Supporting Information

Metallaphotoredox Difluoromethylation of Aryl Bromides

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1) General Information

Commercial reagents were used without prior purification unless otherwise indicated. Photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ was prepared according to the literature procedure.[1] Na_2CO_3, K_2CO_3, and LiOH used in difluoromethylation reactions were dried in the oven at 120 ºC prior to use. Tris(trimethylsilyl)silane was purified via distillation under reduced pressure. All reaction solvents were purified according to the method of Grubbs.[2] $CDCl_3$ was stored over K_2CO_3. Liquid reagents were transferred under N_2 via syringe. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Chromatographic purification of products was typically accomplished on an automated Biotage Isolera™ Spektra System with Silicycle Silia*Sep*™ cartridges (or Silia*Sep*™ C18 cartridges in the case of reverse phase chromatography). Alternatively, forced-flow chromatography on silica gel (Fluka, 230–400 mesh) according to the method of Still,[3] or preparative thin-layer chromatography (PTLC) on Analtech 1 mm silica gel GF plates were employed. Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm or Supelco 0.20 mm silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching, $KMnO_4$ stain, or *p*-anisaldehyde stain. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III NMR 500 MHz and are internally referenced to the residual proteo-solvent signals (7.26 ppm and 77.16 ppm, respectively, for $CDCl_3$; 2.50 ppm and 39.52 ppm, respectively, for DMSO-d_6). ^{19}F NMR spectra were recorded on Bruker NanoBay Avance III HD NMR 400 MHz and are reported unreferenced. Data for ^1H and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift; multiplicity and coupling constants are included only in the case of coupling with ^{19}F nuclei. For ^{19}F NMR analysis of crude reaction mixtures, α,α,α-trifluorotoluene or methyl 4-fluorobenzoate were used as internal standards, added as pure liquids. Liquid chromatography (LC) analysis was performed on an Agilent 1290 Infinity II LC system. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and are reported in wavenumbers (cm^{-1}). High Resolution Mass Spectra were obtained from the Princeton University Mass Spectral Facility.

2) Preparation, Handling and Storage of CF_2HBr Reagent Solution

To an oven-dried 250 mL double-neck round bottom flask equipped with a stir bar and sparged with N_2 while hot was added 60 mL of anhydrous DME. The solvent was degassed by sparging with N_2 while stirring for 20 minutes at room temperature. The flask was then cooled to –20 ºC using an ethylene glycol/dry ice bath. Afterwards, the N_2 inlet was removed and bromodifluoromethane (25 g, 0.19 mol) [available from SynQuest Laboratory, Product #1100-B-01] was slowly bubbled into the solvent using a gas regulator equipped with a long steel needle. (*Note: after a couple of minutes, bromodifluoromethane comes out as a condensed liquid as the needle cools down*.) After the end of addition, the N_2 inlet was re-added. The solution was stirred at 0 ºC for 45 minutes and then (for storage purposes) partitioned via a canula into four oven-dried 25 mL round bottom flasks that were beforehand fitted with rubber septa and kept under N_2. The concentration of the bromodifluoromethane solution was determined by ^{19}F NMR analysis ($CDCl_3$) on an aliquot of the solution against α,α,α-trifluorotoluene as an internal standard (for $PhCF_3$: δ –63.0, s; for CF_2HBr: δ –68.4, d, J = 60.0 Hz). The solution was stored at –20 ºC and handled at 0 ºC to ensure a stable concentration. After each use, the septum was resealed with electrical tape and parafilm to maintain the integrity of the seal.

Using this procedure, 2.0–2.5 M bromodifluoromethane solutions in DME are reliably prepared. Repeated uses over a timeframe of 1 month (several uses/week) caused a smaller than 10% decrease in concentration.

3) Stern-Volmer Fluorescence Quenching Experiments for Silane Reagent

Fluorescence quenching experiments were performed on an Agilent Cary Eclipse Fluorescence Spectrophotometer. In a typical experiment, a 2.5 μM solution of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ in DME was added to the appropriate amount of quencher in a screw-top 1.0 cm quartz cuvette. After degassing by bubbling a stream of nitrogen for 10 minutes, the emission of the sample was collected. All solutions were excited at λ = 380 nm (absorption maximum of the photocatalyst) and the emission intensity at 474 nm was observed (emission maximum). Plots were constructed according to the Stern–Volmer equation $I_0/I = 1 + kq\tau_0[Q]$.

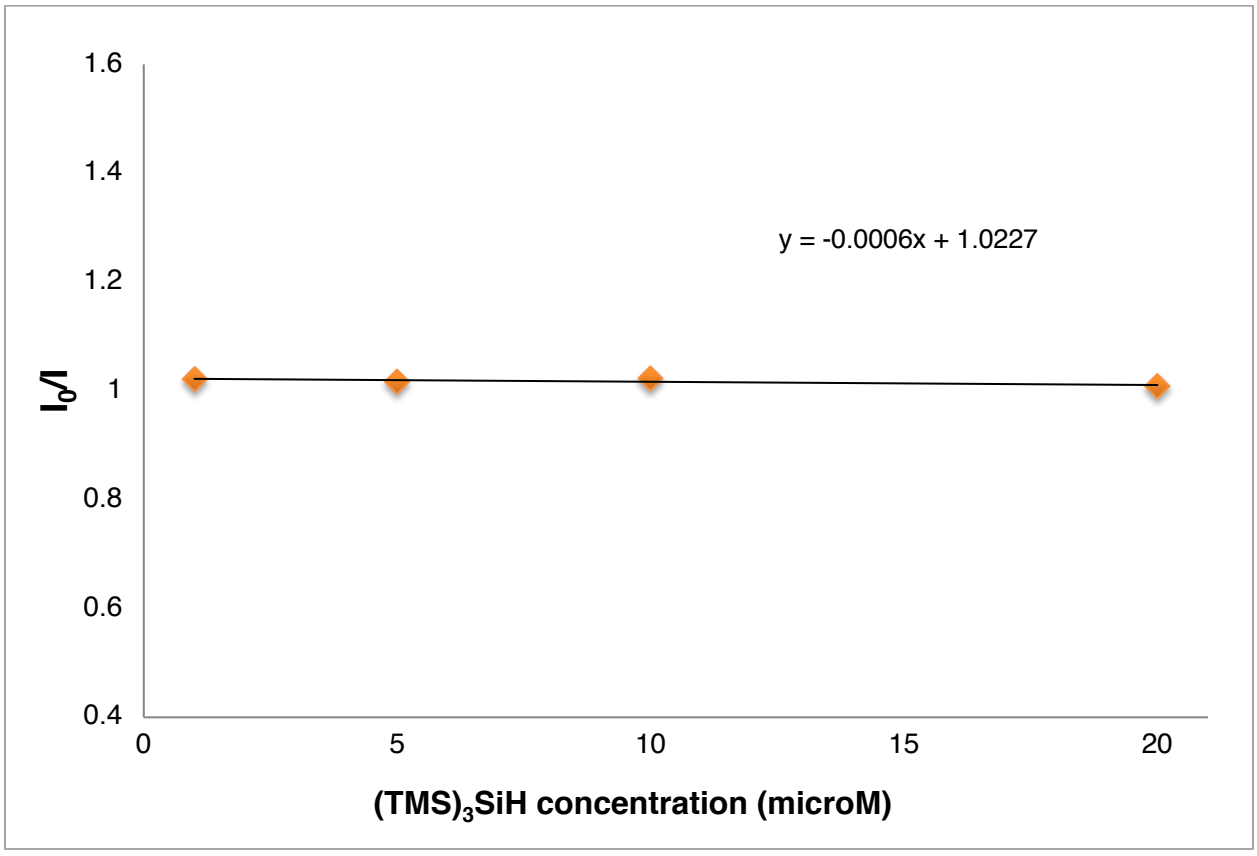


Figure S1. Emission quenching or $^*Ir^{III}$ by $(TMS)_3SiH$

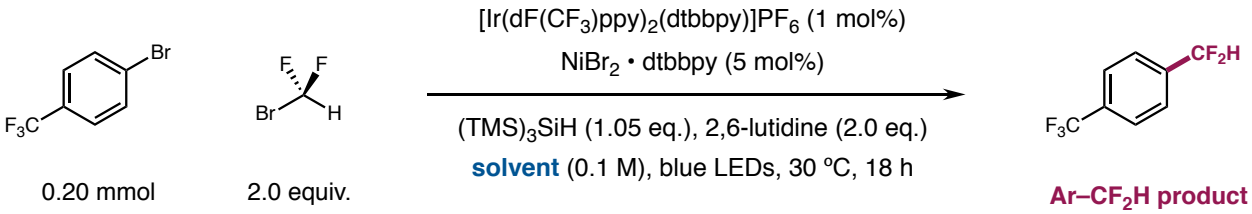
4) Reaction Optimization

Example of procedure for optimization using bromodifluoromethane

To an oven-dried 8 mL vial equipped with a stir bar and sparged with N_2 while hot was added aryl bromide (0.20 mmol, 1.0 equiv.). The vial was then recapped and the headspace was sparged with N_2. Then was added a solution of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 μmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 μmol, 5.0 mol%), and 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 μmol, 5.0 mol%) in DME (2.0 mL, 0.1 M), pre-sonicated separately for 15 minutes. To the vial were then added 2,6-lutidine (46 μL, 0.40 mmol, 2.0 equiv.) and tris(trimethylsilyl)silane (65 μL, 0.21 mmol, 1.05 equiv.). The reaction mixture was degassed by sparging with N_2 while stirring for 15 minutes. Then was added a solution of bromodifluoromethane in DME (0.40 mmol, 2.0 equiv., 155 μL, 2.6 M). The vial was sealed with warm Parafilm and the reaction mixture was then stirred under irradiation with a 34 W or 40 W blue LED Kessil lamp (5 cm distance from vial, with fans and/or a water bath to keep temperature at 30 ºC) for 18 hours. To the reaction vial was then added methyl 4-fluorobenzoate or α,α,α-trifluorotoluene as an internal standard, and the reaction mixture was analyzed via ^{19}F NMR analysis in $CDCl_3$.

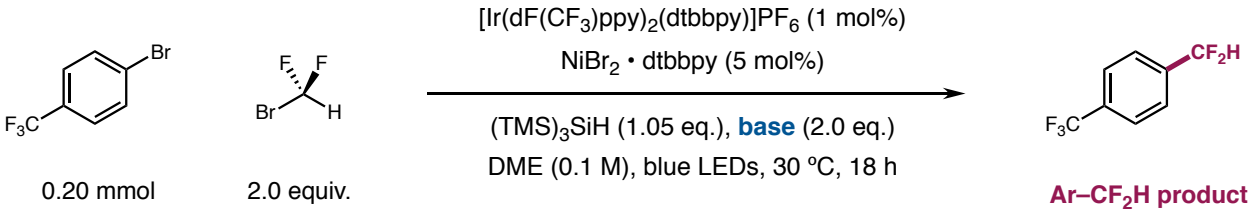
Example of procedure for difluoromethylation using TMS–CF_2Br

To an oven-dried 8 mL vial equipped with a stir bar and sparged with N_2 while hot was added aryl bromide (0.20 mmol, 1.0 equiv.). The vial was then recapped and the headspace was sparged with N_2. Then was added a solution of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 μmol, 1.0 mol%), $Ni(BF_4)_2$• $6H_2O$ (3.4 mg, 10 μmol, 5.0 mol%), and 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 μmol, 5.0 mol%) in DME (2.0 mL, 0.1 M), pre-sonicated separately for 15 minutes. To the vial were then added 2,6-lutidine (93 μL, 0.80 mmol, 4.0 equiv.) and tris(trimethylsilyl)silane (65 μL, 0.21 mmol, 1.05 equiv.). The reaction mixture was degassed by sparging with N_2 while stirring for 15 minutes. Then was added (bromodifluoromethyl)trimethylsilane (62 μL, 0.40 mmol, 2.0 equiv.) and water (3.6 μL, 0.20 mmol, 1.0 equiv.). The vial was sealed with warm Parafilm and the reaction mixture was then stirred under irradiation with a 34 W or 40 W blue Kessil LED lamp (5 cm distance from vial, with fans and/or a water bath to keep temperature at 30 ºC) for 24 hours. To the reaction vial was then added methyl 4-fluorobenzoate as an internal standard, and the reaction mixture was analyzed via ^{19}F NMR analysis in $CDCl_3$.



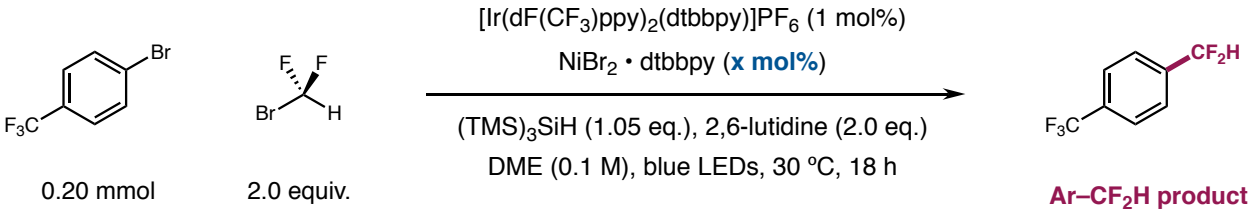
solvent	yield
DME	83%
dioxane	20%
acetone	78%
MeCN	29%
DMA	15%

Figure S2. Evaluation of reaction solvent; yields determined by ^{19}F NMR



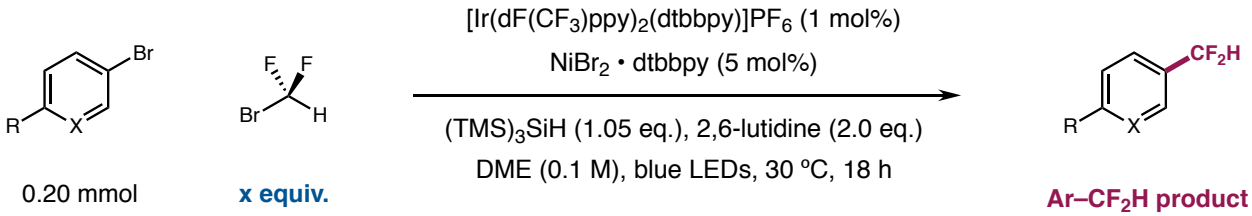
base	yield
2,6-lutidine	84%
quinuclidine	8%
Na_2CO_3	81%
K_3PO_4	54%
LiOH	60%

Figure S3. Evaluation of base; yields determined by ^{19}F NMR



x mol% Ni	yield
1.0	41%
2.0	74%
3.0	80%
5.0	84%
10	86%

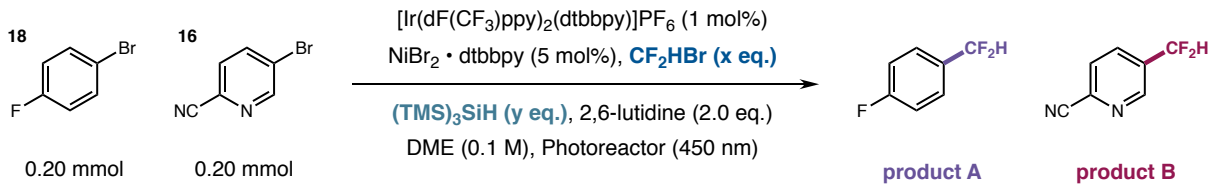
Figure S4. Evaluation of nickel catalyst loading; yields determined by ^{19}F NMR



stoichiometry of CF_2HBr (equiv.)	ArBr	Ar–CF_2H	ArBr	Ar–CF_2H	ArBr	Ar–CF_2H
1.0	4%	52%	3%	77%	1%	74%
2.0	2%	72%	1%	84%	62%	16%
4.0	0%	77%	13%	56%	91%	3%

Figure S5. Effect of CF_2HBr stoichiometry; yields determined by ^{19}F NMR and LC

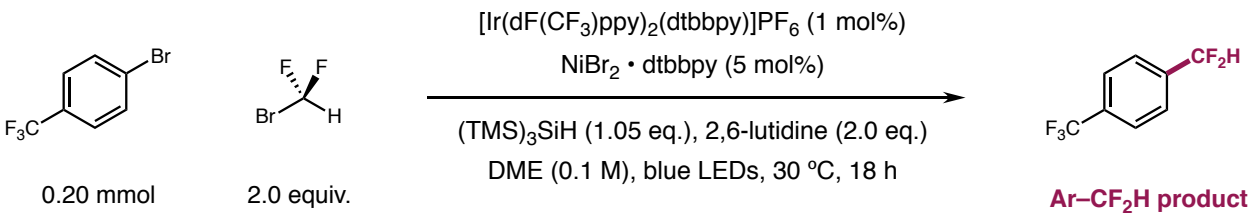
Note: there is a clear correlation between the electronic parameters of the aryl bromide substrate and the optimal stoichiometry of CF_2HBr. The diminishing yields as a function of stoichiometry beyond the optimum are accompanied by recovery of increasing amounts of aryl bromide starting material. This observation is consistent with pathways wherein the nickel catalyst becomes terminally deactivated (potentially via two sequential formal oxidative additions into CF_2HBr) and cannot further perform oxidative addition into the aryl bromide.



reagent stoichiometry		*reaction time = 0.33 h*				*reaction time = 15 h*			
CF_2HBr	$(TMS)_3SiH$	CF_2HBr	**18**	yield A	yield B	CF_2HBr	**18**	yield A	yield B
1.0 eq.	1.05 eq.	75%	99%	0%	29%	15%	53%	18%	55%
2.0 eq.	1.05 eq.	168%	100%	0%	33%	90%	71%	12%	72%
2.0 eq.	2.1 eq.	154%	98%	0%	45%	13%	35%	32%	71%

To minimize error, all reactions were performed in the Integrated Photoreactor, at 450 nm (100% intensity), 1000 rpm stirring and 5000 rpm fan cooling. See: C. C. Le, M. K. Wismer, Z.-C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies, D. W. C. MacMillan, *ACS Cent. Sci.* **2017**, *3*, 647.

Figure S6. Aryl bromide competition experiment; yields determined by ^{19}F NMR



deviation	CF_2HBr	CF_2H_2	ArBr	Ar–CF_2H
none	99%	3%	0%	84%
$Ni(cod)_2$ instead of $NiBr_2$	81%	4%	1%	87%
no light	197%	0%	97%	0%
no photocatalyst	209%	3%	99%	0%
no nickel	111%	50%	98%	0%
no silane	207%	0%	91%	1%
no base	132%	21%	63%	16%

(all values reported relative to initial molar amount of aryl bromide)

Figure S7. Control experiments; yields determined by ^{19}F NMR

Note: the results of control experiments excluding the nickel catalyst are consistent with the proposed ability of the silyl radical generated in situ to perform halogen abstraction from bromodifluoromethane. In the absence of a metal trap, the resultant CF_2H radical is quenched to CF_2H_2 via hydrogen atom transfer with another equivalent of silane or solvent. In the absence of bromide anion, the chain is likely initiated by homolysis of the HF_2C–Br bond under blue light irradiation, which is in accord with the control experiment performed in absence of photocatalyst (see Fig. S8 below).

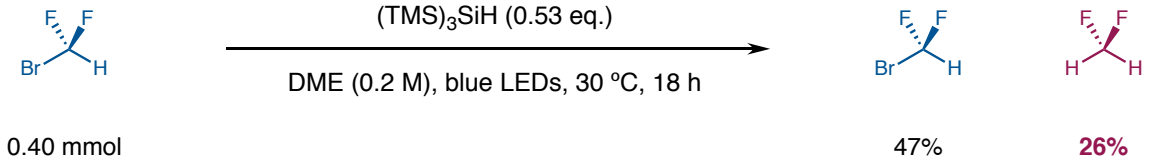
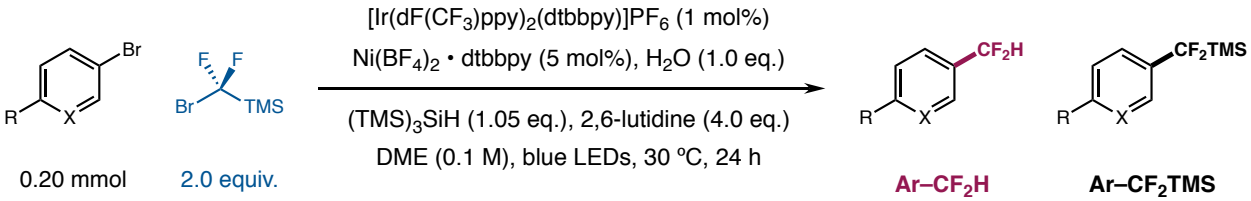


Figure S8. Silane- and light-mediated reduction of CF_2HBr; yields determined by ^{19}F NMR



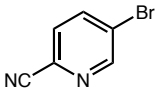
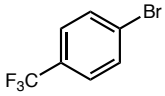
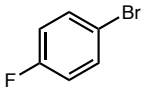
substrate			
yield of Ar–CF_2H	31%	30%	27%
yield of Ar–CF_2TMS	5%	3%	0%

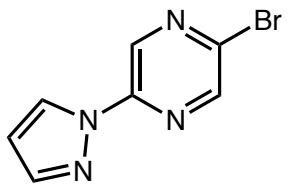
Figure S9. Experiments using TMS–CF_2Br as a CF_2H source; yields determined by ^{19}F NMR

4) Preparation and/or Purification of Aryl Bromides

2-Bromoquinoxaline and 4-bromobenzaldehyde were obtained from commercial sources and purified via flash column chromatography. 2-(4-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained commercially and recrystallized from methanol. All other commercially available aryl bromides were used without prior purification.

The following compounds were prepared according to literature procedures: 2-(5-methoxy-2-methyl-*1H*-indol-3-yl)acetate, [4] 4-bromo-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, [5] and 4-(5-(4-bromophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide.[6]

The syntheses of previously unreported aryl bromides are included below.



2-bromo-5-(1*H*-pyrazol-1-yl)pyrazine (S1)

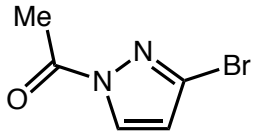
To a 100 mL round bottom flask equipped with a stir bar was added 1*H*-pyrazole (1.19 g, 17.5 mmol, 1.0 equiv.), 2,5-dibromopyrazine (5.00 g, 21.0 mmol, 1.2 equiv.) and K_2CO_3 (7.26 g, 52.5 mmol, 3.0 equiv.). The flask was then fitted with a rubber septum and the headspace was sparged with N_2. Afterwards, to the flask was added anhydrous DMF (25 mL, 0.70 M). The reaction mixture was stirred at 80 ºC for 6 h. Then were added saturated aqueous LiCl solution (25 mL) and EtOAc (50 mL). The mixture was briefly and vigorously stirred, then filtered, and the two layers were separated. The organic layer was washed with brine (3 × 30 mL) and concentrated. Purification by flash column chromatography (1–10% EtOAc/hexanes) provided the title compound as a white crystalline solid (1.80 g, 8.00 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, *J* = 1.3 Hz, 1H), 8.46 – 8.41 (m, 2H), 7.79 (d, *J* = 1.1 Hz, 1H), 6.54 – 6.50 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 144.5, 143.6, 136.1, 135.5, 127.7, 109.1.

IR (film) ν_{max} 3114, 1573, 1531, 1469, 1352, 1194, 1135, 1105, 1044, 1009, 934, 910, 764 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_7H_5BrN_4$ ($[M^*]^+$) 223.9692, found 223.9692.



1-(3-bromo-1*H*-pyrazol-1-yl)ethan-1-one (S2)

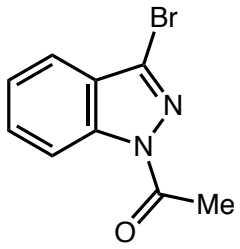
To a 50 mL round bottom flask equipped with a stir bar was added 3-bromo-1*H*-pyrazole (2.0 g, 13.6 mmol, 1.0 equiv.) and 4-(dimethylamino)pyridine (0.166 g, 1.36 mmol, 0.10 equiv.). The flask was then fitted with a rubber septum and the headspace was sparged with N_2. Afterwards, to the flask was added anhydrous DCM (16 mL, 0.85 M), triethylamine (2.84 mL, 20.4 mmol, 1.5 equiv.) and acetic anhydride (1.53 mL, 16.3 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then poured into a saturated aqueous K_2CO_3 solution (30 mL) and extracted three times with DCM. The organic layers were combined and concentrated *in vacuo*. Purification by flash column chromatography (5–10% EtOAc/hexanes) provided the title compound as a white crystalline solid (2.18 g, 11.5 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.8 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H), 2.68 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 132.3, 129.9, 113.3, 21.7.

IR (film) ν_{max} 3133, 3117, 1735, 1511, 1406, 1367, 1188, 1044, 932, 908, 792, 731 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_5H_5BrN_2O$ ($[M^*]^+$) 187.9580, found 187.9589.



1-(3-bromo-1*H*-indazol-1-yl)ethan-1-one (S3)

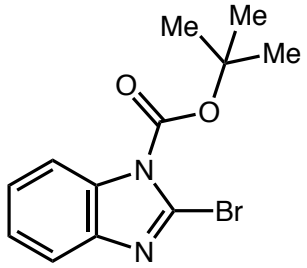
To a 50 mL round bottom flask equipped with a stir bar was added 3-bromo-1*H*-indazole (4.0 g, 20.3 mmol, 1.0 equiv.). The flask was then fitted with a rubber septum and the headspace was sparged with N_2. Afterwards, to the flask was added acetic anhydride (10 mL, 2.0 M) and *N*,*N*-diisopropylethylamine (7.0 mL, 40.6 mmol, 2.0 equiv.). The reaction mixture was refluxed at 140 ºC for 14 h. The reaction mixture was then concentrated to remove most of the solvent, and a saturated aqueous $NaHCO_3$ solution (25 mL) was added. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (3–5% EtOAc/hexanes) provided the title compound as a white solid (3.25 g, 13.6 mmol, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 – 8.38 (m, 1H), 7.66 – 7.58 (m, 2H), 7.42 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 2.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 139.7, 130.8, 130.2, 126.4, 125.2, 120.6, 115.8, 23.1.

IR (film) ν_{max} 3405, 3018, 2933, 1709, 1493, 1372, 1317, 1137, 977, 926, 765, 716 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_9H_7BrN_2O$ ($[M^*]^+$) 237.9736, found 237.9742.



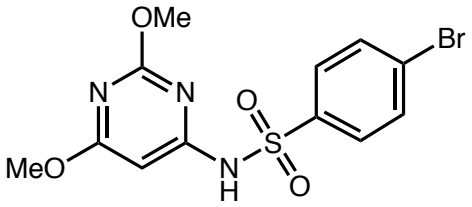
***tert*-butyl 2-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (S4)**

To a 500 mL round bottom flask equipped with a stir bar was added 2-bromo-1*H*-benzo[*d*]imidazole (3.0 g, 15.2 mmol, 1.0 equiv.). The flask was then fitted with a rubber septum and the headspace was sparged with N_2. Afterwards, to the flask was added DMF and acetonitrile (4:3 ratio, 110 mL + 80 mL, 0.08 M) followed by triethylamine (2.55 mL, 18.3 mmol, 1.2 equiv). After 20 minutes, di-*tert*-butyl dicarbonate (6.65 g, 30.5 mmol, 2.0 equiv) was added and the reaction mixture was stirred for another 16 h. Afterwards, the reaction mixture was diluted with EtOAc (200 mL) and washed sequentially with a 0.5 M aqueous HCl solution (200 mL), a saturated aqueous K_2CO_3 solution (200 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc/hexanes) provided the title compound as a white solid (4.00 g, 13.5 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 1H), 7.70 – 7.65 (m, 1H), 7.38 – 7.30 (m, 2H), 1.73 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5, 142.9, 134.0, 127.1, 125.2, 124.7, 119.6, 114.9, 87.0, 28.2. *Note: a minor isomer attributed to the rotation of the Boc group can also be observed in the ^{13}C NMR. Visible peaks: δ 147.3, 141.1, 139.9, 133.5, 124.8, 119.7, 86.8, 28.2.*

Spectroscopic data matches previously reported data.[7]



4-bromo-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (S5)

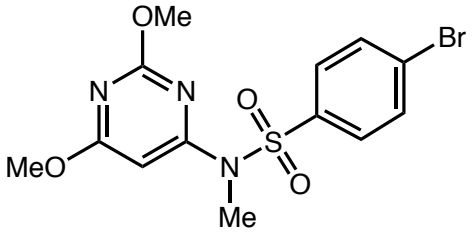
A mixture of 2,6-dimethoxypyrimidin-4-amine (3.05 g, 19.7 mmol, 1.05 equiv.) and 4-bromobenzene-1-sulfonyl chloride (4.78 g, 18.7 mmol, 1.0 equiv.) in pyridine (24 mL) was stirred for 20 hours at room temperature. To the solution was then added H_2O (48 mL) to produce a slurry. After stirring for 1 hour, the slurry was filtered, and the filter cake was washed with water (24 mL), after which the solid was dried *in vacuo* to yield the title compound as a white solid (5.58 g, 14.9 mmol, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 6.21 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 164.6, 158.7, 138.4, 132.6, 129.1, 128.8, 86.0, 55.0, 54.4.

IR (film) ν_{max} 3093, 2950, 1580, 1473, 1363, 1330, 1153, 1088, 1066, 820, 738 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_{12}H_{13}BrN_3O_4S$ ($[M+H]^+$) 373.9805, found 373.9798.



4-bromo-*N*-(2,6-dimethoxypyrimidin-4-yl)-*N*-methylbenzenesulfonamide (S6)

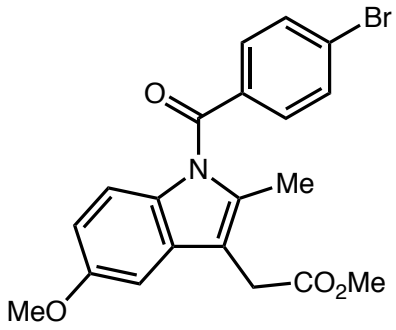
A mixture of 4-bromo-*N*-(2,6-dimethoxypyrimidin-4-yl)benzenesulfonamide (**S5**) (5.58 g, 14.9 mmol, 1.0 equiv.), K_2CO_3 (2.06 g, 14.9 mmol, 1.0 equiv.), and iodomethane (1.39 mL, 22.4 mmol, 1.5 equiv.) in DMF (17 mL) was stirred for 20 hours at room temperature. Afterwards, the reaction mixture was diluted with EtOAc (28 mL) and washed with water (17 mL). The aqueous layer was back-extracted with EtOAc (3 × 17 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (5–66% EtOAc/hexanes) provided the title compound as a white solid (3.62 g, 9.33 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 164.5, 161.3, 137.6, 132.6, 128.8, 128.6, 90.3, 54.9, 54.3, 34.7.

IR (film) ν_{max} 2950, 1571, 1460, 1352, 1208, 1161, 1029, 975, 784, 734 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_{13}H_{15}BrN_3O_4S$ ($[M+H]^+$) 387.9961, found 387.9961.



methyl 2-(1-(4-bromobenzoyl)-5-methoxy-2-methyl-*1H*-indol-3-yl)acetate (S7)

A solution of methyl 2-(5-methoxy-2-methyl-*1H*-indol-3-yl)acetate (0.980 g, 4.20 mmol, 1.0 equiv.), DMAP (0.257 g, 2.10 mmol, 0.50 equiv.), triethylamine (2.93 mL, 21.0 mmol, 5.0 equiv.), and 4-bromobenzoyl chloride (1.106 g, 5.04 mmol, 1.2 equiv.) in DCM (20 mL) was stirred for 48 hours at room temperature. The reaction mixture was washed with aqueous 1 M HCl (30 mL). The aqueous layer was then back-extracted with DCM (10 mL). The combined organic layers were washed with aqueous 1 M HCl (10 mL) and water (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Afterwards, to the residue was added Et_2O (40 mL) to produce a slurry. The slurry was filtered, the filter cake was washed with Et_2O (10 mL), and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (6–88% EtOAc/hexanes) followed by crystallization from 4:1 hexanes/DCM (12.5 mL) provided the title compound as a yellow solid (0.88 g, 2.1 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.67 (s, 2H), 2.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 168.5, 156.2, 136.1, 134.5, 132.2, 131.4, 130.9, 130.8, 127.9, 115.1, 112.7, 111.7, 101.4, 55.8, 52.3, 30.3, 13.5.

IR (film) ν_{max} 2952, 1735, 1679, 1587, 1477, 1356, 1314, 1220, 1165, 1069, 1011, 830, 734 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_{20}H_{18}BrNNaO_4$ ($[M+Na]^+$) 438.0311, found 438.0307.

6) General Procedures for Difluoromethylation of Aryl Bromides

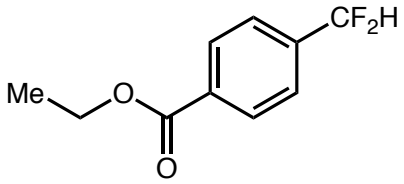
General Procedure A (liquid base)

To an oven-dried 8 mL vial equipped with a stir bar and sparged with N_2 while hot was added aryl bromide (0.50 mmol, 1.0 equiv.). The vial was then recapped and the headspace was sparged with N_2. Then was added a solution of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), and 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%) in DME (5.0 mL, 0.1 M), pre-sonicated separately for 15 minutes. To the vial were afterwards added 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.) and tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.). The reaction mixture was degassed by sparging with N_2 while stirring for 15 minutes. Then was added a solution of bromodifluoromethane in DME (1.0 mmol, 2.0 equiv., 0.44 mL, 2.3 M). The vial was sealed with warm Parafilm and the reaction mixture was then stirred under irradiation with a 34 W or 40 W blue LED Kessil lamp (5 cm distance from vial, with fans and/or a water bath to keep temperature at 30 ºC) for 18 hours. Work-up and purification for each substrate are described below.

General Procedure B (solid base)

To an oven-dried 8 mL vial equipped with a stir bar and sparged with N_2 while hot were added aryl bromide (0.50 mmol, 1.0 equiv.) and solid base (1.5 mmol, 3.0 equiv.). The vial was then recapped and the headspace was sparged with N_2. Then was added a solution of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), and 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%) in DME (5.0 mL, 0.1 M), pre-sonicated separately for 15 minutes. To the vial was afterwards added tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.). The reaction mixture was degassed by sparging with N_2 while stirring for 15 minutes. Then was added a solution of bromodifluoromethane in DME (1.0 mmol, 2.0 equiv., 0.44 mL, 2.3 M). The vial was sealed with warm Parafilm and the reaction mixture was then stirred under irradiation with a 34 W or 40 W blue LED Kessil lamp (5 cm distance from vial, with fans and/or a water bath to keep temperature at 30 ºC) for 18 hours. Work-up and purification for each substrate are described below.

7) Experimental Data for Difluoromethylarene Products



ethyl 4-(difluoromethyl)benzoate (19)

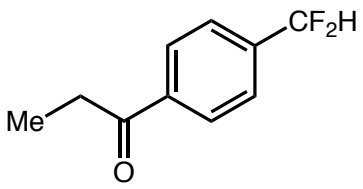
Prepared following general procedure A using ethyl 4-bromobenzoate (115 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (2–10% Et_2O/pentane) provided the title compound as a colorless oil (83.1 mg, 0.415 mmol, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 6.69 (t, *J* = 56.1 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 138.5 (t, *J* = 22.3 Hz), 132.8, 130.1, 125.7 (t, *J* = 6.1 Hz), 114.2 (t, *J* = 239.7 Hz), 61.5, 14.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.2 (d, *J* = 56.2 Hz, 2F).

Spectroscopic data matches previously reported data.[8]



1-(4-(difluoromethyl)phenyl)propan-1-one (20)

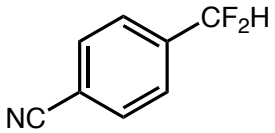
Prepared following general procedure A using 1-(4-bromophenyl)propan-1-one (10 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (0–20% Et_2O/pentane) provided the title compound as a white solid (74.2 mg, 0.403 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 56.1 Hz, 1H), 3.03 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.2, 138.9 (t, *J* = 1.7 Hz), 138.4 (t, *J* = 22.4 Hz), 128.5, 126.0 (t, *J* = 6.0 Hz), 114.1 (t, *J* = 239.7 Hz), 32.2, 8.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.2 (d, *J* = 56.3 Hz, 2F).

Spectroscopic data matches previously reported data.[9]



4-(difluoromethyl)-bennzonitrile (21)

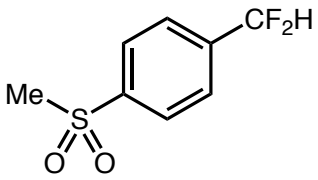
Prepared following general procedure A using 4-bromobenzonitrile (91.0 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, an 84% yield of the desired product was observed via ^{19}F NMR analysis against α,α,α-trifluorotoluene. To the reaction vial was added sodium acetate (205 mg, 2.5 mmol, 5.0 equiv.). After sonication for 2 h, the reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (2–20% EtOAc/hexanes) provided the title compound as slightly yellow oil (57.1 mg, 0.373 mmol, 75% yield). The discrepancy between the isolated and crude NMR yields is likely due to the volatility of the difluoromethylarene product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 6.69 (t, *J* = 55.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7 (t, *J* = 22.9 Hz), 132.7, 126.5 (t, *J* = 6.1 Hz), 118.0, 114.9 (t, *J* = 2.1 Hz), 113.4 (t, *J* = 240.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –113.1 (d, *J* = 55.8 Hz, 2F).

Spectroscopic data matches previously reported data.[10]



1-(difluoromethyl)-4-(methylsulfonyl)benzene (22)

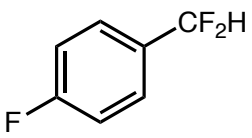
Prepared following general procedure A using 1-bromo-4-(methylsulfonyl)benzene (118 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial were added KF/alumina (40% wt, 1.5 g) and tetrabutylammonium bromide (0.4 g). After vigorous stirring for 30 minutes, the reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (10–30% EtOAc/hexanes) provided the title compound as a white solid (85.6 mg, 0.415 mmol, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 6.73 (t, *J* = 55.8 Hz, 1H), 3.07 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9 (t, *J* = 2.0 Hz), 139.6 (t, *J* = 22.8 Hz), 128.1, 126.9 (t, *J* = 6.0 Hz), 113.5 (t, *J* = 240.7 Hz), 44.5.

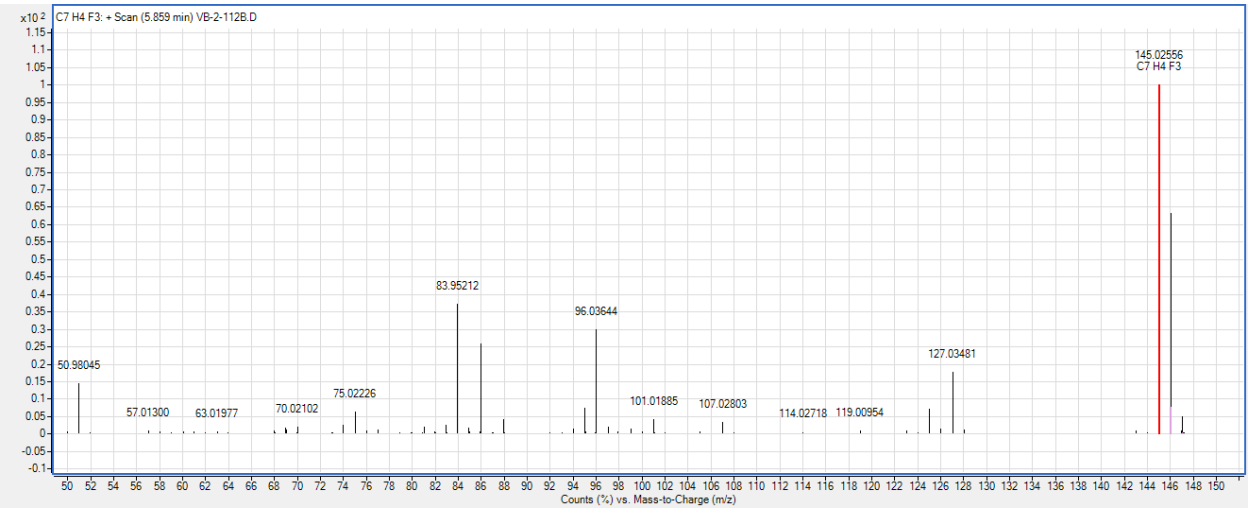
^{19}F NMR (376 MHz, $CDCl_3$) δ –112.8 (d, *J* = 55.8 Hz, 2F).

Spectroscopic data matches previously reported data.[9]



1-(difluoromethyl)-4-fluorobenzene (23)

Prepared following general procedure A using 1-bromo-4-fluorobenzene (87.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.61 mmol, 1.2 equiv., 0.29 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 80% was observed (average of two trials: 80.3% and 80.5% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_7H_4F_3$ ($[M–H]^+$) 145.0260, found 145.0256.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.6 (d, J = 56.1 Hz, 2.8 Hz, 2F), –111.7 (m, 1F).

Spectroscopic data matches previously reported data.[11,12]

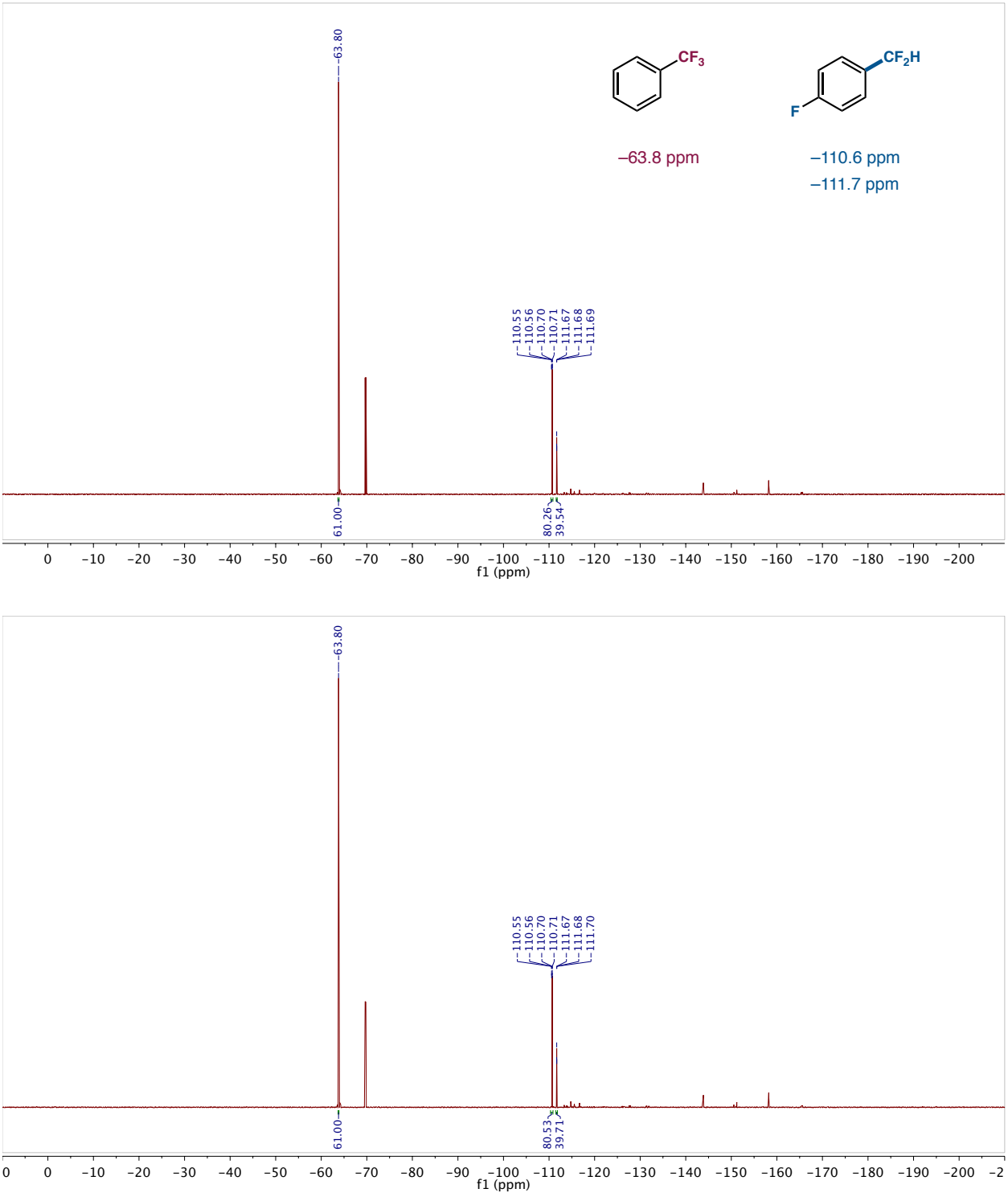
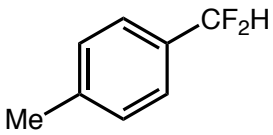
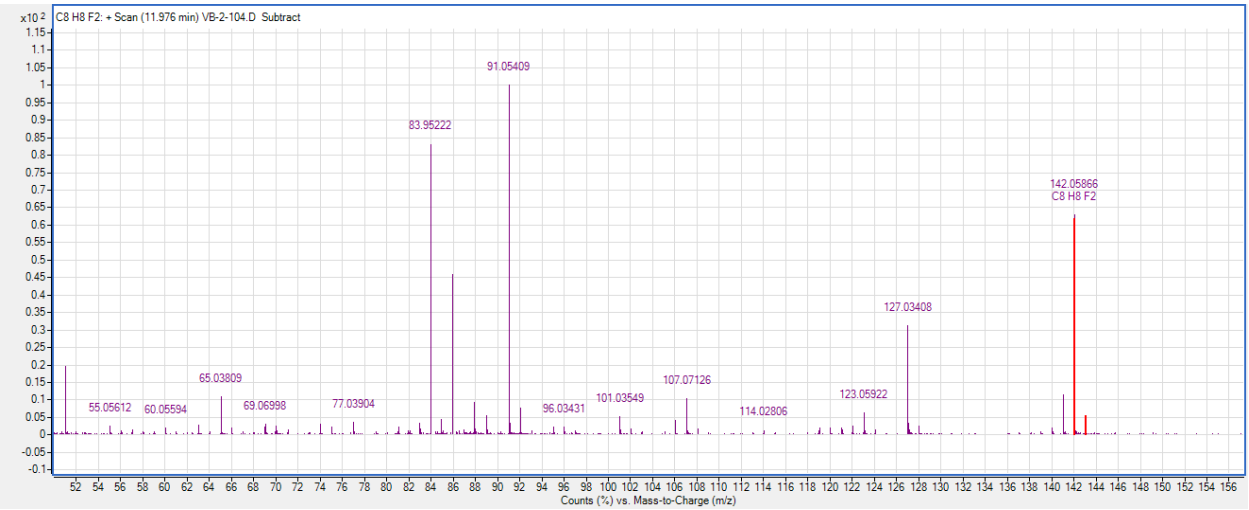


Figure S10. ^{19}F NMR assay difluoromethylarene **23**



1-(difluoromethyl)-4-methylbenzene (24)

Prepared following general procedure A using 1-bromo-4-methylbenzene (85.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.50 mmol, 1.0 equiv., 0.25 mL, 2.0 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 67% was observed (average of two trials: 67.3% and 66.6% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_8F_2$ ($[M^*]^+$) 142.0589, found 142.0587.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.8 (d, J = 56.3 Hz, 2F).

Spectroscopic data matches previously reported data.[10,13]

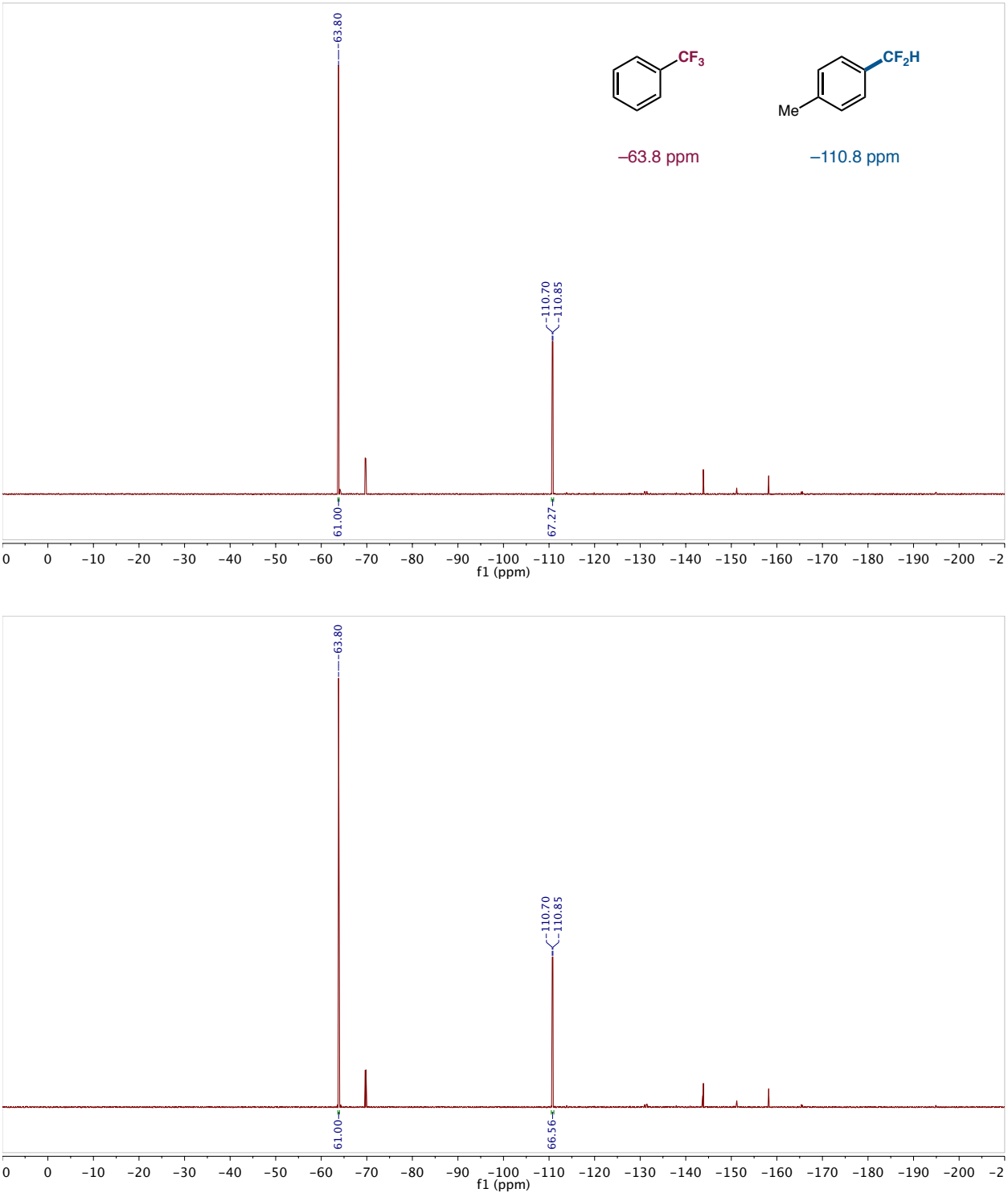
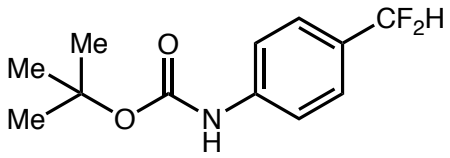


Figure S11. ^{19}F NMR assay for difluoromethylarene **24**



***tert*-butyl (4-(difluoromethyl)phenyl)carbamate (25)**

Prepared following general procedure A using *tert*-butyl (4-bromophenyl)carbamate (136 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.50 mmol, 1.0 equiv., 0.28 mL, 1.8 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added sodium acetate (205 mg, 2.5 mmol, 5.0 equiv.). After sonication for 1.5 h, the reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (2–20% EtOAc/hexanes) provided the title compound as a white solid (89.4 mg, 0.368 mmol, 74% yield).

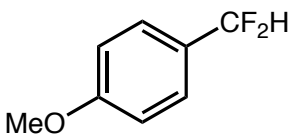
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 4H), 6.62 (br s, 1H), 6.59 (t, J = 56.7 Hz, 1H), 1.52 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 140.7 (t, J = 1.9 Hz), 128.9 (t, J = 22.7 Hz), 126.6 (t, J = 6.1 Hz), 118.2, 114.8 (t, J = 237.8 Hz), 81.2, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.3 (d, J = 56.7 Hz, 2F).

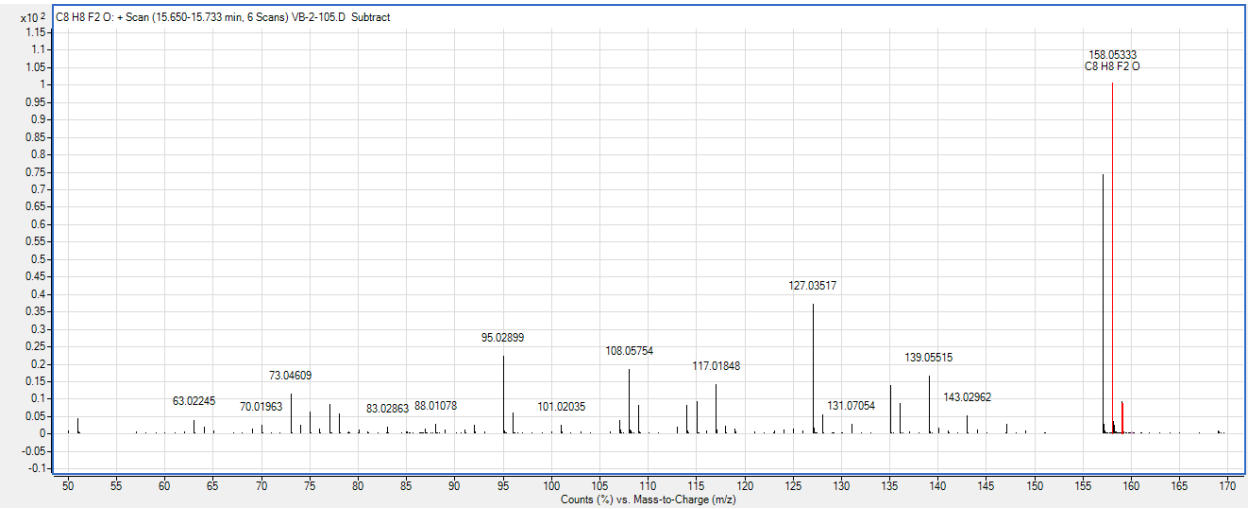
IR (film) ν_{max} 3364, 2988, 1694, 1598, 1510, 1372, 1303, 1156, 1059, 1015, 836, 765 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_8F_2NO_2$ ($[M–C_4H_9+2H]^+$) 188.0518, found 188.0522.



1-(difluoromethyl)-4-methoxybenzene (26)

Prepared following general procedure A using 1-bromo-4-methoxybenzene (93.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.50 mmol, 1.0 equiv., 0.25 mL, 2.0 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 55% was observed (average of two trials: 54.9% and 54.7% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_8F_2O$ ($[M^*]^+$) 158.0538, found 158.0533.

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.1 (d, J = 56.5 Hz, 2F).

Spectroscopic data matches previously reported data.[14]

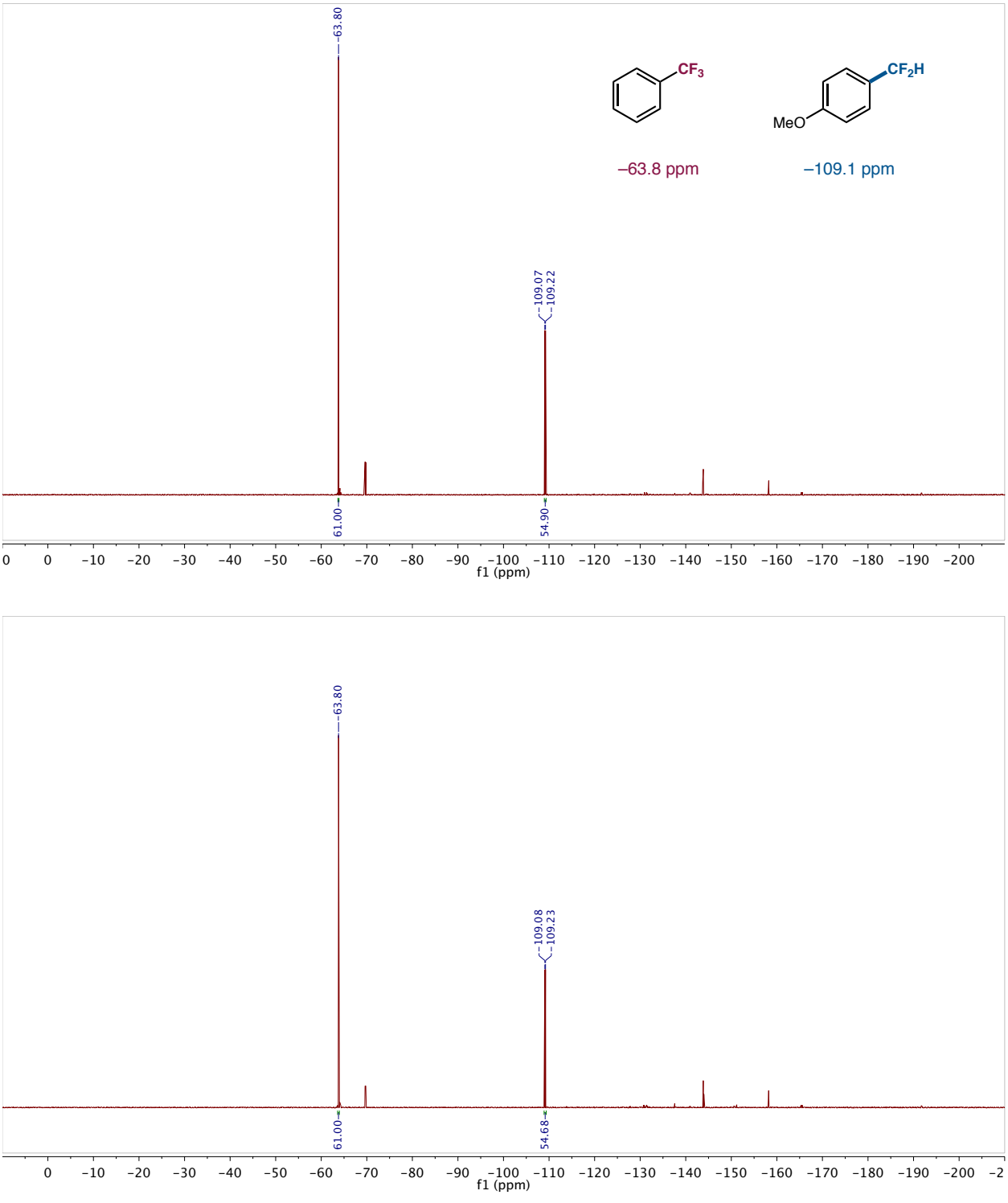
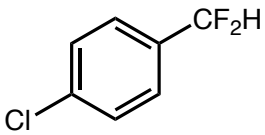
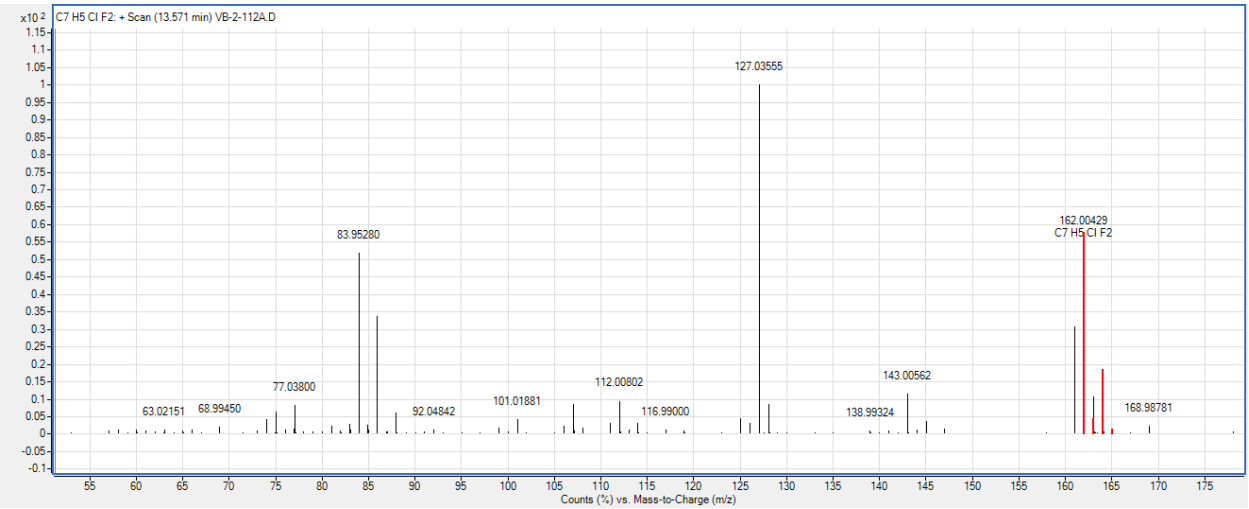


Figure S12. ^{19}F NMR assay for difluoromethylarene **26**



1-chloro-4-(difluoromethyl) benzene (27)

Prepared following general procedure A using 1-bromo-4-chlorobenzene (95.7 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.61 mmol, 1.2 equiv., 0.29 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 80% was observed (average of two trials: 79.0% and 81.7% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_7H_5ClF_2$ ($[M^*]^+$) 162.0042, found 162.0043.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.9 (d, J = 56.1 Hz, 2F).

Spectroscopic data matches previously reported data.[15]

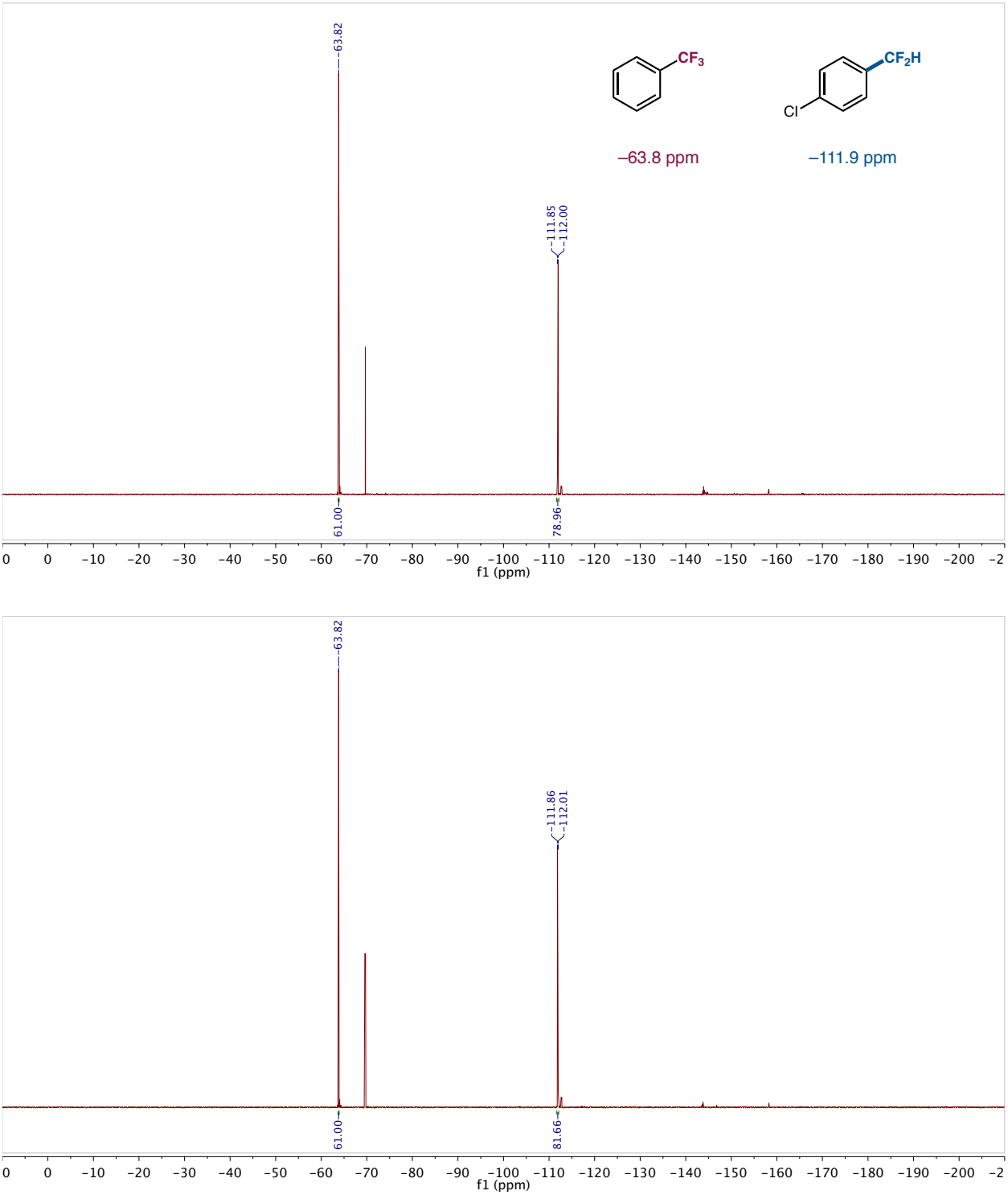
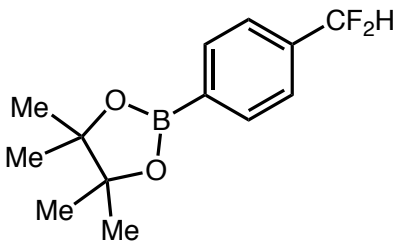
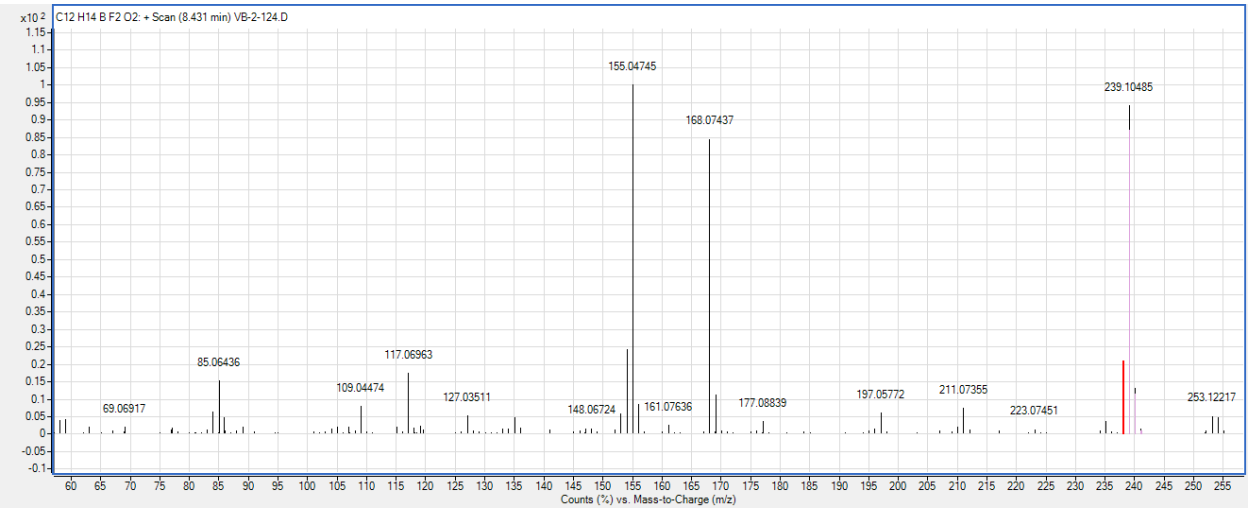


Figure S13. ^{19}F NMR assay for difluoromethylarene **27**



2-(4-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28)

Prepared following general procedure A using 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (142 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.60 mmol, 1.2 equiv., 0.23 mL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the instability of the desired product to chromatographic purification.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 μL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 85% was observed (average of two trials: 85.8% and 85.1% yield).



Crude HRMS (GC-EI-TOF) *m/z* calcd. for $C_{12}H_{14}BF_2O_2$ ($[M–CH_3]^+$) 239.1049, found 239.1049.

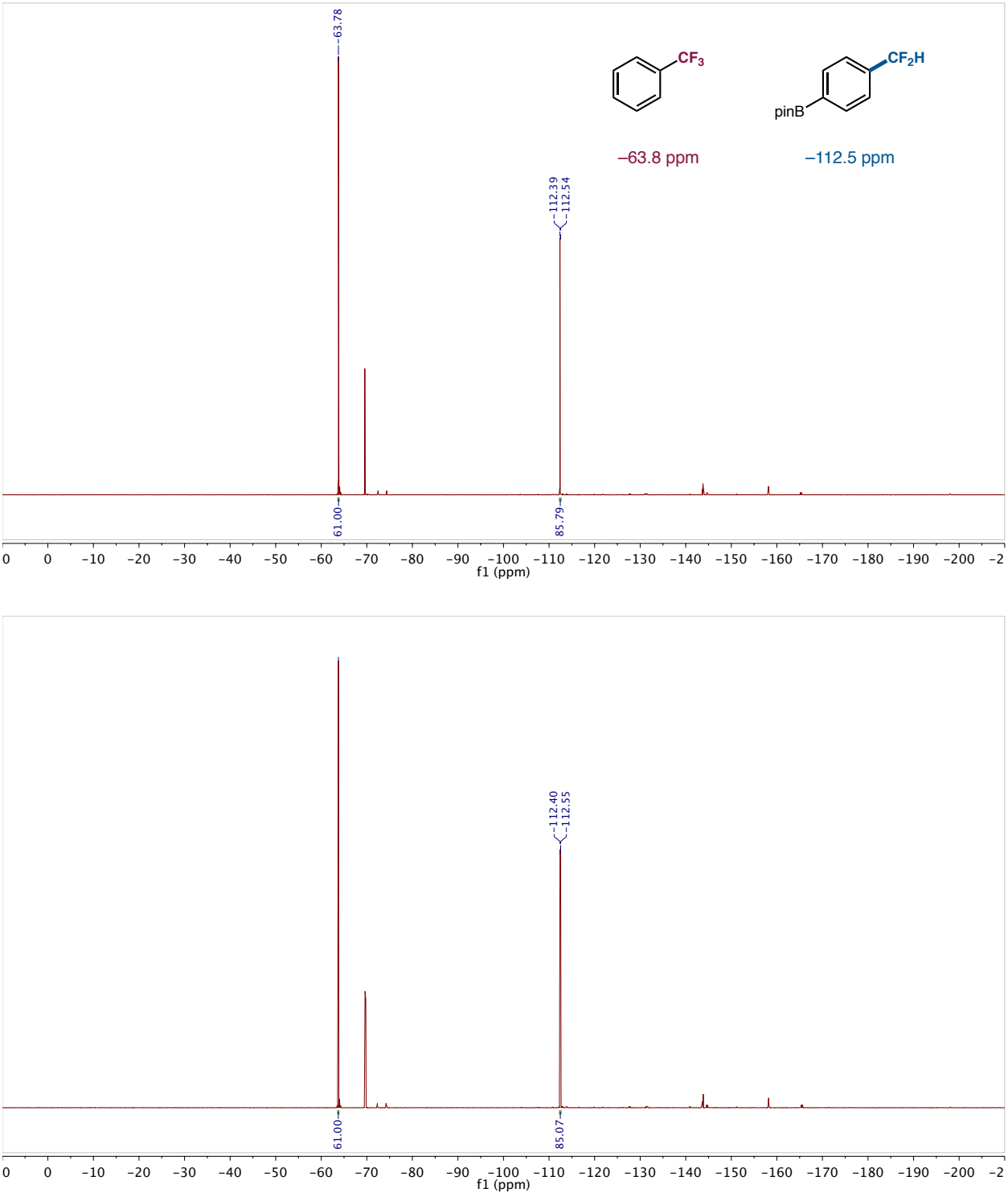


Figure S14. ^{19}F NMR assay for difluoromethylarene **28**

A purified sample of the product could be obtained for spectroscopic characterization. After 18 h, the crude reaction mixture was diluted with pentane, filtered through a cotton plug, and concentrated *in vacuo*. Purification by flash column chromatography (0–5% Et_2O/pentane) provided the title compound as a white solid (23.3 mg, 0.982 mmol, 18% yield). The discrepancy between the isolated and crude NMR yields is likely due to the instability of the difluoromethylarene product to silica gel.

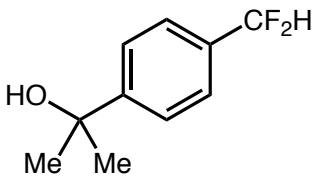
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 6.65 (t, *J* = 56.4 Hz, 1H), 1.35 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9 (t, *J* = 22.2 Hz), 135.2, 124.9 (t, *J* = 6.0 Hz), 114.8 (t, *J* = 239.0 Hz), 84.3, 25.0. (*Note: signal for aromatic carbon ipso to boron is absent.*)

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.5 (d, *J* = 56.5 Hz, 2F).

IR (film) ν_{max} 2978, 1619, 1519, 1401, 1357, 1327, 1217, 1142, 1088, 1019, 962, 856, 655 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_{12}H_{14}BF_2O_2$ ($[M–CH_3]^+$) 239.1049, found 239.1047.



2-(4-(difluoromethyl)phenyl)propan-2-ol (29)

Prepared following general procedure A using 2-(4-bromophenyl)propan-2-ol (108 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.51 mmol, 1.0 equiv., 195 μL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was diluted with Et_2O (10 mL) and washed with 0.3 M aqueous HCl (15 mL) in order to remove excess 2,6-lutidine. The aqueous layer was then back-extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification twice by flash column chromatography (7–60% Et_2O/pentane and 5–30% acetone/pentane, respectively) provided the title compound as a slightly yellow oil (66.2 mg, 0.356 mmol, 71% yield).

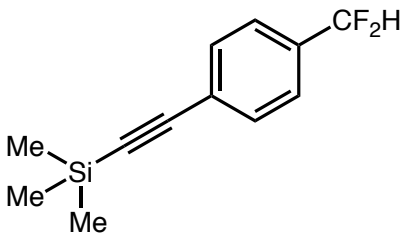
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.64 (t, *J* = 56.5 Hz, 1H), 1.83 (s, 1H), 1.59 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0 (t, *J* = 2.0 Hz), 132.9 (t, *J* = 22.4 Hz), 125.6 (t, *J* = 6.0 Hz), 124.9, 114.9 (t, *J* = 238.3 Hz), 72.6, 31.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.2 (d, *J* = 56.5 Hz, 2F).

IR (film) ν_{max} 3383, 2977, 1618, 1417, 1371, 1222, 1171, 1097, 1069, 1016, 955, 830, 702 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_9H_9F_2O$ ($[M–CH_3]^+$) 171.0616, found 171.0613.



((4-(difluoromethyl)phenyl)ethynyl)trimethylsilane (30)

Prepared following general procedure A using ((4-bromophenyl)ethynyl)trimethylsilane (127 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.60 mmol, 1.2 equiv., 0.29 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (100% heptanes) provided the title compound as a low melting slightly yellow solid (83.7 mg, 0.373 mmol, 75% yield).

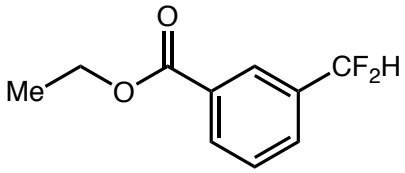
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 6.63 (t, *J* = 56.4 Hz, 1H), 0.26 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2 (t, *J* = 22.5 Hz), 132.3, 125.9 (t, *J* = 2.1 Hz), 125.6 (t, *J* = 6.1 Hz), 114.4 (t, *J* = 239.1 Hz), 104.1, 96.3, 0.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.4 (d, *J* = 56.4 Hz, 2F).

IR (film) ν_{max} 3660, 2980, 2890, 2158, 1611, 1374, 1249, 1214, 1076, 1029, 842, 760, 659 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_{12}H_{14}F_2Si$ ($[M^*]^+$) 224.0827, found 224.0830.



ethyl 3-(difluoromethyl)benzoate (31)

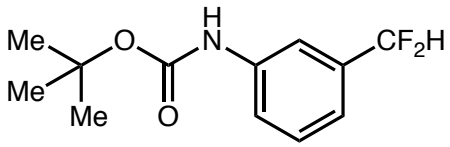
Prepared following general procedure A using ethyl 3-bromobenzoate (115 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.49 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (1–10% Et_2O/pentane) provided the title compound as a colorless oil (78.2 mg, 0.391 mmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.13 (m, 2H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 6.69 (t, *J* = 56.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 134.8 (t, *J* = 22.8 Hz), 131.9 (t, *J* = 1.8 Hz), 131.3, 129.8 (t, *J* = 5.7 Hz), 129.1, 127.0 (t, *J* = 6.3 Hz), 114.3 (t, *J* = 239.4 Hz), 61.5, 14.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.2 (d, *J* = 56.0 Hz, 2F).

Spectroscopic data matches previously reported data.[14]



***tert*-butyl (3-(difluoromethyl)phenyl)carbamate (32)**

Prepared following general procedure A using *tert*-butyl (3-bromophenyl)carbamate (136 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.50 mmol, 1.0 equiv., 0.31 mL, 1.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial were added KF/alumina (40% wt, 1.5 g) and tetrabutylammonium bromide (0.4 g). After vigorous stirring for 30 minutes, the reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (2–20% EtOAc/hexanes) provided the title compound as a white solid (88.2 mg, 0.363 mmol, 73% yield).

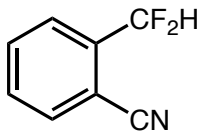
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 6.61 (br s, 1H), 6.60 (t, J = 56.4 Hz, 1H), 1.52 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 139.0, 135.4 (t, J = 22.4 Hz), 129.5, 120.6, 120.1 (t, J = 6.1 Hz), 115.7 (shouldered br s), 114.6 (t, J = 239.1 Hz), 81.1, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.8 (d, J = 56.5 Hz, 2F).

IR (film) ν_{max} 3325, 2981, 1700, 1603, 1533, 1446, 1368, 1234, 1153, 1026, 871, 750 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_8F_2NO_2$ ($[M–C_4H_9+2H]^+$) 188.0518, found 188.0518.



2-(difluoromethyl)benzonitrile (33)

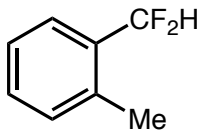
Prepared following general procedure A using 2-bromobenzonitrile (91.0 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.40 mL, 2.5 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, an 83% yield of the desired product was observed via ^{19}F NMR analysis against α,α,α-trifluorotoluene. To the reaction vial were added KF/alumina (40% wt, 1.5 g) and tetrabutylammonium bromide (0.4 g). After vigorous stirring for 6 hours, the reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (0–30% Et_2O/pentane) provided the title compound as a slightly yellow oil (56.2 mg, 0.367 mmol, 73% yield). The discrepancy between the isolated and crude NMR yields is likely due to the volatility of the difluoromethylarene product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 3H), 7.65 – 7.59 (m, 1H), 6.93 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9 (t, *J* = 23.3 Hz), 133.5, 133.4, 131.4 (t, *J* = 1.8 Hz), 126.6 (t, *J* = 5.8 Hz), 115.9, 112.3 (t, *J* = 240.1 Hz), 110.8 (t, *J* = 5.3 Hz).

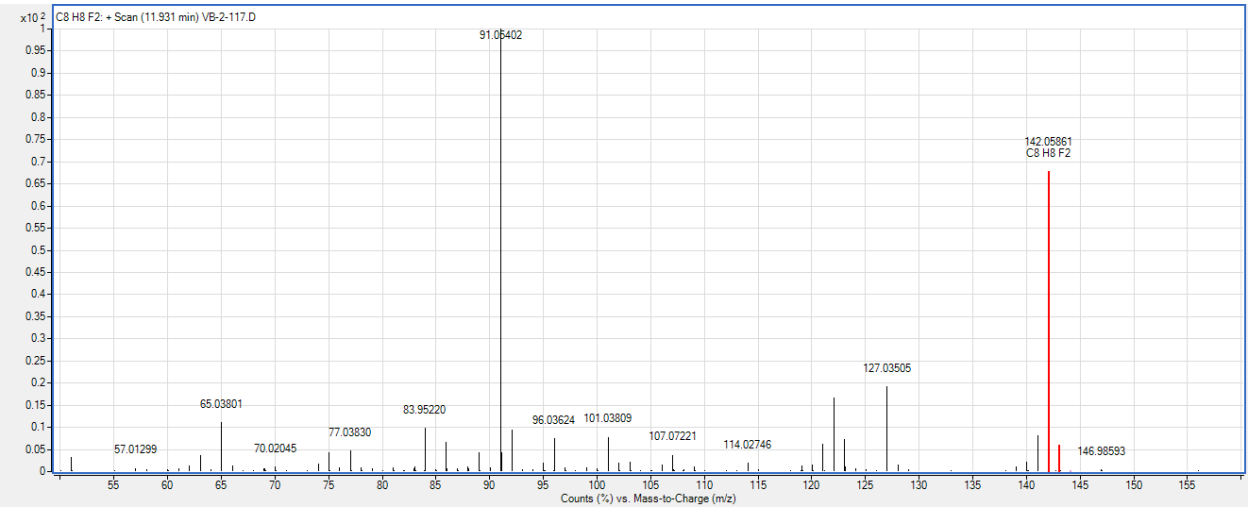
^{19}F NMR (376 MHz, $CDCl_3$) δ –112.1 (d, *J* = 54.6 Hz, 2F).

Spectroscopic data matches previously reported data.[15]



1-(difluoromethyl)-2-methylbenzene (34)

Prepared following general procedure A using 1-bromo-2-methylbenzene (85.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.50 mmol, 1.0 equiv., 0.24 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (15.4 mg, 50 µmol, 10 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (13.4 mg, 50 µmol, 10 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 42 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 60% was observed (average of two trials: 57.7% and 61.8% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_8F_2$ ($[M^*]^+$) 142.0589, found 142.0586.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.3 (d, J = 55.2 Hz, 2F).

Spectroscopic data matches previously reported data.[16]

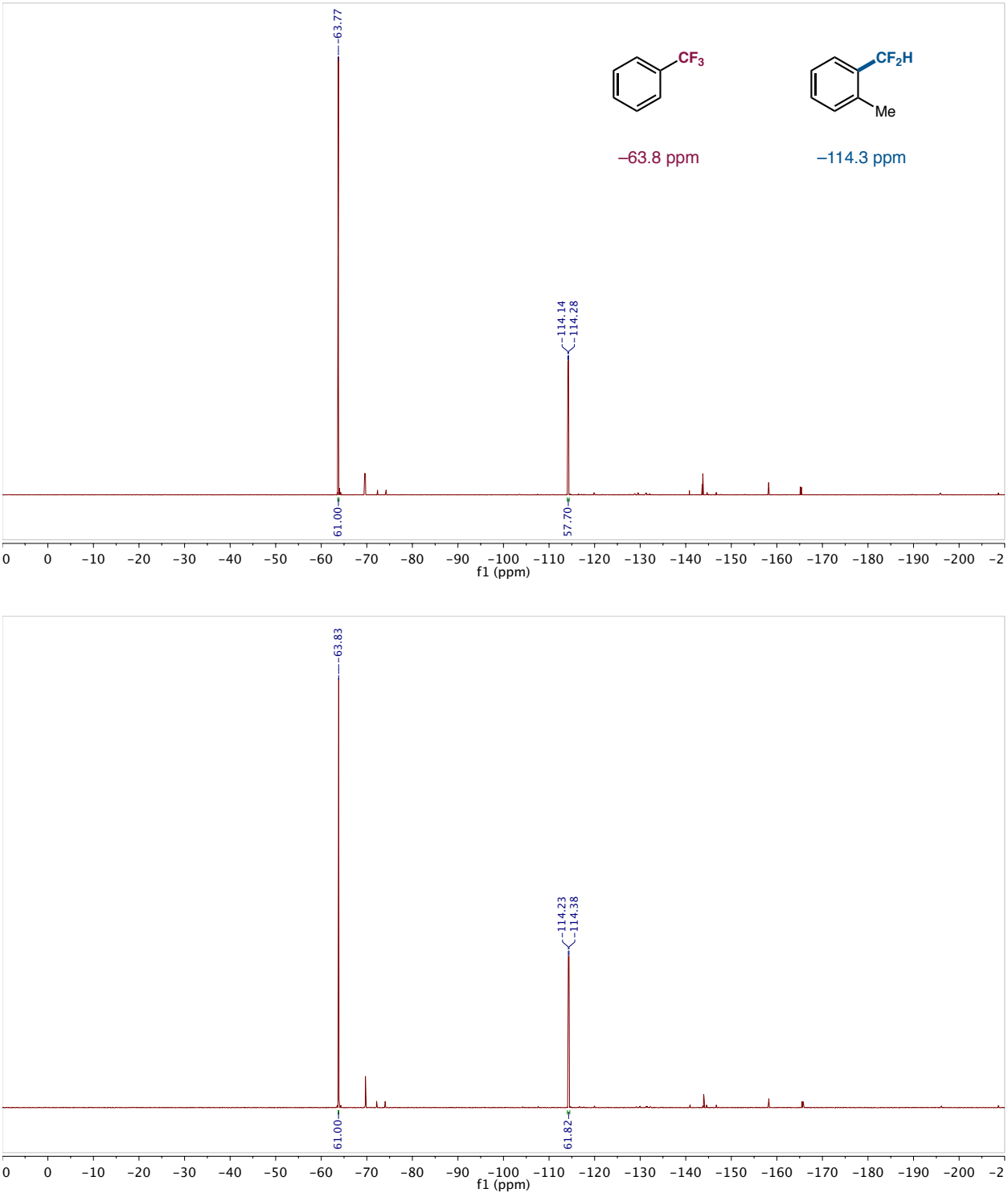
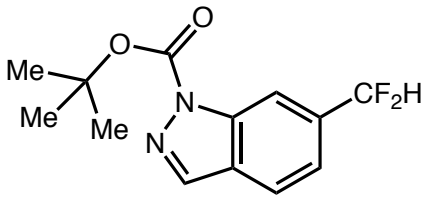


Figure S15. ^{19}F NMR assay for difluoromethylarene **34**



***tert*-butyl 6-(difluoromethyl)-1*H*-indazole-1-carboxylate (35)**

Prepared following general procedure A using *tert*-butyl 6-bromo-1*H*-indazole-1-carboxylate (149 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.51 mmol, 1.0 equiv., 195 µL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification twice by flash column chromatography (2–30% acetone/hexanes and 10–60% Et_2O/pentane, respectively) provided the title compound as a viscous colorless oil that solidified to a white solid over several weeks (92.6 mg, 0.345 mmol, 69% yield).

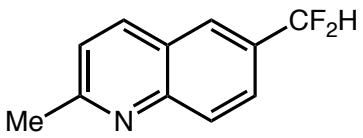
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.21 (d, *J* = 0.5 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 56.2 Hz, 1H), 1.73 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 139.4, 139.3, 135.1 (t, *J* = 22.3 Hz), 127.3 (t, *J* = 1.6 Hz), 121.9, 120.9 (t, *J* = 5.2 Hz), 114.7 (t, *J* = 239.8 Hz), 112.7 (t, *J* = 7.5 Hz), 85.6, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.7 (d, *J* = 56.2 Hz, 2F).

IR (film) ν_{max} 2998, 2980, 1744, 1729, 1474, 1425, 1382, 1347, 1300, 1257, 1155, 1121, 1065, 1030, 998, 951, 855, 816, 748 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_7F_2N_2$ ($[M+2H–Boc]^+$) 169.0572, found 169.0575.



6-(difluoromethyl)-2-methylquinoline (36)

Prepared following general procedure A using 6-bromo-2-methylquinoline (111 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.75 mmol, 1.5 equiv., 0.38 mL, 2.0 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. The crude product was subjected to reverse phase chromatography (0–80% MeCN/H_2O). After removing the acetonitrile from the combined product fractions *in vacuo*, the remaining aqueous layer was basified with K_2CO_3 and back-extracted with DCM (3 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (10–80% Et_2O/pentane) provided the title compound as a white solid (72.5 mg, 0.375 mmol, 75% yield).

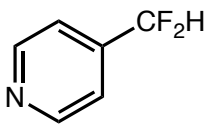
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (overlapping d, J = 8.7 Hz, 1H), 8.08 (overlapping d, J = 8.4 Hz, 1H), 7.91 (m, 1H), 7.78 (dd, J = 8.9, 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.80 (t, J = 56.3 Hz, 1H), 2.76 (s, 3H).

Quantitative ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 148.8 (t, J = 1.6 Hz), 136.7, 131.6 (t, J = 22.5 Hz), 129.8, 125.9 (overlapping t, J = 4.8 Hz), 125.8 (overlapping s), 125.6 (t, J = 7.3 Hz), 123.0, 114.7 (t, J = 238.9 Hz), 25.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ –110.2 (d, J = 56.3 Hz, 2F).

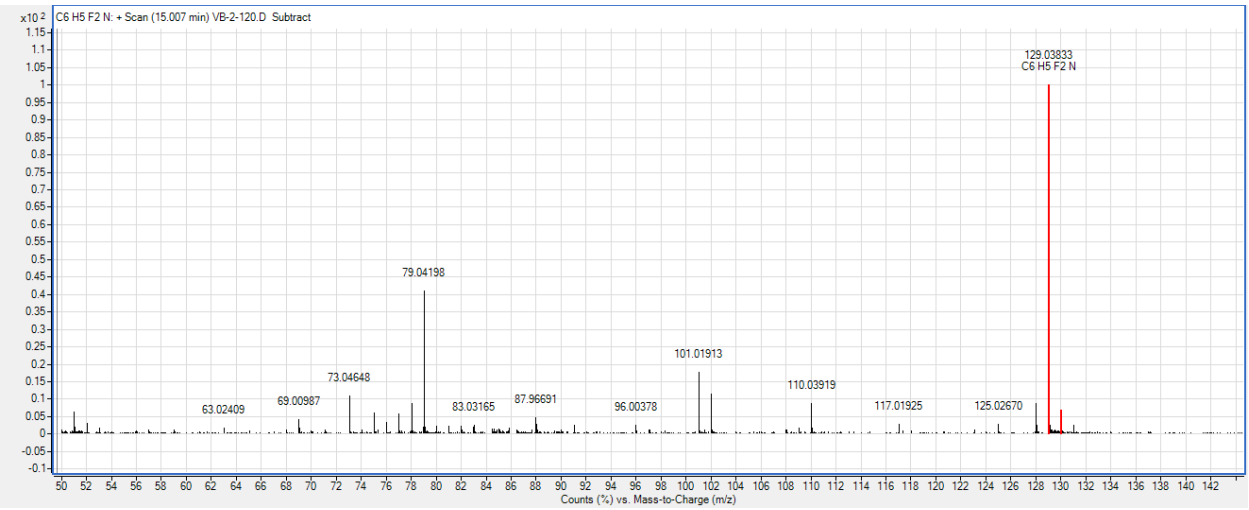
IR (film) ν_{max} 2923, 1603, 1483, 1364, 1329, 1233, 1167, 1079, 1007, 900, 838, 786 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_{11}H_9F_2N$ ($[M^*]^+$) 193.0698, found 193.0693.



4-(difluoromethyl)pyridine (37)

Prepared following general procedure B using 4-bromopyridin-1-ium chloride (97.4 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), dry Na_2CO_3 (265 mg, 2.5 mmol, 5.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). The reaction vial was kept only 1–2 cm away from the light source. Fans were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was then back-extracted with EtOAc three times. To the combined organic layers was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in DMSO-d_6. A yield of 54% was observed (average of two trials: 55.3% and 52.1% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_6H_5F_2N$ ($[M^*]^+$) 129.0385, found 129.0383.

^{19}F NMR (376 MHz, DMSO-d_6) δ –116.9 (d, J = 55.4 Hz).

Spectroscopic data matches previously reported data.[17]

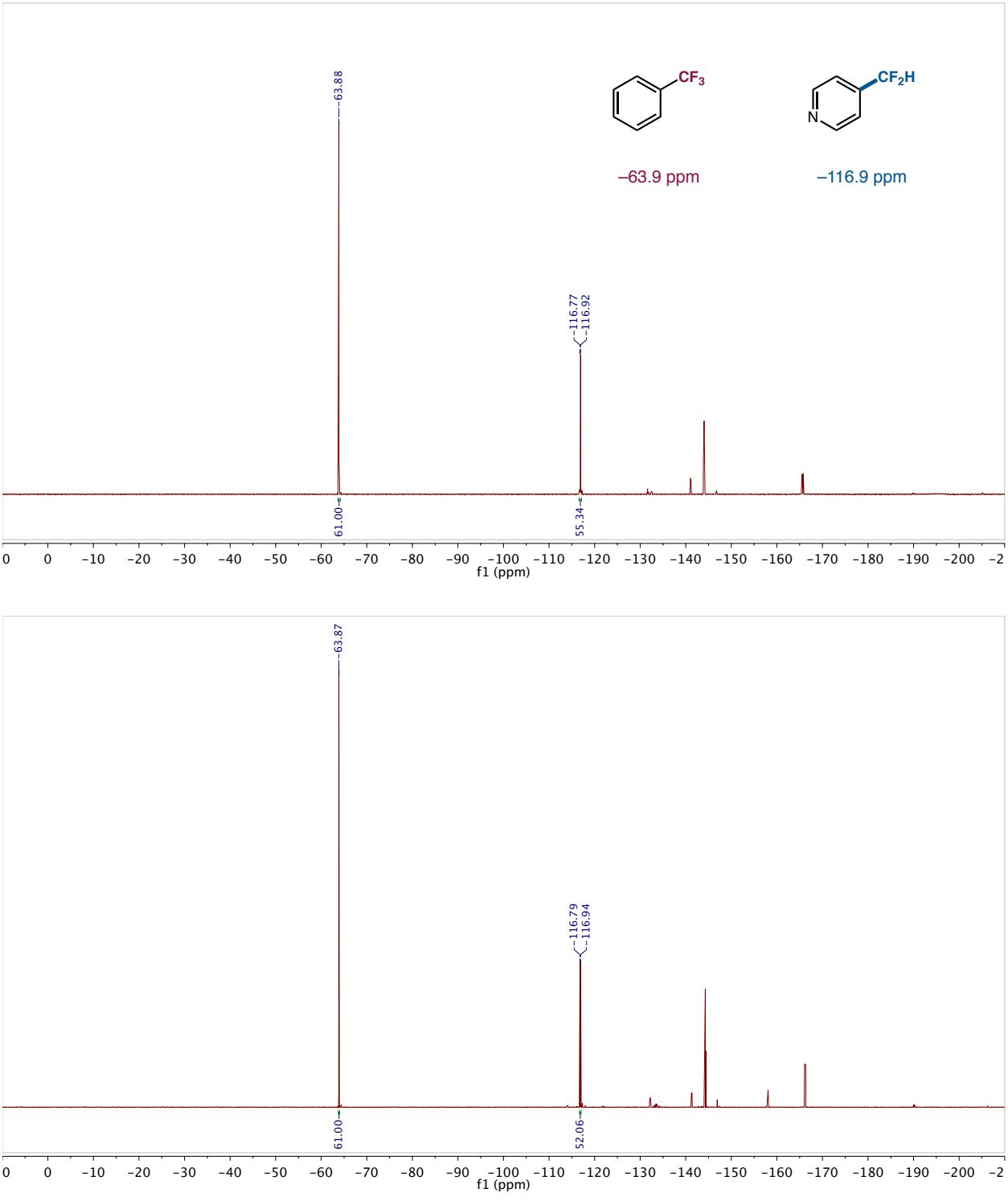
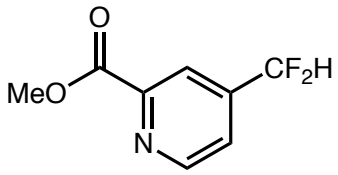


Figure S16. ^{19}F NMR assay for difluoromethylarene **37**



methyl 4-(difluoromethyl)picolinate (38)

Prepared following general procedure A using methyl 4-bromopicolinate (107.4 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.40 mL, 2.5 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (161 μL, 0.52 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (33% EtOAc/hexanes) provided the title compound as a yellow oil (66.3 mg, 0.354 mmol, 71% yield).

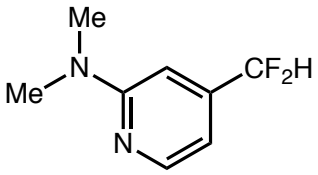
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 4.9 Hz, 1H), 8.25 (s, 1H), 7.61 (d, *J* = 5.4 Hz, 1H), 6.70 (t, *J* = 55.4 Hz, 1H), 4.03 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 150.7, 149.0, 143.7 (t, *J* = 23.9 Hz), 123.2 (t, *J* = 5.7 Hz), 121.7 (t, *J* = 6.0 Hz), 112.5 (t, *J* = 241.7 Hz), 53.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.1 (d, *J* = 55.4 Hz, 2F).

IR (film) ν_{max} 2956, 1724, 1445, 1366, 1303, 1211, 1131, 1039, 977, 783 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_8F_2NO_2$ ($[M+H]^+$) 188.0518, found 188.0517.



4-(difluoromethyl)-*N,N*-dimethylpyridin-2-amine (39)

Prepared following general procedure A using 4-bromo-*N,N*-dimethylpyridin-2-amine (101.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.47 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.7 mg, 5.1 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (118 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (164 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (25% EtOAc/hexanes) provided the title compound as a yellow oil (72.7 mg, 0.422 mmol, 84% yield).

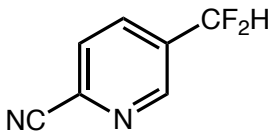
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.1 Hz, 1H), 6.62 (d, *J* = 5.1 Hz, 1H), 6.57 (s, 1H), 6.52 (t, *J* = 56.1 Hz, 1H), 3.11 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 148.9, 143.3 (t, *J* = 22.6 Hz), 113.8 (t, *J* = 240.3 Hz), 107.4 (t, *J* = 5.4 Hz), 101.9 (t, *J* = 6.8 Hz), 38.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.3 (d, *J* = 56.2 Hz, 2F).

IR (film) ν_{max} 2930, 1610, 1508, 1418, 1312, 1223, 1169, 1033, 996, 905, 843, 810, 763 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_{11}F_2N_2$ ($[M+H]^+$) 173.0885, found 173.0884.



5-(difluoromethyl)picolinonitrile (40)

Prepared following general procedure A using 5-bromopicolinonitrile (91.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.5 mmol, 3.0 equiv., 0.84 mL, 1.8 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added acetic acid (0.29 mL, 5.0 mmol, 10 equiv.) in order to protonate the excess 2,6-lutidine. After stirring for 5 minutes, the reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (5–30% EtOAc/hexanes) provided the title compound as a white solid (58.1 mg, 0.377 mmol, 75% yield).

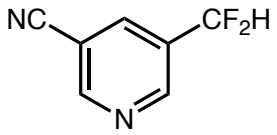
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 55.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7 (t, *J* = 6.5 Hz), 136.1 (t, *J* = 2.1 Hz), 134.7 (t, *J* = 5.7 Hz), 133.2 (t, *J* = 23.5 Hz), 128.4, 116.6, 112.3 (t, *J* = 241.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.3 (d, *J* = 55.2 Hz, 2F).

IR (film) ν_{max} 2980, 2242, 1583, 1471, 1417, 1366, 1231, 1080, 1025, 947, 859, 754 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_7H_4F_2N_2$ ($[M^*]^+$) 154.0337, found 154.0335.



5-(difluoromethyl)-nicotinonitrile (41)

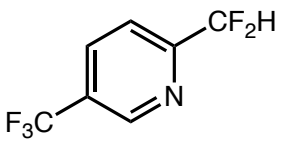
Prepared following general procedure A using 5-bromonicotinonitrile (91.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.39 mL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (116 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was diluted with Et_2O (15 mL) and washed with aqueous 2% formic acid solution (10 mL) in order to remove excess 2,6-lutidine. The aqueous layer was then back-extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (10–80% Et_2O/pentane) provided the title compound as a white solid (52.9 mg, 0.343 mmol, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.96 (s, 1H), 8.13 (s, 1H), 6.77 (t, J = 55.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4 (t, J = 1.9 Hz), 150.5 (t, J = 6.4 Hz), 136.8 (t, J = 5.8 Hz), 130.6 (t, J = 23.9 Hz), 115.7, 112.1 (t, J = 241.6 Hz), 110.5.

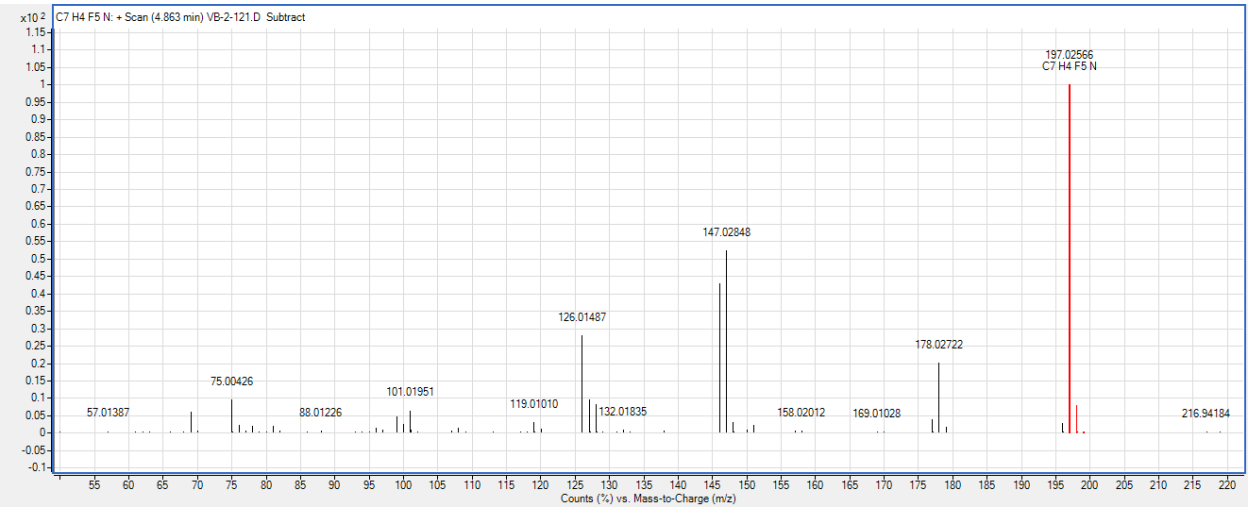
^{19}F NMR (376 MHz, $CDCl_3$) δ –113.9 (d, J = 55.3 Hz, 2F).

Spectroscopic data matches previously reported data.[18]



2-(difluoromethyl)-5-(trifluoromethyl)pyridine (42)

Prepared following general procedure B using 2-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5 mol%), dry LiOH (36 mg, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was then back-extracted with EtOAc three times. To the combined organic layers was added methyl 4-fluorobenzoate (25.0 µL, 0.193 mmol, 0.387 equiv., 0.193 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 46% was observed (average of two trials: 46.4% and 45.5% yield).



HRMS (GC-EI-TOF) *m/z* calcd. for $C_7H_4F_5N$ ($[M^*]^+$) 197.0258, found 197.0256.

^{19}F NMR (376 MHz, $CDCl_3$) δ –63.8 (s, 3F), –118.1 (d, J = 55.1 Hz, 2F).

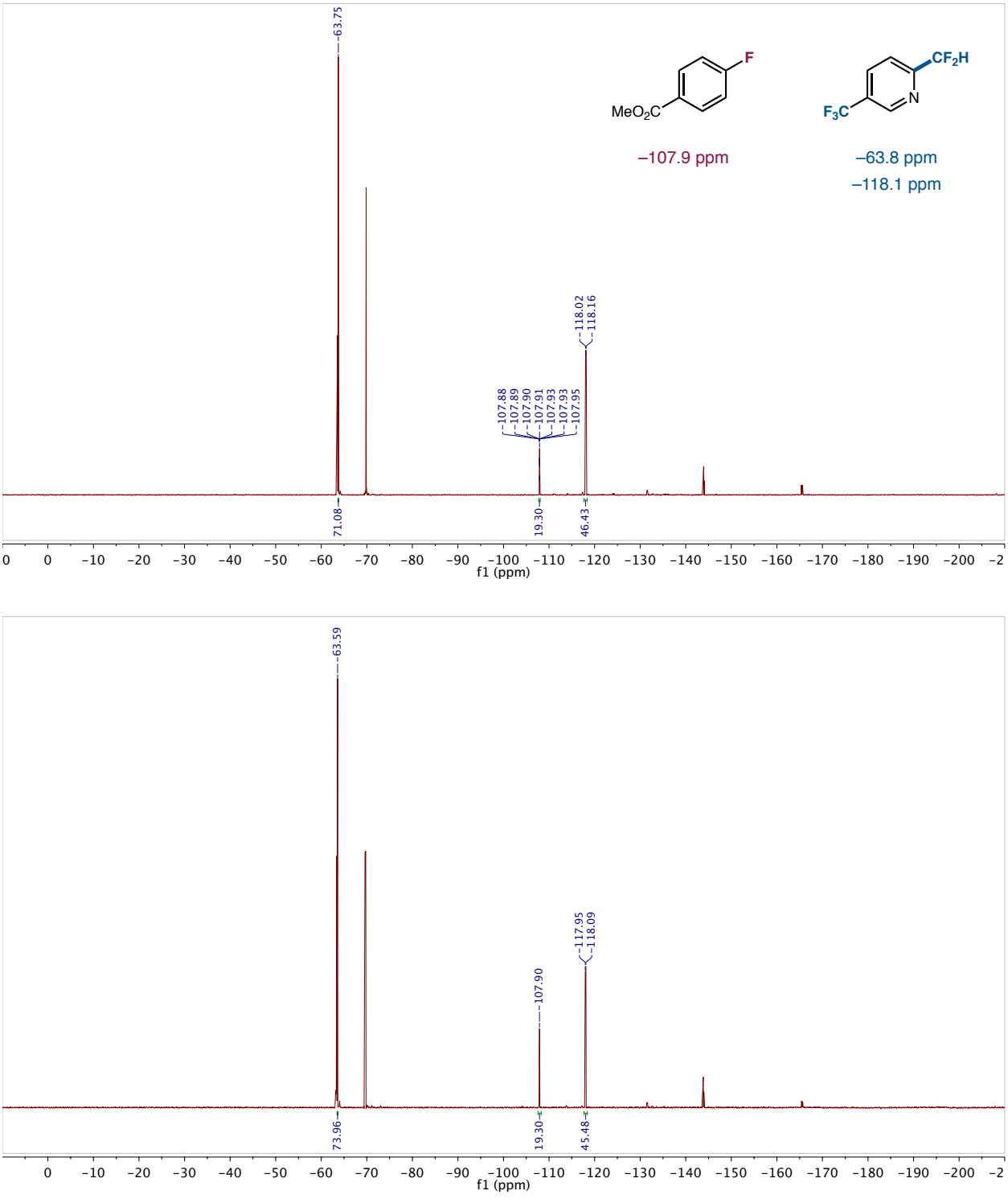
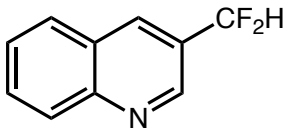


Figure S17. ^{19}F NMR assay for difluoromethylarene **42**



3-(difluoromethyl)quinoline (43)

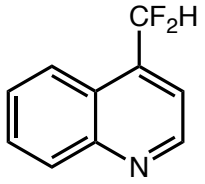
Prepared following general procedure B using 3-bromoquinoline (104.7 mg, 0.503 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.48 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), dry Na_2CO_3 (160 mg, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (6–88% EtOAc/hexanes) provided the title compound as a yellow oil (68.9 mg, 0.385 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.31 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.82 (t, J = 7.3 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 6.89 (t, J = 55.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2 (t, J = 1.6 Hz), 147.3 (t, J = 5.3 Hz), 134.2 (t, J = 6.7 Hz), 131.3, 129.7, 128.6, 127.9, 127.4 (t, J = 22.9 Hz), 127.1, 113.9 (t, J = 239.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.5 (d, J = 55.9 Hz, 2F).

Spectroscopic data matches previously reported data.[18]



4-(difluoromethyl)quinoline (44)

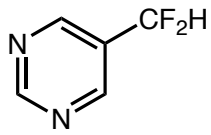
Prepared following general procedure B using 4-bromoquinoline (108.5 mg, 0.52 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.50 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.9 mg, 5.2 μmol, 1.0 mol%), $NiBr_2$•glyme (8.1 mg, 26 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (7 mg, 26 μmol, 5.0 mol%), dry Na_2CO_3 (166 mg, 1.6 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (169 μL, 0.55 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by preparative thin layer chromatography (17% acetone/hexanes) provided the title compound as a yellow solid (73.2 mg, 0.409 mmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (d, *J* = 4.3 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.80 (m, 1H), 7.67 (m, 1H), 7.60 (d, *J* = 4.3 Hz, 1H), 7.17 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 148.8, 137.9 (t, *J* = 21.8 Hz), 130.6, 130.1, 128.0, 124.3 (t, *J* = 3.2 Hz), 123.4, 118.1 (t, *J* = 7.7 Hz), 113.4 (t, *J* = 240.4 Hz).

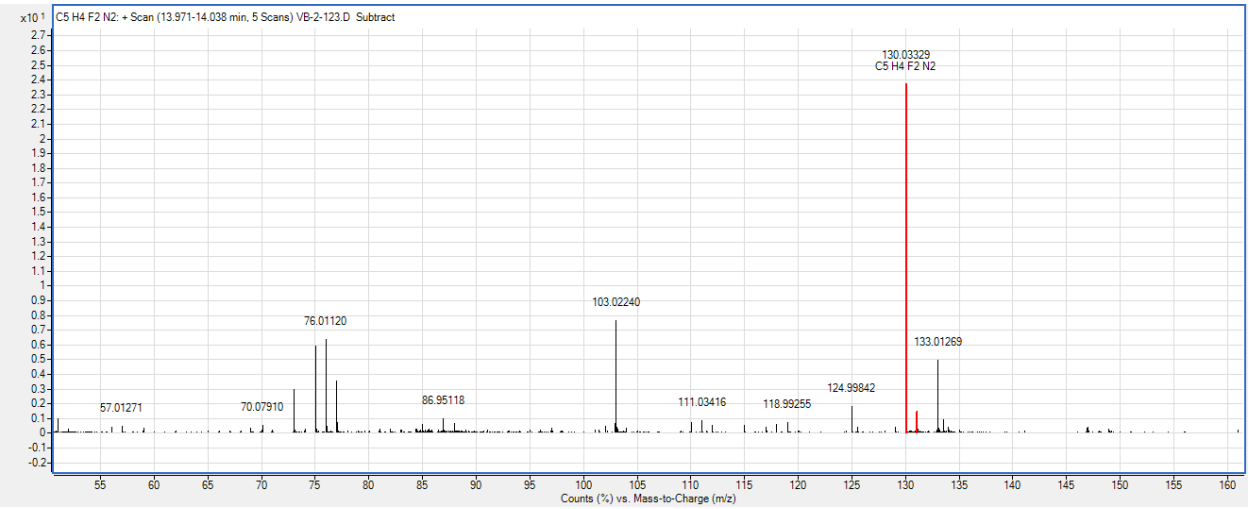
^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1 (d, *J* = 54.7 Hz, 2F).

Spectroscopic data matches with previously reported data.[18]



5-(difluoromethyl)pyrimidine (45)

Prepared following general procedure A using 5-bromopyrimidine (79.5 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.39 mL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was then back-extracted with EtOAc three times. To the combined organic layers was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in DMSO-d_6. A yield of 65% was observed (average of two trials: 65.7% and 64.1% yield).



Crude HRMS (GC-EI-TOF) *m/z* calcd. for $C_5H_4F_2N_2$ ($[M^*]^+$) 130.0337, found 130.0333.

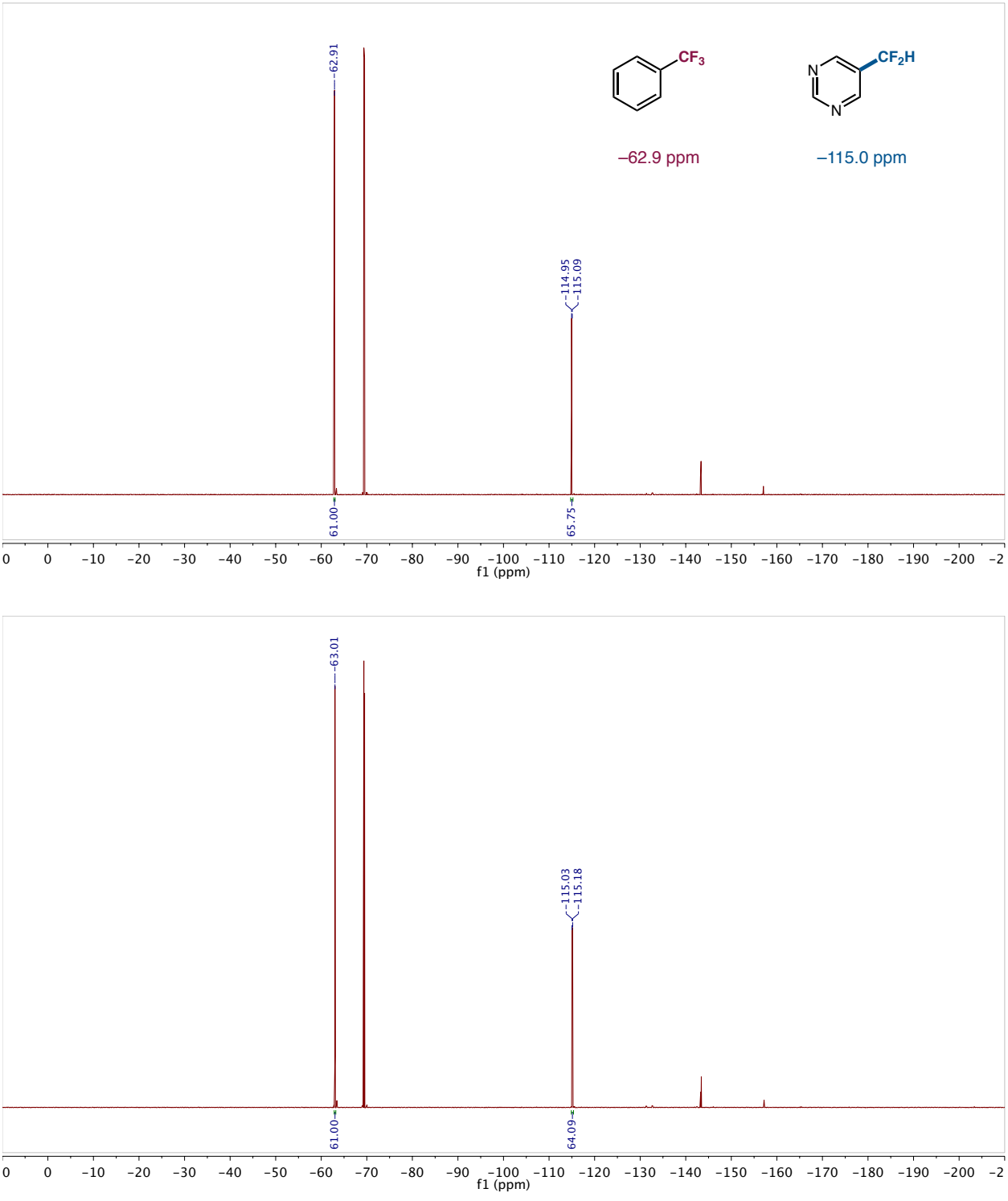


Figure S18. ^{19}F NMR assay for difluoromethylarene **45**

A purified sample of the product could be obtained for spectroscopic characterization. After 18 h, the crude reaction mixture was diluted with Et_2O (15 mL) and washed with aqueous 2% formic acid solution (10 mL) in order to remove excess 2,6-lutidine. The aqueous layer was then back-extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and carefully concentrated *in vacuo*. Purification by flash column chromatography (15–100% Et_2O/pentane) provided the title compound as a yellow oil (11.2 mg, 0.086 mmol, 17% yield). The discrepancy between the isolated and crude NMR yields is likely due to the volatility of the difluoromethylarene product.

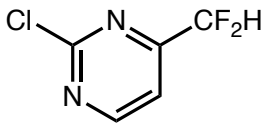
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.91 (s, 2H), 6.77 (t, J = 55.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7 (t, J = 2.1 Hz), 154.7 (t, J = 6.0 Hz), 128.3 (t, J = 24.0 Hz), 112.1 (t, J = 240.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.5 (d, J = 55.2 Hz, 2F).

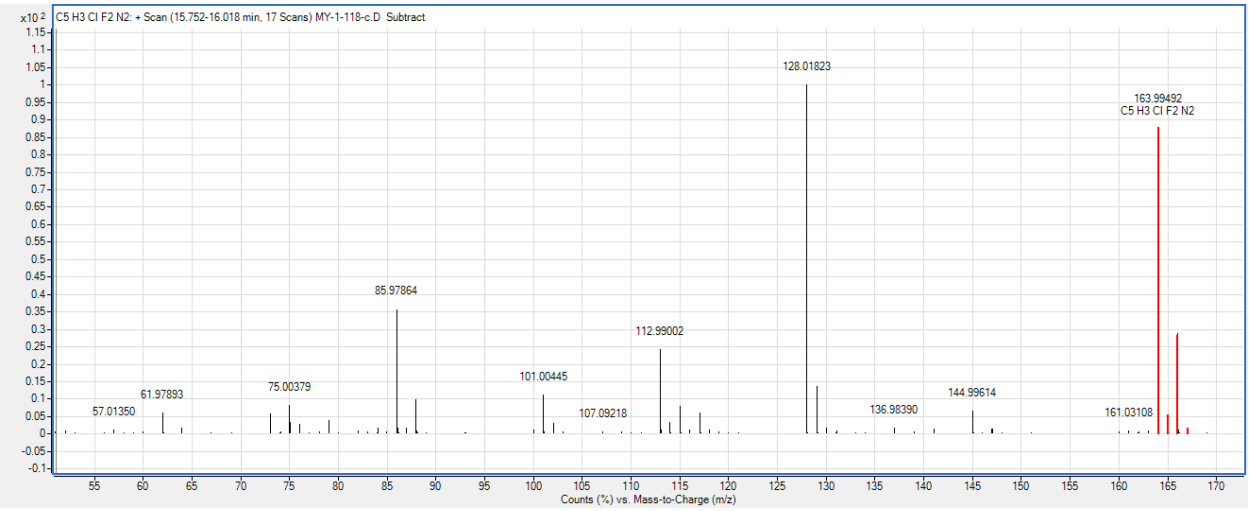
IR (film) ν_{max} 2959, 1720, 1594, 1572, 1418, 1382, 1244, 1114, 1037, 926, 845, 726 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_5H_4F_2N_2$ ($[M^*]^+$) 130.0337, found 130.0334.



2-chloro-4-(difluoromethyl)pyrimidine (46)

Prepared following general procedure A using 4-bromo-2-chloropyrimidine (97.0 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.40 mL, 2.5 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.52 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction mixture was added α,α,α-trifluorotoluene (100 µL, 0.814 mmol, 1.63 equiv., 2.44 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 66% was observed (average of two trials: 66.4% and 66.0% yield).



Crude HRMS (GC-EI-TOF) *m/z* calcd. for $C_5H_3ClF_2N_2$ ($[M^*]^+$) 163.9947, found 163.9949.

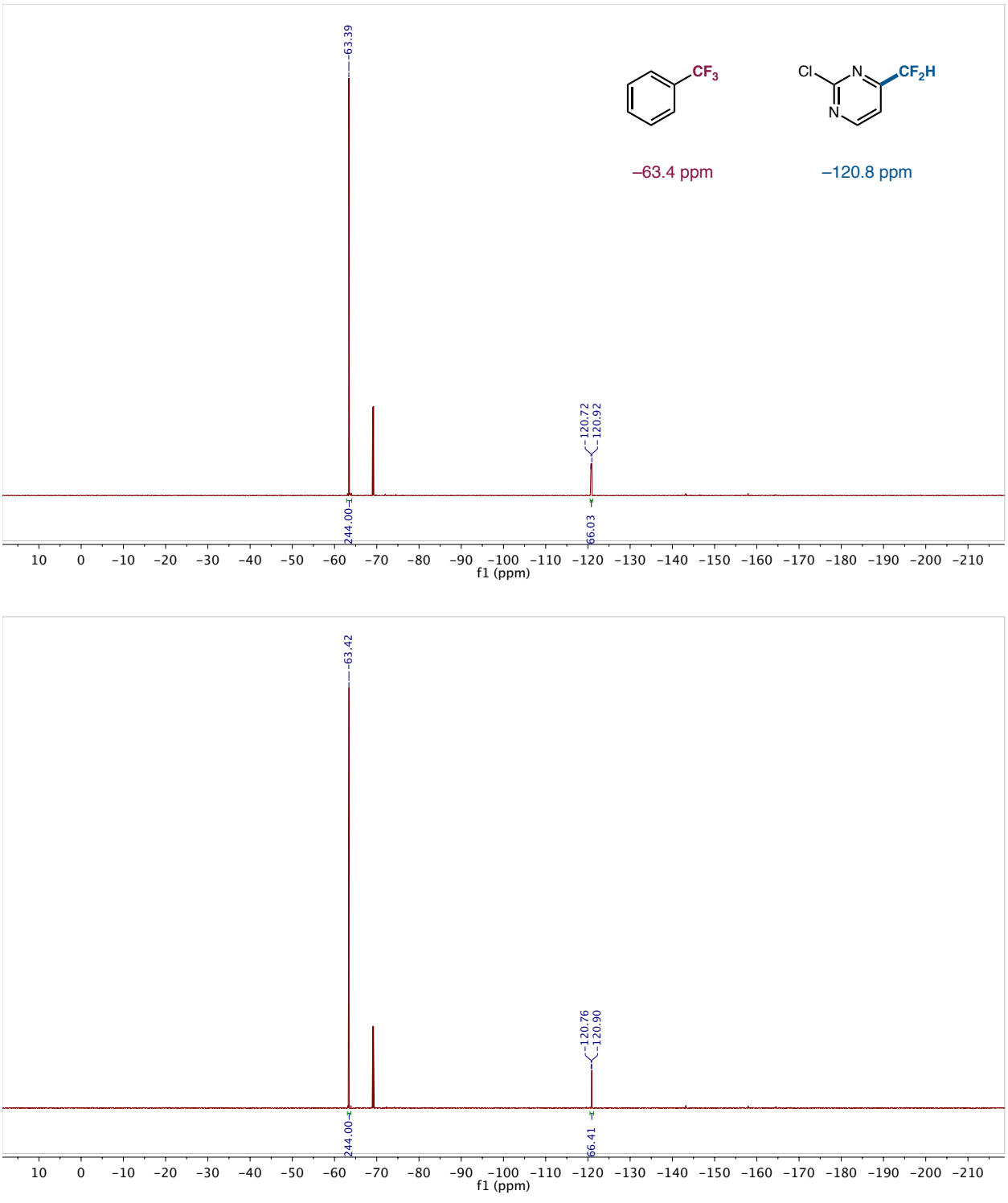


Figure S19. ^{19}F NMR assay for difluoromethylarene **46**

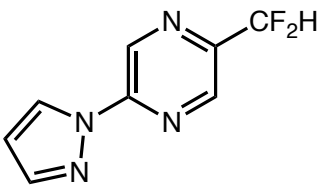
A purified sample of the product could be obtained for spectroscopic characterization. After 18 h, the crude reaction mixture was diluted with DCM (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with DCM (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification twice by preparative thin layer chromatography (33% DCM/hexanes and 9% acetone/hexanes, respectively) provided the title compound as a colorless oil (45.1 mg, 0.274 mmol, 55% yield). The discrepancy between the isolated and crude NMR yields is likely due to the volatility of the difluoromethylarene product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, *J* = 5.0 Hz, 1H), 7.59 (d, *J* = 5.0 Hz, 1H), 6.53 (t, *J* = 54.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2 (t, *J* = 27.6 Hz), 161.8 (t, *J* = 1.5 Hz), 161.6, 115.6 (t, *J* = 2.9 Hz), 111.7 (t, *J* = 242.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –119.4 (d, *J* = 54.3 Hz, 2F).

Spectroscopic data matches previously reported data.[19]



2-(difluoromethyl)-5-(*1H*-pyrazol-1-yl)pyrazine (47)

Prepared following general procedure A using 2-bromo-5-(*1H*-pyrazol-1-yl)pyrazine (113.4 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.76 mmol, 1.5 equiv., 0.36 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 μmol, 2.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 μmol, 2.0 mol%), 2,6-lutidine (117 μL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (163 μL, 0.53 mmol, 1.05 equiv.), and acetone (5.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification twice by preparative thin layer chromatography (14% EtOAc/hexanes and 33% DCM/hexanes, respectively) provided the title compound as a white solid (59.0 mg, 0.301 mmol, 60% yield).

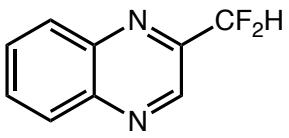
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.67 (s, 1H), 8.54 (d, J = 2.7 Hz, 1H), 7.83 (s, 1H), 6.75 (t, J = 54.9 Hz, 1H), 6.55 (t, J = 1.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 145.0 (t, J = 26.6 Hz), 144.0, 139.7 (t, J = 3.7 Hz), 134.8, 128.0, 113.2 (t, J = 240.2 Hz), 109.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.4 (d, J = 54.8 Hz, 2F).

IR (film) ν_{max} 3127, 1596, 1547, 1499, 1437, 1397, 1380, 1091, 1043, 1019, 939, 867, 779 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_8H_6F_2N_4$ ($[M^*]^+$) 196.0555, found 196.0553.



2-(difluoromethyl)quinoxaline (48)

Prepared following general procedure B using 2-bromoquinoxaline (105 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.49 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), dry Na_2CO_3 (265 mg, 2.5 mmol, 5.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (1–25% Et_2O/pentane) provided the title compound as a white solid (55.1 mg, 0.306 mmol, 61% yield).

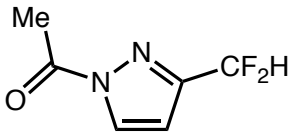
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.82 (m, 2H), 6.84 (t, *J* = 54.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2 (t, *J* = 27.1 Hz), 143.6, 141.9 (t, *J* = 2.4 Hz), 141.2, 131.7, 131.2, 129.8, 129.7, 114.2 (t, *J* = 241.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.2 (d, *J* = 54.5 Hz, 2F).

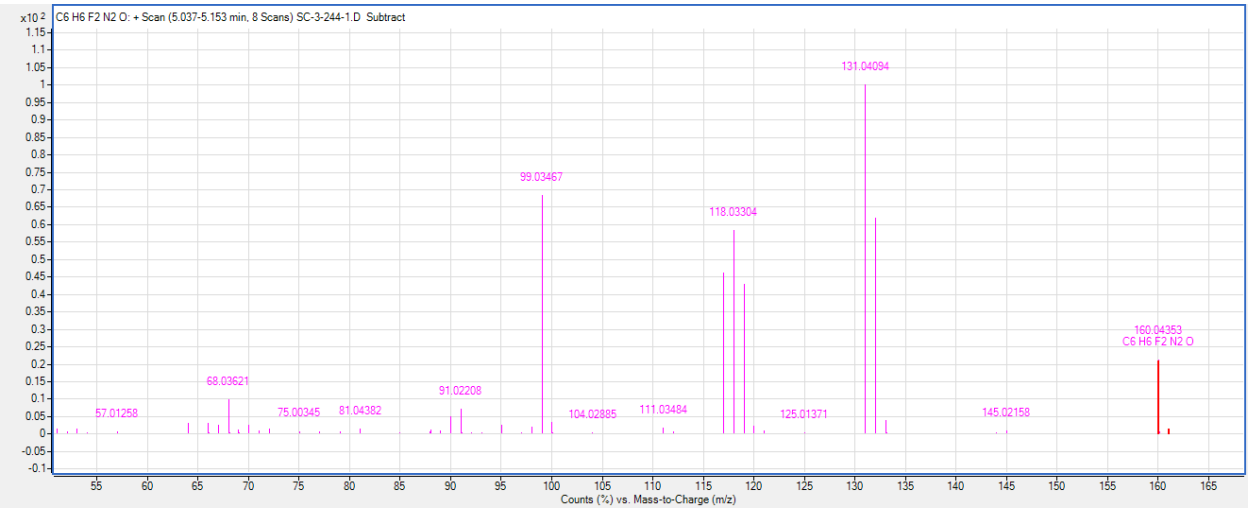
HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_9H_6F_2N_2$ ($[M^*]^+$) 180.0494, found 180.0495.

Spectroscopic data matches previously reported data.[20]



1-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)ethan-1-one (49)

Prepared following general procedure A in a 20 mL vial, using 1-(3-bromo-1*H*-pyrazol-1-yl)ethan-1-one (**S2**) (95.0 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.65 mmol, 1.3 equiv., 0.26 mL, 2.5 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (15 mg, 50 µmol, 10 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (13 mg, 50 µmol, 10 mol%), *N*,*N*-diisopropylethylamine (261 µL, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. The reaction was performed in duplicate. *Yield was determined by ^{19}F NMR due to the high volatility of the desired product.* After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (50.0 µL, 0.407 mmol, 0.814 equiv., 1.22 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A yield of 51% was observed (average of two trials: 49.7% and 51.6% yield).



HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_6H_6F_2N_2O$ ($[M^*]^+$) 160.0443, found 160.0435.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.7 (d, *J* = 54.5 Hz, 2F).

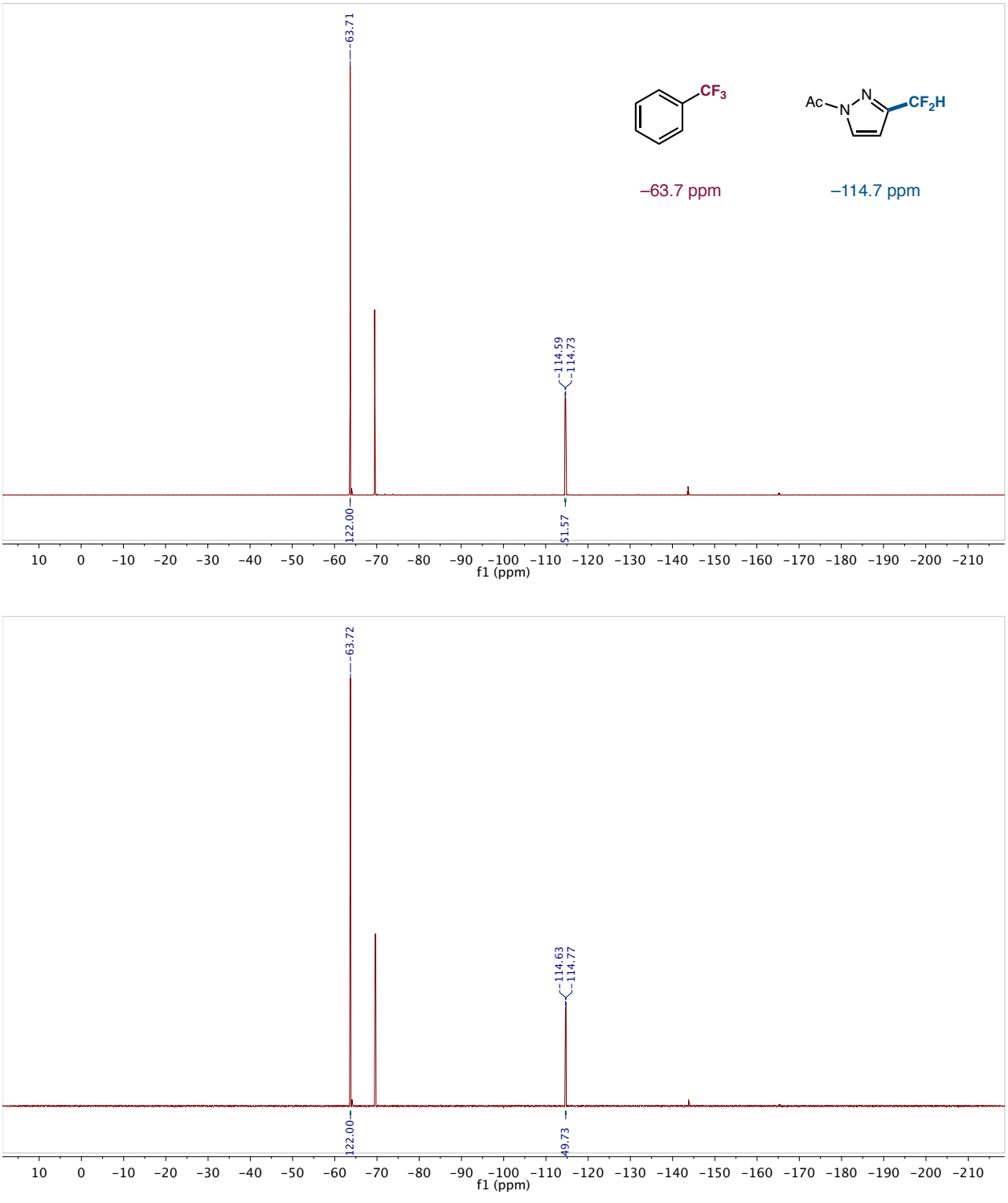
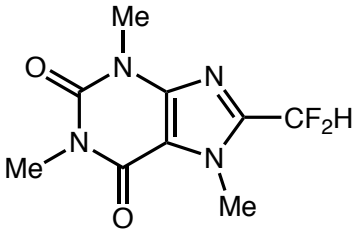


Figure S20. ^{19}F NMR assay for difluoromethylarene **49**



8-(difluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (50)

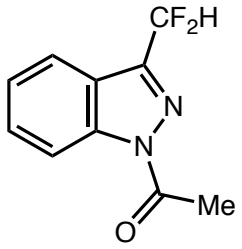
Prepared following general procedure B in a 20 mL vial, using 8-bromo-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (137 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.50 mL, 2.0 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), quinuclidine (111 mg, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (0–100% EtOAc/hexanes) provided the title compound as a white solid (92.1 mg, 0.377 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (t, *J* = 52.2 Hz, 1H), 4.15 (s, 3H), 3.55 (s, 3H), 3.40 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 151.5, 147.0, 142.9 (t, *J* = 27.4 Hz), 109.9 (t, *J* = 238.0 Hz), 109.6, 33.0 (t, *J* = 2.6 Hz), 29.9, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1 (d, *J* = 52.4 Hz, 2F).

Spectroscopic data matches previously reported data.[21]



1-(3-(difluoromethyl)-1*H*-indazol-1-yl)ethan-1-one (51)

Prepared following general procedure B in a 20 mL vial, using 1-(3-bromo-1*H*-indazol-1-yl)ethan-1-one (**S3**) (120 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.63 mmol, 1.3 equiv., 0.24 mL, 2.6 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), quinuclidine (167 mg, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. After 18 h, the crude reaction mixture was poured into a saturated aqueous K_2CO_3 solution (15 mL) and extracted three times with EtOAc (3 × 15 mL). The organic layers were combined and concentrated *in vacuo*. Purification by flash column chromatography (2–8% Et_2O/pentane), followed by reverse phase column chromatography (20–100% MeCN/H_2O) and back-extraction of the appropriate fractions with Et_2O (3 × 20 mL) provided the title compound as a white solid (73.4 mg, 0.349 mmol, 70% yield).

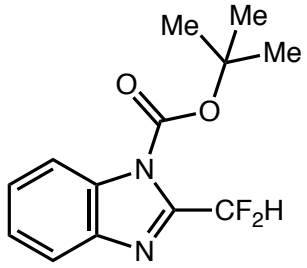
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.45 – 7.39 (m, 1H), 6.93 (t, *J* = 53.8 Hz, 1H), 2.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 144.3 (t, *J* = 30.8 Hz), 140.3, 130.4, 125.4, 122.4, 120.9, 115.8, 111.8 (t, *J* = 234.9 Hz), 23.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.1 (d, *J* = 53.9 Hz, 2F).

IR (film) ν_{max} 2921, 2851, 1731, 1536, 1432, 1374, 1317, 1134 1093, 1025, 937, 795, 749 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_{10}H_8F_2N_2O$ ($[M^*]^+$) 210.0599, found 210.0599.



***tert*-butyl 2-(difluoromethyl)-1*H*-benzo[*d*]imidazole-1-carboxylate (52)**

Prepared following general procedure B in a 20 mL vial, using *tert*-butyl 2-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (**S4**) (149 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.5 mmol, 3.0 equiv., 0.62 mL, 2.4 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), dry K_2CO_3 (207 mg, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (0–25% EtOAc/hexanes) provided the title compound as a white solid (74.2 mg, 0.277 mmol, 55% yield).

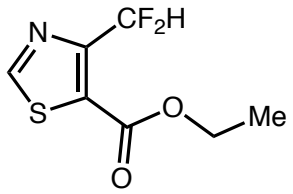
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.43 – 7.38 (m, 1H), 7.24 (t, *J* = 53.3 Hz, 1H), 1.72 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7, 145.9 (t, *J* = 26.8 Hz), 141.5, 133.1, 126.8, 125.2, 121.6, 115.2, 108.4 (t, *J* = 240.7 Hz), 87.4, 28.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ –118.6 (d, *J* = 53.3 Hz, 2F).

IR (film) ν_{max} 2978, 2925, 1747, 1353, 1304, 1149, 1134, 1113, 1080, 1045, 897, 760, 742 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_7F_2N_2$ ($[M–Boc+2H]^+$) 169.0572, found 169.0576.



ethyl 4-(difluoromethyl)thiazole-5-carboxylate (53)

Prepared following general procedure B in a 20 mL vial, using ethyl 4-bromothiazole-5-carboxylate (118 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (0.75 mmol, 1.5 equiv., 0.31 mL, 2.4 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), DABCO (168 mg, 1.5 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification twice by flash column chromatography (0–35% Et_2O/pentane and 0–5% acetone/pentane, respectively) provided the title compound as a white solid (59.3 mg, 0.285 mmol, 57% yield).

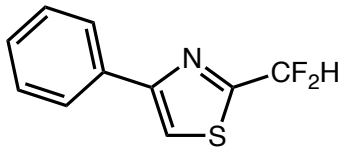
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.42 (t, J = 53.8 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 157.2, 153.1 (t, J = 23.6 Hz), 129.3 (t, J = 5.8 Hz), 108.2 (t, J = 238.4 Hz), 62.8, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.6 (d, J = 53.8 Hz, 2F).

IR (film) ν_{max} 3101, 2992, 1715, 1542, 1373, 1271, 1234, 1089, 1019, 959, 847, 787, 765 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_7H_8F_2NO_2S$ ($[M+H]^+$) 208.0238, found 208.0246.



2-(difluoromethyl)-4-phenylthiazole (54)

Prepared following general procedure B using 2-bromo-4-phenylthiazole (120 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.48 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 μmol, 5.0 mol%), quinuclidine (111 mg, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 μL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans were used for cooling. After 18 h, the crude reaction mixture was filtered through a silica plug, eluting with Et_2O, and concentrated *in vacuo*. Purification by flash column chromatography (0–3% acetone/pentane) followed by preparative thin layer chromatography (5% acetone/pentane) provided the title compound as a colorless oil (48.0 mg, 0.227 mmol, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.64 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 6.93 (t, *J* = 54.8 Hz, 1H).

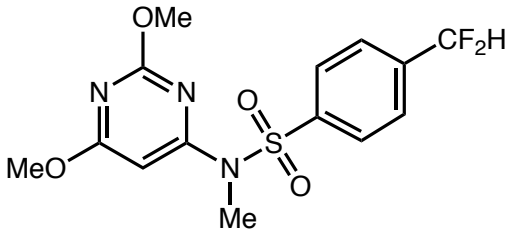
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6 (t, *J* = 30.6 Hz), 156.5, 133.6, 129.0, 128.9, 126.6, 115.1 (t, *J* = 1.5 Hz), 110.9 (t, *J* = 239.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –108.7 (d, *J* = 54.7 Hz, 2F).

IR (film) ν_{max} 3113, 3067, 2927, 1503, 1462, 1339, 1092, 1041, 857, 738, 690, 674 cm^{-1}.

HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_{10}H_7F_2NS$ ($[M^*]^+$) 211.0262, found 211.0260.

8) Experimental Data for CF_2H Analogues of Pharmaceuticals



4-(difluoromethyl)-*N*-(2,6-dimethoxypyrimidin-4-yl)-*N*-methylbenzenesulfonamide (55)

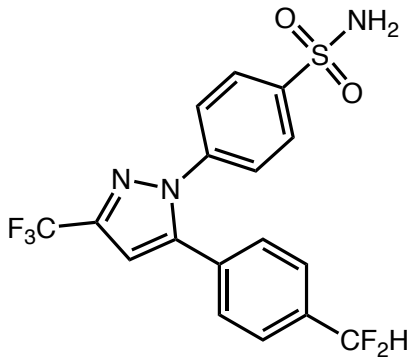
Prepared following general procedure A using 4-bromo-*N*-(2,6-dimethoxypyrimidin-4-yl)-*N*-methylbenzenesulfonamide (**S6**) (191 mg, 0.49 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.57 mL, 1.7 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 μmol, 1.0 mol%), $NiBr_2$•glyme (7.6 mg, 25 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.6 mg, 25 μmol, 5.0 mol%), 2,6-lutidine (172 μL, 1.48 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (159 μL, 0.52 mmol, 1.05 equiv.), and DME (10 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (25% EtOAc/hexanes) followed by crystallization from DCM/hexanes provided the title compound as a white solid (117.1 mg, 0.326 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 6.67 (t, *J* = 55.9 Hz, 1H), 6.60 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.45 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 164.5, 161.3, 141.0 (t, *J* = 2.0 Hz), 139.1 (t, *J* = 22.8 Hz), 127.8, 126.6 (t, *J* = 6.0 Hz), 113.4 (t, *J* = 240.7 Hz), 90.3, 54.9, 54.3, 34.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.9 (d, *J* = 55.9 Hz, 2F).

Spectroscopic data matches previously reported data.[22]



4-(5-(4-(difluoromethyl)phenyl)-3-(trifluoromethyl)-*1H*-pyrazol-1-yl)benzenesulfonamide (56)

Prepared following general procedure A using 4-(5-(4-bromophenyl)-3-(trifluoromethyl)-*1H*-pyrazol-1-yl)benzenesulfonamide (133.6 mg, 0.30 mmol, 1.0 equiv.), bromodifluoromethane (0.32 mmol, 1.1 equiv., 0.17 mL, 1.9 M in DME), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (3.4 mg, 3.0 μmol, 1.0 mol%), $NiBr_2$•glyme (6.9 mg, 22 μmol, 7.5 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.0 mg, 22 μmol, 7.5 mol%), 2,6-lutidine (105 μL, 0.90 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (97 μL, 0.31 mmol, 1.05 equiv.), and DME (6.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (33% EtOAc/hexanes), followed by reverse phase chromatography (20–100% MeCN/H_2O) provided the title compound as a white solid (80.0 mg, 0.192 mmol, 64% yield).

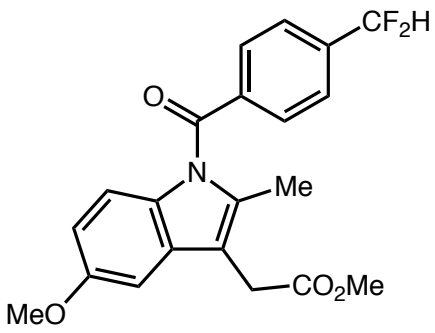
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 1H), 6.66 (t, *J* = 56.2 Hz, 1H), 5.20 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4 (q, *J* = 38.9 Hz), 144.1, 142.2, 141.9, 135.6 (t, *J* = 22.7 Hz), 131.1 (t, *J* = 2.0 Hz), 129.3, 127.8, 126.5 (t, *J* = 6.0 Hz), 125.7, 121.0 (q, *J* = 269.3 Hz), 114.1 (t, *J* = 239.6 Hz), 107.2 (m).

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.5 (3F), –111.8 (d, *J* = 56.2 Hz, 2F).

IR (film) ν_{max} 3263, 1596, 1473, 1337, 1273, 1235, 1159, 1133, 1022, 976, 841, 736 cm^{-1}.

HRMS (ESI-TOF) *m*/*z* calcd. for $C_{17}H_{13}F_5N_3O_2S$ ($[M+H]^+$) 418.0643, found 418.0643.



methyl 2-(1-(4-(difluoromethyl)benzoyl)-5-methoxy-2-methyl-*1H*-indol-3-yl)acetate (57)

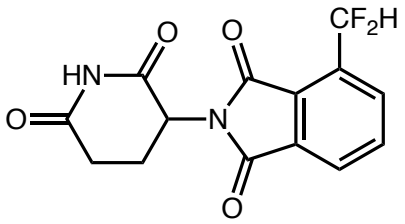
Prepared following general procedure A using methyl 2-(1-(4-bromobenzoyl)-5-methoxy-2-methyl-*1H*-indol-3-yl)acetate (**S7**) (125.2 mg, 0.30 mmol, 1.0 equiv.), bromodifluoromethane (0.60 mmol, 2.0 equiv., 0.29 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (3.4 mg, 3.0 μmol, 1.0 mol%), $NiBr_2$•glyme (4.6 mg, 15 μmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (4.0 mg, 15 μmol, 5.0 mol%), 2,6-lutidine (105 μL, 0.90 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (97 μL, 0.32 mmol, 1.05 equiv.), and DME (6.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (33% EtOAc/Hexane) provided the title compound as a yellow solid (96.0 mg, 0.248 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.74 (t, *J* = 56.0 Hz, 1H), 6.66 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.67 (s, 2H), 2.37 (s, 3H).

Quantitative ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 168.6, 156.3, 138.4 (t, *J* = 22.6 Hz), 138.0 (t, *J* = 1.8 Hz), 136.1, 130.9, 130.1, 126.2 (overlapping t, *J* = 6.0 Hz), 126.2 (overlapping s), 115.2, 114.0 (t, *J* = 240.1 Hz), 112.9, 111.8, 101.5, 55.8, 52.3, 30.3, 13.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.3 (d, *J* = 56.0 Hz, 2F).

Spectroscopic data matches previously reported data.[22]



4-(difluoromethyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (58)

Prepared following general procedure A using 4-bromo-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (101.4 mg, 0.30 mmol, 1.0 equiv.), bromodifluoromethane (0.59 mmol, 2.0 equiv., 0.28 mL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (3.4 mg, 3.0 μmol, 1.0 mol%), $NiBr_2$•glyme (4.6 mg, 15 μmol, 3.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (4.0 mg, 15 μmol, 3.0 mol%), 2,6-lutidine (105 μL, 0.90 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (97 μL, 0.32 mmol, 1.05 equiv.) and DMA (6.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was diluted with DCM (40 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was back-extracted with DCM (2 × 20 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (33% EtOAc/hexanes), followed by reverse phase chromatography (20–100% MeCN/H_2O) provided the title compound as a white solid (68.5 mg, 0.222 mmol, 74% yield).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 11.18 (s, 1H), 8.14 – 8.07 (m, 2H), 8.07 – 7.99 (m, 1H), 7.58 (t, J = 54.5 Hz, 1H), 5.19 (dd, J = 12.9, 5.4 Hz, 1H), 2.99 – 2.84 (m, 1H), 2.67 – 2.51 (m, 2H), 2.11 – 2.01 (m, 1H).

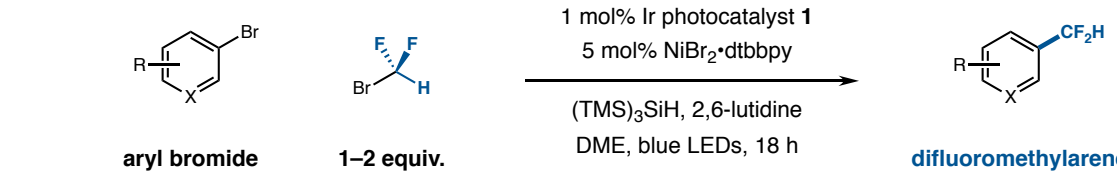
^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 172.8, 169.7, 166.4, 166.0, 135.7, 132.0, 131.1 (t, J = 24.1 Hz), 130.7 (t, J = 5.5 Hz), 128.4 (t, J = 5.7 Hz), 125.8, 110.5 (t, J = 237.1 Hz), 49.2, 30.9, 21.9.

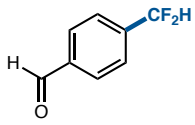
^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ –112.9 (dd, J_{FF} = 303.2, J_{FH} = 54.8 Hz, 1F), –113.9 (dd, J_{FF} = 303.2, J_{FH} = 54.8 Hz, 1F). *Note: an AB splitting pattern for each of the F atoms is observed. The diastereotopicity of the two atoms likely stems from intramolecular hydrogen bonding between the CF_2H group and the neighboring carbonyl, rendering rotation slow on the NMR time scale.*

IR (film) ν_{max} 3296, 2923, 1779, 1705, 1386, 1263, 1195, 1104, 1038, 779, 726 cm^{-1}.

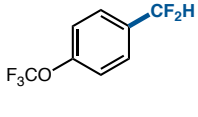
HRMS (ESI-TOF) *m*/*z* calcd. for $C_{14}H_{11}F_2N_2O_4$ ($[M+H]^+$) 309.0681, found 309.0681.

9) Additional Examples for Difluoromethylation of Aryl Bromides

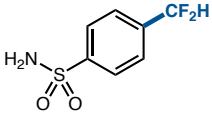




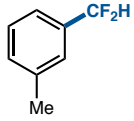
S8, 67% yield



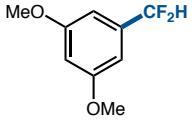
S9, 64% yield



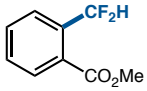
S10, 84% yield



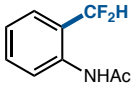
S11, 72% yield



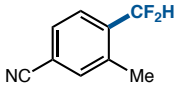
S12, 69% yield



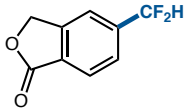
S13, 43% yield*



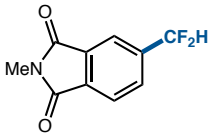
S14, 47% yield*



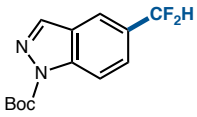
S15. 60% yield



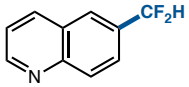
S16, 86% yield



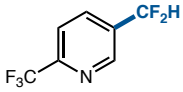
S17, 87% yield



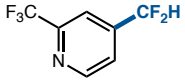
S18, 49% yield



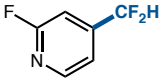
S19, 83% yield



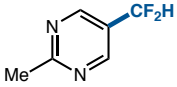
S20, 79% yield



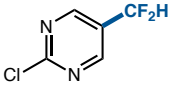
S21, 75% yield



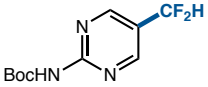
S22, 67% yield



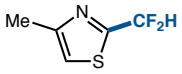
S23, 68% yield



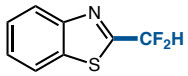
S24, 38% yield



S25, 50% yield

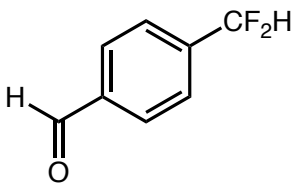


S26, 41% yield*



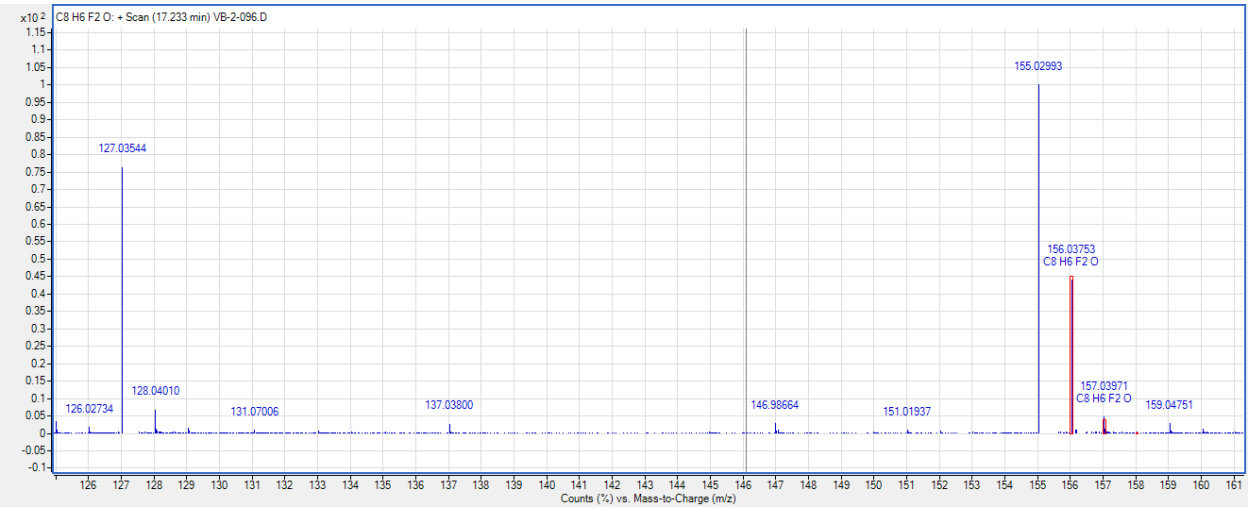
S27, 39% yield*

Figure S21. Additional examples for difluoromethylation of aryl bromides. All yields determined by ^{19}F NMR of crude reaction mixture. *Performed with deviations from standard conditions (*vide infra*).



4-(difluoromethyl)benzaldehyde (S8)

Prepared following general procedure A using 4-bromobenzaldehyde (92.6 mg, 0.50 mmol, 1.0 equiv.), bromodifluoromethane (1.0 mmol, 2.0 equiv., 0.52 mL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (5.6 mg, 5.0 µmol, 1.0 mol%), $NiBr_2$•glyme (7.7 mg, 25 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (6.7 mg, 25 µmol, 5.0 mol%), 2,6-lutidine (116 µL, 1.0 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (162 µL, 0.53 mmol, 1.05 equiv.), and DME (5.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (25.0 µL, 0.203 mmol, 0.407 equiv., 0.610 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 67% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_6F_2O$ ($[M^*]^+$) 156.0381, found 156.0375.

^{19}F NMR (376 MHz, $CDCl_3$) δ –113.4 (d, J = 55.7 Hz, 2F).

Spectroscopic data matches previously reported data.[14]

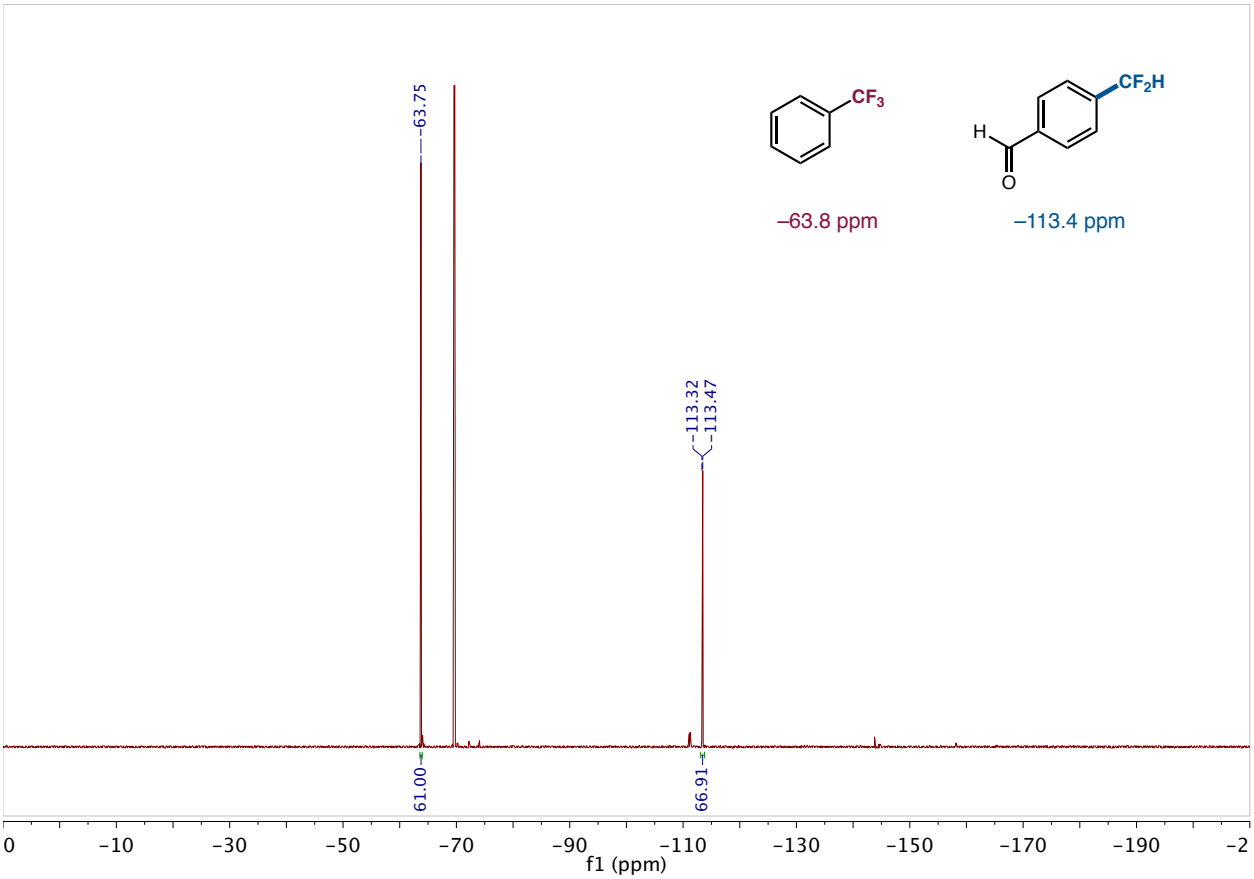
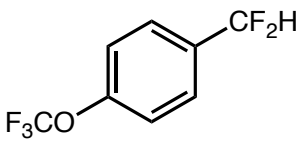
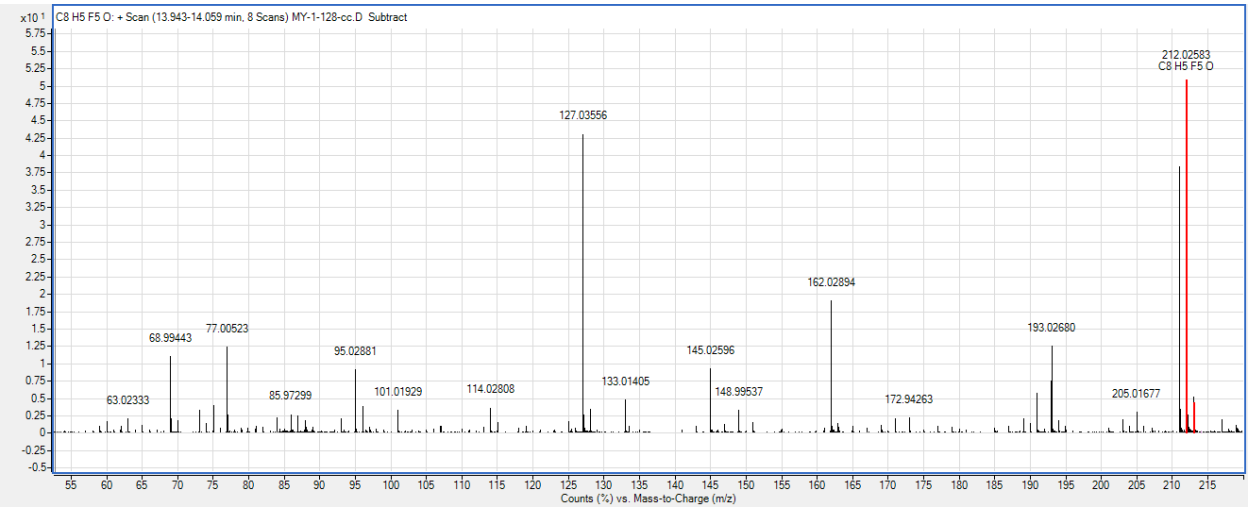


Figure S22. ^{19}F NMR assay for difluoromethylarene **S8**



1-(difluoromethyl)-4-(trifluoromethoxy)benzene (S9)

Prepared following general procedure A using 1-bromo-4-(trifluoromethoxy)benzene (48.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added methyl 4-fluorobenzoate (20.0 µL, 0.154 mmol, 0.772 equiv., 0.386 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 64% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_5F_5O$ ($[M^*]^+$) 212.0255, found 212.0258.

^{19}F NMR (376 MHz, $CDCl_3$) δ –58.8 (s, 3F), –111.7 (d, J = 56.0 Hz, 2F).

Spectroscopic data matches previously reported data.[23]

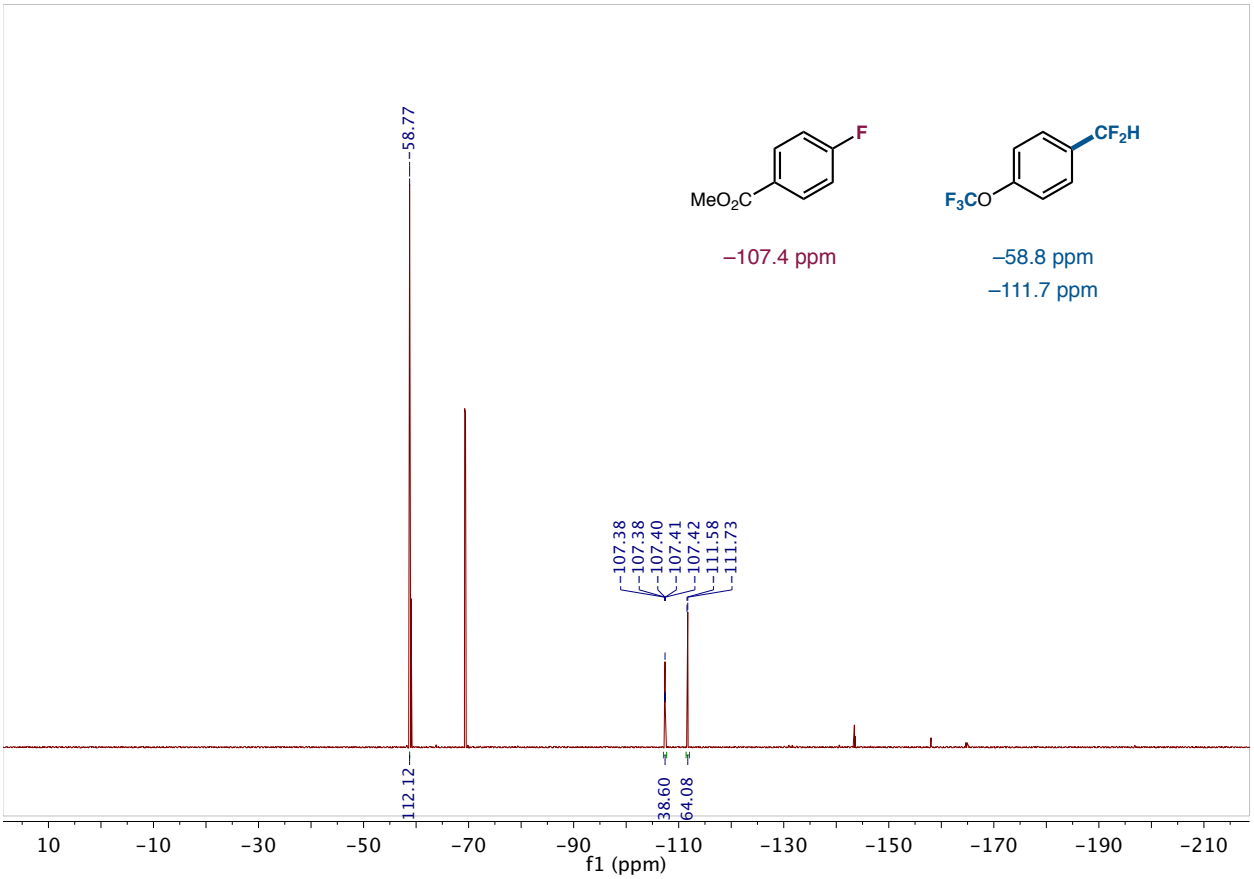
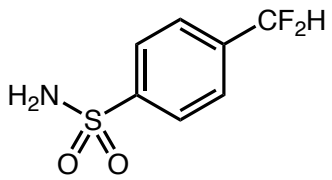
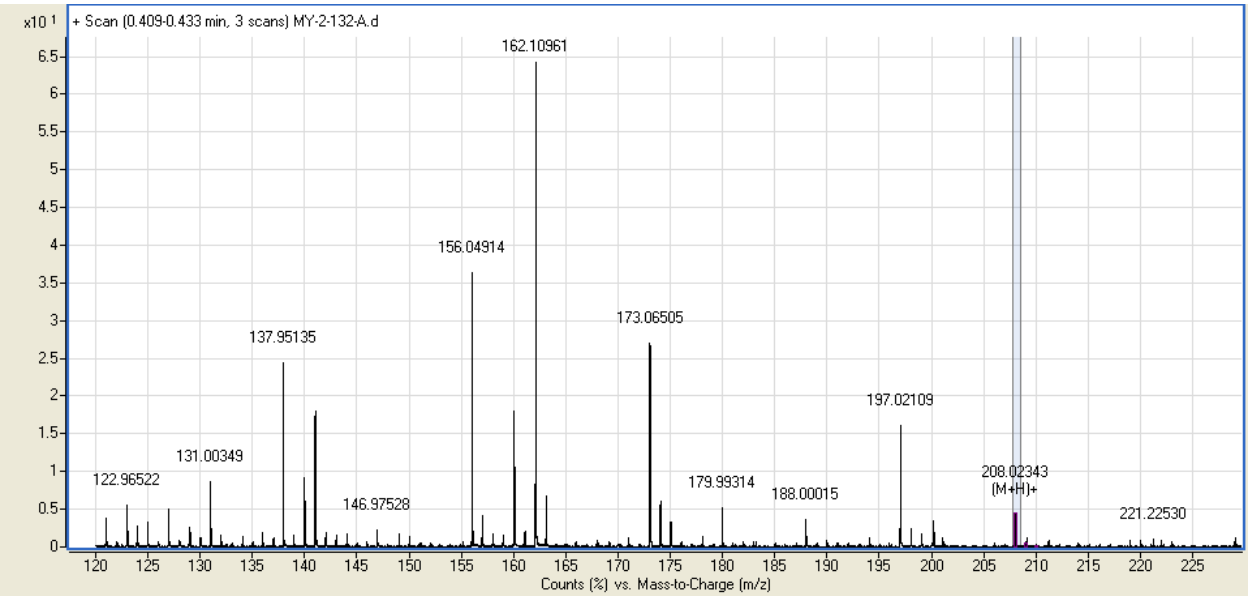


Figure S23. ^{19}F NMR assay for difluoromethylarene **S9**



4-(difluoromethyl)benzenesulfonamide (S10)

Prepared following general procedure A using 4-bromobenzenesulfonamide (47.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 84% was recorded.



HRMS (ESI-TOF) *m/z* calcd. for $C_7H_8F_2NO_2S$ ($[M+H]^+$) 208.0238, found 208.0234.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.8 (d, J = 55.9 Hz, 2F).

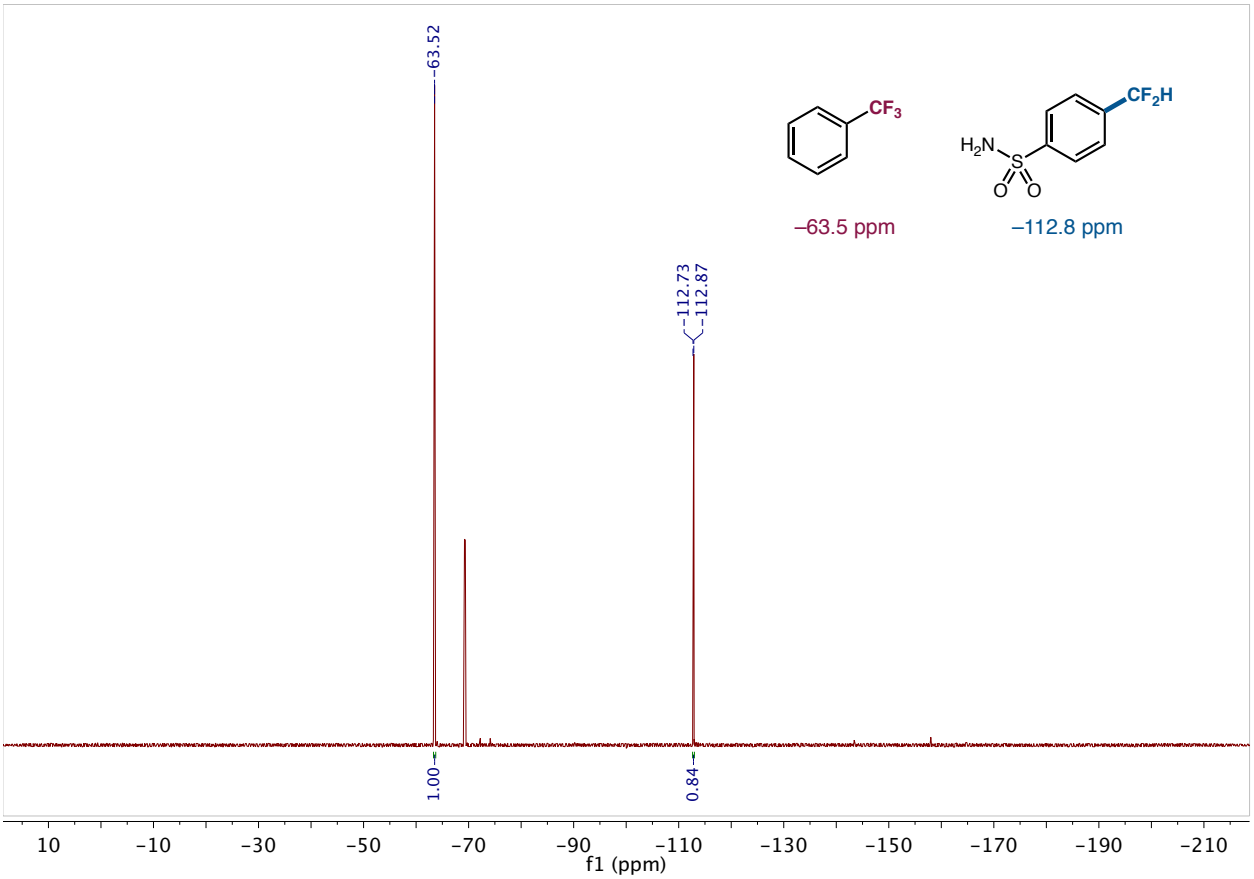
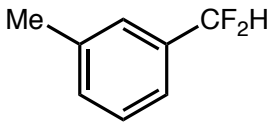
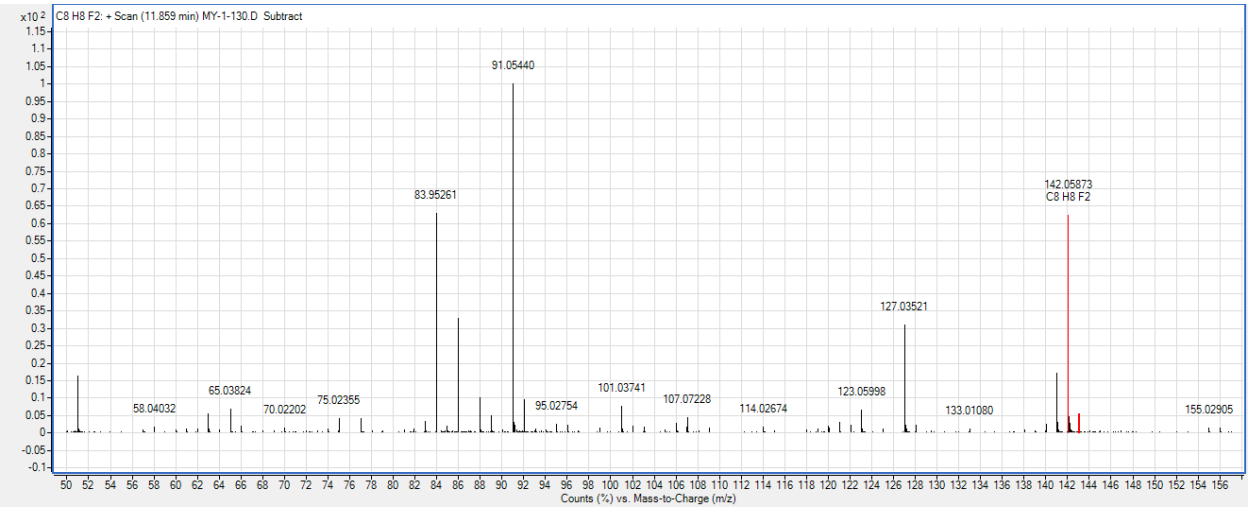


Figure S24. ^{19}F NMR assay for difluoromethylarene **S10**



1-(difluoromethyl)-3-methylbenzene (S11)

Prepared following general procedure A using 1-bromo-3-methylbenzene (34.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 95 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 72% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_8H_8F_2$ ($[M^*]^+$) 142.0589, found 142.0587.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.2 (d, J = 56.3 Hz, 2F).

Spectroscopic data matches previously reported data.[16]

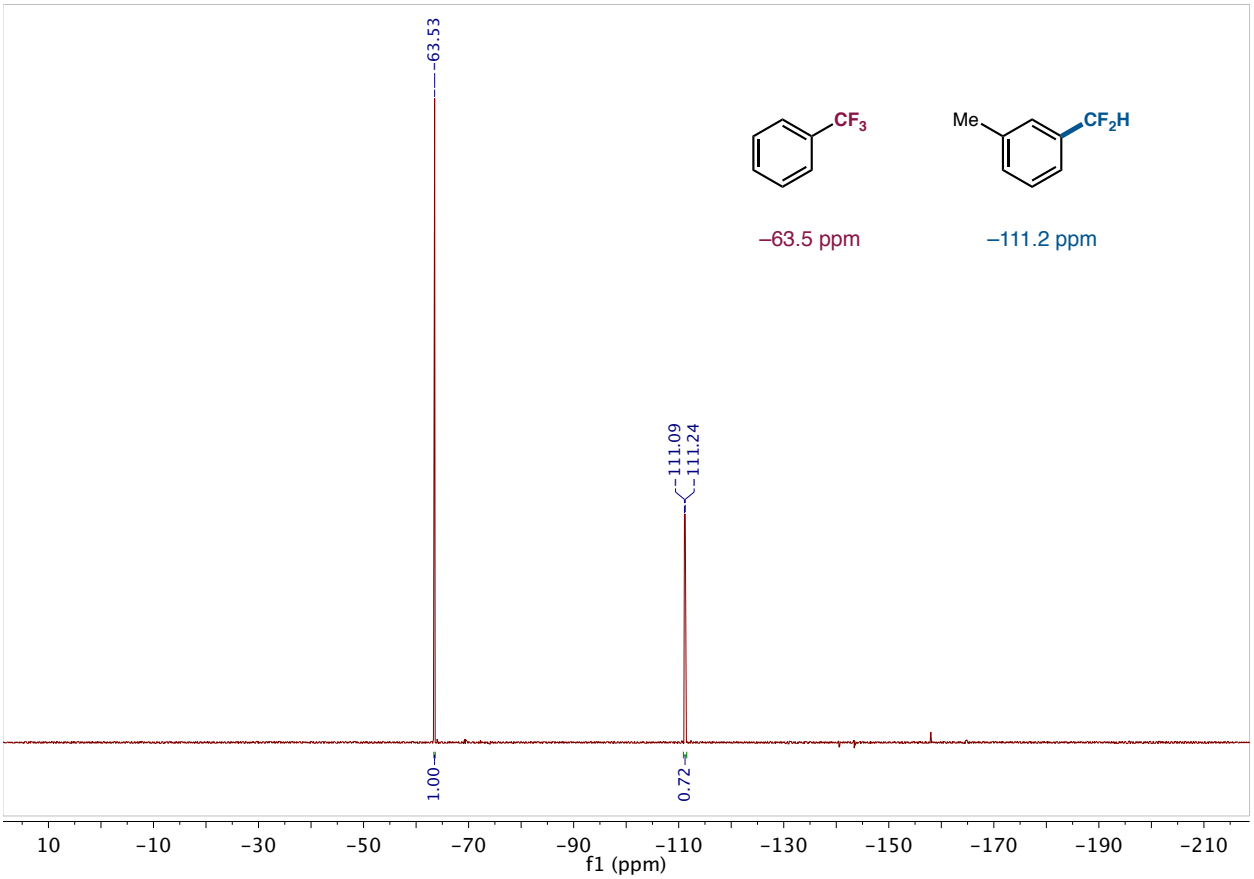
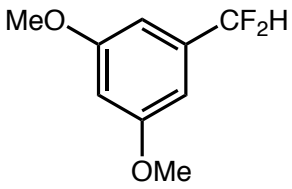
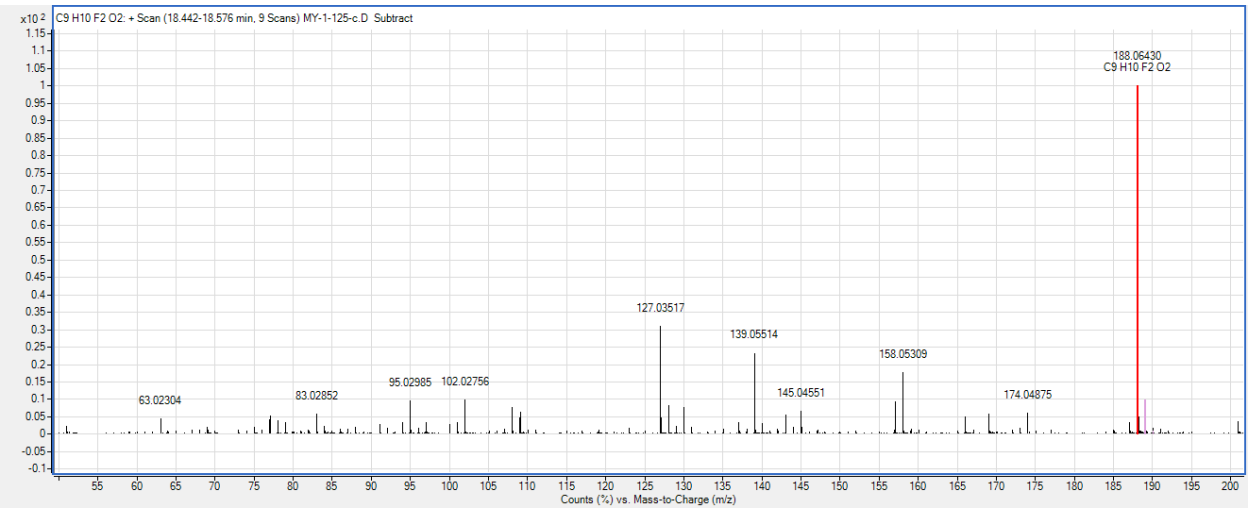


Figure S25. ^{19}F NMR assay for difluoromethylarene **S11**



1-(difluoromethyl)-3,5-dimethoxybenzene (S12)

Prepared following general procedure A using 1-bromo-3,5-dimethoxybenzene (43.4 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 95 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 69% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_9H_{10}F_2O_2$ ($[M^*]^+$) 188.0643, found 188.0643.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.6 (d, J = 56.4 Hz, 2F).

Spectroscopic data matches previously reported data.[14]

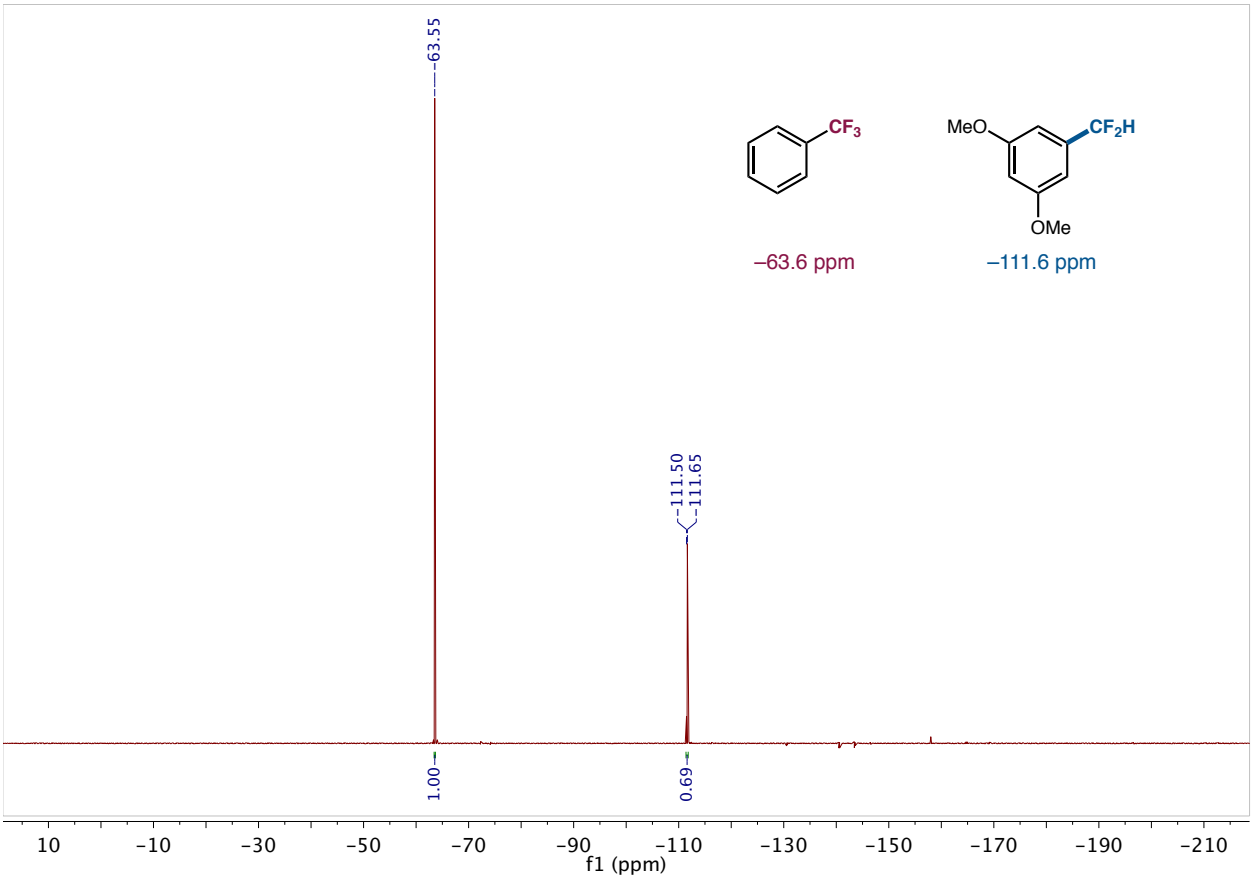
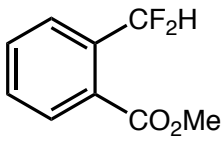
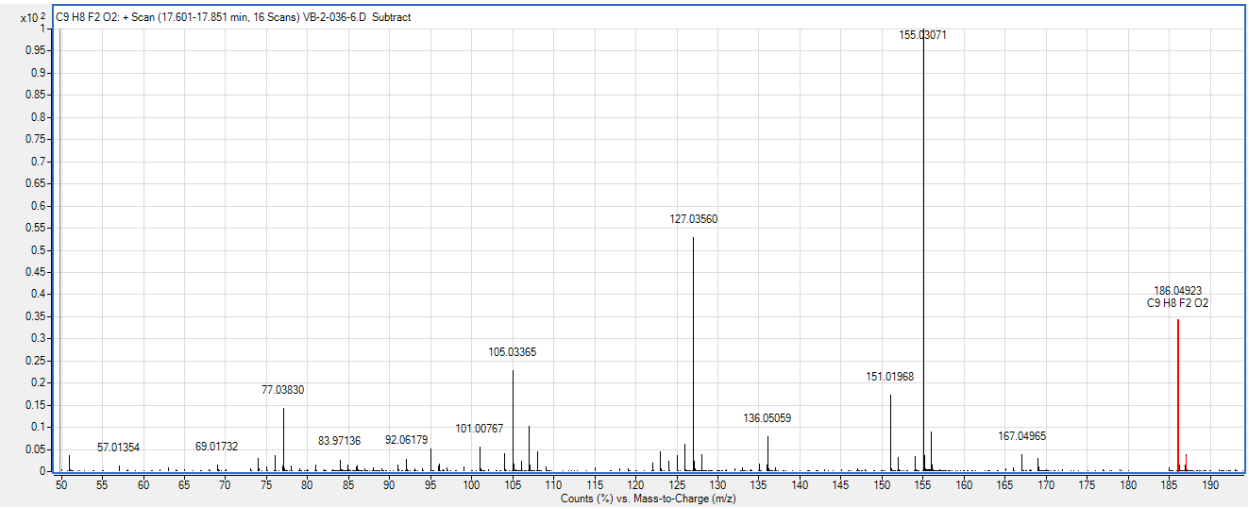


Figure S26. ^{19}F NMR assay for difluoromethylarene **S12**



methyl 2-(difluoromethyl)benzoate (S13)

Prepared following general procedure A using methyl 2-bromobenzoate (43.0 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 87 µL, 2.3 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (6.2 mg, 20 µmol, 10 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (5.4 mg, 20 µmol, 10 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). The reaction was performed in the Integrated Photoreactor at 5200 rpm fan speed and 1000 rpm stirring speed, under irradiation with 450 nm light at 100% intensity.[24] After 12 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 43% was recorded. By comparison, a crude NMR yield of 32% was observed when the reaction was performed in the standard Kessil lamp setup over 42 h.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_9H_8F_2O_2$ ($[M^*]^+$) 186.0487, found 186.0492.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.5 (d, J = 55.6 Hz, 2F).

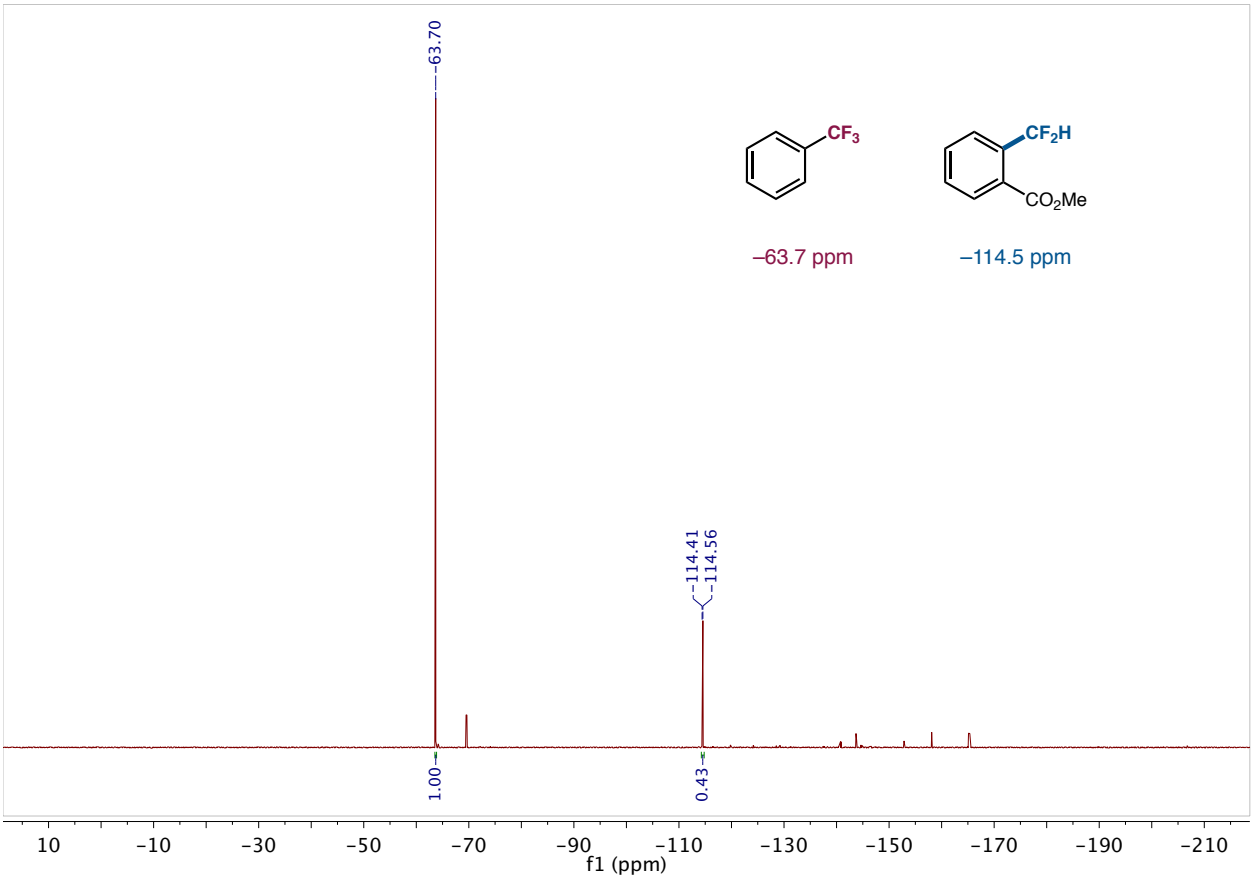
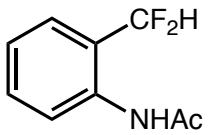
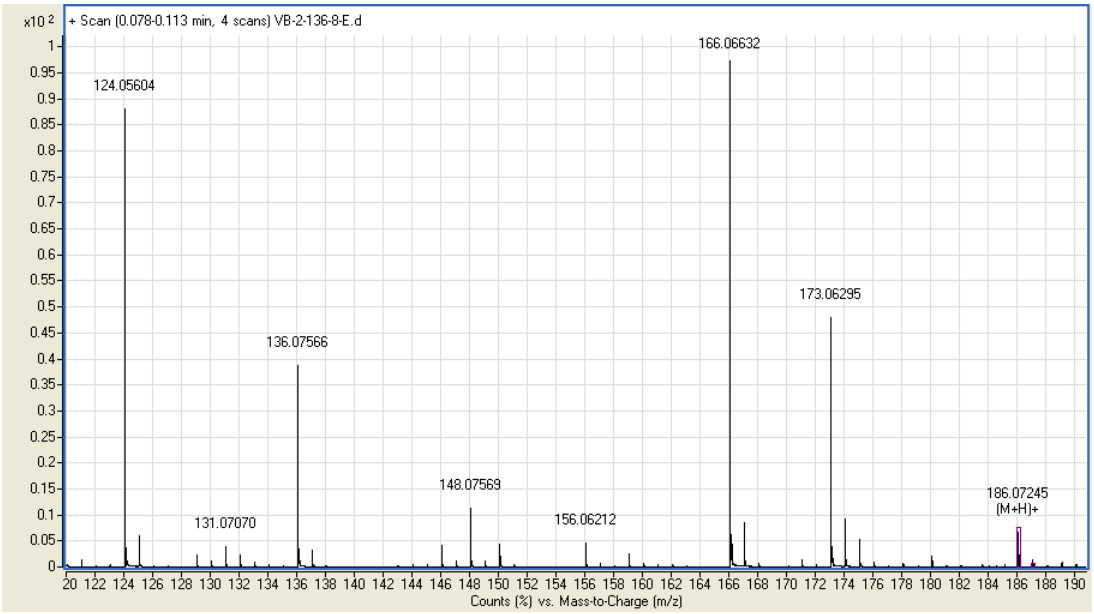


Figure S27. ^{19}F NMR assay for difluoromethylarene **S13**



***N*-(2-(difluoromethyl)phenyl)acetamide (S14)**

Prepared following general procedure A using *N*-(2-bromophenyl)acetamide (42.7 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 87 µL, 2.3 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (6.2 mg, 20 µmol, 10 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (5.4 mg, 20 µmol, 10 mol%), 2,6-lutidine (67 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). The reaction was performed in the Integrated Photoreactor at 5200 rpm fan speed and 1000 rpm stirring speed, under irradiation with 450 nm light at 100% intensity.[24] After 12 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 47% was recorded. By comparison, a crude NMR yield of 45% was observed when the reaction was performed in the standard Kessil lamp setup over 42 h.



HRMS (ESI-TOF) *m/z* calcd. for $C_9H_{10}F_2NO$ ($[M+H]^+$) 186.0725, found 186.0725.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.7 (d, *J* = 55.3 Hz, 2F).

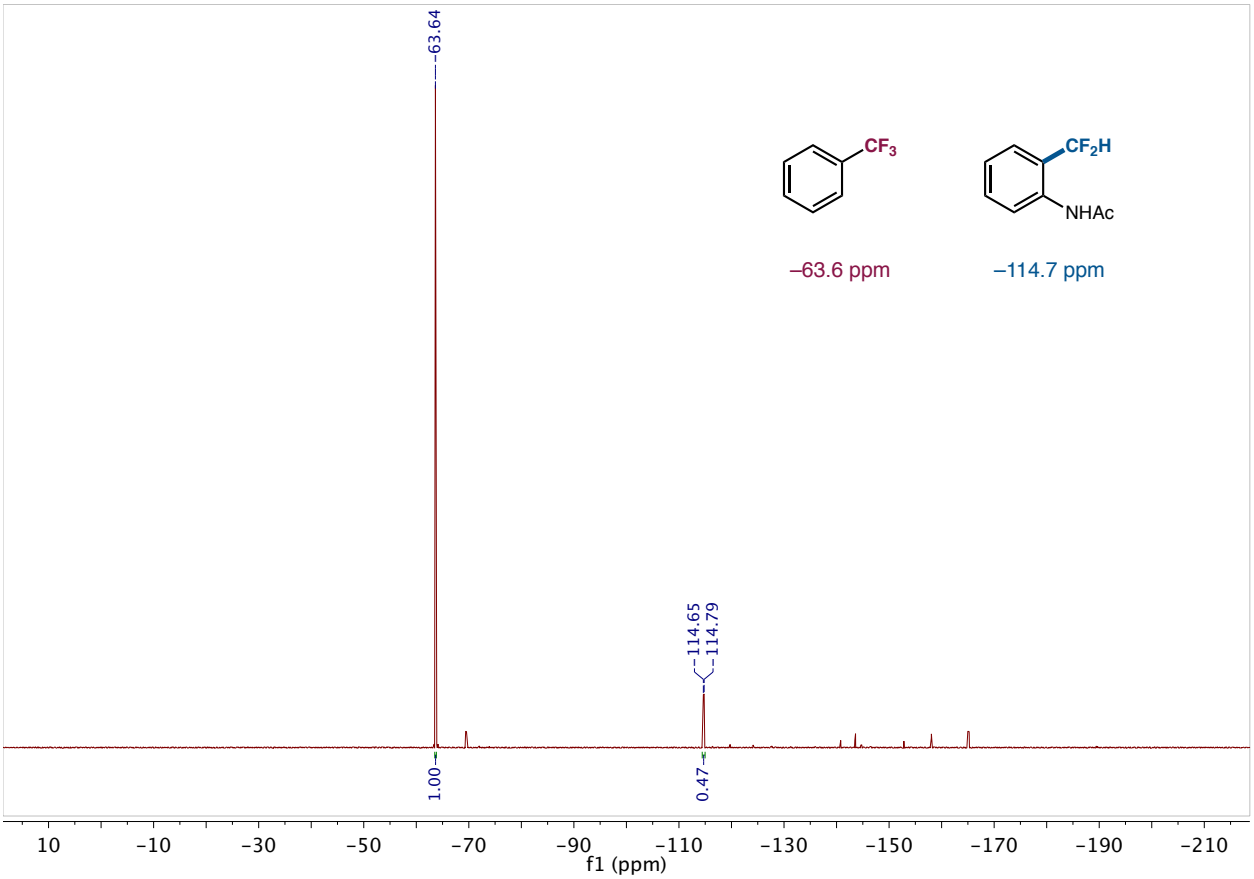
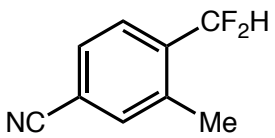
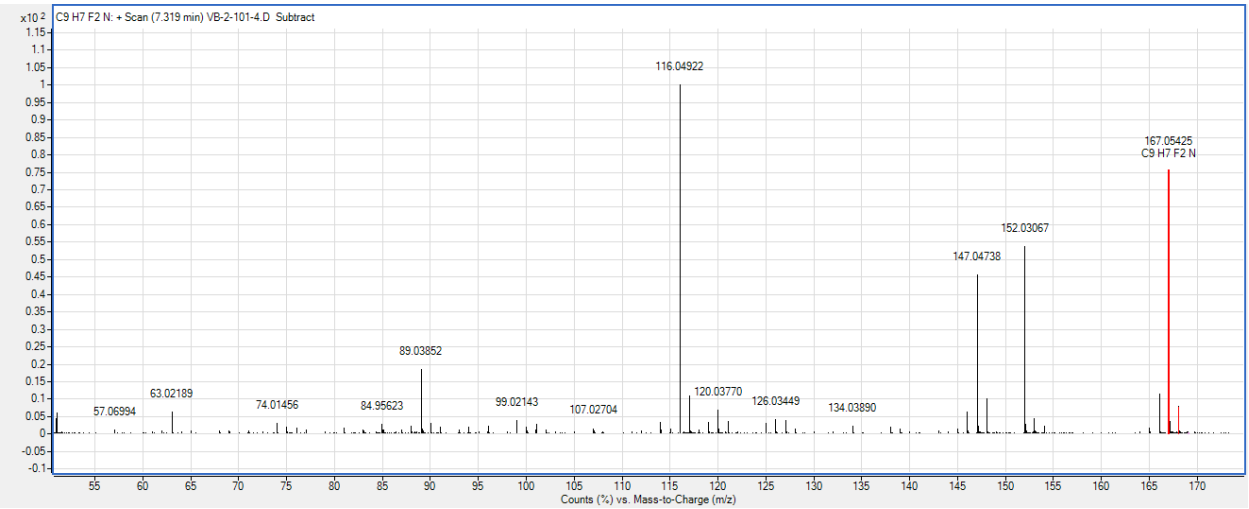


Figure S28. ^{19}F NMR assay for difluoromethylarene **S14**



4-(difluoromethyl)-3-methylbenzonitrile (S15)

Prepared following general procedure A using 4-bromo-3-methylbenzonitrile (39.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 104 µL, 1.9 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (67 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 60% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_9H_7F_2N$ ($[M^*]^+$) 167.0541, found 167.0543.

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ –117.1 (d, *J* = 54.4 Hz, 2F).

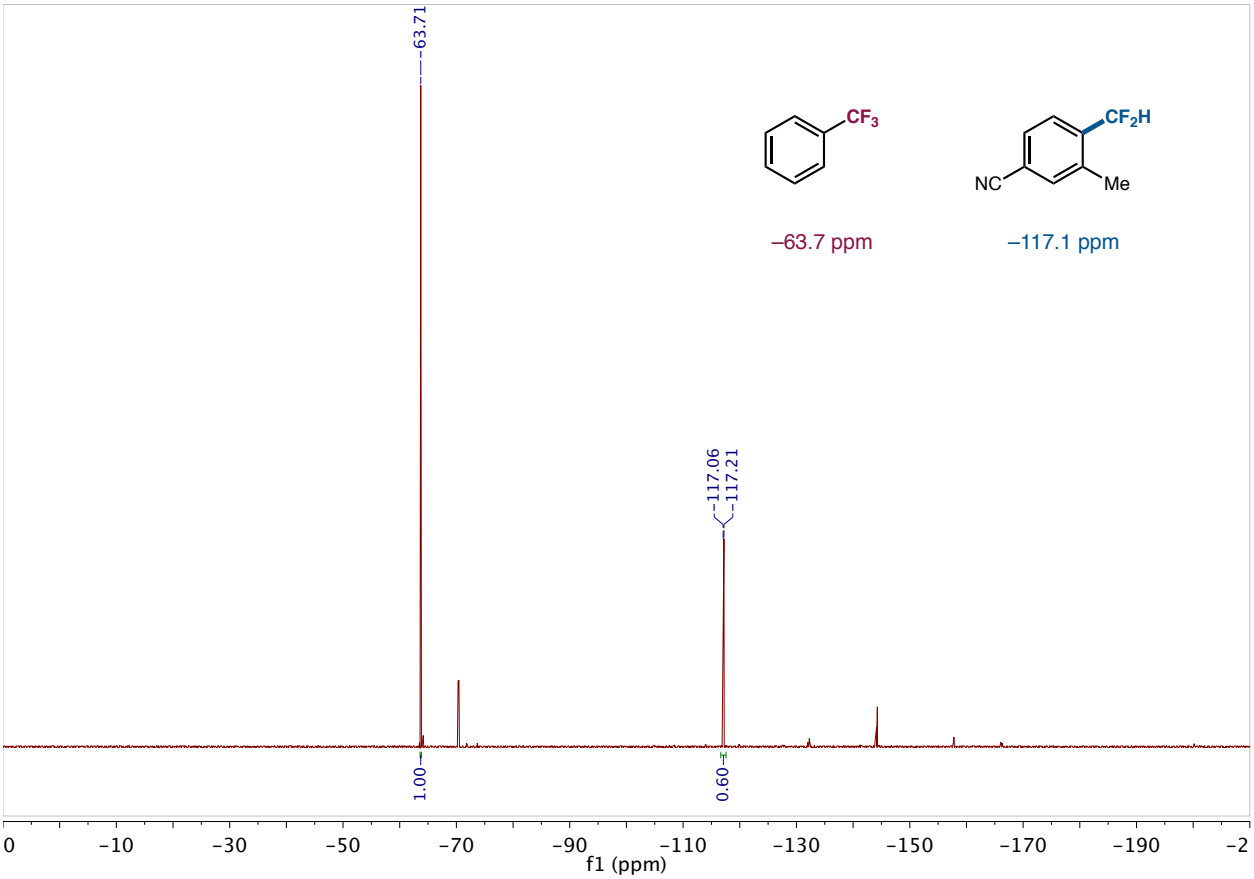
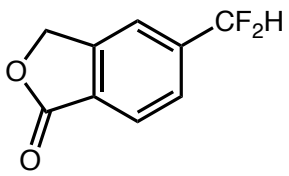
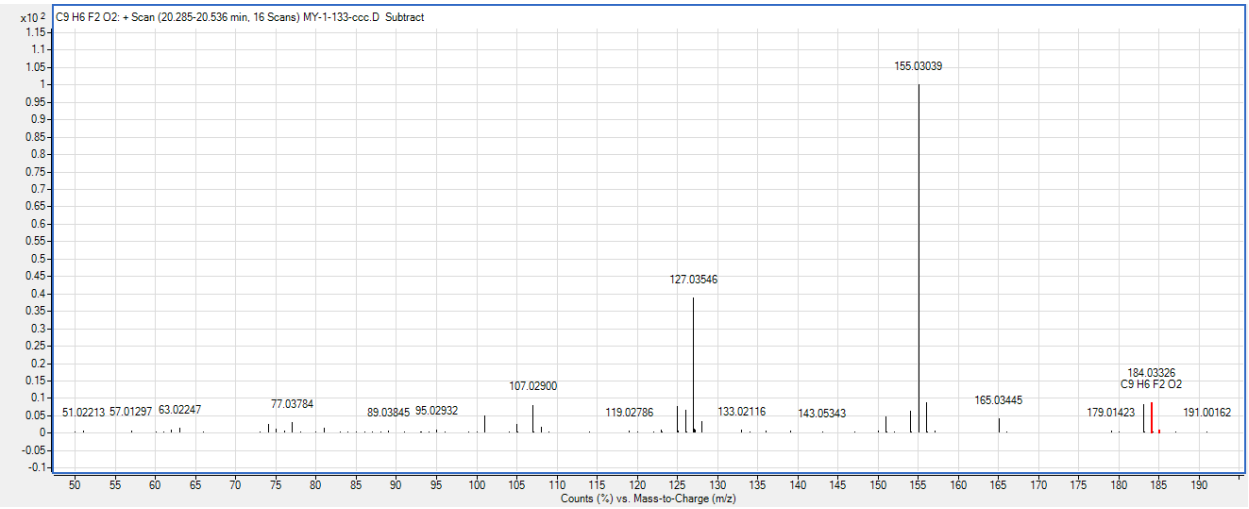


Figure S29. ^{19}F NMR assay for difluoromethylarene **S15**



5-(difluoromethyl)isobenzofuran-1(*3H*)-one (S16)

Prepared following general procedure A using 5-bromoisobenzofuran-1(*3H*)-one (42.6 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 86% was recorded.



HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_9H_6F_2O_2$ ($[M^*]^+$) 184.0330, found 184.0333.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.6 (d, J = 55.7 Hz, 2F).

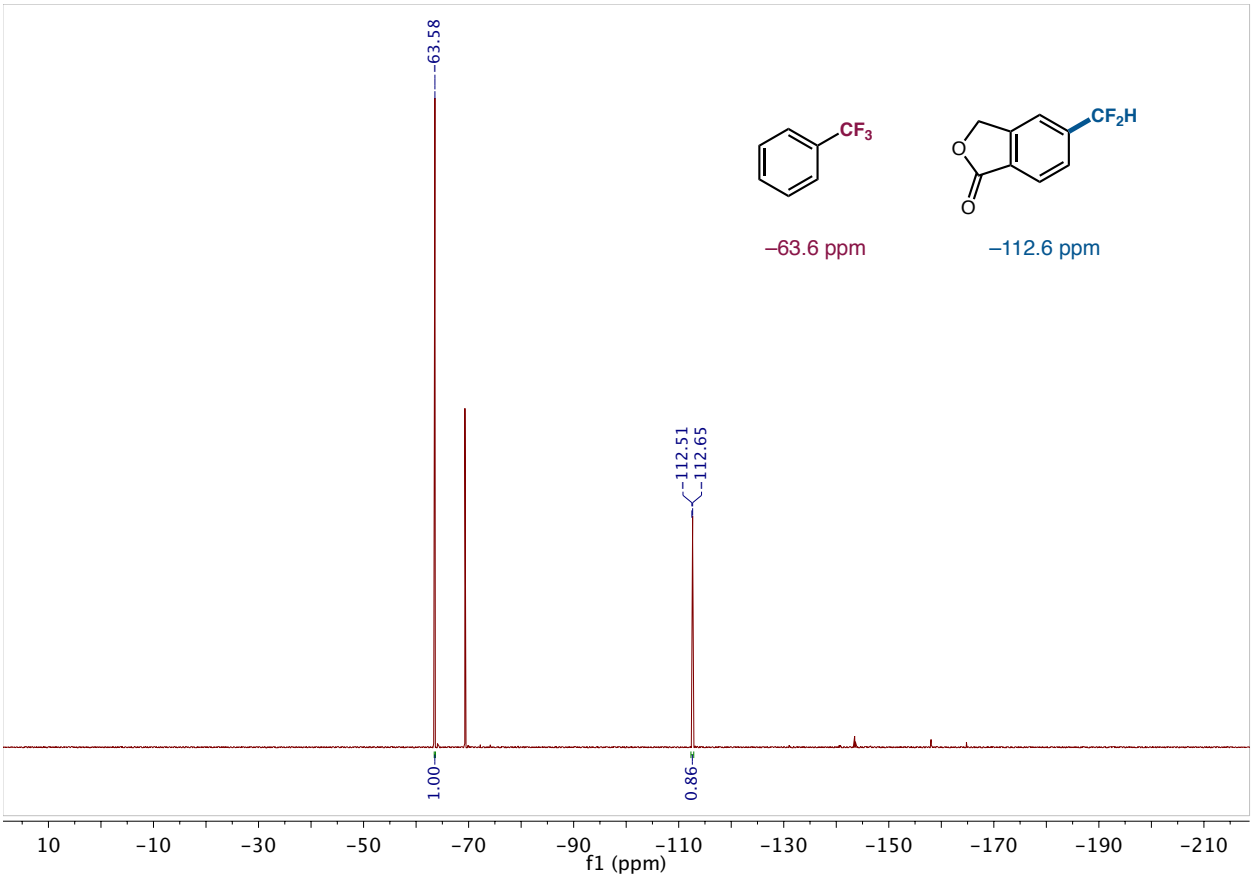
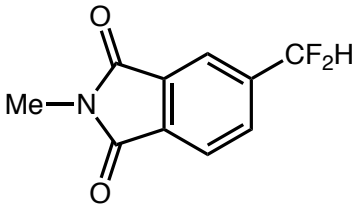
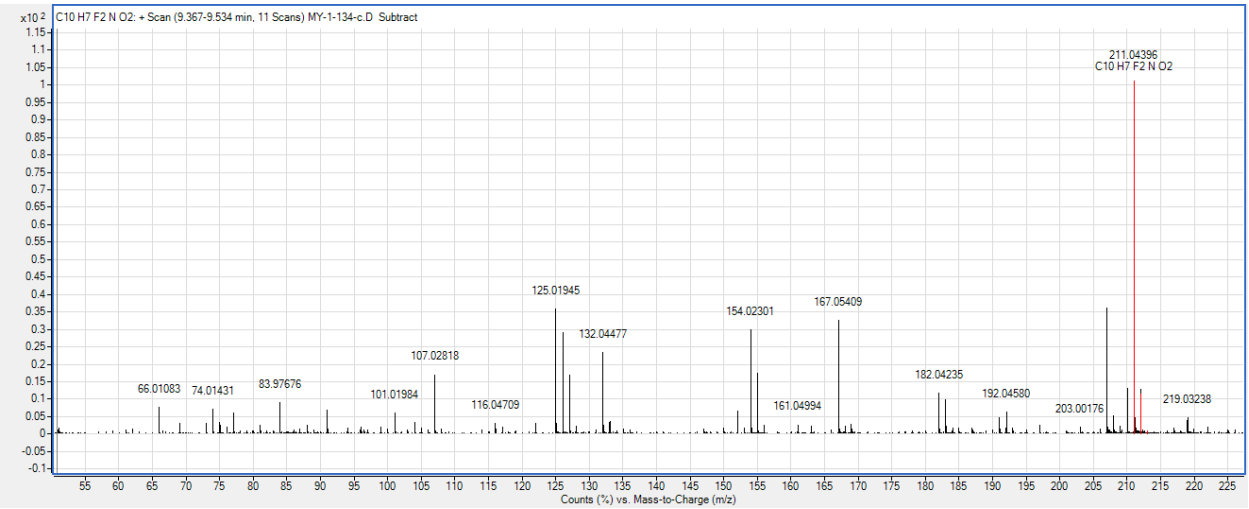


Figure S30. ^{19}F NMR assay for difluoromethylarene **S16**



5-(difluoromethyl)-2-methylisoindoline-1,3-dione (S17)

Prepared following general procedure A using 5-bromo-2-methylisoindoline-1,3-dione (48.0 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 87% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_{10}H_7F_2NO_2$ ($[M^*]^+$) 211.0439, found 211.0440.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.9 (d, J = 55.5 Hz, 2F).

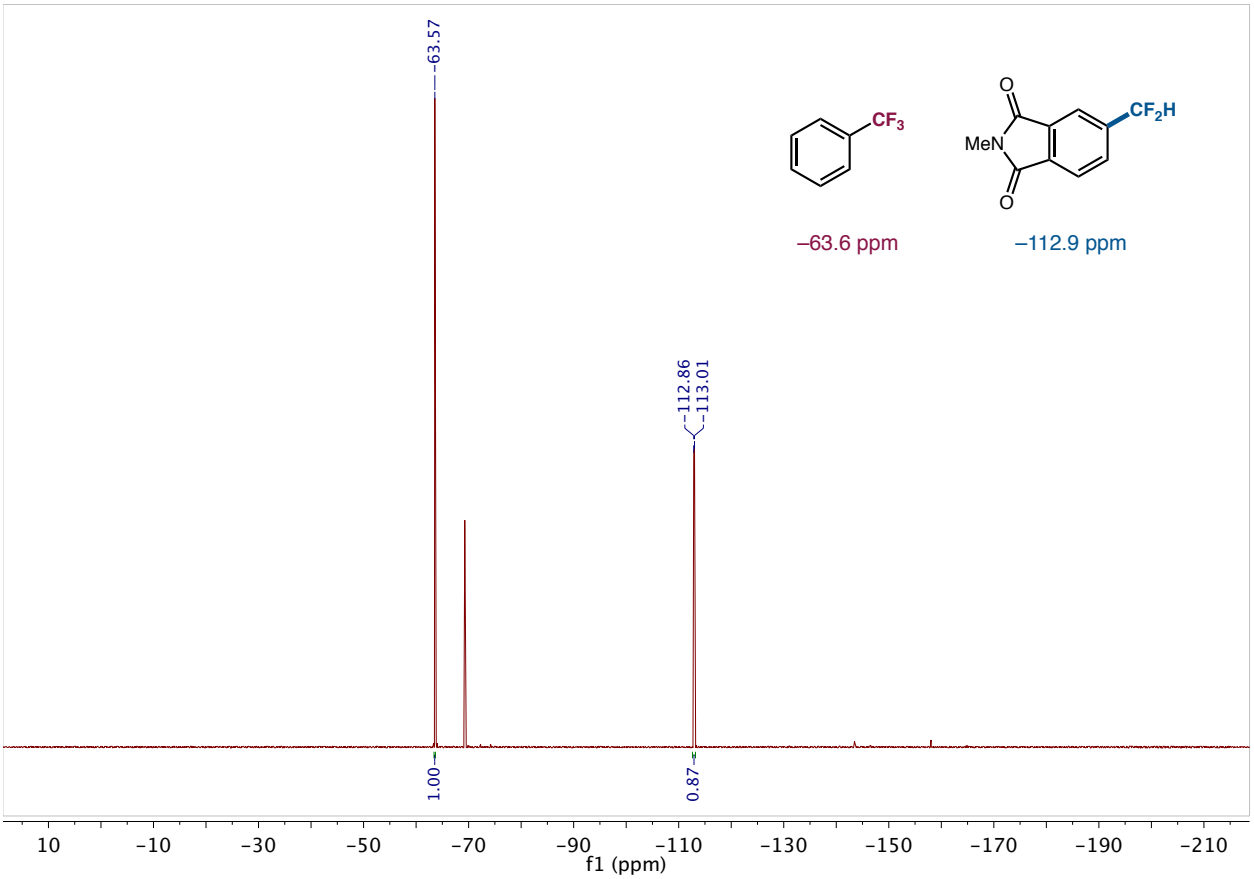
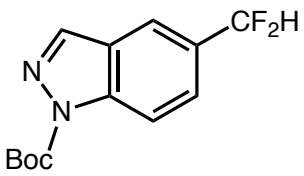
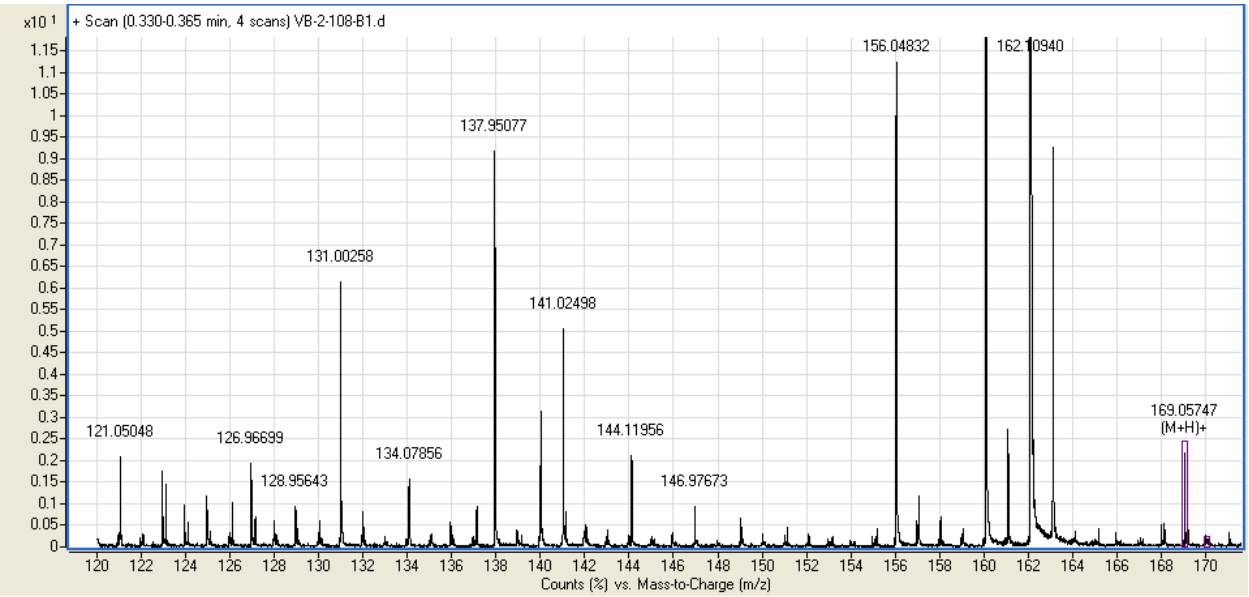


Figure S31. ^{19}F NMR assay for difluoromethylarene **S17**



***tert*-butyl 5-(difluoromethyl)-1*H*-indazole-1-carboxylate (S18)**

Prepared following general procedure A using *tert*-butyl 5-bromo-1*H*-indazole-1-carboxylate (59.3 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 1.0 equiv., 97 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (67 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 49% was recorded.



HRMS (ESI-TOF) *m*/*z* calcd. for $C_8H_7F_2N_2$ ($[M–Boc+2H]^+$) 169.0572, found 169.0575.

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.6 (d, J = 56.2 Hz, 2F).

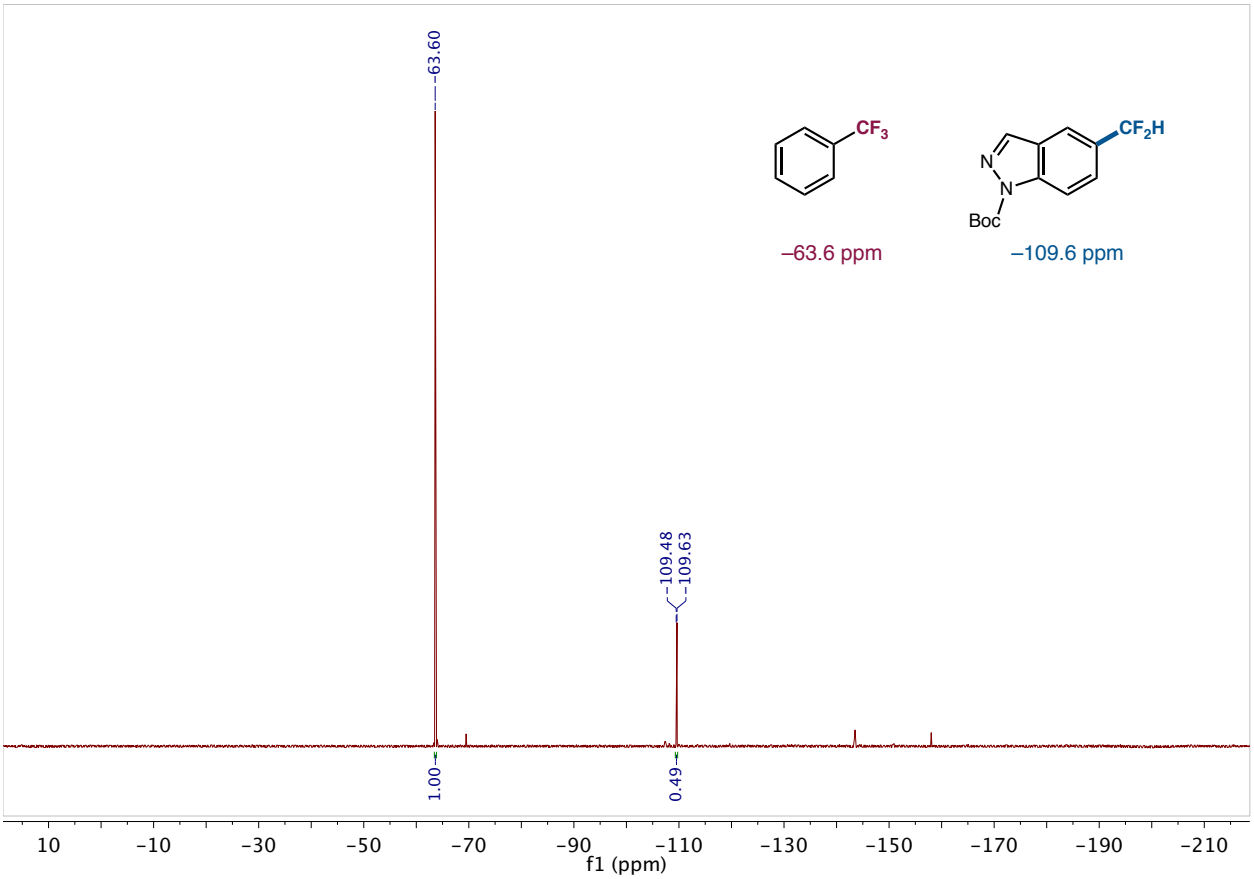
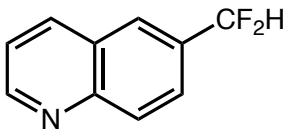
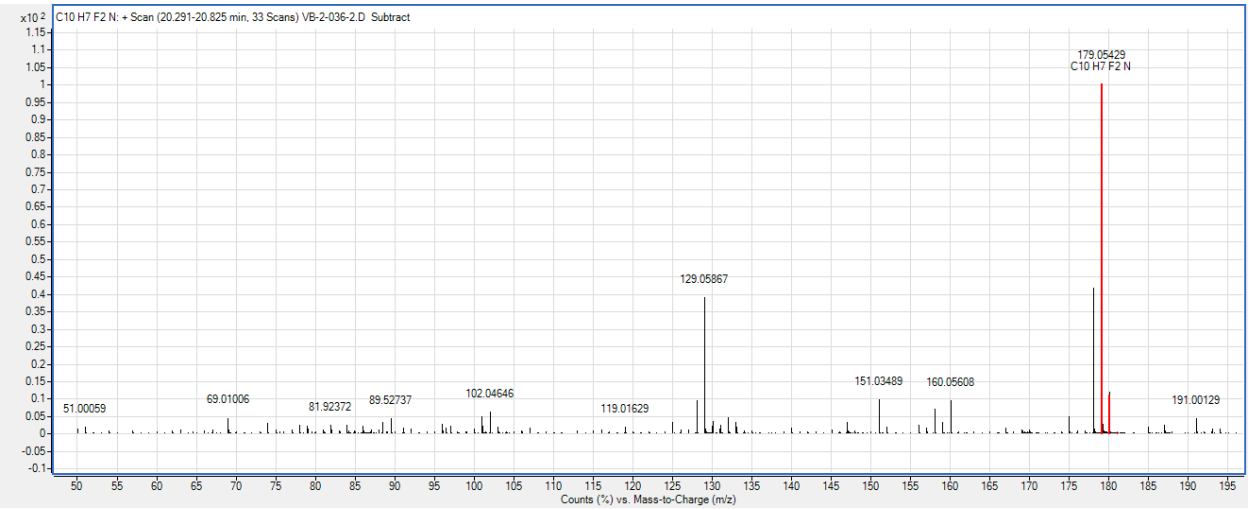


Figure S32. ^{19}F NMR assay for difluoromethylarene **S18**



6-(difluoromethyl)quinoline (S19)

Prepared following general procedure A using 6-bromoquinoline (41.8 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.24 mmol, 1.2 equiv., 103 µL, 2.3 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (67 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 83% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_{10}H_7F_2N$ ($[M^*]^+$) 179.0541, found 179.0543.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.3 (d, J = 56.1 Hz, 2F).

Spectroscopic data matches previously reported data.[25]

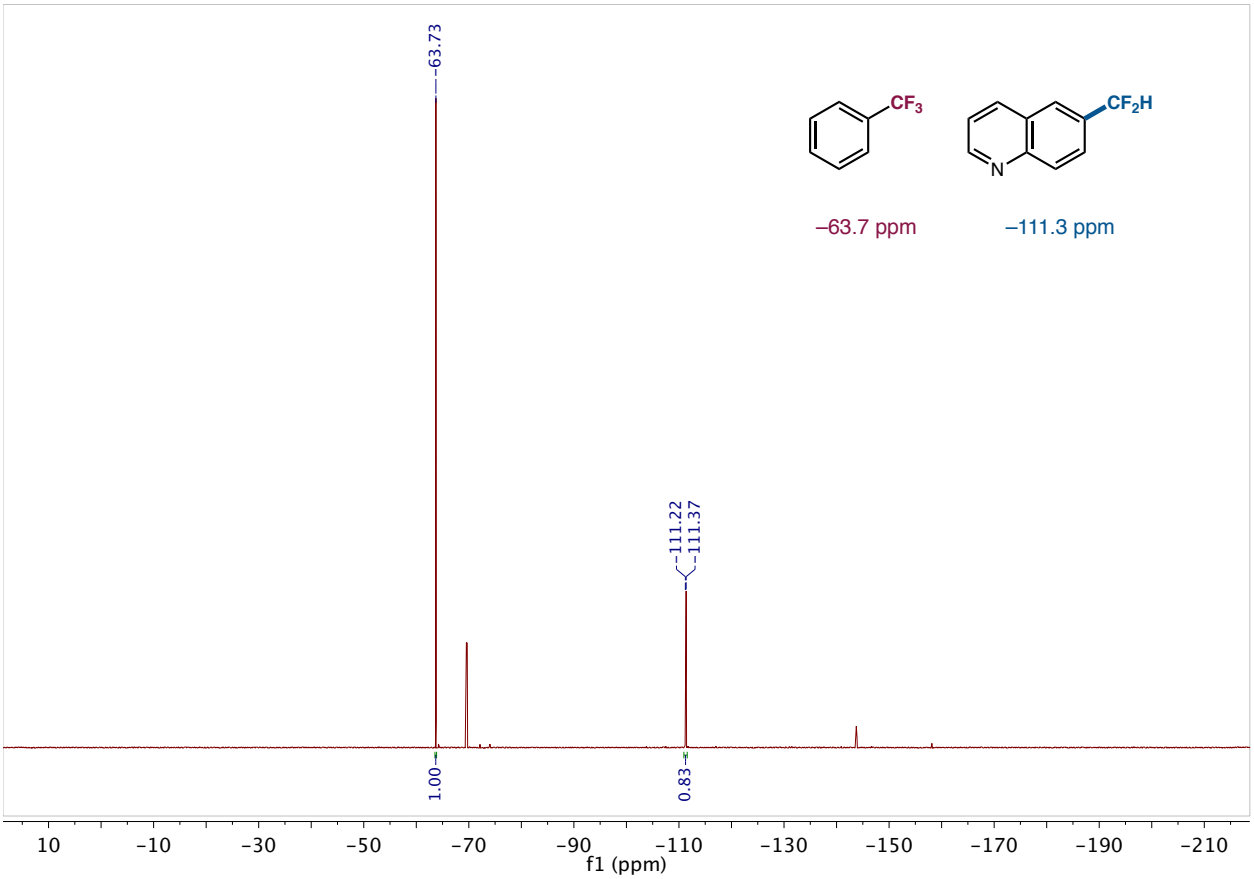
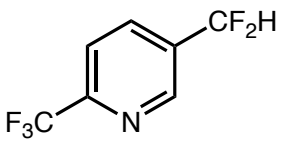
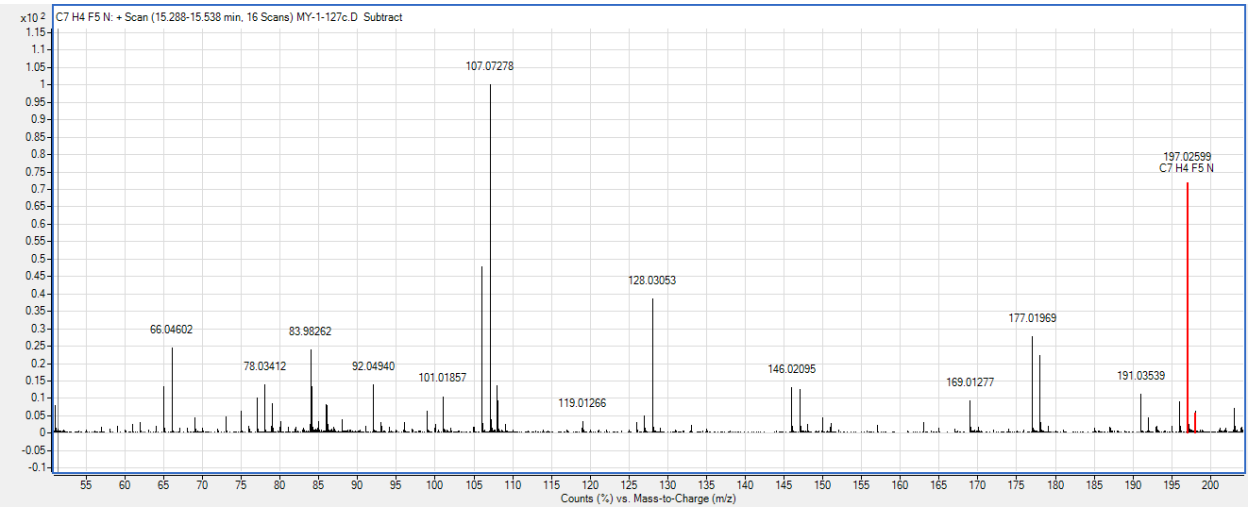


Figure S33. ^{19}F NMR assay for difluoromethylarene **S19**



5-(difluoromethyl)-2-(trifluoromethyl)pyridine (S20)

Prepared following general procedure A using 5-bromo-2-(trifluoromethyl)pyridine (45.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was then back-extracted with EtOAc (3 × 1 mL). To the combined organic layers was added methyl 4-fluorobenzoate (20.0 µL, 0.154 mmol, 0.772 equiv., 0.386 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 79% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_7H_4F_5N$ ($[M^*]^+$) 197.0258, found 197.0260.

^{19}F NMR (376 MHz, $CDCl_3$) δ –69.1 (s, 3F), –114.7 (d, J = 55.2 Hz, 2F).

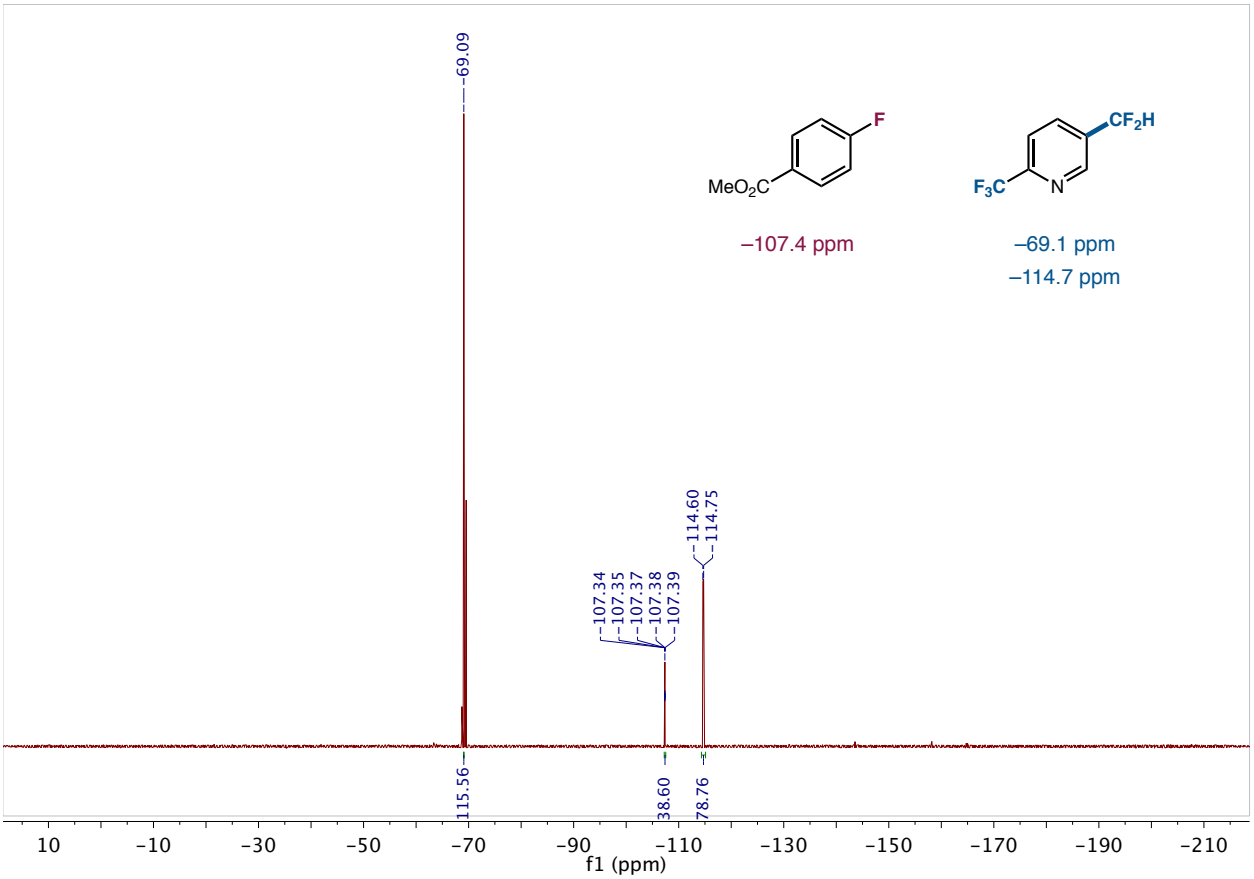
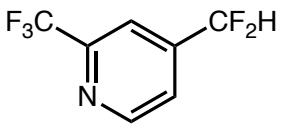
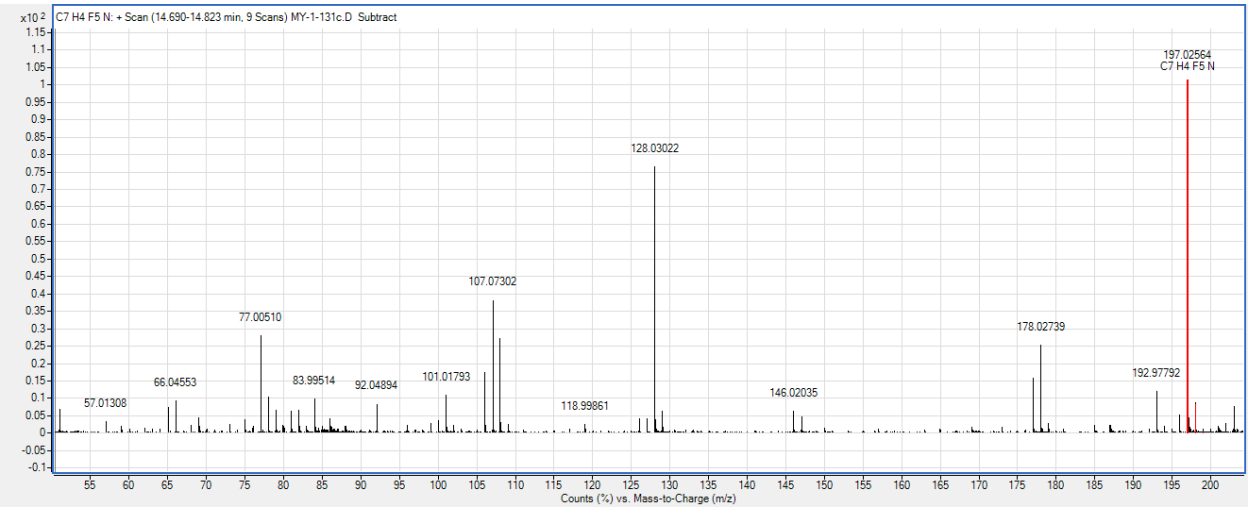


Figure S34. ^{19}F NMR assay for difluoromethylarene **S20**



4-(difluoromethyl)-2-(trifluoromethyl)pyridine (S21)

Prepared following general procedure A using 4-bromo-2-(trifluoromethyl)pyridine (45.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was then back-extracted with EtOAc (3 × 1 mL). To the combined organic layers was added methyl 4-fluorobenzoate (20.0 µL, 0.154 mmol, 0.772 equiv., 0.386 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 75% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_7H_4F_5N$ ($[M^*]^+$) 197.0258, found 197.0256.

^{19}F NMR (376 MHz, $CDCl_3$) δ –69.1 (s, 3F), –117.2 (d, J = 55.1 Hz, 2F).

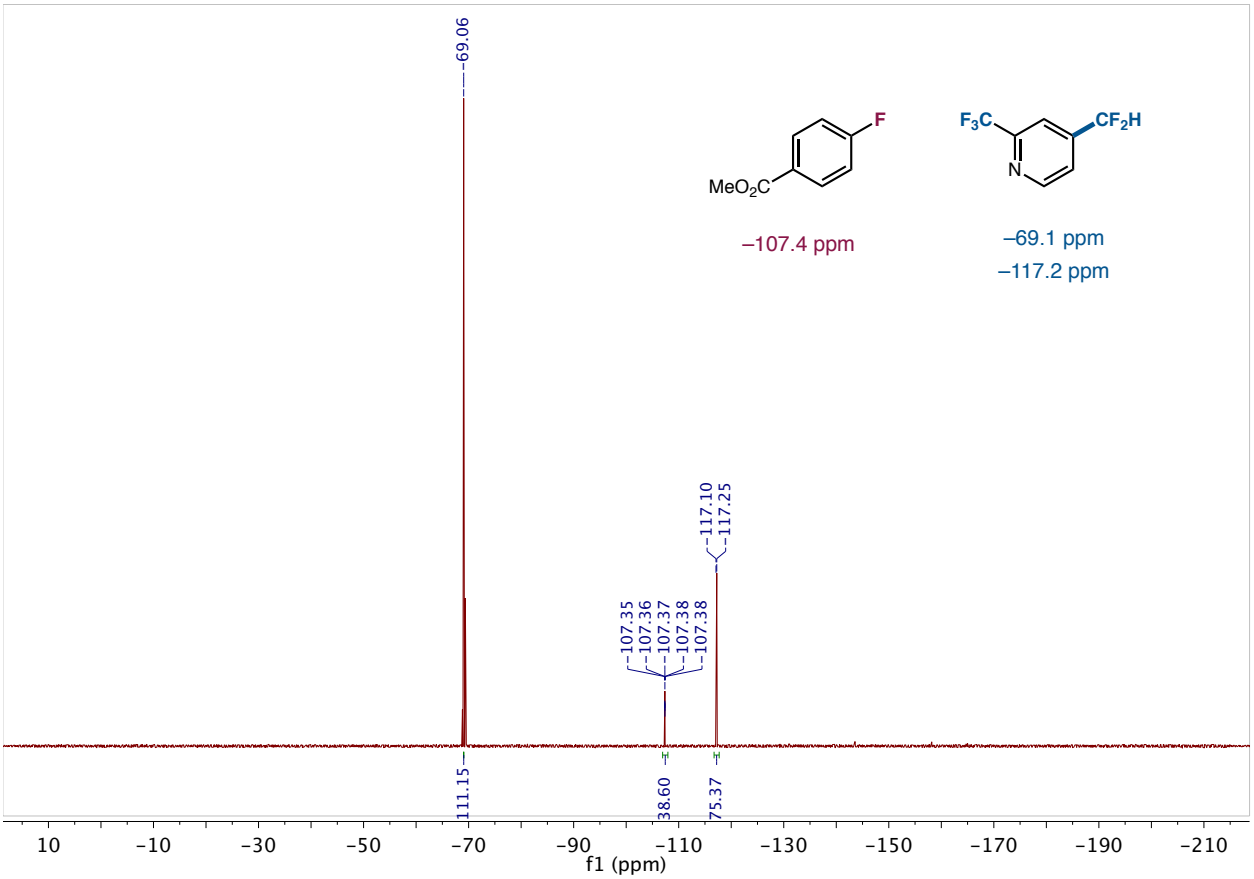
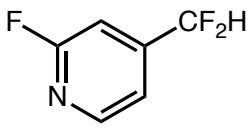
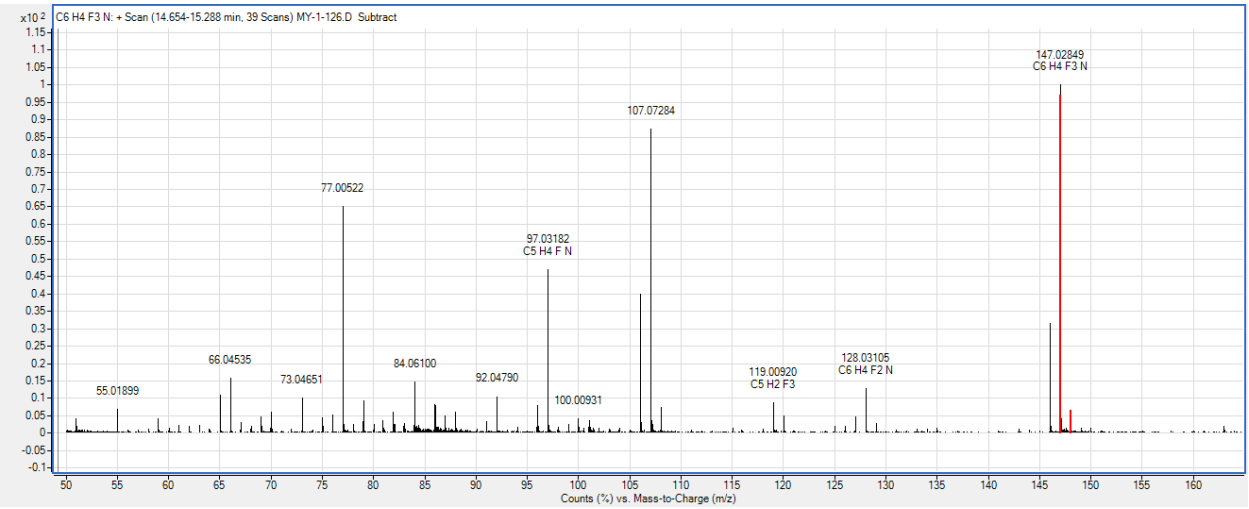


Figure S35. ^{19}F NMR assay for difluoromethylarene **S21**



4-(difluoromethyl)-2-fluoropyridine (S22)

Prepared following general procedure A using 4-bromo-2-fluoropyridine (35.2 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was then back-extracted with EtOAc (3 × 1 mL). To the combined organic layers was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 67% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_6H_4F_3N$ ($[M^*]^+$) 147.0290, found 147.0285.

^{19}F NMR (376 MHz, $CDCl_3$) δ –67.2 (m, 1F), –116.9 (d, J = 55.2 Hz, 2F).

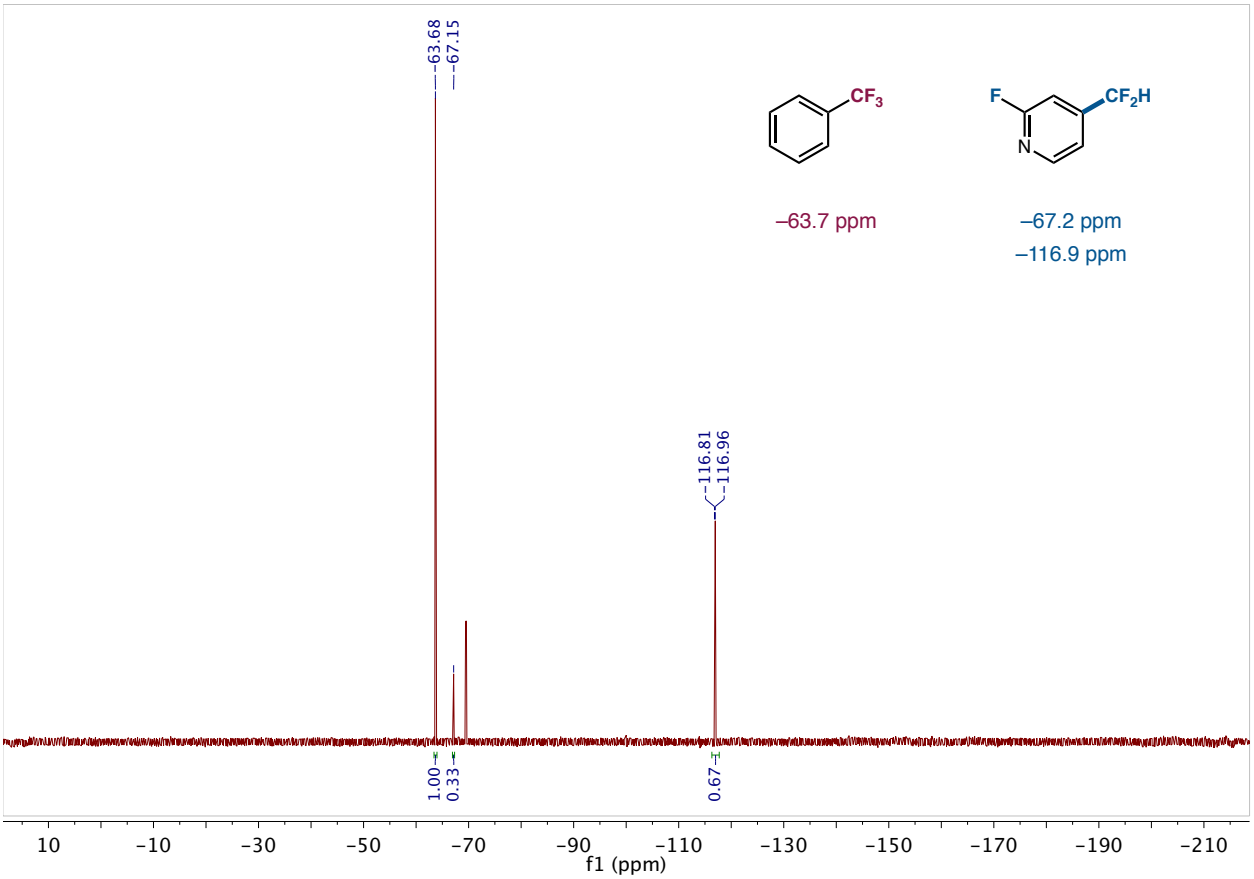
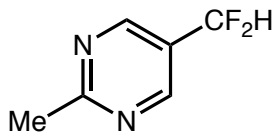
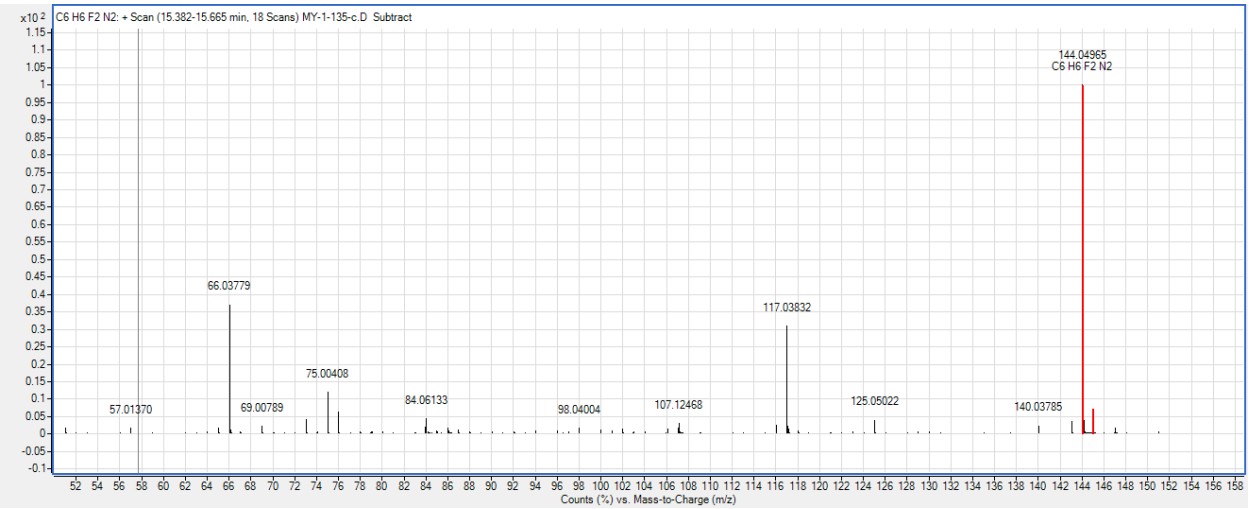


Figure S36. ^{19}F NMR assay for difluoromethylarene **S22**



5-(difluoromethyl)-2-methylpyrimidine (S23)

Prepared following general procedure A using 5-bromo-2-methylpyrimidine (34.8 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.30 mmol, 1.5 equiv., 130 µL, 2.3 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 68% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_6H_6F_2N_2$ ($[M^*]^+$) 144.0494, found 144.0497.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.7 (d, J = 55.1 Hz, 2F).

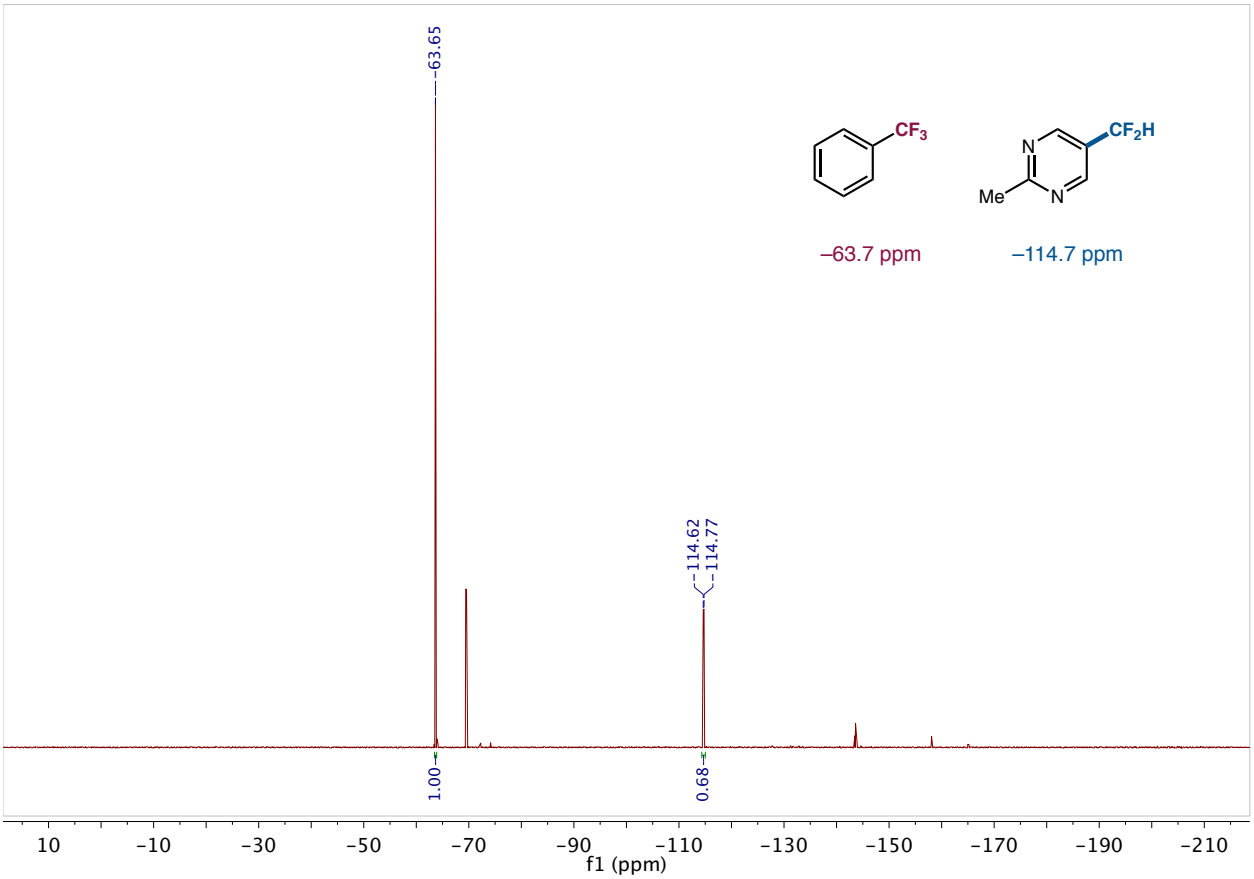
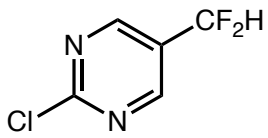
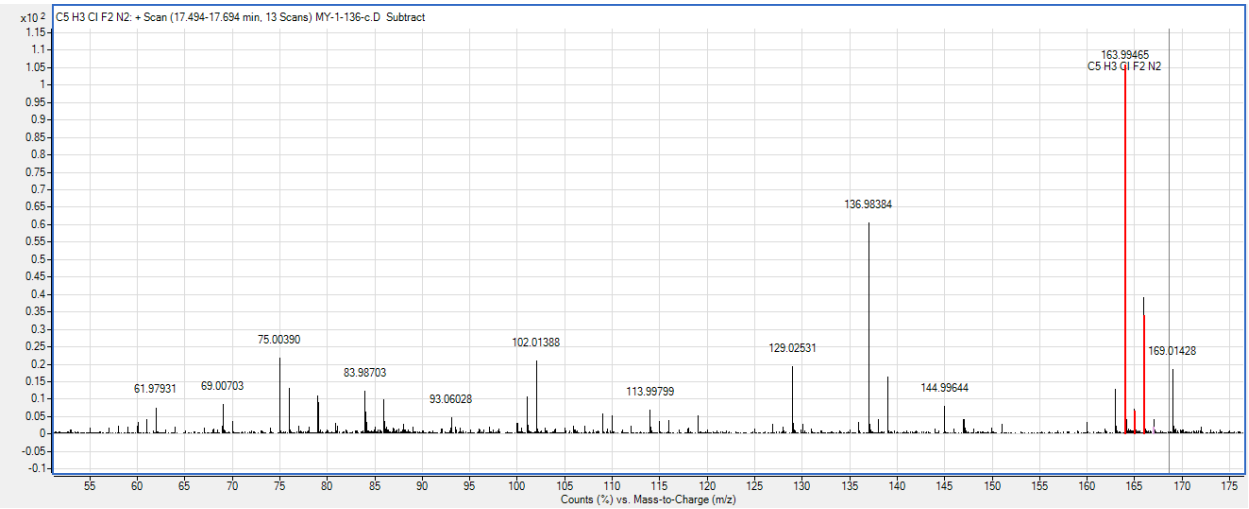


Figure S37. ^{19}F NMR assay for difluoromethylarene **S23**



2-chloro-5-(difluoromethyl)pyrimidine (S24)

Prepared following general procedure A using 5-bromo-2-chloropyrimidine (38.6 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.30 mmol, 1.5 equiv., 130 µL, 2.3 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (67 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (2.0 mL). Fans and a water bath were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 38% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_5H_3ClF_2N_2$ ($[M^*]^+$) 163.9947, found 163.9947.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.5 (d, J = 54.7 Hz, 2F).

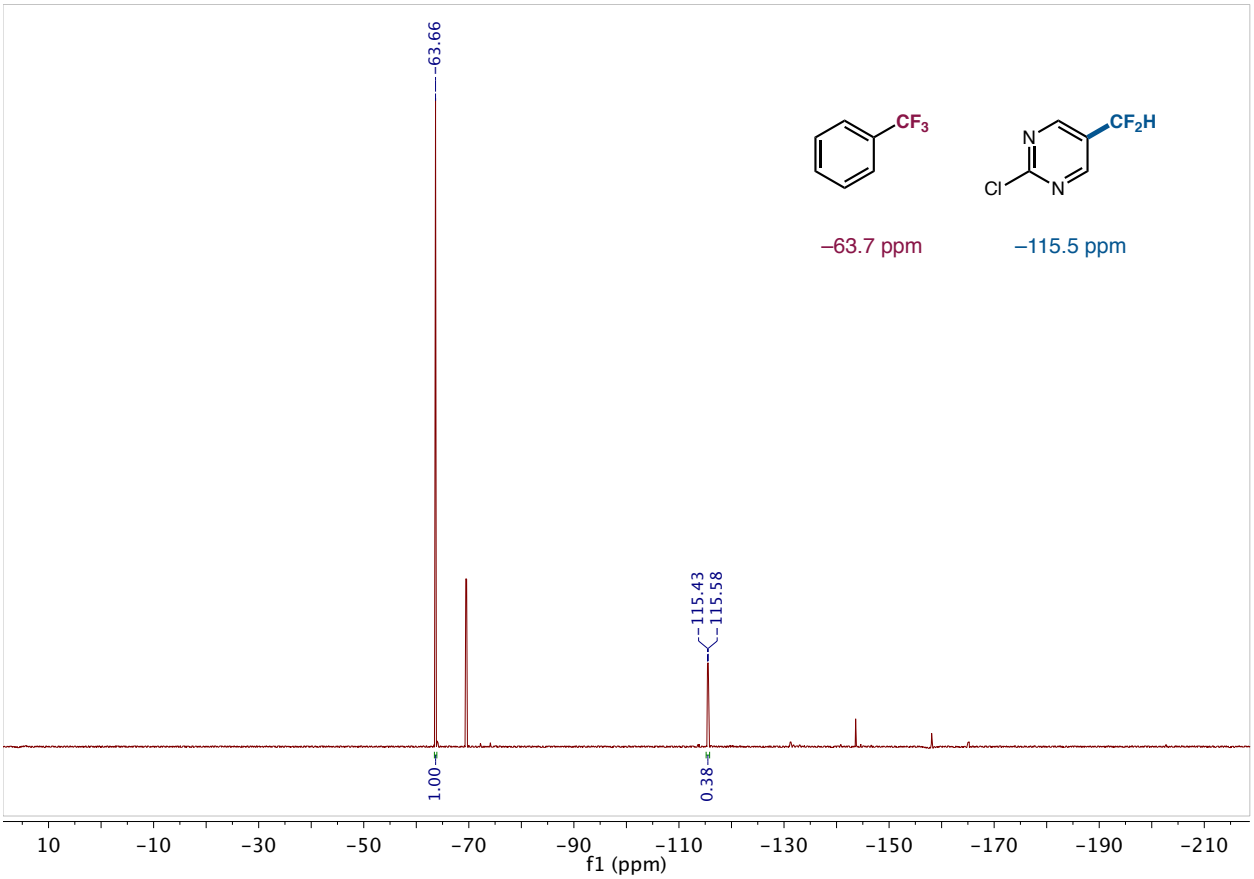
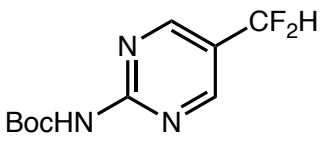
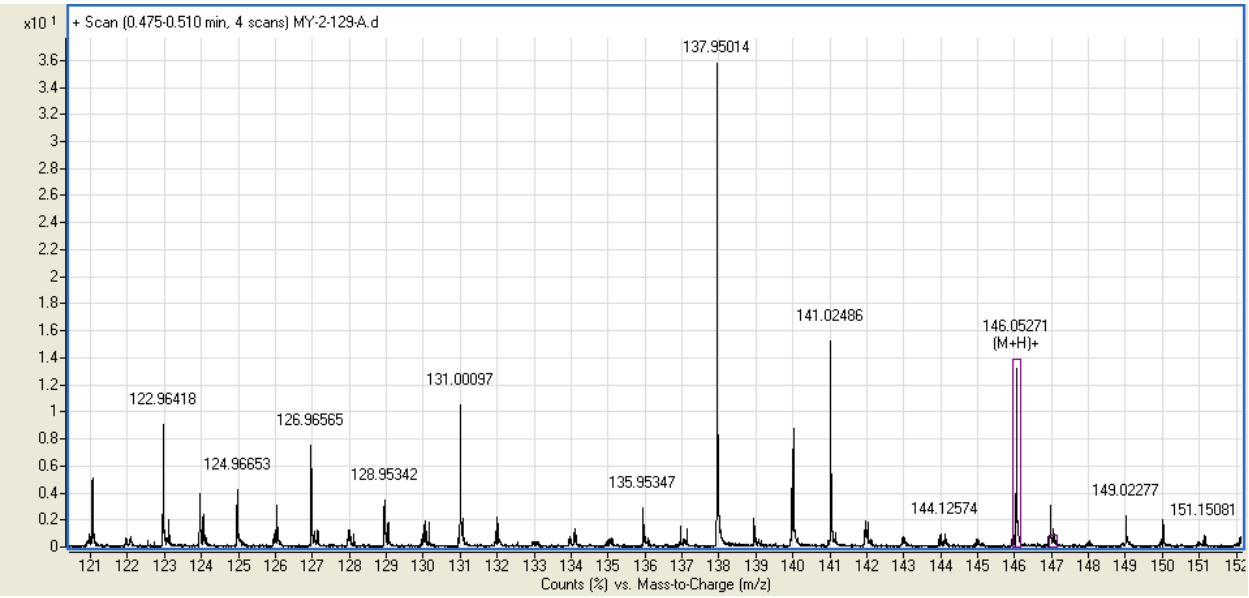


Figure S38. ^{19}F NMR assay for difluoromethylarene **S24**



tert-butyl (5-(difluoromethyl)pyrimidin-2-yl)carbamate (S25)

Prepared following general procedure A using tert-butyl (5-bromopyrimidin-2-yl)carbamate (54.8 mg, 0.20 mmol, 1.0 equiv.), bromodifluoromethane (0.40 mmol, 2.0 equiv., 190 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.2 mg, 2.0 µmol, 1.0 mol%), $NiBr_2$•glyme (3.1 mg, 10 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10 µmol, 5.0 mol%), 2,6-lutidine (47 µL, 0.40 mmol, 2.0 equiv.), tris(trimethylsilyl)silane (65 µL, 0.21 mmol, 1.05 equiv.), and DME (4.0 mL). Fans were used for cooling. After 18 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was then back-extracted with EtOAc (3 × 1 mL). To the combined organic layers was added α,α,α-trifluorotoluene (16.5 µL, 0.134 mmol, 0.67 equiv., 1.0 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 50% was recorded.



HRMS (ESI-TOF) *m/z* calcd. for $C_5H_6F_2N_3$ ($[M–Boc+2H]^+$) 146.0524, found 146.0527.

^{19}F NMR (376 MHz, $CDCl_3$) δ –113.4 (d, J = 55.3 Hz, 2F).

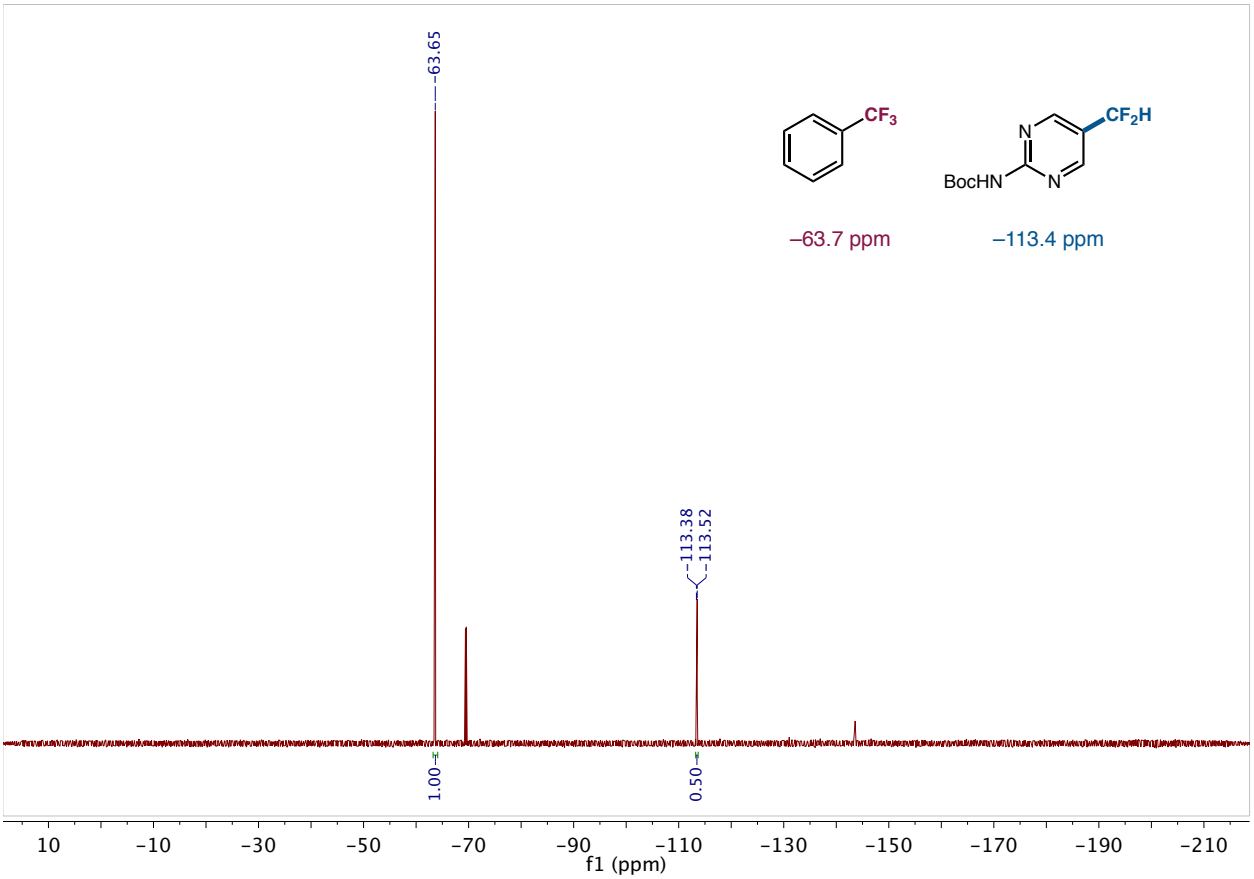
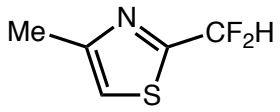
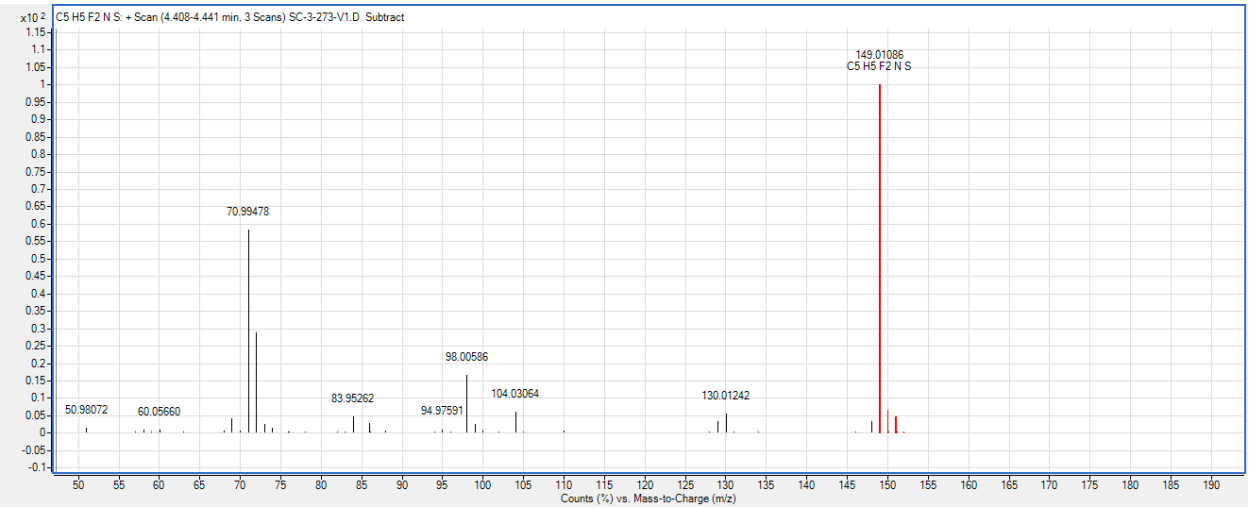


Figure S39. ^{19}F NMR assay for difluoromethylarene **S25**



2-(difluoromethyl)-4-methylthiazole (S26)

Prepared following general procedure A using 2-bromo-4-methylthiazole (11 µL, 0.10 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 2.0 equiv., 95 µL, 2.1 M in DME), [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (1.1 mg, 1.0 µmol, 1.0 mol%), $NiBr_2$•glyme (1.5 mg, 5.0 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (1.3 mg, 5.0 µmol, 5.0 mol%), quinuclidine (44 mg, 0.40 mmol, 4.0 equiv.), tris(trimethylsilyl)silane (32 µL, 0.11 mmol, 1.05 equiv.), and DME (1.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (10.0 µL, 0.081 mmol, 0.814 equiv., 1.22 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 41% was recorded.



HRMS (GC-EI-TOF) *m/z* calcd. for $C_5H_5F_2NS$ ([M*]$^+$) 149.0105, found 149.0109.

^{19}F NMR (376 MHz, $CDCl_3$) δ –109.9 (d, *J* = 54.9 Hz, 2F).

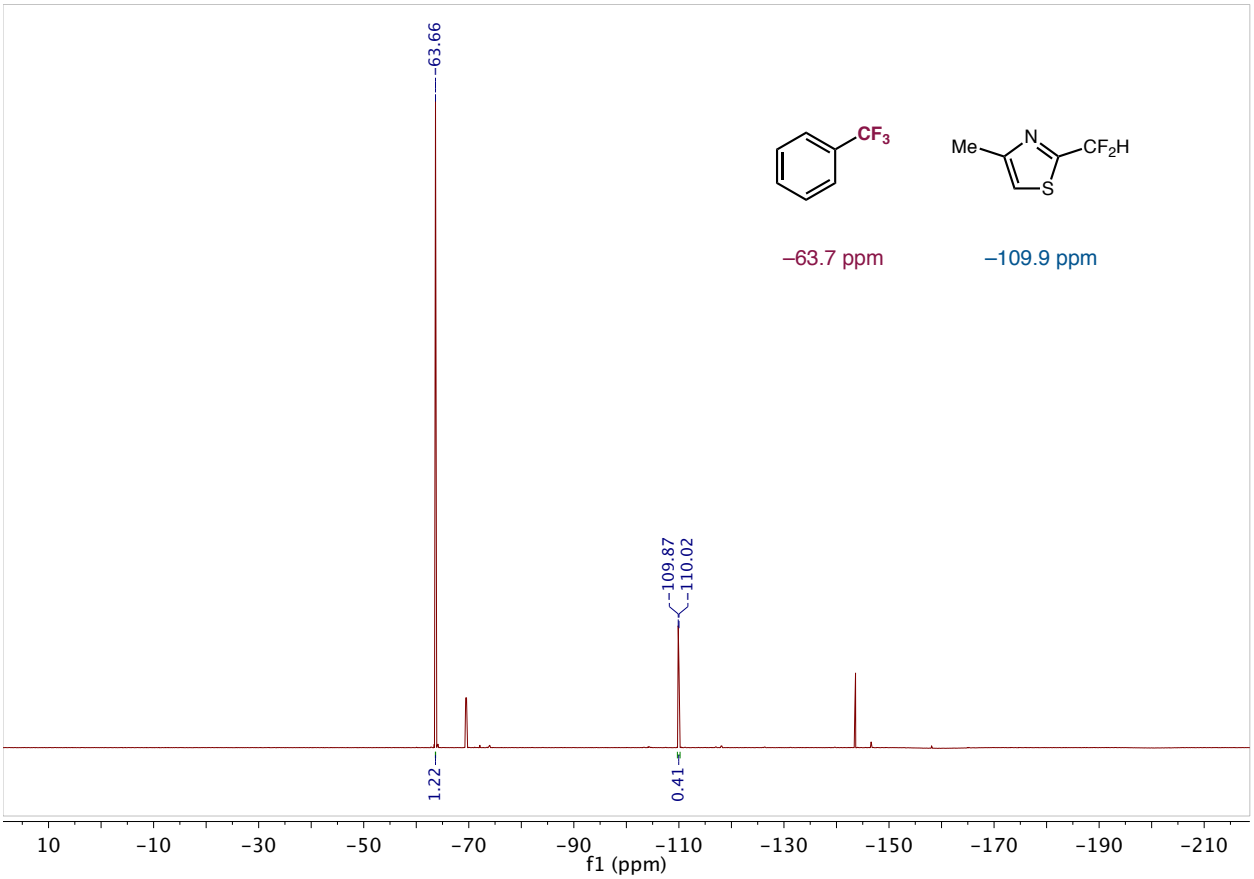
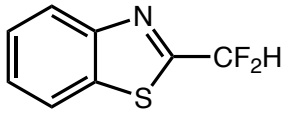
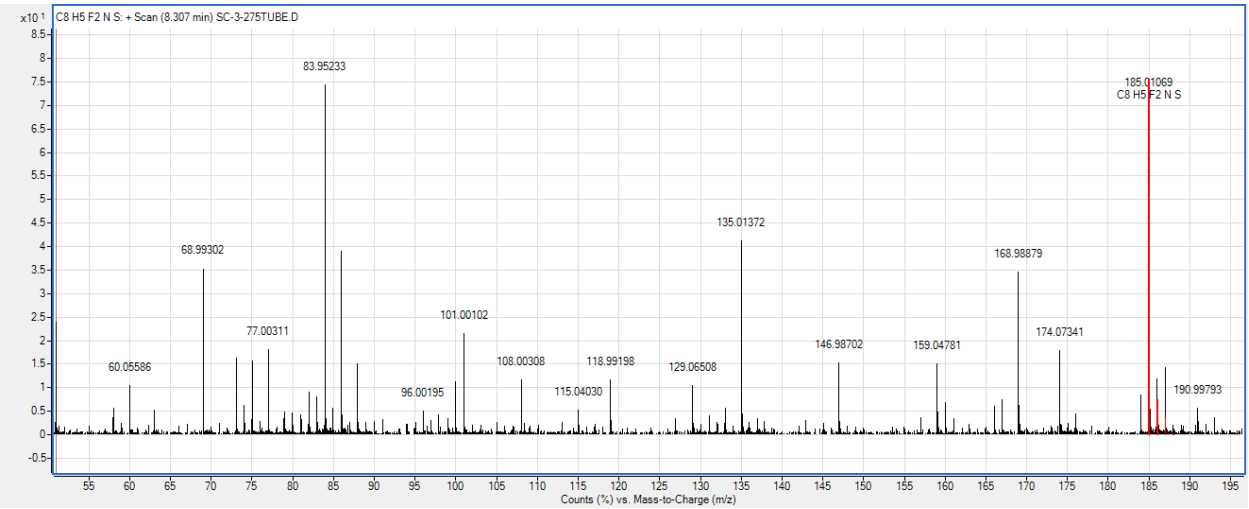


Figure S40. ^{19}F NMR assay for difluoromethylarene **S26**



2-(difluoromethyl)benzo[*d*]thiazole (S27)

Prepared following general procedure A using 2-bromobenzo[*d*]thiazole (21.0 mg, 0.10 mmol, 1.0 equiv.), bromodifluoromethane (0.20 mmol, 2.0 equiv., 95 µL, 2.1 M in DME), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (1.1 mg, 1.0 µmol, 1.0 mol%), $NiBr_2$•glyme (1.5 mg, 5.0 µmol, 5.0 mol%), 4,4'-di-tert-butyl-2,2'-bipyridine (1.3 mg, 5.0 µmol, 5.0 mol%), anhydrous LiOH (7.2 mg, 0.30 mmol, 3.0 equiv.), tris(trimethylsilyl)silane (32 µL, 0.11 mmol, 1.05 equiv.), and DME (1.0 mL). Fans were used for cooling. After 18 h, to the reaction vial was added α,α,α-trifluorotoluene (10.0 µL, 0.081 mmol, 0.814 equiv., 1.22 equiv. "CF_2H") as an internal standard for ^{19}F NMR analysis in $CDCl_3$. A crude NMR yield of 39% was recorded.



HRMS (GC-EI-TOF) *m*/*z* calcd. for $C_8H_5F_2NS$ ($[M^*]^+$) 185.0105, found 185.0107.

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.3 (d, J = 54.3 Hz, 2F).

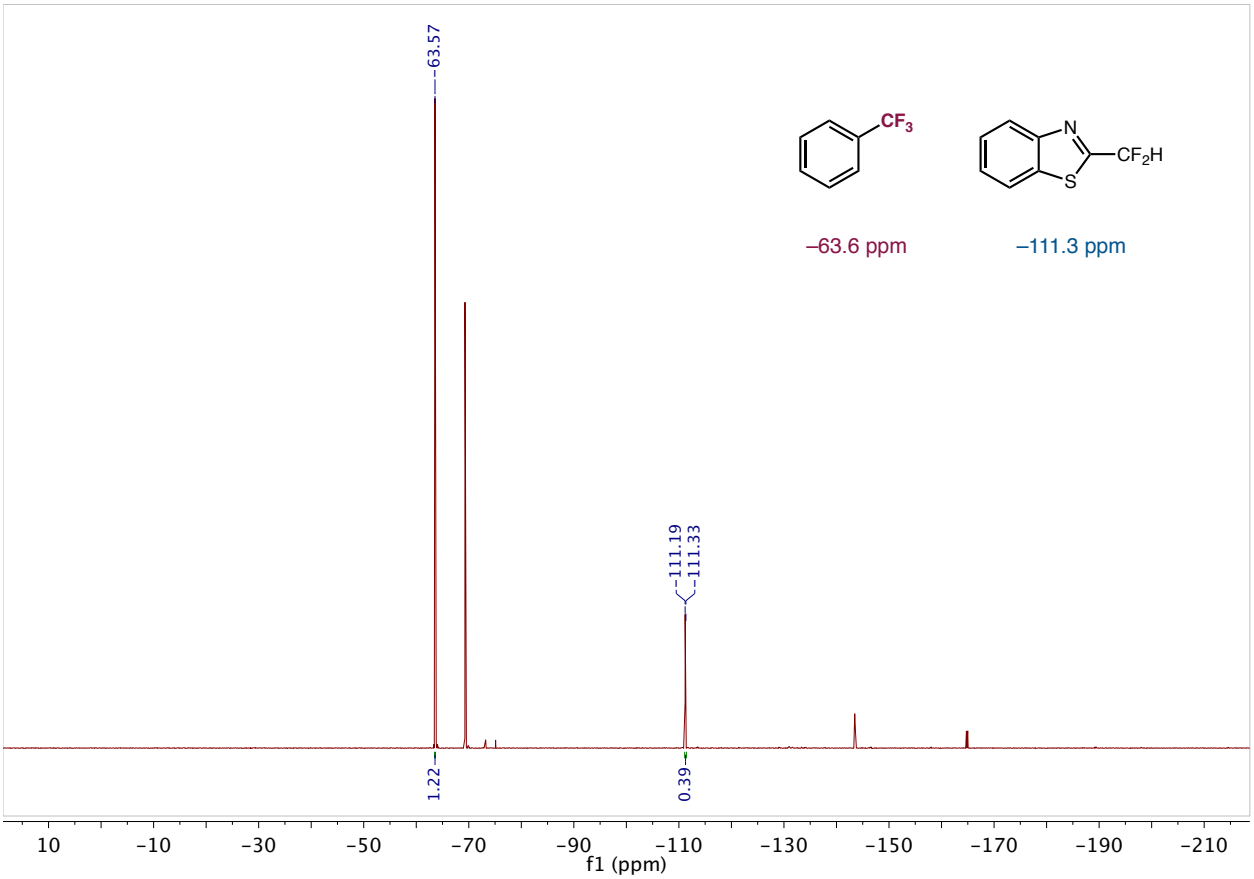
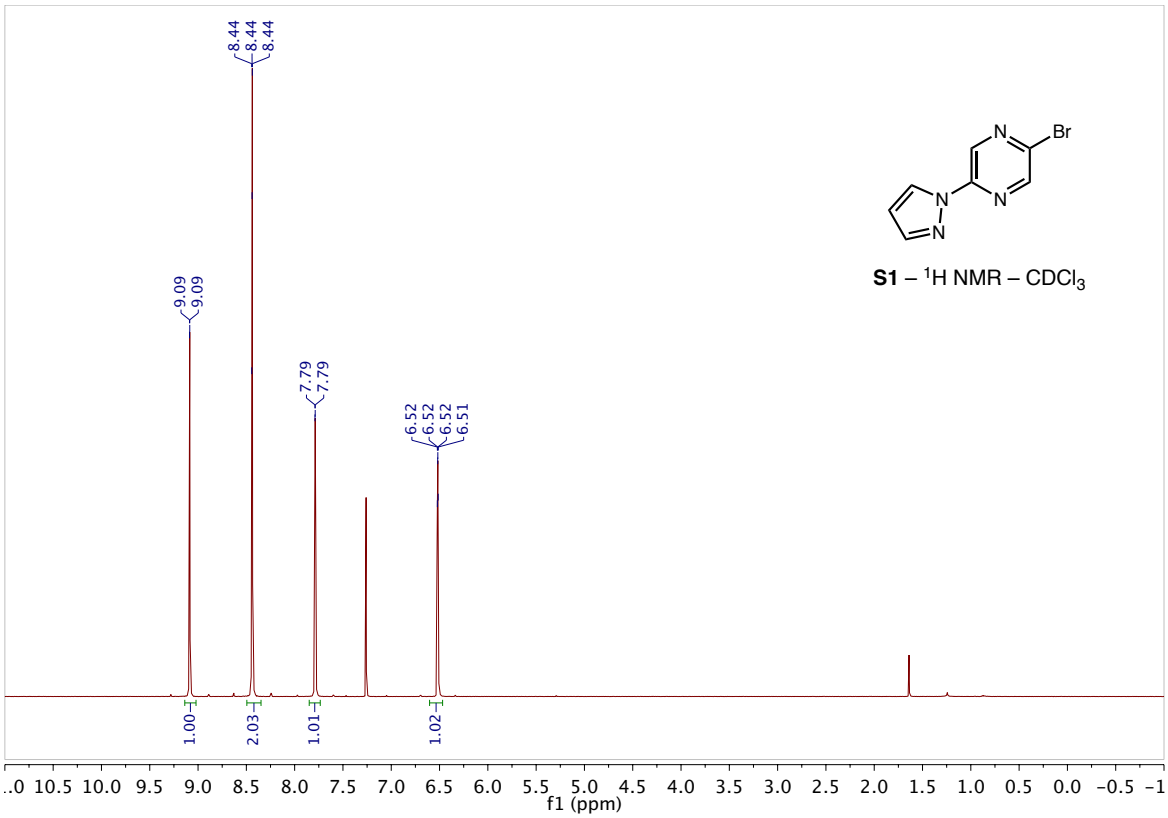
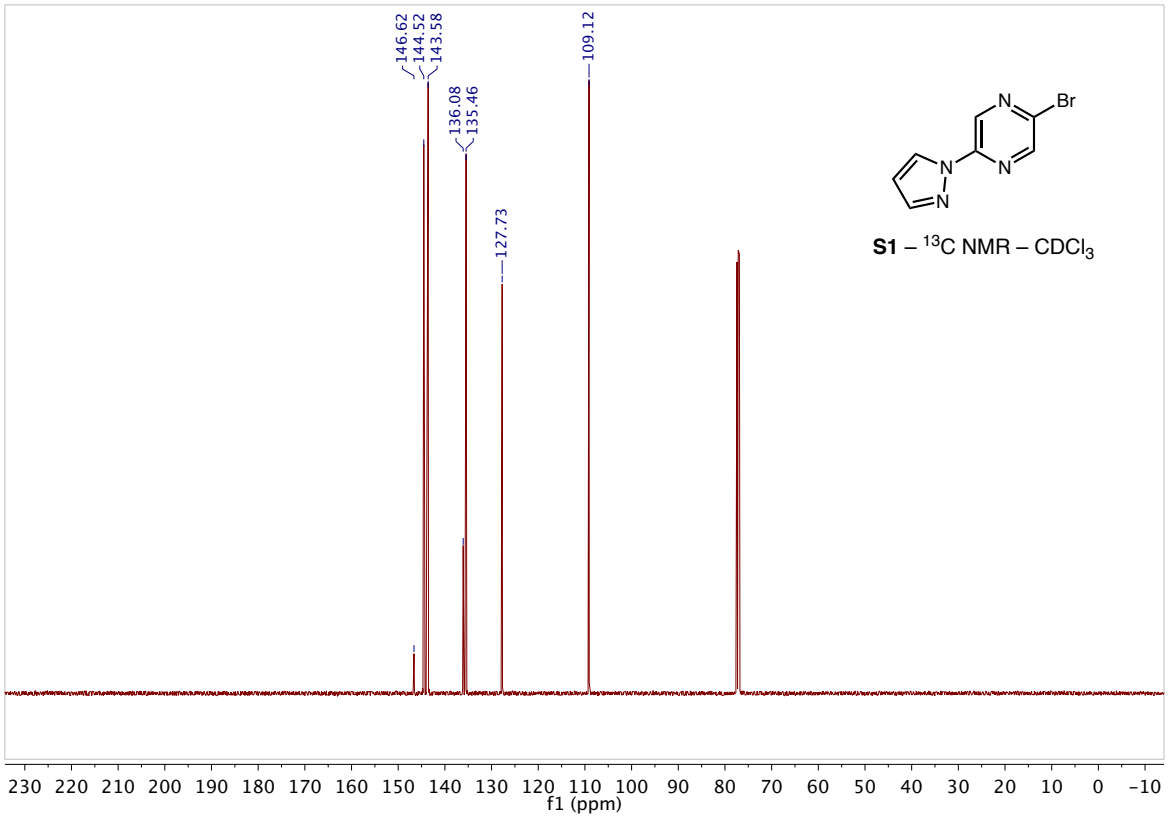


Figure S41. ^{19}F NMR assay for difluoromethylarene **S27**

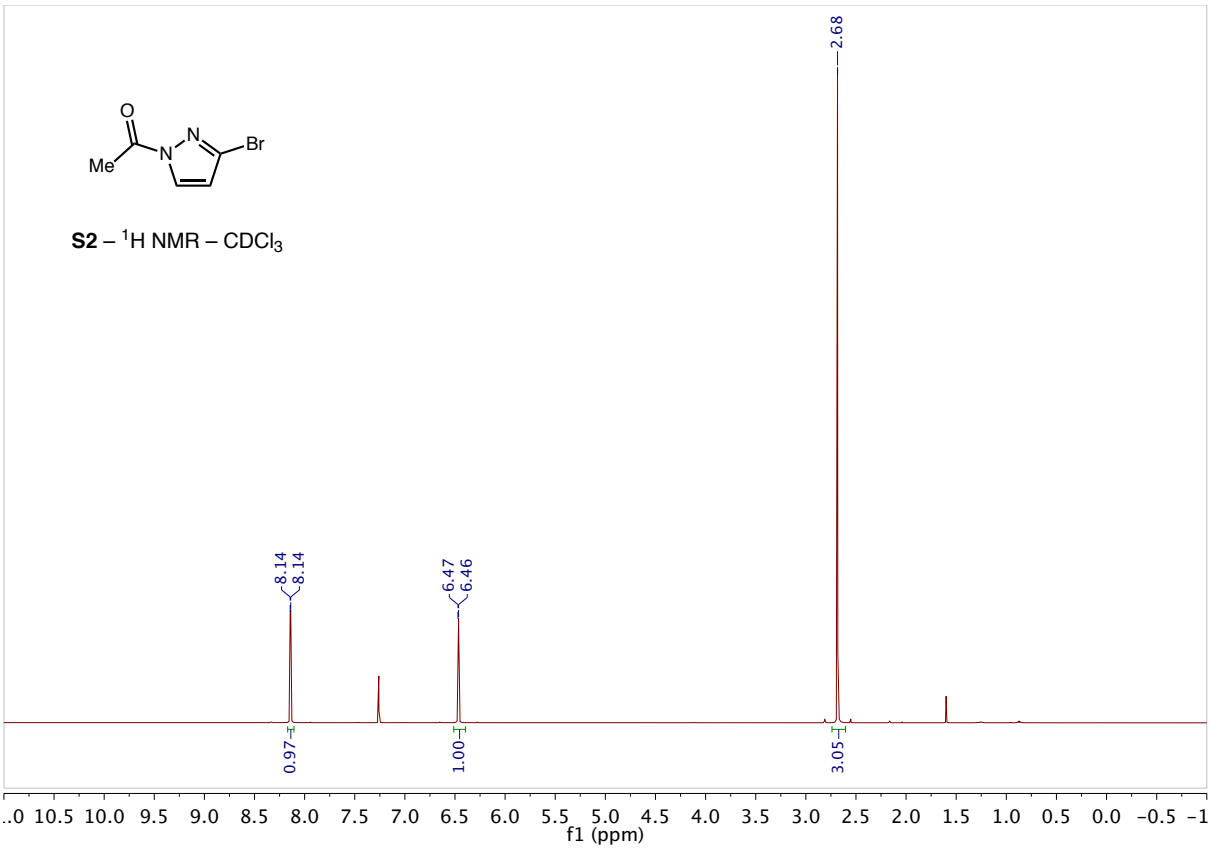
10) NMR Spectral Data



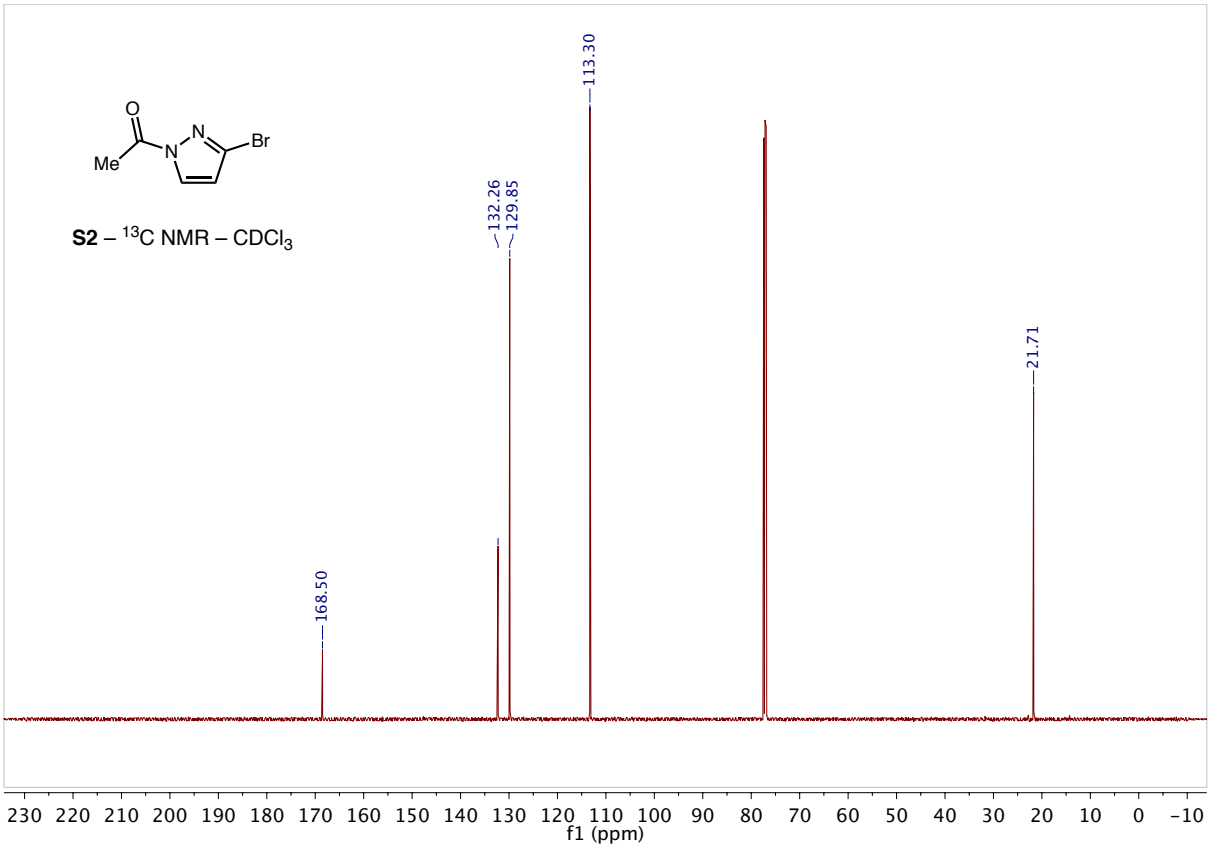
S1 – ^{1}H NMR – $CDCl_3$



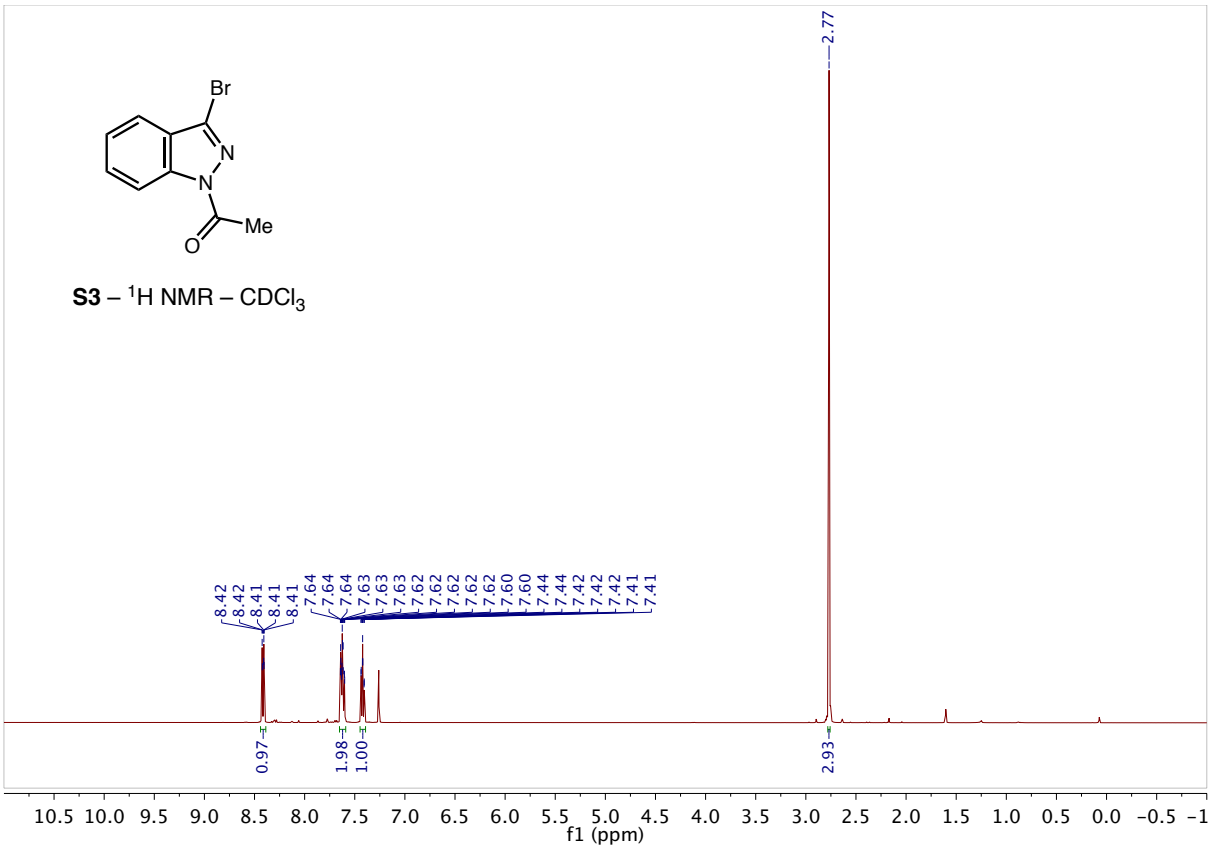
S1 – ^{13}C NMR – $CDCl_3$



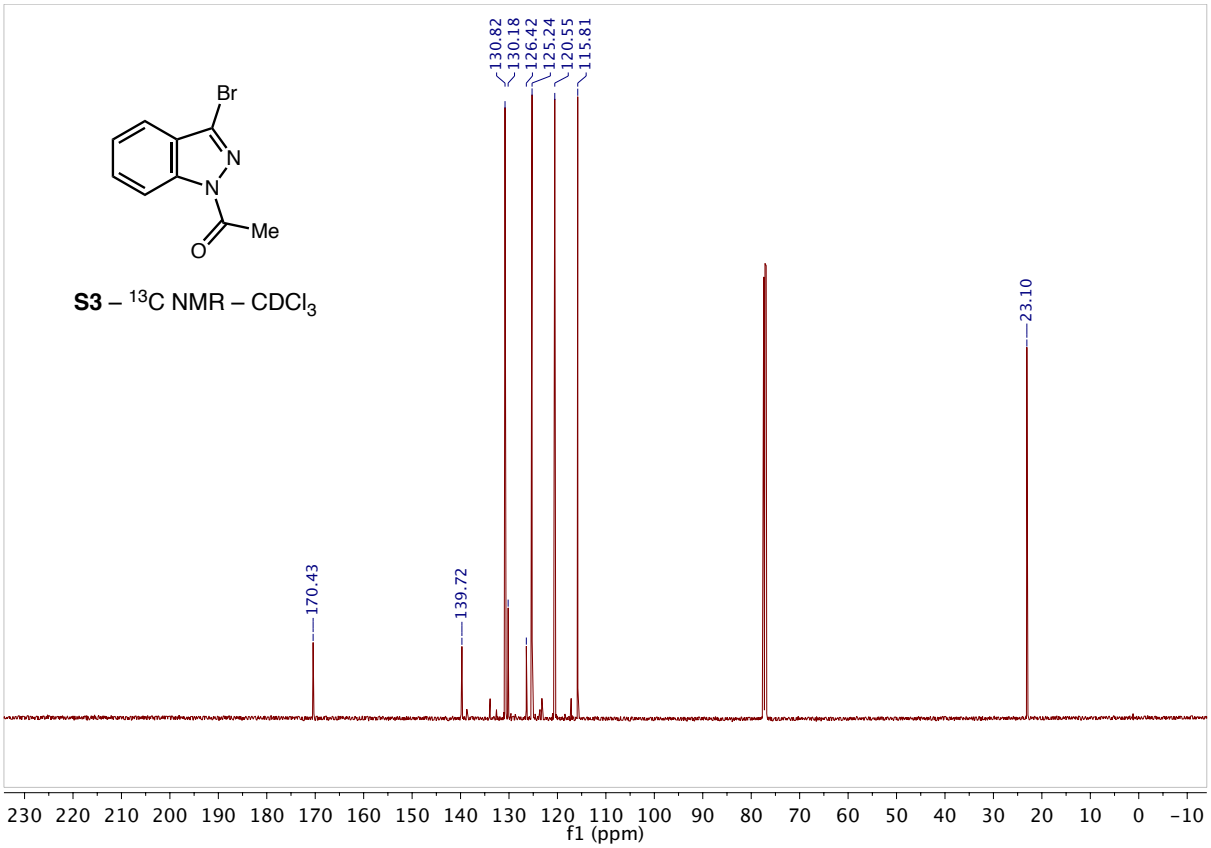
S2 – ^{1}H NMR – $CDCl_3$



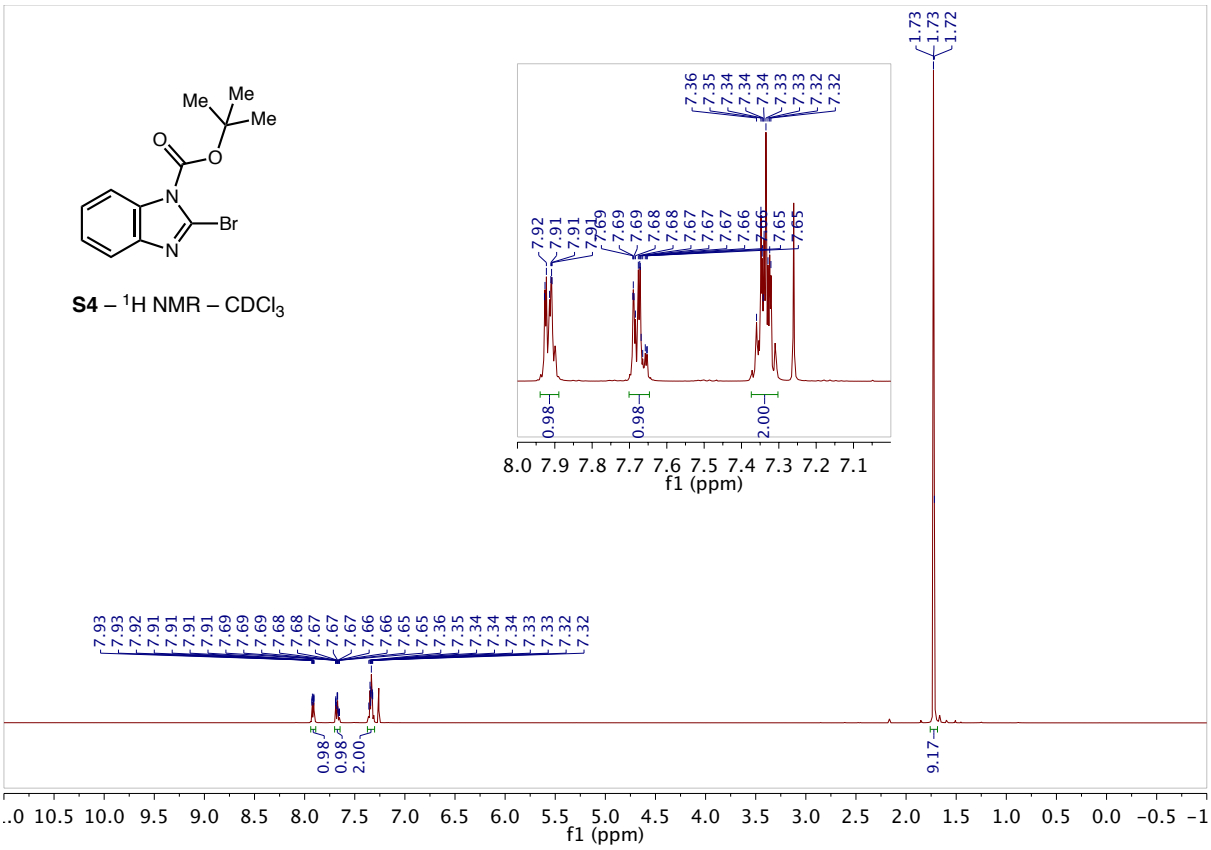
S2 – ^{13}C NMR – $CDCl_3$



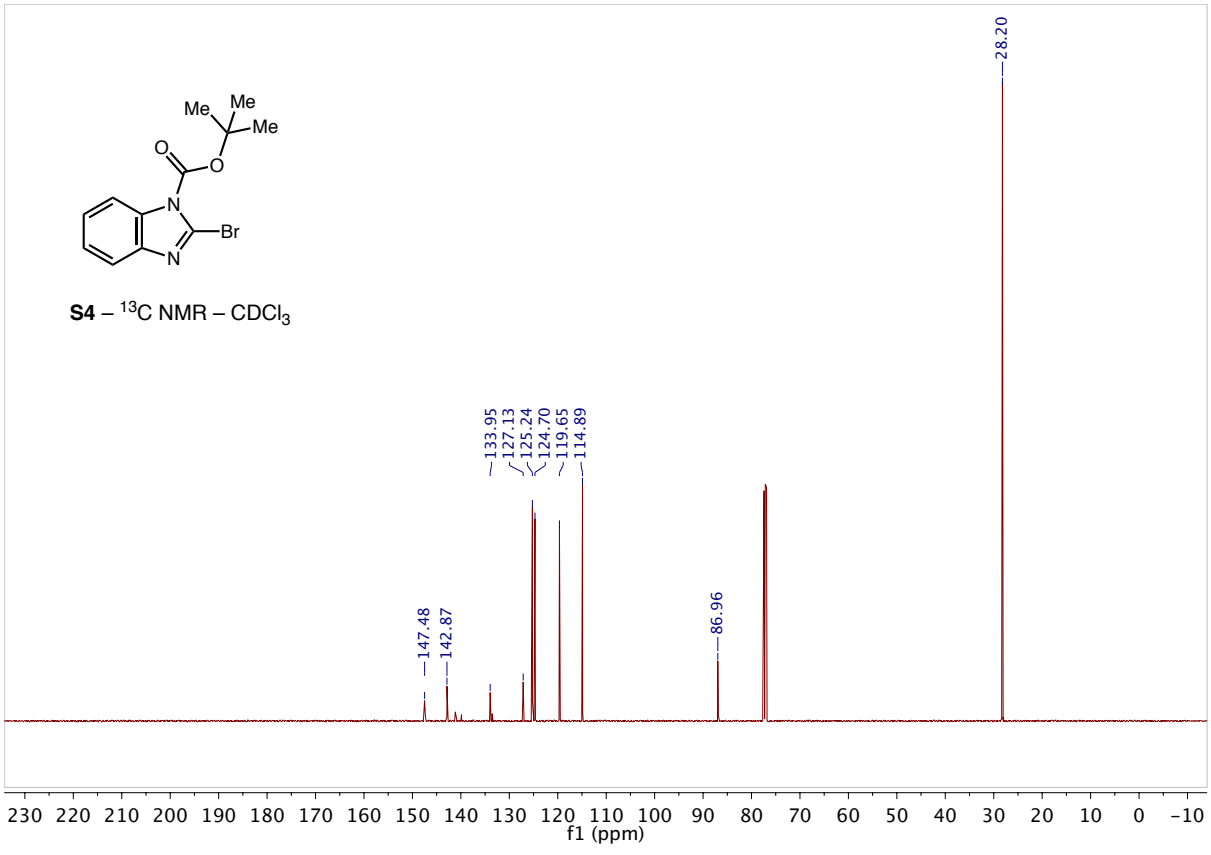
S3 – ^{1}H NMR – $CDCl_3$



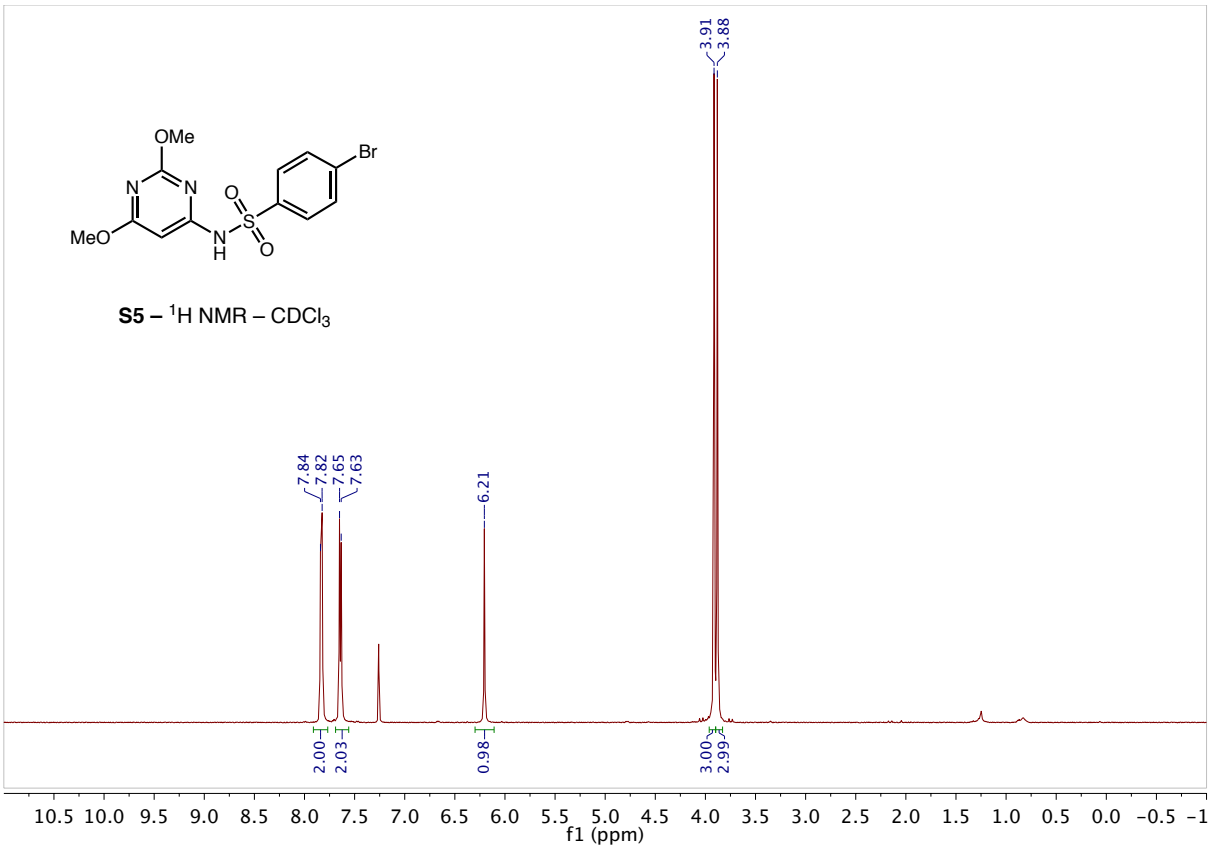
S3 – ^{13}C NMR – $CDCl_3$



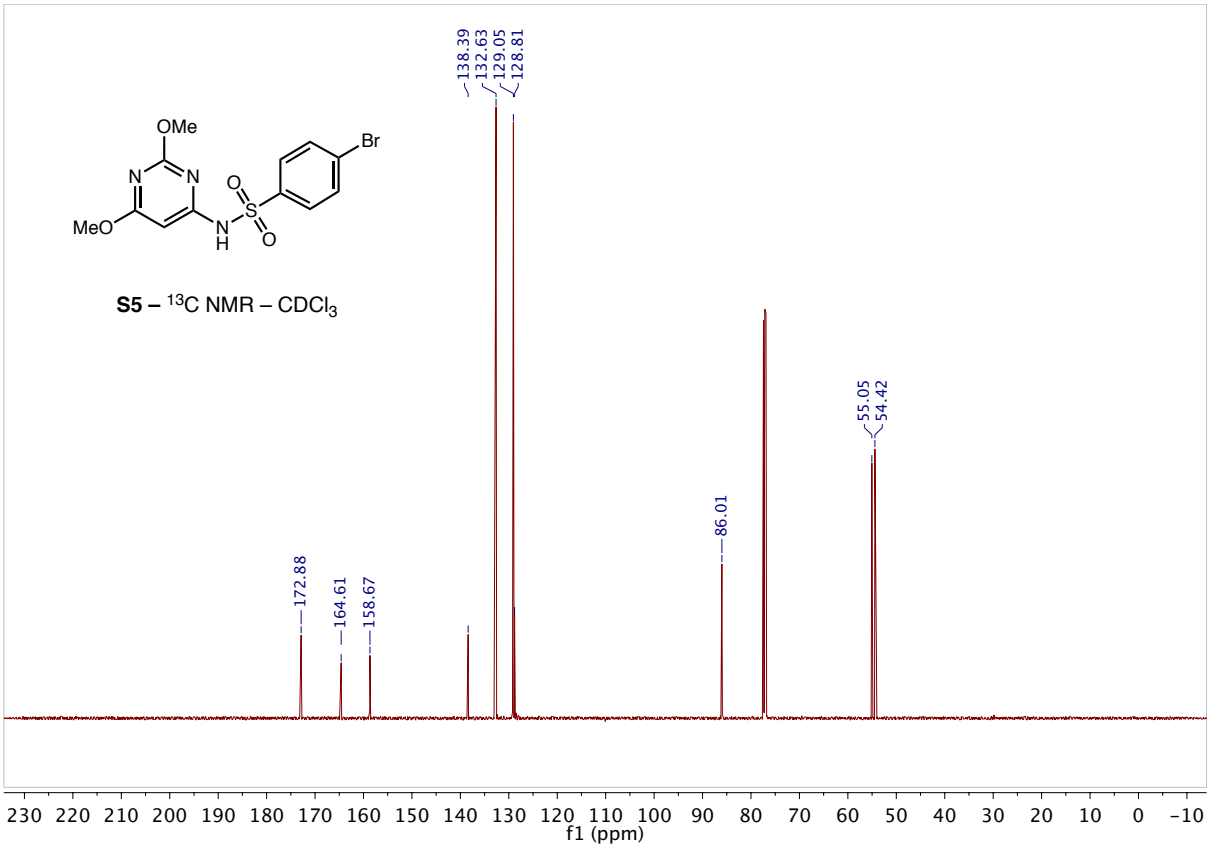
S4 – ^{1}H NMR – $CDCl_3$



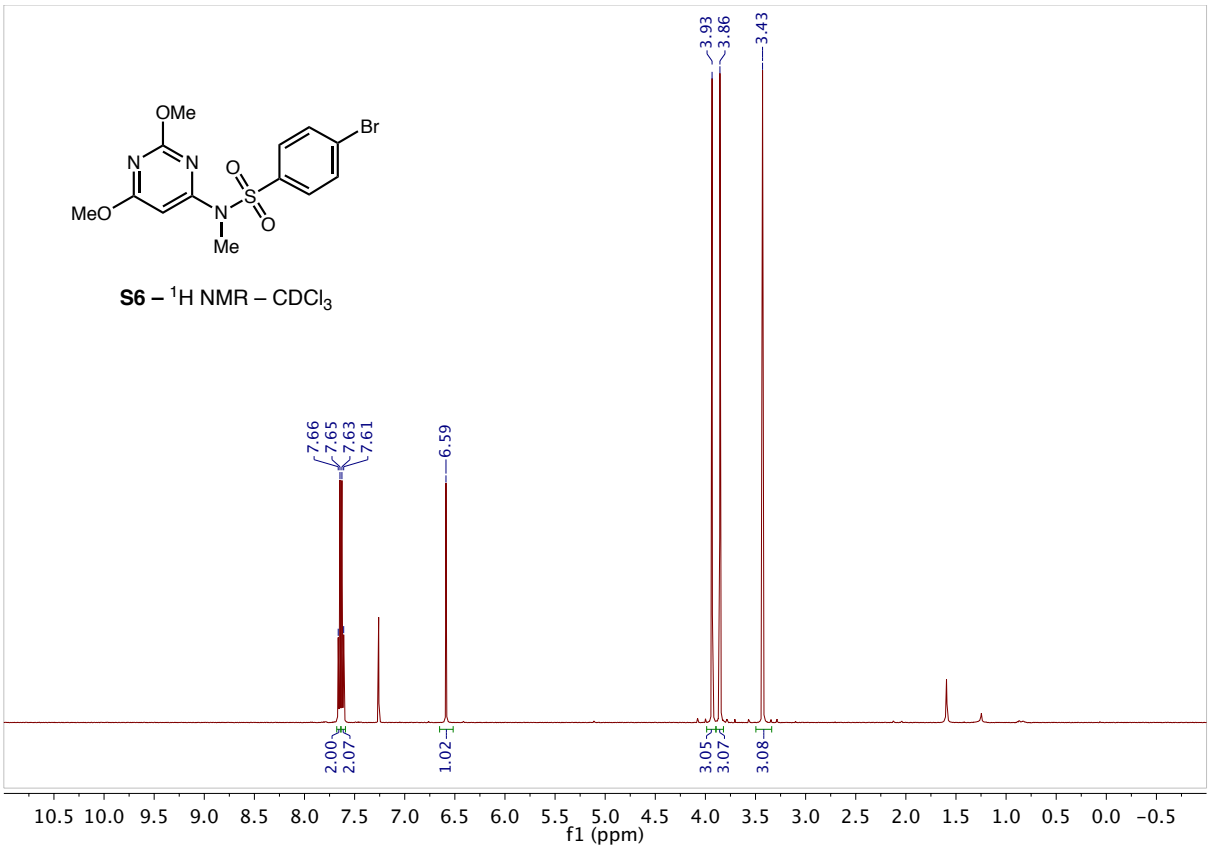
S4 – ^{13}C NMR – $CDCl_3$



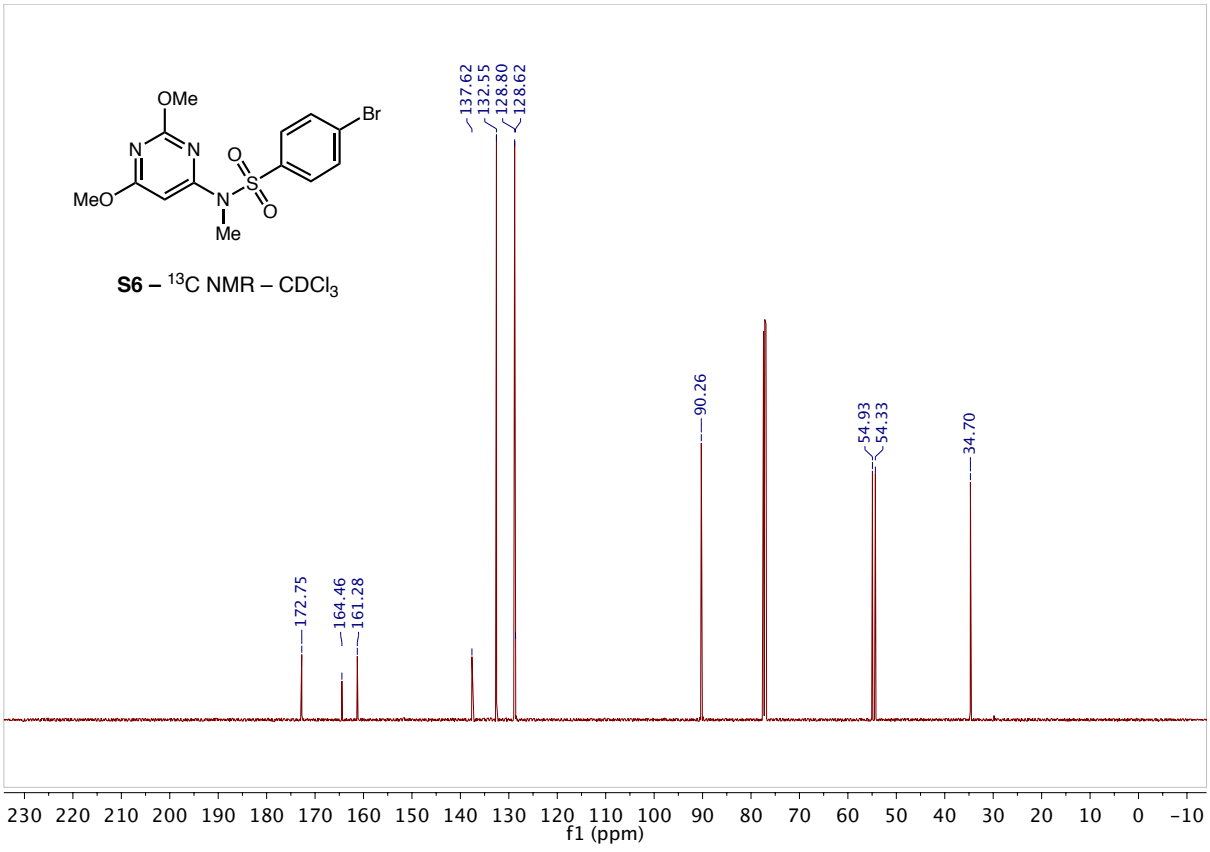
S5 – ^{1}H NMR – $CDCl_3$



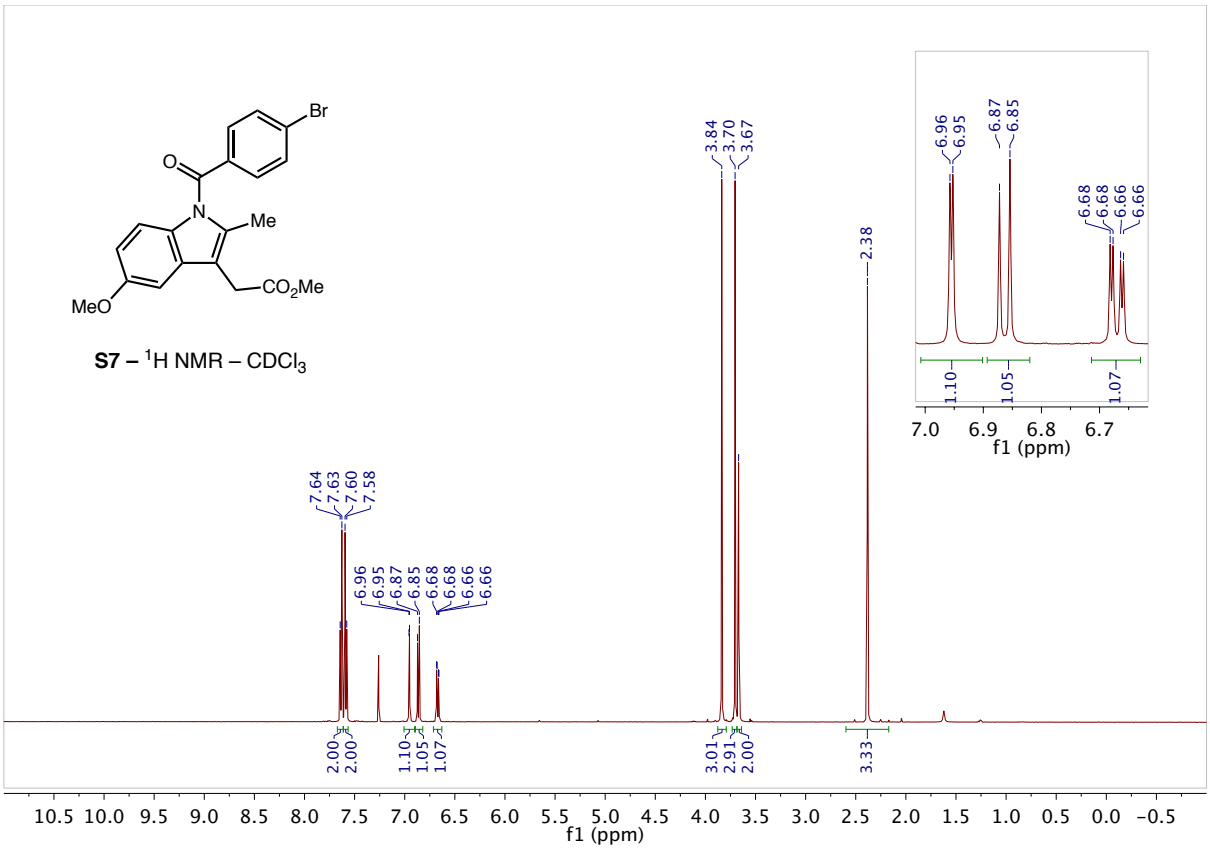
S5 – ^{13}C NMR – $CDCl_3$



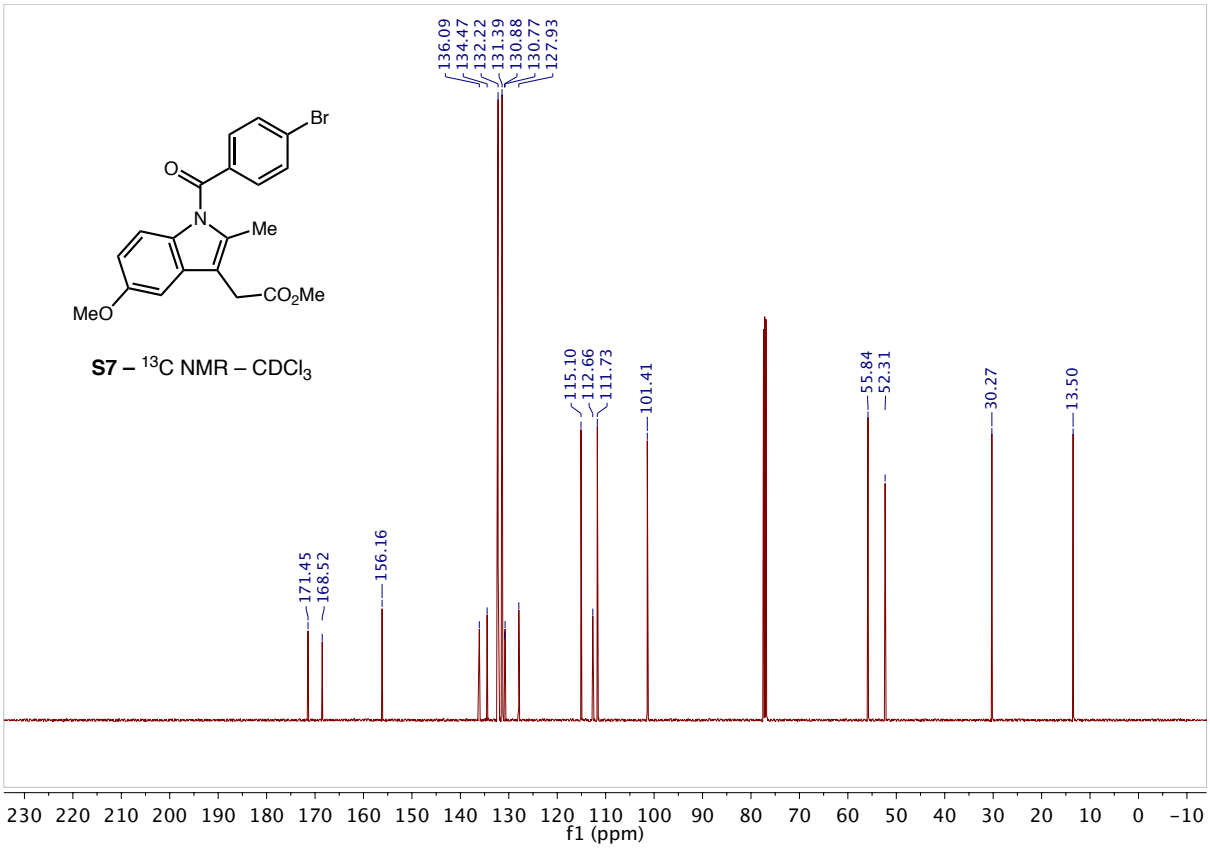
S6 – ^{1}H NMR – $CDCl_3$



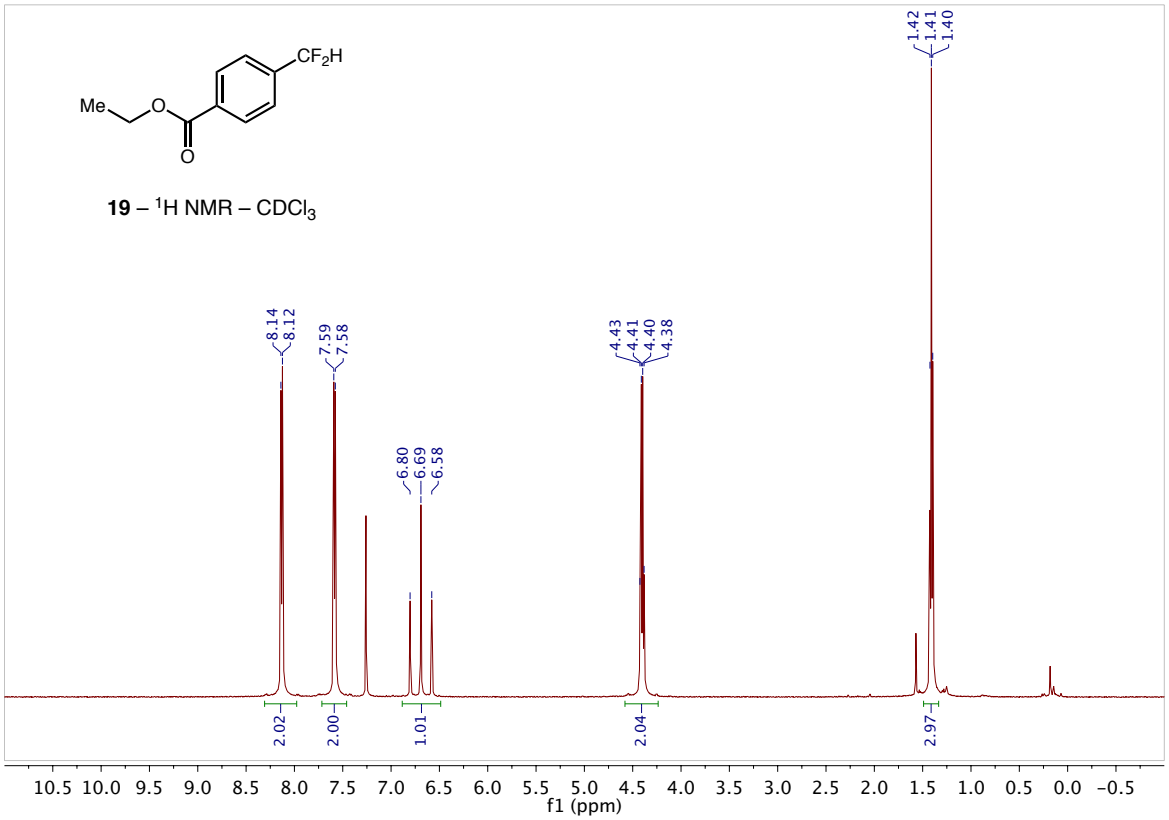
S6 – ^{13}C NMR – $CDCl_3$

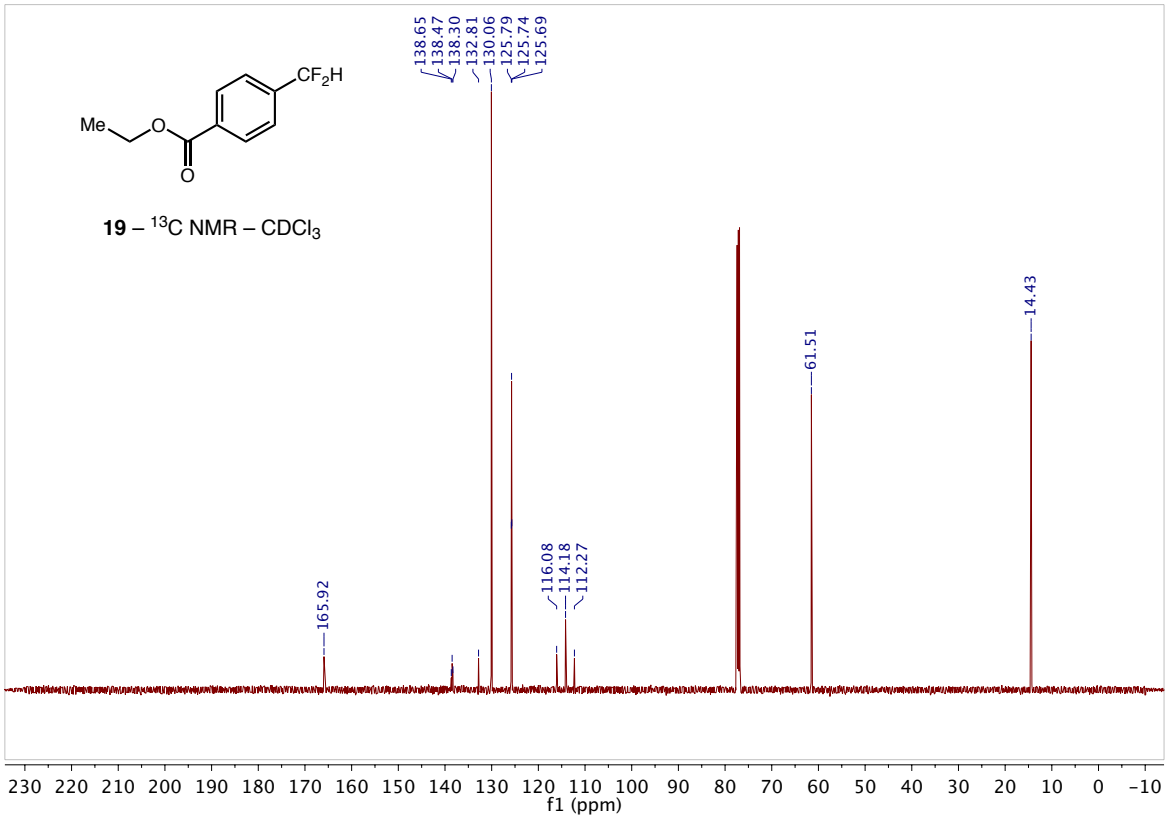


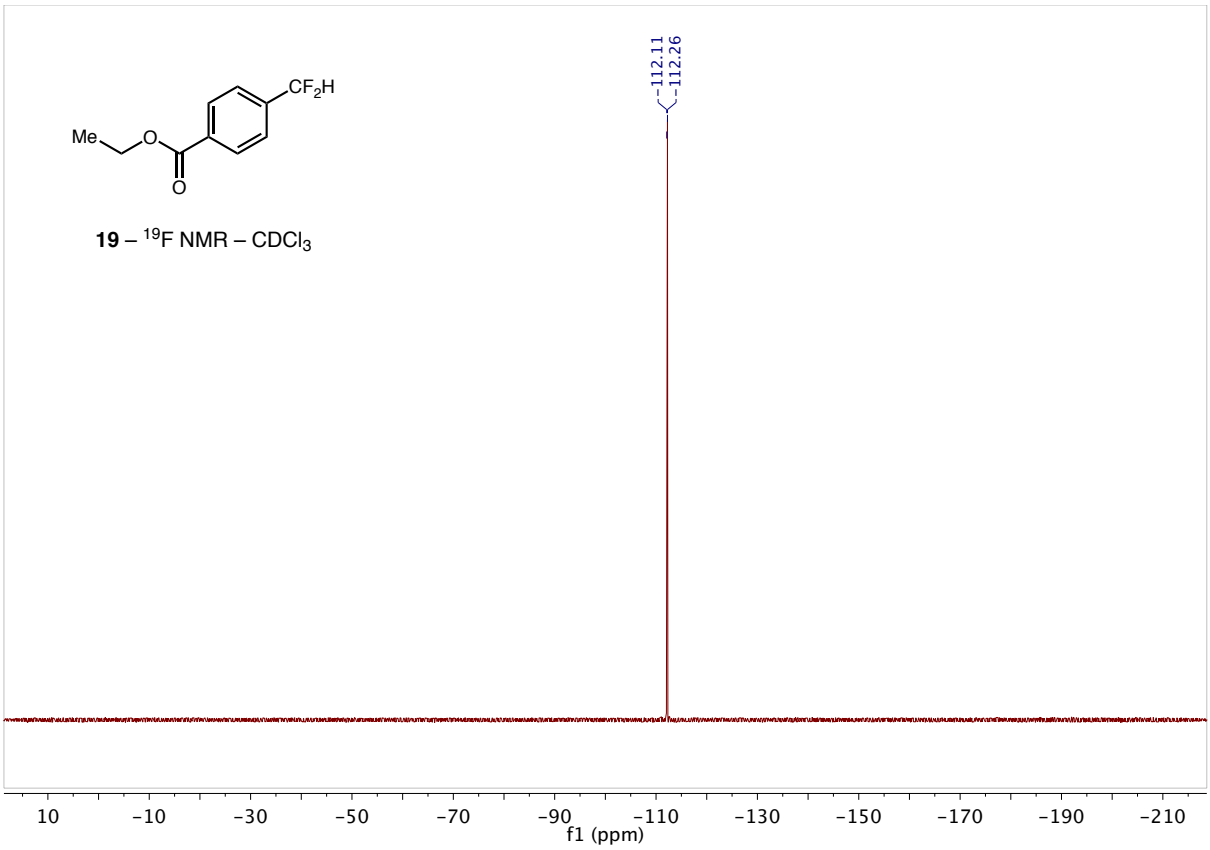
S7 – ^{1}H NMR – $CDCl_3$



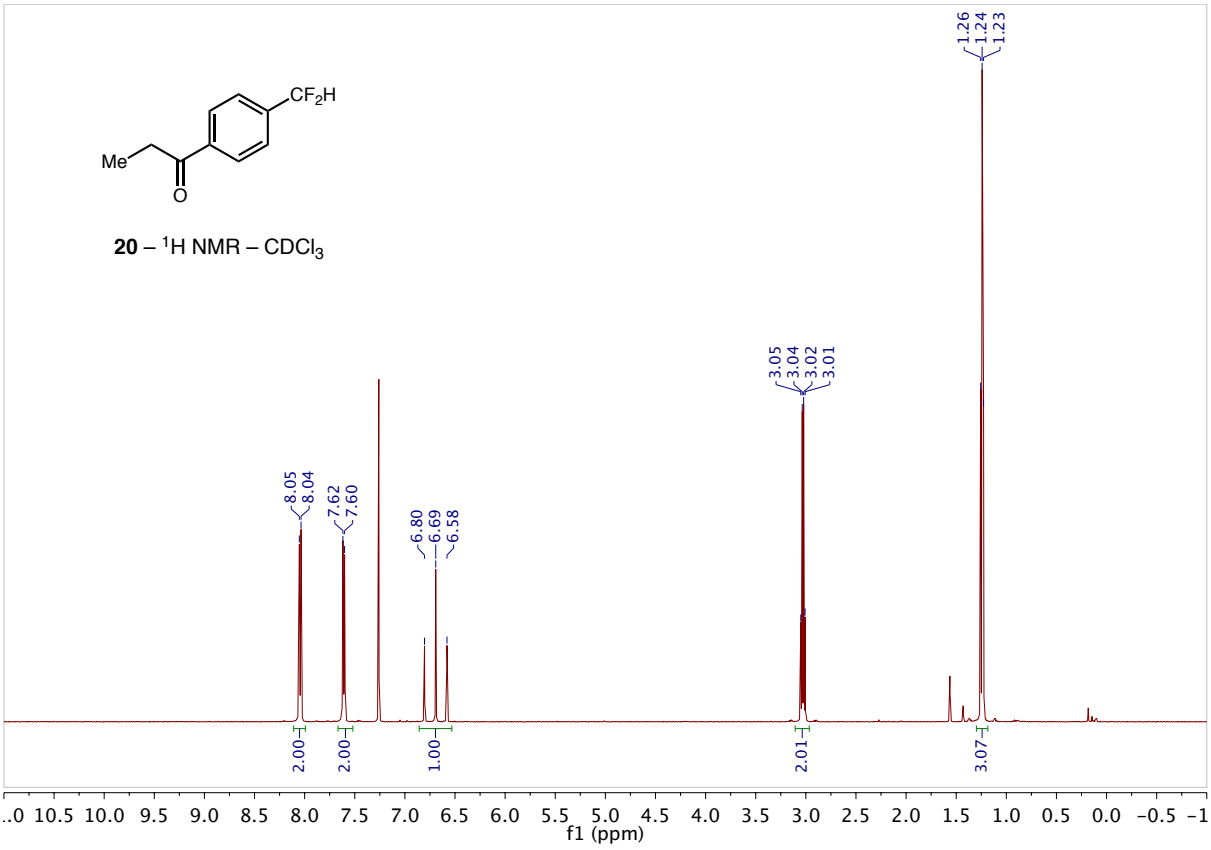
S7 – ^{13}C NMR – $CDCl_3$


CF2H
Me
O
O
19 – 1H NMR – CDCl3
8.14
8.12
7.59
7.58
6.80
6.69
6.58
4.43
4.41
4.40
4.38
1.42
1.41
1.40
2.02
2.00
1.01
2.04
2.97
f1 (ppm)

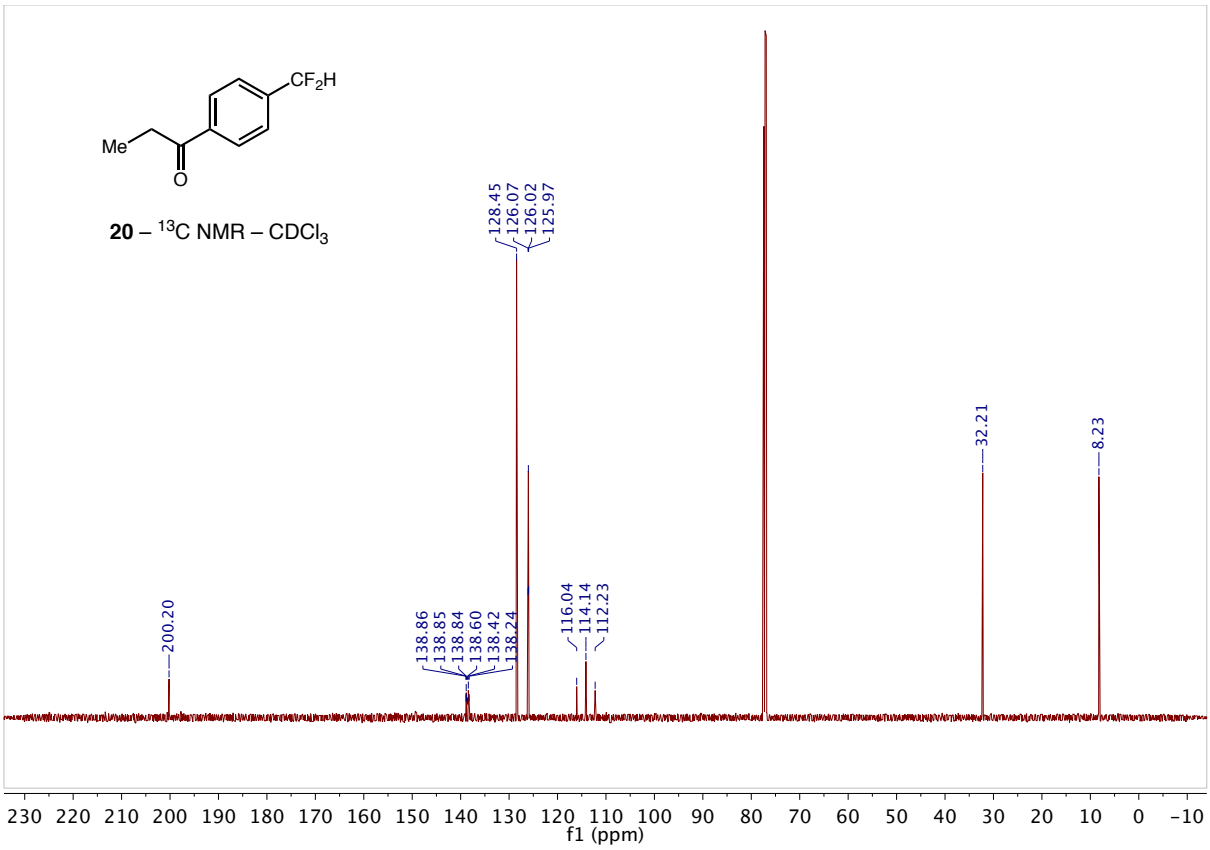

CF2H
Me
O
O
19 – 13C NMR – CDCl3
138.65
138.47
138.30
132.81
130.06
125.79
125.74
125.69
116.08
114.18
112.27
165.92
61.51
14.43
f1 (ppm)

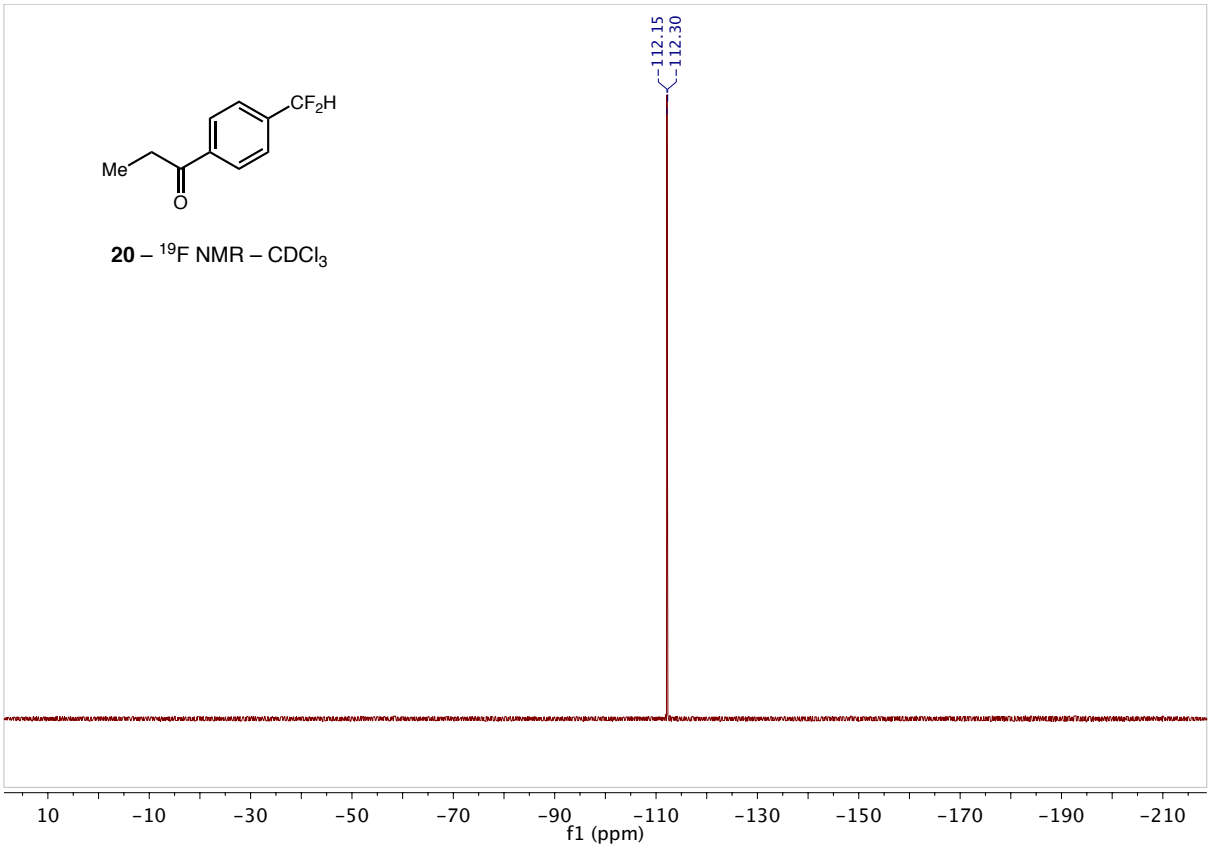


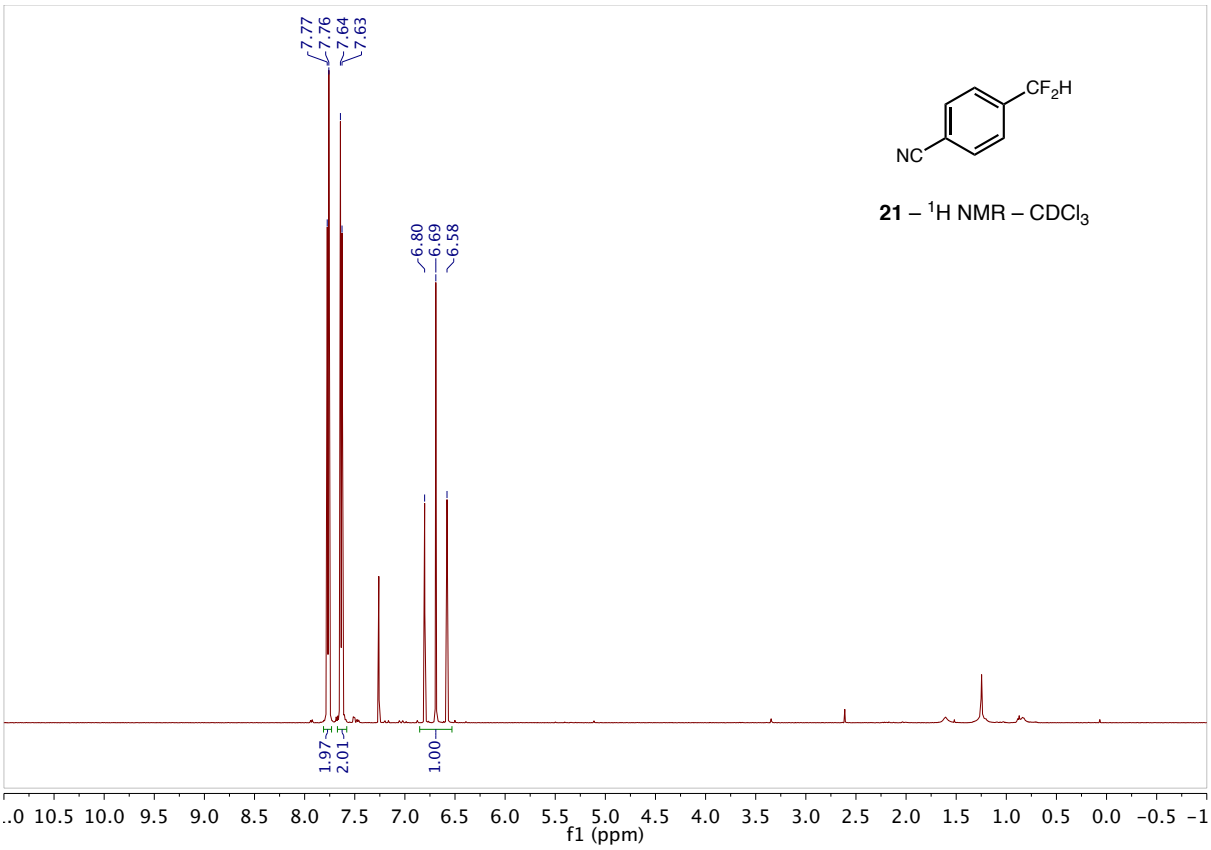
19 – ^{19}F NMR – $CDCl_3$

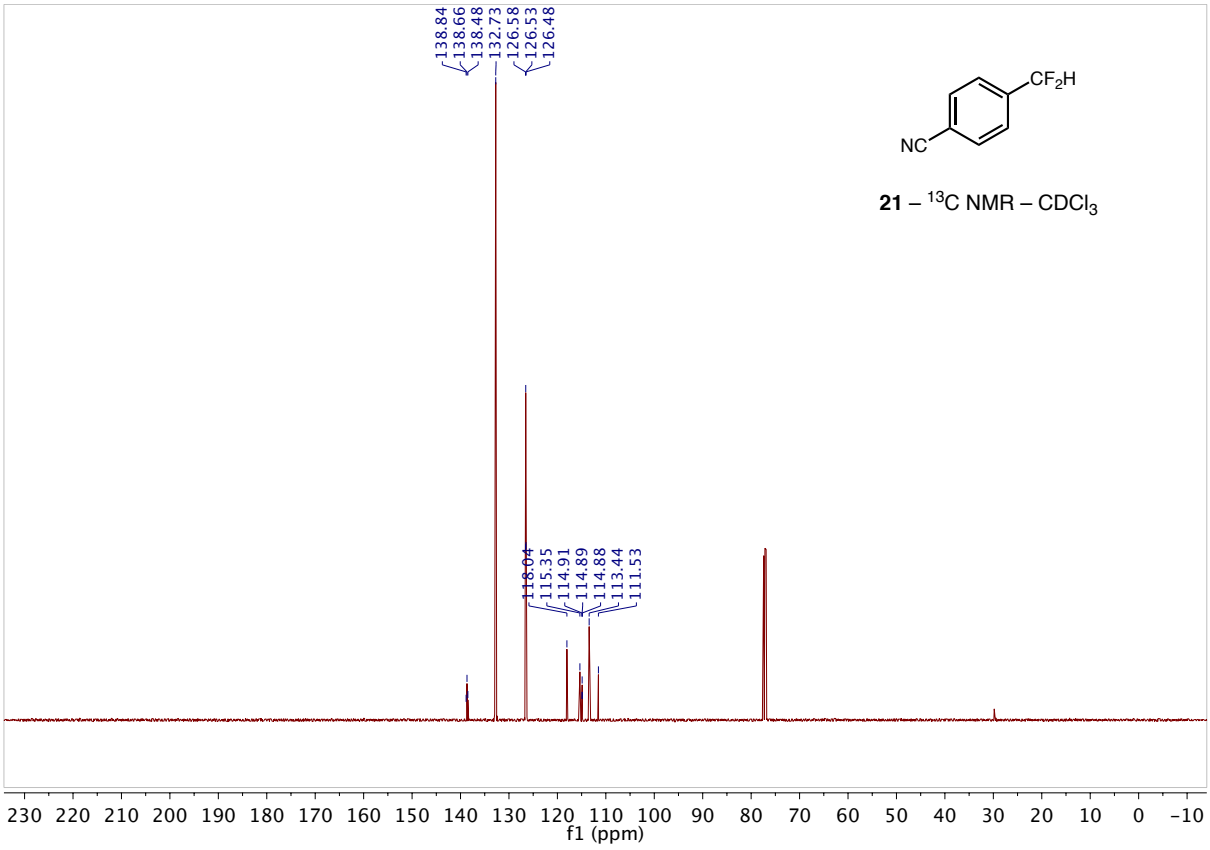


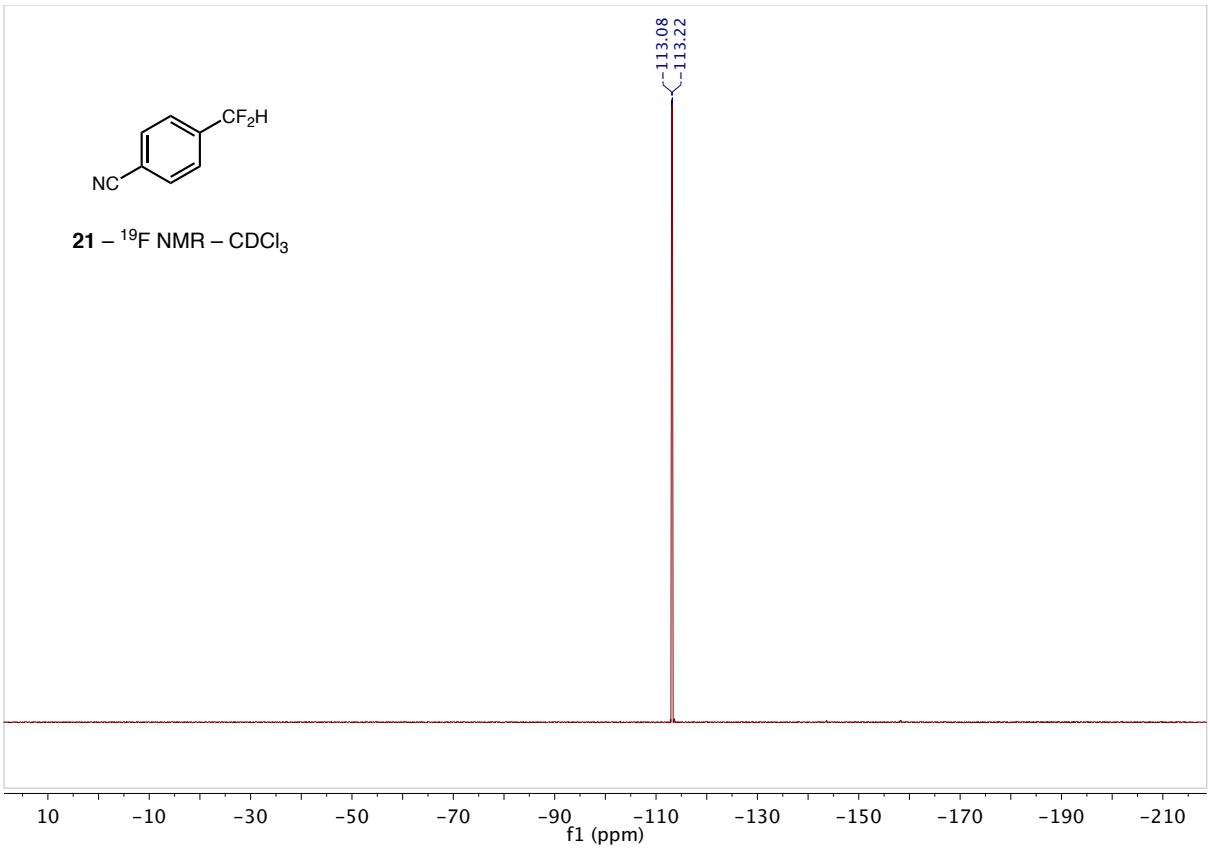
20 – ^{1}H NMR – $CDCl_3$


CF2H
Me
O
20 – 13C NMR – CDCl3
128.45
126.07
126.02
125.97
32.21
8.23
200.20
138.86
138.85
138.84
138.60
138.42
138.24
116.04
114.14
112.23
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

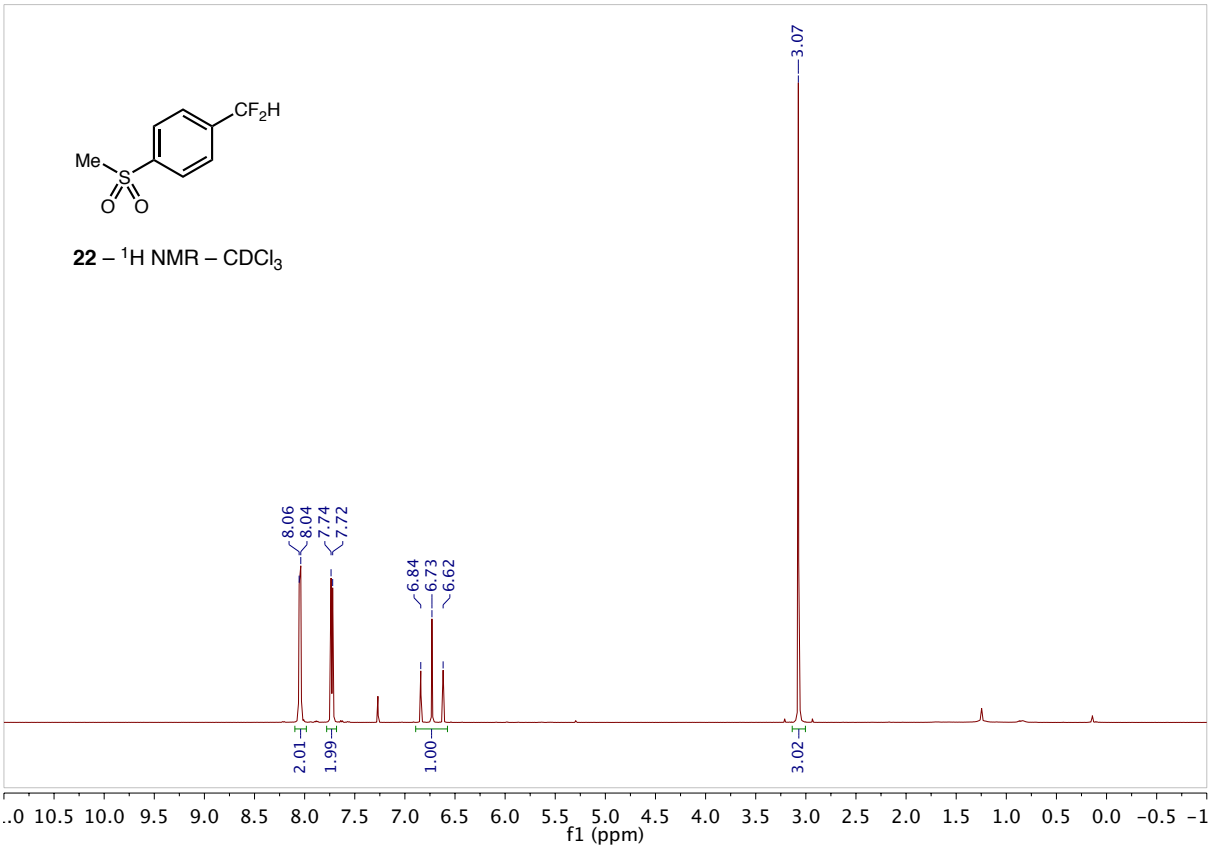

CF2H
Me
O
20 – 19F NMR – CDCl3
112.15
112.30
10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210
f1 (ppm)


7.77
7.76
7.64
7.63
6.80
6.69
6.58
1.97
2.01
1.00
CF2H
NC
21 – 1H NMR – CDCl3
f1 (ppm)

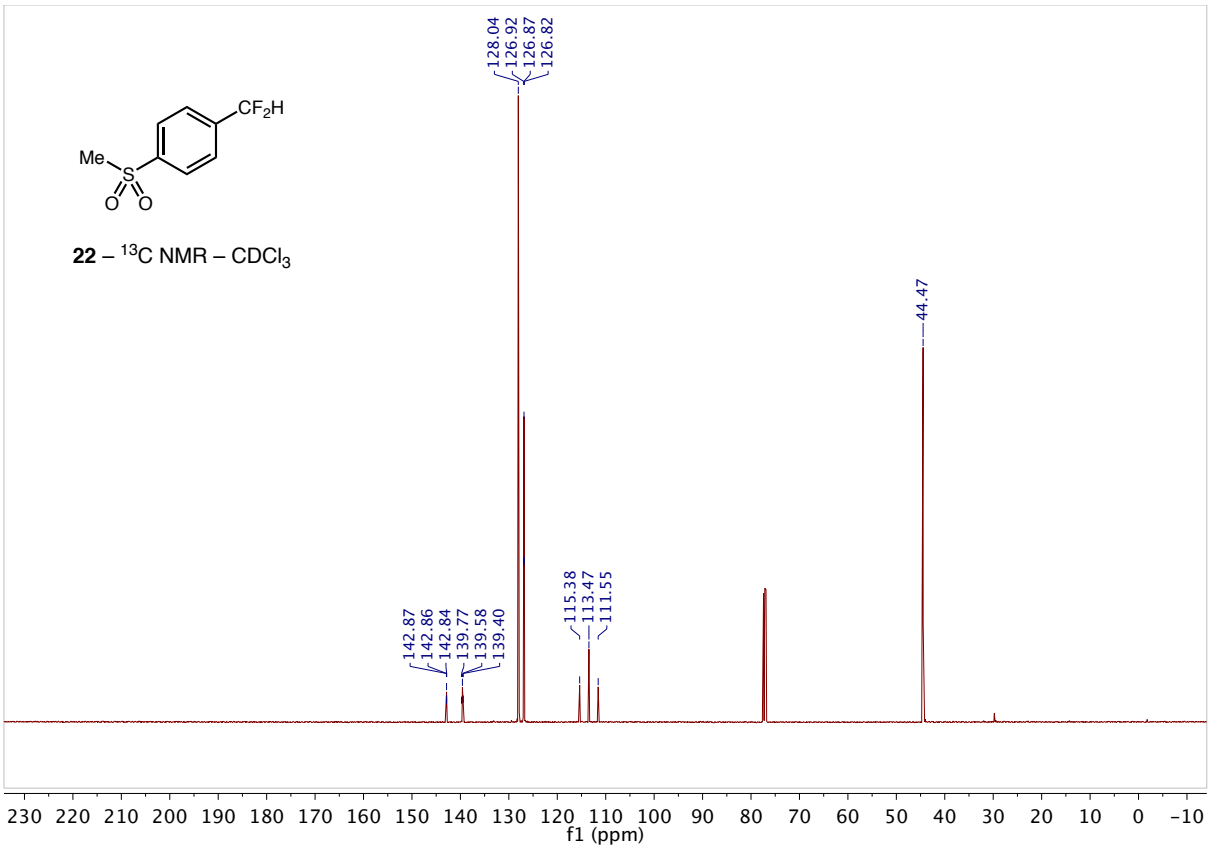

138.84
138.66
138.48
132.73
126.58
126.53
126.48
118.04
115.35
114.91
114.89
114.88
113.44
111.53
CF2H
NC
21 – 13C NMR – CDCl3
f1 (ppm)

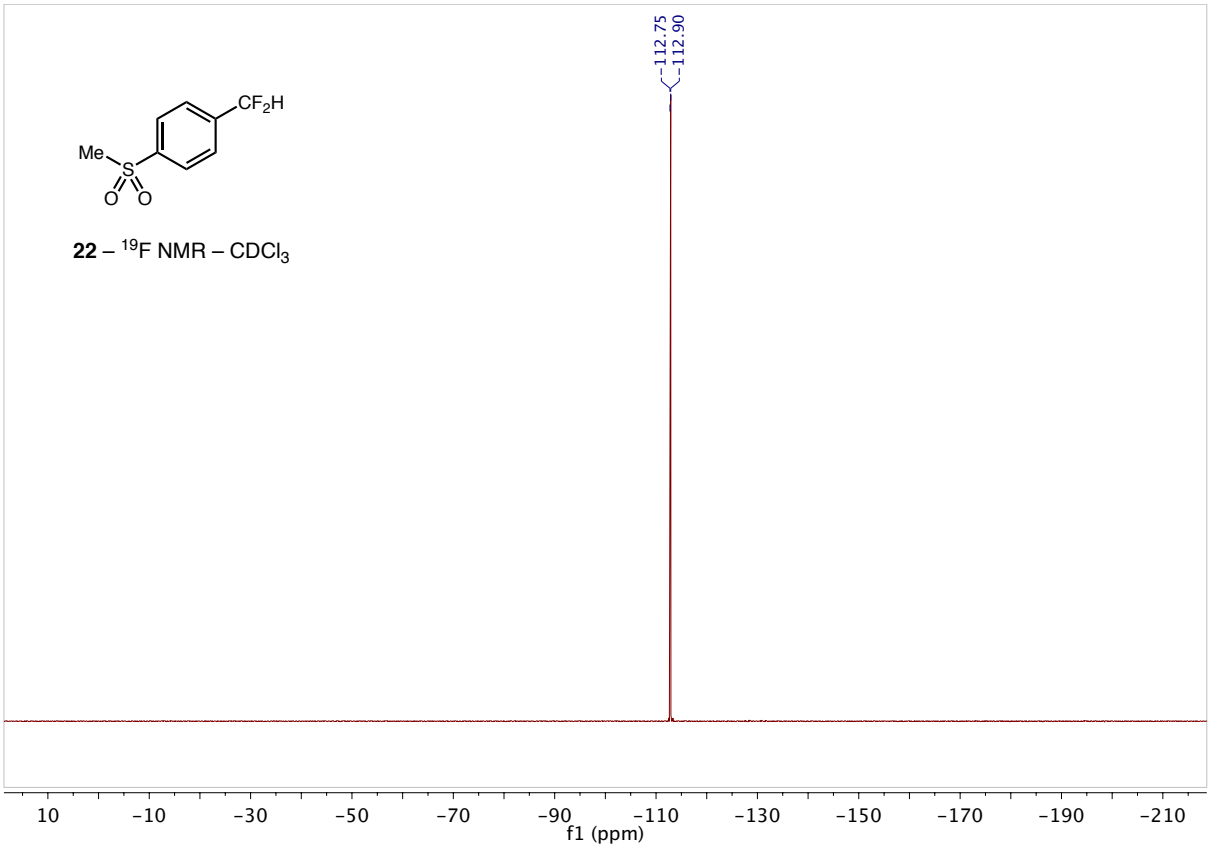


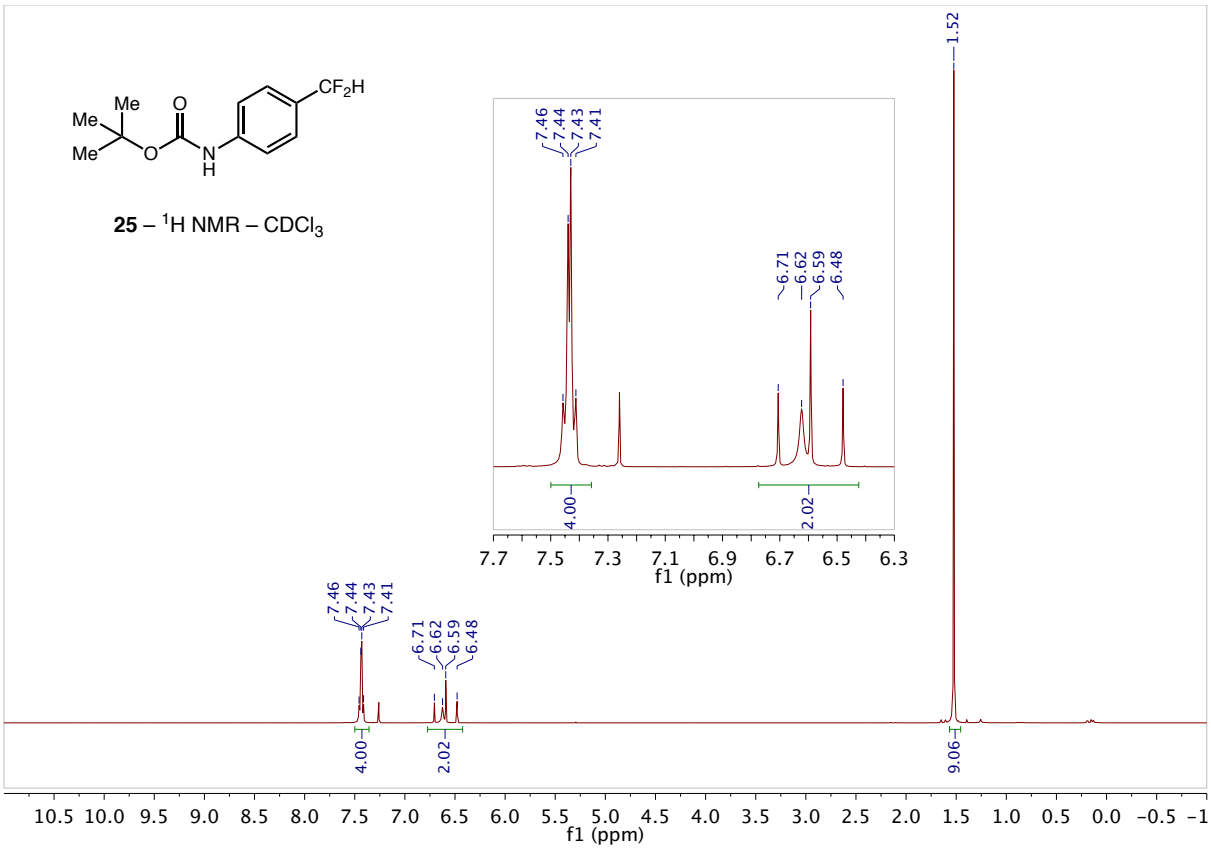
21 – ^{19}F NMR – $CDCl_3$

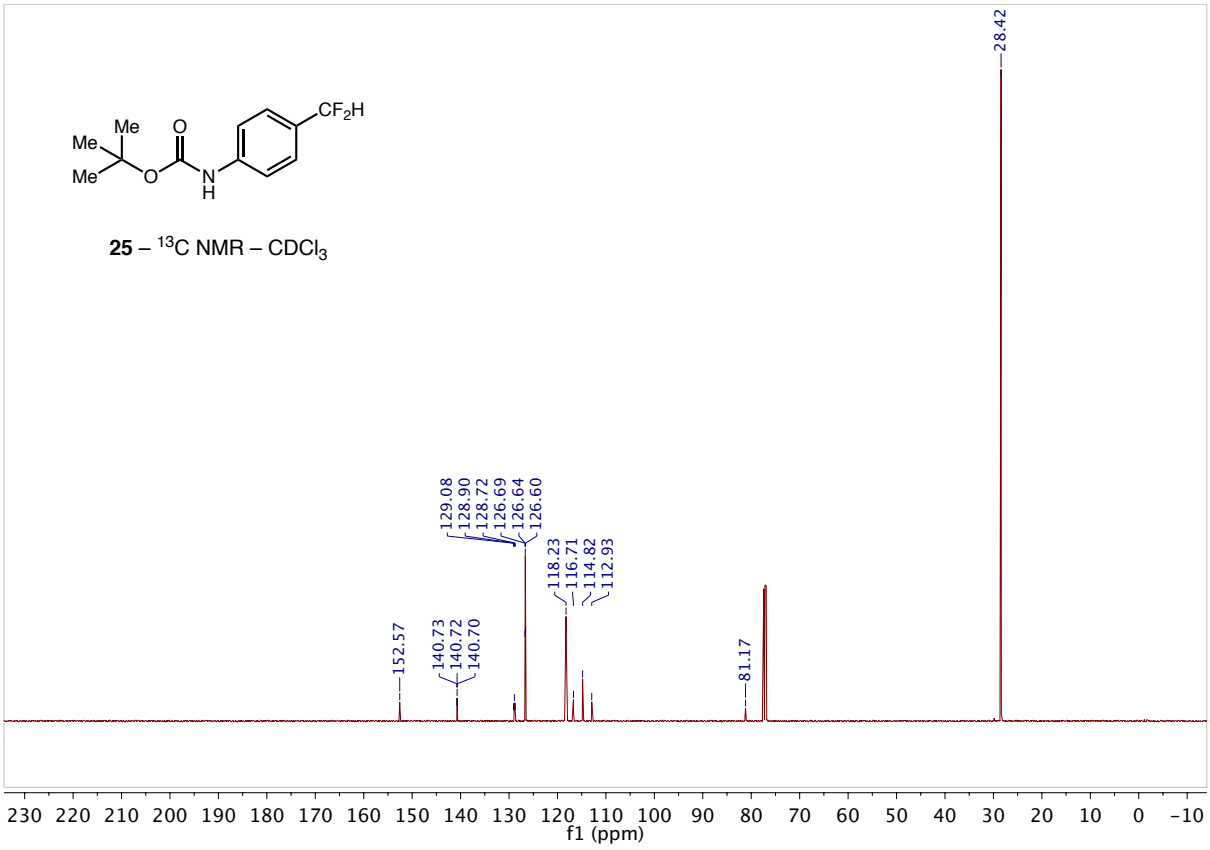


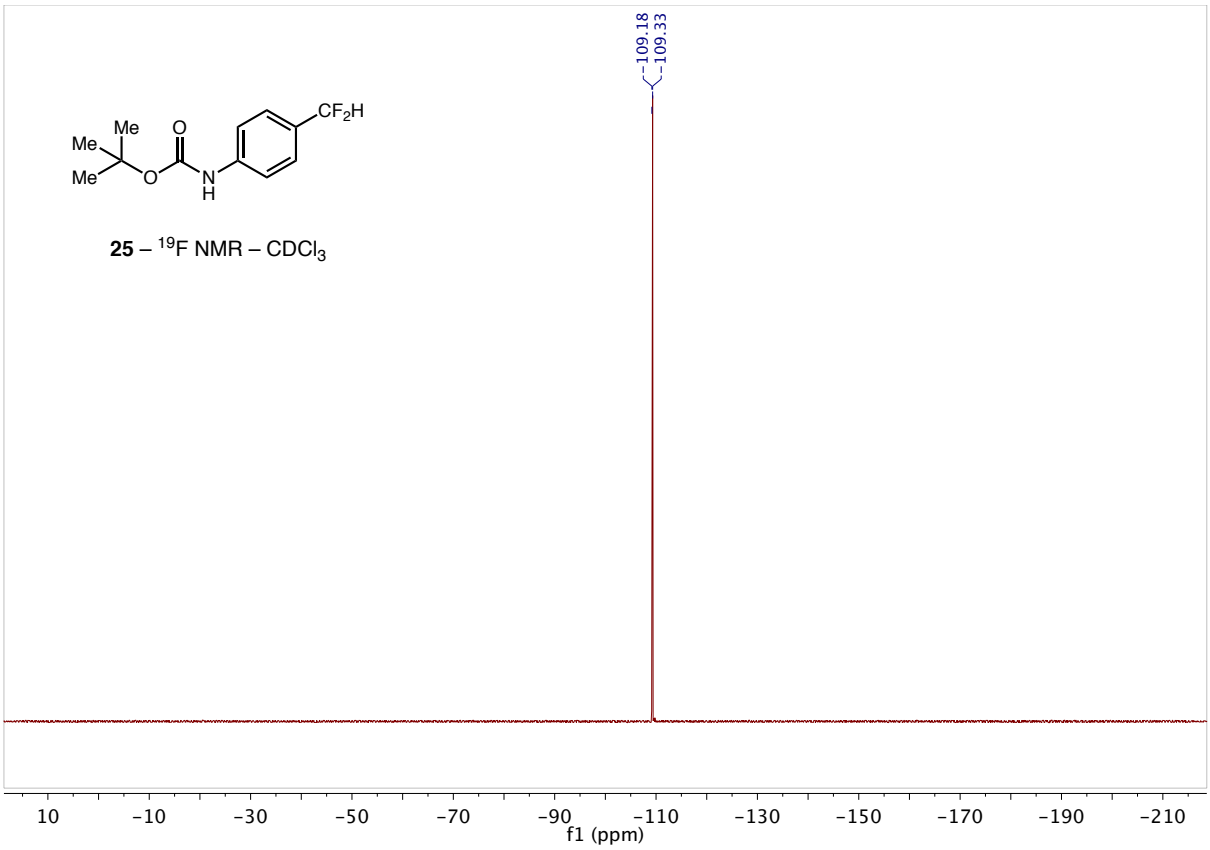
22 – ^{1}H NMR – $CDCl_3$


128.04
126.92
126.87
126.82
CF2H
Me
S
O
O
22 – 13C NMR – CDCl3
44.47
142.87
142.86
142.84
139.77
139.58
139.40
115.38
113.47
111.55
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

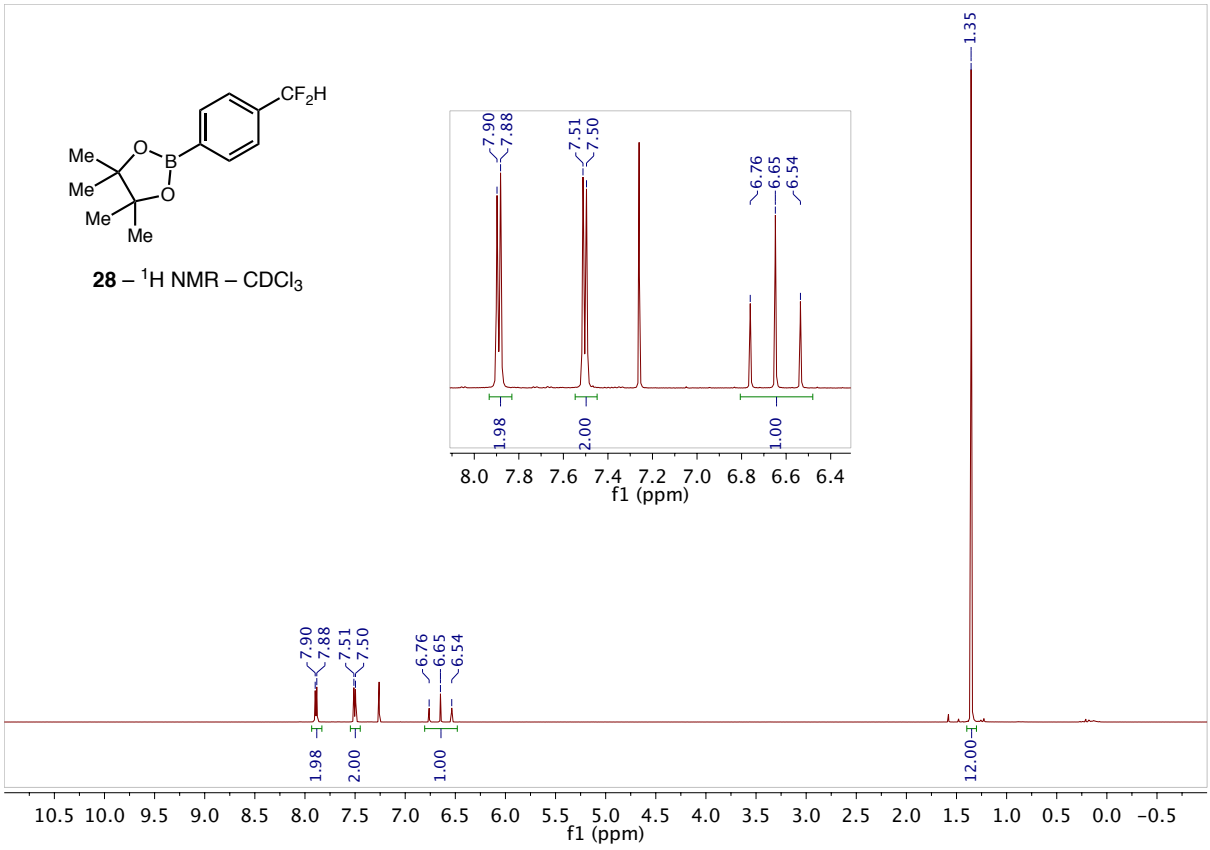

-112.75
-112.90
CF2H
Me
S
O
O
22 – 19F NMR – CDCl3
10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210
f1 (ppm)


Me
Me
Me
O
O
N
H
CF2H
25 – 1H NMR – CDCl3
7.46
7.44
7.43
7.41
6.71
6.62
6.59
6.48
1.52
4.00
2.02
9.06
f1 (ppm)

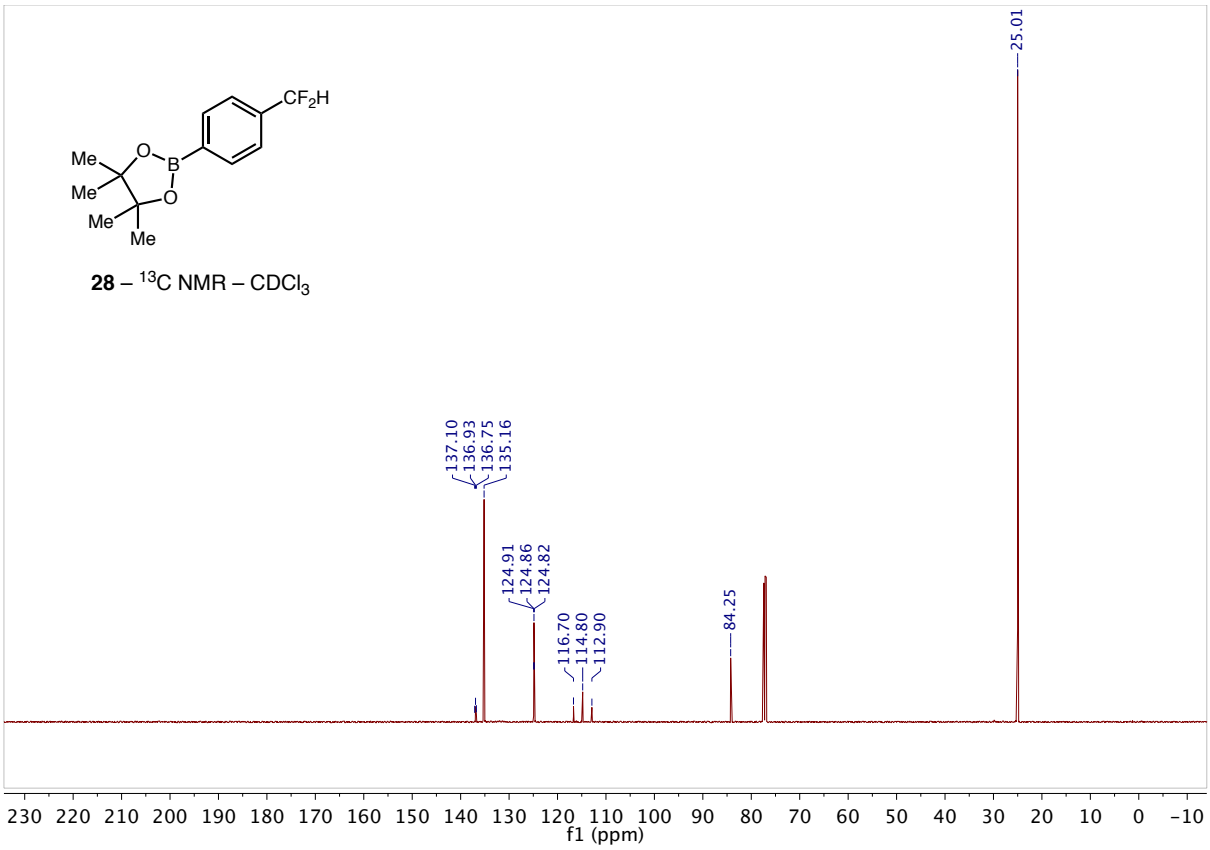

Me
Me
Me
O
O
N
H
CF2H
25 – 13C NMR – CDCl3
28.42
129.08
128.90
128.72
126.69
126.64
126.60
118.23
116.71
114.82
112.93
152.57
140.73
140.72
140.70
81.17
f1 (ppm)



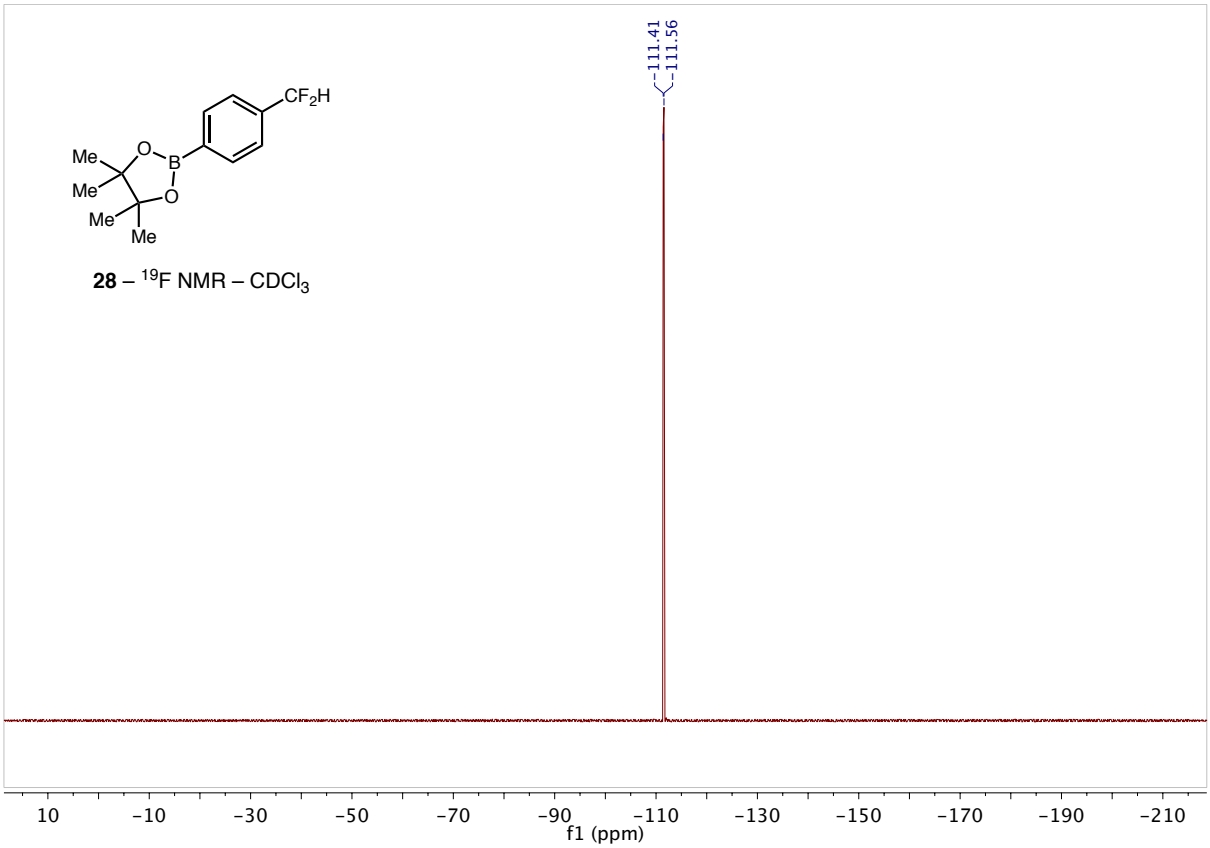
25 – ^{19}F NMR – $CDCl_3$



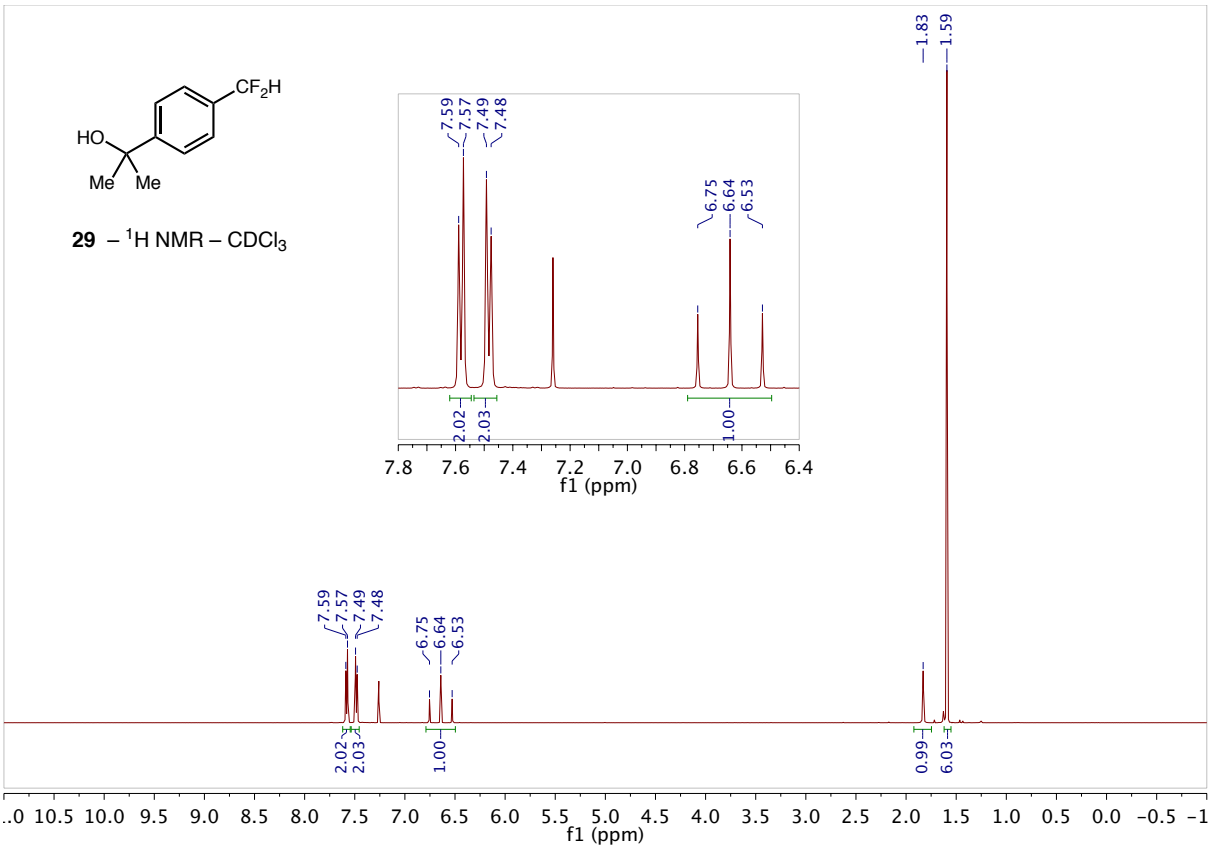
28 – ^{1}H NMR – $CDCl_3$

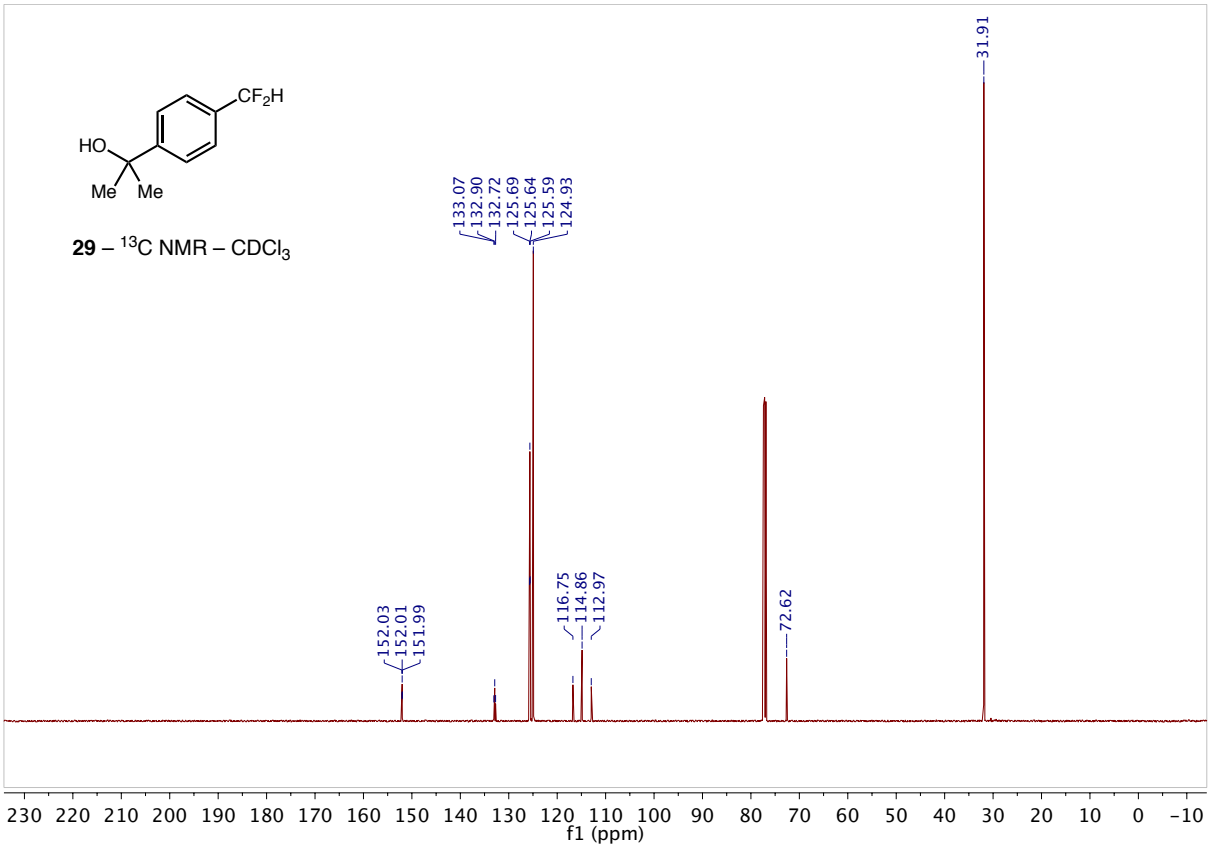


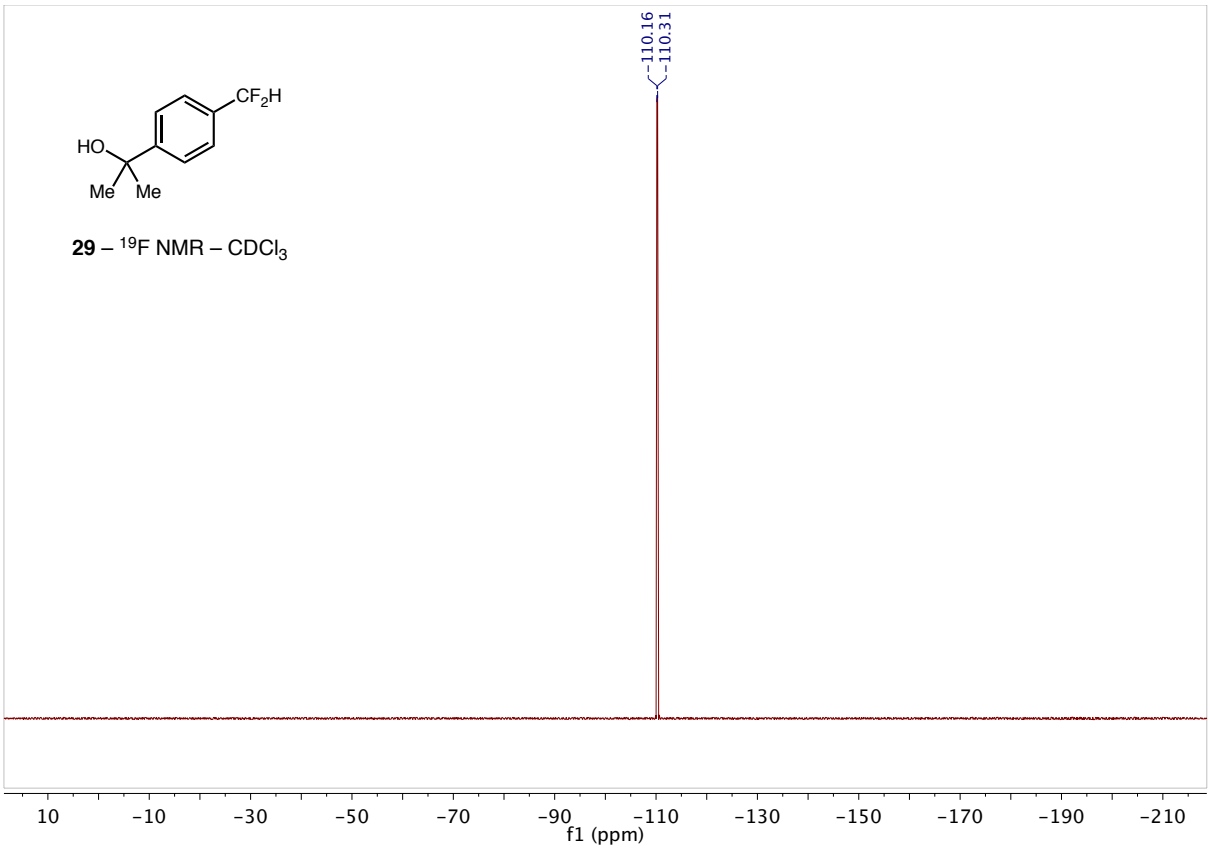
28 – ^{13}C NMR – $CDCl_3$



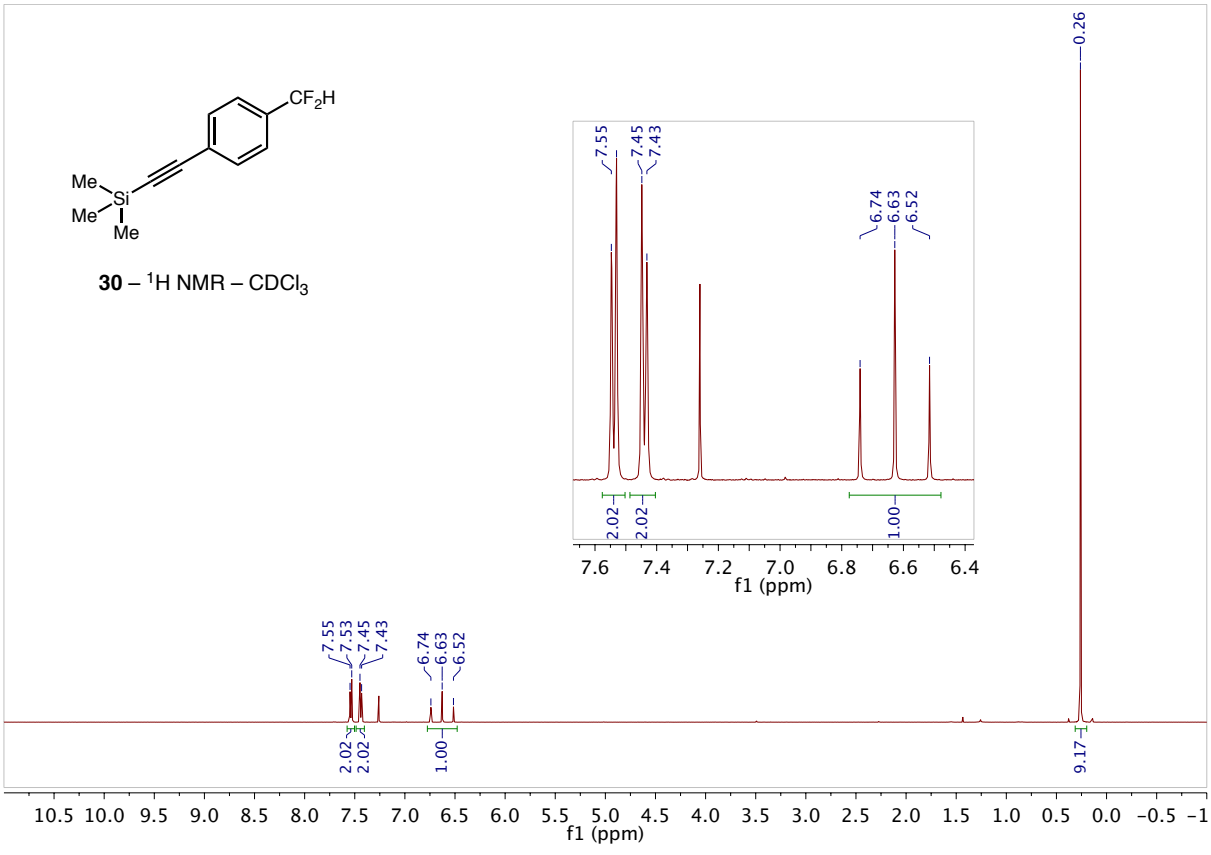
28 – ^{19}F NMR – $CDCl_3$


CF2H
HO
Me Me
29 – 1H NMR – CDCl3
7.59
7.57
7.49
7.48
6.75
6.64
6.53
1.83
1.59
2.02
2.03
1.00
0.99
6.03
f1 (ppm)

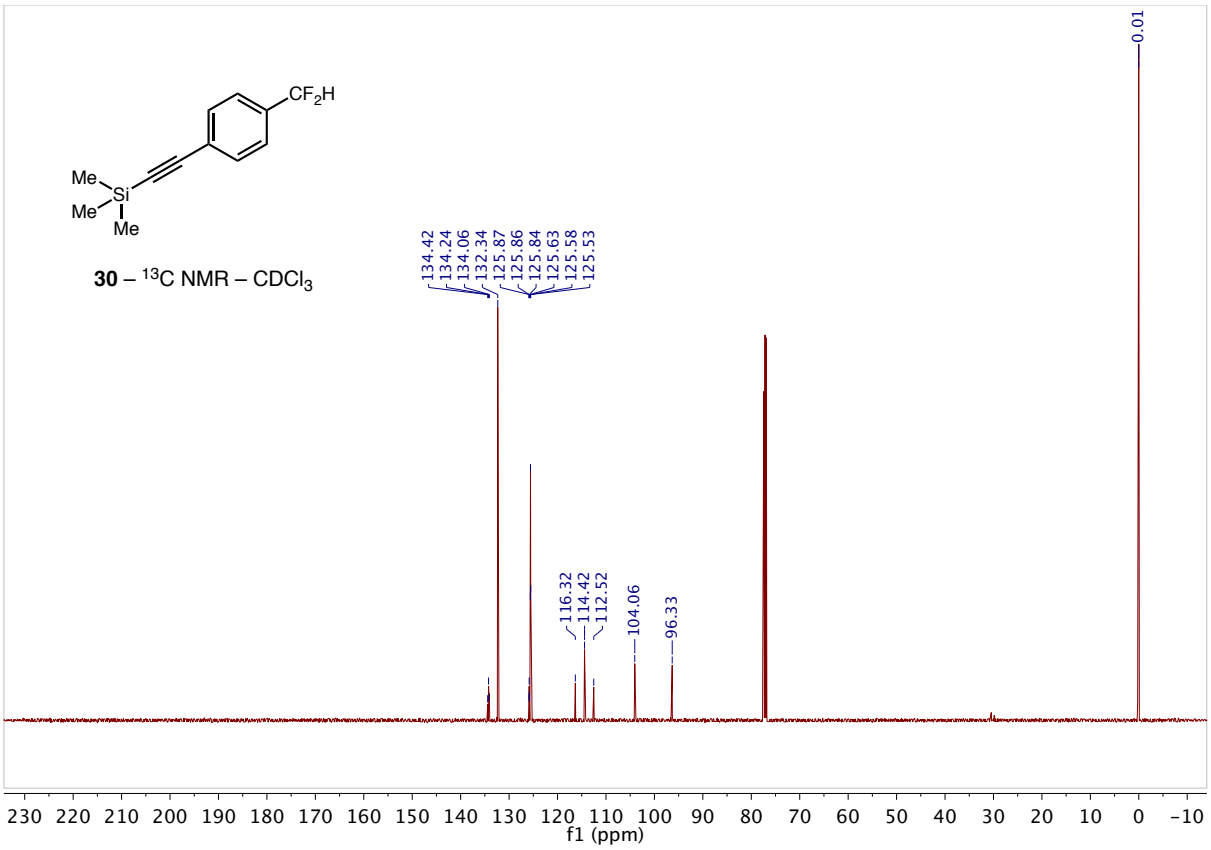

CF2H
HO
Me Me
29 – 13C NMR – CDCl3
133.07
132.90
132.72
125.69
125.64
125.59
124.93
152.03
152.01
151.99
116.75
114.86
112.97
72.62
31.91
f1 (ppm)



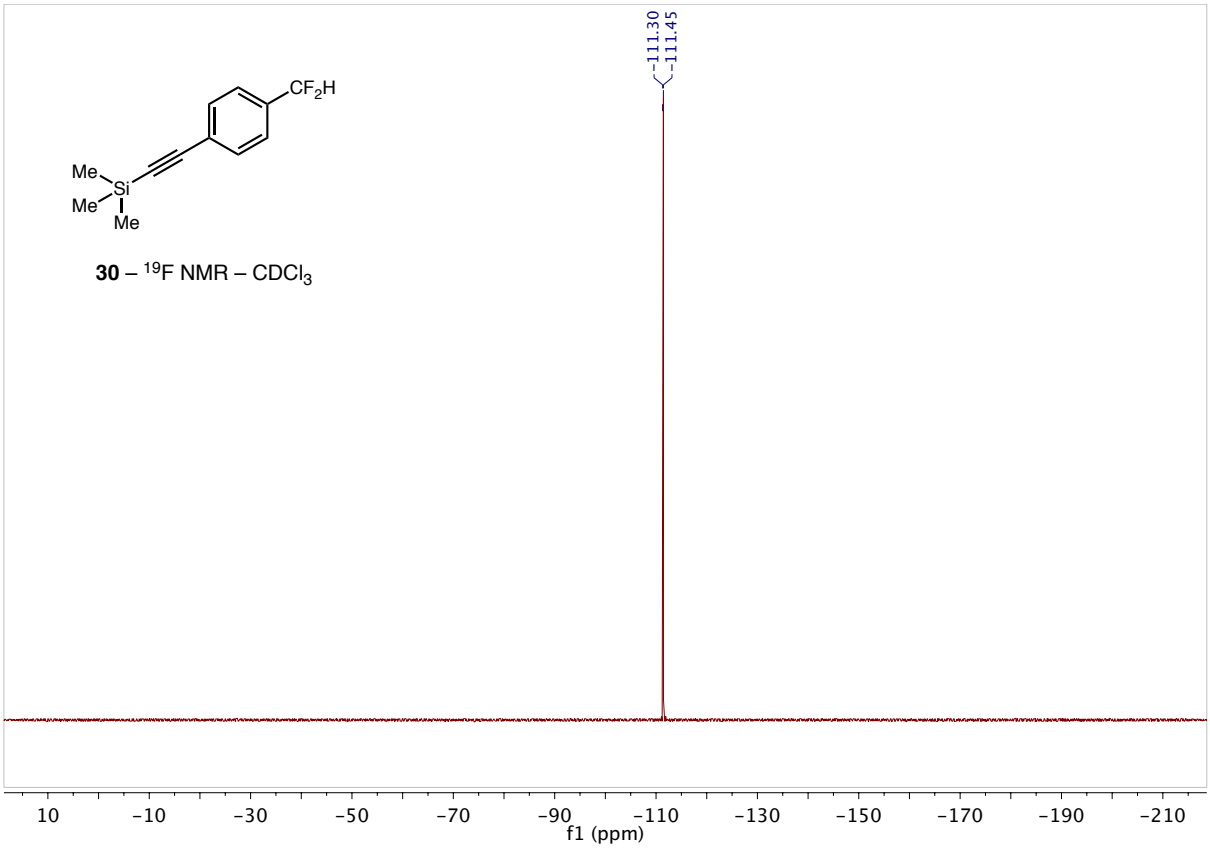
29 – ^{19}F NMR – $CDCl_3$



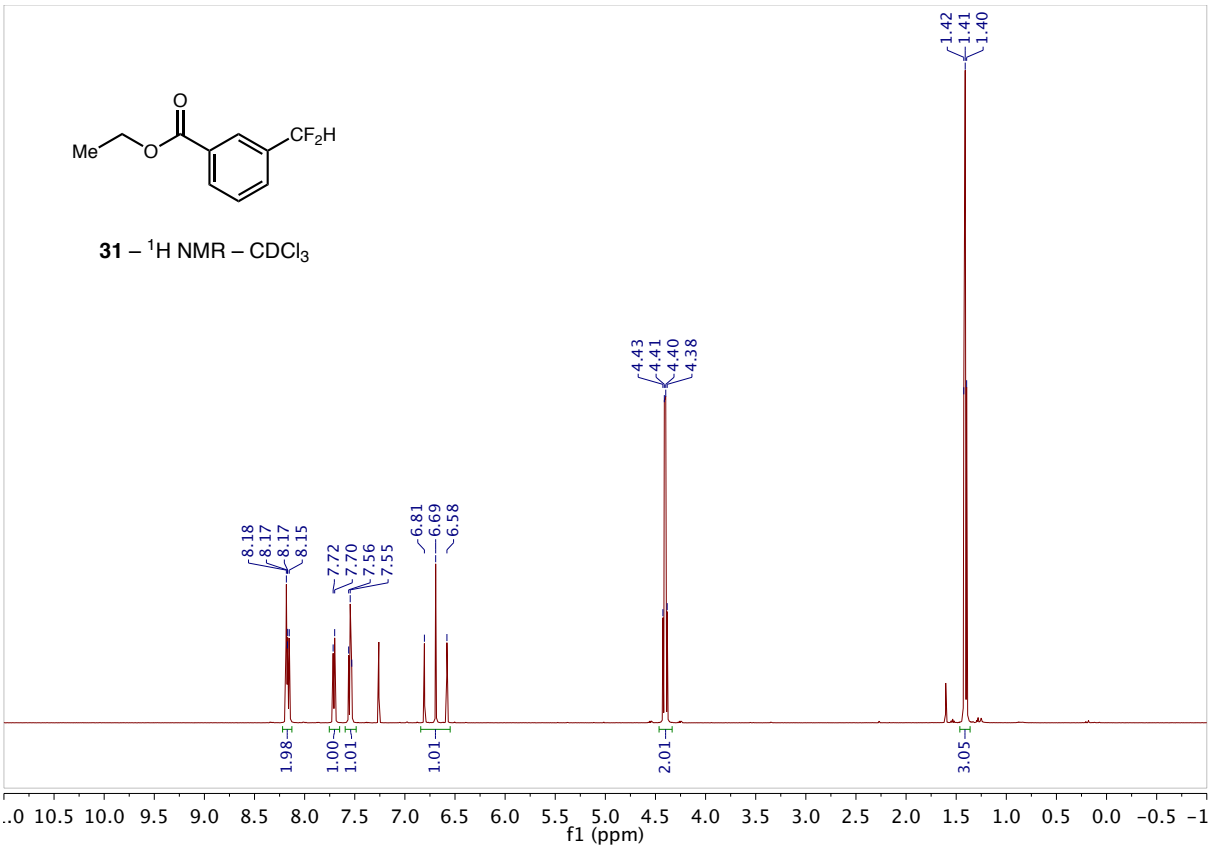
30 – ^{1}H NMR – $CDCl_3$

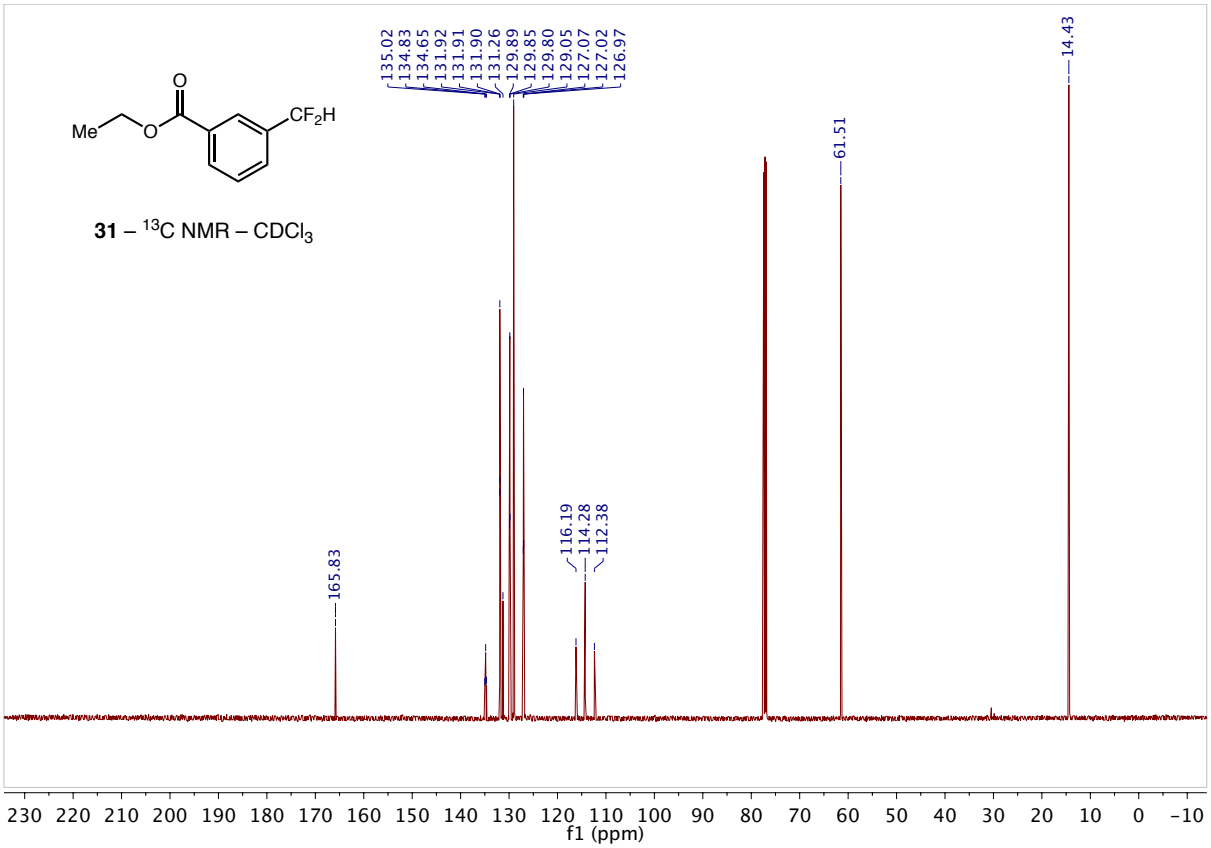


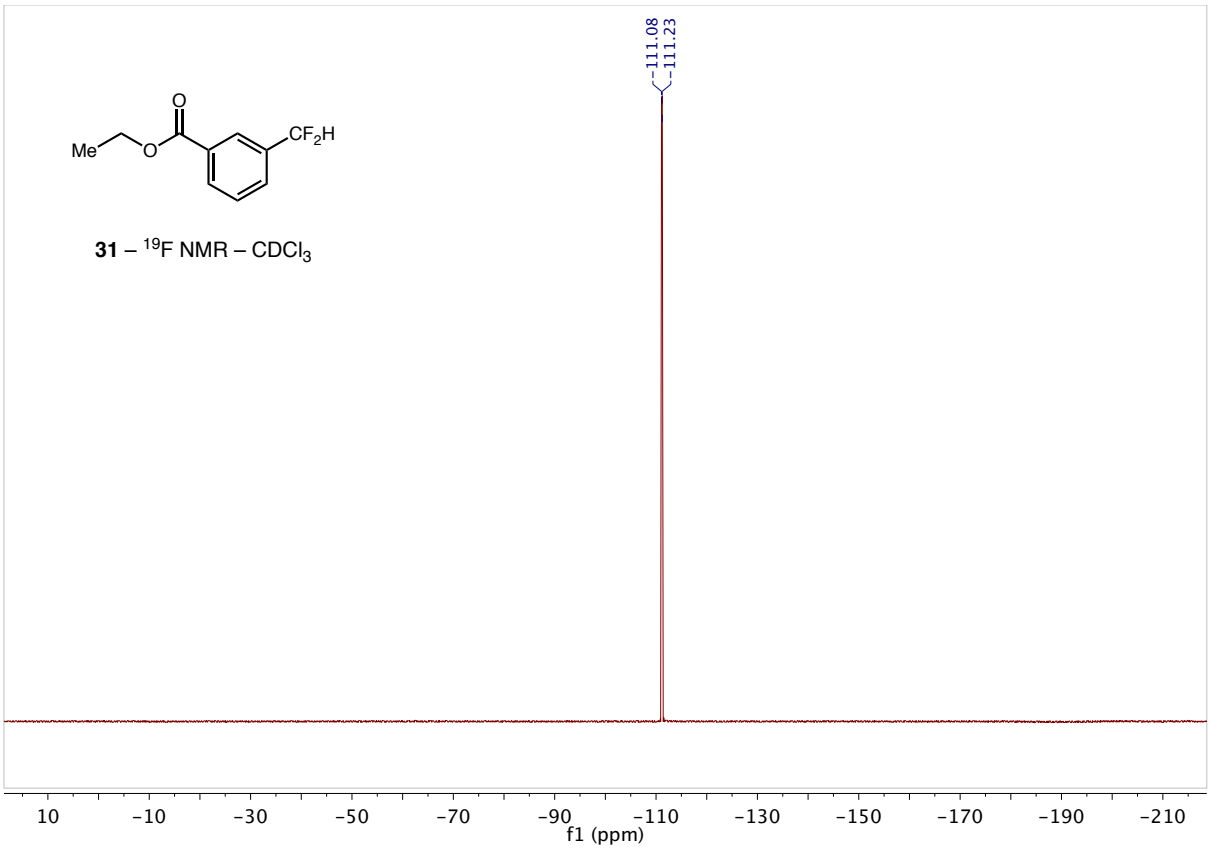
30 – ^{13}C NMR – $CDCl_3$



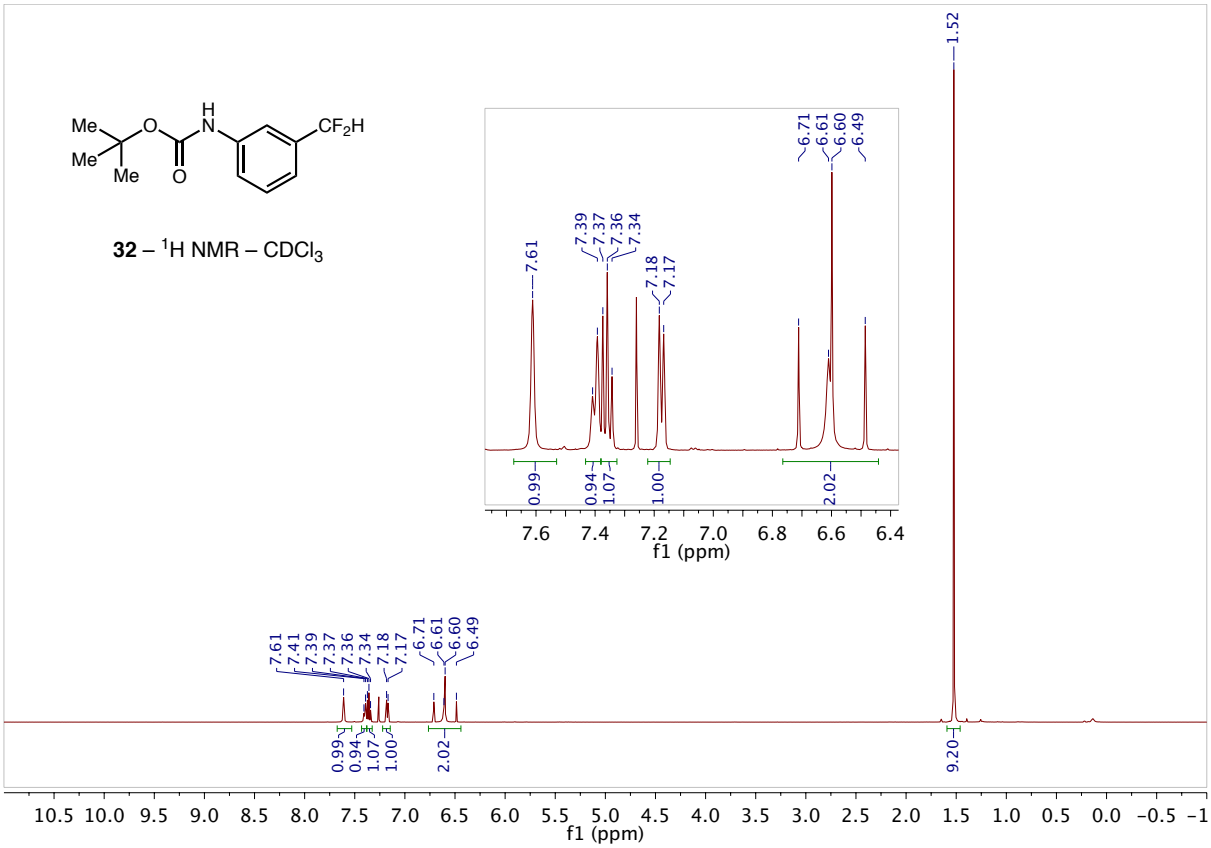
30 – ^{19}F NMR – $CDCl_3$


Me
O
O
CF2H
31 – 1H NMR – CDCl3
1.42
1.41
1.40
4.43
4.41
4.40
4.38
8.18
8.17
8.17
8.15
7.72
7.70
7.56
7.55
6.81
6.69
6.58
1.98
1.00
1.01
1.01
2.01
3.05
f1 (ppm)

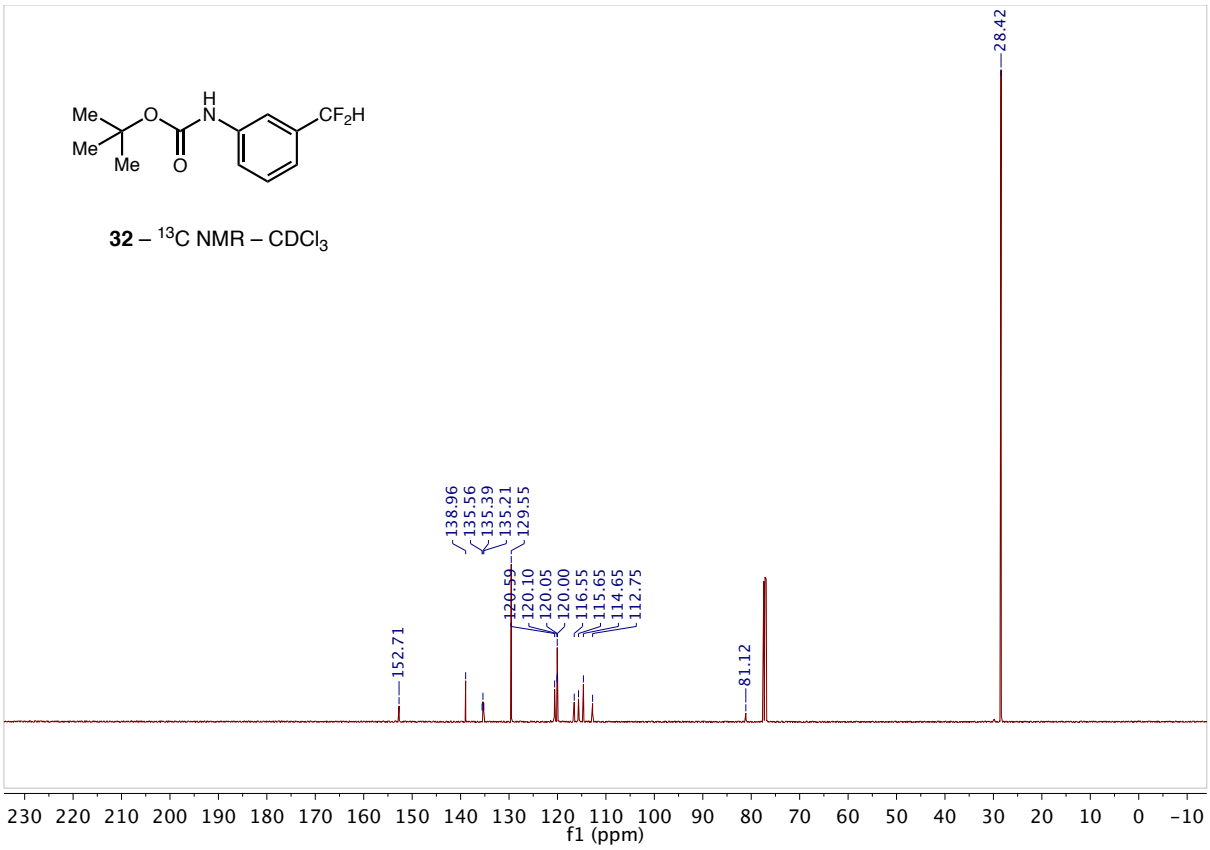

Me
O
O
CF2H
31 – 13C NMR – CDCl3
135.02
134.83
134.65
131.92
131.91
131.90
131.26
129.89
129.85
129.80
129.05
127.07
127.02
126.97
14.43
61.51
116.19
114.28
112.38
165.83
f1 (ppm)



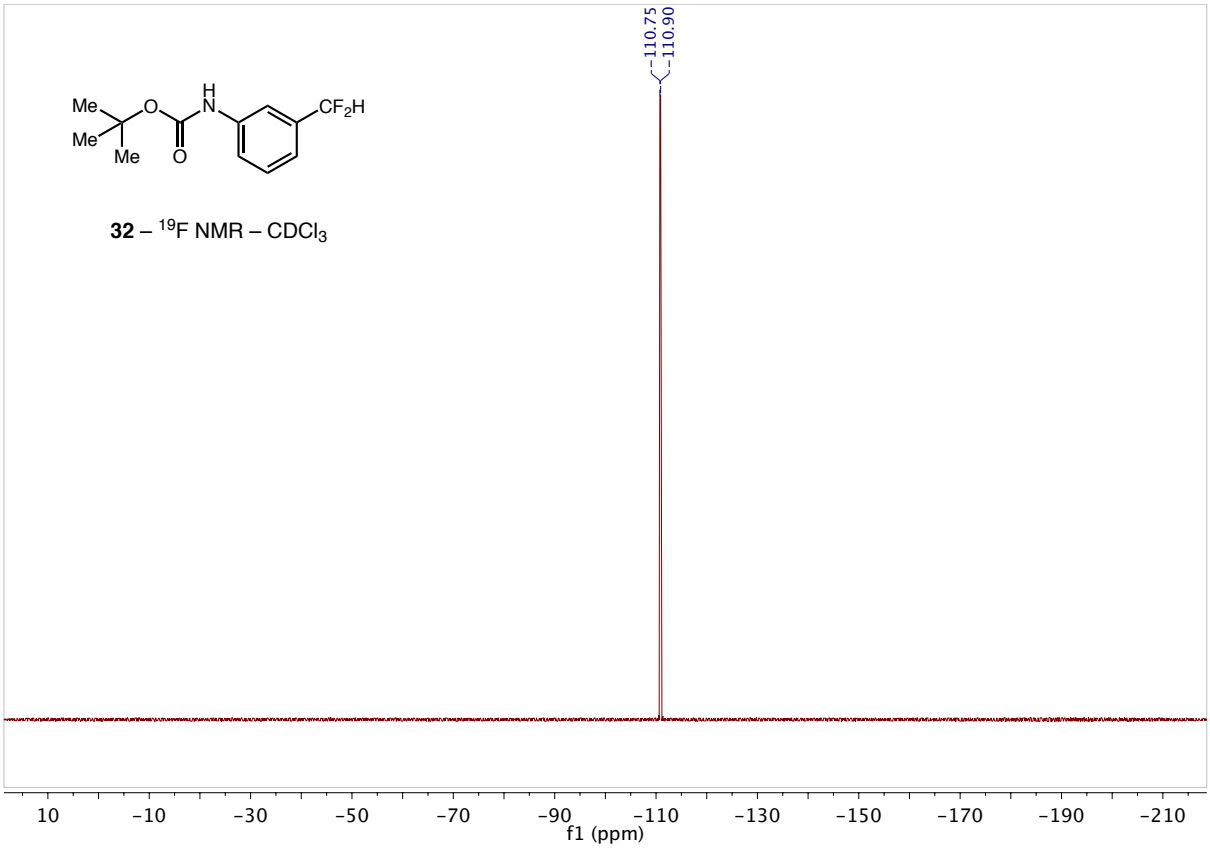
31 – ^{19}F NMR – $CDCl_3$



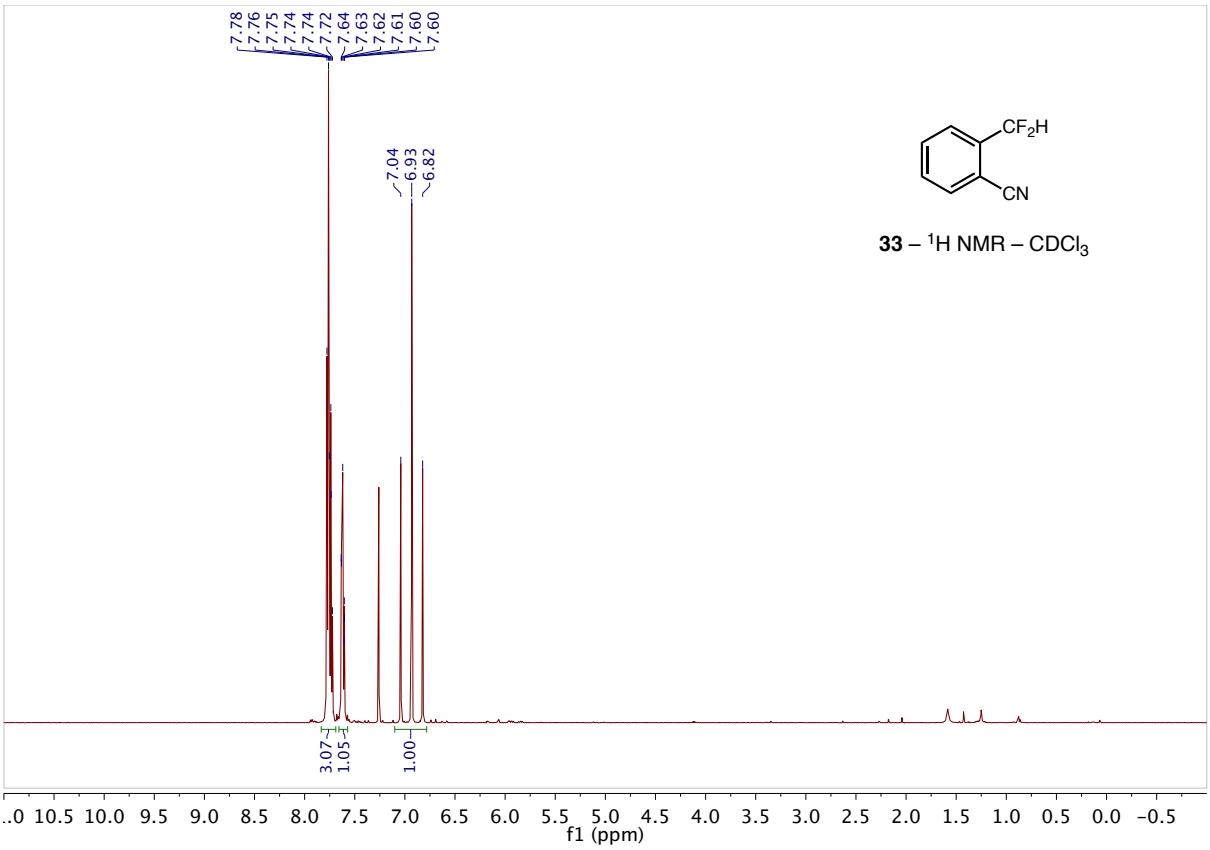
32 – ^{1}H NMR – $CDCl_3$



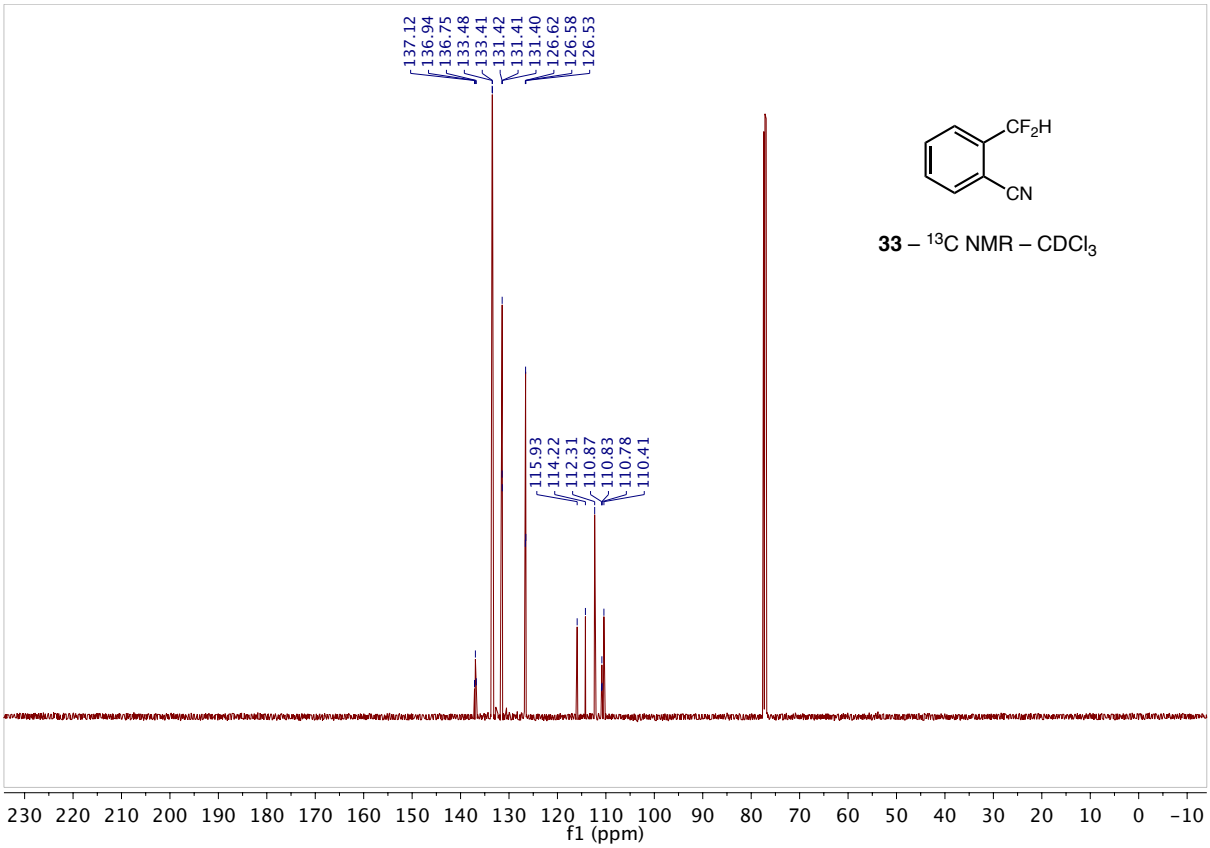
32 – ^{13}C NMR – $CDCl_3$



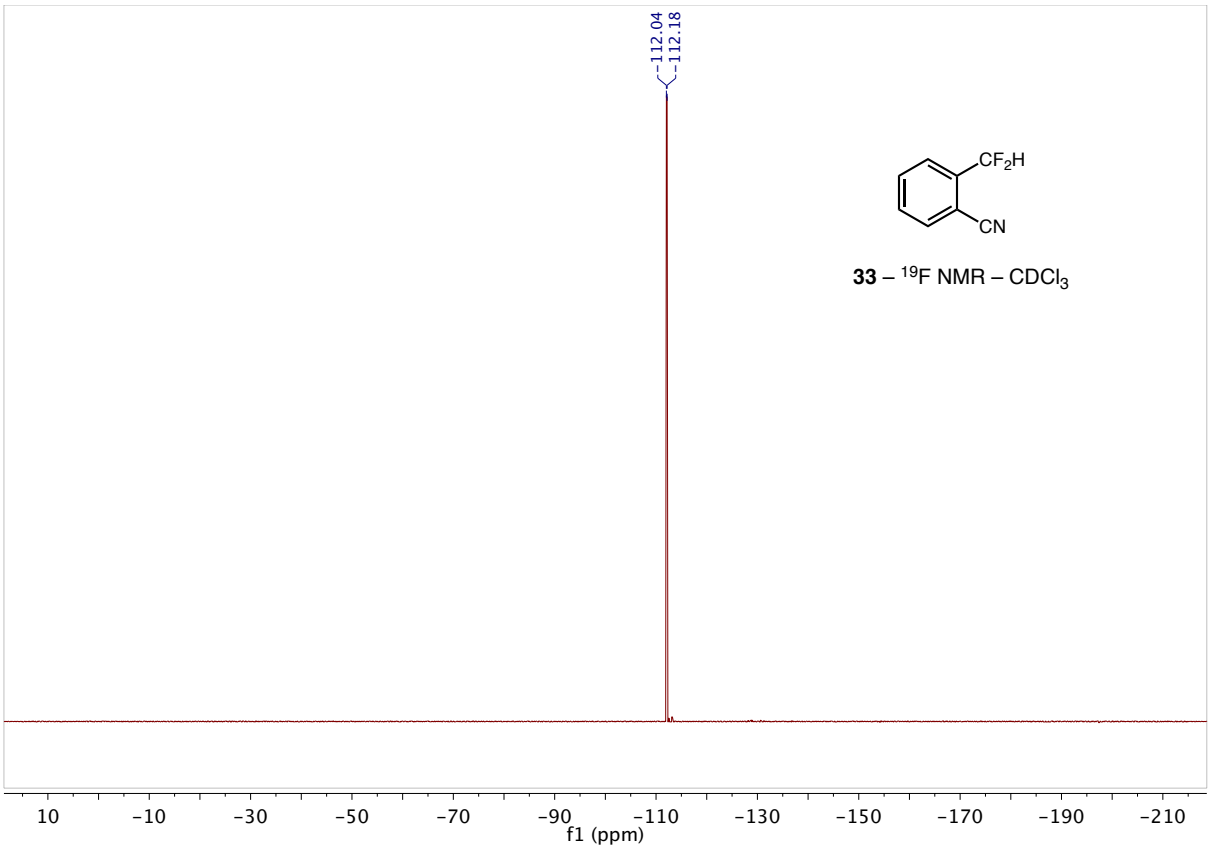
32 – ^{19}F NMR – $CDCl_3$



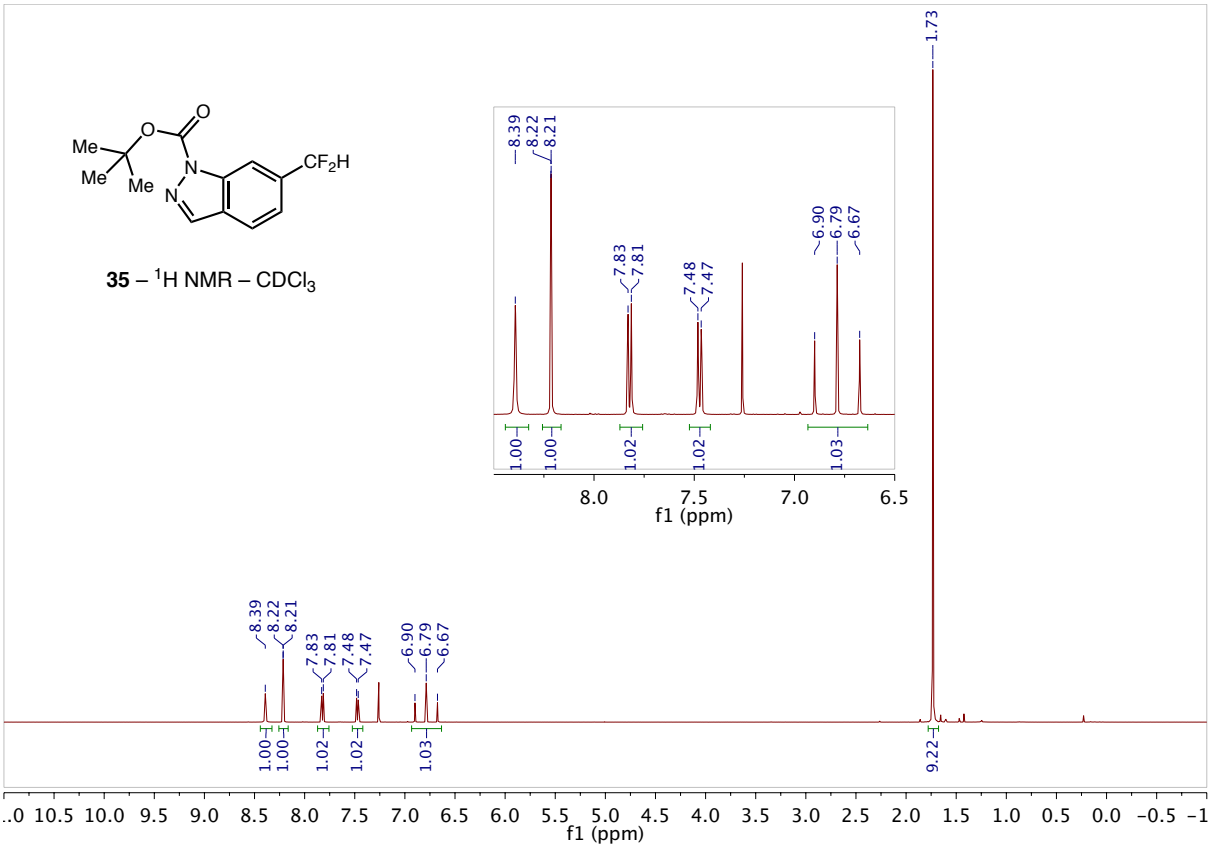
33 – ^{1}H NMR – $CDCl_3$



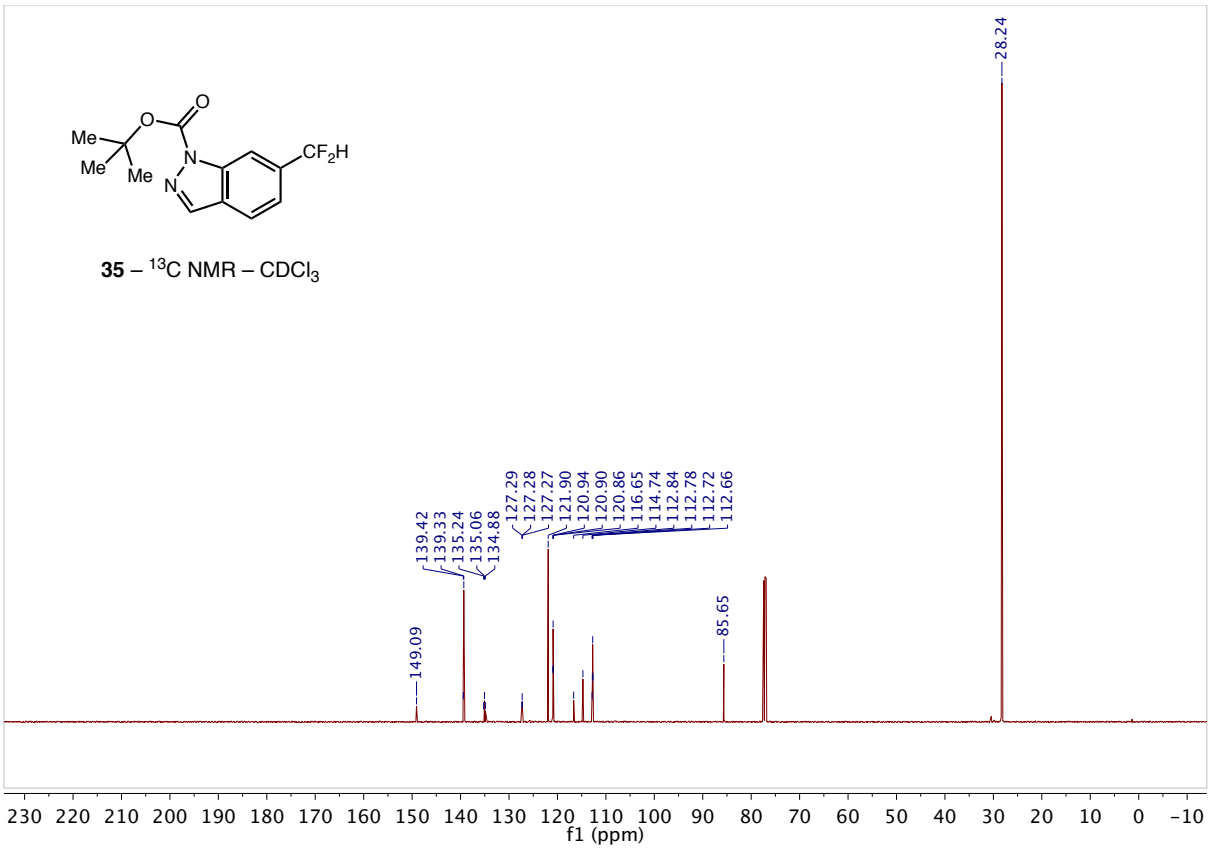
33 – ^{13}C NMR – $CDCl_3$



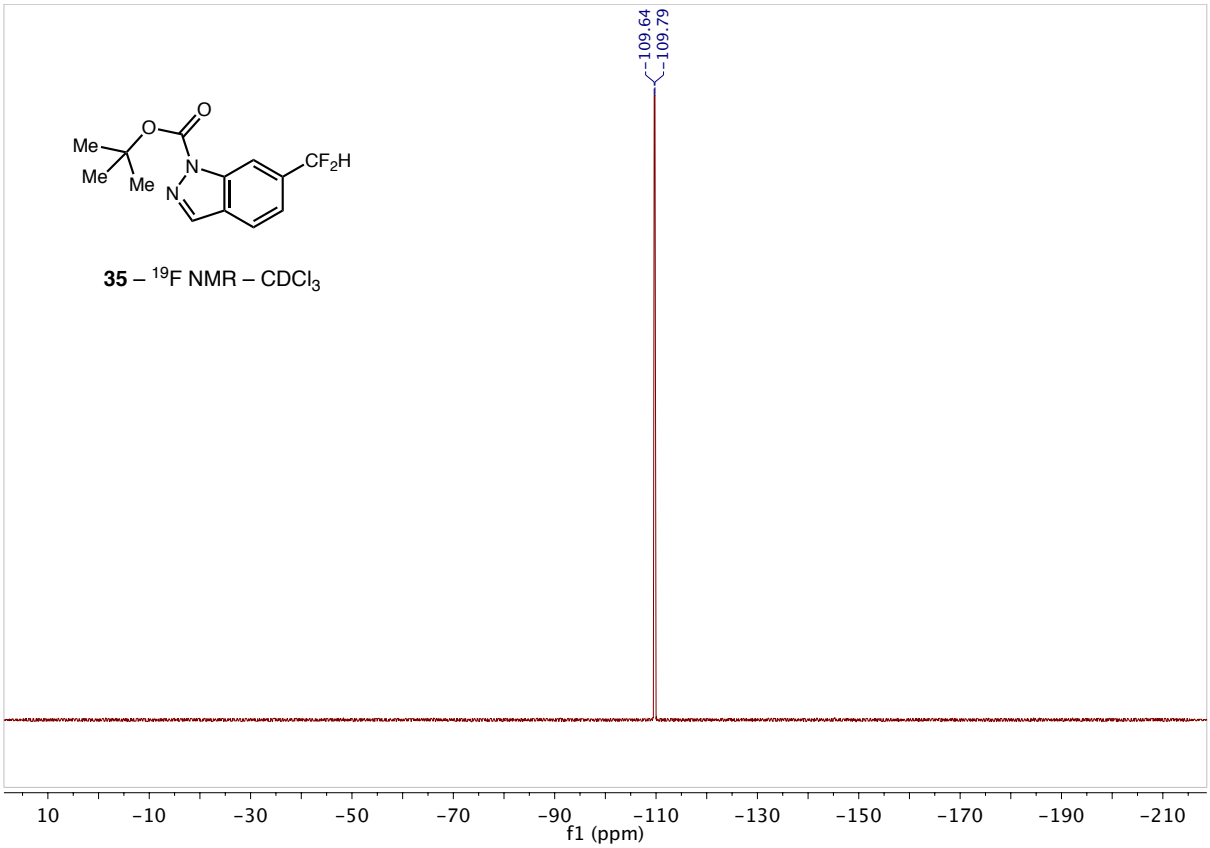
33 – ^{19}F NMR – $CDCl_3$



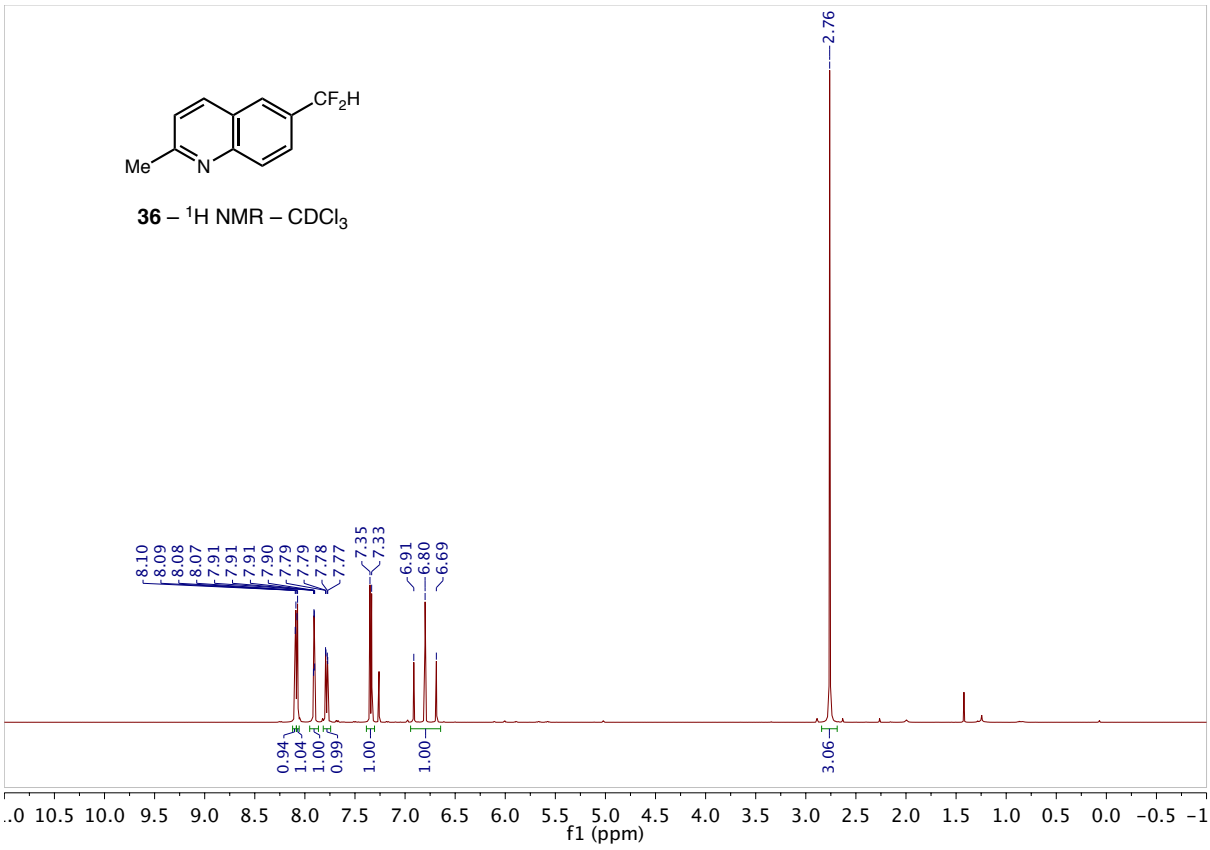
35 – ^{1}H NMR – $CDCl_3$

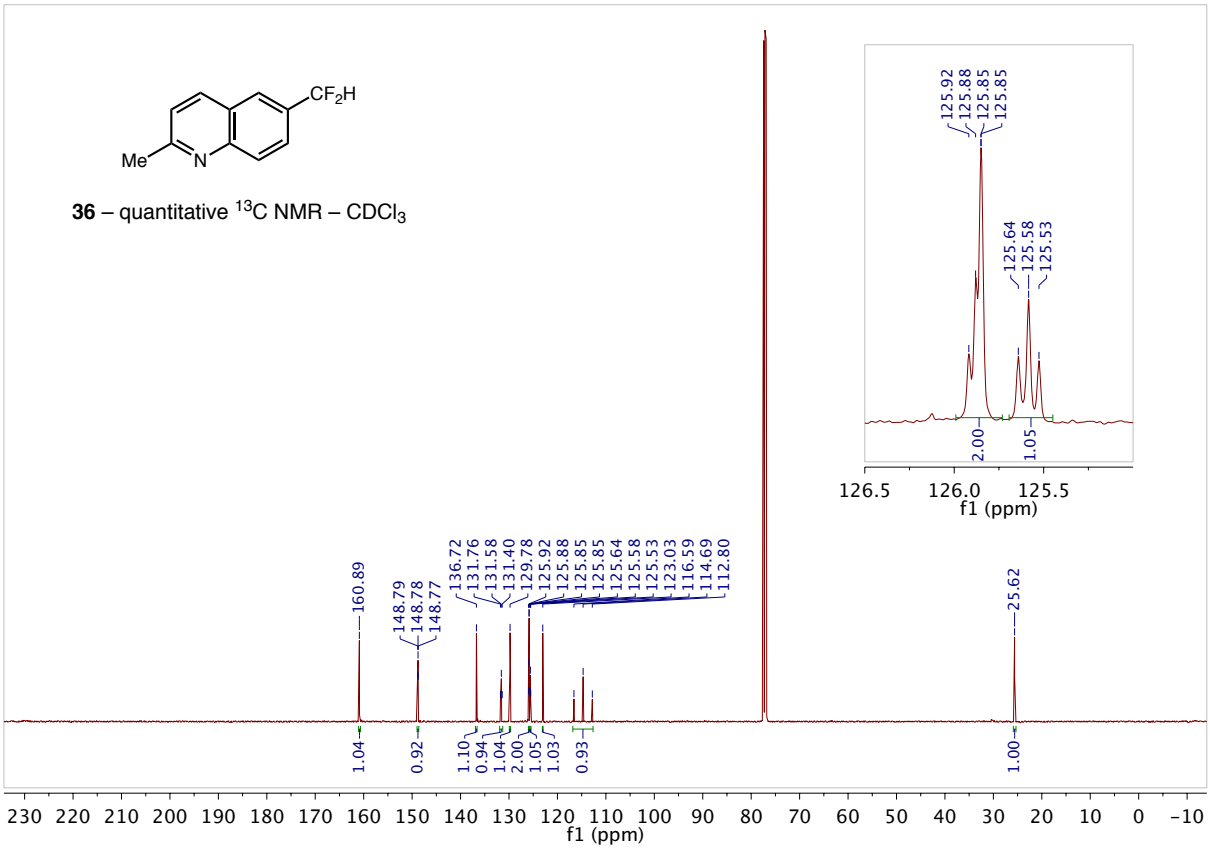


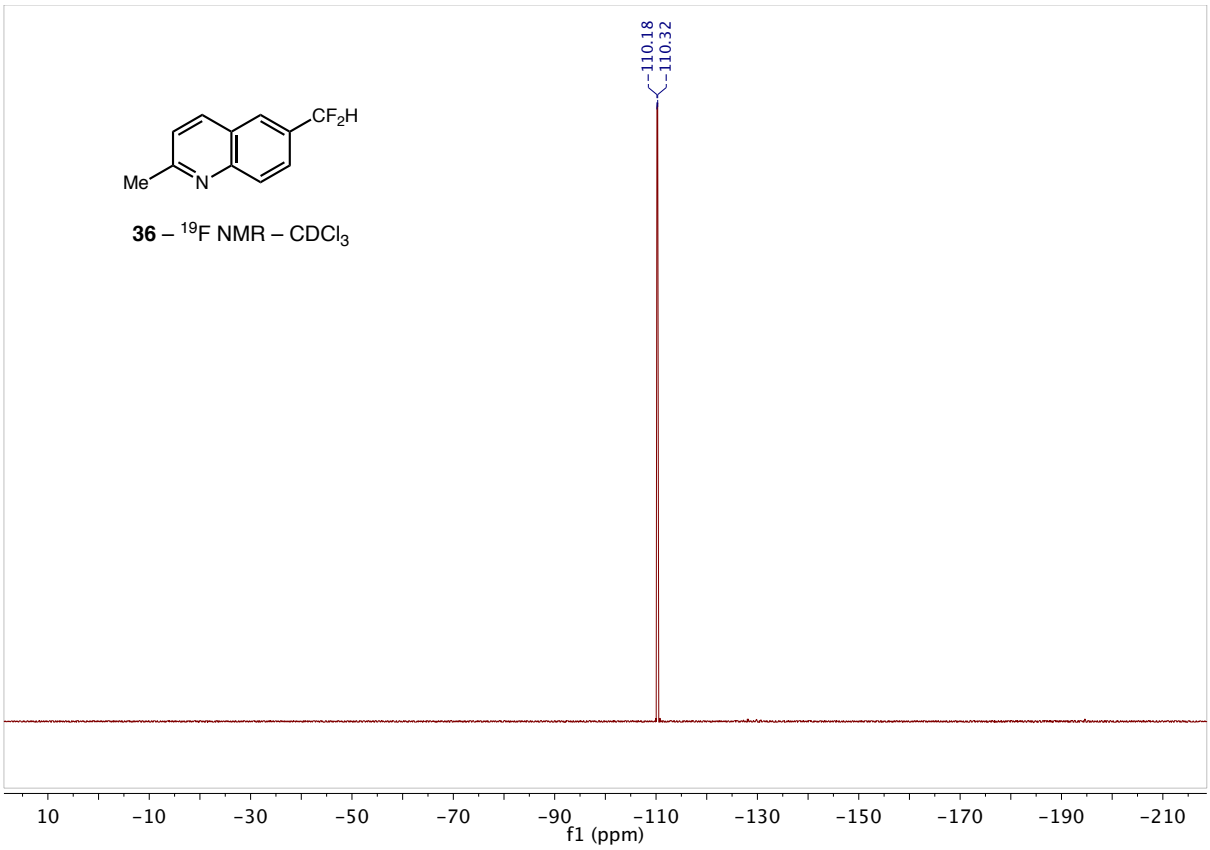
35 – ^{13}C NMR – $CDCl_3$



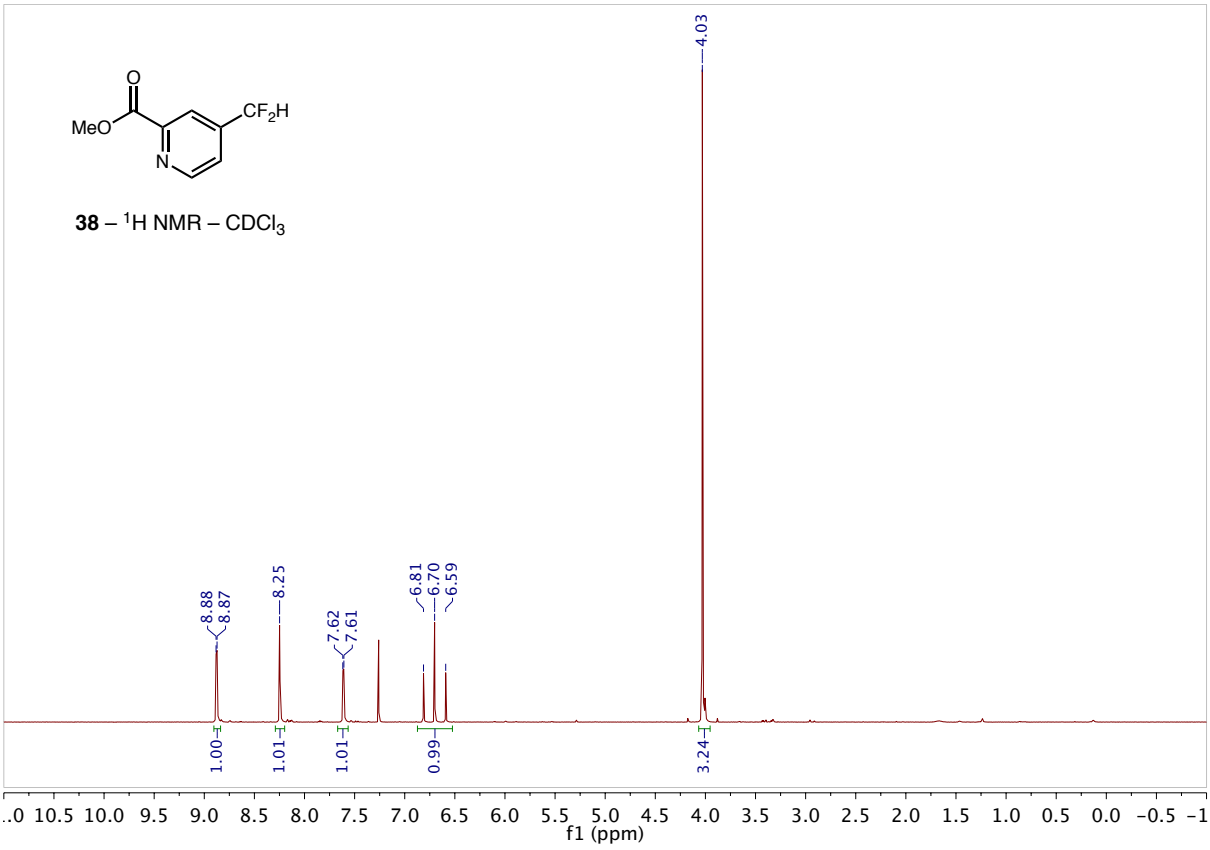
35 – ^{19}F NMR – $CDCl_3$


CF2H
Me
N
36 – 1H NMR – CDCl3
2.76
8.10
8.09
8.08
8.07
7.91
7.91
7.90
7.79
7.79
7.78
7.77
7.35
7.33
6.91
6.80
6.69
0.94
1.04
1.00
0.99
1.00
1.00
3.06
f1 (ppm)

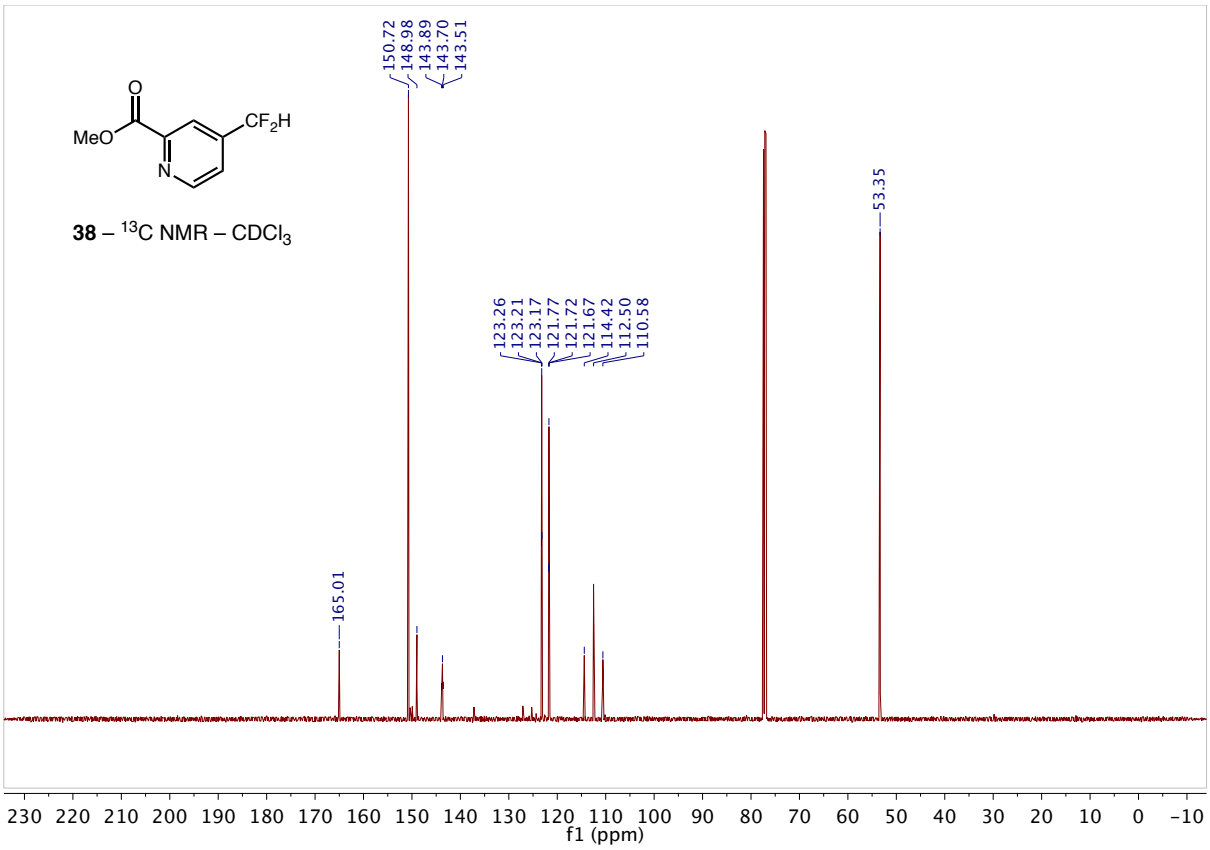

CF2H
Me
N
36 – quantitative 13C NMR – CDCl3
125.92
125.88
125.85
125.85
125.64
125.58
125.53
2.00
1.05
126.5
126.0
125.5
f1 (ppm)
160.89
148.79
148.78
148.77
136.72
131.76
131.58
131.40
129.78
125.92
125.88
125.85
125.85
125.64
125.58
125.53
123.03
116.59
114.69
112.80
25.62
1.04
0.92
1.10
0.94
1.04
2.00
1.05
1.03
0.93
1.00
f1 (ppm)



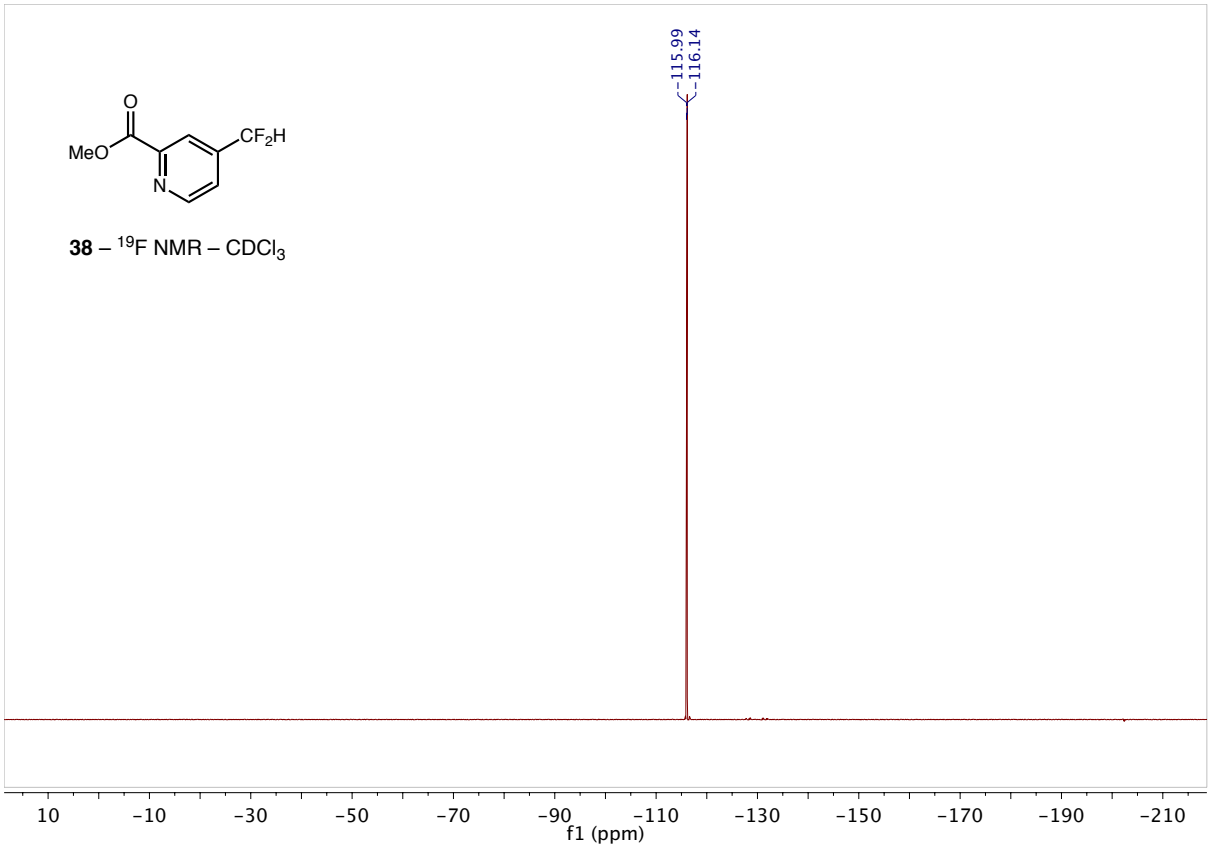
36 – ^{19}F NMR – $CDCl_3$



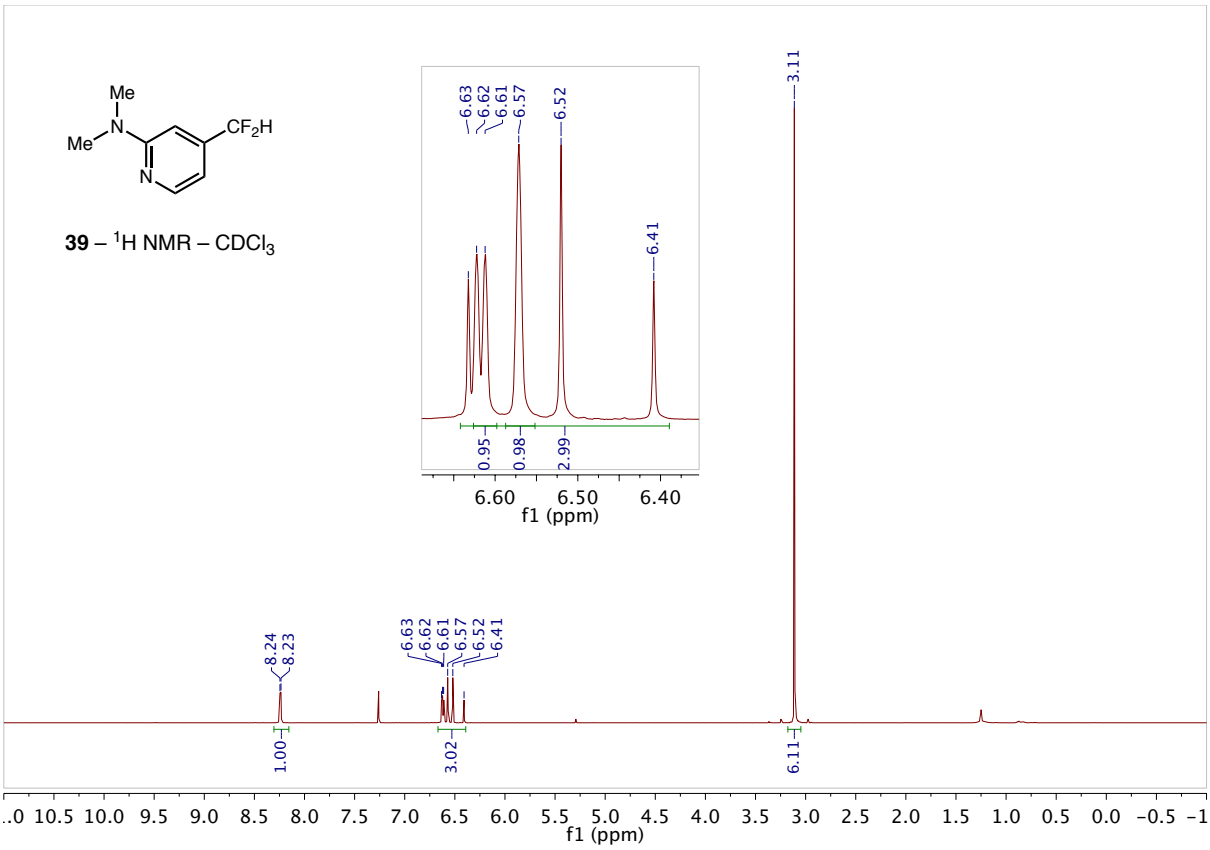
38 – ^{1}H NMR – $CDCl_3$

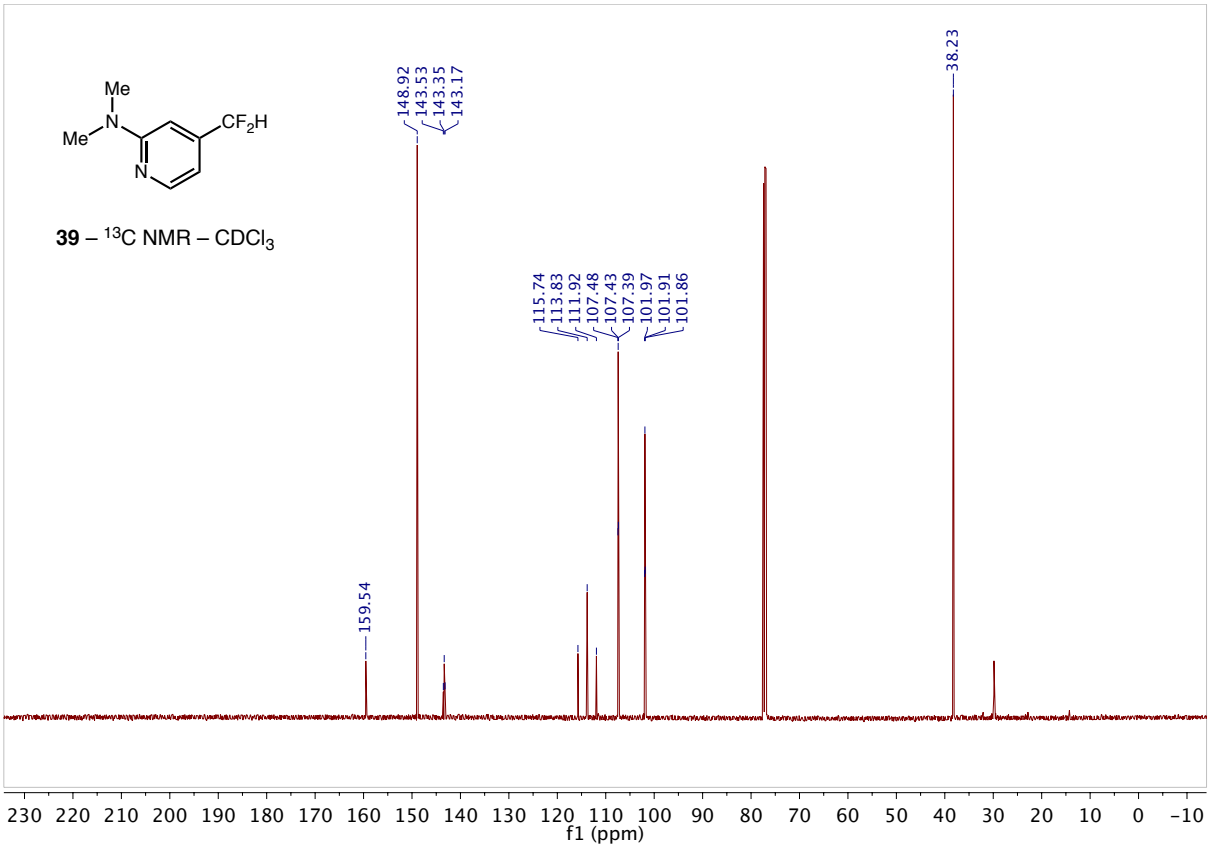


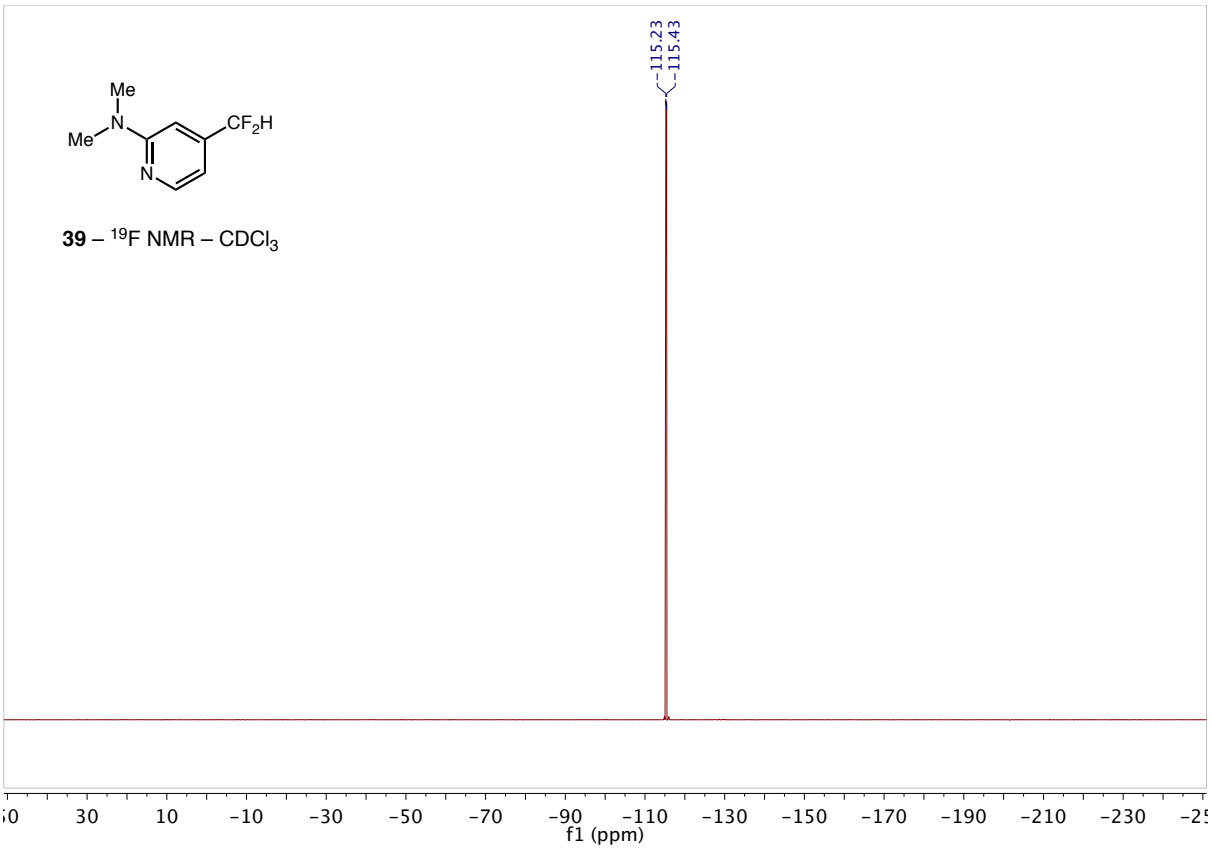
38 – ^{13}C NMR – $CDCl_3$



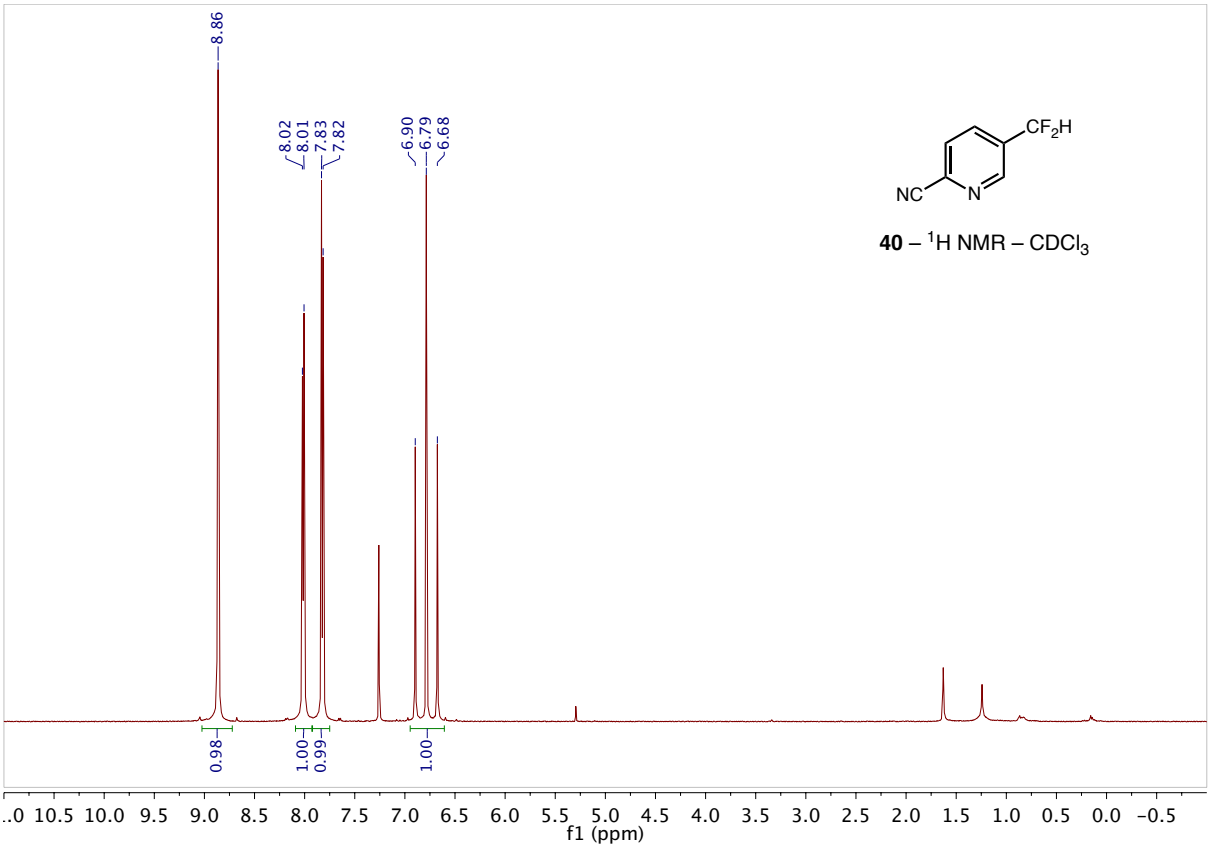
38 – ^{19}F NMR – $CDCl_3$


Me
N
Me
CF2H
N
39 – 1H NMR – CDCl3
6.63
6.62
6.61
6.57
6.52
6.41
3.11
0.95
0.98
2.99
6.60
6.50
6.40
f1 (ppm)
8.24
8.23
1.00
3.02
6.11
f1 (ppm)

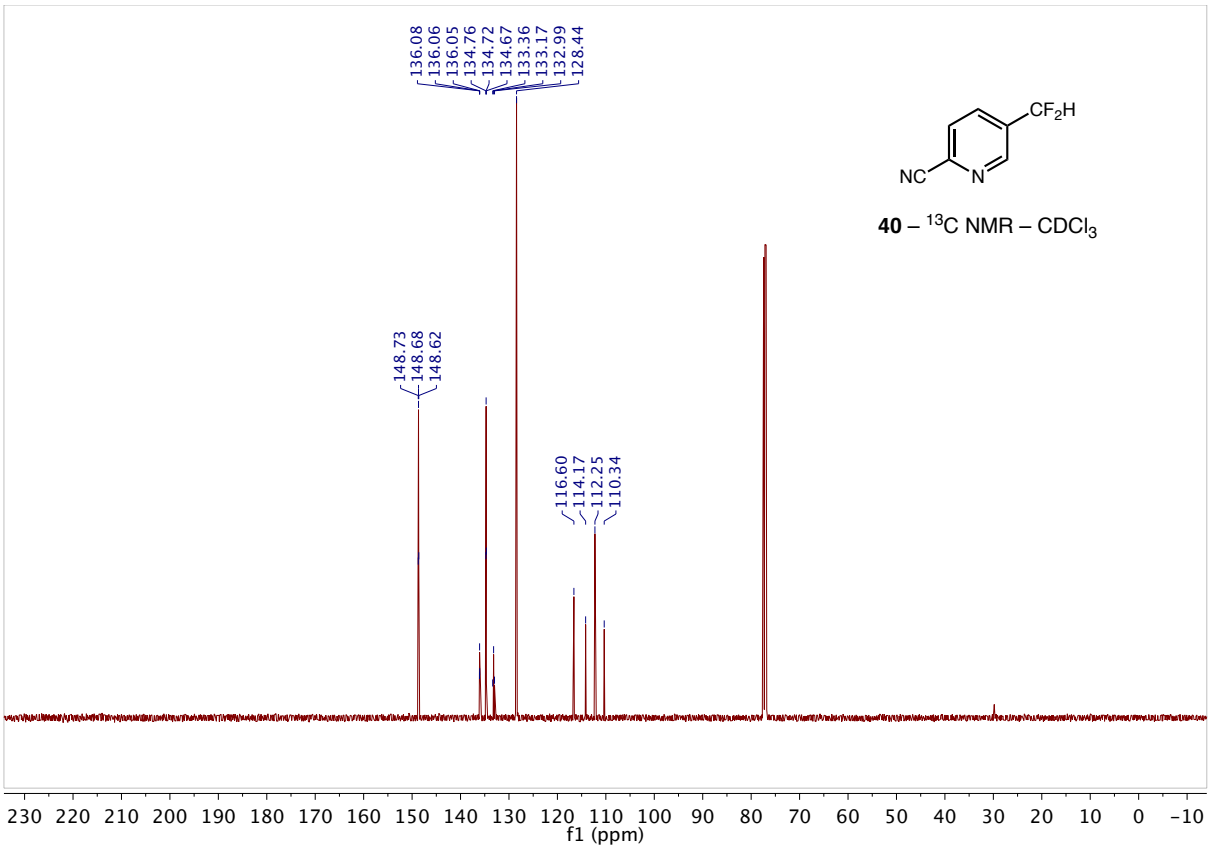

Me
N
Me
CF2H
N
39 – 13C NMR – CDCl3
148.92
143.53
143.35
143.17
38.23
115.74
113.83
111.92
107.48
107.43
107.39
101.97
101.91
101.86
159.54
f1 (ppm)



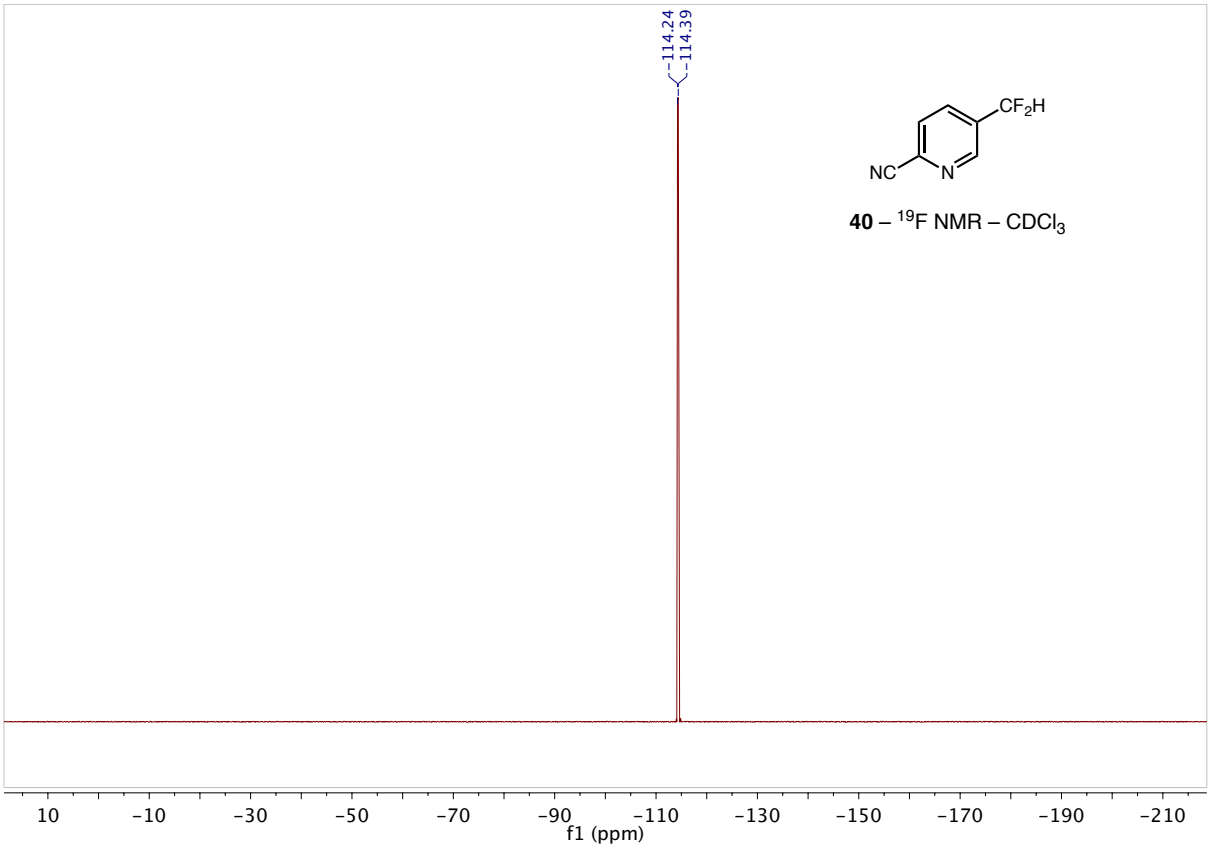
39 – ^{19}F NMR – $CDCl_3$



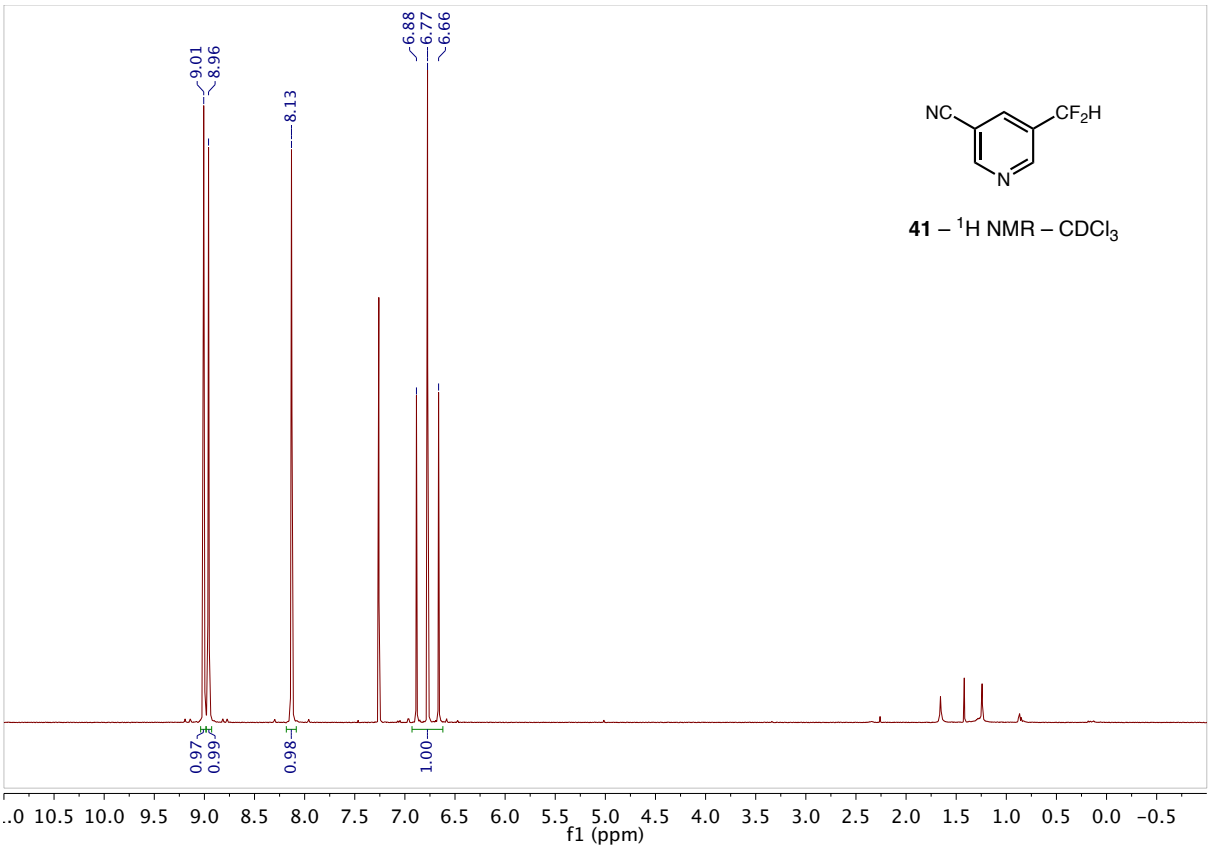
40 – ^{1}H NMR – $CDCl_3$

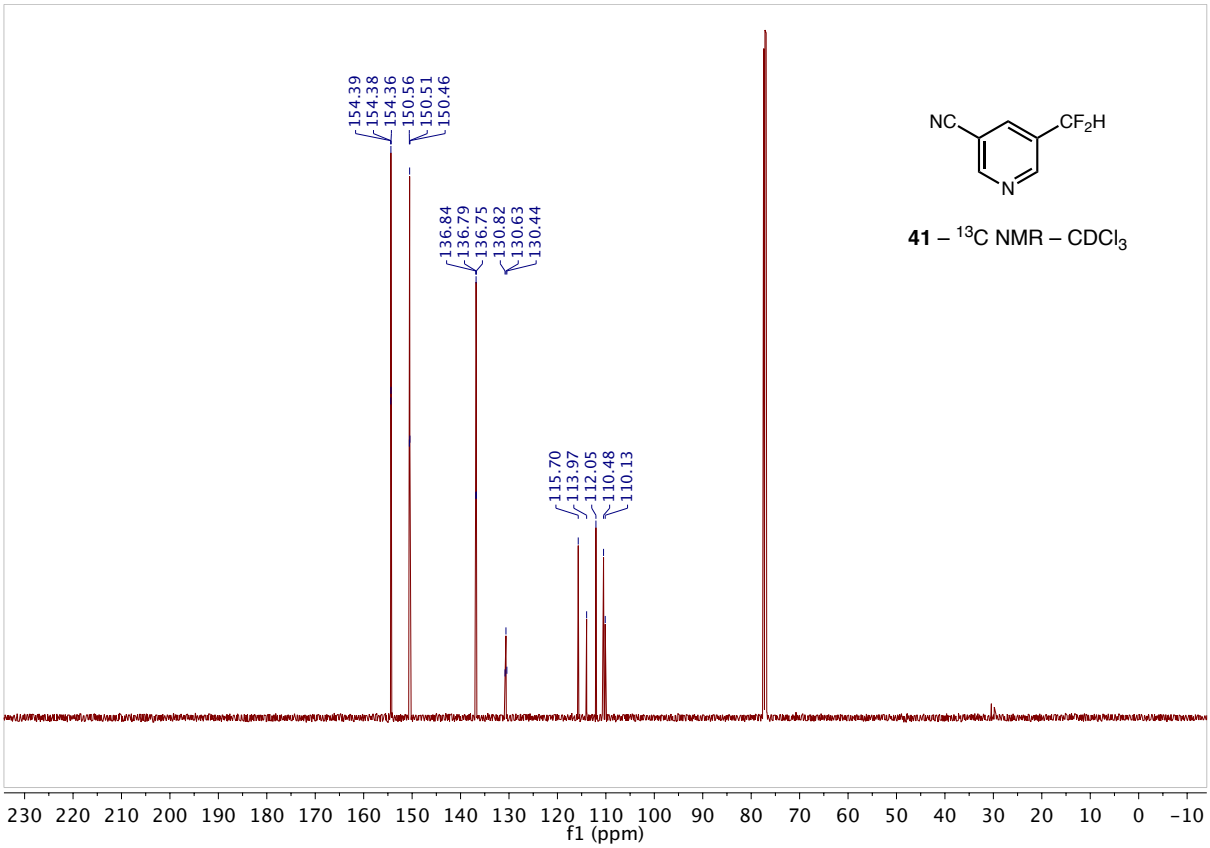


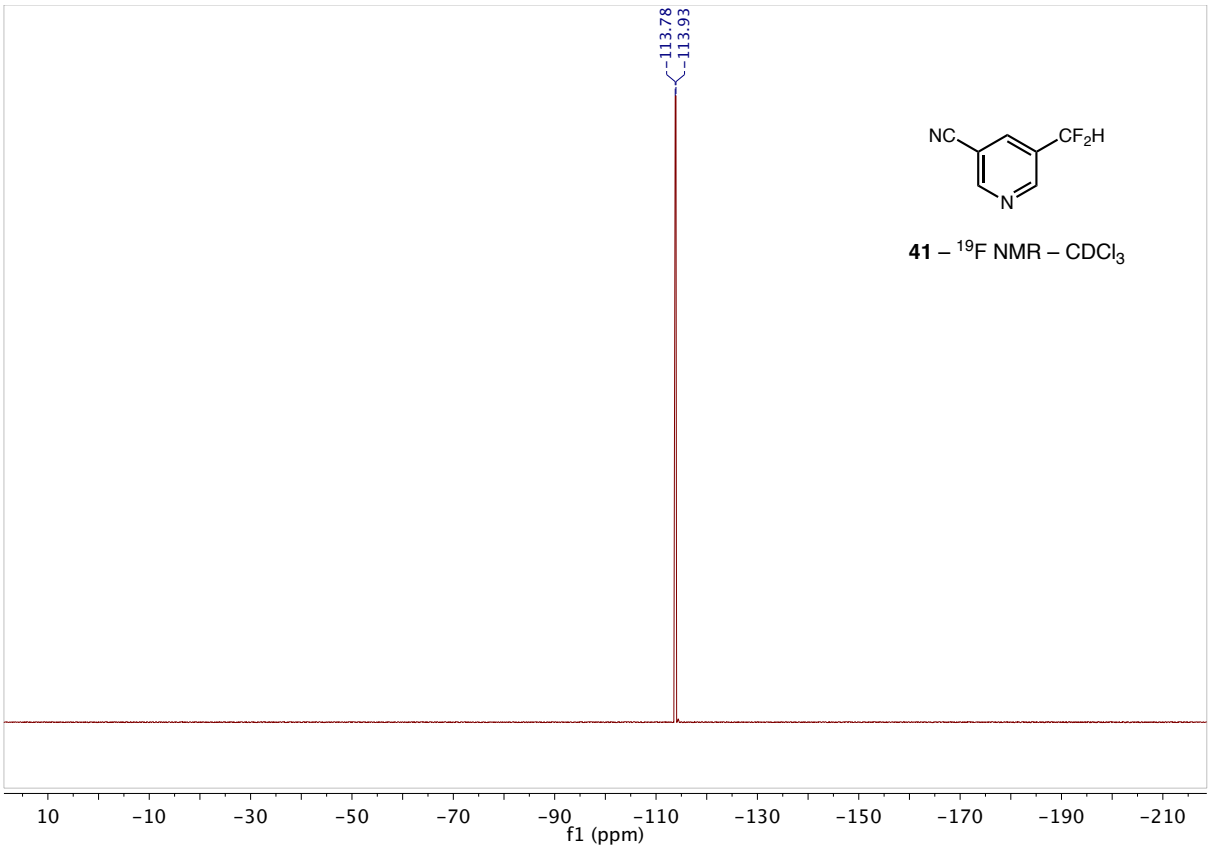
40 – ^{13}C NMR – $CDCl_3$



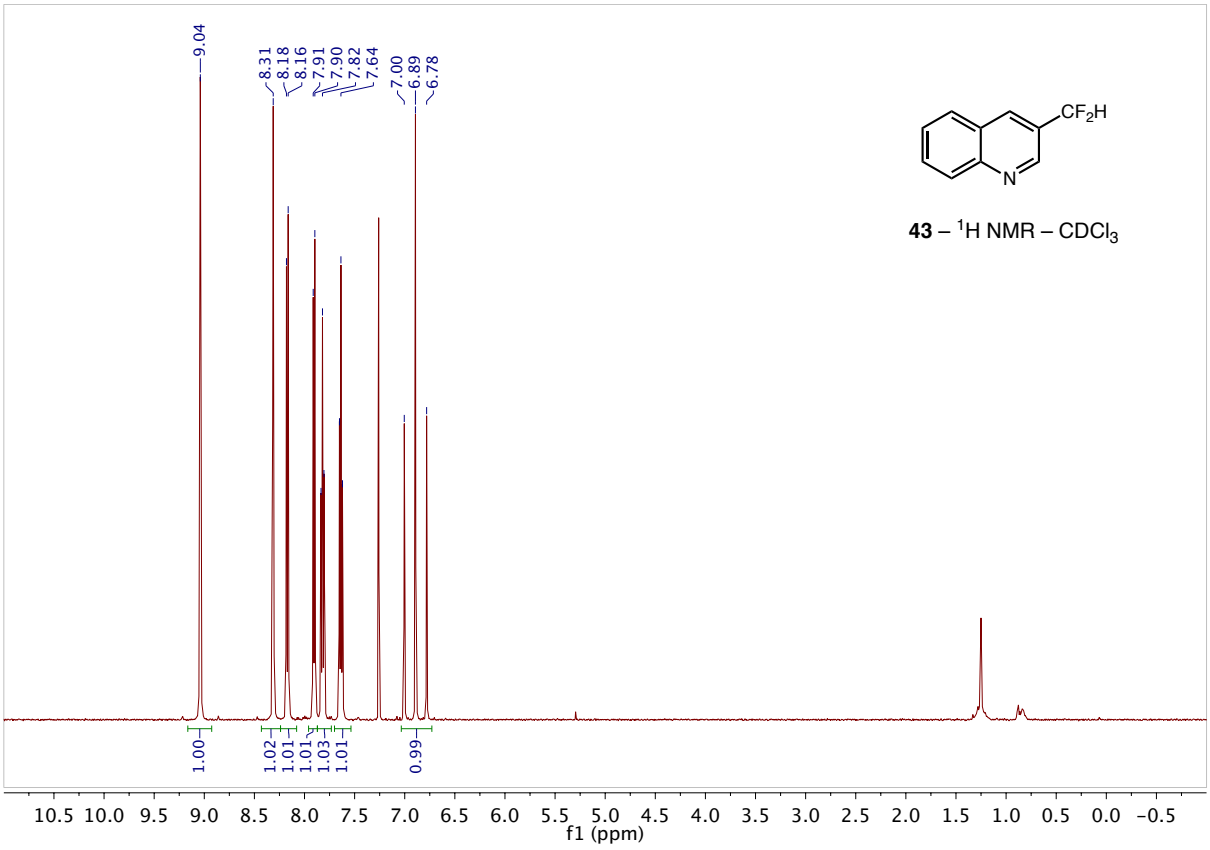
40 – ^{19}F NMR – $CDCl_3$


9.01
8.96
8.13
6.88
6.77
6.66
0.97
0.99
0.98
1.00
NC
CF2H
N
41 – 1H NMR – CDCl3
f1 (ppm)

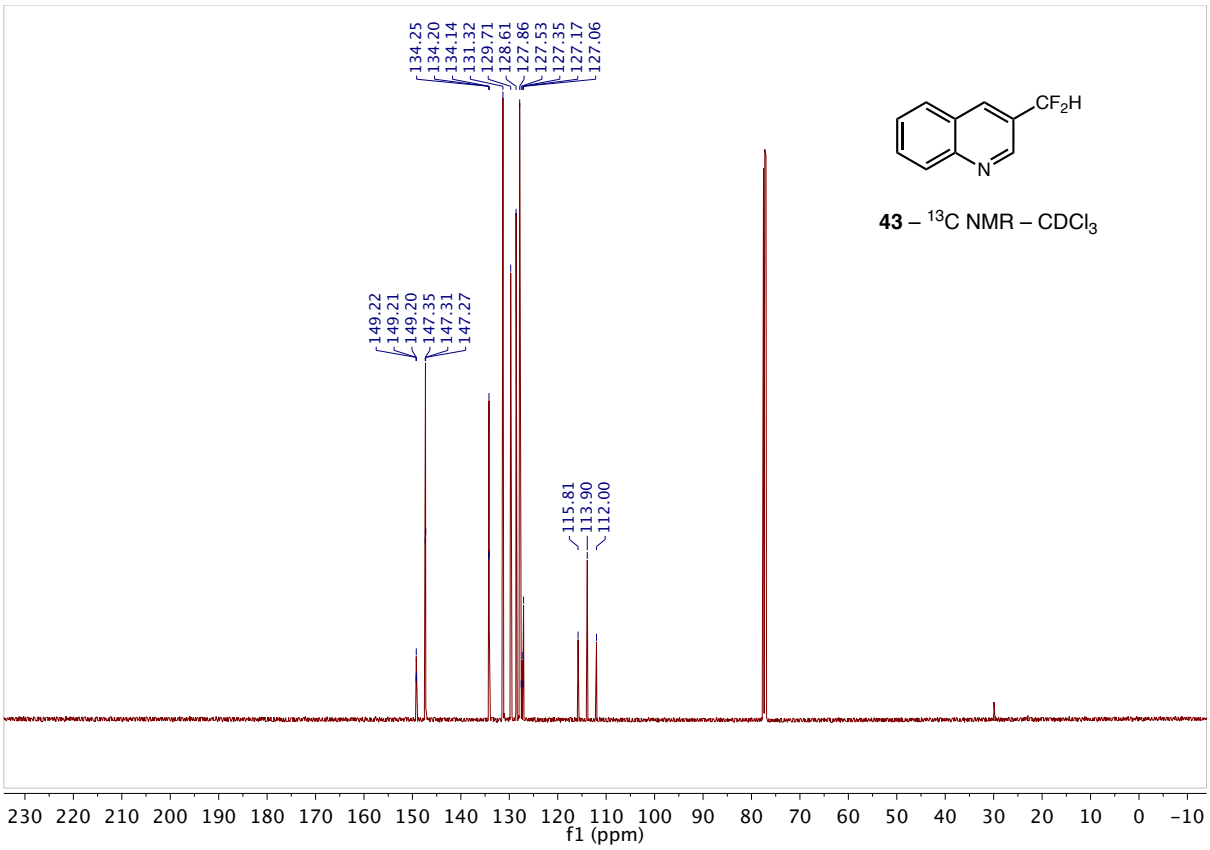

154.39
154.38
154.36
150.56
150.51
150.46
136.84
136.79
136.75
130.82
130.63
130.44
115.70
113.97
112.05
110.48
110.13
NC
CF2H
N
41 – 13C NMR – CDCl3
f1 (ppm)



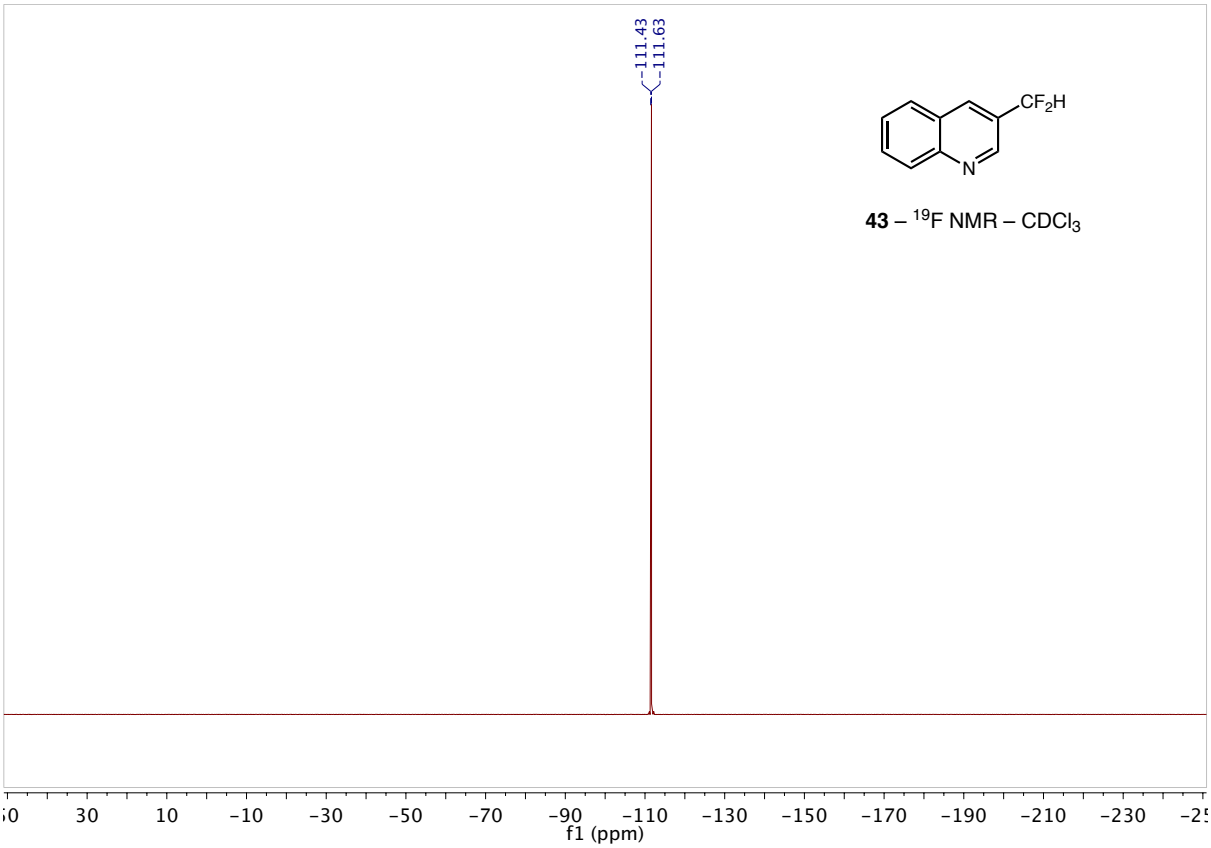
41 – ^{19}F NMR – $CDCl_3$



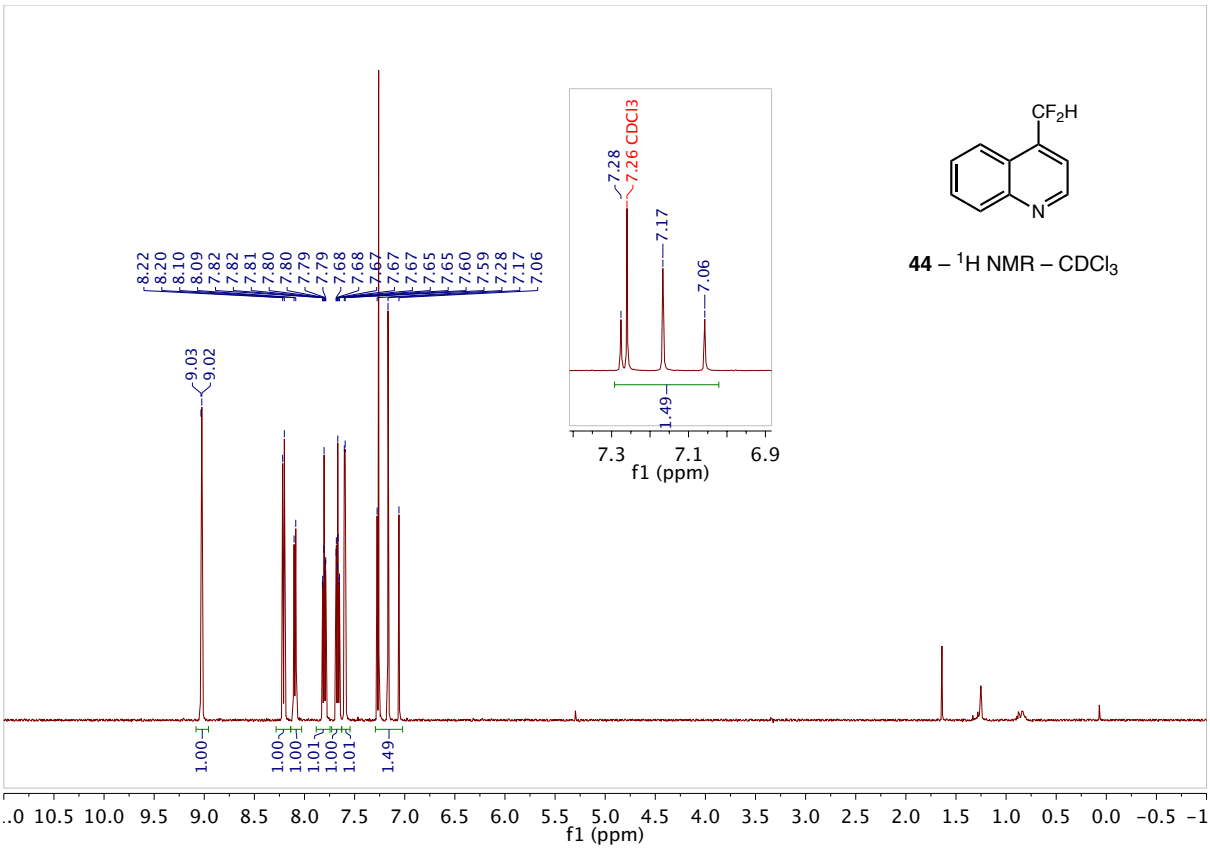
43 – ^{1}H NMR – $CDCl_3$

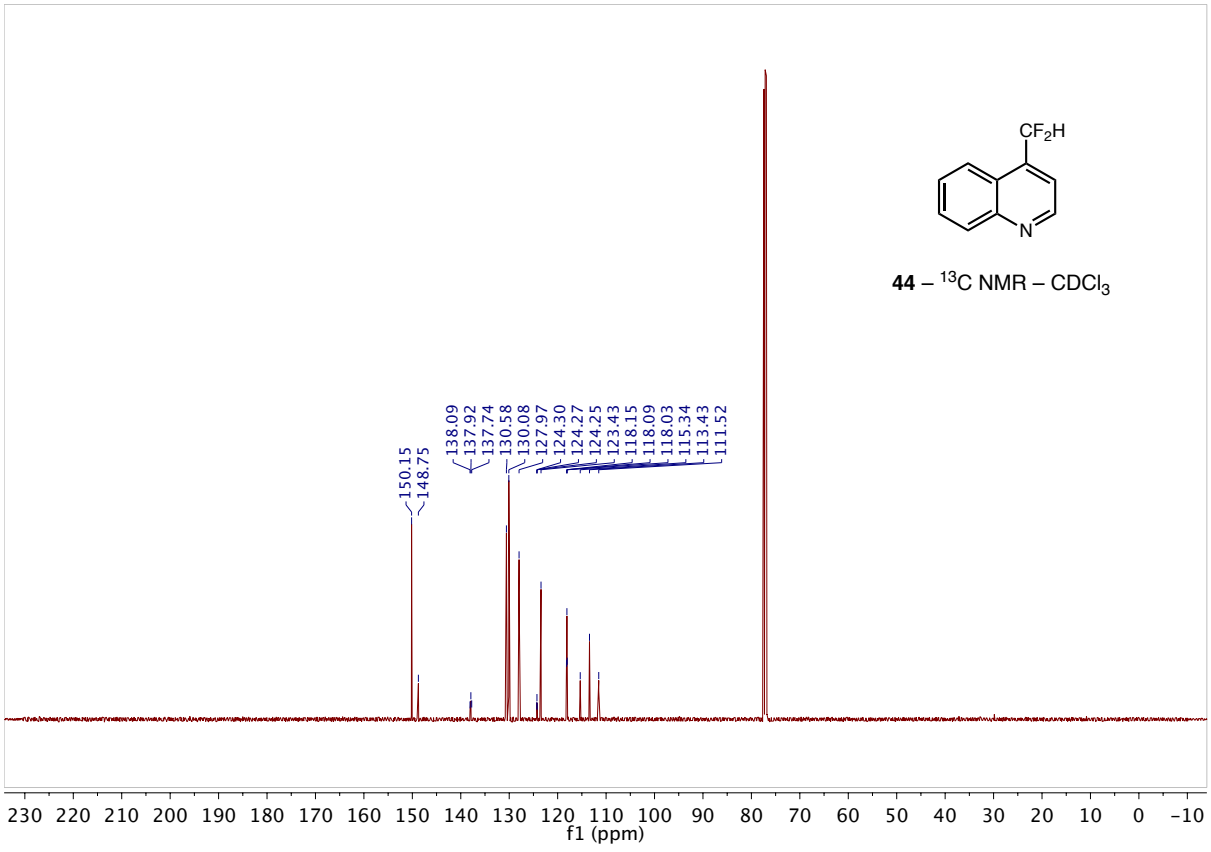


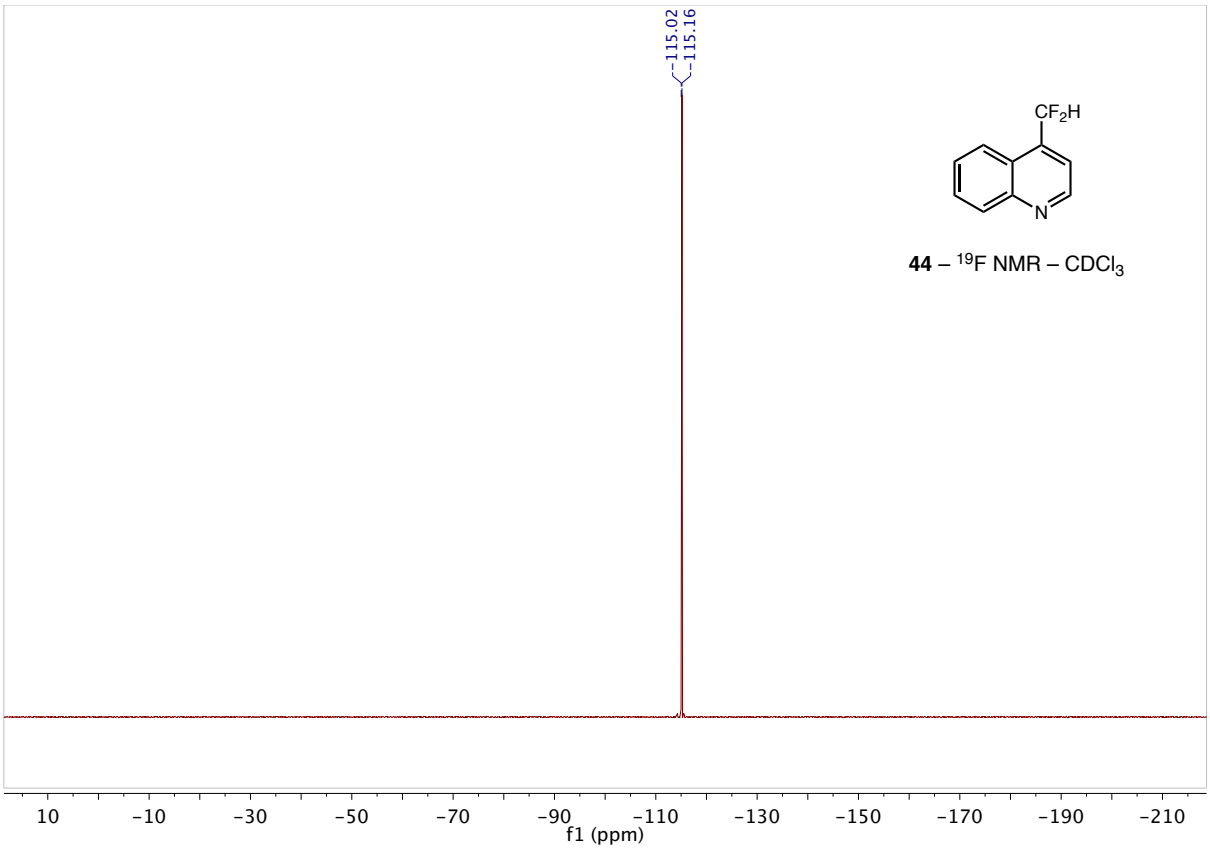
43 – ^{13}C NMR – $CDCl_3$



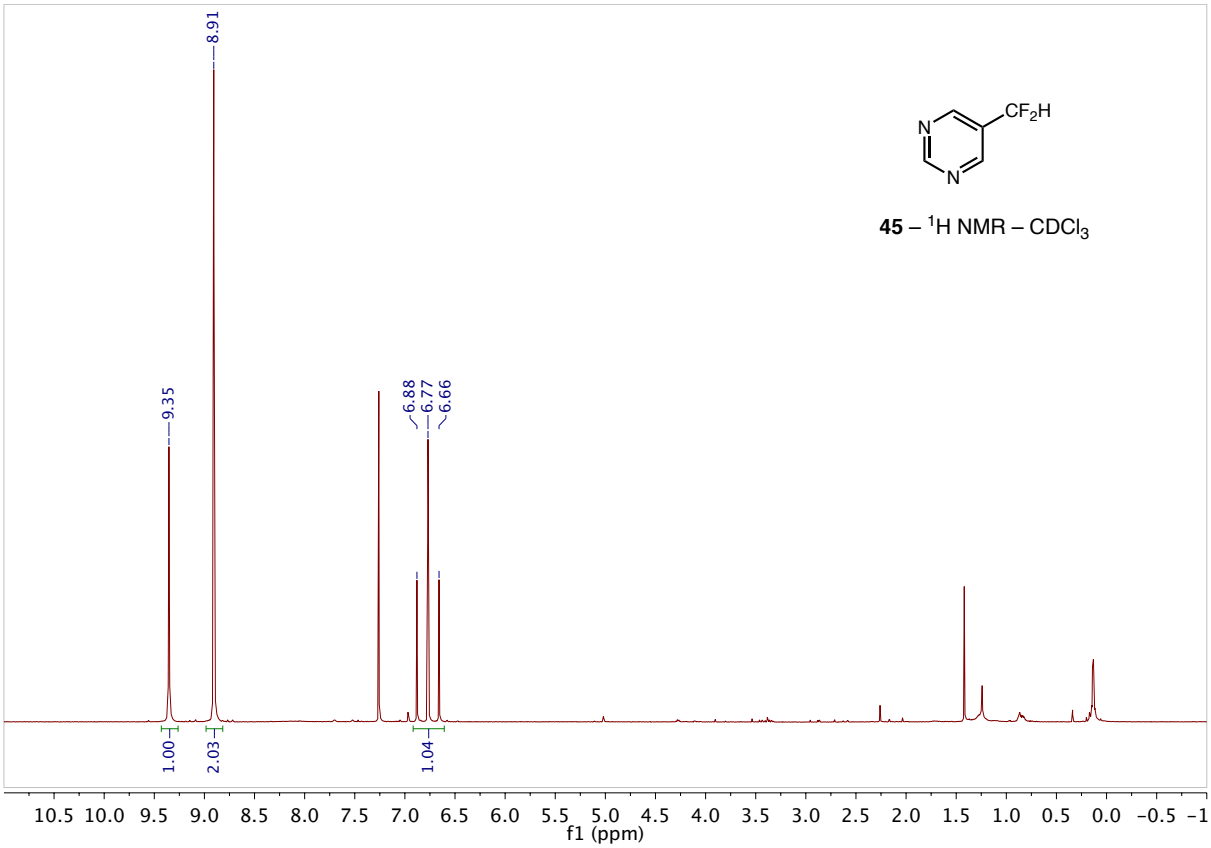
43 – ^{19}F NMR – $CDCl_3$


CF2H
N
44 – 1H NMR – CDCl3
7.28
7.26 CDCl3
7.17
7.06
1.49
7.3
7.1
6.9
f1 (ppm)
8.22
8.20
8.10
8.09
7.82
7.82
7.81
7.80
7.80
7.79
7.79
7.68
7.68
7.67
7.67
7.67
7.65
7.65
7.60
7.59
7.28
7.17
7.06
9.03
9.02
1.00
1.00
1.00
1.01
1.00
1.01
1.49
f1 (ppm)

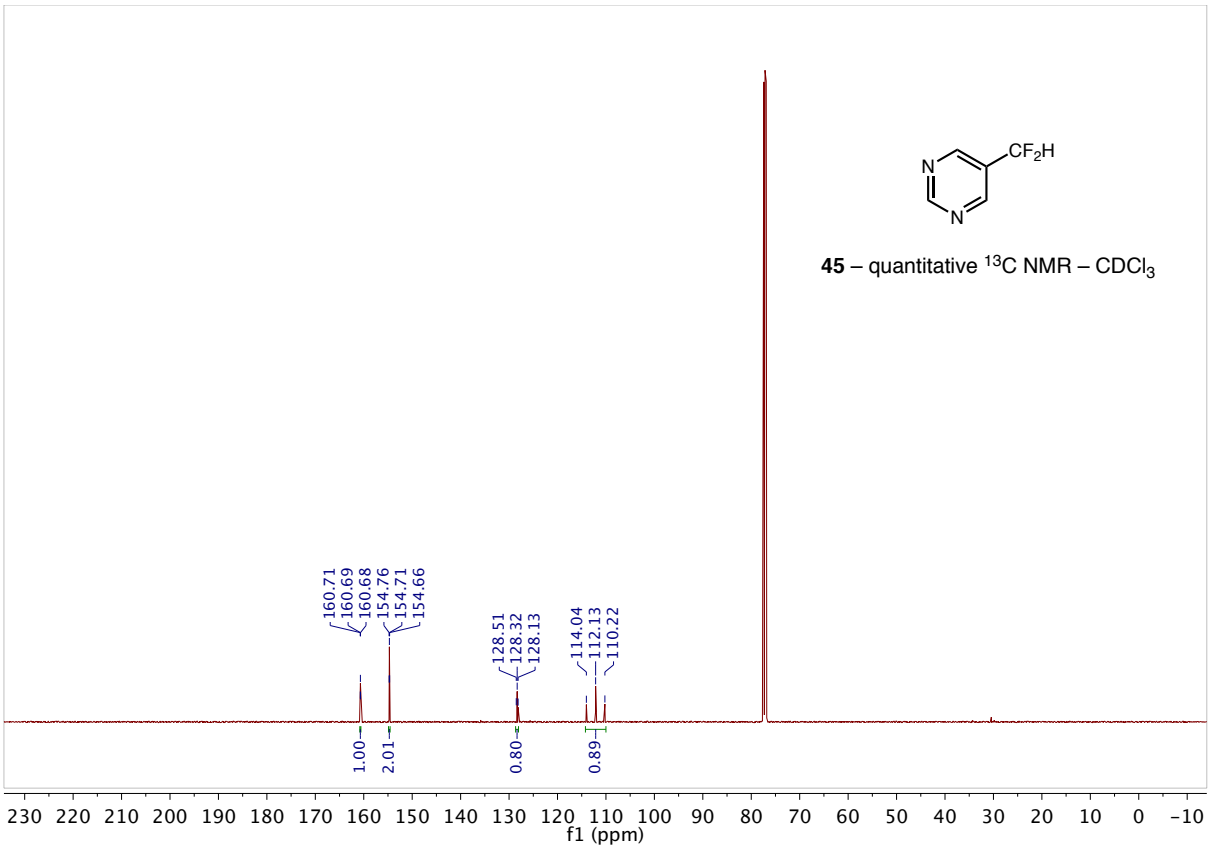

CF2H
N
44 – 13C NMR – CDCl3
150.15
148.75
138.09
137.92
137.74
130.58
130.08
127.97
124.30
124.27
124.25
123.43
118.15
118.09
118.03
115.34
113.43
111.52
f1 (ppm)



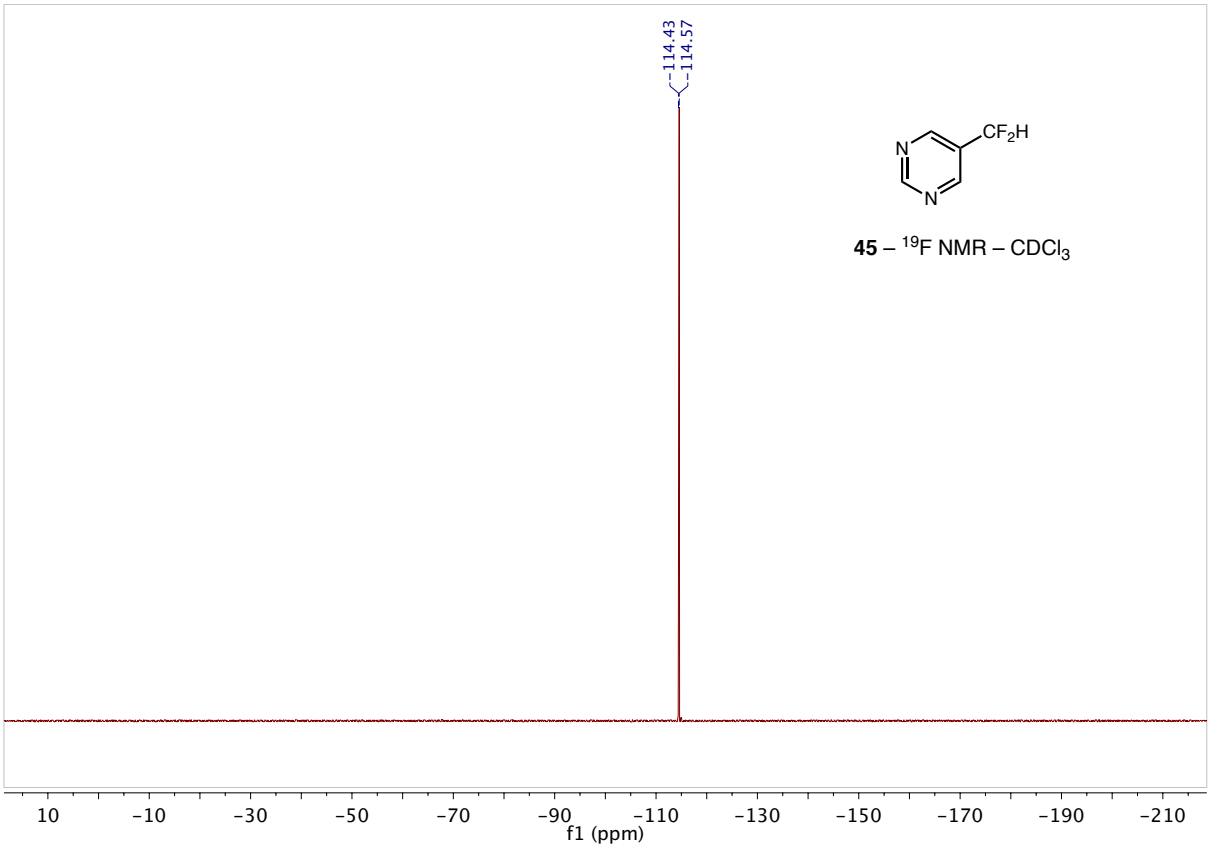
44 – ^{19}F NMR – $CDCl_3$



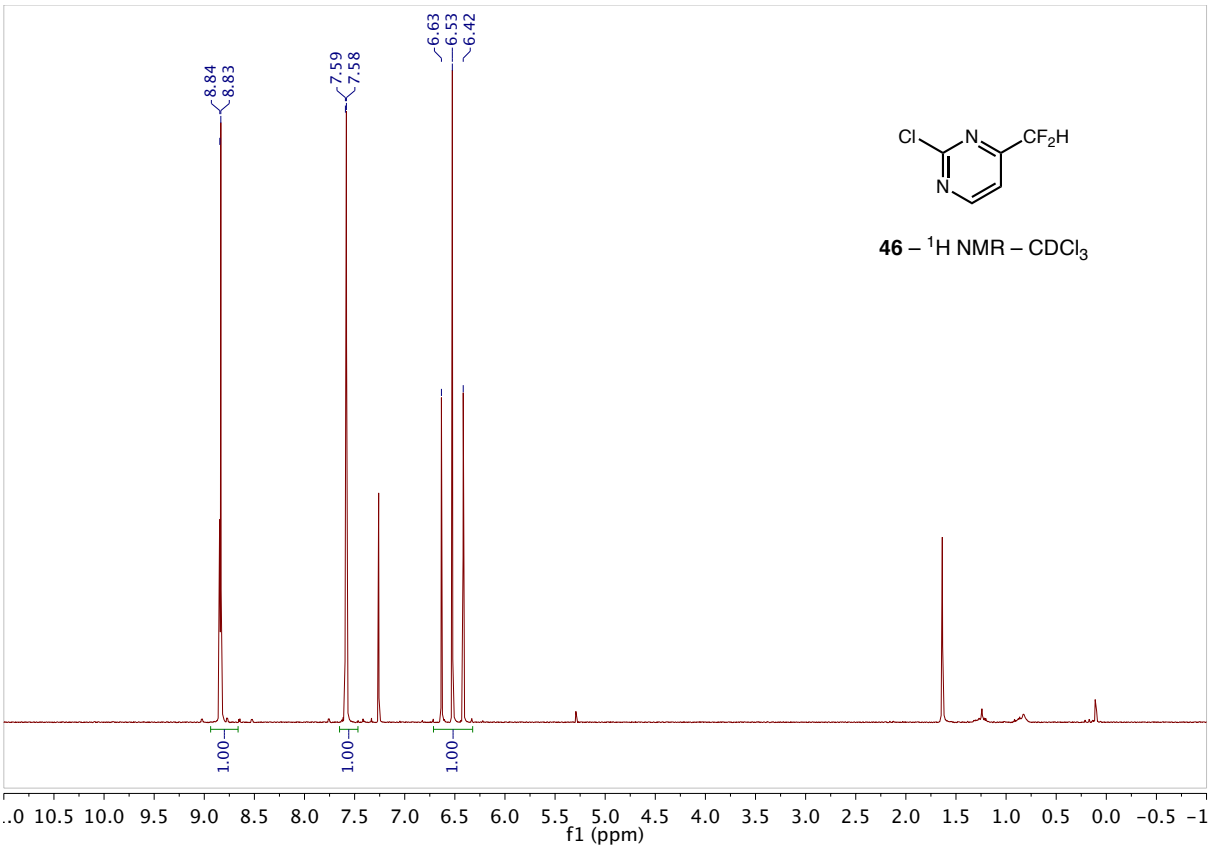
45 – ^{1}H NMR – $CDCl_3$

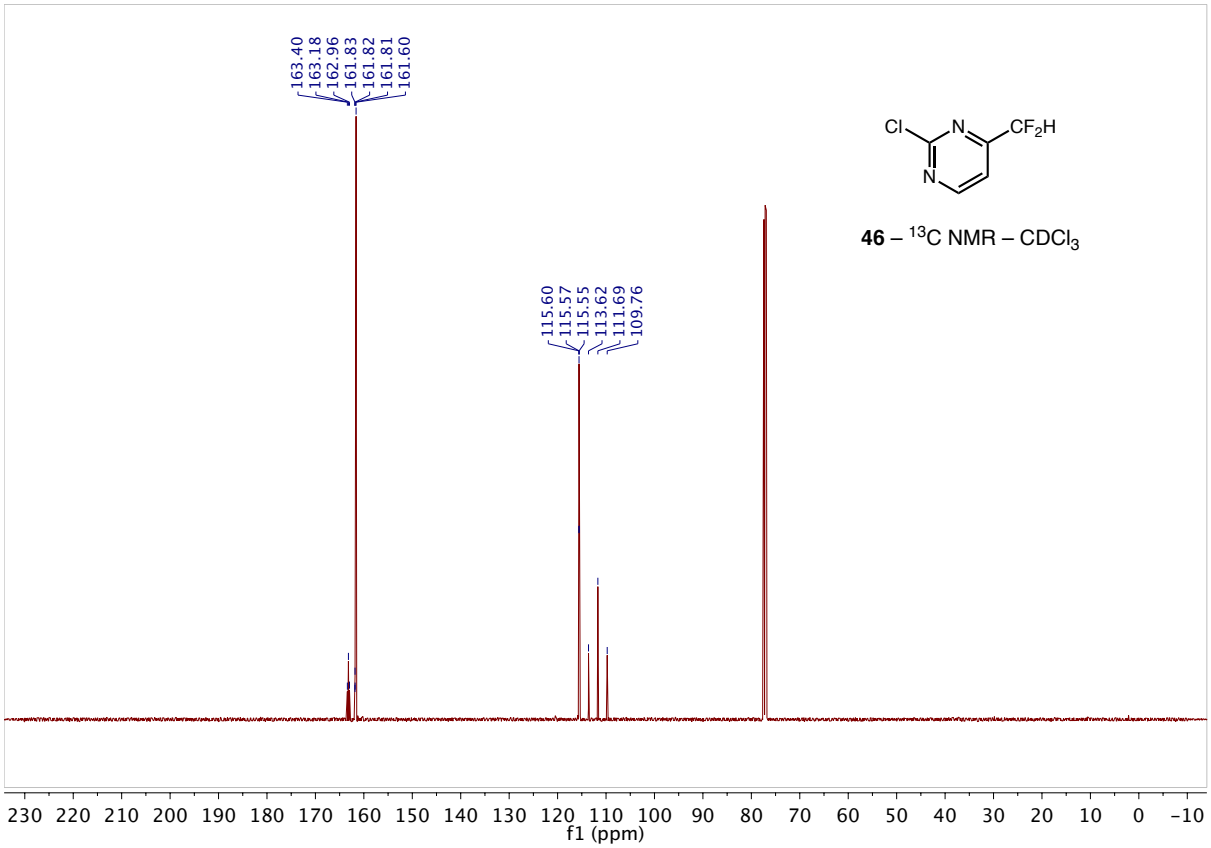


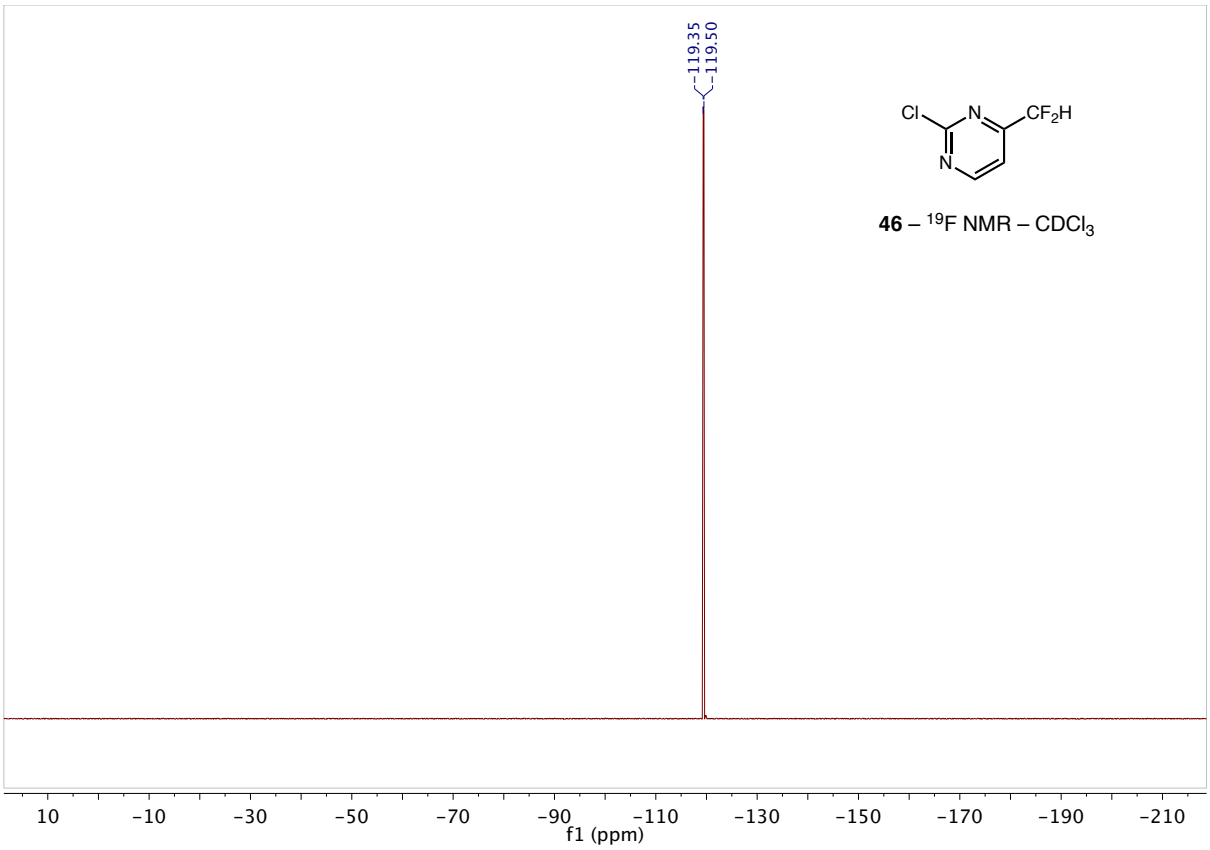
45 – quantitative ^{13}C NMR – $CDCl_3$



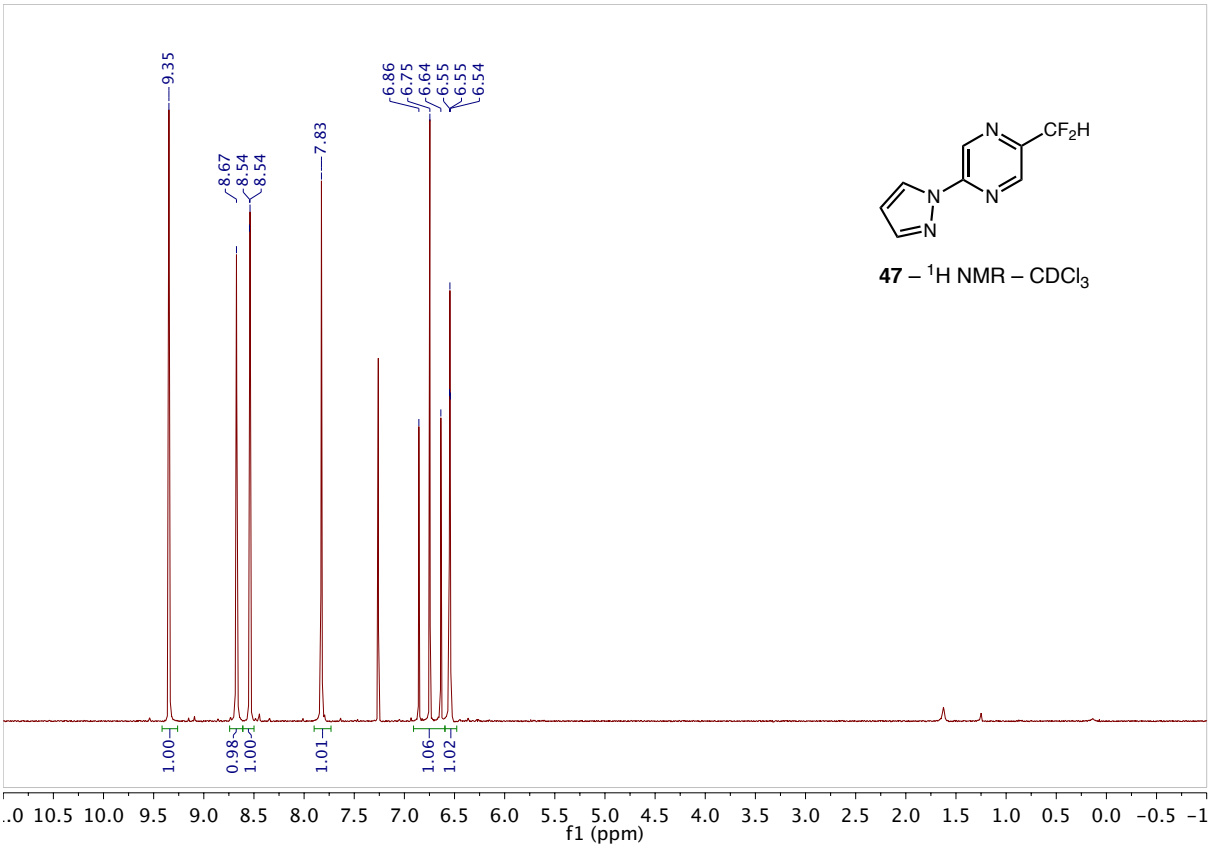
45 – ^{19}F NMR – $CDCl_3$


8.84
8.83
7.59
7.58
6.63
6.53
6.42
1.00
1.00
1.00
Cl
N
CF2H
N
46 – 1H NMR – CDCl3
f1 (ppm)

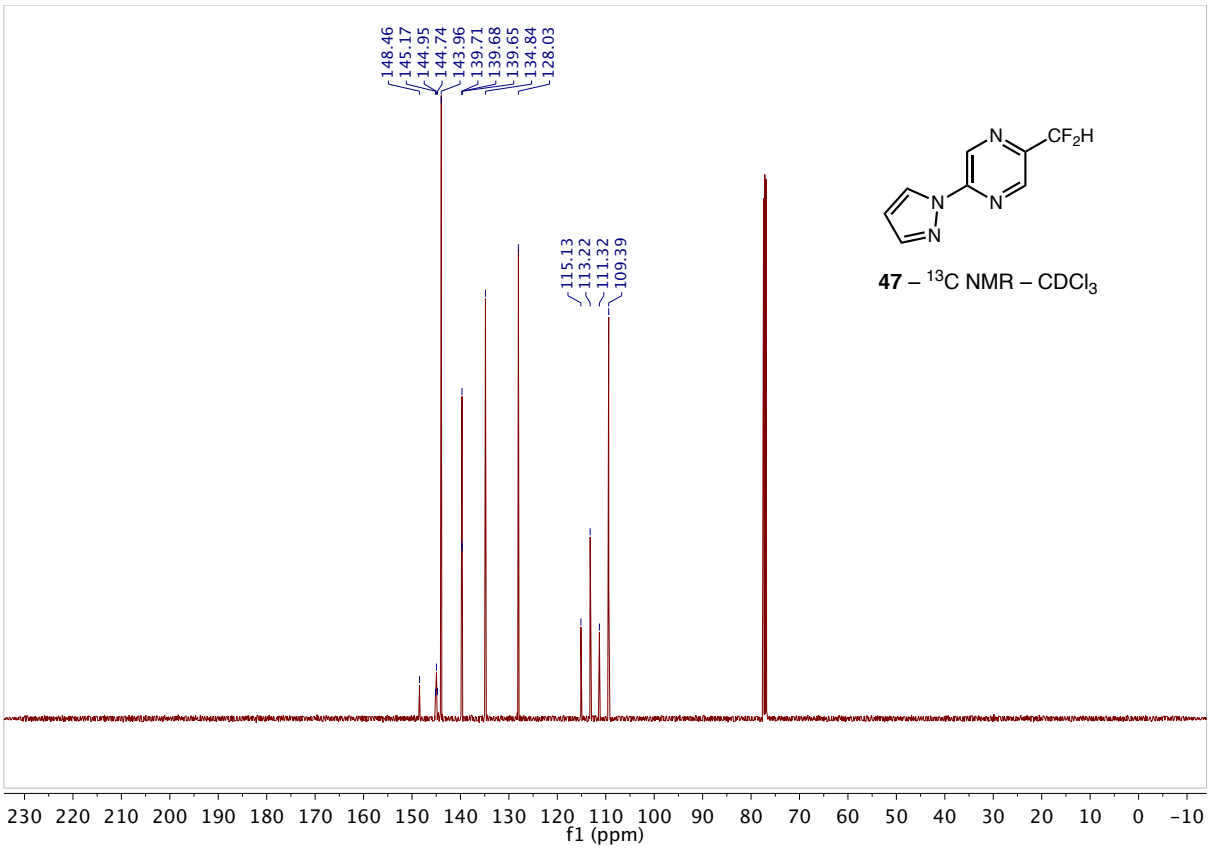

163.40
163.18
162.96
161.83
161.82
161.81
161.60
115.60
115.57
115.55
113.62
111.69
109.76
Cl
N
CF2H
N
46 – 13C NMR – CDCl3
f1 (ppm)



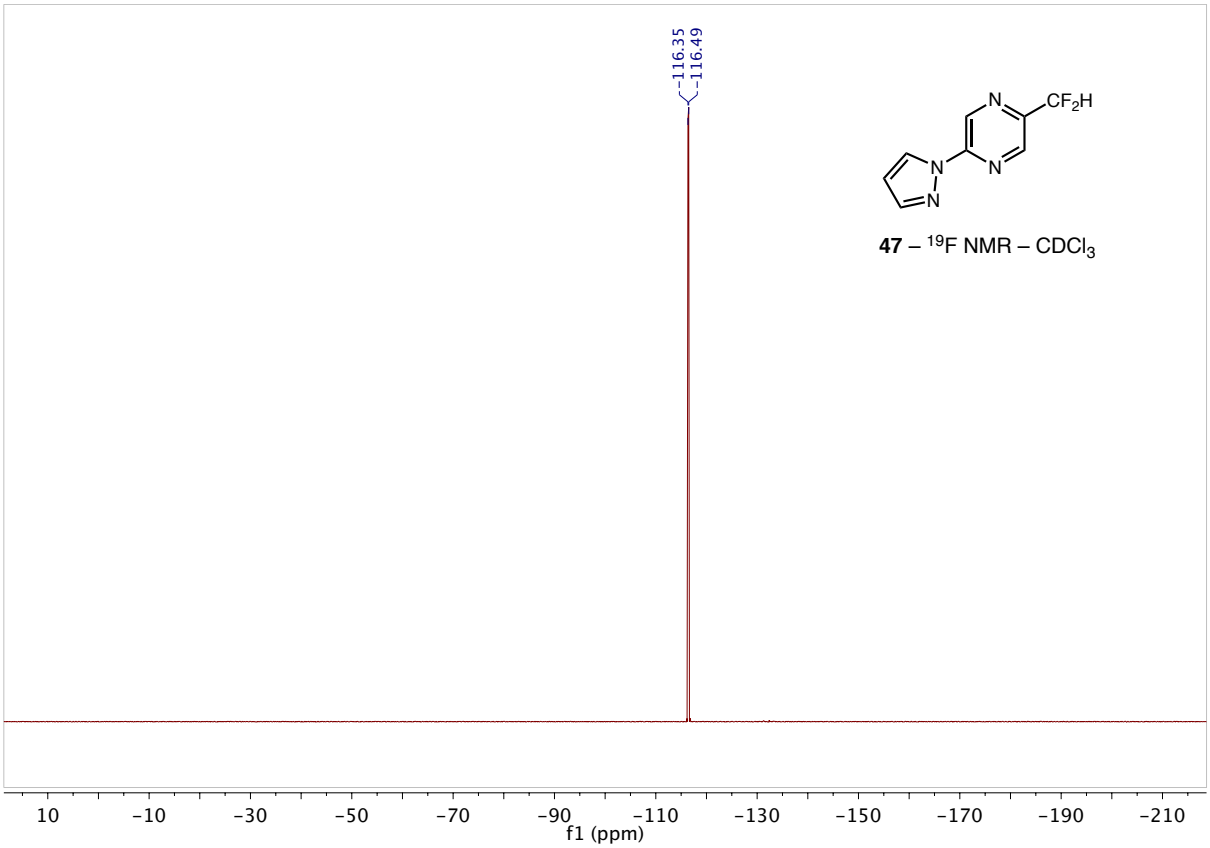
46 – ^{19}F NMR – $CDCl_3$



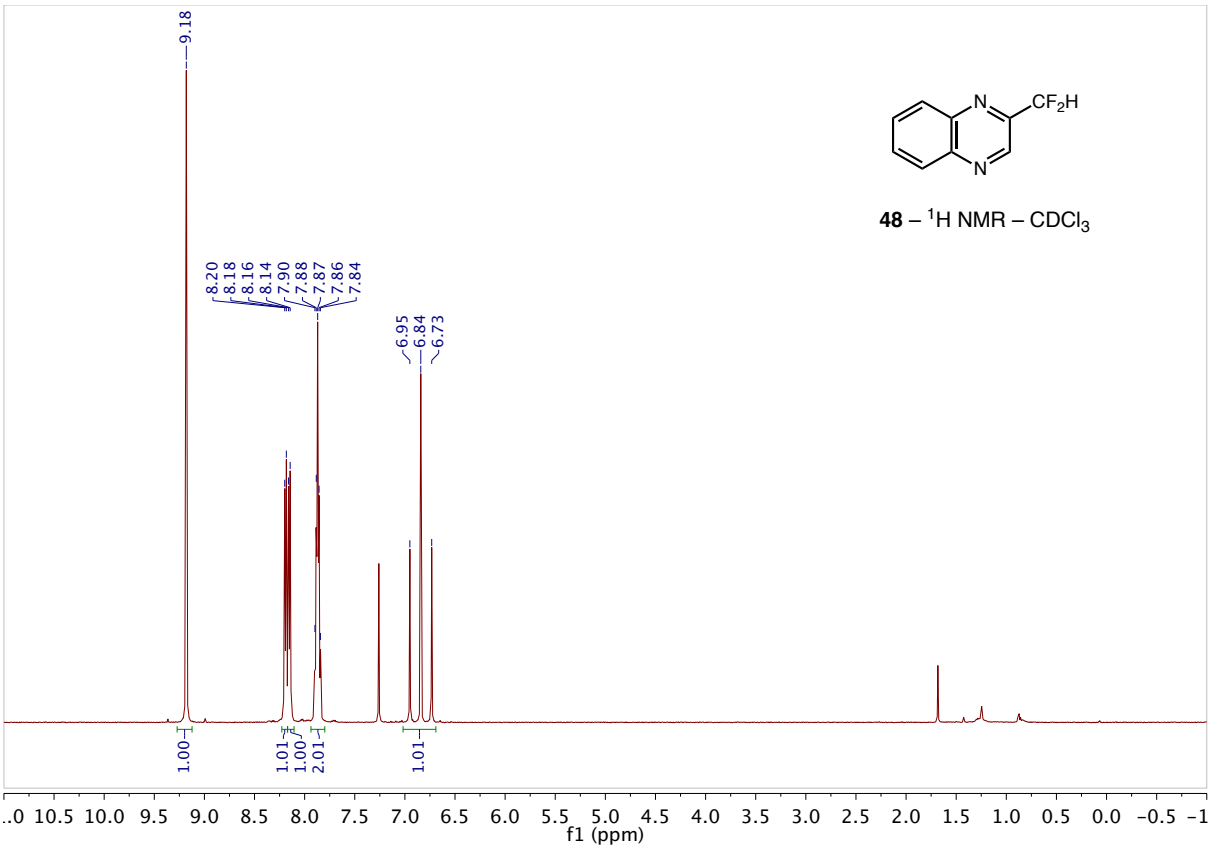
47 – ^{1}H NMR – $CDCl_3$



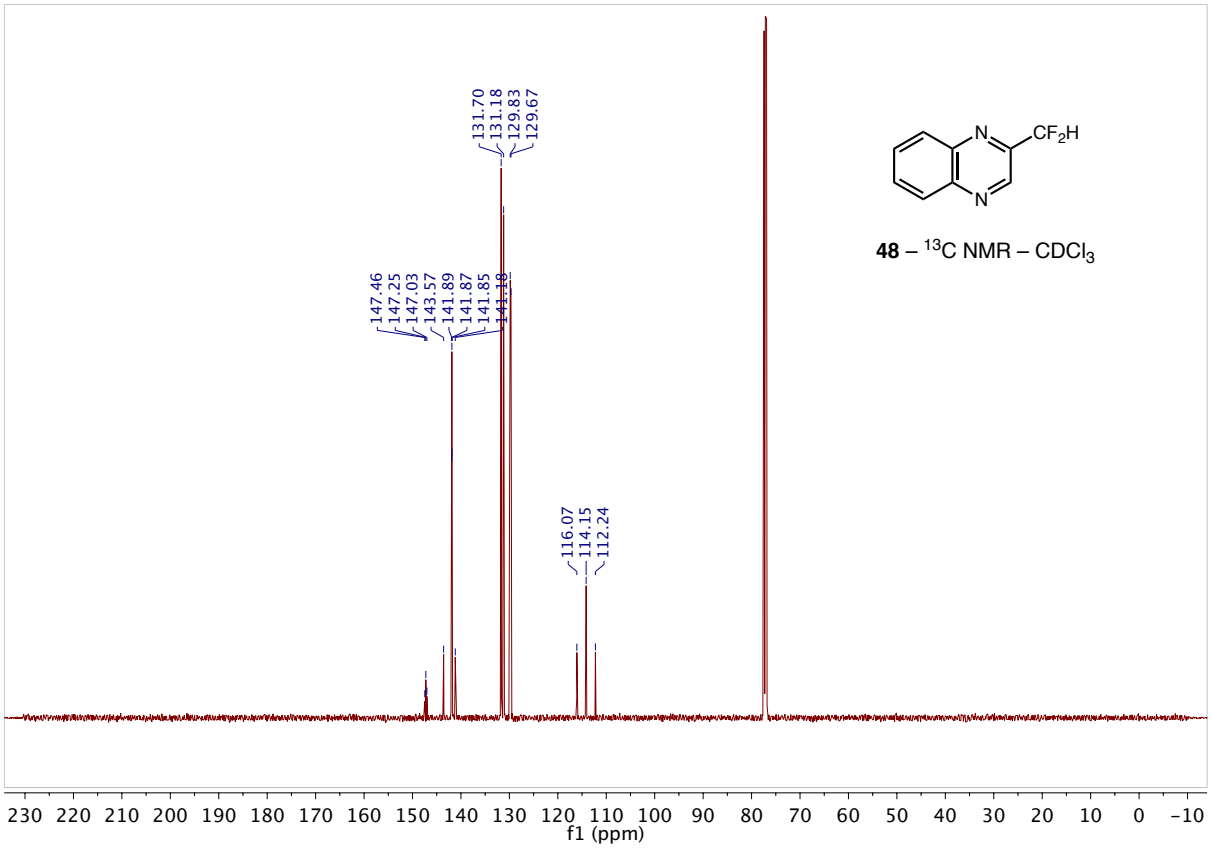
47 – ^{13}C NMR – $CDCl_3$



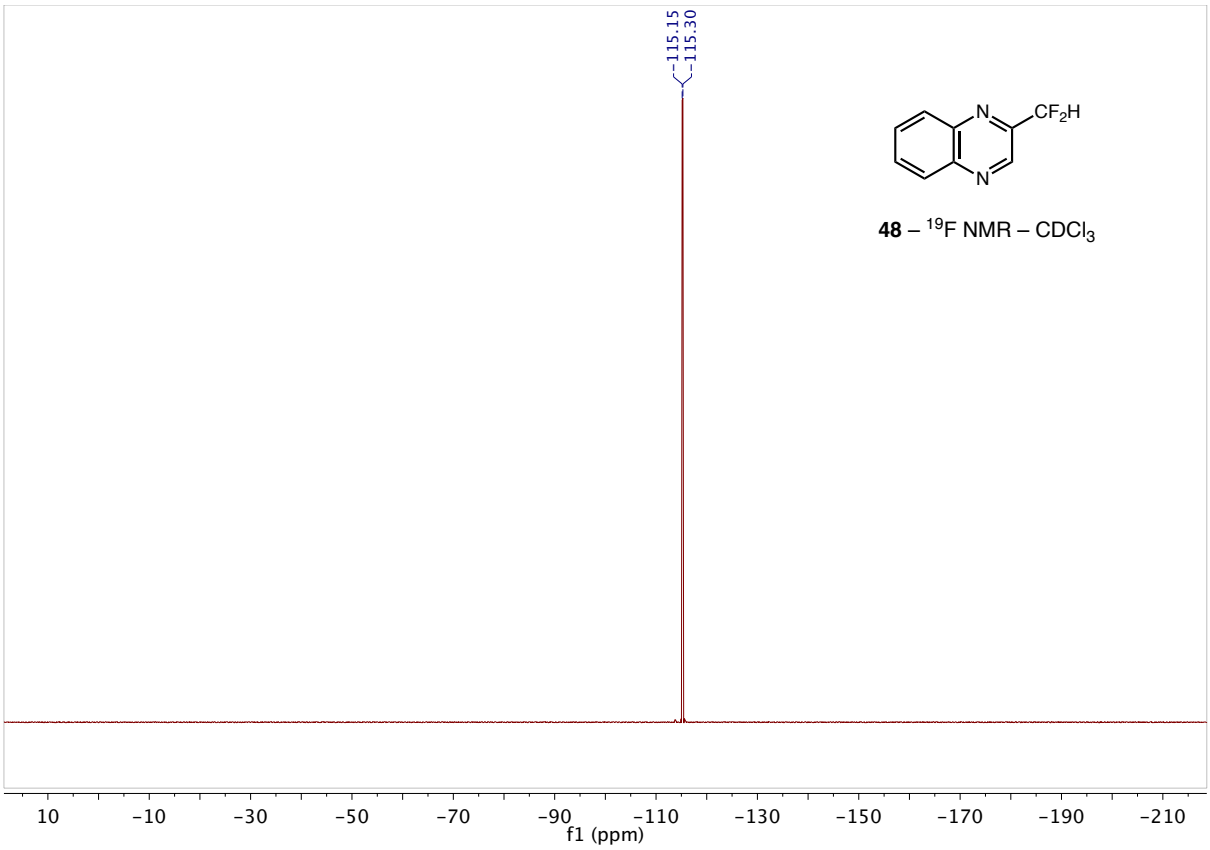
47 – ^{19}F NMR – $CDCl_3$



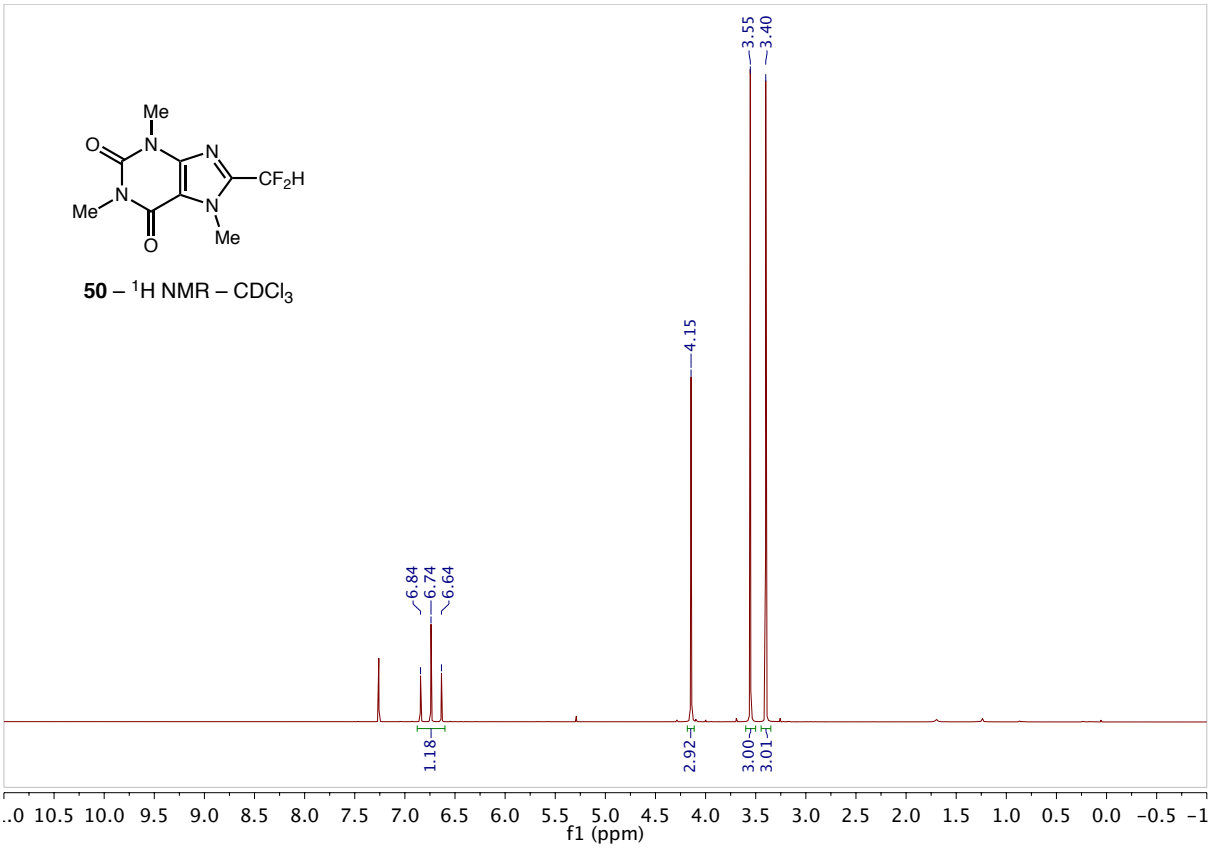
48 – ^{1}H NMR – $CDCl_3$



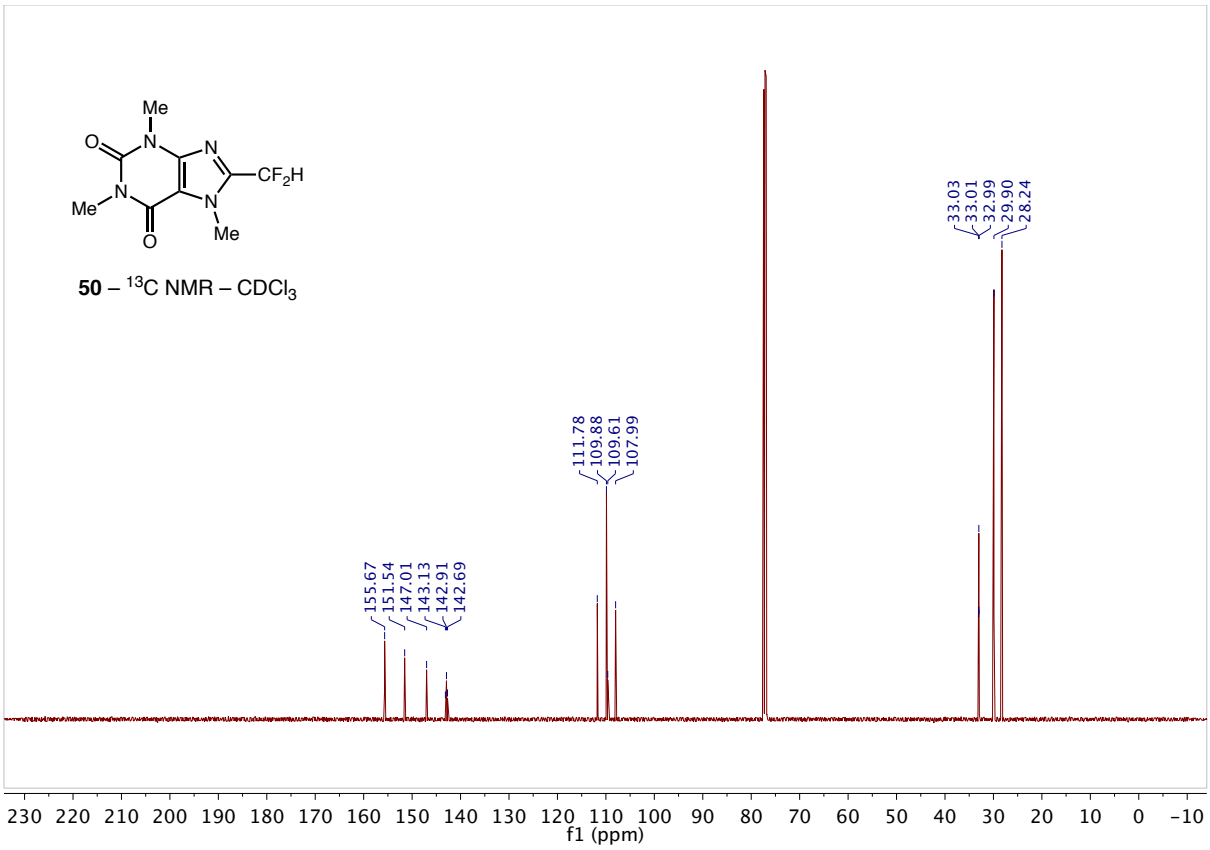
48 – ^{13}C NMR – $CDCl_3$



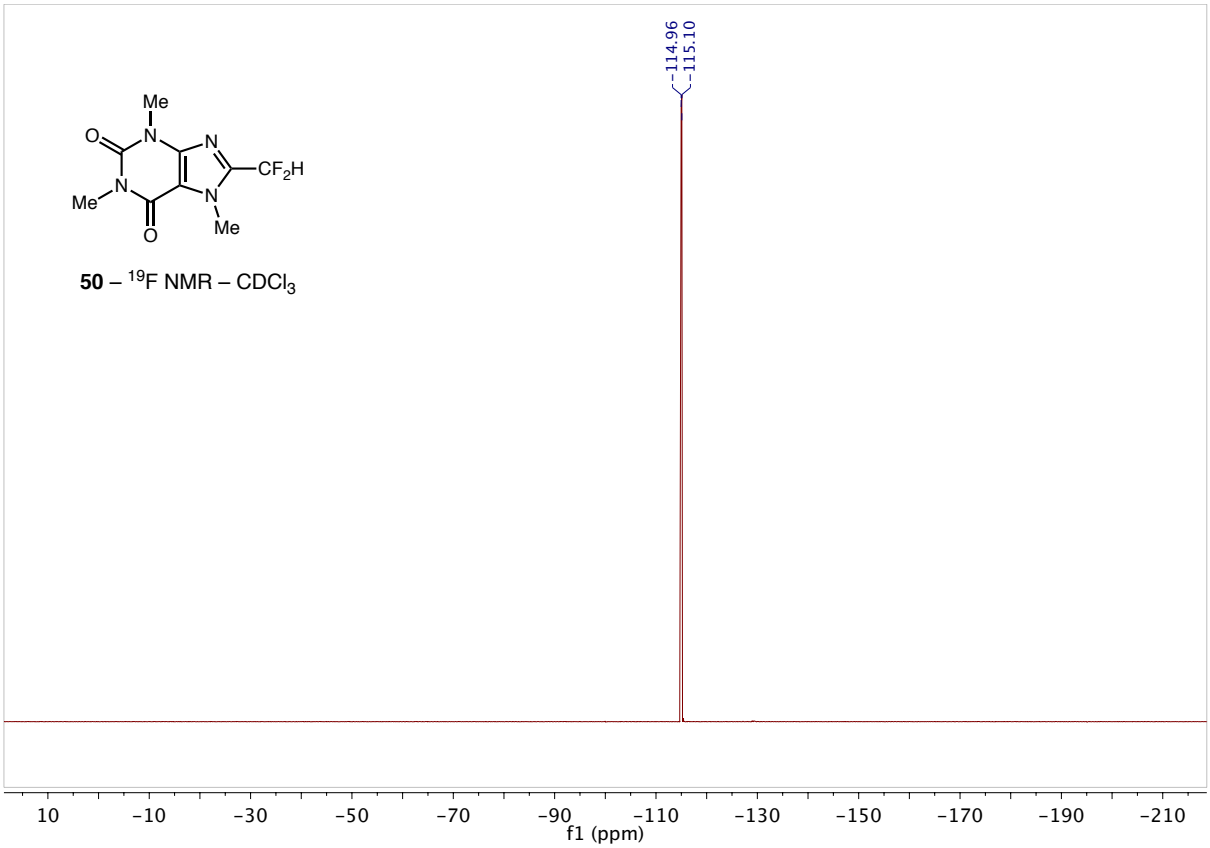
48 – ^{19}F NMR – $CDCl_3$



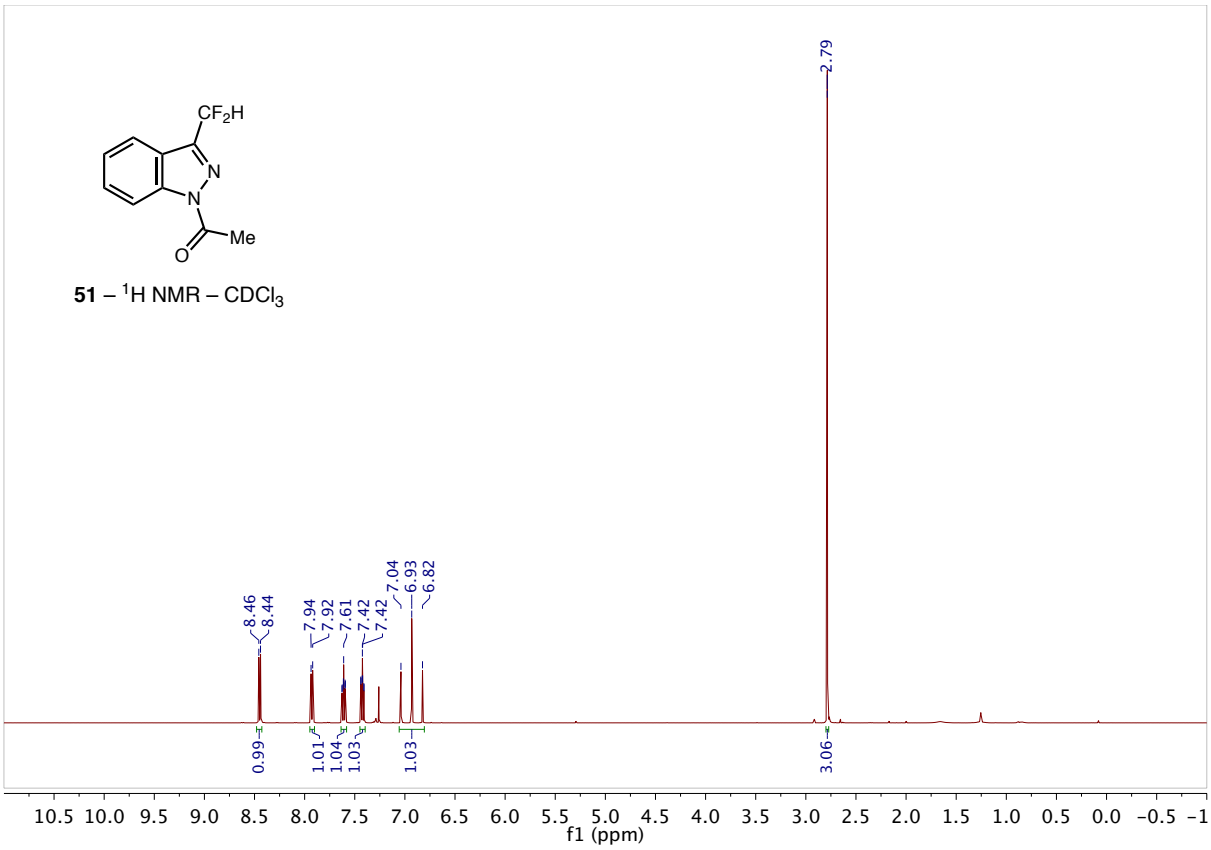
50 – ^{1}H NMR – $CDCl_3$



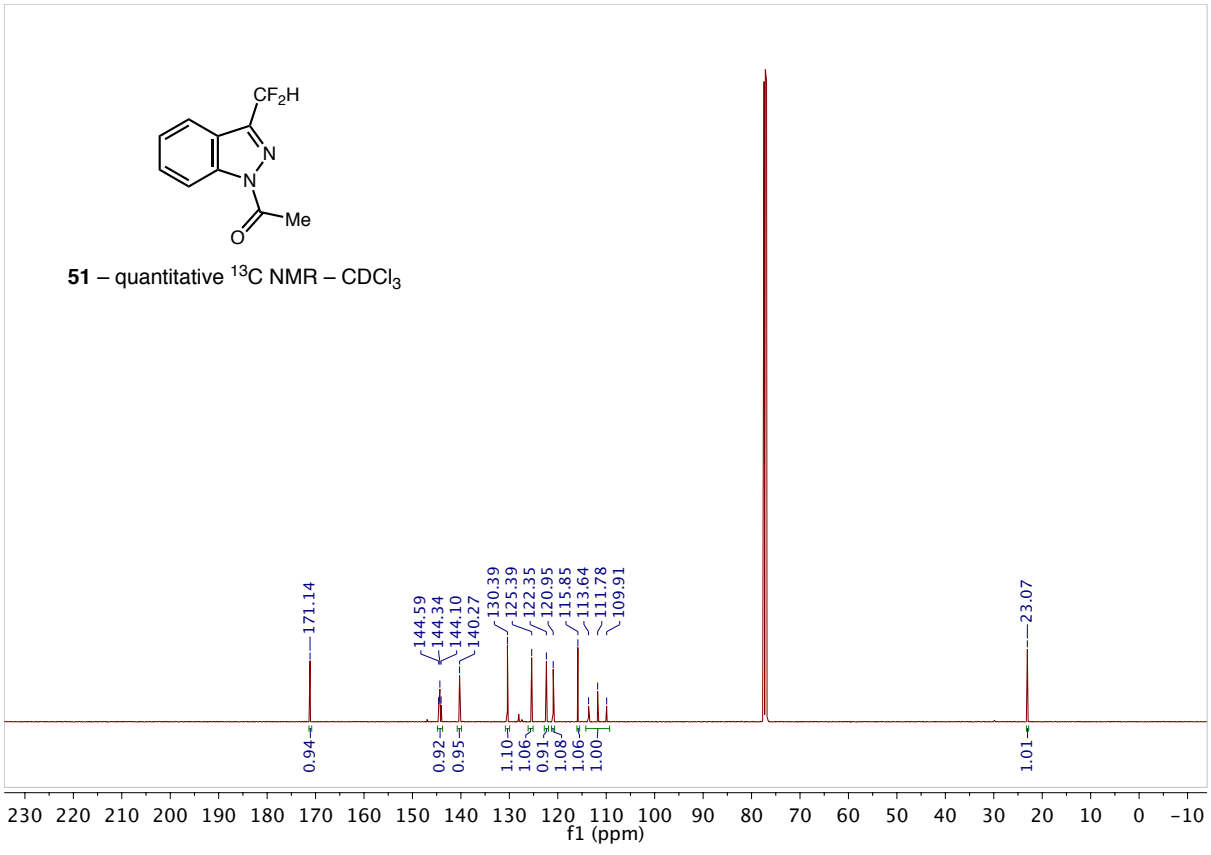
50 – ^{13}C NMR – $CDCl_3$



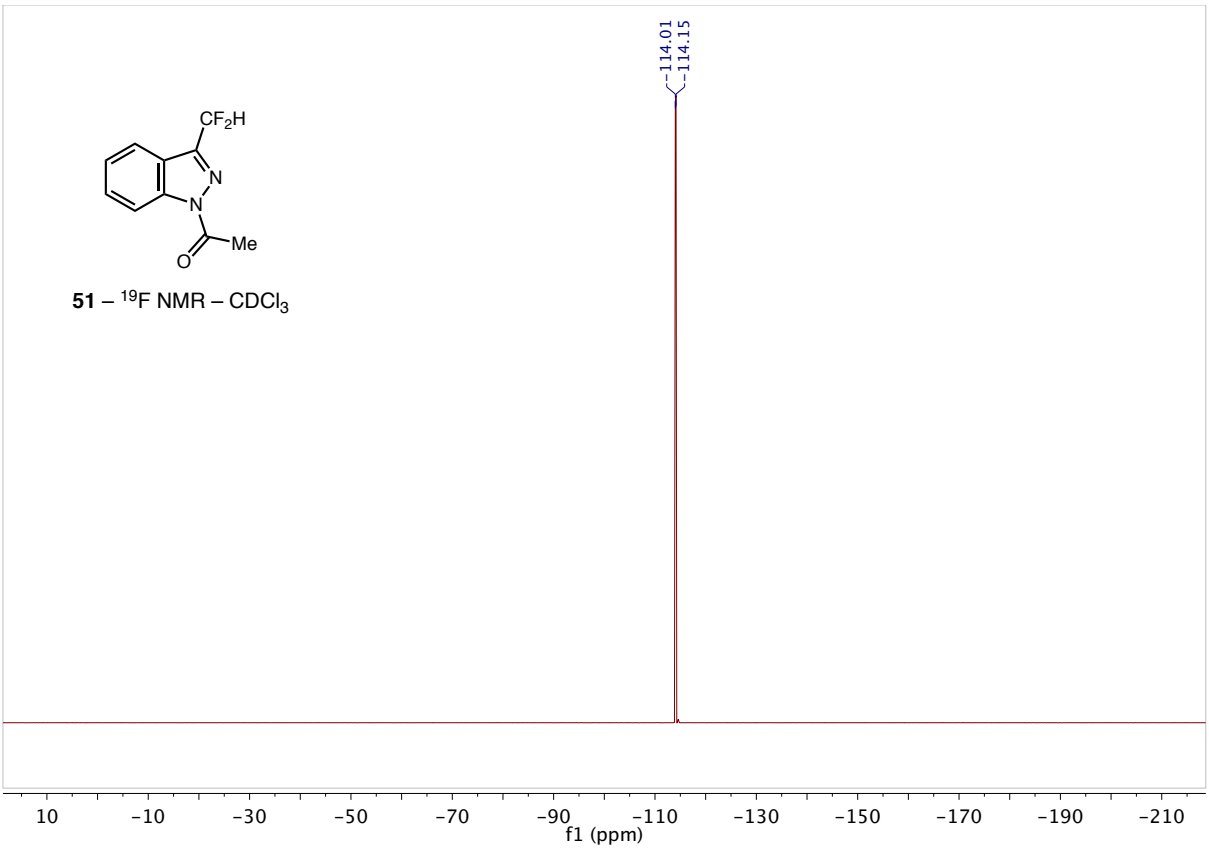
50 – ^{19}F NMR – $CDCl_3$



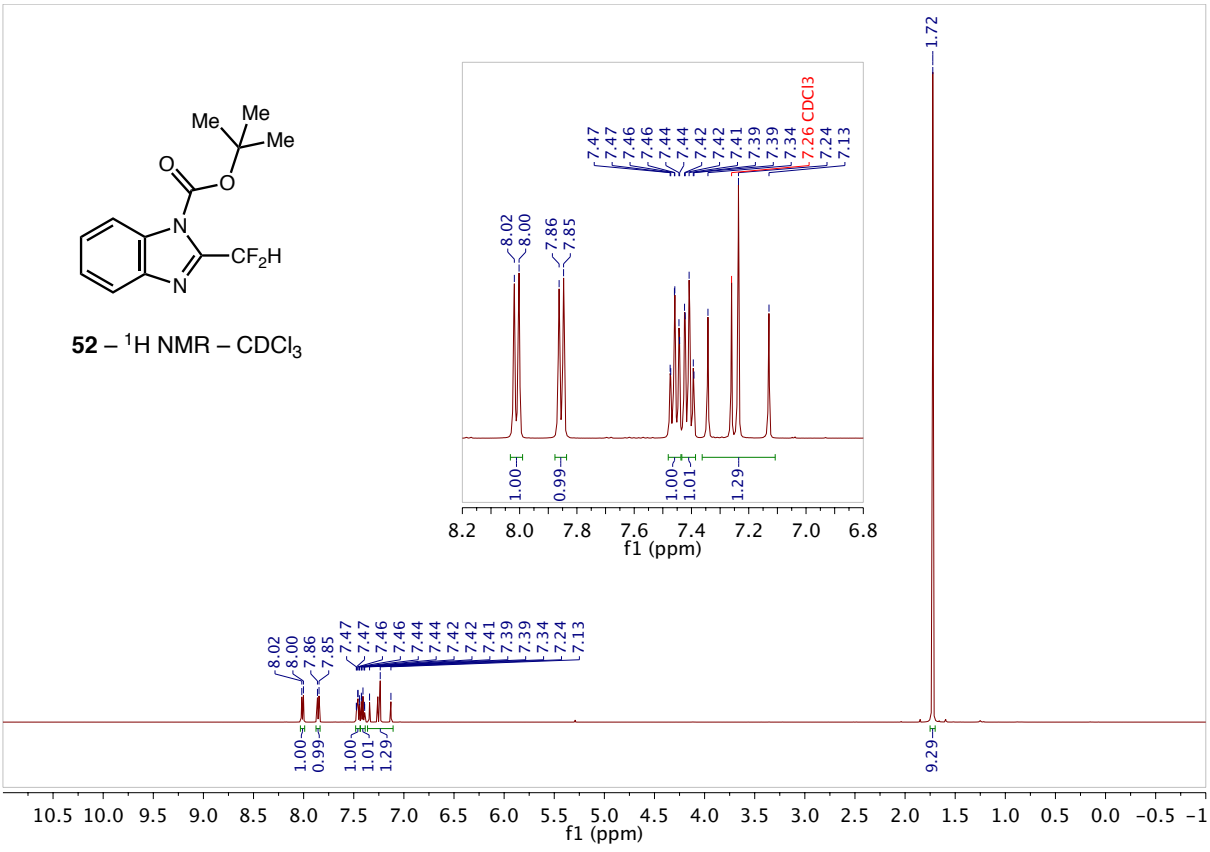
51 – ^{1}H NMR – $CDCl_3$



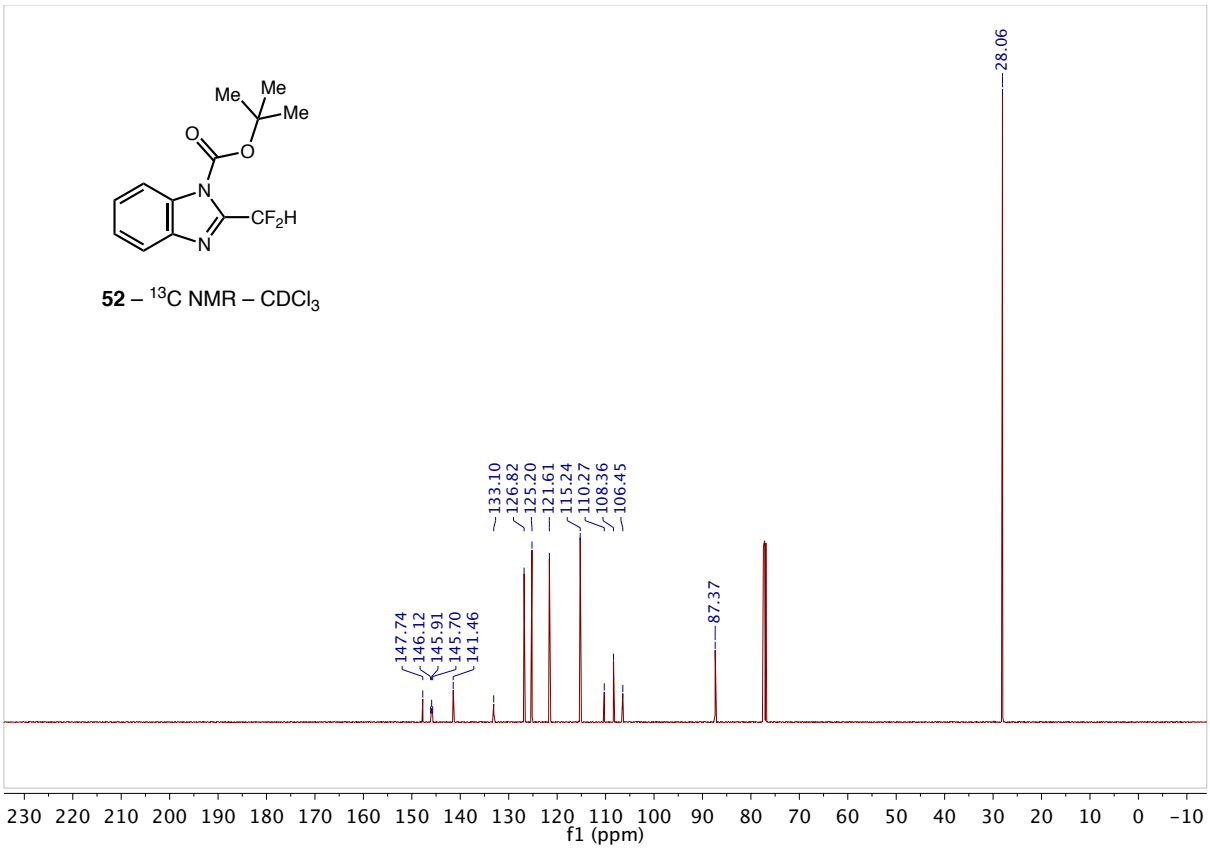
51 – quantitative ^{13}C NMR – $CDCl_3$



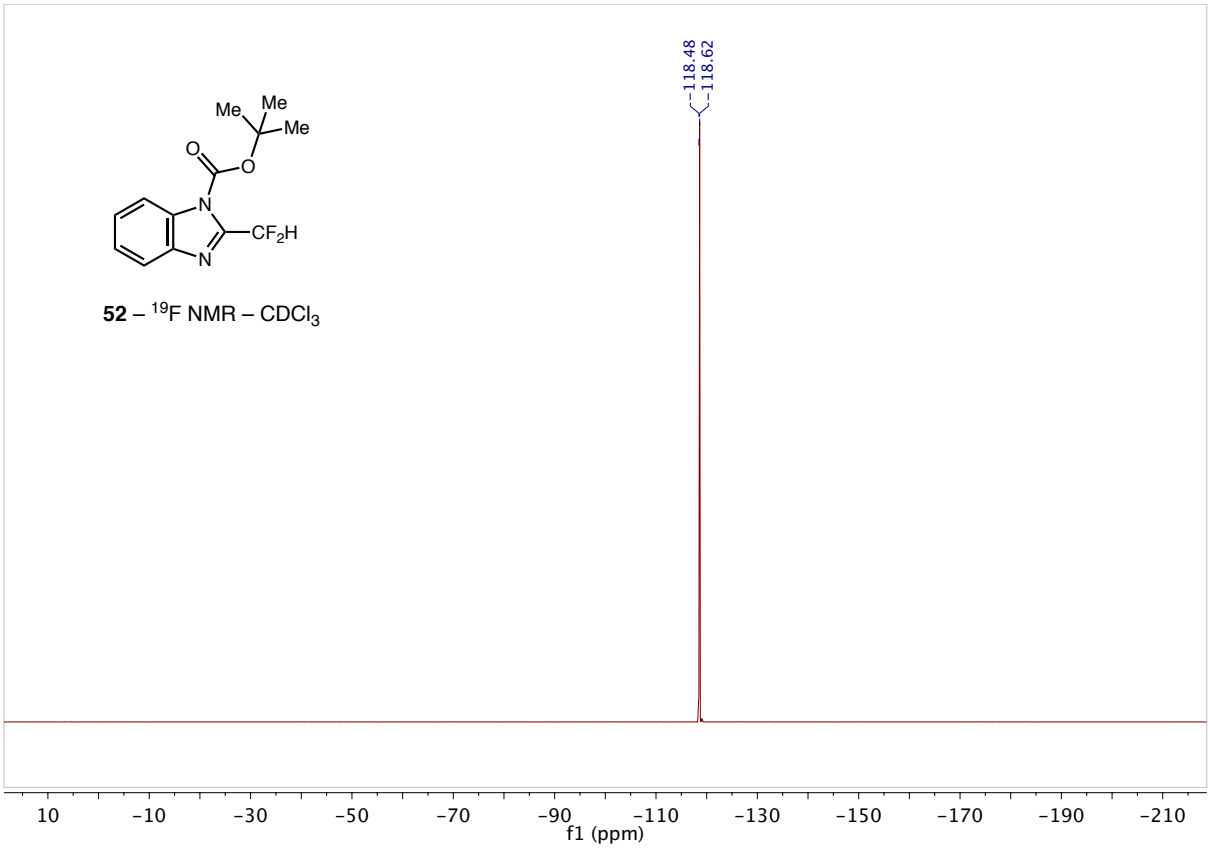
51 – ^{19}F NMR – $CDCl_3$



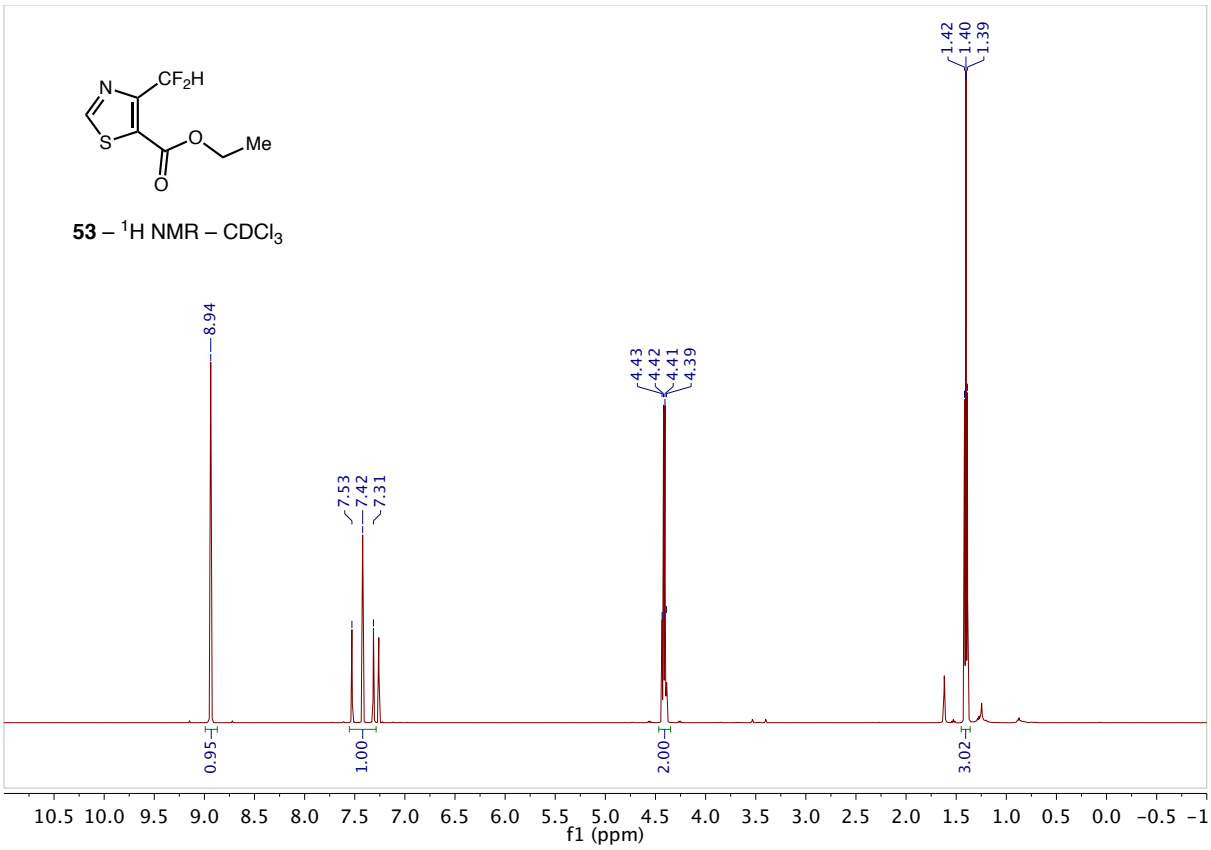
52 – ^{1}H NMR – $CDCl_3$

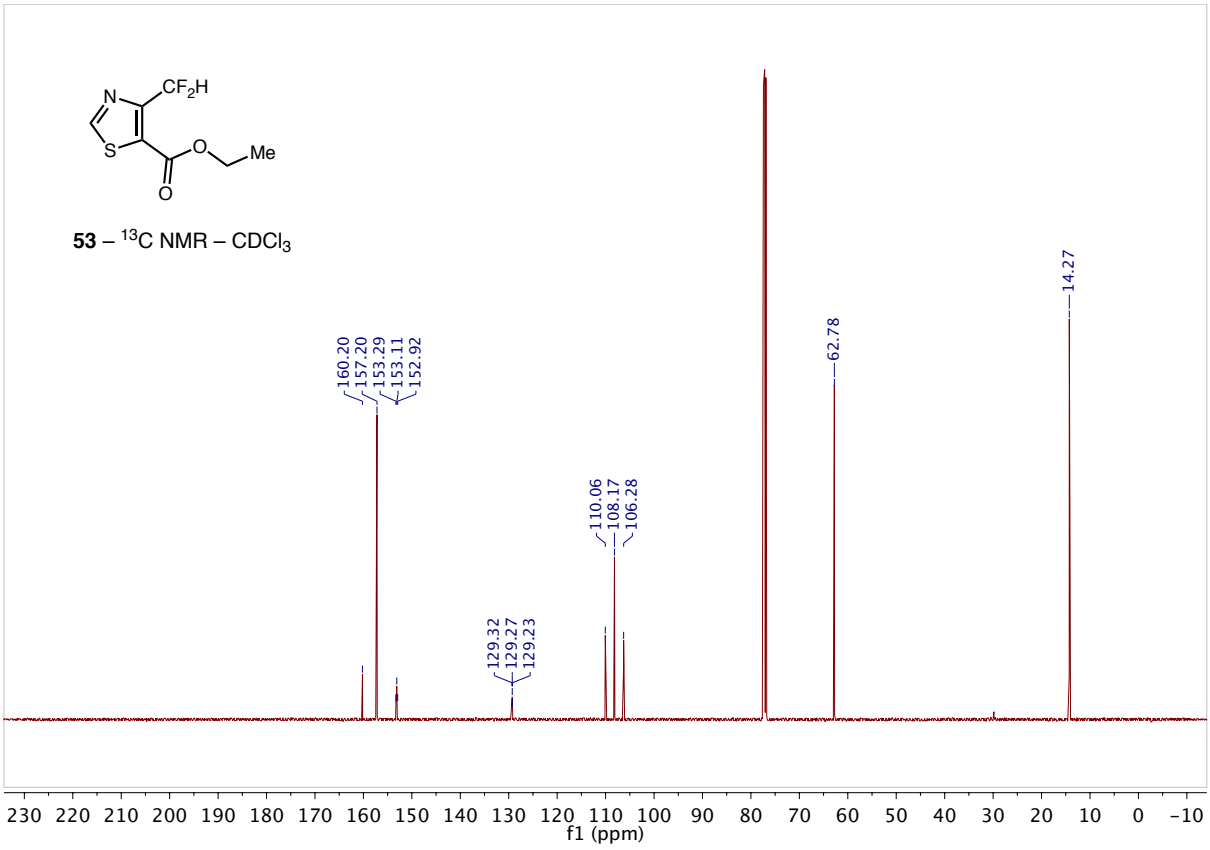


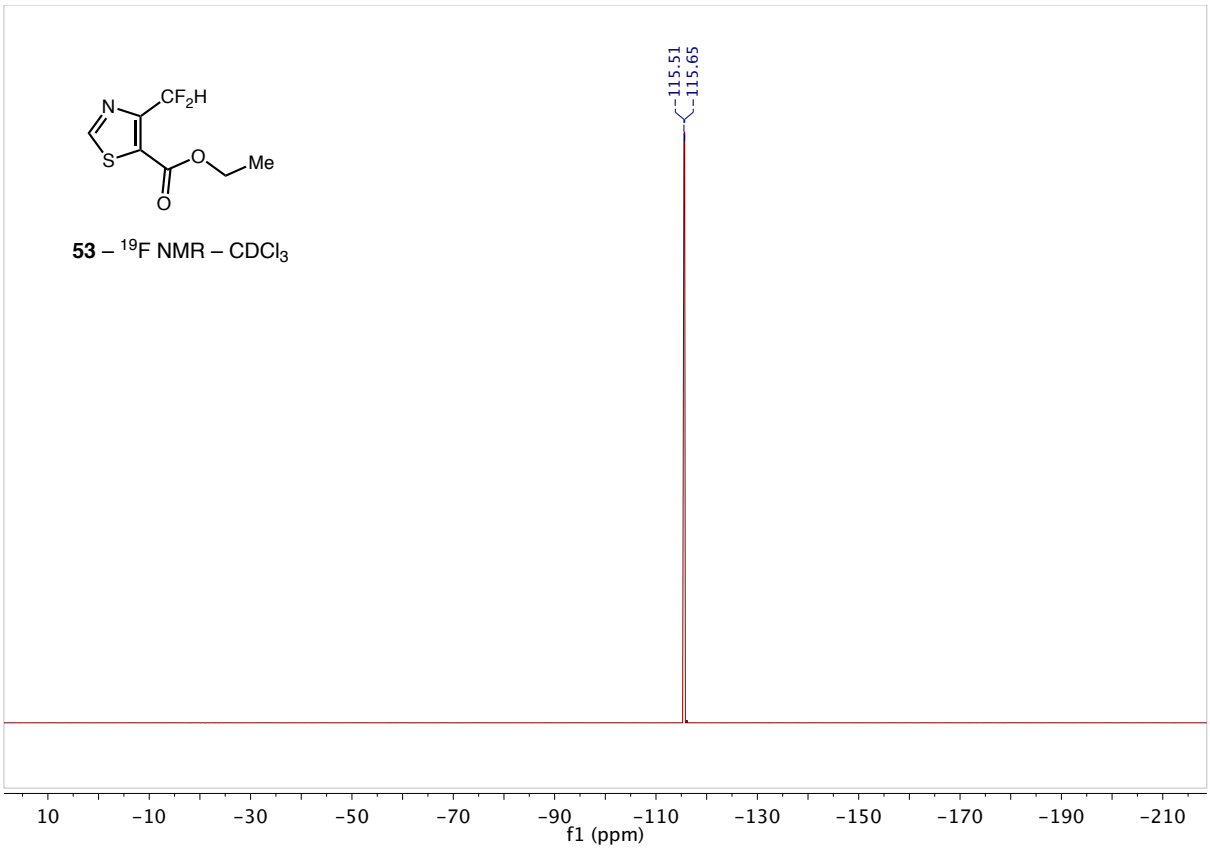
52 – ^{13}C NMR – $CDCl_3$



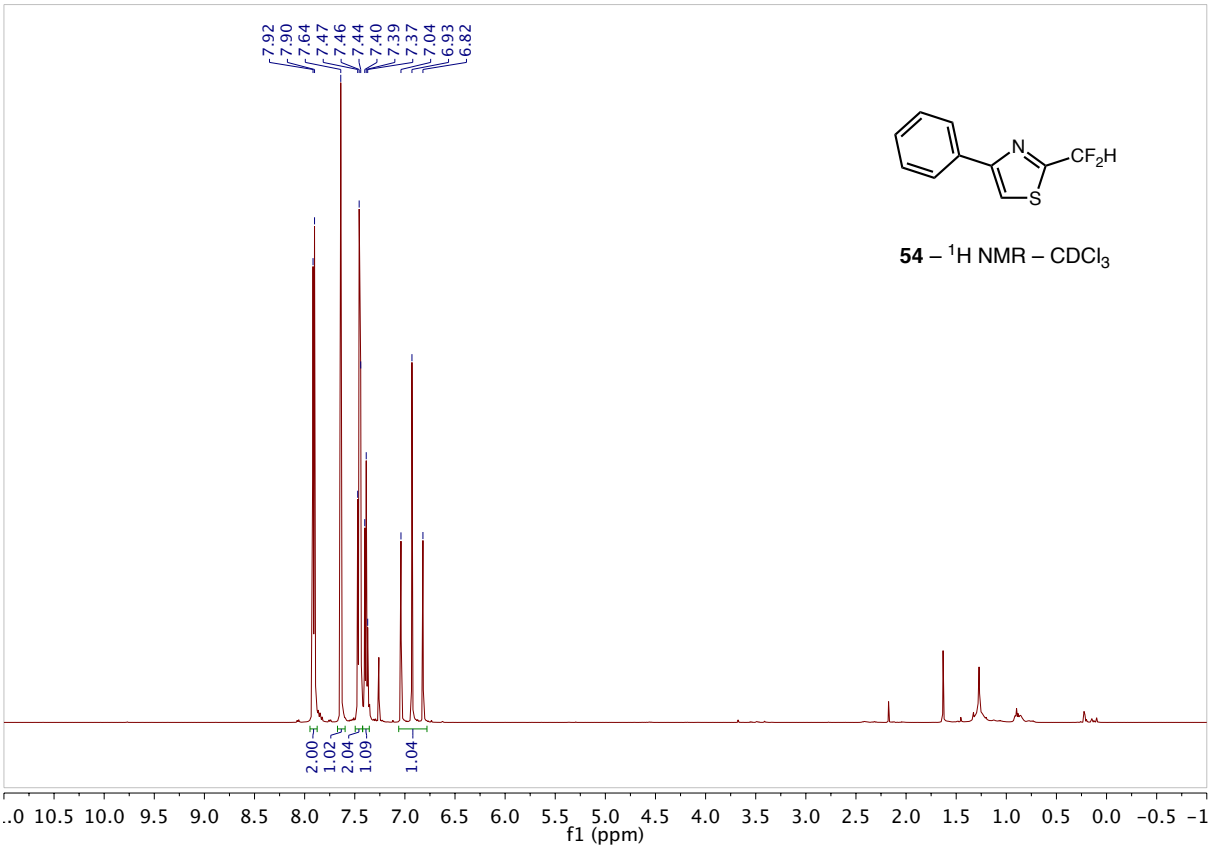
52 – ^{19}F NMR – $CDCl_3$


CF2H
N
S
O
O
Me
53 – 1H NMR – CDCl3
8.94
7.53
7.42
7.31
4.43
4.42
4.41
4.39
1.42
1.40
1.39
0.95
1.00
2.00
3.02
f1 (ppm)

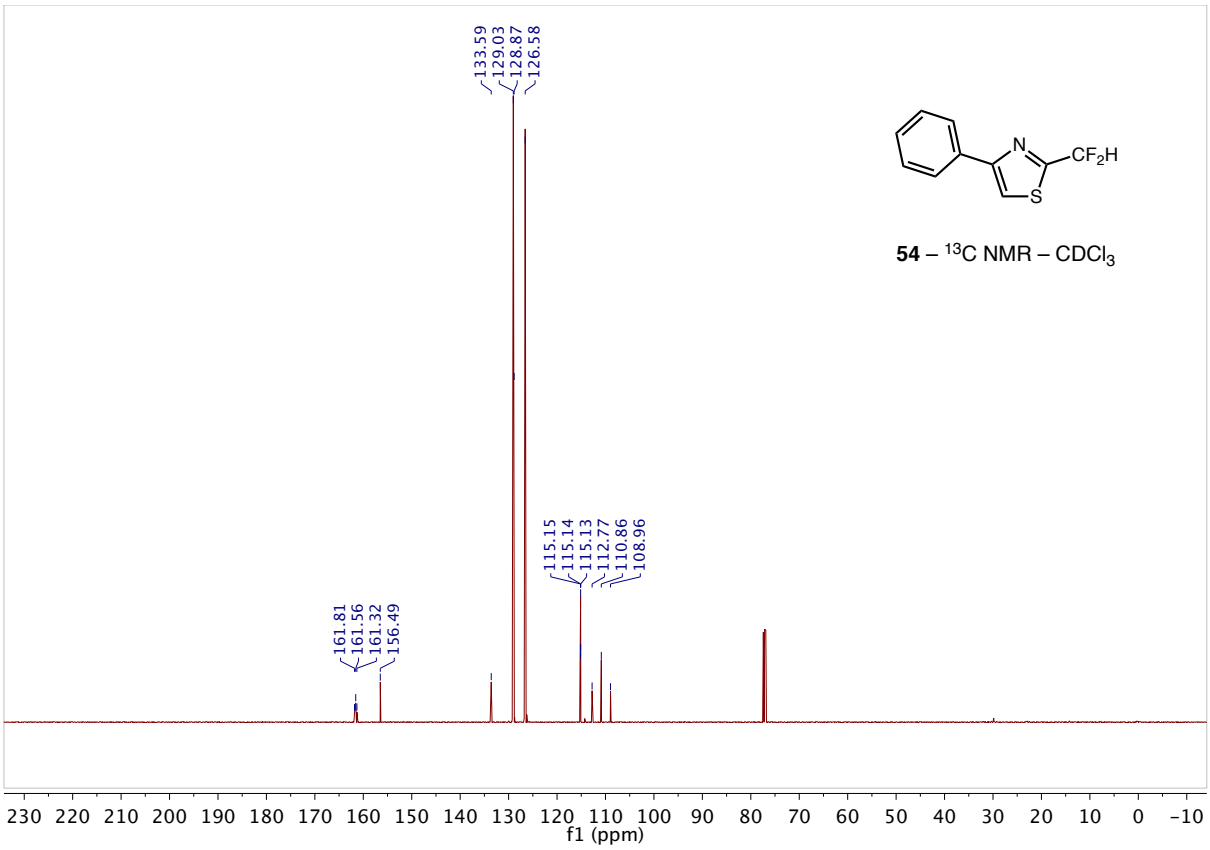

CF2H
N
S
O
O
Me
53 – 13C NMR – CDCl3
160.20
157.20
153.29
153.11
152.92
129.32
129.27
129.23
110.06
108.17
106.28
62.78
14.27
f1 (ppm)



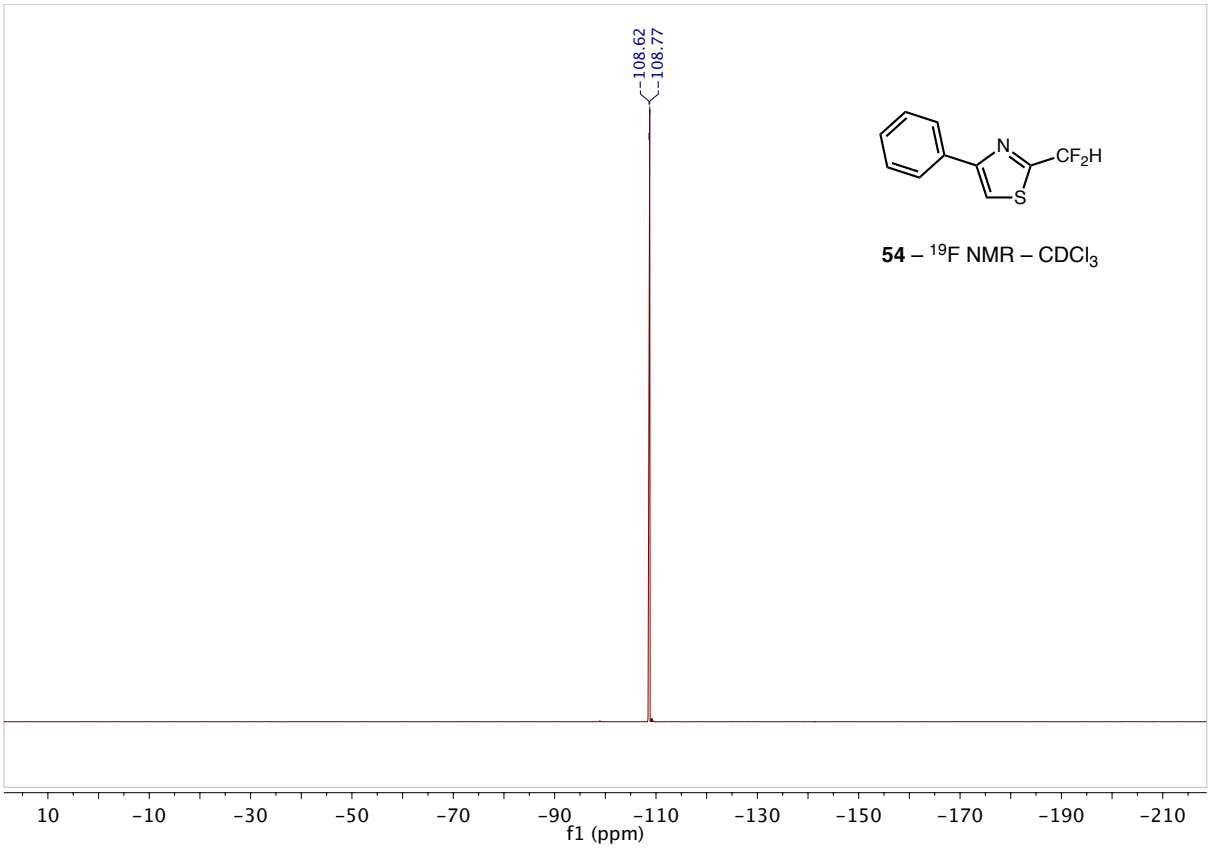
53 – ^{19}F NMR – $CDCl_3$



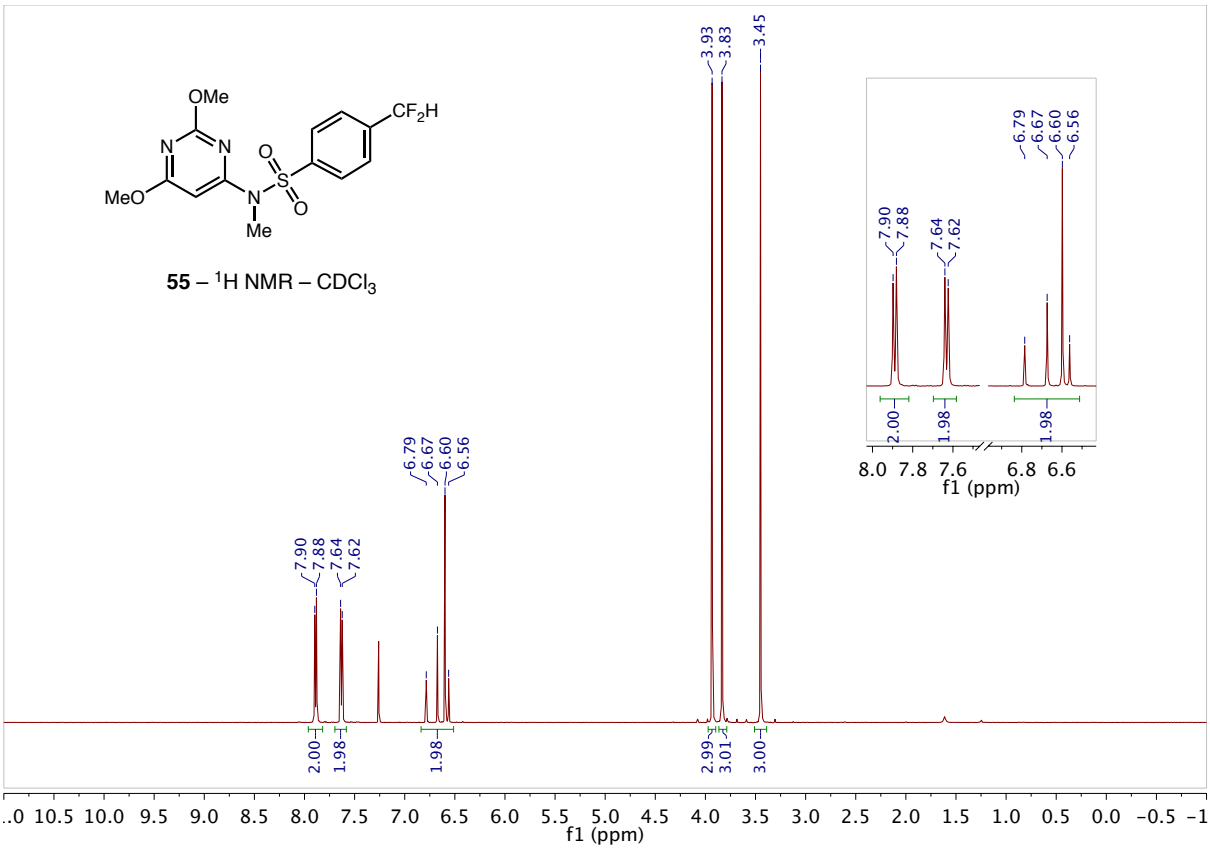
54 – ^{1}H NMR – $CDCl_3$

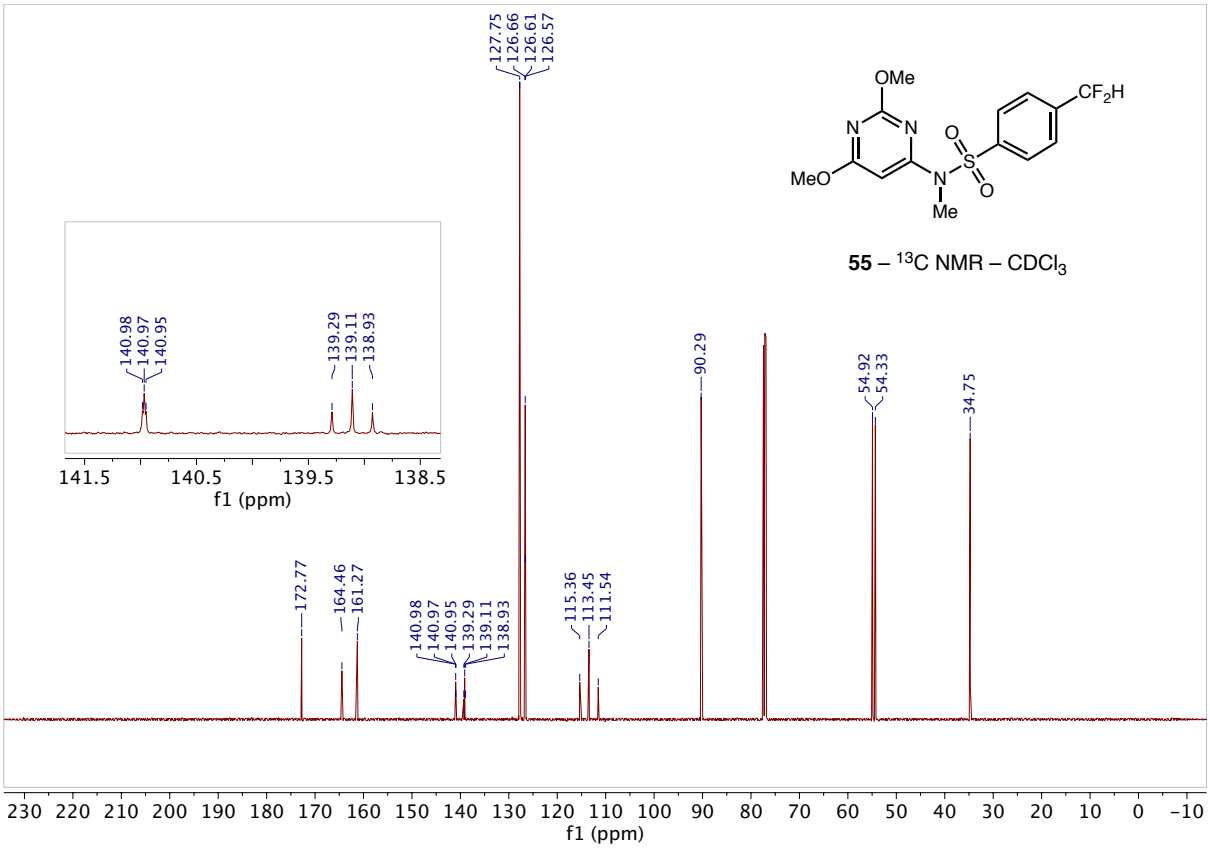


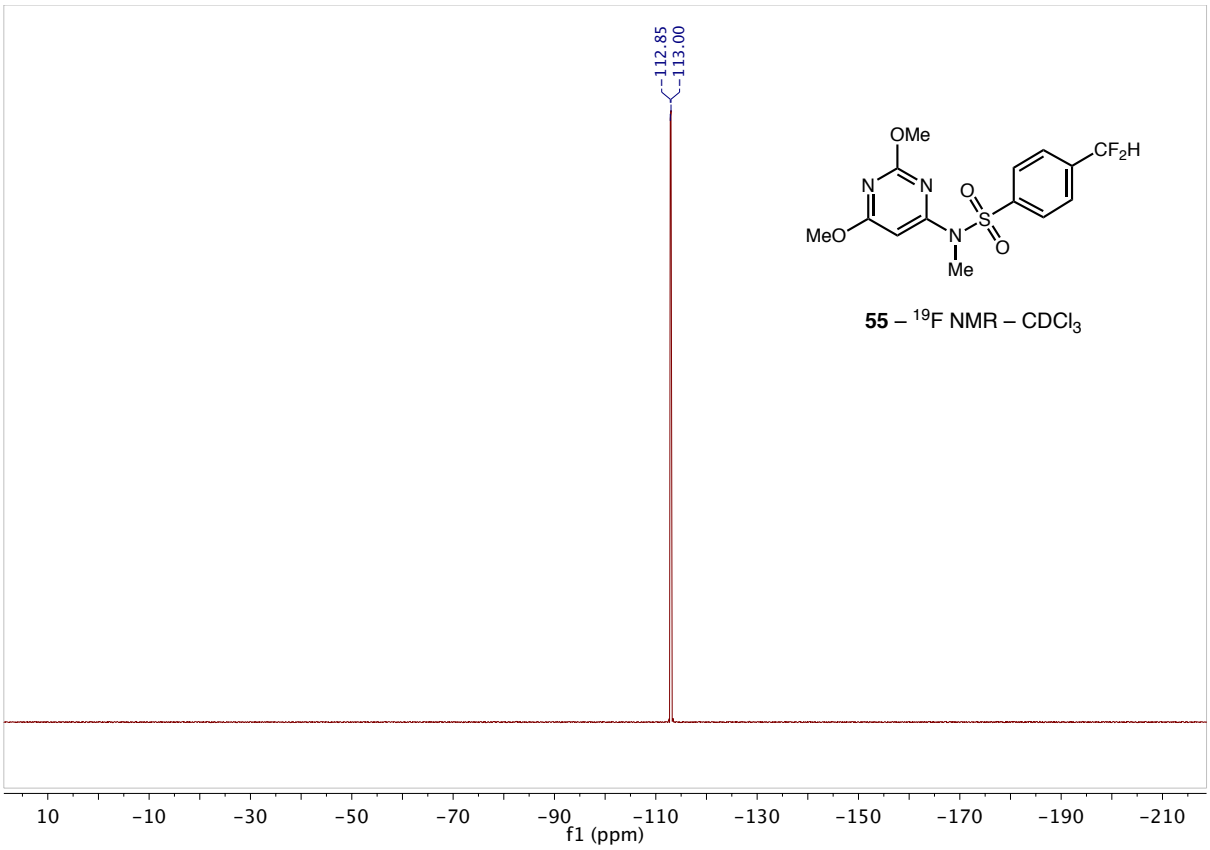
54 – ^{13}C NMR – $CDCl_3$



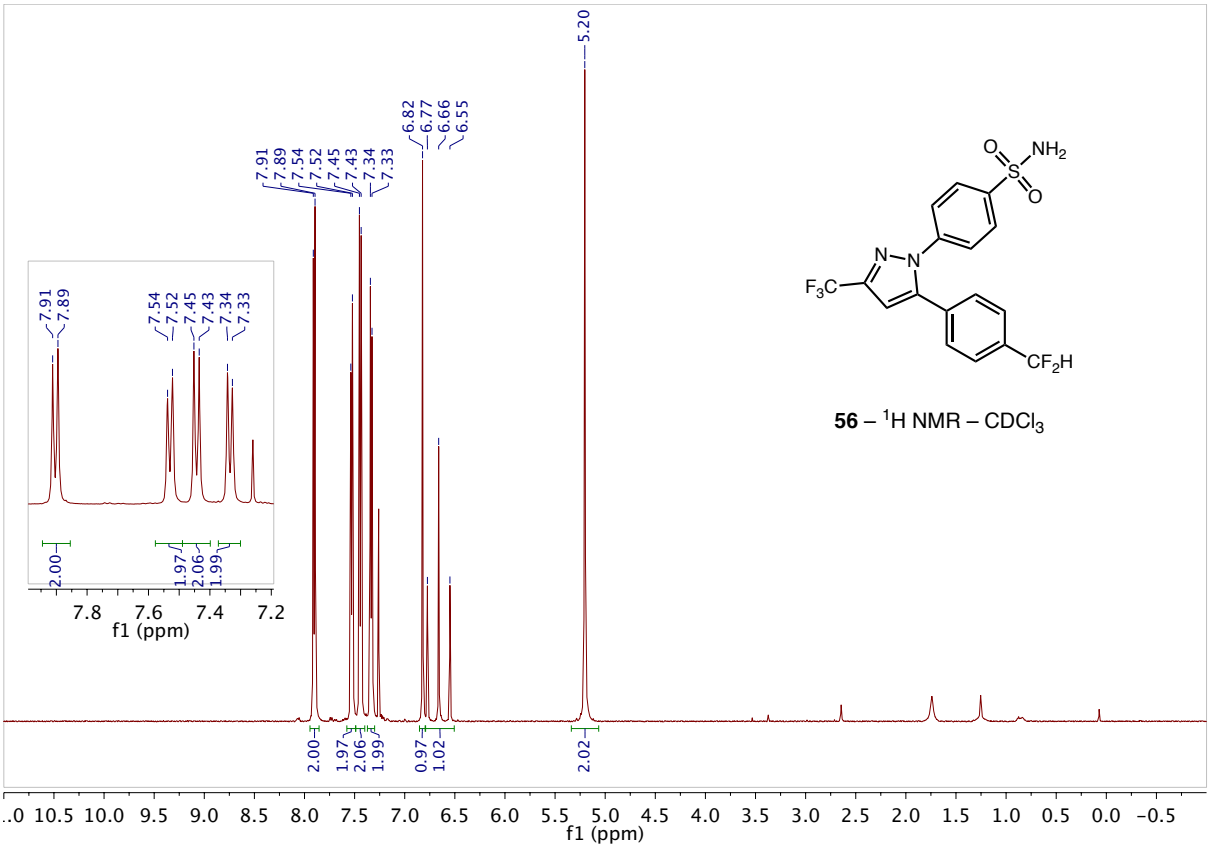
54 – ^{19}F NMR – $CDCl_3$


OMe
N
N
MeO
O
S
O
N
Me
CF2H
55 – 1H NMR – CDCl3
3.93
3.83
3.45
6.79
6.67
6.60
6.56
7.90
7.88
7.64
7.62
2.00
1.98
1.98
2.99
3.01
3.00
f1 (ppm)

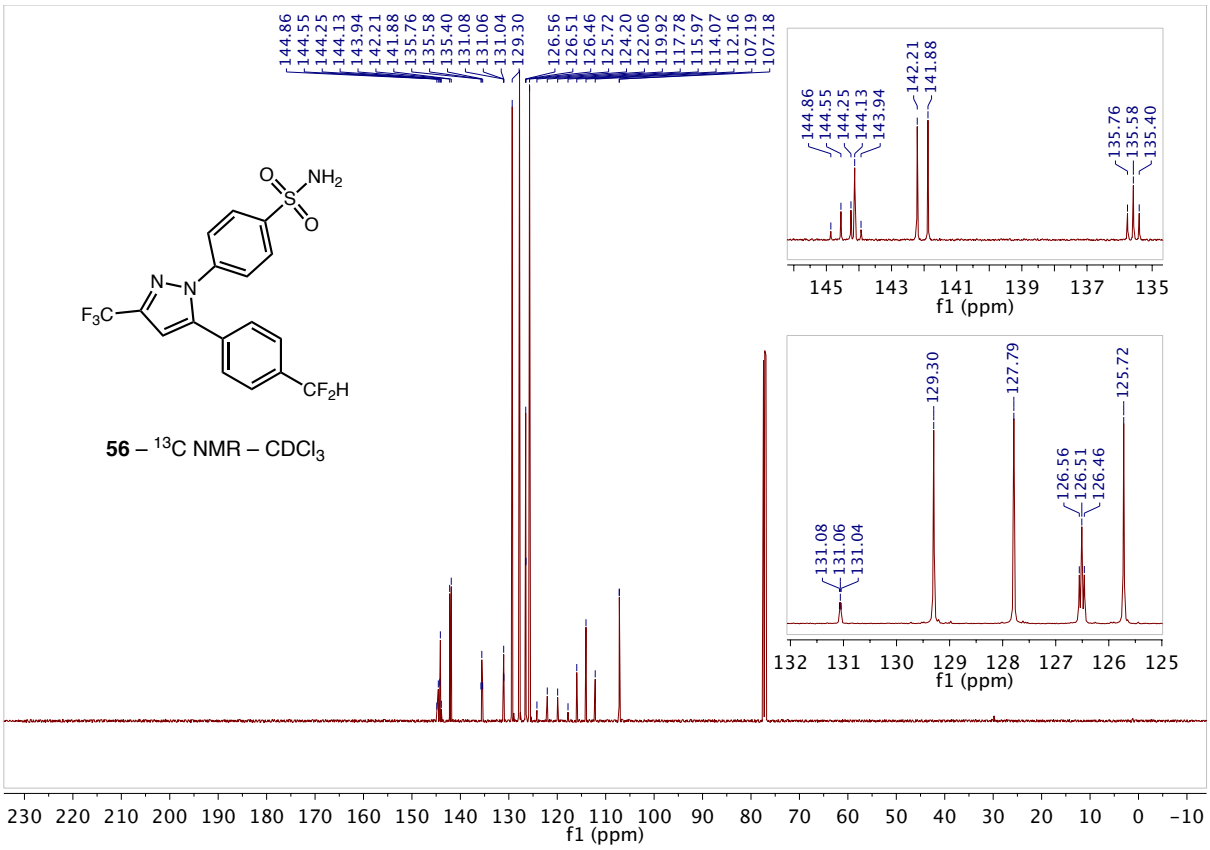

127.75
126.66
126.61
126.57
OMe
N
N
MeO
O
S
O
N
Me
CF2H
55 – 13C NMR – CDCl3
140.98
140.97
140.95
139.29
139.11
138.93
f1 (ppm)
90.29
54.92
54.33
34.75
172.77
164.46
161.27
140.98
140.97
140.95
139.29
139.11
138.93
115.36
113.45
111.54
f1 (ppm)



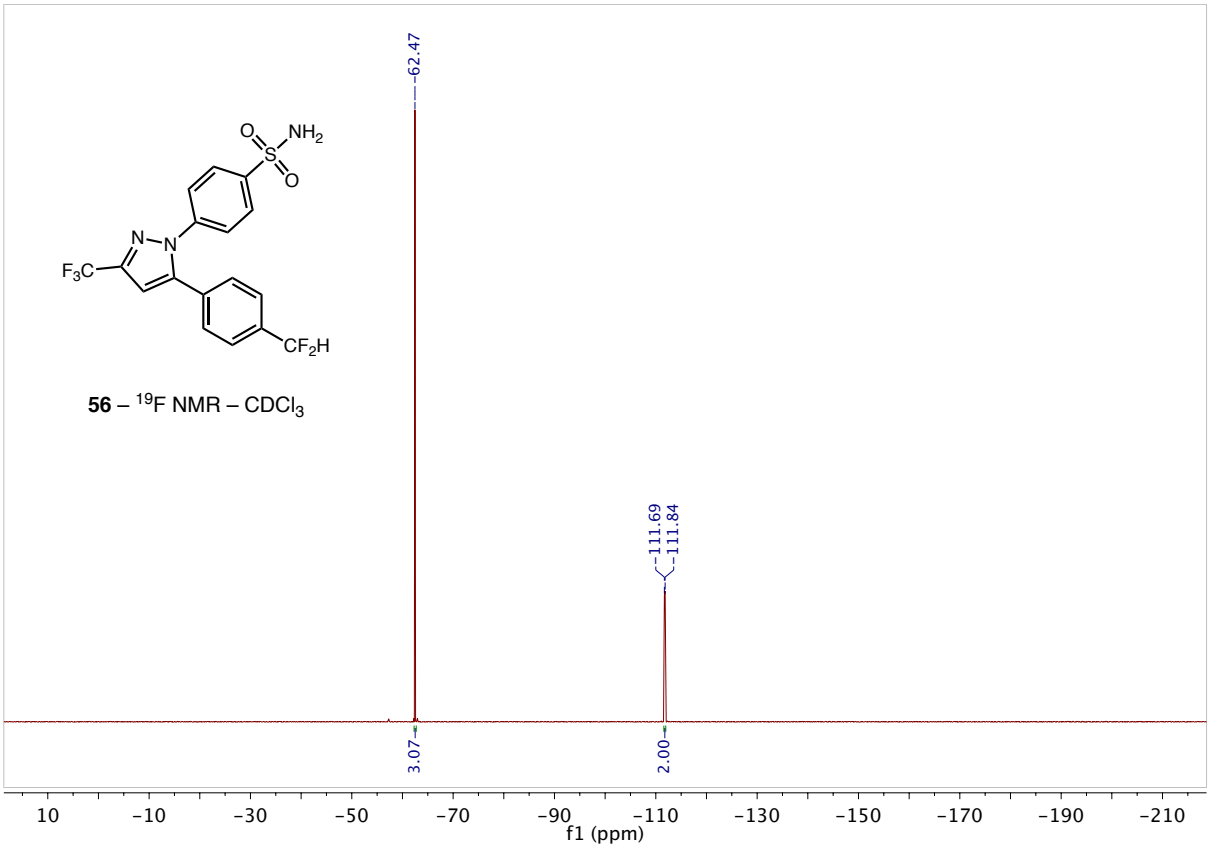
55 – ^{19}F NMR – $CDCl_3$



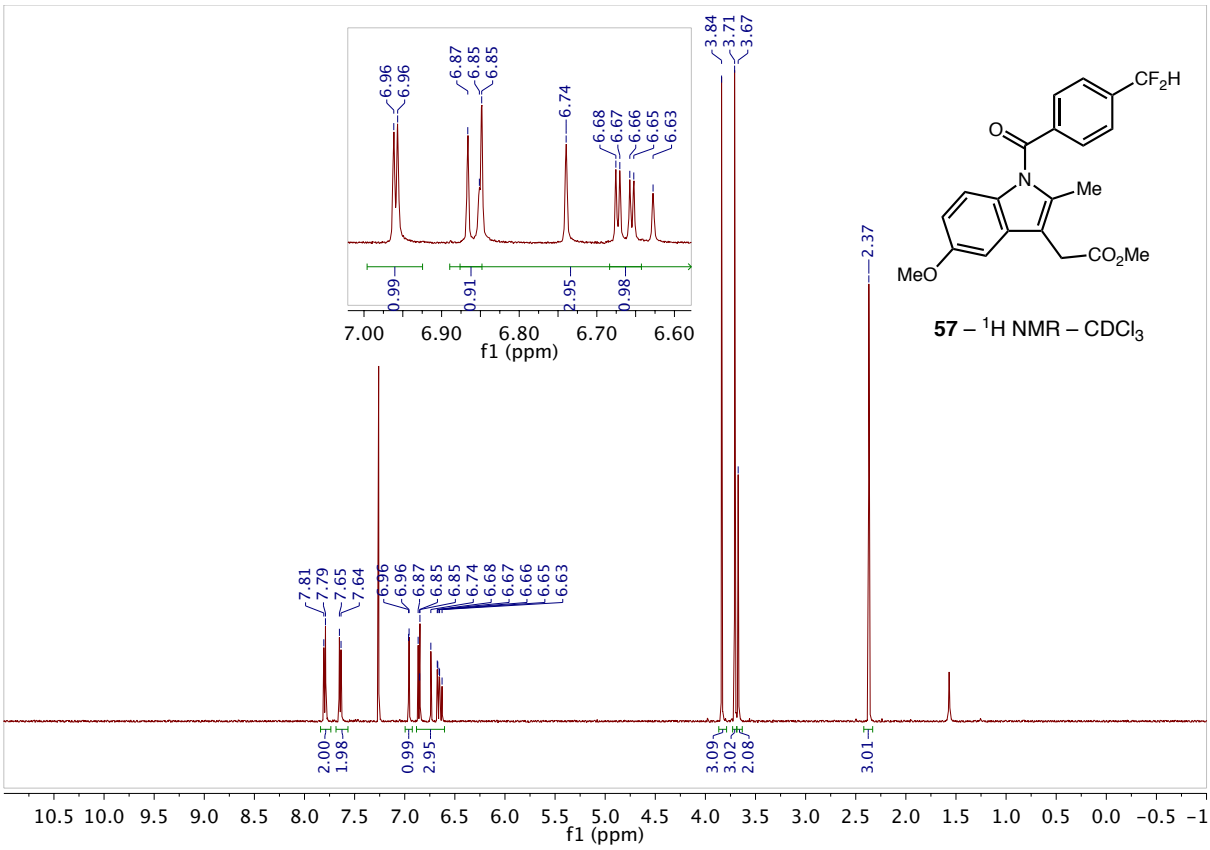
56 – ^{1}H NMR – $CDCl_3$

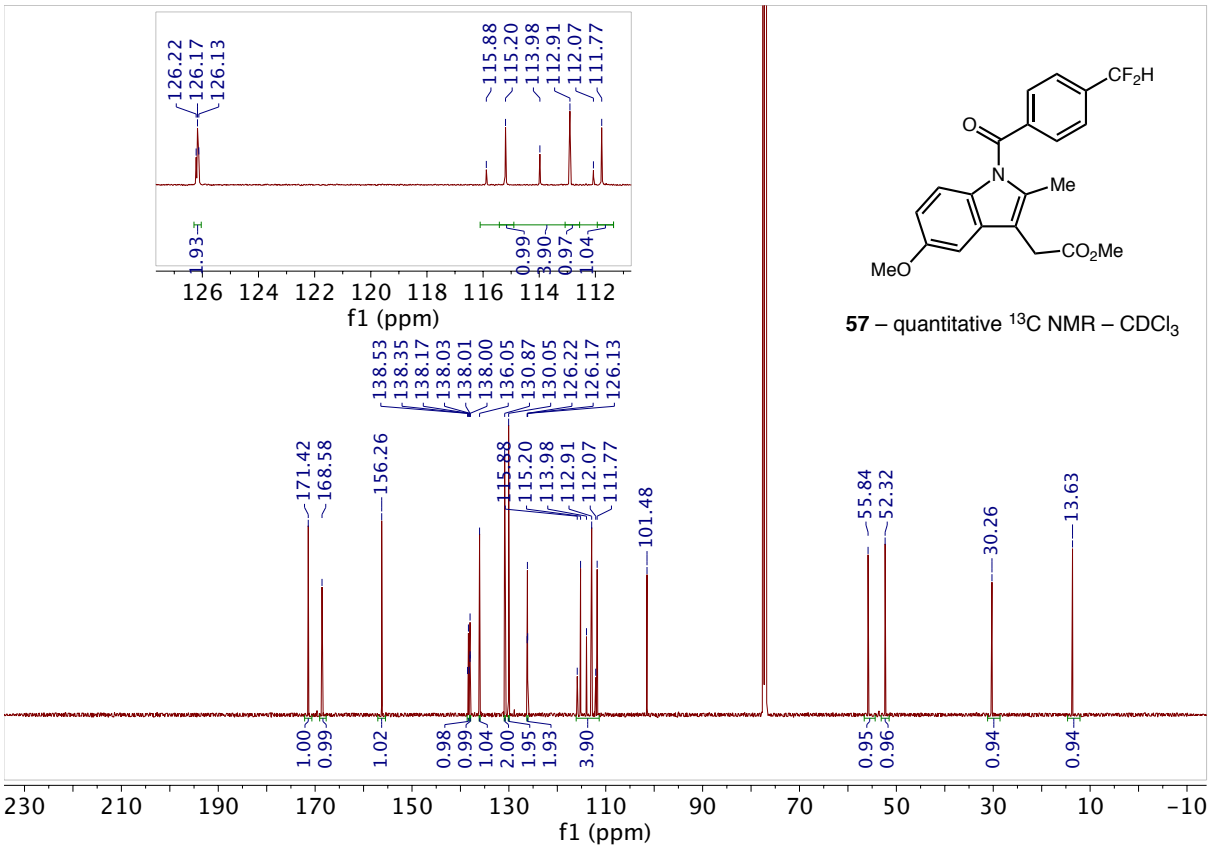


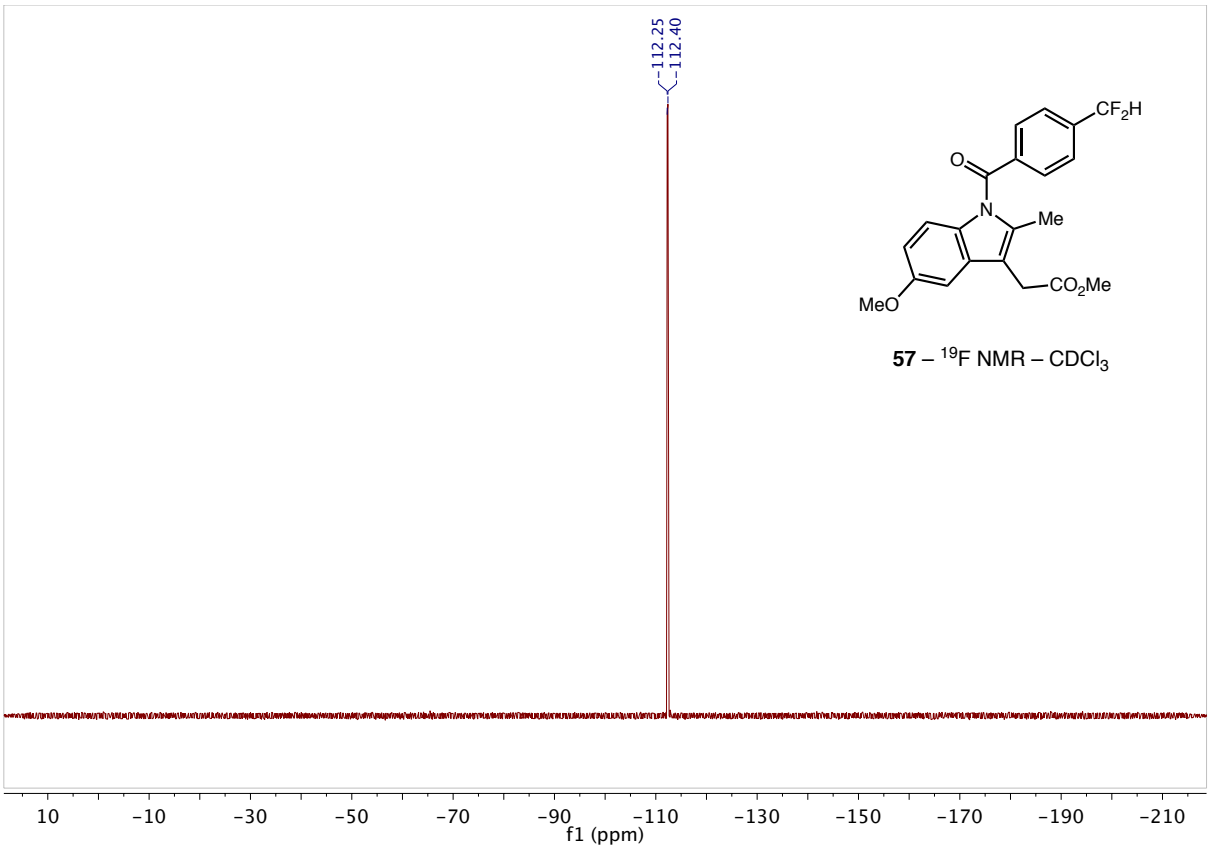
56 – ^{13}C NMR – $CDCl_3$



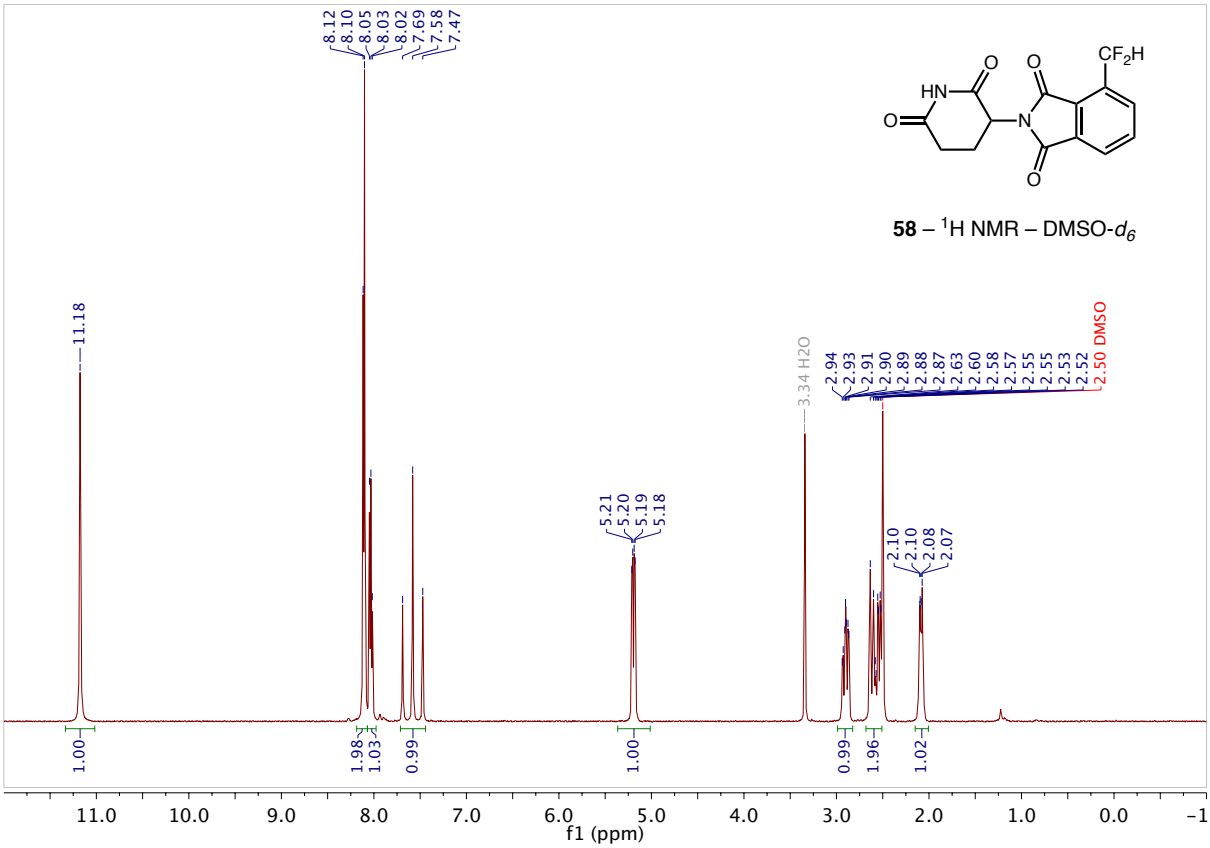
56 – ^{19}F NMR – $CDCl_3$


CF2H
O
N
Me
CO2Me
MeO
57 – 1H NMR – CDCl3
f1 (ppm)

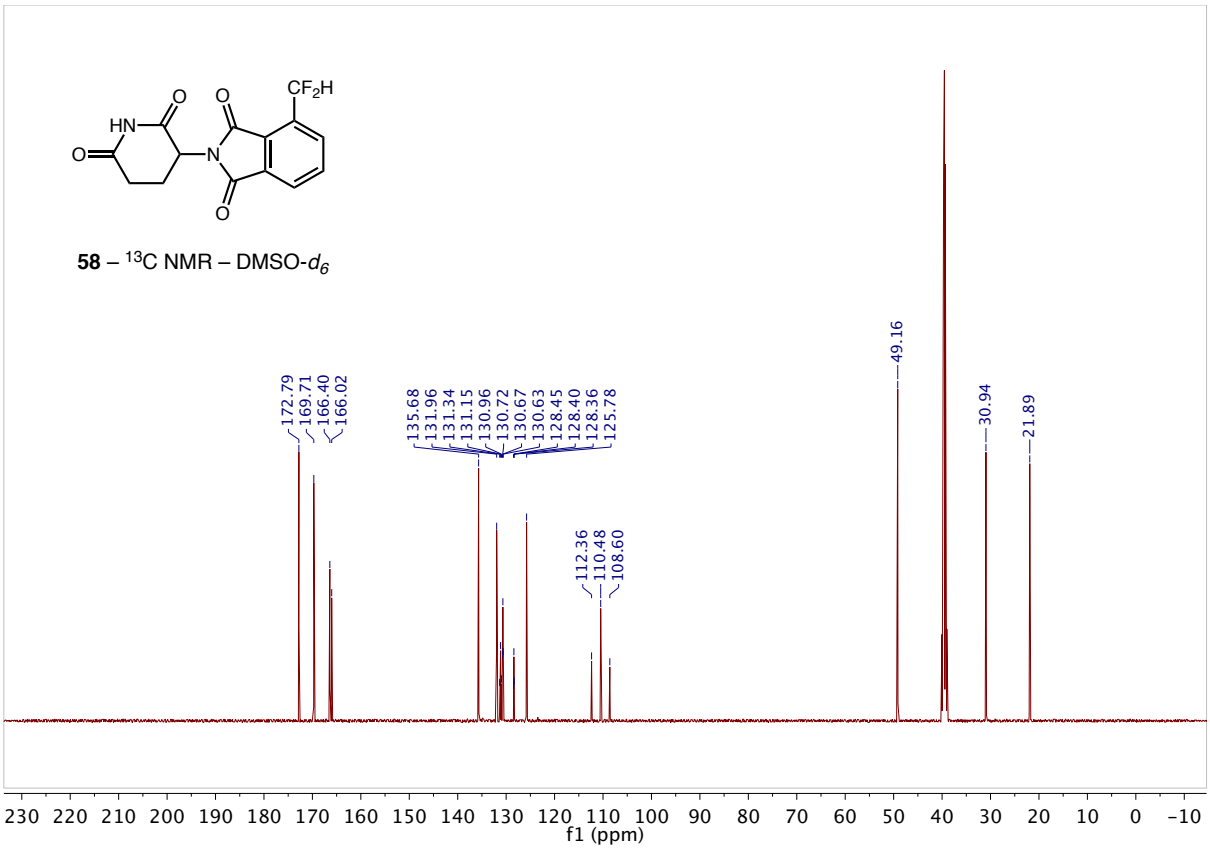

CF2H
O
N
Me
CO2Me
MeO
57 – quantitative 13C NMR – CDCl3
f1 (ppm)

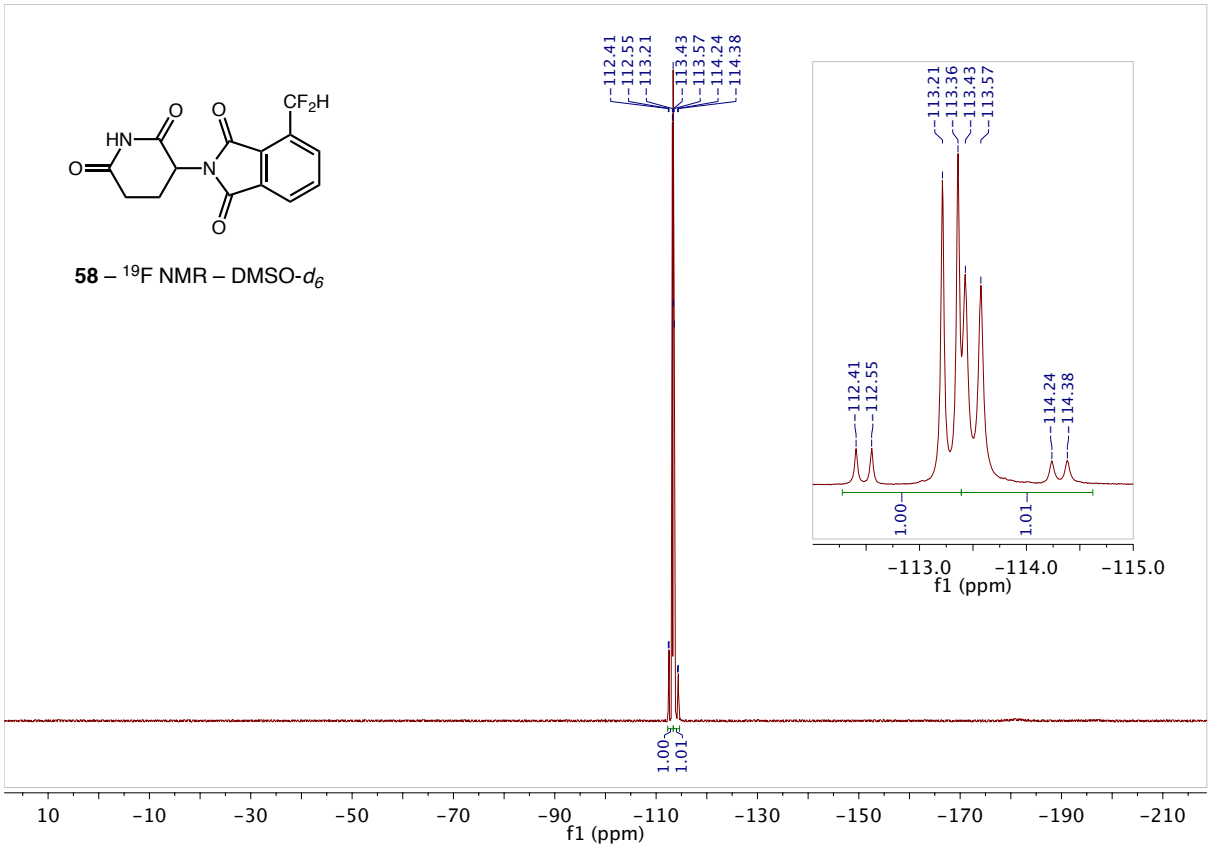


57 – ^{19}F NMR – $CDCl_3$



58 – ^{1}H NMR – DMSO-d_6


CF2H
HN
O
N
O
O
O
58 – 13C NMR – DMSO-d6
172.79
169.71
166.40
166.02
135.68
131.96
131.34
131.15
130.96
130.72
130.67
130.63
128.45
128.40
128.36
125.78
112.36
110.48
108.60
49.16
30.94
21.89
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CF2H
HN
O
N
O
O
O
58 – 19F NMR – DMSO-d6
-112.41
-112.55
-113.21
-113.43
-113.57
-114.24
-114.38
1.00
1.01
-113.21
-113.36
-113.43
-113.57
-112.41
-112.55
-114.24
-114.38
1.00
1.01
-113.0
-114.0
-115.0
f1 (ppm)
10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210
f1 (ppm)

11) References Cited

[1] Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, Jr., R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.

[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[3] Still, W. C.; Kahn, M; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[4] Kalgutkar, A. S.; Crews, B. C.; Saleh, S.; Prudhomme, D.; Marnett, L. *J. Bioorg. Med. Chem*. **2005**, *13*, 6810.

[5] Zhou, B.; Hu, J.; Xu, F.; Chen, Z.; Bai, L.; Fernandez-Salas, E.; Lin, M.; Liu, L.; Yang, C.-Y.; Zhao, Y; McEachern, D.; Przybranowski, S.; Wen, B.; Sun, D.; Wang, S. *J. Med. Chem.* **2018**, *61*, 462.

[6] Heijnen, D.; Tosi, F.; Vila, D.; Stuart, M. C. A.; Elsinga, P. H.; Szymanski, W.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 3354.

[7] Nadipuram, A. K.; David, W. M.; Kumar, D.; Kerwin, S. M. *Org. Lett.* **2002**, *4*, 4543.

[8] Serizawa, H.; Ishii, K.; Aikawa, K.; Mikami, K. *Org. Lett.* **2016**, *18*, 3686.

[9] Lu, C.; Lu, H.; Wu, J.; Shen, H. C.; Hu, T.; Gu, Y.; Shen, Q. *J. Org. Chem.* **2018**, *83*, 1077.

[10] Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984.

[11] Ma, J.-J.; Yi, W.-B.; Lu, G.-P.; Cai, C. *Org. Biomol. Chem.* **2015**, *13*, 2890.

[12] Xia, J. B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494.

[13] Hu, C. M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 335.

[14] Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44.

[15] Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 12090.

[16] Gu, Y.; Chang, D.; Leng, X.; Gu, Y.; Shen, Q. *Organometallics* **2015**, *34*, 3065.

[17] Haas, A.; Spitzer, M.; Lieb, M. *Chem. Ber.* **1988**, *121*, 1329.

[18] Lu, C.; Gu, Y.; Wu, J.; Gu, Y.; Shen, Q. *Chem. Sci.* **2017**, *8*, 4848.

[19] Sakamoto, R.; Kashiwagi, H.; Maruoka, K. *Org. Lett.* **2017**, *19*, 5126.

[20] Thanh, T. T.; Christensen, S. B.; Nielsen, J. *Chem. Eur. J.* **2017**, *23*, 18125.

[21] Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494.

[22] Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918.

[23] Góme, A. B.; Cortés González, M. A.; Lübcke, M.; Johansson, M. J.; Schou, M.; Szabó, K. J. *J. Fluor. Chem.* **2017**, *194*, 51.

[24] Le, C. C.; Wismer, M. K.; Shi, Z. C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. *ACS Cent. Sci.* **2017**, *3*, 647.

[25] Ge, S.; Chaładaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149.