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Flow Technology Enabled Preparation of C3-Heterosubstituted 1-azabicyclo[1.1.0]butanes and Azetidines: Accessing Unexplored Chemical Space in Strained Heterocyclic Chemistry

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Supporting Information

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1. General methods

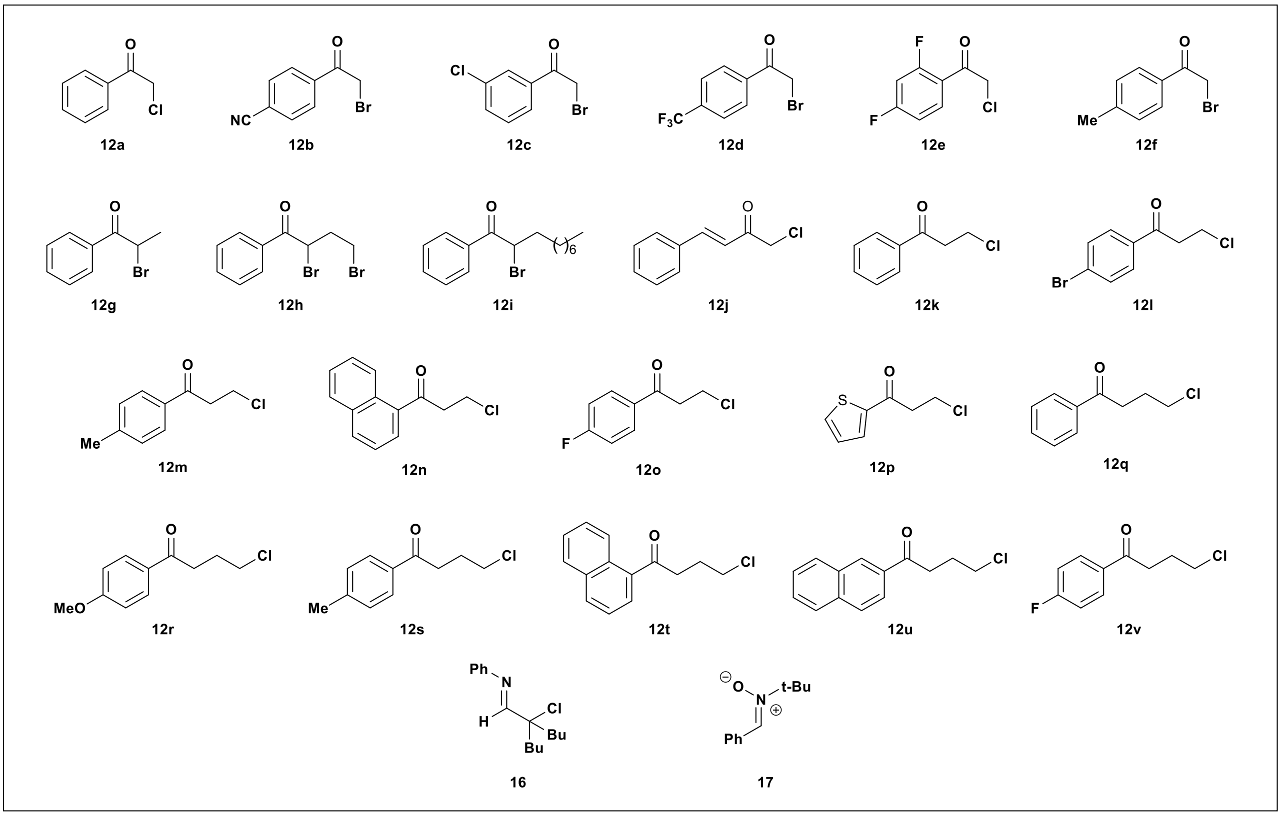
Infrared spectra of the compounds were recorded in reciprocal centimeters (cm^{-1}) by using a PerkinElmer 283 spectrometer. Melting points were measured with Büchi melting point B-545. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Mercury 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F) and an Agilent 500 spectrometer (500 MHz for ^{1}H, 126 MHz for ^{13}C, 470 MHz for ^{19}F). The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 77.00 ppm (^{13}C in $CDCl_3$). Spin-spin coupling constants (*J*) are given in Hz. As far as possible, unambiguous assignment of all resonances was performed by combined application of 2D NMR techniques, *i.e.* HSQC and COSY experiments. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet and bs = broad singlet), coupling constant (in Hz), integration and assignment]. NOESY experiments were performed for structural evaluations of the products. High resolution mass spectrometry (HRMS) spectra were performed on Agilent 6530 accurate mass Q-TOF instrument and Excalibur data system. Diastereomeric ratio was assessed by ^{1}H NMR analysis on the reaction crude. Silica (70−230 mesh and 230−400 mesh) was used for flash chromatography on glass columns. TLC was carried out on a 0.25 mm precoated silica gel thick plates (Merck) with a fluorescence indicator F-254; the spots were visualized under UV light (λ = 254 nm) and/or KMnO4 (aq.) was used as revealing system.

Chemicals were purchased from Sigma-Aldrich, Fluorochem, TCI Europe and Alfa Aesar unless otherwise specified. THF was distilled prior to use. Organolithium reagents were titrated prior to use (using N-benzylbenzamide as titrating agent).[1]

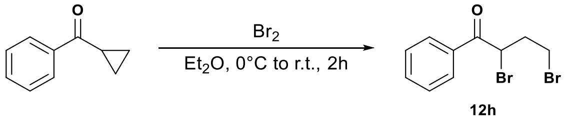
Flow equipment: General fluidic connections were achieved using PFA tubing (Bola), with PEEK or PTFE fittings (Idex). Stainless steel microtube reactors (1.0 mm ID, length R1 250 cm and R2 200 cm) and stainless-steel T-connectors (M1 0.5 mm and M2 1.0 mm through hole) were employed. Flow microreactor systems were immersed in a cooling bath (0 °C). Solutions of the reaction components were pumped using syringe pumps Harvard PHD 2000, equipped with gastight syringes purchased from SGE.

2. Electrophiles collection

The following compounds are available from Sigma-Aldrich, TCI Europe, Fluorochem and Alfa Aesar except for **12h**, **12i**, **12j**, **12m**, **12n**, **12p**, **12s**, **12t**, **12u** and **16** which have been prepared.

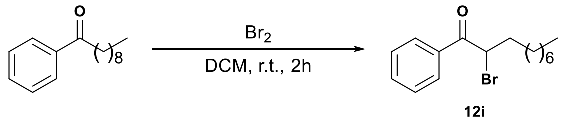


2.1 Procedure for the preparation of 2,4-dibromo-1-phenylbutan-1-one 12h



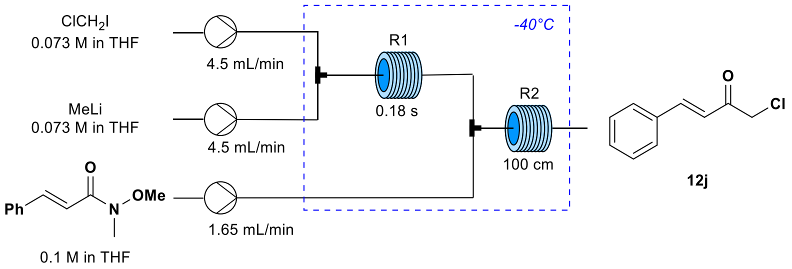
To a solution of cyclopropyl(phenyl)methanone (585 mg, 4 mmol) in diethyl ether (4 mL) at 0°C, Br_2 (230 µL, 4.5 mmol) was added dropwise. The reaction was allowed to warm. After stirring for 2 hours, the crude was poured into a solution of $Na_2S_2O_5$ (1M, 5 mL). The mixture was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained as colourless oil (923 mg, 75%) and used without further purifications. The data are consistent with literature.[2]

2.2 Procedure for the preparation of 2-bromo-1-phenyldecan-1-one 12i



To a solution of 1-phenyldecan-1-one (930 mg, 4 mmol) in DCM (7 mL), Br_2 (205 µL, 4 mmol) was added dropwise. After stirring for 2 hours at room temperature, the crude was poured in a solution of $Na_2S_2O_5$ (1M, 7 mL). The mixture was extracted with DCM (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography on silica gel afforded the desired product (859 mg, 69%) as pale yellow oil. R_f = 0.4 (Hexane/EtOAc 9:1). The data are consistent with literature.[3]

2.3 Flow procedure for the preparation of (E)-1-Chloro-4-phenylbut-3-en-2-one 12j

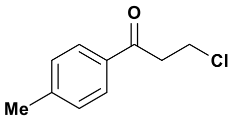


Compound **12j** was synthetized following a reported flow procedure,[4] starting from chloroiodomethane, MeLi and *N*-methoxy-*N*-methylcinnamamide. Compound **12j** was obtained as yellow oil (70 %). The data are consistent with literature.[4]

2.4 General procedure for the preparation of ketones 12m, 12n, 12p, 12s, 12t, 12u (Friedel-Craft acylation)

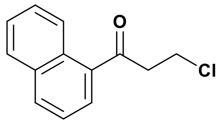
To a stirring suspension of $AlCl_3$ (6.6 mmol, 1.1 equivalent) in DCM (20 mL), 3-chloropropionyl chloride or 4-chlorobutyryl chloride (6.6 mmol, 1.1 equivalent) was added dropwise at 0°C. After 10 minutes, a solution of aromatic substrate (6 mmol, 1 equivalent) in DCM (15 mL) was added to the suspension. The crude was warmed at room temperature and stirred for 2-6 hours. The reaction was monitored by TLC. After the completion of the reaction, the crude was diluted with ice cold water (20 mL). The organic phase was washed with HCl 1M (15 mL), $NaHCO_3$ sat (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Colum chromatography on silica gel afforded the desired product.

3-chloro-1-(p-tolyl)propan-1-one 12m



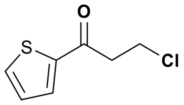
Starting from 3-chloropropionyl chloride and toluene, **12m** was obtained as pale yellow oil (668 mg, 61 %) after column chromatography on silica gel (hexane/EtOAc 9:1, R_f 0.4). The data are consistent with literature.[5]

3-chloro-1-(naphthalen-1-yl)propan-1-one 12n



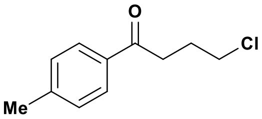
Starting from 3-chloropropionyl chloride and naphthalene, **12n** was obtained as yellow oil (722 mg, 55 %) after column chromatography on silica gel (hexane/EtOAc 8:2, R_f 0.5). The data are consistent with literature.[6]

3-chloro-1-(5-iodothiophen-2-yl)propan-1-one 12p



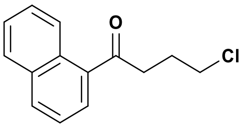
Starting from 3-chloropropionyl chloride and thiophene, **12p** was obtained as waxy yellow solid (1.28 g, 71 %) after column chromatography on silica gel (hexane/EtOAc 8:2, R_f 0.5). The data are consistent with literature.[7]

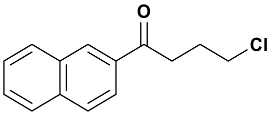
4-chloro-1-(p-tolyl)butan-1-one 12s



Starting from 4-chlorobutyryl chloride and toluene, **12s** was obtained as white solid (696 mg, 59 %) after column chromatography on silica gel (hexane/EtOAc 9:1, R_f 0.5). The data are consistent with literature.[8]

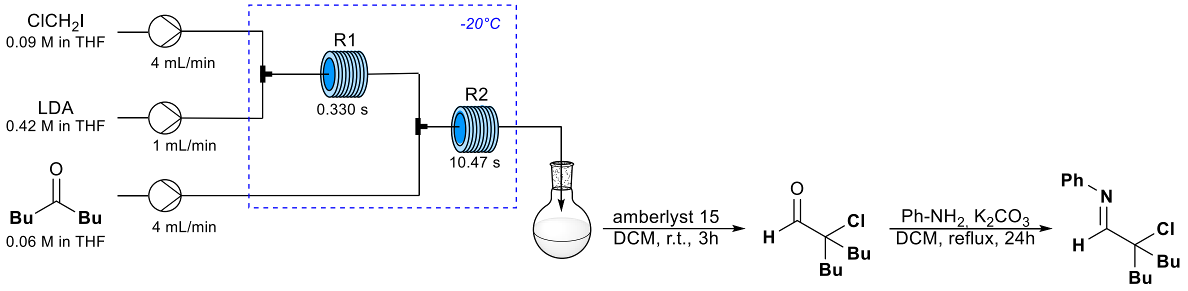
4-chloro-1-(naphthalen-1-yl)butan-1-one 12t and **4-chloro-1-(naphthalen-2-yl)butan-1-one 12u**





Starting from 4-chlorobutyryl chloride and naphtalene, mixture of **12t** and **12u** was obtained. After column chromatography on silica gel (hexane/EtOAc 9:1) **12t** (R_f 0.55, 810 mg, 58 %) and **12u** (R_f 0.45, 475 mg, 34 %) were obtained as colorless oils. The data are consistent with literature.[9]

2.5 Procedure for the preparation of 2-butyl-2-chloro-N-phenylhexan-1-imine 16

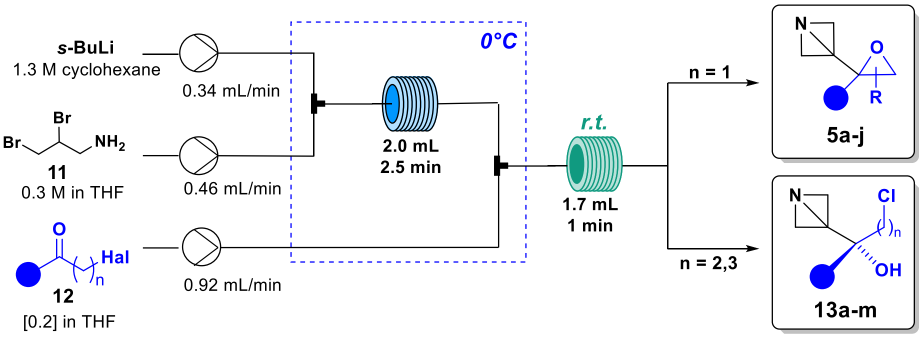


16

Imine **16** was prepared with a flow-batch approach. 2-Butyl-2-chlorohexanal was prepared following a reported flow procedure,[10] starting from chloroiodomethane, LDA and nonan-5-one, and obtained as yellow oil (91 %). The data are consistent with literature.[10] The crude was used without further purification. To a solution of the aldehyde (763 mg, 4 mmol) in DCM (10 mL), aniline (0.364 mL, 4 mmol) and K_2CO_3 (663 mg, 4.8 mmol) were added, and the mixture was refluxed for 24 hours. The crude was diluted with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained as a colorless oil (776 mg, 73 %) and used without further purification.

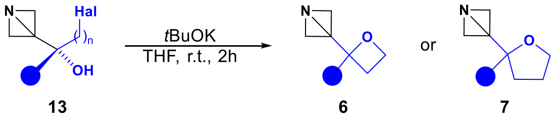
3. General procedures for the preparation of C3-functionalized ABBs and azetidines

3.1 General procedure 1 (GP1) for the preparation of 3-(oxiran-2-yl)-1-azabicyclo[1.1.0]butanes 5 and 1-(1-azabicyclo[1.1.0]butan-3-yl)-chloroalcohol 13



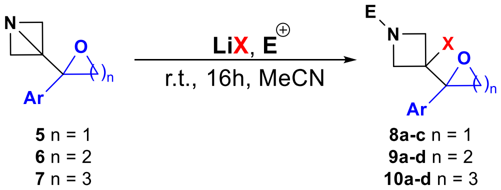
3-(oxiran-2-yl)-1-azabicyclo[1.1.0]butanes **5a-j** and 1-(1-azabicyclo[1.1.0]butan-3-yl)-chloroalcohol **13a-m** were prepared following the reported flow procedure,[11] starting from sec-BuLi, 2,3-dibromopropan-1-amine and the corresponding haloketone. After steady state was reached, the crude was collected for 3 minutes while being quenched with water. The desired product was obtained washing the crude with ethyl ether or after column chromatography on silica gel.

3.2 General procedure 2 (GP2) for the preparation of 3-(oxetan-2-yl)-1-azabicyclo[1.1.0]butanes 6 and 3-(tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butanes 7



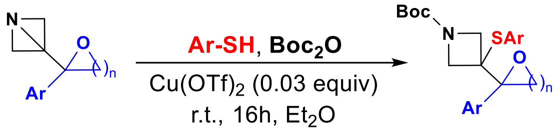
To a solution of alcohol **13** (0.2 mmol) in THF (2 mL), potassium *tert*-butoxide (0.6 mmol, 67 mg) was added. After stirring for 2 hours, the reaction crude was diluted with water (1 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

3.3 General procedure 3 (GP3) for the C3 halogenation of ABBs



To a solution of ABB **5-7** (0.25 mmol) in acetonitrile (2.5 mL), lithium salt (0.75 mmol, unless otherwise specified) and electrophile (Boc_2O or tosyl chloride, 0.5 mmol) were added. After stirring for 16 hours, the reaction crude was diluted with water (2 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography on silica gel afforded the desired product.

3.4 General procedure 4 (GP4) for the C3 thiolation of ABBs



5 n = 1
6 n = 2
7 n = 3

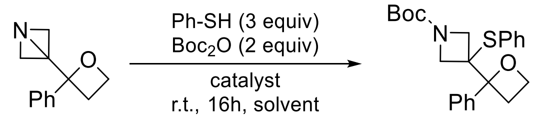
8d-e n = 1
9e-f n = 2
10e-f n = 3

To a solution of ABB **5-7** (0.25 mmol) in ethyl ether (2.5 mL), aromatic thiol (0.75 mmol), Boc$_2$O (0.5 mmol) and Cu(OTf)$_2$ (0.0075 mmol) were added. After stirring for 16 hours, the reaction crude was diluted with water (2 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Column chromatography on silica gel afforded the desired product.

4. Optimization of C3 thiolation

Table S1

Optimization of the C3 thiolation of ABBs involving **6a** and thiophenol.



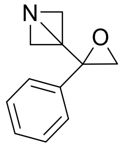
6a **9e**

Entry	Catalyst	Solvent	Variation of conditions	**9e** NMR yield[a]
1	$FeCl_3$ (20%)	DCM	Ph-SH (1 equiv), reflux	0 %
2[b]	$FeCl_3$ (20%)	DCM	Ph-SH (1 equiv), reflux	7 %
3[b]	Na_2CO_3 (1 equiv)	MeCN	Ph-SH (1 equiv), reflux	S.M.
4[b]	Cs_2CO_3 (2 equiv)	MeCN	Ph-SH (1 equiv), reflux	S.M.
5[b]	BF_3 (2 equiv)	MeCN	Ph-SH (1 equiv), reflux	0 %
6[b]	/	DCM	Ph-SH (1 equiv), reflux	S.M.
7[b]	$Cu(OTf)_2$ (0.03 equiv)	Et_2O	Ph-SH (1 equiv)	32 %
8	$Cu(OTf)_2$ (0.03 equiv)	Et_2O	/	84 %

[a] Dibromomethane was used as internal standard. [b] Two-steps reaction: a solution of **6a**, Ph-SH and catalyst was stirred for 16 h; then Boc_2O was added, and the solution was stirred for 1h.

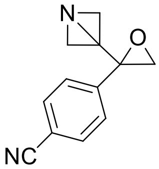
5. Characterization of compounds

3-(2-phenyloxiran-2-yl)-1-azabicyclo[1.1.0]butane 5a



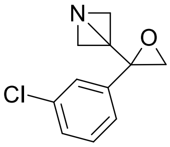
Following the GP1 with **12a** as electrophile, **5a** was obtained as a pale yellow oil (47 mg, 65 %). The data are consistent with literature.[11]

4-(2-(1-azabicyclo[1.1.0]butan-3-yl)oxiran-2-yl)benzonitrile 5b



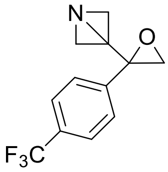
Following the GP1 with **12b** as electrophile, **5b** was obtained as a pale yellow oil (41 mg, 50%) after column chromatography (R_f = 0.3, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2917, 2849, 2230, 1610, 1505, 1403, 1221, 1122, 1047, 916, 836, 733. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H, Ar-H), 3.19 (d, *J* = 5.7 Hz, 1H, OCH_2), 2.88 (d, *J* = 5.7 Hz, 1H, OCH_2), 2.40 (s, 2H, NCH_2), 1.46 (s, 1H, NCH_2), 1.36 (s, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8 (Ar-C_q), 132.4 (2 x Ar-C), 127.3 (2 x Ar-C), 118.6 (CN), 112.4 (Ar-C_q), 57.0 (Oxiranyl-C_q), 55.2 (OCH_2), 54.15 (NCH_2), 54.04 (NCH_2), 30.8 (NC_q). HRMS *m/z* calculated for $C_{12}H_{10}N_2NaO$ $[M+Na]^+$ 221.0691; found 221.0686.

3-(2-(3-chlorophenyl)oxiran-2-yl)-1-azabicyclo[1.1.0]butane 5c



Following the GP1 with **12c** as electrophile, **5c** was obtained as a pale yellow oil (51 mg, 60 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3061, 2953, 1694, 1599, 1573, 1476, 1428, 1336, 1220, 1079, 929, 882, 787, 691. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.49 (m, 1H, Ar-H), 7.41 – 7.38 (m, 1H, Ar-H), 7.31 – 7.28 (m, 2H, Ar-H), 3.13 (d, *J* = 5.8 Hz, 1H, OCH_2), 2.89 (d, *J* = 5.8 Hz, 1H, OCH_2), 2.43 – 2.35 (m, 2H, NCH_2), 1.44 (d, *J* = 2.2 Hz, 1H, NCH_2), 1.34 (d, *J* = 2.2 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (Ar-C_q), 134.6 (Ar-C_q), 129.9 (Ar-C), 128.6 (Ar-C), 126.8 (Ar-C), 124.8 (Ar-C), 56.9 (Oxiranyl-C_q), 54.9 (OCH_2), 54.1 (NCH_2), 54.0 (NCH_2), 31.1 (NC_q). HRMS *m/z* calculated for $C_{11}H_{10}ClNNaO$ $[M+Na]^+$ 230.0349; found 230.0345.

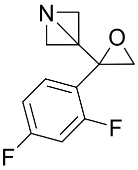
3-(2-(4-(trifluoromethyl)phenyl)oxiran-2-yl)-1-azabicyclo[1.1.0]butane 5d



Following the GP1 with **12d** as electrophile, **5d** was obtained as a pale yellow oil (70 mg, 70%) after column chromatography (R_f = 0.3, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3430, 2917, 1620, 1407, 1325, 1223, 1166, 1122, 1068, 1016, 924, 842, 730. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 4H, Ar-H), 3.18 (d, *J* = 5.8 Hz, 1H, OCH_2), 2.89 (d, *J* = 5.8 Hz, 1H, OCH_2), 2.45 – 2.36 (m, 2H, NCH_2), 1.44 (d, *J* = 1.7 Hz, 1H, NCH_2), 1.35 (d, *J* = 1.7

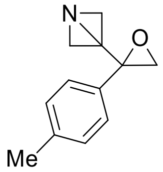
Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5 (Ar-C_q), 130.6 (q, $^{2}J_{C-F}$ = 32.5 Hz, Ar-C_q), 127.0 (2 x Ar-C), 125.5 (q, $^{3}J_{C-F}$ = 3.8 Hz, 2 x Ar-C), 124.1 (q, J = 272.1 Hz, CF_3), 57.1 (Oxiranyl-C_q), 55.0 (OCH_2), 54.1 (NCH_2), 53.9 (NCH_2), 31.1 (NC_q). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.68 (3F). HRMS *m/z* calculated for $C_{12}H_{10}F_3NNaO$ $[M+Na]^+$ 264.0612; found 264.0622.

3-(2-(2,4-difluorophenyl)oxiran-2-yl)-1-azabicyclo[1.1.0]butane 5e



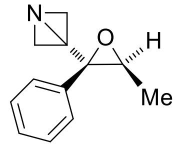
Following the GP1 with **12e** as electrophile, **5e** was obtained as a pale yellow oil (55 mg, 64 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3062, 2924, 1615, 1505, 1427, 1349, 1271, 1141, 1101, 966, 930, 851, 819, 615. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (td, J = 8.3, 6.5 Hz, 1H, Ar-H), 6.88 (td, J = 8.4, 2.4 Hz, 1H, Ar-H), 6.85 – 6.79 (m, 1H, Ar-H), 3.18 (d, J = 5.6 Hz, 1H, OCH_2), 2.99 (d, J = 5.6 Hz, 1H, OCH_2), 2.41 (dd, J = 6.4, 2.6 Hz, 1H, NCH_2), 2.27 (dd, J = 6.4, 2.5 Hz, 1H, NCH_2), 1.30 (t, J = 3.1 Hz, 2H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (dd, $^{1}J_{C-F}$ = 250.1, $^{3}J_{C-F}$ = 11.6 Hz, Ar-CF), 160.8 (dd, $^{1}J_{C-F}$ = 250.3, $^{3}J_{C-F}$ = 12.1 Hz, Ar-CF), 130.4 (dd, $^{3}J_{C-F}$ = 9.8, 5.4 Hz, Ar-C), 120.4 (dd, $^{2}J_{C-F}$ = 15.2, $^{4}J_{C-F}$ = 3.8 Hz, Ar-C_q), 111.66 (dd, $^{2}J_{C-F}$ = 21.4, $^{4}J_{C-F}$ = 3.7 Hz), 104.0 (t, $^{2}J_{C-F}$ = 25.3 Hz, Ar-C), 54.7 (Oxiranyl-C_q), 54.0 (NCH_2), 53.6 (NCH_2), 53.4 (OCH_2), 32.1 (NC_q). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.96 – -109.23 (m, 1F), -111.51 (q, J = 8.2 Hz, 1F). HRMS *m/z* calculated for $C_{11}H_9F_2NNaO$ $[M+Na]^+$ 232.0550; found 232.0545.

3-(2-(p-tolyl)oxiran-2-yl)-1-azabicyclo[1.1.0]butane 5f



Following the GP1 with **12f** as electrophile, **5f** was obtained as a pale yellow oil (55 mg, 71 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3233, 2920, 1666, 1513, 1417, 1255, 1218, 1182, 1097, 1073, 912, 820, 720. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H, Ar-H), 7.17 (d, J = 7.9 Hz, 2H, Ar-H), 3.12 (d, J = 5.8 Hz, 1H, OCH_2), 2.92 (d, J = 5.8 Hz, 1H, OCH_2), 2.40 – 2.37 (m, 2H, NCH_2), 2.35 (s, 3H, CH_3), 1.41 – 1.39 (m, 1H, NCH_2), 1.31 (d, J = 2.5 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2 (Ar-C_q), 134.4 (Ar-C_q), 129.2 (2 x Ar-C), 126.5 (2 x Ar-C), 57.2 (Oxiranyl-C_q), 54.7 (OCH_2), 53.94 (NCH_2), 53.93 (NCH_2), 31.6 (NC_q), 21.3 (CH_3). HRMS *m/z* calculated for $C_{12}H_{13}NNaO$ $[M+Na]^+$ 210.0895; found 210.0892.

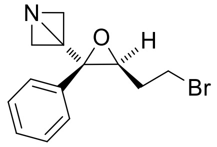
3-((2S*,3S*)-3-methyl-2-phenyloxiran-2-yl)-1-azabicyclo[1.1.0]butane 5g



Following the GP1 with **12g** as electrophile, **5g** was obtained as a pale yellow oil (dr > 95:5, 50 mg, 64 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3433, 1638, 1447, 1275, 1261, 1044, 934, 815, 764, 750, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.32 – 7.28 (m, 1H), 3.37 (q, J = 5.4 Hz, 1H, OCH), 2.31 (s, 2H, NCH_2), 1.27 (s, 1H, NCH_2), 1.23 (s, 1H, NCH_2) 1.04 (d, J = 5.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1 (Ar-C_q), 128.3 (2 x Ar-C), 128.1 (Ar-C), 127.6 (2 x Ar-C), 62.4

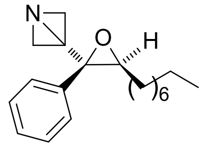
(Oxiranyl-C$_q$), 59.5 (O*C*HCH$_3$), 53.7 (NCH$_2$), 53.1 (NCH$_2$), 32.9 (NC$_q$), 14.3 (OCH*C*H$_3$). HRMS *m/z* calculated for $C_{12}H_{13}NNaO$ [M+Na]$^+$ 210.0895; found 210.0906.

3-((2S*,3S*)-3-(2-bromoethyl)-2-phenyloxiran-2-yl)-1-azabicyclo[1.1.0]butane 5h



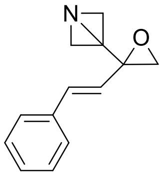
Following the GP1 with **12h** as electrophile, **5h** was obtained as a pale yellow oil (dr > 95:5, 53 mg, 46 %) after column chromatography (R$_f$ = 0.3, hexane/EtOAc 8:2). FT-IR ν$_{max}$/cm^{-1} 3056, 2918, 2849, 1494, 1448, 1266, 1219, 1127, 1076, 1046, 939, 909, 735, 701. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.39 – 7.30 (m, 3H, Ar-H), 3.47 – 3.43 (m, 1H, OCH), 3.42 – 3.33 (m, 2H, CH$_2$Br), 2.40 – 2.32 (m, 2H, NCH$_2$), 1.91 – 1.83 (m, 1H, C*H$_2$*CH$_2$Br), 1.76 – 1.68 (m, 1H, C*H$_2$*CH$_2$Br), 1.33 (d, *J* = 1.5 Hz, 1H, NCH$_2$), 1.27 (d, *J* = 1.5 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 134.7 (Ar-C$_q$), 128.44 (2 x Ar-C), 128.37 (Ar-C), 127.4 (2 x Ar-C), 62.5 (Oxiranyl-C$_q$), 62.1 (OCH), 53.9 (NCH$_2$), 53.4 (NCH$_2$), 32.7 (NC$_q$), 31.6 (*C*H$_2$CH$_2$Br), 29.2 (CH$_2$Br). HRMS *m/z* calculated for $C_{26}H_cBr_2N_2NaO_2$ [2M+Na]$^+$ 583.0415 ; found 583.0407.

3-((2S*,3S*)-3-octyl-2-phenyloxiran-2-yl)-1-azabicyclo[1.1.0]butane 5i



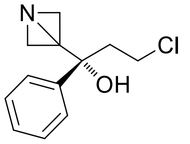
Following the GP1 with **12i** as electrophile, **5i** was obtained as a pale yellow oil (dr > 95:5, 78 mg, 66 %) after column chromatography (R$_f$ = 0.3, hexane/EtOAc 8:2). FT-IR ν$_{max}$/cm^{-1} 2925, 2855, 1604, 1495, 1449, 1400, 1217, 1126, 1075, 929, 907, 767, 734, 700. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44 – 7.27 (m, 5H, Ar-H), 3.23 (t, *J* = 6.0 Hz, 1H, OCH), 2.34 – 2.31 (m, 2H, NCH$_2$), 1.45 – 1.15 (m, 16H, 14 x (CH$_2$)$_7$ and 2 x NCH$_2$), 0.85 (t, *J* = 6.8 Hz, 3H, CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 135.4 (Ar-C$_q$), 128.2 (2 x Ar-C), 128.0 (Ar-C), 127.4 (2 x Ar-C), 63.9 (OCH), 62.2 (Oxiranyl-C$_q$), 53.7 (NCH$_2$), 53.3 (NCH$_2$), 32.9 (NC$_q$), 31.9 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 28.3 (CH$_2$), 26.1 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$). HRMS *m/z* calculated for $C_{19}H_{28}NO$ [M+H]$^+$ 286.2171; found 286.2177.

(E)-3-(2-styryloxiran-2-yl)-1-azabicyclo[1.1.0]butane 5j



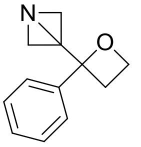
Following the GP1 with **12j** as electrophile, **5j** was obtained as a pale yellow oil (41 mg, 50 %) after column chromatography (R$_f$ = 0.2, hexane/EtOAc 7:3). FT-IR ν$_{max}$/cm^{-1} 2919, 2111, 1645, 1494, 1449, 1261, 1157, 1074, 968, 749, 695. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 – 7.38 (m, 2H, Ar-H), 7.35 – 7.30 (m, 2H, Ar-H), 7.29 – 7.25 (m, 1H, Ar-H), 6.94 (d, *J* = 16.1 Hz, 1H, CH=CH), 6.24 (d, *J* = 16.1 Hz, 1H, CH=CH), 3.07 (d, *J* = 5.8 Hz, 1H, OCH$_2$), 2.91 (d, *J* = 5.8 Hz, 1H, OCH$_2$), 2.48 (dd, *J* = 6.4, 2.7 Hz, 1H, NCH$_2$), 2.42 (dd, *J* = 6.4, 2.6 Hz, 1H, NCH$_2$), 1.42 (dd, *J* = 2.6, 0.6 Hz, 1H, NCH$_2$), 1.37 (d, *J* = 2.7 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.1 (Ar-C$_q$), 133.7 (CH=CH), 128.8 (2 x Ar-C), 128.4 (Ar-C), 126.7 (2 x Ar-C), 125.8 (CH=CH), 56.4 (Oxiranyl-C$_q$), 54.8 (OCH$_2$), 54.2 (NCH$_2$), 54.0 (NCH$_2$), 34.0 (NC$_q$). HRMS *m/z* calculated for $C_{13}H_{13}NNaO$ [M+Na]$^+$222.0895; found 222.0894.

1-(1-azabicyclo[1.1.0]butan-3-yl)-3-chloro-1-phenylpropan-1-ol 13a



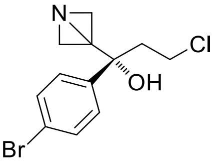
Following the GP1 with **12k** as electrophile, **13a** was obtained as a waxy yellow solid (74 mg, 80%) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 3177, 2930, 1634, 1446, 1255, 1446, 1255, 1213, 1066, 912, 829, 747, 703, 670. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48 – 7.46 (m, 2H, Ar-H), 7.38 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.31 – 7.28 (m, 1H, Ar-H), 3.63 (td, *J* = 11.0, 5.2 Hz, 1H, CH$_2$C*H*$_2$Cl), 3.23 (td, *J* = 11.0, 5.0 Hz, 1H, CH$_2$C*H*$_2$Cl), 2.61 (dd, *J* = 6.6, 2.5 Hz, 1H, NCH$_2$), 2.49 (ddd, *J* = 13.6, 11.3, 5.0 Hz, 1H, C*H*$_2$CH$_2$Cl), 2.33 (ddd, *J* = 13.6, 11.3, 5.2 Hz, 1H, C*H*$_2$CH$_2$Cl), 2.28 (dd, *J* = 6.6, 2.6 Hz, 1H, NCH$_2$), 1.42 (d, *J* = 2.3 Hz, 1H, NCH$_2$), 1.27 (d, *J* = 2.5 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.8 (Ar-C$_q$), 128.6 (2 x Ar-C), 127.7 (Ar-C$_q$), 125.6 (2 x Ar-C), 72.8 (COH), 54.4 (NCH$_2$), 53.9 (NCH$_2$), 44.0 (*C*H$_2$CH$_2$Cl), 39.7 (CH$_2$*C*H$_2$Cl), 37.9 (NC$_q$). HRMS *m/z* calculated for $C_{12}H_{15}ClNO$ [M+H]$^+$ 224.0842; found 224.1436.

3-(2-phenyloxetan-2-yl)-1-azabicyclo[1.1.0]butane 6a



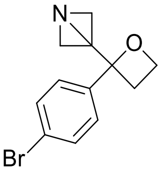
Following the GP2 with **13a**, **6a** was obtained as a pale yellow oil (29 mg, 78 %) without further purification. FT-IR ν_{max}/cm^{-1} 3058, 2948, 2888, 1492, 1448, 1259, 1134, 1075, 1000, 967, 880, 816, 765, 699. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 – 7.41 (m, 2H, Ar-H), 7.40 – 7.35 (m, 2H, Ar-H), 7.30 – 7.26 (m, 1H, Ar-H), 4.63 – 4.57 (m, 1H, OCH$_2$), 4.56 – 4.50 (m, 1H, OCH$_2$), 2.93 – 2.85 (m, 1H, OCH$_2$C*H$_2$*), 2.80 – 2.72 (m, 1H, OCH$_2$C*H$_2$*), 2.54 - 2.50 (m, 1H, NCH$_2$), 2.42 – 2.38 (m, 1H, NCH$_2$), 1.31 (d, *J* = 1.7 Hz, 1H, NCH$_2$), 1.25 (t, *J* = 2.3 Hz, 1H, NCH$_2$).^{13}C NMR (126 MHz, CDCl$_3$) δ 144.1 (Ar-C$_q$), 128.3 (2 x Ar-C), 127.5 (Ar-C), 124.6 (2 x Ar-C), 84.5 (OC$_q$), 65.9 (O*C*H$_2$CH$_2$), 53.1 (NCH$_2$), 52.2 (NCH$_2$), 35.3 (NC$_q$), 31.6 (OCH$_2$*C*H$_2$). HRMS *m/z* calculated for $C_{12}H_{14}NO$ [M+H]$^+$ 188.1075; found 188.1067.

1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(4-bromophenyl)-3-chloropropan-1-ol 13b



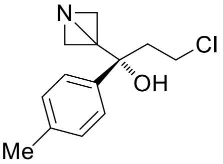
Following the GP1 with **12l** as electrophile, **13b** was obtained as a waxy yellow solid (87 mg, 70 %) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 3400, 1642, 1487, 1448, 1397, 1255, 1132, 1073, 826, 702, 684. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52 – 7.48 (m, 2H, Ar-H), 7.38 – 7.34 (m, 2H, Ar-H), 3.62 (td, *J* = 11.0, 5.2 Hz, 1H, CH$_2$C*H*$_2$Cl), 3.24 (s, OH), 3.20 (td, *J* = 10.9, 5.0 Hz, 1H, CH$_2$C*H*$_2$Cl), 2.61 (dd, *J* = 6.7, 2.3 Hz, 1H, NCH$_2$), 2.47 – 2.39 (m, 1H, C*H*$_2$CH$_2$Cl), 2.33 - 2.28 (m, 2H, 1H C*H*$_2$CH$_2$Cl and 1H NCH$_2$), 1.43 (d, *J* = 2.4 Hz, 1H, NCH$_2$), 1.26 (d, *J* = 2.5 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.1 (Ar-C$_q$), 131.7 (2 x Ar-C), 127.5 (2 x Ar-C), 121.8 (Ar-C$_q$), 72.6 (COH), 54.02 (NCH$_2$), 53.91 (NCH$_2$), 43.8 (*C*H$_2$CH$_2$Cl), 39.4 (CH$_2$*C*H$_2$Cl), 37.8 (NC$_q$). HRMS *m/z* calculated for $C_{12}H_{13}BrCl_2NO$ [M+Cl]$^-$ 337.9543; found 337.9533.

3-(2-(4-bromophenyl)oxetan-2-yl)-1-azabicyclo[1.1.0]butane 6b



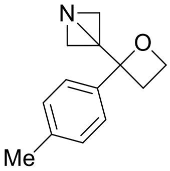
Following the GP2 with **13b**, **6b** was obtained as a pale yellow oil (34 mg, 65 %) without further purification. FT-IR ν_{max}/cm^{-1} 2950, 2888, 1486, 1448, 1395, 1134, 1072, 1009, 967, 881, 820, 700. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.55 – 7.49 (m, 2H, Ar-H), 7.35 – 7.29 (m, 2H, Ar-H), 4.67 – 4.49 (m, 2H, OC*H*$_2$CH$_2$), 2.91 (ddd, *J* = 10.9, 8.7, 6.6 Hz, 1H, OCH$_2$C*H*$_2$), 2.73 (ddd, *J* = 10.9, 8.8, 6.8 Hz, 1H, OCH$_2$C*H*$_2$), 2.52 (dd, *J* = 6.6, 2.9 Hz, 1H, NCH$_2$), 2.39 (dd, *J* = 6.6, 2.6 Hz, 1H, NCH$_2$), 1.34 (d, *J* = 2.1 Hz, 1H, NCH$_2$), 1.28 (d, *J* = 2.7 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.2 (Ar-C$_q$), 131.6 (2 x Ar-C), 126.6 (2 x Ar-C), 121.7 (Ar-C$_q$), 84.4 (OC$_q$), 66.0 (O*C*H$_2$CH$_2$), 53.2 (NCH$_2$), 52.4 (NCH$_2$), 35.1 (NC$_q$), 31.7 (OCH$_2$*C*H$_2$). HRMS *m/z* calculated for $C_{12}H_{12}BrNNaO$ [M+Na]$^+$ 288.0000; found 287.9994.

1-(1-azabicyclo[1.1.0]butan-3-yl)-3-chloro-1-(p-tolyl)propan-1-ol 13c



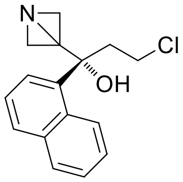
Following the GP1 with **12m** as electrophile, **13c** was obtained as a waxy yellow solid (79 mg, 80 %) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 3270, 2951, 2920, 1674, 1606, 1513, 1450, 1208, 1182, 1098, 914, 821, 721. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.18 (d, *J* = 8.2 Hz, 2H, Ar-H), 3.64 (td, *J* = 11.1, 5.1 Hz, 1H, CH$_2$C*H$_2$*Cl), 3.23 (td, *J* = 11.1, 4.9 Hz, 1H, CH$_2$C*H$_2$*Cl), 2.62 (dd, *J* = 6.6, 2.4 Hz, 1H, NCH$_2$), 2.49 – 2.41 (m, 1H, C*H$_2$*CH$_2$Cl), 2.37 – 2.26 (m, 1H NCH$_2$ and 1H C*H$_2$*CH$_2$Cl), 2.35 (s, 3H, CH$_3$), 1.41 (d, *J* = 2.5 Hz, 1H, NCH$_2$), 1.24 (d, *J* = 2.6 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 138.9 (Ar-C$_q$), 137.3 (Ar-C$_q$), 129.2 (2 x Ar-C), 125.5 (2 x Ar-C), 72.6 (COH), 53.8 (NCH$_2$), 53.6 (NCH$_2$), 43.8 (*C*H$_2$CH$_2$Cl), 39.8 (CH$_2$*C*H$_2$Cl), 38.2 (NCq), 21.1 (CH$_3$). HRMS *m/z* calculated for $C_{13}H_{16}ClNNaO$ [M+Na]$^+$ 260.0818; found 260.0818.

3-(2-(p-tolyl)oxetan-2-yl)-1-azabicyclo[1.1.0]butane 6c



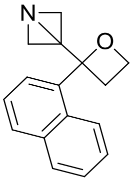
Following the GP2 with **13c**, **6c** was obtained as a pale yellow oil (23 mg, 56 %) without further purification. FT-IR ν_{max}/cm^{-1} 3432, 2949, 29191673, 1513, 1448, 1225, 1181, 1134, 1019, 968, 817, 726. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.32 (m, 2H, Ar-H), 7.21 (d, *J* = 7.9 Hz, 2H, Ar-H), 4.61 (ddd, *J* = 8.7, 6.8, 5.7 Hz, 1H, OC*H$_2$*CH$_2$), 4.57 – 4.52 (m, 1H, OC*H$_2$*CH$_2$), 2.88 (ddd, *J* = 10.8, 8.7, 6.5 Hz, 1H, OCH$_2$C*H$_2$*), 2.76 (ddd, *J* = 10.8, 8.8, 6.8 Hz, 1H, OCH$_2$C*H$_2$*), 2.54 (dd, *J* = 6.6, 3.0 Hz, 1H, NCH$_2$), 2.41 (dd, *J* = 6.6, 2.6 Hz, 1H, NCH$_2$), 2.36 (s, 3H, CH$_3$), 1.33 (d, *J* = 2.6 Hz, 1H, NCH$_2$), 1.26 (d, *J* = 3.0 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.3 (Ar-C$_q$), 137.3 (Ar-C$_q$), 129.1 (2 x Ar-C), 124.6 (2 x Ar-C), 84.6 (OC$_q$), 66.0 (OCH$_2$), 53.2 (NCH$_2$), 52.3 (NCH$_2$), 35.5 (NC$_q$), 31.7 (OCH$_2$*C*H$_2$), 21.3 (CH$_3$). HRMS *m/z* calculated for $C_{13}H_{15}NNaO$ [M+Na]$^+$ 224.1051; found 224.1049.

1-(1-azabicyclo[1.1.0]butan-3-yl)-3-chloro-1-(naphthalen-1-yl)propan-1-ol 13d



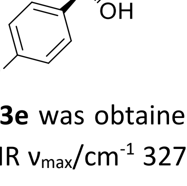
Following the GP1 with **12n** as electrophile, **13d** was obtained as a waxy yellow solid (96 mg, 85 %) after washing the crude with ethyl ether (4 mL). FT-IR ν$_{max}$/cm^{-1} 3400, 2918, 1723, 1674, 1509, 1325, 1278, 1133, 909, 803, 779, 733. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.41 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.92 – 7.87 (m, 2H, Ar-H), 7.82 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.54 – 7.44 (m, 3H, Ar-H), 3.61 (ddd, *J* = 11.2, 10.4, 5.0 Hz, 1H, CH$_2$C*H*$_2$Cl), 3.06 – 2.94 (m, 1H CH$_2$C*H*$_2$Cl and 1H C*H*$_2$CH$_2$Cl), 2.92 (dd, *J* = 6.5, 2.4 Hz, 1H, NCH$_2$), 2.74 (bs, 1H, OH), 2.50 (ddd, *J* = 12.6, 11.0, 5.0 Hz, 1H, C*H*$_2$CH$_2$Cl), 2.10 (dd, *J* = 6.5, 2.4 Hz, 1H, NCH$_2$), 1.70 (d, *J* = 2.5 Hz, 1H, NCH$_2$), 1.43 (d, *J* = 2.4 Hz, 1H, NCH$_2$). ^{13}C NMR δ (126 MHz, CDCl$_3$) δ 137.4 (Ar-C$_q$), 134.6 (Ar-C$_q$), 130.0 (Ar-C$_q$), 129.6 (Ar-C), 129.3 (Ar-C), 125.8 (Ar-C), 125.5 (Ar-C), 125.4 (Ar-C), 125.3 (Ar-C), 124.7 (Ar-C), 72.9 (COH), 57.9 (NCH$_2$), 55.5 (NCH$_2$), 43.9 (*C*H$_2$CH$_2$Cl), 40.1 (CH$_2$*C*H$_2$Cl), 38.5 (NC$_q$). HRMS *m/z* calculated for $C_{16}H_{16}ClNNaO$ [M+Na]$^+$ 296.0818; found 296.0830.

3-(2-(naphthalen-1-yl)oxetan-2-yl)-1-azabicyclo[1.1.0]butane 6d



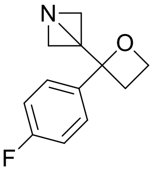
Following the GP2 with **13d**, **6d** was obtained as a pale yellow oil (43 mg, 90 %) without further purification. FT-IR ν$_{max}$/cm^{-1} 2921, 2103, 1644, 1463, 1393, 1248, 1133, 965, 802, 778, 735. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 – 7.85 (m, 1H, Ar-H), 7.81 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.72 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.55 – 7.45 (m, 3H, Ar-H), 4.72 (dd, *J* = 14.1, 7.0 Hz, 1H, OC*H*$_2$CH$_2$), 4.57 (dd, *J* = 14.8, 6.3 Hz, 1H, OC*H*$_2$CH$_2$), 3.28 (dd, *J* = 17.1, 8.8 Hz, 1H, OCH$_2$C*H*$_2$), 3.15 (dd, *J* = 17.7, 9.0 Hz, 1H, OCH$_2$C*H*$_2$), 2.63 (d, *J* = 6.4 Hz, 1H, NCH$_2$), 2.21 (d, *J* = 6.2 Hz, 1H, NCH$_2$), 1.43 (s, 1H, NCH$_2$), 1.36 (s, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.2 (Ar-C$_q$), 134.1 (Ar-C$_q$), 129.3 (Ar-C$_q$), 129.1 (Ar-C), 128.5 (Ar-C), 125.8 (Ar-C), 125.6 (Ar-C), 125.4(Ar-C), 124.9 (Ar-C), 123.2 (Ar-C), 84.8 (OC$_q$), 66.7 (O*C*H$_2$CH$_2$), 54.21 (NCH$_2$), 53.39 (NCH$_2$), 35.7 (NC$_q$), 32.7 (OCH$_2$*C*H$_2$). HRMS *m/z* calculated for $C_{16}H_{15}NNaO$ [M+Na]$^+$ 260.1051; found 260.1046.

1-(1-azabicyclo[1.1.0]butan-3-yl)-3-chloro-1-(4-fluorophenyl)propan-1-ol 13e



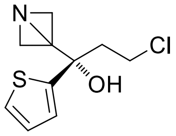
Following the GP1 with **12o** as electrophile, **13e** was obtained as a waxy yellow solid (84 mg, 84 %) after washing the crude with ethyl ether (4 mL). FT-IR ν$_{max}$/cm^{-1} 3272, 2954, 1603, 1508, 1412, 1225, 1159, 1078, 915, 838, 816, 721 ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48– 7.43 (m, 2H, Ar-H), 7.08 – 7.04 (m, 2H, Ar-H), 3.62 (td, *J* = 11.0, 5.2 Hz, 1H, ClCH$_2$), 3.22 (td, *J* = 11.0, 5.1 Hz, 1H, ClCH$_2$), 2.59 (dd, *J* = 6.6, 2.4 Hz, 1H, NCH$_2$), 2.44 (ddd, *J* = 13.6, 11.2, 5.1 Hz, 1H, ClCH$_2$C*H*$_2$), 2.34 – 2.23 (m, 1H NCH$_2$ and 1H ClCH$_2$C*H*$_2$), 1.43 (d, *J* = 2.3 Hz, 1H, NCH$_2$), 1.27 (d, *J* = 2.5 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.3 (d, $^1J_{C\text{-}F}$ = 246.5 Hz, Ar-C$_q$), 137.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C$_q$), 127.4 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 x Ar-C), 115.4 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, 2 x Ar-C), 72.6 (COH), 54.1 (NCH$_2$), 53.9 (NCH$_2$), 44.0 (ClCH$_2$*C*H$_2$), 39.5 (Cl*C*H$_2$CH$_2$), 37.8 (NC$_q$). ^{19}F NMR (282 MHz, CDCl$_3$) -114.96 – -115.15 (m, 1F). HRMS *m/z* calculated for $C_{12}H_{14}ClFNO$ [M+H]$^+$ 242.0748; found 242.0740.

3-(2-(4-fluorophenyl)oxetan-2-yl)-1-azabicyclo[1.1.0]butane 6e



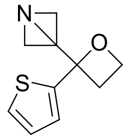
Following the GP2 with **13e**, **6e** was obtained as a pale yellow oil (32 mg, 79 %) without further purification. FT-IR ν_{max}/cm^{-1} 3391, 2954, 2891, 1602, 1508, 1411, 1226, 1157, 1134, 969, 837, 817. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H, Ar-H), 7.10 – 7.04 (m, 2H, Ar-H), 4.64 – 4.59 (m, 1H, OCH_2), 4.57 – 4.51 (m, 1H, OCH_2), 2.94 – 2.87 (m, 1H, OCH_2CH_2), 2.78 – 2.71 (m, 1H, OCH_2CH_2), 2.51 (dd, J = 6.6, 2.9 Hz, 1H, NCH_2), 2.39 (dd, J = 6.6, 2.6 Hz, 1H, NCH_2), 1.34 (d, J = 2.5 Hz, 1H, NCH_2), 1.28 (d, J = 3.2 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, $^{1}J_{C\text{-}F}$ = 246.0 Hz, Ar-C_q), 139.9 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, Ar-C_q), 126.5 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, 2 x Ar-C), 115.3 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, 2 x Ar-C), 84.4 (OC_q), 66.0 (OCH_2), 53.2 (NCH_2), 52.3 (NCH_2), 35.3 (NC_q), 31.7 (OCH_2CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.02 -115.10 (m, 1F). HRMS m/z calculated for $C_{12}H_{13}FNO$ $[M+H]^+$ 206.0981; found 206.1015.

1-(1-azabicyclo[1.1.0]butan-3-yl)-3-chloro-1-(thiophen-2-yl)propan-1-ol 13f



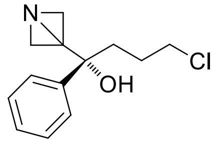
Following the GP1 with **12p** as electrophile, **13f** was obtained as a waxy yellow solid (76 mg, 80 %) after column chromatography (R_f = 0.3, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3400, 1651, 1404, 1233, 1190, 1077, 893, 848, 829, 701. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.26 (m, 1H, Ar-H), 7.03 – 6.99 (m, 2H, Ar-H), 3.71 (td, J = 10.8, 5.6 Hz, 1H, $ClCH_2$), 3.48 (td, J = 10.8, 5.2 Hz, 1H, $ClCH_2$), 2.57 – 2.50 (m, 2H, 1H $ClCH_2CH_2$ and 1H NCH_2), 2.48 – 2.41 (m, 1H, $ClCH_2CH_2$), 2.35 (dd, J = 6.6, 2.6 Hz, 1H, NCH_2), 1.38 (d, J = 2.5 Hz, 1H, NCH_2), 1.33 (d, J = 2.6 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (Ar-C_q), 127.2 (Ar-C), 125.1 (Ar-C), 124.0 (Ar-C), 72.5 (COH), 54.4 (NCH_2), 53.3 (NCH_2), 44.4 ($ClCH_2CH_2$), 39.6 ($ClCH_2CH_2$), 37.9 (NC_q).

3-(2-(thiophen-2-yl)oxetan-2-yl)-1-azabicyclo[1.1.0]butane 6f



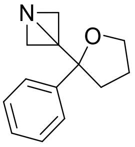
Following the GP2 with **13f**, **6f** was obtained as a pale yellow oil (32 mg, 82 %) without further purification. FT-IR ν_{max}/cm^{-1} 2917, 2849, 2099, 1644, 1435, 1241, 1132, 949, 868, 818, 702. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 5.0, 1.3 Hz, 1H, Ar-H), 7.15 (dd, J = 3.6, 1.2 Hz, 1H, Ar-H), 7.04 (dd, J = 5.1, 3.5 Hz, 1H, Ar-H), 4.67 – 4.60 (m, 1H, OCH_2), 4.59 – 4.53 (m, 1H, OCH_2), 2.90 – 2.84 (m, 2H, OCH_2CH_2), 2.70 (dd, J = 6.5, 3.0 Hz, 1H, NCH_2), 2.48 (dd, J = 6.5, 2.5 Hz, 1H, NCH_2), 1.42 (d, J = 2.4 Hz, 1H, NCH_2), 1.38 (d, J = 3.1 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4 (Ar-C_q), 127.2 (Ar-C), 125.8 (Ar-C), 124.0 (Ar-C), 82.6 (OC_q), 66.0 (OCH_2), 53.6 (NCH_2), 52.3 (NCH_2), 35.1 (NC_q), 32.7 (OCH_2CH_2). HRMS m/z calculated for $C_{10}H_{11}NNaOS$ $[M+Na]^+$ 216.0459; found 216.0454.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-phenylbutan-1-ol 13g



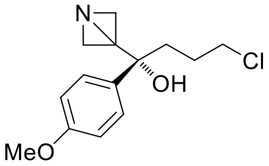
Following the GP1 with **12q** as electrophile, **13g** was obtained as a waxy white solid (93 mg, 95 %) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 3400, 1654, 1637, 1447, 1310, 1131, 1068, 910, 824, 768, 704, 616. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 – 7.46 (m, 2H, Ar-H), 7.38 – 7.35 (m, 2H, Ar-H), 7.29 – 7.26 (m, 1H, Ar-H), 3.46 (t, *J* = 6.4 Hz, 2H, $CH_2CH_2C\mathit{H_2}Cl$), 2.81 (bs, OH), 2.63 (dd, *J* = 6.6, 2.6 Hz, 1H, NCH_2), 2.30 (dd, *J* = 6.6, 2.7 Hz, 1H, NCH_2), 2.19 – 2.11 (m, 1H, $CH_2C\mathit{H_2}CH_2Cl$), 1.99 – 1.86 (m, 1H $CH_2C\mathit{H_2}CH_2Cl$ and 1H $C\mathit{H_2}CH_2CH_2Cl$), 1.60 – 1.51 (m, 1H, $C\mathit{H_2}CH_2CH_2Cl$), 1.41 (d, *J* = 2.4 Hz, 1H, NCH_2), 1.24 (d, *J* = 2.7 Hz, 1H, NCH_2). ^{13}C-NMR (126 MHz, CDCl$_3$) δ 142.8 (Ar-C$_q$), 128.3 (2 x Ar-C), 127.4 (Ar-C), 125.7 (2 x Ar-C), 73.0 (OH-C$_q$), 54.1 (NCH_2), 53.96 (NCH_2), 45.6 ($CH_2CH_2\mathit{C}H_2Cl$), 38.1 ($CH_2\mathit{C}H_2CH_2Cl$), 31.7 (NC$_q$), 26.7 ($\mathit{C}H_2CH_2CH_2Cl$). HRMS *m/z* calculated for $C_{13}H_{17}ClNO$ [M+H]$^+$ 238.0999; found 238.0995.

3-(2-phenyltetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7a



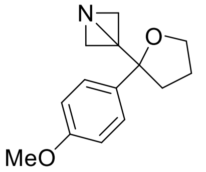
Following the GP2 with **13g**, **7a** was obtained as a pale yellow oil (27 mg, 67 %) without further purification. FT-IR ν_{max}/cm^{-1} 3434, 3058, 2947, 1668, 1448, 1386, 1225, 1132, 1057, 992, 820, 768, 703. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 – 7.44 (m, 2H, Ar-H), 7.36 – 7.32 (m, 2H, Ar-H), 7.29 – 7.24 (m, 1H, Ar-H overlapping CHCl$_3$), 4.06 (dd, *J* = 14.4, 7.6 Hz, 1H, $OC\mathit{H_2}CH_2CH_2$), 3.99 (td, *J* = 7.8, 6.0 Hz, 1H, $OC\mathit{H_2}CH_2CH_2$), 2.36 (dd, *J* = 6.6, 3.0 Hz, 1H, NCH_2), 2.31 – 2.25 (m, 1H, $OCH_2C\mathit{H_2}CH_2$), 2.23 (dd, *J* = 6.6, 2.8 Hz, 1H, NCH_2), 2.21 – 2.14 (m, 1H, $OCH_2C\mathit{H_2}CH_2$), 2.09 – 2.01 (m, 1H, $OCH_2CH_2C\mathit{H_2}$), 1.94 – 1.85 (m, 1H, $OCH_2CH_2C\mathit{H_2}$), 1.17 (d, *J* = 2.7 Hz, 1H, NCH_2), 1.13 (d, *J* = 3.0 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.1 (Ar-C$_q$), 128.3 (2 x Ar-C), 127.3 (Ar-C), 125.7 (2 x Ar-C), 83.4 (OC$_q$) 68.9 ($O\mathit{C}H_2CH_2CH_2$), 52.8 (NCH_2), 52.3 (NCH_2), 36.3 ($OCH_2\mathit{C}H_2CH_2$), 35.9 (NC$_q$), 26.0 ($OCH_2CH_2\mathit{C}H_2$). HRMS *m/z* calculated for $C_{13}H_{16}NO$ [M+H]$^+$ 202,1232; found 202.1225.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-(4-methoxyphenyl)butan-1-ol 13h



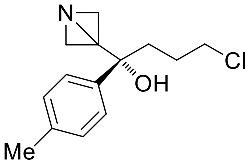
Following the GP1 with **12r** as electrophile, **13h** was obtained as a waxy white solid (109 mg, 99 %) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 3293, 2956, 1722, 1610, 1512, 1462, 1250, 1175, 1101, 1033, 913, 833, 764, 748. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 3.46 (t, *J* = 6.4 Hz, 2H, CH_2Cl), 2.58 (dd, *J* = 6.6, 2.5 Hz, 1H, NCH_2), 2.29 (dd, *J* = 6.6, 2.6 Hz, 1H, NCH_2), 2.14 – 2.06 (m, 1H, $C\mathit{H_2}CH_2Cl$), 1.98 – 1.84 (m, 2H, 1H $CH_2C\mathit{H_2}CH_2Cl$ and 1H $C\mathit{H_2}CH_2CH_2Cl$), 1.62 – 1.53 (m, 1H, $C\mathit{H_2}CH_2CH_2Cl$), 1.38 (d, *J* = 2.4 Hz, 1H, NCH_2), 1.22 (d, *J* = 2.5 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.8 (Ar-C$_q$), 135.9 (Ar-C$_q$), 126.9 (2 x Ar-C), 113.7 (2 x Ar-C), 72.6 (COH), 55.4 (OCH_3), 53.8 (bs, NCH_2), 53.7 (bs, NCH_2), 45.6 (CH_2Cl), 38.2 (NC$_q$), 38.0 ($\mathit{C}H_2CH_2Cl$), 26.8 ($\mathit{C}H_2CH_2CH_2Cl$). HRMS *m/z* calculated for $C_{14}H_{18}ClNNaO_2$ [M+Na]$^+$ 290.0918; found 290.0867.

3-(2-(4-methoxyphenyl)tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7b



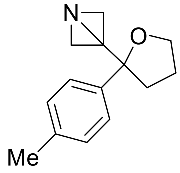
Following the GP2 with **13h**, **7b** was obtained as a pale yellow oil (36 mg, 77 %) without further purification. FT-IR ν$_{max}$/cm^{-1} 2949, 1722, 1610, 1510, 1462, 1247, 1175, 1100, 1057, 1034, 960, 832, 730. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.87 (d, *J* = 8.8 Hz, 2H, Ar-H), 4.05 – 4.00 (m, 1H, OCH$_2$), 3.99 – 3.92 (m, 1H, OCH$_2$), 3.79 (s, 3H, CH$_3$), 2.32 (dd, *J* = 6.6, 3.0 Hz, 1H, NCH$_2$), 2.28 – 2.17 (m, 2H, 1H OCH$_2$C*H*$_2$ and 1H, NCH$_2$), 2.18 – 2.11 (m, 1H, OCH$_2$C*H*$_2$), 2.08 – 1.98 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.94 – 1.84 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.14 (d, *J* = 2.7 Hz, 1H, NCH$_2$), 1.12 (d, *J* = 2.7 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.8 (Ar-C$_q$), 136.1 (Ar-*C*$_q$), 126.9 (2 x Ar-C), 113.6 (2 x Ar-C), 83.1 (OC$_q$), 68.7 (OCH$_2$), 55.4 (O*C*H$_3$), 52.7 (NCH$_2$), 52.3 (NCH$_2$), 36.2 (OCH$_2$*C*H$_2$), 35.9 (NC$_q$), 26.0 (OCH$_2$CH$_2$*C*H$_2$). HRMS *m/z* calculated for $C_{14}H_{17}NNaO_2$ [M+Na]$^+$ 254.1151; found 254.1156.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-(p-tolyl)butan-1-ol 13i



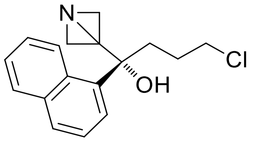
Following the GP1 with **12s** as electrophile, **13i** was obtained as a white solid (62 mg, 60 %) after washing the crude with ethyl ether (4 mL). M.p. 110-112°C. FT-IR ν$_{max}$/cm^{-1} 3247, 2920, 2851, 1661, 1510, 1439, 1384, 1218, 1105, 1043, 820, 740. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.17 (d, *J* = 8.0 Hz, 2H, Ar-H), 3.45 (t, *J* = 6.4 Hz, 2H, CH$_2$CH$_2$C*H*$_2$Cl), 2.64 – 2.60 (m, 1H, NCH$_2$), 2.34 (s, 3H, CH$_3$), 2.32 – 2.28 (m, 1H, NCH$_2$), 2.11 (ddd, *J* = 14.5, 11.6, 4.7 Hz, 1H, CH$_2$C*H*$_2$CH$_2$Cl), 1.97 – 1.85 (m, 1H CH$_2$C*H*$_2$CH$_2$Cl and 1H C*H*$_2$CH$_2$CH$_2$Cl), 1.62 – 1.52 (m, 1H, C*H*$_2$CH$_2$CH$_2$Cl), 1.39 (d, *J* = 2.6 Hz, 1H, NCH$_2$), 1.21 (d, *J* = 2.7 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.9 (Ar-C$_q$), 136.9 (Ar-C$_q$), 129.0 (2 x Ar-C), 125.6 (2 x Ar-C), 72.8 (COH), 53.72 (NCH$_2$), 53.70 (NCH$_2$), 45.6 (CH$_2$CH$_2$*C*H$_2$Cl), 38.3 (NC$_q$), 37.9 (CH$_2$*C*H$_2$CH$_2$Cl), 26.7 (*C*H$_2$CH$_2$CH$_2$Cl), 21.1 (CH$_3$). HRMS *m/z* calculated for $C_{14}H_{18}ClNNaO$ [M+Na]$^+$ 274.0975; found 274.0978.

3-(2-(p-tolyl)tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7c



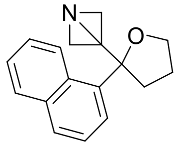
Following the GP2 with **13i**, **7c** was obtained as a pale yellow oil (33 mg, 77 %) without further purification. FT-IR ν$_{max}$/cm^{-1} 2945, 2874, 1721, 1667, 1511, 1455, 1408, 1183, 1131, 1058, 1021, 959, 816. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 – 7.32 (m, 2H, Ar-H), 7.15 (d, *J* = 7.9 Hz, 2H, Ar-H), 4.04 (dd, *J* = 14.3, 7.6 Hz, 1H, OC*H*$_2$CH$_2$CH$_2$), 3.97 (td, *J* = 7.8, 5.9 Hz, 1H, OC*H*$_2$CH$_2$CH$_2$), 2.36 – 2.32 (m, 1H, NCH$_2$), 2.34 (s, 3H, CH$_3$) 2.28 – 2.21 (m, 1H NCH$_2$ and 1H OCH$_2$C*H*$_2$CH$_2$), 2.16 (ddd, *J* = 12.3, 7.9, 6.0 Hz, 1H, OCH$_2$C*H*$_2$CH$_2$), 2.08 – 1.99 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.94 – 1.84 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.16 (d, *J* = 2.9 Hz, 1H, NCH$_2$), 1.12 (d, *J* = 3.2 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.1 (Ar-C$_q$), 136.8 (Ar-C$_q$), 128.9 (2 x Ar-C), 125.6 (2 x Ar-C), 83.3 (OC$_q$), 68.8 (O*C*H$_2$CH$_2$CH$_2$), 52.7 (NCH$_2$), 52.3 (NCH$_2$), 36.2 (OCH$_2$*C*H$_2$CH$_2$), 35.9 (NC$_q$), 26.0 (OCH$_2$CH$_2$*C*H$_2$), 21.2 (CH$_3$). HRMS *m/z* calculated for $C_{14}H_{17}NNaO$ [M+Na]$^+$ 238.1208; found 238.1209.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-(naphthalen-1-yl)butan-1-ol 13j



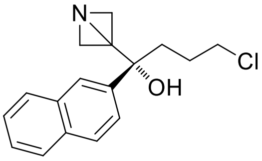
Following the GP1 with **12t** as electrophile, **13j** was obtained as a pale yellow oil (77 mg, 65 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3429, 2091, 1644, 1509, 1444, 1389, 1280, 1216, 1174, 1133, 1074, 904, 802, 779. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.91 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.89 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.80 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.53 – 7.43 (m, 3H, Ar-H), 3.42 – 3.31 (m, 2H, CH_2Cl), 2.94 (dd, *J* = 6.5, 2.2 Hz, 1H, NCH_2), 2.69 – 2.62 (m, 1H, $CH_2C\mathit{H}_2CH_2Cl$), 2.20 – 2.11 (m, 2H, 1H $CH_2C\mathit{H}_2CH_2Cl$ and 1H NCH_2), 1.90 – 1.79 (m, 1H, $C\mathit{H}_2CH_2CH_2Cl$), 1.68 (d, *J* = 1.9 Hz, 1H, NCH_2), 1.40 (d, *J* = 1.5 Hz, 1H, NCH_2), 1.37 – 1.28 (m, 1H, $C\mathit{H}_2CH_2CH_2Cl$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4 (Ar-C_q), 134.6 (Ar-C_q), 130.1 (Ar-C_q), 129.5 (Ar-C), 128.9 (Ar-C), 125.8 (Ar-C), 125.6 (Ar-C), 125.3 (Ar-C), 125.2 (Ar-C), 125.0 (Ar-C), 73.3 (COH), 57.3 (NCH_2), 55.6 (NCH_2), 45.4 (CH_2Cl), 38.6 (NC_q), 38.1 ($CH_2\mathit{C}H_2CH_2Cl$), 27.4 ($\mathit{C}H_2CH_2CH_2Cl$). HRMS *m/z* calculated for $C_{17}H_{18}ClNNaO$ [M+Na]$^+$ 310.0975; found 310.0969.

3-(2-(naphthalen-1-yl)tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7d



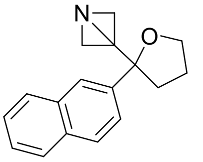
Following the GP2 with **13j**, **7d** was obtained as a pale yellow oil (45 mg, 90 %) without further purification. FT-IR ν_{max}/cm^{-1} 3433, 2102, 1645, 1509, 1393, 1297, 1252, 1132, 1072, 1054, 920, 821, 802, 778, 732. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.88 – 7.83 (m, 2H, Ar-H), 7.77 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.50 – 7.43 (m, 3H, Ar-H), 4.12 (td, *J* = 7.7, 5.6 Hz, 1H, OCH_2), 3.97 (dd, *J* = 15.1, 7.0 Hz, 1H, OCH_2), 2.69 (ddd, *J* = 12.6, 8.3, 6.0 Hz, 1H, $OCH_2C\mathit{H}_2CH_2$), 2.60 – 2.53 (m, 1H, $OCH_2C\mathit{H}_2CH_2$), 2.47 (dd, *J* = 6.6, 2.9 Hz, 1H, NCH_2), 2.13 (dd, *J* = 6.6, 2.9 Hz, 1H, NCH_2), 2.12 – 2.04 (m, 1H, $OCH_2CH_2C\mathit{H}_2$), 1.96 – 1.86 (m, 1H, $OCH_2CH_2C\mathit{H}_2$), 1.25 (d, *J* = 2.9 Hz, 1H, NCH_2), 1.16 (d, *J* = 2.9 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7 (Ar-C_q), 134.6 (Ar-C_q), 130.6 (Ar-C_q), 129.1 (Ar-C), 128.6 (Ar-C), 126.4 (Ar-C), 125.39 (Ar-C), 125.37 (Ar-C), 125.22 (Ar-C), 123.9 (Ar-C), 83.9 (OC_q), 68.3 (OCH_2), 53.99 (NCH_2), 53.14 (NCH_2), 37.4 ($OCH_2\mathit{C}H_2$), 36.4 (NC_q), 26.7 ($OCH_2CH_2\mathit{C}H_2$). HRMS *m/z* calculated for $C_{17}H_{17}NNaO$ [M+Na]$^+$ 274.1208; found 274.1214.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-(naphthalen-2-yl)butan-1-ol 13k



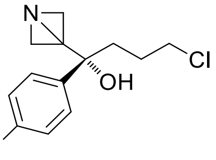
Following the GP1 with **12u** as electrophile, **13k** was obtained as a pale yellow oil (89 mg, 75 %) after column chromatography (R_f = 0.3, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3400, 2099, 1508, 1445, 1309, 1178, 1131, 902, 857, 819, 752, 647. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H, Ar-H), 7.92 – 7.80 (m, *J* = 7.9 Hz, 3H, Ar-H), 7.55 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.52 – 7.46 (m, 2H, Ar-H), 3.55 – 3.38 (m, 2H, CH_2Cl), 2.68 (dd, *J* = 6.5, 2.7 Hz, 1H, NCH_2), 2.33 – 2.24 (m, 2H, 1H NCH_2 and 1H $CH_2C\mathit{H}_2CH_2Cl$), 2.08 – 2.01 (m, 1H, $CH_2C\mathit{H}_2CH_2Cl$), 1.98 – 1.88 (m, 1H, $C\mathit{H}_2CH_2CH_2Cl$), 1.60 – 1.49 (m, 1H, $C\mathit{H}_2CH_2CH_2Cl$), 1.46 (s, 1H, NCH_2), 1.28 (d, *J* = 2.0 Hz, 1H, NCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.2 (Ar-C_q), 133.2 (Ar-C_q), 132.7 (Ar-C_q), 128.4 (Ar-C), 128.1 (Ar-C), 127.7 (Ar-C), 126.4 (Ar-C), 126.2 (Ar-C), 124.6 (Ar-C), 124.0 (Ar-C), 73.2 (COH), 54.4 (NCH_2), 54.1 (NCH_2), 45.5 (CH_2Cl), 38.2 (NC_q), 37.9 ($CH_2\mathit{C}H_2CH_2Cl$), 26.8 ($\mathit{C}H_2CH_2CH_2Cl$). HRMS *m/z* calculated for $C_{17}H_{18}ClNNaO$ [M+Na]$^+$ 310.0975; found 310.0976.

3-(2-(naphthalen-2-yl)tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7e



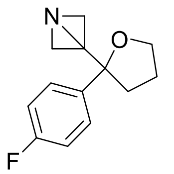
Following the GP2 with **13k**, **7e** was obtained as a pale yellow oil (45 mg, 90 %) without further purification. FT-IR ν$_{max}$/cm^{-1} 3432, 2110, 1647, 1507, 1462, 1272, 1193, 1131, 1058, 906, 857, 820, 749. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (s, 1H, Ar-H), 7.88 – 7.80 (m, 3H, Ar-H), 7.54 (dd, *J* = 8.6, 1.8 Hz, 1H, Ar-H), 7.51 – 7.43 (m, 2H, Ar-H), 4.15 – 4.04 (m, 2H, OCH$_2$), 2.39 (dd, *J* = 6.6, 3.0 Hz, 1H, NCH$_2$) 2.38 – 2.33 (m, 1H, OCH$_2$C*H*$_2$), 2.32 – 2.25 (m, 2H, 1H OCH$_2$C*H*$_2$ and 1H NCH$_2$), 2.13 – 2.05 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.98 – 1.88 (m, 1H, OCH$_2$CH$_2$C*H*$_2$), 1.20 (d, *J* = 2.7 Hz, 1H, NCH$_2$), 1.16 (d, *J* = 3.0 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.5 (Ar-C$_q$), 133.2 (Ar-C$_q$), 132.7 (Ar-C$_q$), 128.3 (Ar-C), 128.0 (Ar-C), 127.7 (Ar-C), 126.2 (Ar-C), 126.0 (Ar-C), 124.3 (Ar-C), 124.2 (Ar-C), 83.6 (OC$_q$), 69.0 (O*C*H$_2$CH$_2$CH$_2$), 52.8 (NCH$_2$), 52.5 (NCH$_2$), 36.2 (OCH$_2$*C*H$_2$CH$_2$), 35.9 (NC$_q$), 26.1 (OCH$_2$CH$_2$*C*H$_2$). HRMS *m/z* calculated for $C_{17}H_{17}NNaO$ [M+Na]$^+$ 274.1208; found 274.1209.

1-(1-azabicyclo[1.1.0]butan-3-yl)-4-chloro-1-(4-fluorophenyl)butan-1-ol 13l



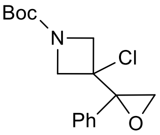
Following the GP1 with **12v** as electrophile, **13l** was obtained as a pale yellow waxy solid (86 mg, 81 %) after washing the crude with ethyl ether (4 mL). FT-IR ν$_{max}$/cm^{-1} 2956, 2917, 1686, 1601, 1506, 1414, 1306, 1225, 1157, 1012, 908, 834. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 – 7.43 (m, 2H, Ar-H), 7.04 (t, *J* = 8.7 Hz, 2H, Ar-H), 3.46 (t, *J* = 6.2 Hz, 2H, CH$_2$Cl), 2.61 (dd, *J* = 6.6, 2.5 Hz, 1H, NCH$_2$), 2.33 – 2.30 (m, 1H, NCH$_2$), 2.14 – 2.05 (m, 1H, C*H*$_2$CH$_2$Cl), 1.97 – 1.85 (m, 2H, 1H CH$_2$C*H*$_2$CH$_2$Cl and 1H C*H*$_2$CH$_2$CH$_2$Cl), 1.58 – 1.47 (m, 1H, C*H*$_2$CH$_2$CH$_2$Cl), 1.41 (d, *J* = 2.4 Hz, 1H, NCH$_2$), 1.23 (d, *J* = 2.6 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.1 (d, $^1J_{C\text{-}F}$ = 245.7 Hz, Ar-CF), 138.7 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C$_q$), 127.5 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 x Ar-C), 115.2 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, 2 x Ar-C), 72.6 (COH), 53.9 (NCH$_2$), 53.6 (NCH$_2$), 45.4 (CH$_2$Cl), 38.2 (NC$_q$), 38.0 (*C*H$_2$CH$_2$Cl), 26.6 (*C*H$_2$CH$_2$CH$_2$Cl). ^{19}F NMR (470 MHz, CDCl$_3$) δ -115.63 – -115.75 (m, 1F).

3-(2-(4-fluorophenyl)tetrahydrofuran-2-yl)-1-azabicyclo[1.1.0]butane 7f



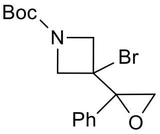
Following the GP2 with **13l**, **7f** was obtained as a pale yellow oil (43 mg, 99 %) without further purification. FT-IR ν$_{max}$/cm^{-1} 1644, 1506, 1296, 1221, 1157, 1131, 1055, 1015, 960, 835, 744. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.47 – 7.34 (m, 2H, Ar-H), 7.07 – 6.95 (m, 2H, Ar-H), 4.09 – 3.91 (m, 2H, OCH$_2$), 2.35 – 1.81 (m, 6H, 4H C*H*$_2$C*H*$_2$CH$_2$O and 2H NCH$_2$), 1.16 (d, *J* = 2.7 Hz, 1H, NCH$_2$), 1.13 (d, *J* = 2.9 Hz, 1H, NCH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.1 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, Ar-C$_q$), 139.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C$_q$), 127.4 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 x Ar-C), 115.0 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, Ar-C), 83.2 (OC$_q$), 68.8 (OCH$_2$), 52.7 (bs, NCH$_2$), 52.3 (bs, NCH$_2$), 36.4 (OCH$_2$*C*H$_2$), 35.7 (NC$_q$), 26.0 (OCH$_2$CH$_2$*C*H$_2$). ^{19}F NMR (282 MHz, CDCl$_3$) δ -115.93 – -116.03 (m, 1F). HRMS *m/z* calculated for $C_{13}H_{14}FNNaO$ [M+Na]$^+$ 242.0957; found 242.0958.

tert-butyl 3-chloro-3-(2-phenyloxiran-2-yl)azetidine-1-carboxylate 8a



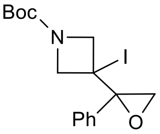
Following the GP3 with **5a**, LiCl (0.25 mmol) and Boc$_2$O, **8a** was obtained as a pale yellow oil (70 mg, 90 %) after column chromatography (R_f = 0.55, hexane/EtOAc 7:3). **FT-IR** ν_{max}/cm^{-1} 2979, 1809, 1706, 1394, 1368, 1258, 1156, 1119, 1073, 912, 734, 700. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.52 – 7.48 (m, 2H, Ar-H), 7.39 - 7.34 (m, 3H, Ar-H), 4.34 (d, *J* = 9.4 Hz, 2H, NCH$_2$), 4.02 (d, *J* = 9.2, 2H, NCH$_2$), 3.05 (d, *J* = 4.4 Hz, 1H, OCH$_2$), 3.02 (d, *J* = 4.5 Hz, 1H, OCH$_2$), 1.44 (s, 9H, 3 x CH$_3$). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 156.1 (C=O), 135.0 (Ar-C$_q$), 128.8 (Ar-C), 128.4 (2 x Ar-C), 127.9 (2 x Ar-C), 80.5 (O*C*(CH$_3$)$_3$), 63.4, 61.1, 60.6, 52.8 (OCH$_2$), 28.5 (3 x CH$_3$). **HRMS** *m/z* calculated for $C_{16}H_{20}ClNNaO_3$ [M+Na]$^+$ 332.1024; found 332.1030.

tert-butyl 3-bromo-3-(2-phenyloxiran-2-yl)azetidine-1-carboxylate 8b



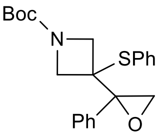
Following the GP3 with **5a**, LiBr (0.25 mmol) and Boc$_2$O, **8b** was obtained as a pale yellow oil (78 mg, 88 %) after column chromatography (R_f = 0.5, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2979, 1809, 1718, 1455, 1407, 1372, 1263, 1118, 1101, 872, 845, 728. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 – 7.51 (m, 2H, Ar-H), 7.40 – 7.32 (m, 3H, Ar-H), 4.49 (d, *J* = 10.2 Hz, 2H, NCH$_2$), 4.21 – 4.15 (m, 2H, NCH$_2$), 3.11 – 3.03 (m, 2H, OCH$_2$), 1.45 (s, 9H, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.2 (C=O), 146.9 (Ar-Cq), 128.8 (2 x Ar-C), 128.4 (2 x Ar-C), 128.1 (Ar-C), 85.3 (OC$_q$), 80.5 (O*C*(CH$_3$)$_3$), 61.5 (2 x NCH$_2$), 54.8 (CBr), 53.7 (OCH$_2$), 28.5 (3 x CH$_3$). HRMS *m/z* calculated for $C_{16}H_{20}BrNNaO_3$ [M+Na]$^+$ 376.0524; found 376.0518.

tert-butyl 3-iodo-3-(2-phenyloxiran-2-yl)azetidine-1-carboxylate 8c



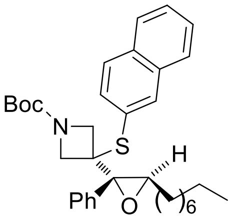
Following the GP3 with **5a**, LiI (0.25 mmol) and Boc$_2$O, **8c** was obtained as a pale yellow oil (75 mg, 75 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 2976, 2931, 1713, 1448, 1392, 1280, 1256, 1163, 1063, 859, 756, 699. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.54 – 7.49 (m, 2H, Ar-H), 7.40 – 7.33 (m, 3H, Ar-H), 4.66 (d, *J* = 9.6 Hz, 1H, NCH$_2$), 4.64 (d, *J* = 10.8 Hz, 1H, NCH$_2$), 4.32 (dd, *J* = 9.5, 1.1 Hz, 1H, NCH$_2$), 4.27 (d, *J* = 10.4 Hz, 1H, NCH$_2$), 3.13 (d, *J* = 4.5 Hz, 1H, OCH$_2$), 3.04 (d, *J* = 4.3 Hz, 1H, OCH$_2$), 1.45 (s, 9H, 3 x CH$_3$).^{13}C NMR (126 MHz, CDCl$_3$) δ 156.3 (C=O), 136.2 (Ar-C$_q$), 128.8 (2 x Ar-C), 128.5 (Ar-C), 128.3 (2 x Ar-C), 80.5 (O*C*(CH$_3$)$_3$), 63.7 (bs, NCH$_2$), 62.9 (Oxiranyl-C$_q$), 54.8 (OCH$_2$), 31.0 (C$_q$I), 28.5 (3 x CH$_3$). HRMS *m/z* calculated for $C_{16}H_{20}INNaO_3^+$ [M+Na]$^+$ 424.0386; found 424.0380.

tert-butyl 3-(2-phenyloxiran-2-yl)-3-(phenylthio)azetidine-1-carboxylate 8d



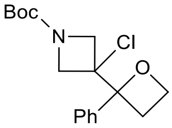
Following the GP4 with **5a** and thiophenol, **8d** was obtained as a pale yellow oil (81 mg, 85 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2976, 1703, 1474, 1392, 1367, 1256, 1140, 1025, 915, 859, 752, 697. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 (d, *J* = 6.6 Hz, 2H, Ar-H), 7.52 – 7.48 (m, 2H, Ar-H), 7.39 – 7.31 (m, 6H, Ar-H), 4.19 (d, *J* = 9.5 Hz, 1H, NCH_2), 4.09 (d, *J* = 8.5 Hz, 1H, NCH_2), 3.95 (d, *J* = 8.6 Hz, 1H, NCH_2) 3.82 (d, *J* = 9.5 Hz, 1H, NCH_2), 2.86 (d, *J* = 4.5 Hz, 1H, OCH_2), 2.66 (d, *J* = 4.4 Hz, 1H, OCH_2), 1.40 (s, 9H, CH_3).^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (C=O), 136.6 (Ar-C_q), 135.7 (2 x Ar-C), 130.9 (Ar-C_q), 129.4 (Ar-C), 129.2 (2 x Ar-C), 128.4 (Ar-C), 128.3 (2 x Ar-C), 128.0 (2 x Ar-C), 80.0 (O*C*(CH_3)$_3$), 74.2 (OC_qPh), 57.7 (NCH_2), 56.6 (NCH_2), 52.5 (OCH_2), 49.9 (SC_q), 28.5 (3 x CH_3). HRMS *m/z* calculated for $C_{22}H_{25}NNaO_3S$ [M+Na]$^+$ 406.1453; found 406.1442.

***tert*-butyl 3-(naphthalen-2-ylthio)-3-((2S*,3R*)-3-octyl-2-phenyloxiran-2-yl)azetidine-1-carboxylate 8e**



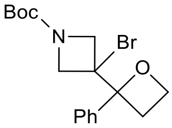
Following the GP4 with **5i** and naphthalene-2-thiol, **8e** was obtained as a waxy yellow solid (99 mg, 73 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3056, 2925, 1704, 1698, 1455, 1393, 1255, 1150, 1078, 943, 915, 859, 816, 746. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.82 (td, *J* = 9.1, 8.5, 4.1 Hz, 3H, Ar-H), 7.66 – 7.61 (m, 2H, Ar-H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar-H), 7.55 – 7.50 (m, 2H, Ar-H), 7.42 – 7.34 (m, 3H, Ar-H), 4.18 (d, *J* = 9.1 Hz, 1H, NCH_2), 4.14 (bs, 1H, NCH_2), 4.04 (bs, 1H, NCH_2), 3.68 (d, *J* = 9.1 Hz, 1H, NCH_2), 2.88 – 2.82 (m, 1H, OCH), 1.34 (s, 9H, 3 x CH_3), 1.29 – 1.00 (m, 14H, (CH_2)$_7$), 0.87 (t, *J* = 7.2 Hz, 3H, (CH_2)$_7$C*H*$_3$).^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (C=O), 134.6 (Ar-C), 133.6 (Ar-C_q), 133.2 (Ar-C_q), 131.4 (Ar-C), 129.0 (2 x Ar-C), 128.8 (2 x Ar-C), 128.2 (Ar-C_q), 128.0 (3 x Ar-C), 127.9 (Ar-C_q), 127.8 (Ar-C), 127.1 (Ar-C), 126.9 (Ar-C), 79.8 (O*C*(CH_3)$_3$), 65.5 (OC_qPh), 61.7 (OCH), 57.3 (bs, 2 x NCH_2), 51.2 (SC_q), 31.9 ((CH_2)$_7$), 29.4 ((CH_2)$_7$), 29.3 ((CH_2)$_7$), 29.2 ((CH_2)$_7$), 29.1 ((CH_2)$_7$), 28.4 (3 x CH_3), 26.1 ((CH_2)$_7$), 22.7 ((CH_2)$_7$), 14.2 (CH_2*C*H_3). HRMS *m/z* calculated for $C_{34}H_{43}NNaO_3S$ [M+Na]$^+$ 568.2861; found 568.2864.

***tert*-butyl 3-chloro-3-(2-phenyloxetan-2-yl)azetidine-1-carboxylate 9a**



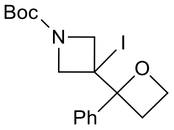
Following the GP3 with **6a**, LiCl and Boc_2O, **9a** was obtained as a pale yellow oil (74 mg, 92 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2974, 2890, 1706, 1448, 1392, 1366, 1275, 1159, 997, 965, 859, 753, 704. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H, Ar-H), 7.40 – 7.35 (m, 2H, Ar-H), 7.35 – 7.30 (m, 1H, Ar-H), 4.86 (d, *J* = 9.1 Hz, 1H, NCH_2), 4.60 – 4.51 (m, 2H, OCH_2), 4.41 (d, *J* = 10.1 Hz, 1H, NCH_2), 4.22 (dd, *J* = 9.3, 1.0 Hz, 1H, NCH_2), 3.75 (d, *J* = 10.0 Hz, 1H, NCH_2), 2.99 (dd, *J* = 9.8, 1.9 Hz, 1H, OCH_2C*H*$_2$), 2.86 (dd, *J* = 8.7, 6.0 Hz, 1H, OCH_2C*H*$_2$), 1.46 (s, 9H, 3 x CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3 (C=O), 141.0 (Ar-C_q), 128.0 (Ar-C), 127.8 (2 x Ar-C), 126.6 (2 x Ar-C), 87.1 (oxetanyl-OC_q), 80.3 (O*C*(CH_3)$_3$), 66.2 (CCl) 65.3 (OCH_2), 60.5 (bs, NCH_2), 59.2 (bs, NCH_2) 30.6 (OCH_2*C*H_2), 28.5 (3 x CH_3). HRMS *m/z* calculated for $C_{17}H_{22}ClNNaO_3$ [M+Na]$^+$ 346.1180; found 346.1185.

***tert*-butyl 3-bromo-3-(2-phenyloxetan-2-yl)azetidine-1-carboxylate 9b**



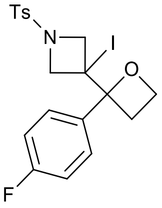
Following the GP3 with **6a**, LiBr and Boc$_2$O, **9b** was obtained as a pale yellow oil (78 mg, 85 %) after column chromatography (R$_f$ = 0.5, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2975, 2888, 1706, 1448, 1390, 1366, 1274, 1161, 962, 859, 751, 702. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 – 7.47 (m, 2H, Ar-H), 7.40 – 7.36 (m, 2H, Ar-H), 7.35 – 7.32 (m, 1H, Ar-H), 4.98 (d, *J* = 9.3 Hz, 1H, , NCH$_2$), 4.59 (d, *J* = 10.3 Hz, 1H, NCH$_2$), 4.56 – 4.48 (m, 2H, OCH$_2$), 4.37 (dt, *J* = 23.2, 11.6 Hz, 1H, NCH$_2$), 3.92 (d, *J* = 10.3 Hz, 1H, NCH$_2$), 3.02 - 2.96 (m, 1H, OCH$_2$C*H*$_2$), 2.91 - 2.86 (m, 1H, OCH$_2$C*H*$_2$), 1.46 (s, 9H, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.4 (C=O), 141.3 (Ar-C$_q$), 128.0 (Ar-C), 127.7 (2 x Ar-C), 126.8 (2 x Ar-C), 87.4 (oxetanyl-OC$_q$), 80.4 (O*C*(CH$_3$)$_3$), 64.7 (OCH$_2$), 61.7 (bs, NCH$_2$) 59.9 (CBr), 59.4 (bs, NCH$_2$), 31.2 (OCH$_2$*C*H$_2$), 28.5 (3 x CH$_3$). HRMS *m/z* calculated for $C_{17}H_{22}BrNNaO$ [M+Na]$^+$ 390.0675; found 390.0667.

***tert*-butyl 3-iodo-3-(2-phenyloxetan-2-yl)azetidine-1-carboxylate 9c**



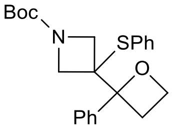
Following the GP3 with **6a**, LiI and Boc$_2$O, **9c** was obtained as a pale yellow oil (74 mg, 71 %) after column chromatography (R$_f$ = 0.5, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 3422, 2975, 2887, 1704, 1968 1448, 1392, 1271, 1161, 959, 859, 749, 702, 607. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.51 - 7.47 (m, 2H, Ar-H), 7.39 – 7.36 (m, 2H, Ar-H), 7.34 – 7.30 (m, 1H, Ar-H), 5.09 (d, *J* = 9.3 Hz, 1H, NCH$_2$), 4.80 (d, *J* = 10.3 Hz, 1H, NCH$_2$), 4.50 (dd, *J* = 9.5, 1.1 Hz, 1H, NCH$_2$), 4.48 – 4.44 (m, 1H, OCH$_2$), 4.43 – 4.36 (m, 1H, OCH$_2$), 4.07 (dd, *J* = 10.3 Hz, 1H, NCH$_2$), 3.01 – 2.93 (m, 1H, OCH$_2$C*H*$_2$), 2.93 – 2.86 (m, 1H, OCH$_2$C*H*$_2$), 1.46 (s, 9H, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.4 (C=O), 142.3 (Ar-C$_q$), 128.0 (Ar-C), 127.7 (2 x Ar-C), 127.0 (2 x Ar-C), 88.7 (oxetanyl-OC$_q$), 80.4 (O*C*(CH$_3$)$_3$), 64.5 (bs, NCH$_2$), 63.8 (OCH$_2$), 62.1 (bs, NCH$_2$), 40.5 (C$_q$I), 31.9 (OCH$_2$*C*H$_2$), 28.5 (3 x CH$_3$). HRMS *m/z* calculated for $C_{17}H_{22}INNaO_3$ [M+Na]$^+$ 438.0537; found 438.0537.

3-(2-(4-fluorophenyl)oxetan-2-yl)-3-iodo-1-tosylazetidine 9d



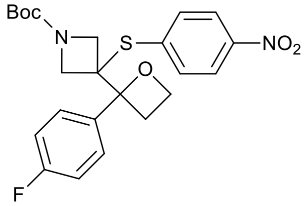
Following the GP3 with **6e**, LiI and tosyl chloride, **9d** was obtained as a pale yellow oil (110 mg, 90 %) after column chromatography (R$_f$ = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 2917, 1735, 1599, 1508, 1347, 1223, 1159, 1094, 958, 816, 676. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.39 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.34 – 7.29 (m, 2H, Ar-H), 7.04 – 6.97 (m, 2H, Ar-H), 4.88 (d, *J* = 9.1 Hz, 1H, NCH$_2$), 4.59 (d, *J* = 9.8 Hz, 1H, NCH$_2$), 4.29 – 4.21 (m, 3H, 1H NCH$_2$ and 2H OCH$_2$), 3.86 (d, *J* = 9.8 Hz, 1H, NCH$_2$), 2.88 (dt, *J* = 11.8, 8.5 Hz, 1H, OCH$_2$C*H*$_2$), 2.78 – 2.71 (m, 1H, OCH$_2$C*H*$_2$), 2.46 (s, 3H, CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.4 (d, $^1J_{C-F}$ = 247.6 Hz, Ar-C$_q$), 144.7 (Ar-C$_q$), 137.8 (d, $^4J_{C-F}$ = 3.2 Hz, Ar-C$_q$), 131.7 (Ar-C$_q$), 129.9 (2 x Ar-C), 128.6 (d, $^3J_{C-F}$ = 8.2 Hz, 2 x Ar-C), 128.5 (2 x Ar-C), 114.7 (d, $^2J_{C-F}$ = 21.6 Hz, 2 x Ar-C), 87.9 (OC$_q$), 64.1 (NCH$_2$), 63.5 (OCH$_2$), 62.1 (NCH$_2$), 38.5 (C$_q$I), 31.5 (OCH$_2$*C*H$_2$), 21.8 (CH$_3$). ^{19}F NMR (282 MHz, CDCl$_3$) -113.93 – -114.03 (m, 1F). HRMS *m/z* calculated for $C_{19}H_{19}FINNaO_3S$ [M+Na]$^+$ 510.0012; found 510.0014.

***tert*-butyl 3-(2-phenyloxetan-2-yl)-3-(phenylthio)azetidine-1-carboxylate 9e**



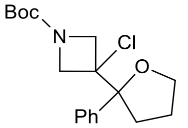
Following the GP4 with **6a** and thiophenol, **9e** was obtained as a pale yellow oil (77 mg, 78 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3435, 2529, 2080, 1645, 1447, 1393, 1366, 1257, 1145, 963, 750, 666. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.50 (m, 2H, Ar-H), 7.42 – 7.38 (m, 4H, 4 x Ar-H), 7.36 – 7.31 (m, 2H, Ar-H), 7.31 – 7.27 (m, 2H, Ar-H), 4.62 – 4.46 (m, 3H, 2H OCH_2 and 1H NCH_2), 4.40 (d, *J* = 9.7 Hz, 1H, NCH_2), 4.04 – 3.92 (m, 1H, NCH_2), 3.77 – 3.63 (m, 1H, NCH_2), 3.07 (bs, 1H, OCH_2CH_2), 2.86 – 2.81 (m, 1H, OCH_2CH_2), 1.34 (s, 9H, 3 x CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1 (C=O), 142.5 (Ar-C_q), 136.3 (2 x Ar-C), 131.1 (Ar-Cq), 129.2 (Ar-C), 129.1 (2 x Ar-C), 127.9 (2 x Ar-C), 127.8 (Ar-C) 126.3 (2 x Ar-C), 88.4 (oxetanyl-OC_q), 79.7 ($OC(CH_3)_3$), 65.4 (OCH_2), 56.1 (bs, NCH_2), 54.2 (C_qSPh), 31.4 (OCH_2CH_2), 28.5 (3 x CH_3). HRMS *m/z* calculated for $C_{23}H_{27}NO_3S$ $[M+Na]^+$ 420.1604; found 420.1611.

***tert*-butyl 3-(2-(4-fluorophenyl)oxetan-2-yl)-3-((4-nitrophenyl)thio)azetidine-1-carboxylate 9f**



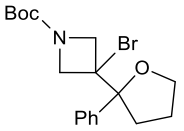
Following the GP4 with **6e** and 4-nitrobenzenethiol, **9f** was obtained as a waxy yellow solid (75 mg, 65 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2976, 2250, 1699, 1597, 1578, 1513, 1393, 1342, 1157, 964, 853, 731. ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 2H, Ar-H), 7.43 – 7.36 (m, 2H, Ar-H), 7.31 – 7.24 (m, 2H, Ar-H), 7.04 (t, *J* = 8.6 Hz, 2H, Ar-H), 4.64 – 4.47 (m, 4H, 2H NCH_2 and 2H OCH_2), 3.97 (d, *J* = 9.1 Hz, 1H, NCH_2), 3.87 (bs, 1H, NCH_2), 3.22 – 3.12 (m, 1H, OCH_2CH_2), 2.84 (ddd, *J* = 11.5, 8.4, 5.6 Hz, 1H, OCH_2CH_2), 1.40 (s, 9H, 3 x CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C-F}$ = 247.6 Hz, C-F), 155.9 (C=O), 146.8 (Ar-C_q), 142.3 (Ar-C_q), 138.3 (d, $^4J_{C-F}$ = 3.3 Hz, Ar-C_q), 131.7 (2 x Ar-C), 127.8 (d, $^3J_{C-F}$ = 8.1 Hz, 2 x Ar-C), 123.8 (2 x Ar-C) 115.2 (d, $^2J_{C-F}$ = 21.5 Hz, 2 x Ar-C), 88.5 (oxetanyl-OC_q), 80.6 ($OC(CH_3)_3$), 65.3 (OCH_2), 57.0 (bs, NCH_2), 55.6 (bs, NCH_2), 54.1 (C_qSAr), 31.5 (OCH_2CH_2), 28.5 (3 x CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.82 – -113.99 (m, 1F). HRMS *m/z* calculated for $C_{23}H_{25}FN_2NaO_5S$ $[M+Na]^+$ 483.1366; found 483.1363.

***tert*-butyl 3-chloro-3-(2-phenyltetrahydrofuran-2-yl)azetidine-1-carboxylate 10a**



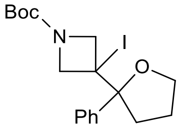
Following the GP3 with **7a**, $ZnCl_2$ and Boc_2O, **10a** was obtained as a pale yellow oil (80 mg, 95 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 2980, 1703, 1447, 1416, 1365, 1255, 1161, 1139, 1056, 859, 754, 707. ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H, Ar-H), 7.36 – 7.28 (m, 3H, Ar-H), 4.49 (d, *J* = 9.1 Hz, 1H, NCH_2), 4.42 (d, *J* = 9.8 Hz, 1H, NCH_2), 4.10 – 4.02 (m, 2H, 1H NCH_2 and 1H OCH_2), 3.94 (td, *J* = 8.3, 4.7 Hz, 1H, OCH_2), 3.67 (d, *J* = 9.8 Hz, 1H, NCH_2), 2.53 (ddd, *J* = 12.4, 7.7, 3.0 Hz, 1H, $OCH_2CH_2CH_2$), 2.12 – 2.04 (m, 1H, $OCH_2CH_2CH_2$), 2.03 – 1.92 (m, 1H, $OCH_2CH_2CH_2$), 1.80 – 1.69 (m, Hz, 1H, $OCH_2CH_2CH_2$), 1.45 (s, 9H, 3 x CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4 (C=O), 140.2 (Ar-C_q), 127.9 (2 X Ar-C), 127.8 (Ar-C), 127.6 (2 x Ar-C), 87.6 (tetrahydrofuranyl-OC_q), 80.0 ($OC(CH_3)_3$), 69.1 (OCH_2), 67.4 (CCl), 61.0 (bs, NCH_2), 34.4 ($OCH_2CH_2CH_2$), 28.5 (3 x CH_3), 25.7 ($OCH_2CH_2CH_2$). HRMS *m/z* calculated for $C_{19}H_{26}BrNNaO_3$ $[M+Na]^+$ 360.1342; found 360.1331.

***tert*-butyl 3-bromo-3-(2-phenyltetrahydrofuran-2-yl)azetidine-1-carboxylate 10b**



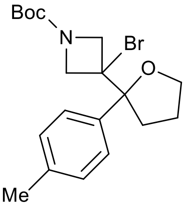
Following the GP3 with **7a**, LiBr and Boc$_2$O, **10b** was obtained as a pale yellow oil (81 mg, 85 %) after column chromatography (R_f = 0.4, hexane/EtOAc 8:2). FT-IR ν_{max}/cm^{-1} 2965, 1720, 1578, 1455, 1408, 1455, 1263, 1117, 1100, 1017, 874, 727. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.38 – 7.28 (m, 3H, Ar-H), 4.61 (dd, *J* = 20.7, 9.7 Hz, 2H, NCH$_2$), 4.25 (d, *J* = 9.4, 1H, NCH$_2$), 4.08 (q, *J* = 7.8 Hz, 1H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2CH_2}$), 3.96 (td, *J* = 8.3, 4.6 Hz, 1H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2CH_2}$), 3.87 (d, *J* = 10.1 Hz, 1H, NCH$_2$), 2.62 – 2.55 (m, 1H, $\mathrm{OCH_2C}\mathit{H}_2\mathrm{CH_2}$), 2.15 – 2.05 (m, 1H, $\mathrm{OCH_2C}\mathit{H}_2\mathrm{CH_2}$), 2.03 – 1.94 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.79 – 1.70 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.45 (s, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.5 (C=O) 140.5 (Ar-Cq), 127.9 (Ar-C), 127.8 (2 x Ar-C), 127.7 (2 x Ar-C), 87.8 (OC$_q$Ph), 80.1 ($\mathrm{O}\mathit{C}\mathrm{(CH_3)_3}$), 69.2 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_2CH_2}$), 62.0 (bs, 2 x NCH$_2$), 60.9 (CBr), 35.0 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.5 (3 x CH$_3$), 25.7 ($\mathrm{OCH_2CH_2}\mathit{C}\mathrm{H_2}$). HRMS *m/z* calculated for $C_{18}H_{24}BrNNaO_3$ [M+Na]$^+$ 404.0832; found 404.0833.

***tert*-butyl 3-iodo-3-(2-phenyltetrahydrofuran-2-yl)azetidine-1-carboxylate 10c**



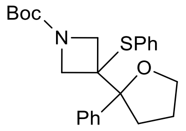
Following the GP3 with **7a**, LiI and Boc$_2$O, **10c** was obtained as a pale yellow oil (84 mg, 78 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2974, 1718, 447, 1407, 1263, 1119, 1100, 1047, 1018, 913, 727, 702. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.38 – 7.28 (m, 3H Ar-H), 4.81 – 4.75 (m, 2H, NCH$_2$), 4.41 (d, *J* = 9.6 Hz, 1H, NCH$_2$), 4.13 – 4.04 (m, 2H, 1H NCH$_2$ and 1H OCH$_2$), 3.97 (td, *J* = 8.3, 4.6 Hz, 1H, OCH$_2$), 2.62 (ddd, *J* = 12.3, 7.7, 2.8 Hz, 1H, $\mathrm{OCH_2C}\mathit{H}_2$), 2.18 – 2.09 (m, 1H, $\mathrm{OCH_2C}\mathit{H}_2$), 2.06 – 1.96 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.84 – 1.72 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.45 (s, 9H, CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.5 (C=O), 141.6 (Ar-C$_q$), 127.9 (3 x Ar-C), 127.7 (2 x Ar-C), 88.4 (tetrahydrofuranyl-OC$_q$), 80.1 ($\mathrm{O}\mathit{C}\mathrm{(CH_3)_3}$), 69.3 (OCH$_2$), 64.6 (bs, 2 x NCH$_2$), 40.9 (IC), 35.5 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2}$), 28.5 (3 x CH$_3$), 25.8 ($\mathrm{OCH_2CH_2}\mathit{C}\mathrm{H_2}$). HRMS *m/z* calculated for $C_{18}H_{24}INNaO_3$ [M+Na]$^+$ 452.0693; found 452.0692.

***tert*-butyl 3-bromo-3-(2-(p-tolyl)tetrahydrofuran-2-yl)azetidine-1-carboxylate 10d**



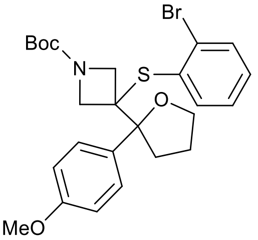
Following the GP3 with **7c**, LiBr and Boc$_2$O, **10d** was obtained as a pale yellow oil (91 mg, 92 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 3419, 1702, 1409, 1365, 1225, 1156, 1050, 975, 938, 860, 805, 767. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.2 Hz, 2H, Ar-H), 4.60 (dd, *J* = 15.2, 9.8 Hz, 2H, NCH$_2$), 4.24 (dd, *J* = 9.4, 1.2 Hz, 1H, NCH$_2$), 4.06 (dd, *J* = 15.5, 7.8 Hz, 1H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2CH_2}$), 3.94 (td, *J* = 8.3, 4.6 Hz, 1H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2CH_2}$), 3.87 (d, *J* = 10.1 Hz, 1H, NCH$_2$), 2.56 (ddd, *J* = 12.5, 7.7, 2.9 Hz, 1H, $\mathrm{OCH_2C}\mathit{H}_2\mathrm{CH_2}$), 2.34 (s, 3H, Ar-CH$_3$), 2.11 – 2.02 (m, 1H, $\mathrm{OCH_2C}\mathit{H}_2\mathrm{CH_2}$), 2.01 – 1.93 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.80 – 1.70 (m, 1H, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.44 (s, 9H, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.5 (C=O), 137.6 (Ar-C$_q$), 137.5 (Ar-C$_q$), 128.6 (2 x Ar-C), 127.6 (2 x Ar-C), 87.7 (OC$_q$Ar), 80.0 ($\mathrm{O}\mathit{C}\mathrm{(CH_3)_3}$), 69.2 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_2CH_2}$), 61.9 (bs, 2 x NCH$_2$), 61.1 (CBr), 35.0 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_2CH_2}$), 28.5 (3 x CH$_3$), 25.7 ($\mathrm{OCH_2CH_2}\mathit{C}\mathrm{H_2}$), 21.2 (Ar-CH$_3$). HRMS *m/z* calculated for $C_{19}H_{26}BrNNaO_3$ [M+Na]$^+$ 418.0994; found 418.1007.

***tert*-butyl-3-(2-phenyltetrahydrofuran-2-yl)-3-(phenylthio)azetidine-1-carboxylate 10e**



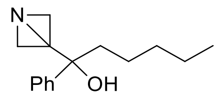
Following the GP4 with **7a** and thiophenol, **10e** was obtained as a pale yellow oil (92 mg, 90 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). **FT-IR** ν_{max}/cm^{-1} 2979, 1810, 1719, 1450, 1408, 1372, 1263, 1213, 1119, 912, 730. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.52 – 7.47 (m, 1H, Ar-H), 7.39 – 7.19 (m, 7H, Ar-H overlapping $CHCl_3$ signal), 4.35 – 4.22 (m, 2H, NCH_2), 4.04 (q, *J* = 7.7 Hz, 1H, OCH_2), 3.97 – 3.83 (m, 2H, 1H NCH_2 and 1H OCH_2), 3.71 – 3.54 (m, 1H, NCH_2), 2.59 – 2.51 (m, 1H, $OCH_2C\mathit{H}_2$), 2.20 – 2.09 (m, 1H, $OCH_2C\mathit{H}_2$), 2.02 - 1.94 (m, 1H, $OCH_2CH_2C\mathit{H}_2$), 1.81 – 1.69 (m, 1H, $OC\mathit{H}_2CH_2C\mathit{H}_2$), 1.30 (s, 9H, 3 x CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.1 (C=O), 141.7 (Ar-C_q), 136.5 (2 x Ar-C), 131.3 (Ar-C_q), 129.2 (Ar-C), 129.0 (2 x Ar-C), 128.0 (Ar-C), 127.7 (2 x Ar-C), 127.3 (2 x Ar-C), 88.4 (tetrahydrofuranyl-OC_q), 79.4 ($O\mathit{C}(CH_3)_3$), 68.3 (OCH_2), 57.3 (bs, 2 x NCH_2), 54.9 (C_qSPh), 34.6 (OCH_2CH_2), 28.4 (3 x CH_3), 25.7 ($OCH_2CH_2\mathit{C}H_2$). **HRMS** *m/z* calculated for $C_{24}H_{29}NNaO_3S$ $[M+H]^+$ 434.1760; found 434.1763.

tert-butyl 3-((2-bromophenyl)thio)-3-(2-(4-methoxyphenyl)tetrahydrofuran-2-yl)azetidine-1-carboxylate 10f



Following the GP4 with **7b** and 2-bromothiophenol, **10f** was obtained as a waxy yellow solid (108 mg, 83 %) after column chromatography (R_f = 0.4, hexane/EtOAc 7:3). FT-IR ν_{max}/cm^{-1} 2975, 1698, 1609, 1510, 1444, 1299, 1250, 1177, 1054, 912, 829, 755, 732. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 6.8, 2.6 Hz, 1H, Ar-H), 7.54 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.30 – 7.25 (m, 1H, Ar-H), 7.19 – 7.12 (m, 2H, Ar-H), 6.89 – 6.85 (m, 2H, Ar-H), 4.37 (d, *J* = 9.7 Hz, 1H, NCH_2), 4.25 – 4.17 (m, 1H, NCH_2), 4.04 (q, *J* = 7.7 Hz, 1H, OCH_2), 3.87 (td, *J* = 8.3, 5.0 Hz, 1H, OCH_2), 3.84 – 3.63 (m, 5H, 2H NCH_2 and 3H OCH_3), 2.60 (ddd, *J* = 12.7, 7.9, 3.1 Hz, 1H, $OCH_2C\mathit{H}_2$), 2.28 – 2.17 (m, 1H, $OCH_2C\mathit{H}_2$), 2.05 – 1.95 (m, 1H, $OCH_2CH_2C\mathit{H}_2$), 1.82 – 1.70 (m, 1H, $OCH_2CH_2C\mathit{H}_2$), 1.31 (bs, 9H, 3 x CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C=O), 156.1 (Ar-C_q), 137.2 (Ar-C), 133.7 (Ar-C), 133.2 (Ar-C_q), 131.4 (Ar-C_q), 130.3 (Ar-C), 128.6 (2 x Ar-C), 127.9 (Ar-C), 113.4 (2 x Ar-C), 88.2 (tetrahydrofuranyl-OC_q), 79.4 ($O\mathit{C}(CH_3)_3$), 68.3 (OCH_2), 57.8 (bs, NCH_2), 56.8 (bs, NCH_2), 56.2 (C_qSPh), 55.3 (OCH_3), 34.3 (OCH_2CH_2), 28.5 (3 x CH_3), 25.8 ($OCH_2CH_2\mathit{C}H_2$). HRMS *m/z* calculated for $C_{25}H_{30}BrNNaO_4S$ $[M+H]^+$ 542.0977; found 542.0966.

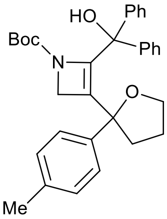
1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylhexan-1-ol 14



To a stirred solution of **5a** (40 mg, 0.23 mmol) in dry ethyl ether (3 mL) at -78°C, butylmagnesium chloride (2.0 M in ethyl ether, 0.138 mL) was added dropwise. The reaction mixture was allowed to warm at room temperature in 15 minutes and quenched with water (1 mL). The crude was extracted with EtOAc (3 x 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound **14** was obtained as a pale yellow oil (29 mg, 55 %) after column chromatography (R_f = 0.6, hexane/EtOAc 6:4). FT-IR ν_{max}/cm^{-1} 3270, 2928, 1494, 1447, 1217, 1129, 1068, 1034, 920, 825, 705. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H, Ar-H), 7.38 – 7.33 (m, 2H, Ar-H), 7.29 – 7.24 (m, 1H, Ar-H overlapping $CHCl_3$), 2.56 (dd, *J* = 6.7, 2.7 Hz, 1H, NCH_2), 2.27 (dd, *J* = 6.7, 2.8 Hz, 1H, NCH_2), 1.96 (ddd, *J* = 13.7, 12.1, 4.5

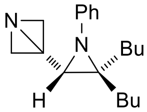
Hz, 1H, pentyl-CH$_2$), 1.80 (ddd, *J* = 13.7, 11.9, 4.5 Hz, 1H, pentyl-CH$_2$), 1.46 – 1.34 (m, 2H, 1H pentyl-CH$_2$ and 1H NCH$_2$), 1.30 – 1.15 (m, 5H, 4H pentyl-CH$_2$ and 1H NCH$_2$), 1.10 – 1.00 (m, 1H, pentyl-CH$_2$), 0.82 (t, *J* = 6.9 Hz, 3H, pentyl-CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.5 (Ar-C$_q$), 128.2 (2 x Ar-C), 127.1 (Ar-C), 125.8 (2 x Ar-C), 73.3 (C$_q$OH), 54.1 (NCH$_2$), 54.0 (NCH$_2$), 40.8 (pentyl-CH$_2$), 38.0 (NC$_q$), 32.2 (pentyl-CH$_2$), 22.9 (pentyl-CH$_2$), 22.6 (pentyl-CH$_2$), 14.1 (pentyl-CH$_3$). HRMS *m/z* calculated for $C_{15}H_{22}NO$ [M+H]$^+$ 232.1701; found 232.1702.

***tert*-butyl 4-(hydroxydiphenylmethyl)-3-(2-(p-tolyl)tetrahydrofuran-2-yl)azete-1(2H)-carboxylate 15**



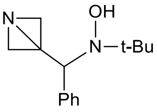
To a stirred solution of **10d** (60 mg, 0.15 mmol) and benzophenone (55 mg, 0.3 mmol) in dry THF (2 mL) at -78°C, LDA (2.0 M in THF/heptane/ethylbenzene, 0.175 mL) was added dropwise. The reaction mixture was allowed to warm at room temperature in 15 minutes and quenched with water (1 mL). The crude was extracted with EtOAc (3 x 3 mL) and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Compound **15** was obtained as a pale yellow oil (63 mg, 85 %) after column chromatography (R$_f$ = 0.6, hexane/EtOAc 8:2). FT-IR ν$_{max}$/cm^{-1} 3272, 1673, 1448, 1416, 1368, 1239, 1156, 1047, 910, 873, 813, 758, 700. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48 – 7.44 (m, 2H, Ar-H), 7.35 – 7.23 (m, 8H, Ar-H), 7.09 (s, 4H, Ar-H), 4.10 (s, 1H, NCH$_2$), 3.66 – 3.52 (m, 2H, OCH$_2$), 2.33 (s, 3H, CH$_3$), 1.67 – 1.46 (m, 4H, OCH$_2$C*H$_2$*C*H$_2$*), 1.28 (s, 9H, 3 x CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 152.1 (C=O), 145.8 (C$_q$), 144.2 (C$_q$), 143.6 (C$_q$), 141.3 (C$_q$), 136.8 (C$_q$), 128.9 (2 x Ar-C), 128.5 (2 x Ar-C), 128.2 (2 x Ar-C), 128.0 (2 x Ar-C), 127.9 (C$_q$), 127.8 (2 x Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 125.5 (2 x Ar-C), 83.8 (C$_q$), 81.3 (C$_q$), 77.6 (C$_q$), 66.6 (OCH$_2$), 55.0 (NCH$_2$), 36.2 (OCH$_2$*C*H$_2$), 28.3 (3 x CH$_3$), 25.7 (OCH$_2$CH$_2$*C*H$_2$), 21.2 (Ar-CH$_3$). HRMS *m/z* calculated for $C_{32}H_{35}NNaO_4$ [M+Na]$^+$ 520.2464; found 520.2475.

3-(3,3-dibutyl-1-phenylaziridin-2-yl)-1-azabicyclo[1.1.0]butane 18



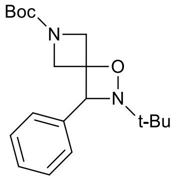
Following the GP1 with **16** as electrophile, **18** was obtained as a pale yellow oil (94 mg, 80 %) after column chromatography (R$_f$ = 0.6, hexane/EtOAc 8:2). FT-IR ν$_{max}$/cm^{-1} 2956, 2930, 1598, 1488, 1455, 1287, 1263, 1172, 1127, 946, 765, 696. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 – 7.15 (m, 2H, Ar-H), 6.93 (tt, *J* = 7.4, 1.1 Hz, 1H, Ar-H), 6.87 – 6.83 (m, 2H, Ar-H), 2.53 (dd, *J* = 6.4, 2.9 Hz, 1H, NCH$_2$), 2.45 (dd, *J* = 6.4, 2.5 Hz, 1H, NCH$_2$), 2.33 (s, 1H, aziridinyl-CH), 1.89 – 1.78 (m, 2H, butyl-CH$_2$), 1.65 – 1.57 (m, 2H, butyl-CH$_2$), 1.53 – 1.15 (m, 9H, 7H butyl-CH$_2$ and 2H NCH$_2$), 0.97 (t, *J* = 7.3 Hz, 3H, butyl-CH$_3$), 0.84 (t, *J* = 7.2 Hz, 3H, butyl-CH$_3$), 0.56 – 0.48 (m, 1H, butyl-CH$_2$). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.0 (Ar-C$_q$), 128.9 (2 x Ar-C), 121.9 (Ar-C), 120.5 (2 x Ar-C), 54.5 (NCH$_2$), 54.1 (NCH$_2$), 50.5 (aziridinyl-C$_q$), 48.1 (aziridinyl-CH), 31.69 (butyl-CH$_2$), 31.65 (butyl-CH$_2$), 29.2 (ABB-C$_q$), 29.0 (butyl-CH$_2$), 28.4 (butyl-CH$_2$), 23.3 (butyl-CH$_2$), 22.8 (butyl-CH$_2$), 14.3 (butyl-CH$_3$), 14.2 (butyl-CH$_3$). HRMS *m/z* calculated for $C_{19}H_{29}N_2$ [M+H]$^+$ 285.2331; found 285.2340.

N-((1-azabicyclo[1.1.0]butan-3-yl)(phenyl)methyl)-N-(*tert*-butyl)hydroxylamine 19



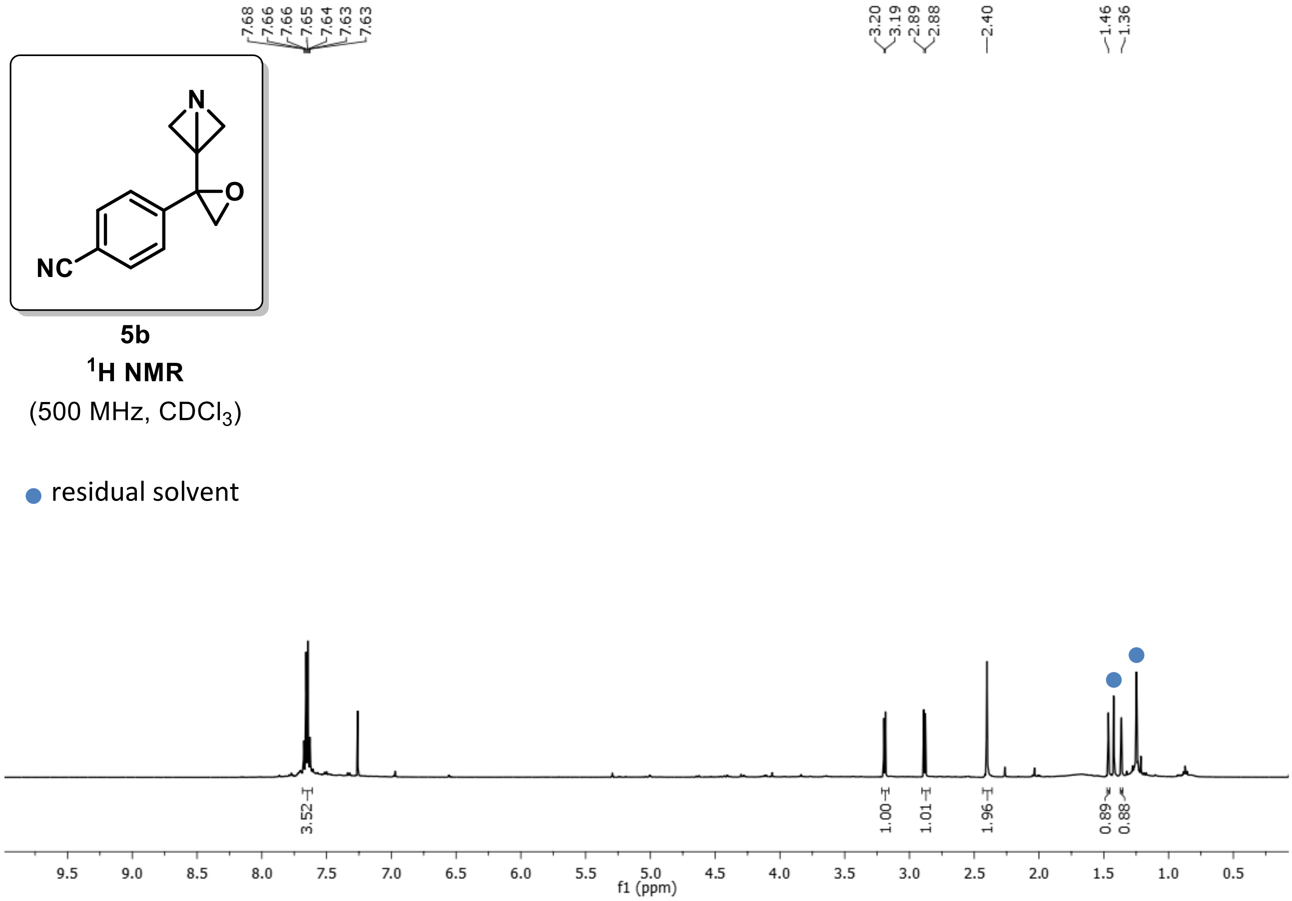
Following the GP1 with **17** as electrophile, **19** was obtained as a white waxy solid (91 mg, 95%) after washing the crude with ethyl ether (4 mL). FT-IR ν_{max}/cm^{-1} 2971, 2934, 1703, 1453, 1363, 1327, 1219, 1075, 1028, 939, 901, 833, 701. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H, Ar-H), 7.34 – 7.22 (m, 3H, Ar-H), 5.16 (bs, 1H, OH), 4.47 (s, 1H, CHPh), 2.38 (dd, *J* = 6.6, 2.8 Hz, 1H, NCH_2), 2.15 (dd, *J* = 6.6, 2.8 Hz, 1H, NCH_2), 1.29 (d, *J* = 2.8 Hz, 1H, NCH_2), 1.12 (d, *J* = 2.8 Hz, 1H, NCH_2), 1.07 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6 (Ar-C_q), 128.9 (2 x Ar-C), 127.3 (2 x Ar-C), 126.6 (Ar-C), 63.2 (CHPh), 59.0 ($\mathit{C}(CH_3)_3$), 54.6 (NCH_2), 51.9 (NCH_2), 32.2 (NC_q), 26.1 ($C(\mathit{C}H_3)_3$). HRMS *m/z* calculated for $C_{14}H_{21}N_2O$ $[M+H]^+$ 233.1654; found 233.1646.

tert-butyl 2-(tert-butyl)-3-phenyl-1-oxa-2,6-diazaspiro[3.3]heptane-6-carboxylate 20



To a stirred solution of **19** (60 mg, 0.26 mmol) and Boc_2O (85 mg, 0.39 mmol) in DCM (2.5 mL), Amberlyst 15 (40 mg) was added. After stirring for 16h at room temperature, the mixture was filtered and the solvent was removed under reduced pressure. Compound **20** was obtained as a pale yellow oil (64 mg, 74 %) after column chromatography (R_f = 0.3, hexane/EtOAc 9:1). FT-IR ν_{max}/cm^{-1} 2974, 2934, 1704, 1478, 1455, 1393, 1366, 1173, 1100, 898, 766, 700. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.41 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.36 – 7.31 (m, 1H, Ar-H), 4.91 (s, 1H, CHPh), 4.21 (dd, *J* = 10.8, 1.6 Hz, 1H, NCH_2), 4.06 (dd, *J* = 10.7, 1.7 Hz, 1H, NCH_2), 3.90 (dd, *J* = 10.8, 1.6 Hz, 1H, NCH_2), 3.65 (d, *J* = 10.3 Hz, 1H, NCH_2), 1.36 (s, 9H, $OC(CH_3)_3$), 1.07 (s, 9H, $NC(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (C=O), 137.4 (Ar-C_q), 129.0 (2 x Ar-C), 128.6 (Ar-C), 127.6 (2 x Ar-C), 80.9 ($O\mathit{C}(CH_3)_3$), 79.9 (spiro-C_q), 68.2 (CHPh), 62.7 (bs, NCH_2), 59.2 ($N\mathit{C}(CH_3)_3$), 59.1 (bs, NCH_2), 28.4 ($OC(\mathit{C}H_3)_3$), 23.4 ($NC(\mathit{C}H_3)_3$). HRMS *m/z* calculated for $C_{19}H_{28}N_2NaO_3$ $[M+Na]^+$ 355.1998; found 355.2003.

6. Copy of NMR spectra

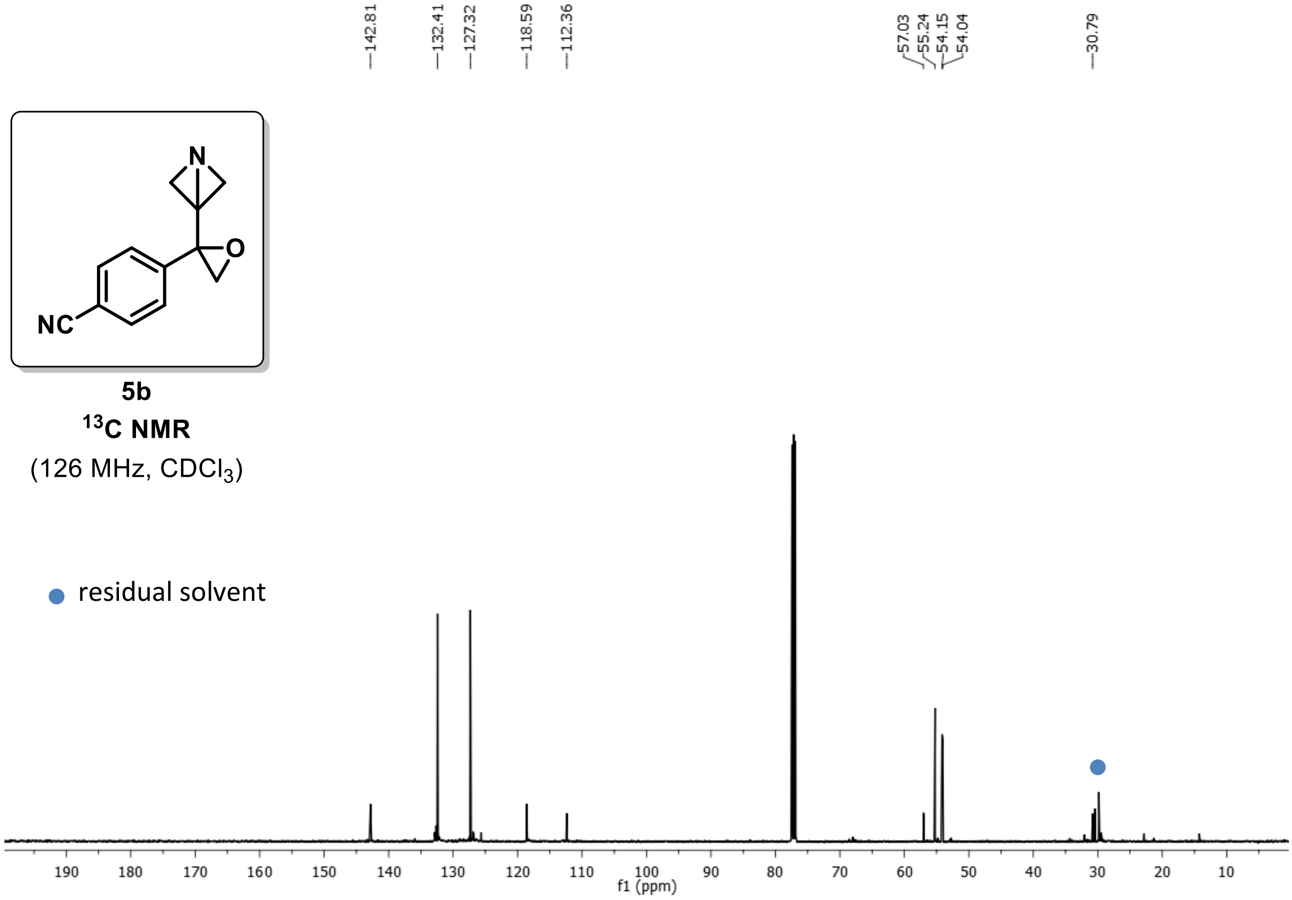


5b

^{1}H NMR

(500 MHz, $CDCl_3$)

● residual solvent

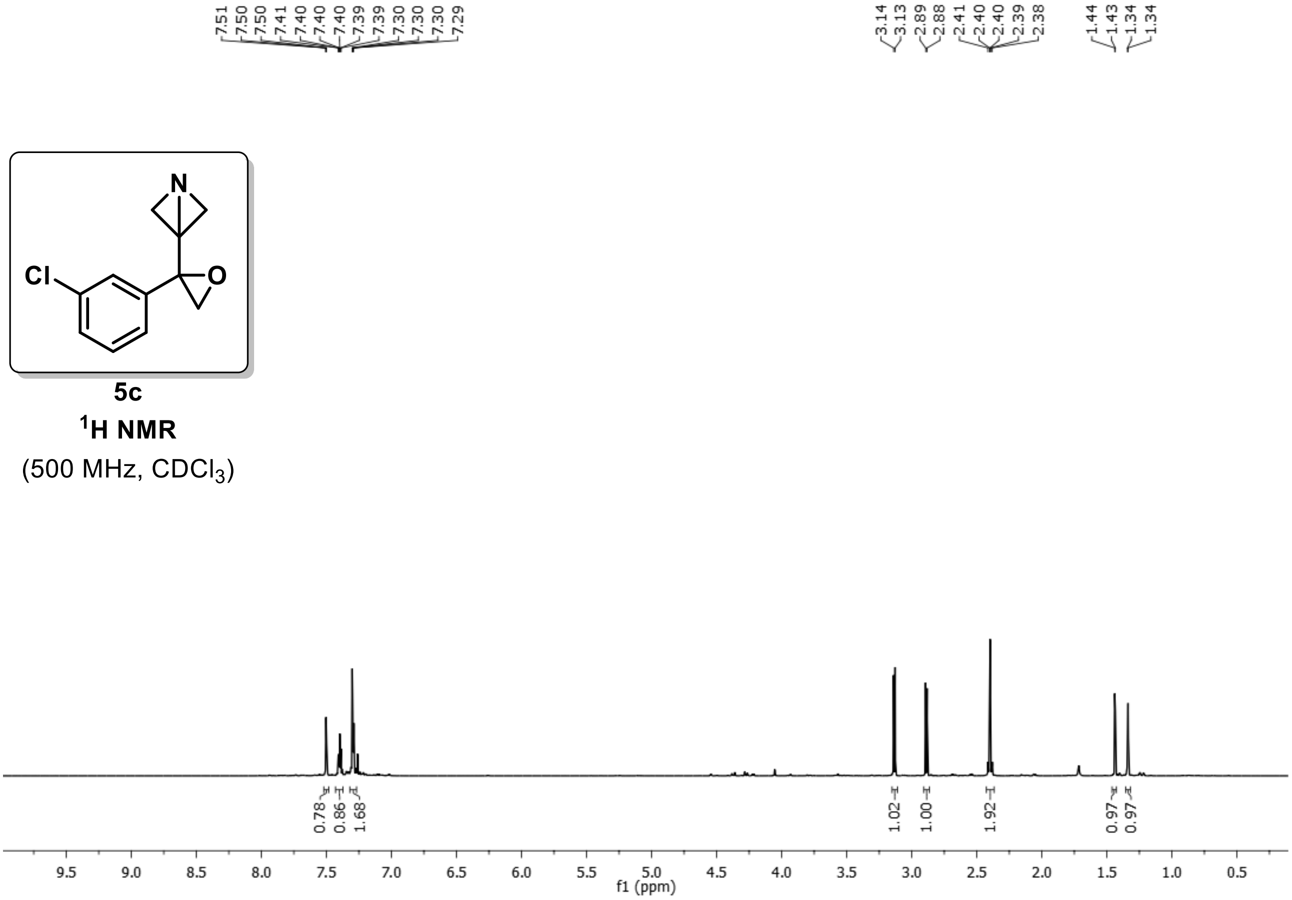


5b

^{13}C NMR

(126 MHz, $CDCl_3$)

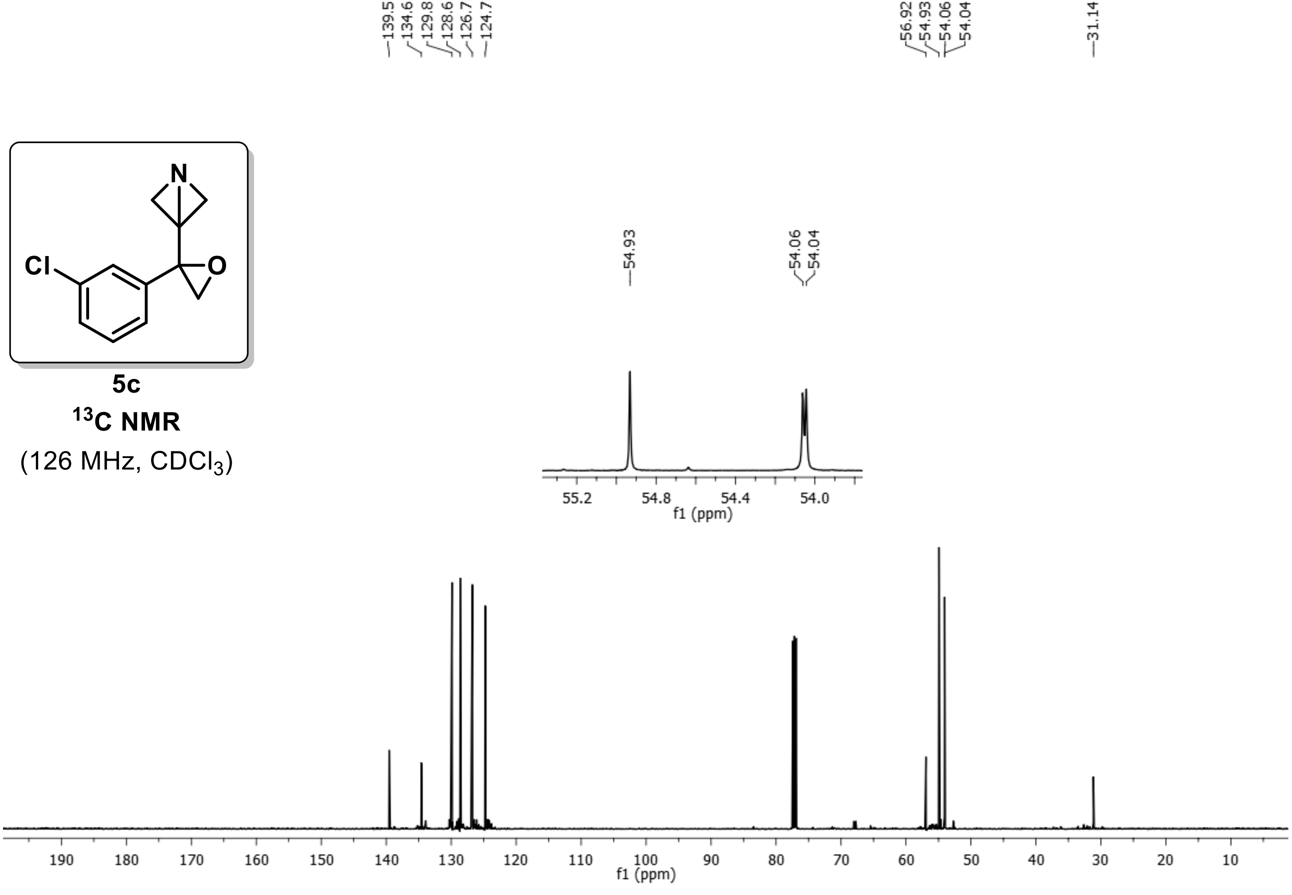
● residual solvent



5c

^{1}H NMR

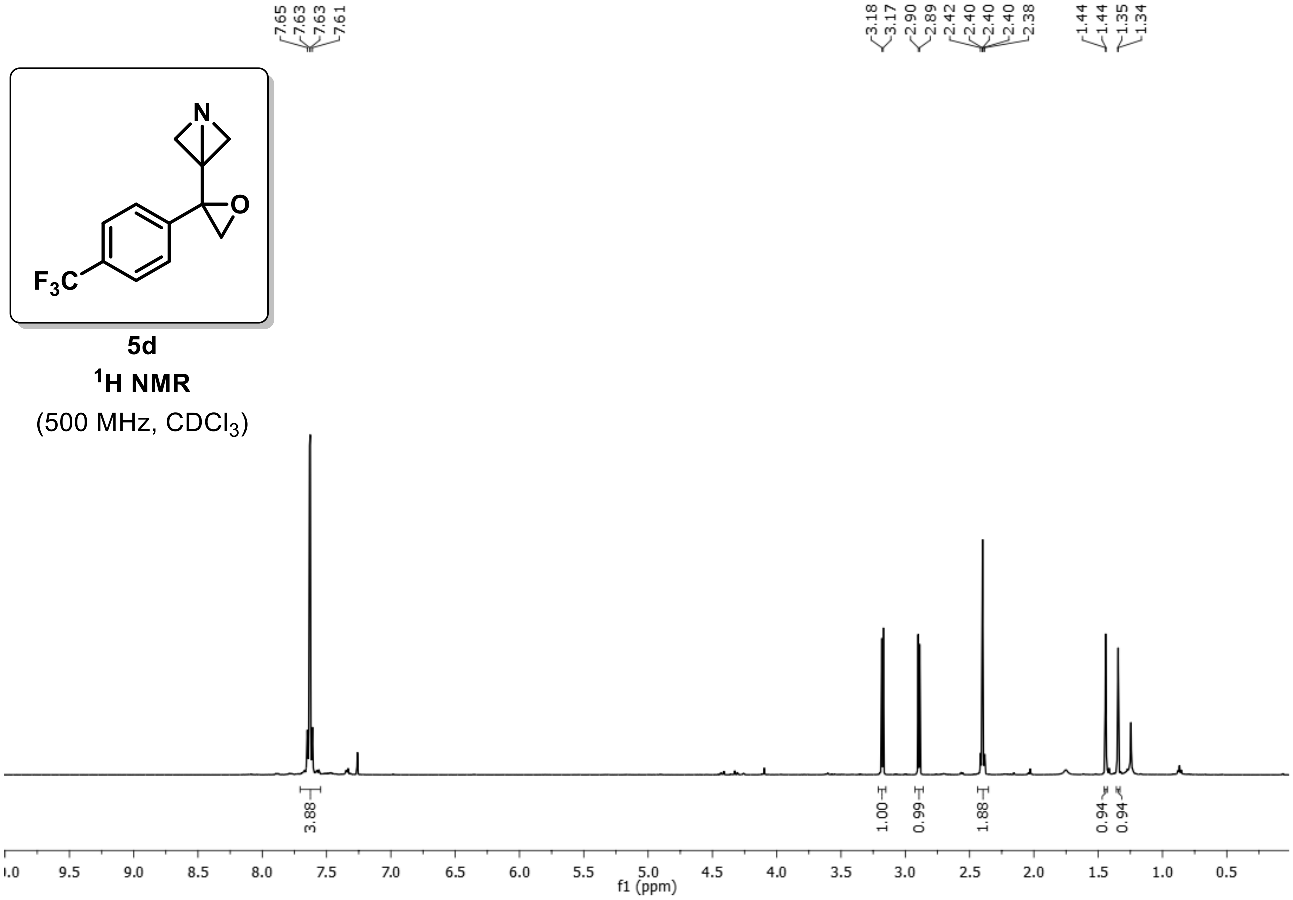
(500 MHz, $CDCl_3$)



5c

^{13}C NMR

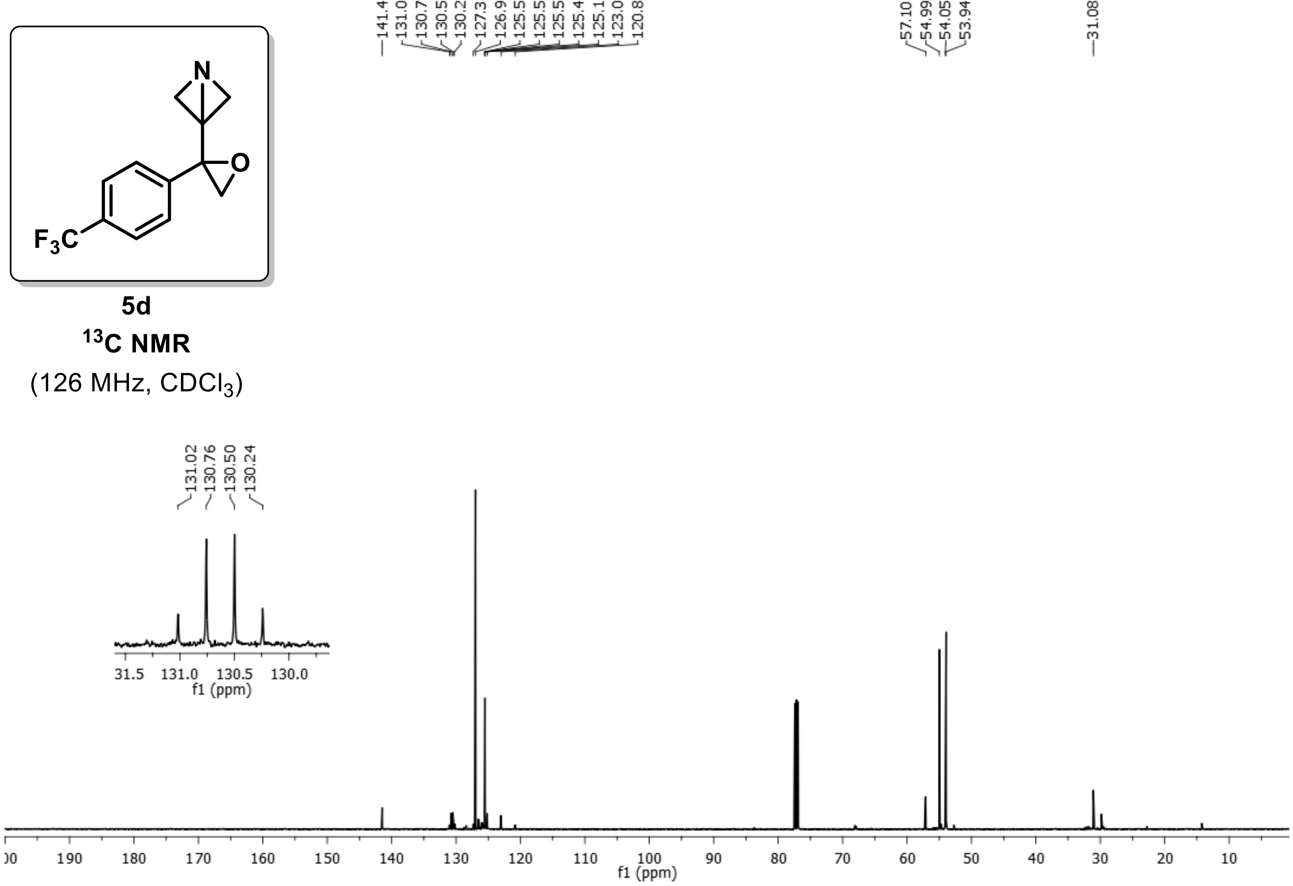
(126 MHz, $CDCl_3$)



5d

^{1}H NMR

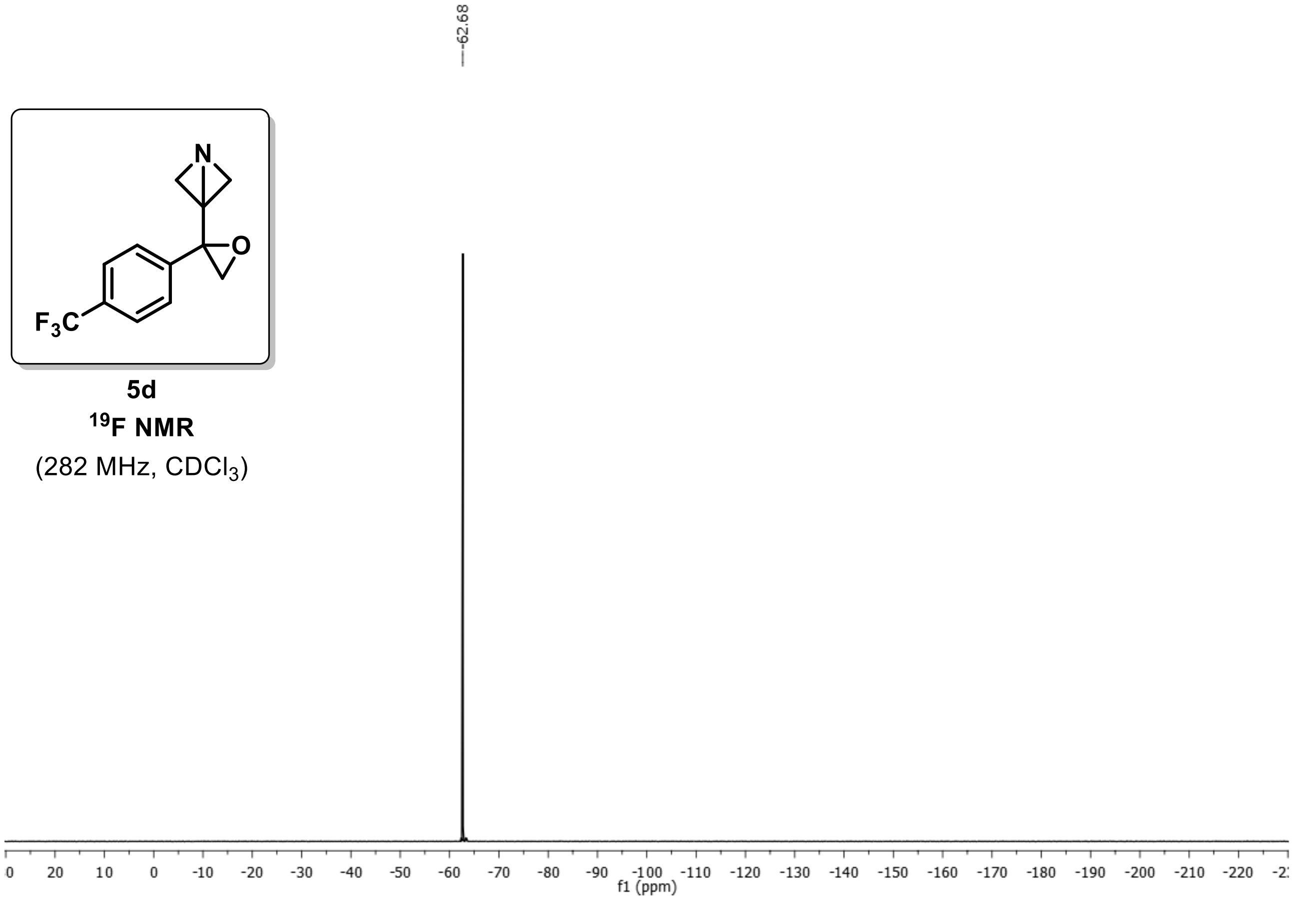
(500 MHz, CDCl$_3$)



5d

^{13}C NMR

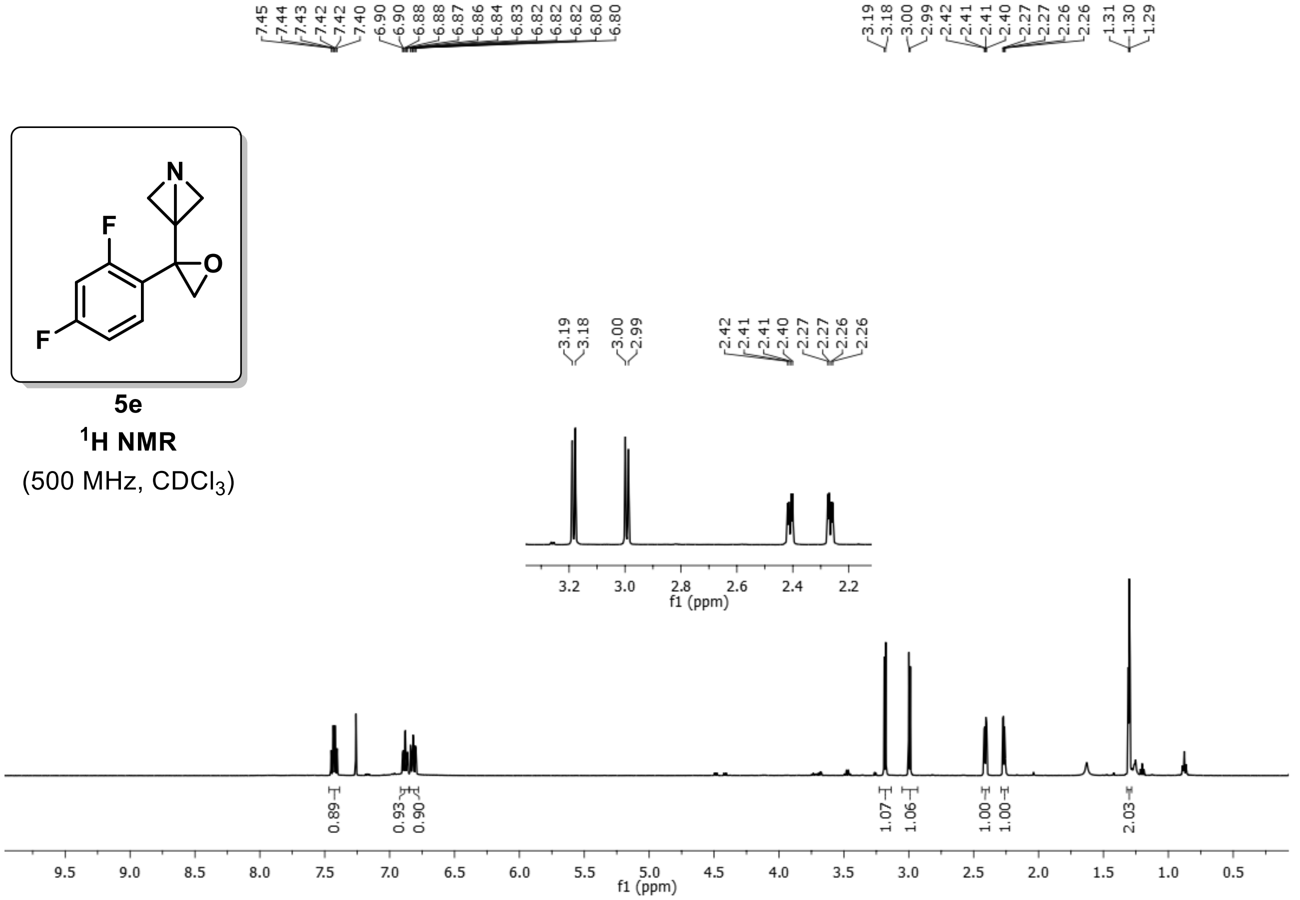
(126 MHz, CDCl$_3$)



5d

^{19}F NMR

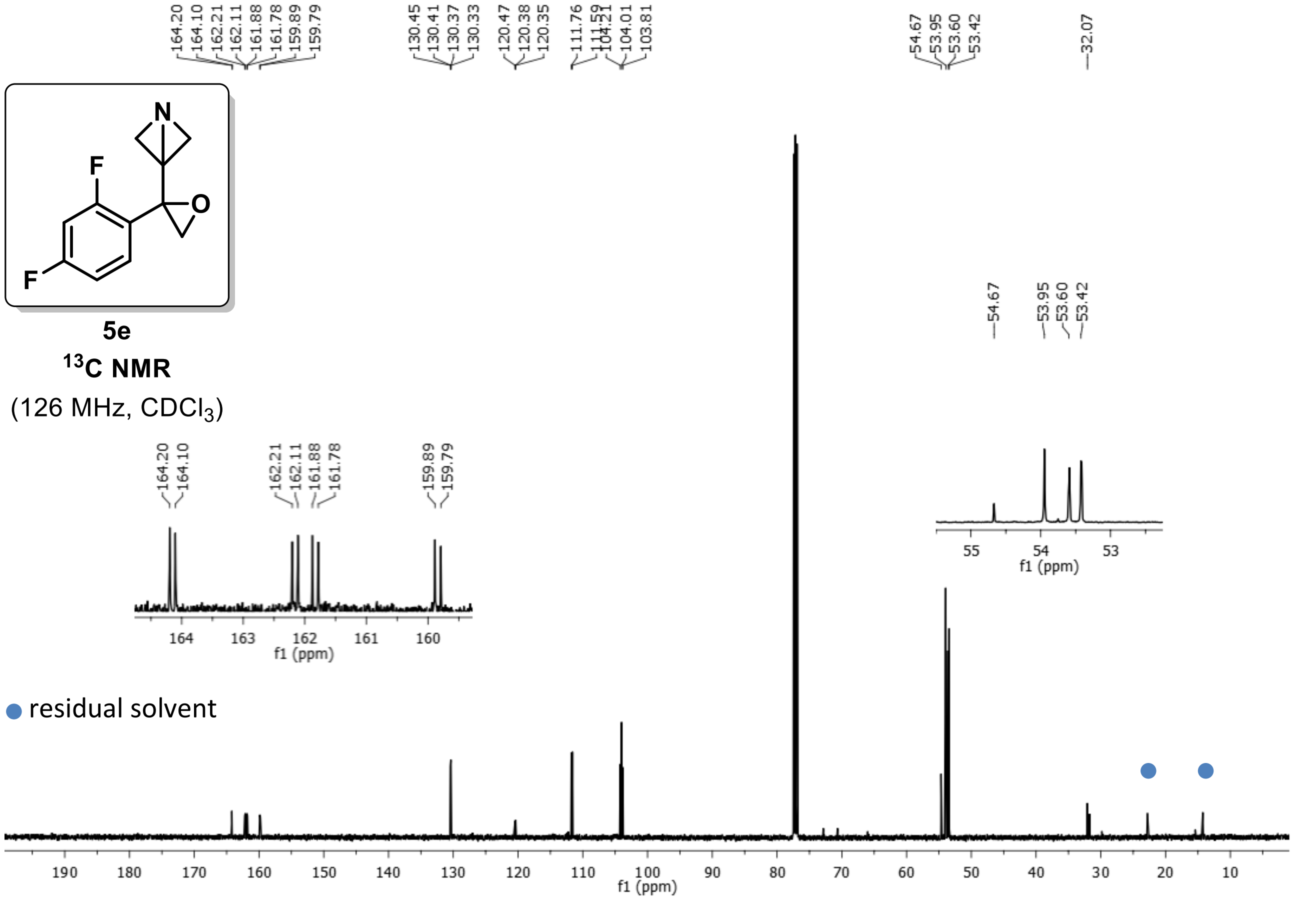
(282 MHz, $CDCl_3$)



5e

^{1}H NMR

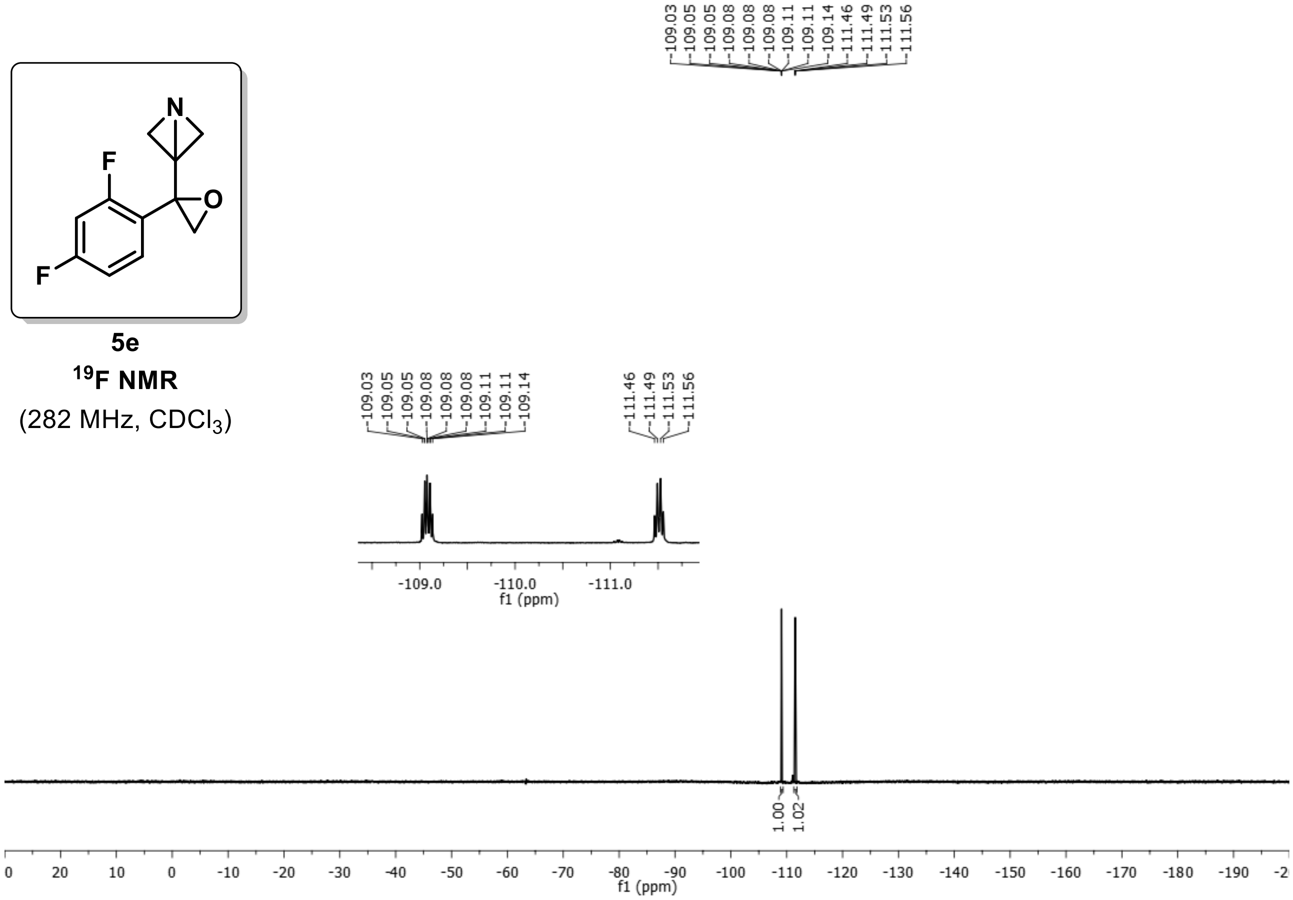
(500 MHz, $CDCl_3$)



5e

^{13}C NMR

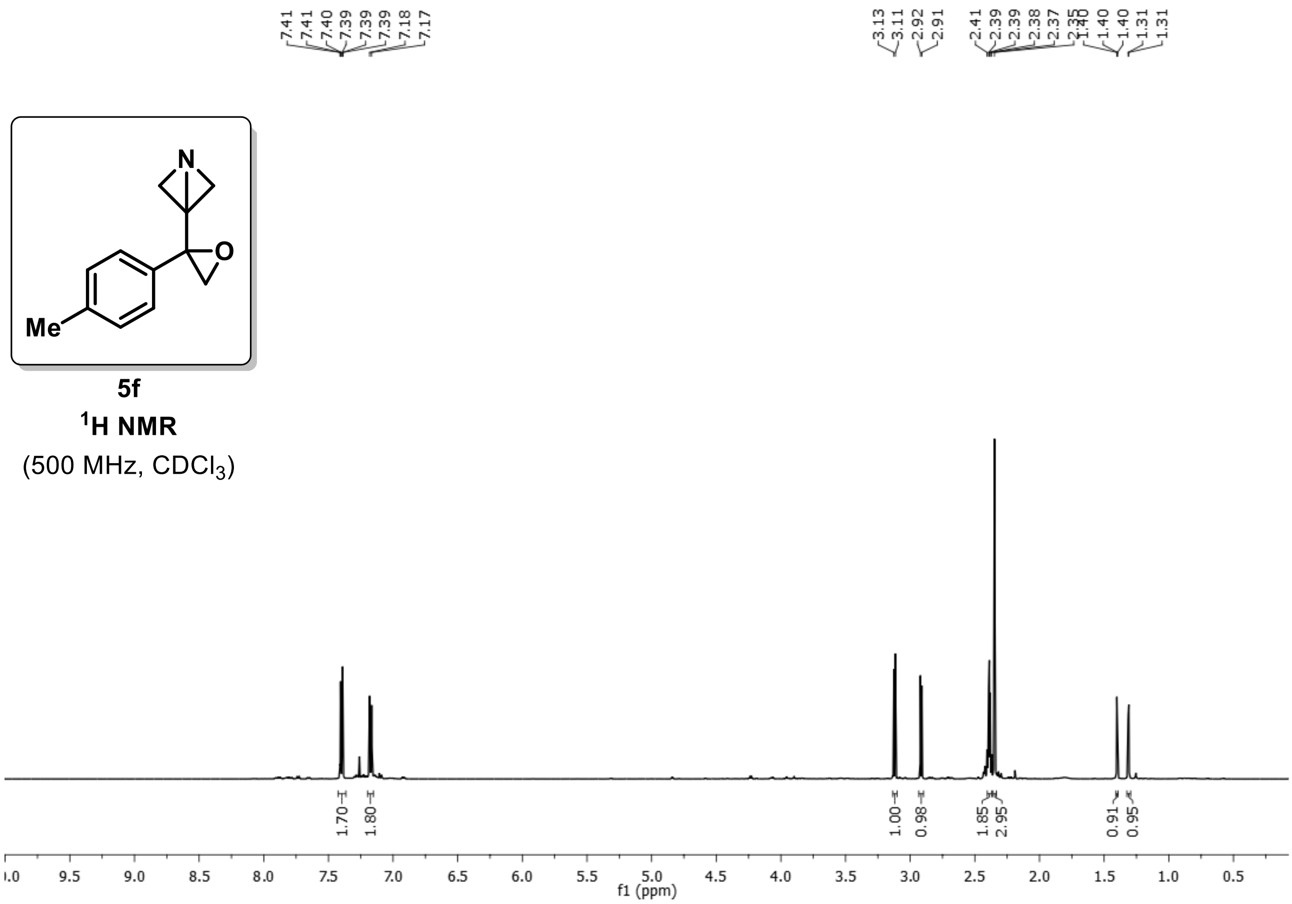
(126 MHz, $CDCl_3$)



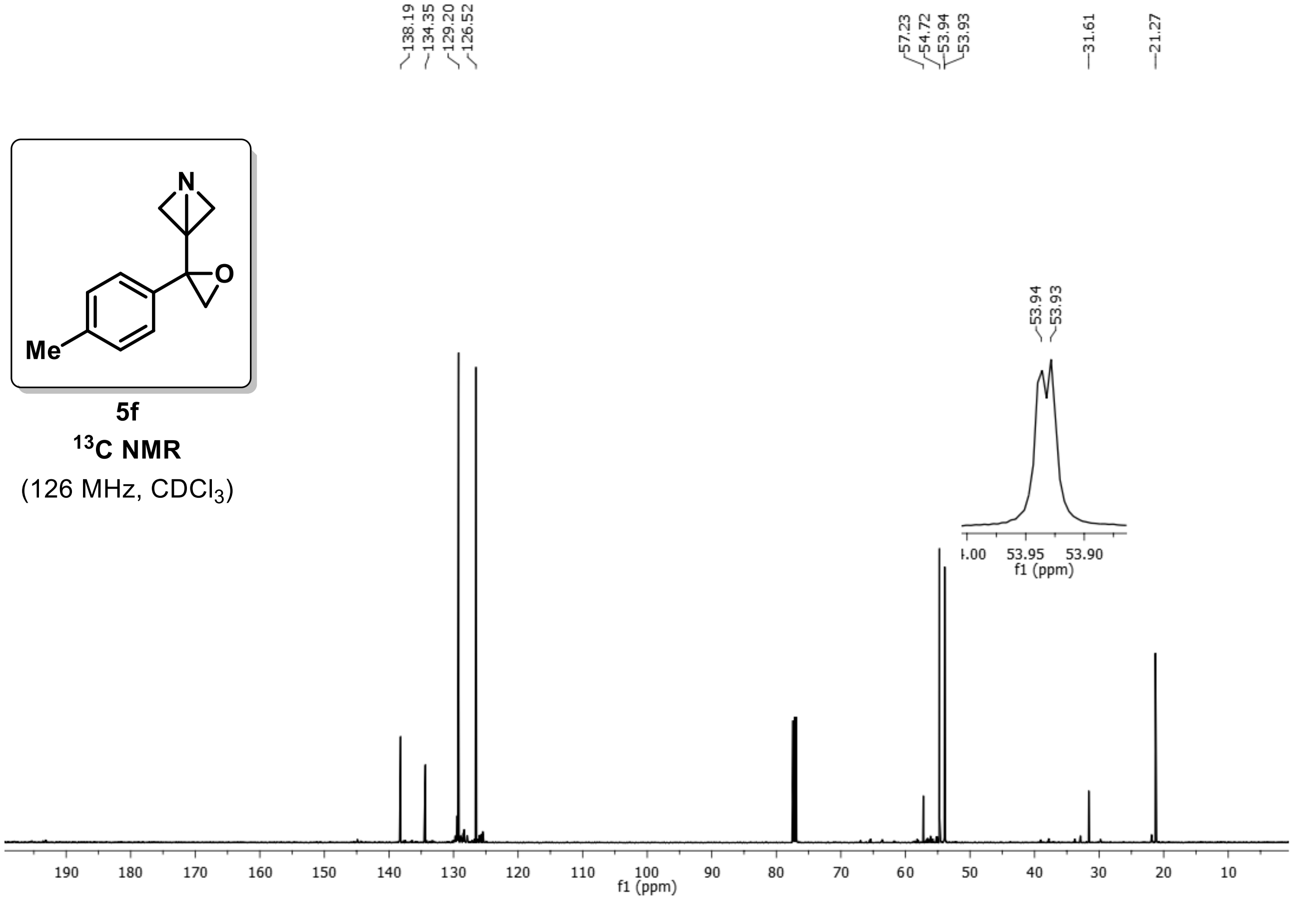
5e

^{19}F NMR

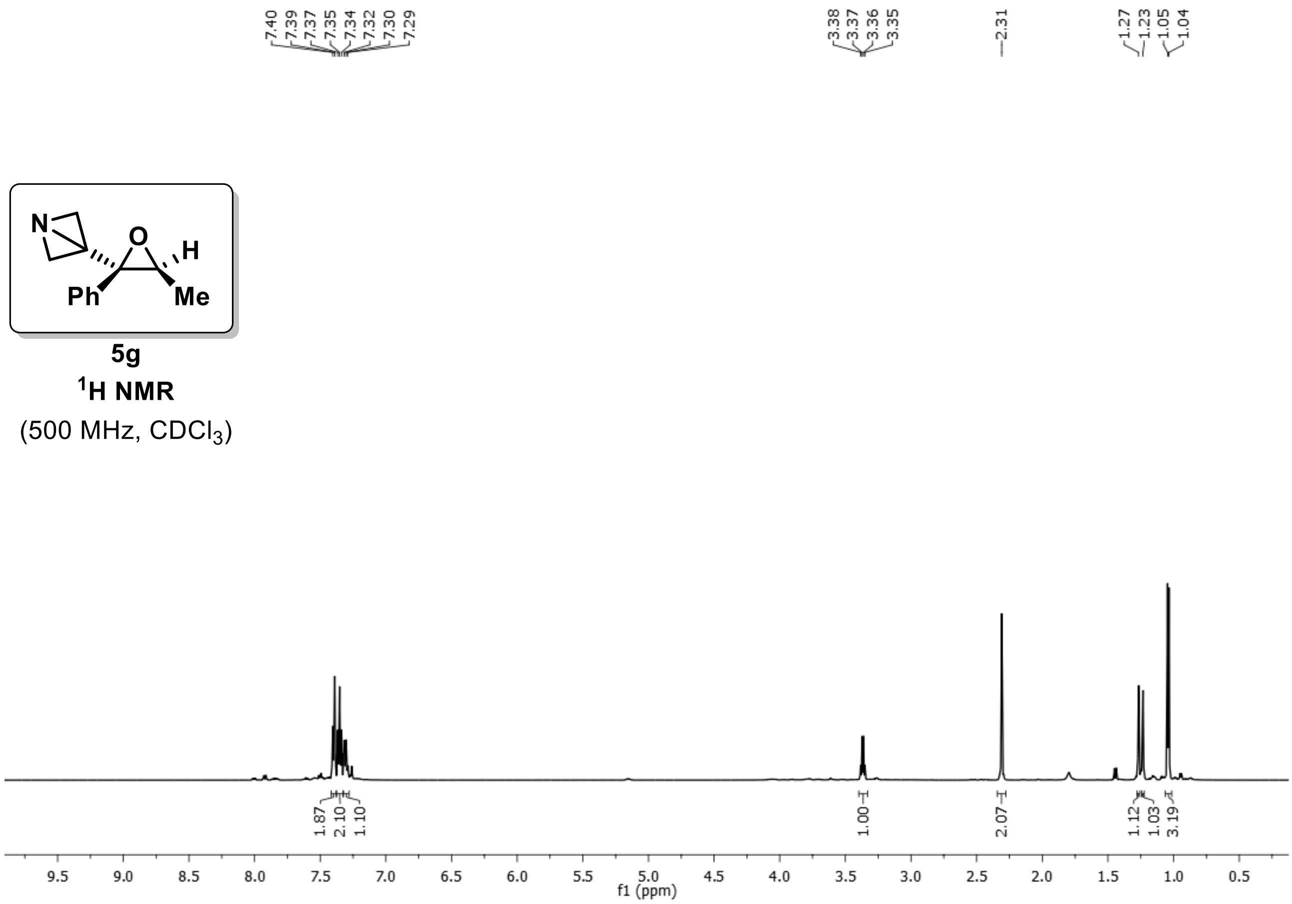
(282 MHz, $CDCl_3$)



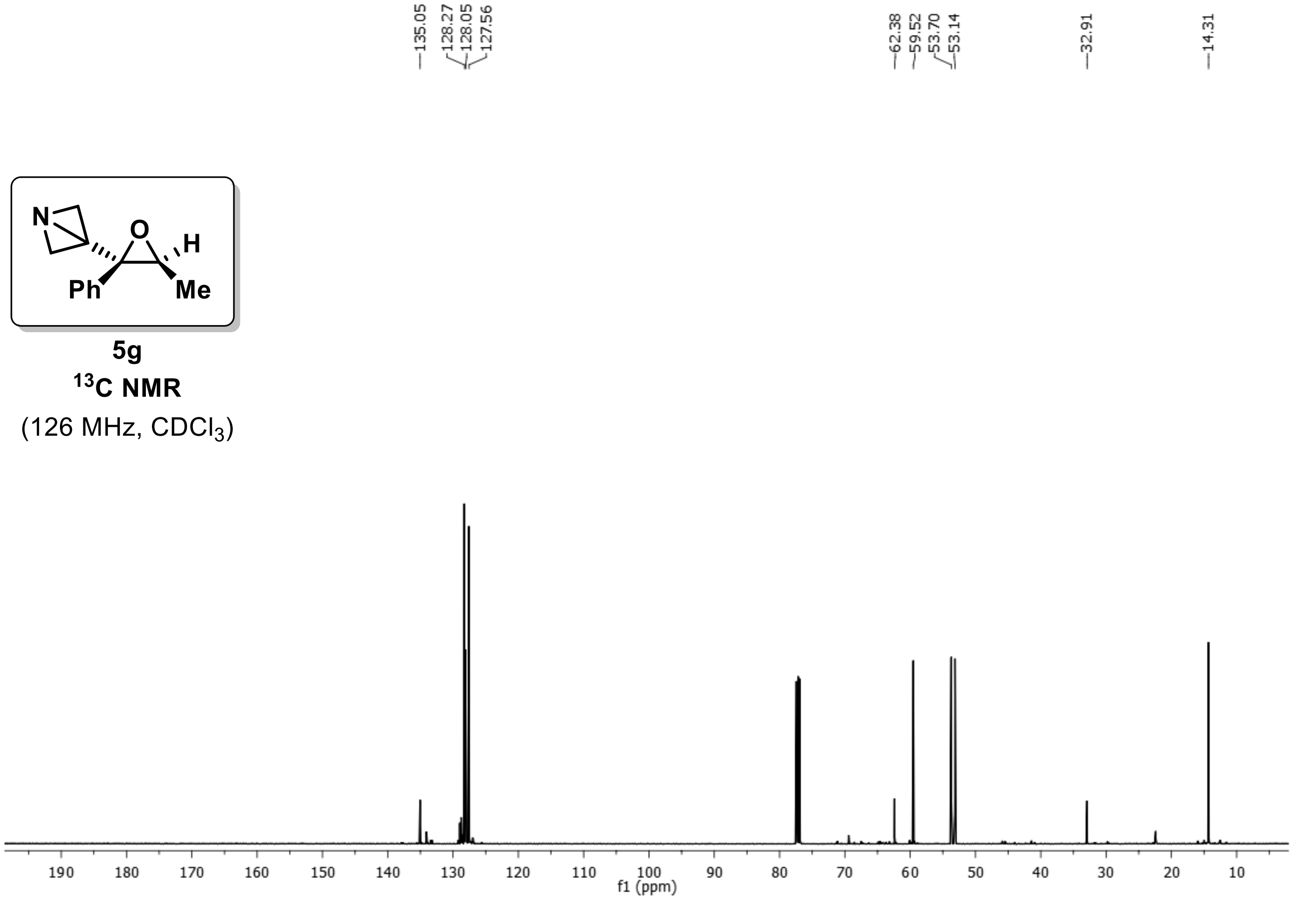
5f
^{1}H NMR
(500 MHz, $CDCl_3$)



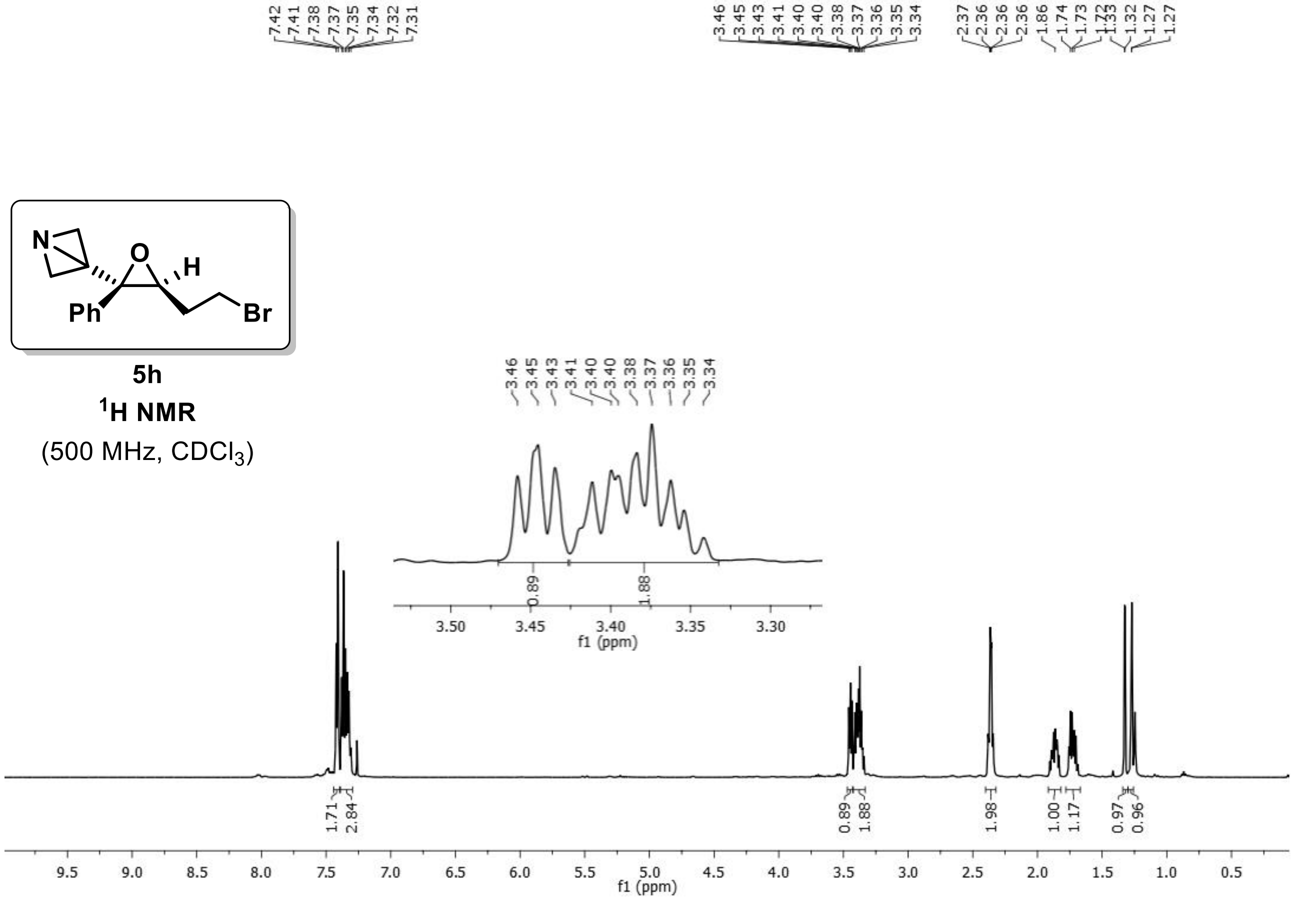
5f
^{13}C NMR
(126 MHz, $CDCl_3$)



5g
^{1}H NMR
(500 MHz, CDCl$_3$)



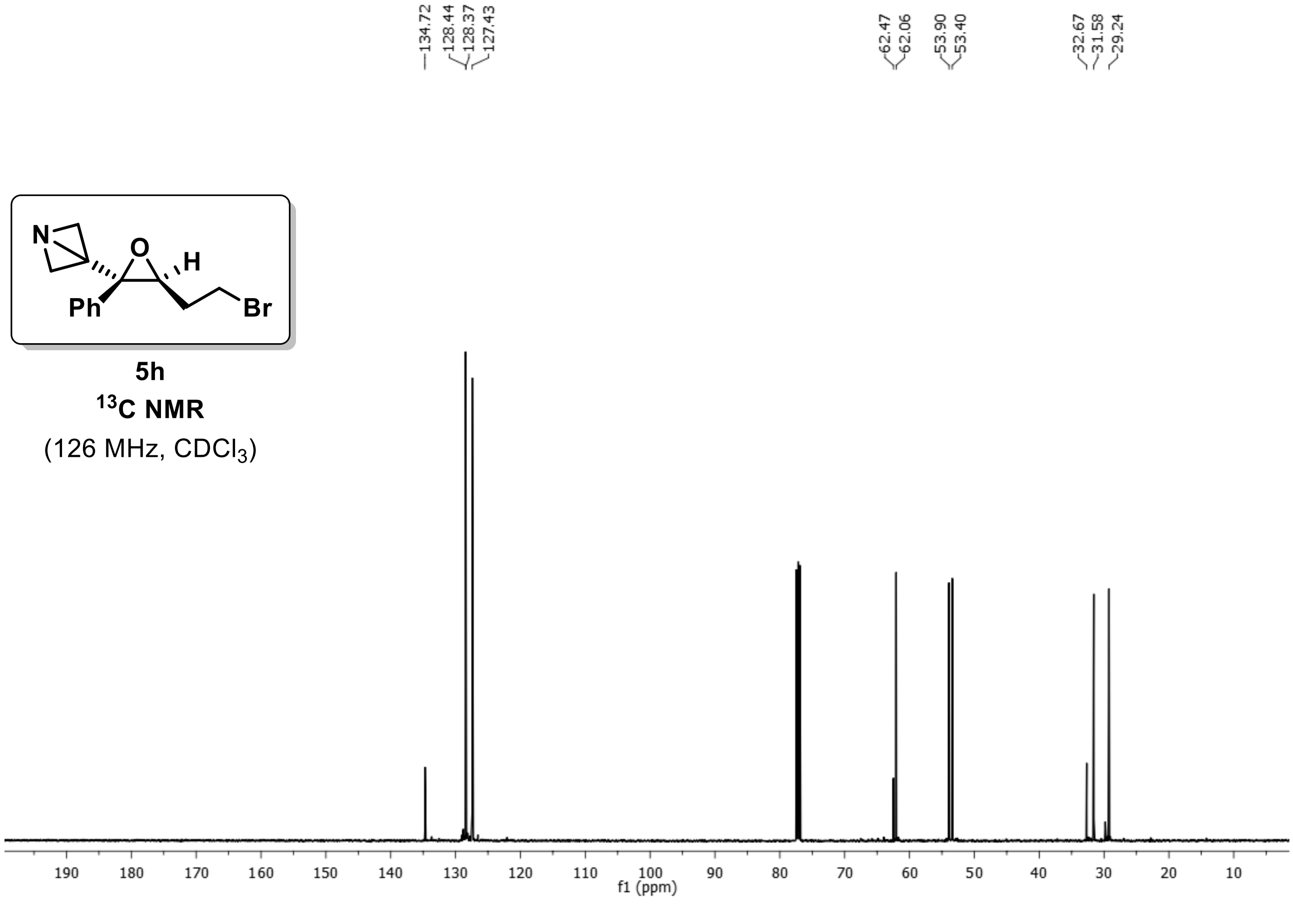
5g
^{13}C NMR
(126 MHz, CDCl$_3$)



5h

^{1}H NMR

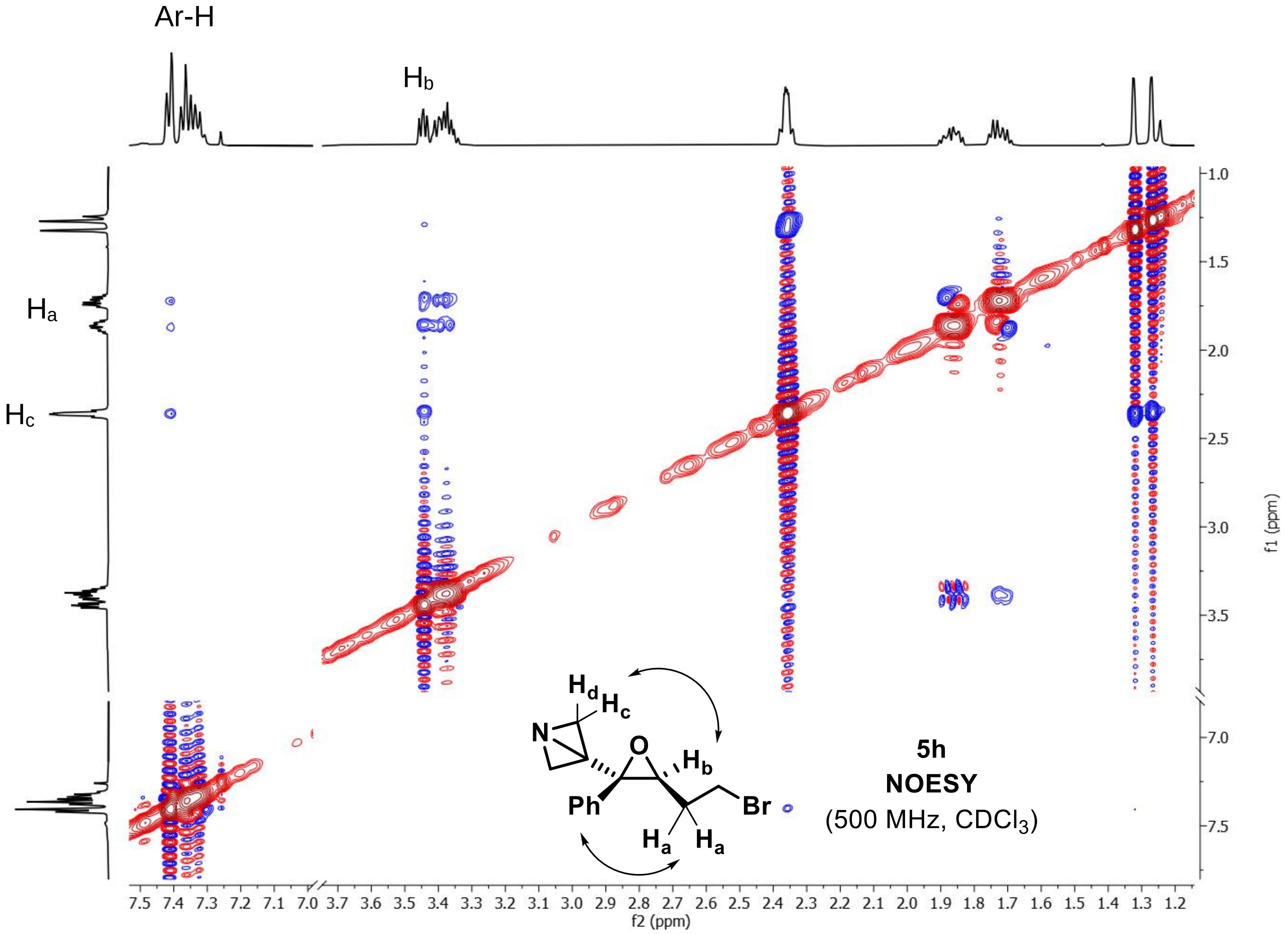
(500 MHz, CDCl$_3$)



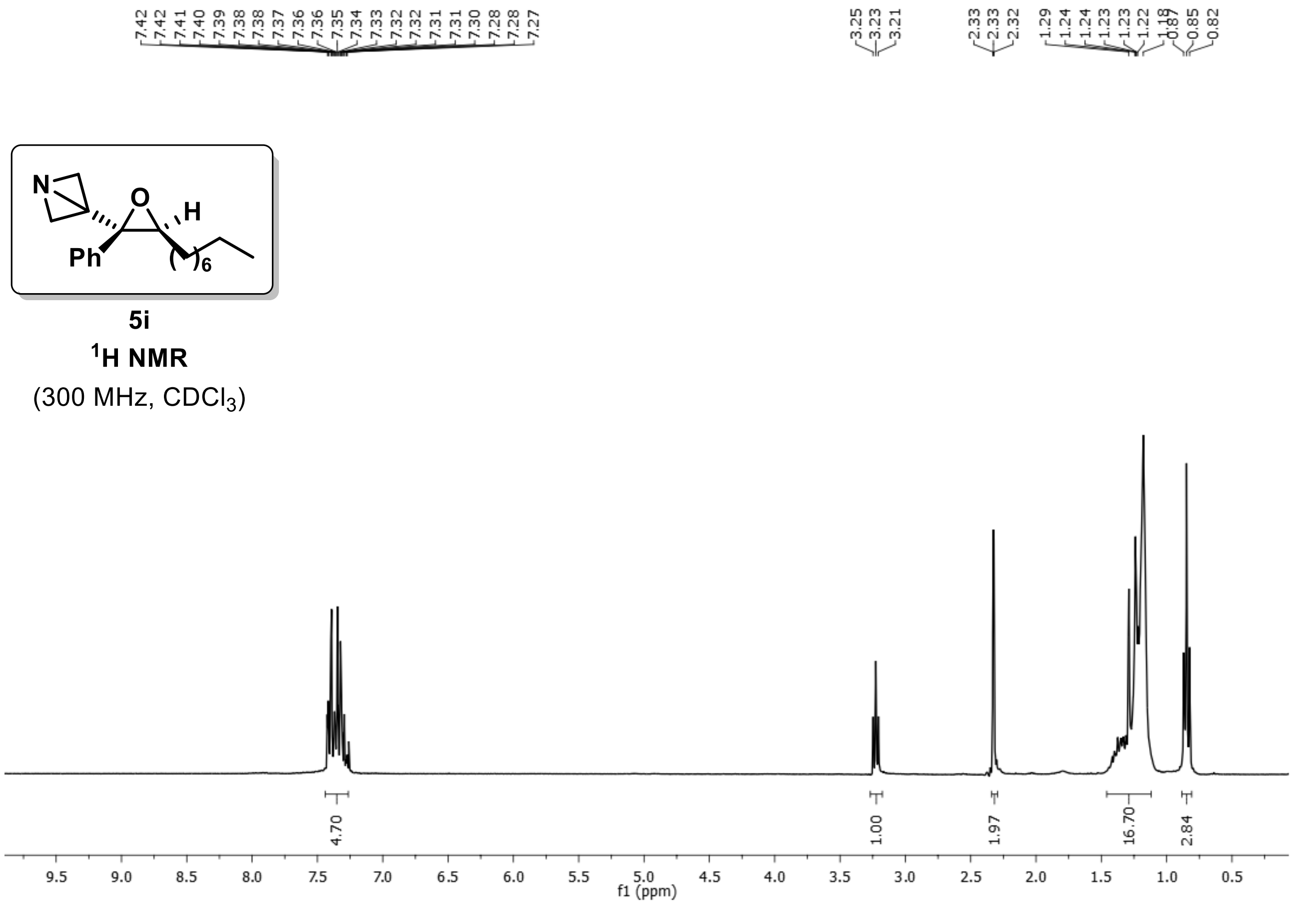
5h

^{13}C NMR

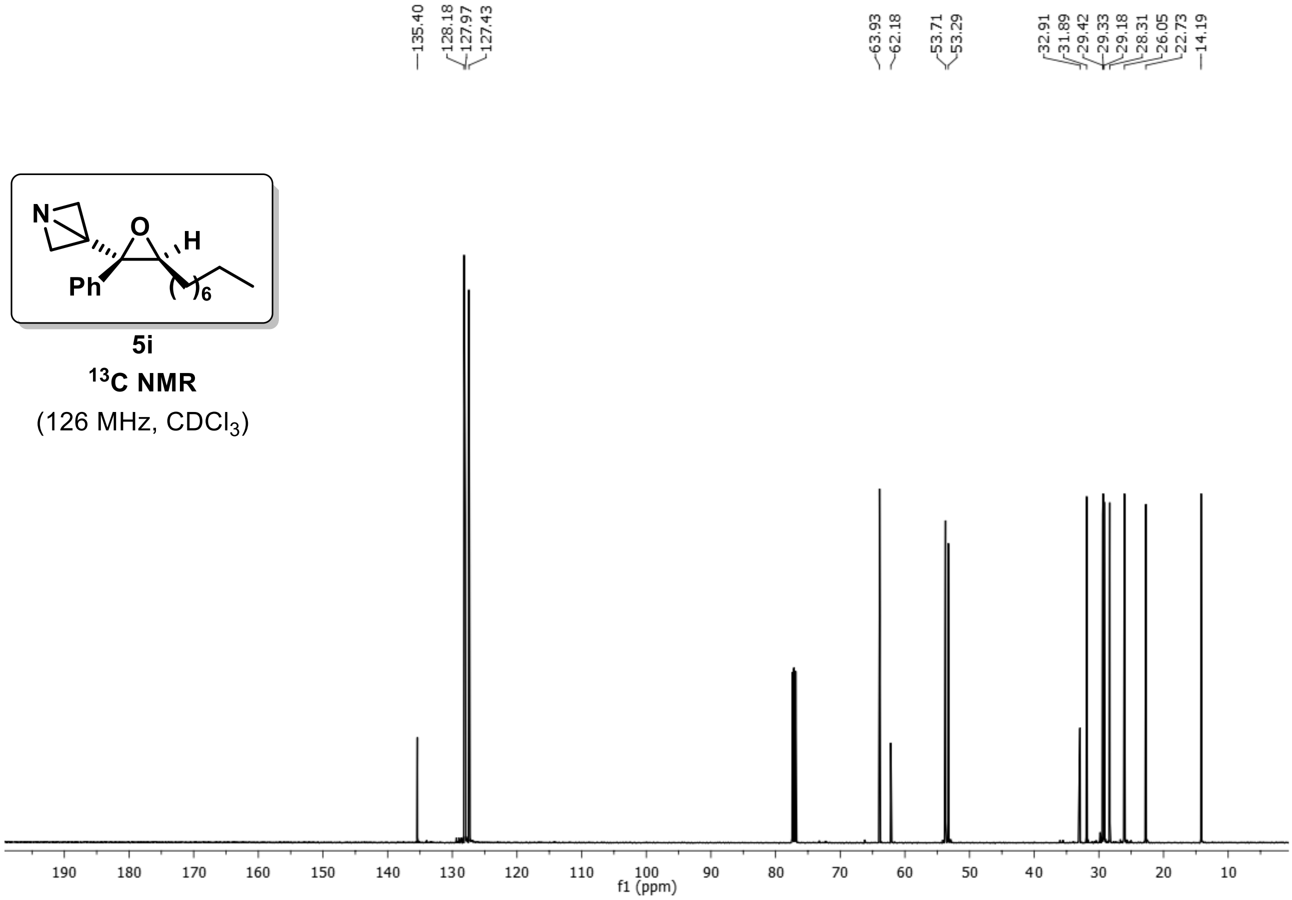
(126 MHz, CDCl$_3$)

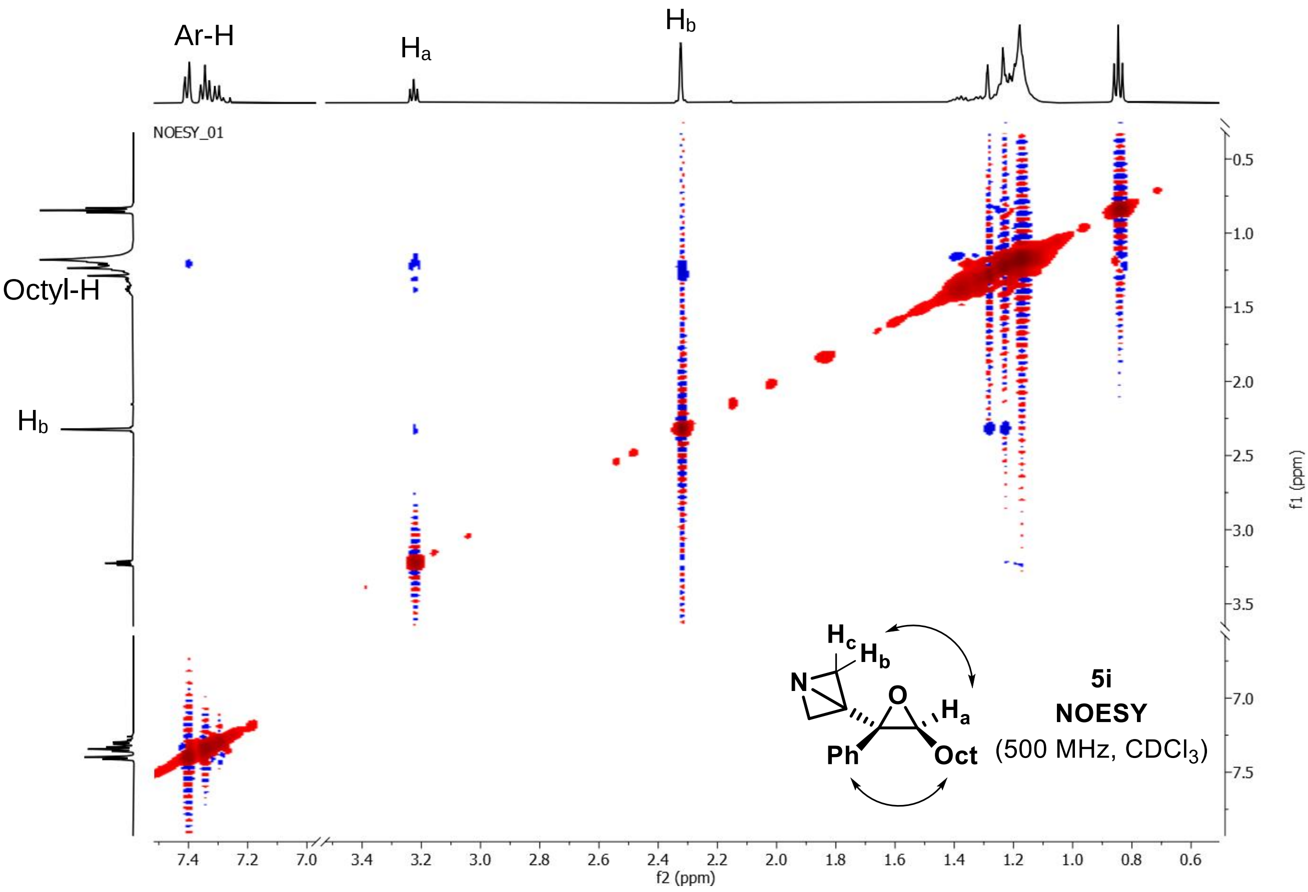


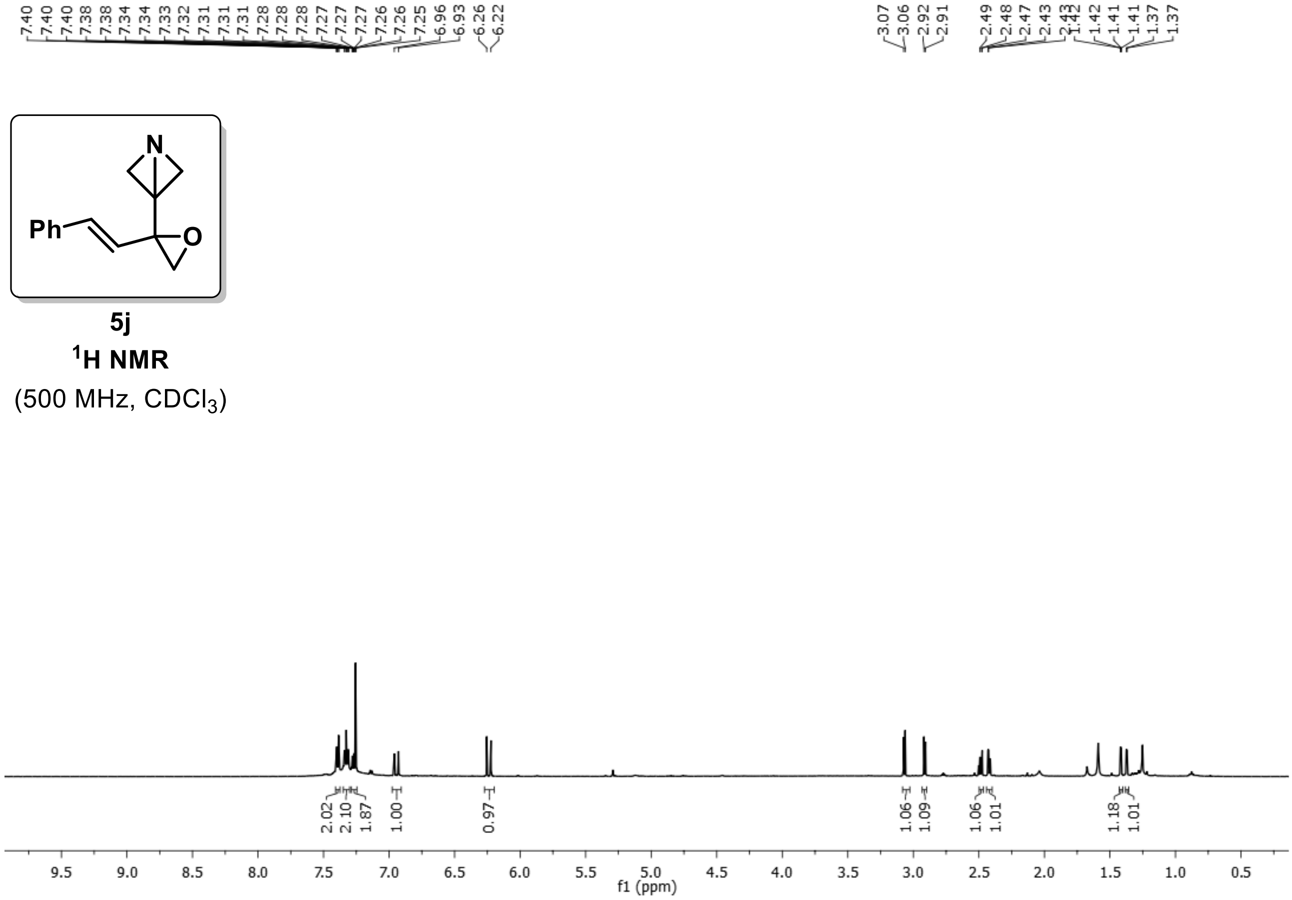
5h
NOESY
(500 MHz, $CDCl_3$)



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


135.40
128.18
127.97
127.43
63.93
62.18
53.71
53.29
32.91
31.89
29.42
29.33
29.18
28.31
26.05
22.73
14.19
N
O
H
Ph
6
5i
^{13}C NMR
(126 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

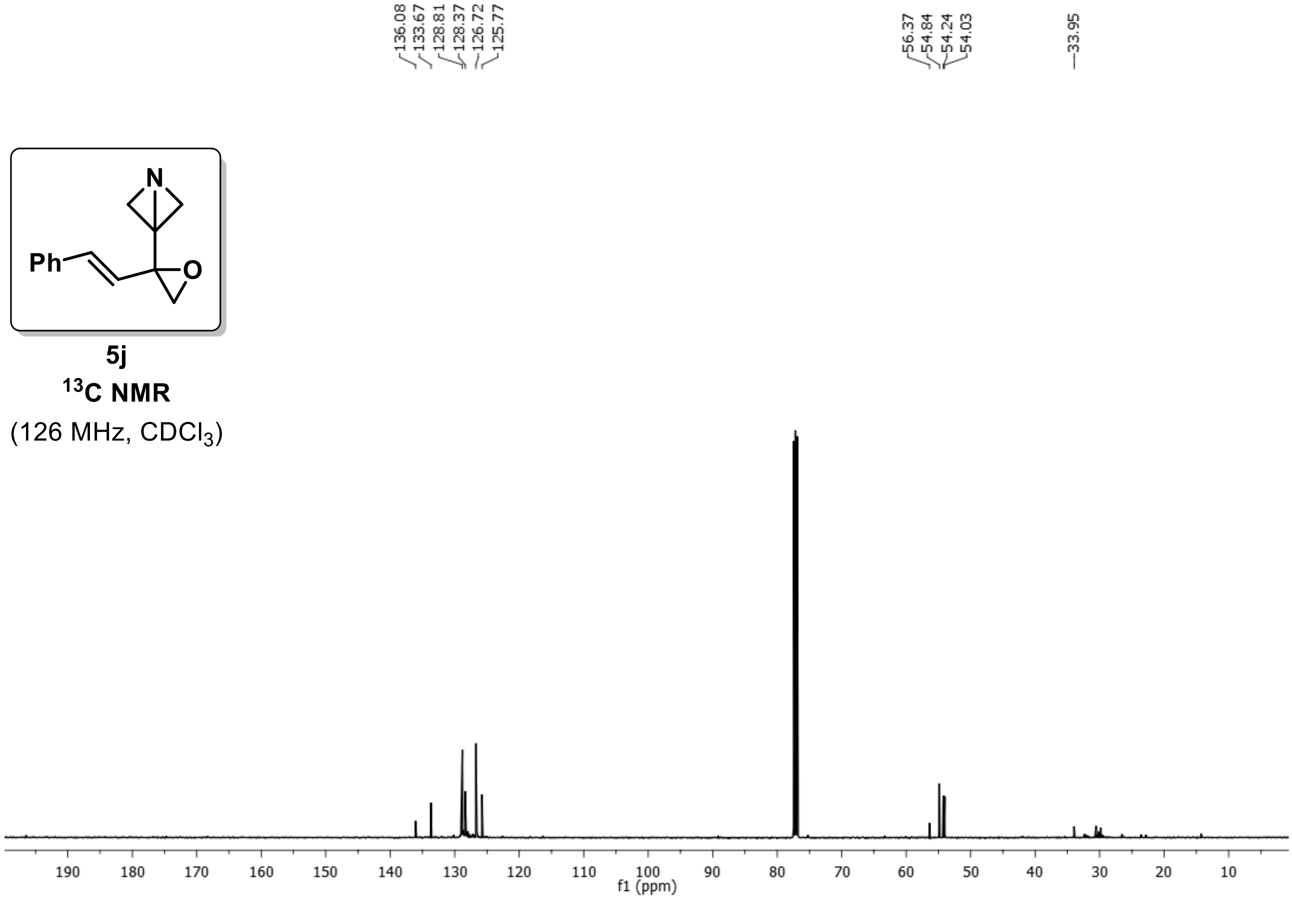

Ar-H
H$_a$
H$_b$
NOESY_01
Octyl-H
H$_b$
H$_c$
H$_b$
N
O
H$_a$
Ph
Oct
5i
NOESY
(500 MHz, CDCl$_3$)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
7.0
7.5
f1 (ppm)
7.4
7.2
7.0
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f2 (ppm)



5j

^{1}H NMR

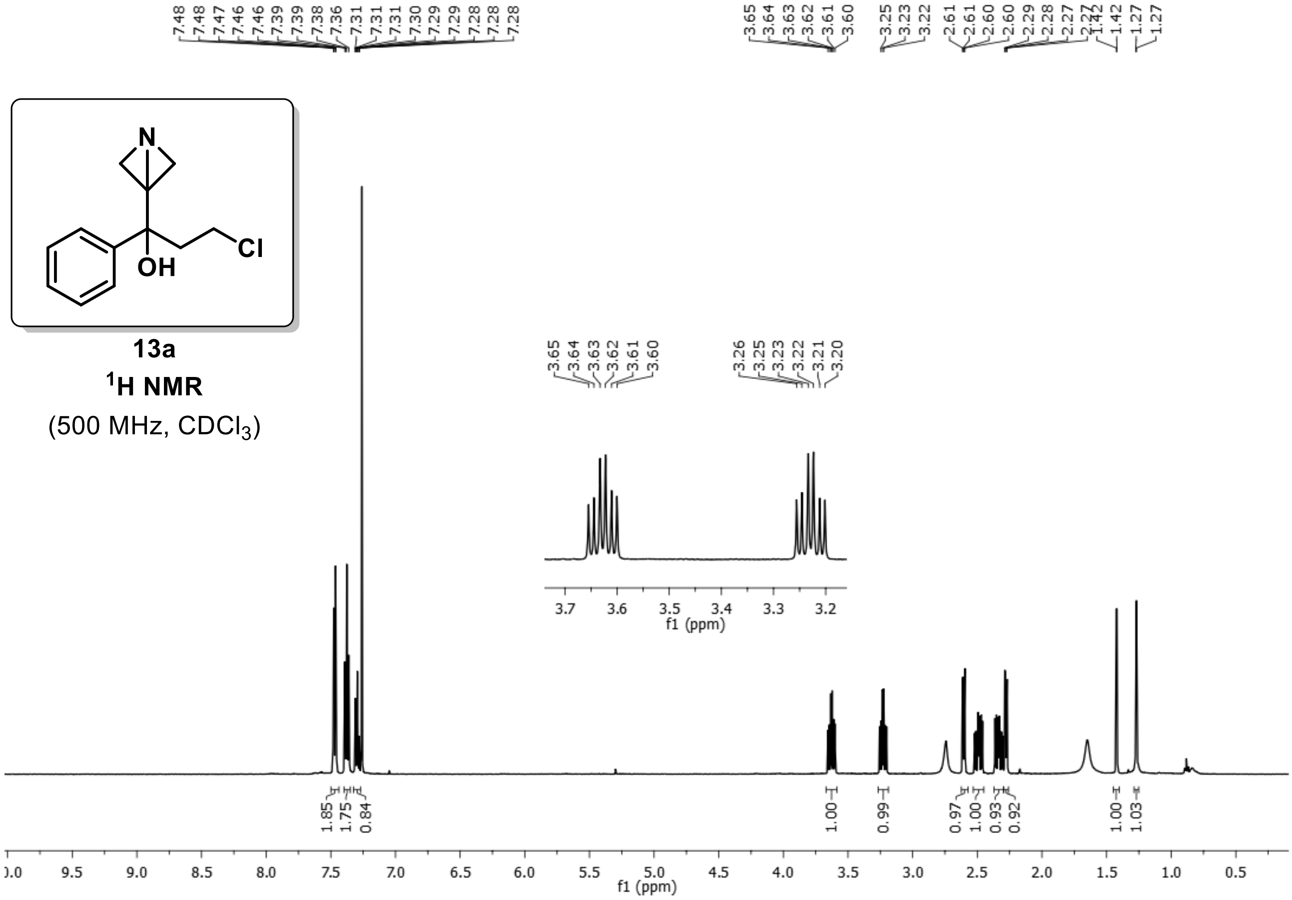
(500 MHz, $CDCl_3$)



5j

^{13}C NMR

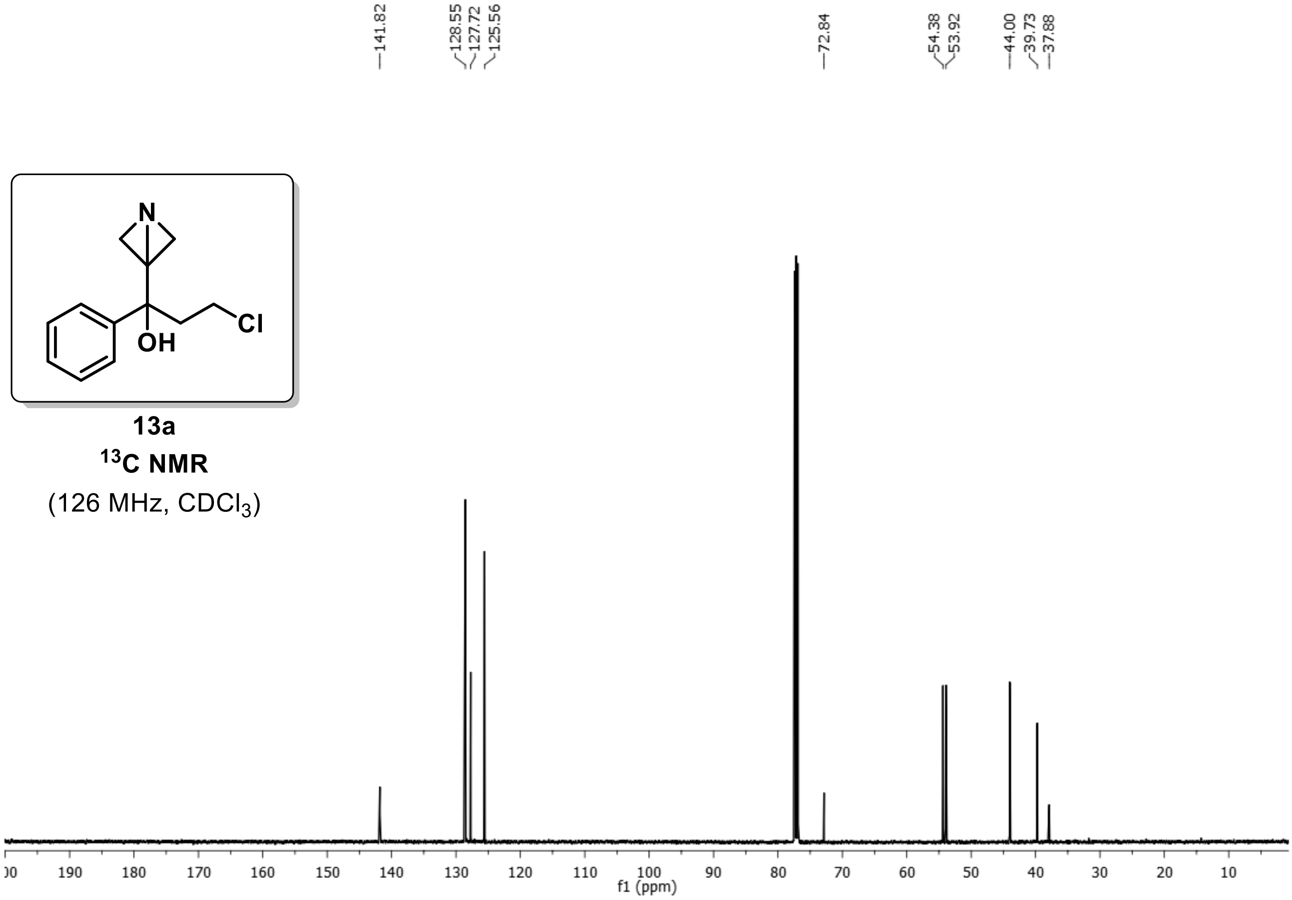
(126 MHz, $CDCl_3$)



13a

^{1}H NMR

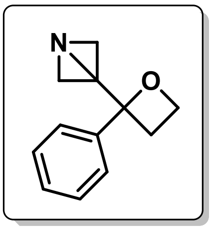
(500 MHz, CDCl$_3$)



13a

^{13}C NMR

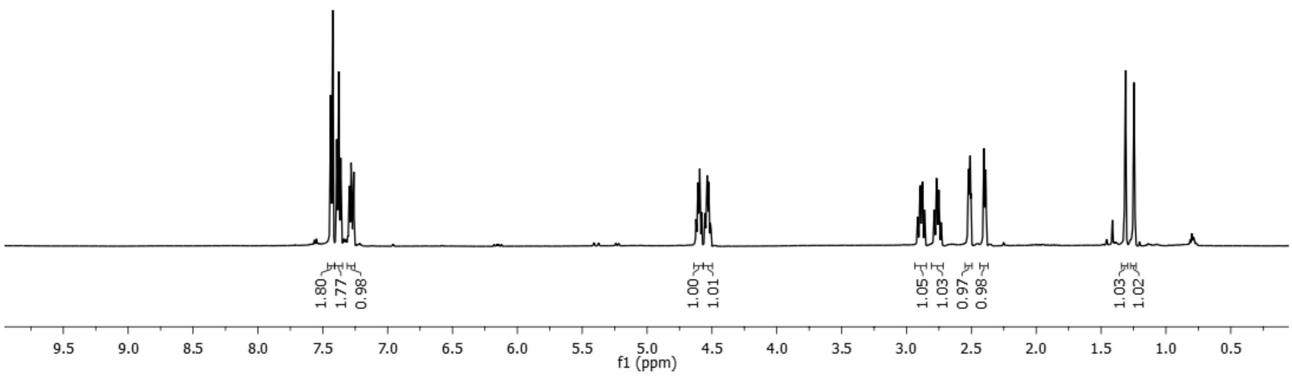
(126 MHz, CDCl$_3$)

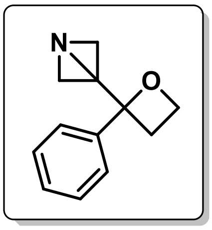


6a

^{1}H NMR

(500 MHz, $CDCl_3$)

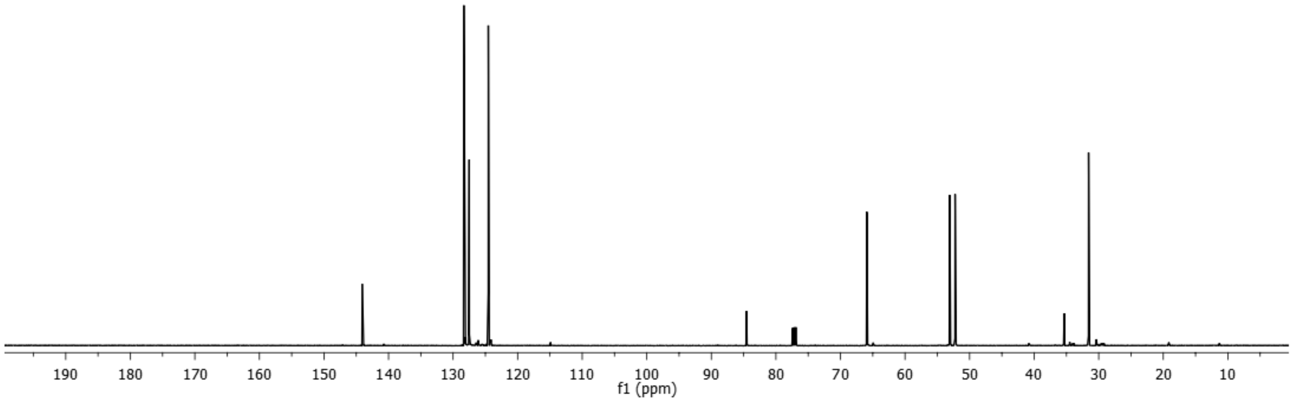


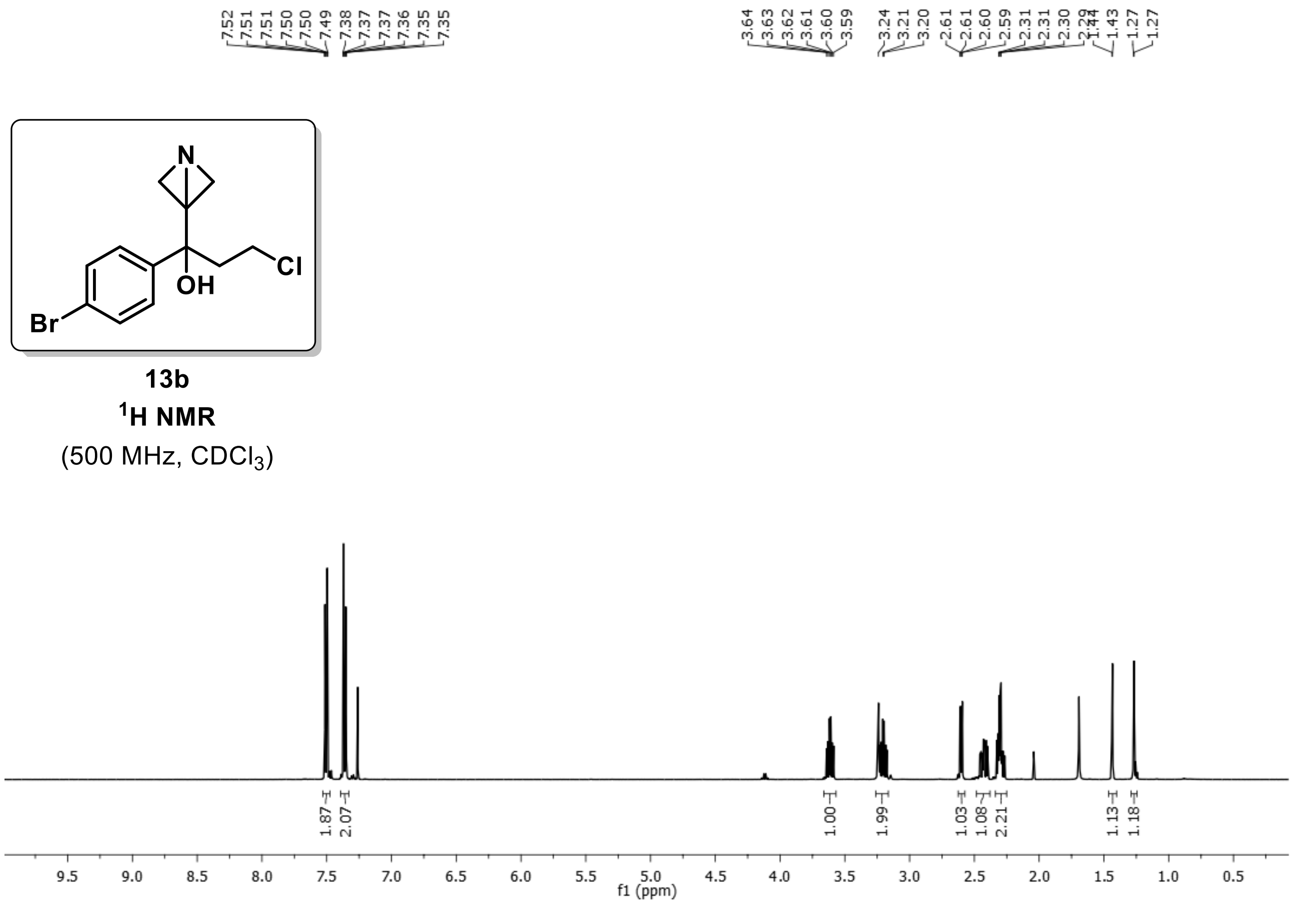


6a

^{13}C NMR

(126 MHz, $CDCl_3$)

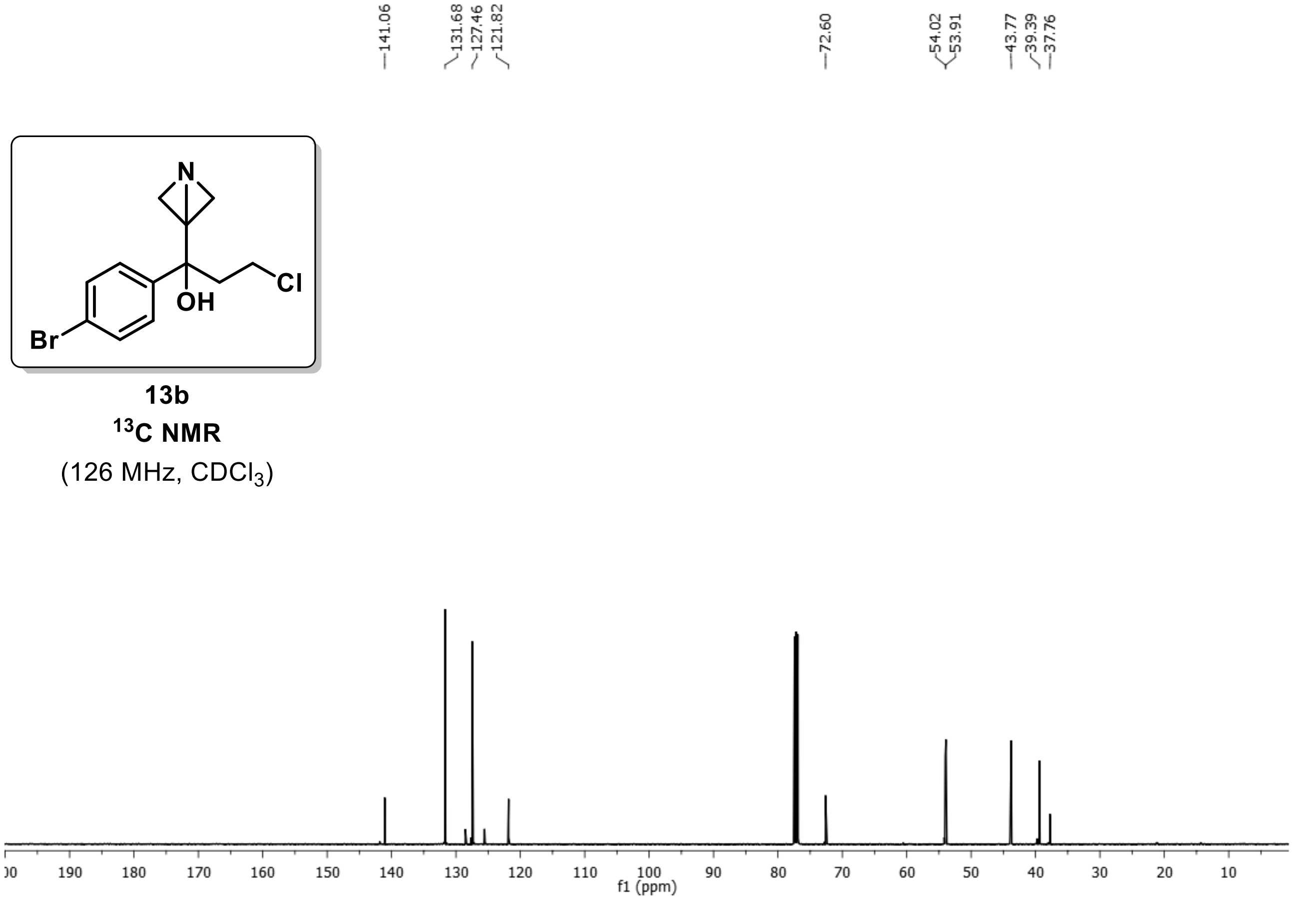




13b

^{1}H NMR

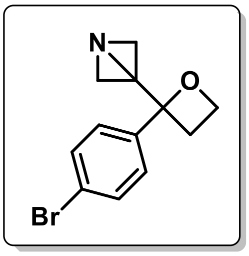
(500 MHz, $CDCl_3$)



13b

^{13}C NMR

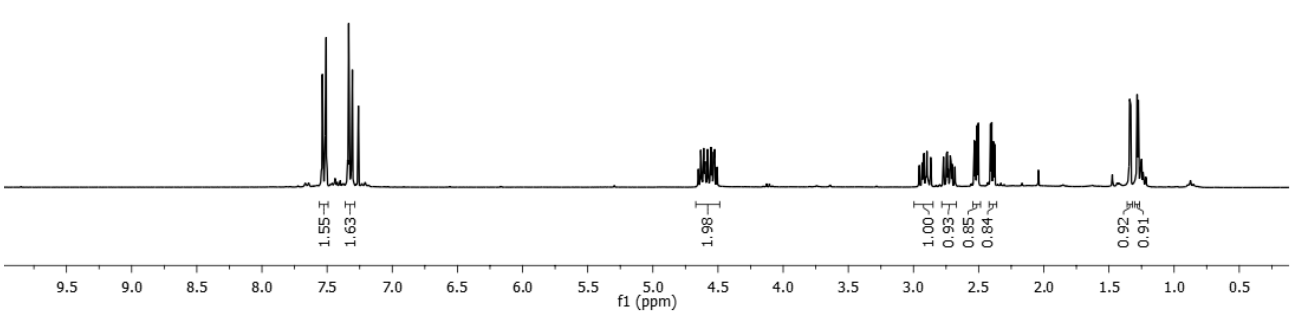
(126 MHz, $CDCl_3$)

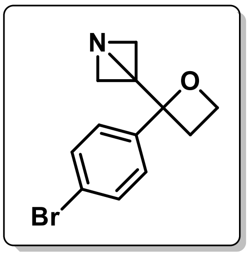


6b

^{1}H NMR

(500 MHz, $CDCl_3$)

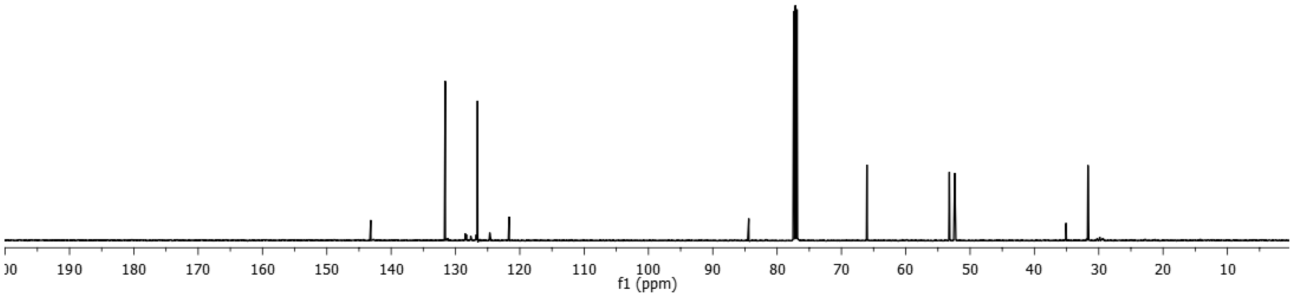


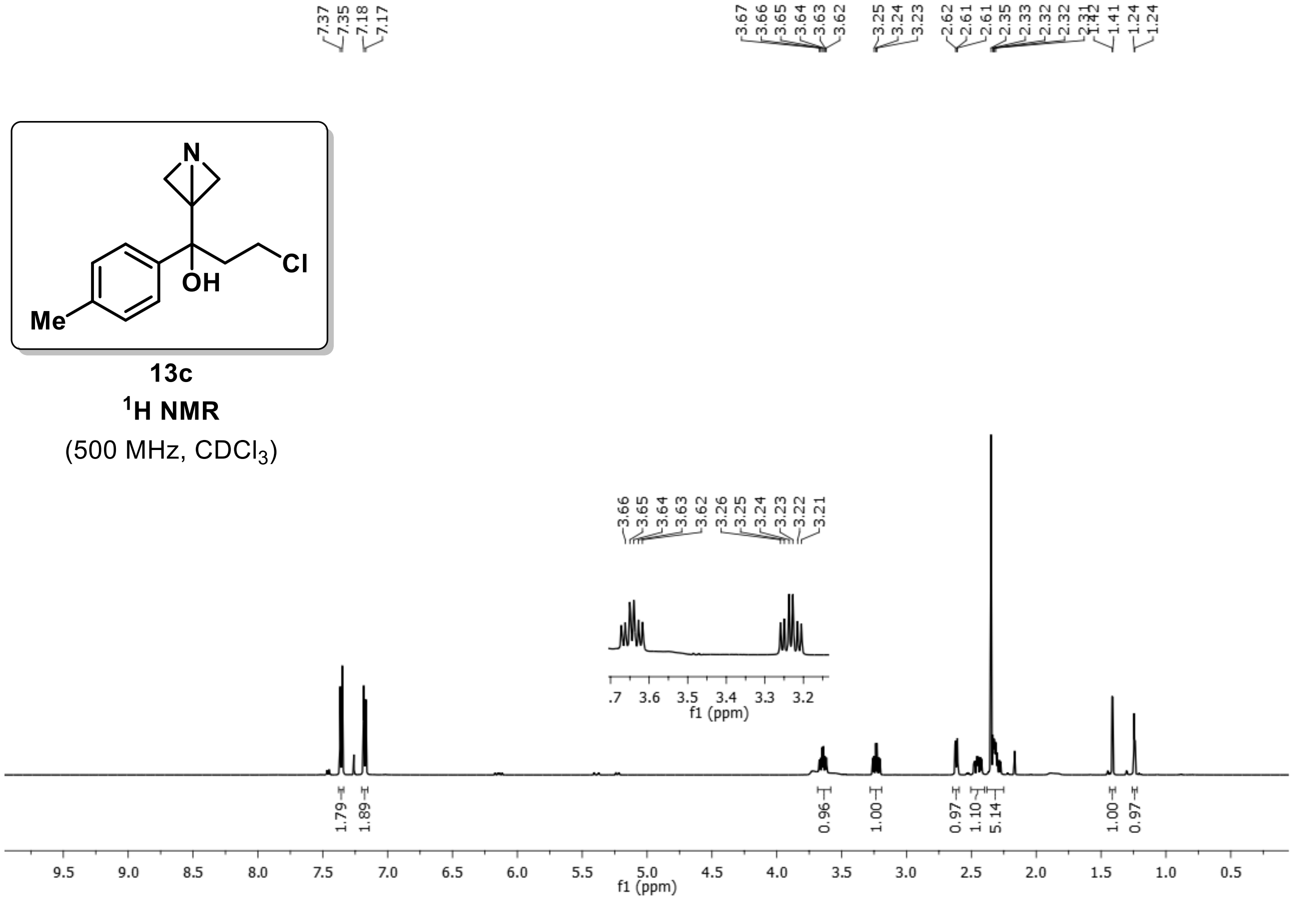


6b

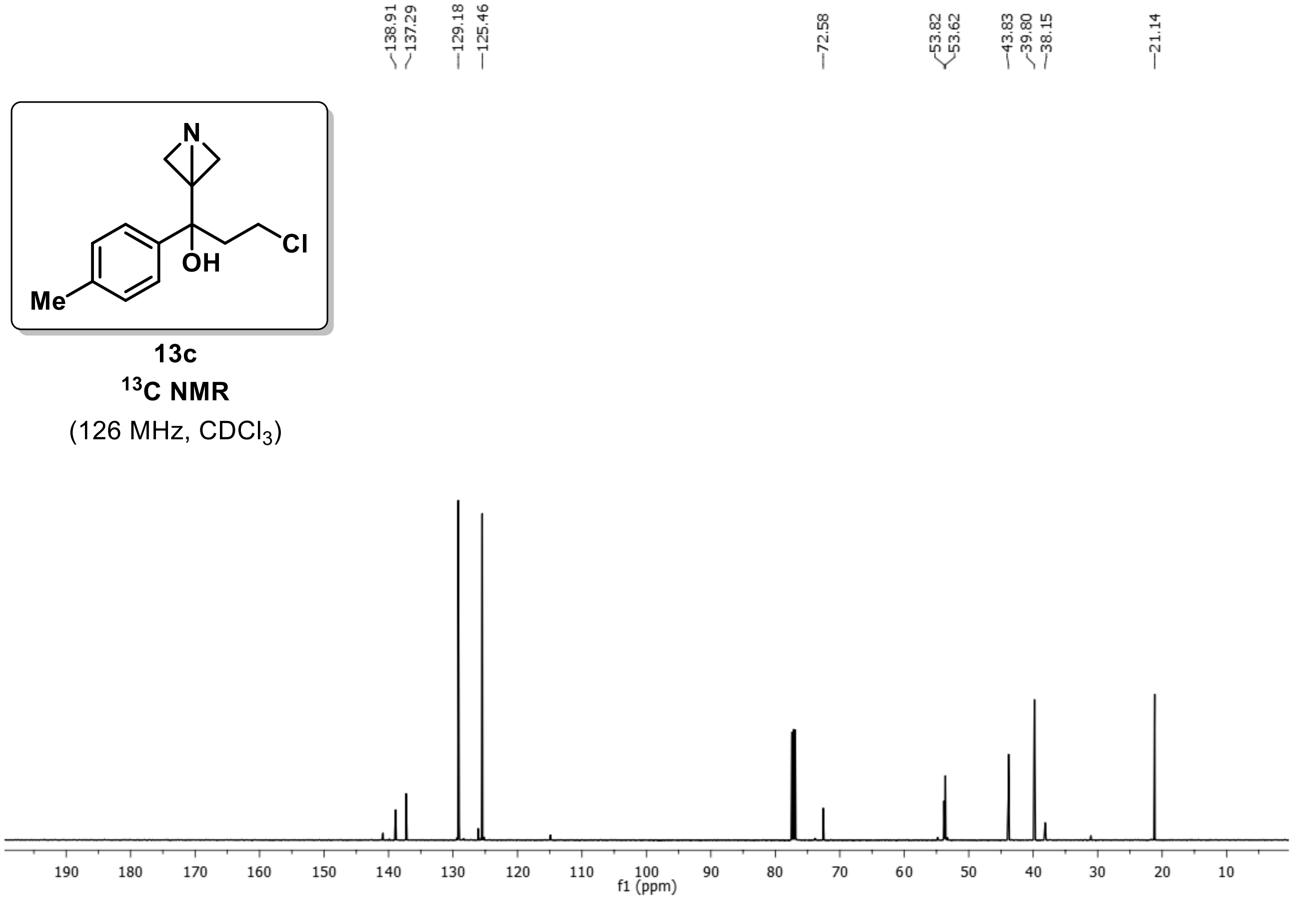
^{13}C NMR

(126 MHz, $CDCl_3$)

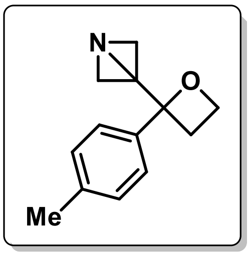




13c
^{1}H NMR
(500 MHz, $CDCl_3$)



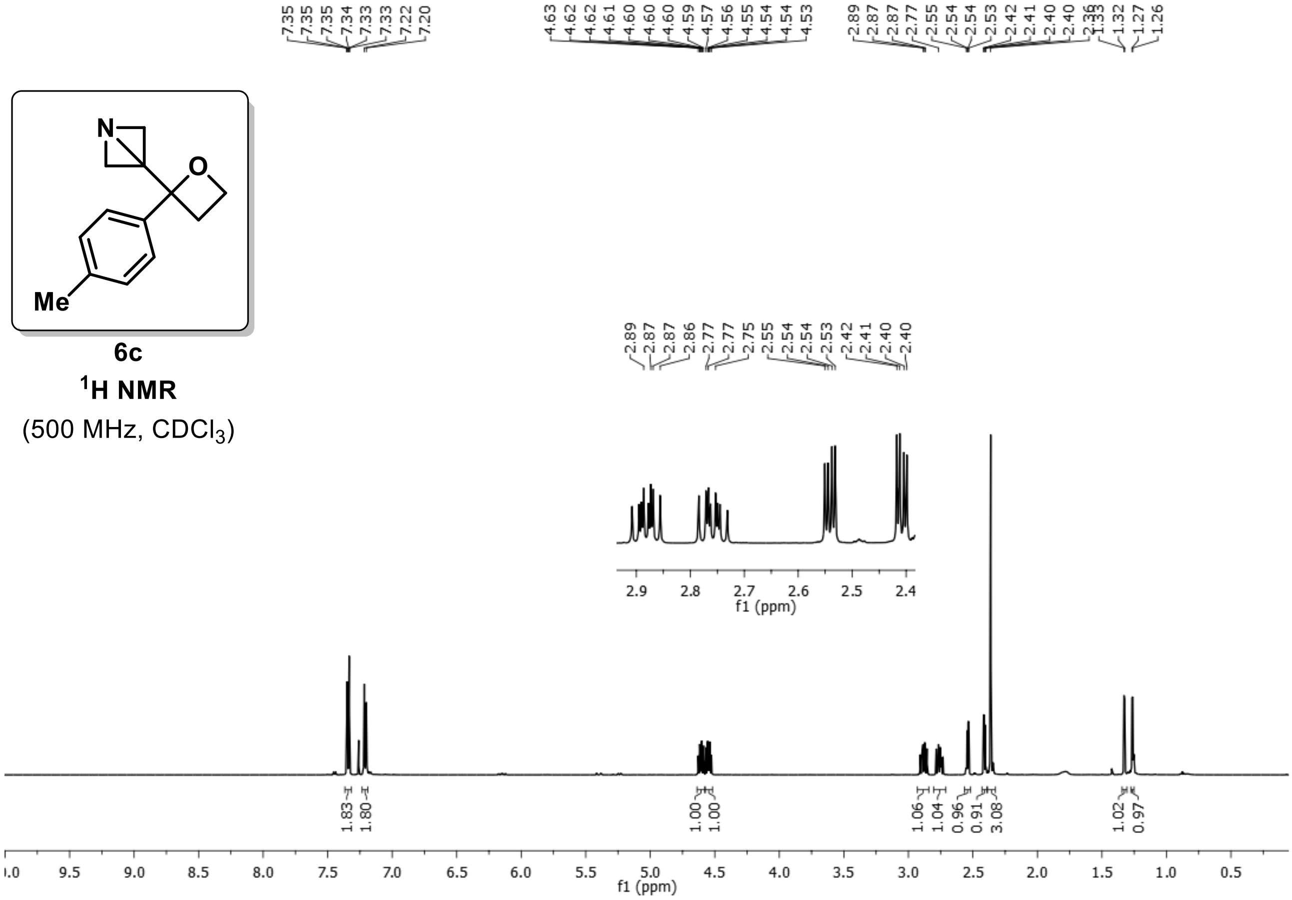
13c
^{13}C NMR
(126 MHz, $CDCl_3$)

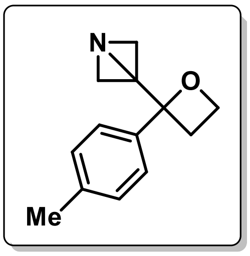


6c

^{1}H NMR

(500 MHz, $CDCl_3$)

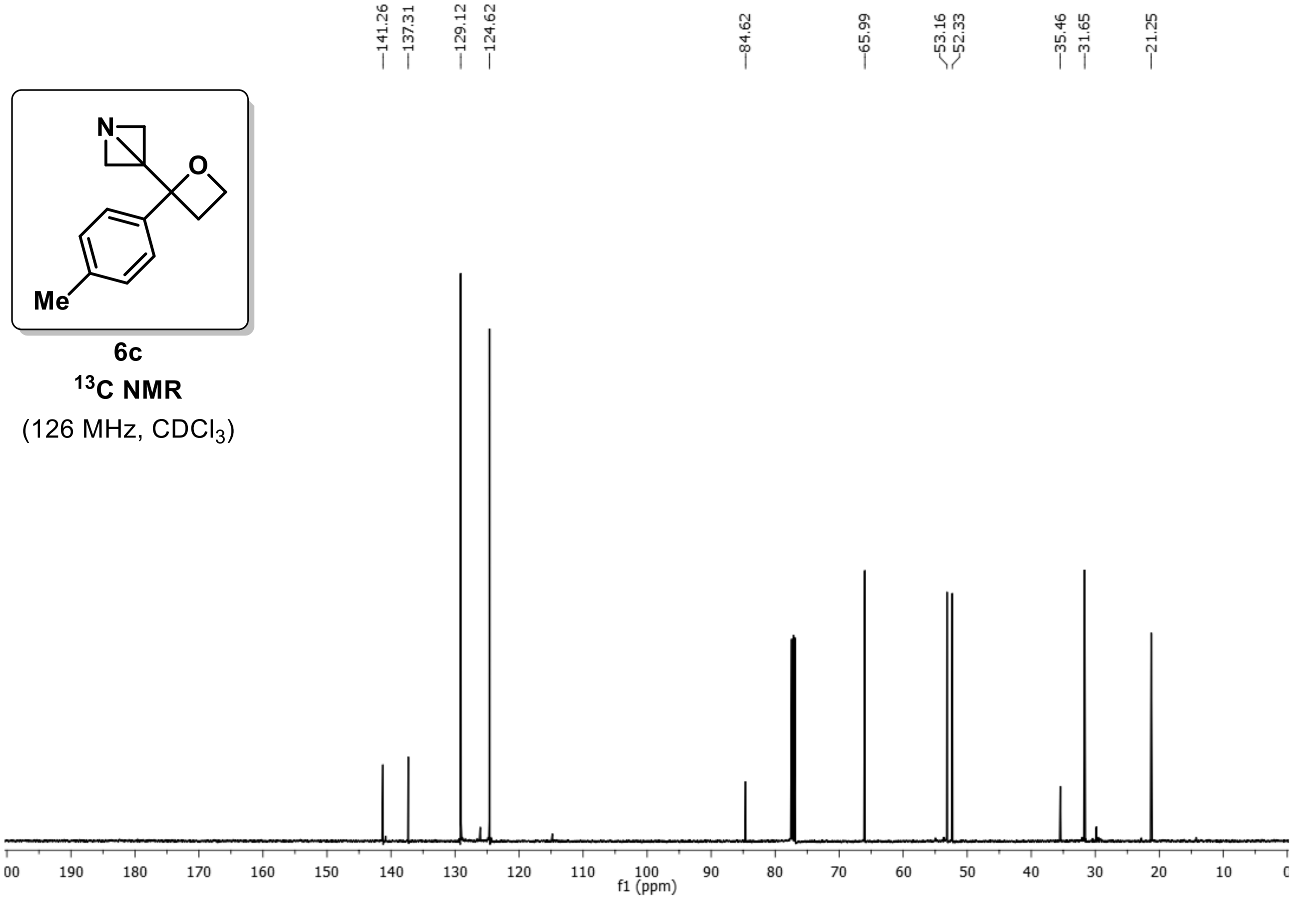


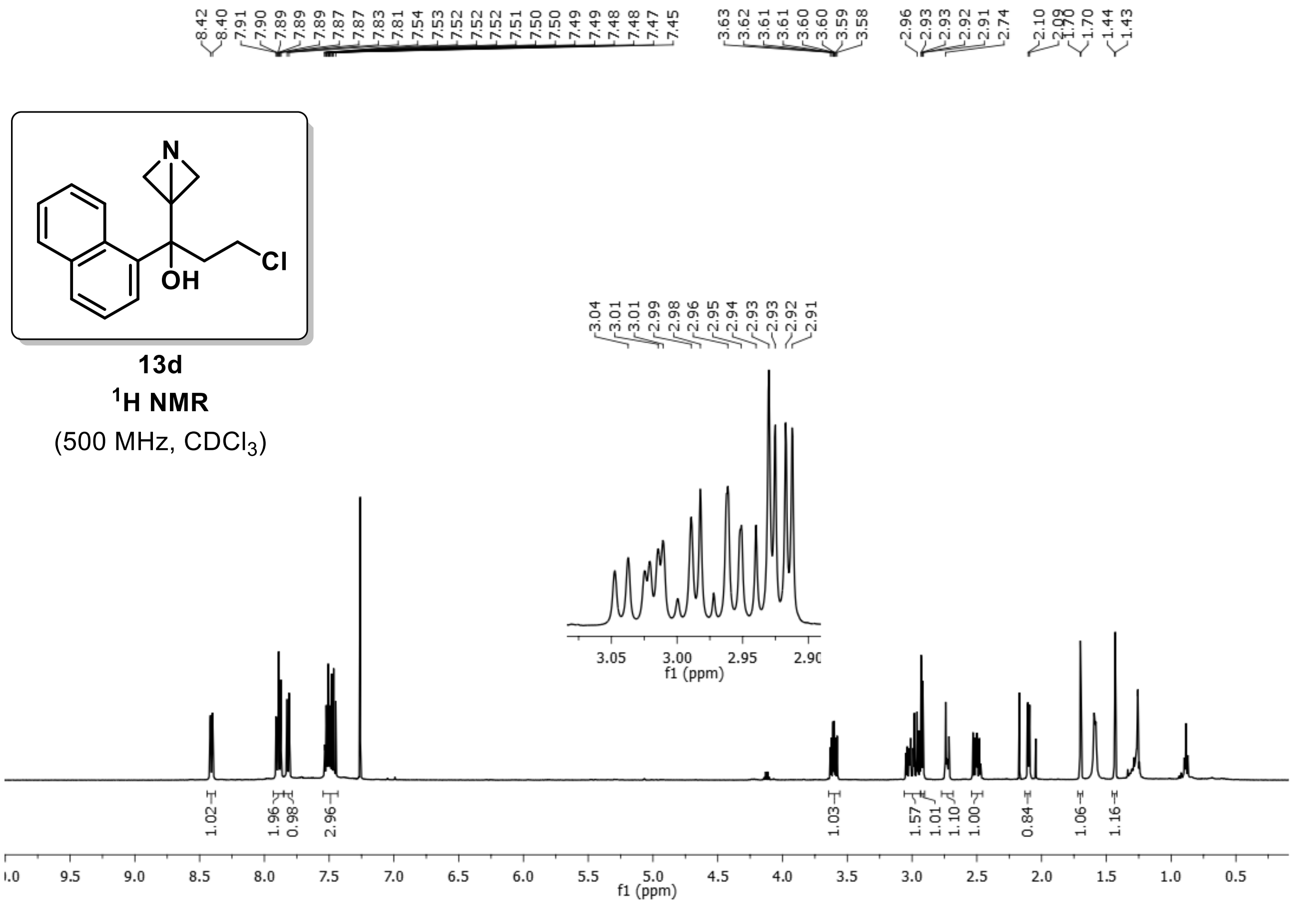


6c

^{13}C NMR

(126 MHz, $CDCl_3$)

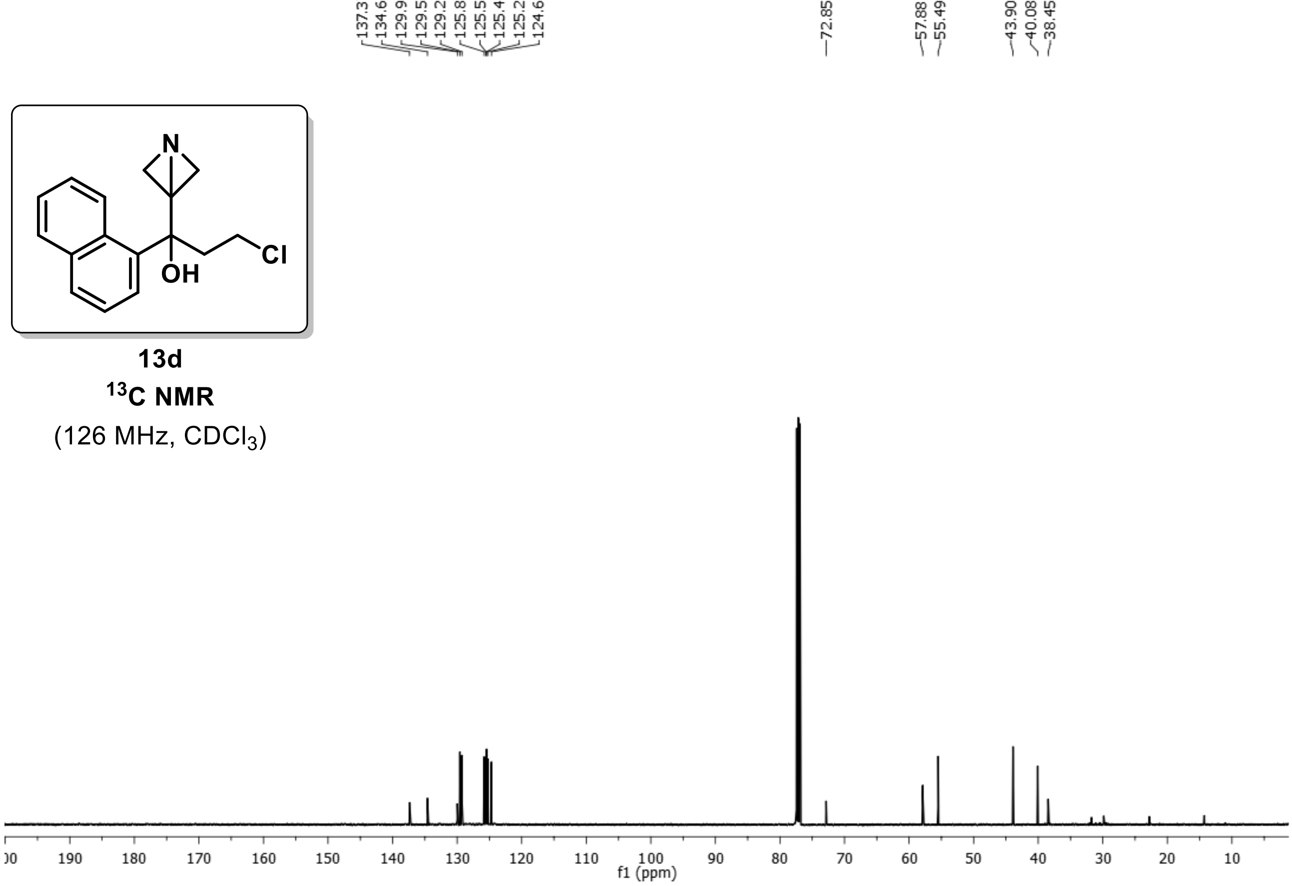




13d

^{1}H NMR

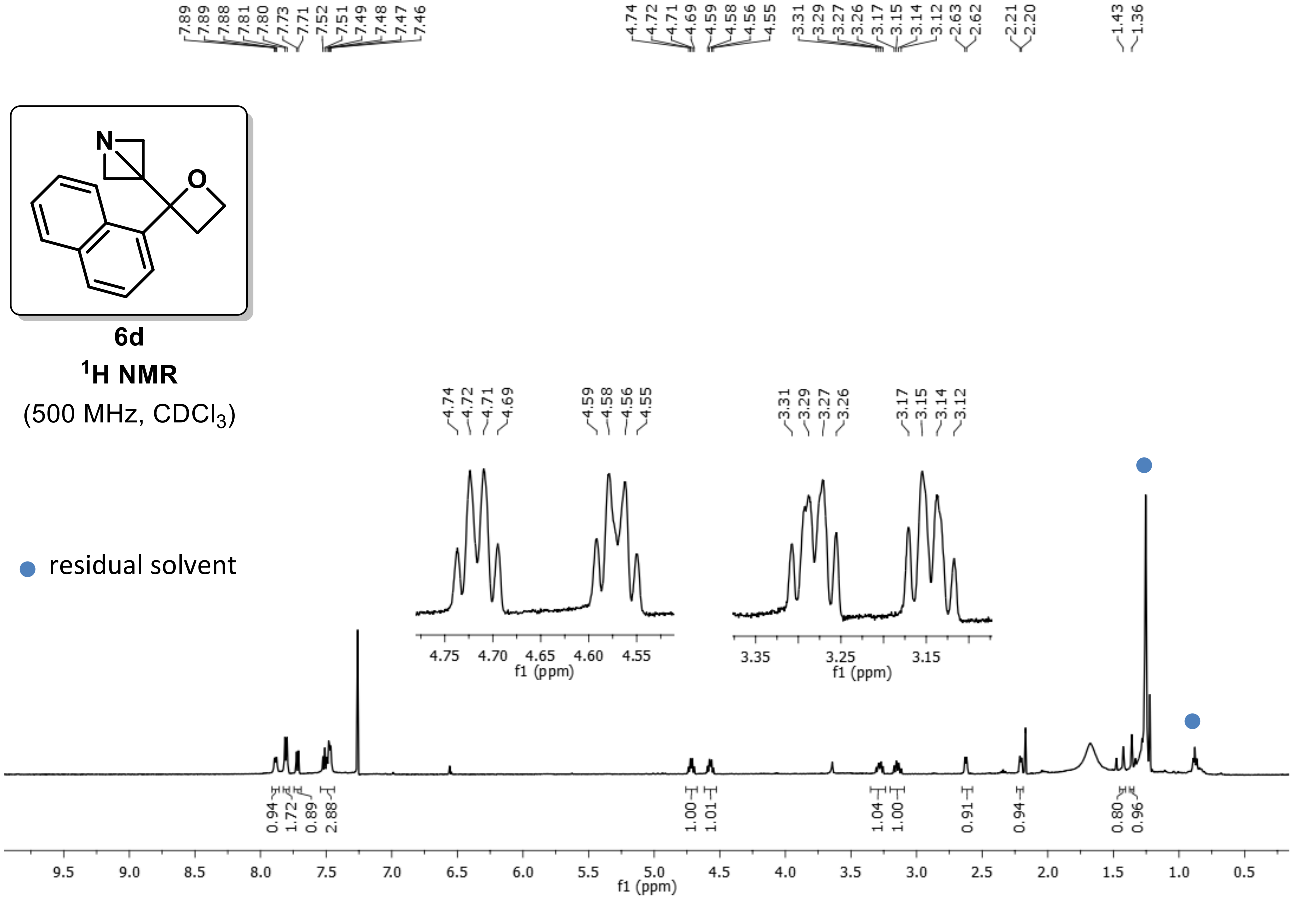
(500 MHz, $CDCl_3$)



13d

^{13}C NMR

(126 MHz, $CDCl_3$)

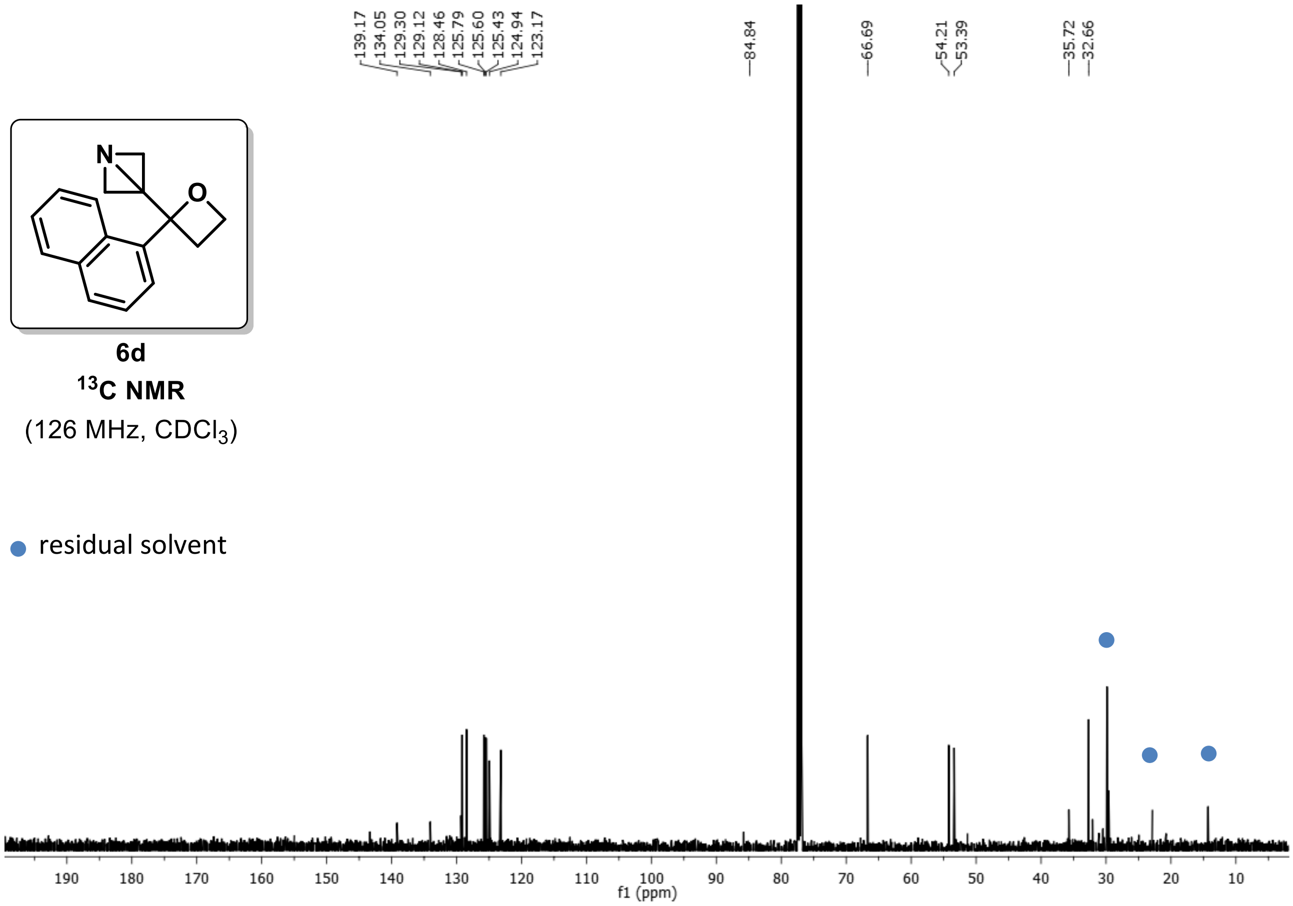


6d

^{1}H NMR

(500 MHz, $CDCl_3$)

● residual solvent

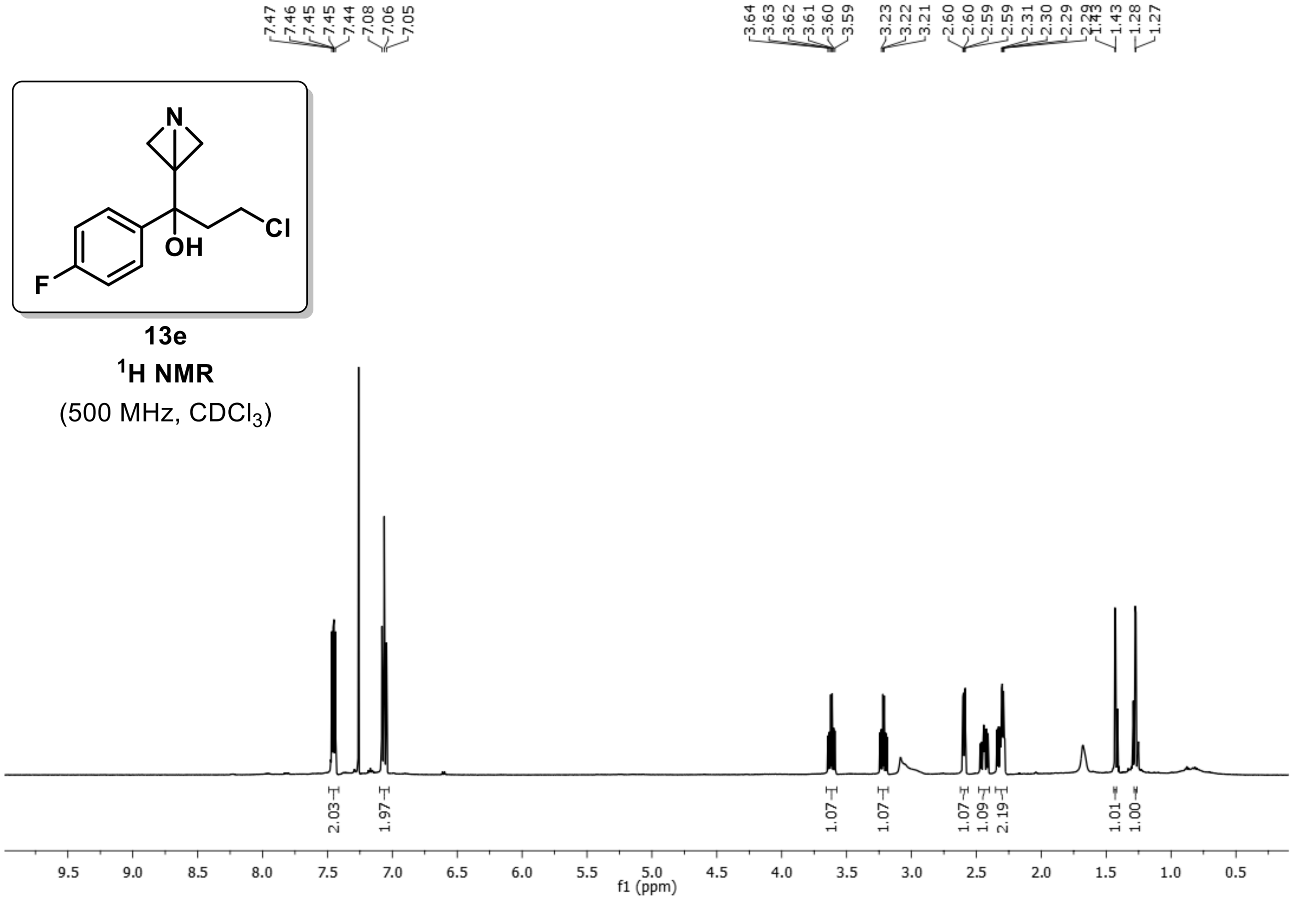


6d

^{13}C NMR

(126 MHz, $CDCl_3$)

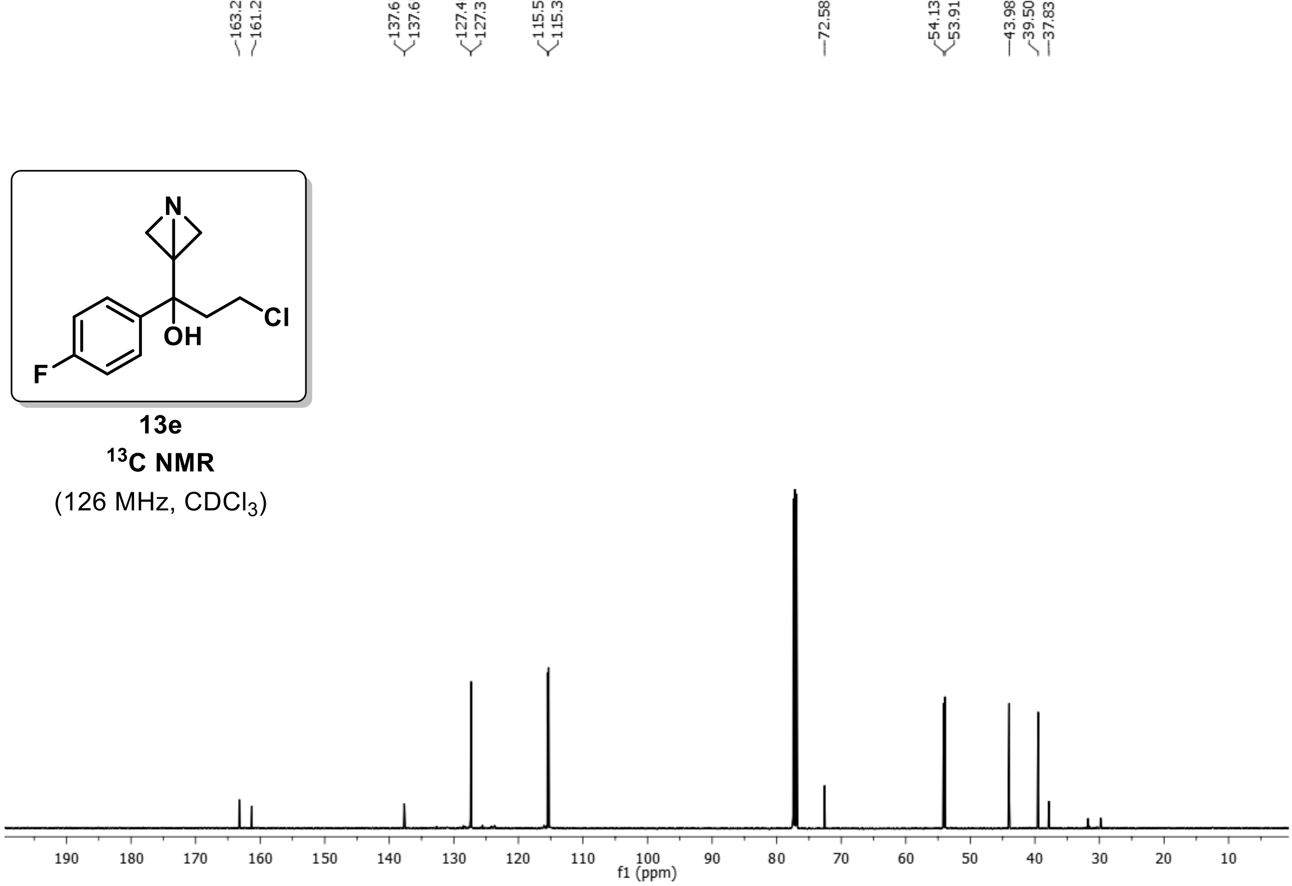
● residual solvent



13e

^{1}H NMR

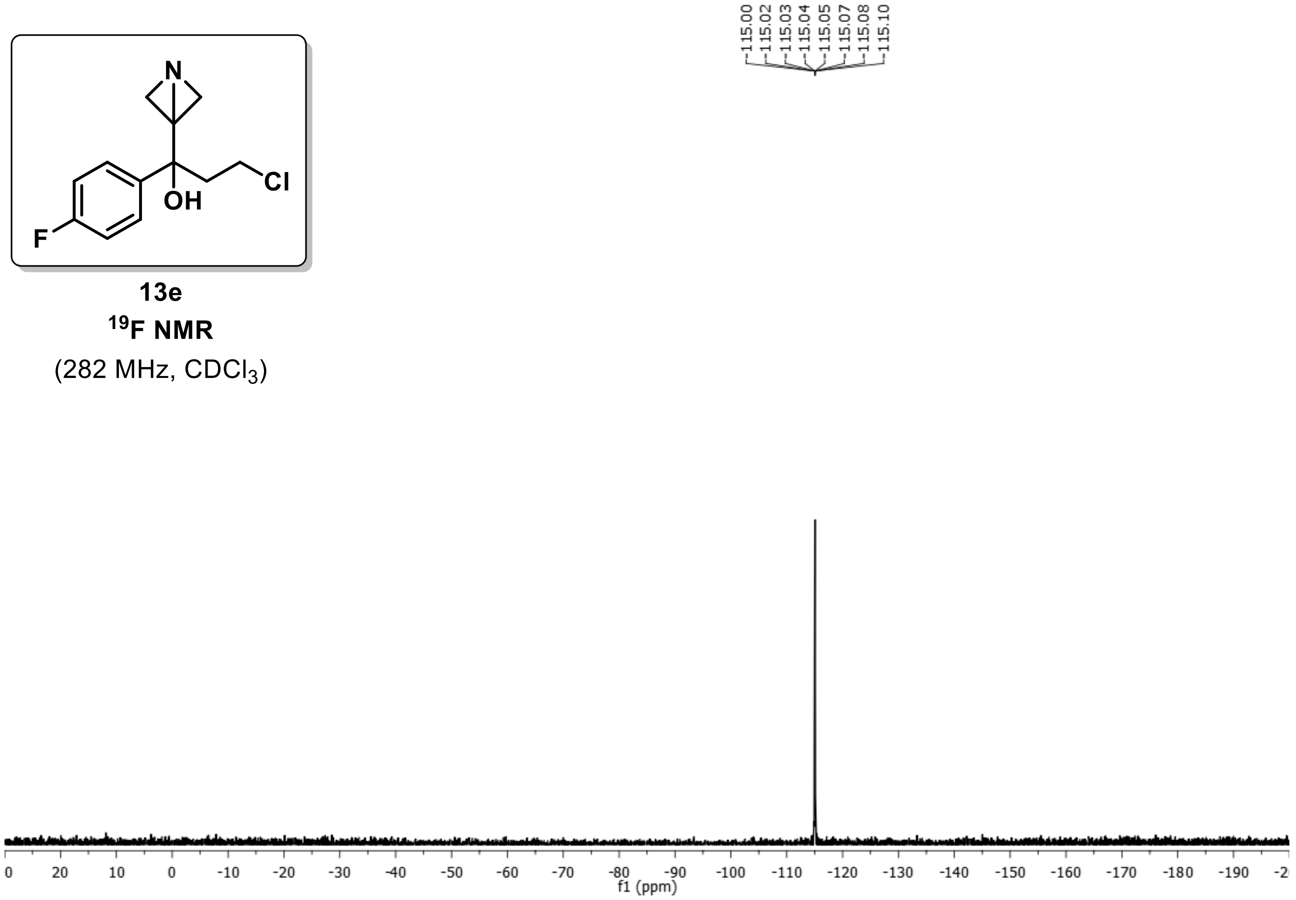
(500 MHz, $CDCl_3$)



13e

^{13}C NMR

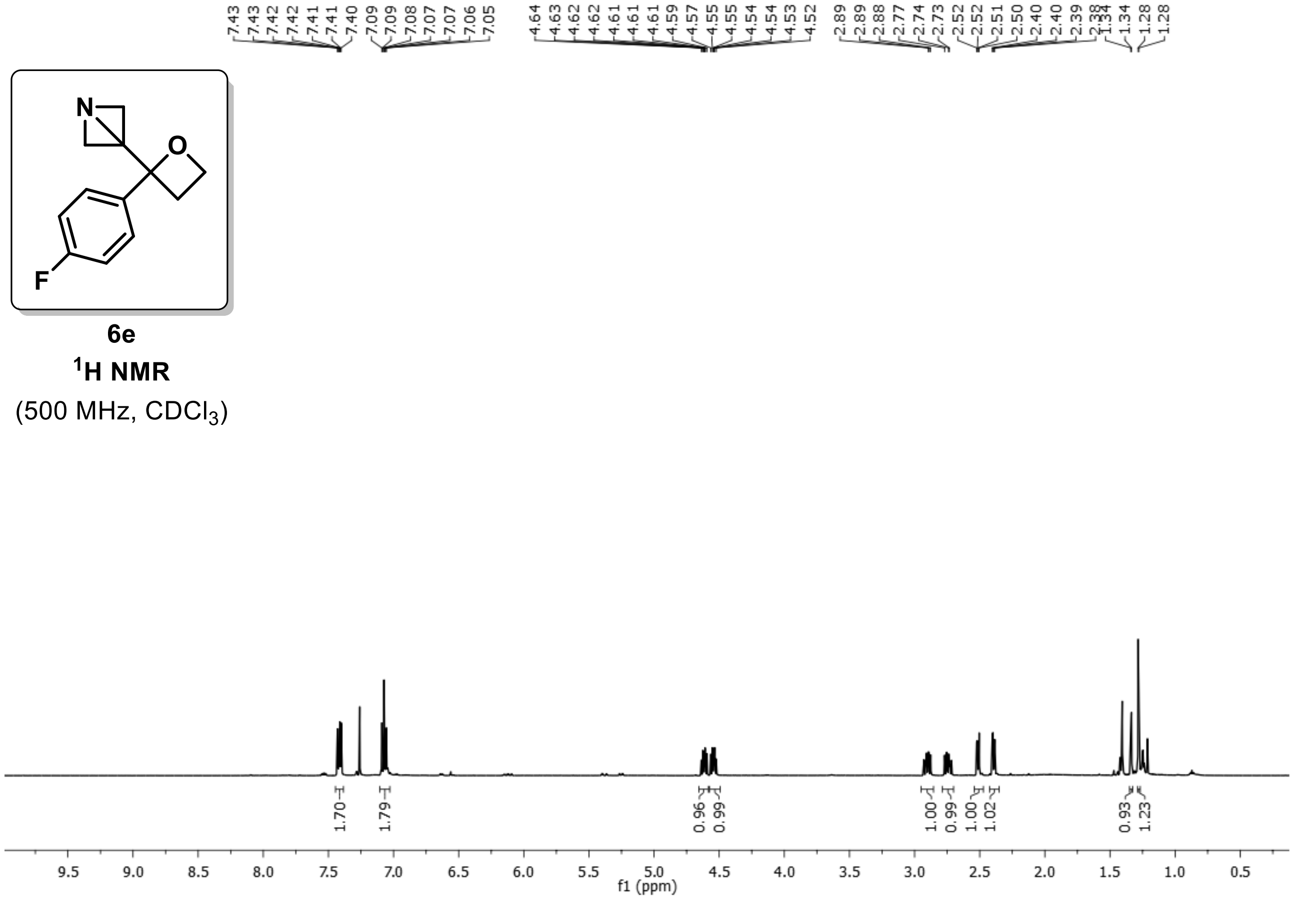
(126 MHz, $CDCl_3$)



13e

^{19}F NMR

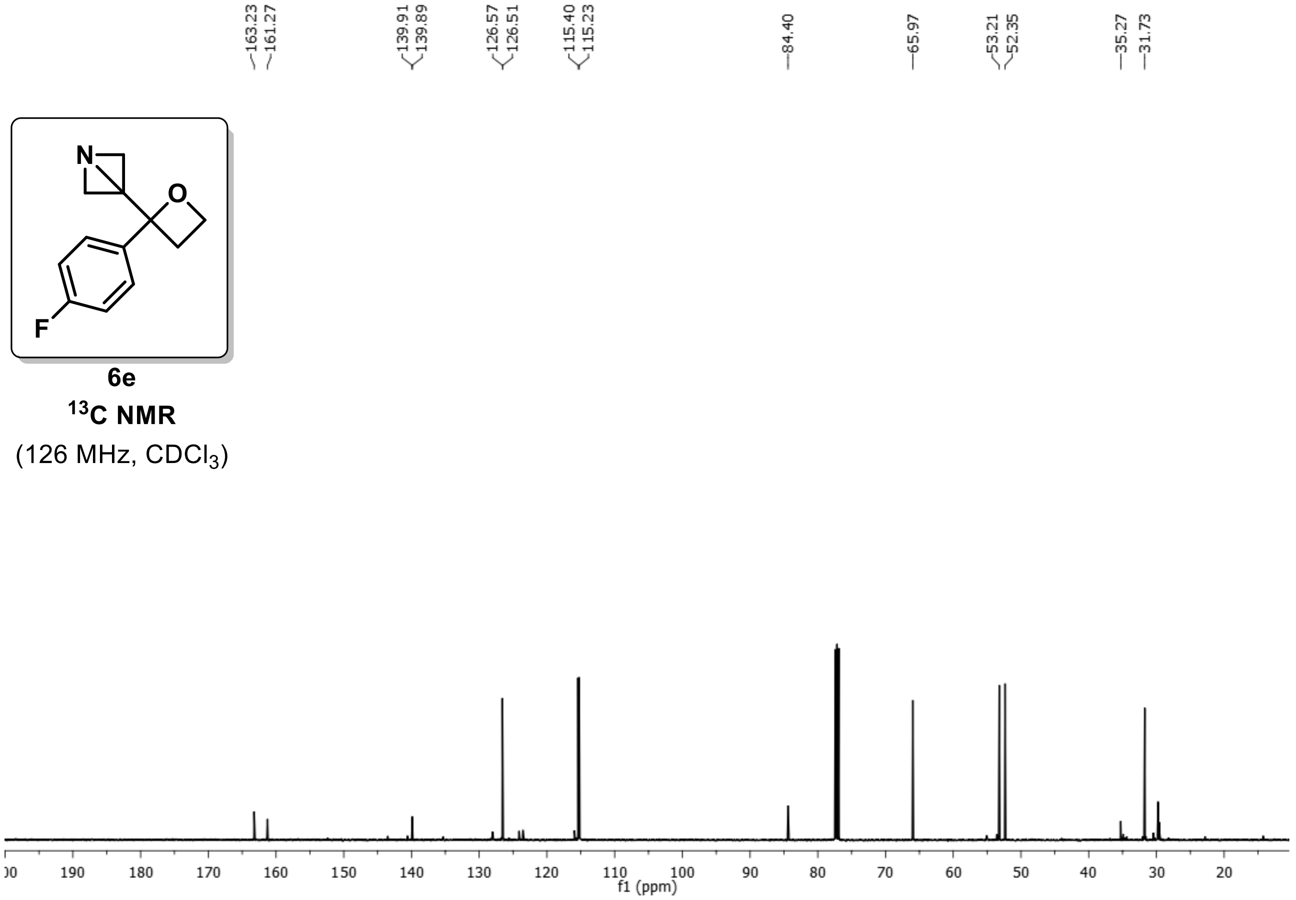
(282 MHz, $CDCl_3$)



6e

^{1}H NMR

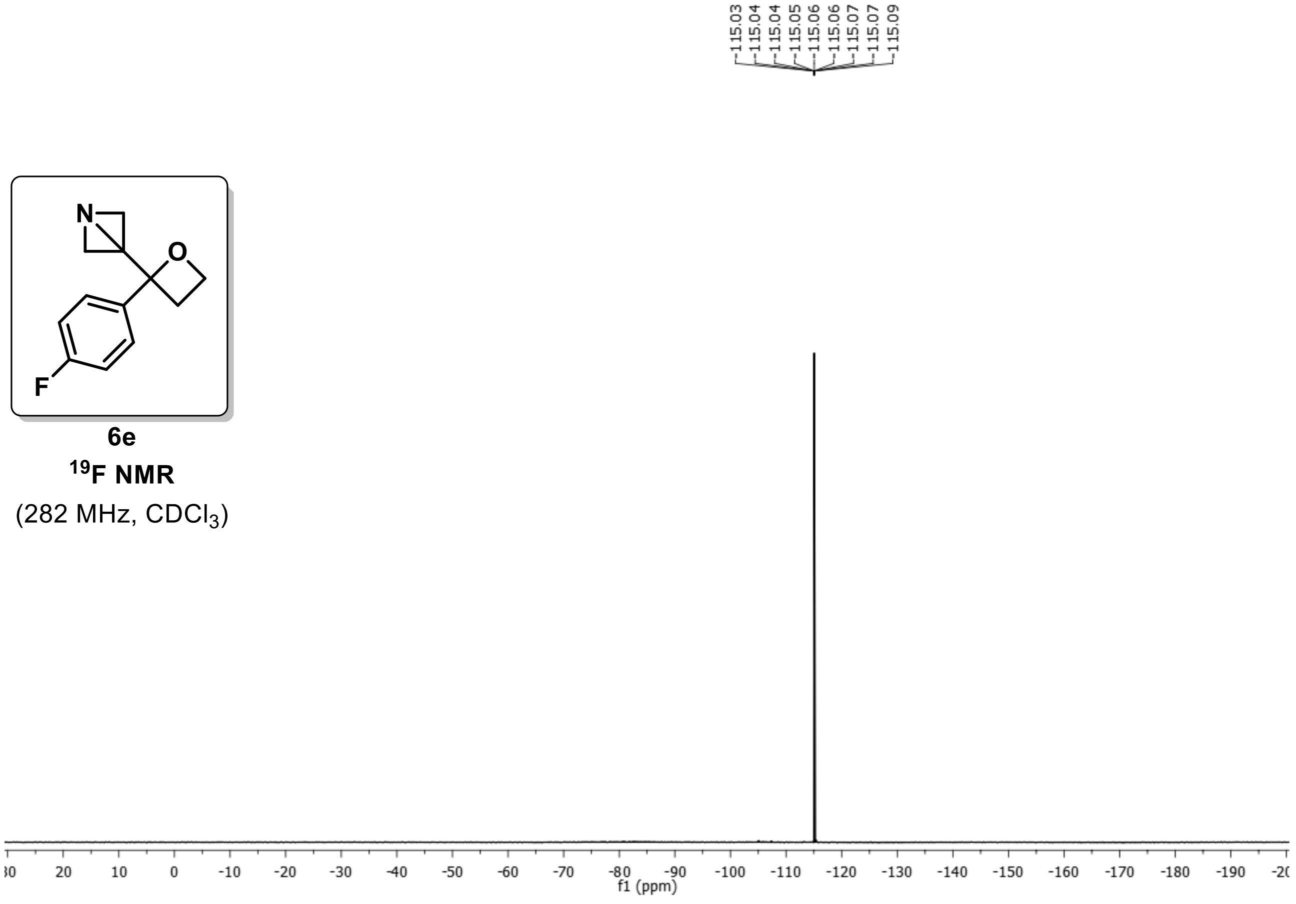
(500 MHz, $CDCl_3$)



6e

^{13}C NMR

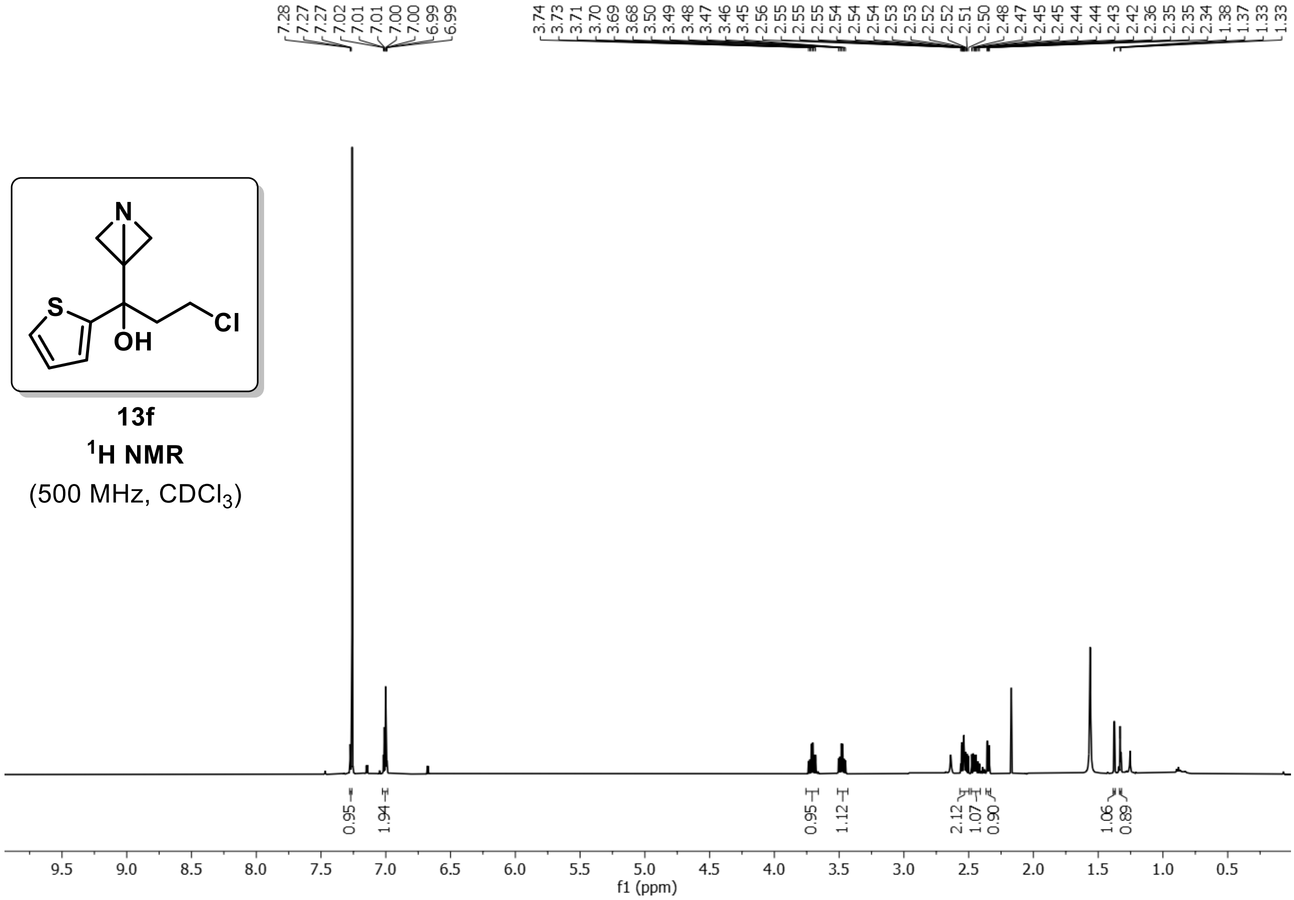
(126 MHz, $CDCl_3$)



6e

^{19}F NMR

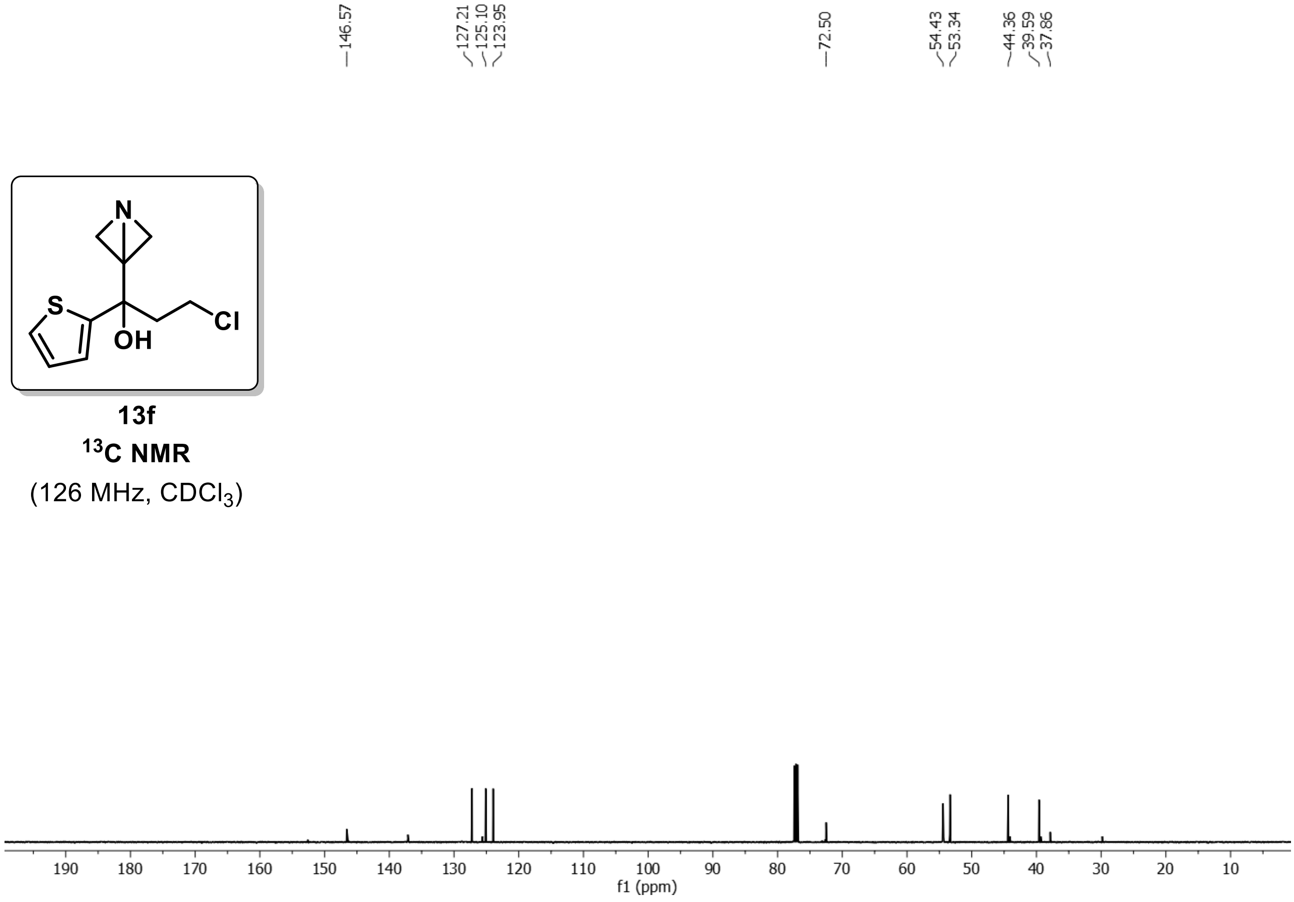
(282 MHz, $CDCl_3$)



13f

^{1}H NMR

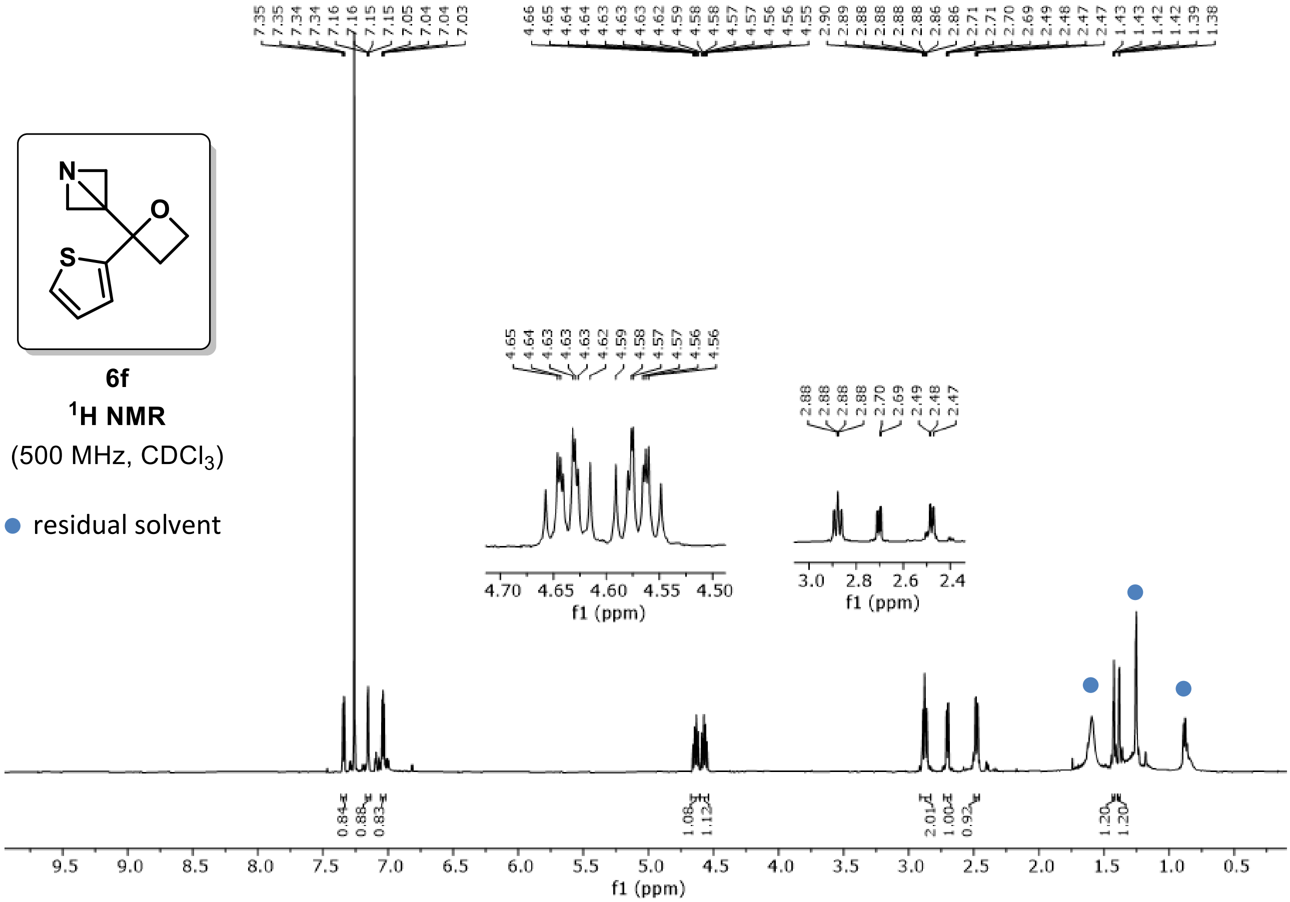
(500 MHz, $CDCl_3$)



13f

^{13}C NMR

(126 MHz, $CDCl_3$)

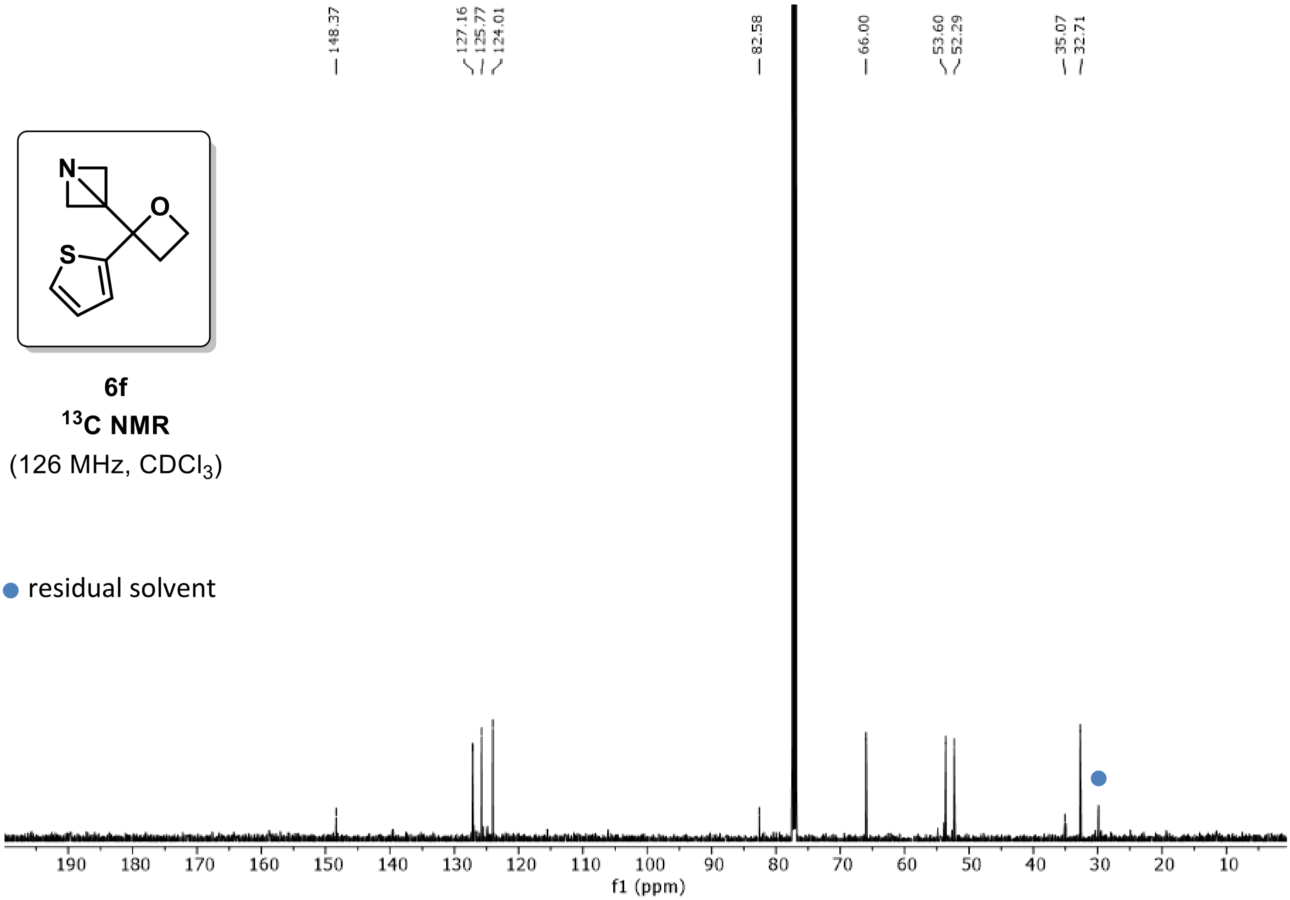


6f

^{1}H NMR

(500 MHz, $CDCl_3$)

● residual solvent

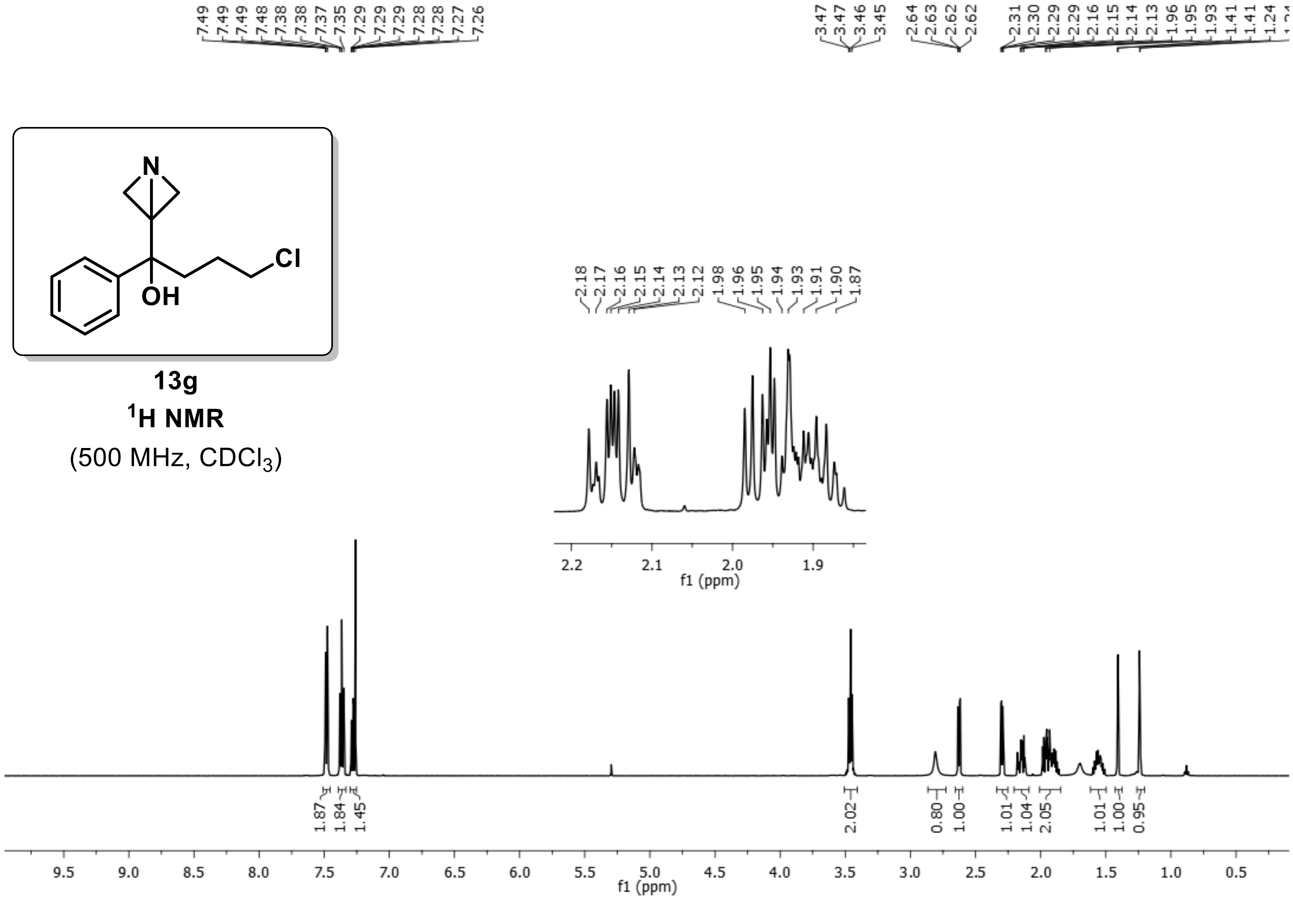


6f

^{13}C NMR

(126 MHz, $CDCl_3$)

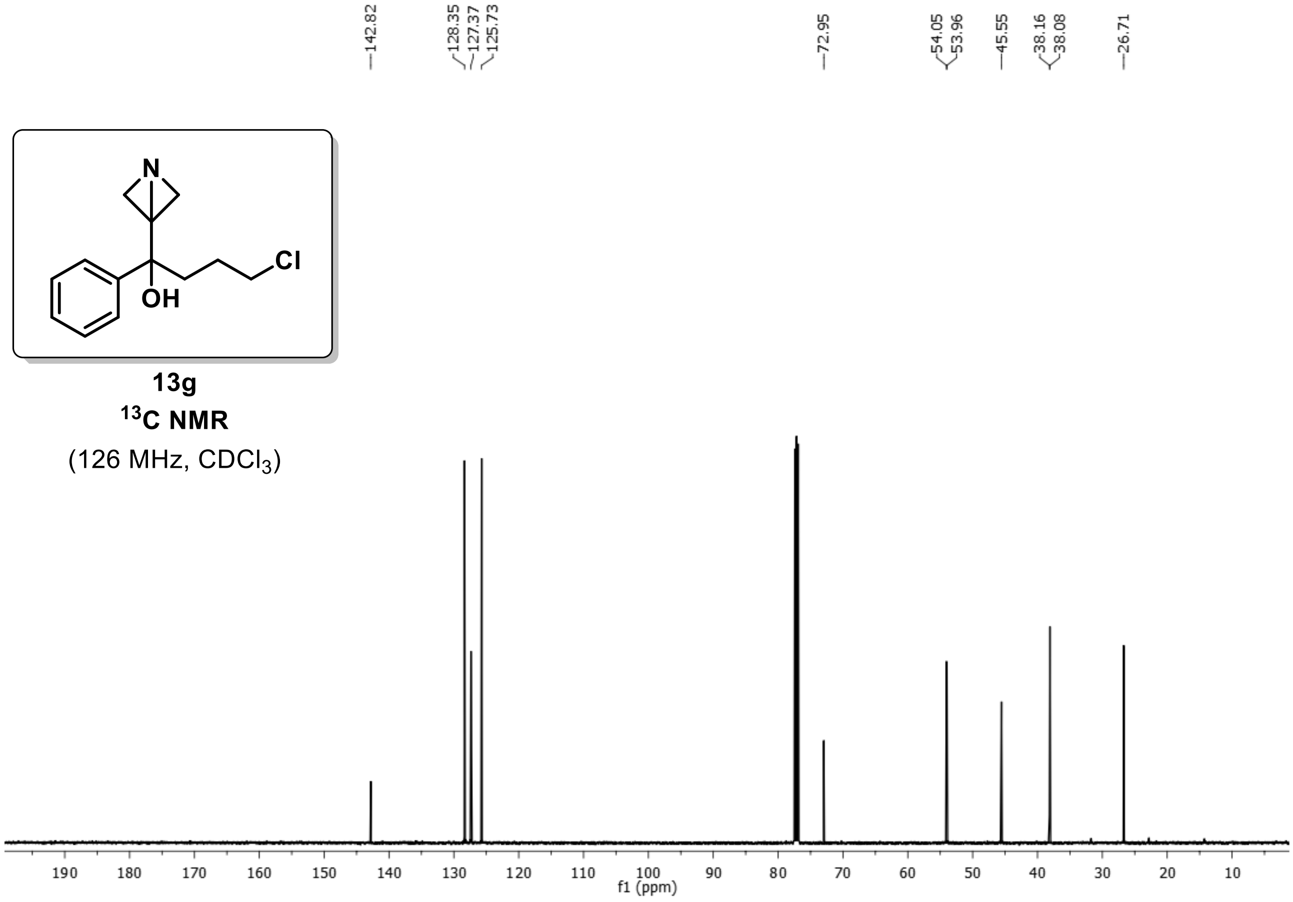
● residual solvent



13g

^{1}H NMR

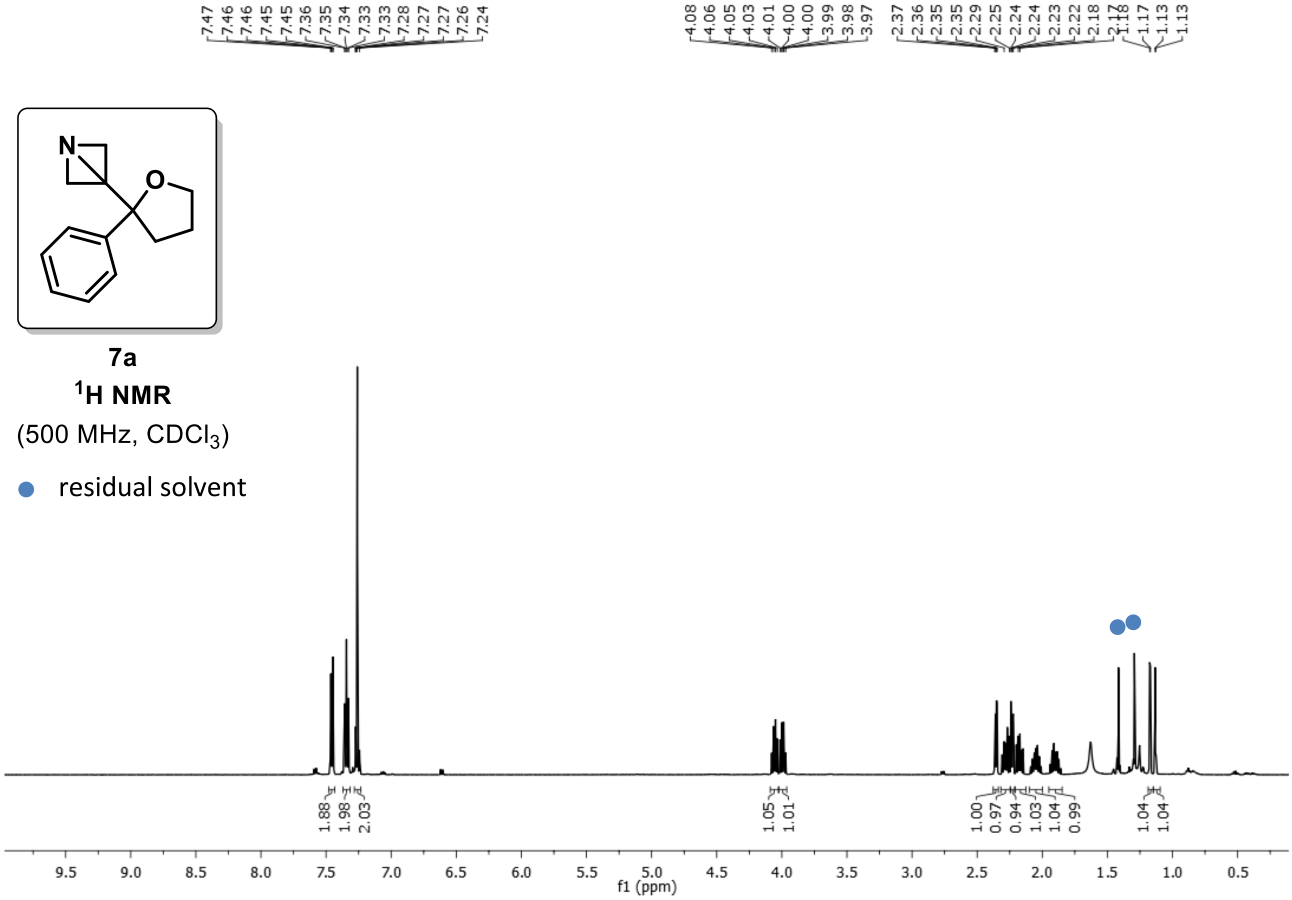
(500 MHz, $CDCl_3$)



13g

^{13}C NMR

(126 MHz, $CDCl_3$)

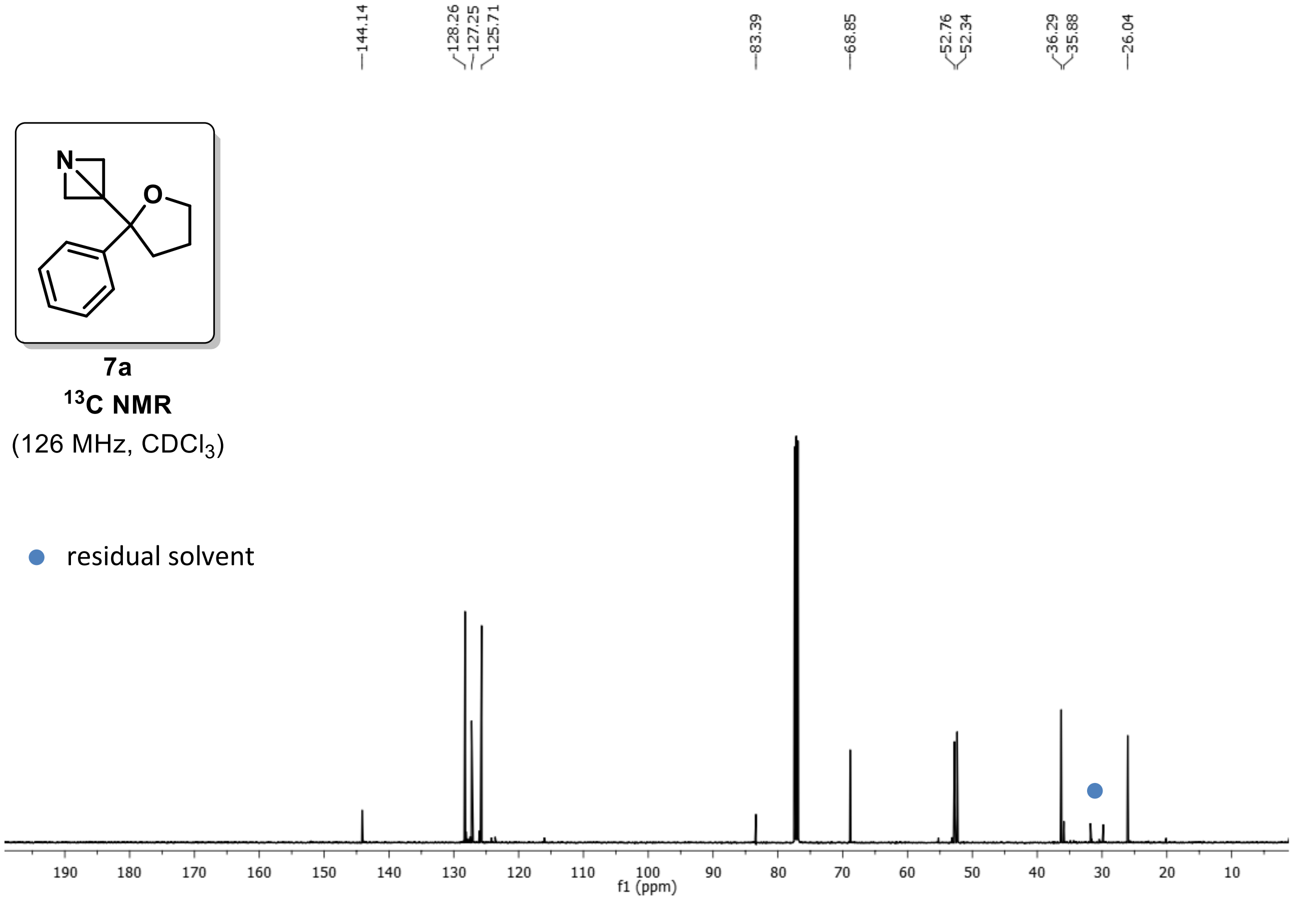


7a

^{1}H NMR

(500 MHz, $CDCl_3$)

● residual solvent

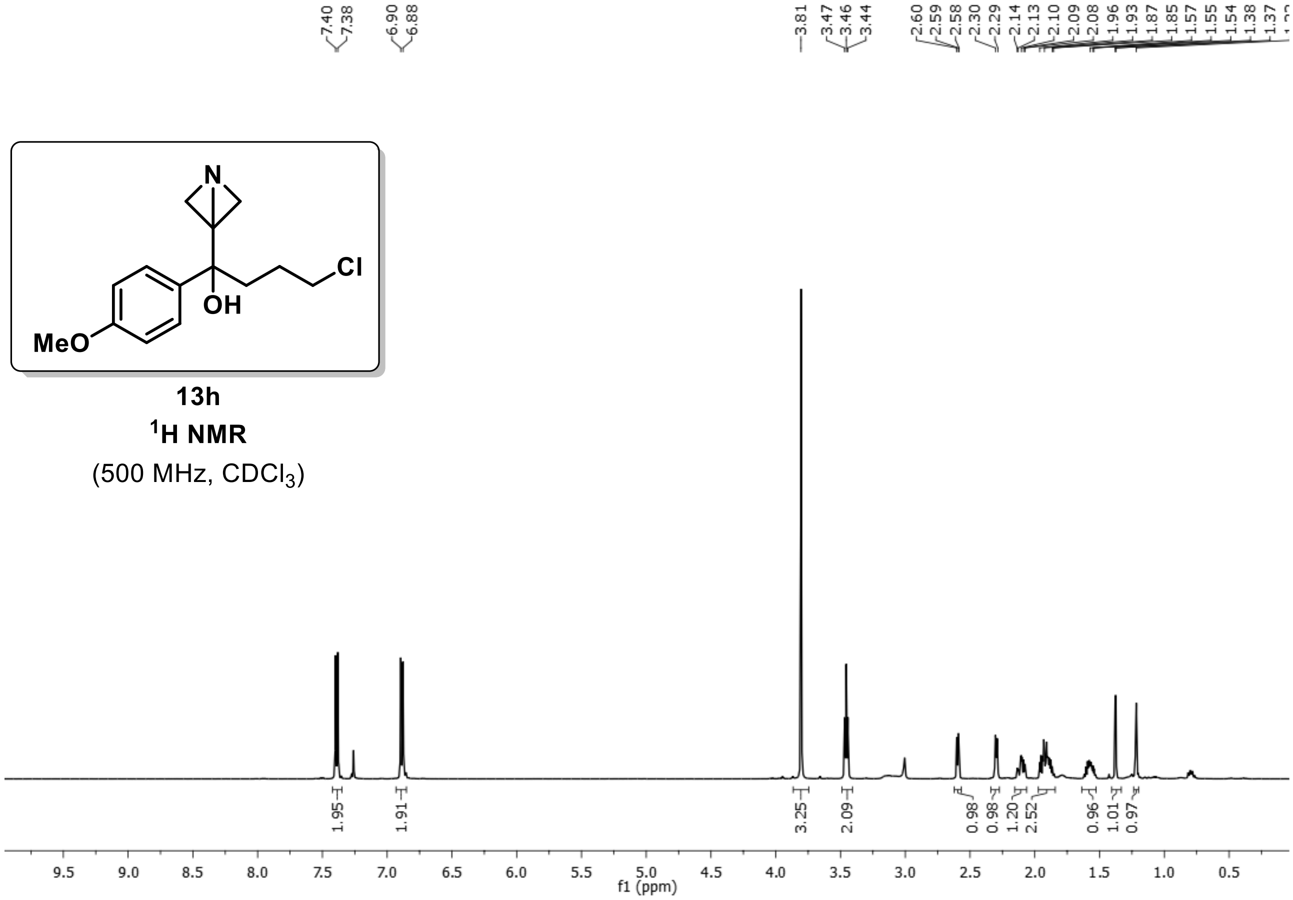


7a

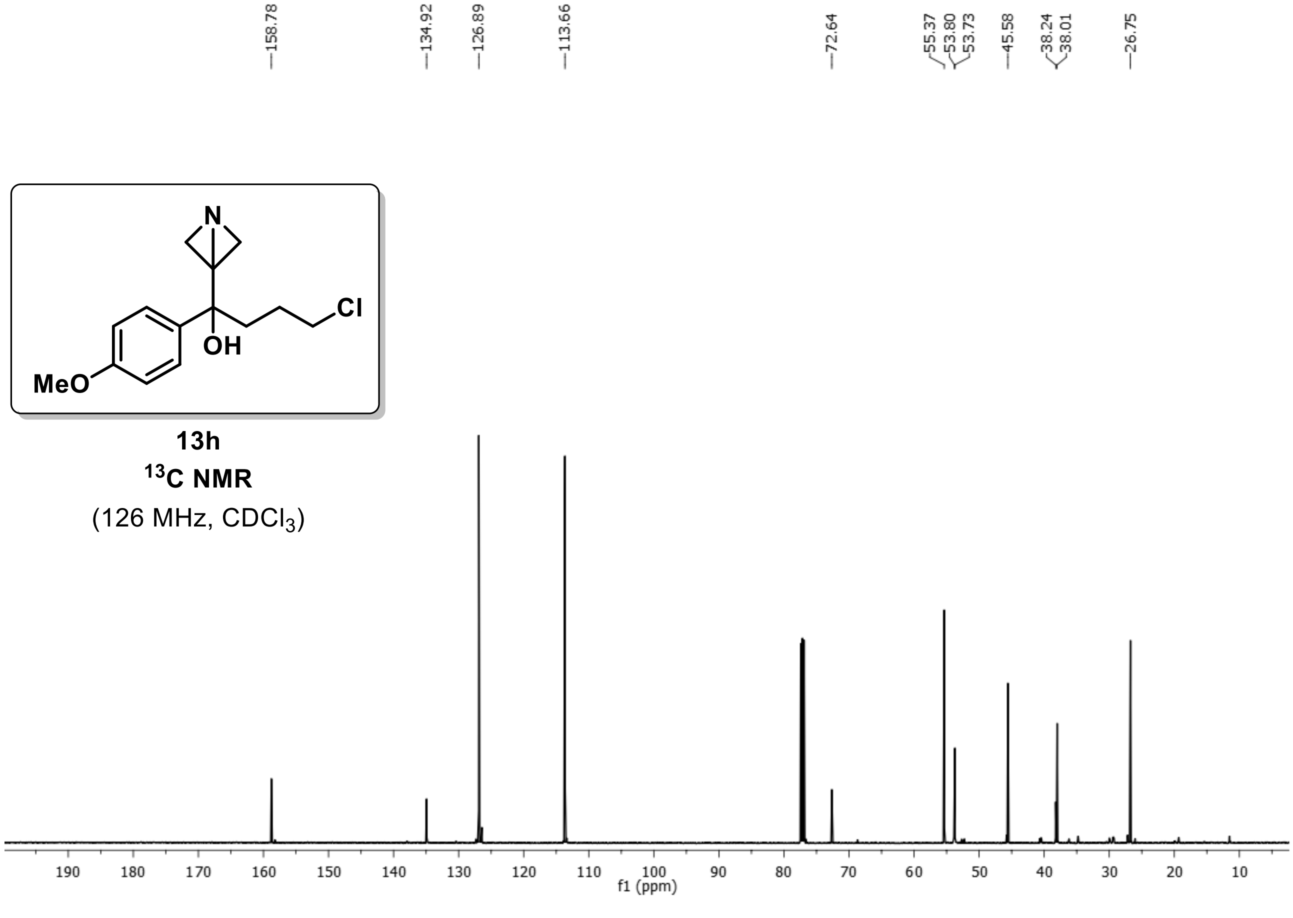
^{13}C NMR

(126 MHz, $CDCl_3$)

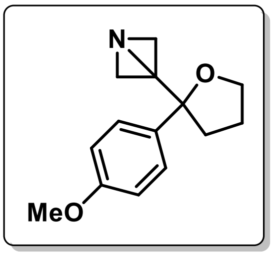
● residual solvent



13h
^{1}H NMR
(500 MHz, $CDCl_3$)



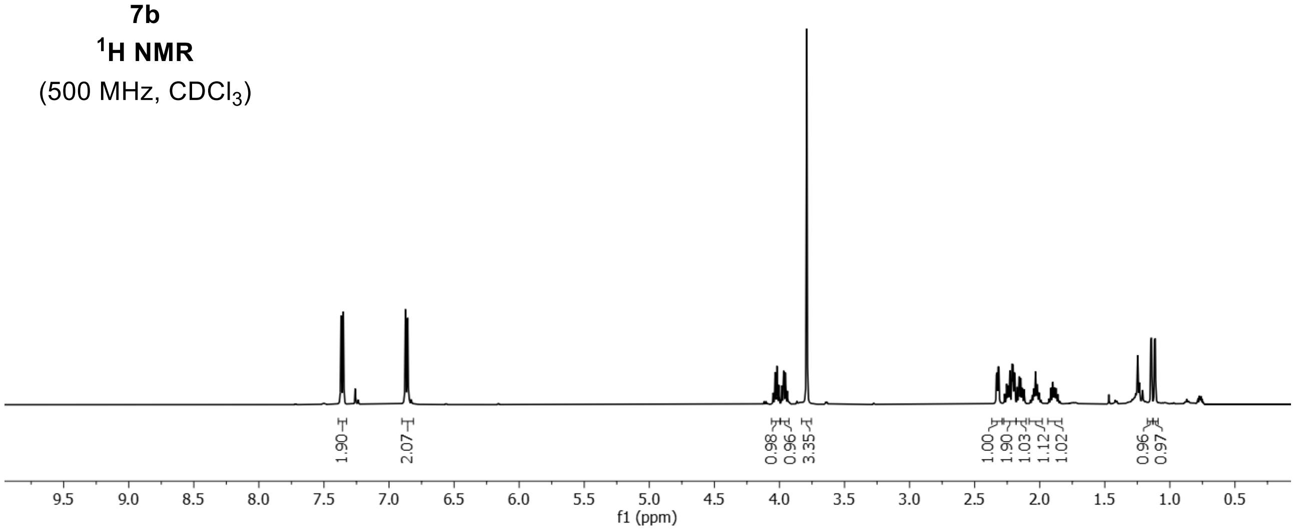
13h
^{13}C NMR
(126 MHz, $CDCl_3$)

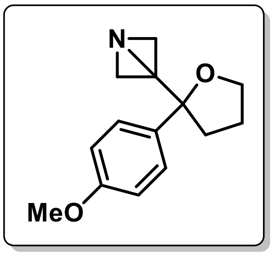


7b

^{1}H NMR

(500 MHz, $CDCl_3$)

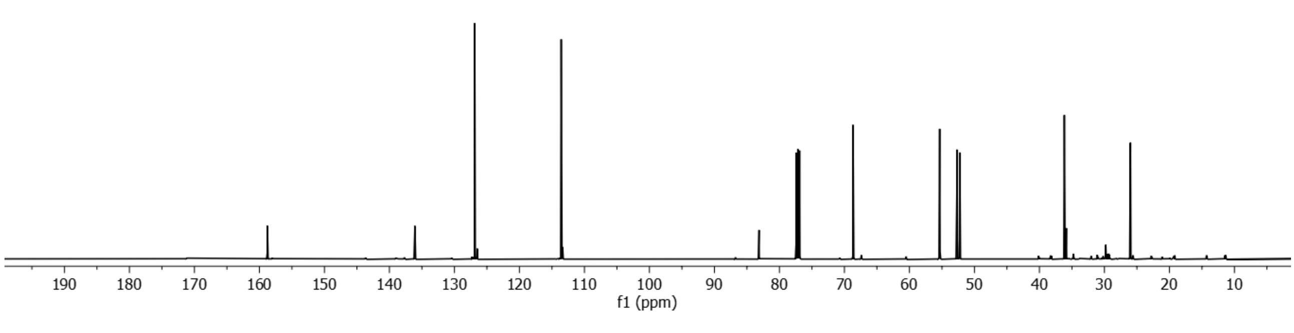


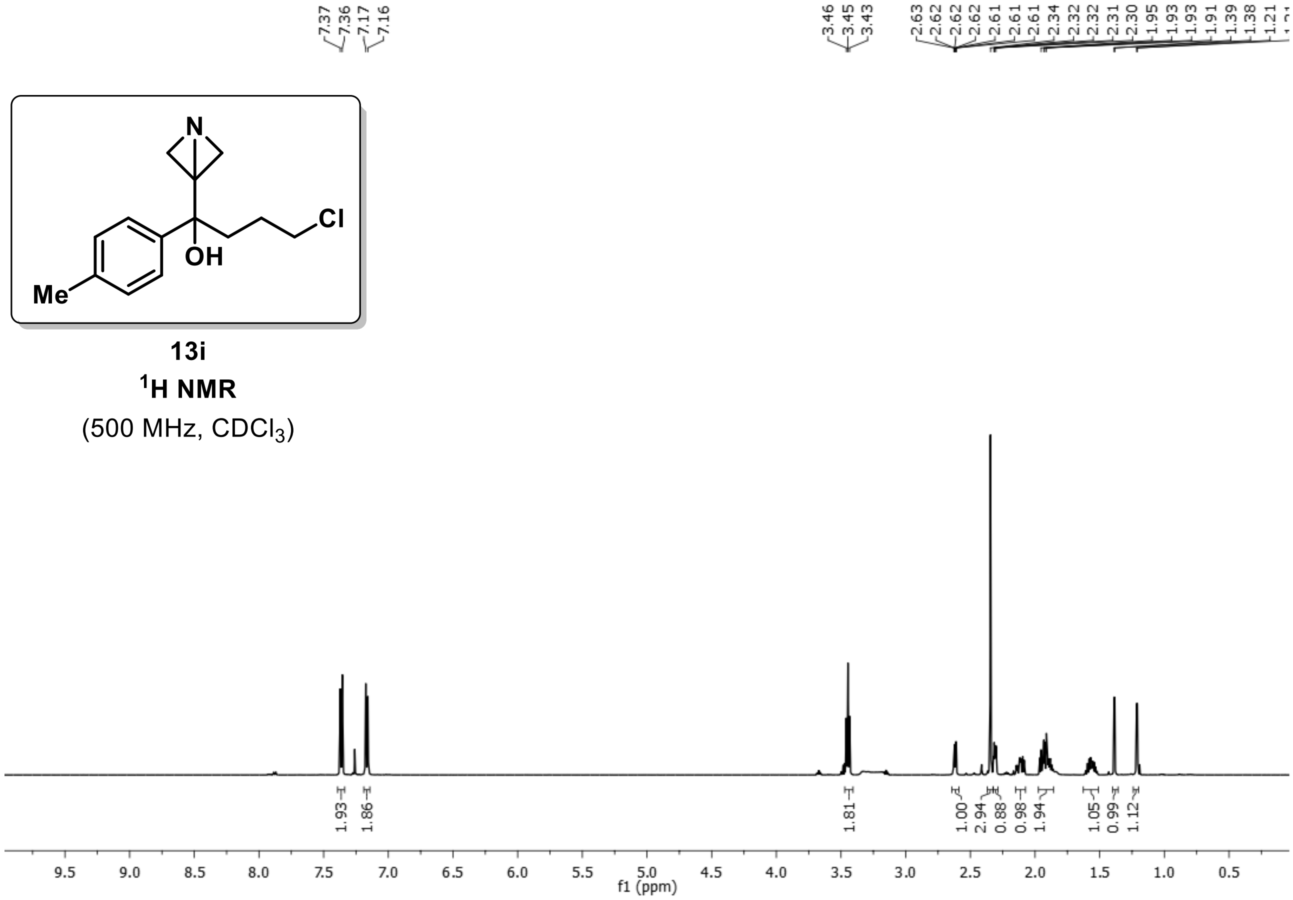


7b

^{13}C NMR

(126 MHz, $CDCl_3$)

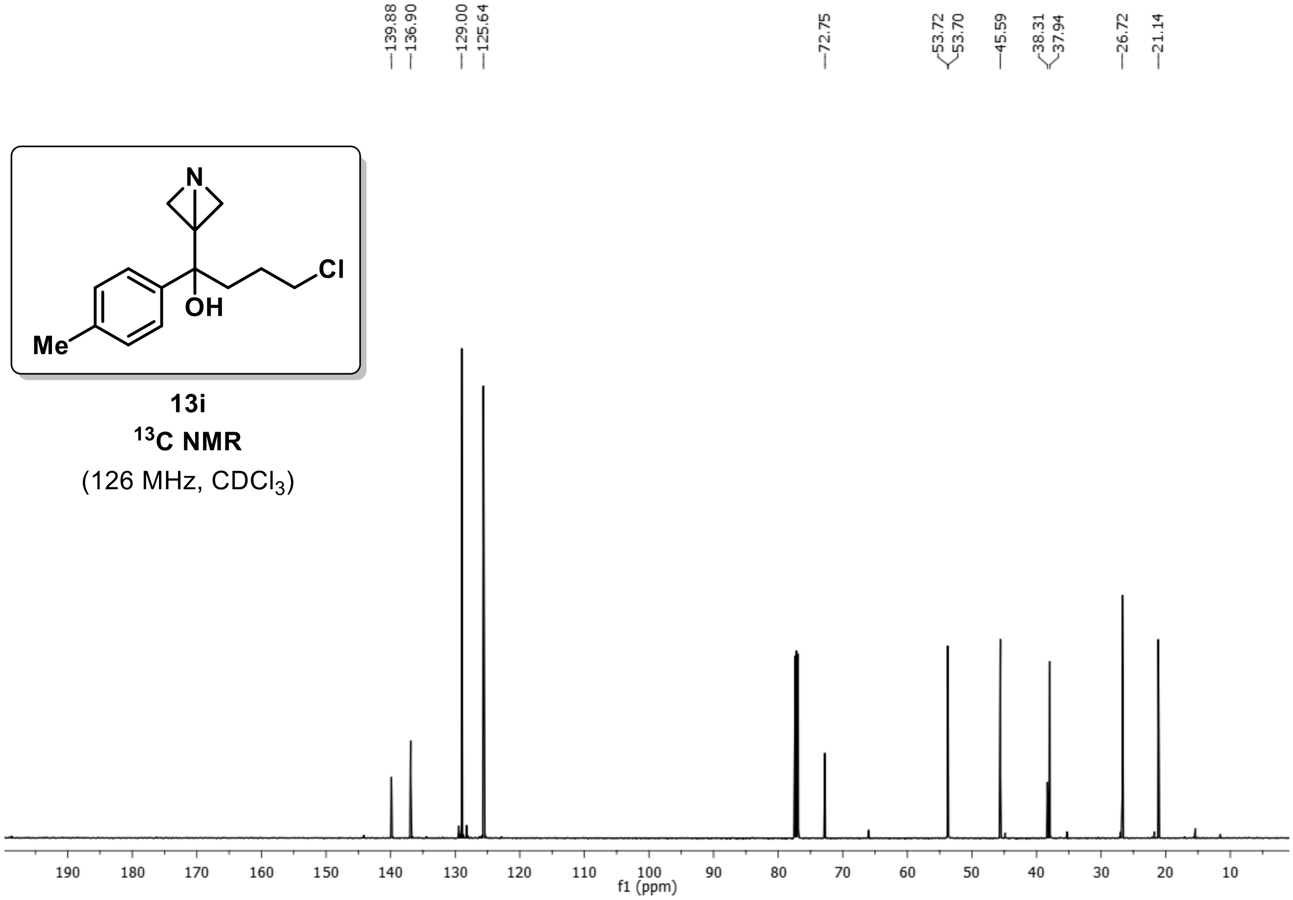




13i

^{1}H NMR

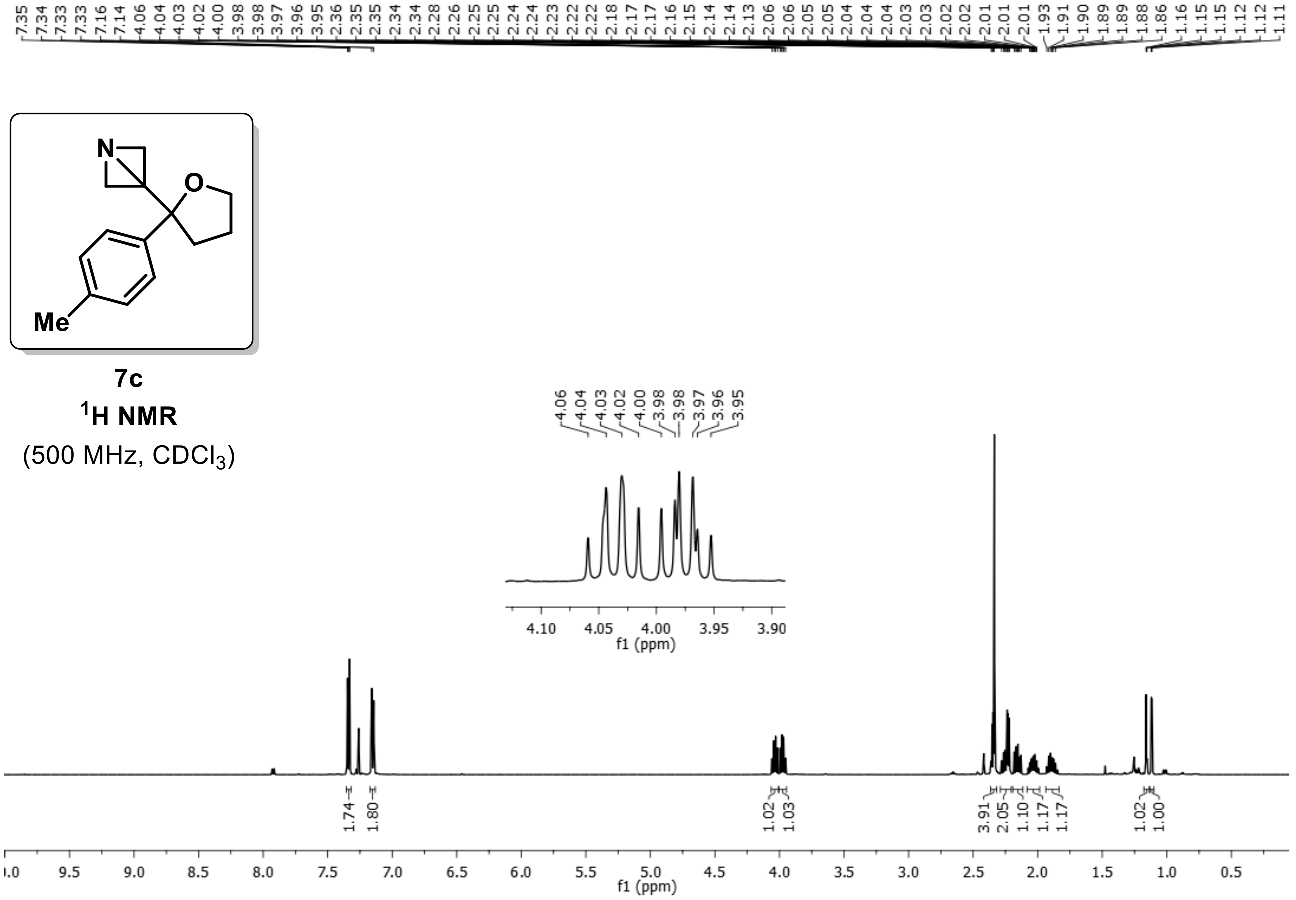
(500 MHz, $CDCl_3$)



13i

^{13}C NMR

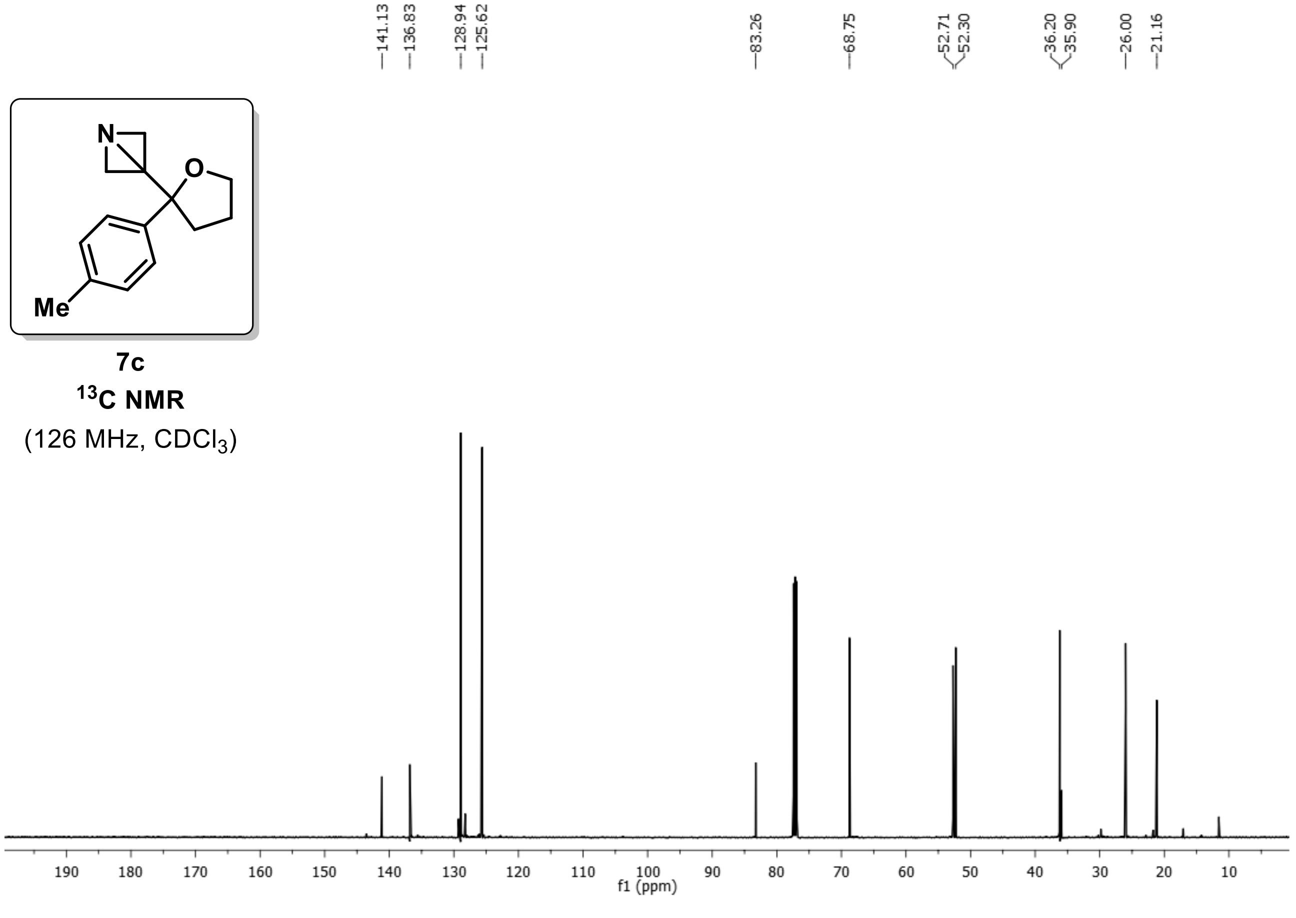
(126 MHz, $CDCl_3$)



7c

^{1}H NMR

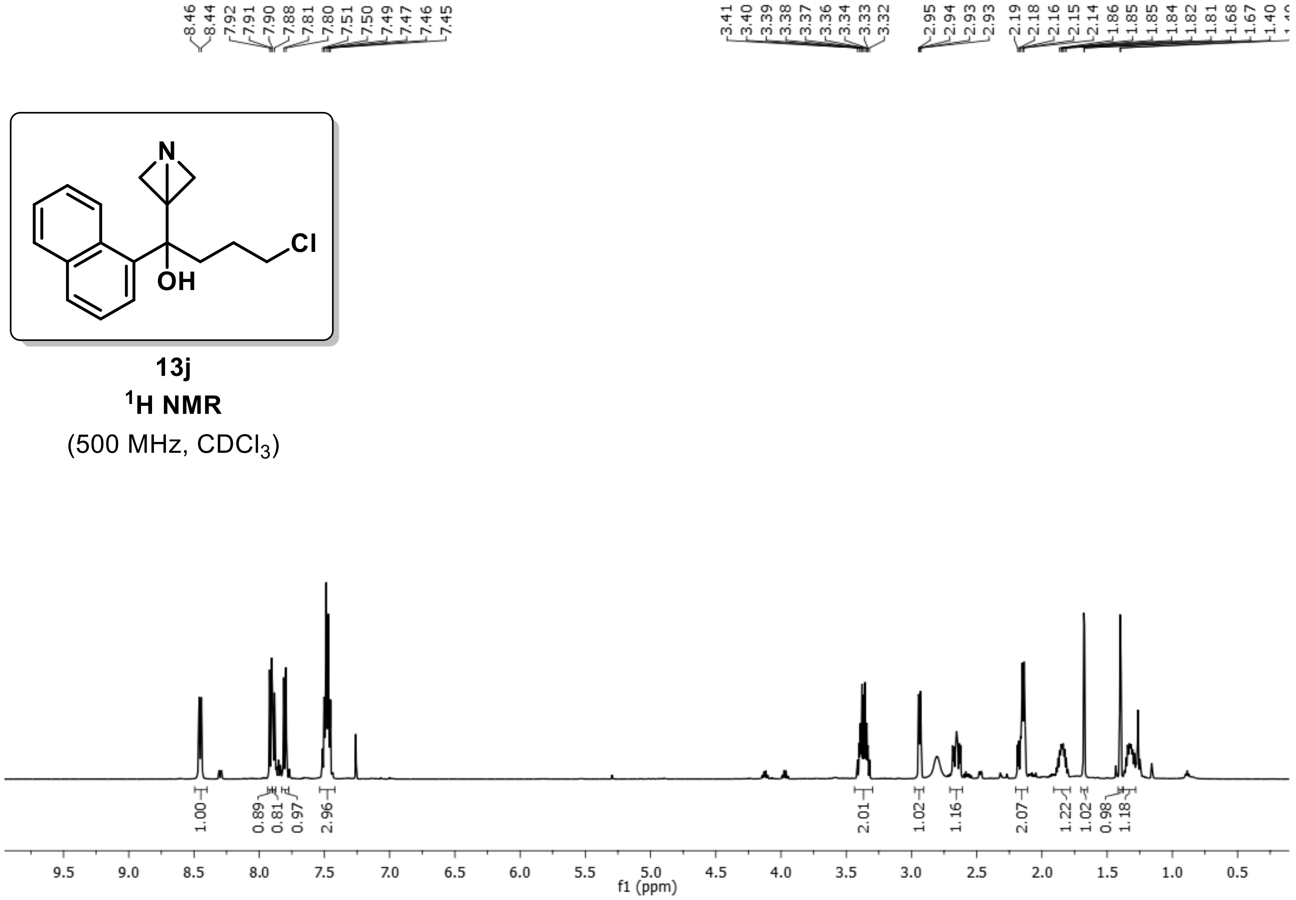
(500 MHz, $CDCl_3$)



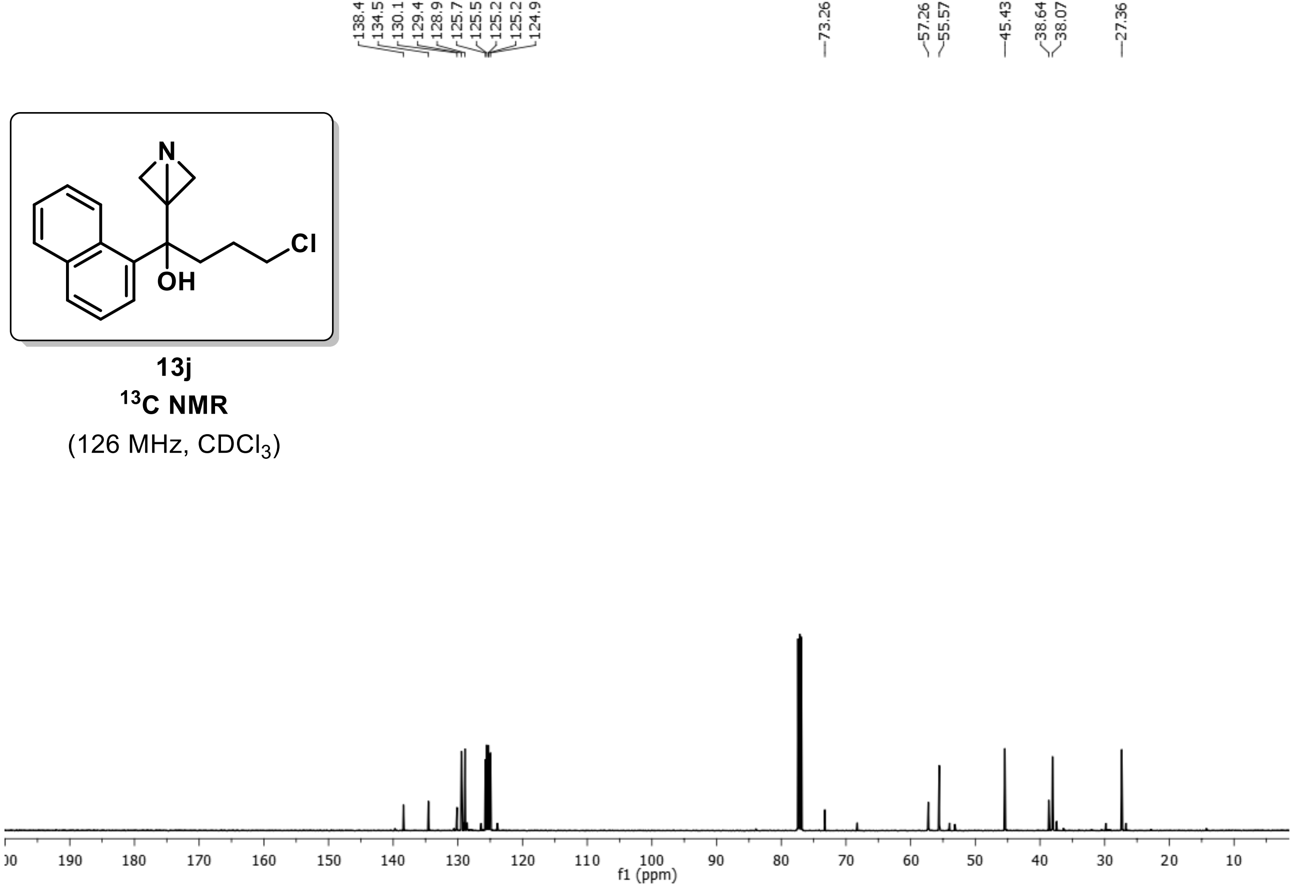
7c

^{13}C NMR

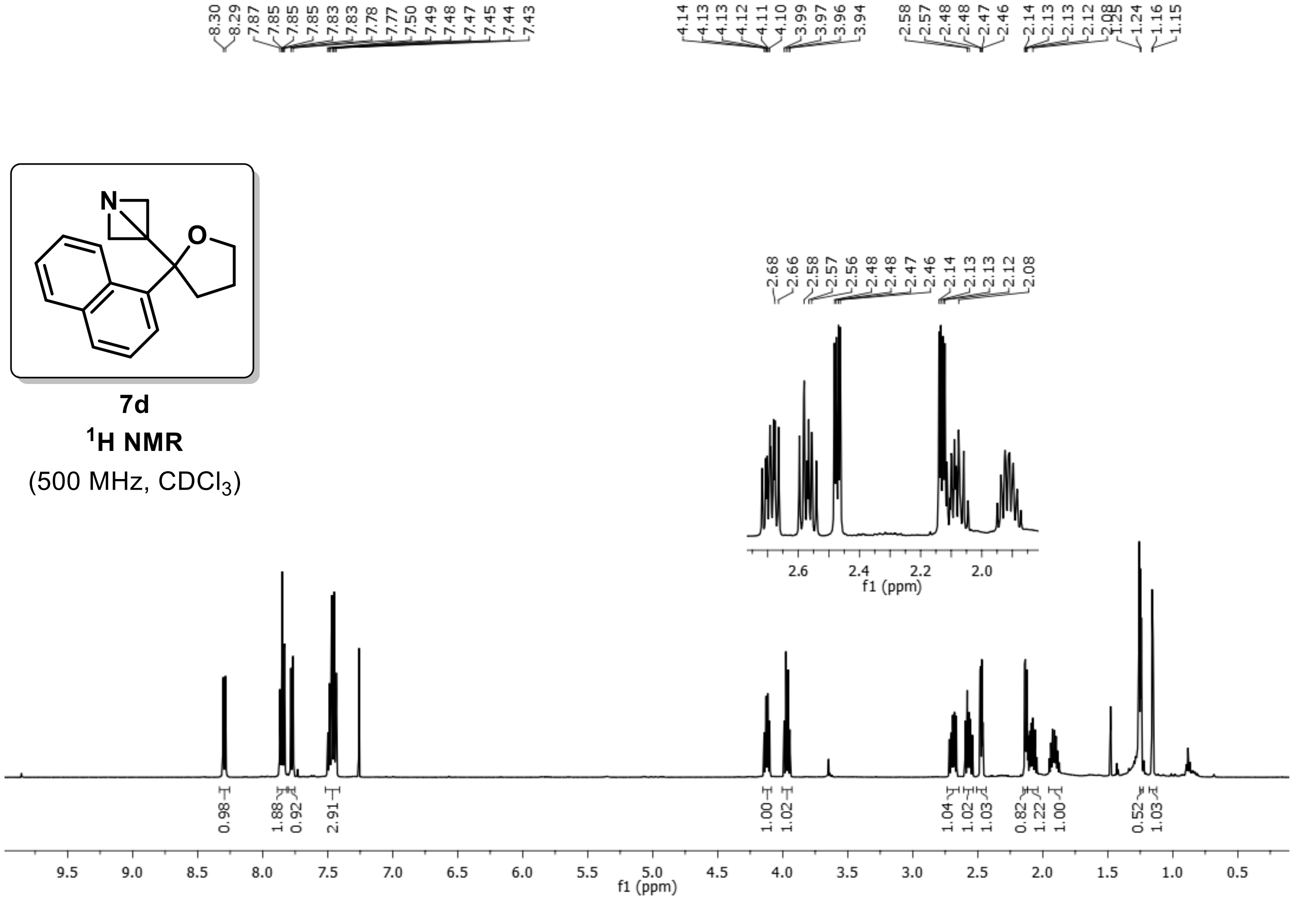
(126 MHz, $CDCl_3$)



13j
^{1}H NMR
(500 MHz, $CDCl_3$)



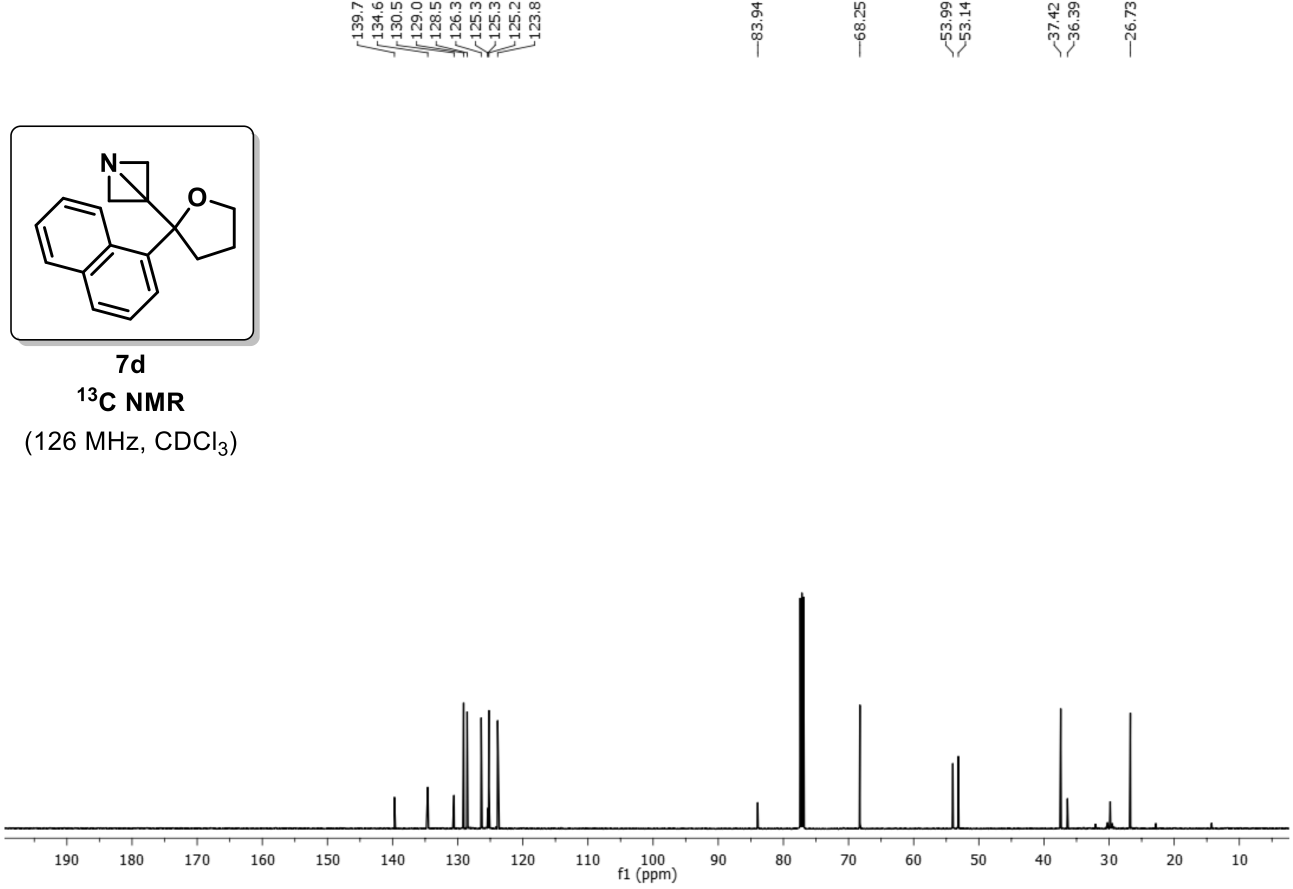
13j
^{13}C NMR
(126 MHz, $CDCl_3$)



7d

^{1}H NMR

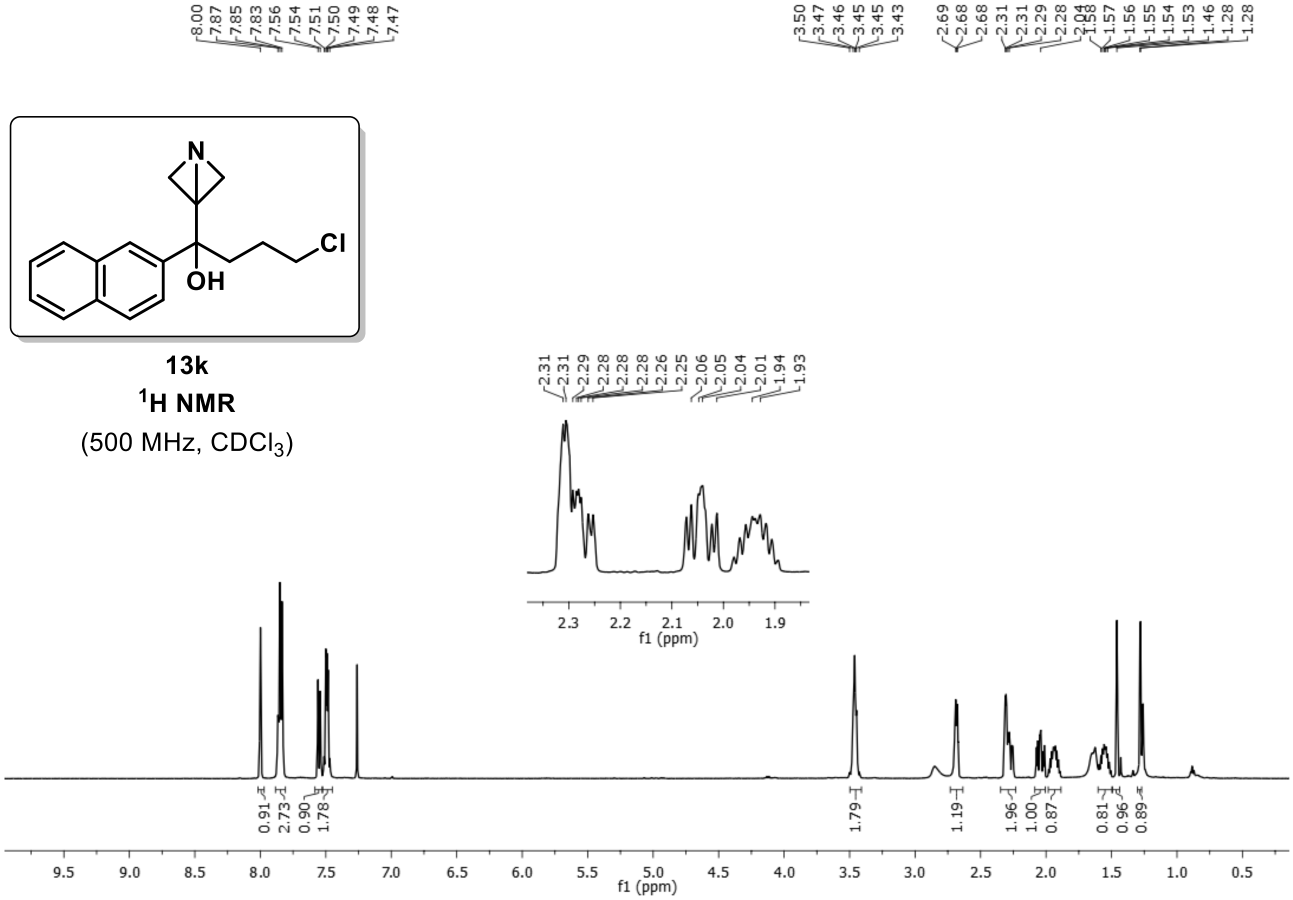
(500 MHz, $CDCl_3$)



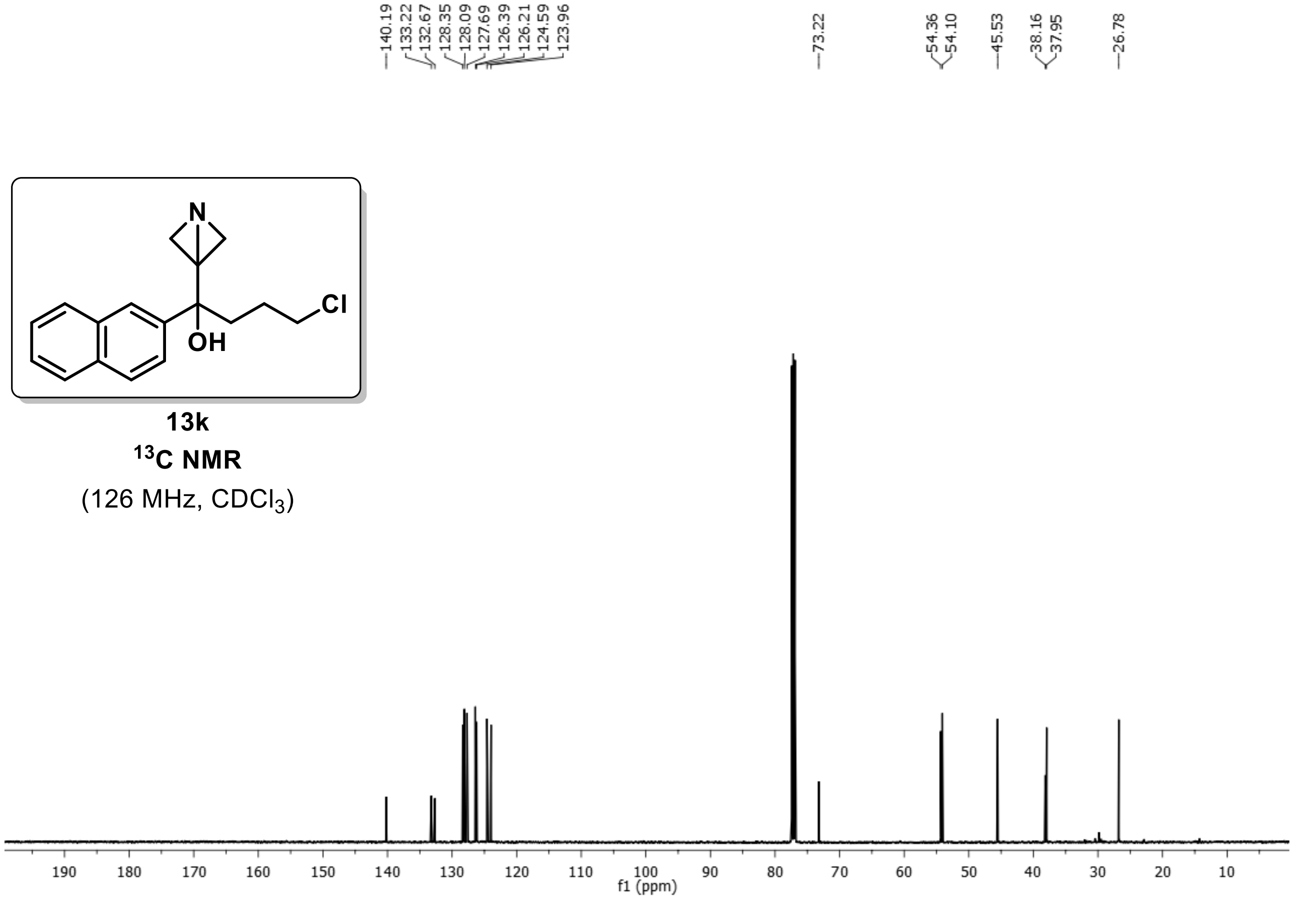
7d

^{13}C NMR

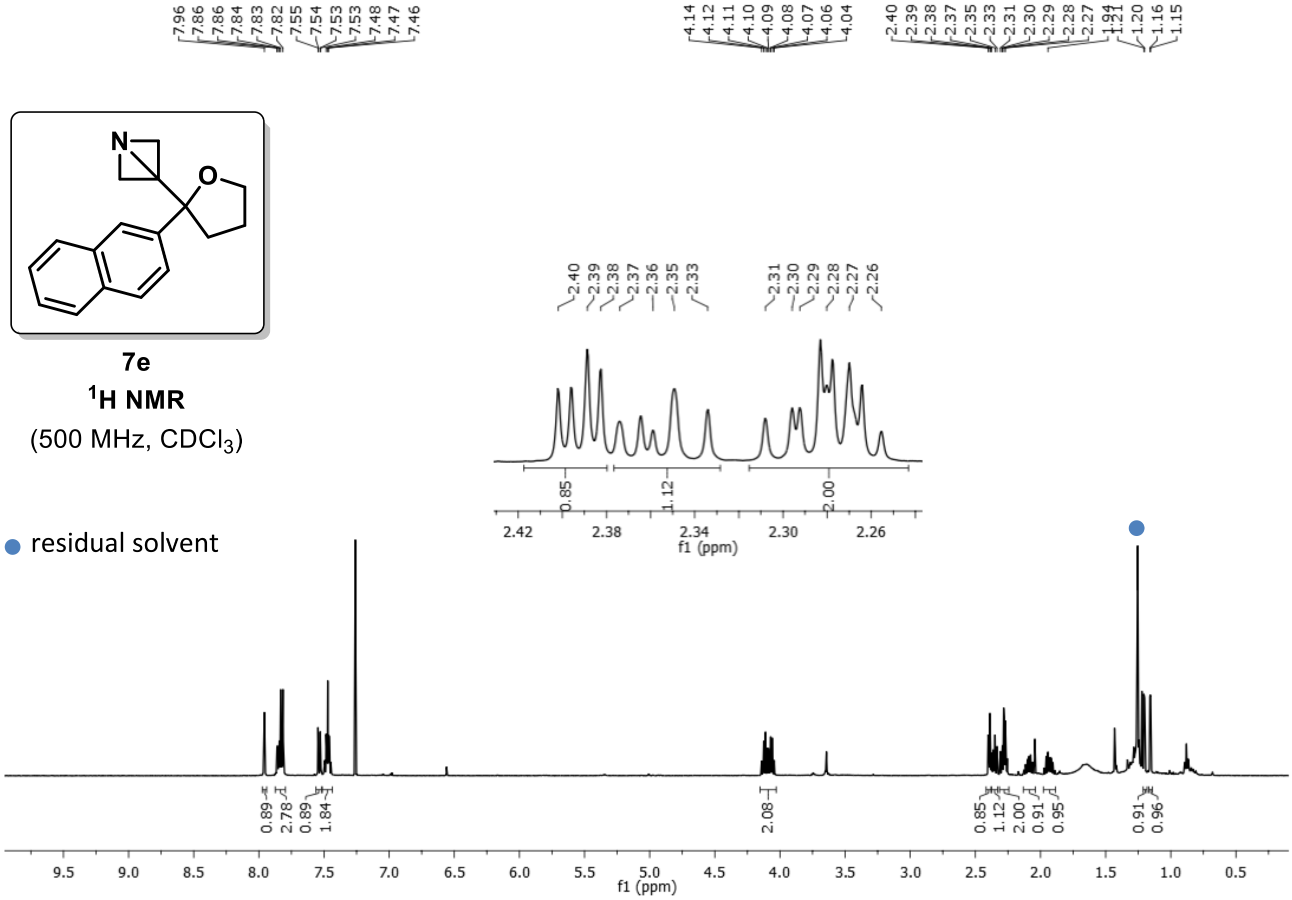
(126 MHz, $CDCl_3$)



13k
^{1}H NMR
(500 MHz, $CDCl_3$)



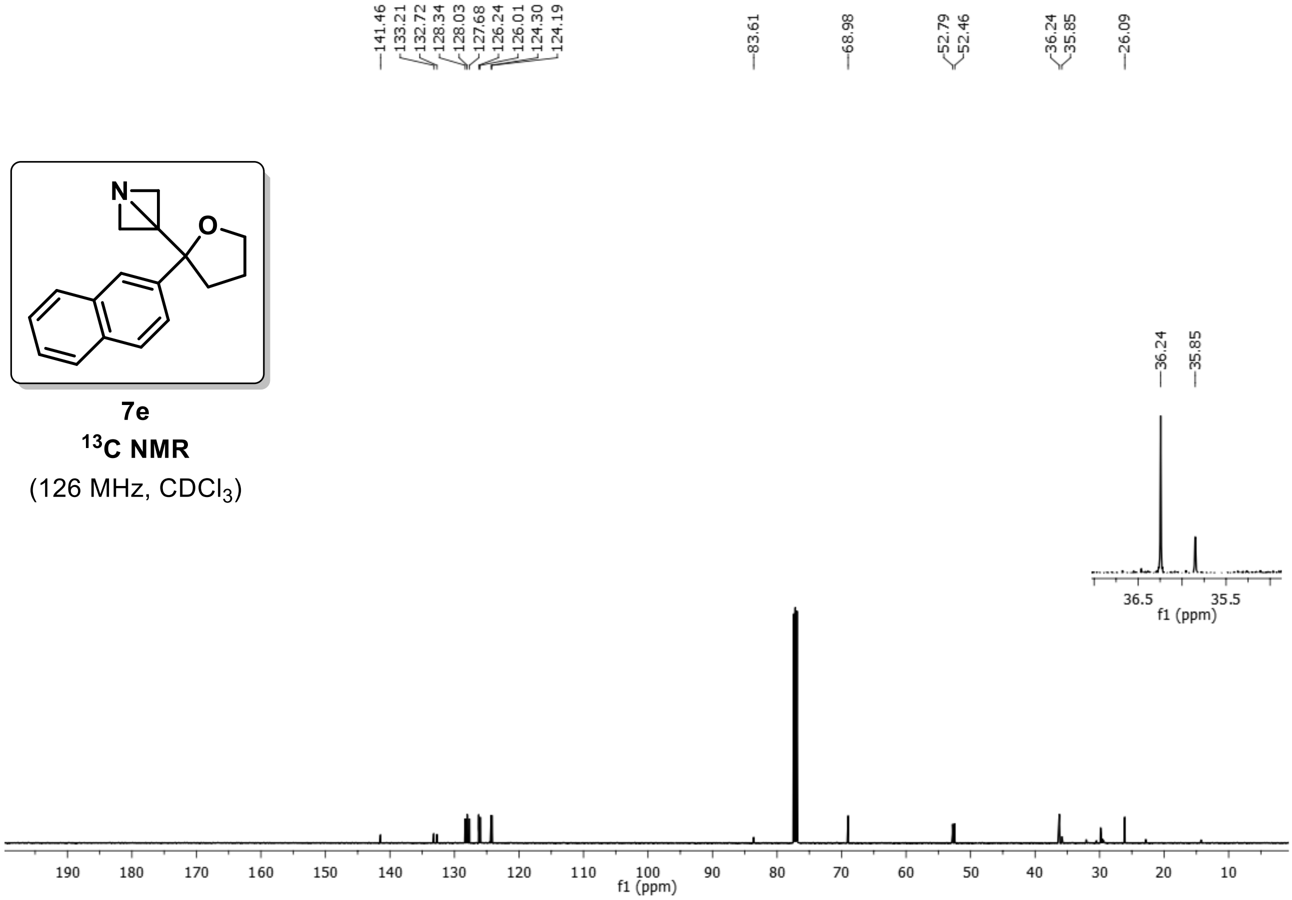
13k
^{13}C NMR
(126 MHz, $CDCl_3$)



7e

^{1}H NMR

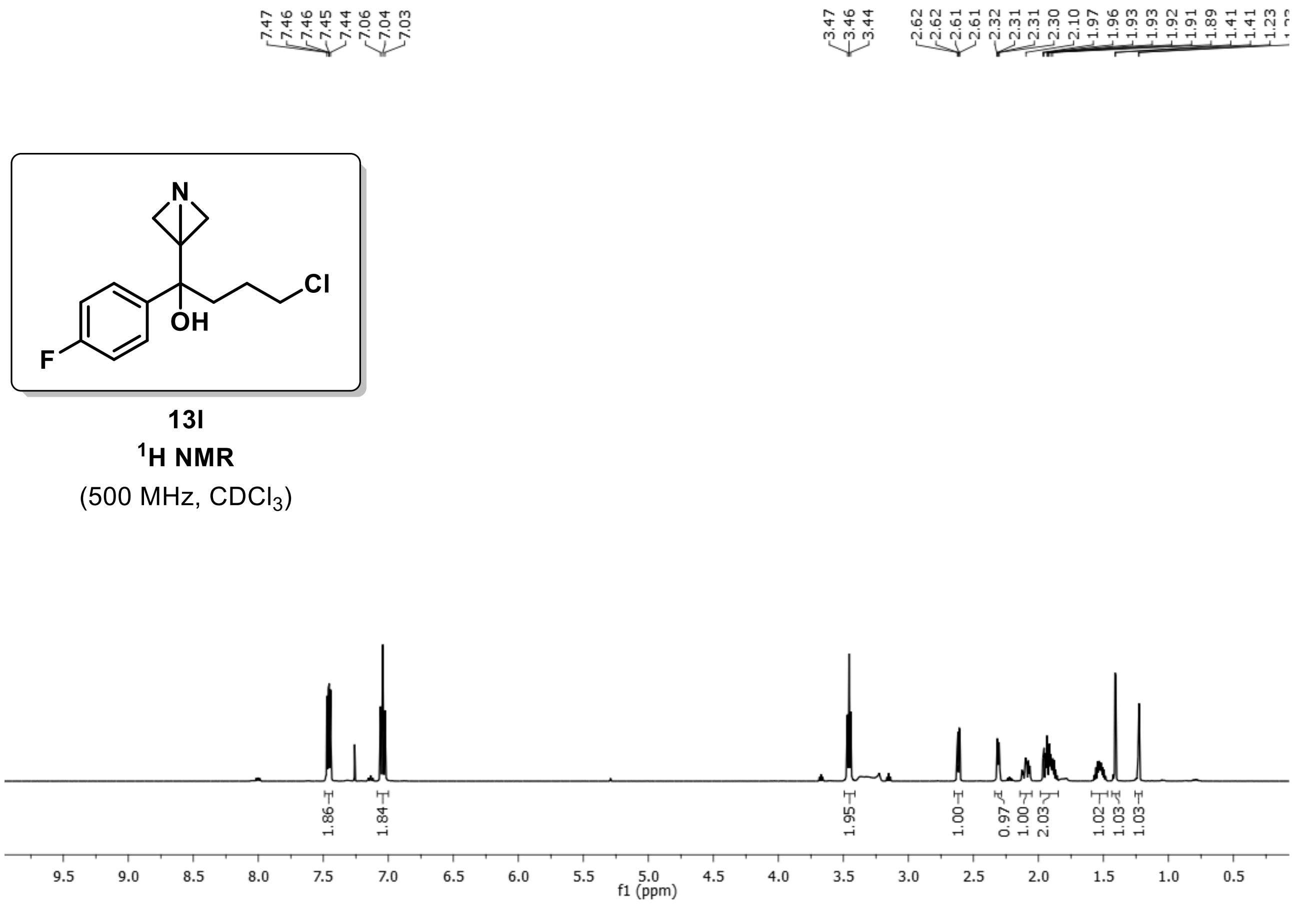
(500 MHz, $CDCl_3$)



7e

^{13}C NMR

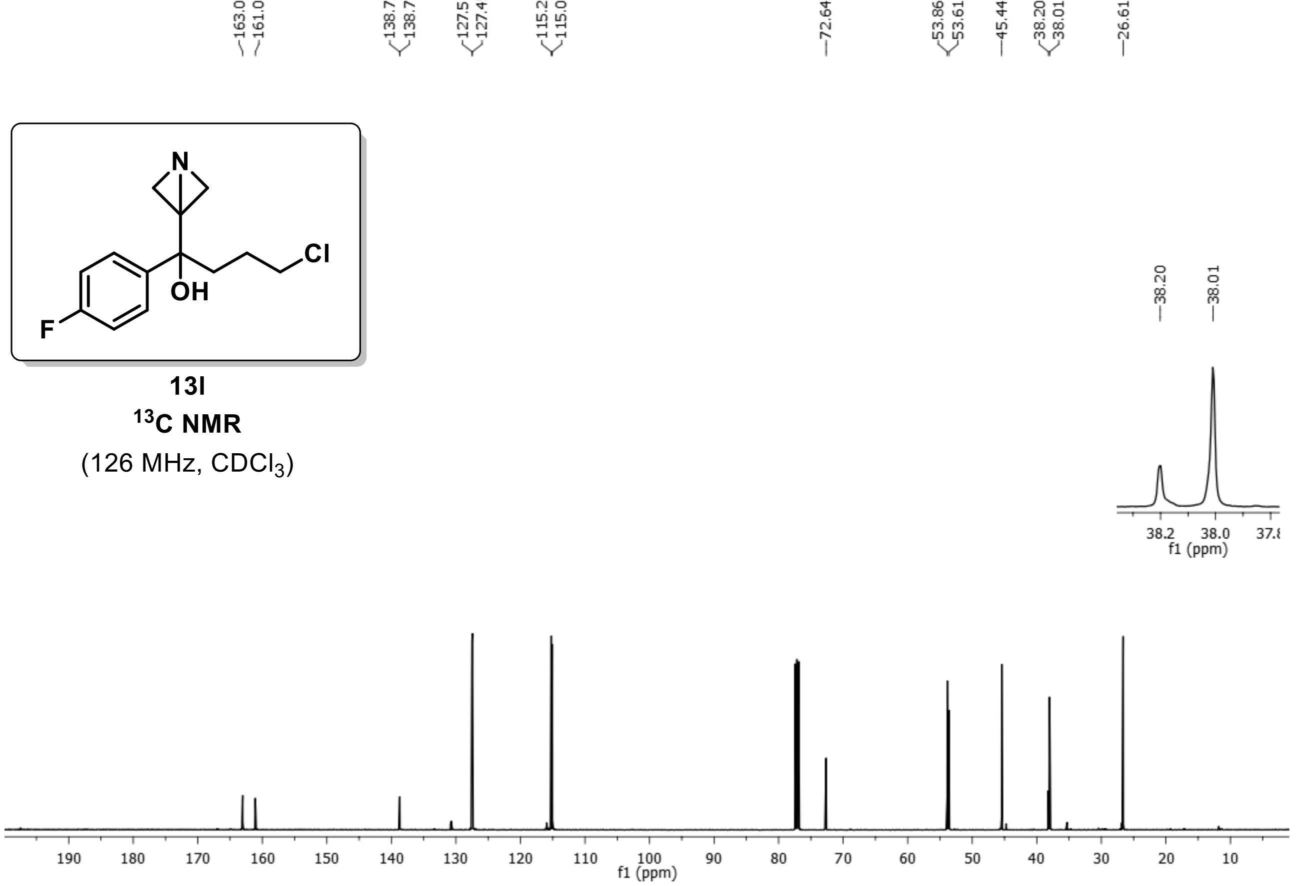
(126 MHz, $CDCl_3$)



13l

^{1}H NMR

(500 MHz, $CDCl_3$)



13l

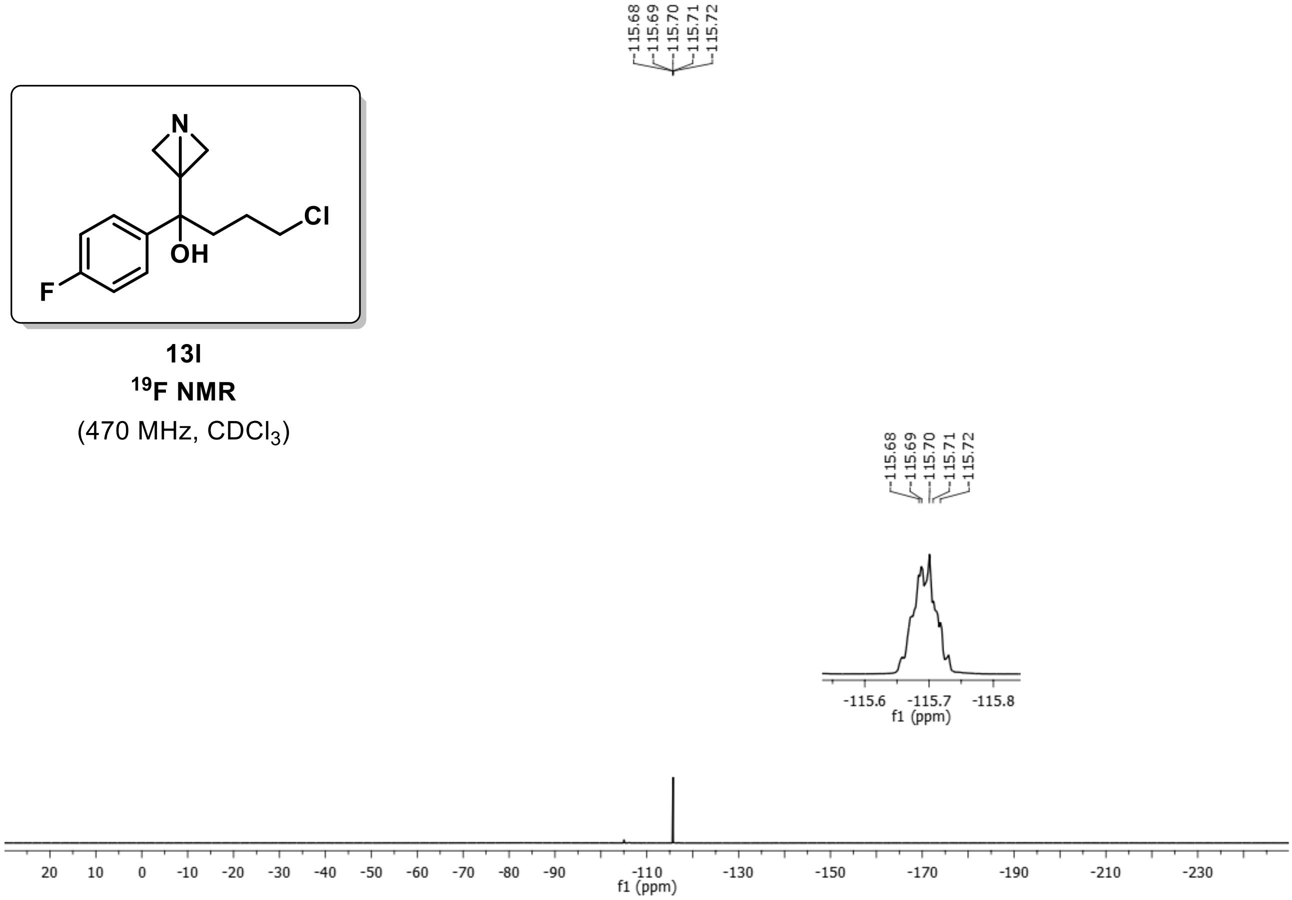
^{13}C NMR

(126 MHz, $CDCl_3$)

13l

^{19}F NMR

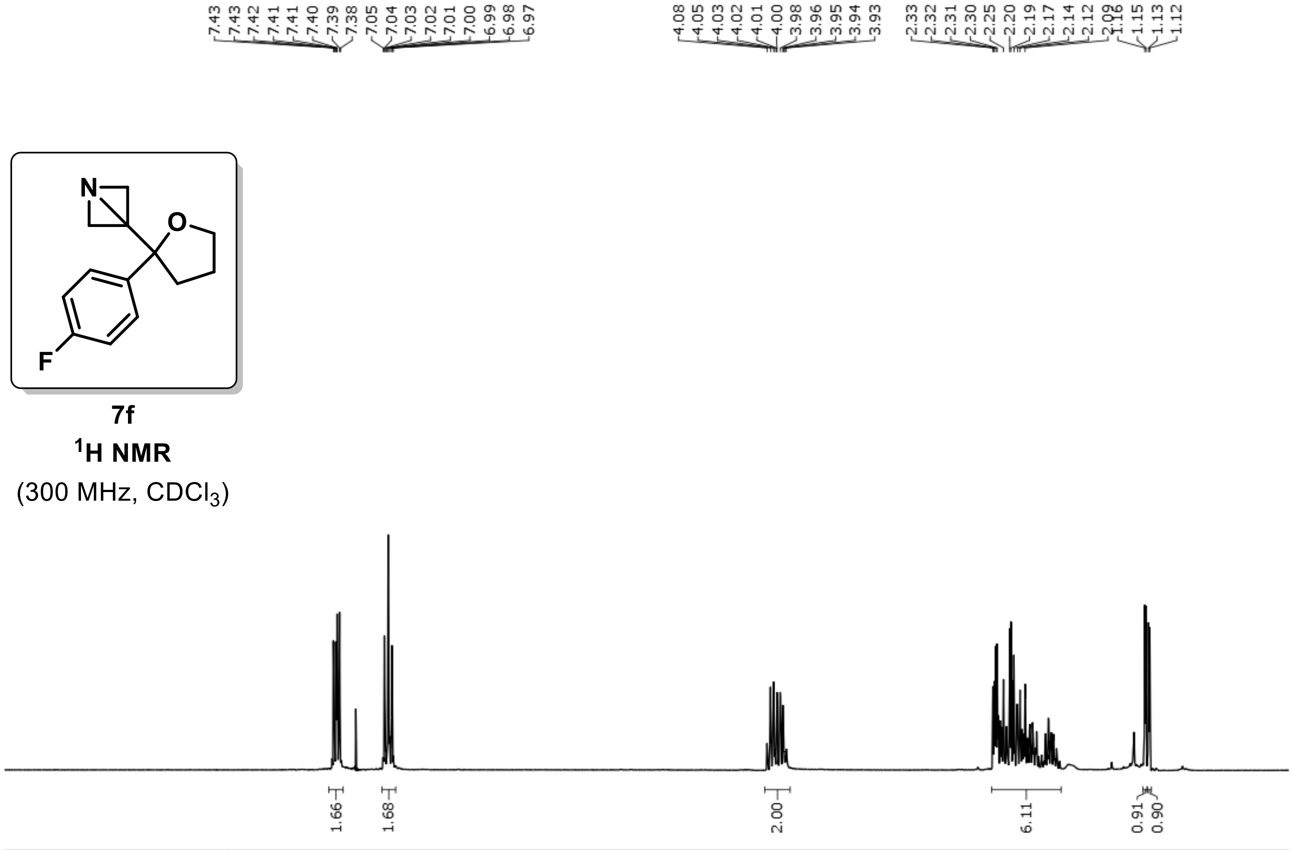
(470 MHz, $CDCl_3$)

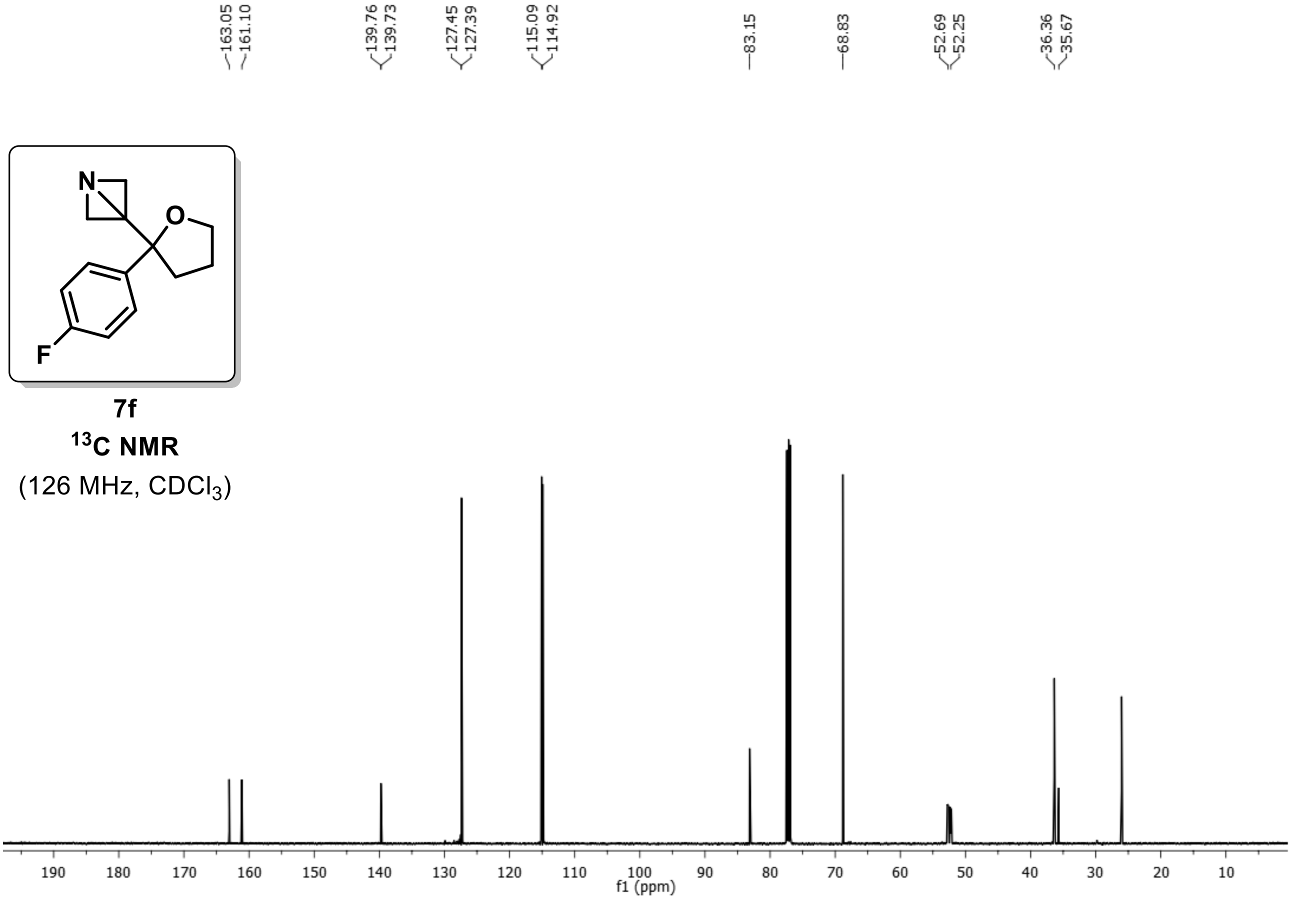


7f

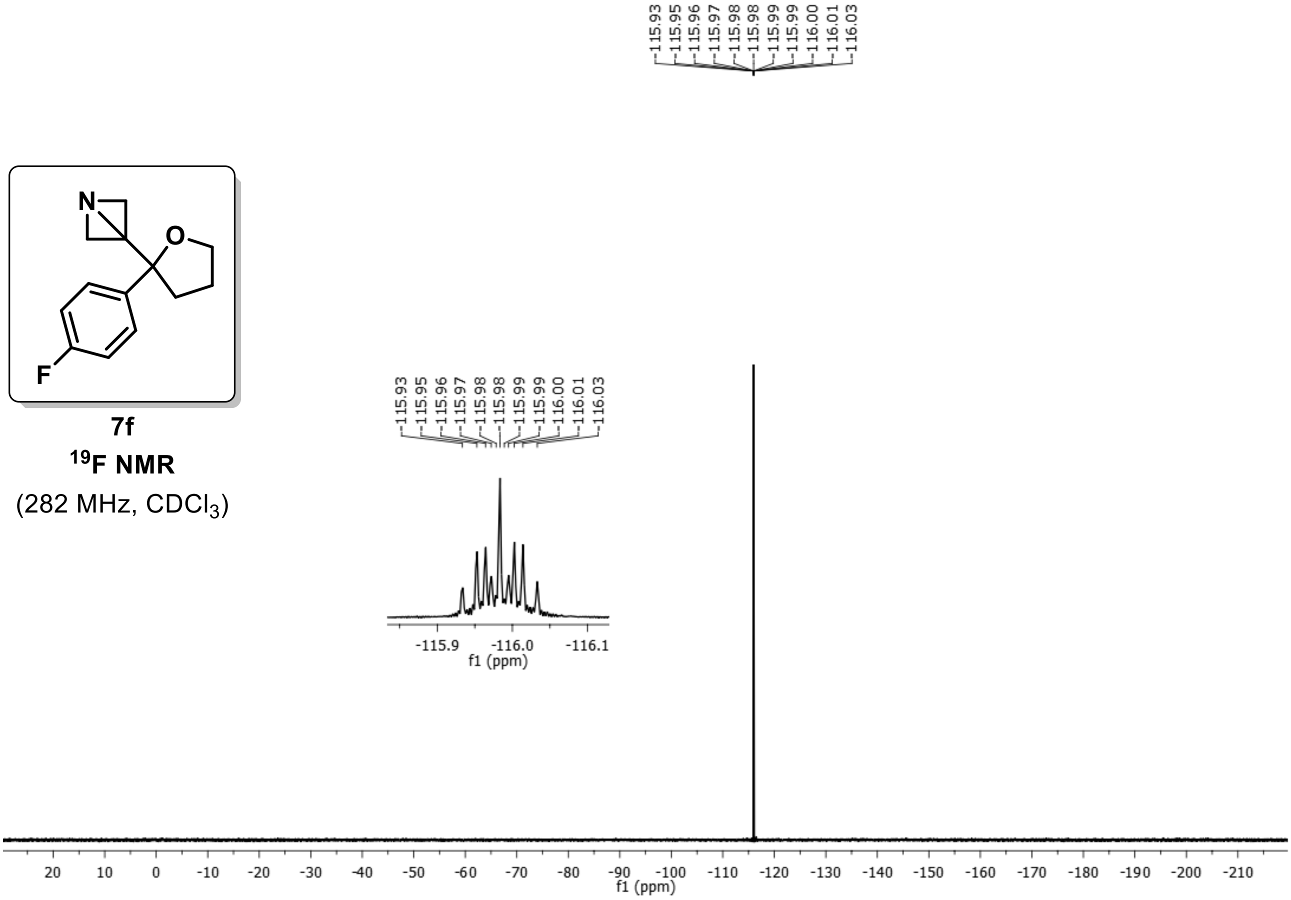
^{1}H NMR

(300 MHz, $CDCl_3$)

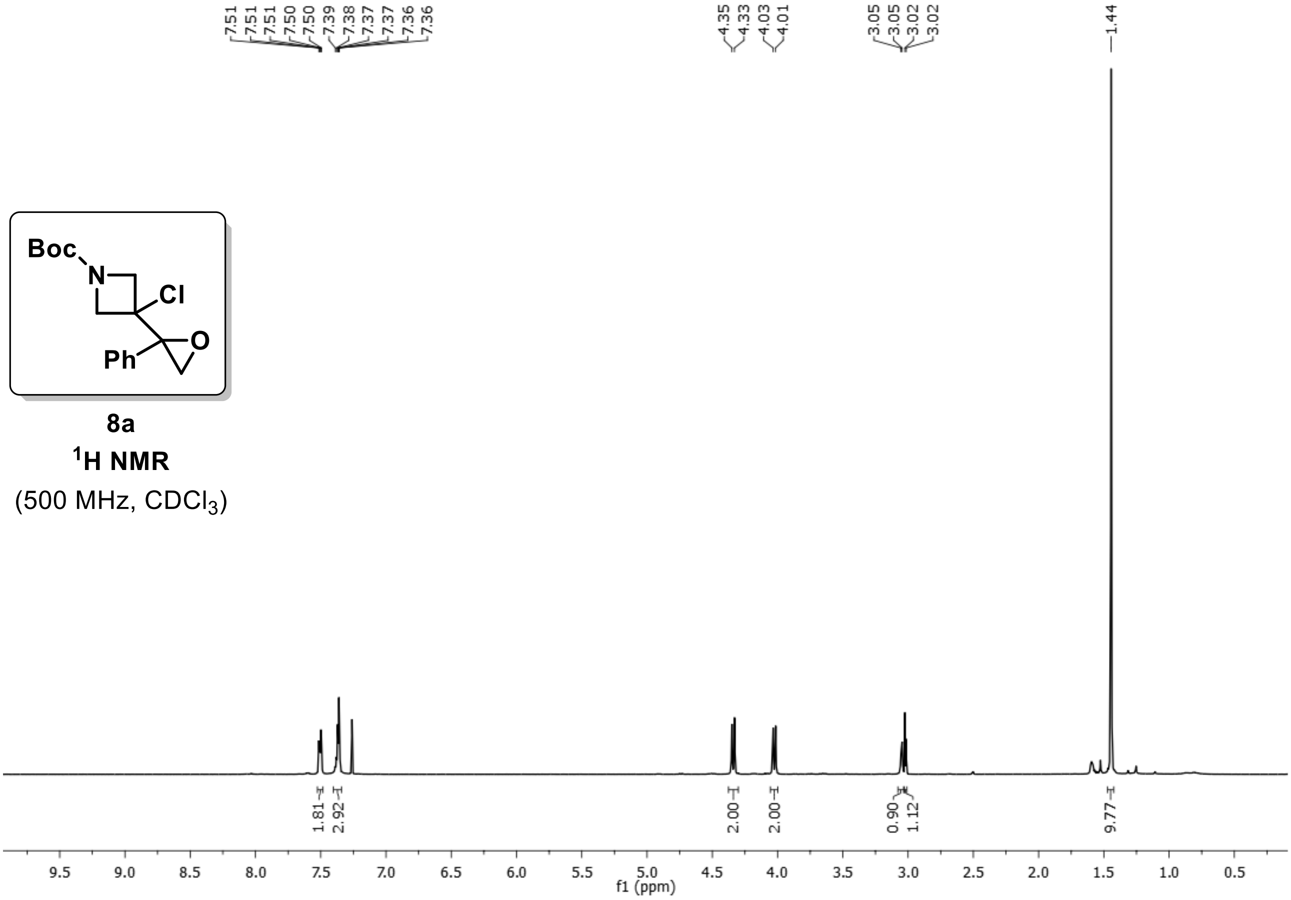




7f
^{13}C NMR
(126 MHz, $CDCl_3$)



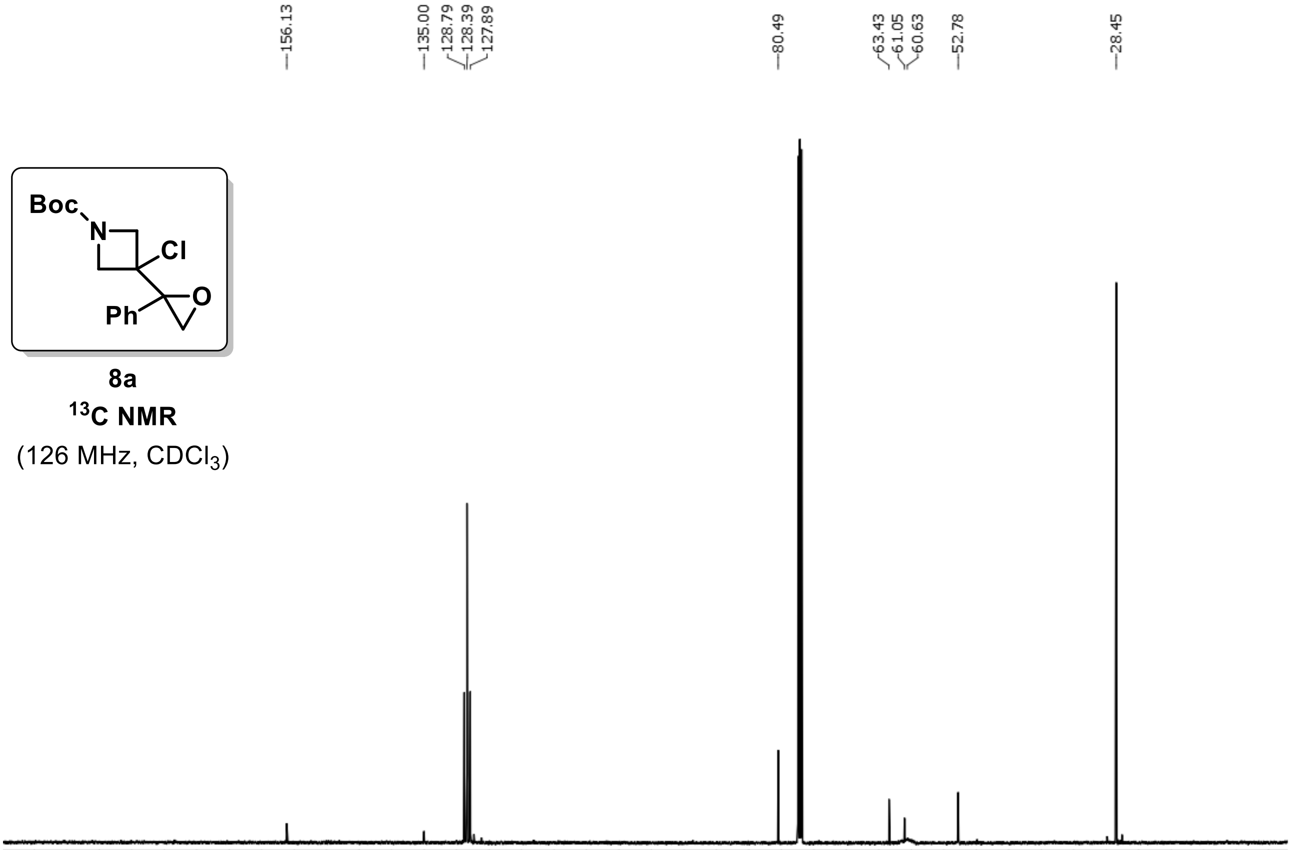
7f
^{19}F NMR
(282 MHz, $CDCl_3$)



8a

^{1}H NMR

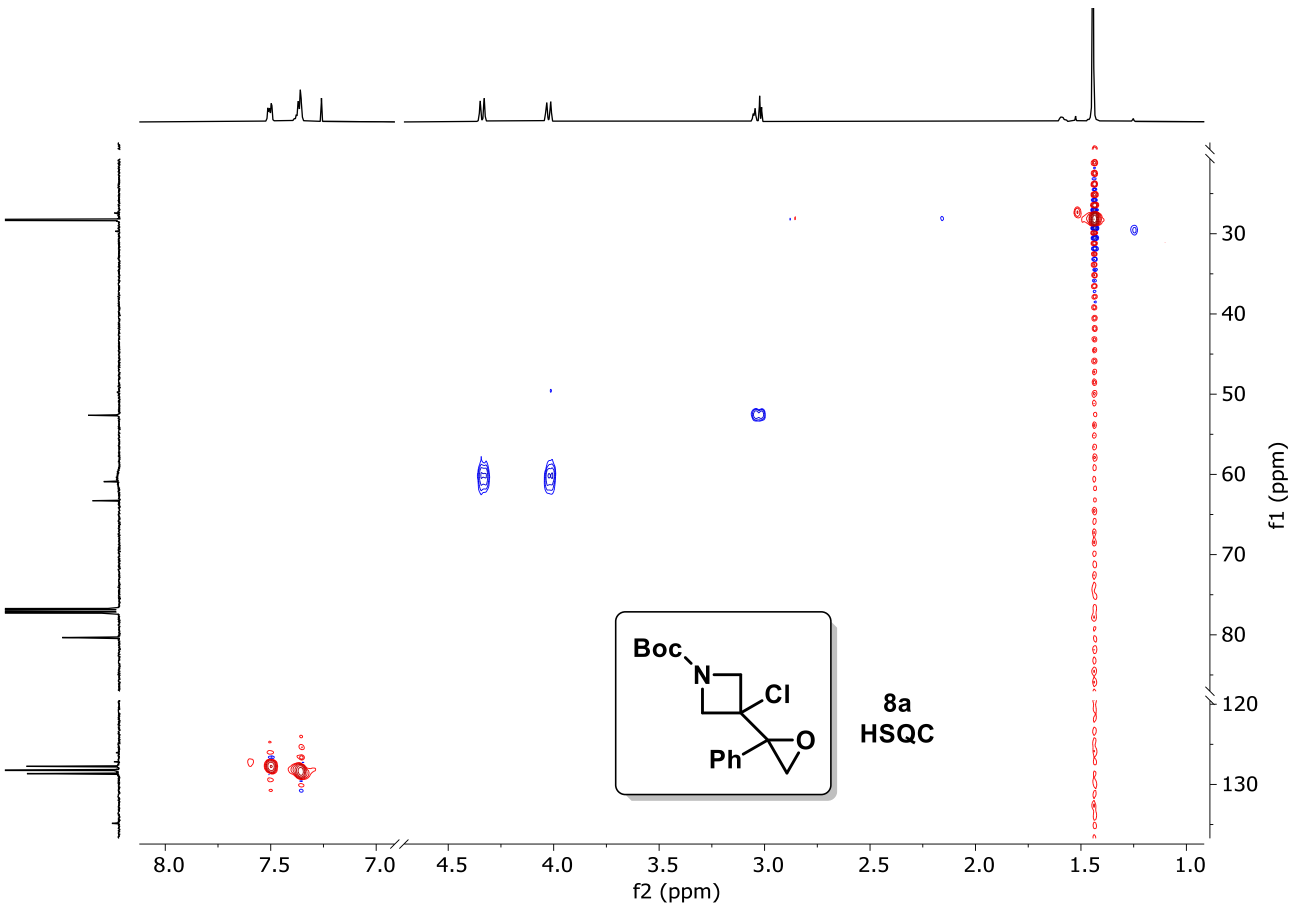
(500 MHz, $CDCl_3$)



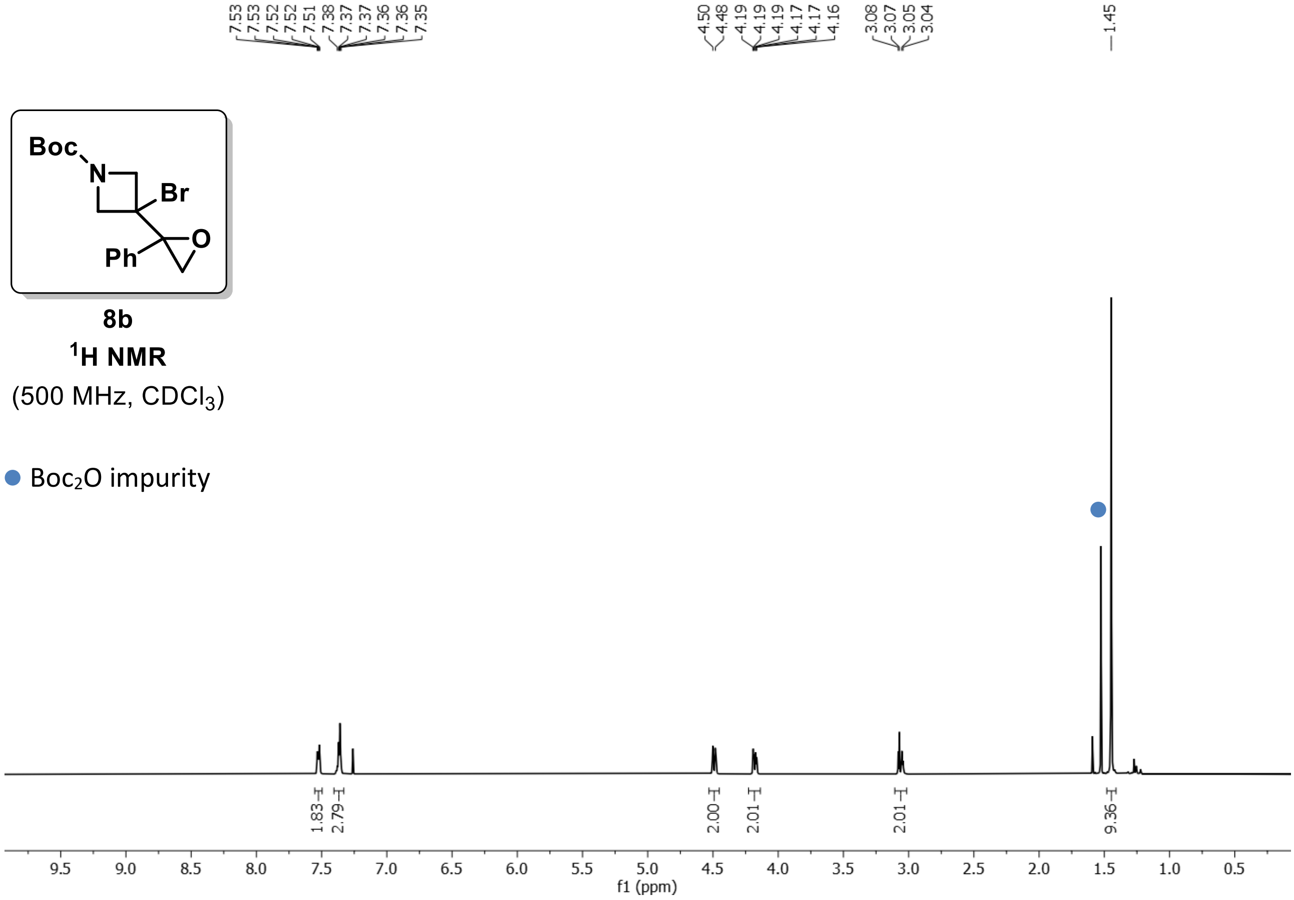
8a

^{13}C NMR

(126 MHz, $CDCl_3$)

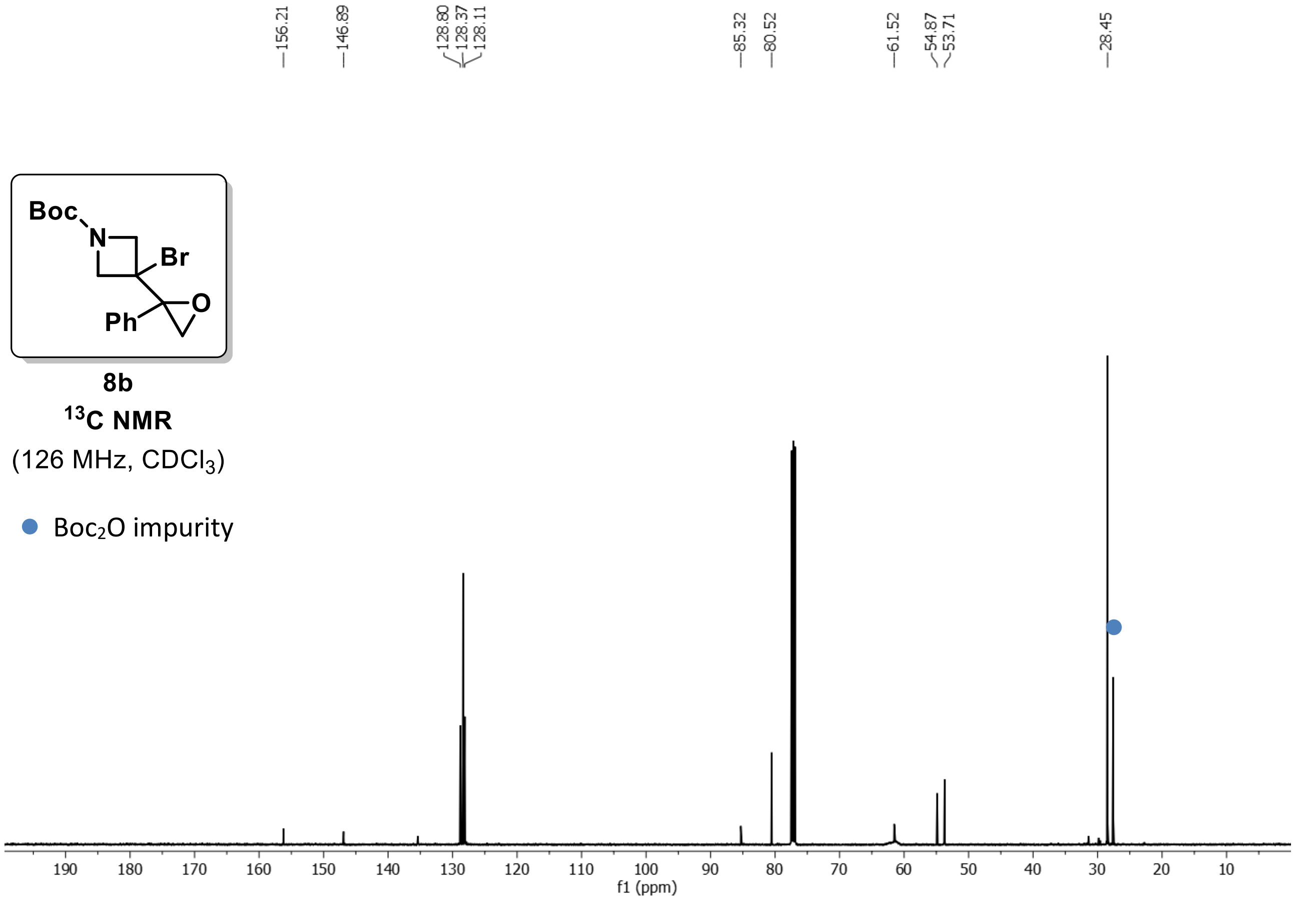


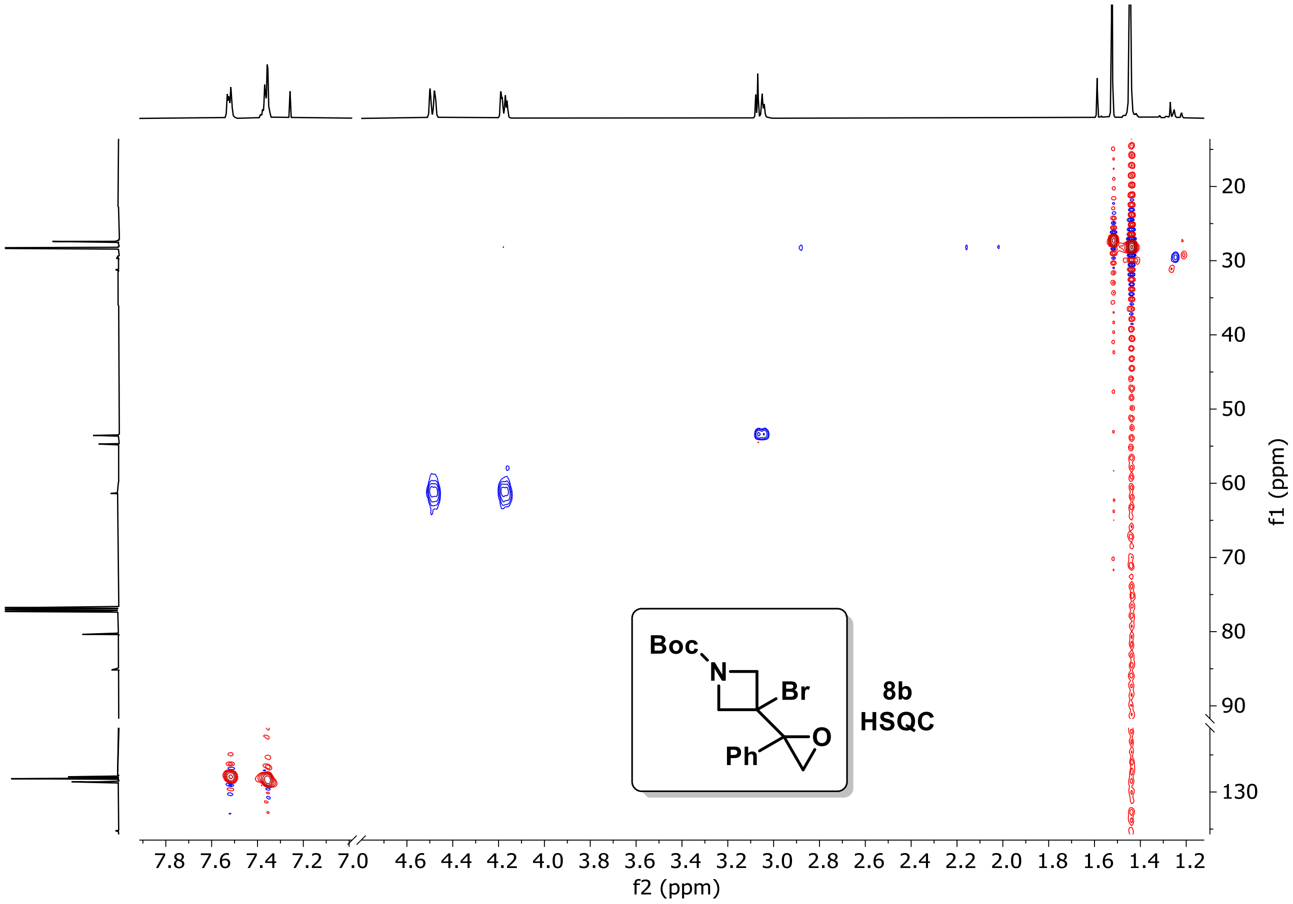
8a
HSQC



8b
^{1}H NMR
(500 MHz, $CDCl_3$)

● Boc_2O impurity

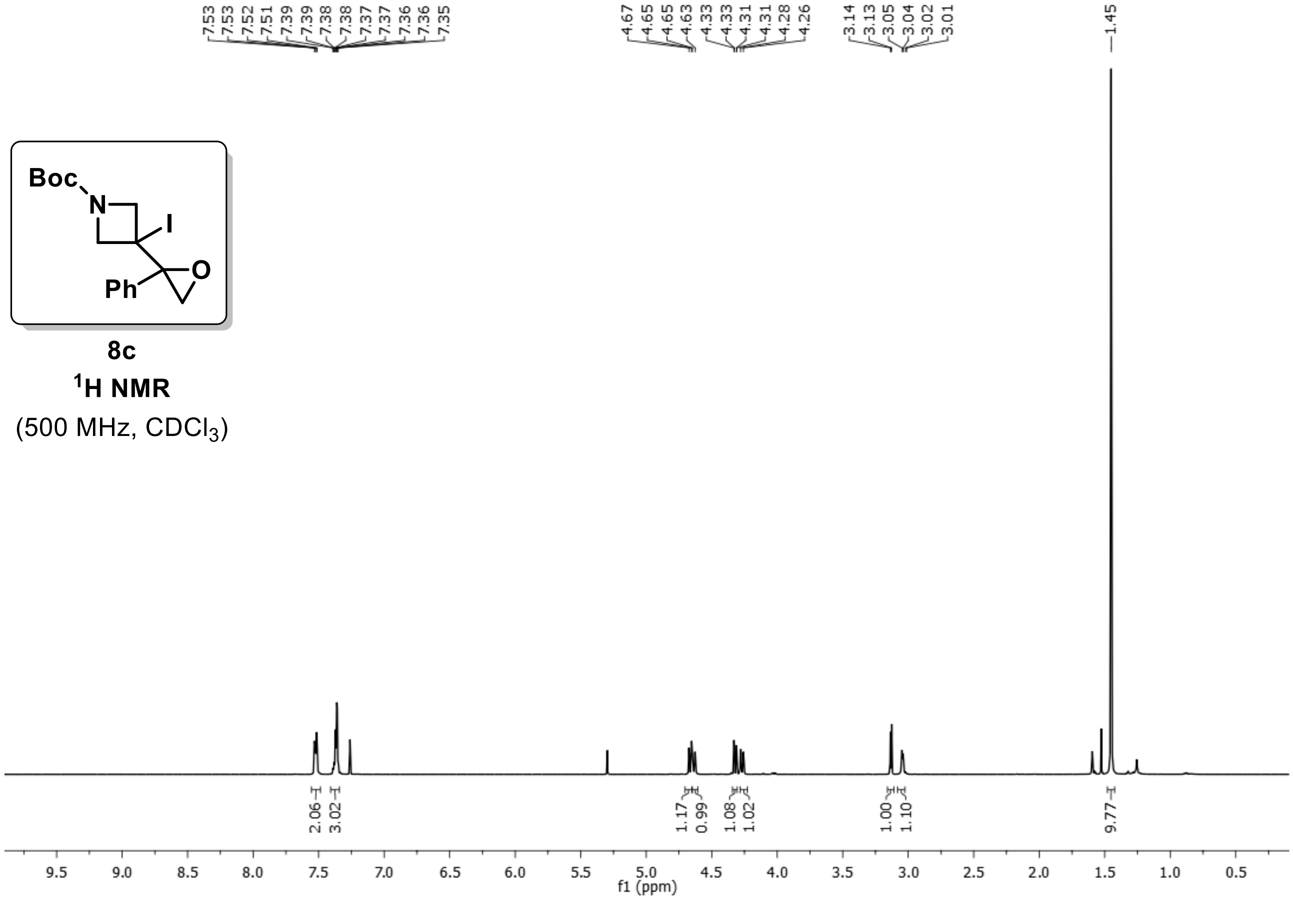

156.21
146.89
128.80
128.37
128.11
85.32
80.52
61.52
54.87
53.71
28.45
Boc
N
Br
Ph
O
8b
^{13}C NMR
(126 MHz, $CDCl_3$)
● Boc_2O impurity
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Boc
N
Br
Ph
O
8b
HSQC
20 30 40 50 60 70 80 90 130
f1 (ppm)
7.8 7.6 7.4 7.2 7.0 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f2 (ppm)

8c

^{1}H NMR

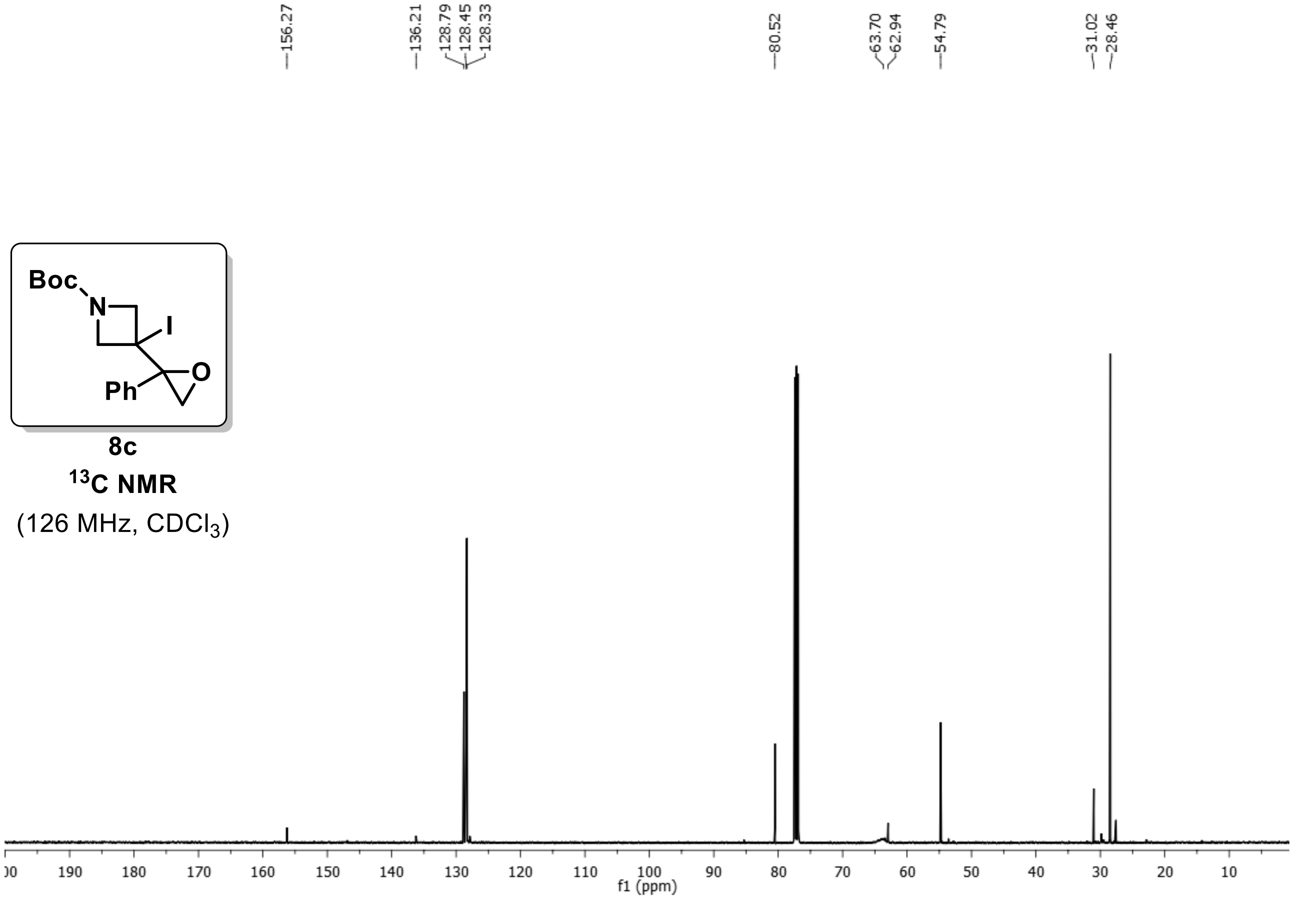
(500 MHz, $CDCl_3$)

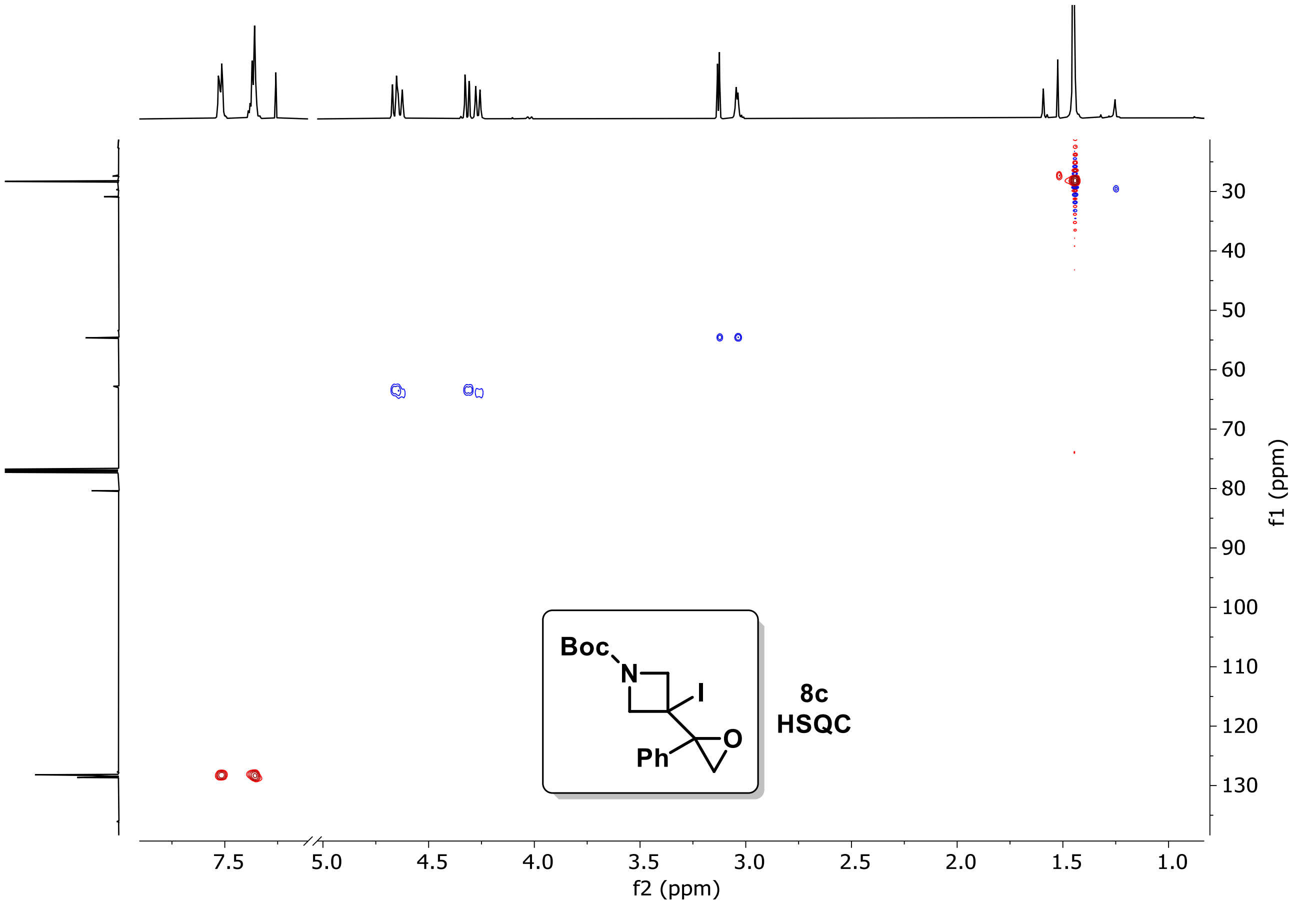


8c

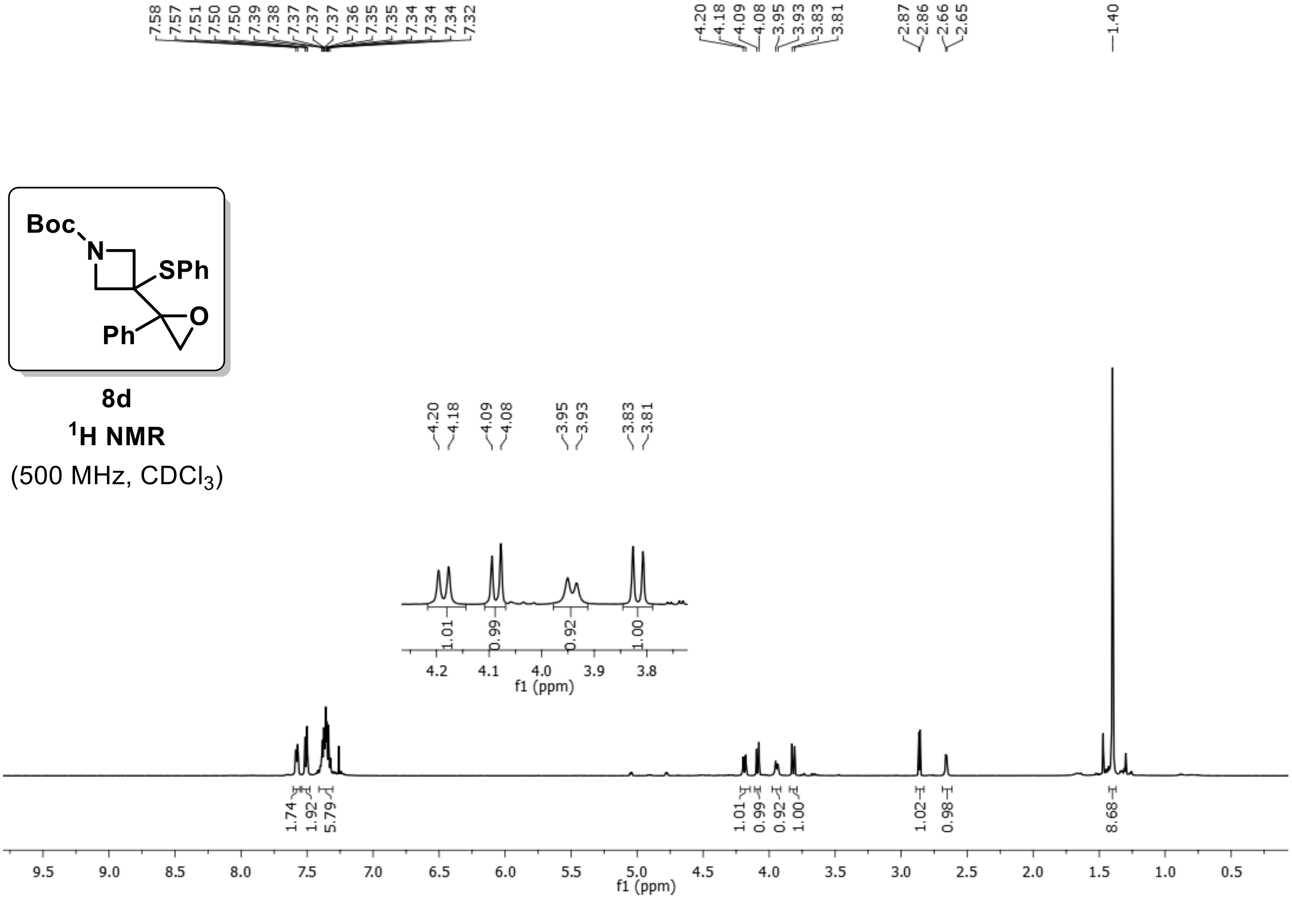
^{13}C NMR

(126 MHz, $CDCl_3$)

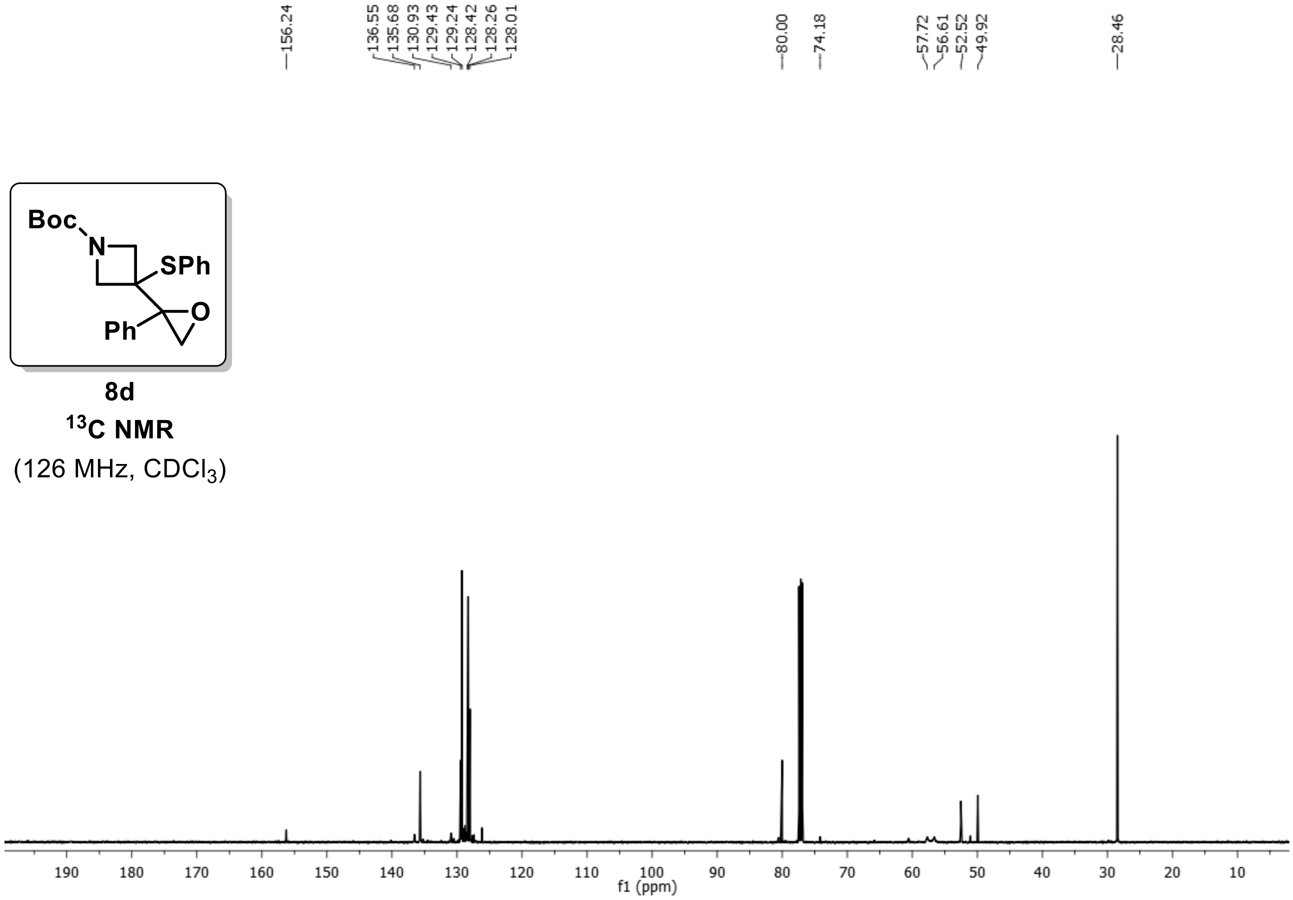




8c
HSQC



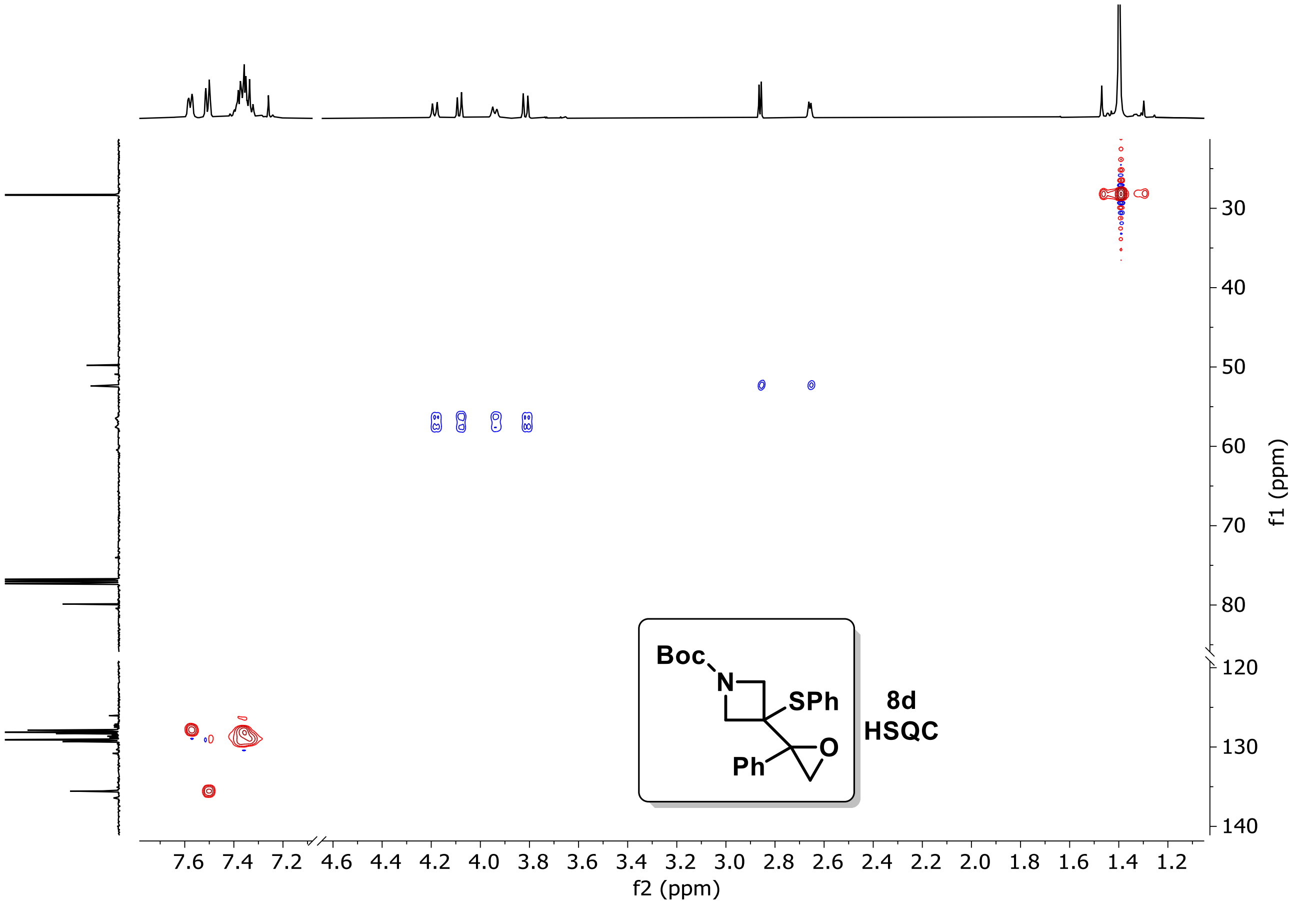
8d
^{1}H NMR
(500 MHz, $CDCl_3$)



8d

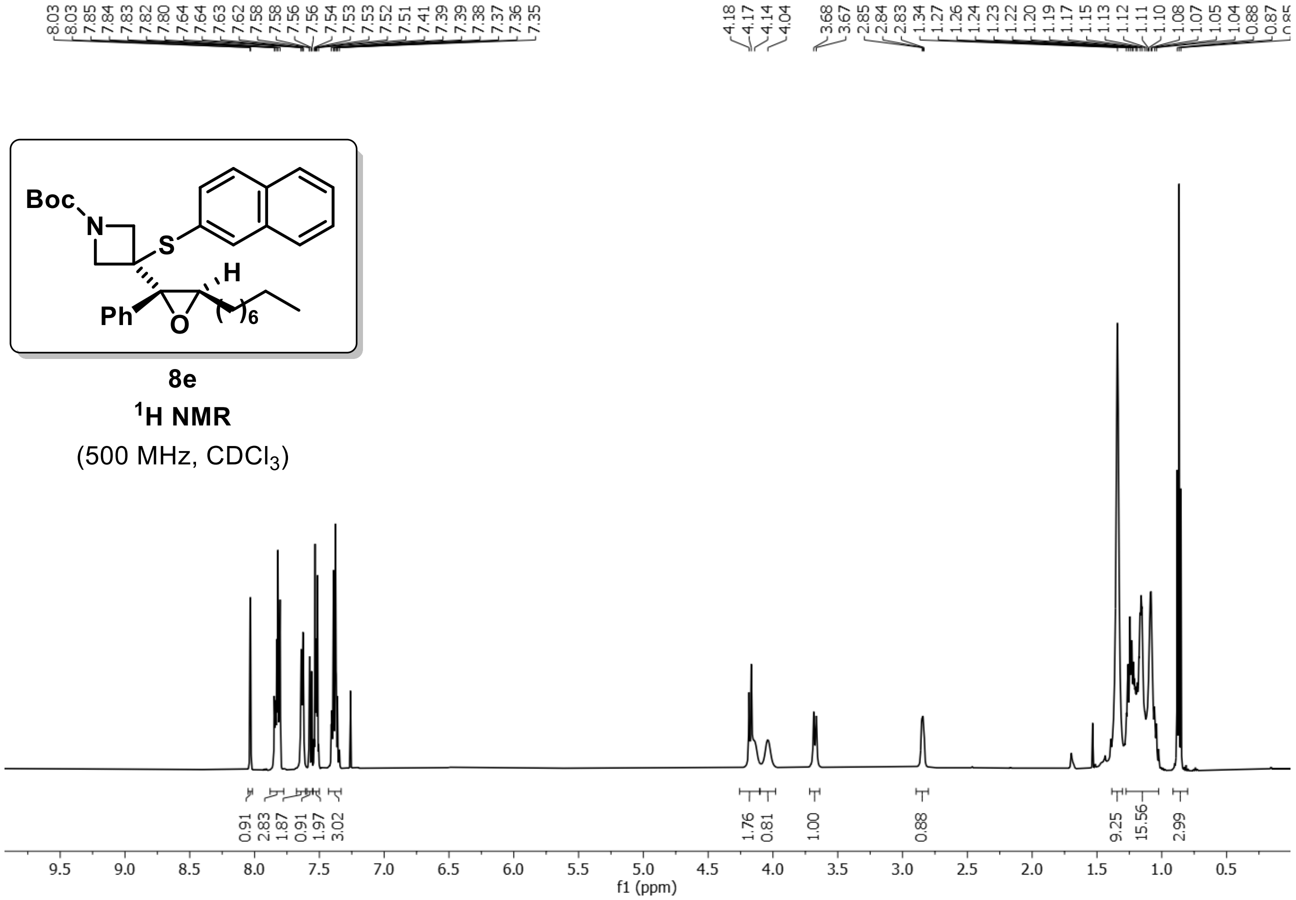
^{13}C NMR

(126 MHz, CDCl$_3$)



8d

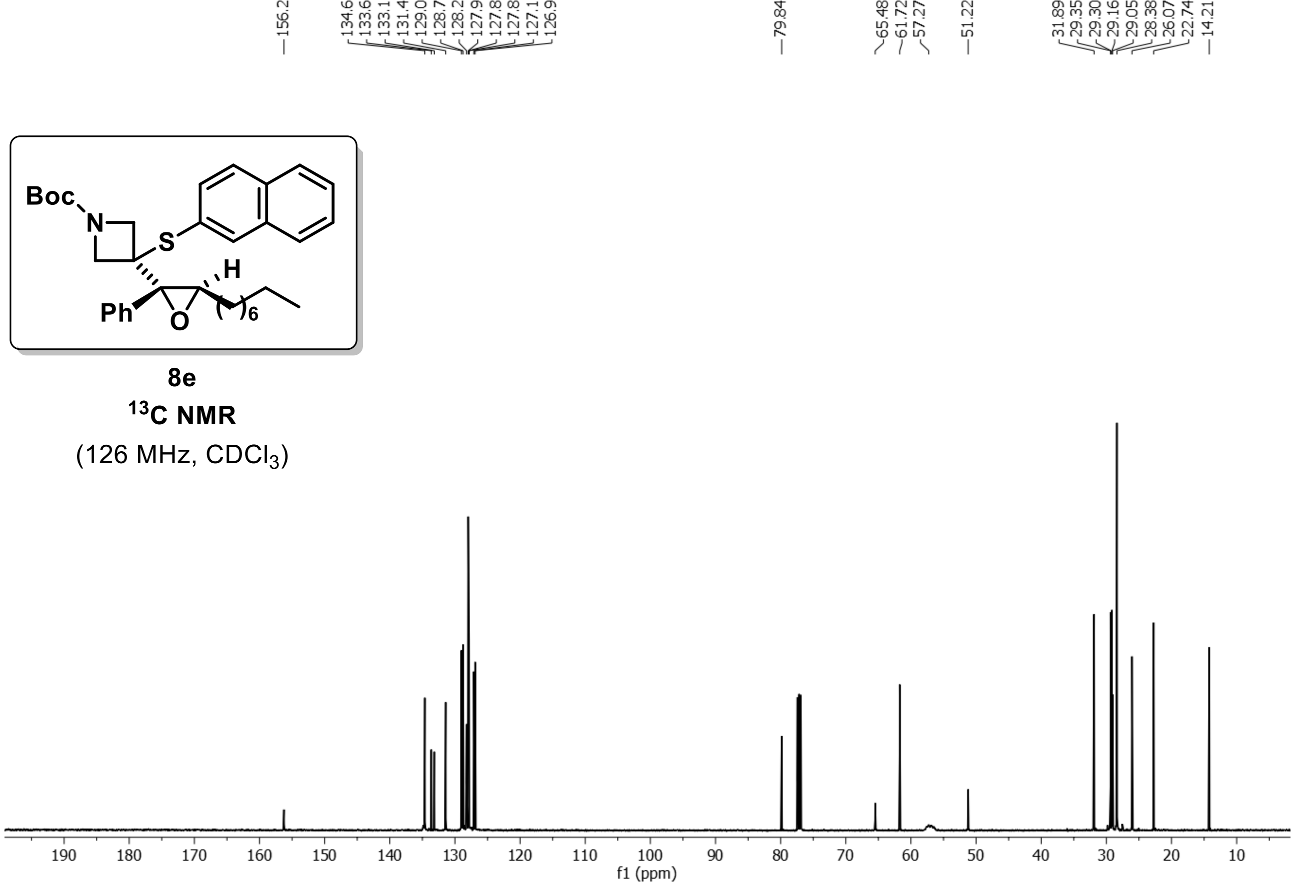
HSQC



8e

^{1}H NMR

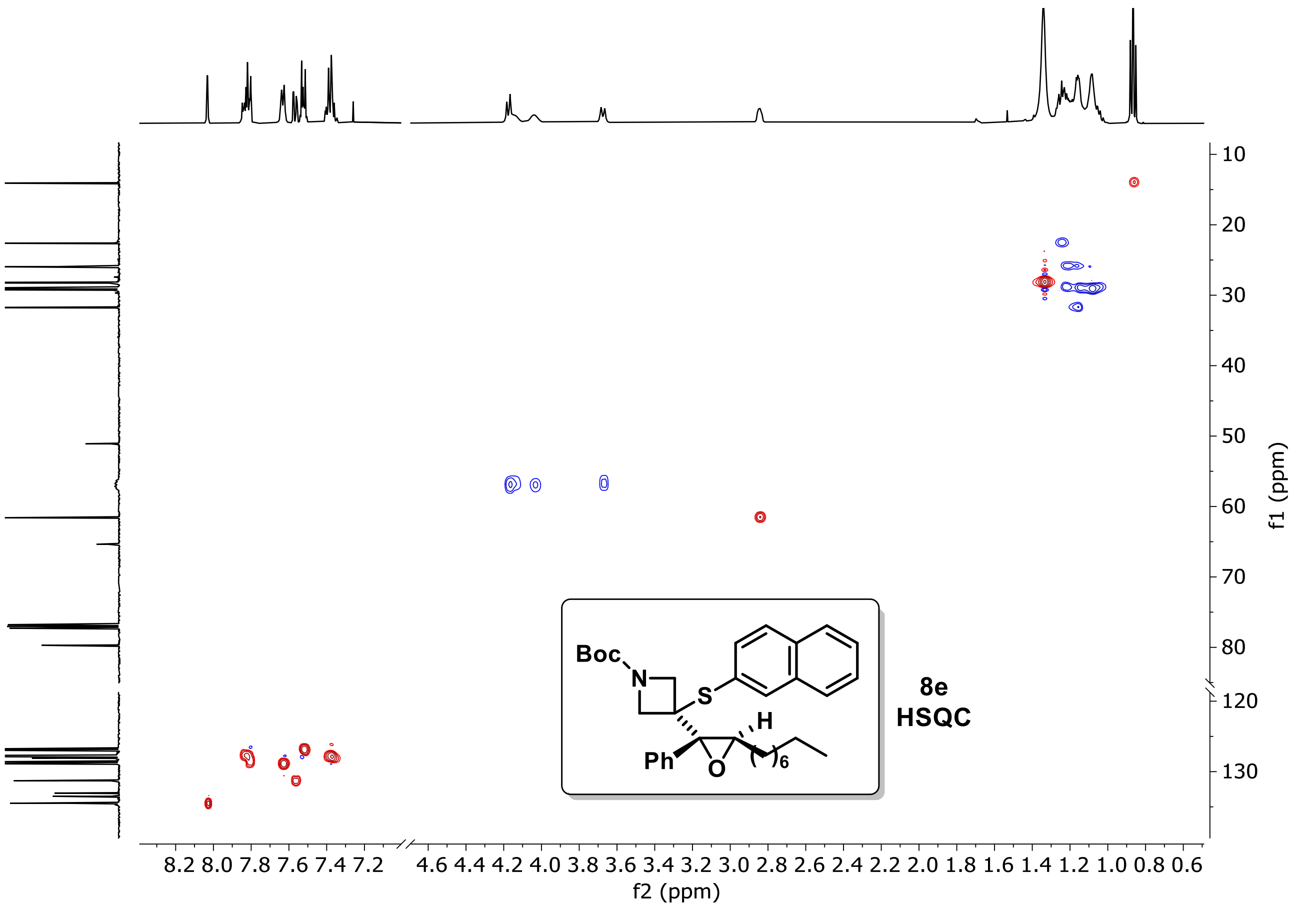
(500 MHz, $CDCl_3$)



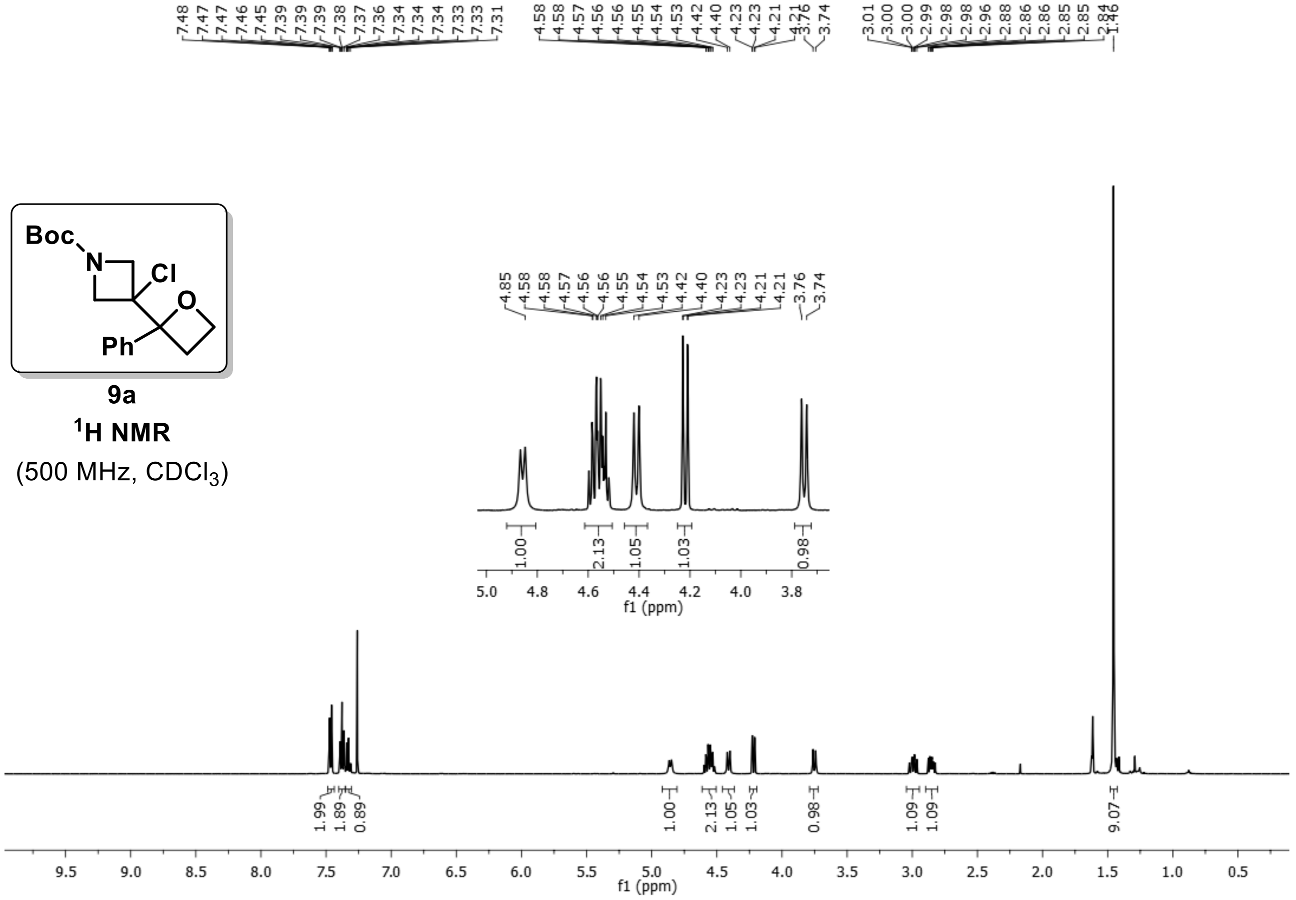
8e

^{13}C NMR

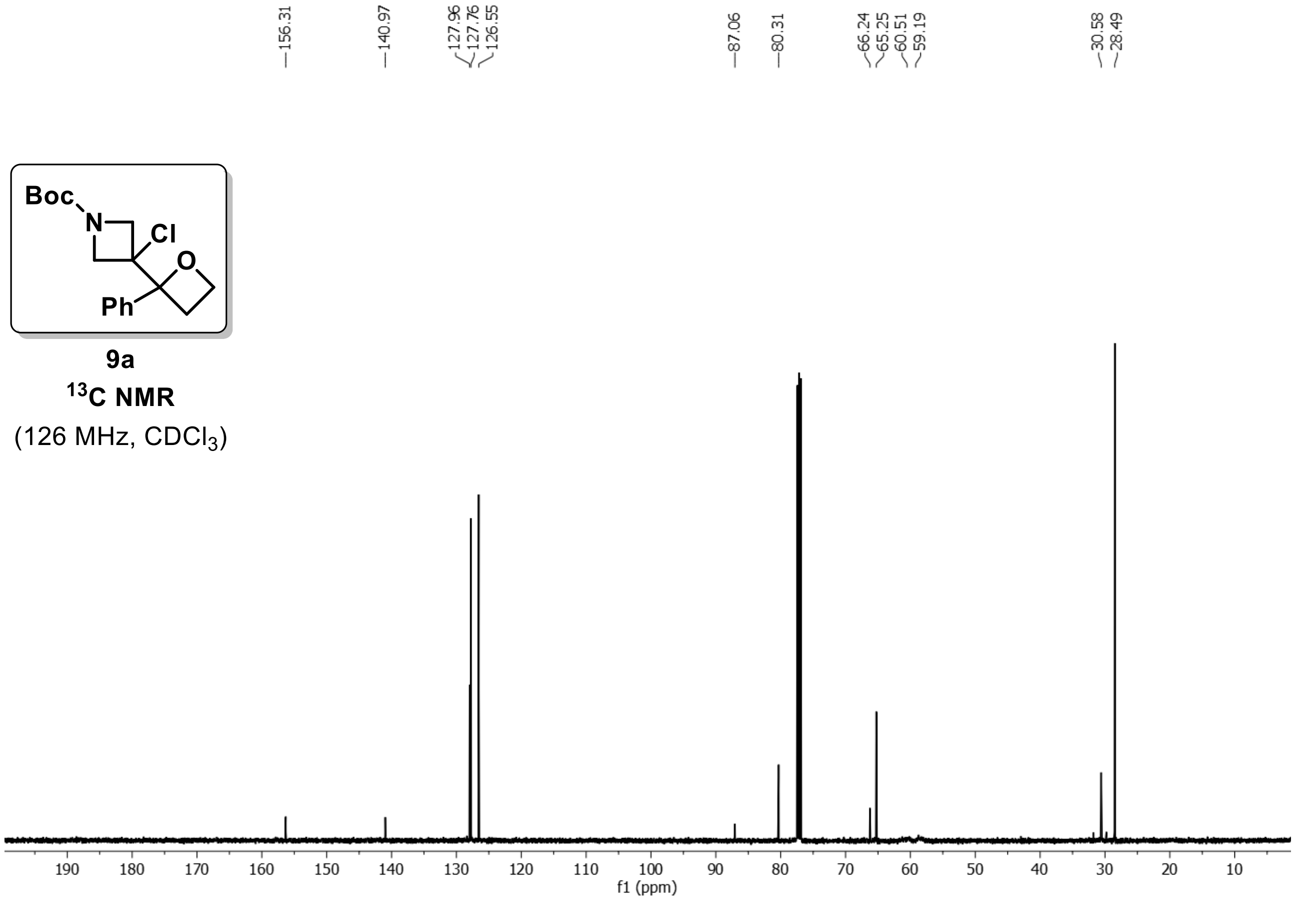
(126 MHz, $CDCl_3$)



8e
HSQC
Boc
N
S
H
Ph
O
6
10
20
30
40
50
60
70
80
120
130
f1 (ppm)
8.2 8.0 7.8 7.6 7.4 7.2
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)



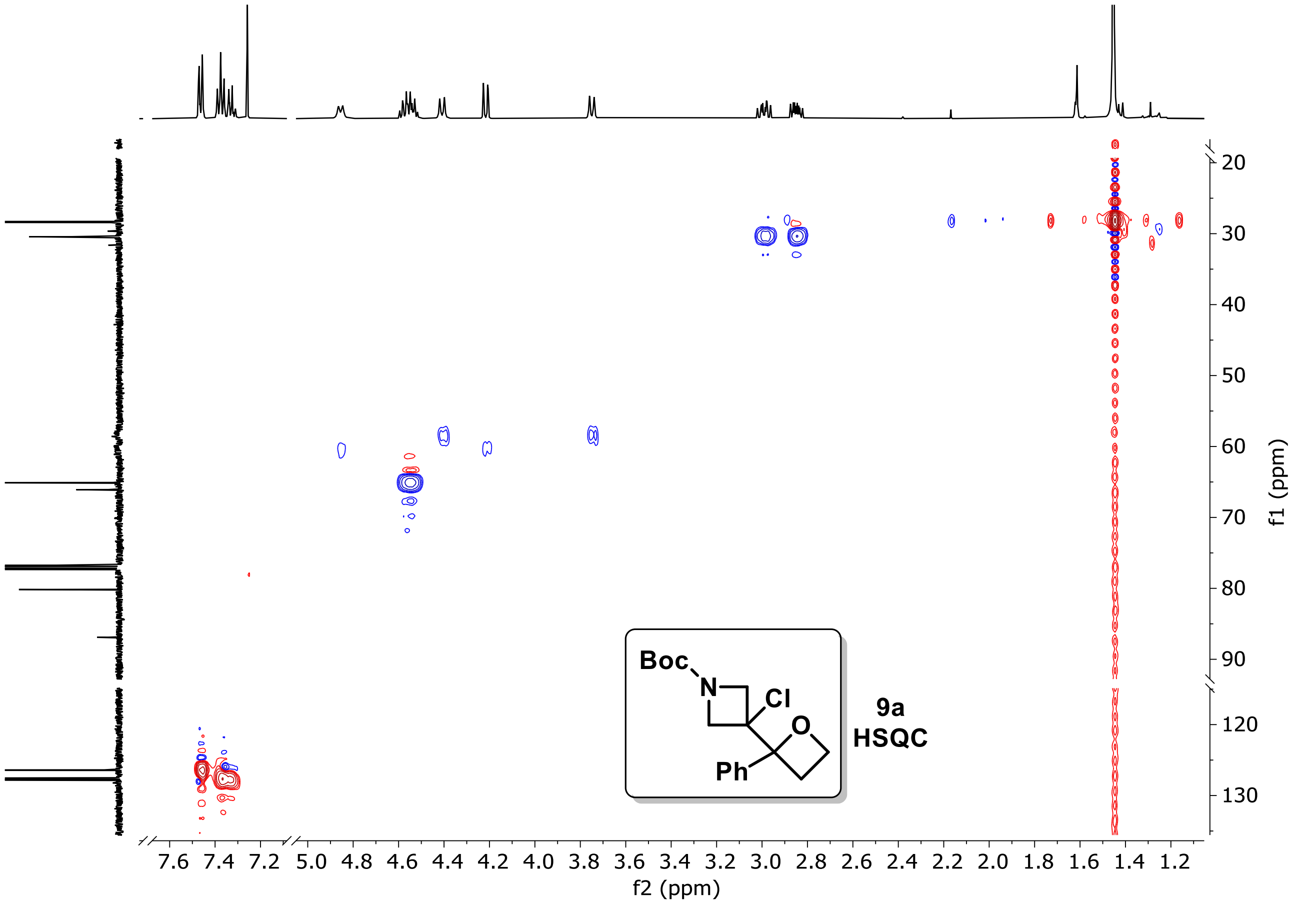
9a
^{1}H NMR
(500 MHz, CDCl$_3$)
Boc
N
Cl
O
Ph
7.48 7.47 7.47 7.46 7.45 7.39 7.39 7.39 7.38 7.37 7.36 7.34 7.34 7.34 7.33 7.33 7.31
4.58 4.58 4.57 4.56 4.56 4.55 4.54 4.53 4.42 4.40 4.23 4.23 4.21 4.21 3.76 3.74
3.01 3.00 3.00 2.99 2.98 2.98 2.96 2.88 2.86 2.86 2.85 2.85 2.84 1.46
4.85 4.58 4.58 4.57 4.56 4.56 4.55 4.54 4.53 4.42 4.40 4.23 4.23 4.21 4.21 3.76 3.74
1.00 2.13 1.05 1.03 0.98
5.0 4.8 4.6 4.4 4.2 4.0 3.8
f1 (ppm)
1.99 1.89 0.89 1.00 2.13 1.05 1.03 0.98 1.09 1.09 9.07
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
f1 (ppm)



9a

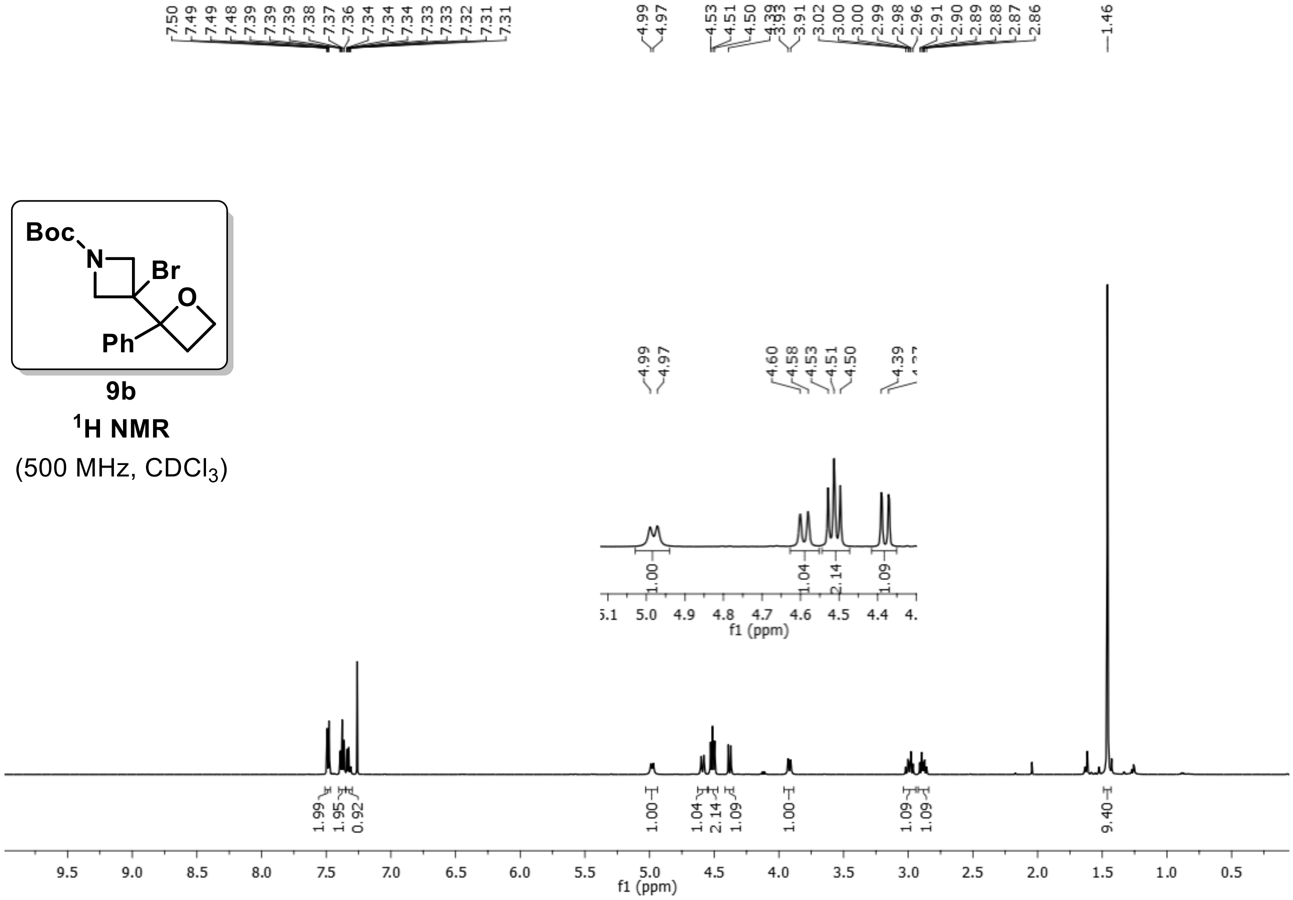
^{13}C NMR

(126 MHz, $CDCl_3$)



9a

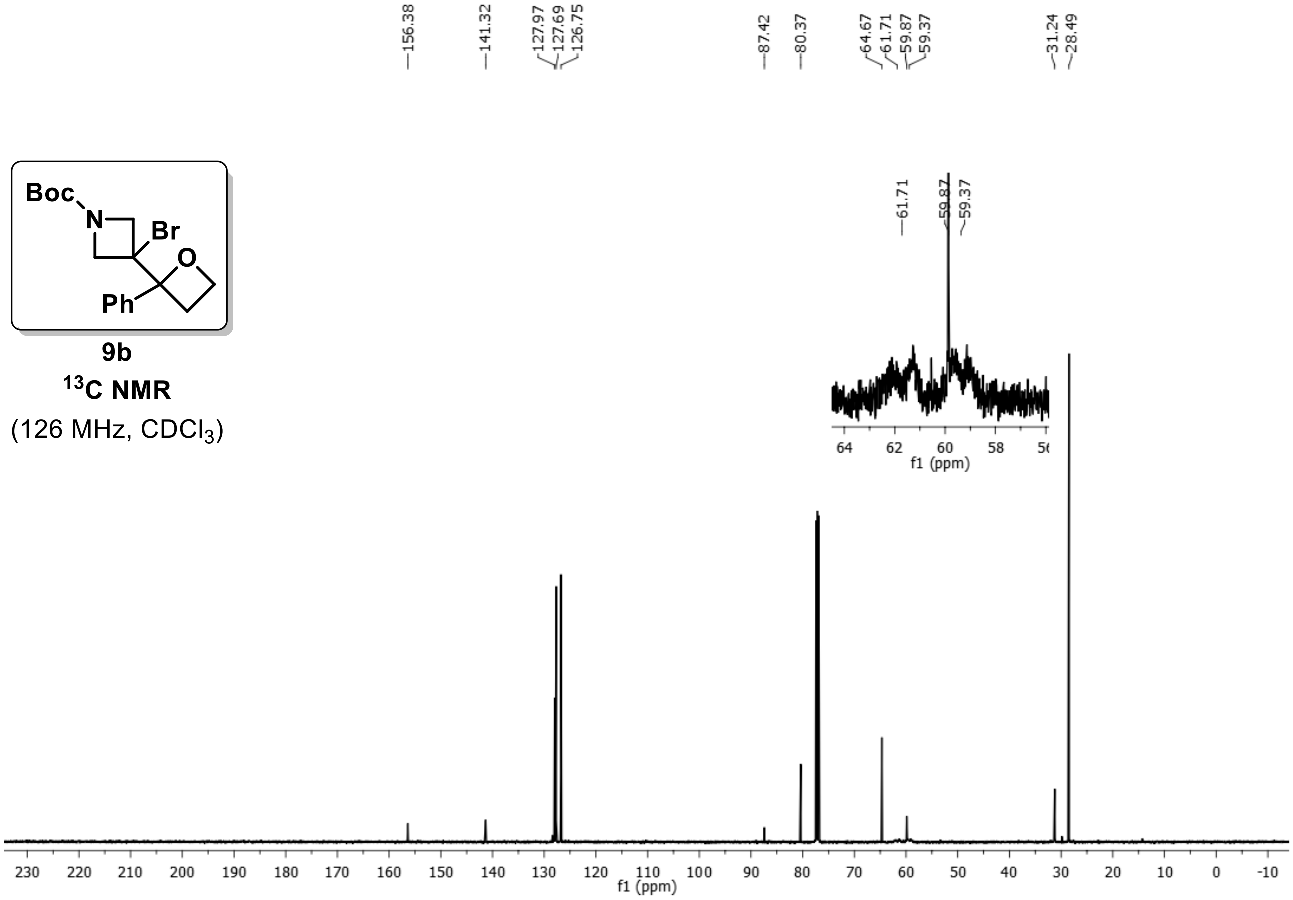
HSQC



9b

^{1}H NMR

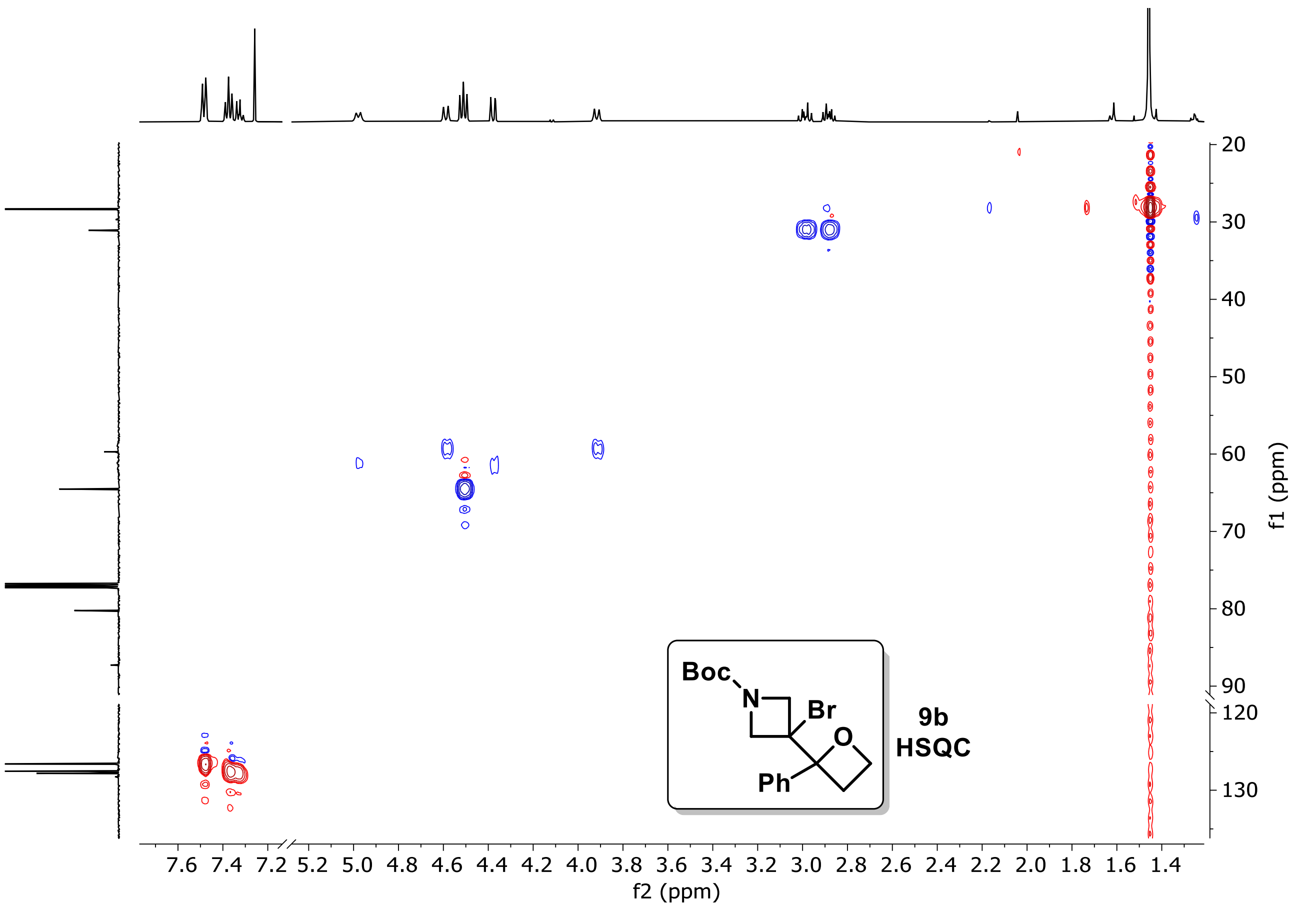
(500 MHz, $CDCl_3$)



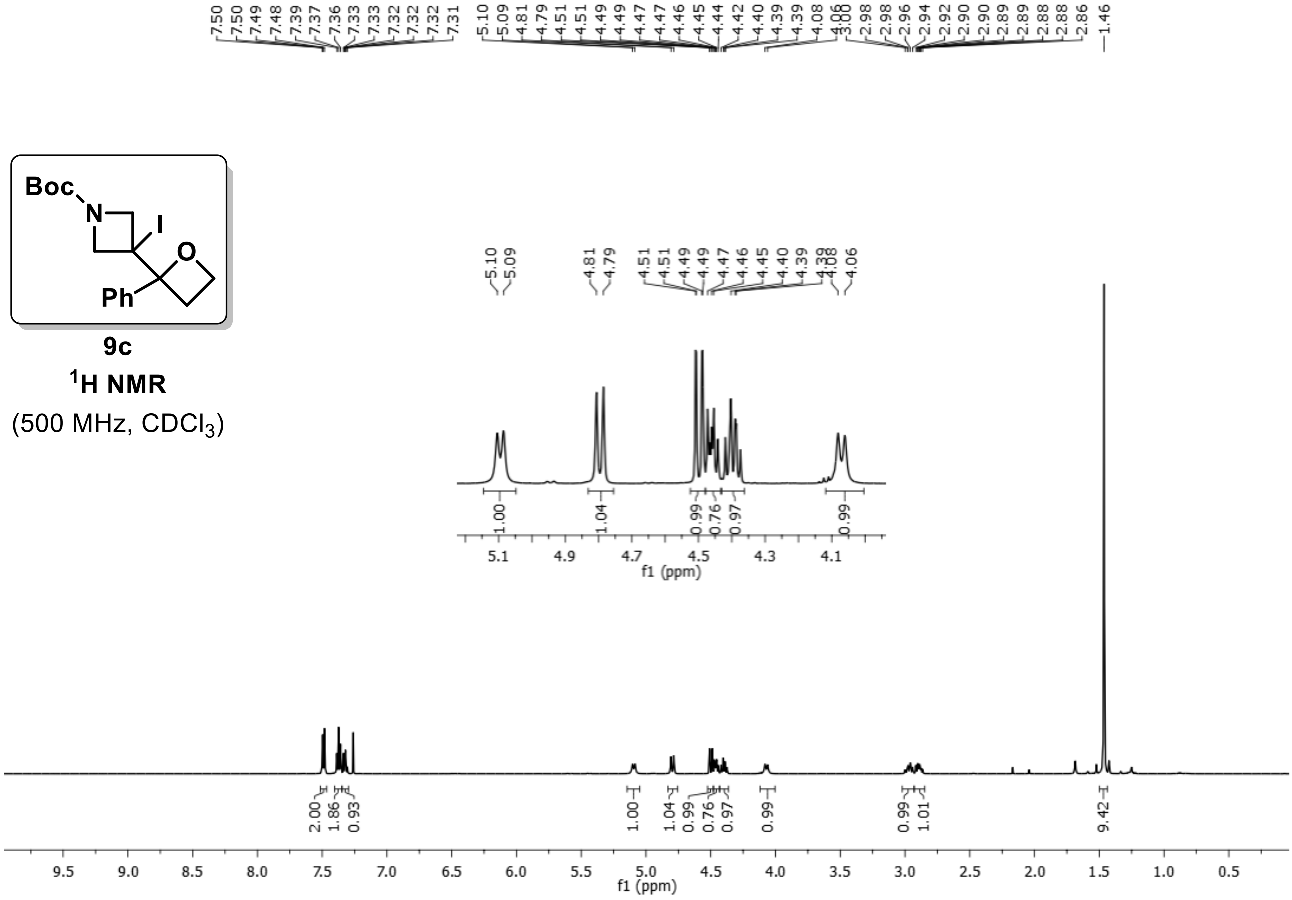
9b

^{13}C NMR

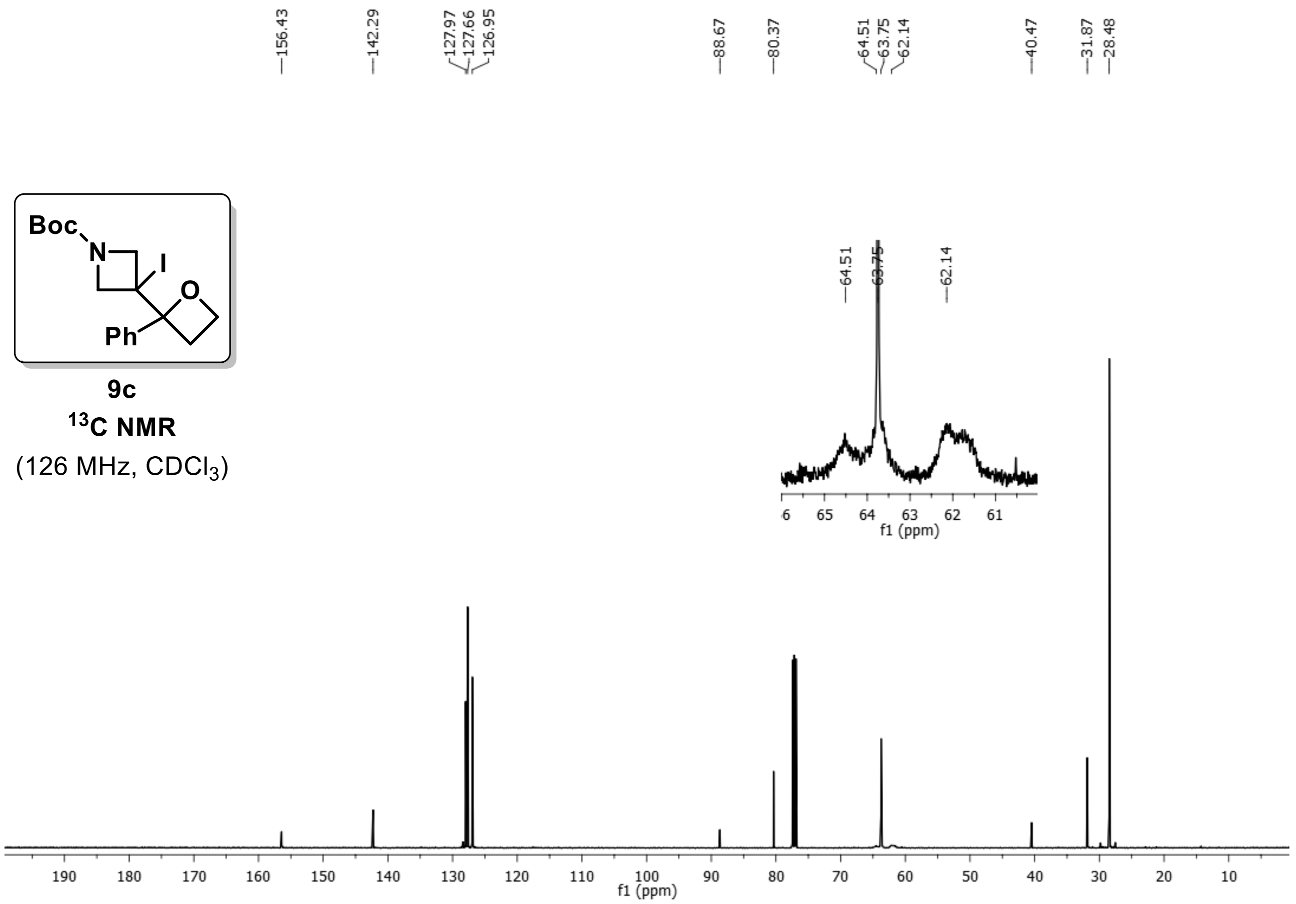
(126 MHz, $CDCl_3$)



9b
HSQC



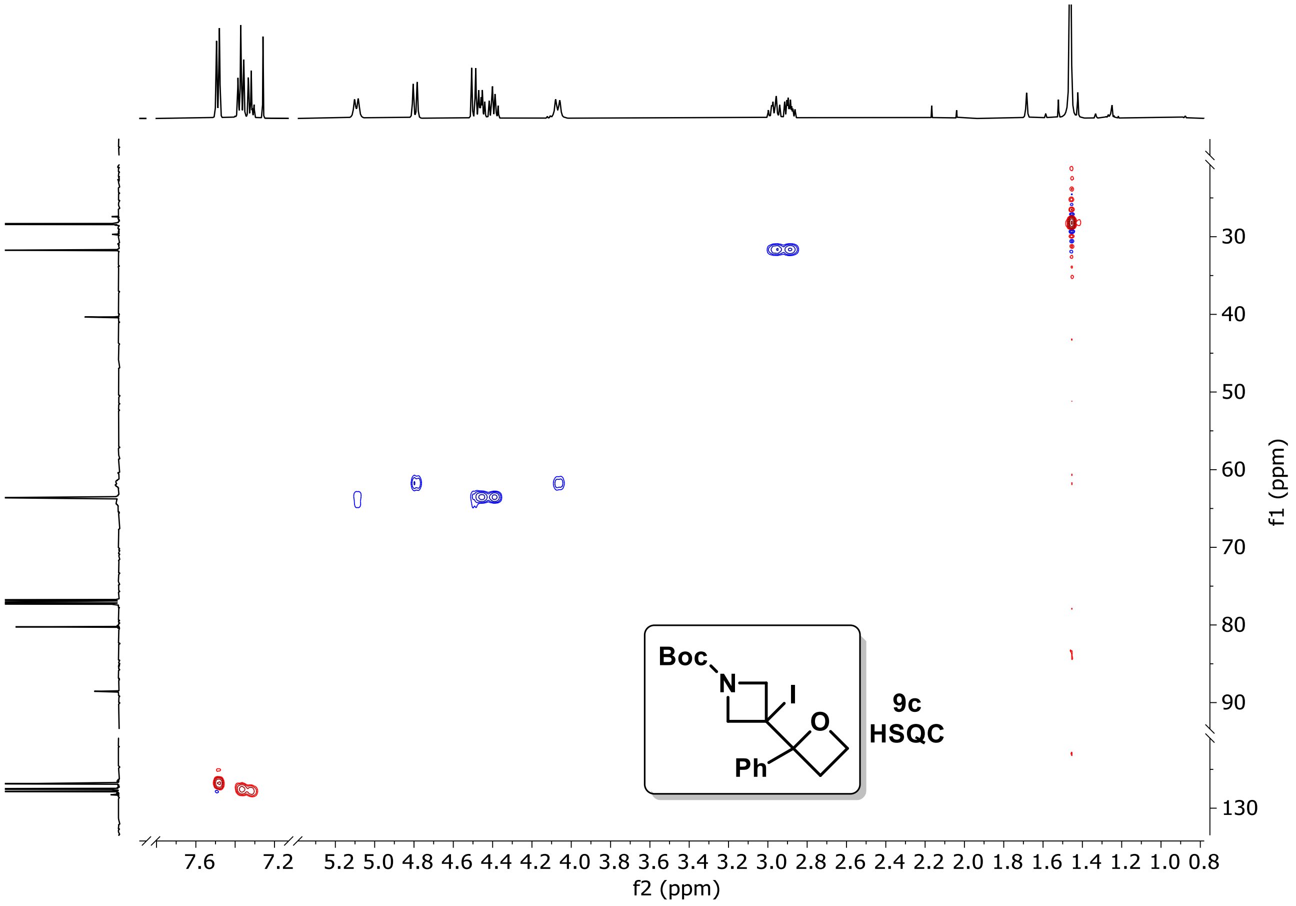
9c
^{1}H NMR
(500 MHz, $CDCl_3$)



9c

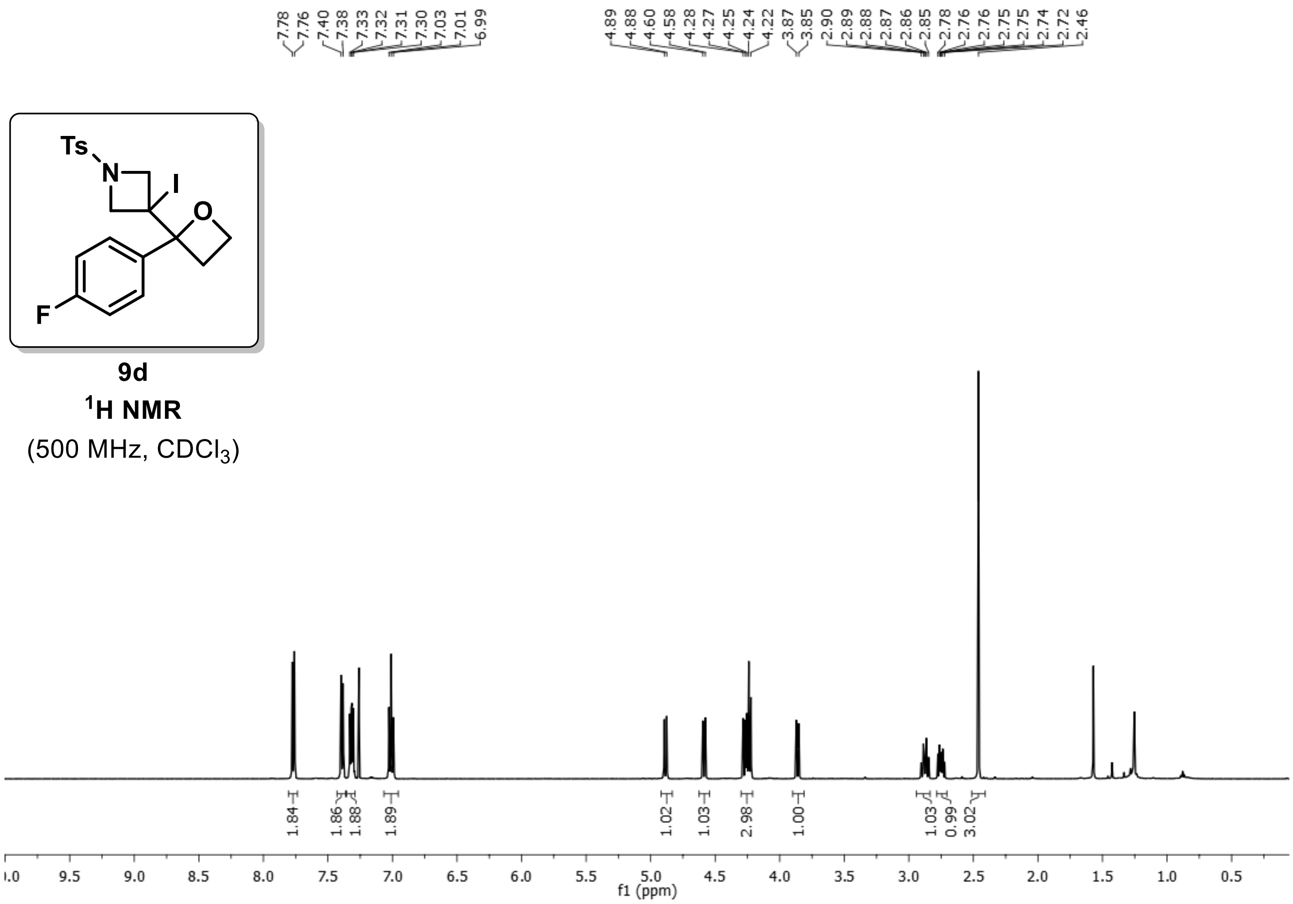
^{13}C NMR

(126 MHz, $CDCl_3$)



9c

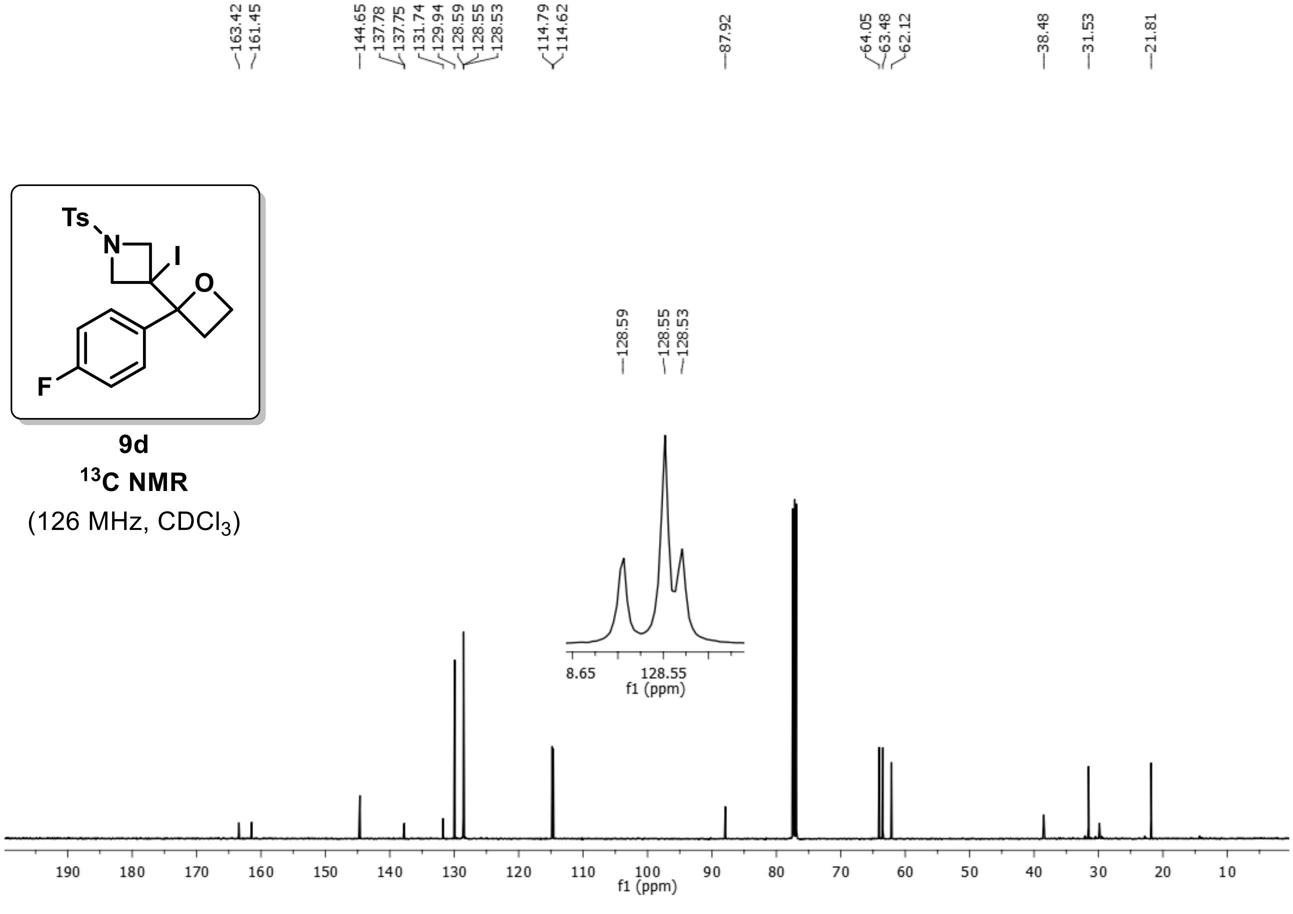
HSQC



9d

^{1}H NMR

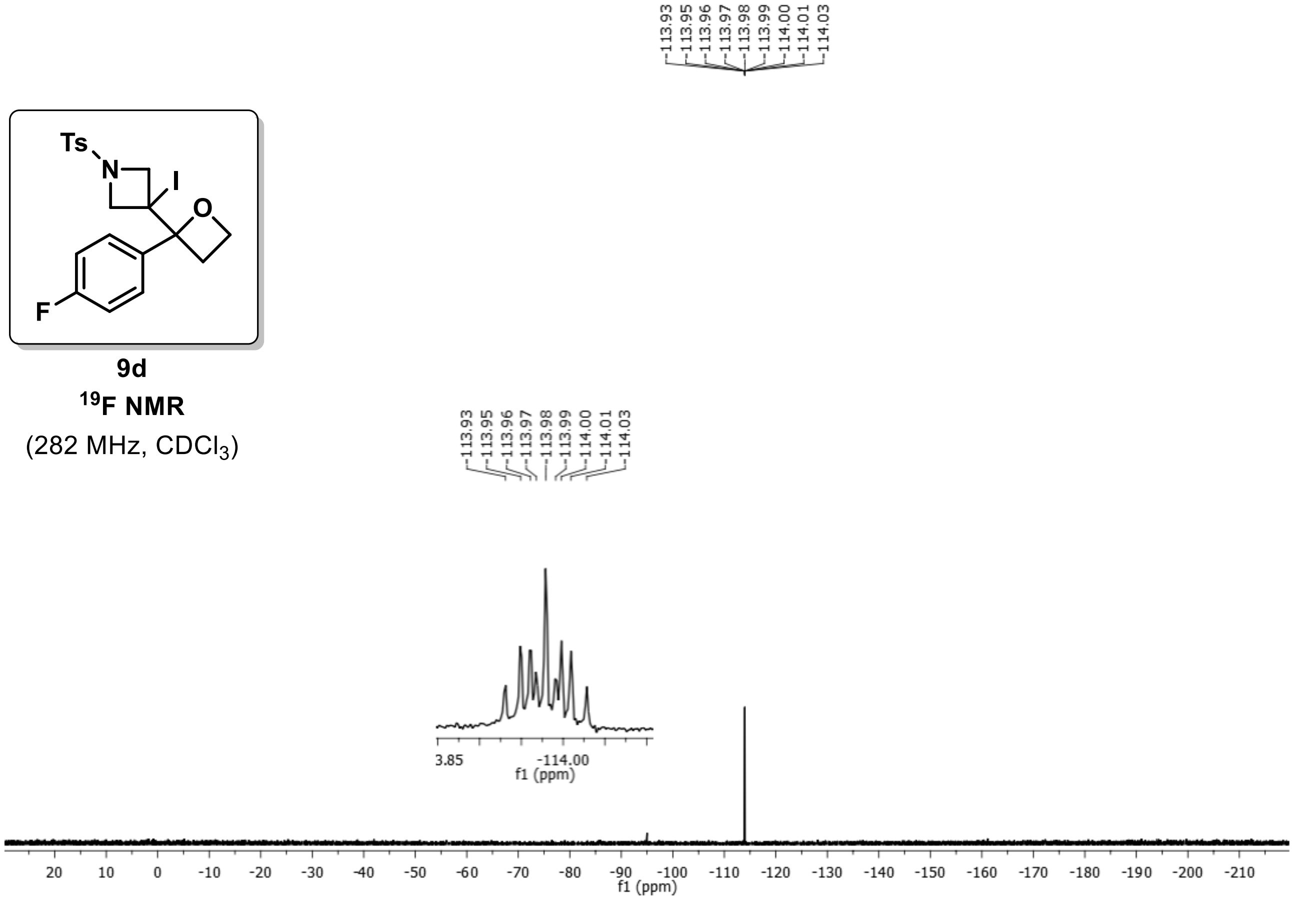
(500 MHz, $CDCl_3$)



9d

^{13}C NMR

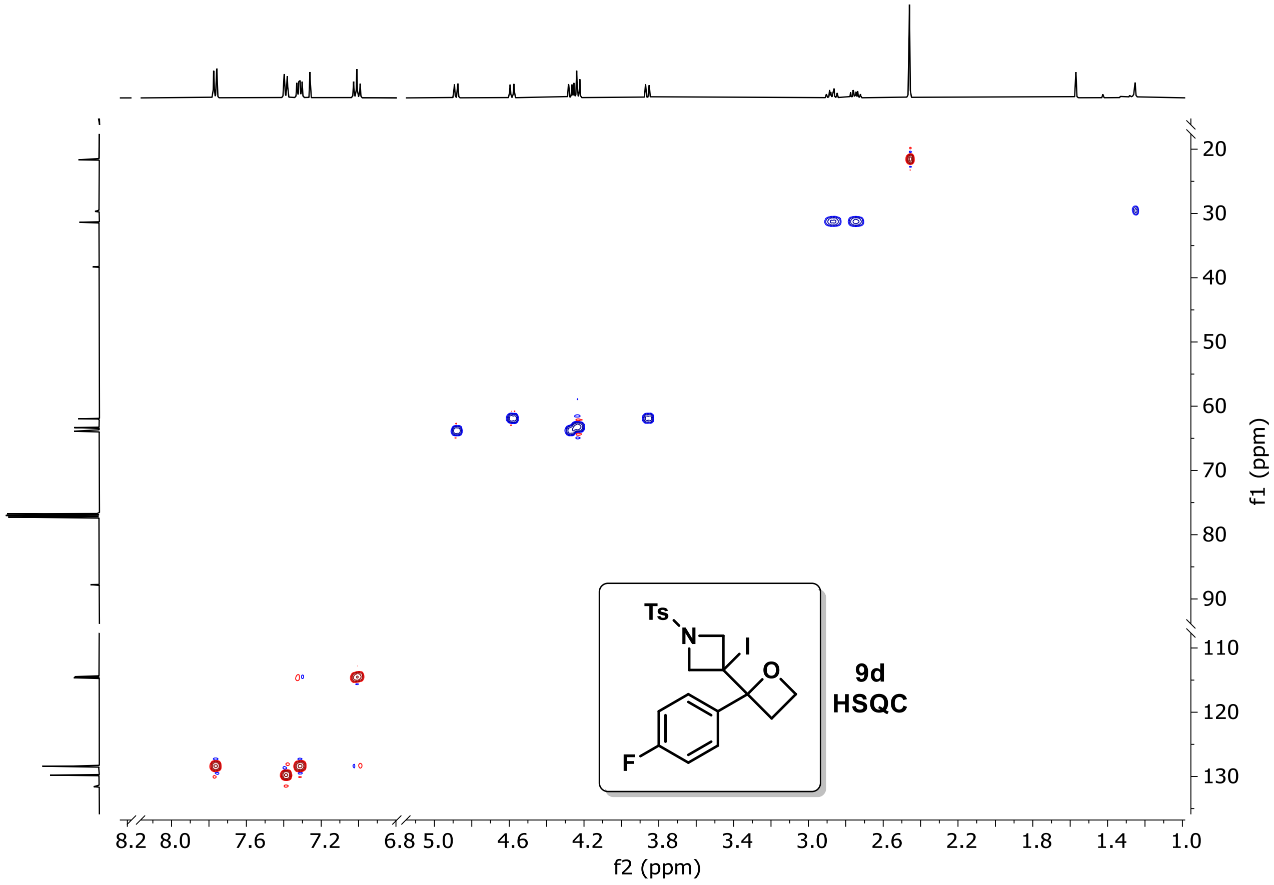
(126 MHz, $CDCl_3$)



9d

^{19}F NMR

(282 MHz, $CDCl_3$)



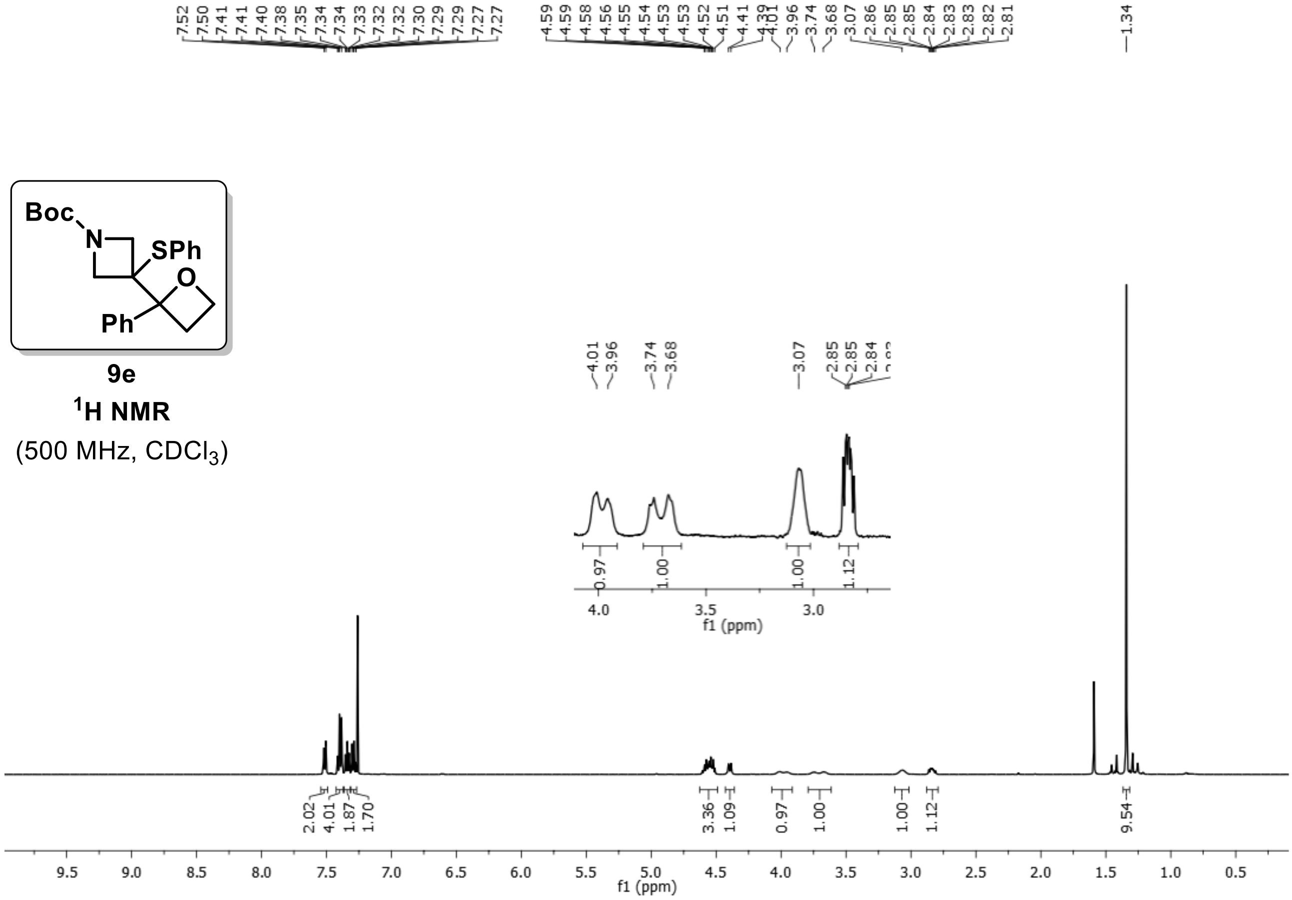
9d

HSQC

9e

^{1}H NMR

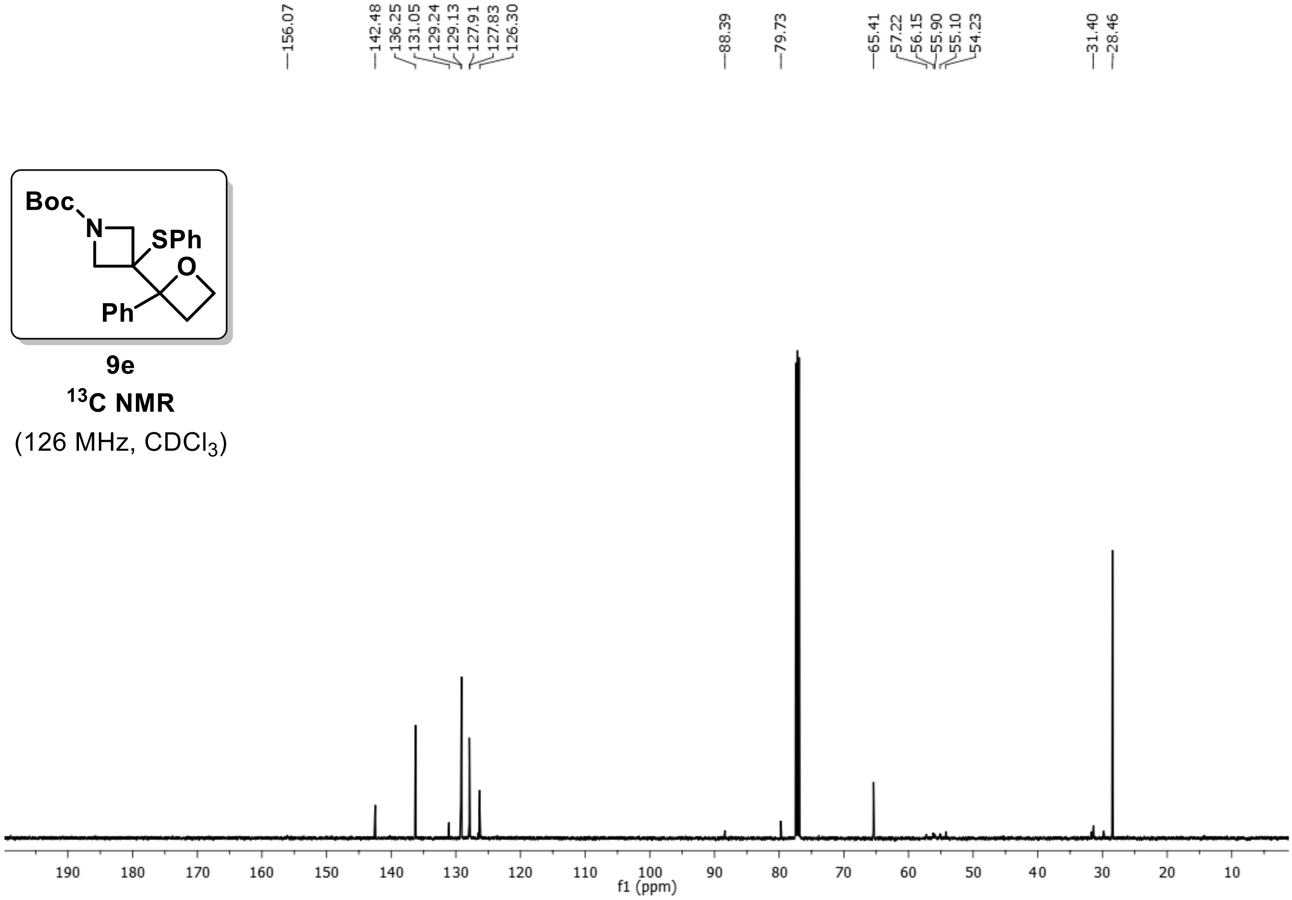
(500 MHz, $CDCl_3$)

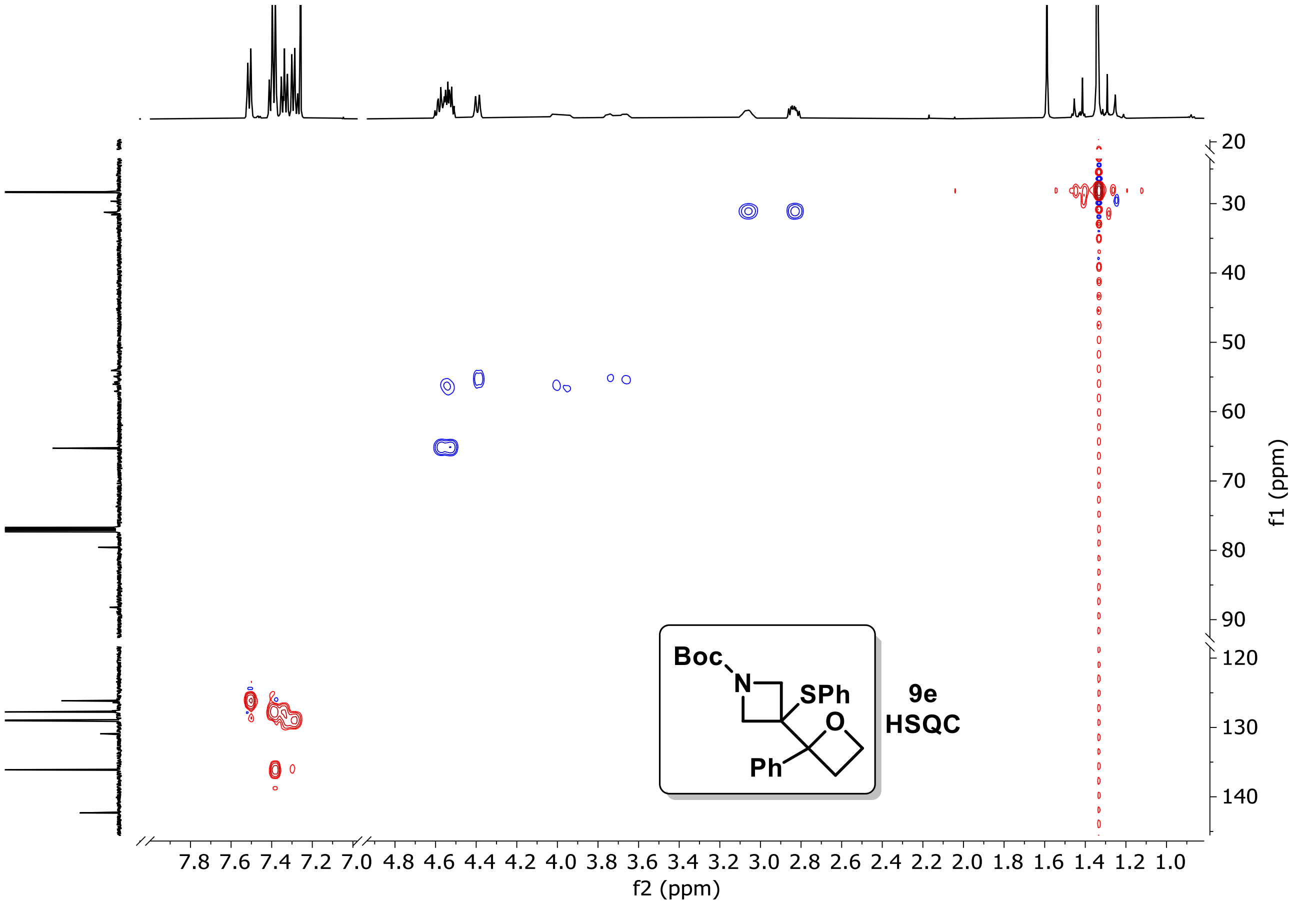


9e

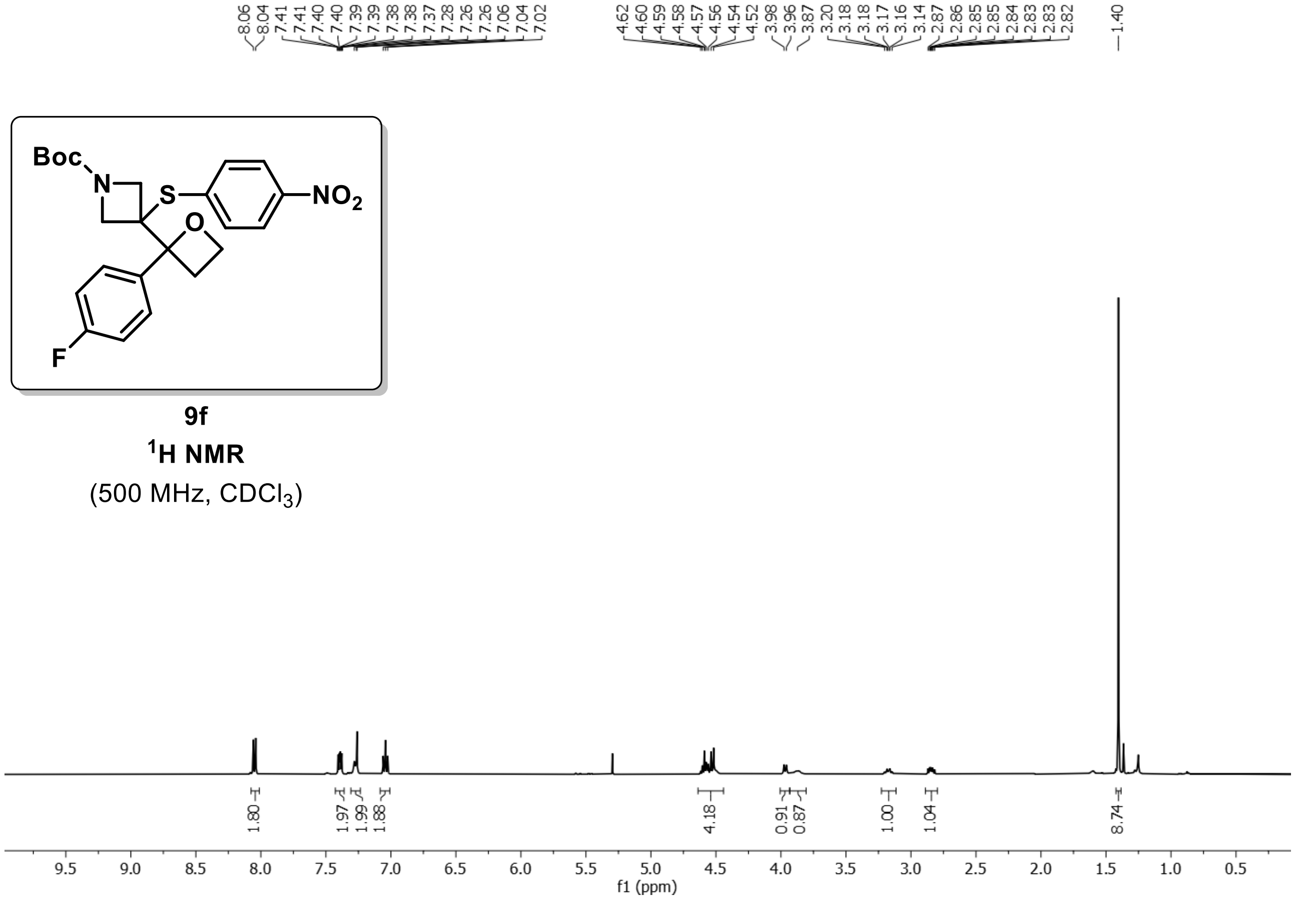
^{13}C NMR

(126 MHz, $CDCl_3$)

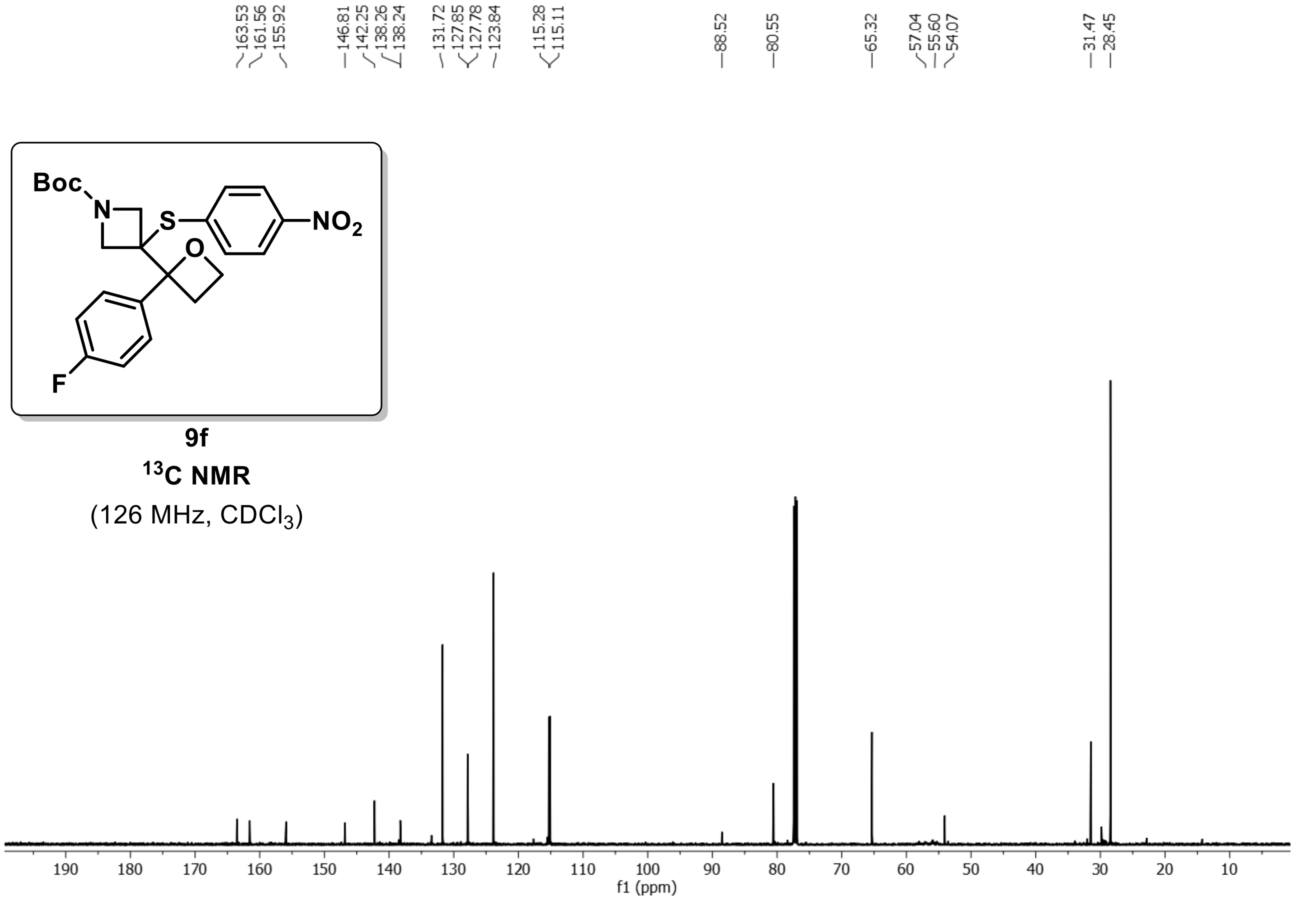




9e
HSQC



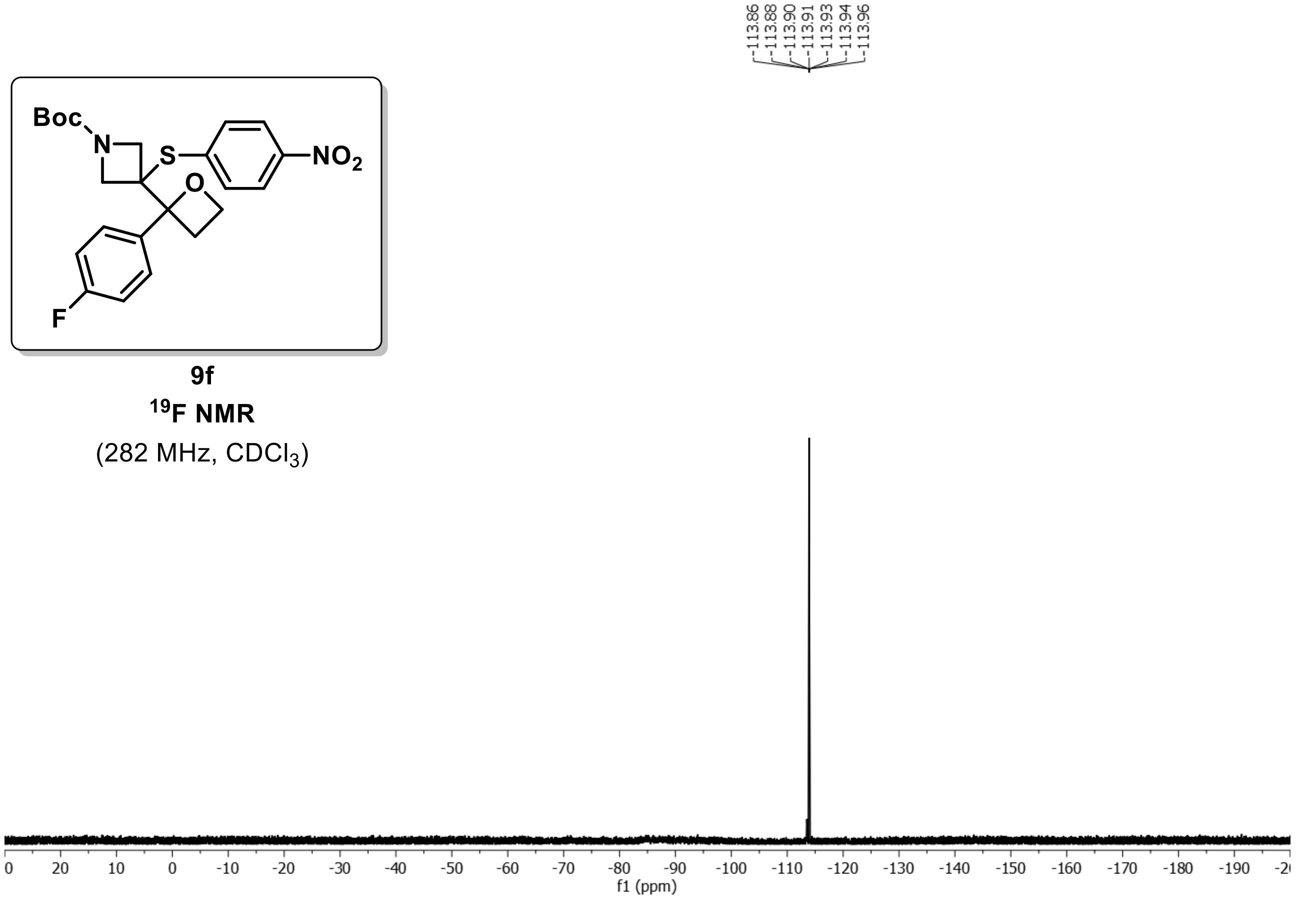
9f
^{1}H NMR
(500 MHz, $CDCl_3$)



9f

^{13}C NMR

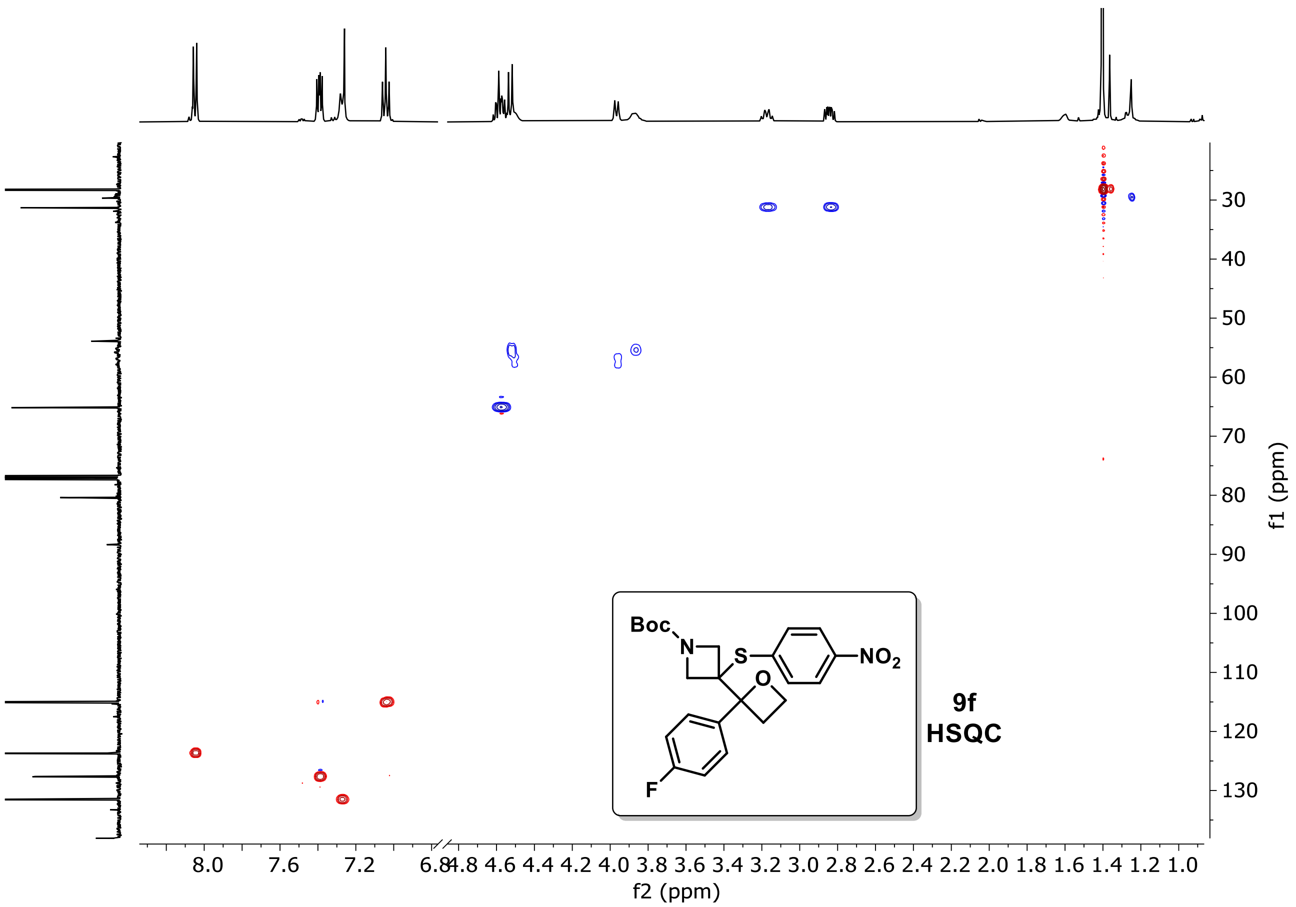
(126 MHz, CDCl$_3$)



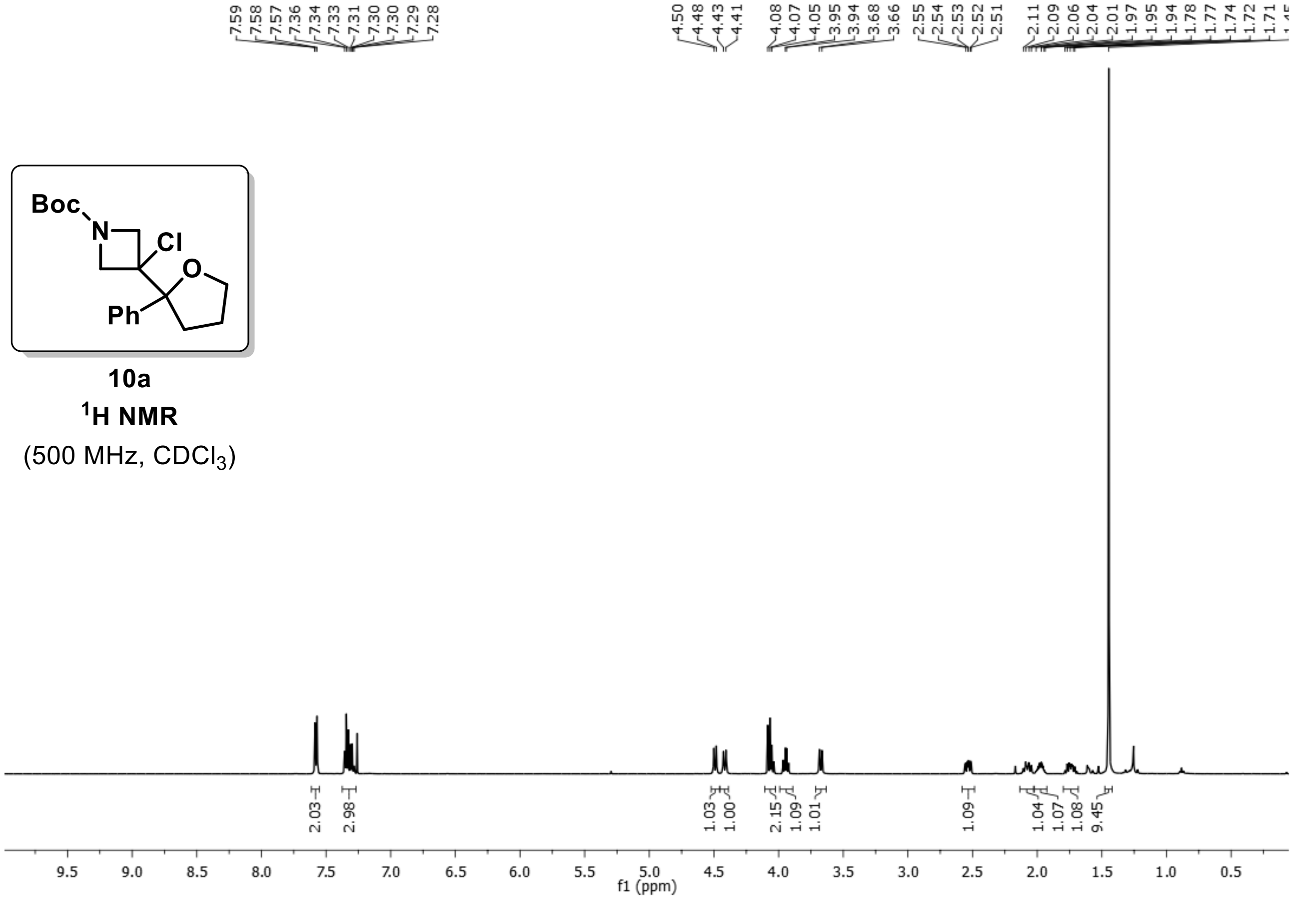
9f

^{19}F NMR

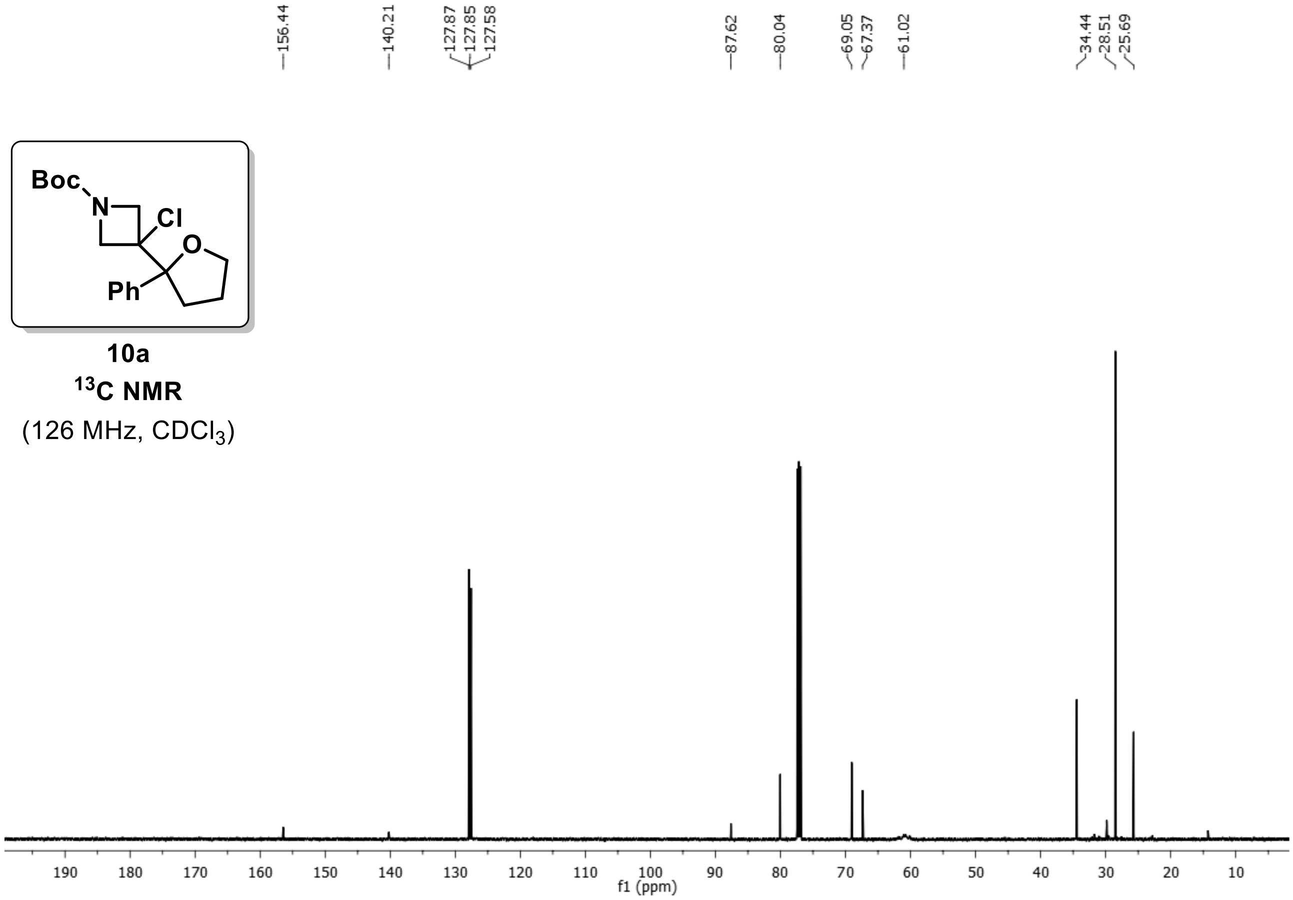
(282 MHz, CDCl$_3$)



9f
HSQC



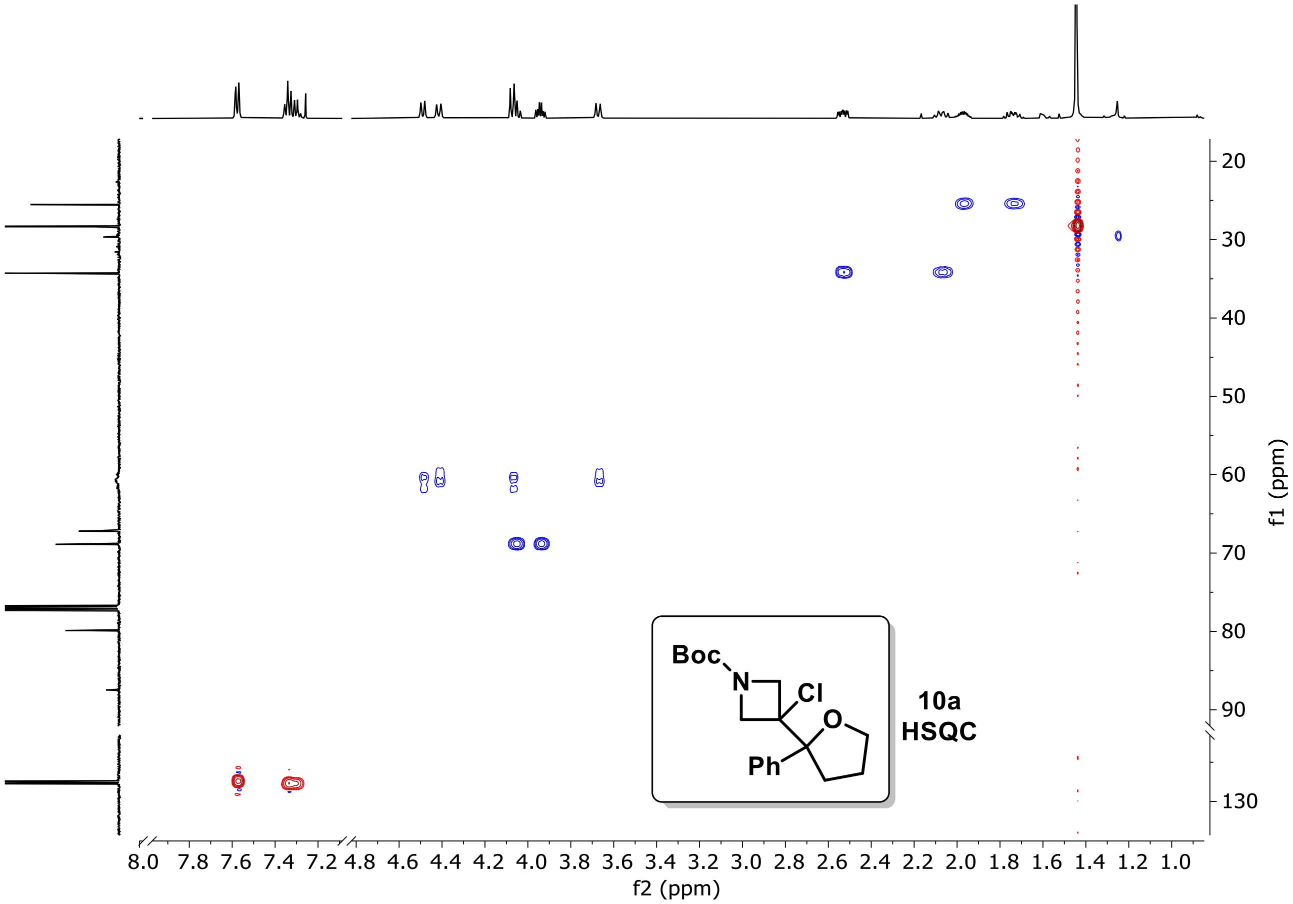
10a
^{1}H NMR
(500 MHz, $CDCl_3$)



10a

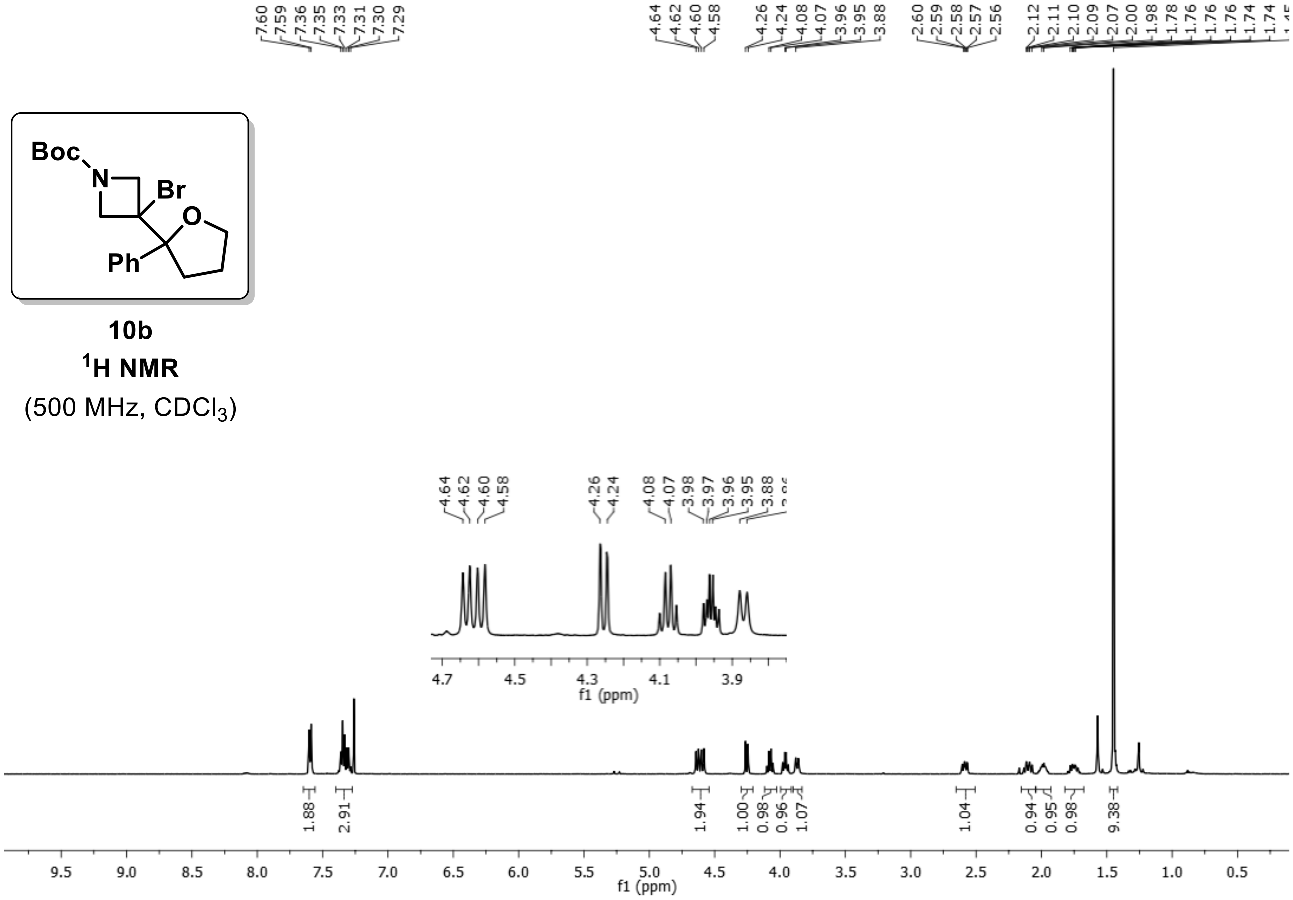
^{13}C NMR

(126 MHz, $CDCl_3$)



10a

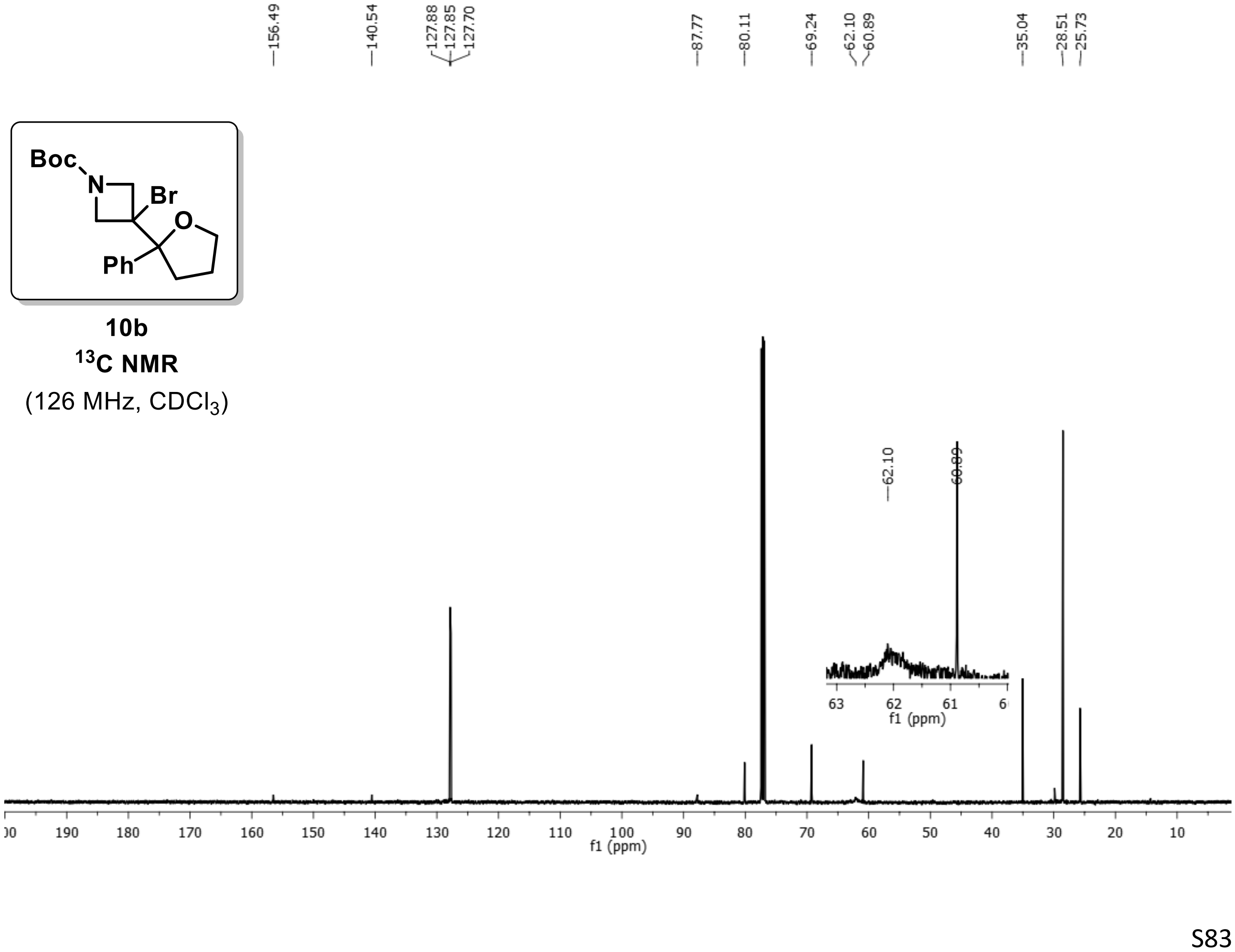
HSQC



10b

^{1}H NMR

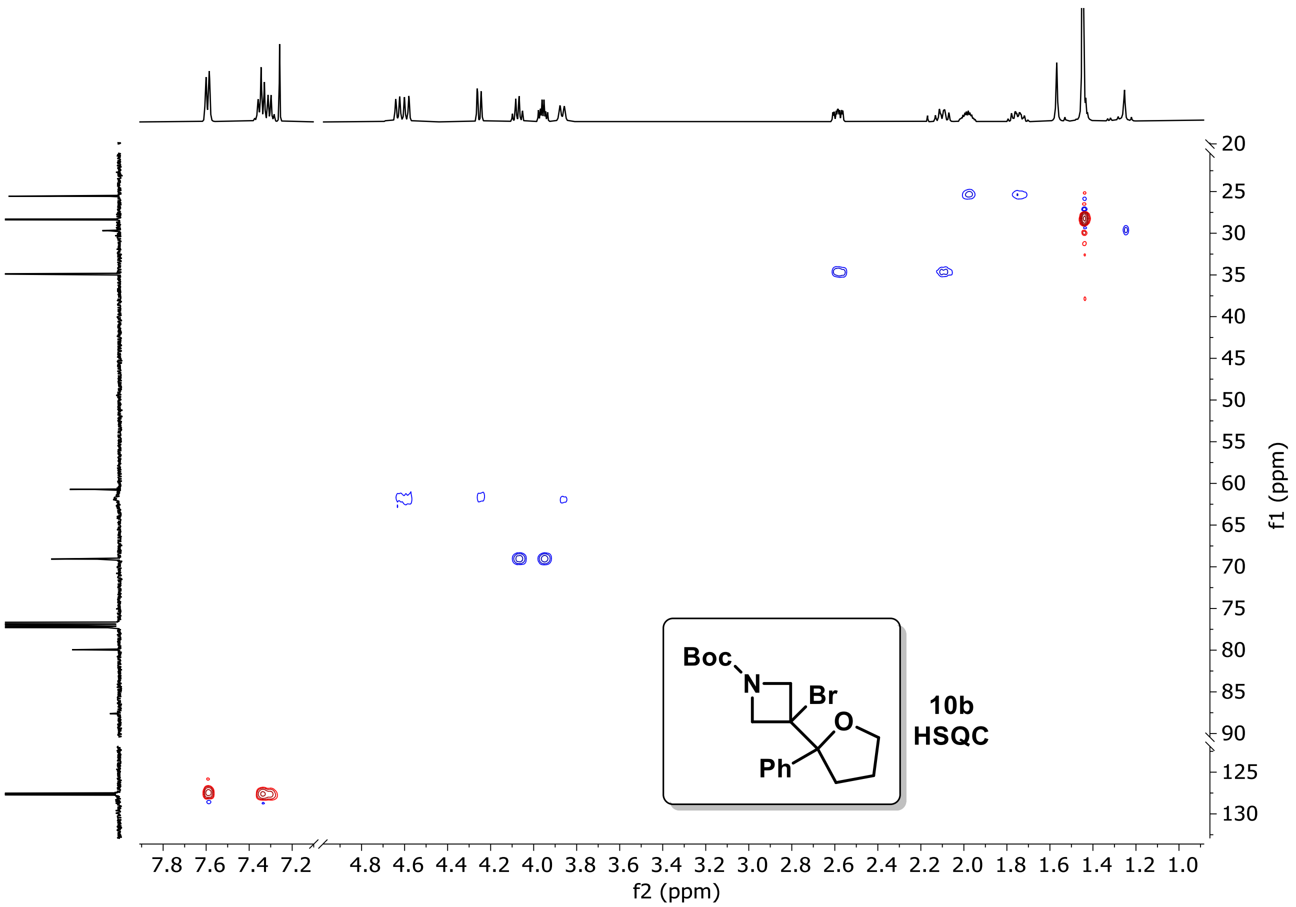
(500 MHz, $CDCl_3$)



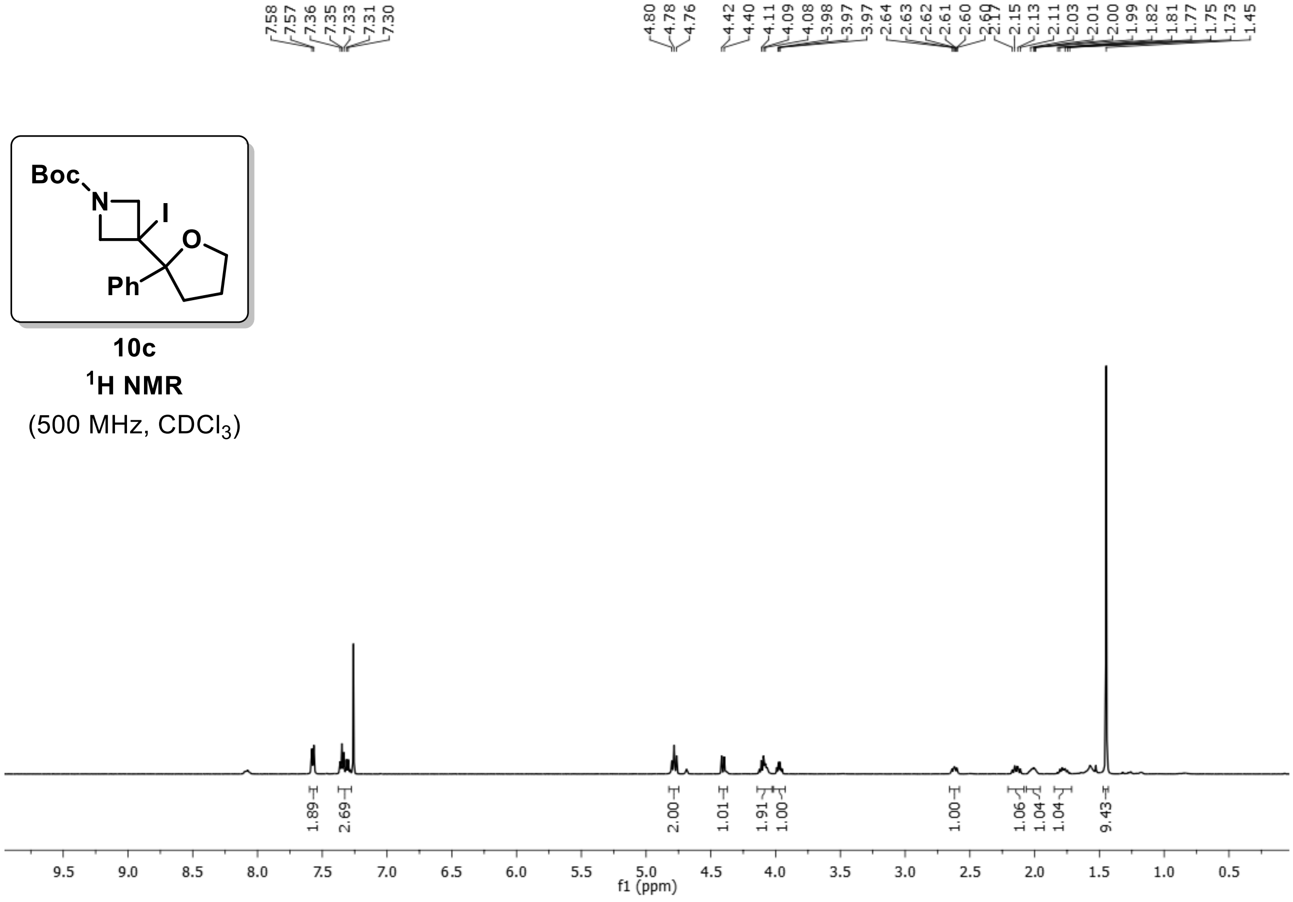
10b

^{13}C NMR

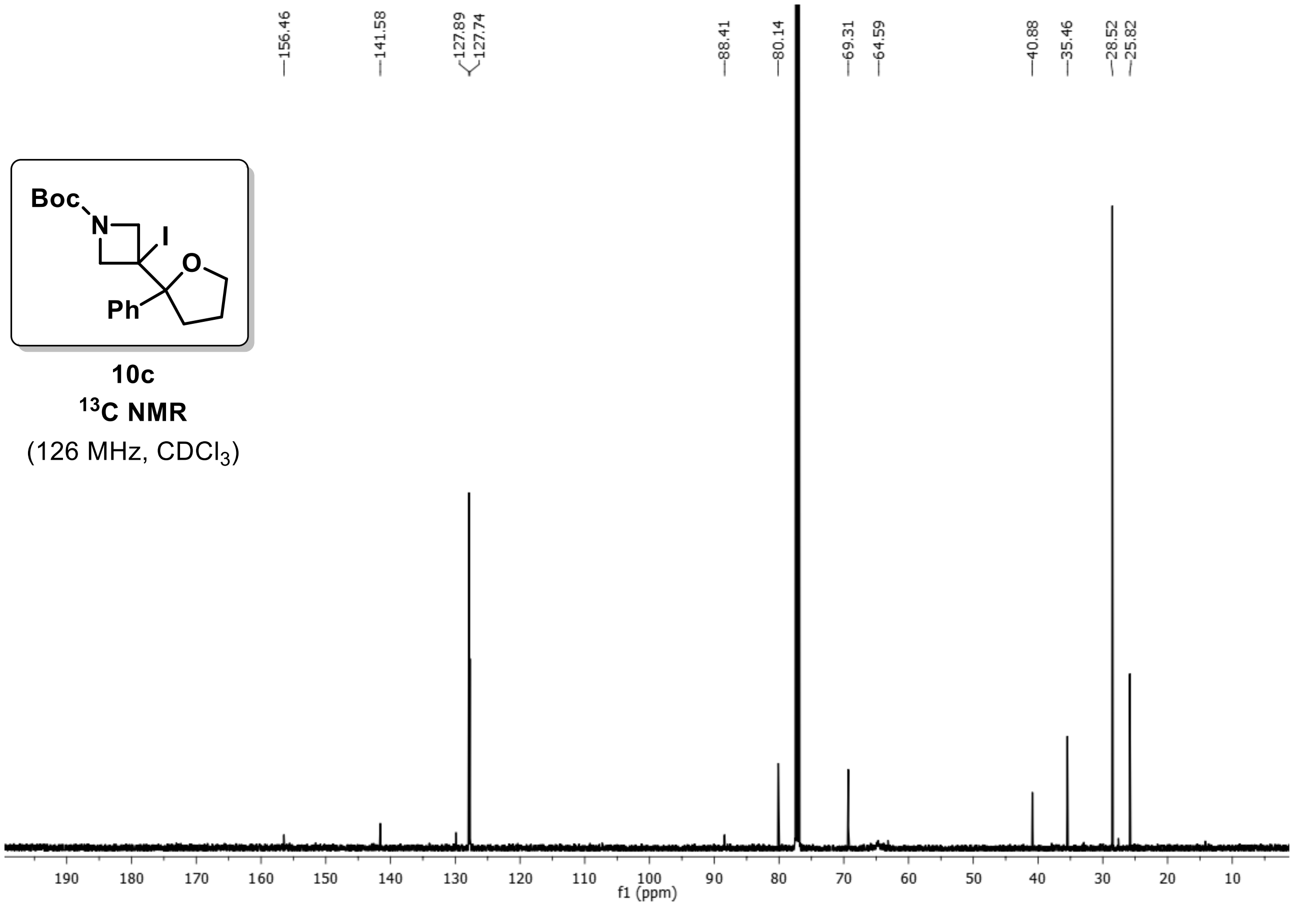
(126 MHz, $CDCl_3$)



10b
HSQC



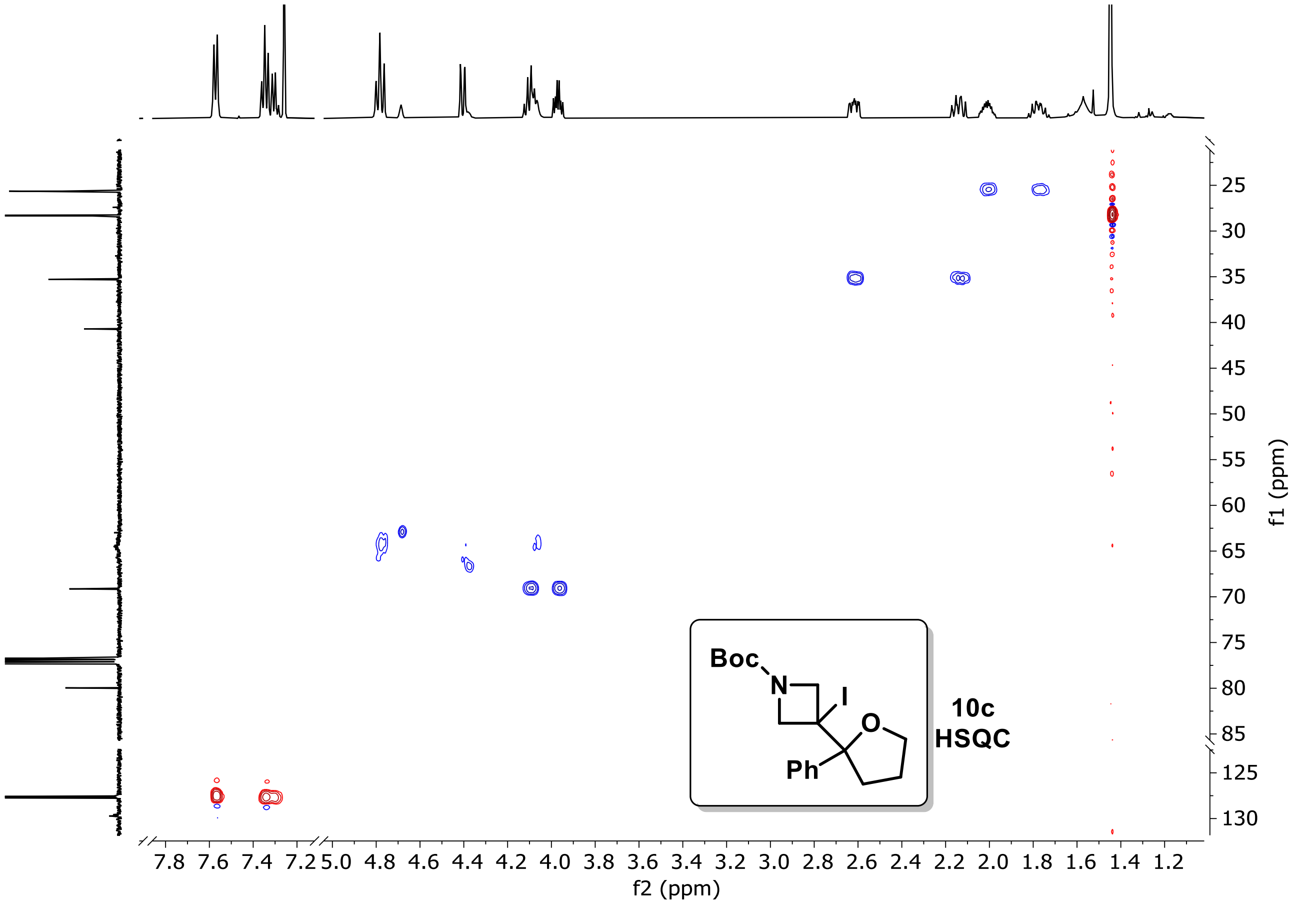
10c
^{1}H NMR
(500 MHz, $CDCl_3$)



10c

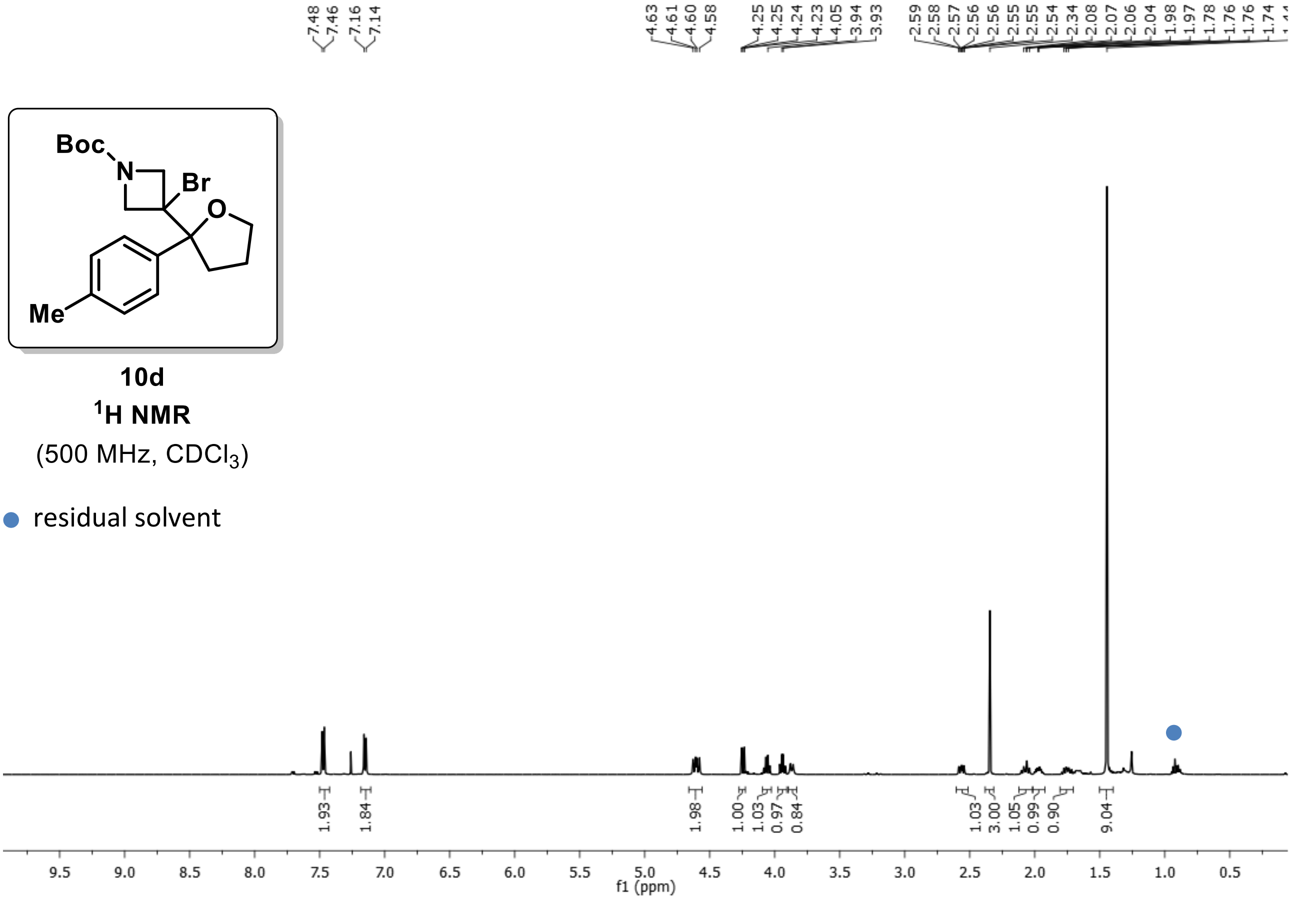
^{13}C NMR

(126 MHz, $CDCl_3$)



10c

HSQC

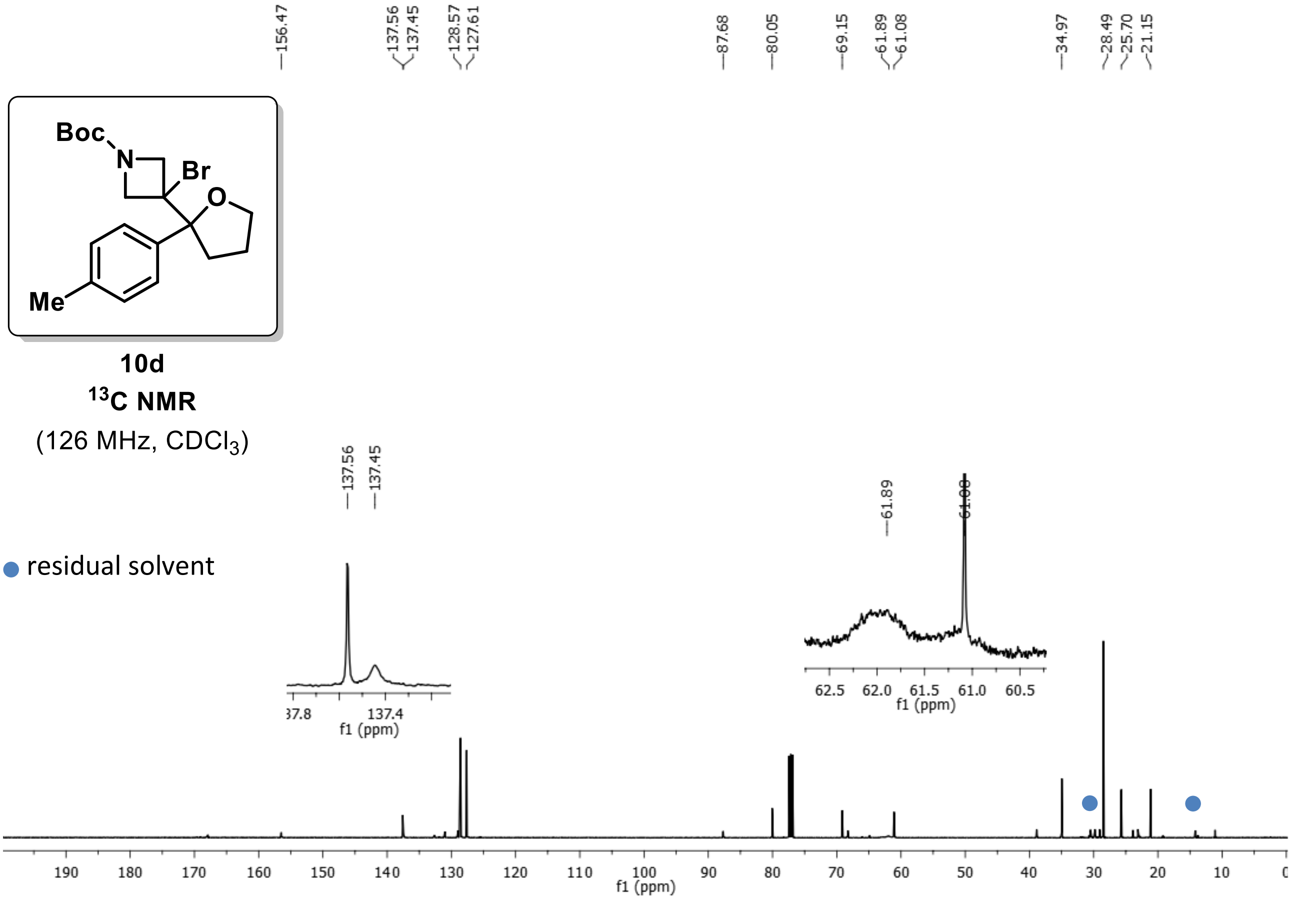


10d

^{1}H NMR

(500 MHz, $CDCl_3$)

● residual solvent

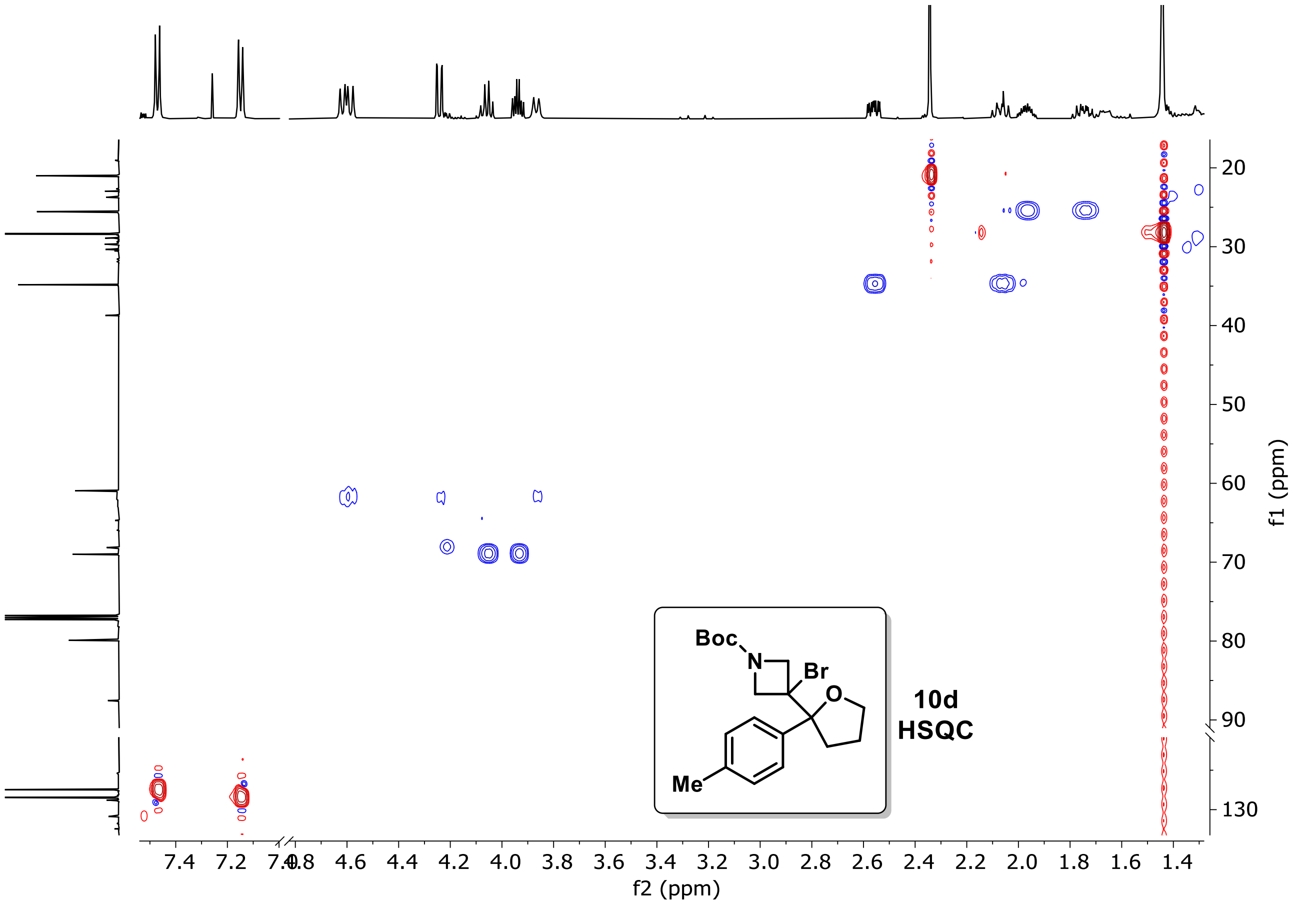


10d

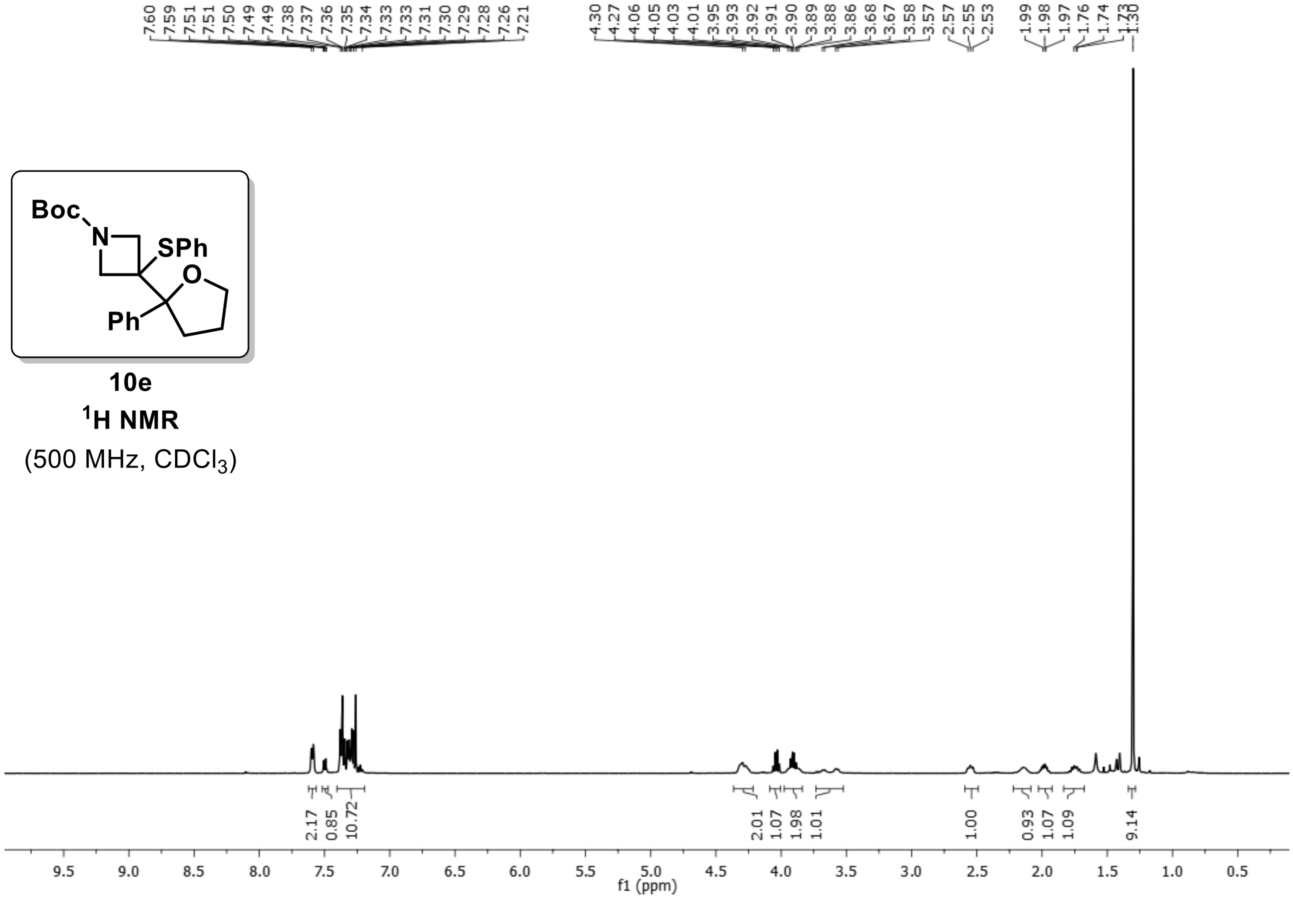
^{13}C NMR

(126 MHz, $CDCl_3$)

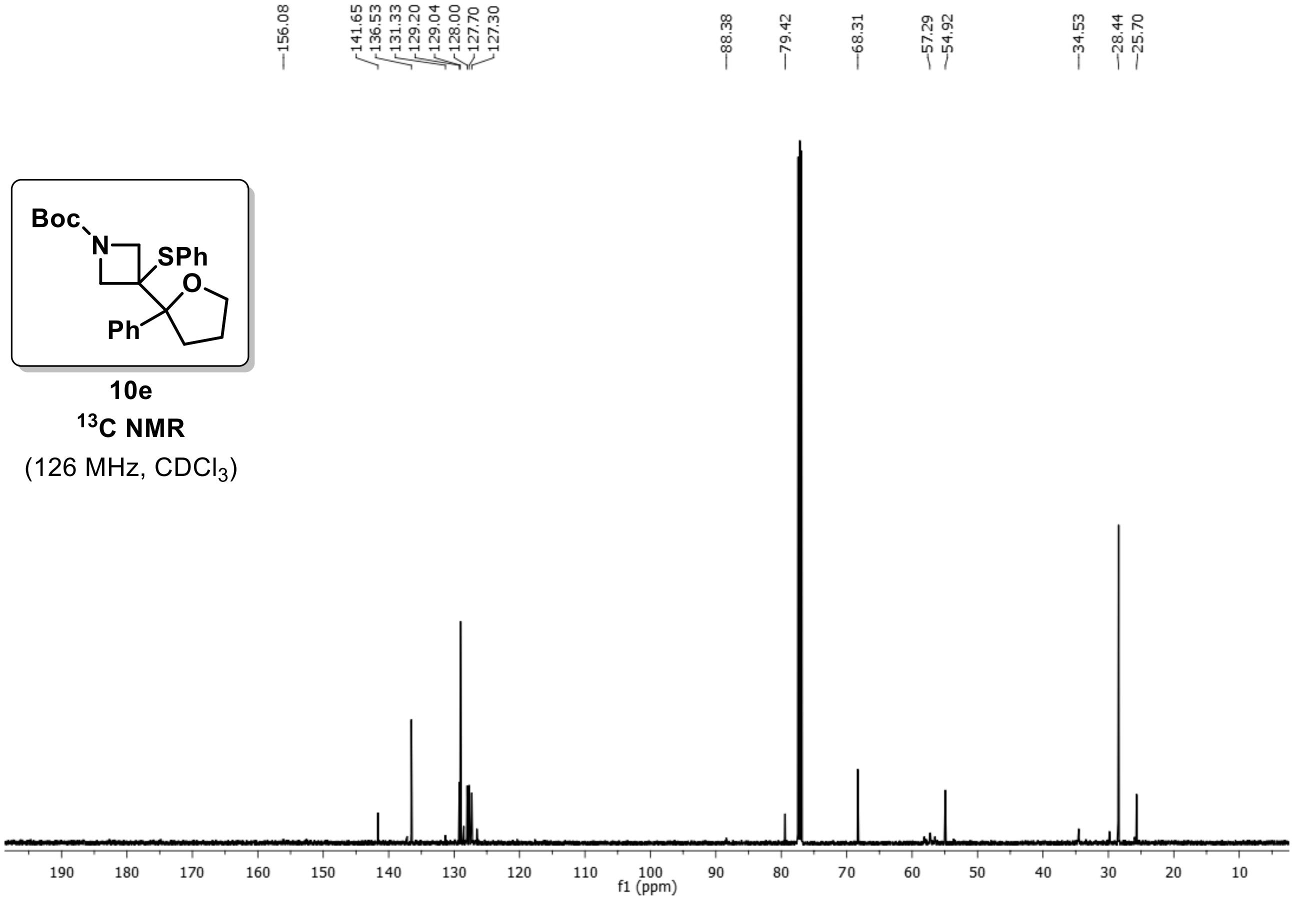
● residual solvent



10d
HSQC



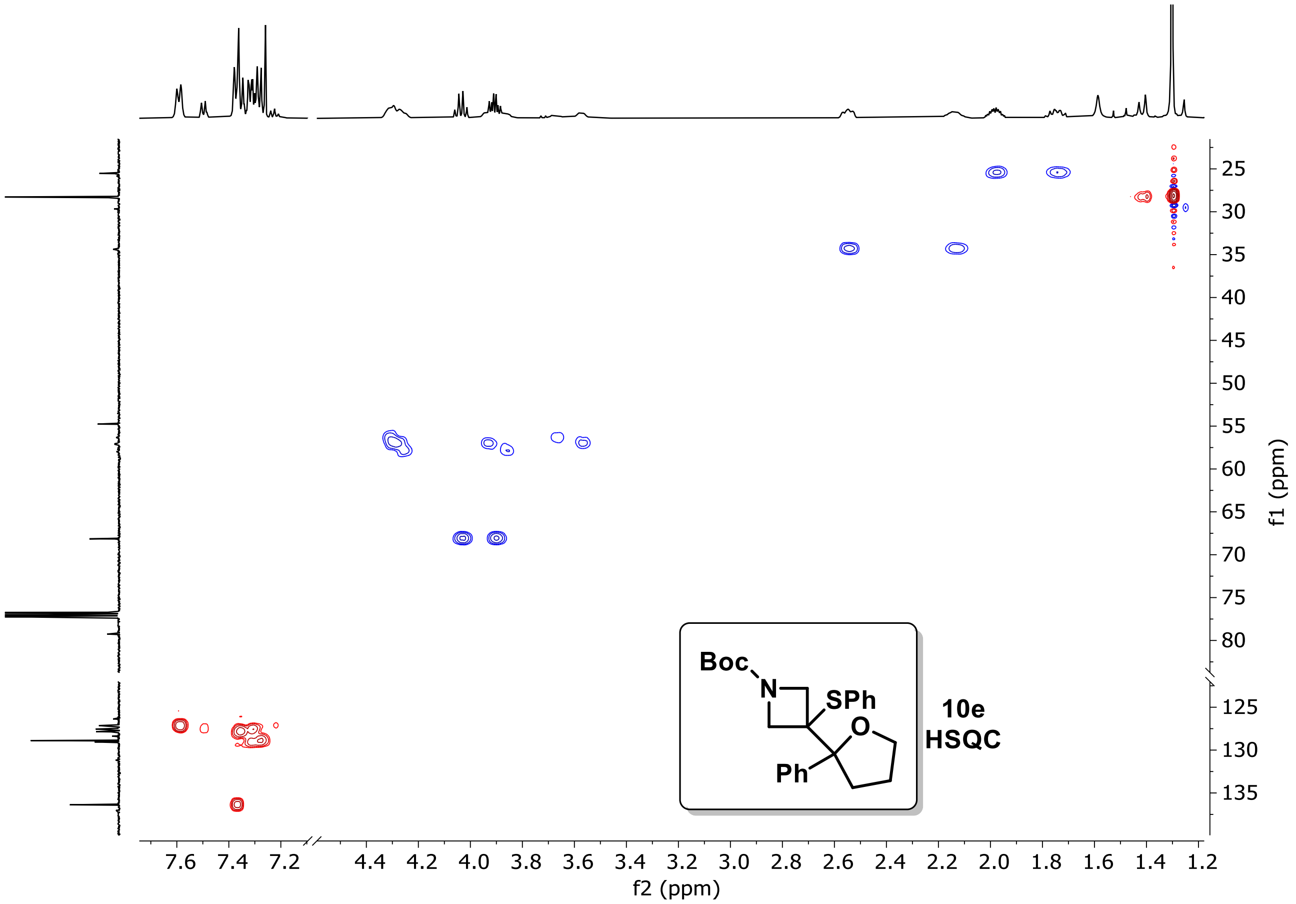
10e
^{1}H NMR
(500 MHz, $CDCl_3$)



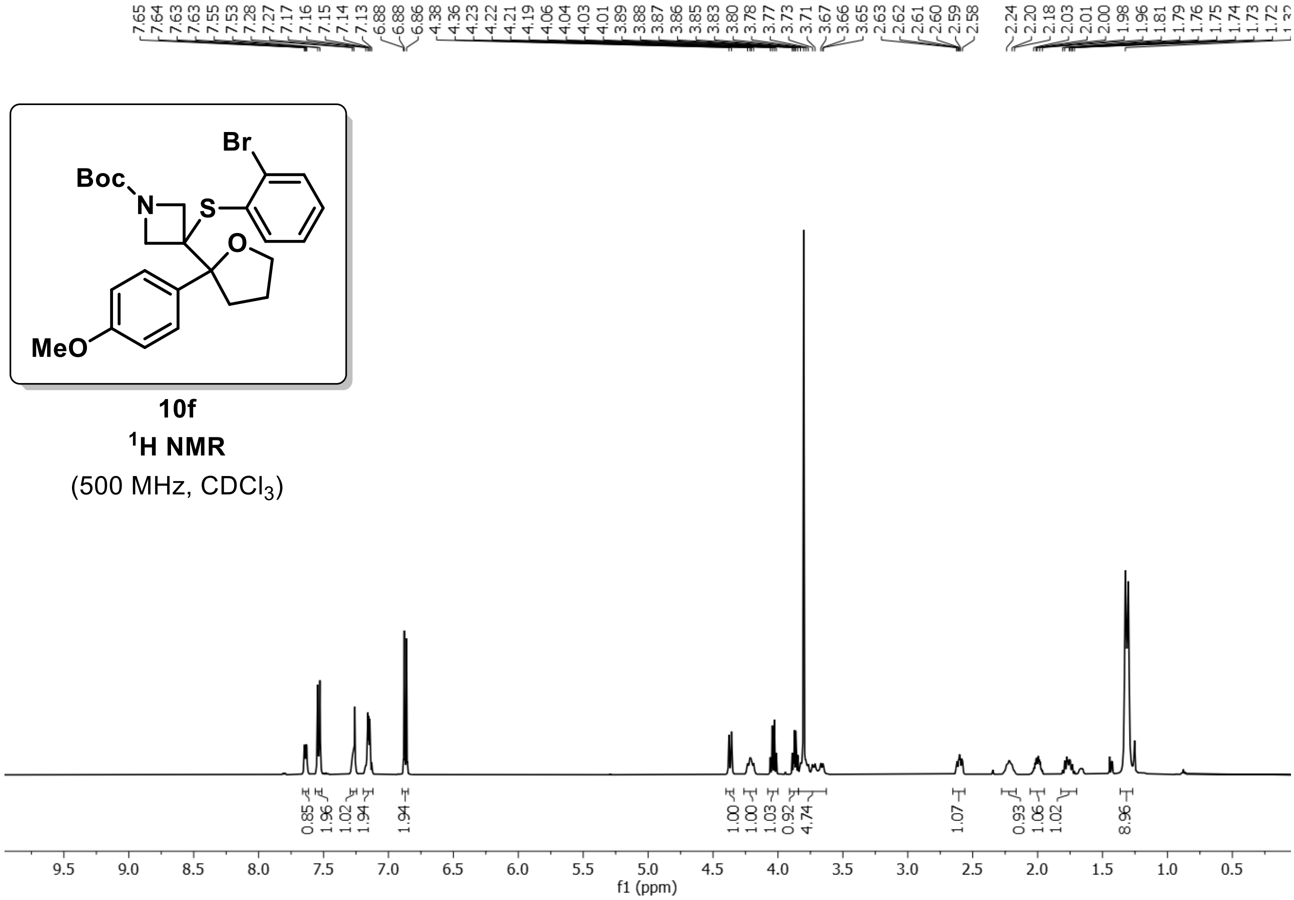
10e

^{13}C NMR

(126 MHz, $CDCl_3$)



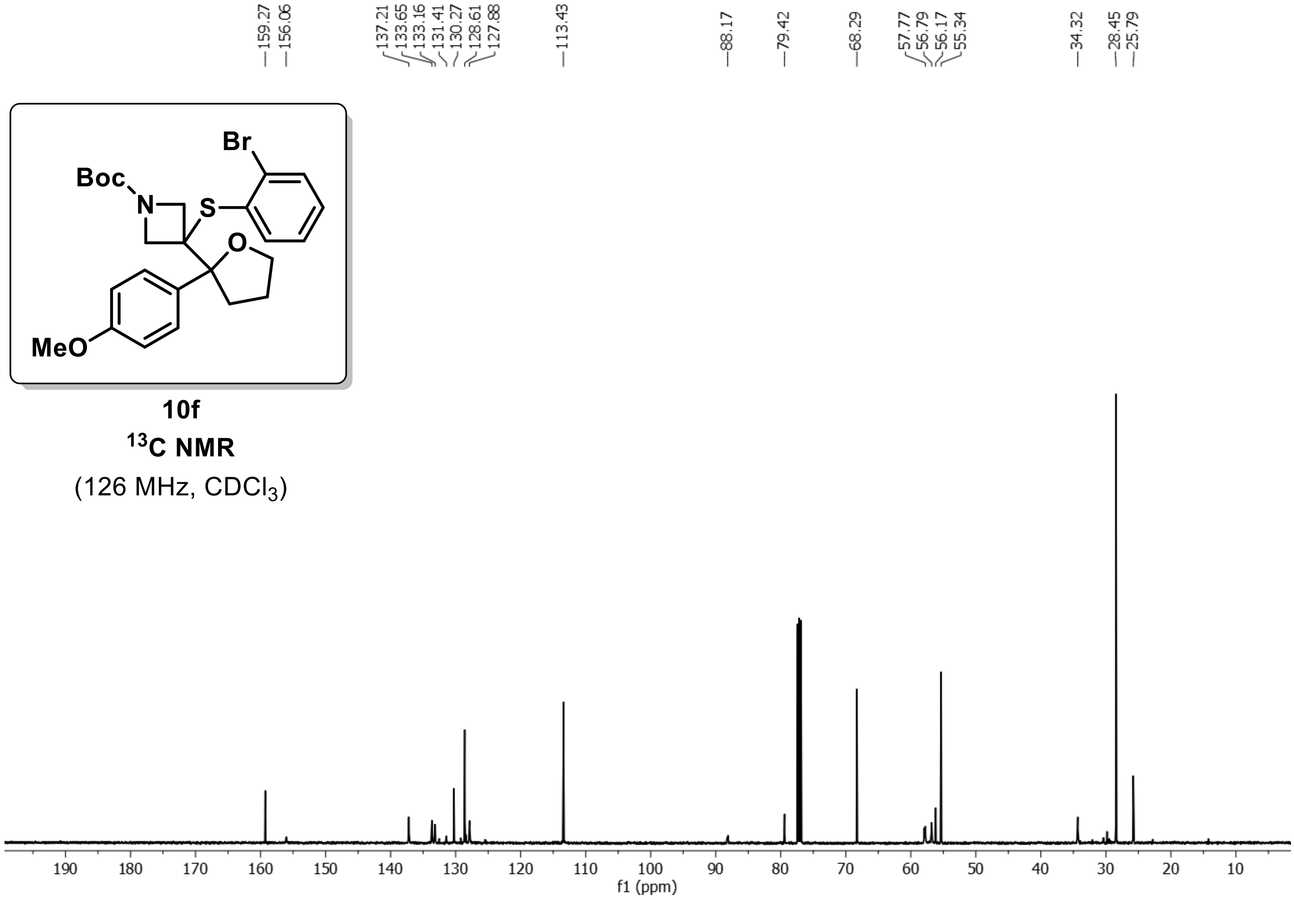
10e
HSQC



10f

^{1}H NMR

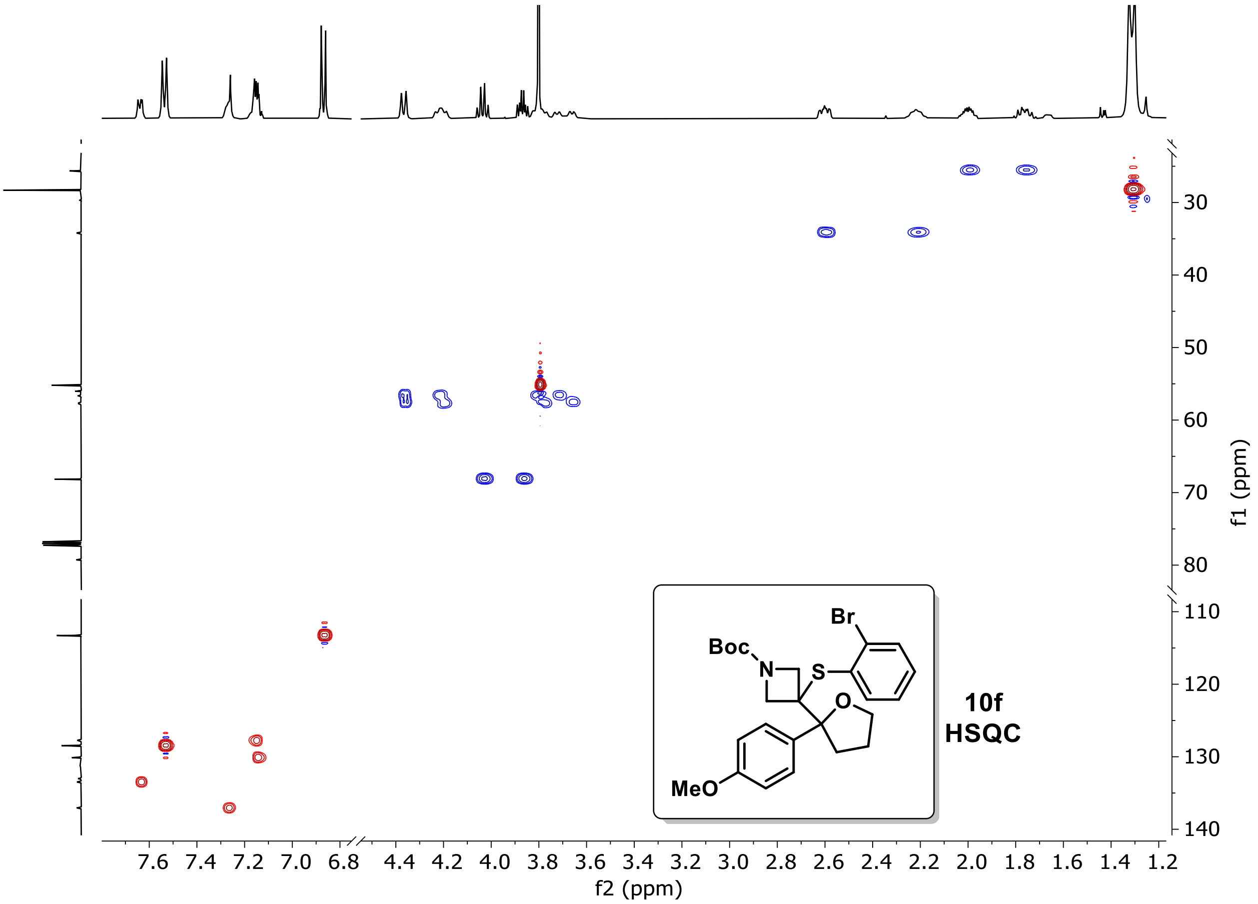
(500 MHz, $CDCl_3$)



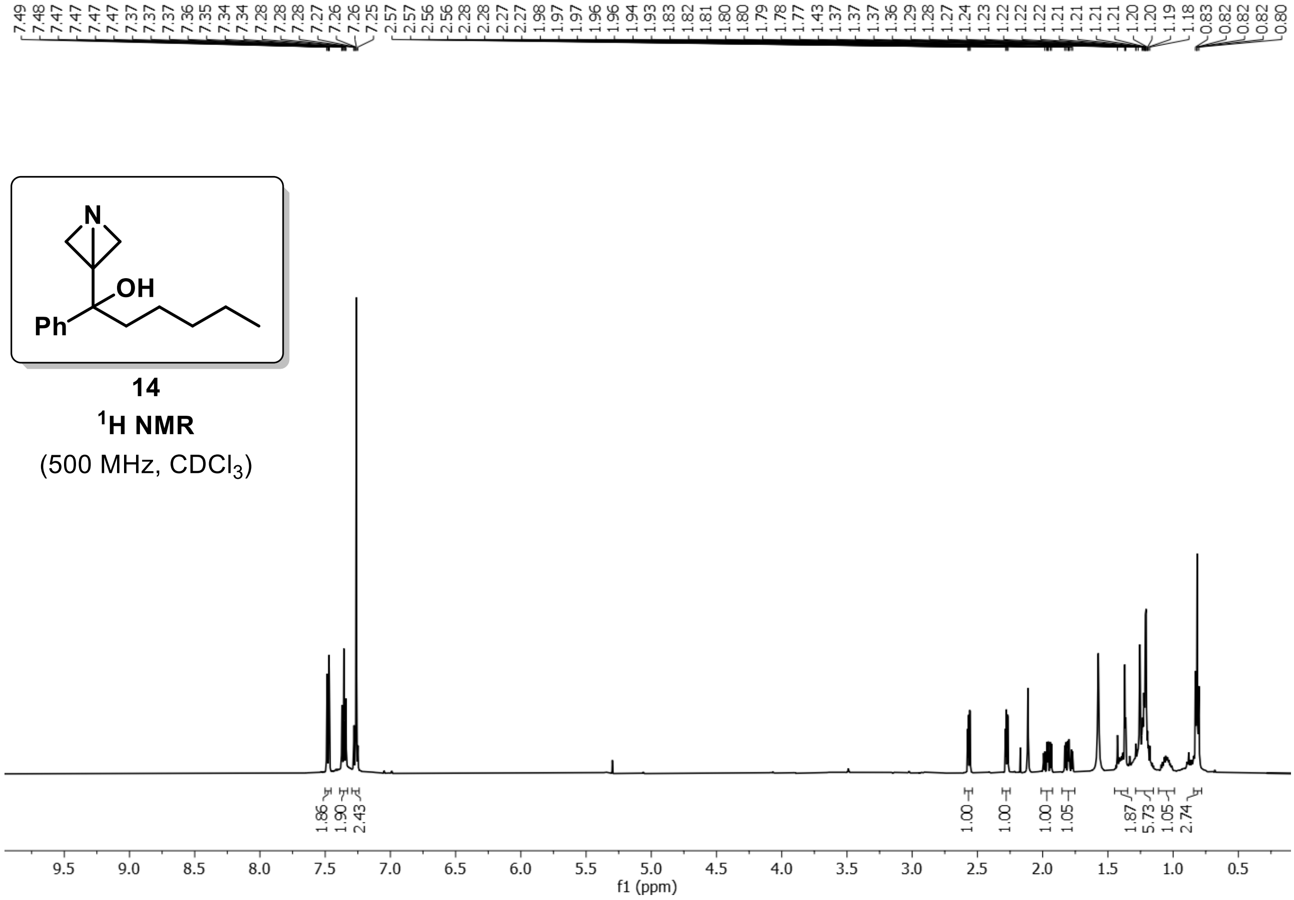
10f

^{13}C NMR

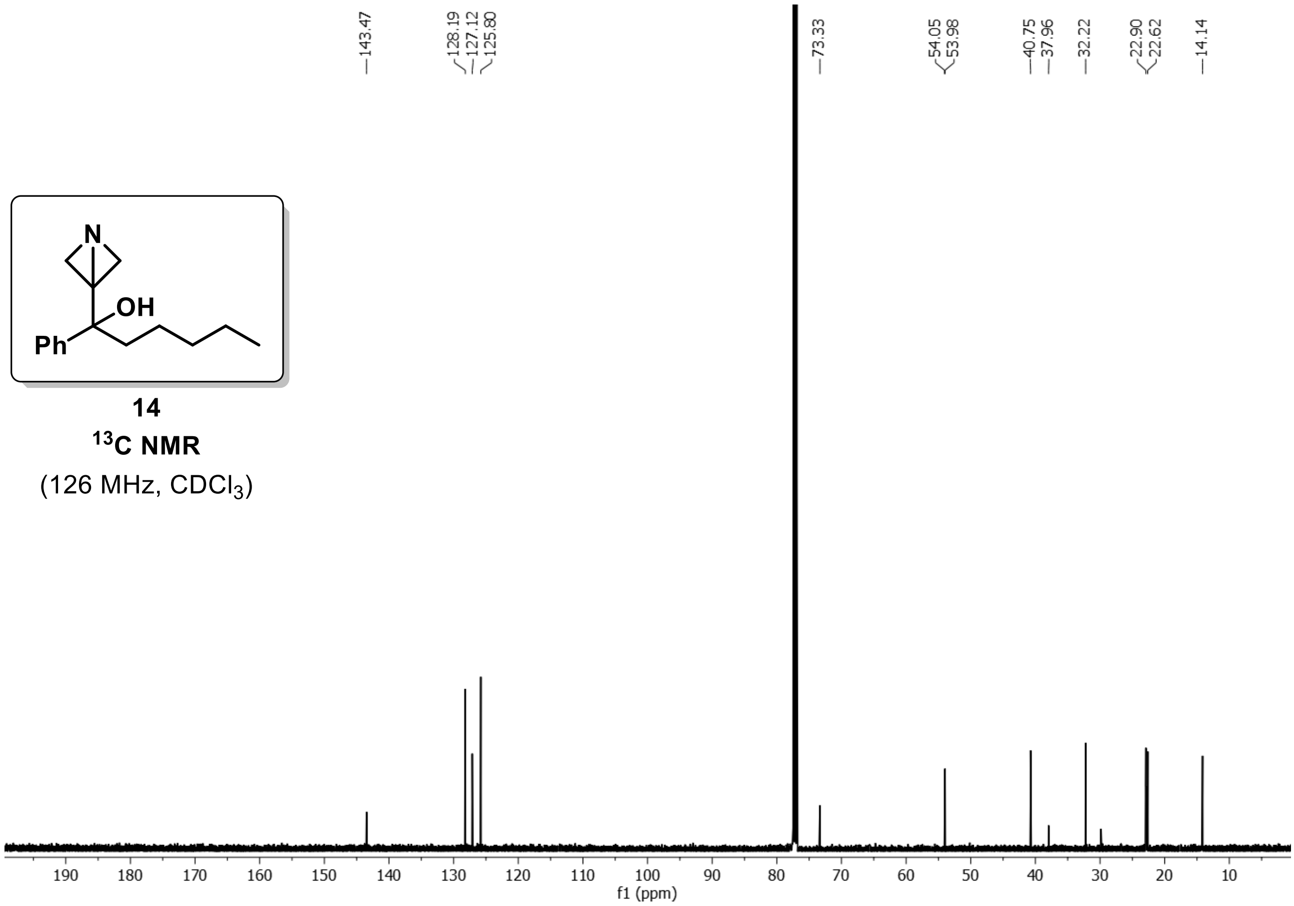
(126 MHz, $CDCl_3$)



10f
HSQC



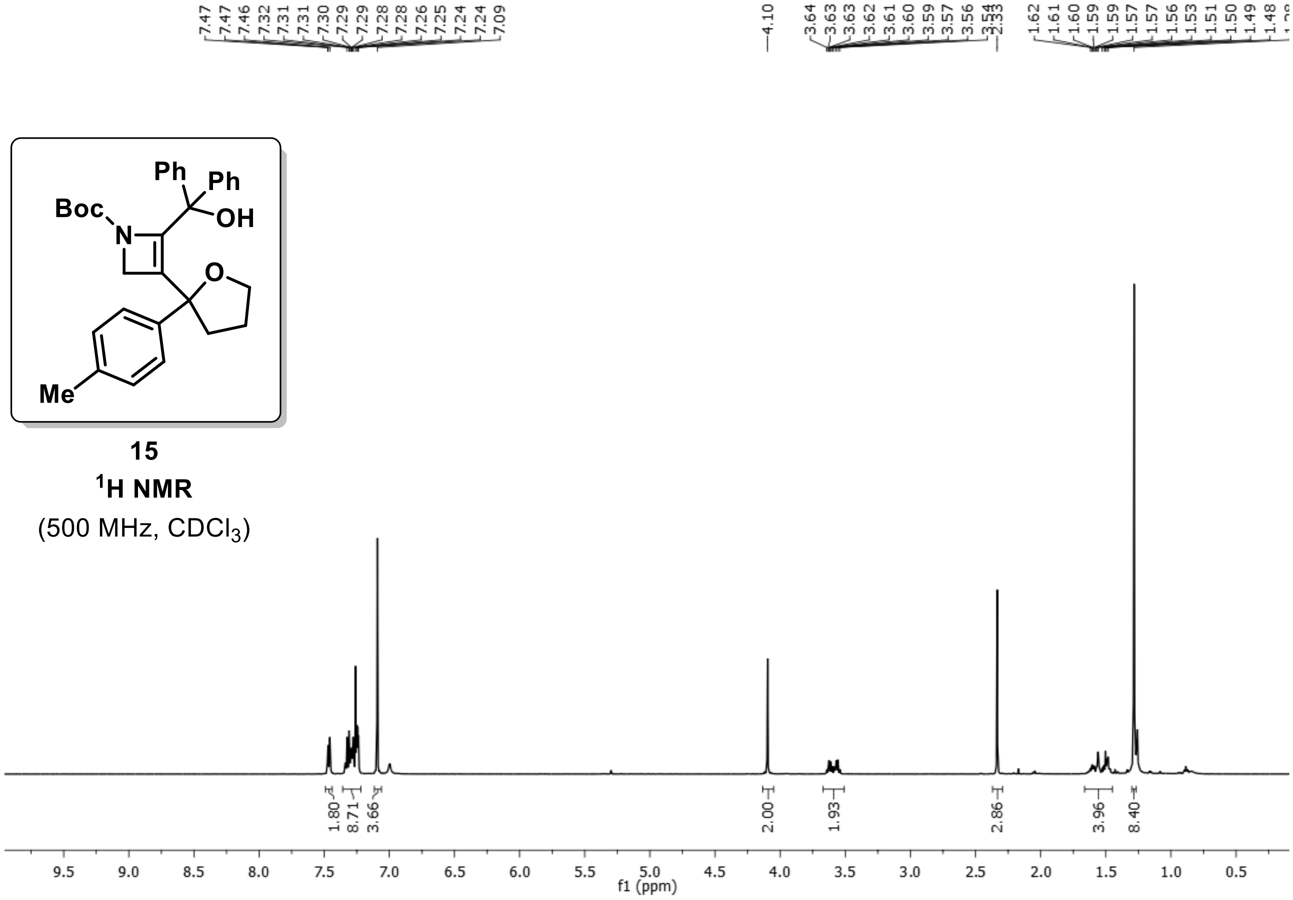
14
^{1}H NMR
(500 MHz, $CDCl_3$)



14

^{13}C NMR

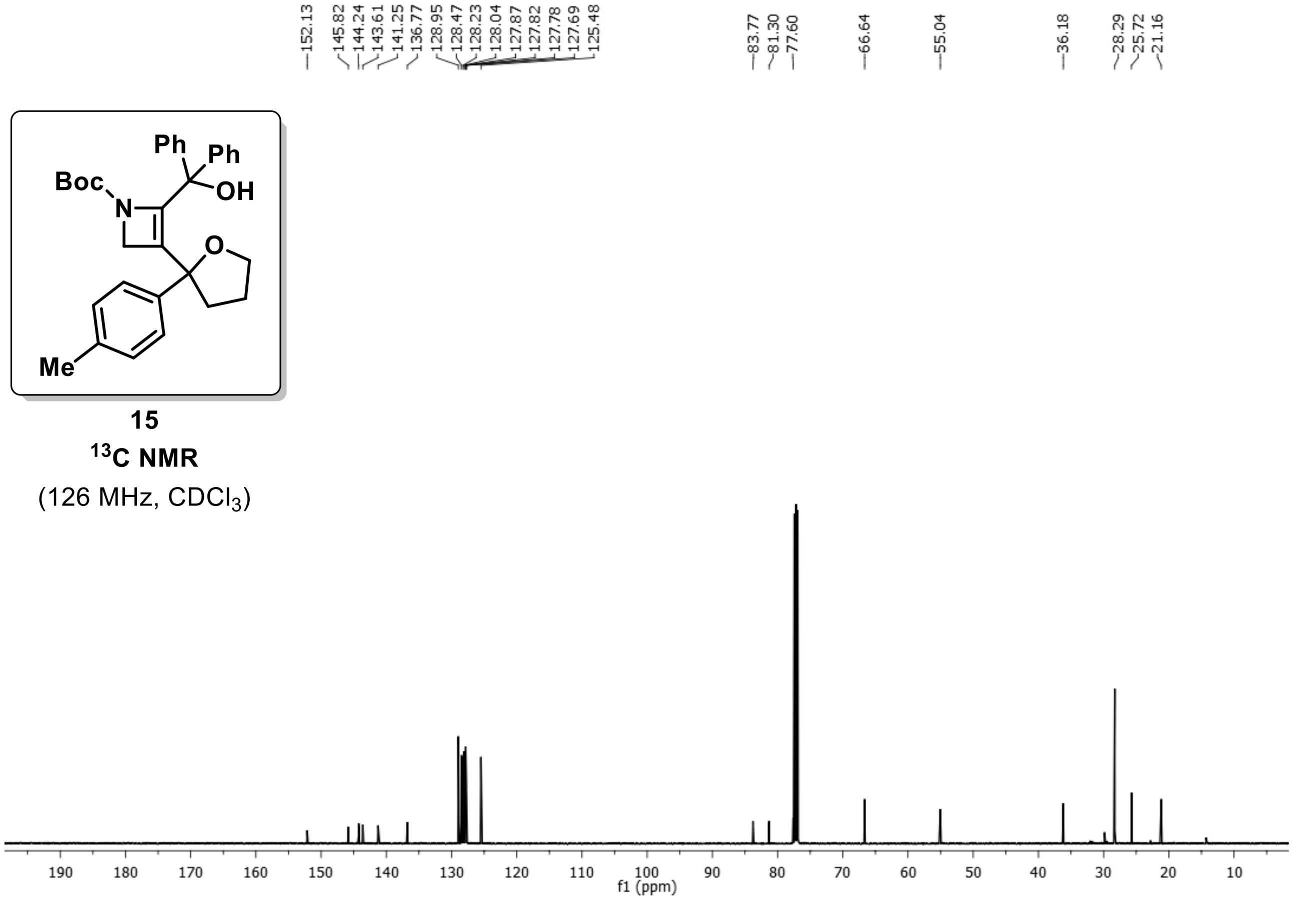
(126 MHz, $CDCl_3$)



15

^{1}H NMR

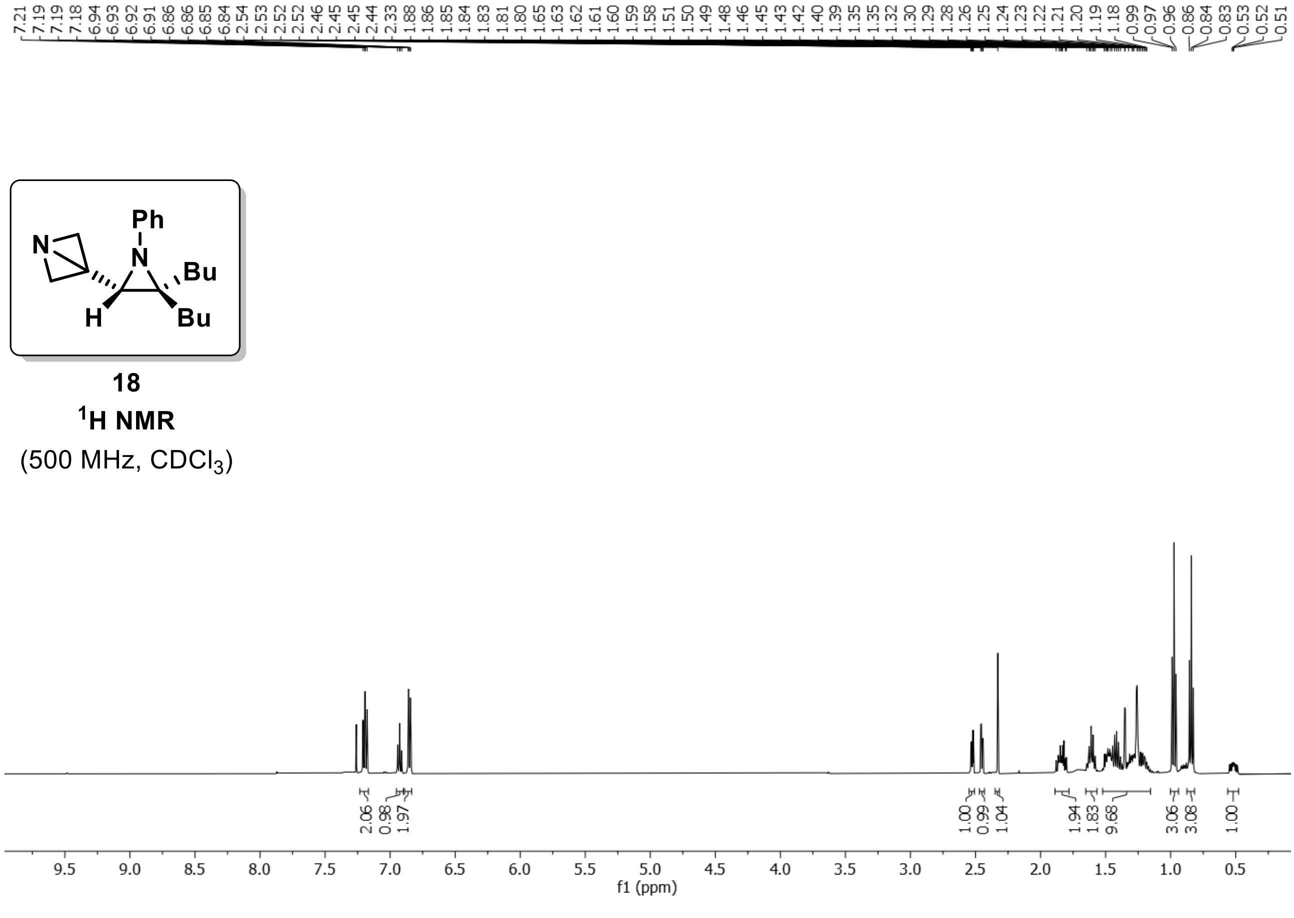
(500 MHz, $CDCl_3$)



15

^{13}C NMR

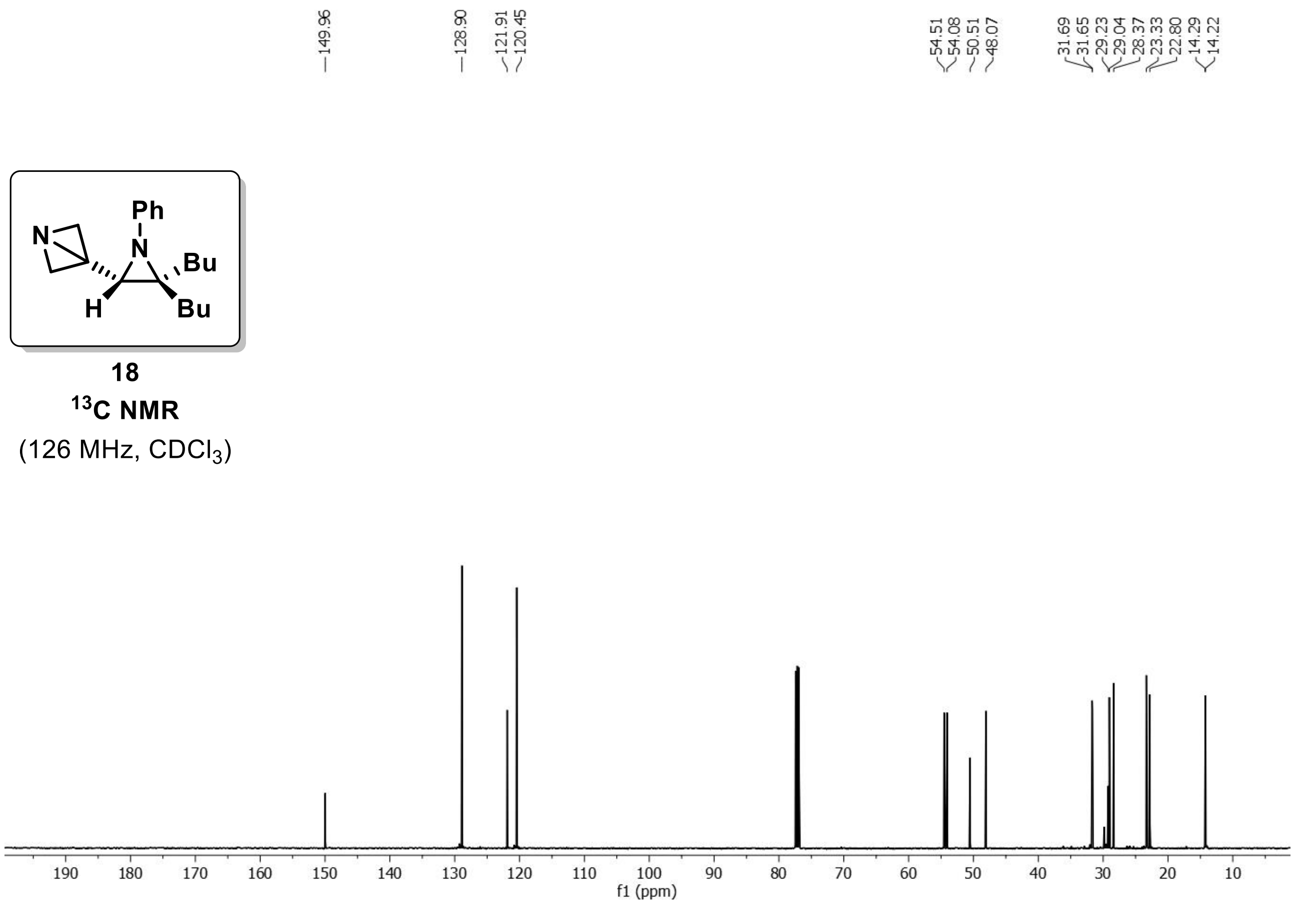
(126 MHz, $CDCl_3$)



18

^{1}H NMR

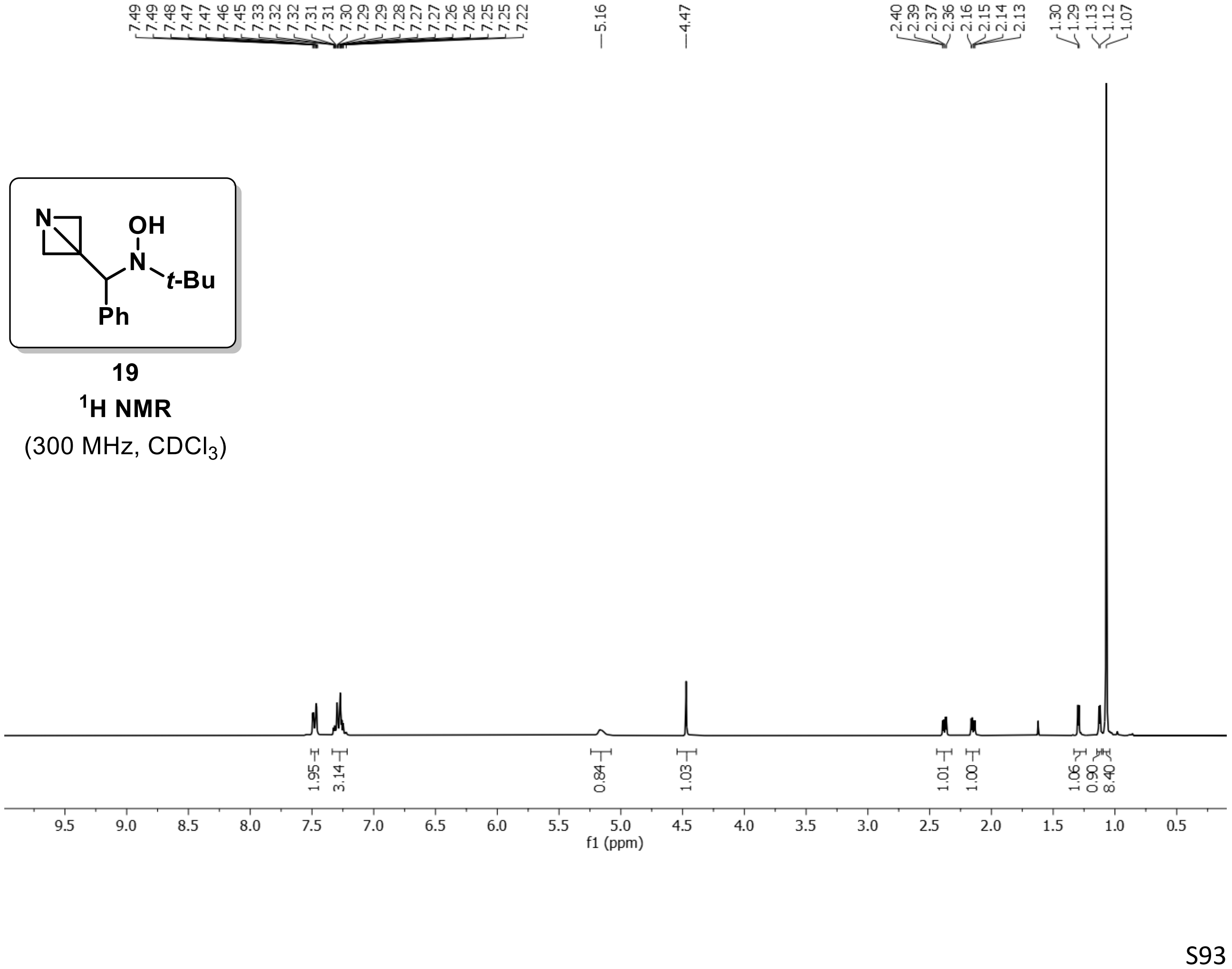
(500 MHz, $CDCl_3$)



18

^{13}C NMR

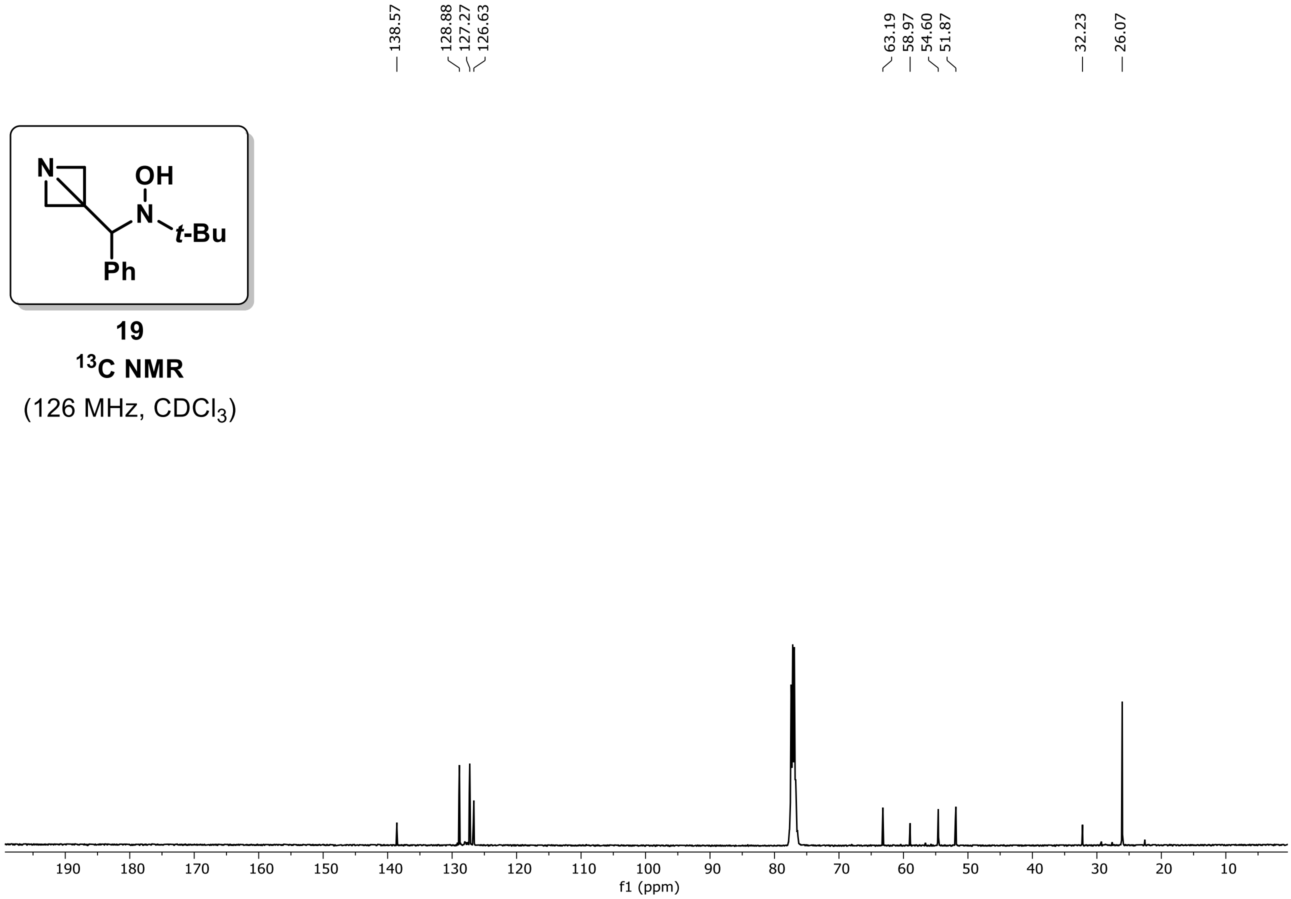
(126 MHz, $CDCl_3$)



19

^{1}H NMR

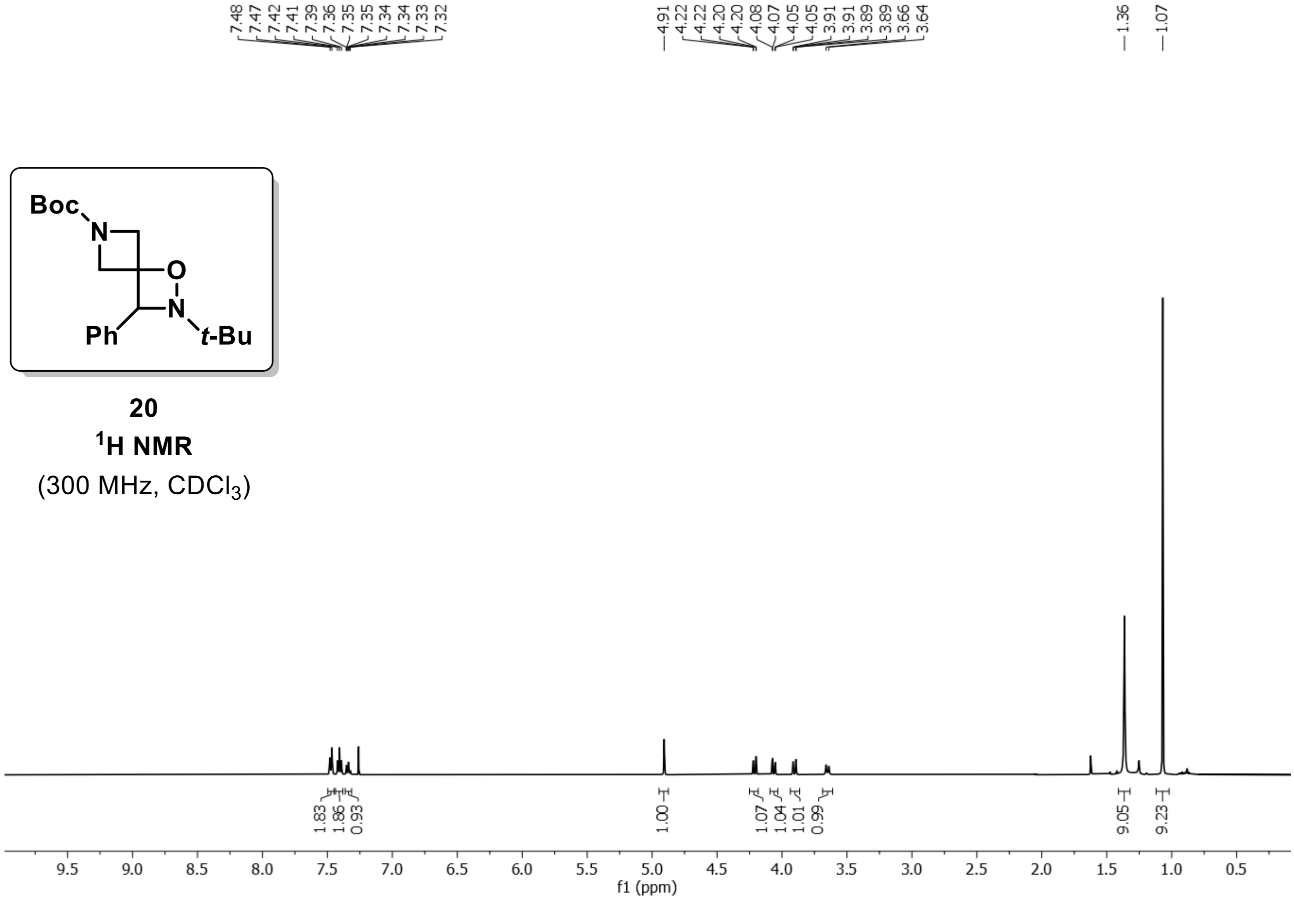
(300 MHz, $CDCl_3$)



19

^{13}C NMR

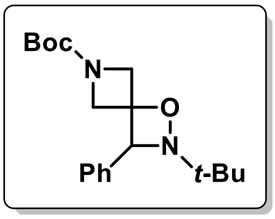
(126 MHz, $CDCl_3$)



20

^{1}H NMR

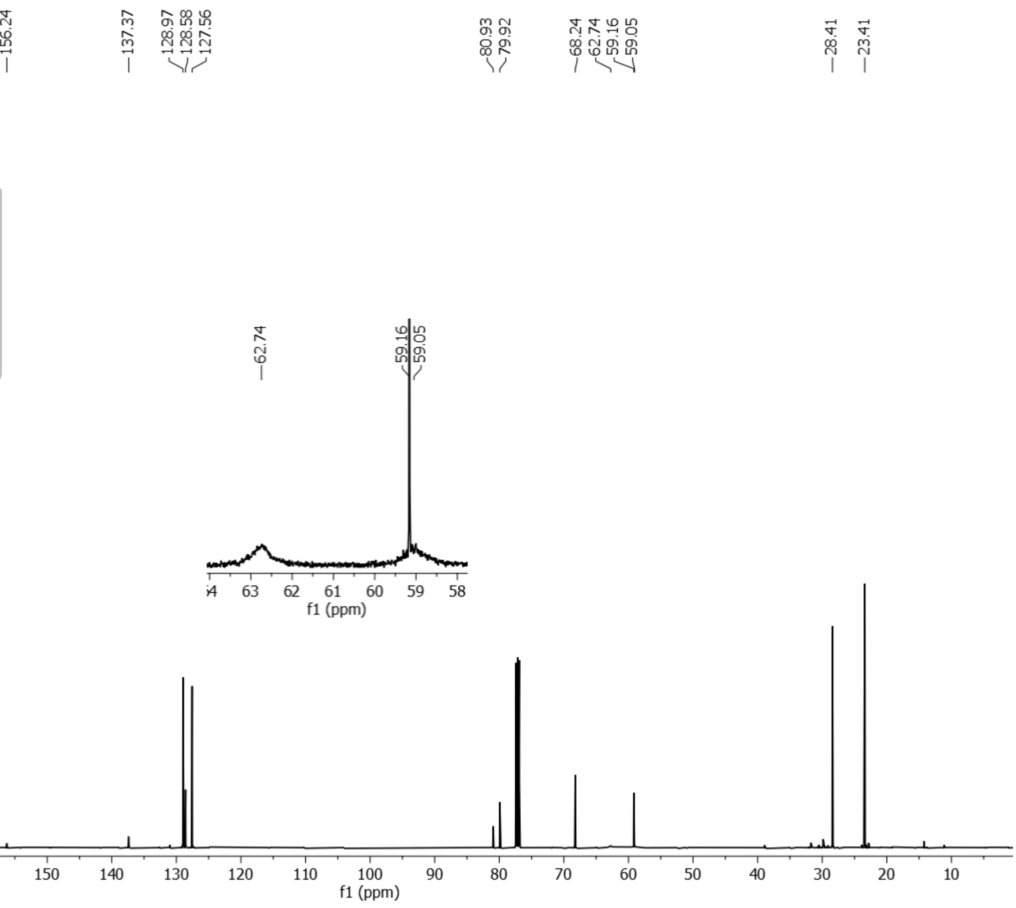
(300 MHz, $CDCl_3$)



20

^{13}C NMR

(126 MHz, $CDCl_3$)



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