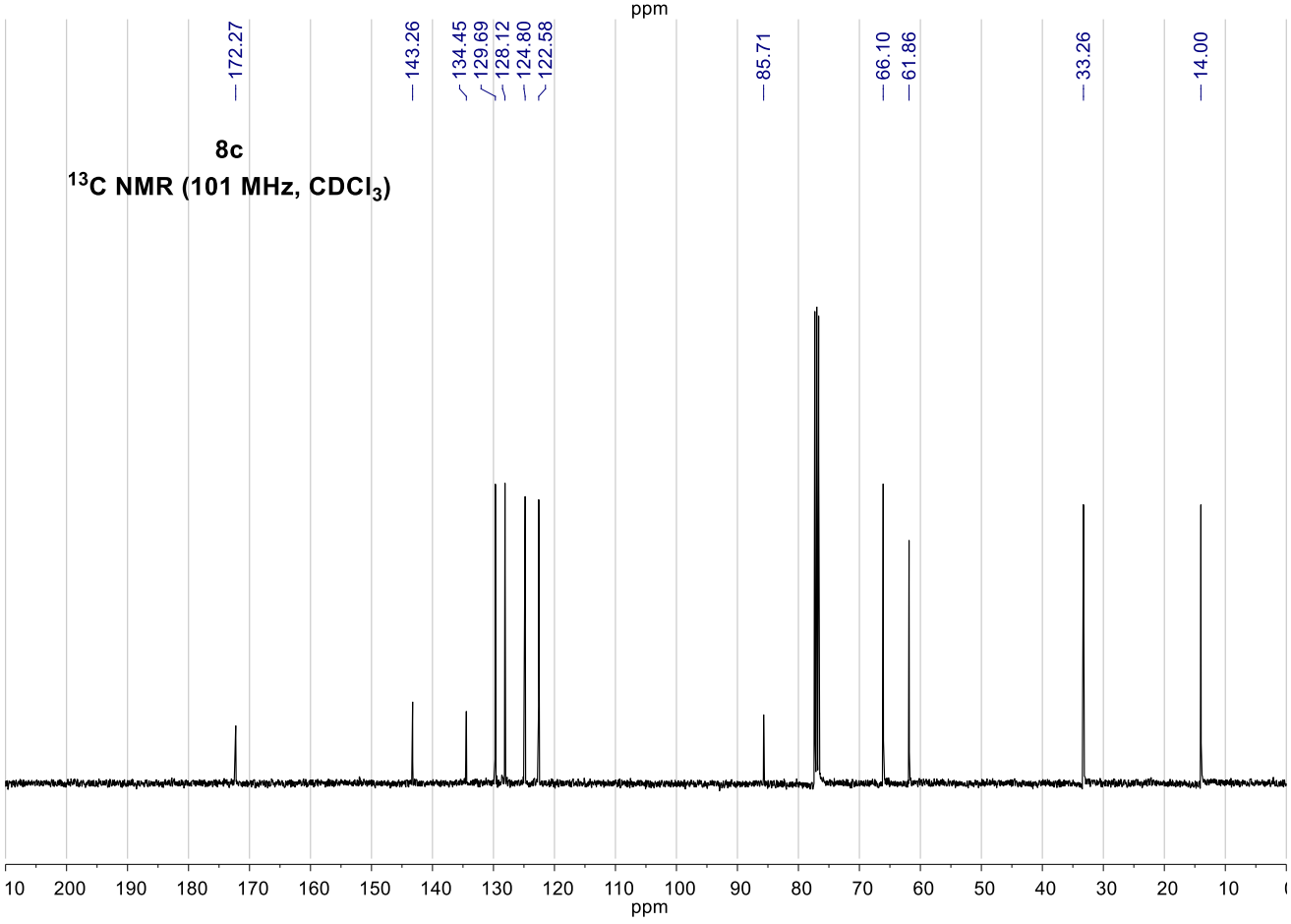

7.53 7.52 7.52 7.51 7.50 7.50 7.42 7.42 7.41 7.40 7.40 7.40 7.38 7.38 7.35 7.34 7.34 7.33
4.69 4.69 4.68 4.67 4.67 4.66 4.65 4.60 4.59 4.58 4.58 4.57 4.56 4.56
4.26 4.25 4.24 4.24 4.22 4.22 4.21 4.20 3.43 3.41 3.41 3.40 3.39 3.38 3.38 3.36 2.95 2.93 2.93 2.92 2.91 2.90 2.90 2.88 1.27 1.25 1.23
O
EtO2C
8a
1H NMR (400 MHz, CDCl3)
1.85 1.87 0.90 1.00 0.97 1.88 0.99 0.99 2.96
ppm

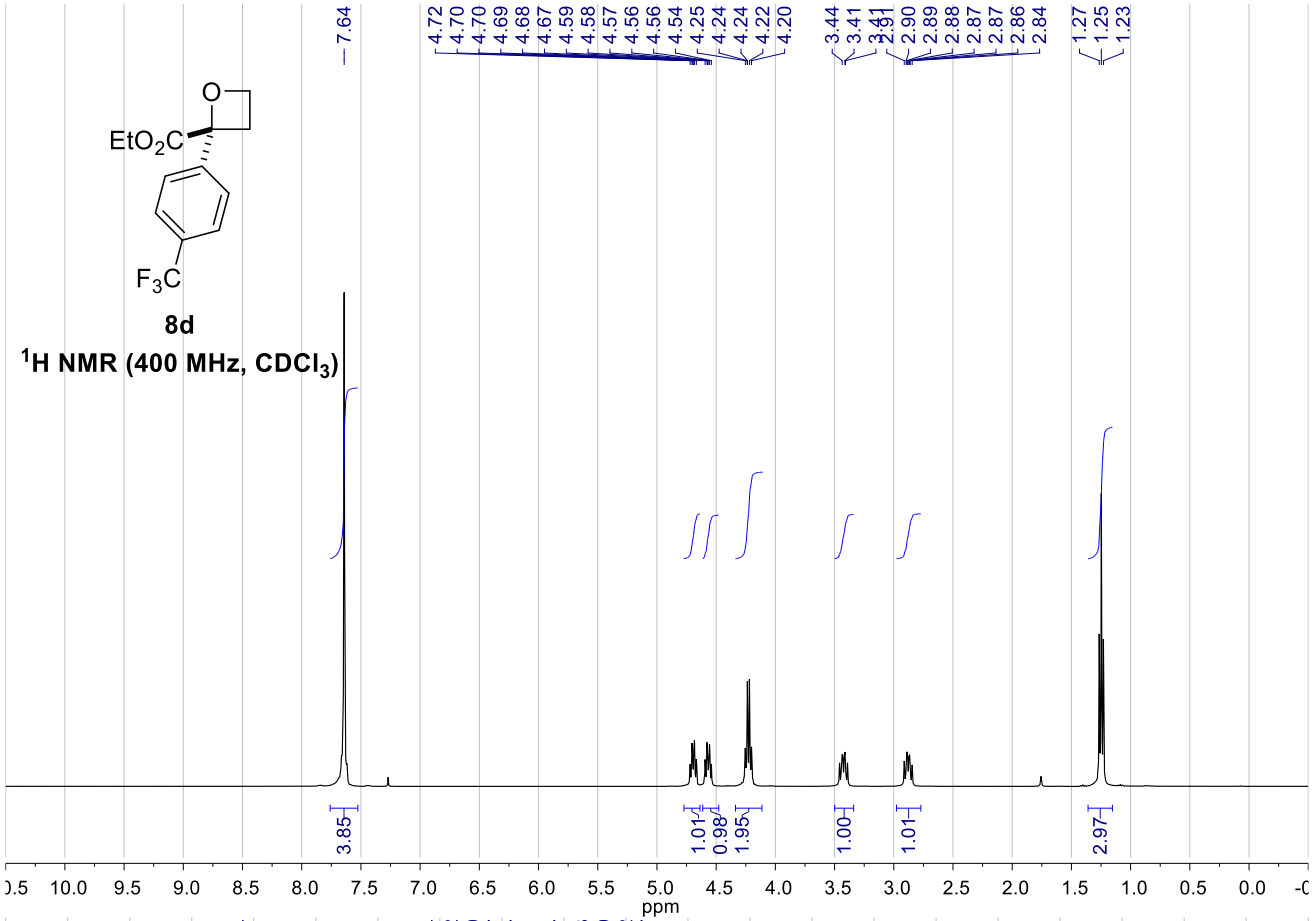

172.79
141.14
128.25
127.83
124.29
86.17
65.94
61.55
33.19
13.95
8a
13C NMR (101 MHz, CDCl3)
ppm

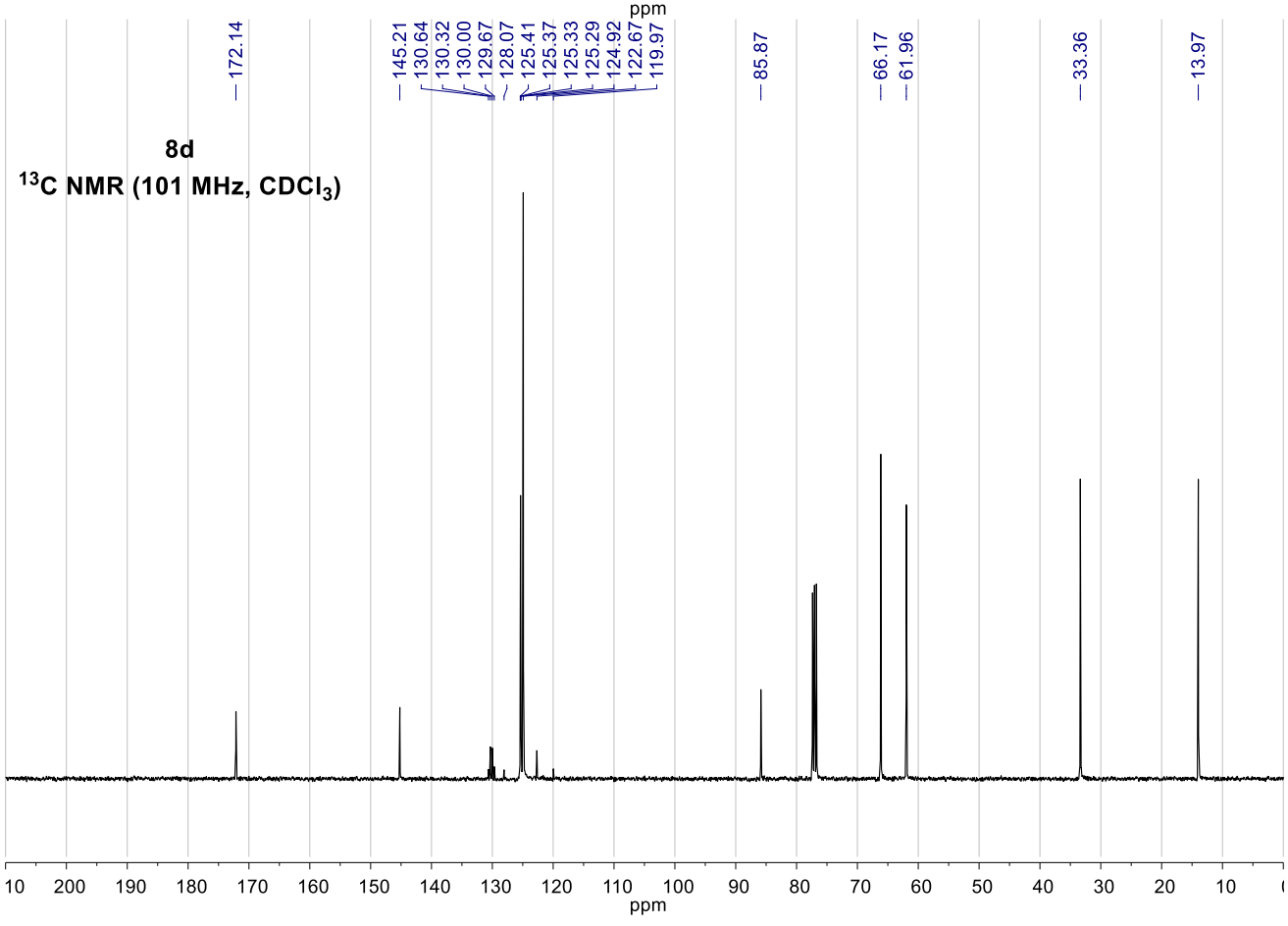

7.52 7.51 7.50 7.50 7.49 7.41 7.40 7.40 7.39 7.38 7.37 7.37 7.33 7.33 7.32 7.31 7.29
5.09 5.07 5.05 4.67 4.66 4.65 4.65 4.57 4.56 4.56 4.55 4.54
3.37 3.36 3.35 3.34 2.93 2.92 2.91 2.91 2.90 2.89 2.89 2.87
1.24 1.23 1.22 1.21
O
iPrO2C
8b
1H NMR (400 MHz, CDCl3)
1.98 2.02 1.01 1.00 1.09 1.04 1.08 1.09 6.35
ppm

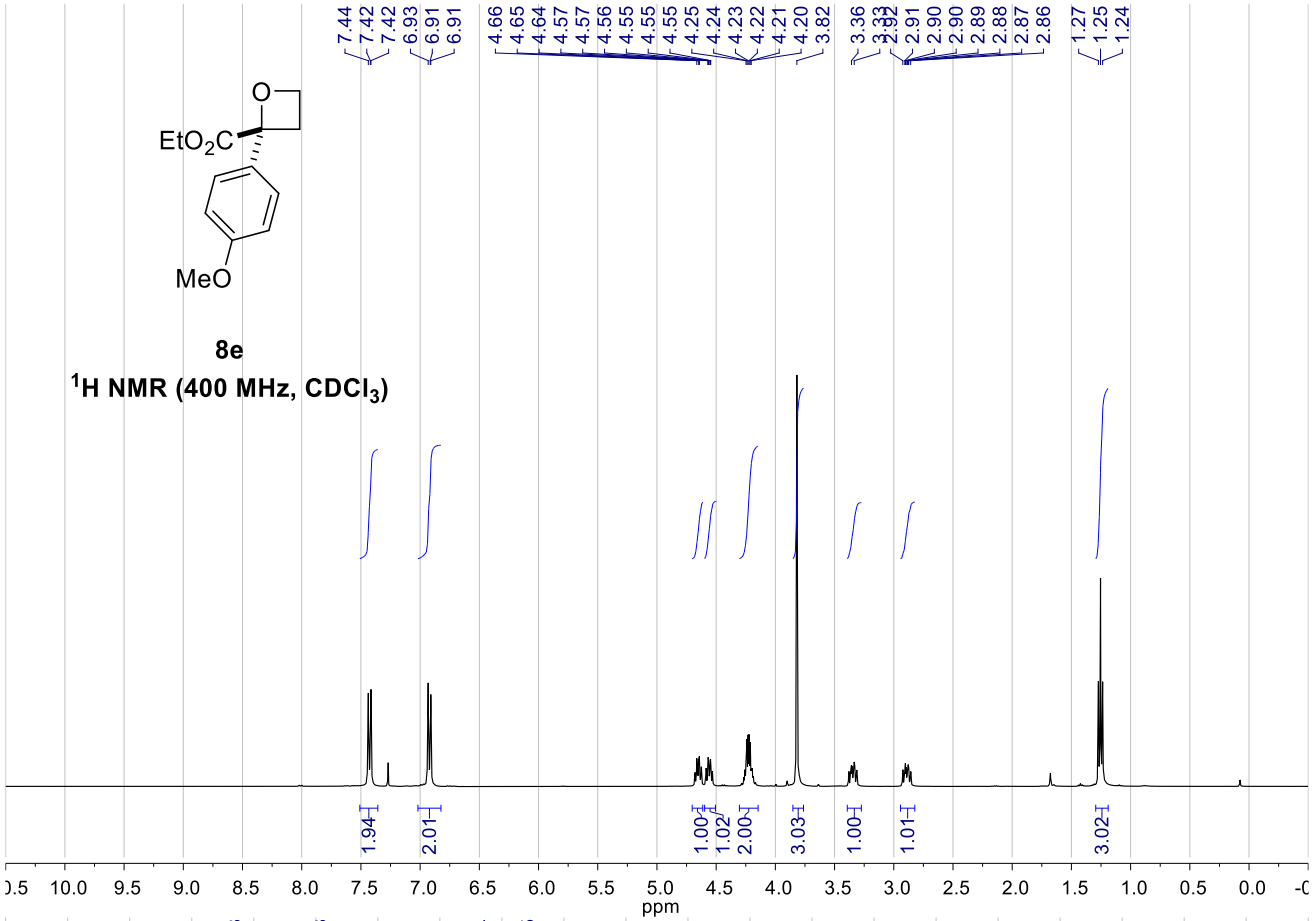

172.31
141.25
128.20
127.77
124.34
86.15
69.10
65.86
33.16
21.48
8b
13C NMR (101 MHz, CDCl3)
ppm

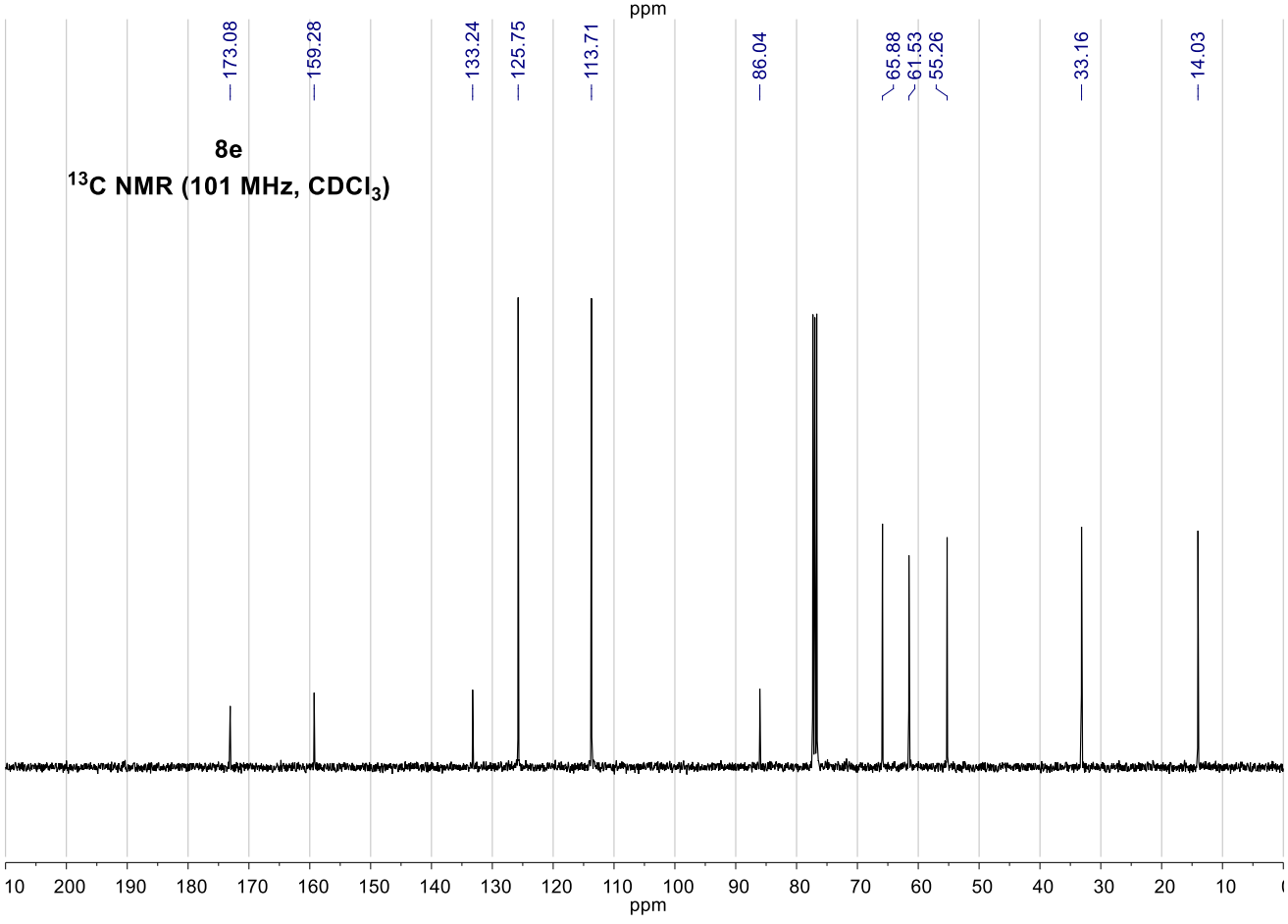

7.54 7.53 7.53 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.33 7.31 7.31 7.30 7.29 7.29 4.70 4.69 4.69 4.68 4.67 4.67 4.67 4.65 4.60 4.59 4.58 4.58 4.57 4.56 4.56 4.55 4.27 4.27 4.25 4.25 4.23 4.23 4.22 4.21 3.43 3.41 3.40 3.40 3.39 3.38 3.38 3.36 2.90 2.89 2.88 2.88 2.87 2.86 2.85 2.84 1.28 1.26 1.25
O
EtO2C
Cl
8c
1H NMR (400 MHz, CDCl3)
0.91 2.88 1.00 1.02 1.97 1.01 1.02 3.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

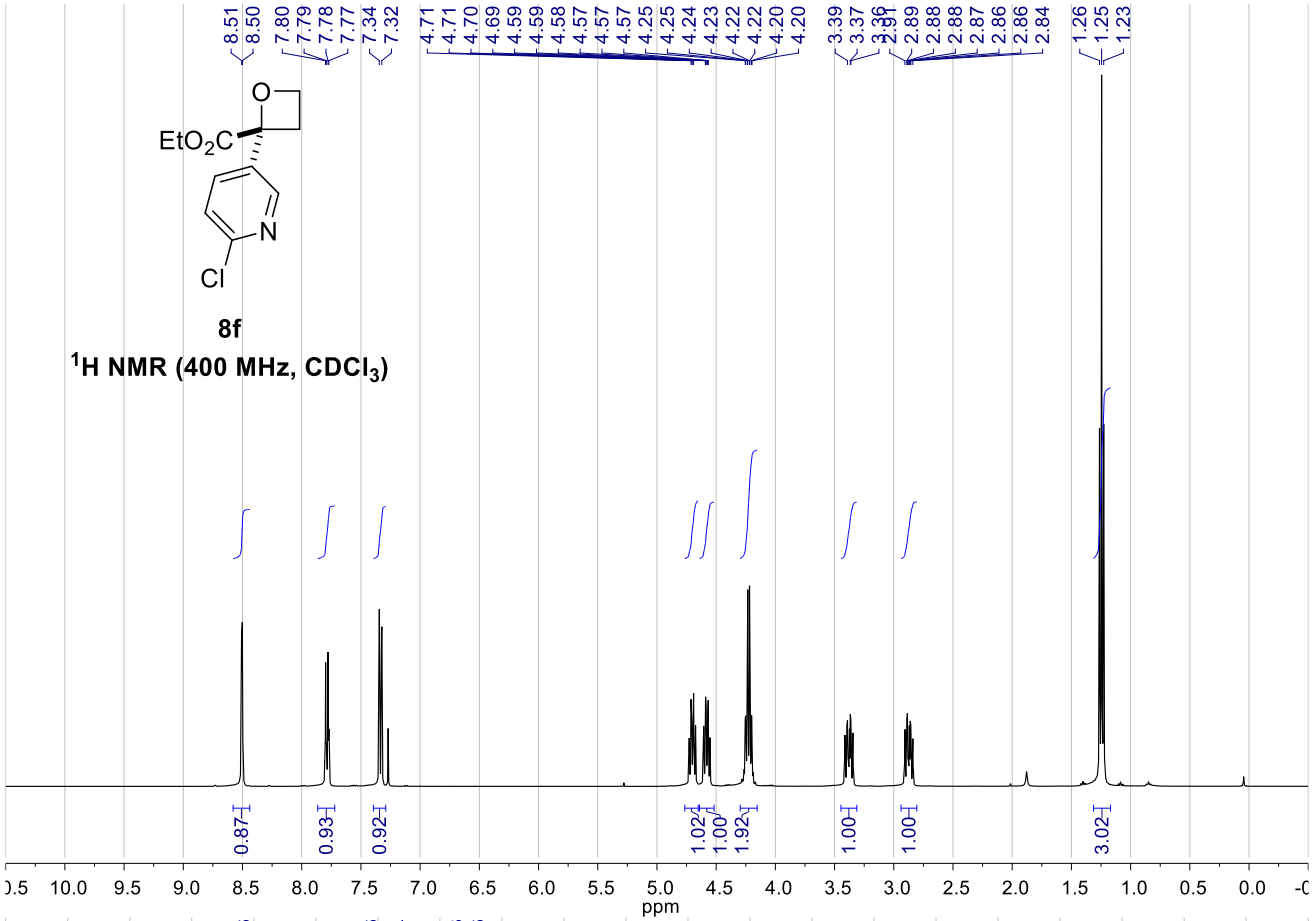

172.27 143.26 134.45 129.69 128.12 124.80 122.58 85.71 66.10 61.86 33.26 14.00
8c
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

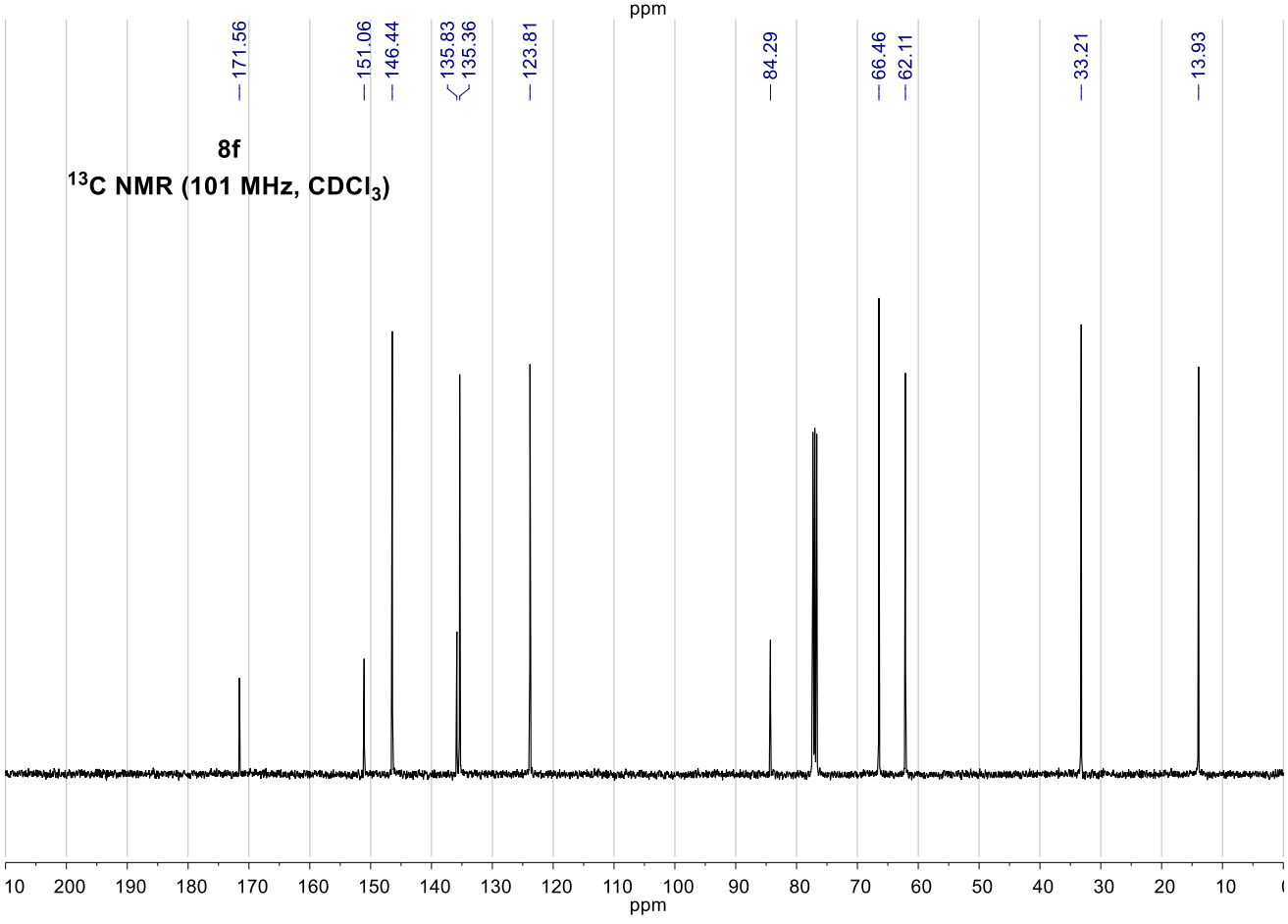

7.64
4.72
4.70
4.70
4.69
4.68
4.67
4.59
4.58
4.57
4.56
4.56
4.54
4.25
4.24
4.24
4.22
4.20
3.44
3.41
3.41
2.91
2.90
2.89
2.88
2.87
2.87
2.86
2.84
1.27
1.25
1.23
O
EtO2C
F3C
8d
1H NMR (400 MHz, CDCl3)
3.85
1.01
0.98
1.95
1.00
1.01
2.97
ppm

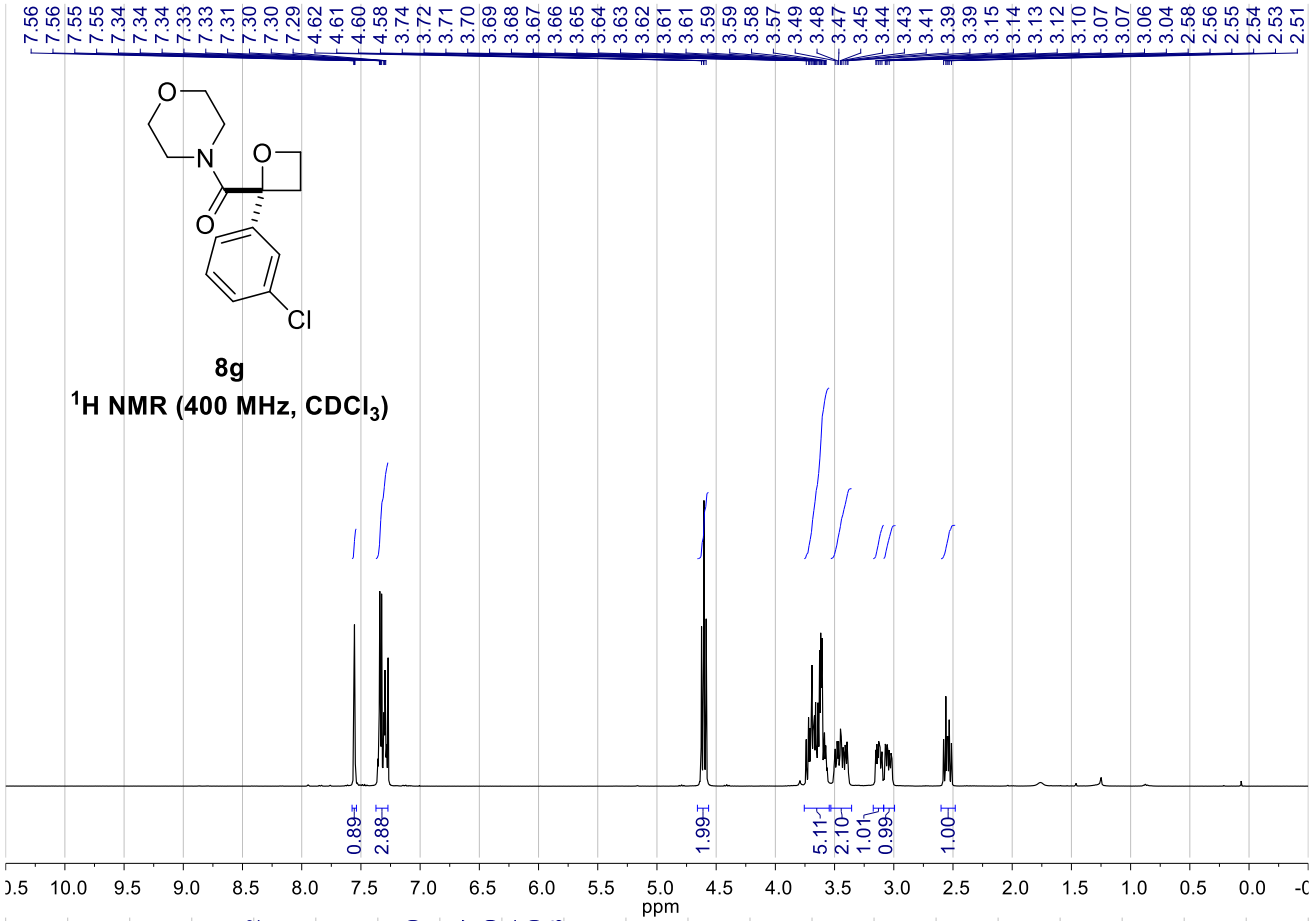

172.14
145.21
130.64
130.32
130.00
129.67
128.07
125.41
125.37
125.33
125.29
124.92
122.67
119.97
85.87
66.17
61.96
33.36
13.97
8d
13C NMR (101 MHz, CDCl3)
ppm

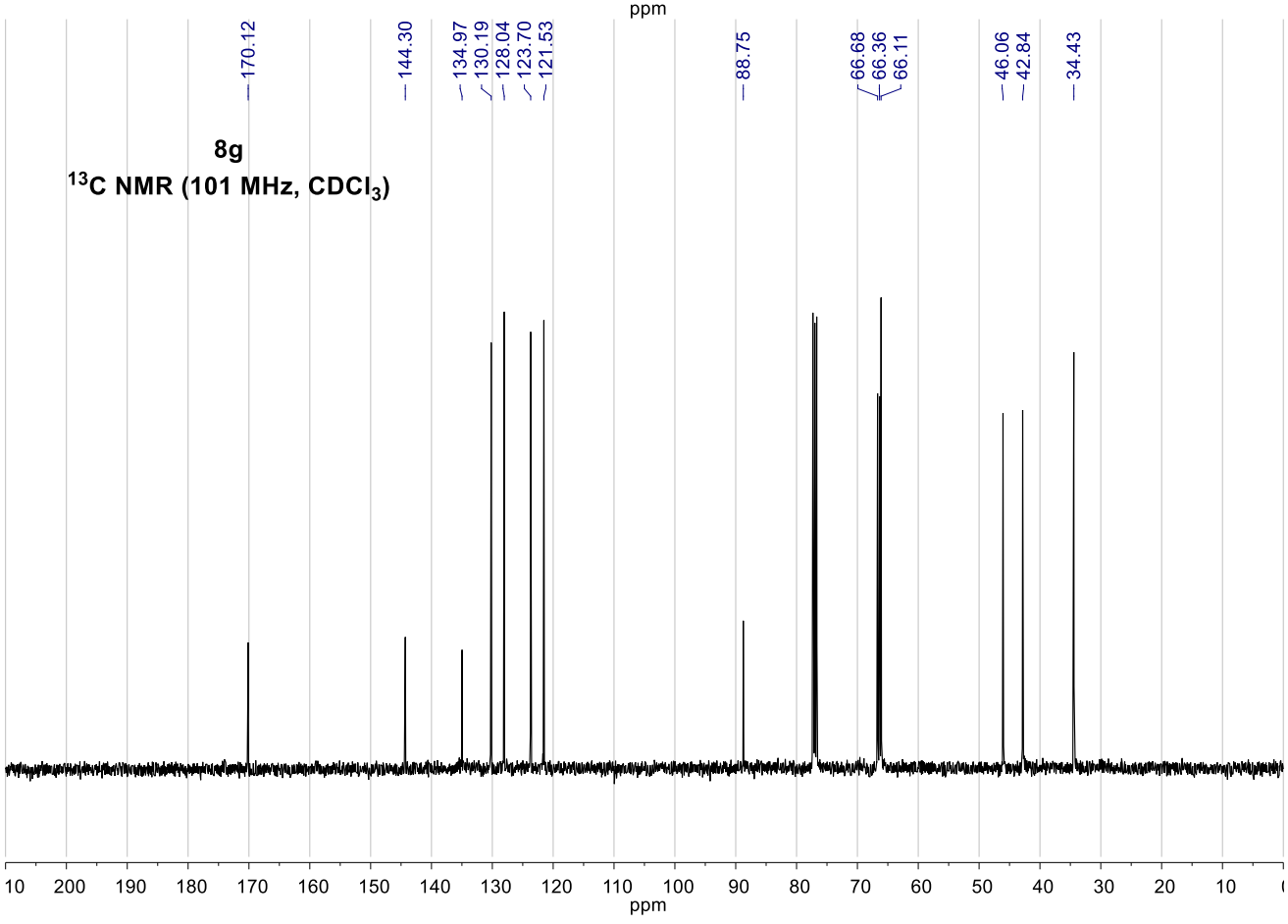

7.44
7.42
7.42
6.93
6.91
6.91
4.66
4.65
4.64
4.57
4.57
4.56
4.55
4.55
4.55
4.25
4.24
4.23
4.22
4.21
4.20
3.82
3.36
2.91
2.90
2.90
2.89
2.88
2.87
2.86
1.27
1.25
1.24
O
EtO2C
MeO
8e
1H NMR (400 MHz, CDCl3)
1.94
2.01
1.00
1.02
2.00
3.03
1.00
1.01
3.02
ppm

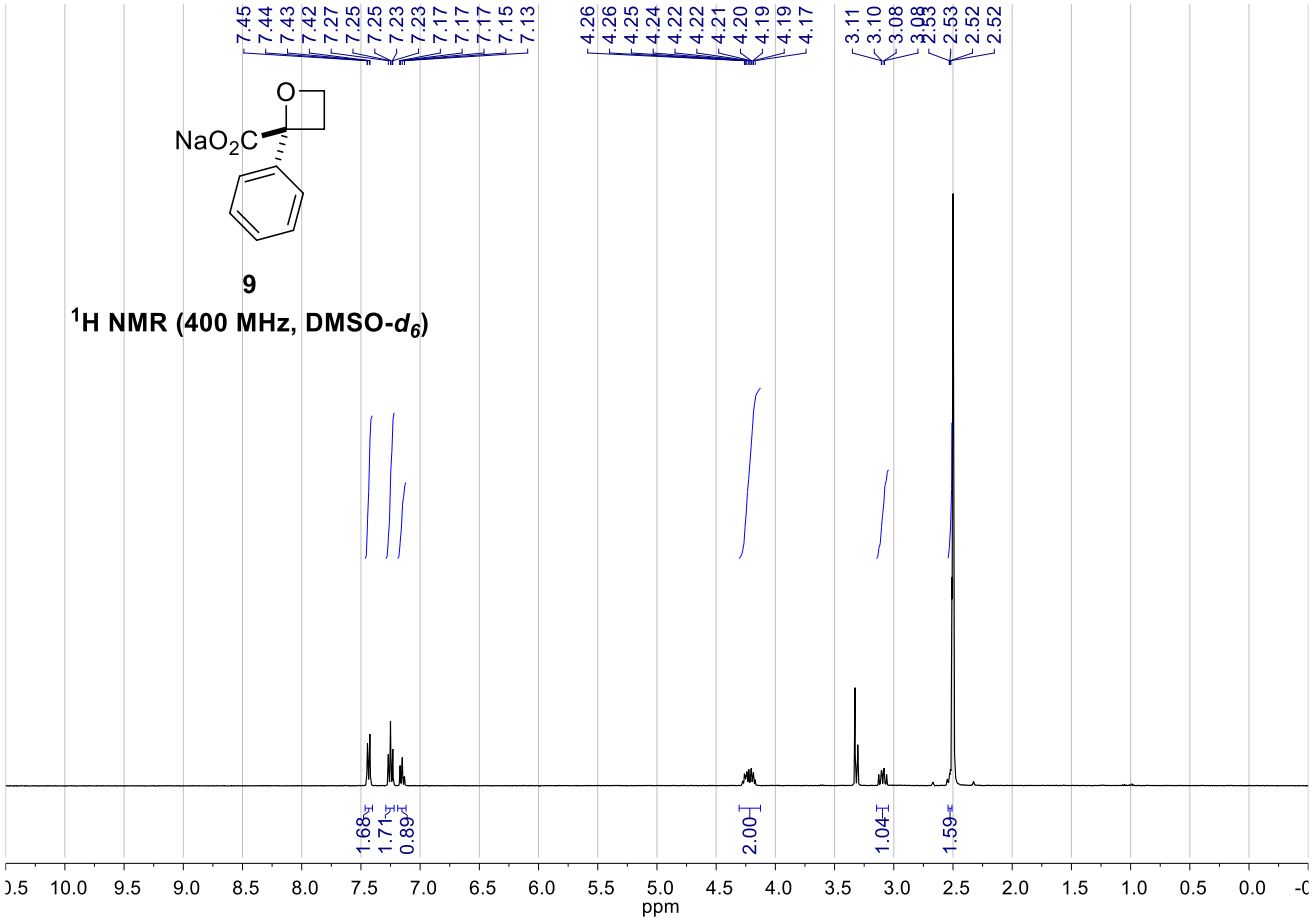

173.08
159.28
133.24
125.75
113.71
86.04
65.88
61.53
55.26
33.16
14.03
8e
13C NMR (101 MHz, CDCl3)
ppm

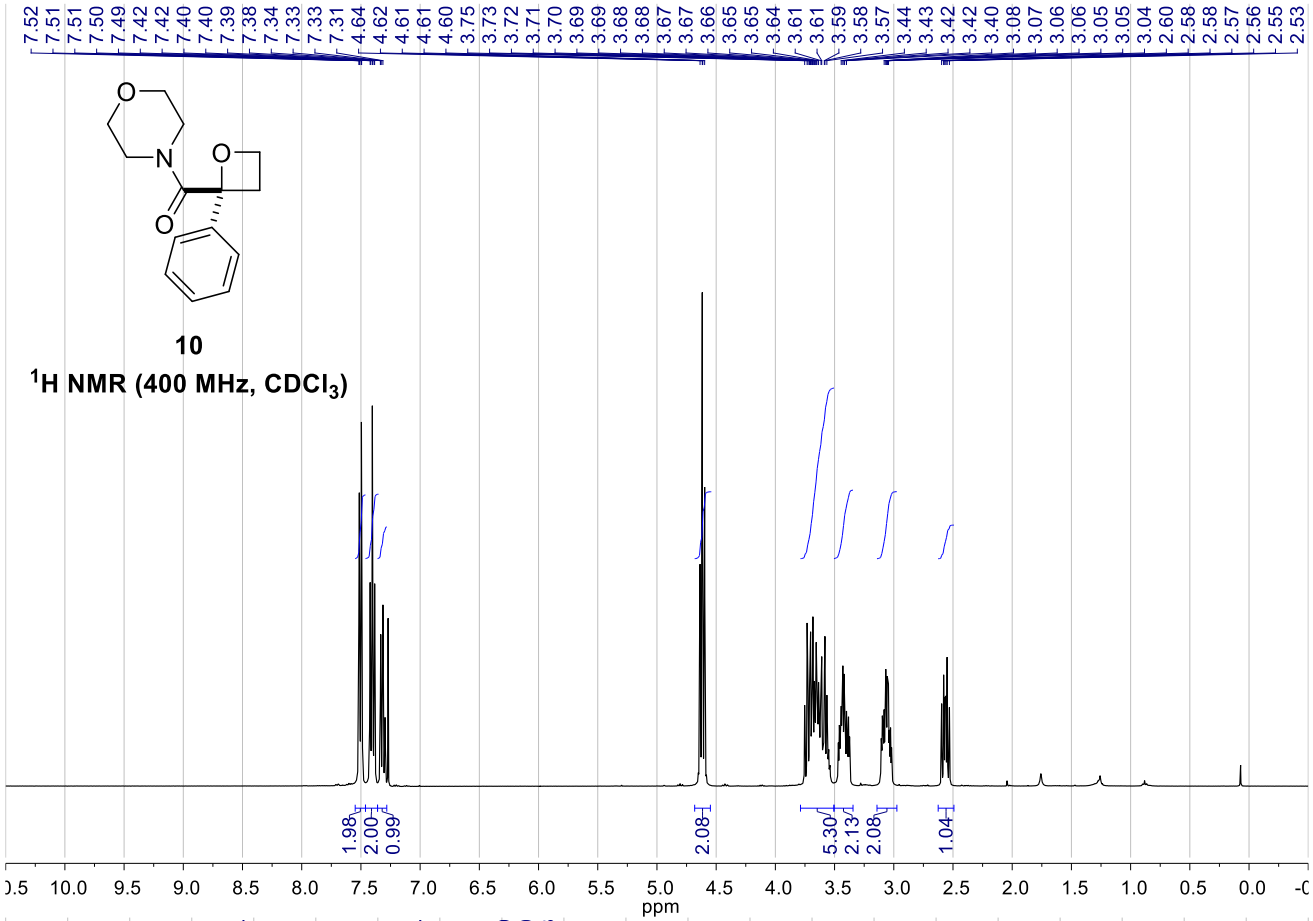

8.51
8.50
7.80
7.79
7.78
7.77
7.34
7.32
4.71
4.71
4.70
4.69
4.59
4.59
4.58
4.57
4.57
4.57
4.25
4.25
4.24
4.23
4.22
4.22
4.20
4.20
3.39
3.37
3.36
3.35
2.89
2.88
2.88
2.87
2.86
2.86
2.84
1.26
1.25
1.23
O
EtO2C
N
Cl
8f
1H NMR (400 MHz, CDCl3)
0.87
0.93
0.92
1.02
1.00
1.92
1.00
1.00
3.02
ppm

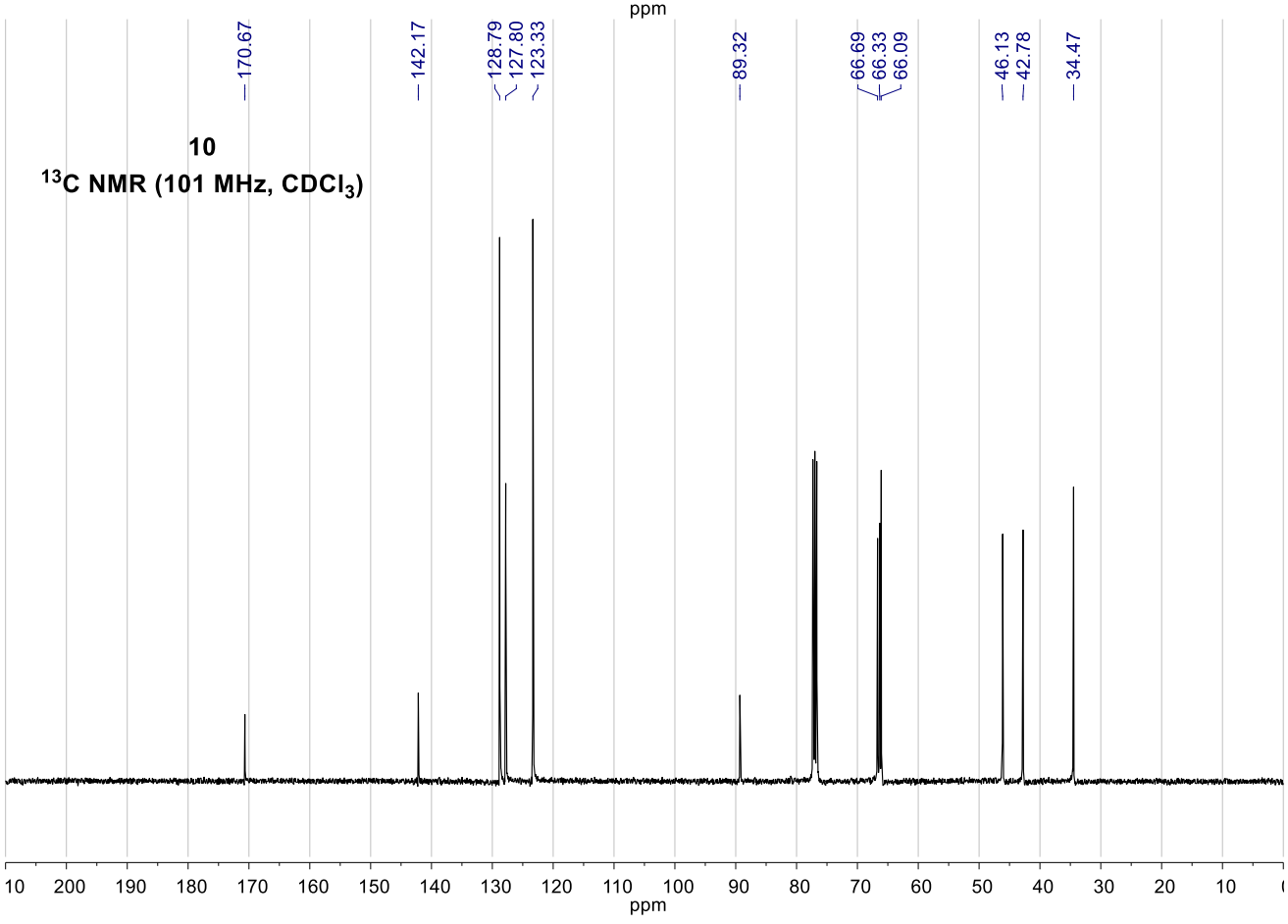

171.56
151.06
146.44
135.83
135.36
123.81
84.29
66.46
62.11
33.21
13.93
8f
13C NMR (101 MHz, CDCl3)
ppm

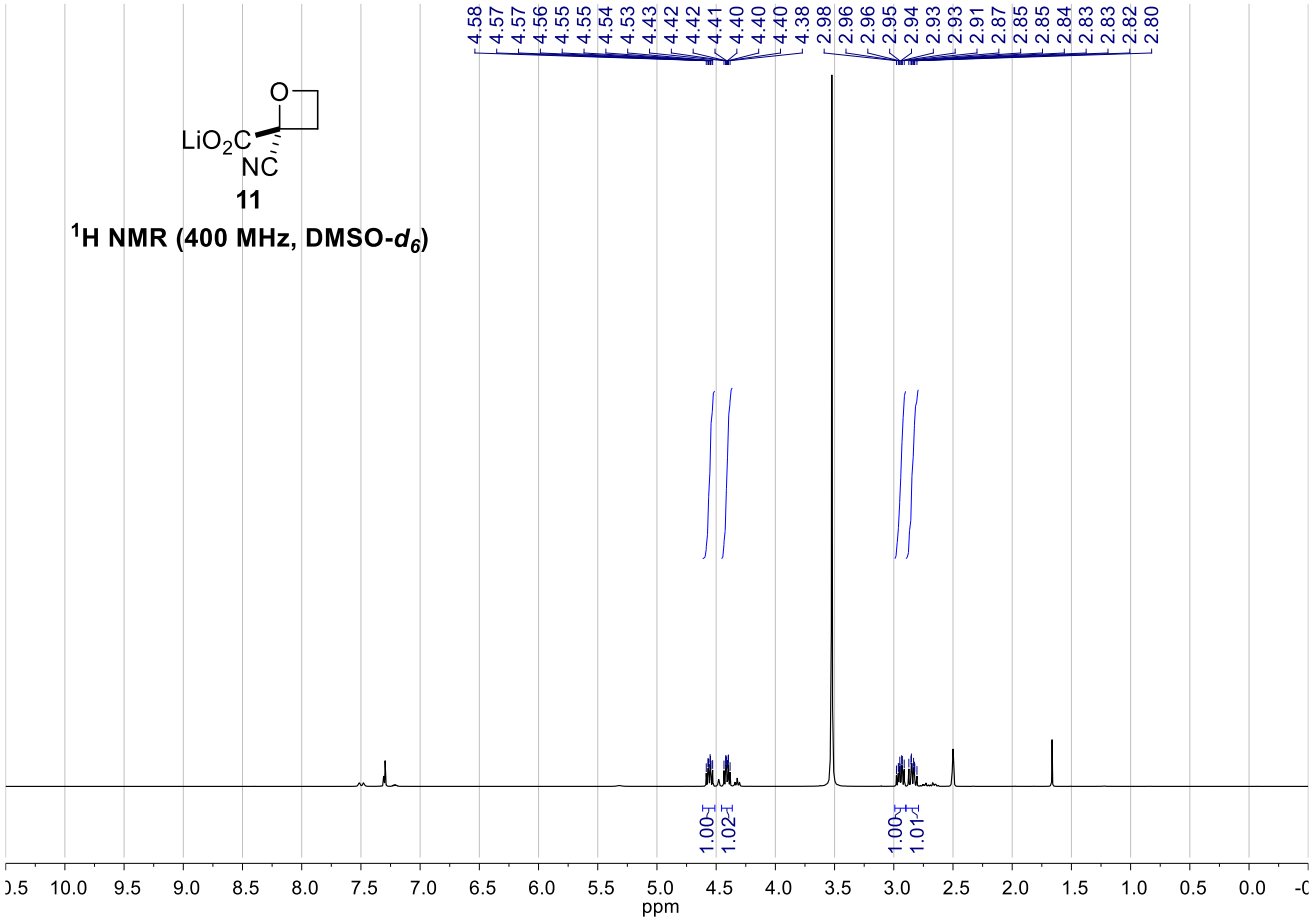

7.56 7.56 7.55 7.55 7.34 7.34 7.34 7.33 7.33 7.31 7.30 7.30 7.29 4.62 4.61 4.60 4.58 3.74 3.72 3.71 3.70 3.69 3.68 3.67 3.66 3.65 3.64 3.63 3.62 3.61 3.61 3.59 3.59 3.58 3.57 3.49 3.48 3.47 3.45 3.44 3.43 3.41 3.39 3.39 3.15 3.14 3.13 3.12 3.10 3.07 3.07 3.06 3.04 2.58 2.56 2.55 2.54 2.53 2.51
O
N
O
O
Cl
8g
^{1}H NMR (400 MHz, CDCl$_3$)
0.89 2.88 1.99 5.11 2.10 1.01 0.99 1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

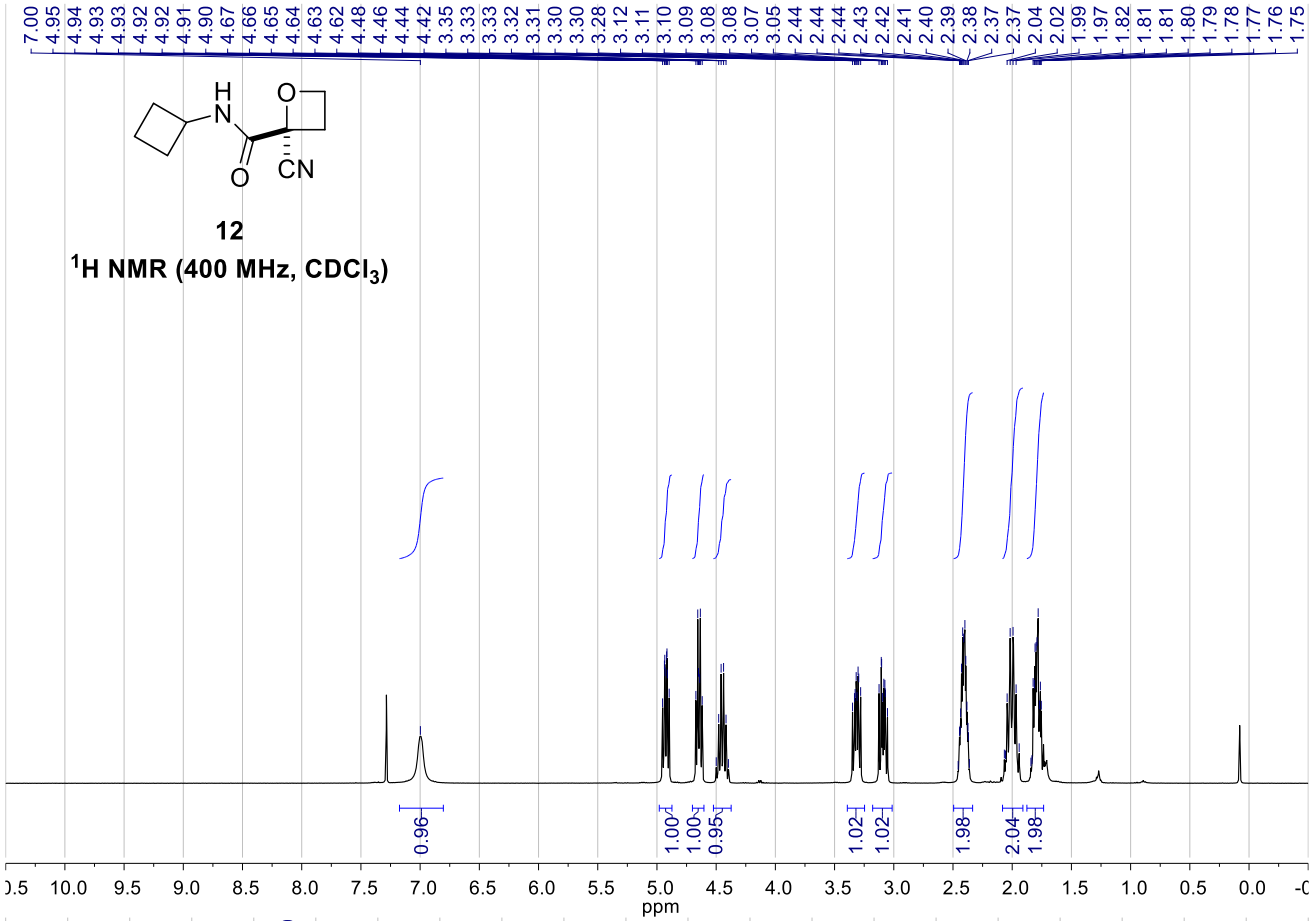

170.12 144.30 134.97 130.19 128.04 123.70 121.53 88.75 66.68 66.36 66.11 46.06 42.84 34.43
8g
^{13}C NMR (101 MHz, CDCl$_3$)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

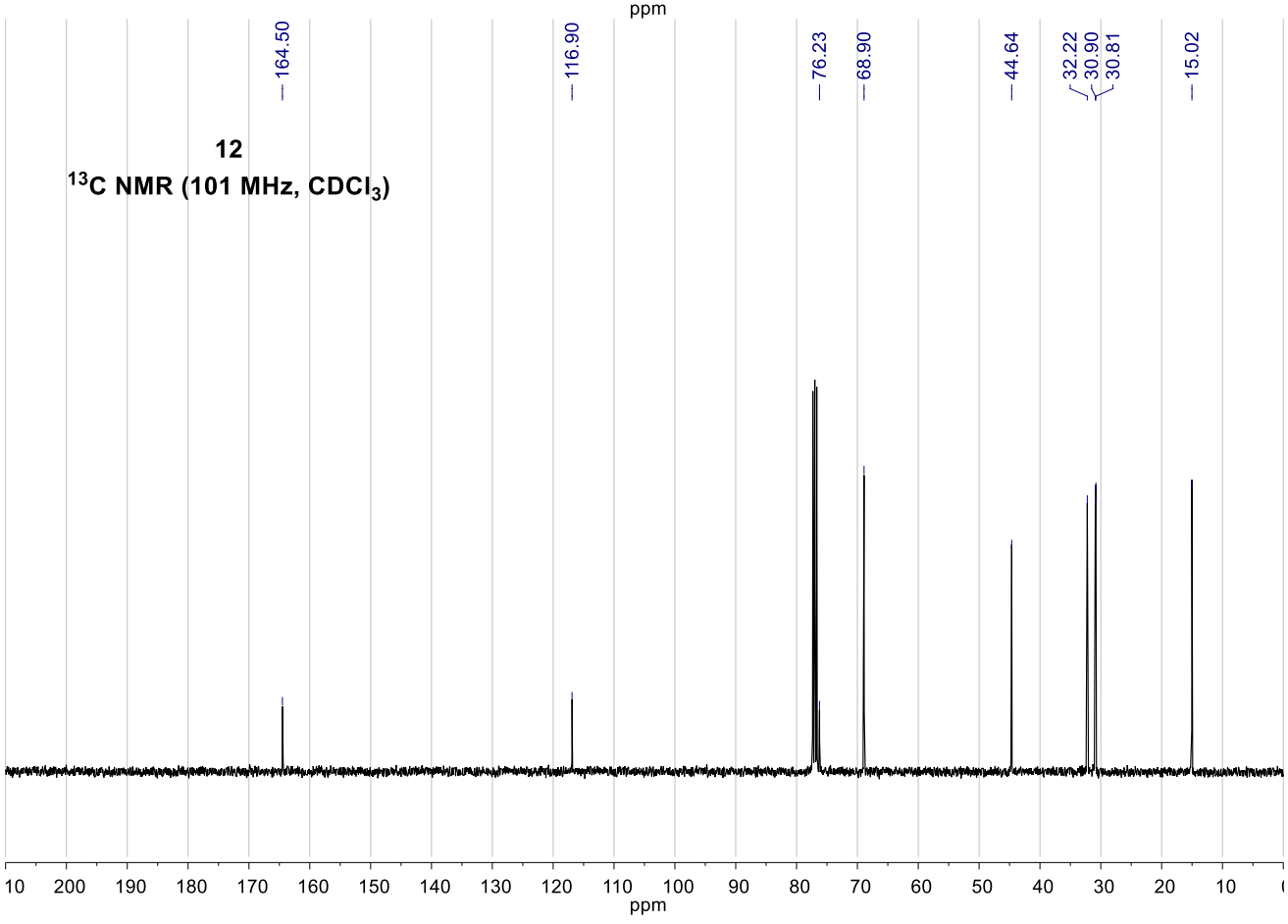

7.45
7.44
7.43
7.42
7.27
7.25
7.25
7.23
7.23
7.17
7.17
7.17
7.15
7.13
4.26
4.26
4.25
4.24
4.22
4.22
4.21
4.20
4.19
4.19
4.17
3.11
3.10
3.08
2.53
2.53
2.52
2.52
O
NaO2C
9
1H NMR (400 MHz, DMSO-d6)
1.68
1.71
0.89
2.00
1.04
1.59
ppm

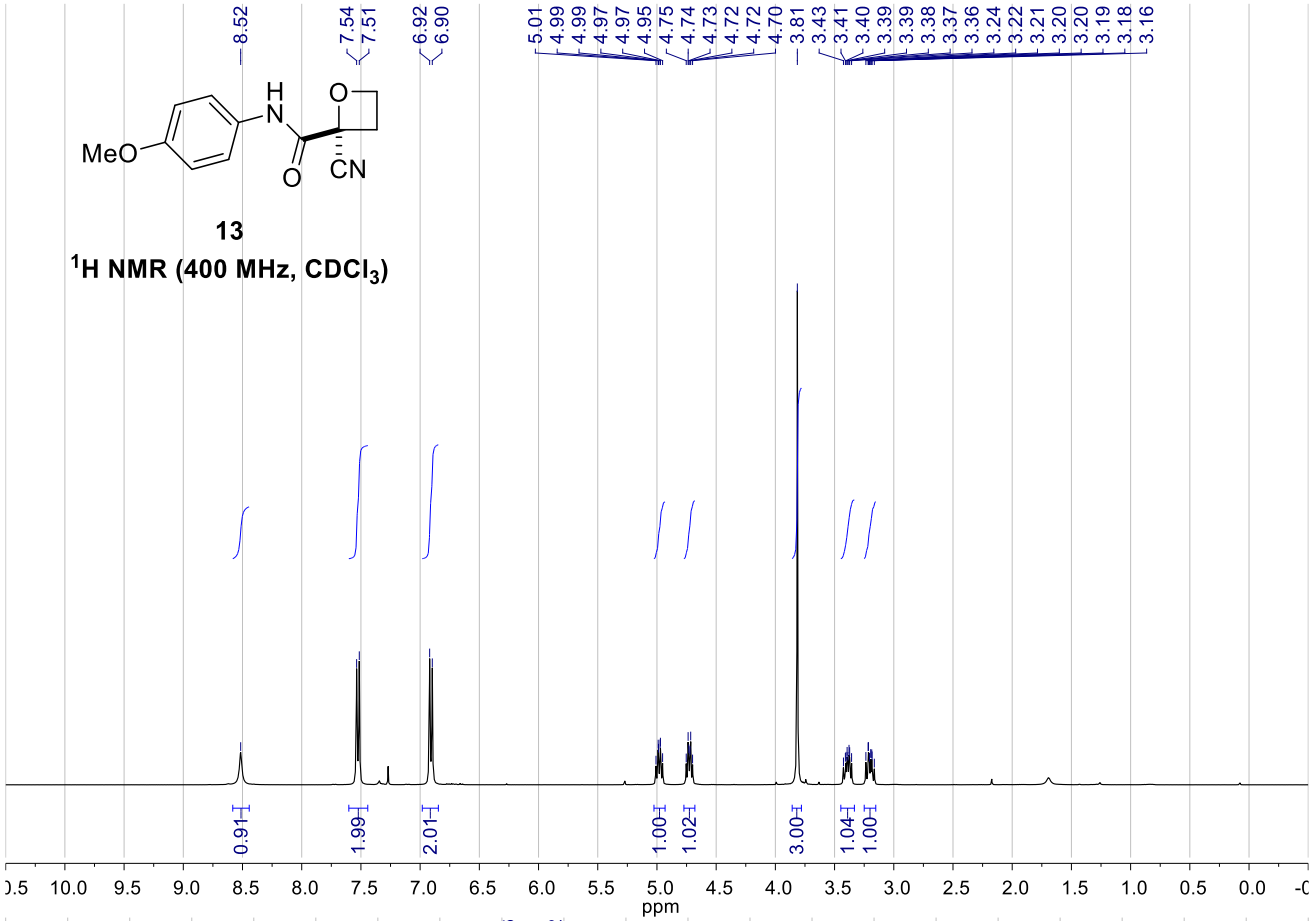

7.52 7.51 7.51 7.50 7.49 7.42 7.42 7.40 7.40 7.39 7.38 7.34 7.33 7.33 7.31 4.64 4.62 4.61 4.61 4.60 3.75 3.73 3.72 3.71 3.70 3.69 3.69 3.68 3.68 3.67 3.67 3.66 3.65 3.65 3.64 3.61 3.61 3.59 3.58 3.57 3.44 3.43 3.42 3.42 3.40 3.08 3.07 3.06 3.06 3.05 3.05 3.04 2.60 2.58 2.58 2.57 2.56 2.55 2.53
O
N
O
O
10
^{1}H NMR (400 MHz, CDCl$_3$)
1.98 2.00 0.99 2.08 5.30 2.13 2.08 1.04
ppm

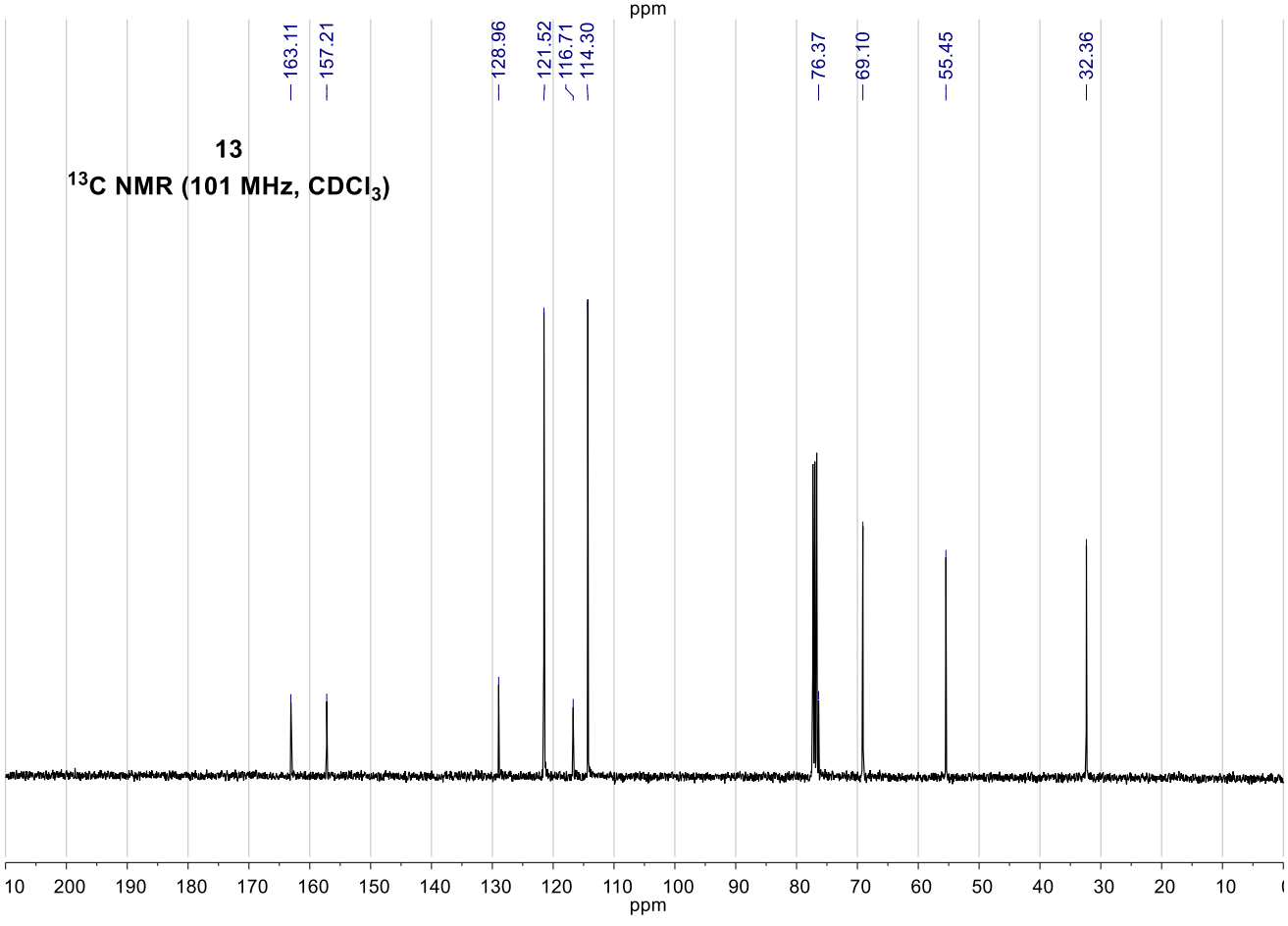

170.67 142.17 128.79 127.80 123.33 89.32 66.69 66.33 66.09 46.13 42.78 34.47
10
^{13}C NMR (101 MHz, CDCl$_3$)
ppm

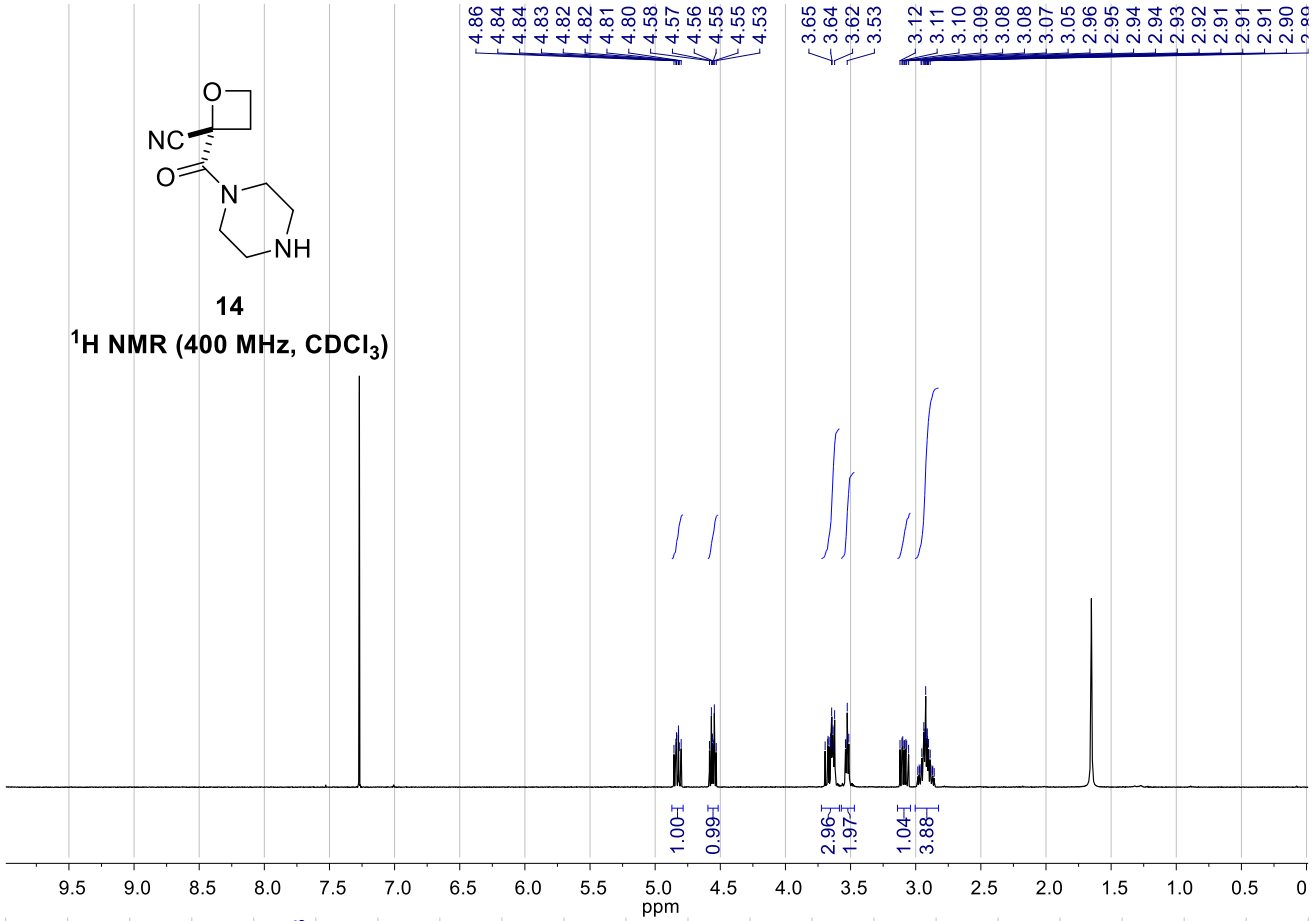

4.58
4.57
4.57
4.56
4.55
4.55
4.54
4.53
4.43
4.42
4.42
4.41
4.40
4.40
4.40
4.38
2.98
2.96
2.96
2.95
2.94
2.93
2.93
2.91
2.87
2.85
2.85
2.84
2.83
2.83
2.82
2.80
O
LiO2C
NC
11
1H NMR (400 MHz, DMSO-d6)
1.00
1.02
1.00
1.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

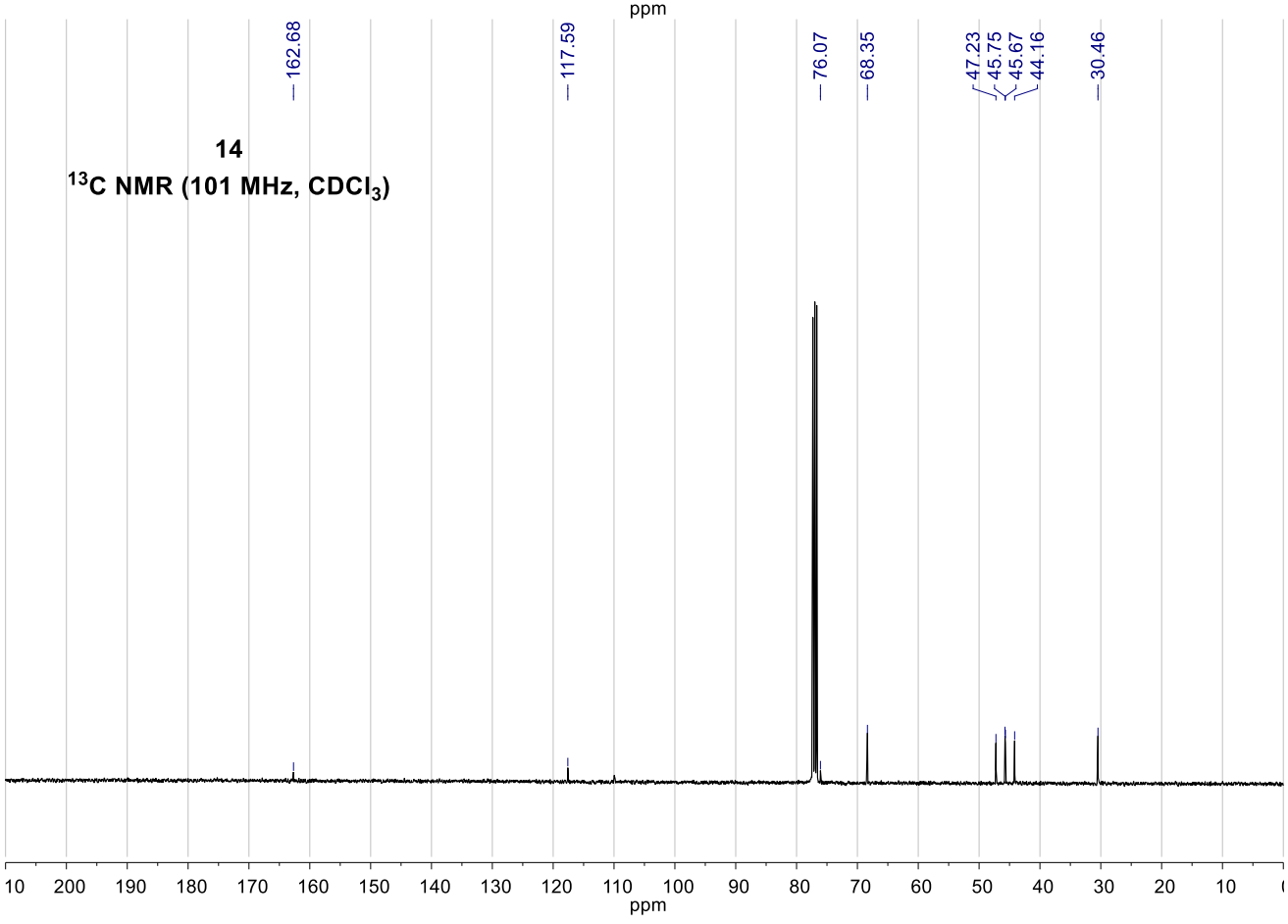

12
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


12
^{13}C NMR (101 MHz, CDCl$_3$)
ppm


8.52
7.54
7.51
6.92
6.90
5.01
4.99
4.99
4.97
4.97
4.95
4.75
4.74
4.73
4.72
4.72
4.70
3.81
3.43
3.41
3.40
3.39
3.39
3.38
3.37
3.36
3.24
3.22
3.21
3.20
3.20
3.19
3.18
3.16
MeO
H
N
O
O
CN
13
^{1}H NMR (400 MHz, CDCl$_3$)
0.91
1.99
2.01
1.00
1.02
3.00
1.04
1.00
ppm

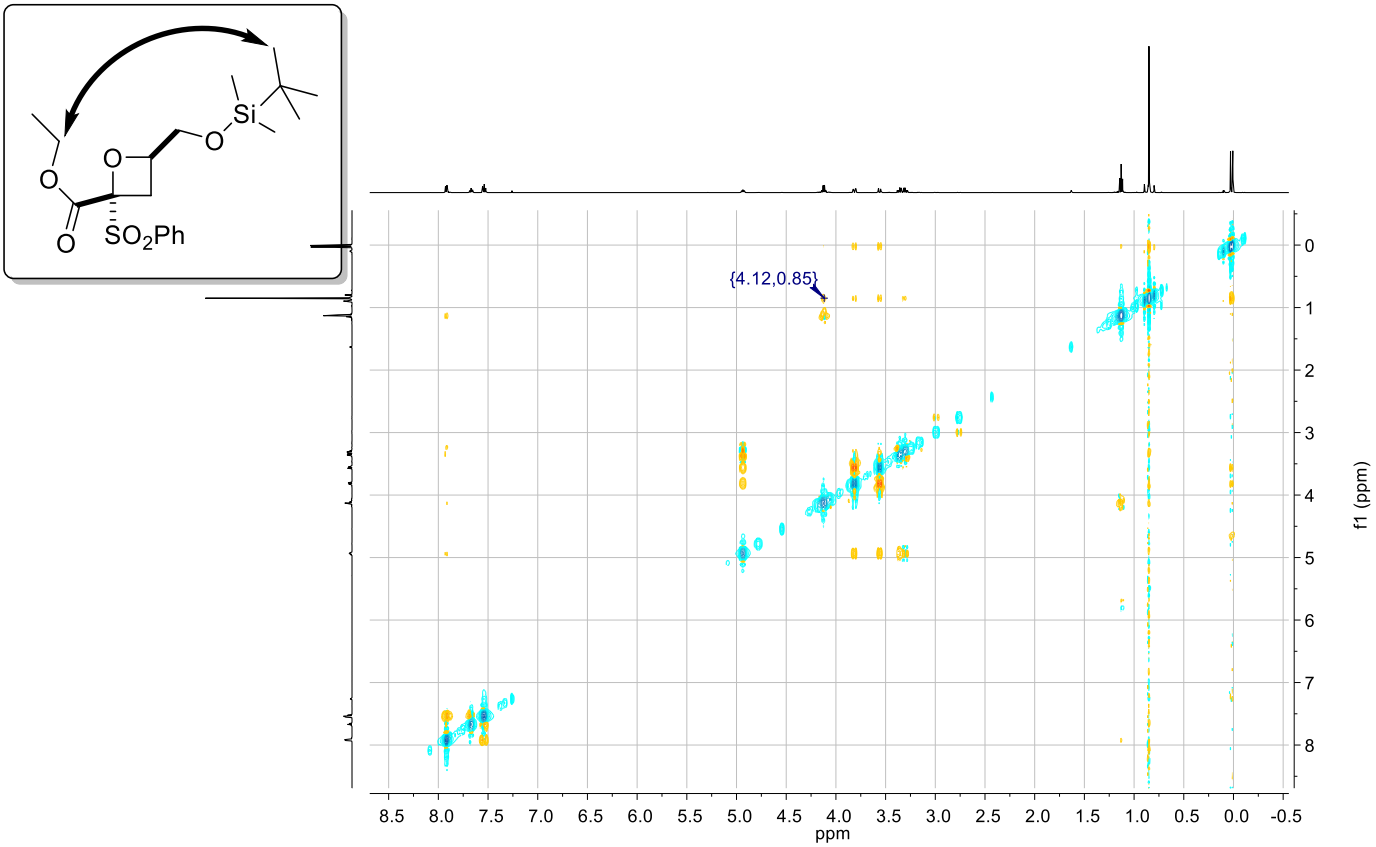

163.11
157.21
128.96
121.52
116.71
114.30
76.37
69.10
55.45
32.36
13
^{13}C NMR (101 MHz, CDCl$_3$)
ppm


4.86
4.84
4.84
4.83
4.82
4.82
4.81
4.80
4.58
4.57
4.56
4.55
4.55
4.53
3.65
3.64
3.62
3.53
3.12
3.11
3.10
3.09
3.08
3.08
3.07
3.05
2.96
2.95
2.94
2.94
2.93
2.92
2.91
2.91
2.90
O
NC
O
N
NH
14
^{1}H NMR (400 MHz, CDCl$_3$)
1.00
0.99
2.96
1.97
1.04
3.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm

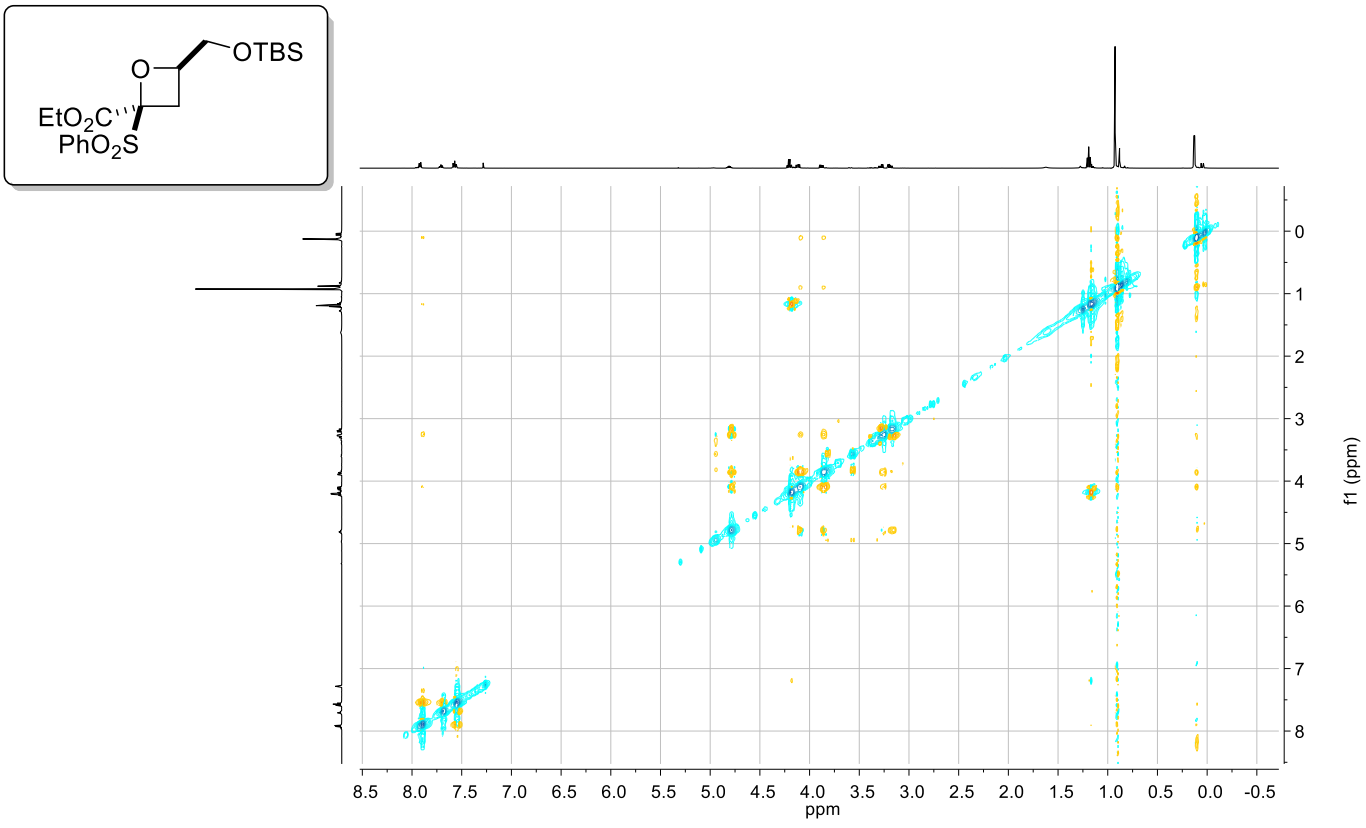

162.68
117.59
76.07
68.35
47.23
45.75
45.67
44.16
30.46
14
^{13}C NMR (101 MHz, CDCl$_3$)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

NOESY and Selective NOE Spectra for Oxetanes 5a, 5d, 5f and 5h

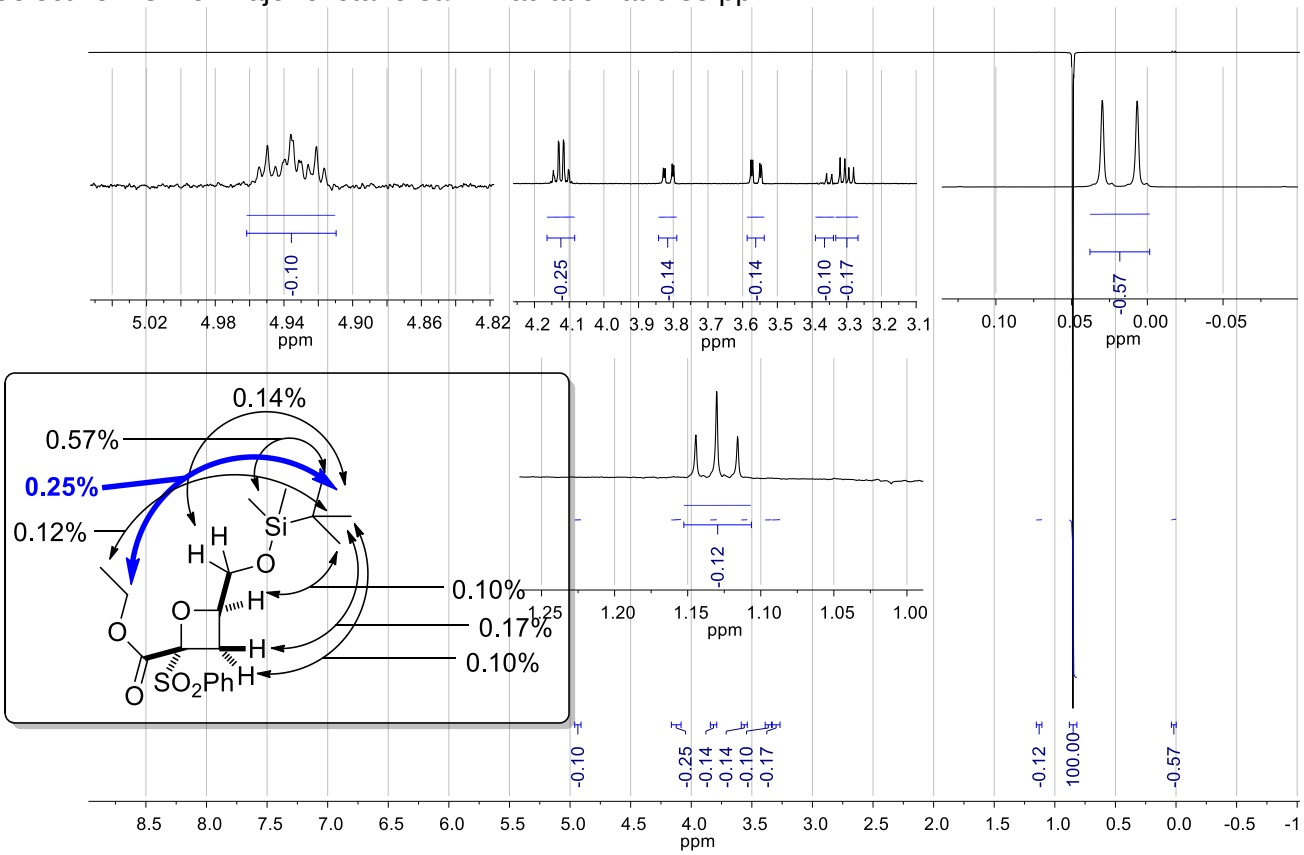
NOESY NMR of major oxetane **5a**



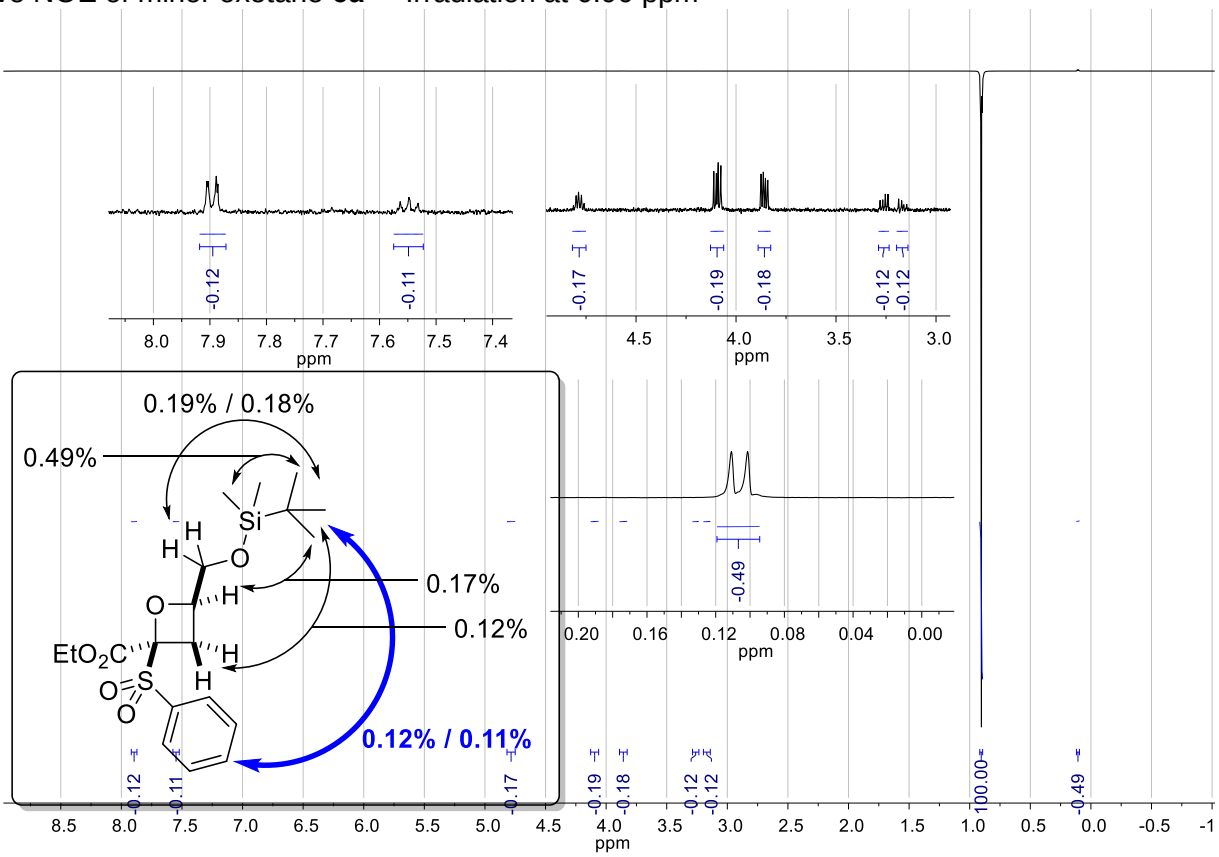
NOESY NMR of minor oxetane **5a'**



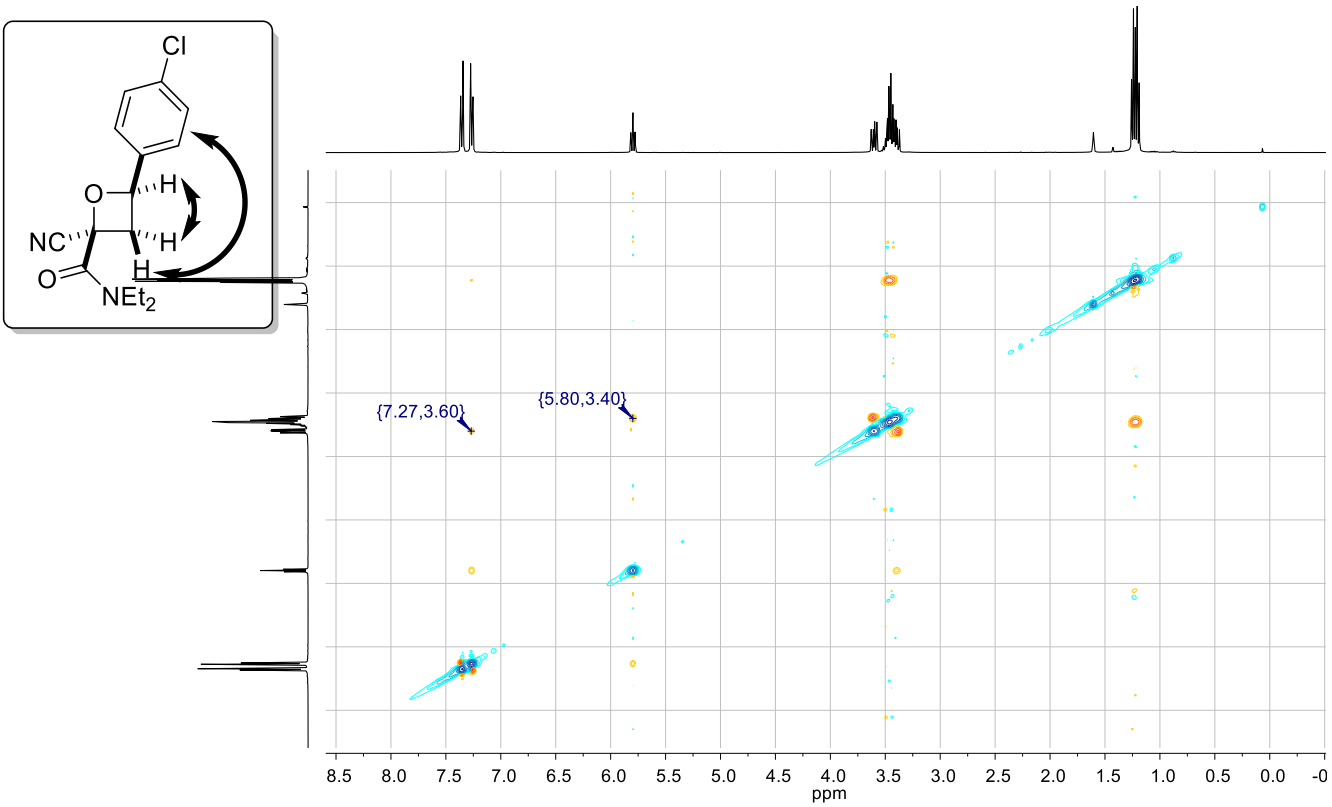
Selective NOE of major oxetane **5a** – Irradiation at 0.85 ppm



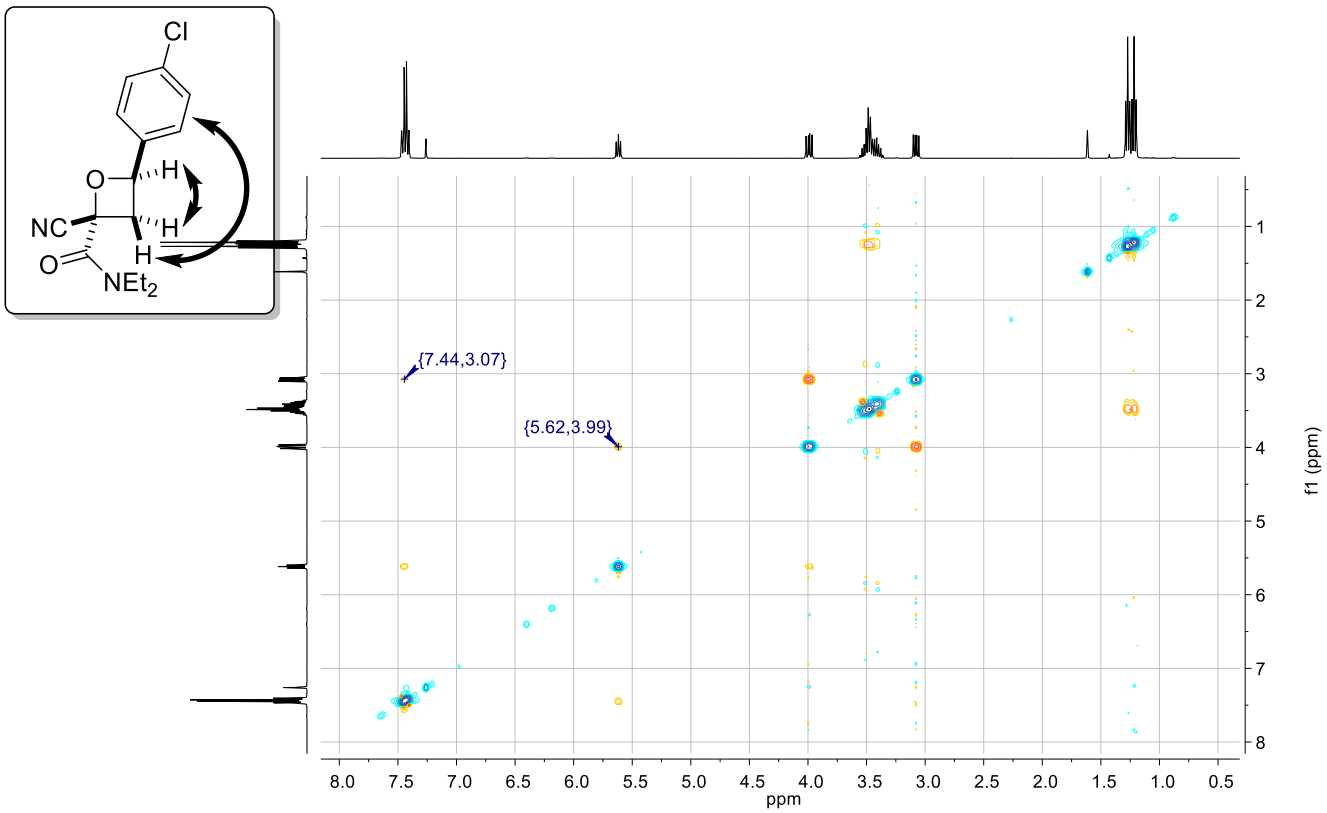
Selective NOE of minor oxetane **5a'** – Irradiation at 0.90 ppm



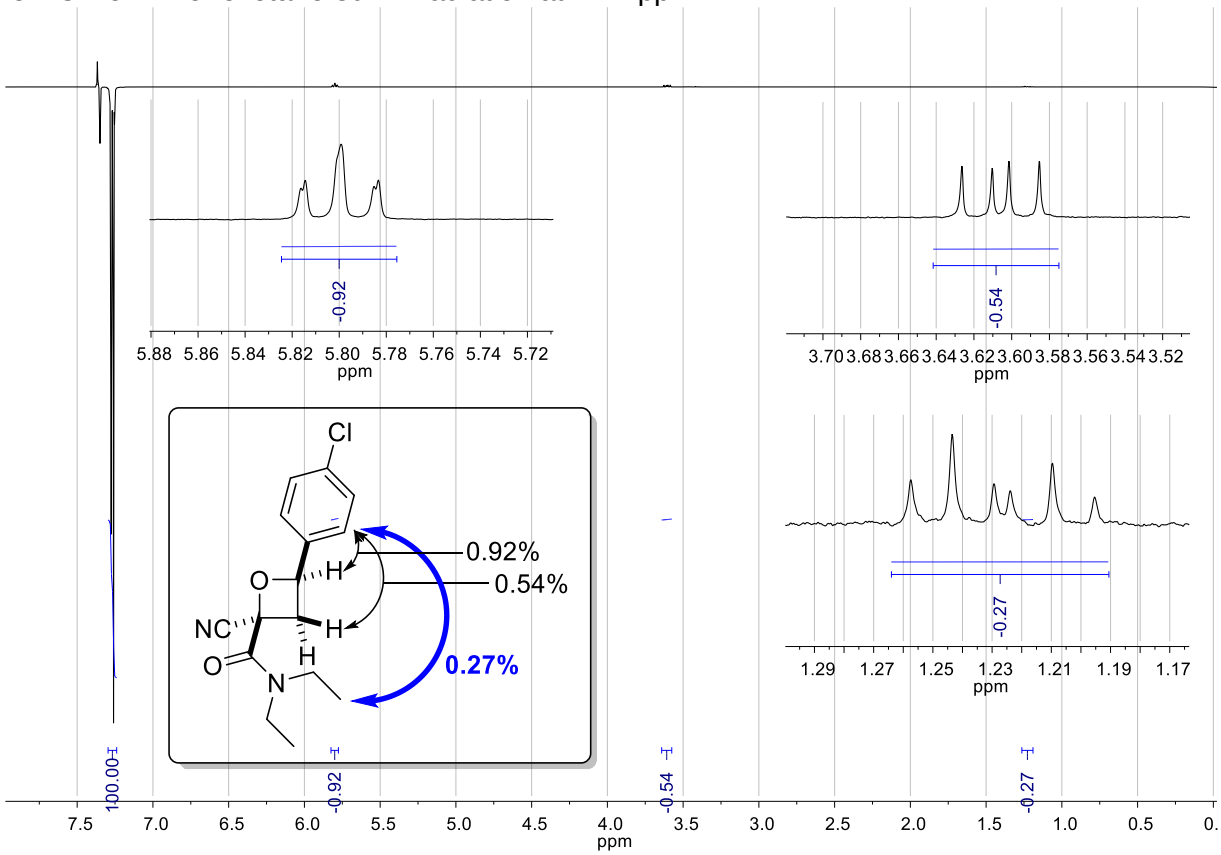
NOESY NMR of minor oxetane **5d**



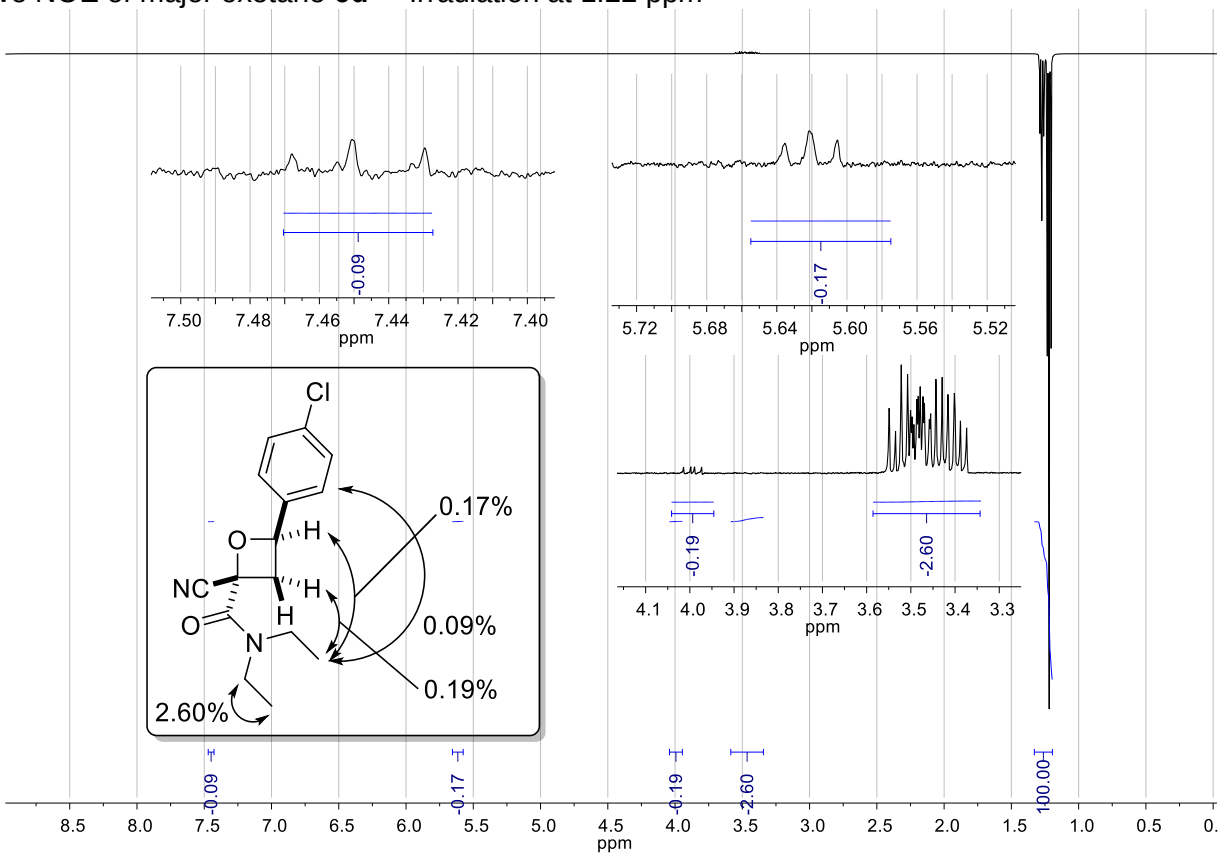
NOESY NMR of major oxetane **5d'**



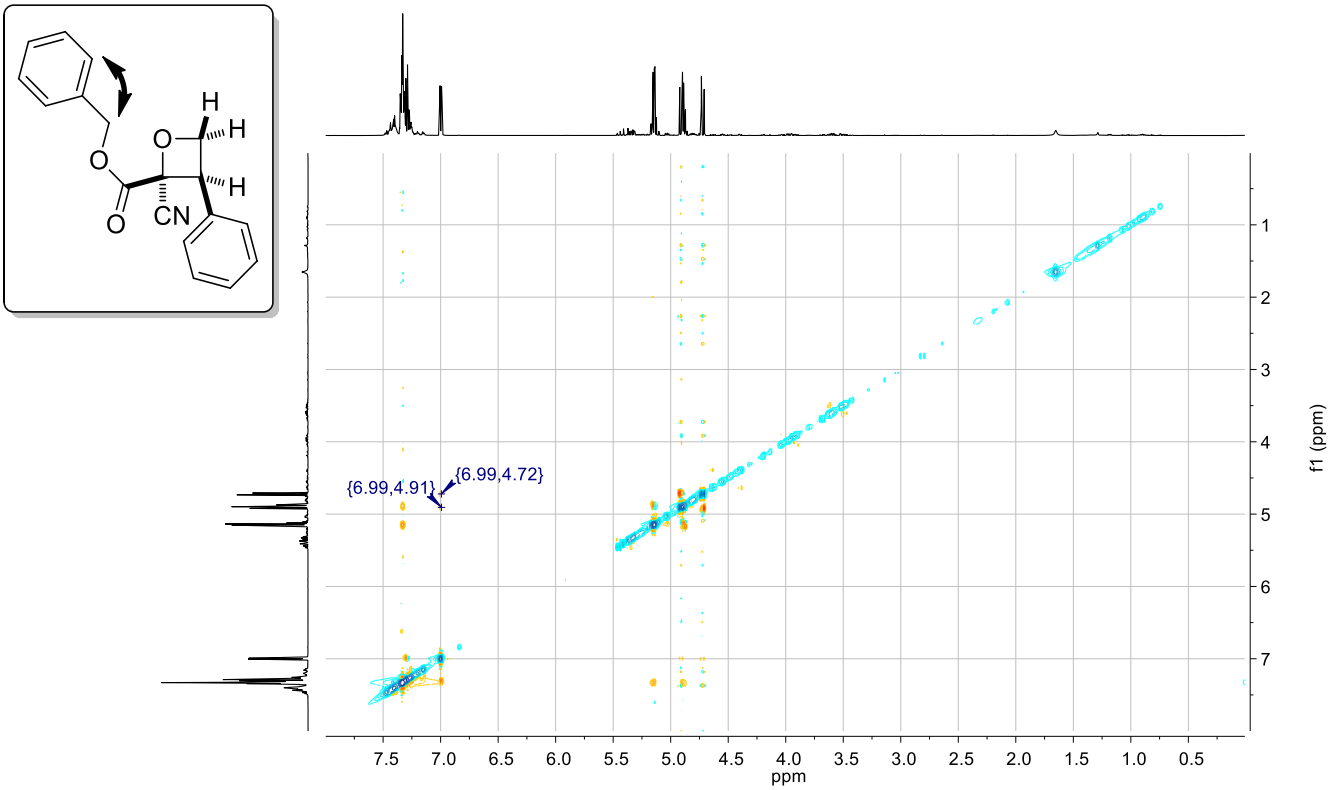
Selective NOE of minor oxetane **5d** – Irradiation at 7.27 ppm



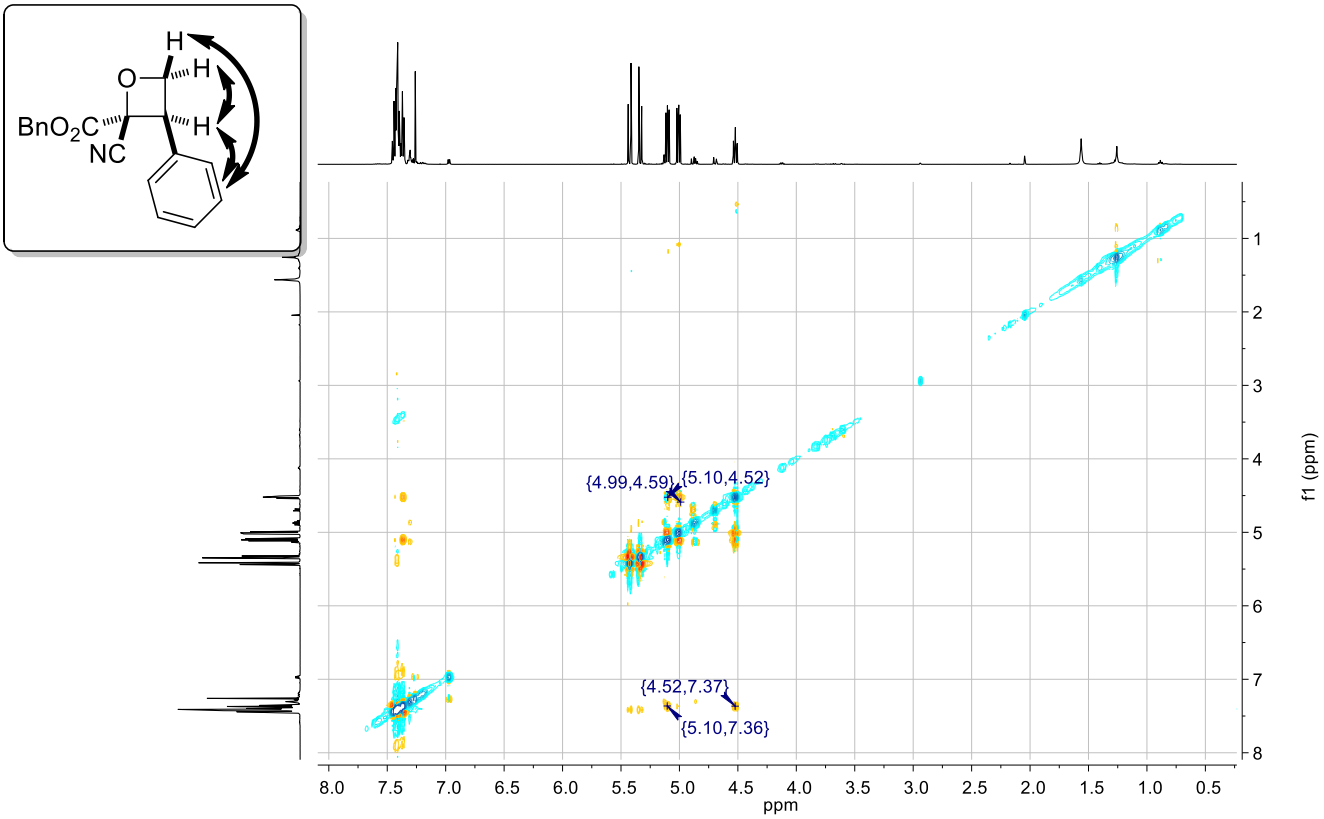
Selective NOE of major oxetane **5d'** – Irradiation at 1.22 ppm



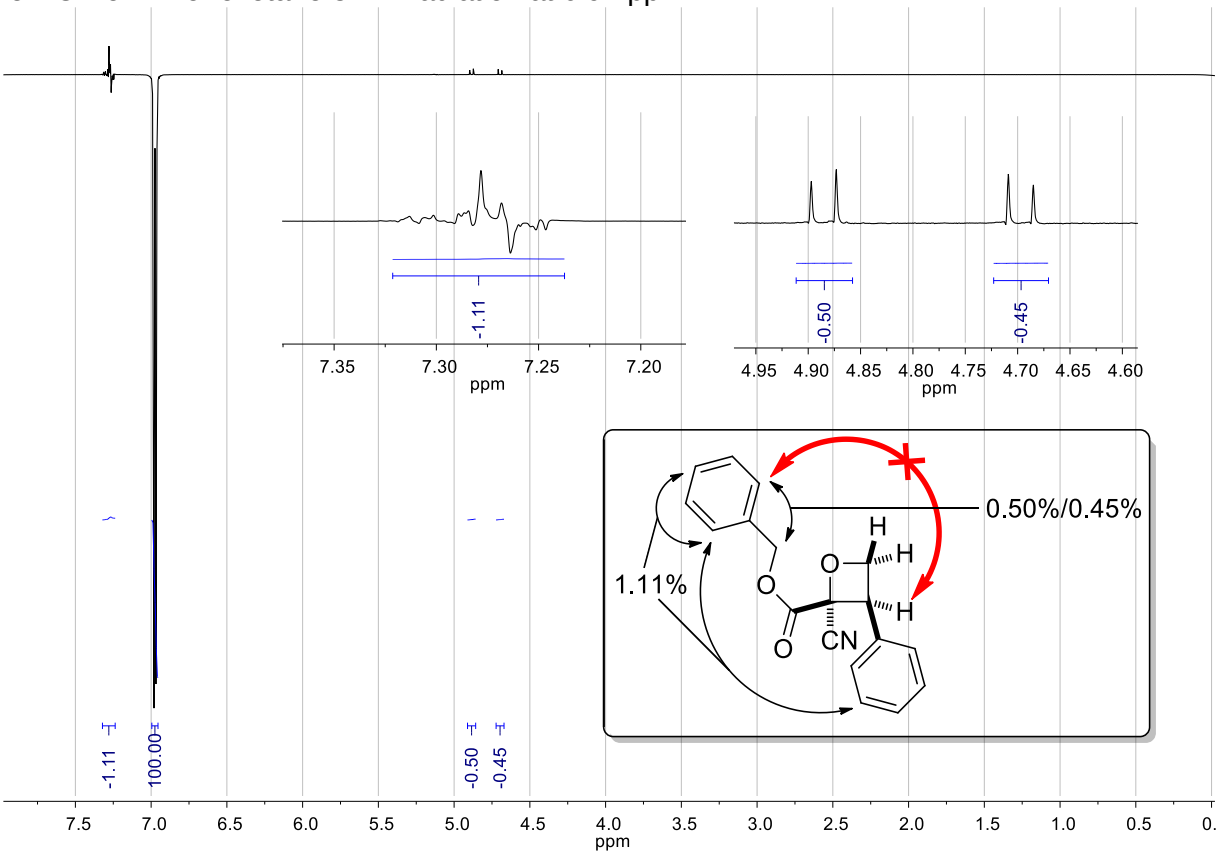
NOESY NMR of minor oxetane **5f**



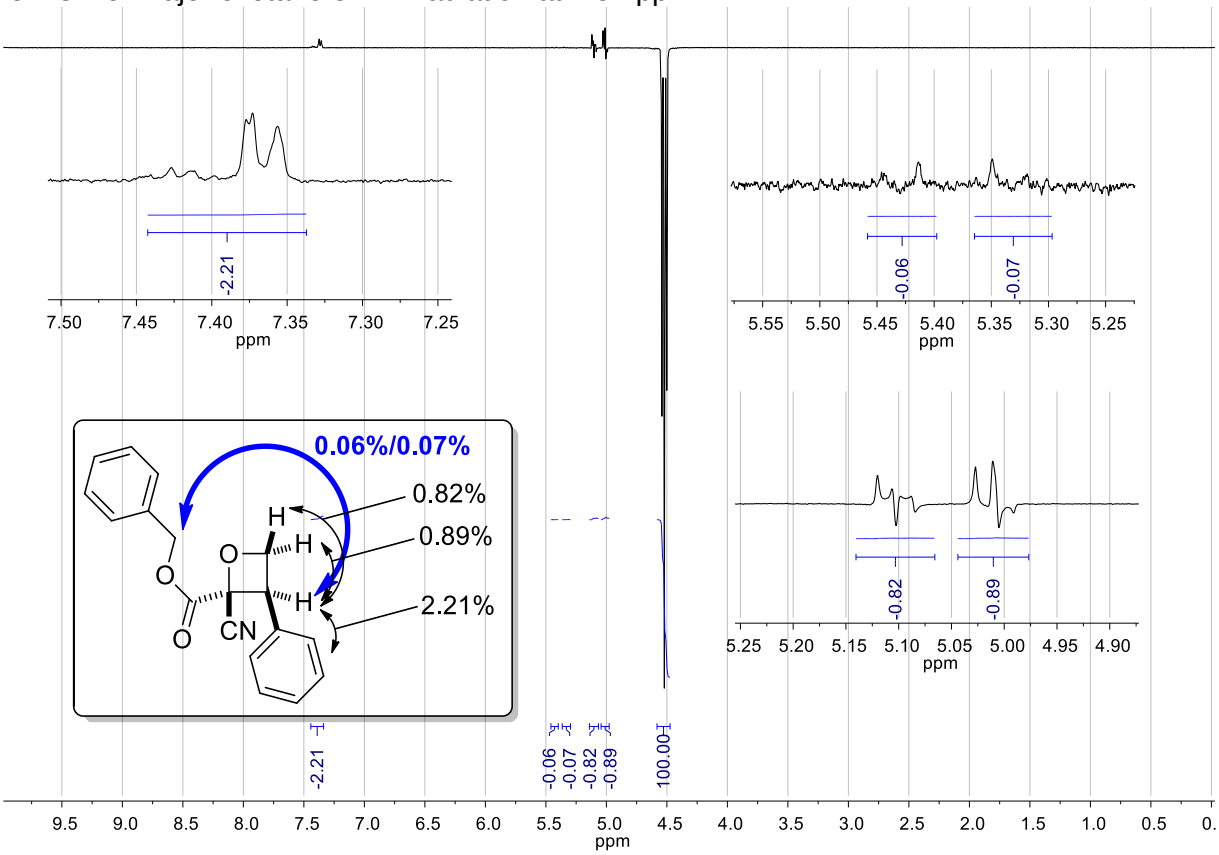
NOESY NMR of major oxetane **5f'**



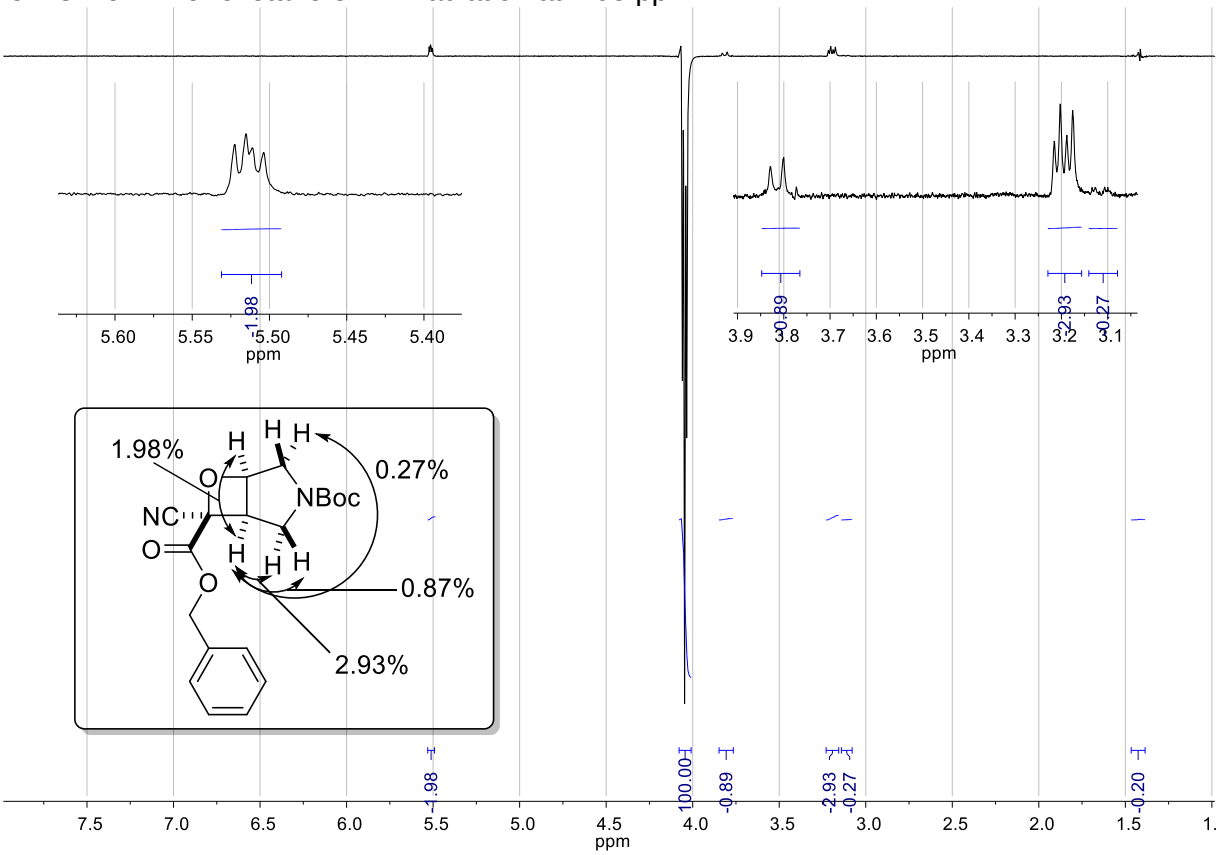
Selective NOE of minor oxetane **5f** – Irradiation at 6.97 ppm



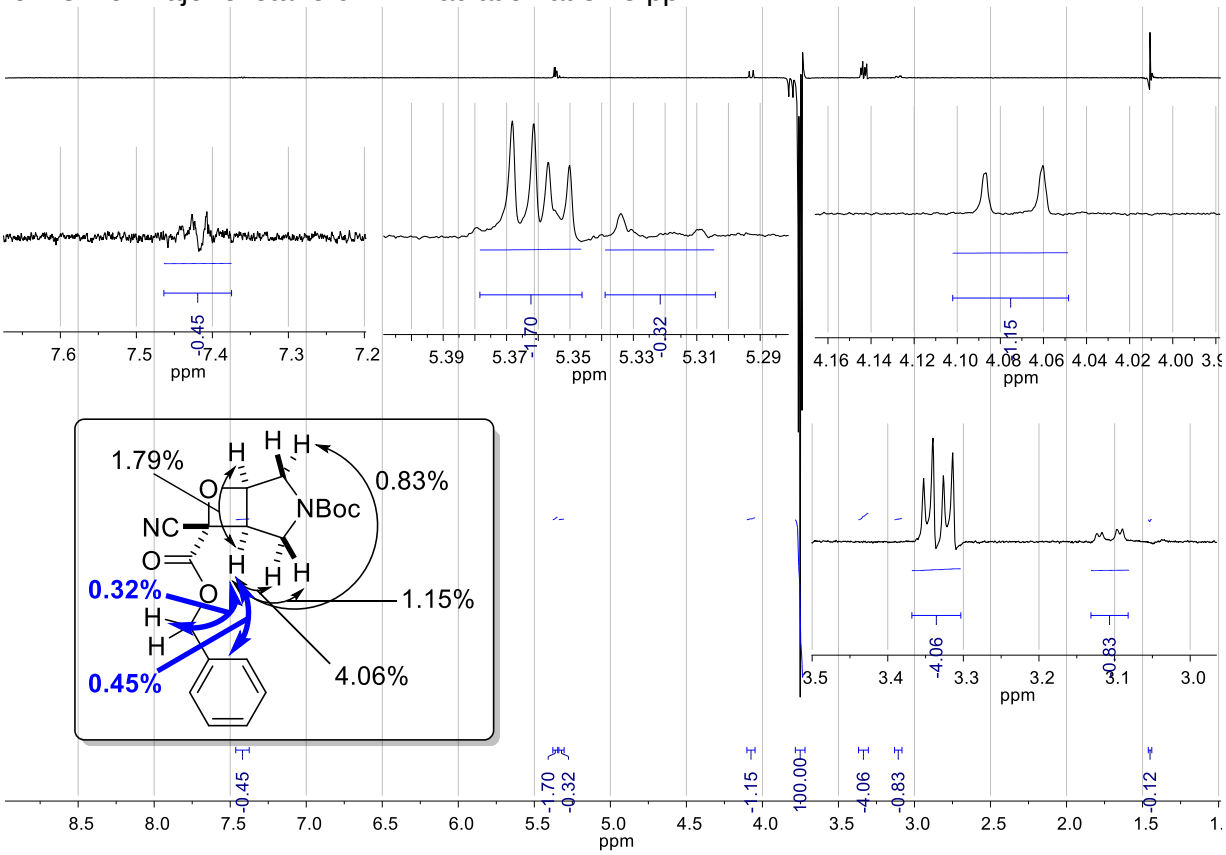
Selective NOE of major oxetane **5f'** – Irradiation at 4.52 ppm



Selective NOE of minor oxetane **5h** – Irradiation at 4.05 ppm



Selective NOE of major oxetane **5h'** – Irradiation at 3.75 ppm



The relative stereochemistry for the major isomer of oxetane **5b** as indicated in table 2 was assigned by analogy to that observed for oxetane **5a**.

The relative stereochemistry for the major isomers of oxetanes **5c** and **5e** as indicated in table 2 were assigned by analogy to that observed for oxetane **5d**.

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