Supporting Information

Copper-Catalyzed Difluoromethylation of Aryl Iodides with (Difluoromethyl)zinc Reagent

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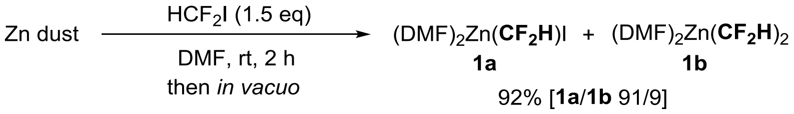
General Information:

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on Bruker AV300M (300 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million relative to the singlet (δ = 7.26) for $CHCl_3$ as an internal standard in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million relative to the central line of the triplet (δ = 77.0) for $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million relative to the singlet (δ = -63.24) for benzotrifluoride (BTF) as an external standard. IR spectra were measured on a JASCO FT/IR-4200 spectrometer. Mass spectra were measured on a JEOL JMS-T100CS (Accu-TOF) spectrometer. Diethylzinc solution (1.0 M in hexanes) and zinc dust (powder, <150 μm, 99.995% trace metals basis) were purchased from Aldrich. Difluoroiodomethane was synthesized employing published procedure.[1]

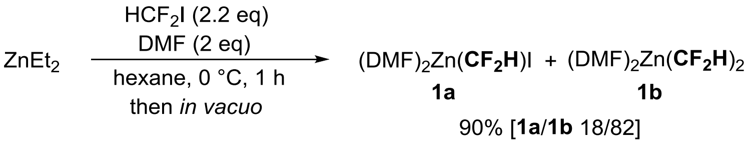
Synthetic Procedure of Zinc Reagent 1 from Zn Dust and HCF_2I (Scheme 2)



To a suspension of zinc powder (without activation, 33 mg, 0.50 mmol) in DMF or DMF-d_7 (1.0 mL) was added dropwise difluoroiodomethane (DMF solution 1.0-1.5 M, 750-500 μL, 0.50 mmol) at -40 °C under argon atmosphere. After the reaction mixture was stirred for 2 hours at room temperature, the resulting solution was filtered through a short plug with celite under argon atmosphere to remove unreacted elemental zinc. The DMF solution of $(DMF)_2Zn(CF_2H)I$ **1a** and $(DMF)_2Zn(CF_2H)_2$ **1b** were obtained, and the yield (total 92% yield) was determined by ^{19}F NMR analysis using (trifluoromethoxy)benzene as an internal standard. The concentration of zinc reagent solution (0.4-0.5 M) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

^{1}H NMR (300 MHz, DMF-d_7) δ 6.11 (t, J_{HF} = 43.5 Hz, 1H, $(DMF)_2Zn(CF_2H)I$), 6.13 (t, J_{HF} = 43.5 Hz, 2H, $(DMF)_2Zn(CF_2H)_2$); ^{13}C NMR (75 MHz, DMF-d_7) δ 143.2 (t, J_{CF} = 270.3 Hz, CF_2H, $(DMF)_2Zn(CF_2H)I$), 144.26 (tt, J_{CF} = 268.5, 3.0 Hz, CF_2H, $(DMF)_2Zn(CF_2H)_2$); ^{19}F NMR (282 MHz, DMF-d_7) δ -126.9 (d, J_{FH} = 44.0 Hz, 2F, $(DMF)_2Zn(CF_2H)I$), -127.0 (d, J_{FH} = 41.2 Hz, 4F, $(DMF)_2Zn(CF_2H)_2$), in a 91/9 ratio.

Synthetic Procedure of Zinc Reagent 1 from $ZnEt_2$ and HCF_2I (Scheme 3a)



To a mixture of DMF (31 μL, 0.40 mmol) in hexane (2.0 mL) was added dropwise difluoroiodomethane (THF solution 1.0-1.5 M, 440-290 μL, 0.44 mmol) at -40 °C. Diethylzinc (1.0 M in hexanes, 200 μL, 0.20 mmol) was added dropwise at -40 °C under argon atmosphere. After the reaction mixture was stirred at 0 °C for 1 hour, remaining difluoroiodomethane and solvents were removed in vacuo to give $(DMF)_2Zn(CF_2H)I$ **1a** and $(DMF)_2Zn(CF_2H)_2$ **1b** as a colorless gelled liquid. The yield (total 90% yield) was determined by ^{19}F NMR analysis using (trifluoromethoxy)benzene as an internal standard. DMF (0.4 mL) was added to the obtained

$(DMF)_2Zn(CF_2H)I$ **1a** and $(DMF)_2Zn(CF_2H)_2$ **1b** at room temperature under argon atmosphere. The concentration of the zinc reagent solution (0.4-0.5 M in DMF) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

^1H NMR (300 MHz, THF-d_8) δ 2.82 (s, 6H), 2.95 (s, 6H), 6.06 (t, J_{HF} = 43.5 Hz, 2H, $(DMF)_2Zn(CF_2H)_2$), 6.08 (t, J_{HF} = 43.5 Hz, 1H, $(DMF)_2Zn(CF_2H)I$), 7.96 (s, 2H); ^{13}C NMR (75 MHz, THF-d_8) δ 31.5, 36.7, 142.7 (tt, J_{CF} = 267.3, 4.2 Hz, CF_2H), 164.2; ^{19}F NMR (282 MHz, THF-d_8) δ -129.3 (d, J_{FH} = 42.6 Hz, 2F, $(DMF)_2Zn(CF_2H)I$), -130.1 (d, J_{FH} = 45.1 Hz, 4F, $(DMF)_2Zn(CF_2H)_2$), in a 18/82 ratio.

Optimization of Reaction Conditions for Synthetic Procedure of Zinc Reagent 1

$$\mathrm{ZnEt_2} \xrightarrow[\substack{\text{ligand (2 eq)} \\ \text{solvent, Y °C, 1 h} \\ \text{then } \textit{in vacuo}}]{\substack{\mathrm{HCF_2I}\text{ (2.2 eq)} \\ \text{[1.0-1.5 M, X solution]}}} \underset{\mathbf{1a}}{(\mathrm{DMF})_2\mathrm{Zn}(\mathbf{CF_2H})\mathrm{I}} + \underset{\mathbf{1b}}{(\mathrm{DMF})_2\mathrm{Zn}(\mathbf{CF_2H})_2}$$

entry	X	ligand	solvent	Y	yield [**1a**/**1b**][a]
1	DMF	-	hexane	-20	45% [38:62]
2	DMF	-	hexane	0	57% [31:69]
3	DMF	-	hexane	rt	41% [35:65]
4	DMF	-	DMF	0	38% [45:55]
5	hexane	DMF	hexane	0	69% [27:73]
6	hexane	-	hexane	0	2% [48:52][b]
7	toluene	DMF	hexane	0	82% [22:78]
8	**THF**	**DMF**	**hexane**	**0**	**90% [18:82]**
9	1,4-dioxane	DMF	hexane	rt	61% [30:70]
10	1,4-dioxane	DMF	1,4-dioxane	rt	68% [29:71]

[a] Yield was determined by ^{19}F NMR analysis using BTF as an internal standerd.
[b] Zn reagent without DMF ligand was observed.

Synthetic Procedure of Zinc Reagent 2 from $ZnEt_2$ and HCF_2I (Scheme 3b)

$$\mathrm{ZnEt_2} \xrightarrow[\substack{\text{2) DMPU (2 eq)} \\ \text{0 °C, 30 min} \\ \text{then } \textit{in vacuo}}]{\substack{\text{1) }\mathrm{HCF_2I}\text{ (2.2 eq)} \\ \text{DMF (2 eq)} \\ \text{hexane, 0 °C, 1 h}}} \underset{\mathbf{2a}}{(\mathrm{DMPU})_2\mathrm{Zn}(\mathbf{CF_2H})\mathrm{I}} + \underset{\mathbf{2b}}{(\mathrm{DMPU})_2\mathrm{Zn}(\mathbf{CF_2H})_2}$$

88% [**2a**/**2b** 18/82]

To a mixture of DMF (31 μL, 0.40 mmol) in hexane (2.0 mL) was added dropwise difluoroiodomethane (THF solution 1.0-1.5 M, 440-290 μL, 0.44 mmol) at -40 °C. Diethylzinc (1.0 M in hexanes, 200 μL, 0.20 mmol) was added dropwise at -40 °C under argon atmosphere. After the reaction mixture was stirred at 0 °C for 1 hour, and then DMPU (48 μL, 0.40 mmol) was added dropwise at the same temperature. After stirring for 30 min at 0 °C, remaining difluoroiodomethane and solvents were removed in vacuo to give $(DMPU)_2Zn(CF_2H)I$ **2a** and $(DMPU)_2Zn(CF_2H)_2$ **2b** as a colorless gelled liquid. The yield (total 88% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Various solvents (0.4 mL) were added to the obtained $(DMPU)_2Zn(CF_2H)I$ **2a** and $(DMPU)_2Zn(CF_2H)_2$ **2b** at room temperature under argon atmosphere. The concentration of the zinc reagent solution (0.4-0.5 M) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

^1H NMR (300 MHz, DMF-d_7) δ 1.92 (quin, J = 5.9 Hz, 4H), 2.82 (s, 12H), 3.23 (t, J = 5.9 Hz, 8H), 6.13 (t, J_{HF} = 43.3 Hz, 2H, $(DMPU)_2Zn(CF_2H)_2$), 6.16 (t, J_{HF} = 43.4 Hz, 1H, $(DMPU)_2Zn(CF_2H)I$); ^{13}C NMR (75 MHz, DMF-d_7) δ 22.4, 35.1, 47.9, 144.2 (tt, J_{CF} = 268.1, 3.2 Hz, CF_2H), 156.6; ^{19}F NMR (282 MHz, DMF-d_7) δ -126.9 (d, J_{FH} = 42.6 Hz, 2F, $(DMPU)_2Zn(CF_2H)I$), -127.1 (d, J_{FH} = 45.1 Hz, 4F, $(DMPU)_2Zn(CF_2H)_2$), in a 18/82 ratio.

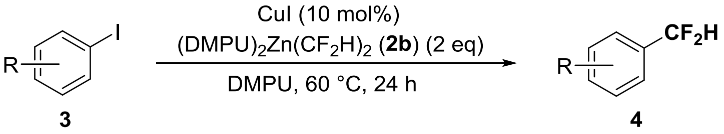
Investigation for Thermal Stability of Zinc Reagents (Table 1)

A mixture of $(DMF)_2Zn(CF_2H)_2$ (DMF solution 0.40-0.50 M, 250-200 μL, 0.1 mmol) in DMF (1.0 mL) or $(DMPU)_2Zn(CF_2H)_2$ reagent (DMF solution 0.40-0.5 M, 250-200 μL, 0.1 mmol) in DMF (1.0 mL) or $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40-0.5 M, 250-200 μL, 0.1 mmol) in DMPU (1.0 mL) was filled into a NMR tube under argon atmosphere. The decomposition of zinc reagents was monitored by ^{19}F NMR analysis using benzotrifluoride (10 μL, 0.08 mmol) as an internal standard at 60 °C.

Copper-Catalyzed Difluoromethylation of Aryl Iodides

Aryl iodide substrates: **3g** and **3n-o** were purchased from Aldrich. **3b-d**, **3f**, **3h-i**, and **3k** were purchased from TCI. **3a** and **3m** were purchased from Wako Pure Chemical Industries, Ltd. **3e** was purchased from Kanto Chemical Co., Inc. **3j**[2] and **3l**[3] was synthesized employing published procedure.

Typical Procedure for Copper-Catalyzed Difluoromethylation of Aryl Iodides with $(DMPU)_2Zn(CF_2H)_2$ Reagent (Scheme 4)

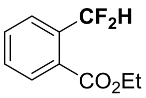


To a mixture of aryl iodide **3** (0.3 mmol) and CuI (5.7 mg, 0.03 mmol, 10 mol%) in DMPU (2.0 mL) was added $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40-0.50 M, 1.5-1.2 mL, 0.6 mmol) at room temperature. After stirring for 24 hours at 60 °C under argon atmosphere, the reaction mixture was quenched by 1N HCl aq. (5.0 mL), and then Et_2O (5.0 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (5.0 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting crude reside was purified by silica-gel column chromatography to give the difluoromethylated products **4**.

Gram-Scale Experiment (Table 2, entry 2)

To a mixture of aryl iodide **3a** (1.35 g, 5 mmol) and CuI (95.2 mg, 0.5 mmol) in DMPU (30 mL) was added $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40 M, 25 mL, 10 mmol) at room temperature. After stirring for 24 hours at 60 °C under argon atmosphere, the reaction mixture was quenched by 1N HCl aq. (70 mL), and then pentane/Et_2O (45 mL/5 mL) was added. The organic layer was separated, and the aqueous layer was extracted with pentane/Et_2O (45 mL/5 mL × 3). The combined organic layer was washed with brine (70 mL), dried over Na_2SO_4, and evaporated. The resulting crude reside was purified by silica-gel column chromatography (pentane/Et_2O = 40/1) to give the product **4a** (855.1 mg, 85% yield) as a yellow liquid.

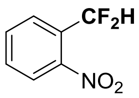
Ethyl 2-(difluoromethyl)benzoate (4a)



The title compound was obtained from ethyl 2-iodobenzoate **3a** following the procedure above. The yield of the compound (90% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 40/1) gave the compound (55.3 mg, 92% yield) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.1 Hz, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.54 (t, J_{HF} = 55.6 Hz, 1H), 7.54 (apt, *J* = 7.3 Hz, 1H), 7.64 (apt, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 61.6, 112.0 (t, J_{CF} = 236.2 Hz, *C*F_2H), 125.8 (t, J_{CF} = 8.1 Hz), 129.1 (t, J_{CF} = 5.3 Hz), 130.3 (t, J_{CF} = 1.8 Hz), 130.8, 132.5, 135.2 (t, J_{CF} = 22.2 Hz), 166.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.7 (d, J_{FH} = 55.7 Hz, 2F); HRMS (APCI-TOF) calcd for $C_{10}H_{11}F_2O_2$ $[M+H]^+$: 201.0727, found: 201.0731; FT-IR (neat, cm^{-1}) 1040, 1105, 1145, 1206, 1370, 1452, 1585, 1605, 1725, 2934, 2986, 3081.

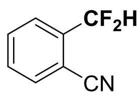
1-(Difluoromethyl)-2-nitrobenzene (4b)



The title compound was obtained from 1-iodo-2-nitrobenzene **3b** following the procedure above. The yield (78% yield) was determined by ^{19}F NMR analysis using (trifluoromethoxy)benzene as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 9/1) gave the compound (38.9 mg, 75% yield) as a pale yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, J_{HF} = 54.9 Hz, 1H), 7.67 (apt, *J* = 7.7 Hz, 1H), 7.77 (apt, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.7 (t, J_{CF} = 238.5 Hz, *C*F_2H), 125.1, 127.0 (t, J_{CF} = 8.4 Hz), 129.1 (t, J_{CF} = 23.6 Hz), 131.6 (t, J_{CF} = 1.7 Hz), 134.1, 147.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.0 (d, J_{FH} = 54.6 Hz, 2F); HRMS (APCI-TOF) calcd for $C_7H_5F_2NO_2$ $[M]^{-\bullet}$: 173.0288, found: 173.0291; FT-IR (neat, cm^{-1}) 1056, 1106, 1206, 1369, 1538, 2871, 2930, 3093.

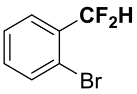
2-(Difluoromethyl)benzonitrile (4c)



The title compound was obtained from 2-iodobenzonitrile **3c** following the procedure above. The yield (62% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 9/1) gave the compound (27.7 mg, 60% yield) as a pale yellow liquid. The product (**4c**) is known compound and the following data are identical to those given in corresponding literature.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (t, J_{HF} = 54.6 Hz, 1H), 7.58-7.63 (m, 1H), 7.70-7.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.5 (t, J_{CF} = 5.1 Hz), 112.2 (t, J_{CF} = 238.5 Hz, *C*F_2H), 115.7, 126.4 (t, J_{CF} = 5.9 Hz), 131.2 (t, J_{CF} = 1.7 Hz), 133.2, 133.3, 136.6 (t, J_{CF} = 23.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.7 (d, J_{FH} = 54.6 Hz, 2F).

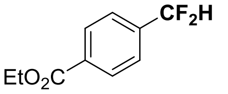
1-Bromo-2-(difluoromethyl)benzene (4d)



The title compound was obtained from 1-bromo-2-iodobenzene **3d** following the procedure above. The yield (40% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the compound (28.4 mg, 46% yield) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (t, J_{HF} = 54.9 Hz, 1H), 7.34 (apt, J = 7.8 Hz, 1H), 7.42 (apt, J = 7.5 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.8 (t, J_{CF} = 236.9 Hz, CF_2H), 121.6 (t, J_{CF} = 6.4 Hz), 127.1 (t, J_{CF} = 6.1 Hz), 127.7, 132.1 (t, J_{CF} = 1.9 Hz), 133.1, 133.3 (t, J_{CF} = 23.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.6 (d, J_{FH} = 54.6 Hz, 2F); HRMS (APCI-TOF) calcd for $C_7H_4{}^{79}BrF_2$ [M-H]$^-$: 204.9464, found: 204.9455; FT-IR (neat, cm^{-1}) 1047, 1134, 1213, 1278, 1377, 1447, 1597, 2926, 3075.

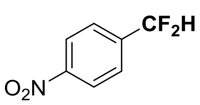
Ethyl 4-(difluoromethyl)benzoate (4e)



The title compound was obtained from ethyl 4-iodobenzoate **3e** following the procedure above. The yield (58% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 40/1) gave the compound (36.4 mg, 61% yield) as a colorless liquid. The product (**4e**) is known compound and the following data are identical to those given in corresponding literature.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.68 (t, J_{HF} = 56.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 8.12 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.3, 114.0 (t, J_{CF} = 238.5 Hz, CF_2H), 125.6 (t, J_{CF} = 6.8 Hz), 129.9, 132.7, 138.3 (t, J_{CF} = 21.8 Hz), 165.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.2 (d, J_{FH} = 54.9 Hz, 2F).

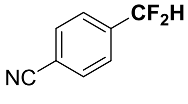
1-(Difluoromethyl)-4-nitrobenzene (4f)



The title compound was obtained from 1-iodo-4-nitrobenzene **3f** following the procedure above. The yield of the compound (61% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 9/1) gave the compound (31.3 mg, 60% yield) as a yellow liquid. The product (**4f**) is known compound and the following data are identical to those given in corresponding literature.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (t, J_{HF} = 55.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 8.29 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.2 (t, J_{CF} = 239.3 Hz, CF_2H), 123.9, 126.8 (t, J_{CF} = 6.0 Hz), 140.1 (t, J_{CF} = 23.3 Hz), 149.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.0 (d, J_{FH} = 55.2 Hz, 2F).

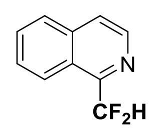
4-(Difluoromethyl)benzonitrile (4g)



The title compound was obtained from 4-iodobenzonitrile **3g** following the procedure above. The yield (83% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 9/1) gave the compound (36.8 mg, 80% yield) as a yellow liquid. The product (**4g**) is known compound and the following data are identical to those given in corresponding literature.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (t, J_{HF} = 55.2 Hz, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.3 (t, J_{CF} = 239.3 Hz, CF_2H), 114.6 (t, J_{CF} = 1.8 Hz), 117.8, 126.3 (t, J_{CF} = 6.0 Hz), 132.4, 138.4 (t, J_{CF} = 23.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (d, J_{FH} = 56.3 Hz, 2F).

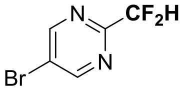
1-(Difluoromethyl)isoquinoline (4h)



The title compound was obtained from 1-iodoisoquinoline **3h** following the procedure above. The yield (88% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane/Et_2O = 9/1) gave the compound (50.4 mg, 94% yield) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (t, J_{HF} = 54.4 Hz, 1H), 7.64-7.76 (m, 3H), 7.88 (d, *J* = 8.1 Hz, 1H), 8.47-8.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.8 (t, J_{CF} = 240.7 Hz, CF_2H), 123.5, 125.1 (t, J_{CF} = 3.8 Hz), 125.1, 127.3, 128.2, 130.6, 137.0, 141.1, 151.1 (t, J_{CF} = 26.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.0 (d, J_{FH} = 54.3 Hz, 2F); HRMS (APCI-TOF) calcd for $C_{10}H_8F_2N$ $[M+H]^+$: 180.0625, found: 180.0617; FT-IR (neat, cm^{-1}) 1035, 1114, 1206, 1370, 1460, 1585, 1629, 1725, 2927, 3060.

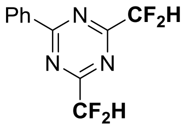
5-Bromo-2-(difluoromethyl)pyrimidine (4i)



The title compound was obtained from 5-bromo-2-iodopyrimidine **3i** following the procedure above. The yield (92% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (hexane/AcOEt = 9/1) gave the compound (57.1 mg, 91% yield) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (t, J_{HF} = 54.3 Hz, 1H), 8.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.6 (t, J_{CF} = 241.4 Hz, CF_2H), 122.0, 158.6, 158.8 (t, J_{CF} = 25.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -118.4 (d, J_{FH} = 54.6 Hz, 2F); HRMS (APCI-TOF) calcd for $C_5H_4{}^{79}BrF_2N_2$ $[M+H]^+$: 208.95259, found: 208.95267; FT-IR (neat, cm^{-1}) 1059, 1120, 1173, 1384, 1443, 1551, 1724, 2855, 2927, 2960, 3049.

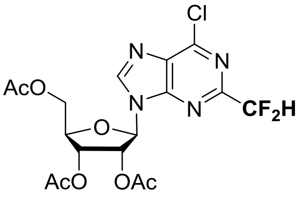
2,4-Bis(difluoromethyl)-6-phenyl-1,3,5-triazine (4j)



The title compound was obtained from 2,4-diiodo-6-phenyl-1,3,5-triazine **3j** with (TMEDA)$Zn(CF_2H)_2$ reagent (4 equiv) following the procedure above. The yield (89% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (hexane/AcOEt = 9/1) gave the compound (63.9 mg, 83% yield) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (t, J_{HF} = 53.7 Hz, 1H), 7.56 (apt, *J* = 7.2 Hz, 2H), 7.65-7.71 (m, 1H), 8.63 (dd, *J* = 8.6, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.9 (t, J_{CF} = 243.0 Hz, CF_2H), 129.1, 129.8, 133.3, 134.6, 169.7 (t, J_{CF} = 25.5 Hz), 174.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -121.9 (d, J_{FH} = 54.6 Hz, 2F); HRMS (APCI-TOF) calcd for $C_{11}H_6F_4N_3$ $[M-H]^-$: 256.04978, found: 256.04939; FT-IR (KBr, cm^{-1}) 1071, 1152, 1181, 1393, 1499, 1566, 1721, 2987, 3056.

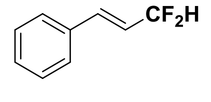
(2*R*,3*R*,4*R*,5*R*)-2-(acetoxymethyl)-5-(6-chloro-2-(difluoromethyl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4k)



The title compound was obtained from (2*R*,3*R*,4*R*,5*R*)-2-(acetoxymethyl)-5-(6-chloro-2-iodo-9*H*-purin-9-yl) tetra hydrofuran-3,4-diyl diacetate **3k** following the procedure above. The yield (88% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography

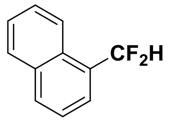
(hexane/AcOEt = 1/1) gave the compound (125.2 mg, 90% yield) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.08 (s, 3H), 2.16 (s, 3H), 4.40-4.42 (m, 2H), 4.48-4.52 (m, 1H), 5.64 (apt, J = 5.1 Hz, 1H), 5.84 (apt, J = 5.4 Hz, 1H), 6.26 (d, J = 5.1 Hz, 2H), 6.71 (t, J_{HF} = 54.4 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.5, 20.6, 62.9, 70.5, 73.4, 80.8, 87.0, 111.4 (t, J_{CF} = 241.5 Hz, CF_2H), 132.8, 145.0, 151.3, 152.1, 154.5 (t, J_{CF} = 26.3 Hz), 169.4, 169.5, 170.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.6 (d, J_{FH} = 54.6 Hz, 2F); HRMS (APCI-TOF) calcd for $C_{17}H_{17}ClF_2N_4NaO_7$ [M+Na]$^+$: 485.06515, found: 485.06623; FT-IR (KBr, cm^{-1}) 1058, 1154, 1227, 1375, 1496, 1568, 1593, 1750, 2956, 2988, 3058, 3118.

(*E*)-(3,3-Difluoroprop-1-en-1-yl)benzene (4l)



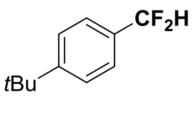
The title compound was obtained from (*E*)-(2-iodovinyl)benzene **3l** following the procedure above. The yield (99% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane) gave the compound (38.4 mg, 84% yield; low boiling point compound) as a colorless liquid. The product (**4l**) is known compound and the following data are identical to those given in corresponding literature.[6]
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06-6.46 (m, 2H), 6.85-6.93 (m, 1H), 7.35-7.47 (m, 5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.7 (dd, J_{FH} = 54.7, 6.5 Hz, 2F).

1-(Difluoromethyl)naphthalene (4m)



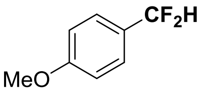
The title compound was obtained from 1-iodonaphthalene **3m** following the procedure above. The yield (49% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (pentane only) gave the compound (25.3 mg, 47% yield) as a colorless liquid. The product (**4m**) is known compound and the following data are identical to those given in corresponding literature.[4]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J_{HF} = 55.2 Hz, 1H), 7.49-7.64 (m, 3H), 7.70 (d, J = 7.2 Hz, 1H), 7.91-7.99 (m, 2H), 8.19 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.4 (t, J_{CF} = 237.0 Hz, CF_2H), 123.5 (t, J_{CF} = 1.4 Hz), 124.6, 124.8 (t, J_{CF} = 8.6 Hz), 126.4, 127.2, 128.8, 129.5 (t, J_{CF} = 20.6 Hz), 129.7 (t, J_{CF} = 2.6 Hz), 131.5 (t, J_{CF} = 1.8 Hz), 133.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.9 (d, J_{FH} = 54.6 Hz, 2F).

1-(*tert*-Butyl)-4-(difluoromethyl)benzene (4n)



The title compound was obtained from 1-(*tert*-butyl)-4-iodobenzene **3n** following the procedure above. The yield (14% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. The product (**4n**) is known compound and the following data are identical to those given in corresponding literature.[7]
^{19}F NMR (282 MHz, $CDCl_3$) δ -109.8 (d, J_{FH} = 56.0 Hz, 2F).

1-(Difluoromethyl)-4-methoxybenzene (4o)

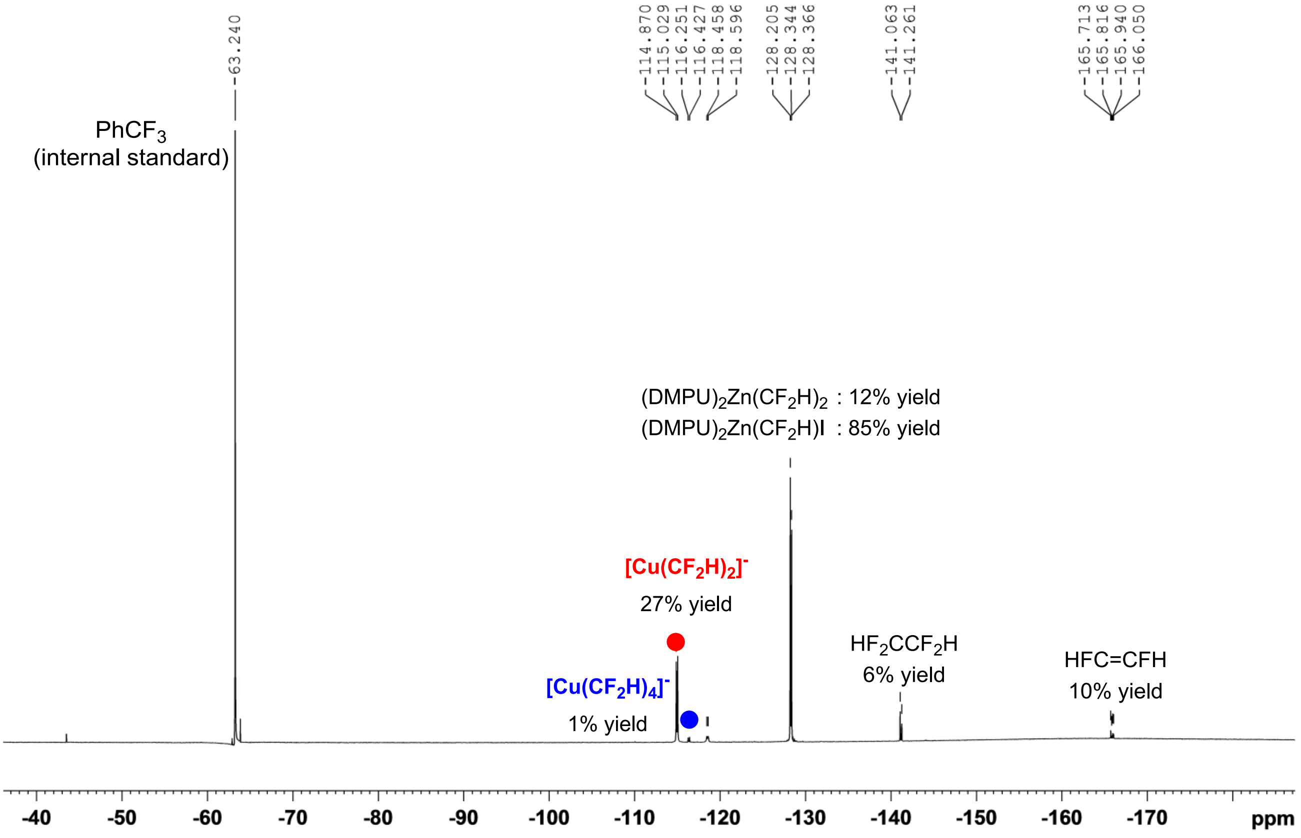


The title compound was obtained from 1-iodo-4-methoxybenzene **3o** following the procedure above. The yield (5% yield) was determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. The product (**4o**) is known

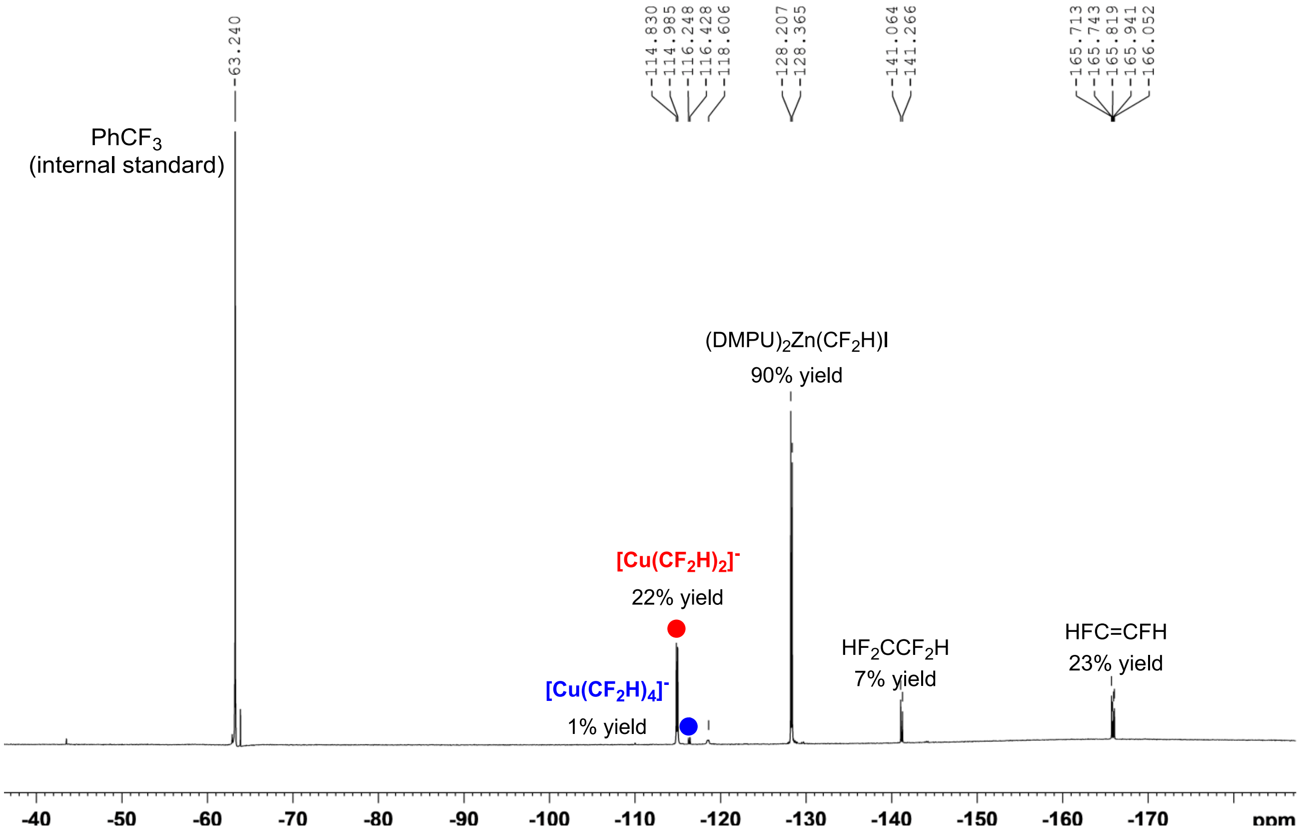
compound and the following data are identical to those given in corresponding literature.[8]
^{19}F NMR (282 MHz, $CDCl_3$) δ -108.2 (d, J_{FH} = 57.4 Hz, 2F).

Observation of Copper Species by ^{19}F NMR spectrum (Scheme 5a)

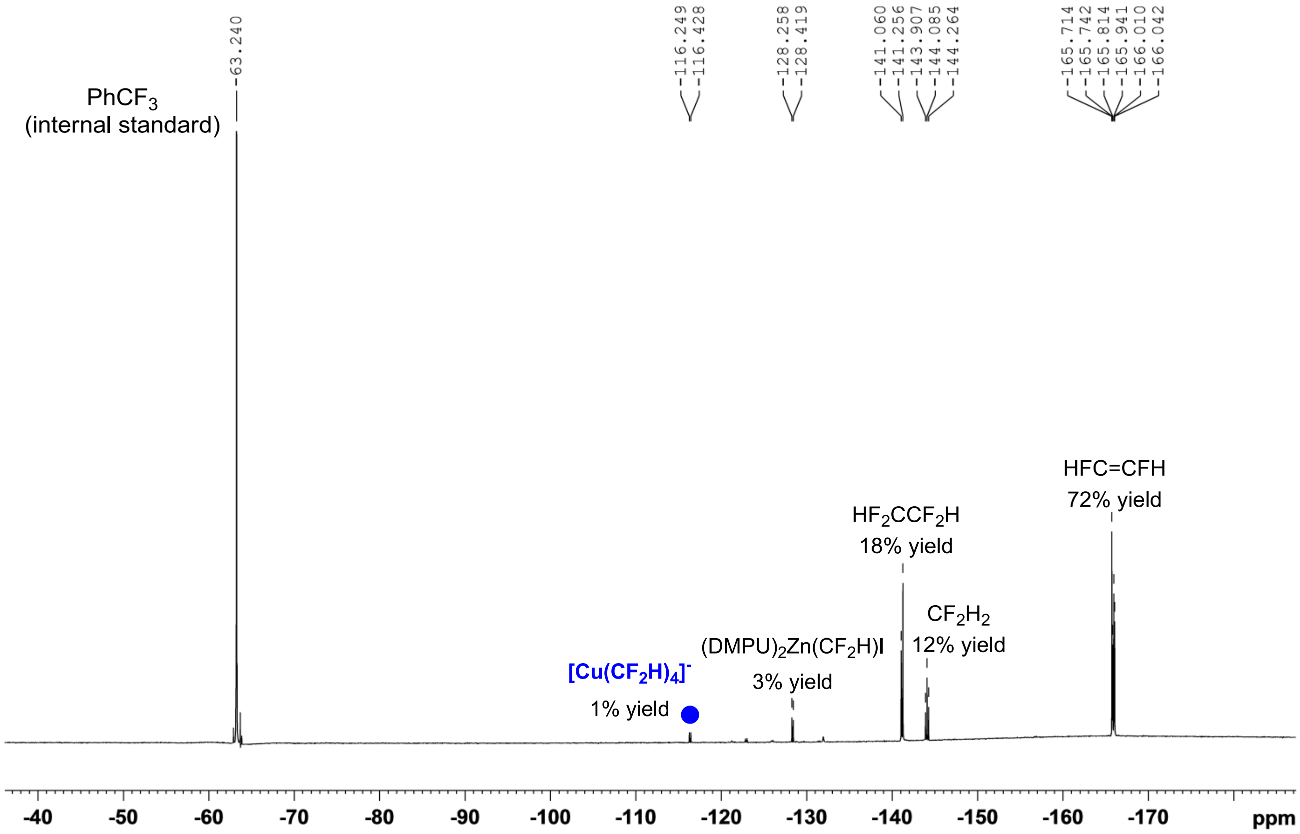
To a mixture of CuI (19 mg, 0.1 mmol) in DMPU (1.0 mL) was added $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40-0.50 M, 250-200 μL, 0.1 mmol) at room temperature. After the reaction mixture was stirred for 15 min at room temperature, the generation of cuprate species was monitored by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard and sealed capillary filled with DMF-*d*$_7$ for signal lock under argon atmosphere. Two doublet peaks of the cuprate species, $[Cu(CF_2H)_2]^-$ (δ_F -114.9; d, J_{FH} = 44.8 Hz) and $[Cu(CF_2H)_4]^-$ (δ_F -116.3; d, J_{FH} = 49.6 Hz) were observed in 27% and 1% yields, respectively. Additionally, HF_2CCF_2H and HFC=CFH were observed in 6% and 10% yields, respectively. After 1 hour, $Cu(CF_2H)_2]^-$, $[Cu(CF_2H)_4]^-$, HF_2CCF_2H, and HFC=CFH were observed in 22%, 1%, 7%, and 23% yields, respectively. $[Cu(CF_2H)_2]^-$, $[Cu(CF_2H)_4]^-$, HF_2CCF_2H, and HFC=CFH were assigned based on the ^{19}F NMR chemical shifts given in corresponding literature.[9] After the reaction mixture was stirred for 1 hour at 60 °C, $[Cu(CF_2H)_4]^-$, HF_2CCF_2H, HFC=CFH, and CF_2H_2 were observed in 1%, 18%, 74%, and 12% yields, respectively, and thus $[Cu(CF_2H)_2]^-$ was not observed.



^{19}F NMR spectra after 15 minutes of addition of $(DMPU)_2Zn(CF_2H)_2$ to CuI at rt in DMPU



^{19}F NMR spectra after 1 h of addition of $(DMPU)_2Zn(CF_2H)_2$ to CuI at rt in DMPU

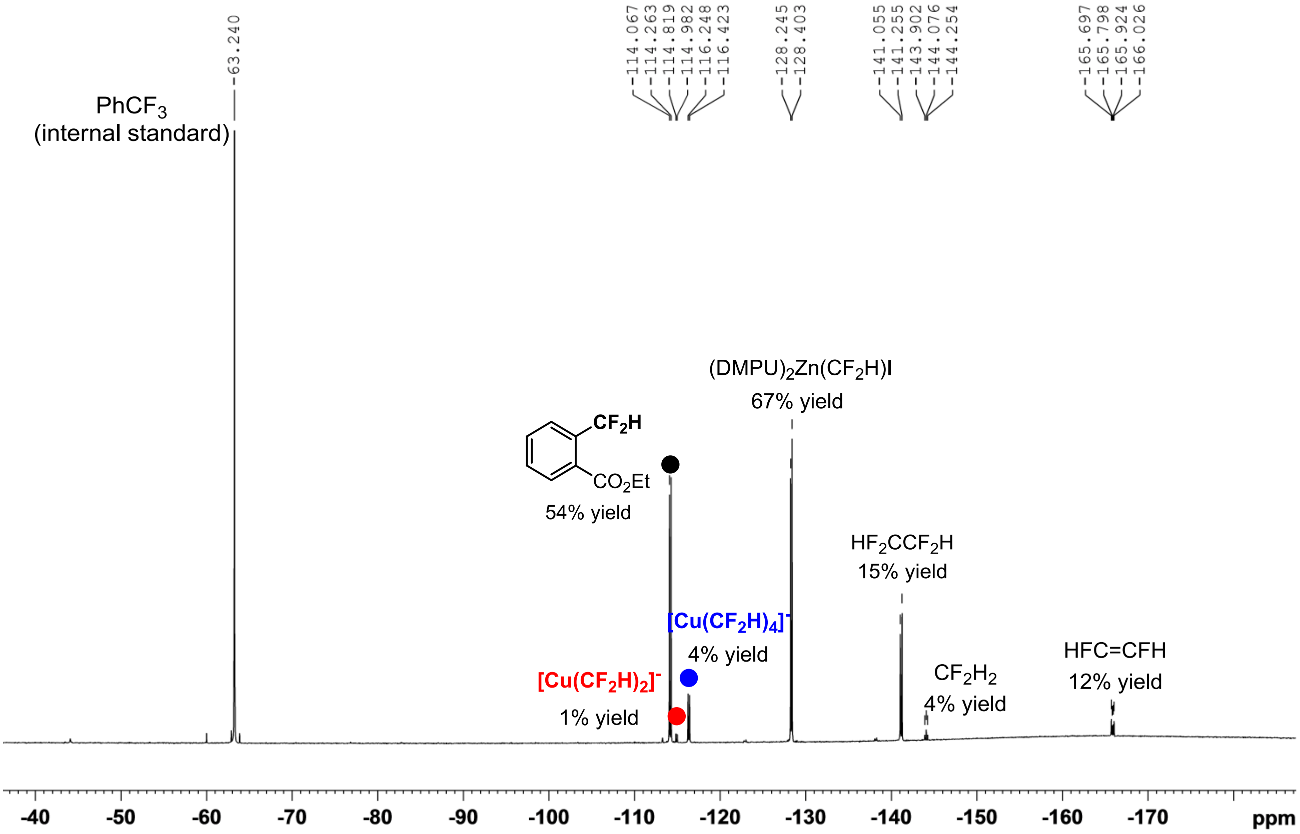


^{19}F NMR spectra after 1 h of addition of $(DMPU)_2Zn(CF_2H)_2$ to CuI at 60 °C in DMPU

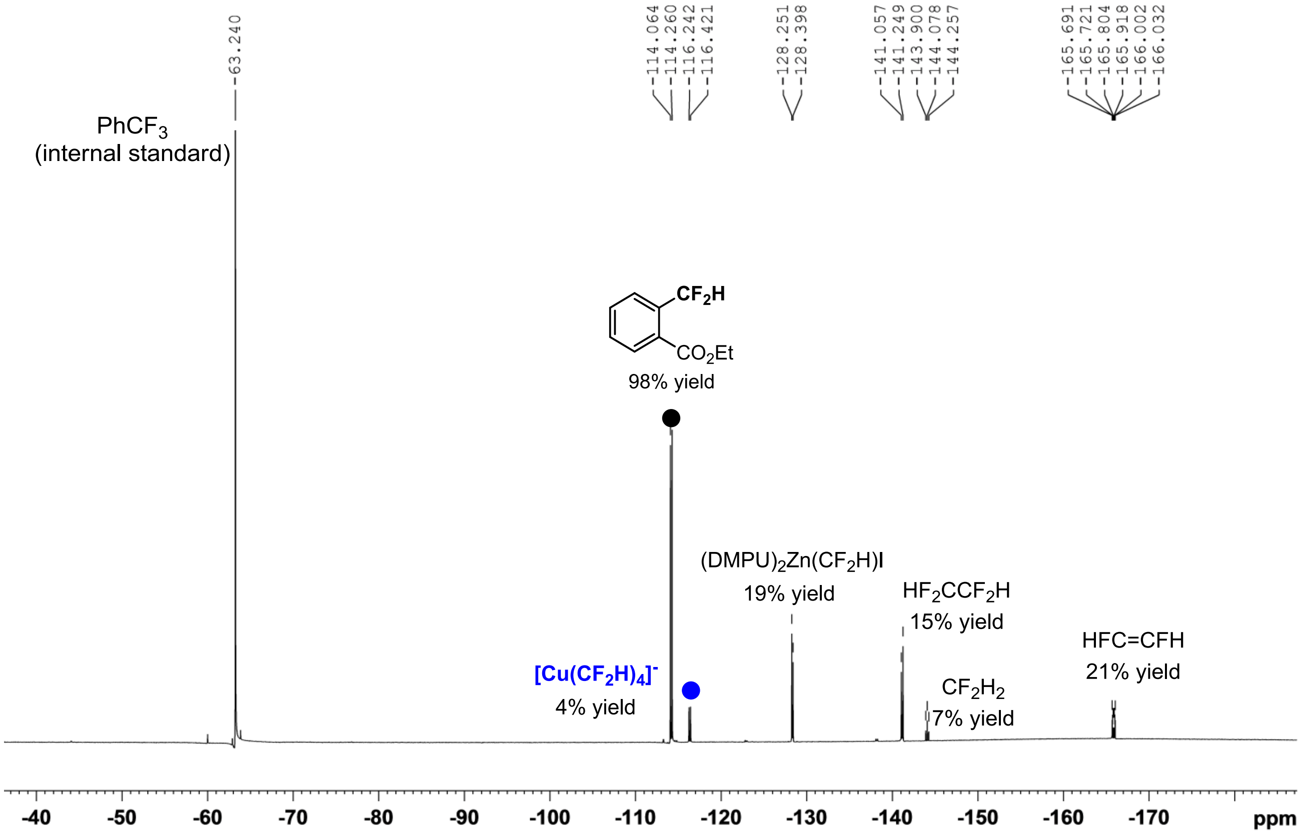
Observation of Reaction of Copper Species and ArI by ^{19}F NMR spectrum (Scheme 5b)

(A) At room temperature

To a mixture of CuI (19 mg, 0.1 mmol) in DMPU (1.0 mL) was added $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40-0.50 M, 250-200 µL, 0.1 mmol) at room temperature. After the reaction mixture was stirred for 15 min at room temperature, the generation of cuprate species was monitored by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard and sealed capillary filled with DMF-*d*$_7$ for signal lock under argon atmosphere. Ethyl 2-iodobenzoate **3a** (27.6 mg, 0.1 mmol) was added to the mixture of pre-generated cuprate species at room temperature. After 1 hour at room temperature, the generation of the difluoromethylated product **4a** (54% yield) and consumption of $[Cu(CF_2H)_2]^-$ were observed. After 24 hours, the yield of **4a** (98% yield) was determined by ^{19}F NMR analysis. However, $[Cu(CF_2H)_4]^-$ remained in 4% yield.



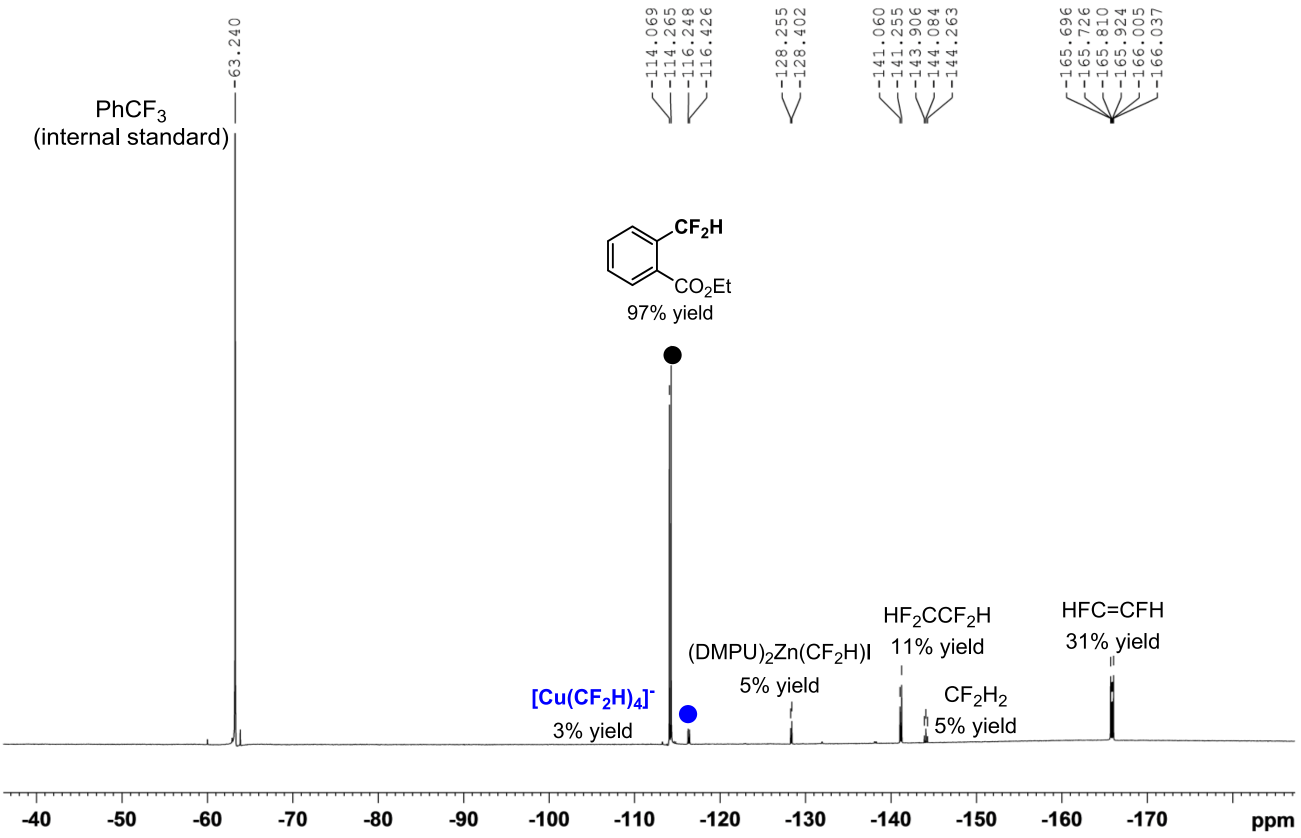
^{19}F NMR spectra after 1 h of addition of ArI to cuprate species at rt in DMPU



^{19}F NMR spectra after 12 h of addition of ArI to cuprate species at rt in DMPU

(B) At 60 °C

To a mixture of CuI (19 mg, 0.1 mmol) in DMPU (1.0 mL) was added $(DMPU)_2Zn(CF_2H)_2$ reagent (DMPU solution 0.40-0.50 M, 250-200 μL, 0.1 mmol) at room temperature. After the reaction mixture was stirred for 15 min at room temperature, the generation of cuprate species was monitored by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard and sealed capillary filled with DMF-d_7 for signal lock under argon atmosphere. Ethyl 2-iodobenzoate **3a** (27.6 mg, 0.1 mmol) was added to the mixture of pre-generated cuprate species at room temperature. After 1 hour at 60 °C, the generation of the difluoromethylated product **4a** (97% yield) and consumption of $[Cu(CF_2H)_2]^-$ were observed. However, $[Cu(CF_2H)_4]^-$ remained in 3% yield.



^{19}F NMR spectra after 1 h of addtion of ArI to cuprate species at 60 °C in DMPU

References

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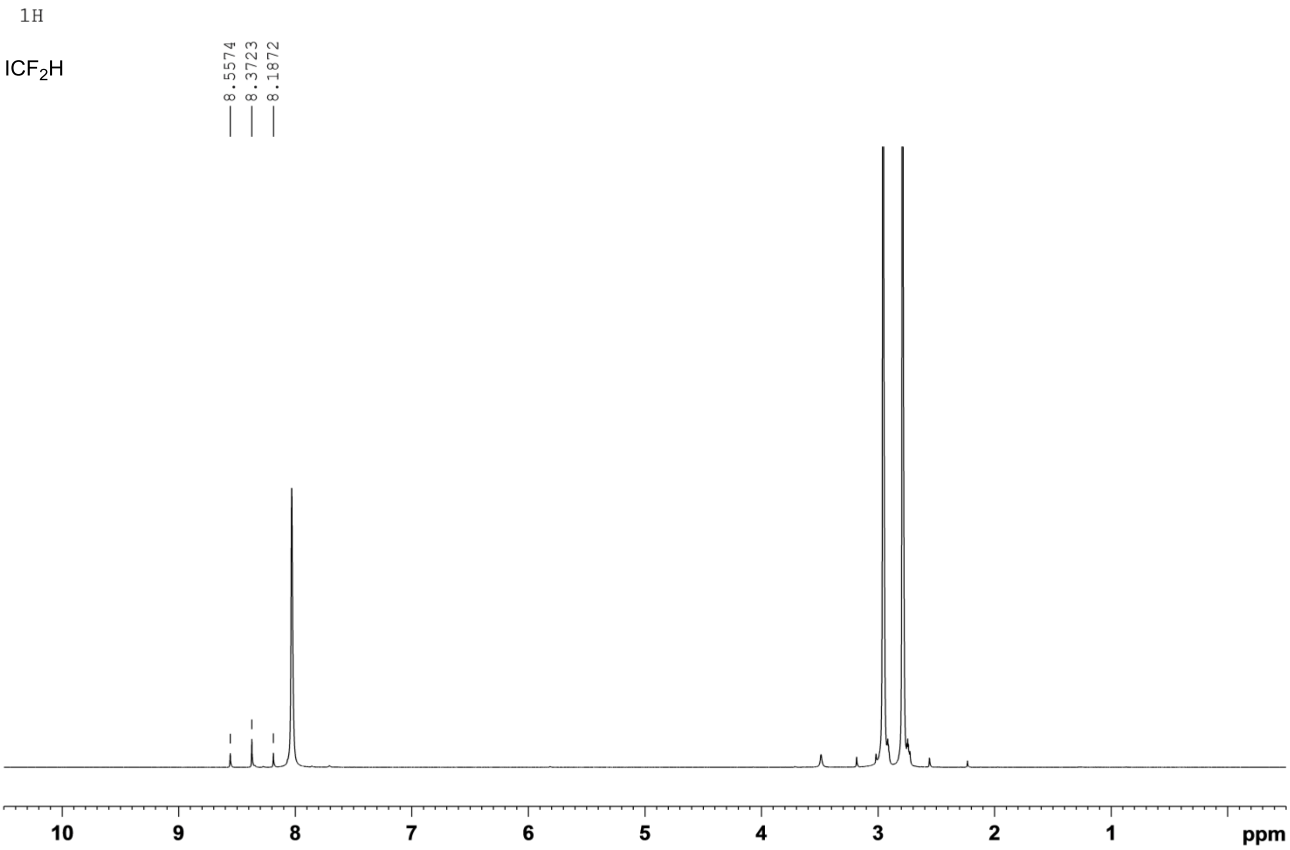
d) Ellerman, D. D.; Brown, L. C.; Williams, D. *J. Mol. Spect.* **1961**, *7*, 307.


1H
ICF$_2$H
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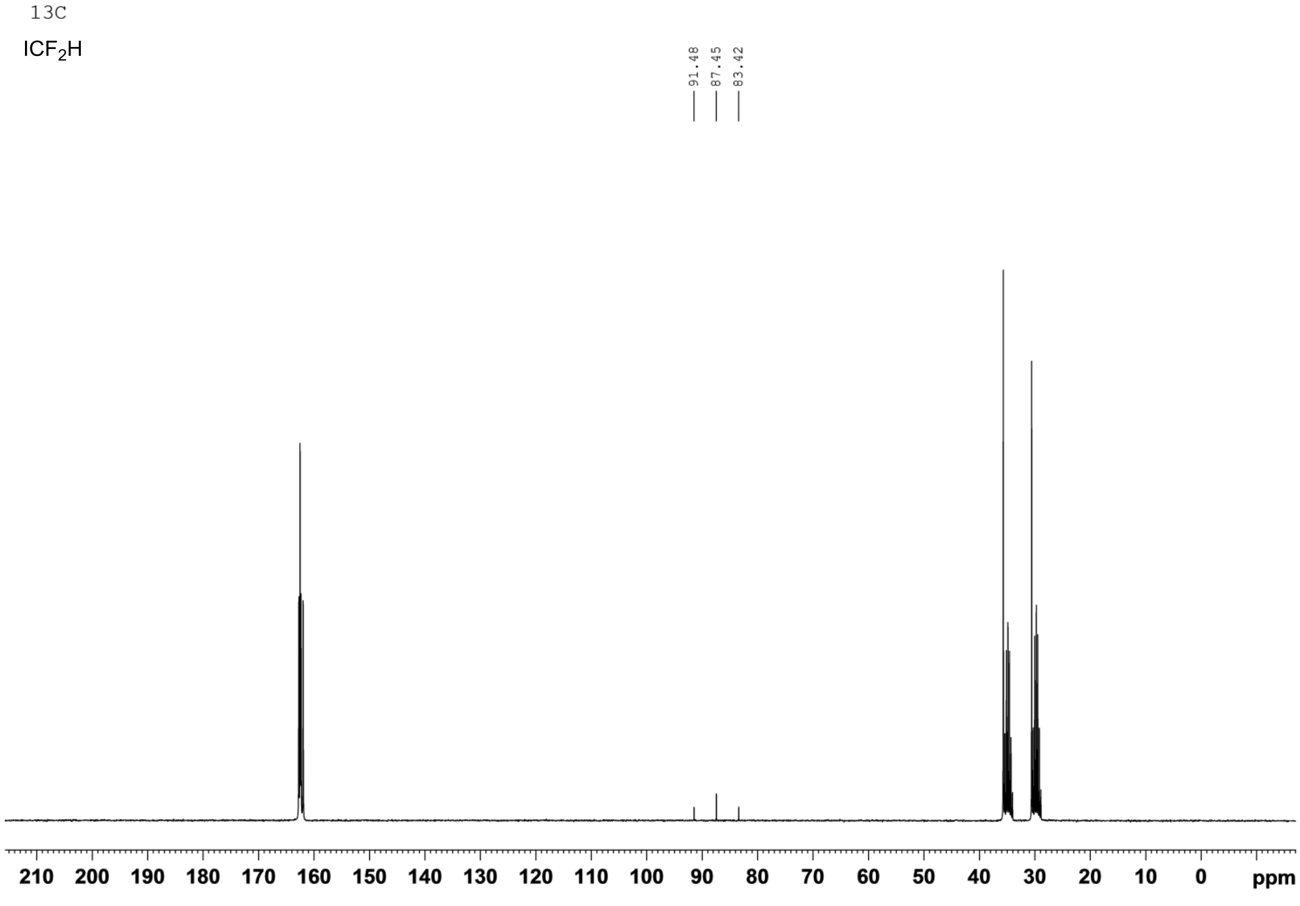
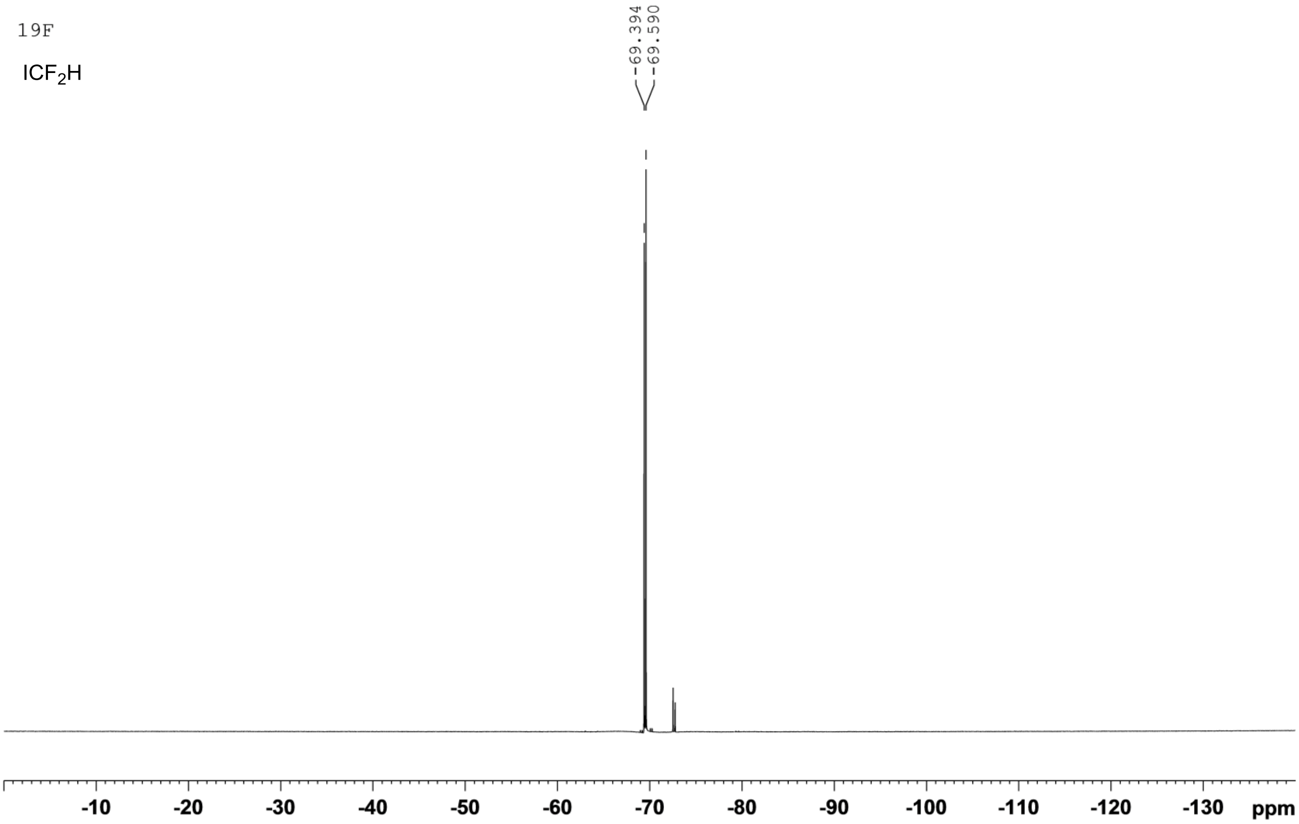
8.1872
10
9
8
7
6
5
4
3
2
1
ppm


13C
ICF$_2$H
91.48
87.45
83.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


19F
ICF$_2$H
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-69.590
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-30
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-50
-60
-70
-80
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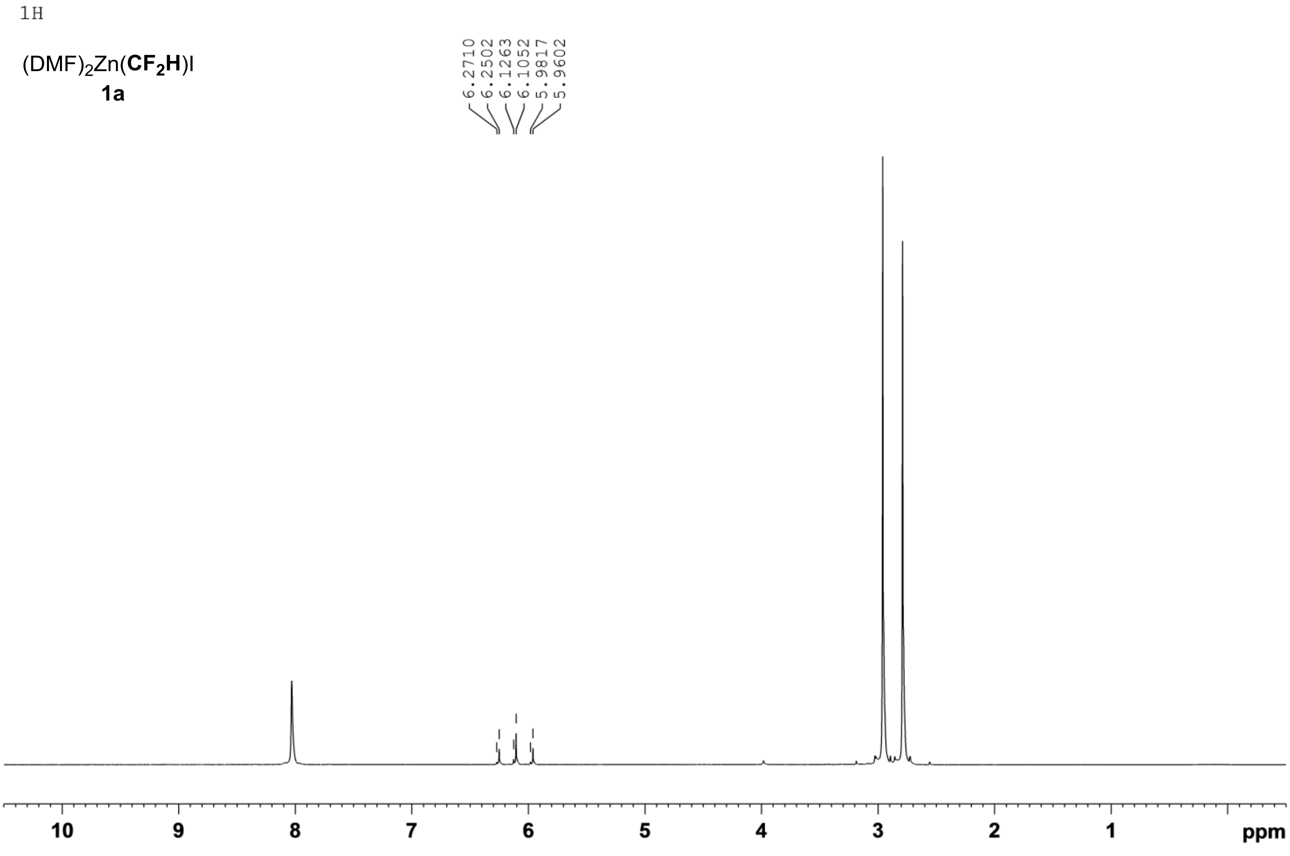
-100
-110
-120
-130
ppm


1H
(DMF)$_2$Zn(**CF$_2$H**)I
1a
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6.2502
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5.9817
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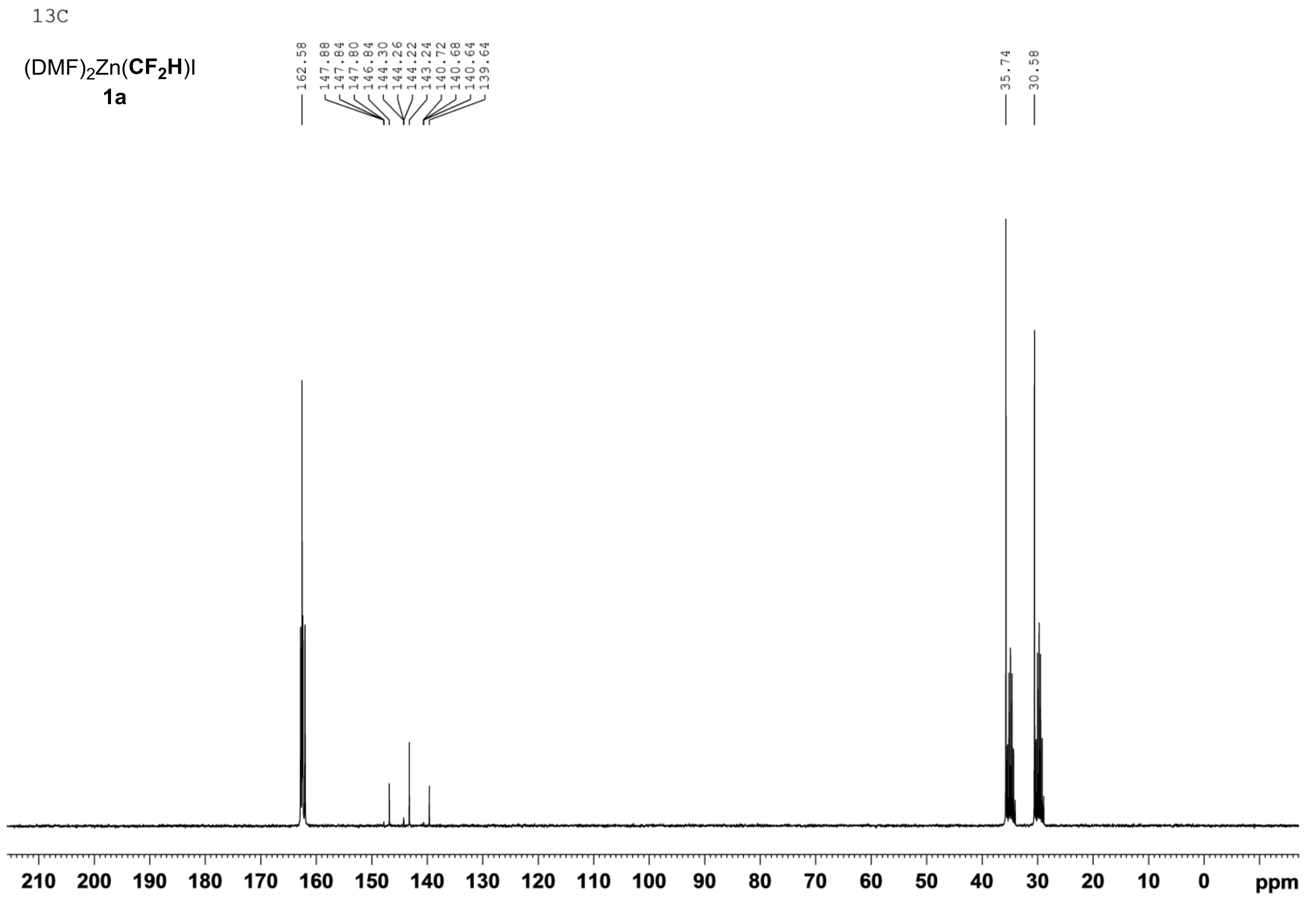
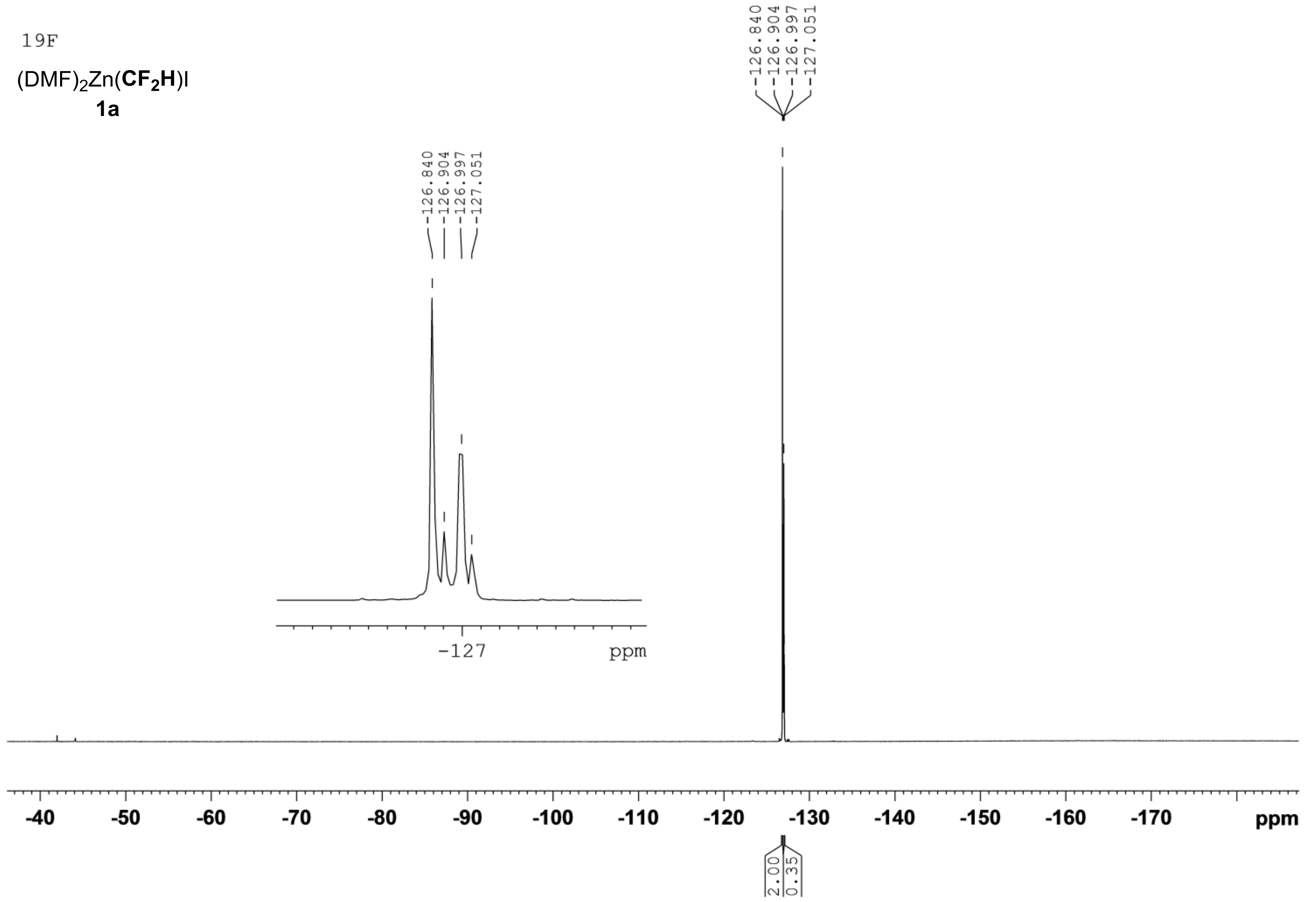
10
9
8
7
6
5
4
3
2
1
ppm


13C

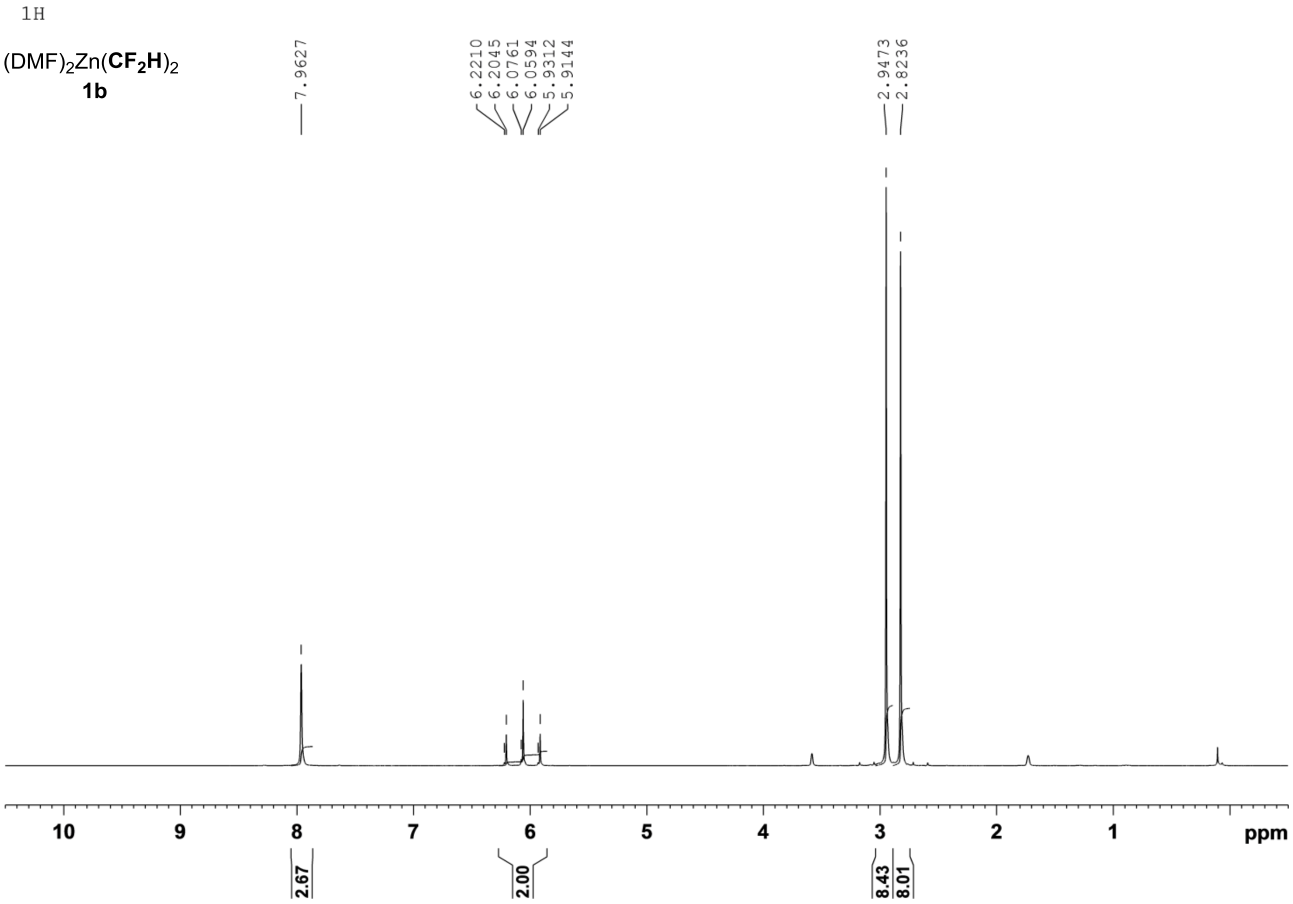
$(DMF)_2Zn(\mathbf{CF_2H})I$

1a

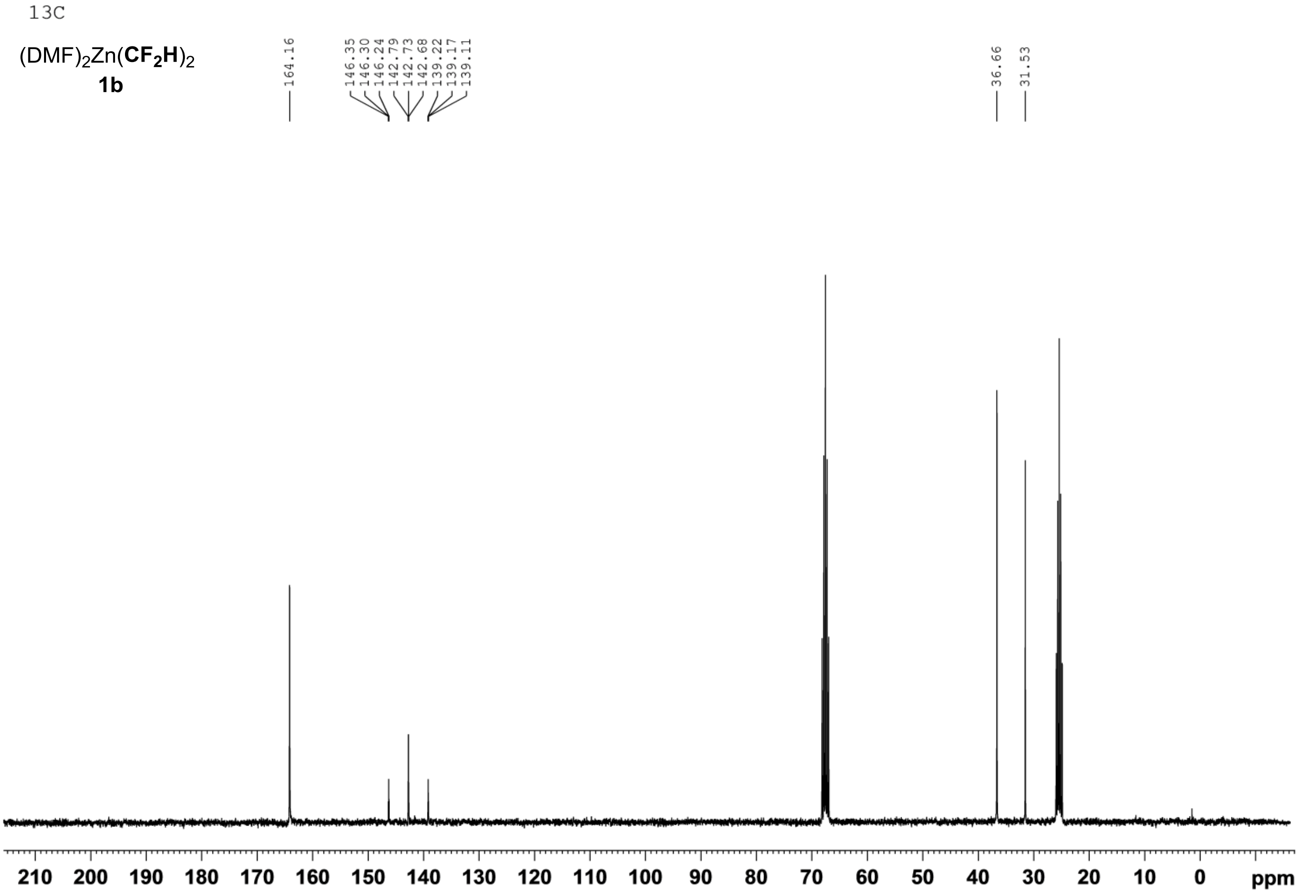

19F

$(DMF)_2Zn(\mathbf{CF_2H})I$

1a

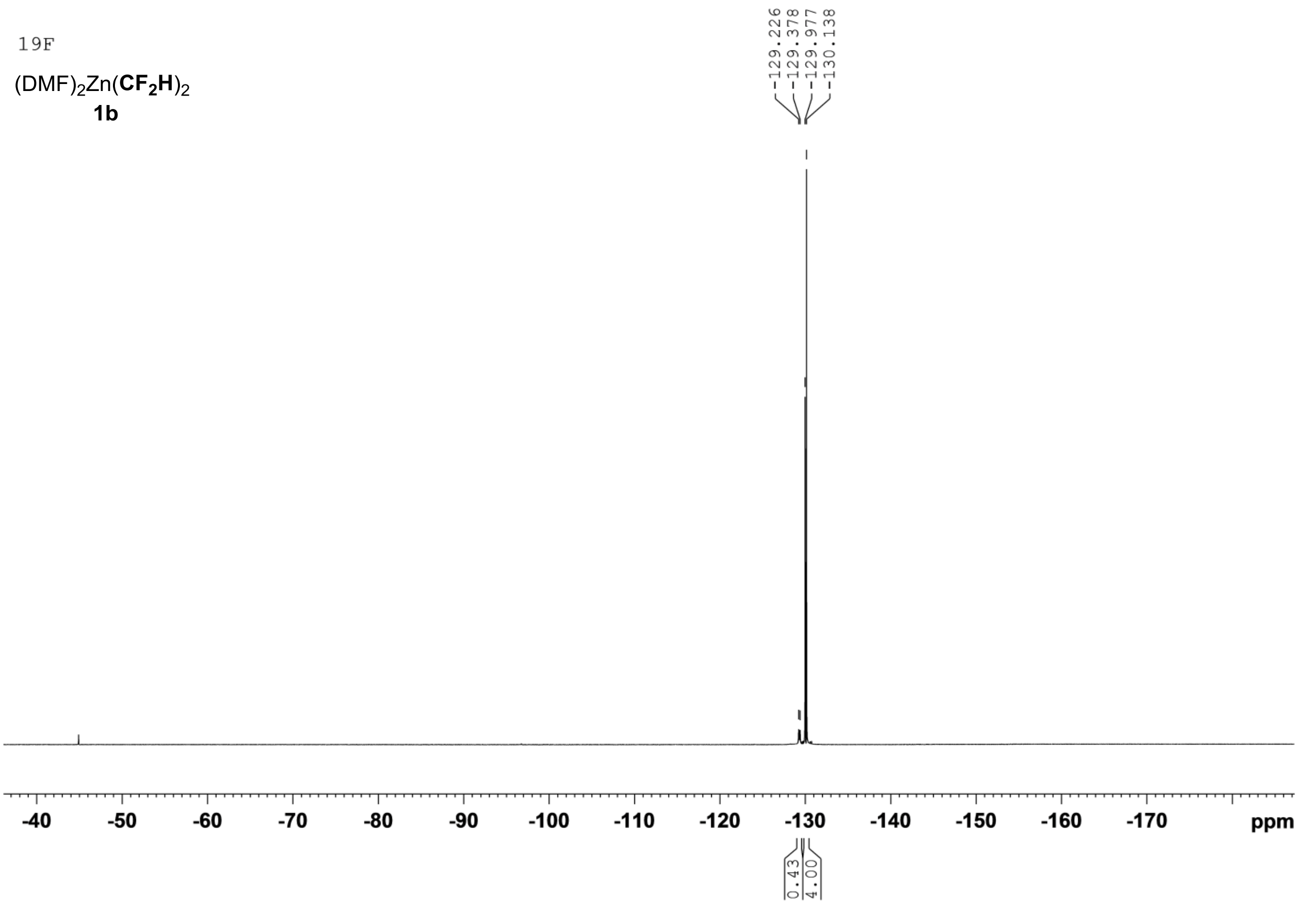


$(DMF)_2Zn(\mathbf{CF_2H})_2$
1b

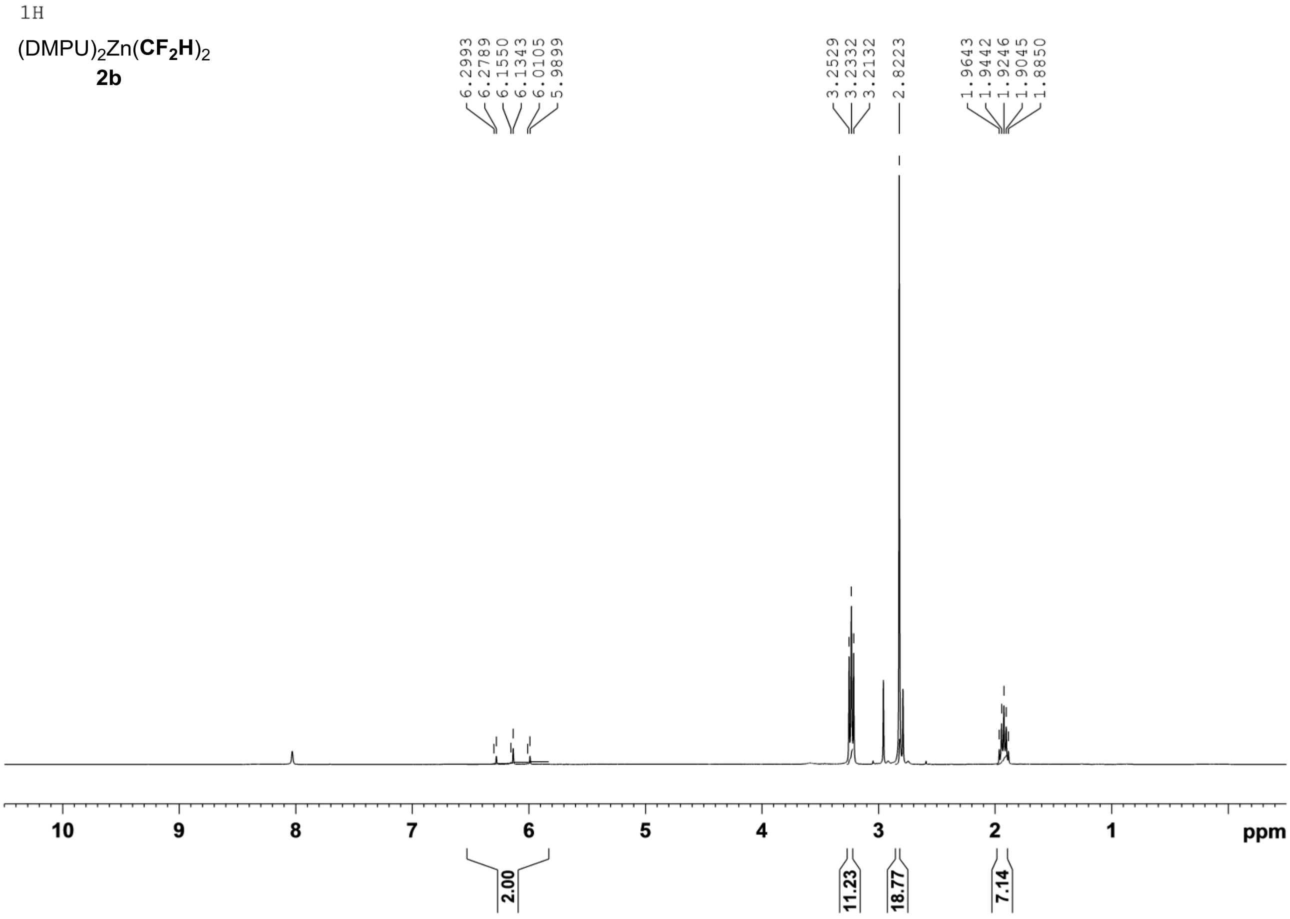


$(DMF)_2Zn(\mathbf{CF_2H})_2$
1b

$(DMF)_2Zn(\mathbf{CF_2H})_2$
1b



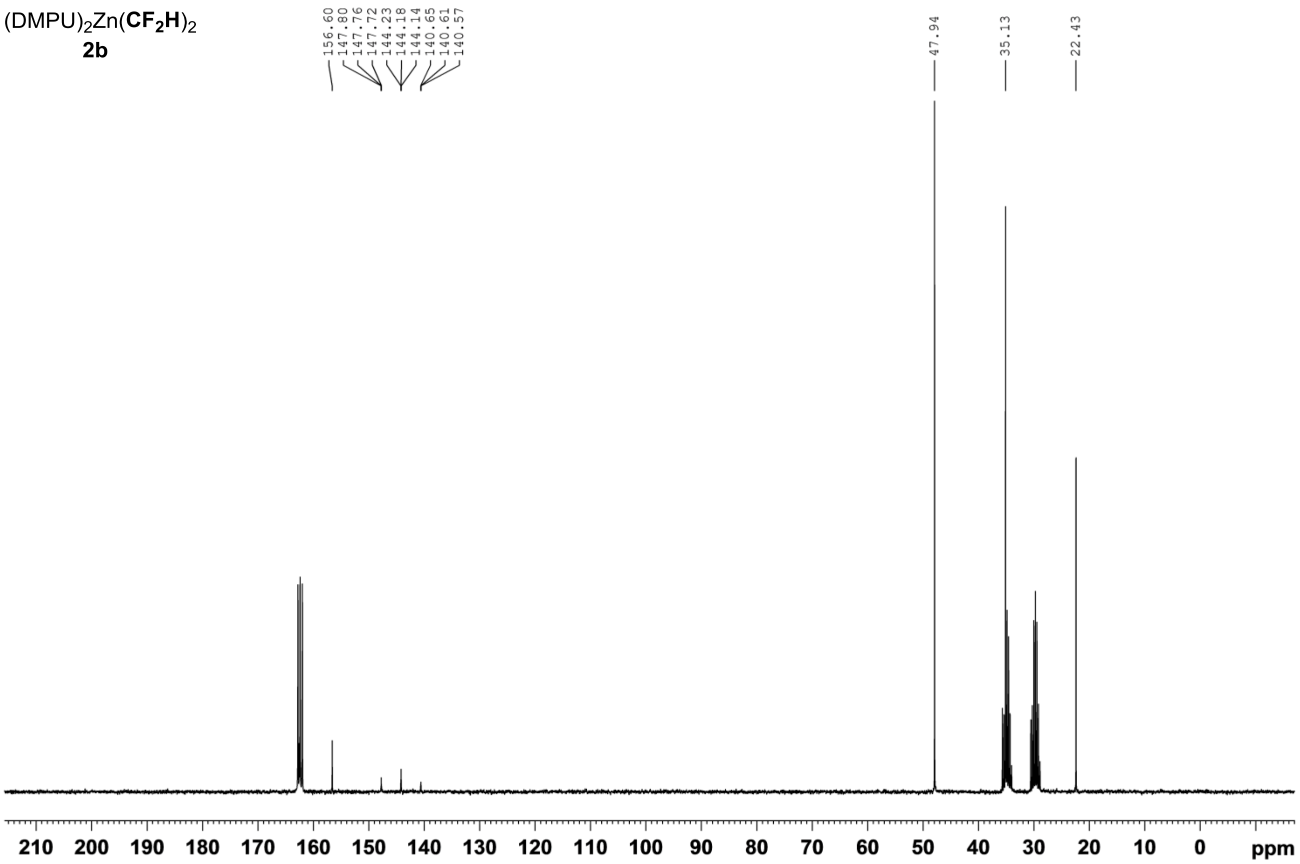
$(DMPU)_2Zn(\mathbf{CF_2H})_2$
2b



13C

(DMPU)$_2$Zn(**CF$_2$H**)$_2$

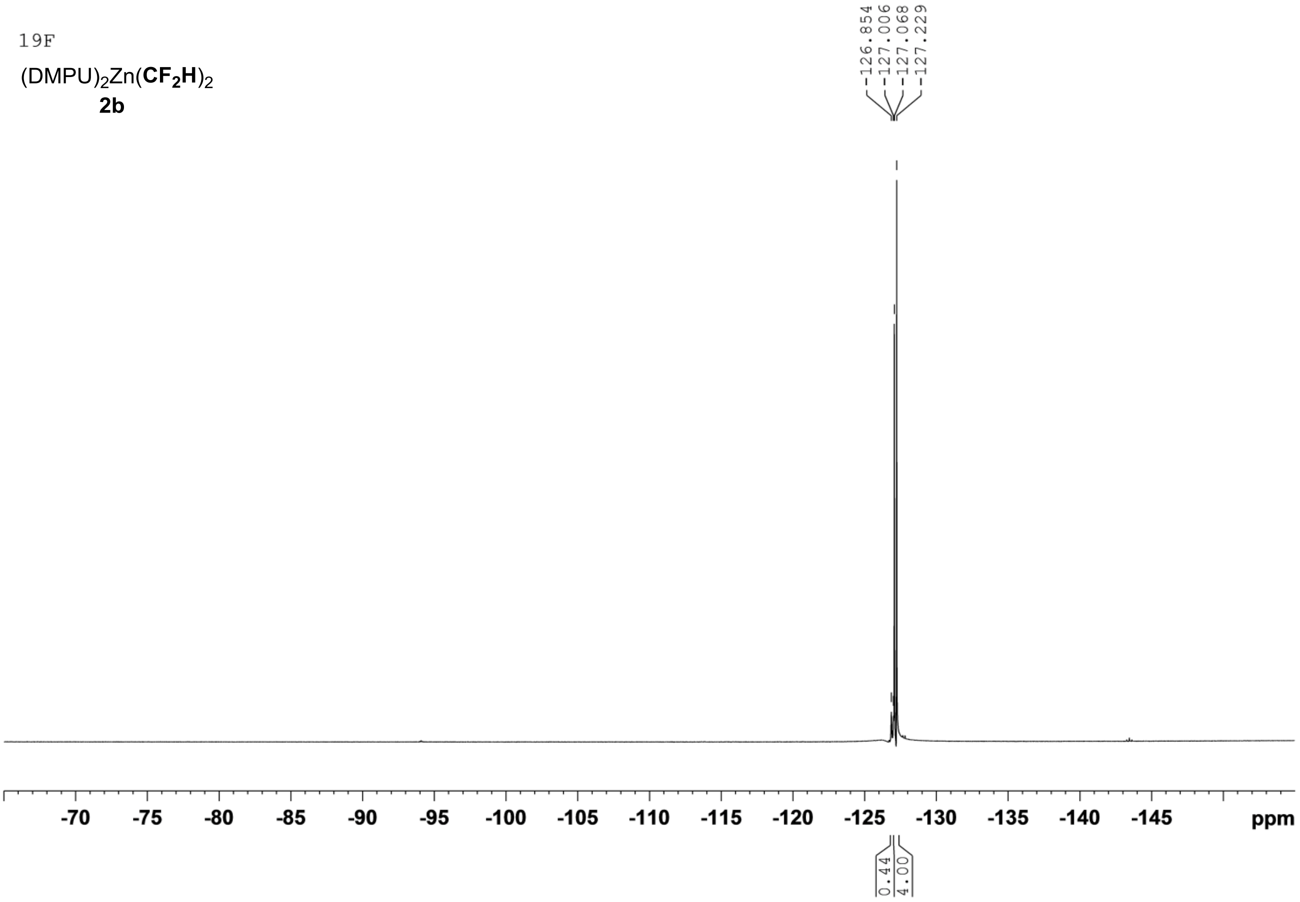
2b

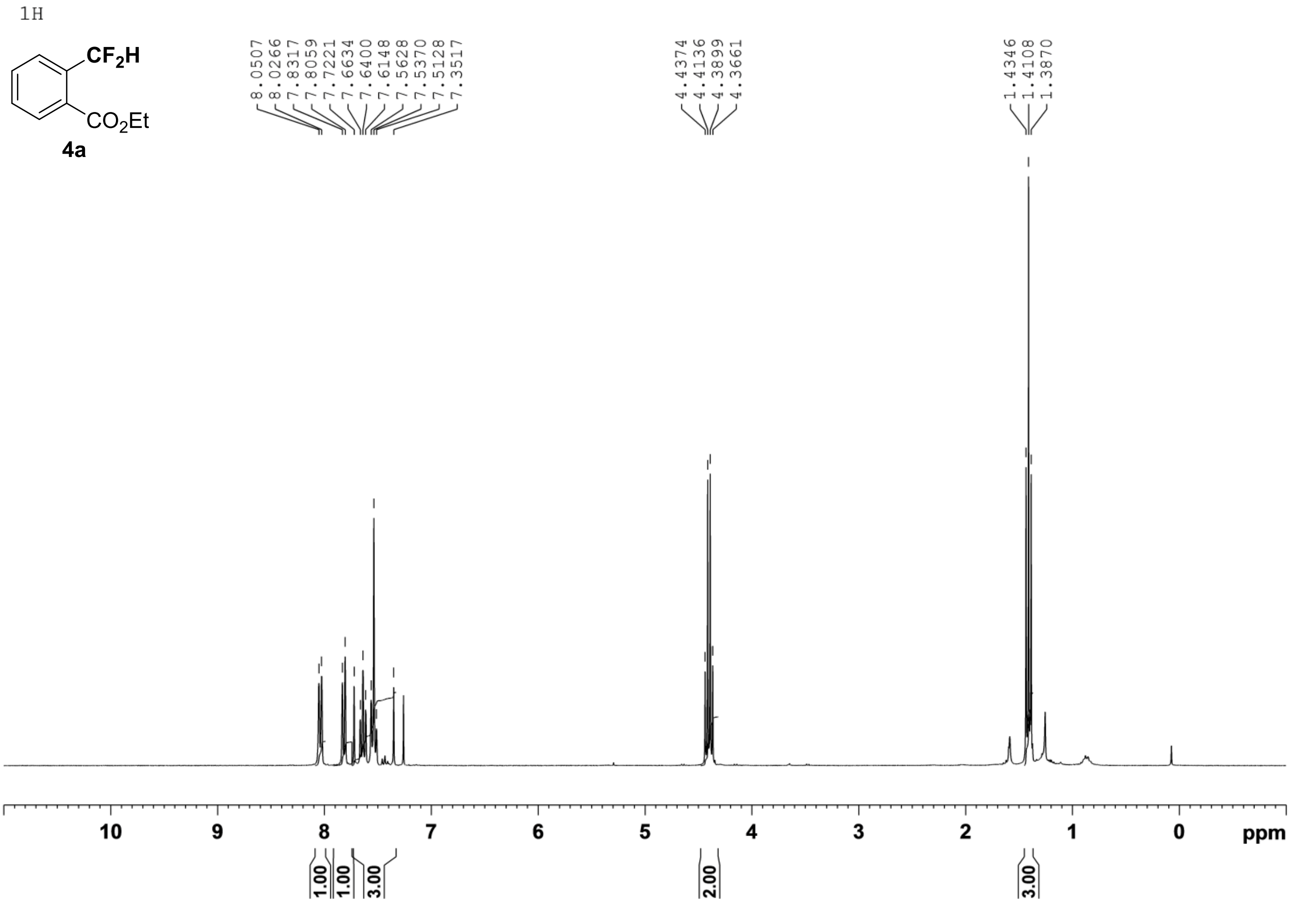


19F

(DMPU)$_2$Zn(**CF$_2$H**)$_2$

2b




1H
CF$_2$H
CO$_2$Et
4a
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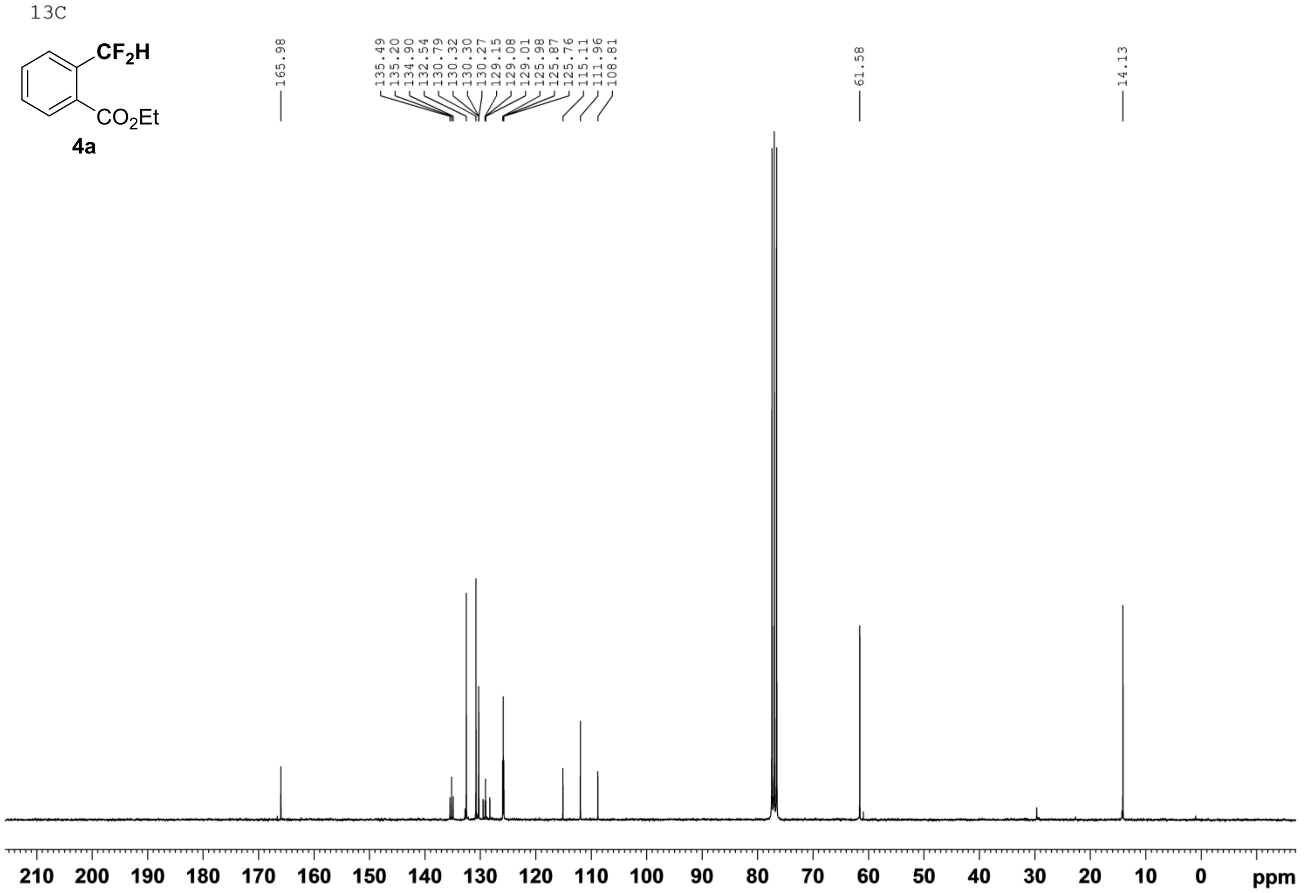
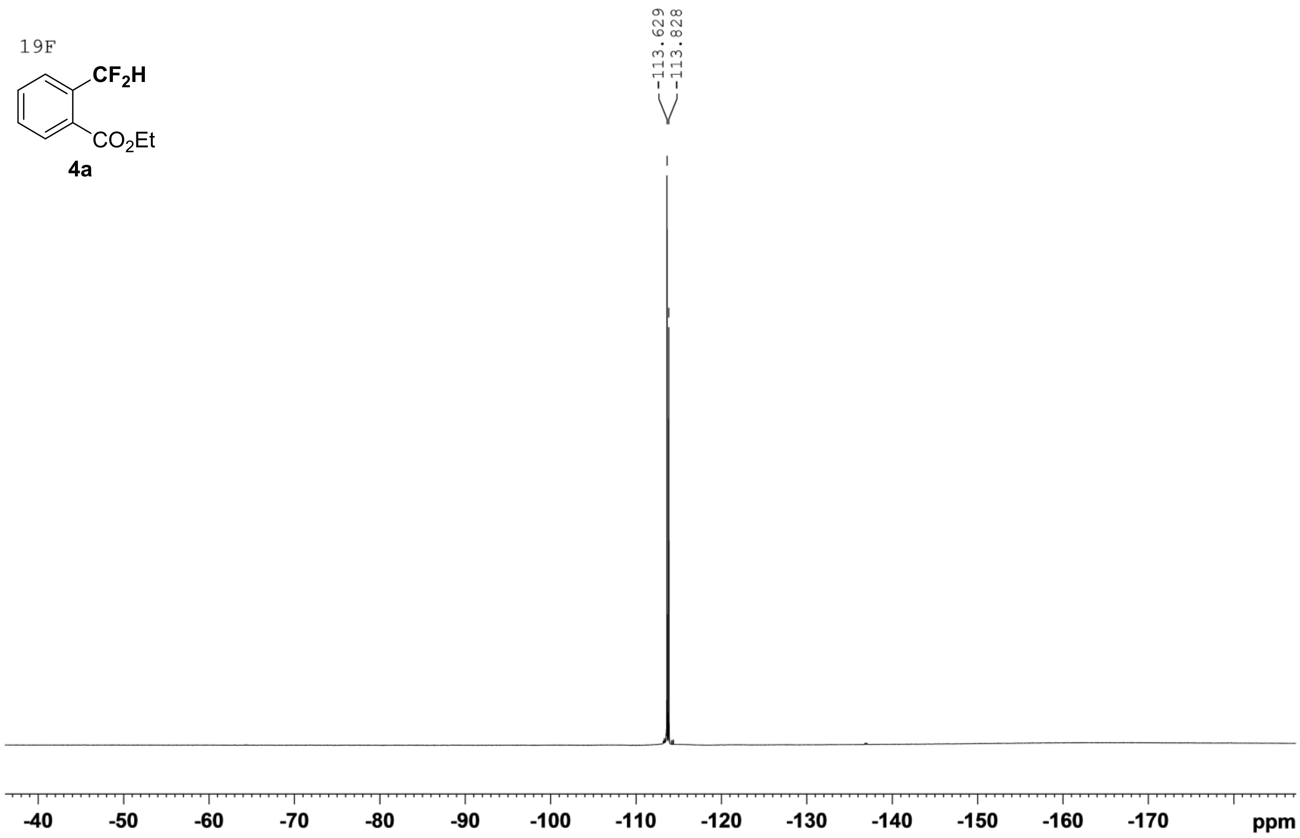
8.0266
7.8317
7.8059
7.7221
7.6634
7.6400
7.6148
7.5628
7.5370
7.5128
7.3517
4.4374
4.4136
4.3899
4.3661
1.4346
1.4108
1.3870
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.00
3.00
2.00
3.00


13C
CF$_2$H
CO$_2$Et
4a
165.98
135.49
135.20
134.90
132.54
130.79
130.32
130.30
130.27
129.15
129.08
129.01
125.98
125.87
125.76
115.11
111.96
108.81
61.58
14.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


19F
CF2H
CO2Et
4a
-113.629
-113.828
-40
-50
-60
-70
-80
-90
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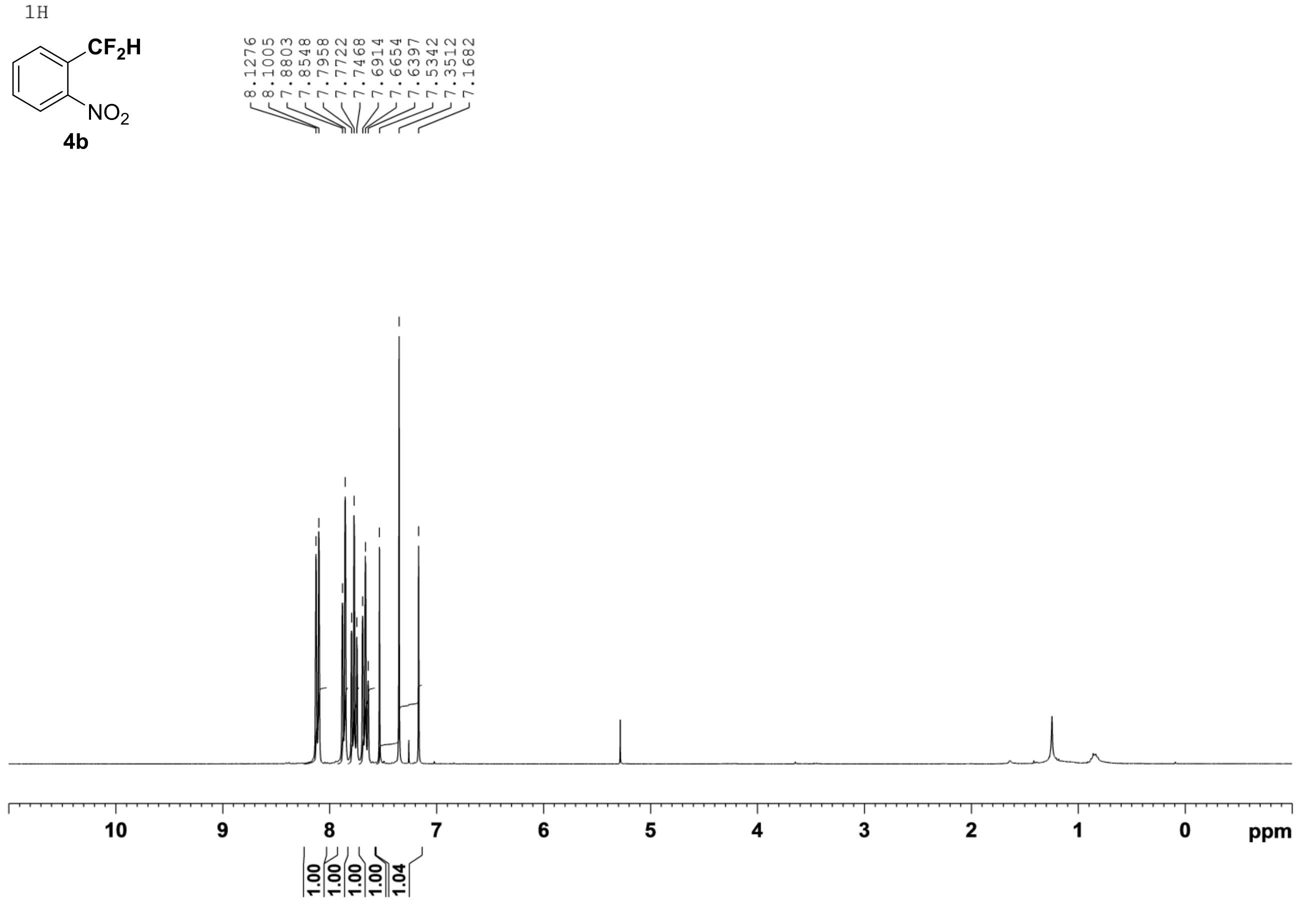
-140
-150
-160
-170
ppm


1H
CF2H
NO2
4b
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8.1005
7.8803
7.8548
7.7958
7.7722
7.7468
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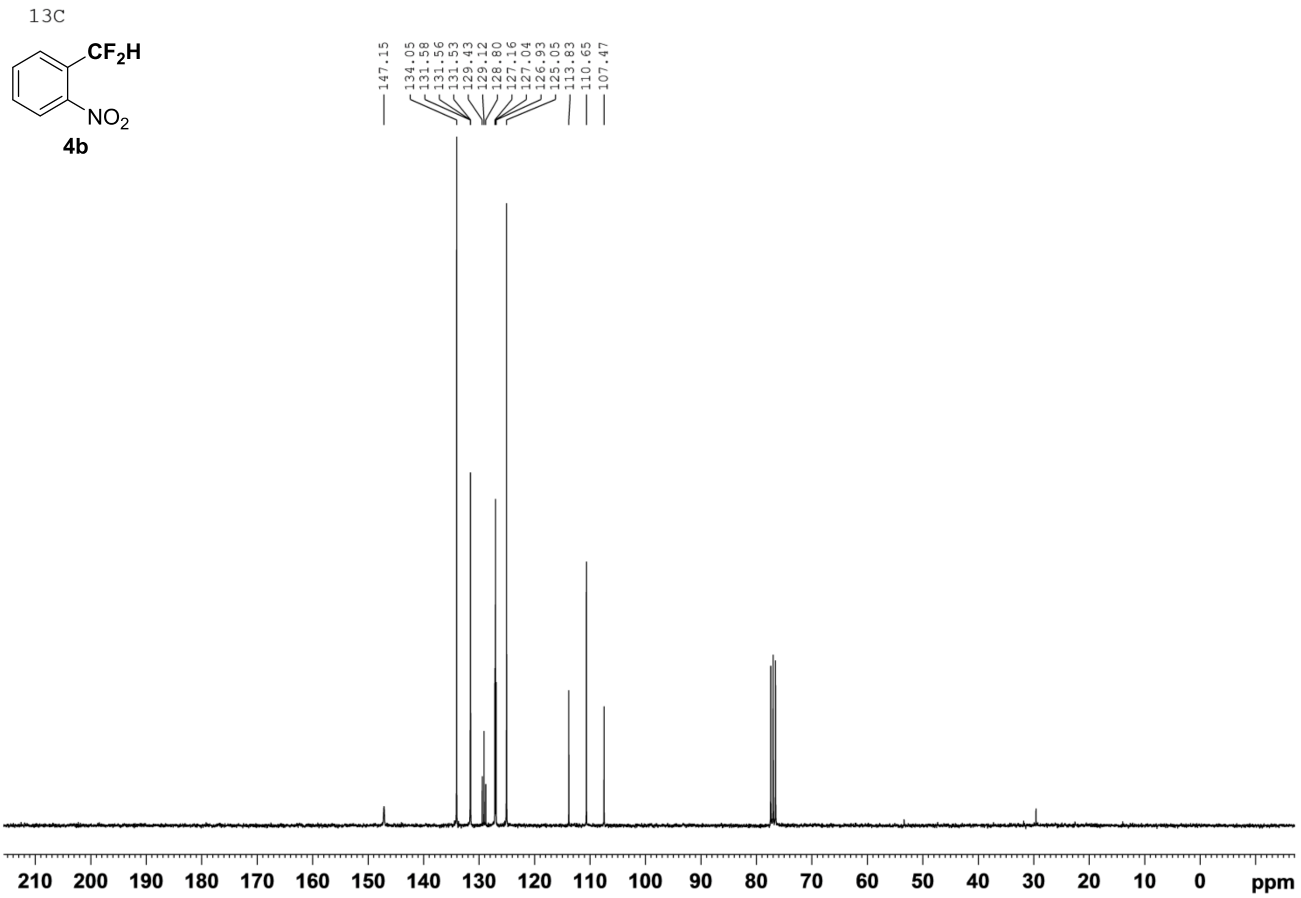
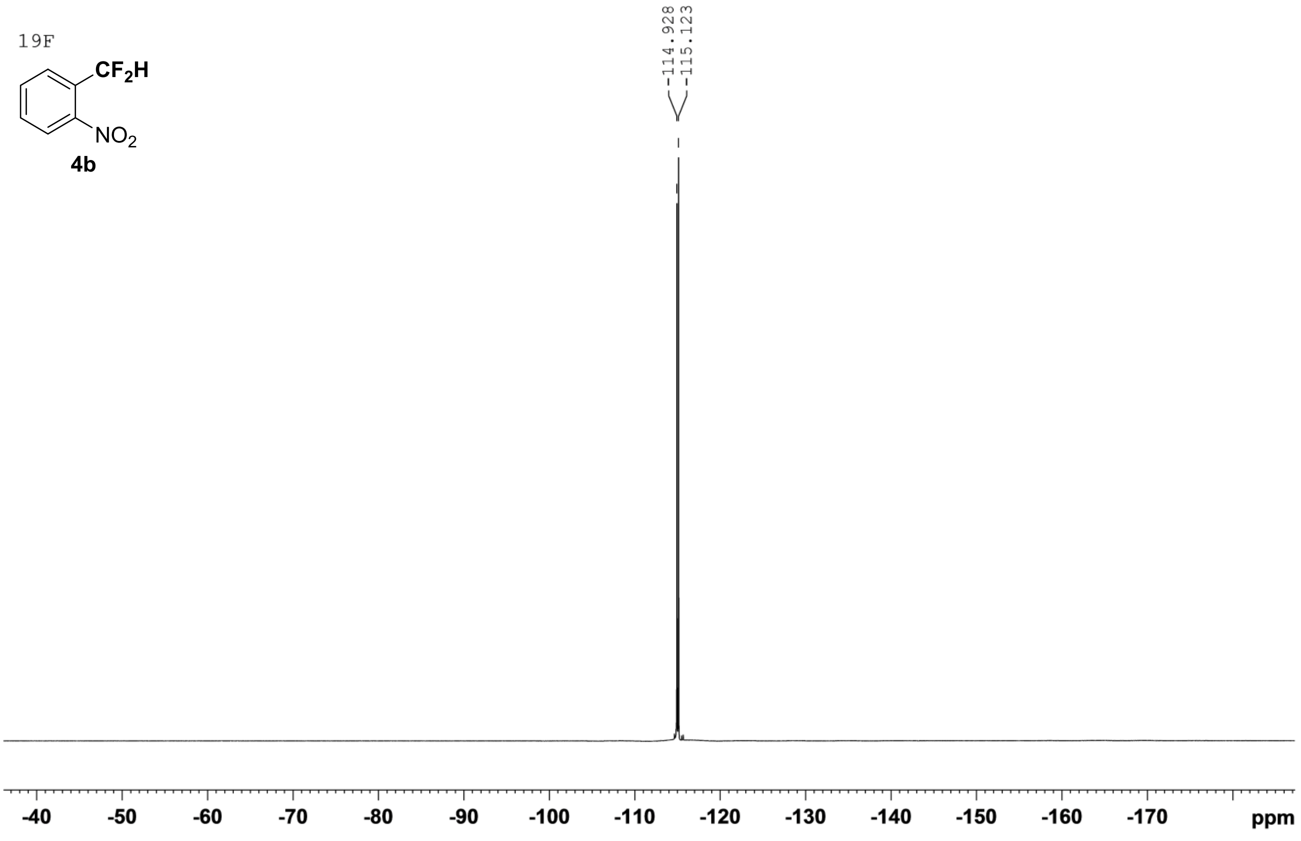
7.6654
7.6397
7.5342
7.3512
7.1682
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.00
1.00
1.04


13C
CF2H
NO2
4b
147.15
134.05
131.58
131.56
131.53
129.43
129.12
128.80
127.16
127.04
126.93
125.05
113.83
110.65
107.47
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


19F
CF2H
NO2
4b
-114.928
-115.123
-40
-50
-60
-70
-80
-90
-100
-110
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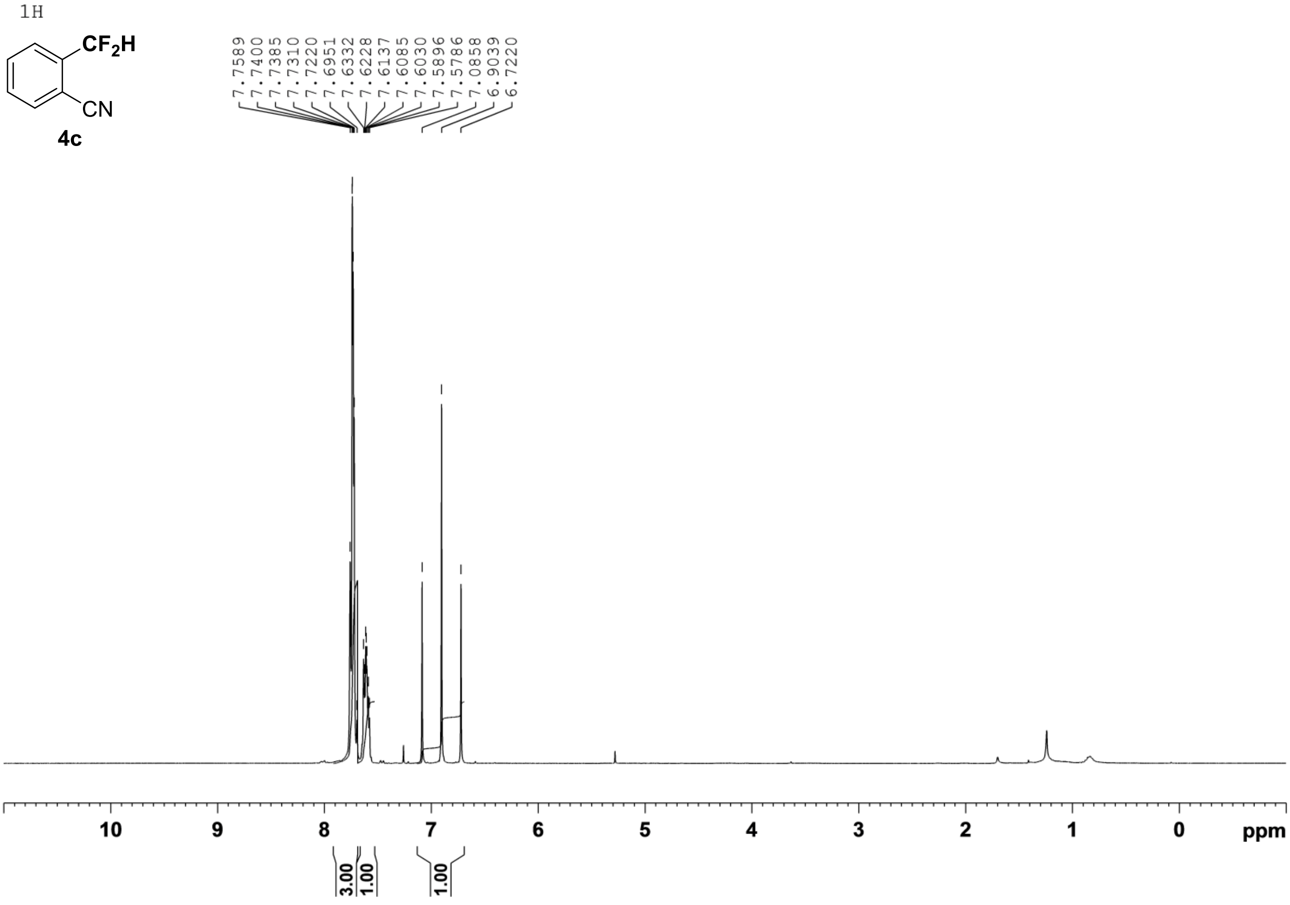
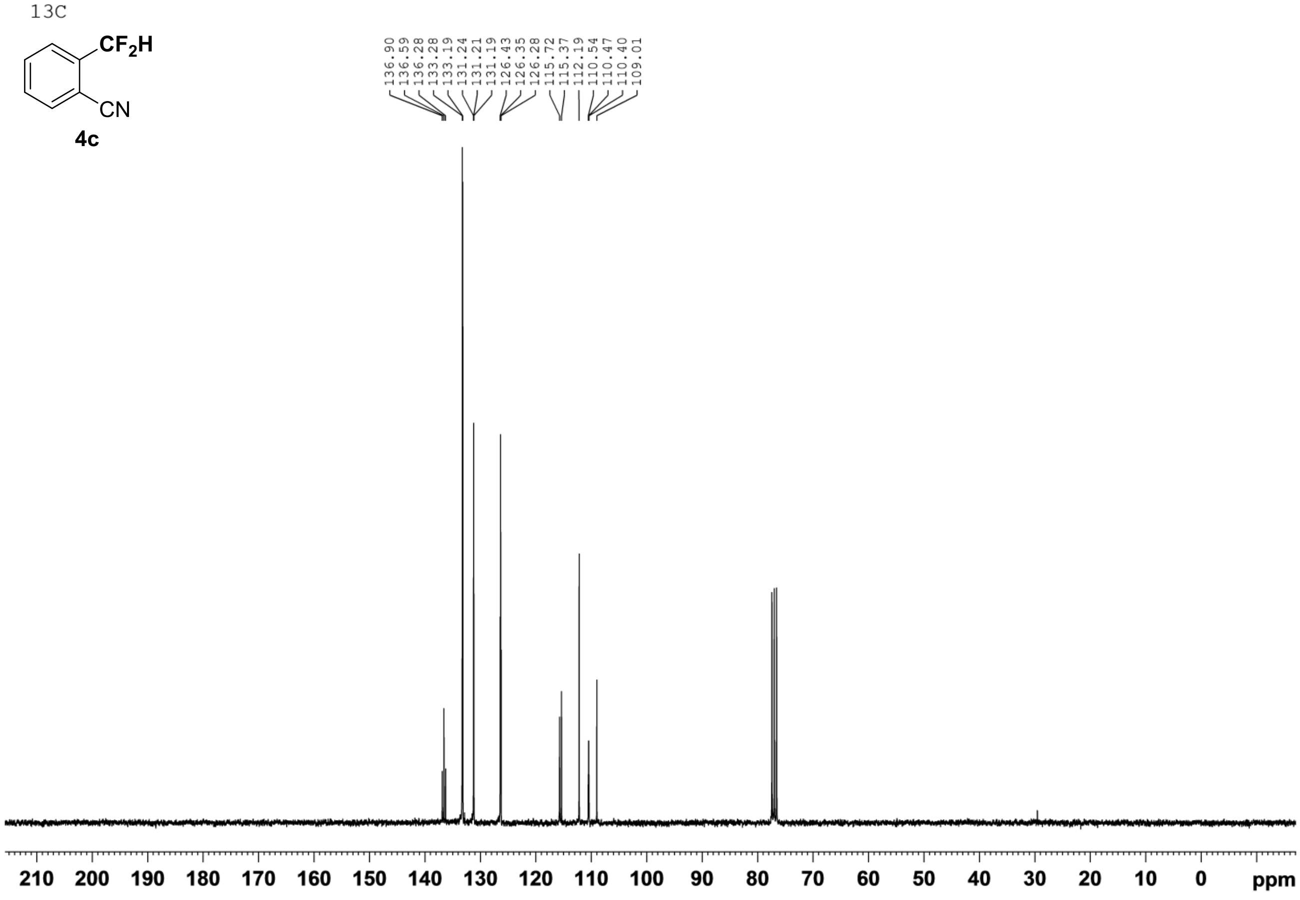
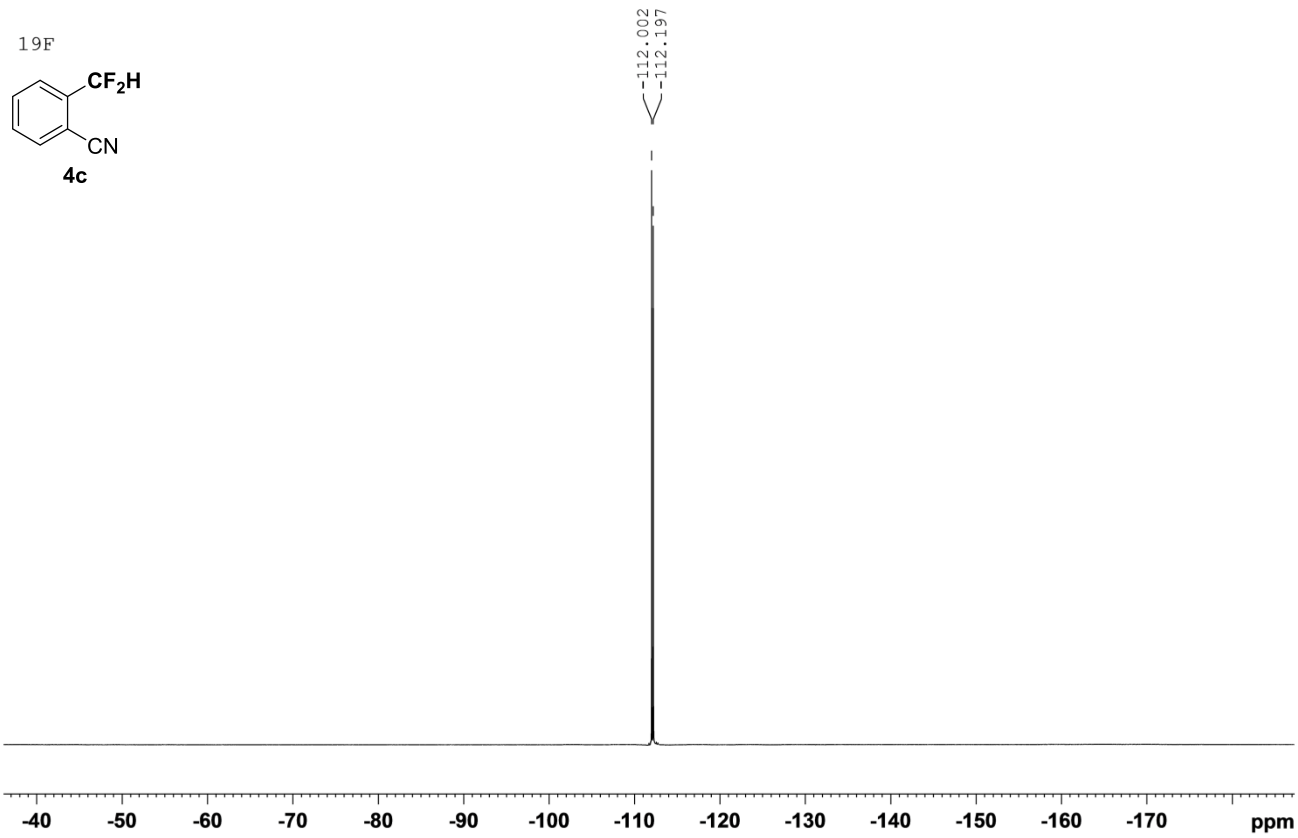
-130
-140
-150
-160
-170
ppm


1H
CF2H
CN
4c
7.7589
7.7400
7.7385
7.7310
7.7220
7.6951
7.6332
7.6228
7.6137
7.6085
7.6030
7.5896
7.5786
7.0858
6.9039
6.7220
10
9
8
7
6
5
4
3
2
1
0
ppm
3.00
1.00
1.00


13C
CF2H
CN
4c
136.90
136.59
136.28
133.28
133.19
131.24
131.21
131.19
126.43
126.35
126.28
115.72
115.37
112.19
110.54
110.47
110.40
109.01
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


19F
CF2H
CN
4c
-112.002
-112.197
-40
-50
-60
-70
-80
-90
-100
-110
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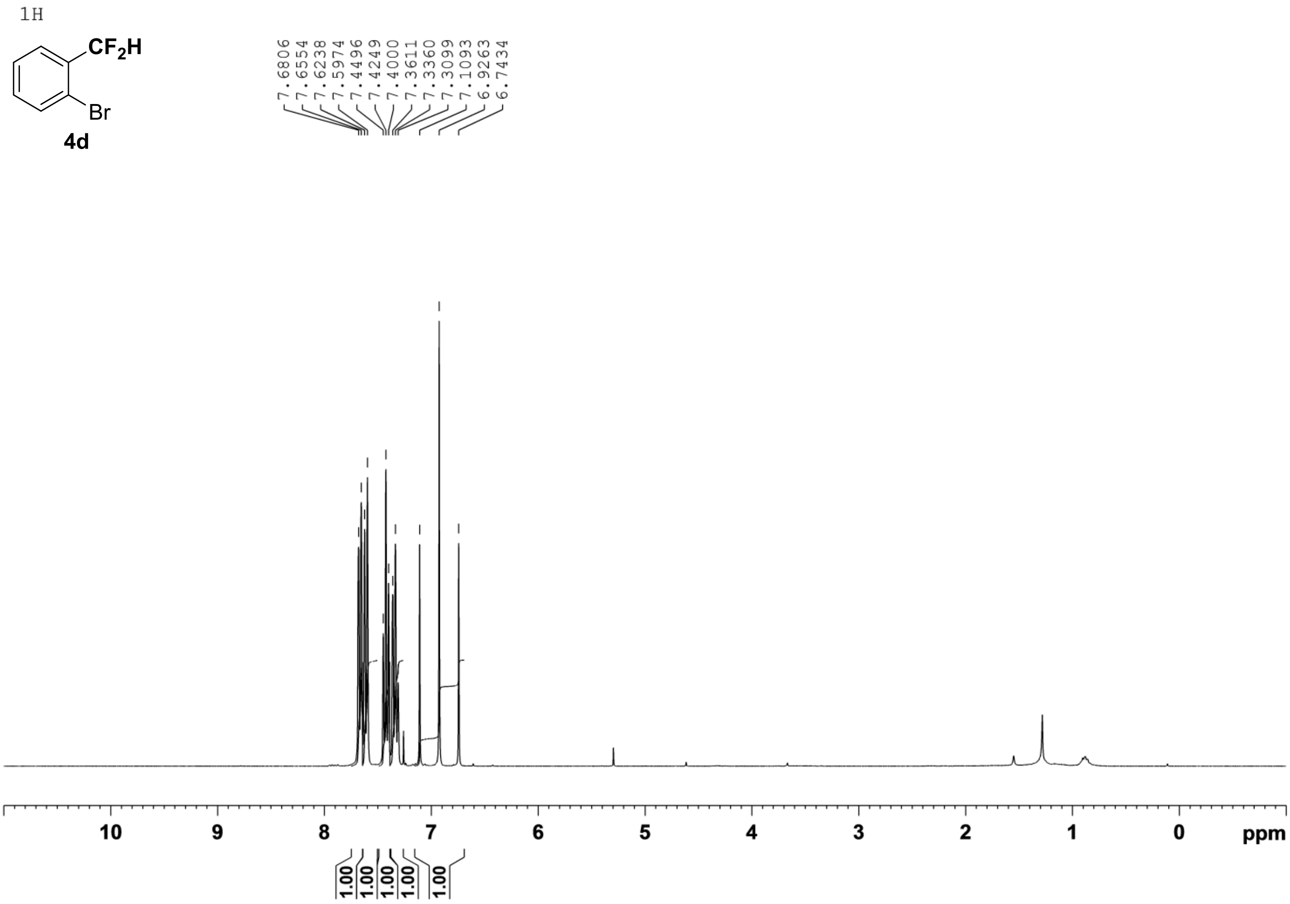
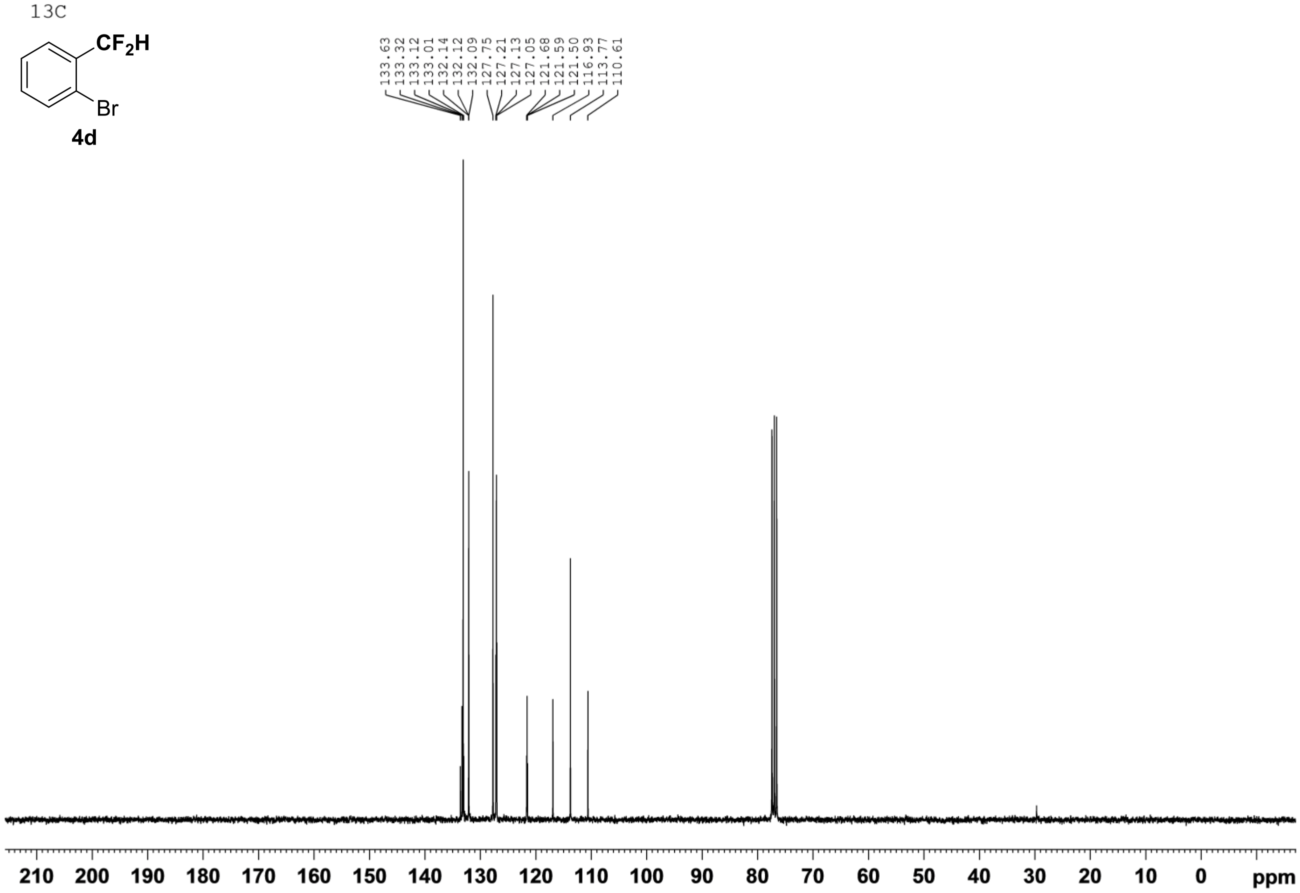
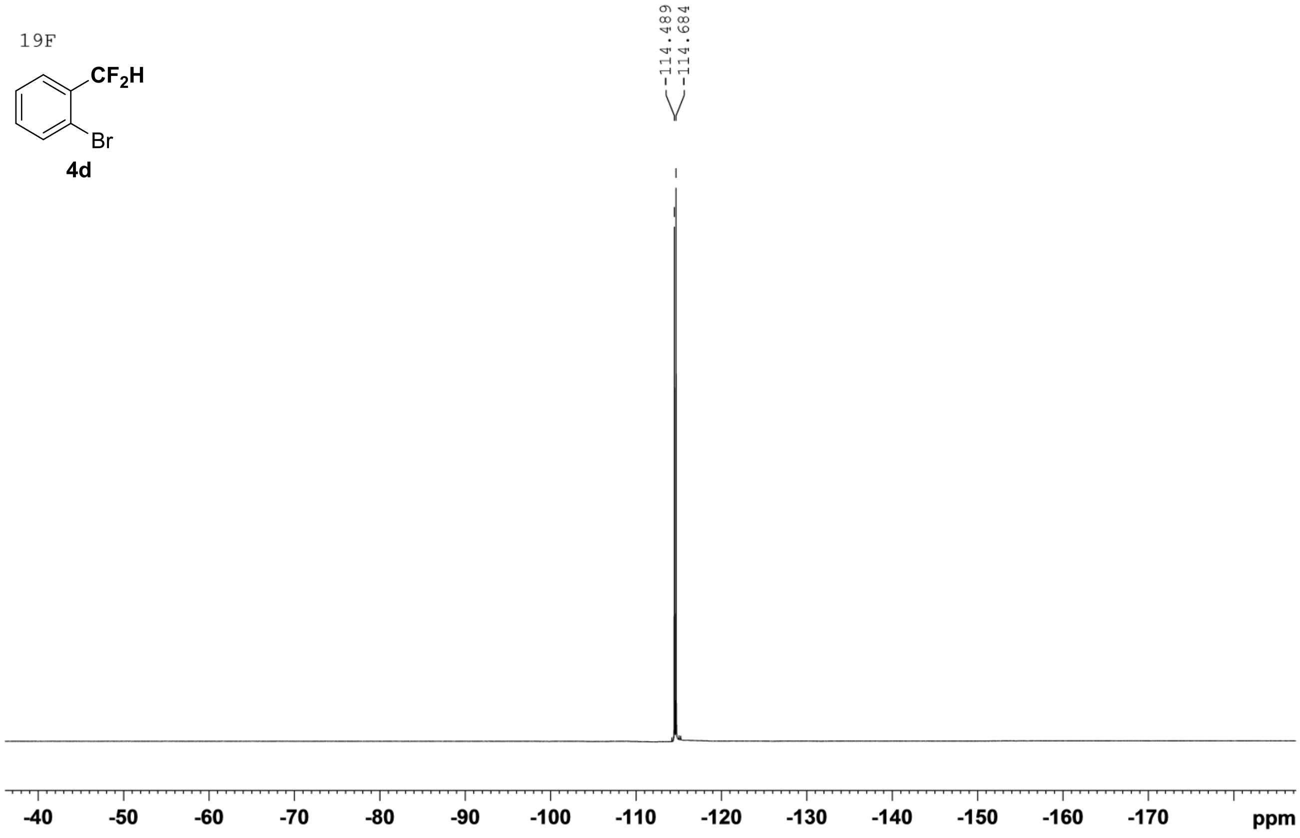
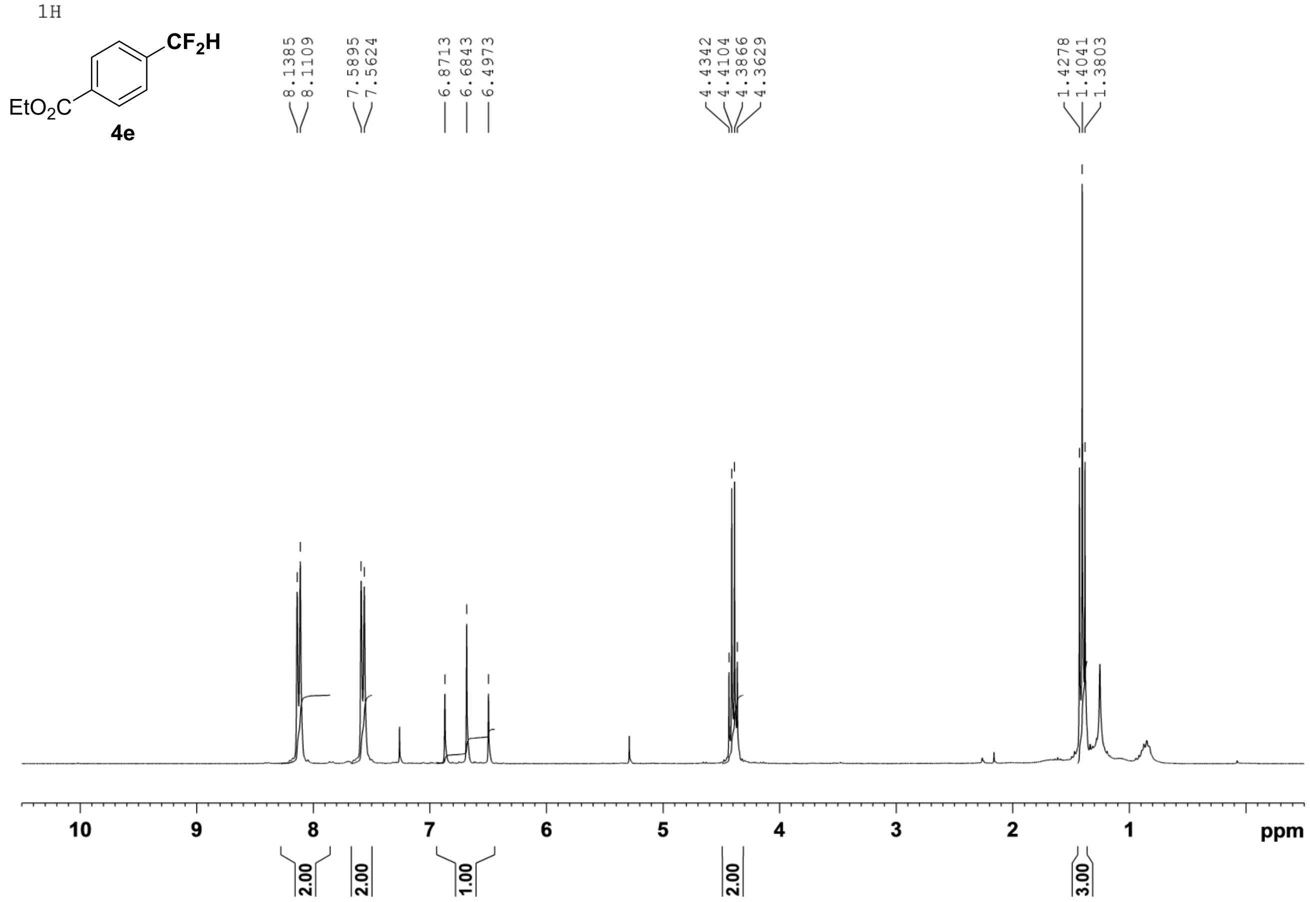
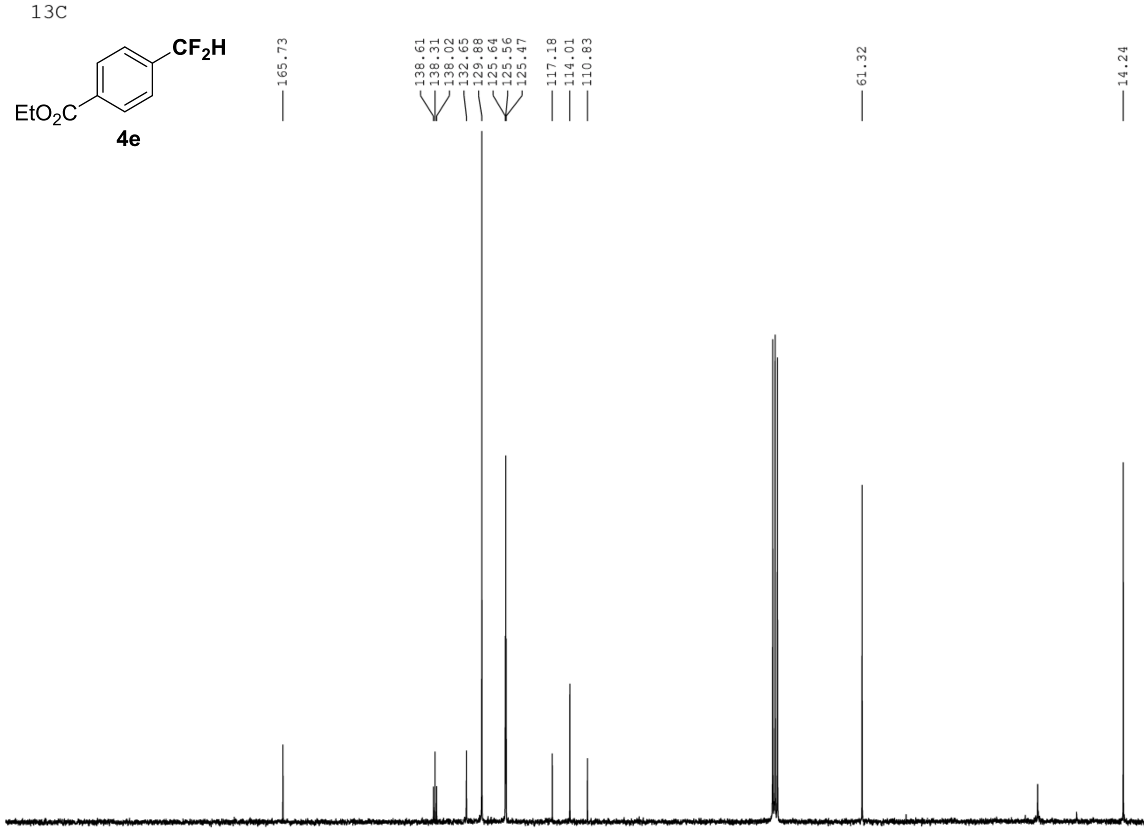
-130
-140
-150
-160
-170
ppm

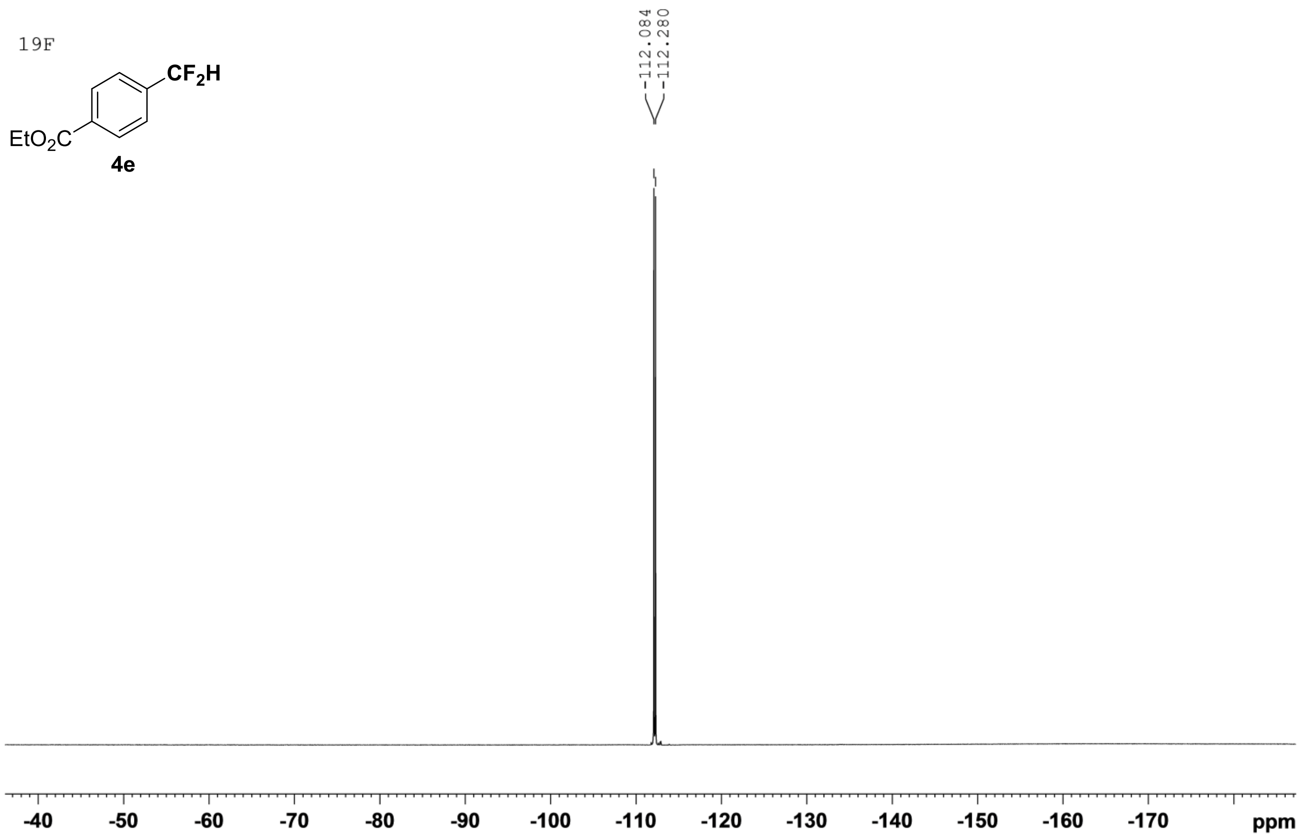

1H
CF2H
Br
4d
7.6806
7.6554
7.6238
7.5974
7.4496
7.4249
7.4000
7.3611
7.3360
7.3099
7.1093
6.9263
6.7434
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.00
1.00
1.00

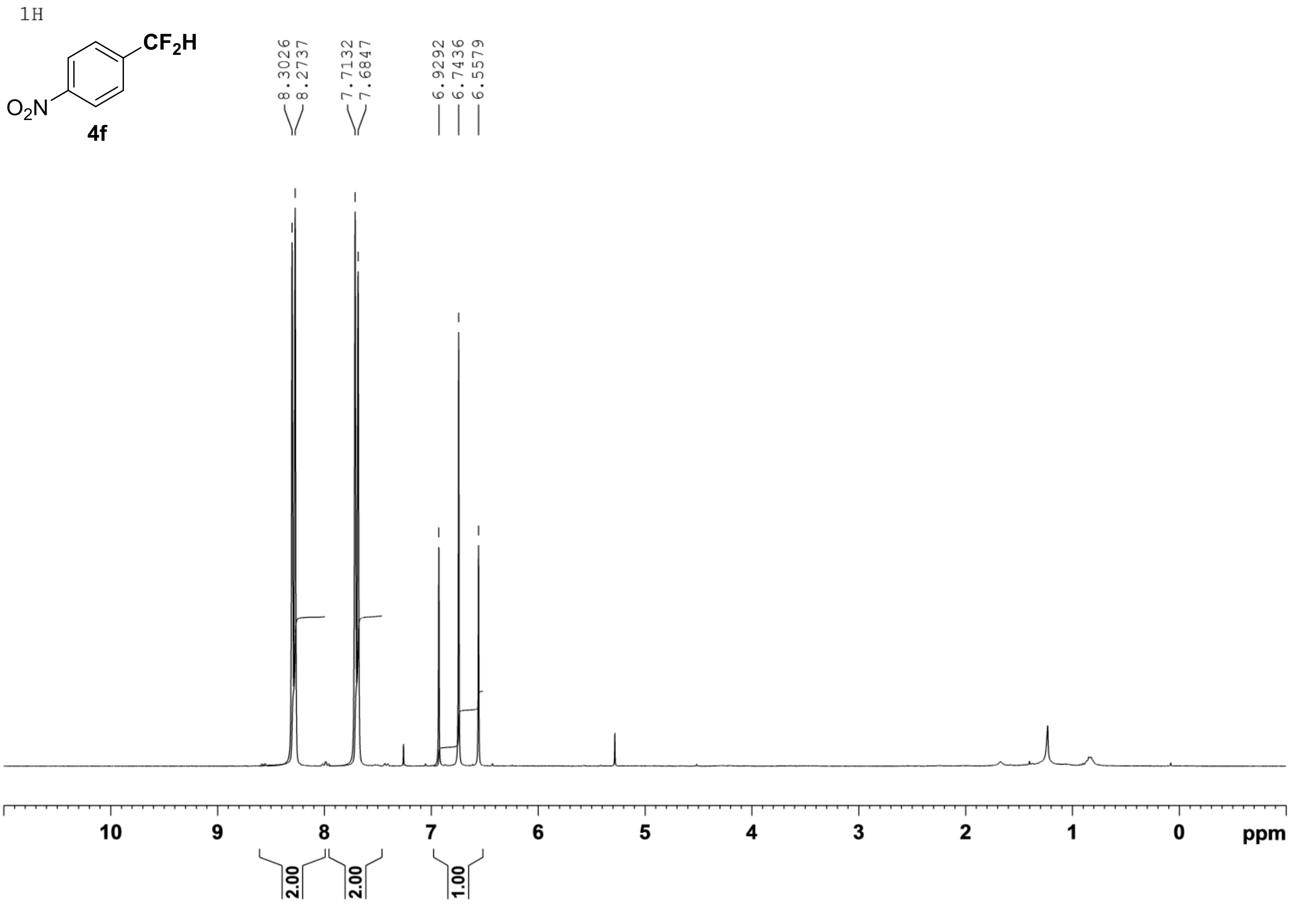

13C
CF2H
Br
4d
133.63
133.32
133.12
133.01
132.14
132.12
132.09
127.75
127.21
127.13
127.05
121.68
121.59
121.50
116.93
113.77
110.61
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

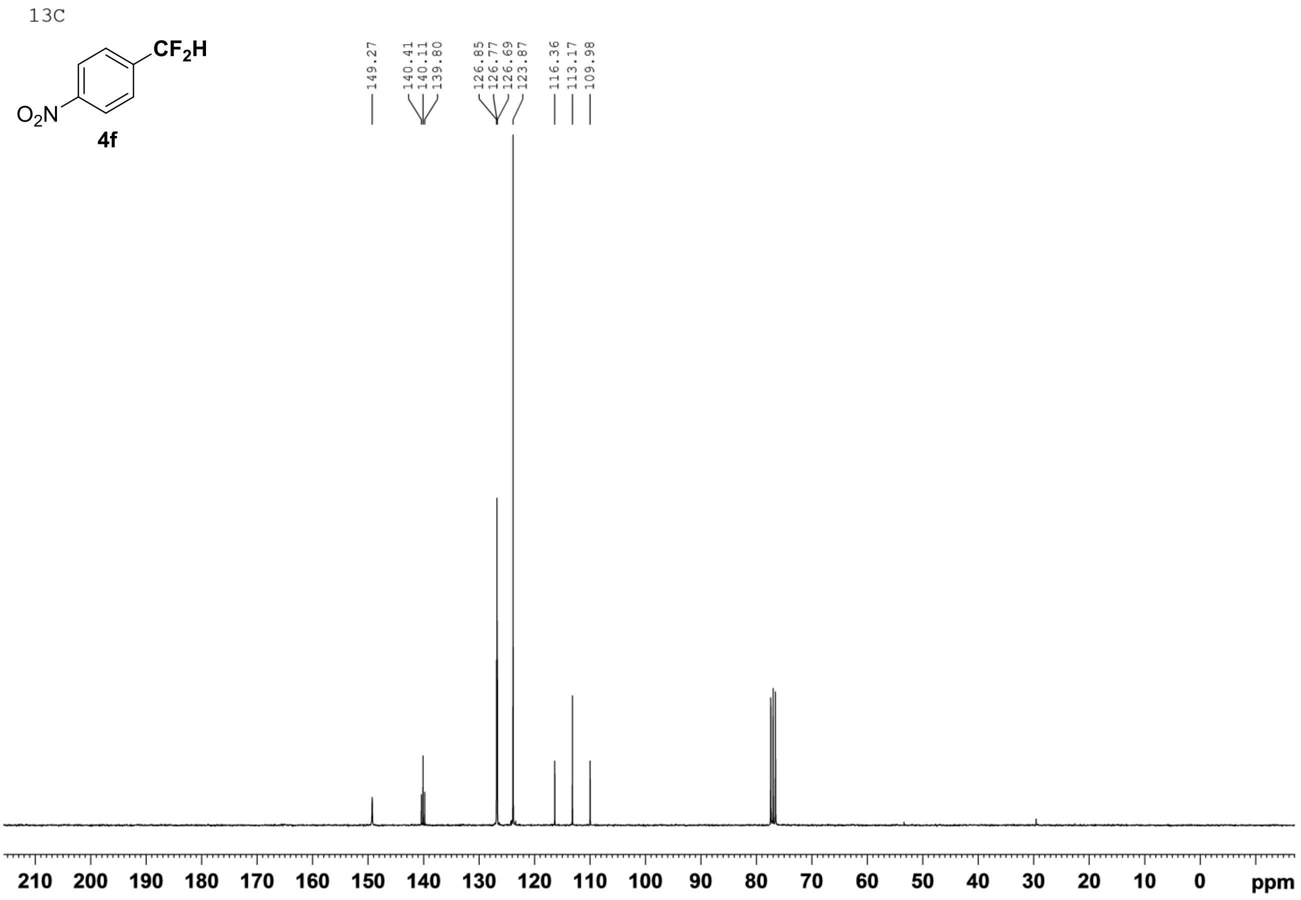

19F
CF2H
Br
4d
-114.489
-114.684
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm

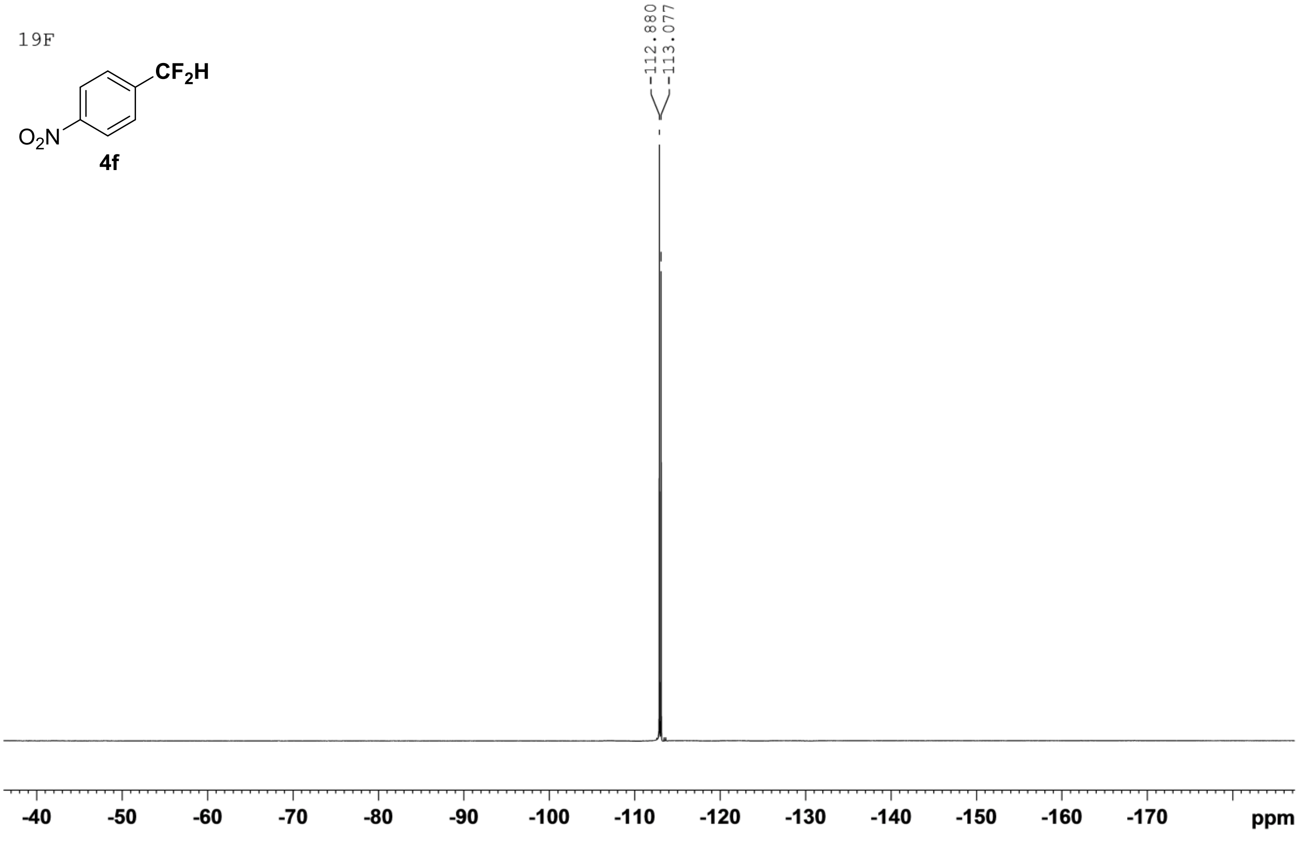

1H
CF2H
EtO2C
4e
8.1385
8.1109
7.5895
7.5624
6.8713
6.6843
6.4973
4.4342
4.4104
4.3866
4.3629
1.4278
1.4041
1.3803
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
1.00
2.00
3.00


13C
CF2H
EtO2C
4e
165.73
138.61
138.31
138.02
132.65
129.88
125.64
125.56
125.47
117.18
114.01
110.83
61.32
14.24
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


19F
CF_2H
EtO_2C
4e
-112.084
-112.280
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm


1H
CF_2H
O_2N
4f
8.3026
8.2737
7.7132
7.6847
6.9292
6.7436
6.5579
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.00
1.00


13C
CF$_2$H
O$_2$N
4f
149.27
140.41
140.11
139.80
126.85
126.77
126.69
123.87
116.36
113.17
109.98
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


19F
CF$_2$H
O$_2$N
4f
-112.880
-113.077
-40
-50
-60
-70
-80
-90
-100
-110
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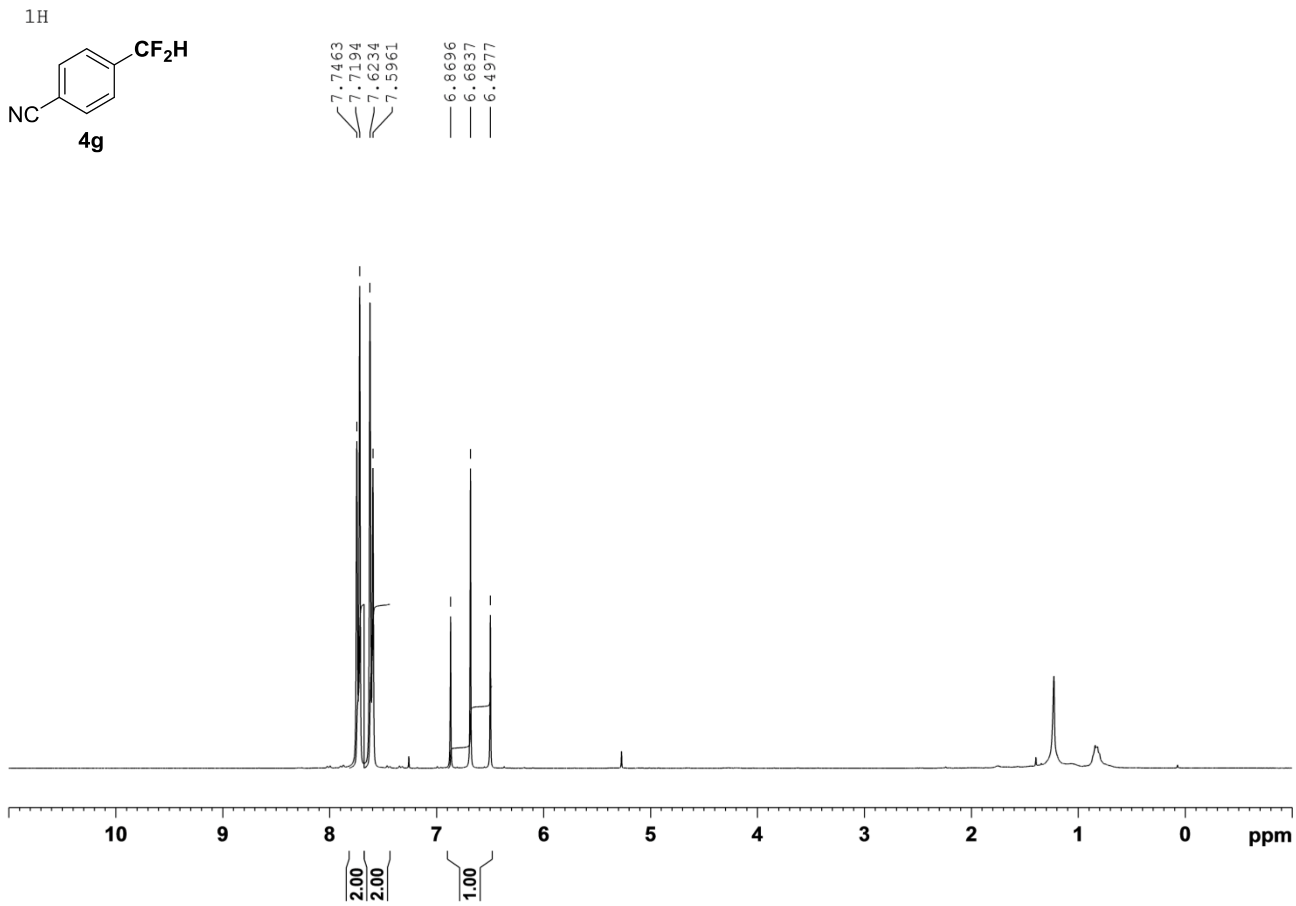
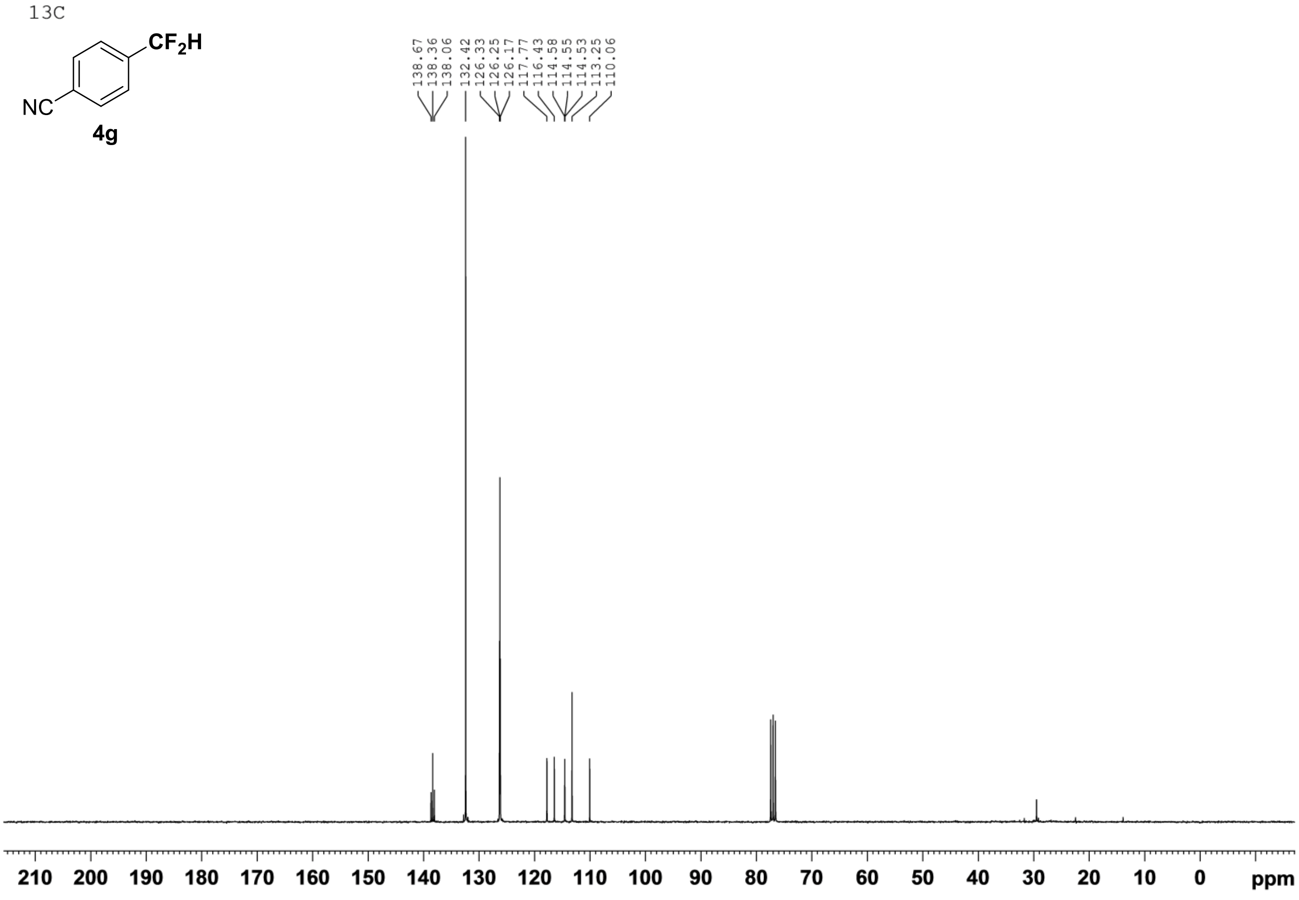
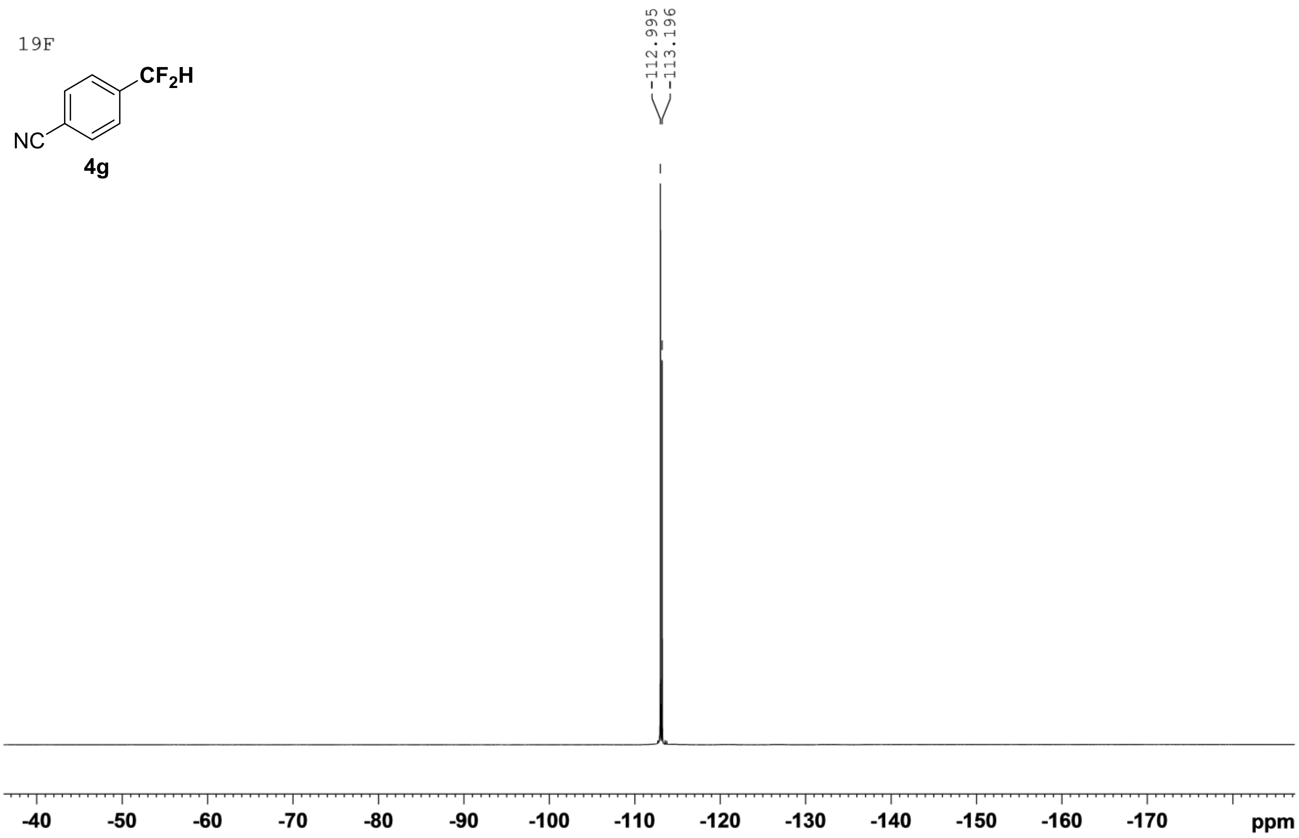
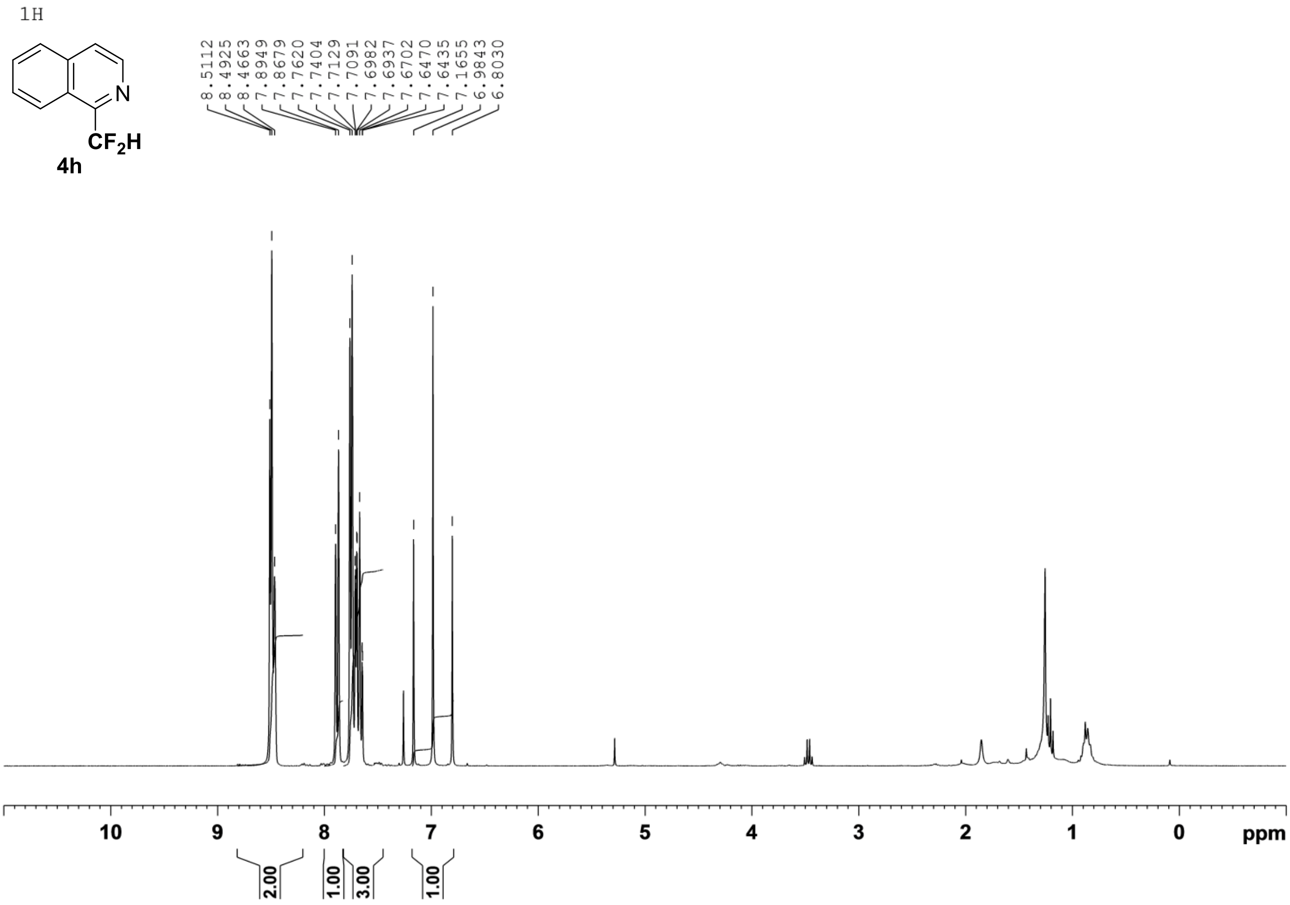
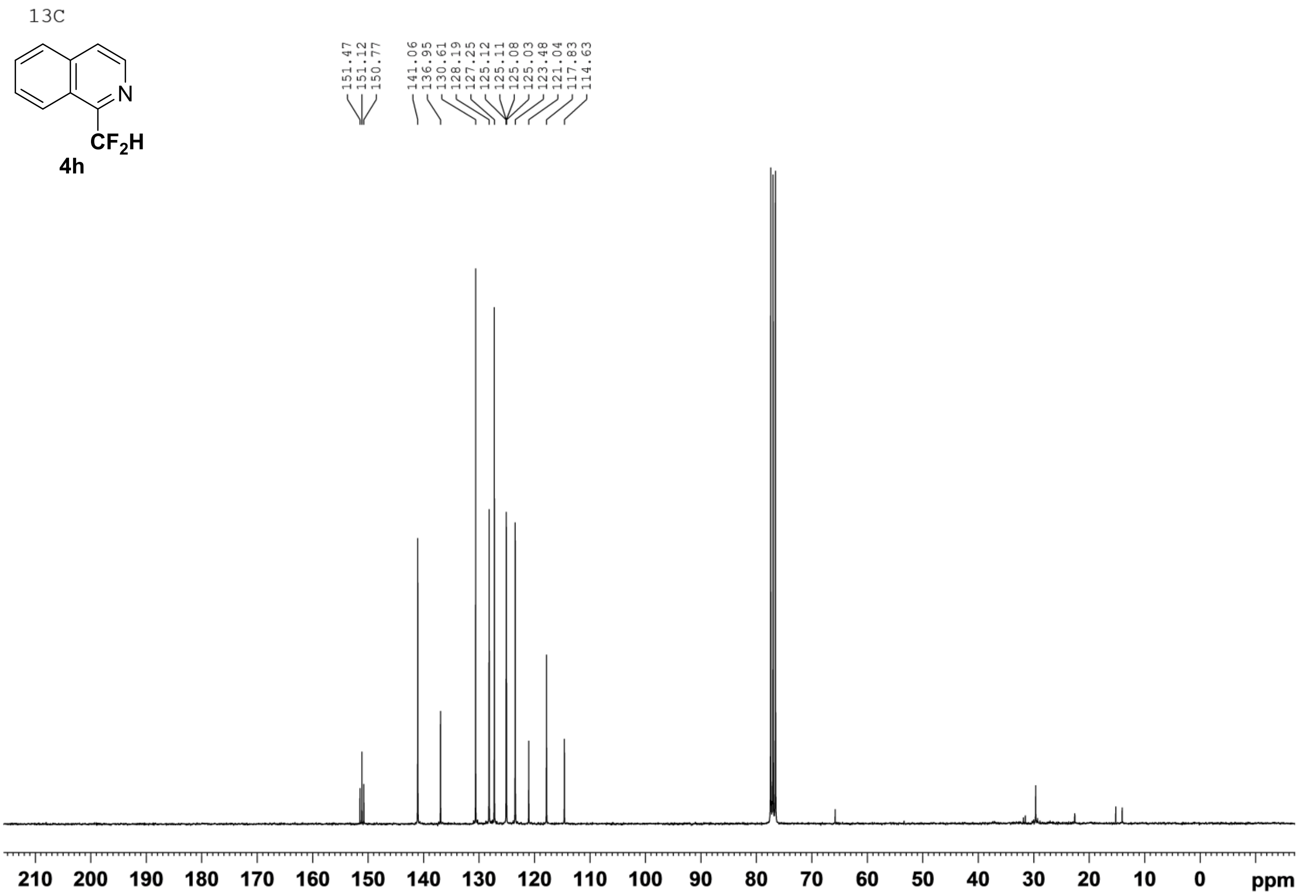
-130
-140
-150
-160
-170
ppm

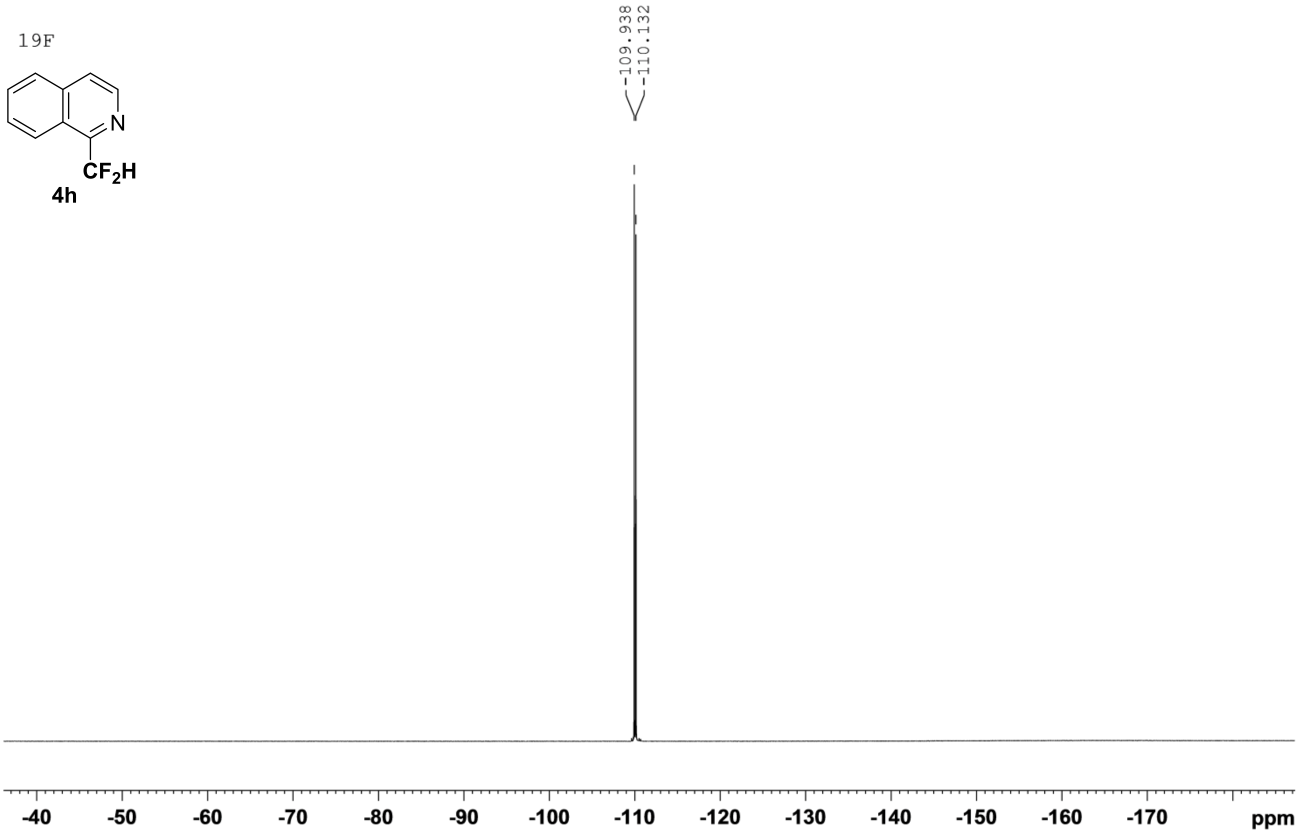

1H
CF2H
NC
4g
7.7463
7.7194
7.6234
7.5961
6.8696
6.6837
6.4977
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.00
1.00

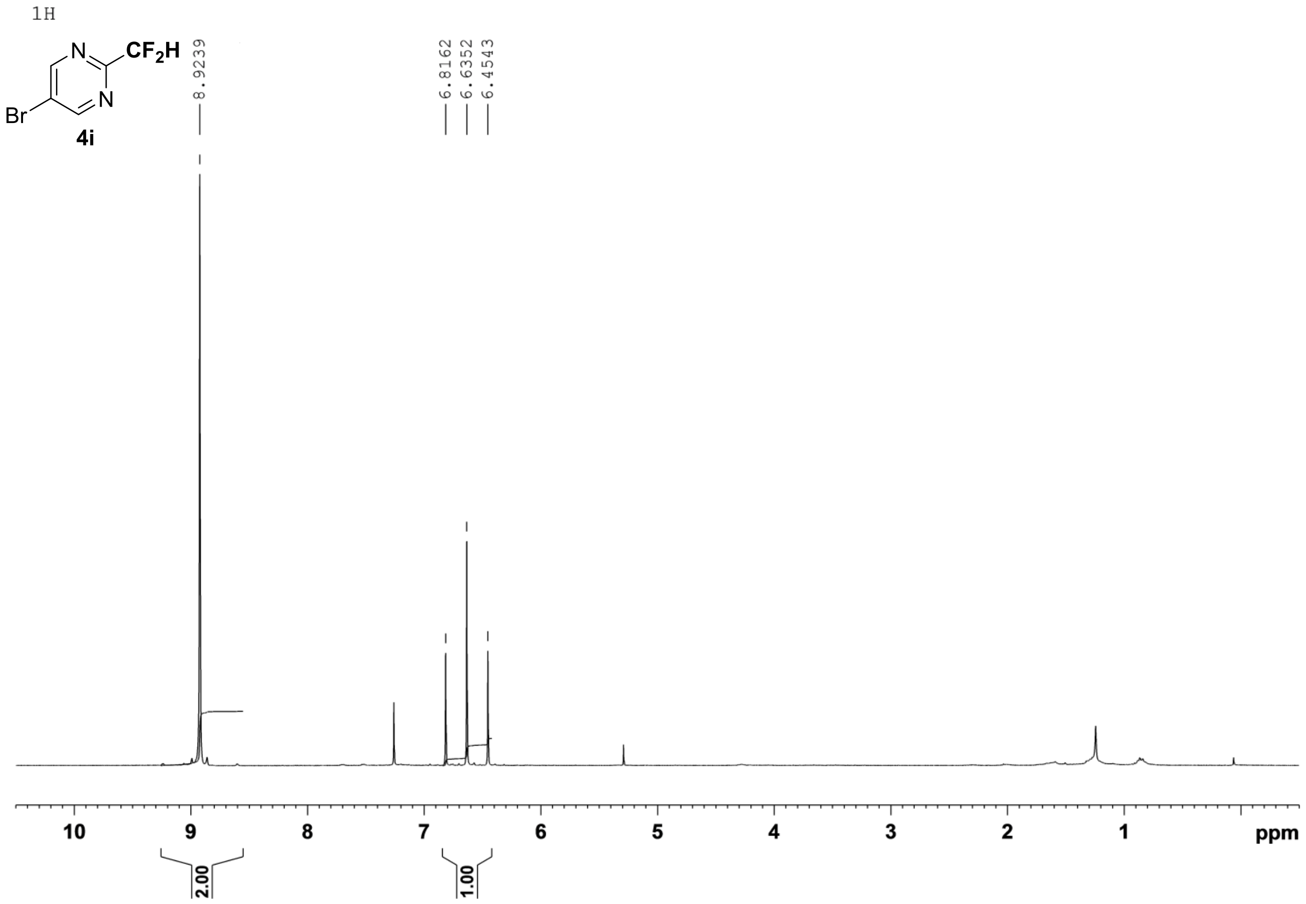

13C
CF2H
NC
4g
138.67
138.36
138.06
132.42
126.33
126.25
126.17
117.77
116.43
114.58
114.55
114.53
113.25
110.06
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

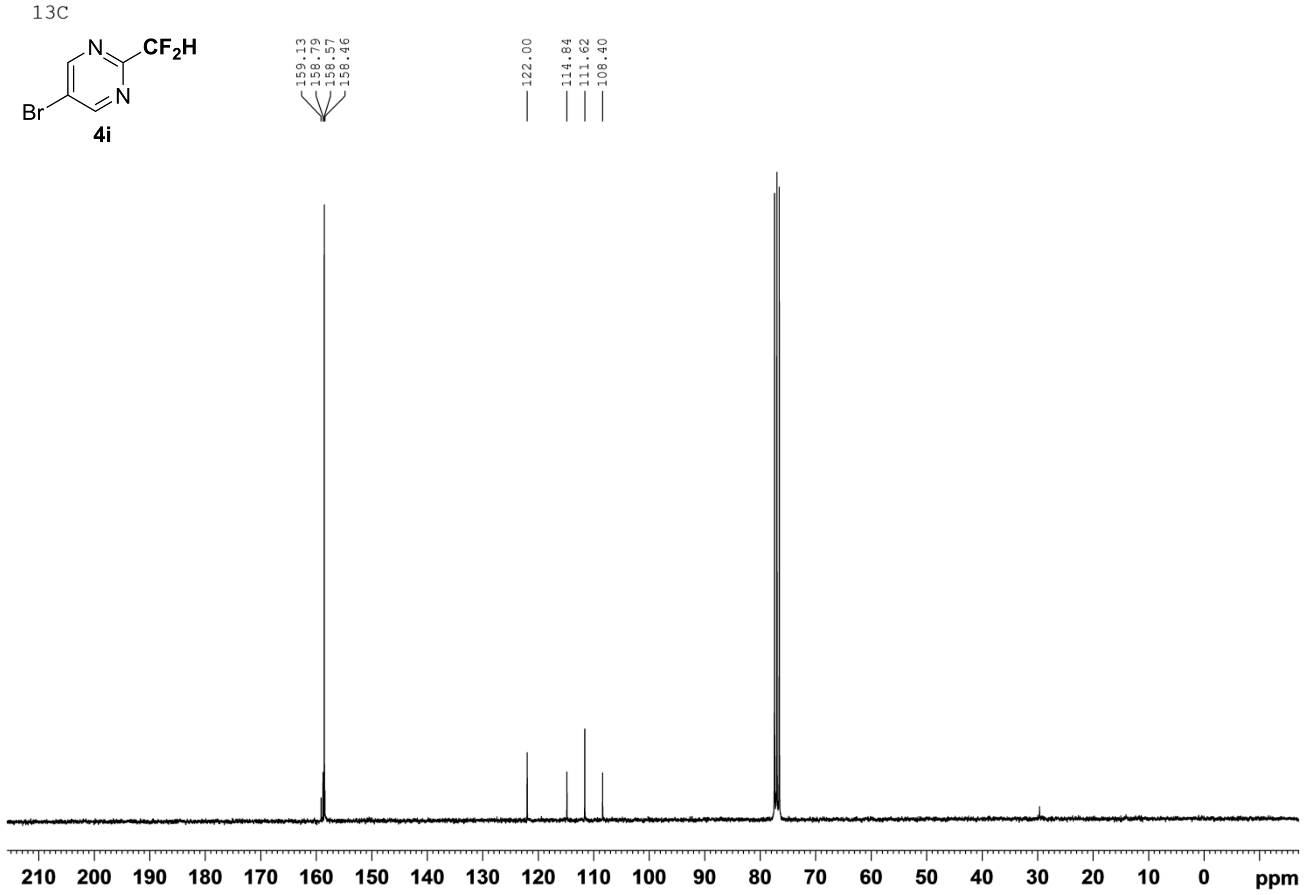

19F
CF2H
NC
4g
-112.995
-113.196
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm

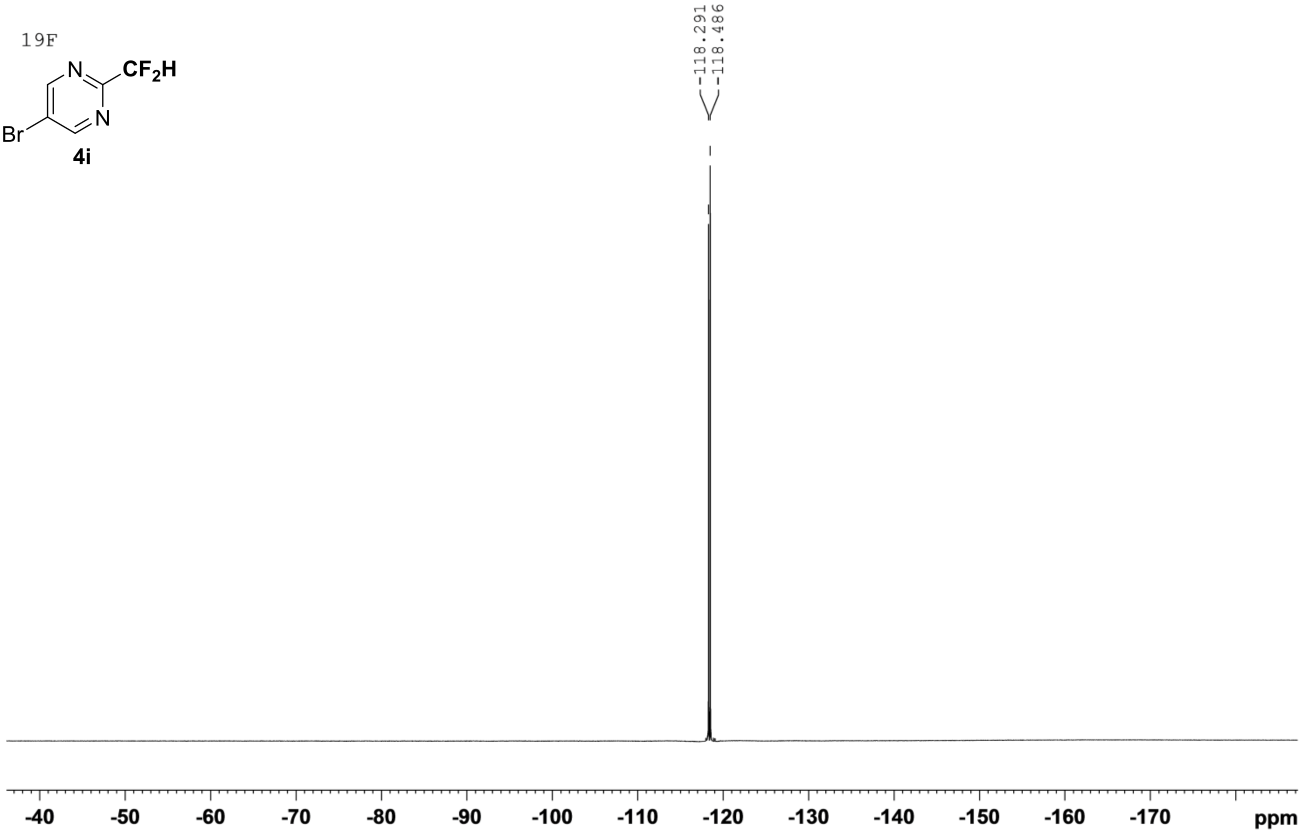

1H
N
CF2H
4h
8.5112
8.4925
8.4663
7.8949
7.8679
7.7620
7.7404
7.7129
7.7091
7.6982
7.6937
7.6702
7.6470
7.6435
7.1655
6.9843
6.8030
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.00
3.00
1.00

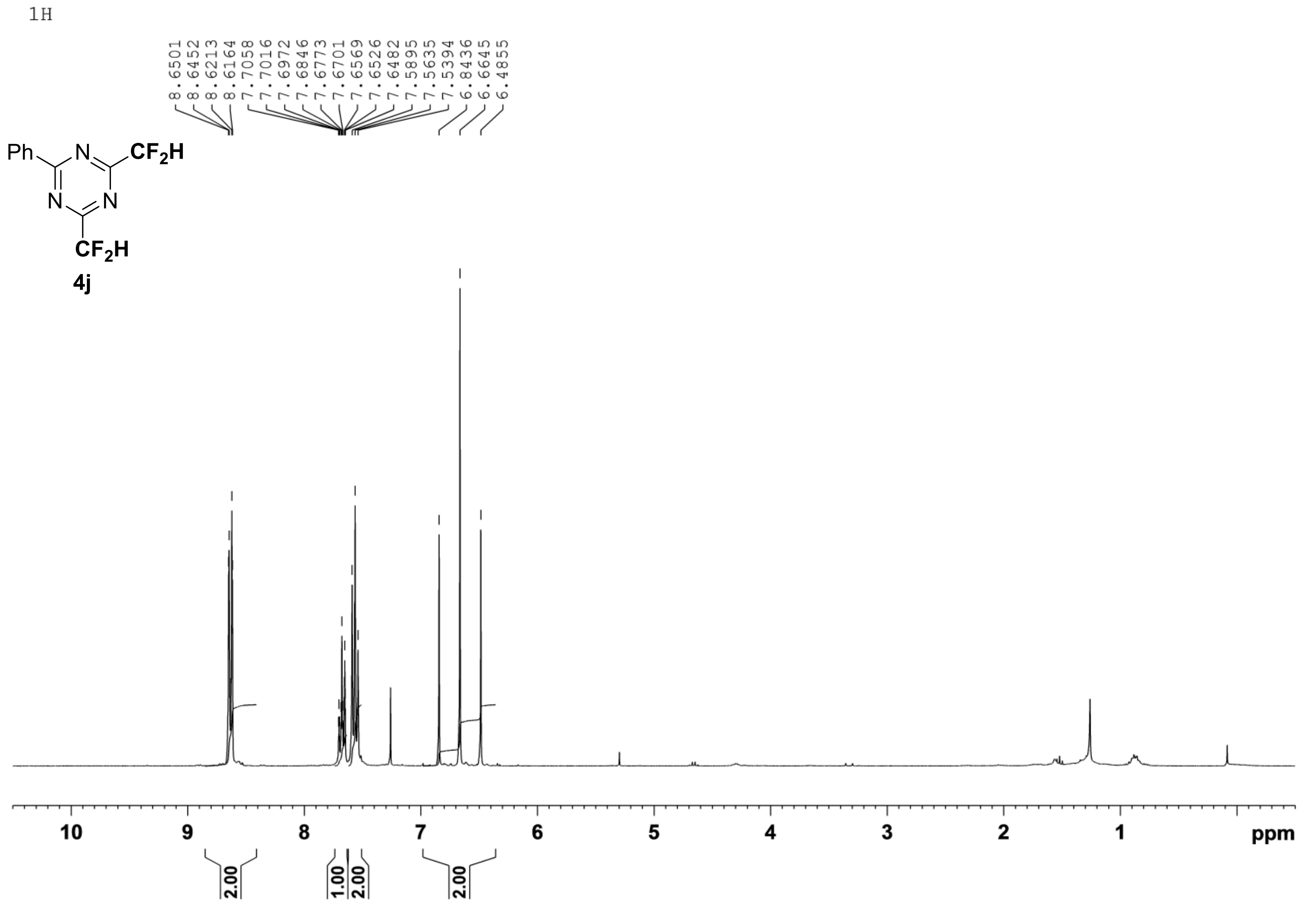

13C
N
CF2H
4h
151.47
151.12
150.77
141.06
136.95
130.61
128.19
127.25
125.12
125.11
125.08
125.03
123.48
121.04
117.83
114.63
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

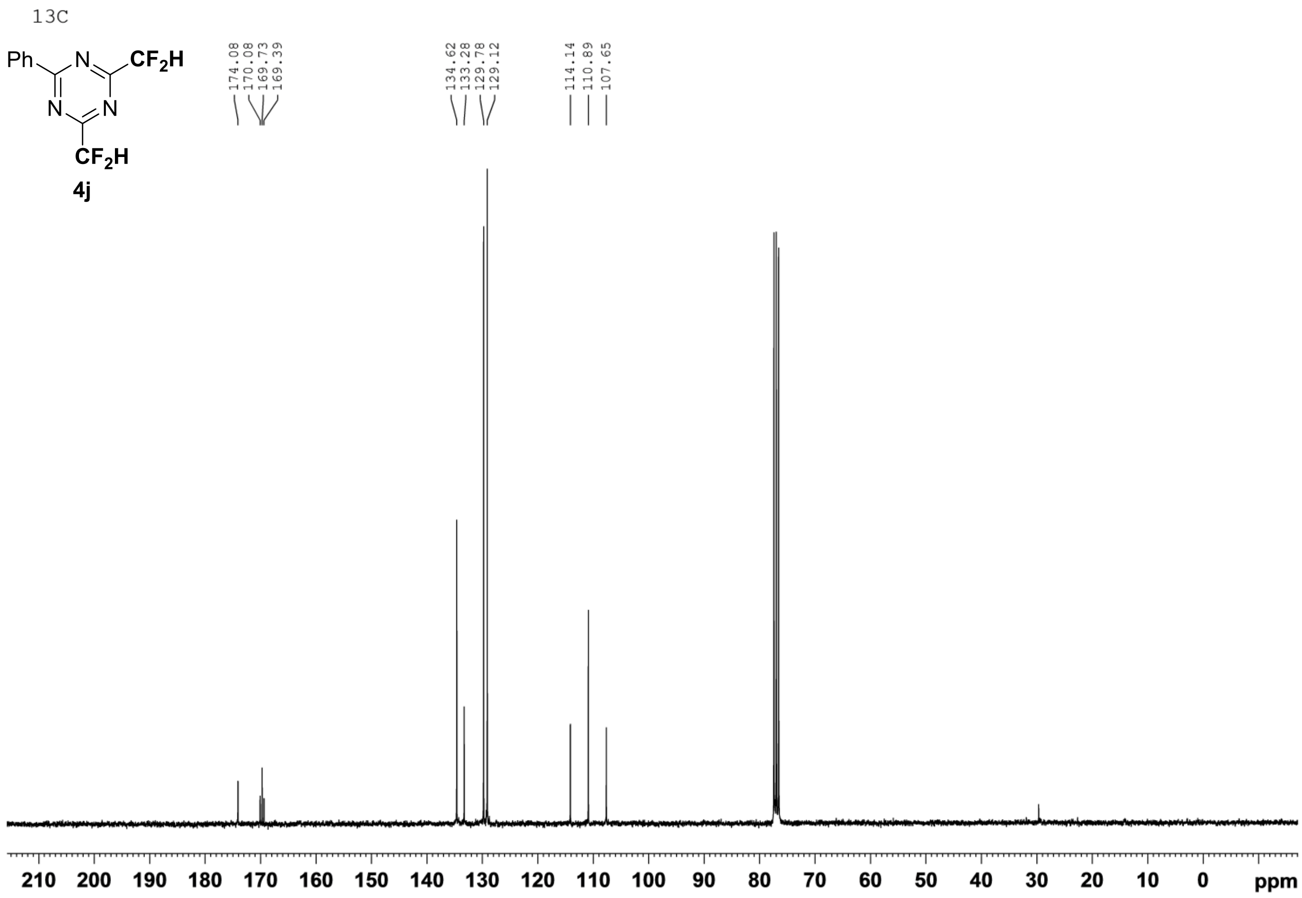

19F
N
CF2H
4h
-109.938
-110.132
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm

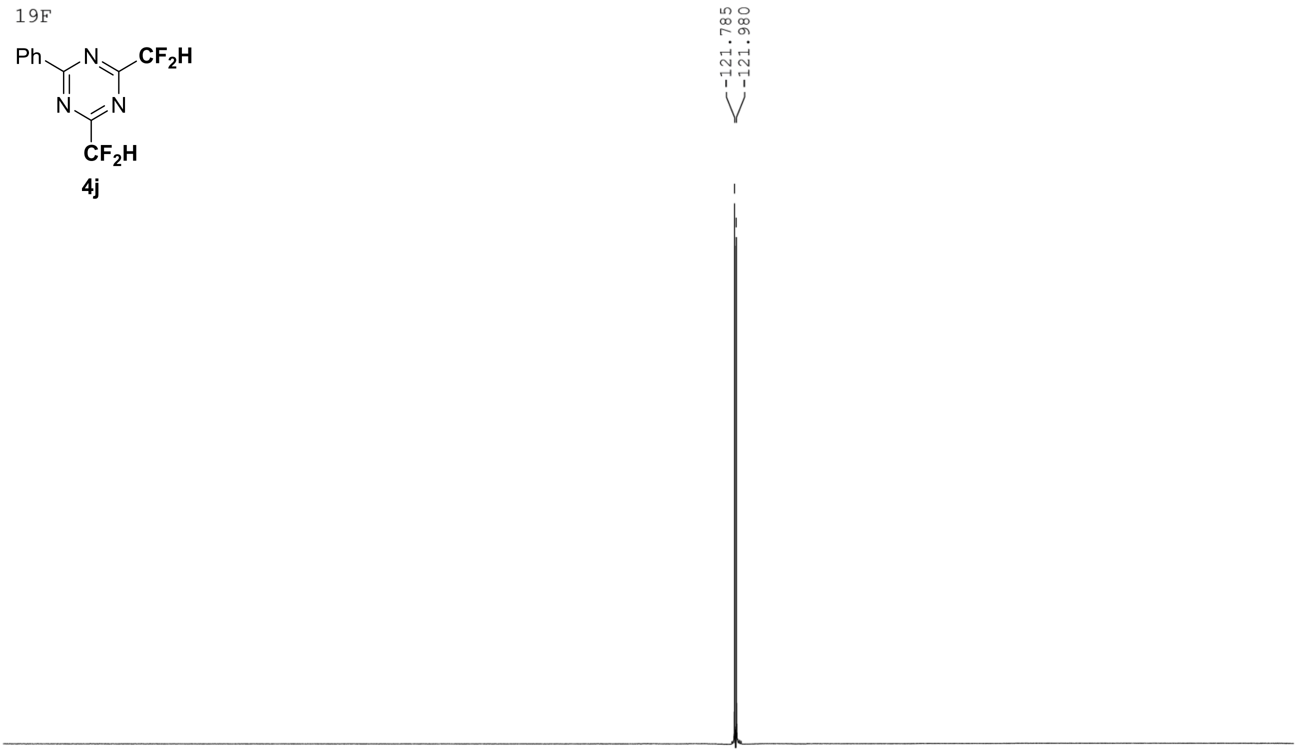

1H
N
CF2H
N
Br
4i
8.9239
6.8162
6.6352
6.4543
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.00


13C
N
CF2H
N
Br
4i
159.13
158.79
158.57
158.46
122.00
114.84
111.62
108.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

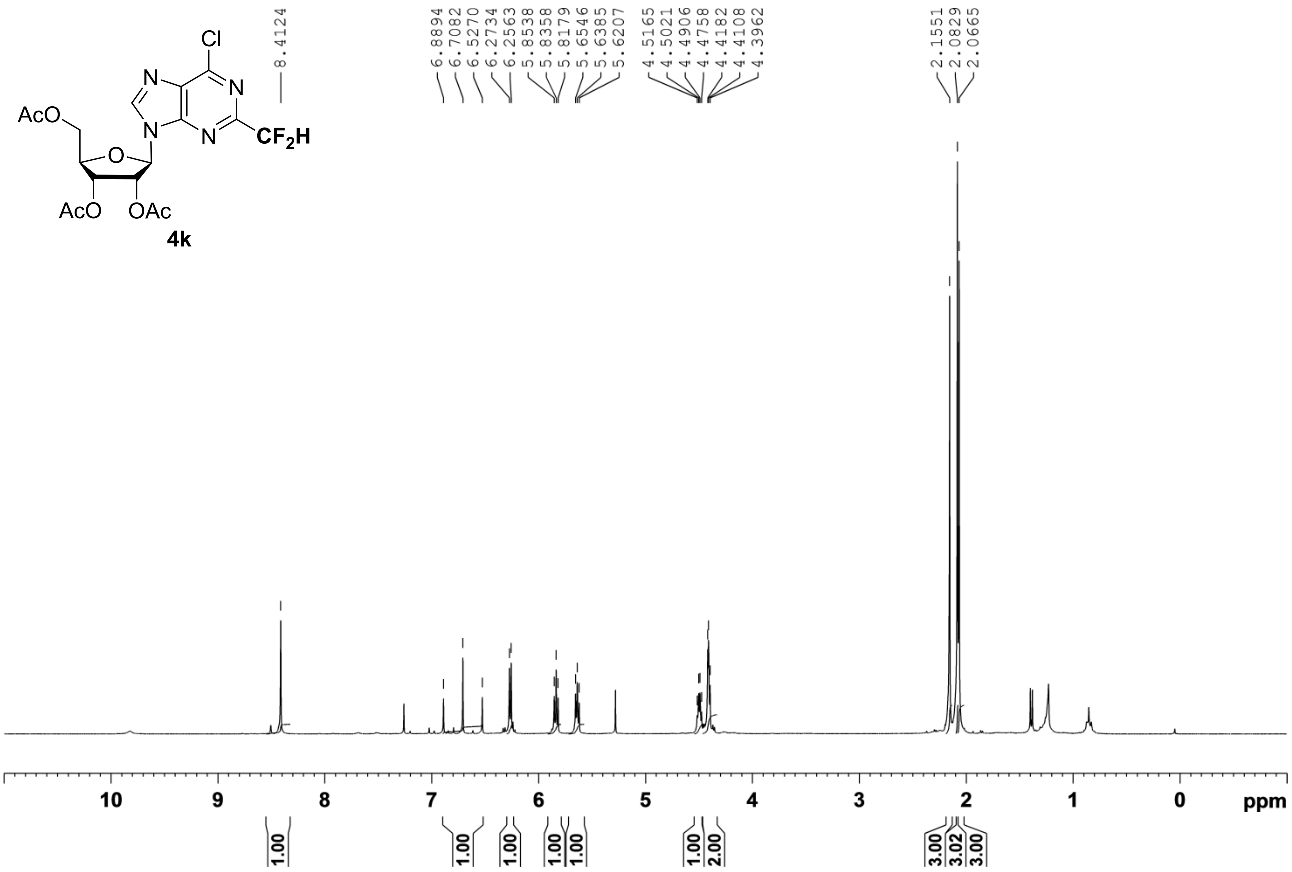

19F
4i
Br
N
N
CF2H
-118.291
-118.486
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm


1H
4j
Ph
N
N
N
CF2H
CF2H
8.6501
8.6452
8.6213
8.6164
7.7058
7.7016
7.6972
7.6846
7.6773
7.6701
7.6569
7.6526
7.6482
7.5895
7.5635
7.5394
6.8436
6.6645
6.4855
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.00
2.00
2.00

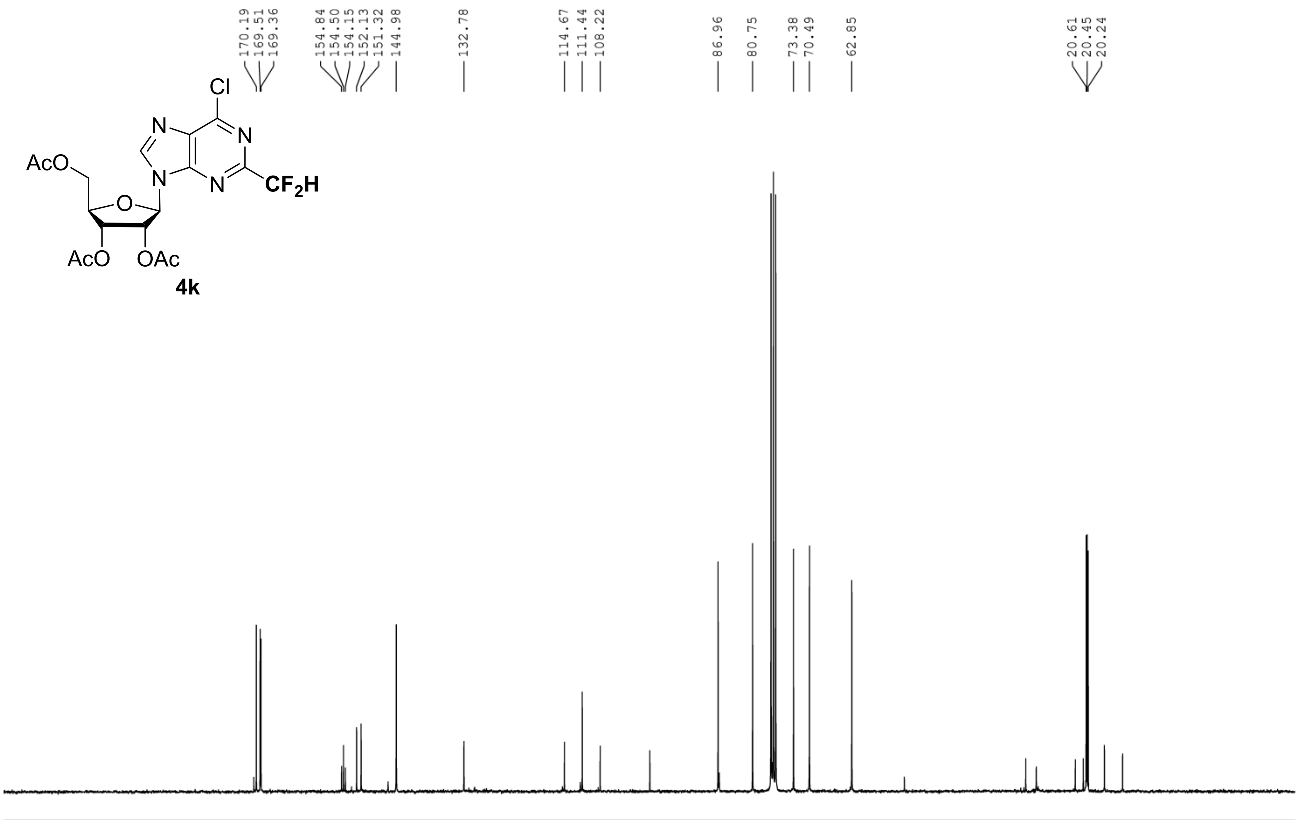

13C
Ph
N
N
N
CF2H
CF2H
4j
174.08
170.08
169.73
169.39
134.62
133.28
129.78
129.12
114.14
110.89
107.65
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

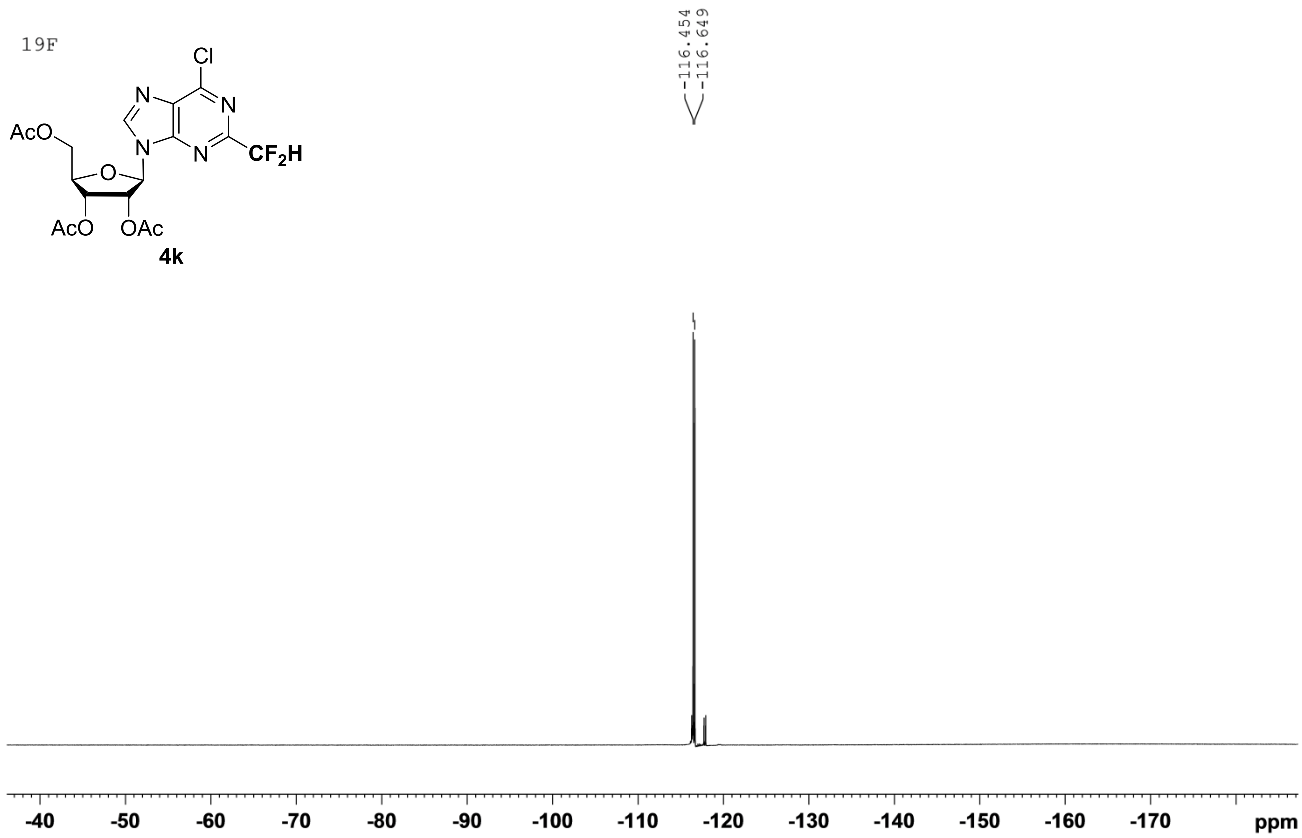

19F
Ph
N
N
N
CF2H
CF2H
4j
-121.785
-121.980
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm

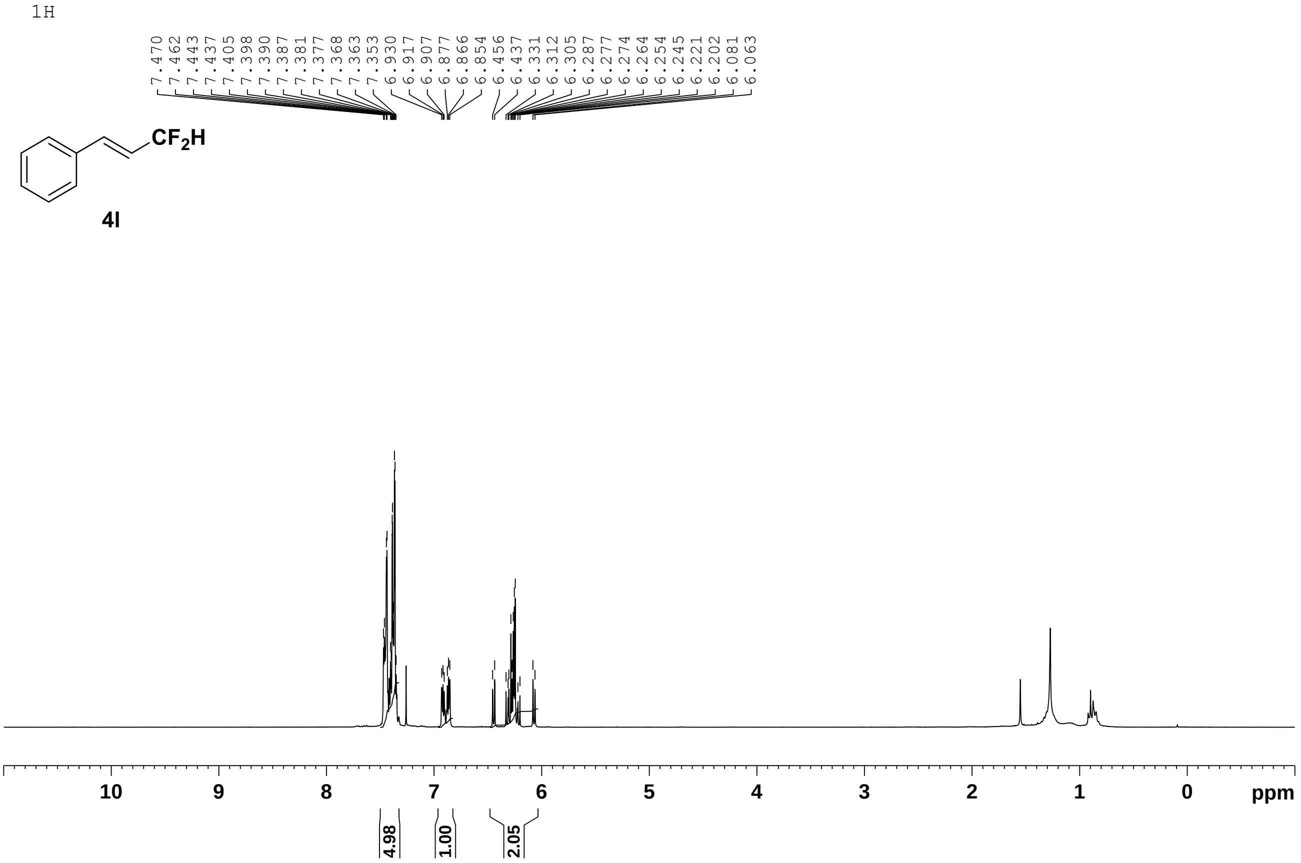
1H

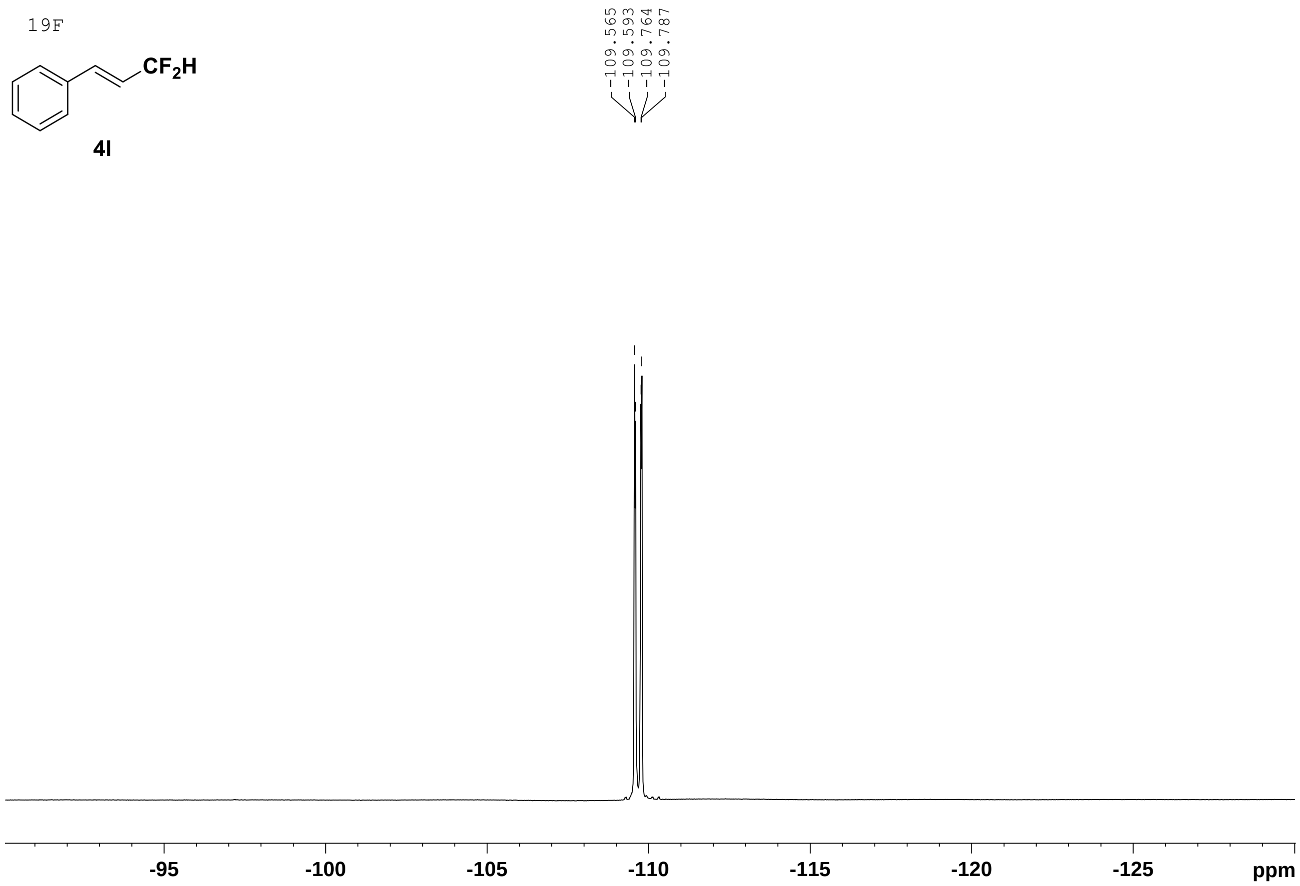

Cl
N
N
N
N
AcO
O
CF2H
AcO
OAc
4k
8.4124
6.8894
6.7082
6.5270
6.2734
6.2563
5.8538
5.8358
5.8179
5.6546
5.6385
5.6207
4.5165
4.5021
4.4906
4.4758
4.4182
4.4108
4.3962
2.1551
2.0829
2.0665
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.00
1.00
1.00
1.00
2.00
3.00
3.02
3.00

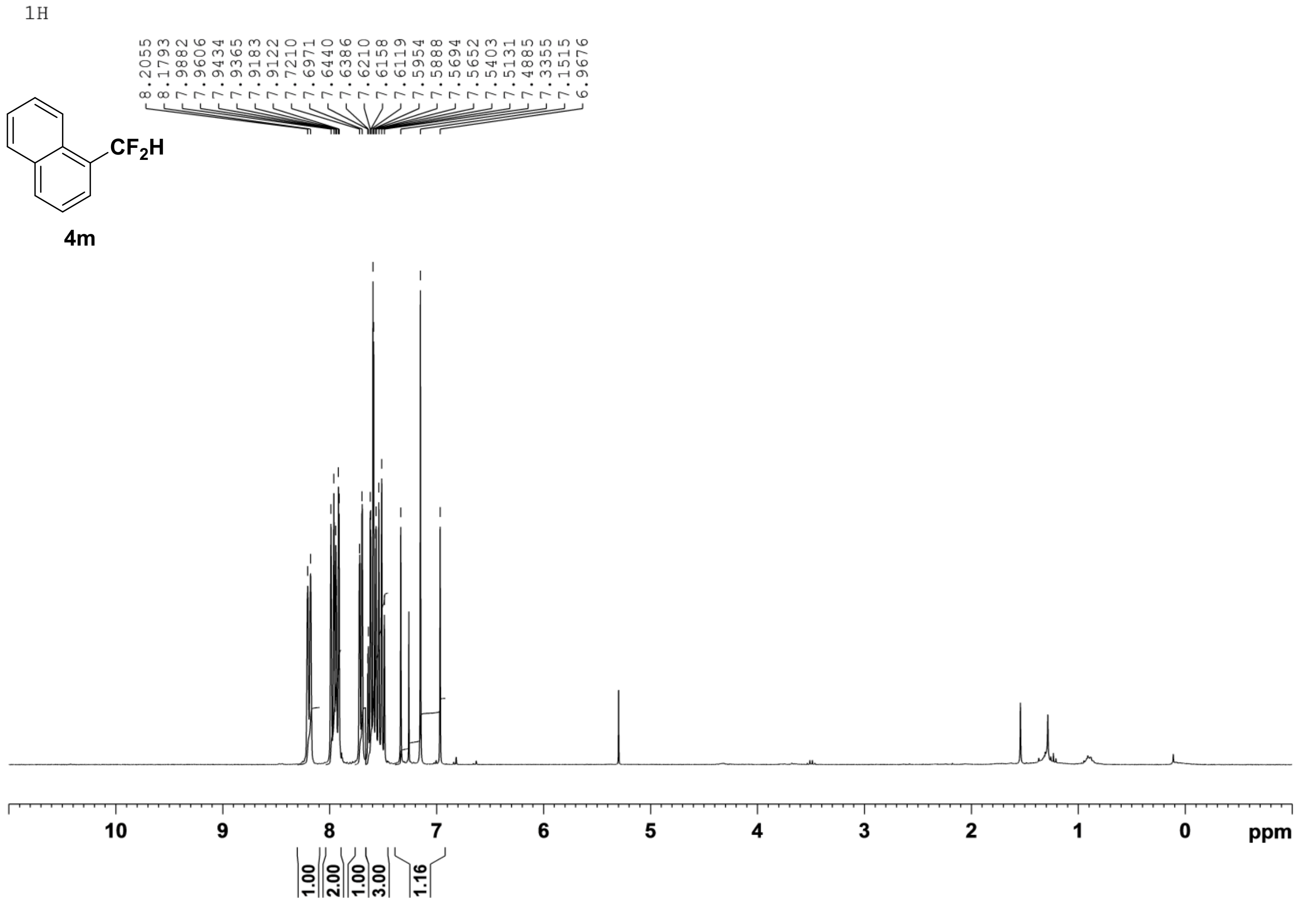
13C

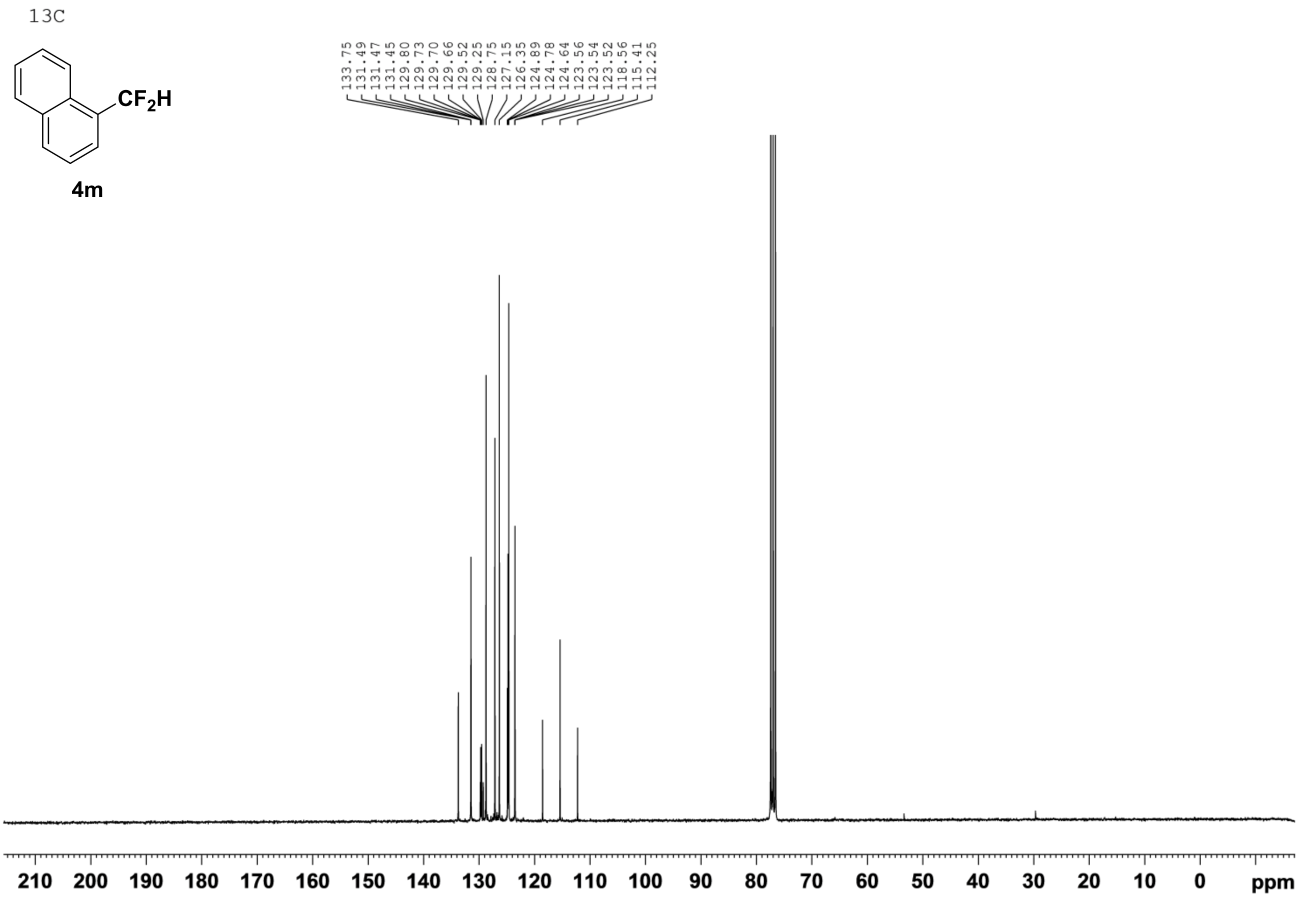

170.19
169.51
169.36
154.84
154.50
154.15
152.13
151.32
144.98
132.78
114.67
111.44
108.22
86.96
80.75
73.38
70.49
62.85
20.61
20.45
20.24
Cl
N
N
N
N
AcO
O
CF2H
AcO
OAc
4k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

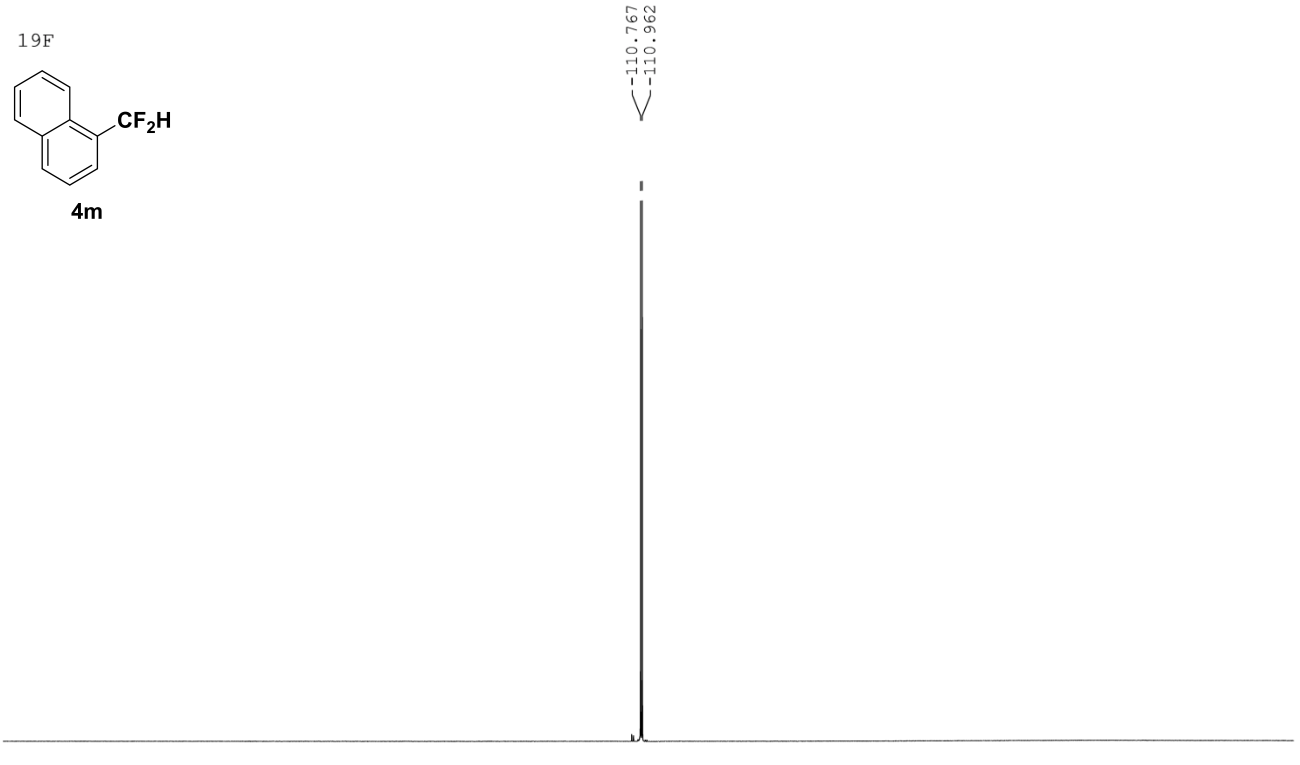

19F
4k
AcO
AcO
OAc
Cl
N
N
N
N
O
CF2H
-116.454
-116.649
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm

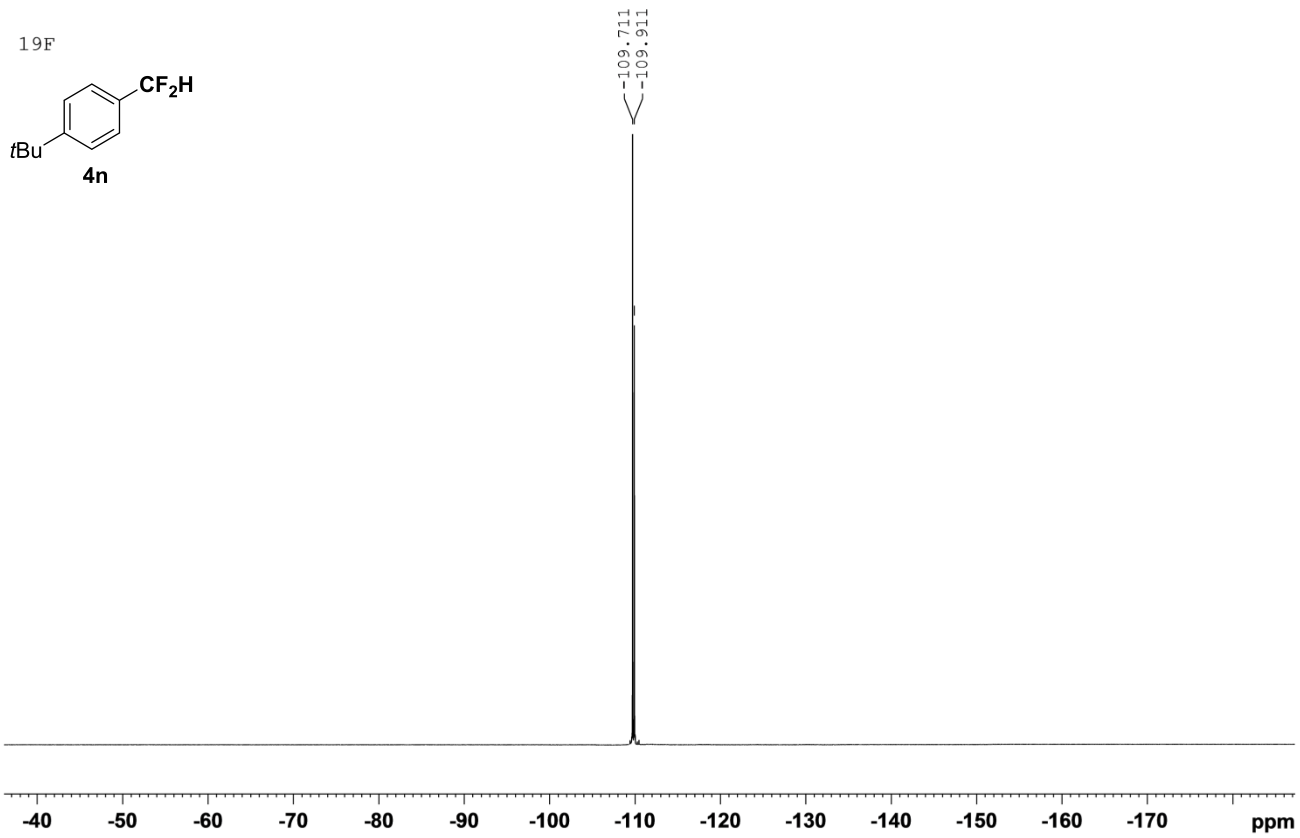

1H
4l
CF2H
7.470
7.462
7.443
7.437
7.405
7.398
7.390
7.387
7.381
7.377
7.368
7.363
7.353
6.930
6.917
6.907
6.877
6.866
6.854
6.456
6.437
6.331
6.312
6.305
6.287
6.277
6.274
6.264
6.254
6.245
6.221
6.202
6.081
6.063
10
9
8
7
6
5
4
3
2
1
0
ppm
4.98
1.00
2.05

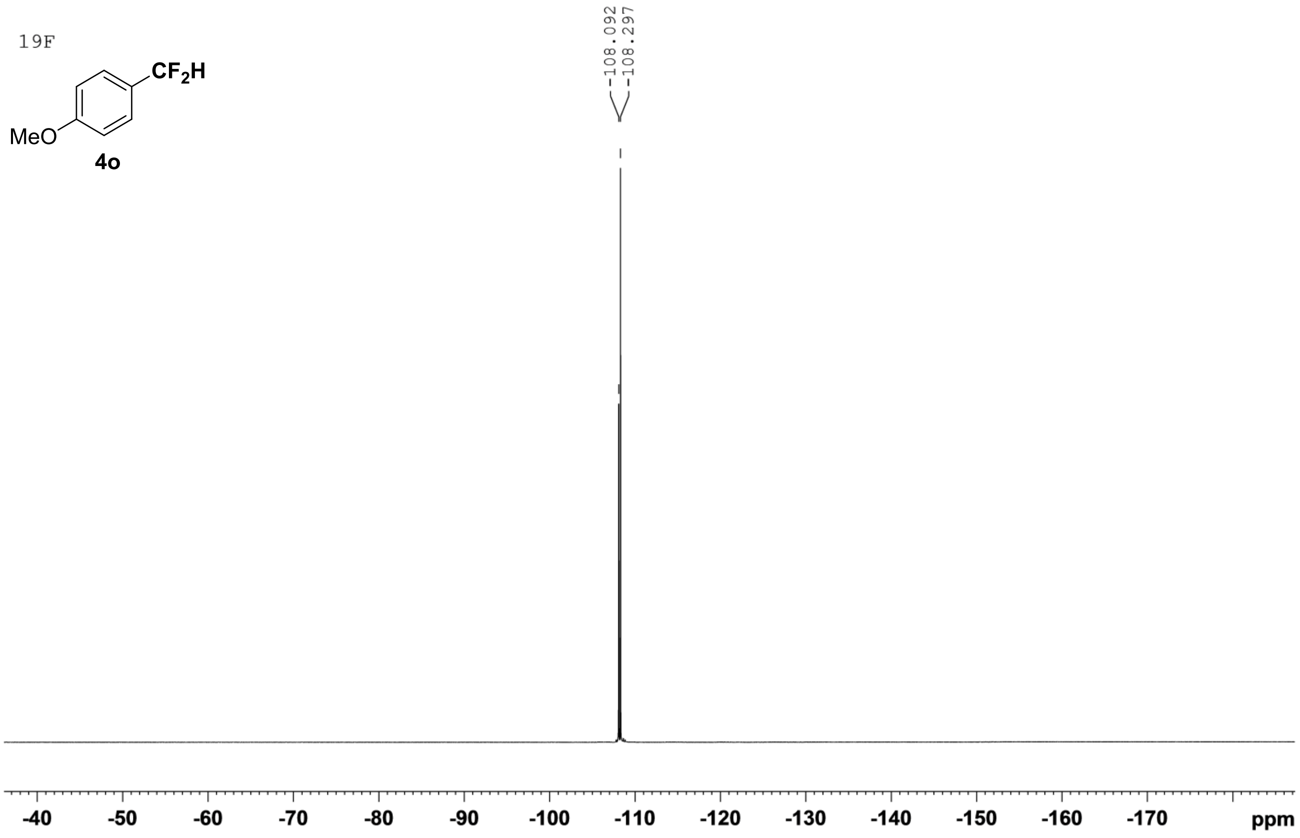

19F
CF2H
4l
-109.565
-109.593
-109.764
-109.787
-95
-100
-105
-110
-115
-120
-125
ppm


1H
CF2H
4m
8.2055
8.1793
7.9882
7.9606
7.9434
7.9365
7.9183
7.9122
7.7210
7.6971
7.6440
7.6386
7.6210
7.6158
7.6119
7.5954
7.5888
7.5694
7.5652
7.5403
7.5131
7.4885
7.3355
7.1515
6.9676
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.00
1.00
3.00
1.16


13C
CF2H
4m
133.75
131.49
131.47
131.45
129.80
129.73
129.70
129.66
129.52
129.25
128.75
127.15
126.35
124.89
124.78
124.64
123.56
123.54
123.52
118.56
115.41
112.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


19F
CF2H
4m
-110.767
-110.962
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 ppm


19F
CF$_2$H
*t*Bu
4n
-109.711
-109.911
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm


19F
CF$_2$H
MeO
4o
-108.092
-108.297
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm