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SUPPLEMENTARY INFORMATION

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Electrolytic deuteration of unsaturated bonds without using D_2

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Supplementary Information

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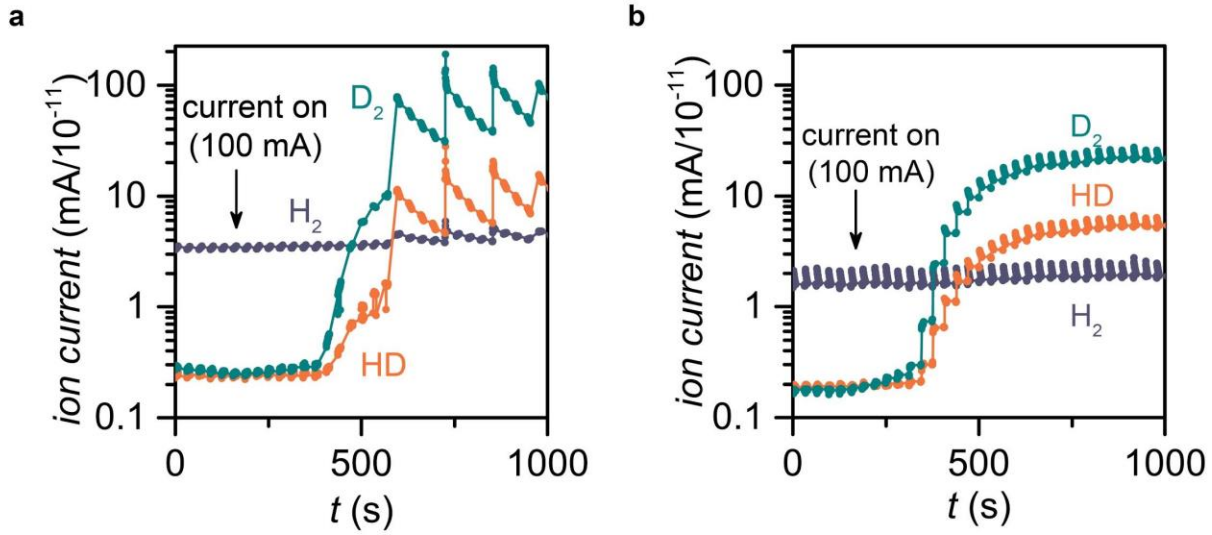
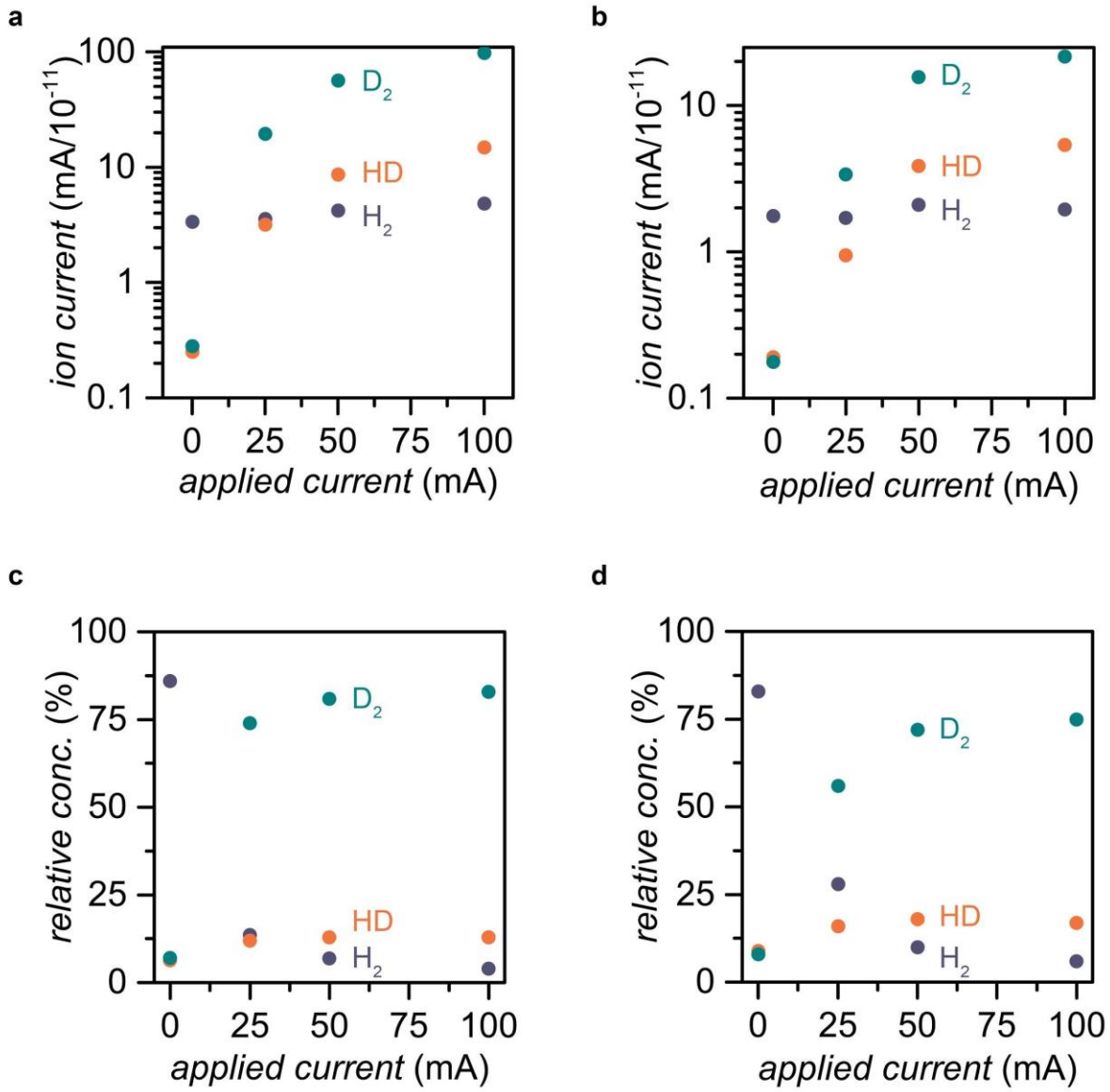
Deuterium permeation studies

A small signal at 2 m/z for H_2 gas (10^{-11} mA ion current) was detected in the absence of applied current which was attributed to trace amounts of H_2 in the air. An order of magnitude lower ion current (10^{-12} mA) was detected at 3 and 4 m/z (HD and D_2, respectively), a value right at the detection limit of the instrument. A constant current of 100 mA was applied at 200 s and a negligible change in ion current was detected for H_2 in both the chemical and electrochemical compartments. The ion current for HD increased by one order of magnitude and for D_2 by two orders of magnitude in both the electrochemical and chemical compartments (Supplementary Figure 1).

The evolution of HD is attributed to trace amounts of hydrogen in the D_2SO_4 and D_2O electrolyte. Hydrogen gas evolution was negligible because the amount of deuterium formed electrochemically is significantly greater than that of hydrogen making the statistical probability of combining two hydrogen atoms very low. The amount of D_2 evolved as well as the D_2/HD and D_2/H_2 production ratio increased with an applied current of 25, 50, and 100 mA in both electrochemical and chemical compartment (Supplementary Figure 2). The sawtooth pattern is attributed to D_2 gas bubbles releasing from the palladium membrane. Over time, D_2 bubbles accumulate on the surface of the palladium membrane due to the reactor design which occludes the surface of the palladium and decreases surface area. The release of these bubbles increases surface area and the potential returns to its original value.

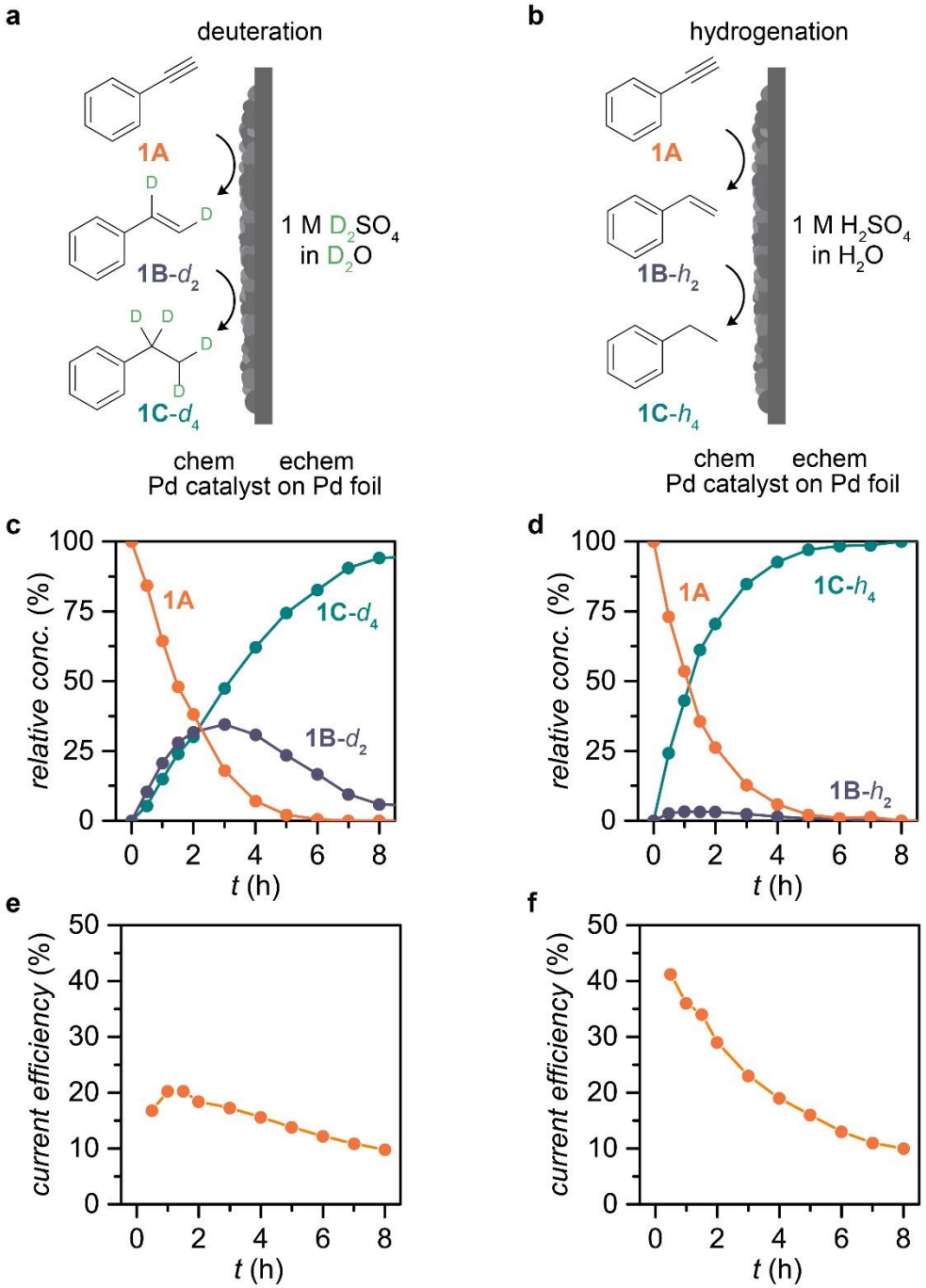


Supplementary Figure 1. **Deuterium (D_2), hydrogen deuteride (HD), and hydrogen (H_2) evolution on both sides of the palladium membrane.** atm MS measurements of D_2, HD, and H_2 evolution from **a**, the electrochemical compartment with 1.0 M D_2SO_4, and **b**, chemical compartment with dichloromethane at 100 mA as a function of time.

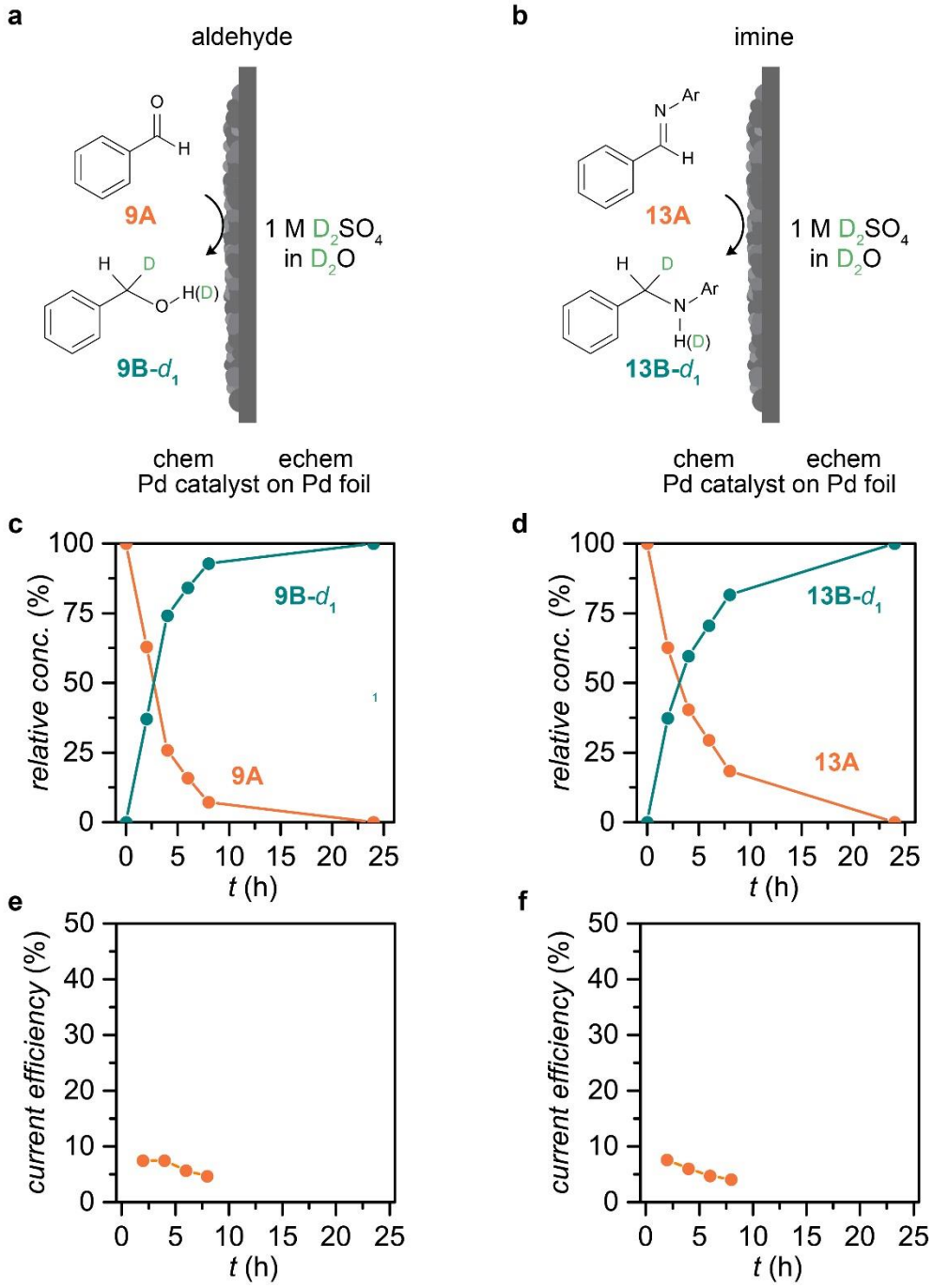


Supplementary Figure 2. **Relative and absolute deuterium (D_2), hydrogen deuteride (HD), and hydrogen (H_2) evolution on both sides of the palladium membrane at different flow currents.** atm MS measurements of D_2, HD, and H_2 evolution from **a**, the electrochemical compartment with 1 M D_2SO_4 and **b**, the chemical compartment with dichloromethane at 25, 50, and 100 mA. Relative concentrations of D_2, HD and H_2 in **c**, the electrochemical compartment and **d**, the chemical compartment.

Kinetic studies



Supplementary Figure 3. **Product distribution for palladium membrane deuteration and hydrogenation of phenylacetylene.** Reaction cell setup of **a**, deuteration and **b**, hydrogenation reactions of phenylacetylene (**1A**) at 100 mA applied current. Reagent (**1A**) consumption and product (**1B** and **1C**) formation during the deuteration and hydrogenation reactions for **c**, deuteration and **d**, hydrogenation. Current efficiency determined for **e**, deuteration and **f**, hydrogenation.



Supplementary Figure 4. **Product distribution for palladium membrane deuteration of benzaldehyde and *N*-benzylideneaniline.** Reaction cell setup of deuteration of **a**, benzaldehyde (**9A**) and **b**, *N*-benzylideneaniline (**13A**) at 100 mA applied current. Reactant consumption and product formation during the deuteration reaction for **c**, benzaldehyde (**9A**) and **d**, *N*-benzylideneaniline (**13A**). Current efficiency determined for deuteration of **e**, benzaldehyde (**9A**) and **f**, *N*-benzylideneaniline (**13A**).

General procedure for palladium membrane deuteration of alkynes

All reactions were performed using either dichloromethane (DCM, **1**, **2**, **4**–**8**) or methanol (MeOH, **3**) from a solvent purification system prior to use. All reactions were carried out in air at room temperature. A chemical compartment with a magnetic stir bar was oven-dried at 110 ^{o}C overnight prior to use and was charged with substrate (0.75 mmol) and solvent (30 mL). 1 M D_2SO_4 in D_2O electrolyte solution (35 mL) was added to the electrochemical compartment and a constant current of 100 mA was applied for 24 h. Both reaction mixture and electrolyte solution were stirred at a constant rate throughout the experiment. Reaction aliquots were sampled every 1 h to monitor the reaction profile by GC-MS. After 24 h, the reaction mixture was concentrated in vacuo and the desired product was isolated.

Ethylbenzene-*d*$_4$ (1C). According to the general procedure, phenylacetylene (76.8 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as light yellow liquid (81.2 mg, 95% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.26-7.31 (m, 2H), 7.37-7.41 (m, 3H), 1.21 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 2.64 (s, 2D), 1.23 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 144.3, 128.4, 127.9, 125.7, 28.3 (m), 14.9 (m). The current efficiency was determined by comparing the number of electrons used to generate alkane to the total number of electrons consumed to reduce deuterons over a given period of time.

Propylbenzene-*d*$_4$ (2C). According to the general procedure, 3-phenyl-1-propyne (87.2 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a colorless liquid (85.5 mg, 92% yield). The starting material contains 250 ppm BHT (butylated hydroxytoluene) inhibitor. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.35 (m, 2H), 7.22–7.25 (m, 3H), 2.63 (m, 2H), 1.00 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 1.68 (s, 2D), 0.97 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 142.7, 128.5, 128.2, 125.6, 37.8, 23.7 (m), 13.1 (m).

3-ethylpyridine-d_4 (3C). According to the general procedure, 3-ethynylpyridine (77.3 mg, 0.75 mmol) was dissolved in MeOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a yellow liquid (74.9 mg, 90% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 8.36 (s, 1H), 8.31 (s, 1H,), 7.67 (d, *J* = 7 Hz, 1H), 7.31 (br t, *J* = 7 Hz, 1H), 1.17 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 2.53 (s, 2D), 1.12 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, CD_3OD): 149.4, 147.2, 141.6, 137.7, 125.2, 26.0 (m), 15.2 (m).

Bibenzyl-d_4 (4C). According to the general procedure, diphenylacetylene (133.6 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a white solid (136.7 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.34 (m, 4H), 7.22–7.26 (m, 6H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 2.92 (s, 2D), 1.12 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 141.7, 128.5, 128.4, 125.9, 37.2 (m).

Octane-d_4 (5C). According to the general procedure, 1-octyne (82.5 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a colorless liquid (75.3 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (m, 10H), 0.90 (m, 4H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 1.24 (s, 2D), 0.90 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 31.9, 29.3, 22.7 (m), 14.1 (m).

1-chlorohexane-d_4 (6C). According to the general procedure, 6-chloro-1-hexyne (87.0 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a colorless liquid (81.8 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (t, *J* = 7 Hz, 2H), 1.79 (m, 2H), 1.44 (m, 2H), 1.31 (m, 2H), 0.87 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 1.29 (s, 2D), 0.87 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 45.8, 33.2, 31.4, 27.1, 22.3 (m), 13.8 (m).

1-hexanol-d_4 (7C). According to the general procedure, 5-hexyn-1-ol (73.6 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a colorless liquid (77.9 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, *J* = 7 Hz, 2H), 1.58 (quint, *J* = 7 Hz, 2H), 1.34 (m, 4H), 0.87 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 1.76 (s, OD) 1.27 (s, 2D), 0.85 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 62.8, 32.7, 31.5, 25.4, 22.4 (m), 13.5 (m).

Methyl-4-ethylbenzoate-d_4 (8C). According to the general procedure, methyl-ethynylbenzoate (119.5 mg, 0.75 mmol) was dissolved in DCM (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as orange liquid (115.2 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8 Hz, 2H), 3.91 (s, 3H), 1.23 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 2.69 (s, 2D), 1.24 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 167.3, 149.8, 129.8, 128.0, 127.8, 52.1, 28.6 (m), 14.6 (m).

General procedure for palladium membrane deuteration of aldehydes and imines

All reactions were performed using either ethanol (EtOH, **9**, **10**, **13**–**17**) or MeOH–H_2O (1:1) mixture (**11**, **12**). EtOH used for imine deuterations was dried over activated molecular sieve prior to use. Imines were prepared by stirring equal equivalents of corresponding amine and aldehyde in MeOH at room temperature for 1 h, and removing the solvent with rotary evaporation. The crude imines were purified by recrystallization in either cold MeOH or hexanes, and dried under high-vacuum. Impurities were not detectable by ^{1}H NMR spectroscopy for all synthesized imines.

To suppress the formation of the deoxygenated product, Pd foils used for aldehyde deuteration were soaked in 10 vol. % ethylenediamine in EtOH and rinsed with EtOH (10 mL × 3)[1]. Over the course of the deuteration reaction, no residual EDA was detectable with ^{1}H NMR. All reactions were carried out in the open air at room temperature. The chemical compartment with a magnetic stir bar was oven dried at 110 ℃ overnight prior to use and was charged with substrate (0.75 mmol) and solvent (30 mL). 1 M D_2SO_4 in D_2O electrolyte solution (35 mL) was added to the electrochemical compartment and a constant current of 100 mA was applied for 24 h. Both reaction mixture and electrolyte solution were stirred at a constant rate throughout the experiment. Reaction aliquots were sampled every 2 h to monitor the reaction profile by ^{1}H NMR spectroscopy. After 24 h, the reaction mixture was concentrated in vacuo and the desired product was isolated.

Benzyl alcohol-d_1 (9B). According to the general procedure, benzaldehyde (79.6 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford desired product as a colorless liquid (69.6 mg, 85% yield). ^{1}H NMR (400 MHz, CD_2Cl_3): δ 7.27–7.43 (m, 5H), 4.62 (m, 1H), 2.68 (br s, 1H); ^{2}H NMR (61 MHz, CH_2Cl_2): δ 4.66 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 141.2, 128.5, 127.5, 127.0, 64.6 (m). The current efficiency was determined by comparing the number of electrons used to generate alcohol to the total number of electrons consumed to reduce deuterons over a given period of time.

4-chlorobenzyl alcohol-d_1 (10B). According to the general procedure, 4-chlorobenzaldehyde (105.4 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford desired product as a white solid (105.5 mg, 98 % yield). ^{1}H NMR (400 MHz, CD_2Cl_3): δ 7.25–7.38 (m, 4H), 4.64 (m, 1H), 1.81 (br s, 1H); ^{2}H NMR (61 MHz, CH_2Cl_2): δ 4.59 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 140.3, 133.5, 129.1, 128.8, 64.5 (m).

4-methylbenzyl alcohol-d_1 (11B). According to the general procedure, 4-methylbenzaldehyde (90.4 mg, 0.75 mmol) was dissolved in 50:50 (v:v) MeOH:H_2O (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford desired product as a white solid (79.4 mg, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.20 (m, 2H), 7.20–7.27 (m, 2H), 4.59 (m, 1H), 2.34 (s, 3H), 1.78 (br s, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.59 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 138.3, 137.4, 129.2, 127.1, 64.8 (m), 20.9.

4-hydroxybenzyl alcohol-d_1 (12B). According to the general procedure, 4-hydroxybenzaldehyde (91.6 mg, 0.75 mmol) was dissolved in 50:50 (v:v) MeOH:H_2O (30 mL). After 48 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a beige solid (84.5 mg, 90 % yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.16 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 4.47 (m, 1H); ^{2}H NMR (61 MHz, CH_3OH): δ 4.44 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, CD_3OD): 158.2, 133.7, 130.1, 116.4, 65.2 (m).

***N*-benzylaniline-d_1 (13B)**. According to the general procedure, *N*-benzylideneaniline (135.9 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a yellow liquid (125.6 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.44 (m, 5H), 7.16 (t, J = 7.9 Hz, 2H), 6.58-6.73 (m, 3H), 4.33 (m, 1H), 4.15 (br s, 1H); ^{2}H NMR (61 MHz, CH_2Cl_2): δ 4.34 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 148.8, 140.3, 129.7, 129.1, 128.0, 127.7, 117.9, 113.3, 48.3 (m). The current efficiency was determined by comparing the number of electrons used to generate amine to the total number of electrons consumed to reduce deuterons over a given period of time.

***N*-benzyl-*p*-toluidine-d_1 (14B)**. According to the general procedure, *N*-benzylidene-*p*-toluidine (146.4 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as light pink liquid (127.8 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.56 (m, 5H), 6.99 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 8.1 Hz, 2H), 4.31 (m, 1H), 4.00 (br s, 1H), 2.25 (s, 3H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.31 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 146.6, 140.5, 130.2, 129.1, 128.0, 127.6, 127.1, 113.5, 48.6 (m), 20.6.

***N*-(*p*-chlorobenzyl)aniline-d_1 (15B)**. According to the general procedure, *N*-(4-chlorobenzylidene)aniline (161.8 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as brown liquid (145.3 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.40 (m, 4H), 7.15 (t, *J* = 7.3, 1.9 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 2H), 4.69 (br s, 1H), 4.30 (m, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.34 (s, 1D);^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 147.5, 138.1, 138.1, 132.7, 129.2, 128.6, 117.9, 113.2, 47.4 (m).

***N*-(4-Chlorobenzyl)-3,5-dimethylaniline-d_1 (16B)**. According to the general procedure, *N*-(4-Chlorobenzylidene)-3,5-dimethylaniline (182.8 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as brown liquid (177.7 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.37 (m, 4H), 6.40 (s, 1H), 6.29 (s, 2H), 4.28 (m, 1H), 2.19 (s, 6H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.29 (s, 1D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 147.6, 139.0, 138.5, 132.7, 129.0, 128.7, 120.1, 111.3, 47.3 (m), 21.3.

3-ethyl-*N*-phenyl--3,5-dimethylaniline-d_3 (17B). According to the general procedure, *N*-(3-Vinylbenzylidene)aniline (189.9 mg, 0.75 mmol) was dissolved in EtOH (30 mL). After 24 h of deuteration, the reaction mixture in the chemical compartment was concentrated to afford the desired product as brown liquid (167.2 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.38 (m, 4H), 6.39 (s, 1H), 6.31 (s, 2H), 4.28 (m, 1.03H), 4.01(br s. 1H) 2.66 (m, 1H), 2.24 (s, 6H), 1.25 (m, 2.00H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 4.26 (s, 1D), 2.63 (s, 1D), 1.21 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 148.6, 144.8, 140.0, 140.0, 138.9, 128.6, 127.3, 126.7, 124.9, 119.4, 110.8, 48.3 (m), 28.9 (m), 21.3, 15.3 (m).

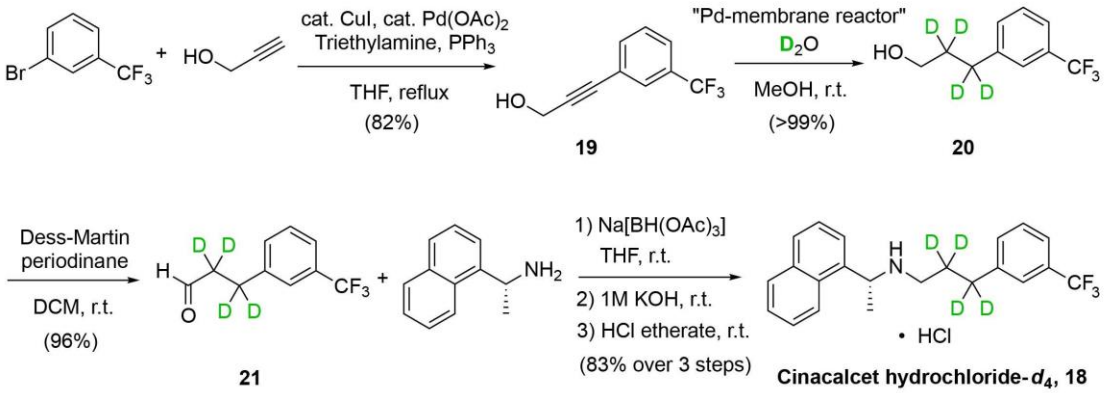
Synthesis of cinacalcet hydrochloride-d_4

Cinacalcet hydrochloride-d_4 (18). A solution of (R)-(+)-1-(1-Naphthyl)ethylamine (130 mg, 0.76 mmol) and **21** (175 mg, 0.84 mmol) in 20 mL anhydrous THF was stirred under N_2 at room temperature for 1 hour. Sodium triacetoxyborohydride (288 mg, 1.36 mmol) in 10 mL anhydrous THF was slowly added to the solution and the mixture was stirred at room temperature for 20 h before the reaction was quenched with 10 mL 1M NaOH solution in water. The mixture was concentrated under reduced pressure to around 20 mL and extracted three times with 10 mL dichloromethane. The organic phase was combined, washed with 10 mL brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum yielding the crude free base cinacalcet which was purified using a basic alumina column (hexanes/ethyl acetate = 4:1). The purified free base was immediately converted into its hydrochloride salt by dissolution in diethyl ether and reaction with an excess amount of HCl etherate solution. The white precipitate was collected by vacuum filtration and was dried under vacuum. A white powder was obtained (280 mg, 83% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.97 (m, 2H), 7.77 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.56–7.68 (m, 3H), 7.36–7.48 (m, 4H), 5.38 (q, *J* = 6.8 Hz, 1H), 3.08 (d, J = 12.1 Hz, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 1.80 (d, J = 7.4 Hz, 3H); ^{2}H NMR (61 MHz, CD_3OD): δ 2.65 (s, 2D), 1.99 (s, 2D); $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD): 142.9, 135.5, 134.2, 133.2, 132.1, 131.8 (q, $^2J_{CF}$ = 31.5 Hz), 131.0, 130.4, 128.5, 127.6, 126.6, 125.9 (q, $^3J_{CF}$ = 3.6 Hz), 125.6 (q, $^1J_{CF}$ = 272.0 Hz), 124.9, 124.1 (q, $^3J_{CF}$ = 3.9 Hz), 123.0, 54.2, 46.6, 32.5 (m), 27.9 (m), 20.1; $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD, internal standard $CFCl_3$): δ -63.75 (s, 3F); ESI-MS $[M\text{-}Cl]^-$, cald. for $C_{22}H_{18}D_4F_3N$, 362.20; found, 362.210.

3-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (19). A solution of trimethylamine (6.50 g, 64.1 mmol) in 100 mL anhydrous THF was degassed with N_2 for 30 min in a 250 mL three-neck round bottom flask. CuI (244 mg, 1.28 mmol), $Pd(OAc)_2$ (287 mg, 1.28 mmol) and triphenylphosphine (673 mg, 2.56 mmol) were added and the solution was degassed for another 15 min. Propargyl alcohol (1.72 g, 30.8 mmol) and 3-bromobenzotrifluoride (5.77 g, 25.6 mmol) were added via syringe and the reaction mixture was heated at 70 °C. After 20 h, the mixture was concentrated under vacuum after which 100 mL of deionized water was added. The mixture was extracted three times with 50 mL hexanes and the organic phase was combined, washed with 20 mL of brine and dried over anhydrous $MgSO_4$. The crude product obtained after evaporation of the solvent was distilled under reduced pressure to yield a light yellow liquid (4.20 g, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.54-7.59 (m, 2H), 7.43 (t, J = 7.3 Hz, 1H), 4.51 (s, 2H), 2.33 (br s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 134.9, 131.0 (q, $^2J_{CF}$ = 32.5 Hz), 129.0, 128.5 (q, $^3J_{CF}$ = 3.8 Hz), 125.1 (q, $^3J_{CF}$= 3.8 Hz), 124.2 (q, $^1J_{CF}$ = 272.5 Hz), 122.4, 88.9, 84.3, 51.5; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$): δ -62.73 (s, 3F).

3-(Trifluoromethyl)benzenepropanol-*d*$_4$ (20). 3-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (560 mg, 2.8 mmol) was dissolved in MeOH (30 mL). 1 M D_2SO_4 in D_2O was added to the electrochemical compartment and a constant current of 100 mA was applied. After 24 h, the reaction mixture in the chemical compartment was concentrated to afford the desired product as a clear colorless liquid (606 mg, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.47 (m, 2H), 7.35–7.41 (m, 2H), 3.67 (s, 2H), 1.58 (br s, 1H); ^{2}H NMR (61 MHz, $CHCl_3$): δ 2.73 (s, 2D), 1.86 (s, 2D); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 142.8, 132.0, 130.7 (q, $^2J_{CF}$ = 32.2 Hz) 128.9, 125.1 (q, $^3J_{CF}$ = 3.9 Hz), 124.3 (q, $^1J_{CF}$ = 272.3 Hz) 122.8 (q, $^3J_{CF}$ = 3.8 Hz), 61.8, 33.2 (m), 31.1 (m); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$, internal standard $CFCl_3$): δ -62.28 (s, 3F)

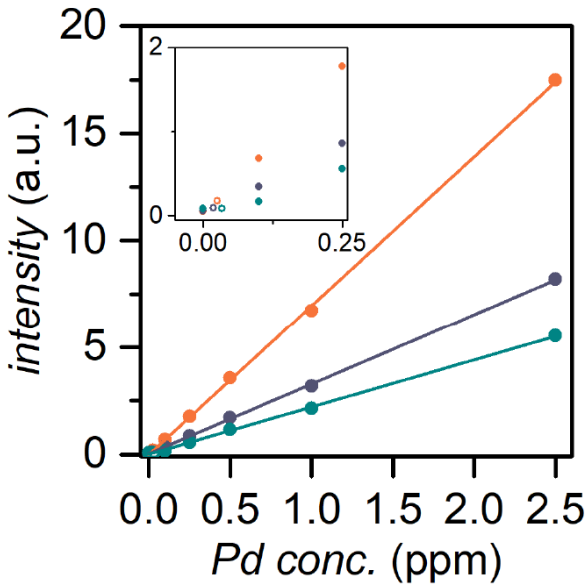
3-(Trifluoromethyl)benzenepropanal-d_4 (21). A suspension of Dess-Martin periodinane (2.36 g, 5.57 mmol) in DCM (20 mL) was slowly added to 3-(trifluoromethyl)benzenepropanol-d_4 (580 mg, 2.79 mmol) in DCM (50 mL). The reaction mixture was stirred in air for 1 h at room temperature and washed with 20 mL 1 M KOH solution, 20 mL saturated $Na_2S_2O_3$, 20 mL brine and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum and the resulting crude product was purified using silica column (hexanes/ethyl acetate = 4:1). A clear liquid was obtained (560 mg, 96% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.79 (s, 1H), 7.45–7.50 (m, 2H), 7.41–7.45 (m, 2H); ^{2}H NMR (61 MHz, CH_2Cl_2): δ 2.91 (s, 2D), 2.72 (s, 2D); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2): 201.3, 142.1, 132.4, 130.9 (q, $^2J_{CF}$ = 32.0 Hz) 129.4, 125.4 (q, $^3J_{CF}$ = 3.6 Hz), 124.7 (q, $^1J_{CF}$ = 273.4 Hz) 123.4 (q, $^3J_{CF}$ = 3.9 Hz), 44.5 (m), 27.5 (m); ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2, internal standard $CFCl_3$): δ -62.63 (s, 3F)



Supplementary Figure 5. Synthesis of cinacalcet hydrochloride-d_4 (**18**).

ICP-OES residual palladium study

ICP-OES studies were performed by preparing a calibration curve with a 1000 mg/mL Pd in 5% HCl stock standard solution. The calibration curve ranged from 0.1 ppm to 25 ppm and 3 emission lines (340 nm, orange; 361 nm, purple; 324 nm, teal) were used for calibration and sample measurement. The sample was prepared by removing the content of the reaction mixture of 1-hexyne hydrogenation in DCM solvent after 24 h of reaction at 100 mA applied current. Solvent and product were removed under vacuum and the flask was treated with 1 mL 40% HNO_3 for 72 h. Subsequently, 7 mL dH_2O was added to the flask to yield a 5% HNO_3 matrix for measurement. ICP-OES measurements of the sample yielded results of 0.026±0.008 ppm, or 0.007±0.002 ppm in the original 30 mL reaction mixture (7±2 ppb).



Supplementary Figure 6. ICP-OES calibration curves (solid dots) and sample measurements (hollow dots) for 3 emission lines at 340 nm (orange), 361 nm (purple) and 324 nm (teal). A line of best fit is plotted on each of the calibration curves and was used to determine the sample concentration. The inset shows a region between 0 and 0.25 ppm Pd concentration in which the unknown sample resides.

Costs of deuterium reagents

The cost of the deuterium reagent for palladium membrane deuteration was calculated by determination of the amount of D_2O consumed to deuterate 0.75 mmol. Complete conversion took 8 hr; therefore, the cost of deuterium source for the palladium membrane deuteration was estimated by amount of D_2O consumed during the electrolysis for 8 h at 100 mA. Theoretically, the electrolyte (D_2SO_4) does not get consumed by electrolysis; however, the electrolyte may need to be replaced at some point in practice. The cost of electrolyte (D_2SO_4, Sigma Aldrich) was estimated by the numbers of reactions we have run (~50 times) using one preparation of electrolyte solution). The prices of D_2O and D_2SO_4 from different suppliers (Sigma Aldrich, Acros Organics, Cambridge Isotope Laboratories) were averaged. Error bars represent + 1 standard deviation of the mean cost for at least 3 suppliers.

$$\begin{aligned} &\#\ of\ moles\ of [\![D]\!]\_2\ O\ consumed\ during\ electrolysis\ for\ 8\ hr \\ &\quad = ((charge\ passed\ through\ for\ 8\ h\ at\ 100\ mA))/(2 \\ &\quad \times (Faraday's\ constant)) \end{aligned}$$

$$= 0.100 C/sec \times 8h \times (3600\ sec)/1h \times mol/(96485\ C) \times 1/2 = 14\ mmol \quad (1)$$

$$Cost\ of\ [\![14\ mmol\ D]\!]\_2\ O\ =\ price\ of\ [\![D\_2\ O]\!]\_\ per\ mol\ \times 14\ mmol$$

$$= ((23.0\ USD)/mol) \times 0.014\ mol\ = 0.32\ USD \quad (2)$$

$$Cost\ of\ D\_2\ [\![SO]\!]\_4\ to\ prepare\ 1\ M\ D\_2\ [\![SO]\!]\_4\ \ solution\ (35\ mL)$$

$$\begin{aligned} &= (price\ of\ [\![D\_2\ SO]\!]\_4\ per\ mol) \\ &\quad \times (\ \#\ of\ moles\ of\ D\_2\ [\![SO]\!]\_4\ \ in\ 35\ mL\ of\ 1\ M\ D\_2\ [\![SO]\!]\_4) \end{aligned}$$

$$= ((141\ USD)/mol) \times 0.035\ mol\ = 4.9\ USD \quad (3)$$

$$Cost\ of\ D\_2\ [\![SO]\!]\_4\ \ per\ reaction$$

$$\begin{aligned} &= (Cost\ of\ D\_2\ [\![SO]\!]\_4\ to\ prepare\ 1\ M\ D\_2\ [\![SO]\!]\_4\ \ solution\ (35\ mL)\ ) \\ &\quad /(\#\ of\ reactions\ used) = (4.9\ USD)/50 = 0.10\ USD \end{aligned} \quad (4)$$

Total cost of the deuterium reagent per reaction = cost of D_2O + D_2SO_4 = **0.42 USD** (5)

The costs of the deuterium reagents for reductive deuteration (RD) was calculated based on the procedure commonly used for (RD) with D_2 gas and deuterium transfer reagent ($NaBD_4$). The cost of D_2 gas was estimated by the amount of D_2 gas required (20 mol equivalents) to deuterate 0.75 mmol of phenylacetylene[2]. The cost of $NaBD_4$ was estimated by the amount of $NaBD_4$ required to deuterate 0.75 mmol of benzaldehyde (2 mol equivalent)[3]. The prices of D_2 gas (Sigma Aldrich, Cambridge Isotope Laboratories) and $NaBD_4$ (Sigma Aldrich, Eurisotop, Cambridge Isotope Laboratories) from different suppliers were averaged. Error bars represent + 1 standard deviation of the mean cost for at least 3 suppliers.

$$\#\ of\ mmoles\ of [\![D]\!]\_2\ \ gas\ required = \ 0.75\ mmol \times 20\ = 15\ mmol \tag{6}$$

$$\begin{aligned} volume\ of [\![D]\!]\_2\ \ gas\ required & \\ = \ & ((\#\ of\ moles\ of\ [\![D]\!]\_2\ \ gas\ required)) \\ & /((\#\ of\ moles\ in\ 1\ L\ of [\![D]\!]\_2\ \ gas\ at\ 297\ K)) = \\ = \ & ((0.015\ mol))/((0.040\ mol \cdot L\text{^}(=1))) = 0.38\ L \end{aligned} \tag{7}$$

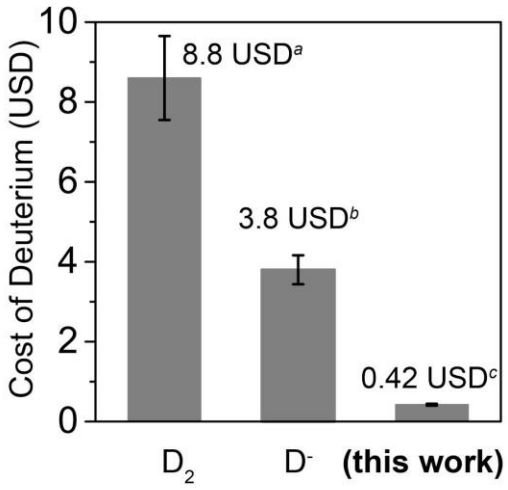
$$Cost\ of\ D\_2\ \ gas\ = \ (price\ of\ [\![1\ L\ D]\!]\_2\ \ gas) \times \text{(volume of } D_2 \text{ gas required)}$$

$$= (\ \ (23.1\ USD)/L) \times (0.38\ L) = \textbf{8.8 USD} \tag{8}$$

$$\#\ of\ mmoles\ of [\![NaBD]\!]\_4\ \ required = \ 0.75\ mmol \times 2\ = 1.5\ mmol \tag{9}$$

$$Cost\ of\ NaBD\_4\ \ = \ (price\ of\ NaBD\_4\ \ per\ mol) \times (\#\ of\ moles\ of\ NaBD\_4\ \ required)$$

$$= ((2534\ USD)/mol) \times 0.0015\ mol\ = \textbf{3.8 USD} \tag{10}$$



Supplementary Figure 7. **Costs of deuterium reagent.** The cost was estimated by the amount of deuterium reagents typically required to deuterate 0.75 mmol phenylacetylene and benzaldehyde for [a]RD of phenylacetylene with D_2 gas (20 mol equivalents), [b]RD of benzaldehyde with $NaBD_4$ (2 mol equivalents), [c]Pd membrane deuteration of phenylacetylene and benzaldehyde with D_2O that is consumed for electrolysis at −100 mA for 8 h. Error bars represent + 1 standard deviation of the mean cost for at least 3 suppliers. Detailed calculation is described in Supplementary Note.

We also compared the cost to deuterate cinacalcet precursor, 3-(Trifluoromethyl)phenyl)prop-2-yn-1-ol (**19**), with RD using D_2 gas and the Pd membrane reactor. Deuteration of **19** took ~8h for completion and we made an assumption that the same amount of D_2 gas would be required to deuterate **19** as it takes for phenylacetylene (shown above). Therefore, the estimated costs for each deuterium atom added to the cinacalcet hydrochloride-d_4 **18** with a palladium reactor or traditional RD using D_2 gas are 0.42 USD and 8.8 USD, respectively. Deuterium atoms added with the membrane reactor have 5% the cost as compared to traditional RD methods using D_2 gas.

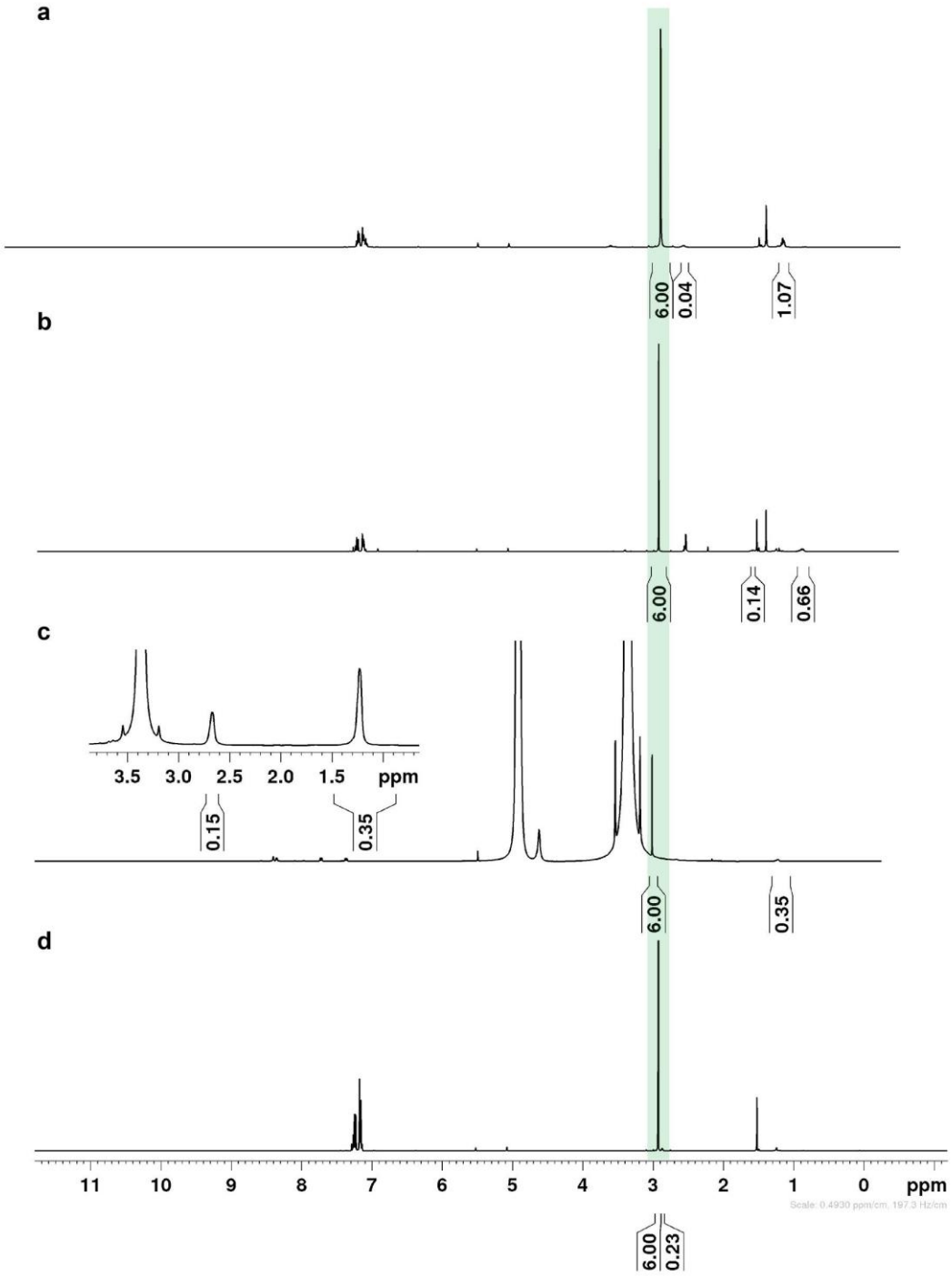
Deuterium incorporation study

Solvent suppression ^{1}H NMR (**1C**, **2C**, **4C**–**8C**, **20**) in $CDCl_3$ and ^{1}H NMR in CD_3OD (**3C**, **18**) and CD_2Cl_2 (**21**) were used to quantify deuterium incorporation of substrates. After 24 h, 500 µL of reaction mixture (0.025 M in DCM **1C**, **2C**, **4C**–**8C**, **20** MeOH **3C**) was sampled, and 125 µL of 0.1 M dimethylsulfone in $CDCl_3$ (**1C**, **2C**, **4C**–**8C**) and CD_3OD (**3C**) was added. The DCM solvent signal (~δ 5.3 ppm) was suppressed using Bruker solvent suppression pulse program (zggpw5) for **1C**, **2C**, **4C**–**8C**, **20**. For **3C**, **18**, **20**, and **21**, isolated product was dissolved in CD_3OD or CD_2Cl_2 (300 µL, 0.1 M), and 300 µL of 0.1 M dimethylsulfone in corresponding solvent was added. The amount of deuterium incorporated was determined by comparing two aliphatic proton signals for each substrate, a methylene (CH_2) proton signal and a methyl (CH_3) proton signal for **1C**–**3C** and **5C**–**8C**, and two methylene proton signals for **4C**, **18**, **20**, **21**, to the internal standard dimethyl (6H) signal. The percentage of the incorporation was determined relative to the theoretical amount of deuterium that can be added by the reaction (*i.e.* two deuterium atoms each for alkyne carbons).

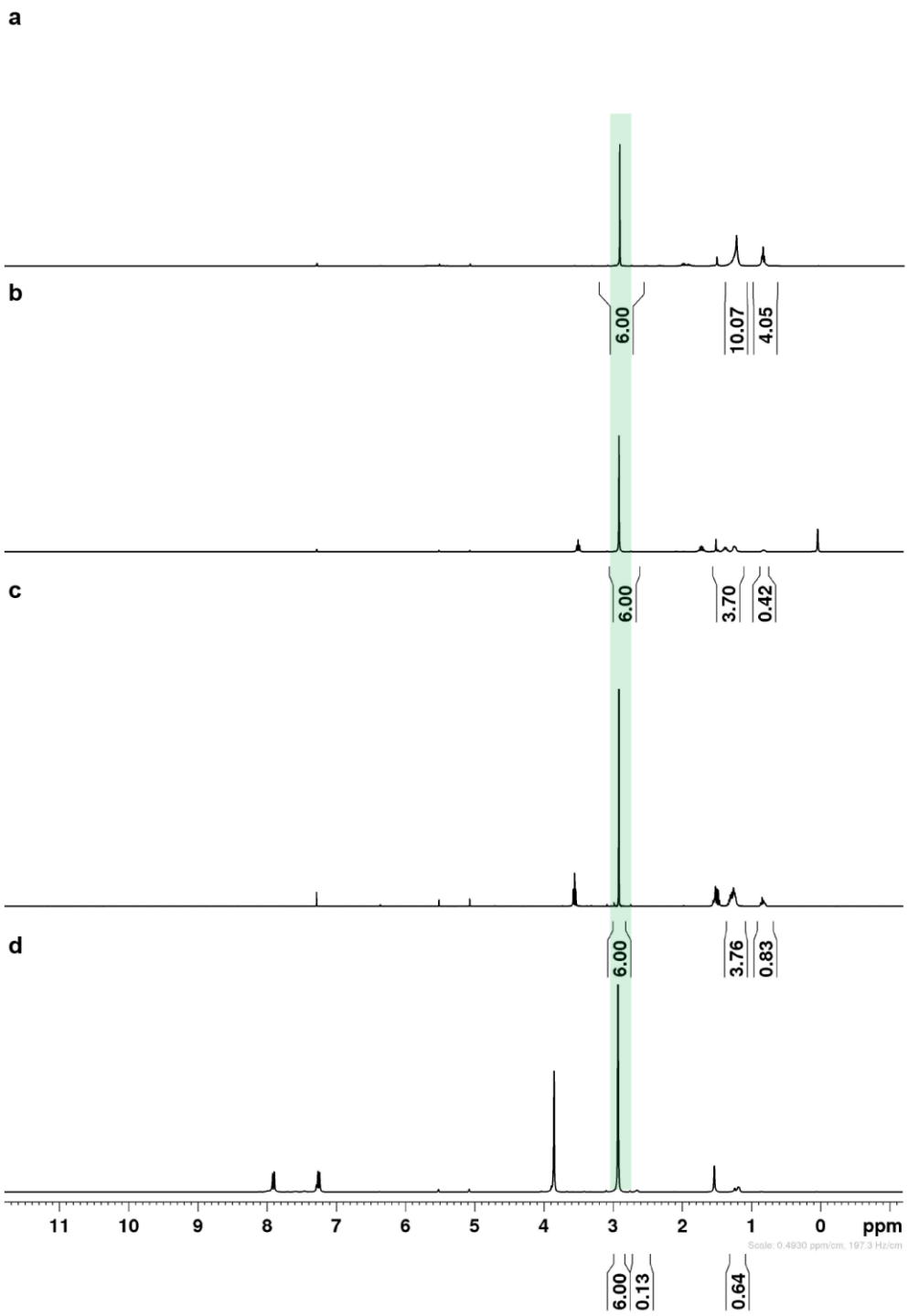
For example, a methylene signal of phenylacetylene **1C** was integrated as 0.04 H and a methyl peak was integrated as 1.07 H relative to the internal standard signal (Supplementary Figure 8a). The methylene carbon contains 1.96 D (98 % incorporation) and the methyl carbon contains 1.93 D (97 % incorporation) which give 3.8 D per molecule.

For **3C**, the CH_2 proton signal was overlapped with the solvent signal in the ^{1}H NMR of the reaction mixture. A CH_3 proton signal was compared to the internal standard in the reaction mixture (Supplementary Figure 8c) and the integrated CH_3 proton signal was used to integrate the CH_2 proton signal in the ^{1}H NMR spectrum of final product after solvent had been removed (Supplementary Figure 8c, inset).

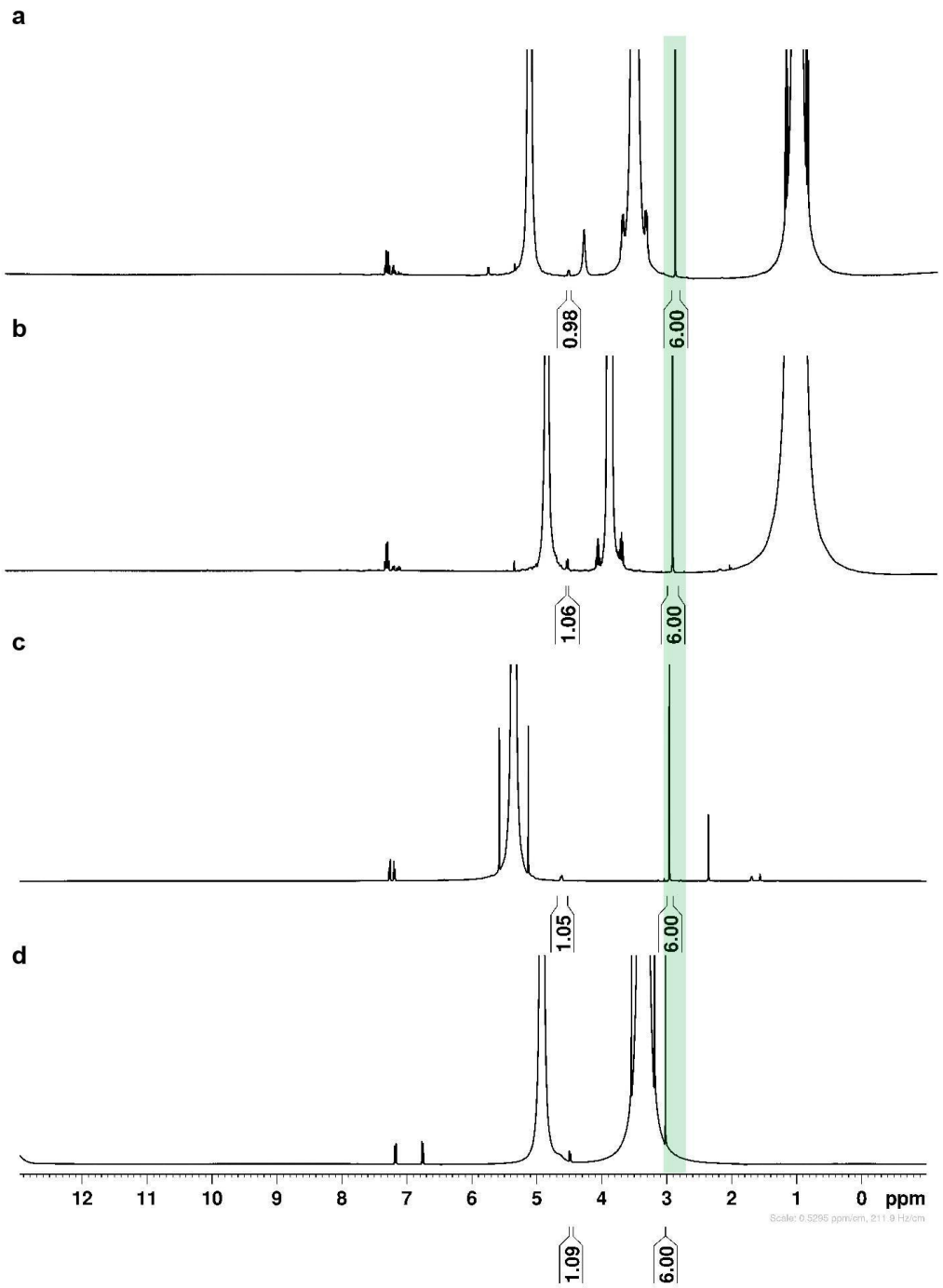
^{1}H NMR in CD_3OD (**12B**) and CD_2Cl_2 (**9B**–**11B**, **13B**–**17B**) were used to quantify deuterium incorporation of aldehyde and imine substrates. After 24 h, 500 µL of reaction mixture (0.025 M in ethanol **9B**, **10B**, **14B**–**16B**) was sampled, and 125 µL of 0.1 M dimethylsulfone in CD_2Cl_2 (**9B**, **10B**, **14B**–**16B**) was added. For **11B**, **12B**, and **17B**, isolated product was dissolved in CH_2Cl_2 or CH_3OH (500 µL, 0.025 M), and 125 µL of 0.1 M dimethylsulfone in corresponding deuterated solvent was added. For **13B**, the isolated product was dissolved in CD_2Cl_2 (300 µL, 0.1 M), and 300 µL of 0.1 M dimethylsulfone in corresponding solvent was added. The amount of deuterium incorporated was determined by comparing one α–proton to hydroxyl (**9B**–**12B**) or amine group (**13B**–**17B**) signals for each substrate to the internal standard dimethyl (6H) signal. The percentage of the incorporation was determined relative to the theoretical amount of deuterium that can be added by the reaction (*i.e.* one deuterium atom each for α-proton to hydroxyl and amine group).



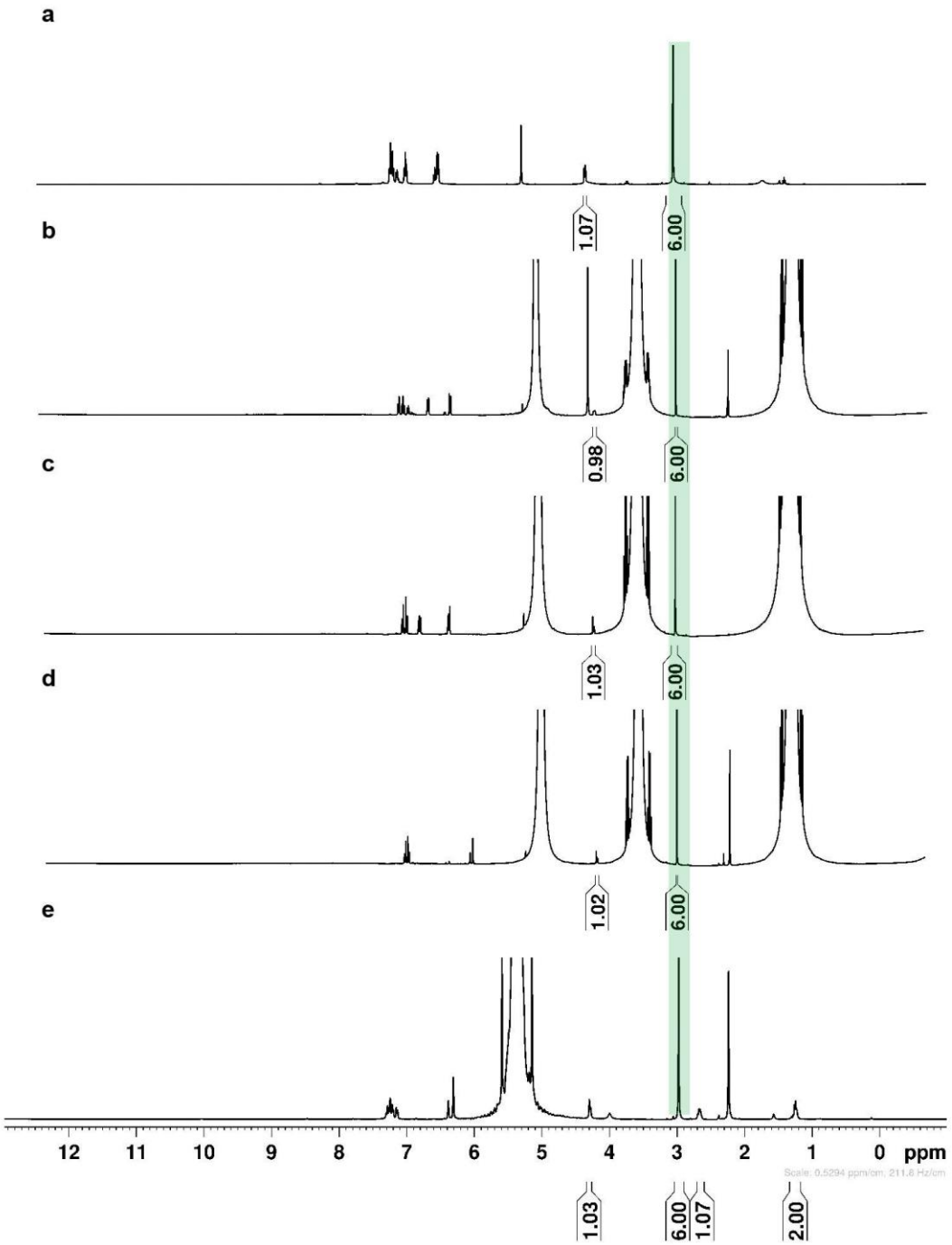
Supplementary Figure 8. ^{1}H NMR spectrum of **a**, ethylbenzene-d_4 (**1C**), **b**, propylbenzene-d_4 (**2C**), **c**, 3-ethylpyridine-d_4 (**3C**), and **d**, bibenzyl-d_4 (**4C**) with one equivalent of dimethylsulfone as an internal standard (green).



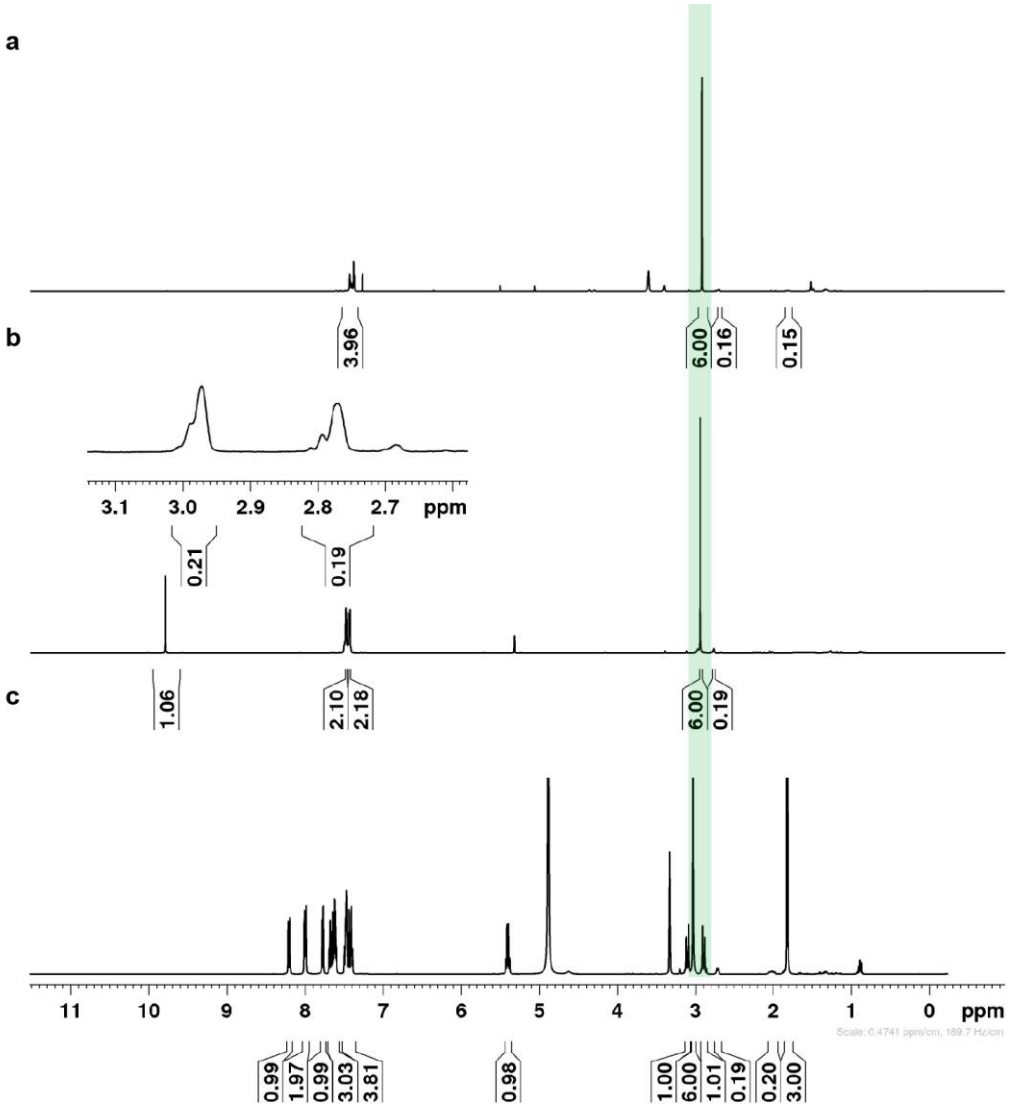
Supplementary Figure 9. ^{1}H NMR spectrum of **a**, octane-d_4 (**5C**), **b**, 1-chlorohexane-d_4 (**6C**), **c**, 1-hexanol-d_4 (**7C**), and **d,** methyl-4-ethylbenzoate-d_4 (**8C**) with one equivalent of dimethylsulfone as an internal standard (green).



Supplementary Figure 10. ^{1}H NMR spectrum of **a**, benzyl alcohol-d_1 (**9B**), **b**, 4-chlorobenzyl alcohol-d_1 (**10B**), **c**, 4-methylbenzyl alcohol-d_1 (**11B**), and **d,** 4-hydroxybenzyl alcohol-d_1 (**12B**) with one equivalent of dimethylsulfone as an internal standard (green).



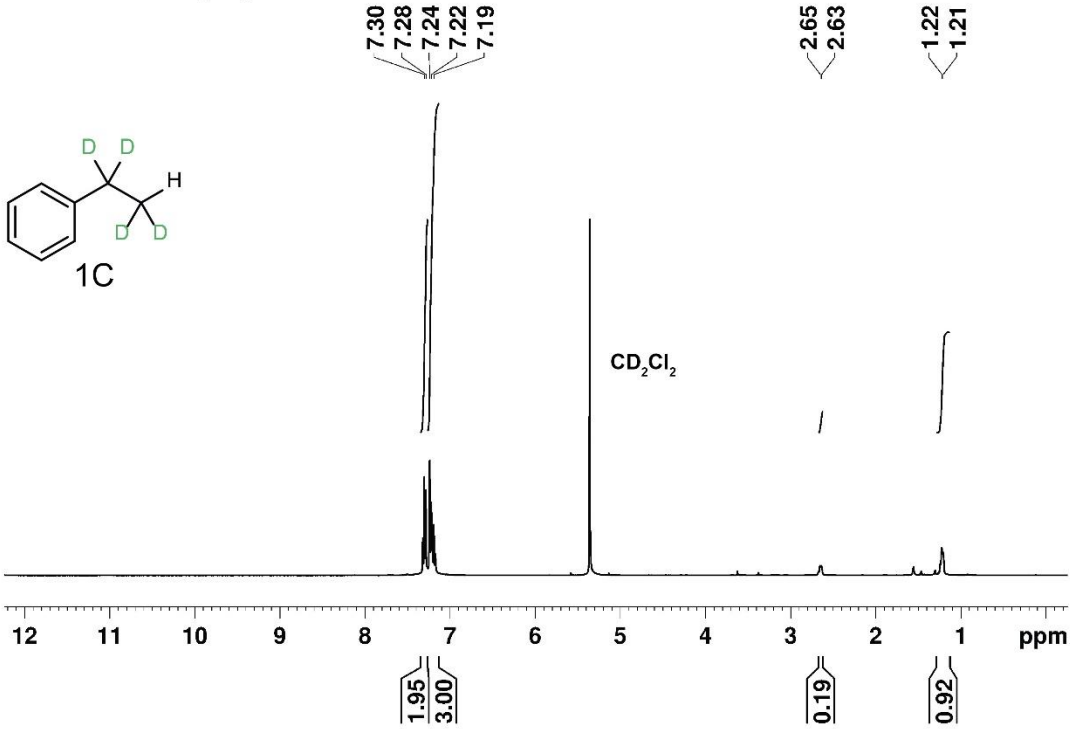
Supplementary Figure 11. ^{1}H NMR spectrum of **a**, *N*-benzylaniline-d_1 (**13B**), **b**, *N*-benzyl-*p*-toluidine-d_1 (**14B**), **c**, *N*-(*p*-chlorobenzyl)aniline-d_1 (**15B**), **d,** *N*-(4-Chlorobenzyl)-3,5-dimethylaniline-d_1 (**16B**) and **e**, 3-ethyl-*N*-phenyl-3,5-dimethylaniline-d_3 (**17B**) with one equivalent of dimethylsulfone as an internal standard (green).



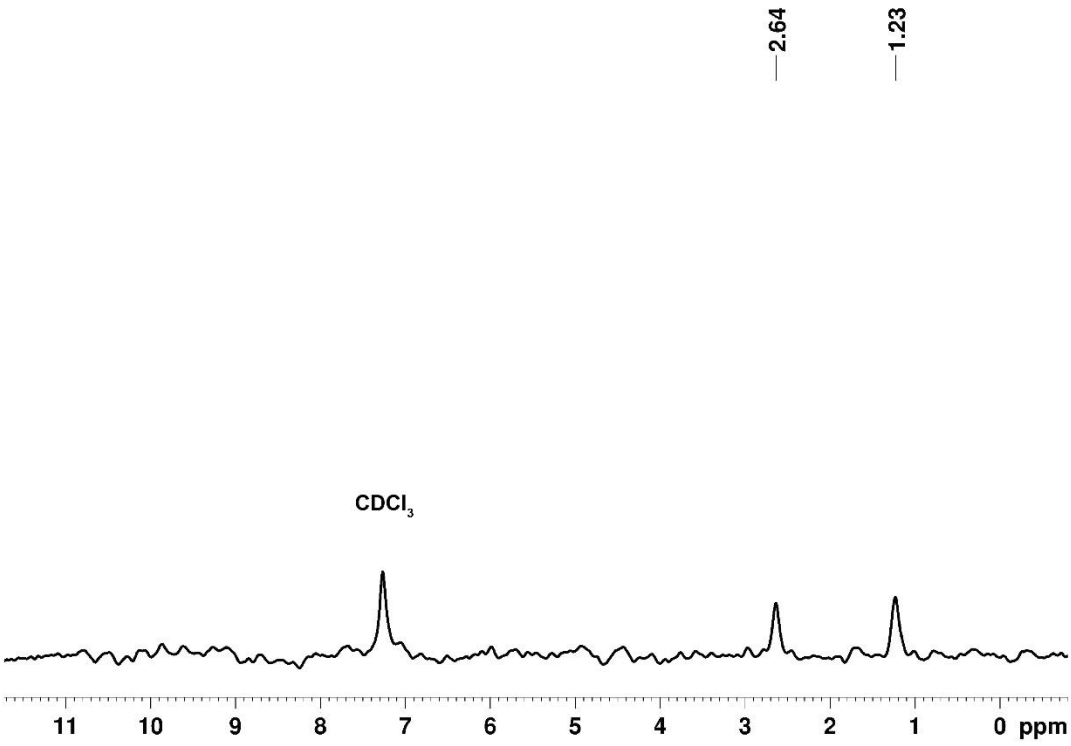
Supplementary Figure 12. ^{1}H NMR spectrum of **a**, 3-(trifluoromethyl)benzenepropanol-d_4 (**20**) **b**, 3-(trifluoromethyl)benzenepropanal-d_4 (**21**), and **c**, cinacalcet hydrochloride-d_4 (**18**) with one equivalent of dimethylsulfone as an internal standard (green).

NMR spectra

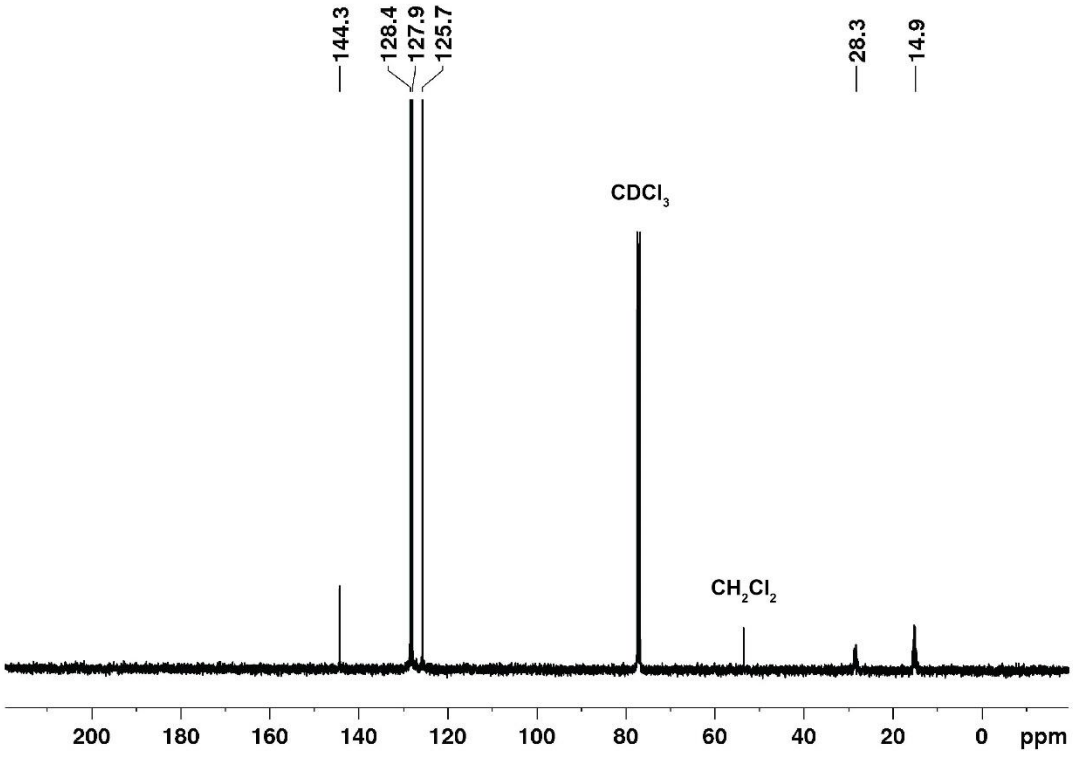
^{1}H NMR (400 MHz, CD_2Cl_2)



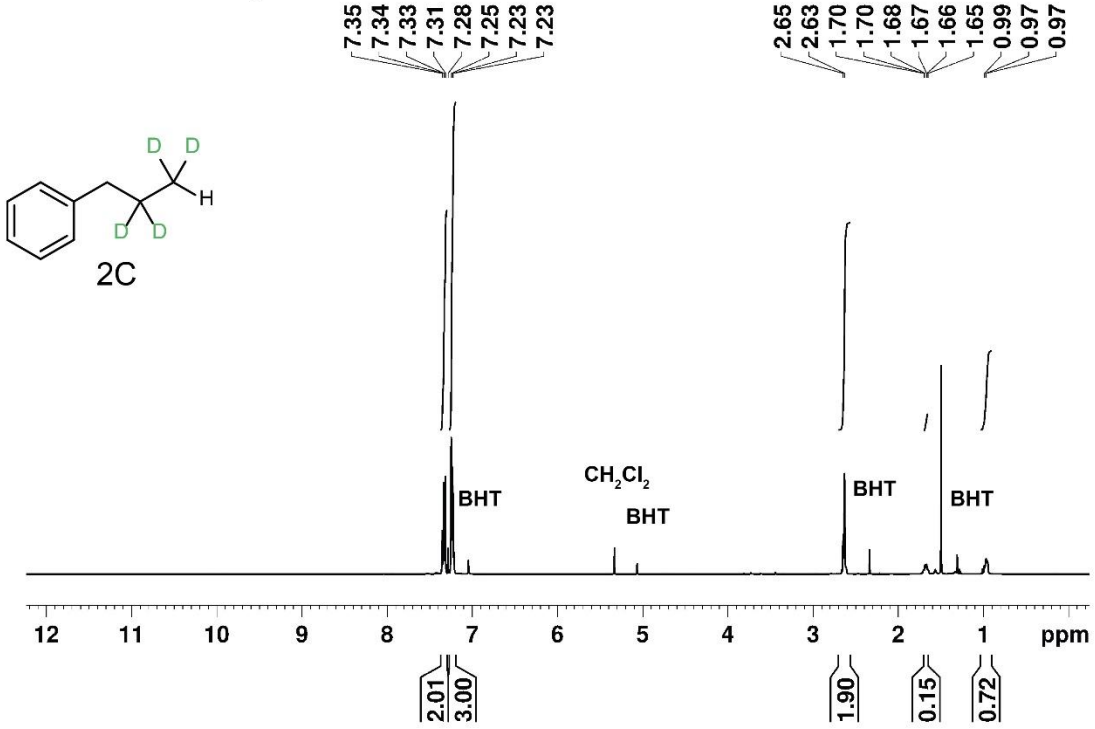
^{2}H NMR (61 MHz, $CHCl_3$)



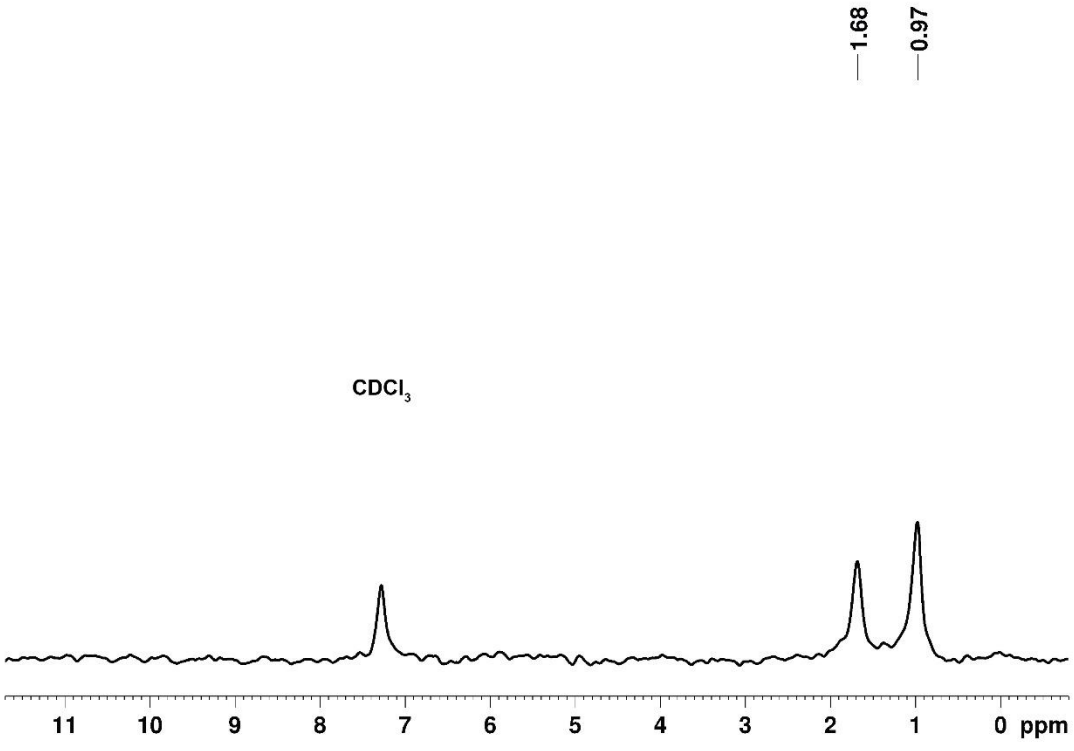
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



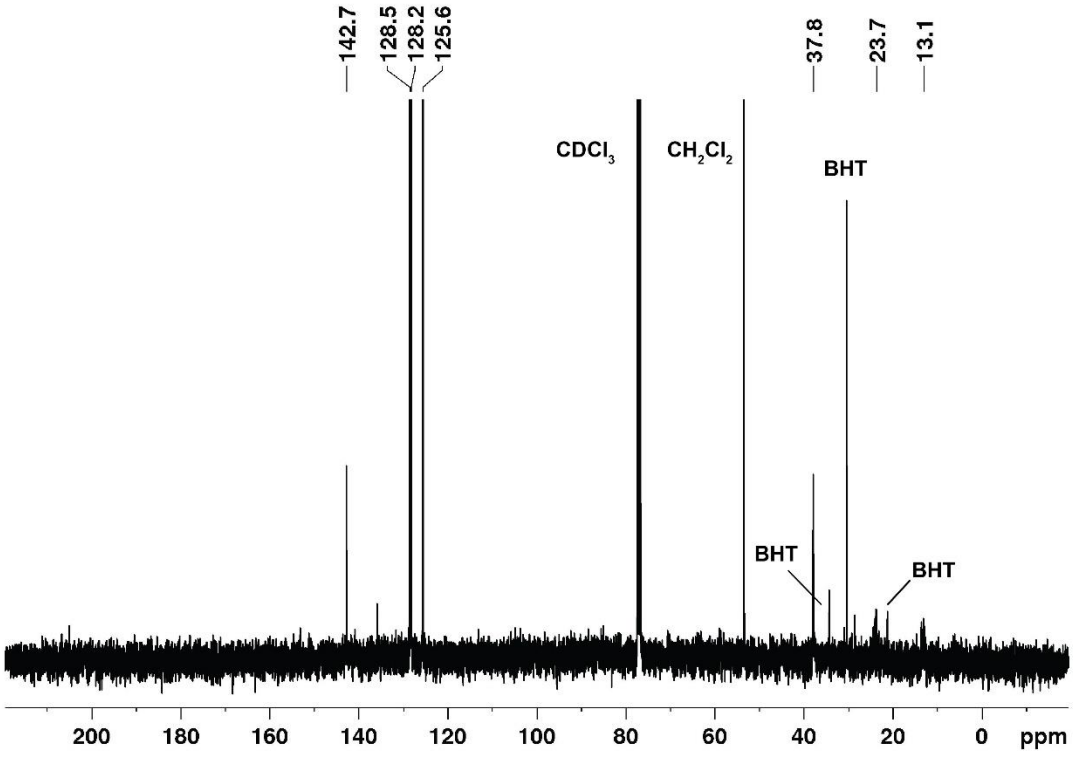
^{1}H NMR (400 MHz, $CDCl_3$) BHT is an inhibitor in starting material 3-phenyl-1-propyne.



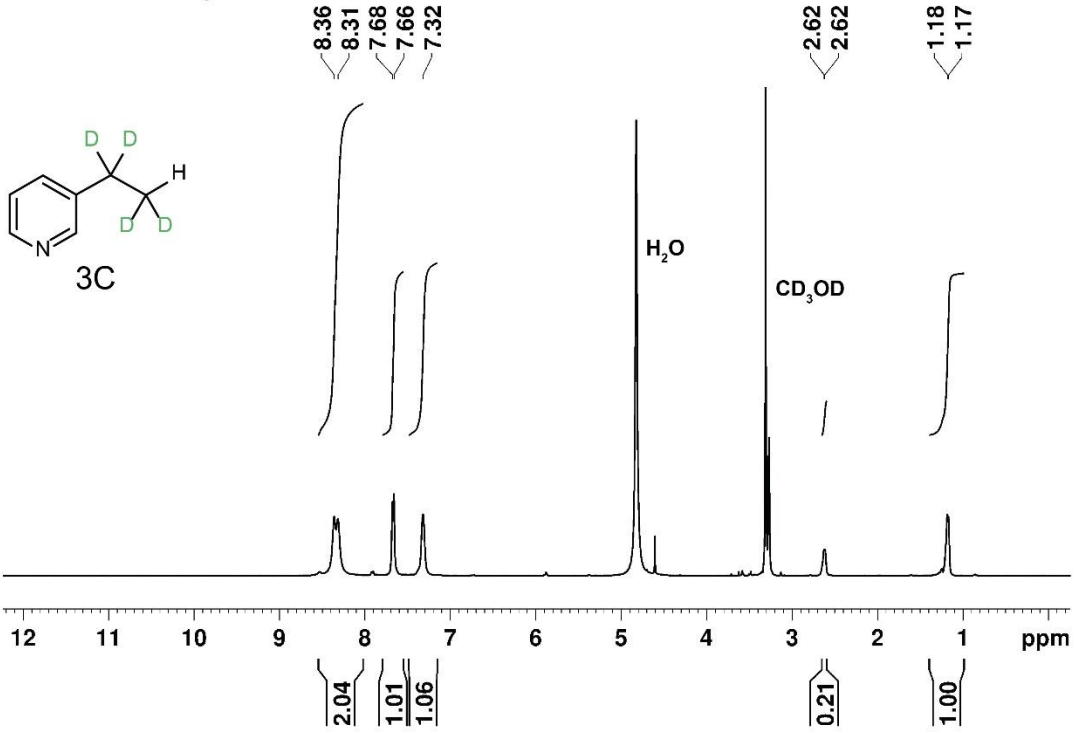
^{2}H NMR (61 MHz, $CHCl_3$)



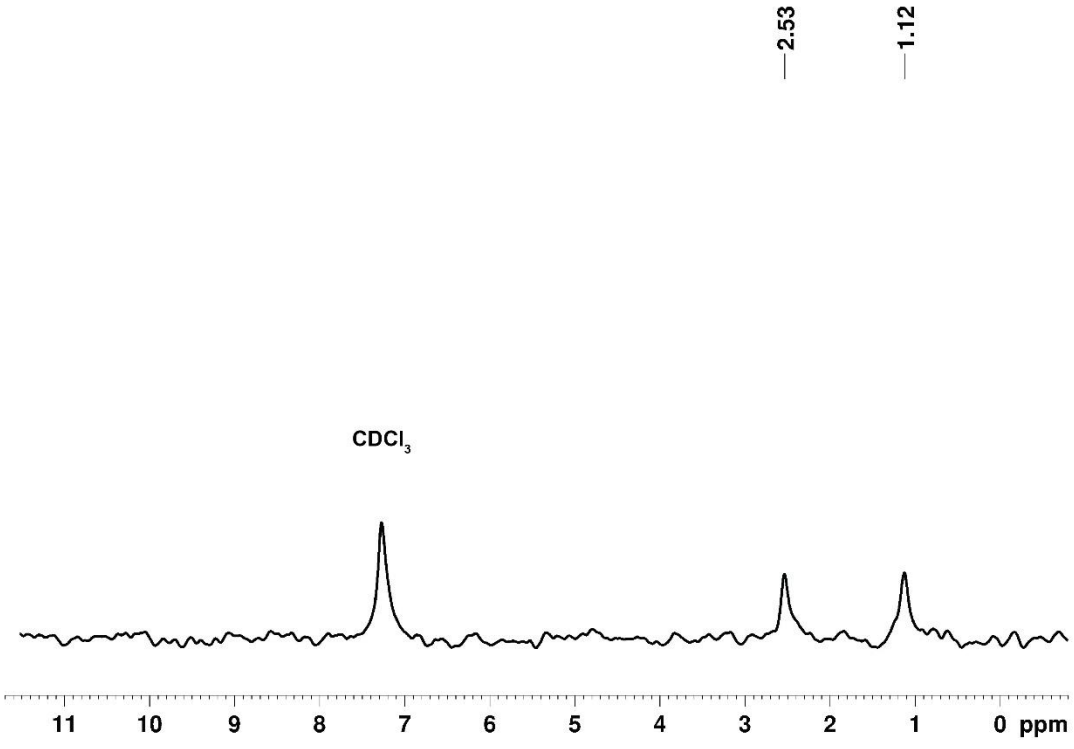
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



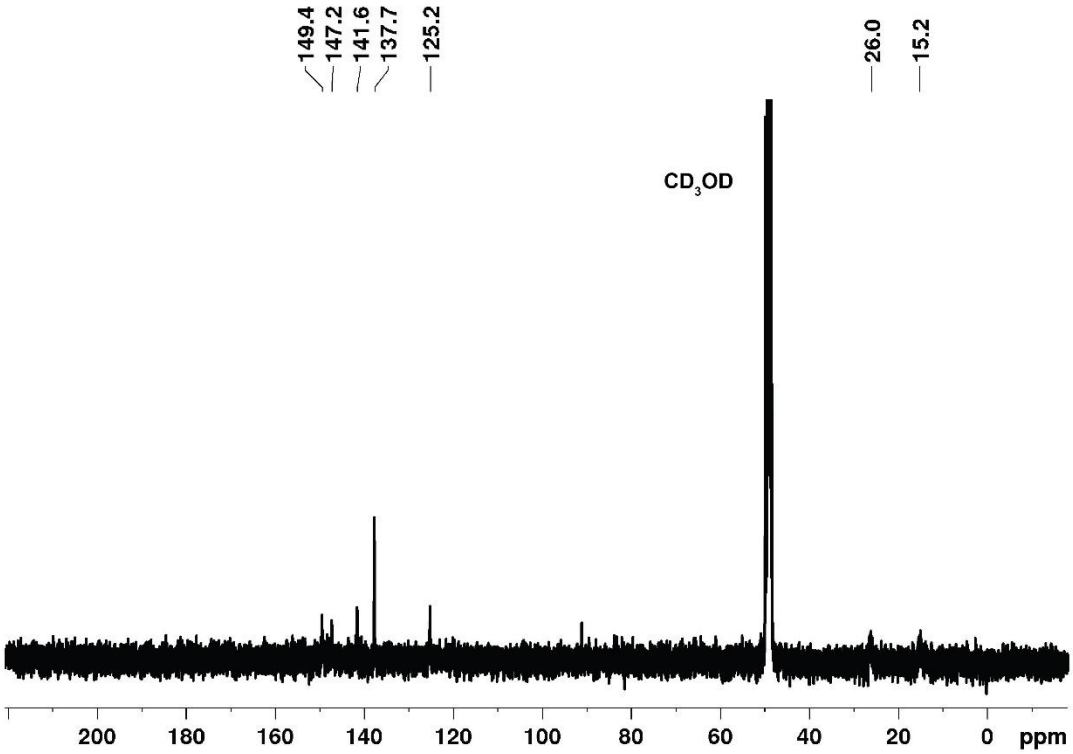
^{1}H NMR (400 MHz, CD_3OD)



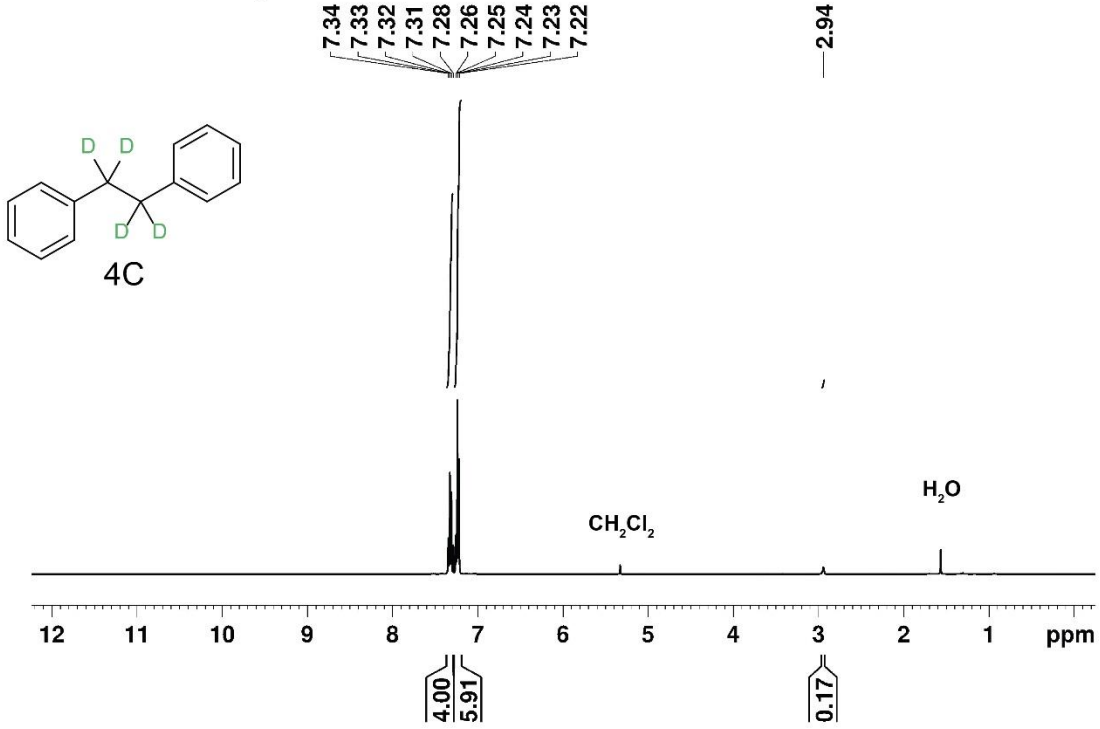
^{2}H NMR (61 MHz, $CHCl_3$)



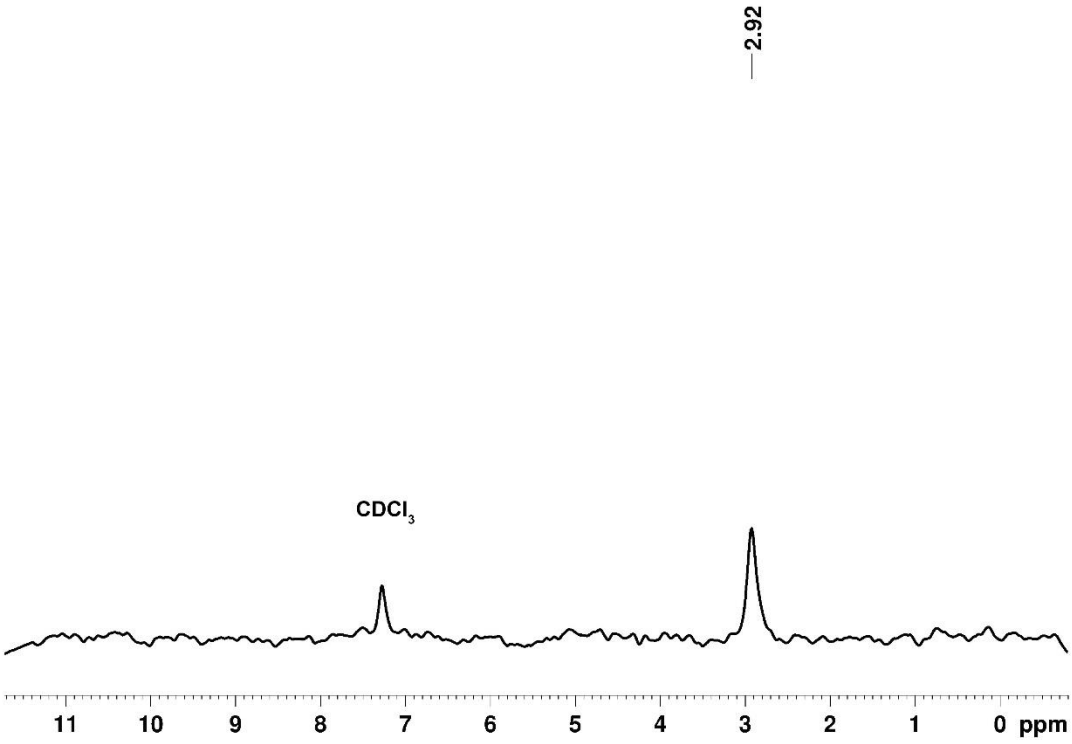
$^{13}C\{^{1}H\}$NMR (101 MHz, CD_3OD)



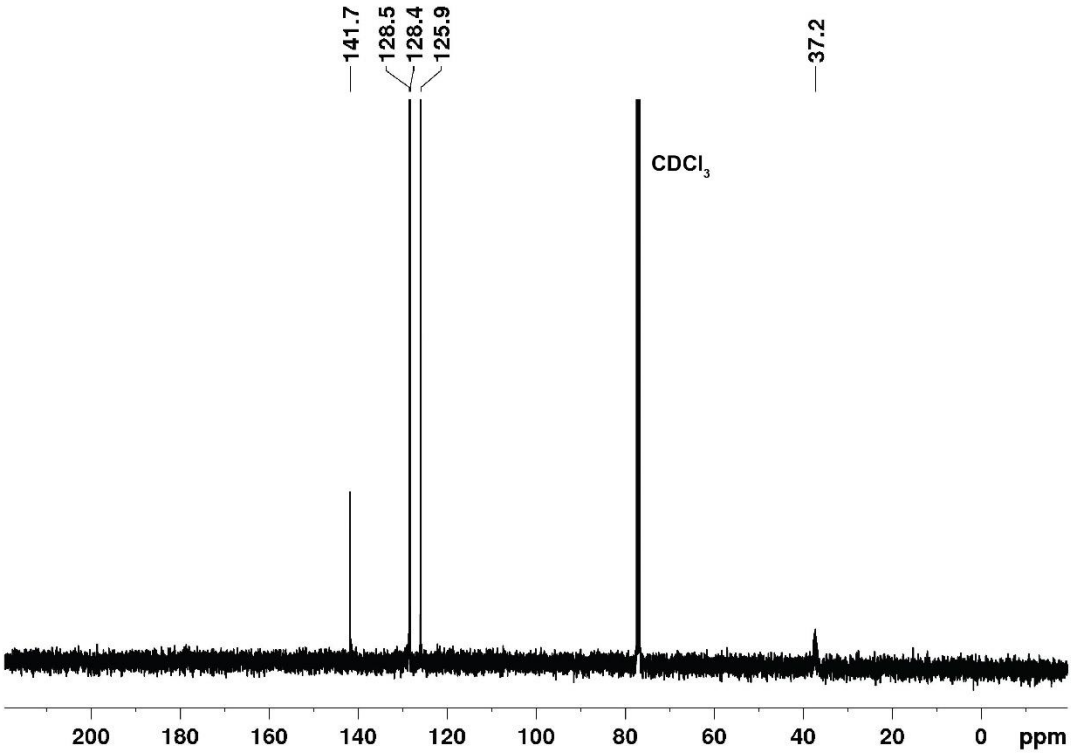
^{1}H NMR (400 MHz, $CDCl_3$)



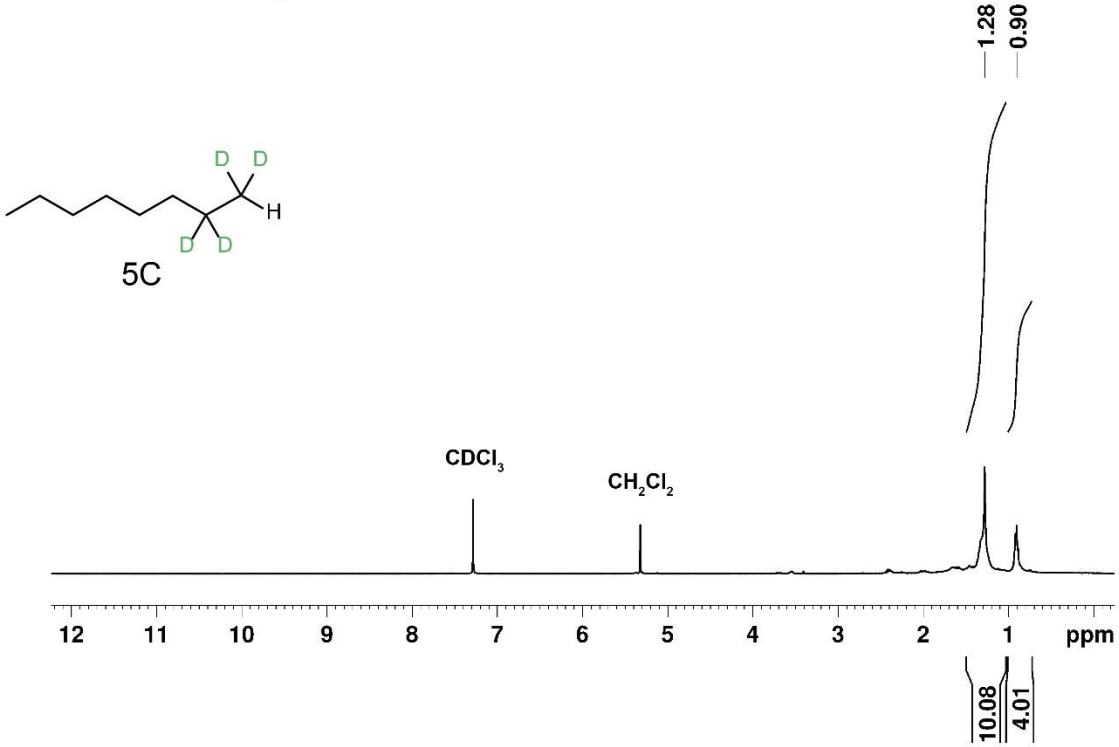
^{2}H NMR (61 MHz, $CHCl_3$)



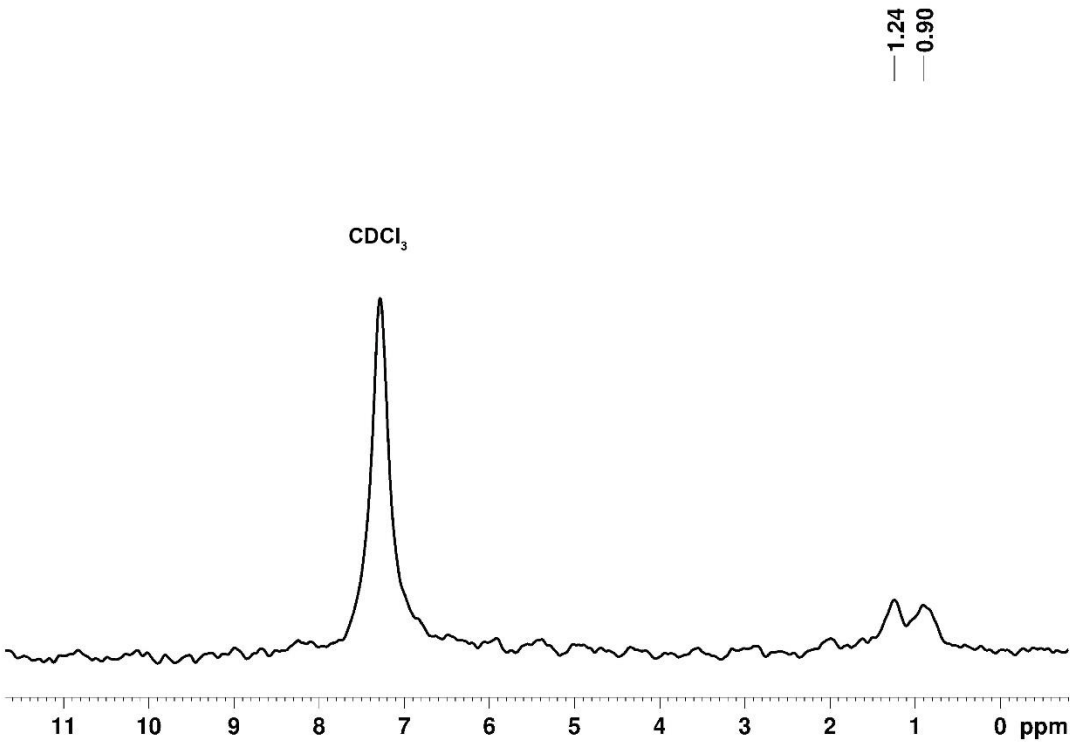
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



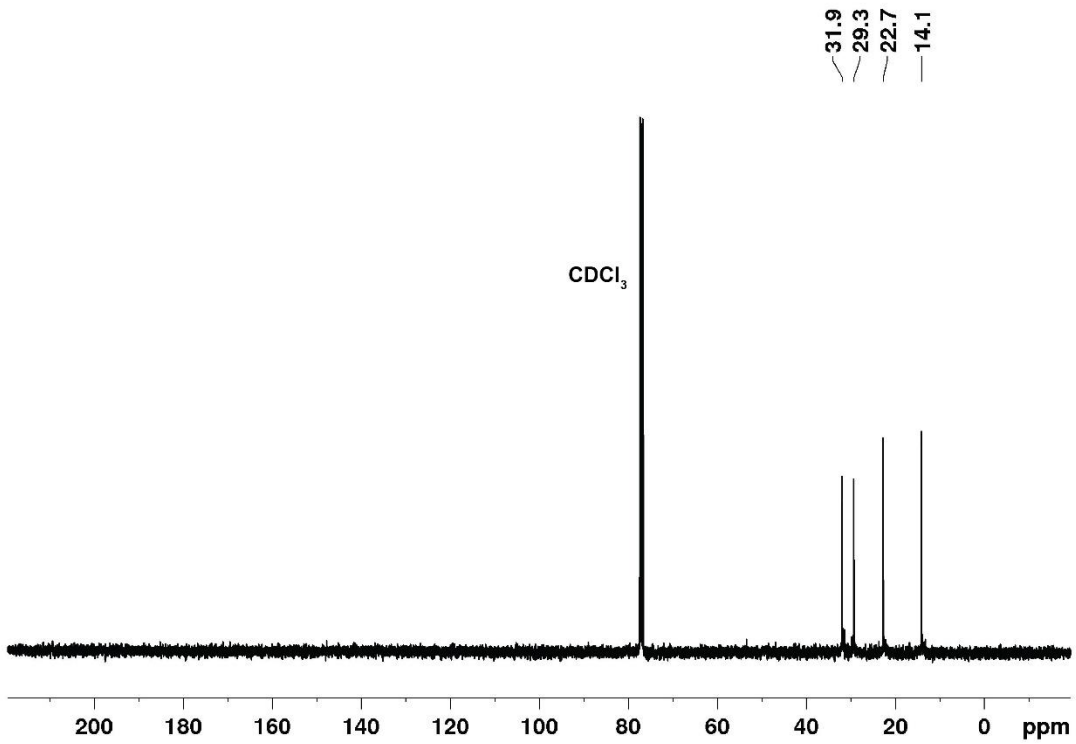
^{1}H NMR (400 MHz, $CDCl_3$)



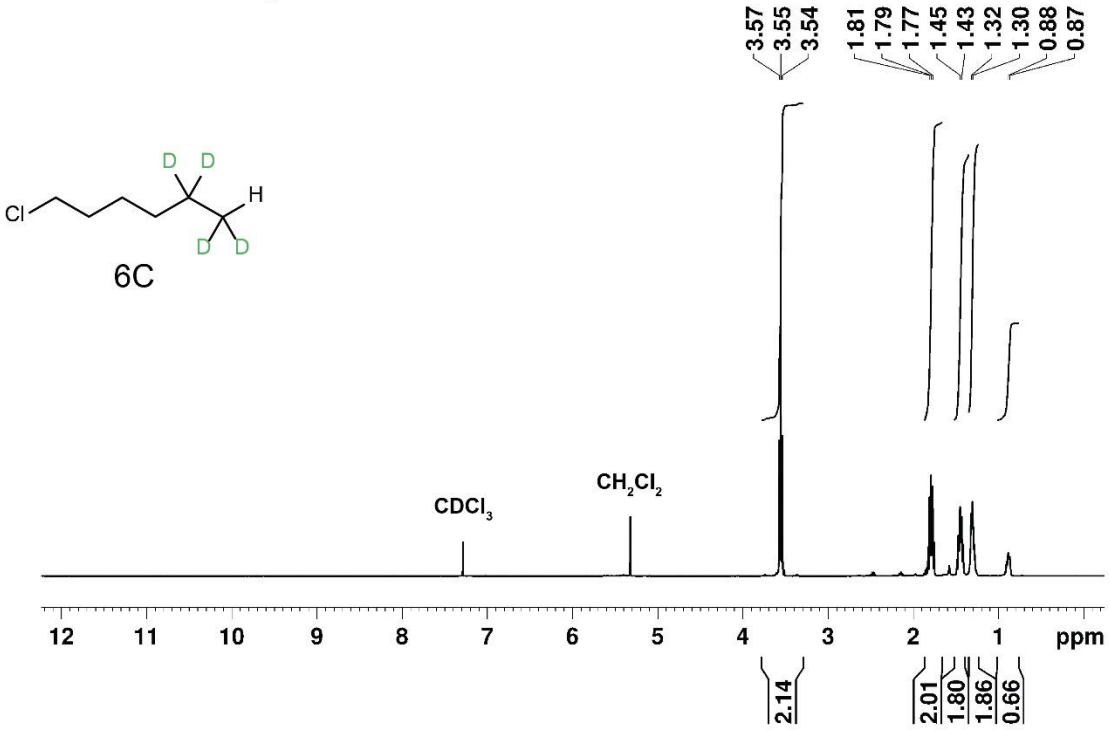
^{2}H NMR (61 MHz, $CHCl_3$)



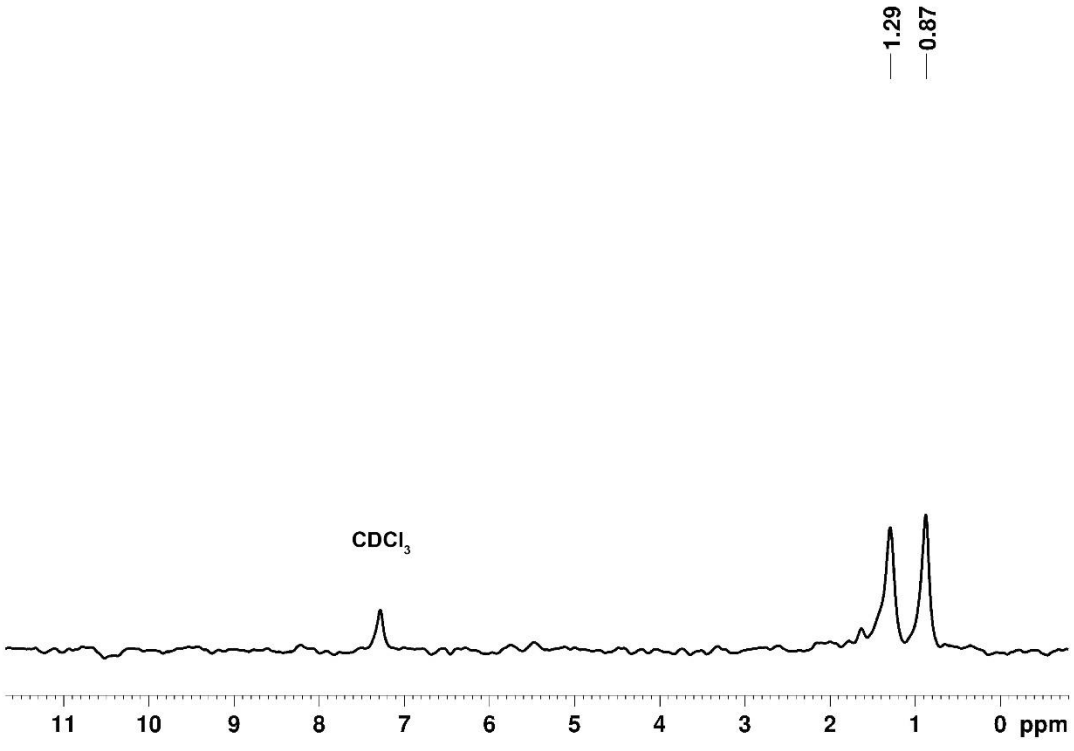
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



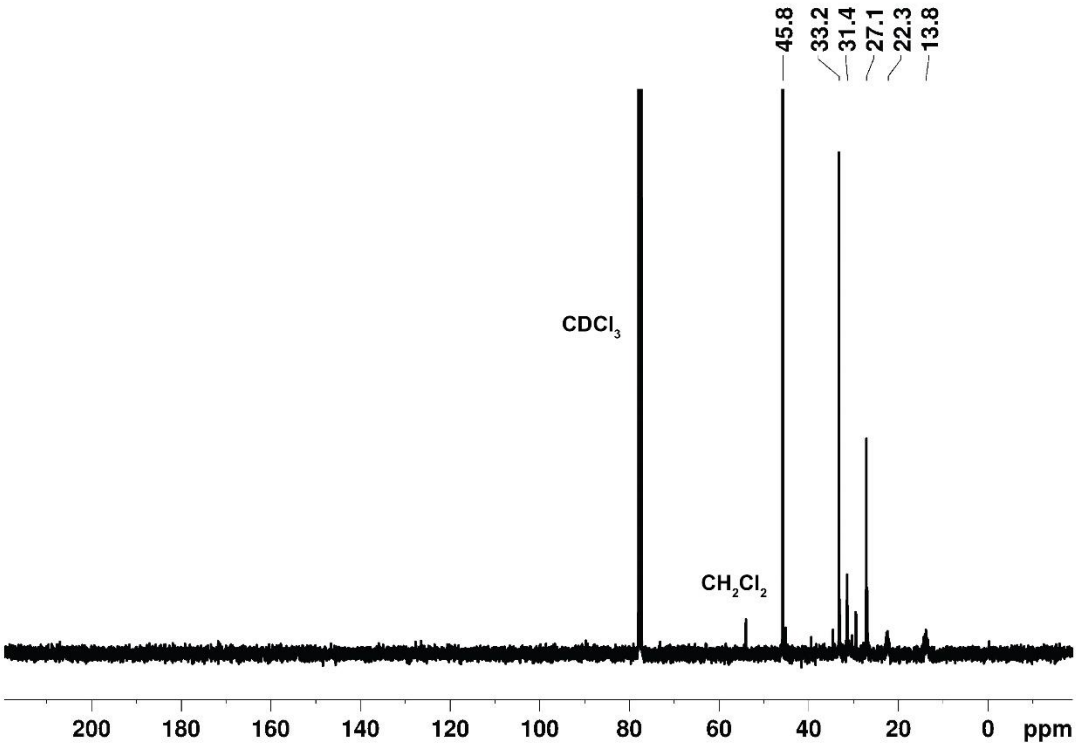
^{1}H NMR (400 MHz, $CDCl_3$)



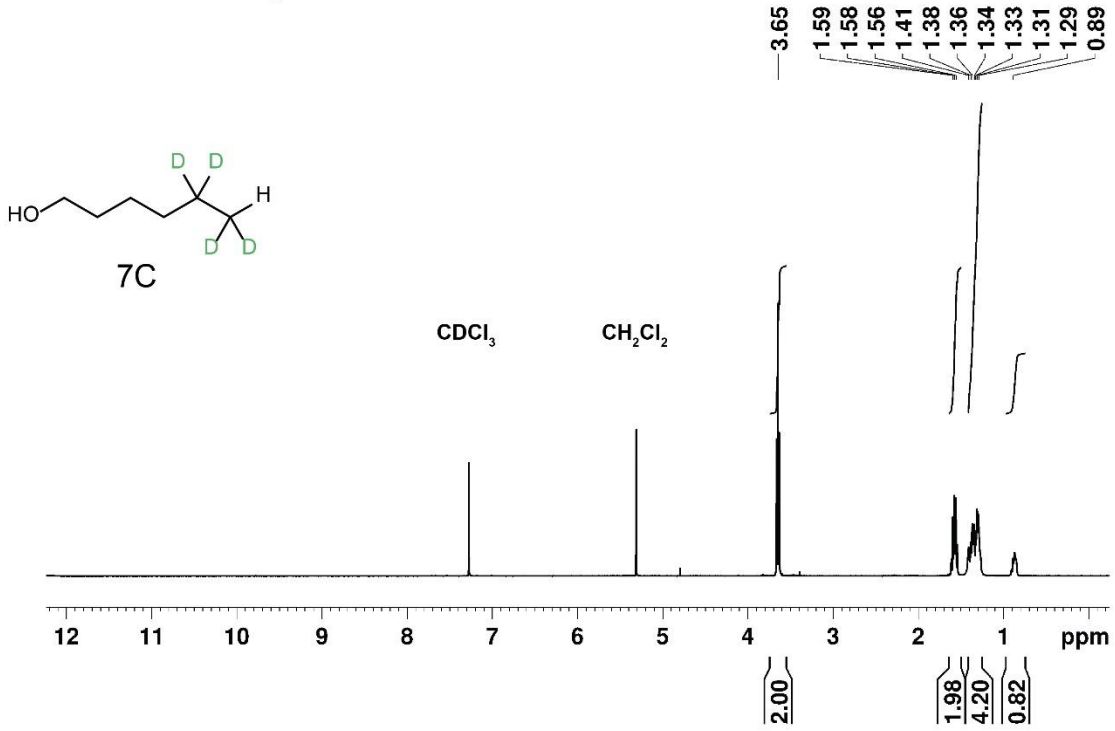
^{2}H NMR (61 MHz, $CHCl_3$)



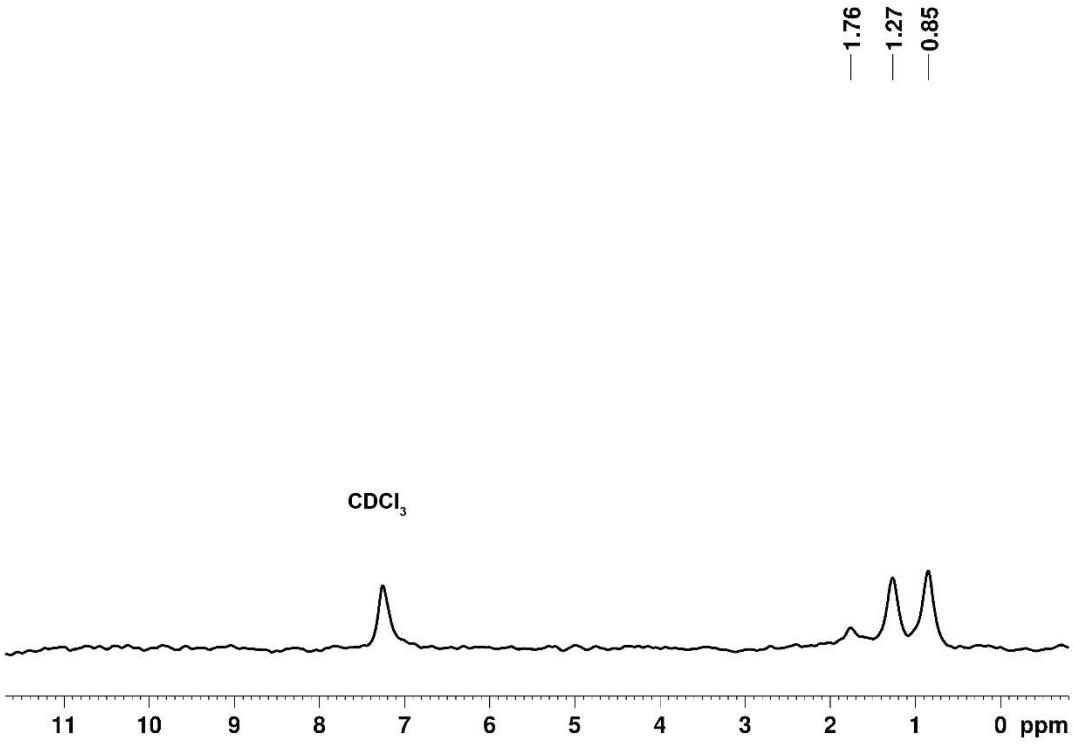
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



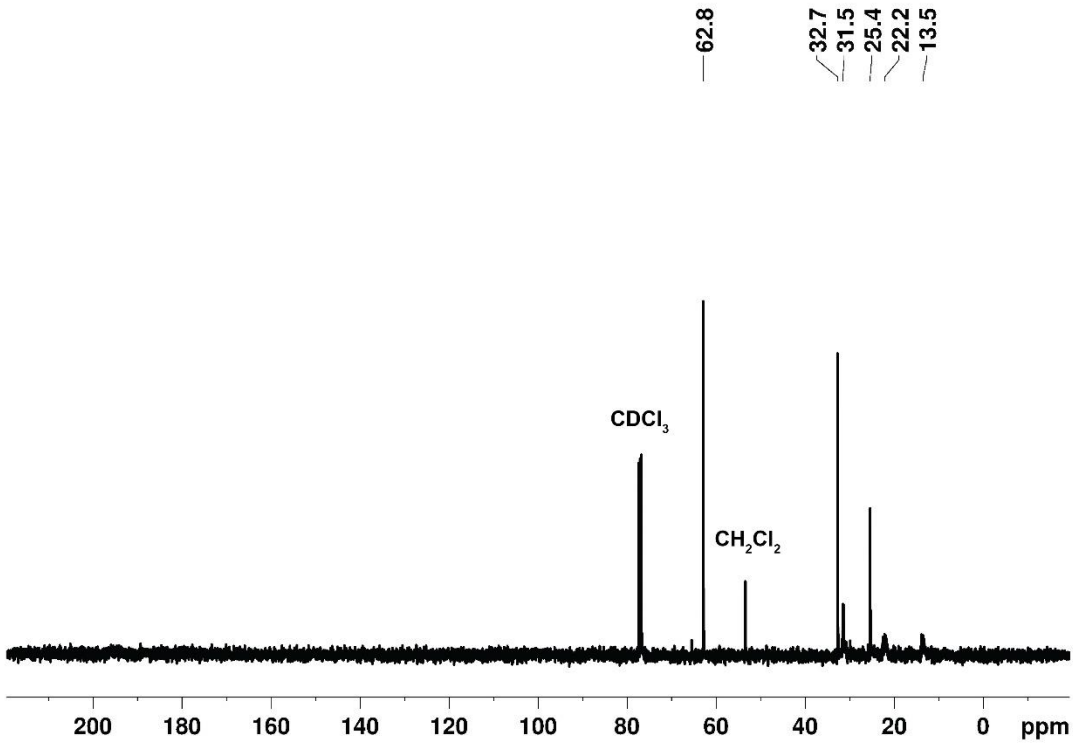
^{1}H NMR (400 MHz, $CDCl_3$)



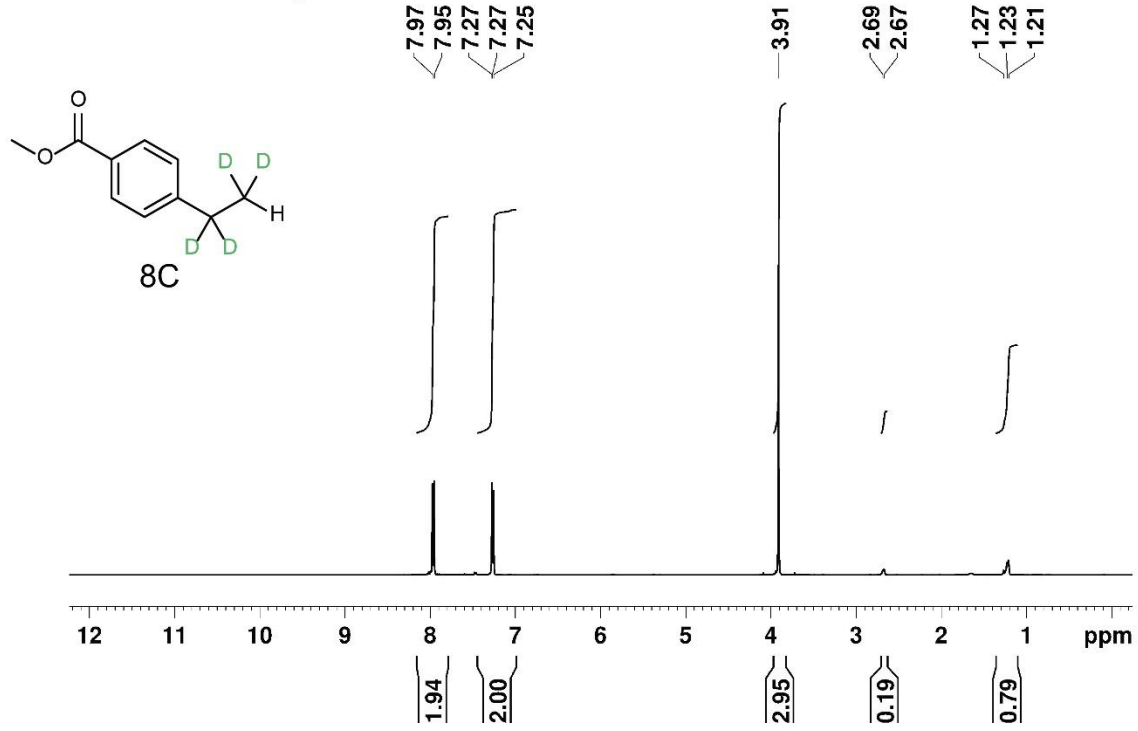
^{2}H NMR (61 MHz, $CHCl_3$)



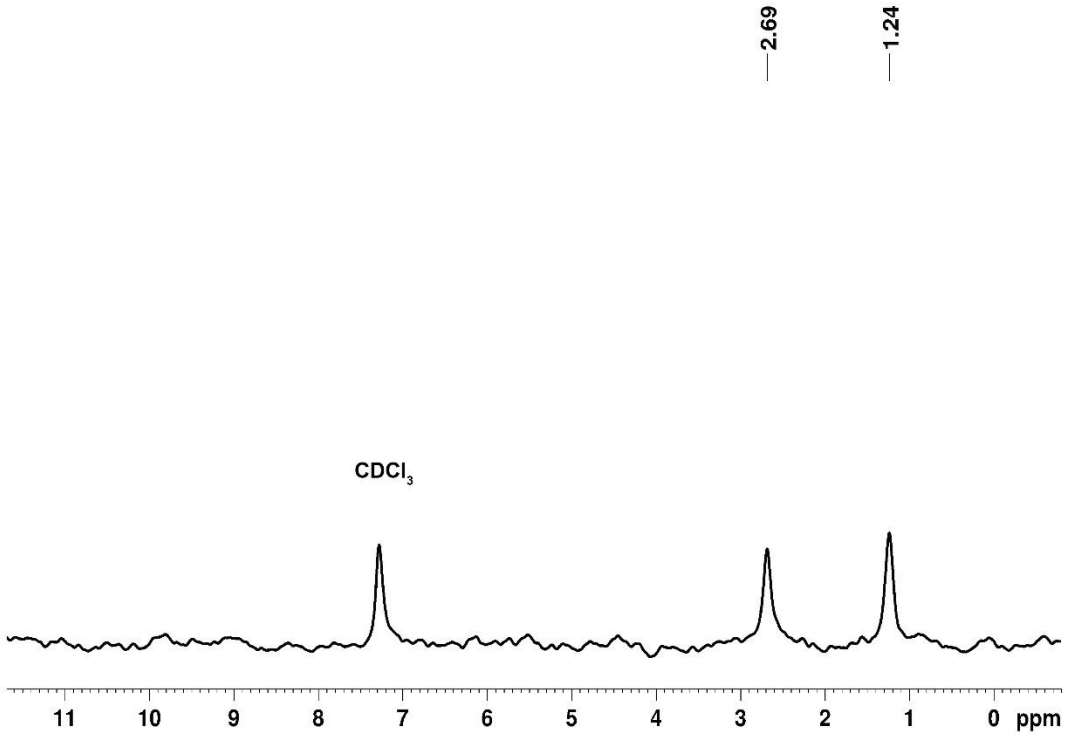
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



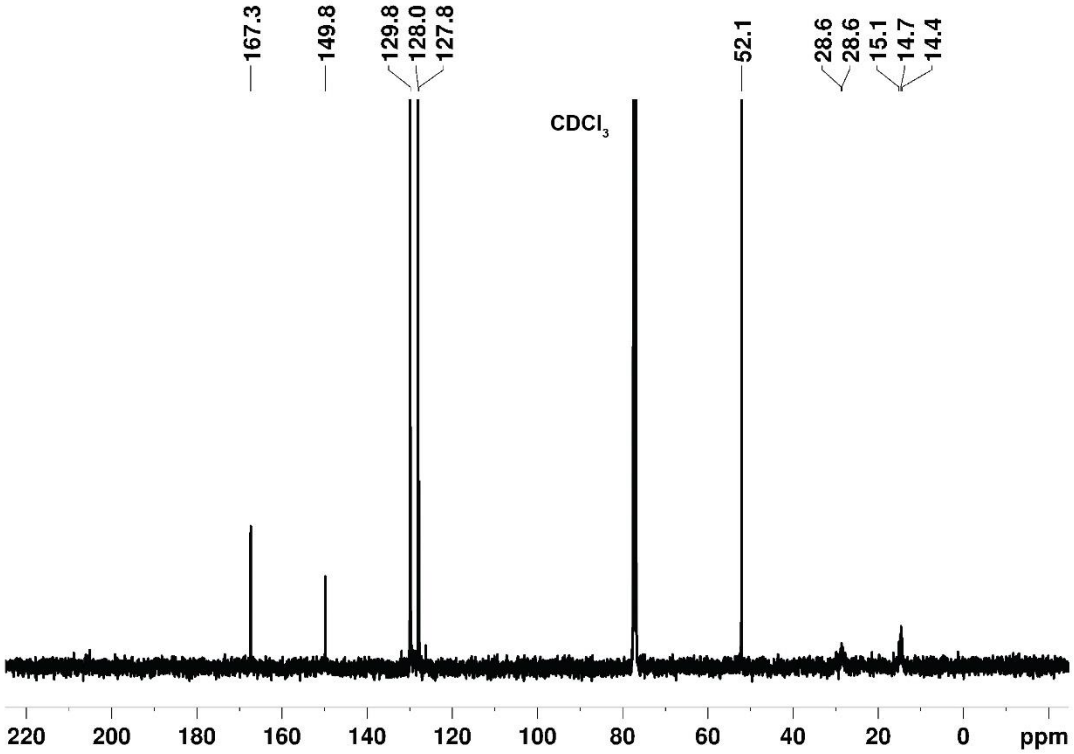
^{1}H NMR (400 MHz, $CDCl_3$)



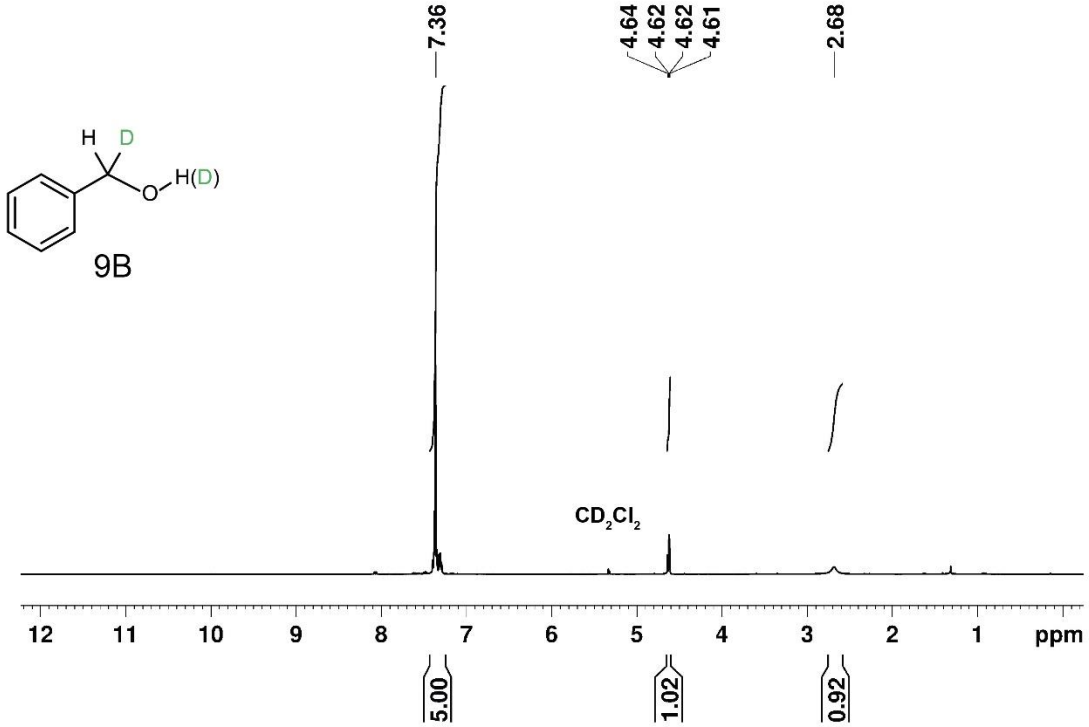
^{2}H NMR (61 MHz, $CHCl_3$)



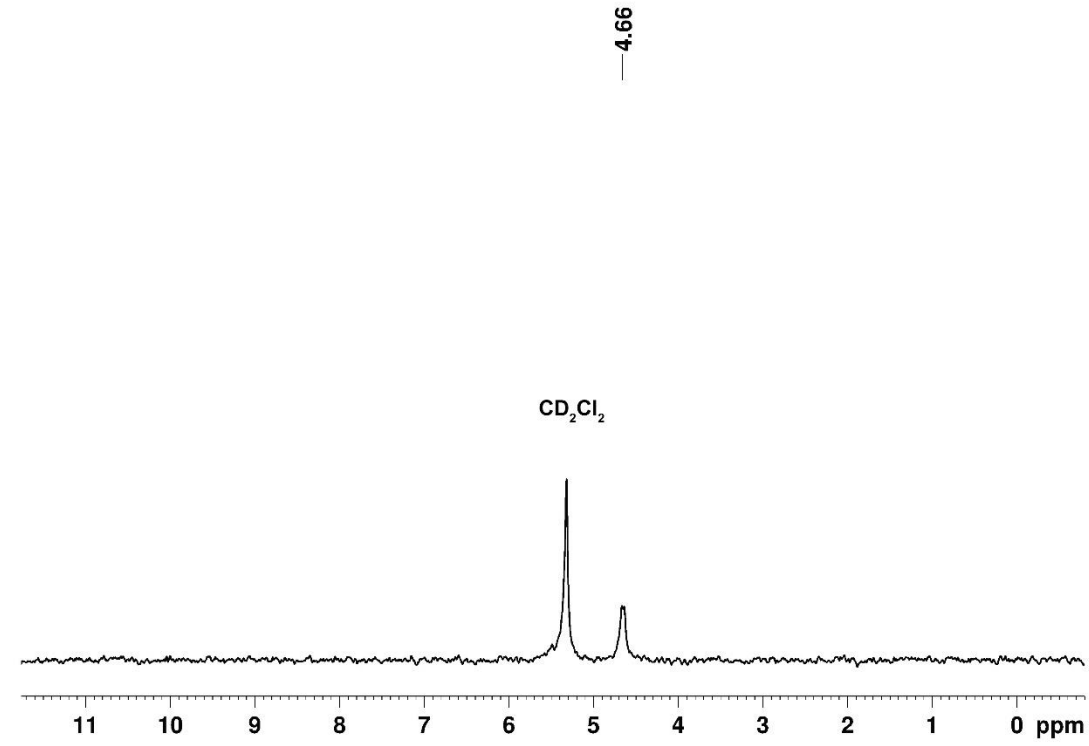
$^{13}C\{^{1}H\}$NMR (101 MHz, $CDCl_3$)



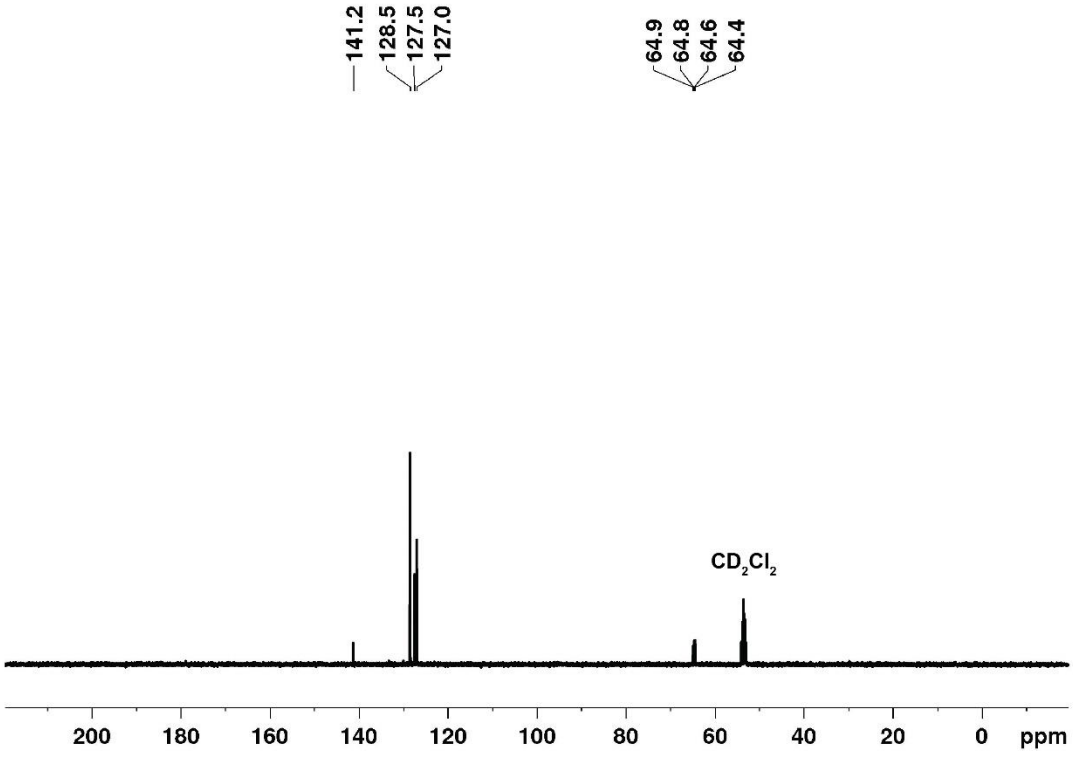
^{1}H NMR (400 MHz, CD_2Cl_2)



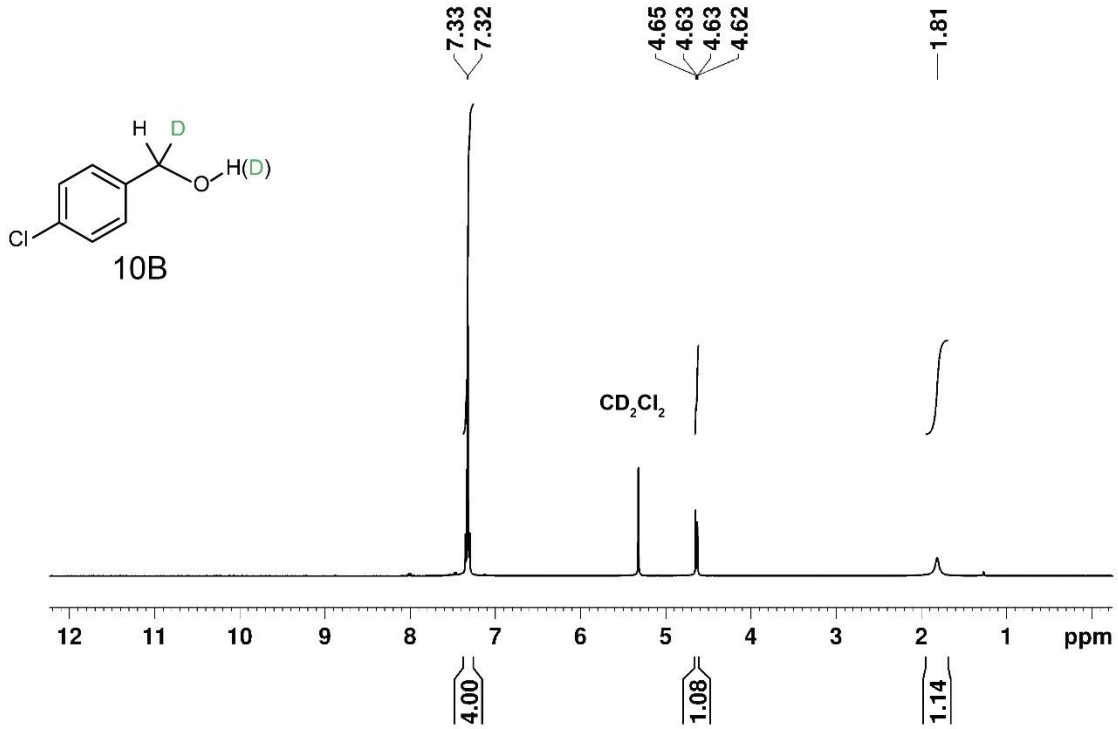
^{2}H NMR (61 MHz, CH_2Cl_2)



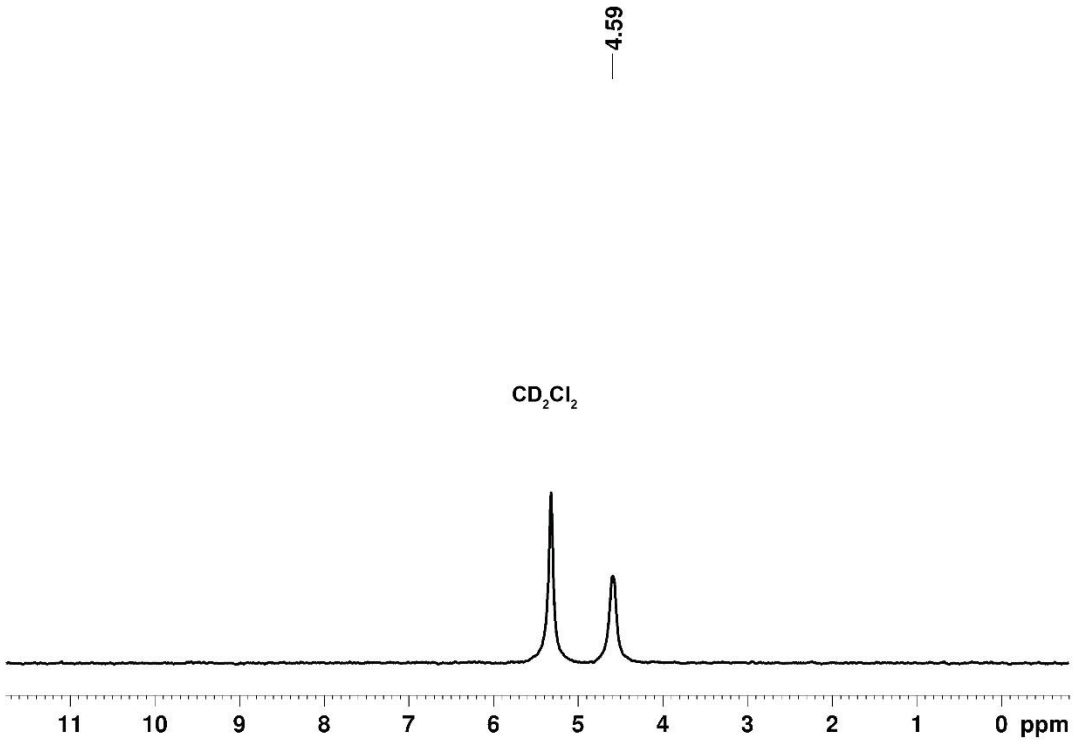
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



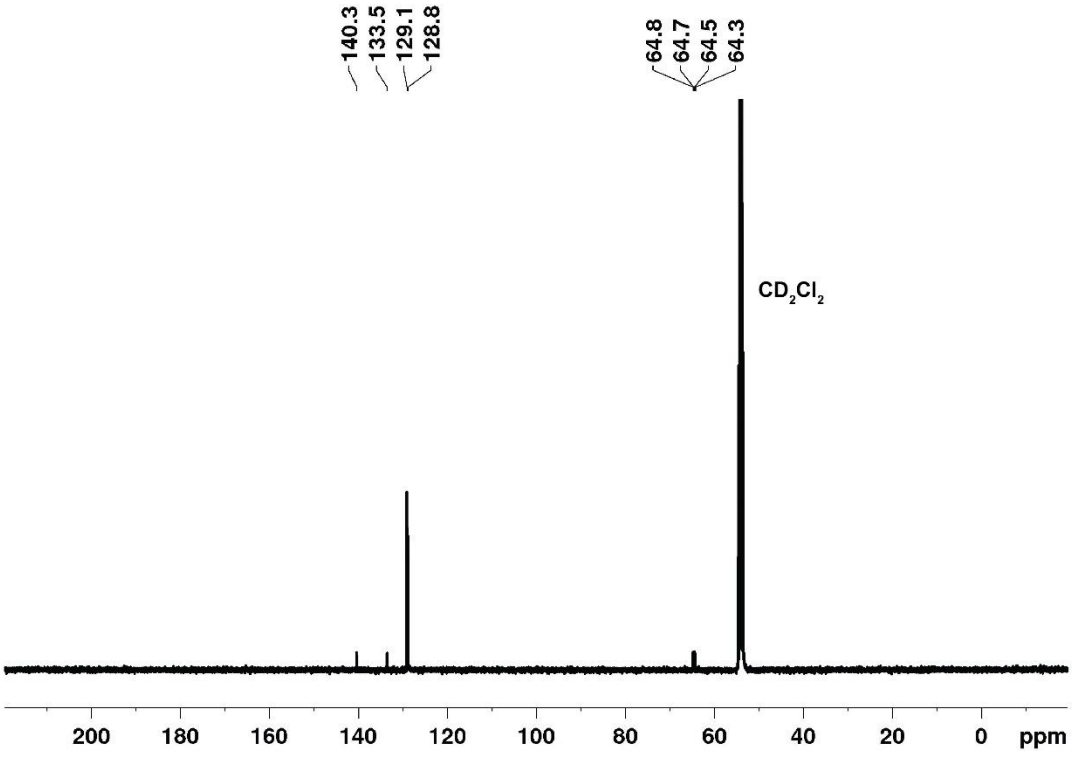
^{1}H NMR (400 MHz, CD_2Cl_2)



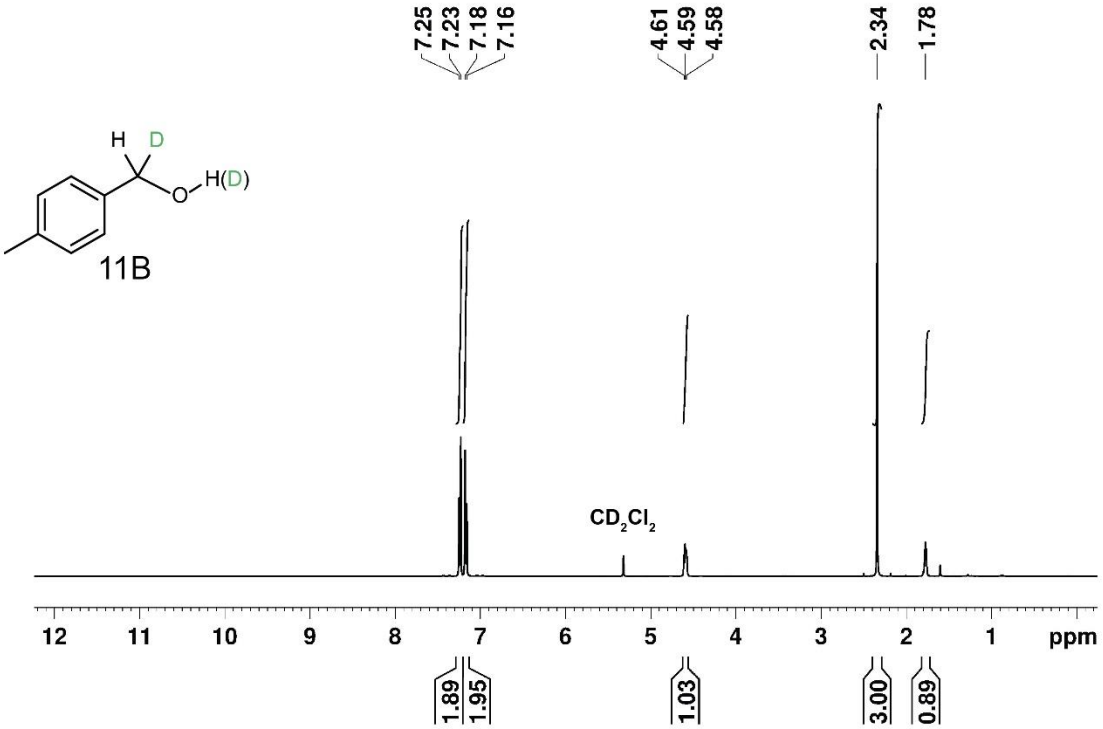
^{2}H NMR (61 MHz, CH_2Cl_2)



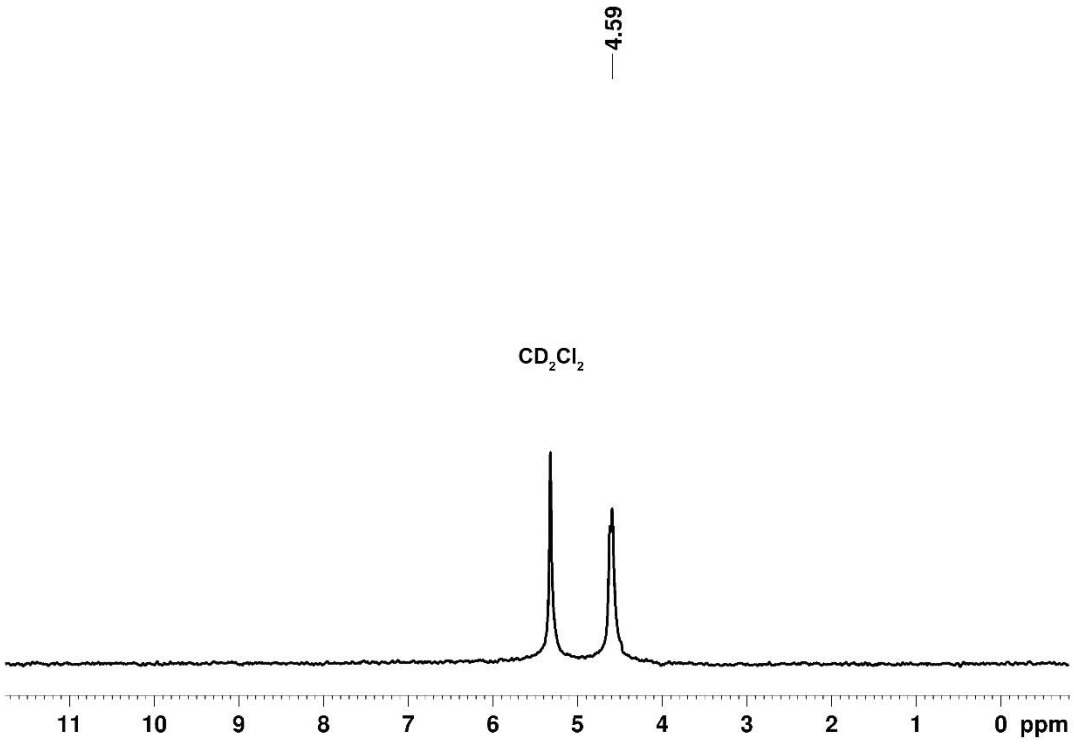
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



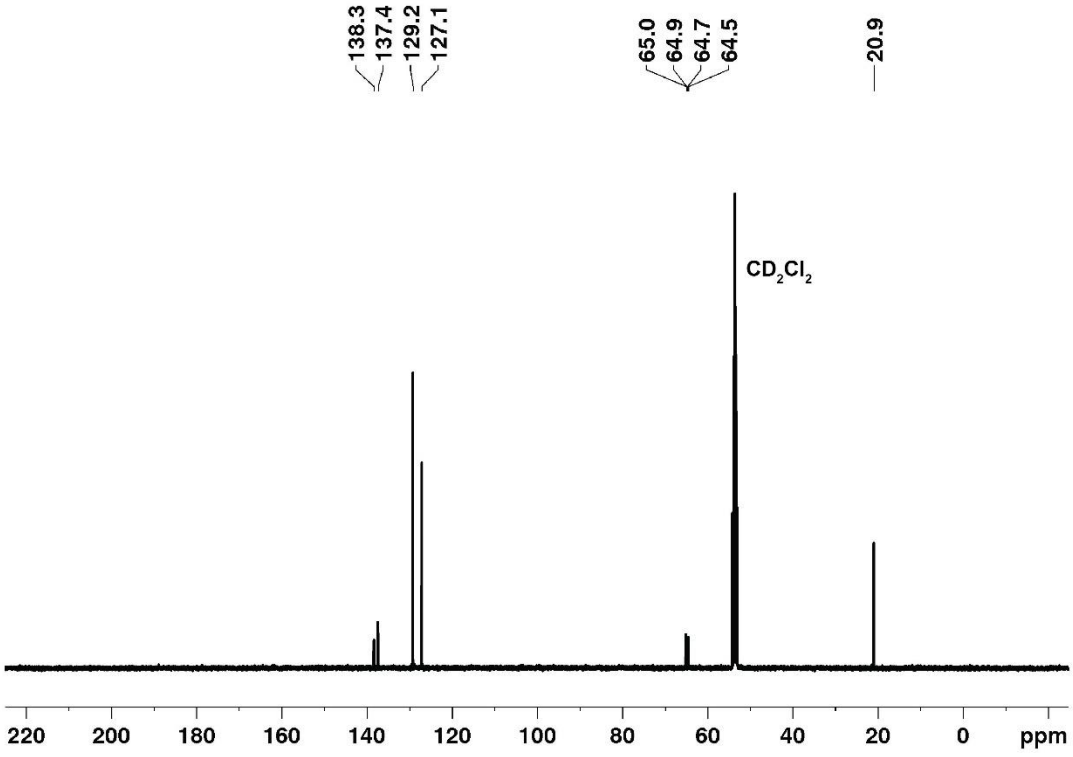
^{1}H NMR (400 MHz, CD_2Cl_2)



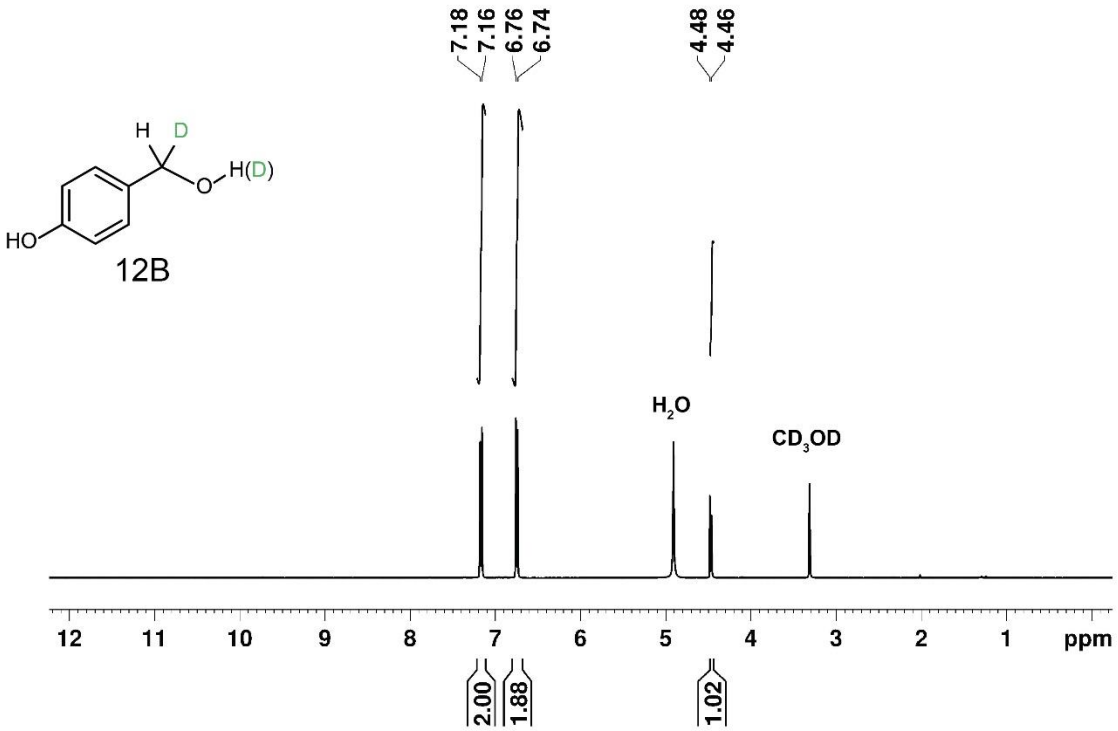
^{2}H NMR (61 MHz, CH_2Cl_2)



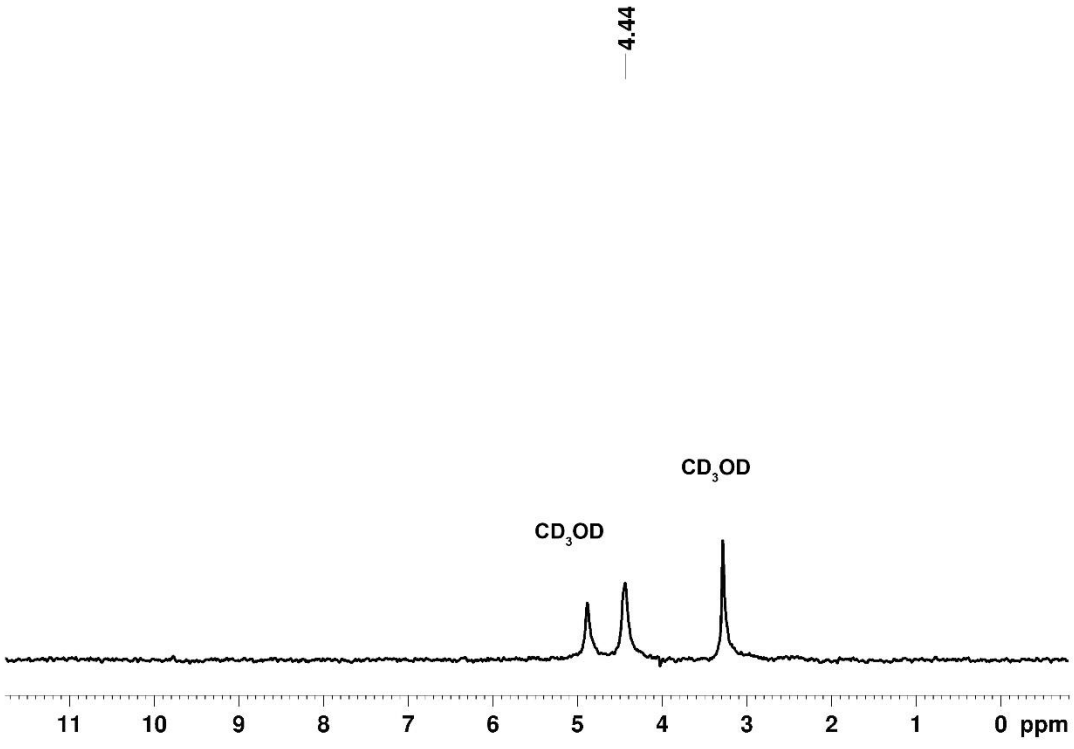
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



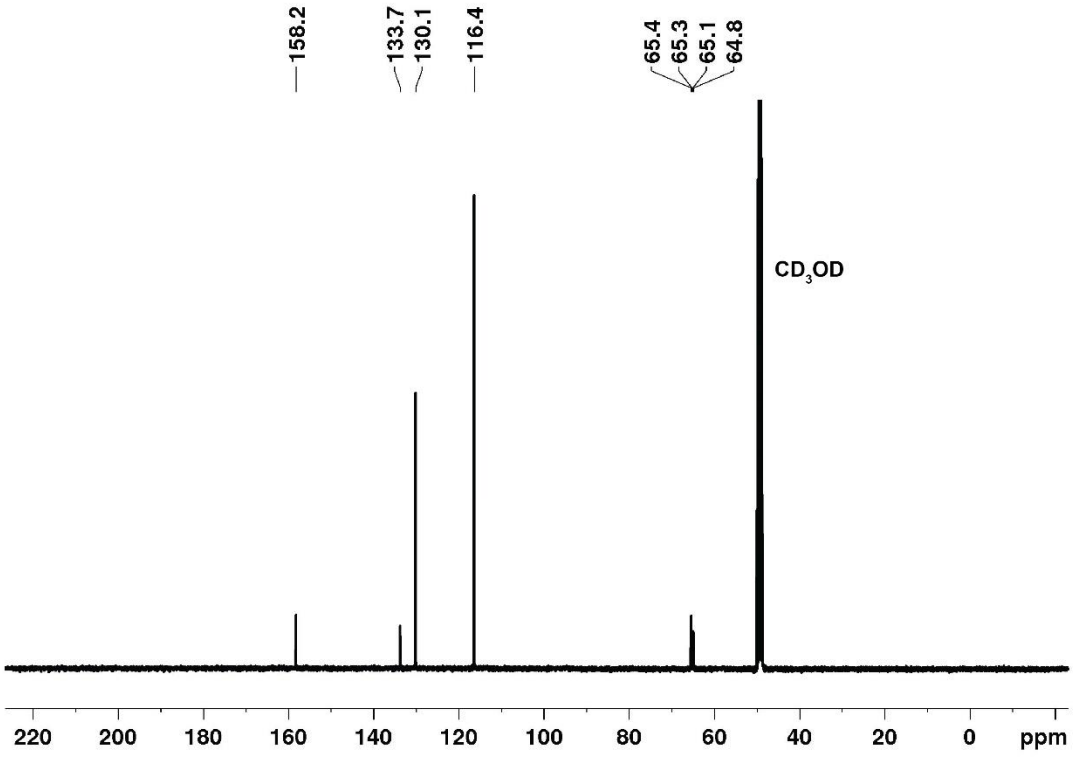
^{1}H NMR (400 MHz, CD_3OD)



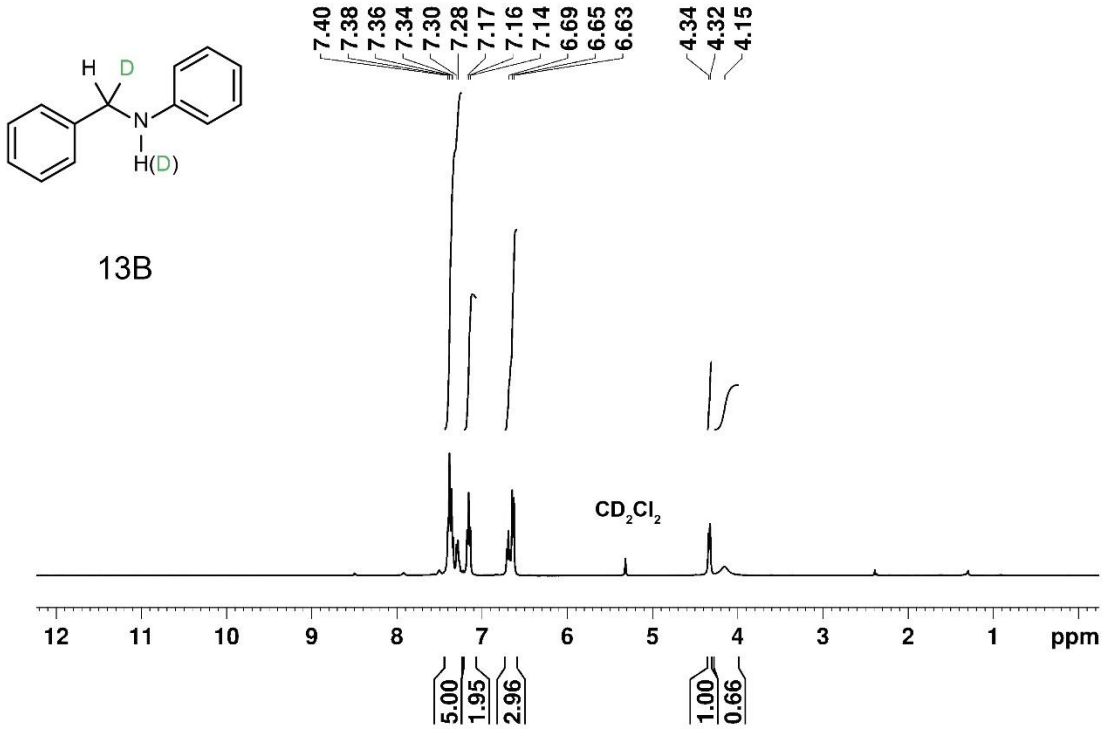
^{2}H NMR (61 MHz, CH_3OH)



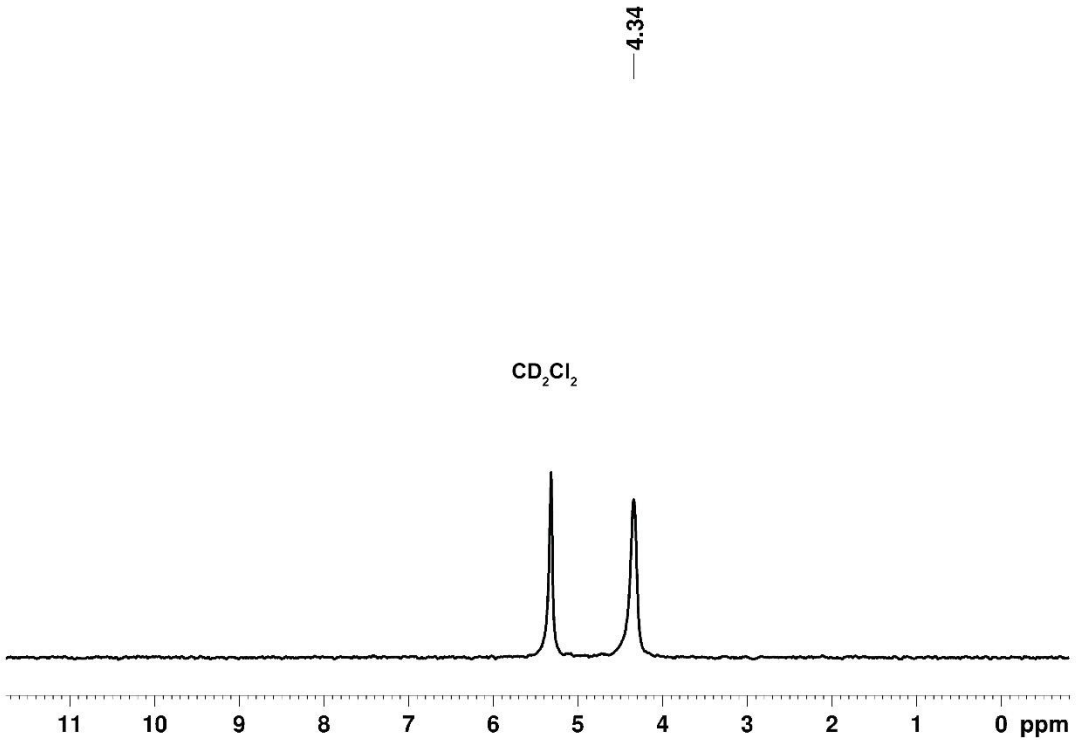
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD)



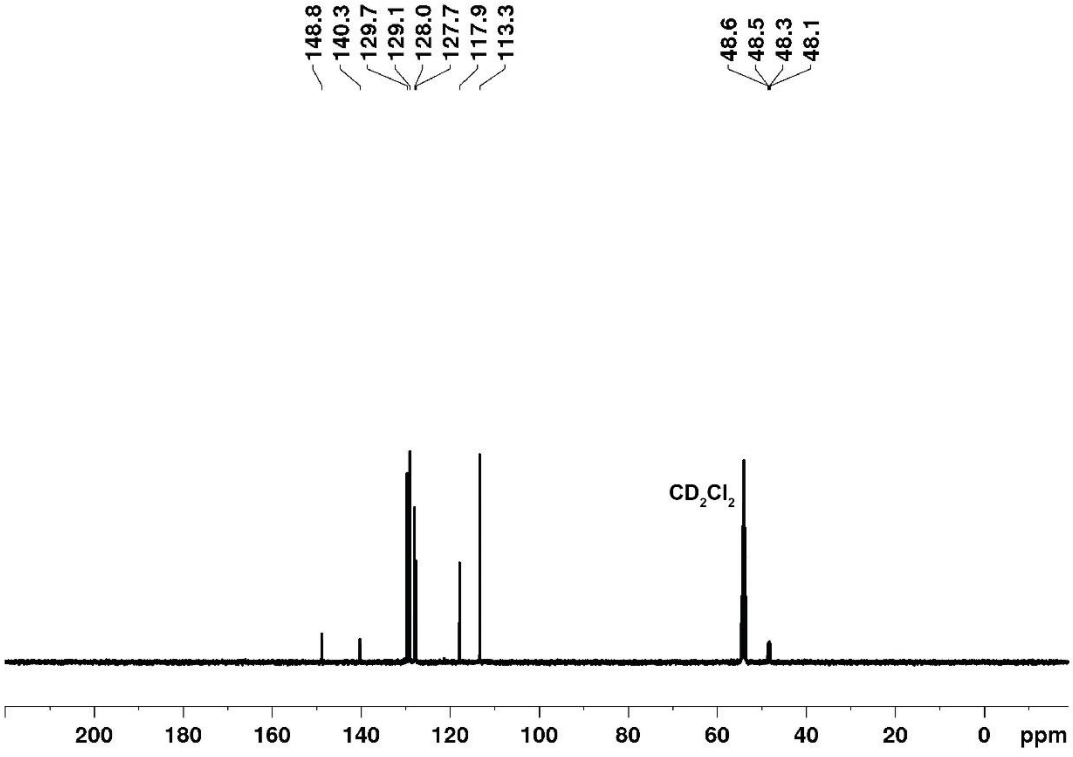
^{1}H NMR (400 MHz, CD_2Cl_2)



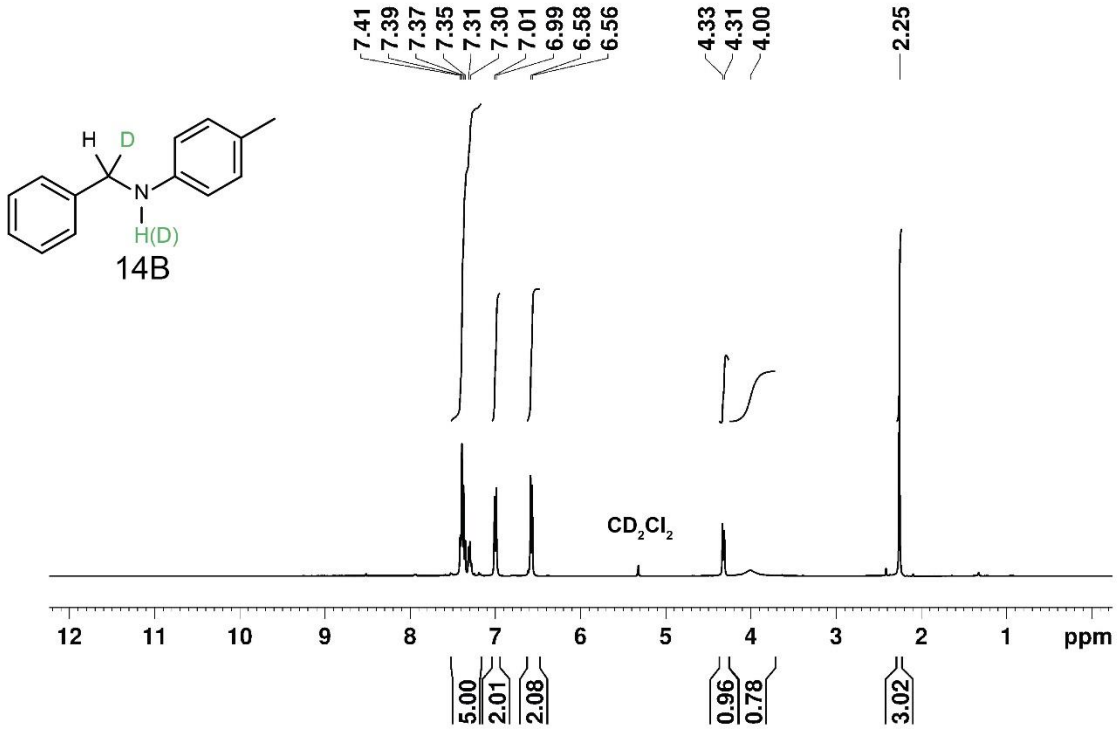
^{2}H NMR (61 MHz, CH_2Cl_2)



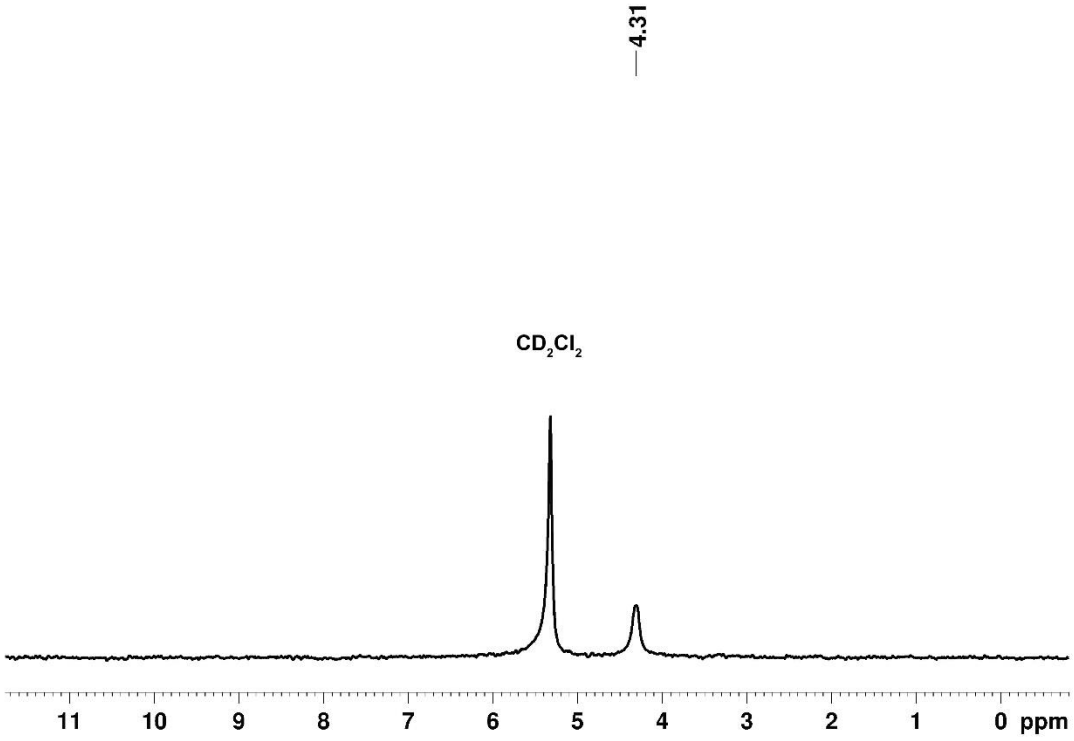
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



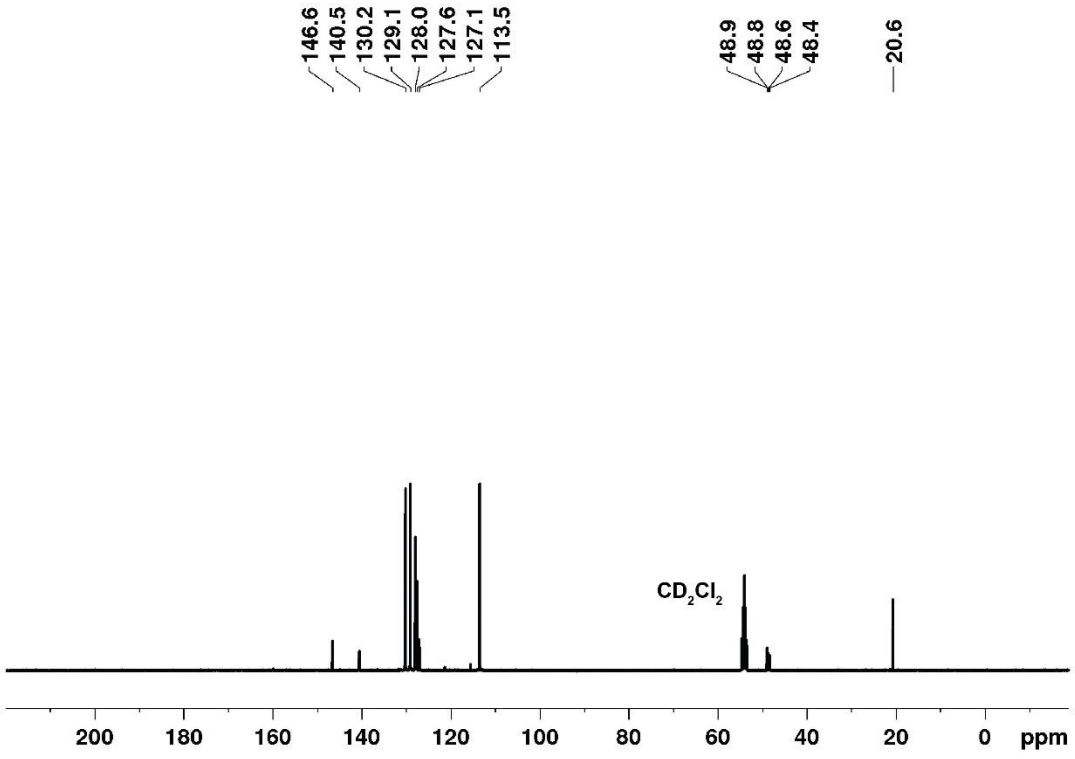
^{1}H NMR (400 MHz, CD_2Cl_2)



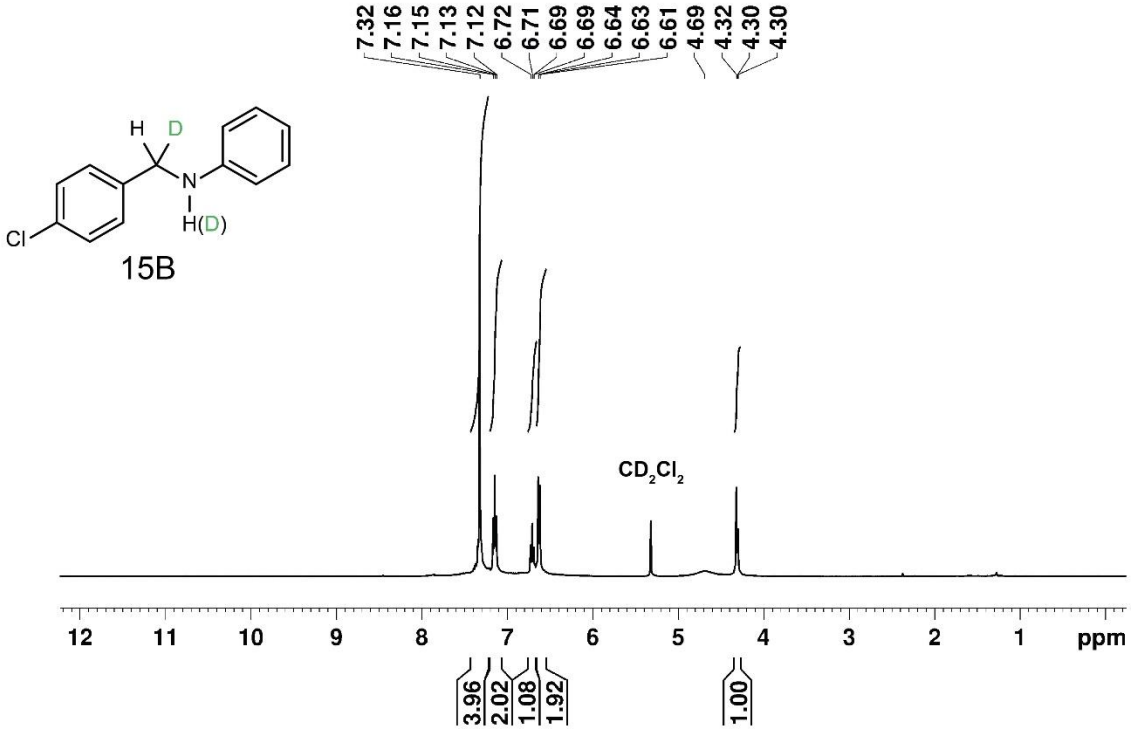
^{2}H NMR (61 MHz, CH_2Cl_2)



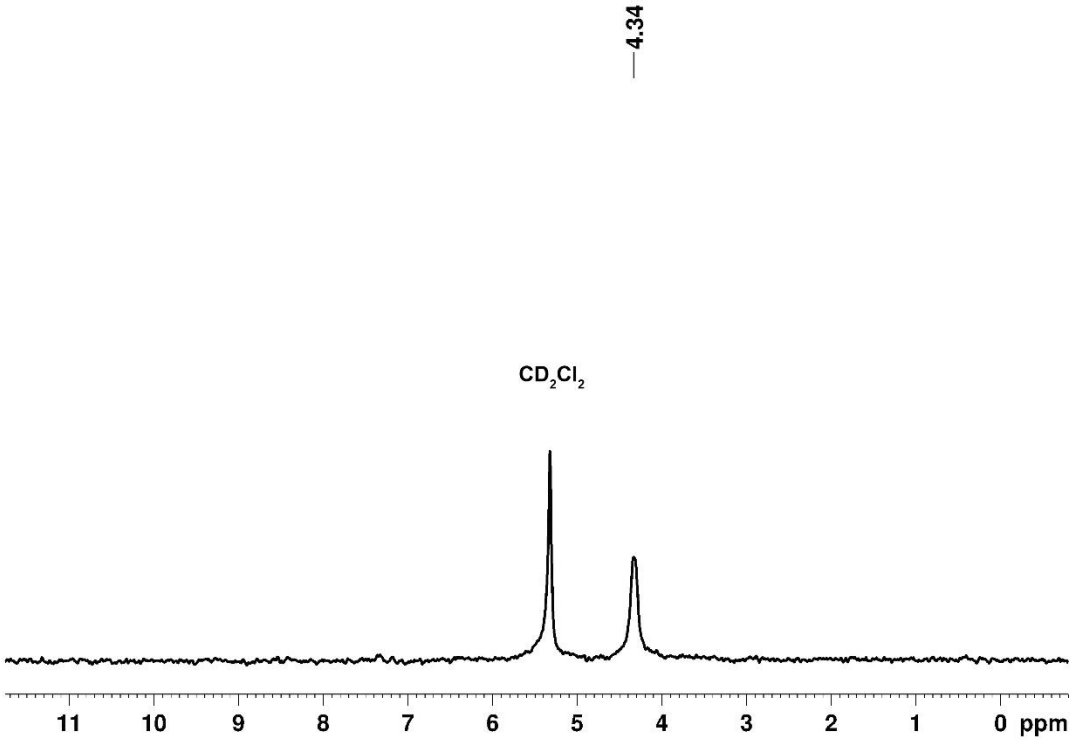
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



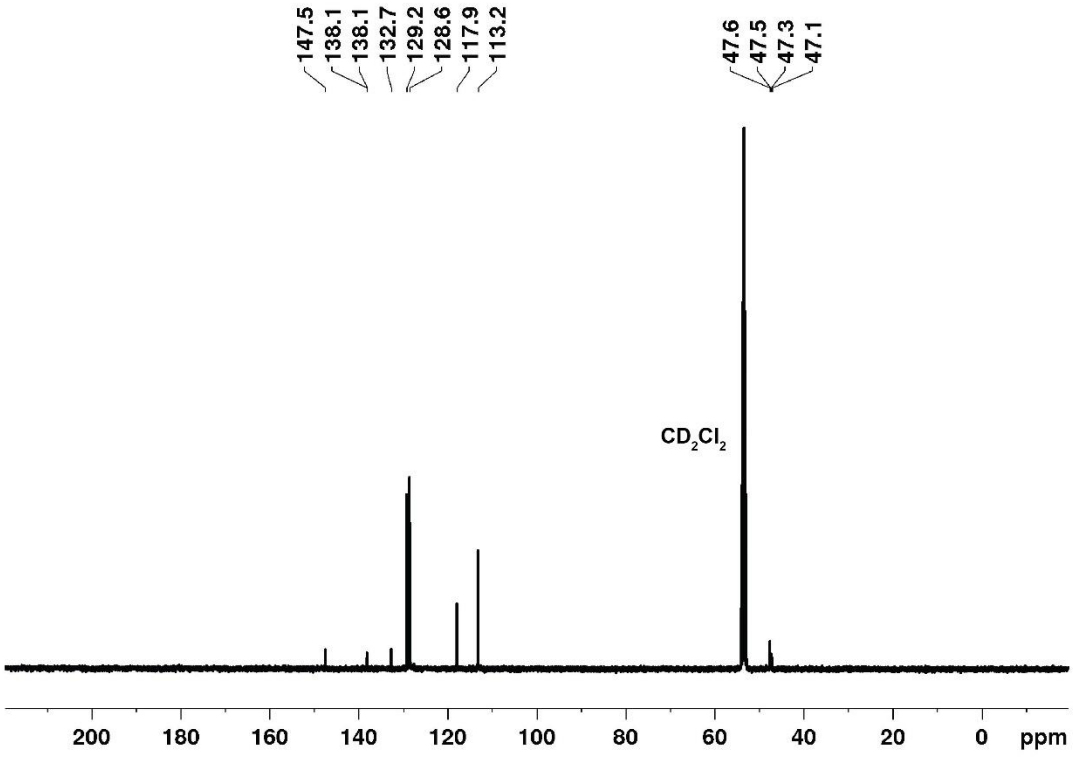
^{1}H NMR (400 MHz, CD_2Cl_2)



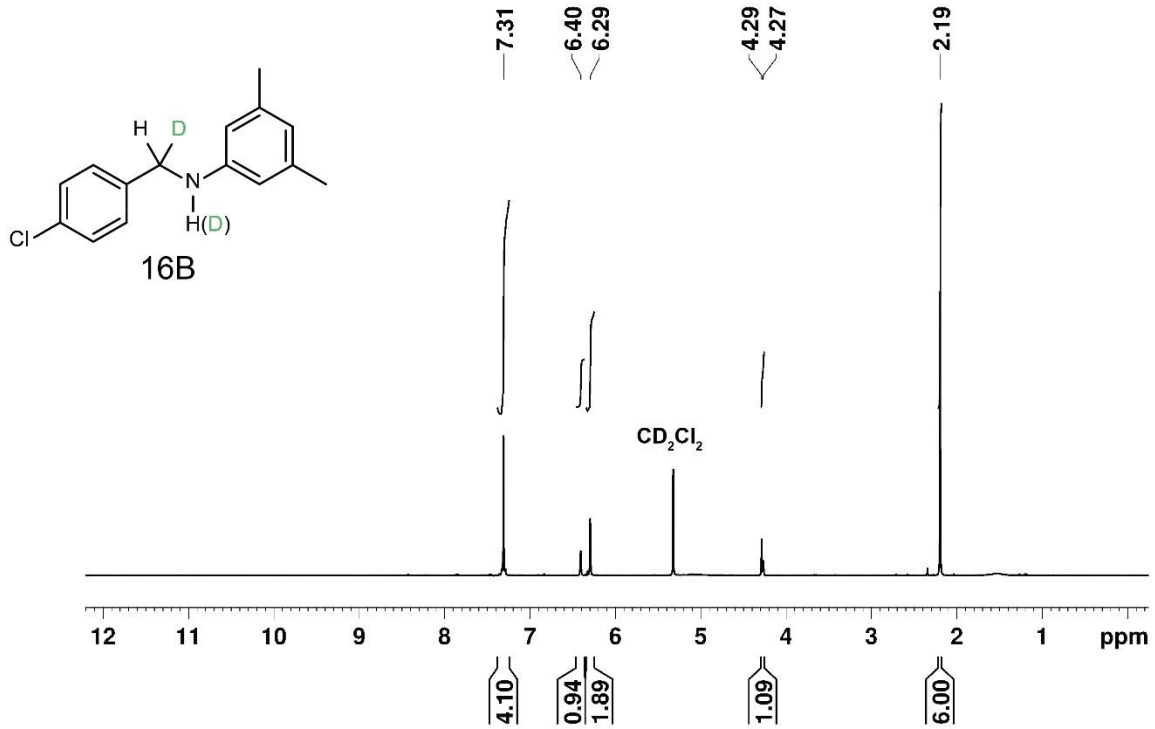
^{2}H NMR (61 MHz, CH_2Cl_2)



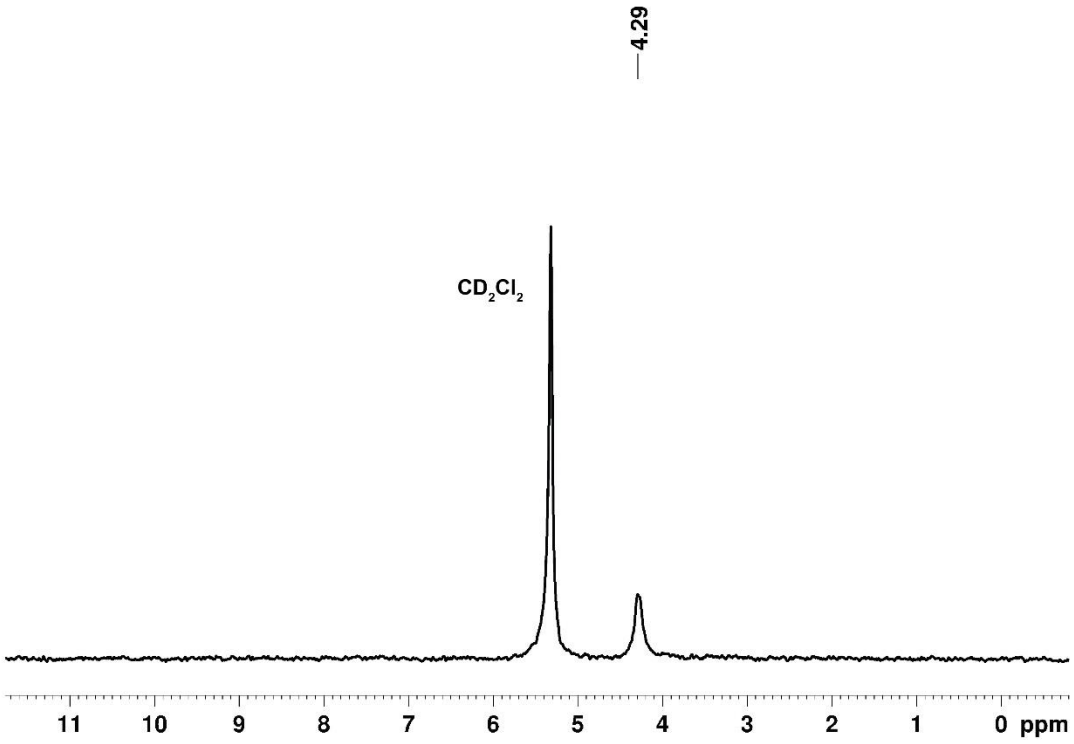
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



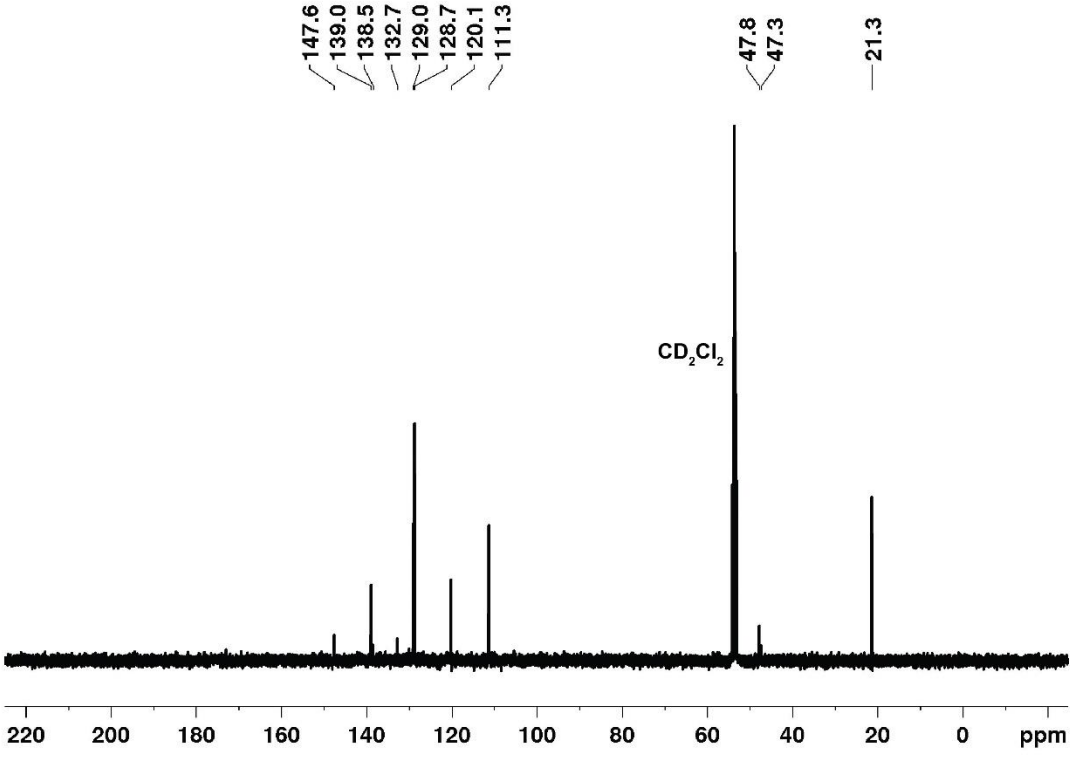
^{1}H NMR (400 MHz, CD_2Cl_2)



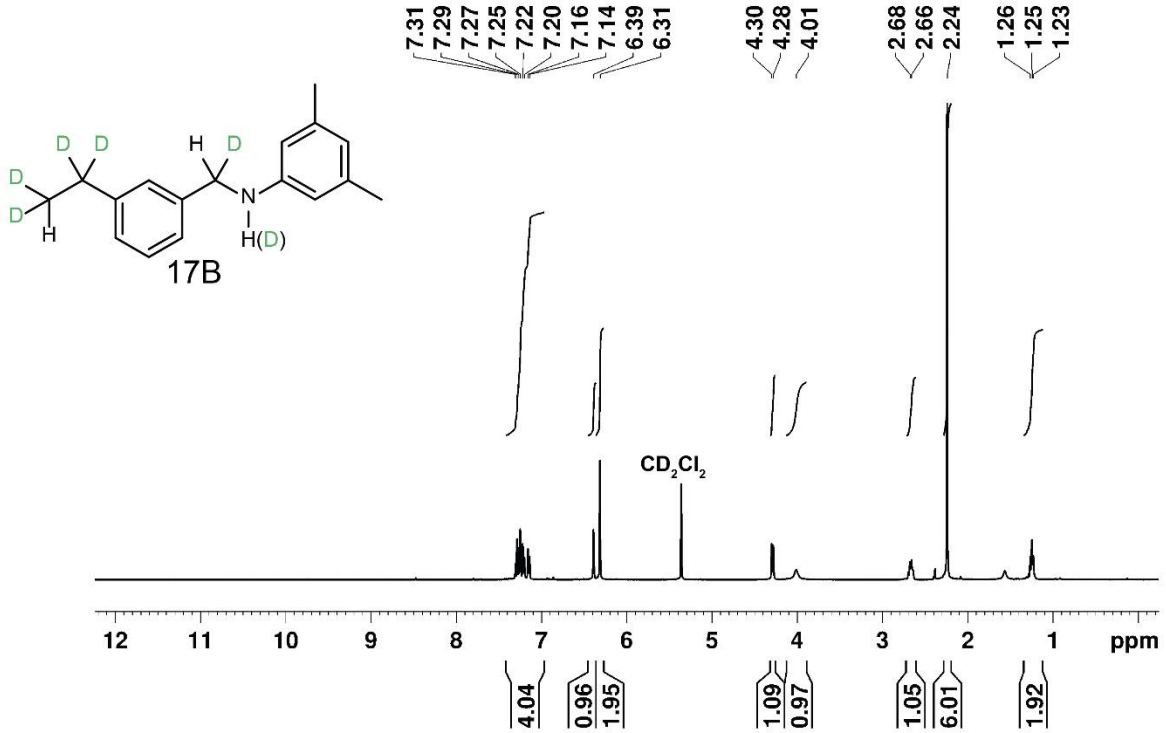
^{2}H NMR (61 MHz, CH_2Cl_2)



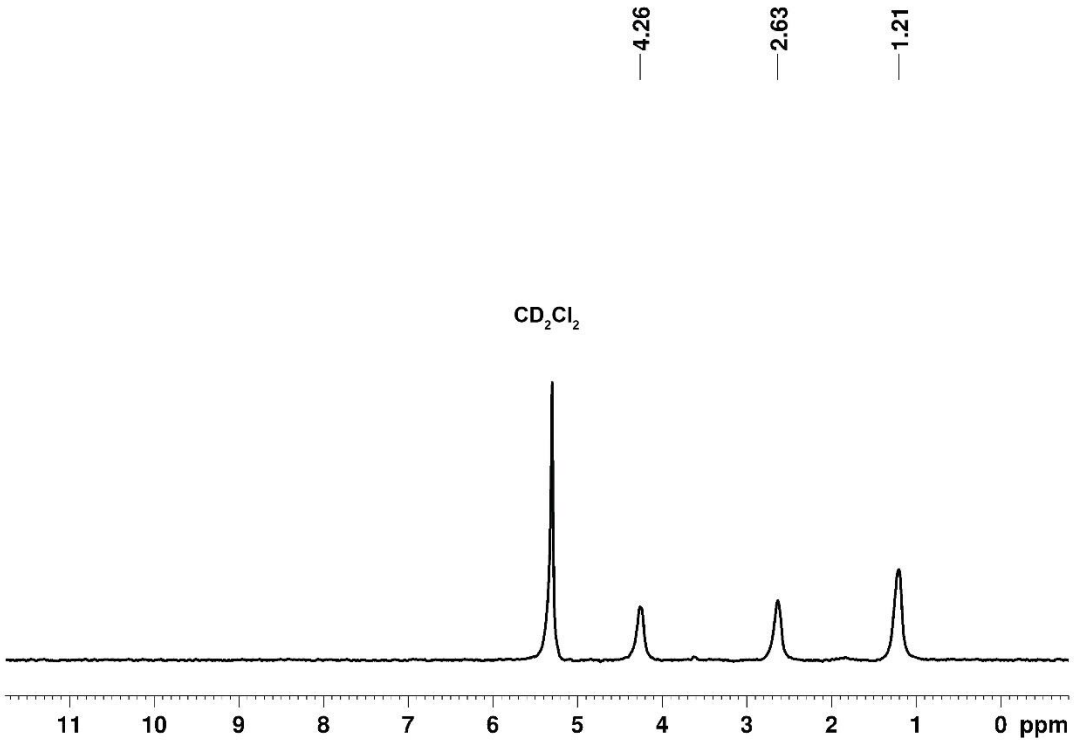
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



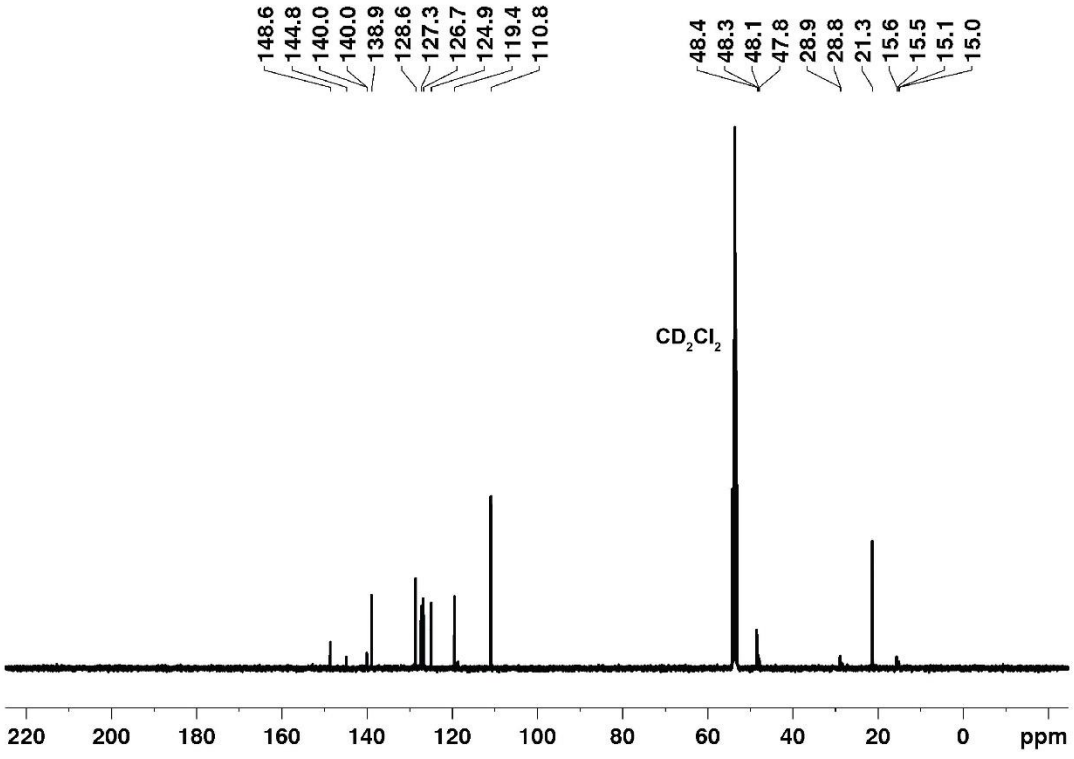
^{1}H NMR (400 MHz, CD_2Cl_2)



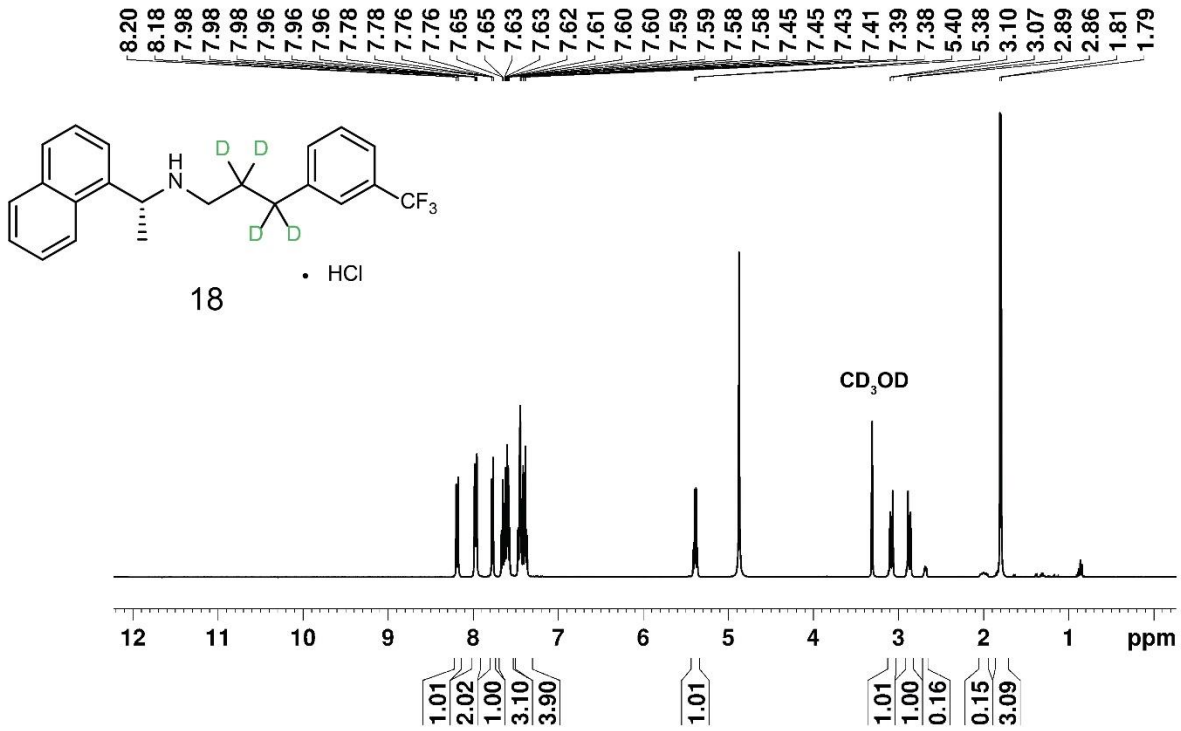
^{2}H NMR (61 MHz, CH_2Cl_2)



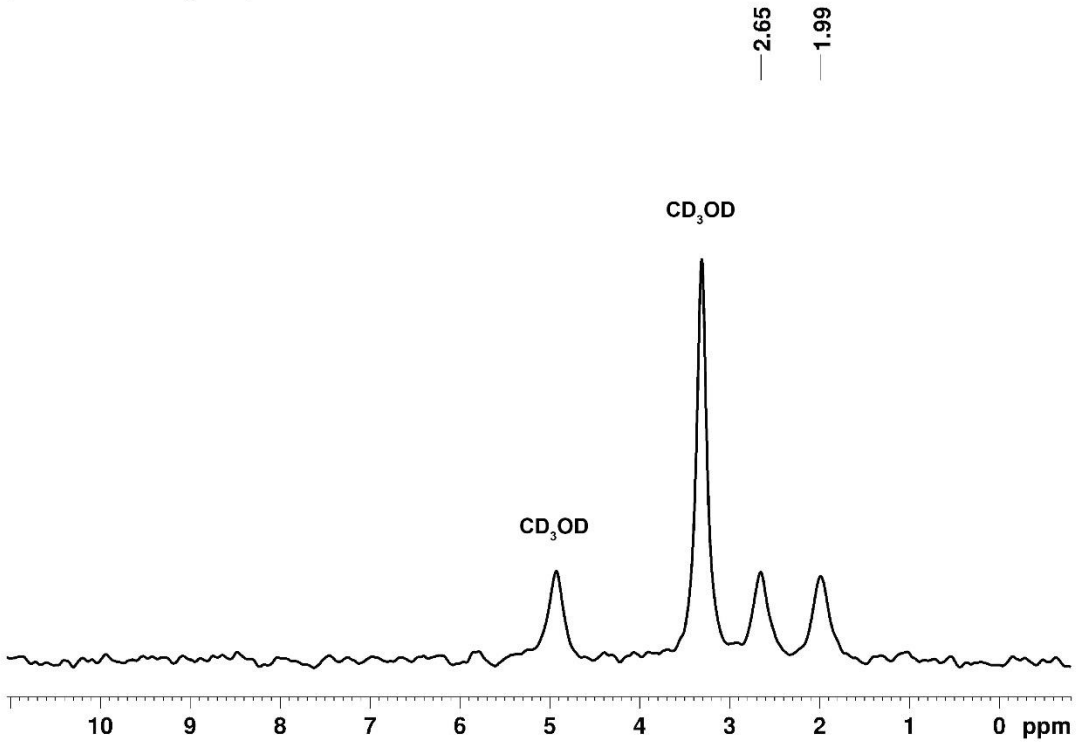
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



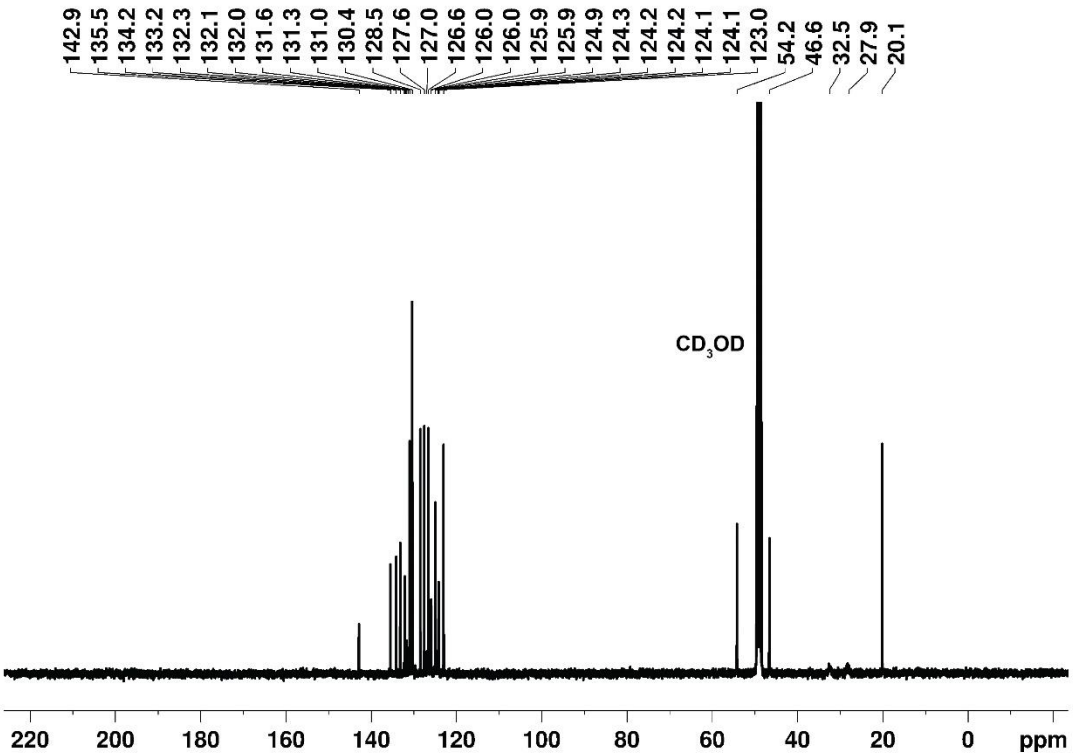
^{1}H NMR (400 MHz, CD_3OD)



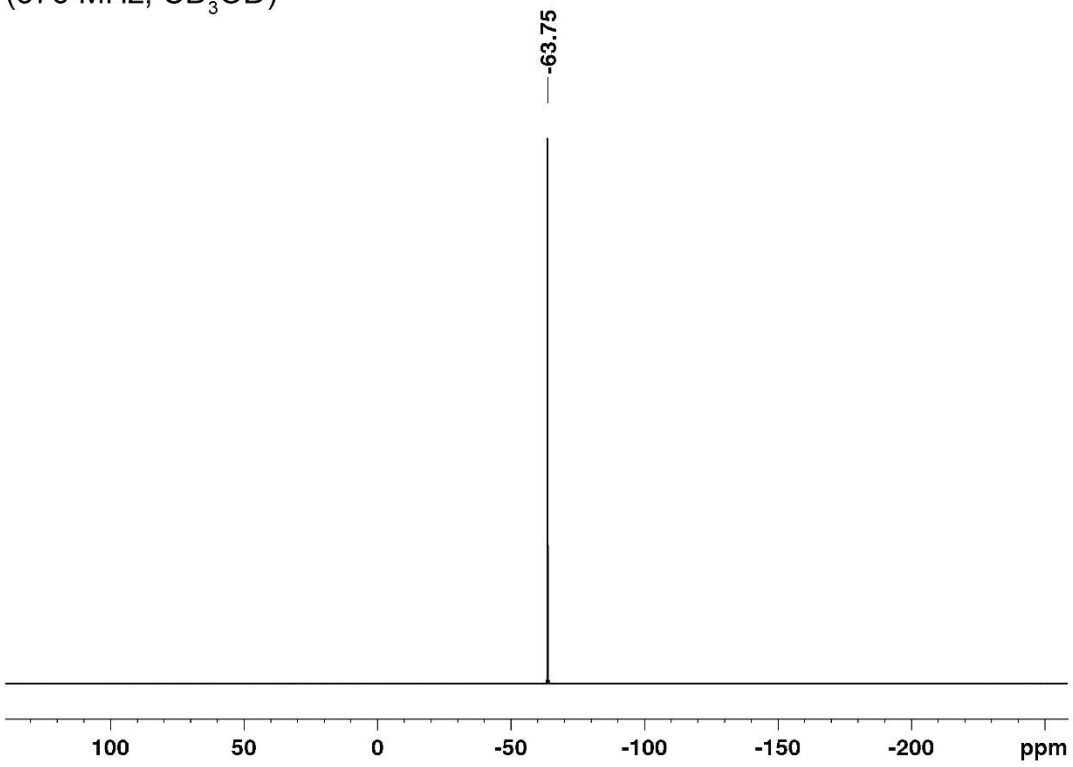
^{2}H NMR (61 MHz, CH_3OH)



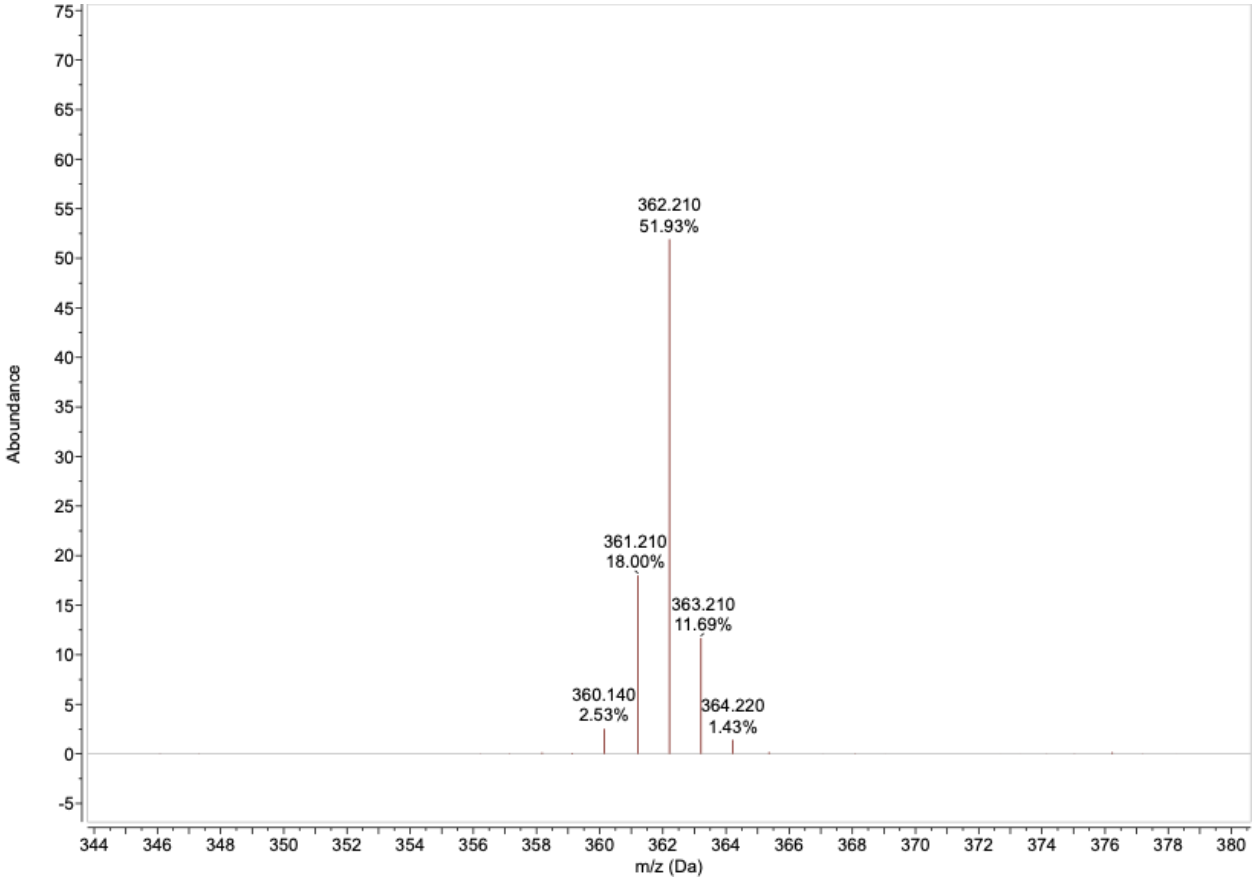
$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD)



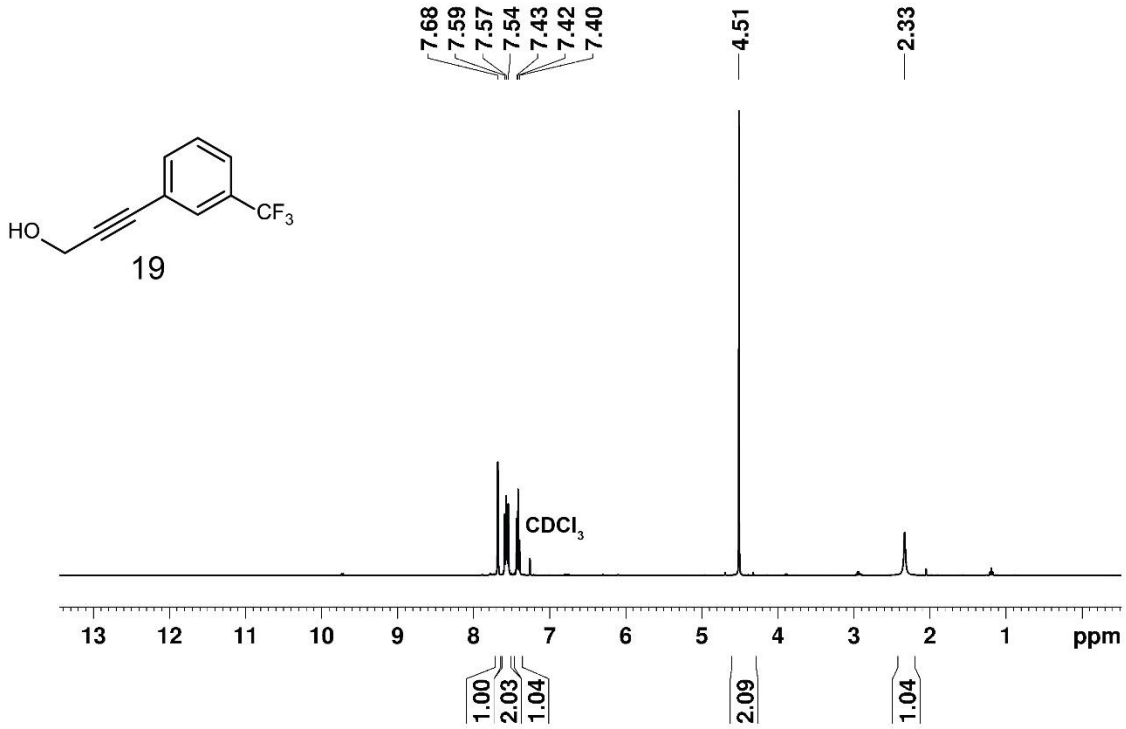
^{19}F NMR (376 MHz, CD_3OD)



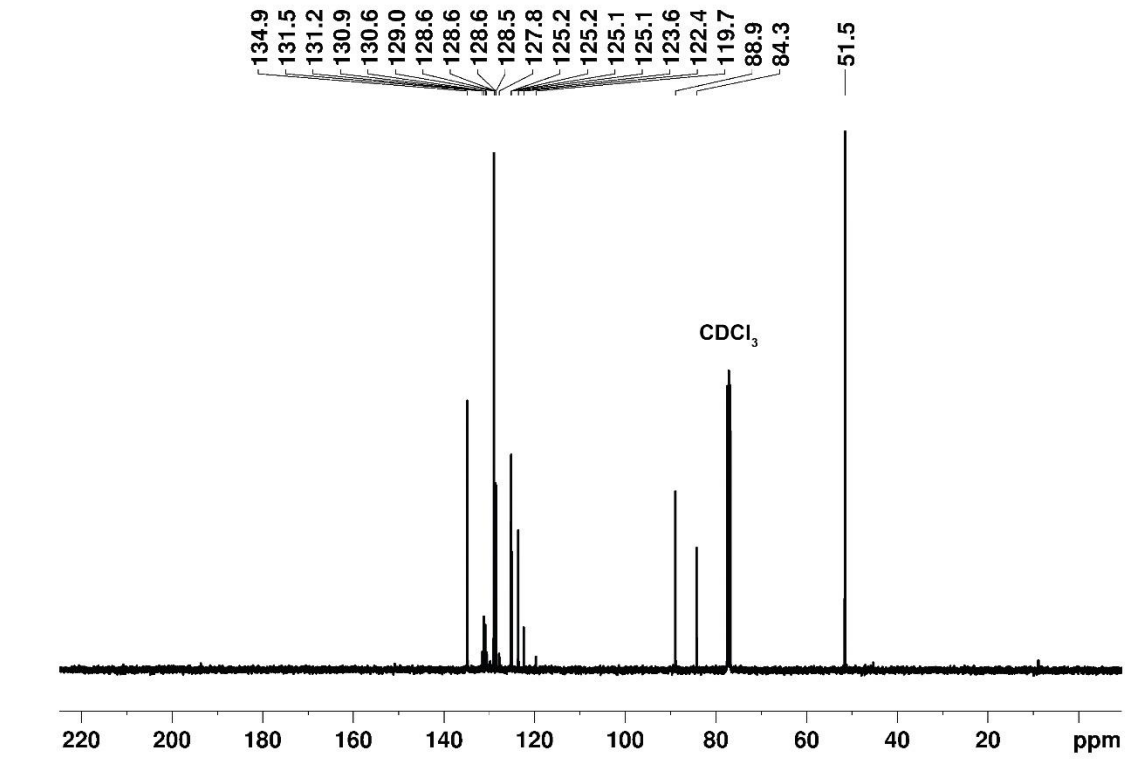
ESI–MS: m/z = 362.20



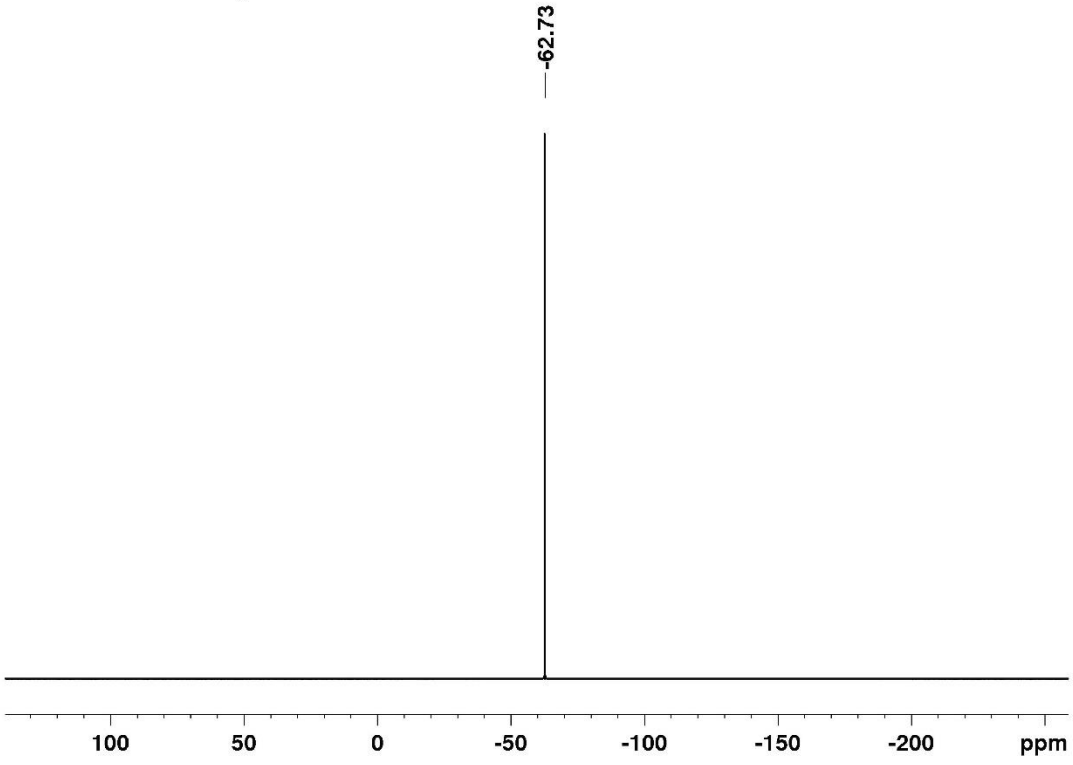
^{1}H NMR (400 MHz, $CDCl_3$)



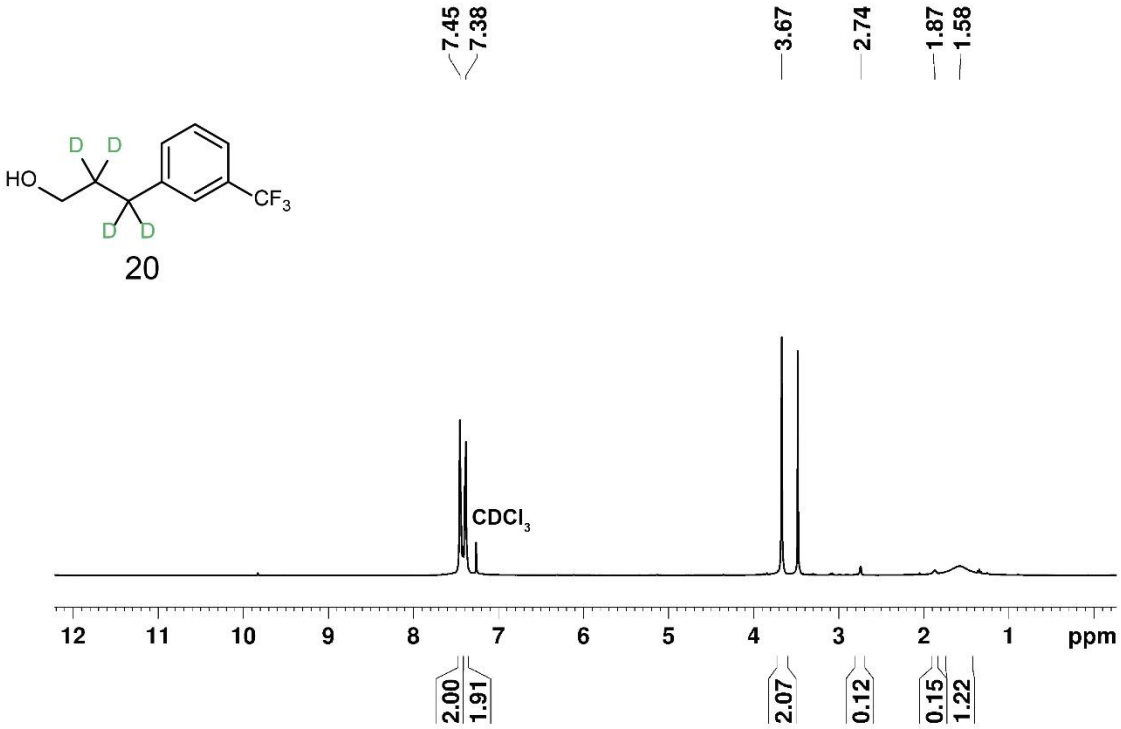
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



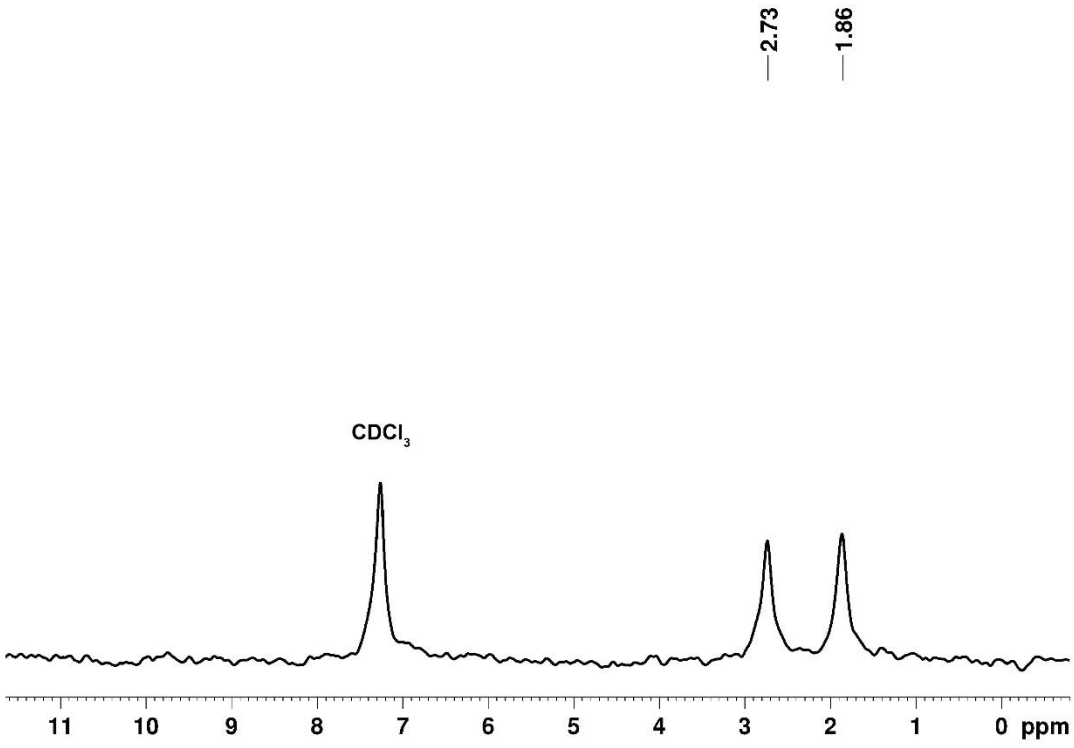
^{19}F NMR (376 MHz, $CDCl_3$)



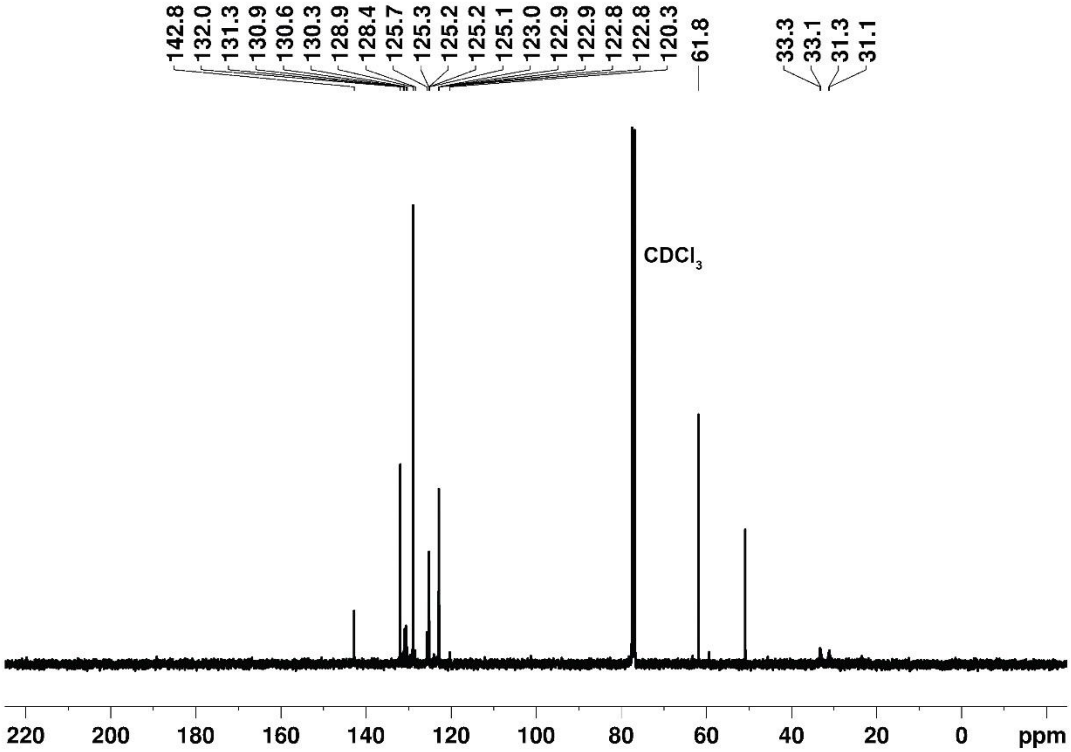
^{1}H NMR (400 MHz, $CDCl_3$)



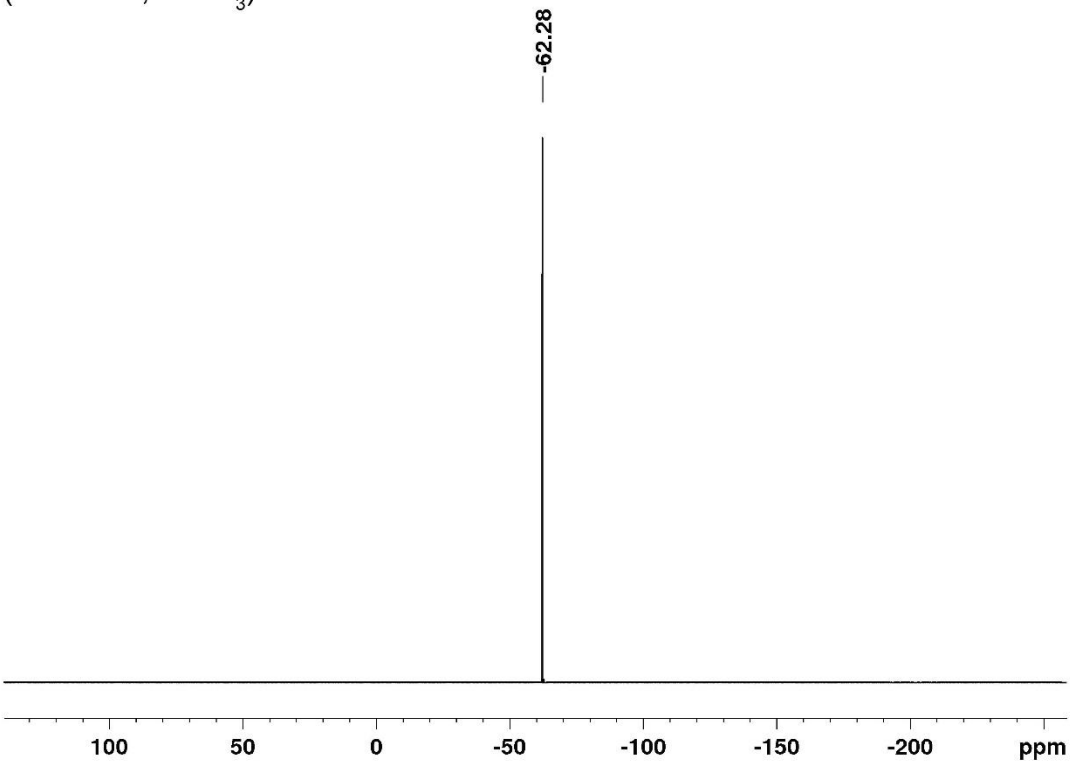
^{2}H NMR (61 MHz, $CHCl_3$)



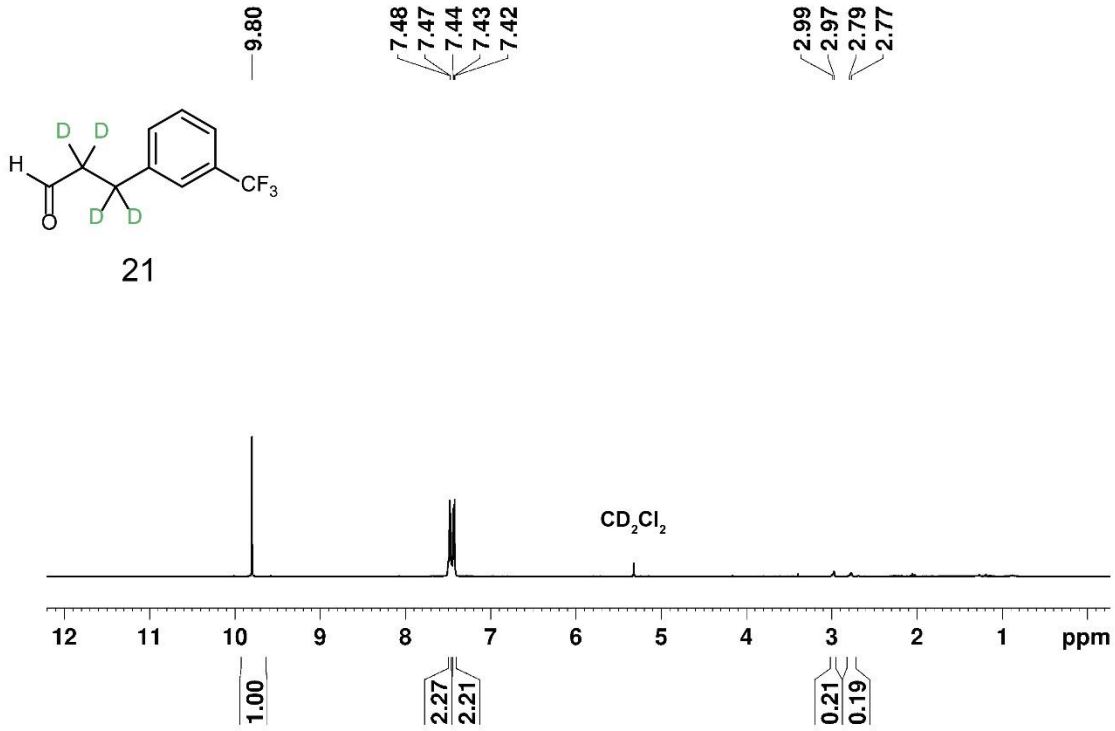
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, CD_2Cl_2)



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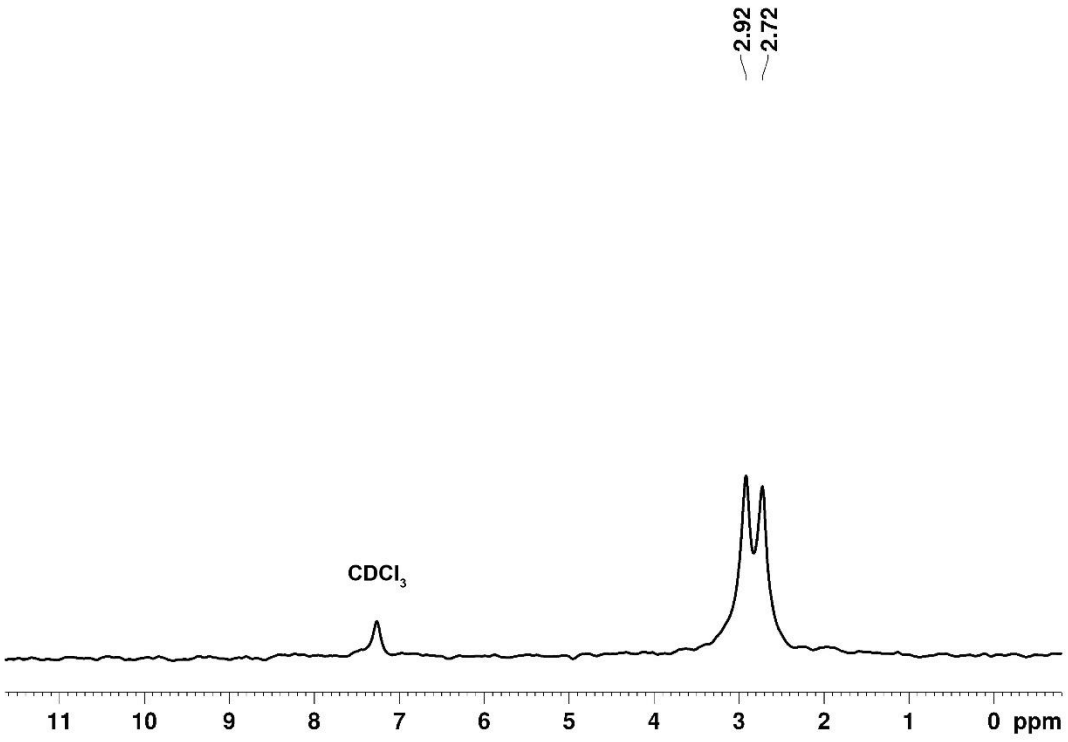
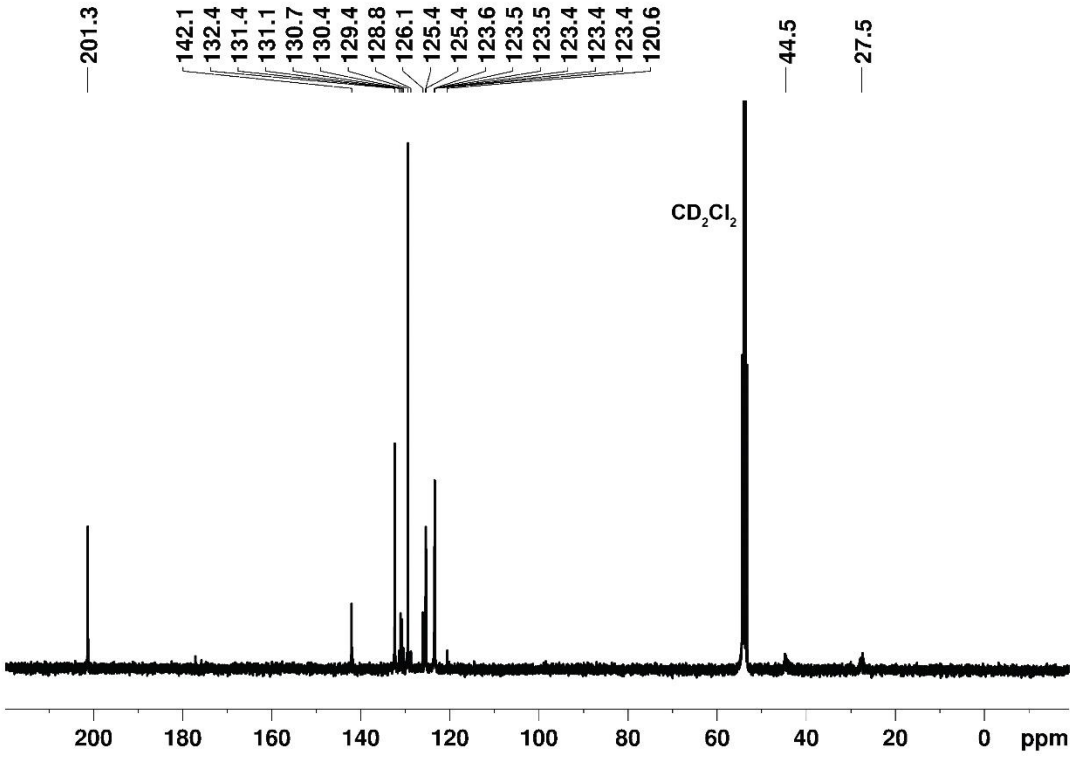
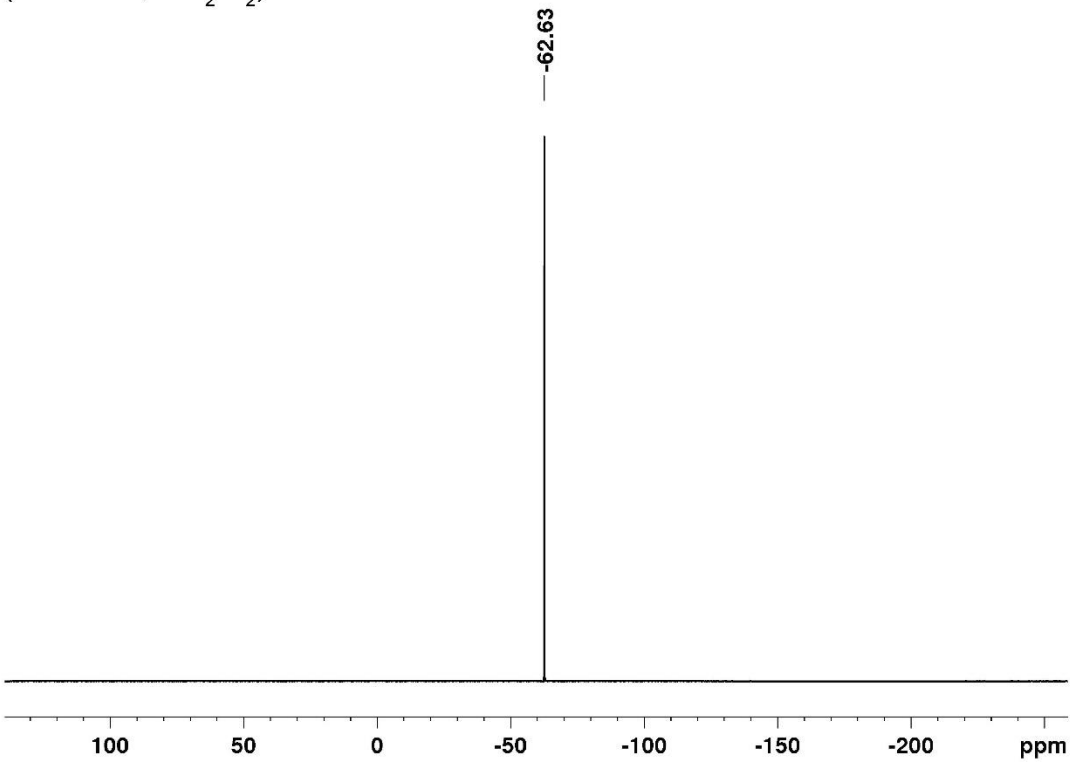
^{2}H NMR (61 MHz, $CHCl_3$)



$^{13}C\{^{1}H\}$ NMR (101 MHz, CD_2Cl_2)



^{19}F NMR (376 MHz, CD_2Cl_2)



Supplementary References

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