

# One-pot synthesis of difluoromethyl ketones by a difluorination/fragmentation process

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## Supporting Information

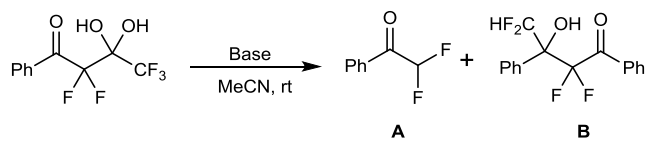
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## General Information

Solvents and commercially available reagents were purchased from standard chemical suppliers (Fisher, Sigma-Aldrich, VWR, Fluorochem) and used as received without further purification or drying. Reactions were performed under an atmosphere of dry nitrogen gas. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin or potassium permanganate as appropriate. Flash column chromatography was carried out using silica gel (Apollo Scientific 60Å particle size 40-63 micron). Melting points are uncorrected. Infra-red spectra were recorded on a Bruker Alpha-P ATR instrument on the neat compound. NMR spectra were recorded on a Bruker DPX-300, Bruker Avance III HD 300 MHz or Bruker Avance III HD 500 MHz instrument. For  $^1\text{H}$  NMR spectra, chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ( $\text{CDCl}_3$  at 7.26 ppm,  $\text{d}_6$ -acetone at 2.05 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants ( $J$ ) are quoted to the nearest 0.1 Hz. For proton decoupled  $^{13}\text{C}$  NMR spectra, chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ( $\text{CDCl}_3$  at 77.16 ppm,  $\text{d}_6$ -acetone at 29.92 ppm). Assignments were made using DEPT or PENDANT pulse sequences. For proton-decoupled  $^{19}\text{F}$  NMR spectra, chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) downfield of  $\text{CFCl}_3$ , using residual protonated solvent as internal standard ( $\text{CFCl}_3$  at 376.38 MHz with respect to tetramethylsilane at 400.00 MHz). Low resolution mass spectra were recorded using electrospray ionization (ESI) techniques on an Agilent 6130R instrument. High resolution mass spectra were recorded using electrospray ionization (ESI) techniques on a Bruker Maxis instrument.

## Optimisation Studies

### Base optimization



| Base (1 equiv.)   | Conversion / % | % A | % B |
|-------------------|----------------|-----|-----|
| LiOH              | 100            | 72  | 28  |
| NaOH              | 81             | 43  | 57  |
| KOH               | 31             | 52  | 48  |
| Et <sub>3</sub> N | 100            | 100 | 0   |
| LiOH <sup>a</sup> | 100            | 83  | 17  |

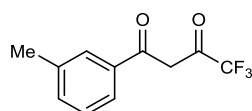
All ratios determined by integration of crude <sup>19</sup>F NMR spectra. <sup>a</sup> Solvent was MeCN/H<sub>2</sub>O (9:1).

## Preparation of 1-trifluoromethyl-1,3-diketones\*

\* Several 1-trifluoromethyl-1,3-diketones used are reported compounds. Data agrees with literature

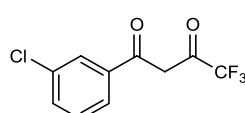
### General Procedure A:

Sodium hydride (0.24 g, 6.0 mmol, 60 % dispersion in mineral oil) was first suspended in hexane and stirred for 15 minutes to remove the mineral oil. The stirring was ceased and the hexane decanted off by pipette. The appropriate methyl ketone (5 mmol) was dissolved in THF (10 ml) and added to the sodium hydride at 0 °C. Ethyl trifluoroacetoacetate (0.72 ml, 6 mmol) was then added dropwise with stirring and the solution allowed to warm to room temperature. After stirring for 16 hours, HCl (2 M, 10 ml) was added and the mixture extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and evaporated to yield the desired 1-trifluoromethyl-1,3-diketone.



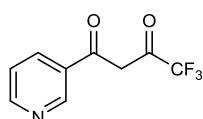
#### 4,4,4-trifluoro-1-(m-tolyl)butane-1,3-dione (6h)

The title compound was prepared according to General Procedure A from 3'-methylacetophenone (0.68 ml, 5 mmol), without further purification to give an orange oil (0.92 g, 80%). IR 1582, 1263, 1150, 1076, 1000, 785 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77-7.73 (2H, m), 7.46-7.42 (1H, m), 7.40 (1H, t, *J* = 7.5 Hz), 6.57 (1H, s), 2.44 (3H, s); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.5 (C), 177.2 (C, q, *J* = 36.2 Hz), 139.0 (C), 134.9 (CH), 132.8 (C), 128.9 (CH), 128.1 (CH), 124.9 (CH), 117.2 (C, q, *J* = 283 Hz), 92.3 (CH, q, *J* = 1.8 Hz), 21.3 (s); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -76.5 (3F, s); HRMS (ES-) Exact mass calculated for C<sub>11</sub>H<sub>9</sub>O<sub>2</sub>F<sub>3</sub> [M-H]<sup>-</sup>: 229.0482, found: 229.0478.



#### 1-(3-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (6l)

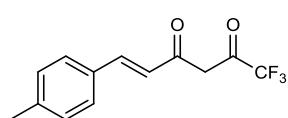
The title compound was prepared according to General Procedure A from 3'-chloroacetophenone (0.52 ml, 5 mmol), without further purification to give an orange oil (0.81 g, 65%). IR 1586, 1566, 1473, 1285, 1195, 1146, 1119, 1069, 920, 809 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.92 (1H, s), 7.82 (1H, d, *J* = 7.8 Hz), 7.59 (1H, dd, *J* = 7.9, 1.0 Hz), 7.46 (1H, t, *J* = 7.9 Hz), 6.54 (1H, s); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 184.5 (C), 177.6 (C, q, *J* = 36.5 Hz), 135.4 (C), 134.6 (C), 133.9 (CH), 130.3 (CH), 127.6 (CH), 125.6 (CH), 117.0 (C, q, *J* = 283 Hz), 92.6 (CH, q, *J* = 1.9 Hz); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -76.5 (3F, s); HRMS (ES-) Exact mass calculated for C<sub>10</sub>H<sub>6</sub>O<sub>2</sub>F<sub>3</sub><sup>35</sup>Cl [M-H]<sup>-</sup>: 248.9936, found: 248.9937.



#### 4,4,4-trifluoro-1-(pyridin-3-yl)butane-1,3-dione (6m)

The title compound was prepared according to General Procedure A from 3-acetylpyridine (0.55 ml, 5 mmol), without further purification to give a pale yellow

solid (0.84 g, 77%). IR 2751, 1639, 1609, 1519, 1291, 1119, 1064, 771, 720  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6$ -acetone)  $\delta$  9.17 (1H, s), 8.73 (1H, d,  $J$  = 3.9 Hz), 8.35 (1H, d,  $J$  = 8.0 Hz), 7.50 (1H, dd,  $J$  = 7.9, 4.9 Hz), 6.92 (1H, s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{d}_6$ -acetone)  $\delta$  186.0 (C), 177.1 (C, q,  $J$  = 34.7), 155.3 (CH), 149.9 (CH), 136.1 (CH), 129.8 (C), 124.9 (CH), 118.2 (C, q,  $J$  = 283 Hz), 94.3 (CH);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -76.5 (3F, s); HRMS (ES-) Exact mass calculated for  $\text{C}_9\text{H}_6\text{NO}_2\text{F}_3$   $[\text{M}-\text{H}]^-$ : 216.0273, found: 216.0278.



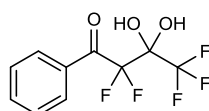
**(E)-1,1,1-trifluoro-6-(p-tolyl)hex-5-ene-2,4-dione (6p)**

The title compound was prepared according to General Procedure A from 3-acetylpyridine (310 mg, 1.93 mmol), sodium hydride (93 mg, 2.32 mmol, 60% in mineral oil) and ethyl trifluoroacetate (0.28 ml, 2.32 mmol) in THF (10 ml), without further purification to give a brown solid (361 mg, 73%). IR 1617, 1588, 1572, 1449, 1258, 1195, 1144, 1107, 977, 872, 811, 716  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (1H, d,  $J$  = 15.8 Hz), 7.47 (2H, d,  $J$  = 8.1 Hz), 7.23 (2H, d,  $J$  = 8.1 Hz), 6.54 (1H, d,  $J$  = 15.8 Hz), 6.02 (1H, s), 2.40 (3H, s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  181.5 (C), 180.1 (C, q,  $J$  = 36.0 Hz), 143.9 (CH), 141.9 (C), 131.5 (C), 129.9 (2 x CH), 128.6 (2 x CH), 120.0 (CH), 116.8 (C, q,  $J$  = 285 Hz), 95.4 (CH), 21.6 ( $\text{CH}_3$ );  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -77.0 (3F, s); HRMS (ES+) Exact mass calculated for  $\text{C}_{13}\text{H}_{11}\text{O}_2\text{F}_3$   $[\text{M}+\text{Na}]^+$ : 279.0603, found: 279.0602.

## Difluorination of 1-trifluoromethyl-1,3-diketones

### General Procedure B:

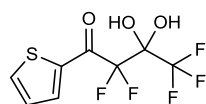
To a solution of 4,4,4-trifluorobutan-1,3-dione in MeCN was added Selectfluor and the mixture was heated under reflux conditions for 24 hours. The mixture was diluted with EtOAc (50 ml), filtered through a Celite plug, and concentrated in vacuo. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (35 ml) and water (35 ml) was added, and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 15 ml). The organic phase was dried with  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford the 2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one.



**2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one (4a)**

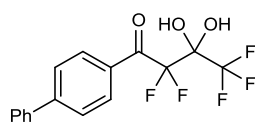
The title compound was prepared according to General Procedure B from 4,4,4-trifluoro-1-phenylbutane-1,3-dione (2.16 g, 10 mmol) and Selectfluor<sup>TM</sup> (8.86 g, 25 mmol) in acetonitrile (40 ml), without further purification to give a pale yellow solid (2.21 g, 82%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (2H, dd,  $J$  = 8.5, 1.2 Hz), 7.72 (1H, m), 7.54 (2H, m), 4.89 (2H, br s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  191.6 (C, t,  $J$  = 29.1 Hz), 135.6 (CH), 131.8 (C), 130.6 (2 x CH), 128.9 (2 x CH), 121.0 (C, q,

$J = 288$  Hz), 111.3 (C, t,  $J = 269$  Hz), 92.9 (C, qt, 32.7, 26.9 Hz);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.7 (3F, t,  $J = 11.2$  Hz), -112.5 (2F, q,  $J = 11.2$  Hz) HRMS (ES+) Exact mass calculated for  $\text{C}_{10}\text{H}_7\text{O}_3\text{F}_5$   $[\text{M}+\text{Na}]^+$ : 293.0208, found: 293.0206.



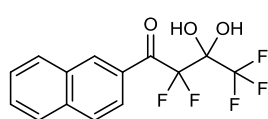
**2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(thiophen-2-yl)butan-1-one (4b)**

The title compound was prepared according to General Procedure B from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (1.11 g, 5 mmol) and Selectfluor<sup>TM</sup> (4.43 g, 12.5 mmol) in acetonitrile (20 ml), without further purification to give a dark brown solid (1.38 g, 100% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (1H, m), 7.97 (1H, dd,  $J = 4.9, 0.9$  Hz), 7.29 (1H, m), 4.86 (2H, br s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  183.6 (C, t,  $J = 29.1$  Hz), 139.2 (CH), 138.1 (CH, t,  $J = 6$  Hz), 137.4 (C), 129.5 (CH), 120.9 (C, q,  $J = 289$  Hz), 111.0 (C, t,  $J = 267$  Hz), 93.2-92.4 (C, m);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.7 (3F, t,  $J = 10.3$  Hz), -114.4 (2F, q,  $J = 10.3$  Hz); HRMS (ES+) Exact mass calculated for  $\text{C}_8\text{H}_5\text{O}_3\text{F}_5\text{S}$   $[\text{M}+\text{Na}]^+$ : 298.9772, found: 298.9775. Data consistent with that previously reported.<sup>1</sup>



**1-([1,1'-biphenyl]-4-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (4c)**

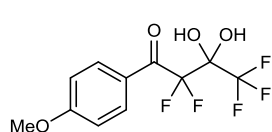
The title compound was prepared according to General Procedure B from 1-([1,1'-biphenyl]-4-yl)-4,4,4-trifluorobutane-1,3-dione (292 mg, 1 mmol) and Selectfluor<sup>TM</sup> (886 mg, 2.5 mmol) in acetonitrile (15 ml), without further purification to give a pale yellow solid (337 mg, 97%). IR 3326, 1676, 1601, 1407, 1261, 1206, 1153, 1116, 1070, 814  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (2H, d,  $J = 8.2$  Hz), 7.74 (2H, d,  $J = 8.7$  Hz), 7.65 (2H, d,  $J = 7$  Hz), 7.53-7.46 (3H, m), 5.15 (2H, br s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  190.9 (C, t,  $J = 29.1$  Hz), 148.3 (C), 139.1 (C), 131.4 (2 x CH, t,  $J = 3.5$  Hz), 130.4 (C), 129.2 (2 x CH), 129.0 (CH), 127.4 (4 x CH), 121.1 (C, q,  $J = 288$  Hz), 111.7 (C, t,  $J = 268$  Hz), 92.9 (C, qt,  $J = 32.9, 27.1$  Hz);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.5 (3F, t,  $J = 11.5$  Hz), -112.4 (2F, q,  $J = 11.5$  Hz); HRMS (ES+) Exact mass calculated for  $\text{C}_{16}\text{H}_{11}\text{O}_3\text{F}_5$   $[\text{M}+\text{Na}]^+$ : 369.0518, found: 369.0521.



**2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (4d)**

The title compound was prepared according to General Procedure B from 4,4,4-Trifluoro-1-(2-naphthyl)-1,3-butanedione (1.33 g, 5 mmol) and Selectfluor<sup>TM</sup> (4.43 g, 12.5 mmol) in acetonitrile (20 ml), without further purification to give a light brown solid (1.19 g, 74%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.73 (1H, s), 8.05-7.99 (2H, m), 7.93-7.88 (2H, m), 7.68 (1H, ddd,  $J = 8.1, 6.9, 1.2$  Hz), 7.62-7.59 (1H, m), 4.77 (2H, br s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  191.3 (C, t,  $J = 29.1$  Hz), 136.5 (C), 134.1 (CH, t,  $J = 5$  Hz), 132.1 (C), 130.4 (CH), 130.2 (CH), 128.9 (CH), 128.9 (C), 127.9 (CH), 127.4 (CH), 124.5 (CH), 121.0 (C, q,  $J = 288$  Hz), 111.4 (C, t,  $J = 268$  Hz), 93.4-92.6 (C, m);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.0 (3F, t,  $J = 10.6$  Hz), -111.1 (2F, q,  $J = 10.6$  Hz); HRMS (ES+)

Exact mass calculated for  $C_{14}H_9O_3F_5$   $[M+Na]^+$ : 343.0364, found: 343.0360. Data consistent with that previously reported.<sup>2</sup>



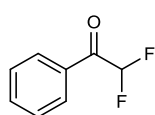
**2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(4-methoxyphenyl)butan-1-one**  
**(4e)**

The title compound was prepared according to General Procedure B from 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (246 mg, 1 mmol) and Selectfluor<sup>TM</sup> (886 mg, 2.5 mmol) in acetonitrile (15 ml), and purified by column chromatography (40% EtOAc/hexane) to give a yellow oil (210 mg, 70%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.12 (2H, d,  $J$  = 9.1 Hz), 6.98 (2H, d,  $J$  = 9.1 Hz), 5.03 (2H, br s), 3.91 (3H, s); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  189.5 (C, t,  $J$  = 28.1 Hz), 165.7 (C), 133.5 (2 x CH, t,  $J$  = 3.5 Hz), 124.4 (C), 121.0 (q,  $J$  = 286 Hz), 114.3 (2 x CH), 111.4 (C, t,  $J$  = 268 Hz), 93.6-92.4 (C, qt,  $J$  = 33.1, 27.7 Hz), 55.7 (CH<sub>3</sub>); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -81.0 (3F, t,  $J$  = 11.0 Hz), -111.4 (2F, q,  $J$  = 11.0 Hz); HRMS (ES+) Exact mass calculated for  $C_{11}H_9O_4F_5$   $[M+Na]^+$ : 323.0313, found: 323.0314. Data consistent with that previously reported.<sup>3</sup>

## Fragmentation of 2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one compounds

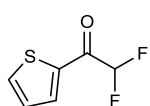
### General Procedure C:

To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **1a-e** (1 mmol) in MeCN, Et<sub>3</sub>N (1.5 mmol) was added dropwise and stirred at room temperature for 24 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and 2M HCl (15 mL) was added. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), and the organic phase was dried with MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the  $\alpha,\alpha$ -difluoroketone.

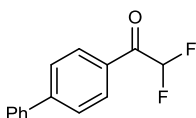


**2,2-difluoro-1-phenylethan-1-one (5a)**

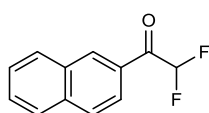
The title compound was prepared according to General Procedure C from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one (270 mg, 1 mmol) without further purification to give a yellow oil (120 mg, 77%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.06 (2H, d,  $J$  = 7.6 Hz), 7.66 (1H, m), 7.51 (2H, t,  $J$  = 7.9 Hz), 6.31 (1H, t,  $J$  = 53.4 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  187.7 (C, t,  $J$  = 25.1 Hz), 135.0 (CH), 131.5 (C), 129.6 (2 x CH, t,  $J$  = 3.0 Hz), 129.0 (2 x CH), 111.1 (CH, t,  $J$  = 253 Hz); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -122.8 (2F, s). Data consistent with that previously reported.<sup>4</sup>

**2,2-difluoro-1-(thiophen-2-yl)ethan-1-one (5b)**

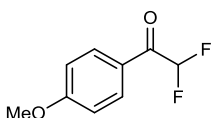
The title compound was prepared according to general procedure C from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(thiophen-2-yl)butan-1-one (2.26 g, 8.18 mmol) without further purification to give a brown oil (1.26 g, 95%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03-7.99 (1H, m), 7.85 (1H, dd,  $J = 4.9, 0.9$  Hz), 7.24 (1H, dd,  $J = 4.0, 0.9$  Hz), 6.29 (1H, t,  $J = 53.9$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  181.1 (C, t,  $J = 26.1$  Hz), 137.7 (C), 136.8 (CH), 135.6 (CH, t,  $J = 4.0$  Hz), 128.9 (CH), 110.9 (CH, t,  $J = 254$  Hz);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.8 (2F, s); HRMS (ES+) Exact mass calculated for  $\text{C}_6\text{H}_4\text{OF}_2\text{S}$   $[\text{M}+\text{Na}]^+$ : 184.9841, found: 184.9843.

**1-([1,1'-biphenyl]-4-yl)-2,2-difluoroethan-1-one (5c)**

The title compound was prepared according to General Procedure C from 1-([1,1'-biphenyl]-4-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one (336 mg, 0.97 mmol) without further purification to give a white solid (208 mg, 92%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.17 (2H, d,  $J = 8.5$  Hz), 7.76 (2H, m), 7.67-7.63 (2H, m), 7.52-7.44 (3H, m), 6.34 (1H, t,  $J = 53.4$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  187.2 (C, t,  $J = 25.1$  Hz), 147.6 (C), 139.4 (C), 130.3 (2 x CH, t,  $J = 2.5$  Hz), 130.2 (C), 129.1 (2 x CH), 128.7 (CH), 127.6 (2 x CH), 127.4 (2 x CH), 111.3 (CH, t,  $J = 254$  Hz);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.8 (2F, s); HRMS (ES+) Exact mass calculated for  $\text{C}_{14}\text{H}_{10}\text{OF}_2$   $[\text{M}+\text{Na}]^+$ : 255.0592, found: 255.0590.

**2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one (5d)**

The title compound was prepared according to General Procedure C from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (320 mg, 1 mmol) without further purification to give a pale brown solid (188 mg, 91%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (1H, s), 8.09-7.90 (4H, m), 7.69-7.59 (2H, m), 6.42 (1H, t,  $J = 53.7$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  187.6 (C, t,  $J = 25.1$  Hz), 136.3 (C), 132.5 (CH, t,  $J = 4.0$  Hz), 132.3 (C), 130.0 (CH), 129.7 (CH), 129.0 (CH), 128.8 (C), 127.9 (CH), 127.3 (CH), 124.1 (CH), 111.4 (CH, t,  $J = 254.0$  Hz);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.2 (2F, s). Data consistent with that previously reported.<sup>4</sup>

**2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one (5e)**

The title compound was prepared according to General Procedure C from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(4-methoxyphenyl)butan-1-one (33 mg, 0.12 mmol) without further purification to give a yellow oil (17 mg, 76%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (2H, d,  $J = 9.0$  Hz), 6.99 (2H, dm,  $J = 9.0$  Hz), 6.27 (1H, t,  $J = 53.6$  Hz), 3.90 (3H, s);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  188.5

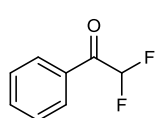


(C, t,  $J = 27.1$  Hz), 164.7 (C), 132.2 (2 x CH), 124.5 (C), 113.8 (2 x CH), 111.4 (CH, t,  $J = 254$  Hz), 55.6 (CH<sub>3</sub>); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -121.5 (2F, s); HRMS (ES+) Exact mass calculated for C<sub>9</sub>H<sub>8</sub>O<sub>2</sub>F<sub>2</sub> [M+Na]<sup>+</sup>: 209.0385, found: 209.0383. Data consistent with that previously reported.<sup>5</sup>

## One-pot fluorination / fragmentation process

### General Procedure D

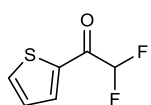
Selectfluor (0.425 g, 1.2 mmol) was added to the appropriate 1-trifluoromethyl-1,3-diketone derivative **1** (0.5 mmol) and dissolved in acetonitrile (5 ml). The mixture was heated to reflux for 3 hours, followed by the addition of water (18  $\mu$ l, 1.0 mmol) then heated to reflux for a further 15 minutes. The solution was cooled to room temperature, triethylamine (0.348 ml, 2.5 mmol) was added and the mixture stirred for 16 hours. After this period the solvent was evaporated and the residue purified by flash column chromatography to yield the desired  $\alpha,\alpha$ -difluoromethyl ketone.



#### 2,2-difluoro-1-phenylethan-1-one (5a)

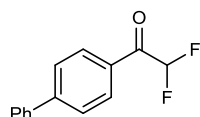
The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-phenylbutane-1,3-dione (108 mg, 0.5 mmol) and purified by flash column chromatography (5% Et<sub>2</sub>O / Pentane) to give a yellow oil (70 mg, 90%). Data as above.

The title compound was also prepared on a 5 mmol scale using a modification of General Procedure D, using 4,4,4-trifluoro-1-phenylbutane-1,3-dione (1.08 g, 5 mmol), Selectfluor (3.90 g, 11 mmol), followed by the addition of water (0.18 ml, 10 mmol) and triethylamine (3.48 ml, 25 mmol). This gave after purification by flash column chromatography (5% Et<sub>2</sub>O / Pentane) a yellow oil (0.54 g, 69%). Data as above.



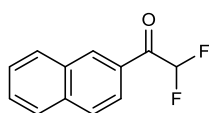
#### 2,2-difluoro-1-(thiophen-2-yl)ethan-1-one (5b)

The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (111 mg, 0.5 mmol) and purified by flash column chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a yellow oil (79 mg, 97%). Data as above.

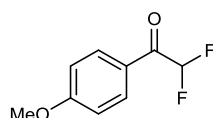


#### 1-([1,1'-biphenyl]-4-yl)-2,2-difluoroethan-1-one (5c)

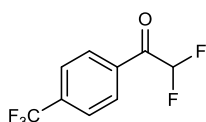
The title compound was prepared according to General Procedure D from 1-([1,1'-biphenyl]-4-yl)-4,4,4-trifluorobutane-1,3-dione (146 mg, 0.5 mmol) and purified by flash column chromatography (5% Et<sub>2</sub>O / Pentane) to give a white solid (86 mg, 74%). Data as above.

**2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one (5d)**

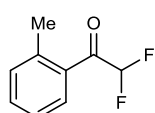
The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (133 mg, 0.5 mmol) and purified by flash column chromatography (5% Et<sub>2</sub>O / Pentane) to give a light brown solid (101.6 mg, 99%). Data as above.

**2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one (5e)**

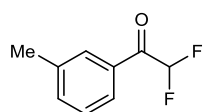
The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(4-methoxyphenyl)butane-1,3-dione (123 mg, 0.5 mmol) and purified by flash column chromatography (5% Et<sub>2</sub>O / Pentane) to give a yellow oil (76.5 mg, 82%). Data as above.

**2,2-difluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one (5f)**

The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(4-(trifluoromethyl)phenyl)butane-1,3-dione (142 mg, 0.5 mmol) and purified by flash column chromatography (5% Et<sub>2</sub>O / Pentane) to give a yellow oil (68 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.20 (2H, d, *J* = 8.2 Hz), 7.80 (2H, d, *J* = 8.2 Hz), 6.27 (1H, t, *J* = 53.3 Hz). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.9 (C, t, *J* = 26.5 Hz), 136.0 (C, q, *J* = 33.0 Hz), 134.0 (C), 130.1 (2 x CH, t, *J* = 2.4 Hz), 126.0 (2 x CH, q, *J* = 3.7 Hz), 123.3 (C, q, *J* = 273 Hz), 111.3 (CH, t, *J* = 254 Hz). <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -63.5 (3F, s), -121.7 (2F, s); HRMS (ES-) Exact mass calculated for C<sub>9</sub>H<sub>5</sub>F<sub>5</sub>O [M-H]<sup>-</sup>: 223.0188, found: 223.0188.

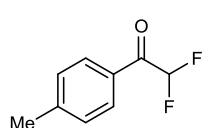
**2,2-difluoro-1-(o-tolyl)ethan-1-one (5g)**

The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(o-tolyl)butane-1,3-dione (115 mg, 0.5 mmol) and purified by flash column chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a pale yellow oil (54 mg, 63%). IR 1704, 1602, 1571, 1457, 1235, 1147, 1121, 1054, 965, 724, 649 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.88 (1H, dd, *J* = 8.2, 1.4 Hz), 7.50 (1H, td, *J* = 7.6, 1.1 Hz), 7.36-7.31 (2H, m), 6.27 (1H, t, *J* = 53.8 Hz), 2.56 (3H, d, *J* = 8.4 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 189.7 (C, t, *J* = 24 Hz), 141.5 (C), 133.4 (CH), 132.5 (CH), 130.9 (C), 130.2 (CH, t, *J* = 4.0 Hz), 125.8 (CH), 110.7 (CH, t, *J* = 254 Hz), 21.7 (CH<sub>3</sub>); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.8 (2F, s); HRMS (ES-) Exact mass calculated for C<sub>9</sub>H<sub>8</sub>F<sub>2</sub>O [M-H]<sup>-</sup>: 169.0470, found: 169.0467.

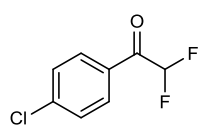
**2,2-difluoro-1-(m-tolyl)ethan-1-one (5h)**

The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(m-tolyl)butane-1,3-dione (115 mg, 0.5 mmol) and purified by flash column

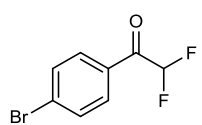
chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a yellow oil (59 mg, 70%). IR 1707, 1605, 1586, 1280, 1264, 1202, 1131, 1058, 746, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.92 – 7.83 (2H, m), 7.48 (1H, d, *J* = 7.6 Hz), 7.41 (1H, t, *J* = 7.9 Hz), 6.29 (1H, t, *J* = 54 Hz), 2.44 (3H, s). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 187.7 (C, t, *J* = 25 Hz), 138.9 (C), 135.7 (CH), 131.5 (C, t, *J* = 1.5 Hz), 130.0 (CH, t, *J* = 1.9 Hz), 128.8 (CH), 126.8 (CH, t, *J* = 2.4 Hz), 111.1 (CH, t, *J* = 254 Hz), 21.3 (CH<sub>3</sub>). <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -122.1 (2F, s); HRMS (ES<sup>-</sup>) Exact mass calculated for C<sub>9</sub>H<sub>8</sub>F<sub>2</sub>O [M-H]<sup>-</sup>: 169.0470, found: 169.0471.

**2,2-difluoro-1-(*p*-tolyl)ethan-1-one (5i)**

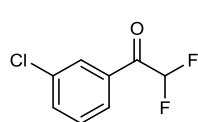
The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(*p*-tolyl)butane-1,3-dione (115 mg, 0.5 mmol) and purified by flash column chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a cream solid (71 mg, 84%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (2H, d, *J* = 8.1 Hz), 7.33 (2H, d, *J* = 8.1 Hz), 6.28 (1H, t, *J* = 53.6 Hz), 2.45 (3H, s). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 187.2 (C, t, *J* = 25 Hz), 146.2 (C), 129.8 (2 x CH, t, *J* = 2.2 Hz), 129.7 (2 x CH), 129.1 (C, t, *J* = 1.6 Hz), 111.3 (CH, t, *J* = 254 Hz), 21.9 (CH<sub>3</sub>); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.9 (2F, s). Data consistent with that previously reported.<sup>5</sup>

**1-(4-chlorophenyl)-2,2-difluoroethan-1-one (5j)**

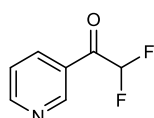
The title compound was prepared according to General Procedure D from 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (125 mg, 0.5 mmol) and purified by flash column chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a yellow oil (71 mg, 75%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.02 (2H, d, *J* = 8.8 Hz), 7.53 – 7.49 (2H, m), 6.24 (1H, t, *J* = 53.5 Hz). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.6 (C, t, *J* = 25.9 Hz), 141.7 (C), 131.1 (2 x CH, t, *J* = 2.4 Hz), 129.7 (C, t, *J* = 2.1 Hz), 129.4 (2 x CH), 111.4 (CH, t, *J* = 254.2 Hz); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.6 (2F, s). Data consistent with that previously reported.<sup>6</sup>

**1-(4-bromophenyl)-2,2-difluoroethan-1-one (5k)**

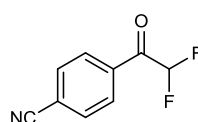
The title compound was prepared according to General Procedure D from 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (148 mg, 0.5 mmol) and purified by flash column (2.5% Et<sub>2</sub>O / Pentane) to give a yellow oil (98 mg, 84%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.94 (2H, d, *J* = 8.7 Hz), 7.68 (2H, d, *J* = 8.7 Hz), 6.24 (1H, t, *J* = 53.7 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.9 (C, t, *J* = 25.1 Hz), 132.4 (2 x CH), 131.2 (C), 131.1 (2 x CH), 130.6 (C), 111.3 (CH, t, *J* = 255.0 Hz); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.6 (2F, s); HRMS (ES<sup>+</sup>) Exact mass calculated for C<sub>8</sub>H<sub>5</sub>OF<sub>2</sub><sup>79</sup>Br [M+H]<sup>+</sup>: 234.9399, found: 234.9400. Data consistent with that previously reported.<sup>5</sup>

**1-(3-chlorophenyl)-2,2-difluoroethan-1-one (5l)**

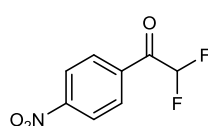
The title compound was prepared according to General Procedure D from 1-(3-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (125 mg, 0.5 mmol) and purified by flash column chromatography (2.5% Et<sub>2</sub>O / Pentane) to give a colorless oil (85 mg, 89%). IR 2976, 1714, 1429, 1393, 1236, 1141, 1076, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.05 (1H, s), 7.97 (1H, d, *J* = 7.9 Hz), 7.65 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz), 7.49 (1H, t, *J* = 7.9 Hz), 6.25 (1H, t, *J* = 53.4 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.6 (C, t, *J* = 26.1 Hz), 135.4 (C), 134.9 (CH), 132.8 (C, t, *J* = 2.0 Hz), 130.3 (CH), 129.6 (CH, t, *J* = 2.3 Hz), 127.8 (CH, t, *J* = 2.6 Hz), 111.1 (CH, t, *J* = 254 Hz); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.7 (2F, s).

**2,2-difluoro-1-(pyridin-3-yl)ethan-1-one (5m)**

The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(pyridin-3-yl)butane-1,3-dione (109 mg, 0.5 mmol) and purified by flash column chromatography (Et<sub>2</sub>O) to give a yellow oil (59 mg, 75%). IR 1709, 1602, 1587, 1128, 1050, 1025, 717, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.27 (1H, d, *J* = 0.8 Hz), 8.87 (1H, dd, *J* = 4.8, 1.6 Hz), 8.35 (1H, d, *J* = 8.0 Hz), 7.49 (1H, ddd, *J* = 8.0, 4.9, 0.6 Hz), 6.25 (1H, t, *J* = 53.3 Hz). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 187.1 (C, t, *J* = 26.9 Hz), 154.9 (CH), 150.8 (CH, t, *J* = 3.3 Hz), 136.9 (CH, t, *J* = 2.2 Hz), 127.2 (C, t, *J* = 2.1 Hz), 123.9 (CH), 111.3 (CH, t, *J* = 254 Hz); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -122.0 (2F, s); HRMS (ES<sup>-</sup>) Exact mass calculated for C<sub>7</sub>H<sub>5</sub>F<sub>2</sub>ON [M-H]<sup>-</sup>: 156.0266, found: 156.0266.

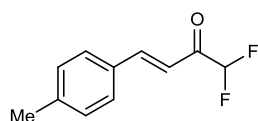
**4-(2,2-difluoroacetyl)benzonitrile (5n)**

The title compound was prepared according to General Procedure D from 4-(4,4,4-trifluoro-3-oxobutanoyl)benzonitrile (121 mg, 0.5 mmol) and purified by flash column chromatography (20% Et<sub>2</sub>O / Pentane) to give a yellow oil (63 mg, 70%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.19 (2H, d, *J* = 8.7 Hz), 7.86 – 7.82 (2H, m), 6.26 (1H, t, *J* = 53.3 Hz). <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.7 (C, t, *J* = 26.8 Hz), 134.2 (C, t, *J* = 2.2 Hz), 132.7 (2 x CH), 130.1 (2 x CH, t, *J* = 2.5 Hz), 118.1 (C), 117.5 (C), 111.3 (CH, t, *J* = 255 Hz); <sup>19</sup>F NMR (376.6 MHz, CDCl<sub>3</sub>) δ -121.5 (2F, s). Data consistent with that previously reported.<sup>7</sup>

**2,2-difluoro-1-(4-nitrophenyl)ethan-1-one (5o)**

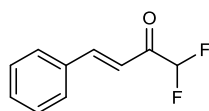
The title compound was prepared according to General Procedure D from 4,4,4-trifluoro-1-(4-nitrophenyl)butane-1,3-dione (131 mg, 0.5 mmol) and purified by flash column chromatography (40% Et<sub>2</sub>O / Pentane) to give a brown oil (86 mg, 85%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.39 – 8.35 (2H, m), 8.26 (2H, d, *J* = 9.0 Hz), 6.29 (1H, t, *J* = 53.2 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 186.5 (C, t, *J* = 26.9 Hz), 151.2 (C), 135.6 (C, t, *J* = 2.3 Hz), 130.8 (2 x CH, t, *J* = 2.5 Hz),

124.0 (2 x CH), 111.2 (CH, t,  $J$  = 254 Hz);  $^{19}\text{F}$  NMR (376.6 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.6 (2F, s). Data consistent with that previously reported.<sup>8</sup>



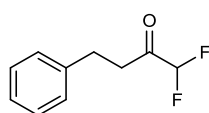
**(E)-1,1-difluoro-4-(p-tolyl)but-3-en-2-one (5p)**

The title compound was prepared according to General Procedure D from (E)-1,1,1-trifluoro-6-(p-tolyl)hex-5-ene-2,4-dione (121 mg, 0.5 mmol) and purified by flash column chromatography (2.5%  $\text{Et}_2\text{O}$  / Pentane) to give a yellow oil (61 mg, 62%). IR 1701, 1594, 1568, 1209, 1105, 1052, 985, 809  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (1H, d,  $J$  = 16.0 Hz), 7.52 (2H, d,  $J$  = 8.0 Hz), 7.24 (2H, d,  $J$  = 8.0 Hz), 7.01 (1H, d,  $J$  = 16.0 Hz), 5.92 (1H, t,  $J$  = 54.1 Hz), 2.40 (3H, s).  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  187.8 (t,  $J$  = 25.6 Hz, C), 148.2 (CH), 142.6 (C), 131.1 (C), 129.9 (2 x CH), 129.0 (2 x CH), 116.8 (CH), 110.6 (t,  $J$  = 253 Hz, CH);  $^{19}\text{F}$  NMR (376.6 MHz,  $\text{CDCl}_3$ )  $\delta$  -126.0 (2F, s); HRMS (ES-) Exact mass calculated for  $\text{C}_{11}\text{H}_{10}\text{F}_2\text{O}$   $[\text{M}-\text{H}]^-$ : 195.0627, found: 195.0625.



**(E)-1,1-difluoro-4-phenylbut-3-en-2-one (5q)**

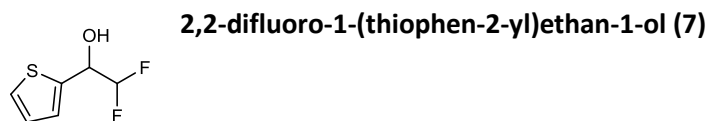
The title compound was prepared according to General Procedure D from (E)-1,1,1-trifluoro-6-phenylhex-5-ene-2,4-dione (121 mg, 0.5 mmol) and purified by flash column chromatography (10%  $\text{Et}_2\text{O}$  / Pentane) to give a yellow oil (62 mg, 68%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (1H, d,  $J$  = 16.1 Hz), 7.67 – 7.61 (2H, m), 7.50 – 7.41 (3H, m), 7.06 (1H, d,  $J$  = 16.1 Hz), 5.93 (1H, t,  $J$  = 54.0 Hz).  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  187.8 (C, t,  $J$  = 25.8 Hz), 148.2 (CH), 133.7 (C), 131.8 (CH), 129.1 (2 x CH), 129.0 (2 x CH), 117.9 (CH), 110.6 (CH, t,  $J$  = 253 Hz);  $^{19}\text{F}$  NMR (376.6 MHz,  $\text{CDCl}_3$ )  $\delta$  -126.0 (2F, s). Data consistent with that previously reported.<sup>7</sup>



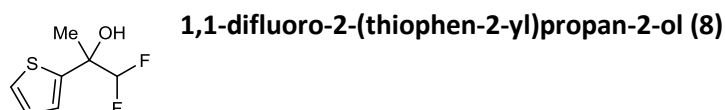
**1,1-difluoro-4-phenylbutan-2-one (5r)**

The title compound was prepared according to General Procedure D from 1,1,1-trifluoro-6-phenylhexane-2,4-dione (122 mg, 0.5 mmol) and purified by flash column chromatography (10%  $\text{Et}_2\text{O}$  / Pentane) to give a yellow oil (52 mg, 56%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (2H, t,  $J$  = 7.4 Hz), 7.25 – 7.18 (3H, m), 3.04 – 2.99 (2H, m), 2.99 – 2.94 (2H, m).  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  199.0 (C, t,  $J$  = 26.4 Hz), 139.9 (C), 128.6 (2 x CH), 128.3 (2 x CH), 126.5 (CH), 109.8 (CH, t,  $J$  = 253 Hz), 37.7 ( $\text{CH}_2$ ), 28.3 ( $\text{CH}_2$ ).  $^{19}\text{F}$  NMR (376.6 MHz,  $\text{CDCl}_3$ )  $\delta$  -127.0 (2F, s). Data consistent with that previously reported.<sup>7</sup>

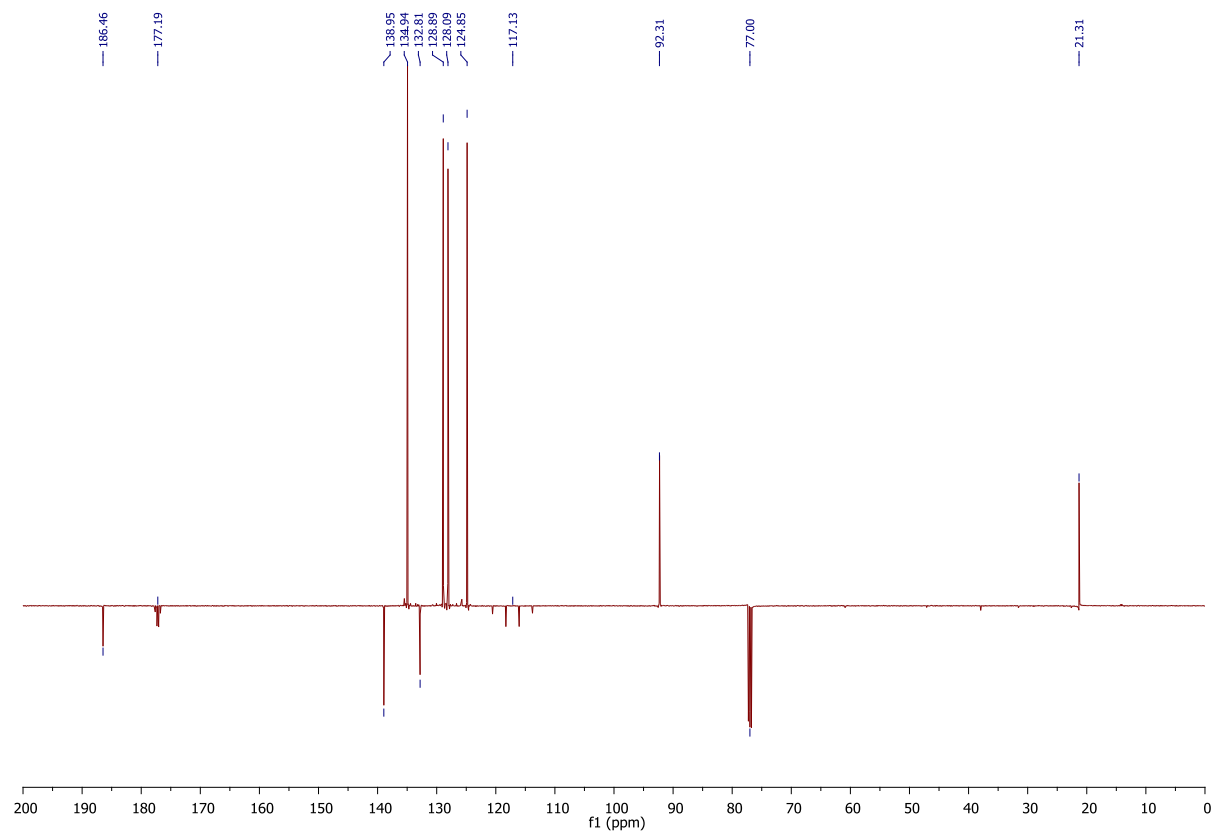
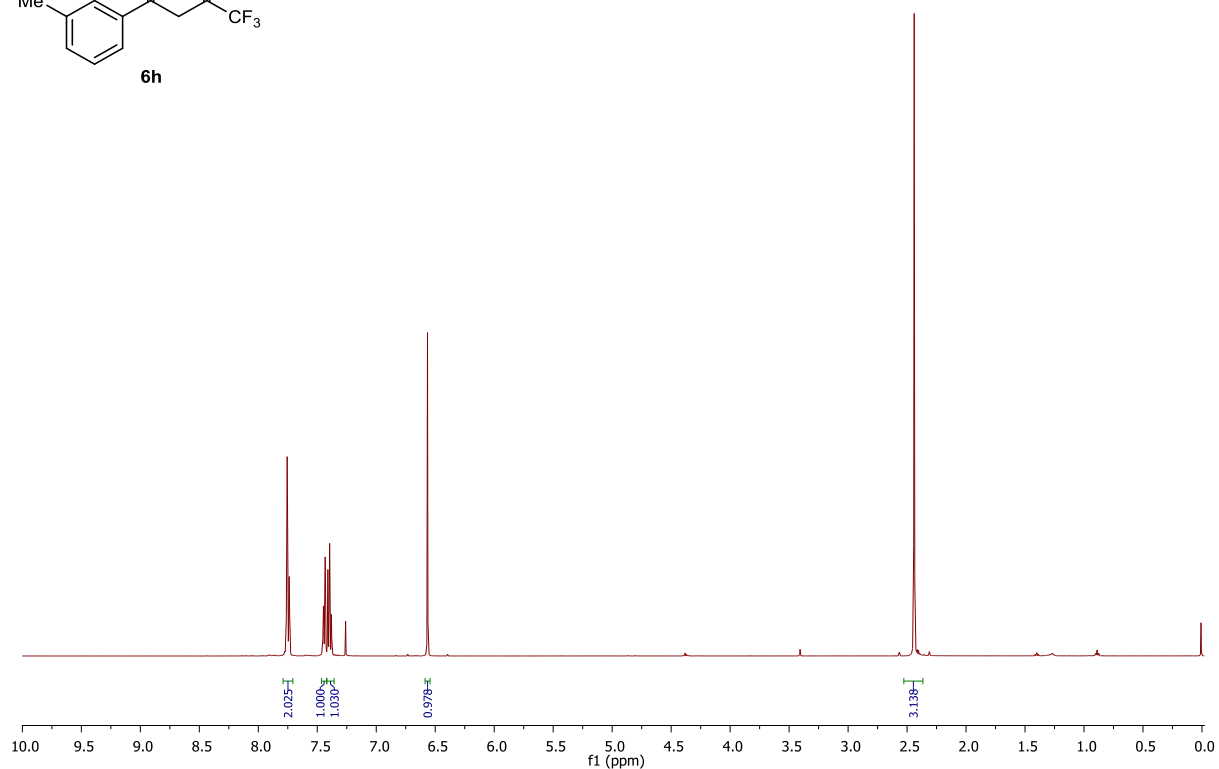
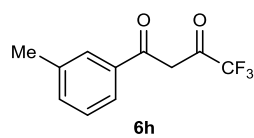
## Transformations of difluoromethyl ketones

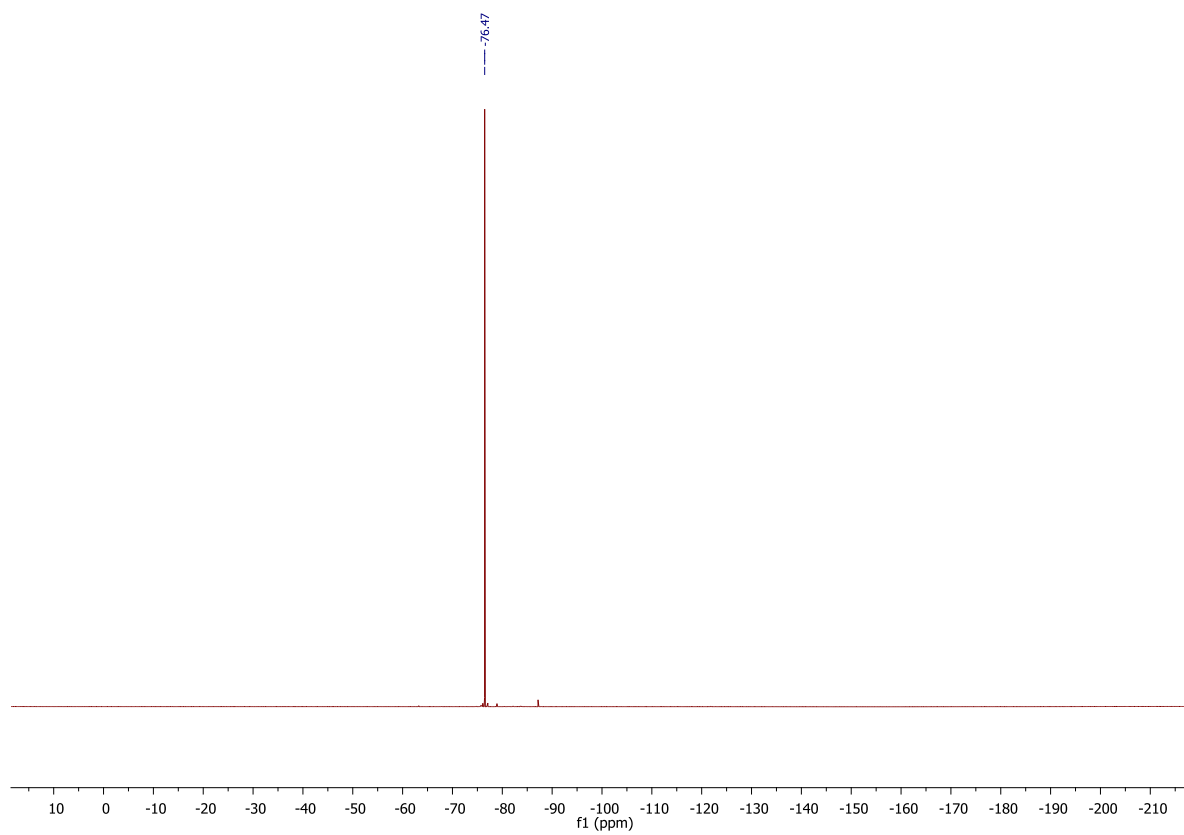
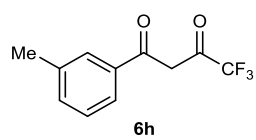


To a solution of 2,2-difluoro-1-(thiophen-2-yl)ethan-1-one (81 mg, 0.5 mmol) in EtOH (3 mL) at 0 °C was added NaBH<sub>4</sub> (23 mg, 0.6 mmol) and stirred for 6 hours. The mixture was quenched with water, and EtOH removed in vacuo. The solution was acidified with 0.2 M HCl and extracted with EtOAc. The organic phase was dried with MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a brown oil (78 mg, 95%). IR 3371 (O–H stretch), 1437, 1366, 1135, 1118, 1037, 761, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38 (1H, dd, *J* = 5.2, 1.2 Hz), 7.14 (1H, d, *J* = 3.4 Hz), 7.05 (1H, dd, *J* = 5.0, 3.5 Hz), 5.82 (1H, td, *J* = 55.9, 4.3 Hz), 5.07 (1H, td, *J* = 10.1, 4.3 Hz), 3.01 (1H, br s); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 138.3 (C, t, *J* = 4.0 Hz), 127.1 (CH), 126.6 (CH), 126.6 (CH), 115.1 (CH, t, *J* = 246.0 Hz), 70.0 (CH, t, *J* = 25.1 Hz); <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ -126.6 (1F, d, *J* = 284 Hz), 127.7 (1F, d, *J* = 284 Hz); HRMS (ES<sup>+</sup>) Exact mass calculated for C<sub>6</sub>H<sub>6</sub>OF<sub>2</sub>S [M+Na]<sup>+</sup>: 187.0000, found: 187.0002.

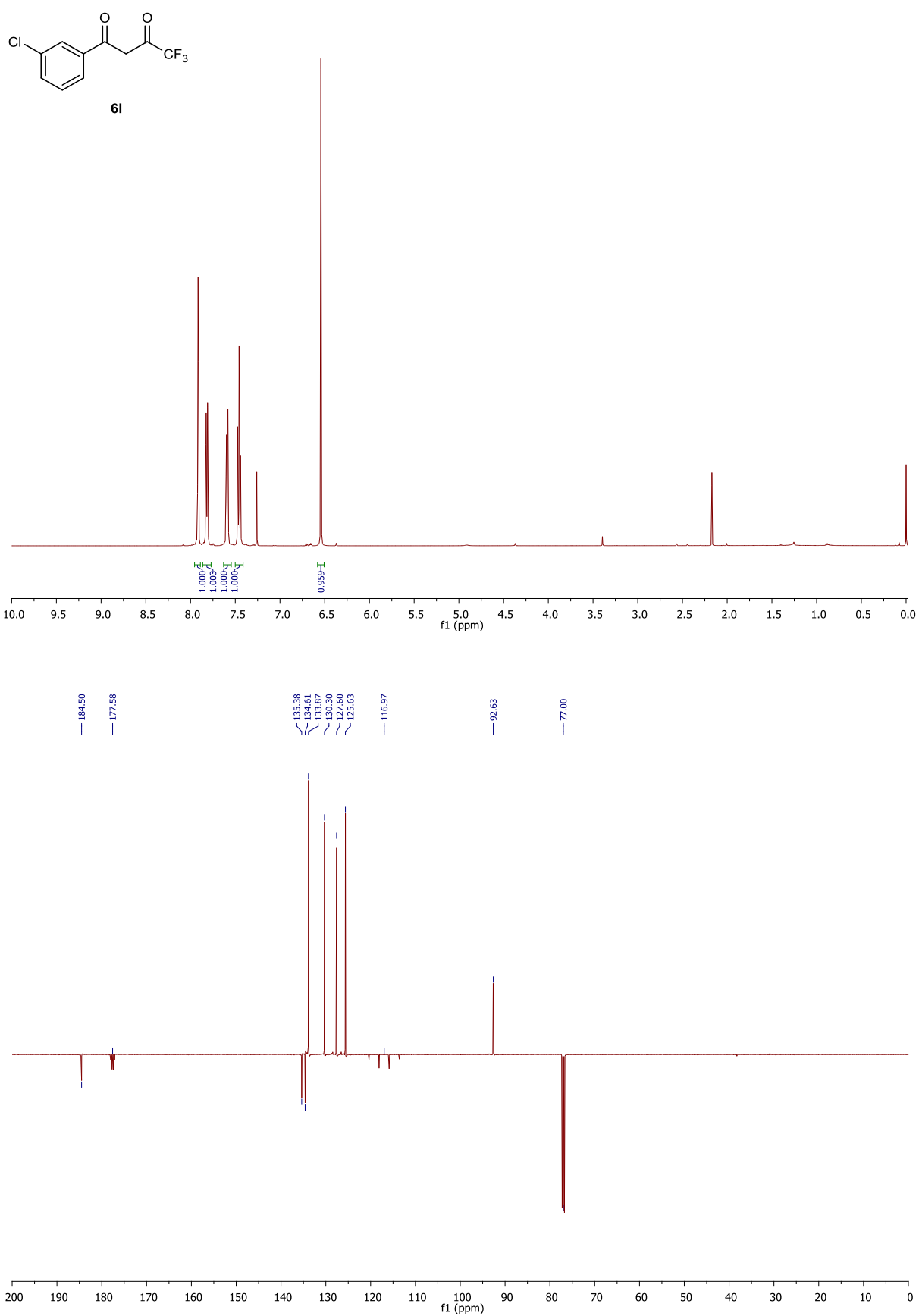


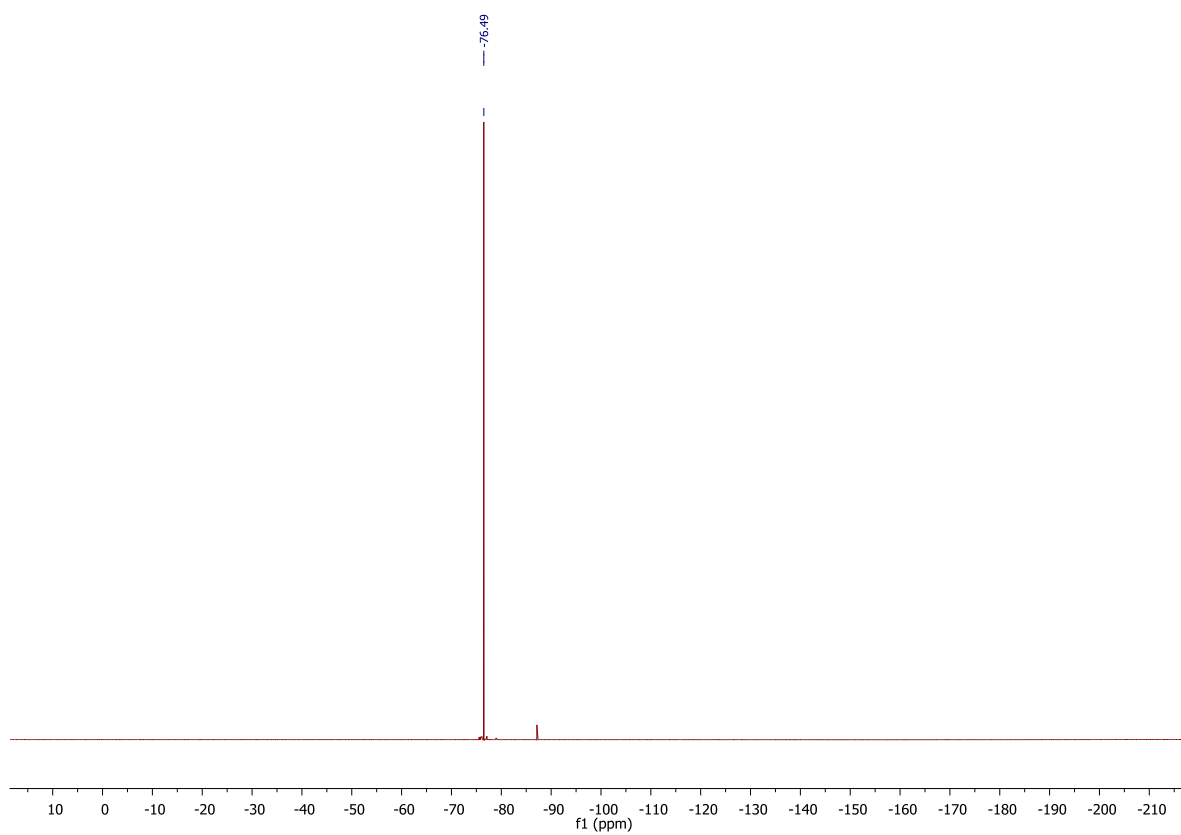
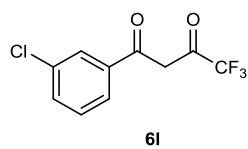
To a solution of 2,2-difluoro-1-(thiophen-2-yl)ethan-1-one (81 mg, 0.5 mmol) in THF (5 mL) under nitrogen at room temperature was added MeMgBr (3M in Et<sub>2</sub>O) (0.2 mL, 0.6 mmol) and stirred for 6 hours. The reaction was quenched with 0.2 M HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The organic phase was dried with MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give a dark brown oil (72 mg, 81%). IR 3450, 2988, 1384, 1241, 1065, 1047, 1020, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.33 (1H, dd, *J* = 3.7, 1.2 Hz), 7.09 (1H, d, *J* = 3.4 Hz), 7.04 (1H, dd, *J* = 3.7, 1.2 Hz), 5.75 (1H, t, *J* = 56.2 Hz), 2.62 (1H, br s), 1.72 (3H, t, *J* = 1.7 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 144.4 (C), 127.3 (CH), 126.8 (CH), 125.0 (CH), 116.3 (CH, t, *J* = 250.0 Hz), 73.8 (C, t, *J* = 23.1 Hz), 23.1 (CH<sub>3</sub>, t, *J* = 2.0 Hz); <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ -128.8 (1F, d, *J* = 276 Hz), 130.1 (1F, d, *J* = 276 Hz); HRMS (ES<sup>+</sup>) Exact mass calculated for C<sub>7</sub>H<sub>8</sub>OF<sub>2</sub>S [M+Na]<sup>+</sup>: 201.0156, found: 201.0160.

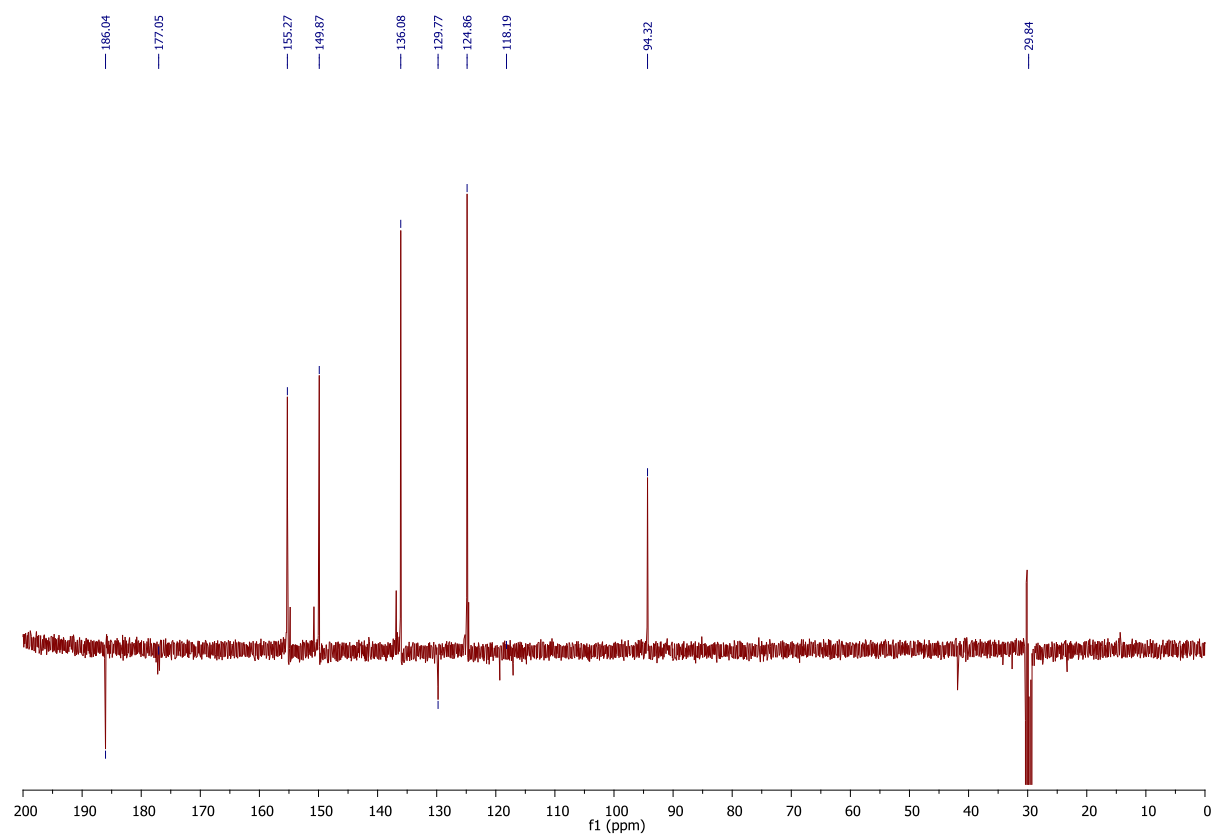
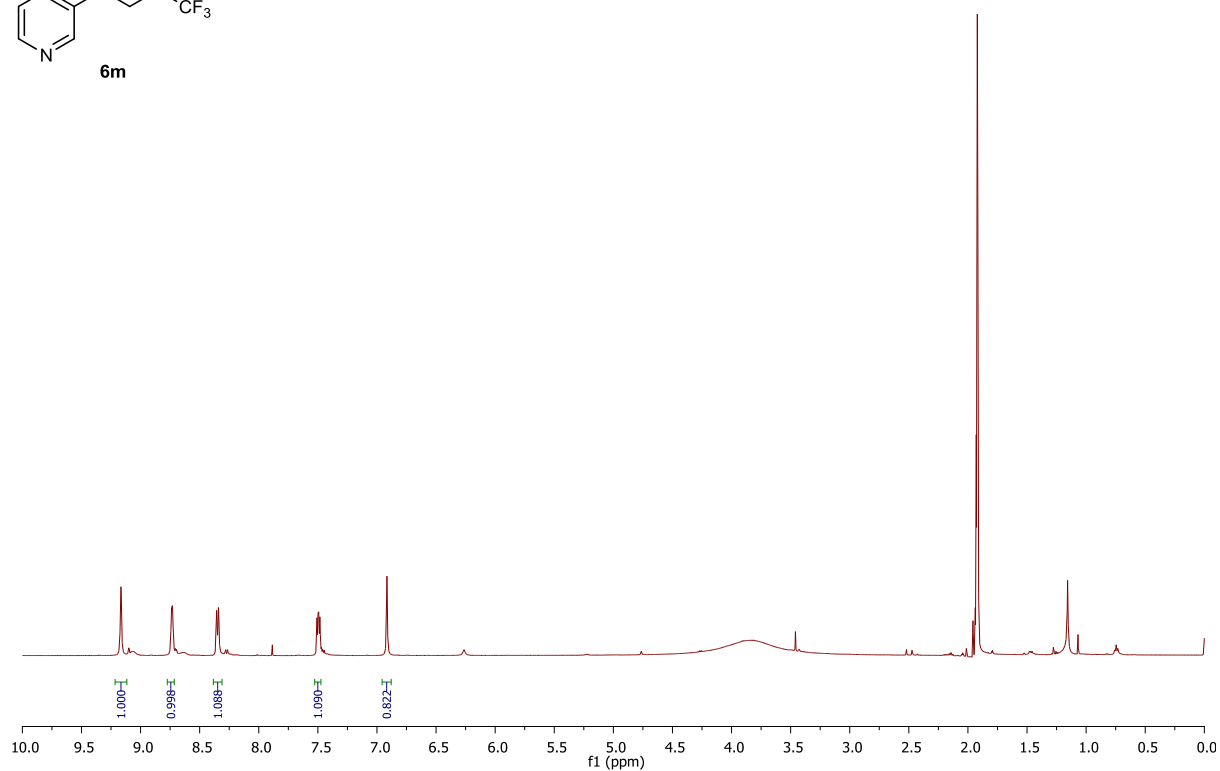
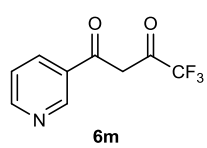
Copies of  $^1\text{H}$   $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra for all new compounds

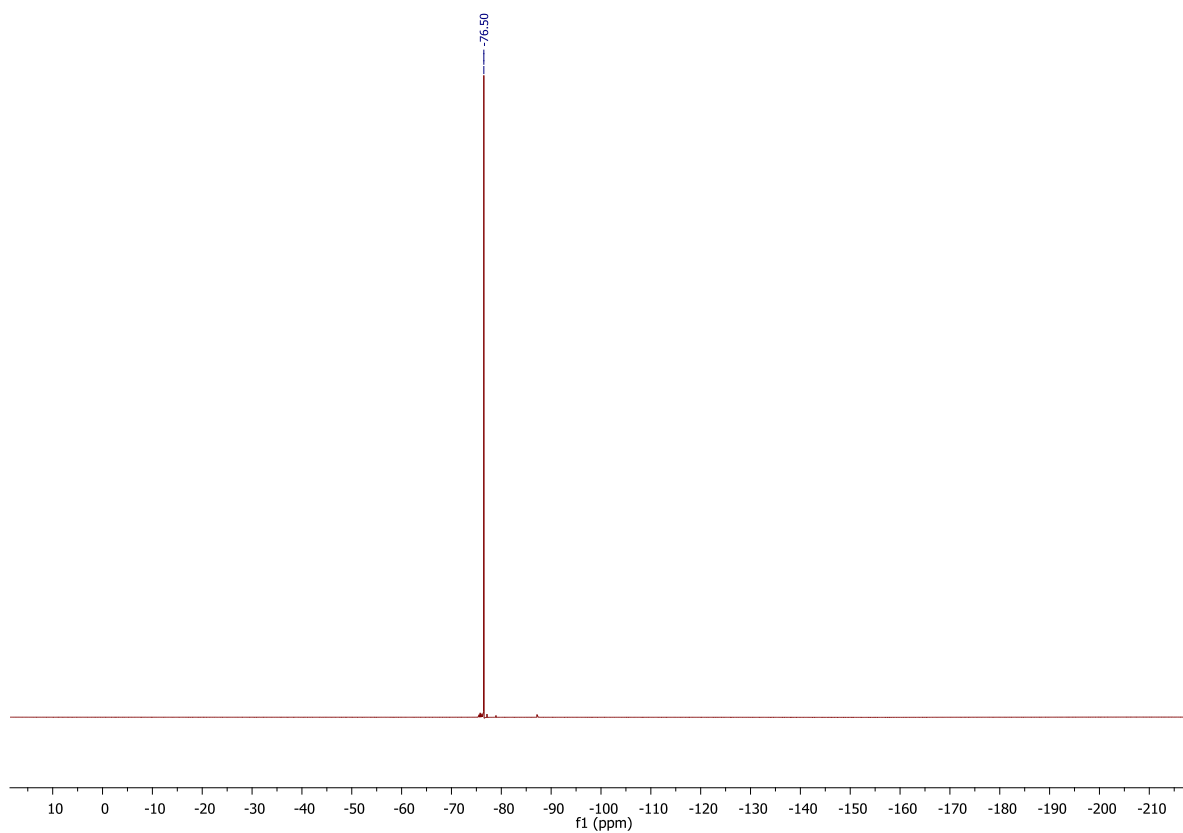
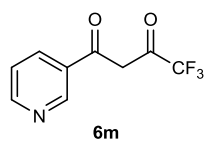


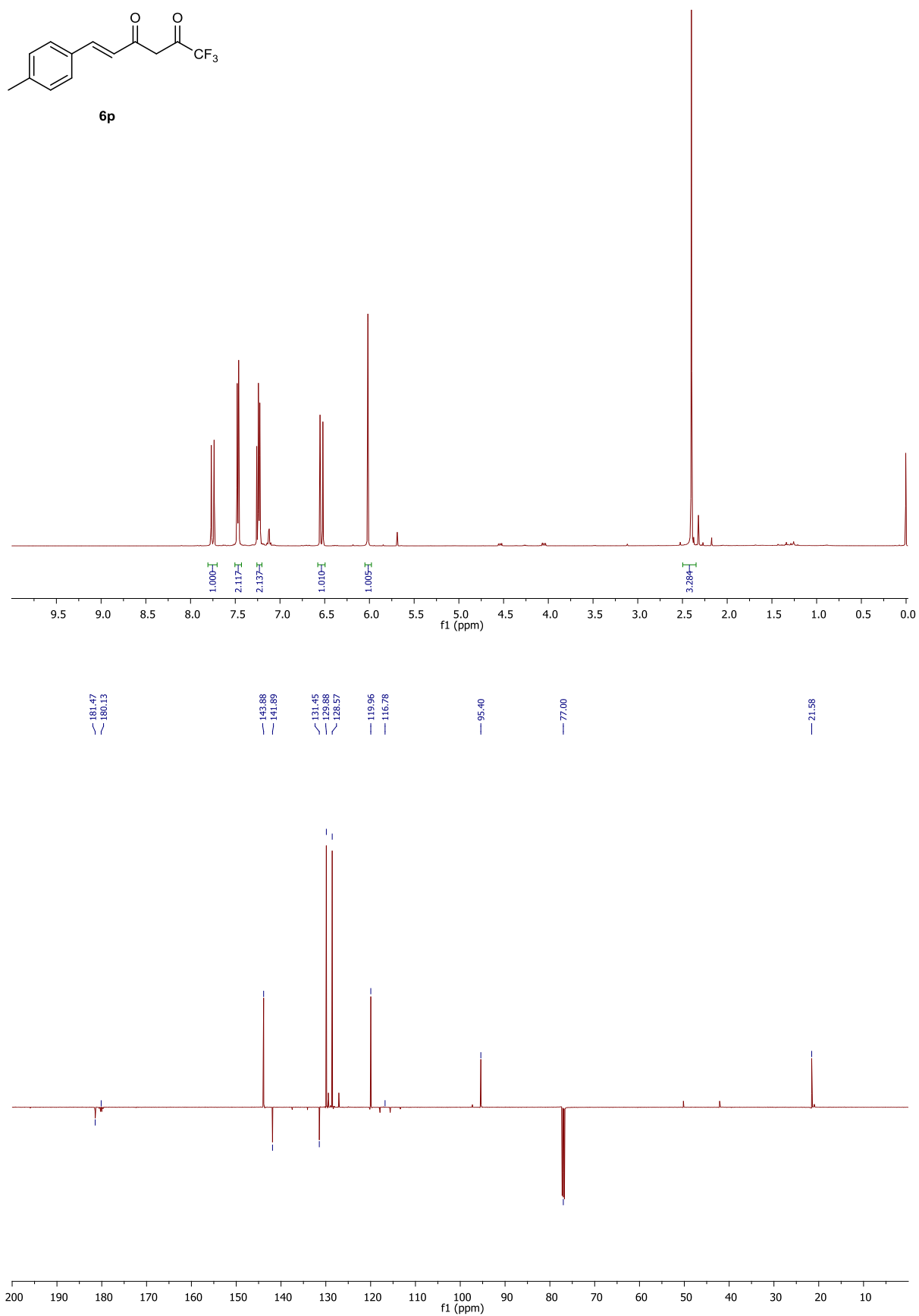


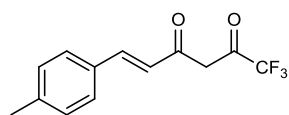
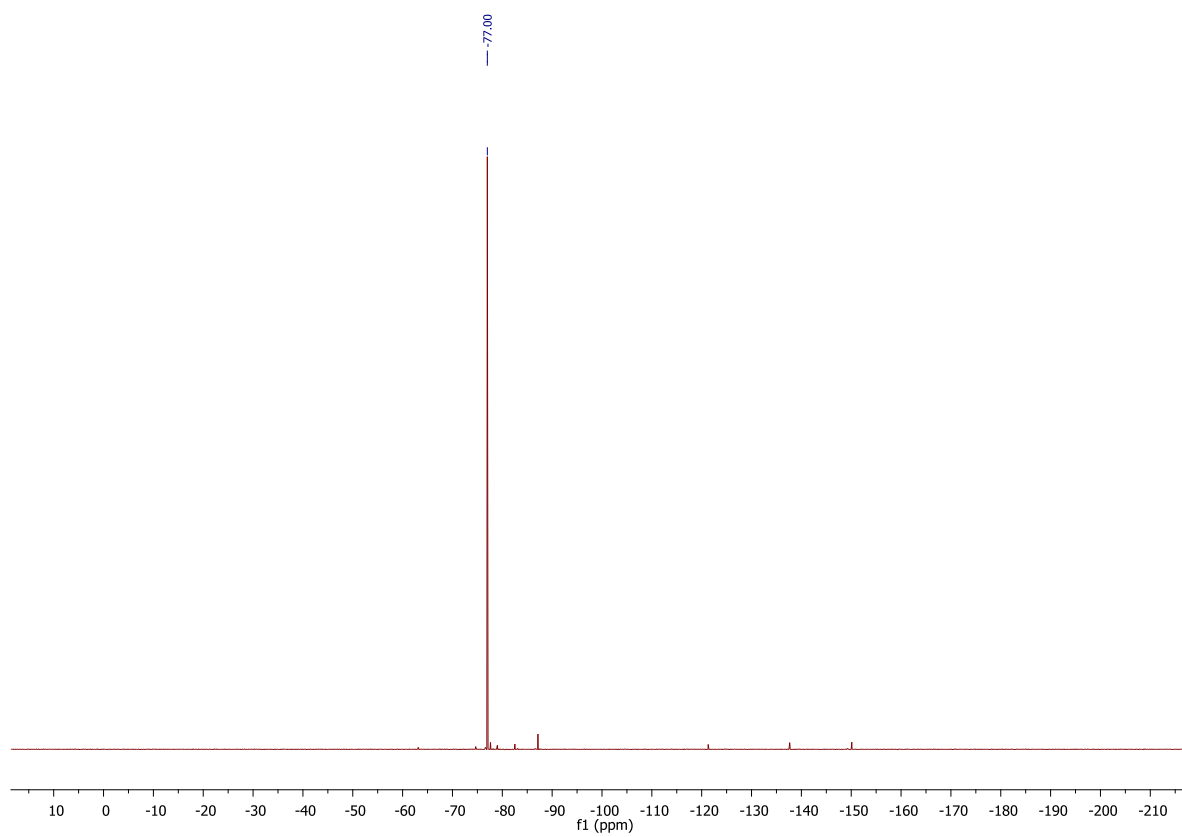


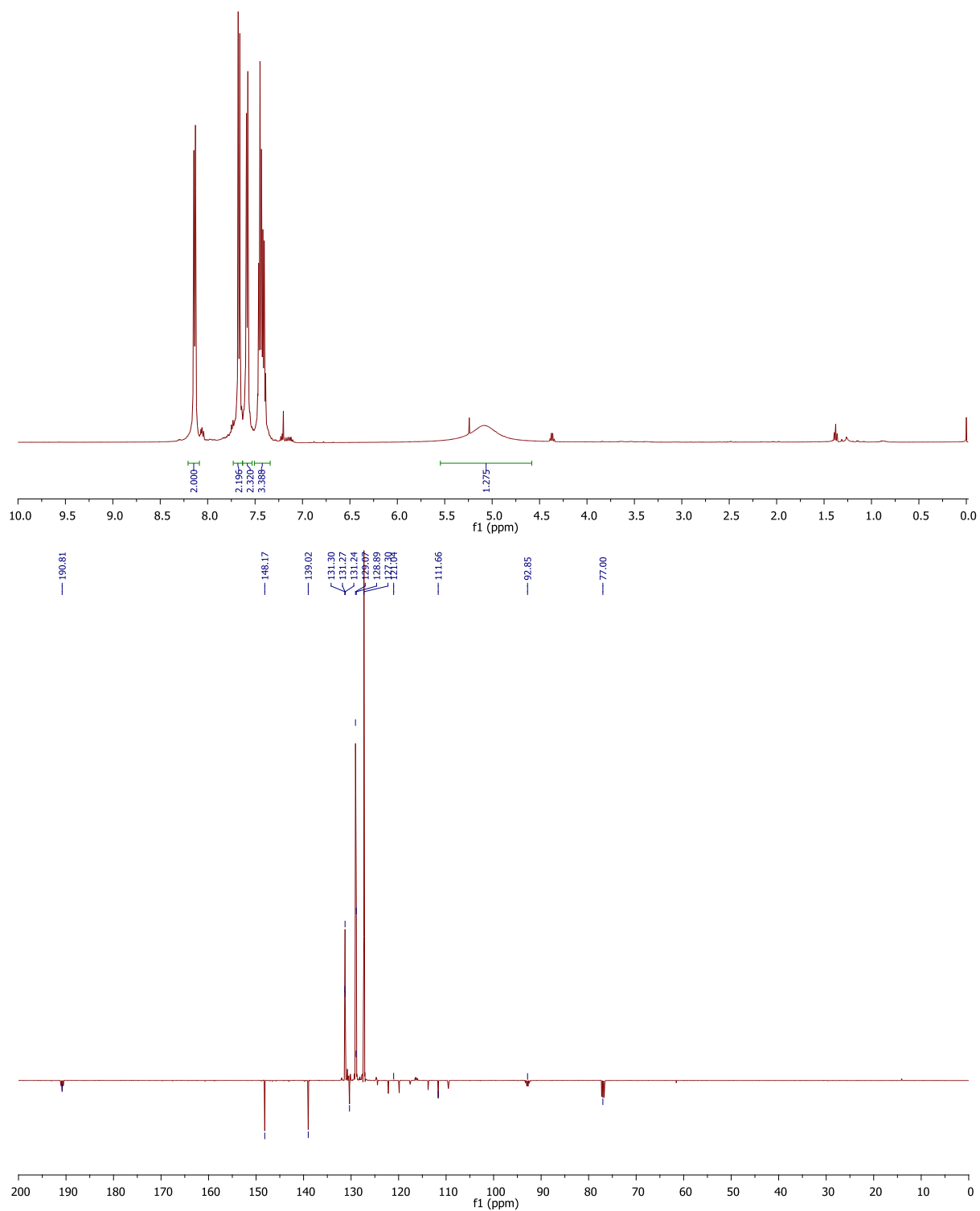
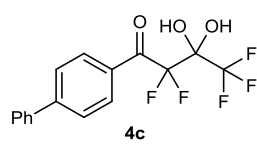


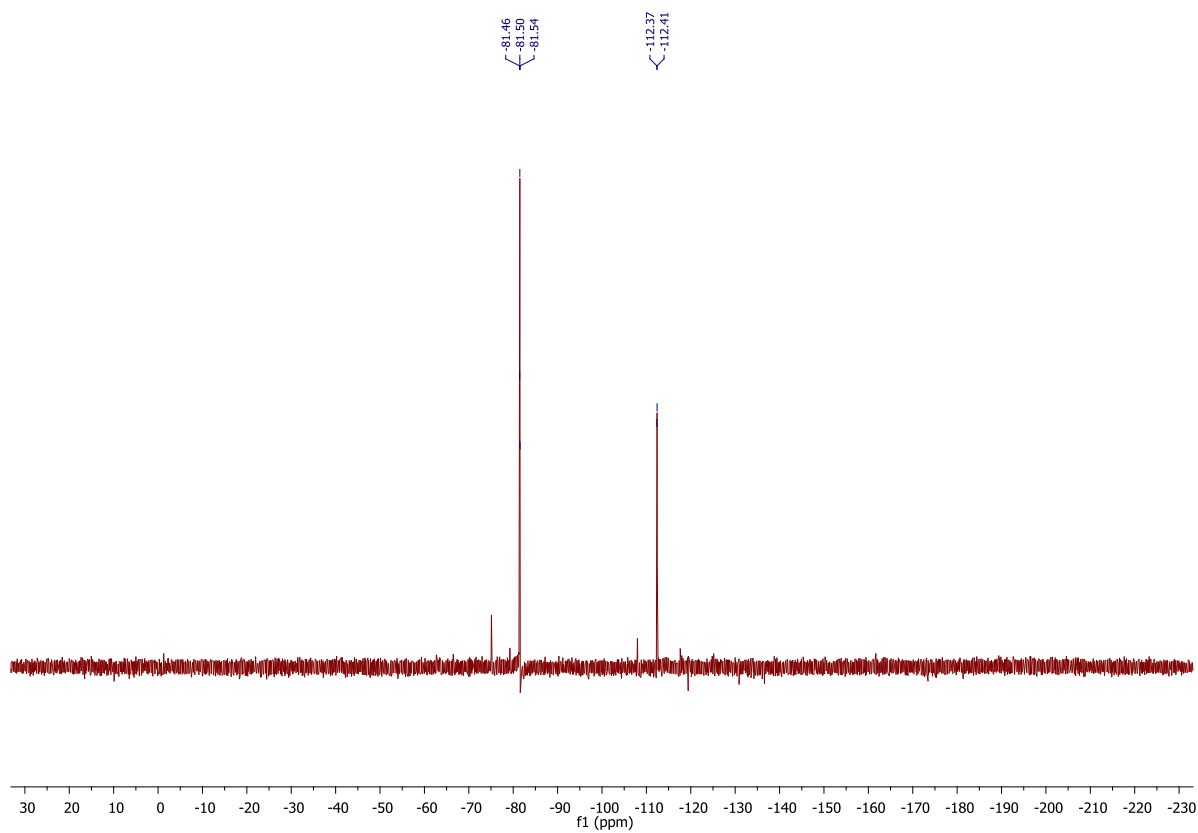
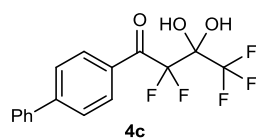




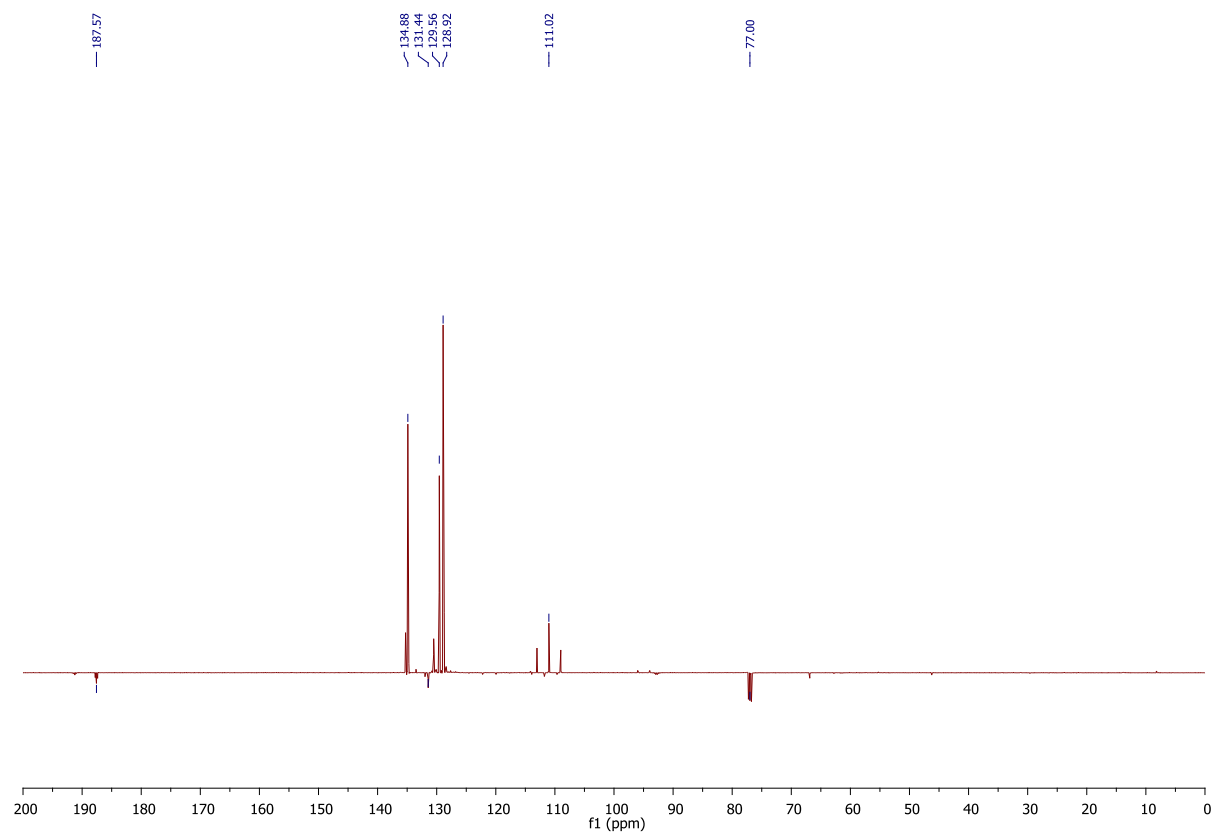
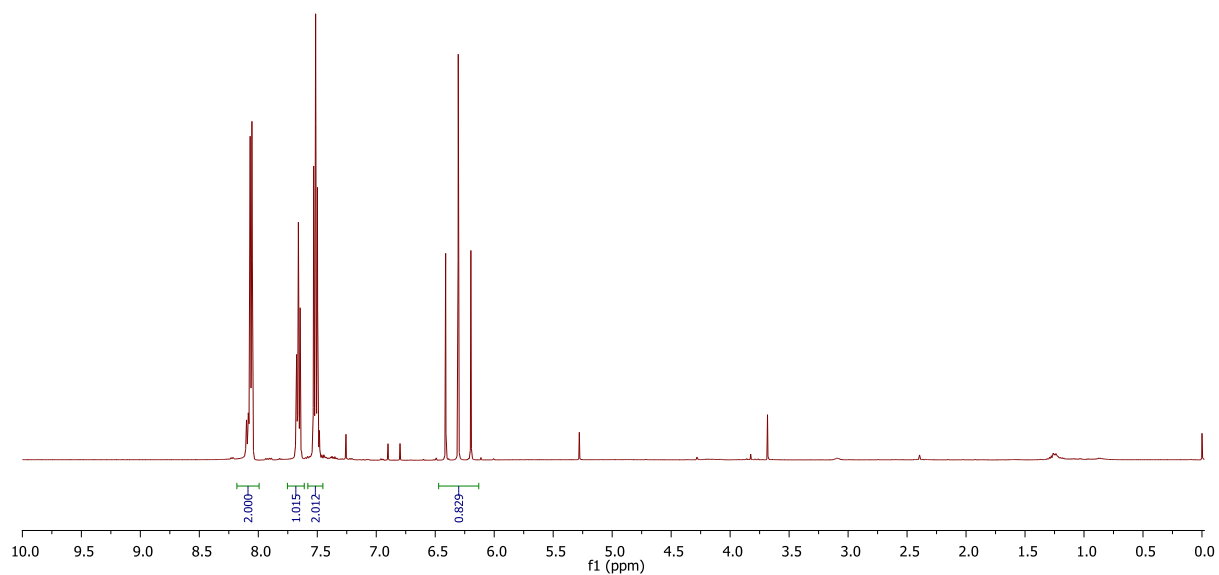
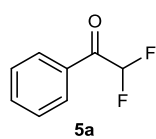


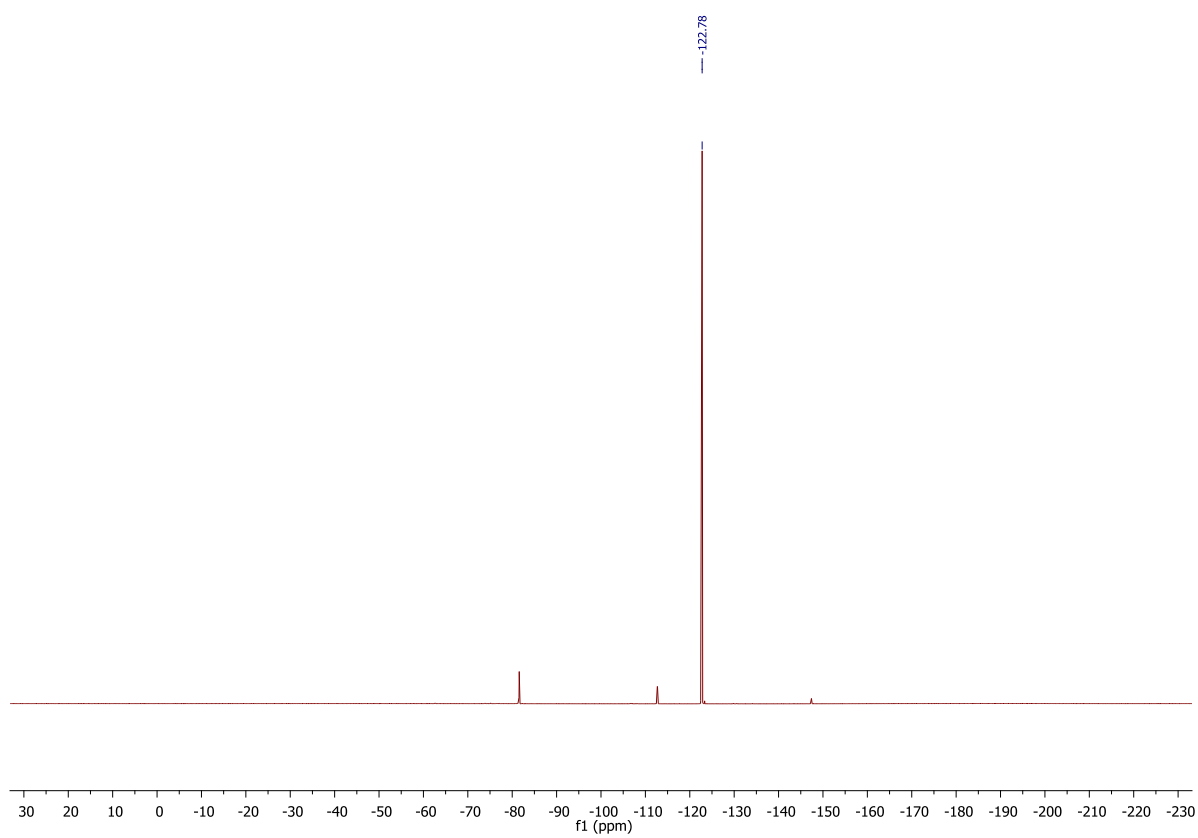
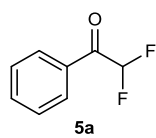
**6p**

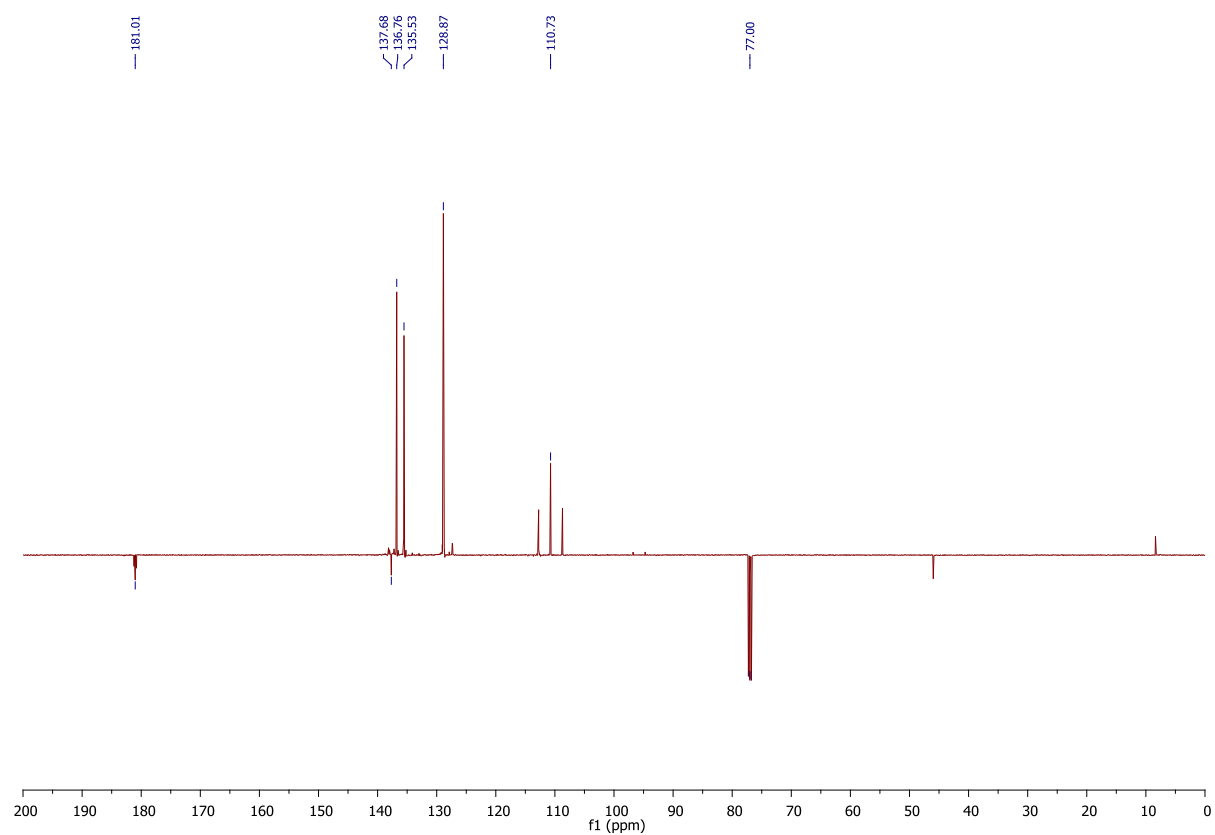
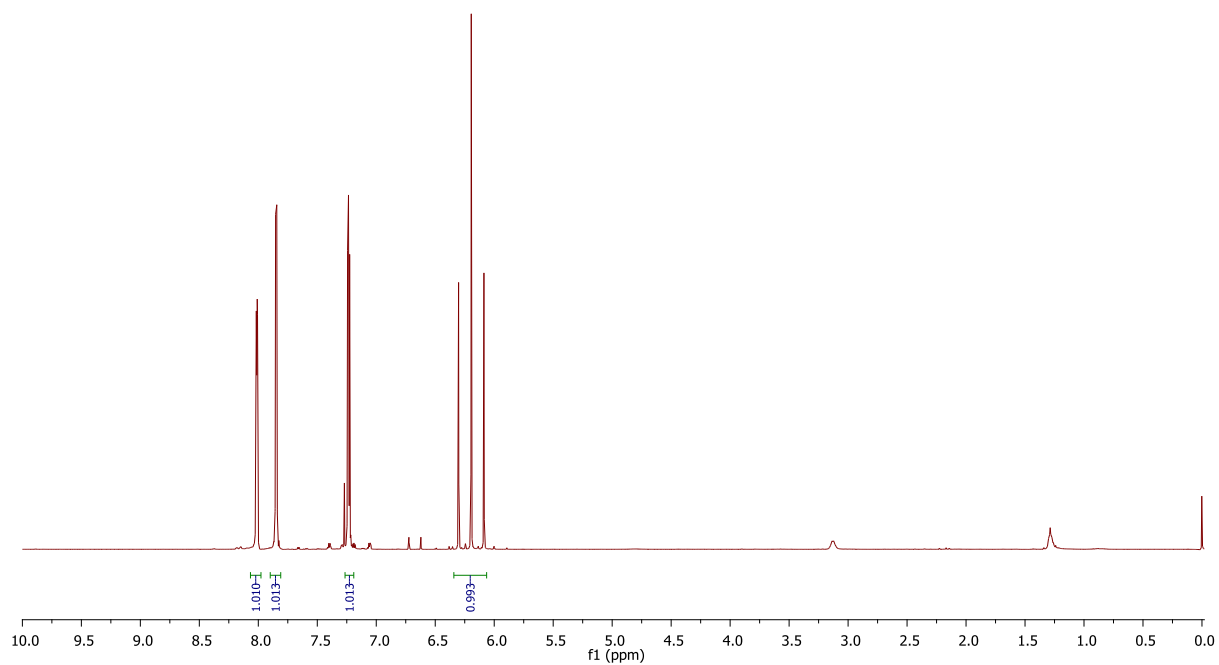
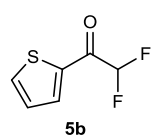


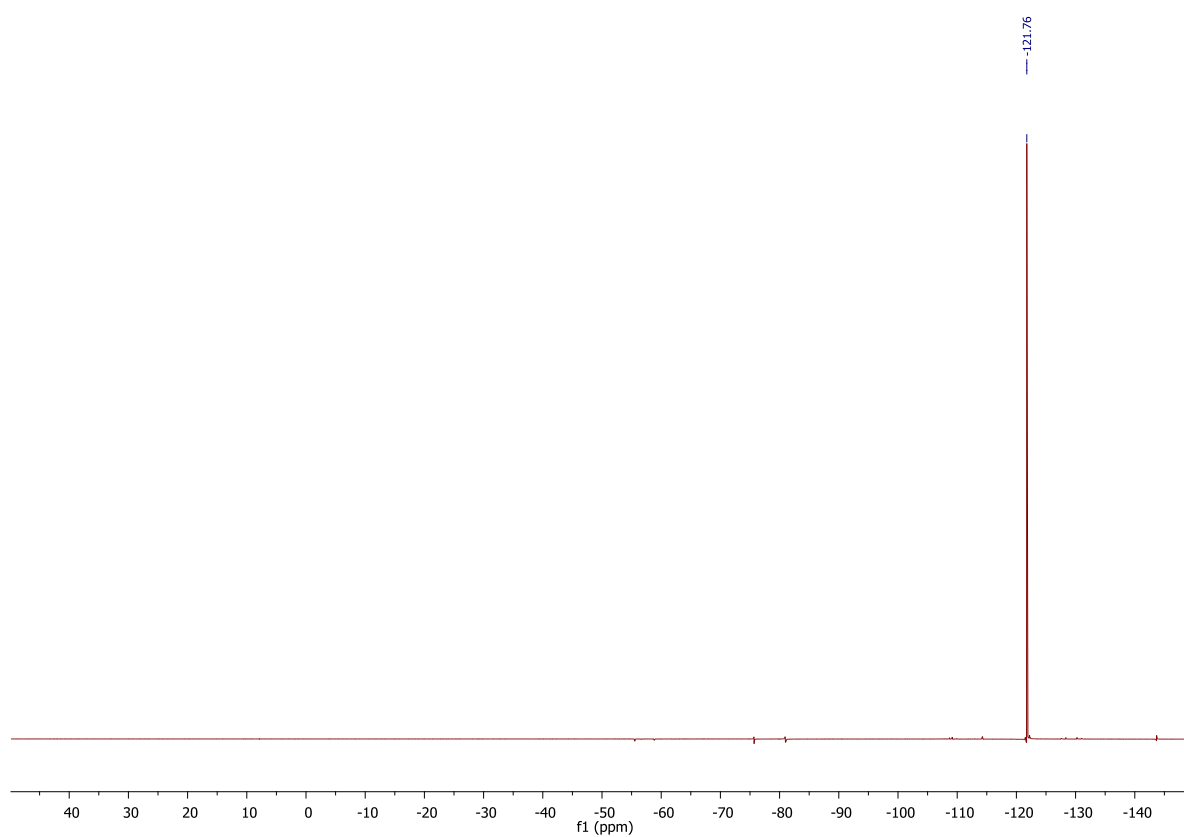
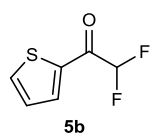


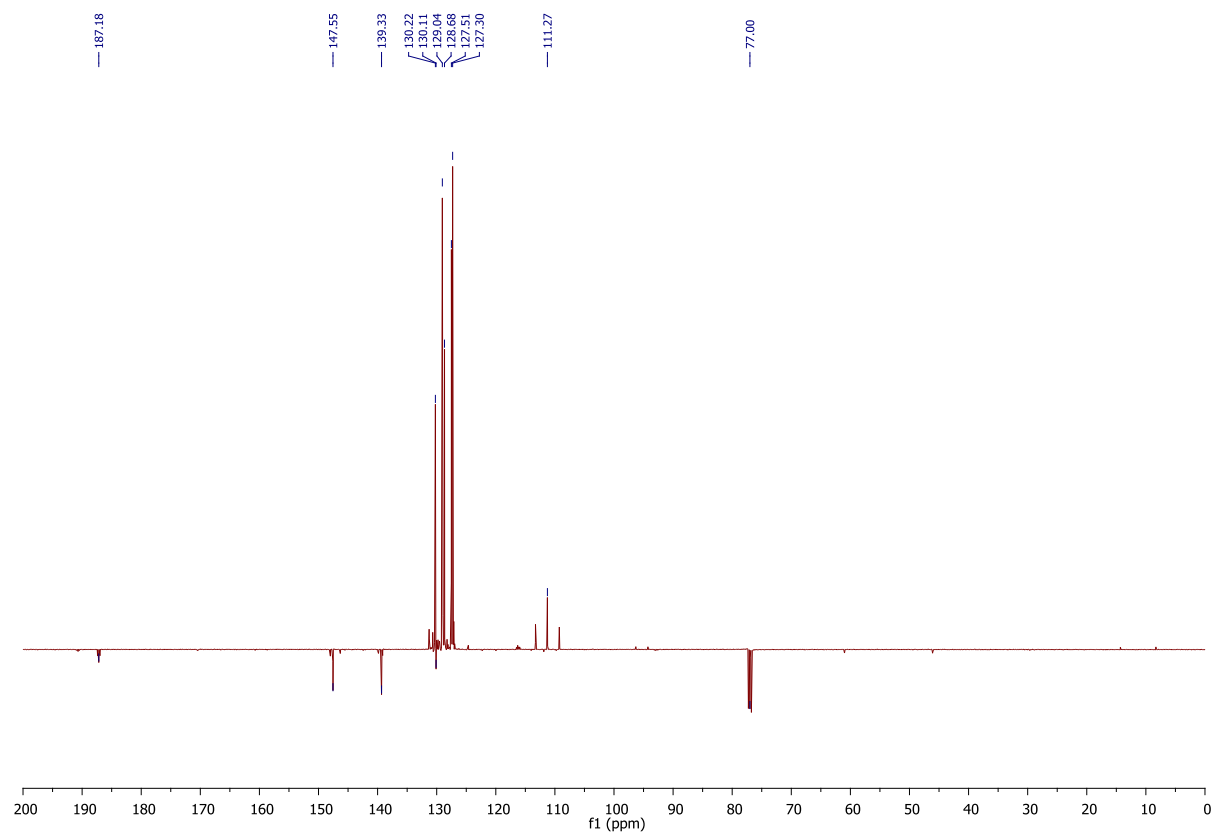
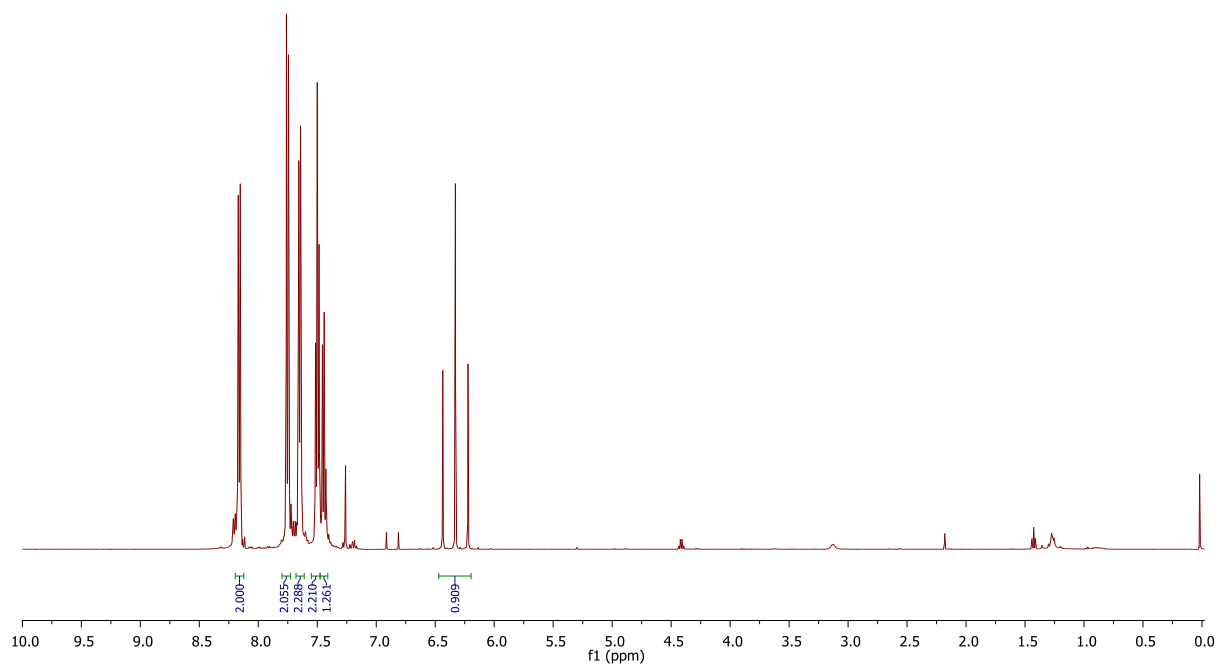
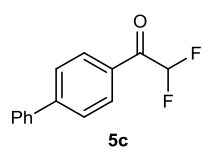


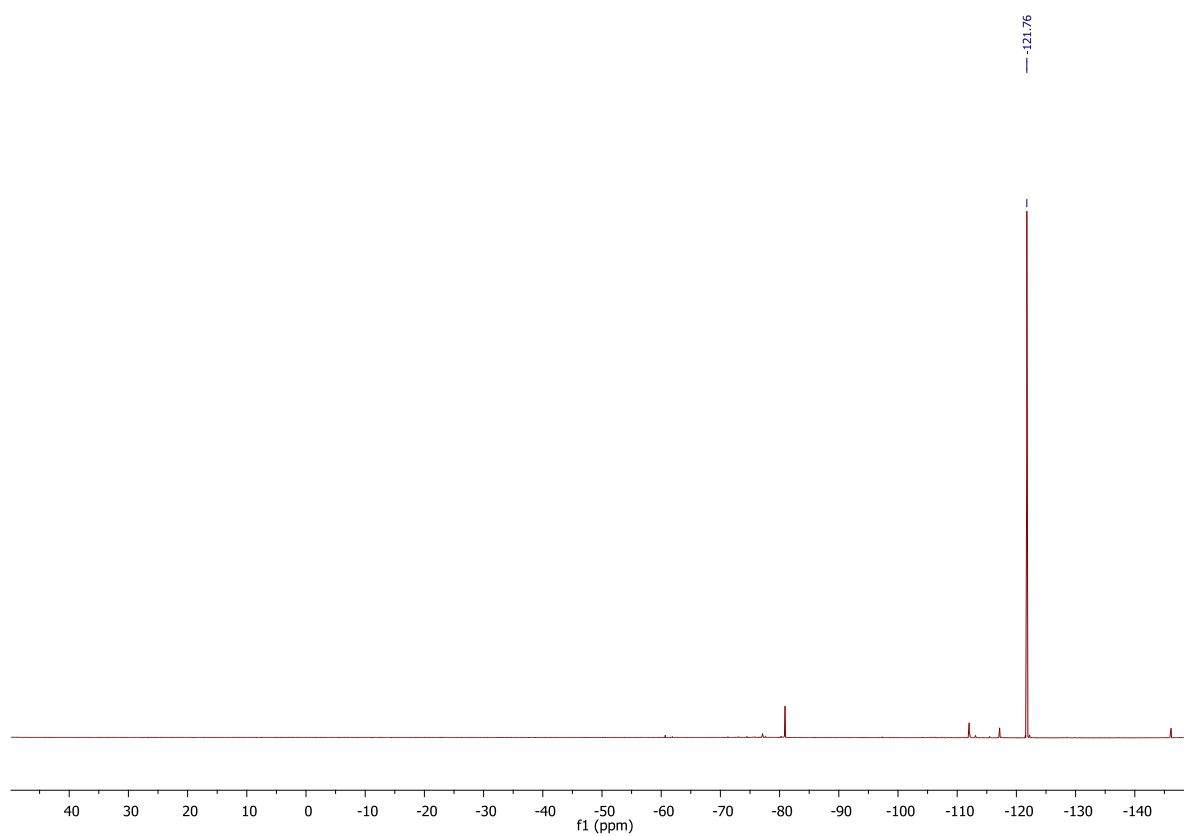
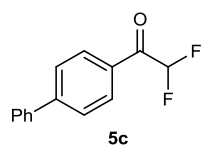


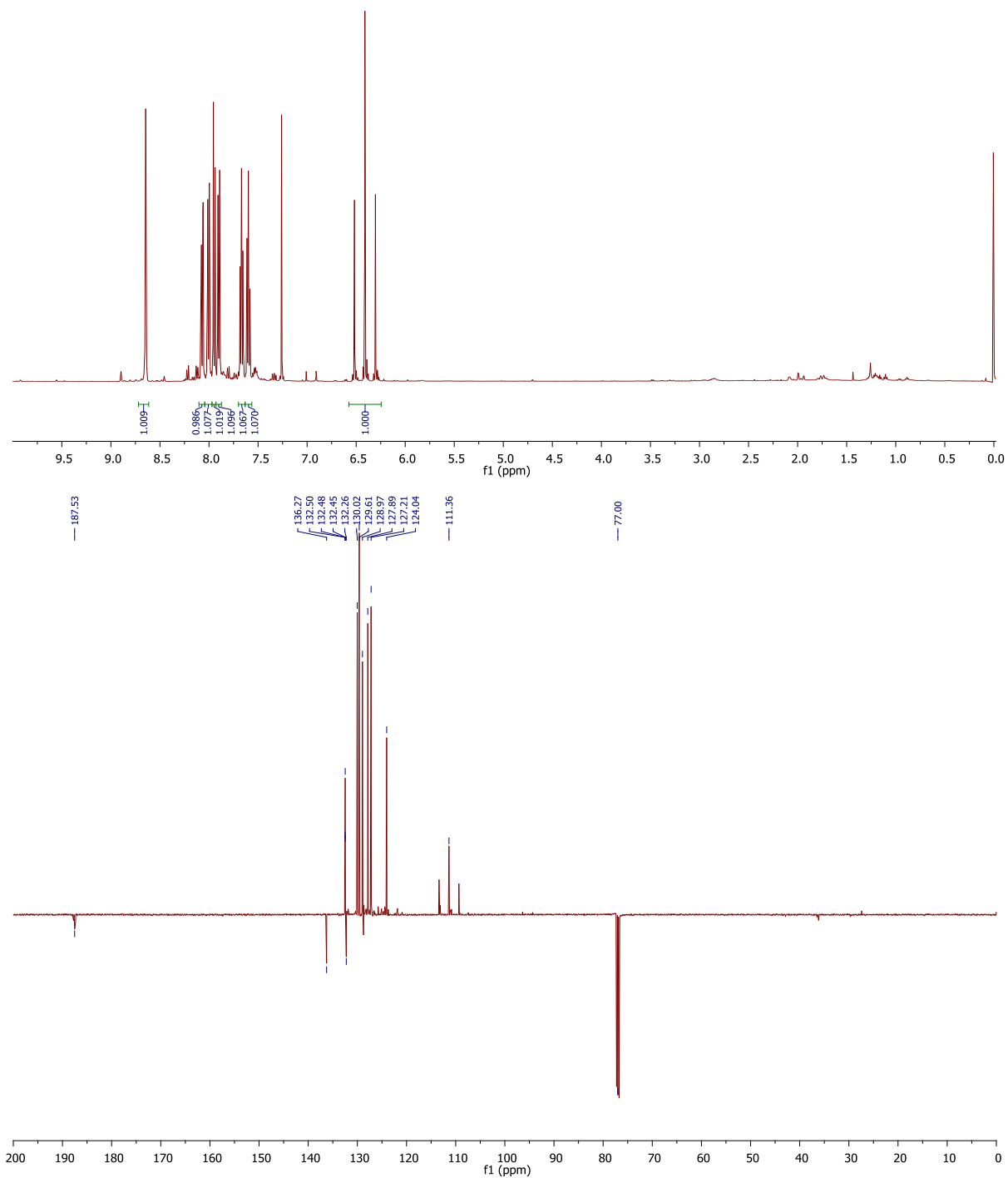
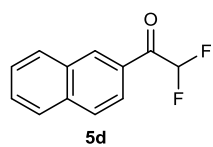


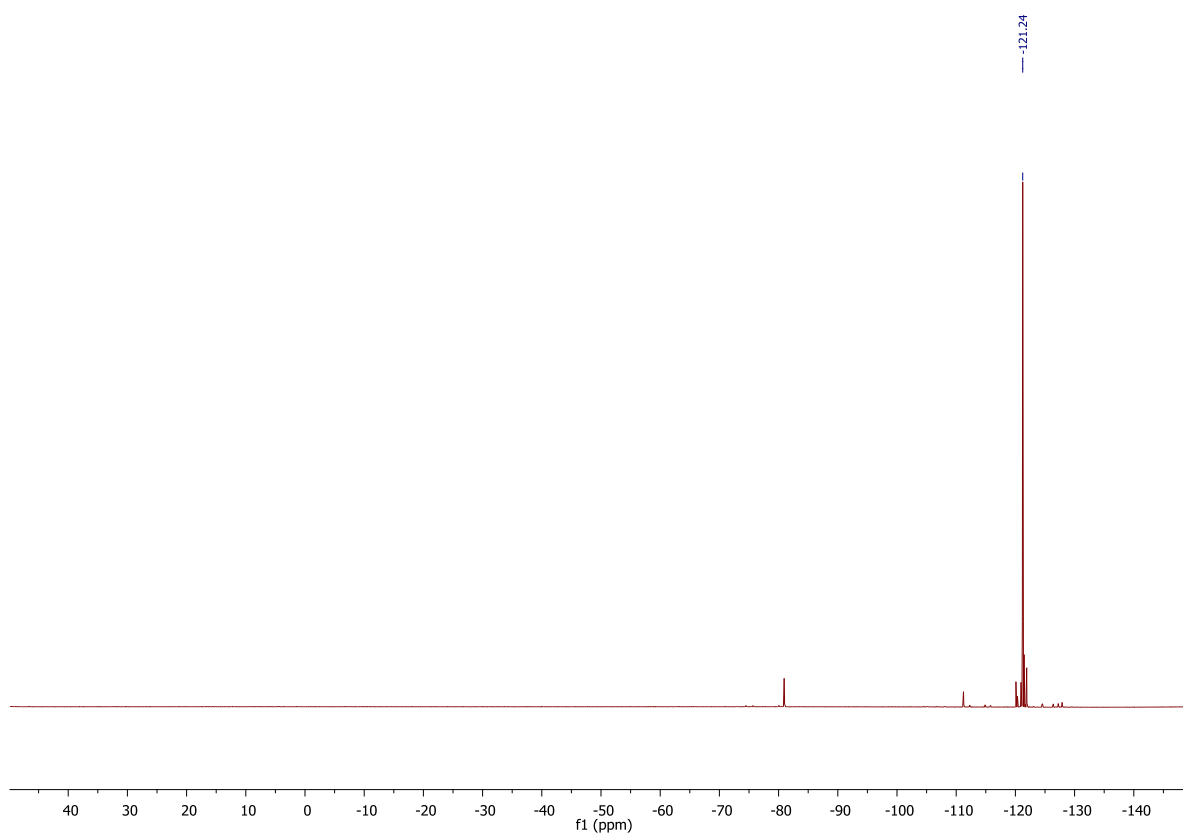
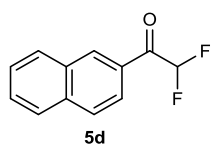




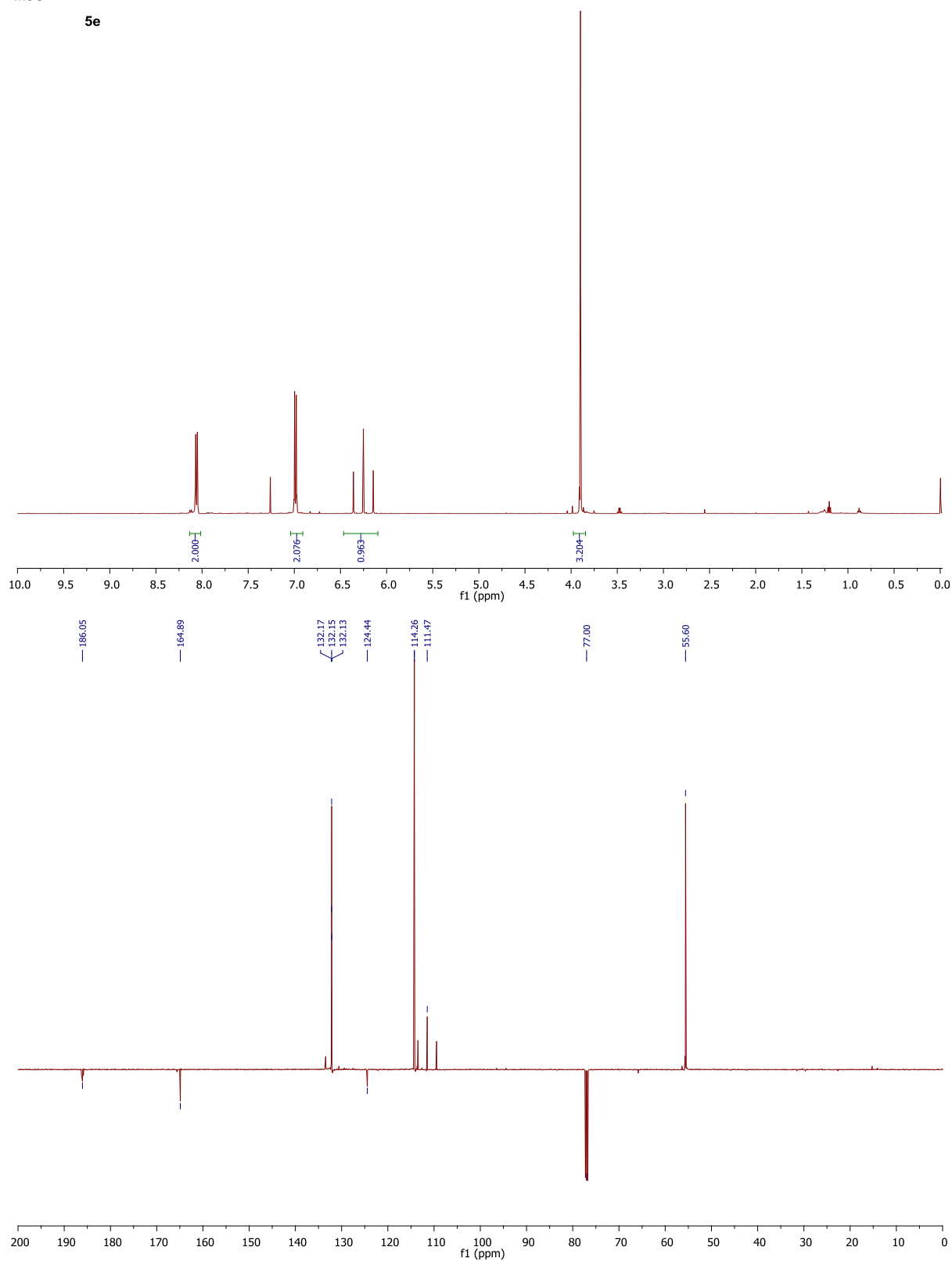
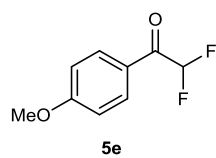


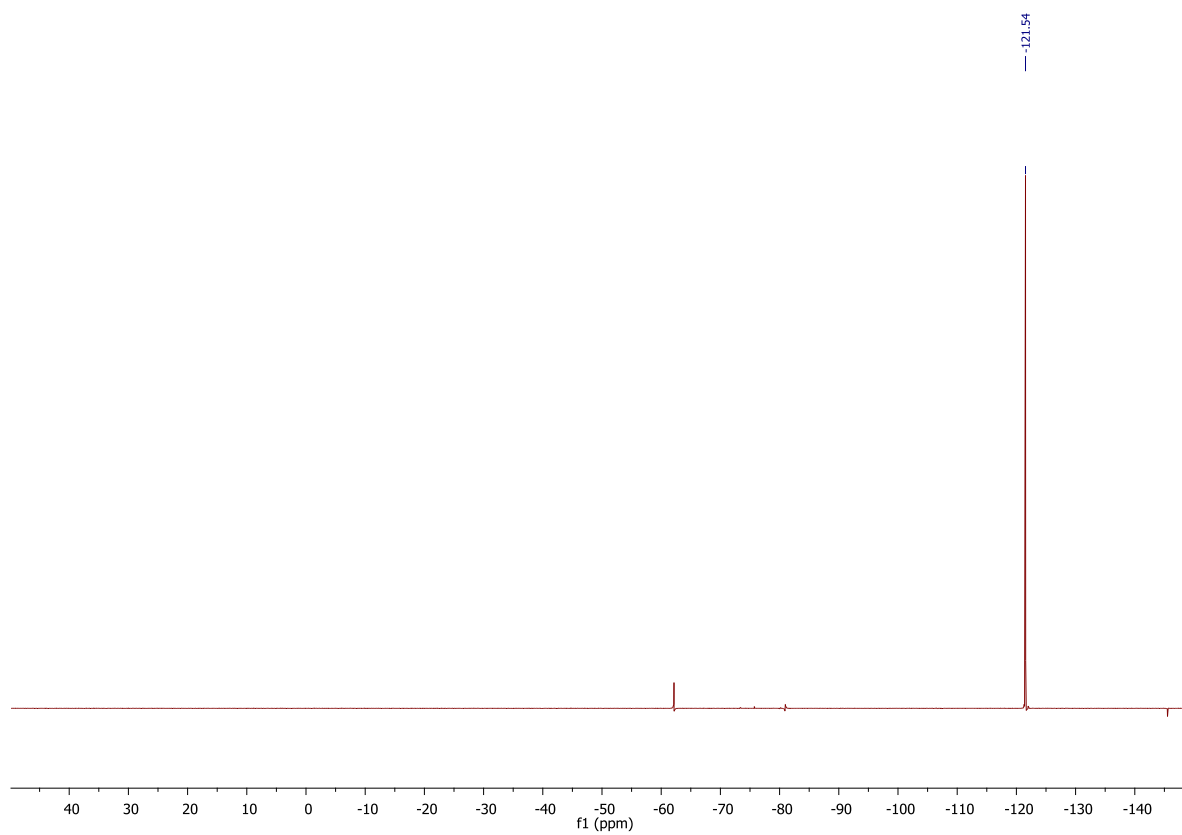
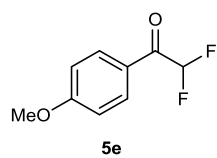


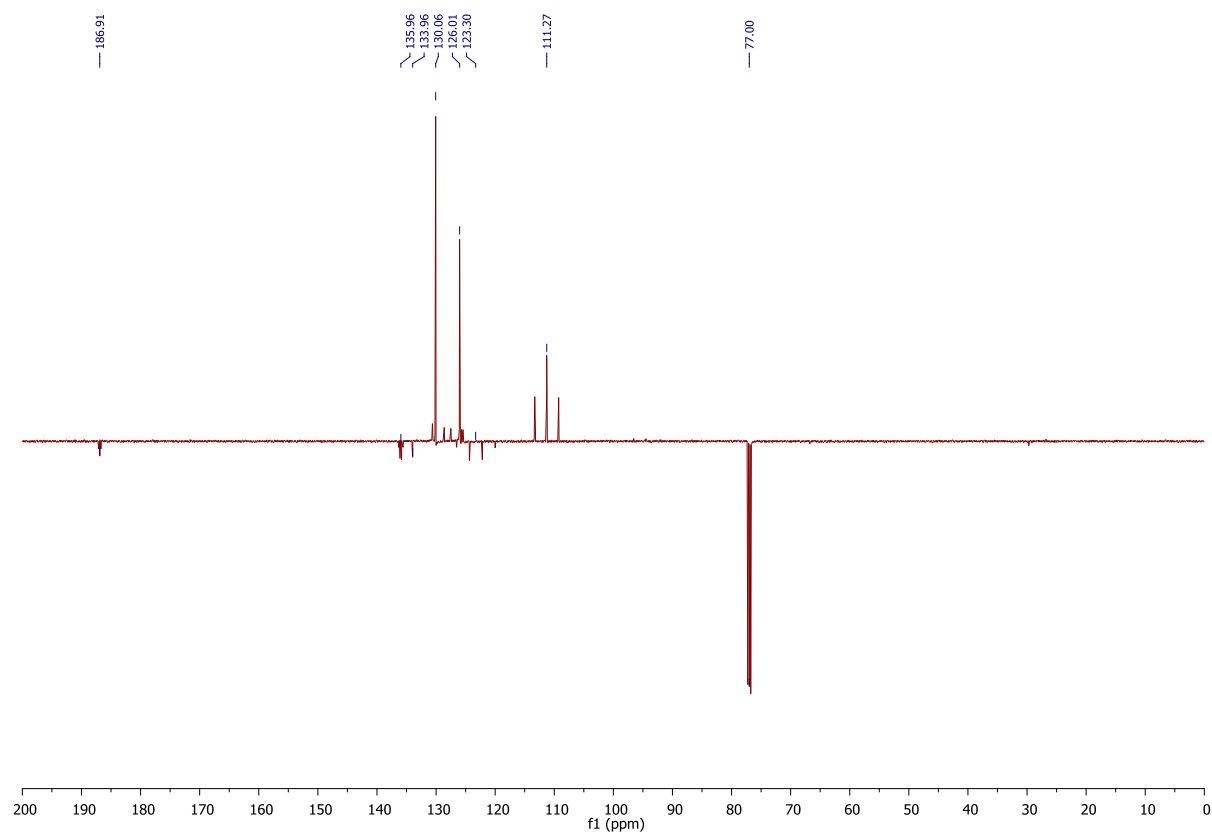
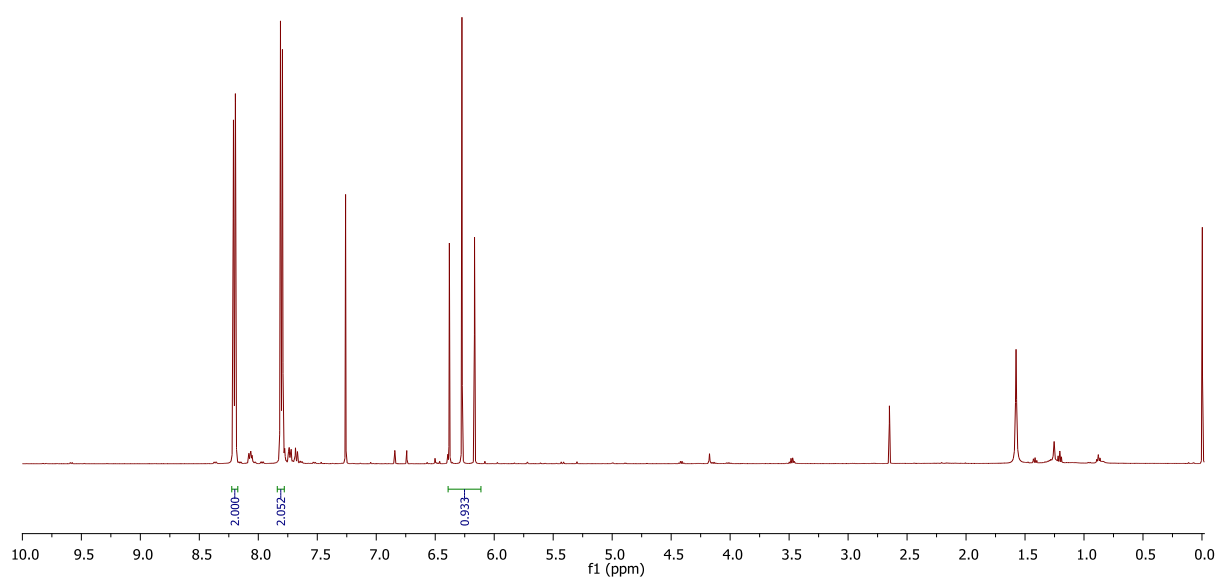
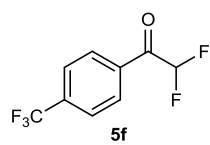


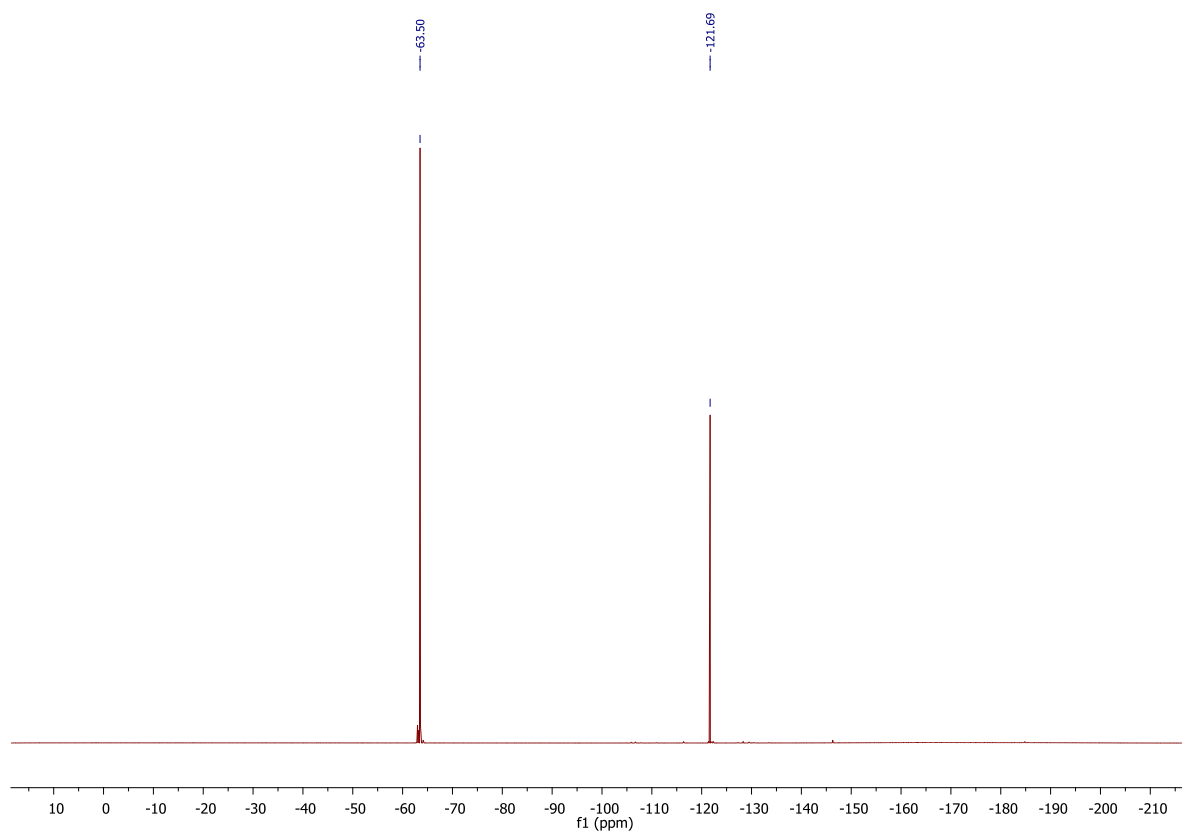
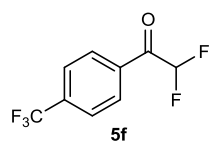


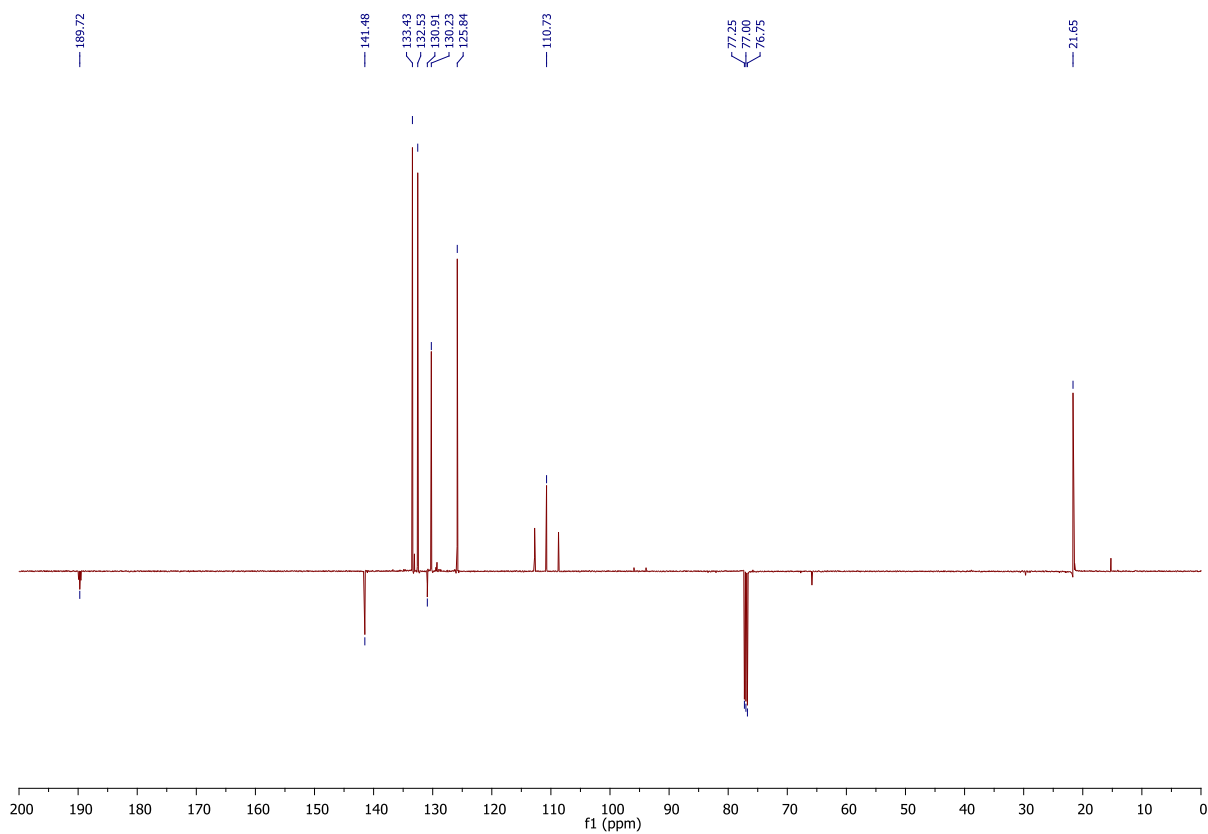
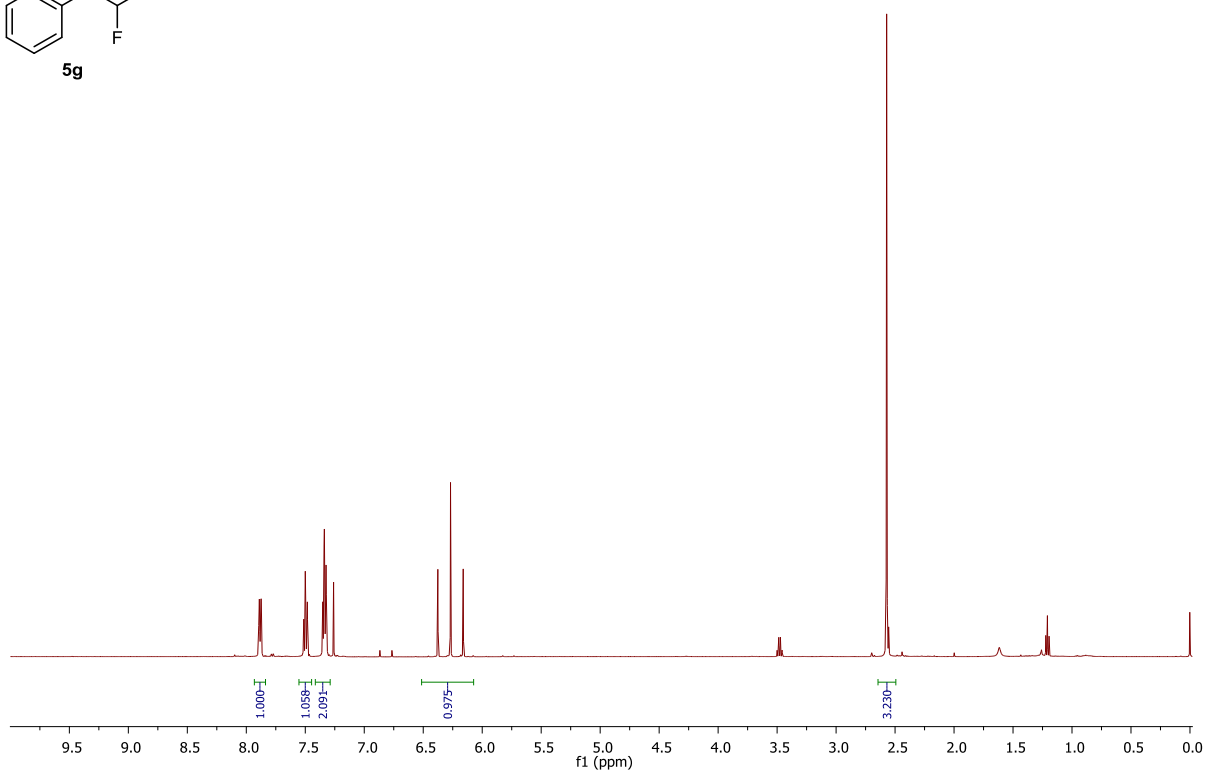
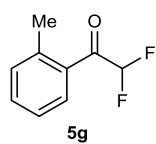


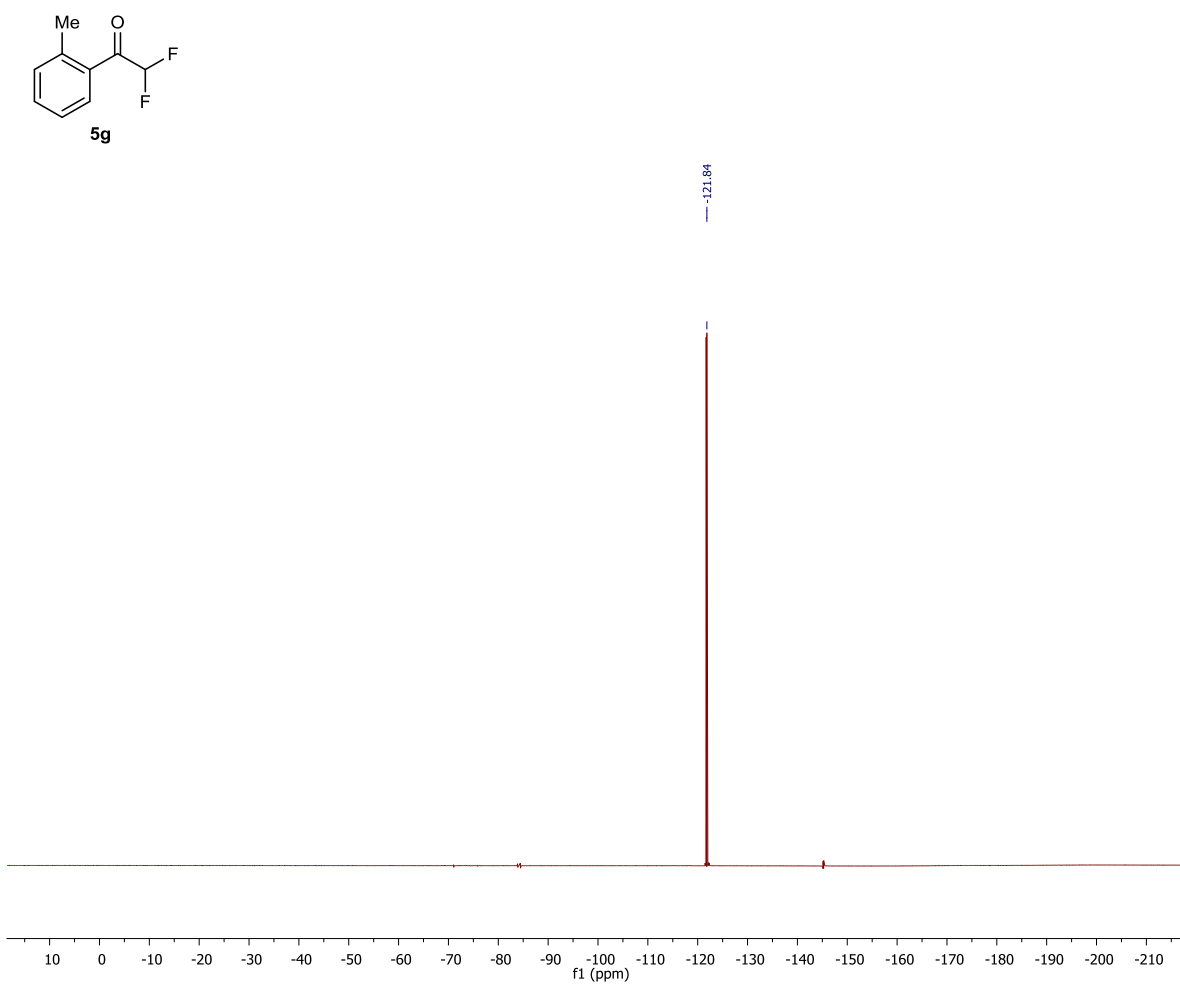


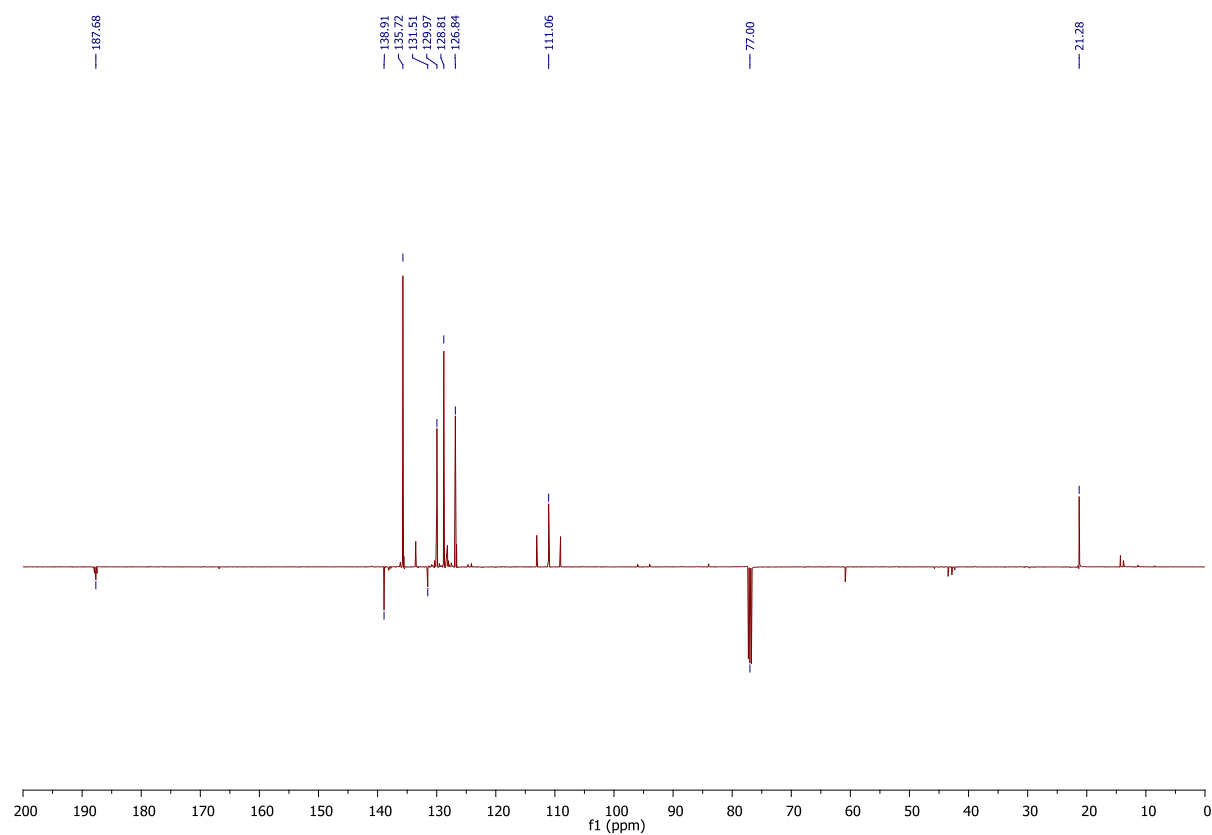
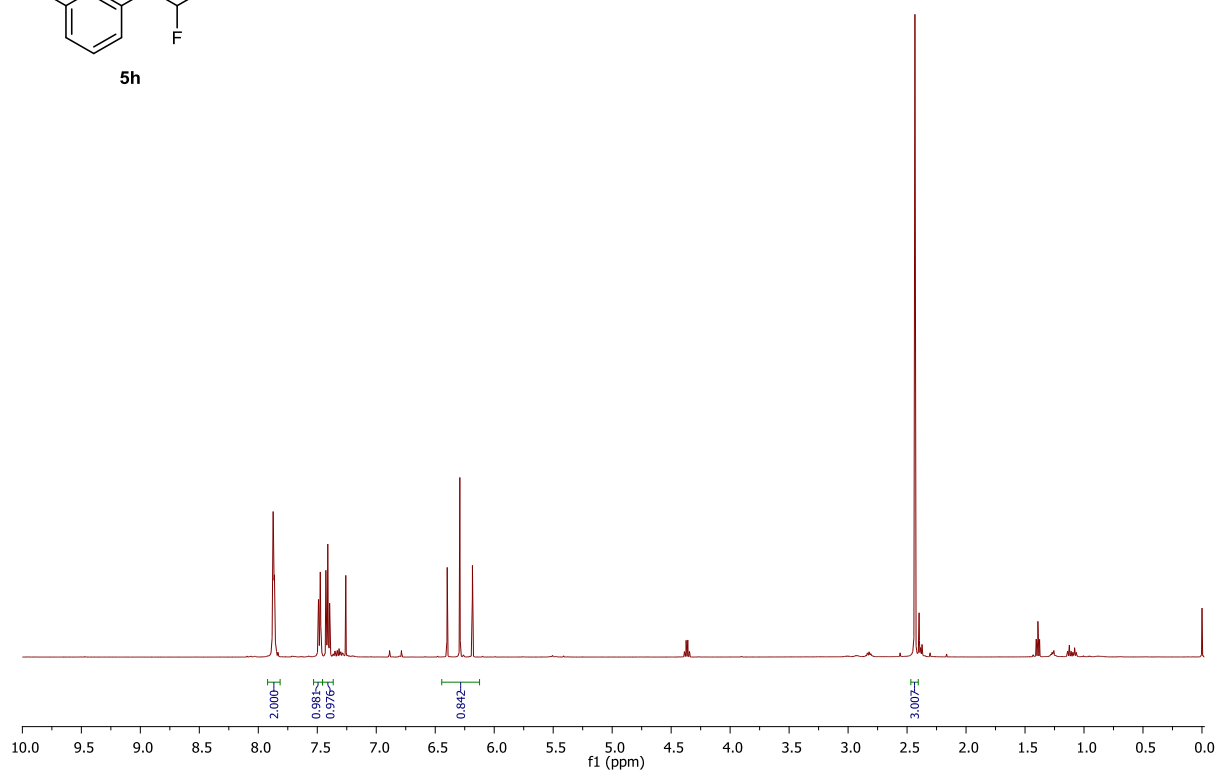
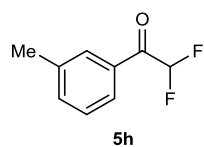


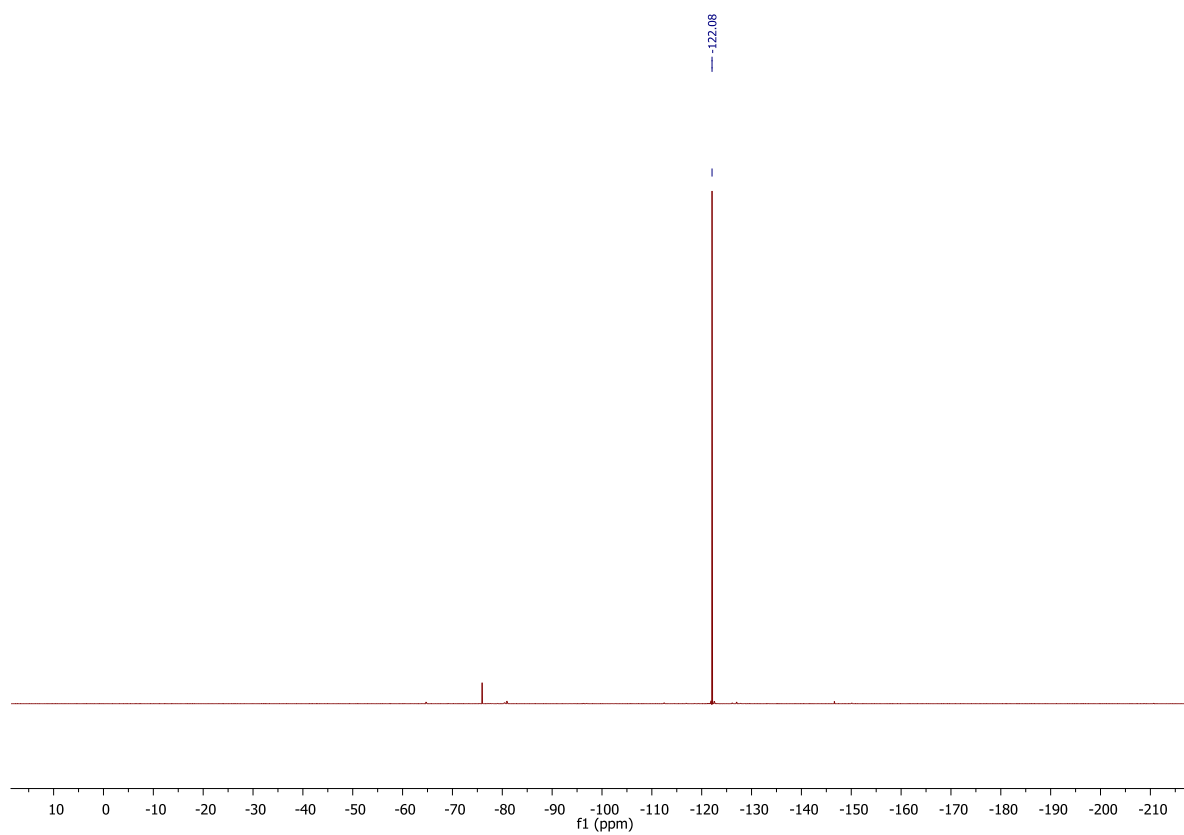
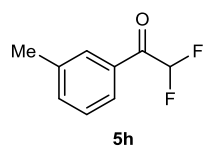




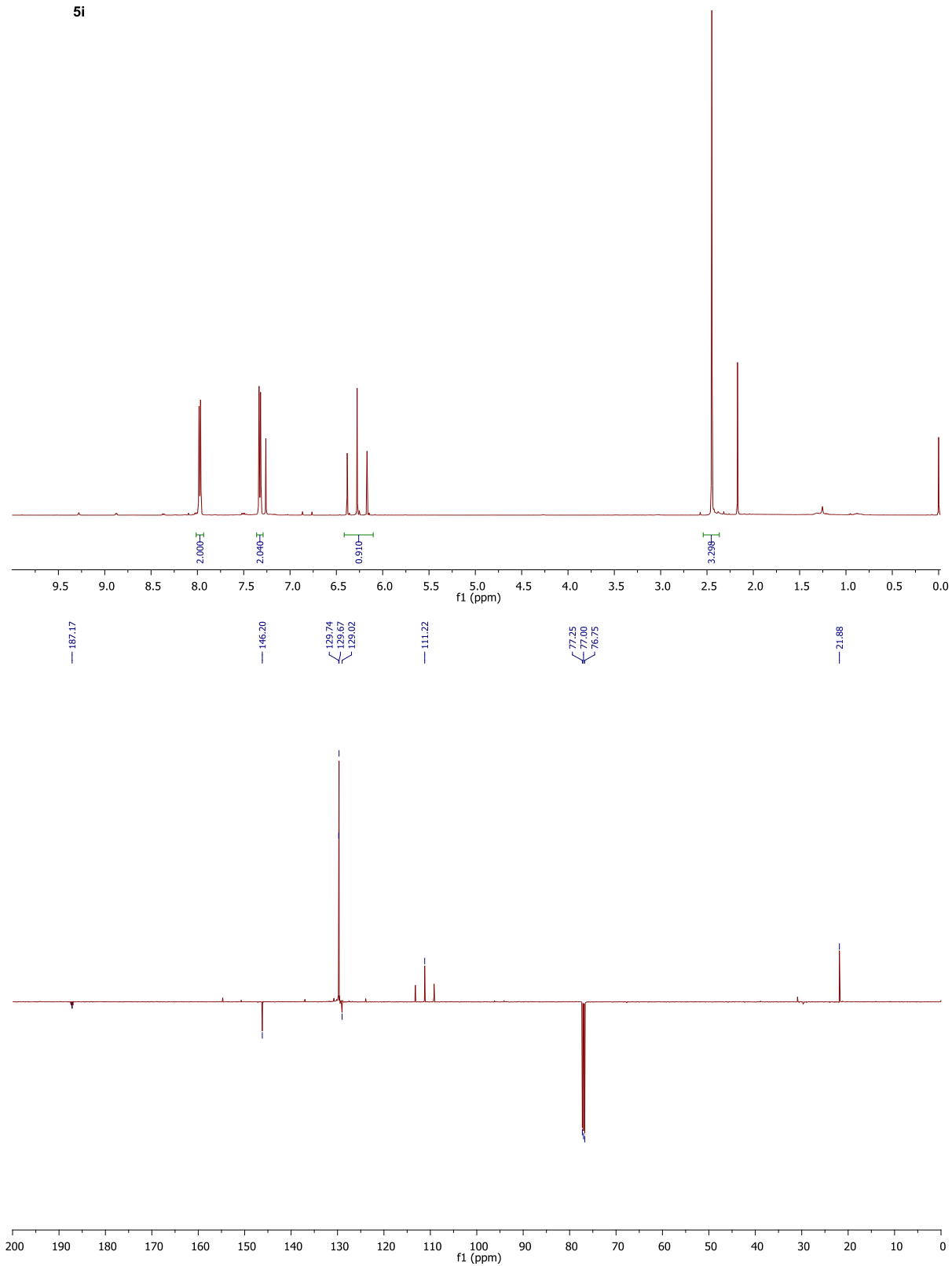
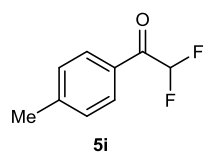


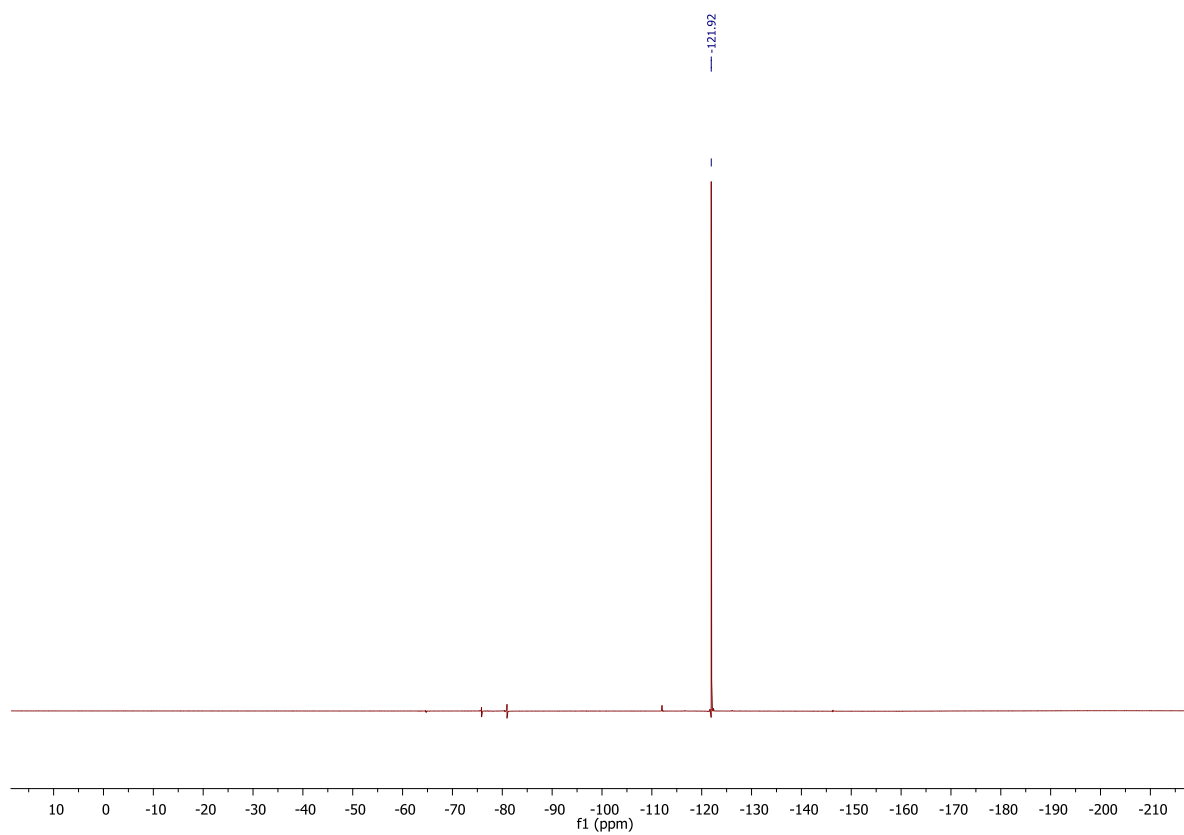
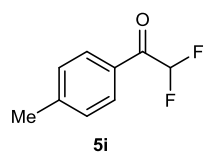


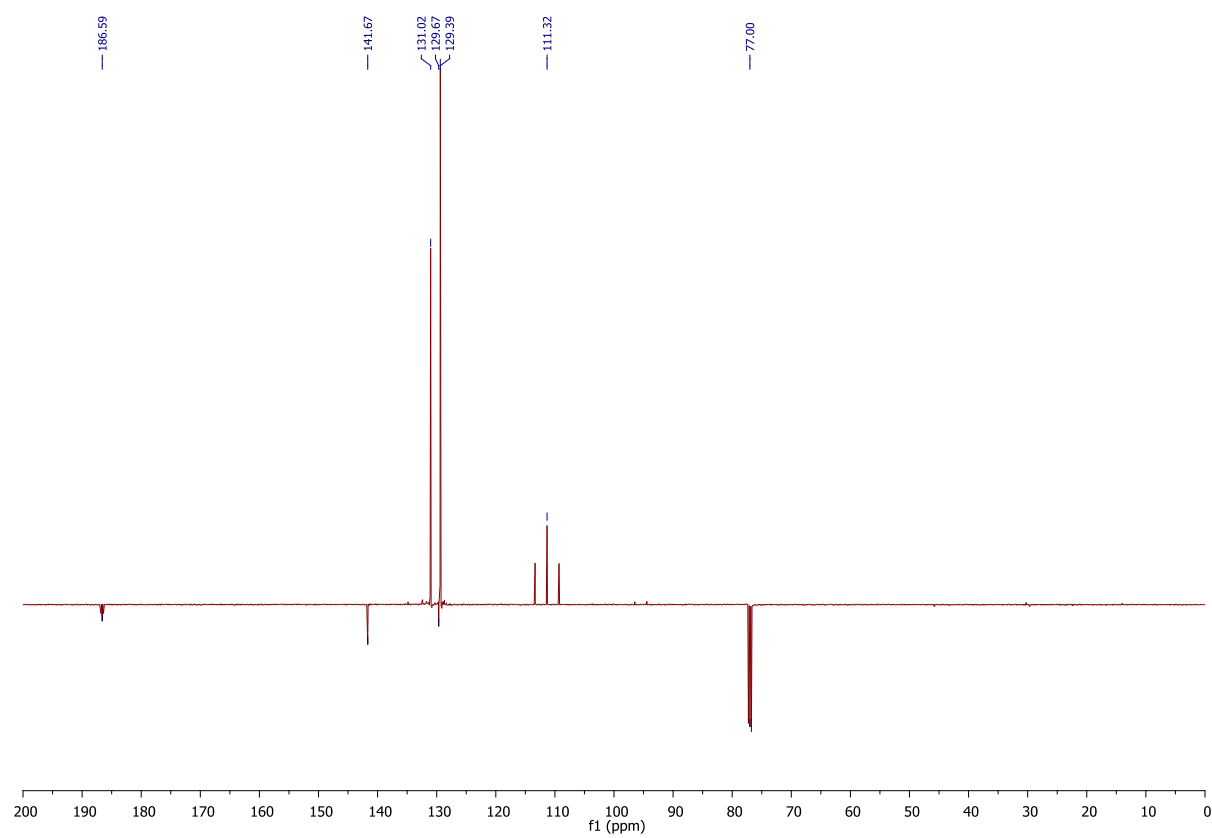
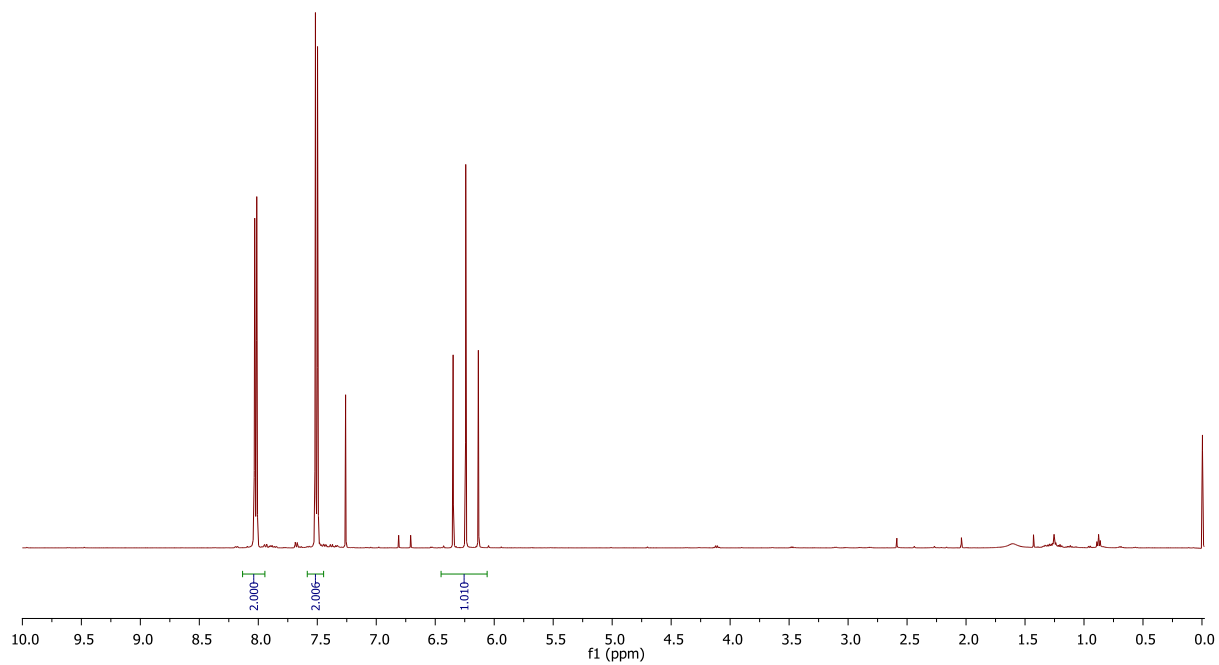
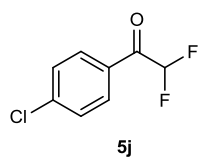


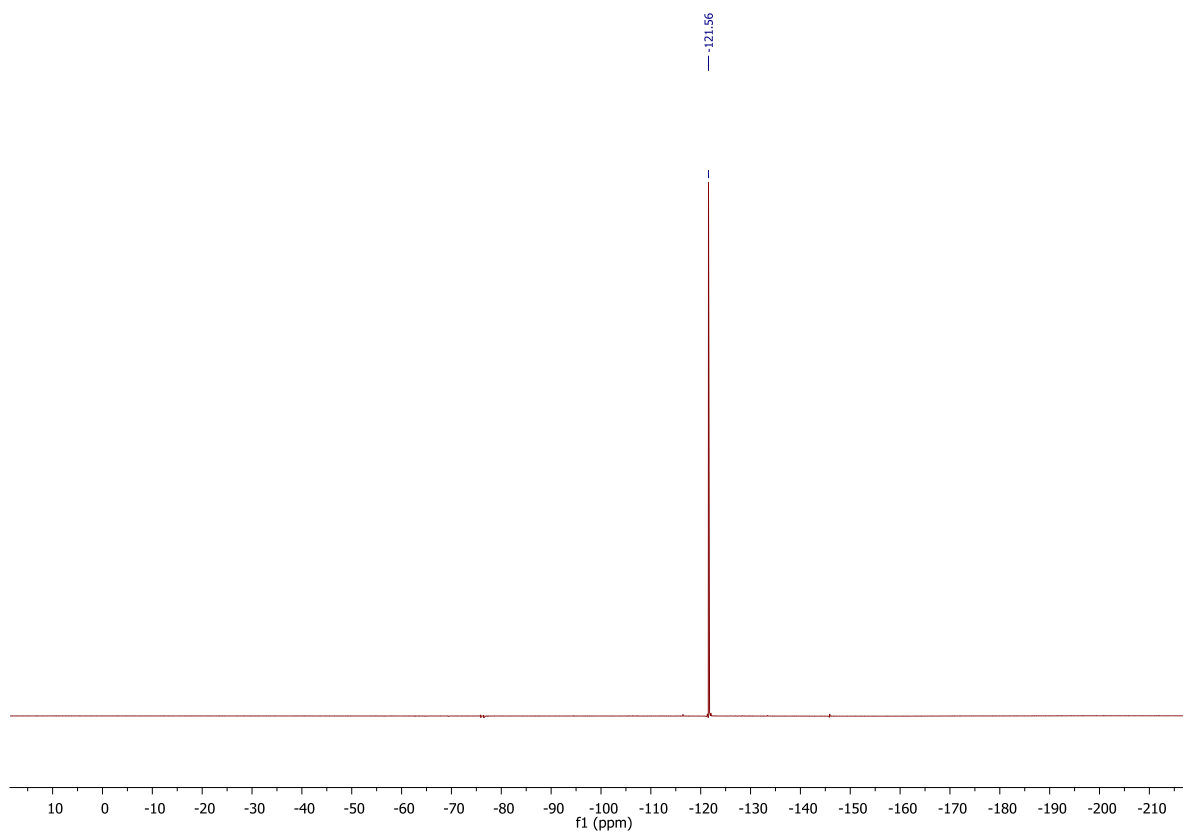
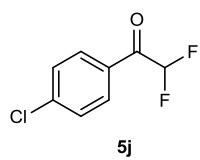


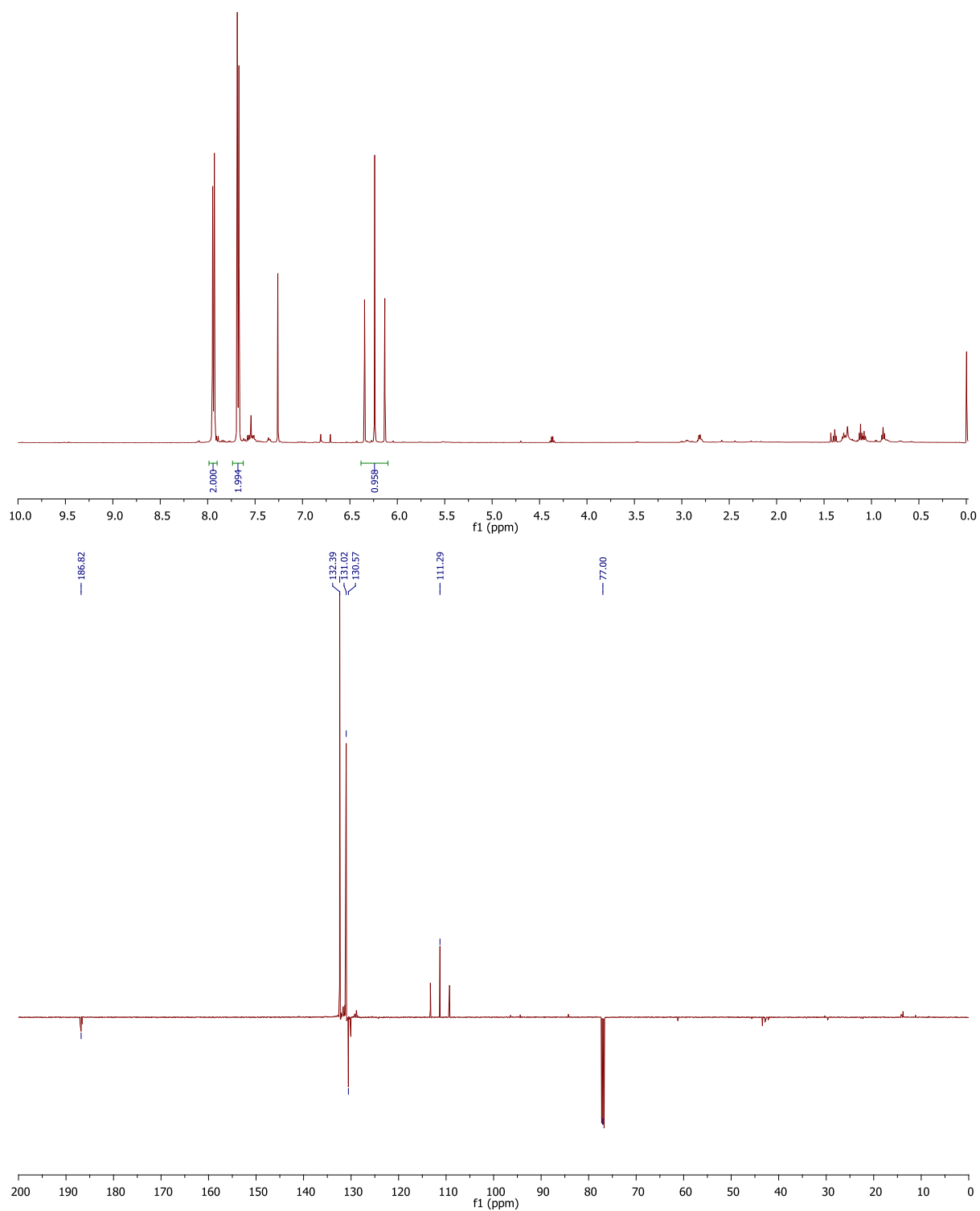
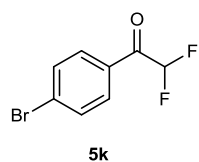


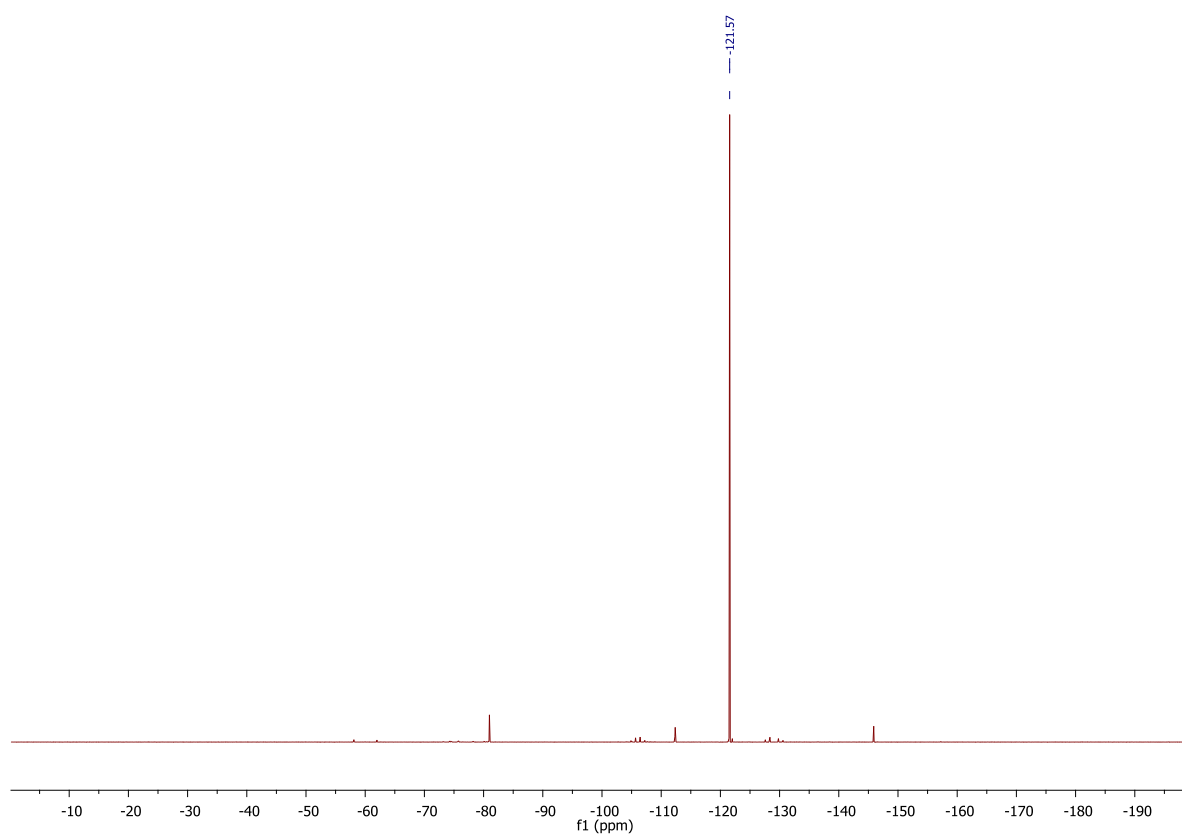
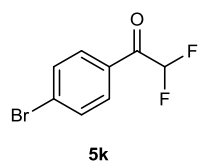


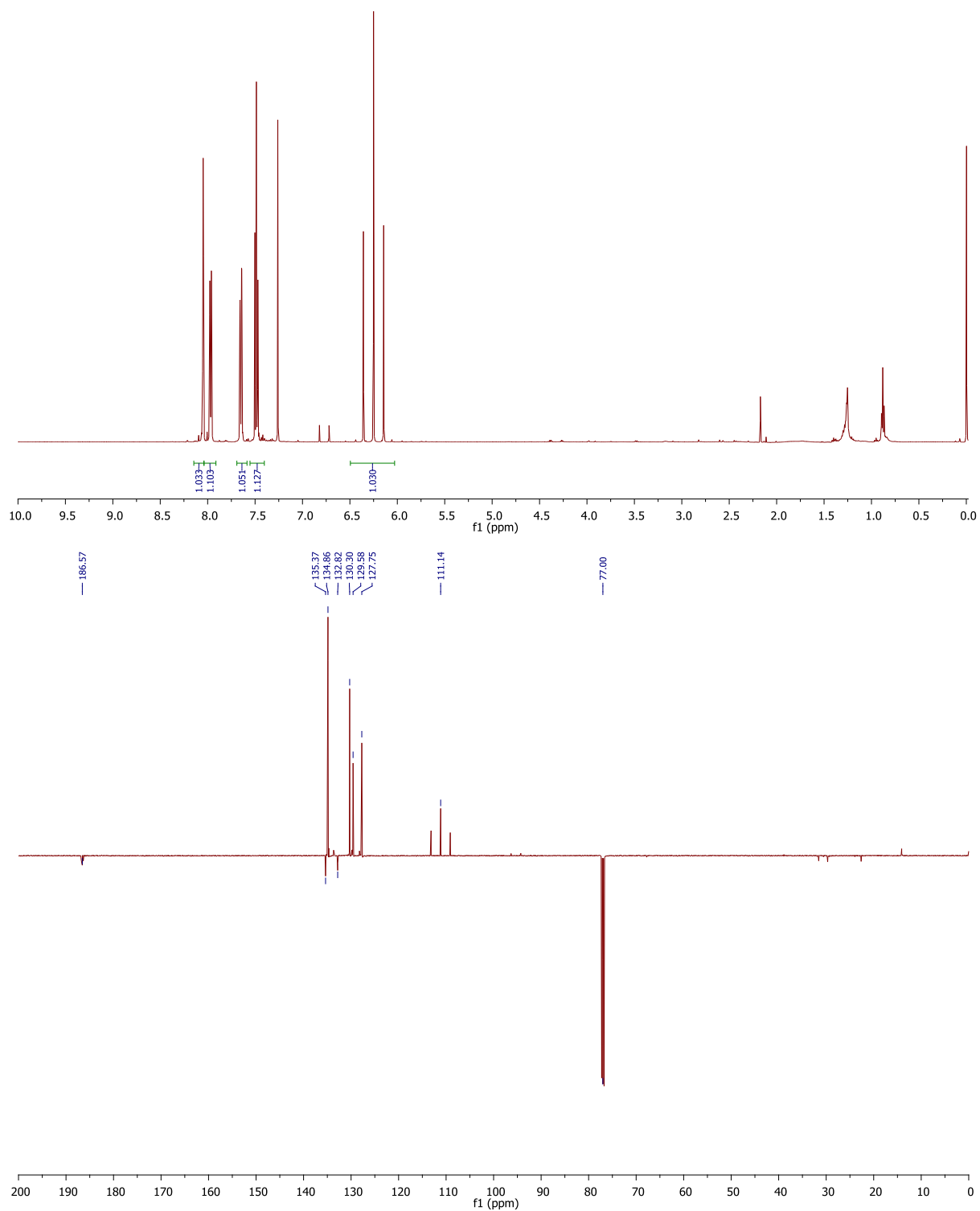
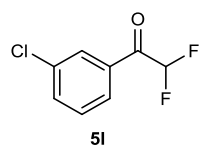


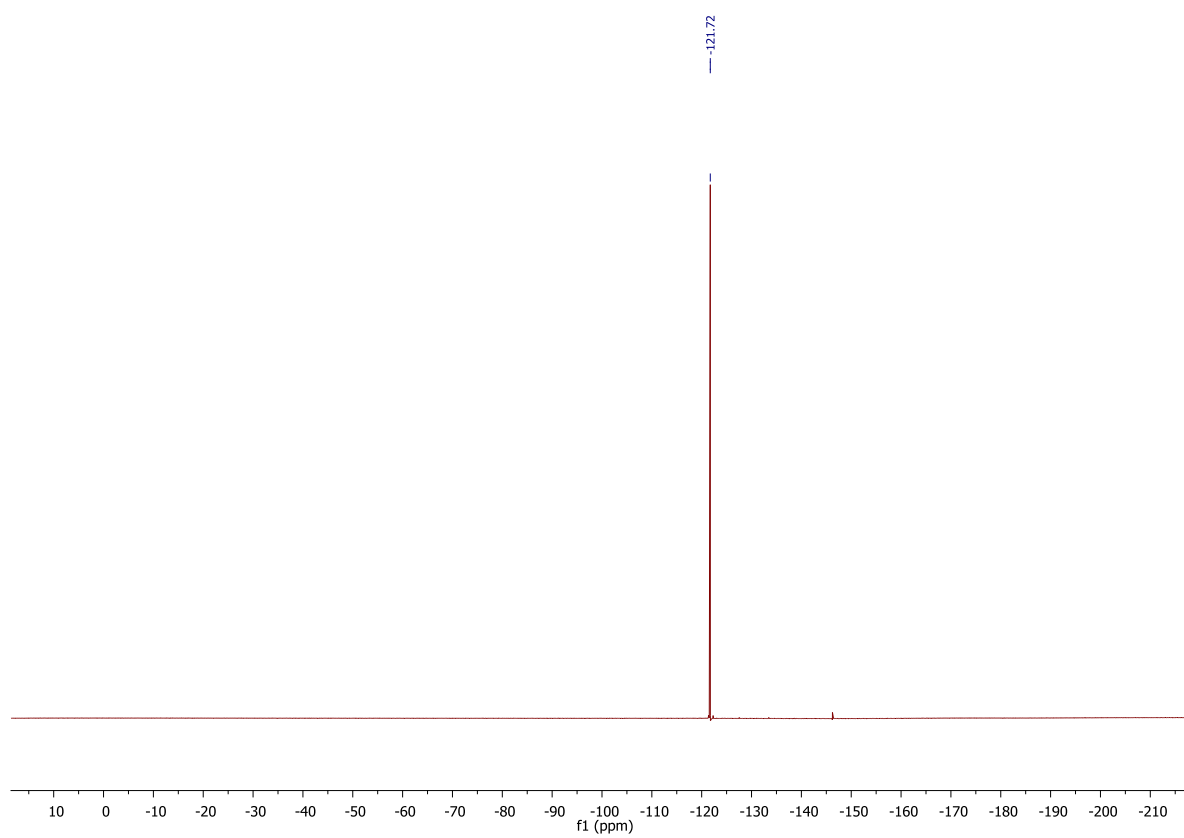
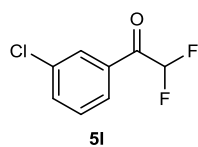




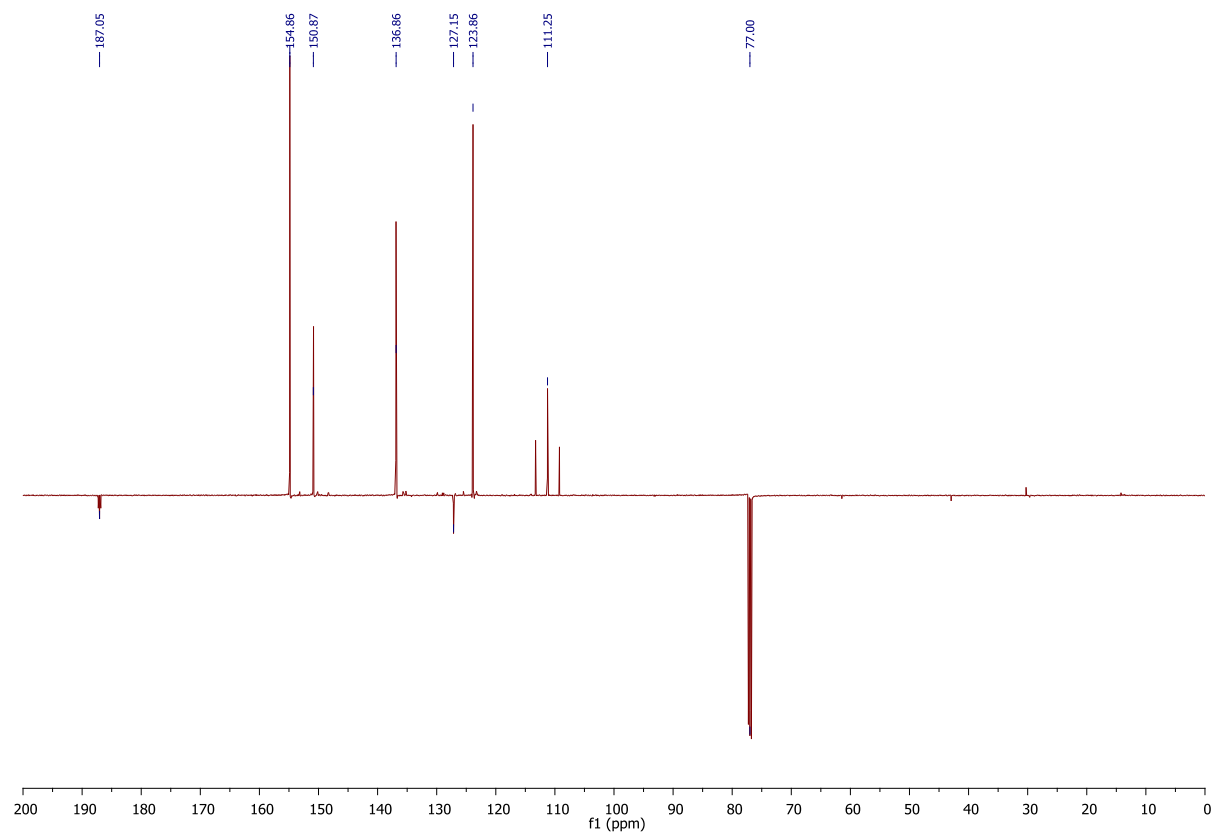
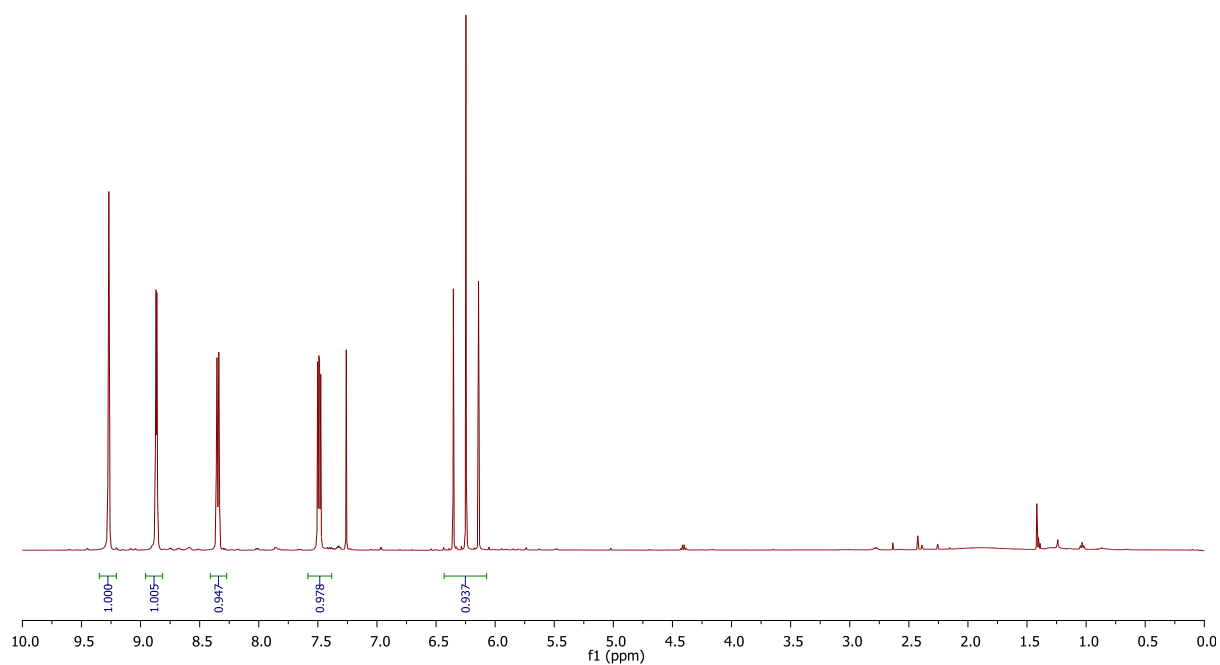
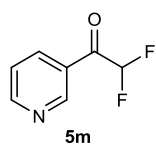


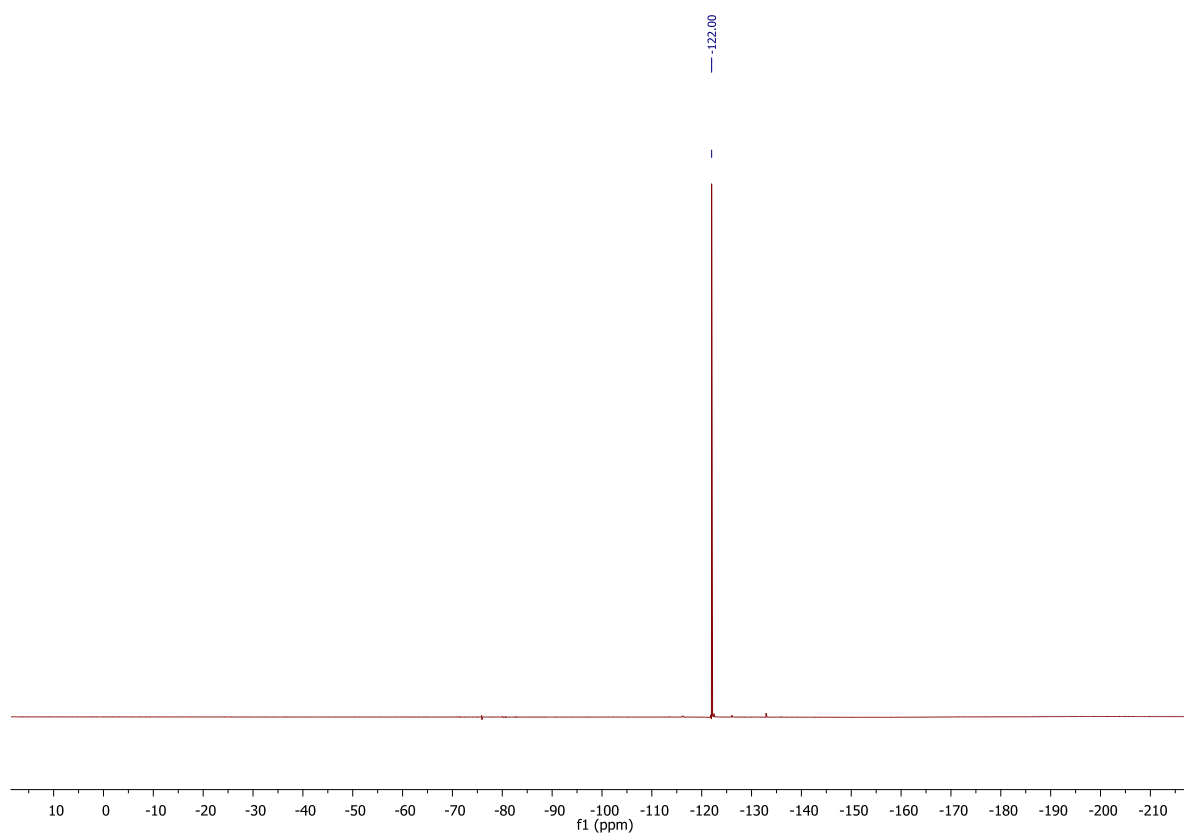
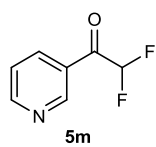


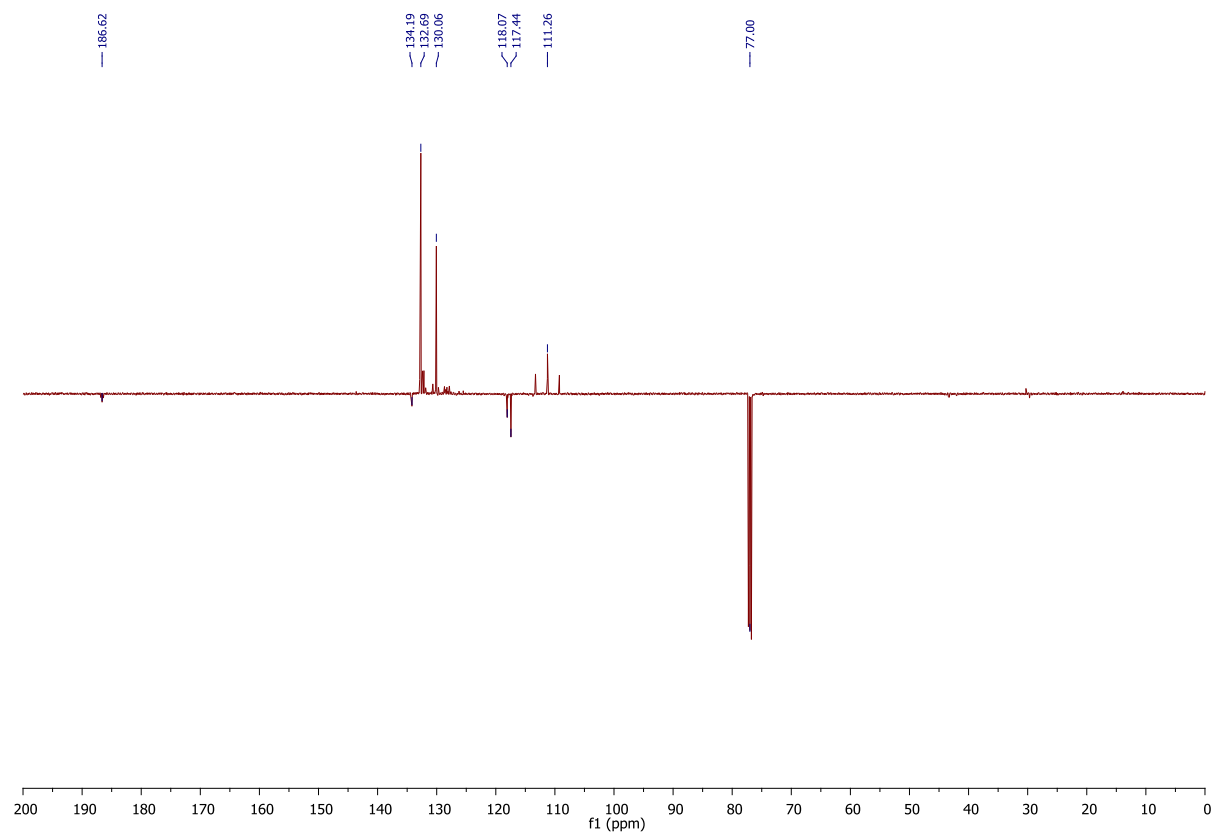
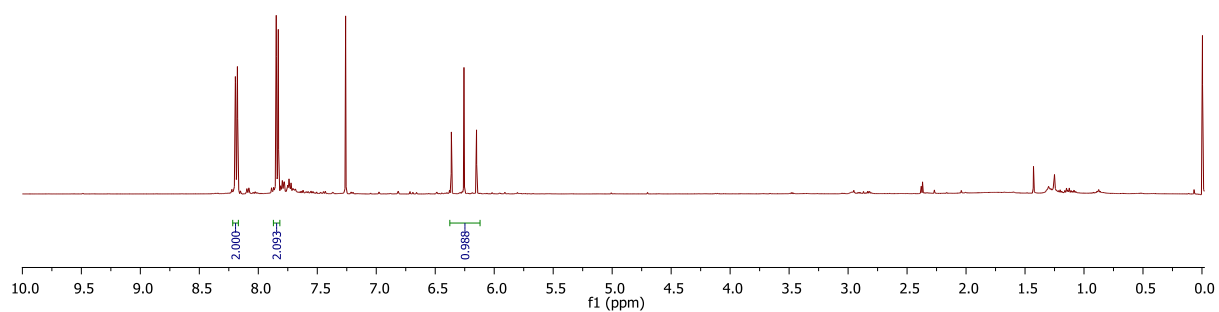
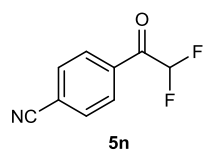


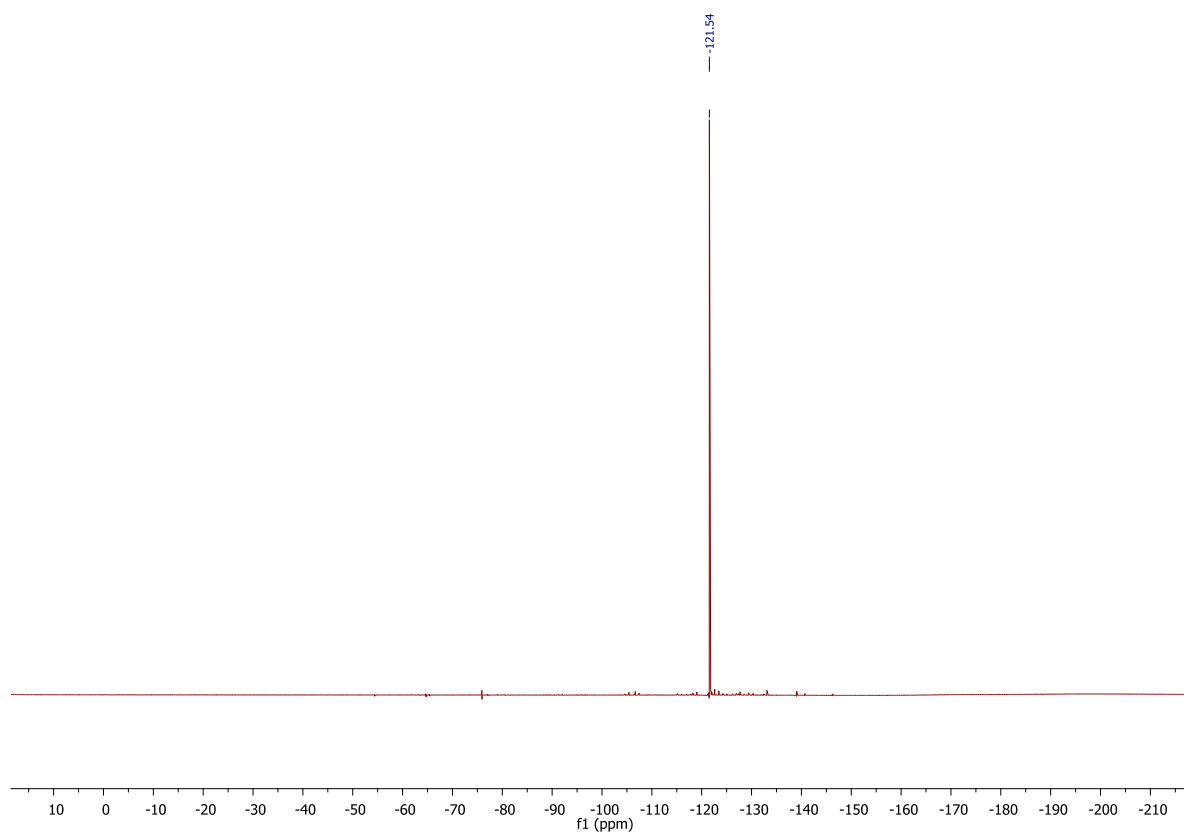
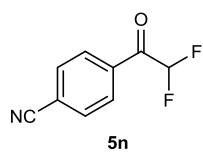


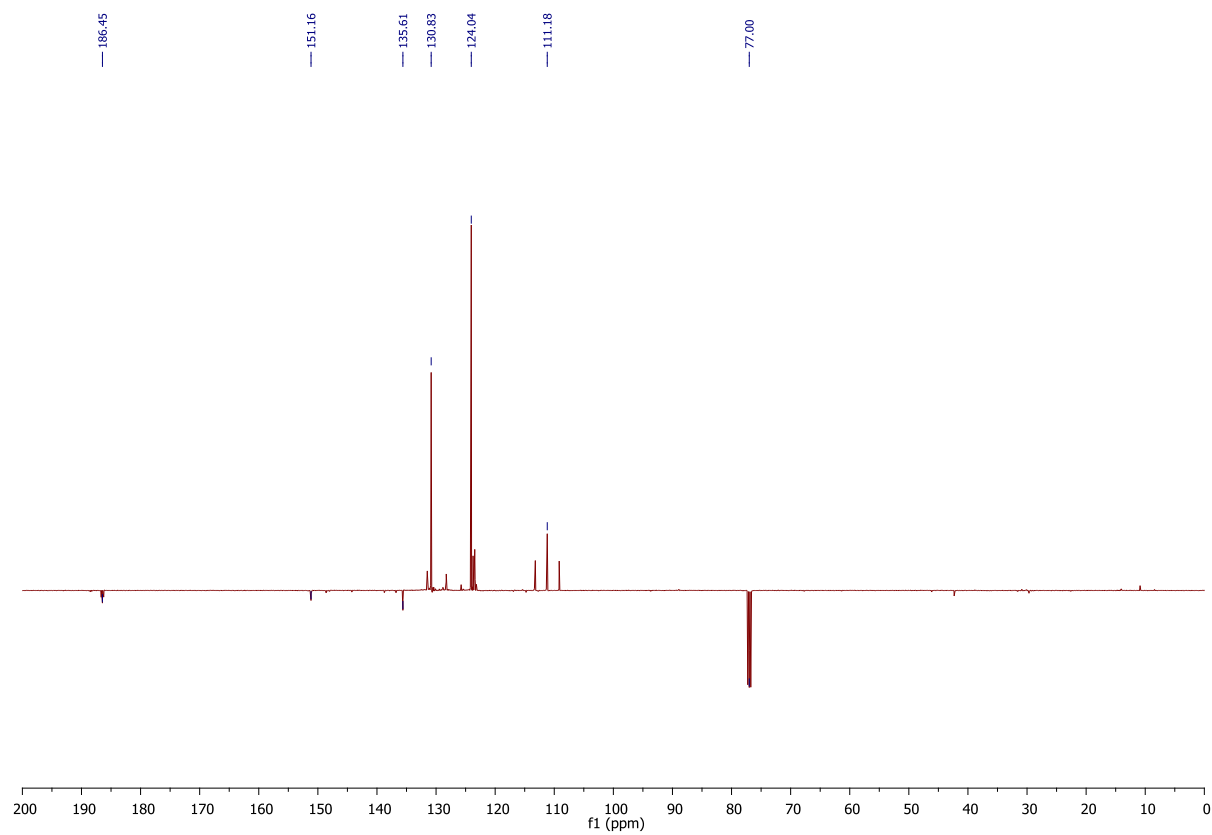
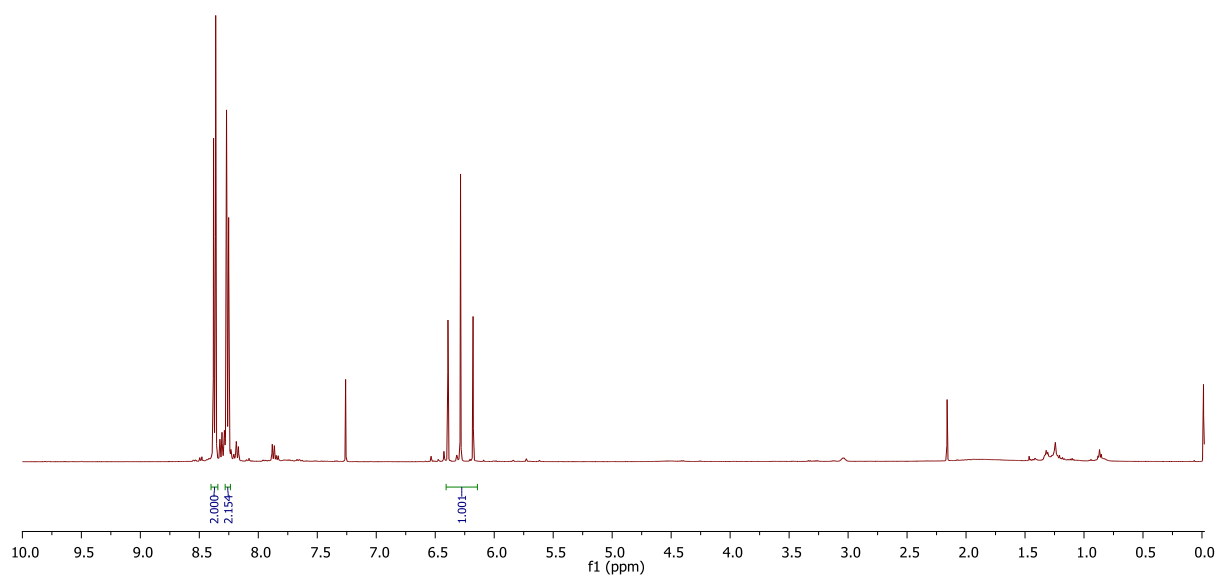
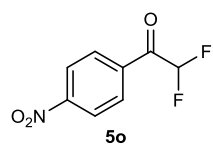


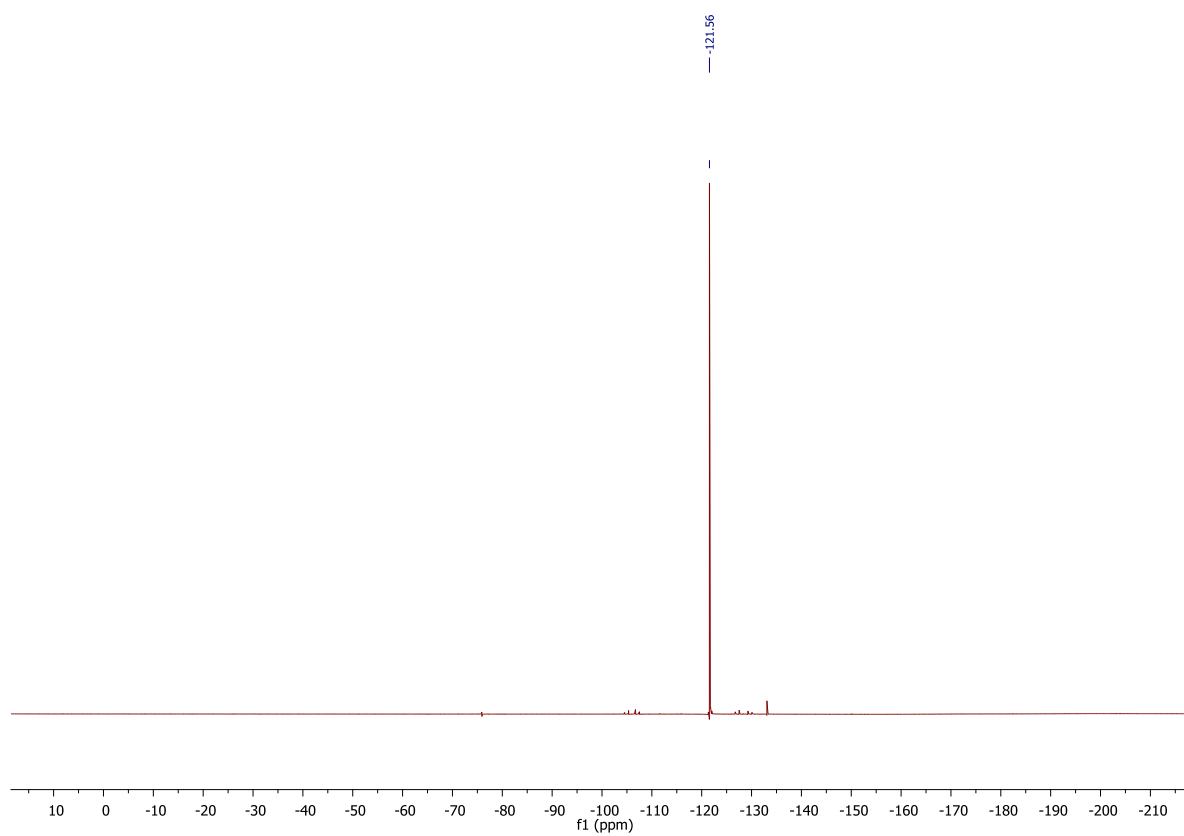
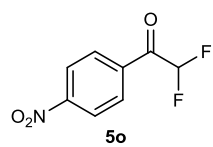


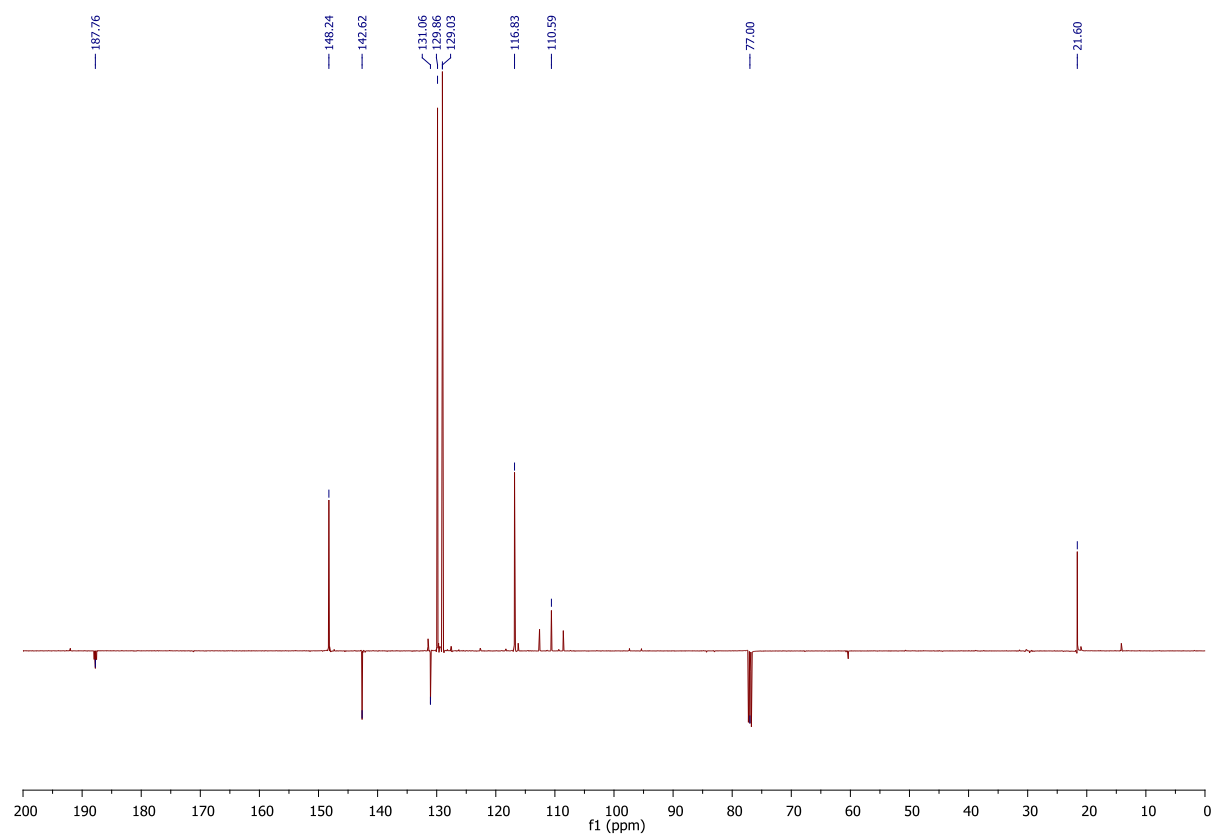
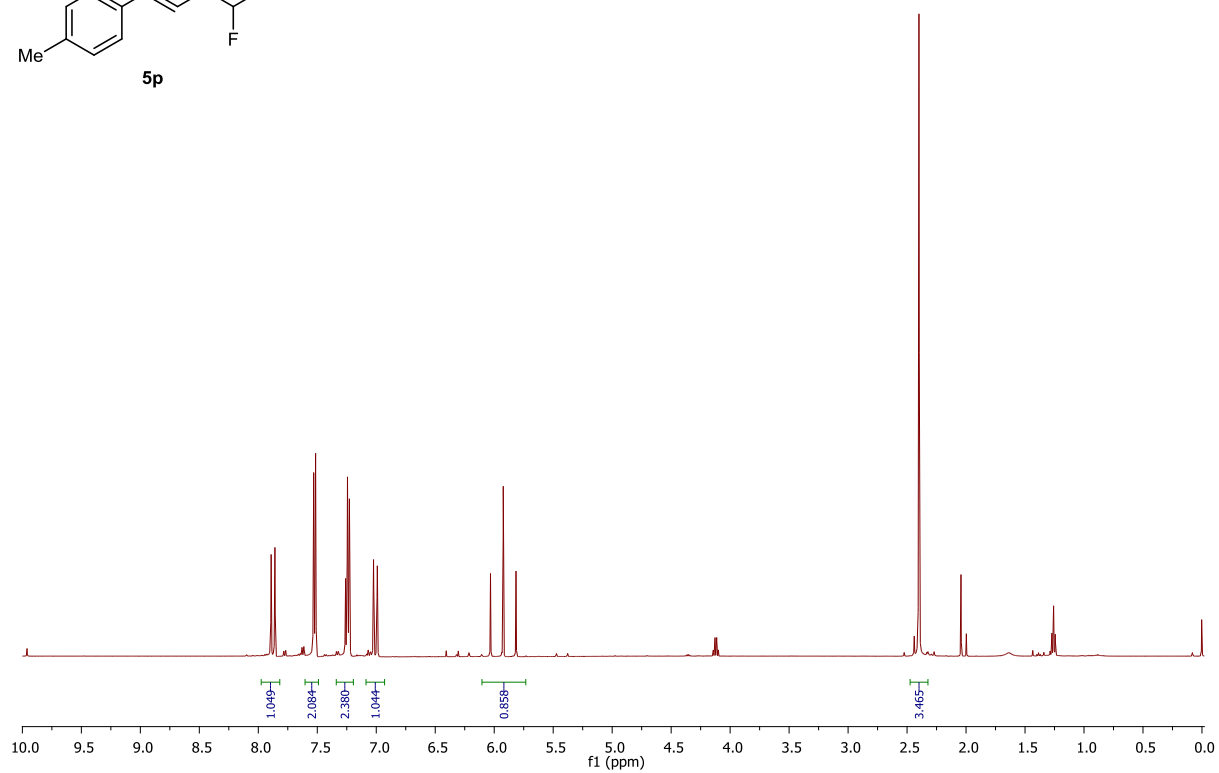
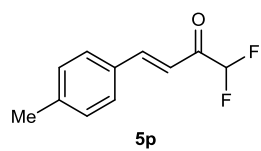


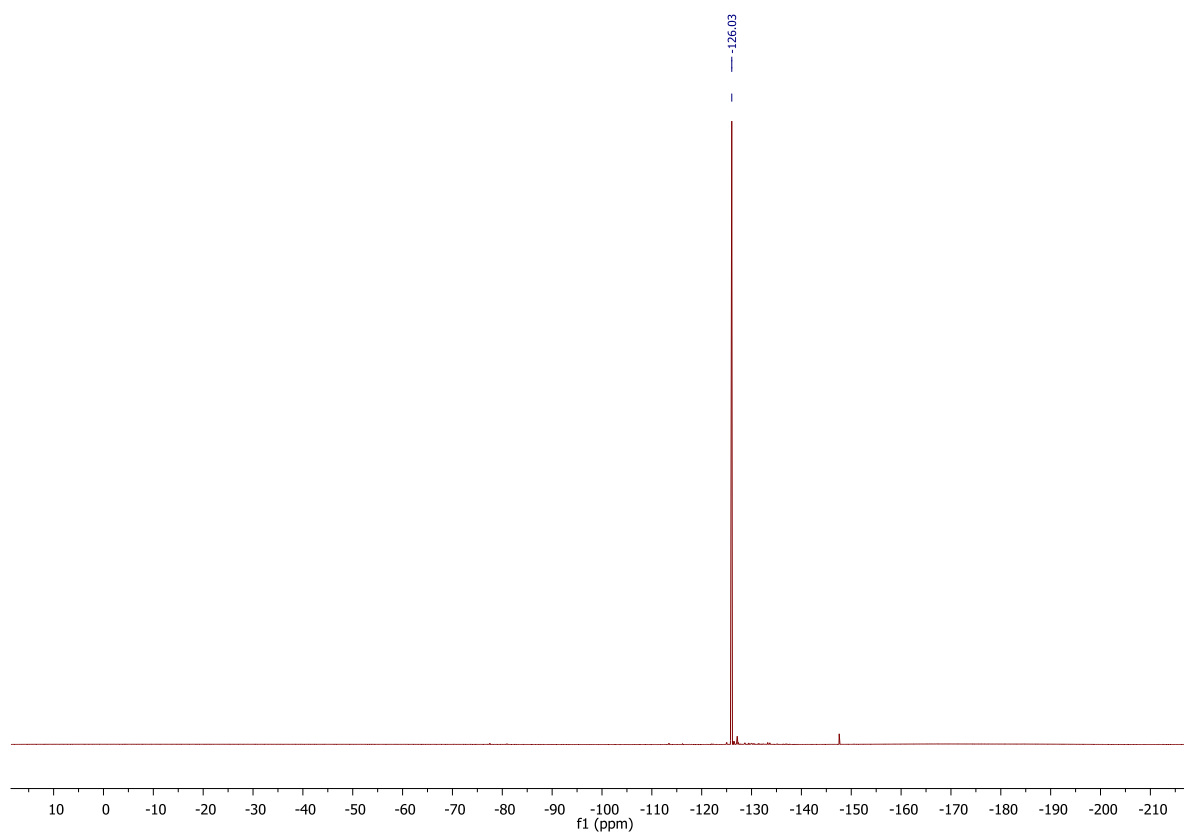
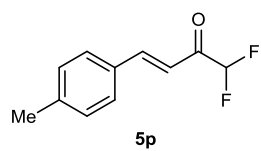




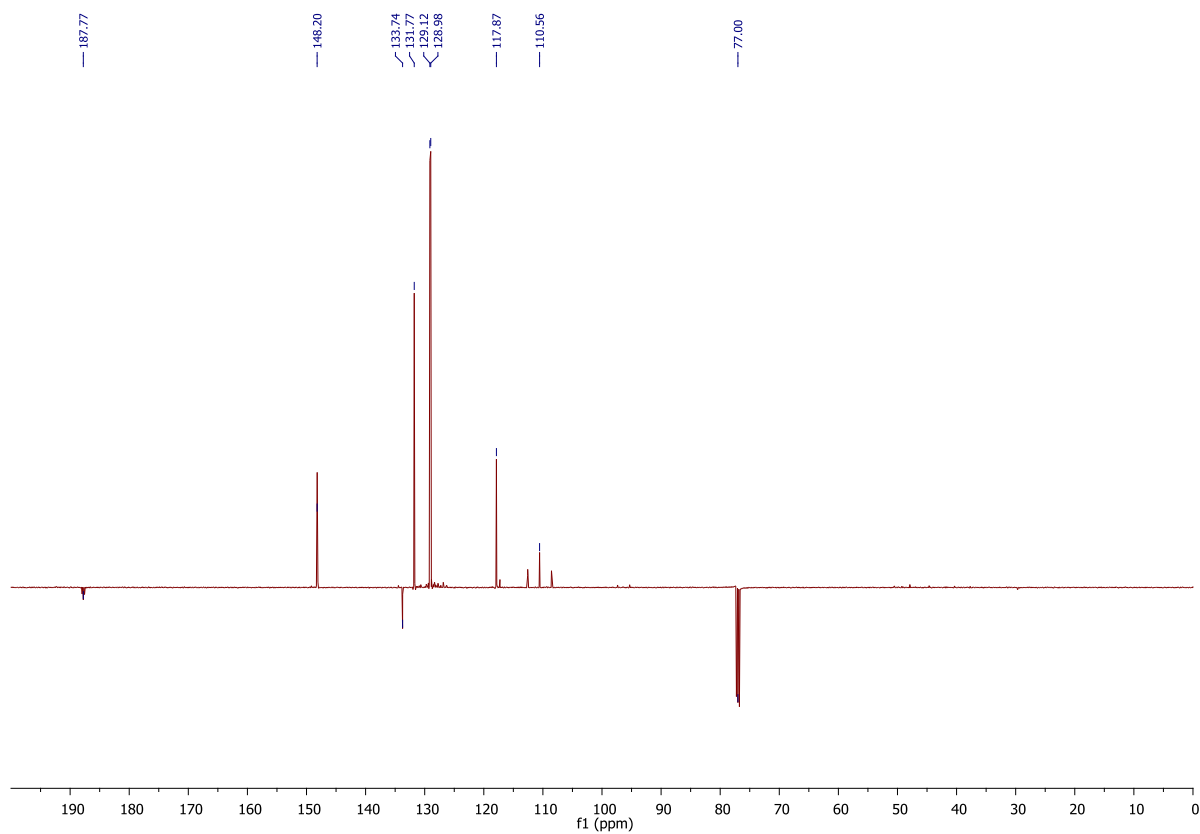
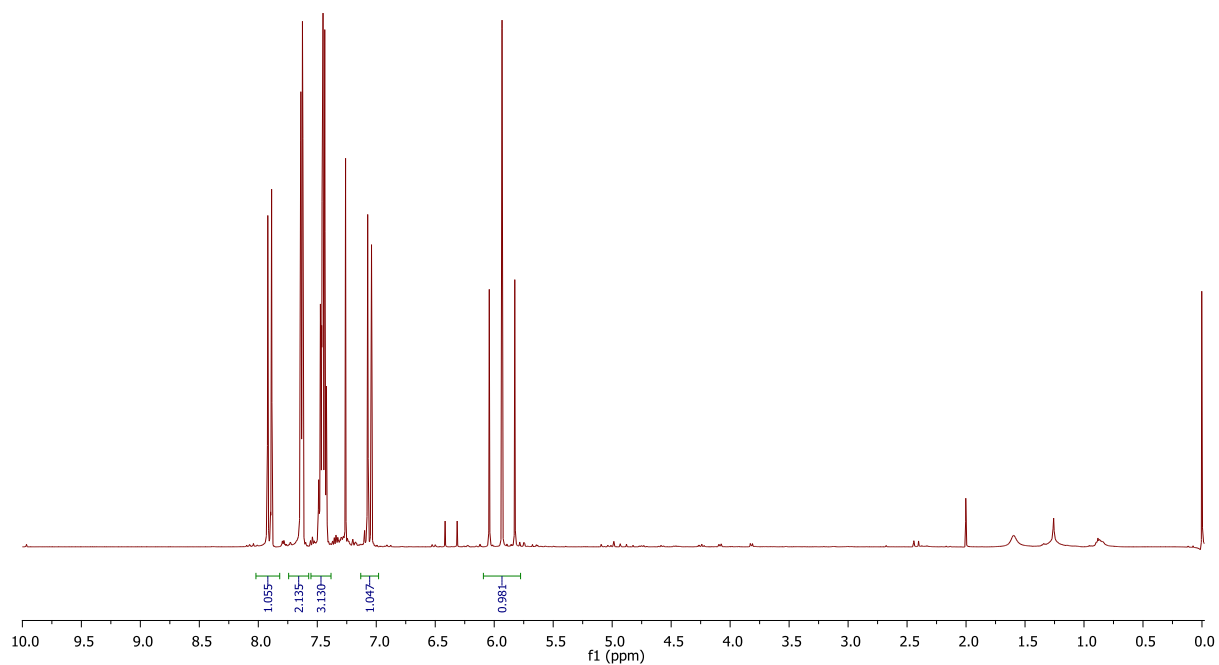
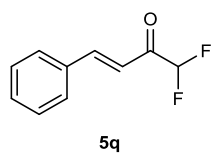


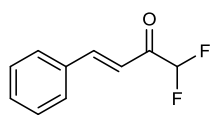




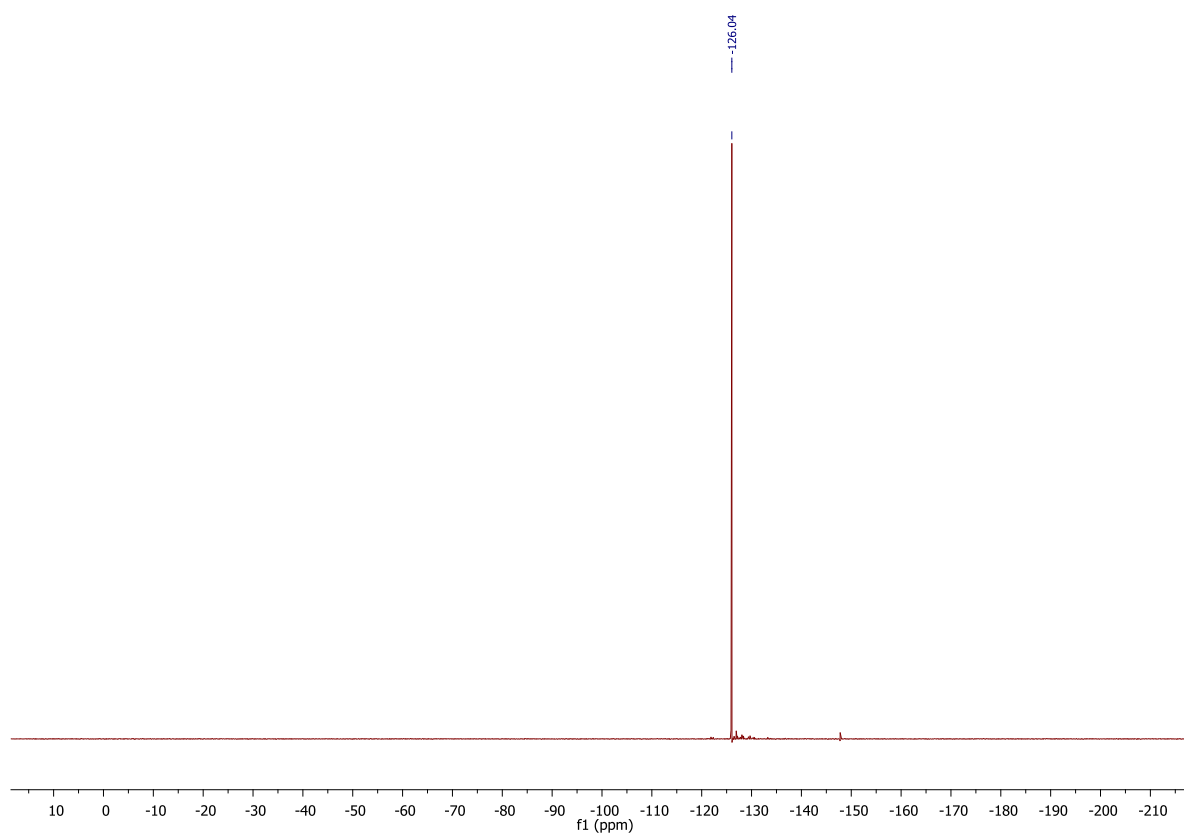


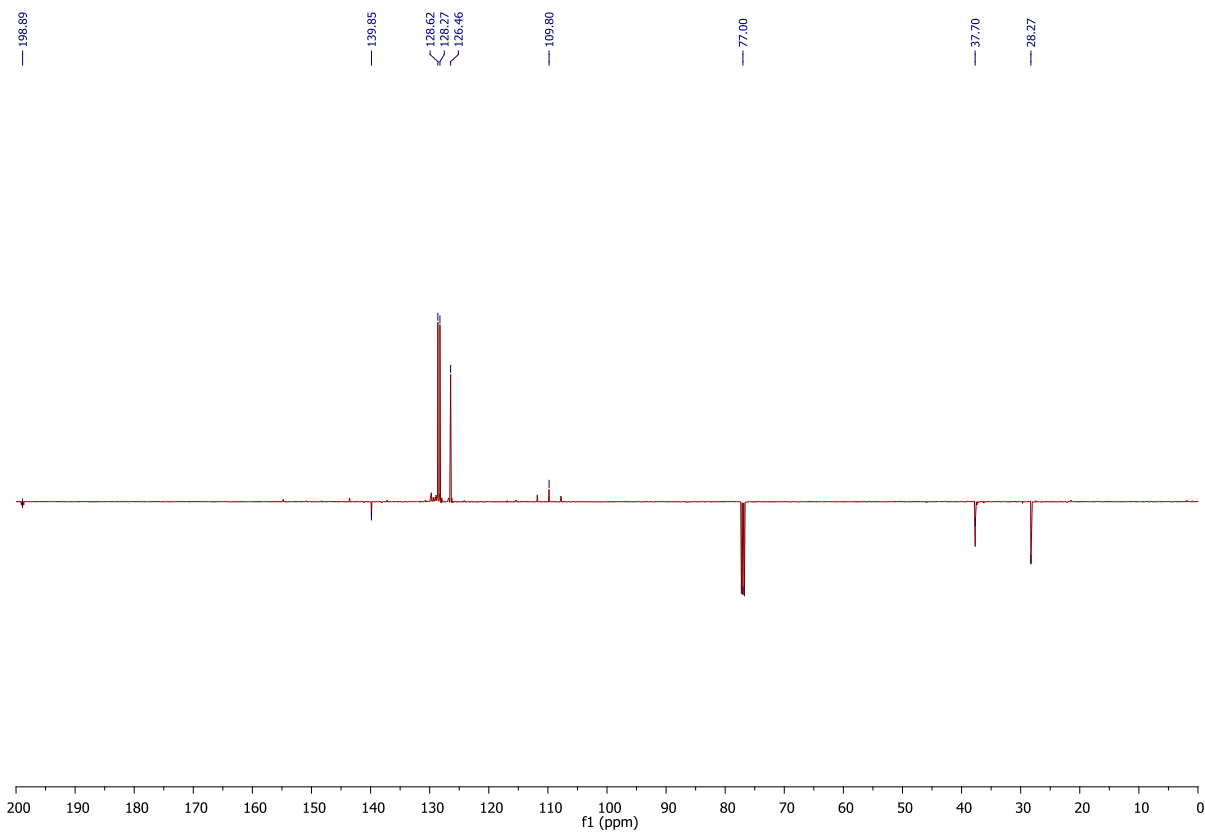
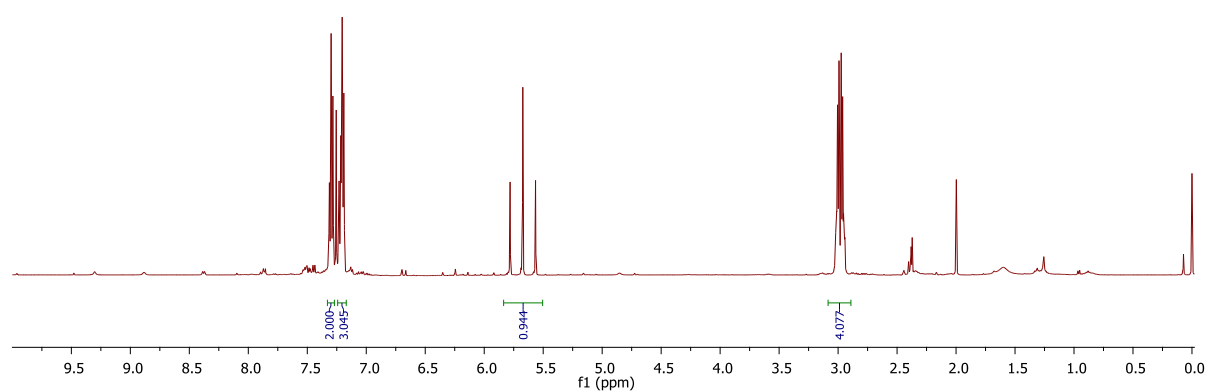
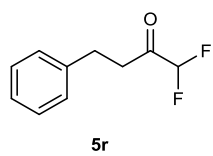


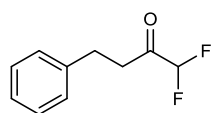
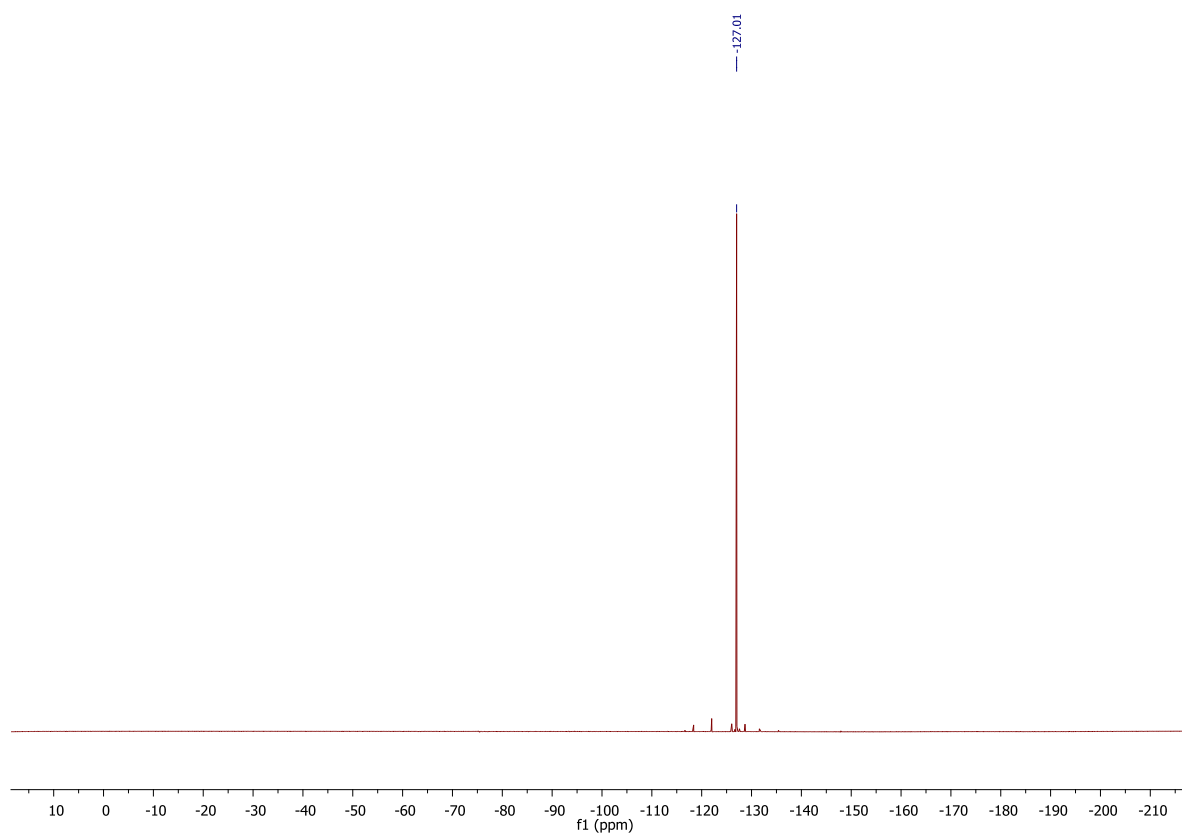


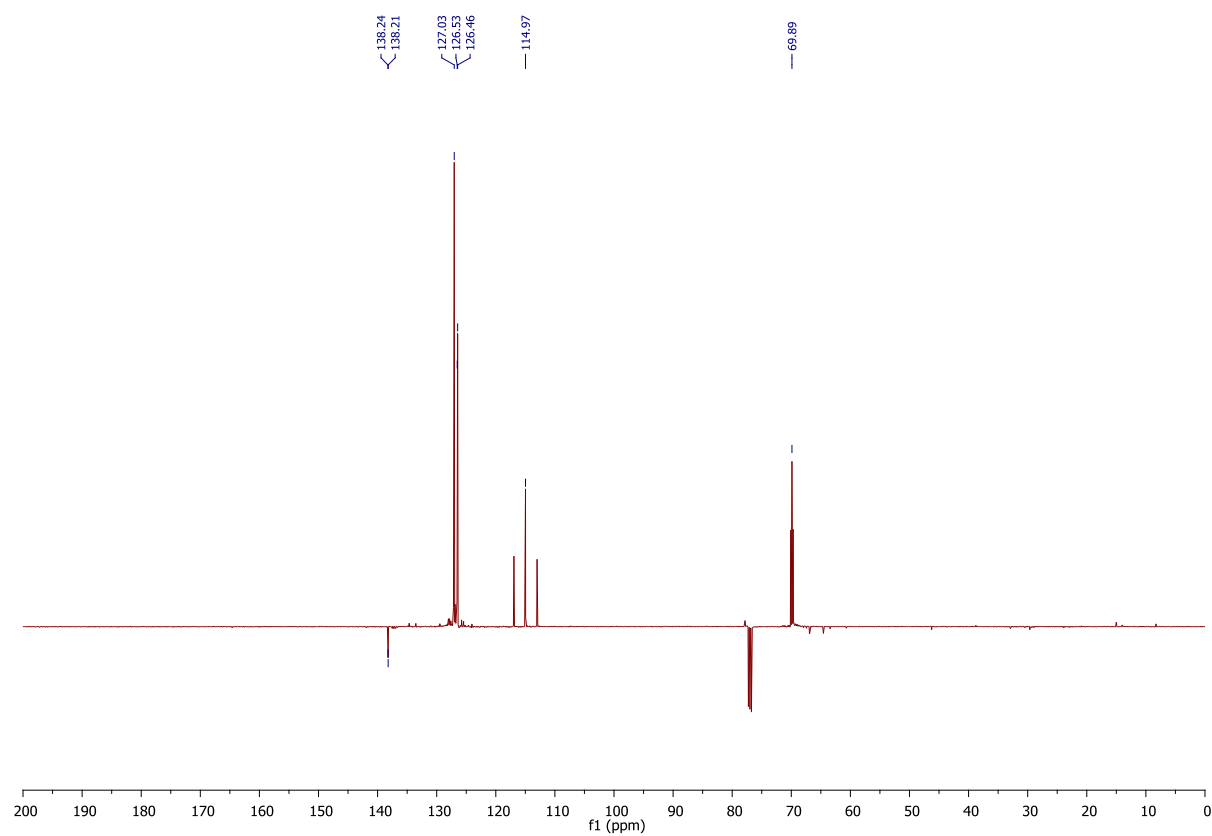
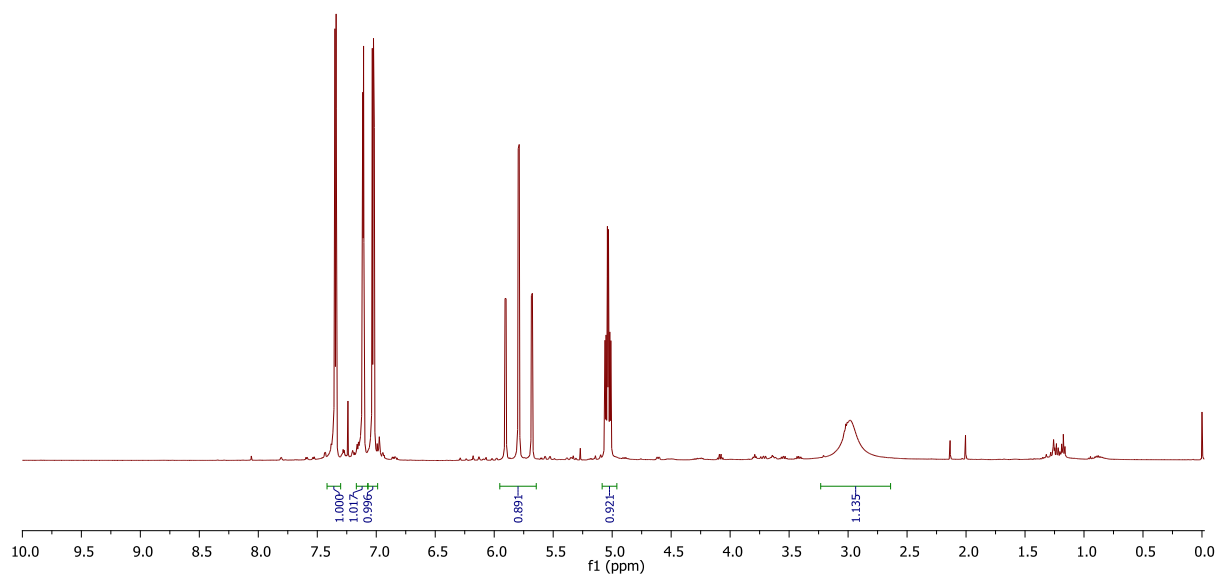
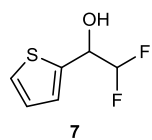


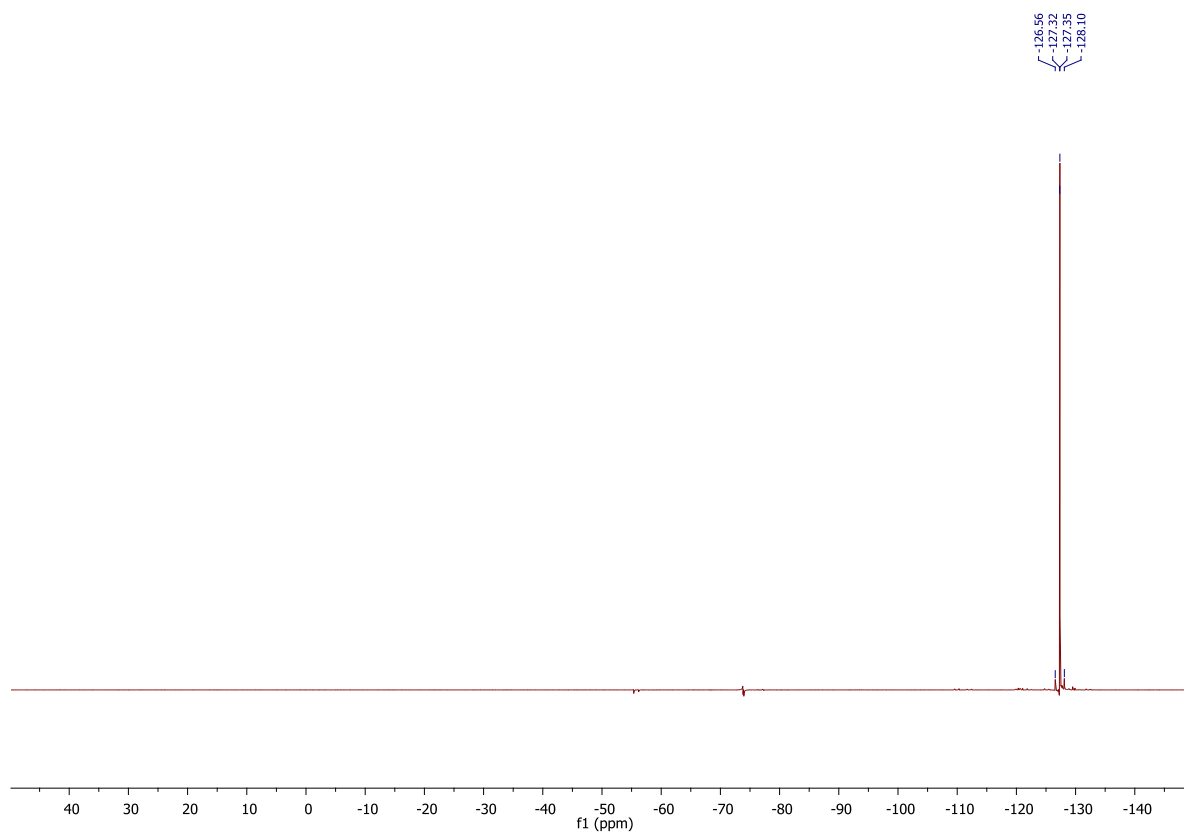
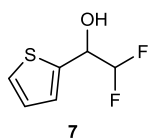
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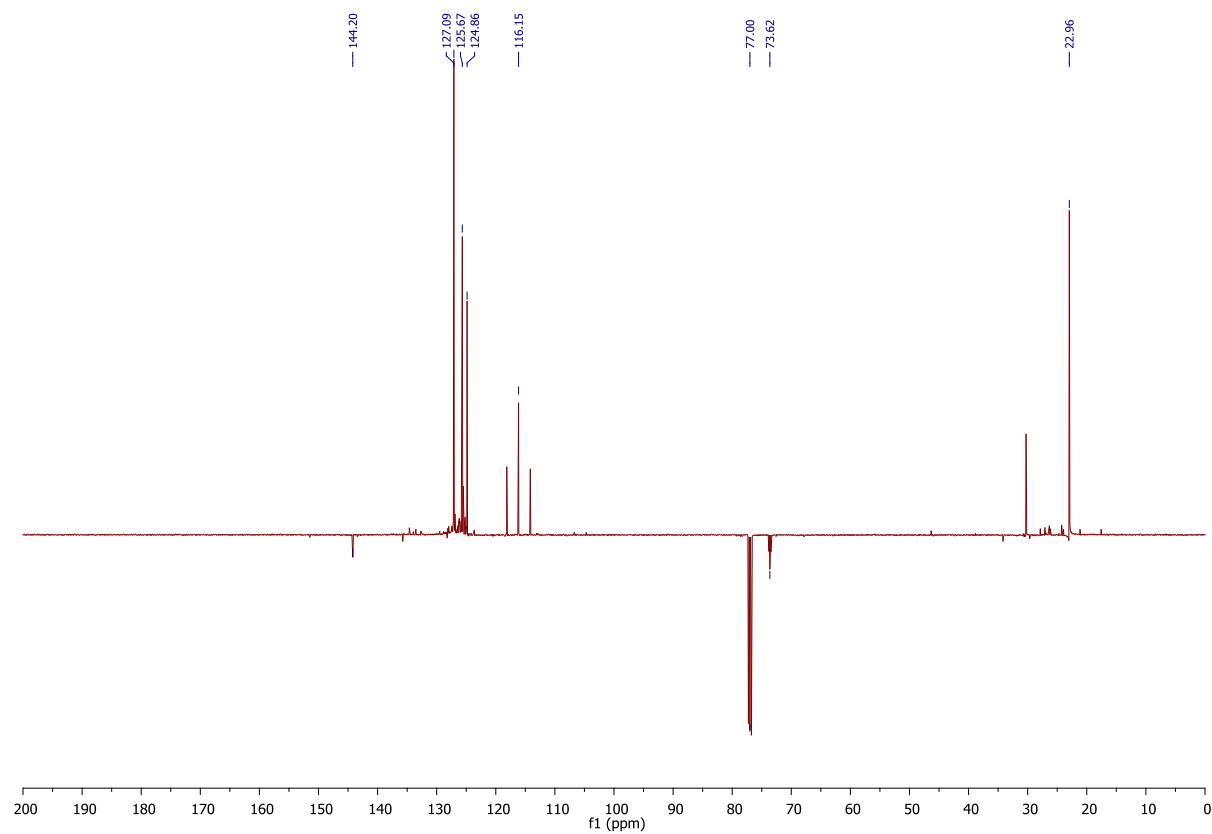
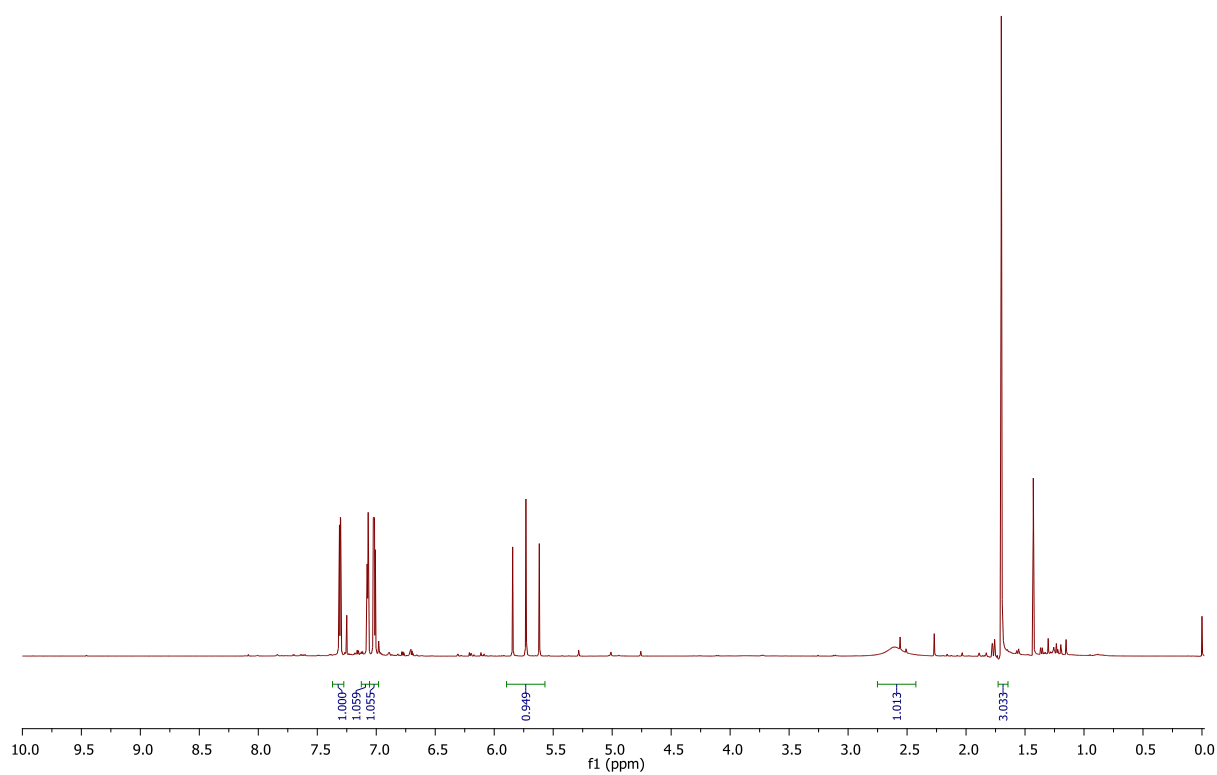
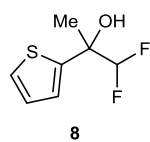


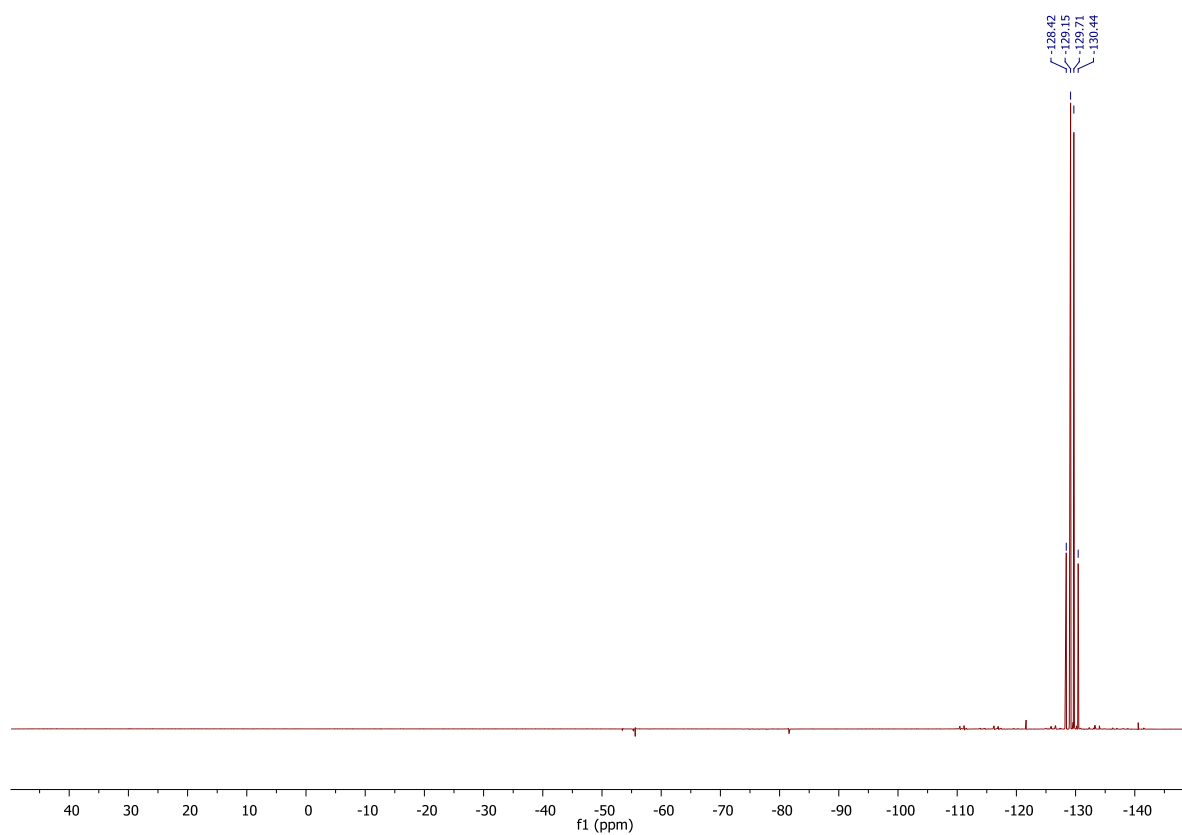
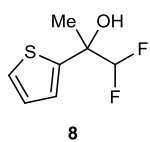


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