Supporting Information

Highly Enantioselective, Hydrogen-Bond-Donor Catalyzed Additions to Oxetanes

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Contents

General Information

Methods:

All reactions were performed in round bottom flasks under a nitrogen (N_2) atmosphere unless otherwise noted. Catalytic experiments were performed under N_2, in oven-dried 1- or 2-dram vials with septum-lined caps. Stainless steel gas-tight syringes were used to transfer air- and moisture-sensitive liquids. Reactions were monitored by thin-layer chromatography (TLC) on Silica Gel 60 F254 plates (EMD) and visualized under UV light (254 nm) or with cerium ammonium molybdate or $KMnO_4$ upon heating. Flash chromatography was performed using SiliaFlash P60 (230-400 mesh, SiliCycle), and was conducted on a Biotage Isolera automated chromatography system.

Materials and Reagents:

Commercial reagents were purchased from Sigma-Aldrich, MilliporeSigma, Alfa Aesar, Strem, Oakwood, Matrix Scientific, Synthonix, Chem-Impex, Cambridge Isotope Laboratories, or TCI and used as received unless otherwise noted. Reaction solvents (*t*-BuOMe, Et_2O, THF, 1,4-dioxane, CH_2Cl_2, toluene, and DMF) were dried by passing through columns of activated alumina. Deuterated solvents $CDCl_3$ and $(CD_3)_2SO$ (Cambridge Isotope Laboratories), and HPLC solvents (EMD) were used without purification.

Instrumentation:

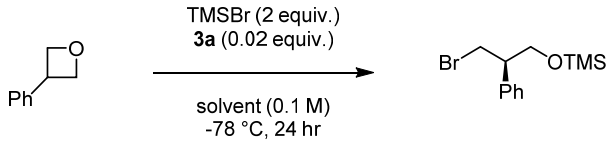
Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded on a Varian Inova 500 (500 MHz), Inova 600 (600 MHz), or Inova 400 (400 MHz) spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Proton resonances are referenced to residual protium in the NMR solvent ($CHCl_3$ = 7.26 ppm, DMSO = 2.50 ppm). Carbon resonances are referenced to the carbon resonances of the NMR solvent ($CDCl_3$ = 77.16 ppm, $(CD_3)_2SO$ = 39.52 ppm). Chemical shifts for fluorine-19 nuclear magnetic resonance (19F NMR) were recorded on Varian Inova 400 (400 MHz) or Inova 500 (500 MHz) spectrometer and are reported in parts per million downfield from chlorotrifluoromethane. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration. Infrared (IR) spectra were obtained using a Bruker Alpha FTIR spectrometer equipped with an attenuated total reflectance (ATR) single reflection unit. Optical rotations ([α]) were measured using a 1 mL cell with a 0.5 dm path length on a Jasco DIP 370 digital polarimeter at 589 nm (sodium D line) at ambient temperature. Mass spectral (MS) data were obtained by submission to the Harvard FAS Division of Science Small Molecule Mass Spectrometry facility. High-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1200 series quaternary HPLC system with commercially available ChiralPak and ChiralCel columns. Enantioenriched and racemic samples were injected as solutions in 5 : 1 hexanes : *i*-PrOH. GC analysis was performed using an Agilent 7890A GC system with commercially-available Chirasil-Dex CB and Agilent HP-5 columns. Supercritical fluid chromatography (SFC) analysis was performed using a JASCO SFC-4000 SFC system with commercially-available ChiralPak columns.

Abbreviations Used:

acac = acetoacetonate, aq = aqueous, boc = *tert*-butyloxycarbonyl, BRSM = based on recovered starting material, c = concentration (in grams/100 mL), calc = calculated, cm^{-1} = wavenumber, DMF = dimethylformamide, dppf = bis(diphenylphosphino)ferrocene, d.r. = diastereomer ratio, e.e. = enantiomeric excess, ent = enantiomer, equiv = equivalents, FTIR = Fourier-transform infrared spectroscopy, GC = gas chromatography, hr = hours, HATU = 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, HMDS = hexamethyldisilazne, HPLC = high-performance liquid chromatography, min = minutes, m/z = mass to charge ratio, n/d = not determined, NMR = nuclear magnetic resonance, Ph = phenyl, phth = phthalyl, pin = pinacol, *p*-Ts = para-toluenesulfonyl, r.t. = room temperature, sat = saturated, 2-Me-THF = 2-methyltetrahydrofuran, THF = tetrahydrofuran, TLC = thin layer chromatography, TMEDA = tetramethylethylenediamine, TMS = trimethylsilyl, Tol = tolyl, wt = weight, xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

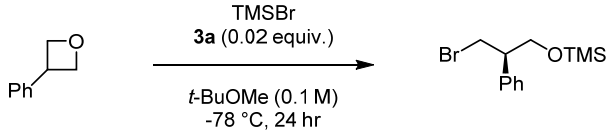
Reaction Development and Optimization

General Procedure A (reaction optimization and development at 0.1 mmol scale): An oven-dried 1-dram vial was equipped with a magnetic stir-bar and closed with a screw-cap containing a rubber septum. The vial was charged with oxetane **1a** (13.4 mg, 0.1 mmol, 1 equiv.), catalyst **3a** (1.4 mg, 0.002 mmol, 0.02 equiv.), mesitylene as an internal standard (10 uL, 0.072 mmol, 0.72 equiv.), and *t*-BuOMe (1 mL, 0.1 M). The headspace of the vial was flushed with nitrogen for 15 seconds and then the vial was cooled to -78 °C in a dry ice-acetone bath, allowing 10 minutes for the temperature to equilibrate. A micro-syringe was flushed with TMSBr 3x or until the solution in the syringe was clear, and then TMSBr (26 uL, 0.2 mmol, 2 equiv.) was added dropwise to the reaction being careful to ensure no TMSBr froze to the side of the vial. The reaction was allowed to continue stirring at -78 °C for 1 hour, after which it was transferred to a -80 °C freezer and continued without stirring for an additional 23 hours. The reaction was then quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.1 mL). After an additional 5 minutes at -80 °C, the reaction was allowed to warm to room temperature and diluted with Et_2O (2 mL). A 1 mL aliquot of the reaction was run through a syringe filter and subjected to chiral GC analysis to determine enantiomeric excess, and where applicable, conversion relative to mesitylene.



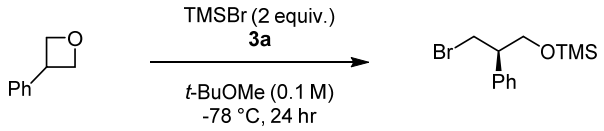
entry	reaction solvent	conversion (%)	e.e. (%)
1	*t*-BuOMe	100	96
2	Et_2O	85	93
3	Toluene	99	0
4	CH_2Cl_2	100	2

Figure S1 – Optimization of reaction solvent. All reactions were conducted according to General Procedure A, with the reaction solvent being modified.



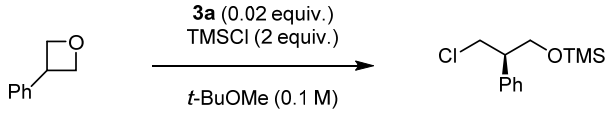
entry	TMSBr loading (eq.)	conversion (%)	e.e. (%)
1	1	84	96
2	2	100	96
3	3	100	96
4	4	100	96

Figure S2 – Optimization of TMSBr loading. All reactions were conducted according to General Procedure A, with the loading of TMSBr being modified.



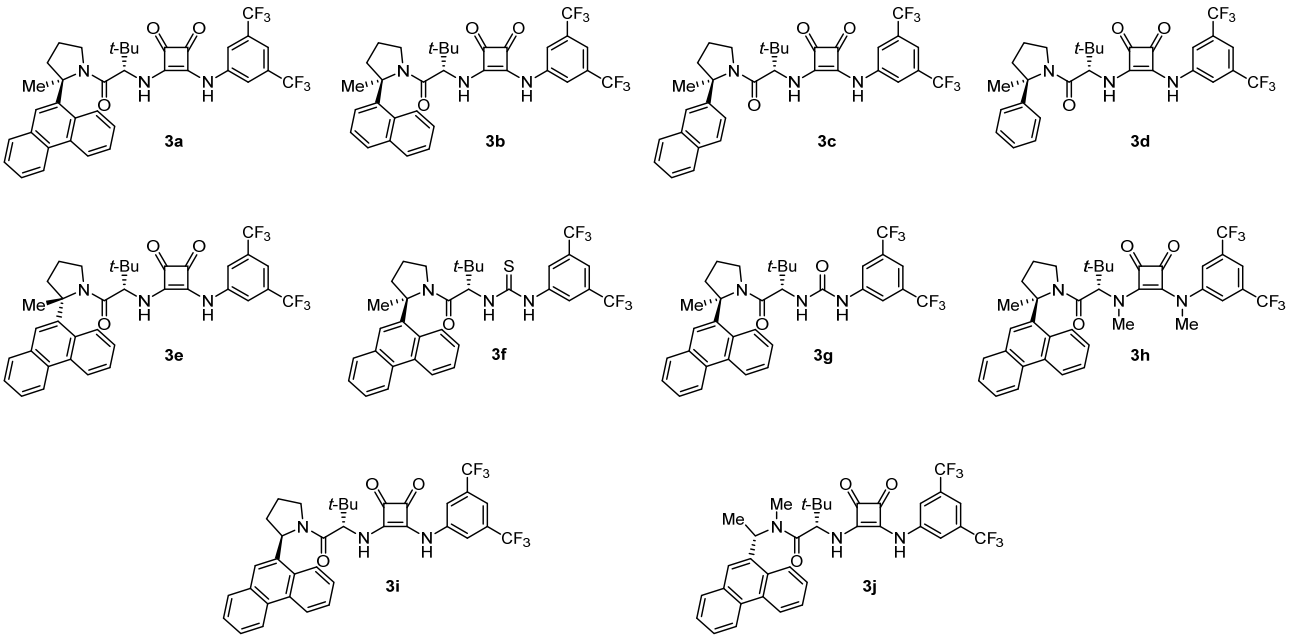
entry	loading of **3a** (mol%)	run 1 - conversion (%)	run 1 - e.e. (%)	run 2 - e.e. (%)	run 3 - e.e. (%)
1	5	100	97	—	97
2	1	99	96	96	—
3	0.5	86	96	94	97
4	0.1	42	91	95	—
5	0.05	56	73	91	87
6	0.01	27	43	86	—

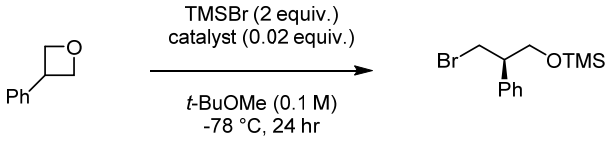
Figure S3 – Optimization of catalyst loading. All reactions were conducted according to General Procedure A, with the loading of catalyst **3a** being modified. We suspect that the irreproducibility at low catalyst loadings is due to variable contribution from an HBr-catalyzed background pathway which varies with the amount of adventitious water.



entry	temperature	conversion (%)	e.e. (%)
1	-30 °C	14	97
2	4 °C	51	92

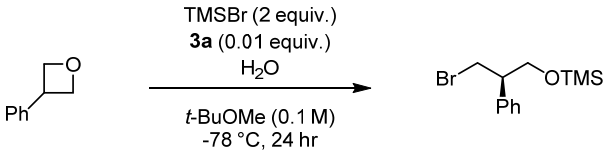
Figure S4 – Highly enantioselective oxetane openings can be performed with TMSCl. All reactions were conducted according to General Procedure A, with the following modifications: the reactions were run using TMSCl in place of TMSBr and at the indicated temperature. All reactions were run for 18 hours. In all cases, conversion of **1a** relative to mesitylene was determined by GC analysis. The enantiomeric enrichment was determined by GC using the standard procedure for brominated silyl ether **2a**. While TMSCl could effect highly enantioselective oxetane openings in the presence of **3a**, the reaction was far slower than that with TMSBr.





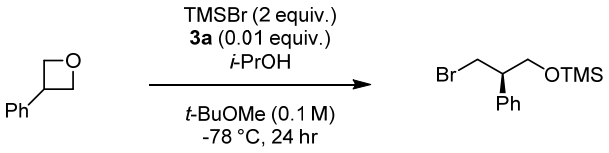
entry	catalyst	run 1 - e.e. (%)	run 2 - e.e. (%)	run 3 - e.e. (%)
1	**3a**	98	96	97
2	**3b**	90	88	94
3	**3c**	79	91	91
4	**3d**	51	70	83
5	**3e**	-15	—	—
6	**3f**	80	86	87
7	**3g**	18	77	93
8	**3h**	12	—	—
9	**3i**	93	91	—
10	**3j**	49	—	—

Figure S5 – Catalyst optimization for enantioselectivity. All reactions were conducted according to General Procedure A.



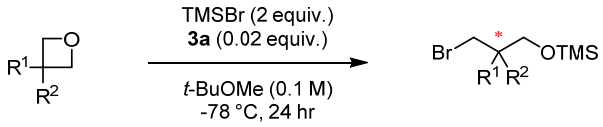
entry	loading of H_2O (mol%)	e.e. (%)
1	2	98
2	4	98
3	6	95
4	8	93

Figure S6 – Effect of added H_2O on enantioselectivity (375 mg scale reactions). A round-bottom flask was equipped with a magnetic stir-bar and flame dried 2x under vacuum. The flask was then charged with catalyst **3a** (0.01 equiv.) and oxetane **1a** (1 equiv.), which were dissolved in *t*-BuOMe (0.1 M) under an atmosphere of nitrogen. The appropriate volume of water was then added to the reaction, being careful to ensure that the water was added directly to the solvent and did not adhere to the side of the flask. The solution was stirred at room temperature for 1 minute and then cooled to -78 °C in a dry ice-acetone bath, allowing 15 minutes for the temperature to equilibrate before TMSBr (0.74 mL, 5.59 mmol, 2 equiv.) was added to the reaction dropwise. The reaction was allowed to continue stirring at -78 °C for 24 hours, after which it was quenched by the addition of Et_3N (2.5 mL / 1 mL of TMSBr). This was allowed to continue stirring at -78 °C for 2 minutes to ensure complete silylation of any residual bromohydrin, after which MeOH (2.5 mL / 1 mL of TMSBr) was added to complete the quench. The reaction was then passed through a short celite plug to remove the solids. The product (**2a**) was subjected to chiral GC analysis to determine enantiomeric excess.



entry	loading of *i*-PrOH (mol%)	e.e. (%)
1	1	98
2	10	94
3	50	23

Figure S7 – Effect of added *i*-PrOH on enantioselectivity. All reactions were conducted according to General Procedure A with the following modification: the indicated loading of *i*-PrOH was added to the reaction.



entry	product	screening scale run(s) - e.e. (%)	0.4 mmol scale run(s) - e.e. (%)
1	**2a**	96, 97, 98	98, 98
2	**2b**	91[a]	92
3	**2c**	98[a]	98
4	**2d**	–68[a,b]	73
5	**2e**	–97[a,b]	98
6	**2f**	100	98[c], 99
7	**2g**	95[a]	96
8	**2h**	–91[a,b]	93
9	**2i**	–98[a,b]	97
10	**2j**	–96[a,b,d]	94, 96, 96
11	**2k**	–92[b,e,f]	89[f], 91[f]
12	**2l**	87[d]	90
13	**2m**	95[d]	95, 96[c]
14	**2n**	98[a]	97, 99
15	**2o**	—	93, 94
16	**2p**	–81[b,e]	82, 85
17	**2q**	80[c,e,f], 81[e,f], –81[b,e,f]	82[f,g,h]
18	**2r**	–91[b,e,f], –91[b,e,f], 92[e,f]	92[f,g,h]
19	**2s**	89[c,e,f]	91[f,g,h], 91[f,g,h]
20	**2t**	82[c,e,f]	88[f,g,h]
21	**2u**	89[g,i]	88[g,i]
22	**2v**	58[g], –64[b,e], –77[b,e], –78[b,e]	67[c,g], 77[c,g]

Figure S8 – Reproducibility of e.e. for the enantioselective reaction. Screening scale refers to 0.05 mmol of substrate unless otherwise noted. Deviations from standard conditions are as follows: a) 2.5 mol% **3a** was used; b) ent **3a** was used; c) 48 hour reaction time; d) reaction run on 0.1 mmol scale; e) 5 mol% **3a** was used; f) reaction run at −25 °C; g) 7.5 mol% **3a** was used; h) 72 hour reaction time; i) reaction run at −65 °C. Greater variability in e.e. is expected for products **2k** and **2q-v** due to imperfect control over temperature for reactions run in cryocools.

Kinetic Isotope Effect Experiments

General procedure for KIE experiments:

A stock solution was prepared consisting of ~1 : 1 $^{12}C_2$- and $^{13}C_2$- oxetane **1a** (0.3 mmol $^{12}C_2$-**1a** and 0.3 mmol $^{13}C_2$-**2a**) and mesitylene (60 uL) in *t*-BuOMe (6 mL, 0.1 M total oxetane). 4 mL (0.4 mmol total **1a**, 1 equiv.) of this stock solution was added to an oven-dried 2-dram vial which had been charged with catalyst **3a** (5.4 mg, 0.008 mmol, 0.02 equiv.) and a magnetic stir-bar, and closed with a screw-cap containing a rubber septum. The remainder of the stock solution was set aside to use as the R_0 sample. The headspace of the vial was flushed with nitrogen for 15 seconds and then the vial was cooled to -78 °C in a dry ice-acetone bath, allowing 15 minutes for the temperature to equilibrate. A micro-syringe was flushed with TMSBr 3x or until the solution in the syringe was clear, and then TMSBr (42 uL, 0.32 mmol, 0.8 equiv.) was added dropwise to the reaction being careful to ensure no TMSBr froze to the side of the vial. The reaction was allowed to continue stirring at -78 °C for 3 days, after which it was quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.4 mL). After an additional 5 minutes at -78 °C, the reaction was allowed to warm to room temperature and an aliquot was removed for GC analysis to determine conversion and enantiomeric enrichment of the product. The remainder of the crude reaction mixture was diluted with Et_2O and saturated aqueous $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried briefly (~10 minutes) over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to recover the unreacted oxetane **1a** starting material for NMR analysis of the R_f sample. An aliquot of the R_0 sample was removed for GC measurement and the remainder of the sample was purified by flash column chromatography to recover pure oxetane **1a** for NMR analysis of the R_0 sample.

Sample measurement for KIE experiments:

GC measurements of aliquots of the crude R_0 and R_f samples were conducted using either the standard chiral GC conditions for product **2a** or using an achiral GC (HP-5 – 30m x 0.32 mm x 0.25 µm, 40 °C for 2 minutes, 40→225 °C at 25°/min, 7 psi). Conversion was determined relative to the mesitylene internal standard. Six GC runs were recorded for each sample. The e.e. of the product in the R_f sample was then measured using the standard chiral GC conditions for product **2a**.

The ratio of ^{12}C to ^{13}C in the 2- and 4-positions of the 3-phenyloxetane was determined through ^1H-NMR analysis of the protons bound to those carbons and their ^{13}C satellite peaks.[1] NMR measurements of the purified R_0 and R_f samples were conducted in 600 uL of $CDCl_3$ each at nearly-identical concentration (as determined by integration of the benzylic proton relative to the solvent residual peak). The spectra were recorded on a Varian NMR probe (600 MHz) at room temperature. In order to obtain reproducible and quantitative results spectra were recorded without sample spinning using a calibrated ninety-degree pulse with the transmitter offset frequency set to -90.8 Hz. An acquisition time of 2.5 seconds and relaxation delay of 30 seconds were used. Six spectra were recorded for each sample.

Data analysis for KIE experiments:

All GC spectra were normalized such that the area under the mesitylene peak was set to 1000 units.

All spectra were processed using Mestrenova. Spectra were aligned by setting the solvent residual peak to 7.26 ppm, and then phased using Mestrenova's automatic phase correction followed by a manual phase correction. Then a third-order polynomial baseline correction was applied. All NMR spectra were normalized such that the integral of the benzylic proton (H^c in Fig. S10) was set to 2000 units.

The kinetic isotope effect was computed using the following formula:

$$\frac{k_{12}}{k_{13}} = \frac{\ln\left(1 - F_{12}\right)}{\ln\left(\left(1 - F_{12}\right) * \frac{R_f}{R_0}\right)}$$

where:

$$R_0 = \frac{[13C\ Oxetane]}{[12C\ Oxetane]}\ in\ the\ stock\ solution\ of\ starting\ material\ added\ to\ the\ reaction$$

$$R_f = \frac{[13C\ Oxetane]}{[12C\ Oxetane]}\ in\ the\ starting\ material\ recovered\ from\ a\ reaction\ run\ to\ partial\ conversion$$

and F_{12} is the fractional conversion of ^{12}C oxetane given by:

$$1 - F_{12} = \left(1 - F\right) * \frac{1 + R_0}{1 + R_f}\ \ where\ F\ is\ the\ fractional\ conversion\ in\ total\ oxetane$$

Error was determined using the following formula:[2]

$$\Delta KIE = KIE * \sqrt{\left(\frac{\Delta KIE_F}{KIE}\right)^2 + \left(\frac{\Delta KIE_R}{KIE}\right)^2}$$

where:

$$\Delta KIE_F = \frac{-\ln\left(R_f/R_0\right)}{\left(1 - F_{12}\right) * ln^2\left(\left(1 - F_{12}\right) * R_f/R_0\right)} * \Delta F_{12}$$

$$\Delta KIE_R = \frac{-\ln\left(1 - F_{12}\right)}{\left(R_f/R_0\right) * ln^2\left(\left(1 - F_{12}\right) * R_f/R_0\right)} * \Delta\left(R_f/R_0\right)$$

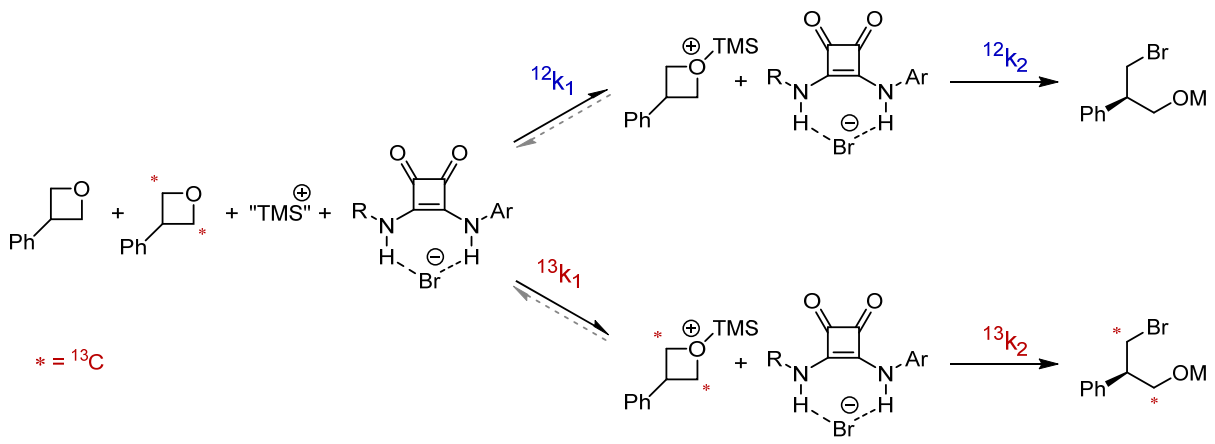


Figure S9 – Identification of the enantiodetermining step via a one-pot competition kinetic isotope effect experiment. Based on chemical intuition, we expected that C-Br bond formation (k_2) would be the enantiodetermining step of the transformation. However, we have previously encountered unexpected enantiodetermining steps in methods developed by our lab, with the asymmetric Strecker reaction providing a particularly relevant example.[3] In that transformation, which occurs by imine activation via protonation followed by C-C bond formation through cyanide delivery, the activation/rearrangement step was found to be enantiodetermining instead of the anion delivery step. Thus, we felt it was necessary to consider the possibility that oxetane activation (k_1) could be irreversible, and thus, potentially enantiodetermining. To probe this, a one-pot competition kinetic isotope effect experiment was conducted using an ~ 1 : 1 ratio of 2,4-^{12}C and 2,4-^{13}C oxetane **1a**. If oxetane activation is irreversible then the KIE will reflect $^{12}k_1/^{13}k_1$. Since that step occurs on oxygen, the isotope effect at carbon will be secondary, and therefore, should be small (i.e. <1.02). However, if the activation of any particular molecule of oxetane is reversible, then the KIE will primarily reflect the relative rates of bromide delivery (k_2) to the two isotopologues (more precisely, it will reflect both k_2 and the equilibrium isotope effect for the activation of ^{12}C vs ^{13}C oxetanes, but the latter effect is expected to be small). Because bromide substitution occurs directly at the labeled/unlabeled carbon, $^{12}k_2/^{13}k_2$ will reflect a primary carbon KIE, which is expected to be significantly larger (typically 1.03-1.08) than that for irreversible oxetane activation. The observation of a large, primary KIE unambiguously indicates that oxetane activation must be reversible, and thus, cannot be enantiodetermining. Consequently, we have assigned anion delivery as the enantiodetermining step.

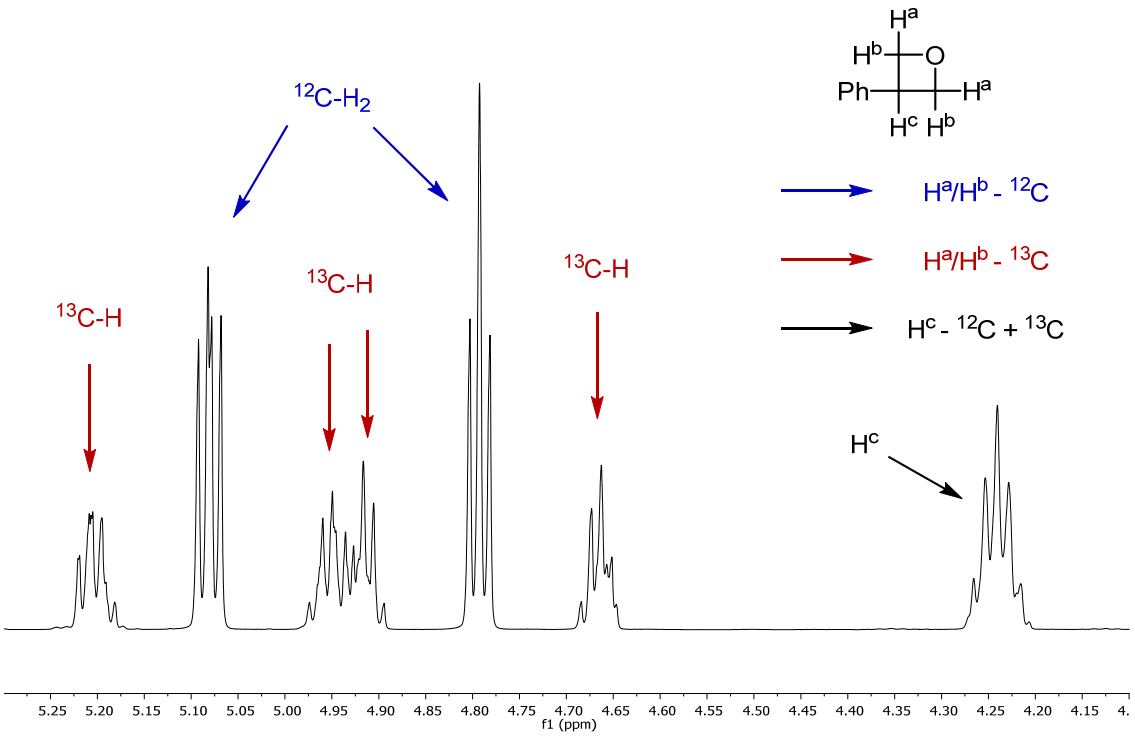


Figure S10 – Representative ^{1}H NMR spectrum showing the peaks of interest. The protons corresponding to H^a and H^b for ^{12}C oxetane are located in the ranges 5.11-5.05 ppm and 4.85-4.76 ppm, each of which integrates for 2 protons/molecule of $^{12}C_2$ oxetane. For $^{13}C_2$ oxetane these peaks are split by coupling to the ^{13}C, giving resonances in the ranges 5.23-5.18 ppm, 4.98-4.88 ppm (2 overlapping resonances), and 4.71-4.63 ppm which integrate for 1, 2, and 1 protons/molecule of $^{13}C_2$ oxetane respectively. The benzylic proton (H^c) is located at 4.29-4.17 ppm and is common to both $^{12}C_2$ and $^{13}C_2$ oxetane. This peak was used to normalize integrations across multiple measurements (the integral H^c was set to 2000 units in each spectrum).

Run 1: R_0 Sample						
Measurement	**Normalized [Oxetane]**	**Normalized ^{12}C-H int.**		**Normalized ^{13}C-H int.**		
		5.107-5.051 (2H)	**4.853-4.758 (2H)**	**5.230-5.177 (1H)**	**4.983-4.884 (2H)**	**4.709-4.632 (1H)**
1	1211.10	2074.60	2082.68	993.31	1979.08	982.90
2	1213.45	2071.37	2081.78	990.36	1976.44	983.96
3	1214.60	2071.51	2082.53	990.69	1976.98	983.74
4	1216.06	2068.53	2082.34	988.25	1975.17	984.26
5	1221.83	2067.38	2083.43	987.05	1974.53	984.26
6	1215.28	2066.09	2084.23	985.82	1974.07	983.56

Property	**Value**	**Standard deviation**
Normalized [Oxetane]	1215.39	3.60
Normalized ^{12}C-H	1038.19	3.55
Normalized ^{13}C-H	987.02	2.89

Figure S11 – Tabulated data for R_0 sample for run 1. The R_0 sample for run 1 was prepared according to the general procedure for KIE experiments. The concentration of oxetane to mesitylene was measured using the achiral GC method described above. For details on how the reaction was conducted see Fig. S12.

Run 1: R_f Sample						
Measurement	**Normalized [Oxetane]**	**Normalized ^{12}C-H int.**		**Normalized ^{13}C-H int.**		
		5.107-5.051 (2H)	**4.853-4.758 (2H)**	**5.230-5.177 (1H)**	**4.983-4.884 (2H)**	**4.709-4.632 (1H)**
1	743.60	2011.18	2023.44	1019.40	2034.69	1010.36
2	746.63	2009.36	2023.42	1018.01	2033.50	1010.66
3	751.93	2008.13	2023.61	1017.45	2033.10	1010.32
4	752.85	2007.01	2025.65	1016.89	2033.61	1010.50
5	752.31	2004.56	2025.06	1015.27	2032.30	1009.74
6	758.07	2002.60	2027.45	1013.32	2032.22	1009.59

Property	**Value**	**Standard deviation**
Normalized [Oxetane]	750.90	5.09
Normalized ^{12}C-H	1007.98	4.76
Normalized ^{13}C-H	1014.51	3.37

Figure S12 – Tabulated data for R_f sample for run 1. Run 1 was conducted using the stock solution described in Fig. S11 and was run according to the general procedure for KIE experiments with the following modification: a higher concentration of TMSBr (106 uL, 2 equiv.) was added and the reaction was quenched after 8 hours. The concentration of oxetane relative to mesitylene was determined using the achiral GC method described above. Chiral GC analysis of the crude reaction mixture revealed that **2a** was formed in 96% enantiomeric enrichment.

Run 2: R_0 Sample						
Measurement	**Normalized [Oxetane]**	**Normalized ^{12}C-H int.**		**Normalized ^{13}C-H int.**		
		5.107-5.051 (2H)	**4.853-4.758 (2H)**	**5.230-5.177 (1H)**	**4.983-4.884 (2H)**	**4.709-4.632 (1H)**
1	1088.54	2236.13	2242.33	896.10	1795.76	900.64
2	1089.45	2235.20	2240.47	895.29	1794.93	900.39
3	1082.25	2235.59	2241.19	895.70	1795.30	900.48
4	1073.58	2235.58	2241.57	896.25	1795.63	899.82
5	1082.17	2235.90	2241.38	896.62	1795.72	899.71
6	1088.04	2232.13	2237.50	892.95	1792.15	900.56

Property	**Value**	**Standard deviation**
Normalized [Oxetane]	1084.00	6.02
Normalized ^{12}C-H	1118.96	1.66
Normalized ^{13}C-H	897.74	2.19

Figure S13 – Tabulated data for R_0 sample for run 2. The R_0 sample for run 2 was prepared according to the general procedure for KIE experiments with the following modifications: the stock solution of oxetane consisted of 0.4 mmol each of $^{12}C_2$-**1a** and $^{13}C_2$-**1a**, with 80 uL of mesitylene in *t*-BuOMe (8 mL, 0.1 M total oxetane). The standard chiral GC method was used to determine the total concentration of oxetane relative to mesitylene. For details on how the reaction was conducted see Fig. S14.

Run 2: R_f Sample						
Measurement	**Normalized [Oxetane]**	**Normalized ^{12}C-H int.**		**Normalized ^{13}C-H int.**		
		5.107-5.051 (2H)	**4.853-4.758 (2H)**	**5.230-5.177 (1H)**	**4.983-4.884 (2H)**	**4.709-4.632 (1H)**
1	153.68	1942.15	1948.22	970.06	1960.41	989.41
2	159.16	1944.68	1948.49	970.76	1960.33	988.69
3	156.10	1944.09	1948.67	971.04	1959.96	988.76
4	156.01	1943.44	1946.38	969.62	1958.77	988.47
5	156.26	1942.41	1946.81	971.09	1959.14	988.14
6	155.28	1942.53	1947.24	969.06	1958.37	988.92

Property	**Value**	**Standard deviation**
Normalized [Oxetane]	156.08	1.78
Normalized ^{12}C-H	972.71	1.25
Normalized ^{13}C-H	979.58	7.77

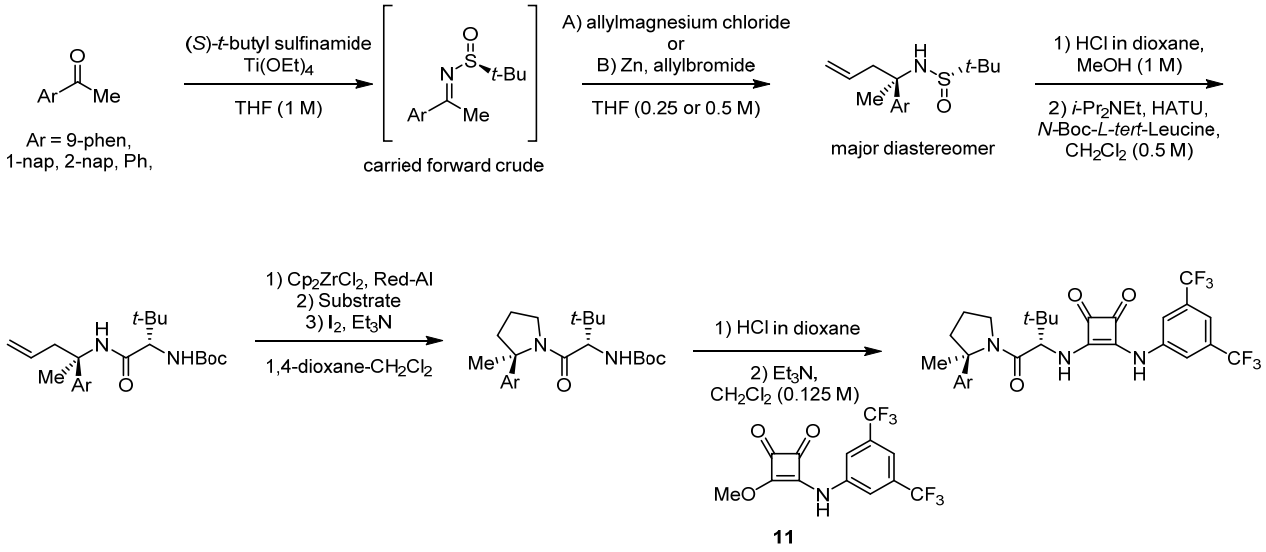
Figure S14 – Tabulated data for R_f sample for run 2. Run 2 was conducted according to the general procedure for KIE experiments with the following modifications: 3 mL of the stock solution described in Fig. S13 (0.3 mmol total **1a**, 1 equiv.) and 5 mol% of **3a** were used (the TMSBr loading remained 0.8 equiv. relative to 0.3 mmol total **1a**). The standard chiral GC method was used to determine the concentration of oxetane relative to mesitylene after the reaction was quenched, and also to determine that **2a** was formed in 97% enantiomeric enrichment.

KIE measurements				
Property	Run 1		Run 2	
	Value	Error	Value	Error
R_f/R_0	1.0587	0.0077	1.255	0.011
$1–F_{12}$	0.6007	0.0063	0.1293	0.0020
KIE	**1.126**	0.018	**1.125**	0.005

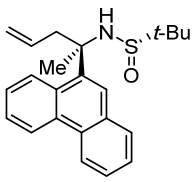
Figure S15 – Tabulated data for KIEs. All values were calculated using the equations described above. Data for run 1 are drawn from Fig. S11 and S12. Data for run 2 are drawn from Fig. S13 and S14. The average KIE over the two samples is 1.126(9). The measured KIEs are very large even for a primary $^{12}C/^{13}C$ KIE, potentially indicating tunneling by the carbon atom during the bromide delivery step.

Synthesis and Characterization of Catalysts

Catalysts **3a**-**3d** were prepared according to the general procedure described below. Allylation procedure B, based on a previously reported method,[4] was used for the synthesis of catalysts **3c** and **3d** as it provided excellent d.r. and good yield. For the optimal catalyst **3a** and 1-naphthyl pyrrolidine **3b** it was necessary to use allylation procedure A, as procedure B provided poor d.r. and low yield with those substrates. 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **11** was prepared according to a literature procedure.[5] A representative procedure is described for the synthesis of optimal catalyst **3a** and for allylation procedure B en route to catalyst **3c.** This route and the characterization data for catalysts **3a**-**3d** collected for this publication were previously reported by our lab.[6]



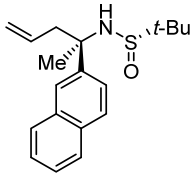
Allylation procedure A (used for catalysts 3a and 3b):



12

(S)-2-methyl-N-((R)-2-(phenanthren-9-yl)pent-4-en-2-yl)propane-2-sulfinamide (12): To 9-phenanthryl methylketone (7.82 g, 35.5 mmol, 1 equiv.) was added *(S)*-*t*-butyl sulfinamide (4.73 g, 39.1 mmol, 1.1 equiv.) and THF (35 mL, 1 M). Then $Ti(OEt)_4$ (16.4 mL, 78 mmol, 2.2 equiv.) was added and the solution was heated to reflux. After 48 hours, the solution was cooled to room temperature and was then diluted with EtOAc and quenched by the addition of saturated aqueous Na_2SO_4 (8.2 mL). The resulting slurry was stirred for 10 minutes. $MgSO_4$ was added and the slurry was stirred for an additional 10 minutes, after which it was filtered through a plug of celite in a Buchner funnel. The filter cake was rinsed 2x with EtOAc and the filtrate was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and carried forward crude assuming quantitative yield. In a separate flask, a solution of allylmagnesium chloride (14.7 mL of a 2.0 M solution in THF, 2.45 equiv.) was added to THF (50 mL, 0.25 M). The crude ketimine was then added over 5 minutes as a solution in THF (35.5 mmol in 20 mL of THF, 1 equiv.). The reaction was stirred at room temperature for 2 hours after which it was quenched by the addition of water and diluted with Et_2O. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash column chromatography to yield **12** (7.47 g, 20.43 mmol, 58% yield over two steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.85 (dd, J = 8.4, 1.4 Hz, 1H), 8.76 (dd, J = 8.3, 1.5 Hz, 1H), 8.64 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H), 7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.68 – 7.53 (m, 4H), 5.60 (ddt, J = 17.2, 10.0, 7.4 Hz, 1H), 5.15 (dq, J = 17.1, 1.5 Hz, 1H), 5.08 (dd, J = 10.2, 2.1 Hz, 1H), 3.90 (s, 1H), 3.09 (d, J = 7.4 Hz, 2H), 2.14 (s, 3H), 1.16 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.7, 133.1, 131.7, 130.9, 130.4, 129.7, 129.3, 128.6, 128.2, 127.2, 126.8, 125.9, 125.4, 123.4, 122.2, 119.8, 62.0, 56.1, 47.0, 30.5, 23.0 ppm; **FT-IR** (thin-film): 3220, 3075, 2977, 2961, 2867, 1494, 1472, 1450, 1386, 1365, 1145, 1054, 994, 909, 895, 854, 835, 794, 767, 748, 730, 617 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{23}H_{28}NOS$ $[M+H]^+$ 366.1886, found 366.1884; $[\alpha]_D$ = 75.6° (c = 1.0, $CHCl_3$).

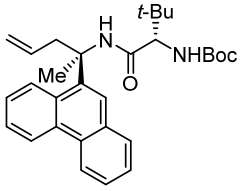
Allylation procedure B (used for catalysts 3c-3g):



13

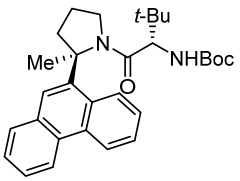
(S)-2-methyl-N-((R)-2-(naphthalen-2-yl)pent-4-en-2-yl)propane-2-sulfinamide (13): Homoallyl sulfinamide **13** was prepared using a procedure based on a previous literature report.[4] To 2-acetonaphthone (1.70 g, 10 mmol, 1 equiv.) was added *(S)*-*t*-butyl sulfinamide (1.33 g, 11 mmol, 1.1 equiv.) and THF (10 mL, 1 M). Then $Ti(OEt)_4$ (4.6 mL, 22 mmol, 2.2 equiv.) was added and the solution was heated to reflux. After 24 hours, the solution was cooled to room temperature, diluted with EtOAc and quenched by the addition of saturated aqueous Na_2SO_4. The resulting slurry was stirred for 15 minutes after which $MgSO_4$ was added and the solution was stirred for an additional 5 minutes. The slurry was then filtered through a plug of celite in a Buchner funnel. The filter cake was rinsed 2x with EtOAc and the filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Then zinc powder (719 mg, 11 mmol, 1.1 equiv.) was added to the crude ketimine and the solids were placed under an atmosphere of nitrogen. The solids were suspended in THF (20 mL, 0.5 M) and TMSCl (60 uL, 0.5 mmol, 0.05 equiv.) was added to activate the zinc metal. The suspension was stirred for 15 minutes, at which point the flask was placed in a room-temperature water bath and then allylbromide (0.95 mL, 11 mmol, 1.1 equiv.) was added over 1 minute and the reaction was allowed to continue overnight. The following day the reaction was diluted with EtOAc and quenched by the addition of saturated aqueous $NaHCO_3$. The resulting biphasic solution was stirred until the two layers cleanly separated and a white precipitate was visible (about 3 hours) and then the organic layer was removed. The aqueous layer was extracted 2x with EtOAc and then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. NMR analysis of the crude reaction mixture revealed a 95 : 5 diastereomer ratio, which was purified by flash column chromatography to yield major diastereomer **13** (2.06 g, 6.53 mmol, 65% yield over the two steps). The spectral data were consistent with a previous literature repot of the enantiomeric compound.[4] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.0 Hz, 1H), 7.85 – 7.80 (m, 3H), 7.57 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.52 – 7.45 (m, 2H), 5.59 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.20 (ddt, *J* = 17.0, 2.3, 1.3 Hz, 1H), 5.13 (dd, *J* = 10.1, 2.1 Hz, 1H), 3.81 (s, 1H), 2.76 (d, *J* = 7.4 Hz, 2H), 1.89 (s, 3H), 1.24 (s, 9H) ppm; $[\alpha]_D = 70.8^o$ (c = 1.0, $CHCl_3$).

Representative procedure for the synthesis of catalyst 3a:



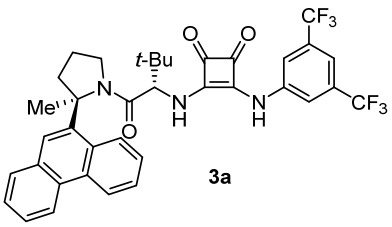
14

tert-butyl ((S)-3,3-dimethyl-1-oxo-1-(((R)-2-(phenanthren-9-yl)pent-4-en-2-yl)amino)butan-2-yl)carbamate (14): Sulfinamide **12** (7.47 g, 20.43 mmol, 1 equiv.) was dissolved in MeOH (20.4 mL, 1 M) and cooled to 0 °C. Then HCl (10.2 mL of a 4 M solution in dioxane, 2 equiv.) was added, after which the reaction was allowed to warm to room temperature. After 60 minutes, TLC indicated complete consumption of the starting material, so the reaction was sparged with nitrogen for 30 minutes to remove the HCl and then concentrated under vacuum. The solids were dissolved in water and Et_2O, the organic layer was removed, and the aqueous layer was washed 3x with Et_2O. Then 2 M aqueous NaOH was added to the aqueous layer until it reached a pH of 14, and the basic aqueous layer was extracted 5x with CH_2Cl_2. The combined CH_2Cl_2 extractions were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and carried forward crude assuming quantitative yield. The crude amine was dissolved in CH_2Cl_2 (41 mL, 0.5 M) and the solution was cooled to 0 °C. To this was added sequentially *i*-Pr_2NEt (5.2 mL, 30.6 mmol, 1.5 equiv.), *N*-Boc-*L*-*tert*-Leucine (5.20 g, 22.47 mmol, 1.1 equiv.), and HATU (8.55 g, 22.47 mmol, 1.1 equiv.). After 15 minutes the ice bath was removed, and the reaction was allowed to continue at room temperature. After 36 hours the reaction was diluted with Et_2O and quenched by the addition of water. The aqueous layer was removed, and the organic layer was washed 2x with 1 M aqueous HCl and then 2x with sat. aq. $NaHCO_3$. The organic layer was then washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash column chromatography to yield **14** (9.35 g, 19.70 mmol, 96% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.53 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.82 (s, 1H), 7.64 – 7.51 (m, 4H), 6.29 (s, 1H), 5.67 (dtd, *J* = 15.9, 9.3, 5.8 Hz, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H), 5.00 (d, *J* = 9.7 Hz, 1H), 3.82 (d, *J* = 9.6 Hz, 1H), 3.25 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.95 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.06 (s, 3H), 1.39 (s, 9H), 0.98 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.9, 156.0, 137.5, 133.3, 131.8, 131.3, 130.3, 129.5, 129.3, 126.9, 126.8, 126.1, 126.03, 125.98, 125.87, 124.0, 122.4, 120.1, 79.7, 62.8, 59.1, 45.1, 34.7, 28.5, 26.7, 26.0 ppm; **FT-IR** (thin-film): 3404, 3329, 3074, 2974, 2871, 1701, 1675, 1495, 1455, 1391, 1366, 1317, 1248, 1169, 1059, 1006, 912, 865, 766, 746, 728 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{30}H_{39}N_2O_3$ $[M+H]^+$ 475.2955, found 475.2953; $[\alpha]_D = -70.0^o$ (c = 1.0, $CHCl_3$).



15

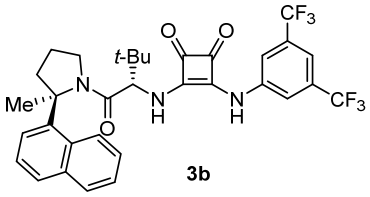
tert-butyl ((S)-3,3-dimethyl-1-((R)-2-methyl-2-(phenanthren-9-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)carbamate (15): A suspension of Schwartz's reagent was generated using a procedure based on a previous literature report.[7] Zirconocene dichloride (17.9 g, 61.2 mmol, 4.2 equiv.) was suspended in 1,4-dioxane (300 mL) under an atmosphere of nitrogen. A solution of Red-Al (10.3 mL of a >60 wt% solution in toluene, 30.6 mmol, 2.1 equiv.) was added dropwise, and the resulting suspension was allowed to continue stirring at room temperature. After 2 hours, the suspension was cooled to 0 °C and then homoallyl amide **14** was added dropwise as a solution in CH_2Cl_2 (6.93 g in 10 mL OF CH_2Cl_2, 14.6 mmol, 1 equiv.) The ice-bath was removed upon completion of the addition, and the reaction was allowed to continue at room temperature overnight. The following morning, the reaction was cooled to 0 °C and I_2 (15.2 g, 59.9 mmol, 4.1 equiv.) and Et_3N (10.2 mL, 73.2 mmol, 5 equiv.) were added simultaneously. The ice-bath was removed upon completion of the addition, and the reaction was allowed to continue at room temperature for 3 hours. The reaction was then transferred to a large flask using additional CH_2Cl_2 to ensure transfer of all solids and concentrated under vacuum onto a sufficient quantity of silica gel to form a fine tan powder. The impregnated silica was added to the top of a silica plug and eluted using a large volume of Et_2O. The filtrate was then washed with saturated aqueous $Na_2S_2O_3$ and the organic layer was removed. The aqueous layer was extracted 2x with Et_2O and then the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum and purified by flash column chromatography to yield **15** (3.76 g, 7.92 mmol, 54% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.61 (d, *J* = 8.3 Hz, 1H), 8.08 (br s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.65 (m, 1H), 7.62 – 7.48 (m, 4H), 5.40 – 4.73 (m, 1H), 4.44 (d, *J* = 10.0 Hz, 1H), 4.33 (q, *J* = 8.6 Hz, 1H), 4.07 (br s, 1H), 2.79 (dt, *J* = 16.5, 8.1 Hz, 1H), 2.36 – 1.91 (m, 6H), 1.46 (s, 9H), 1.03 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) two of the aryl carbon peaks and one of the alkyl carbon peaks could not be located and are believed to be under other peaks δ 169.8, 155.8, 137.6 (br), 131.7, 131.4, 130.1, 129.1, 126.45, 126.42, 126.0, 125.4, 125.1, 123.9, 122.2, 79.3, 68.0, 58.3, 48.9, 40.4, 35.4, 28.5, 26.4, 23.2 ppm; **FT-IR** (thin-film): 3440, 2973, 2870, 1710, 1647, 1494, 1452, 1412, 1392, 1366, 1328, 1303, 1232, 1167, 1060, 1006, 907, 765, 747, 727 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{30}H_{39}N_2O_3$ $[M+H]^+$ 475.2955, found 475.2955; $[\alpha]_D = -49.6°$ (c = 1.0, $CHCl_3$).



3a

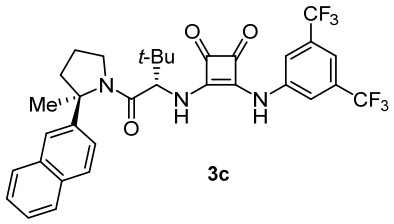
3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((S)-3,3-dimethyl-1-((R)-2-methyl-2-(phenanthren-9-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)amino)cyclobut-3-ene-1,2-dione (3a): Following a previously reported procedure,[8] Boc-protected amine **15** (400 mg, 0.84 mmol, 1 equiv.) was cooled to 0 °C and then HCl (4 mL of a 4 M solution in dioxane, 19 equiv.) was added dropwise over 2 minutes. The ice-bath was removed, and the reaction was allowed to continue for 1.5 hours, at which point TLC indicated complete consumption of the starting material. The reaction was then sparged with nitrogen to remove HCl and then concentrated under vacuum. The solids were suspended in CH_2Cl_2 (6.8 mL, 0.125 M) and Et_3N was added (0.35 mL, 2.53 mmol, 3 equiv.) to freebase the ammonium salt. After 15 minutes, squaric ester **11** (286 mg, 0.84 mmol, 1 equiv.) was added, and the reaction was allowed to continue for 48 hours. Then an aqueous solution of NaOH (6.8 mL, 1 M) was added and the biphasic solution was stirred vigorously for 12 hours. The reaction as then diluted with CH_2Cl_2 and water, and the organic layer was removed. The aqueous layer was extracted 3x with CH_2Cl_2 and then the combined organic layers were washed with a 1:1 mixture of water and brine, dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography to yield squaramide **3a** (400 mg, 0.59 mmol, 70% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.76 (d, *J* = 8.2 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 2H), 7.97 – 7.72 (m, 4H), 7.70 (s, 1H), 7.61 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.55 (s, 1H), 7.42 – 7.18 (m, 2H), 5.00 – 4.83 (m, 1H), 4.30 (q, *J* = 9.3 Hz, 1H), 4.16 – 4.03 (m, 1H), 2.57 (q, *J* = 10.9 Hz, 1H), 2.46 – 2.12 (m, 2H), 2.10 – 1.93 (m, 4H), 0.99 (s, 9H) ppm; **^{13}C NMR** (126 MHz, DMSO-d_6) one of the aryl carbon peaks could not be located and is believed to be under another peak, one of the alkyl carbon peaks could not be located and is believed to be under the DMSO solvent residual (compare to the peak at 40.4 in 1-naphthyl catalyst **3b**) δ 184.7, 180.6, 168.9, 167.2, 162.9, 141.0, 138.2, 131.5 (q, *J* = 33.0 Hz), 131.0, 130.9, 129.3, 128.7, 128.6, 126.7, 126.6, 125.23, 125.16, 124.4, 123.8, 123.1 (q, *J* = 273.5 Hz), 122.3, 117.7 (d, *J* = 4.1 Hz), 115.2 – 114.3 (m), 67.3, 61.2, 48.1, 35.1, 25.7, 25.0, 23.0 ppm; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.82 ppm; **FT-IR** (thin-film): 3226, 3057, 2967, 1792, 1695, 1631, 1608, 1582, 1558, 1473, 1418, 1378, 1277, 1179, 1133, 907, 883, 726, 680 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{37}H_{34}F_6N_3O_3$ $[M+H]^+$ 682.2499, found 682.2493; $[\alpha]_D = -127.2°$ (c = 1.0, $CHCl_3$).

Characterization of sub-optimal catalysts:



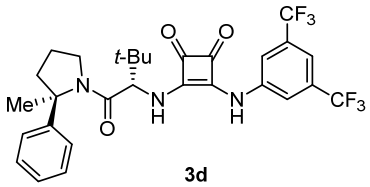
3b

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((S)-3,3-dimethyl-1-((R)-2-methyl-2-(naphthalen-1-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)amino)cyclobut-3-ene-1,2-dione (3b): Prepared according to the route described above from commercially available 1-acetonaphthone using procedure A for the allylation. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 7.99 (s, 2H), 7.90 – 7.76 (m, 3H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.66 (s, 1H), 7.56 – 7.47 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.12 (m, 2H), 4.92 (d, *J* = 10.1 Hz, 1H), 4.24 (q, *J* = 9.1 Hz, 1H), 4.11 – 4.03 (m, 1H), 2.50 – 2.42 (m, 1H), 2.32 – 2.21 (m, 1H), 2.16 – 2.04 (m, 1H), 2.01 – 1.91 (s, 4H), 0.99 (s, 9H) ppm; **^{13}C NMR** (126 MHz, DMSO-d_6) one of the aryl carbon peaks could not be located and is believed to be under another peak δ 184.6, 180.5, 168.9, 167.0, 162.9, 141.0, 140.3, 134.4, 131.5 (q, *J* = 33.0 Hz), 129.4, 129.0, 127.5, 125.0, 124.4, 124.3, 123.7, 123.1 (q, *J* = 272.8 Hz), 117.7 (d, *J* = 4.1 Hz), 115.2 – 114.4 (m), 67.3, 61.2, 48.1, 40.4, 35.2, 25.7, 24.8, 23.0 ppm; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.93 ppm; **FT-IR** (thin-film): 3219, 2054, 2967, 1793, 1697, 1631, 1608, 1583, 1560, 1475, 1420, 1379, 1278, 1181, 1135, 929, 909, 882, 797, 777, 732, 702, 680 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{33}H_{32}F_6N_3O_3$ $[M+H]^+$ 632.2342, found 632.2335; $[\alpha]_D = -107^o$ (c = 1.0, $CHCl_3$).



3c

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((S)-3,3-dimethyl-1-((R)-2-methyl-2-(naphthalen-2-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)amino)cyclobut-3-ene-1,2-dione (3c): Prepared according to the route described above from commercially available 2-acetonaphthone using procedure B for the allylation. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.20 (d, *J* = 10.0 Hz, 1H), 8.08 (s, 2H), 7.82 – 7.71 (m, 3H), 7.71 – 7.57 (m, 2H), 7.44 – 7.33 (m, 2H), 7.30 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 5.07 (d, *J* = 9.9 Hz, 1H), 4.15 (ddd, *J* = 9.9, 7.5, 5.1 Hz, 1H), 3.89 (dt, *J* = 9.9, 7.2 Hz, 1H), 2.09 (ddd, *J* = 12.5, 8.5, 6.4 Hz, 1H), 2.03 (dt, *J* = 12.3, 6.0 Hz, 1H), 2.00 – 1.91 (m, 4H), 1.83 (tdd, *J* = 14.1, 11.7, 5.5 Hz, 1H), 1.03 (s, 9H) ppm; **^{13}C NMR** (126 MHz, DMSO-d_6) δ 184.6, 180.6, 169.3, 167.5, 162.7, 143.7, 141.2, 132.7, 131.5, 131.4 (q, *J* = 33.0 Hz), 127.8, 127.5, 127.1, 125.6, 125.3, 123.8, 123.2 (q, *J* = 272.8 Hz), 123.1, 117.9 (d, *J* = 4.7 Hz), 115.0 – 114.1 (m), 67.0, 61.5, 49.7, 43.7, 35.8, 25.8, 24.2, 22.3 ppm; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.95 ppm; **FT-IR** (thin-film): 3213, 3058, 2968, 1792, 1696, 128, 1607, 1581, 1557, 1473, 1420, 1377, 1276, 1178, 1131, 928, 908, 883, 815, 731, 702, 680 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{33}H_{32}F_6N_3O_3$ $[M+H]^+$ 632.2342, found 632.2344; $[\alpha]_D = 49.8^o$ (c = 1.0, $CHCl_3$).



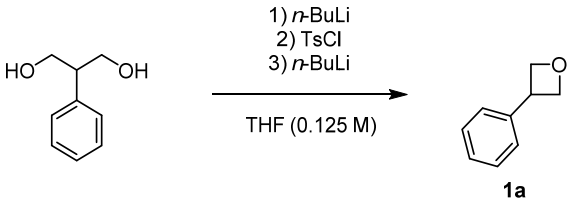
3d

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((S)-3,3-dimethyl-1-((R)-2-methyl-2-phenylpyrrolidin-1-yl)-1-oxobutan-2-yl)amino)cyclobut-3-ene-1,2-dione (3d): Prepared according to the route described above from commercially available acetophenone using procedure B for the allylation. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.25 (d, *J* = 10.0 Hz, 1H), 8.08 (s, 2H), 7.63 (s, 1H), 7.22 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.20 – 7.16 (m, 2H), 7.13 – 7.09 (m, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 4.03 (ddd, *J* = 9.5, 7.5, 4.0 Hz, 1H), 3.82 (ddd, *J* = 9.9, 8.3, 6.8 Hz, 1H), 2.04 (ddd, *J* = 12.0, 9.8, 6.1 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.84 (s, 3H), 1.76 – 1.66 (m, 1H), 1.02 (s, 9H) ppm; **^{13}C NMR** (126 MHz, DMSO-d_6) δ 184.5, 180.4, 169.1, 167.4, 162.5, 146.0, 141.1, 131.4 (q, *J* = 33.0 Hz), 127.8, 125.7, 124.8, 123.2 (q, *J* = 272.9 Hz), 117.9 (d, *J* = 4.0 Hz), 114.7, 67.0, 61.4, 49.6, 44.0, 36.0, 25.7, 24.6, 22.0 ppm; **^{19}F NMR** (376 MHz, DMSO-d_6) δ -61.87 ppm; **FT-IR** (thin-film): 3226, 3060, 2970, 1794, 1697, 1630, 1602, 1584, 1557, 1476, 1422, 1379, 1277, 1180, 1134, 929, 882, 761, 733, 699, 681 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{29}H_{30}F_6N_3O_3$ $[M+H]^+$ 582.2186, found 582.2185; $[\alpha]_D = 6.2^o$ (c = 1.0, $CHCl_3$).

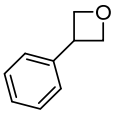
Synthesis and Characterization of Substrates

Synthesis of 3-substituted oxetanes from 2-substiuted 1,3-propane diols:

Known oxetanes **1a**[9] and **1p**[10] and novel oxetanes $^{13}C_2$-**1a**, **1n**, **1o**, and **1u** were prepared from the corresponding propane-1,3-diol derivatives according to a literature procedure.[11]

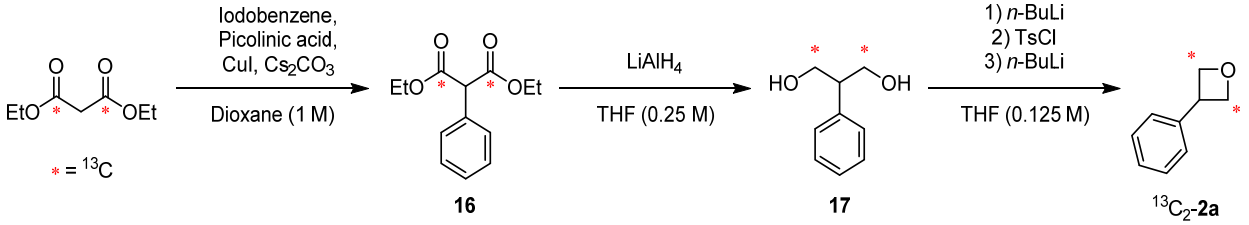


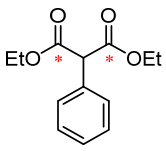
1a



1a

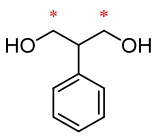
3-phenyloxetane (1a): 2-phenylpropane-1,3-diol (3.5 g, 23 mmol, 1 equiv.) was dissolved in THF (180 mL, 0.125 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (9.2 mL of a 2.5 M solution, 23 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 15 minutes before *p*-toluenesulfonyl chloride (4.38 g, 23 mmol, 1 equiv.) was added in 3 portions. The reaction was allowed to continue at 0 °C, gradually turning clear. After 1 hour, a solution of *n*-BuLi in hexanes (9.2 mL of a 2.5 M solution, 23 mmol, 1 equiv.) was added over 1.5 minutes, and the reaction was then warmed to 50 °C and allowed to continue overnight. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1a** (1.78 g, 13.27 mmol, 58% yield). The spectral data were consistent with a previous literature report[9]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43-7.35 (m, 4H), 7.28 (td, *J* = 7.2, 1.5 Hz, 1H), 5.08 (dd, *J* = 8.3, 6.1 Hz, 2H), 4.79 (t, *J* = 6.4 Hz, 2H), 4.27-4.21 (m, 1H) ppm.





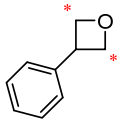
16

diethyl 2-phenylmalonate-(1,3-$^{13}C_2$) (16): Based on a previously-reported literature procedure,[12] copper(I) iodide (119 mg, 0.624 mmol, 0.1 equiv.), picolinic acid (154 mg, 1.249 mmol, 0.2 equiv.), and Cs_2CO_3 (6.10 g, 18.73 mmol, 3 equiv.) were placed under an atmosphere of nitrogen and then suspended in dioxane (6.24 mL, 1 M). The suspension was sparged with nitrogen for 10 minutes and then iodobenzene (1.75 mL, 15.61 mmol, 2.5 equiv.) was added followed immediately by diethyl malonate-(1,3-$^{13}C_2$) (1.0 g, 6.24 mmol, 1 equiv.). The reaction was then heated to 50 °C and stirred vigorously. After 15 hours, the reaction was allowed to cool to room temperature, diluted with Et_2O, and quenched with saturated aqueous NH_4Cl. The organic layer was removed, and then the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography to yield diester **16** (1.373 g, 5.81 mmol, 93% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.38 – 7.31 (m, 3H), 4.61 (t, *J* = 8.4 Hz, 1H), 4.22 (dddq, *J* = 14.1, 10.7, 7.0, 3.5 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H) ppm.



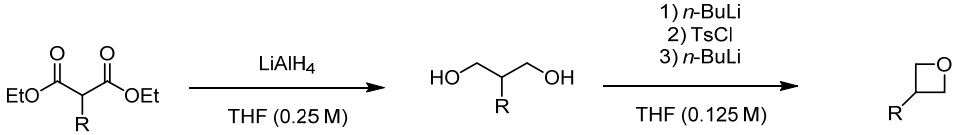
17

2-phenylpropane-1,3-diol-(1,3-$^{13}C_2$) (17): $LiAlH_4$ (654 mg, 17.2 mmol, 3 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (27.7 mL, 0.20 M). Then a solution of diethyl 2-phenylmalonate-(1,3-$^{13}C_2$) (**16**) in THF (1.37 g, 5.75 mmol, 1 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice-bath melted. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 650 uL of water, 650 uL of a 15% aqueous NaOH solution, and 1.96 mL of water. The slurry was filtered through celite and washed with warm ethyl acetate as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield diol **17** (0.662 g, 4.29 mmol, 75% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.29 – 7.27 (m, 1H), 7.25 – 7.22 (m, 2H), 4.02 (ddddd, *J* = 138, 10.9, 7.7, 5.7, 3.9 Hz, 2H), 3.96 (ddq, *J* = 143.9, 10.8, 5.4 Hz, 2H), 3.12 (tt, *J* = 7.6, 5.5 Hz, 1H), 2.00 (td, *J* = 5.7, 2.9 Hz, 2H) ppm.

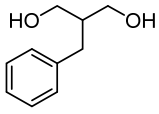


$^{13}C_2$-**1a**

3-phenyloxetane-(2,4-$^{13}C_2$) ($^{13}C_2$-1a): 2-phenylpropane-1,3-diol-(1,3-$^{13}C_2$) (**17**) (0.662 g, 4.29 mmol, 1 equiv.) was dissolved in THF (30 mL, 0.14 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (1.71 mL of a 2.5 M solution, 4.28 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 30 minutes before a solution of *p*-toluenesulfonyl chloride in THF (0.819 g in 5 mL of THF, 4.29 mmol, 1 equiv.) was added. The reaction was allowed to continue at 0 °C for 1 hour, at which point a solution of *n*-BuLi in hexanes (1.71 mL of a 2.5 M solution, 4.28 mmol, 1 equiv.) was added dropwise. The reaction was then warmed to 60 °C and allowed to continue for 12 hours. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane $^{13}C_2$-**1a** (272 mg, 2.00 mmol, 46% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 4H), 7.30 – 7.25 (m, 1H), 5.26 – 5.19 (m, 1H), 4.97 – 4.90 (m, 2H), 4.67 – 4.61 (m, 1H), 4.24 (dddd, *J* = 15.3, 8.6, 4.2, 2.4 Hz, 1H) ppm; **HRMS** (FTMS + p EI) calculated for $C_7{}^{13}C_2H_{10}O\bullet$ $[M\bullet]^+$ 136.0793, found 136.0793.

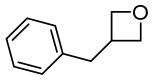


R = Bn, Cp



18

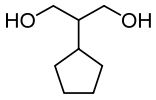
2-benzylpropane-1,3-diol (18): $LiAlH_4$ (854 mg, 22.5 mmol, 2.25 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (40 mL, 0.25 M). Then diethyl 2-benzylmalonate (2.35 mL, 10 mmol, 1 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice-bath melted. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 850 uL of water, 850 uL of a 15% aqueous NaOH solution, and 2.55 mL of water. The reaction was then allowed to warm to room temperature and continue stirring for 2 hours, at which point $MgSO_4$ was added. After an additional 10 minutes of stirring, the slurry was filtered through a pad of celite using a large volume of additional Et_2O as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield diol **18** (1.41 g, 8.49 mmol, 85% yield). The spectral data were consistent with a previous literature report[13]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 3.81 (dt, *J* = 10.2, 4.4 Hz, 2H), 3.68 (ddd, *J* = 11.3, 6.8, 4.9 Hz, 2H), 2.63 (d, *J* = 7.5 Hz, 2H), 2.23 – 2.10 (br, 2H), 2.07 (ddp, *J* = 11.1, 7.4, 3.5 Hz, 1H) ppm.



1p

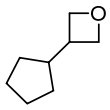
3-benzyloxetane (1p): 2-benzylpropane-1,3-diol (**18**) (1.411 g, 8.49 mmol, 1 equiv.) was dissolved in THF (68 mL, 0.125 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (3.4 mL of a 2.5 M solution, 8.49 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 15 minutes before *p*-toluenesulfonyl chloride (1.618 g, 8.49 mmol, 1 equiv.) was added in a single portion. The reaction was allowed to continue at 0 °C, gradually turning clear. After 1 hour, a solution of *n*-BuLi in hexanes (3.4 mL of a 2.5 M solution, 8.49 mmol, 1 equiv.) was added over 1.5 minutes, and the reaction was then warmed to 50 °C and allowed to continue overnight. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was

removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1p** (628 mg, 4.24 mmol, 50% yield). The spectral data were consistent with a previous literature report[10]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.23-7.19 (m, 1H), 7.14-7.11 (m, 2H), 4.79 (dd, *J* = 7.7, 6.0 Hz, 2H), 4.48 (t, *J* = 6.1 Hz, 2H), 3.31 (pt, *J* = 7.8, 6.2 Hz, 1H), 3.02 (d, *J* = 8.0 Hz, 2H) ppm.

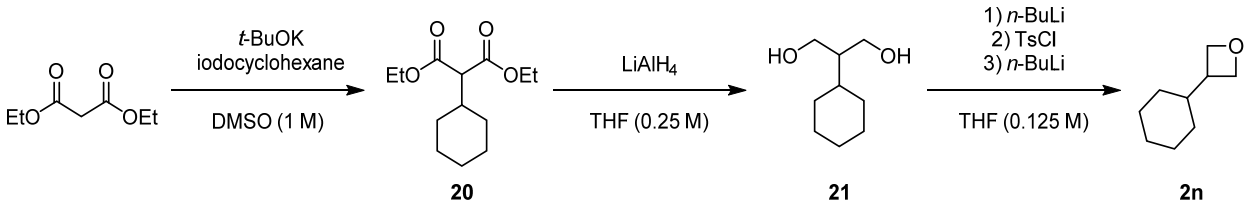


19

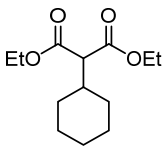
2-cyclopentylpropane-1,3-diol (19): $LiAlH_4$ (3.74 g, 98.56 mmol, 2.25 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (75 mL, 0.25 M). Then diethyl 2-cyclopentylmalonate (10.0 g, 43.80 mmol, 1 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice-bath melted. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 3.7 mL of water, 3.7 mL of a 15% aqueous NaOH solution, and 11.2 mL of water. The reaction was then allowed to warm to room temperature and continue stirring for 2 hours, at which point $MgSO_4$ was added. After an additional 10 minutes of stirring, the slurry was filtered through a pad of celite using a large volume of additional Et_2O as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield diol **19** (3.31 g, 22.95 mmol, 52% yield). The spectral data were consistent with a previous literature report[14]: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.92 (dd, J = 10.6, 3.2 Hz, 2H), 3.73 (dd, J = 10.6, 7.6 Hz, 2H), 2.23 (s, 2H), 1.85 – 1.75 (m, 2H), 1.74 – 1.43 (m, 6H), 1.16 (p, J = 8.8 Hz, 2H) ppm.


1o

3-cyclopentyloxetane (1o): 2-cyclopentylpropane-1,3-diol (**19**) (0.851 g, 5.90 mmol, 1 equiv.) was dissolved in THF (47 mL, 0.125 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (2.36 mL of a 2.5 M solution, 5.90 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 15 minutes before *p*-toluenesulfonyl chloride (1.18 g, 5.90 mmol, 1 equiv.) was added in a single portion. The reaction was allowed to continue at 0 °C, gradually turning clear. After 1 hour, a solution of *n*-BuLi in hexanes (2.36 ml of a 2.5 M solution, 5.90 mmol, 1 equiv.) was added over 1.5 minutes, and the reaction was then warmed to 50 °C and allowed to continue overnight. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1o** (314 mg, 2.49 mmol, 42% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 7.9, 5.9 Hz, 2H), 4.41 (t, *J* = 6.1 Hz, 2H), 2.84 (dtt, *J* = 9.6, 7.9, 6.3 Hz, 1H), 2.24 (dp, *J* = 9.6, 7.8 Hz, 1H), 1.80 – 1.66 (m, 2H), 1.66 – 1.47 (m, 4H), 1.11 – 1.01 (m, 2H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 77.0, 43.4, 40.2, 29.8, 25.4 ppm; **FT-IR** (thin-film): 2944, 2863, 1488, 1451, 1369, 1178, 1136, 1098, 978, 898, 834 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_8H_{15}O$ $[M+H]^+$ 127.1117, found 127.1119.

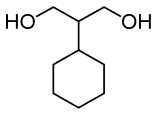


20 **21** **2n**


20

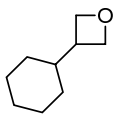
diethyl 2-cyclohexylmalonate (20): Following a literature procedure[15] potassium *tert*-butoxide (1.35 g, 12.00 mmol, 1.2 equiv.) was dissolved in DMSO (10 mL, 1 M). Then diethylmalonate (1.52 mL, 10 mmol, 1 equiv.) and iodocyclohexane (1.94 mL, 15 mmol, 1.5 equiv.) were added sequentially, and the reaction was heated to 80 °C and allowed to continue overnight under an atmosphere of nitrogen. The following day, the reaction was allowed to cool to room temperature and quenched by the addition of water (5 mL) and acetic acid (2 mL). The reaction was diluted with Et_2O, the organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were then washed 5x with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography, but it still contained I_2, so the product was dissolved in Et_2O and washed with saturated aqueous sodium thiosulfate. The organic layer was removed, and the aqueous layer was extracted 2x w/ Et_2O. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, concentrated, and re-purified by flash column chromatography to yield diester **20** (1.73 g, 7.14 mmol, 71% yield). The spectral data were

consistent with a previous literature report[15]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 4H), 3.13 (d, *J* = 9.1 Hz, 1H), 2.08 (dddd, *J* = 14.8, 11.8, 8.9, 3.2 Hz, 1H), 1.78 – 1.61 (m, 5H), 1.35 – 1.22 (m, 8H), 1.16 (tt, *J* = 12.9, 3.2 Hz, 1H), 1.05 (qd, *J* = 13.0, 12.0, 3.8 Hz, 2H) ppm.



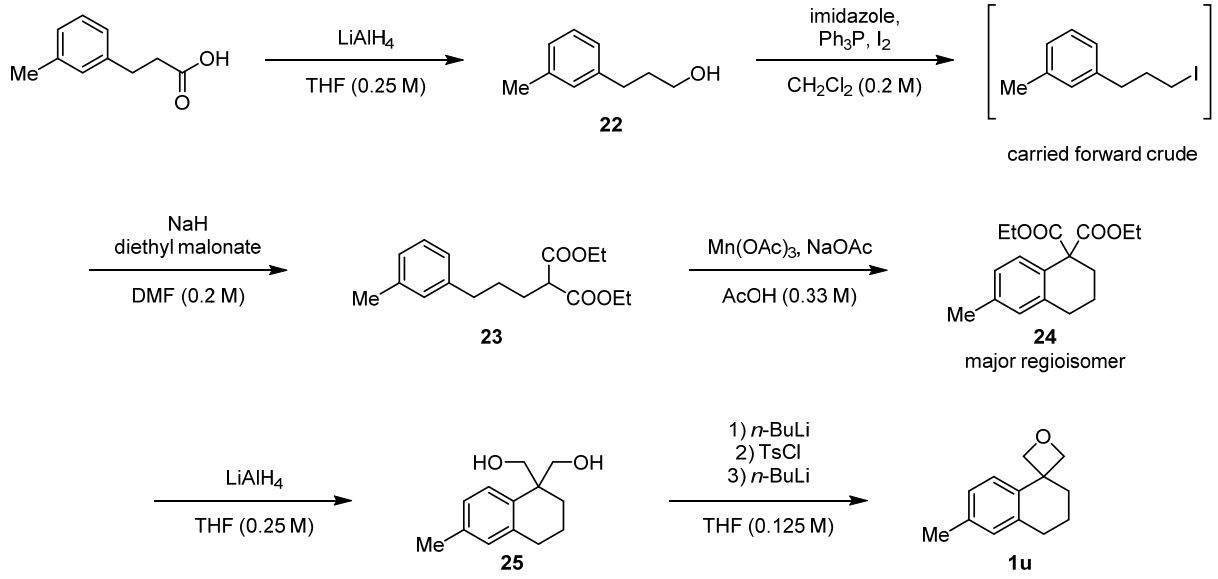
21

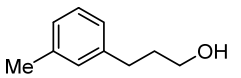
2-cyclohexylpropane-1,3-diol (21): $LiAlH_4$ (610 mg, 16.07 mmol, 2.25 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (18.6 mL). A solution of diethyl 2-cyclohexylmalonate (**20**) (1.73 g in 5 mL of THF, 7.14 mmol, 1 equiv.) was added dropwise using an additional 2x 2.5 mL of THF to aid transfer (giving a 0.25 M overall solution in THF), and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice-bath melted. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 610 uL of water, 610 uL of a 15% aqueous NaOH solution, and 1.83 mL of water. The reaction was then allowed to warm to room temperature and continue stirring for 2 hours, at which point $MgSO_4$ was added. After an additional 10 minutes of stirring, the slurry was filtered through a pad of celite using a large volume of additional Et_2O as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield diol **21** (1.00 g, 6.32 mmol, 88% yield). The spectral data were consistent with a previous literature report[13]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.87 (ddd, *J* = 10.6, 5.3, 3.7 Hz, 2H), 3.81 (ddd, *J* = 10.6, 7.6, 4.6 Hz, 2H), 2.17 (t, *J* = 5.0 Hz, 2H), 1.78 – 1.69 (m, 4H), 1.65 (dtt, *J* = 13.1, 3.4, 1.7 Hz, 1H), 1.60 – 1.54 (m, 1H), 1.42 (tdt, *J* = 12.0, 6.3, 3.1 Hz, 1H), 1.23 (qt, *J* = 13.8, 3.8 Hz, 2H), 1.13 (qt, *J* = 12.7, 3.2 Hz, 1H), 1.01 (qd, *J* = 12.7, 11.9, 3.8 Hz, 2H) ppm.



1n

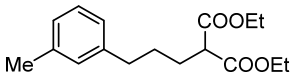
3-cyclohexyloxetane (1n): 2-cyclohexylpropane-1,3-diol (**21**) (1 g, 6.32 mmol, 1 equiv.) was dissolved in THF (50 mL, 0.125 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (2.53 mL of a 2.5 M solution, 6.32 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 15 minutes before *p*-toluenesulfonyl chloride (1.205 g, 6.32 mmol, 1 equiv.) was added in a single portion. The reaction was allowed to continue at 0 °C, gradually turning clear. After 1 hour, a solution of *n*-BuLi in hexanes (2.53 mL of a 2.5 M solution, 6.32 mmol, 1 equiv.) was added over 1.5 minutes, and the reaction was then warmed to 50 °C and allowed to continue overnight. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1n** (582 mg, 4.15 mmol, 66% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.72 (ddd, *J* = 8.0, 5.9, 1.2 Hz, 2H), 4.46 (ddd, *J* = 7.0, 6.0, 1.2 Hz, 2H), 2.80 – 2.61 (m, 1H), 1.79 – 1.55 (m, 6H), 1.31 – 1.19 (m, 2H), 1.19 – 1.09 (m, 1H), 0.86 – 0.71 (m, 2H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 76.6, 41.8, 41.1, 29.9, 26.4, 26.0 ppm; **FT-IR** (thin-film): 2922, 2852, 1719, 1449, 1270, 1178, 980, 885 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_9H_{17}O$ $[M+H]^+$ 141.1274, found 141.1275.





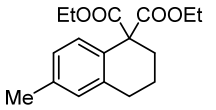
22

3-(m-tolyl)propan-1-ol (22): $LiAlH_4$ (1.16 g, 30.4 mmol, 2 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (30 mL). A solution of 3-(m-tolyl)propanoic acid (2.5 g in 30 mL THF, 15.2 mmol, 0.5 M, 1 equiv.) was added dropwise (giving a 0.25 M overall solution in THF). The reaction was allowed to proceed for 45 minutes, gradually warming as the ice-bath melted, before it was transferred to an oil-bath and refluxed overnight. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 1.16 mL of water, 1.16 mL of a 15% aqueous NaOH solution, and 3.48 mL of water. The reaction was then allowed to warm to room temperature and continue stirring for 2 hours, at which point $MgSO_4$ was added. After an additional 10 minutes of stirring, the slurry was filtered through a pad of celite using a large volume of additional Et_2O as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield alcohol **22** (2.26 g, 15.0 mmol, 99% yield). The spectral data were consistent with a previous literature report[16]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.5 Hz, 1H), 7.04-6.99 (m, 3H), 3.72-3.65 (m, 2H), 2.68 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.34 (s, 3H), 1.90 (dtd, *J* = 9.1, 7.5, 7.0, 5.9 Hz, 2H), 1.33-1.25 (br, 1H) ppm.



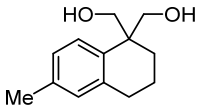
23

diethyl 2-(3-(m-tolyl)propyl)malonate (23): Alcohol **22** (2.21 g, 14.71 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (59 mL, 0.25 M) and cooled to 0 °C. Imidazole (1.40 g, 20.60 mmol, 1.4 equiv.), Ph_3P (5.02 g, 19.13 mmol, 1.3 equiv.), and I_2 (5.04 g, 19.86 mmol, 1.35 equiv.) were added sequentially and the reaction was allowed to proceed at 0 °C for 1.5 hours, at which point TLC indicated complete consumption of the starting alcohol. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ and diluted with Et_2O. The aqueous layer was removed, and the organic layer was washed 2x with saturated aqueous NH_4Cl, followed by brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was then suspended in hexanes and filtered through a 1-inch silica plug which was rinsed with additional hexanes. The filtrate from the plug was then concentrated under vacuum to yield the alkyl iodide (3.78 g, 14.53 mmol 99% yield), which was carried forward immediately without further purification. In a separate flask a dispersion of NaH (2.91 g of a 60 wt% dispersion, 72.6 mmol, 5.0 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in DMF (60 mL). Diethyl malonate (11.25 mL, 74.1 mmol, 5.1 equiv.) was added dropwise, and the reaction was allowed to warm to room temperature. After 1 hour the reaction was again cooled to 0 °C and a solution of the crude iodide (3.78 g in 12.6 mL of DMF, 14.53 mmol, 1 equiv.) was added dropwise (giving a 0.2 M overall solution in DMF), and the reaction was heated to 60 °C overnight. The following day, the reaction was allowed to cool to room temperature, diluted with Et_2O, and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was removed, and the organic layer was washed 5x with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by column chromatography to yield diester **23** (3.30 g, 11.29 mmol, 78% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 1H), 7.02 – 6.94 (m, 3H), 4.22 – 4.16 (m, 4H), 3.34 (td, *J* = 7.6, 1.2 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 1.99 – 1.90 (m, 2H), 1.69 – 1.60 (m, 2H), 1.26 (td, *J* = 7.1, 1.1 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5, 141.8, 138.0, 129.3, 128.4, 126.7, 125.5, 61.4, 52.0, 35.5, 29.2, 28.5, 21.5, 14.2 ppm; **FT-IR** (thin-film): 2981, 2936, 2863, 1748, 1729, 1609, 1462, 1446, 1368, 1335, 1297, 1237, 1208, 1776, 1142, 1096, 1025, 862, 782, 739, 670 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{17}H_{24}O_4$• $[M•]^+$ 292.1669, found 292.1669.



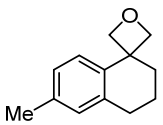
24

diethyl 6-methyl-3,4-dihydronaphthalene-1,1(2H)-dicarboxylate (24): Manganese(III) acetate dihydrate (7.45 g, 27.8 mmol, 2.5 equiv.) and NaOAc (2.28 g, 27.8 mmol, 2.5 equiv.) were added to a Schlenk flask and suspended in AcOH (28 mL). Then malonate **23** (3.25 g, 11.12 mmol, 1 equiv.) was added using an additional 5 mL of AcOH to aid transfer (giving a 0.33 M overall solution in AcOH). The reaction was then heated to 70 °C and allowed to continue overnight, with the solids gradually going into solution as the reaction proceeded. The following day, the reaction was cooled to room temperature and diluted with EtOAc and water. The aqueous layer was removed and the organic layer was washed sequentially with water, 2x with 1 M aqueous NaOH, saturated aqueous $Na_2S_2O_3$, and brine and then dried over Na_2SO_4, filtered, and concentrated under vacuum to give an ~4.4 : 1 mixture of the 6-methyl and 8-methyl regioisomeric products, which were separable by flash column chromatography to yield desired regioisomer **24** (1.97 g, 6.78 mmol, 61% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.92 (s, 1H), 4.29 – 4.15 (m, 4H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.46 – 2.35 (m, 2H), 2.30 (s, 3H), 1.83 (dtd, *J* = 11.7, 6.4, 3.4 Hz, 2H), 1.26 (td, *J* = 7.1, 1.8 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.9, 137.3, 137.0, 130.4, 130.0, 129.2, 126.7, 61.7, 58.8, 31.3, 29.4, 21.1, 20.0, 14.1 ppm; **FT-IR** (thin-film): 2979, 2939, 2872, 1725, 1504, 1445, 1389, 1365, 1286, 1241, 1188, 1152, 1130, 1084, 1045, 1026, 893, 857, 820, 768 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{17}H_{22}O_4$• $[M•]^+$ 290.1513, found 290.1513.



25

(6-methyl-1,2,3,4-tetrahydronaphthalene-1,1-diyl)dimethanol (25): $LiAlH_4$ (579 mg, 15.27 mmol, 2.25 equiv.) was cooled to 0 °C under an atmosphere of nitrogen and suspended in THF (17 mL). A solution of cyclic malonate **24** (1.97 g in 5 mL of THF, 6.78 mmol, 1 equiv.) was added dropwise using an additional 2x 2.5 mL of THF to aid transfer (giving a 0.25 M overall solution in THF), and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice-bath melted. The following day, the reaction was cooled to 0 °C, diluted with Et_2O, and worked up according to Fieser's protocol by the careful sequential addition of 580 uL of water, 580 uL of a 15% aqueous NaOH solution, and 1.74 mL of water. The reaction was then allowed to warm to room temperature and continue stirring for 2 hours, at which point $MgSO_4$ was added. After an additional 10 minutes of stirring, the slurry was filtered through a pad of celite using a large volume of additional Et_2O as a rinse. The filtrate was concentrated under vacuum and purified by flash column chromatography to yield diol **25** (1.16 g, 5.62 mmol, 83% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 1H), 6.99 (dtd, *J* = 8.1, 1.4, 0.7 Hz, 1H), 6.96 – 6.93 (m, 1H), 3.92 (dd, *J* = 11.0, 5.8 Hz, 2H), 3.80 – 3.71 (m, 2H), 2.74 (t, *J* = 6.3 Hz, 2H), 2.28 (d, *J* = 0.8 Hz, 3H), 1.98 – 1.90 (m, 4H), 1.88 – 1.76 (m, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7, 136.2, 134.5, 130.4, 127.0, 126.8, 70.1, 43.1, 30.6, 27.9, 21.0, 19.2 ppm; **FT-IR** (thin-film): 3334 (br), 3002, 2927, 2871, 1615, 1498, 1454, 1432, 1109, 1045, 1015, 987, 909, 853, 814, 729, 557 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{13}H_{18}O_2Na$ $[M+Na]^+$ 229.1199, found 229.1206.

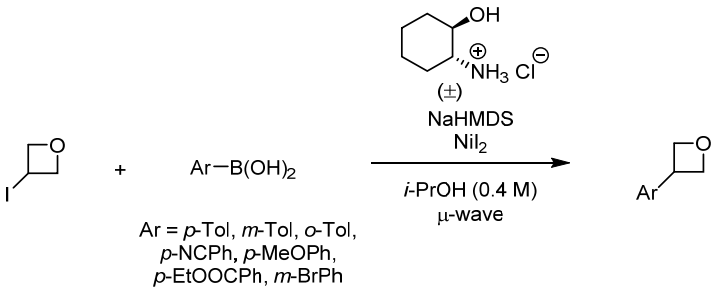


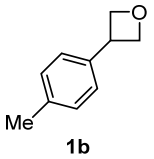
1u

6-methyl-3,4-dihydro-2H-spiro[naphthalene-1,3'-oxetane] (1u): Diol **25** (1.10 g, 5.33 mmol, 1 equiv.) was dissolved in THF (42.7 mL, 0.125 M) and cooled to 0 °C. A solution of *n*-BuLi in hexanes (2.13 mL of a 2.5 M solution, 5.33 mmol, 1 equiv.) was added dropwise, and the resulting suspension was stirred at 0 °C for 15 minutes before *p*-toluenesulfonyl chloride (1.02 g, 5.33 mmol, 1 equiv.) was added in a single portion. The reaction was allowed to continue at 0 °C, gradually turning clear. After 1 hour, a solution of *n*-BuLi in hexanes (2.13 ml of a 2.5 M solution, 5.33 mmol, 1 equiv.) was added over 1.5 minutes, and the reaction was then warmed to 50 °C and allowed to continue overnight. The following day, the reaction was cooled to room temperature, diluted with Et_2O and quenched by the addition of water. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1u** (425.3 mg, 2.259 mmol, 42% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.13 (dt, *J* = 8.0, 1.3 Hz, 1H), 6.90 (t, *J* = 1.4 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 2H), 4.63 (d, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 6.3 Hz, 2H), 2.32 (s, 3H), 2.22 – 2.15 (m, 2H), 1.76 – 1.69 (m, 2H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.8, 136.5, 136.3, 129.6, 127.7, 126.6, 85.8, 42.2, 35.8, 30.1, 21.0, 20.3 ppm; **FT-IR** (thin-film): 3001, 2923, 2861, 1614, 1501, 1487, 1446, 1432, 1275, 1154, 1043, 984, 951, 908, 891, 877, 816, 559 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{13}H_{16}O\bullet$ $[M\bullet]^+$ 188.1196, found 188.1194.

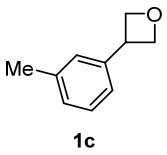
Synthesis of 3-aryl oxetanes via cross coupling with 3-iodooxetane:

Known oxetanes **1b**,[9] **1e**,[9] **1f**,[9] and **1h**[17] and novel oxetanes **1c** and **1d** were prepared from 3-iodooxetane using a previously reported Ni-catalyzed cross-coupling.[9] Known oxetane **1g**[18] was prepared using the Ni-catalyzed cross-coupling followed by treatment with NaOEt to correct for partial transesterification during the cross-coupling.

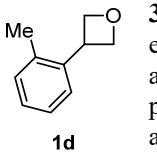




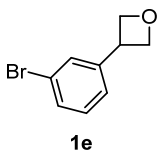
3-(*p*-tolyl)oxetane (1b): Following a literature procedure[9] *p*-tolylboronic acid (1.36 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1b** (565 mg, 3.81 mmol, 76% yield). The spectral data were consistent with a previous literature report[9]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.18 (dt, *J* = 7.7, 0.7 Hz, 2H), 5.06 (dd, *J* = 8.4, 6.0 Hz, 2H), 4.77 (dd, *J* = 6.9, 6.0 Hz, 2H), 4.20 (tt, *J* = 8.3, 6.9 Hz, 1H), 2.35 (s, 3H) ppm.



3-(*m*-tolyl)oxetane (1c): Following a literature procedure[9] *m*-tolylboronic acid (1.36 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1c** (482 mg, 3.25 mmol, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 1H), 7.24-7.21 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.11-7.07 (m, 1H), 5.07 (dd, *J* = 8.4, 5.9 Hz, 2H), 4.78 (dd, *J* = 6.8, 6.0 Hz, 2H), 4.20 (tt, *J* = 8.3, 6.8 Hz, 1H), 2.38 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.4, 138.3, 128.5, 127.7, 127.4, 123.7, 78.8, 40.2, 21.3 ppm; **FT-IR** (thin-film): 3024, 2961, 2871, 1608, 1590, 1491, 1460, 982, 930, 864, 783, 702, 443 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{10}H_{13}O$ $[M+H]^+$ 149.0961, found 149.0961.

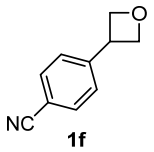


3-(*o*-tolyl)oxetane (1d): Following a literature procedure[9] *o*-tolylboronic acid (1.36 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1d** (467 mg, 3.15 mmol, 63% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.7 Hz, 1H), 7.28-7.24 (m, 1H), 7.20-7.14 (m, 2H), 5.04 (dd, *J* = 8.5, 5.8 Hz, 2H), 4.88 (dd, *J* = 7.6, 5.8 Hz, 2H), 4.52 (p, *J* = 8.0 Hz, 1H), 2.17 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.0, 135.6, 130.2, 126.8, 126.3, 125.4, 77.5, 37.5, 19.4 ppm; **FT-IR** (thin-film): 3021, 2946, 2870, 1491, 1460, 1014, 979, 913, 839, 753, 722, 580, 547, 456, 438 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{10}H_{13}O$ $[M+H]^+$ 149.0961, found 149.0962.



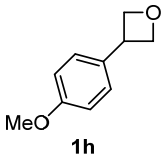
3-(3-bromophenyl)oxetane (1e): Following a literature procedure[9] *m*-bromophenylboronic acid (2.01 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1e** (201 mg, 0.94 mmol, 19% yield). The spectral data were consistent with a previous literature report[9]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (t, *J* = 1.8 Hz, 1H), 7.41 (ddd,

J = 7.9, 2.0, 1.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 5.07 (dd, *J* = 8.3, 6.1 Hz, 2H), 4.74 (t, *J* = 6.4 Hz, 2H), 4.19 (tt, *J* = 8.3, 6.6 Hz, 1H) ppm.



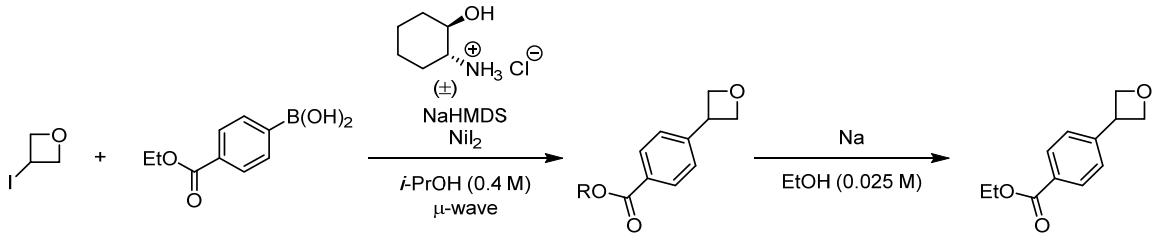
1f

4-(oxetan-3-yl)benzonitrile (1f): Following a literature procedure[9] *p*-cyanophenylboronic acid (1.47 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1f** (339 mg, 2.13 mmol, 43% yield). The spectral data were consistent with a previous literature report[9]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 2H), 7.53-7.50 (m, 2H), 5.11 (dd, *J* = 8.3, 6.2 Hz, 2H), 4.72 (t, *J* = 6.3 Hz, 2H), 4.26 (tt, *J* = 8.3, 6.4 Hz, 1H) ppm.



1h

3-(4-methoxyphenyl)oxetane (1h): Based on a literature procedure[9] *p*-methoxyphenylboronic acid (1.52 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield oxetane **1h** (548 mg, 3.34 mmol, 67% yield). The spectral data were consistent with a previous literature report[17]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 6.93-6.89 (m, 2H), 5.05 (dd, *J* = 8.4, 6.0 Hz, 2H), 4.75 (dd, *J* = 6.8, 6.0 Hz, 2H), 4.19 (ddd, *J* = 15.3, 8.4, 6.8 Hz, 1H), 3.81 (s, 3H) ppm.



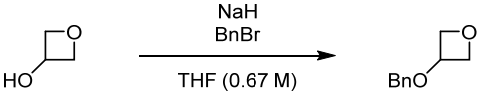
1g

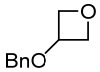
ethyl-4-(oxetan-3-yl)benzoate (1g): Based on a literature procedure[9] *p*-ethoxycarbonylphenylboronic acid (1.94 g, 10 mmol, 2 equiv.), NaHMDS (1.83 g, 10 mmol, 2 equiv.), NiI_2 (94 mg, 0.3 mmol, 0.06 equiv.), and *trans*-2-aminocyclohexanol hydrochloride (46 mg, 0.3 mmol, 0.06 equiv.) were added to a microwave vial and placed under an atmosphere of argon. The solids were suspended in argon-sparged *i*-PrOH (10 mL) and stirred under an atmosphere of argon for 10 minutes. A solution of 3-iodooxetane (0.92 g in 2.5 mL of *i*-PrOH, 5 mmol, 2 M, 1 equiv.) was added, and the vial was sealed under an atmosphere of argon. The reaction was then heated to 80 °C in a microwave reactor for 20 minutes, after which it was allowed to cool to room temperature, diluted with EtOH, and filtered through a plug of celite topped with a Kimwipe using additional EtOH as a rinse. The crude product was concentrated under vacuum and purified by flash column chromatography to yield an inseparable mixture of the desired ethyl and undesired isopropyl esters (740 mg of a ~3.3 : 1 mixture of ethyl and isopropyl esters). Sodium ethoxide was prepared in a separate flask by the gradual addition of sodium metal (116 mg, 5.04 mmol, 1.5 equiv.) to anhydrous ethanol (124 mL) being careful to avoid a significant exotherm. Once all the metal had dissolved, an ethanolic solution of the oxetanyl esters (740 mg of

mixed ester in 5 mL of ethanol, 3.36 mmol, 1 equiv.) was added using an additional 2x 2.5 mL ethanol rinse to aid transfer (giving a 0.025 M overall solution in ethanol) and the reaction was allowed to continue overnight under an atmosphere of nitrogen. The following day, it was quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was removed and the aqueous layer was extracted 3x w/ Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude oil containing a mixture of ethyl and isopropyl esters (~9.4 : 1 ethyl to isopropyl). Since conversion to the desired ethyl ester was incomplete, the material was resubmitted to identical transesterification conditions for 36 hours, worked up identically, and purified by flash column chromatography to yield oxetane **1g** (619 mg, 3.00 mmol, 60% yield over all steps). The spectral data were consistent with a previous literature report[18]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06-8.03 (m, 2H), 7.48-7.45 (m, 2H), 5.10 (dd, *J* = 8.3, 6.1 Hz, 2H), 4.77 (t, *J* = 6.3 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.28 (tt, *J* = 8.4, 6.6 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm.

Synthesis of benzyl protected oxetanols:

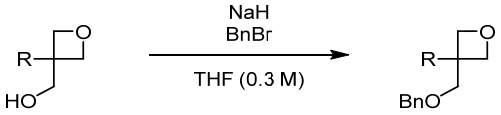
Known oxetanes **1j**[19], and **1v**[20] and novel oxetanes **1l** and **1s** were prepared by benzyl protection of the corresponding alcohols, which are commercially available. Novel oxetanes **1q**, **1r**, and **1t** were prepared by the addition of aryl Grignard reagents into 3-oxetanone followed by benzyl protection of the resulting alcohol.



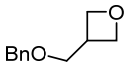


1j

3-(benzyloxy)oxetane (1j): A dispersion of NaH (600 mg of a 60 wt% dispersion, 15.0 mmol, 1.5 equiv.) was suspended in THF (15 mL, 0.67 M) at 0 °C and then oxetan-3-ol (0.64 mL, 10 mmol, 1 equiv.) was added dropwise. After 30 minutes, benzyl bromide (1.4 mL, 12.0 mmol, 1.2 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1j** (1.038 g, 6.32 mmol, 63% yield). The spectral data were consistent with a previous literature report[19]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.74-4.68 (m, 2H), 4.67-4.61 (m, 3H), 4.46 (s, 2H) ppm.

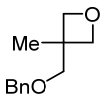


R = H, Me



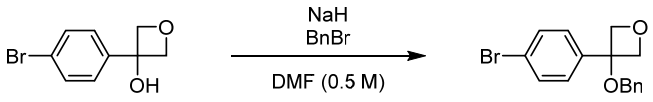
1l

3-((benzyloxy)methyl)oxetane (1l): A dispersion of NaH (300 mg of a 60 wt% dispersion, 7.5 mmol, 1.5 equiv.) was suspended in THF (16.7 mL, 0.3 M) at 0 °C and then oxetan-3-ylmethanol (441 mg, 5 mmol, 1 equiv.) was added dropwise. After 30 minutes, benzyl bromide (0.65 mL, 5.5 mmol, 1.1 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1l** (0.3795 g, 2.13 mmol, 43% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.32 – 7.28 (m, 1H), 4.80 (ddd, *J* = 7.8, 6.2, 0.6 Hz, 2H), 4.55 (s, 2H), 4.46 (t, *J* = 6.0 Hz, 2H), 3.71 (d, *J* = 6.9 Hz, 2H), 3.29 – 3.21 (m, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.2, 128.5, 127.82, 127.77, 74.7, 73.3, 71.8, 35.0 ppm; **FT-IR** (thin-film): 3030, 2961, 2869, 1496, 1454, 1369, 1206, 1091, 1028, 975, 859, 736, 697, 607 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{11}H_{15}O_2$ $[M+H]^+$ 179.1067, found 179.1067.

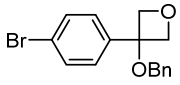


1v

3-((benzyloxy)methyl)-3-methyloxetane (1v): A dispersion of NaH (900 mg of a 60 wt% dispersion, 22.5 mmol, 1.5 equiv.) was suspended in THF (50 mL, 0.3 M) at 0 °C and then (3-methyloxetan-3-yl)methanol (1.53 g, 15 mmol, 1 equiv.) was added dropwise. After 30 minutes, benzyl bromide (2.0 mL, 16.5 mmol, 1.1 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1v** (2.28 g, 11.85 mmol, 79% yield). The spectral data were consistent with a previous literature report[20]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38-7.32 (m, 4H), 7.32-7.28 (m, 1H), 4.58 (s, 2H), 4.53 (d, *J* = 5.7 Hz, 2H), 4.36 (d, *J* = 5.7 Hz, 2H), 3.53 (s, 2H), 1.34 (s, 3H) ppm.

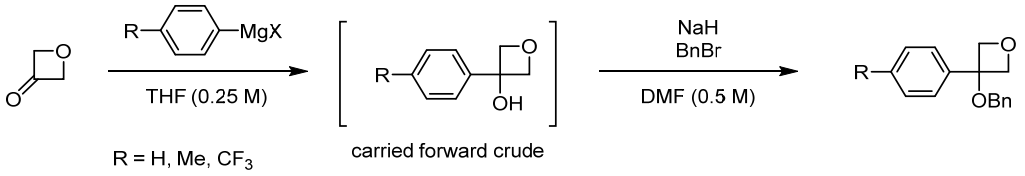


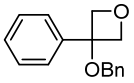
1s



1s

3-(benzyloxy)-3-(4-bromophenyl)oxetane (1s): A dispersion of NaH (65 mg of a 60 wt% dispersion, 1.64 mmol, 1.5 equiv.) was suspended in DMF (0.75 mL) at 0 °C, and a solution of 3-(*p*-bromophenyl)oxetan-3-ol (250 mg in 0.75 mL of DMF, 1.09 mmol, 1 equiv.) was added dropwise using an additional 2x 0.5 mL of DMF to aid transfer. After 30 minutes, benzyl bromide (0.26 mL, 2.18 mmol, 2 equiv.) was added dropwise, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was removed, and the organic layer was washed 5x with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1s** (340 mg, 1.07 mmol, 98% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 7.44 – 7.41 (m, 2H), 7.38 – 7.28 (m, 5H), 5.02 – 4.99 (m, 2H), 4.84 – 4.80 (m, 2H), 4.26 (s, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.2, 137.6, 132.1, 128.6, 127.9, 127.8, 127.6, 122.3, 81.1, 80.4, 66.6 ppm; **FT-IR** (thin-film): 3063, 3031, 2949, 2874, 1591, 1486, 1454, 1397, 1382, 1284, 1173, 1136, 1075, 1059, 1026, 1008, 983, 882, 822, 736, 696, 547 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{16}H_{14}BrO_2$ $[M-H]^+$ 317.0172, found 317.0168.

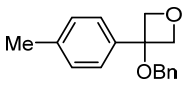




1q

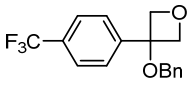
3-(benzyloxy)-3-phenyloxetane (1q): Oxetan-3-one (0.59 mL, 10 mmol, 1 equiv.) was dissolved in THF (40 mL, 0.25 M) and cooled to 0 °C. A solution of phenylmagnesium bromide (3.7 mL of 3 M solution in THF, 11 mmol, 1.1 equiv.) was added dropwise and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 3-phenyloxetan-3-ol which was carried forward crude. In a separate flask, a dispersion of NaH (600 mg of a 60 wt% dispersion, 15.0 mmol, 1.5 equiv.) was suspended in DMF (10 mL) at 0 °C, and a solution of the crude 3-phenyloxetan-3-ol (assumed 1.50 g in 5 mL of DMF, 10 mmol, 1 equiv.) was added dropwise, using an additional 2x 2.5 mL of DMF to aid transfer (giving a 0.5 M overall solution in DMF). After 30 minutes, benzyl bromide (2.38 mL, 20.0 mmol, 2 equiv.) was added over 1 minute, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was removed, and the organic layer was washed 5x with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1q**

(1.30 g, 5.41 mmol, 54% yield over the two steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.49-7.44 (m, 2H), 7.40-7.33 (m, 5H), 7.33-7.28 (m, 1H), 5.04-5.01 (m, 2H), 4.92-4.90 (m, 2H), 4.27 (s, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.9, 137.9, 128.8, 128.4, 128.1, 127.7, 127.5, 126.0, 81.1, 80.7, 66.3 ppm; **FT-IR** (thin-film): 3088, 3061, 3030, 2949, 2874, 1716, 1496, 1448, 1383, 1277, 1175, 1134, 1060, 1022, 983, 882, 758, 737, 700, 550 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{16}H_{17}O_2$ $[M+H]^+$ 241.1223, found 241.1222.



1r

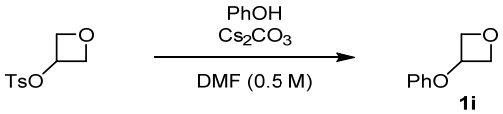
3-(benzyloxy)-3-(*p*-tolyl)oxetane (1r): Oxetan-3-one (0.59 mL, 10 mmol, 1 equiv.) was dissolved in THF (40 mL, 0.25 M) and cooled to 0 °C. A solution of p-tolylmagnesium bromide (11 mL of 1 M solution in THF, 11 mmol, 1.1 equiv.) was added over 1 minute and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 3-*p*-tolyloxetan-3-ol which was carried forward crude. In a separate flask, a dispersion of NaH (600 mg of a 60 wt% dispersion, 15.0 mmol, 1.5 equiv.) was suspended in DMF (10 mL) at 0 °C, and a solution of the crude 3-*p*-tolyloxetan-3-ol (assumed 1.64 g in 5 mL of DMF, 10 mmol, 1 equiv.) was added dropwise, using an additional 2x 2.5 mL of DMF to aid transfer (giving a 0.5 M overall solution in DMF). After 30 minutes, benzyl bromide (2.38 mL, 20.0 mmol, 2 equiv.) was added over 1 minute, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was removed, and the organic layer was washed 5x with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1r** (1.44 g, 5.66 mmol, 57% yield over the two steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.37 – 7.32 (m, 4H), 7.31 – 7.25 (m, 3H), 5.01 – 4.98 (m, 2H), 4.9-4.87 (m, 2H), 4.24 (s, 2H), 2.39 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.0, 137.9, 136.9, 129.5, 128.5, 127.7, 127.6, 126.0, 81.3, 80.7, 66.3, 21.2 ppm; **FT-IR** (thin-film): 3030, 2948, 2873, 1608, 1514, 1497, 1454, 1381, 1276, 1172, 1131, 1116, 1062, 1026, 1017, 981, 911, 882, 816, 732, 696, 545 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{17}H_{17}O_2$ $[M-H]^+$ 253.1223, found 253.1224.



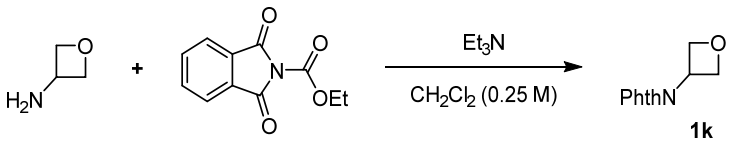
1t

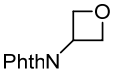
3-(benzyloxy)-3-(4-(trifluoromethyl)phenyl)oxetane (1t): Magnesium turnings (292 mg, 12 mmol, 1.2 equiv.) were flame-dried under vacuum, placed under an atmosphere of nitrogen, and then covered with a minimal volume of THF (3 mL). A drop of 1,2-dibromoethane was added followed by the gradual, simultaneous addition of 1-iodo-4-(trifluoromethyl)benzene (1.76 mL, 12 mmol, 1.2 equiv.) and THF (9 mL), being careful to avoid a significant exotherm. The reaction was allowed to continue for 2 hours, at which point no solid magnesium was visible. In a separate flask oxetan-3-one (0.59 mL, 10 mmol, 1 equiv.) was dissolved in THF (40 mL, 0.25 M) and cooled to 0 °C. The solution of Grignard (~1 M) was then added dropwise to the solution of oxetan-3-one, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was removed, and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 3-*p*-(trifluoromethyl)phenyloxetan-3-ol which was carried forward crude. In a separate flask, a dispersion of NaH (600 mg of a 60 wt% dispersion, 15.0 mmol, 1.5 equiv.) was suspended in DMF (10 mL) at 0 °C, and a solution of the crude 3-*p*-(trifluoromethyl)phenyloxetan-3-ol (assumed 2.18 g in 5 mL of DMF, 10 mmol, 1 equiv.) was added dropwise, using an additional 2x 2.5 mL of DMF to aid transfer (giving a 0.5 M overall solution in DMF). After 30 minutes, benzyl bromide (2.38 mL, 20.0 mmol, 2 equiv.) was added over 1 minute, and the reaction was allowed to continue overnight, gradually warming to room temperature as the ice bath melted. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was removed, and the organic layer was washed 5x with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1t** (1.24 g, 4.01 mmol, 40% yield over the two steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 4H), 7.39 – 7.29 (m, 5H), 5.07 – 5.04 (m, 2H), 4.85 – 4.82 (m, 2H), 4.30 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.3, 137.5, 130.5 (q, J = 32.6 Hz), 128.7, 128.0, 127.6, 126.5, 126.0 (q, J = 3.8 Hz), 124.1 (q, J = 272.1 Hz), 81.1, 80.4, 66.8 ppm; **^{19}F NMR** (376 MHz, $CDCl_3$) δ −62.62 ppm; **FT-IR** (thin-film): 2950, 2876, 1497, 1453, 1415, 1387, 1339, 1175, 1156, 1113, 1093, 1077, 1060, 1016, 979, 882, 845, 831, 750, 702, 603 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{17}H_{16}F_3O_2$ $[M+H]^+$ 309.1097, found 309.1095.

Syntheses of other substrates:

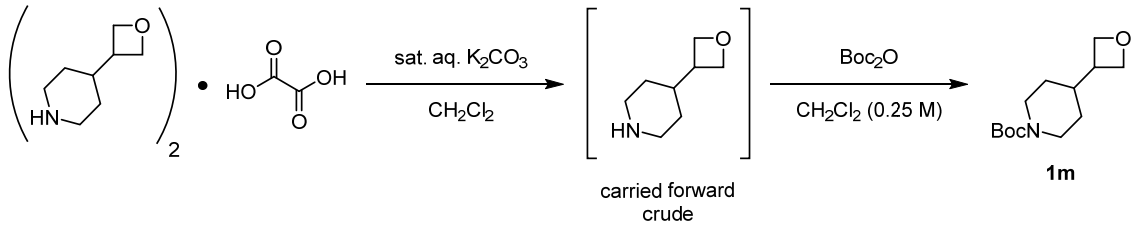


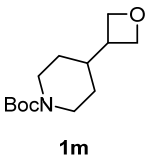
3-phenoxyoxetane (1i): Oxetan-3-yl 4-methylbenzenesulfonate (913 mg, 4 mmol, 1 equiv.) was dissolved in DMF (8 mL, 0.5 M) to which was added phenol (452 mg, 4.8 mmol, 1.2 equiv.) and Cs_2CO_3 (5.21 g, 16 mmol, 4 equiv.). The reaction was heated to 85 °C and allowed to continue at that temperature for 3 days. The reaction was then allowed to cool to room temperature, and it was diluted with Et_2O and 10% aqueous LiCl. The aqueous layer was removed, and the organic layer was washed 3x with 10% aqueous LiCl, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography to yield oxetane **1i** (601 mg, 2.48 mmol, 62% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.99 (td, J = 7.4, 1.1 Hz, 1H), 6.73 – 6.68 (m, 2H), 5.24 – 5.18 (m, 1H), 4.97 (ddd, J = 7.1, 6.2, 1.0 Hz, 2H), 4.80 – 4.75 (m, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7, 129.8, 121.6, 114.6, 78.2, 70.1 ppm; **FT-IR** (thin-film): 3042, 2948, 2874, 1599, 1587, 1489, 1372, 1291, 1235, 1174, 1124, 1090, 1077, 1038, 1025, 972, 879, 811, 751, 690, 587, 512, 474 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_9H_{10}O_2$• $[M•]^+$ 150.0675, found 150.0674.





2-(oxetan-3-yl)isoindoline-1,3-dione (1k): Oxetan-3-amine (0.35 mL, 5 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (20 mL, 0.25 M) and cooled to 0 °C. Triethylamine (0.70 mL, 5 mmol, 1 equiv.) was added followed by Nefkens' reagent (1.10 g, 5 mmol, 1 equiv.). The ice-bath was then removed and the reaction was allowed to continue stirring under nitrogen. After 48 hours, the reaction diluted with CH_2Cl_2, and the organic layer was washed sequentially with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield oxetane **1k** (521 mg, 2.56 mmol, 51% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.77 – 7.73 (m, 2H), 5.42 – 5.34 (m, 1H), 5.34 – 5.29 (m, 2H), 4.93 – 4.89 (m, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 134.4, 131.8, 123.6, 75.3, 44.3 ppm; **FT-IR** (thin-film): 2964, 2898, 1772, 1705, 1486, 1466, 1389, 1046, 969, 884, 724, 531 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{11}H_9NO_3$ $[M+H]^+$ 204.0655, found 204.0654.





tert-butyl 4-(oxetan-3-yl)piperidine-1-carboxylate (1m): 4-(oxetan-3-yl)piperidine hemioxalate (125 mg, 0.336 mmol, 0.5 equiv.) was dissolved in CH_2Cl_2 and free-based with saturated aqueous potassium carbonate in a separatory funnel. The organic layer was removed, and the aqueous layer was extracted 5x with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and carried forward crude assuming complete conversion to two equivalents of 4-(oxetan-3-yl)piperidine. The free amine was then re-dissolved in CH_2Cl_2 (1.3 mL, 0.25 M) and then Boc_2O (165 mg, 0.755 mmol, 1.125 equiv.) was added. The reaction was allowed to continue stirring overnight under an atmosphere of nitrogen. The following day, the reaction was concentrated and purified by flash column

chromatography to yield oxetane **1m** (155 mg, 0.642 mmol, 96% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 7.9, 6.1 Hz, 2H), 4.46 (t, *J* = 6.2 Hz, 2H), 4.31 – 3.85 (br, 2H), 2.77 – 2.62 (m, 3H), 1.86 – 1.75 (m, 1H), 1.61 – 1.53 (m, 2H), 1.45 (s, 9H), 1.00 (qd, *J* = 12.4, 4.5 Hz, 2H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 79.5, 75.8, 44.8 – 42.5 (br), 40.3, 40.0, 28.9, 28.5 ppm; **FT-IR** (thin-film): 2972, 2931, 2860, 1685, 1447, 1414, 1364, 1276, 1235, 1158, 1093, 1018, 978, 883, 811, 771 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{13}H_{23}NO_3Na$ $[M+Na]^+$ 264.1570, found 264.1567.

Reaction Scope and Derivatizations

General procedures for preparative-scale squaramide catalyzed oxetane opening:

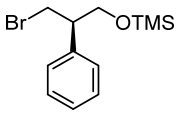
General Procedures B and C differ only in the reaction workup and purification. Oxetanes **1f**, **1k**, **1m**, **1u**, and **1v** required deviations from these procedures. General Procedure D, which has both elevated temperatures and higher catalyst loadings, was used for tertiary alcohol derivatives **1q-t** due to their reduced reactivity.

General Procedure B (reaction with purification by silica plug): An oven-dried 2-dram vial was equipped with a magnetic stir-bar and closed with a screw-cap containing a rubber septum. The vial was charged with oxetane (0.4 mmol, 1 equiv.), squaramide **3a** (5.4 mg, 0.008 mmol, 0.02 equiv.), and *t*-BuOMe (4 mL, 0.1 M). The headspace of the vial was flushed with nitrogen for 15 seconds and then the vial was cooled to -78 °C in a dry ice-acetone bath, allowing 15 minutes for the temperature to equilibrate. A micro-syringe was flushed with TMSBr 3x or until the solution in the syringe was clear, and then TMSBr (106 uL, 0.8 mmol, 2 equiv.) was added dropwise to the reaction being careful to ensure no TMSBr froze to the side of the vial. The reaction was allowed to continue stirring at -78 °C for 24 hours, after which it was quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.4 mL). After an additional 5 minutes at -78 °C, the reaction diluted with 2 mL of hexanes. The crude mixture was run through a 2-inch silica plug topped with 4 mL of hexanes using an additional 20 mL of a 30% solution of Et_2O in hexanes to rinse the plug. The filtrate from the plug was concentrated under vacuum to yield the product, generally requiring no further purification. When possible, e.e. was determined by chiral GC using the TMS-protected product. Otherwise, a pipette-tip of the product was dissolved in Et_2O (1 mL) and aqueous 1 M HCl was added (1 mL). The resulting biphasic solution was stirred vigorously for ~30 minutes to deprotect the silyl ether, and then the organic layer was removed, dried over Na_2SO_4, filtered, concentrated under vacuum, and analyzed by chiral HPLC.

General Procedure C (reaction with aqueous workup and column chromatography): An oven-dried 2-dram vial was equipped with a magnetic stir-bar and closed with a screw-cap containing a rubber septum. The vial was charged with oxetane (0.4 mmol, 1 equiv.), squaramide **3a** (5.4 mg, 0.008 mmol, 0.02 equiv.), and *t*-BuOMe (4 mL, 0.1 M). The headspace of the vial was flushed with nitrogen for 15 seconds and then the vial was cooled to -78 °C in a dry ice-acetone bath, allowing 15 minutes for the temperature to equilibrate. A micro-syringe was flushed with TMSBr 3x or until the solution in the syringe was clear, and then TMSBr (106 uL, 0.8 mmol, 2 equiv.) was added dropwise to the reaction being careful to ensure no TMSBr froze to the side of the vial. The reaction was allowed to continue stirring at -78 °C for 24 hours, after which it was quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.4 mL). After an additional 5 minutes at -78 °C, the reaction was diluted with Et_2O and saturated aqueous $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried briefly (~10 minutes) over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield the product. To determine the e.e., a pipette-tip of the product was dissolved in Et_2O (1 mL) and aqueous 1 M HCl was added (1 mL). The resulting biphasic solution was stirred vigorously for ~30 minutes to deprotect the silyl ether, and then the organic layer was removed, dried over Na_2SO_4, filtered, concentrated under vacuum, and analyzed by chiral HPLC.

General Procedure D (reaction of 3-(benzyloxy)-3-aryloxetanes): An oven-dried 2-dram vial was equipped with a magnetic stir-bar and closed with a screw-cap containing a rubber septum. The vial was charged with oxetane (0.4 mmol, 1 equiv.), squaramide **3a** (20.4 mg, 0.030 mmol, 0.075 equiv.), and *t*-BuOMe (4 mL, 0.1 M). The headspace of the vial was flushed with nitrogen for 15 seconds and then the vial was cooled to -78 °C in a dry ice-acetone bath, allowing 15 minutes for the temperature to equilibrate. A micro-syringe was flushed with TMSBr 3x or until the solution in the syringe was clear, and then TMSBr (106 uL, 0.8 mmol, 2 equiv.) was added dropwise to the reaction being careful to ensure no TMSBr froze to the side of the vial. The reaction was allowed to continue stirring at -78 °C for 1 hour after which it was transferred to a -25 °C cryocool and allowed to continue for an additional 71 hours. The reaction was then quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.4 mL). After an additional 5 minutes at -25 °C, the reaction was diluted with 2 mL of hexanes. The crude mixture was run through a 2-inch silica plug topped with 4 mL of hexanes using an additional 20 mL of 30% ether in hexanes as a rinse. The filtrate from the plug was concentrated under vacuum and purified by flash column chromatography to yield the desired product. To determine the e.e., a pipette-tip of the product was dissolved in Et_2O (1 mL) and aqueous 3 M HCl was added (1 mL). The resulting biphasic solution was stirred vigorously for ~30 minutes to deprotect the silyl ether, and then the organic layer was removed, dried over Na_2SO_4, filtered, concentrated under vacuum, and analyzed by chiral HPLC.

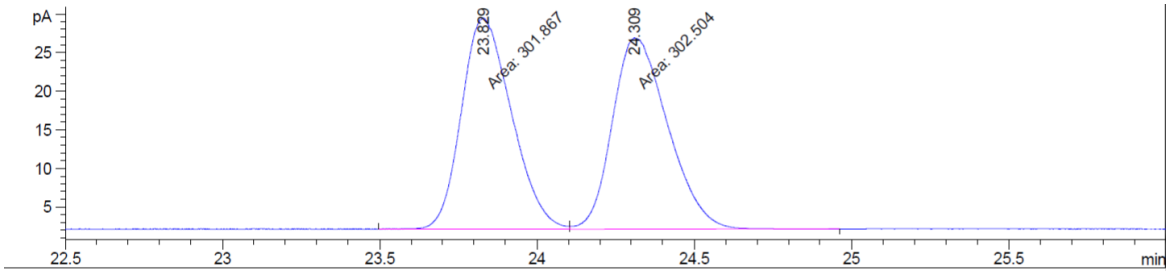
Characterization data for products:



2a

(R)-(3-bromo-2-phenylpropoxy)trimethylsilane (2a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a** (111.0 mg, 0.386 mmol, 97% yield). **2a** was determined to be of 98% e.e. by chiral GC analysis (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi, t_r(major)= 24.3 min, t_r(minor)= 23.9 min). The absolute configuration of this compound was assigned by X-ray crystallographic analysis of its triazole derivative **26a** (see below). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.21 (m, 2H), 3.90 – 3.82 (m, 2H), 3.79 (dd, *J* = 10.3, 7.0 Hz, 1H), 3.64 (dd, *J* = 10.0, 7.3 Hz, 1H), 3.14 (qd, *J* = 6.9, 5.0 Hz, 1H), 0.08 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.4, 128.6, 128.1, 127.4, 64.8, 50.2, 35.1, −0.5 ppm; **FT-IR** (thin-film): 2957, 2903, 2868, 1495, 1453, 1382, 1251, 1098, 872, 841, 753, 699, 533 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{12}H_{19}BrOSi$ $[M+H]^+$ 287.0461, found 287.0464; $[\alpha]_D$ = –38.0º (c = 1.0, $CHCl_3$).

Racemic sample: GC (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi)



Signal 2: FID2 B, Back Signal

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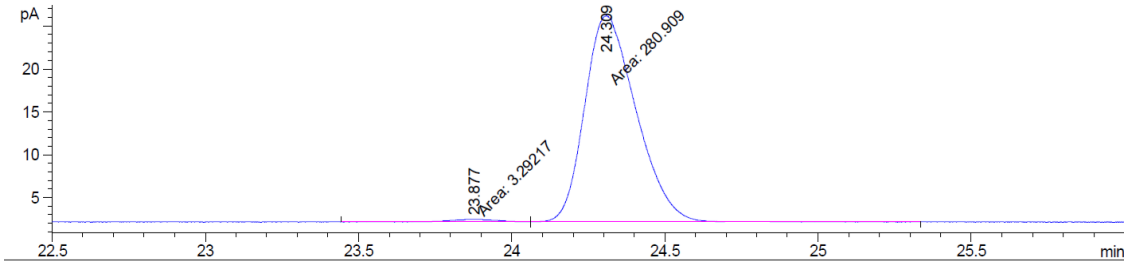
1	23.829	MF	0.1839	301.86725	27.35132	49.94733
2	24.309	FM	0.2037	302.50391	24.74771	50.05267

Enantioenriched sample: GC (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi), 98% e.e.



Signal 2: FID2 B, Back Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.877	MF	0.1787	3.29217	3.07066e-1	1.15839
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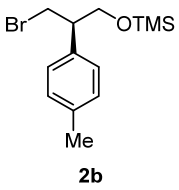
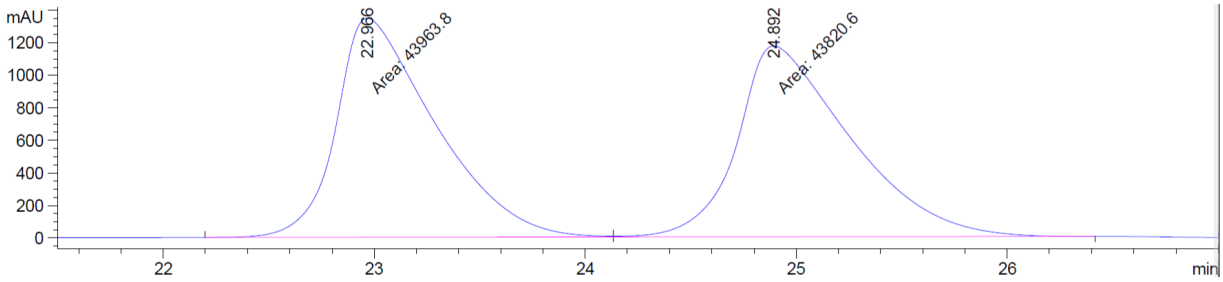


2b

(R)-(3-bromo-2-(p-tolyl)propoxy)trimethylsilane (2b): Oxetane **1b** (59.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2b** (121.0 mg, 0.40 mmol, 100% yield). **2b** was determined to be of 92% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak IB, 2% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 23.4 min, t_r(minor)= 25.7 min). The absolute configuration of **2b** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 4H), 3.87 – 3.81 (m, 2H), 3.77 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.62 (dd, *J* = 9.9, 7.4 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.33 (s, 3H), 0.09 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.3, 136.9, 129.3, 127.9, 64.8, 49.8, 35.3, 21.2, -0.5 ppm; **FT-IR** (thin-film): 2956, 2921, 2867, 1515, 1434, 1381, 1250, 1092, 926, 868, 837, 813, 747, 537 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{13}H_{20}BrOSi$ $[M-H]^+$ 299.0461, found 299.0461; $[\alpha]_D = -37.6°$ (c = 1.0, $CHCl_3$).

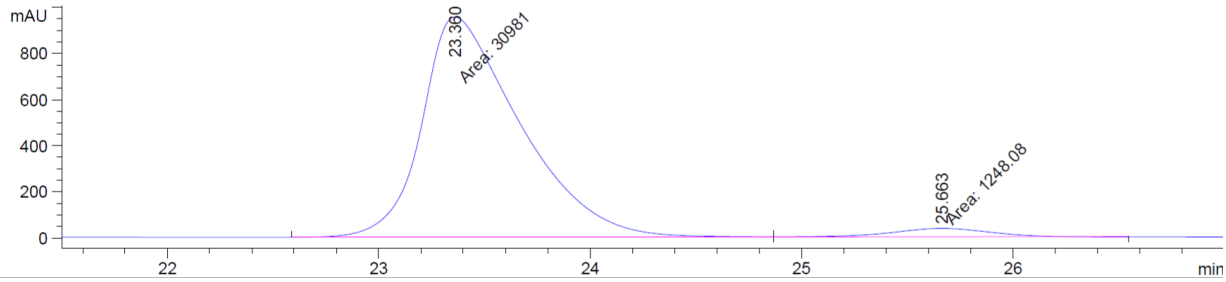
Racemic sample: HPLC (ChiralPak IB, 2% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.966	MF	0.5442	4.39638e4	1346.48755	50.0816
2	24.892	FM	0.6224	4.38206e4	1173.37927	49.9184

Enantioenriched sample: HPLC (ChiralPak IB, 2% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 92% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.360	MF	0.5396	3.09810e4	956.91705	96.1275
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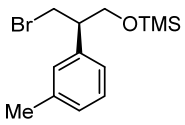
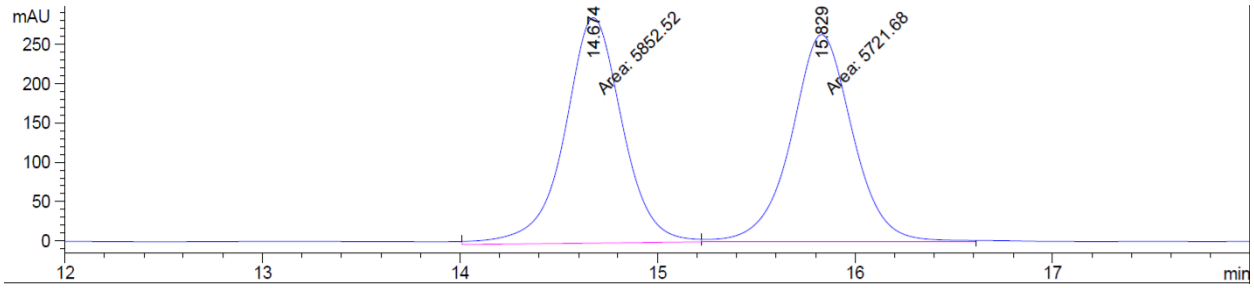


2c

(R)-(3-bromo-2-(m-tolyl)propoxy)trimethylsilane (2c): Oxetane **1c** (59.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2c** (117 mg, 0.39 mmol, 97% yield). **2c** was determined to be of 98% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 14.2 min, t_r(minor)= 15.3 min). The absolute configuration of **2c** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 – 7.20 (m, 1H), 7.10 – 7.07 (m, 1H), 7.04 – 7.01 (m, 2H), 3.88 – 3.82 (m, 2H), 3.77 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.62 (dd, *J* = 9.9, 7.4 Hz, 1H), 3.11 (qd, *J* = 7.1, 5.1 Hz, 1H), 2.35 (s, 3H), 0.08 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.2, 138.1, 128.9, 128.4, 128.1, 125.1, 64.8, 50.2, 35.1, 21.6, -0.4 ppm; **FT-IR** (thin-film): 3024, 2956, 2919, 2867, 1608, 1490, 1434, 1381, 1250, 1091, 944, 867, 837, 785, 747, 702, 444 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{13}H_{20}BrOSi$ $[M-H]^+$ 299.0461, found 299.0461; $[\alpha]_D = -36.4^o$ (c = 1.0, $CHCl_3$).

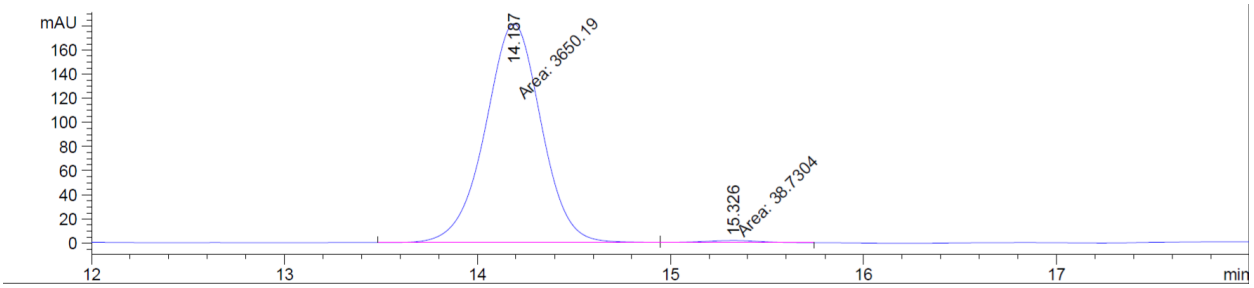
Racemic sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

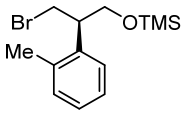
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.674	MM	0.3405	5852.52148	286.46936	50.5652
2	15.829	MM	0.3620	5721.67627	263.42648	49.4348

Enantioenriched sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 98% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

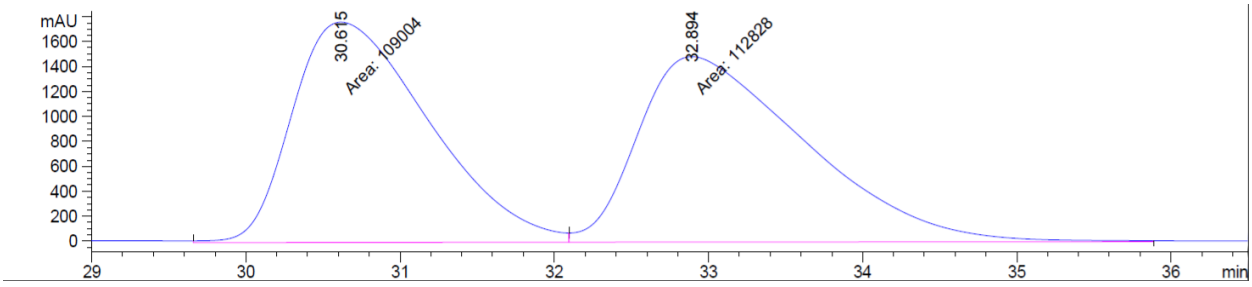
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.187	MF	0.3358	3650.18579	181.18057	98.9501
2	15.326	FM	0.3473	38.73040	1.85851	1.0499



2d

(R)-(3-bromo-2-(o-tolyl)propoxy)trimethylsilane (2d): Oxetane **1d** (59.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B, but due to incomplete conversion, it was necessary to purify the crude product by flash column chromatography to yield **2d** (87.4 mg, 0.29 mmol, 72% yield). **2d** was determined to be of 73% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralCel OD-H, 3% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 33.3 min, t_r(minor)= 31.1 min). The absolute configuration of **2d** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 4H), 3.88 (dd, *J* = 9.9, 6.1 Hz, 1H), 3.81 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.76 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.61 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.47 (tdd, *J* = 7.4, 6.1, 5.0 Hz, 1H), 2.36 (s, 3H), 0.08 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.6, 136.5, 130.6, 127.1, 126.3, 126.2, 64.6, 45.3, 34.8, 19.9, -0.5 ppm; **FT-IR** (thin-film): 3022, 2955, 2901, 2867, 1492, 1462, 1250, 1092, 999, 944, 925, 869, 838, 748, 723, 657, 455 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{13}H_{20}BrOSi$ $[M-H]^+$ 299.0461, found 299.0461; $[\alpha]_D$ = –29.6° (c = 1.0, $CHCl_3$).

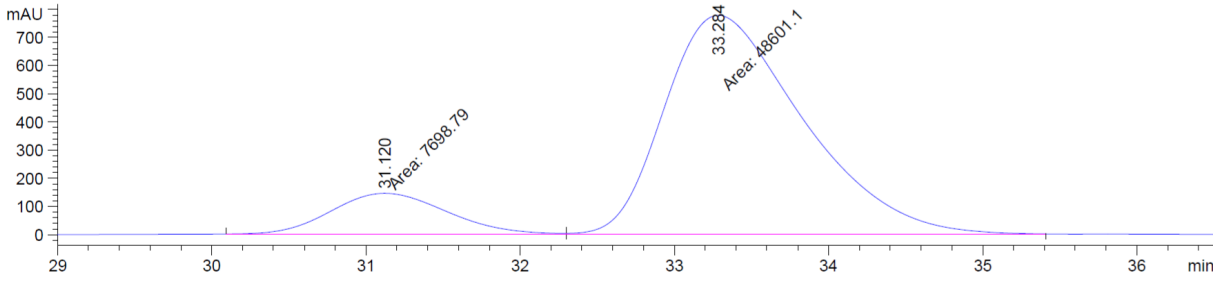
Racemic sample: HPLC (ChiralCel OD-H, 3% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

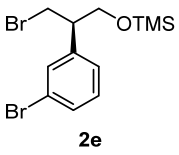
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.615	MF	1.0279	1.09004e5	1767.40015	49.1381
2	32.894	FM	1.2637	1.12828e5	1488.02905	50.8619

Enantioenriched sample: HPLC (ChiralCel OD-H, 3% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 73% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

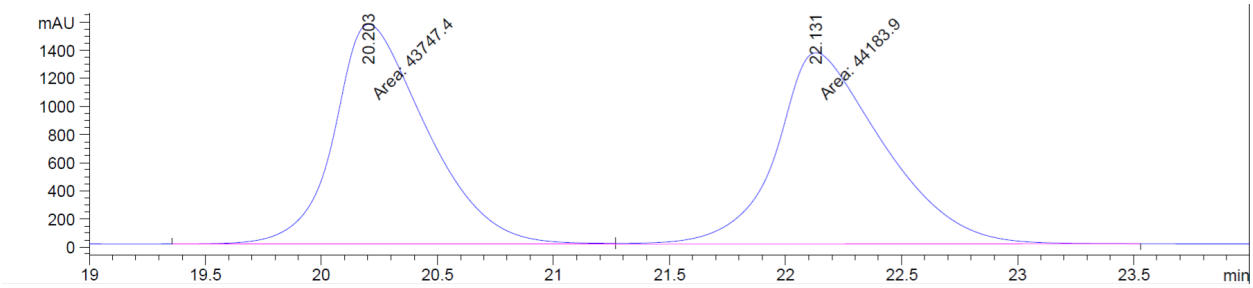
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.120	MF	0.8785	7698.79053	146.05885	13.6746
2	33.284	FM	1.0412	4.86011e4	777.95697	86.3254



2e

(R)-(3-bromo-2-(3-bromophenyl)propoxy)trimethylsilane (2e): Oxetane **1e** (85 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2e** (141 mg of a 12.5 : 1 mixture of silylated : desilylated product, 0.39 mmol combined, 98% yield of combined silylated and desilylated products). **2e** was determined to be of 98% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak IB, 3% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 20.2 min, t_r(minor)= 22.3 min). The absolute configuration of **2e** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.16 (dt, *J* = 7.7, 1.5 Hz, 1H), 3.87 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.82 – 3.75 (m, 2H), 3.59 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.10 (qd, *J* = 6.6, 4.8 Hz, 1H), 0.08 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 131.2, 130.4, 130.1, 126.9, 122.6, 64.4, 49.8, 34.3, -0.5 ppm; **FT-IR** (thin-film): 2957, 2906, 2870, 1595, 1567, 1477, 1428, 1381, 1251, 1098, 997, 942, 867, 841, 782, 749, 694, 657, 439 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{12}H_{17}Br_2OSi$ $[M-H]^+$ 362.9410, found 362.9408; $[\alpha]_D = -33^o$ (c = 1.0, $CHCl_3$).

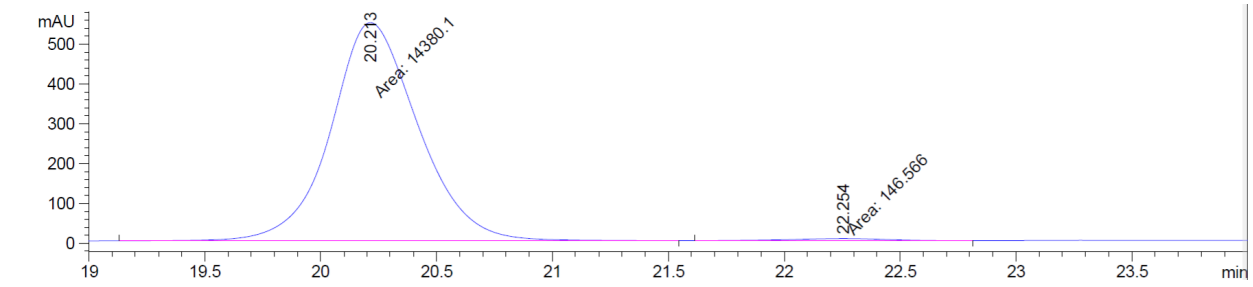
Racemic sample: HPLC (ChiralPak IB, 3% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

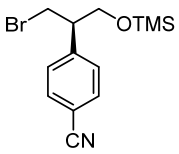
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.203	MF	0.4657	4.37474e4	1565.55688	49.7517
2	22.131	FM	0.5404	4.41839e4	1362.67834	50.2483

Enantioenriched sample: HPLC (ChiralPak IB, 3% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 98% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

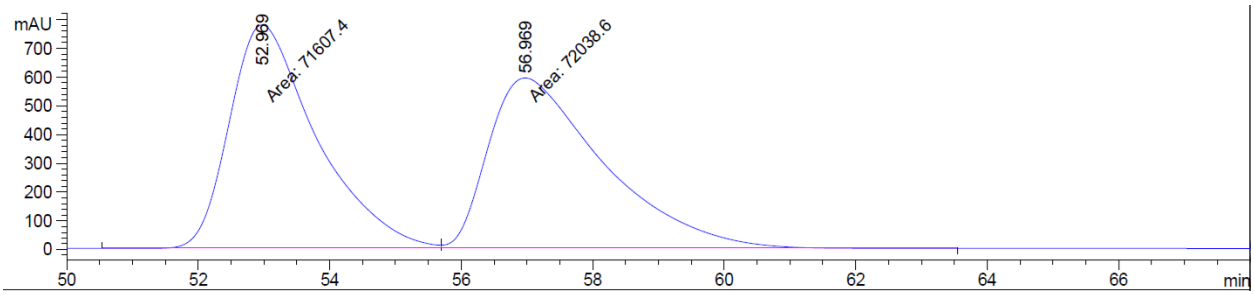
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.213	MM	0.4377	1.43801e4	547.58612	98.9911
2	22.254	MM	0.4780	146.56618	5.11043	1.0089



2f

(R)-4-(1-bromo-3-((trimethylsilyl)oxy)propan-2-yl)benzonitrile (2f): Oxetane **1f** (63.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure C with the following modification: the reaction was run for 48 hours. The reaction yielded **2f** (112.8 mg, 0.36 mmol, 90% yield). **2f** was determined to be of 98% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 58.5 min, t_r(minor)= 54.2 min). The absolute configuration of **2f** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.37 – 7.34 (m, 2H), 3.89 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.61 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.22 – 3.17 (m, 1H), 0.07 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.9, 132.2, 129.0, 118.8, 111.2, 64.1, 50.1, 33.6, -0.6 ppm; **FT-IR** (thin-film): 2957, 2901, 2871, 2229, 1609, 1506, 1252, 1099, 871, 841, 749, 564 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{13}H_{19}BrNOSi$ $[M+H]^+$ 312.0414, found 312.0404; $[\alpha]_D = -36.8^o$ (c = 1.0, $CHCl_3$).

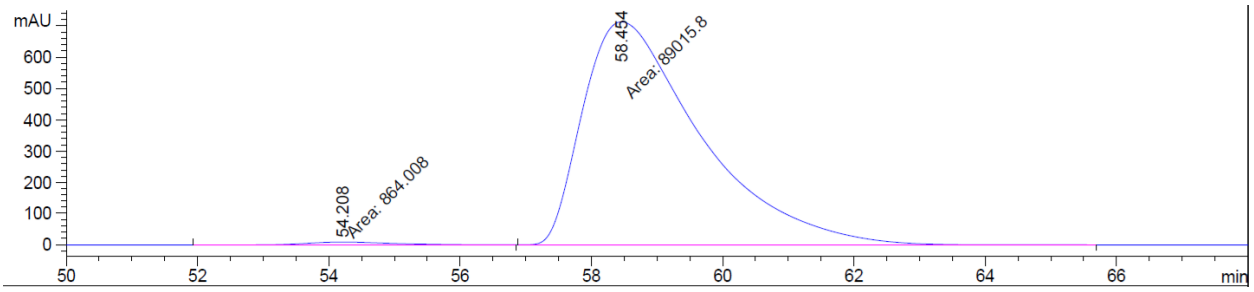
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm)



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

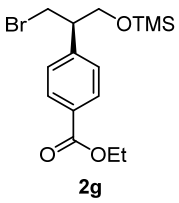
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.969	MF	1.5344	7.16074e4	777.78027	49.8499
2	56.969	FM	2.0242	7.20386e4	593.14807	50.1501

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm), 98% e.e.



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

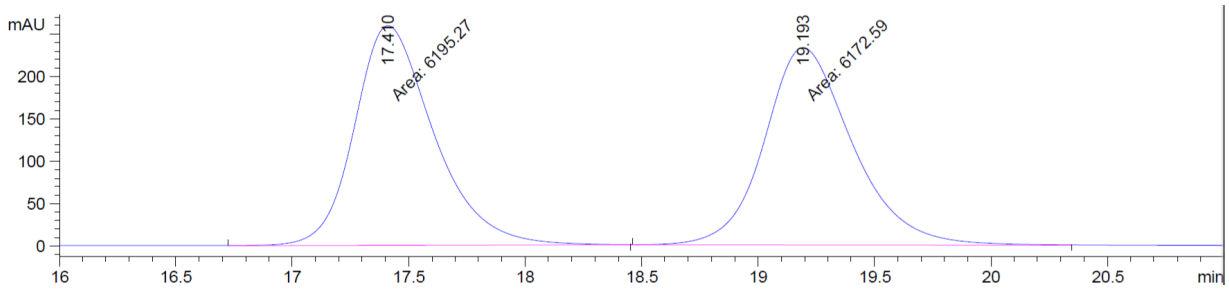
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.208	MM	1.5577	864.00775	9.24429	0.9613
2	58.454	MM	2.0777	8.90157e4	714.05865	99.0387



2g

ethyl (R)-4-(1-bromo-3-((trimethylsilyl)oxy)propan-2-yl)benzoate (2g): Oxetane **1g** (82 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2g** (136 mg, 0.38 mmol, 95% yield). **2g** was determined to be of 96% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 18.6 min, t_r(minor)= 17.0 min). The absolute configuration of **2g** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.32 – 7.28 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.89 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.63 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.20 (qd, *J* = 6.6, 4.9 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.07 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 145.5, 129.8, 129.6, 128.1, 64.4, 61.0, 50.1, 34.2, 14.4, -0.6 ppm; **FT-IR** (thin-film): 2957, 2905, 2870, 1716, 1611, 1367, 1275, 1251, 1182, 1101, 1022, 870, 841, 749, 707, 537 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{15}H_{24}BrO_3Si$ $[M+H]^+$ 359.0673, found 359.0672; $[\alpha]_D$ = –27.8º (c = 1.0, $CHCl_3$).

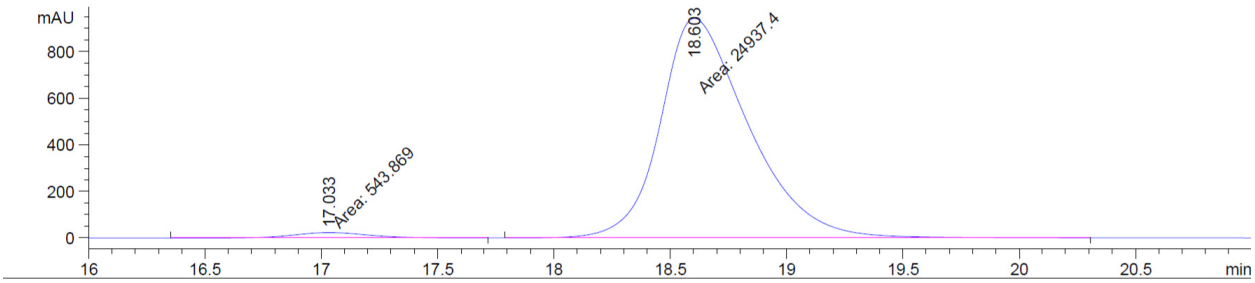
Racemic sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm)



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

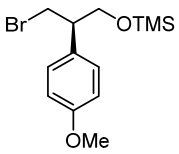
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.410	MM	0.3977	6195.27441	259.61163	50.0917
2	19.193	MM	0.4417	6172.59277	232.93501	49.9083

Enantioenriched sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm), 96% e.e.



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

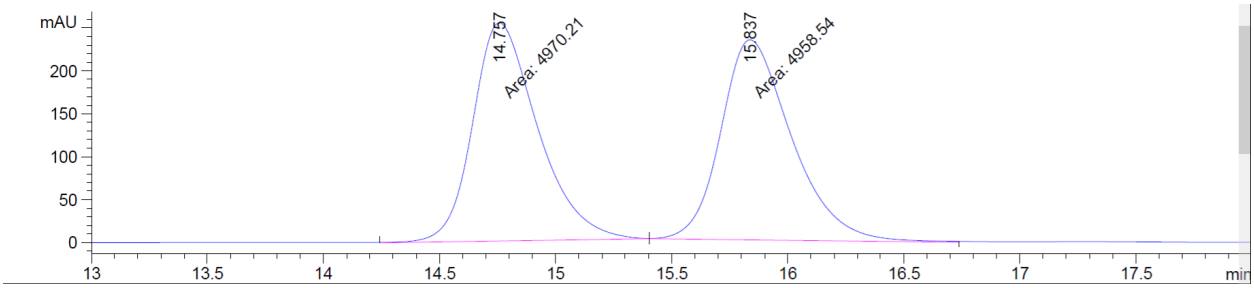
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.033	MM	0.3860	543.86902	23.48250	2.1344
2	18.603	MM	0.4405	2.49374e4	943.42413	97.8656



2h

(R)-(3-bromo-2-(4-methoxyphenyl)propoxy)trimethylsilane (2h): Oxetane **1h** (65.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2h** (126 mg, 0.40 mmol, 99% yield). **2h** was determined to be of 93% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 15.5 min, t_r(minor)= 14.6 min). The absolute configuration of **2h** was assigned by analogy to **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 – 7.13 (m, 2H), 6.89 – 6.84 (m, 2H), 3.87 – 3.80 (m, 2H), 3.80 (s, 3H), 3.76 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.60 (dd, *J* = 9.9, 7.3 Hz, 1H), 3.09 (qd, *J* = 6.9, 5.0 Hz, 1H), 0.08 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 132.4, 129.0, 113.9, 64.8, 55.3, 49.3, 35.5, -0.5 ppm; **FT-IR** (thin-film): 2999, 2956, 2904, 2869, 2835, 1611, 1513, 1465, 1444, 1303, 1249, 1180, 1093, 1036, 870, 840, 748, 547 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{13}H_{21}BrO_2Si^{\bullet}$ $[M^{\bullet}]^+$ 316.0489, found 316.0488; $[\alpha]_D$ = –29.8º (c = 1.0, $CHCl_3$).

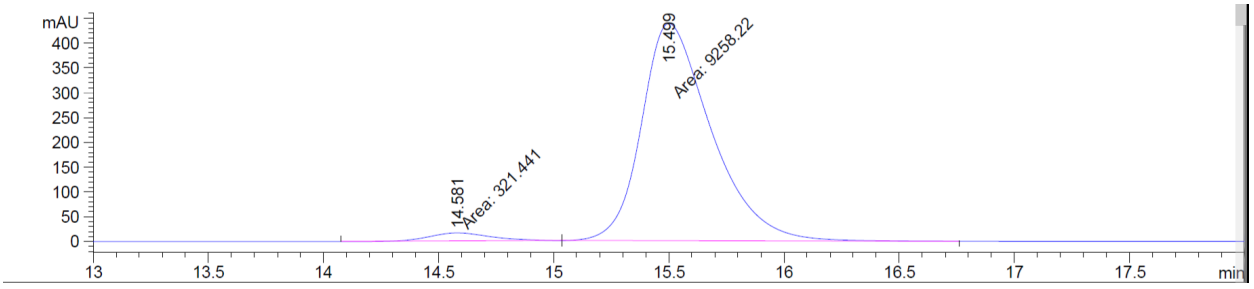
Racemic sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 220 nm)



Signal 4: DAD1 D, Sig=220,16 Ref=450,100

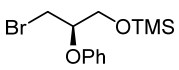
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.757	MM	0.3256	4970.20947	254.38033	50.0588
2	15.837	MM	0.3544	4958.54004	233.16539	49.9412

Enantioenriched sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 220 nm), 93% e.e.



Signal 4: DAD1 D, Sig=220,16 Ref=450,100

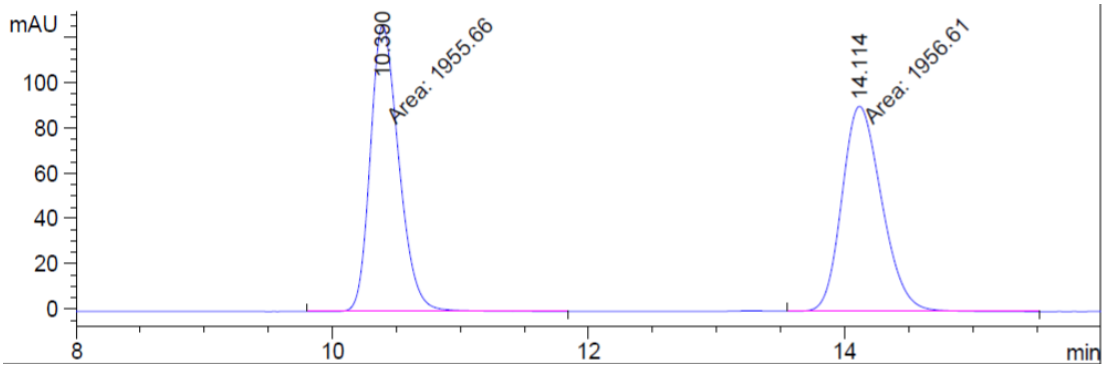
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.581	MM	0.3209	321.44141	16.69322	3.3555
2	15.499	MM	0.3521	9258.21973	438.28241	96.6445



2i

(R)-(3-bromo-2-phenoxypropoxy)trimethylsilane (2i): Oxetane **1i** (60.1 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure C to yield **2i** (108.5 mg, 0.36 mmol, 89% yield). **2i** was determined to be of 97% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralCel OD-H, 10% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 10.3 min, t_r(minor)= 13.7 min). The absolute configuration of **2i** was assigned by analogy to **2a**, **2o**, and **2w**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 2H), 7.05 – 6.88 (m, 3H), 4.51 – 4.44 (m, 1H), 4.00 – 3.78 (m, 2H), 3.76 – 3.63 (m, 1H), 3.63 – 3.56 (m, 1H), 0.16 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.6, 129.8, 121.9, 116.5, 78.0, 62.3, 31.1, -0.3 ppm; **FT-IR** (thin-film): 2957, 1599, 1494, 1238, 1107, 902, 869, 842, 723, 692, 650 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{12}H_{19}BrO_2Si^{\bullet}$ $[M^{\bullet}]^+$ 302.0332, found 302.033; $[\alpha]_D$ = –23.8 (c = 1.0, $CHCl_3$).

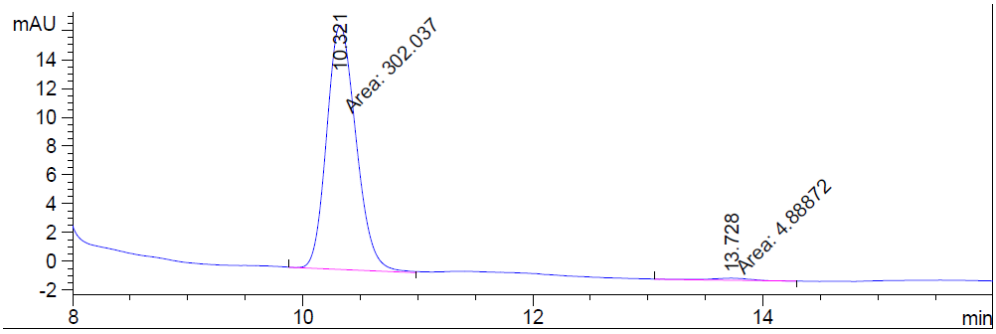
Racemic sample: HPLC (ChiralCel OD-H, 10% *i*-PrOH in hexanes, 1 mL/min, 254 nm)



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

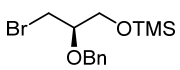
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.390	MM	0.2582	1955.65857	126.25317	49.9879
2	14.114	MM	0.3601	1956.60889	90.55547	50.0121

Enantioenriched sample: HPLC (ChiralCel OD-H, 10% *i*-PrOH in hexanes, 1 mL/min, 254 nm), 97% e.e.



Signal 2: DAD1 B, Sig=254,4 Ref=450,100

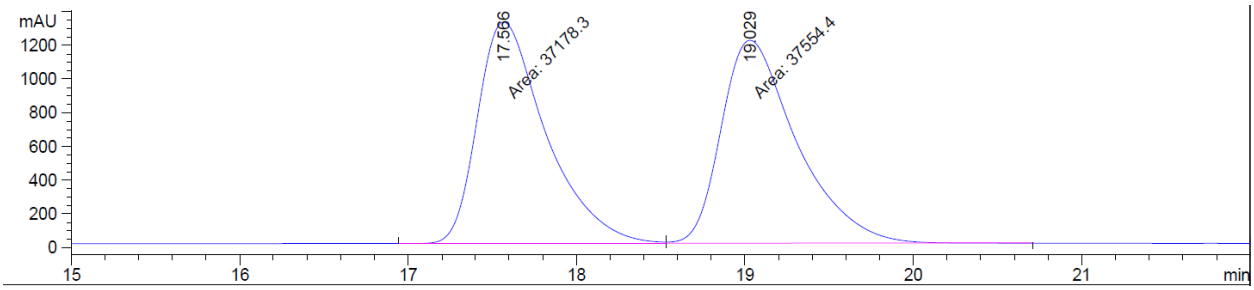
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.321	MM	0.2965	302.03717	16.97544	98.4072
2	13.728	MM	0.4881	4.88872	1.66925e-1	1.5928



2j

(R)-(2-(benzyloxy)-3-bromopropoxy)trimethylsilane (2j): Oxetane **1j** (65.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B with the following modification: due to incomplete conversion the reaction was purified by flash column chromatography. The reaction yielded **2j** (111.5 mg, 0.351 mmol, 88% yield). **2j** was determined to be of 96% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 17.2 min, t_r(minor)= 18.7 min). The absolute configuration of **2j** was assigned by analogy to **2w**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.31 – 7.27 (m, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 3.75 – 3.61 (m, 3H), 3.58 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.49 (dd, *J* = 10.6, 4.7 Hz, 1H), 0.12 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.1, 128.6, 128.02, 127.96, 78.5, 72.3, 62.6, 32.5, -0.4 ppm; **FT-IR** (thin-film): 2954, 2917, 2862, 1252, 1099, 1071, 871, 842, 744, 698 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{13}H_{20}BrO_2Si$ $[M-H]^+$ 315.0410, found 315.0409; $[\alpha]_D = -10.3°$ (c = 1.0, $CHCl_3$).

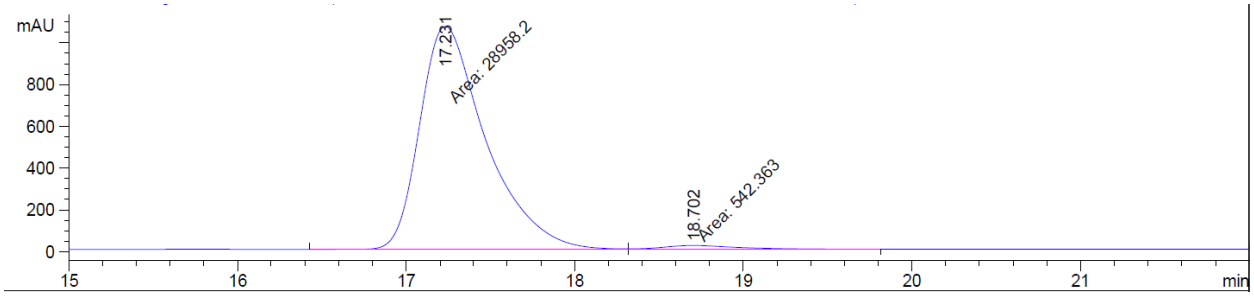
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

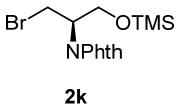
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.566	MF	0.4713	3.71783e4	1314.86340	49.7484
2	19.029	FM	0.5192	3.75544e4	1205.47534	50.2516

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 96% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

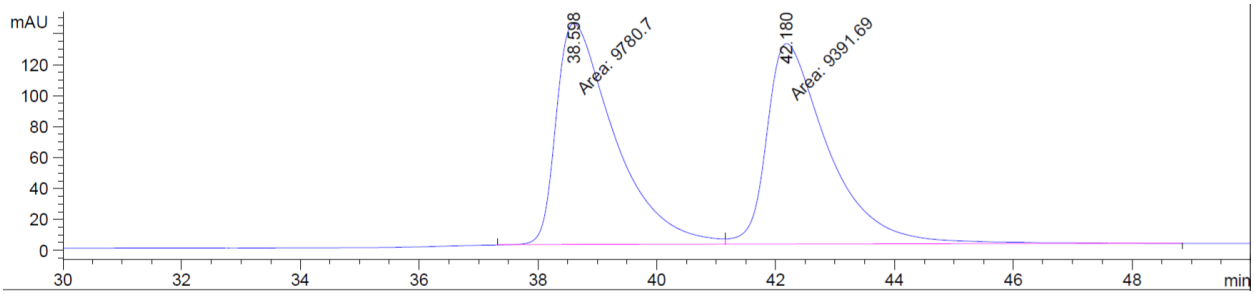
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.231	MF	0.4529	2.89582e4	1065.54163	98.1615
2	18.702	FM	0.5042	542.36340	17.92952	1.8385



2k

(R)-2-(1-bromo-3-((trimethylsilyl)oxy)propan-2-yl)isoindoline-1,3-dione (2k): Oxetane **1k** (81.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure C with the following modification: the reaction was conducted at –25 ºC due to the insolubility of the oxetane starting material. The reaction yielded **2k** (115.4 mg, 0.32 mmol, 81% yield). **2k** was determined to be of 91% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 37.4 min, t_r(minor)= 42.0 min). The absolute configuration of **2k** was assigned by analogy to **2a**, **2o**, and **2w**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.76 – 7.72 (m, 2H), 4.63 (dtd, *J* = 10.1, 7.3, 5.1 Hz, 1H), 4.05 – 3.97 (m, 2H), 3.94 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.80 (dd, *J* = 10.6, 5.2 Hz, 1H), 0.07 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.2, 134.3, 131.8, 123.6, 61.3, 55.1, 29.5, -0.5 ppm; **FT-IR** (thin-film) 2956, 1776, 1708, 1613, 1468, 1430, 1380, 1361, 1336, 1251, 1100, 1053, 1012, 866, 839, 750, 717, 530 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{14}H_{18}BrNO_3Si$ $[M+H]^+$ 356.0312, found 356.0308; $[\alpha]_D$ = – 3.1 (c = 1.0, $CHCl_3$).

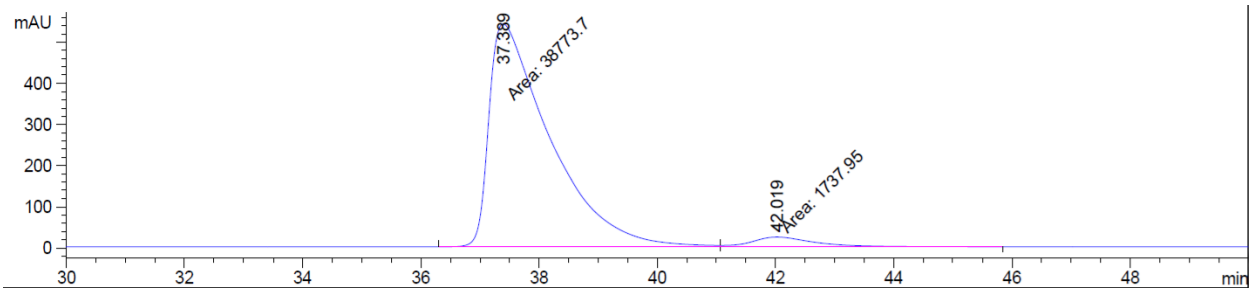
Racemic sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm)



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

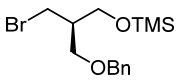
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.598	MF	1.1406	9780.70215	142.92007	51.0145
2	42.180	FM	1.2088	9391.68750	129.49091	48.9855

Enantioenriched sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 230 nm), 91% e.e.



Signal 2: DAD1 B, Sig=230,4 Ref=450,100

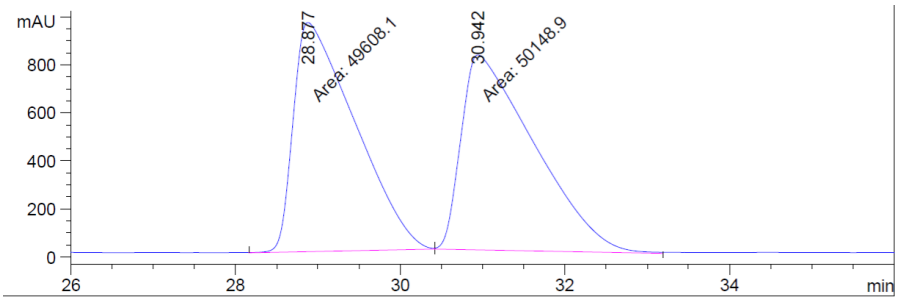
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.389	MF	1.1928	3.87737e4	541.75299	95.7100
2	42.019	FM	1.2261	1737.94653	23.62377	4.2900



2l

(R)-(3-(benzyloxy)-2-(bromomethyl)propoxy)trimethylsilane (2l): Oxetane **1l** (71 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2l** (124.1 mg, 0.375 mmol, 94% yield). **2l** was determined to be of 90% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralCel OJ-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 29.5 min, t_r(minor)= 32.1 min). The absolute configuration of **2l** was assigned by analogy to **2a**, **2o**, and **2w**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.32 – 7.27 (m, 1H), 4.52 (s, 2H), 3.68 (ddd, *J* = 10.2, 5.4, 1.1 Hz, 1H), 3.62 (ddd, *J* = 10.2, 6.5, 1.1 Hz, 1H), 3.57 (dt, *J* = 5.6, 1.1 Hz, 2H), 3.57 – 3.53 (m, 1H), 3.52 – 3.47 (m, 1H), 2.23 – 2.15 (m, 1H), 0.12 (d, *J* = 1.1 Hz, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.4, 128.5, 127.74, 127.70, 73.4, 69.1, 61.4, 43.7, 33.2, -0.4 ppm; **FT-IR** (thin-film): 3031, 2955, 2901, 2864, 1454, 1363, 1251, 1087, 869, 838, 746, 697 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{14}H_{24}BrO_2Si$ $[M+H]^+$ 331.0723, found 331.0724; $[\alpha]_D = -1.2°$ (c = 1.0, $CHCl_3$).

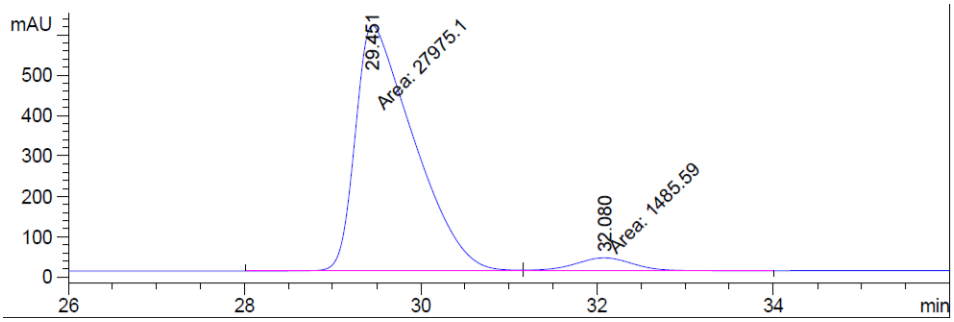
Racemic sample: HPLC (ChiralCel OJ-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

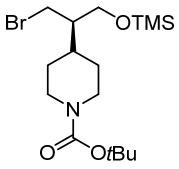
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.877	MM	0.8667	4.96081e4	954.00372	49.7289
2	30.942	MM	1.0290	5.01489e4	812.25208	50.2711

Enantioenriched sample: HPLC (ChiralCel OJ-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 90% e.e.



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

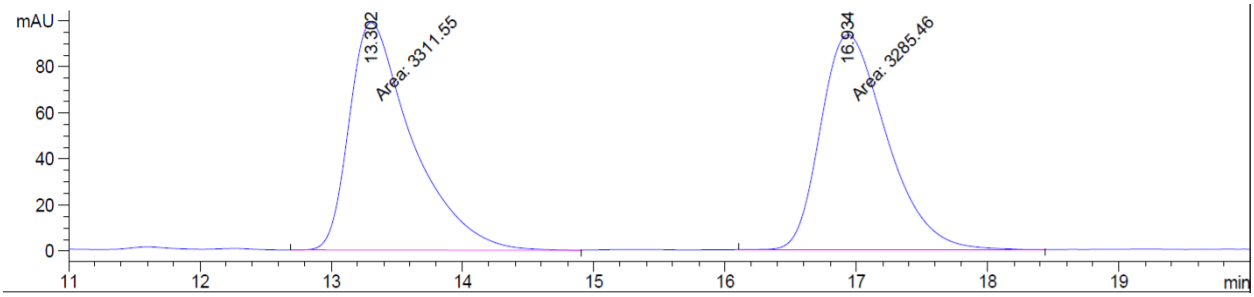
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.451	MF	0.7661	2.79751e4	608.57654	94.9574
2	32.080	FM	0.7710	1485.59302	32.11270	5.0426



2m

tert-butyl (R)-4-(1-bromo-3-((trimethylsilyl)oxy)propan-2-yl)piperidine-1-carboxylate (2m): Oxetane **1m** (97 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure C with the following modification: the reaction was run for 48 hours. The reaction yielded **2m** (150.2 mg, 0.38 mmol, 95% yield). **2m** was determined to be of 96% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 17.4 min, t_r(minor)= 14.0 min). The absolute configuration of **2m** was assigned by analogy to **2a** and **2o**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.12 (br, 2H), 3.73 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.68 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.55 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.52 – 3.47 (m, 1H), 2.72 – 2.61 (m, 2H), 1.77 – 1.65 (m, 2H), 1.63 – 1.55 (m, 2H), 1.45 (s, 9H), 1.29 – 1.12 (m, 2H), 0.12 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 79.4, 60.8, 47.0, 45.3 – 42.8 (br), 35.6, 34.3, 29.5 (br), 28.5, -0.5 ppm; **FT-IR** (thin-film): 2955, 1691, 1467, 1422, 1392, 1364, 1250, 1165, 1081, 1020, 867, 838, 747 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{16}H_{33}BrNO_3Si$ $[M+H]^+$ 394.1408, found 394.1408; $[\alpha]_D$ = +0.6º (c = 1.0, $CHCl_3$).

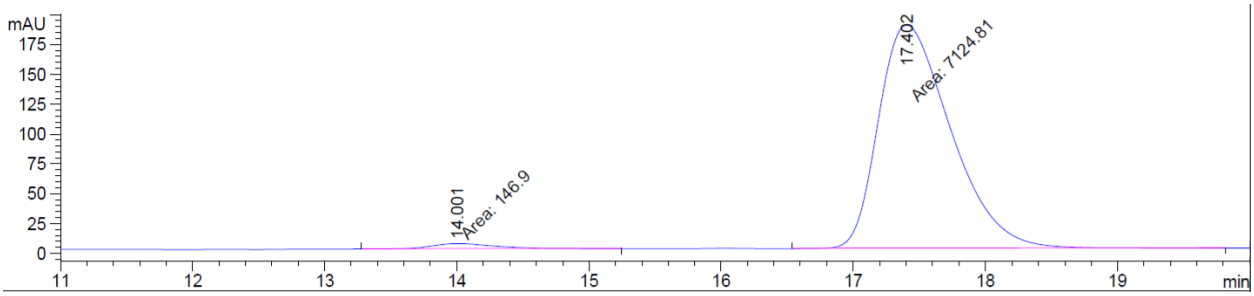
Racemic sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

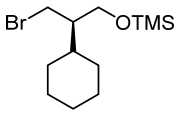
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.302	MM	0.5580	3311.54810	98.90836	50.1977
2	16.934	MM	0.5861	3285.46265	93.42296	49.8023

Enantioenriched sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 96% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

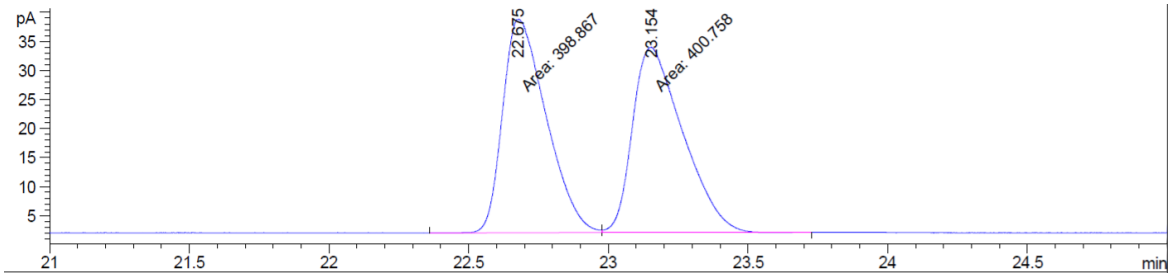
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.001	MM	0.5579	146.89992	4.38868	2.0202
2	17.402	MM	0.6339	7124.81445	187.33537	97.9798



2n

(R)-(3-bromo-2-cyclohexylpropoxy)trimethylsilane (2n): Oxetane **1n** (56.1 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B with the following modification: due to incomplete conversion the reaction was purified by flash column chromatography. The reaction yielded **2n** (97.5 mg, 0.33 mmol, 83% yield). **2n** was determined to be of 99% e.e. by chiral GC analysis (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi, t_r(major)= 22.9 min, t_r(minor)= 22.6 min). The absolute configuration of **2n** was assigned by analogy to **2a** and **2o**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.67 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.56 – 3.50 (m, 2H), 1.78 (ddq, *J* = 12.1, 3.5, 1.8 Hz, 1H), 1.76 – 1.69 (m, 3H), 1.65 (dddd, *J* = 12.6, 5.0, 3.2, 1.5 Hz, 1H), 1.62 – 1.55 (m, 1H), 1.49 – 1.42 (m, 1H), 1.30 – 1.18 (m, 2H), 1.14 (qt, *J* = 12.6, 3.3 Hz, 1H), 1.04 – 0.95 (m, 2H), 0.12 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 61.2, 47.7, 37.0, 35.2, 30.5, 30.4, 26.64, 26.57, 26.53, -0.4 ppm; **FT-IR** (thin-film) 2922, 2853, 1449, 1432, 1250, 1085, 1024, 996, 944, 891, 875, 839, 747, 684, 655, 625 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{12}H_{26}BrOSi$ $[M-H]^+$ 293.0931, found 293.0931; $[\alpha]_D = -2.2°$ (c = 1.0, $CHCl_3$).

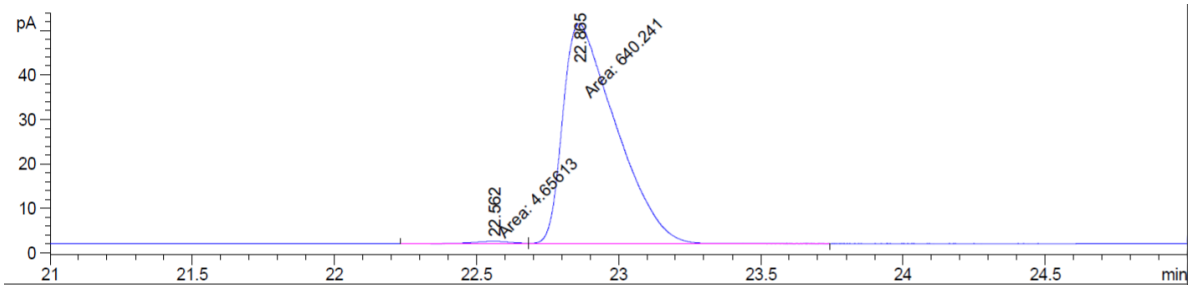
Racemic sample: GC (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi)



Signal 2: FID2 B, Back Signal

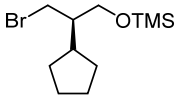
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.675	MF	0.1808	398.86673	36.77726	49.88176
2	23.154	FM	0.2089	400.75766	31.97166	50.11824

Enantioenriched sample: GC (CP-Chirasil-Dex CB – 25m x 0.25 mm x 0.25 µm, 125 °C for 25 minutes, 125→150 °C at 1°/min, 150→200 °C at 5°/min, 7 psi), 99% e.e.



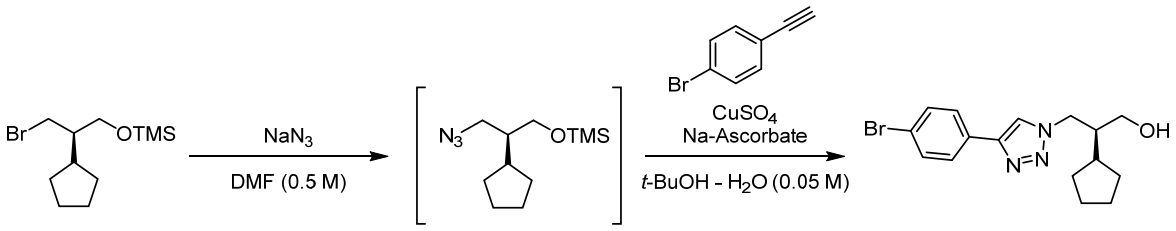
Signal 2: FID2 B, Back Signal

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.562	MF	0.1514	4.65613	5.12565e-1	0.72200
2	22.865	FM	0.2158	640.24121	49.45528	99.27800

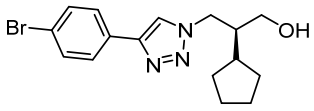


2o

(R)-(3-bromo-2-cyclopentylpropoxy)trimethylsilane (2o): Oxetane **1o** (50 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2o** (102.0 mg, 0.36 mmol, 91% yield). Separation conditions could not be identified to allow for the direct determination of the e.e. of **2o**, but its triazole derivative **26o** was determined to be of 93% e.e. by chiral HPLC analysis (see below). The absolute configuration of this compound was assigned by X-ray crystallographic analysis of its triazole derivative **26o**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.76 (dd, *J* = 9.8, 2.8 Hz, 1H), 3.71 – 3.67 (m, 1H), 3.56 – 3.50 (m, 2H), 1.92 – 1.83 (m, 1H), 1.83 – 1.71 (m, 2H), 1.69 – 1.59 (m, 2H), 1.59 – 1.47 (m, 3H), 1.20 – 1.07 (m, 2H), 0.12 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 62.0, 48.2, 39.7, 36.7, 30.9, 30.8, 25.3, 24.8, -0.4 ppm; **FT-IR** (thin-film): 2953, 2910, 2870, 1470, 1451, 1431, 1251, 1093, 872, 839, 747 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{11}H_{24}BrOSi$ $[M+H]^+$ 279.0774, found 279.0775; $[\alpha]_D = -3.4^o$ (c = 1.0, $CHCl_3$).



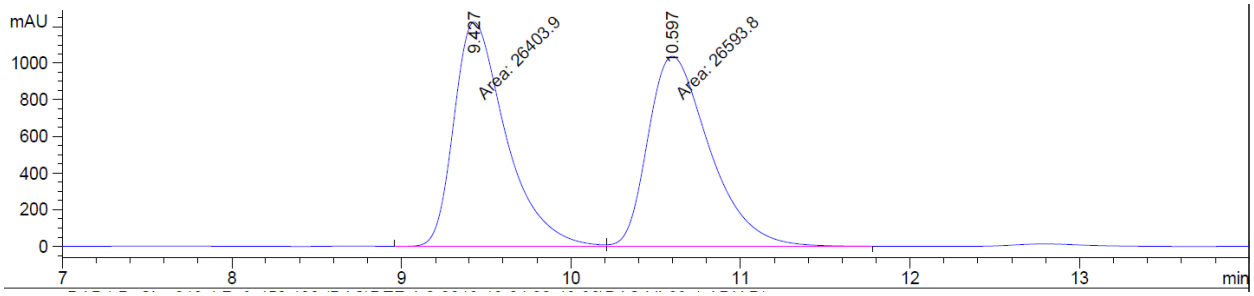
2o carried forward crude 26o



26o

(S)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-cyclopentylpropan-1-ol (26o): Alkyl bromide **2o** (50 mg, 0.179 mmol, 1 equiv.) was dissolved in DMF (1.4 mL, 0.125 M) and then sodium azide (47 mg, 0.716 mmol, 4 equiv.) was added. The reaction was allowed to proceed overnight at room temperature with vigorous stirring. The following day, the reaction was diluted with Et_2O and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was removed and the organic layer was washed 3x with saturated aqueous $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was carried forward assuming complete conversion by dissolving it in a 1 : 1 mixture of *t*-BuOH and water (1.79 mL of each solvent, 0.05 M overall). Then 1-bromo-4-ethynylbenzene (39 mg, 0.215 mmol, 1.2 equiv.), copper(II) sulfate pentahydrate (11 mg, 0.045 mmol, 0.25 equiv.), and sodium ascorbate (18 mg, 0.090 mmol, 0.5 equiv.) were added and the reaction was allowed to continue overnight at room temperature with vigorous stirring. The following day, the reaction was diluted with EtOAc and water. The organic layer was removed, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to yield triazole **26o** (54.5 mg, 0.156 mmol, 87% yield over both steps). **26o** was determined to be of 93% e.e. by chiral HPLC analysis (ChiralPak AD-H, 20% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 9.4 min, t_r(minor)= 10.7 min). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.58 (dd, *J* = 13.9, 4.4 Hz, 1H), 4.49 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.54 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.47 (dd, *J* = 11.4, 6.3 Hz, 1H), 2.84 – 2.66 (br, 1H), 1.97 (dtd, *J* = 11.3, 7.4, 3.0 Hz, 1H), 1.87 (dtt, *J* = 10.8, 7.2, 4.1 Hz, 1H), 1.79 (dtd, *J* = 10.0, 7.2, 2.7 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.69 – 1.61 (m, 2H), 1.60 – 1.45 (m, 2H), 1.25 (ddd, *J* = 14.2, 10.6, 6.4 Hz, 1H), 1.14 (dq, *J* = 11.7, 8.7 Hz, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.6, 132.1, 129.6, 127.3, 122.1, 121.2, 61.2, 50.3, 47.3, 39.2, 31.2, 30.9, 25.1, 25.0 ppm; **FT-IR** (thin-film): 3382 (br), 3134, 2952, 2868, 1549, 1481, 1453, 1402, 1357, 1226, 1194, 1070, 1052, 1011, 973, 824, 512 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{16}H_{21}BrN_3O$ $[M+H]^+$ 350.0863, found 350.0860; $[\alpha]_D = +6.0^o$ (c = 1.0, $CHCl_3$). A crystal suitable for X-ray diffraction of the HCl salt of **26o** was grown by vapor diffusion of an ethereal solution of HCl into a solution of triazole **26o** in diethyl ether, allowing for the assignment of the absolute configuration of **2o** (see section **SI-X-Ray crystallography** for crystallographic details).

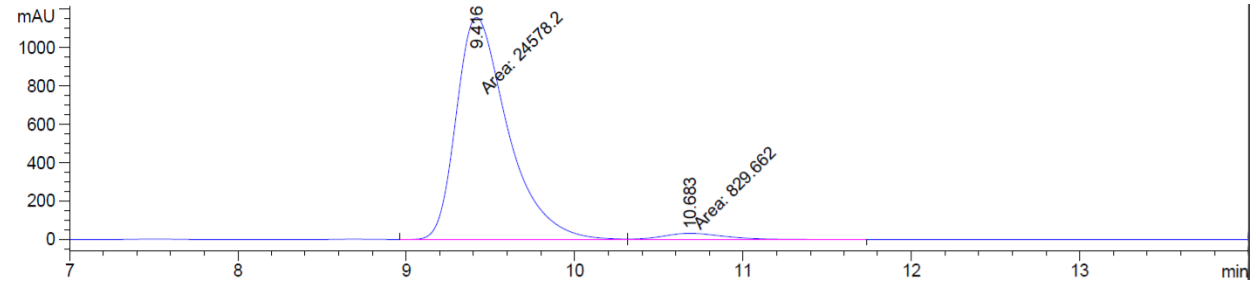
Racemic sample: HPLC (ChiralPak AD-H, 20% *i*-PrOH in hexanes, 1 mL/min, 230 nm)



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

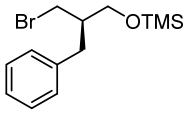
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.427	MF	0.3581	2.64039e4	1229.04126	49.8208
2	10.597	FM	0.4252	2.65938e4	1042.48926	50.1792

Enantioenriched sample: HPLC (ChiralPak AD-H, 20% *i*-PrOH in hexanes, 1 mL/min, 230 nm), 93% e.e.



Signal 3: DAD1 C, Sig=230,4 Ref=450,100

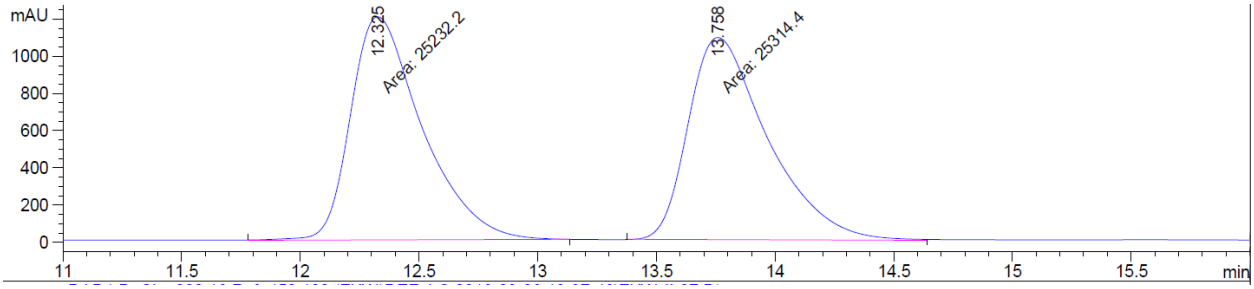
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.416	MF	0.3545	2.45782e4	1155.51648	96.7346
2	10.683	FM	0.4280	829.66180	32.30447	3.2654



2p

(R)-(2-benzyl-3-bromopropoxy)trimethylsilane (2p): Oxetane **1p** (59.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2p** (106.4 mg, 0.35 mmol, 88% yield). **2p** was determined to be of 85% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 14.2 min, t_r(minor)= 12.6 min). The absolute configuration of **2p** was assigned by analogy to **2a** and **2o**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 3.61 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.58 – 3.52 (m, 2H), 3.39 (dd, *J* = 9.9, 5.1 Hz, 1H), 2.72 – 2.63 (m, 2H), 2.10 (tddd, *J* = 11.7, 9.1, 5.8, 4.6 Hz, 1H), 0.12 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.5, 129.3, 128.6, 126.4, 62.9, 44.5, 36.0, 35.6, -0.4 ppm; **FT-IR** (thin-film) 3064, 3028, 2956, 2903, 2865, 1604, 1496, 1470, 1454, 1250, 1090, 1040, 978, 874, 837, 740, 699 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{10}H_{13}BrO$ $[M\text{-}TMS+H_2]^+$ 229.0223, found 229.0221; $[\alpha]_D = -2.3°$ (c = 1.0, $CHCl_3$).

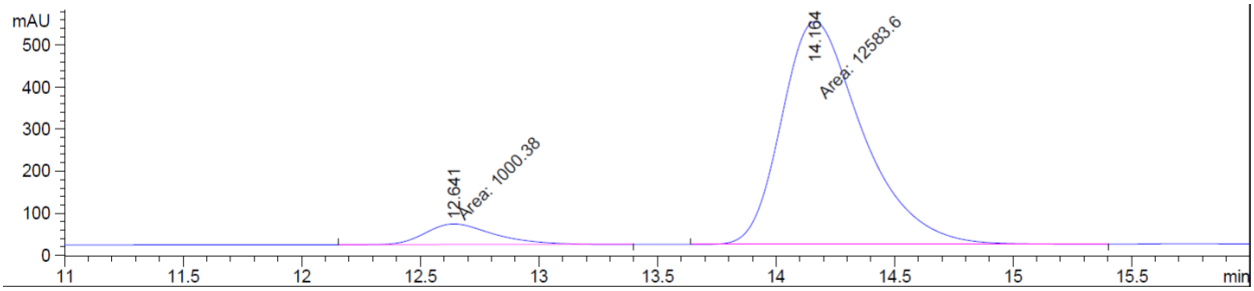
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

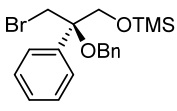
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.325	MM	0.3501	2.52322e4	1201.07080	49.9187
2	13.758	MM	0.3879	2.53144e4	1087.66833	50.0813

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 85% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

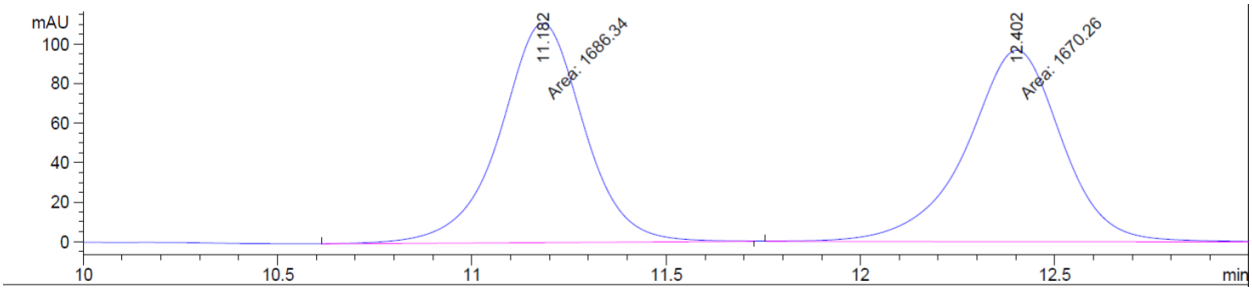
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.641	MM	0.3383	1000.37946	49.28965	7.3644
2	14.164	MM	0.3955	1.25836e4	530.24762	92.6356



2q

(R)-(2-(benzyloxy)-3-bromo-2-phenylpropoxy)trimethylsilane (2q): Oxetane **1q** (96.1 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure D to yield **2q** (92.4 mg, 0.24 mmol, 59% yield, 83% yield BRSM). **2q** was determined to be of 82% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 12.0 min, t_r(minor)= 10.9 min). The absolute configuration of **2q** was assigned by analogy to **2t**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.40 – 7.26 (m, 8H), 4.44 (d, J = 10.6 Hz, 1H), 4.31 (d, J = 10.6 Hz, 1H), 4.19 (d, J = 10.7 Hz, 1H), 4.12 (d, J = 9.9 Hz, 1H), 3.92 (dd, J = 10.7, 1.0 Hz, 1H), 3.80 (dd, J = 9.9, 1.0 Hz, 1H), −0.02 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.1, 138.4, 128.45, 128.42, 128.0, 127.8, 127.6, 127.2, 79.9, 66.0, 65.0, 36.2, -0.6 ppm; **FT-IR** (thin-film): 3089, 3063, 3032, 2955, 2875, 1496, 1447, 1251, 1155, 1107, 1068, 1028, 871, 838, 746, 730, 696, 590, 560 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{19}H_{26}BrO_2Si$ $[M+H]^+$ 393.0880, found 393.0873; $[\alpha]_D$ = +41.4° (c = 1.0, $CHCl_3$).

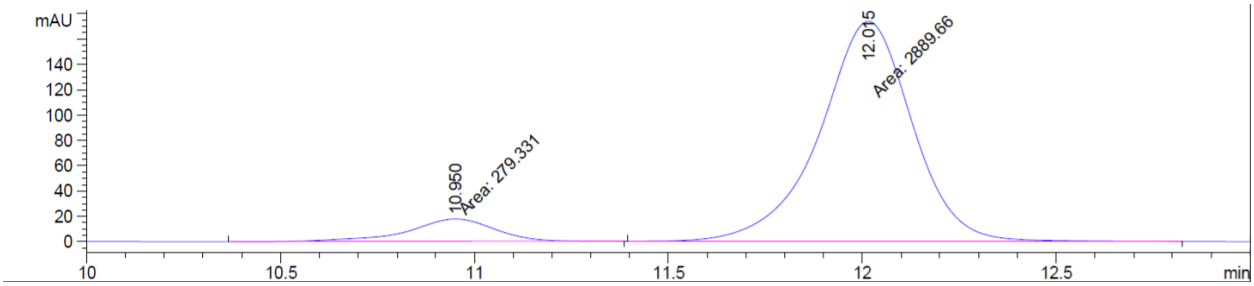
Racemic sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

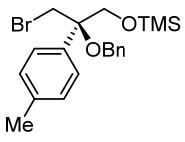
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.182	MM	0.2527	1686.33630	111.21729	50.2395
2	12.402	MM	0.2869	1670.26025	97.04285	49.7605

Enantioenriched sample: HPLC (ChiralPak IB, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 82% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

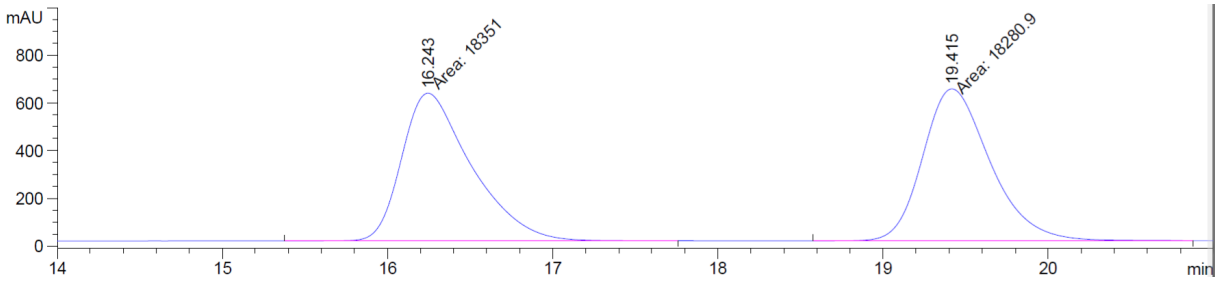
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.950	MM	0.2619	279.33066	17.77384	8.8145
2	12.015	MM	0.2771	2889.65698	173.78247	91.1855



2r

(R)-(2-(benzyloxy)-3-bromo-2-(p-tolyl)propoxy)trimethylsilane (2r): Oxetane **1r** (101.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure D to yield **2r** (125.9 mg, 0.31 mmol, 77% yield). **2r** was determined to be of 92% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 16.2 min, t_r(minor)= 19.4 min). The absolute configuration of **2r** was assigned by analogy to **2t**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 2H), 4.41 (d, *J* = 10.6 Hz, 1H), 4.30 (d, *J* = 10.7 Hz, 1H), 4.14 (dd, *J* = 10.7, 0.8 Hz, 1H), 4.10 (d, *J* = 9.9 Hz, 1H), 3.92 – 3.89 (m, 1H), 3.81 (dd, *J* = 10.0, 0.8 Hz, 1H), 2.36 (s, 3H), 0.00 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.5, 137.6, 136.9, 129.1, 128.4, 127.8, 127.5, 127.0, 79.8, 65.8, 64.9, 36.4, 21.2, -0.6 ppm; **FT-IR** (thin-film): 3031, 2955, 2923, 2873, 1512, 1498, 1454, 1425, 1382, 1250, 1158, 1105, 1069, 1028, 872, 839, 824, 746, 734, 695, 667, 562, 547, 480 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{20}H_{27}BrO_2SiNa$ $[M+Na]^+$ 429.0856, found 429.0851; $[\alpha]_D$ = +44.4° (c = 1.0, $CHCl_3$).

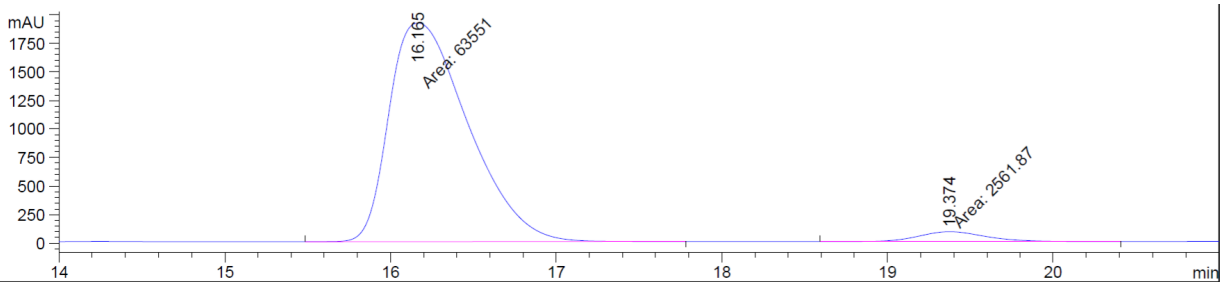
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

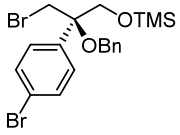
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.243	MM	0.4927	1.83510e4	620.80194	50.0957
2	19.415	MM	0.4773	1.82809e4	638.35321	49.9043

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 92% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

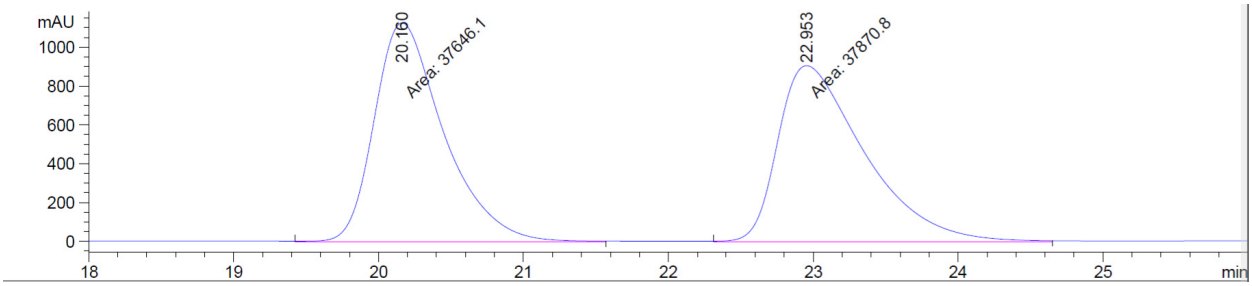
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.165	MM	0.5525	6.35510e4	1917.15662	96.1250
2	19.374	MM	0.4877	2561.87378	87.55840	3.8750



2s

(R)-(2-(benzyloxy)-3-bromo-2-(4-bromophenyl)propoxy)trimethylsilane (2s): Oxetane **1s** (127.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure D to yield **2s** (133.3 mg, 0.28 mmol, 71% yield, 95% yield BRSM). **3s** was determined to be of 91% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 20.2 min, t_r(minor)= 23.3 min). The absolute configuration of **2s** was assigned by analogy to **2t**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.39 – 7.27 (m, 7H), 4.44 (d, *J* = 10.6 Hz, 1H), 4.29 (d, *J* = 10.5 Hz, 1H), 4.12 (d, *J* = 10.8 Hz, 1H), 4.09 (d, *J* = 9.9 Hz, 1H), 3.86 (dd, *J* = 10.9, 1.0 Hz, 1H), 3.74 (dd, *J* = 10.0, 1.0 Hz, 1H), 0.01 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.3, 138.1, 131.6, 129.0, 128.5, 127.8 (this peak was revealed upon application of nonstandard exponential apodization), 127.7, 122.1, 79.7, 65.8, 65.1, 35.7, -0.6 ppm; **FT-IR** (thin-film): 3065, 3032, 2955, 2923, 2874, 1589, 1486, 1454, 1425, 1397, 1251, 1159, 1110, 1074, 1009, 872, 841, 750, 735, 696, 621, 557 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{19}H_{24}Br_2O_2SiNa$ $[M+Na]^+$ 492.9805, found 492.9800; $[\alpha]_D$ = +50.6° (c = 1.0, $CHCl_3$).

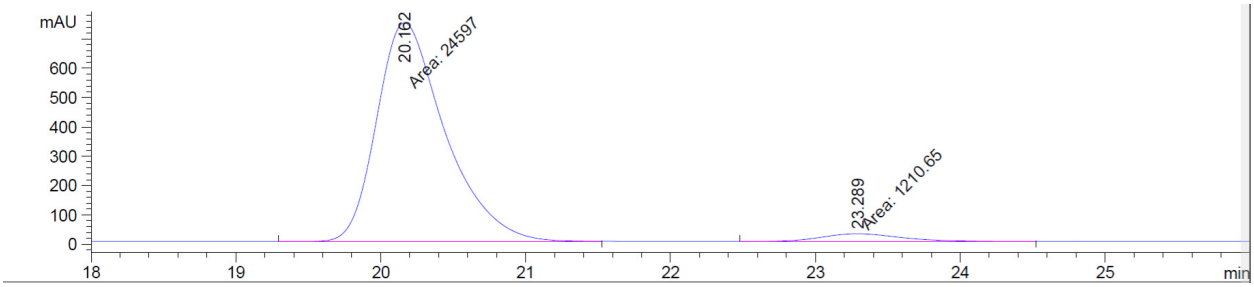
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

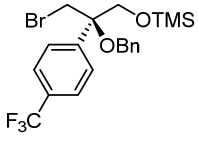
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.160	MM	0.5559	3.76461e4	1128.75415	49.8512
2	22.953	MM	0.6939	3.78708e4	909.57452	50.1488

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 91% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.162	MM	0.5489	2.45970e4	746.92047	95.3090
2	23.289	MM	0.7187	1210.64600	28.07631	4.6910

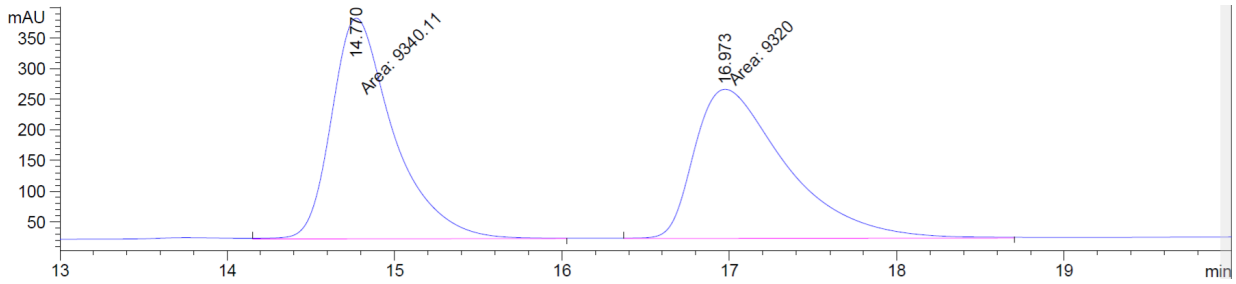


2t

(R)-(2-(benzyloxy)-3-bromo-2-(4-(trifluoromethyl)phenyl)propoxy)trimethylsilane (2t): Oxetane **1t** (123.3 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure D to yield **2t** (110.4 mg, 0.24 mmol, 60% yield, 85% yield BRSM). **2t** was determined to be of 88% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 14.8 min, t_r(minor)= 17.0 min). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 – 7.63 (m, 2H), 7.60 – 7.57 (m, 2H), 7.40 – 7.34 (m, 4H), 7.32 – 7.28 (m, 1H), 4.48, (d, J = 10.6 Hz, 1H), 4.31 (d, J = 10.5 Hz, 1H), 4.17 (d, J = 10.9 Hz, 1H), 4.12 (d, J = 10.0 Hz, 1H), 3.89 (dd, J = 10.9, 1.0 Hz, 1H), 3.77 (dd, J = 10.0, 1.0 Hz, 1H), 0.00 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 138.0, 130.2 (q, J = 32.6 Hz), 128.6, 127.8, 127.8, 127.6, 125.3 (q, J = 3.7 Hz), 124.2 (q, J = 272.1 Hz), 79.9, 66.0, 65.2, 35.5, −0.7 ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ −62.62 ppm; **FT-IR** (thin-film): 3033, 2957, 2875, 1618, 1498, 1455, 1410, 1327, 1252, 1165, 1111, 1070, 1016, 872, 842, 745, 696, 612, 460 cm^{-1}; **HRMS** (FTMS + p APCI corona) calculated for $C_{20}H_{24}BrF_3O_2SiNa$ $[M+Na]^+$ 483.0573, found 483.0572; $[\alpha]_D$ = +37.6° (c = 1.0, $CHCl_3$). A crystal

suitable for X-ray diffraction grew spontaneously upon allowing a sample of **2t** that had been concentrated from Et_2O to stand on the bench, allowing for the assignment of its absolute configuration (see section **SI-X-Ray crystallography** for crystallographic details).

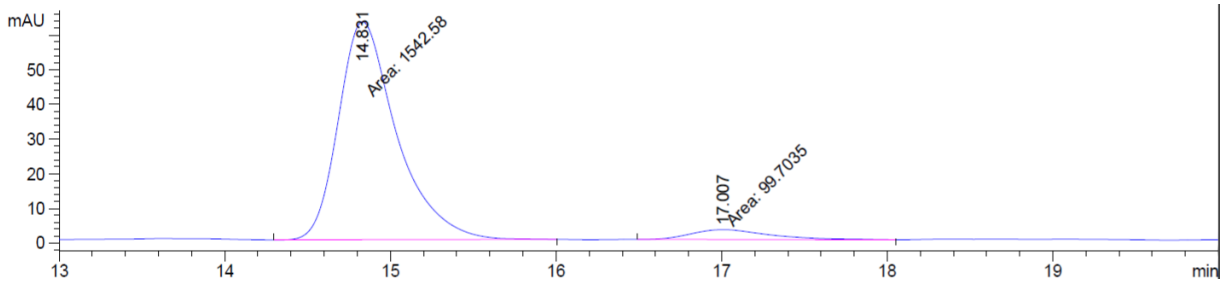
Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

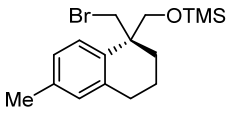
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.770	MM	0.4310	9340.11426	361.14682	50.0539
2	16.973	MM	0.6361	9320.00391	244.19301	49.9461

Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 88% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.831	MM	0.4082	1542.58252	62.98191	93.9290
2	17.007	MM	0.5693	99.70345	2.91901	6.0710

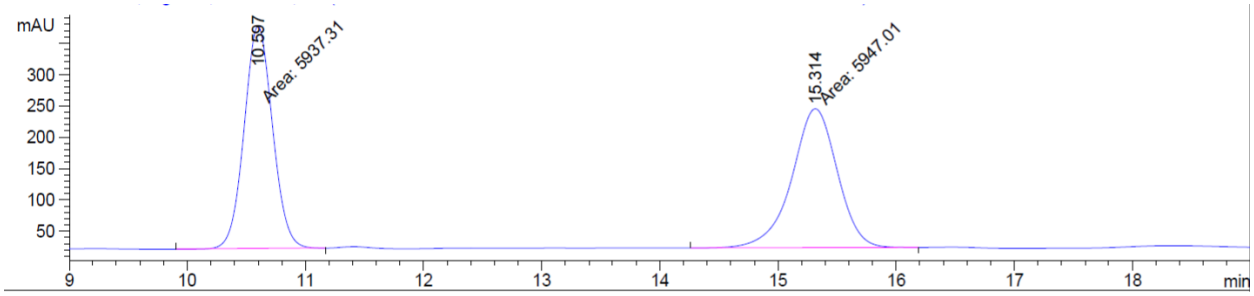


2u

(S)-((1-(bromomethyl)-6-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)trimethylsilane (2u): Oxetane **1u** (75 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B with the following modifications: 7.5 mol% of catalyst **3a** was used, the reaction was run at −65 °C, and 3 M HCl was required for the deprotection of the silyl ether for HPLC analysis. Since trace starting material remained in the crude product, it was purified by flash column chromatography to yield **2u** (121.6 mg, 0.36 mmol, 89% yield). **2u** was determined to be of 88% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 15.3 min, t_r(minor)= 10.4 min). The absolute configuration of this compound was assigned by X-ray crystallographic analysis of its triazole derivative **26u** (see below). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.92 (s, 1H), 3.83 (dd, *J* = 10.3, 0.9 Hz, 1H), 3.74 –

3.68 (m, 2H), 3.56 (dd, J = 10.2, 1.0 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.29 (s, 3H), 1.96 (ddd, J = 12.7, 10.2, 2.9 Hz, 1H), 1.87 – 1.69 (m, 3H), 0.09 (s, 9H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.1, 136.2, 135.2, 130.0, 127.5, 126.8, 68.3, 42.8, 42.6, 30.5, 28.9, 21.1, 19.2, -0.5 ppm; **FT-IR** (thin-film) 3004, 2936, 2864, 1614, 1498, 1458, 1250, 1096, 1079, 1023, 872, 836, 746, 704, 639, 562 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{16}H_{24}BrOSi$ $[M-H]^+$ 339.0774, found 339.0773; $[\alpha]_D$ = +38.8° (c = 1.0, $CHCl_3$).

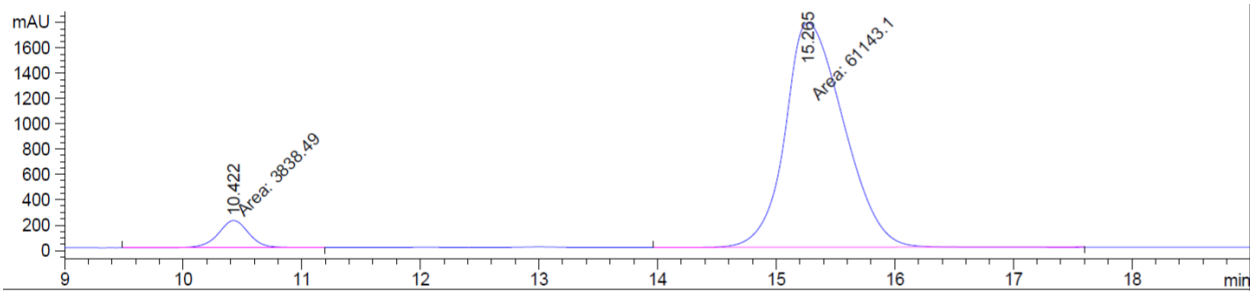
Racemic sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

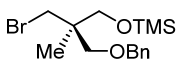
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.597	MM	0.2789	5937.31055	354.83820	49.9592
2	15.314	MM	0.4474	5947.01416	221.55240	50.0408

Enantioenriched sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 88% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.422	MM	0.2985	3838.49194	214.35403	5.9070
2	15.265	MM	0.5743	6.11431e4	1774.39746	94.0930

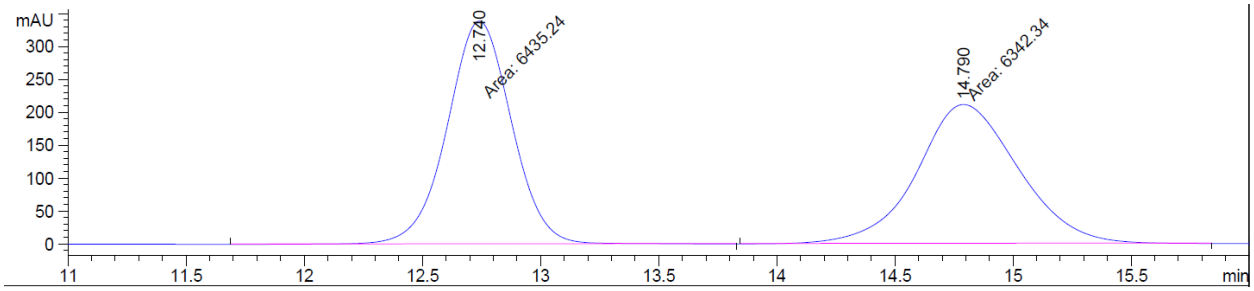


2v

(R)-(3-(benzyloxy)-2-(bromomethyl)-2-methylpropoxy)trimethylsilane (2v): Oxetane **1v** (76.9 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B with the following modifications: 7.5 mol% of catalyst **3a** was used, the reaction was run for 48 hours, and 3 M HCl was required for deprotection of the silyl ether for HPLC analysis. The reaction yielded **2v** (133.5 mg, 0.39 mmol, 97% yield). **2v** was determined to be of 67% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 13.7 min, t_r(minor)= 11.9 min).

The absolute configuration of this compound was assigned by analogy to chlorohydrin analogue **28** formed via the opening of **1v** with TMSCl catalyzed by squaramide **3a** (see below). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.30 – 7.26 (m, 1H), 4.50 (s, 2H), 3.50 – 3.43 (m, 4H), 3.35 (s, 2H), 1.01 (s, 3H), 0.09 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7, 128.4, 127.6, 127.5, 73.5, 73.2, 65.5, 41.2, 40.0, 18.7, -0.4 ppm; **FT-IR** (thin-film): 2957, 2901, 2860, 1497, 1474, 1427, 1386, 1364, 1251, 1086, 1028, 874, 840, 746, 697, 661, 608 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{15}H_{26}BrO_2Si$ $[M+H]^+$ 345.0880, found 345.0878; $[\alpha]_D = -21°$ (c = 1.0, $CHCl_3$).

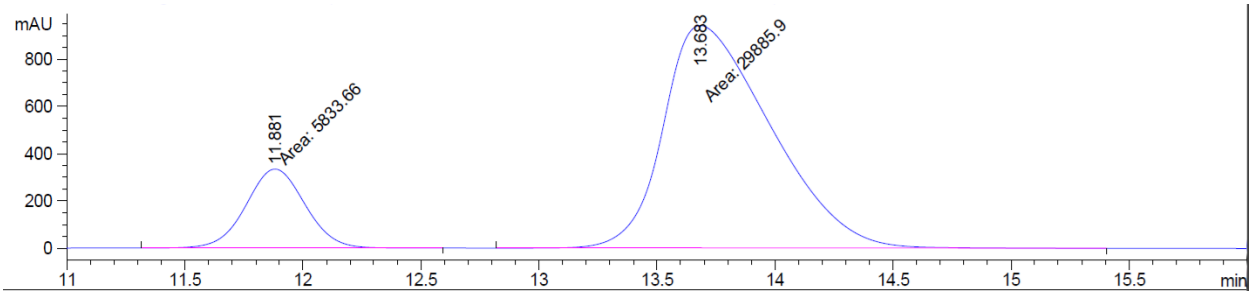
Racemic sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

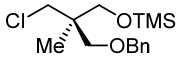
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.740	MM	0.3165	6435.23682	338.83606	50.3635
2	14.790	MM	0.5000	6342.34473	211.43150	49.6365

Enantioenriched sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 67% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

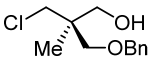
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.881	MM	0.2908	5833.66357	334.31403	16.3318
2	13.683	MM	0.5283	2.98859e4	942.84674	83.6682



27

(R)-(3-(benzyloxy)-2-(chloromethyl)-2-methylpropoxy)trimethylsilane (27): Oxetane **1v** (76.9 mg, 0.4 mmol, 1 equiv.) and squaramide **3a** (20.5 mg, 0.03 mmol, 0.075 equiv.) were weighed into an oven-dried 2-dram vial equipped with a magnetic stir bar and closed with a screw-cap containing a rubber septum. The compounds were dissolved in *t*-BuOMe (4 mL, 0.1 M) and the headspace of the vial was flushed with nitrogen for 15 seconds after which the vial was cooled to -78 °C in a dry

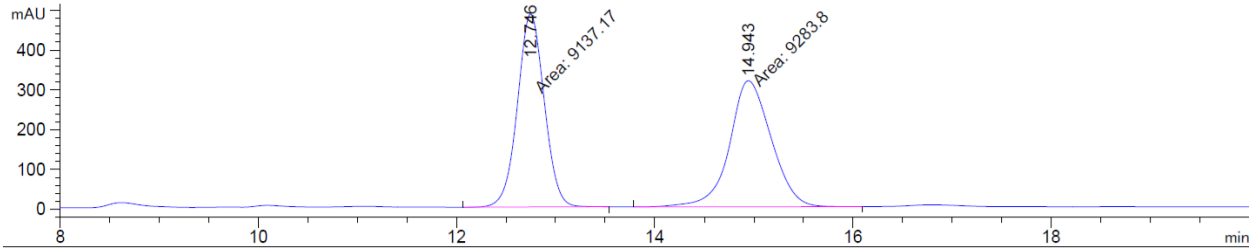
ice-acetone bath, allowing 15 minutes for the temperature to equilibrate. Then TMSCl was added (0.1 mL, 0.8 mmol, 2 equiv.). The reaction was allowed to continue stirring at -78 °C for 30 minutes, after which it was transferred to a -30 °C freezer and allowed to continue for 5 days without stirring. The reaction was then quenched by the addition of a 1:1 solution of *i*-PrOH-Et_3N (0.4 mL). After an additional 5 minutes at -30 °C, the reaction was diluted with Et_2O and saturated aqueous $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield **27** (35.5 mg, 0.12 mmol, 30% yield). The e.e. and absolute configuration of this compound was assigned by its desilylated derivative **28** (see below). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.32 – 7.26 (m, 1H), 4.51 (s, 2H), 3.60 – 3.54 (m, 2H), 3.50 – 3.45 (m, 2H), 3.37 – 3.32 (m, 2H), 1.00 (s, 3H), 0.10 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.8, 128.4, 127.6, 127.5, 73.5, 72.7, 65.0, 49.2, 41.9, 17.8, -0.5 ppm; **FT-IR** (thin-film): 3031, 2956, 2901, 2862, 1726, 1497, 1475, 1454, 1434, 1408, 1364, 1251, 1206, 1086, 1028, 872, 839, 746, 733, 697, 608 cm^{-1}; **HRMS** (FTMS + p ESI) calculated for $C_{15}H_{26}ClO_2Si$ $[M+H]^+$ 301.1385, found 301.1387; $[\alpha]_D = -1.6°$ (c = 1.0, $CHCl_3$).



28

(S)-3-(benzyloxy)-2-(chloromethyl)-2-methylpropan-1-ol (28): Silyl-protected chlorohydrin **27** (35.5 mg, 0.12 mmol, 1 equiv.) was dissolved in THF (1.2 mL, 0.1 M) and cooled to 0 °C in an ice-bath. A solution of tetrabutylammonium fluoride (0.18 mL of a 1 M solution in THF, 0.18 mmol, 1 equiv.) was added, and then the ice-bath was removed allowing the reaction to warm to room temperature. After 45 minutes at room temperature, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and diluted with Et_2O. The organic layer was removed and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography to yield **28** (22.8 mg, 0.10 mmol, 84% yield). **28** was determined to be of 69% e.e. by chiral HPLC analysis (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 14.6 min, t_r(minor)= 12.9 min). The spectral data and sign of the optical rotation were consistent with previous literature reports for the (S)-enantiomer of this compound[21,22], allowing the assignment of the absolute configuration. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.31 (m, 3H), 4.53 (s, 2H), 3.72 (d, *J* = 10.9 Hz, 1H), 3.66 – 3.61 (m, 2H), 3.56 (dd, *J* = 11.2, 1.1 Hz, 1H), 3.51 (dd, *J* = 9.1, 1.1 Hz, 1H), 3.44 (d, *J* = 9.1 Hz, 1H), 2.52 (br, 1H) 0.93 (s, 3H) ppm; $[\alpha]_D = +3.8°$ (c = 1.0, $CHCl_3$).

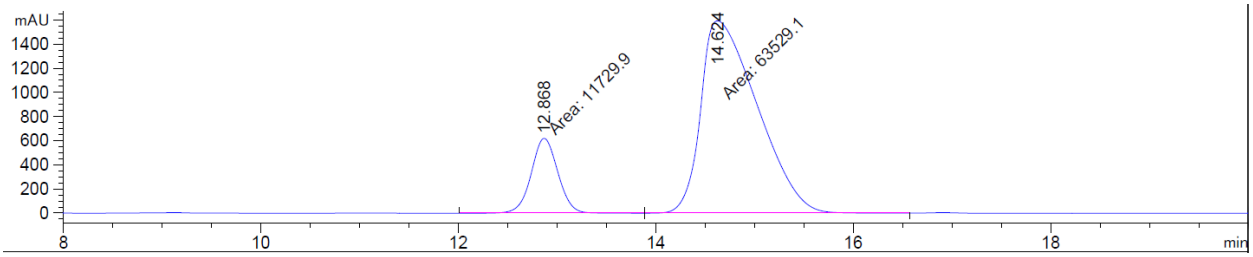
Racemic sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.746	MM	0.3139	9137.17383	485.07922	49.6020
2	14.943	MM	0.4880	9283.79785	317.05579	50.3980

Enantioenriched sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 69% e.e.

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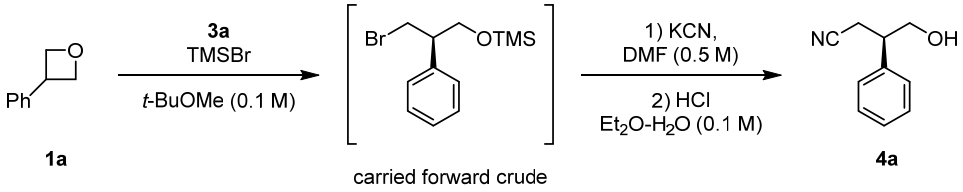
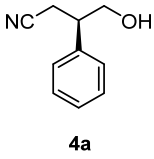
Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|-------|
   1  12.868 MM    0.3145 1.17299e4   621.63062  15.5861
   2  14.624 MM    0.6634 6.35291e4  1595.98853  84.4139
```

Procedures and characterization data for derivatizations of products:

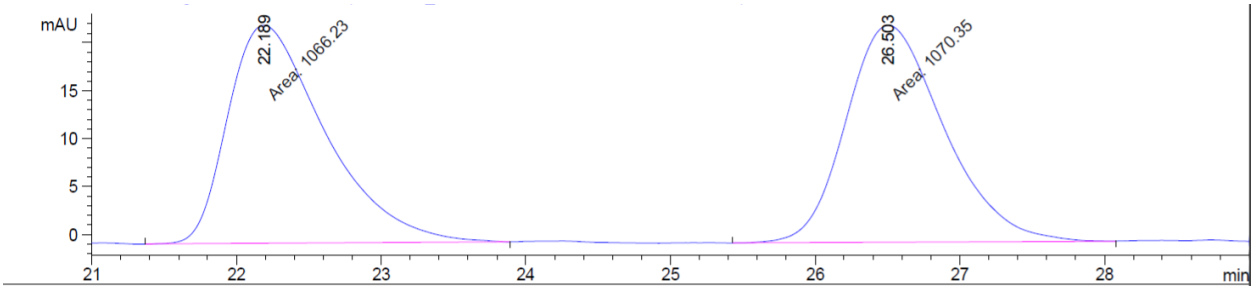




4a

(R)-4-hydroxy-3-phenylbutanenitrile (4a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a**, which was immediately carried forward crude. The crude alkyl bromide **2a** was dissolved in DMF (0.8 mL, 0.5 M) and KCN (78 mg, 1.2 mmol, 3 equiv.) was added. The solution was heated to 50 °C for three days after which it was cooled to room temperature and diluted with Et_2O and saturated aqueous $NaHCO_3$. The aqueous layer was removed, and the organic layer was washed 2x with saturated aqueous $NaHCO_3$ to ensure removal of any unreacted KCN. The organic layer was then concentrated under vacuum, and the resulting oil was dissolved in Et_2O (2 mL, 0.2 M) and aqueous 1 M HCl (2 mL) was added. The biphasic solution was stirred vigorously until TLC indicated complete conversion of the TMS-protected product to the free alcohol (~30 minutes) and then the reaction was diluted with Et_2O and water. The organic layer was removed and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield nitrile **4a** (40.3 mg, 0.25 mmol, 62% yield from 3-phenyloxetane). **4a** was determined to be of 97% e.e. by chiral HPLC analysis (ChiralPak AS-H, 10% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 21.7 min, t_r(minor)= 26.8 min). The absolute configuration of **4a** was assigned based on that of **2a**. The spectral data and the sign of the optical rotation were consistent with a previous literature report[10]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.28 – 7.25 (m, 2H), 3.95 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.88 (dd, *J* = 10.9, 6.9 Hz, 1H), 3.20 (p, *J* = 6.6 Hz, 1H), 2.86 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.73 (dd, *J* = 16.8, 7.6 Hz, 1H), 1.53 (s, 1H) ppm; $[\alpha]_D = -30.0^o$ (c = 1.0, $CHCl_3$).

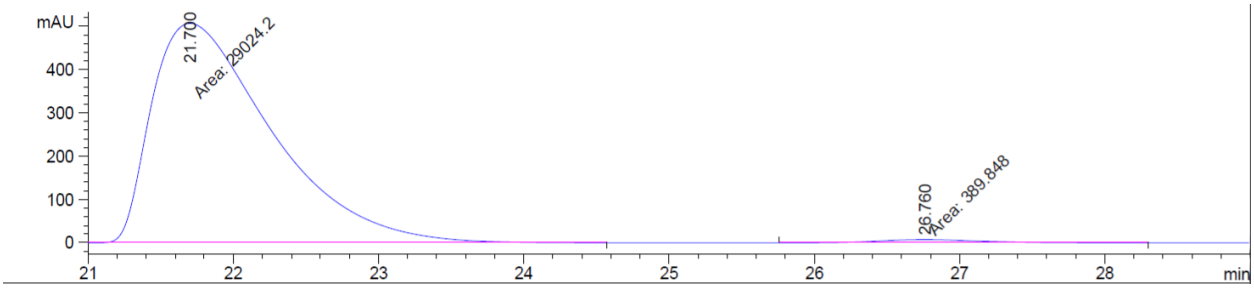
Racemic sample: HPLC (ChiralPak AS-H, 10% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

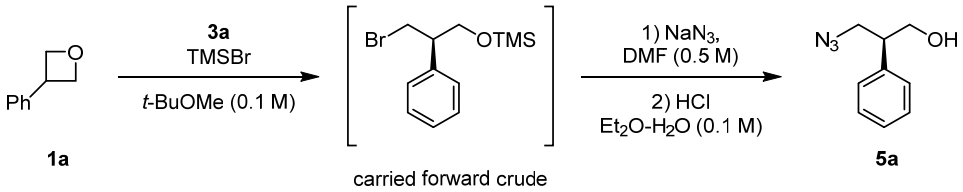
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.189	MM	0.7801	1066.22876	22.77945	49.9035
2	26.503	MM	0.7869	1070.35254	22.67056	50.0965

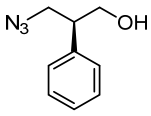
Enantioenriched sample: HPLC (ChiralPak AS-H, 10% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.700	MM	0.9540	2.90242e4	507.05762	98.6746
2	26.760	MM	0.8620	389.84848	7.53753	1.3254

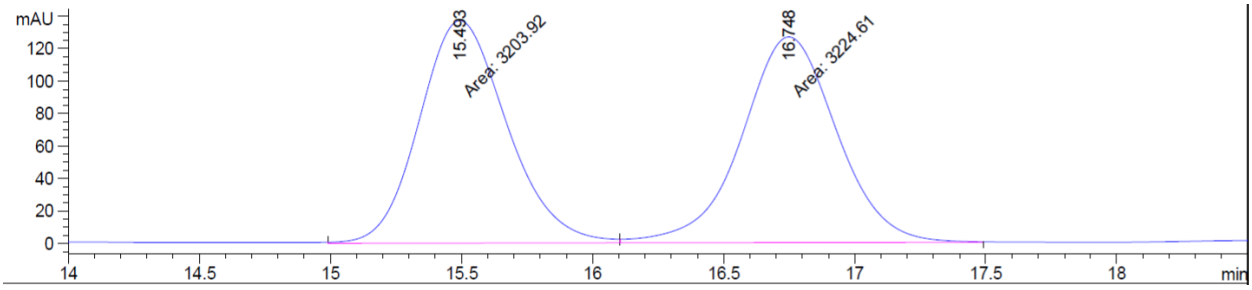




5a

(S)-3-azido-2-phenylpropan-1-ol (5a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a**, which was immediately carried forward crude. The crude alkyl bromide **2a** was dissolved in DMF (0.8 mL, 0.5 M) and NaN_3 (104 mg, 1.6 mmol, 4 equiv.) was added. The solution was allowed to stir at room temperature for three days after which it was diluted with Et_2O and saturated aqueous $NaHCO_3$. The aqueous layer was removed, and the organic layer was washed 2x with saturated aqueous $NaHCO_3$ to ensure removal of any unreacted NaN_3. The organic layer was then concentrated under vacuum, and the resulting oil was dissolved in Et_2O (2 mL, 0.2 M) and aqueous 1 M HCl (2 mL) was added. The biphasic solution was stirred vigorously until TLC indicated complete conversion of the TMS-protected product to the free alcohol (~30 minutes) and then the reaction was diluted with Et_2O and water. The organic layer was removed and the aqueous layer was extracted 3x with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield **5a** (58.2 mg, 0.33 mmol, 82% yield from 3-phenyloxetane). **5a** was determined to be of 97% e.e. by chiral HPLC analysis (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 17.0 min, t_r(minor)= 15.8 min). The absolute configuration of **5a** was assigned based on that of **2a**. The spectral data and the sign of the optical rotation were consistent with a previous literature report[10]: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.31 – 7.28 (m, 1H), 7.26 – 7.24 (m, 2H), 3.93 – 3.86 (m, 2H), 3.72 – 3.62 (m, 2H), 3.08 (p, J = 6.6 Hz, 1H), 1.50 (s, 1H) ppm; $[\alpha]_D = -18.0^o$ (c = 1.0, $CHCl_3$).

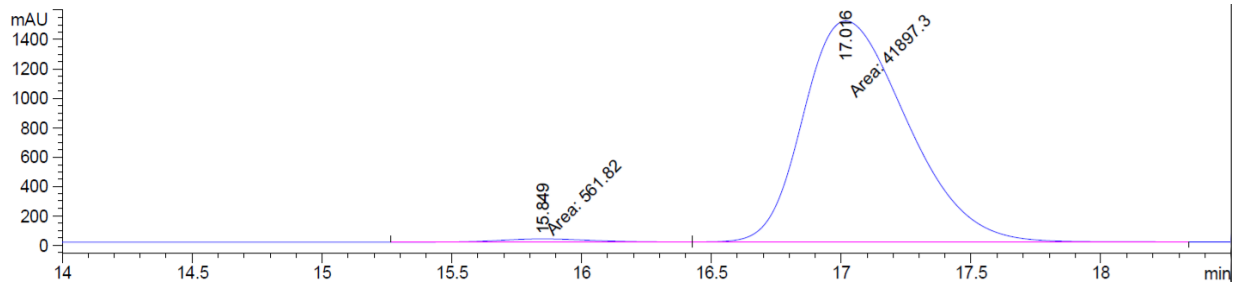
Racemic sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

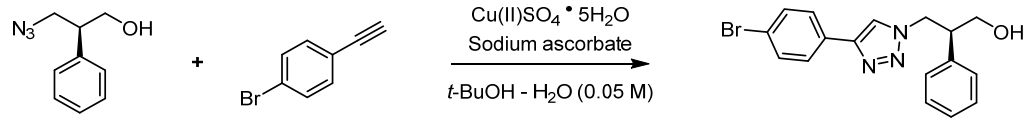
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.493	MF	0.3887	3203.92285	137.39435	49.8391
2	16.748	FM	0.4230	3224.61182	127.06793	50.1609

Enantioenriched sample: HPLC (ChiralPak AS-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.

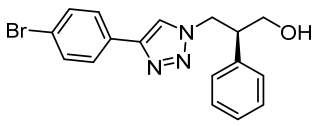


Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.849	MF	0.4238	561.81952	22.09209	1.3232
2	17.016	FM	0.4641	4.18973e4	1504.69788	98.6768



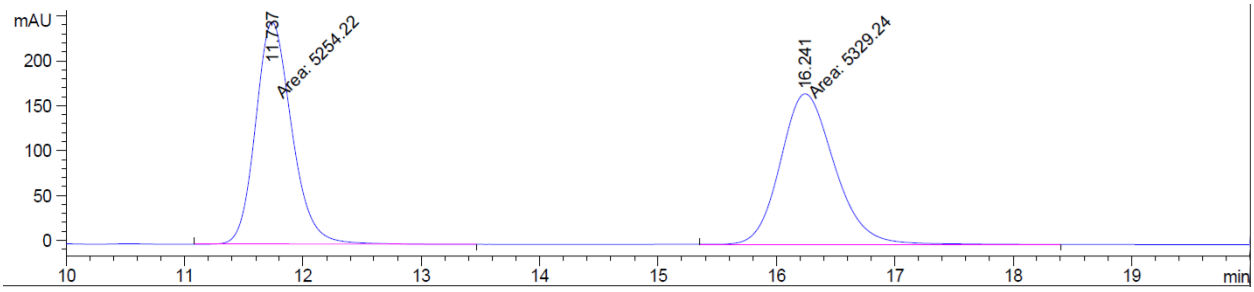
6a **26a**



26a

(S)-3-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)-2-phenylpropan-1-ol (26a): Azide **5a** (30 mg, 0.17 mmol, 1 equiv.) was dissolved in a 1 : 1 mixture of *t*-BuOH and water (1.69 mL of each solvent, 0.05 M overall). Then 1-bromo-4-ethynylbenzene (37 mg, 0.20 mmol, 1.2 equiv.), copper(II) sulfate pentahydrate (10.6 mg, 0.042 mmol, 0.25 equiv.), and sodium ascorbate (17 mg, 0.085 mmol, 0.5 equiv.) were added and the reaction was allowed to continue overnight at room temperature with vigorous stirring. The following day, the reaction was diluted with EtOAc and water. The organic layer was removed, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to yield triazole **26a** (61.0 mg, 0.17 mmol, 100% yield). **26a** was determined to be of 97% e.e. by chiral HPLC analysis (ChiralCel OJ-H, 30% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 16.4 min, t_r(minor)= 11.7 min). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.44 (s, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.17 (d, *J* = 6.8 Hz, 2H), 4.88 (dd, *J* = 13.8, 6.8 Hz, 1H), 4.65 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.87 (d, *J* = 5.9 Hz, 2H), 3.43 (p, *J* = 6.5 Hz, 1H), 2.63 – 2.46 (br, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.5, 138.6, 132.1, 129.5, 129.1, 128.0, 127.9, 127.3, 122.1, 120.8, 63.7, 52.3, 48.7 ppm; **FT-IR** (thin-film): 3354 (br), 3133, 3087, 3063, 3030, 2929, 2874, 1495, 1481, 1454, 1401, 1360, 1226, 1193, 1069, 1049, 1011, 975, 908, 819, 764, 732, 700, 543, 514 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{17}H_{17}BrN_3O$ $[M+H]^+$ 358.0550, found 358.0548; $[\alpha]_D$ = –65.8° (c = 1.0, $CHCl_3$). A crystal suitable for X-ray diffraction of the HCl salt of **26a** was grown by vapor diffusion of an ethereal solution of HCl into a solution of triazole **26a** in diethyl ether, allowing for the assignment of the absolute configuration of **2a** (see section **SI-X-Ray crystallography** for crystallographic details).

Racemic sample: HPLC (ChiralCel OJ-H, 30% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

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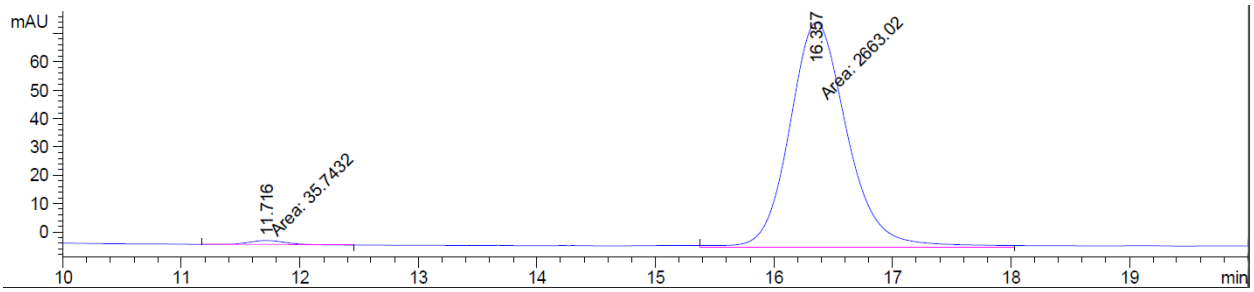
2	16.241	MM	0.5308	5329.23682	167.33211	50.3544

Enantioenriched sample: HPLC (ChiralCel OJ-H, 30% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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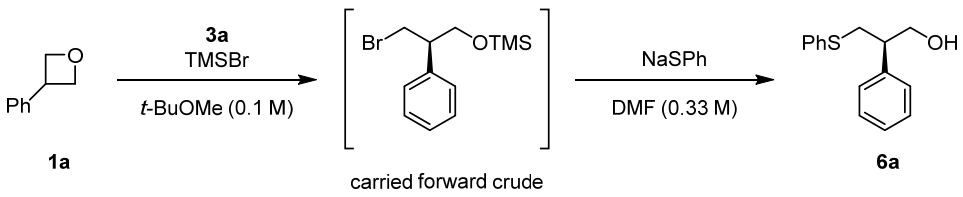
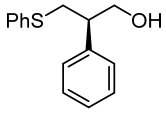
2	16.357	MM	0.5608	2663.02222	79.14651	98.6756

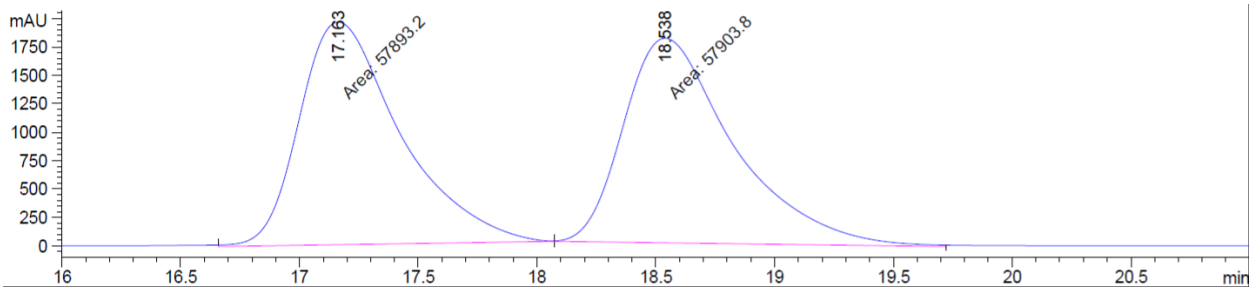




6a

(R)-2-phenyl-3-(phenylthio)propan-1-ol (6a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a** which was immediately carried forward crude. The crude alkyl bromide **2a** was dissolved in DMF (1.2 mL, 0.33 M) and NaSPh (79 mg, 0.6 mmol, 1.5 equiv.) was added. The solution was allowed to stir at room temperature overnight, after which it was diluted with Et_2O and saturated aqueous $NaHCO_3$. The aqueous layer was removed, and the organic layer was washed 2x with saturated aqueous $NaHCO_3$, then washed with brine, dried over $MgSO_4$, filtered, and concentrated. An NMR of the crude product revealed a mixture of silylated and desilylated material, so the crude oil was dissolved in Et_2O (2 mL, 0.2 M) and aqueous 2 M HCl (2 mL) was added. The biphasic solution was stirred vigorously until TLC indicated complete conversion of the TMS-protected product to the free alcohol (~1 hour) and then the reaction was diluted with Et_2O and water. The aqueous layer was removed, and the organic layer was washed with saturated aqueous $NaHCO_3$ followed by brine, dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography to yield thioether **6a** (87.2 mg, 0.36 mmol, 89% yield from 3-phenyloxetane). **6a** was determined to be of 97% e.e. by chiral HPLC analysis (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 17.9 min, t_r(minor)= 19.3 min). The absolute configuration of **6a** was assigned based on that of **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.30 – 7.26 (m, 3H), 7.25 – 7.21 (m, 2H), 7.21 – 7.16 (m, 1H), 3.96 – 3.89 (m, 2H), 3.34 (dd, *J* = 13.1, 7.8 Hz, 1H), 3.24 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.07 (p, *J* = 6.7 Hz, 1H), 1.61 – 1.36 (br, 1H) ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.0, 136.3, 129.3, 129.0, 128.8, 128.0, 127.3, 126.1, 66.1, 47.5, 36.2 ppm; **FT-IR** (thin-film): 3364 (br), 3058, 3027, 2923, 2873, 1582, 1494, 1480, 1452, 1438, 1087, 1052, 1024, 906, 736, 689, 537, 473 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{15}H_{16}OS^{\bullet}$ $[M^{\bullet}]^+$ 244.0916, found 244.0915; $[\alpha]_D = -54.6^{\circ}$ (c = 1.0, $CHCl_3$).

Racemic sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)

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Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak RetTime Type  Width     Area      Height     Area
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   1  17.163 MM    0.4919 5.78932e4  1961.43469  49.9954
   2  18.538 MM    0.5355 5.79038e4  1802.13635  50.0046
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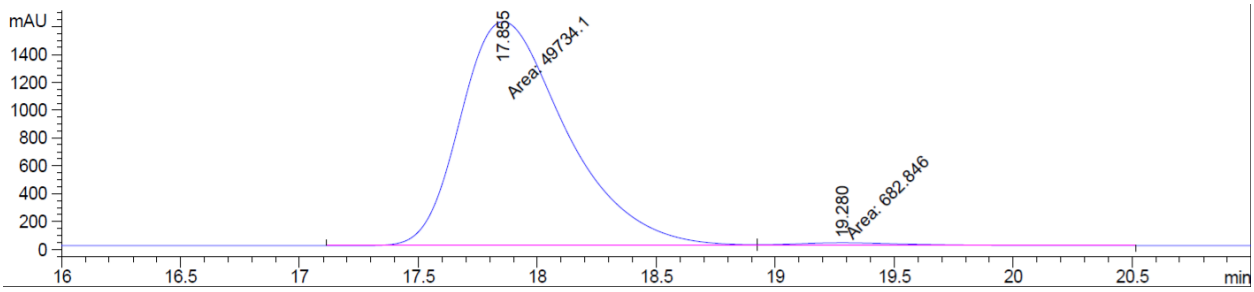
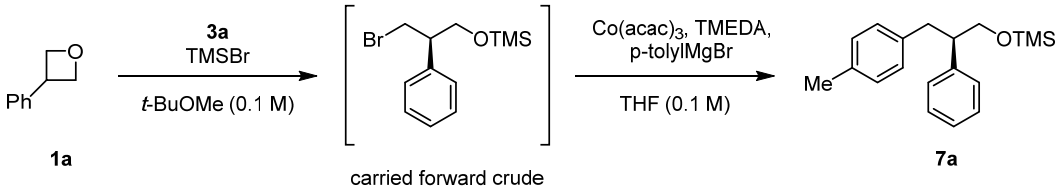
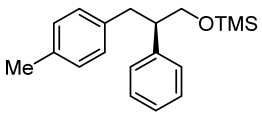
Enantioenriched sample: HPLC (ChiralPak AD-H, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.855	MF	0.5153	4.97341e4	1608.62207	98.6456
2	19.280	FM	0.5700	682.84619	19.96699	1.3544

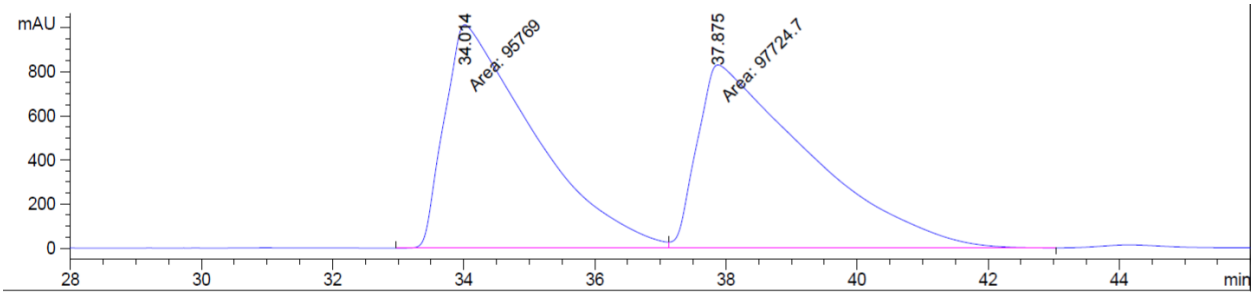




7a

(R)-trimethyl(2-phenyl-3-(p-tolyl)propoxy)silane (7a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a** which was immediately carried forward crude following a procedure reported by Cahiez.[23] The crude alkyl bromide **2a**, cobalt(III) acetylacetone (7.1 mg, 0.02 mmol, 0.05 equiv.) and TMEDA (3.0 uL, 0.02 mmol, 0.05 equiv.) were added to an oven-dried 2-dram vial, placed under an atmosphere of nitrogen, and dissolved in THF (4.0 mL, 0.1 M). The solution was cooled to 0 °C and then p-tolylmagnesium bromide (0.44 mL of a 1 M solution in THF, 0.44 mmol, 1.1 equiv.) was added at a rate of 10 uL/min using a syringe pump. After the addition was complete, the reaction was allowed to continue stirring at 0 °C for 30 minutes, after which it was quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was removed, and the aqueous layer was extracted 3x with Et_2O. Then the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography to yield **7a** (96.1 mg, 0.32 mmol, 80% yield from 3-phenyloxetane). **7a** was determined to be of 97% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralCel OJ-H, 4% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 34.7 min, t_r(minor)= 40.3 min). The absolute configuration of **7a** was assigned based on that of **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 6.99 (d, J = 7.7 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 3.71 (d, J = 6.3 Hz, 2H), 3.12 (dd, J = 13.6, 6.3 Hz, 1H), 3.01 (dq, J = 8.4, 6.3 Hz, 1H), 2.82 (dd, J = 13.6, 8.4 Hz, 1H), 2.27 (s, 3H), 0.02 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.9, 137.5, 135.2, 129.1, 128.9, 128.4, 128.2, 126.4, 66.6, 50.3, 38.0, 21.1, -0.4 ppm; **FT-IR** (thin-film): 3027, 2954, 2920, 2860, 1064, 1515, 1494, 1451, 1382, 1249, 1100, 1078, 1008, 953, 872, 836, 809, 746, 697, 580, 562, 546, 522, 499 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{19}H_{26}OSi^{\bullet}$ $[M^{\bullet}]^+$ 298.1747, found 298.1747; $[\alpha]_D = -71.0^o$ (c = 1.0, $CHCl_3$).

Racemic sample: HPLC (ChiralCel OJ-H, 4% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

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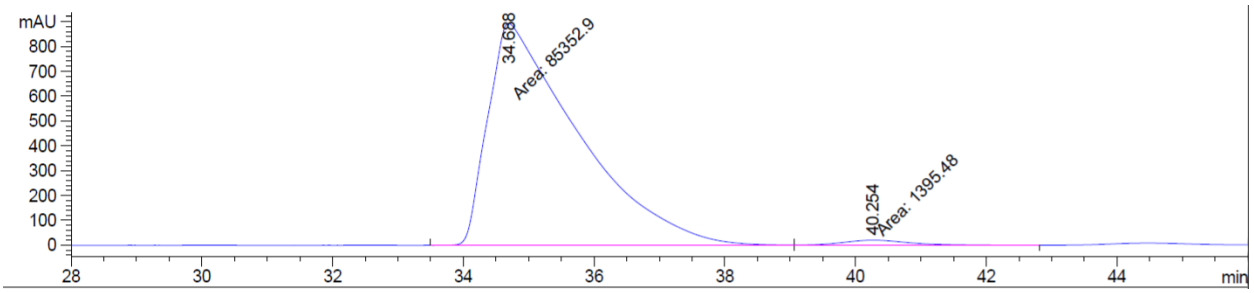
1	34.014	MF	1.5759	9.57690e4	1012.84924	49.4946
2	37.875	FM	1.9620	9.77247e4	830.15088	50.5054

Enantioenriched sample: HPLC (ChiralCel OJ-H, 4% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

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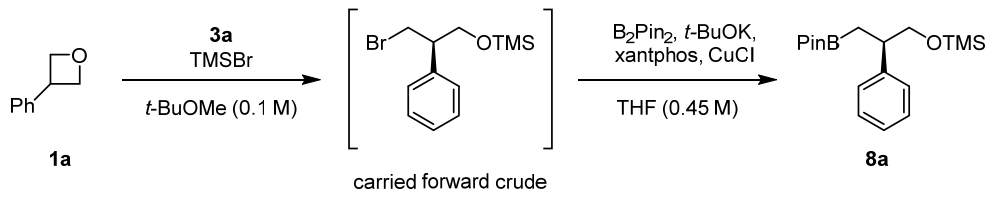
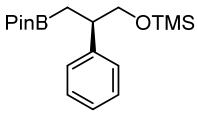
2	40.254	MM	1.1550	1395.48474	20.13612	1.6087

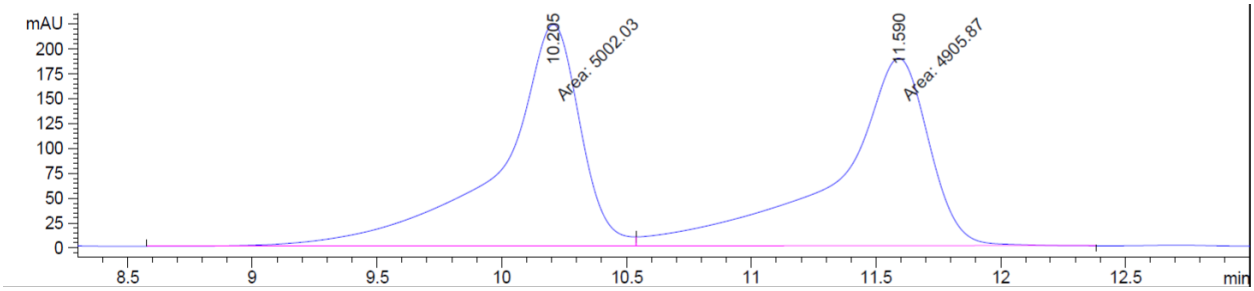




8a

(R)-trimethyl(2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (8a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a** which was immediately carried forward crude following a procedure based on that previously reported by Ito.[24] Copper(I) chloride (7.9 mg, 0.08 mmol, 0.2 equiv.), xantphos (46.3 mg, 0.08 mmol, 0.2 equiv.), and B_2Pin_2 (122 mg, 0.48 mmol, 1.2 equiv.) were added to an oven-dried 0.5-dram vial, placed under an atmosphere of nitrogen, and suspended in an argon-sparged solution of *t*-BuOK (0.48 mL of a 1 M solution in THF, 0.48 mmol, 1.2 equiv.). The crude bromide from the first step (**2a**) was then added dropwise as a solution in argon-sparged THF (assumed 115 mg in 0.4 mL of THF, 0.4 mmol, 1 M, 1 equiv.), and the reaction was allowed to proceed under an atmosphere of nitrogen. After 48 hours, the reaction was run through a silica plug, eluting with 1:1 hexanes-Et_2O and the filtrate was concentrated under vacuum and purified by flash column chromatography to yield boronic ester **8a** (88.6 mg, 0.26 mmol, 66% yield from 3-phenyloxetane). **8a** was determined to be of 94% e.e. by chiral HPLC analysis of the free alcohol which was formed by briefly stirring the silylated product with 1 M aqueous HCl (ChiralPak IC, 5% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 11.7 min, t_r(minor)= 10.4 min). We suspect that the measured decrease in e.e. reflects poor chromatographic separation of the enantiomers causing an underestimation of the enantiomeric enrichment, but we cannot rule out the possibility that a small amount of epimerization occurred under the reaction conditions. The absolute configuration of **8a** was assigned based on that of **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.23 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 3.65 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.57 (dd, *J* = 9.9, 7.3 Hz, 1H), 3.02 (dq, *J* = 9.3, 6.7 Hz, 1H), 1.31 (dd, *J* = 15.5, 6.6 Hz, 1H), 1.11-1.05 (m, 1H), 1.10 (s, 6H), 1.07 (s, 6H), 0.02 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 128.08, 128.06, 126.2, 83.0, 69.3, 44.0, 24.8, 24.7, 15.8–14.0 (br), −0.4 ppm; **FT-IR** (thin-film): 2978, 2958, 1453, 1370, 1320, 1250, 1213, 1145, 1096, 969, 873, 839, 748, 698, 535 cm^{-1}; **HRMS** (FTMS + p CI) calculated for $C_{18}H_{30}BO_3Si$ $[M-H]^+$ 333.2052, found 333.2049; $[\alpha]_D = -22.2^o$ (c = 1.0, $CHCl_3$).

Racemic sample: HPLC (ChiralPak IC, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 3: DAD1 C, Sig=210,4 Ref=450,100

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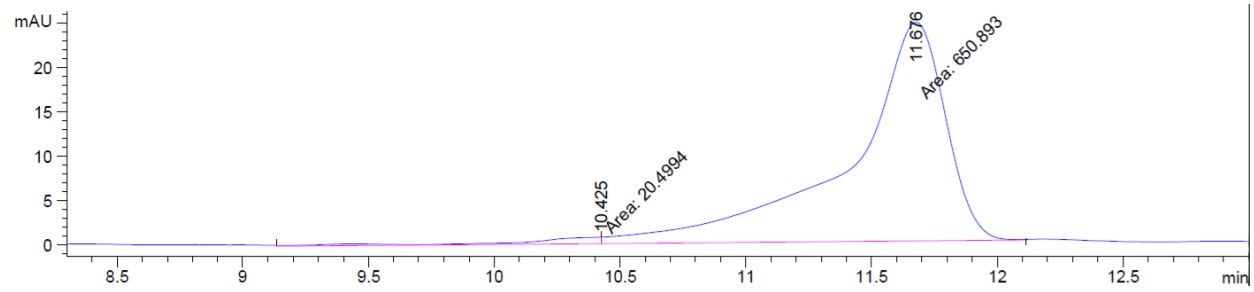
2	11.590	FM	0.4327	4905.86523	188.97437	49.5147

Enantioenriched sample: HPLC (ChiralPak IC, 5% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 94% e.e.

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Signal 3: DAD1 C, Sig=210,4 Ref=450,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.425 MF    0.4427   20.49944 7.71783e-1   3.0533
   2  11.676 FM    0.4407  650.89276   24.61829  96.9467
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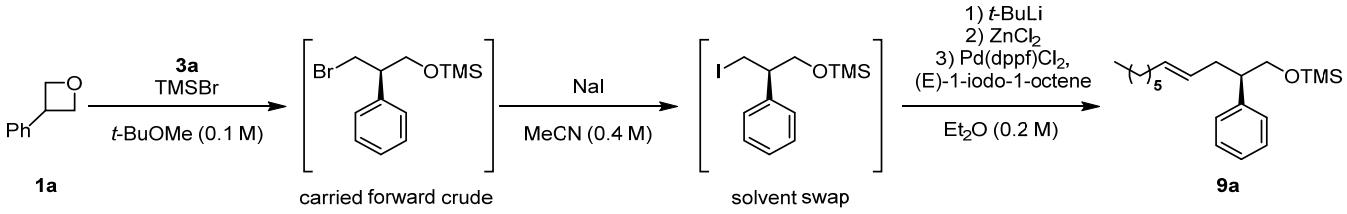
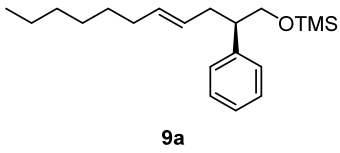
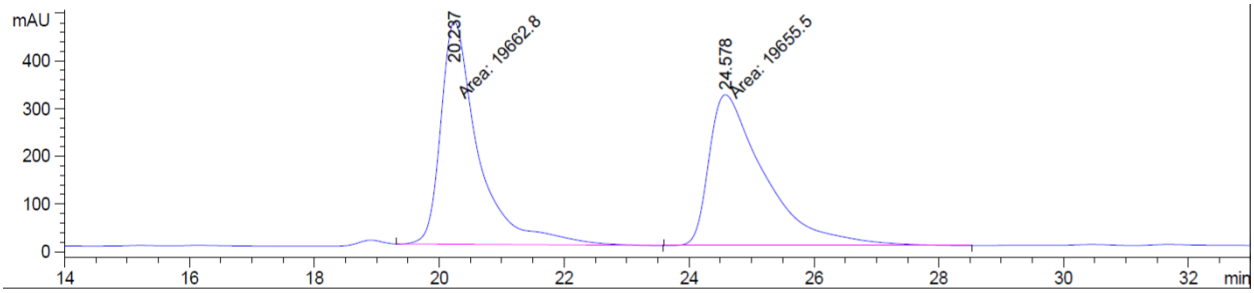




(R,E)-trimethyl((2-phenylundec-4-en-1-yl)oxy)silane (9a): Oxetane **1a** (53.7 mg, 0.4 mmol, 1 equiv.) underwent reaction according to General Procedure B to yield **2a** which was immediately carried forward crude. Alkyl bromide **2a** and NaI (90 mg, 0.60 mmol, 1.5 equiv.) were added to an oven-dried 2-dram vial, placed under an atmosphere of nitrogen, and dissolved in acetonitrile (1.0 mL, 0.4 M). The solution was then heated to 55 °C and allowed to react overnight at that temperature with vigorous stirring in a sealed vial for 24 hours. The solution was then allowed to cool to room temperature and the acetonitrile was removed under vacuum. The solids were then re-suspended in Et_2O (2.0 mL, 0.2 M) under an atmosphere of nitrogen and cooled to -78 °C in a dry-ice acetone bath. The temperature was allowed to equilibrate for 5 minutes, after which *t*-BuLi (0.52 mL of a 1.7 M solution in pentane, 0.88 mmol, 2.2 equiv.) was added dropwise. The reaction was allowed to proceed for 5 minutes, after which a solution of $ZnCl_2$ (0.44 mL of a 1 M solution in Et_2O, 0.44 mmol, 1.1 equiv.) was added. The vial was transferred to an ice-bath and allowed to proceed at 0 °C for 20 minutes, after which $Pd(dppf)Cl_2$ was added followed immediately by a solution of (E)-1-iodo-1-octene (2.0 mL of a 0.24 M solution in THF, 0.48 mmol, 1.2 equiv.). The ice-bath was then removed and the reaction was allowed to proceed overnight at room temperature. The following day the reaction was diluted with Et_2O and filtered through a celite plug. The filtrated was then concentrated and purified by flash column chromatography to yield **9a** (79.9 mg, 0.25 mmol, 63% yield from 3-phenyloxetane). **9a** was determined to be of 97% e.e. by chiral HPLC analysis of the deprotected alcohol (ChiralPak AD-H, 2% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 26.6 min, t_r(minor)= 21.6 min). The absolute configuration of **9a** was assigned based on that of **2a**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 5.37 (dtt, *J* = 14.7, 6.6, 1.2 Hz, 1H), 5.31 – 5.24 (m, 1H), 3.68 (d, *J* = 6.5 Hz, 2H), 2.77 (dq, *J* = 8.7, 6.4 Hz, 1H), 2.51 (dddd, *J* = 14.1, 7.1, 6.0, 1.1 Hz, 1H), 2.27 (dddd, *J* = 14.1, 8.8, 6.5, 1.2 Hz, 1H), 1.93 – 1.86 (m, 2H), 1.32 – 1.14 (m, 8H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.02 (s, 9H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.1, 132.4, 128.3, 128.2, 128.0, 126.4, 67.1, 48.8, 35.3, 32.7, 31.9, 29.6, 28.8, 22.8, 14.3, -0.4 ppm; **FT-IR** (thin-film): 3063, 3029, 2956, 2924, 2854, 1604, 1495, 1467, 1453, 1379,

1261, 1250, 1104, 1082, 967, 873, 839, 755, 698 cm^{-1}; **HRMS** (FTMS + p EI) calculated for $C_{20}H_{34}OSi^{\bullet}$ $[M^{\bullet}]^{+}$ 318.2373, found 318.2374; $[\alpha]_D = -28.4^{\circ}$ (c = 1.0, $CHCl_3$).

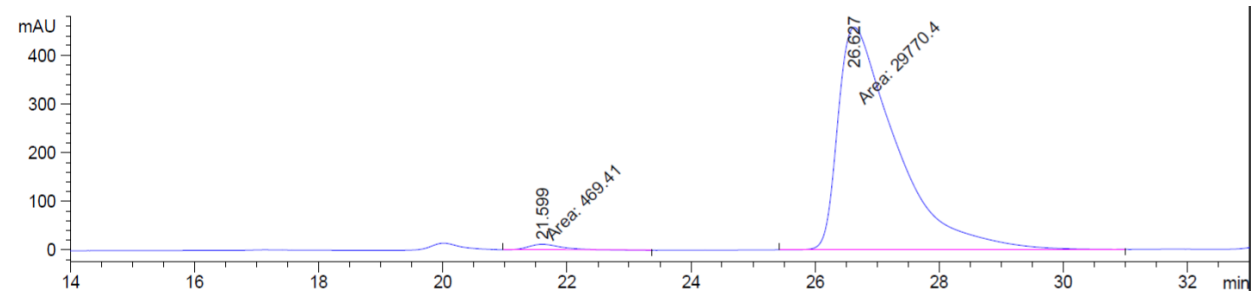
Racemic sample: HPLC (ChiralPak AD-H, 2% *i*-PrOH in hexanes, 1 mL/min, 210 nm)



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

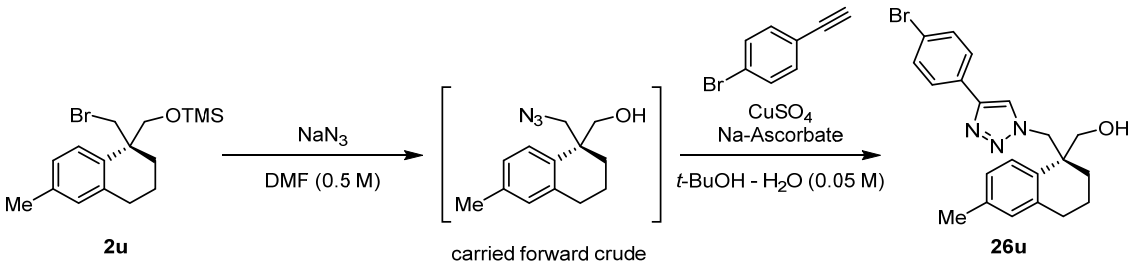
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.237	MM	0.7010	1.96628e4	467.49231	50.0093
2	24.578	MM	1.0352	1.96555e4	316.44034	49.9907

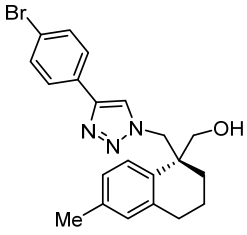
Enantioenriched sample: HPLC (ChiralPak AD-H, 2% *i*-PrOH in hexanes, 1 mL/min, 210 nm), 97% e.e.



Signal 4: DAD1 D, Sig=210,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.599	MM	0.6670	469.41000	11.72877	1.5523
2	26.627	MM	1.0852	2.97704e4	457.23355	98.4477

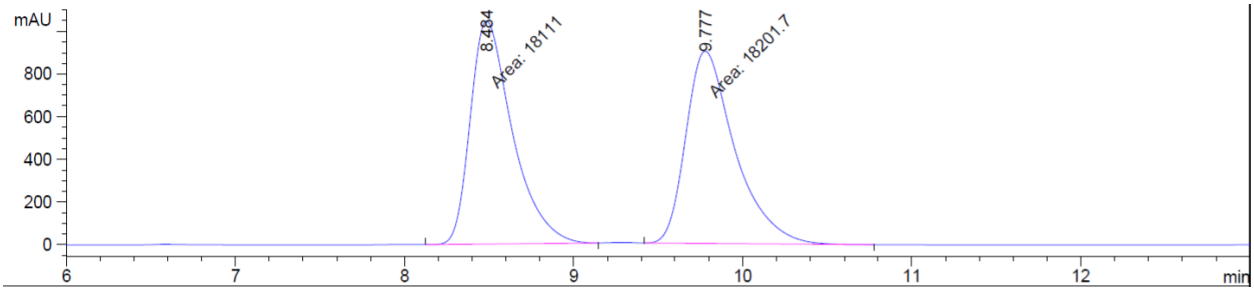




26u

(R)-(1-((4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)methyl)-6-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (26u): Alkyl bromide **2u** (34 mg, 0.10 mmol, 1 equiv.) was dissolved in DMF (1.0 mL, 0.1 M) and then sodium azide (26 mg, 0.40 mmol, 4 equiv.) was added. The reaction was then heated to 100 °C in a sealed container and allowed to proceed overnight at that temperature with vigorous stirring. The following day, the reaction was allowed to cool to room temperature, diluted with Et_2O, and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was removed and the organic layer was washed 2x with saturated aqueous $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was carried forward assuming complete conversion by dissolving it in a 1 : 1 mixture of *t*-BuOH and water (1.0 mL of each solvent, 0.05 M overall). Then 1-bromo-4-ethynylbenzene (21.7 mg, 0.12 mmol, 1.2 equiv.), copper(II) sulfate pentahydrate (6.2 mg, 0.025 mmol, 0.25 equiv.), and sodium ascorbate (9.91 mg, 0.050 mmol, 0.5 equiv.) were added and the reaction was allowed to continue overnight at room temperature with vigorous stirring. The following day, the reaction was diluted with EtOAc and water. The organic layer was removed, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography to yield triazole **26u** (10.2 mg, 0.025 mmol, 25% yield over both steps). **26u** was determined to be of 89% e.e. by chiral HPLC analysis (ChiralPak AD-H, 30% *i*-PrOH in hexanes, 1 mL/min, t_r(major)= 9.5 min, t_r(minor)= 8.3 min). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.43 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.96 (s, 1H), 4.78 (d, *J* = 14.1 Hz, 1H), 4.55 (d, *J* = 14.1 Hz, 1H), 3.78 (d, *J* = 11.7 Hz, 1H), 3.66 (d, *J* = 11.7 Hz, 1H), 2.70 (q, *J* = 6.2, 5.6 Hz, 2H), 2.31 (s, 3H), 1.86 – 1.71 (m, 2H), 1.69 – 1.61 (m, 2H), 1.26 (s, 1H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.5, 138.4, 137.0, 134.1, 132.1, 130.7, 129.6, 127.4, 127.3, 127.2, 122.2, 121.5, 68.5, 56.5, 43.2, 30.4, 29.5, 21.0, 19.0 ppm; **FT-IR** (thin-film): 3348 (br), 3137, 2925, 2869, 1717, 1614, 1549, 1500, 1481, 1455, 1401, 1355, 1231, 1181, 1099, 1069, 1047, 1011, 972, 908, 820, 732, 648, 571, 512 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{21}H_{23}BrN_3O$ $[M+H]^+$ 412.1019, found 412.1030; $[\alpha]_D = -8.2°$ (c = 1.0, $CHCl_3$). A crystal suitable for X-ray diffraction of the HCl salt of **26u** was grown by vapor diffusion of an ethereal solution of HCl into a solution of triazole **26u** in diethyl ether, allowing for the assignment of the absolute configuration of **2u** (see section **SI-X-Ray crystallography** for crystallographic details).

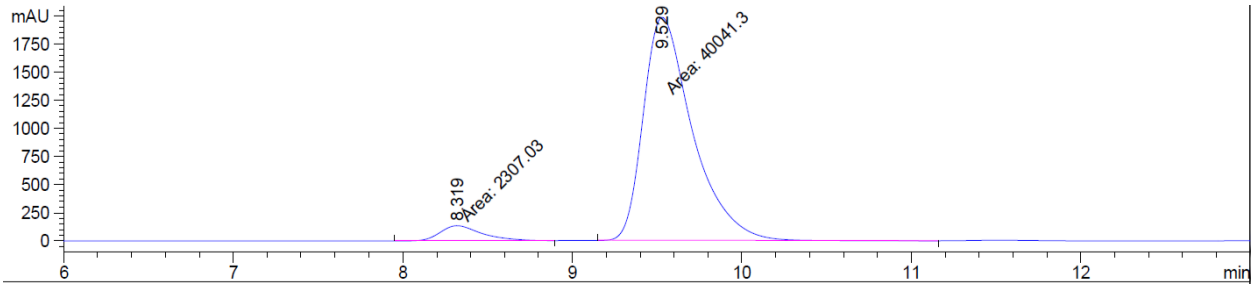
Racemic sample: HPLC (ChiralPak AD-H, 30% *i*-PrOH in hexanes, 1 mL/min, 254 nm)



Signal 1: DAD1 A, Sig=254,4 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.484	MM	0.2888	1.81110e4	1045.04724	49.8750
2	9.777	MM	0.3365	1.82017e4	901.39307	50.1250

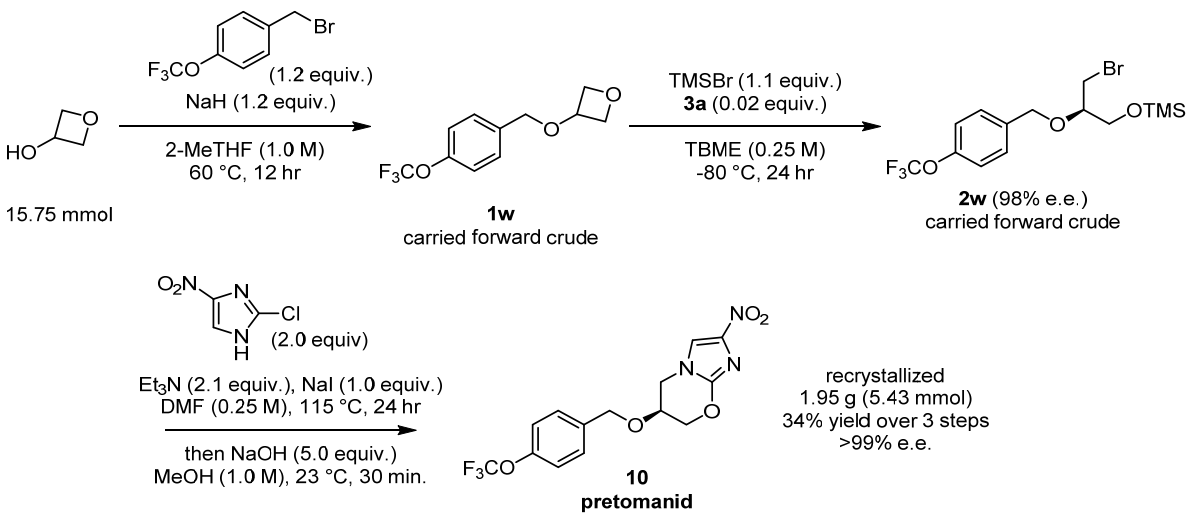
Enantioenriched sample: HPLC (ChiralPak AD-H, 30% *i*-PrOH in hexanes, 1 mL/min, 254 nm), 89% e.e.

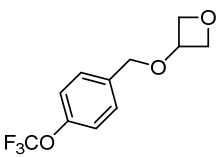


Signal 1: DAD1 A, Sig=254,4 Ref=450,100

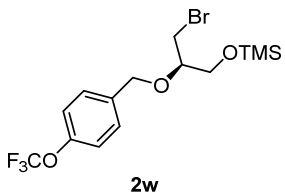
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.319	MM	0.2853	2307.02808	134.76653	5.4477
2	9.529	MM	0.3364	4.00413e4	1983.69531	94.5523

Preparative-Scale Synthesis of Pretomanid



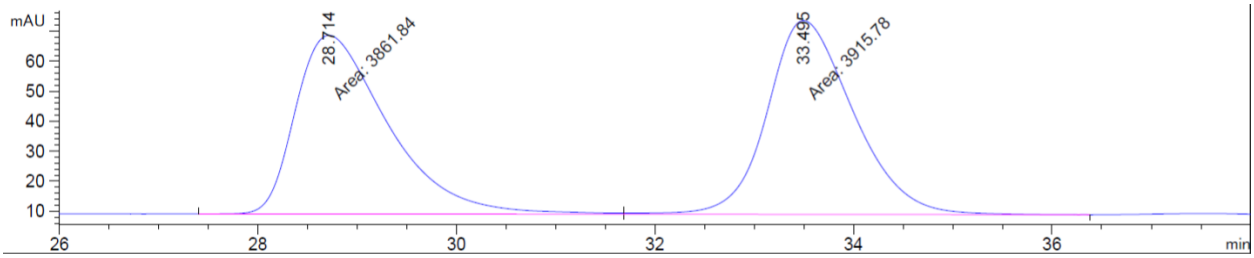


3-((4-(trifluoromethoxy)benzyl)oxy)oxetane (1w): A round-bottom flask with a stir bar was flame-dried under reduced pressure and backfilled with nitrogen gas. The flask was charged with sodium hydride, 60% dispersion in mineral oil (760 mg, 18.9 mmol, 1.2 equiv) and 2-methyltetrahydrofuran (16.0 mL, 1.0 M). The solution was cooled to 0 °C using an ice bath and 3-hydroxyoxetane (1.0 mL, 15.75 mmol, 1.0 equiv) was added dropwise. The mixture was stirred at 0 °C for 1 minute, then 4-(trifluoromethoxy)benzyl bromide (3.0 mL, 18.9 mmol, 1.2 equiv) was added. The reaction was removed from the ice bath and allowed to warm to room temperature, then warmed to 60 °C using an oil bath. The reaction was stirred for 12 h and was then removed from the oil bath. Once the solution was at room temperature, the reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and washed with saturated aqueous NH_4Cl (30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). The resultant organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding benzylated product **1w** as a yellow oil. No further purification was done.



(R)-(3-bromo-2-((4-(trifluoromethoxy)benzyl)oxy)propoxy)trimethylsilane (2w): A round-bottom flask with a stir bar was flame-dried under reduced pressure and backfilled with nitrogen gas. The flask was charged with benzylated intermediate **1w** in *t*-BuOMe (64 mL, 0.25 M) followed by squaramide catalyst **3a** (215 mg, 0.32 mmol, 0.02 equiv). The mixture was stirred at room temperature for 10 minutes and then cooled to –78 °C using an acetone/dry ice bath. The temperature was allowed to equilibrate for 10 minutes and TMSBr (2.3 mL, 17.3 mmol, 1.1 equiv) was added. The reaction was stirred for an additional 10 minutes and was then transferred to a –80 °C freezer. The mixture was aged without stirring for 24 h and then warmed to room temperature. The reaction was transferred into a separatory funnel and saturated aqueous $NaHCO_3$ (30 mL) was added. The layers were separated without agitation and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding bromide product **2w** as a yellow oil. No further purification was done. To determine the e.e. of **2w**: a sample of bromide **2w** (5 mg) was stirred with silica gel (1.5 g) in ethyl acetate (2 mL) for 1 hour to deprotect the silyl ether. The suspension was then filtered over a cotton plug and the filtrate was reduced under reduced pressure. **2w** was determined to be of 98% e.e. by chiral HPLC analysis of the desilylated alcohol (ChiralPak AS-H, 3% i-PrOH in hexanes, 1 mL/min, tr(major)= 34.4 min, tr(minor)= 30.1 min). The absolute configuration of **2w** was assigned following its derivatization to pretomanid (**10**).

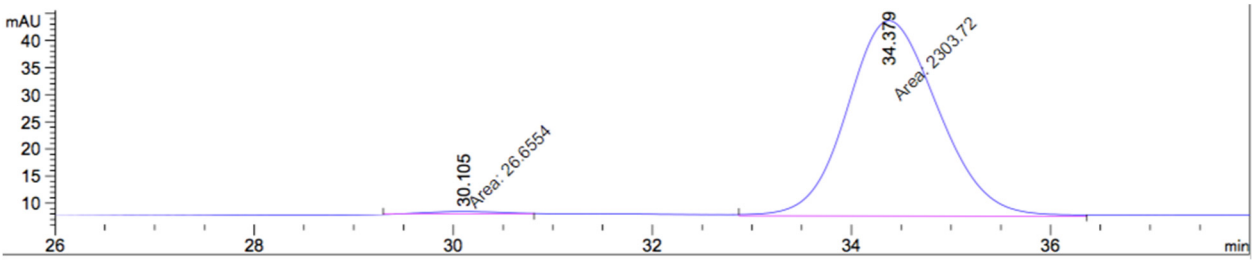
Racemic sample: HPLC (ChiralPak AS-H, 3% *i*-PrOH in hexanes, 1 mL/min, 220 nm)



Signal 4: DAD1 D, Sig=220,16 Ref=450,100

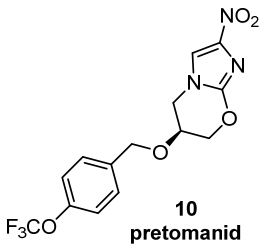
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.714	MF	1.0812	3861.83667	59.52892	49.6532
2	33.495	FM	1.0107	3915.77661	64.57066	50.3468

Enantioenriched sample: HPLC (ChiralPak AS-H, 3% *i*-PrOH in hexanes, 1 mL/min, 220 nm), 98% e.e.



Signal 4: DAD1 D, Sig=220,16 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.105	MM	0.8859	26.65538	5.01458e-1	1.1438
2	34.379	MM	1.0658	2303.71509	36.02395	98.8562

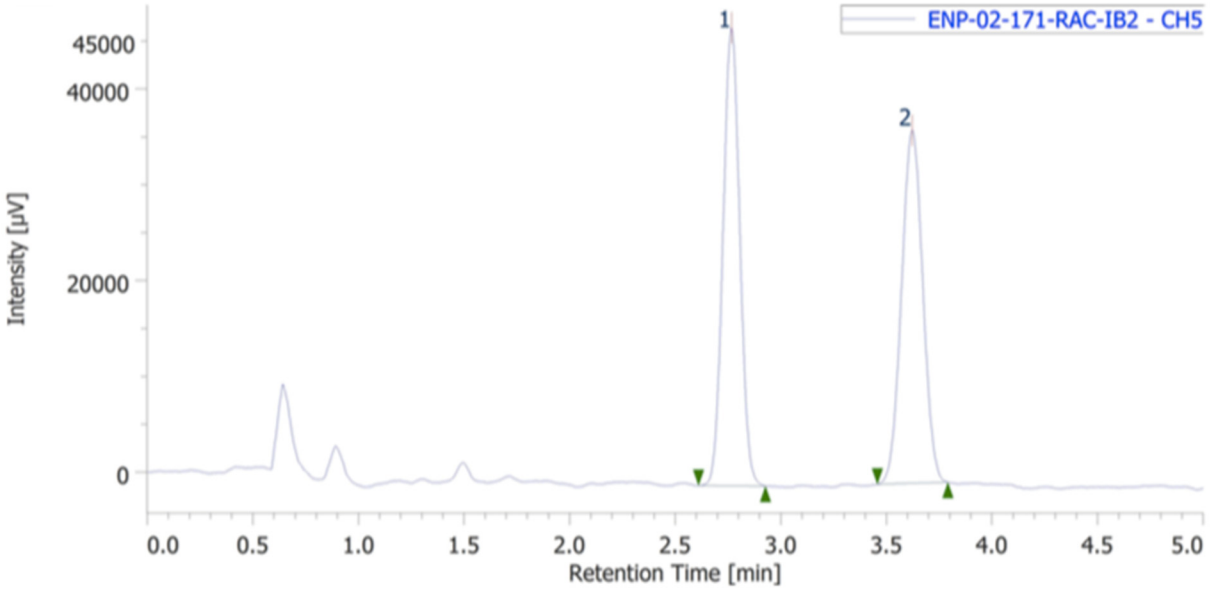


10
pretomanid

Pretomanid (10): A round-bottom flask with a stir bar was flame-dried under reduced pressure and backfilled with nitrogen gas. The flask was charged with substrate **2w** in DMF (63 mL, 0.25 M) followed by 2-chloro-4-nitroimidazole (4.65 g, 31.5 mmol, 2.0 equiv), Et_3N (4.6 mL, 33.1 mmol, 2.1 equiv), and NaI (2.36 g, 15.75 mmol, 1.0 equiv). The mixture was heated to 115 °C using an oil bath and stirred for 24 h. The reaction was removed from the oil bath and allowed to cool. Once at room temperature, NaOH (3.15 g, 78.8 mmol, 5.0 equiv) and MeOH (16 mL, 1.0 M) were added. The mixture was stirred for an additional 0.5 h and the resulting solution was transferred to a separatory funnel containing DI H_2O (200 mL). The layers were separated, and the organic phase was dried over Na_2SO_4. The crude product was purified by recrystallization by dissolving the mixture in isopropyl alcohol (50 mL), adding hexanes (200 mL), and aging in a 5 °C fridge for 6 h. The solution was filtered to afford pretomanid (**10**) as a discolored solid (1.83 g, 5.1 mmol, 32% yield). Concentrating the mother liquor and repeating the recrystallization provided additional pretomanid (**10**) (120 mg, 0.33 mmol, 2% yield) for a total 34% three-step synthesis of pretomanid (**10**) (1.95 g, 5.43 mmol, 34% yield). The spectral data were consistent with those acquired for an authentic sample of the drug from Millipore Sigma: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 4.73 (d, J = 11.9 Hz, 1H), 4.65 – 4.60 (m, 2H), 4.36 (d, J = 12.0 Hz, 1H), 4.21 (dd, J = 12.7, 3.7 Hz, 1H), 4.18 – 4.11 (m, 2H) ppm; Pretomanid (**10**) was determined to be of >99% e.e. by chiral SFC analysis (ChiralPak IB,

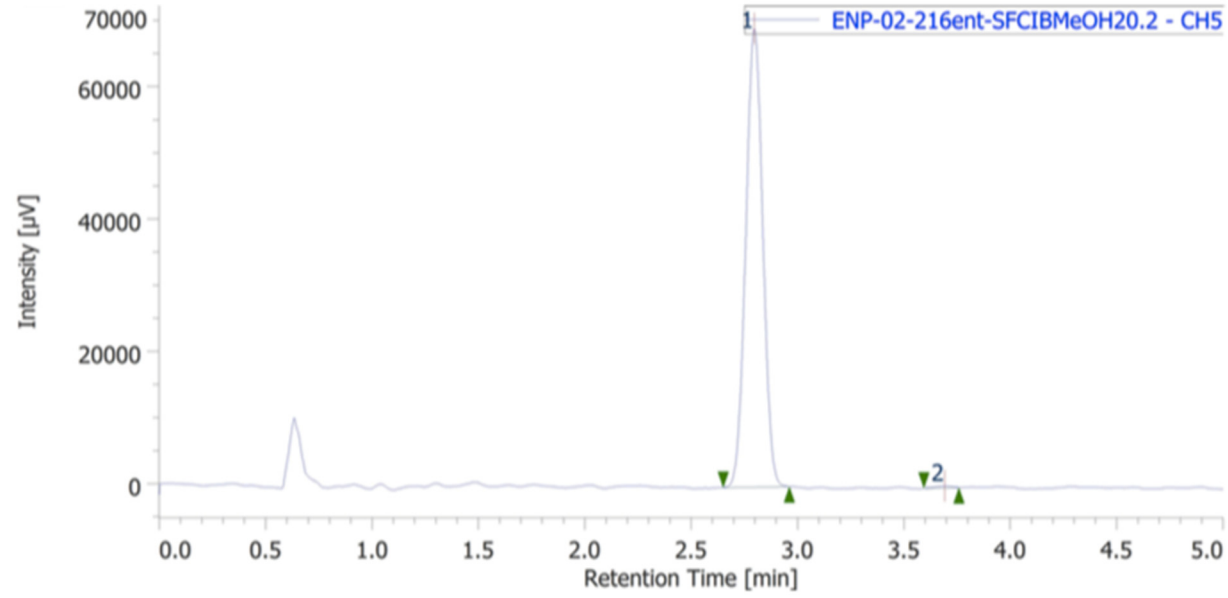
20% MeOH/CO_2, 5 mL/min, tr(major)= 3.6 min, tr(minor)= 2.8 min). The absolute configuration of **10** was assigned by SFC comparison to an authentic sample of the drug from MilliporeSigma.

Racemic sample: SFC (ChiralPak IB, 20% MeOH/CO_2, 5 mL/min, 210 nm)



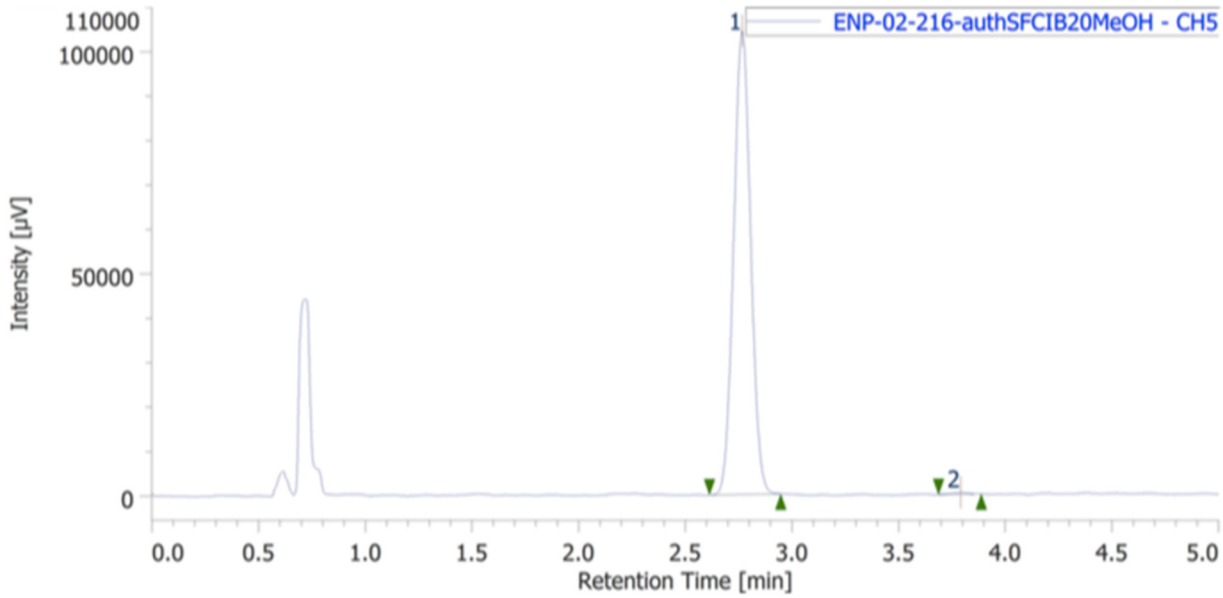
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%
1	Unknown	5	2.767	264985	47790	50.7	56.5
2	Unknown	5	3.620	257922	36820	49.3	43.5

Synthetic, enantioenriched sample: SFC (ChiralPak IB, 20% MeOH/CO_2, 5 mL/min, 210 nm), >99% e.e.



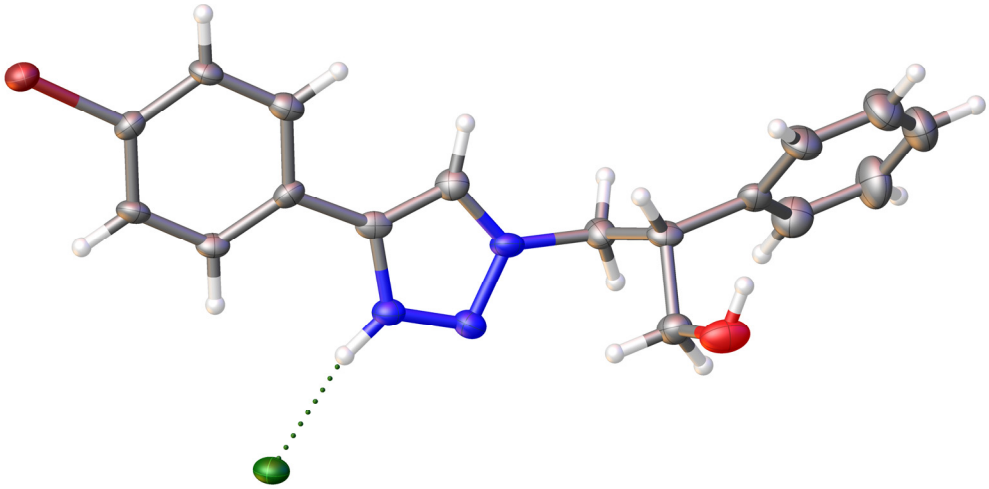
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%
1	Unknown	5	2.797	384897	69244	99.6	99.6
2	Unknown	5	3.690	1610	302	0.417	0.434

Sample from MilliporeSigma: SFC (ChiralPak IB, 20% MeOH/CO_2, 5 mL/min, 210 nm), >99% e.e.



#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%
1	Unknown	5	2.767	578207	104432	99.6	99.6
2	Unknown	5	3.790	2134	385	0.368	0.367

X-Ray Crystallography



26a

X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30°, -55°, -80°, 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A[25] with reflection spot size optimization. Absorption corrections were made with the program SADABS.[25] The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014[26] and SHELXL-2014[27] with OLEX 2 interface.[28] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table **S1**, geometric parameters are shown in Table **S2** and hydrogen-bond parameters are listed in Table **S3**. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[29]

Table S1. Experimental details

	DAS-V-181-1
Crystal data	
Chemical formula	$C_{17}H_{17}BrClN_3O$
M_r	394.69
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	6.9388 (2), 15.0508 (3), 32.5860 (8)
V (Å^3)	3403.10 (15)
Z	8
Radiation type	Cu $K\alpha$
μ (mm^{-1})	4.80
Crystal size (mm)	0.24 × 0.10 × 0.08

Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.608, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	36923, 5929, 5058
R_{int}	0.088
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.596
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.046, 0.100, 1.05
No. of reflections	5929
No. of parameters	423
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.71, -0.59
Absolute structure	Flack x determined using 1910 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.017 (16)

Computer programs: *SAINT* 8.37A,[25] *SHELXT2014*,[26] *SHELXL2014*,[27] Bruker *SHELXTL*.[26,27]

Table S2. Geometric parameters (Å, º)

Br1—C6	1.886 (7)	Br2—C26	1.891 (7)
O1—C17	1.424 (10)	O2—C37	1.428 (10)
O1—H1	0.8400	O2—H2	0.8400
N1—N2	1.329 (8)	N4—N5	1.301 (8)
N1—C1	1.333 (9)	N4—C21	1.359 (9)
N1—C9	1.482 (9)	N4—C29	1.468 (10)
N2—N3	1.321 (9)	N5—N6	1.326 (9)
N3—C2	1.373 (9)	N6—C22	1.370 (9)
N3—H3	0.84 (9)	N6—H6	0.95 (9)
C1—C2	1.365 (10)	C21—C22	1.371 (11)
C1—H1A	0.9500	C21—H21	0.9500
C2—C3	1.474 (10)	C22—C23	1.462 (11)
C3—C8	1.397 (10)	C23—C24	1.399 (10)
C3—C4	1.398 (10)	C23—C28	1.403 (11)

C4—C5	1.390 (11)	C24—C25	1.379 (11)
C4—H4	0.9500	C24—H24	0.9500
C5—C6	1.404 (10)	C25—C26	1.396 (10)
C5—H5	0.9500	C25—H25	0.9500
C6—C7	1.385 (9)	C26—C27	1.393 (10)
C7—C8	1.386 (10)	C27—C28	1.381 (10)
C7—H7	0.9500	C27—H27	0.9500
C8—H8	0.9500	C28—H28	0.9500
C9—C10	1.531 (10)	C29—C30	1.528 (11)
C9—H9A	0.9900	C29—H29A	0.9900
C9—H9B	0.9900	C29—H29B	0.9900
C10—C11	1.526 (10)	C30—C31	1.531 (10)
C10—C17	1.540 (10)	C30—C37	1.538 (10)
C10—H10	1.0000	C30—H30	1.0000
C11—C12	1.388 (12)	C31—C36	1.381 (12)
C11—C16	1.406 (11)	C31—C32	1.386 (12)
C12—C13	1.384 (13)	C32—C33	1.412 (13)
C12—H12	0.9500	C32—H32	0.9500
C13—C14	1.390 (14)	C33—C34	1.375 (14)
C13—H13	0.9500	C33—H33	0.9500
C14—C15	1.376 (15)	C34—C35	1.374 (14)
C14—H14	0.9500	C34—H34	0.9500
C15—C16	1.402 (12)	C35—C36	1.387 (12)
C15—H15	0.9500	C35—H35	0.9500
C16—H16	0.9500	C36—H36	0.9500
C17—H17A	0.9900	C37—H37A	0.9900
C17—H17B	0.9900	C37—H37B	0.9900
C17—O1—H1	109.5	C37—O2—H2	109.5
N2—N1—C1	112.5 (6)	N5—N4—C21	112.7 (6)
N2—N1—C9	119.4 (6)	N5—N4—C29	118.9 (6)
C1—N1—C9	128.1 (6)	C21—N4—C29	128.4 (6)
N3—N2—N1	103.8 (6)	N4—N5—N6	105.4 (6)
N2—N3—C2	112.9 (6)	N5—N6—C22	111.4 (6)
N2—N3—H3	123 (6)	N5—N6—H6	119 (5)
C2—N3—H3	124 (6)	C22—N6—H6	129 (5)
N1—C1—C2	107.1 (6)	N4—C21—C22	105.4 (6)

N1—C1—H1A	126.4	N4—C21—H21	127.3
C2—C1—H1A	126.4	C22—C21—H21	127.3
C1—C2—N3	103.7 (6)	N6—C22—C21	105.1 (7)
C1—C2—C3	132.4 (7)	N6—C22—C23	124.7 (7)
N3—C2—C3	123.9 (7)	C21—C22—C23	130.2 (7)
C8—C3—C4	120.0 (7)	C24—C23—C28	119.5 (8)
C8—C3—C2	122.2 (6)	C24—C23—C22	118.5 (7)
C4—C3—C2	117.7 (7)	C28—C23—C22	122.0 (6)
C5—C4—C3	120.0 (7)	C25—C24—C23	120.1 (7)
C5—C4—H4	120.0	C25—C24—H24	120.0
C3—C4—H4	120.0	C23—C24—H24	120.0
C4—C5—C6	119.1 (6)	C24—C25—C26	119.7 (6)
C4—C5—H5	120.4	C24—C25—H25	120.1
C6—C5—H5	120.4	C26—C25—H25	120.1
C7—C6—C5	121.0 (7)	C27—C26—C25	121.1 (7)
C7—C6—Br1	120.2 (6)	C27—C26—Br2	120.6 (6)
C5—C6—Br1	118.8 (5)	C25—C26—Br2	118.3 (5)
C6—C7—C8	119.6 (7)	C28—C27—C26	118.9 (7)
C6—C7—H7	120.2	C28—C27—H27	120.6
C8—C7—H7	120.2	C26—C27—H27	120.6
C7—C8—C3	120.3 (6)	C27—C28—C23	120.8 (7)
C7—C8—H8	119.9	C27—C28—H28	119.6
C3—C8—H8	119.9	C23—C28—H28	119.6
N1—C9—C10	112.4 (6)	N4—C29—C30	111.5 (7)
N1—C9—H9A	109.1	N4—C29—H29A	109.3
C10—C9—H9A	109.1	C30—C29—H29A	109.3
N1—C9—H9B	109.1	N4—C29—H29B	109.3
C10—C9—H9B	109.1	C30—C29—H29B	109.3
H9A—C9—H9B	107.8	H29A—C29—H29B	108.0
C11—C10—C9	110.5 (7)	C29—C30—C31	109.3 (7)
C11—C10—C17	111.0 (6)	C29—C30—C37	112.4 (6)
C9—C10—C17	109.2 (6)	C31—C30—C37	111.0 (6)
C11—C10—H10	108.7	C29—C30—H30	108.0
C9—C10—H10	108.7	C31—C30—H30	108.0
C17—C10—H10	108.7	C37—C30—H30	108.0
C12—C11—C16	119.2 (8)	C36—C31—C32	118.7 (8)
C12—C11—C10	122.4 (7)	C36—C31—C30	123.1 (7)

C16—C11—C10	118.4 (8)	C32—C31—C30	118.3 (8)
C13—C12—C11	120.8 (8)	C31—C32—C33	120.0 (10)
C13—C12—H12	119.6	C31—C32—H32	120.0
C11—C12—H12	119.6	C33—C32—H32	120.0
C12—C13—C14	120.1 (9)	C34—C33—C32	119.9 (10)
C12—C13—H13	119.9	C34—C33—H33	120.0
C14—C13—H13	119.9	C32—C33—H33	120.0
C15—C14—C13	119.9 (9)	C35—C34—C33	120.2 (10)
C15—C14—H14	120.1	C35—C34—H34	119.9
C13—C14—H14	120.1	C33—C34—H34	119.9
C14—C15—C16	120.6 (9)	C34—C35—C36	119.7 (10)
C14—C15—H15	119.7	C34—C35—H35	120.1
C16—C15—H15	119.7	C36—C35—H35	120.1
C15—C16—C11	119.4 (9)	C31—C36—C35	121.5 (9)
C15—C16—H16	120.3	C31—C36—H36	119.2
C11—C16—H16	120.3	C35—C36—H36	119.2
O1—C17—C10	114.1 (6)	O2—C37—C30	108.7 (6)
O1—C17—H17A	108.7	O2—C37—H37A	110.0
C10—C17—H17A	108.7	C30—C37—H37A	110.0
O1—C17—H17B	108.7	O2—C37—H37B	110.0
C10—C17—H17B	108.7	C30—C37—H37B	110.0
H17A—C17—H17B	107.6	H37A—C37—H37B	108.3
C1—N1—N2—N3	-0.7 (9)	C21—N4—N5—N6	0.8 (9)
C9—N1—N2—N3	179.5 (6)	C29—N4—N5—N6	178.8 (6)
N1—N2—N3—C2	0.9 (8)	N4—N5—N6—C22	-0.6 (8)
N2—N1—C1—C2	0.2 (9)	N5—N4—C21—C22	-0.6 (10)
C9—N1—C1—C2	180.0 (7)	C29—N4—C21—C22	-178.4 (7)
N1—C1—C2—N3	0.3 (9)	N5—N6—C22—C21	0.3 (9)
N1—C1—C2—C3	179.8 (8)	N5—N6—C22—C23	-180.0 (7)
N2—N3—C2—C1	-0.8 (9)	N4—C21—C22—N6	0.2 (9)
N2—N3—C2—C3	179.7 (7)	N4—C21—C22—C23	-179.6 (7)
C1—C2—C3—C8	170.4 (8)	N6—C22—C23—C24	-166.1 (7)
N3—C2—C3—C8	-10.2 (12)	C21—C22—C23—C24	13.6 (12)
C1—C2—C3—C4	-6.0 (13)	N6—C22—C23—C28	13.7 (11)
N3—C2—C3—C4	173.4 (7)	C21—C22—C23—C28	-166.6 (8)
C8—C3—C4—C5	0.4 (12)	C28—C23—C24—C25	1.4 (11)

C2—C3—C4—C5	176.9 (7)	C22—C23—C24—C25	-178.8 (7)
C3—C4—C5—C6	-1.0 (12)	C23—C24—C25—C26	-0.1 (11)
C4—C5—C6—C7	1.9 (12)	C24—C25—C26—C27	-0.8 (12)
C4—C5—C6—Br1	-178.9 (6)	C24—C25—C26—Br2	177.7 (6)
C5—C6—C7—C8	-2.1 (12)	C25—C26—C27—C28	0.2 (12)
Br1—C6—C7—C8	178.7 (6)	Br2—C26—C27—C28	-178.2 (6)
C6—C7—C8—C3	1.5 (12)	C26—C27—C28—C23	1.1 (11)
C4—C3—C8—C7	-0.6 (12)	C24—C23—C28—C27	-1.9 (11)
C2—C3—C8—C7	-176.9 (7)	C22—C23—C28—C27	178.3 (7)
N2—N1—C9—C10	-99.4 (8)	N5—N4—C29—C30	93.8 (8)
C1—N1—C9—C10	80.9 (10)	C21—N4—C29—C30	-88.5 (10)
N1—C9—C10—C11	-164.4 (6)	N4—C29—C30—C31	-166.8 (6)
N1—C9—C10—C17	73.3 (8)	N4—C29—C30—C37	69.5 (8)
C9—C10—C11—C12	-40.8 (10)	C29—C30—C31—C36	-21.5 (9)
C17—C10—C11—C12	80.5 (9)	C37—C30—C31—C36	103.0 (8)
C9—C10—C11—C16	140.9 (7)	C29—C30—C31—C32	158.8 (7)
C17—C10—C11—C16	-97.9 (8)	C37—C30—C31—C32	-76.7 (9)
C16—C11—C12—C13	-1.6 (13)	C36—C31—C32—C33	-0.1 (12)
C10—C11—C12—C13	-179.9 (8)	C30—C31—C32—C33	179.6 (7)
C11—C12—C13—C14	1.3 (16)	C31—C32—C33—C34	1.6 (14)
C12—C13—C14—C15	0.1 (16)	C32—C33—C34—C35	-1.7 (15)
C13—C14—C15—C16	-1.3 (16)	C33—C34—C35—C36	0.4 (15)
C14—C15—C16—C11	1.0 (15)	C32—C31—C36—C35	-1.3 (11)
C12—C11—C16—C15	0.5 (13)	C30—C31—C36—C35	179.1 (7)
C10—C11—C16—C15	178.9 (8)	C34—C35—C36—C31	1.2 (13)
C11—C10—C17—O1	65.9 (8)	C29—C30—C37—O2	58.8 (9)
C9—C10—C17—O1	-172.1 (6)	C31—C30—C37—O2	-64.0 (8)

Table S3. Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O1—H1···O2	0.84	2.36	2.947 (8)	127.3
N3—H3···Cl1	0.84 (9)	2.16 (9)	2.985 (7)	169 (9)
N6—H6···Cl2^{i}	0.95 (9)	2.01 (9)	2.948 (6)	169 (8)
O2—H2···Cl2	0.84	2.42	3.217 (7)	157.7

Symmetry code(s): (i) -*x*+2, *y*-1/2, -*z*+1/2.

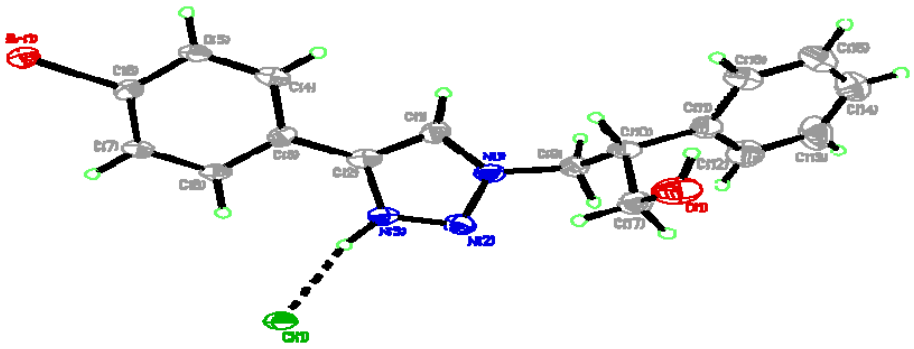


Figure S16. Perspective views showing 50% probability displacement

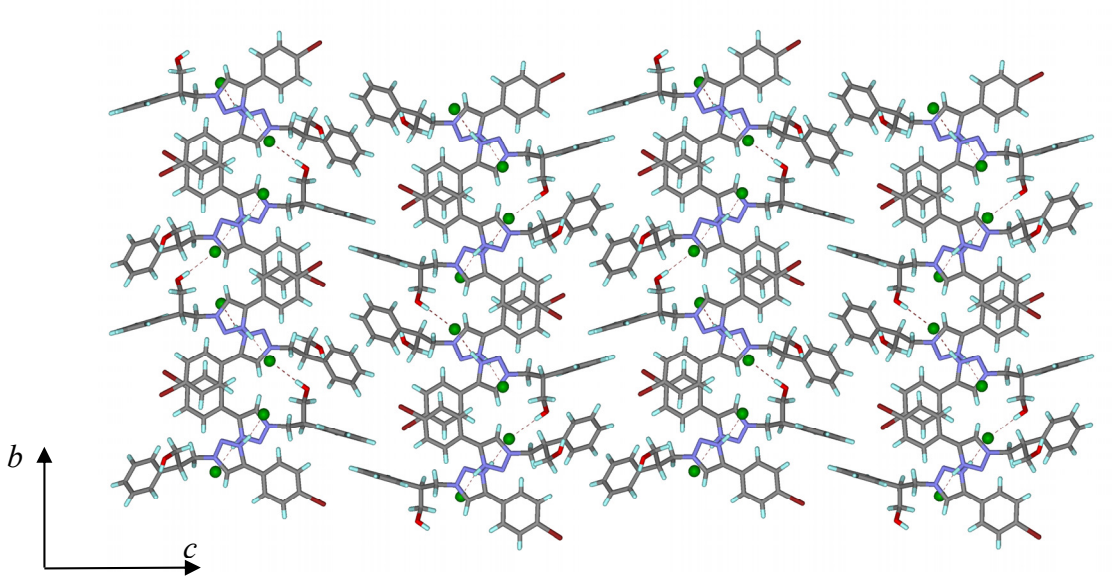
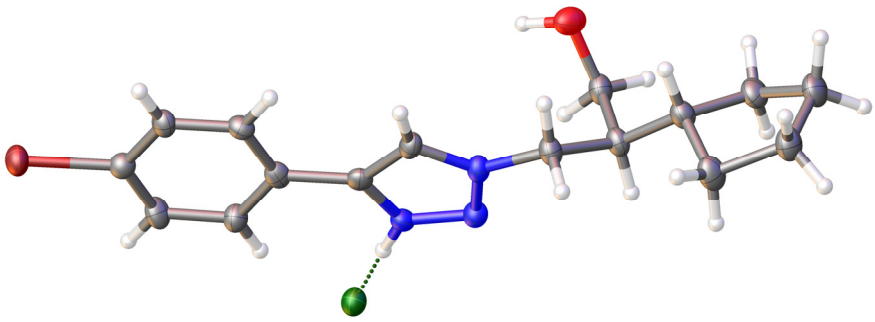


Figure S17. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.



26o

A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at -30°, -55°, -80°, 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V8.37 A[25] with reflection spot size optimization. Absorption corrections were made with the program SADABS.[25] The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014[26] and SHELXL-2014[27] with OLEX 2 interface.[28] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table **S4**, geometric parameters are shown in Table **S5**, and hydrogen-bond parameters are listed in Table **S6**. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[29]

Table S4. Experimental details

	DAS-VI-67
Crystal data	
Chemical formula	$C_{16}H_{21}BrClN_3O$
M_r	386.72
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	7.0227 (3), 15.3766 (6), 15.8486 (6)
β (°)	99.589 (3)
V (Å^3)	1687.50 (12)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	4.82
Crystal size (mm)	0.06 × 0.01 × 0.01
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*

T_{min}, T_{max}	0.510, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	35039, 5720, 5367
R_{int}	0.054
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.595
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.065, 0.171, 1.16
No. of reflections	5720
No. of parameters	401
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.47, -0.66
Flack parameter	-0.01 (3)
Hooft parameter	-0.01 (2)

Computer programs: *SAINT* 8.37A,[25] *SHELXT2014*,[26] *SHELXL2014*,[27] Bruker *SHELXTL*.[26,27]

Table S5. Geometric parameters (Å, º)

Br1—C3	1.881 (9)	Br2—C23	1.897 (9)
O1—C16	1.418 (11)	O2—C36	1.417 (12)
O1—H1	0.8568	O2—H2A	0.8585
N1—N2	1.306 (11)	N4—N5	1.321 (11)
N1—C8	1.351 (11)	N4—C28	1.355 (12)
N1—C9	1.485 (10)	N4—C29	1.488 (11)
N2—N3	1.329 (10)	N5—N6	1.319 (11)
N3—C7	1.350 (12)	N6—C27	1.358 (12)
N3—H3	0.9120	N6—H6	0.9168
C1—C2	1.396 (12)	C21—C26	1.389 (13)
C1—C6	1.401 (12)	C21—C22	1.389 (13)
C1—H1A	0.9500	C21—H21	0.9500
C2—C3	1.397 (15)	C22—C23	1.385 (14)
C2—H2	0.9500	C22—H22	0.9500
C3—C4	1.385 (13)	C23—C24	1.387 (12)
C4—C5	1.381 (12)	C24—C25	1.381 (13)
C4—H4	0.9500	C24—H24	0.9500
C5—C6	1.389 (13)	C25—C26	1.396 (13)

C5—H5	0.9500	C25—H25	0.9500
C6—C7	1.474 (12)	C26—C27	1.475 (12)
C7—C8	1.389 (13)	C27—C28	1.377 (12)
C8—H8	0.9500	C28—H28	0.9500
C9—C10	1.523 (12)	C29—C30	1.525 (12)
C9—H9A	0.9900	C29—H29A	0.9900
C9—H9B	0.9900	C29—H29B	0.9900
C10—C11	1.530 (12)	C30—C31	1.526 (12)
C10—C16	1.532 (11)	C30—C36	1.529 (12)
C10—H10	1.0000	C30—H30	1.0000
C11—C15	1.533 (13)	C31—C35	1.526 (13)
C11—C12	1.537 (12)	C31—C32	1.547 (13)
C11—H11	1.0000	C31—H31	1.0000
C12—C13	1.539 (12)	C32—C33	1.541 (13)
C12—H12A	0.9900	C32—H32A	0.9900
C12—H12B	0.9900	C32—H32B	0.9900
C13—C14	1.551 (13)	C33—C34	1.531 (15)
C13—H13A	0.9900	C33—H33A	0.9900
C13—H13B	0.9900	C33—H33B	0.9900
C14—C15	1.520 (12)	C34—C35	1.520 (13)
C14—H14A	0.9900	C34—H34A	0.9900
C14—H14B	0.9900	C34—H34B	0.9900
C15—H15A	0.9900	C35—H35A	0.9900
C15—H15B	0.9900	C35—H35B	0.9900
C16—H16A	0.9900	C36—H36A	0.9900
C16—H16B	0.9900	C36—H36B	0.9900
C16—O1—H1	110.4	C36—O2—H2A	106.1
N2—N1—C8	113.7 (7)	N5—N4—C28	113.0 (7)
N2—N1—C9	121.4 (7)	N5—N4—C29	116.9 (7)
C8—N1—C9	124.7 (8)	C28—N4—C29	129.9 (8)
N1—N2—N3	103.6 (7)	N6—N5—N4	104.0 (7)
N2—N3—C7	113.4 (7)	N5—N6—C27	112.8 (8)
N2—N3—H3	118.8	N5—N6—H6	117.0
C7—N3—H3	127.6	C27—N6—H6	130.2
C2—C1—C6	119.5 (10)	C26—C21—C22	120.4 (9)
C2—C1—H1A	120.3	C26—C21—H21	119.8

C6—C1—H1A	120.3	C22—C21—H21	119.8
C1—C2—C3	119.5 (9)	C23—C22—C21	118.7 (9)
C1—C2—H2	120.3	C23—C22—H22	120.7
C3—C2—H2	120.3	C21—C22—H22	120.7
C4—C3—C2	120.7 (9)	C22—C23—C24	121.4 (9)
C4—C3—Br1	119.6 (7)	C22—C23—Br2	120.6 (7)
C2—C3—Br1	119.8 (7)	C24—C23—Br2	118.0 (7)
C5—C4—C3	119.8 (9)	C25—C24—C23	119.8 (9)
C5—C4—H4	120.1	C25—C24—H24	120.1
C3—C4—H4	120.1	C23—C24—H24	120.1
C4—C5—C6	120.5 (9)	C24—C25—C26	119.5 (9)
C4—C5—H5	119.8	C24—C25—H25	120.3
C6—C5—H5	119.8	C26—C25—H25	120.3
C5—C6—C1	120.1 (9)	C21—C26—C25	120.2 (9)
C5—C6—C7	119.3 (8)	C21—C26—C27	121.8 (8)
C1—C6—C7	120.6 (9)	C25—C26—C27	117.9 (8)
N3—C7—C8	104.3 (7)	N6—C27—C28	105.1 (8)
N3—C7—C6	126.0 (8)	N6—C27—C26	124.6 (8)
C8—C7—C6	129.7 (8)	C28—C27—C26	130.2 (9)
N1—C8—C7	105.0 (8)	N4—C28—C27	104.9 (8)
N1—C8—H8	127.5	N4—C28—H28	127.5
C7—C8—H8	127.5	C27—C28—H28	127.5
N1—C9—C10	116.0 (7)	N4—C29—C30	114.4 (7)
N1—C9—H9A	108.3	N4—C29—H29A	108.7
C10—C9—H9A	108.3	C30—C29—H29A	108.7
N1—C9—H9B	108.3	N4—C29—H29B	108.7
C10—C9—H9B	108.3	C30—C29—H29B	108.7
H9A—C9—H9B	107.4	H29A—C29—H29B	107.6
C9—C10—C11	106.8 (7)	C29—C30—C31	106.6 (8)
C9—C10—C16	111.7 (7)	C29—C30—C36	112.1 (7)
C11—C10—C16	113.4 (7)	C31—C30—C36	114.4 (8)
C9—C10—H10	108.3	C29—C30—H30	107.8
C11—C10—H10	108.3	C31—C30—H30	107.8
C16—C10—H10	108.3	C36—C30—H30	107.8
C10—C11—C15	115.8 (8)	C35—C31—C30	116.5 (8)
C10—C11—C12	114.4 (8)	C35—C31—C32	103.5 (8)
C15—C11—C12	102.1 (7)	C30—C31—C32	113.6 (8)

C10—C11—H11	108.1	C35—C31—H31	107.6
C15—C11—H11	108.1	C30—C31—H31	107.6
C12—C11—H11	108.1	C32—C31—H31	107.6
C11—C12—C13	104.9 (7)	C33—C32—C31	106.2 (8)
C11—C12—H12A	110.8	C33—C32—H32A	110.5
C13—C12—H12A	110.8	C31—C32—H32A	110.5
C11—C12—H12B	110.8	C33—C32—H32B	110.5
C13—C12—H12B	110.8	C31—C32—H32B	110.5
H12A—C12—H12B	108.8	H32A—C32—H32B	108.7
C12—C13—C14	105.9 (7)	C34—C33—C32	105.1 (8)
C12—C13—H13A	110.5	C34—C33—H33A	110.7
C14—C13—H13A	110.5	C32—C33—H33A	110.7
C12—C13—H13B	110.5	C34—C33—H33B	110.7
C14—C13—H13B	110.5	C32—C33—H33B	110.7
H13A—C13—H13B	108.7	H33A—C33—H33B	108.8
C15—C14—C13	105.8 (8)	C35—C34—C33	103.9 (8)
C15—C14—H14A	110.6	C35—C34—H34A	111.0
C13—C14—H14A	110.6	C33—C34—H34A	111.0
C15—C14—H14B	110.6	C35—C34—H34B	111.0
C13—C14—H14B	110.6	C33—C34—H34B	111.0
H14A—C14—H14B	108.7	H34A—C34—H34B	109.0
C14—C15—C11	105.2 (8)	C34—C35—C31	102.5 (8)
C14—C15—H15A	110.7	C34—C35—H35A	111.3
C11—C15—H15A	110.7	C31—C35—H35A	111.3
C14—C15—H15B	110.7	C34—C35—H35B	111.3
C11—C15—H15B	110.7	C31—C35—H35B	111.3
H15A—C15—H15B	108.8	H35A—C35—H35B	109.2
O1—C16—C10	110.2 (7)	O2—C36—C30	111.0 (8)
O1—C16—H16A	109.6	O2—C36—H36A	109.4
C10—C16—H16A	109.6	C30—C36—H36A	109.4
O1—C16—H16B	109.6	O2—C36—H36B	109.4
C10—C16—H16B	109.6	C30—C36—H36B	109.4
H16A—C16—H16B	108.1	H36A—C36—H36B	108.0
C8—N1—N2—N3	0.7 (9)	C28—N4—N5—N6	-0.5 (9)
C9—N1—N2—N3	176.0 (7)	C29—N4—N5—N6	-176.0 (7)
N1—N2—N3—C7	-0.3 (9)	N4—N5—N6—C27	-0.6 (9)

C6—C1—C2—C3	-1.1 (13)	C26—C21—C22—C23	0.9 (15)
C1—C2—C3—C4	1.4 (14)	C21—C22—C23—C24	-0.8 (15)
C1—C2—C3—Br1	-178.4 (6)	C21—C22—C23—Br2	178.6 (6)
C2—C3—C4—C5	-0.4 (13)	C22—C23—C24—C25	0.0 (15)
Br1—C3—C4—C5	179.3 (6)	Br2—C23—C24—C25	-179.4 (7)
C3—C4—C5—C6	-0.9 (13)	C23—C24—C25—C26	0.6 (14)
C4—C5—C6—C1	1.2 (13)	C22—C21—C26—C25	-0.3 (14)
C4—C5—C6—C7	-178.9 (7)	C22—C21—C26—C27	-178.8 (8)
C2—C1—C6—C5	-0.2 (13)	C24—C25—C26—C21	-0.5 (14)
C2—C1—C6—C7	179.9 (7)	C24—C25—C26—C27	178.1 (8)
N2—N3—C7—C8	-0.2 (9)	N5—N6—C27—C28	1.3 (10)
N2—N3—C7—C6	-179.3 (7)	N5—N6—C27—C26	-179.6 (7)
C5—C6—C7—N3	-176.7 (8)	C21—C26—C27—N6	-7.7 (14)
C1—C6—C7—N3	3.2 (12)	C25—C26—C27—N6	173.8 (9)
C5—C6—C7—C8	4.5 (13)	C21—C26—C27—C28	171.1 (9)
C1—C6—C7—C8	-175.6 (8)	C25—C26—C27—C28	-7.4 (14)
N2—N1—C8—C7	-0.8 (9)	N5—N4—C28—C27	1.3 (9)
C9—N1—C8—C7	-175.9 (7)	C29—N4—C28—C27	176.1 (8)
N3—C7—C8—N1	0.6 (8)	N6—C27—C28—N4	-1.5 (9)
C6—C7—C8—N1	179.6 (7)	C26—C27—C28—N4	179.5 (8)
N2—N1—C9—C10	38.5 (11)	N5—N4—C29—C30	-132.4 (8)
C8—N1—C9—C10	-146.8 (8)	C28—N4—C29—C30	53.0 (12)
N1—C9—C10—C11	173.3 (7)	N4—C29—C30—C31	173.3 (7)
N1—C9—C10—C16	48.8 (11)	N4—C29—C30—C36	47.5 (11)
C9—C10—C11—C15	-173.6 (8)	C29—C30—C31—C35	-175.5 (8)
C16—C10—C11—C15	-50.1 (11)	C36—C30—C31—C35	-51.0 (12)
C9—C10—C11—C12	68.1 (10)	C29—C30—C31—C32	64.2 (11)
C16—C10—C11—C12	-168.4 (8)	C36—C30—C31—C32	-171.3 (8)
C10—C11—C12—C13	163.3 (8)	C35—C31—C32—C33	21.9 (11)
C15—C11—C12—C13	37.4 (10)	C30—C31—C32—C33	149.2 (9)
C11—C12—C13—C14	-21.7 (11)	C31—C32—C33—C34	4.3 (11)
C12—C13—C14—C15	-2.7 (11)	C32—C33—C34—C35	-29.1 (12)
C13—C14—C15—C11	26.3 (11)	C33—C34—C35—C31	43.0 (11)
C10—C11—C15—C14	-164.4 (8)	C30—C31—C35—C34	-165.3 (9)
C12—C11—C15—C14	-39.5 (10)	C32—C31—C35—C34	-39.8 (10)
C9—C10—C16—O1	51.5 (10)	C29—C30—C36—O2	50.0 (11)
C11—C10—C16—O1	-69.2 (10)	C31—C30—C36—O2	-71.4 (10)

Table S6. Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O1—H1···Cl2^{i}	0.86	2.32	3.116 (7)	155.4
N6—H6···Cl2	0.92	2.11	3.018 (9)	170.2
O2—H2A···Cl1^{ii}	0.86	2.41	3.180 (7)	150.0
N3—H3···Cl1	0.91	2.10	3.011 (7)	176.0

Symmetry code(s): (i) -*x*, *y*-1/2, -*z*+1; (ii) -*x*, *y*+1/2, -*z*+1.

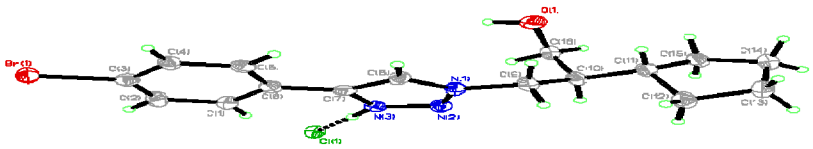


Figure S18. Perspective views showing 50% probability displacement

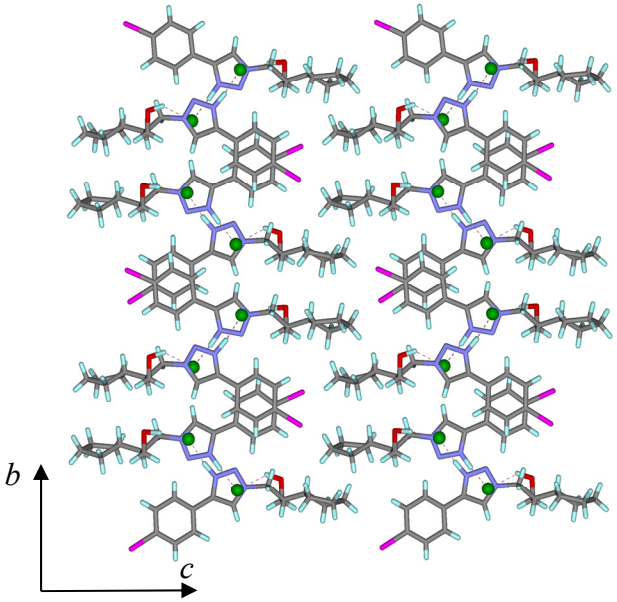
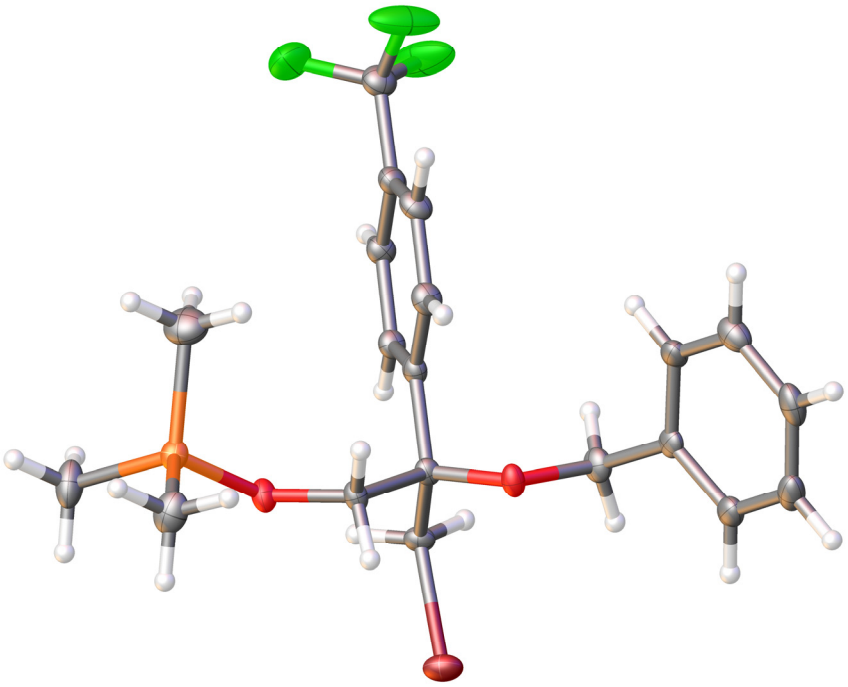


Figure S19. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.



2t

X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A[30] with reflection spot size optimization. Absorption corrections were made with the program SADABS.[30] The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014[26] and SHELXL-2014[27] with OLEX 2 interface.[28] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table **S7** and geometric parameters are shown in Table **S8**. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[29]

Table S7. Experimental details

	DAS-III-249-1
Crystal data	
Chemical formula	$C_{20}H_{24}BrF_3O_2Si$
M_r	461.30
Crystal system, space group	Triclinic, *P*1
Temperature (K)	100
a, *b*, *c* (Å)	9.7525 (2), 10.9189 (2), 11.7345 (2)
α, β, γ (°)	115.1170 (11), 96.8758 (12), 106.1458 (11)
V (Å^3)	1045.39 (4)
Z	2

Radiation type	Mo $K\alpha$
μ (mm^{-1})	2.06
Crystal size (mm)	0.20 × 0.16 × 0.12
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.578, 0.647
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	41662, 9165, 8882
R_{int}	0.023
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.641
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.023, 0.059, 1.03
No. of reflections	9165
No. of parameters	550
No. of restraints	310
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.59, -0.27
Absolute structure	Flack x determined using 4241 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.005 (2)

Computer programs: *SAINT* 8.37A,[25] *SHELXT2014*,[26] *SHELXL2014*,[27] Bruker *SHELXTL*.[26,27]

Table S8. Geometric parameters (Å, º)

Br1—C16	1.944 (3)	Si2—C38	1.860 (4)
Si1—O2	1.663 (2)	O3—C27	1.424 (3)
Si1—C20	1.849 (3)	O3—C28	1.436 (3)
Si1—C19	1.856 (3)	O4—C37	1.423 (3)
Si1—C18	1.857 (4)	C21—C22	1.389 (4)
F1—C15	1.319 (4)	C21—C26	1.391 (4)
F2—C15	1.336 (4)	C21—H21	0.9500
F3—C15	1.319 (4)	C22—C23	1.386 (5)
O1—C8	1.422 (3)	C22—H22	0.9500
O1—C7	1.438 (3)	C23—C24	1.388 (5)

O2—C17	1.418 (3)	C23—H23	0.9500
C1—C2	1.376 (5)	C24—C25	1.395 (4)
C1—C6	1.400 (4)	C24—H24	0.9500
C1—H1	0.9500	C25—C26	1.391 (4)
C2—C3	1.383 (5)	C25—H25	0.9500
C2—H2	0.9500	C26—C27	1.504 (4)
C3—C4	1.379 (5)	C27—H27A	0.9900
C3—H3	0.9500	C27—H27B	0.9900
C4—C5	1.392 (5)	C28—C36	1.523 (4)
C4—H4	0.9500	C28—C29	1.535 (4)
C5—C6	1.391 (4)	C28—C37	1.536 (4)
C5—H5	0.9500	C29—C34	1.395 (4)
C6—C7	1.499 (4)	C29—C30	1.400 (4)
C7—H7A	0.9900	C30—C31	1.377 (4)
C7—H7B	0.9900	C30—H30	0.9500
C8—C16	1.529 (4)	C31—C32	1.394 (4)
C8—C9	1.534 (4)	C31—H31	0.9500
C8—C17	1.540 (4)	C32—C33	1.388 (4)
C9—C14	1.392 (4)	C32—C35B	1.487 (4)
C9—C10	1.397 (4)	C32—C35	1.487 (4)
C10—C11	1.383 (4)	C32—C35A	1.487 (4)
C10—H10	0.9500	C33—C34	1.384 (4)
C11—C12	1.385 (4)	C33—H33	0.9500
C11—H11	0.9500	C34—H34	0.9500
C12—C13	1.394 (4)	C35—F4	1.320 (10)
C12—C15	1.495 (4)	C35—F6	1.324 (8)
C13—C14	1.386 (4)	C35—F5	1.396 (8)
C13—H13	0.9500	C35A—F4A	1.309 (18)
C14—H14	0.9500	C35A—F5A	1.375 (19)
C16—H16A	0.9900	C35A—F6A	1.392 (17)
C16—H16B	0.9900	C35B—F5B	1.223 (13)
C17—H17A	0.9900	C35B—F4B	1.343 (15)
C17—H17B	0.9900	C35B—F6B	1.430 (11)
C18—H18A	0.9800	C36—H36A	0.9900
C18—H18B	0.9800	C36—H36B	0.9900
C18—H18C	0.9800	C37—H37A	0.9900
C19—H19A	0.9800	C37—H37B	0.9900

C19—H19B	0.9800	C38—H38A	0.9800
C19—H19C	0.9800	C38—H38B	0.9800
C20—H20A	0.9800	C38—H38C	0.9800
C20—H20B	0.9800	C39—H39A	0.9800
C20—H20C	0.9800	C39—H39B	0.9800
Br2—C36	1.953 (3)	C39—H39C	0.9800
Si2—O4	1.659 (2)	C40—H40A	0.9800
Si2—C40	1.849 (3)	C40—H40B	0.9800
Si2—C39	1.858 (4)	C40—H40C	0.9800
O2—Si1—C20	105.11 (13)	C22—C21—C26	120.5 (3)
O2—Si1—C19	110.23 (14)	C22—C21—H21	119.8
C20—Si1—C19	111.16 (17)	C26—C21—H21	119.8
O2—Si1—C18	109.67 (14)	C23—C22—C21	120.1 (3)
C20—Si1—C18	111.12 (19)	C23—C22—H22	119.9
C19—Si1—C18	109.48 (17)	C21—C22—H22	119.9
C8—O1—C7	117.1 (2)	C22—C23—C24	119.7 (3)
C17—O2—Si1	121.34 (18)	C22—C23—H23	120.1
C2—C1—C6	120.9 (3)	C24—C23—H23	120.1
C2—C1—H1	119.6	C23—C24—C25	120.3 (3)
C6—C1—H1	119.6	C23—C24—H24	119.9
C1—C2—C3	119.8 (3)	C25—C24—H24	119.9
C1—C2—H2	120.1	C26—C25—C24	120.0 (3)
C3—C2—H2	120.1	C26—C25—H25	120.0
C4—C3—C2	120.5 (3)	C24—C25—H25	120.0
C4—C3—H3	119.8	C21—C26—C25	119.4 (3)
C2—C3—H3	119.8	C21—C26—C27	117.9 (3)
C3—C4—C5	119.8 (3)	C25—C26—C27	122.7 (3)
C3—C4—H4	120.1	O3—C27—C26	110.2 (2)
C5—C4—H4	120.1	O3—C27—H27A	109.6
C6—C5—C4	120.5 (3)	C26—C27—H27A	109.6
C6—C5—H5	119.8	O3—C27—H27B	109.6
C4—C5—H5	119.8	C26—C27—H27B	109.6
C5—C6—C1	118.6 (3)	H27A—C27—H27B	108.1
C5—C6—C7	121.3 (3)	O3—C28—C36	105.6 (2)
C1—C6—C7	119.8 (3)	O3—C28—C29	110.7 (2)
O1—C7—C6	105.7 (2)	C36—C28—C29	106.7 (2)

O1—C7—H7A	110.6	O3—C28—C37	108.6 (2)
C6—C7—H7A	110.6	C36—C28—C37	111.1 (2)
O1—C7—H7B	110.6	C29—C28—C37	113.8 (2)
C6—C7—H7B	110.6	C34—C29—C30	118.6 (3)
H7A—C7—H7B	108.7	C34—C29—C28	122.8 (2)
O1—C8—C16	113.2 (2)	C30—C29—C28	118.6 (2)
O1—C8—C9	109.7 (2)	C31—C30—C29	121.0 (3)
C16—C8—C9	111.0 (2)	C31—C30—H30	119.5
O1—C8—C17	101.7 (2)	C29—C30—H30	119.5
C16—C8—C17	110.7 (2)	C30—C31—C32	119.7 (3)
C9—C8—C17	110.3 (2)	C30—C31—H31	120.2
C14—C9—C10	118.1 (3)	C32—C31—H31	120.2
C14—C9—C8	123.8 (3)	C33—C32—C31	120.1 (3)
C10—C9—C8	118.1 (3)	C33—C32—C35B	120.3 (3)
C11—C10—C9	121.0 (3)	C31—C32—C35B	119.6 (3)
C11—C10—H10	119.5	C33—C32—C35	120.3 (3)
C9—C10—H10	119.5	C31—C32—C35	119.6 (3)
C10—C11—C12	120.4 (3)	C33—C32—C35A	120.3 (3)
C10—C11—H11	119.8	C31—C32—C35A	119.6 (3)
C12—C11—H11	119.8	C34—C33—C32	120.0 (3)
C11—C12—C13	119.4 (3)	C34—C33—H33	120.0
C11—C12—C15	121.9 (3)	C32—C33—H33	120.0
C13—C12—C15	118.7 (3)	C33—C34—C29	120.7 (3)
C14—C13—C12	119.9 (3)	C33—C34—H34	119.7
C14—C13—H13	120.0	C29—C34—H34	119.7
C12—C13—H13	120.0	F4—C35—F6	110.4 (7)
C13—C14—C9	121.2 (3)	F4—C35—F5	103.2 (6)
C13—C14—H14	119.4	F6—C35—F5	101.9 (7)
C9—C14—H14	119.4	F4—C35—C32	114.8 (6)
F3—C15—F1	108.5 (3)	F6—C35—C32	115.0 (4)
F3—C15—F2	104.2 (3)	F5—C35—C32	110.0 (4)
F1—C15—F2	105.0 (3)	F4A—C35A—F5A	105.0 (14)
F3—C15—C12	113.4 (3)	F4A—C35A—F6A	107.9 (14)
F1—C15—C12	113.0 (3)	F5A—C35A—F6A	96.4 (14)
F2—C15—C12	112.0 (3)	F4A—C35A—C32	119.5 (11)
C8—C16—Br1	113.01 (19)	F5A—C35A—C32	111.5 (12)
C8—C16—H16A	109.0	F6A—C35A—C32	113.8 (11)

Br1—C16—H16A	109.0	F5B—C35B—F4B	110.3 (12)
C8—C16—H16B	109.0	F5B—C35B—F6B	110.9 (10)
Br1—C16—H16B	109.0	F4B—C35B—F6B	101.2 (9)
H16A—C16—H16B	107.8	F5B—C35B—C32	116.4 (7)
O2—C17—C8	110.6 (2)	F4B—C35B—C32	110.4 (10)
O2—C17—H17A	109.5	F6B—C35B—C32	106.6 (5)
C8—C17—H17A	109.5	C28—C36—Br2	113.59 (19)
O2—C17—H17B	109.5	C28—C36—H36A	108.8
C8—C17—H17B	109.5	Br2—C36—H36A	108.8
H17A—C17—H17B	108.1	C28—C36—H36B	108.8
Si1—C18—H18A	109.5	Br2—C36—H36B	108.8
Si1—C18—H18B	109.5	H36A—C36—H36B	107.7
H18A—C18—H18B	109.5	O4—C37—C28	109.7 (2)
Si1—C18—H18C	109.5	O4—C37—H37A	109.7
H18A—C18—H18C	109.5	C28—C37—H37A	109.7
H18B—C18—H18C	109.5	O4—C37—H37B	109.7
Si1—C19—H19A	109.5	C28—C37—H37B	109.7
Si1—C19—H19B	109.5	H37A—C37—H37B	108.2
H19A—C19—H19B	109.5	Si2—C38—H38A	109.5
Si1—C19—H19C	109.5	Si2—C38—H38B	109.5
H19A—C19—H19C	109.5	H38A—C38—H38B	109.5
H19B—C19—H19C	109.5	Si2—C38—H38C	109.5
Si1—C20—H20A	109.5	H38A—C38—H38C	109.5
Si1—C20—H20B	109.5	H38B—C38—H38C	109.5
H20A—C20—H20B	109.5	Si2—C39—H39A	109.5
Si1—C20—H20C	109.5	Si2—C39—H39B	109.5
H20A—C20—H20C	109.5	H39A—C39—H39B	109.5
H20B—C20—H20C	109.5	Si2—C39—H39C	109.5
O4—Si2—C40	105.62 (13)	H39A—C39—H39C	109.5
O4—Si2—C39	108.54 (15)	H39B—C39—H39C	109.5
C40—Si2—C39	112.24 (18)	Si2—C40—H40A	109.5
O4—Si2—C38	109.27 (14)	Si2—C40—H40B	109.5
C40—Si2—C38	111.61 (17)	H40A—C40—H40B	109.5
C39—Si2—C38	109.41 (19)	Si2—C40—H40C	109.5
C27—O3—C28	115.1 (2)	H40A—C40—H40C	109.5
C37—O4—Si2	120.28 (17)	H40B—C40—H40C	109.5

C20—Si1—O2—C17	-171.9 (2)	C22—C21—C26—C27	-179.8 (3)
C19—Si1—O2—C17	-52.0 (2)	C24—C25—C26—C21	-0.5 (5)
C18—Si1—O2—C17	68.6 (3)	C24—C25—C26—C27	179.7 (3)
C6—C1—C2—C3	-0.3 (4)	C28—O3—C27—C26	166.3 (2)
C1—C2—C3—C4	1.1 (5)	C21—C26—C27—O3	169.0 (3)
C2—C3—C4—C5	-1.0 (5)	C25—C26—C27—O3	-11.3 (4)
C3—C4—C5—C6	0.1 (4)	C27—O3—C28—C36	167.8 (2)
C4—C5—C6—C1	0.7 (4)	C27—O3—C28—C29	52.7 (3)
C4—C5—C6—C7	-172.9 (3)	C27—O3—C28—C37	-72.9 (3)
C2—C1—C6—C5	-0.6 (4)	O3—C28—C29—C34	-128.9 (3)
C2—C1—C6—C7	173.1 (3)	C36—C28—C29—C34	116.7 (3)
C8—O1—C7—C6	159.2 (2)	C37—C28—C29—C34	-6.3 (4)
C5—C6—C7—O1	95.9 (3)	O3—C28—C29—C30	50.0 (3)
C1—C6—C7—O1	-77.6 (3)	C36—C28—C29—C30	-64.4 (3)
C7—O1—C8—C16	59.3 (3)	C37—C28—C29—C30	172.6 (2)
C7—O1—C8—C9	-65.1 (3)	C34—C29—C30—C31	-0.4 (4)
C7—O1—C8—C17	178.1 (2)	C28—C29—C30—C31	-179.3 (3)
O1—C8—C9—C14	130.1 (3)	C29—C30—C31—C32	0.1 (5)
C16—C8—C9—C14	4.4 (4)	C30—C31—C32—C33	0.1 (5)
C17—C8—C9—C14	-118.7 (3)	C30—C31—C32—C35B	177.6 (3)
O1—C8—C9—C10	-49.8 (3)	C30—C31—C32—C35	177.6 (3)
C16—C8—C9—C10	-175.5 (2)	C30—C31—C32—C35A	177.6 (3)
C17—C8—C9—C10	61.4 (3)	C31—C32—C33—C34	0.1 (5)
C14—C9—C10—C11	0.4 (4)	C35B—C32—C33—C34	-177.5 (3)
C8—C9—C10—C11	-179.7 (3)	C35—C32—C33—C34	-177.5 (3)
C9—C10—C11—C12	0.2 (5)	C35A—C32—C33—C34	-177.5 (3)
C10—C11—C12—C13	-1.1 (4)	C32—C33—C34—C29	-0.4 (4)
C10—C11—C12—C15	179.6 (3)	C30—C29—C34—C33	0.5 (4)
C11—C12—C13—C14	1.3 (4)	C28—C29—C34—C33	179.4 (3)
C15—C12—C13—C14	-179.3 (3)	C33—C32—C35—F4	-138.8 (8)
C12—C13—C14—C9	-0.8 (4)	C31—C32—C35—F4	43.7 (9)
C10—C9—C14—C13	-0.1 (4)	C33—C32—C35—F6	-9.0 (12)
C8—C9—C14—C13	180.0 (3)	C31—C32—C35—F6	173.5 (11)
C11—C12—C15—F3	132.3 (3)	C33—C32—C35—F5	105.4 (7)
C13—C12—C15—F3	-47.0 (4)	C31—C32—C35—F5	-72.2 (8)
C11—C12—C15—F1	8.3 (4)	C33—C32—C35A—F4A	-108.7 (19)
C13—C12—C15—F1	-171.0 (3)	C31—C32—C35A—F4A	73.7 (19)

C11—C12—C15—F2	-110.1 (3)	C33—C32—C35A—F5A	128.4 (18)
C13—C12—C15—F2	70.6 (4)	C31—C32—C35A—F5A	-49.1 (18)
O1—C8—C16—Br1	52.5 (3)	C33—C32—C35A—F6A	21 (2)
C9—C8—C16—Br1	176.26 (18)	C31—C32—C35A—F6A	-156.8 (19)
C17—C8—C16—Br1	-60.9 (3)	C33—C32—C35B—F5B	74.7 (15)
Si1—O2—C17—C8	-142.0 (2)	C31—C32—C35B—F5B	-102.9 (15)
O1—C8—C17—O2	-177.4 (2)	C33—C32—C35B—F4B	-158.7 (10)
C16—C8—C17—O2	-56.9 (3)	C31—C32—C35B—F4B	23.8 (10)
C9—C8—C17—O2	66.4 (3)	C33—C32—C35B—F6B	-49.6 (10)
C40—Si2—O4—C37	167.7 (2)	C31—C32—C35B—F6B	132.9 (10)
C39—Si2—O4—C37	-71.8 (2)	O3—C28—C36—Br2	57.8 (2)
C38—Si2—O4—C37	47.5 (2)	C29—C28—C36—Br2	175.58 (18)
C26—C21—C22—C23	-0.2 (5)	C37—C28—C36—Br2	-59.8 (3)
C21—C22—C23—C24	0.2 (5)	Si2—O4—C37—C28	176.23 (18)
C22—C23—C24—C25	-0.3 (5)	O3—C28—C37—O4	-167.3 (2)
C23—C24—C25—C26	0.5 (5)	C36—C28—C37—O4	-51.6 (3)
C22—C21—C26—C25	0.4 (5)	C29—C28—C37—O4	68.9 (3)

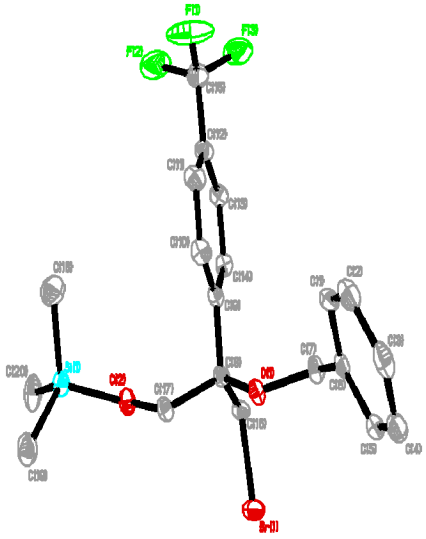


Figure S20. Perspective views showing 50% probability displacement

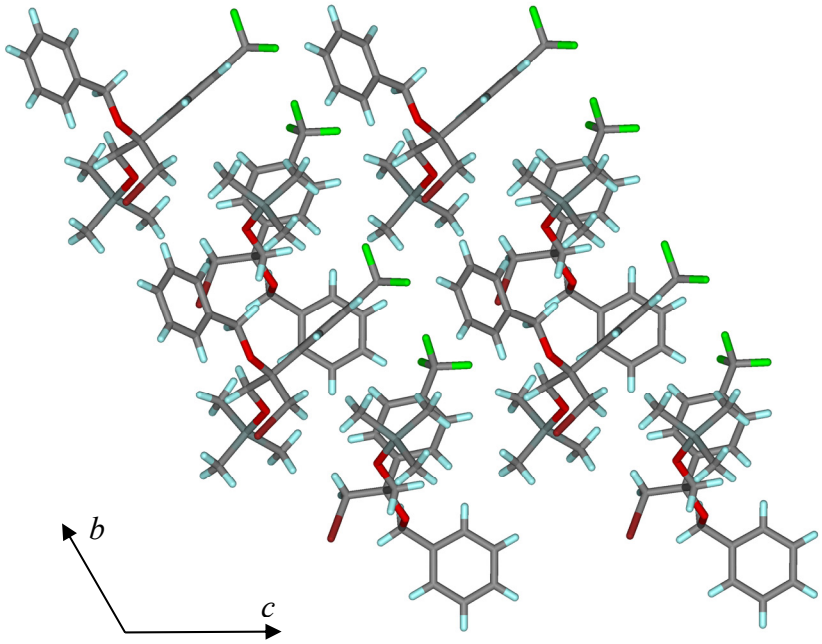
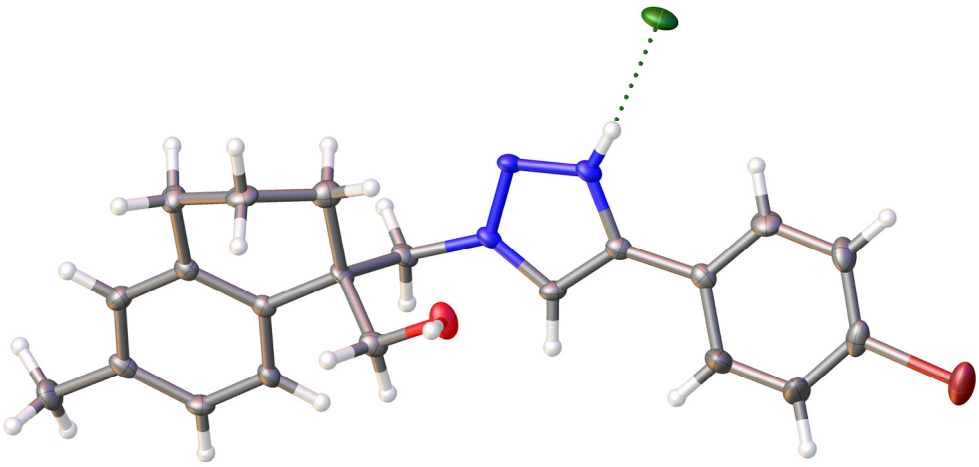


Figure S21. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.



26u

X-ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A[30] with reflection spot size optimization. Absorption corrections were made with the program TWINABS.[30] The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014[26] and SHELXL-2014[27] with OLEX 2 interface.[28] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table **S9**, geometric parameters are shown in Table **S10** and hydrogen-bond parameters are listed in Table **S11**. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0.[29]

Table S9. Experimental details

	DAS-VI-88
Crystal data	
Chemical formula	$C_{23}H_{28}BrClN_3O_{1.50}$
M_r	485.84
Crystal system, space group	Monoclinic, *C*2
Temperature (K)	100
a, *b*, *c* (Å)	31.216 (3), 8.4388 (8), 8.5385 (8)
β (°)	93.3905 (17)
V (Å^3)	2245.4 (4)
Z	4
Radiation type	Mo *K*α
μ (mm^{-1})	1.97
Crystal size (mm)	0.14 × 0.12 × 0.06

Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan twinabs
T_{min}, T_{max}	0.616, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	6527, 6527, 6120
R_{int}	0.032
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.641
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.033, 0.064, 1.04
No. of reflections	6527
No. of parameters	301
No. of restraints	25
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.48, -0.28
Absolute structure	Flack x determined using 1947 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.006 (3)

Computer programs: *SAINT* 8.37A,[25] *SHELXT2014*,[26] *SHELXL2014*,[27] Bruker *SHELXTL*.[26,27]

Table S10. Geometric parameters (Å, º)

Br1—C17	1.897 (4)	C11—H11B	0.9900
O1—C21	1.419 (5)	C12—C13	1.368 (6)
O1—H1	0.93 (5)	C12—H12	0.9500
N1—N2	1.327 (5)	C13—C14	1.470 (6)
N1—C12	1.341 (5)	C14—C15	1.383 (7)
N1—C11	1.472 (5)	C14—C19	1.384 (7)
N2—N3	1.319 (5)	C15—C16	1.381 (7)
N3—C13	1.356 (6)	C15—H15	0.9500
N3—H3	0.82 (6)	C16—C17	1.359 (8)
C1—C2	1.531 (6)	C16—H16	0.9500
C1—C10	1.550 (6)	C17—C18	1.372 (7)
C1—H1A	0.9900	C18—C19	1.383 (7)
C1—H1B	0.9900	C18—H18	0.9500

C2—C3	1.525 (6)	C19—H19	0.9500
C2—H2A	0.9900	C20—H20A	0.9800
C2—H2B	0.9900	C20—H20B	0.9800
C3—C4	1.516 (6)	C20—H20C	0.9800
C3—H3A	0.9900	C21—H21A	0.9900
C3—H3B	0.9900	C21—H21B	0.9900
C4—C9	1.393 (6)	C1S—C2S	1.519 (14)
C4—C5	1.393 (6)	C1S—H1SA	0.9800
C5—C6	1.394 (6)	C1S—H1SB	0.9800
C5—H5	0.9500	C1S—H1SC	0.9800
C6—C7	1.393 (7)	C2S—O1S	1.393 (16)
C6—C20	1.498 (7)	C2S—H2SA	0.9900
C7—C8	1.400 (7)	C2S—H2SB	0.9900
C7—H7	0.9500	O1S—C3S	1.419 (16)
C8—C9	1.386 (7)	C3S—C4S	1.500 (16)
C8—H8	0.9500	C3S—H3SA	0.9900
C9—C10	1.533 (6)	C3S—H3SB	0.9900
C10—C11	1.533 (6)	C4S—H4SA	0.9800
C10—C21	1.549 (5)	C4S—H4SB	0.9800
C11—H11A	0.9900	C4S—H4SC	0.9800
C21—O1—H1	108 (3)	N3—C13—C12	104.5 (4)
N2—N1—C12	112.5 (4)	N3—C13—C14	125.8 (4)
N2—N1—C11	121.3 (4)	C12—C13—C14	129.7 (4)
C12—N1—C11	126.2 (4)	C15—C14—C19	119.3 (4)
N3—N2—N1	103.7 (3)	C15—C14—C13	117.7 (4)
N2—N3—C13	113.1 (4)	C19—C14—C13	123.0 (4)
N2—N3—H3	117 (4)	C16—C15—C14	119.9 (5)
C13—N3—H3	130 (4)	C16—C15—H15	120.0
C2—C1—C10	111.5 (4)	C14—C15—H15	120.0
C2—C1—H1A	109.3	C17—C16—C15	120.2 (5)
C10—C1—H1A	109.3	C17—C16—H16	119.9
C2—C1—H1B	109.3	C15—C16—H16	119.9
C10—C1—H1B	109.3	C16—C17—C18	121.0 (4)
H1A—C1—H1B	108.0	C16—C17—Br1	118.6 (4)
C3—C2—C1	109.4 (4)	C18—C17—Br1	120.3 (4)
C3—C2—H2A	109.8	C17—C18—C19	119.3 (5)

C1—C2—H2A	109.8	C17—C18—H18	120.4
C3—C2—H2B	109.8	C19—C18—H18	120.4
C1—C2—H2B	109.8	C18—C19—C14	120.3 (5)
H2A—C2—H2B	108.2	C18—C19—H19	119.8
C4—C3—C2	111.3 (4)	C14—C19—H19	119.8
C4—C3—H3A	109.4	C6—C20—H20A	109.5
C2—C3—H3A	109.4	C6—C20—H20B	109.5
C4—C3—H3B	109.4	H20A—C20—H20B	109.5
C2—C3—H3B	109.4	C6—C20—H20C	109.5
H3A—C3—H3B	108.0	H20A—C20—H20C	109.5
C9—C4—C5	118.9 (4)	H20B—C20—H20C	109.5
C9—C4—C3	122.2 (4)	O1—C21—C10	113.4 (4)
C5—C4—C3	119.0 (4)	O1—C21—H21A	108.9
C4—C5—C6	123.5 (5)	C10—C21—H21A	108.9
C4—C5—H5	118.2	O1—C21—H21B	108.9
C6—C5—H5	118.2	C10—C21—H21B	108.9
C7—C6—C5	116.5 (5)	H21A—C21—H21B	107.7
C7—C6—C20	121.7 (4)	C2S—C1S—H1SA	109.5
C5—C6—C20	121.7 (5)	C2S—C1S—H1SB	109.5
C6—C7—C8	120.7 (4)	H1SA—C1S—H1SB	109.5
C6—C7—H7	119.6	C2S—C1S—H1SC	109.5
C8—C7—H7	119.6	H1SA—C1S—H1SC	109.5
C9—C8—C7	121.5 (4)	H1SB—C1S—H1SC	109.5
C9—C8—H8	119.2	O1S—C2S—C1S	108.1 (12)
C7—C8—H8	119.2	O1S—C2S—H2SA	110.1
C8—C9—C4	118.6 (4)	C1S—C2S—H2SA	110.1
C8—C9—C10	119.3 (4)	O1S—C2S—H2SB	110.1
C4—C9—C10	122.1 (4)	C1S—C2S—H2SB	110.1
C9—C10—C11	106.3 (3)	H2SA—C2S—H2SB	108.4
C9—C10—C21	107.2 (3)	C2S—O1S—C3S	112.8 (10)
C11—C10—C21	111.8 (4)	O1S—C3S—C4S	109.3 (11)
C9—C10—C1	112.7 (4)	O1S—C3S—H3SA	109.8
C11—C10—C1	108.9 (3)	C4S—C3S—H3SA	109.8
C21—C10—C1	109.9 (3)	O1S—C3S—H3SB	109.8
N1—C11—C10	114.2 (3)	C4S—C3S—H3SB	109.8
N1—C11—H11A	108.7	H3SA—C3S—H3SB	108.3
C10—C11—H11A	108.7	C3S—C4S—H4SA	109.5

N1—C11—H11B	108.7	C3S—C4S—H4SB	109.5
C10—C11—H11B	108.7	H4SA—C4S—H4SB	109.5
H11A—C11—H11B	107.6	C3S—C4S—H4SC	109.5
N1—C12—C13	106.2 (4)	H4SA—C4S—H4SC	109.5
N1—C12—H12	126.9	H4SB—C4S—H4SC	109.5
C13—C12—H12	126.9		
C12—N1—N2—N3	0.1 (5)	C12—N1—C11—C10	99.1 (5)
C11—N1—N2—N3	-179.7 (3)	C9—C10—C11—N1	-169.7 (3)
N1—N2—N3—C13	-0.5 (4)	C21—C10—C11—N1	-53.1 (5)
C10—C1—C2—C3	-63.9 (5)	C1—C10—C11—N1	68.5 (5)
C1—C2—C3—C4	53.2 (5)	N2—N1—C12—C13	0.2 (5)
C2—C3—C4—C9	-19.5 (6)	C11—N1—C12—C13	-180.0 (4)
C2—C3—C4—C5	158.9 (4)	N2—N3—C13—C12	0.6 (5)
C9—C4—C5—C6	2.5 (7)	N2—N3—C13—C14	-177.8 (4)
C3—C4—C5—C6	-175.9 (5)	N1—C12—C13—N3	-0.5 (5)
C4—C5—C6—C7	0.9 (7)	N1—C12—C13—C14	177.9 (4)
C4—C5—C6—C20	-179.4 (5)	N3—C13—C14—C15	169.2 (5)
C5—C6—C7—C8	-2.6 (7)	C12—C13—C14—C15	-8.9 (7)
C20—C6—C7—C8	177.7 (4)	N3—C13—C14—C19	-9.1 (7)
C6—C7—C8—C9	0.9 (7)	C12—C13—C14—C19	172.8 (5)
C7—C8—C9—C4	2.6 (6)	C19—C14—C15—C16	1.2 (9)
C7—C8—C9—C10	-177.4 (4)	C13—C14—C15—C16	-177.2 (5)
C5—C4—C9—C8	-4.2 (6)	C14—C15—C16—C17	-0.3 (10)
C3—C4—C9—C8	174.2 (4)	C15—C16—C17—C18	-0.9 (9)
C5—C4—C9—C10	175.8 (4)	C15—C16—C17—Br1	177.7 (5)
C3—C4—C9—C10	-5.8 (6)	C16—C17—C18—C19	1.1 (8)
C8—C9—C10—C11	57.0 (5)	Br1—C17—C18—C19	-177.4 (4)
C4—C9—C10—C11	-123.0 (4)	C17—C18—C19—C14	-0.2 (8)
C8—C9—C10—C21	-62.7 (5)	C15—C14—C19—C18	-1.0 (8)
C4—C9—C10—C21	117.3 (4)	C13—C14—C19—C18	177.3 (4)
C8—C9—C10—C1	176.2 (4)	C9—C10—C21—O1	-176.8 (4)
C4—C9—C10—C1	-3.7 (6)	C11—C10—C21—O1	67.1 (5)
C2—C1—C10—C9	38.0 (5)	C1—C10—C21—O1	-54.0 (5)
C2—C1—C10—C11	155.8 (4)	C1S—C2S—O1S—C3S	-177.7 (14)
C2—C1—C10—C21	-81.4 (4)	C2S—O1S—C3S—C4S	175.5 (14)
N2—N1—C11—C10	-81.1 (5)		

Table S11. Hydrogen-bond parameters

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
O1—H1···Cl1^{i}	0.93 (5)	2.22 (5)	3.126 (4)	166 (5)
N3—H3···Cl1	0.82 (6)	2.18 (6)	3.003 (4)	174 (6)

Symmetry code(s): (i) -*x*-3/2, *y*-1/2, -*z*-1.

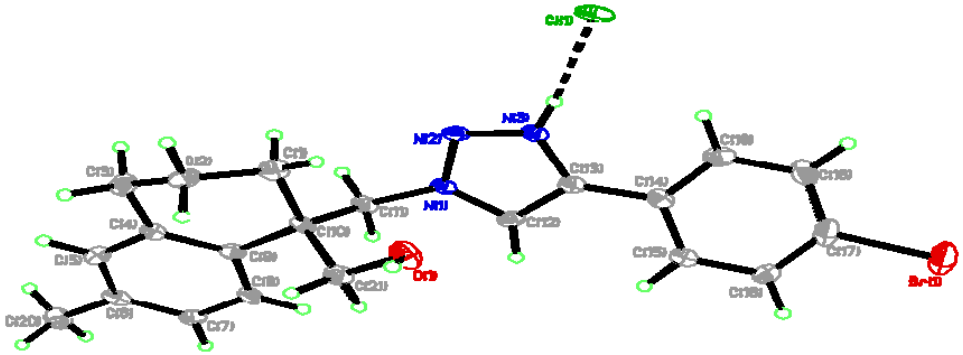


Figure S22. Perspective views showing 50% probability displacement

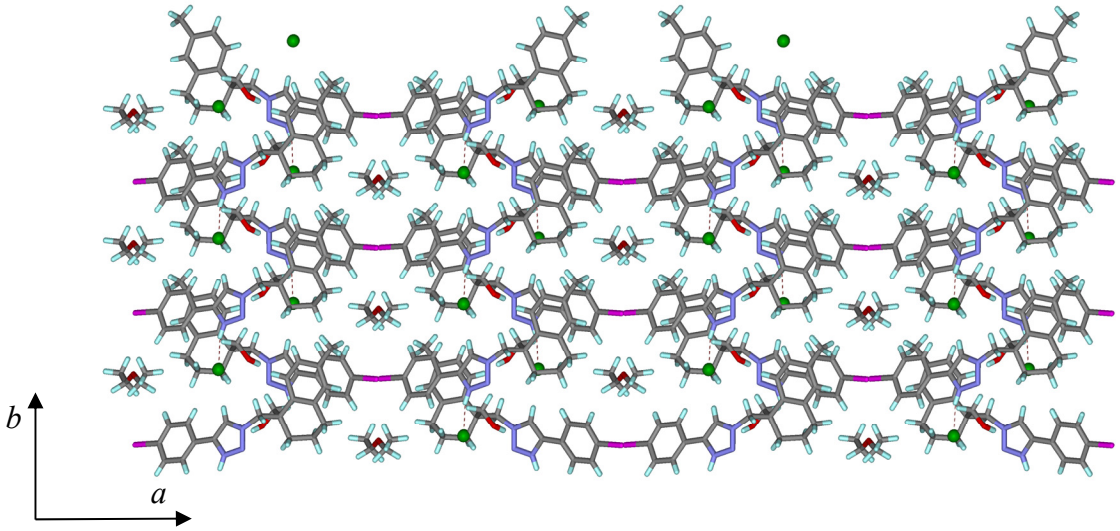
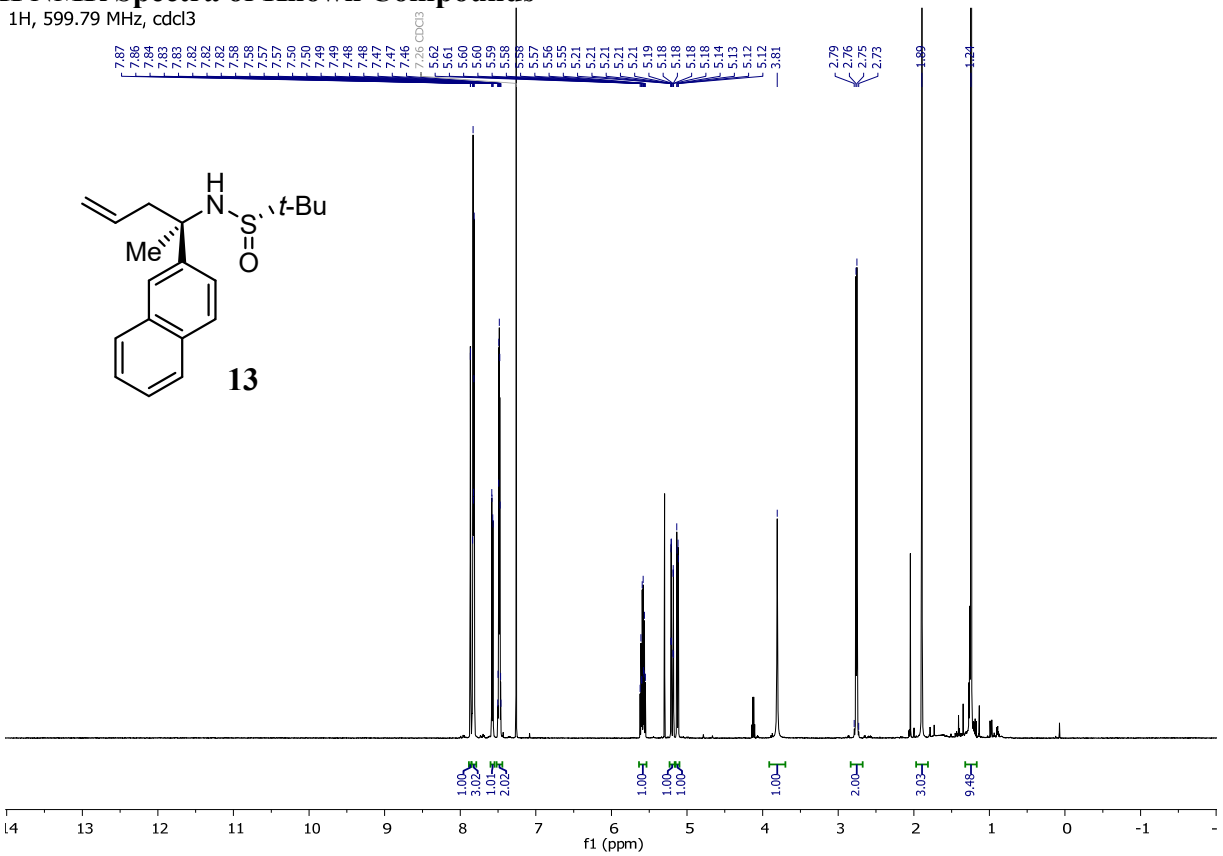
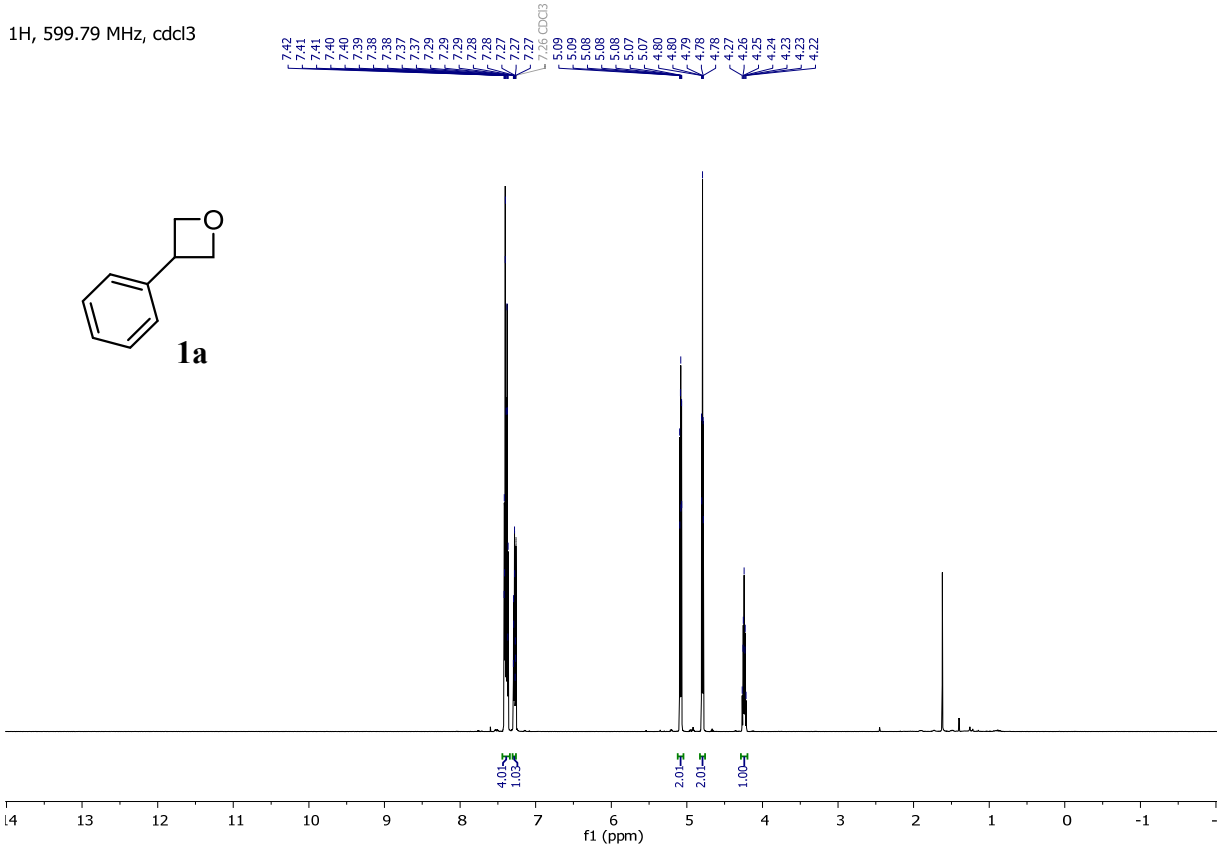


Figure S23. Three-dimensional supramolecular architecture viewed along the *c*-axis direction

^{1}H NMR Spectra of Known Compounds





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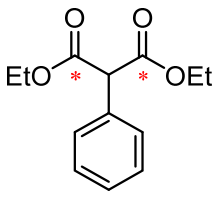
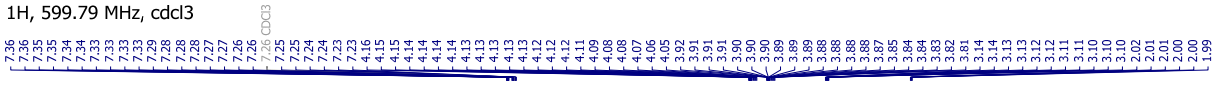
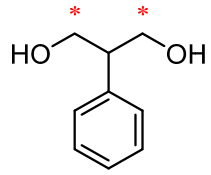


16

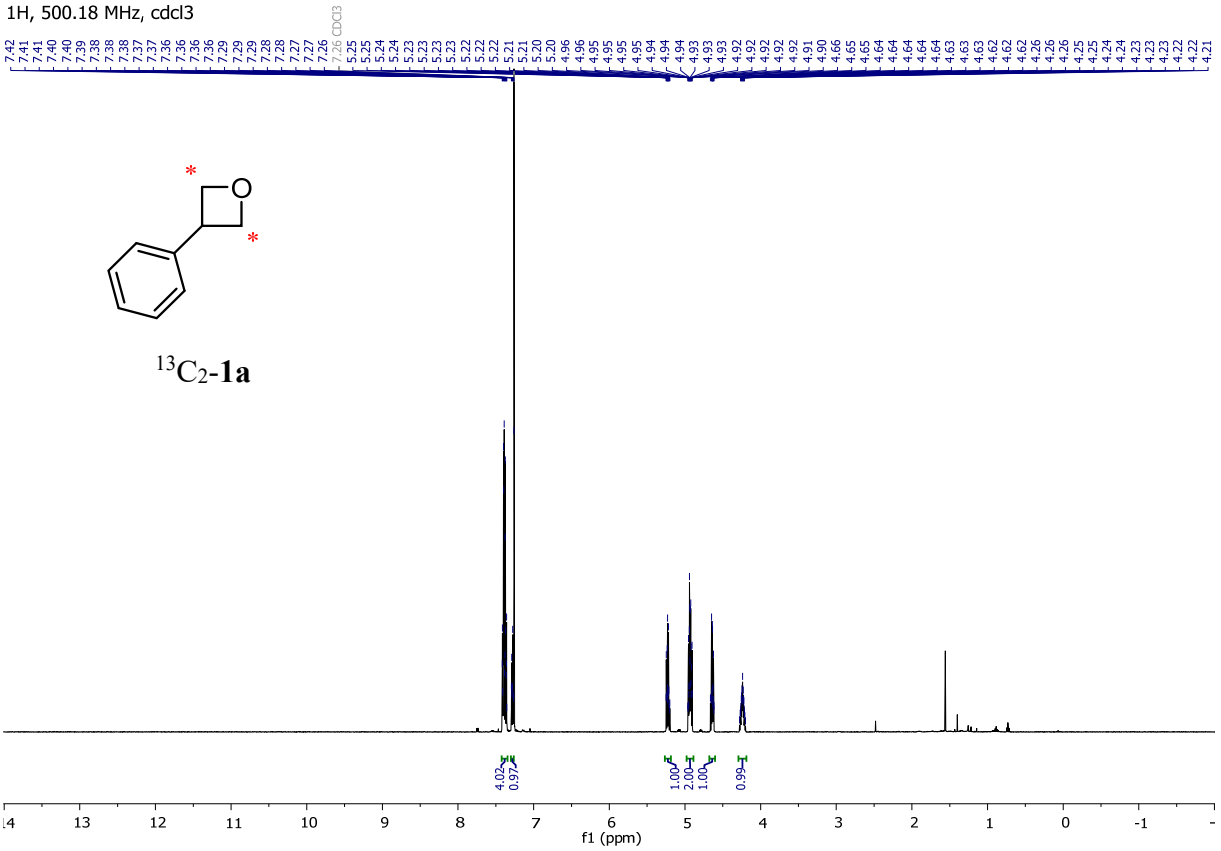
1H, 599.79 MHz, cdcl3





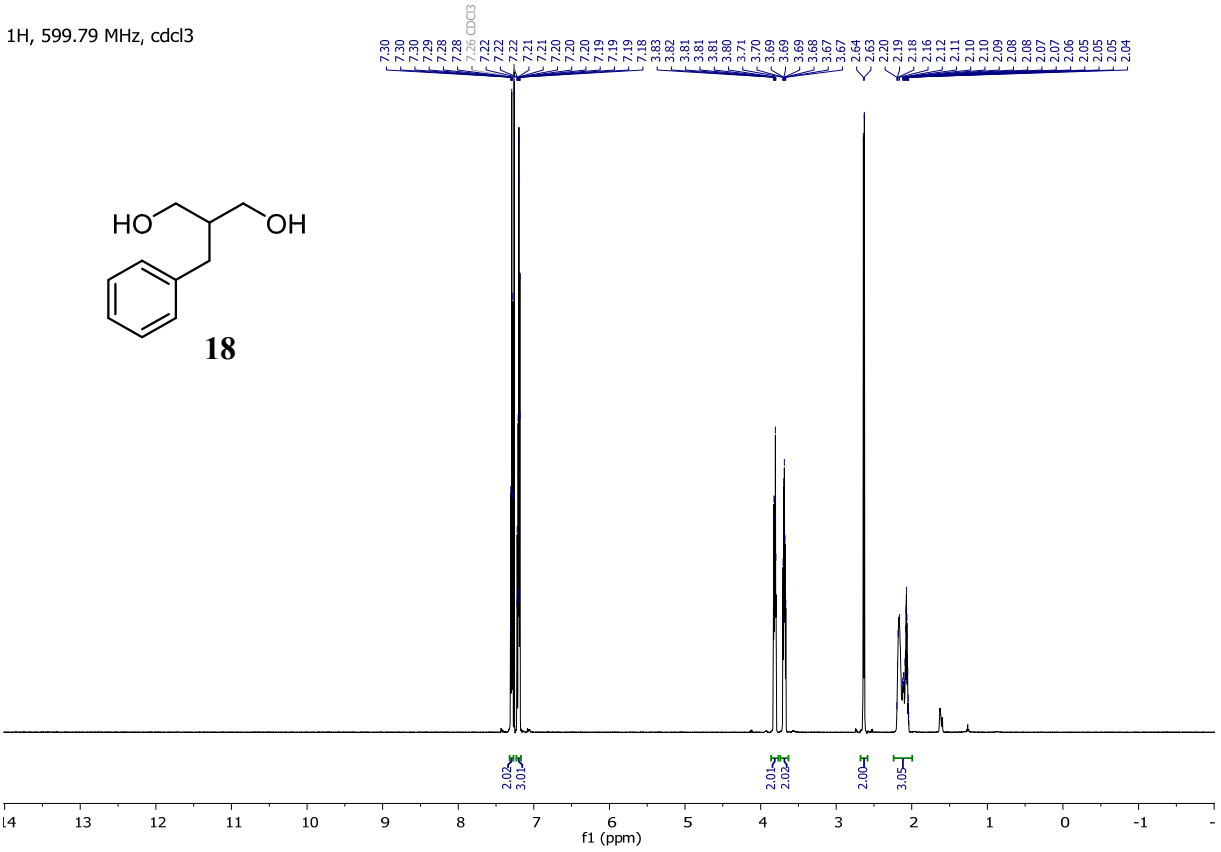
17

1H, 500.18 MHz, cdcl3



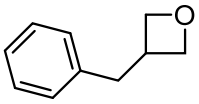
$^{13}C_2$-**1a**

1H, 599.79 MHz, cdcl3



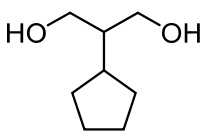
18

1H, 599.79 MHz, cdcl3



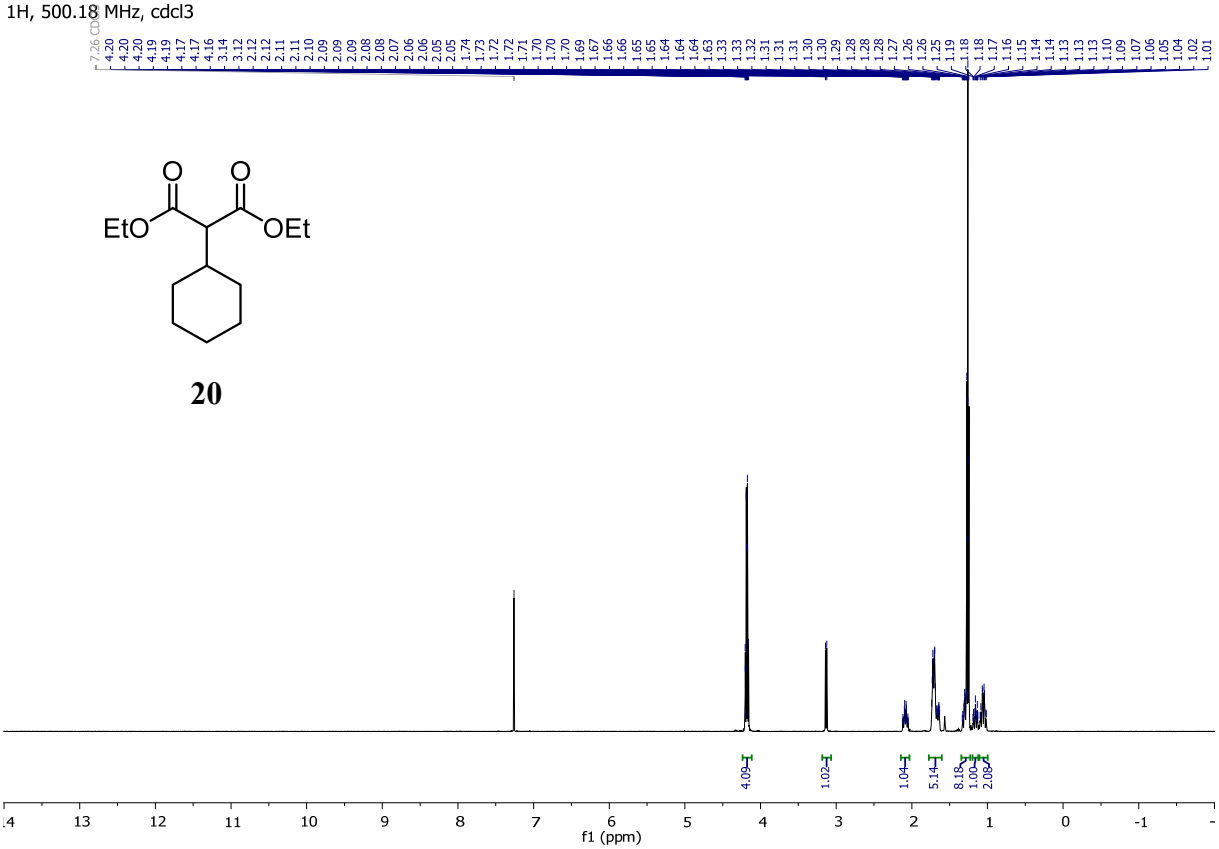
1p

1H, 399.78 MHz, cdcl3



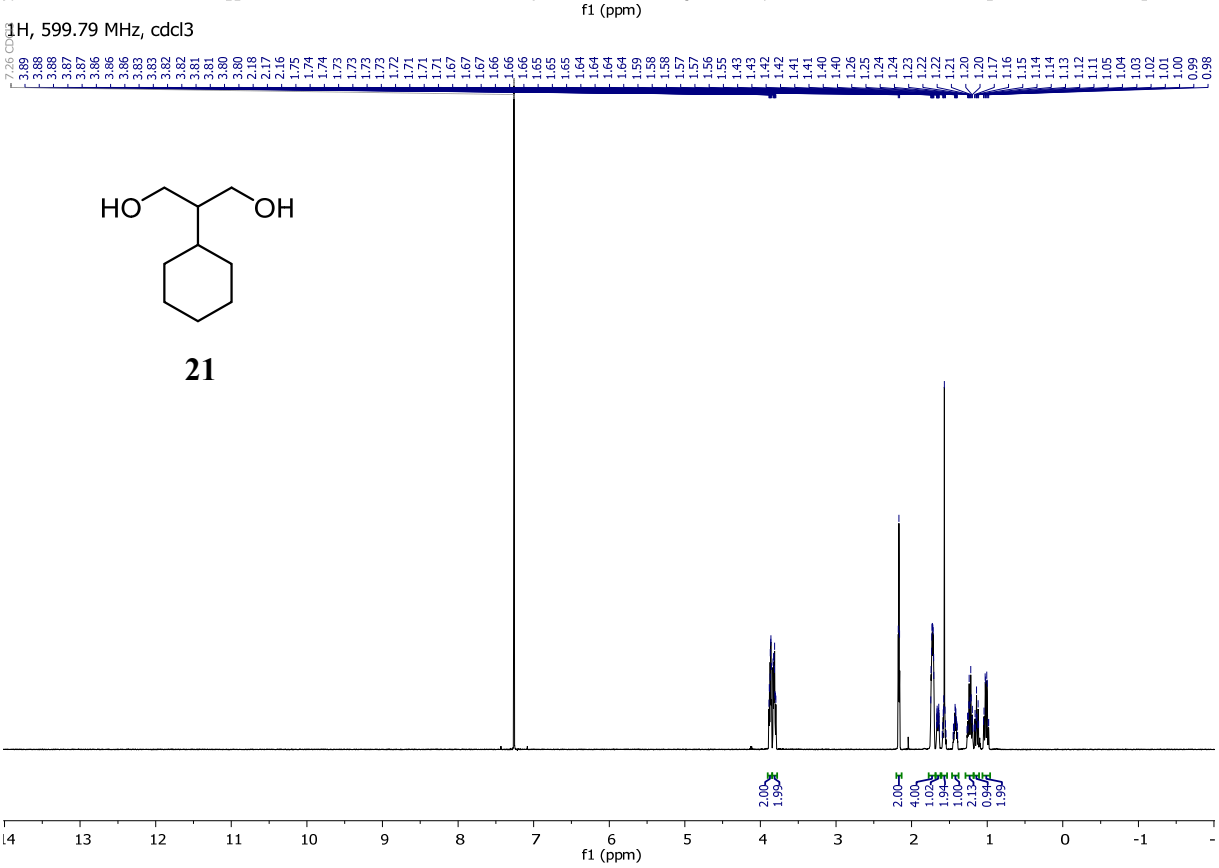
19

1H, 500.18 MHz, cdcl3



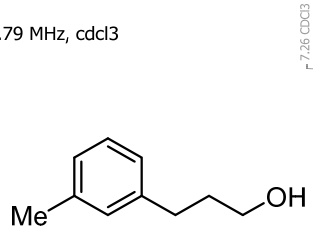
20

1H, 599.79 MHz, cdcl3



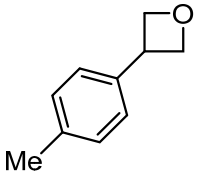
21

1H, 599.79 MHz, cdcl3



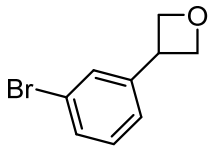
22

1H, 599.79 MHz, cdcl3

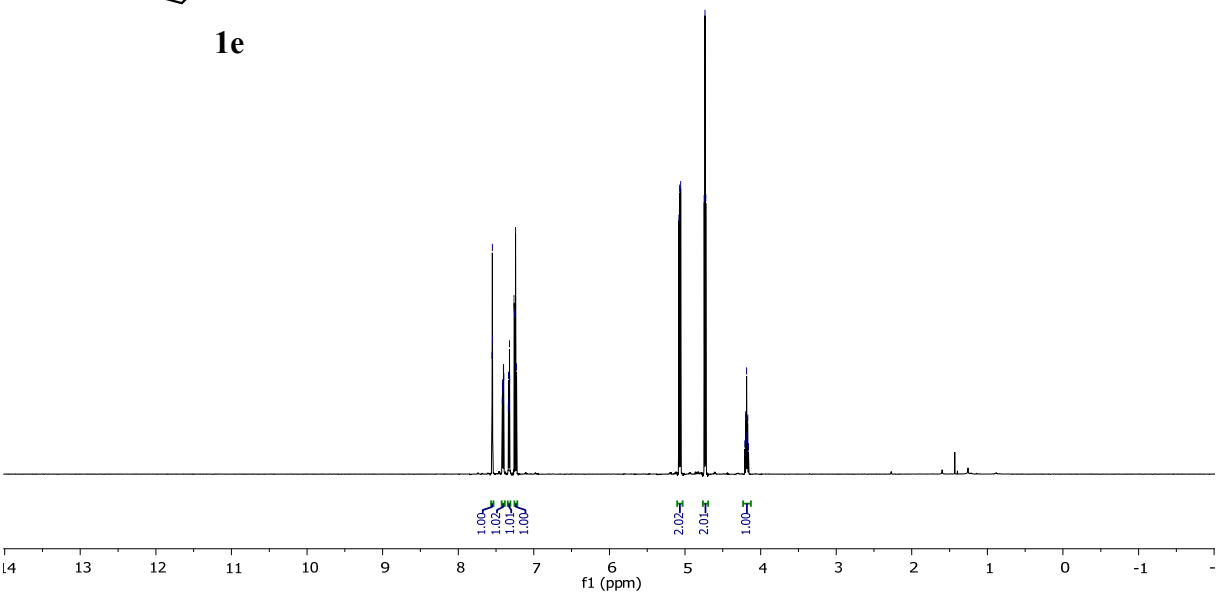


1b

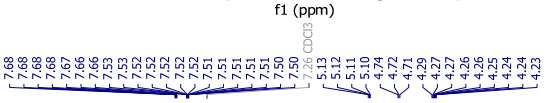
1H, 599.79 MHz, cdcl3

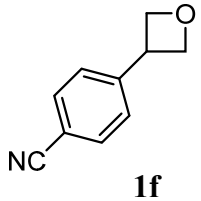


1e



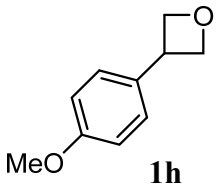
1H, 500.18 MHz, cdcl3





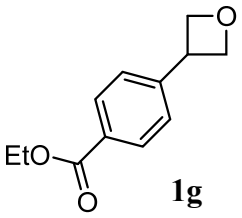
1f

1H, 599.79 MHz, cdcl3



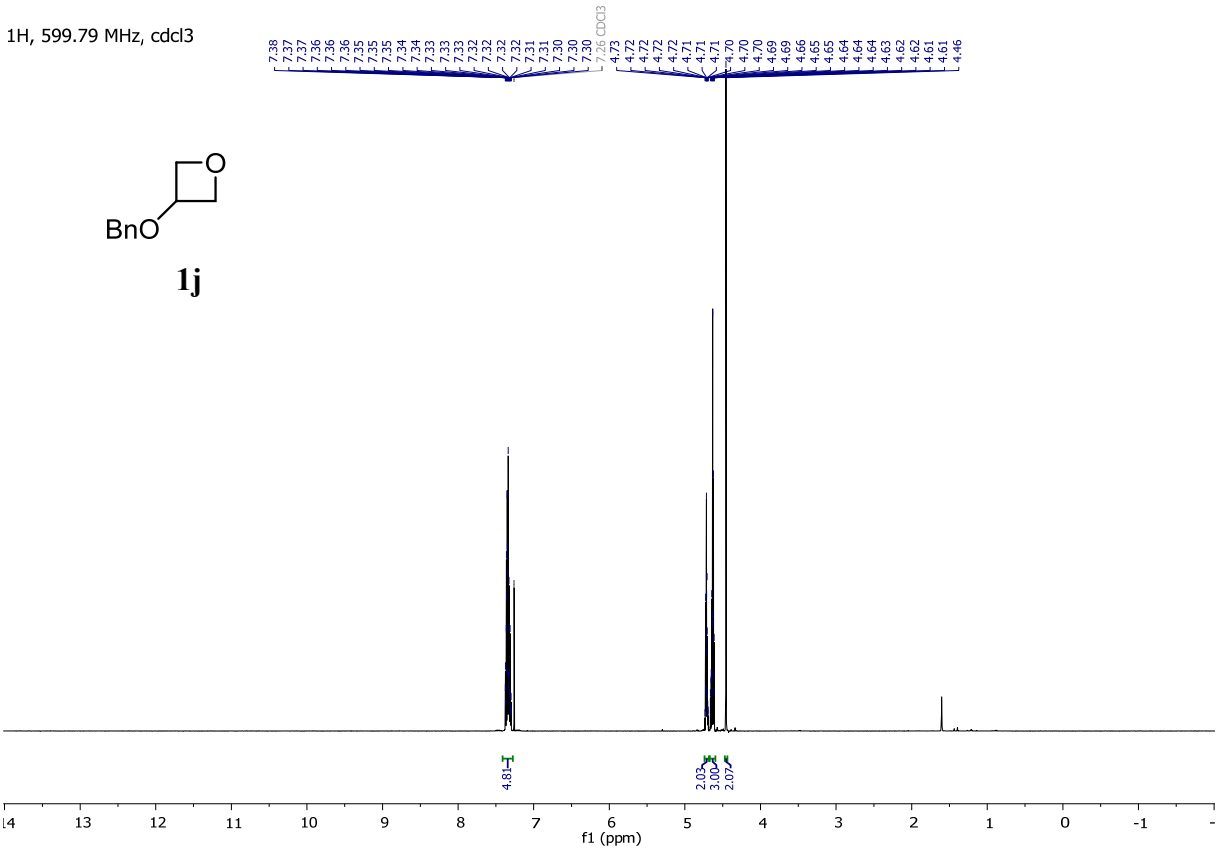
1h

1H, 599.79 MHz, cdcl3



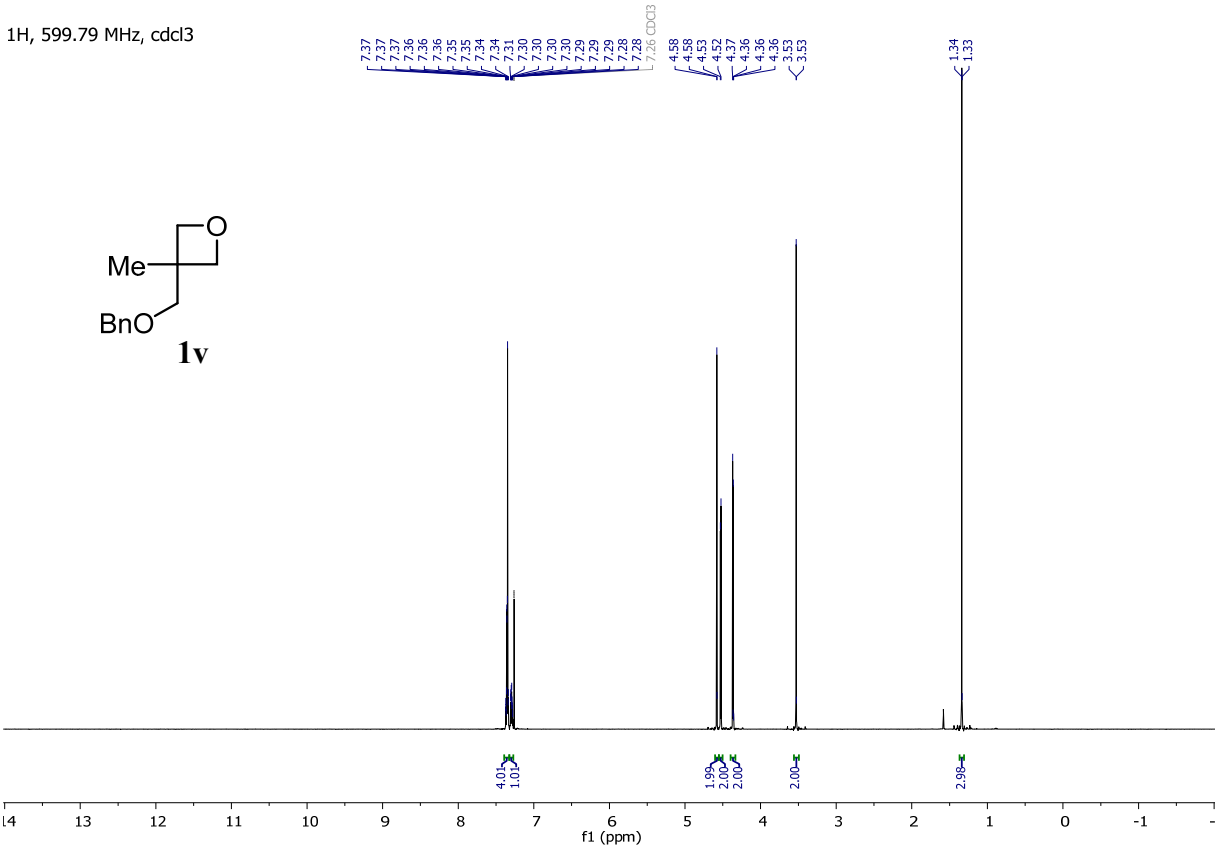
1g

1H, 599.79 MHz, cdcl3



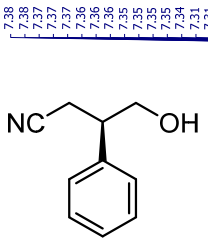
1j

1H, 599.79 MHz, cdcl3



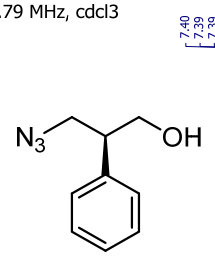
1v

1H, 599.79 MHz, cdcl3



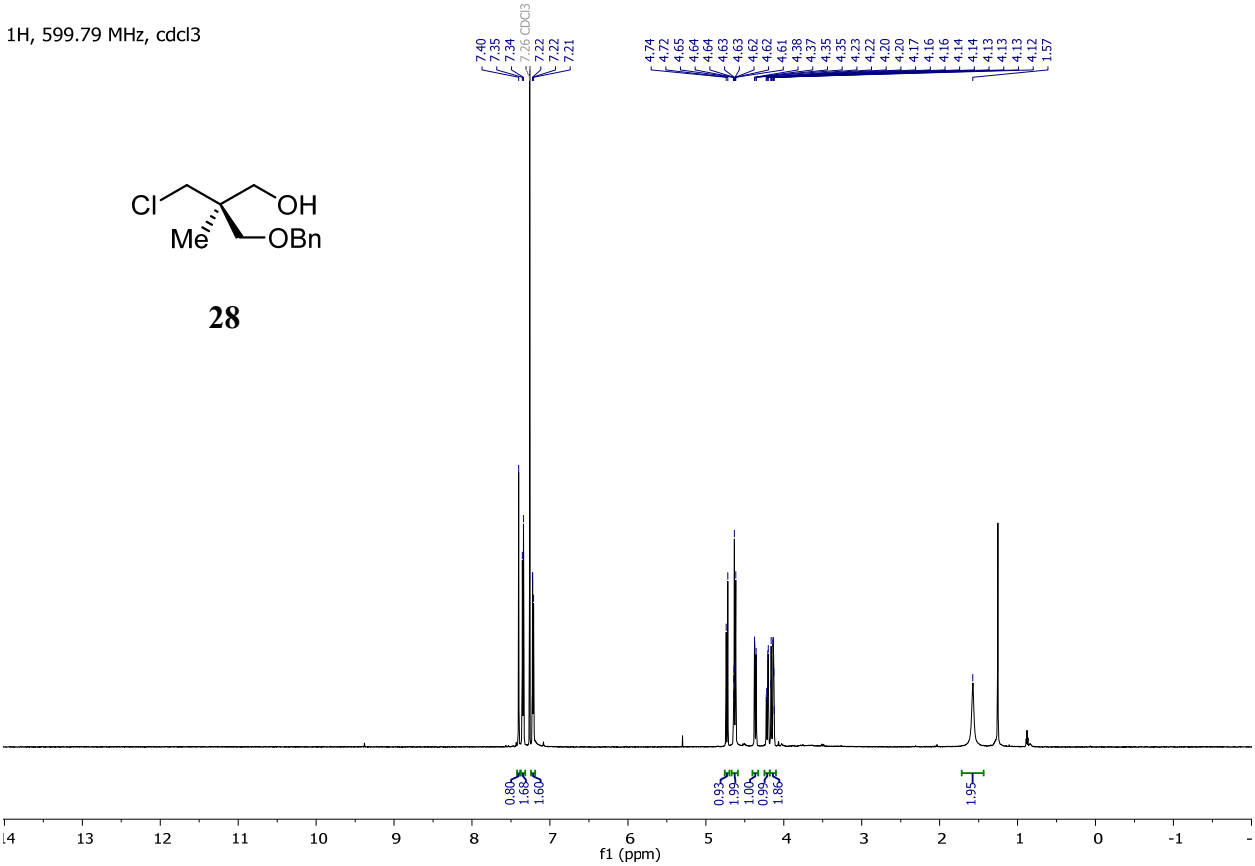
4a

1H, 599.79 MHz, cdcl3



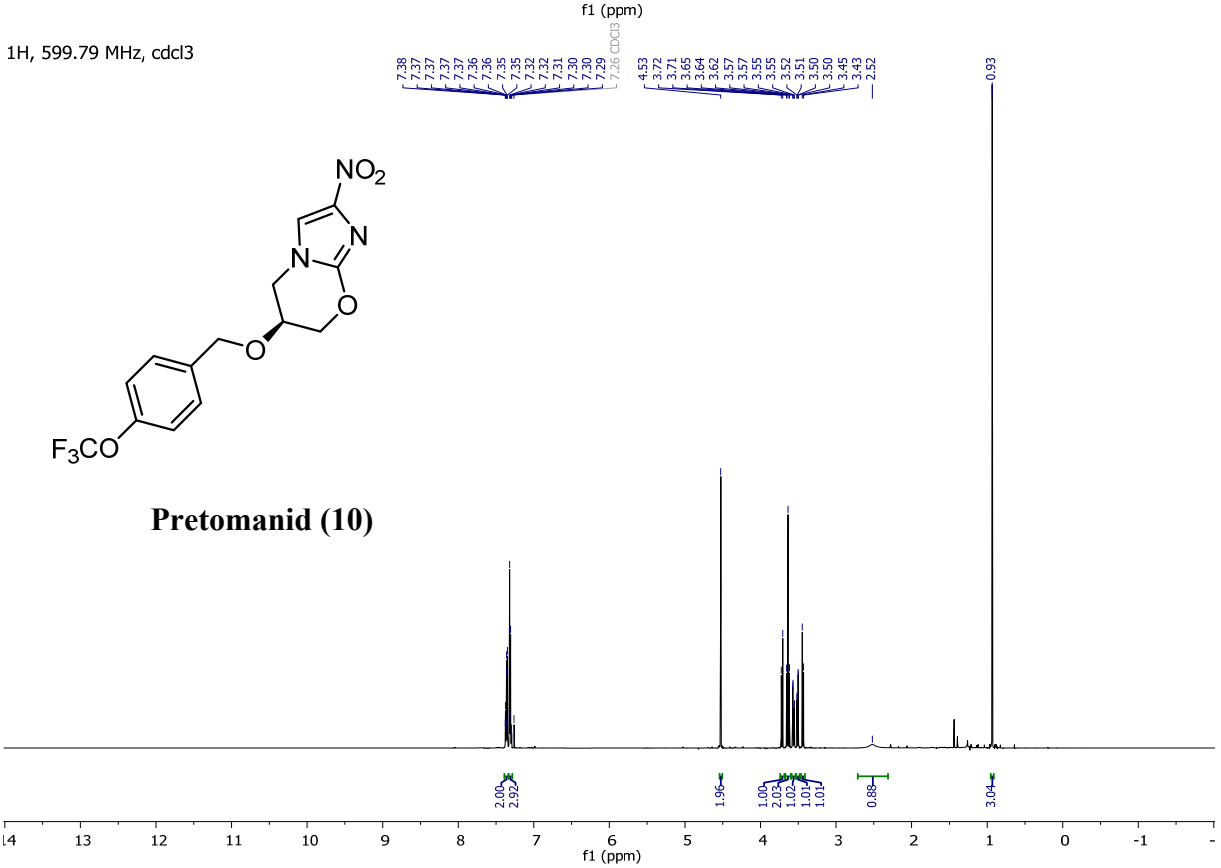
5a

1H, 599.79 MHz, cdcl3

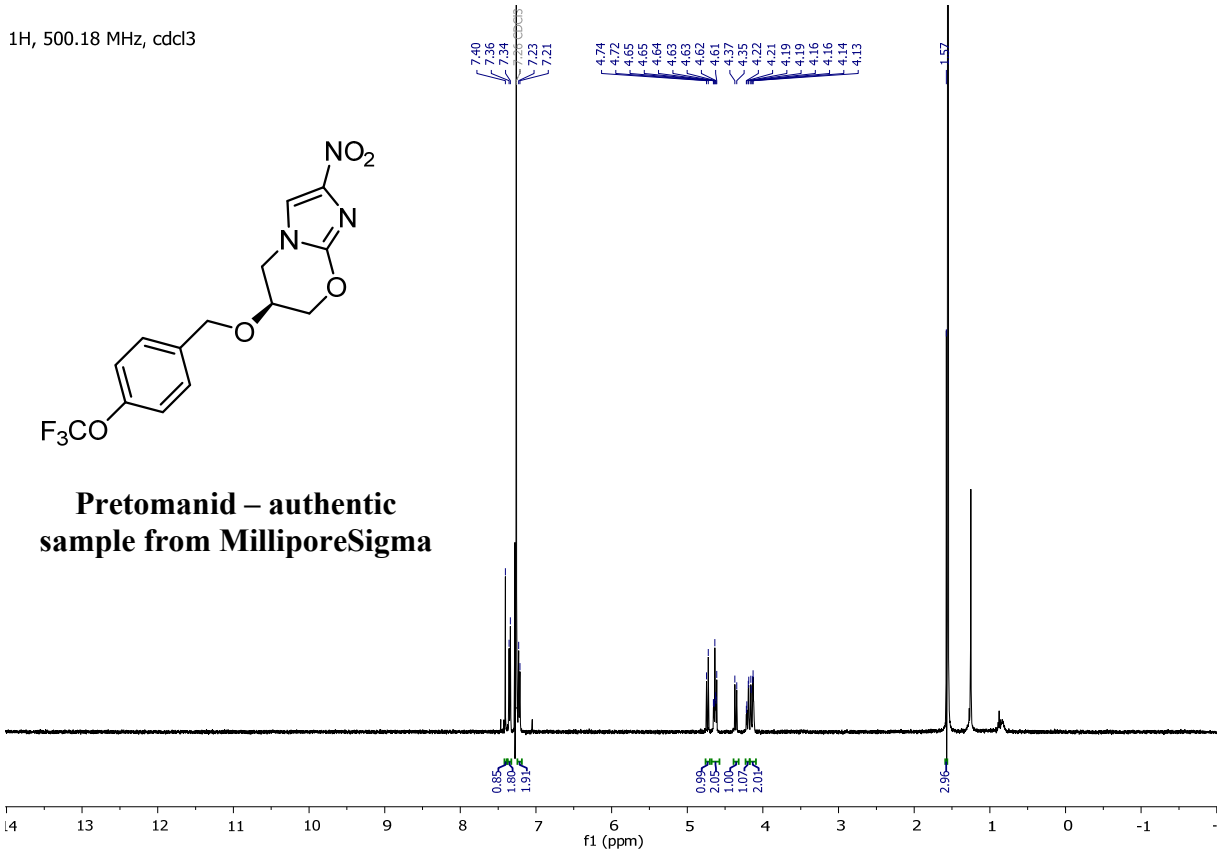


28

1H, 599.79 MHz, cdcl3

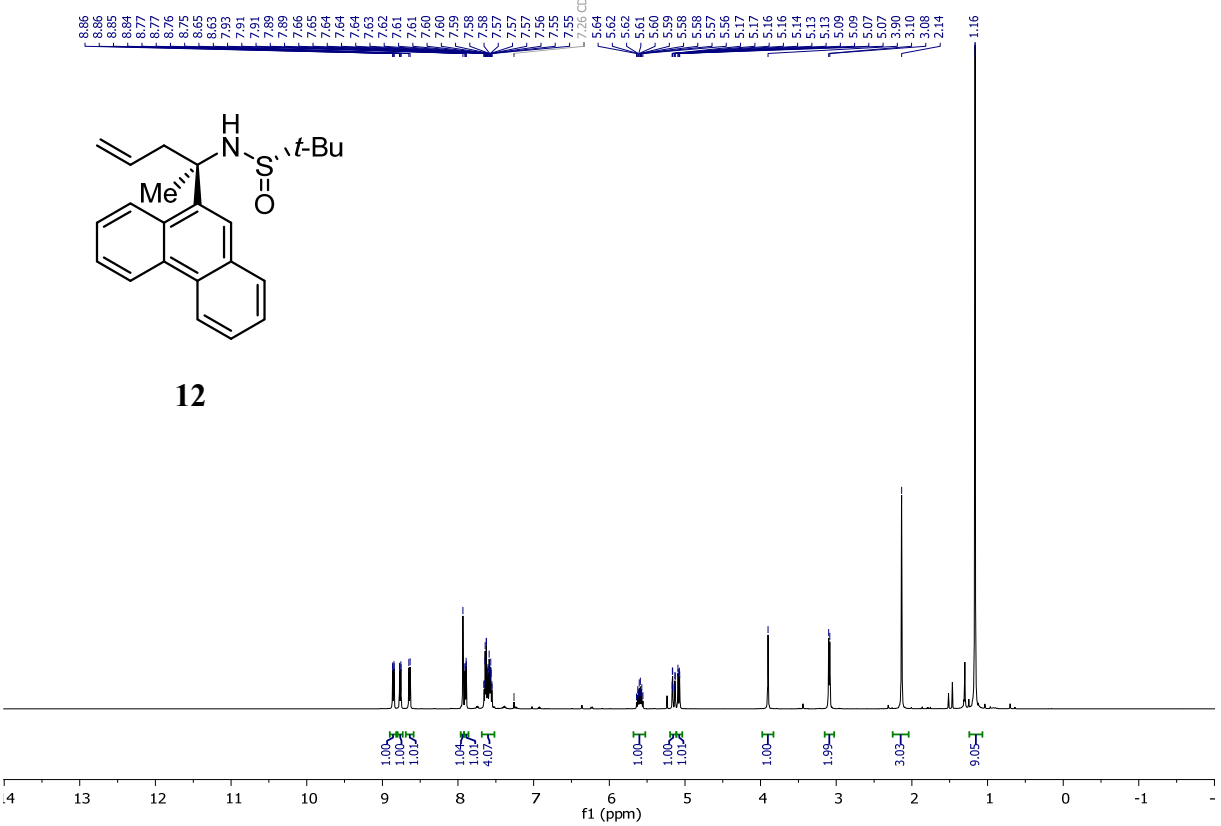


Pretomanid (10)


1H, 500.18 MHz, cdcl3
NO2
N
N
O
O
F3CO
Pretomanid – authentic sample from MilliporeSigma
f1 (ppm)

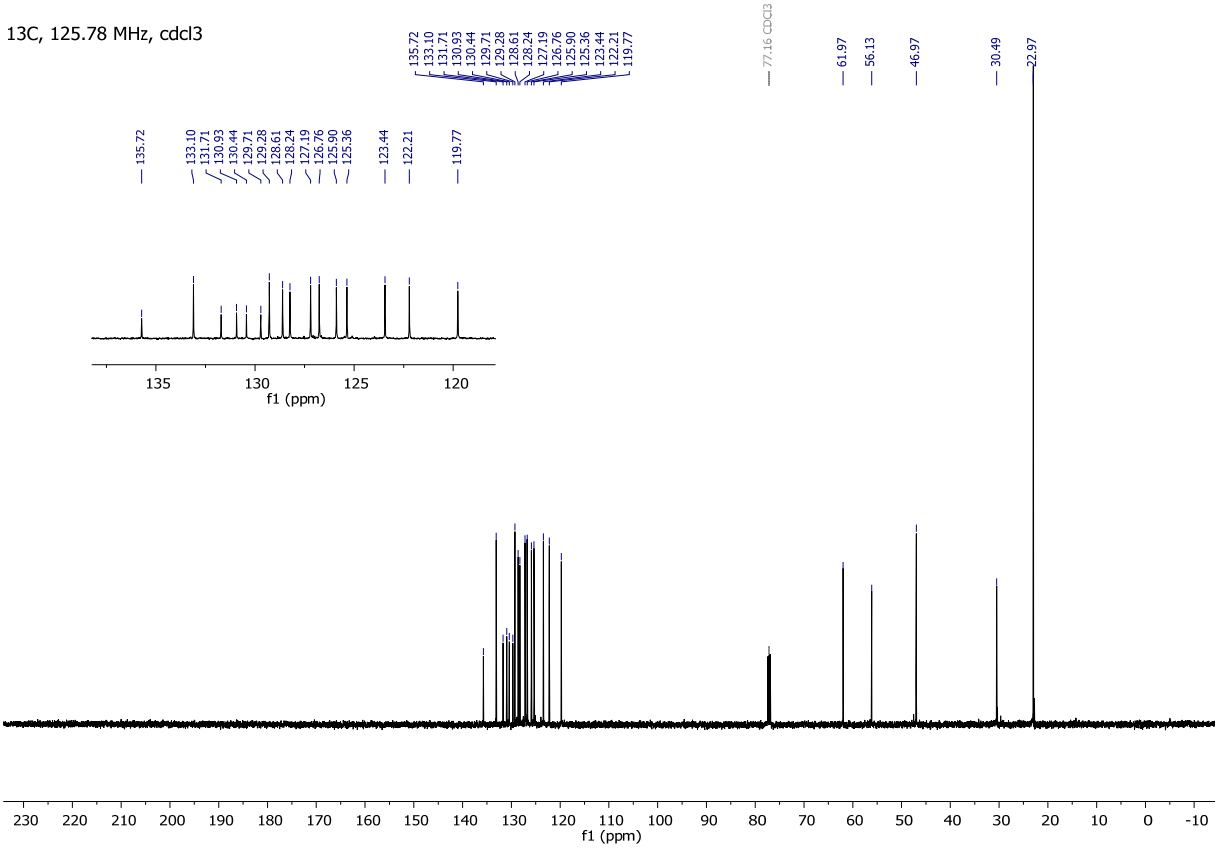
NMR Spectra of Novel Compounds

1H, 500.18 MHz, cdcl3

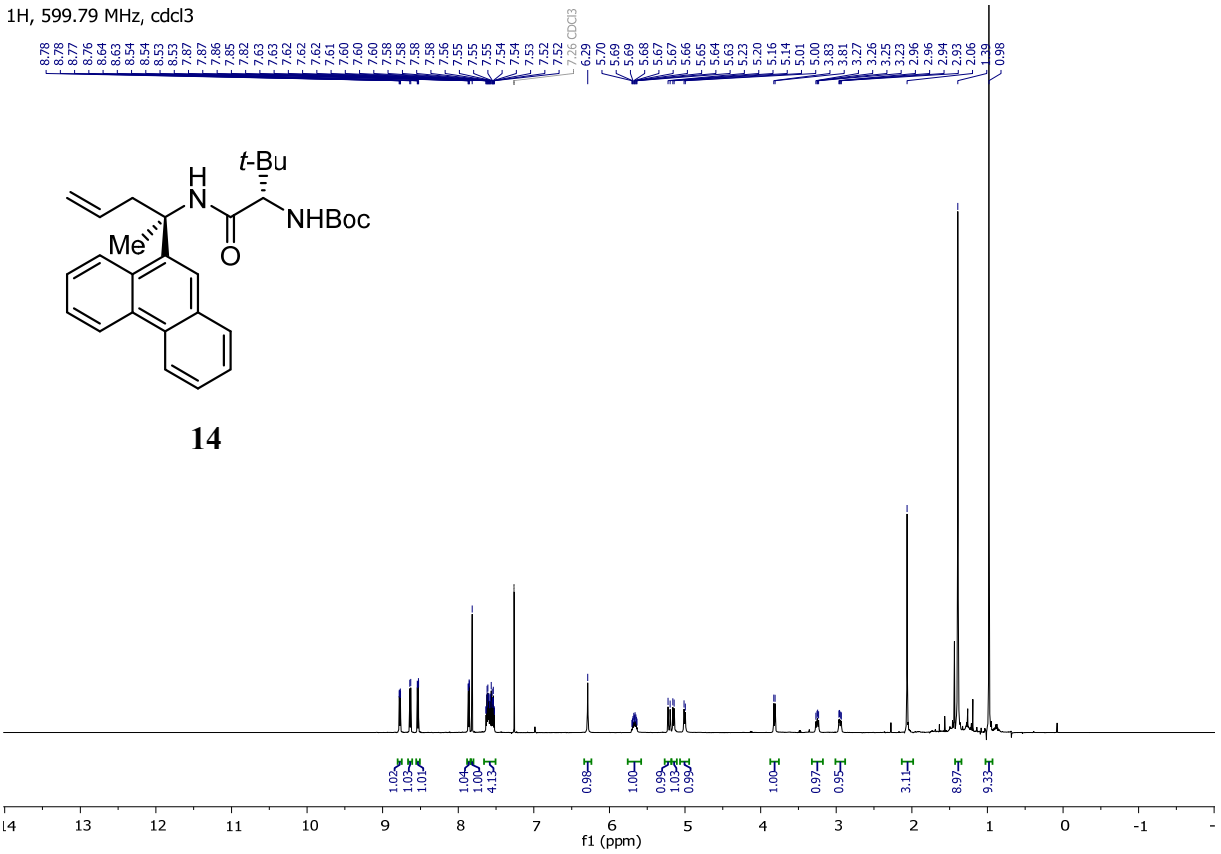


12

13C, 125.78 MHz, cdcl3

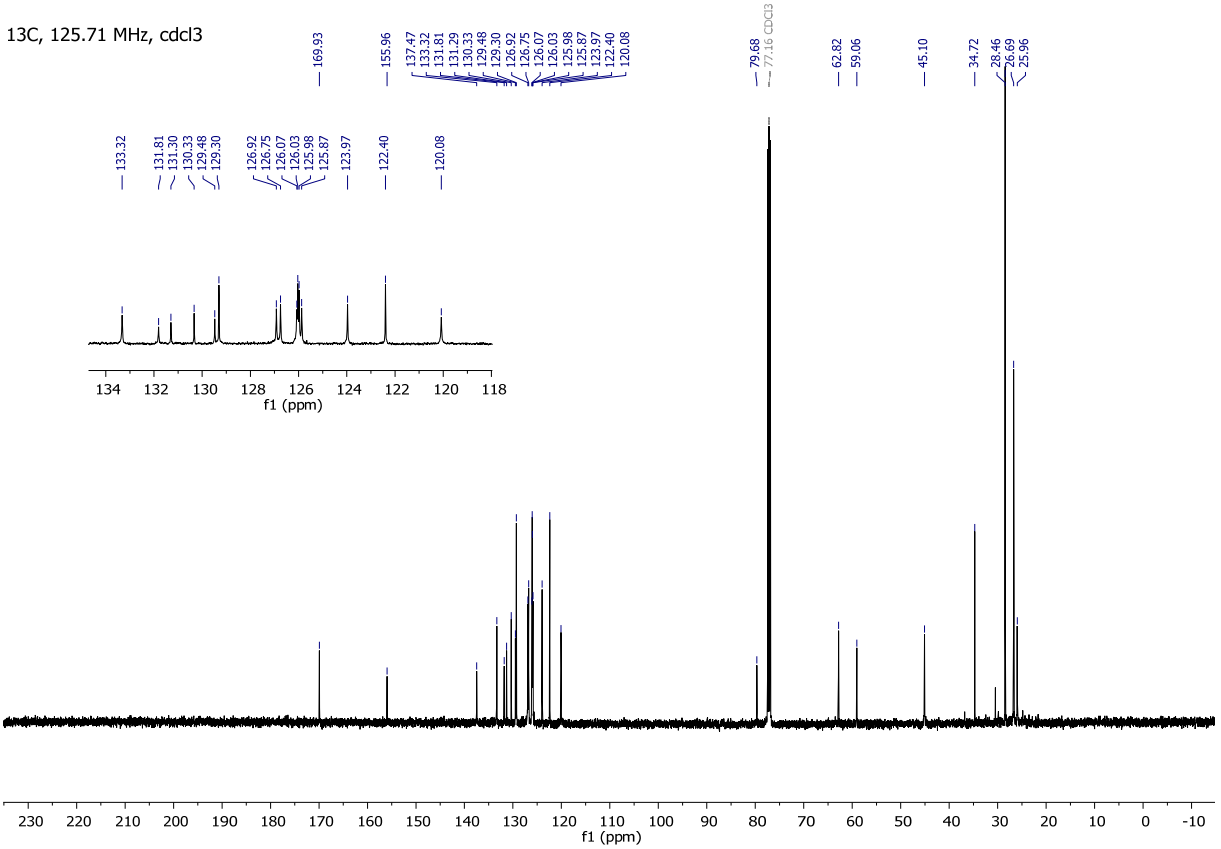


1H, 599.79 MHz, cdcl3

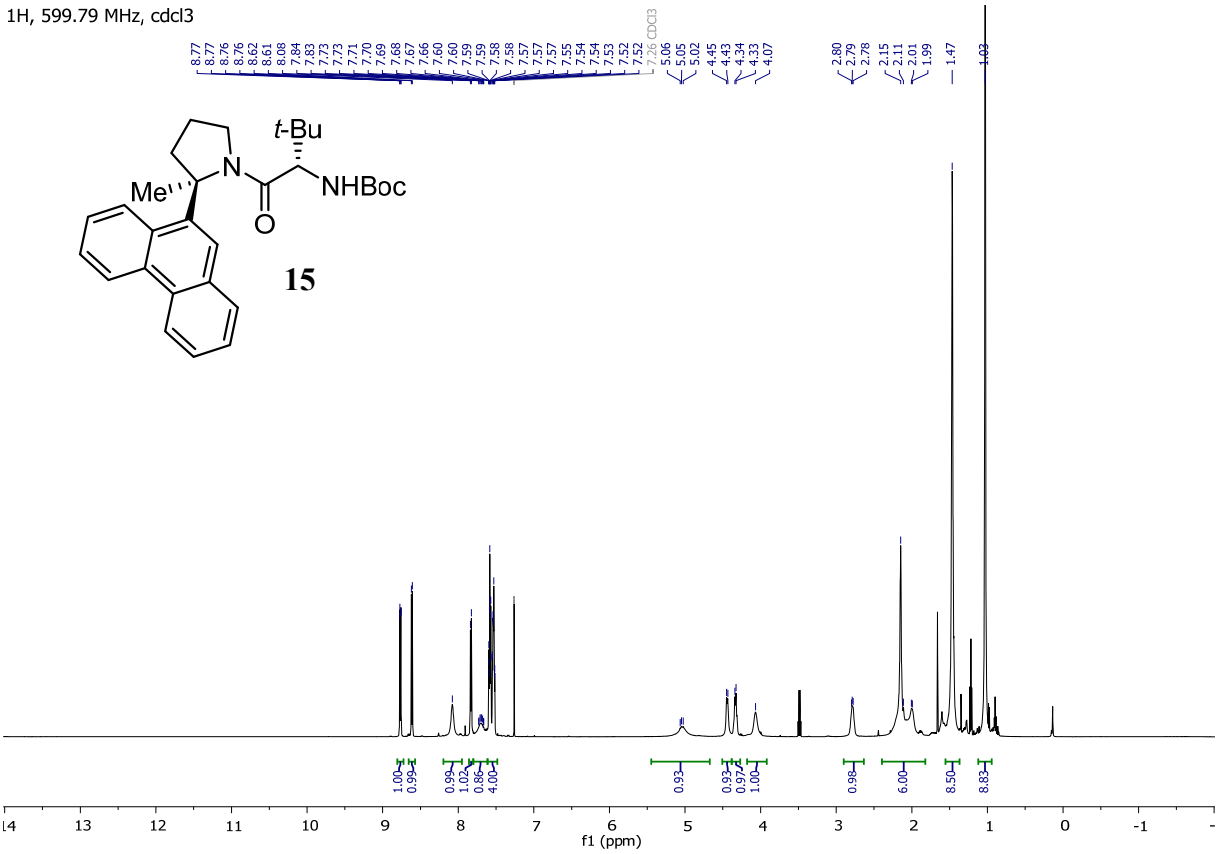


14

13C, 125.71 MHz, cdcl3

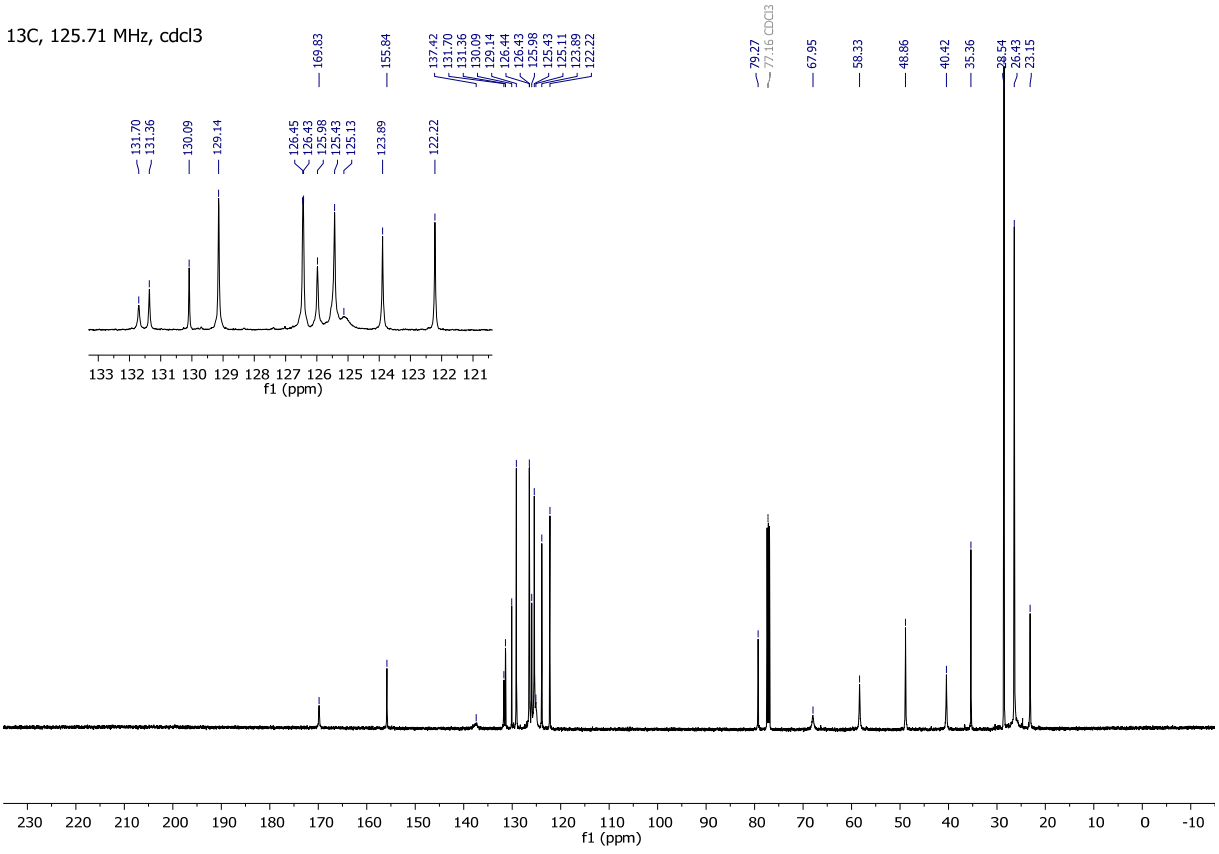


1H, 599.79 MHz, cdcl3

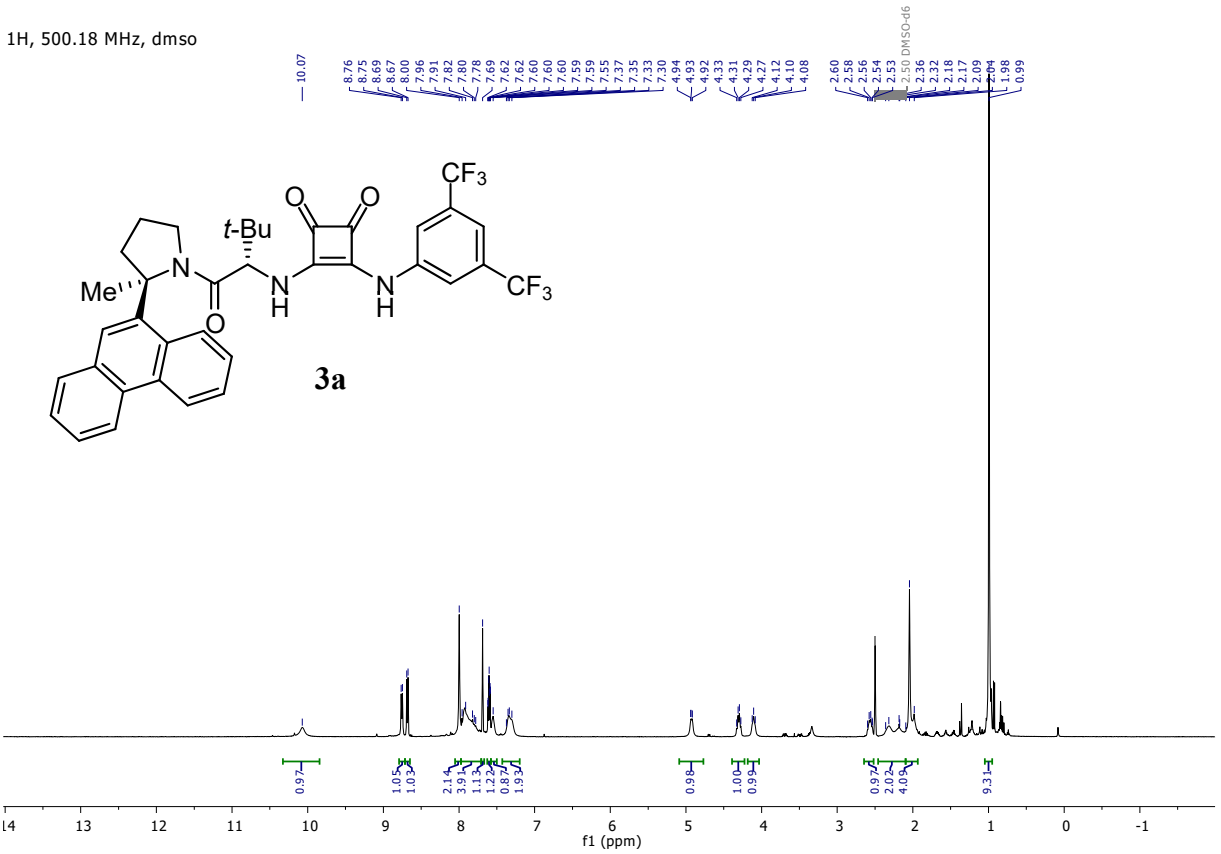


15

13C, 125.71 MHz, cdcl3

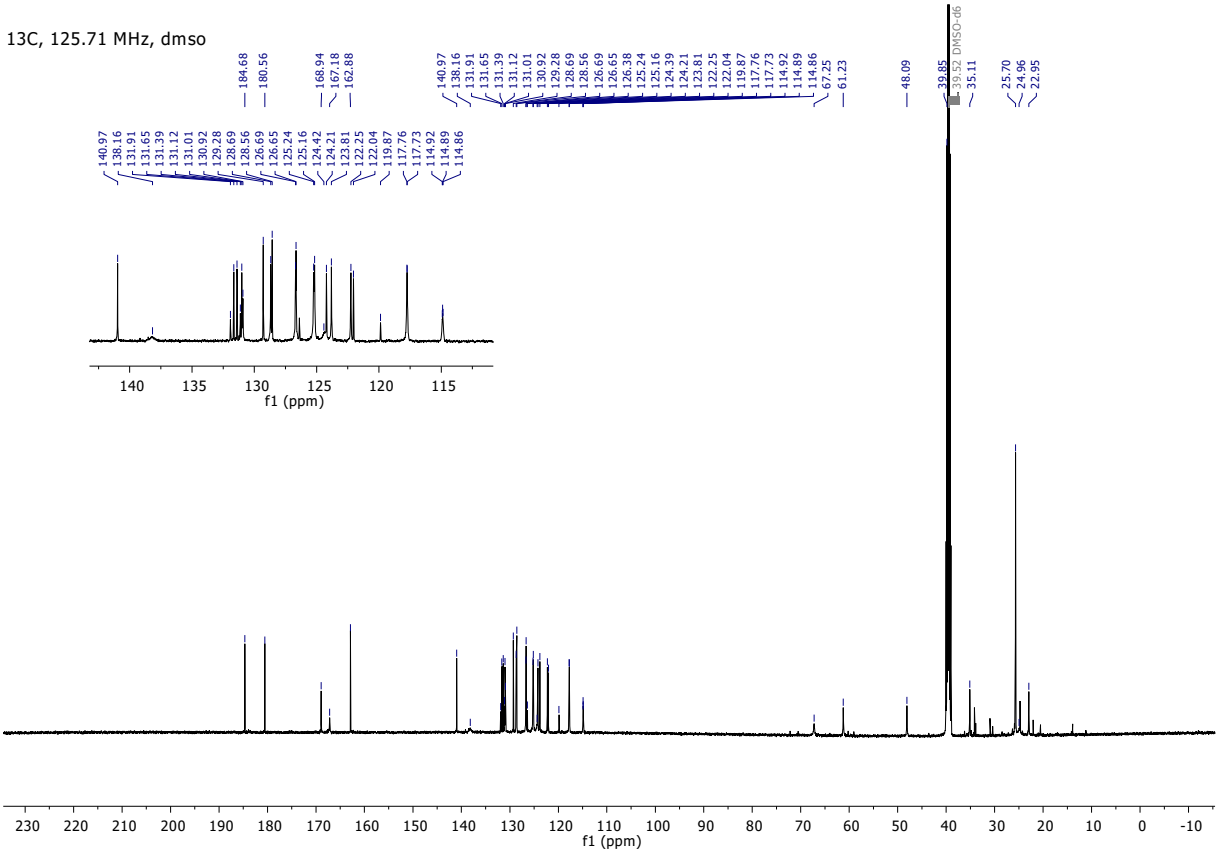


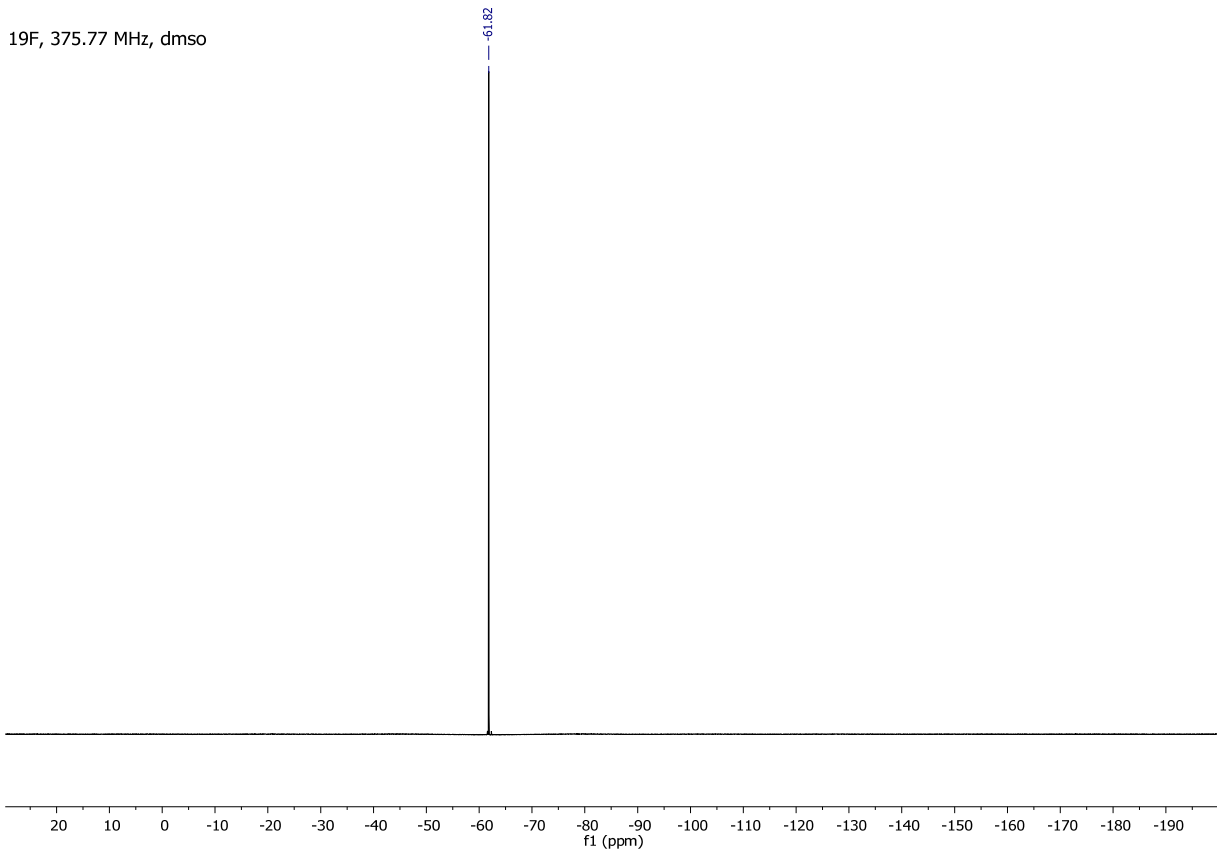
1H, 500.18 MHz, dmso



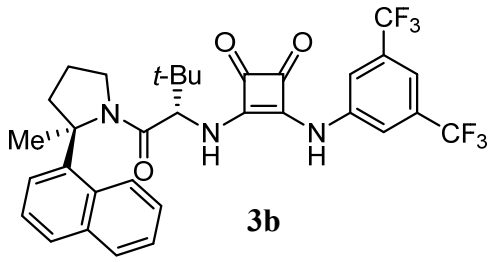
3a

13C, 125.71 MHz, dmso



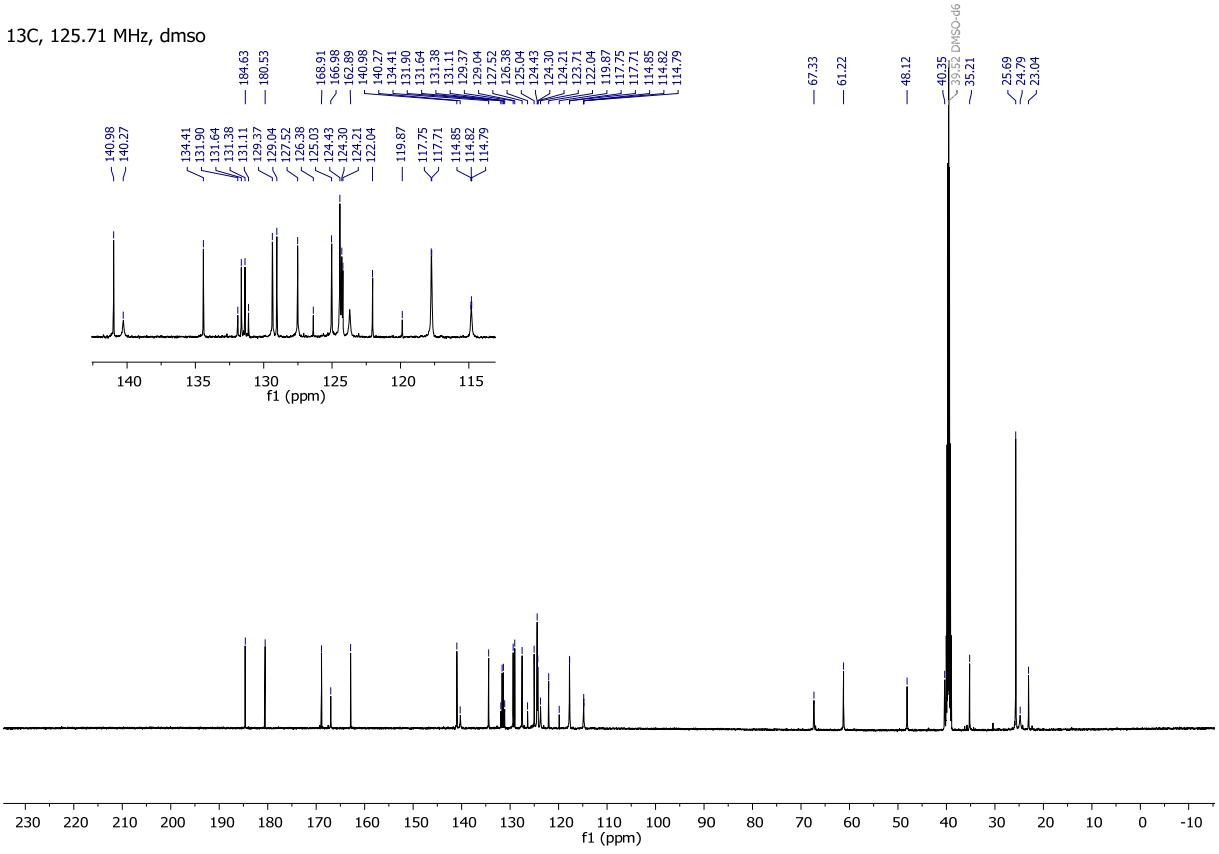

19F, 375.77 MHz, dmso
-61.82
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

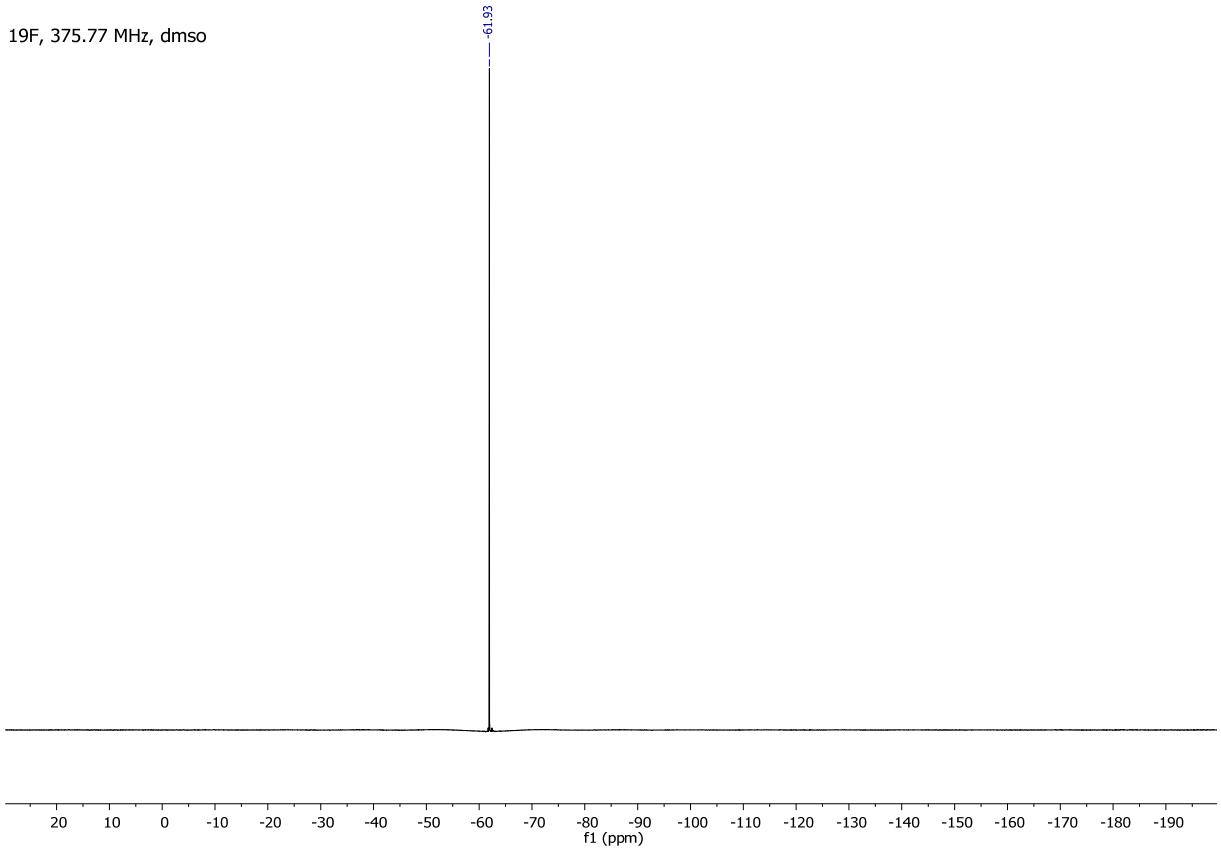
1H, 599.79 MHz, dmso



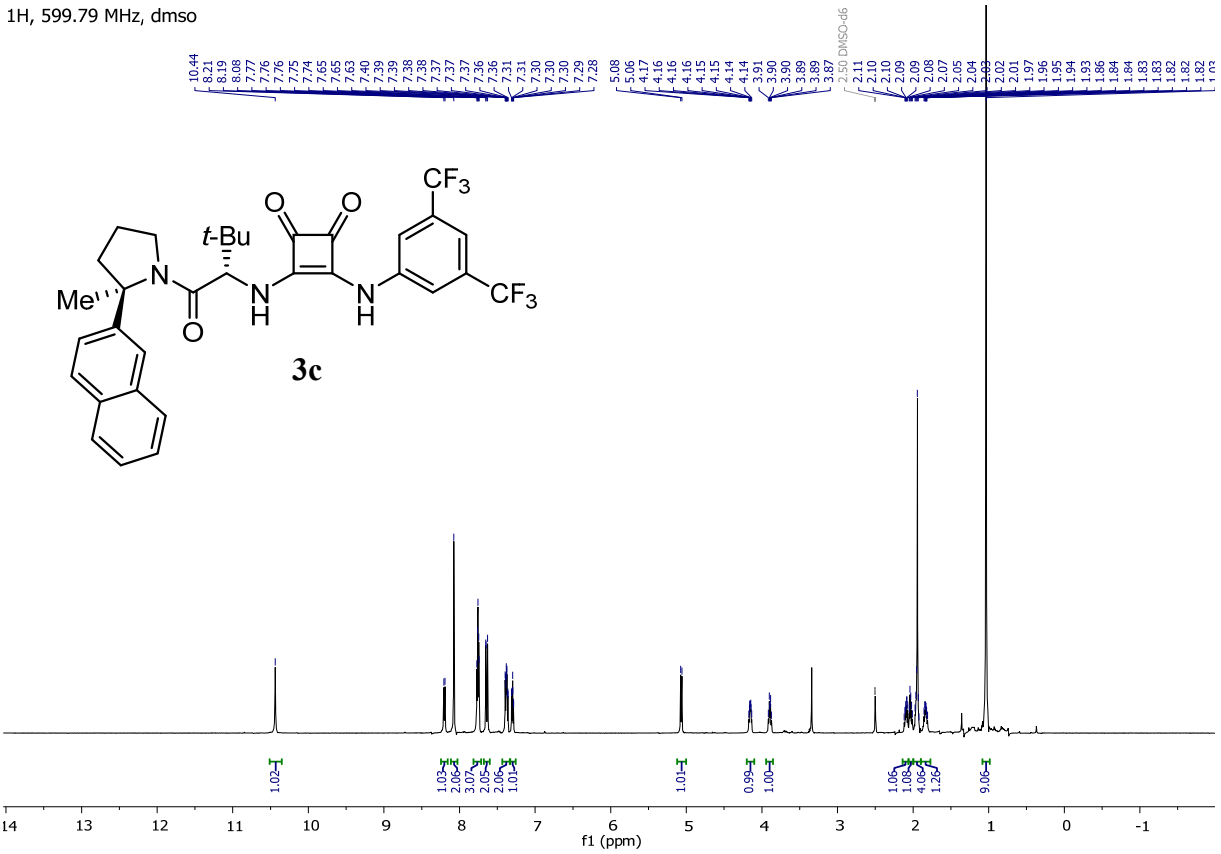
3b

13C, 125.71 MHz, dmso



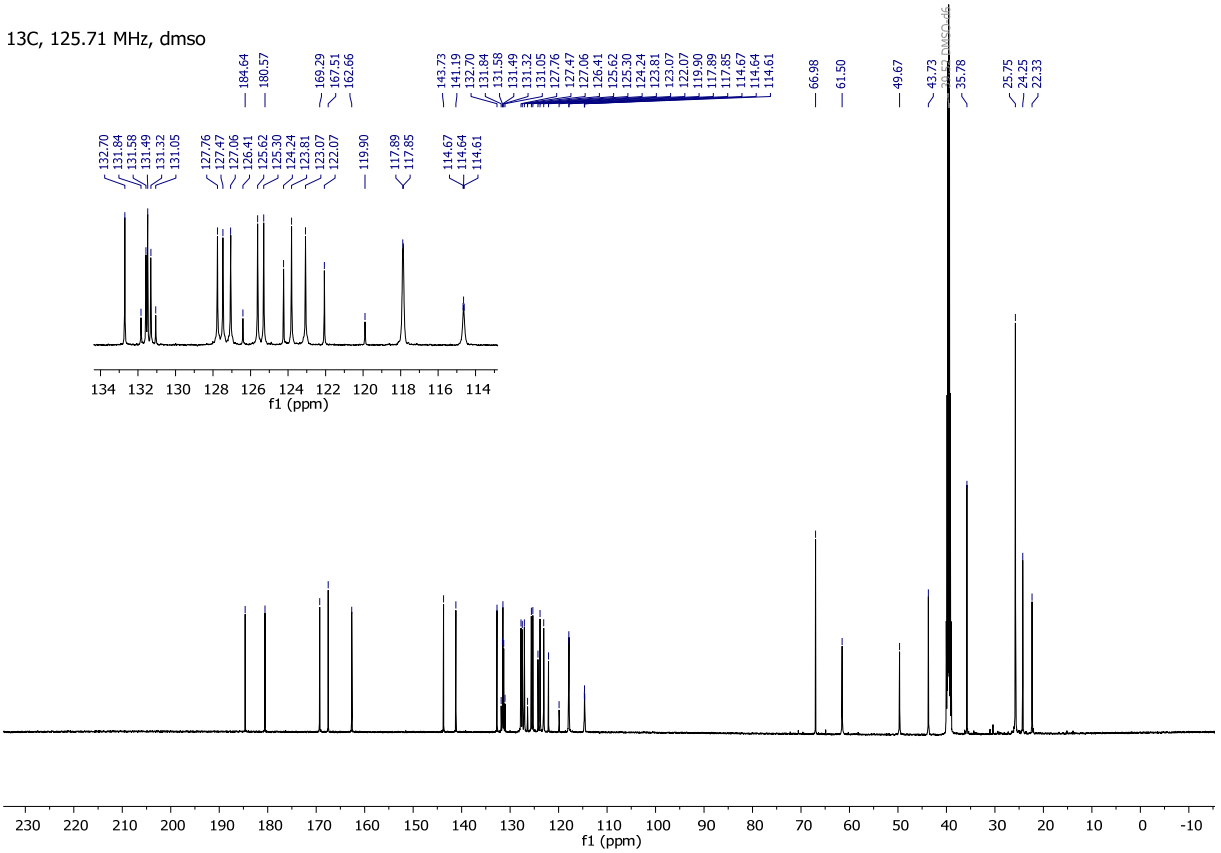

19F, 375.77 MHz, dmso
-61.93
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

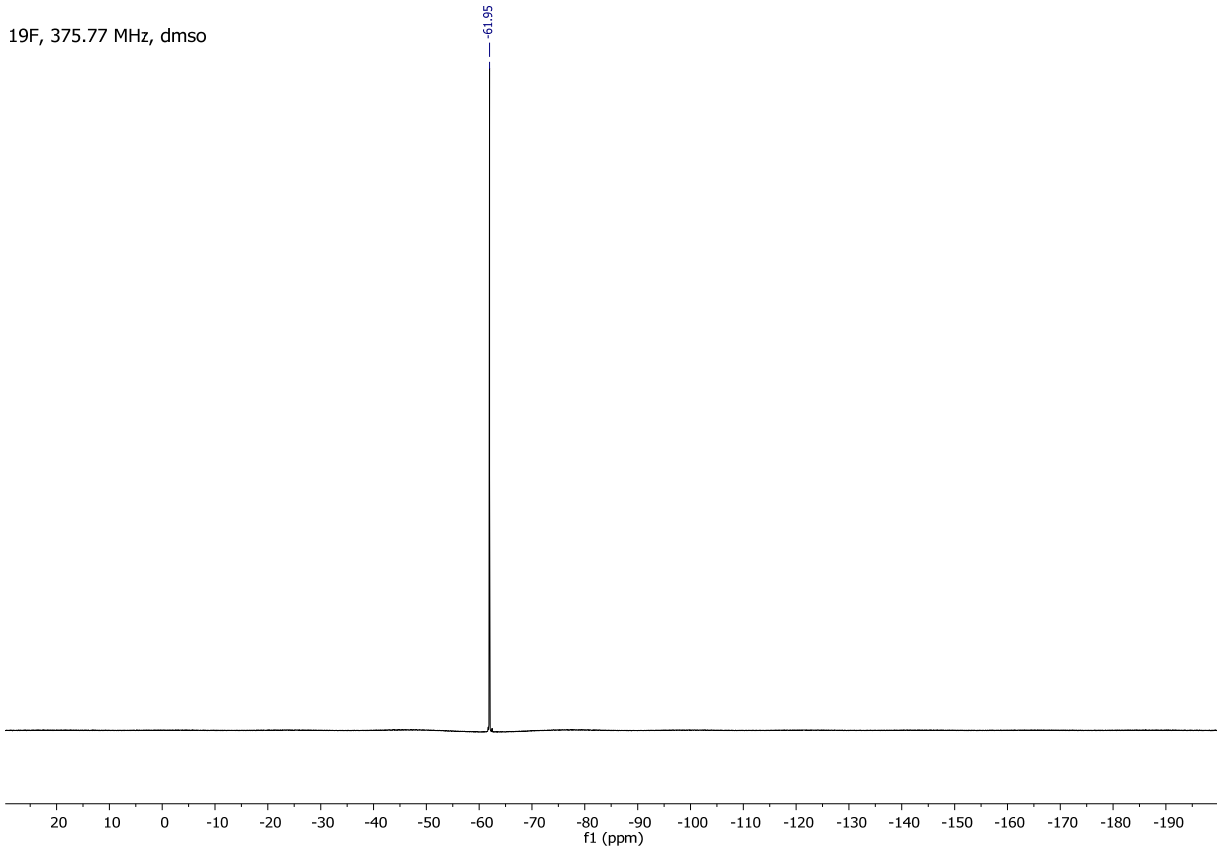
1H, 599.79 MHz, dmso



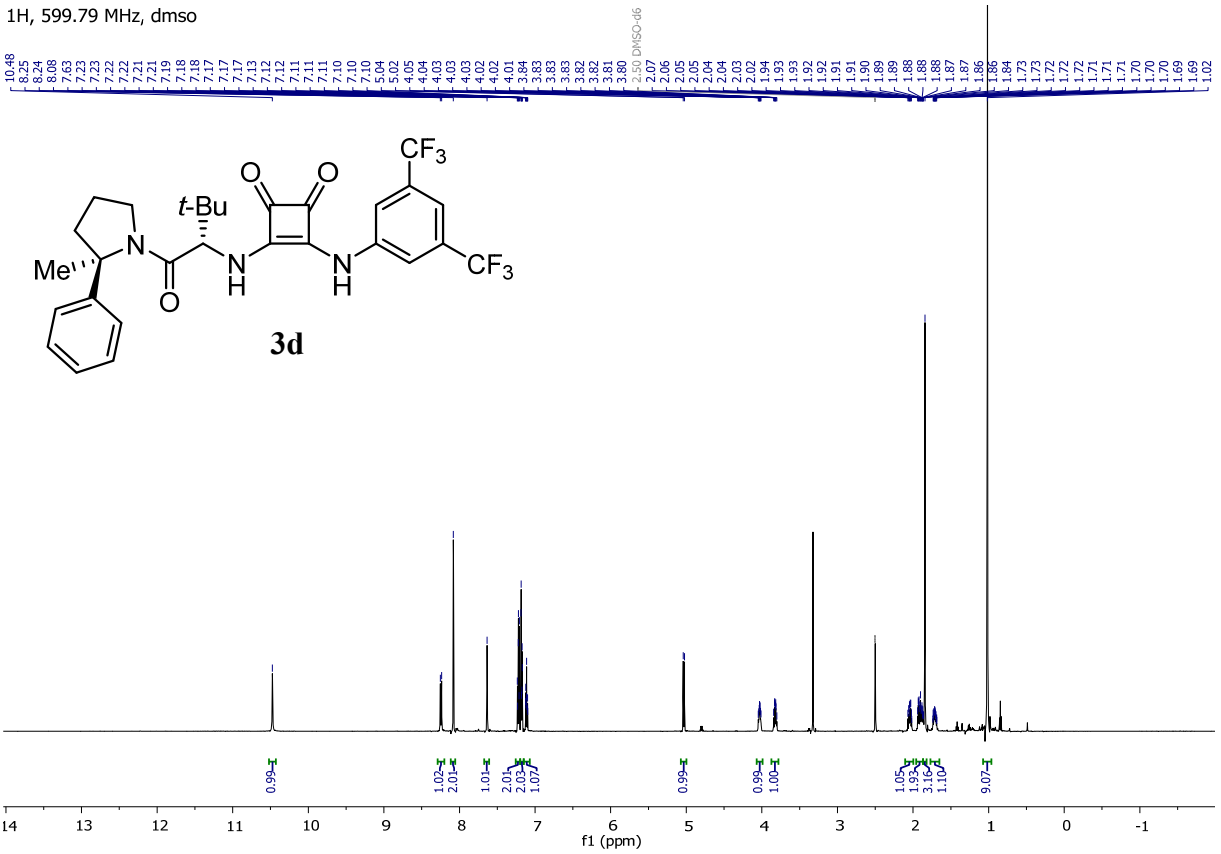
3c

13C, 125.71 MHz, dmso

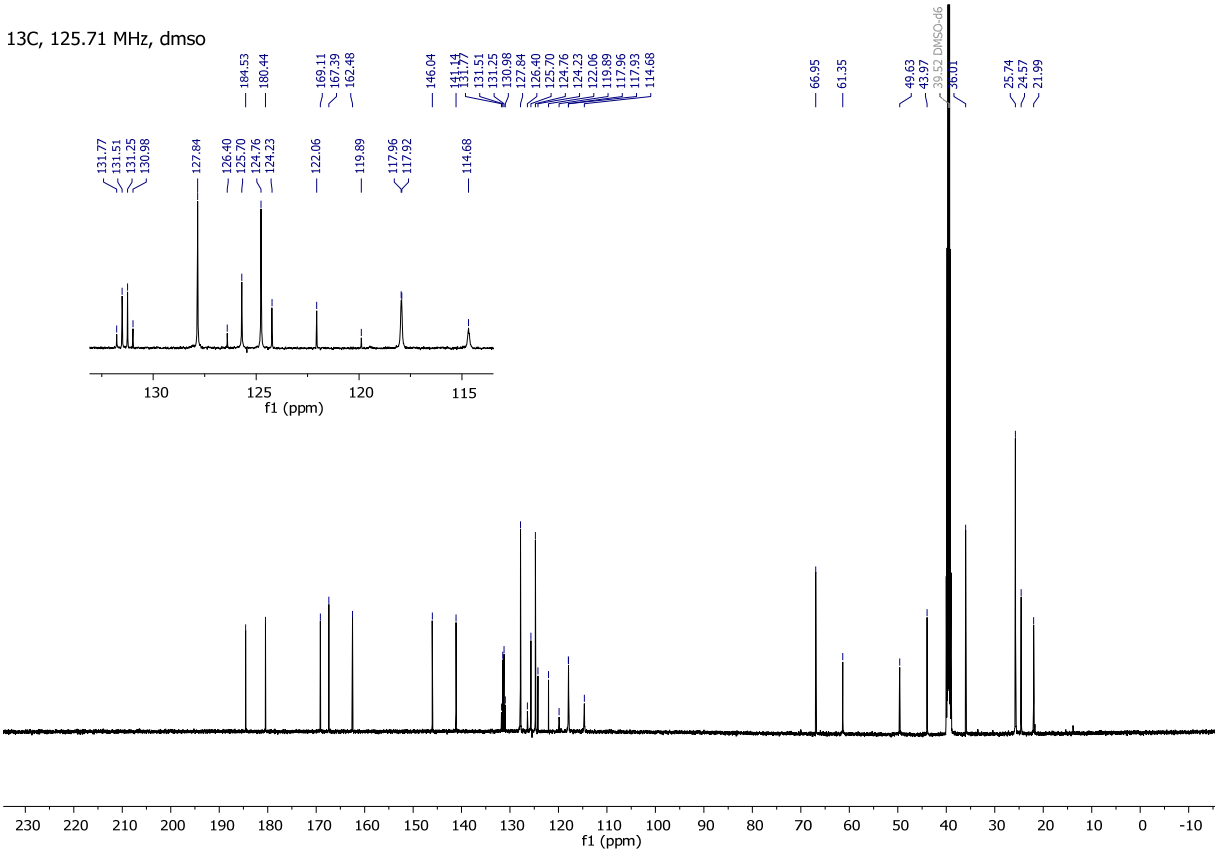


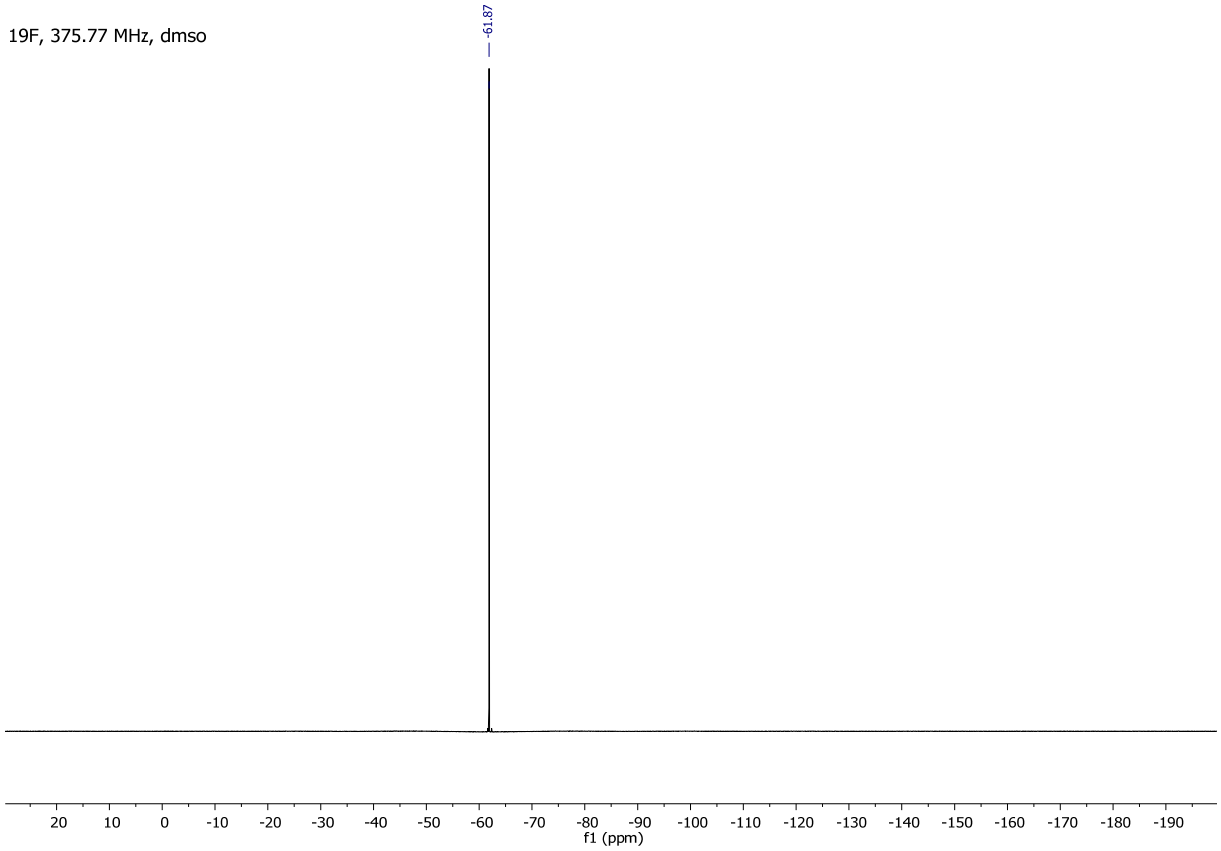

19F, 375.77 MHz, dmso
-61.95
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

1H, 599.79 MHz, dmso

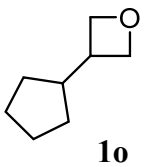


13C, 125.71 MHz, dmso



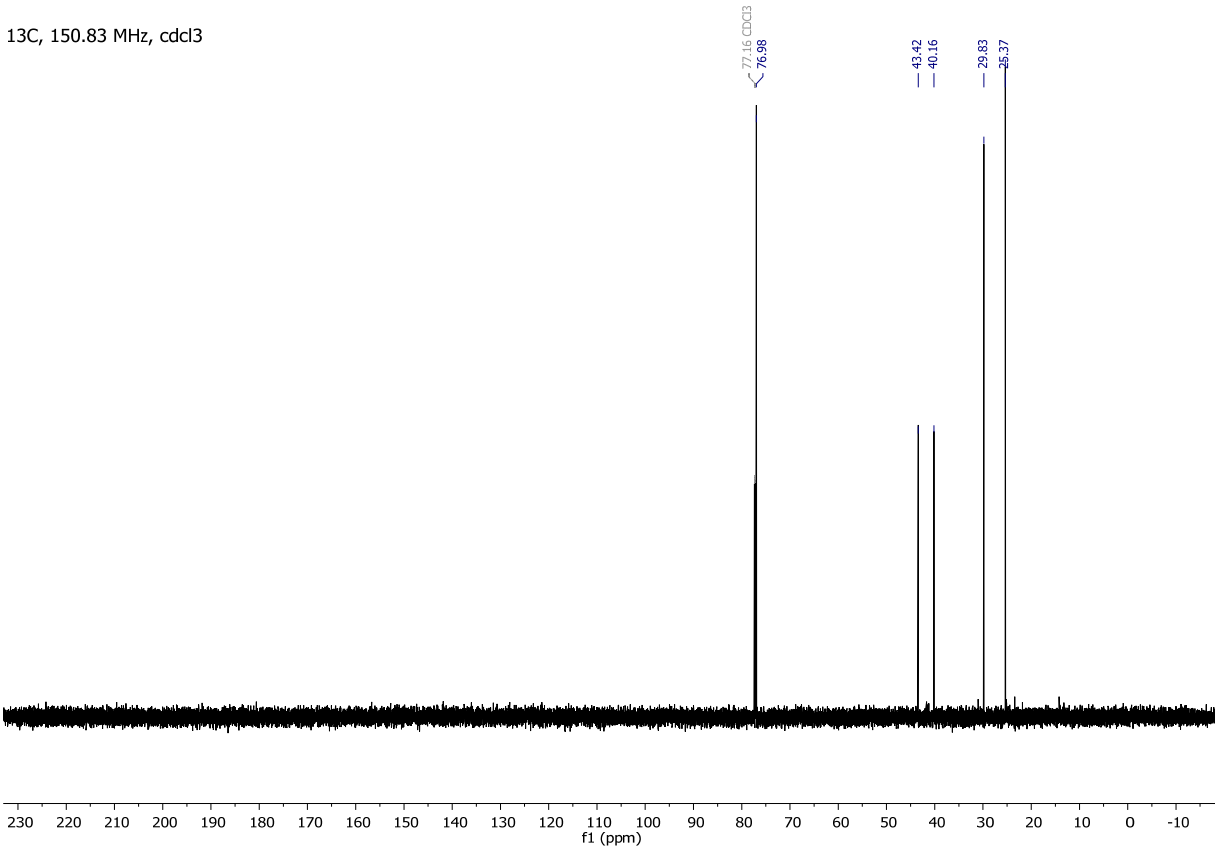

19F, 375.77 MHz, dmso
-61.87
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

1H, 599.79 MHz, cdcl3

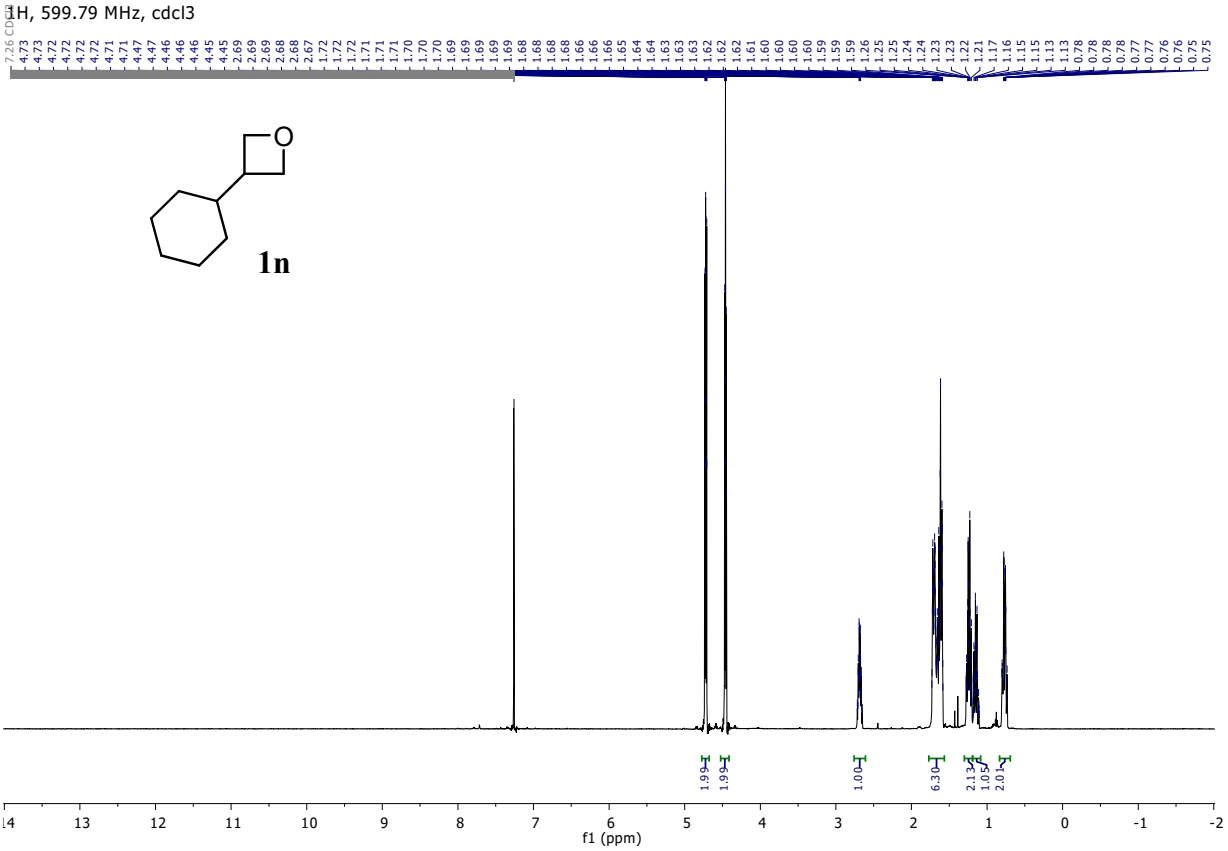


1o

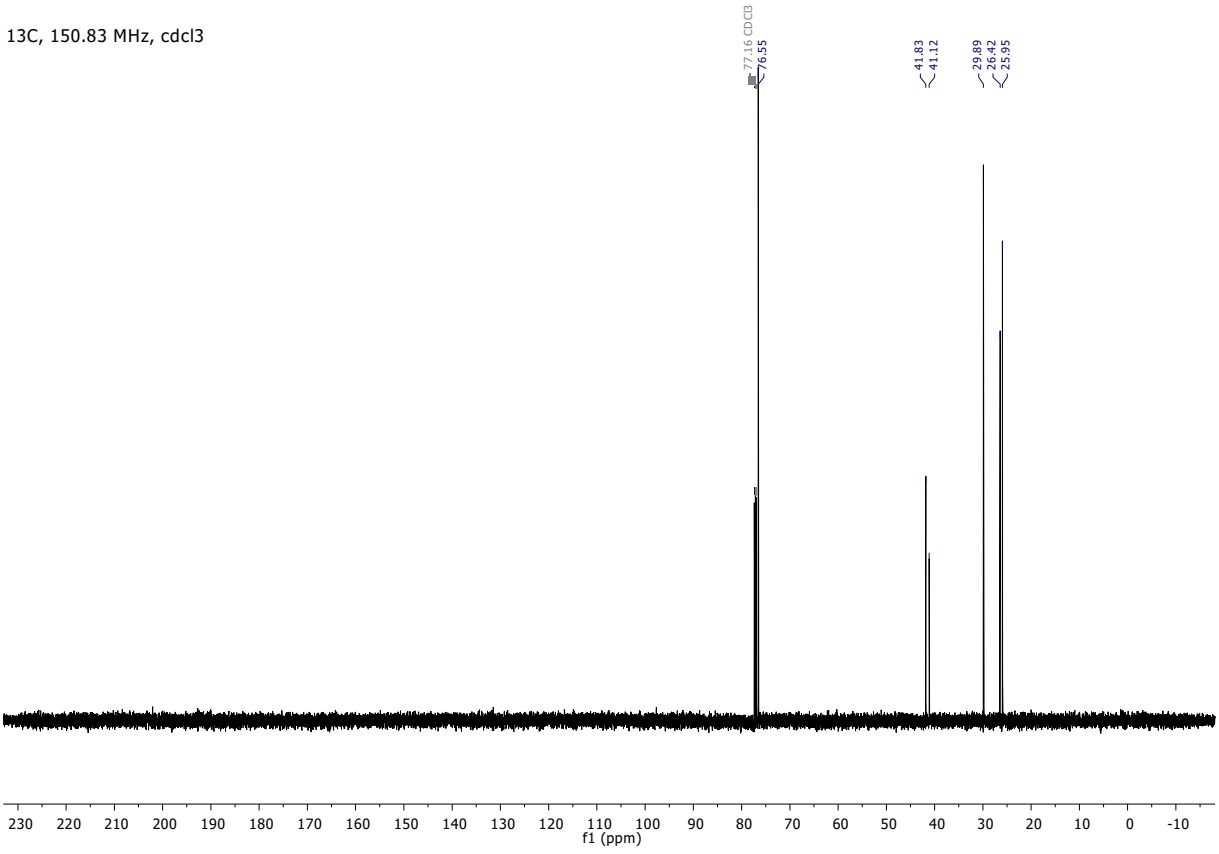
13C, 150.83 MHz, cdcl3



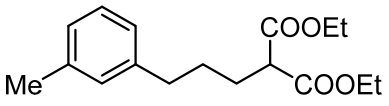
1H, 599.79 MHz, cdcl3



13C, 150.83 MHz, cdcl3

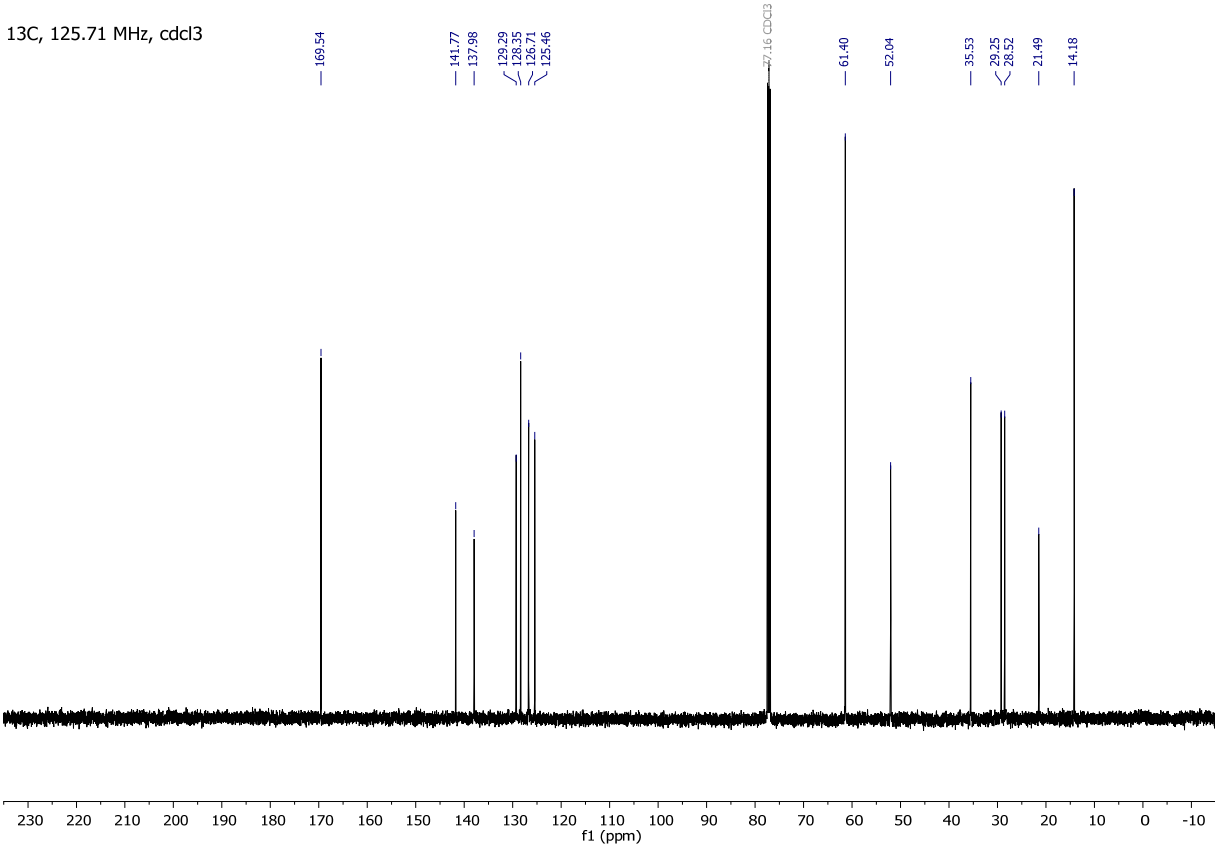


1H, 599.79 MHz, cdcl3

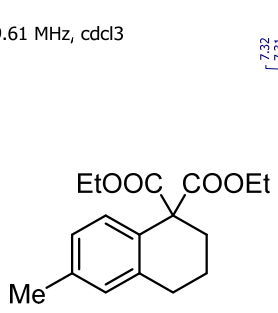


23

13C, 125.71 MHz, cdcl3

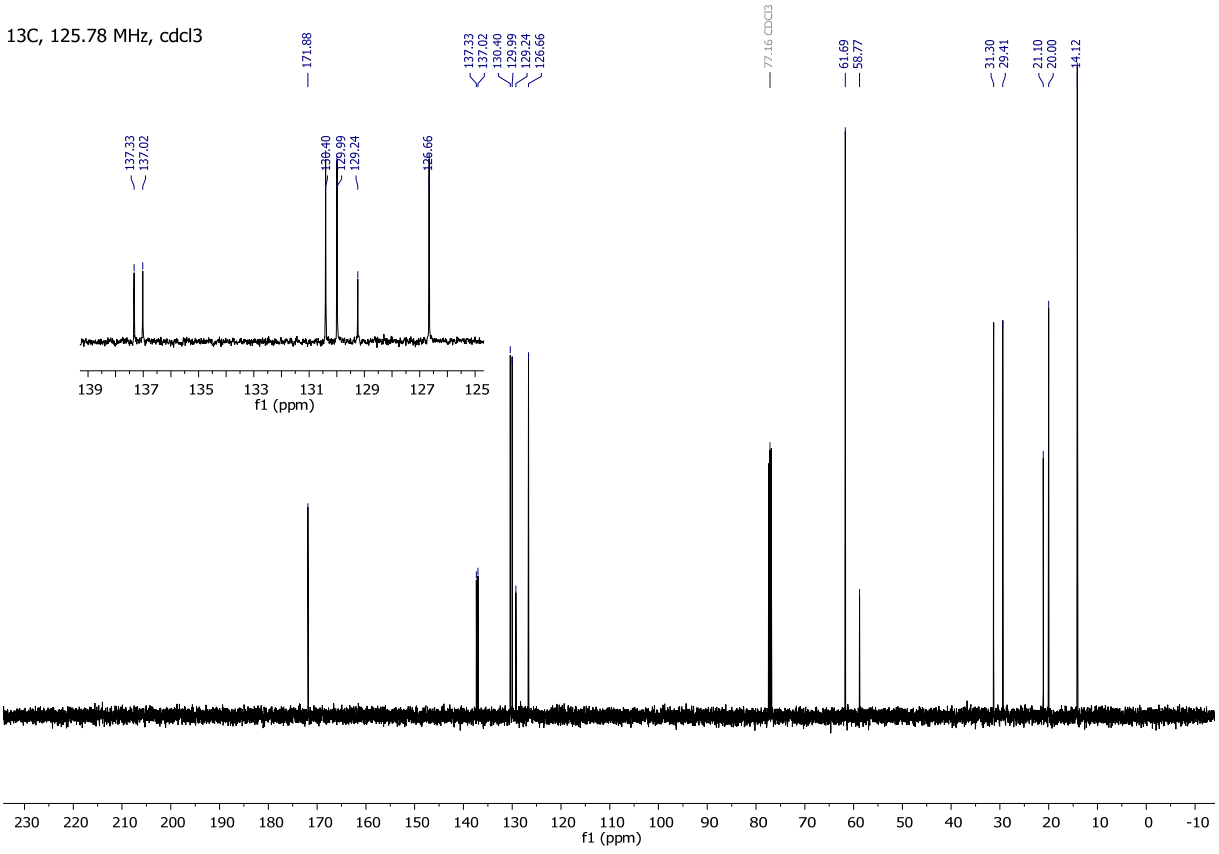


1H, 499.61 MHz, cdcl3

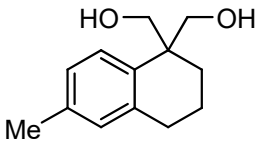


24

13C, 125.78 MHz, cdcl3

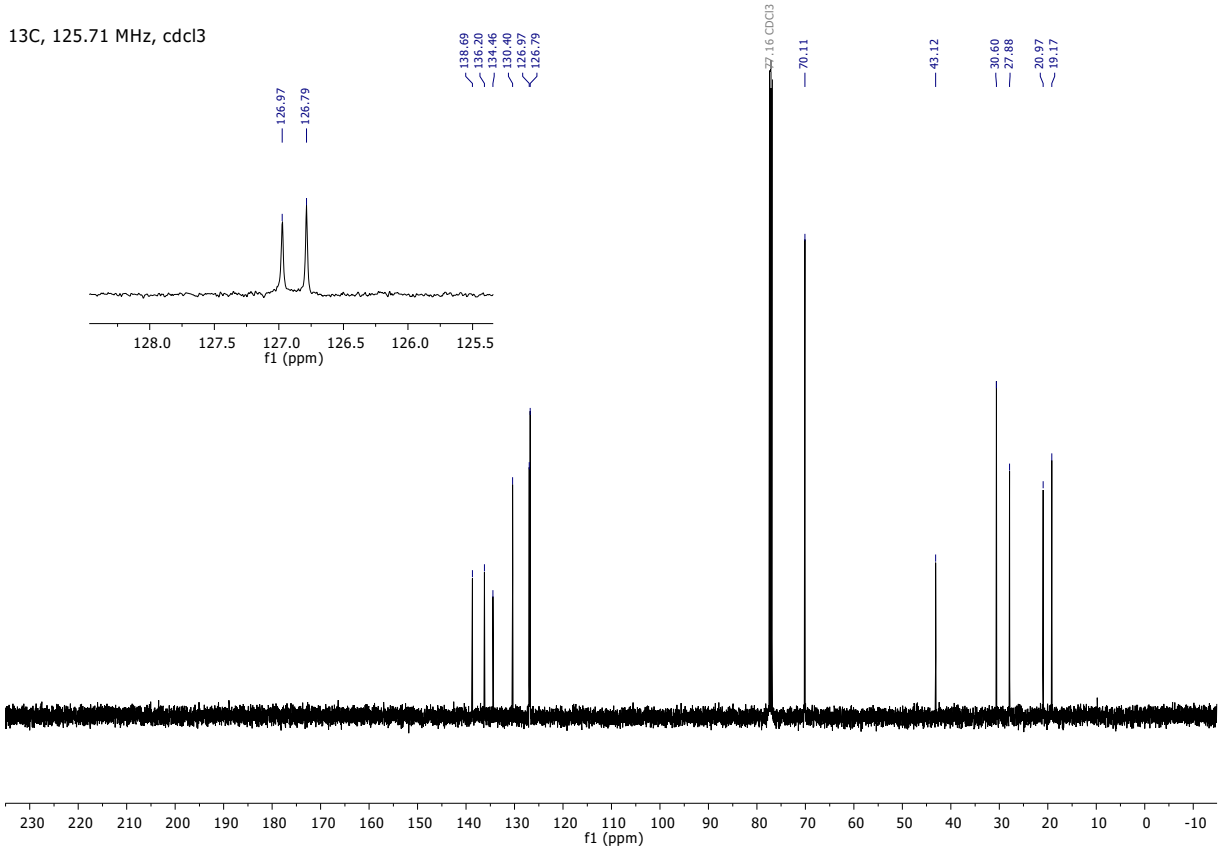


1H, 499.61 MHz, cdcl3

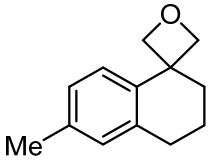


25

13C, 125.71 MHz, cdcl3

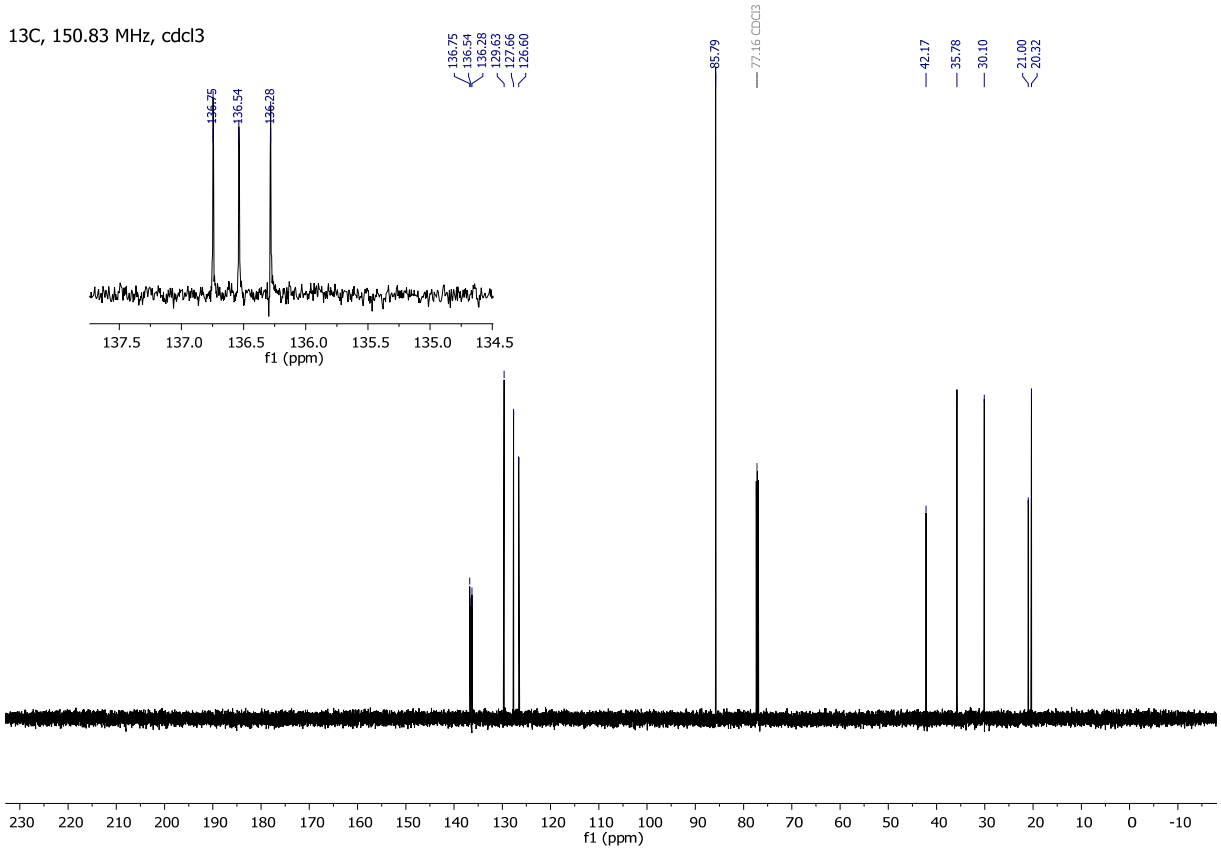


1H, 599.79 MHz, cdcl3

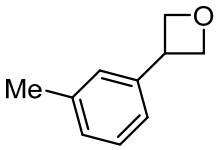


1u

13C, 150.83 MHz, cdcl3

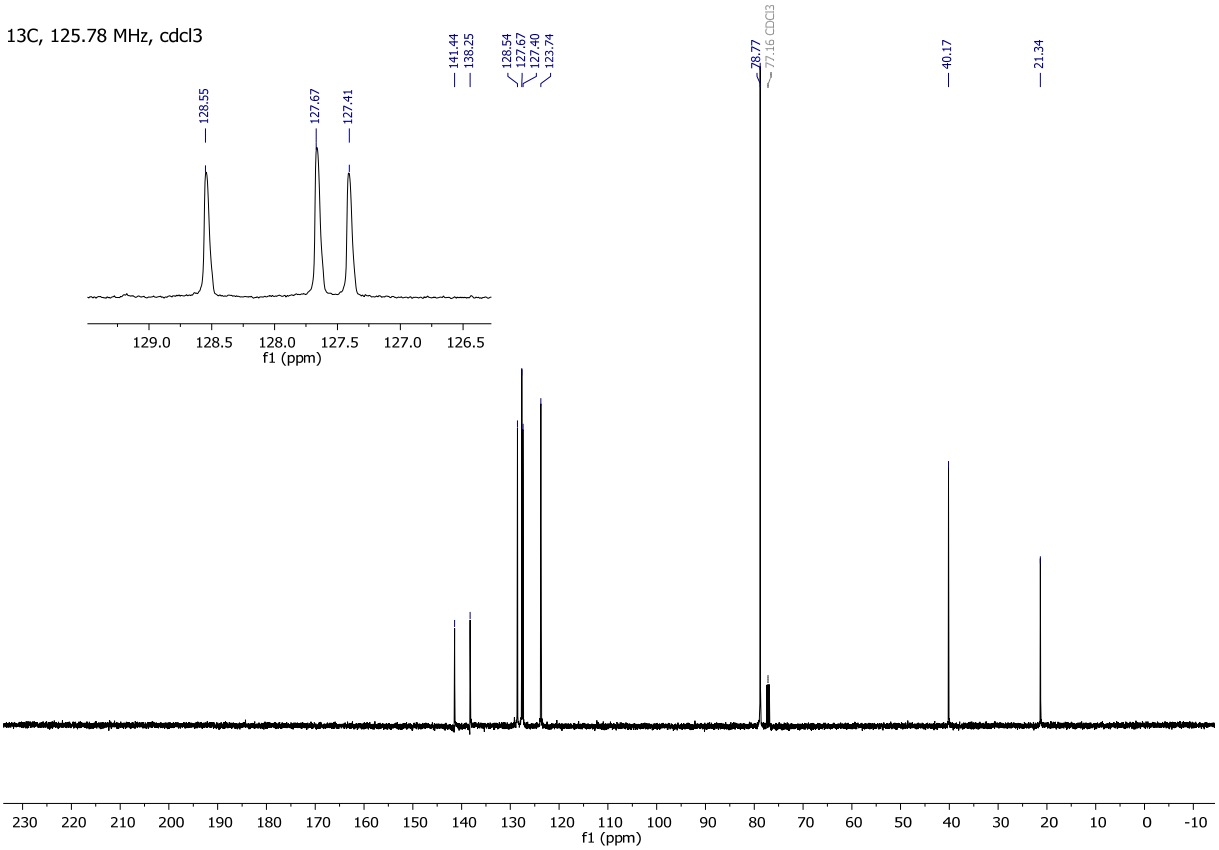


1H, 500.18 MHz, cdcl3

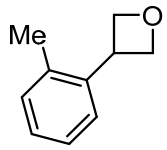


1c

13C, 125.78 MHz, cdcl3

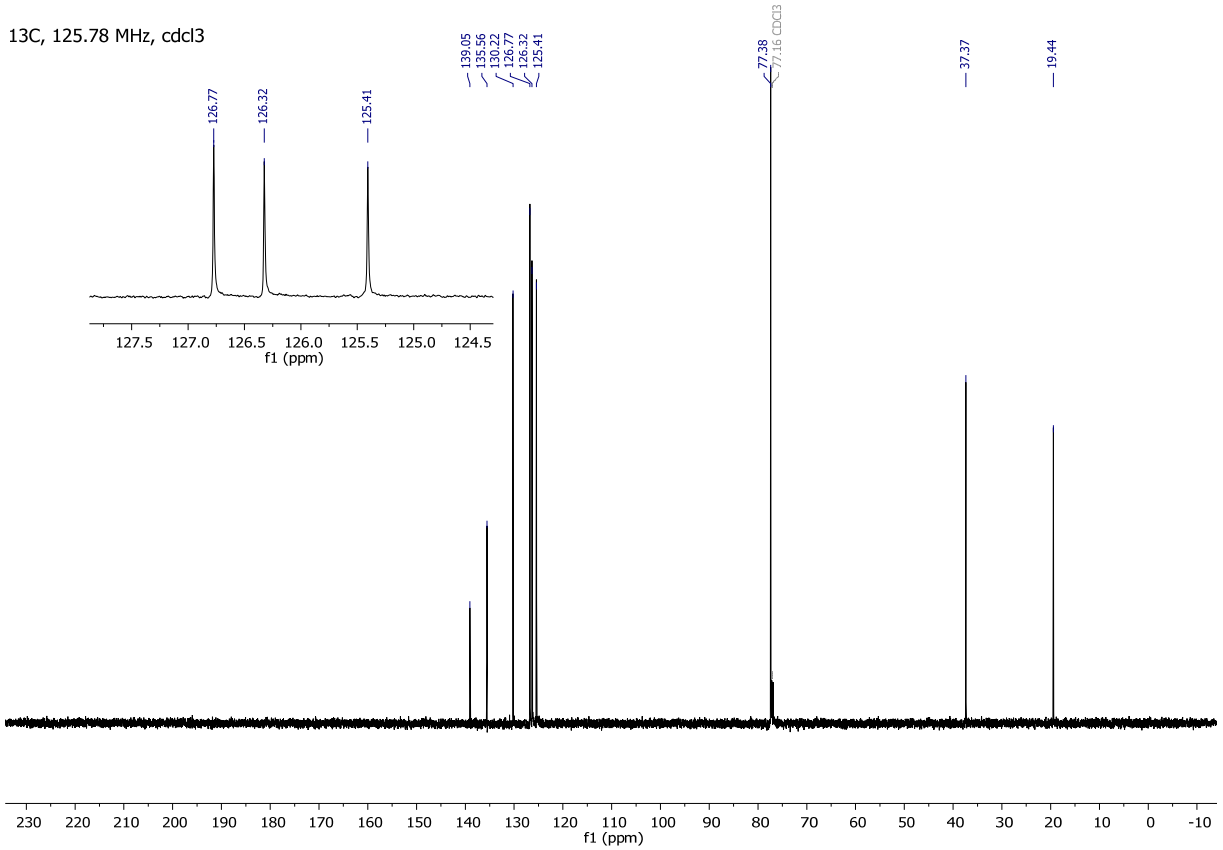


1H, 599.79 MHz, cdcl3



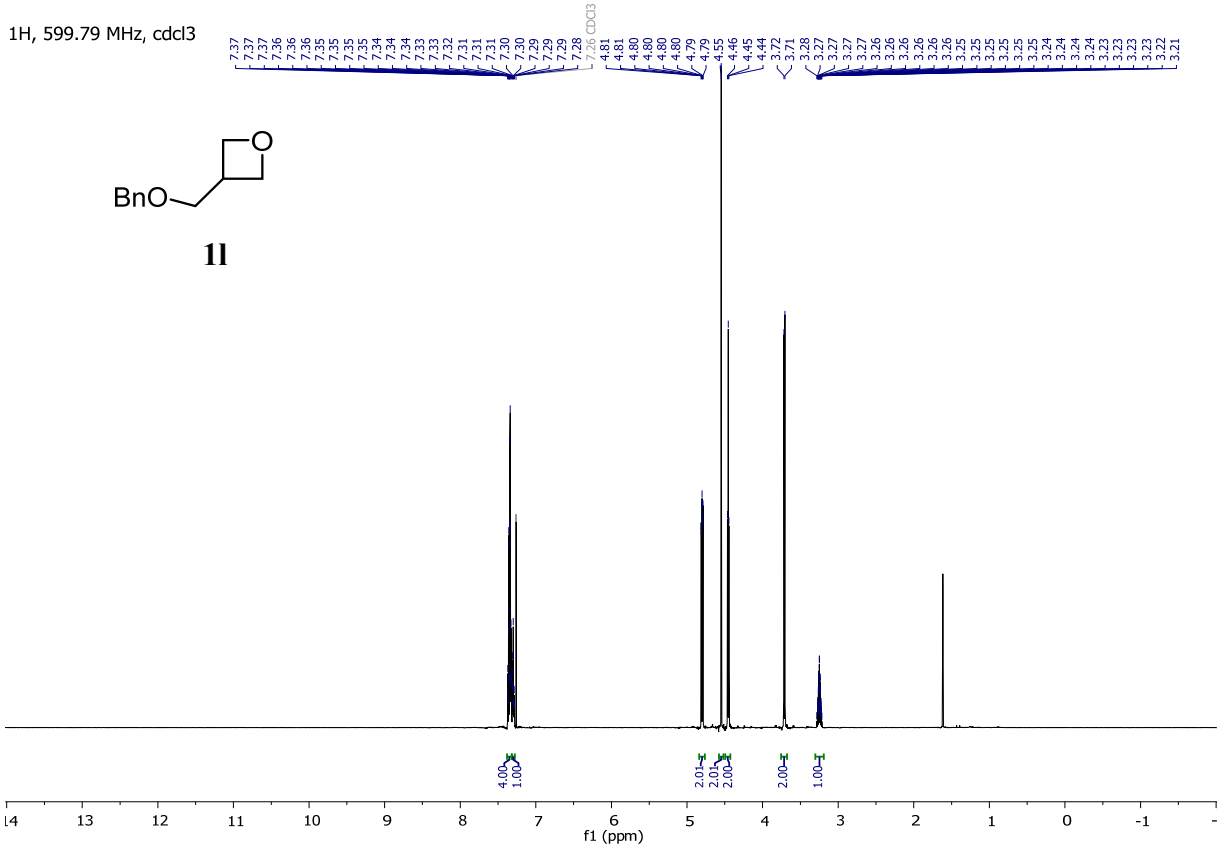
1d

13C, 125.78 MHz, cdcl3

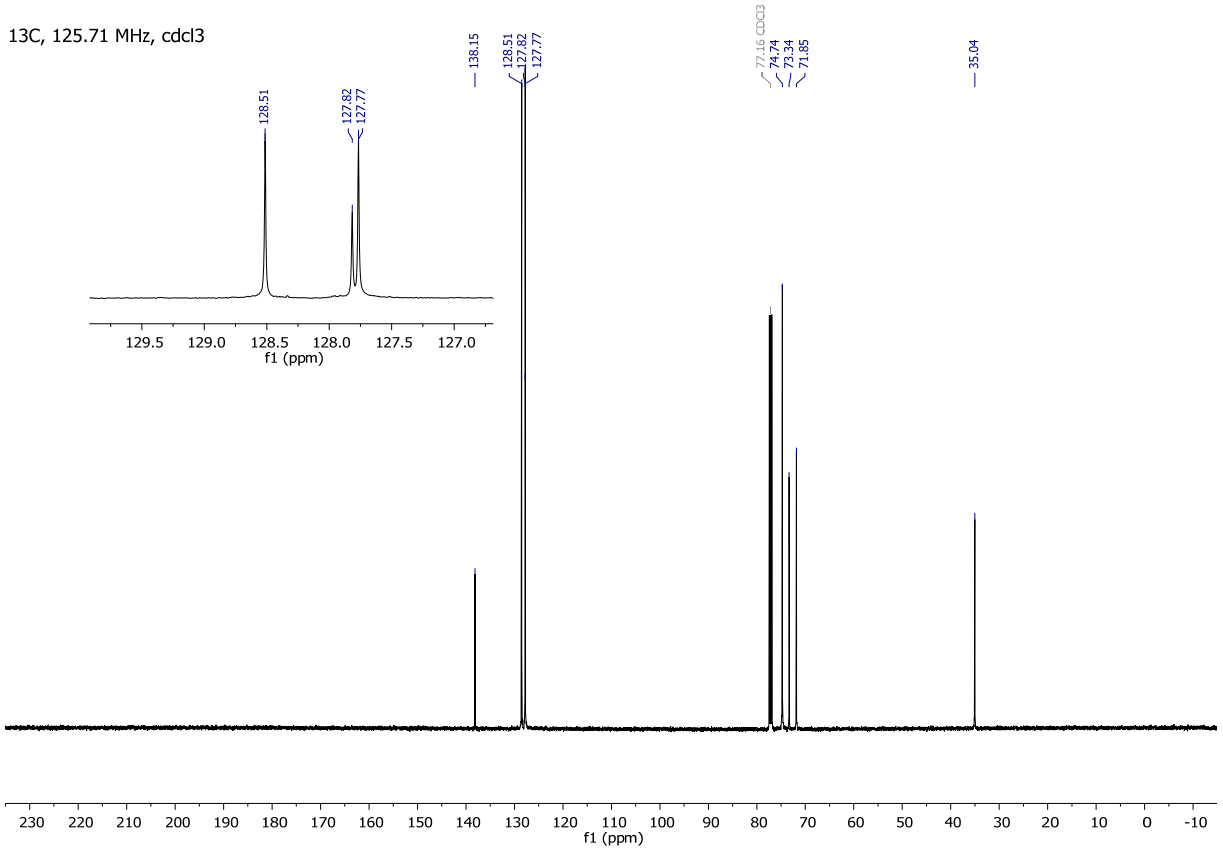


1H, 599.79 MHz, cdcl3

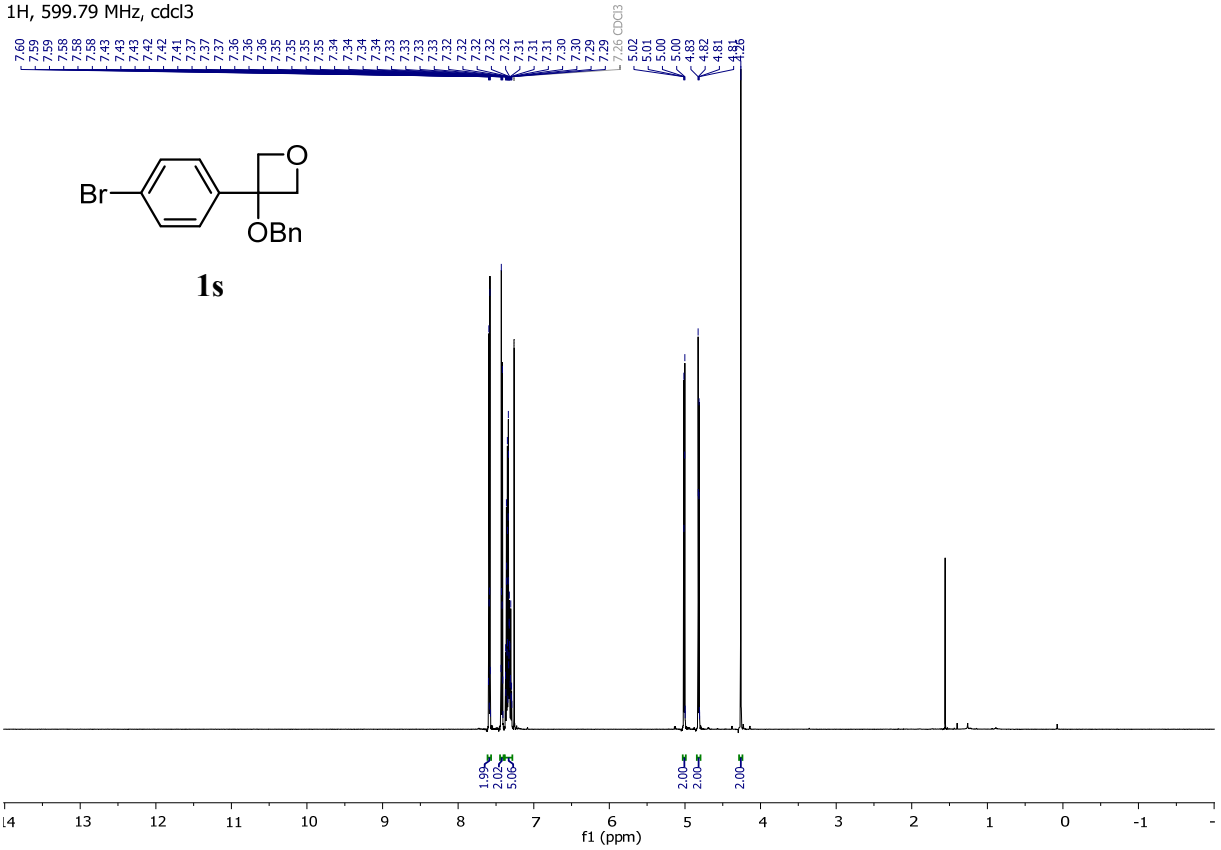
1l



13C, 125.71 MHz, cdcl3

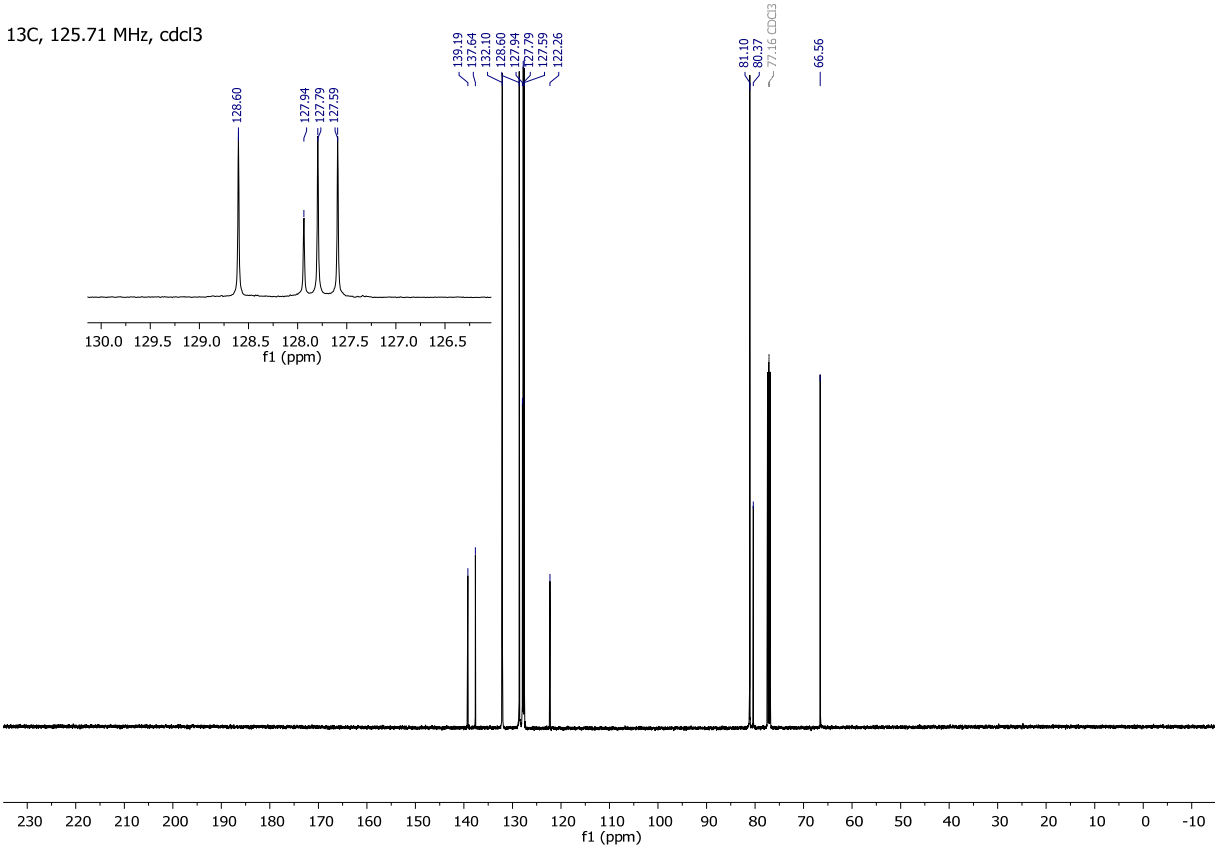


1H, 599.79 MHz, cdcl3

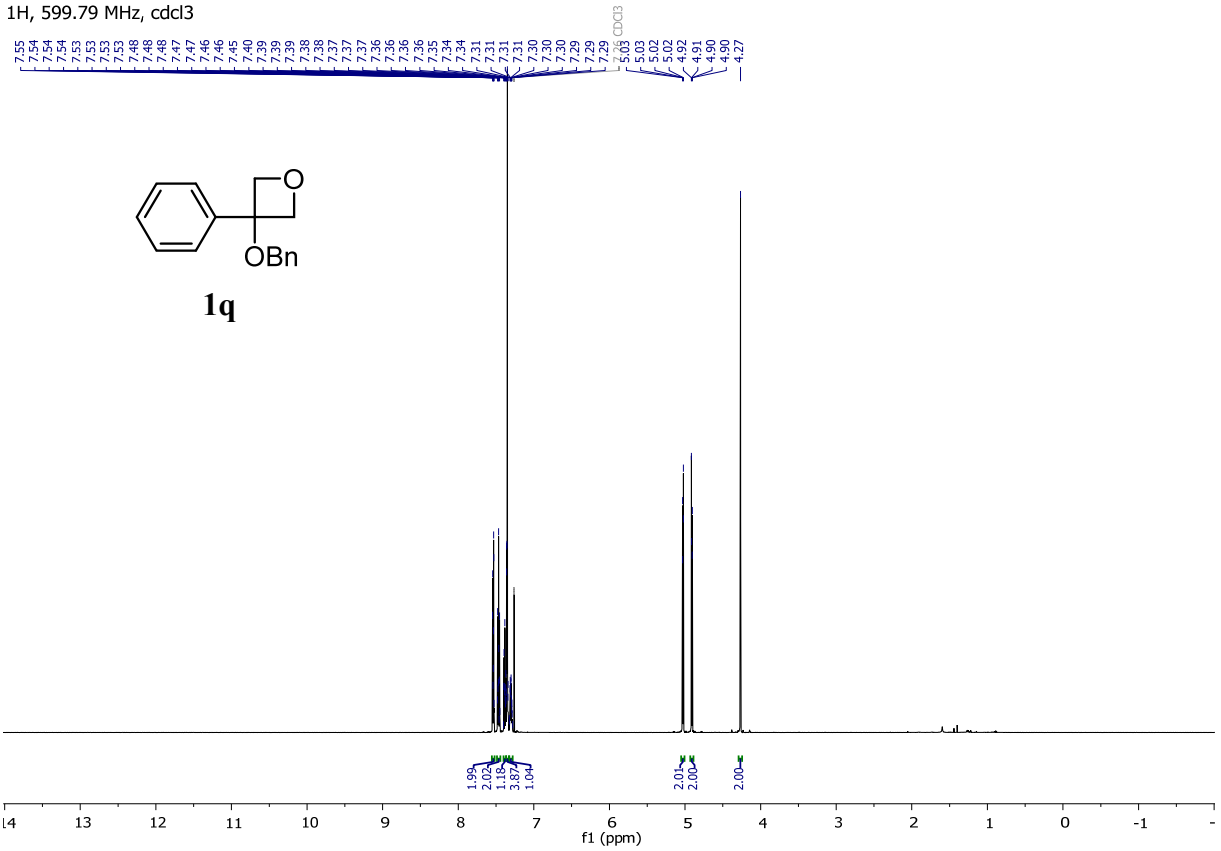


1s

13C, 125.71 MHz, cdcl3

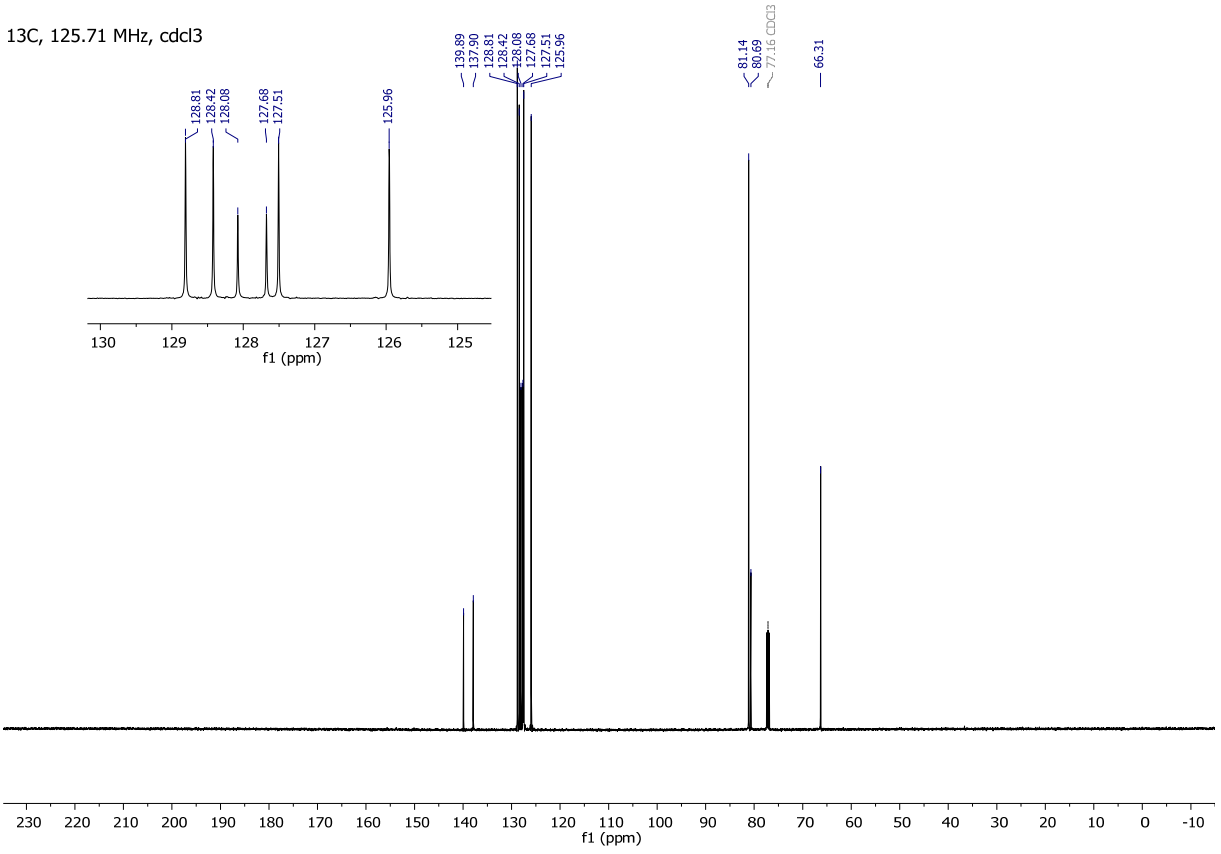


1H, 599.79 MHz, cdcl3

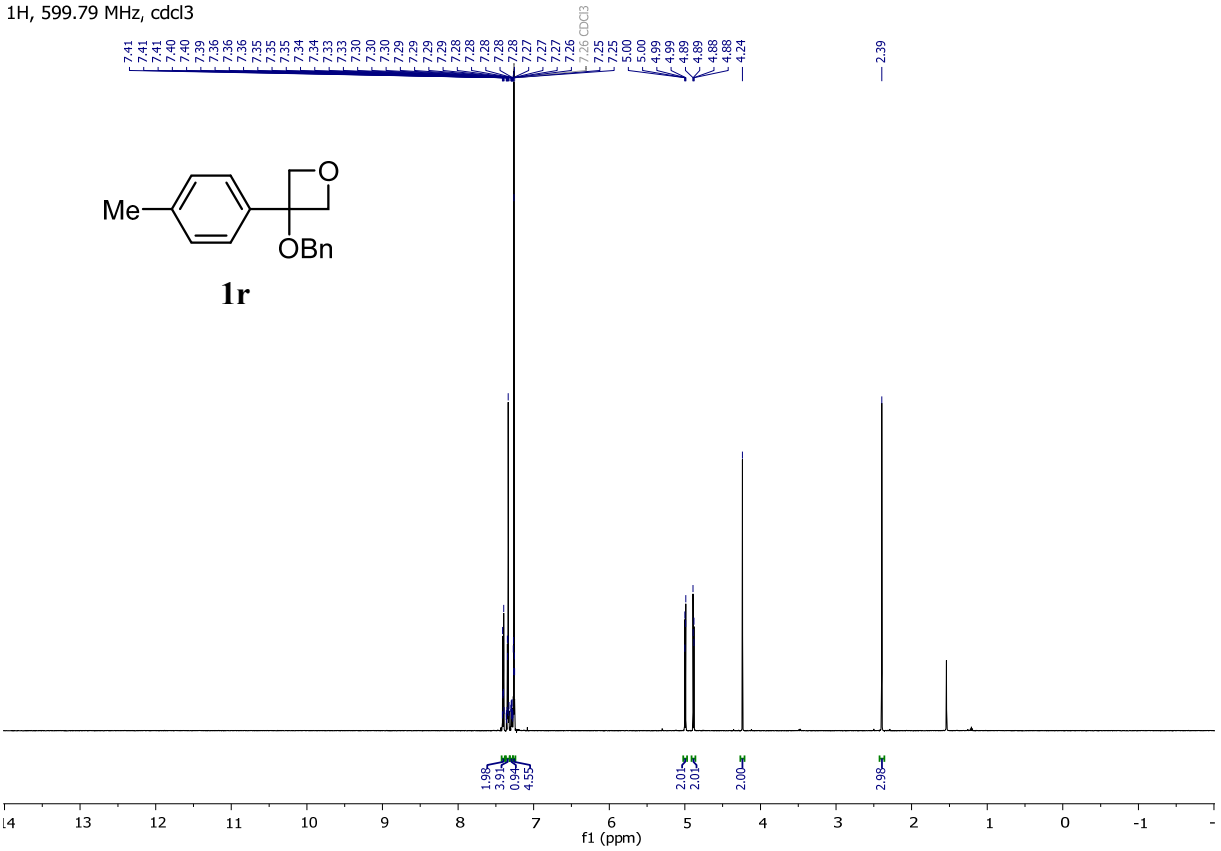


1q

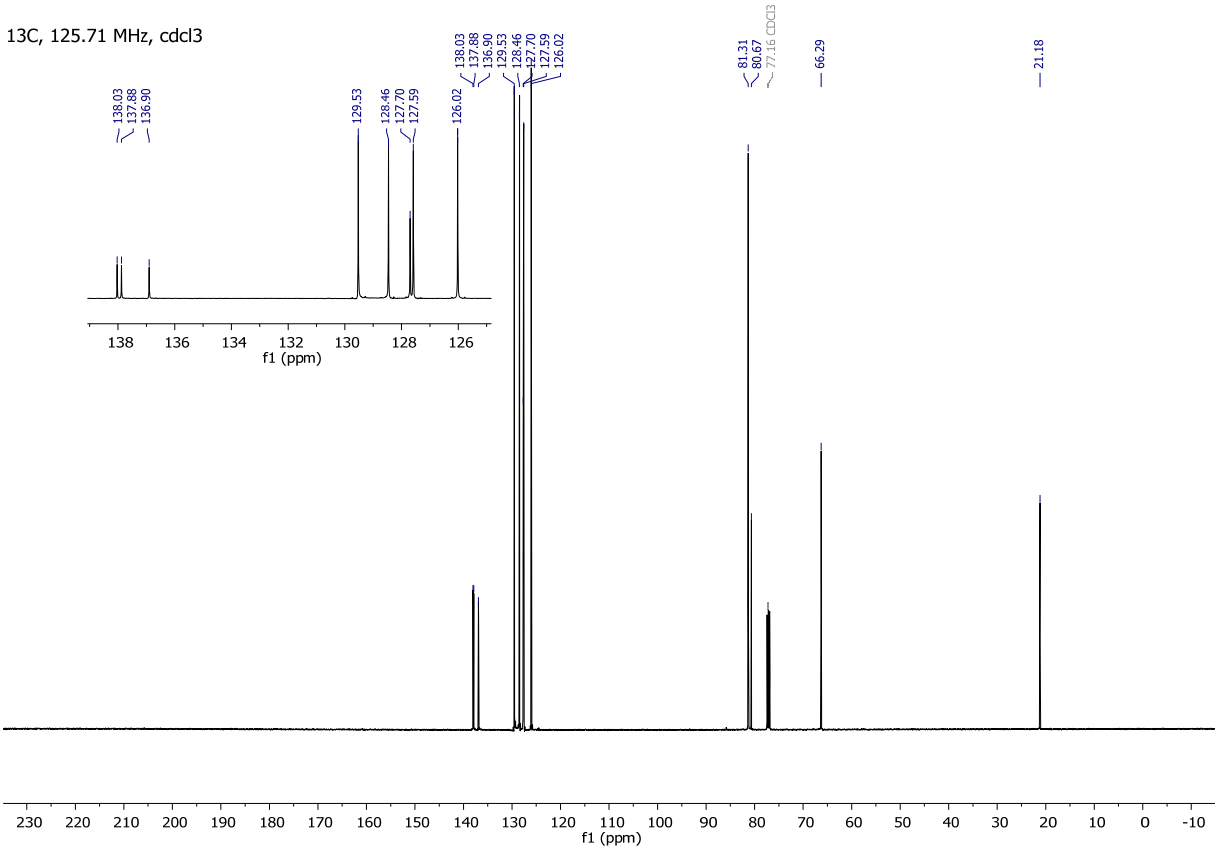
13C, 125.71 MHz, cdcl3



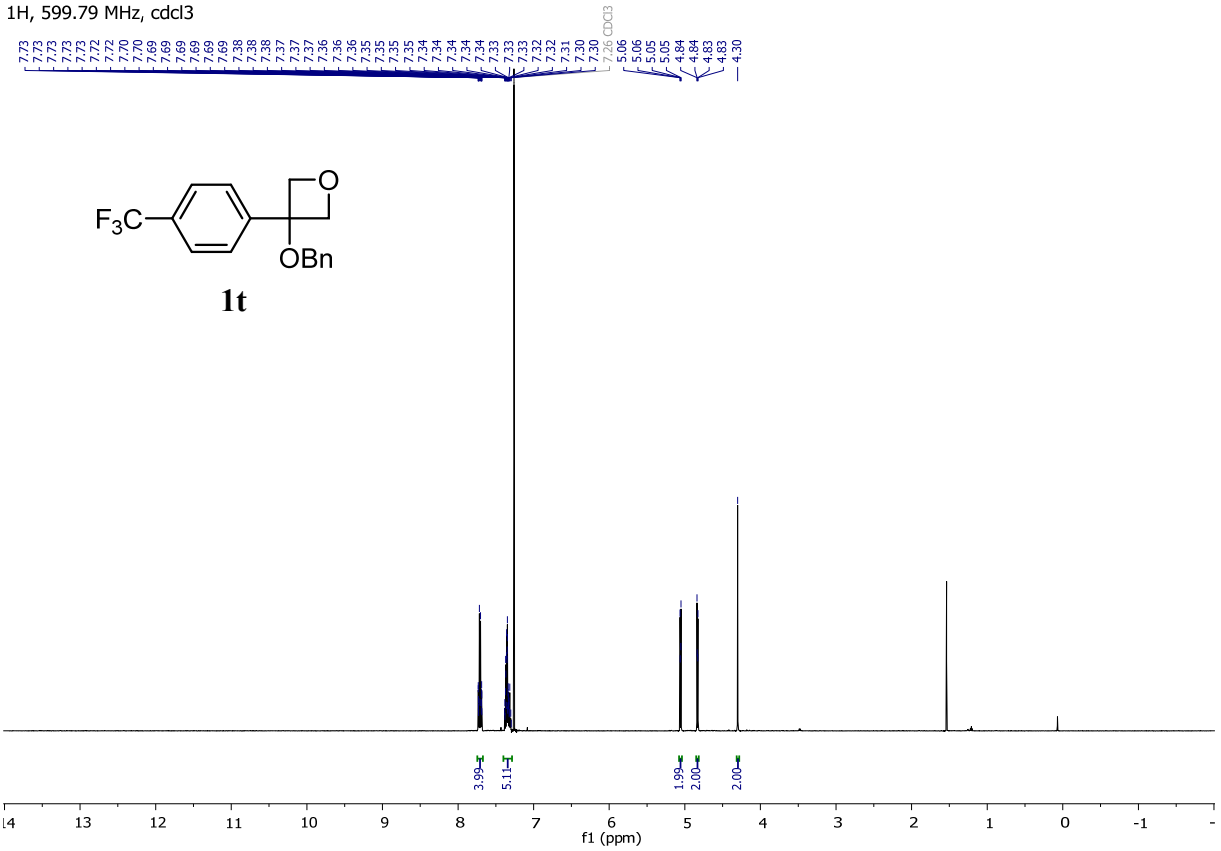
1H, 599.79 MHz, cdcl3



13C, 125.71 MHz, cdcl3

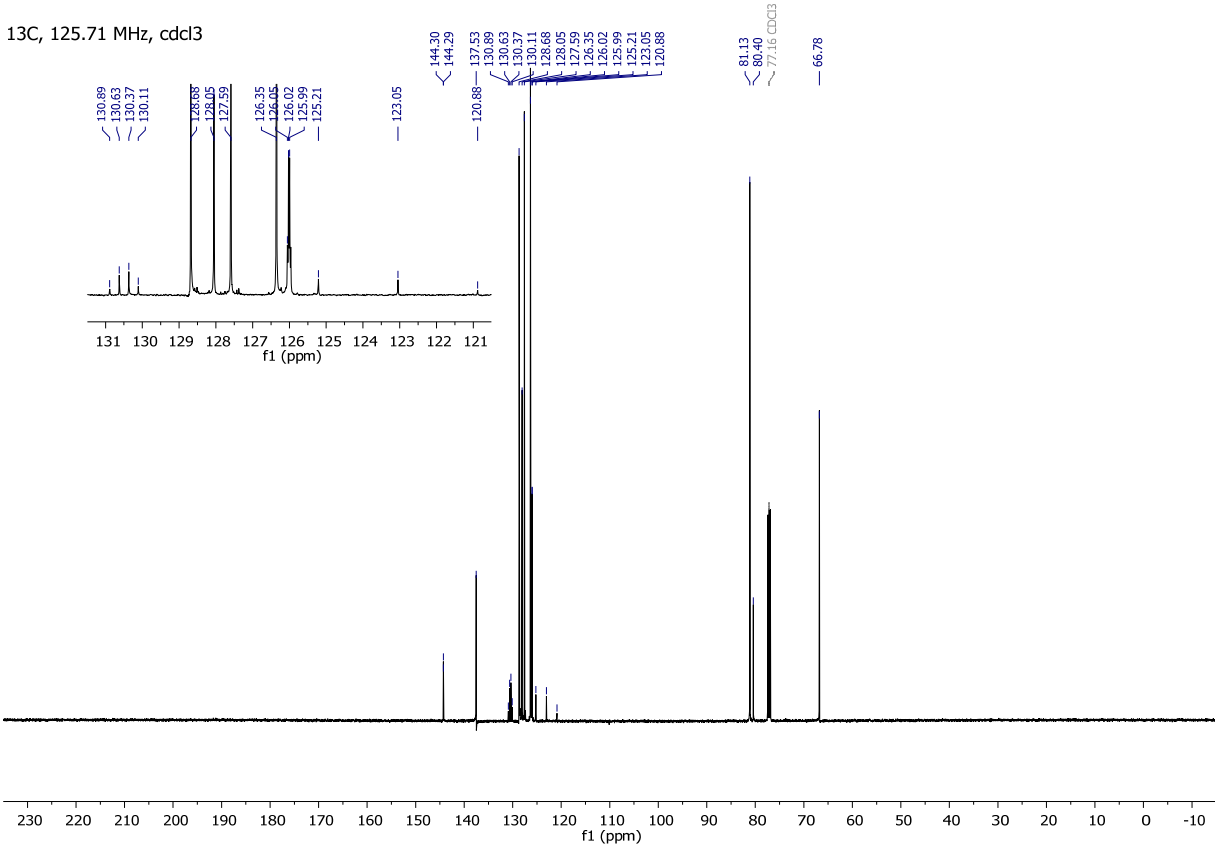


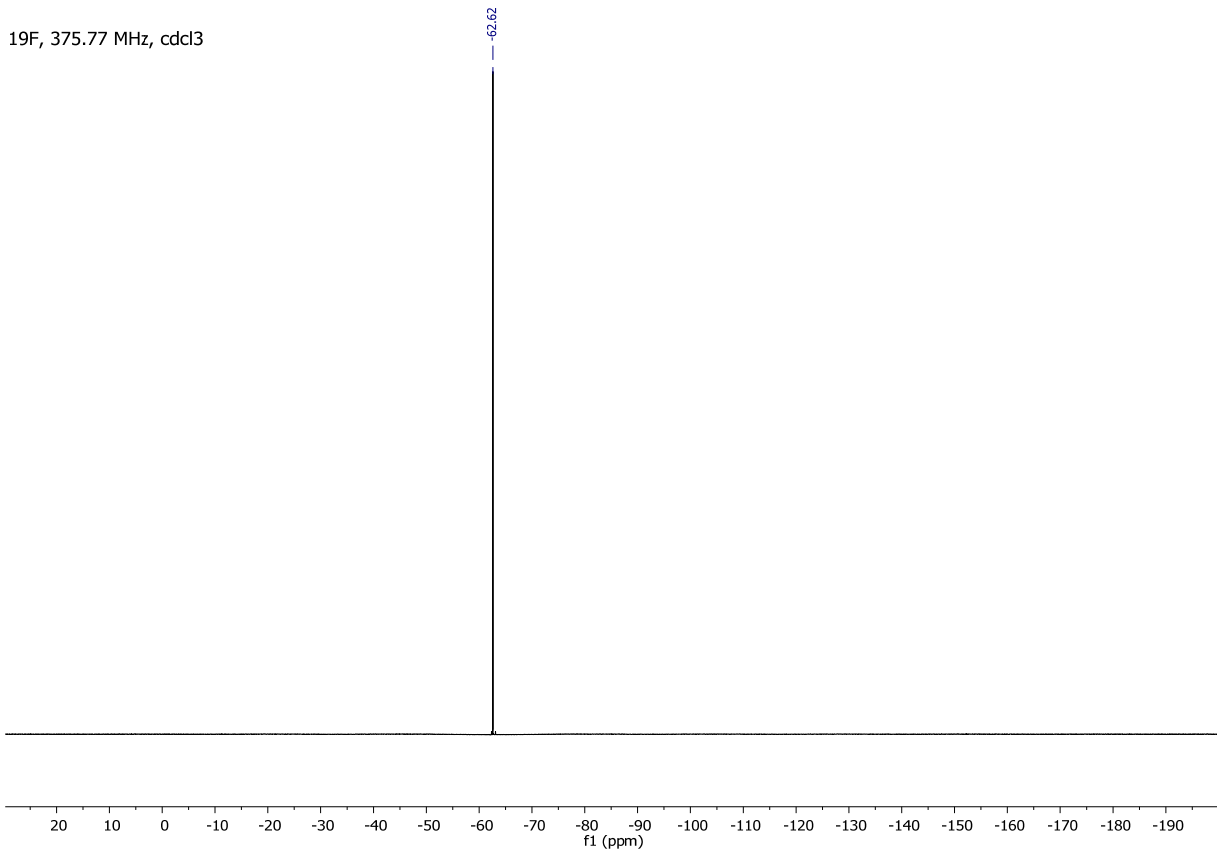
1H, 599.79 MHz, cdcl3



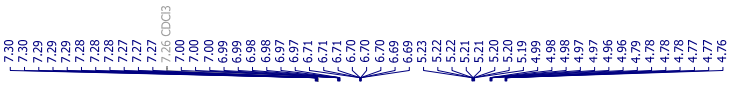
1t

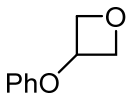
13C, 125.71 MHz, cdcl3



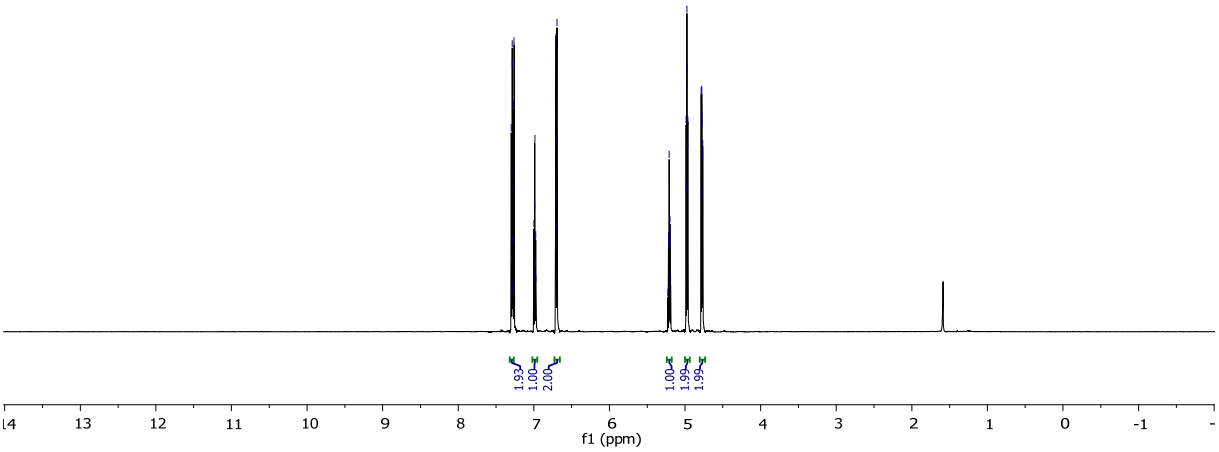

19F, 375.77 MHz, cdcl3
-62.62
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

1H, 599.79 MHz, cdcl3

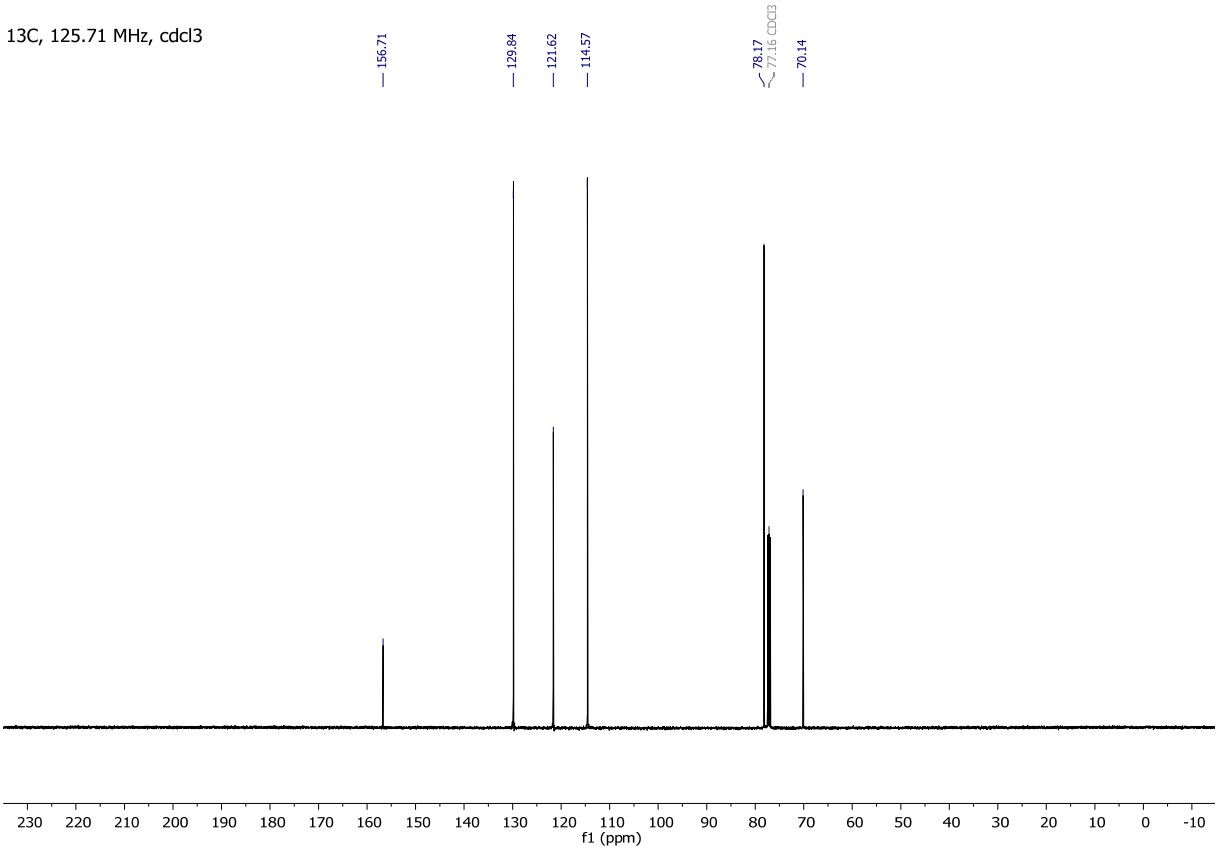




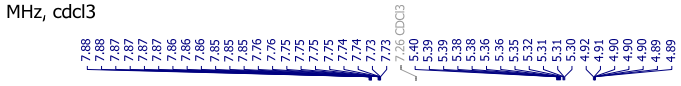
1i

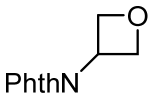


13C, 125.71 MHz, cdcl3

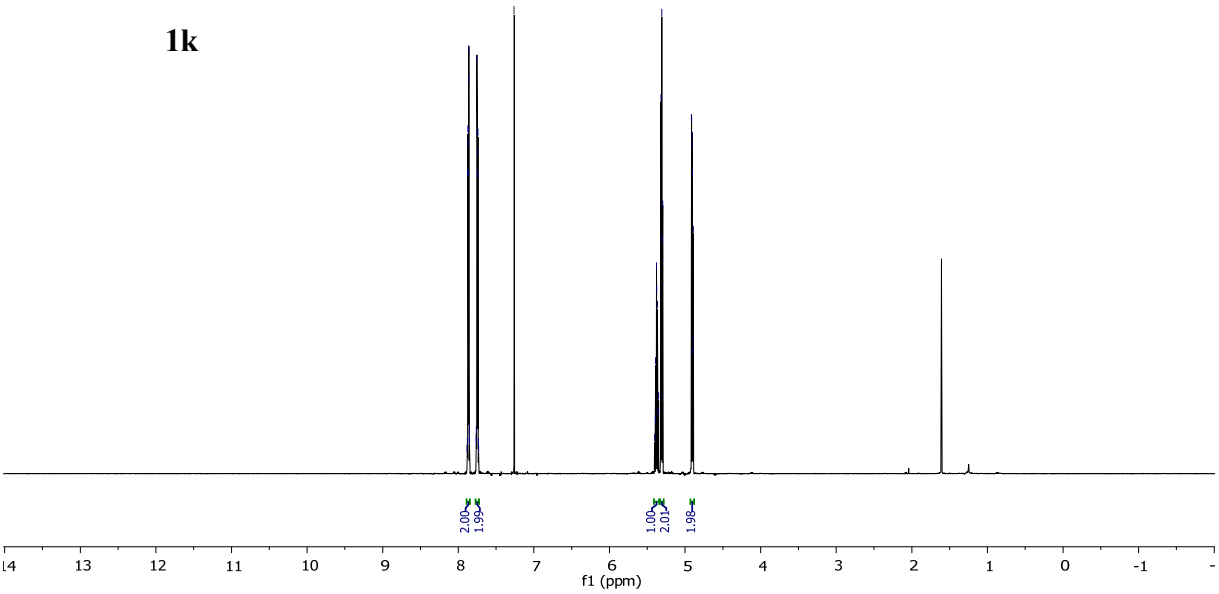


1H, 599.79 MHz, cdcl3

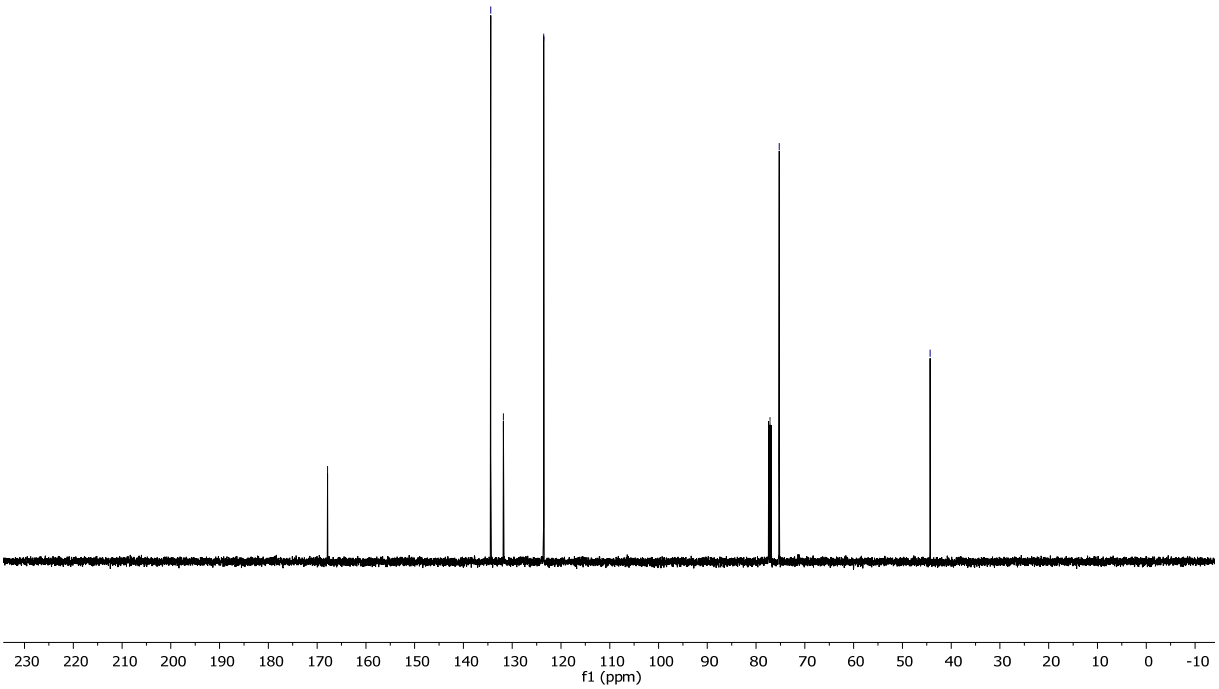




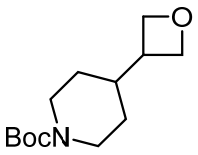
1k



13C, 125.78 MHz, cdcl3

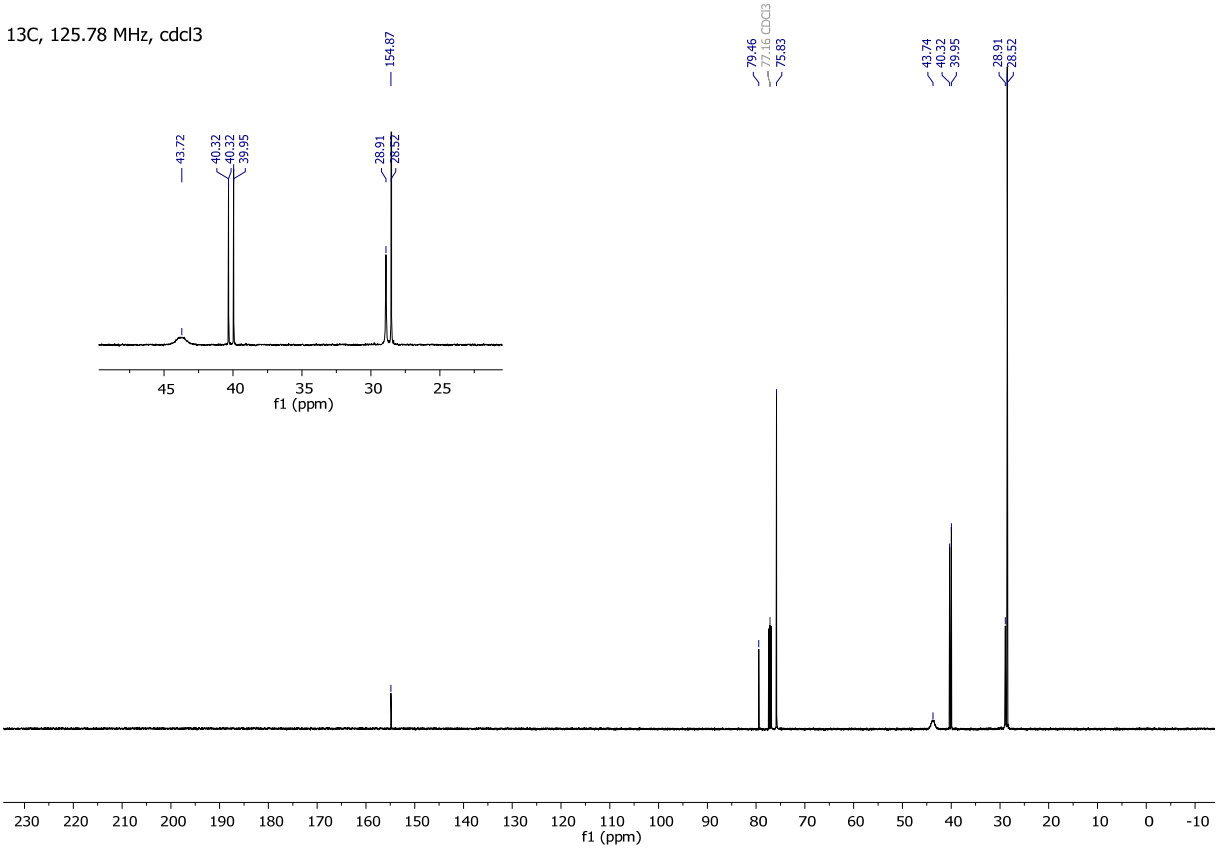


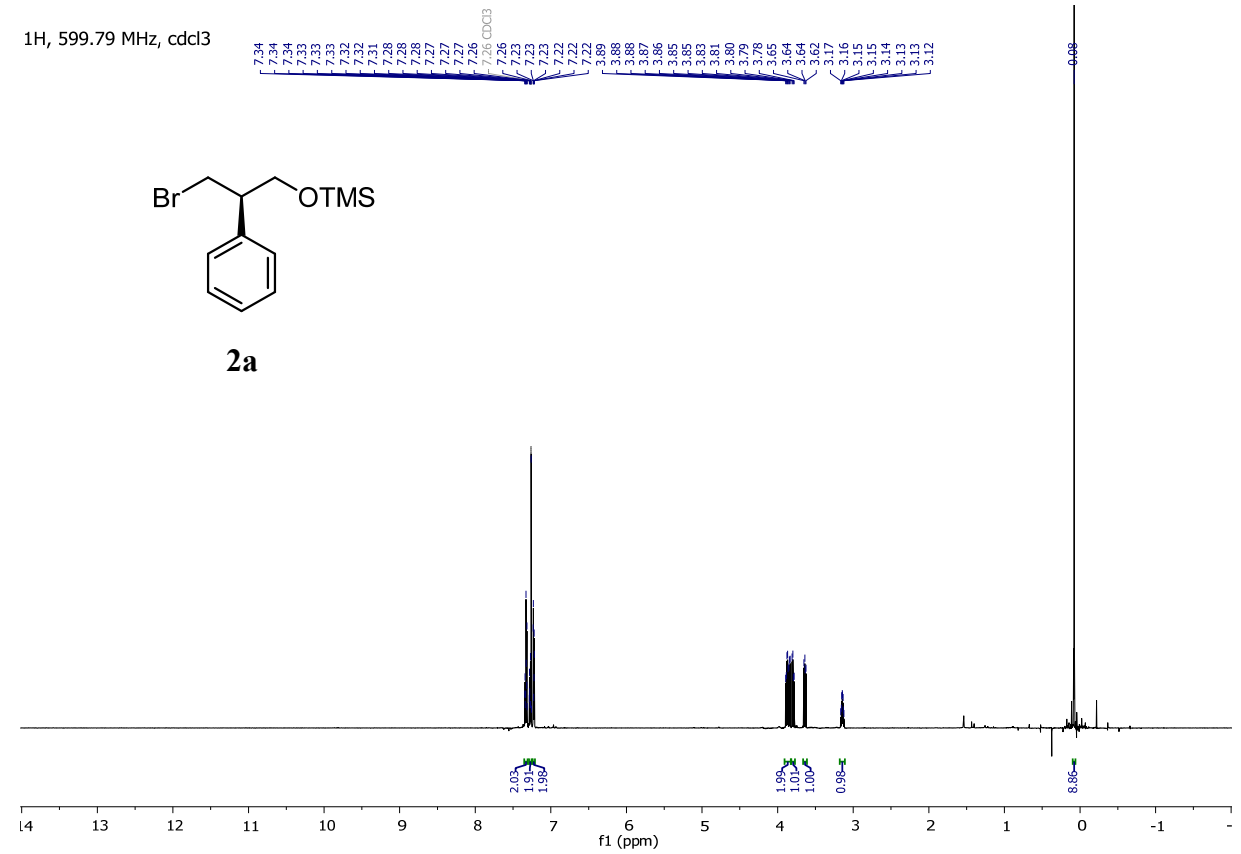
1H, 599.79 MHz, cdcl3

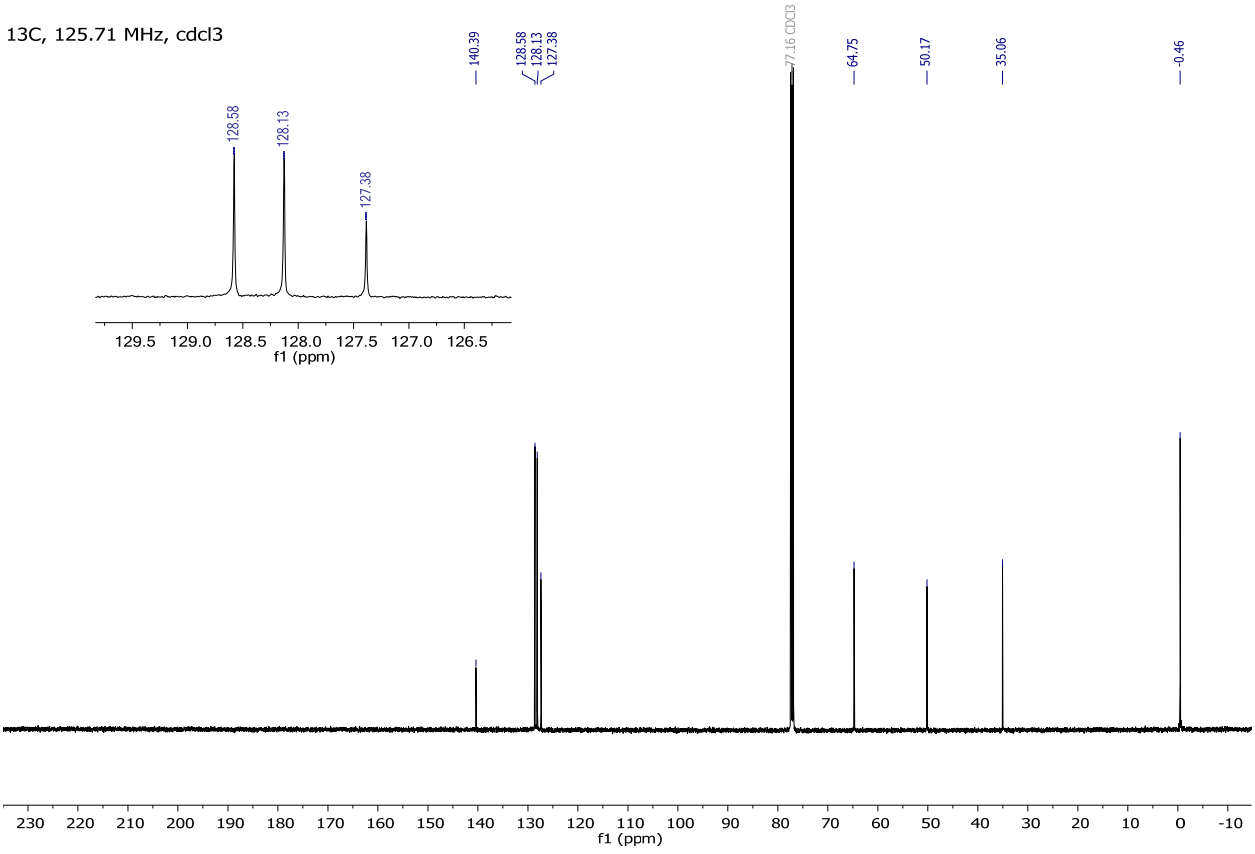


1m

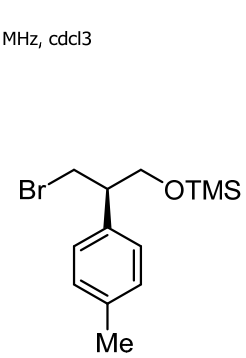
13C, 125.78 MHz, cdcl3




1H, 599.79 MHz, cdcl3
Br
OTMS
2a
f1 (ppm)

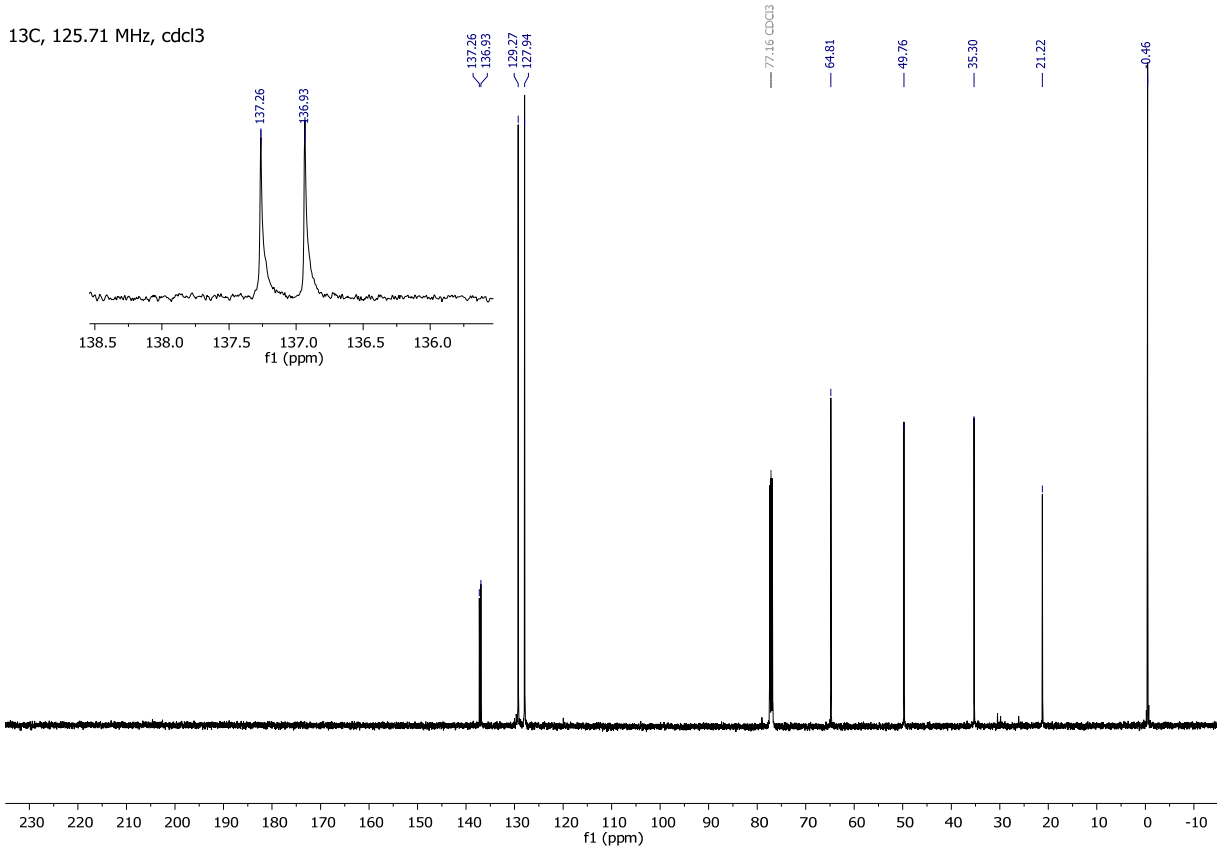

13C, 125.71 MHz, cdcl3
140.39
128.58
128.13
127.38
77.16 CDCl3
64.75
50.17
35.06
-0.46
f1 (ppm)

1H, 599.79 MHz, cdcl3

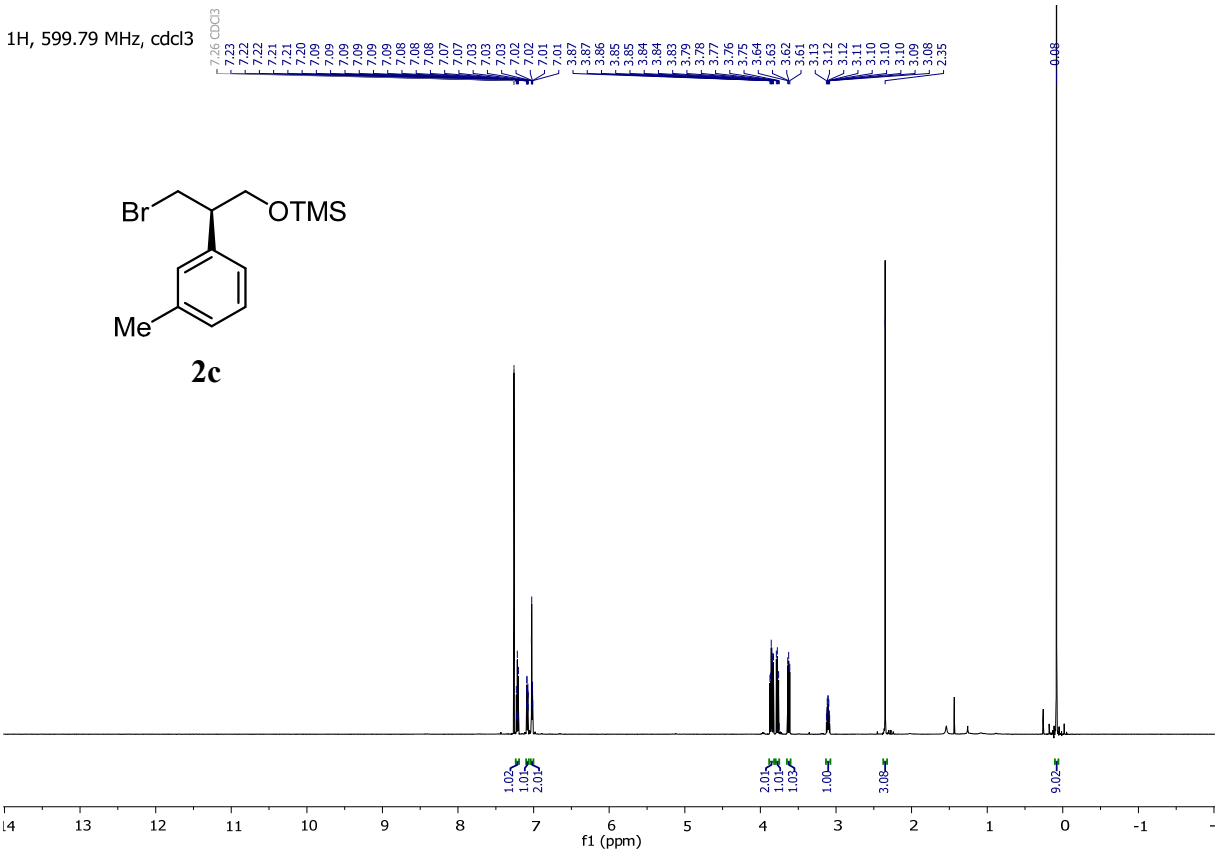


2b

13C, 125.71 MHz, cdcl3

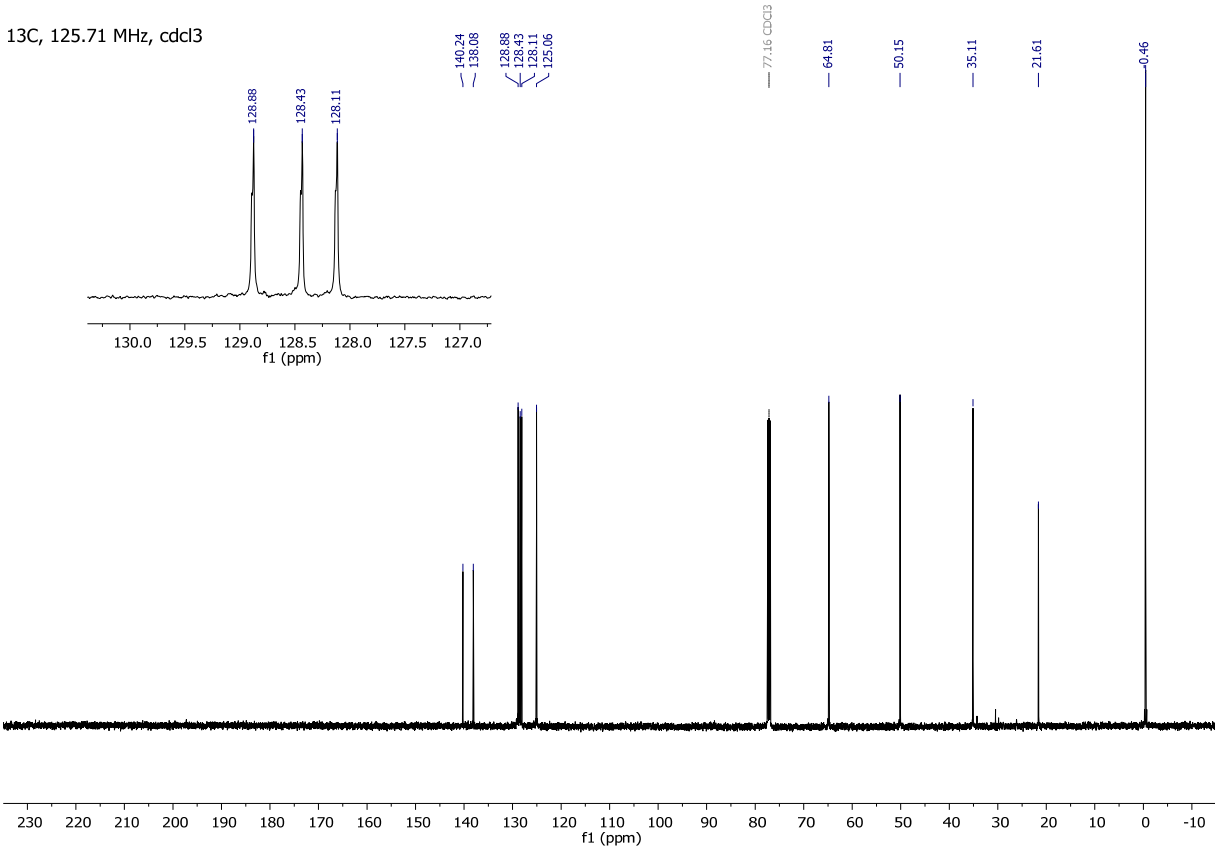


1H, 599.79 MHz, cdcl3

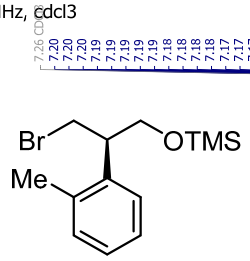


2c

13C, 125.71 MHz, cdcl3

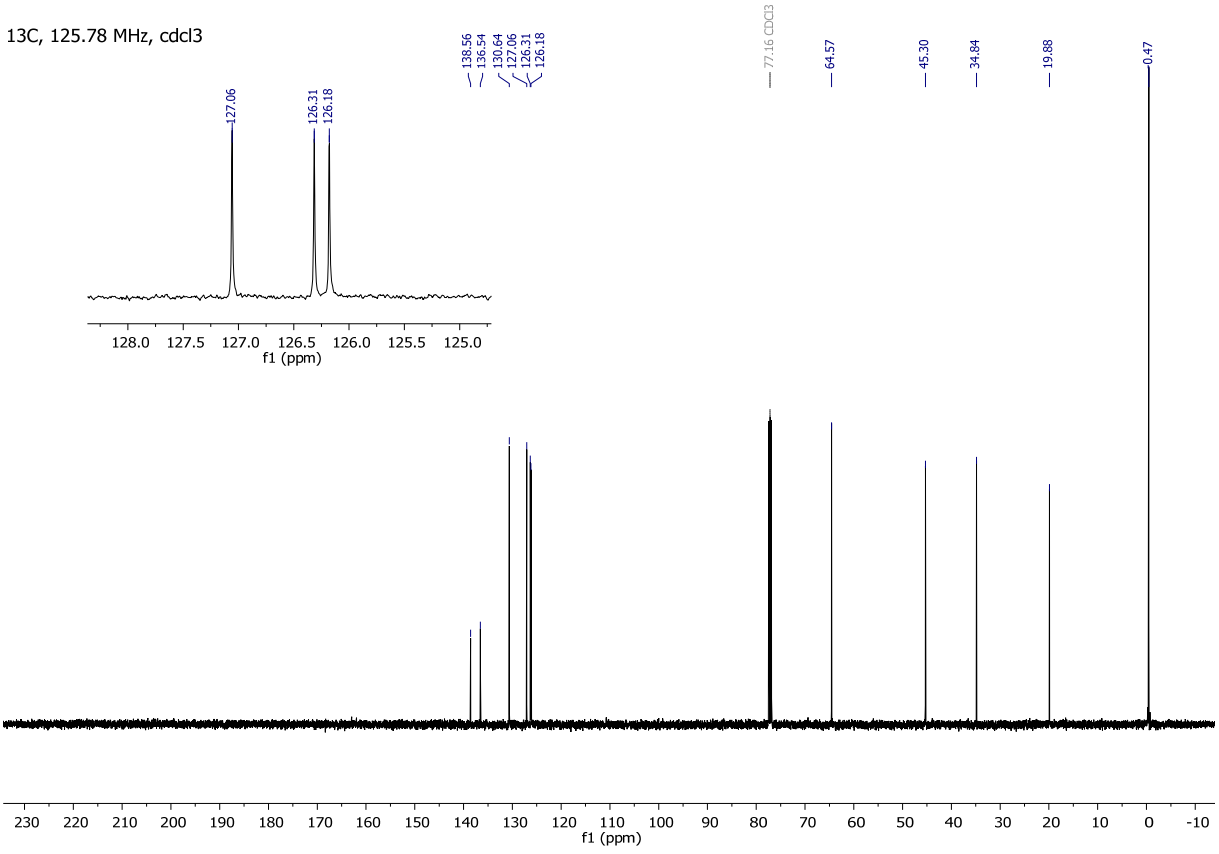


1H, 599.79 MHz, cdcl3

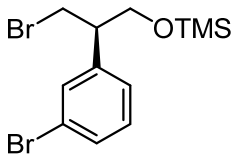


2d

13C, 125.78 MHz, cdcl3

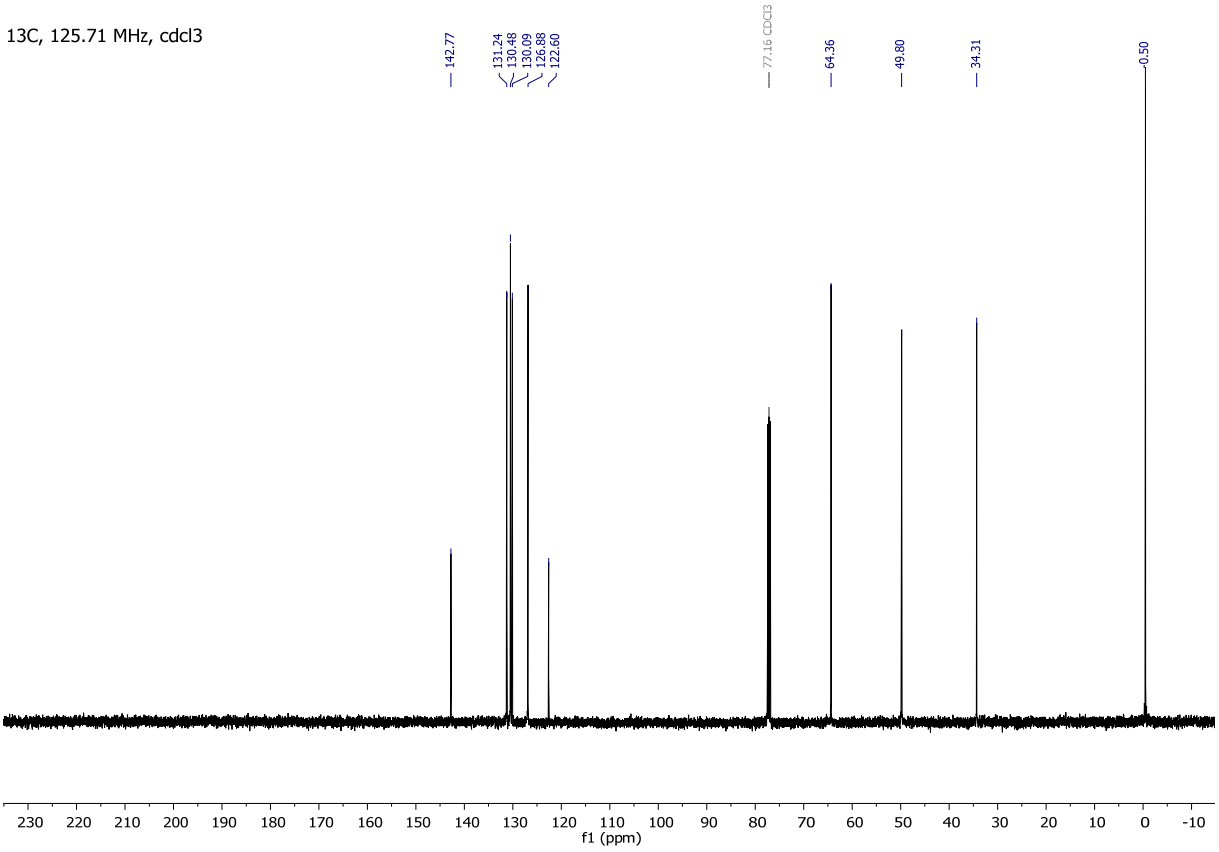


1H, 599.79 MHz, cdcl3

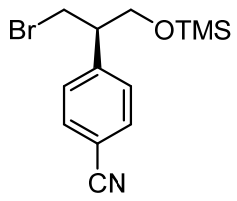


2e

13C, 125.71 MHz, cdcl3

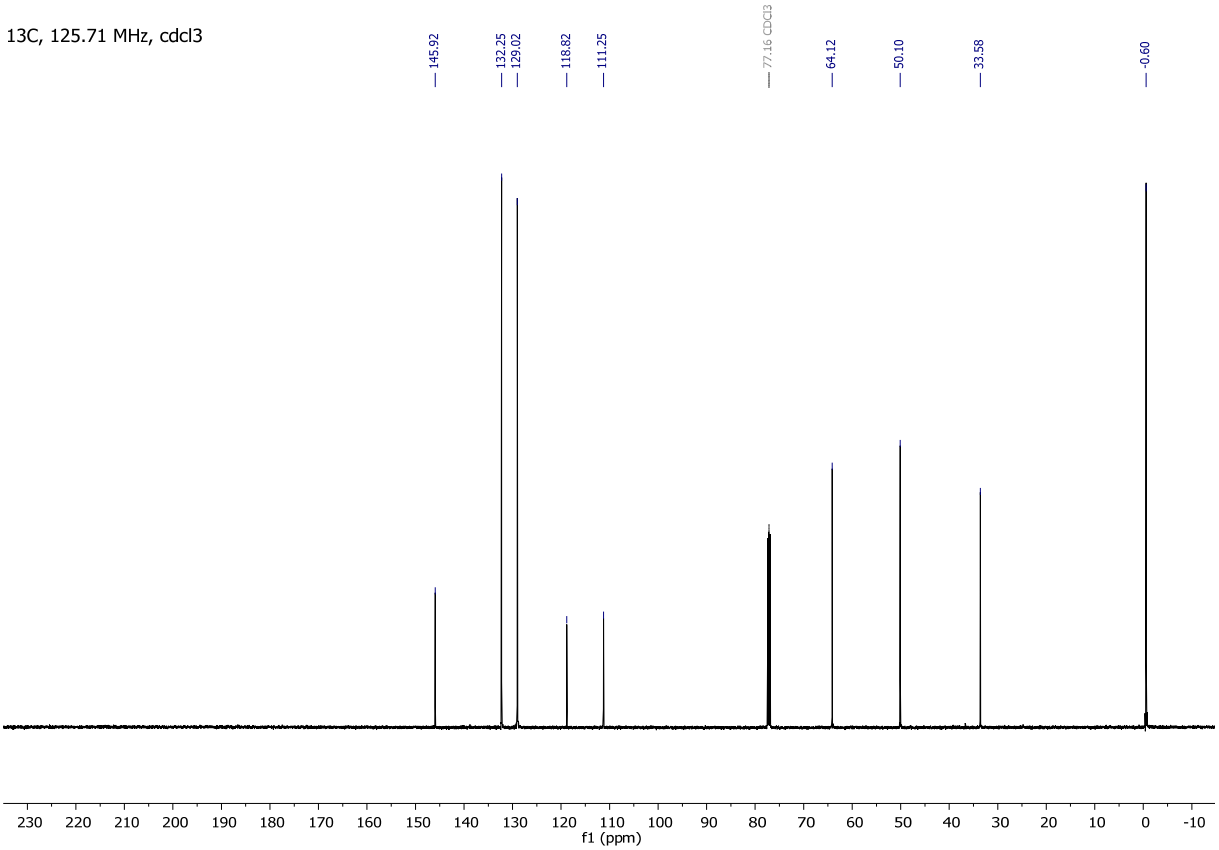


1H, 599.79 MHz, cdcl3

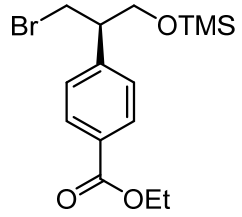


2f

13C, 125.71 MHz, cdcl3

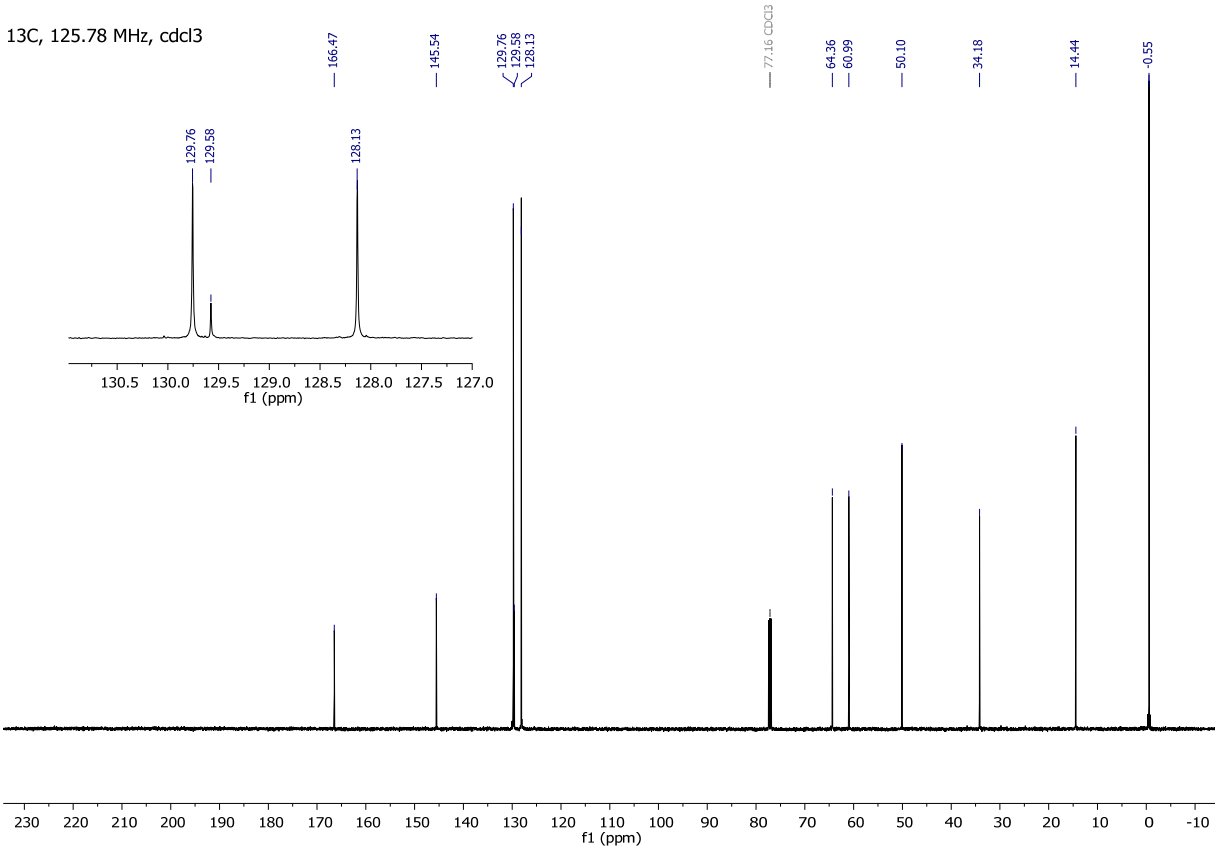


1H, 599.79 MHz, cdcl3

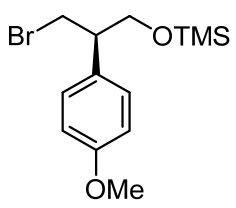


2g

13C, 125.78 MHz, cdcl3

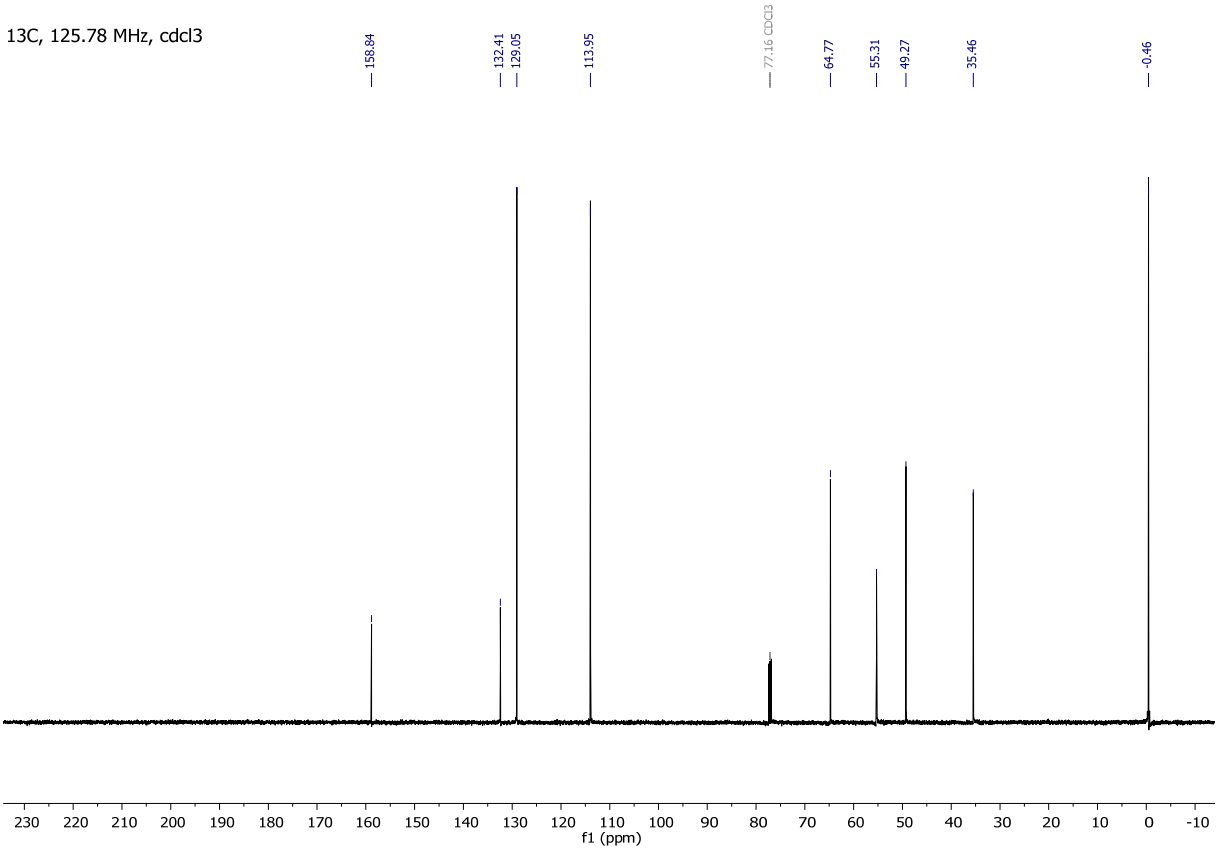


1H, 599.79 MHz, cdcl3

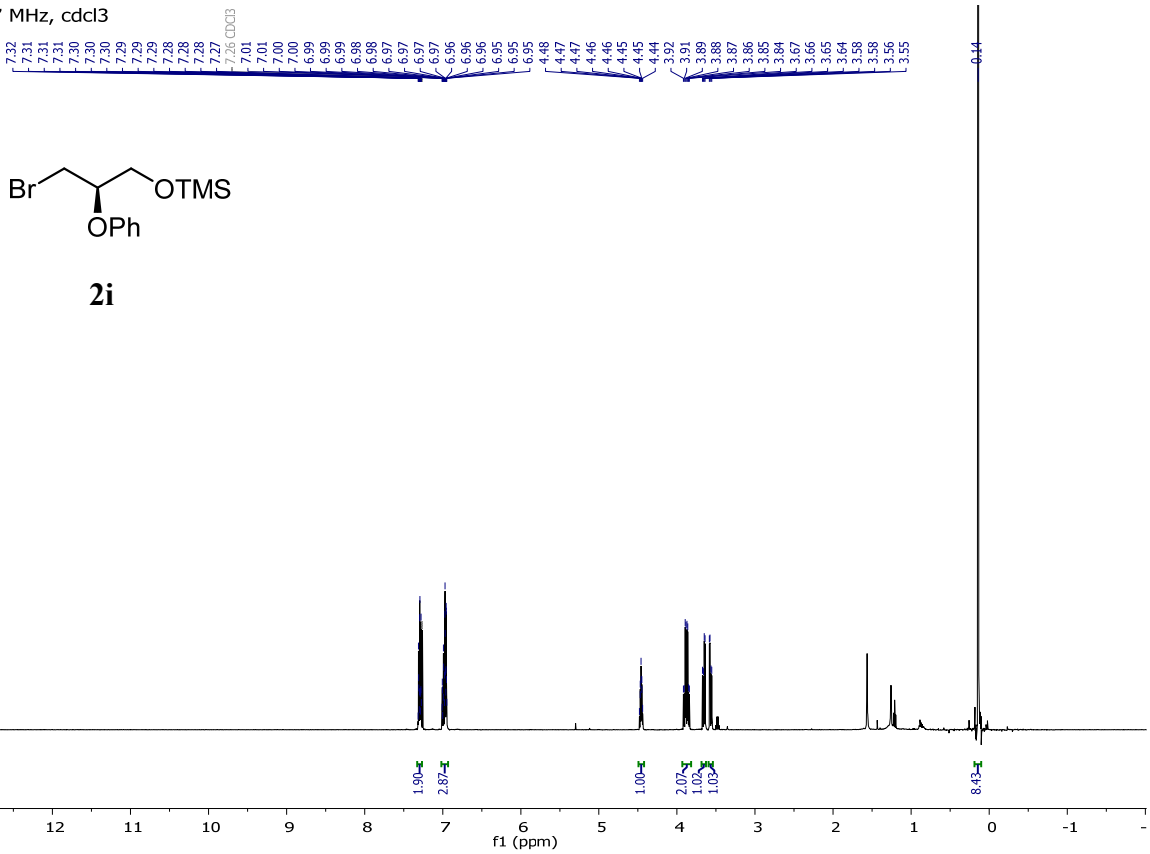


2h

13C, 125.78 MHz, cdcl3

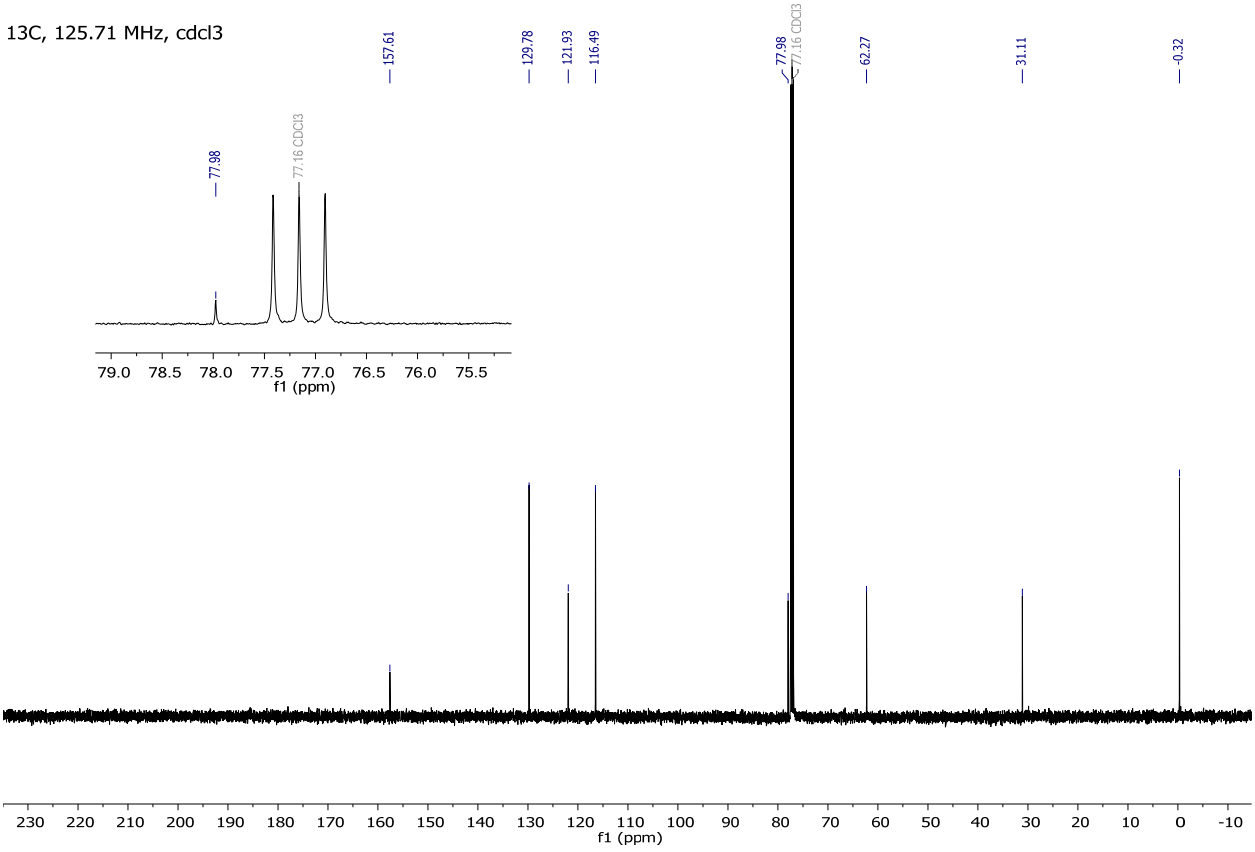


1H, 499.87 MHz, cdcl3

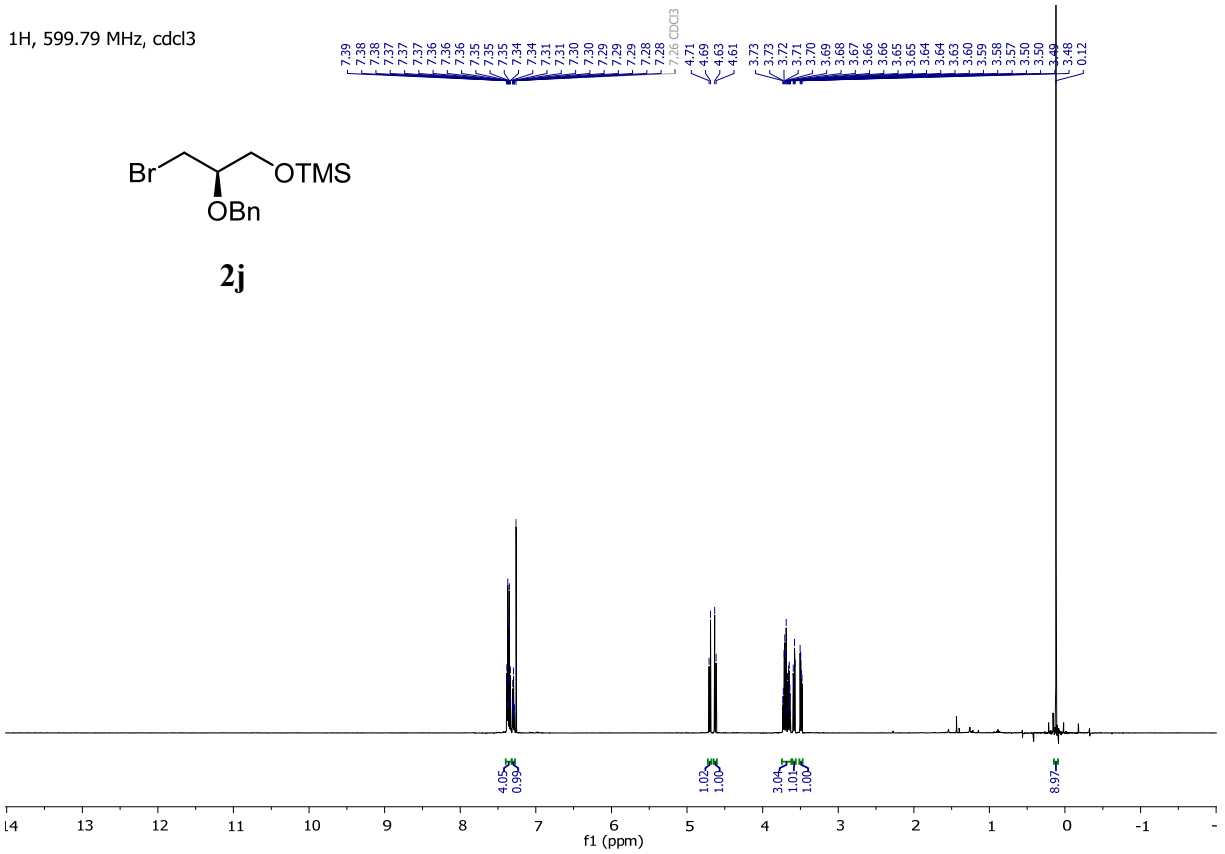


2i

13C, 125.71 MHz, cdcl3

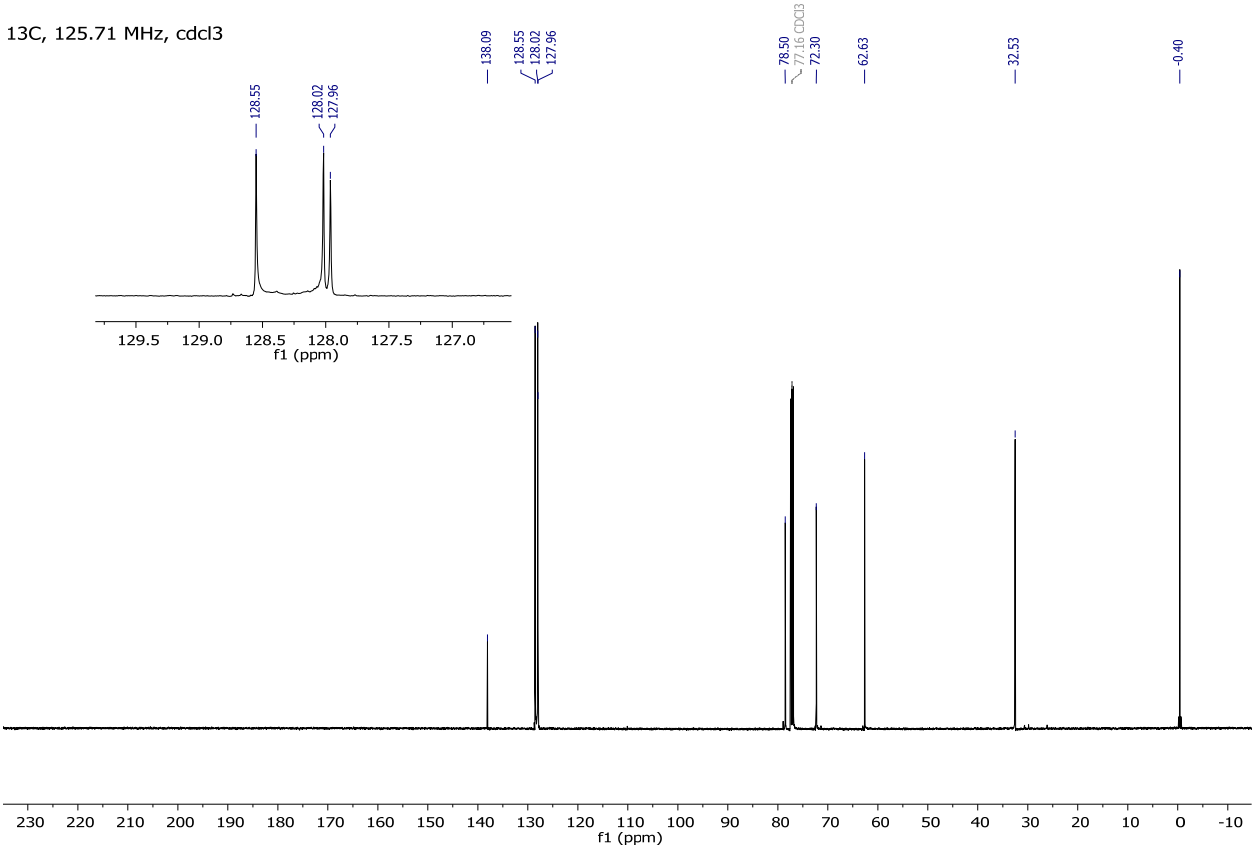


1H, 599.79 MHz, cdcl3

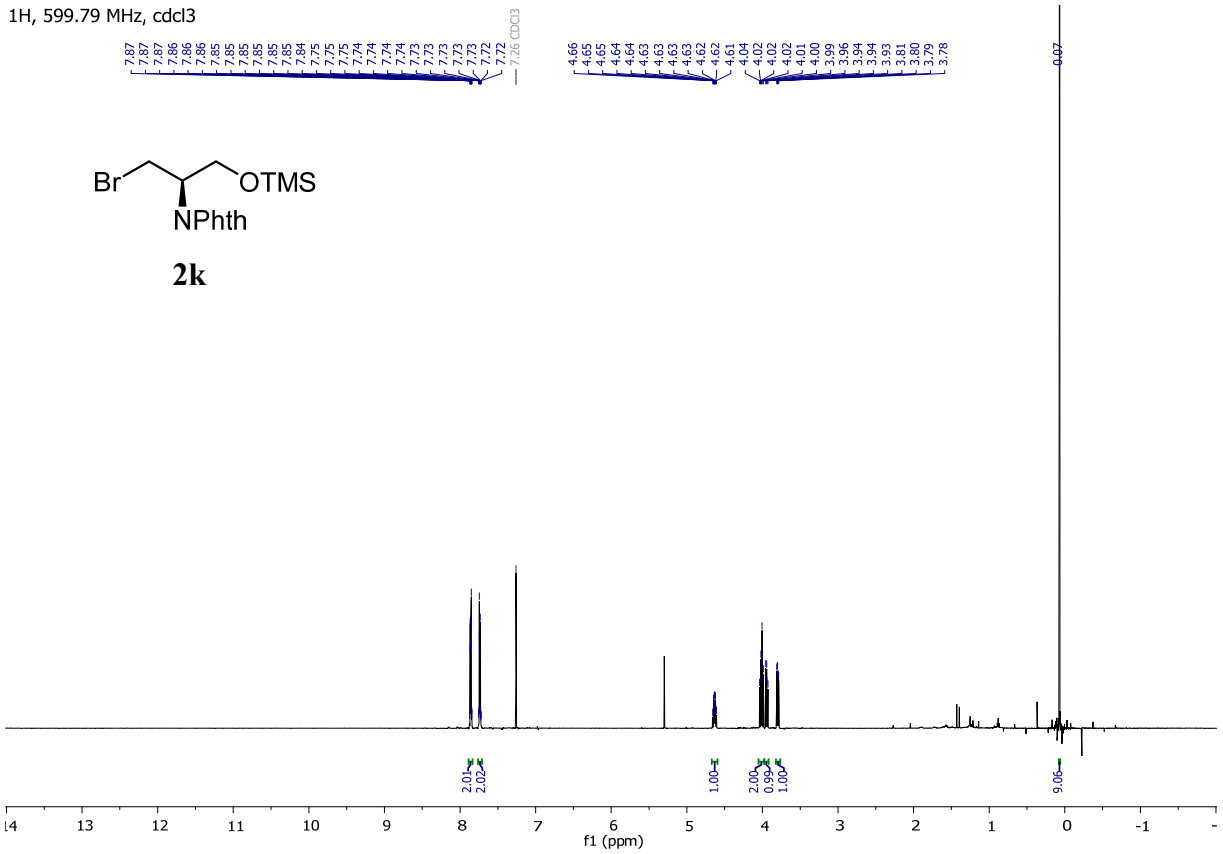


2j

13C, 125.71 MHz, cdcl3

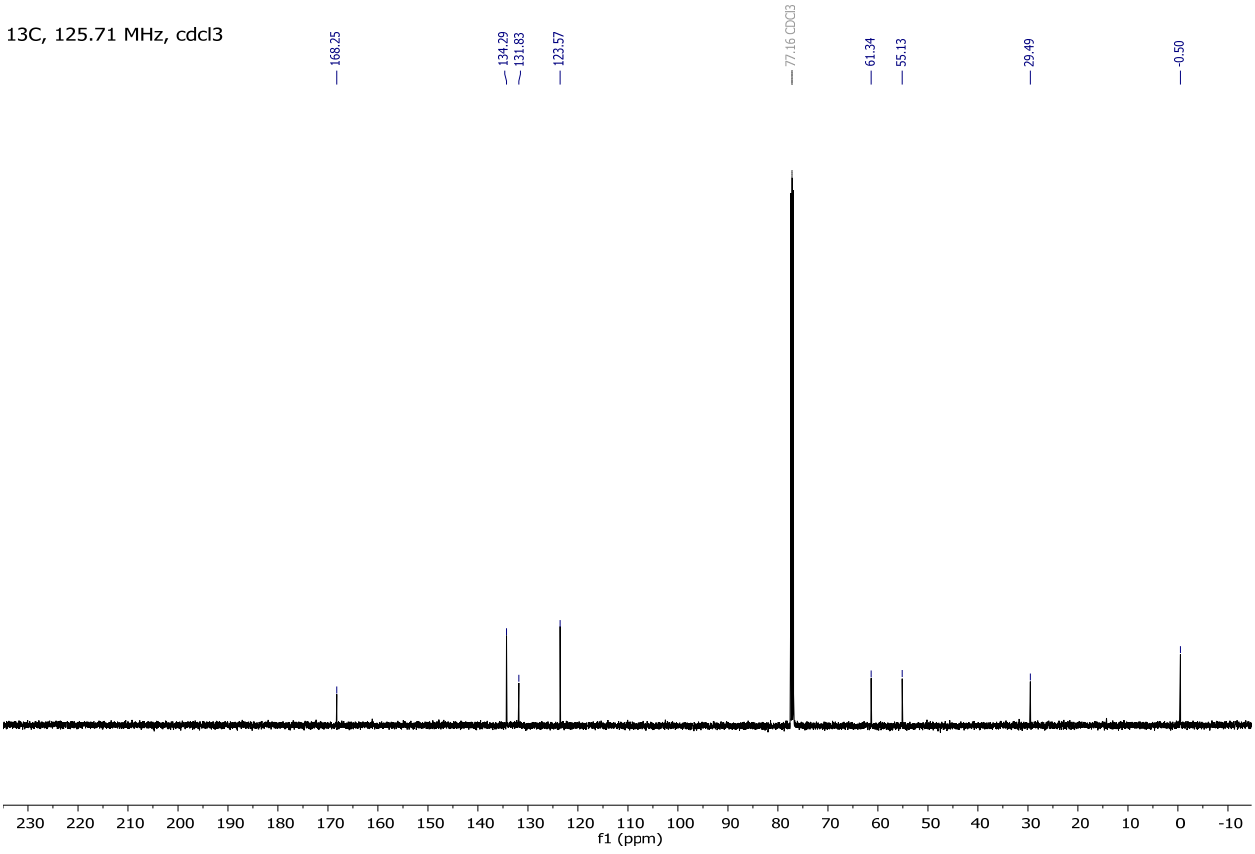


1H, 599.79 MHz, cdcl3

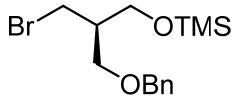


2k

13C, 125.71 MHz, cdcl3



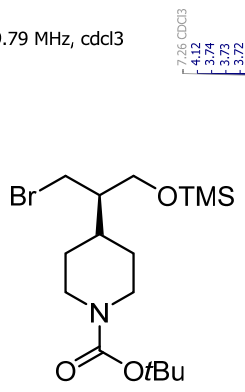
1H, 599.79 MHz, cdcl3



2l

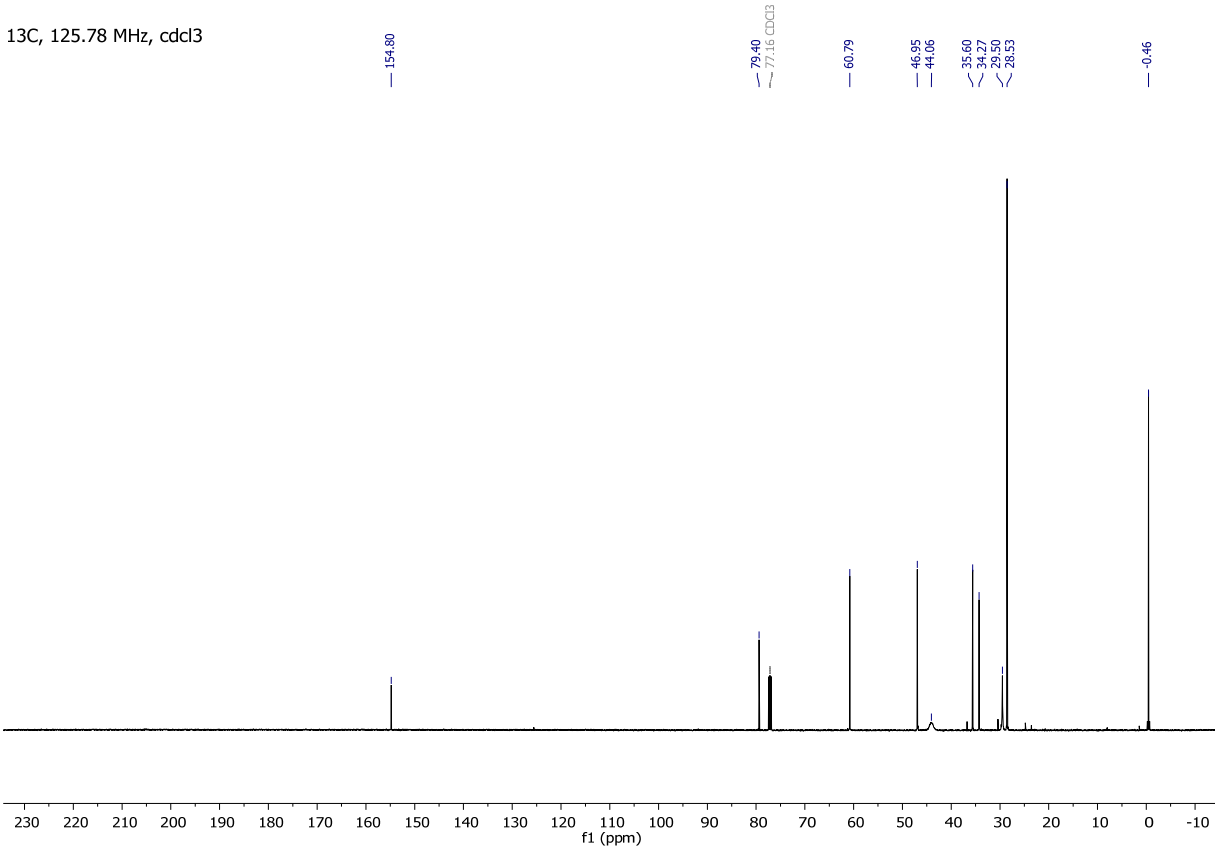
13C, 125.78 MHz, cdcl3

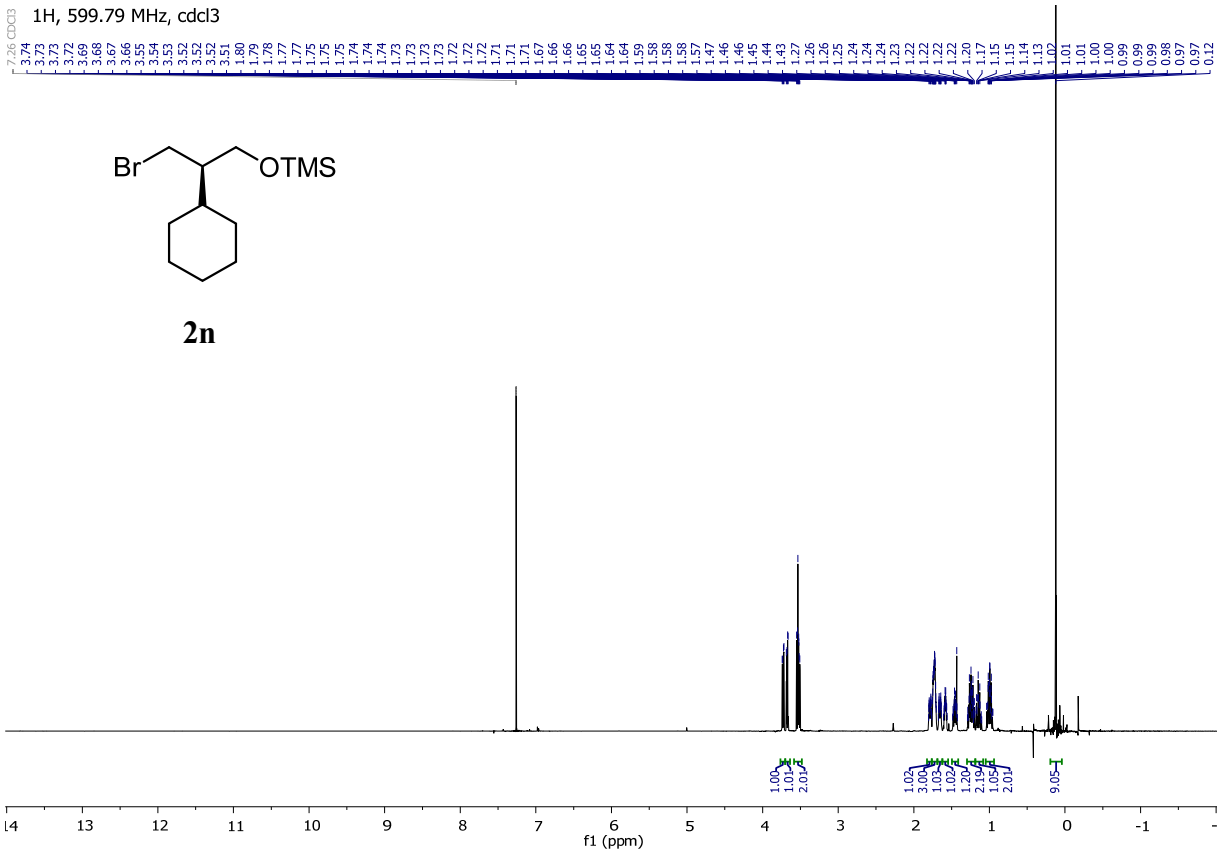
1H, 599.79 MHz, cdcl3



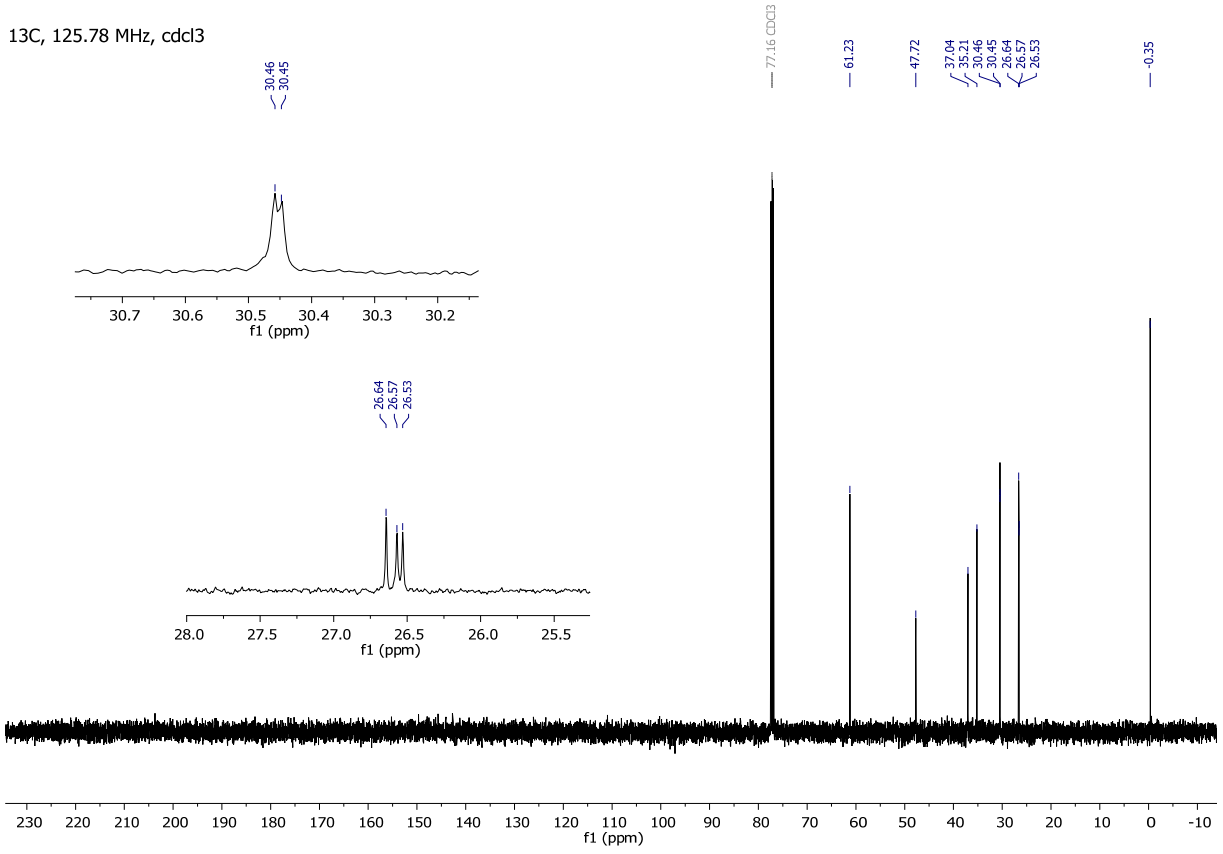
2m

13C, 125.78 MHz, cdcl3

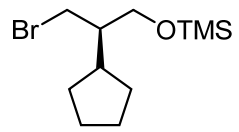



1H, 599.79 MHz, cdcl3
Br
OTMS
f1 (ppm)

2n

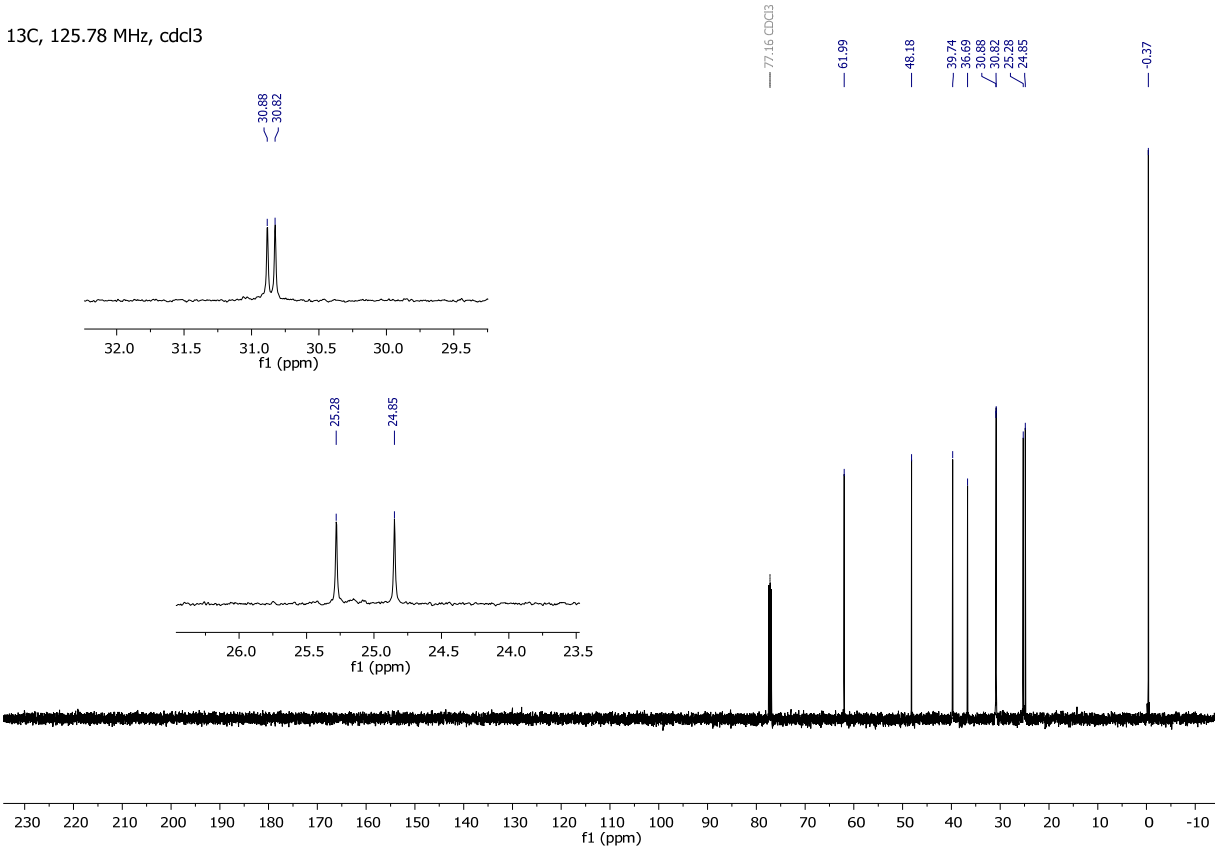

13C, 125.78 MHz, cdcl3
77.16 CDCl3
61.23
47.72
37.04
35.21
30.46
30.45
26.64
26.57
26.53
-0.35
f1 (ppm)

1H, 599.79 MHz, cdcl3

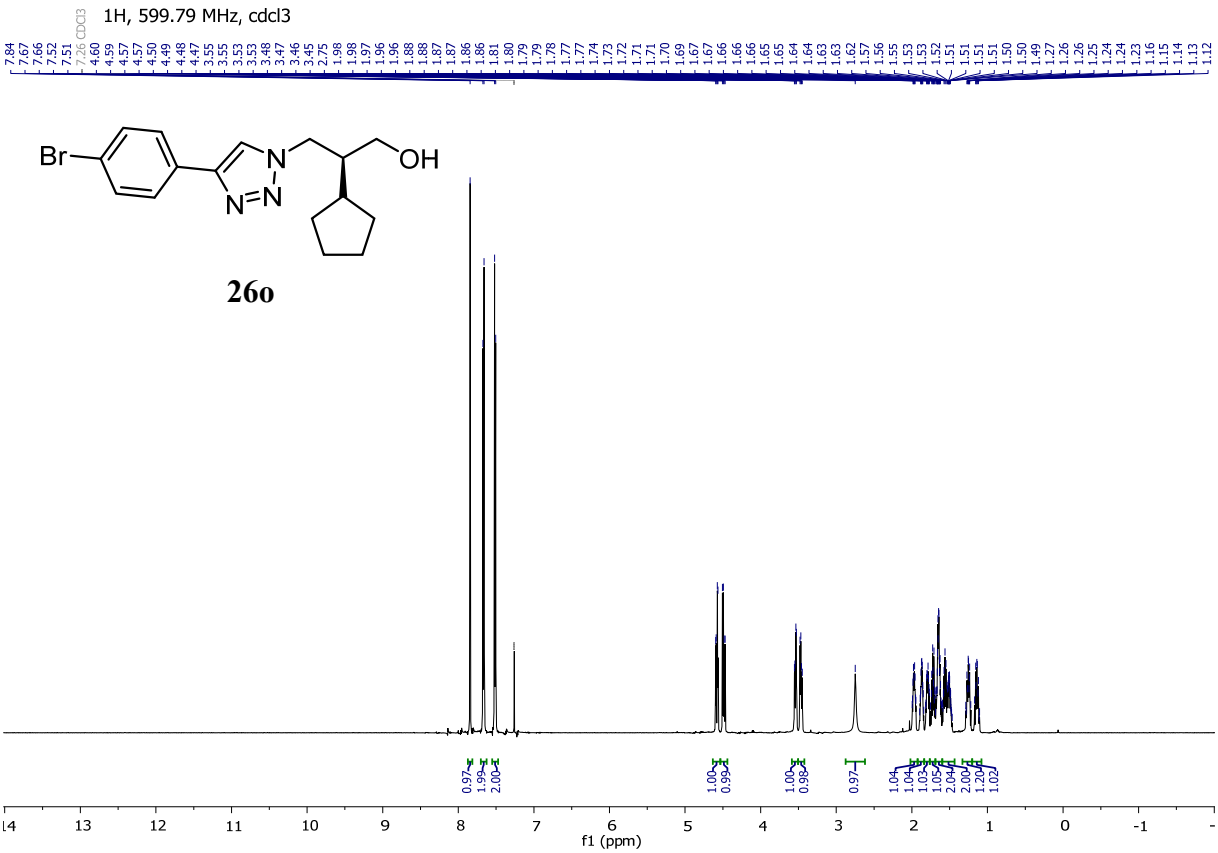


2o

13C, 125.78 MHz, cdcl3

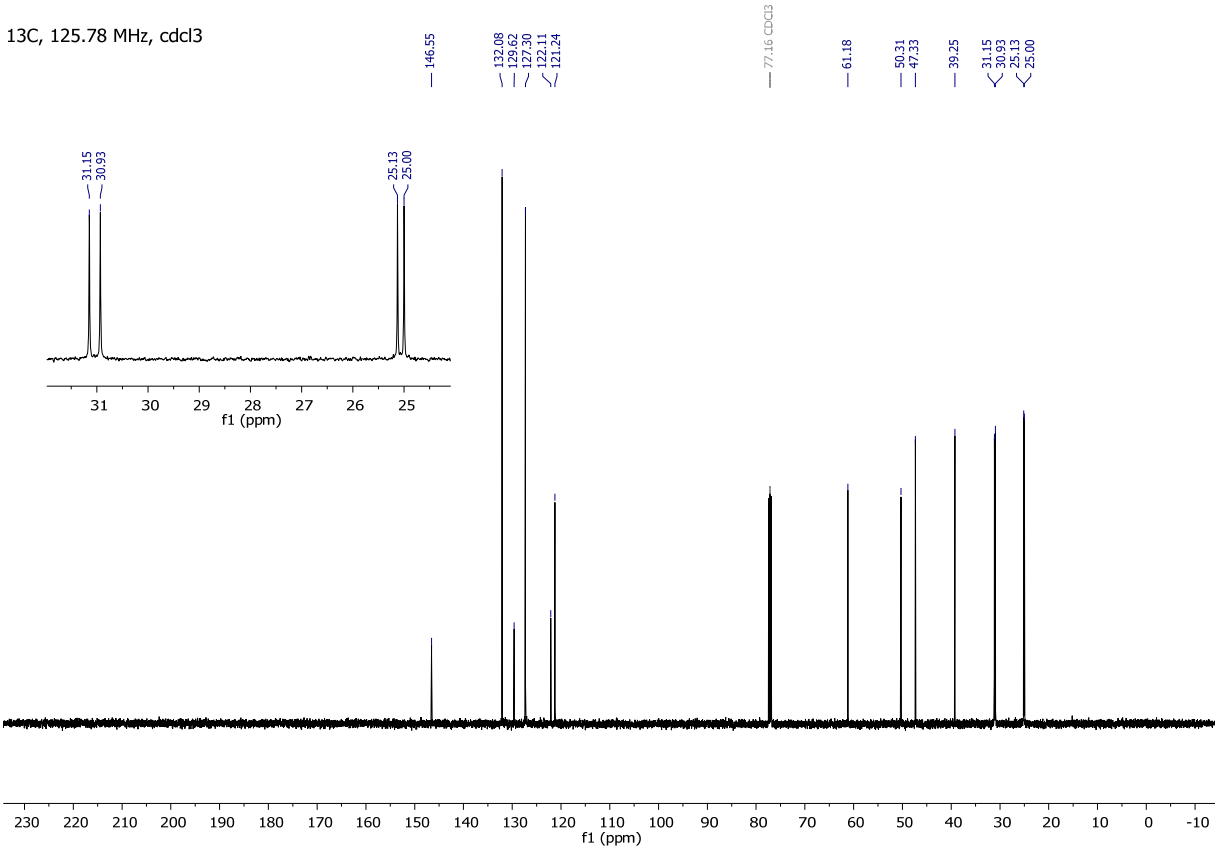


1H, 599.79 MHz, cdcl3

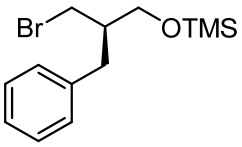


26o

13C, 125.78 MHz, cdcl3

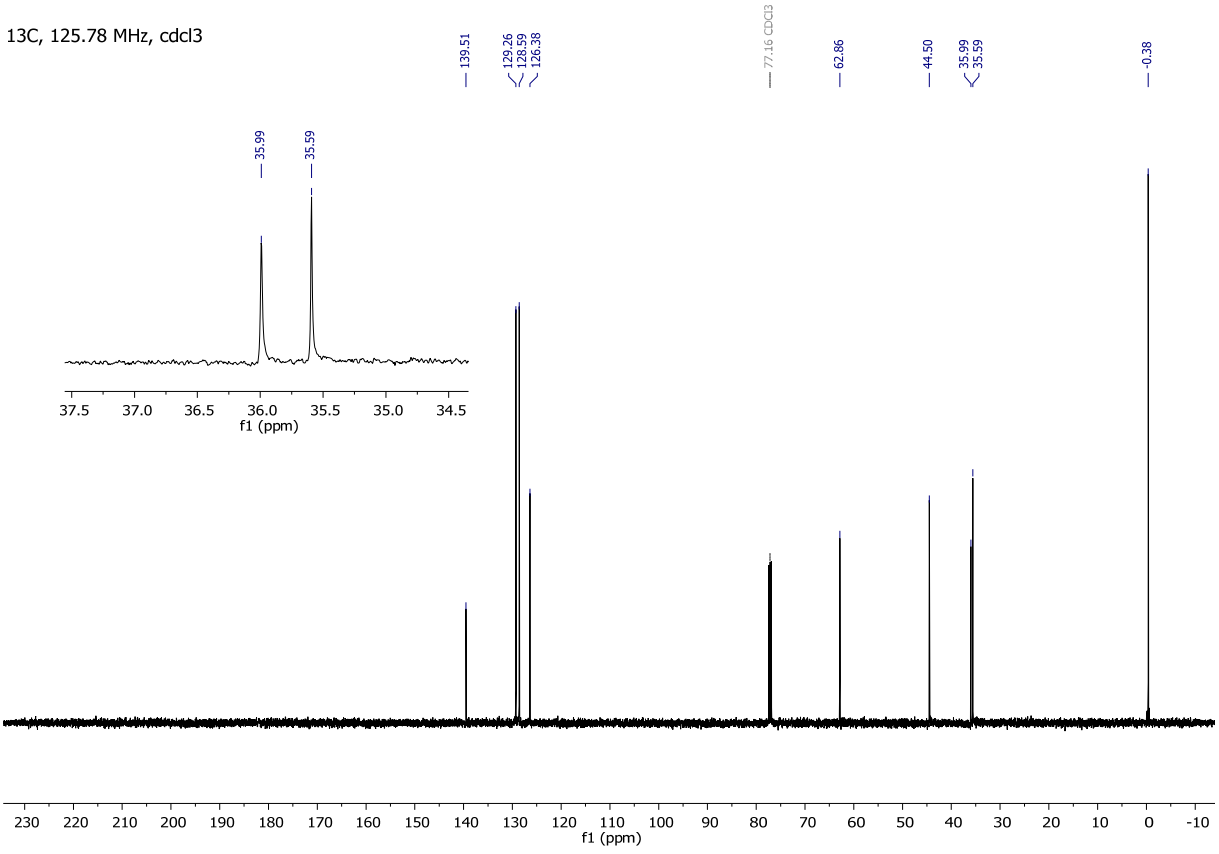


1H, 599.79 MHz, cdcl3

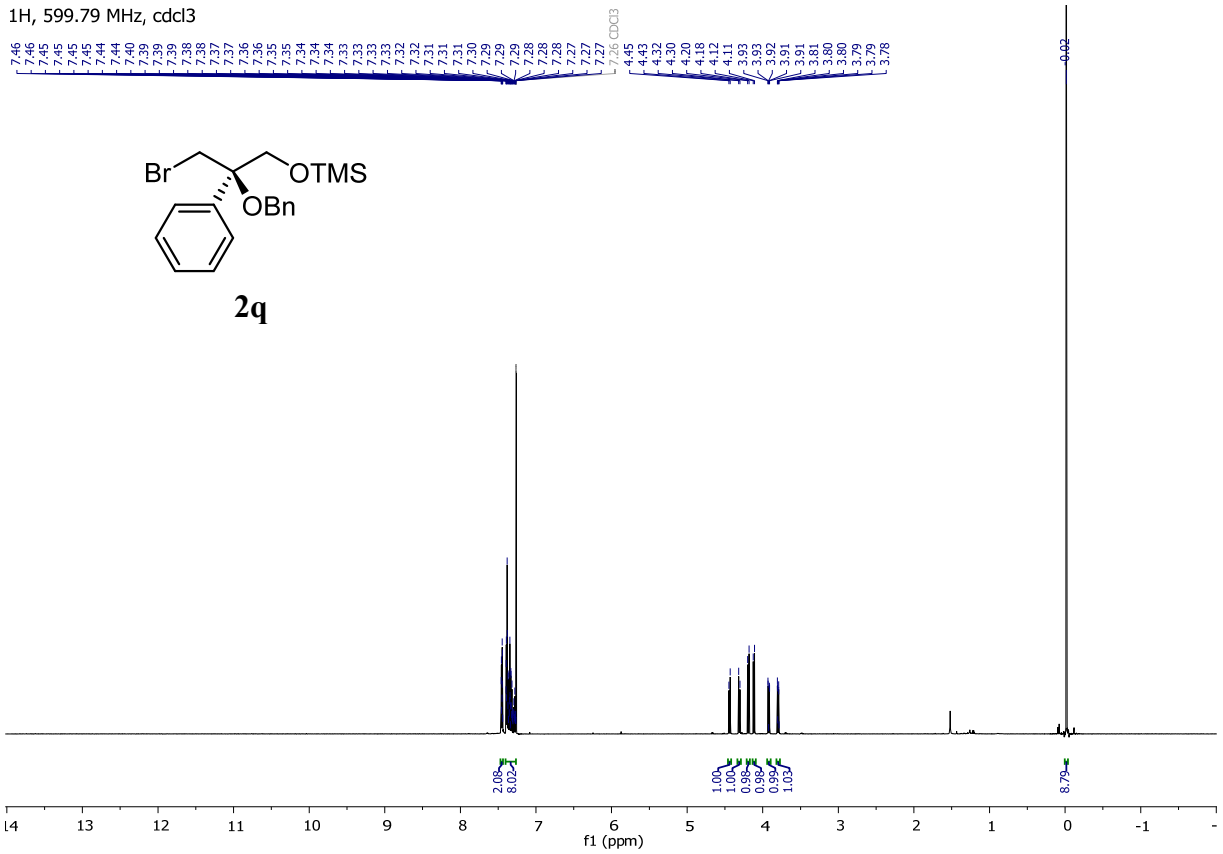


2p

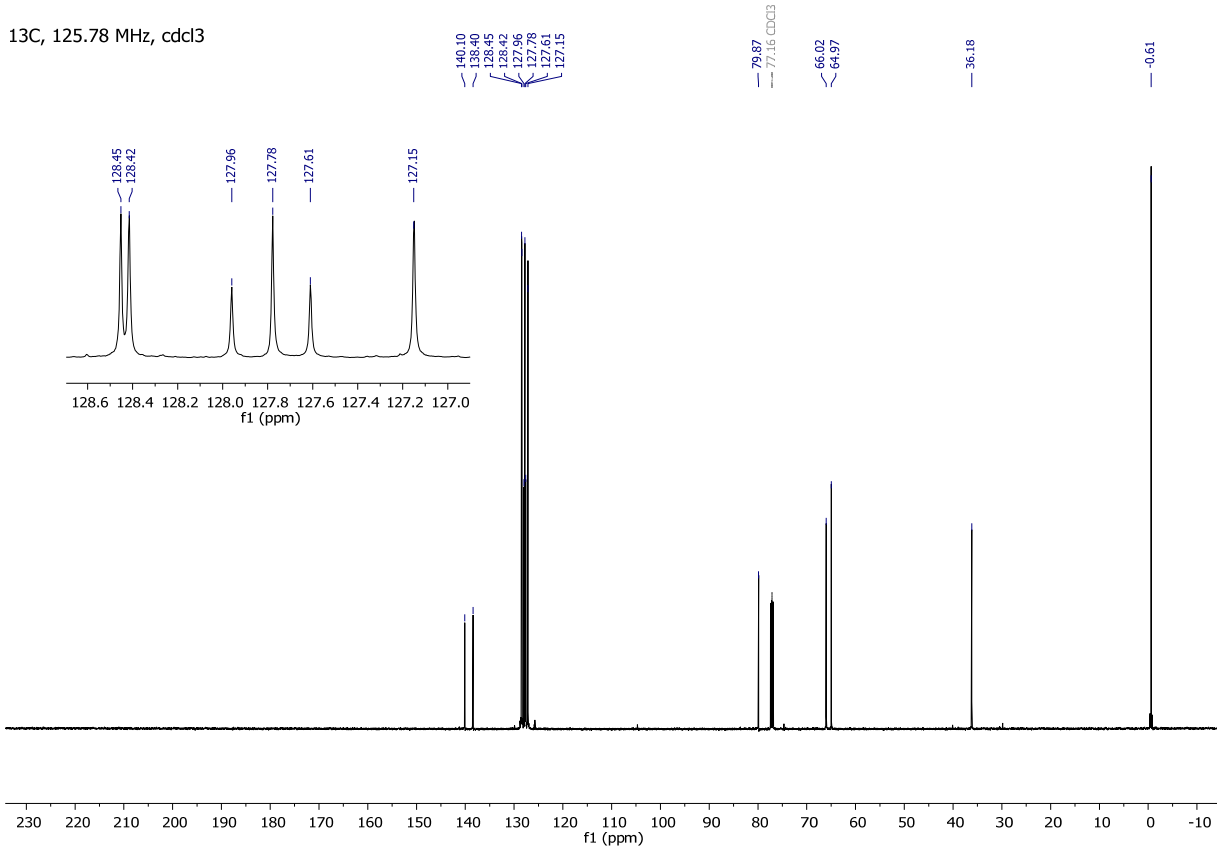
13C, 125.78 MHz, cdcl3



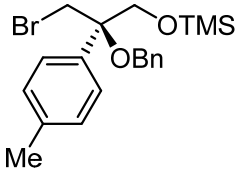
1H, 599.79 MHz, cdcl3



13C, 125.78 MHz, cdcl3

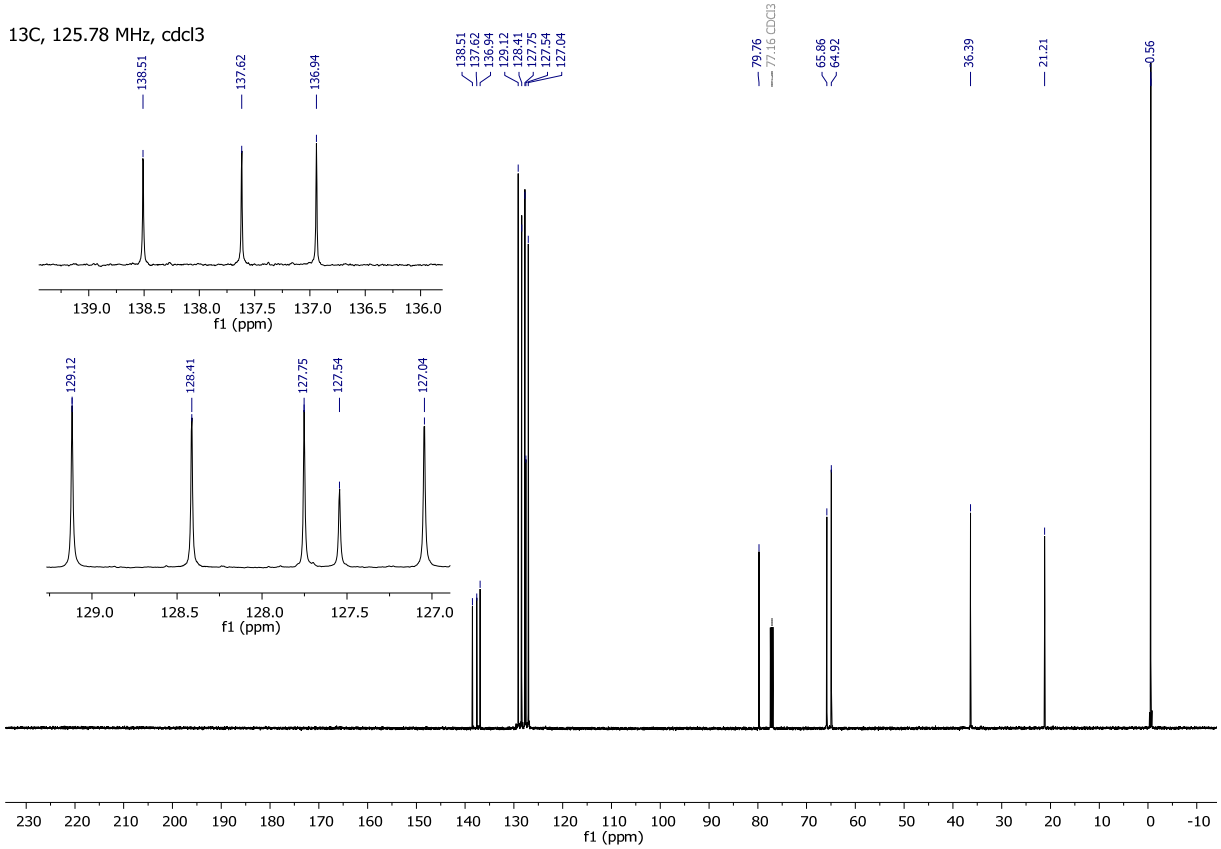


1H, 599.79 MHz, cdcl3

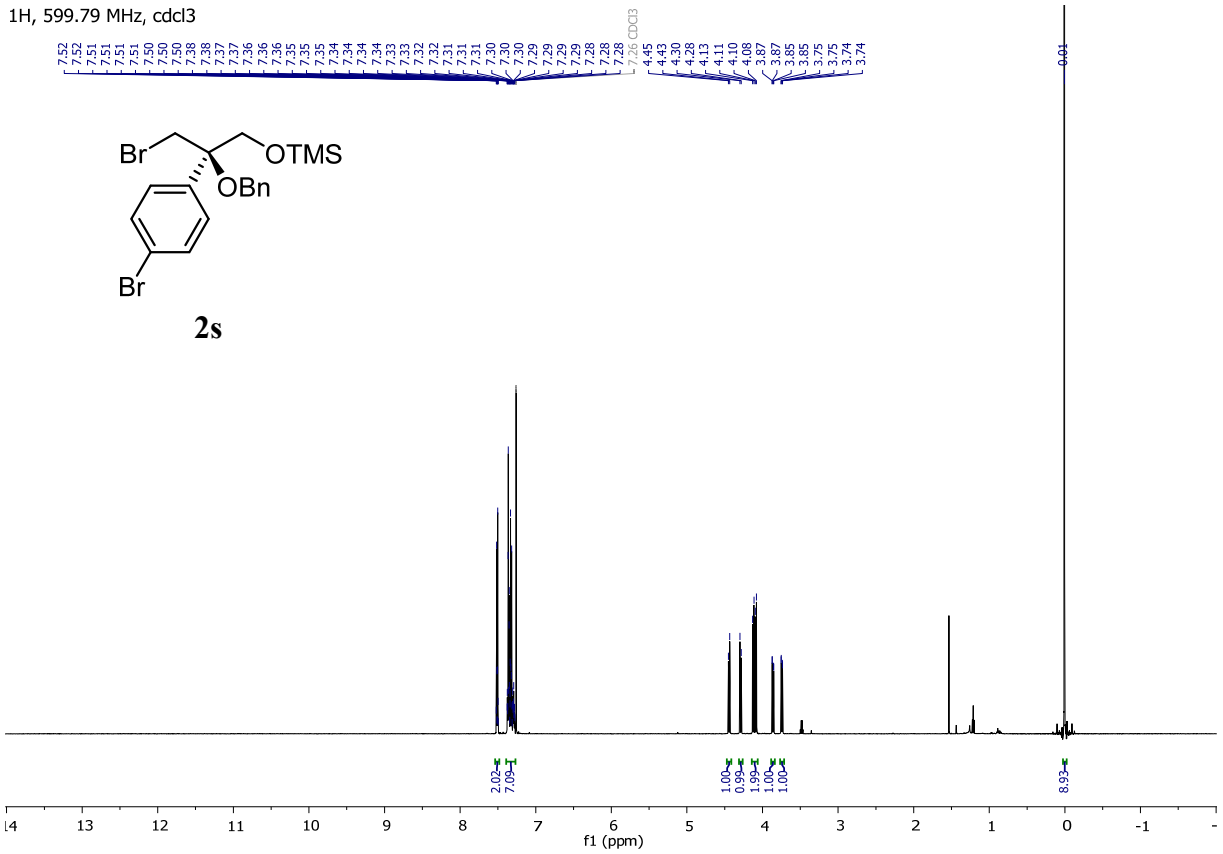


2r

13C, 125.78 MHz, cdcl3

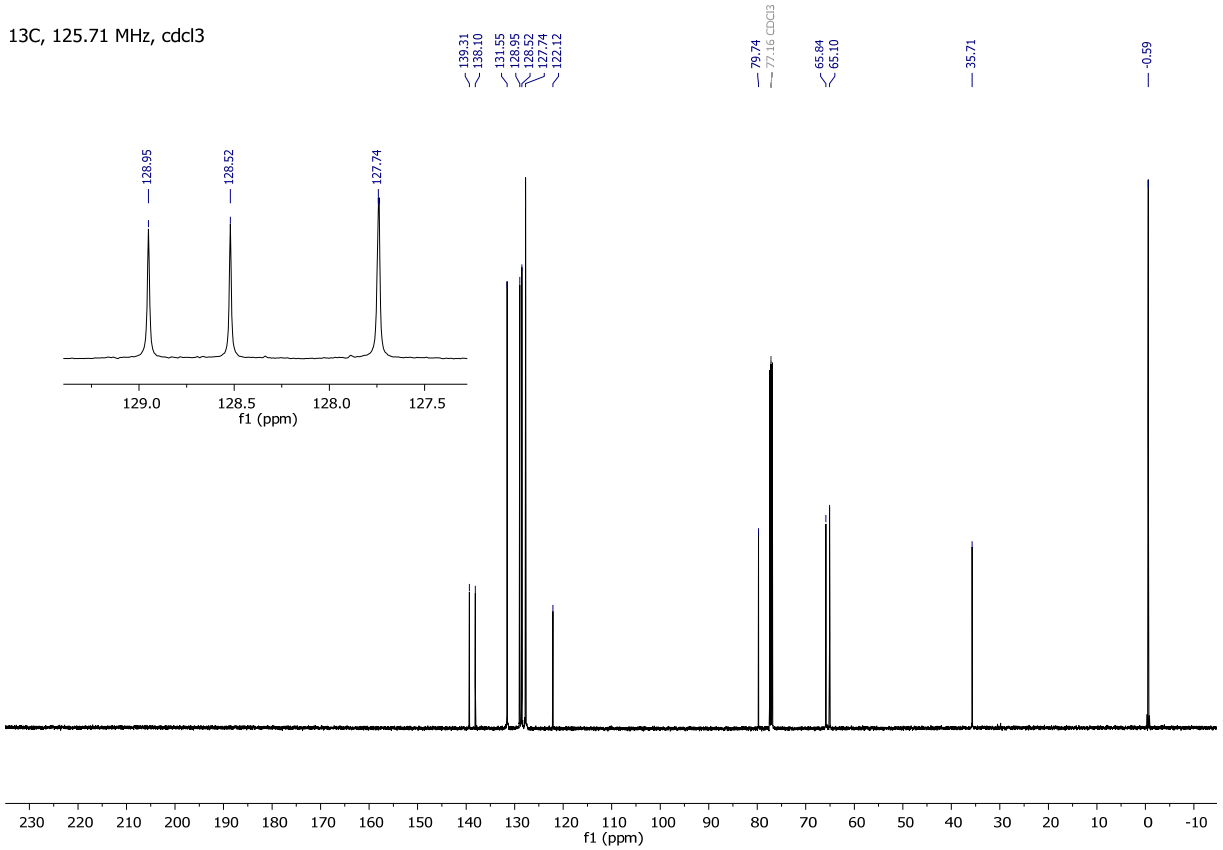


1H, 599.79 MHz, cdcl3

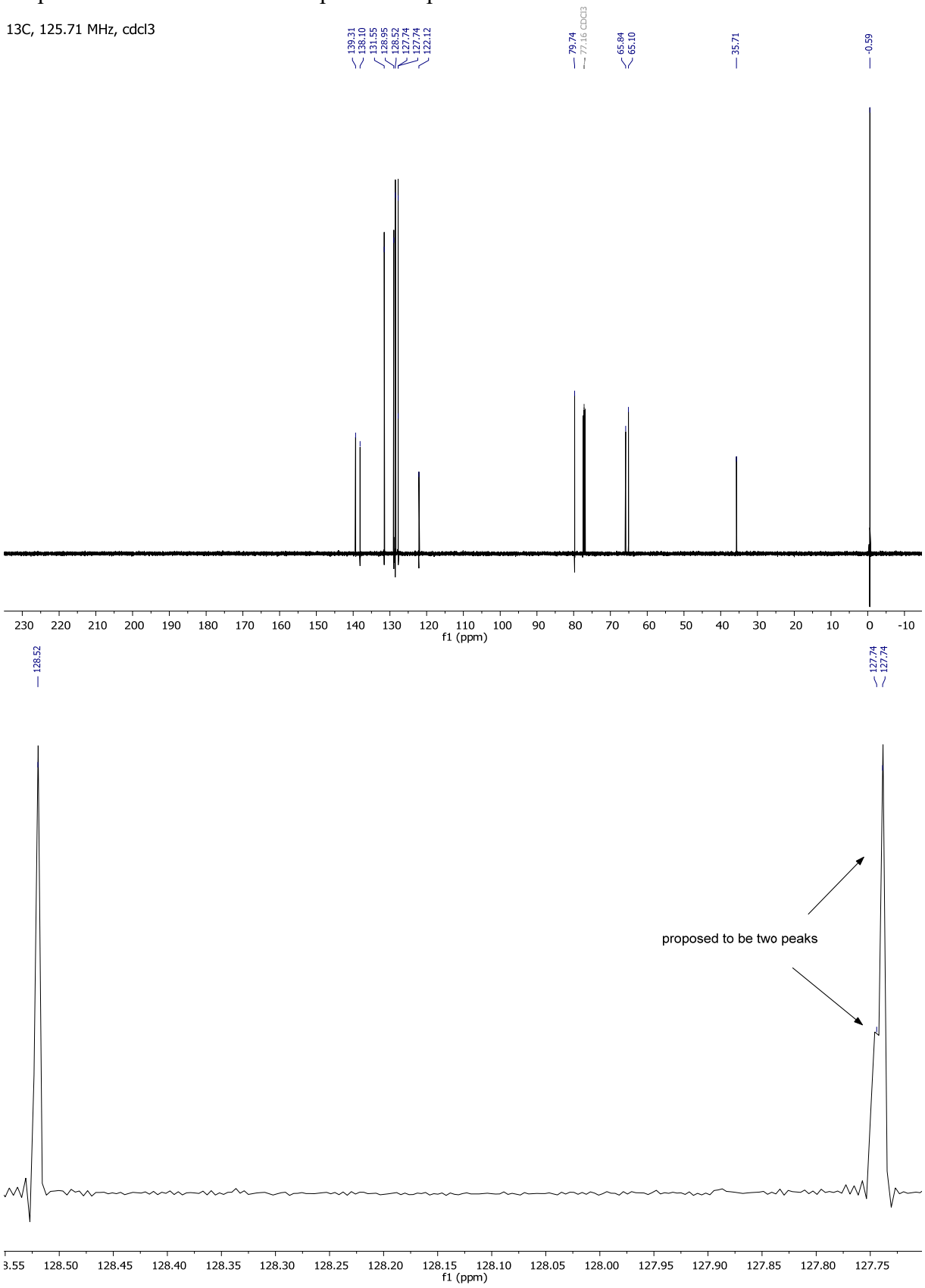


2s

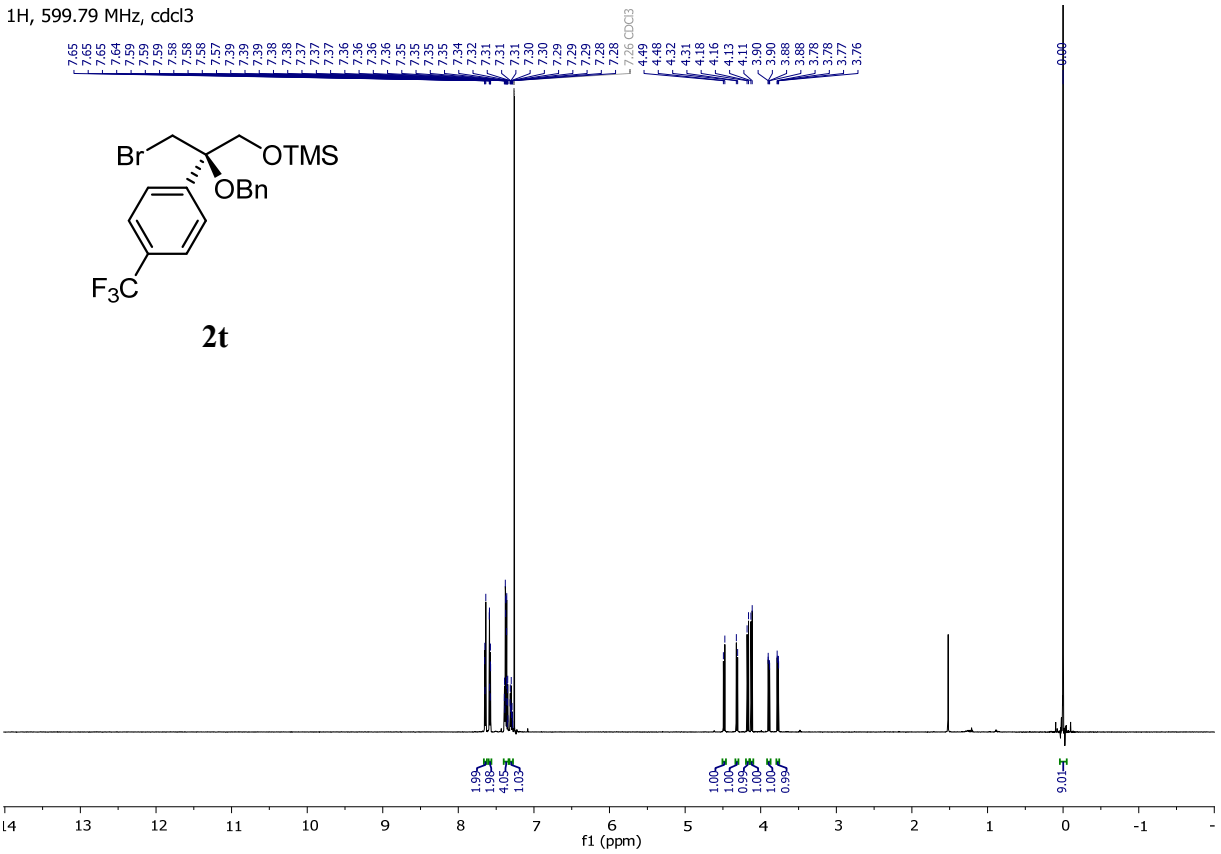
13C, 125.71 MHz, cdcl3



^{13}C spectrum with nonstandard exponential apodization

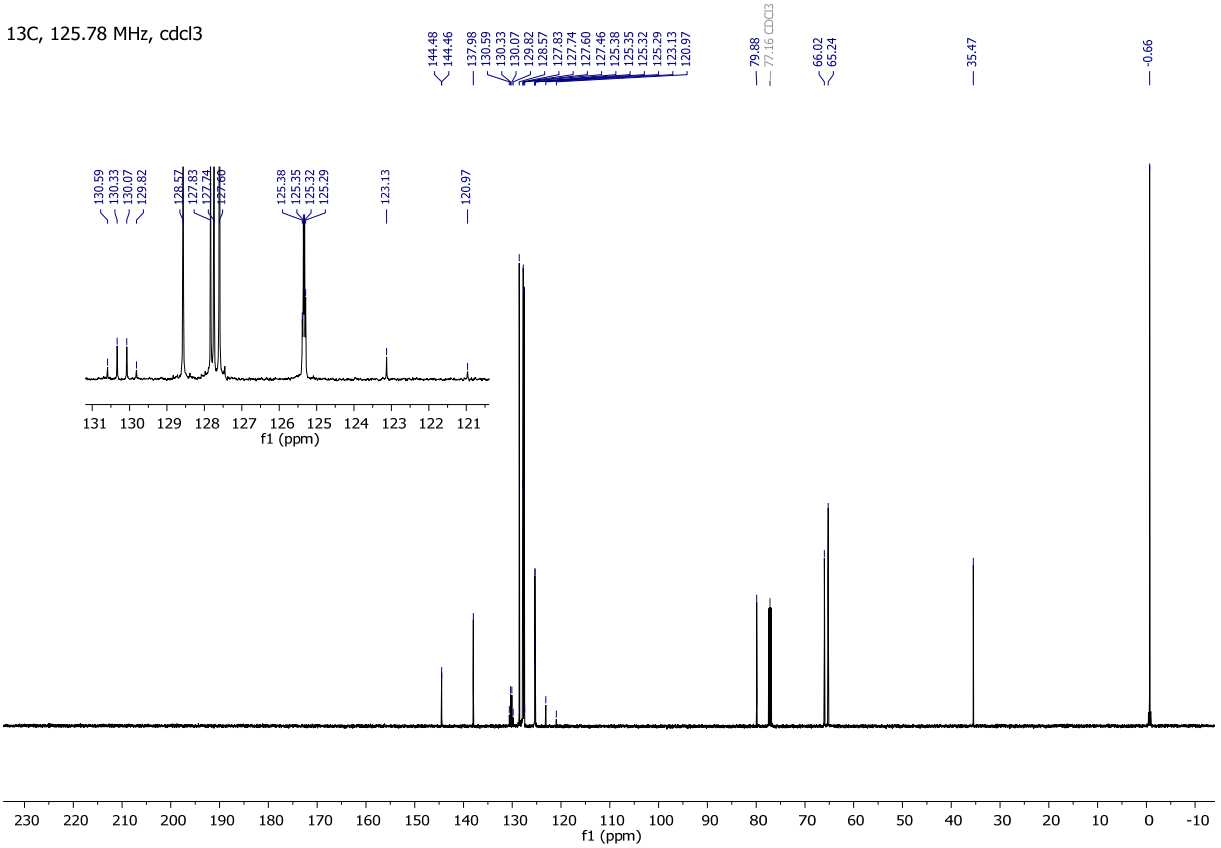


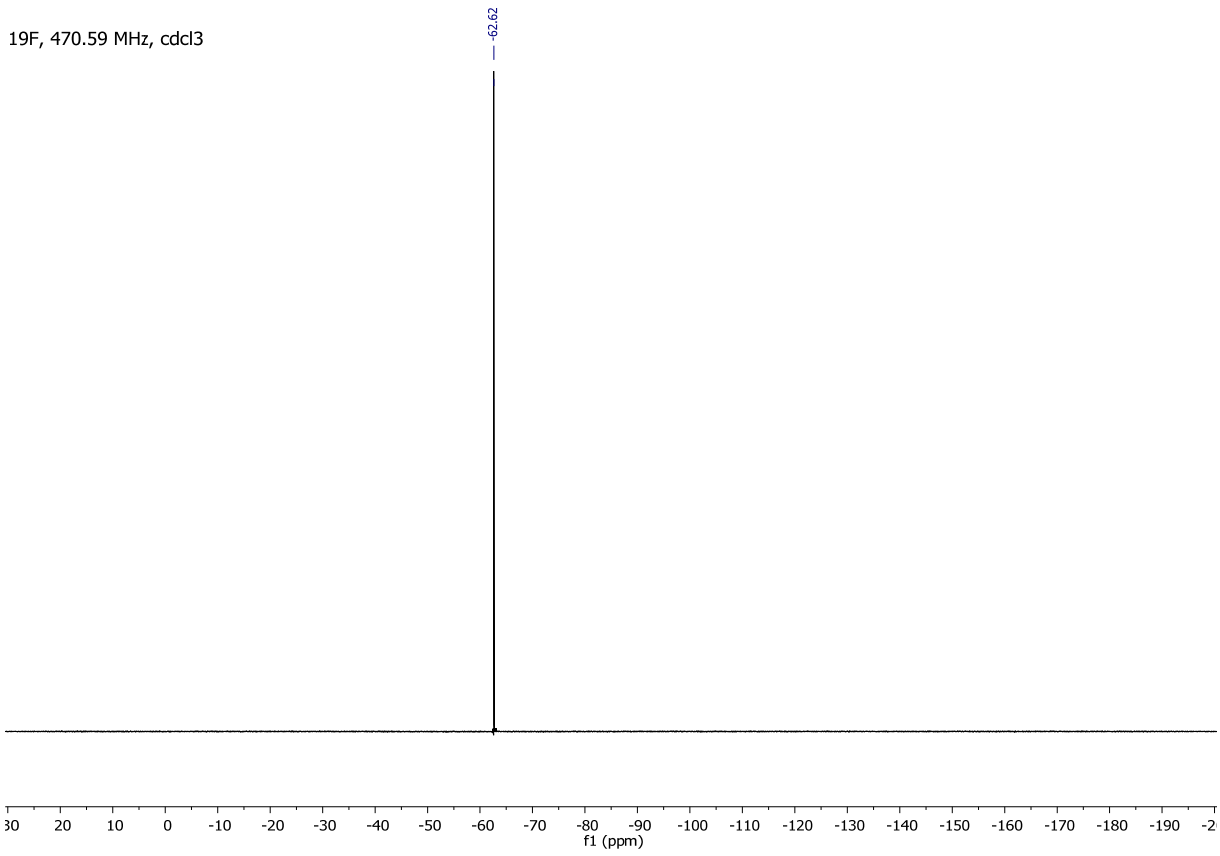
1H, 599.79 MHz, cdcl3

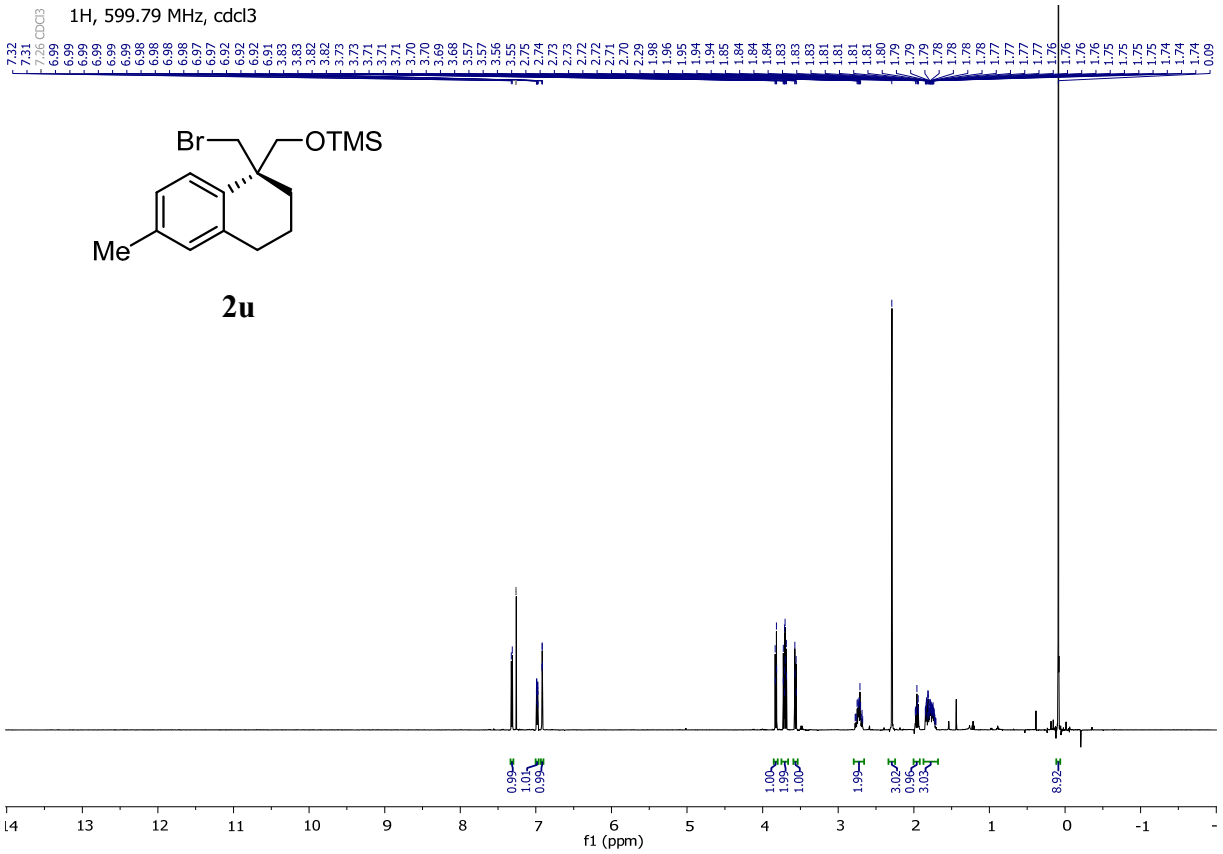


2t

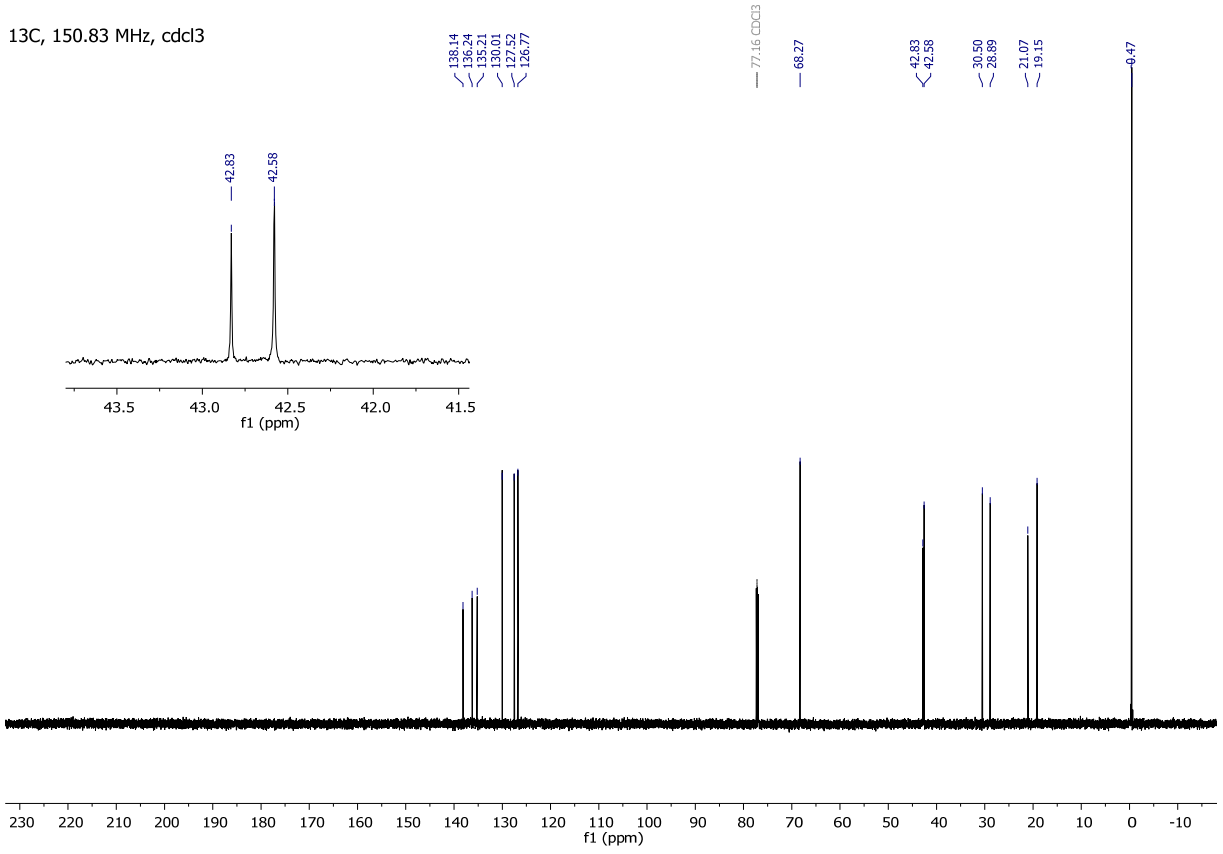
13C, 125.78 MHz, cdcl3



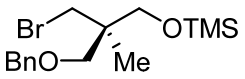

19F, 470.59 MHz, cdcl3
-62.62
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)



2u

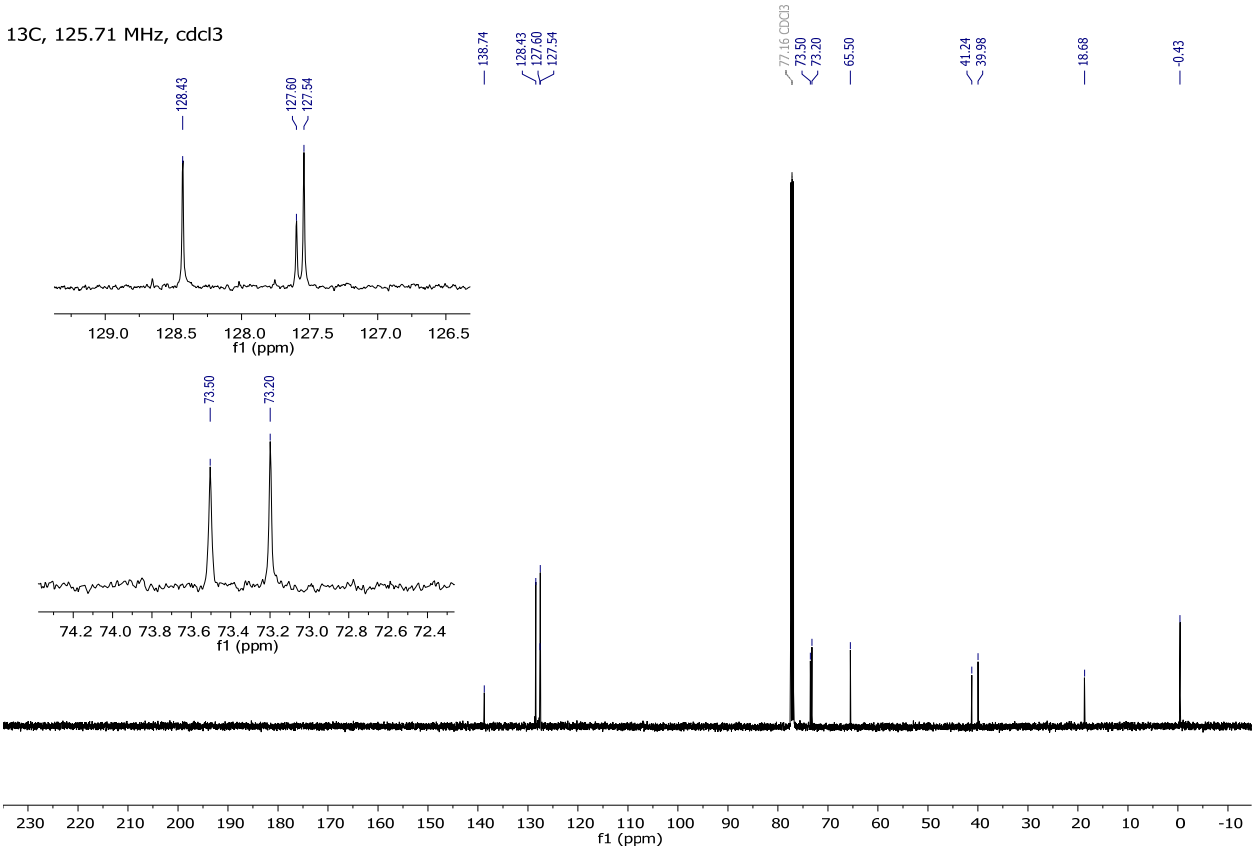


1H, 599.79 MHz, cdcl3

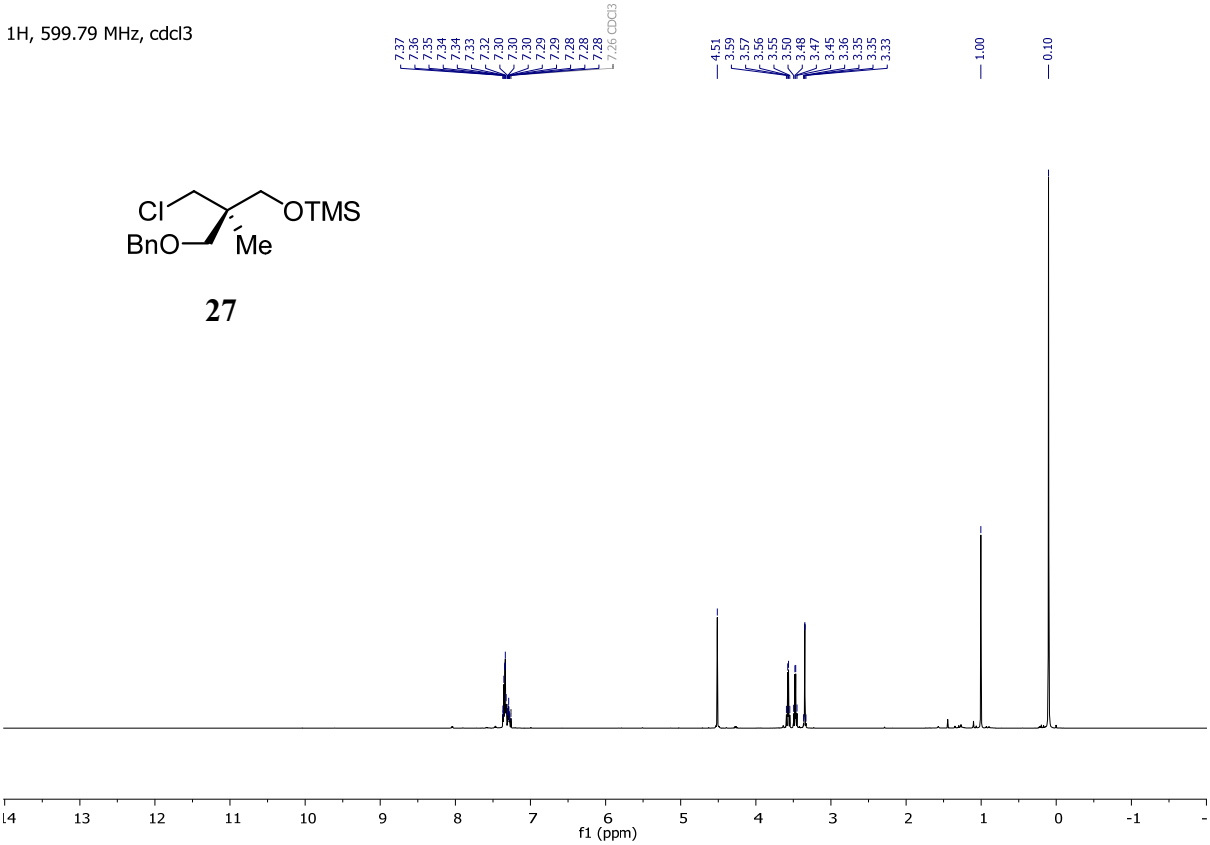


2v

13C, 125.71 MHz, cdcl3

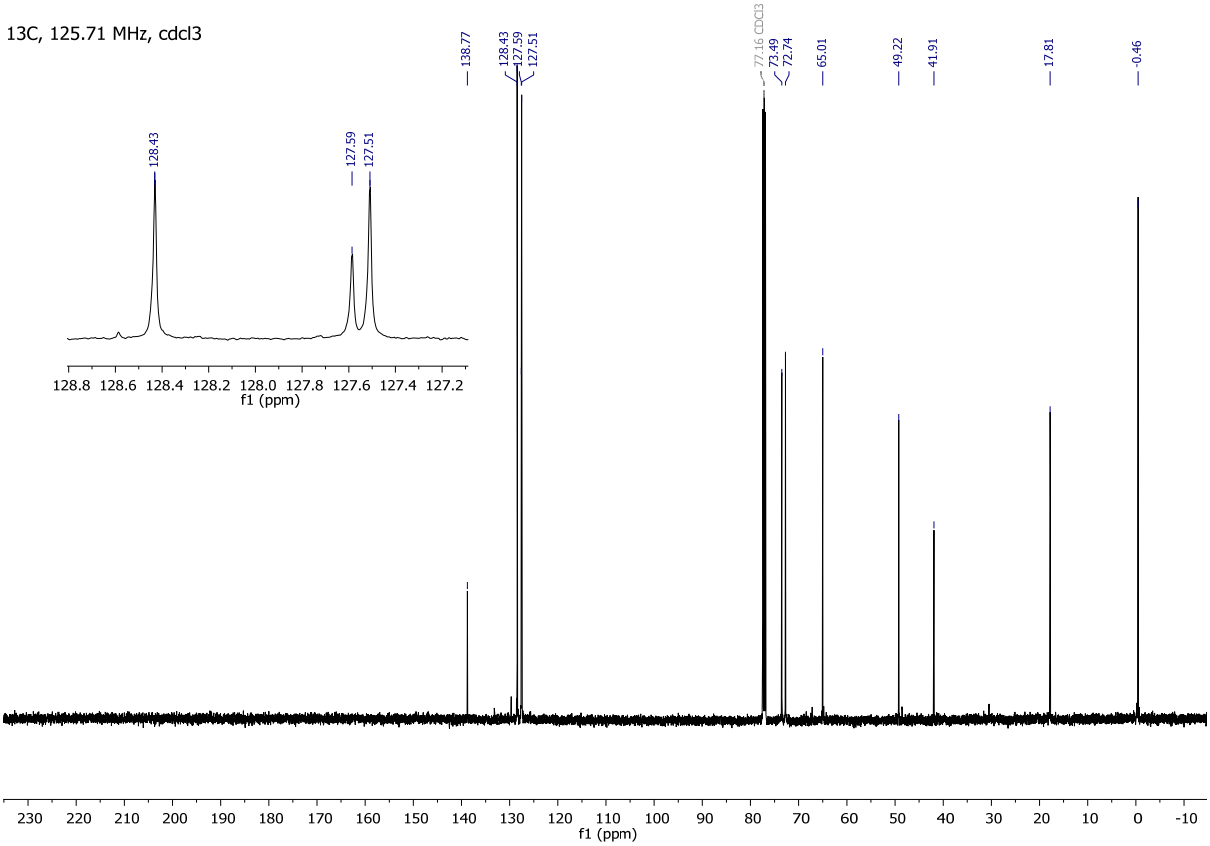


1H, 599.79 MHz, cdcl3

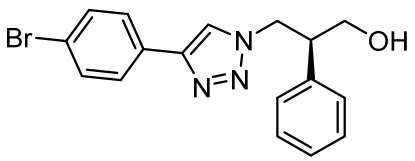


27

13C, 125.71 MHz, cdcl3

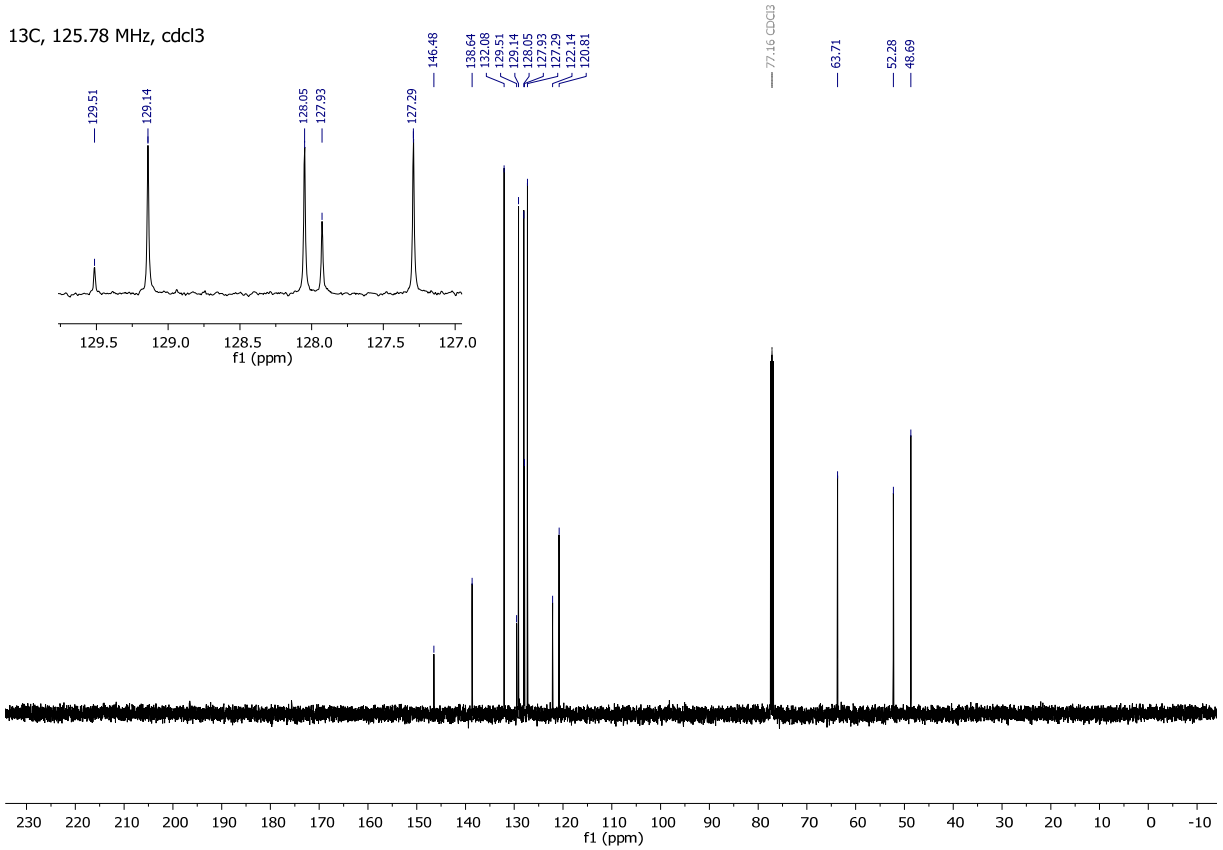


1H, 599.79 MHz, cdcl3

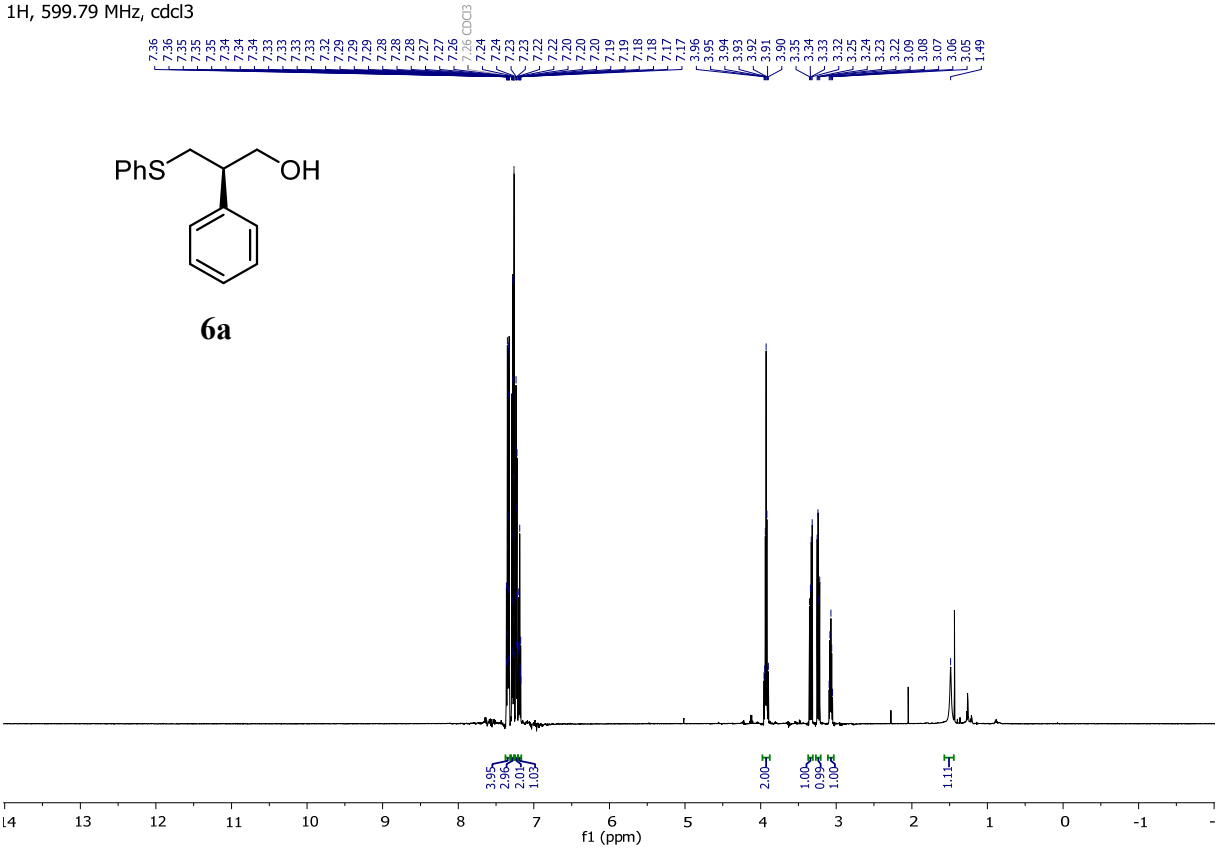


26a

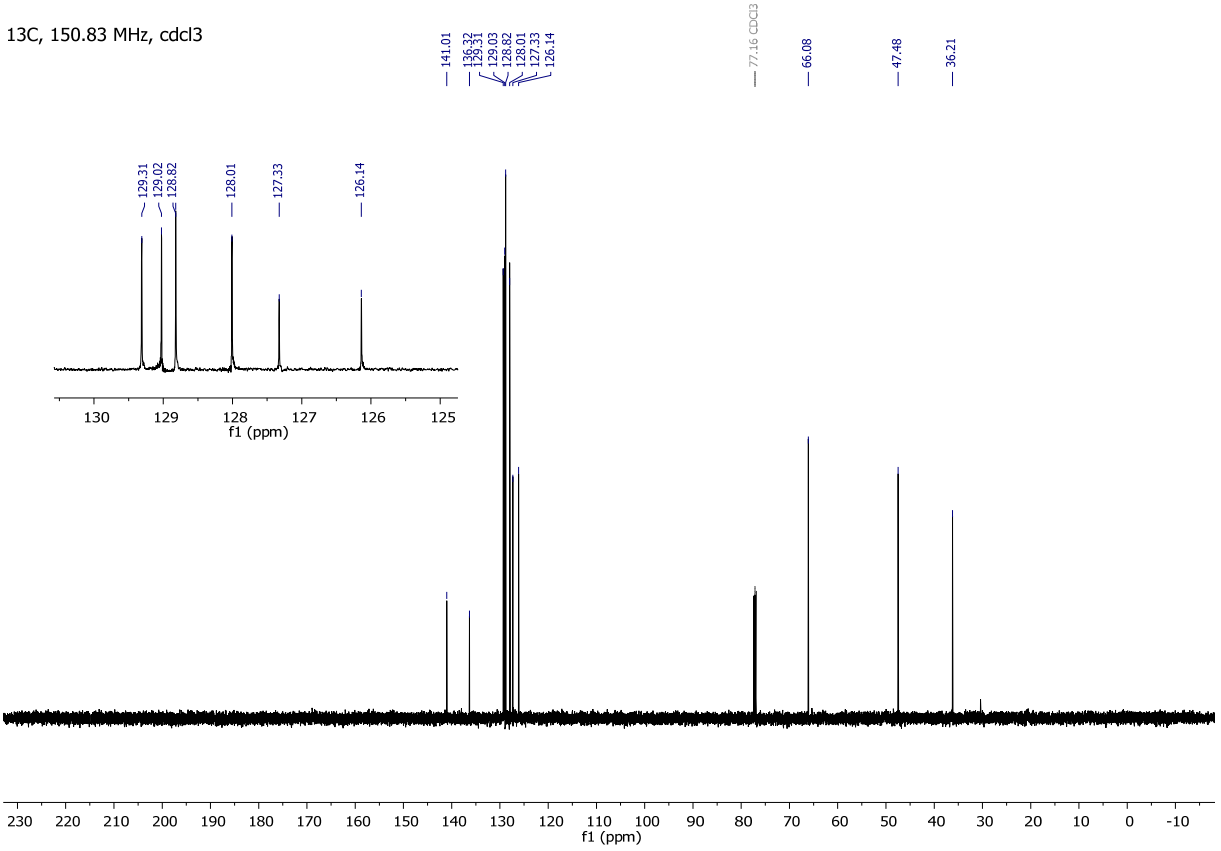
13C, 125.78 MHz, cdcl3



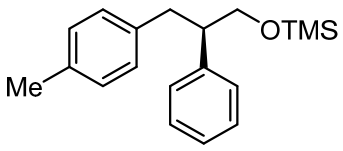
1H, 599.79 MHz, cdcl3



13C, 150.83 MHz, cdcl3

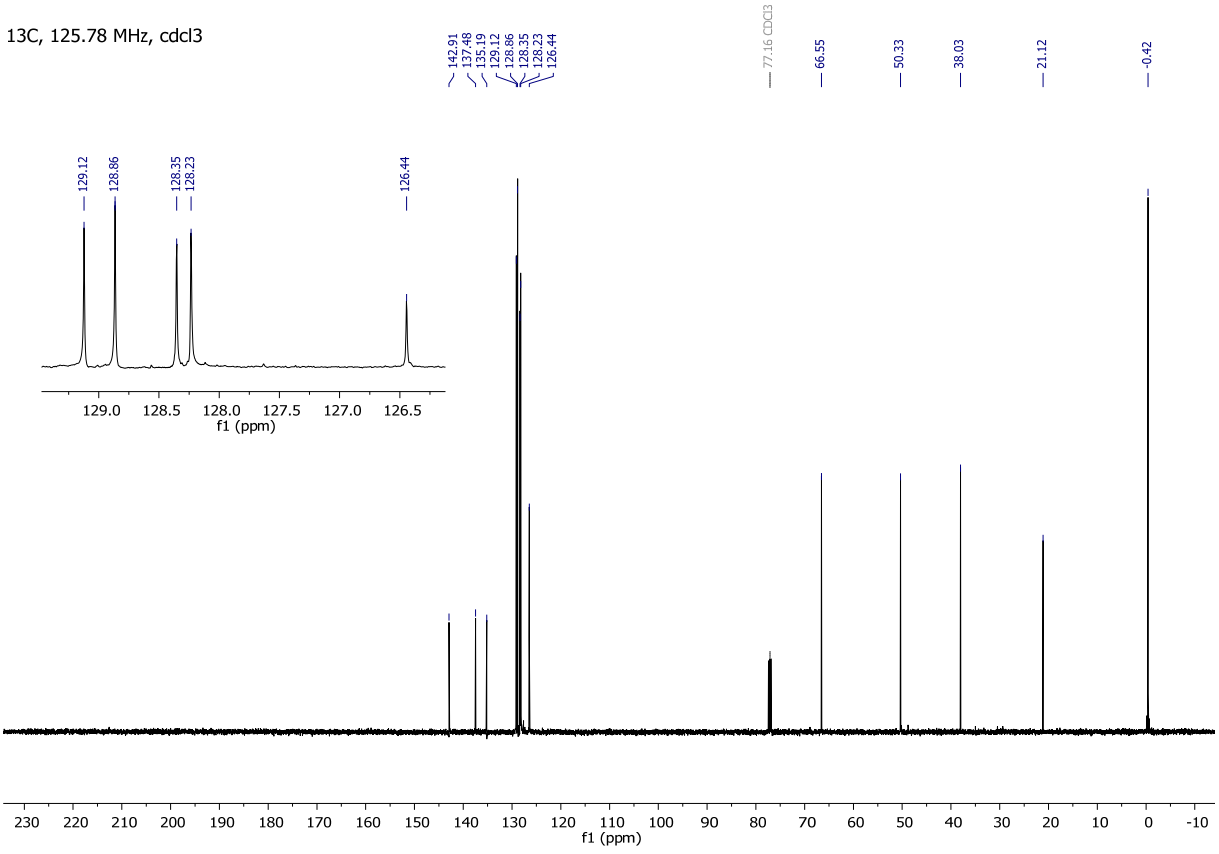


1H, 599.79 MHz, cdcl3

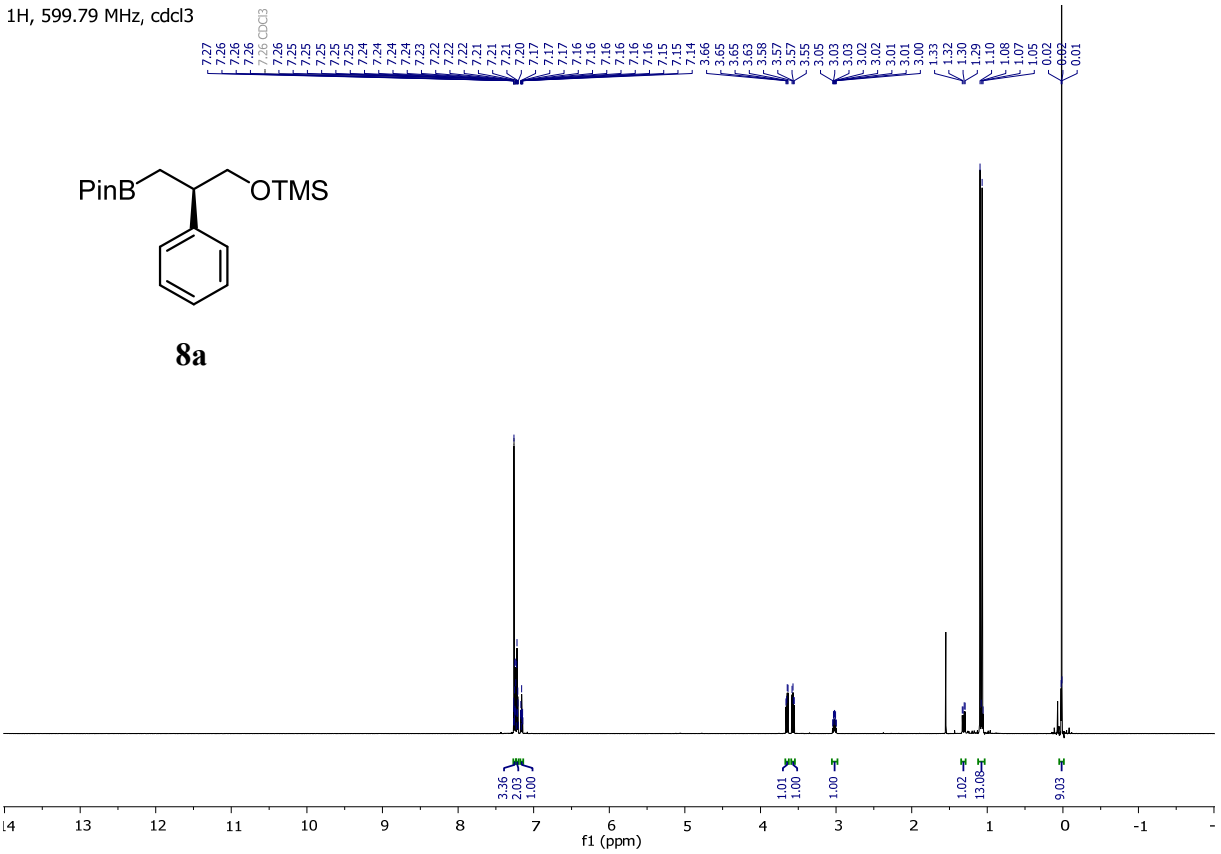


7a

13C, 125.78 MHz, cdcl3

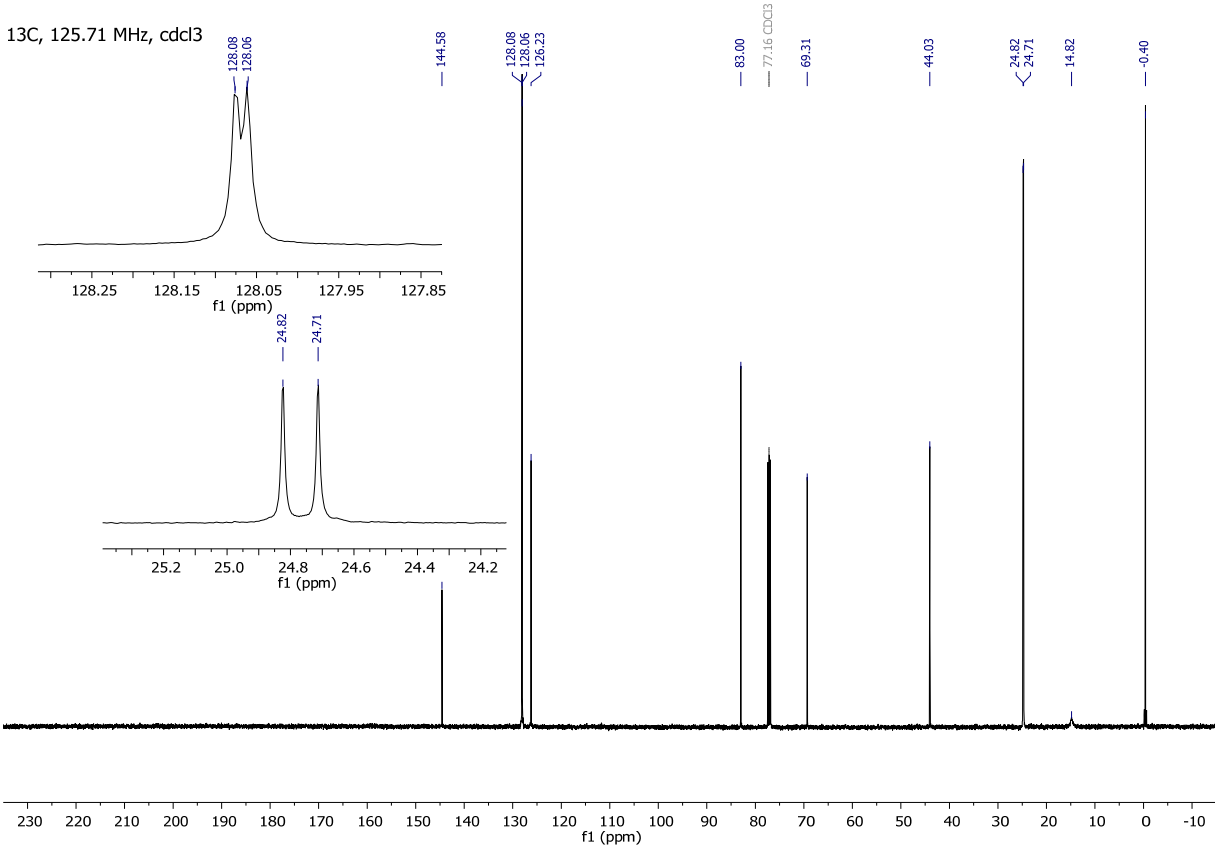


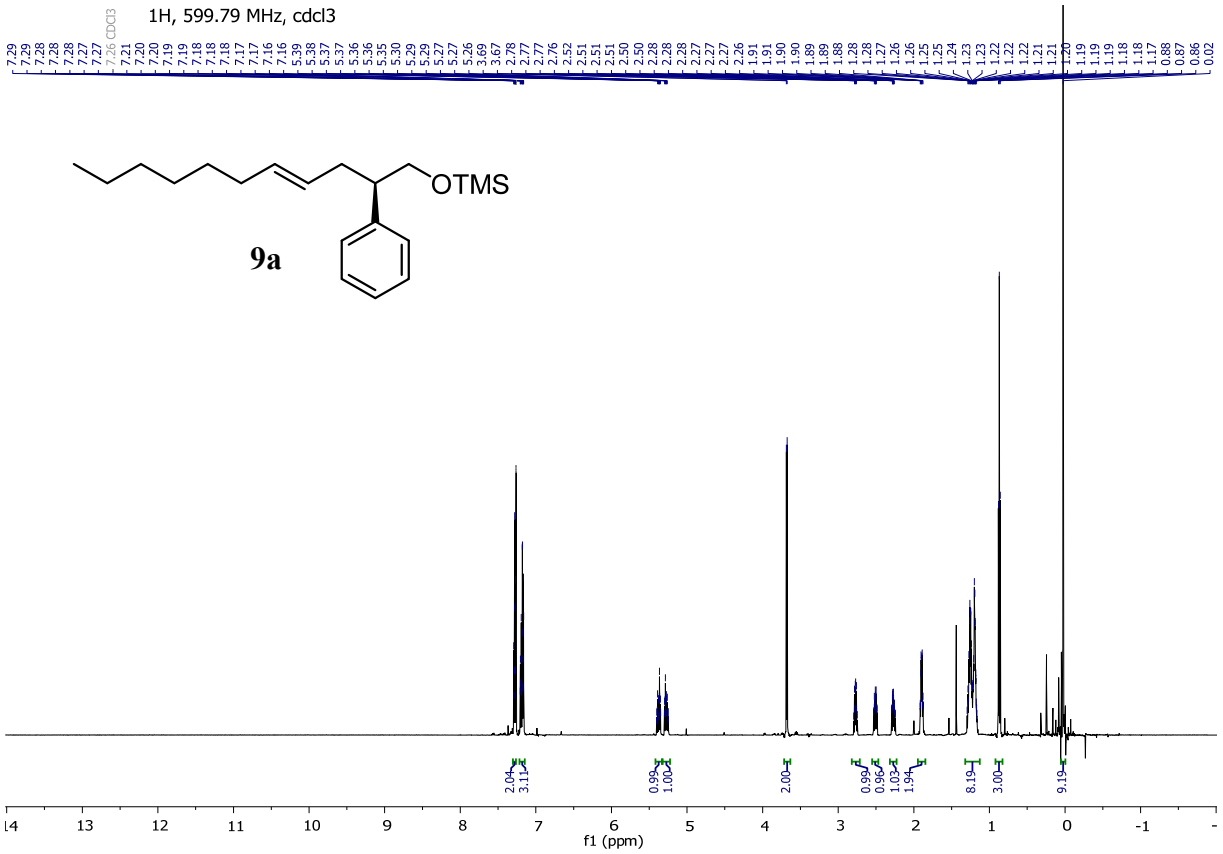
1H, 599.79 MHz, cdcl3

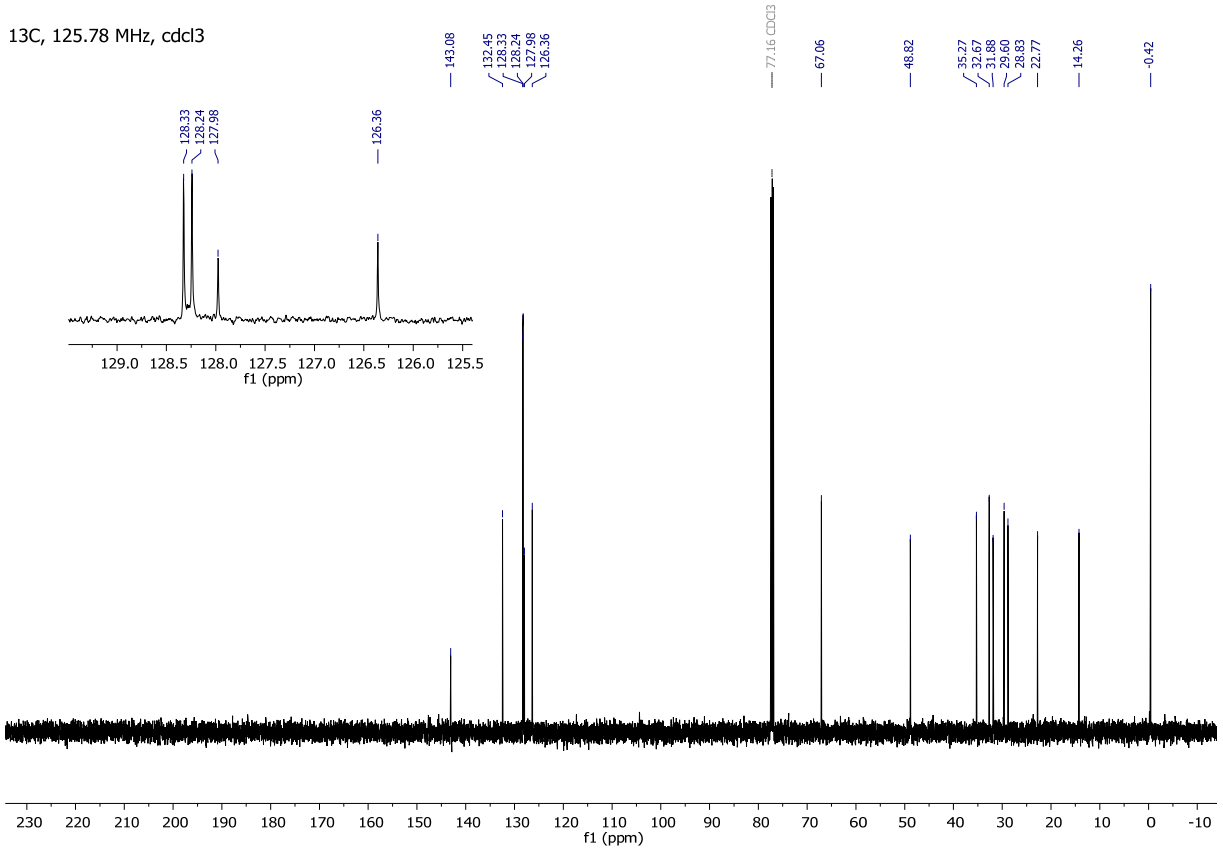


8a

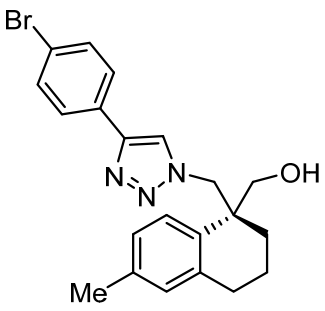
13C, 125.71 MHz, cdcl3




1H, 599.79 MHz, cdcl3
OTMS
9a
f1 (ppm)

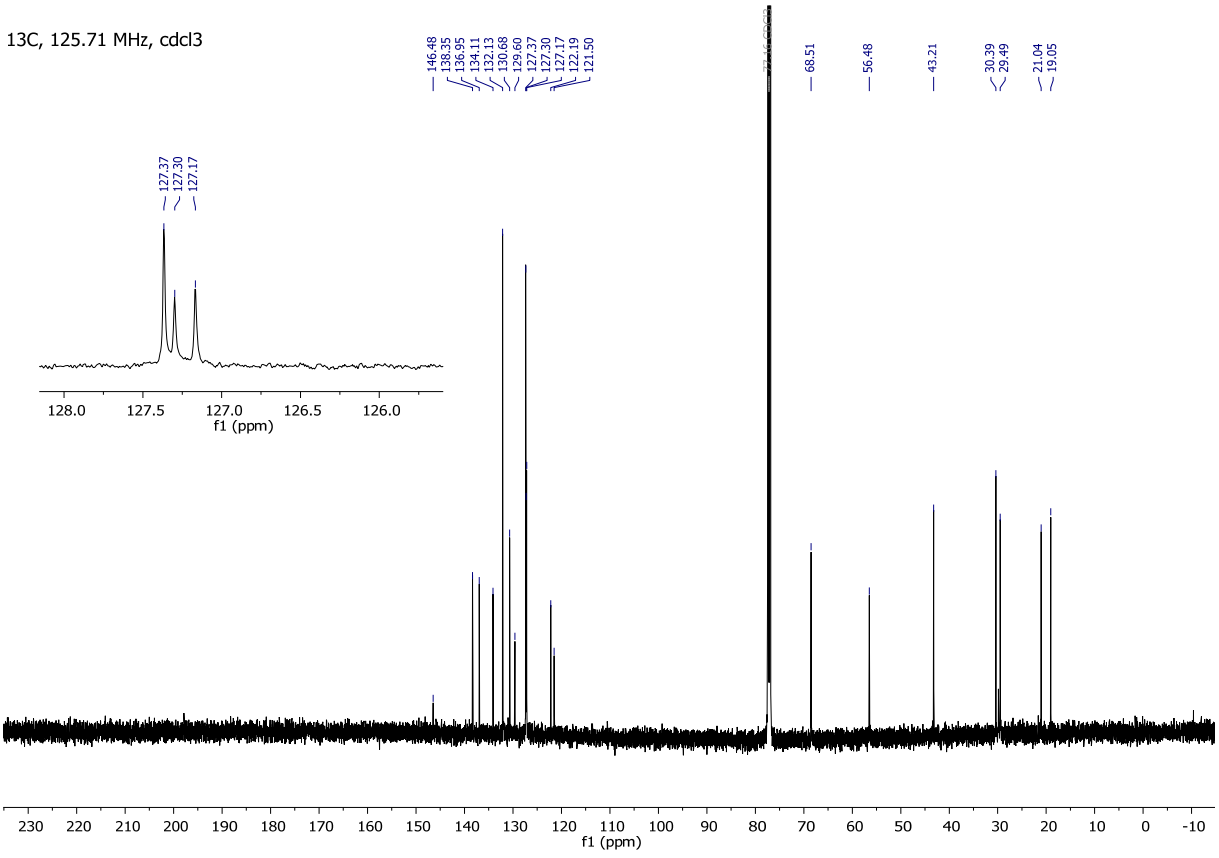

13C, 125.78 MHz, cdcl3
f1 (ppm)

1H, 500.18 MHz, cdcl3



26u

13C, 125.71 MHz, cdcl3



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