nature chemistry

SUPPLEMENTARY INFORMATION

DOI: 10.1038/NCHEM.2746

In the format provided by the authors and unedited.

Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium

Zhang Feng†, Qiao-Qiao Min†, Xia-Pin Fu†, Lun An, and Xingang Zhang*

*Corresponding author. Email: xgzhang@sioc.ac.cn (X. Z.)

†These authors contributed equally

Table of Contents

1. Materials and Methods

General Information: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM400 and AM500 spectrometer and are calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.00 ppm ^{13}C NMR). ^{19}F NMR was recorded on a Bruker AM400 spectrometer ($CFCl_3$ as an external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction. X-ray Photoelectron Spectroscopy (XPS) spectra was recorded on a PHI 5000 VersaProbe spectrometer. The electrospray ionization mass spectrometry (ESI-MS) and the subsequent tandem mass spectrometry (ESI-MS/MS) experiments were performed in Thermo TSQ Quantum AccessTM triple-quadrupole mass spectrometer (Thermo-Fisher Scientific, Waltham, MA, USA). The basic ESI-MS conditions were: spray voltage, 3000 V; capillary temperature, 275 ^{o}C; sheath gas pressure, 2 arb. units; aux gas pressure, 2 arb. units; the collision energy ranged from 5 to 30 eV depending on the dissociation capability of the precursor ions in MS/MS. Data acquisition and analysis were carried out with the Xcalibur software package (Version 2.0, Thermo Fisher Scientific).

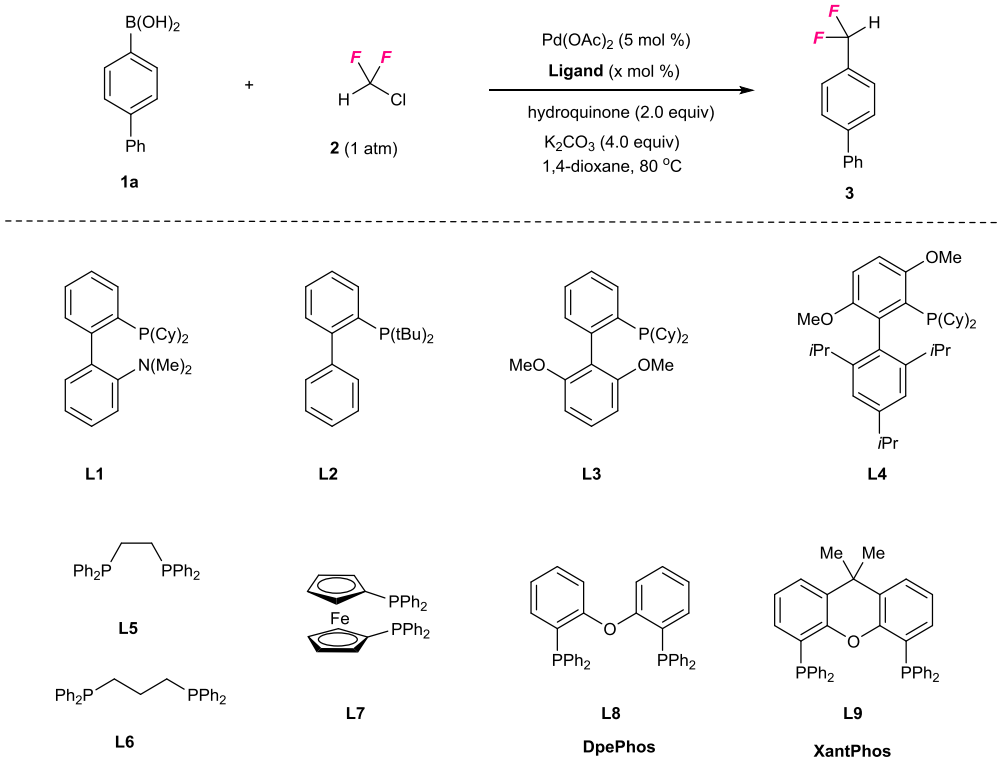
Materials: All reagents were used as received from commercial sources and used without further purification. DMF, DMA, DMPU, DMSO, and DCE were distilled under reduced pressure from CaH_2. 1,4-Dioxane, THF and toluene were distilled from sodium and benzophenone immediately before use. The anhydrous K_2CO_3 was ground into a fine powder and stored at glovebox before used. All (hetero)aryl boronic acids or esters were used from commercial suppliers or prepared using standard literature procedures.

Preparation of $ClCF_2H$ Stock Solution

Anhydrous 1,4-dioxane (100 mL) was added to a Schlenk tube under argon atomosphere (Ar). $ClCF_2H$ gas was then slowly bubbled through the 1,4-dioxane until the total volume of the solution reach the maximum (generally 6 hours). The concentration of the $ClCF_2H$ stock solution was determined by ^{19}F NMR using fluorobenzene as an internal standard (generally 1.7~2.2 mol/L). This solution could be stored at refrigerator (-4 ^{o}C) for one month without loss of $ClCF_2H$.

2. Optimization of Pd-Catalyzed Cross-Coupling of $ClCF_2H$ with Arylborons 1

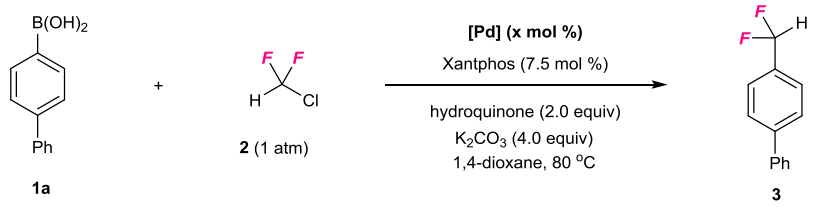
Supplementary Table 1. Optimization of Ligands[a]



Entry	Ligand (x)	**3**, Yield [b]	Entry	Ligand (x)	**3**, Yield [b]
1	PPh_3 (15)	2%	6	**L5** (7.5)	3%
2	**L1** (15)	nd	7	**L6** (7.5)	8%
3	**L2** (15)	nd	8	**L7** (7.5)	1%
4	**L3** (15)	trace	9	**L8** (7.5)	9%
5	**L4** (15)	6%	**10**	**L9 (7.5)**	**16%**

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (1 atm), 1,4-dioxane (2.0 mL), 80 °C, 24 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. nd, not detected.

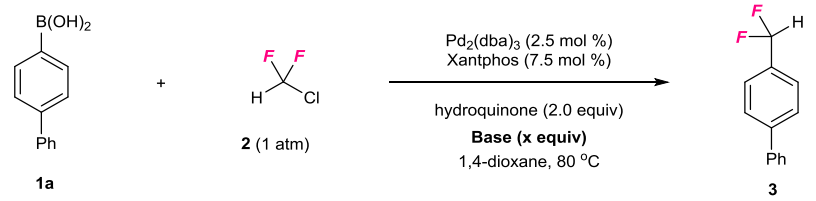
Supplementary Table 2. Optimization of Palladium Catalysts[a]



Entry	[Pd] (x)	**3**, Yield[b]	Entry	[Pd] (x)	**3**, Yield[b]
1	$Pd(OAc)_2$ (5)	16%	6	$[PdCl(C_3H_5)]_2$ (2.5)	16%
2	$Pd(acac)_2$ (5)	3%	7	$PdCl_2(MeCN)_2$ (5)	nd
3	$PdCl_2$(dppf) (5)	18%	8	$PdCl_2(PhCN)_2$ (5)	21%
4	$PdCl_2(PPh_3)_2$ (5)	nd	9	$Pd(PPh_3)_4$ (5)	29%
5	$PdCl_2$(Xantphos) (5)	22%	**10**	**$Pd_2(dba)_3$ (2.5)**	**47%**

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (1 atm), 1,4-dioxane (2.0 mL), 80 °C, 24 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. nd, not detected.

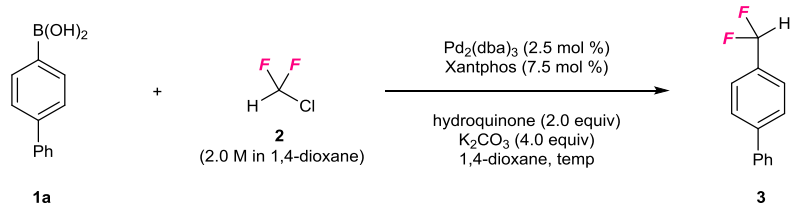
Supplementary Table 3. Optimization of Bases[a]



Entry	Base (x)	**3**, Yield[b]	Entry	Base (x)	**3**, Yield[b]
1	K_2CO_3 (4)	47%	6	*t*-BuOK	nd
2	Cs_2CO_3 (4)	nd	7	*t*-BuONa	nd
3	Na_2CO_3 (4)	3%	8	K_2CO_3 (3)	36%
4	KOAc (4)	nd	9	K_2CO_3 (2)	35%
5	K_3PO_4 (4)	13%	**10**[c]	K_2CO_3 (4)	**49%**

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (1 atm), 1,4-dioxane (2.0 mL), 80 °C, 24 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. [c]Using 2.5 mL of 1,4-dioxane.

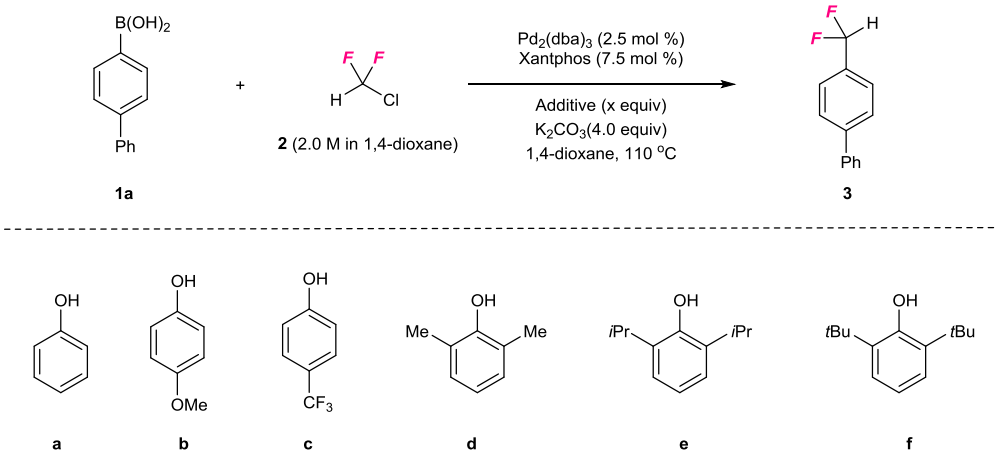
Supplementary Table 4. Optimization of Reaction Parameters[a]



Entry	Temp (°C)	$ClCF_2H$ (equiv)	Time (h)	**3,** Yield [b]
1	80	2	24	21%
2	80	3	24	28%
3	80	4	24	27%
4	80	5	24	34%
5	80	6	24	41%
6	**80**	**6**	**48**	**72%**
7	110	2	12	34%
8	110	3	12	50%
9	110	4	12	66%
10	110	5	12	68%
11	110	6	12	60%
12	110	10	12	76%
13	110	10	24	78%
14	**110**	**2**	**48**	**71%**
15	110	4	48	83%
16	110	6	48	89% (80%)
17	110	8	48	89% (80%)
18	**110**	**10**	**48**	**91% (91%)**
19[c]	110	10	48	nd
20[d]	110	10	48	nd
21[e]	110	10	48	nd

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (2.0 M in dioxane), 1,4-dioxane (2.5 mL), 12-48 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. Value within parentheses is the yield of the isolated product. [c]Reaction run in the absence of [Pd]. [d]Reaction run in the absence of Xantphos. [e]Reaction run in the absence of base.

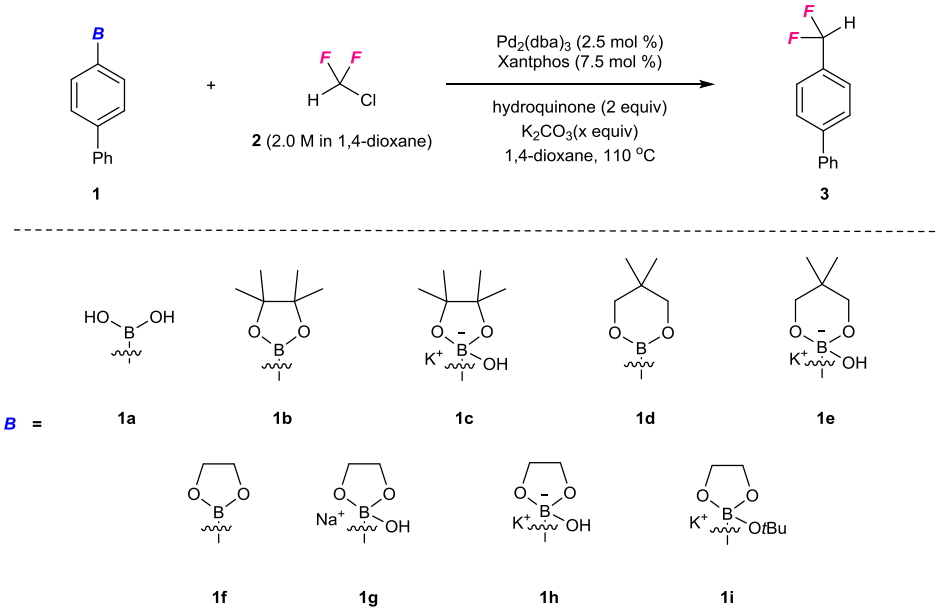
Supplementary Table 5. Optimization of Additives



Entry	Additive (x)	**3**, Yield[b]
1	**a** (2.0)	82%
2	**b** (2.0)	79%
3	**c** (2.0)	32%
4	**d** (2.0)	53%
5	**e** (2.0)	46%
6	**f** (2.0)	13%
7	hydroquinone (2.0)	91%
8	hydroquinone (1.5)	80%
9	hydroquinone (1.0)	79%
10	hydroquinone (0.25)	59%
11	hydroquinone (0.1)	42%
12	none	1%

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (10 equiv, 2.0 M in 1,4-dioxane), 1,4-dioxane (2.5 mL), 110 °C, 48 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard.

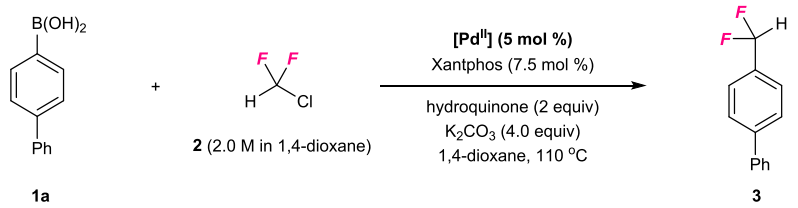
Supplementary Table 6. Optimization of Arylborons[a]



Entry	**1**	K_2CO_3 (x)	**3**, Yield[b]
1	**1a**	4.0	91% (91%)
2	**1b**	4.0	5%
3	**1c**	3.0	8%
4	**1d**	4.0	49%
5	**1e**	3.0	91% (90%)
6	**1f**	4.0	97% (95%)
7	**1g**	3.0	26%
8	**1h**	3.0	96% (95%)
9	**1i**	3.0	94%

[a]Reaction conditions (unless otherwise specified): **1** (0.5 mmol, 1.0 equiv), **2** (10 equiv，2.0 M in 1,4-dioxane), 1,4-dioxane (5 mL), 110 °C, 48 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. Value within parentheses is the yield of the isolated product.

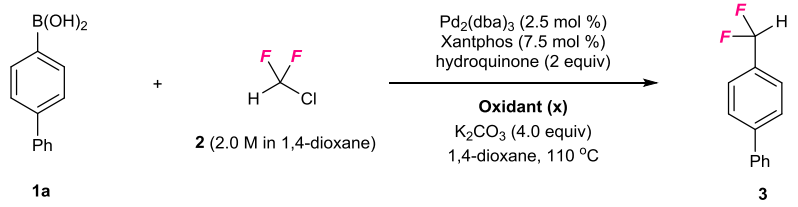
Supplementary Table 7. Investigation of Pd(II)-Catalysts for the Cross-Coupling of 1a with $ClCF_2H$ under Standard Reaction Conditions[a]



Entry	$[Pd^{II}]$	**3**, Yield[b]
1	$PdCl_2(PPh_3)$	87%
2	$PdCl_2$(dppf)	73%
3	$PdCl_2$(Xantphos)	74%
4	$PdCl_2$(PhCN)	73%

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (10 equiv，2.0 M in 1,4-dioxane), 1,4-dioxane (2.5 mL), 110 °C, 48 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard.

Supplementary Table 8. Investigation of Oxidants for the Cross-Coupling of 1a with $ClCF_2H$ under Standard Reaction Conditions[a]

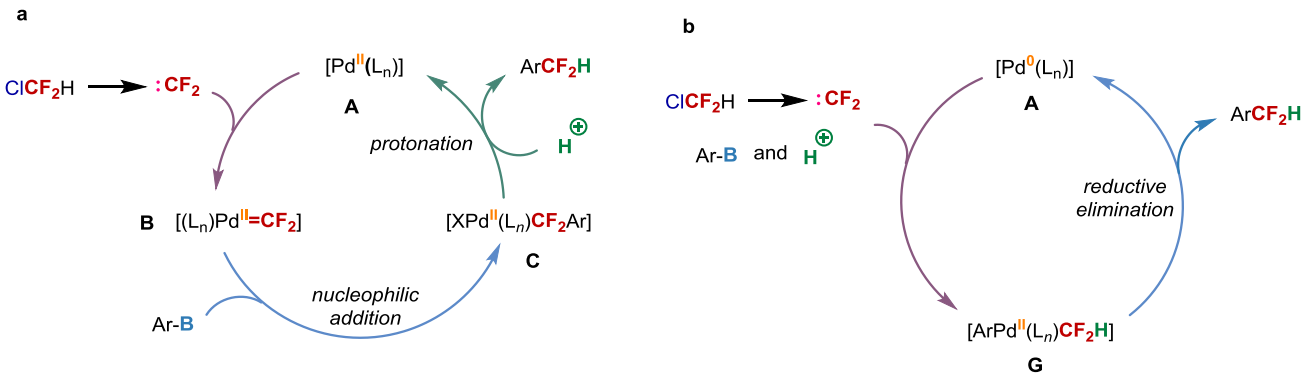


Entry	Oxidant (x)	**3**, Yield[b]
1	Ag_2CO_3 (5 mol %)	77%
2	$FeCl_3$ (5 mol %)	83%
3	BQ (5 mol %)	86%
4	BQ (1 equiv)	40%

[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2** (10 equiv, 2.0 M in 1,4-dioxane), 1,4-dioxane (2.5 mL), 110 °C, 48 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard.

3. Mechanistic Studies

A hypothesized mechanism for palladium-catalyzed difluoroalkylation of (hetero)aryl boronic acids or esters with $ClCF_2H$ is illustrated in Supplementary Fig. 1a. The cross-coupling could be initiated by the formation of palladium difluorocarbene complex (**B**) from the reaction of $Pd^{II}(L_n)$ (**A**) with a difluorocarbene species that was derived from the reaction of $ClCF_2H$ with a Bronsted base (K_2CO_3); next, nucleophilic addition of (hetero)aryl borons with **B** to produce the key intermediate (**C**). As a final step protonation of **C** to deliver the desired difluoromethylated product and release the catalyst **A**. Alternatively, a pathway via a Pd(0)/Pd(II) redox catalytic cycle is also possible for the current cross-coupling (Supplementary Fig. 1b).



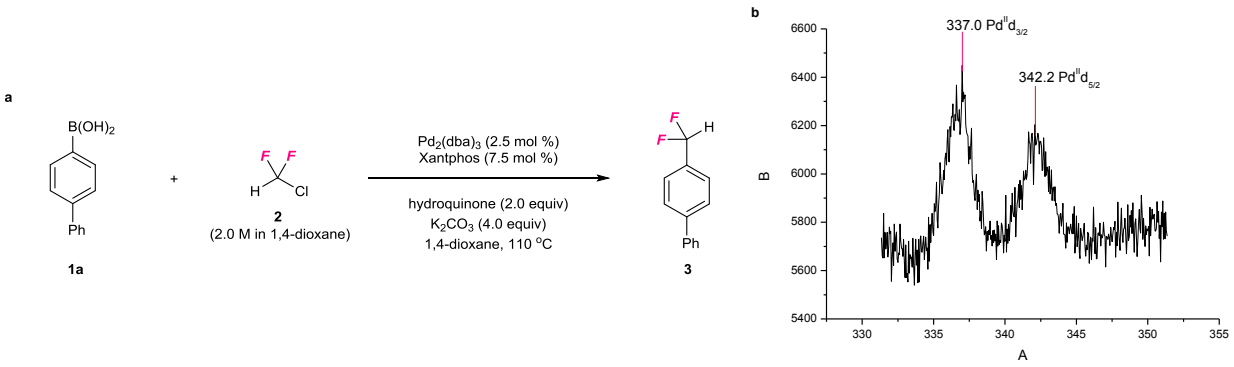
Supplementary Figure 1. Possible mechanisms for the Pd-catalyzed difluoromethylation of arylboronic acids or esters with $ClCF_2H$. a. A possible pathway via a Pd(II) involved catalytic cycle. **b.** A possible pathway via a Pd(0)/Pd(II) redox catalytic cycle.

3.1 X-ray Photoelectron Spectroscopy (XPS) Experiment

The X-ray photoelectron spectroscopy (XPS) analysis of the reaction of **1a** with $ClCF_2H$ under standard reaction conditions (Supplementary Fig. 2) showed that only Pd^{II} species was observed. The XPS showed that peak corresponding to Pd^{II} was observed with the binding energy at 337.0 ev and 342.2 ev, which were negatively shifted by 0.5 ev and 0.7 ev, respectively compared with free $Pd(PPh_3)_2Cl_2$ (Pd^{II} at 337.5 ev, 342.9 ev)[1].

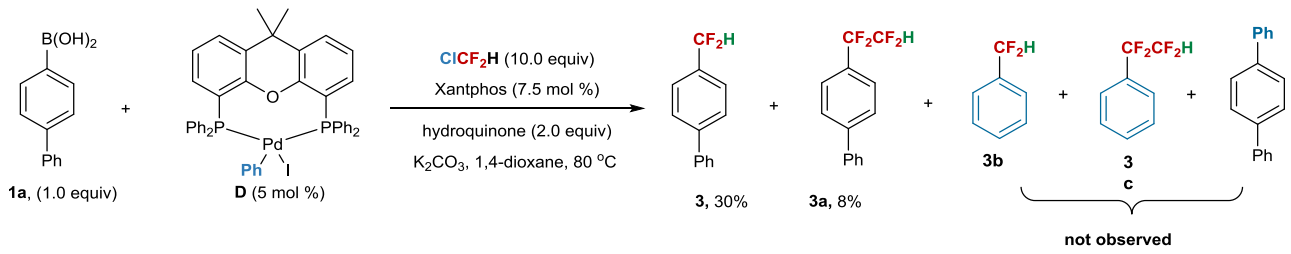
Procedure: To a 25 mL of sealed tube were added anhydrous K_2CO_3 (powder, 1.2 mmol, 4.0 equiv), hydroquinone (0.6 mmol, 2.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), Xantphos (7.5 mol %) and aryl boronic acid **1a** (0.3 mmol, 1equiv) under argon. A solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL, 10

equiv) and fresh distilled 1,4-dioxane (1.0 mL) were added subsequently. The sealed tube was screw capped and heated to 110 °C (oil bath). After stirring for 48 h, the reaction was cooled to room temperature and concentrated under N_2. The resulting mixture was analyzed by X-ray photoelectron spectroscopy (XPS) (**Note**: all the XPS experiments were carried out under N_2).



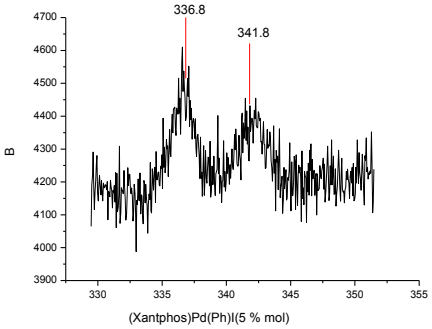
Supplementary Figure 2. X-Ray photoelectron spectroscopy (XPS) analysis of reaction of 1a with 2 under standard reaction donditions. a, Reaction of **1a** with **2** under standard reaction conditions. **b**, XPS of the reaction.

3.2 Reaction of Palladium Complex (D) with 1a



Procedure: To a 25 mL of sealed tube were added anhydrous K_2CO_3 (powder, 1.2 mmol, 4.0 equiv), hydroquinone (0.6 mmol, 2.0 equiv), [PhPd(Xantphos)I] (**D**)[2] (5 mol%) and aryl boronic acid **1a** (0.3 mmol, 1 equiv) under argon. A solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL, 10 equiv) and fresh distilled 1,4-dioxane (1.0 mL) were added subsequently. The sealed tube was screw capped and heated to 110 °C (oil bath) with stirring for 48 h to provide compound **3** and 4-(1,1,2,2-tetrafluoroethyl)-1,1'-biphenyl **3a** (the yields were determined by ^{19}F NMR using fluorobenzene as an internal standard). The XPS analysis of the reaction (Supplementary Fig. 3) showed that only peak corresponding to Pd^{II} was observed with the binding energy at 336.8 ev and 341.8 ev, which were negatively shifted by 0.7 ev and 1.1 ev, respectively compared with free $Pd(PPh_3)_2Cl_2$ (Pd^{II} at 337.5 ev, 342.9 ev)[1].

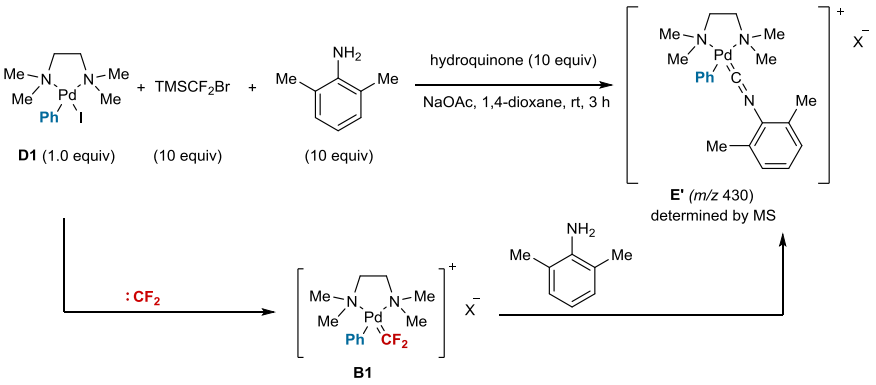
4-(1,1,2,2-Tetrafluoroethyl)-1,1'-biphenyl (3a). [known compound[3]]: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.12-7.69 (m, 2 H), 7.64-7.59 (m, 4 H), 7.49-7.45 (m, 2 H), 7.43-7.38 (m, 1 H), 5.96 (tt, *J* = 54.4 Hz, *J* = 2.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.4 (m，2 F), -134.1 (dt, *J* = 54.2 Hz, *J* = 3.4 Hz, 2 F).



Supplementary Figure 3. X-Ray photoelectron spectroscopy (XPS) analysis of the reaction of palladium complex (D) with 1a

3.3 Mass Spectrometric (MS) Analysis of Aminolysis of the Palladium Difluorocarbene Complex

To probe the possibility that the formation of palladium difluorocarbene complex [$(L_n)Pd^{II}$=CF_2] (**B**) can be derived from the reaction of $Pd^{II}(L_n)$ (**A**) species with difluorocarbene, we conducted mass spectrometric (MS) analysis of aminolysis of the palladium difluorocarbene complex[4] and found that treatment of palladium(II) species [PhPd(TMEDA)(I)] (**D1**)[5] with difluorocarbene precursor $TMSCF_2Br$[6] could provide palladium difluorocarbene complex [PhPd(TMEDA)=CF_2]$^+$ (**B1**).

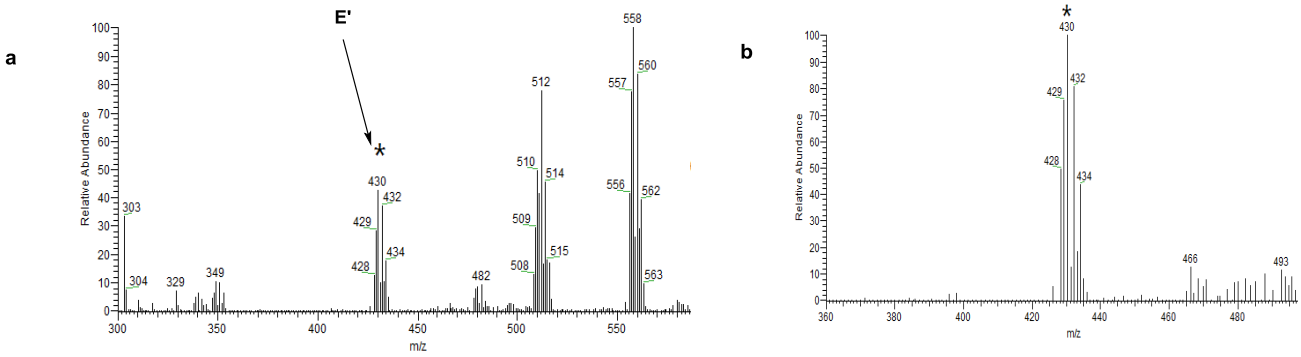


Procedure: Palladium complex (**D1**)[5] (0.05 mmol, 18.4 mg, 1 equiv), hydroquinone (0.5 mmol, 55 mg, 10 equiv) and NaOAc (0.5 mmol, 68 mg, 10 equiv) were added to a 25 mL of Schlenk tube. The mixture was then evacuated and backfilled with Argon for 3 times. Then, 2,6-dimethylaniline (5 mmol,

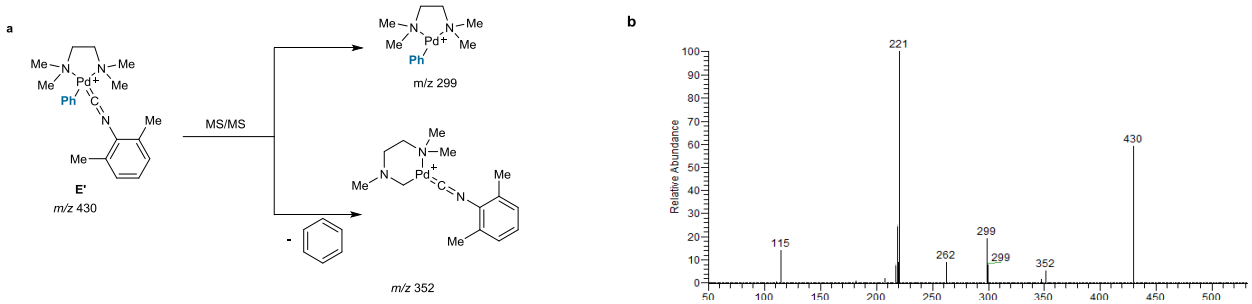
62 μL, 10 equiv), and 1,4-dioxane (2.5 mL) were added. After the resulting mixture was stirred for 5 min at room temperature, $TMSCF_2Br$[6] (0.5 mmol, 10 equiv) was added. The Schlenk tube was screw capped and the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted for the ESI-MS analysis.

General MS Experimental Conditions: The reaction solution was diluted by 200 times with CH_3CN before ESI-MS analysis and the injection speed of the diluted solution was set to 8 μL/min to ESI-MS. We carefully monitored the diluted reaction solution by ESI-MS and found that some Pd complexes are not stable and their signals decreased rapidly (even disappeared from the ESI-MS spectra after 10 min). So the MS experiments should be performed fast. The electrospray ionization tandem mass spectrometry (ESI-MS/MS) method was performed to assign the possible structures of the Pd complexes observed from the diluted reaction solution.

MS analysis of the reaction showed that complex (**D1**) could provide the corresponding aminolysis product $[Ph(TMEDA)Pd=C=N(2,6\text{-dimethylphenyl})]^+$ (**E′**, *m/z* 430) at room temperature (Supplementary Fig. 4). Additionally, the ESI-MS/MS experiment for the cationic palladium complex at *m/z* 430 further support the structure of **E′** (Supplementary Fig. 5).



Supplementary Figure 4. MS analysis of aminolysis of the palladium difluorocarbene complex with palladium complex D1 as a substrate and $TMSCF_2Br$ as a difluorocarbene precursor. **a**, The ESI-MS spectrum in positive ion mode of the diluted reaction solution. A cationic Pd complex at *m/z* 430 corresponding to aminolysis product $[Ph(TMEDA)Pd=C=N(2,6\text{-dimethylphenyl})]^+$ was observed. **b**, The ESI-MS spectrum of the cationic Pd complex at *m/z* 430.

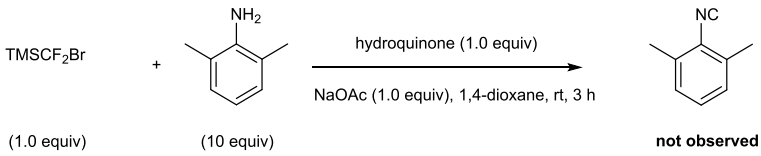


Supplementary Figure 5. ESI-MS/MS experiment for the cationic palladium complex at *m/z* 430. **a**, The proposed fragmentation pattern of the cationic Pd complex [Ph(TMEDA)Pd=C=N(2,6-dimethylphenyl)]$^+$ at *m/z* 430, which supported their structure assignment. **b**, The ESI-MS/MS spectra in positive ion mode of the Pd complexe at *m/z* 430.

Reaction of $TMSCF_2Br$ with 2,6-dimethylaniline

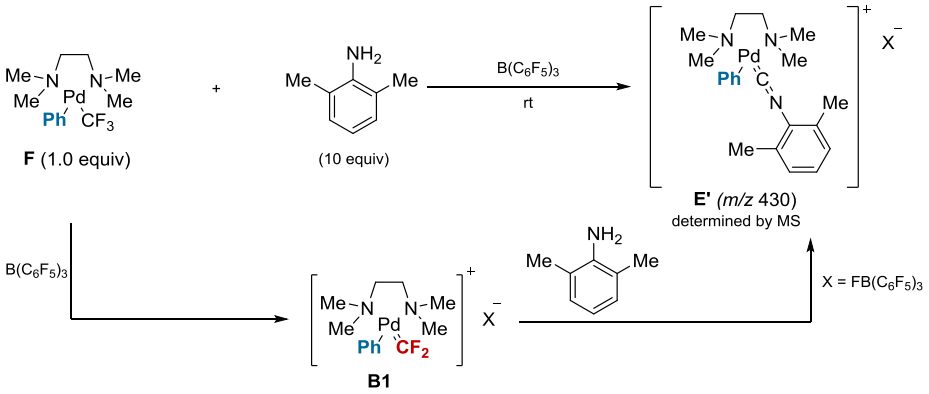
Another possibility for the formation of aminolysis product **E′** is the reaction of **D1** with isocyanide ArNC, which was generated in situ between free difluorocarbene and 2,6-dimethylaniline. However, this possibility is unlikely because we did not observe the isocyanide by treatment of $TMSCF_2Br$ with 2,6-dimethylaniline, for details, see Supplementary Fig. 6.

Procedure: Hydroquinone (0.5 mmol, 55 mg, 1.0 equiv) and NaOAc (0.5 mmol, 68 mg, 1.0 equiv) were added to a 25 mL of Schlenk tube. The mixture was then evacuated and backfilled with Argon for 3 times. Then $TMSCF_2Br$ (0.5 mmol, 1.0 equiv), 2,6-dimethylaniline (5 mmol, 62 μL, 10 equiv), and 1,4-dioxane (2.5 mL) were added subsequently. The Schlenk tube was screw capped and the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted for the GC-MS analysis and showed no isocyanide ArNC was observed.



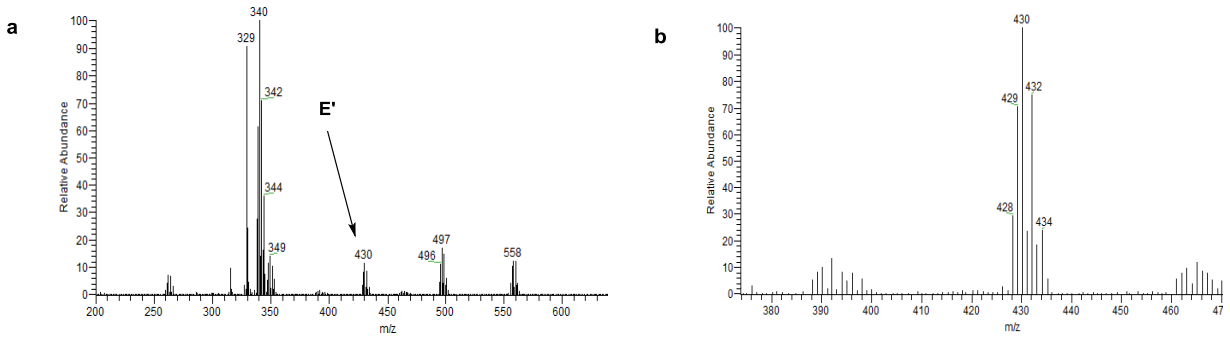
Supplementary Figure 6. **Reaction of $TMSCF_2Br$ with 2,6-dimethylaniline**

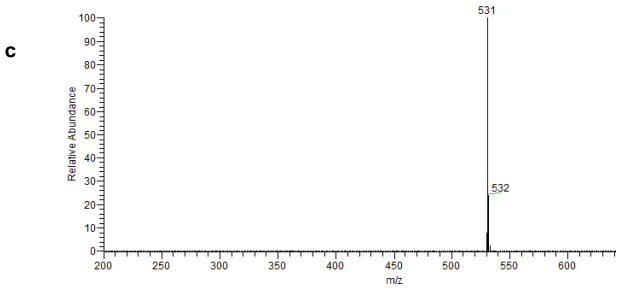
3.4 Experiement of Fluoride Abstraction from Palladium Complex [PhPd(TMEDA)CF_3] (F) with $B(C_6F_5)_3$



It has been demonstrated that cationic metal difluorocarbene species could be produced by fluoride abstraction from the trifluoromethyl ligand with various Lewis acids[7]. To further confirm the formation of palladium difluorocarbene complex, we prepared palladium complex [PhPd(TMEDA)CF_3] (**F**)[8]. Treatment of **F** with Lewis acid $B(C_6F_5)_3$ in the presence of 2,6-dimethylaniline also produced aminolysis product $[Ph(TMEDA)Pd{=}C{=}N(2,6\text{-dimethylphenyl})]^+$ (**E′**, *m/z* 430) (Supplementary Fig. 7), in which the cationic Pd complex at *m/z* 430 have same MS/MS fragmentation pattern with that from Supplementary Fig. 5.

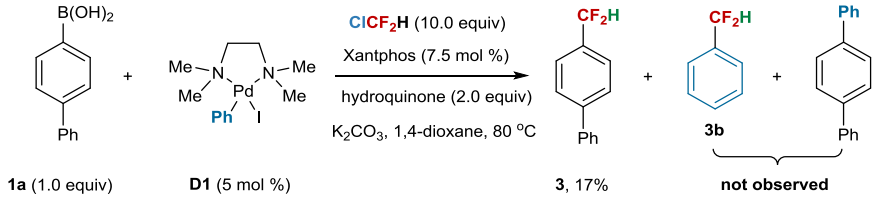
Procedure: To a 20 mL of standard flat bottom scintillation vial were added palladium complex (**F**) (0.05 mmol, 18.4 mg, 1 equiv), 2,6-dimethylaniline (62 µL, 0.5 mol, 10 equiv), and benzene (2.5 mL) in glove box at room temperature. After the mixture was stirred for 5 min, Lewis acid $B(C_6F_5)_3$ (0.05 mmol, 25.6 mg, 1 equiv) was added. The reaction was stirred at room temperature for 1 h. The resulting mixture was diluted for the ESI-MS analysis.





Supplementary Figure 7. MS analysis of cationic Pd complex [Ph(TMEDA)Pd=C=N(2,6-dimethylphenyl)]$^+$. a, The ESI-MS spectrum in positive ion mode of the diluted reaction solution. A cationic Pd complex at *m/z* 430 corresponding to aminolysis product [Ph(TMEDA)Pd=C=N(2,6-dimethylphenyl)]$^+$ was observed. **b**, The ESI-MS spectrum of the cationic Pd complex at *m/z* 430. **c**, The ESI-MS spectrum in negative ion mode of the diluted reaction solution. The $[B(C_6F_5)_3F]^-$ at *m/z* 531 was observed.

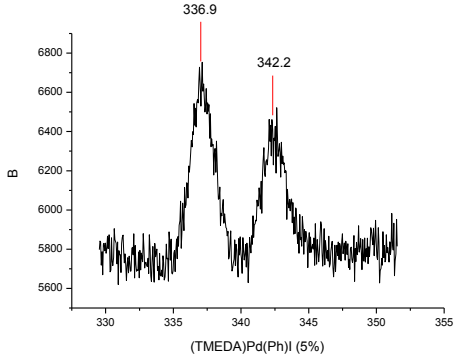
3.5 Cross-Coupling of Arylboronic Acid with $ClCF_2H$ in the Presence of [Ph(TMEDA)Pd(I)]



Procedure: Procedure: To a 25 mL of sealed tube were added anhydrous K_2CO_3 (powder, 1.2 mmol, 4.0 equiv), hydroquinone (0.6 mmol, 2.0 equiv), palladium complex (**D1**) (5 mol%) and aryl boronic acid **1a** (0.3 mmol, 1.0 equiv) under argon. A solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL, 10 equiv) and fresh distilled 1,4-dioxane (1.0 mL) were added subsequently. The sealed tube was screw capped and heated to 80 ^oC (oil bath) with stirring for 36 h. The yield of **3** was determined by ^{19}F NMR using fluorobenzene as an internal standard.

Note: The lower yield of **3** than that use of **D** as a catalyst is because of the low reactivity of **D1**. Increasing the reaction temperature to 110 ^oC, the yield of **3** can be improved to 65%. Again, no triphenyl species was observed.

The XPS analysis of the reaction showed that only Pd(II) species was observed (Supplementary Fig. 8). The XPS showed that peak corresponding to Pd^{II} was observed with the binding energy at 336.9 ev and 342.2 ev, which were negatively shifted by 0.6 ev and 0.7 ev, respectively compared with free $Pd(PPh_3)_2Cl_2$ (Pd^{II} at 337.5 ev, 342.9 ev)[1].



Supplementary Figure 8. X-Ray photoelectron spectroscopy (XPS) analysis of cross-coupling of arylboronic acid with $ClCF_2H$ in the presence of [Ph(TMEDA)PdI]

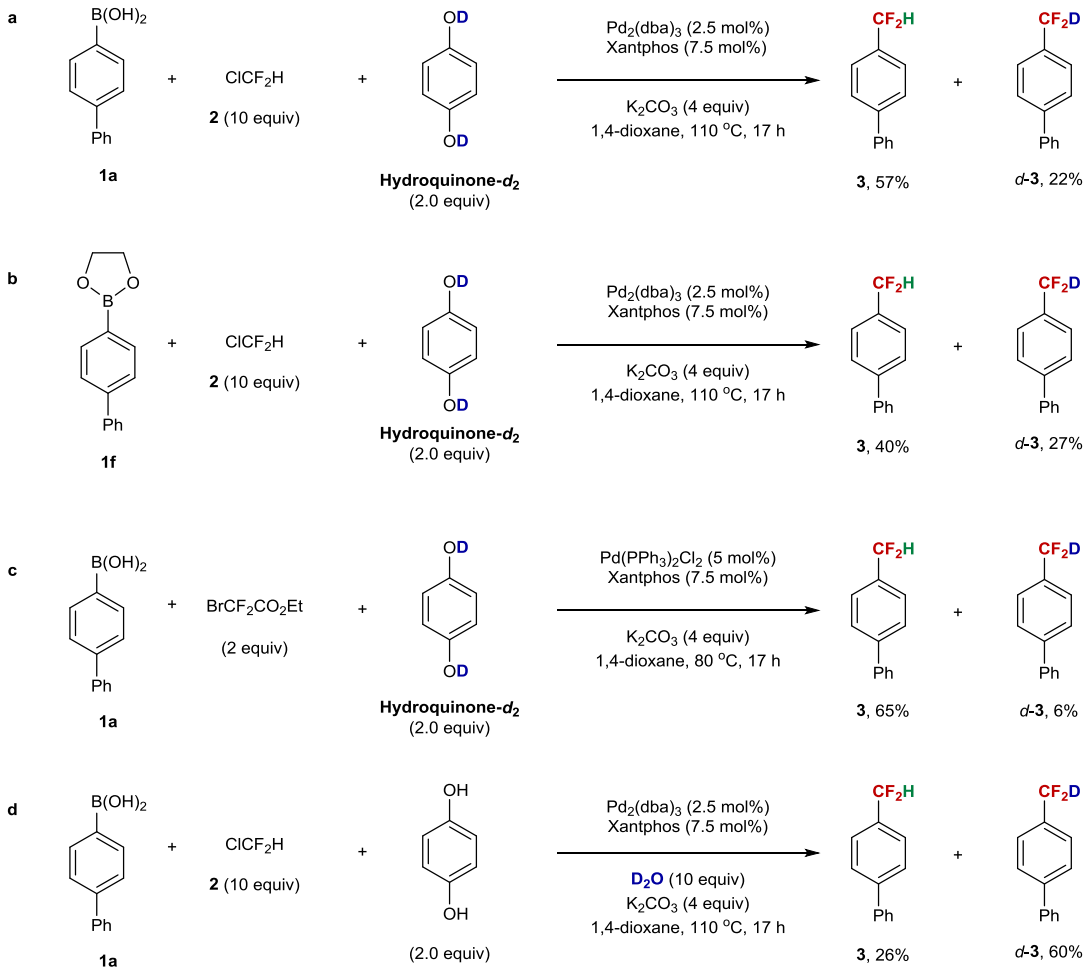
3.6 Experiments to Probe the Proton Source of Pd-Catalyzed Difluoromethylation of Arylborons

A range of experiments with deuterated hydroquinone as an additive were conducted (Supplementary Fig. 9). When arylboronic acid **1a** was treated with $ClCF_2H$ in the presence of deuterated hydroquinone under stdandrd reaction conditions for 17 h, besides the formation of 57% yield of desired product **3**, a 22% yield of deuterated *d*-**3** was also obtained (Supplementary Fig. 9a). Switching **1a** with aryl-Beg **1f** also provided both products **3** and *d*-**3** with high efficiency (Supplementary Fig. 9b). Thus, these results suggested that both hydroquinone and $ClCF_2H$ can serve as proton sources. To probe that whether arylboronic acid was a proton source in the current process, a difluorocarbene precursor $BrCF_2CO_2Et$ instead of $ClCF_2H$ was used. We found that both **3** and *d*-**3** could also be obtained in good yields (Supplementary Fig. 9c). This finding demonstrates that arylboronic acid is also a proton source. Additionally, water can also function as a proton source. When 10 equiv of D_2O was added to the reaction, a 60% yield of *d*-**3** was produced (Supplementary Fig. 9d).

Procedure: To a 25 mL of sealed tube were added anhydrous K_2CO_3 (powder, 1.2 mmol, 4.0 equiv), deuterated hydroquinone (0.6 mmol, 2.0 equiv), palladium catalyst (5 mol%), Xantphos (7.5 mol%) and aryl boronic acid **1a** or Ar-Beg **1f** (0.3 mmol, 1 equiv) under argon. A solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL, 10 equiv) or $BrCF_2CO_2Et$ (0.6 mmol, 2.0 equiv) and fresh distilled 1,4-dioxane (1.0 mL for $ClCF_2H$, 2.5 mL for $BrCF_2CO_2Et$) were added subsequently. The sealed tube was screw capped and heated to 110 ^oC (oil bath, for $ClCF_2H$) or 80 ^oC (oil bath, for $BrCF_2CO_2Et$) with stirring for 3 h. The yields of **3** and *d*-**3** were determined by ^{19}F NMR using fluorobenzene as an

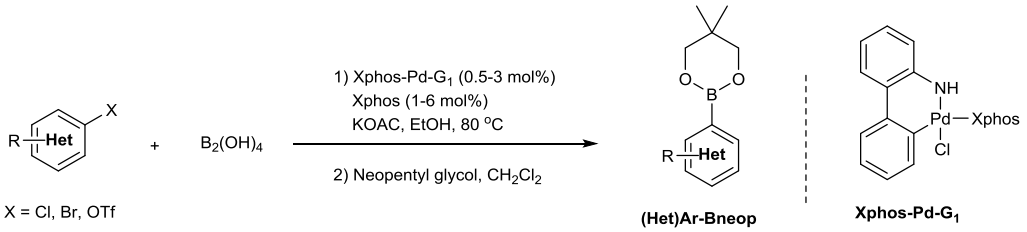
internal standard. The mixture of **3** and *d*-**3:** ^{2}H NMR (77 MHz, $CHCl_3$) δ 7.10 (t, *J* = 8.7 Hz, 1D); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.34 (d, *J* = 56.5 Hz, **CF$_2$**H), -111.06 (t, *J* = 8.6 Hz, **CF$_2$**D). MS (EI): m/z (%) 204 (M^+, 60, compound **3**), 205 (M^+, 100, compound *d*-**3**). HRMS: Calculated for $C_{13}H_9DF_2$ (M^+): 205.0813; Found: 205.0807.

Preparation of Hydroquinone-*d*$_2$: To a 250 mL three necked round flask were add CH_3ONa (1.08 g, 20 mmol, 3.3 equiv), hydroquinone (660 mg, 6 mmol, 1 equiv), and 40 mL of THF under argon at rt. After the resulting mixture was stirred for 2 h, 35% of DCl/D_2O (3.4 mL, 40 mmol, 7 equiv) was added dropwise, and the reaction mixture was stirred overnignt at rt. If the deuteration ratio of *d*-**3**/**3** is not good enough, the produt should be deuterated again with the same procedure described above. The reaction mixture was concentrated to give deuterated hydroquinone (hydroquinone-*d*$_2$ >99%)



Supplementary Figure 9. Experiments to probe the proton source of Pd-catalyzed difluoromethylation of arylborons.

4. General Procedure for the Preparation of Aryl Neopentylglycol Boronate Esters (Ar-Bneop)

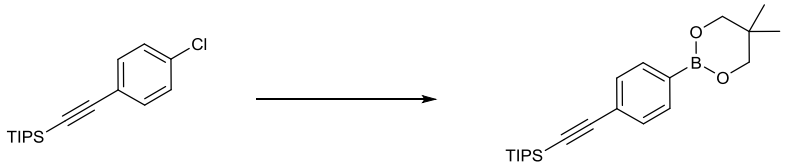


X = Cl, Br, OTf

(Het)Ar-Bneop **Xphos-Pd-G$_1$**

The preparation of (Het)Ar-Bneop is according to the literature[9]. To a 50 mL of Schlenk tube were added anhydrous KOAc (12 mmol, 1.18 g, 3.0 equiv), $B_2(OH)_4$ (8 mmol, 720 mg, 2.0 equiv), (Xphos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) (0.8-6 mol%), XPhos-Pd-G_1 (0.4-3 mol%), and (hetero)aryl halide (4 mmol, 1.0 equiv) or (hetero)aryl trifluoromethanesulfonate (4 mmol, 1.0 equiv) under argon, followed by fresh distilled EtOH (20 mL). The resulting mixture was then heated to 80 °C and stirred for 4 h. The reaction was cooled to room temperature and concentrated. The residue was diluted with ethyl acetate (100 mL) and washed with saturated brine. The organic layer was filtered through a pad of $MgSO_4$ and concentrated. The residue was dissolved in dichloromethane (CH_2Cl_2, 20 mL), and neopentyl glycol (8 mmol, 833 mg, 2.0 equiv) was added. After the resulting mixture was tirred at room temperature for 8 h, the reaction mixture was then diluted with ethyl acetate, filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography to give (Het)Ar-Benop.

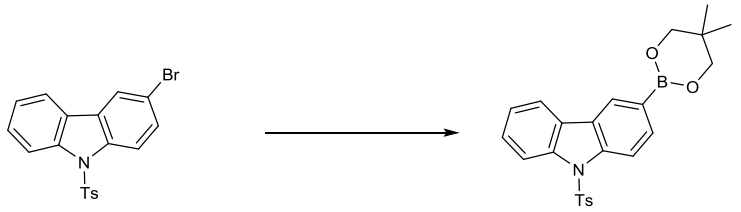
5. Experimental Procedures and Characterization Data for (Het)Ar-Bneop



26b **26a**

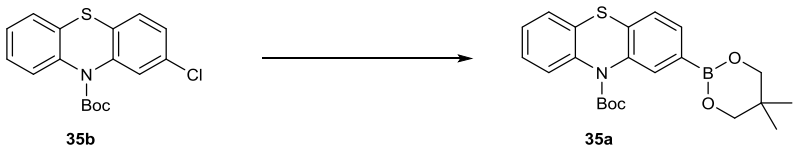
((4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)ethynyl)triisopropylsilane (26a). Xphos (19 mg, 0.04 mmol, 1 mol %), XPhos-Pd-G_1 (15.8 mg, 0.02 mmol, 0.5 mol %) and aryl chloride **26b** (1.17 g, 4.0 mmol, 1.0 equiv) were used. Compound **26a** (1.12 g, 75% yield) was isolated by silica gel chromatography (CH_2Cl_2) as a white solid (m.p. 74-76 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 3.77 (s, 4 H), 1.14 (s, 18 H), 1.14-1.07 (m, 3 H), 1.02 (s, 6

H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 131.1, 125.6, 107.4, 91.5, 72.3, 31.9, 21.9, 18.7, 11.3 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 3075, 2942, 2890, 2865, 2155, 1603 cm^{-1}. MS (EI): *m/z* (%) 370 (M^+), 369 (M^+), 328, 327 (100), 257. HRMS: Calculated for $C_{22}H_{35}O_2Si^{10}B$ (M^+): 369.2536; Found: 369.2528.



34b **34a**

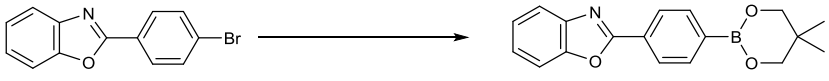
3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-9-tosyl-9*H*-carbazole (34a). Xphos (38.1 mg, 0.08 mmol, 2 mol %), XPhos-Pd-G_1 (31.5 mg, 0.04 mmol, 1 mol %) and heteroaryl bromide **34b** (1.60 g, 4.0 mmol, 1.0 equiv) were used. Compound **34a** (1.42 g, 82% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc = 20:1) as a white solid (m.p. 176-178 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 8.32 (dd, *J* = 8.4 Hz, 3.2 Hz, 2 H), 7.94 (dd, *J* = 8.4 Hz, 3.2 Hz, 2 H), 7.69 (d, *J* = 8.1 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 3.82 (s, 4 H), 2.23 (s, 3 H), 1.05 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.2, 138.4, 134.9, 133.0, 129.6, 127.1, 126.5, 126.4, 125.8, 123.9, 120.0, 115.0, 114.2, 72.4, 31.9, 21.9, 21.4 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 3042, 2959, 2886, 1618, 1598 cm^{-1}. MS (DART): *m/z* (%) 451 [$(M+NH_4)^+$] (100), 450 [$(M+NH_4)^+$]. HRMS: Calculated for $C_{24}H_{28}O_4N_2{}^{10}BS$ [$(M+NH_4)^+$]: 450.1894; Found: 450.1889.



35b **35a**

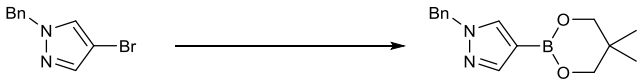
***N*-Boc-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-10*H*-phenothiazine (35a).** Xphos (38.1 mg, 0.08 mmol, 2 mol %), XPhos-Pd-G_1 (31.5 mg, 0.04 mmol, 1 mol %), and heteroaryl chloride **35b** (1.34 g, 4.0 mmol, 1.0 equiv) were used. Compound **35a** (1.29 g, 78% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc = 25:1) as a solid (m.p. 144-146 ^{o}C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.57 (dd, *J* = 7.8 Hz, 0.9 Hz, 1 H), 7.51 (d, *J* = 8.1 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H),

7.25 (td, *J* = 7.8 Hz, 1.4 Hz, 1 H), 7.13 (td, *J* = 7.8 Hz, 1.4 Hz, 1 H), 3.76 (s, 4 H), 1.49 (s, 9 H), 1.01 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 138.7, 137.9, 134.8, 132.4, 131.9, 131.2, 127.3, 127.1, 126.6, 126.5, 125.9, 81.8, 72.3, 31.9, 28.1, 21.8 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 3059, 3003, 2965, 1715, 1598, 1475 cm^{-1}. MS (DART): m/z (%) 429 [$(M+NH_4)^+$] (100), 428 [$(M+NH_4)^+$], 411 (M^+). HRMS: Calculated for $C_{22}H_{30}O_4N_2{}^{10}BS$ [$(M+NH_4)^+$]: 428.2050; Found: 428.2049.



39b **39a**

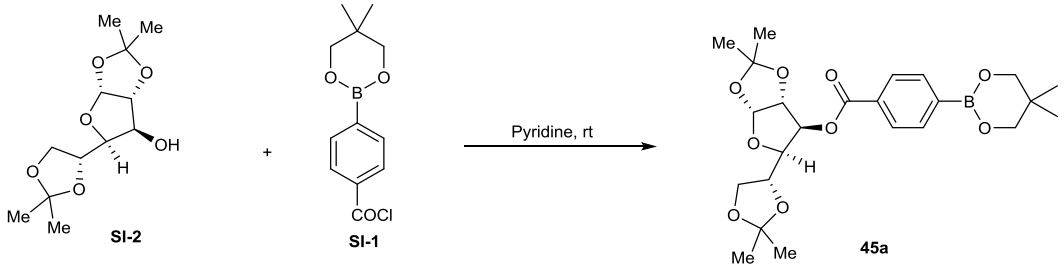
2-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)benzo[*d*]oxazole (39a). Xphos (38.1 mg, 0.08 mmol, 2 mol %), XPhos-Pd-G_1 (31.5 mg, 0.04 mmol, 1 mol %), and heteroaryl bromide **39b** (1.10 g, 4.0 mmol, 1.0 equiv) were used. Compound **39a** (900 mg, 73% yield) was isolated by silica gel chromatography (CH_2Cl_2) as white a solid (m.p. 187-189 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 8.2 Hz, 2 H), 7.79-7.77 (m, 1 H), 7.58-7.56 (m, 1 H), 7.35-7.33 (m, 2 H), 3.78 (s, 4 H), 1.03 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 150.7, 142.1, 134.2, 128.7, 126.5, 125.1, 124.5, 120.0, 110.5, 72.3, 31.8, 21.8 (The carbon bearing boron substituent was not observed). IR(thin film) ν_{max} 3064, 2959, 2936, 2900, 1605, 1570 cm^{-1}. MS (EI): m/z (%) 308 (M^+), 307 (M^+) (100), 221. HRMS: Calculated for $C_{18}H_{18}NO_3{}^{10}B$ (M^+): 306.1416; Found: 306.1414.



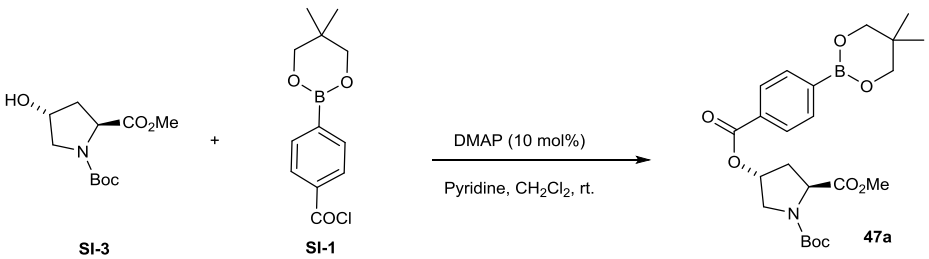
40b **40a**

1-Benzyl-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1*H*-pyrazole (40a). Xphos (114.2 mg, 0.24 mmol, 6 mol %), XPhos-Pd-G_1 (94.4 mg, 0.12 mmol, 3 mol %) and heteroaryl bromide **40b** (948 mg, 4.0 mmol, 1.0 equiv) were used. Compound **40a** (702 mg, 65% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc/Et_3N = 500 : 25 : 1) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1 H), 7.60 (s, 1 H), 7.34-7.28 (m, 3 H), 7.22-7.20 (m, 2 H), 5.30 (s, 2 H), 3.69 (s, 4 H), 0.99 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 136.3, 135.4, 128.7, 128.0, 127.8, 72.0, 55.7, 31.9, 21.9 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 3099, 2960, 2942, 2897,

1603, 1550 cm^{-1}. MS (EI): m/z (%) 270 (M^+), 269 (M^+) (100), 183. HRMS: Calculated for $C_{15}H_{18}N_2O_2{}^{10}B$ [$(M-H)^+$]: 268.1498; Found: 268.1502.

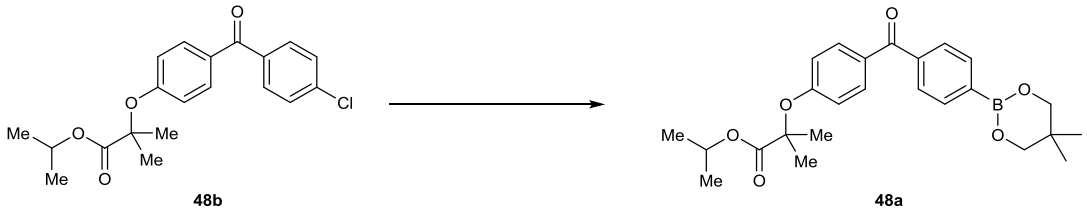


(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3] dioxol-6-yl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (45a). To a 50 mL of Schlenk tube was added **S1-2** (2.60 g, 10 mmol), **SI-1** (3.03 g, 12 mmol) and pyridine (20 mL) at room temperature under argon. After stirring for 24 h, the reaction mixture was concentrated in vacuo. The residual was diluted with ethyl acetate (200 mL) and washed with saturated brine (50 mL). The organic layer was dried with $MgSO_4$ and filtered through a pad of Celite® and concentrated. Compound **45a** (3.0 g, 63% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc =20:1) as white a solid (m.p. 104 - 106 ^oC). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2 H), 7.85 (d, *J* = 8.1 Hz, 2 H), 5.94 (d, *J* = 3.6 Hz, 1 H), 5.48 (d, *J* = 2.8 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.36-4.32 (m, 2 H), 4.12-4.04 (m, 2 H), 3.76 (s, 4 H), 1.53 (s, 3 H), 1.39 (s, 3 H), 1.30 (s, 3 H), 1.24 (s, 3 H), 1.01 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 133.8, 131.0, 128.5, 112.2, 109.3, 105.1, 83.3, 79.9, 76.6, 72.5, 72.3, 67.2, 31.8, 26.7, 26.6, 26.1, 25.1, 21.8 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 2981, 2960, 2935, 2899, 1733, 1507 cm^{-1}. MS (DART): m/z (%) 477 (M^+), 476 (M^+), 419 (100), 379. HRMS: Calculated for $C_{24}H_{34}O_9{}^{10}B$ [$(M+H)^+$]: 476.2327; Found: 476.2329.

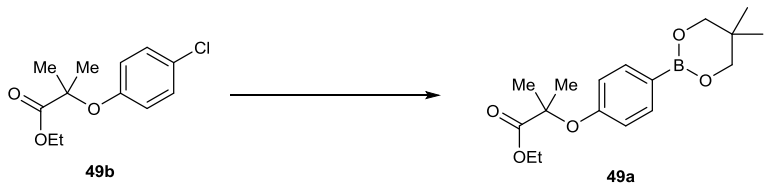


1-(*tert*-Butyl) 2-methyl (2*S*, 4*R*)-4-((4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoyl-) oxy) pyrrolidine-1,2-dicarboxylate (47a). To a 50 mL of Schlenk tube was added **S1-3** (2.21 g, 9 mmol),

SI-1 (1.51 g, 6 mmol), pyridine (1 mL, 12 mmol), DMAP (4-dimethylaminopyridine ,73 mg, 0.6 mmol) and CH_2Cl_2 (30 mL) at room temperature under argon. After stirring for 24 h, the reaction mixture was diluted with ethyl acetate (150 mL) and washed with saturated brine (50 mL), and then the organic layer was dried with $MgSO_4$ and filtered through a pad of Celite® and concentrated. Compound **47a** (2.22 g, 80% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc =20:1) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6, 80 ^{o}C): δ 7.92 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 5.46 (s, 1 H), 4.42 (t, *J* = 7.7 Hz, 1 H), 3.79 (s, 4 H), 3.76-3.68 (m, 4 H), 3.62 (d, *J* = 12.2 Hz, 1 H), 2.62-2.50 (m, 1 H), 2.39-2.24 (m, 1 H), 1.39 (s, 9 H), 0.99 (s, 6 H). ^{13}C NMR (100 MHz, DMSO-d_6, 80 ^{o}C): δ 172.0, 165.1, 152.9, 133.3, 131.0, 127.8, 79.3, 72.5, 71.4, 67.6, 57.0, 51.5, 35.2, 31.1, 27.6, 21.0. IR (thin film) ν_{max} 3489, 2964, 2886, 1751, 1705, 1478 cm^{-1}. MS (DART): m/z (%) 462 (M^+) (100), 461 (M^+). HRMS: Calculated for $C_{23}H_{33}O_8N^{10}B$ [$(M+H)^+$]: 461.2323; Found: 461.2326.

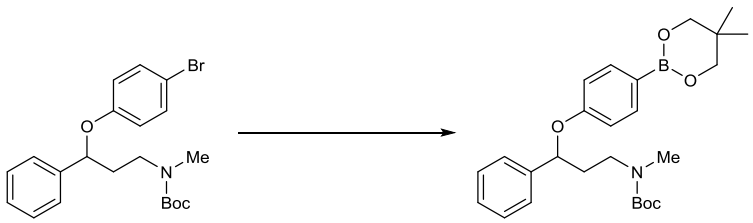


Isopropyl 2-(4-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoyl)phenoxy)-2-methyl-propanoate (48a). KOAc (15 mmol, 1.47 g, 3.0 equiv), $B_2(OH)_4$ (10 mmol, 900 mg, 2.0 equiv), Xphos (19 mg, 0.04 mmol, 0.8 mol%), XPhos-Pd-G_1 (15.8 mg, 0.02 mmol, 0.4 mol%), Fenofibrate **48b** (1.81 g, 5.0 mmol, 1.0 equiv), neopentyl glycol (10 mmol, 1.04 g, 2.0 equiv) and fresh distilled EtOH (25 mL) were used. Compound **48a** (1.87 g, 85% yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc = 40:1) as a white solid (m.p. 122-124 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 5.05 (m, 1 H), 3.75 (s, 4 H), 1.63 (s, 6 H), 1.17 (d, *J* = 6.2 Hz, 6 H), 1.00 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 173.0, 159.4, 139.7, 133.5, 132.0, 130.6, 128.5, 117.0, 79.2, 72.3, 69.2, 31.8, 25.3, 21.8, 21.4 (The carbon bearing boron substituent was not observed). IR(thin film) ν_{max} 3020, 2979, 2953, 2930, 2887, 1729, 1644, 1599 cm^{-1}. MS (DART): m/z (%) 439 (M^+) (100), 438 (M^+). HRMS: Calculated for $C_{25}H_{32}O_6{}^{10}B$ [$(M+H)^+$]: 438.2323; Found: 438.2320.



49b **49a**

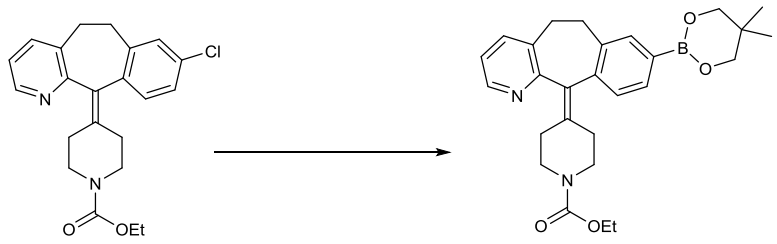
Ethyl 2-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenoxy)-2-methylpropanoate (49a). KOAc (5.89 g, 60 mmol, 2.4 equiv), $B_2(OH)_4$ (3.60 g, 40 mmol, 1.6 equiv), Xphos (95.2 mg, 0.2 mmol, 0.8 mol%), XPhos-Pd-G1 (78.7 mg, 0.1 mmol, 0.4 mol%), Clofibrate **49b** (6.08 g, 25.0 mmol, 1.0 equiv), neopentyl glycol (4.2 g, 40 mmol, 1.6 equiv) and fresh distilled EtOH (100 mL) were used. Compound **49a** (7.51 g, 94 %) was isolated by silica gel chromatography (CH_2Cl_2) as a white solid (m.p. 38-40 ^oC). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.73 (s, 4 H), 1.60 (s, 6 H), 1.21 (t, *J* = 7.1 Hz, 3 H), 1.00 (s, 6 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 157.7, 135.0, 117.4, 78.7, 72.1, 61.3, 31.8, 25.3, 21.8, 13.9 (The carbon bearing boron substituent was not observed). IR(thin film) ν_{max} 2963, 1729, 1601, 1569 cm^{-1}. MS (EI): m/z (%) 320 (M^+), 319 (M^+), 247, 206, 135, 94 (100). HRMS: Calculated for $C_{17}H_{25}O_5{}^{10}B$ (M^+): 319.1831; Found: 319.1825.



50b **50a**

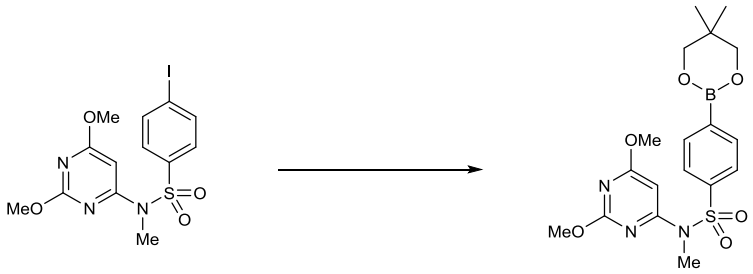
***N*-Boc-3-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenoxy)-*N*-methyl-3-phenylpropan-1-amine (50a).** KOAc (15 mmol, 1.47 g, 3.0 equiv), $B_2(OH)_4$ (10 mmol, 900 mg, 2.0 equiv), Xphos (19 mg, 0.04 mmol, 0.8 mol%), XPhos-Pd-G1 (15.8 mg, 0.02 mmol, 0.4 mol%), heteroaryl bromide **50b** (2.1 g, 5.0 mmol, 1.0 equiv), neopentyl glycol (10 mmol, 1.04 g, 2.0 equiv) and fresh distilled EtOH (40 mL) were used. Compound **50a** (2.05 g, 90 % yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc = 20:1) as a colorless oil. ^1H NMR (400 MHz, DMSO-d_6, 80 ^oC): δ 7.54 (d, *J* = 8.3 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.25 (t, *J* = 7.1 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 5.33 (dd, *J* = 7.5, 4.9 Hz, 1 H), 3.70 (s, 4 H), 3.32 (t, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 2.21 – 1.95 (m, 2 H), 1.35 (s, 9 H), 0.94 (s, 6 H). ^{13}C NMR (101 MHz, DMSO-d_6, 80 ^oC): δ 159.57, 154.47, 141.00, 134.71, 128.06, 127.10, 125.61, 114.76, 78.05, 76.64, 71.19, 44.79, 35.68, 33.61, 31.06, 27.74,

20.99. IR (thin film) ν_{max} 3372, 2964, 2358, 1709, 1602, 1509 cm^{-1}. MS (DART): m/z (%) 454 (M^+) (100), 453 (M^+), 439, 438. HRMS: Calculated for $C_{26}H_{37}O_5N^{10}B$ [$(M+H)^+$]: 453.2796; Found: 453.2793.



51b **51a**

Ethyl 4-(8-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclo-hepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (51a). KOAc (2.94 g, 30 mmol, 3.0 equiv), $B_2(OH)_4$ (1.80 g, 20 mmol, 2.0 equiv), Xphos (38 mg, 0.08 mmol, 0.8 mol%), XPhos-Pd-G1 (31.5 mg, 0.04 mmol, 0.4 mol%), Loratadine **51b** (3.83 g, 10.0 mmol, 1.0 equiv), neopentyl glycol (2.1 g, 20 mmol, 2.0 equiv) and fresh distilled EtOH (50 mL) were used. Compound **51a** (4.06 g, 88 % yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc =4:1) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.61(s, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 7.06 (dd, *J* = 7.6, 4.8 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.80 (m, 2 H), 3.74 (s, 4 H), 3.46-3.30 (m, 2 H), 3.15-3.07 (m, 2H), 2.88-2.81 (m, 2 H), 2.52-2.45 (m, 1 H), 2.36-2.29 (m, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 0.99 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 155.0, 145.8, 141.2, 137.2, 136.27, 136.24, 134.9, 134.2, 133.4, 131.2, 128.0, 121.7, 77.6, 71.8, 60.8, 44.4, 31.38, 31.33, 31.2, 30.3, 30.1, 21.3, 14.3 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 3370, 2961, 2930, 1694, 1605 cm^{-1}. MS (DART): m/z (%) 461 (M^+) (100), 460 (M^+), 406, 405. HRMS: Calculated for $C_{27}H_{34}O_4N_2{}^{10}B$ [$(M+H)^+$]: 460.2642; Found: 460.2638.

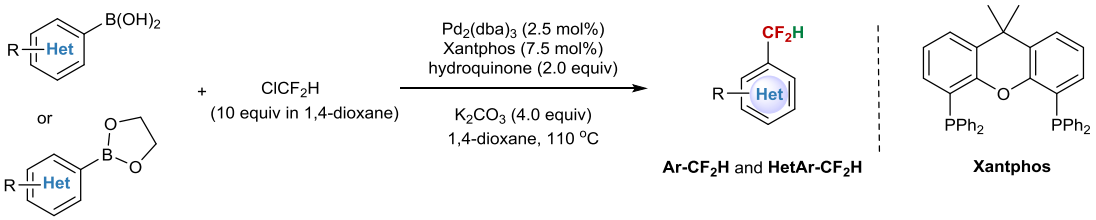


53b **53a**

***N*-(2,6-Dimethoxypyrimidin-4-yl)-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-*N*-methylbenzenesulfonamide (53a).** KOAc (486 mg, 4.95 mmol, 3.0 equiv), $B_2(OH)_4$ (300 mg, 3.3 mmol, 2.0 equiv), Xphos (47 mg, 0.099 mmol, 6 mol%), XPhos-Pd-G1 (39 mg, 0.0495 mmol, 3 mol%), heteroaryl iodide **53b** (0.72 g, 1.65 mmol, 1.0 equiv), neopentyl glycol (290 mg, 2.79 mmol, 1.69 equiv) and fresh distilled EtOH (22 mL) were used. Compound **53a** (450 mg, 65 % yield) was isolated by silica gel chromatography (CH_2Cl_2/EtOAc =15:1) as a white solid (m.p. 118-120 ^oC). ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2 H), 6.60 (s, 1 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 3.74 (s, 4 H), 3.44 (s, 3 H), 0.99 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.2, 161.2, 140.0, 134.4, 125.9, 89.7, 72.3, 54.6, 54.0, 34.4, 31.8, 21.7 (The carbon bearing boron substituent was not observed). MS (DART): m/z (%) 423 (M^+), 422 (M^+) (100), 421 (M^+). HRMS: Calculated for $C_{18}H_{25}O_6N_3{}^{10}BS$ [$(M+H)^+$]: 421.1588; Found: 421.1586.

6. General Procedures for Palladium-Catalyzed Difluoromethylation of Arylborons with $ClCF_2H$

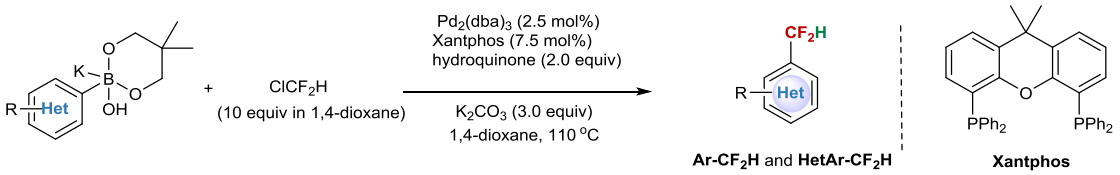
6.1 General Procedure for Palladium-Catalyzed Difluoromethylation of $ArB(OH)_2$ or Ar-Beg with $ClCF_2H$ (General Procedure A)



To a 25 mL of sealed tube were added anhydrous K_2CO_3 (powder, 4.0 equiv), hydroquinone (2.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), Xantphos (7.5 mol %) and $ArB(OH)_2$ (0.3 or 0.5 mmol) or Ar-Beg (0.3 or 0.5 mmol) under argon. A solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL for 0.3 mmol scale or 2.5 mL for 0.5 mmol scale, 10 equiv) and fresh distilled 1,4-dioxane (1.0 mL for 0.3 mmol scale or

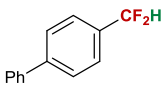
2.5 mL for 0.5 mmol scale) were added subsequently. The sealed tube was screw capped and heated to 110 °C (oil bath). After stirring for 48 h, the reaction was cooled to room temperature and fluorobenzene (1.0 equiv) was added. The yield was determined by ^{19}F NMR before working up. The reaction mixture was then diluted with ethyl acetate, filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography to provide the desired product.

6.2 General Procedure for Palladium-Catalyzed Difluoromethylation of Ar-Bneop·KOH with $ClCF_2H$ (General Procedure B)



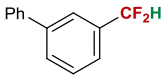
To a 25 mL of sealed tube were added KOH (1.0 equiv) and Ar-Bneop (0.3 or 0.5 mmol) at 0 °C, followed by anhydrous MeOH (2 mL) and fresh distilled 1,4-dioxane (2.0 mL). After stirring at 0 °C for 30 min, the volatile solvents were evacuated to give a solid. Anhydrous K_2CO_3 (powder, 3.0 equiv), hydroquinone (2.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), and Xantphos (7.5 mol %) were then added to the tube under argon, followed by a solution of $ClCF_2H$ in 1,4-dioxane (2.0 M, 1.5 mL for 0.3 mmol scale or 2.5 mL for 0.5 mmol scale, 10 equiv) and fresh distilled 1,4-dioxane (1.0 mL for 0.3 mmol scale or 2.5 mL for 0.5 mmol scale). The sealed tube was screw capped and heated to 110 °C (oil bath). After stirring for 48 h, the reaction was cooled to room temperature and fluorobenzene (1.0 equiv) was added. The yield was determined by ^{19}F NMR before working up. The reaction mixture was then diluted with ethyl acetate, filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography to provide the desired product.

7. Experimental Procedures and Characterization Data for Difluoromethylated Arenes 3-53

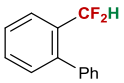


4-(Difluoromethyl)-1,1'-biphenyl (3) [known compound[10]]: The reaction was carried out according to the general procedure A or B on 0.5 mmol scale. The product **3** ($ArB(OH)_2$: 93 mg, 91% yield, ArBeg: 97 mg, 95% yield, ArBneop·KOH: 92 mg, 90% yield) as a white solid (m.p. 78-82 °C) was

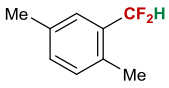
purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2 H), 7.63-7.59 (m, 4 H), 7.51-7.47 (m, 2 H), 7.43-7.39 (m, 1 H), 6.72 (t, *J* = 56.5 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.4 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7 (t, *J* = 2.0 Hz), 140.1, 133.2 (t, *J* = 22.4 Hz), 128.9, 127.9, 127.4, 127.2, 126.0 (t, *J* = 6.0 Hz), 114.7 (t, *J* = 238.5 Hz). MS (EI): *m/z* (%) 204 (M^+)(100), 183, 152, 127. HRMS: Calculated for $C_{13}H_{10}F_2$ (M^+): 204.0751; Found: 204.0754.



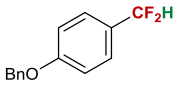
3-(Difluoromethyl)-1,1'-biphenyl (4) [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **4** (44 mg, 72% yield) as an oil was purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.73-7.71 (m, 1 H), 7.63-7.61 (m, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 752-7.46 (m, 3 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 6.72 (t, *J* = 56.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.6 (d, *J* = 56.4 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.2, 134.9 (t, *J* = 22.0 Hz), 129.5 (t, *J* = 1.9 Hz), 129.2, 128.9, 127.8, 127.2, 124.4 (t, *J* = 5.9 Hz), 124.3 (t, *J* = 5.9 Hz), 114.8 (t, *J* = 237.6 Hz). MS (EI): *m/z* (%) 204 (M^+) (100), 183, 152, 84. HRMS: Calculated for $C_{13}H_{10}F_2$ (M^+): 204.0751; Found: 204.0745.



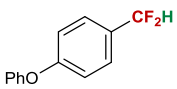
2-(Difluoromethyl)-1,1'-biphenyl (5). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **5** (31 mg, 50% yield) as an oil was purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 1 H), 7.55-7.50 (m, 2 H), 7.46-7.40 (m, 3 H), 7.37-7.36 (m, 3 H), 6.55 (t, *J* = 54.9 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.4 (d, *J* = 54.9 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (t, *J* = 6.6 Hz), 138.6, 131.7 (t, *J* = 22.2 Hz), 130.4 (t, *J* = 1.8 Hz), 130.2, 129.4, 128.4, 127.9, 127.8, 125.6 (t, *J* = 5.2 Hz), 113.1 (t, *J* = 234.6 Hz). MS (EI): *m/z* (%) 204 (M^+) (100), 183, 154, 127. HRMS: Calculated for $C_{13}H_{10}F_2$ (M^+): 204.0751; Found: 204.0757.



2-(Difluoromethyl)-1,4-dimethylbenzene (6). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **6** (24 mg, 51% yield, 78% yield determined by ^{19}F NMR) as an oil was purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 7.11 (d, *J* = 7.7 Hz, 1 H), 6.73 (t, *J* = 55.6 Hz, 1 H), 2.39 (s, 3 H), 2.35 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.9 (d, *J* = 55.6 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.0 (t, *J* = 4.5 Hz), 132.0 (t, *J* = 20.5 Hz), 131.2 (t, *J* = 1.7 Hz), 131.0, 126.3 (t, *J* = 7.3 Hz), 114.5 (t, *J* = 237.7 Hz), 20.9, 18.0. MS (EI): *m/z* (%) 156 (M^+), 141, 105 (100). HRMS: Calculated for $C_9H_{10}F_2$ (M^+): 156.0751; Found: 156.0747.

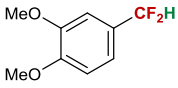


1-(Benzyloxy)-4-(difluoromethyl)benzene (7). [known compound[10]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **7** (64 mg, 91% yield) as a white solid (m.p. 78-80 ^{o}C) was purified with silica gel chromatography (Hexane/EtOAc = 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 4 H), 7.42-7.38 (m, 2 H), 7.36-7.32 (m, 1 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 6.60 (t, *J* = 56.7 Hz, 1 H), 5.10 (s, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.4 (d, *J* = 56.7 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (t, *J* = 1.4 Hz), 136.4, 128.6, 128.1, 127.4, 127.1 (t, *J* = 5.9 Hz), 127.0, 114.9, 114.8 (t, *J* = 236.0 Hz), 70.1. MS (EI): *m/z* (%) 234 (M^+), 141, 131, 91 (100). HRMS: Calculated for $C_{14}H_{12}OF_2$ (M^+): 234.0856; Found: 234.0858.

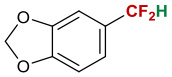


1-(Difluoromethyl)-4-phenoxybenzene (8). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **8** (55 mg, 83% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2 H), 7.38 (t, *J* = 7.9 Hz,

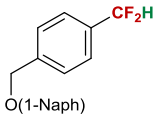
2 H), 7.17 (t, *J* = 7.4 Hz, 1 H), 7.05 (d, *J* = 8.2 Hz, 4 H), 6.63 (t, *J* = 56.6 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.0 (d, *J* = 56.6 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (t, *J* = 2.0 Hz), 156.2, 129.9, 128.9 (t, *J* = 22.6 Hz), 127.3 (t, *J* = 6.0 Hz), 124.1, 119.6, 118.3, 114.6 (t, *J* = 236.8 Hz). MS (EI): *m/z* (%) 220 (M^+)(100), 169, 141, 77. HRMS: Calculated for $C_{13}H_{10}OF_2$ (M^+): 220.0700; Found: 220.0706.



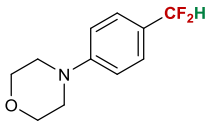
1-(Difluoromethyl)-3,4-dimethoxybenzene (9). [known compound[12]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **9** (47 mg, 82% yield) as a colorless oil was purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 - 7.02 (m, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.56 (t, *J* = 56.7 Hz, 1 H), 3.91 (s, 3 H), 3.90(s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.2 (d, *J* = 56.7 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9 (t, *J* = 2.0 Hz), 149.2, 126.9 (t, *J* = 22.7 Hz), 118.7 (t, *J* = 7.0 Hz), 114.9 (t, *J* = 237.7 Hz), 110.7, 108.0 (t, *J* = 5.3 Hz), 55.91, 55.90. MS (EI): *m/z* (%) 188 (M^+)(100), 173, 169, 145, 130, 125. HRMS: Calculated for $C_9H_{10}O_2F_2$ (M^+): 188.0649; Found: 188.0645.



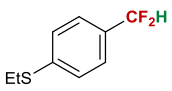
5-(Difluoromethyl)benzo[*d*][1,3]dioxole (10). [known compound[13]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **10** (34 mg, 65% yield; 82% yield determined by ^{19}F NMR) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99-6.97 (m, 2 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 6.54 (t, *J* = 56.6 Hz, 1 H), 6.01 (s, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.0 (d, *J* = 56.6 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5 (t, *J* = 1.4 Hz), 148.0, 128.3 (t, *J* = 22.6 Hz), 120.1 (t, *J* = 7.1 Hz), 114.6 (t, *J* = 238.1 Hz), 108.2, 105.8 (t, *J* = 5.4 Hz), 101.5. MS (EI): *m/z* (%) 172 (M^+), 171 (100), 153, 91, 63. HRMS: Calculated for $C_8H_6O_2F_2$ (M^+): 172.0336; Found: 172.0338.



1-((4-(Difluoromethyl)benzyl)oxy)naphthalene (11). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **11** (72 mg, 84% yield) as a white solid (m.p. 76-80 °C) was purified with silica gel chromatography (Hexane/EtOAc = 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.38 (m, 1 H), 7.87-7.85 (m, 1 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 7.58 (d, *J* = 8.2 Hz, 2 H), 7.56-7.53 (m, 2 H), 7.50 (d, *J* = 8.3 Hz, 1 H), 7.40 (t, *J* = 7.9 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.70 (t, *J* = 56.5 Hz, 1 H), 5.30 (s, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.4 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 140.0 (t, *J* = 2.0 Hz), 134.6, 133.9 (t, *J* = 22.4 Hz), 127.5, 127.4, 126.5, 125.8 (t, *J* = 6.0 Hz), 125.7 (t, *J* = 8.2 Hz), 125.3, 122.0, 120.7, 114.6 (t, *J* = 238.6 Hz), 105.2, 69.4. MS (EI): *m/z* (%) 284 (M^+), 234, 165,141 (100), 115, 91. HRMS: Calculated for $C_{18}H_{14}OF_2$ (M^+): 284.1013; Found: 284.1015.

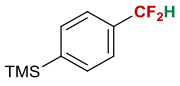


4-(4-(Difluoromethyl)phenyl)morpholine (12). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **12** (48 mg, 74% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 6.58 (t, *J* = 56.9 Hz, 1 H), 3.87 (t, *J* = 4.8 Hz, 4 H), 3.22 (t, *J* = 4.8 Hz, 4 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.2 (d, *J* = 56.9 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8 (t, *J* = 1.5 Hz), 126.7 (t, *J* = 5.9 Hz), 125.2 (t, *J* = 22.8 Hz), 115.1 (t, *J* = 236.8 Hz), 114.8, 66.7, 48.5. MS (EI): *m/z* (%) 213 (M^+), 194, 155 (100), 154, 127. HRMS: Calculated for $C_{11}H_{13}NOF_2$ (M^+): 213.0965; Found: 213.0959.

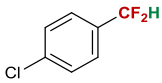


(4-(Difluoromethyl)phenyl)(ethyl)sulfane (13). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **13** (35 mg, 62% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.3 Hz,

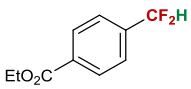
2 H), 6.61 (t, *J* = 56.6 Hz, 1 H), 2.99 (q, *J* = 7.4 Hz, 2 H), 1.35 (t, *J* = 7.4 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.2 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (t, *J* = 2.1 Hz), 131.4 (t, *J* = 22.4 Hz), 127.9, 126.0 (t, *J* = 6.0 Hz), 114.6 (t, *J* = 238.3 Hz), 26.9, 14.1. MS (EI): *m/z* (%) 188 (M^+)(100), 173, 160, 153, 127. HRMS: Calculated for $C_9H_{10}SF_2$ (M^+): 188.0471; Found: 188.0477.



(4-(Difluoromethyl)phenyl)trimethylsilane (14). [known compound[13]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **14** (50 mg, 82% yield) as a colorless oil was purified with silica gel chromatography (Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 2 H), 7.48 (d, *J* = 7.8 Hz, 2 H), 6.62 (t, *J* = 56.6 Hz, 1 H), 0.29 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.9 (d, *J* = 56.6 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.6 (t, *J* = 22.5 Hz), 133.6, 124.7 (t, *J* = 5.9 Hz), 114.8 (t, *J* = 238.6 Hz), -1.3. MS (EI): *m/z* (%) 200 (M^+), 185 (100). HRMS: Calculated for $C_{10}H_{14}SiF_2$ (M^+): 200.0833; Found: 200.0838.

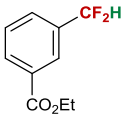


1-Chloro-4-(difluoromethyl)benzene (15). [known compound[13]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylBeg as a coupling partner. Due to the low boiling point of the product, the yield (80%) was determined by ^{19}F NMR using fluorobenzene as an internal standard. The product was characterized by ^{19}F NMR and GC-MS analysis. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.6 (d, *J* = 55.9 Hz, 2 F). GC-MS : *m/z* (%) 162.0 (M^+).

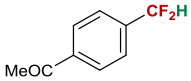


Ethyl 4-(difluoromethyl)benzoate (16). [known compound[13]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **16** (46 mg, 77% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.2 Hz, 2 H), 7.58 (d, *J* = 8.2 Hz, 2 H), 6.69 (t, *J* = 56.1 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (376

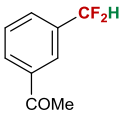
MHz, $CDCl_3$) δ -112.2 (d, *J* = 56.1 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 138.3 (t, *J* = 22.4 Hz), 132.6, 129.9, 125.6 (t, *J* = 6.1 Hz), 114.0 (t, *J* = 239.7 Hz), 61.4, 14.3. IR (thin film) ν_{max} 2983, 2930, 1767, 1723 cm^{-1}. MS (EI): *m/z* (%) 200 (M^+), 172, 155 (100), 127, 105. HRMS: Calculated for $C_{10}H_{10}O_2F_2$ (M^+): 200.0649; Found: 200.0651.



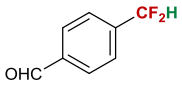
Ethyl 3-(difluoromethyl)benzoate (17). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **17** (47 mg, 78% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.18-8.15 (m, 2 H), 7.71 (d, *J* = 7.7 Hz, 1 H), 7.55 (t, *J* = 7.7 Hz, 1 H), 6.69 (t, *J* = 56.2 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2 (d, *J* = 56.2 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 134.7 (t, *J* = 22.8 Hz), 131.7 (t, *J* = 1.7 Hz), 131.1, 129.7 (t, *J* = 5.7 Hz), 128.9, 126.9 (t, *J* = 6.3 Hz), 114.2 (t, *J* = 239.4 Hz), 61.4, 14.3. IR (thin film) ν_{max} 2983, 1766, 1615 cm^{-1}. MS (EI): *m/z* (%) 200 (M^+), 172, 155 (100), 127, 107. HRMS: Calculated for $C_{10}H_{10}O_2F_2$ (M^+): 200.0649; Found: 200.0648.



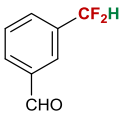
1-(4-(Difluoromethyl)phenyl)ethanone (18) [known compound[14]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **18** (24 mg, 46% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 6.68 (t, *J* = 56.1 Hz, 1 H), 2.62 (s, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.7 (d, *J* = 56.1 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 138.8, 138.5 (t, *J* = 22.1 Hz), 128.6, 125.9 (t, *J* = 6.0 Hz), 113.9 (t, *J* = 238.2 Hz), 26.8. IR (thin film) ν_{max} 3064, 2967, 1767, 1689 cm^{-1}. MS (EI): *m/z* (%) 170 (M^+), 155 (100). HRMS: Calculated for $C_9H_8OF_2$ (M^+): 170.0543; Found: 170.0542.



1-(3-(Difluoromethyl)phenyl)ethanone (19). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **19** (28 mg, 55% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.7 Hz, 1 H), 6.68 (t, *J* = 56.2 Hz, 1 H), 2.63 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.3 (d, *J* = 56.2 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 137.5, 134.9 (t, *J* = 22.7 Hz), 130.5, 129.9 (t, *J* = 5.8 Hz), 129.2, 125.5 (t, *J* = 6.2 Hz), 114.1 (t, *J* = 239.5 Hz), 26.7. MS (EI): *m/z* (%) 170 (M^+), 149, 155 (100), 127, 110. IR (thin film) ν_{max} 3062, 2968, 1760, 1690 cm^{-1}. HRMS: Calculated for $C_9H_8OF_2$ (M^+): 170.0543; Found:170.0539.

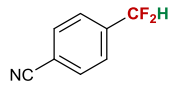


4-(Difluoromethyl)benzaldehyde (20). [known compound[14]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **20** (26 mg, 55% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.96 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 6.71 (t, *J* = 56.0 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.6 (d, *J* = 56.0 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 139.7 (t, *J* = 22.4 Hz), 137.9 (t, *J* = 1.8 Hz), 129.9, 126.3 (t, *J* = 6.1 Hz), 113.8 (t, *J* = 240.1 Hz). MS (EI): *m/z* (%) 156 (M^+), 156 (100). IR (thin film) ν_{max} 3064, 2967, 1767, 1689 cm^{-1}. HRMS: Calculated for $C_8H_6OF_2$ (M^+): 156.0387; Found: 156.0384.

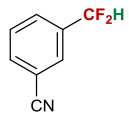


3-(Difluoromethyl)benzaldehyde (21). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **21** (24 mg, 50% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 8.02 (s, 1 H), 8.0 (d, *J* = 7.6 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 6.72 (t, *J* = 56.1 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.7

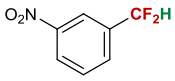
(d, *J* = 56.1 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 136.6, 135.5 (t, *J* = 23.1 Hz), 131.8 (t, *J* = 1.4 Hz), 131.3 (t, *J* = 5.7 Hz), 129.6, 126.8 (t, *J* = 6.2 Hz), 113.8 (t, *J* = 239.8 Hz). MS (EI): *m/z* (%) 156 (M^+), 155 (100). IR (thin film) ν_{max} 3064, 2967, 1767, 1689 cm^{-1}. HRMS: Calculated for $C_8H_6OF_2$ (M^+): 156.0387; Found: 156.0390.



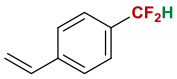
4-(Difluoromethyl)benzonitrile (22). [known compound[15]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **22** (28 mg, 60% yield) as a colorless oil was purified with silica gel chromatography (Hexane /EtOAc = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 6.69 (t, *J* = 55.8 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2 (d, *J* = 55.8 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (t, *J* = 22.9 Hz), 132.6, 126.4 (t, *J* = 6.1 Hz), 117.9, 114.8 (t, *J* = 2.0 Hz), 113.3 (t, *J* = 240.7 Hz). IR (thin film) ν_{max} 3433, 2961, 2874, 2232, 1727 cm^{-1}. MS (EI): *m/z* (%) 153 (M^+), 152 (100), 134, 103. HRMS: Calculated for $C_8H_5NF_2$ (M^+): 153.0390; Found: 153.0389.



3-(Difluoromethyl)benzonitrile (23). [known compound[15]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **23** (39 mg, 85% yield) as a colorless oil was purified with silica gel chromatography (Hexane /EtOAc = 20:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.78 (dd, *J* = 12.5 Hz, 7.9 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 6.69 (t, *J* = 55.9 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.48 (d, *J* = 55.9 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7 (t, *J* = 23.6 Hz), 134.2, 129.9 (t, *J* = 5.8 Hz), 129.7, 129.3 (t, *J* = 6.4 Hz), 117.8, 113.2, 113.1 (t, *J* = 240.6 Hz). IR (thin film) ν_{max} 3433, 2961, 2874, 2232, 1727 cm^{-1}. MS (EI): *m/z* (%) 153 (M^+), 152 (100), 103. HRMS: Calculated for $C_8H_5NF_2$ (M^+): 153.0390; Found: 153.0389.



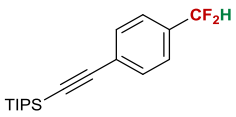
1-(Difluoromethyl)-3-nitrobenzene (24). [known compound[16]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with Ar-Beg as a coupling partner. The product **24** (32 mg, 60% yield) as a light yellow oil was purified with silica gel chromatography (Hexane /CH_2Cl_2 = 10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 8.36 (d, *J* = 8.3 Hz, 1 H), 7.87 (d, J = 7.7 Hz, 1 H), 7.69 (t, J = 8.0 Hz, 1 H), 6.75 (t, *J* = 55.9 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.2 (d, *J* = 55.9 Hz, 2 F). ^{13}C NMR (126 MHz, $CDCl_3$) δ148.3, 136.1 (t, *J* = 23.6 Hz), 131.5 (t, *J* = 5.7 Hz), 130.1, 125.6, 121.0 (t, *J* = 6.5 Hz), 113.1 (t, *J* = 240.8 Hz).



1-(Difluoromethyl)-4-vinylbenzene (25). The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **25** (25 mg, 54% yield; 70% yield determined by ^{19}F NMR) as a colorless oil was purified with silica gel chromatography (n-pentane).

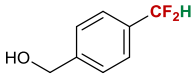
Proceduce for the working up: the reaction mixture was deluted with 5 mL of brine and extracted with 2 mL of n-pentane twice. The combined organic layers were washed with brine for three times (4 mL x 3) and directly subjected to a flash chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 4H), 6.64 (t, *J* = 56.5 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.35 (d, *J* = 10.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.5 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0 (t, *J* = 2.1 Hz), 136.0, 133.6 (t, *J* = 22.4 Hz), 126.4, 125.8 (t, *J* = 6.1 Hz), 115.6, 114.6 (t, *J* = 238.4 Hz). IR (thin film) ν_{max} 3154, 3093, 2926, 2854, 2253, 1632 cm^{-1}. MS (EI): *m/z* (%) 154 (M^+, 100), 127, 104. HRMS: Calculated for $C_9H_8F_2$ (M^+): 154.0594; Found: 154.0591.

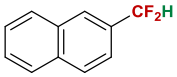


(4-(Difluoromethyl)phenyl)ethynyl)triisopropylsilane (26). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **26a** as a coupling partner. The product **26** (125 mg, 81% yield; 95% yield determined by ^{19}F NMR) as a colorless oil was purified with silica gel chromatography (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4

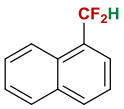
Hz, 2 H), 6.64 (t, *J* = 56.4 Hz, 1 H), 1.17 (s, 18 H), 1.15-1.14 (m, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2 (d, *J* = 56.4 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0 (t, *J* = 22.5 Hz), 132.3, 126.1 (t, *J* = 2.1 Hz), 125.4 (t, *J* = 6.1 Hz), 114.3 (t, *J* = 239.1 Hz), 106.0, 92.7, 18.6, 11.3. IR (thin film) ν_{max} 2944, 2892, 2866, 2158, 1614, 1463. cm^{-1}. MS (EI): *m/z* (%) 308 (M^+), 266, 237, 223, 209, 195 (100), 179. HRMS: Calculated for $C_{18}H_{26}F_2Si$ (M^+): 308.1772; Found: 308.1775.



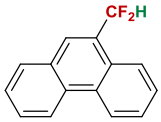
4-(Difluoromethyl)phenyl)methanol (27). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **27** (41 mg, 85% yield) as a colorless oil was purified with silica gel chromatography (Hexane/CH_2Cl_2 = 3:1 to 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 6.65 (t, *J* = 56.5 Hz, 1 H), 4.75 (s, 2 H), 1.80 (s, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.34 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 133.6 (t, *J* = 22.5 Hz), 127.0, 125.8 (t, *J* = 6.1 Hz), 114.6 (t, *J* = 238.5 Hz), 64.7. IR (thin film) ν_{max} 3676, 3649, 3567, 3062, 2962, 2847, 1706, 1618 cm^{-1}. MS (EI): *m/z* (%) 158 (M^+), 127 (100), 107, 77.



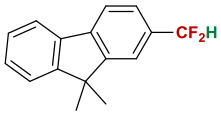
2-(Difluoromethyl)naphthalene (28). [known compound[13]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **28** (48 mg, 90% yield) was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.96-7.89 (m, 3 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.59-7.57 (m, 2 H), 6.83 (t, *J* = 56.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.8 (d, *J* = 56.4 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 134.3 (t, *J* = 1.4 Hz), 132.6, 131.6 (t, *J* = 22.4 Hz), 128.9, 128.5, 127.9, 127.4, 126.8, 125.9 (t, *J* = 7.5 Hz), 122.0 (t, *J* = 4.8 Hz), 115.1 (t, *J* = 238.5 Hz). MS (EI): *m/z* (%) 178 (M^+) (100), 177, 159, 155, 128. HRMS Calculated for for $C_{11}H_8F_2$ (M^+): 178.0594; Found: 178.0598.



1-(Difluoromethyl)naphthalene (29). [known compound[14]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **29** (51 mg, 95% yield) was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 7.94-7.90 (m, 1 H), 7.70 (m, 1 H), 7.65-7.55 (m, 2 H), 7.51 (t, *J* = 7.7 Hz, 1 H), 7.15 (t, *J* = 55.2 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.9 (d, *J* = 55.2 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 131.5 (t, *J* = 1.6 Hz), 129.7 (t, *J* = 2.8 Hz), 129.5 (t, *J* = 20.6 Hz), 128.8, 127.2, 126.4, 124.8 (t, *J* =8.6 Hz), 124.7, 123.6, 115.4 (t, *J* = 238.4 Hz). MS (EI): *m/z* (%) 178 (M^+), 115, 87 (100). HRMS: Calculated for $C_{11}H_8F_2$ (M^+): 178.0594; Found: 178.0597.

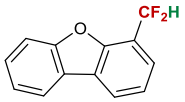


9-(Difluoromethyl)phenanthrene (30). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **30** (64 mg, 93% yield) a white solid (m.p. 116-118 ^{o}C) was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1 H), 8.64 (d, *J* = 8.4 Hz, 1 H), 8.20-8.18 (m, 1 H), 7.93 (s, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.72-7.58 (m, 4 H), 7.12 (t, *J* = 55.2 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.7 (d, *J* = 55.2 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 130.9, 130.2, 129.5, 128.3, 128.0 (t, *J* = 20.5 Hz), 127.9 (t, *J* = 1.8 Hz), 127.2, 127.15, 127.13, 126.8 (t, *J* = 9.4 Hz), 124.5 (t, *J* = 1.6 Hz), 123.3, 122.7, 115.7 (t, *J* = 237.1 Hz). MS (EI): *m/z* (%) 228 (M^+) (100), 207, 178, 152, 89. HRMS: Calculated for $C_{15}H_{10}F_2$ (M^+): 228.0751; Found: 228.0752.

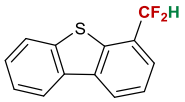


2-(Difluoromethyl)-9,9-dimethyl-9*H*-fluorene (31). The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **31** (68 mg, 92% yield) as a white solid (m.p. 60-62 ^{o}C) was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2 H), 7.61 (s, 1 H), 7.50-7.46 (m, 2 H), 7.39-

7.37 (m, 2 H), 6.73 (t, J = 56.7 Hz, 1 H), 1.52 (s, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.0 (d, J = 56.7 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.09, 154.08, 141.8 (t, J = 2.0 Hz), 138.2, 133.2 (t, J = 22.0 Hz), 128.1, 127.2, 124.8 (t, J = 6.3 Hz), 122.8, 120.6, 120.1, 119.9 (t, J = 5.9 Hz), 115.3 (t, J = 238.4 Hz), 47.1, 27.0. IR(thin film) ν_{max} 3018, 3064, 2963, 2862, 1918, 1618 cm^{-1}. MS (EI): *m/z* (%) 244 (M^+), 229 (100), 209, 193, 178, 152. HRMS: Calculated for $C_{16}H_{14}F_2$ (M^+): 244.1064; Found: 244.1071.

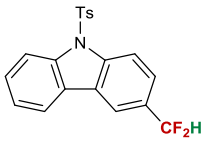


4-(Difluoromethyl)dibenzo[*b,d*]furan (32). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **32** (47 mg, 71% yield) as a colorless oil was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (ddt, J = 7.6 Hz, J = 1.2 Hz, J = 1.2 Hz, 1 H), 7.97 (ddt, J = 7.6 Hz, J = 1.2 Hz, J = 1.2 Hz, 1 H), 7.67 (dd, J = 7.6 Hz, 1.0 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.51 (td, J = 7.6, 1.2 Hz, 1 H), 7.44-7.37 (m, 2 H), 7.23 (t, J = 55.2 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1 (d, J = 55.2 Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 127.8, 125.1, 123.7 (t, J = 5.7 Hz), 123.4, 123.2, 123.1 (t, J = 1.6 Hz), 122.7, 120.8, 118.5 (t, J = 23.8 Hz), 111.9, 111.8 (t, J = 237.4 Hz). MS (EI): *m/z* (%) 218 (M^+), 218 (100), 199, 168, 139. HRMS: Calculated for $C_{13}H_8OF_2$ (M^+): 218.0543; Found: 218.0546.

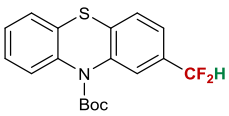


4-(Difluoromethyl)dibenzo[*b,d*]thiophene (33). [known compound[11]]: The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **33** (52 mg, 73% yield) as a colorless oil was purified with silica gel chromatography (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.9 Hz, 1 H), 8.19-8.17 (m, 1 H), 7.90-7.88 (m, 1 H), 7.62 (d, J = 7.4 Hz, 1 H), 7.55-7.48 (m, 3 H), 6.94 (t, J = 55.6 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.3 (d, J = 55.6 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 139.5 (t, J = 1.0 Hz), 136.9, 136.6 (t, J = 3.3 Hz), 134.6, 128.5 (t, J = 22.8 Hz), 127.3, 124.7, 124.4, 124.3 (t, J = 7.0 Hz), 123.7 (t,

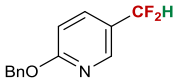
J = 1.8 Hz), 122.6, 121.6, 114.4 (t, *J* = 239.4 Hz). MS (EI): m/z (%) 234 (M+), 215,184 (100), 170, 139. HRMS: Calculated for $C_{13}H_8SF_2$ (M^+): 234.0315; Found: 234.0310.



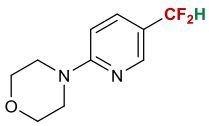
3-(Difluoromethyl)-9-tosyl-9*H*-carbazole (34). The reaction was carried out according to the general procedure A on 0.3 mmol scale or the general procedure B on 0.5 mmol scale. The product **34** ($ArB(OH)_2$: 80 mg, 72% yield; Ar-Bneop: 167 mg, 90% yield) as a off-white solid (m.p. 128-130 ^oC) was purified with silica gel chromatography (Hexane/CH_2Cl_2 = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.80 (t, *J* = 56.6 Hz, 1H), 2.25 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.8 (d, *J* = 56.6 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 145.2, 139.5, 138.7, 134.7, 130.0 (t, *J* = 22.7 Hz), 129.7, 128.0, 126.4, 125.6, 124.6 (t, *J* = 5.9 Hz), 124.1, 120.2, 117.5 (t, *J* = 6.3 Hz), 115.2, 115.0, 114.8 (t, *J* = 238.8 Hz), 21.4. MS (EI): *m/z* (%) 371 (M^+), 352, 216 (100), 197, 155, 91. HRMS: Calculated for $C_{20}H_{15}NO_2SF_2$ (M^+): 371.0792; Found: 371.0791.



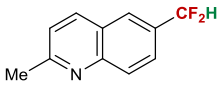
***N*-Boc-2-(difluoromethyl)-10*H*-phenothiazine (35).** The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop as a coupling partner. The product **35** (149 mg, 85% yield) as a off-white solid (m.p. 86-88 ^oC) was purified with silica gel chromatography (Hexane/ CH_2Cl_2 = 2:1). ^1H NMR (400 MHz, DMSO-d_6, 80 ^oC): δ 7.75 (s, 1 H), 7.57 (dd, *J* = 8.0, 2.8 Hz, 2 H), 7.43 (t, *J* = 5.9 Hz, 2 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 7.02 (t, *J* = 55.8 Hz, 1 H), 1.45 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.5 (d, *J* = 56.4 Hz, 2 F). ^{13}C NMR (101 MHz, DMSO-d_6, 80 ^oC) δ 151.1, 138.3, 137.7, 134.2, 132.7 (t, *J* = 22.6 Hz), 130.2, 127.5, 127.02, 126.99, 126.8, 126.2, 124.2 (t, *J* = 6.4 H), 123.2 (t, *J* = 5.9 Hz), 114.0 (t, *J* = 235.4 Hz) , 81.8, 27.4. IR (thin film) ν_{max} 3064, 2980, 2930, 1709, 1607 cm^{-1}. MS (EI): *m/z* (%) 349 (M^+), 293, 250, 243, 199, 57 (100). HRMS: Calculated for $C_{18}H_{17}NO_2SF_2$ (M^+): 349.0948; Found: 349.0943.



2-(Benzyloxy)-5-(difluoromethyl)pyridine (36). The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **36** (63 mg, 89% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1 to 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.75 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.49-7.47 (m, 2 H), 7.43-7.34 (m, 3 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 6.65 (t, *J* = 56.0 Hz, 1 H), 5.44 (s, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (d, *J* = 56.0 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.1, 145.1 (t, *J* = 7.4 Hz), 136.7, 135.9 (t, *J* = 4.5 Hz), 128.5, 128.00, 127.99, 123.6 (t, *J* = 23.3 Hz), 113.7 (t, *J* = 237.6 Hz), 111.4, 68.0. IR (thin film) ν_{max} 3068, 3034, 2957, 2888, 2850, 1615, 1578 cm^{-1}. MS (EI): *m/z* (%) 235 (M^+), 129, 91 (100). HRMS: Calculated for $C_{13}H_{11}NOF_2$ (M^+): 235.0809; Found: 235.0804.

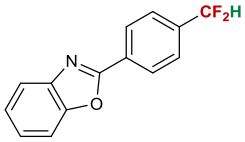


4-(5-(Difluoromethyl)pyridin-2-yl)morpholine (37). The reaction was carried out according to the general procedure A on 0.3 mmol scale with arylboronic acid as a coupling partner. The product **37** (39 mg, 60% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1 to 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 6.66 (d, *J* = 8.8 Hz, 1 H), 6.58 (t, *J* = 56.3 Hz, 1 H), 3.82-3.80 (m, 4 H), 3.59-3.57 (m ,4 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.7 (d, *J* = 56.3 Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 146.0, 134.9 (t, *J* = 4.4 Hz), 119.6 (t, *J* = 23.4 Hz), 114.2 (t, *J* = 236.6 Hz), 106.3, 66.6, 45.2. MS (EI): *m/z* (%) 214 (M^+), 183, 129 (100). IR (thin film) ν_{max} 2996, 2968, 2899, 1614 cm^{-1}. HRMS: Calculated for $C_{10}H_{12}N_2OF_2$ (M^+): 214.0918; Found: 214.0916.

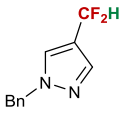


6-(Difluoromethyl)-2-methylquinoline (38). The reaction was carried out according to the general procedure A on 0.3 mmol scale with lithium triisopropyl arylborate salt (HetArB(O*i*Pr)$_3$Li) as a coupling partner. HetArB(O*i*Pr)$_3$Li was prepared according to the literature[17]. The product **38** (29 mg, 50% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.5 Hz, 5.6 Hz, 2 H), 7.90 (d, *J* = 1.1 Hz, 1 H), 7.77 (dd, *J* = 8.8 Hz, 1.5 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 6.79 (t, *J* = 56.3 Hz, 1 H), 2.75 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.3 (d, *J* = 56.3 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 160.7, 148.6, 136.6, 131.5 (t, *J* = 22.5 Hz), 129.6, 125.74 (t, *J* = 4.9 Hz), 125.7, 125.4 (t, *J* = 7.3 Hz), 122.9, 114.5 (t, *J* = 238.9 Hz), 25.4. IR (thin film) ν_{max} 2998, 2360, 1631, 1603 cm^{-1}. MS (EI): *m/z* (%) 193 (M^+)(100), 178, 143. HRMS: Calculated for $C_{11}H_9NF_2$ (M^+): 193.0703; Found: 193.0698.

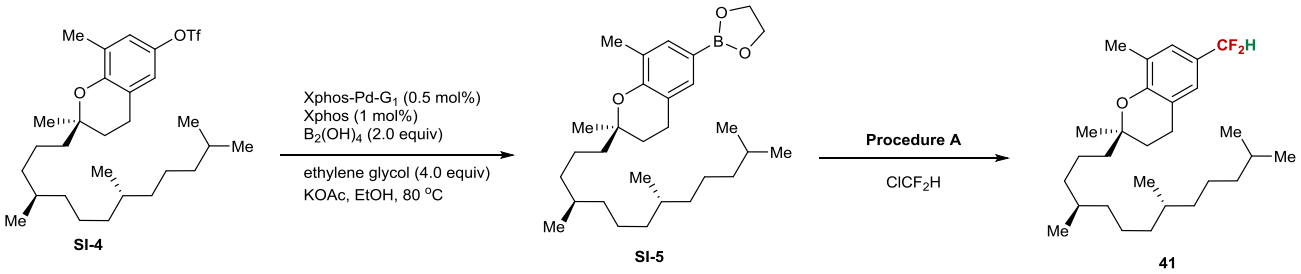


2-(4-(Difluoromethyl)phenyl)benzo[*d*]oxazole (39). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **39a** as a coupling partner. The product **39** (80 mg, 65% yield) as a white solid (m.p. 119-121 ^oC) was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.5 Hz, 2 H), 7.81-7.79 (m, 1 H), 7.68 (d, *J* = 8.2 Hz, 2 H), 7.62-7.60 (m, 1 H), 7.41 -7.37 (m, 2 H), 6.73 (t, *J* = 56.2 Hz, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.3 (d, *J* = 56.2 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 150.8, 142.0, 137.0, 129.4 (t, *J* = 2.0 Hz), 127.9, 126.2 (t, *J* = 6.1 Hz), 125.6, 124.8, 120.3, 114.1 (t, *J* = 239.6 Hz), 110.7. IR (thin film) ν_{max} 3051, 2925, 1711, 1654, 1606 cm^{-1}. MS (EI): *m/z* (%) 245 (M^+) (100), 217, 195, 127, 92, 63. HRMS: Calculated for $C_{14}H_9NOF_2$ (M^+): 245.0652; Found: 245.0658.



1-Benzyl-4-(difluoromethyl)-1*H*-pyrazole (40). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **40a** as a coupling partner. The product **40** (61 mg, 58% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 7.54 (s, 1 H), 7.39-7.34 (m, 3 H), 7.25-7.23 (m, 2 H), 6.68 (t, *J* = 56.8 Hz, 1 H), 5.31 (s, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.4 (d, *J* = 56.8 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2 (t, *J* = 4.6 Hz), 135.5, 129.0, 128.4, 128.0 (t, *J* = 5.7 Hz), 127.9, 117.5 (t, *J* = 26.9 Hz), 110.9 (t, *J* = 233.9 Hz), 56.4. IR (thin film) ν_{max} 3091, 3032, 2960, 1733, 1652,

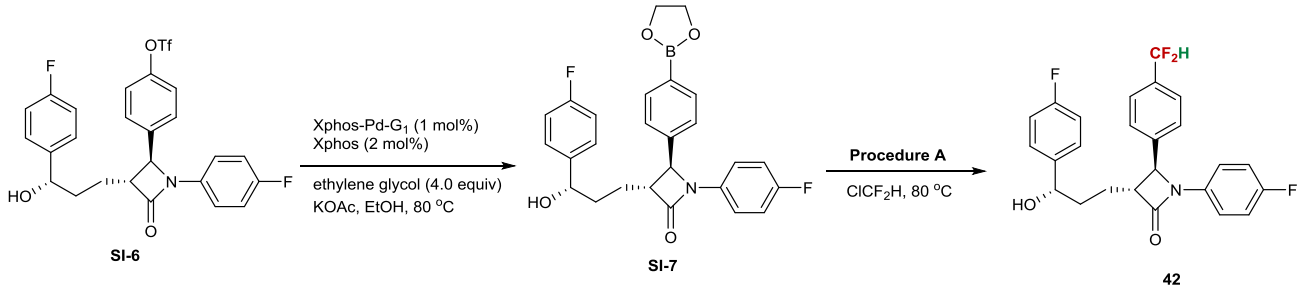
1574 cm^{-1}. MS (EI): *m/z* (%) 208 (M^+), 207, 187, 131, 91(100), 65. HRMS: Calculated for $C_{11}H_{10}N_2F_2$ (M^+): 208.0812; Found: 208.0804.



(*R*)-6-(Difluoromethyl)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (41). The reaction was carried out according to the general procedure A on 0.5 mmol scale with Ar-Beg **SI-5** as a coupling partner, which was prepared from **SI-4**[18] according to the literature[9] without purification and directly used for the difluoromethylation. The product **41** (201 mg, 92% yield 2 steps from **SI-4**) as a colorless oil was purified with silica gel chromatography (Hexane).

Procedure for the preparation of Ar-Beg SI-5: To a 20 mL of Schlenk tube were added anhydrous KOAc (1.5 mmol, 147.5 mg, 3.0 equiv), $B_2(OH)_4$ (1 mmol, 90 mg, 2.0 equiv), Xphos (1 mol%), XPhos Pd-G_1 (0.5 mol%), and **SI-4** (0.5 mmol, 267.4 mg, 1.0 equiv) under argon, followed by ethylene glycol (2 mmol, 124 mg, 4.0 equiv) and fresh distilled EtOH (5 mL). The resulting mixture was then heated to 80 ^oC and stirred for 4 h. The reaction was cooled to room temperature and concentrated. The residue was diluted with dichloromethane (20 mL) and washed with saturated brine. The organic layer was filtered through a pad of $MgSO_4$ and concentrated to give **SI-5** (Ar-Beg), which was directly used without further purification.

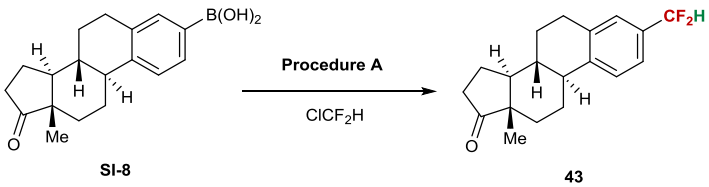
Data for compound **41**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1 H), 7.06 (s, 1 H), 6.53 (t, *J* = 57.0 Hz, 1 H), 2.78 (t , *J* = 6.4 Hz, 2 H), 2.19 (s, 3 H), 1.81(ddd, *J* = 20.7, 13.7, 7.0 Hz, 2 H), 1.61-1.04 (m, 25 H), 0.89-0.85(m, 12 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.3 (d, *J* = 57.0 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (t, *J* = 1.8 Hz), 126.8, 125.4 (t, *J* = 5.7 Hz), 124.7 (t, *J* = 45.0 Hz), 124.4 (t, *J* = 6.1 Hz), 120.5, 115.4 (t, *J* = 236.8 Hz), 76.7, 40.1, 39.4, 37.44, 37.40, 37.38, 37.28, 32.8, 32.7, 30.9, 28.0, 24.8, 24.4, 24.2, 22.7, 22.6, 22.2, 20.9, 19.7, 19.6, 16.1. IR (thin film) ν_{max} 2927, 2867, 1484, 1381 cm^{-1}. MS (EI): *m/z* (%) 436 (M^+), 211 (100), 171. HRMS: Calculated for $C_{28}H_{46}OF_2$ (M^+): 436.3517; Found: 436.3519.



(3*R*,4*S*)-4-(4-(Difluoromethyl)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one (42). [known compound[11]]. The reaction was carried out according to the general procedure A on 0.5 mmol scale with Ar-Beg **SI-7** as a coupling partner at 80 °C for 60 h. Compound **SI-7** was prepared according to the procedure for the preparation of Ar-Beg **SI-5** from **SI-6**[18] without purification and directly used for the difluoromethylation. The product **42** (164 mg, 74% yield 2 steps from **SI-6**) as a white solid (m.p. 144-146 °C) was purified with silica gel chromatography (Hexane/ EtOAc = 4:1).

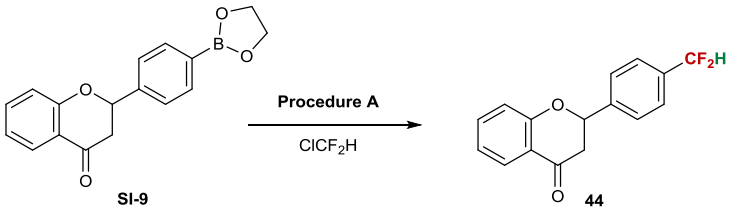
Preparation of SI-7: KOAc (1.5 mmol, 147.5 mg, 3.0 equiv), $B_2(OH)_4$ (1 mmol, 90 mg, 2.0 equiv), Xphos (2 mol%), XPhos Pd-G_1 (1 mol%), **SI-6** (0.5 mmol, 270.8 mg, 1.0 equiv) and ethylene glycol (2 mmol, 124 mg, 4.0 equiv) were used.

Data for compound **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.29 (m, 2 H), 7.23-7.19 (m, 2 H), 7.02 (t, *J* = 8.6 Hz, 2 H), 6.94 (t, *J* = 8.6 Hz, 2 H), 6.64 (t, *J* = 56.4 Hz, 1 H), 4.72 (m, 1 H), 4.68 (d, *J* = 2.4 Hz, 1 H), 3.08 (td, *J* = 6.8 Hz, 2.4 Hz, 1 H), 2.16 (d, *J* = 3.2 Hz, 1 H), 2.06-1.87 (m, 4 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.0 (d, *J* = 56.4 Hz, 2F), -114.7 (m,1F), -117.7 (m,1F). ^{13}C NMR (100 MHz, CDCl3) δ 167.0, 162.2 (d, *J* = 245.8 Hz), 159.1 (d, *J* = 243.8 Hz), 140.4 (t, *J* = 2.0 Hz), 139.9 (d, *J* = 3.1 Hz), 134.8 (t, *J* = 22.7 Hz), 133.6 (d, *J* = 2.8 Hz), 127.4 (d, *J* = 8.1 Hz), 126.6 (t, *J* = 6.0 Hz), 126.2, 118.3 (d, *J* = 7.9 Hz), 116.0 (d, *J* = 22.7 Hz), 115.4 (d, *J* = 21.4 Hz), 114.2 (t, *J* = 239.1 Hz), 73.2, 60.9, 60.5, 36.6, 25.1.

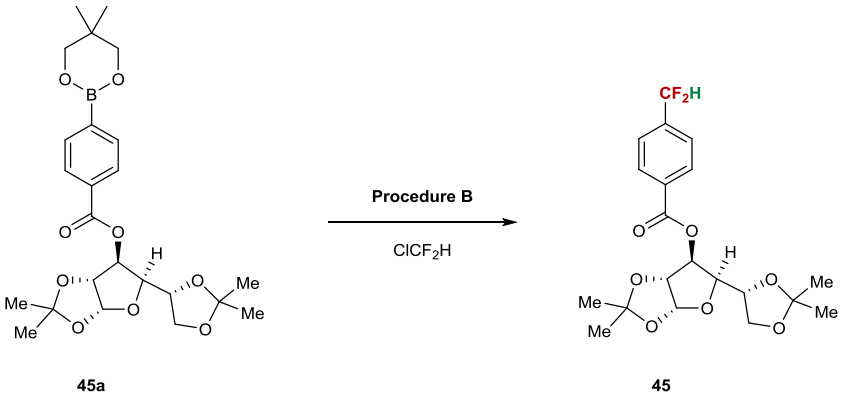


(8*R*,9*S*,13*S*,14*S*)-3-(Difluoromethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (43). [known compound[11]]. The reaction was carried out

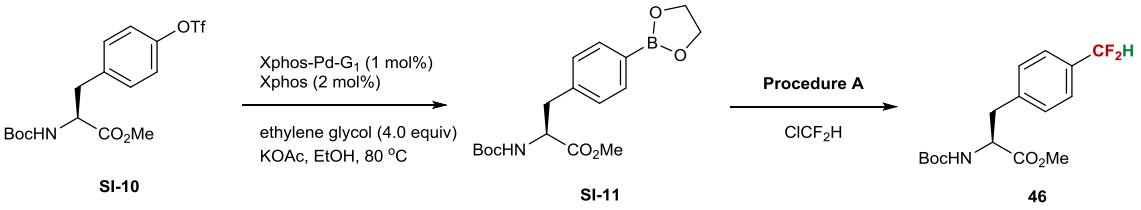
according to the general procedure A on 0.3 mmol scale with arylboronic acid **SI-8** as a coupling partner, which was prepared according to the literature[19]. The product **43** (64 mg, 70% yield) as a white solid (m.p. 59-62 ºC) was purified with silica gel chromatography (Hexane/ EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.24 (s, 1 H), 6.58 (t, *J* = 56.6 Hz, 1 H), 2.97-2.94 (m, 2 H), 2.51 (q, *J* = 8.8 Hz, 1 H), 2.47-2.42 (m, 1 H), 2.32 (t, *J* = 10.0 Hz, 1 H), 2.19-2.12 (m, 1 H), 2.10-2.03 (m, 2 H), 1.99-1.96 (m, 1 H), 1.67-1.42 (m, 6 H), 0.91 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.0 (dd, *J* = 56.6 Hz, *J* = 5.4 Hz, 2 F). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 220.5, 142.5 (t, *J* = 1.9 Hz), 137.0, 131.8 (t, *J* = 22.5 Hz), 126.0 (t, *J* = 5.9 Hz), 125.6, 122.7 (t, *J* = 6.0 Hz), 114.8 (t, *J* = 238.1 Hz), 50.4, 47.8, 44.3, 37.8, 35.7, 31.4, 29.2, 26.2, 25.5, 21.5, 13.7.



2-(4-(Difluoromethyl)phenyl)chroman-4-one (44). [known compound[11]]. The reaction was carried out according to the general procedure A on 0.5 mmol scale with Ar-Beg **SI-9** as a coupling partner, which was prepared from its corresponding arylboronic acid[20]. The product **44** (69 mg, 50% yield) as a white solid (m.p. 61-63 ºC) was purified with silica gel chromatography (Hexane/ EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.4 Hz, 1.5 Hz, 1 H), 7.59 (s, 4 H), 7.52 (td, *J* = 8.4 Hz, J = 1.6 Hz, 1 H), 7.09 (m, 2 H), 6.68 (t, *J* = 56.4 Hz, 1 H), 5.54 (dd, *J* = 13.1 Hz, 3.1 Hz, 1 H), 3.06 (dd, *J* = 16.9 Hz, 13.1 Hz, 1 H), 2.90 (dd, *J* = 16.9 Hz, 3.1 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.9 (d, J = 56.4 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 161.3, 141.5 (t, *J* = 1.8 Hz), 136.3, 134.7 (t, *J* = 22.4 Hz), 127.1, 126.4, 126.1 (t, *J* = 6.0 Hz), 121.9, 120.9, 118.0, 114.4 (t, *J* = 239.0 Hz), 78.9, 44.6. IR (thin film) ν_{max} 3353, 2923, 2853, 1683, 1601, 1465 cm^{-1}. MS (EI): *m/z* (%) 274 (M^+), 257, 147, 120 (100), 92. HRMS: Calculated for $C_{16}H_{12}O_2F_2$ (M^+): 274.0805; Found: 274.0794.



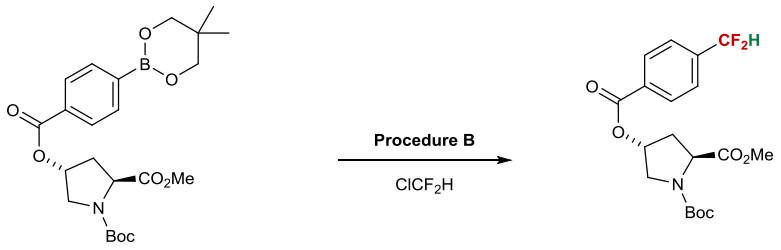
(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl 4-(difluoromethyl)benzoate (45). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **45a** as a coupling partner. The product **45** (186 mg, 90% yield) as a colorless oil was purified with silica gel chromatography (Hexane/ EtOAc = 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.1 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 6.69 (t, *J* = 56.0 Hz, 1 H), 5.95 (d, *J* = 3.7 Hz, 1 H), 5.51 (d, *J* = 2.6 Hz, 1 H), 4.64 (d, *J* = 3.7 Hz, 1 H), 4.33 (m, 2 H), 4.10 (ddd, *J* = 13.1 Hz, 8.6 Hz, 5.0 Hz, 2 H), 1.56 (s, 3 H), 1.41 (s, 3 H), 1.32 (s, 3 H), 1.26 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (d, *J* = 56.0 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 138.9 (t, *J* = 22.5 Hz), 131.7, 130.0, 125.8 (t, *J* = 6.0 Hz), 113.8 (t, *J* = 239.9 Hz), 112.4, 109.4, 105.1, 83.3, 79.9, 76.95, 72.5, 67.3, 26.8, 26.7, 26.1, 25.1. IR (thin film) ν_{max} 2989, 2938, 2898, 1730, 1714, 1457 cm^{-1}. MS (EI): m/z (%) 399 [$(M-CH_3)^+$], 341, 281, 255, 155 (100), 127, 101. HRMS: Calculated for $C_{19}H_{21}O_7F_2$ [$(M-CH_3)^+$]: 399.1255; Found: 399.1256.



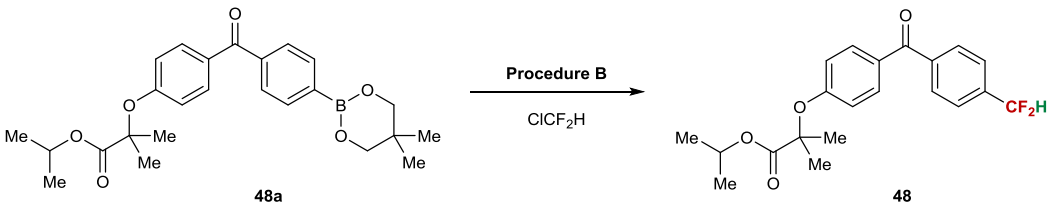
Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate (46). [known compound[11]]. The reaction was carried out according to the general procedure A on 0.5 mmol scale with Ar-Beg **SI-11** as a coupling partner. Compound **SI-11** was prepared according to the procedure for the preparation of Ar-Beg **SI-5** from **SI-10** without purification and directly used for the difluoromethylation. The product **46** (116 mg, 70% yield 2 steps from **SI-10**) as a white solid (m.p. 70-73 °C) was purified with silica gel chromatography (Hexane/ EtOAc = 4:1).

Preparation of SI-11: KOAc (1.5 mmol, 147.5 mg, 3.0 equiv), $B_2(OH)_4$ (1 mmol, 90 mg, 2.0 equiv), Xphos (2 mol%), XPhos Pd-G_1 (1 mol%), **SI-10** (0.5 mmol, 213.7 mg, 1.0 equiv) and ethylene glycol (2 mmol, 124 mg, 4.0 equiv) were used.

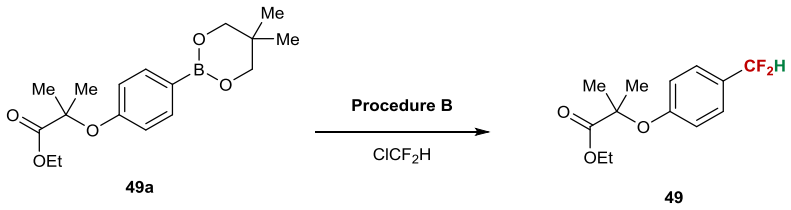
Data for compound **46**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.9 Hz, 2 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 6.60 (t, *J* = 56.5 Hz, 1 H), 5.03 (d, *J* = 7.5 Hz, 1 H), 4.60 (dd, *J* = 13.0 Hz, 6.1 Hz, 1 H), 3.70 (s, 3 H), 3.17 (dd, *J* = 13.7 Hz, 5.5 Hz, 1 H), 3.06 (dd, *J* = 13.6, 6.1 Hz, 1 H), 1.40 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.5 (d, J = 56.5 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 154.9, 139.0 (t, *J* = 2.0 Hz), 133.0 (t, *J* = 22.0 Hz), 129.6, 125.7 (t, *J* = 5.9 Hz), 114.6 (t, *J* = 238.5 Hz), 80.0, 54.2, 52.2, 38.1, 28.2.



1-(*tert*-Butyl) 2-methyl (2*S*, 4*R*)-4-((4-(difluoromethyl)benzoyl)oxy)pyrrolidine-1,2-dicarboxylate (47). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **47a** as a coupling partner. The product **47** (120 mg, 60% yield) as a colorless oil was purified with silica gel chromatography (Hexane/EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) rotameric mixture: δ 8.09 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 6.69 (t, *J* = 56.1 Hz, 1 H), 5.55-5.52 (m, 1 H), 4.53 and 4.43 (t, *J* = 8.0 Hz, 1 H, rotamer), 3.88-3.84 (m, 2 H), 3.77 and 3.76 (s, 3 H, rotamer), 2.58-2.50 (m, 1 H), 2.37-2.30 (m, 1 H), 1.45 and 1.43 (s, 9H, rotamer). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (d, J = 56.1 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis: δ 173.0 (172.7), 165.05 (165.01), 154.2 (153.6), 138.9 (138.8), 131.8 (131.7), 130.0, 125.73 (125.70) (t, *J* = 5.9 Hz), 113.8 (t, *J* = 239.8 Hz), 86.7, 73.7 (73.0), 57.9 (57.6), 52.4 (54.3), 52.2 (52.0), 36.7 (35.6), 28.3 (28.2). IR (thin film) ν_{max} 2978, 2931, 1751, 1701, 1583 cm^{-1}. MS (EI): m/z (%) 326 [$(M-OC_4H_9)^+$], 155, 127(100). HRMS: Calculated for $C_{15}H_{14}NO_5F_2$ [$(M-OC_4H_9)^+$]: 326.0840; Found: 326.0827.

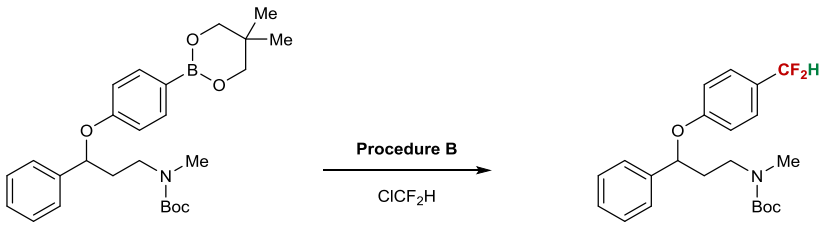


Isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate (48). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **48a** as a coupling partner. The product **48** (151 mg, 80% yield) as a colorless oil was purified with silica gel chromatography (Hexane/ EtOAc = 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 2 H), 7.75 (d, J = 9.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 6.72 (t, *J* = 56.2 Hz, 1 H), 5.09 (hept, *J* = 6.2 Hz, 1 H), 1.66 (s, 6 H), 1.20 (d, *J* = 6.3 Hz, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.9 (d, *J* = 56.2 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 173.1, 159.9, 140.3, 137.3 (t, *J* = 22.5 Hz), 132.1, 130.0, 129.9, 125.5 (t, *J* = 6.0 Hz), 117.2, 114.1 (t, *J* = 239.6 Hz), 79.4, 69.3, 25.3, 21.5. IR (thin film) ν_{max} 2983, 2925, 1730, 1654 cm^{-1}. MS (EI): *m/z* (%) 376 (M^+), 289 (100), 248, 121. HRMS: Calculated for $C_{21}H_{22}O_4F_2$: 376.1486; Found: 376.1472.



Ethyl 2-(4-(difluoromethyl)phenoxy)-2-methylpropanoate (49). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **49a** as a coupling partner. The product **49** (117 mg, 90% yield) as a colorless oil was purified with silica gel chromatography (Hexane/ EtOAc = 8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.2 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 6.58 (t, *J* = 56.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2 H), 1.62 (s, 6 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.9 (d, *J* = 56.7 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 157.4 (t, *J* = 1.9 Hz), 127.7 (t, *J* = 22.7 Hz), 126.7 (t, *J* = 6.0 Hz), 118.3, 114.7 (t, *J* = 237.7 Hz), 79.2, 61.6, 25.3, 14.0. IR(thin film) ν_{max} 2990, 2942, 1735, 1615 cm^{-1}. MS (EI): *m/z* (%) 258 (M^+), 185 (100), 144, 115. HRMS: Calculated for $C_{13}H_{16}O_3F_2$: 258.1068; Found: 258.1069.

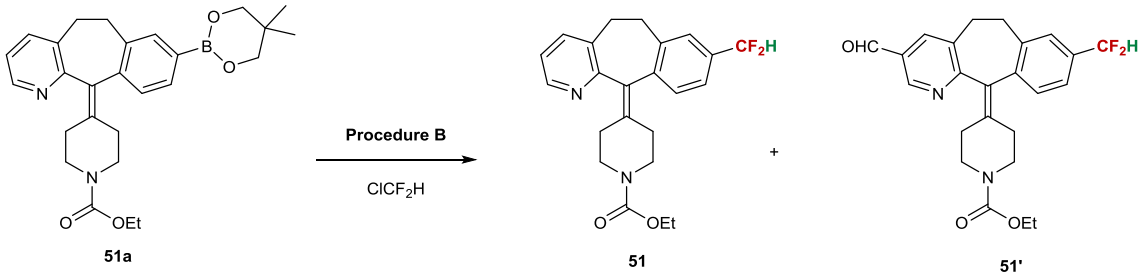
Gram-Scale Synthesis of Ethyl 2-(4-(difluoromethyl)phenoxy)-2-methylpropanoate (49). To a 100 mL of sealed tube were added KOH (336 mg, 6 mmol, 1.0 equiv) and Ar-Bneop (1.92 g, 6 mmol, 1.0 equiv) at 0 °C, followed by anhydrous MeOH (24 mL) and fresh distilled 1,4-dioxane (12 mL). After stirring at 0 °C for 30 min, the volatile solvents were evacuated to give a solid. Anhydrous K_2CO_3 (powder, 2.48 g, 18 mmol, 3.0 equiv), hydroquinone (1.32 g, 12 mmol, 2.0 equiv), $Pd_2(dba)_3$ (82.4 mg, 0.09 mmol, 1.5 mol %), and Xantphos (156.2 mg, 0.045 mmol, 4.5 mol %) were then added to the tube under argon, followed by a solution of $ClCF_2H$ in 1,4-dioxane (30 mL, 2.0 M, 10 equiv) and fresh distilled 1,4-dioxane (20 mL). The sealed tube was screw capped and heated to 110 °C (oil bath). After stirring for 48 h, the reaction was cooled to room temperature and fluorobenzene (1.0 equiv) was added. The yield was determined by ^{19}F NMR before working up. The reaction mixture was then diluted with ethyl acetate (250 mL), and washed with saturated brine (50 mL) for three times, and then the organic layer was dried with $MgSO_4$ and concentrated. The product **49** (1.12 g, 72% yield) as a colorless oil was purified with silica gel chromatography (CH_2Cl_2).



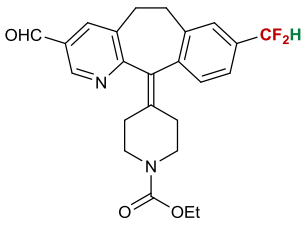
50a 50

***tert*-Butyl (3-(4-(difluoromethyl)phenoxy)-3-phenylpropyl)(methyl)carbamate (50).** The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **50a** as a coupling partner. The product **50** (180 mg, 92% yield) as a colorless oil was purified with silica gel chromatography (Hexane/ EtOAc = 8:1). ^1H NMR (400 MHz, $CDCl_3$) rotameric mixture: δ 7.33-7.30 (m, 5 H), 7.29-7.24 and 7.19-7.15 (m, 1 H, rotamer), 6.87 and 6.82 (d, *J* = 8.0 Hz, 2 H, rotamer), 6.52 (t, *J* = 56.8 Hz, 1 H), 5.16-5.14 and 5.11-5.10 (m , 1 H, rotamer), 3.46 and 3.36 (br, 2 H, rotamer), 2.85 (s, 3H), 2.16 (br, 1 H), 2.12-2.04 (m ,1 H), 1.38 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.4 (d, *J* = 56.8 Hz, 2 F). ^{13}C NMR (125 MHz, $CDCl_3$) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis: δ 159.7, 155.7, 141.0, 129.2, 128.7 (128.6), 127.7 (127.5), 126.9 (t, *J* = 5.9 Hz), 125.6, (120.7) 115.7, 114.7 (t, *J* = 237.4 Hz), 79.3 (78.2), 67.0, (45.8) 45.7, 37.2 (36.7), 34.4,

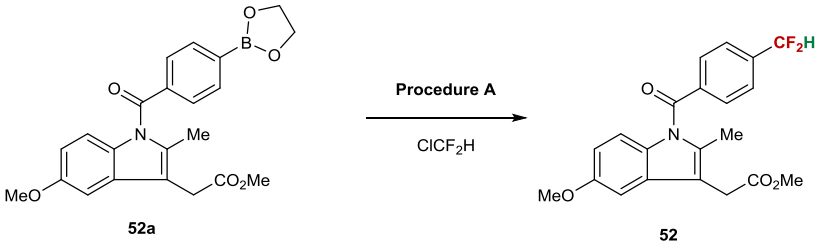
28.3. IR (thin film) ν_{max} 2976, 1694, 1615, 1589 cm^{-1}. MS (EI): *m/z* (%) 391 (M^+), 318, 248, 214, 192, 144, 88 (100). HRMS: Calculated for $C_{22}H_{27}NO_3F_2$: 391.1959; Found: 391.1956.



Ethyl 4-(8-(difluoromethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piper-idine-1-carboxylate (51). The reaction was carried out according to the general procedure B on 0.5 mmol scale with Ar-Bneop **51a** as a coupling partner. After the reaction, a mixture of **51** and **51′** were provided. To the mixture of **51** and **51′** was added MeOH (10 ml), followed by $NaBH_4$ (9.5 mg, 0.25 mmol) at 0 °C. After the reaction was stirred for 1 h, the reaction was quenched with H_2O (1 mL) at same reaction temperature. The resulting mixture was then concentrated. The residue was purified with silica gel chromatography (Hexane/ EtOAc = 4:1 to 2:1) to give product **51** (96 mg, 48% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 3.6 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 14.1 Hz, 2 H), 7.27 (d, *J* = 9.0 Hz, 1 H), 7.10 (dd, *J* = 7.7 Hz, 4.8 Hz, 1 H), 6.58 (t, *J* = 56.5 Hz, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 3.81 (br, 2 H), 3.49-3.34 (m, 2 H), 3.18-3.11 (m, 2 H), 2.91-2.83 (m, 2 H), 2.51-2.44 (m, 1 H), 2.37-2.30 (m, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.3 (d, *J* = 56.5 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 155.5, 146.6, 141.8, 138.3, 137.7, 134.4, 133.41, 133.36 (t, *J* = 22.3 Hz), 129.6, 126.1 (t, *J* = 5.8 Hz), 123.3 (t, *J* = 6.1 Hz), 122.3, 114.6 (t, *J* = 238.6 Hz), 61.3, 44.8, 44.7, 31.7, 31.5, 30.7, 30.5, 14.6. IR (thin film) ν_{max} 2979, 2865, 1697, 1436 cm^{-1}. MS (EI): *m/z* (%) 398 (M^+) (100), 282. HRMS: Calculated for $C_{23}H_{24}N_2O_2F_2$: 398.1806; Found: 398.1812.

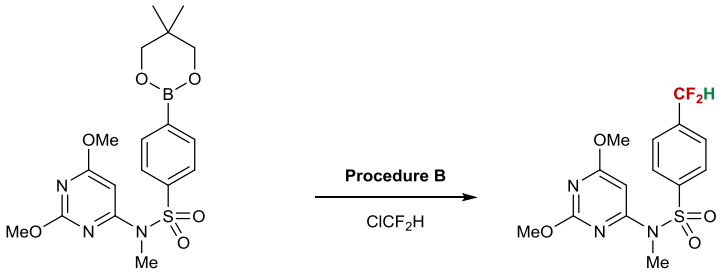


Ethyl 4-(8-(difluoromethyl)-3-formyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(6*H*)-ylidene)pipe-ridine-1-carboxylate (51′). The analytical pure **51′** was purified from the mixture of **51** and **51′** through the reverse phase semi-preparative HPLC (MeCN/H_2O = 50:50 (v/v, containing 0.1% trifluoroacetic acid); Column: Kaseisorb LC ODS 2000 (10.0 mm × 250mm, 5 μm); Flow rate of the Mobile phase: 4.0 mL/min; Wavelength: 220 nm; Temperature: 25 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1 H), 8.86 (d, *J* = 1.8 Hz, 1 H), 7.94 (d, *J* = 1.8 Hz, 1 H), 7.33 (d, *J* = 11.2 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 6.59 (t, J = 56.8 Hz, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.81 (br, 2 H), 3.52 -3.41 (m, 2 H), 3.21-3.17 (m, 2 H), 3.03 -2.87 (m, 2 H), 2.55-2.48 (m, 1 H), 2.45 -2.27 (m, 3 H), 1.25 (t, J = 7.1 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.6 (d, *J* = 56.8 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 162.4, 155.4, 149.3, 140.7, 139.4, 138.1, 137.0, 134.4, 133.9 (t, *J* = 22.4 Hz), 130.3, 129.8, 126.3 (t, *J* = 5.9 Hz), 123.6 (t, *J* = 6.3 Hz), 114.4 (t, *J* = 238.8 Hz), 61.4, 44.73, 44.66, 31.50, 31.48, 30.8, 30.7, 14.7. IR (thin film) ν_{max} 3502, 2979, 2914, 2857, 1697, 1616, 1434 cm^{-1}. MS (EI): *m/z* (%) 426 (M^+) (100), 398, 336, 324, 310, 296, 273. HRMS: Calculated for $C_{24}H_{24}N_2O_3F_2$: 426.1755; Found: 426.1759.



Methyl 2-(1-(4-(difluoromethyl)benzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (52). The reaction was carried out according to the general procedure A on 0.5 mmol scale with Ar-Beg **52a** as a coupling partner, which was prepared from its corresponding arylboronic acid[21]. The product **52** (88 mg, 45% yield) as a yellow oil was purified with silica gel chromatography (Hexane/ EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 2.5 Hz, 1 H), 6.86 (d, *J* = 9.0 Hz, 1 H), 6.74 (t, *J* = 56.0 Hz, 1 H), 6.66 (dd, *J* = 9.0 Hz, 2.5 Hz, 1 H), 3.84 (s,

3 H), 3.71 (s, 3 H), 3.67 (s, 2 H), 2.37 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.3 (d, *J* = 56.0 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.4, 156.1, 138.2 (t, *J* = 22.6 Hz), 137.9 (t, *J* = 1.6 Hz), 135.9, 130.7, 129.9, 126.0 (t, *J* = 6.0 Hz), 115.1, 113.8 (t, *J* = 240.1 Hz), 112.8, 111.6, 110.9, 101.3, 55.7, 52.2, 30.1, 13.5. IR(thin film) ν_{max} 3374, 2954, 2836, 1736, 1683 cm^{-1}. MS (EI): *m/z* (%) 387(M^+), 328, 233, 174 (100). HRMS: Calculated for $C_{21}H_{19}NO_4F_2$: 387.1282; Found: 387.1288.

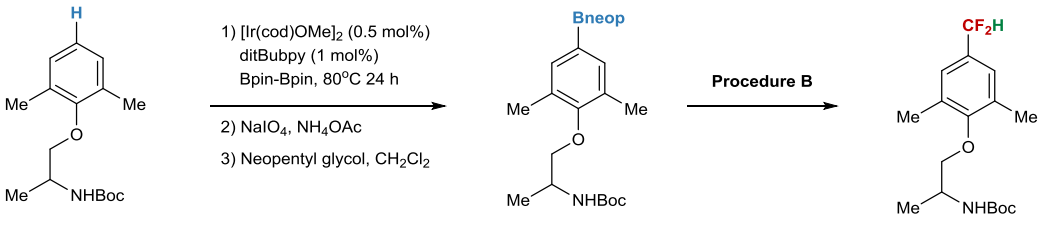


53a 53

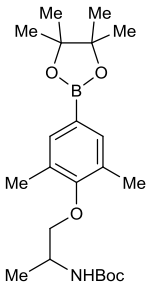
4-(Difluoromethyl)-*N*-(2,6-dimethoxypyrimidin-4-yl)-*N*-methylbenzenesulfonamide (53). The reaction was carried out according to the general procedure B on 0.3 mmol scale with Ar-Bneop **53a** as a coupling partner. The product **53** (78 mg, 72% yield) as a colorless oil was purified with silica gel chromatography (Hexane/ EtOAc = 4:1 to 2:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 2 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 6.68 (t, *J* = 55.9 Hz, 1 H), 6.61 (s, 1 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.46 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.7 (d, *J* = 55.9 Hz, 2 F).^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 164.3, 161.2, 140.9 (t, *J* = 2.1 Hz), 139.0 (t, *J* = 22.9 Hz), 127.6, 126.5 (t, *J* = 6.0 Hz), 113.3 (t, *J* = 240.7 Hz), 90.2, 54.8, 54.2, 34.6. IR (thin film) ν_{max} 3125, 3020, 1588 cm^{-1}. MS (EI): *m/z* (%) 360.1 (M^+, 100). HRMS: Calculated for $C_{14}H_{16}N_3O_4F_2S$: 360.0824; Found: 360.0820.

8. Experimental Procedures and Characterization Data for Compounds 54 and 55

8.1 Experimental Procedures and Characterization Data for Selective C-H Bond Borylation and Difluoromethylation.

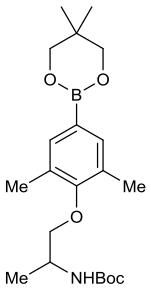


Mexiletine 54a 54



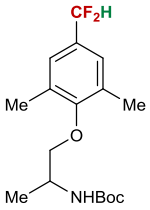
SI-12

***tert*-Butyl (1-(2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)- propan-2-yl)carbamate (SI-12).** According to the literature[22], to a 25 mL of stirred Schlenk tube were added *N*-Boc-Mexiletine (559 mg, 2 mmol), Bpin-Bpin (315 mg, 1.24 mmol), $[Ir(COD)OMe]_2$ (6.63 mg, 0.01 mmol), 4,4'-Bis(*t*-butyl)-2,2'-bipyridine (5.36 mg, 0.02 mmol) and fresh distilled THF (10 mL) under argon. The tube was screw capped and heated to 80 ºC (oil bath). After stirring for 24 h, the reaction was cooled to room temperature. The reaction mixture was then diluted with ethyl acetate (100 mL), filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography (CH_2Cl_2/ EtOAc = 10:1) to give aryl boronate ester **SI-12** (535 mg, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 2H), 4.88 (br, 1H), 3.99 (br, 1H), 3.79 (br, 1H), 3.69 (dd, *J* = 9.0, 3.5 Hz, 1H), 2.26 (s, 6H), 1.46 (s, 9 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.33 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 155.3, 135.7, 130.3, 83.7, 79.3, 74.0, 46.7, 28.4, 24.8, 17.9, 16.0 (The carbon bearing boron substituent was not observed). IR (thin film) ν_{max} 2976, 1715 cm^{-1}. MS (EI): *m/z* (%) 405.3 (M^+), 406.3 (100). HRMS: Calculated for $C_{22}H_{37}NO_5B$: 405.2796; Found: 405.2791.



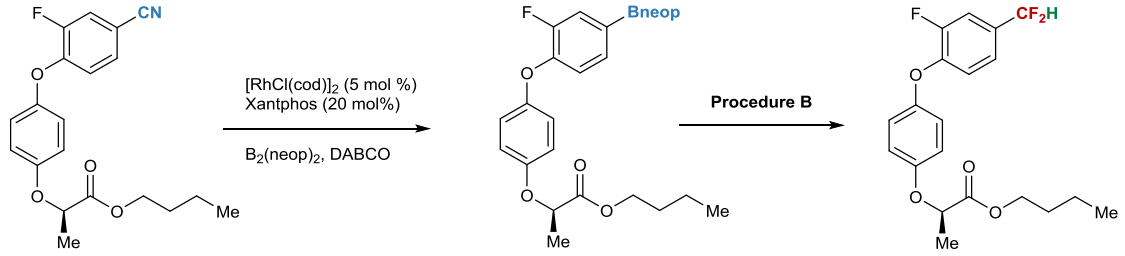
***tert*-Butyl (1-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2,6-dimethylphenoxy)propan -2-yl)carbamate (54a).** To a 25 mL of Schlenk tube were added **SI-12** (365 mg, 0.90 mmol), NH_4OAc (416 mg, 5.4 mmol), $NaIO_4$ (1.16 g, 5.4 mmol), acetone (10 mL) and H_2O (5 mL) under argon. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with saturated brine (20 mL) for three times. The organic layer was

dried with $MgSO_4$ and concentrated. The residue was dissolved in dichloromethane (20 mL), and neopentyl glycol (1.8 mmol, 188 mg, 2.0 equiv) was added. After the resulting mixture was tirred at room temperature for 8 h, the reaction mixture was then diluted with ethyl acetate, filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography (CH_2Cl_2/ EtOAc = 10:1) to give Ar-Bneop **54a** (321 mg, 91% yield 2 steps from **SI-12**) as a white solid (m.p. 157-159 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 2 H), 4.92 (br, 1 H), 3.99 (br, 1 H), 3.78 (br, 1 H), 3.75 (s, 4 H), 3.69 (dd, *J* = 9.0 Hz, 3.5 Hz, 1H), 2.26 (s, 6 H), 1.46 (s, 9 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.01 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 155.3, 134.8, 129.9, 79.2, 74.0, 72.2, 46.7, 31.8, 28.4, 21.8, 17.8, 16.0. IR (thin film) ν_{max} 3407, 2959, 1722 cm^{-1}. MS (EI): *m/z* (%) 391.3(M^+), 392.3 (100). HRMS: Calculated for $C_{21}H_{35}NO_5B$: 381.2639; Found: 391.2639.

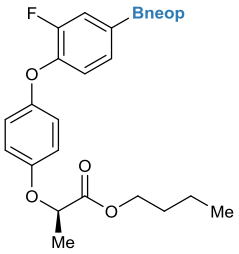


***tert*-Butyl (1-(4-(difluoromethyl)-2,6-dimethylphenoxy)propan-2-yl)carbamate (54).** The reaction was carried out according to the general procedure B on 0.5 mmol scale. The product **54** (125 mg, 76% yield) as white solid (m.p. 80-82 °C) was purified with silica gel chromatography (Hexane/ EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2 H), 6.53 (t, *J* = 56.7 Hz, 1 H), 4.84 (br, 1 H), 4.00 (br, 1 H), 3.79 (br, 1 H), 3.70 (dd, *J* = 9.0 Hz, 3.5 Hz, 1 H), 2.29 (s, 6 H), 1.46 (s, 9 H), 1.38 (d, *J* = 6.8 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.2 (d, *J* = 56.7 Hz, 2 F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (t, *J* = 2.2 Hz), 155.3, 131.5, 129.8 (t, *J* = 22.2 Hz), 126.2 (t, *J* = 5.9 Hz), 114.7 (t, *J* = 238.0 Hz), 79.4, 74.2, 46.6, 28.4, 17.8, 16.2. IR(thin film) ν_{max} 3451, 3354, 2977, 2929, 1705, 1500 cm^{-1}. MS (EI): *m/z* (%) 329 (M^+), 273, 236, 172, 102 (100). HRMS: Calculated for $C_{17}H_{25}NO_3F_2$: 329.1803; Found: 329.1796.

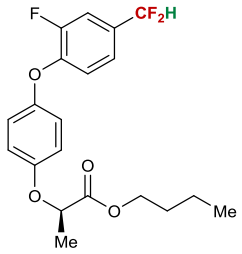
8.2 Experimental Procedures and Characterization Data for Sequential C-CN Bond Borylation and Difluoromethylation.



55a 55



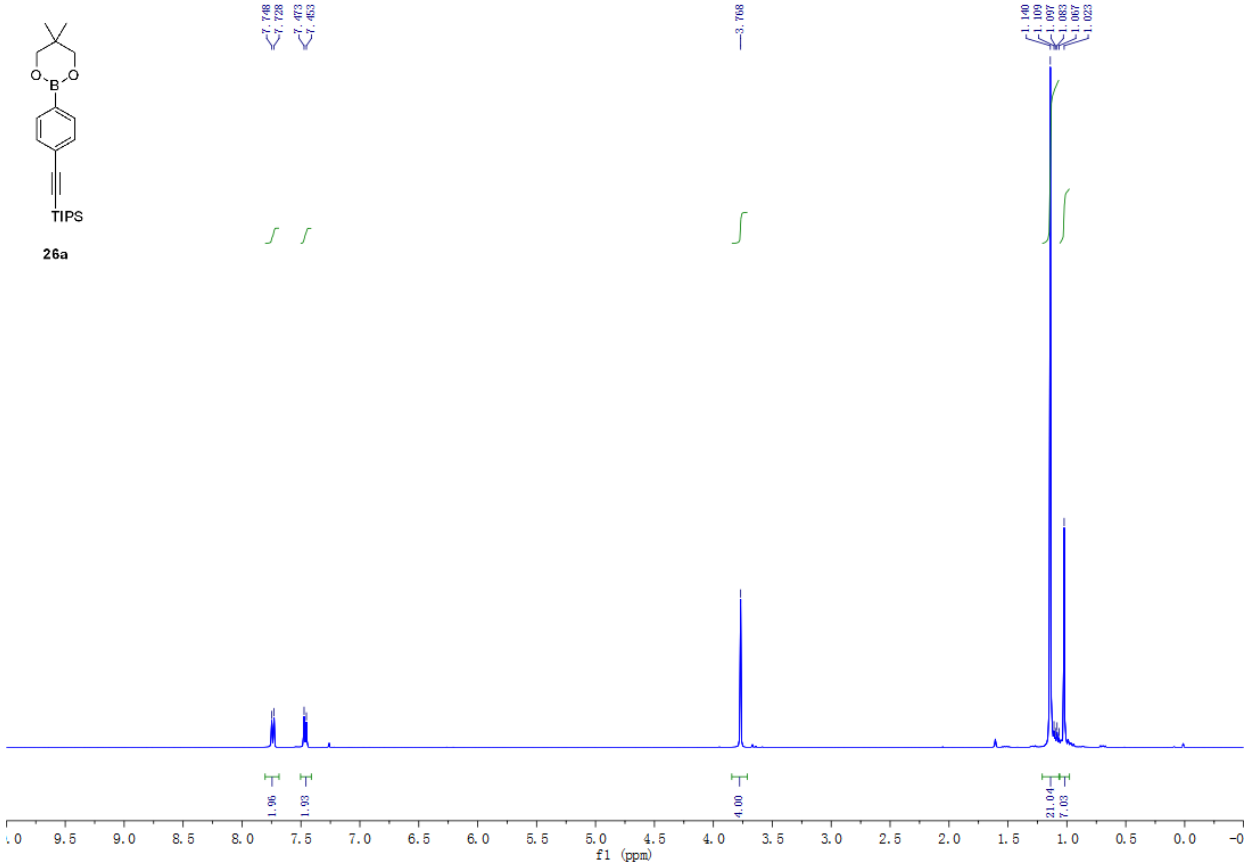
Butyl (*R*)-2-(4-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluorophenoxy)phenoxy)-propanoate (55a). [known compound[23]].According to the literature[23], to an oven-dried 25 mL of stirred sealed tube were added cyhalofop-butyl (1.0 g, 2.8 mmol), bis(neopentylglycolato)diboron (1.9 g, 8.4 mmol), $[RhCl(cod)]_2$ (69 mg, 0.14 mmol), Xantphos (324 mg, 0.56 mmol), DABCO (1,4-diazabicyclooctane, 628 mg, 5.6 mmol), and fresh distilled toluene (5.6 mL) under argon. The tube was screw capped and heated to 100 ºC (oil bath). After stirring for 96 h at 100 ºC, the reaction mixture was cooled to room temperature. The reaction mixture was then diluted with ethyl acetate (100 mL), filtered through a pad of Celite® and concentrated. The residue was purified with silica gel chromatography (Hexane/ EtOAc = 6:1 to 3:1) to give **55a** (1.02 g, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 11.5 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 6.96-6.83 (m, 5 H), 4.70 (q, *J* = 6.7 Hz, 1H), 4.22-4.09 (m, 2 H), 3.75 (s, 4 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.62-1.57 (m, 2 H), 1.34-1.27 (m, 2 H), 1.01 (s, 6 H), 0.89 (t, *J* = 7.4 Hz, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -134.79 (dd, *J* = 11.0, 8.3 Hz, 1 F).

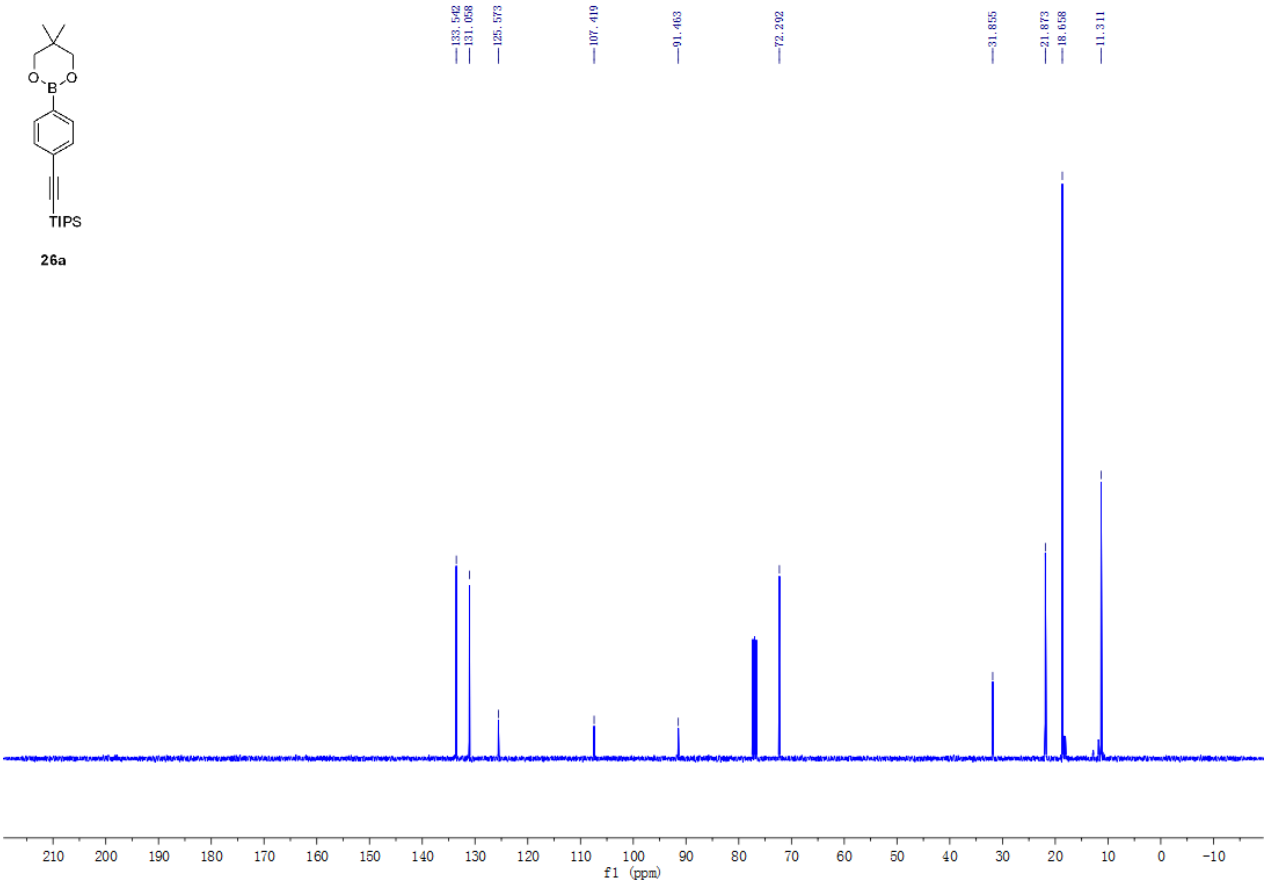


Butyl (*R*)-2-(4-(4-(difluoromethyl)-2-fluorophenoxy)phenoxy)propanoate (55). The reaction was carried out according to the general procedure B on 0.5 mmol scale. The product **55** (172 mg, 90% yield) as a colorless oil was purified with silica gel chromatography (Hexane/CH_2Cl_2 = 6:4 to 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 10.6 Hz, 1 H), 7.17 (d, *J* = 8.3 Hz, 1 H), 6.97-6.91 (m, 3 H), 6.88-6.84 (m, 2 H), 6.59 (t, *J* = 56.4 Hz, 1 H), 4.71 (q, *J* = 6.7 Hz, 1 H), 4.21-4.12 (m, 2 H), 1.62 (d, *J* = 6.7 Hz, 3 H), 1.61-1.59 (m, 2 H), 1.32 (m, 2 H), 0.90 (t, *J* = 7.4 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.86 (d, *J* = 56.4 Hz, 2 F), -130.90 (dd, *J* = 10.0 Hz, 8.7 Hz, 1 F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 154.3, 153.2 (d, *J* = 250.1 Hz), 150.0, 147.5 (dt, *J* = 11.0, 1.9 Hz), 129.7 (td, *J* = 23.3, 6.2 Hz), 121.9 (td, *J* = 6.4, 3.8 Hz), 120.0, 119.4, 116.4, 114.4 (dt, *J* = 20.2, 5.9 Hz), 113.6 (td, *J* = 239.0, 1.6 Hz), 73.2, 65.1, 30.5, 18.9, 18.6, 13.6. IR(thin film) ν_{max} 2962, 2935, 2875, 1752, 1625, 1502 cm^{-1}. MS (EI): *m/z* (%) 382 (M^+), 332, 281, 254, 155, 91 (100). HRMS: Calculated for $C_{20}H_{21}O_4F_3$: 382.1392; Found: 382.1399.

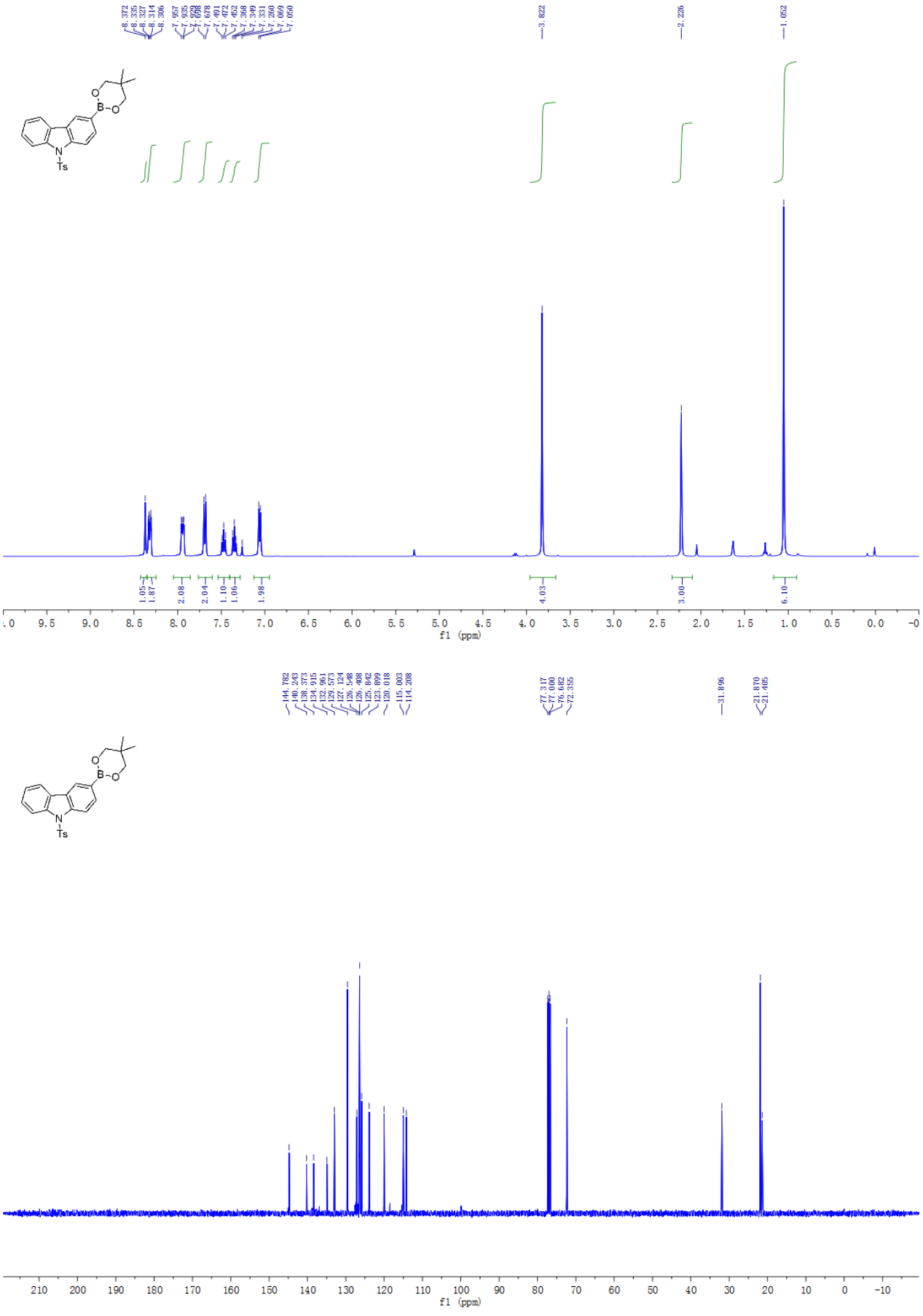
9. Part one: ^{1}H NMR Copies and ^{13}C NMR Copies of ArBneop

((4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)ethynyl)triisopropylsilane (26a)

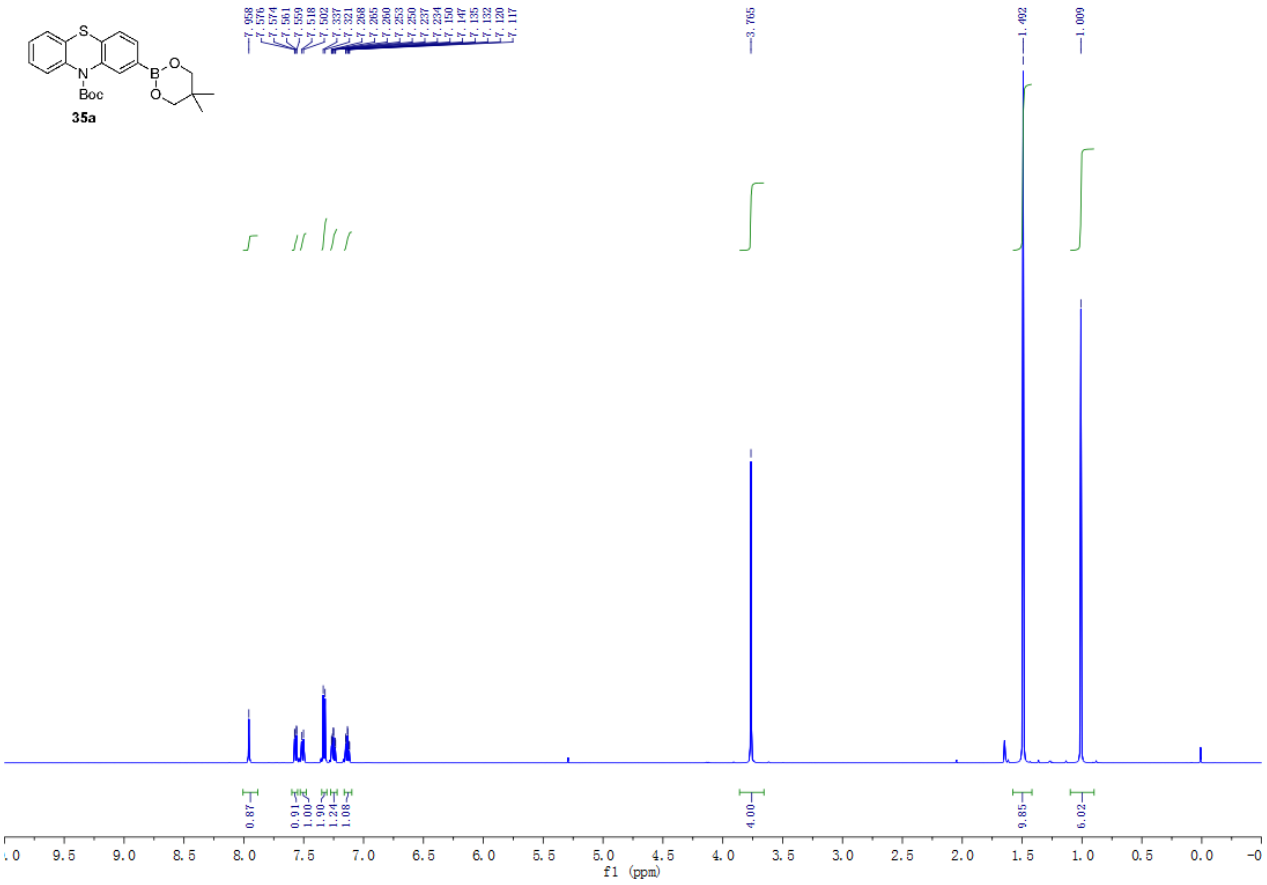


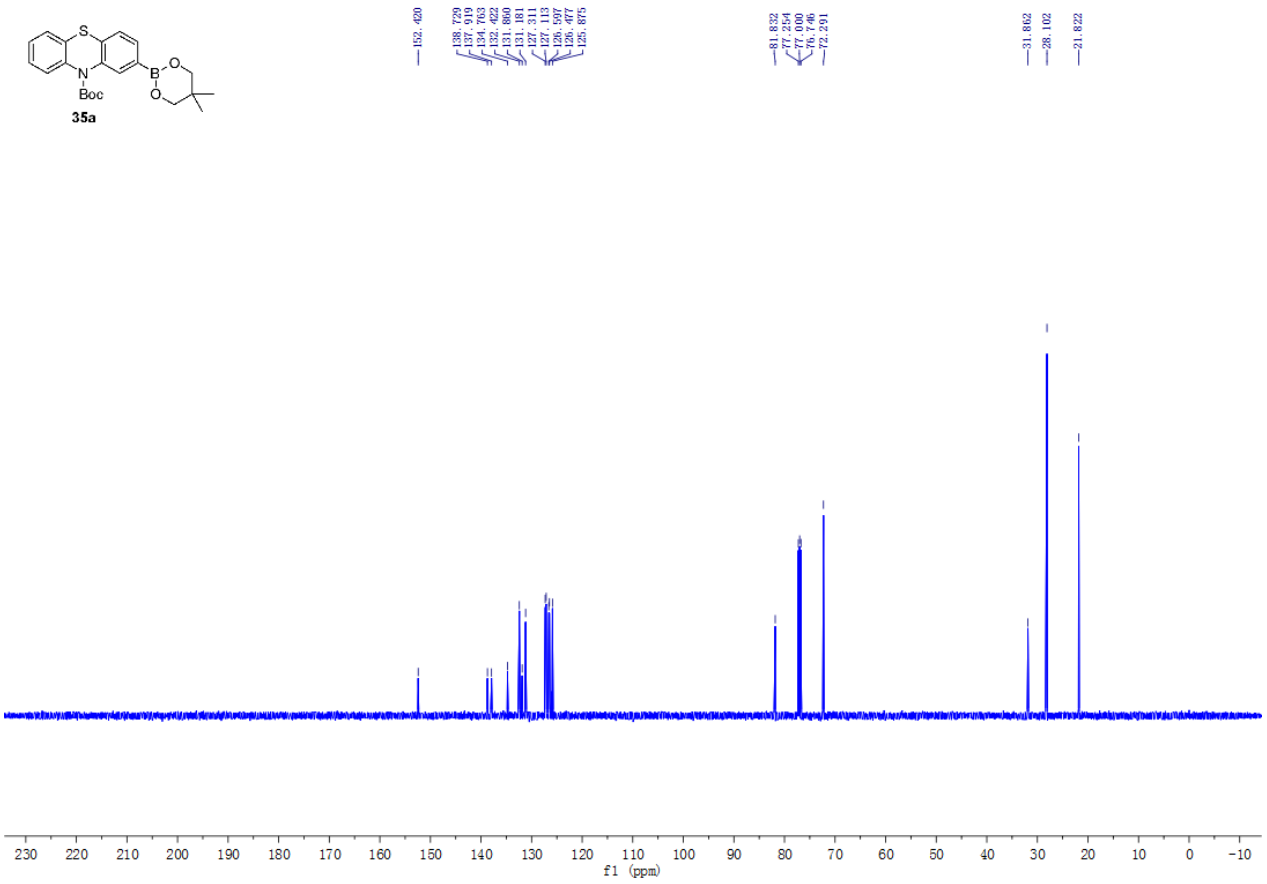


3-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-9-tosyl-9*H*-carbazole (34a)

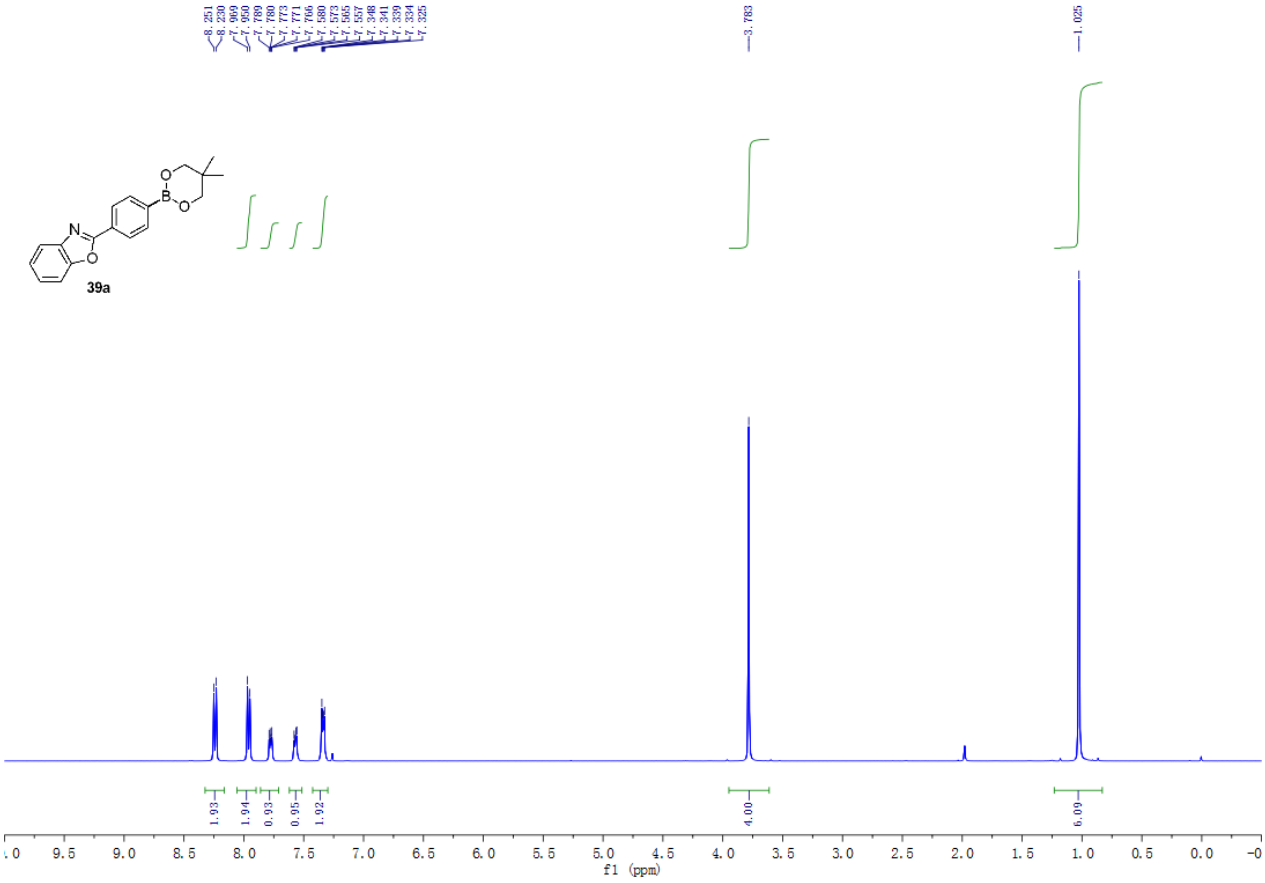


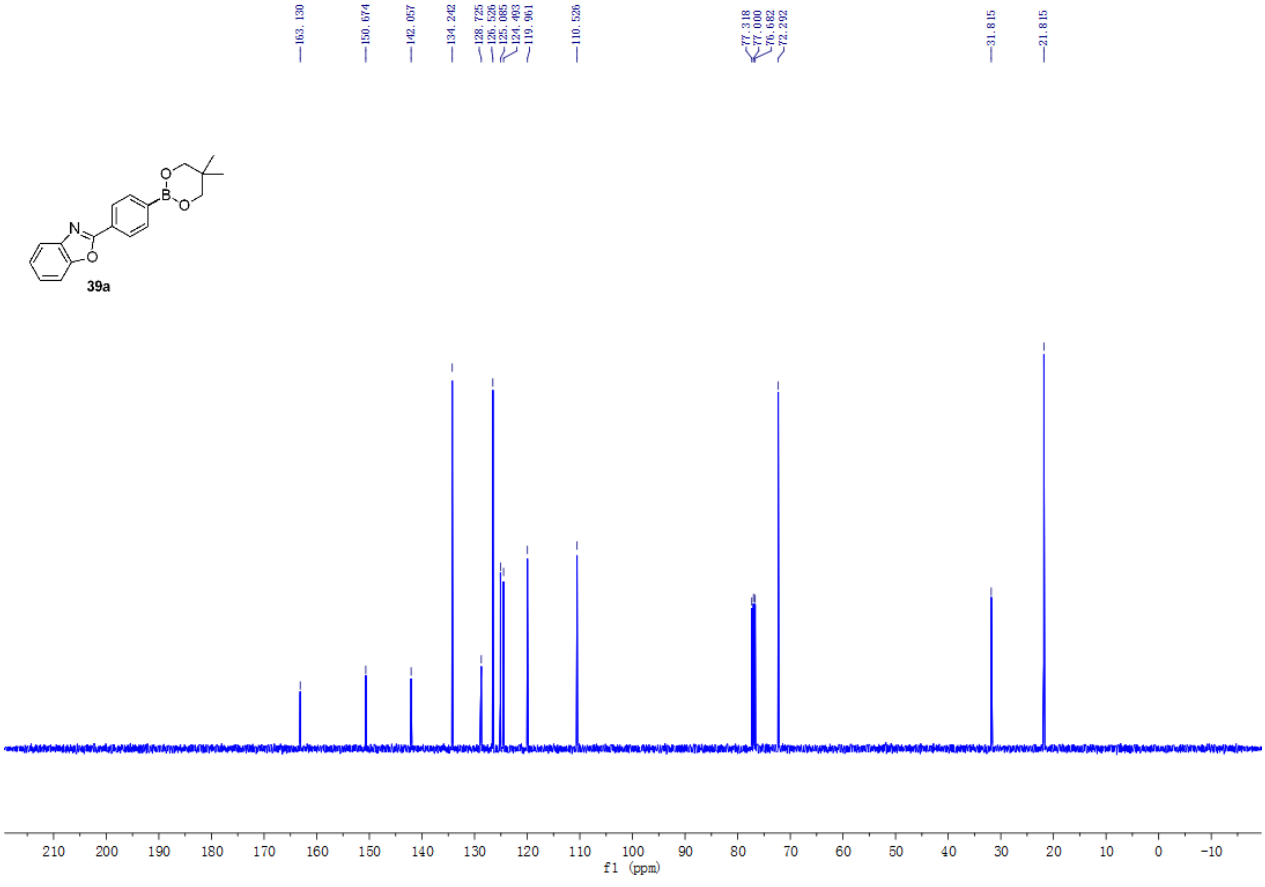
N-Boc-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-10*H*-phenothiazine (35a)



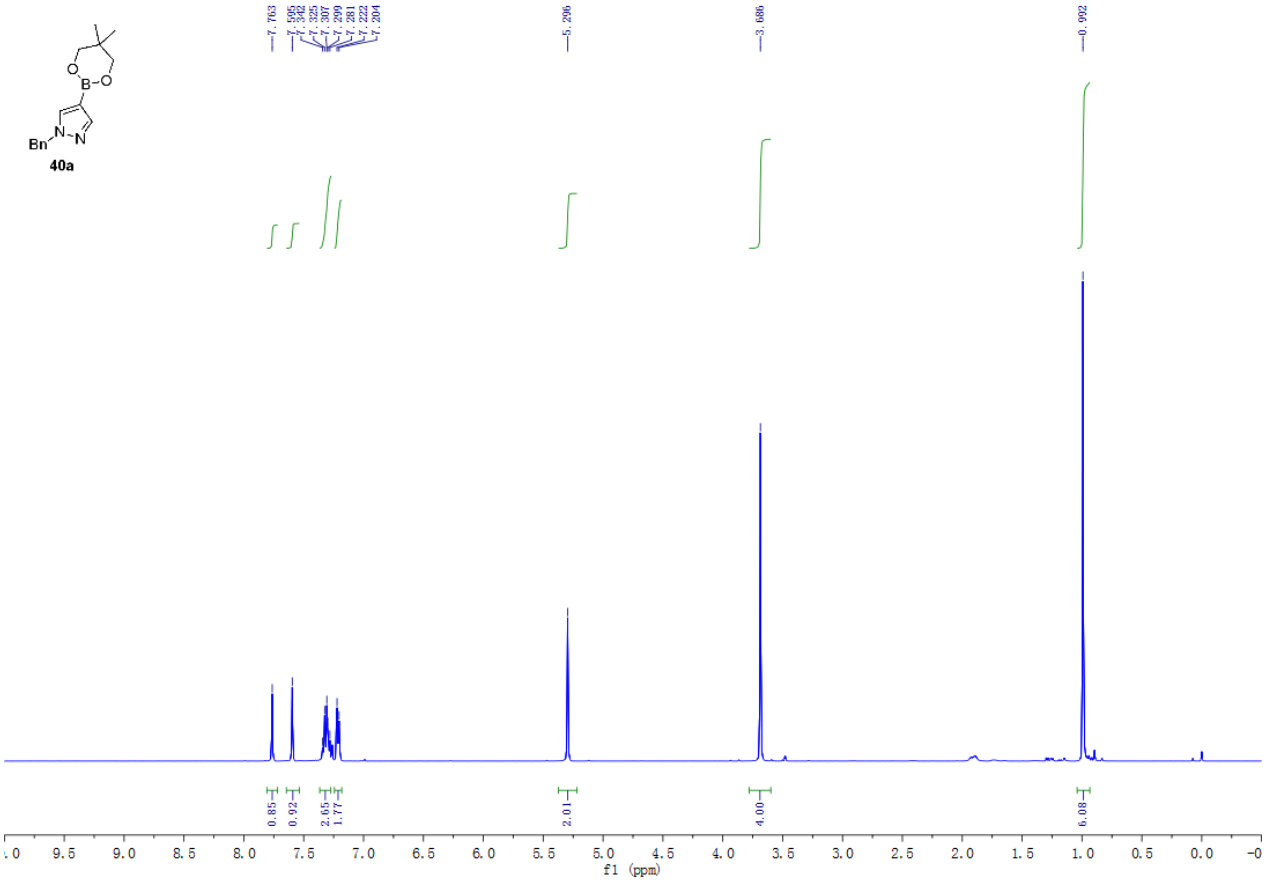


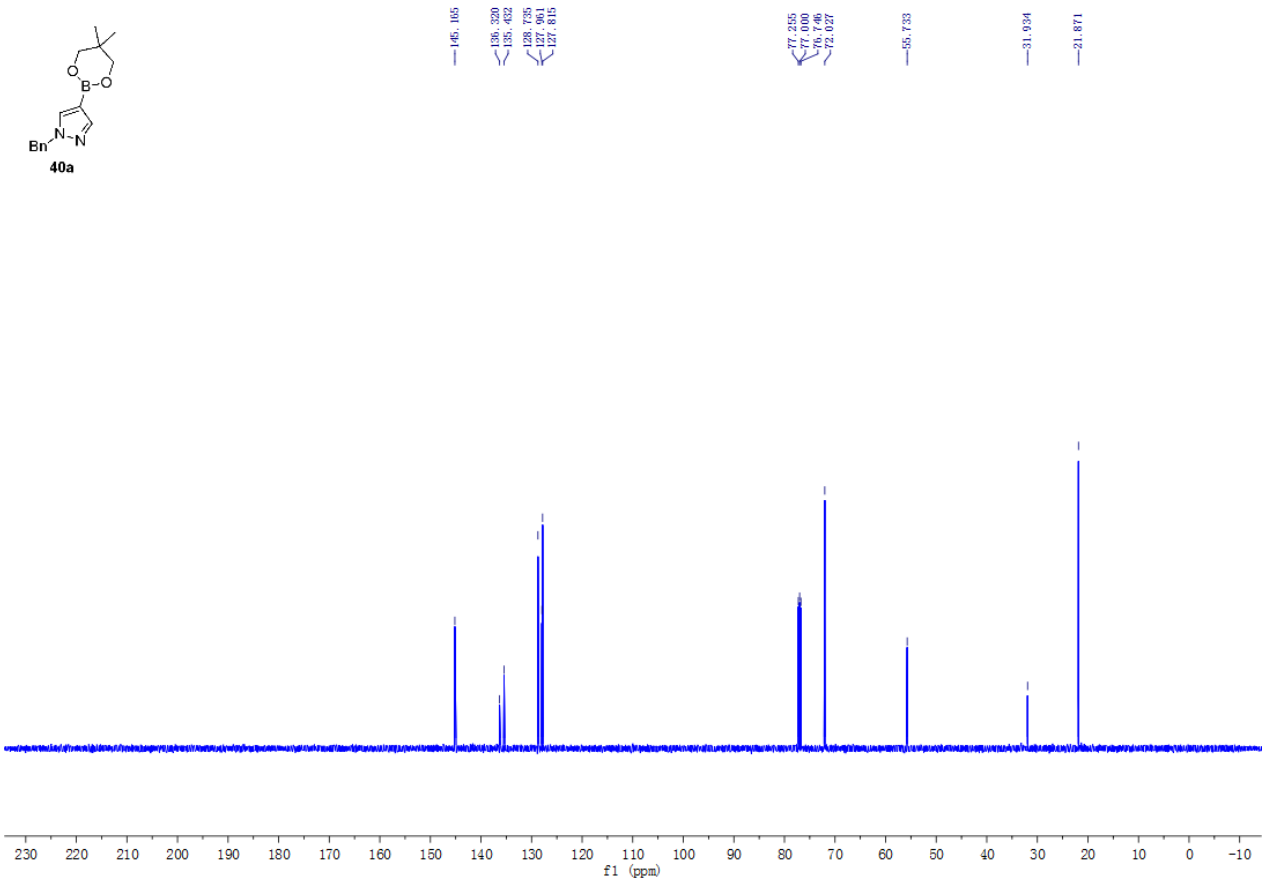
2-(4-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)benzo[*d*]oxazole (39a).



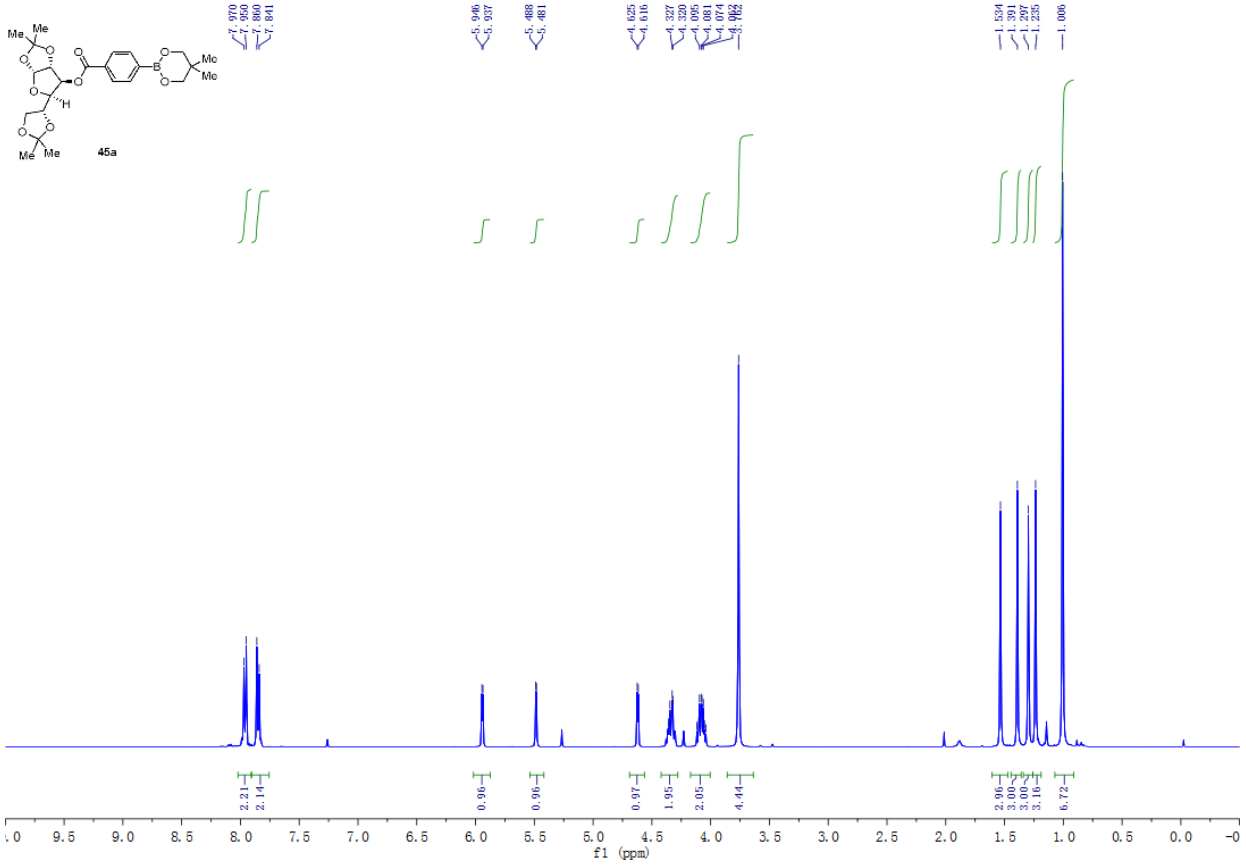


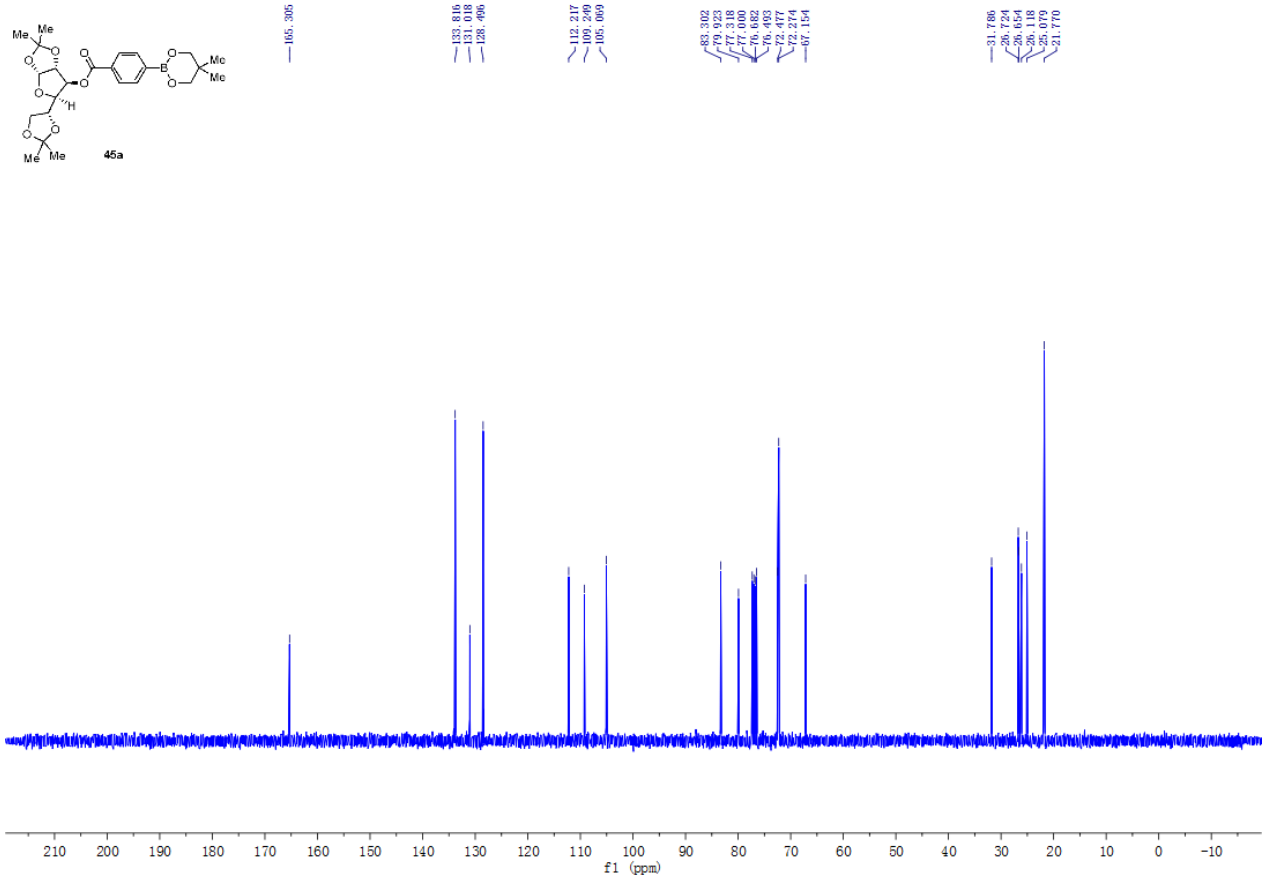
1-Benzyl-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1*H*-pyrazole (40a)



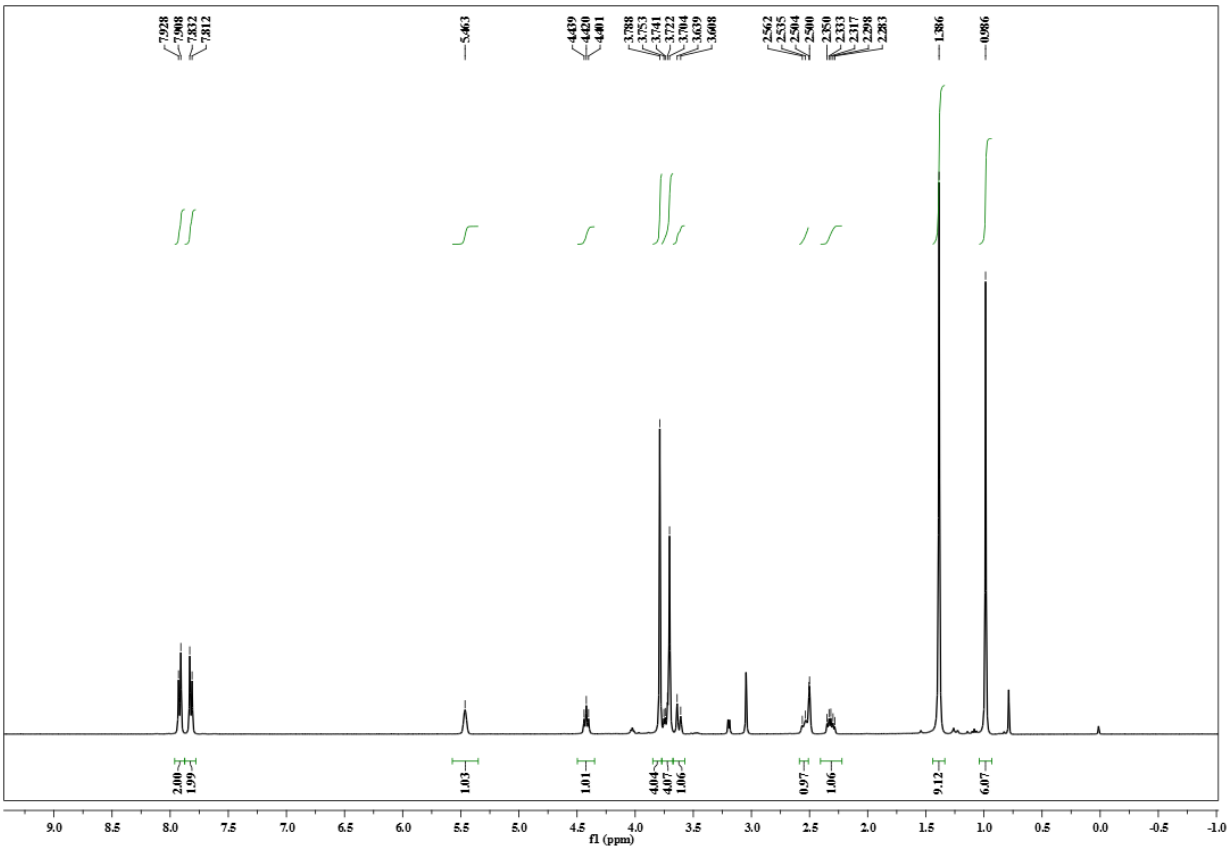


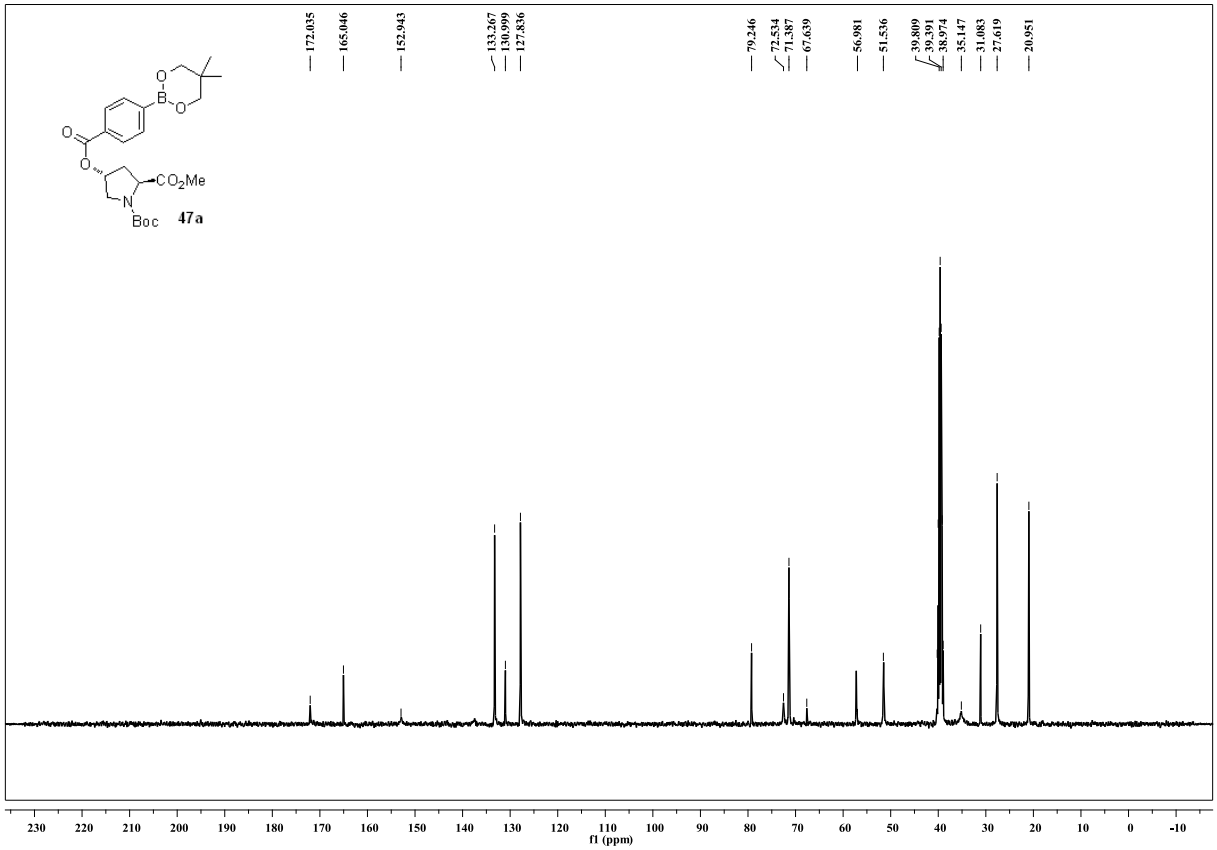
(3a*S*, 5*S*, 6*R*, 6a*S*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofu-ro[2,3-*d*]-[1,3] dioxol-6-yl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (45a).



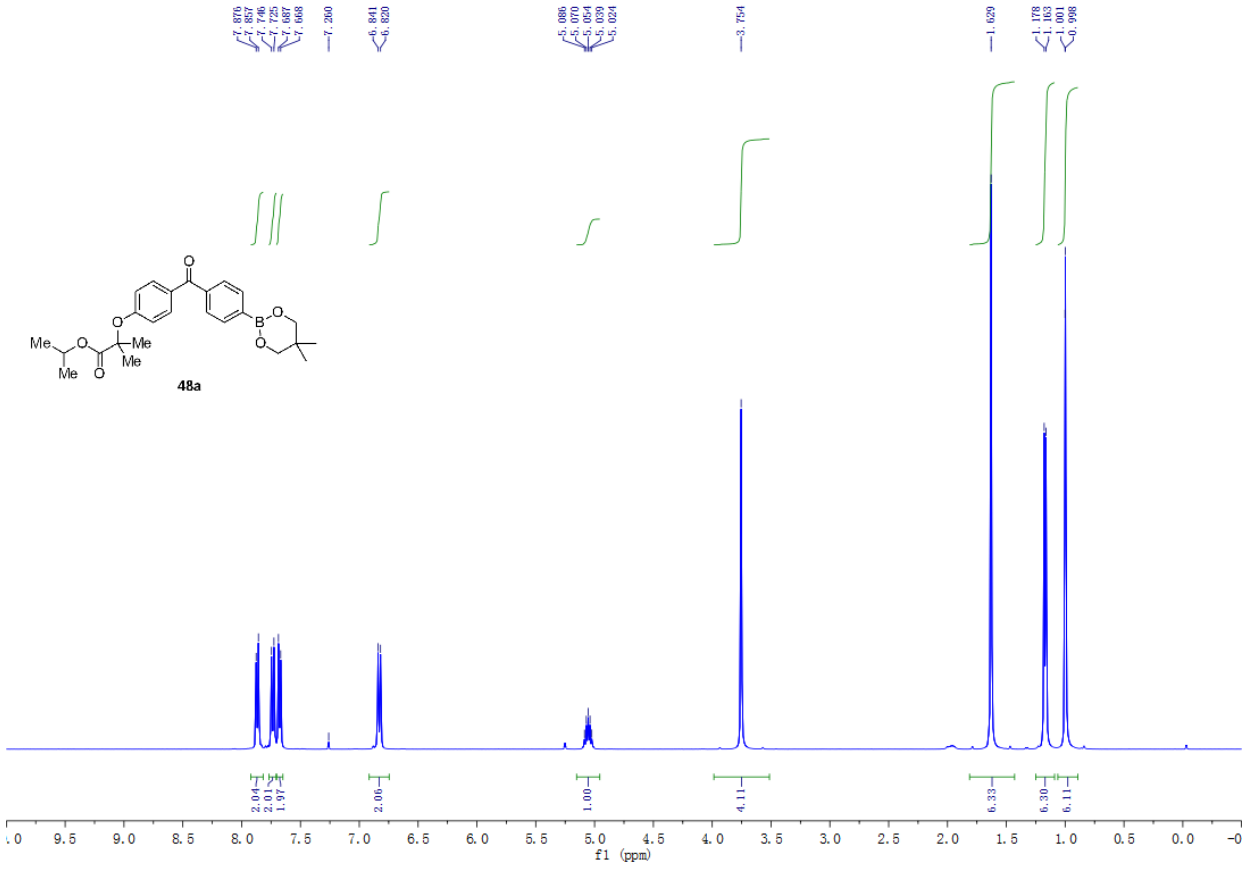


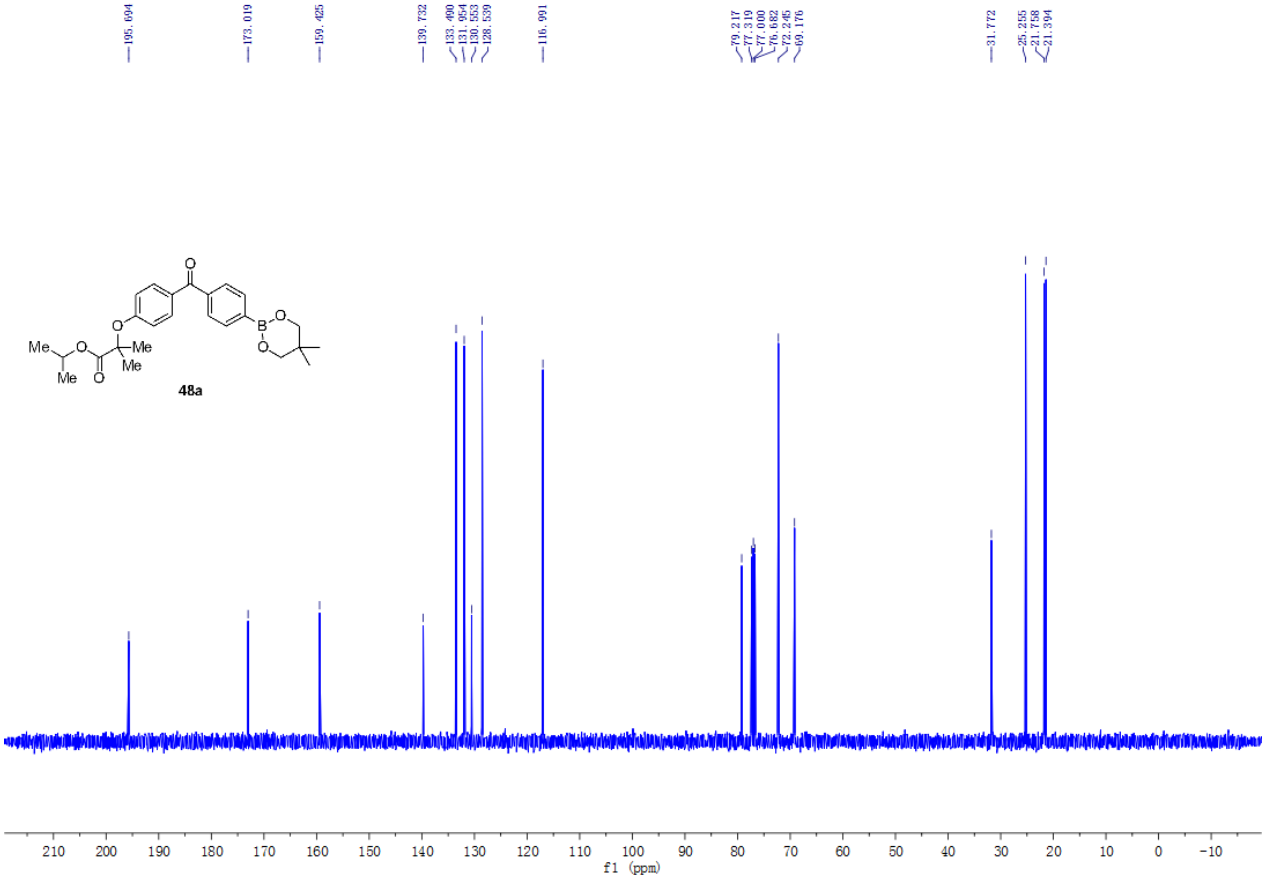
1-(*tert*-Butyl) 2-methyl (2*S*, 4*R*)-4-((4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoyl) oxy) pyrrolidine-1,2-dicarboxylate (47a).



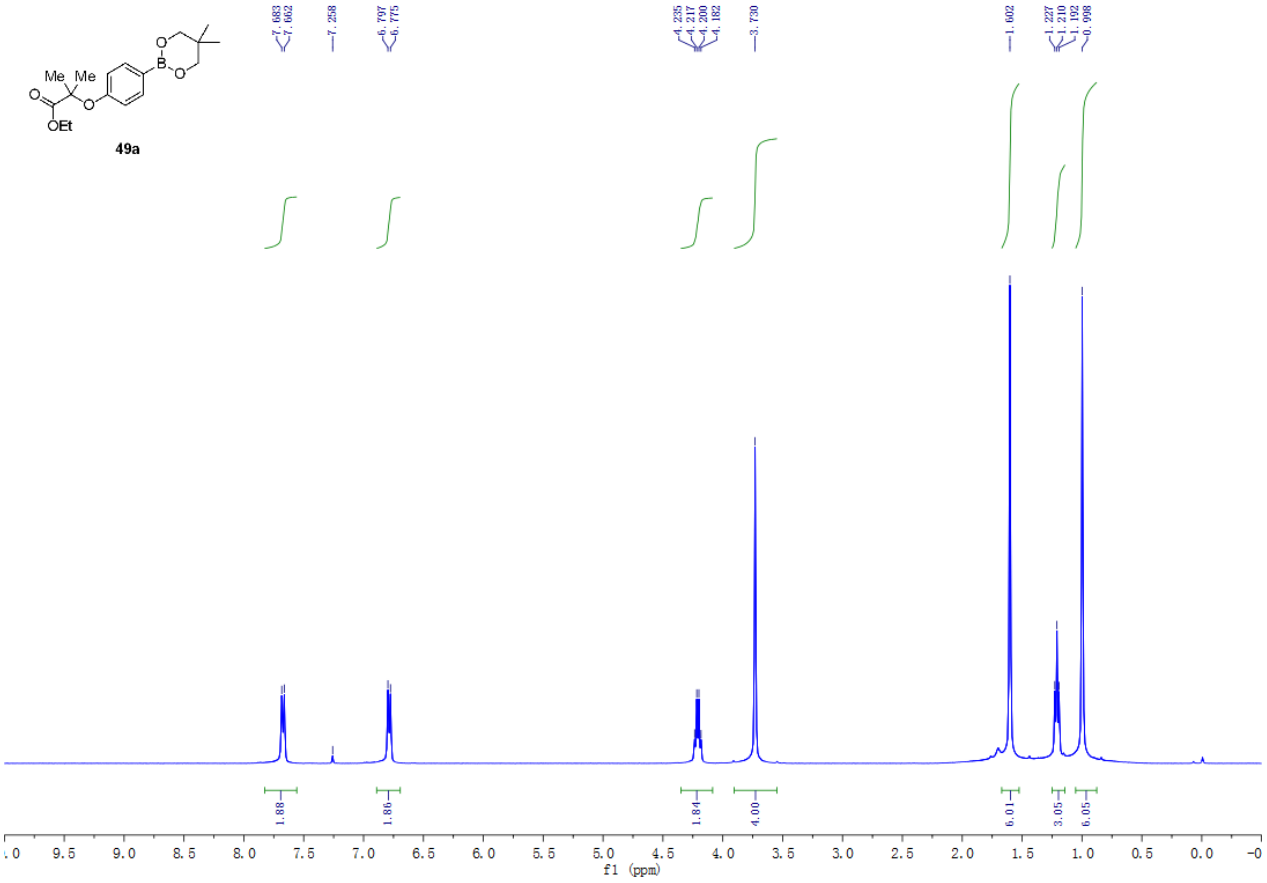


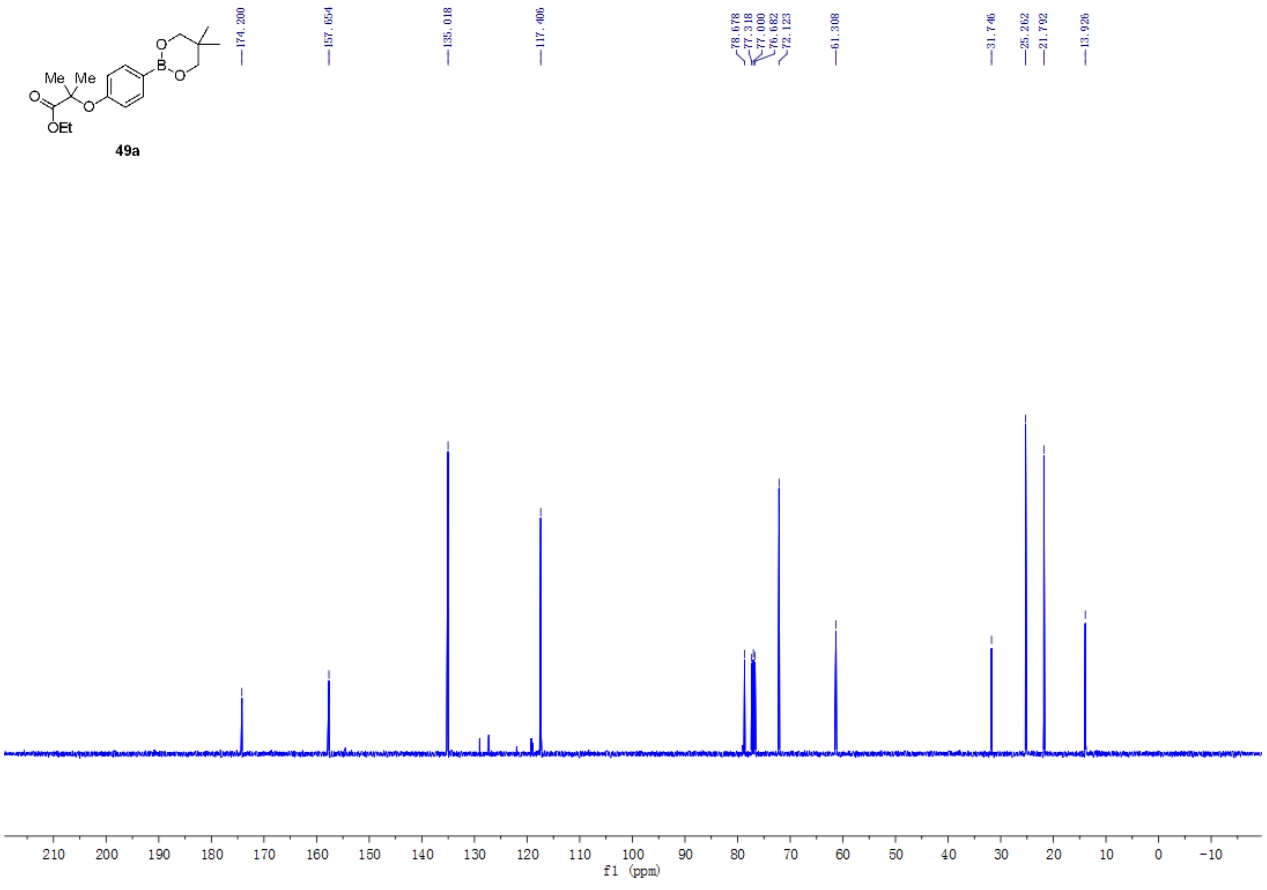
Isopropyl 2-(4-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoyl)phenoxy)-2-methyl-propanoate (48a).



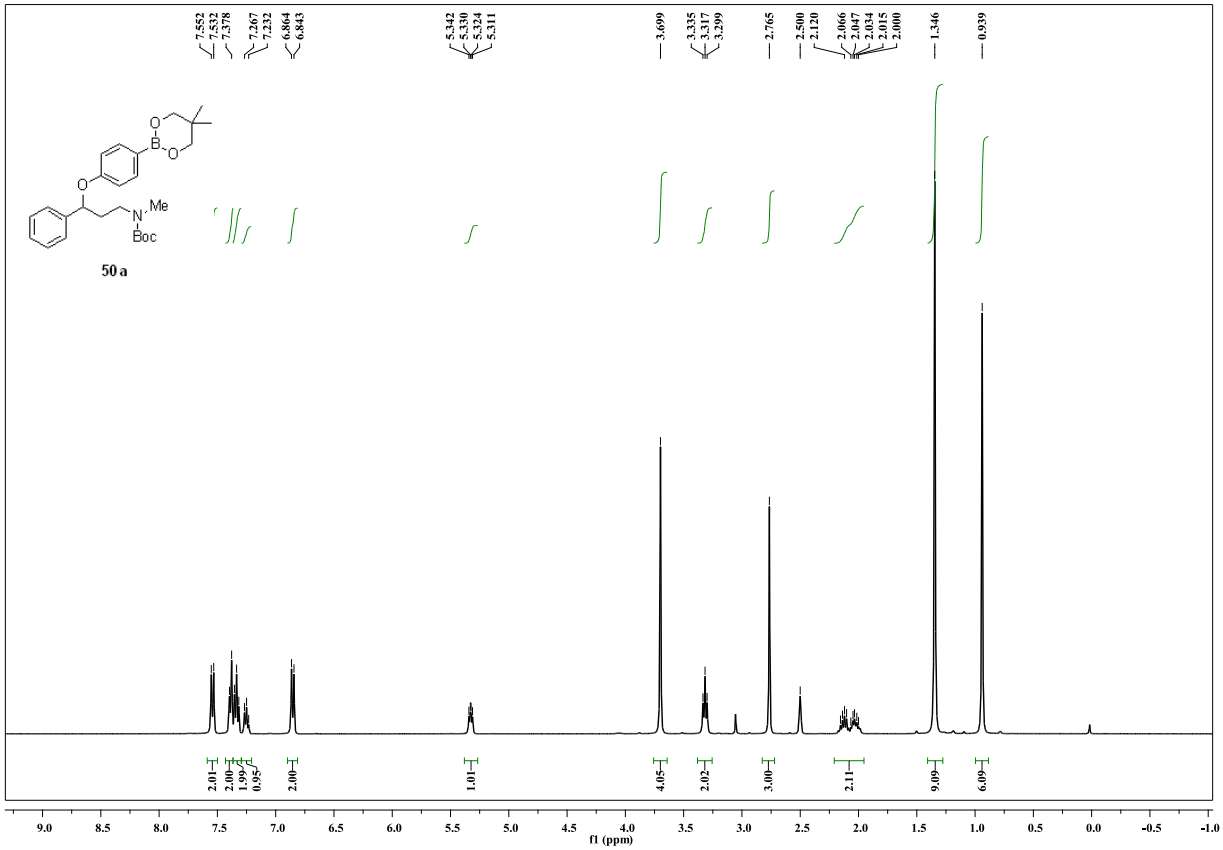


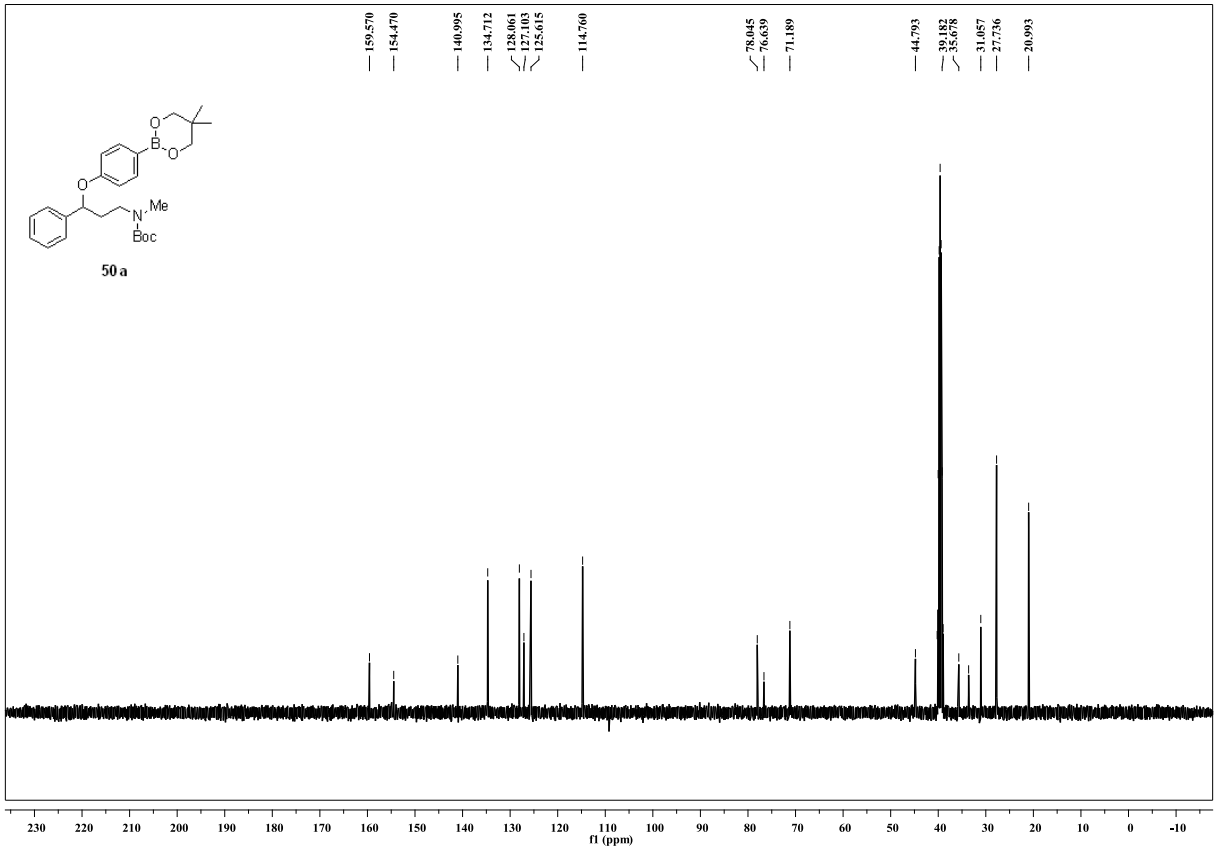
Ethyl 2-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenoxy)-2-methylpropanoate (49a)



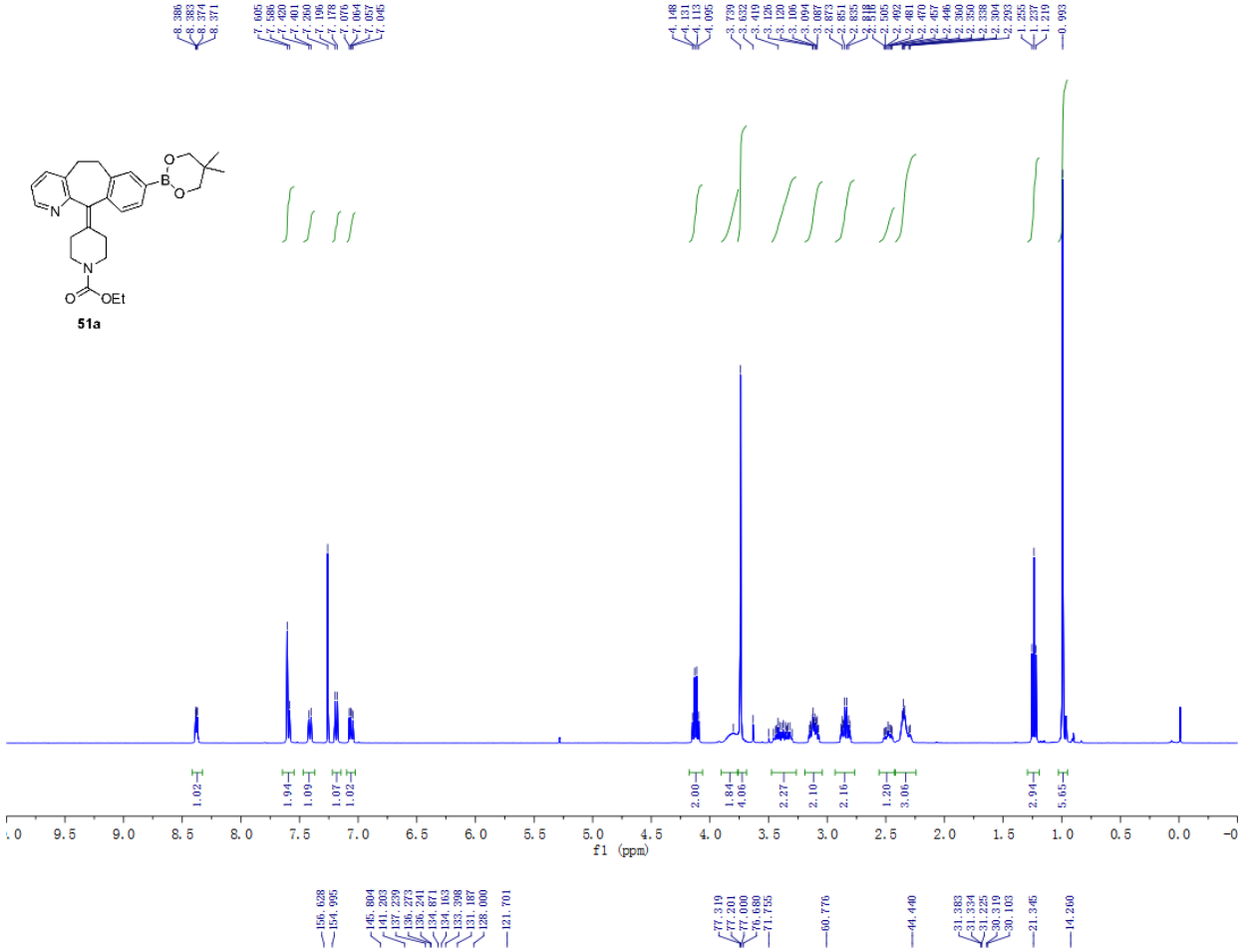


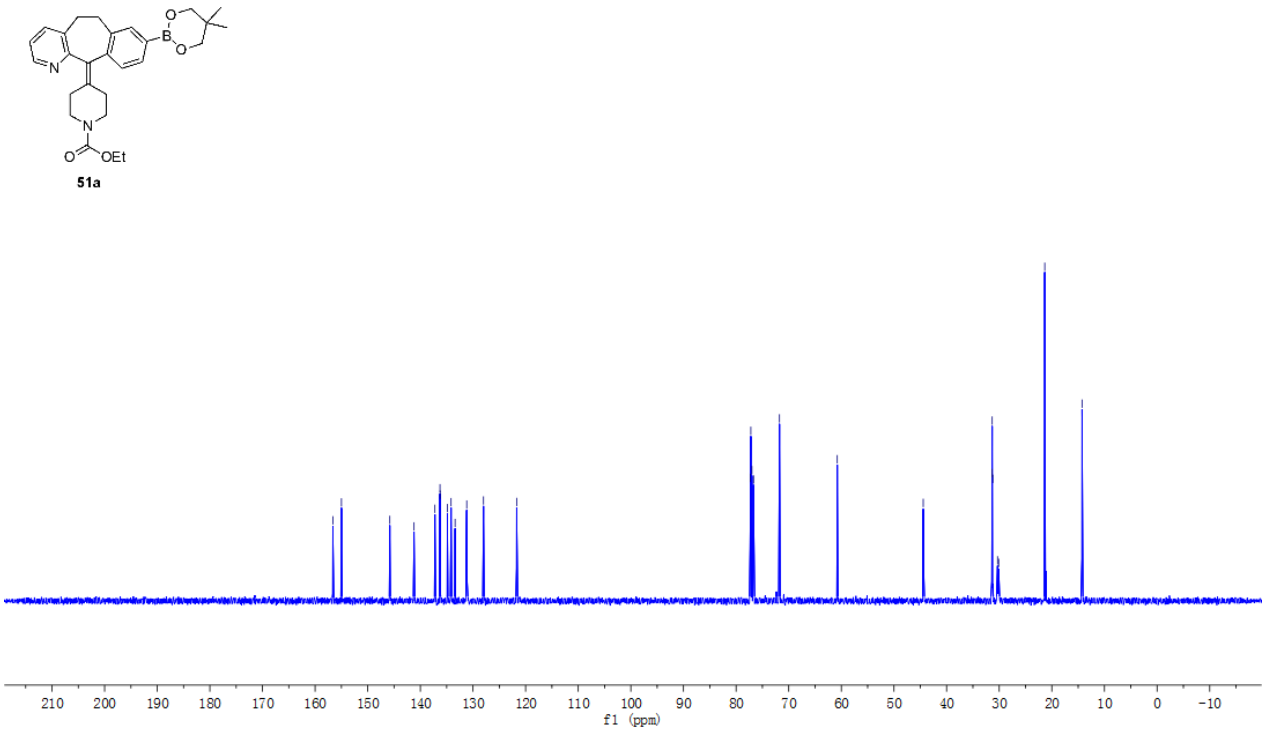
***N*-Boc-3-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenoxy)-*N*-methyl-3-phenylpropan-1-amine (50a).**



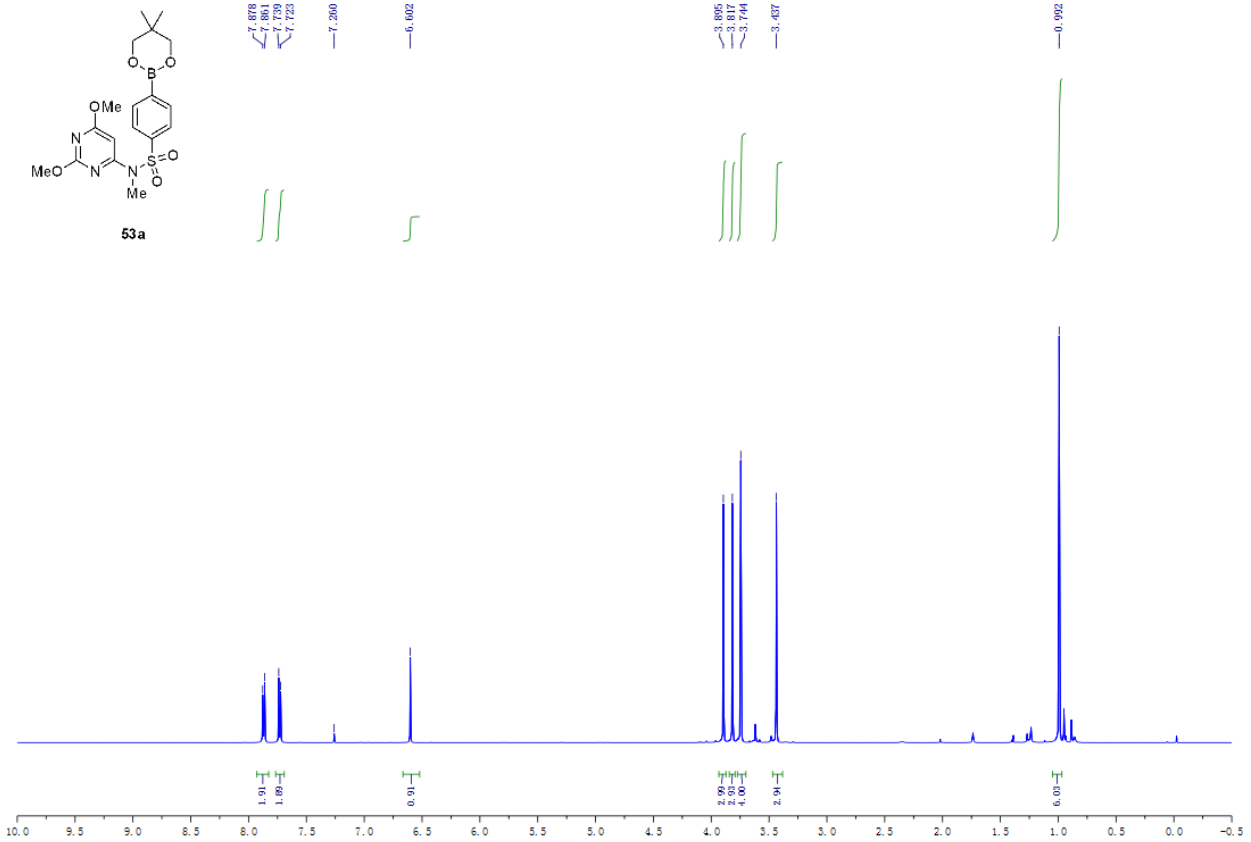


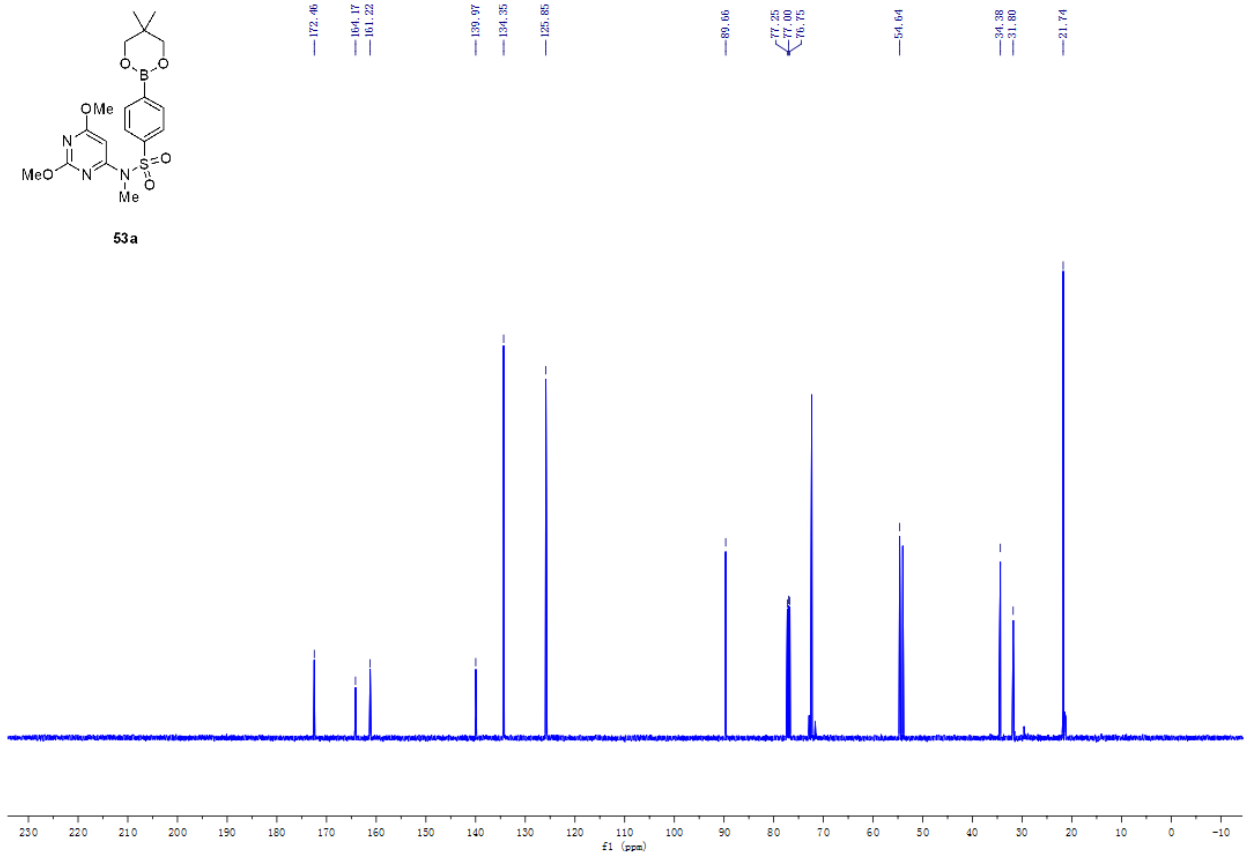
Ethyl 4-(8-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*] pyridin-11-ylidene)piperidine-1-carboxylate (51a).





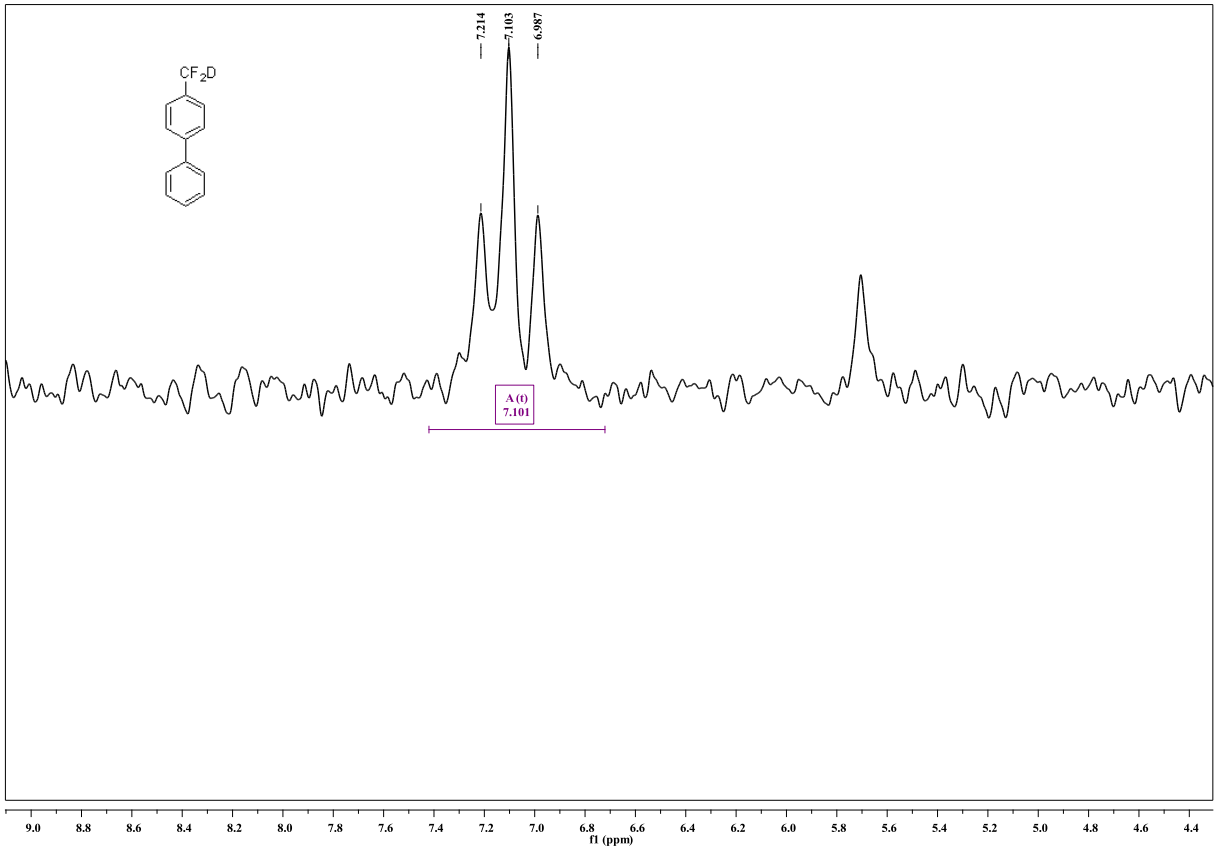
_N_-(2,6-Dimethoxypyrimidin-4-yl)-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-_N_-methylbenzenesulfonamide (53a).

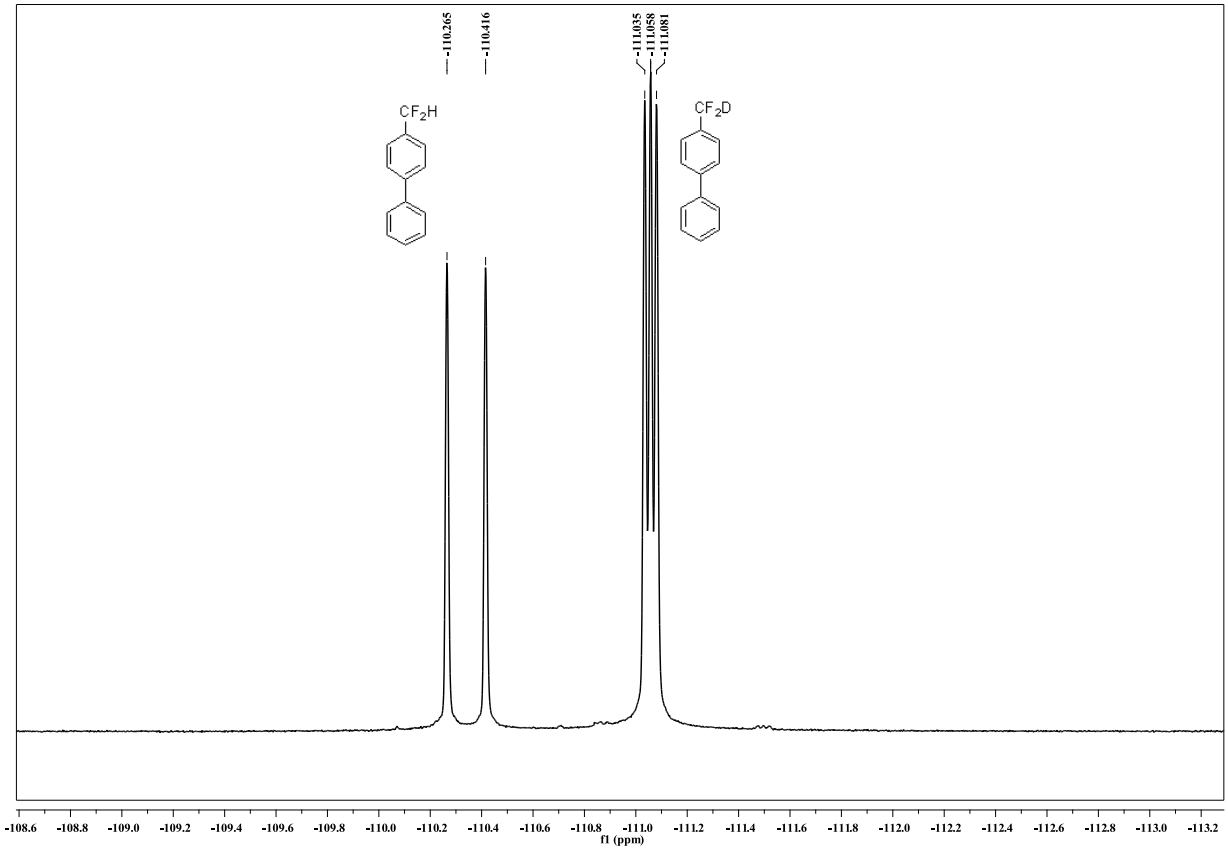




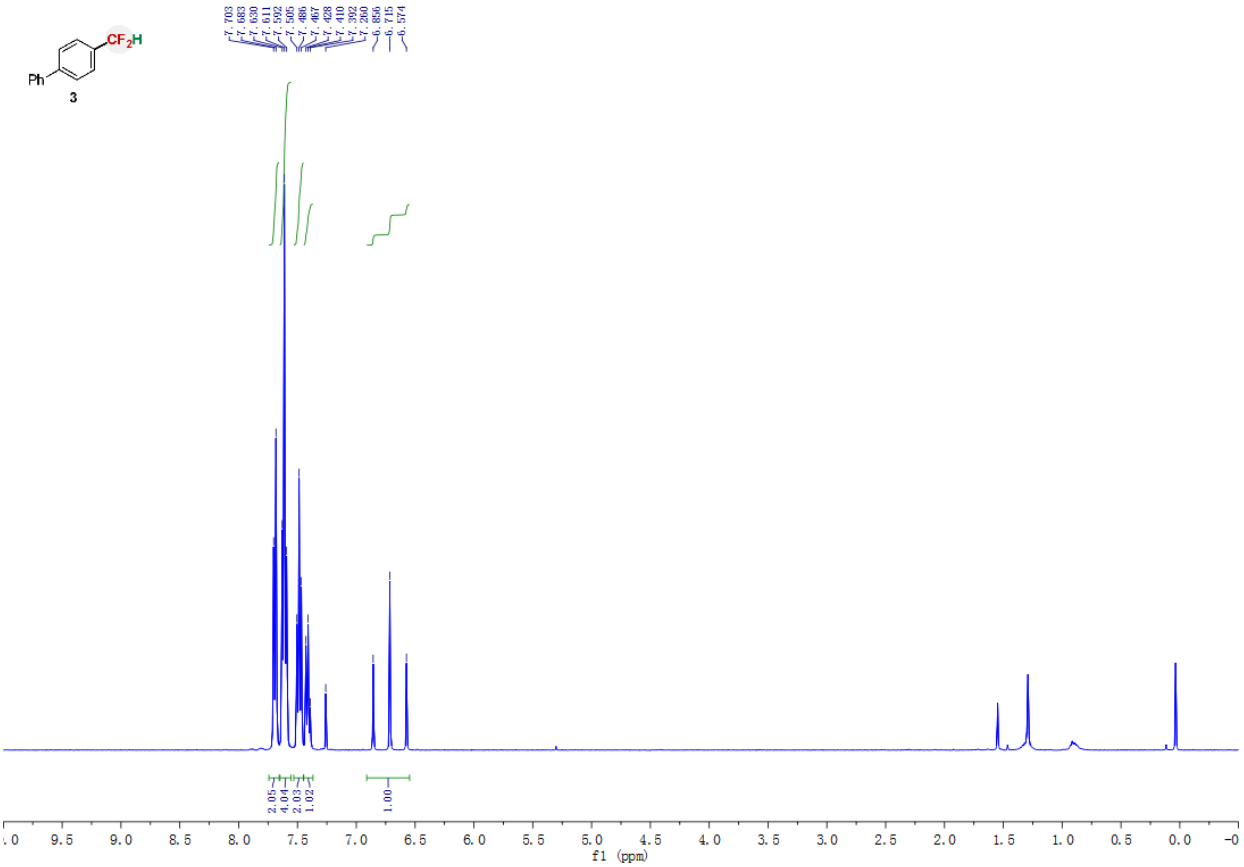
10. Part two: ^{1}H NMR Copies, ^{19}F NMR Copies and ^{13}C NMR Copies of Compounds 3 to 31

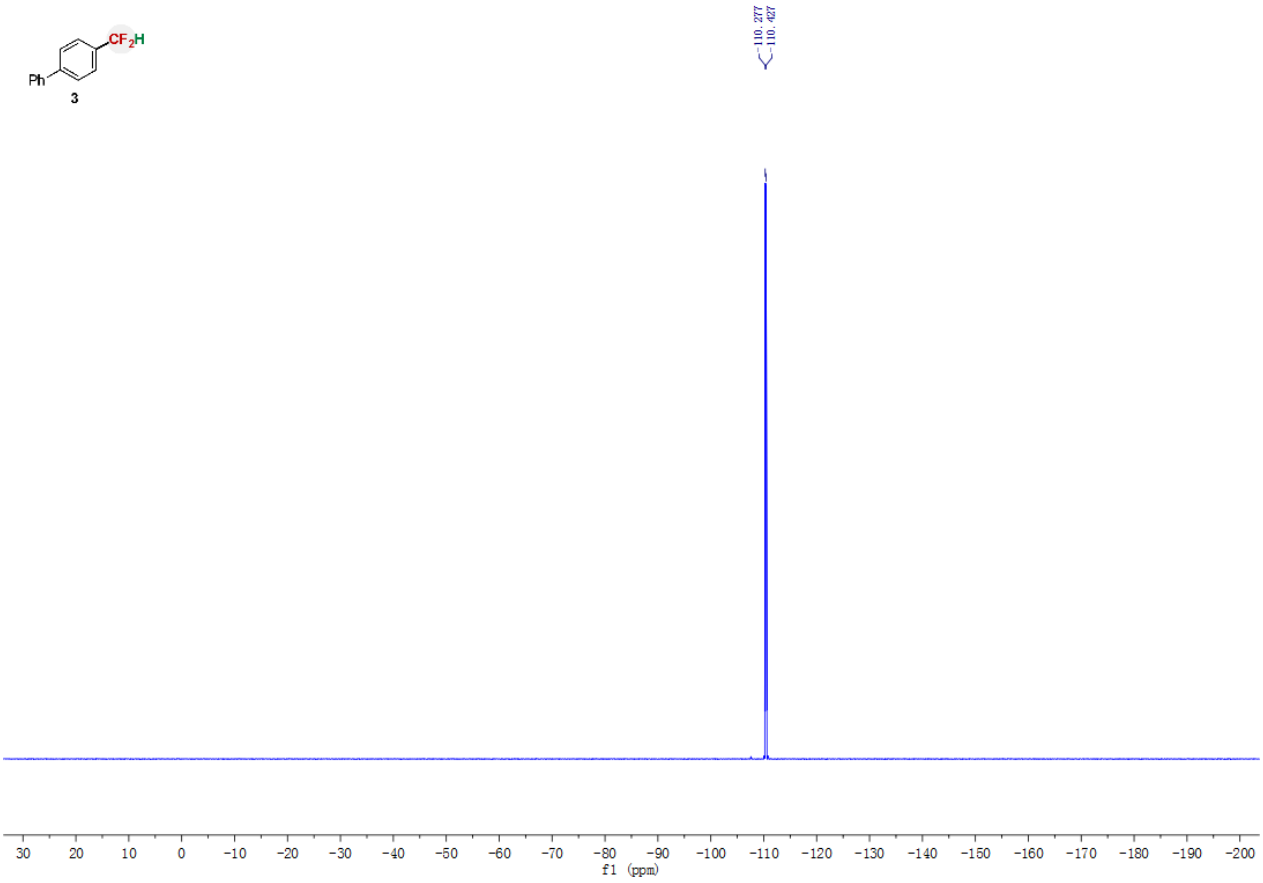
^{2}H NMR and ^{19}F NMR of the mixture of **3** and *d*-**3**

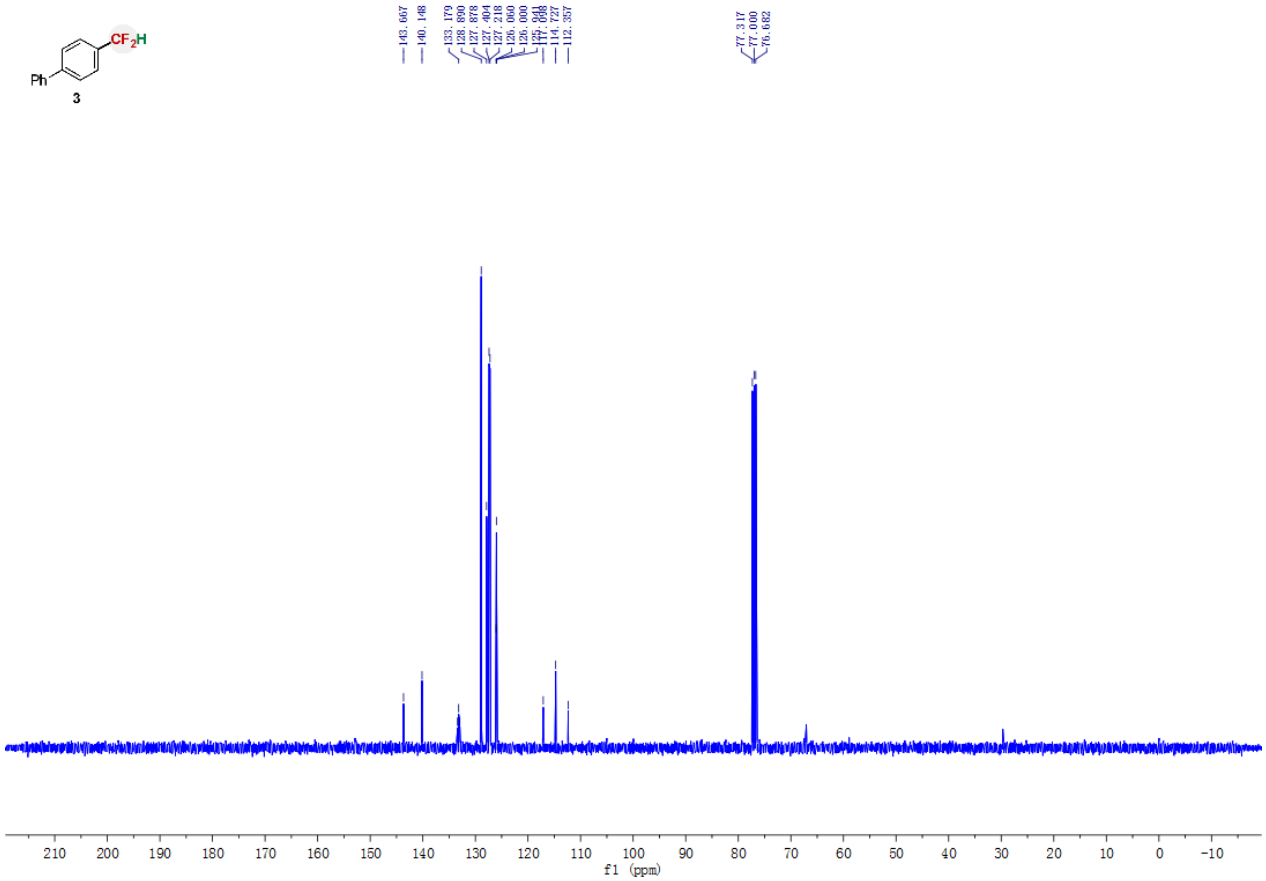




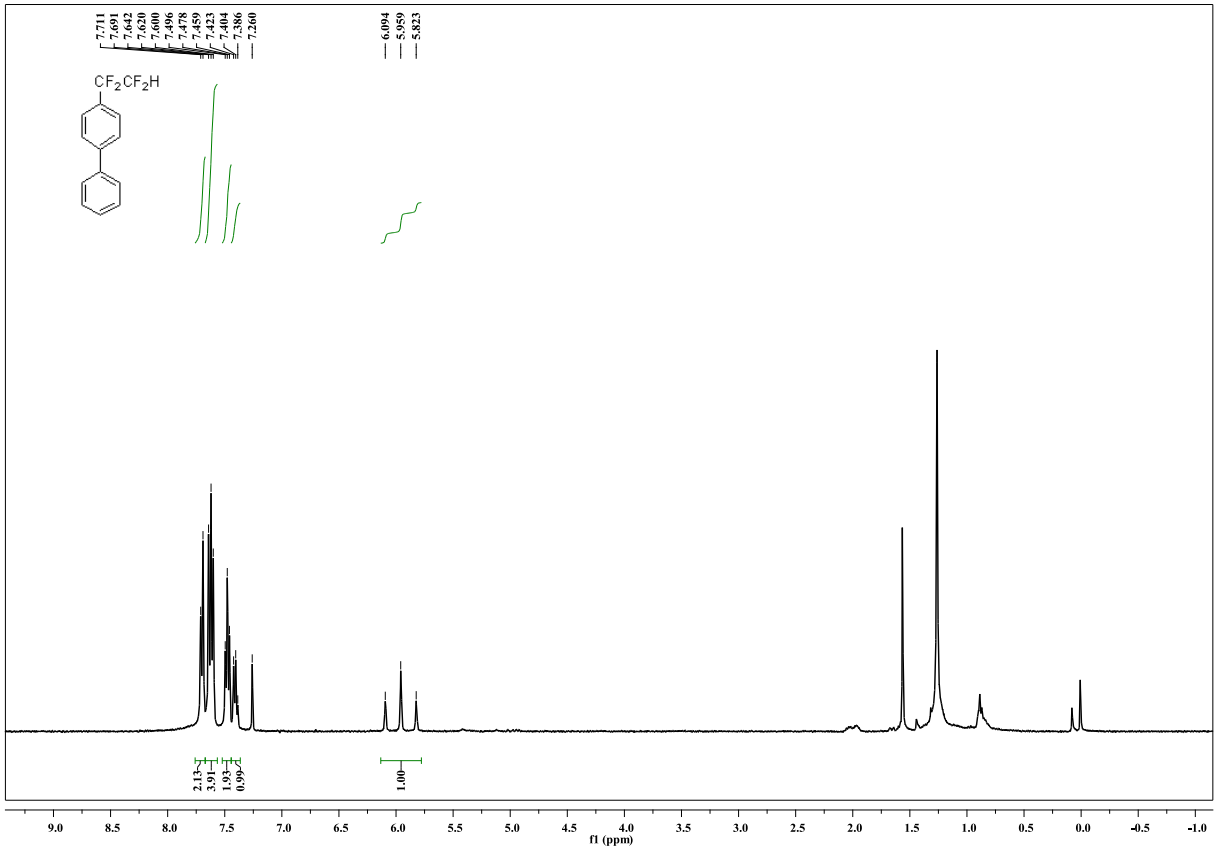
4-(Difluoromethyl)-1,1'-biphenyl (3)

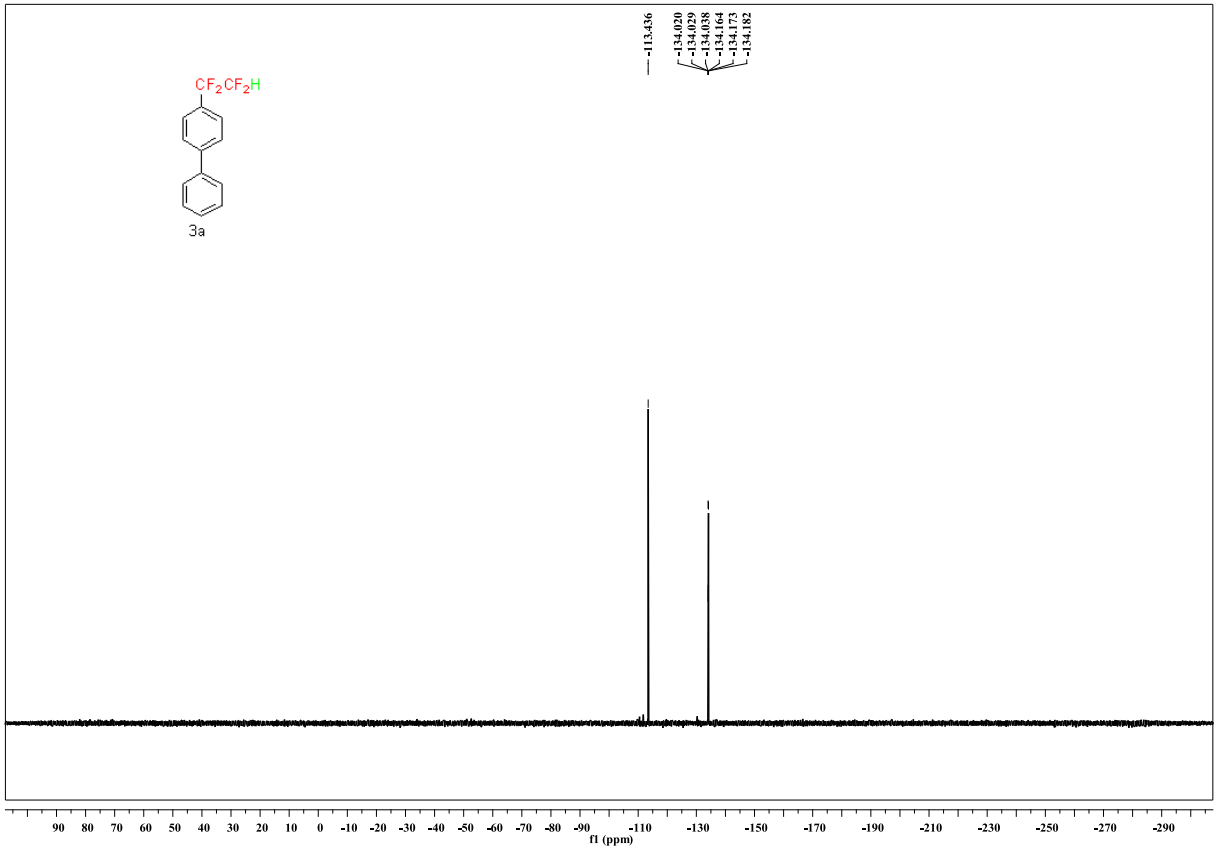




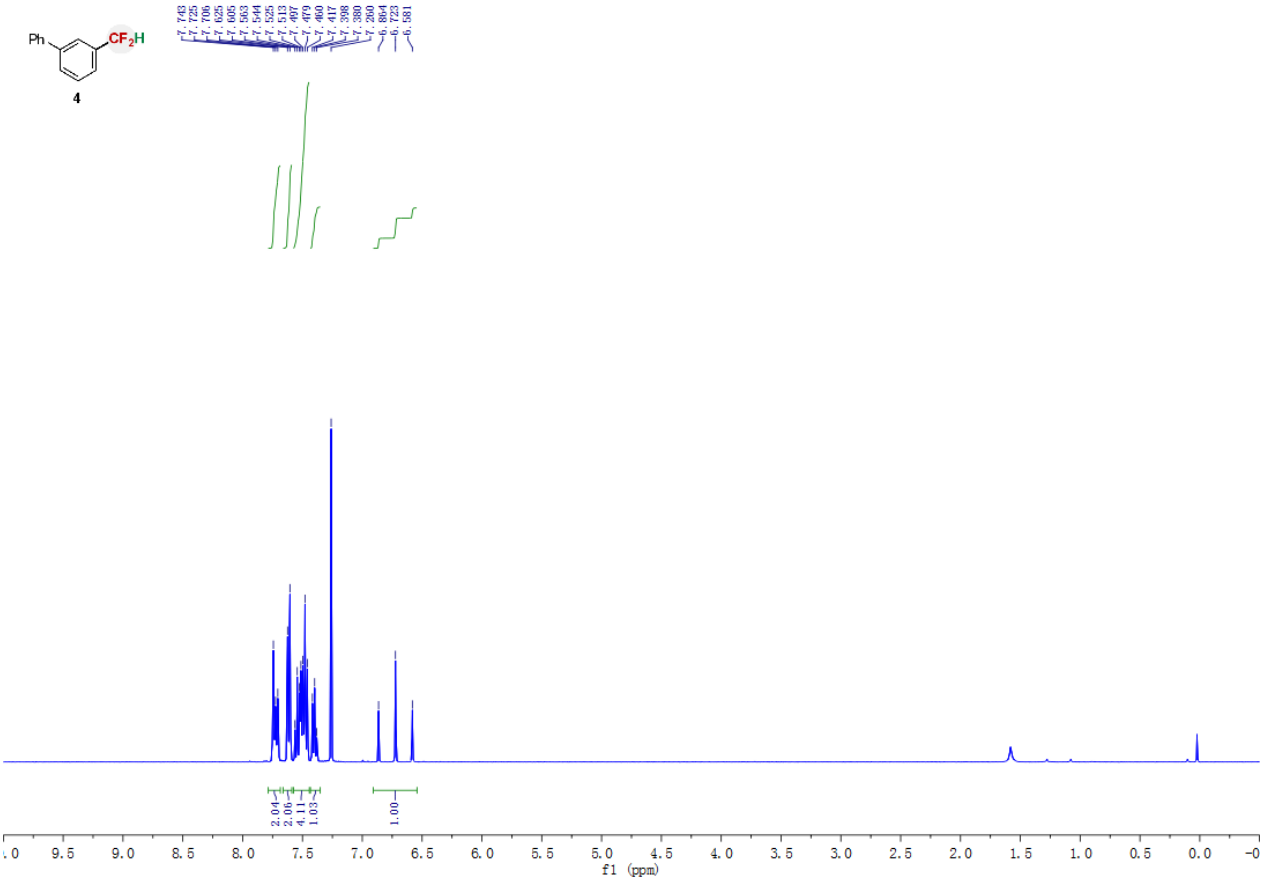


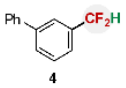
4-(1,1,2,2-Tetrafluoroethyl)-1,1'-biphenyl (3a)





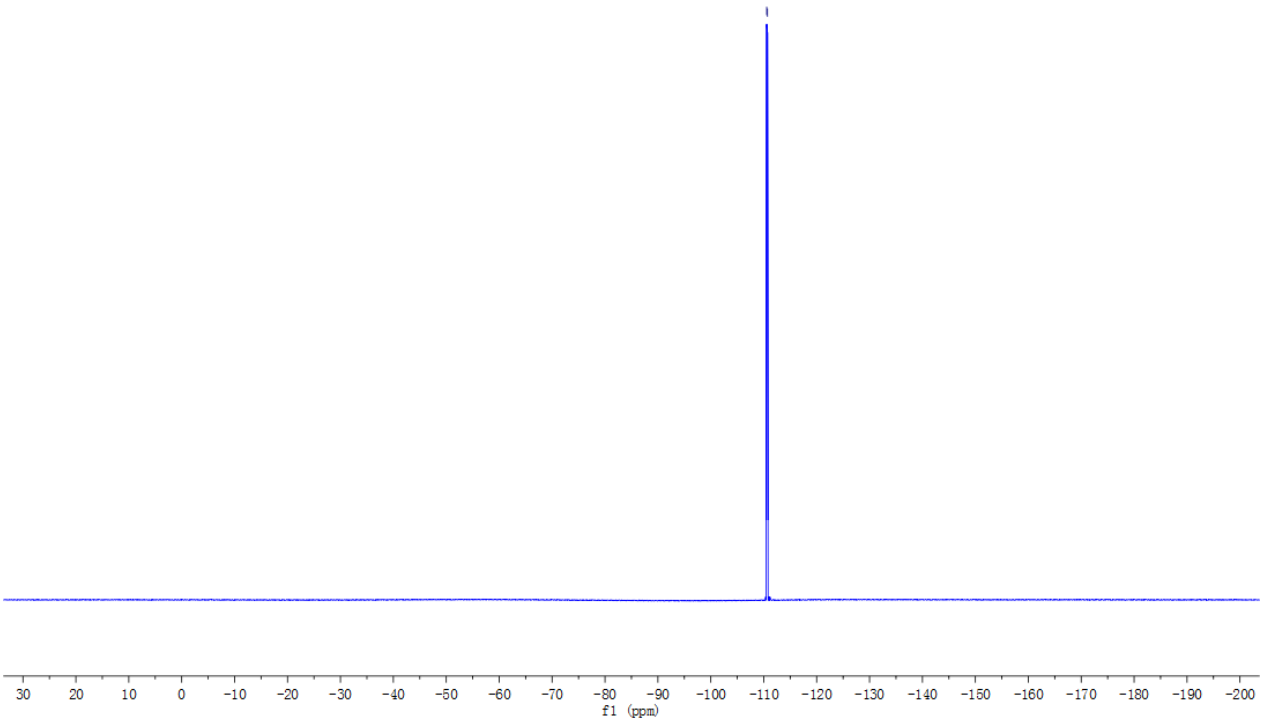
3-(Difluoromethyl)-1,1'-biphenyl (4)

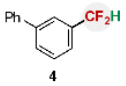



Ph
CF2H

4

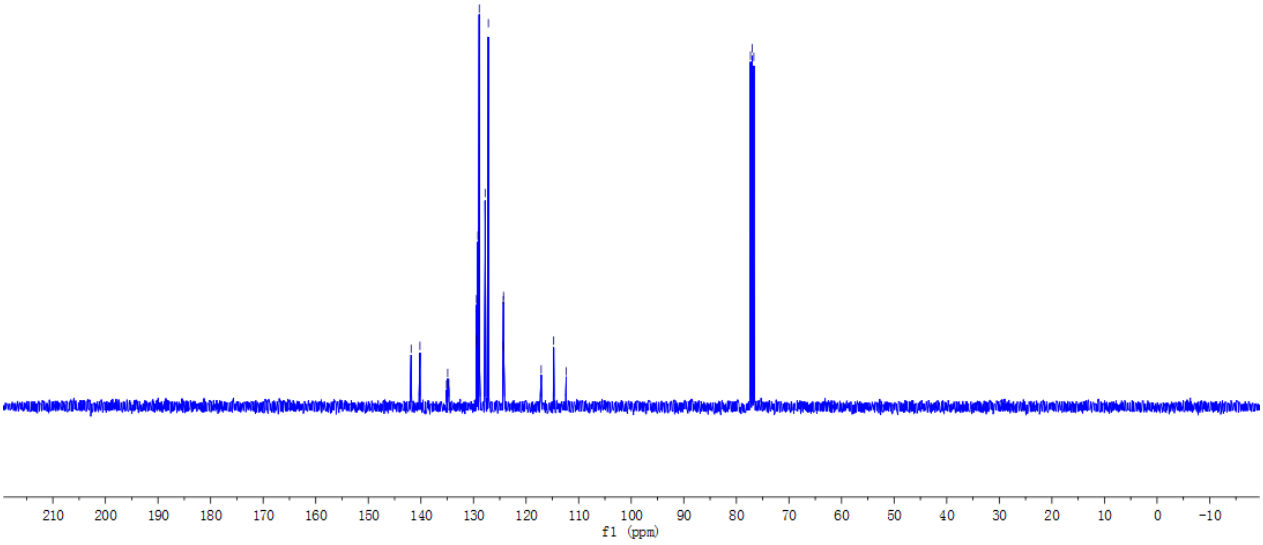

110.500
110.710


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

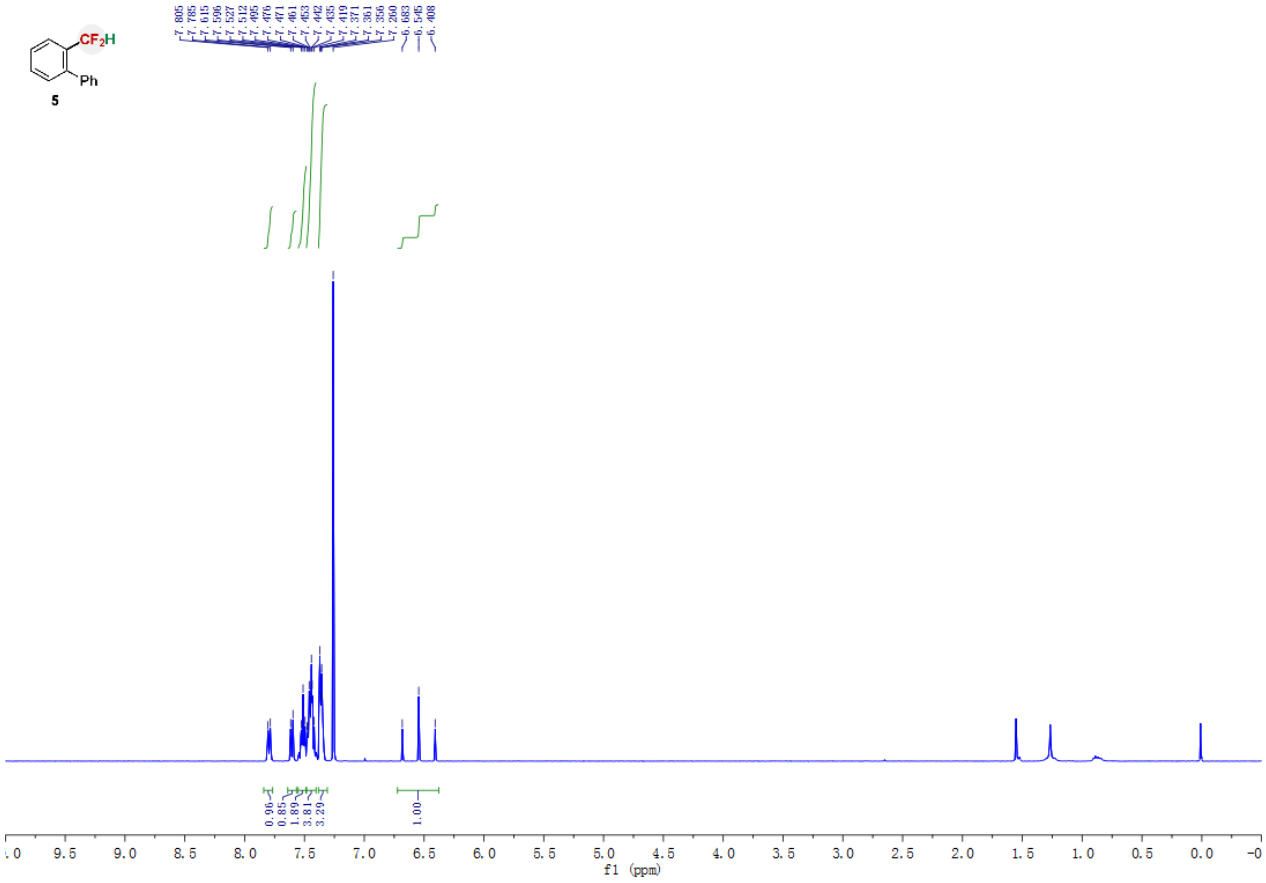

Ph
CF2H

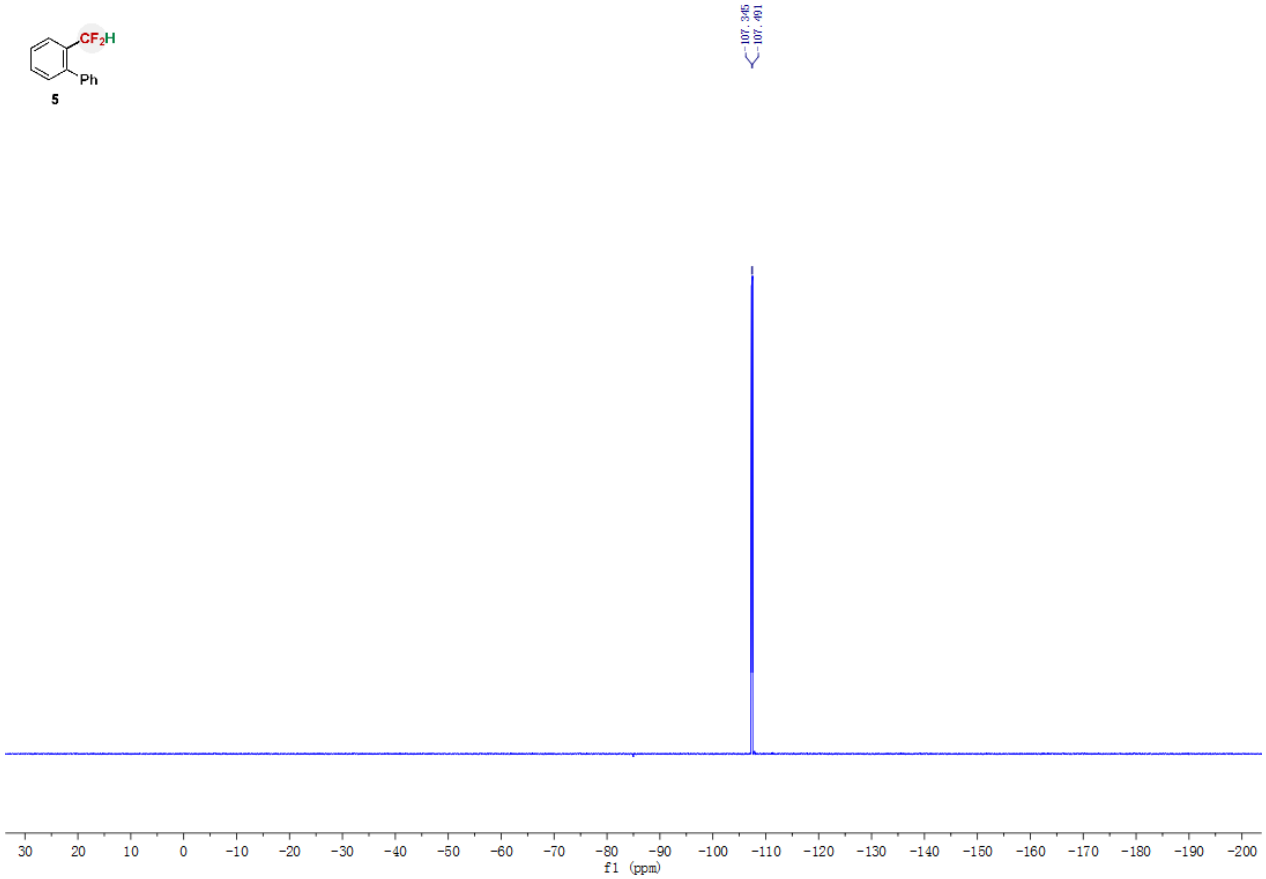
4

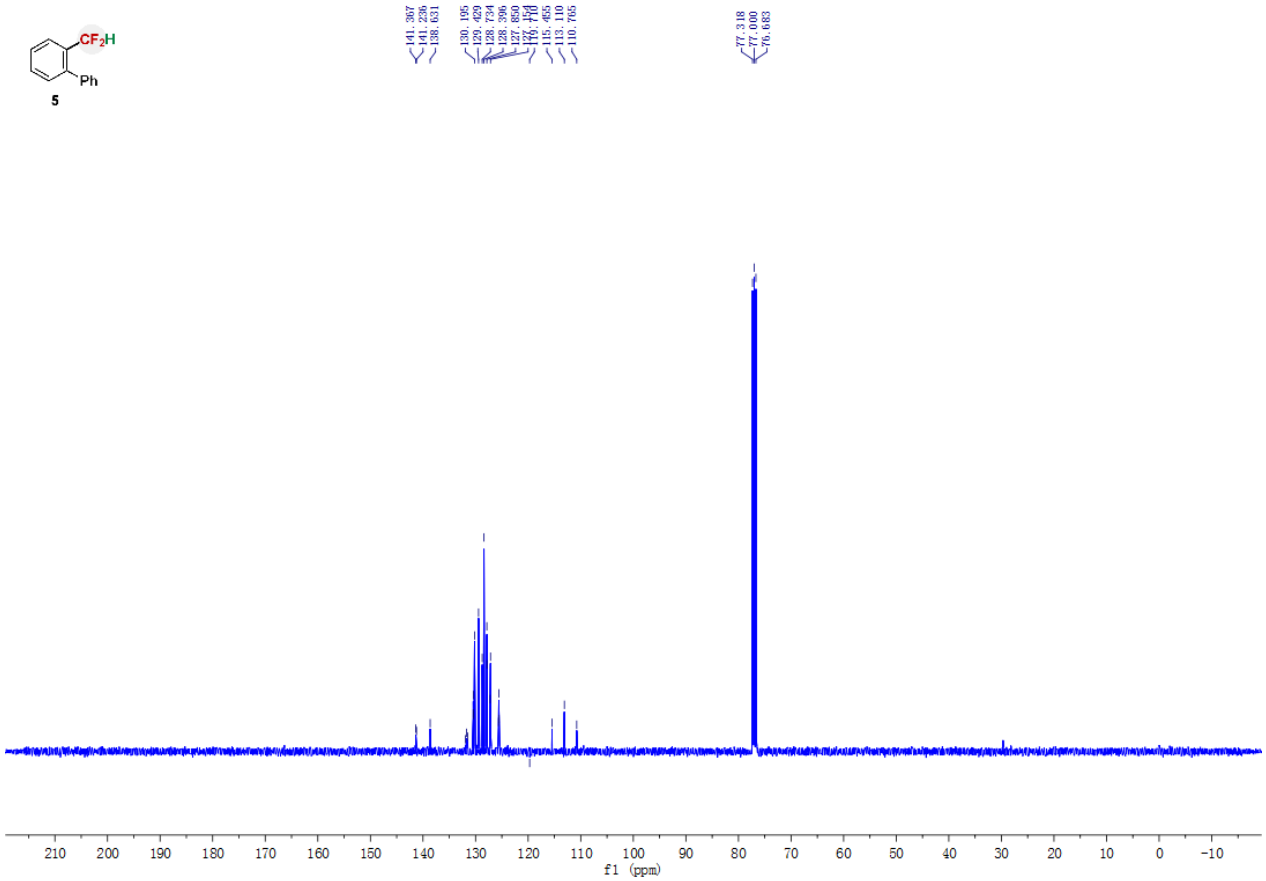

141.655
140.182
134.906
134.685
129.162
128.900
127.784
127.168
114.746
112.371
77.318
77.000
76.683


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

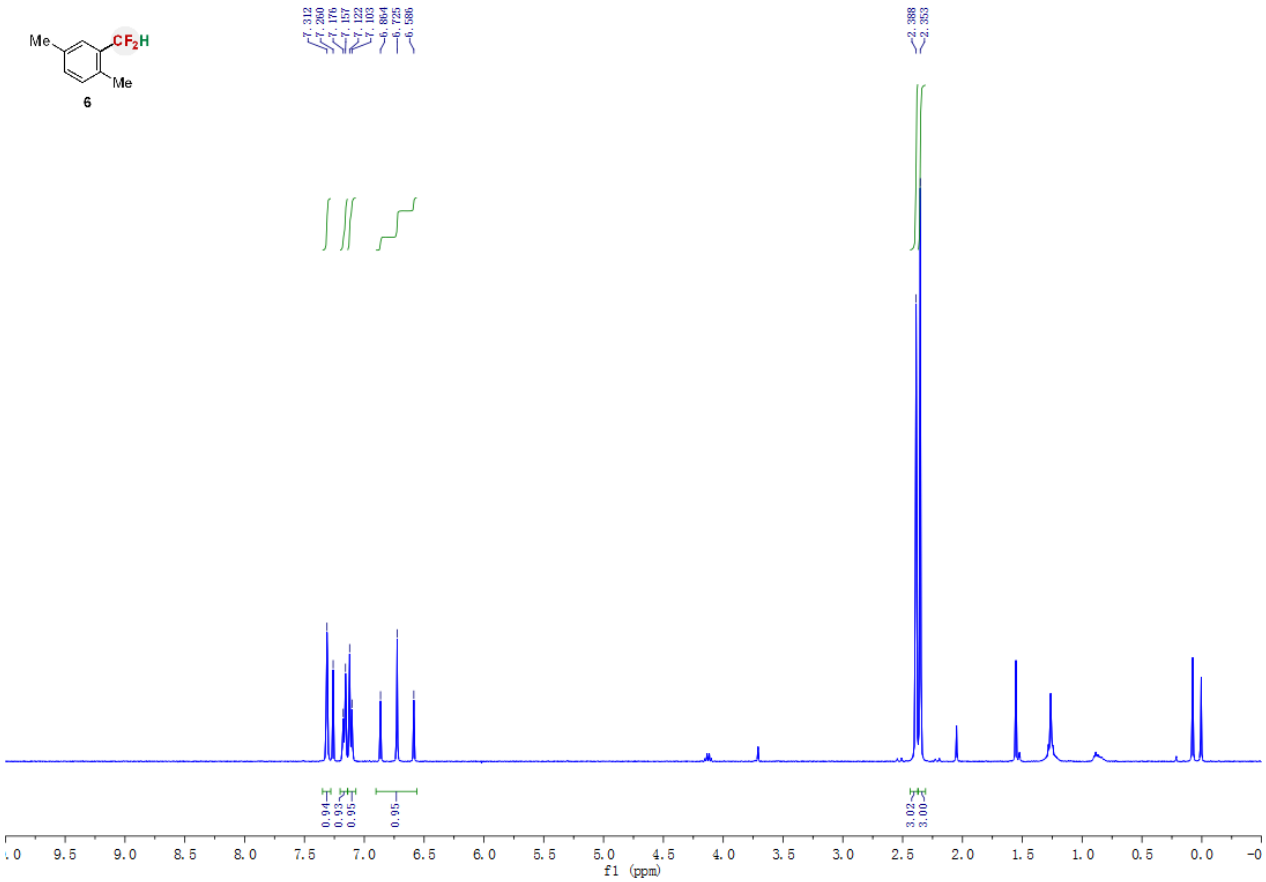
2-(Difluoromethyl)-1,1'-biphenyl (5).

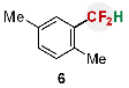






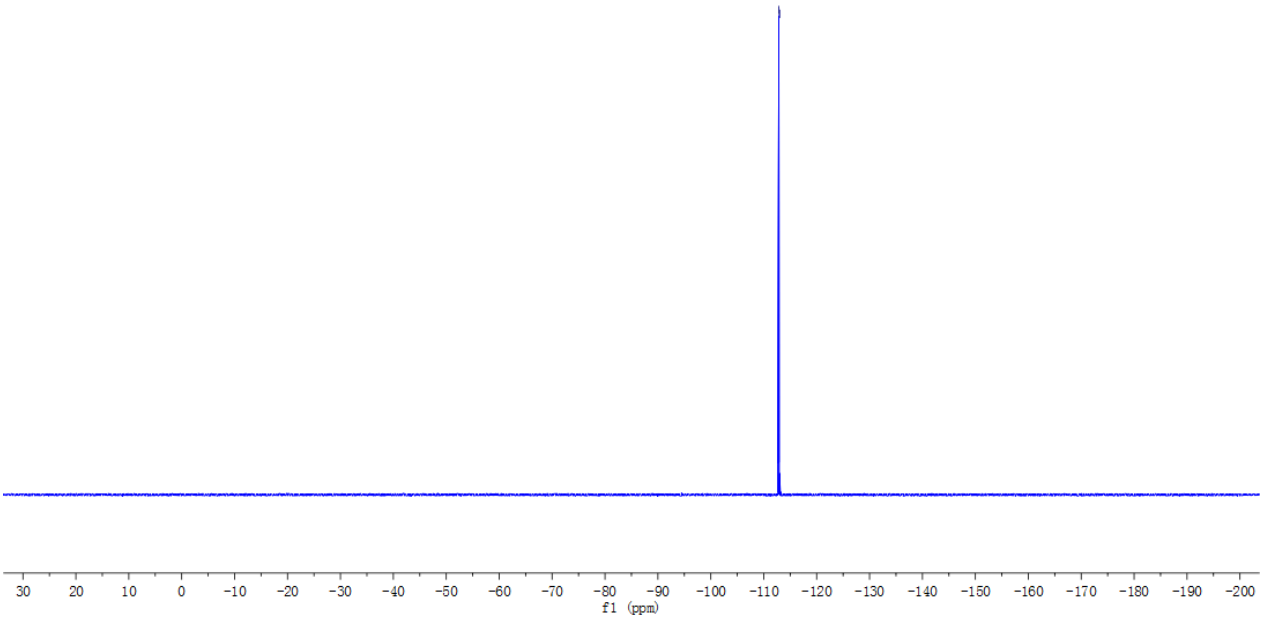
2-(Difluoromethyl)-1,4-dimethylbenzene (6).

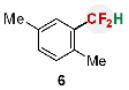



Me
CF2H
Me

6


112.863
113.011


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

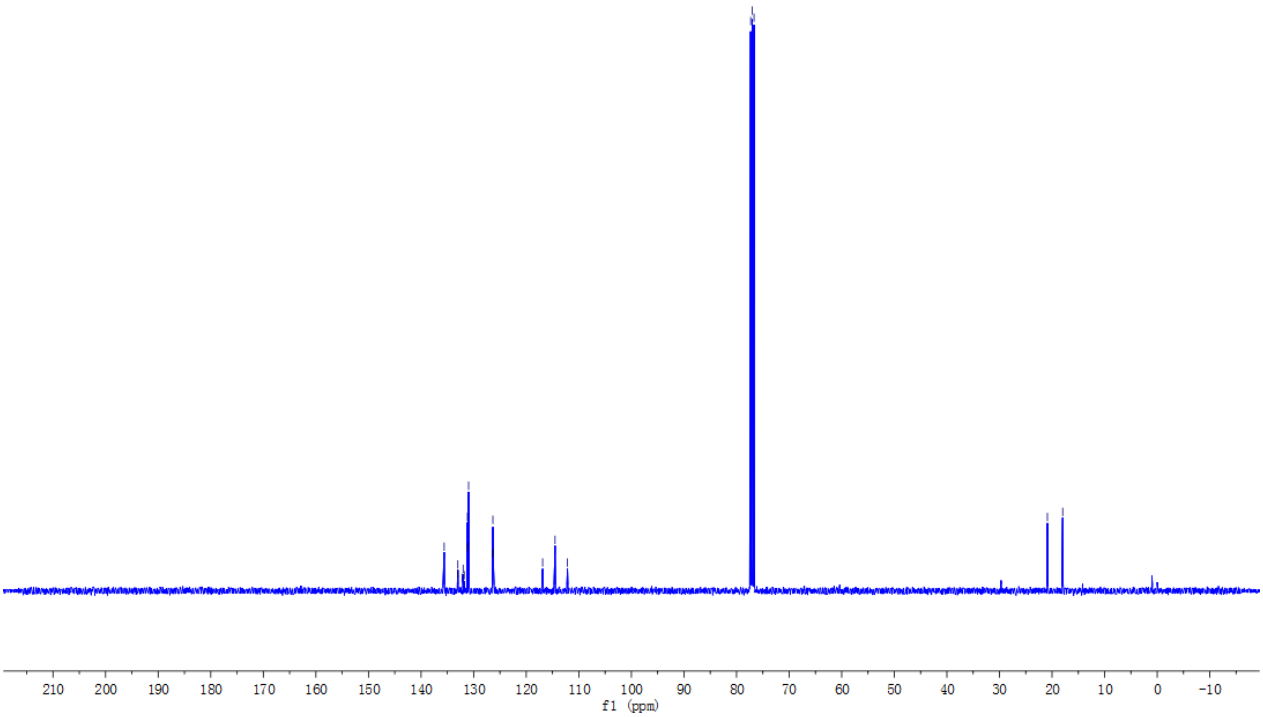

Me
CF2H
Me

6

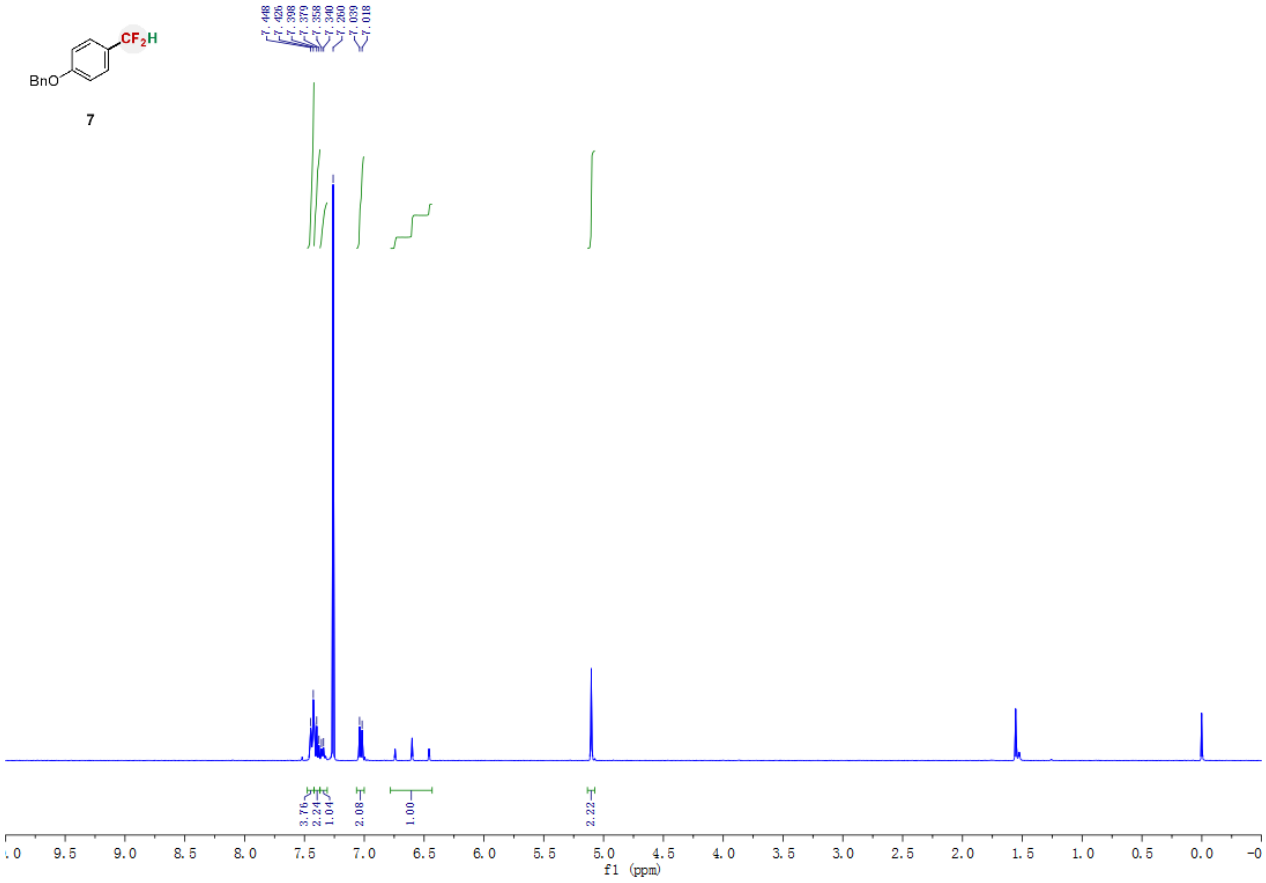

135.602
133.656
133.004
132.999
132.199
131.996
131.791
131.202
131.183
131.163
130.958
126.944
126.544
126.296
116.880
114.519
112.156

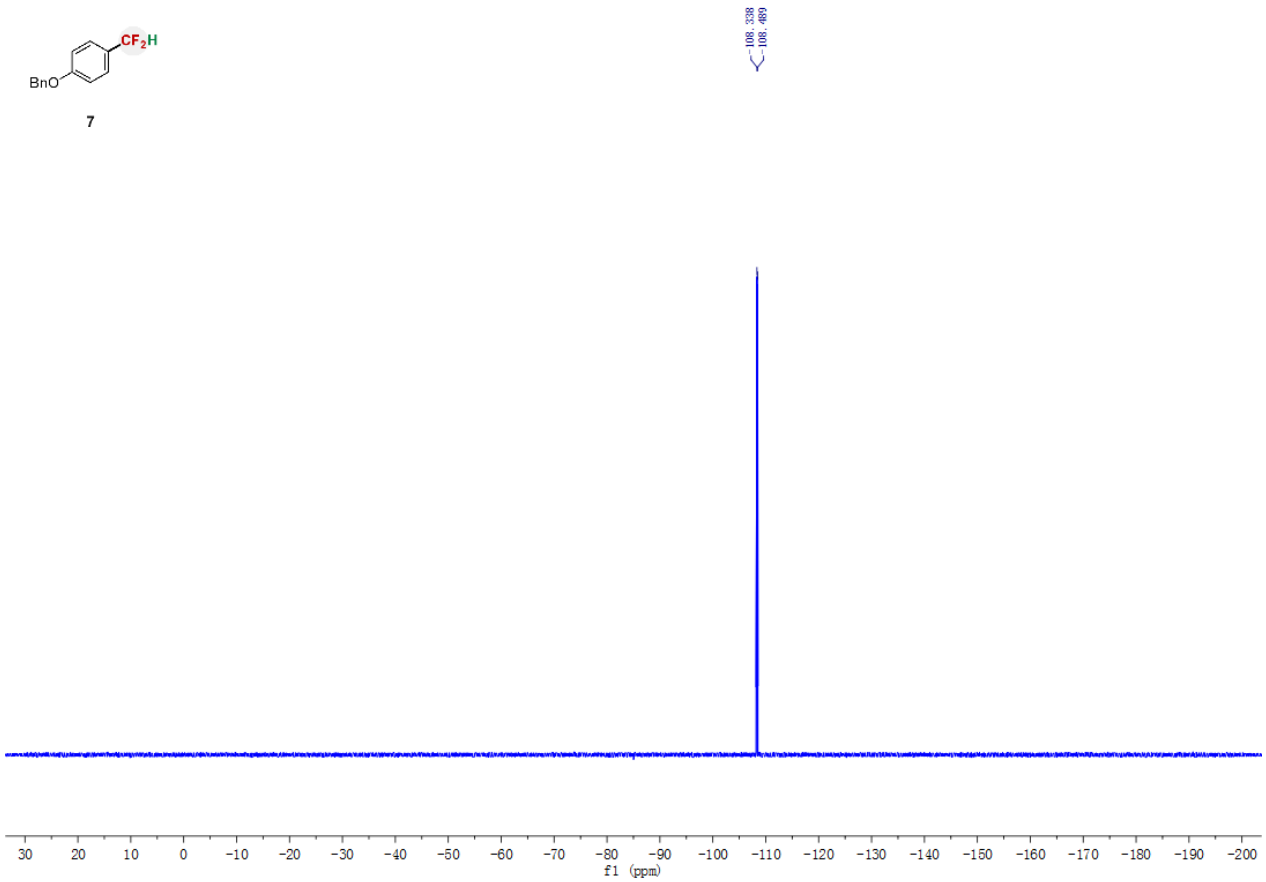

77.317
77.000
76.682

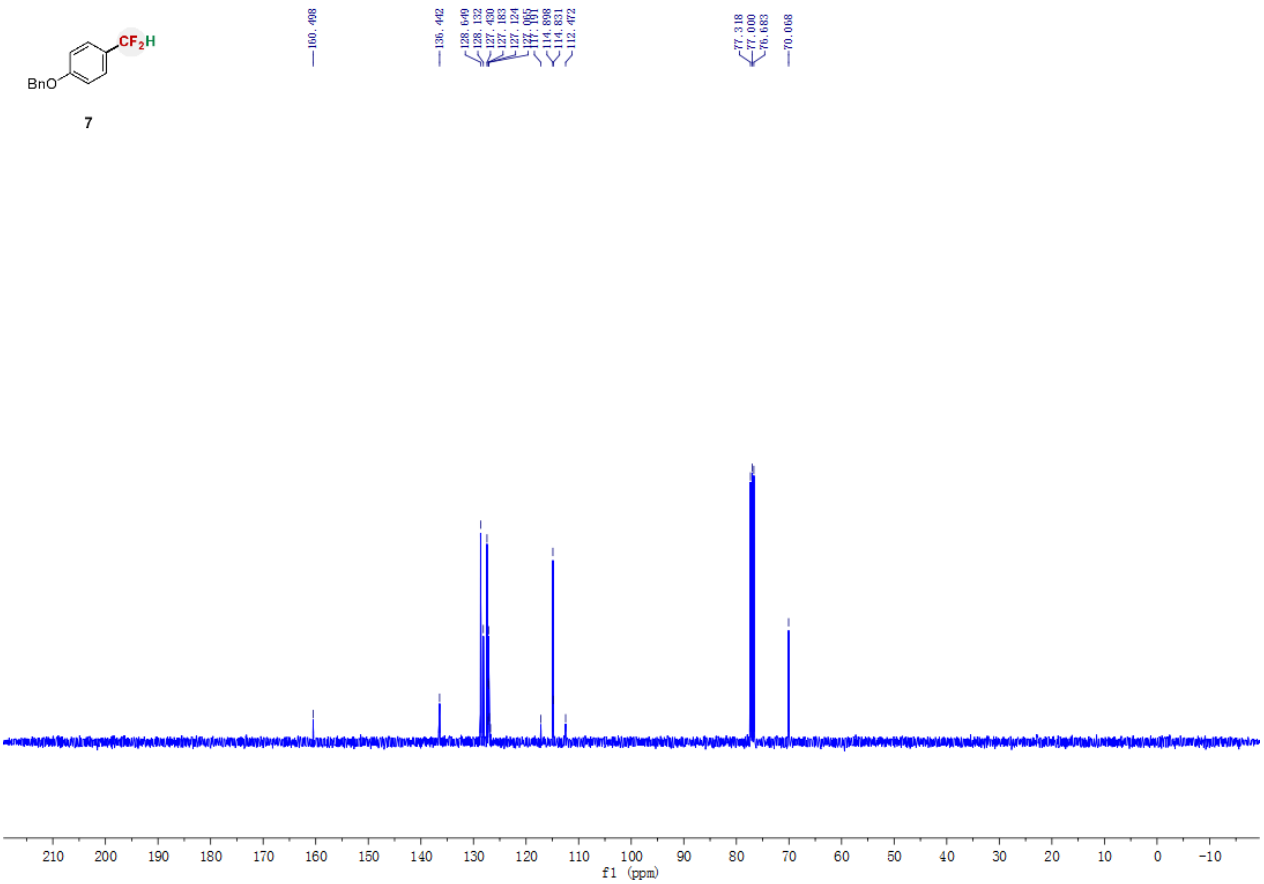

20.884
17.971


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

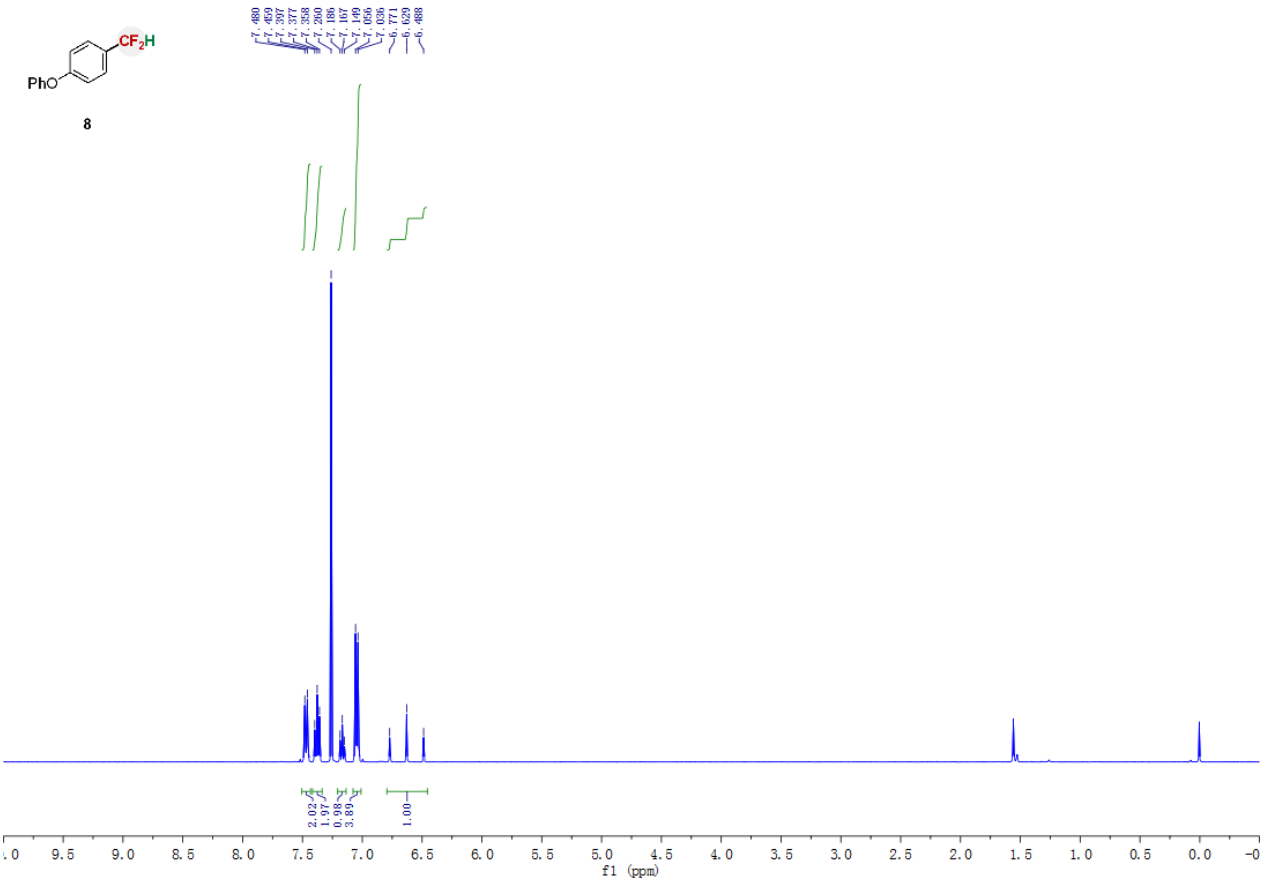
1-(Benzyloxy)-4-(difluoromethyl)benzene (7).

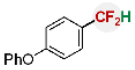






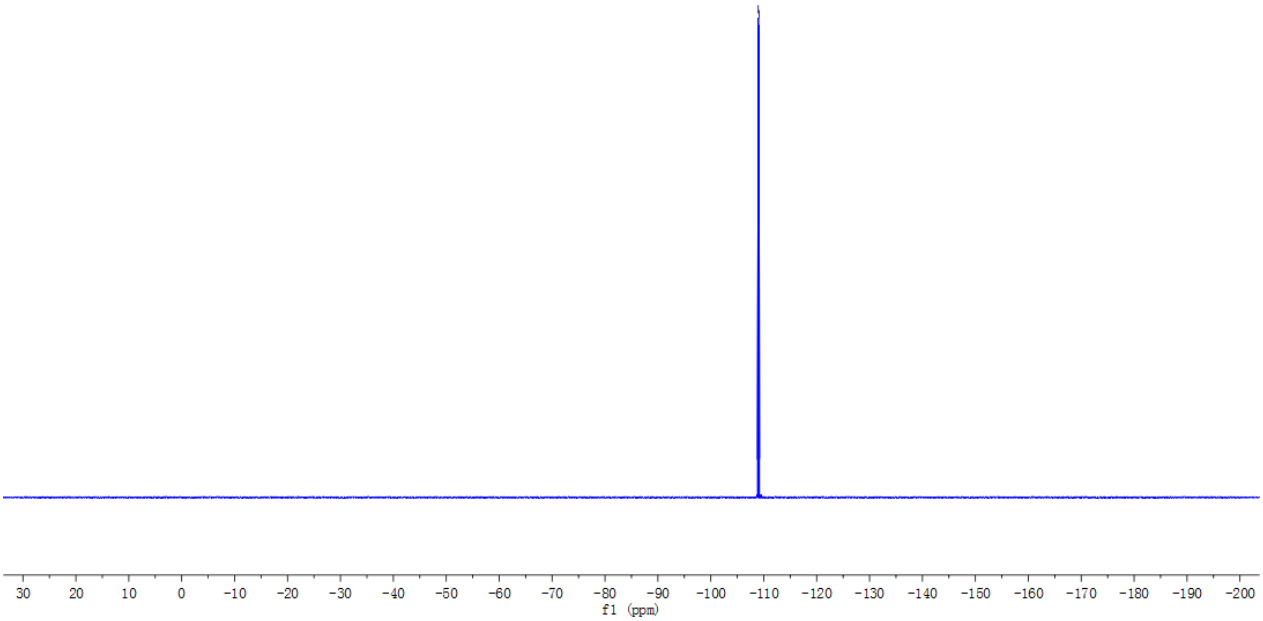
1-(Difluoromethyl)-4-phenoxybenzene (8).

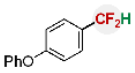



CF2H
PhO

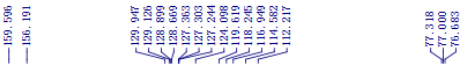
8

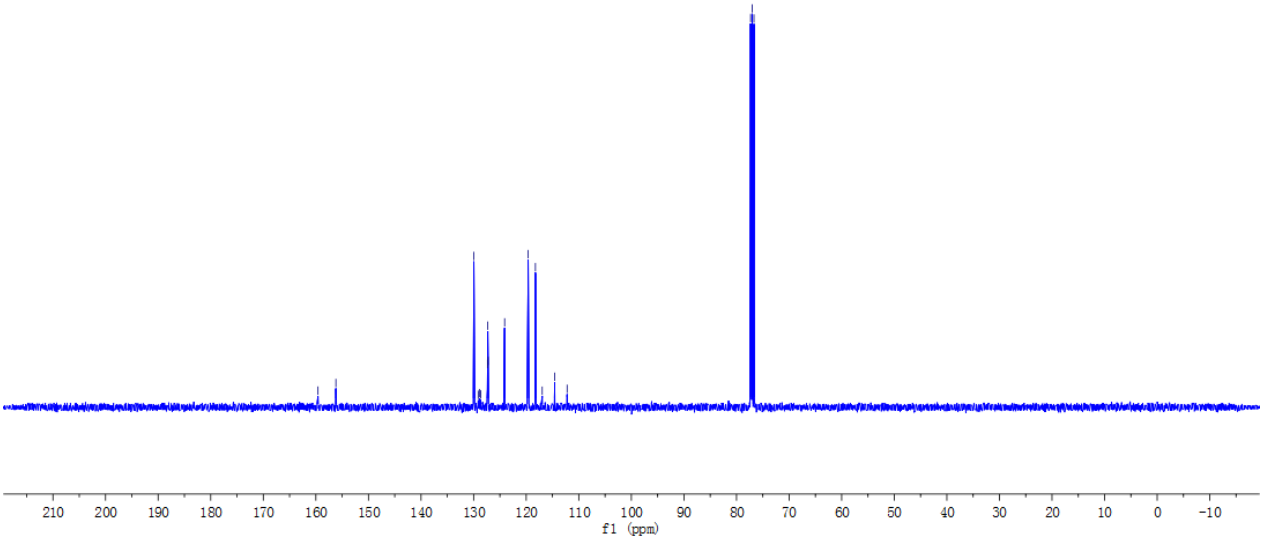

108.902
109.112


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

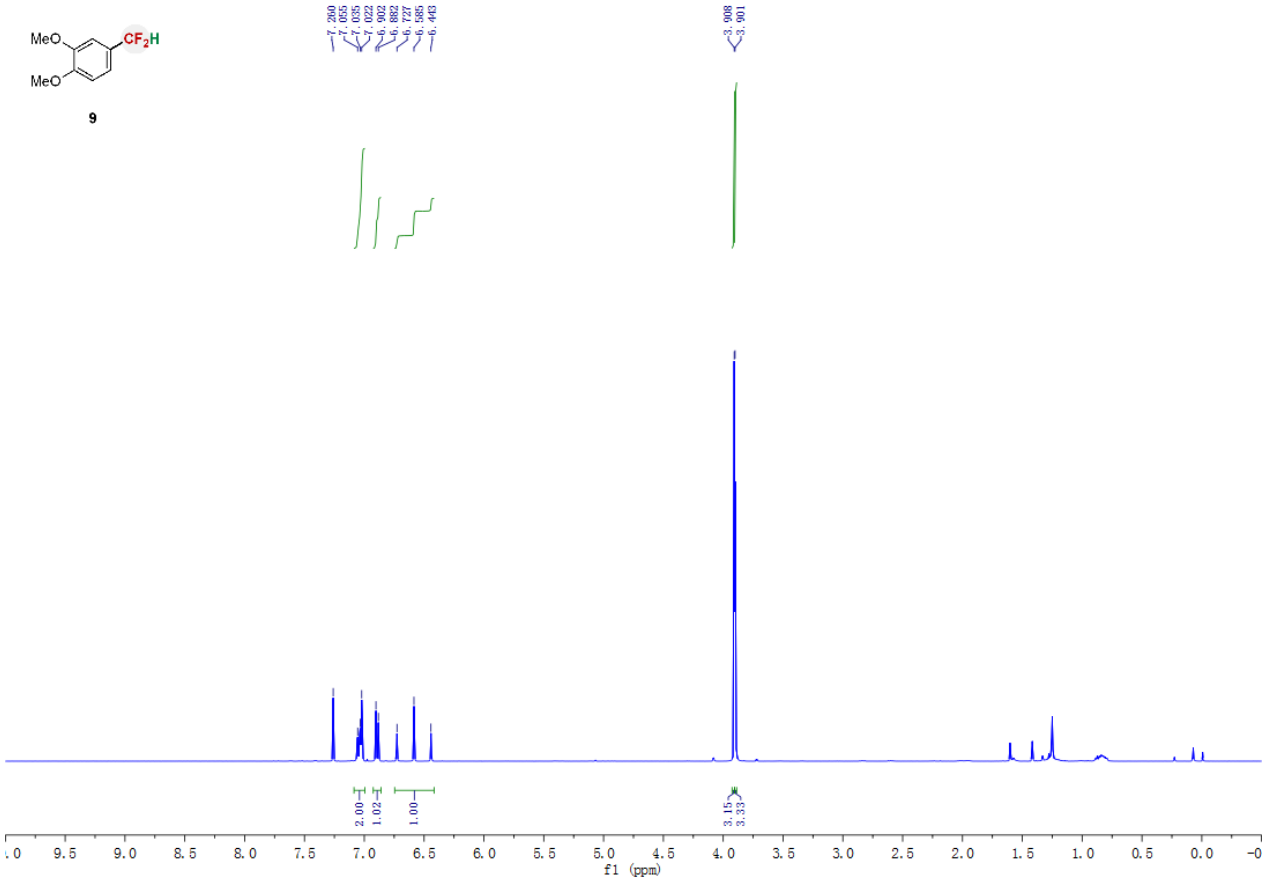

CF2H
PhO

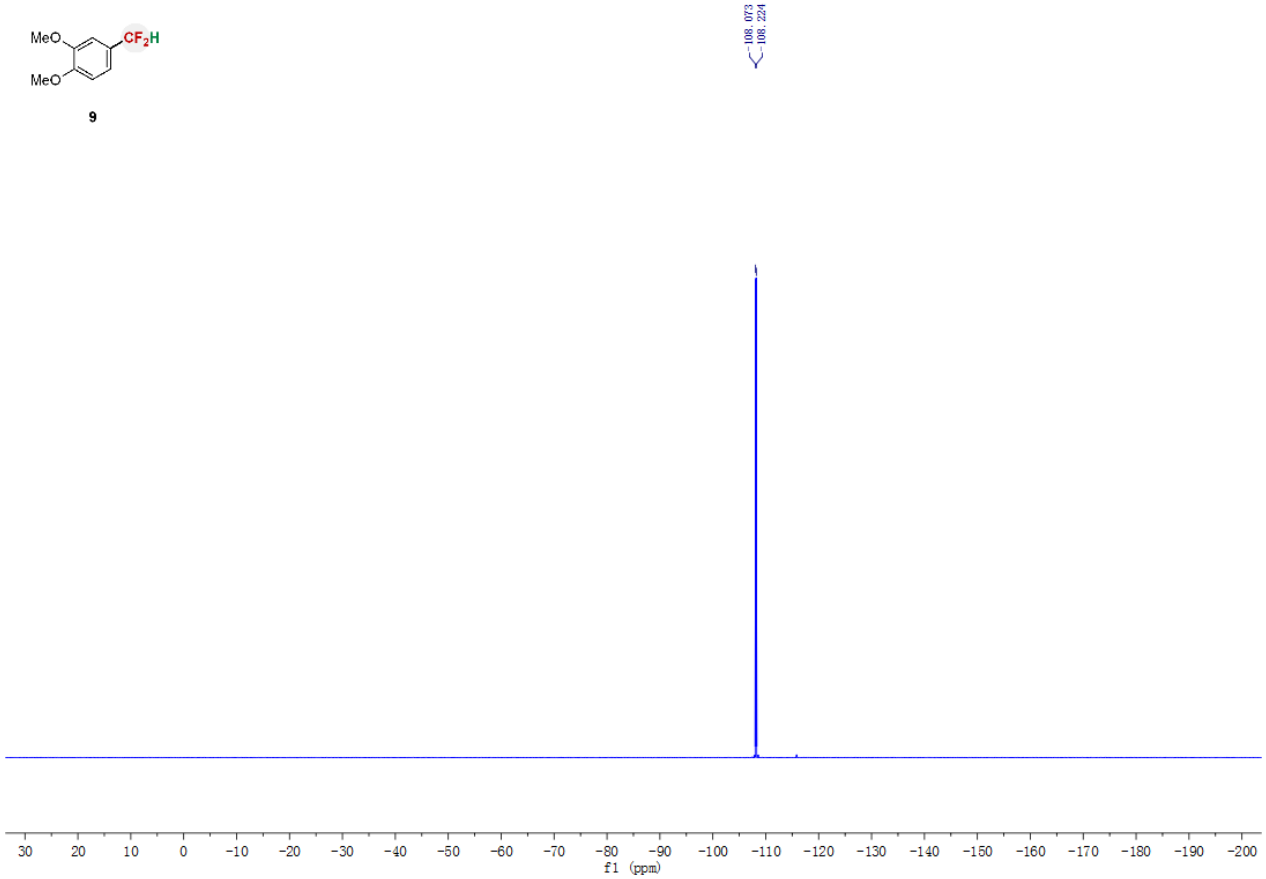
8

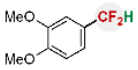

159.596
156.191
129.947
129.126
128.899
128.669
127.363
127.303
127.294
124.098
119.915
118.945
116.949
114.582
112.217
77.318
77.000
76.683


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-(Difluoromethyl)-3,4-dimethoxybenzene (9).

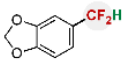




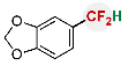


9

5-(Difluoromethyl)benzo[*d*][1,3]dioxole (10).

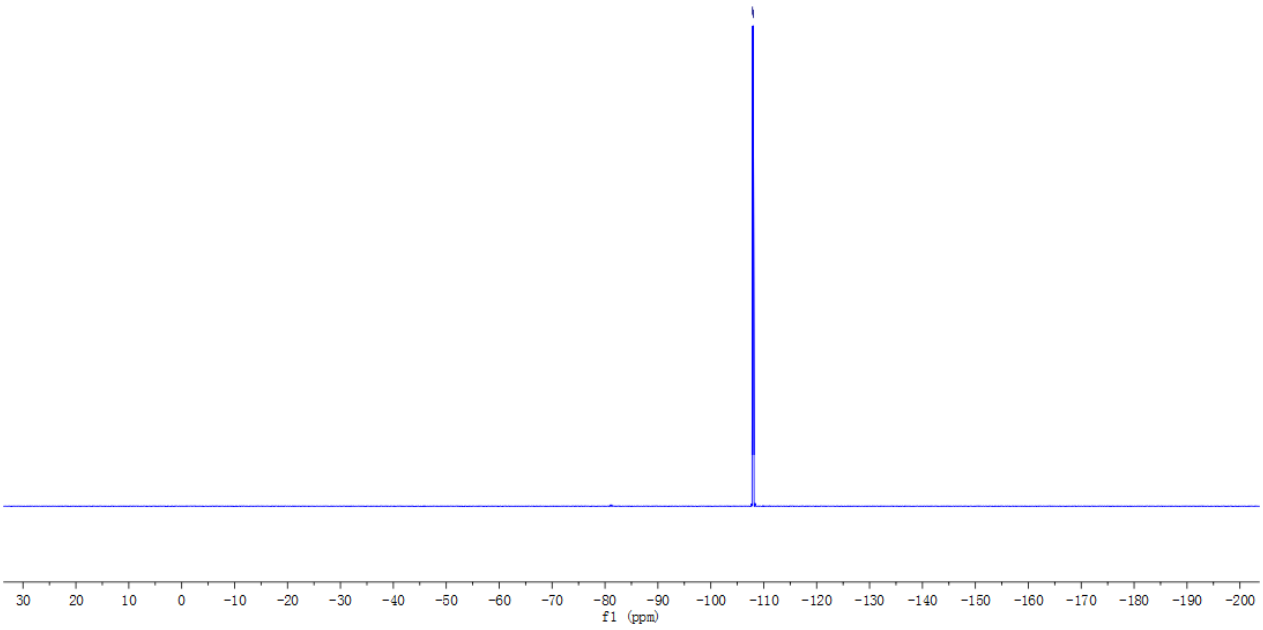


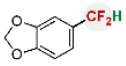
10



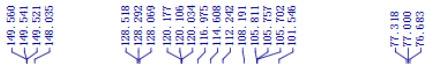
10

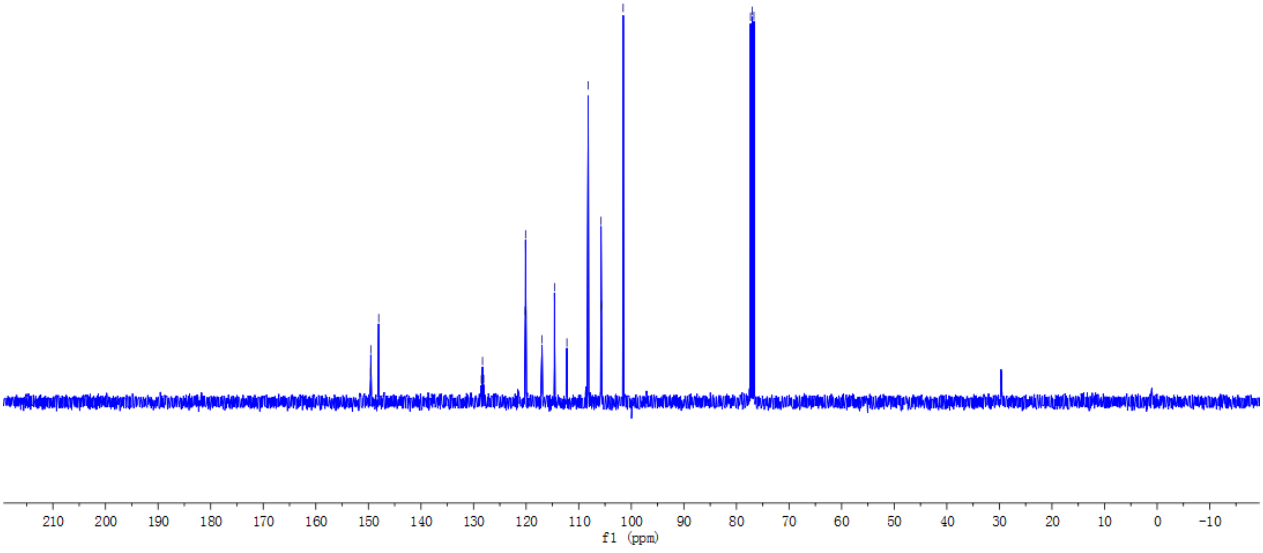

107.870
108.020


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

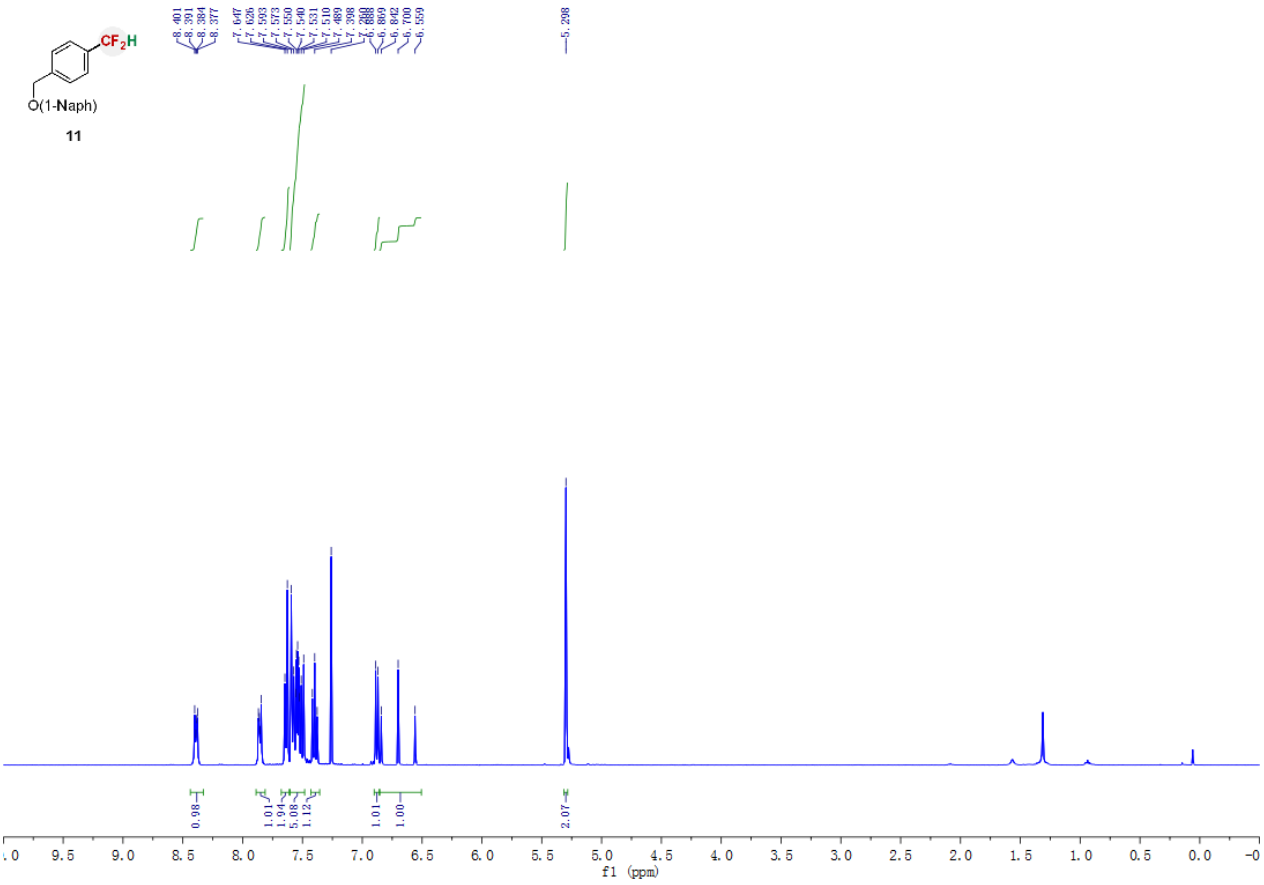


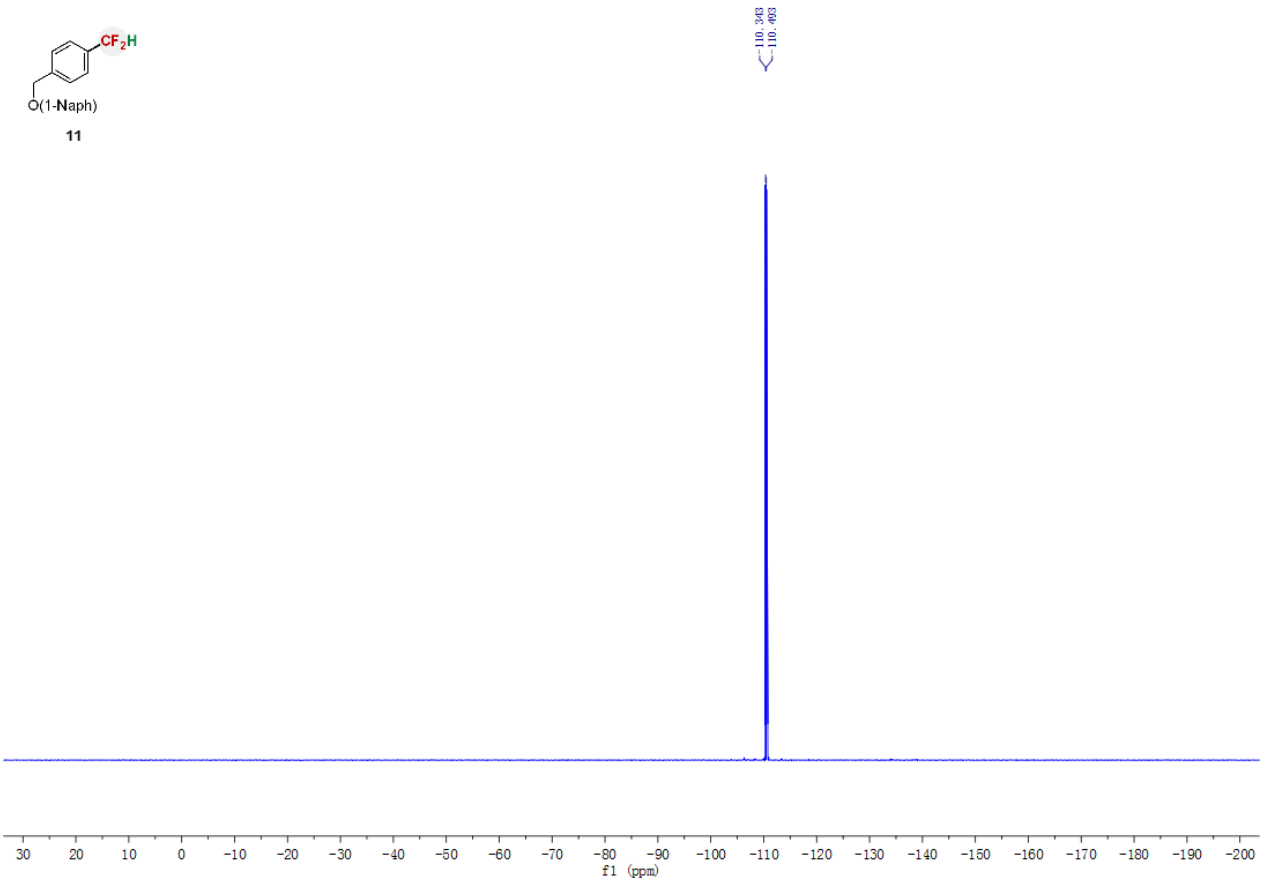
10

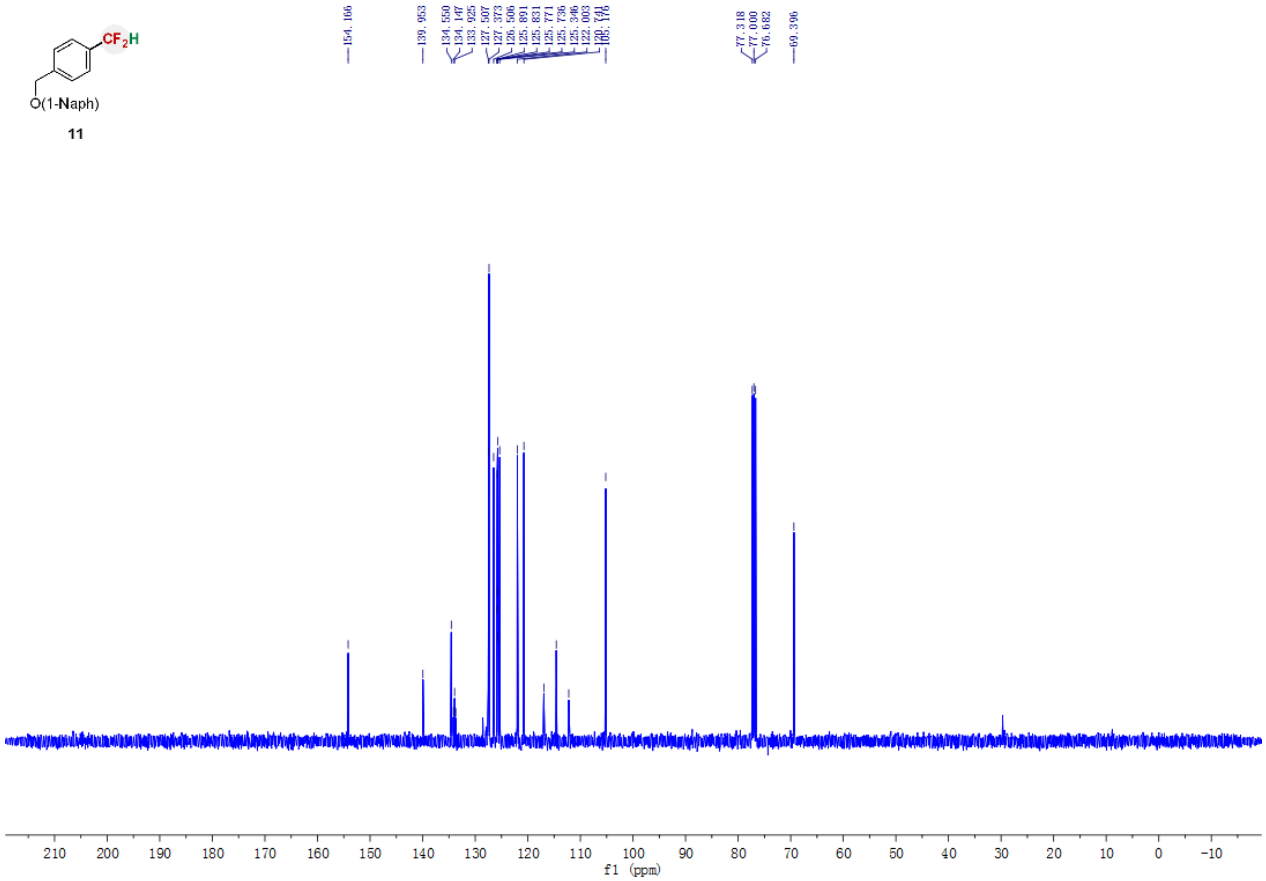

149.560
149.541
149.521
148.035
128.518
128.292
128.069
120.177
120.106
120.034
116.975
114.668
112.292
108.101
105.811
105.757
105.702
101.596
77.318
77.000
76.683


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

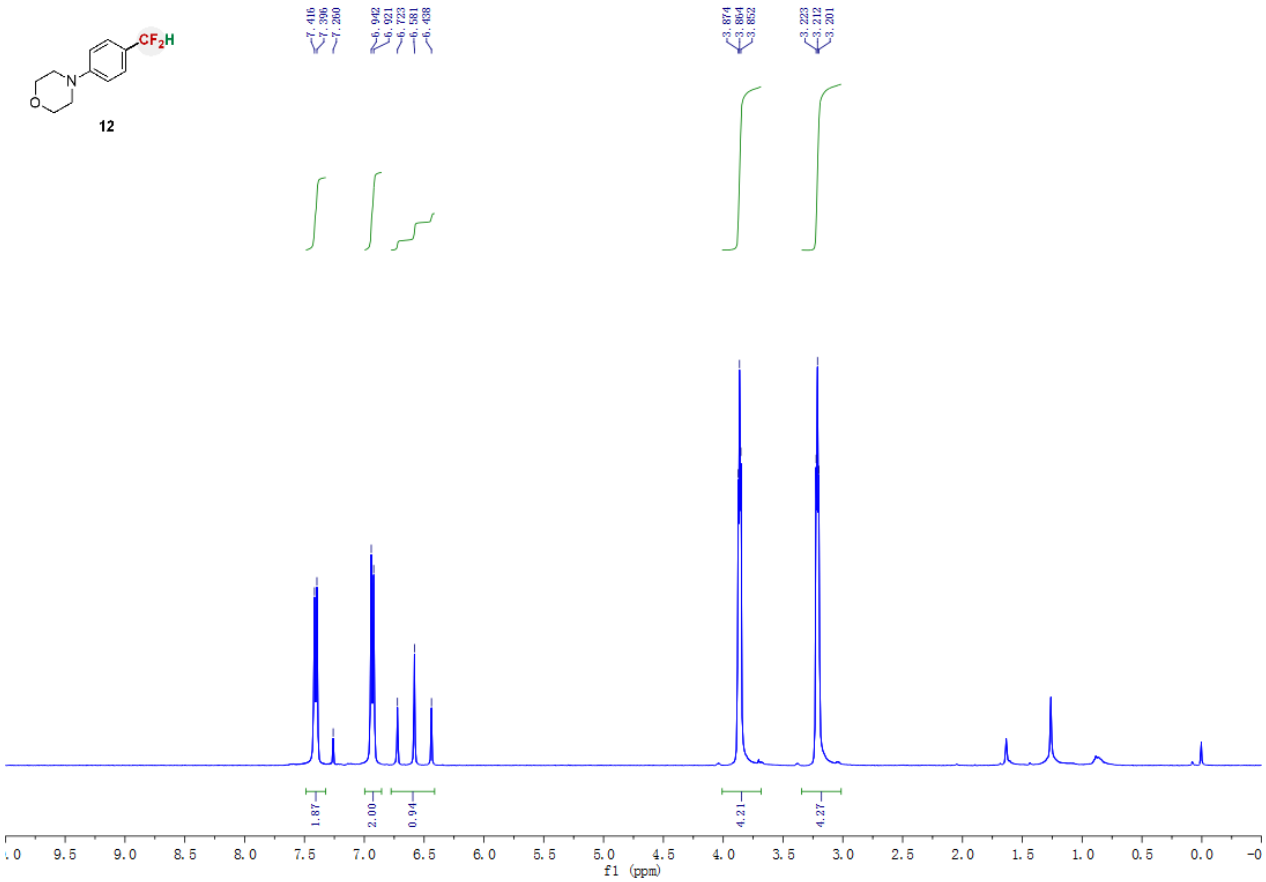
1-((4-(Difluoromethyl)benzyl)oxy)naphthalene (11).

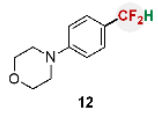




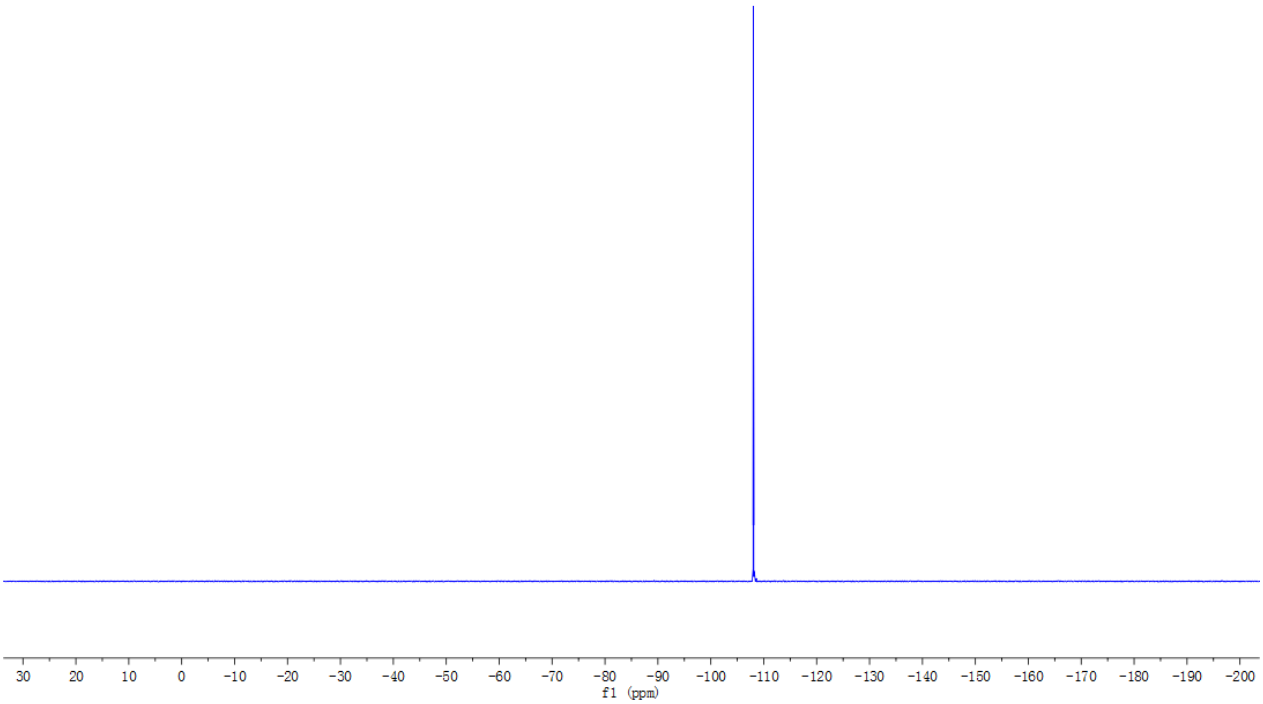


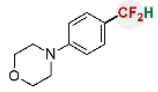
4-(4-(Difluoromethyl)phenyl)morpholine (12).





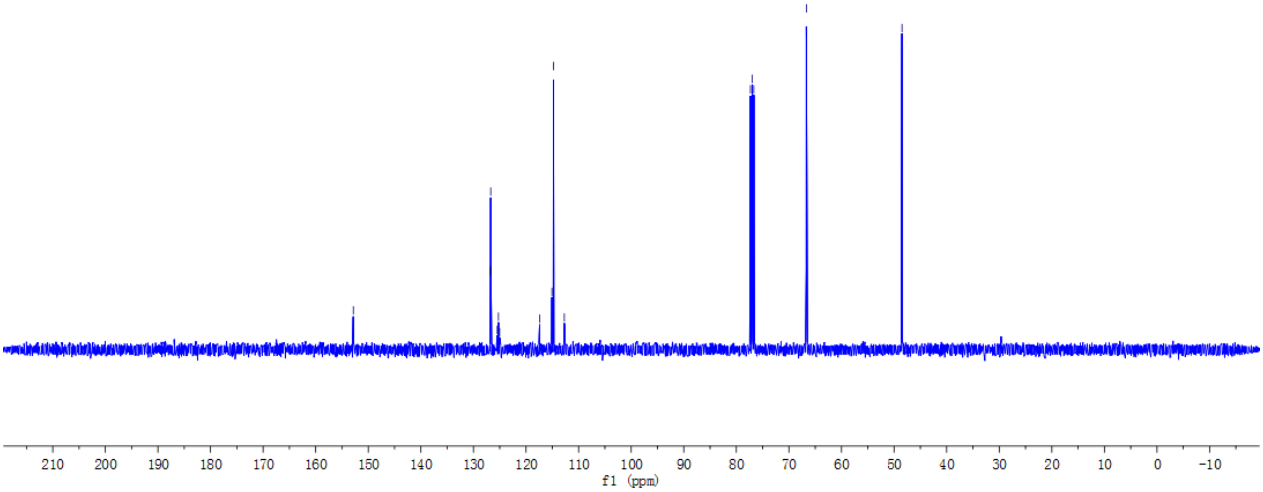
12



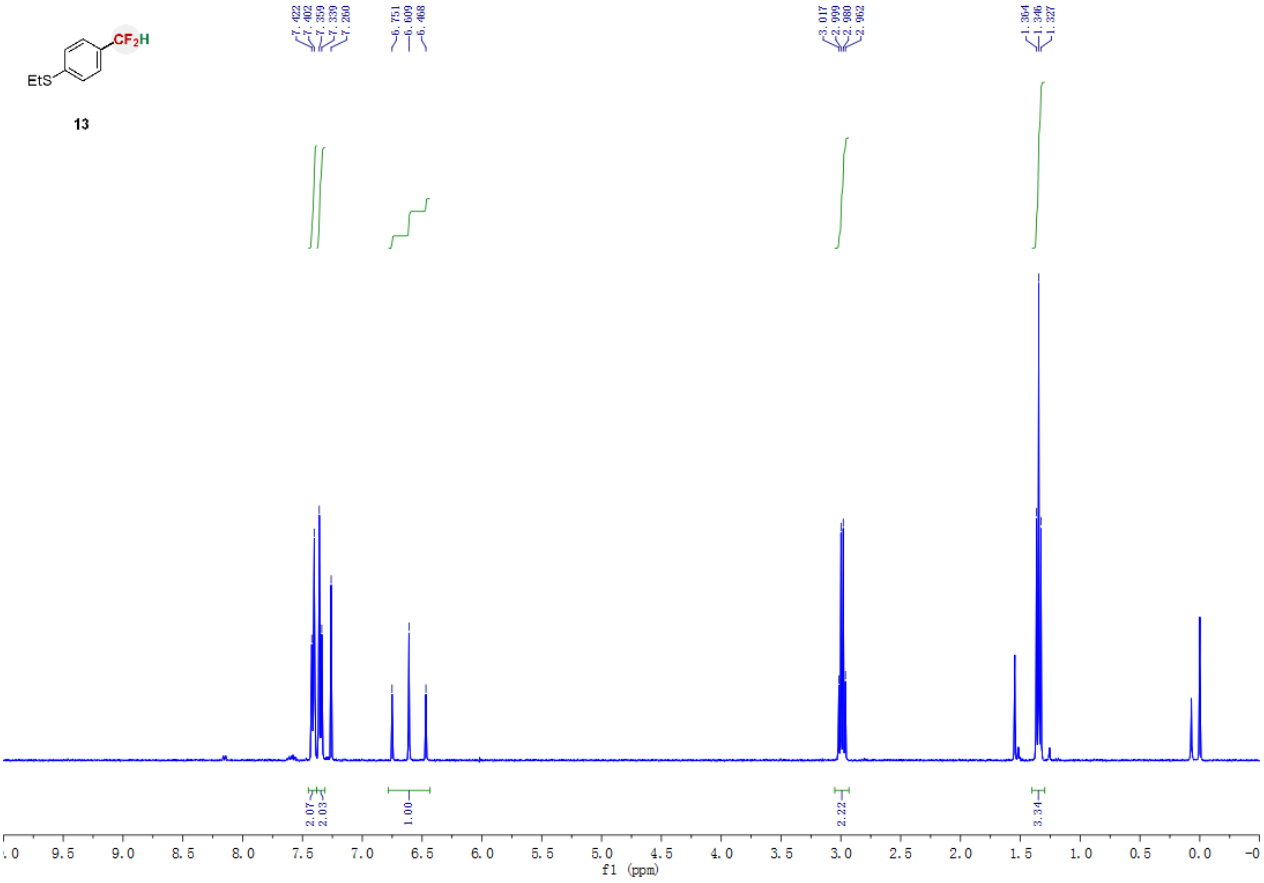


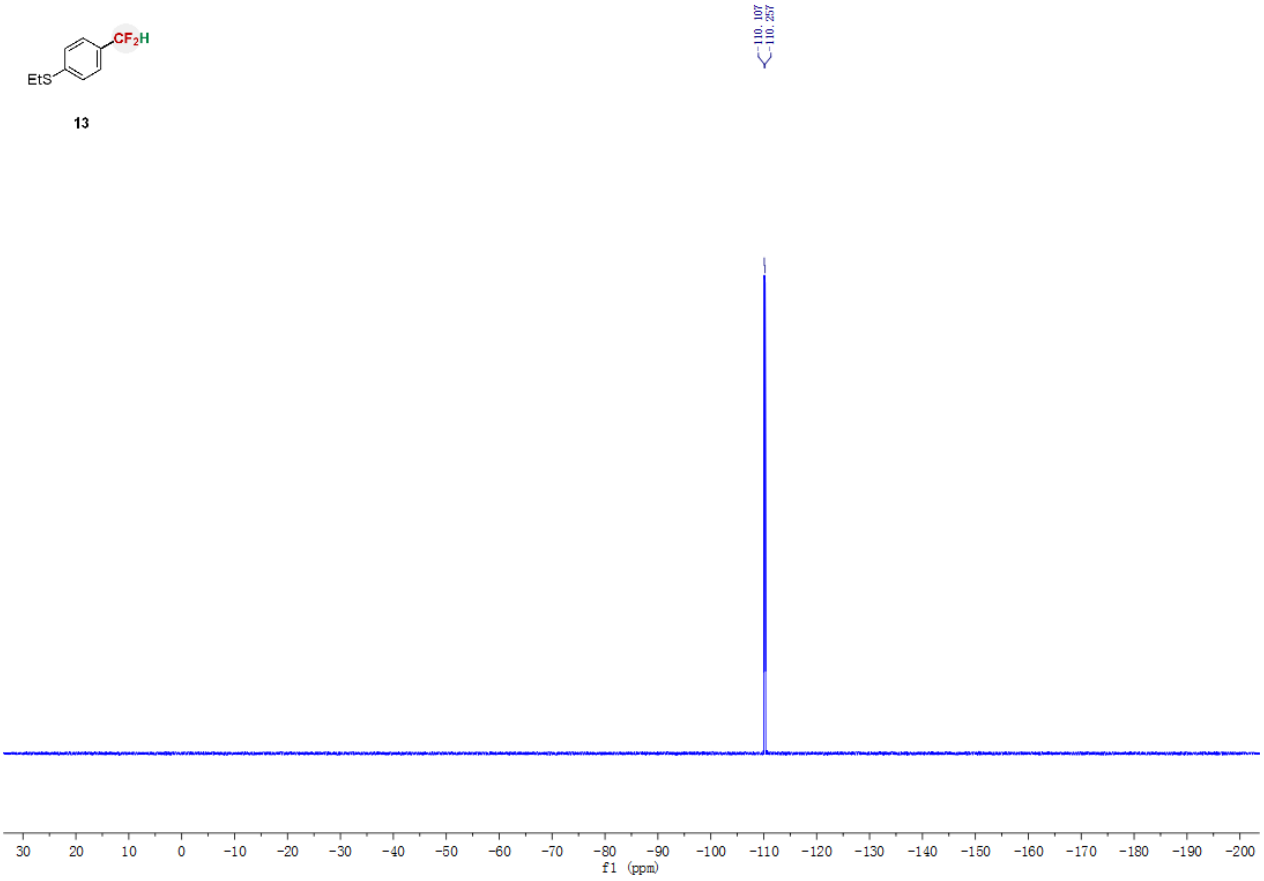
12

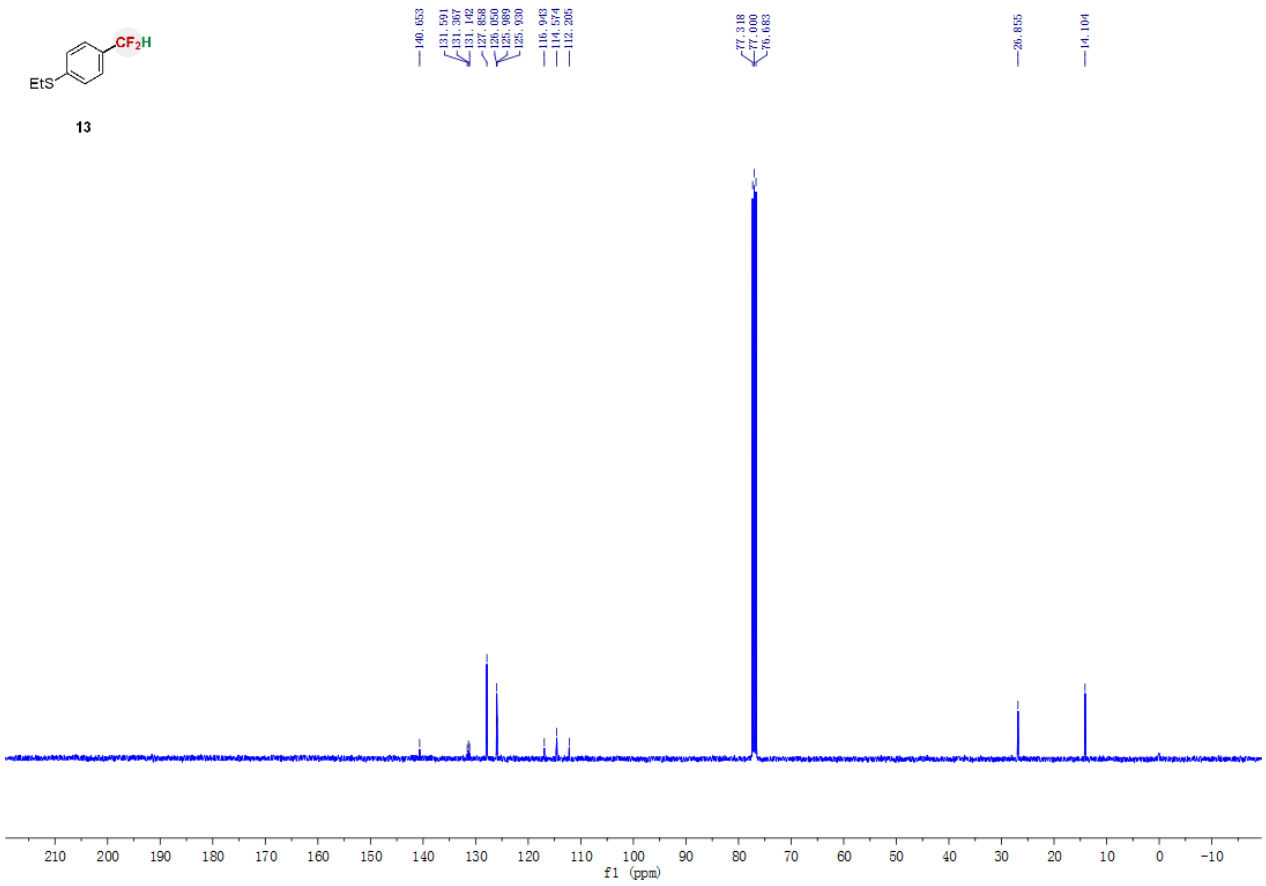
152.845
126.767
126.708
126.650
125.469
125.243
125.017
117.422
115.997
112.781
112.713
77.318
77.000
76.682
66.684
48.494



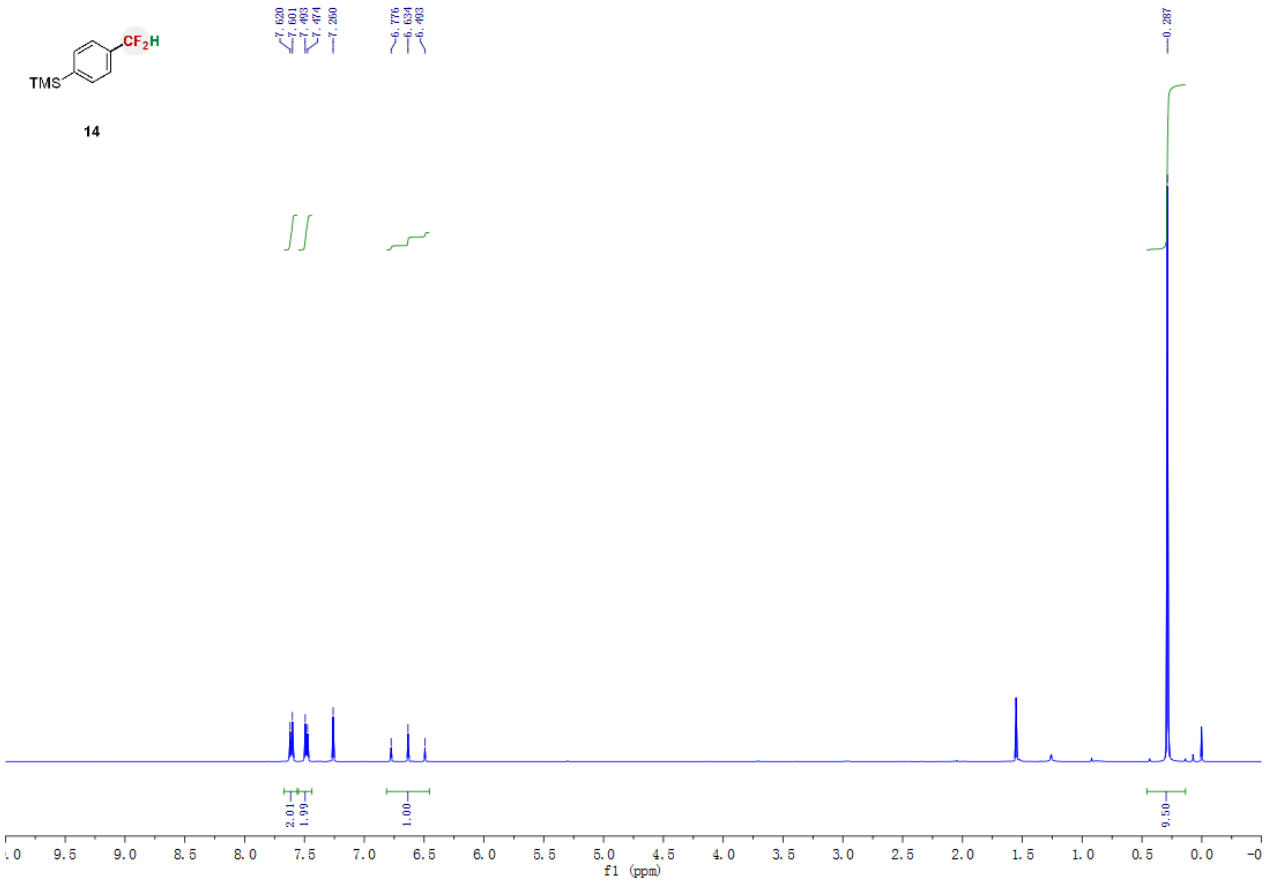
(4-(Difluoromethyl)phenyl)(ethyl)sulfane (13).

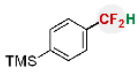






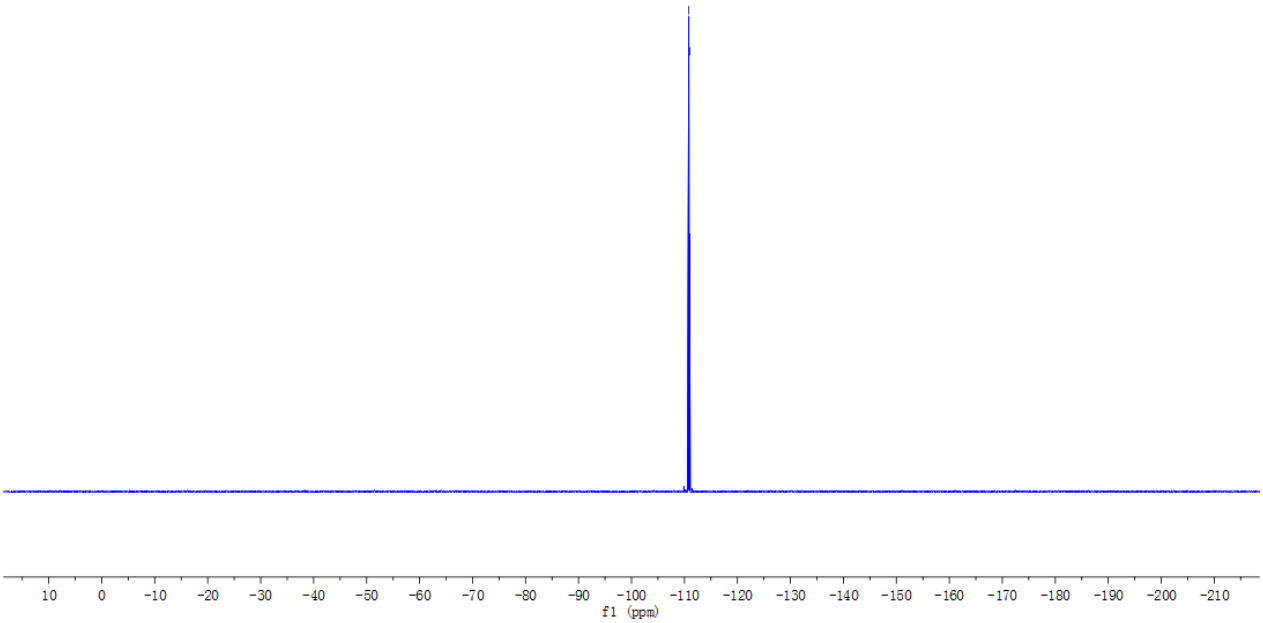
(4-(Difluoromethyl)phenyl)trimethylsilane (14).

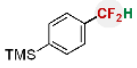



CF2H
TMS

14

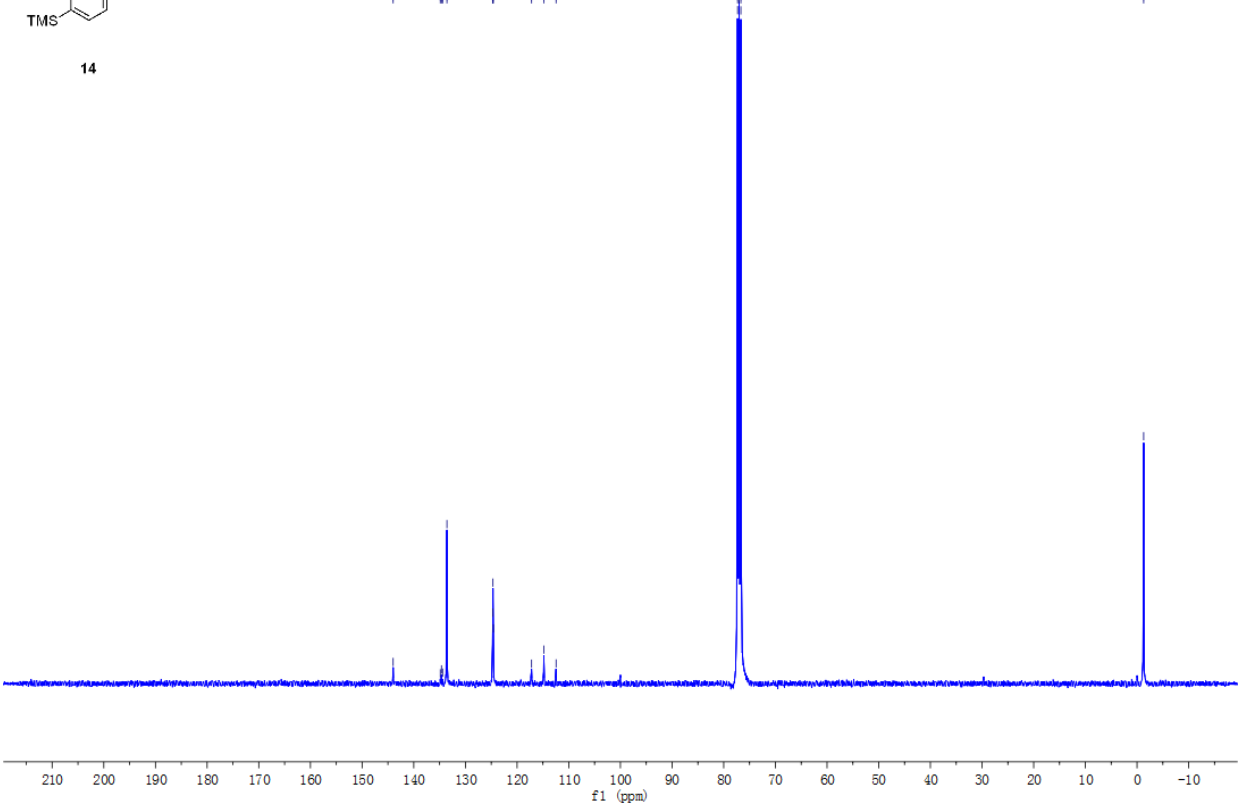

110.821
110.971


10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

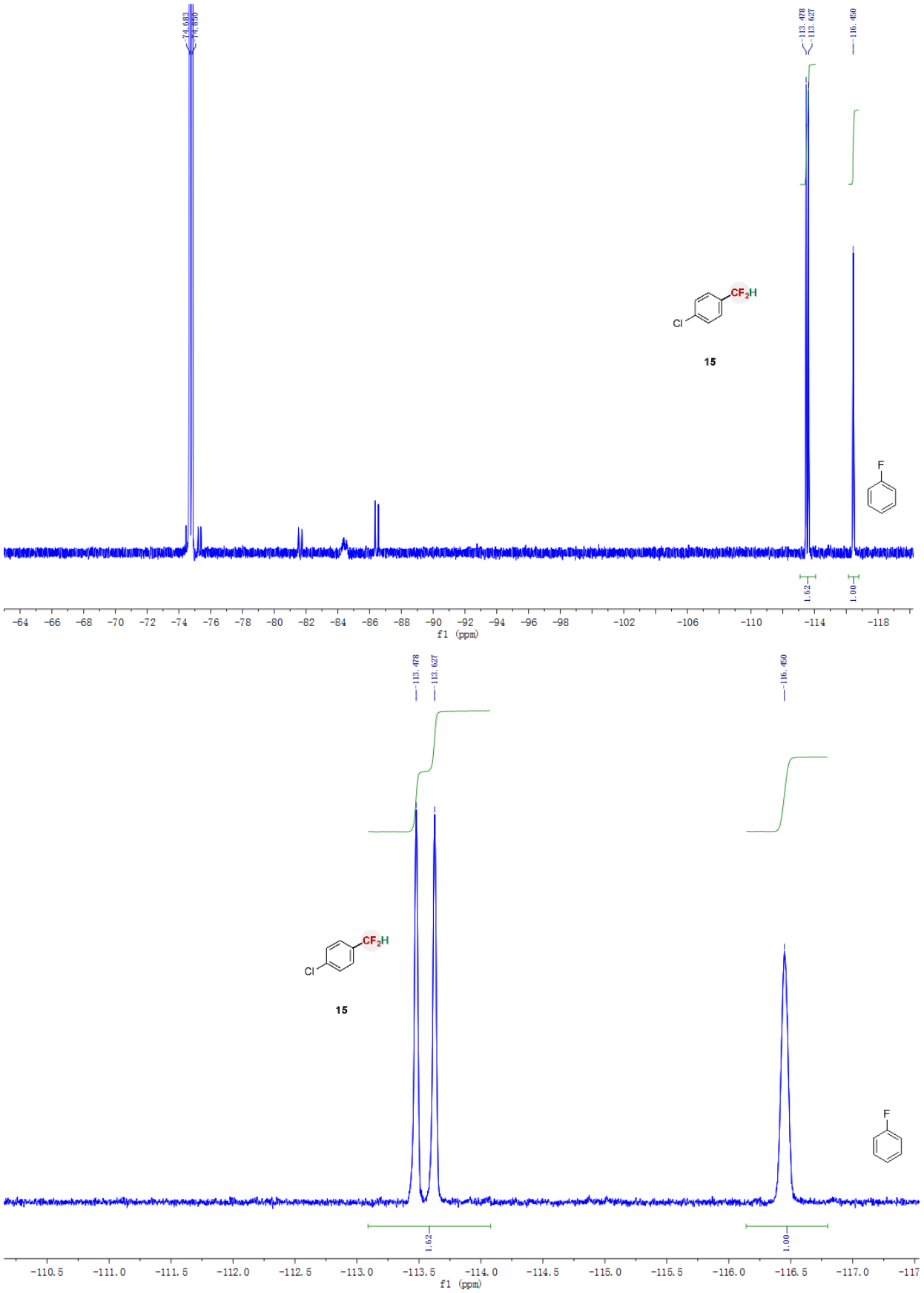

CF2H
TMS

14

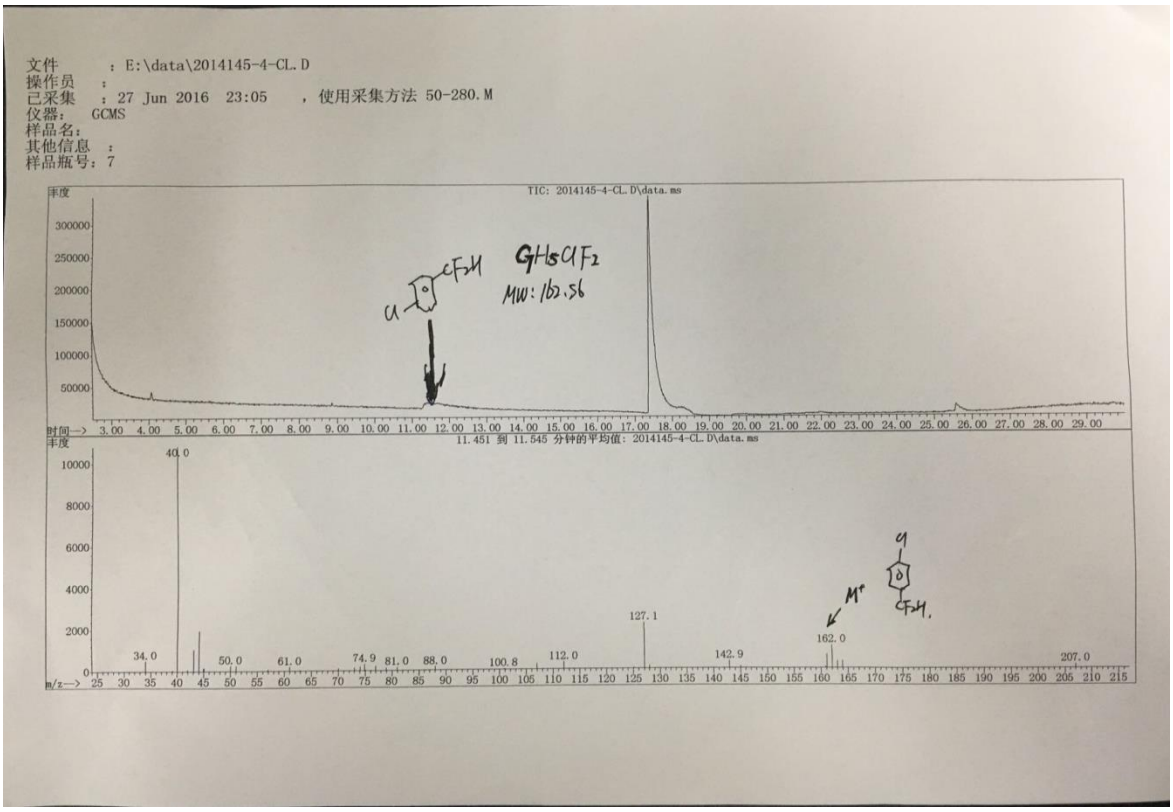

143.990
134.862
134.638
134.416
133.576
124.728
124.669
124.610
117.194
114.823
112.452
77.317
77.000
76.682
1.288


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

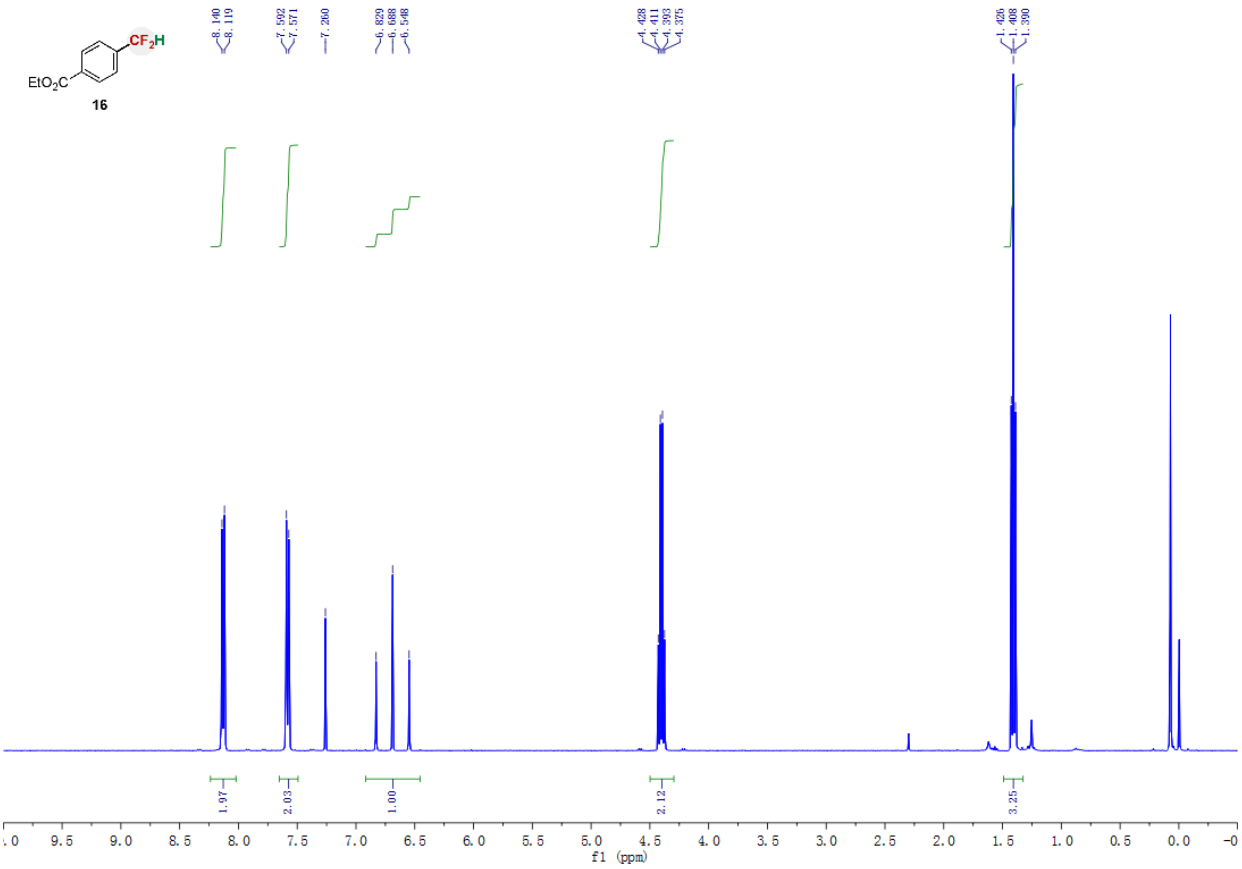
Crude ^{19}F NMR of 1-Chloro-4-(difluoromethyl)benzene (15) using fluorobenzene as internal standard.

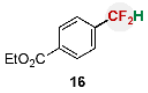


GC-MS of Crude 1-Chloro-4-(difluoromethyl)benzene (15)



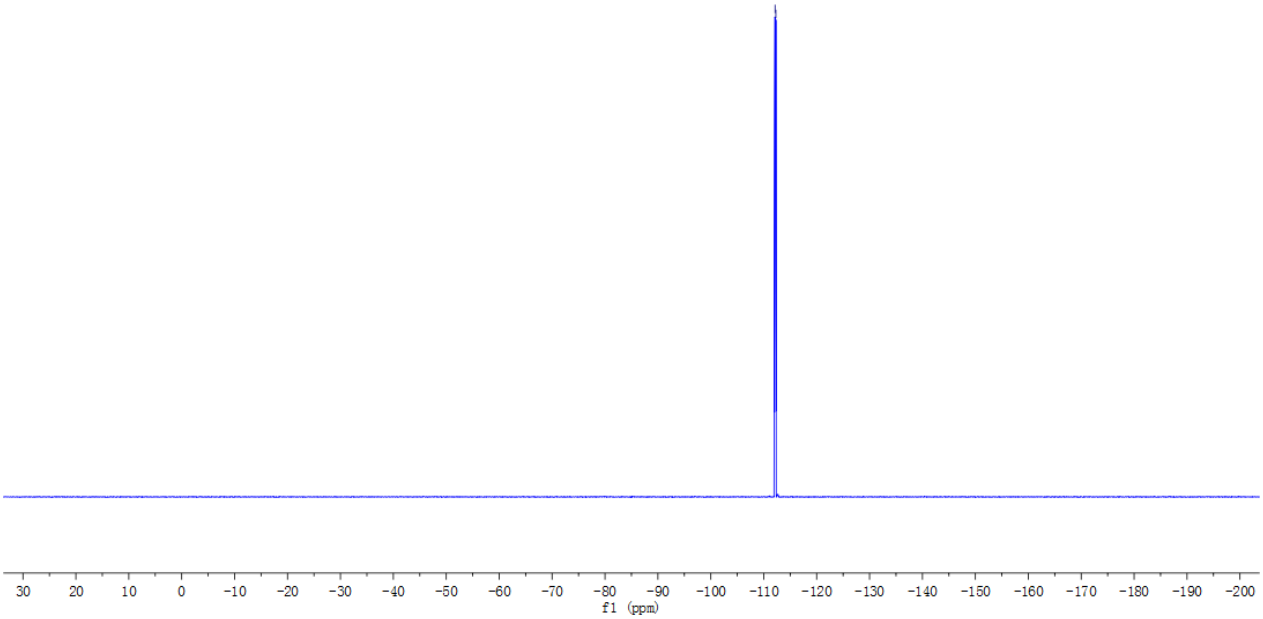
Ethyl 4-(difluoromethyl)benzoate (16).

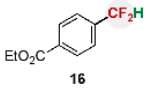



CF2H
EtO2C

16

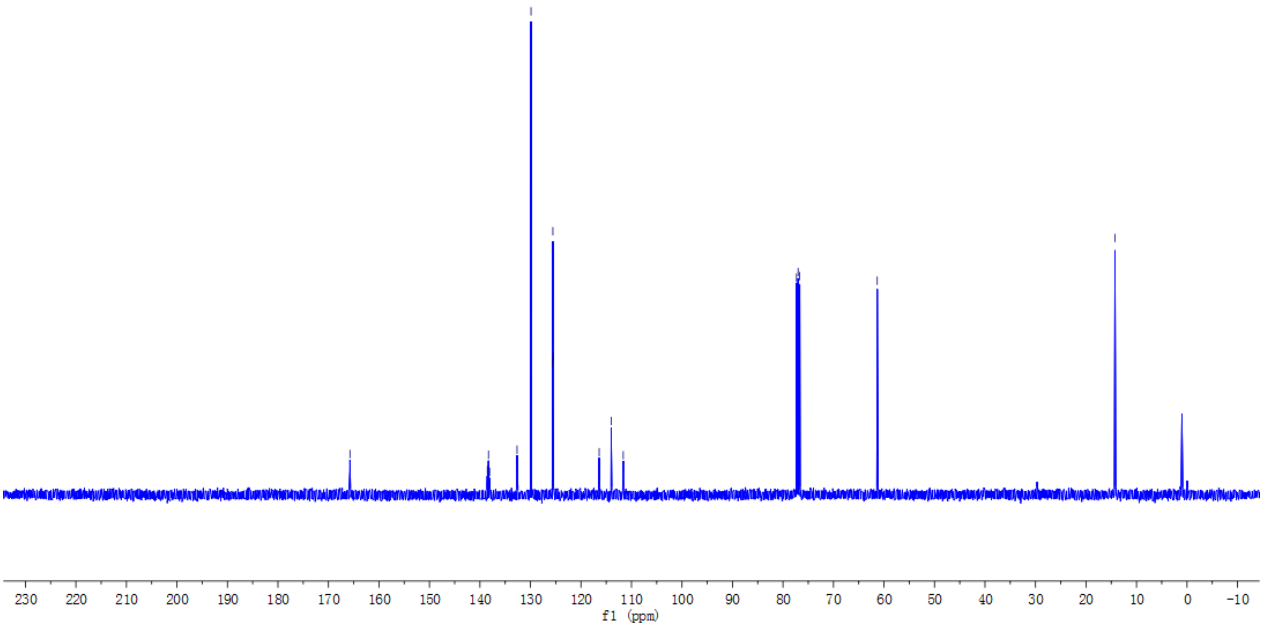

112.142
112.291


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

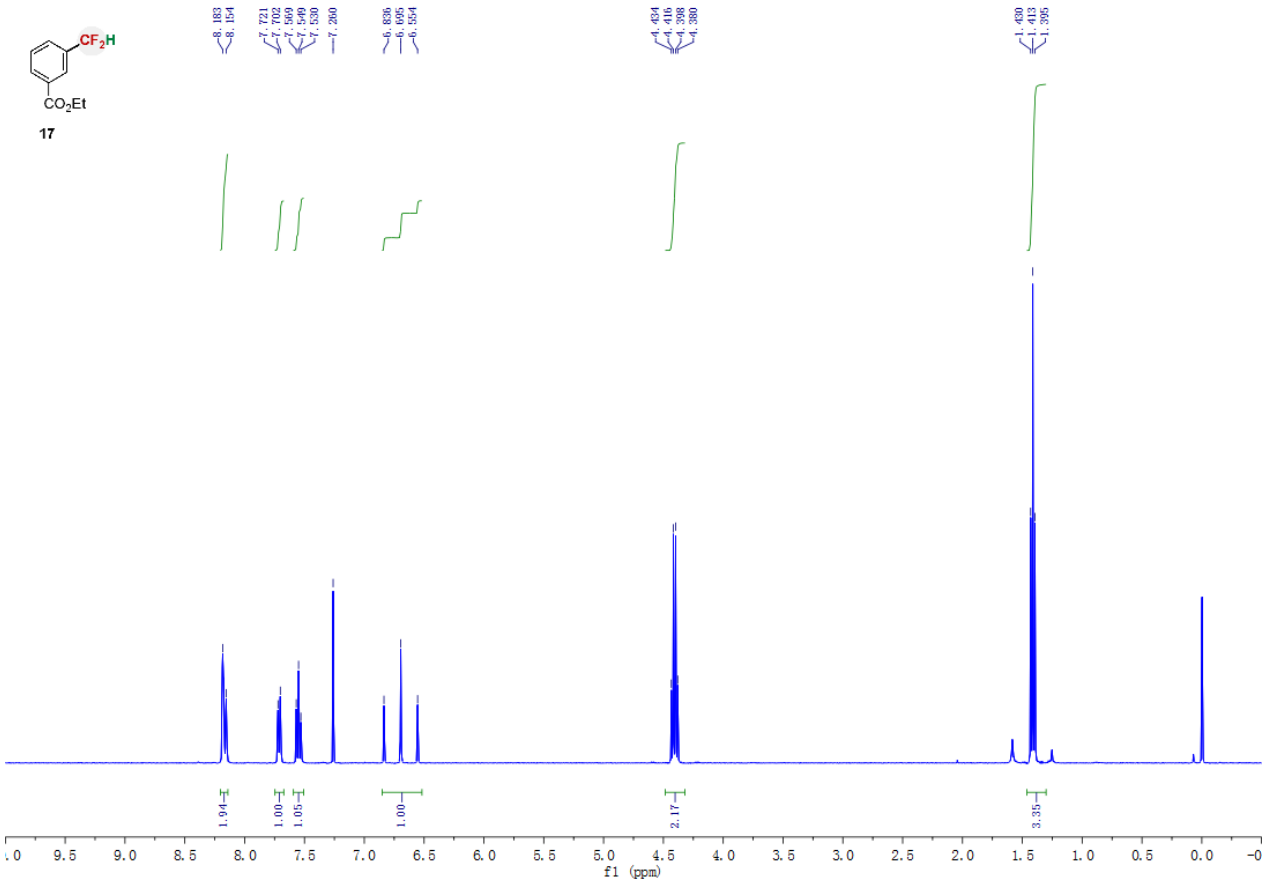

CF2H
EtO2C

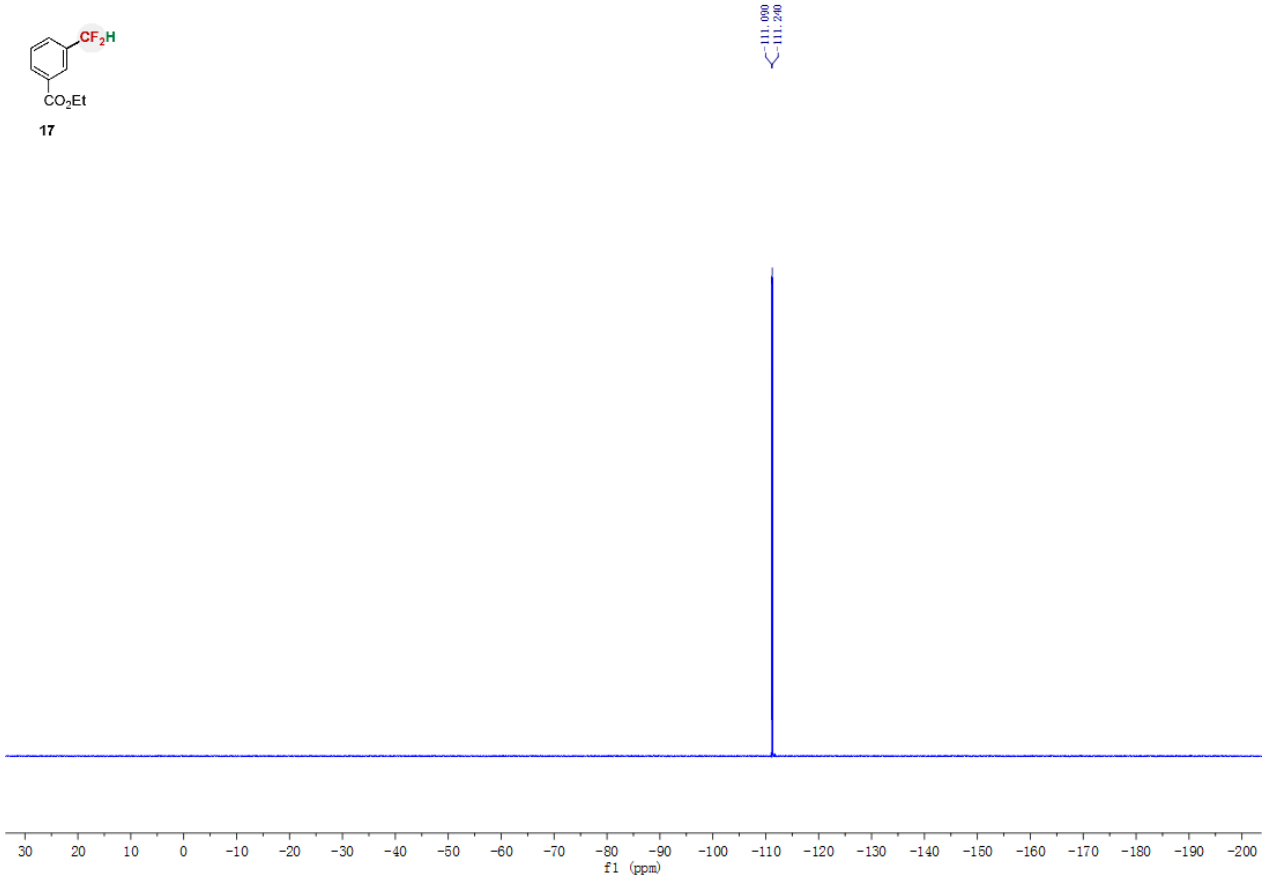
16

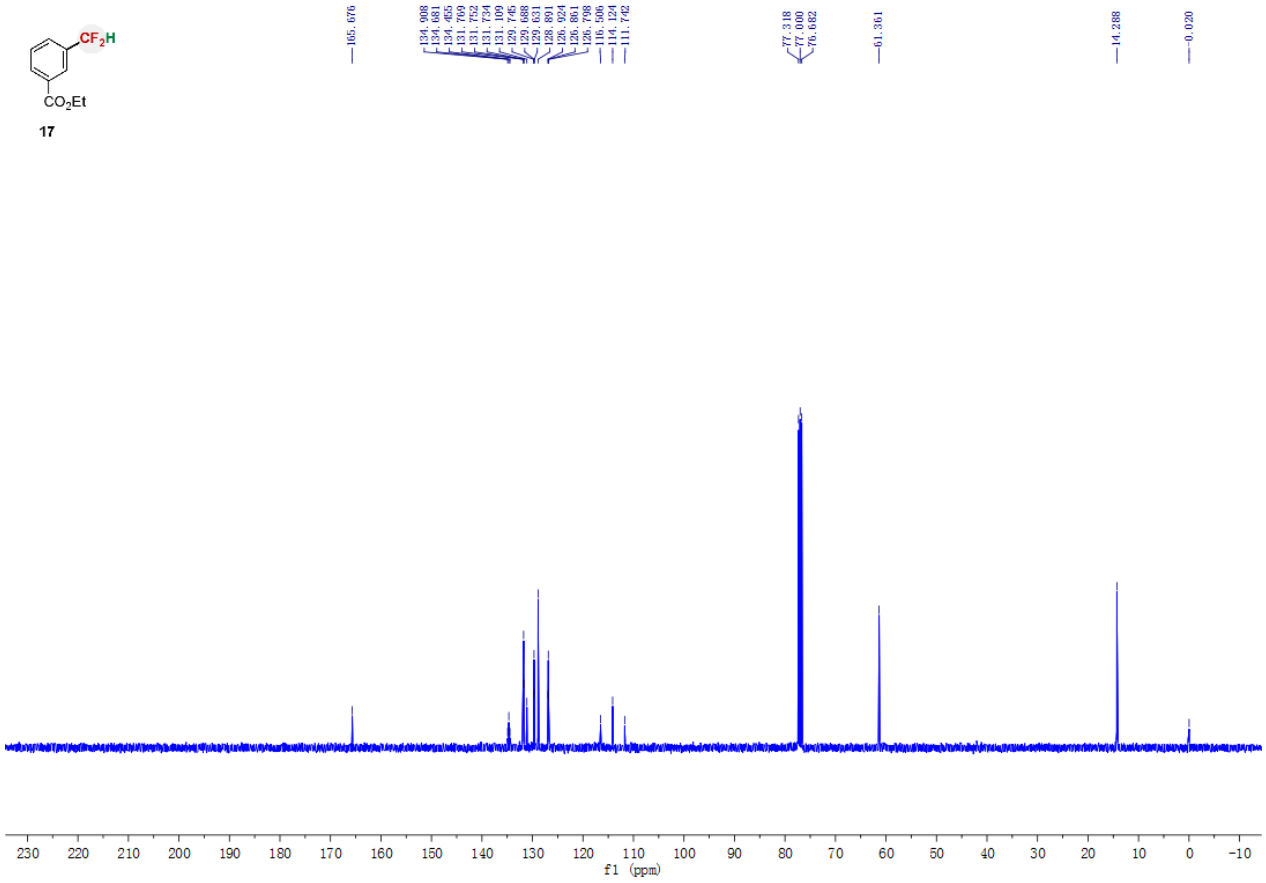

165.737
138.533
138.310
138.086
132.650
129.888
125.623
125.562
125.502
116.394
114.009
111.623
77.318
77.000
76.682
61.334
14.261


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

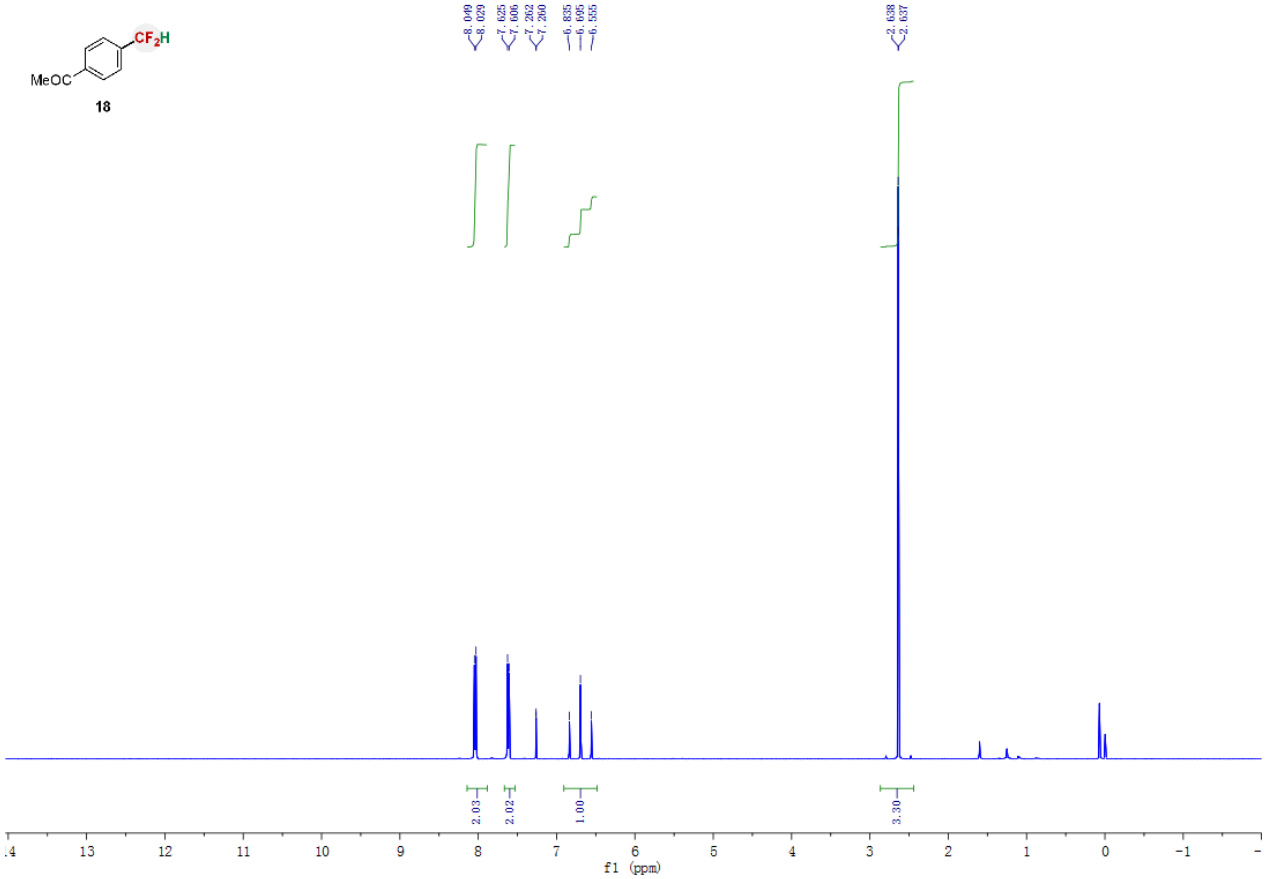
Ethyl 3-(difluoromethyl)benzoate (17).

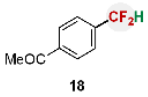






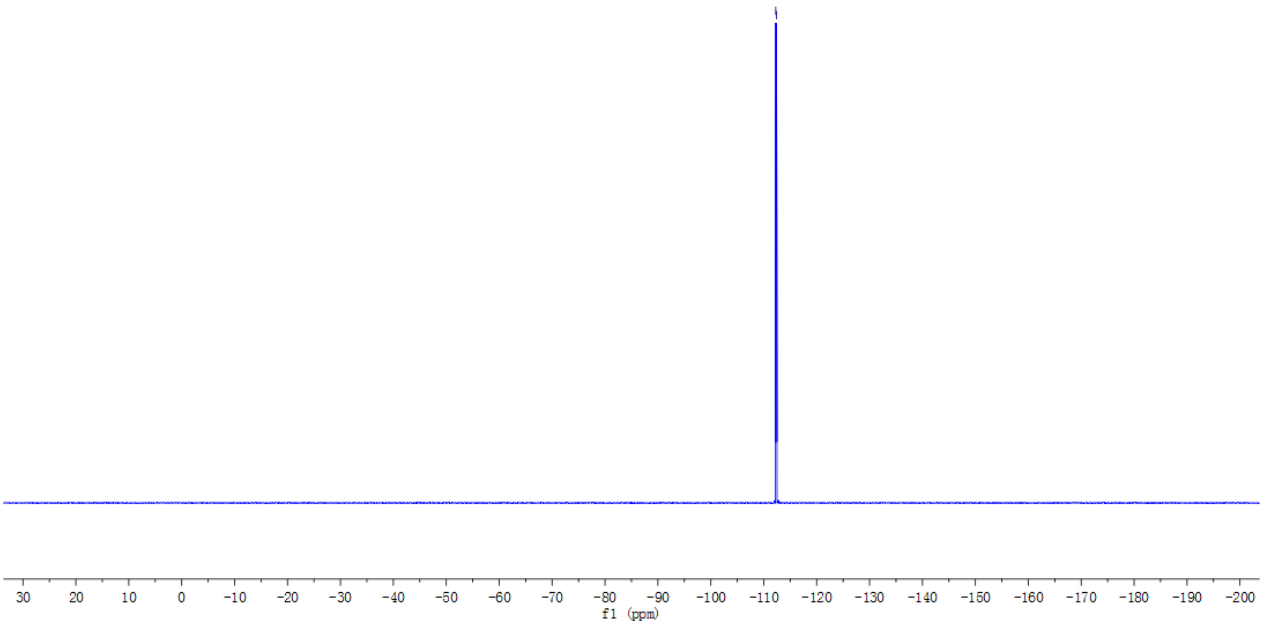
1-(4-(Difluoromethyl)phenyl)ethanone (18)

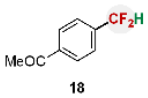



CF2H
MeOC

18

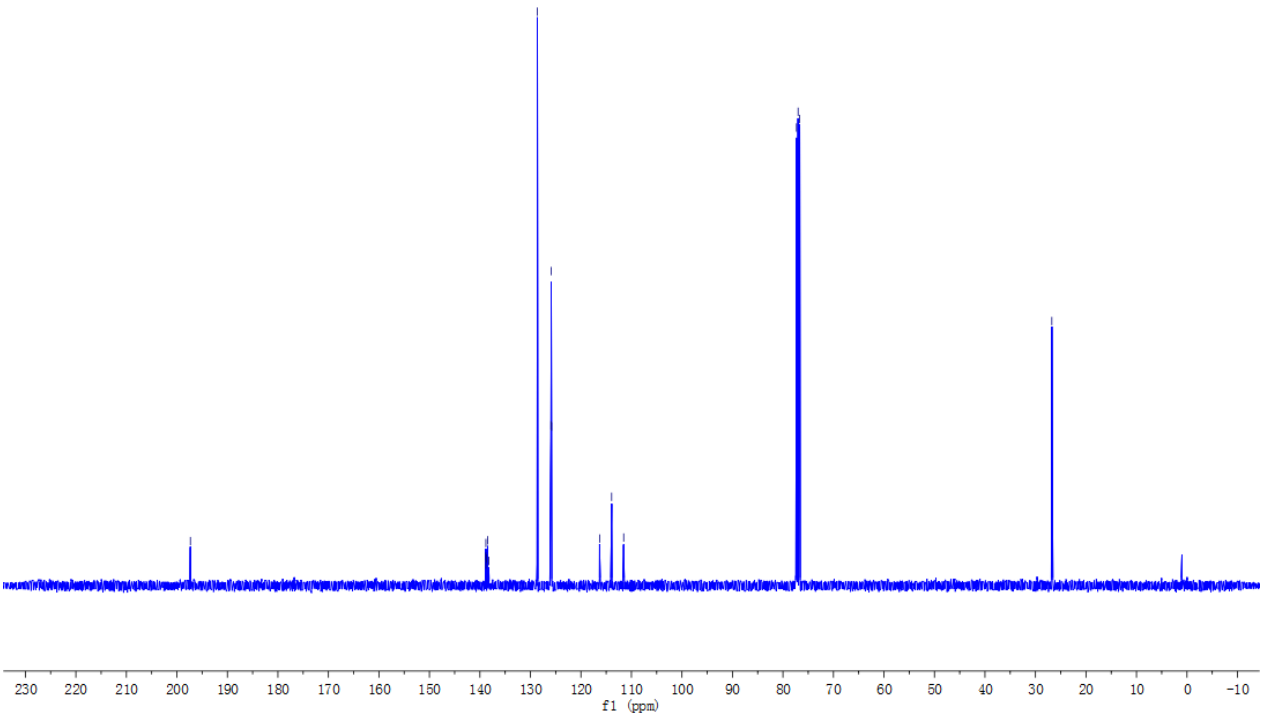

112.268
112.417


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

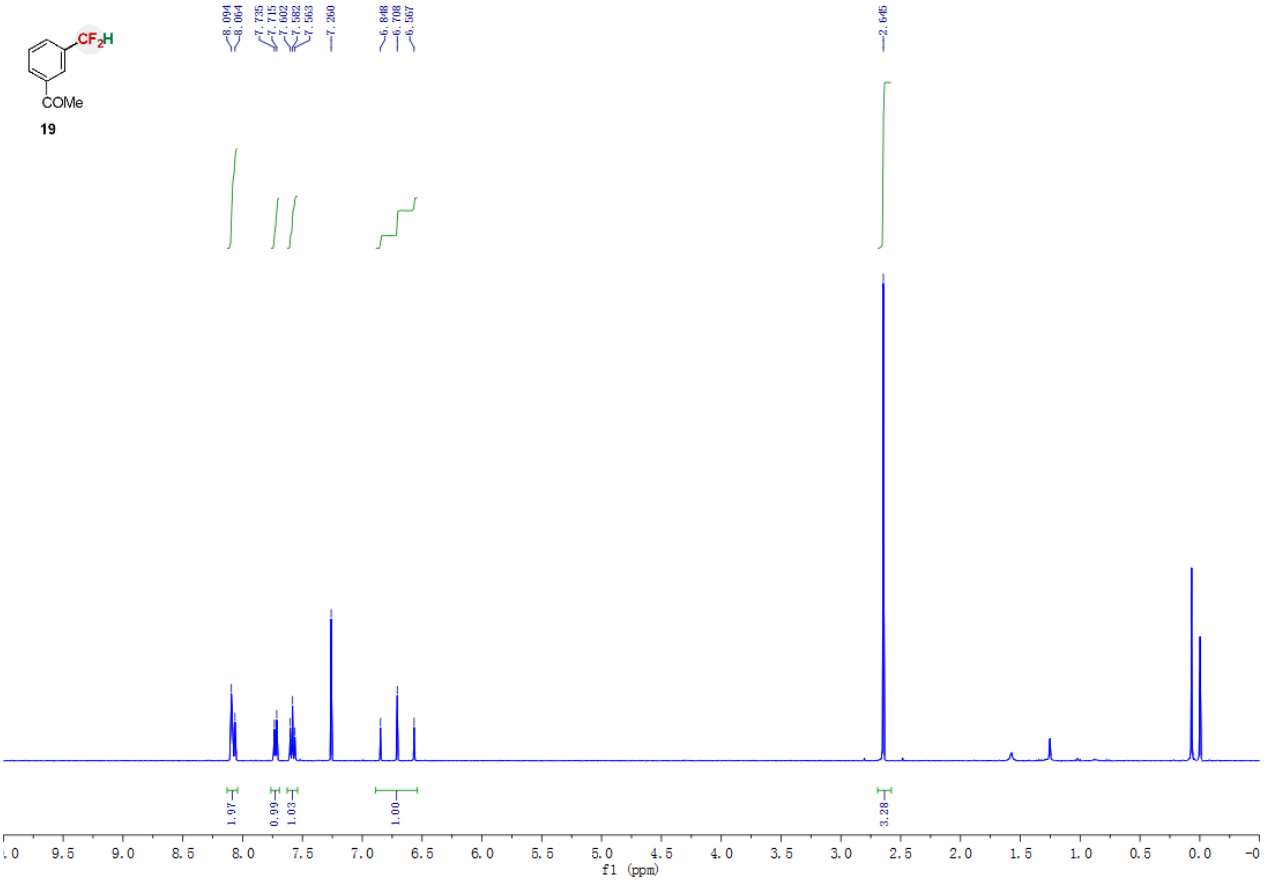

CF2H
MeOC

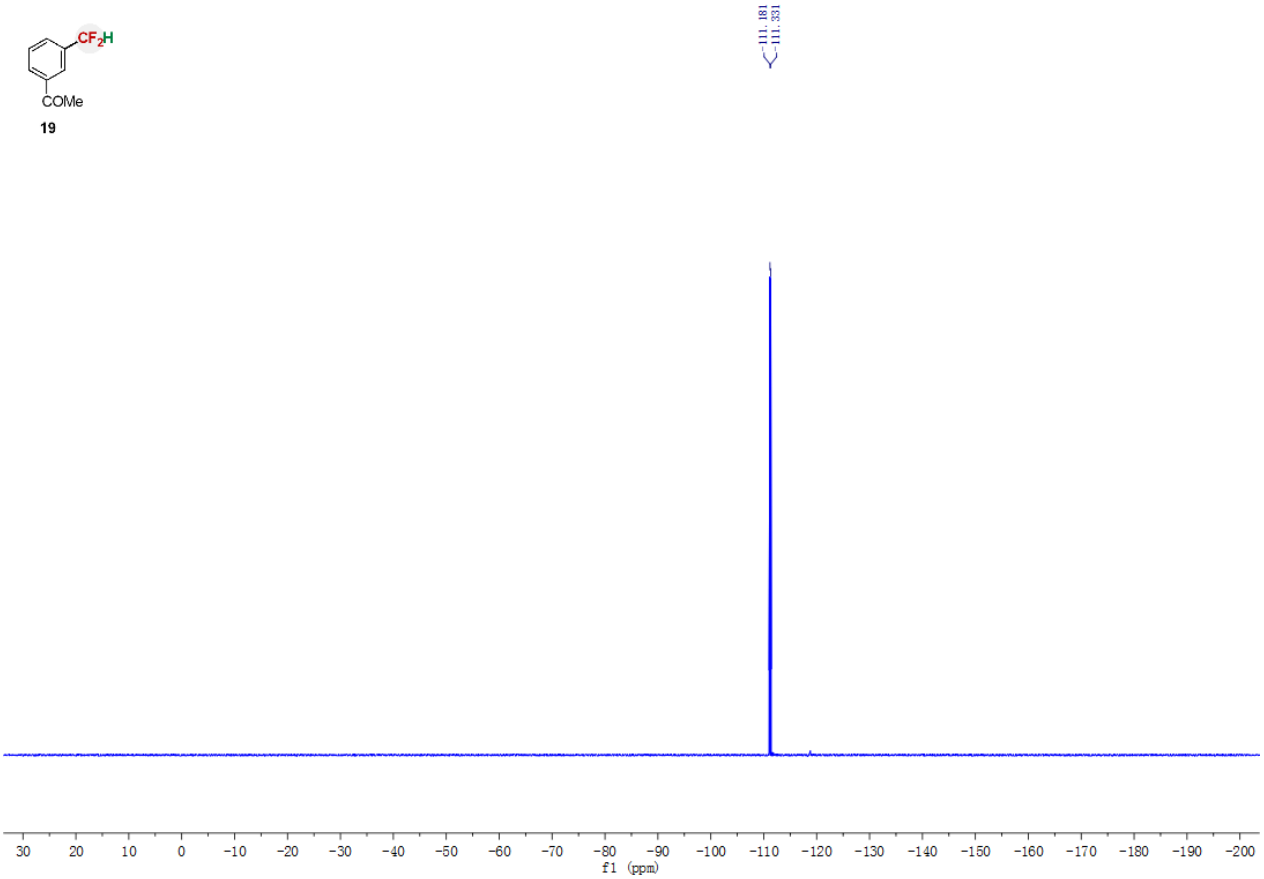
18

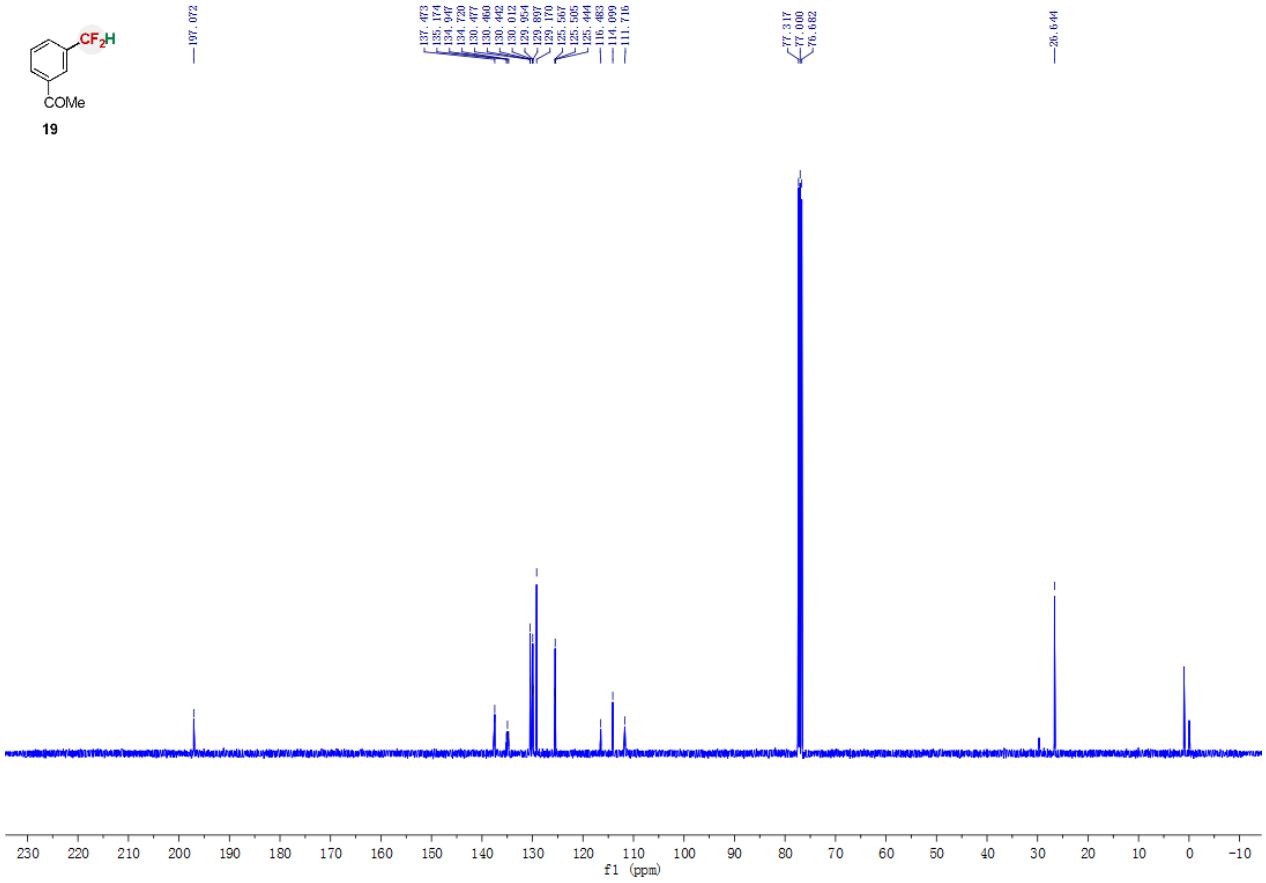

197.325
138.890
138.822
138.694
138.606
138.463
138.240
128.613
125.932
125.872
125.811
116.307
113.921
111.535
77.318
77.000
76.682
26.763


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

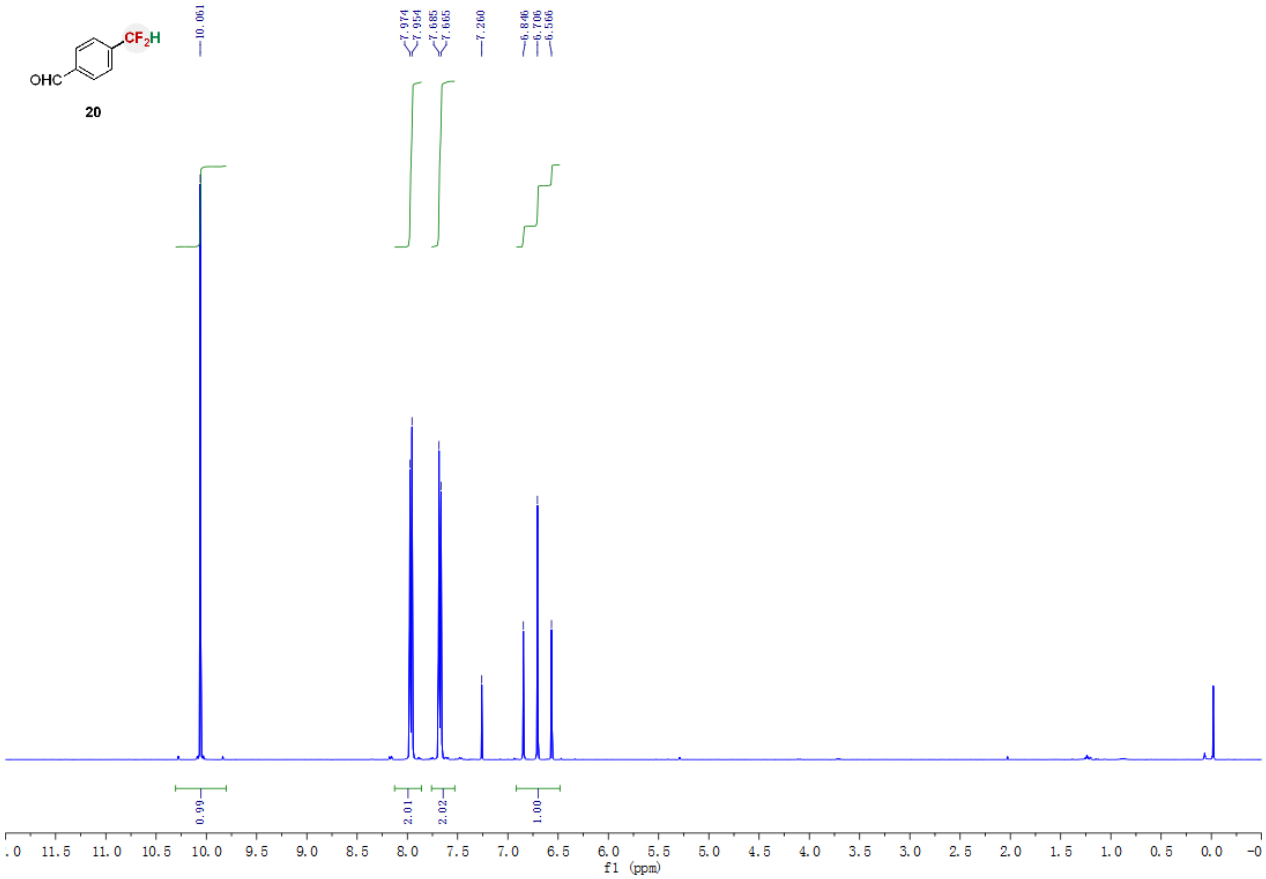
1-(3-(Difluoromethyl)phenyl)ethanone (19).

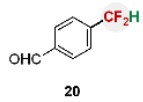






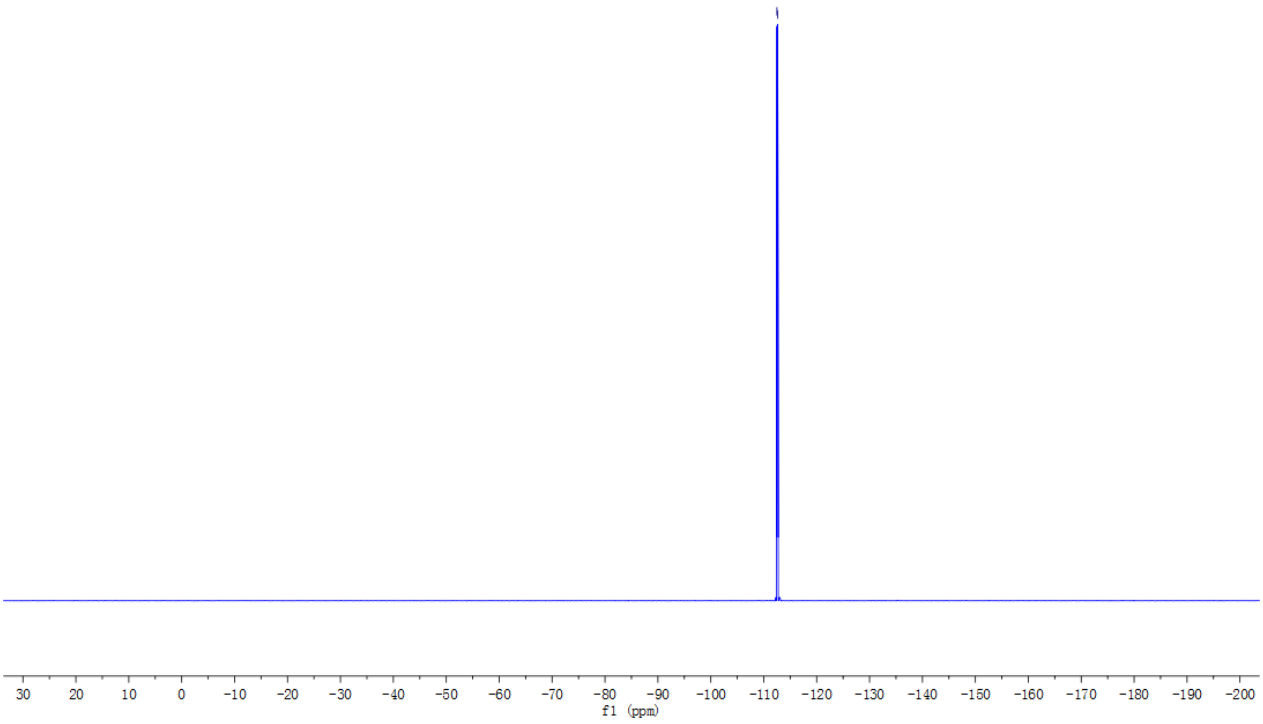
4-(Difluoromethyl)benzaldehyde (20).

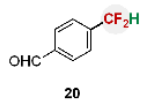



CF2H
OHC

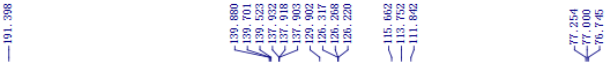
20

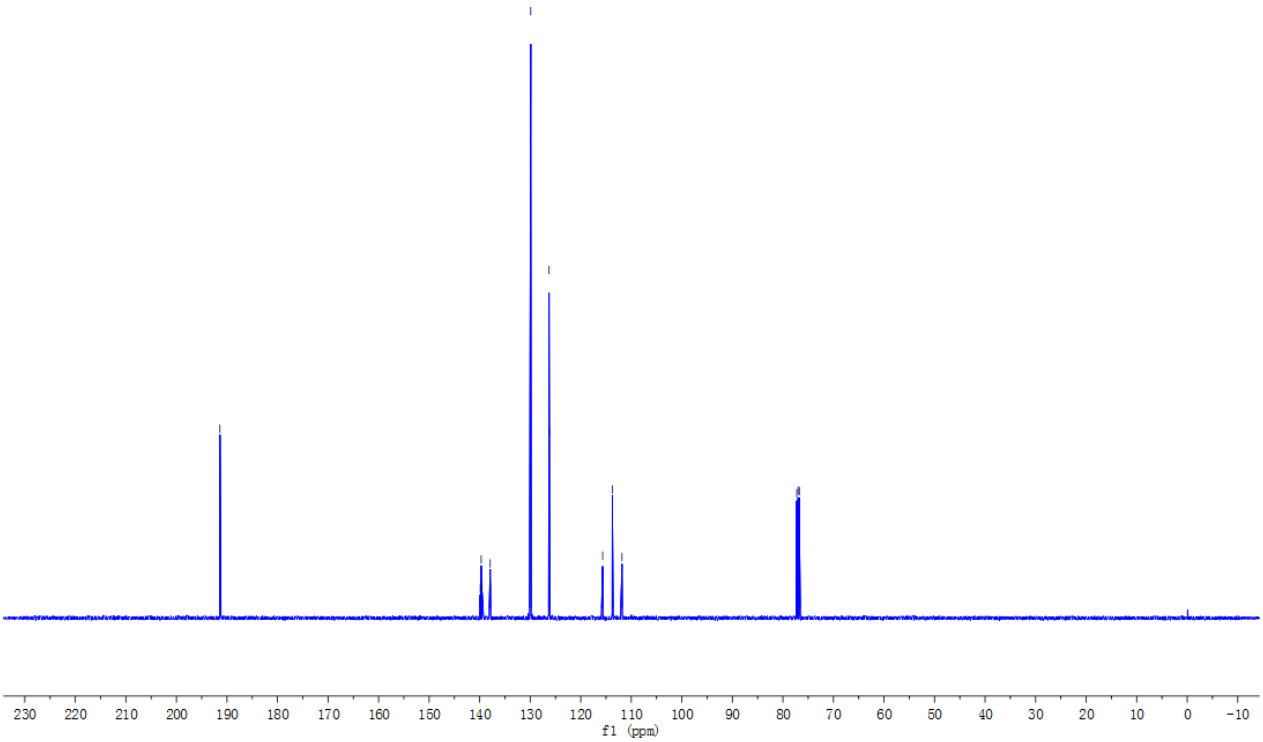

112.493
112.682


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

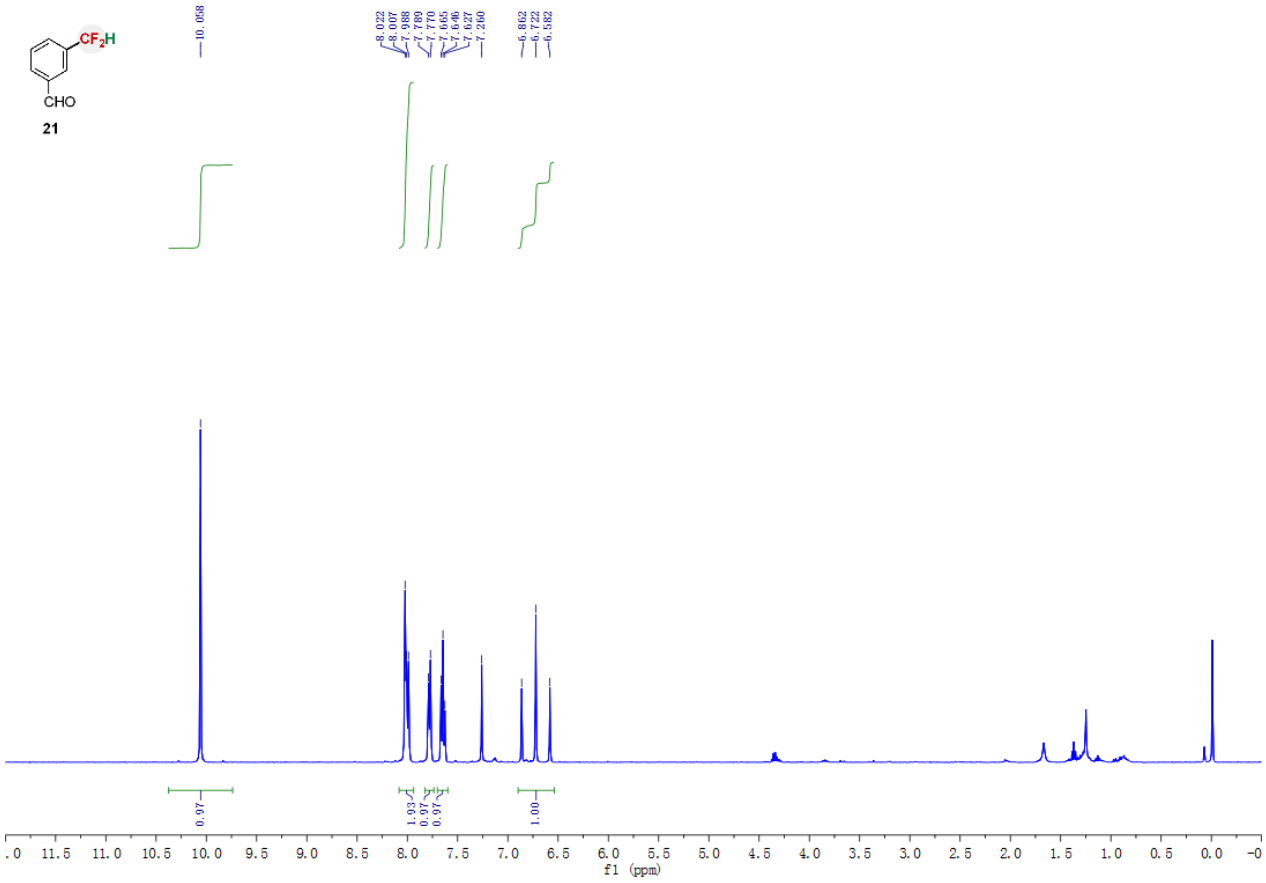

CF2H
OHC

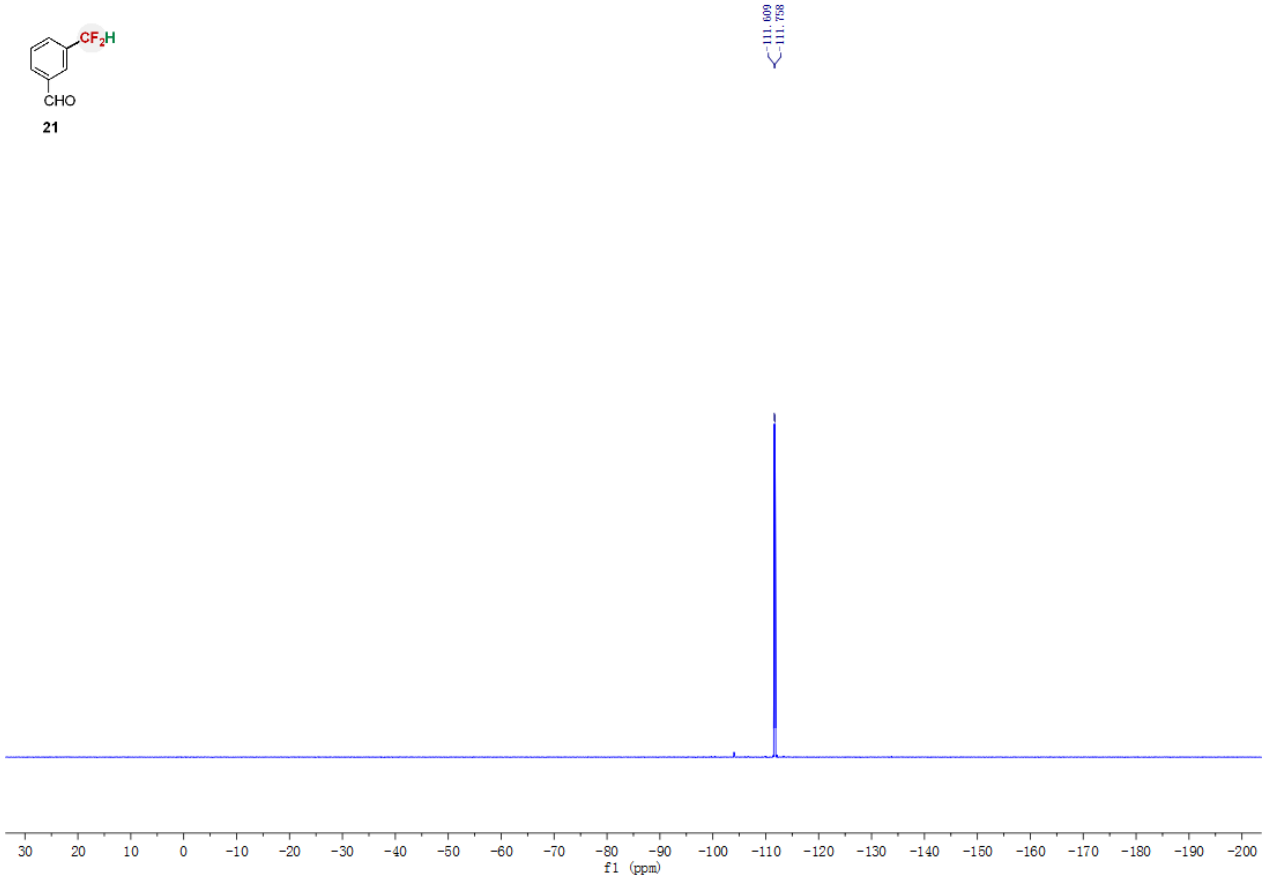
20

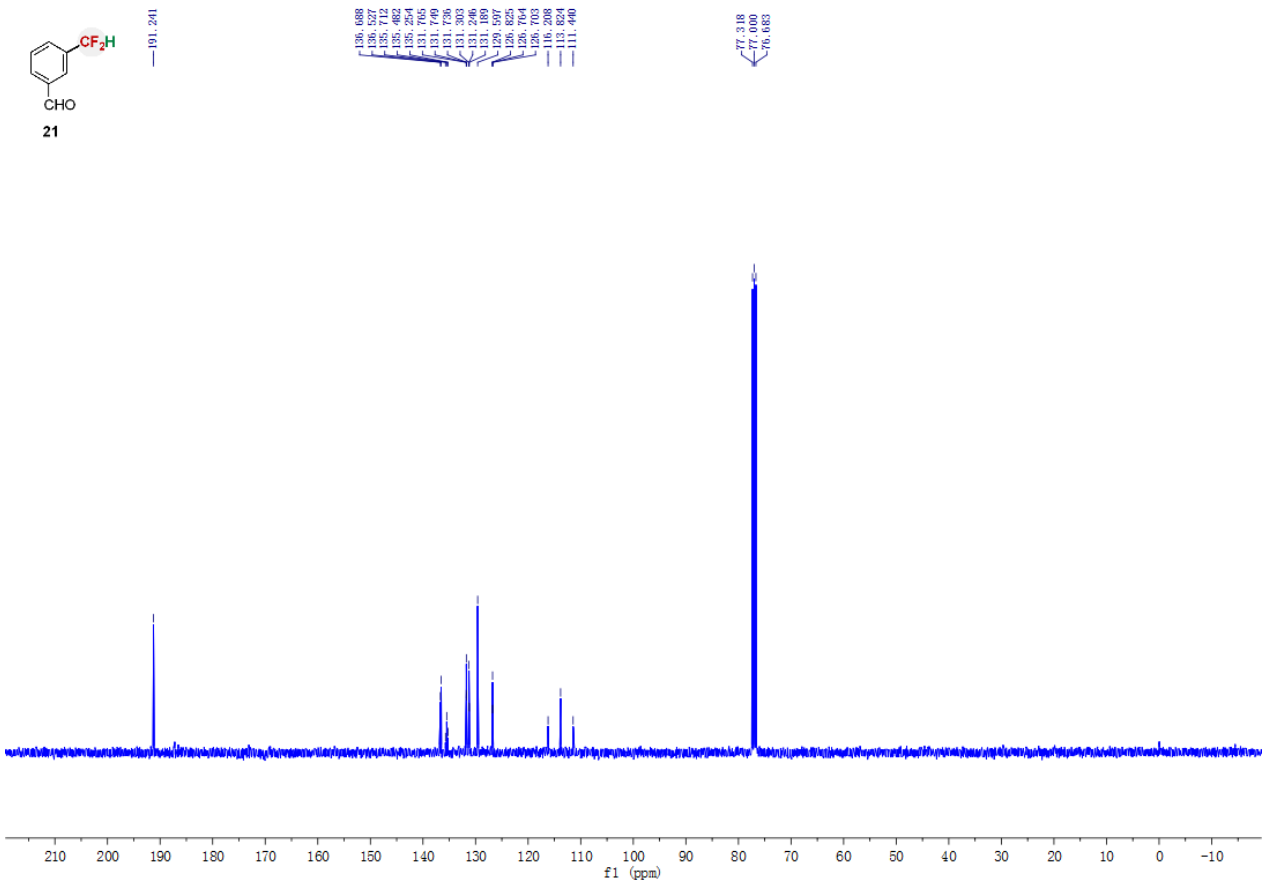

191.398
139.880
139.701
139.523
137.932
137.918
137.903
129.902
126.317
126.298
126.220
115.662
113.752
111.842
77.254
77.000
76.745


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

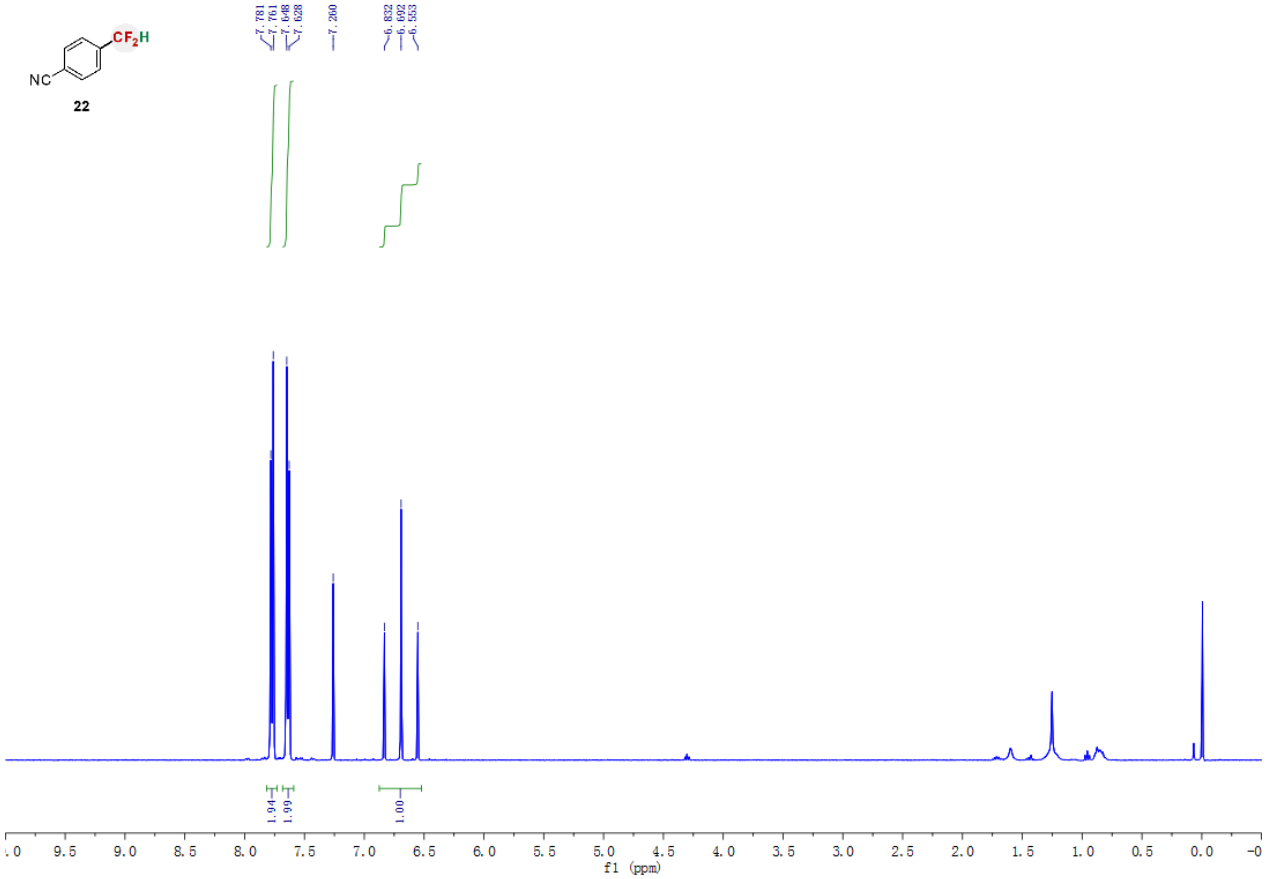
3-(Difluoromethyl)benzaldehyde (21).

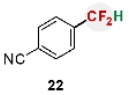






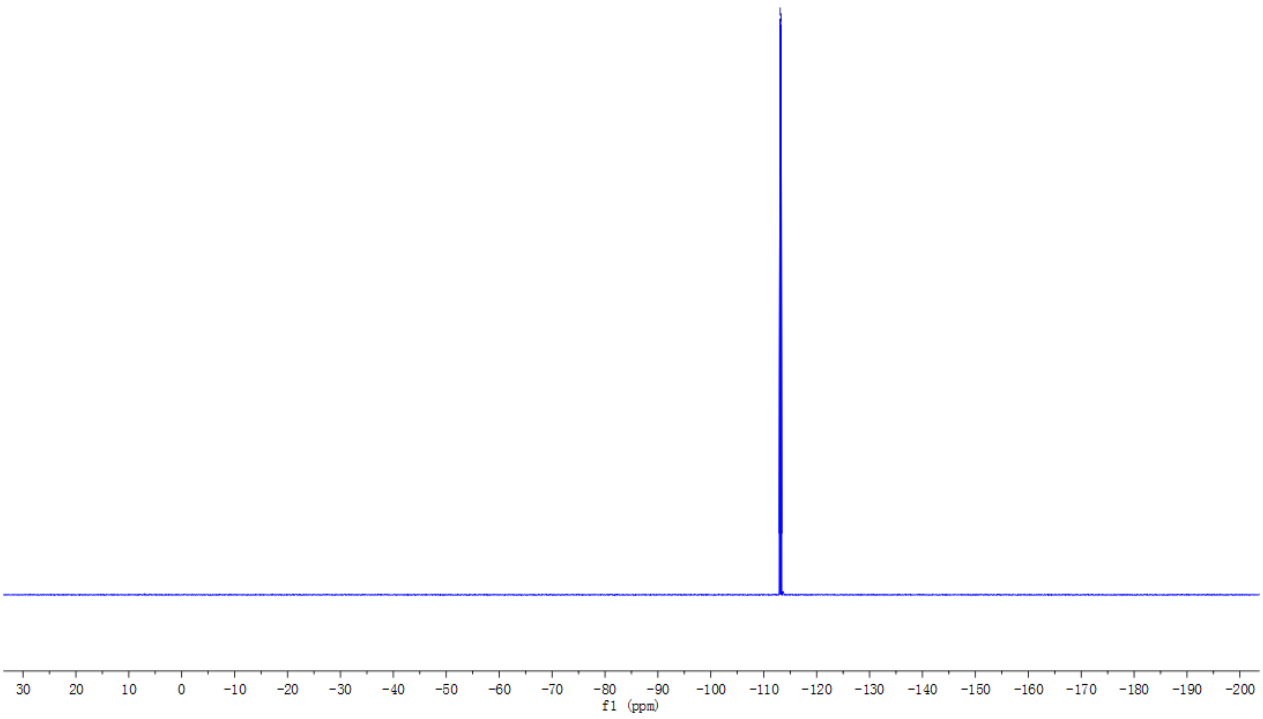
4-(Difluoromethyl)benzonitrile (22).

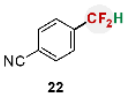



CF2H
NC

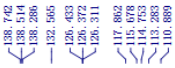
22


113.118
113.267

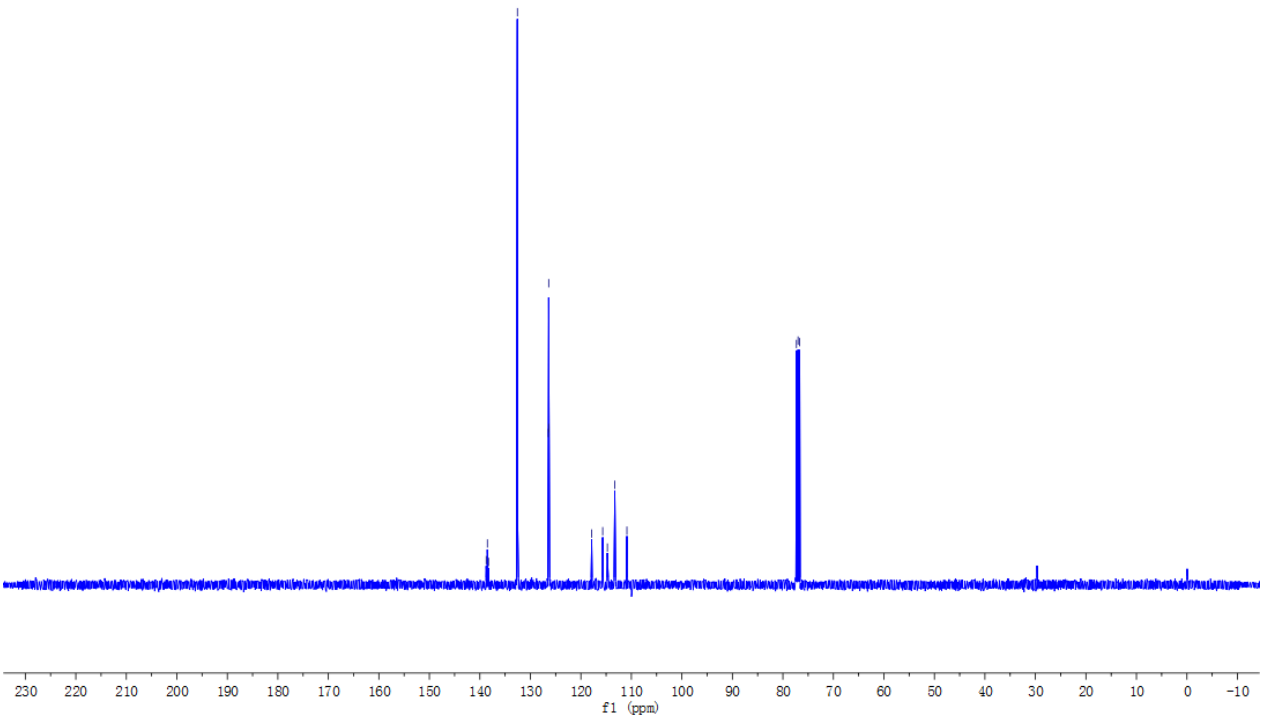

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


CF2H
NC

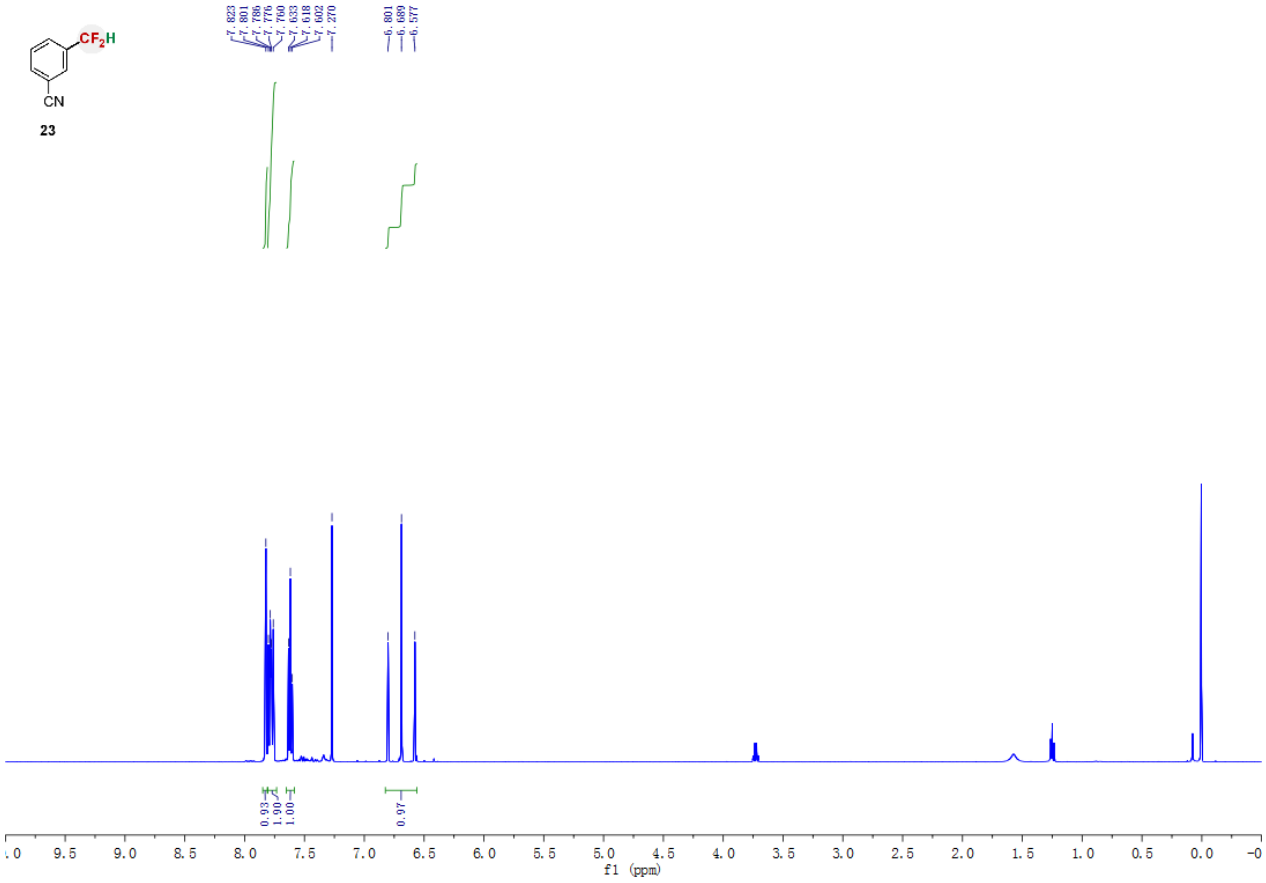
22

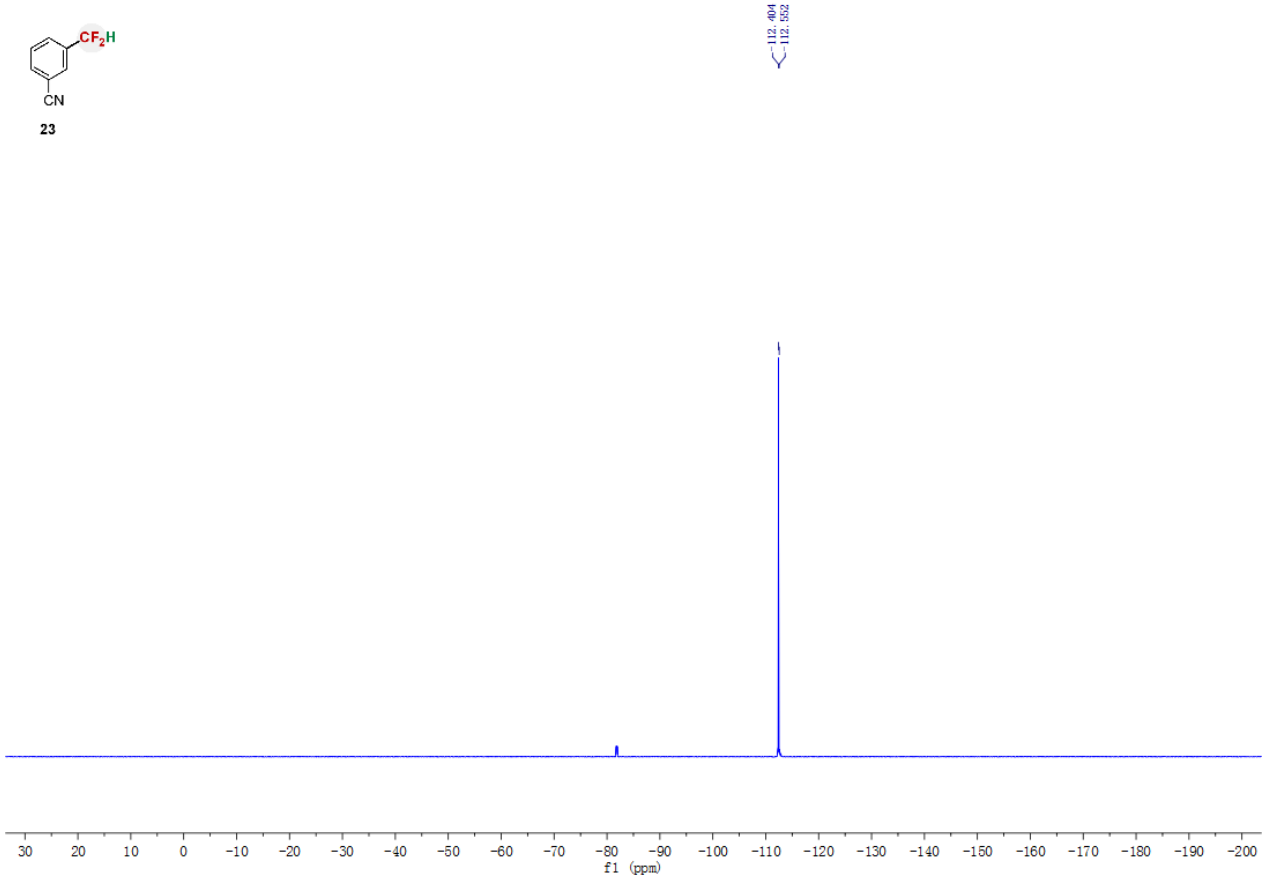

138.742
138.514
138.286
132.565
126.433
126.372
126.311
117.862
115.678
114.753
113.283
110.889

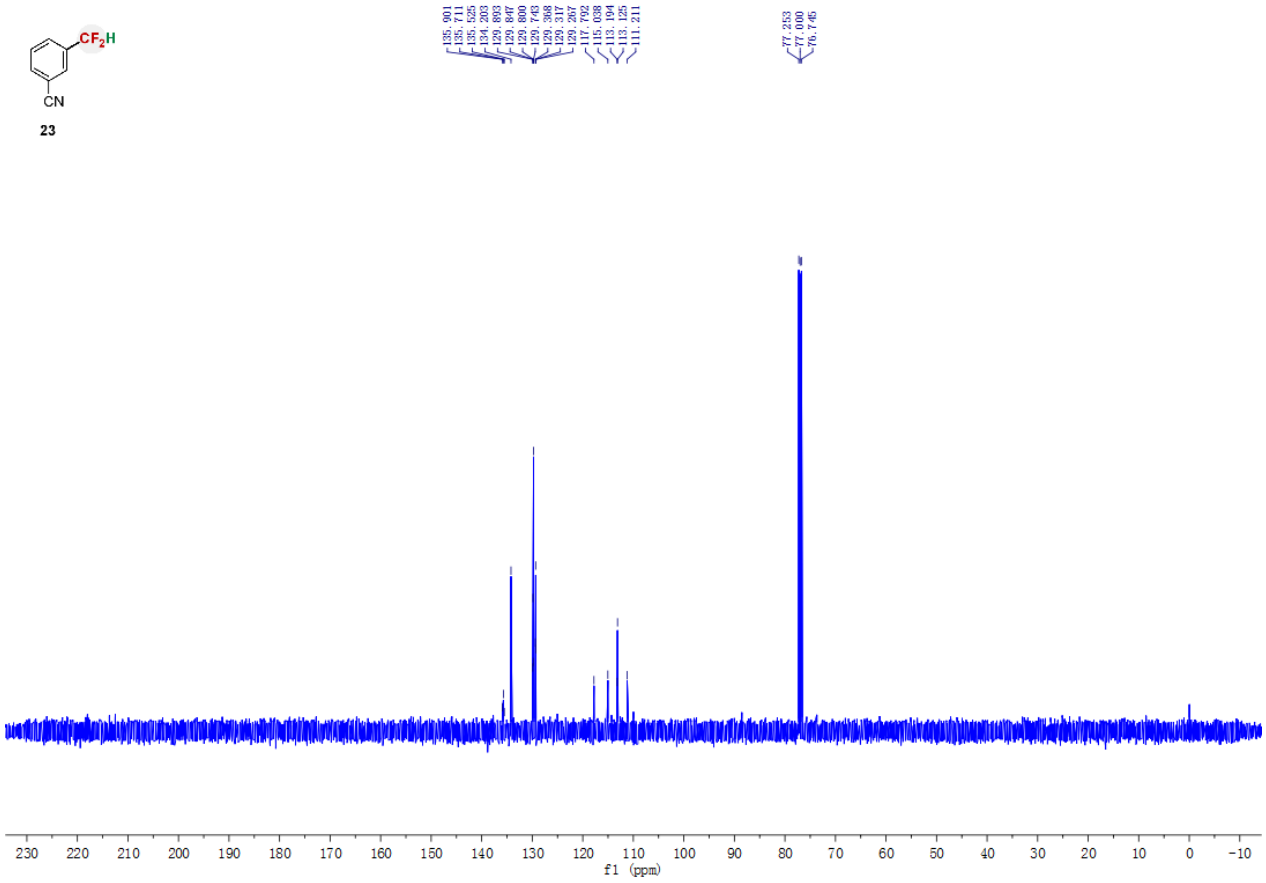

77.318
77.000
76.682


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

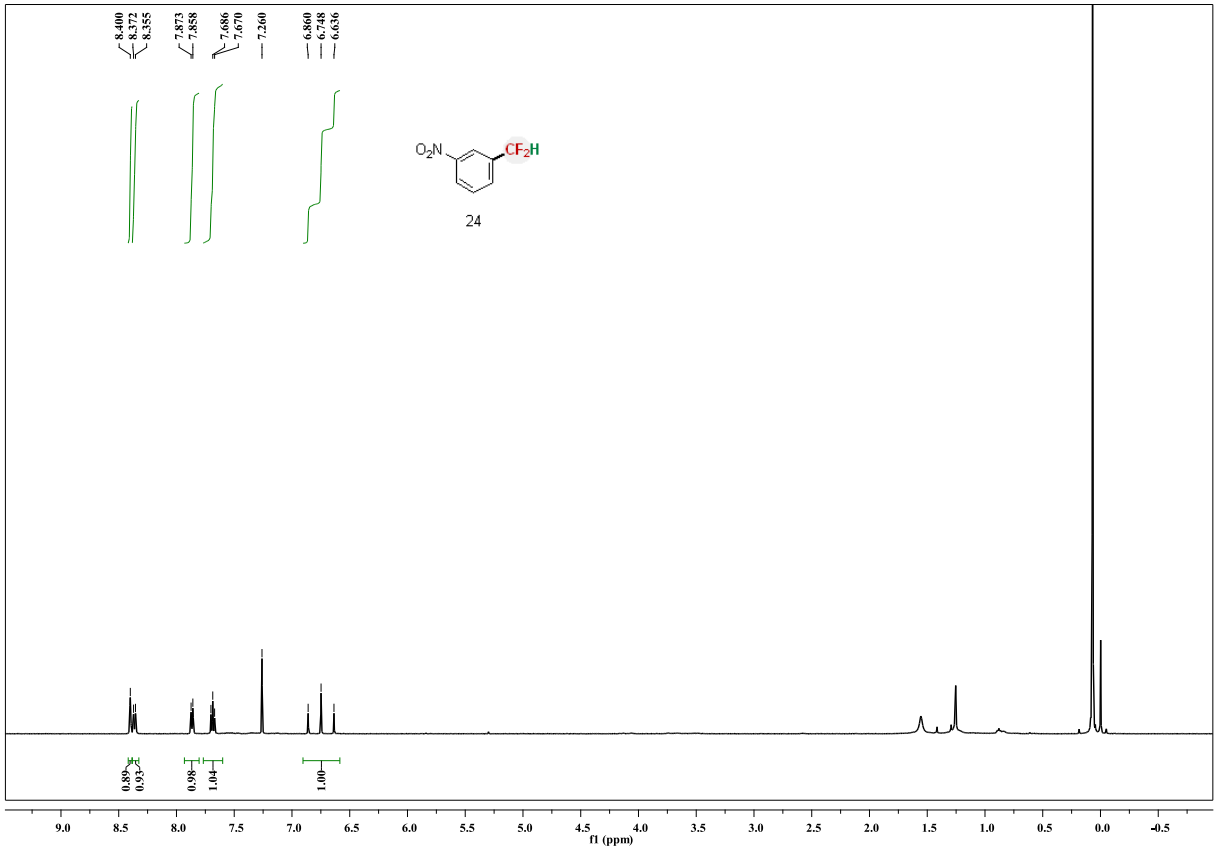
3-(Difluoromethyl)benzonitrile (23).

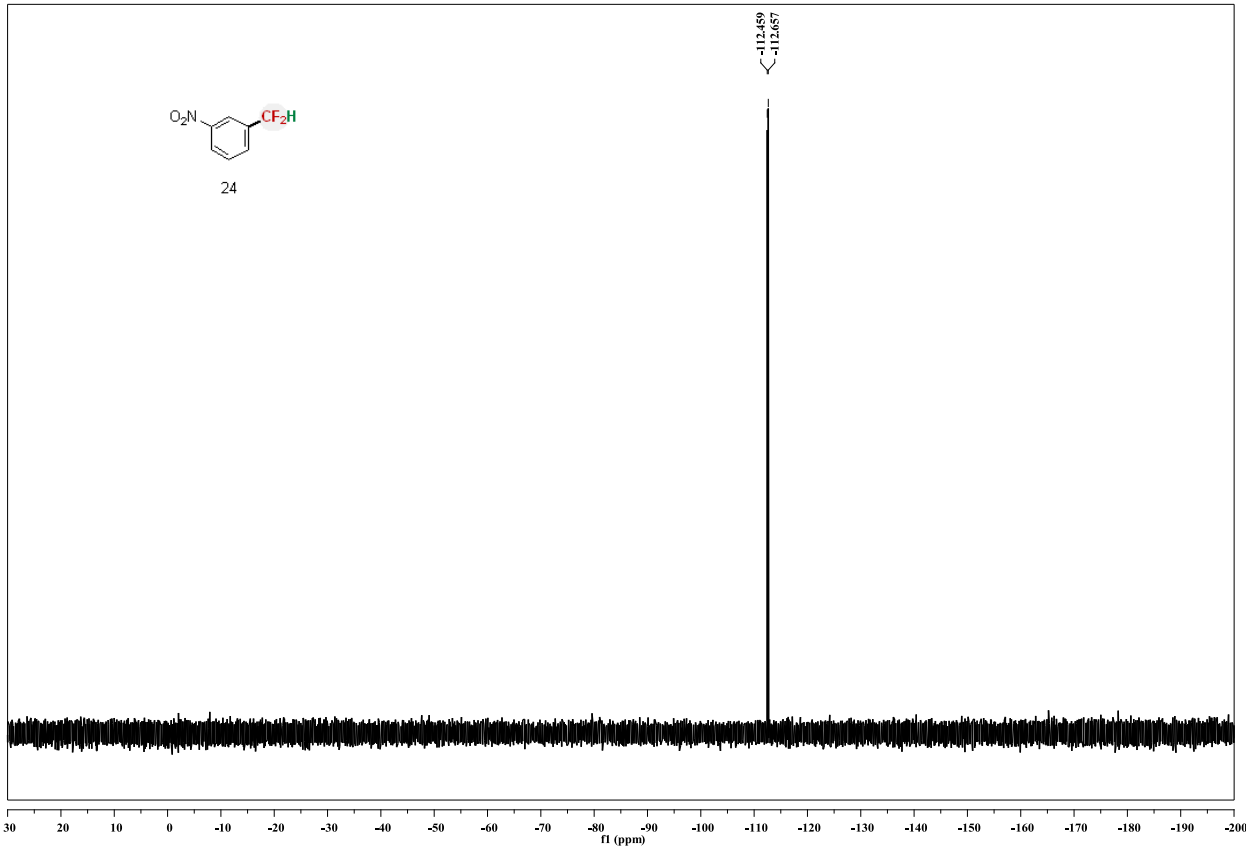


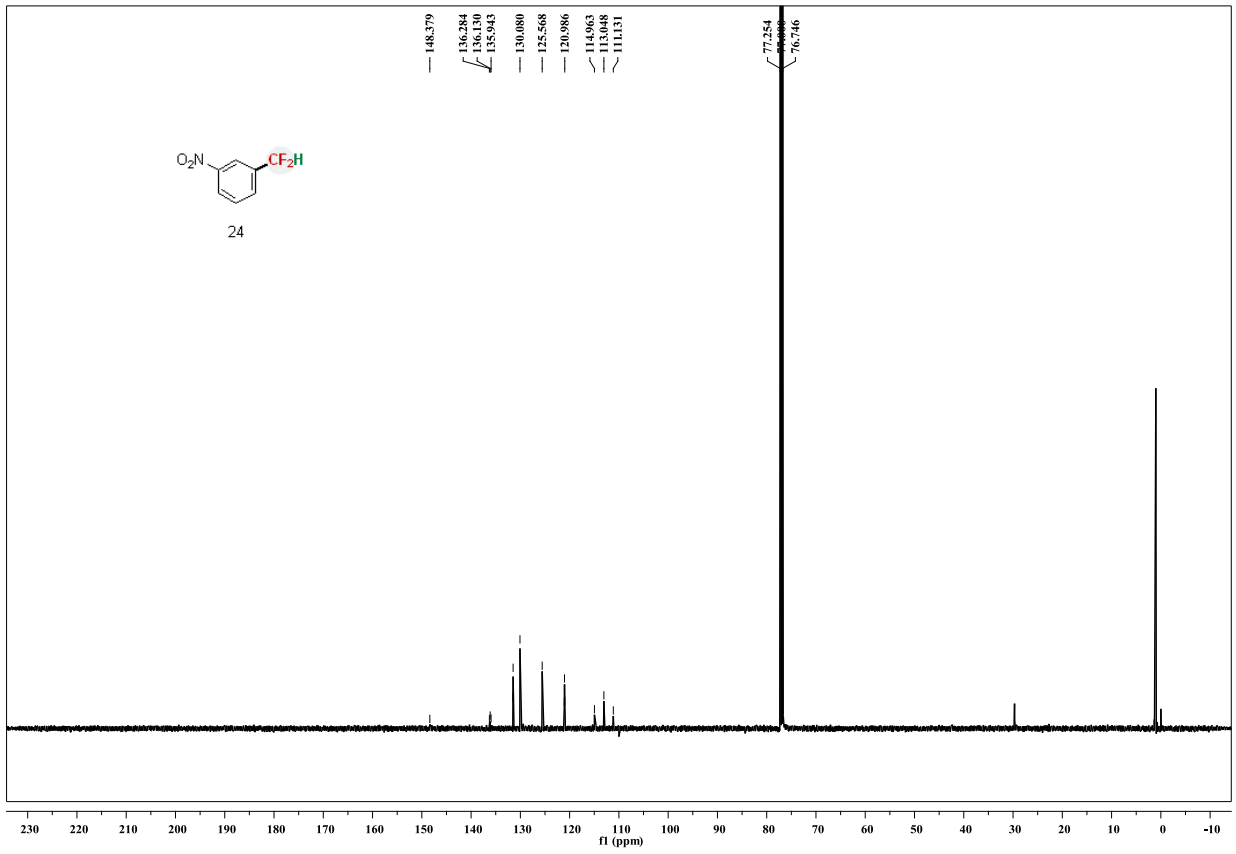




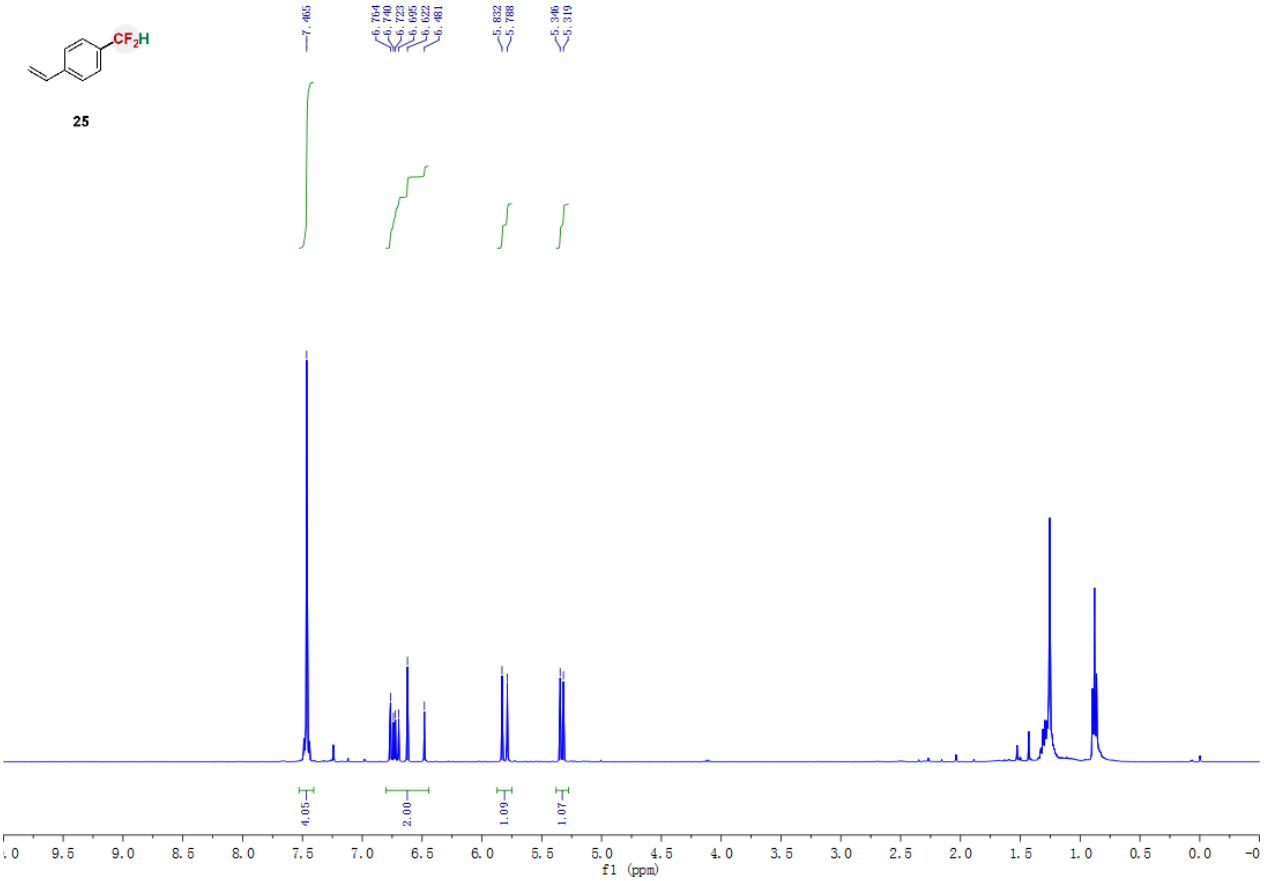
1-(Difluoromethyl)-3-nitrobenzene (24).

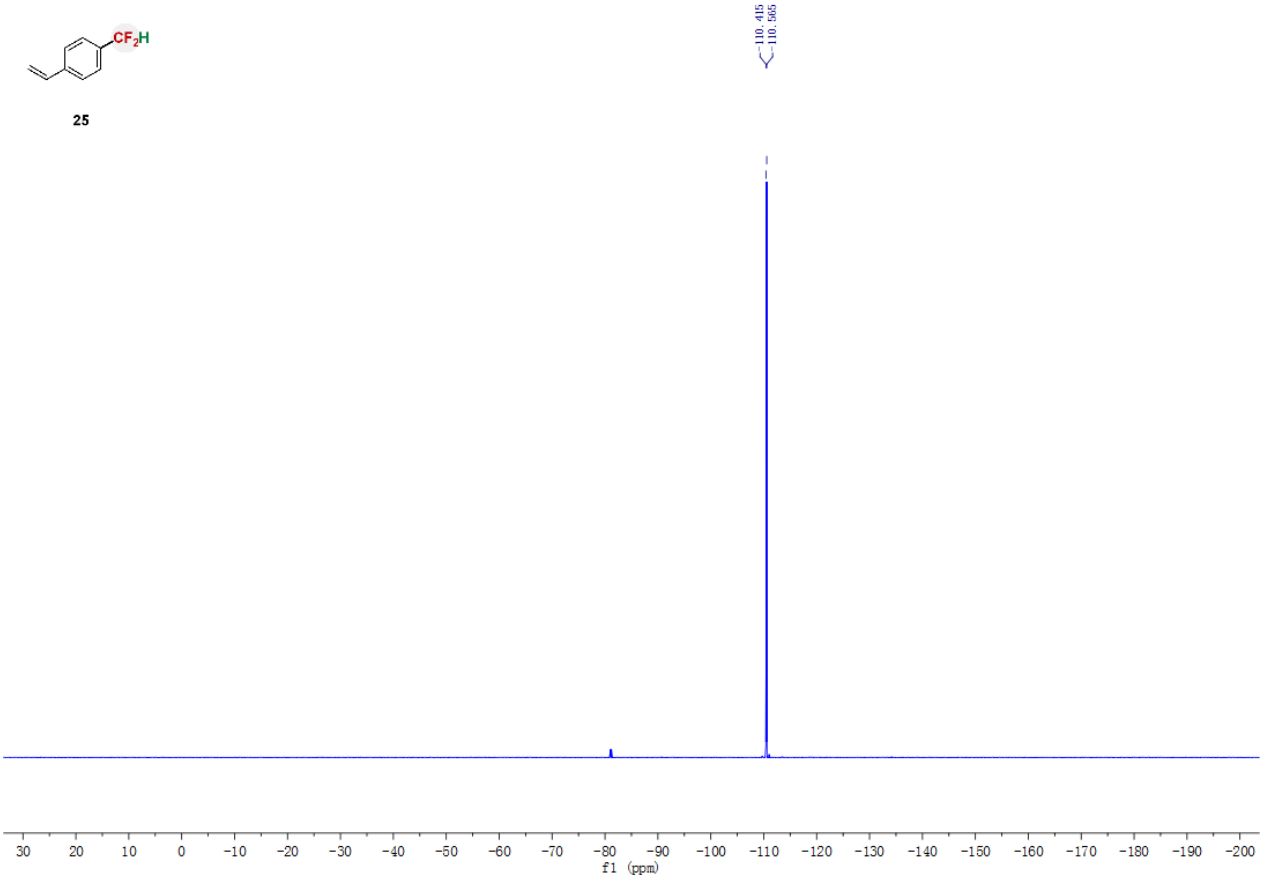


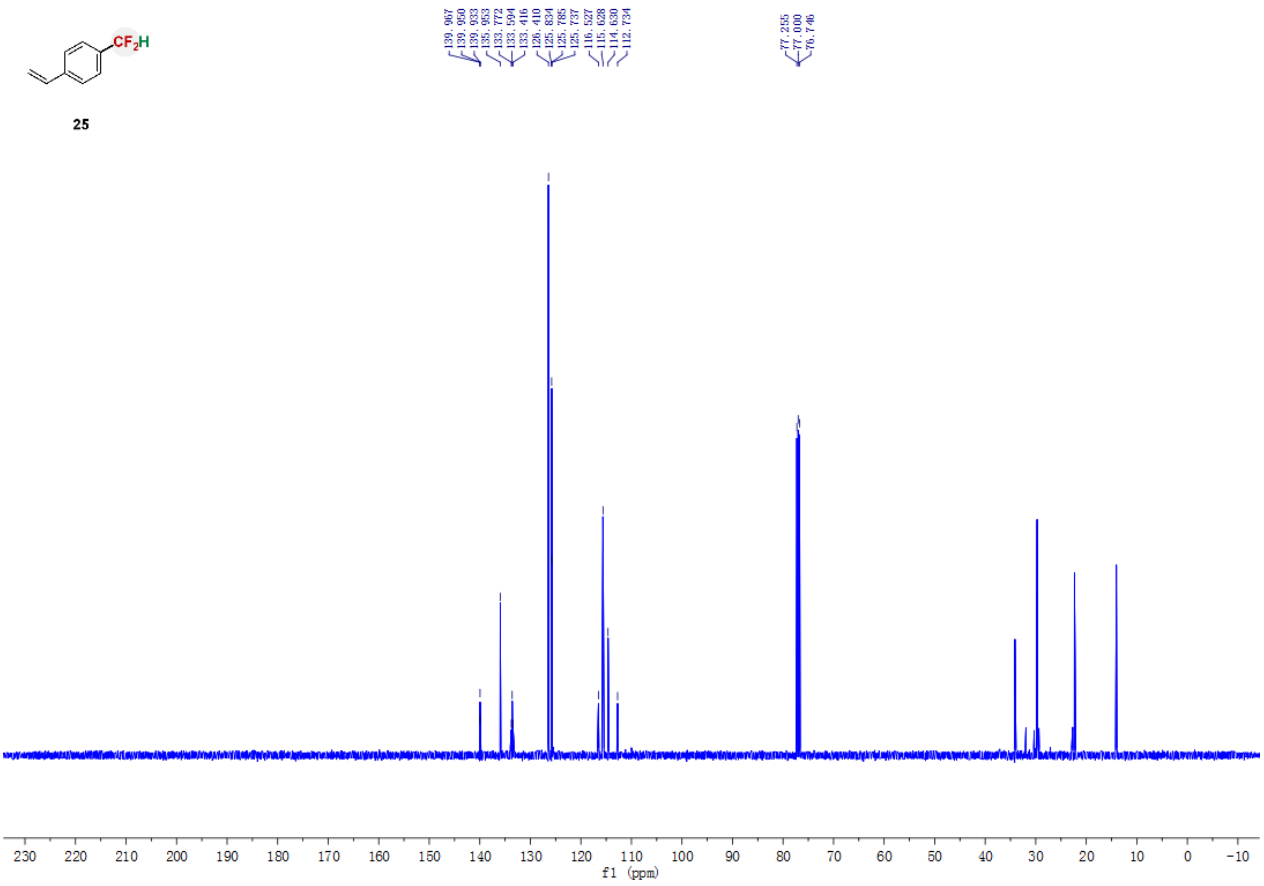

-112.459
-112.657
O2N
CF2H
24
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


148.379
136.284
136.130
135.943
130.080
125.568
120.986
114.963
113.048
111.131
77.254
76.746
O2N
CF2H
24
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

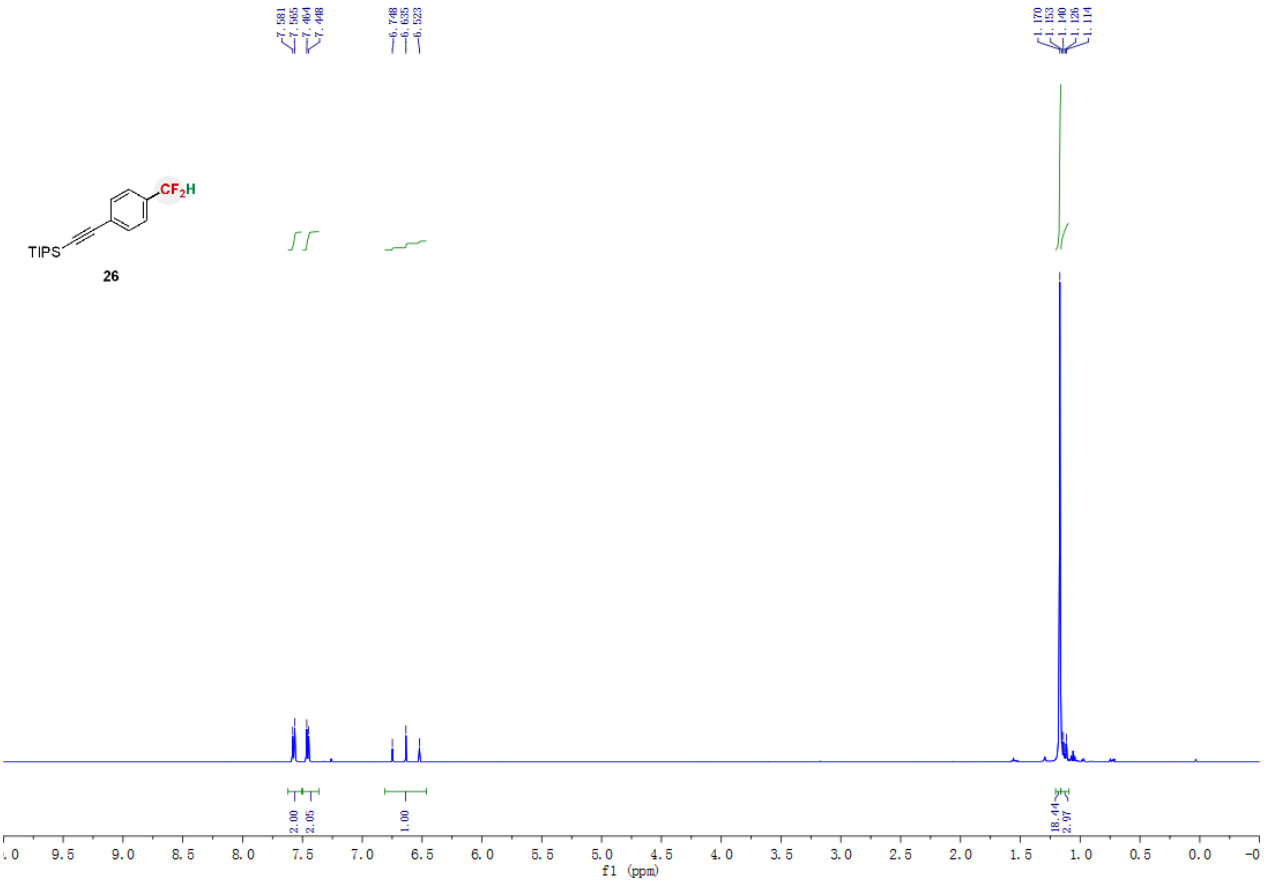
1-(Difluoromethyl)-4-vinylbenzene (25).

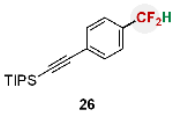






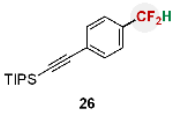
(4-(Difluoromethyl)phenyl)ethynyl)triisopropylsilane (26).




CF2H
TIPS

26

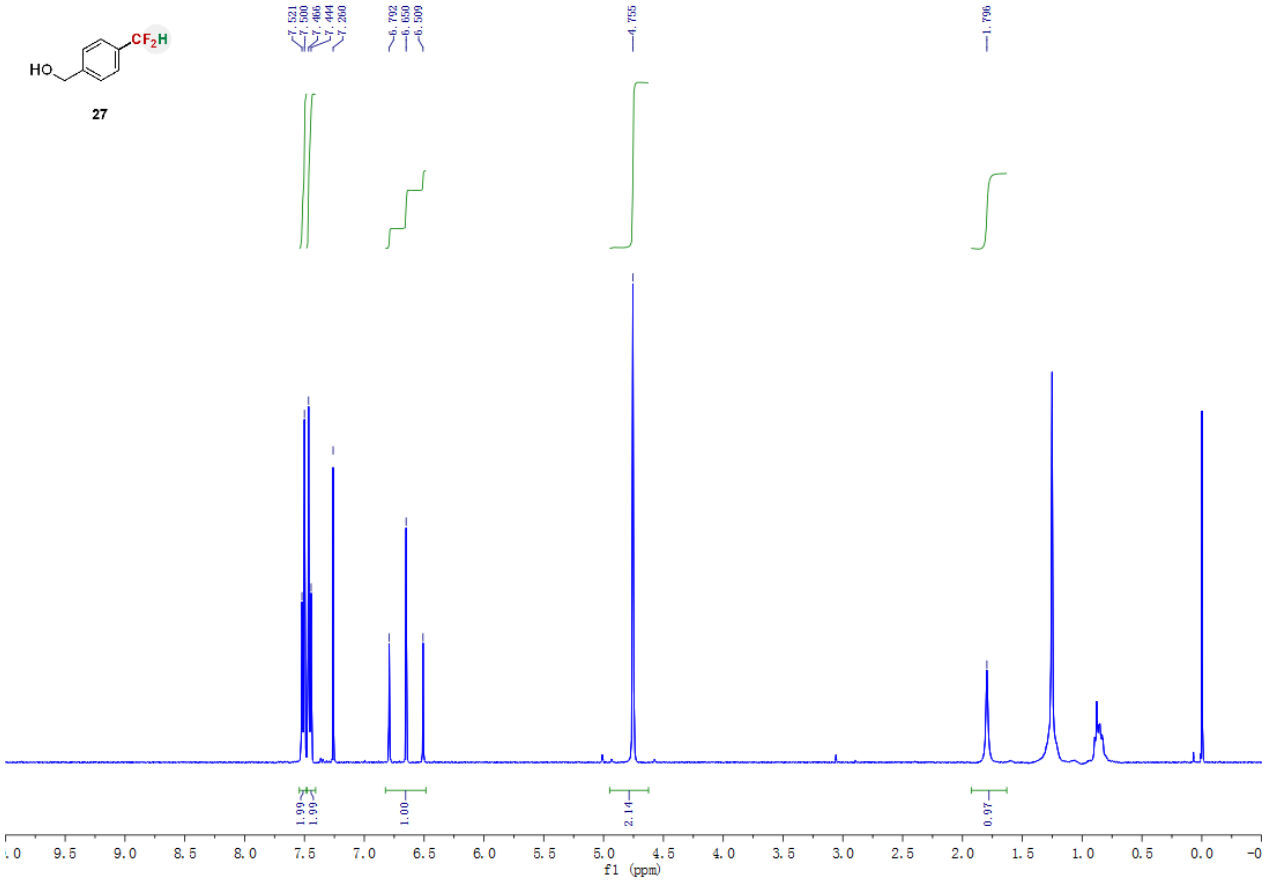
111.158
111.308
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

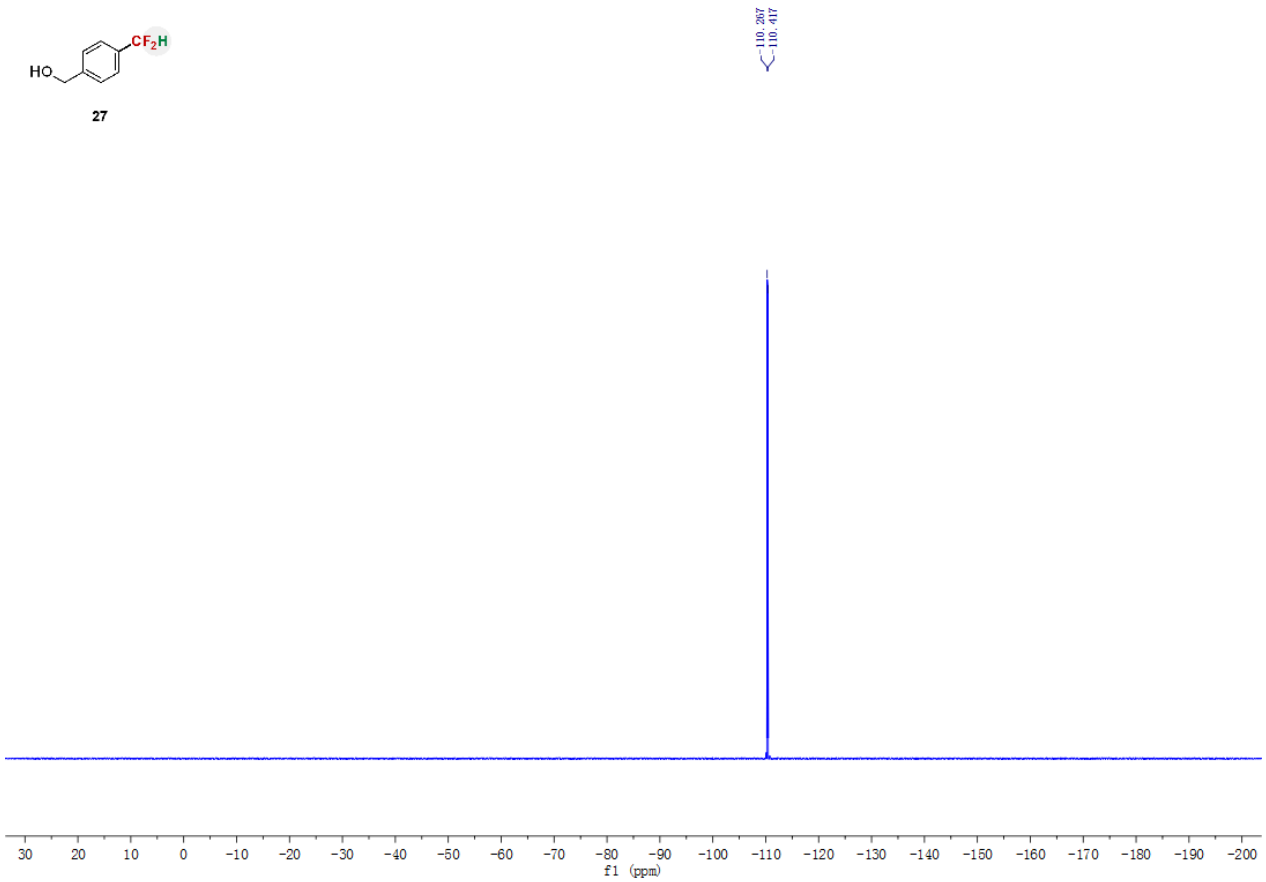

CF2H
TIPS

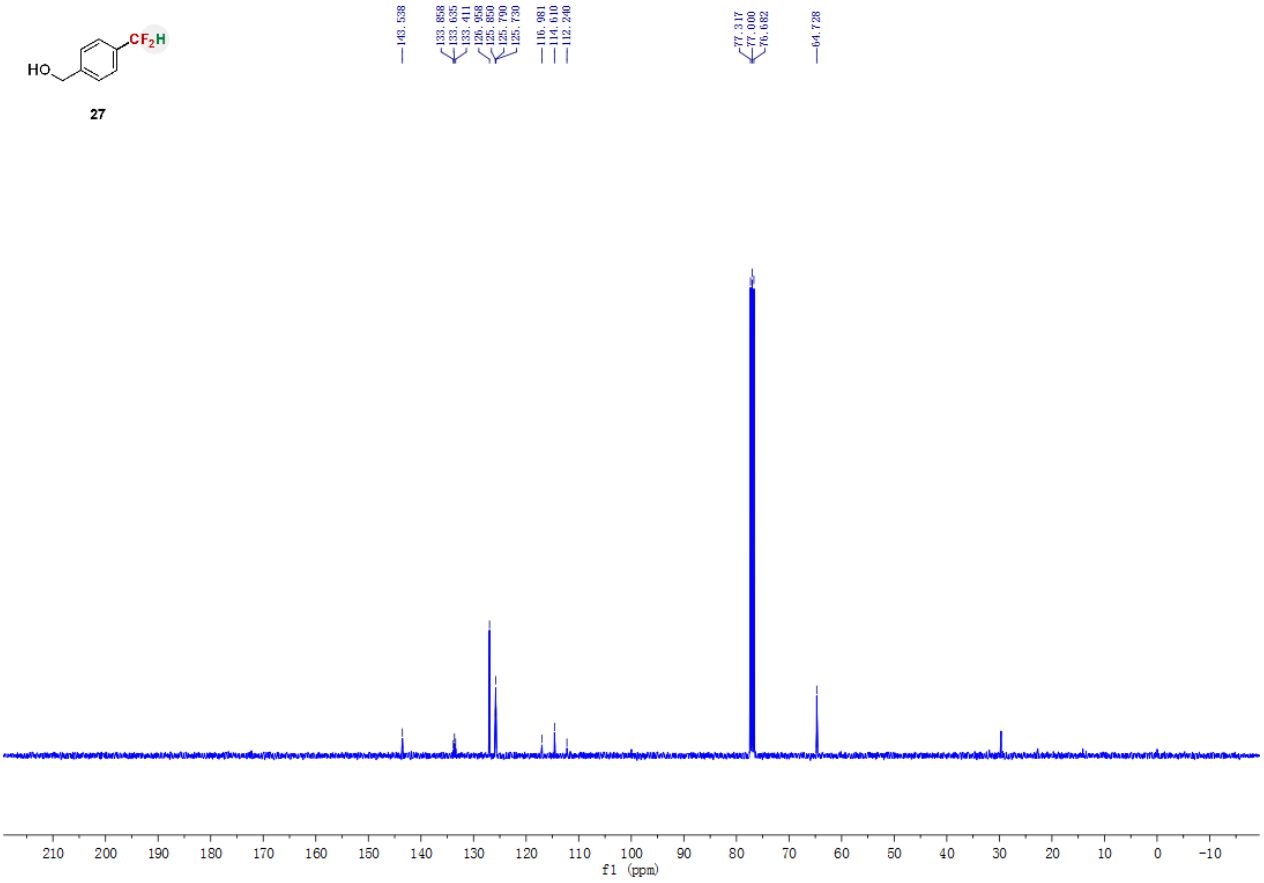
26

134.196
134.037
133.839
132.249
126.120
125.467
125.409
114.303
112.401
105.998
92.698
77.254
77.000
76.745
18.630
11.301
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

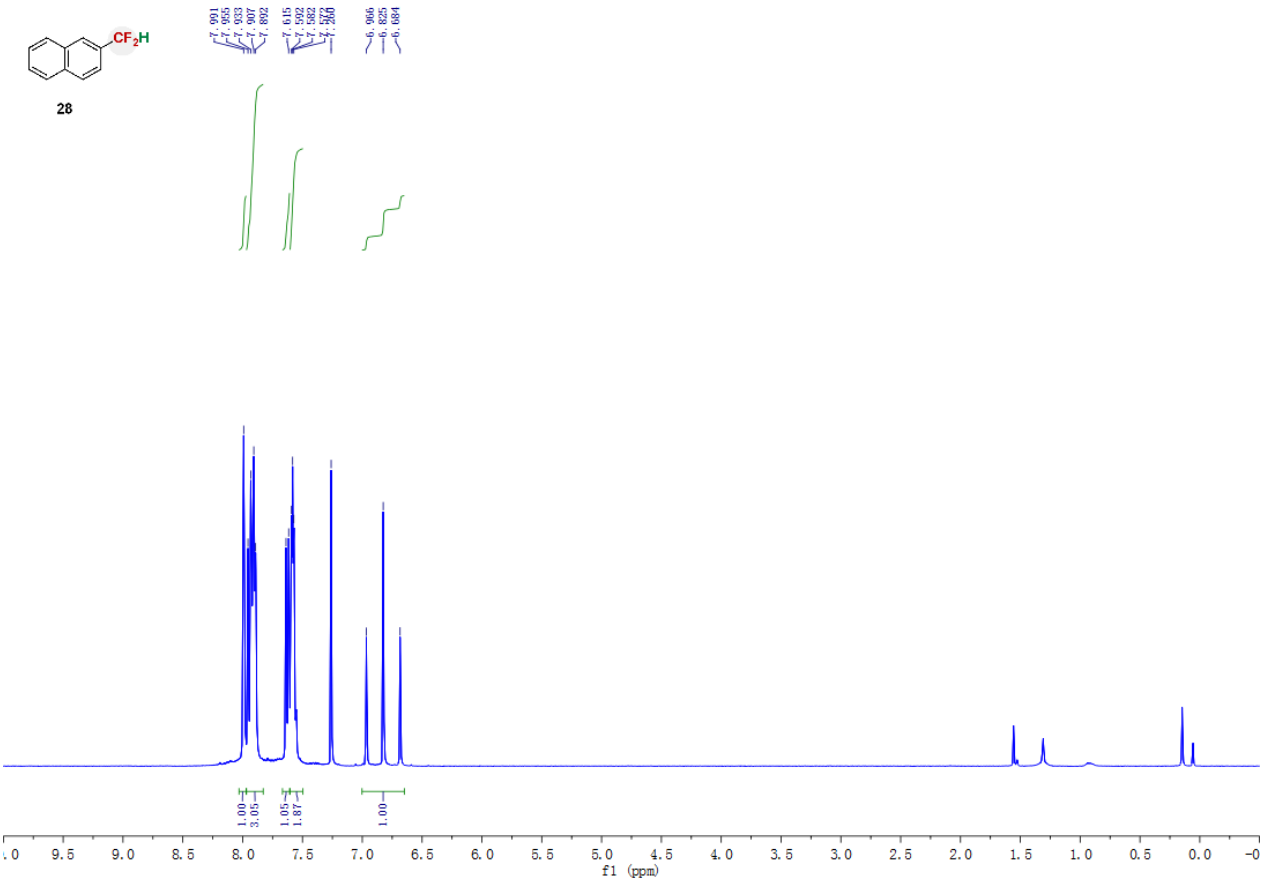
4-(Difluoromethyl)phenyl)methanol (27).

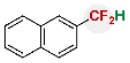






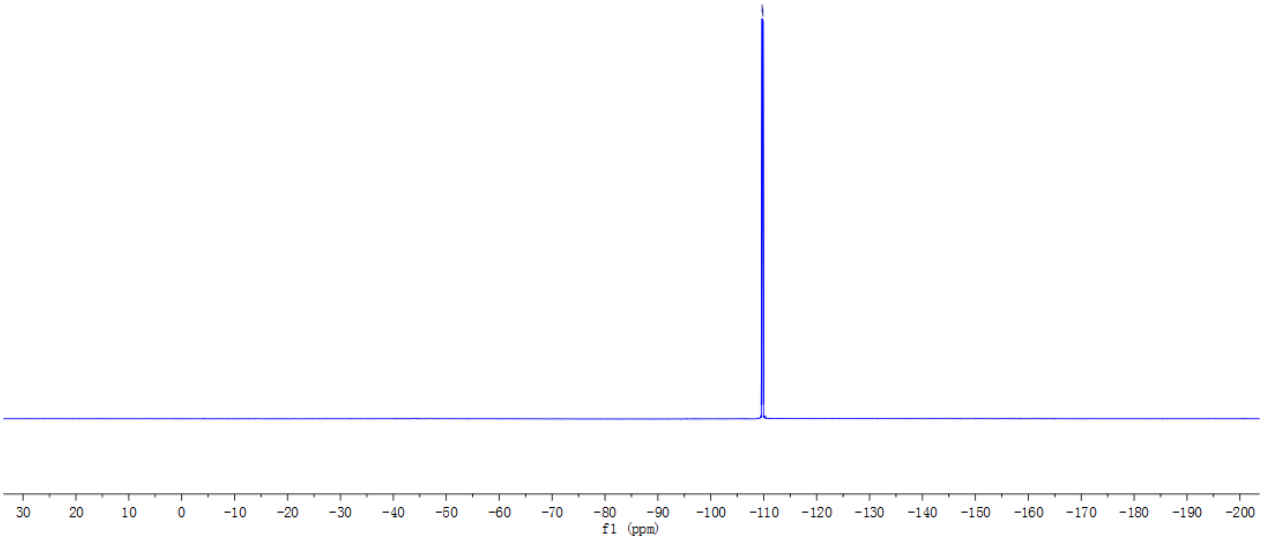
2-(Difluoromethyl)naphthalene (28).

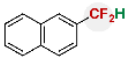



CF2H

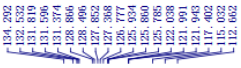
28


109.703
109.853

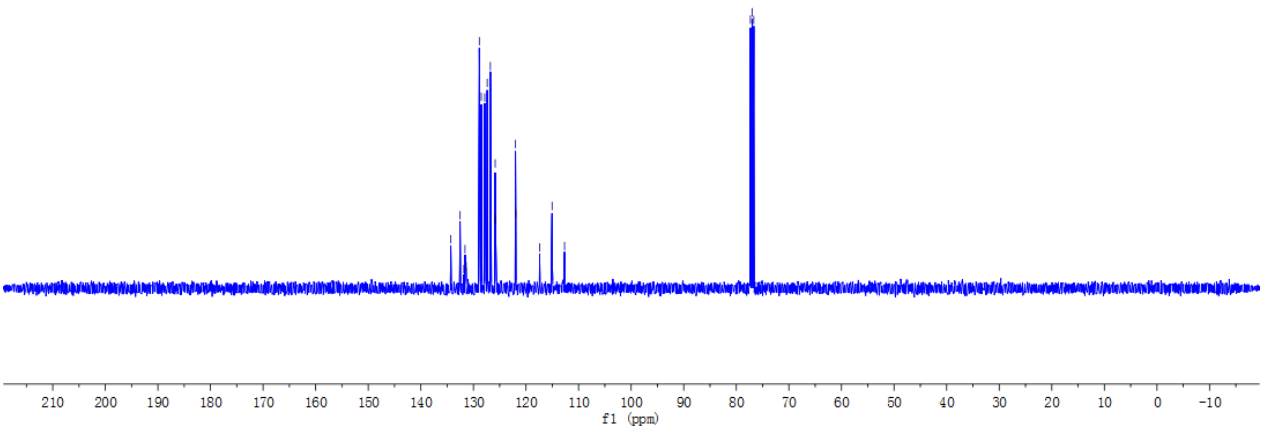

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


CF2H

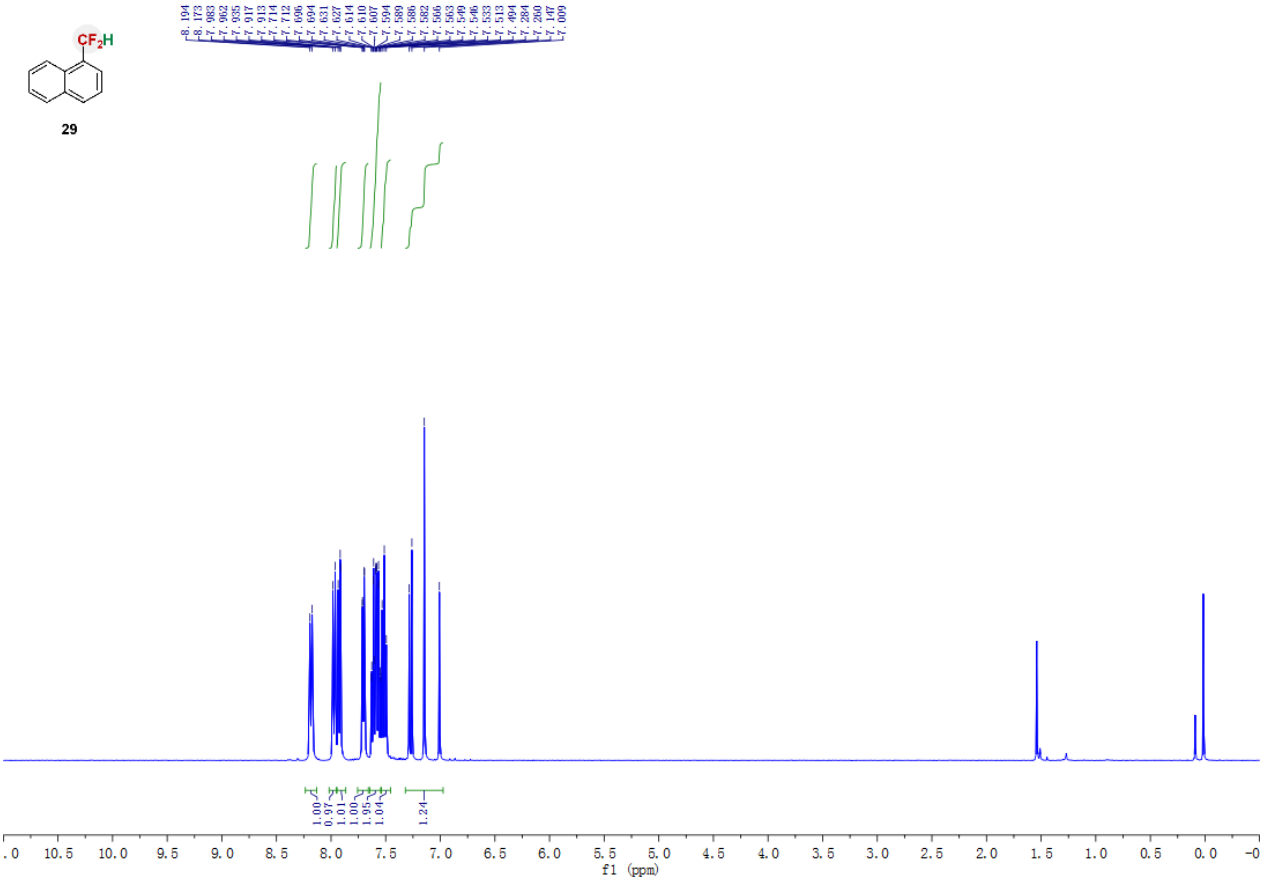
28

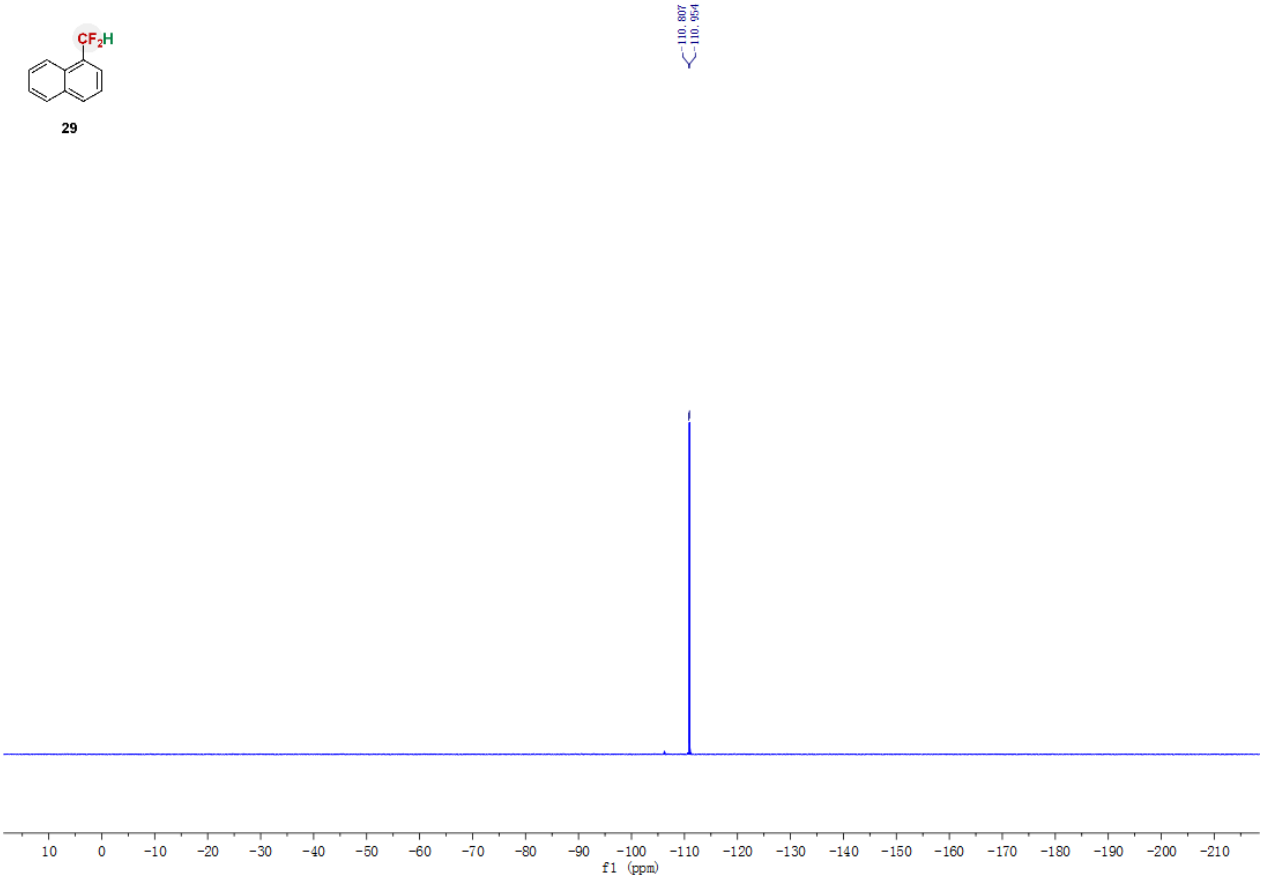

134.292
132.532
131.919
131.596
131.374
128.886
128.496
127.852
127.398
126.777
125.934
125.860
125.765
125.038
121.991
121.943
117.402
115.032
112.662

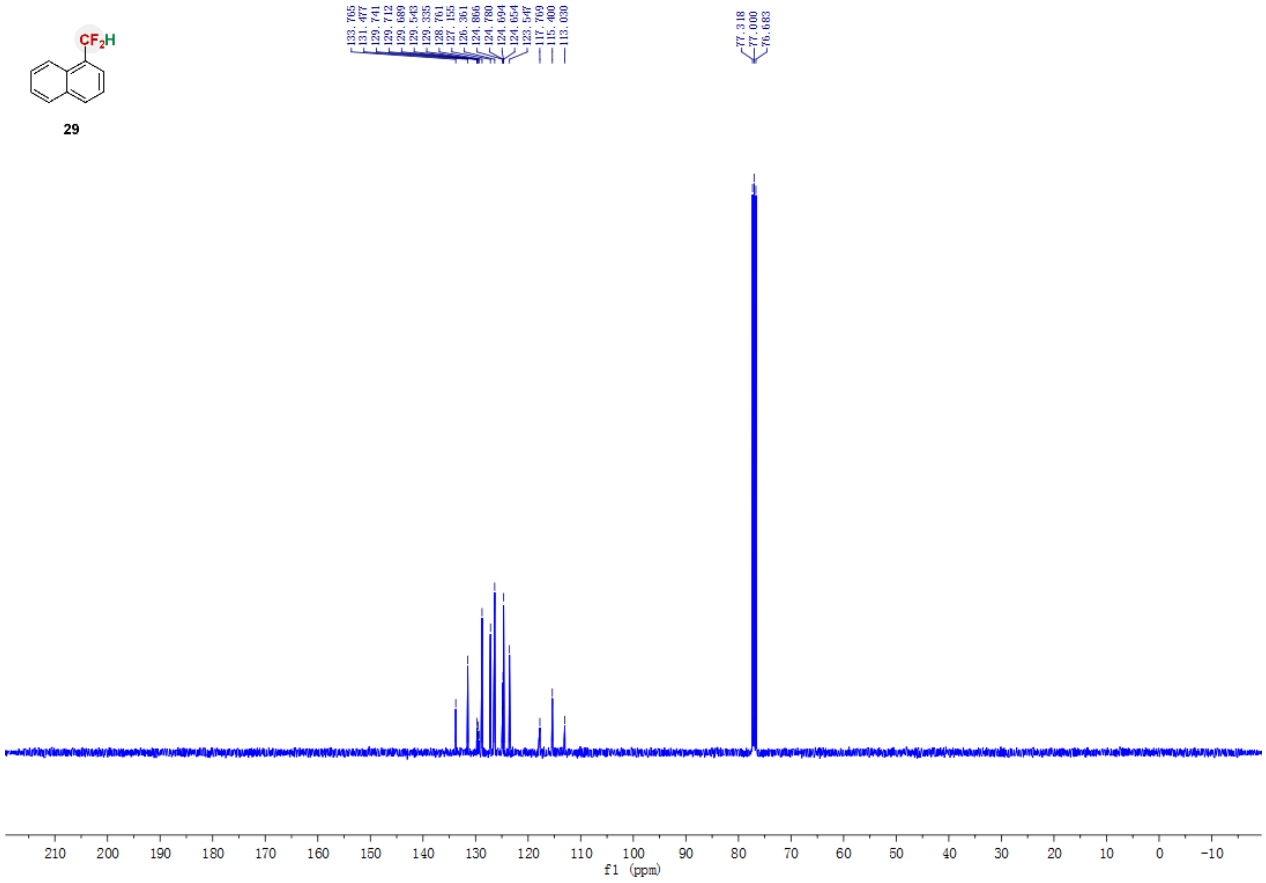

77.318
77.000
76.683


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

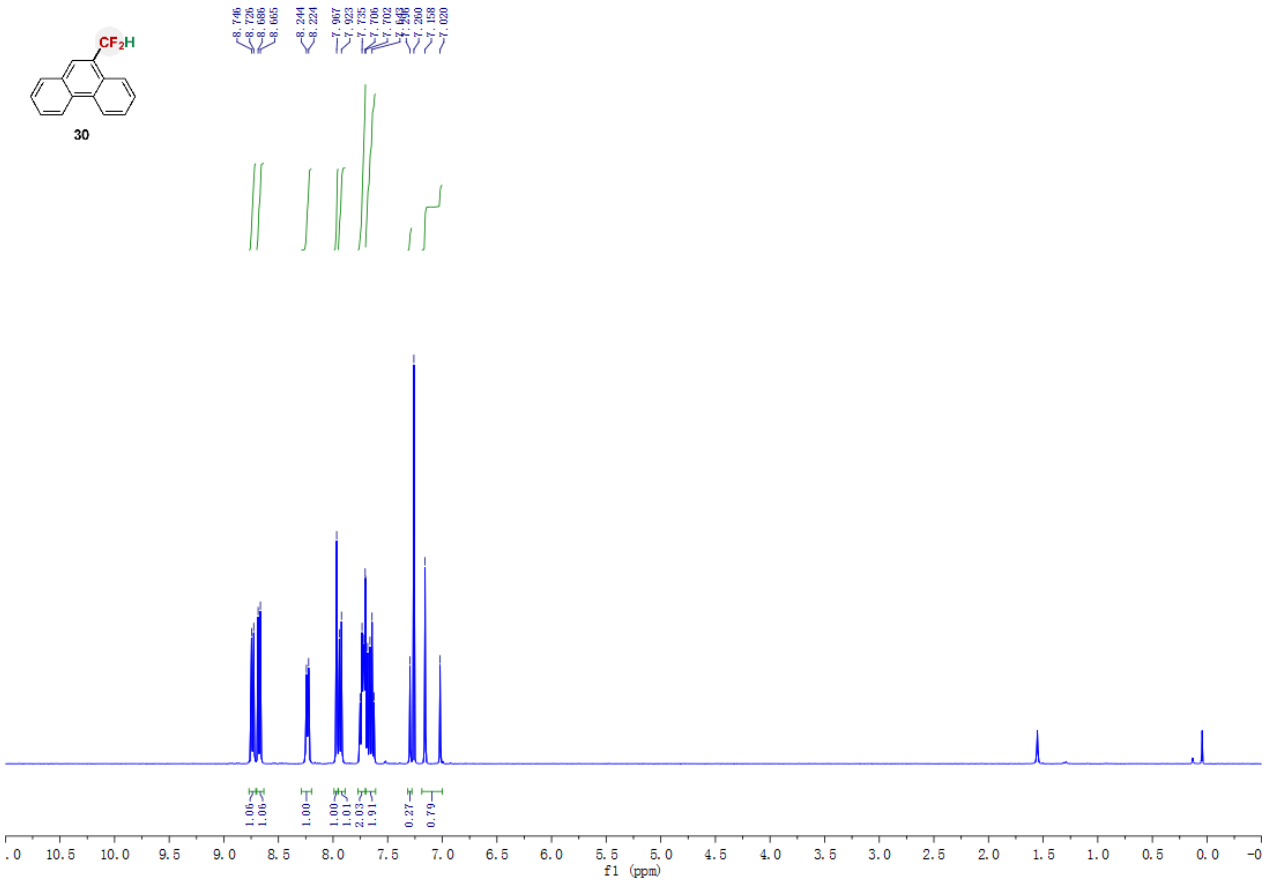
1-(Difluoromethyl)naphthalene (29).

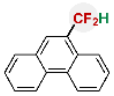






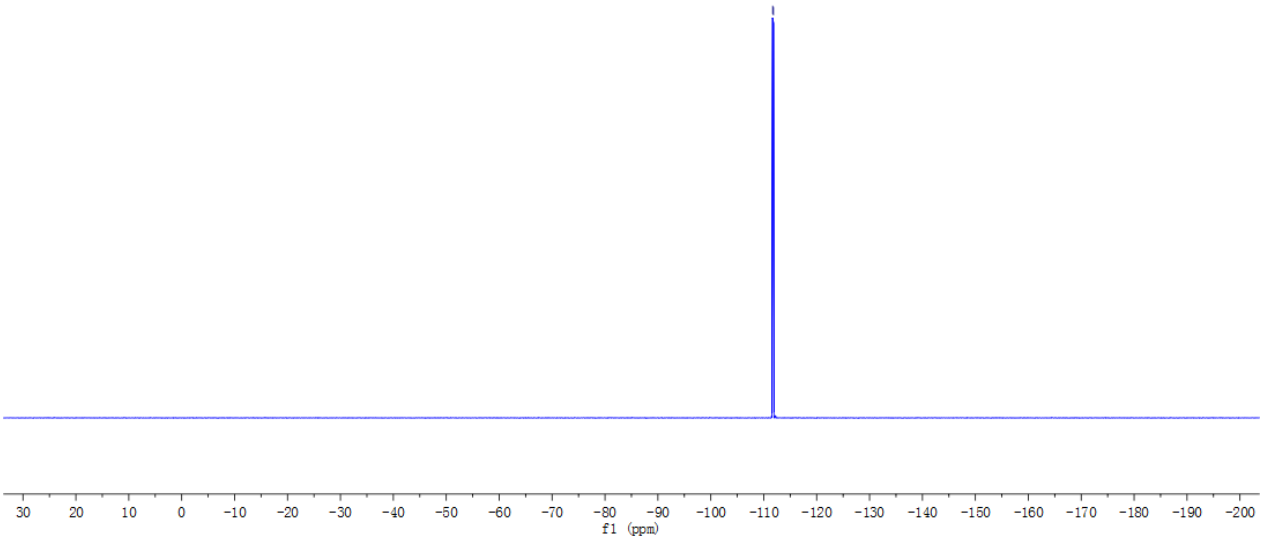
9-(Difluoromethyl)phenanthrene (30).

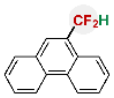



CF2H

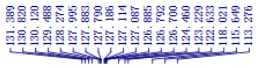
30


111.689
111.835

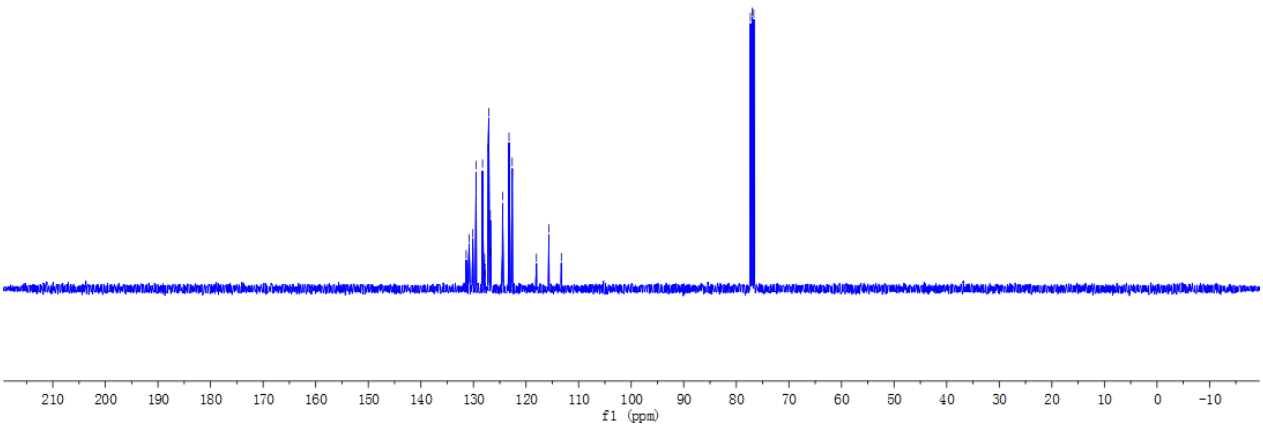

30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


CF2H

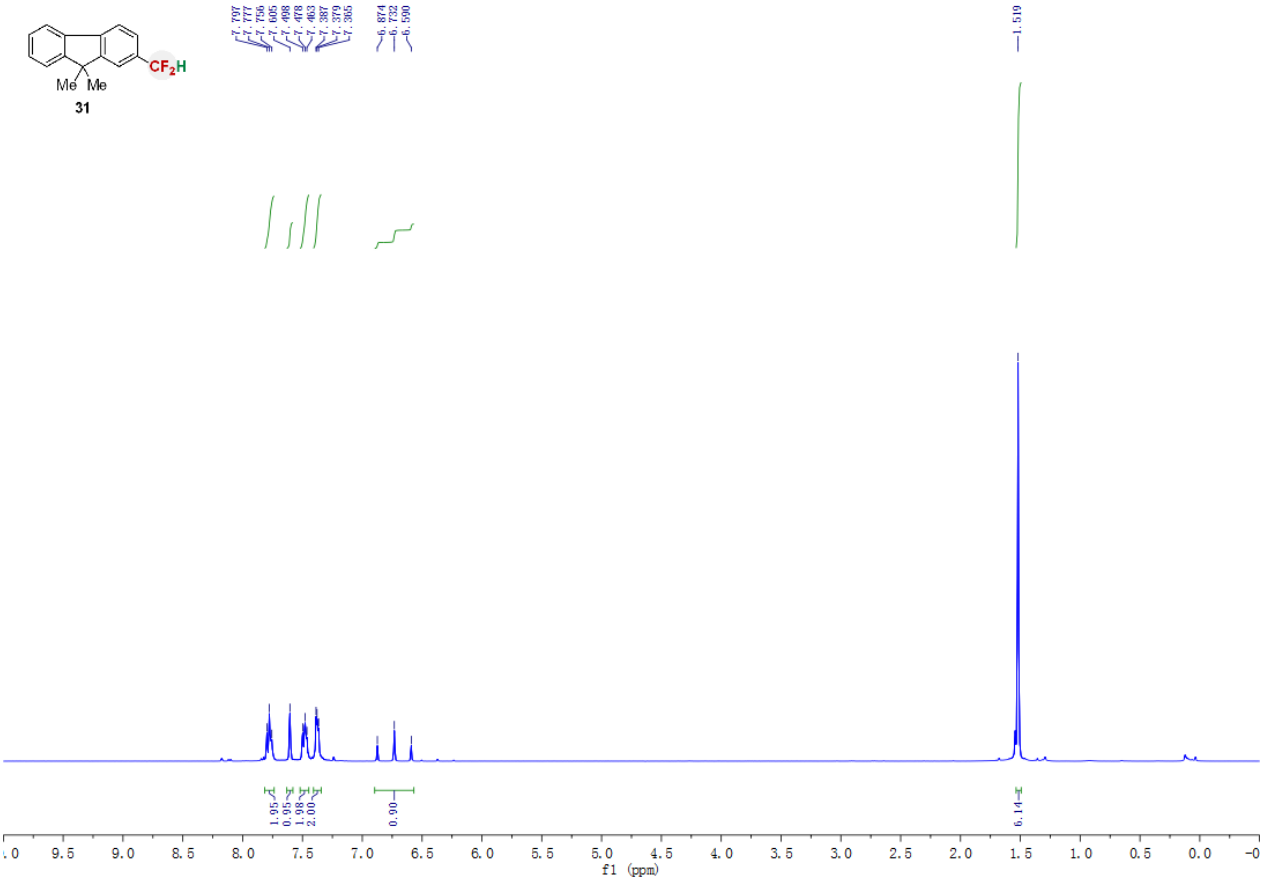
30

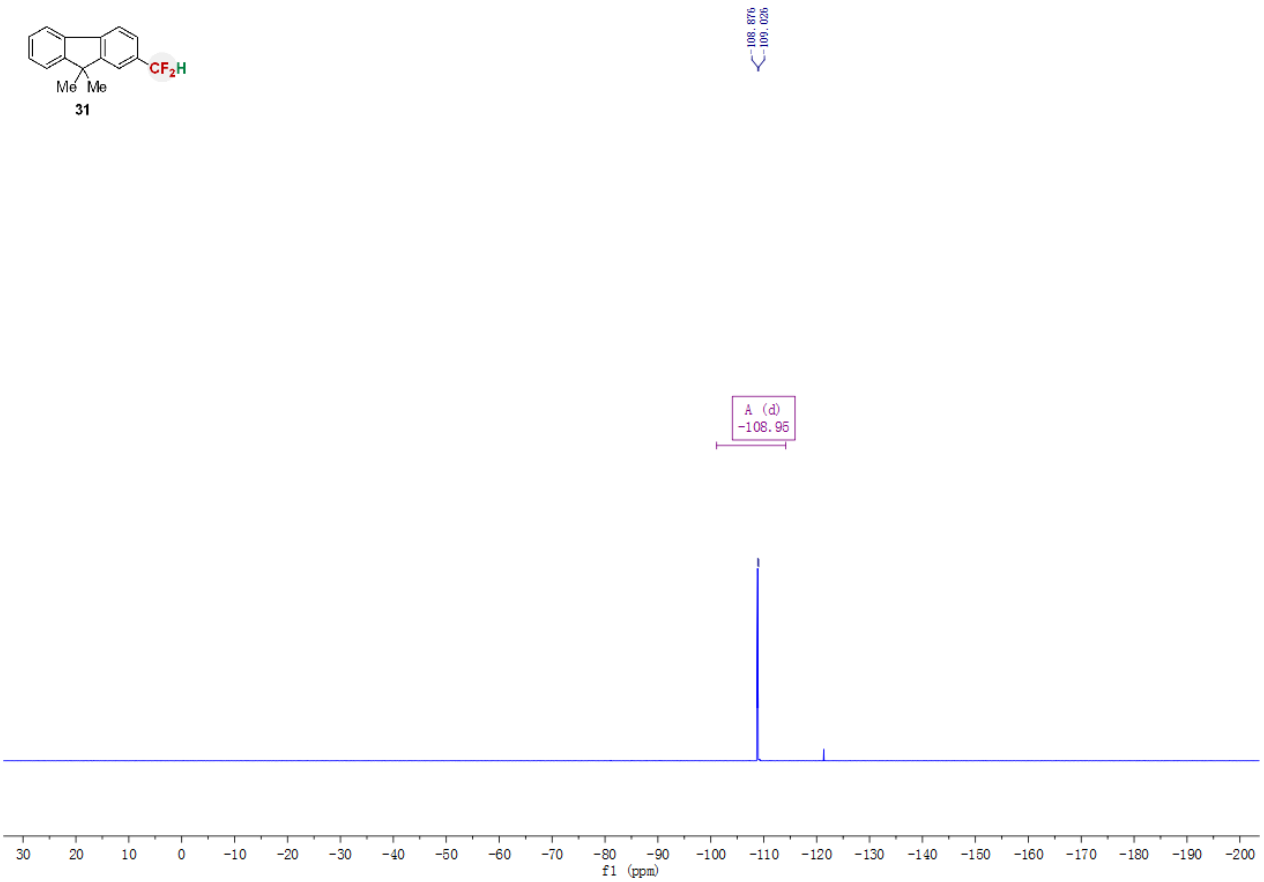

131.389
130.620
130.103
129.488
128.274
127.995
127.883
127.790
127.186
127.114
127.087
126.885
126.702
126.700
124.460
123.229
122.633
118.021
115.649
113.276

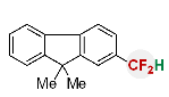

77.318
77.000
76.683


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2-(Difluoromethyl)-9,9-dimethyl-9*H*-fluorene (31).



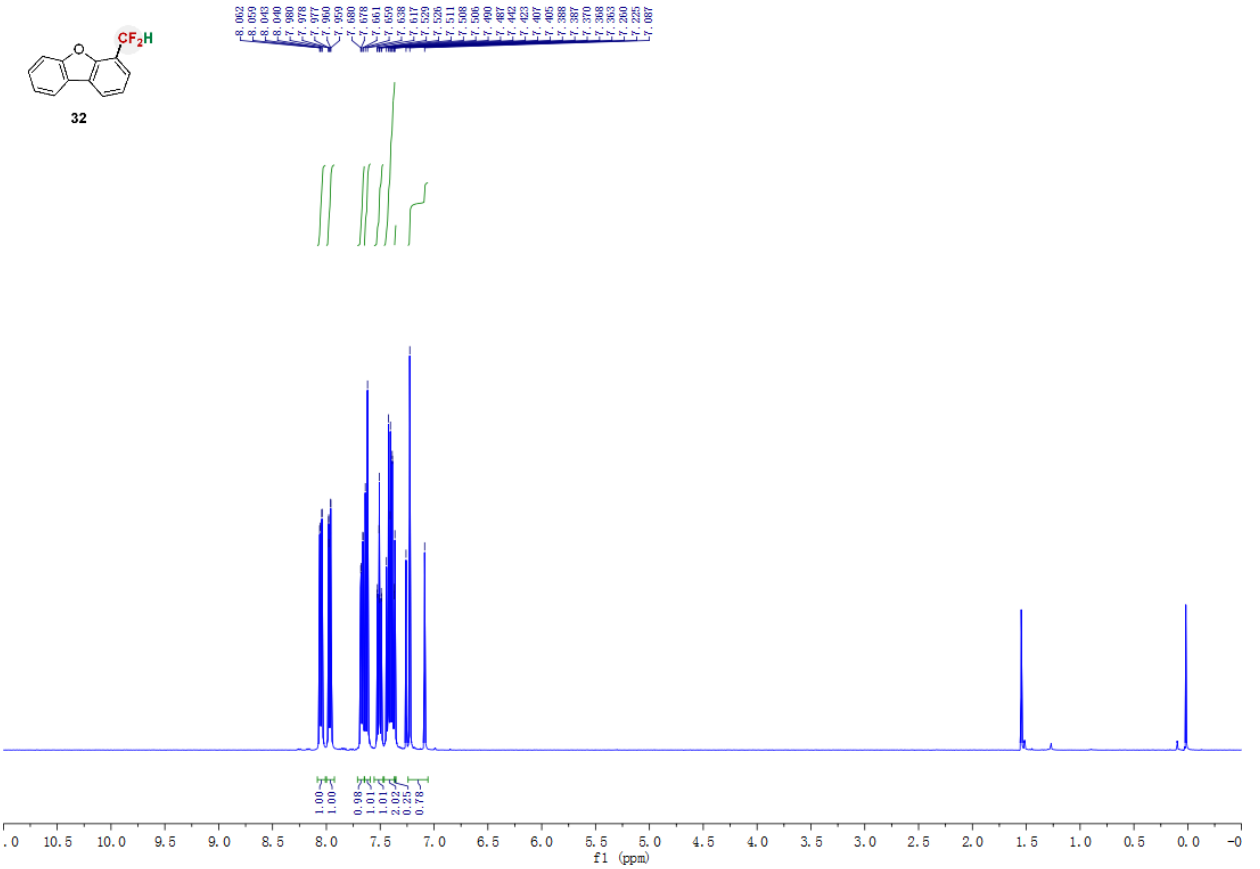


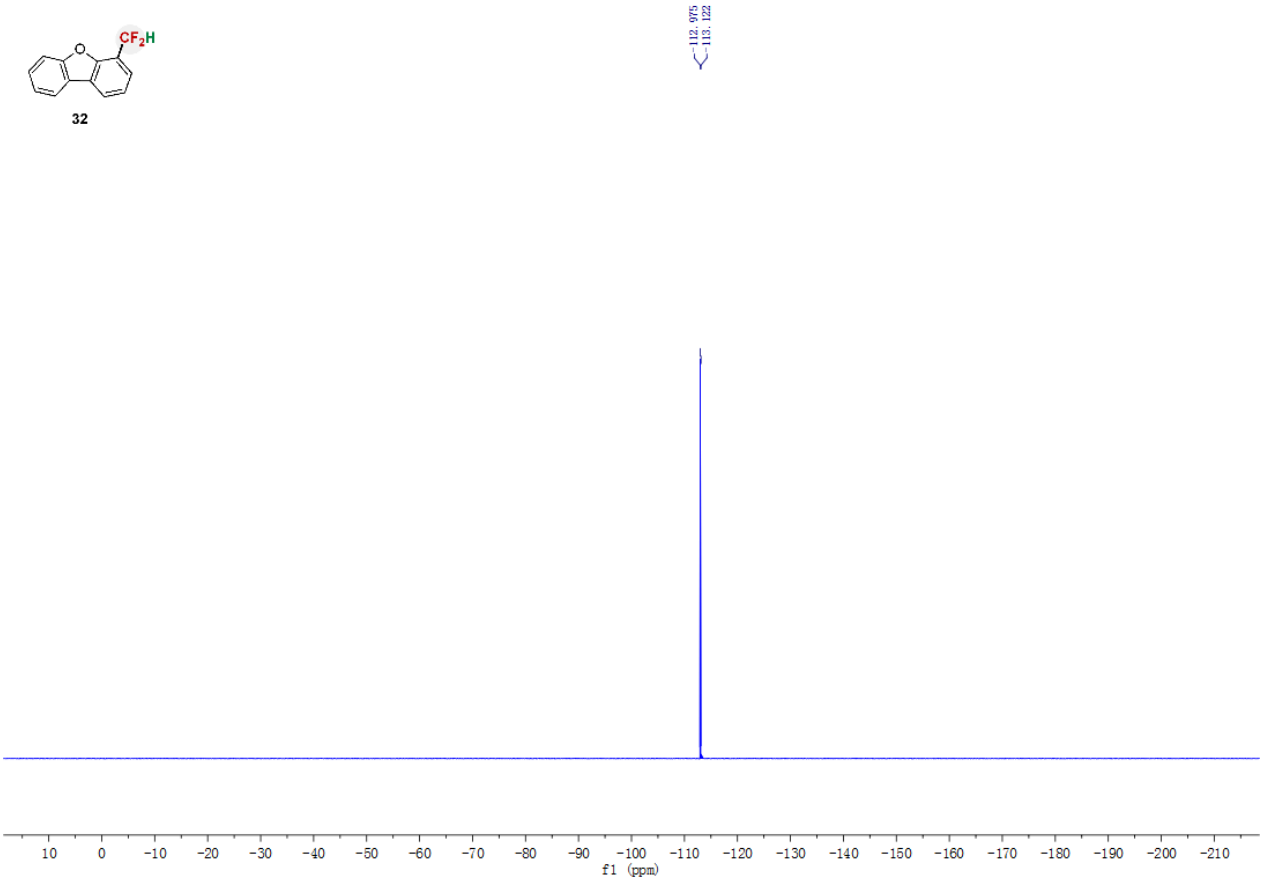

CF2H
Me Me

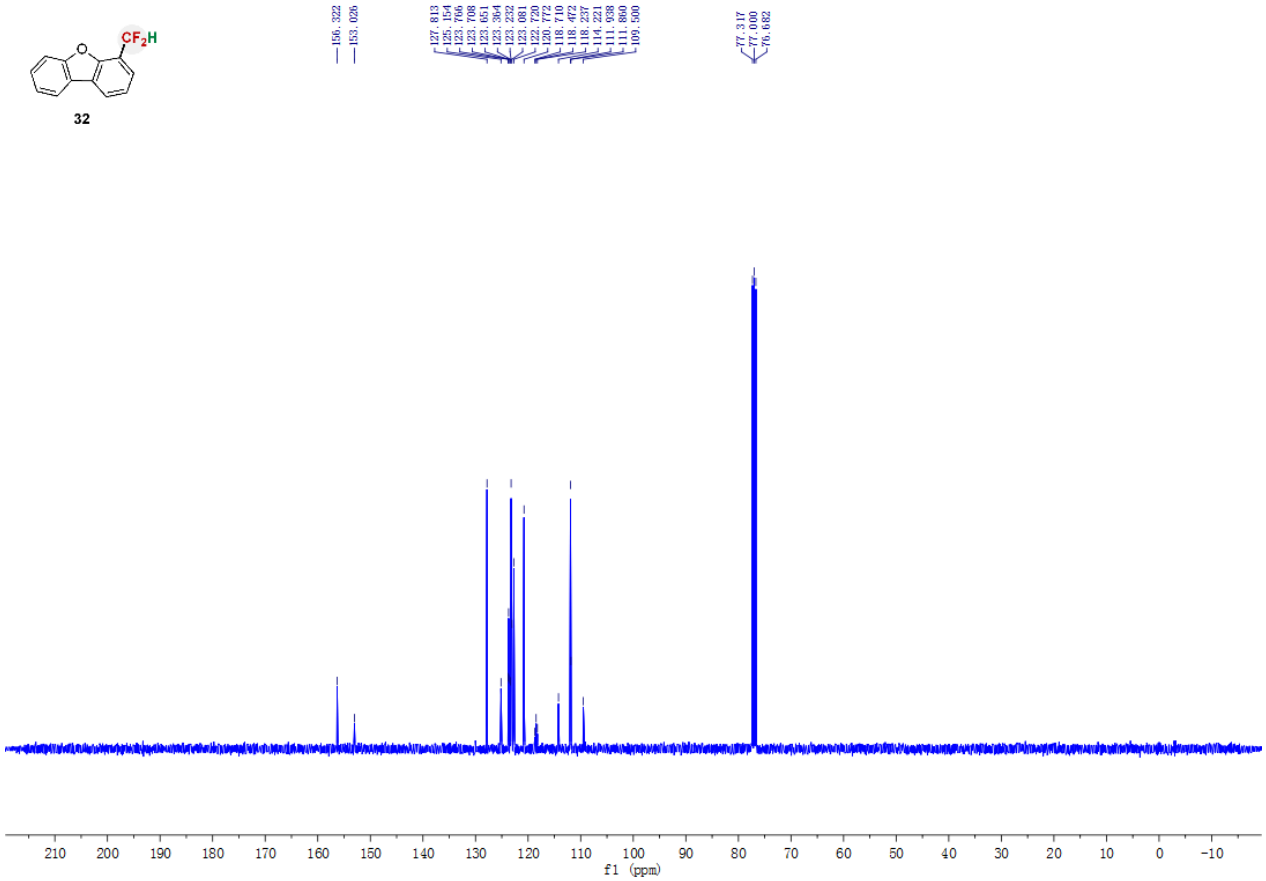
31

154.098
154.084
141.848
141.828
141.808
138.171
135.397
133.178
132.960
128.138
127.214
124.861
124.799
124.735
122.784
120.557
120.141
119.929
119.870
119.811
117.644
115.274
112.985
47.059
27.033
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

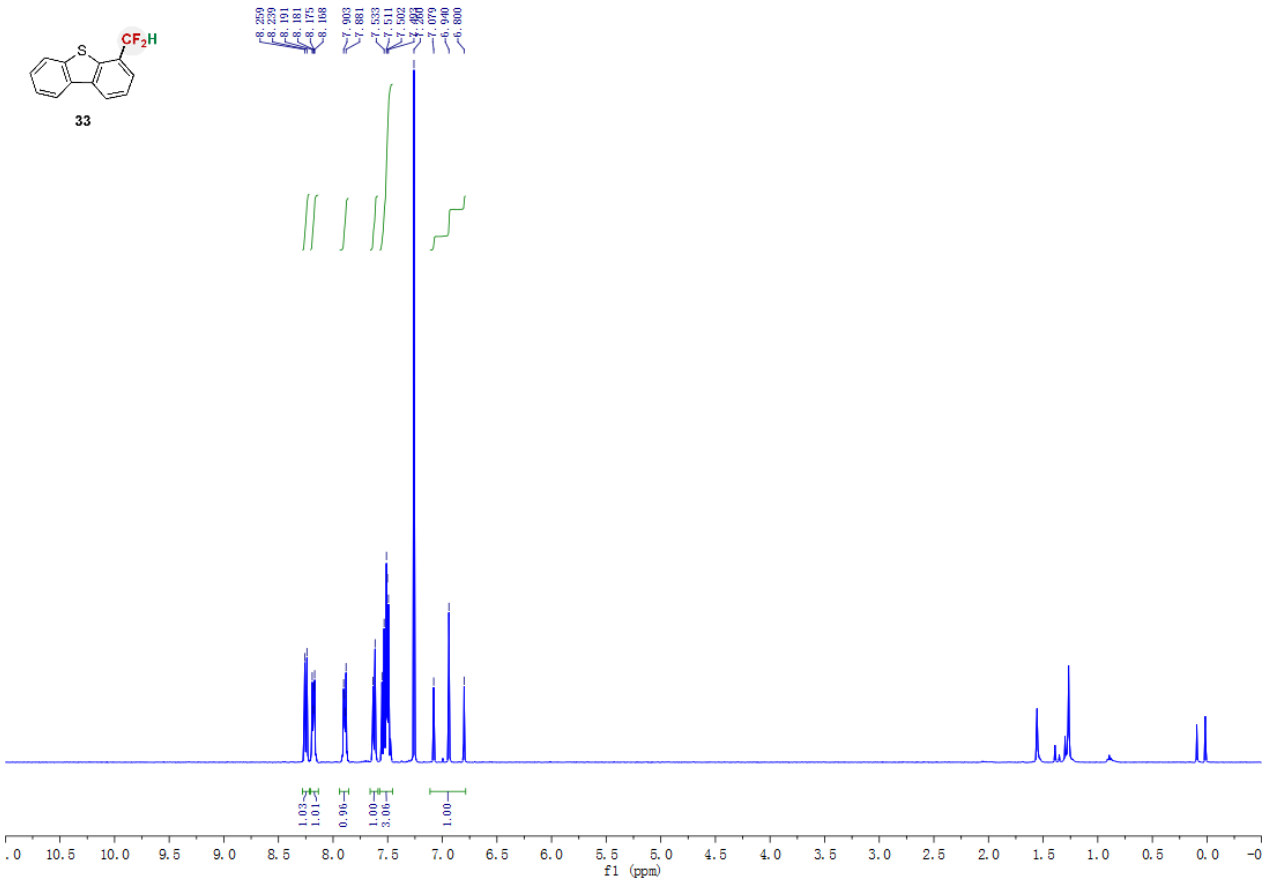
4-(Difluoromethyl)dibenzo[*b*,*d*]furan (32).





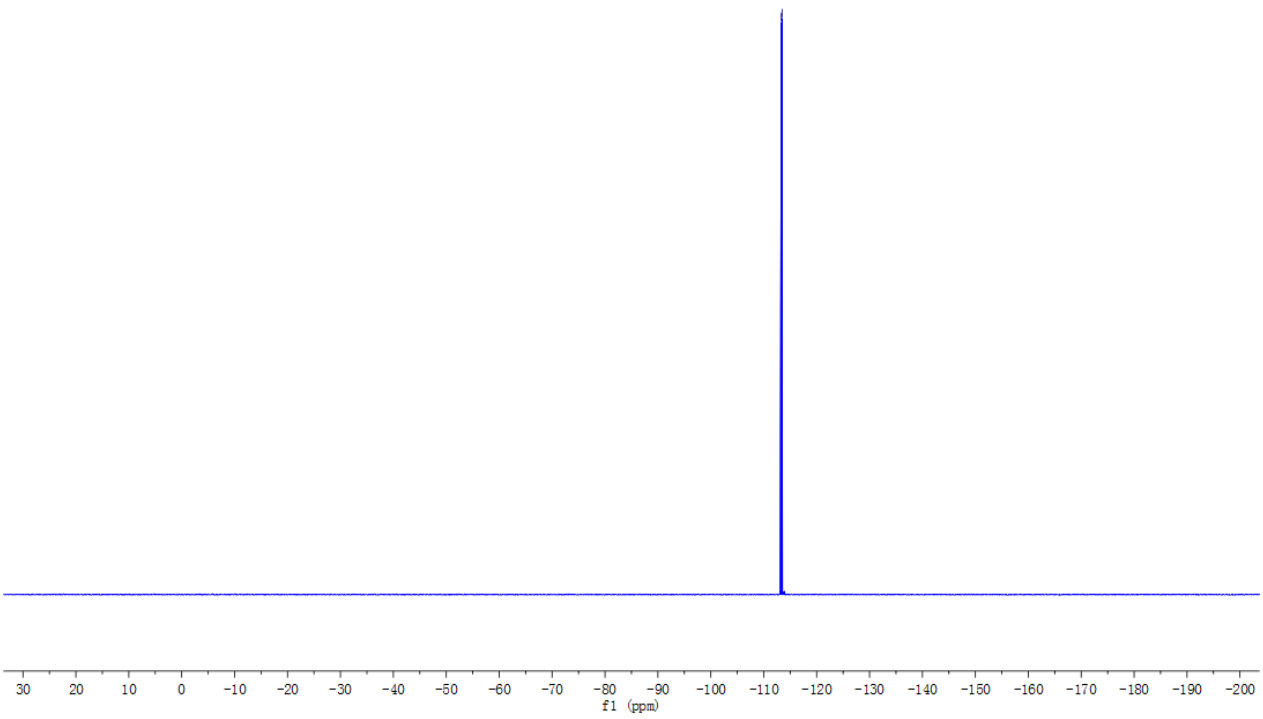


4-(Difluoromethyl)dibenzo[*b*,*d*]thiophene (33).



33

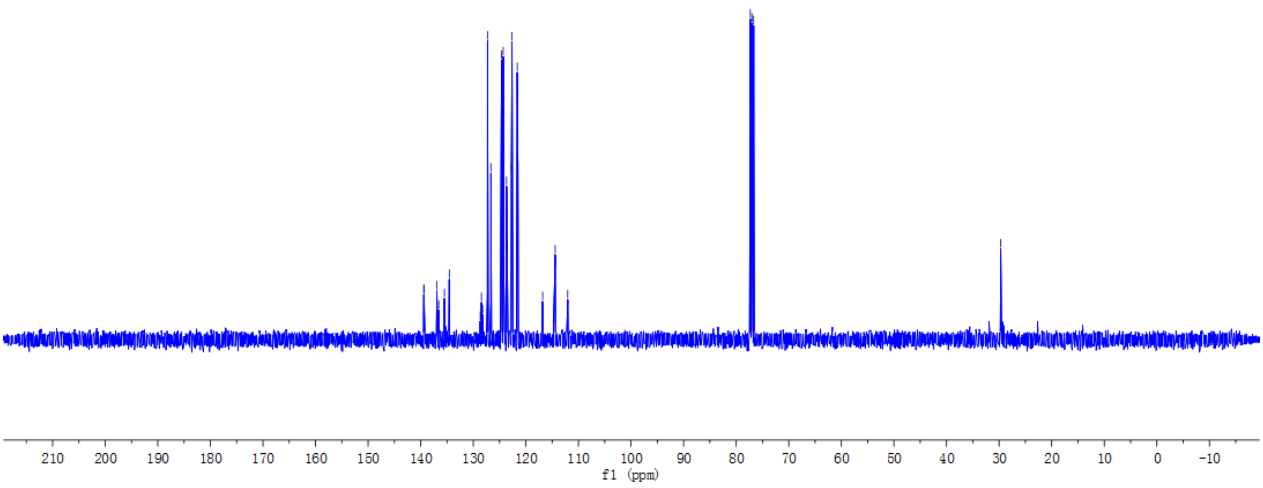

113.321
113.468


30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

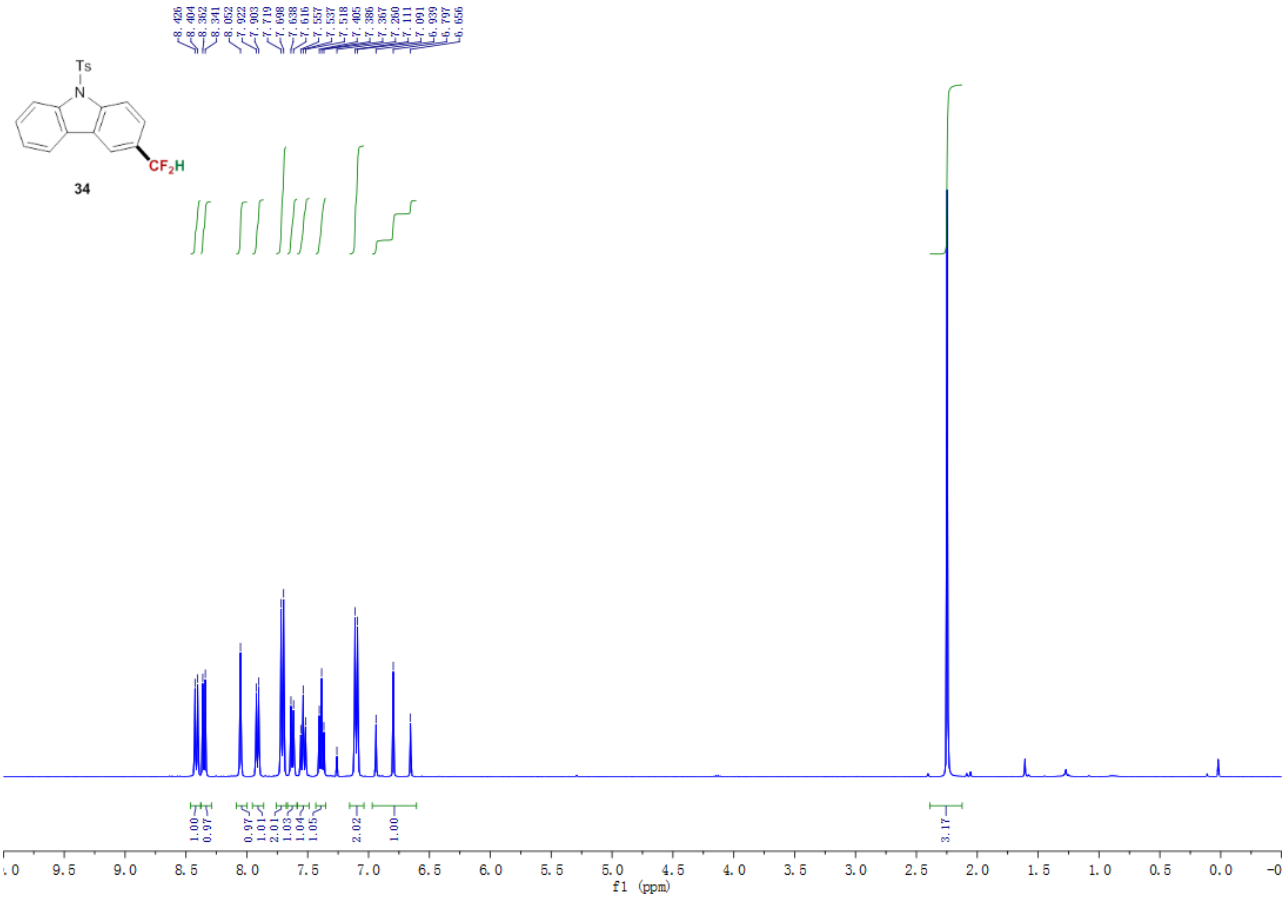
33

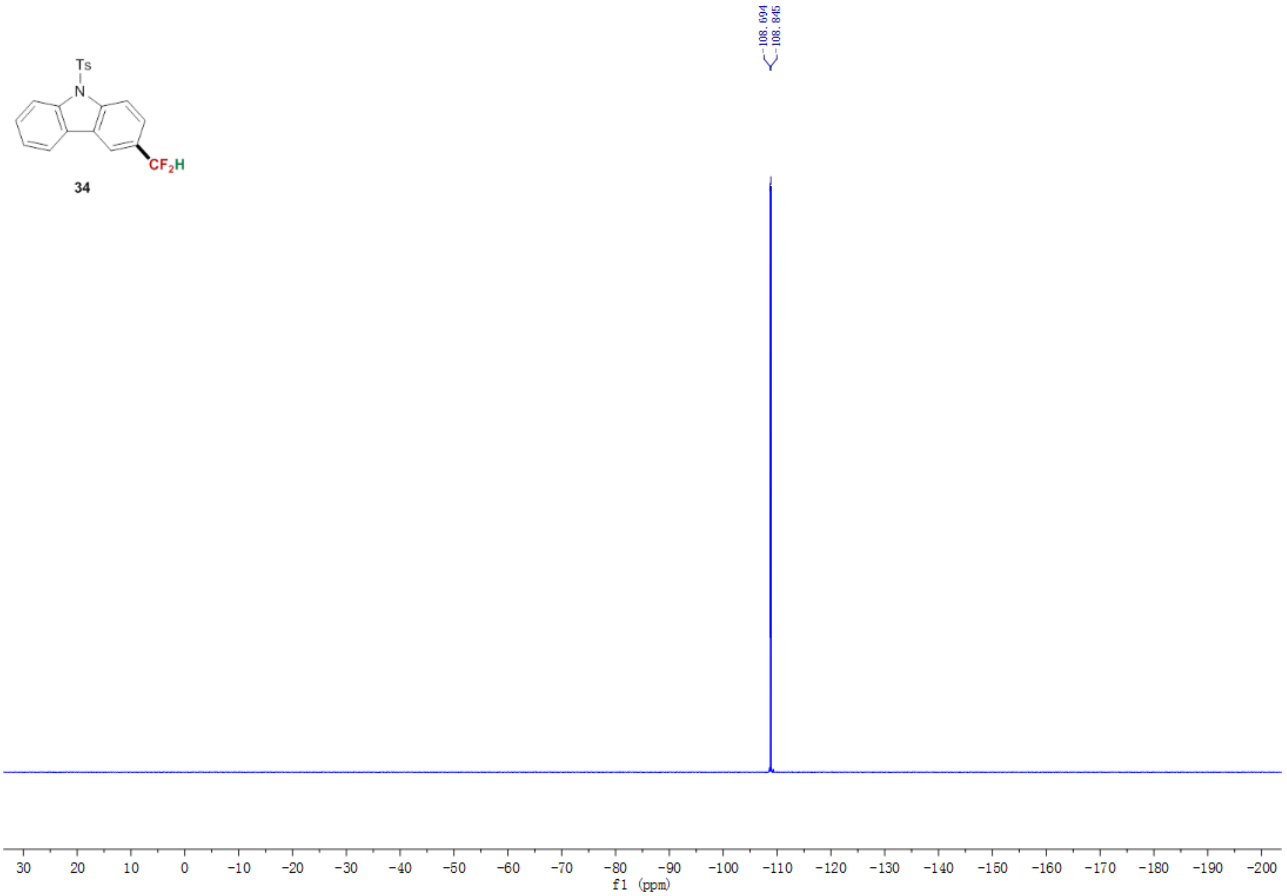

139.418
139.379
136.922
136.772
135.491
134.559
128.674
128.446
128.219
127.294
126.641
124.628
124.310
124.293
124.255
124.184
123.695
123.679
123.663
122.742
122.635
121.631
121.514
116.997
116.826
112.043
77.317
77.000
76.682

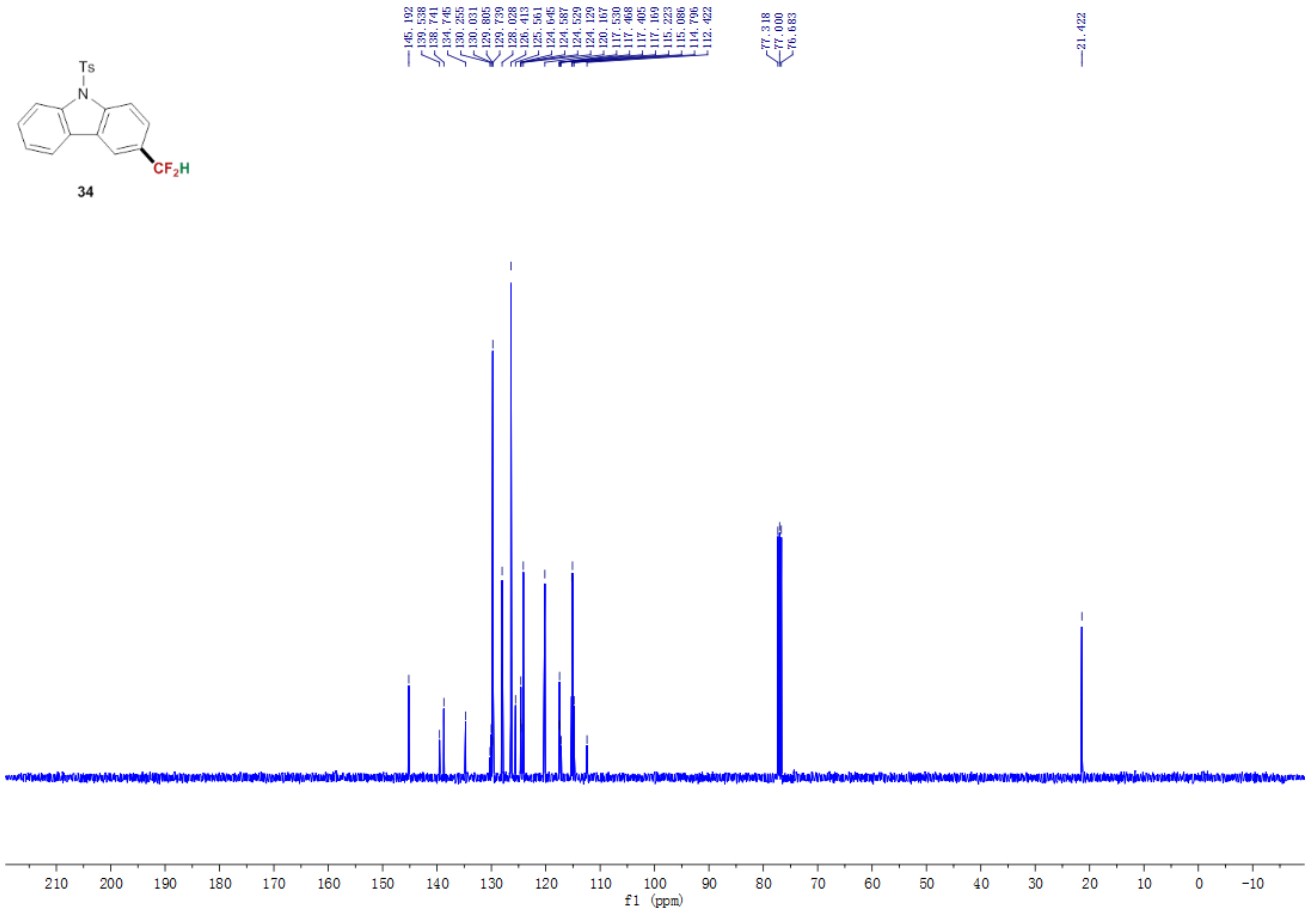
29.691


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

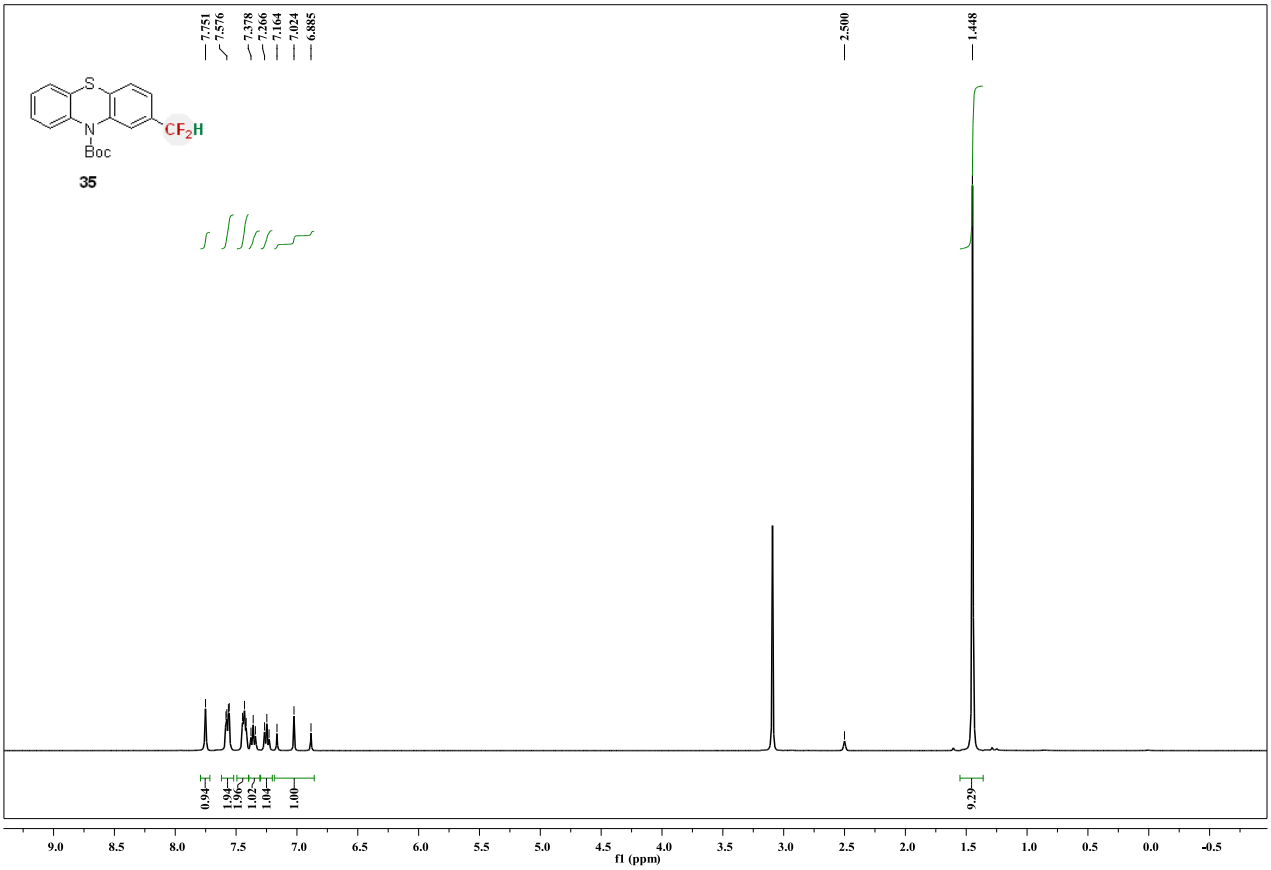
3-(Difluoromethyl)-9-tosyl-9*H*-carbazole (34).

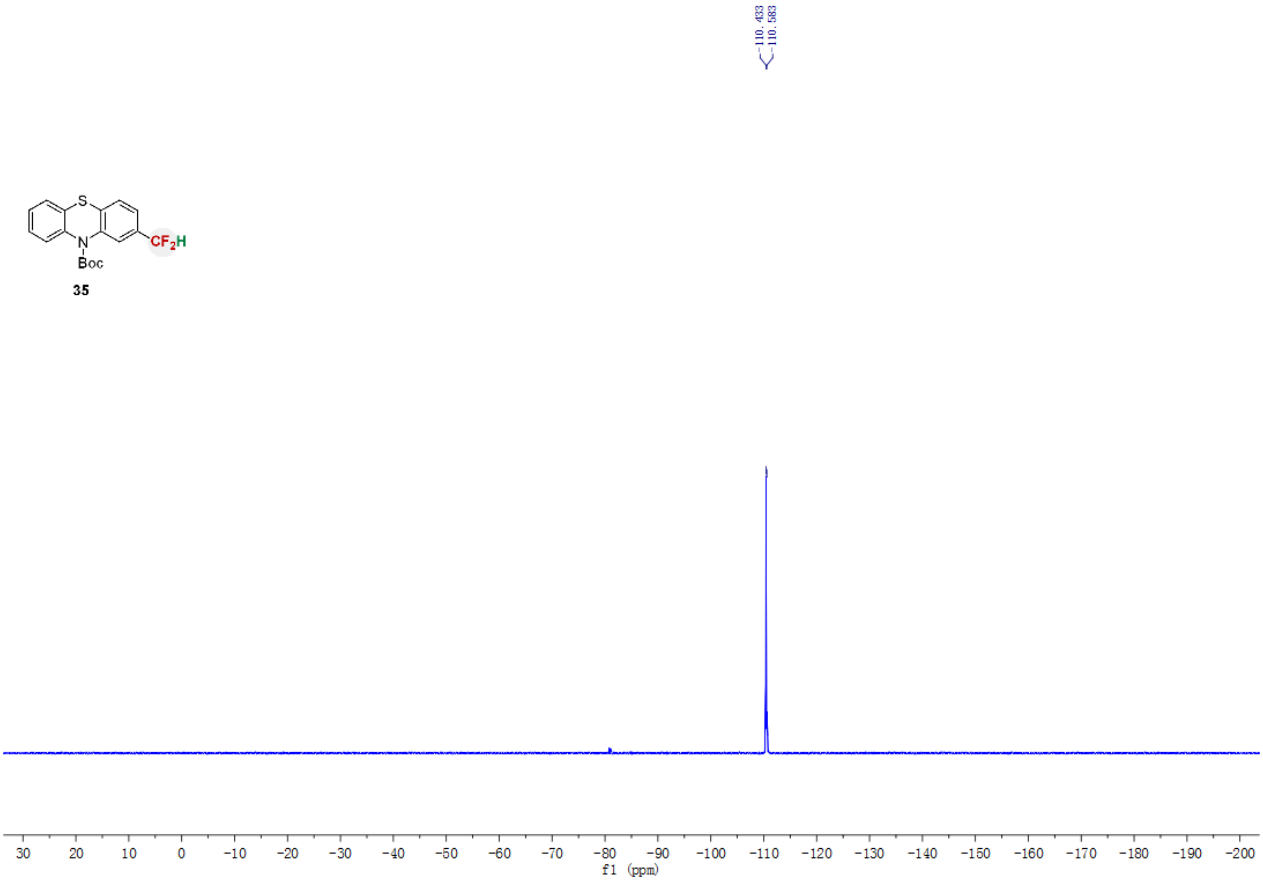


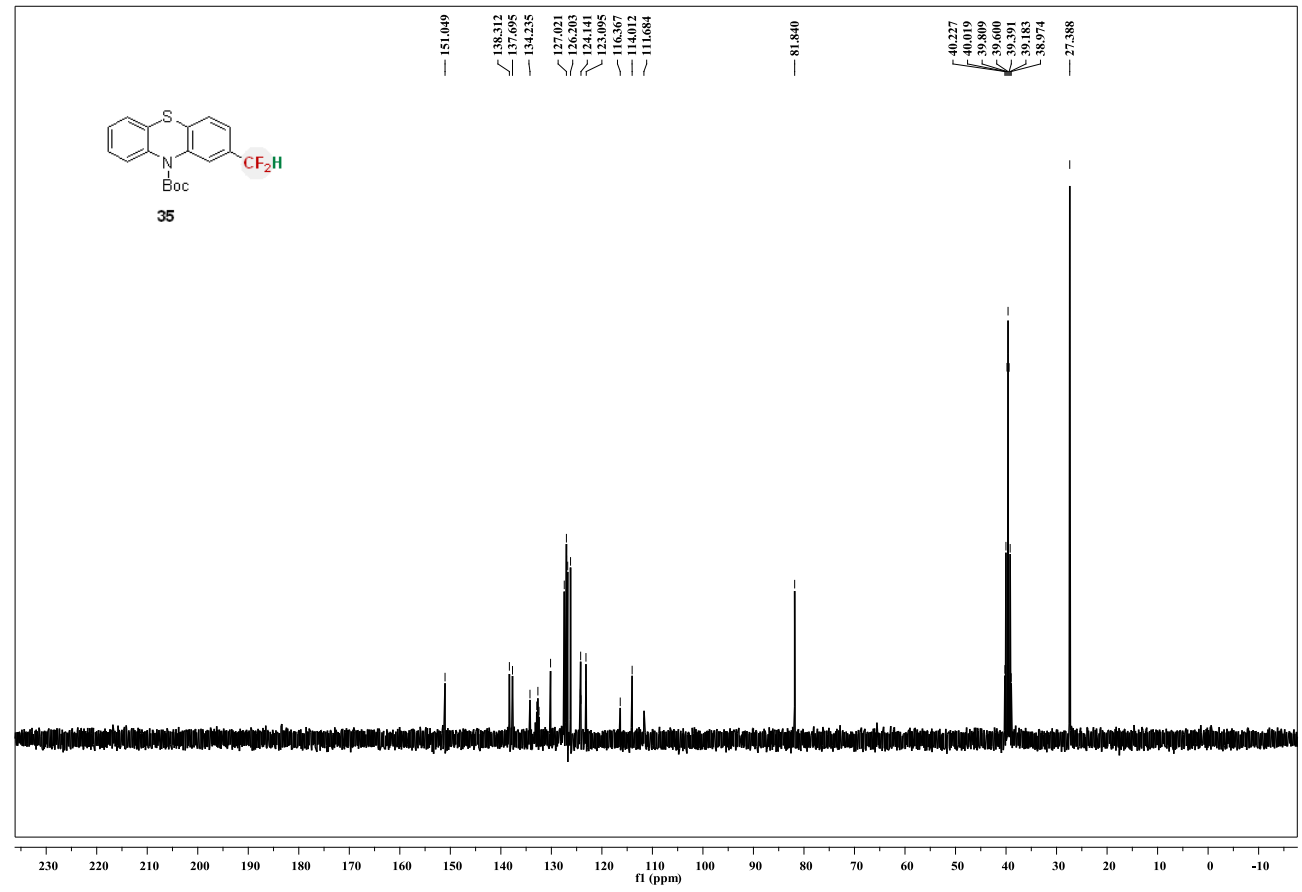




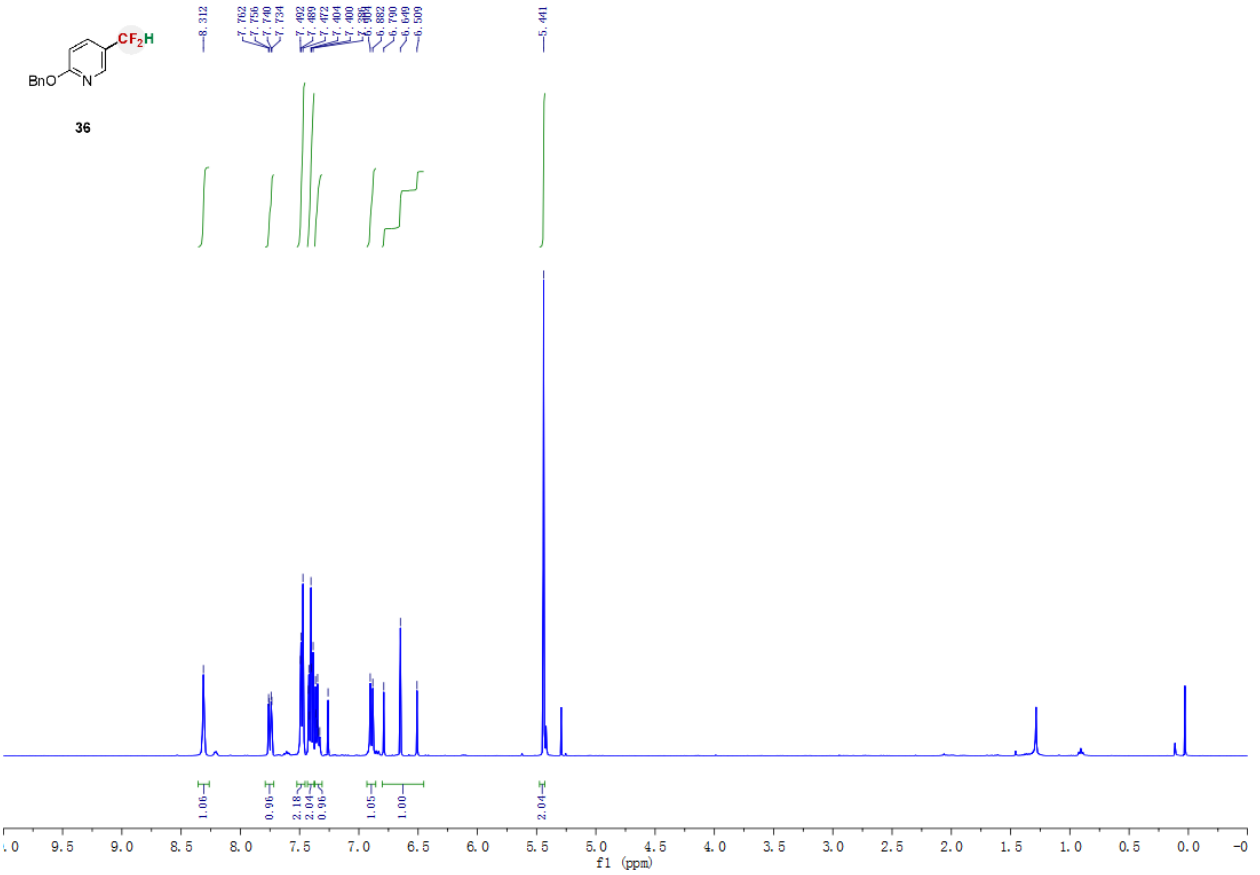
***N*-Boc-2-(difluoromethyl)-10*H*-phenothiazine (35).**

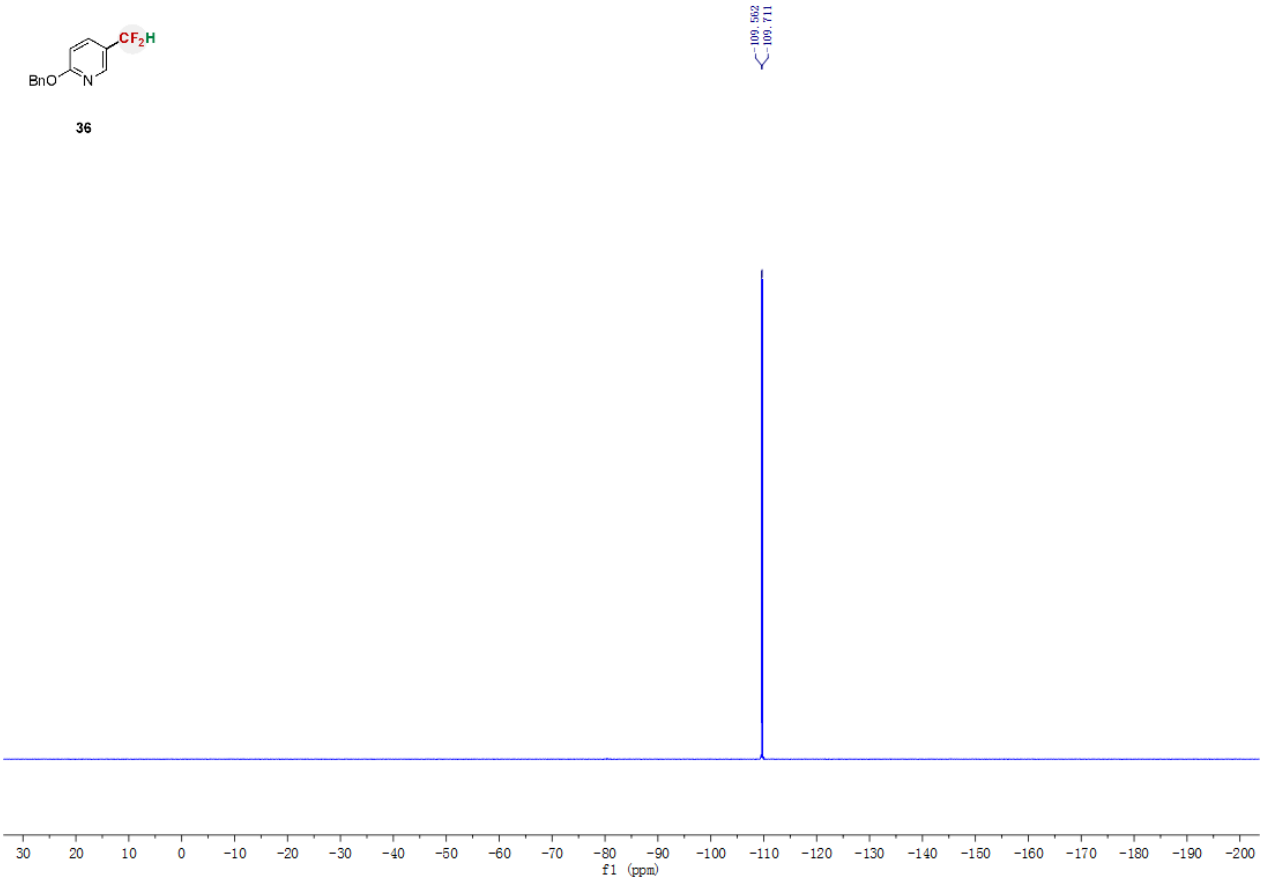


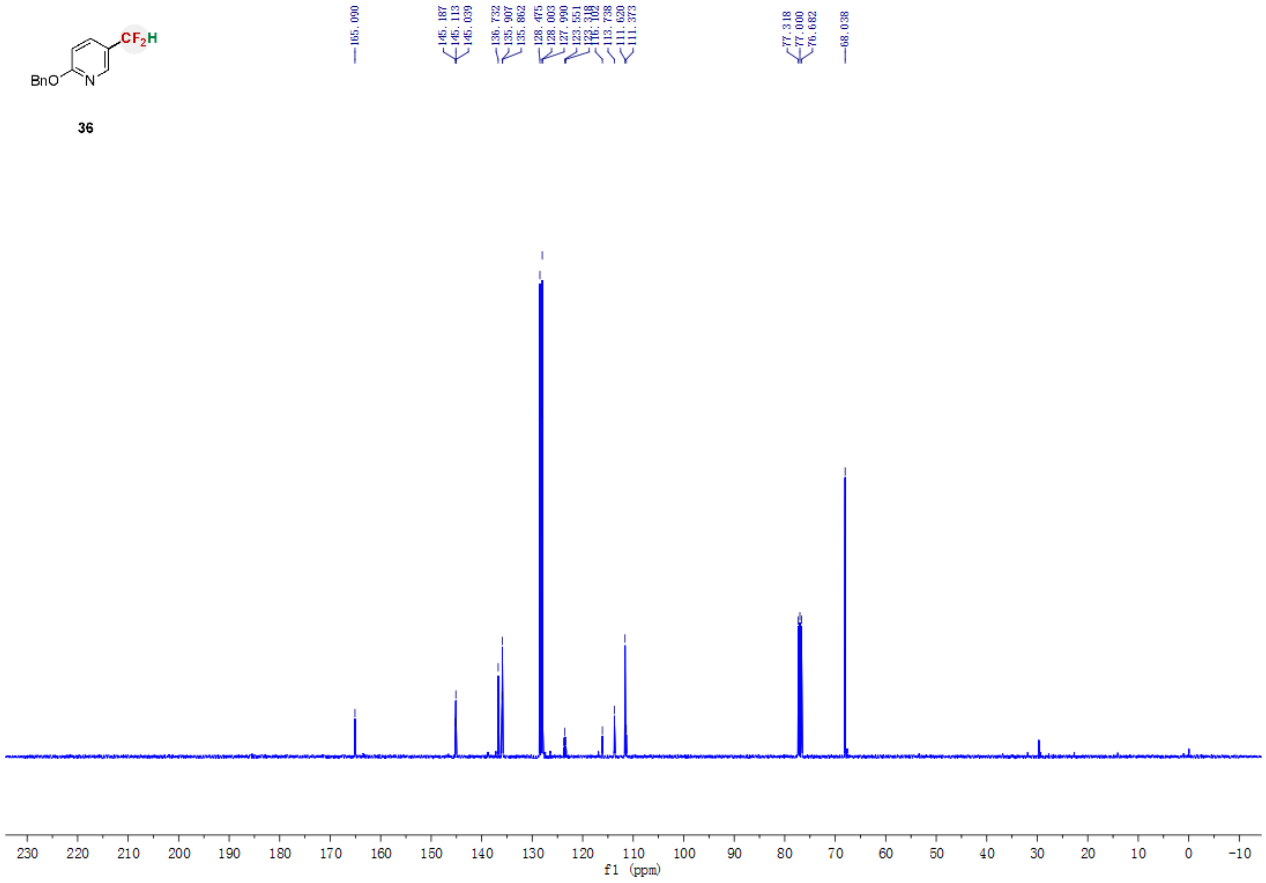

110.433
110.583
CF2H
Boc
35
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


151.049
138.312
137.695
134.235
127.021
126.203
124.141
123.095
116.367
114.012
111.684
81.840
40.227
40.019
39.809
39.600
39.391
39.183
38.974
27.388
CF2H
Boc
35
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

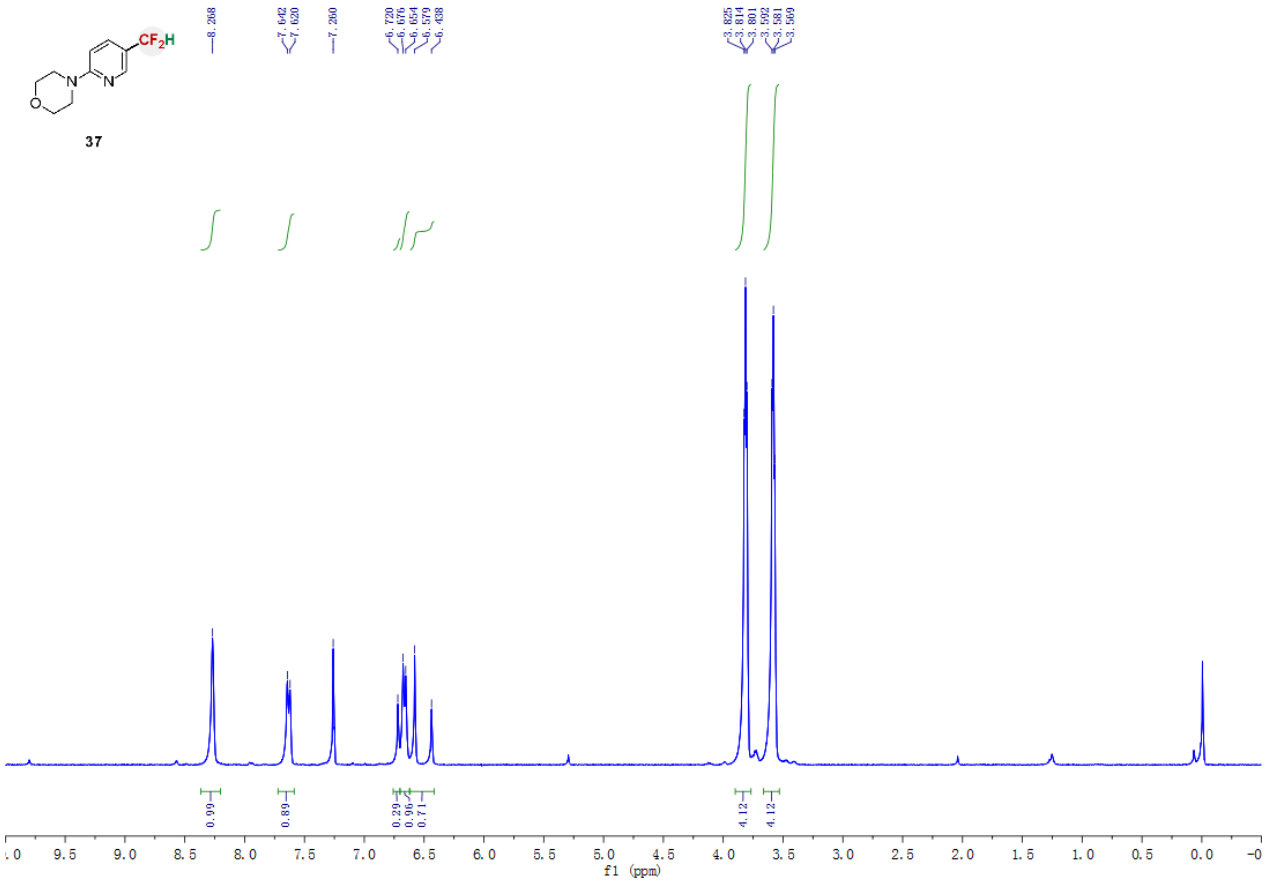
2-(Benzyloxy)-5-(difluoromethyl)pyridine (36).

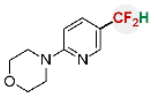






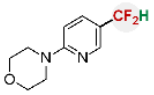
4-(5-(Difluoromethyl)pyridin-2-yl)morpholine (37).





37

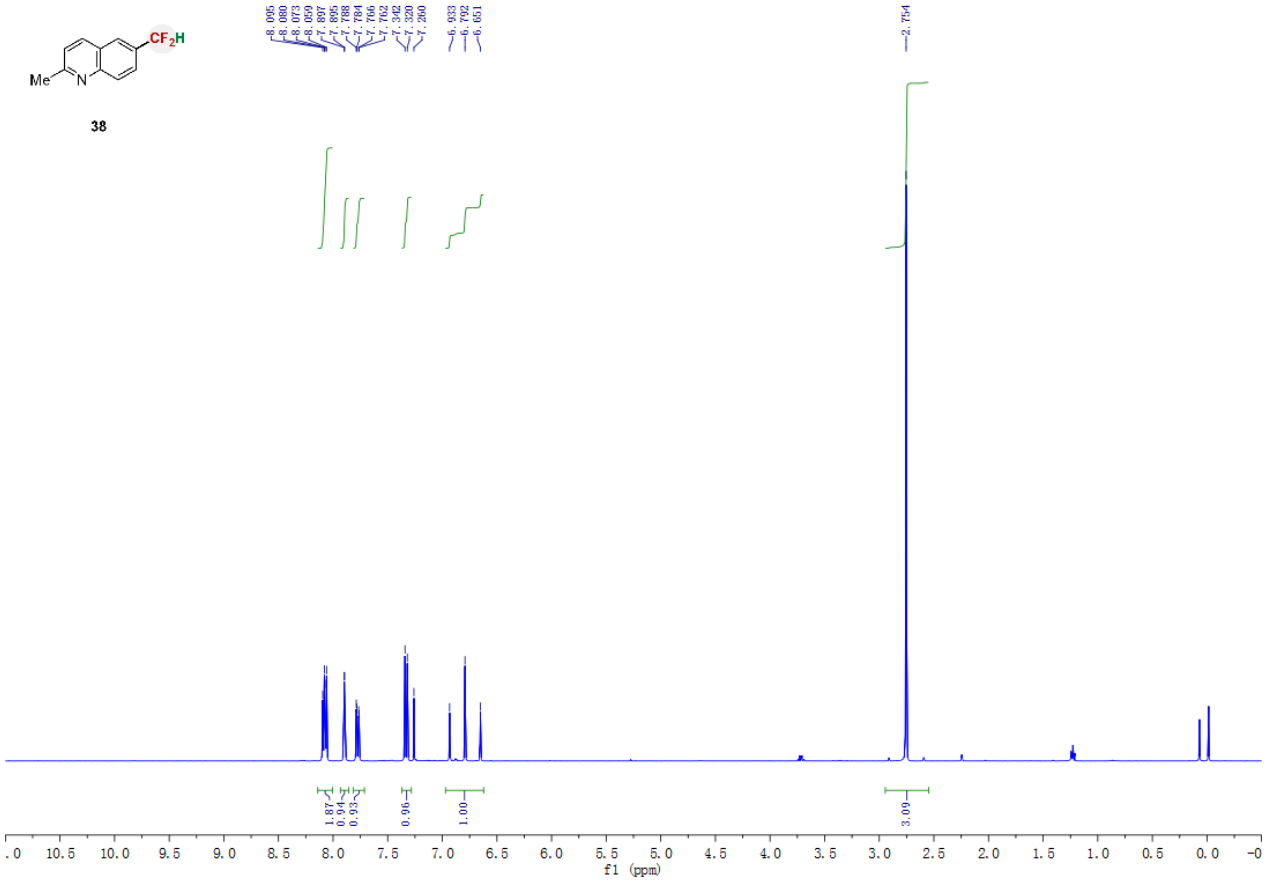
108.619
108.709
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

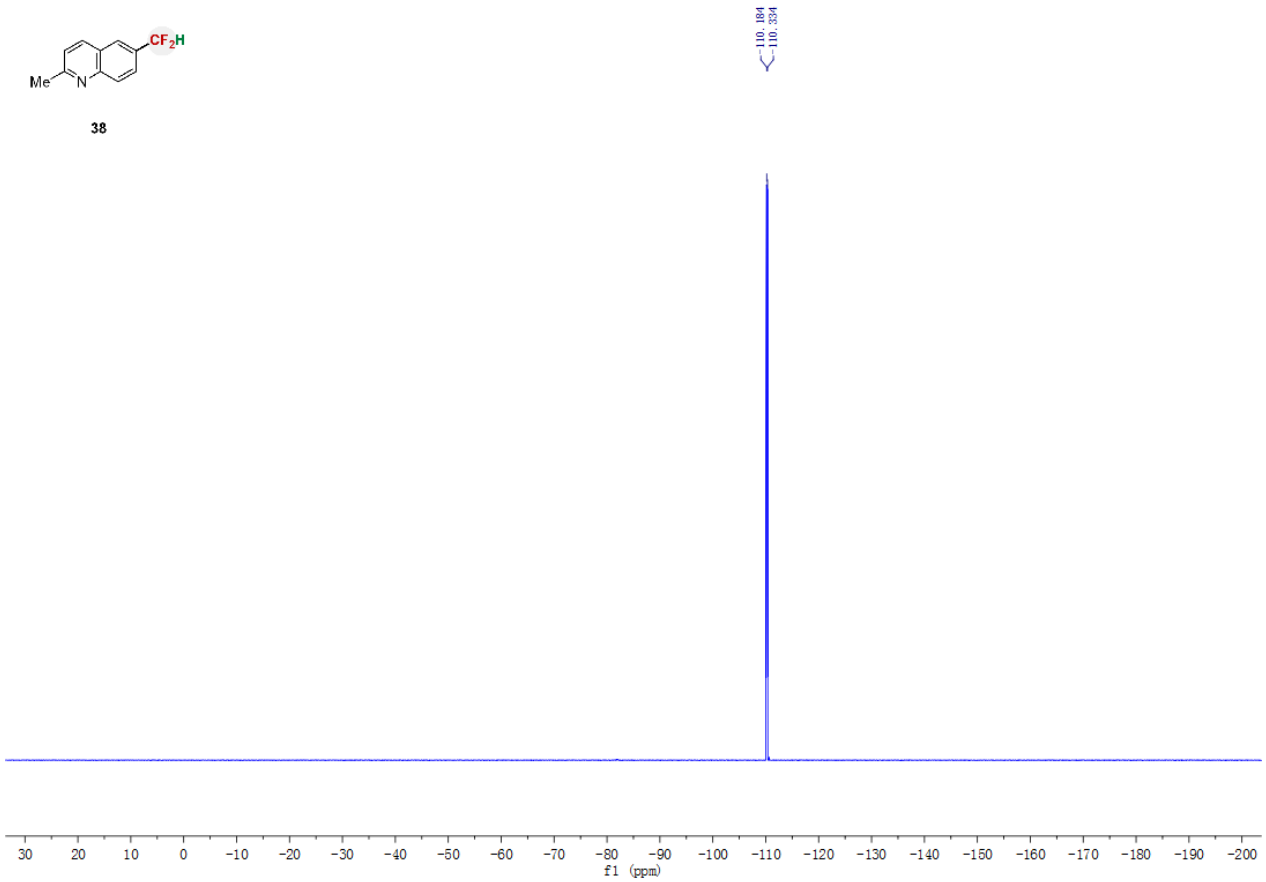


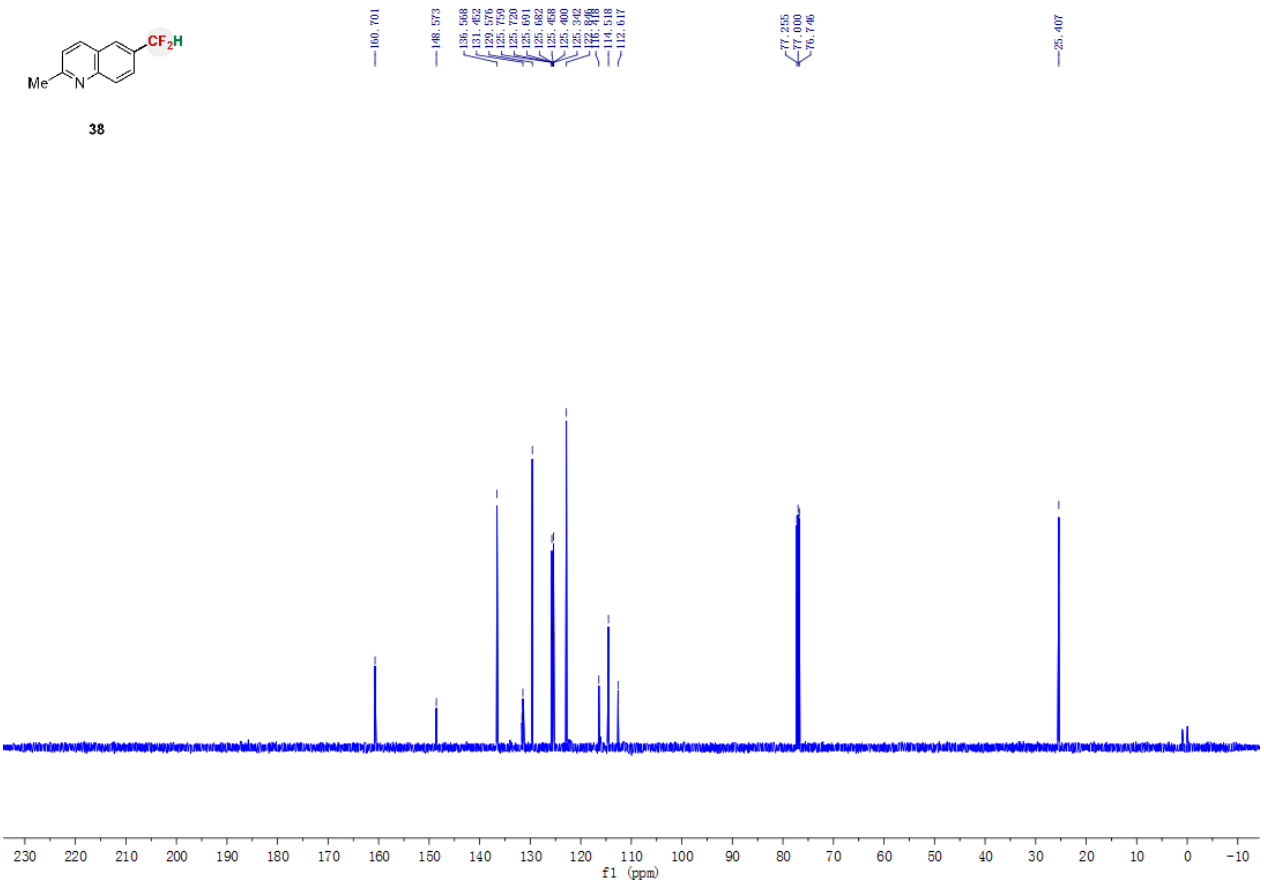
37

160.382
146.031
134.869
119.791
119.558
119.325
116.588
114.233
111.880
106.274
77.318
77.000
76.682
66.591
45.169
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

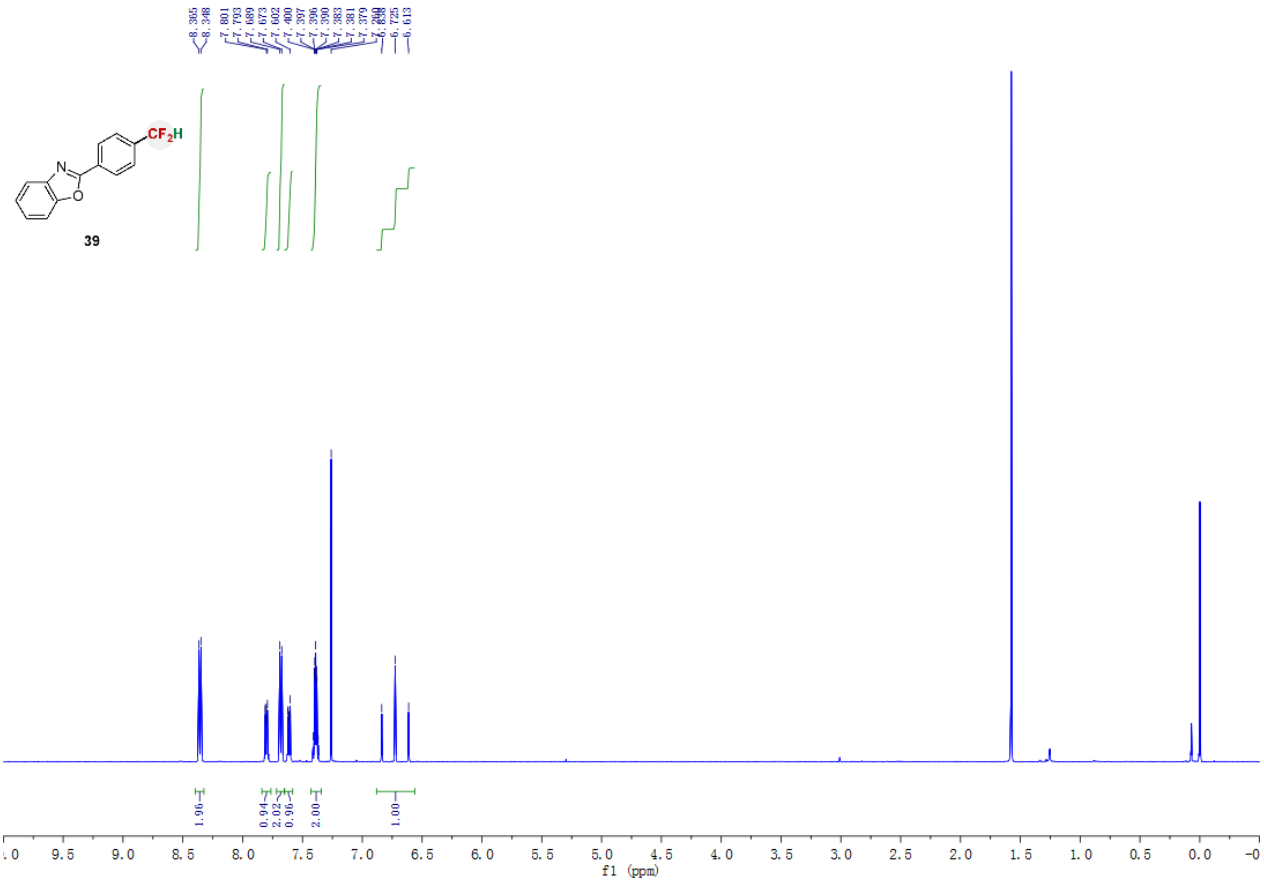
6-(Difluoromethyl)-2-methylquinoline (38).

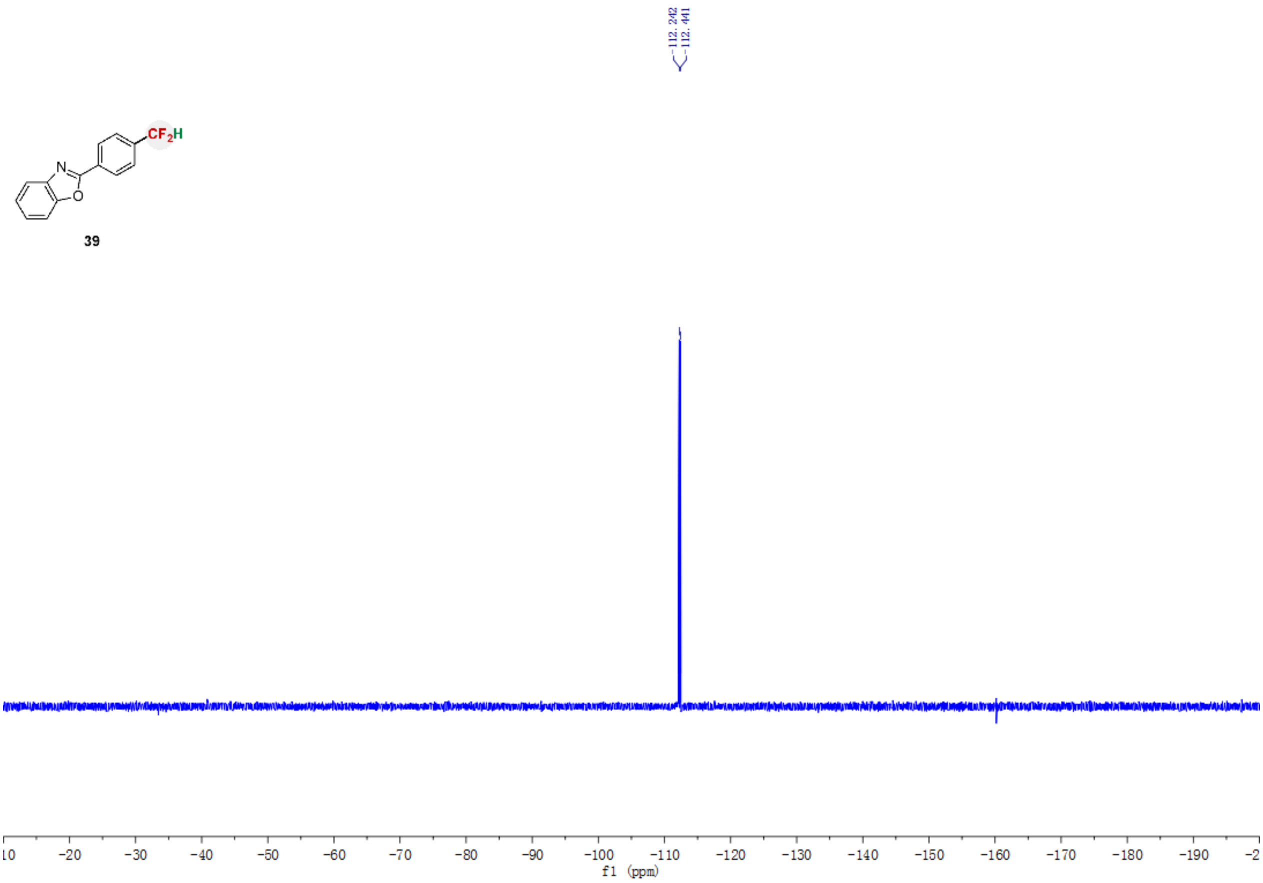


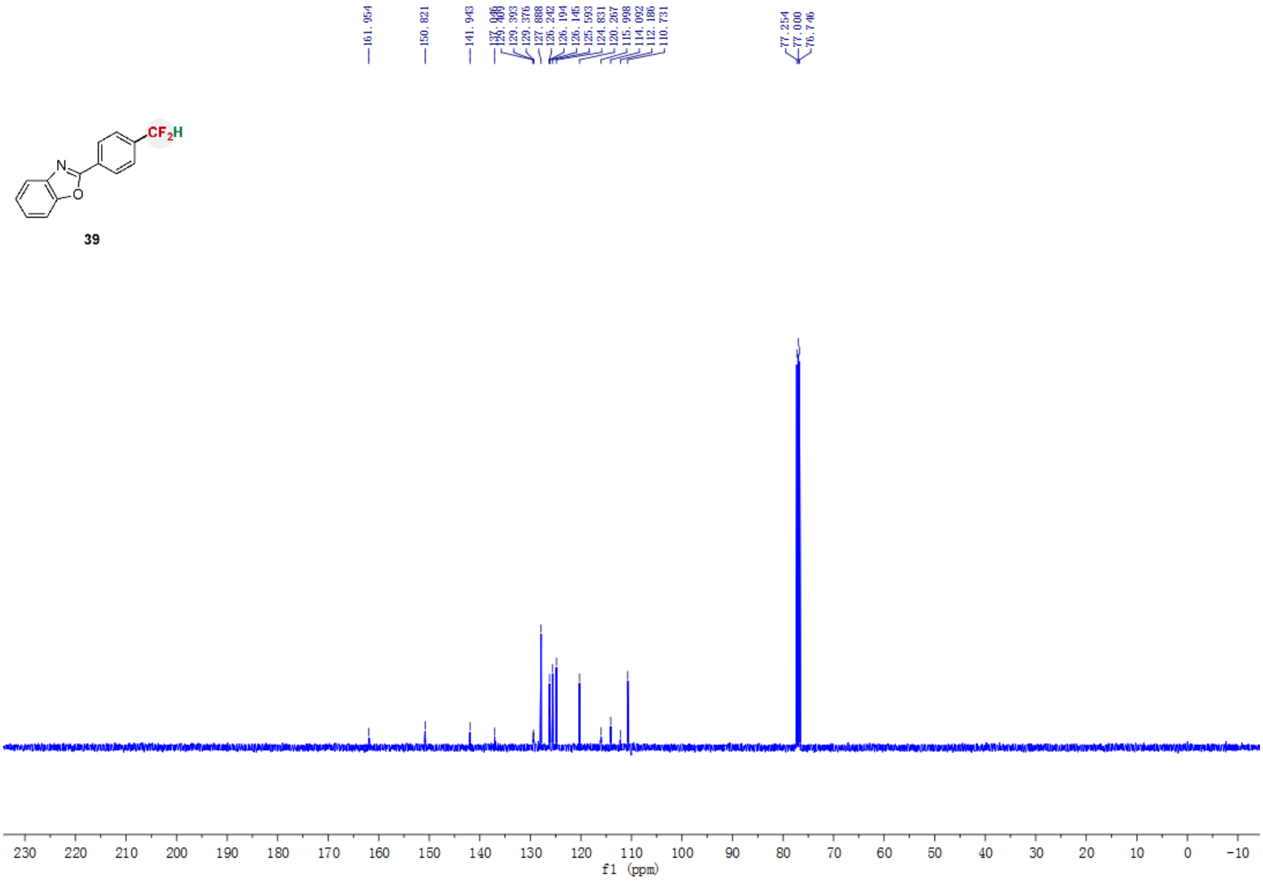




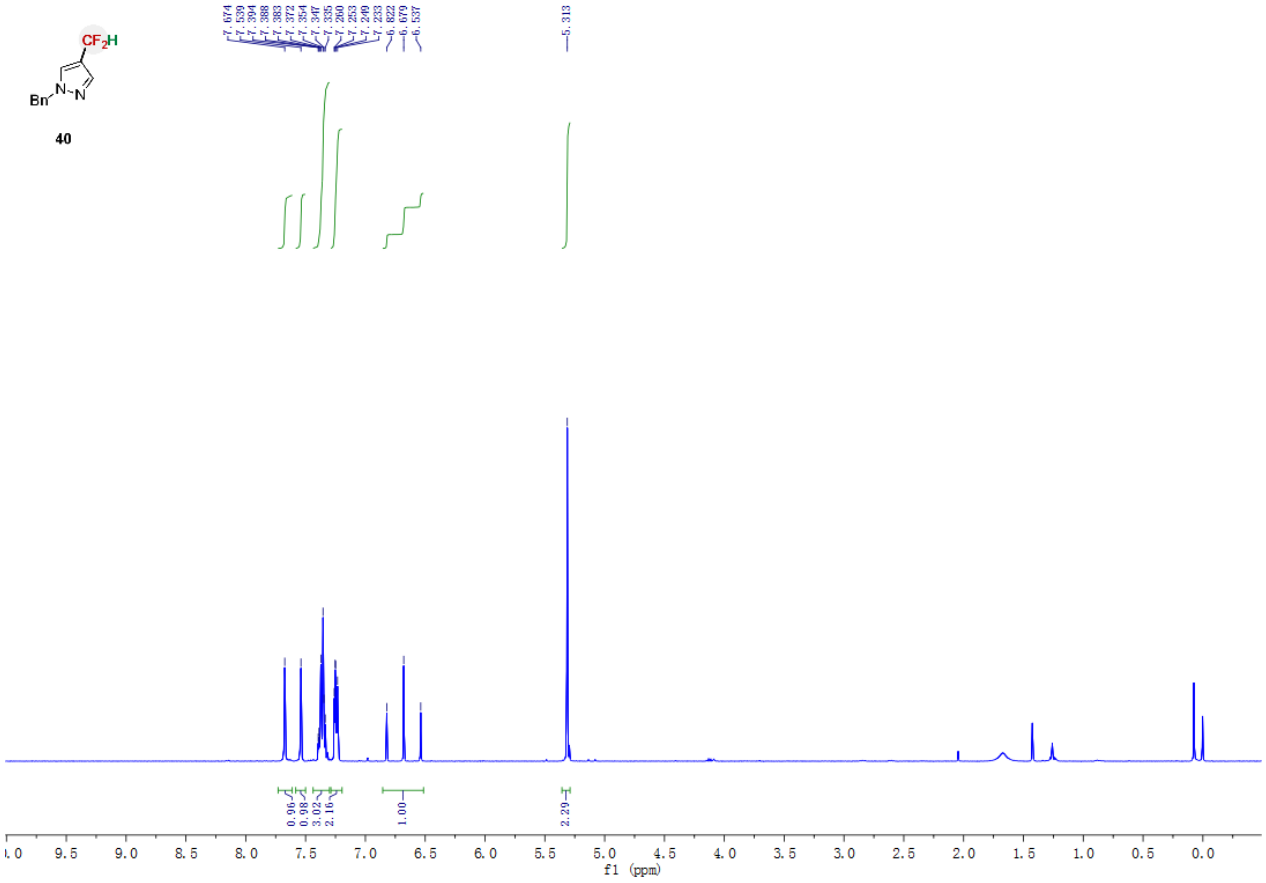
2-(4-(Difluoromethyl)phenyl)benzo[*d*]oxazole (39).

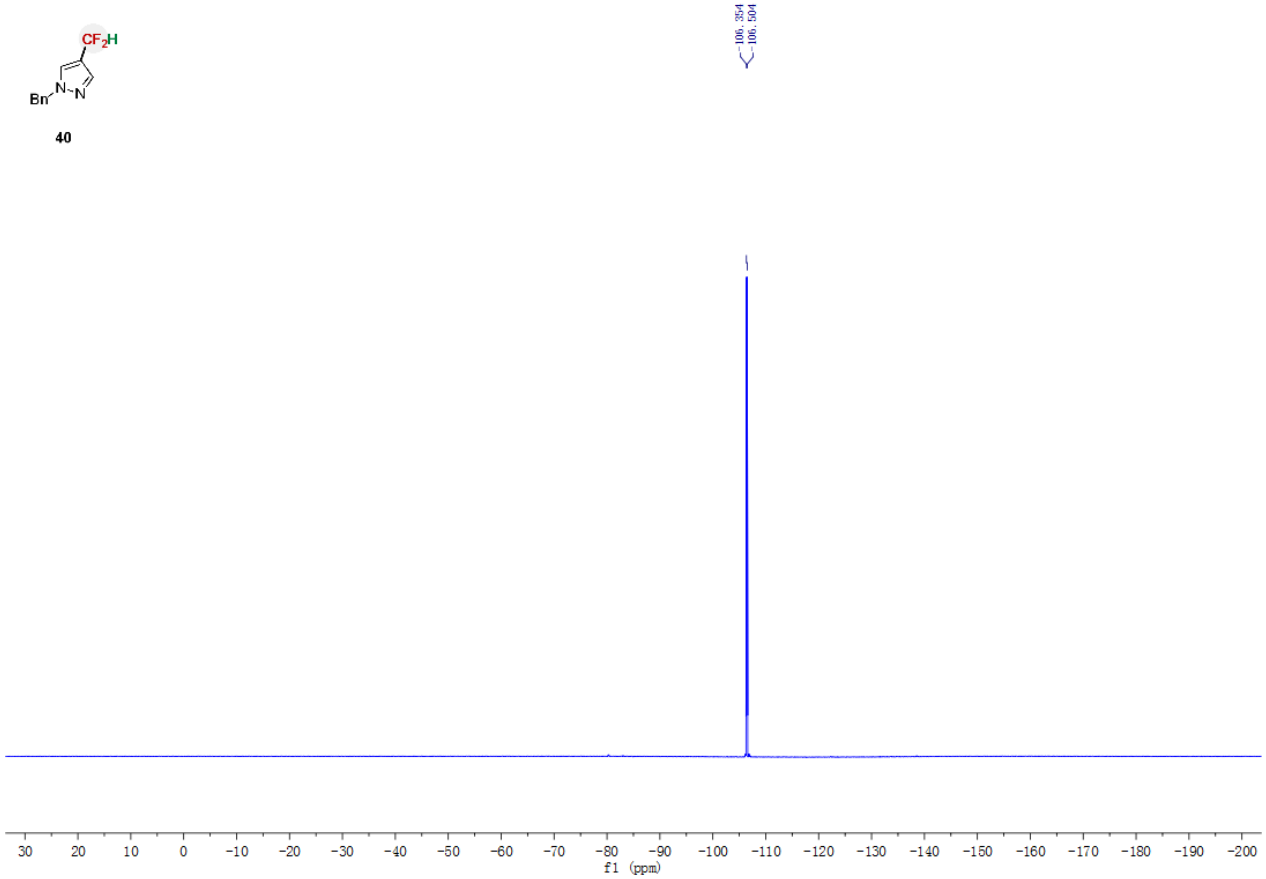



-112.242
-112.441
CF2H
39
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)


161.954
150.821
141.943
129.393
129.376
127.888
126.242
126.194
126.145
125.593
124.831
120.267
115.998
114.092
112.186
110.731
77.254
77.000
76.746
CF2H
39
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-Benzyl-4-(difluoromethyl)-1*H*-pyrazole (40).



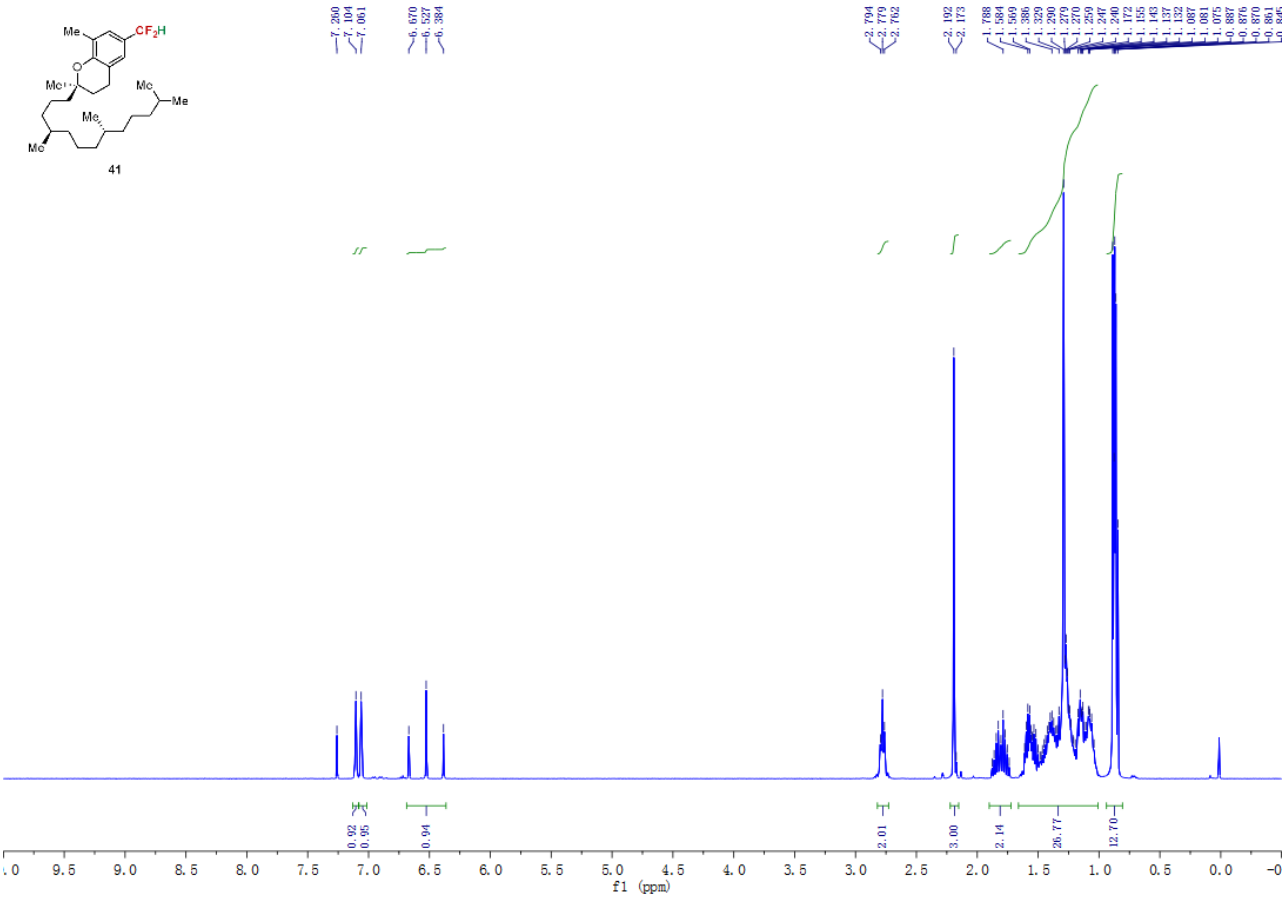


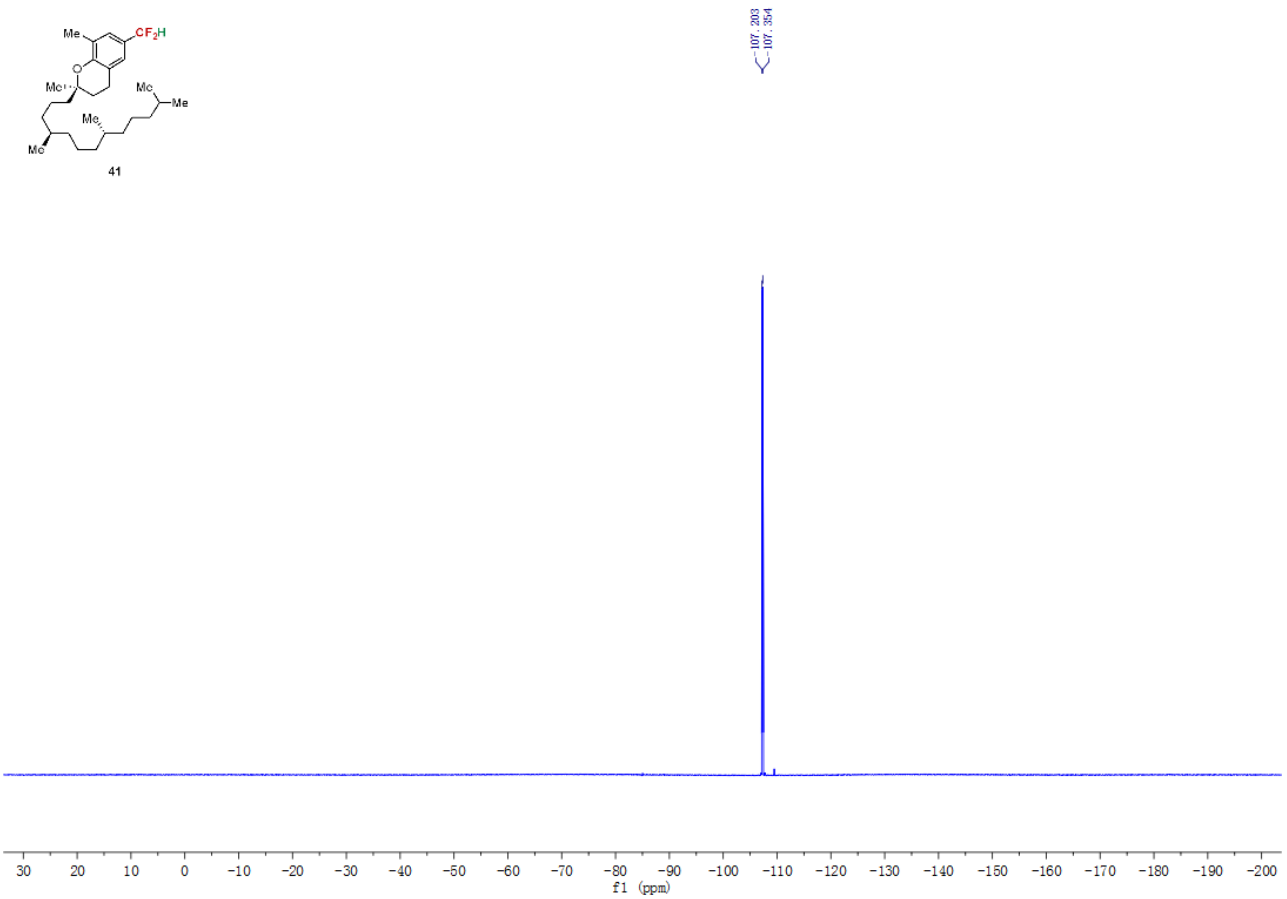

CF2H
Bn
N
N

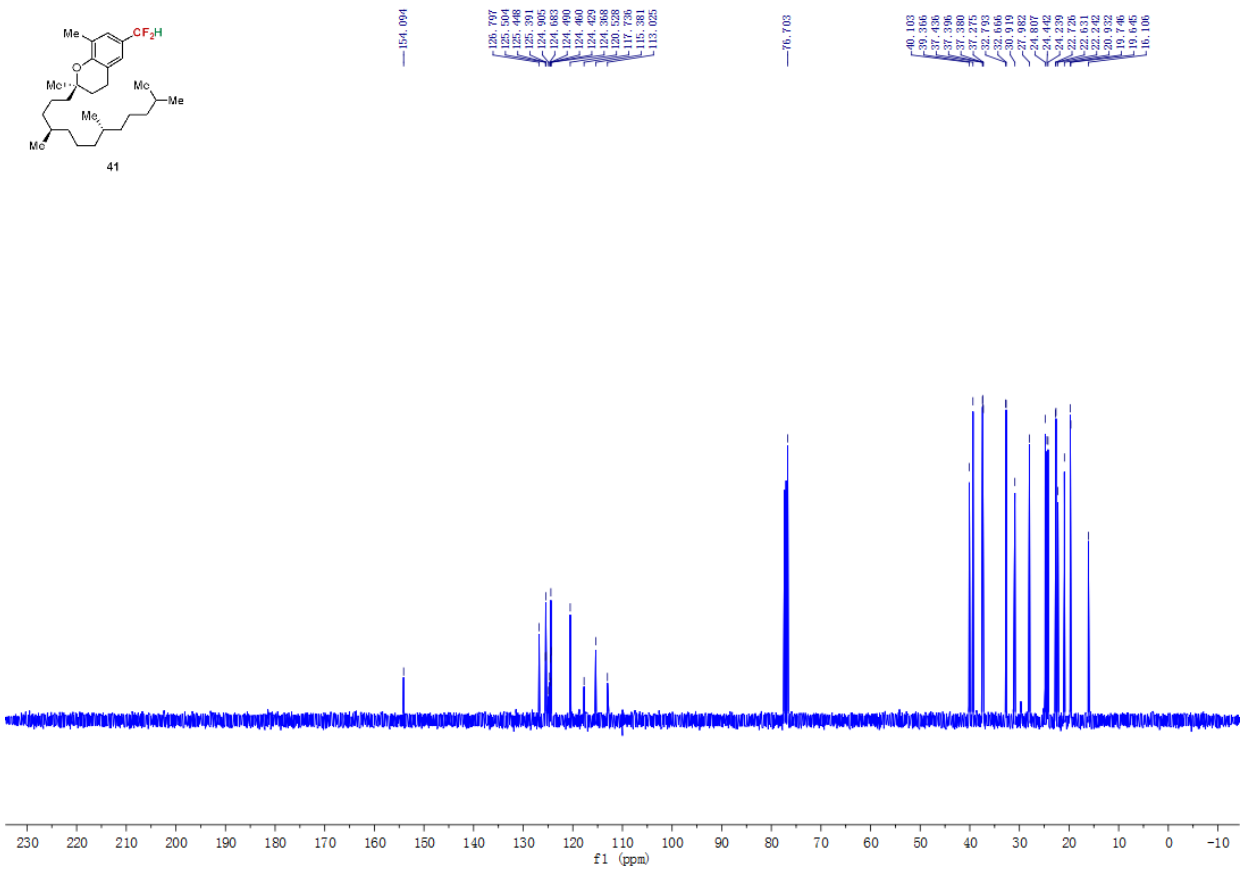
40

137.280
137.244
137.207
135.506
128.960
128.421
128.008
117.504
117.290
112.769
110.908
109.048
77.255
77.000
76.746
56.364
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

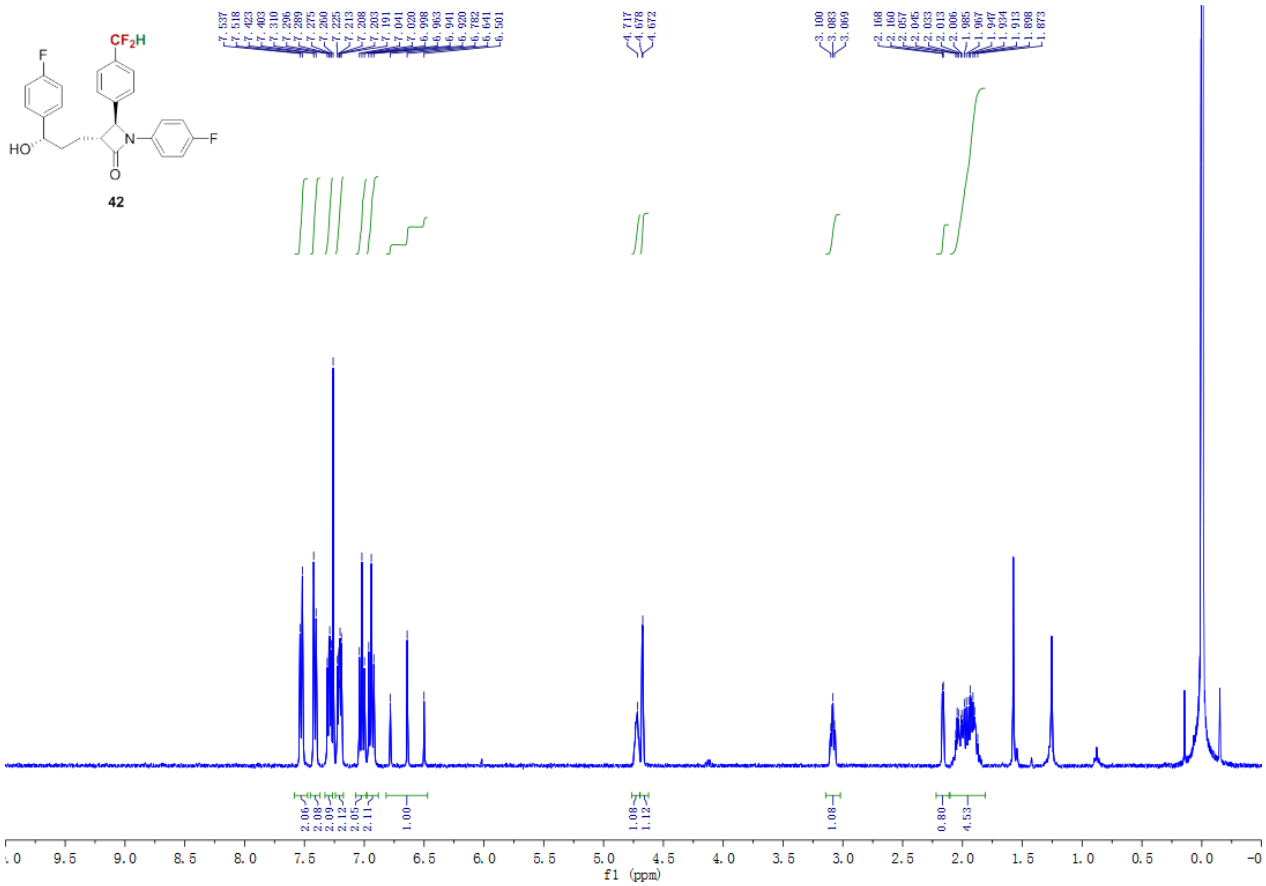
(*R*)-6-(Difluoromethyl)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (41).

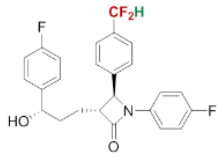




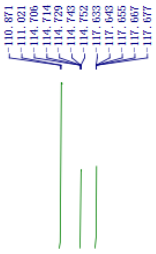


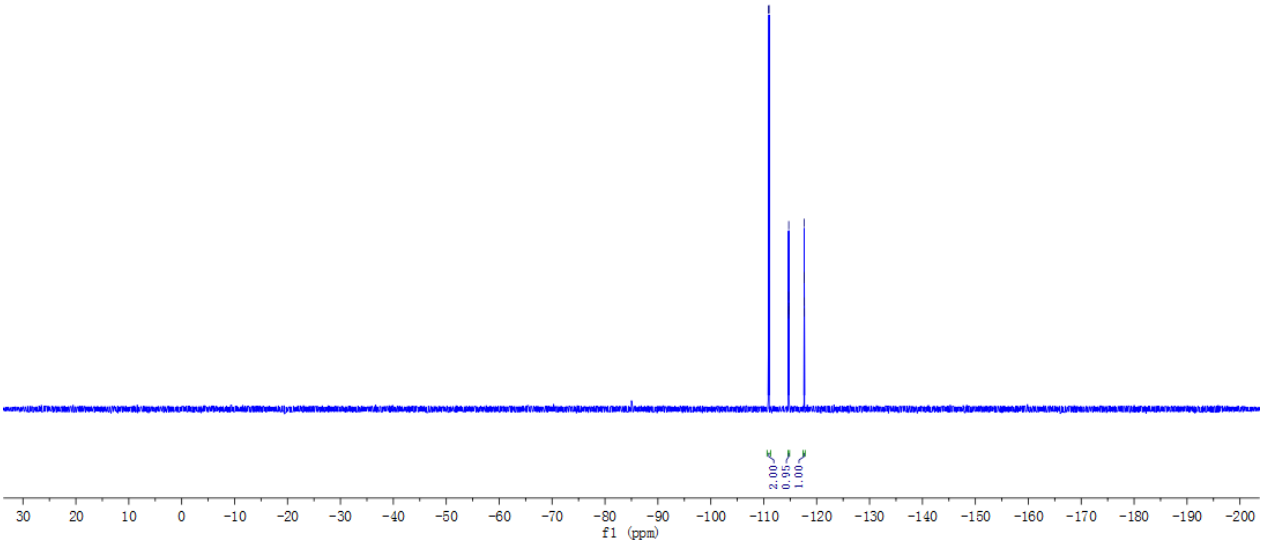
(3*R*,4*S*)-4-(4-(Difluoromethyl)phenyl)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one (42).

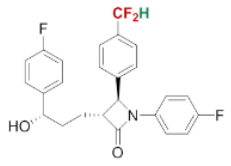



F
CF2H
HO
N
F
O

42

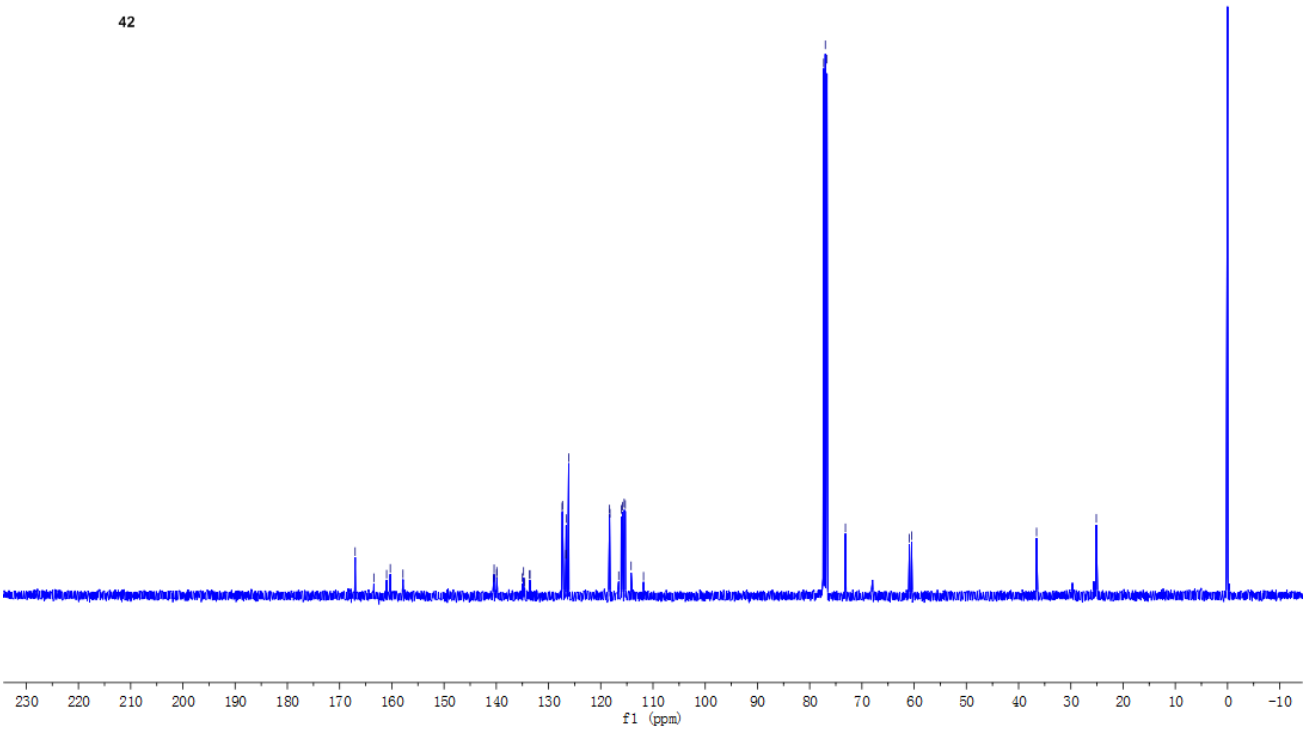

110.871
111.021
114.706
114.714
114.729
114.743
114.752
117.633
117.643
117.655
117.667
117.677


2.00
0.95
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

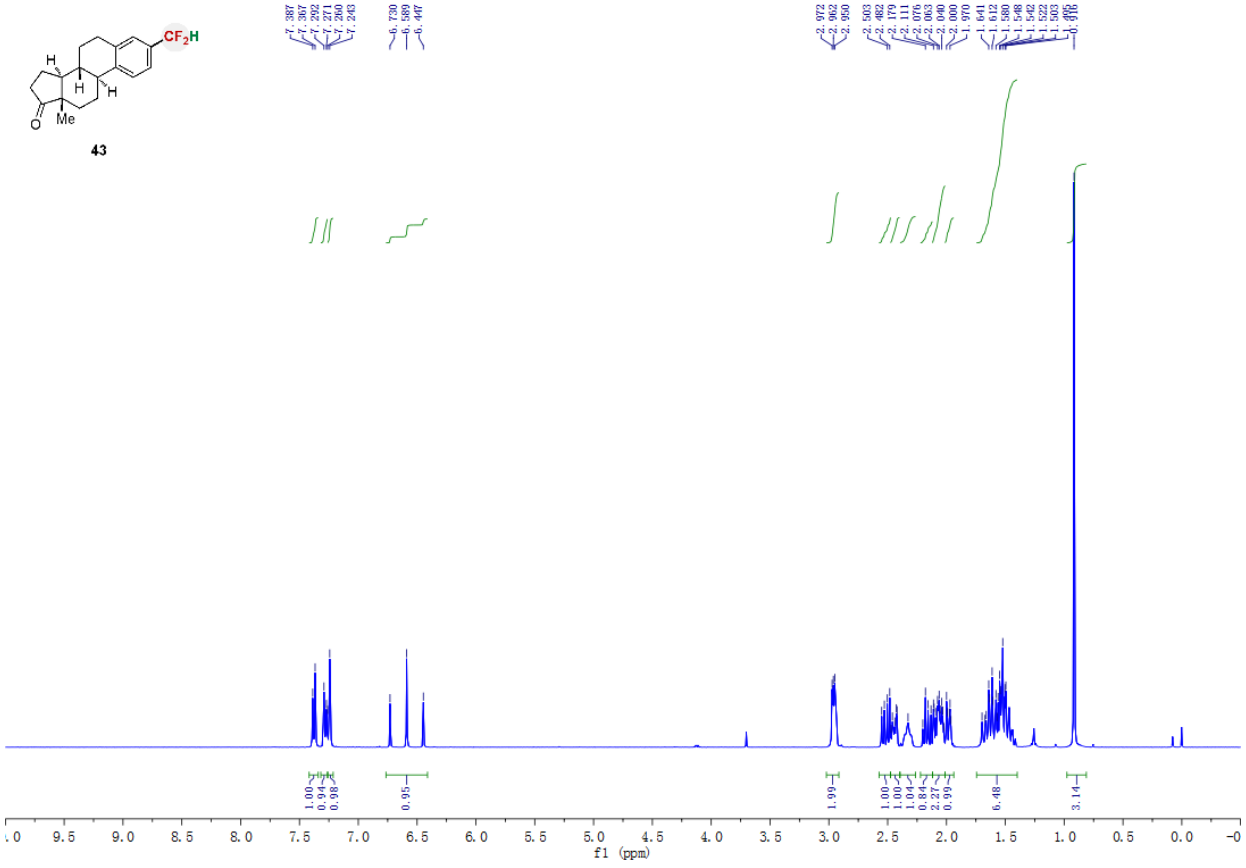

F
CF2H
HO
N
F
O

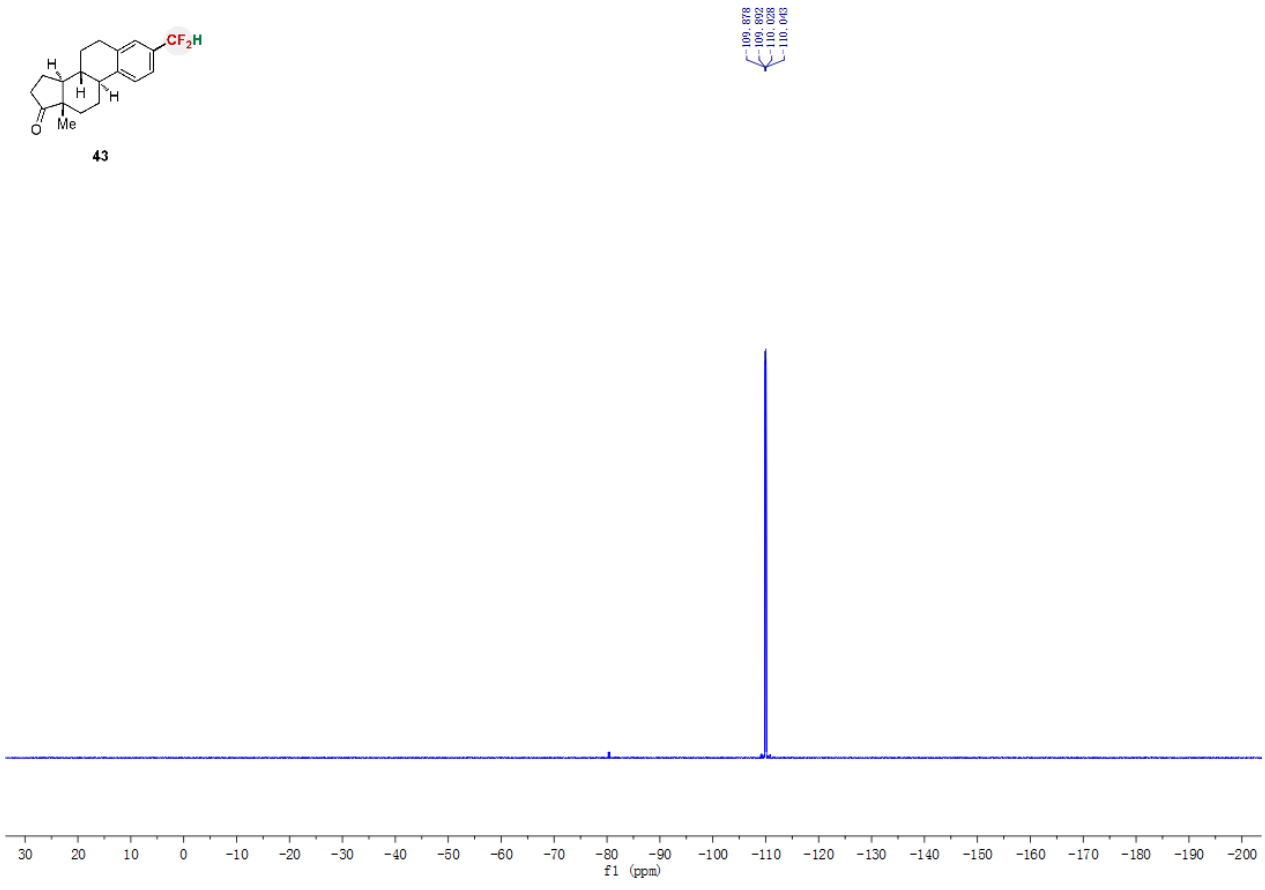
42

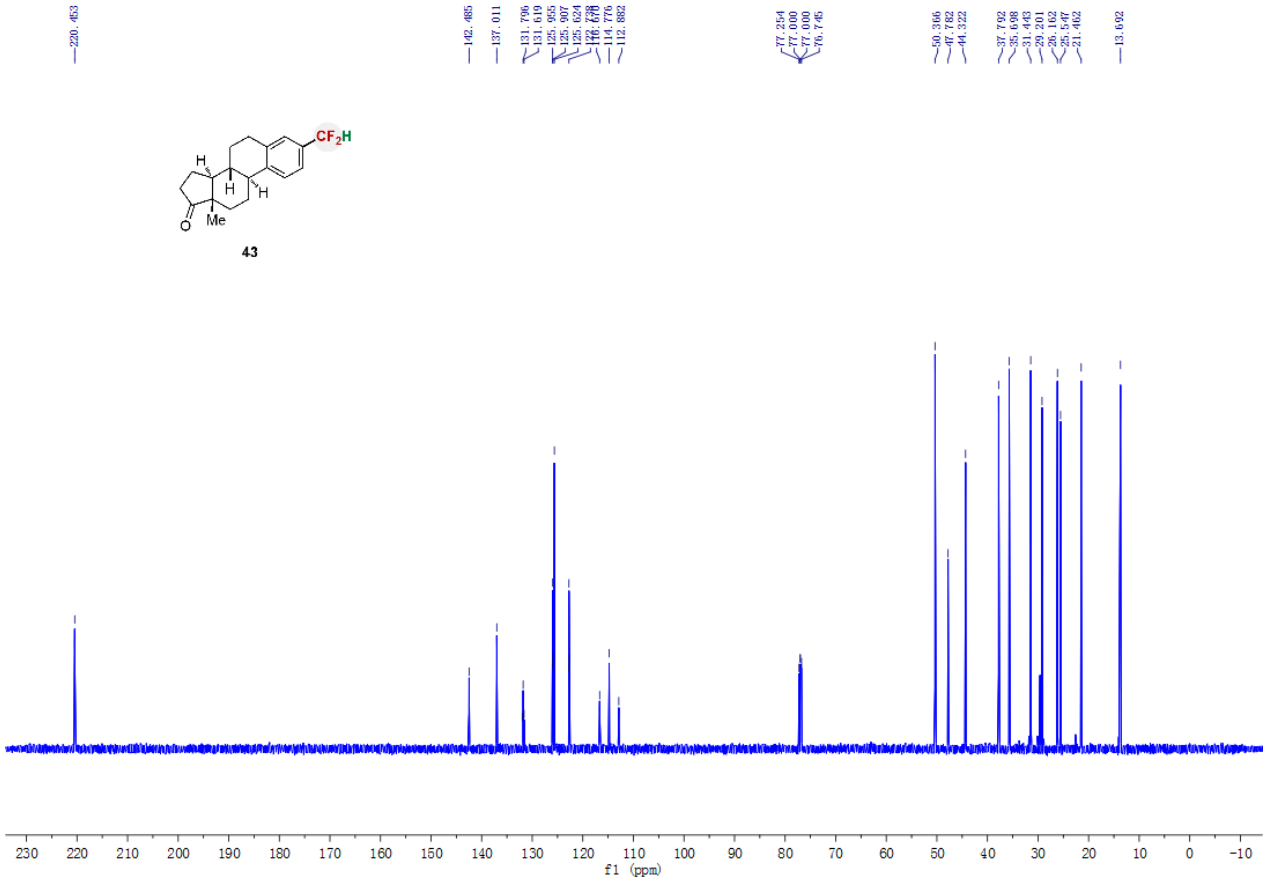

167.022
163.462
160.996
160.280
157.864
140.435
140.415
139.924
139.893
135.006
134.778
134.554
133.604
133.576
127.389
127.309
116.565
116.073
115.847
115.514
115.301
114.187
111.808
77.318
77.000
76.683
73.154
60.907
60.483
36.563
25.128


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

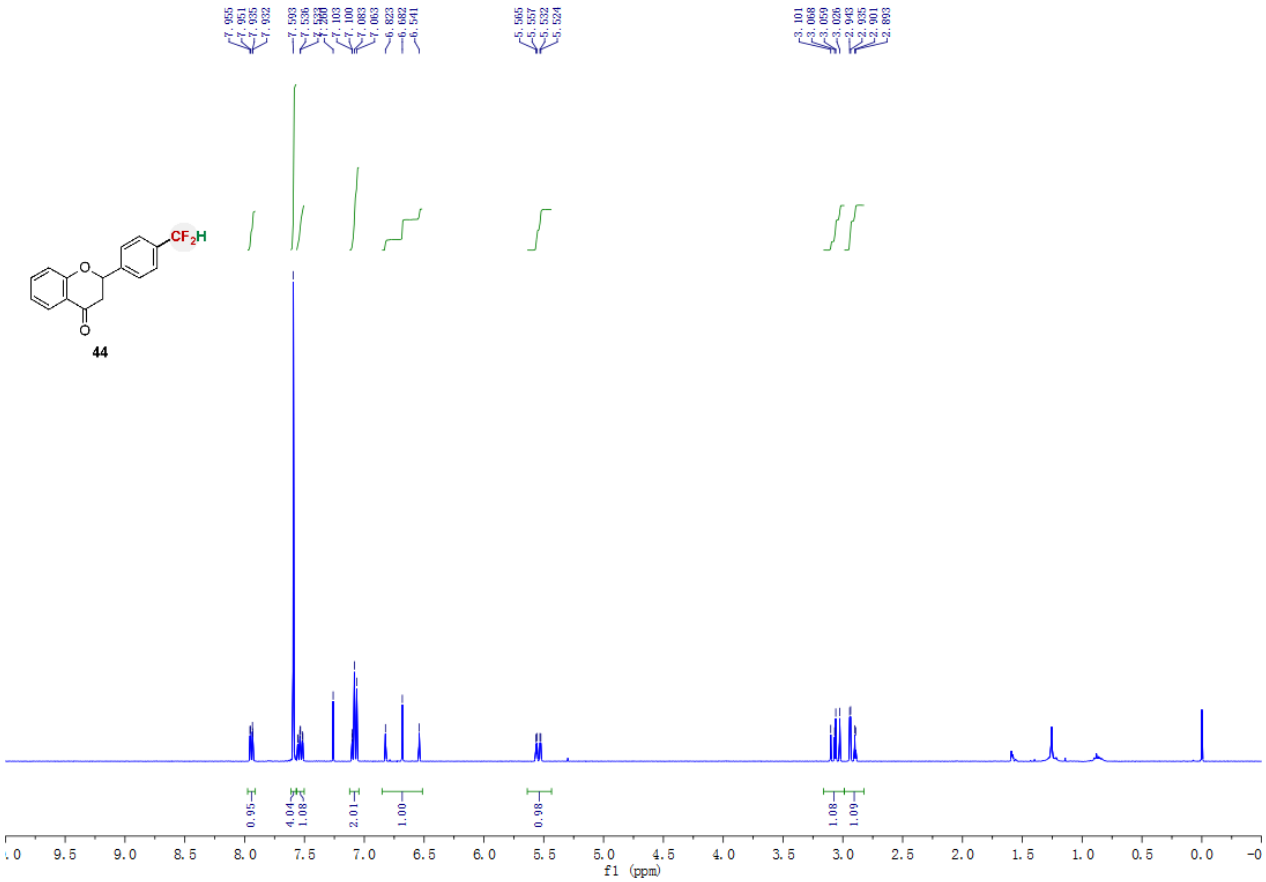
(8*R*,9*S*,13*S*,14*S*)-3-(Difluoromethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (43).

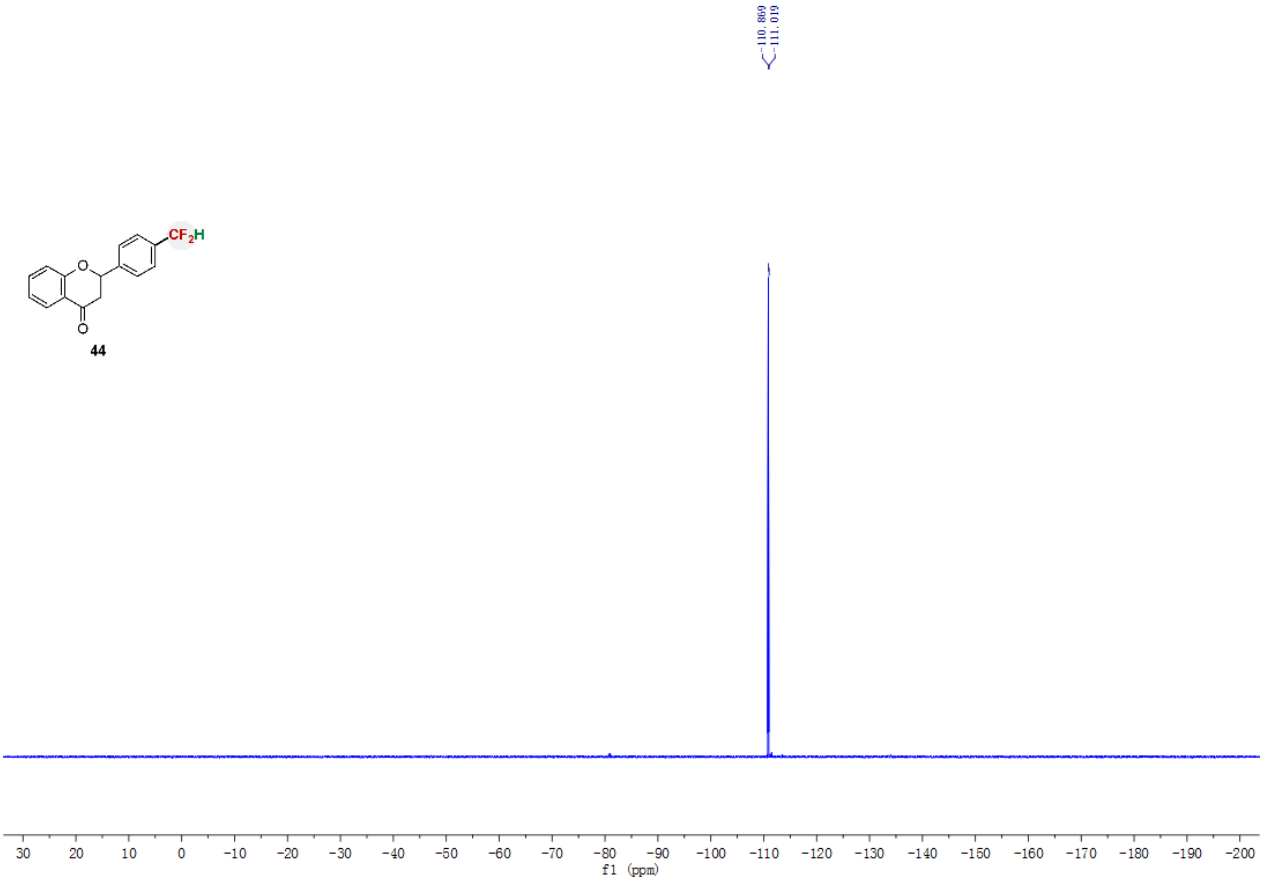


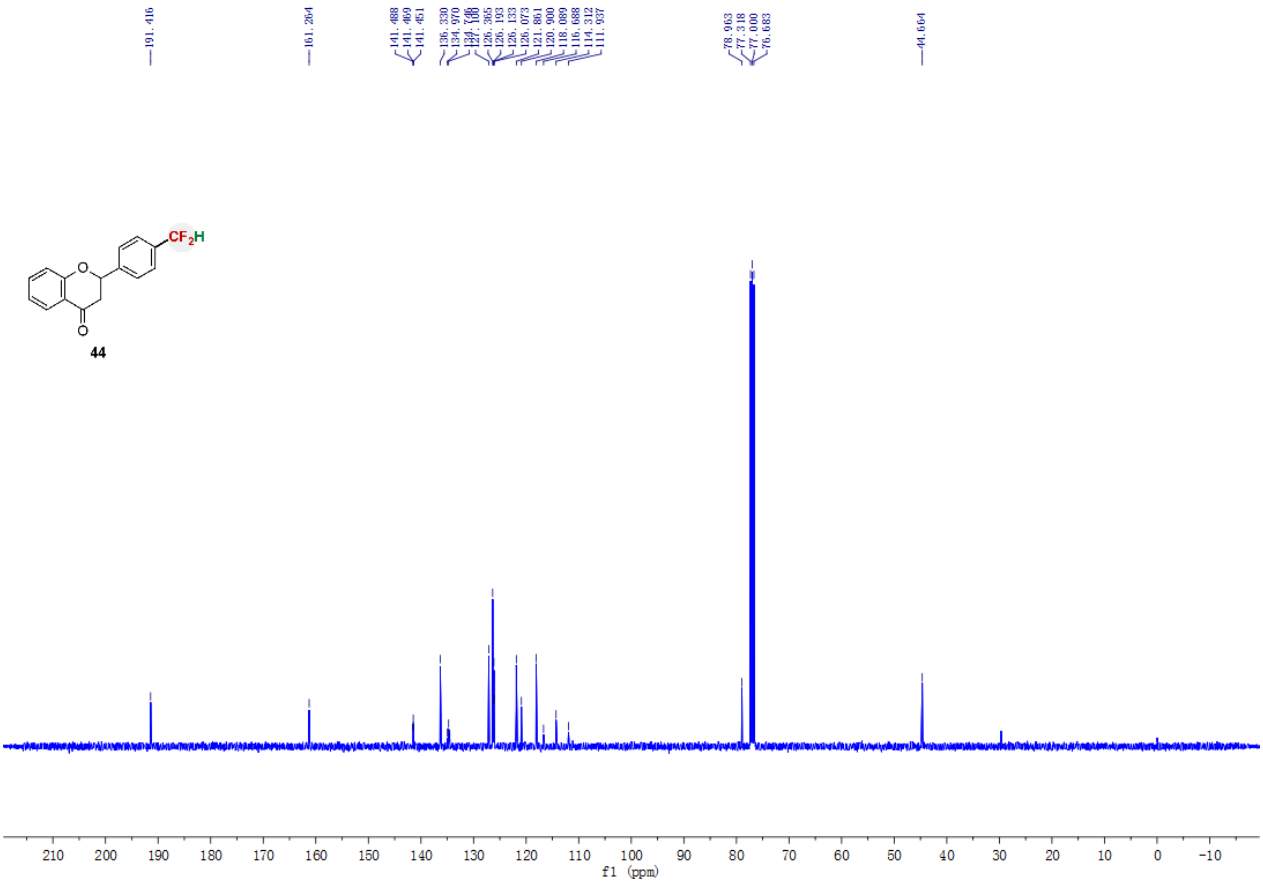




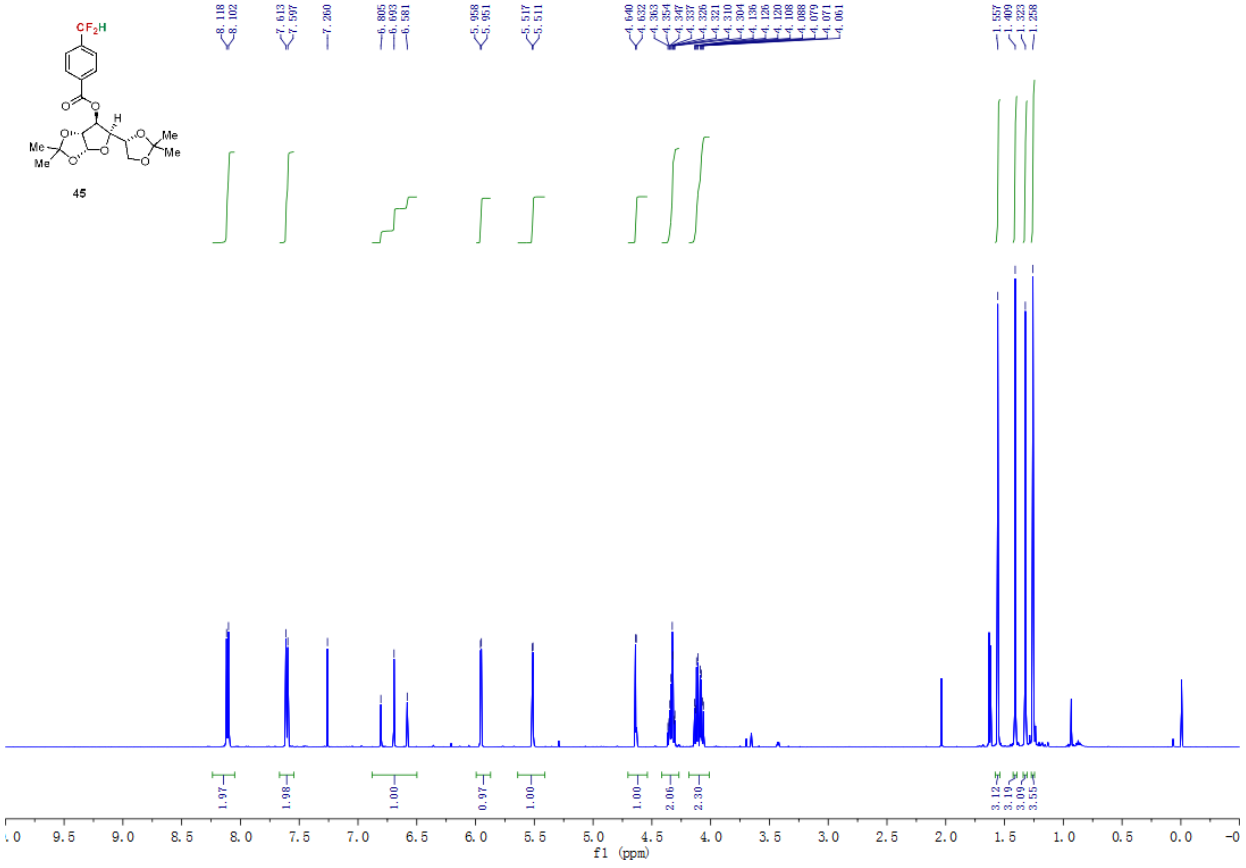
2-(4-(Difluoromethyl)phenyl)chroman-4-one (44).

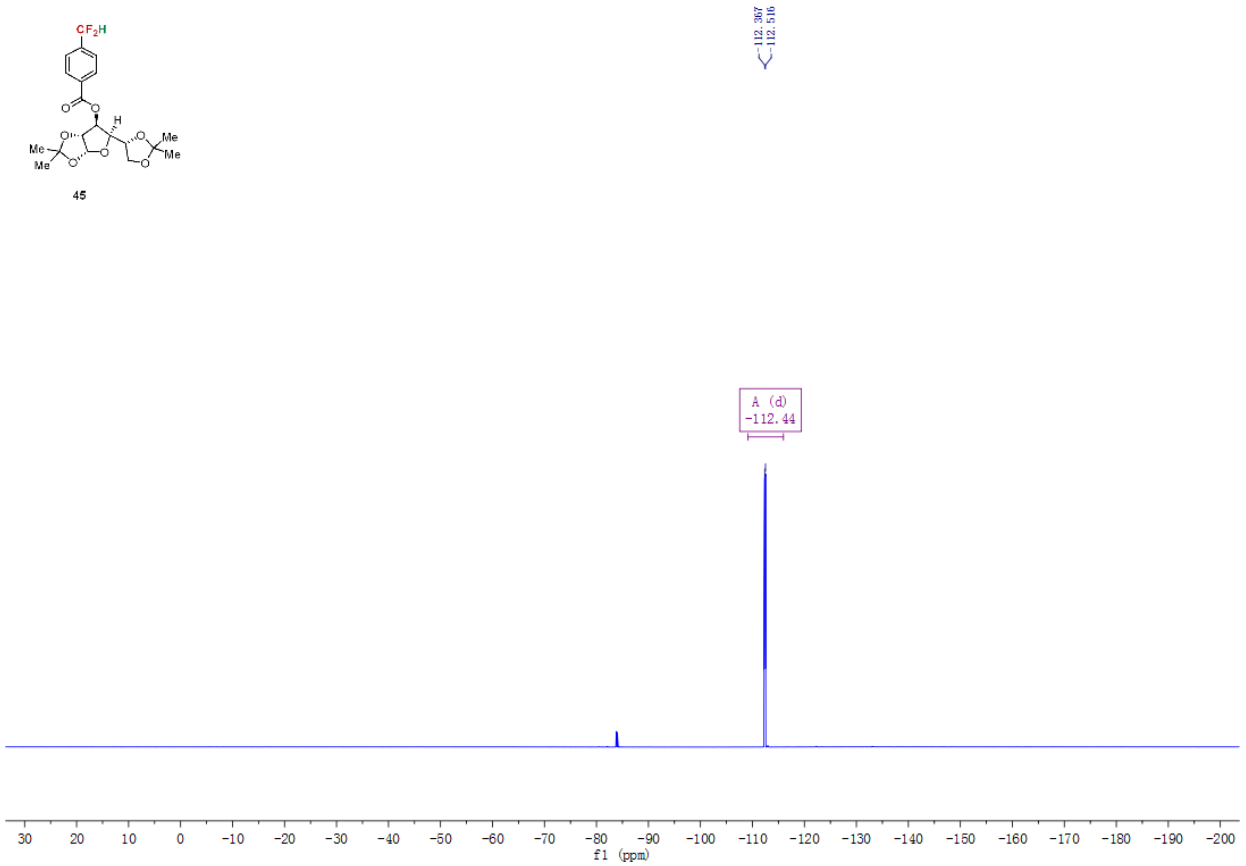


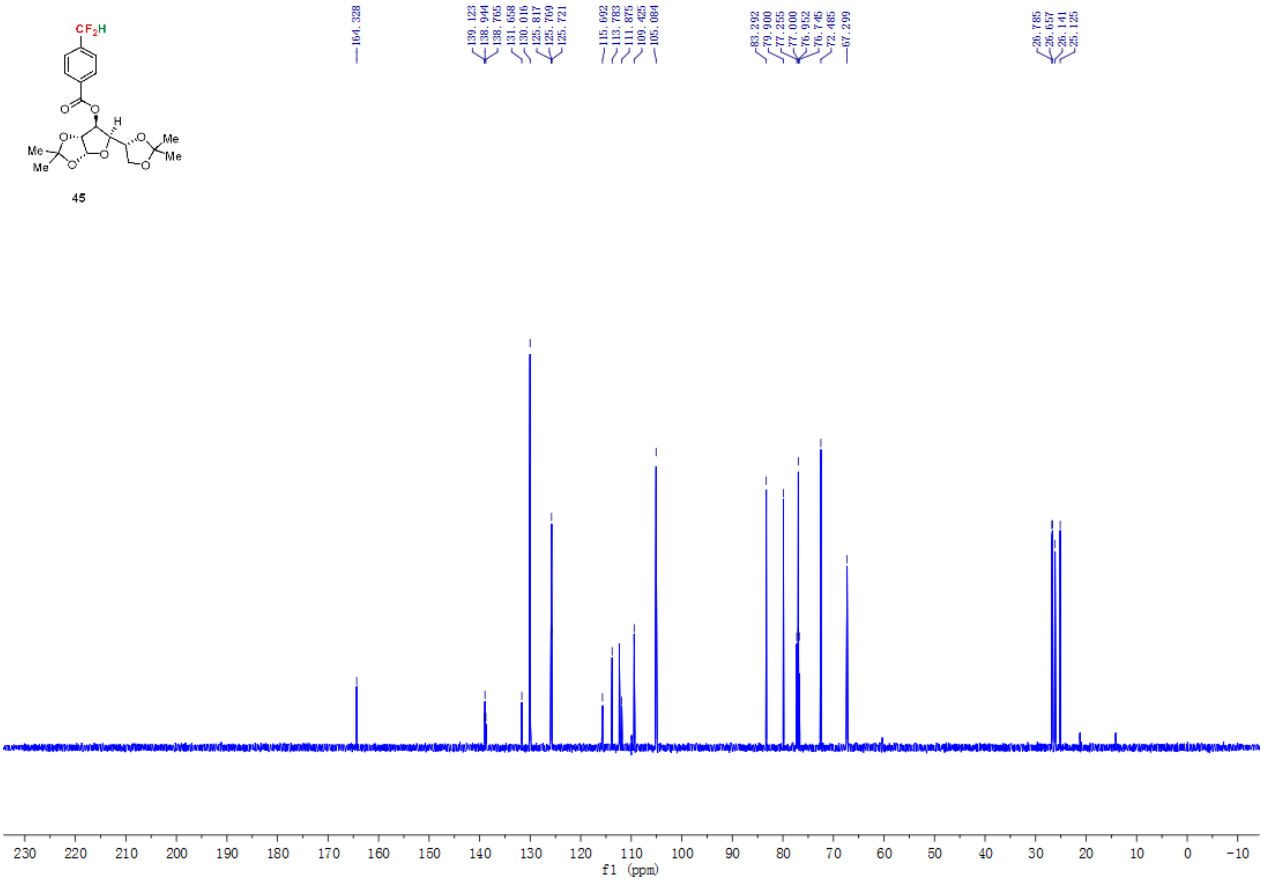

110.889
111.019
CF2H
O
O
44
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


191.416
161.264
141.488
141.469
141.451
136.330
134.970
127.305
126.195
126.133
126.073
121.861
120.900
118.089
116.688
114.312
111.597
78.963
77.318
77.000
76.683
44.664
CF2H
O
O
44
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

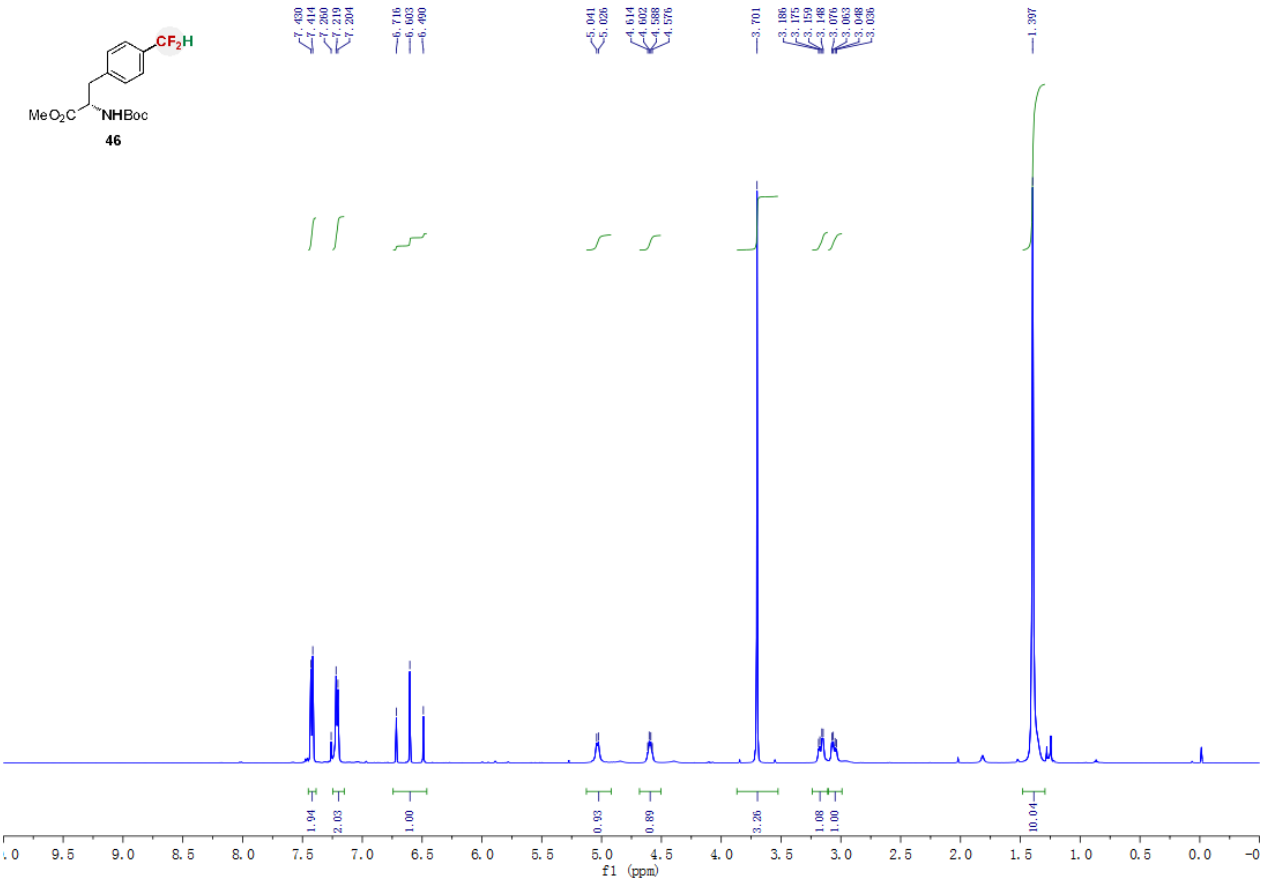
(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl 4-(difluoromethyl)benzoate (45).

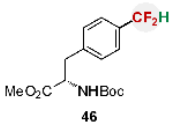






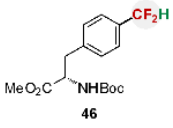
Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate (46).




CF2H
MeO2C
NHBoc

46

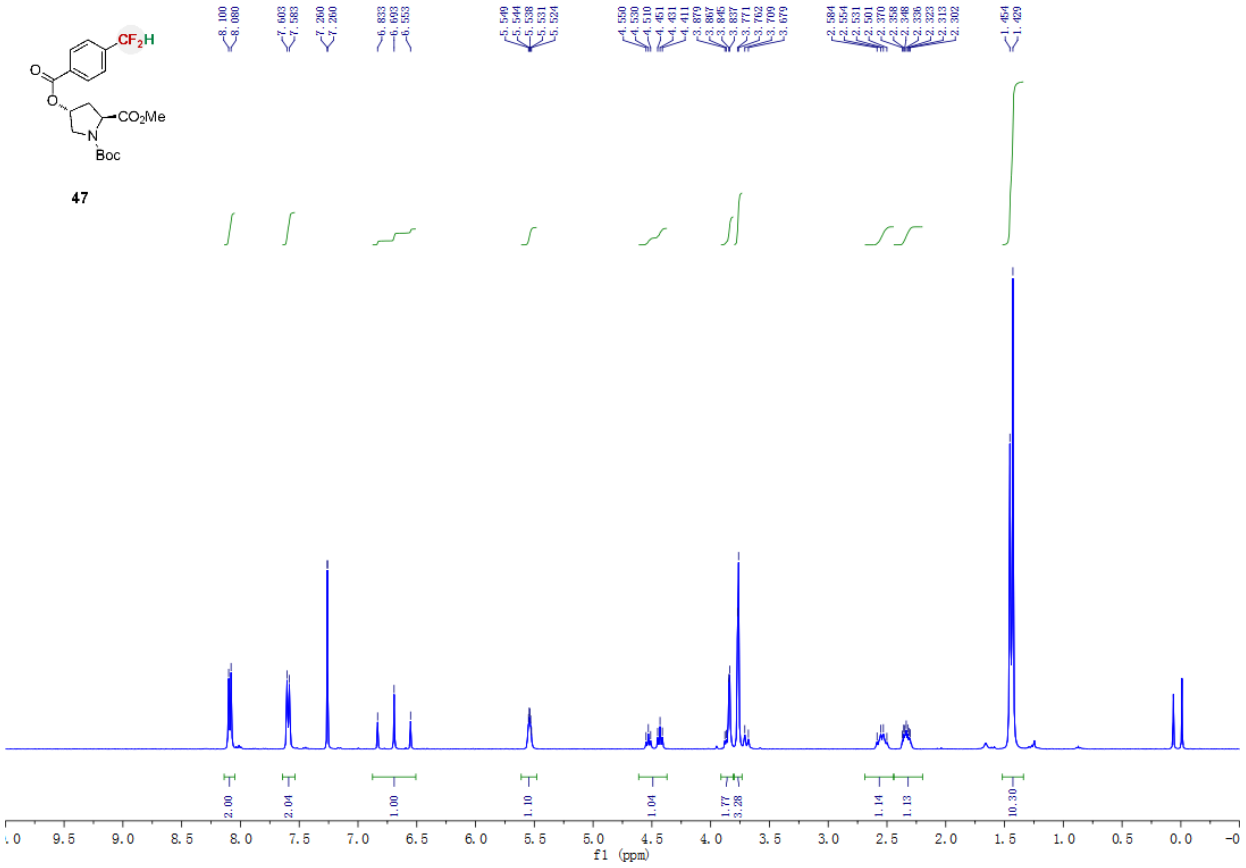
110.469
110.609
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


CF2H
MeO2C
NHBoc

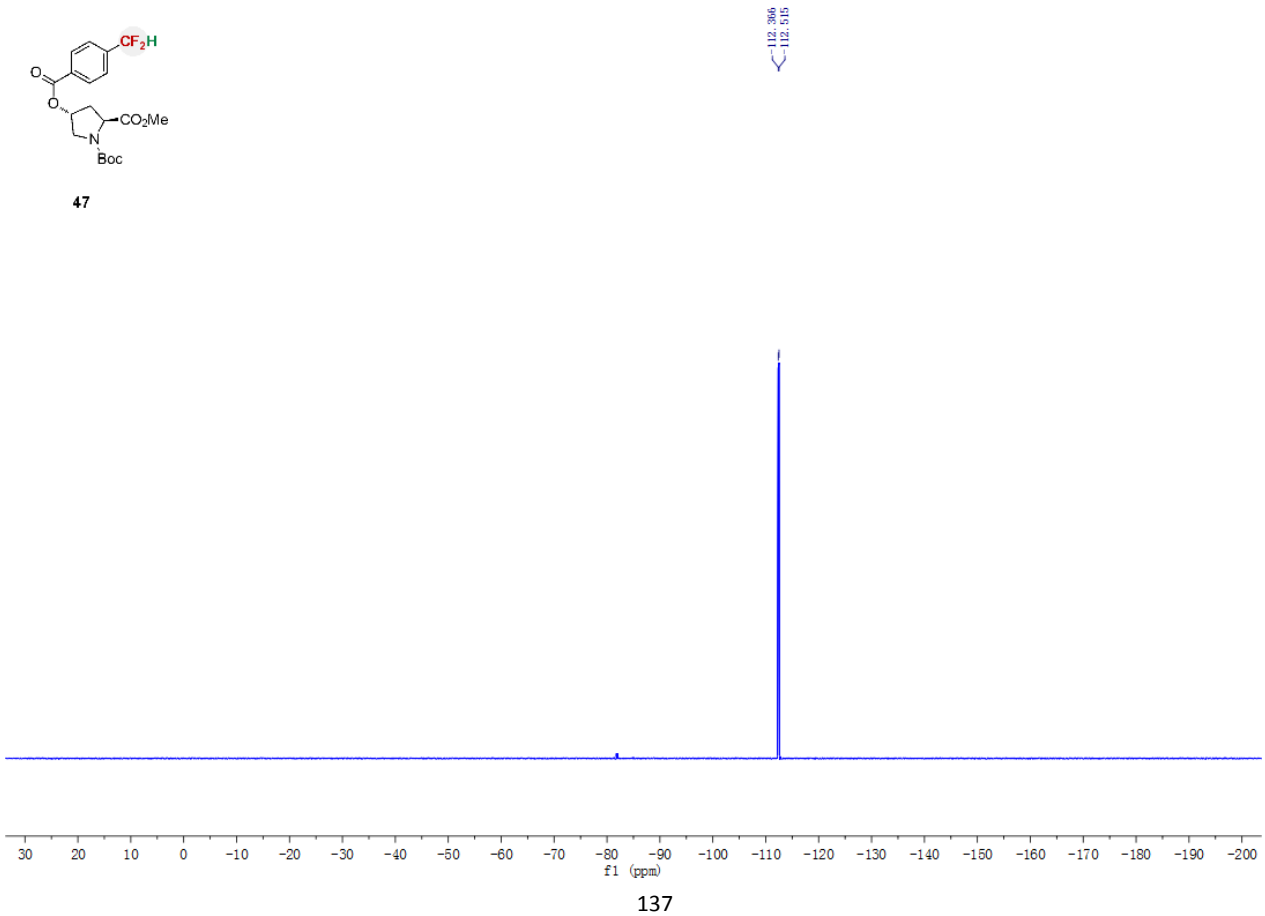
46

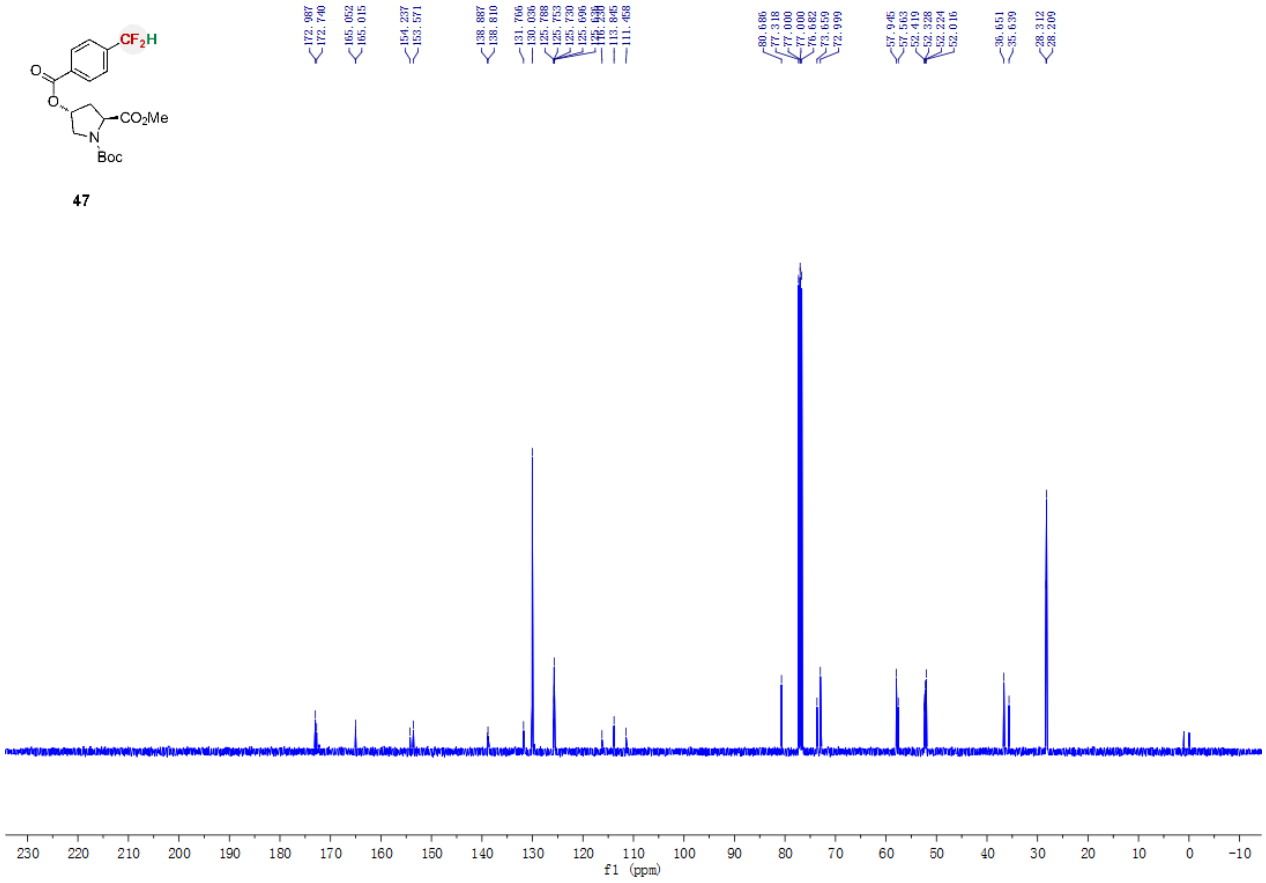
171.983
154.944
139.006
138.989
138.973
133.233
133.061
131.888
129.578
125.713
125.666
125.619
116.464
114.557
112.659
79.987
77.254
77.000
77.000
76.746
54.205
52.231
38.132
28.182
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1-(*tert*-Butyl)2-methyl(2*S*,4*R*)-4-((4-(difluoromethyl)benzoyl)oxy)pyrrolidine-1,2-dicarboxylate (47).

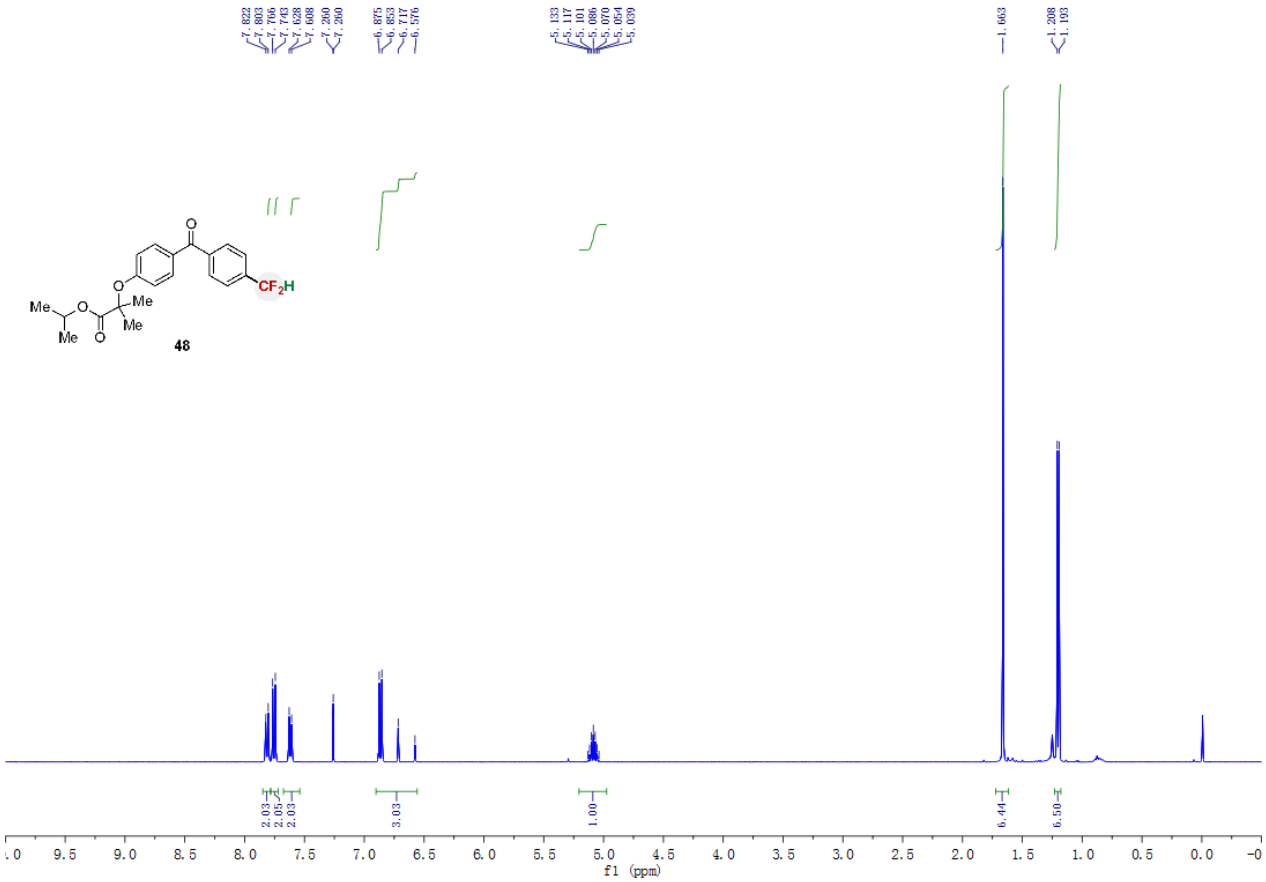


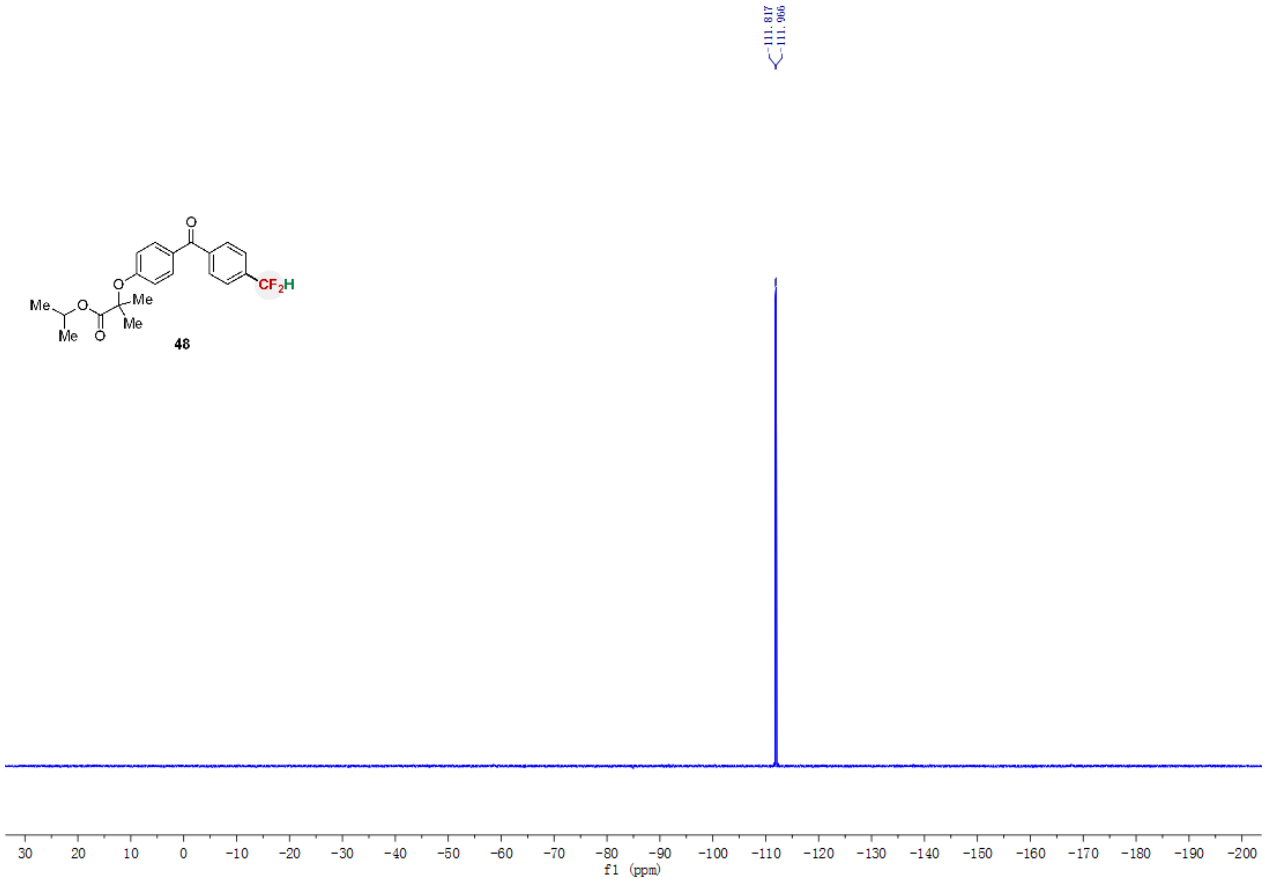
47

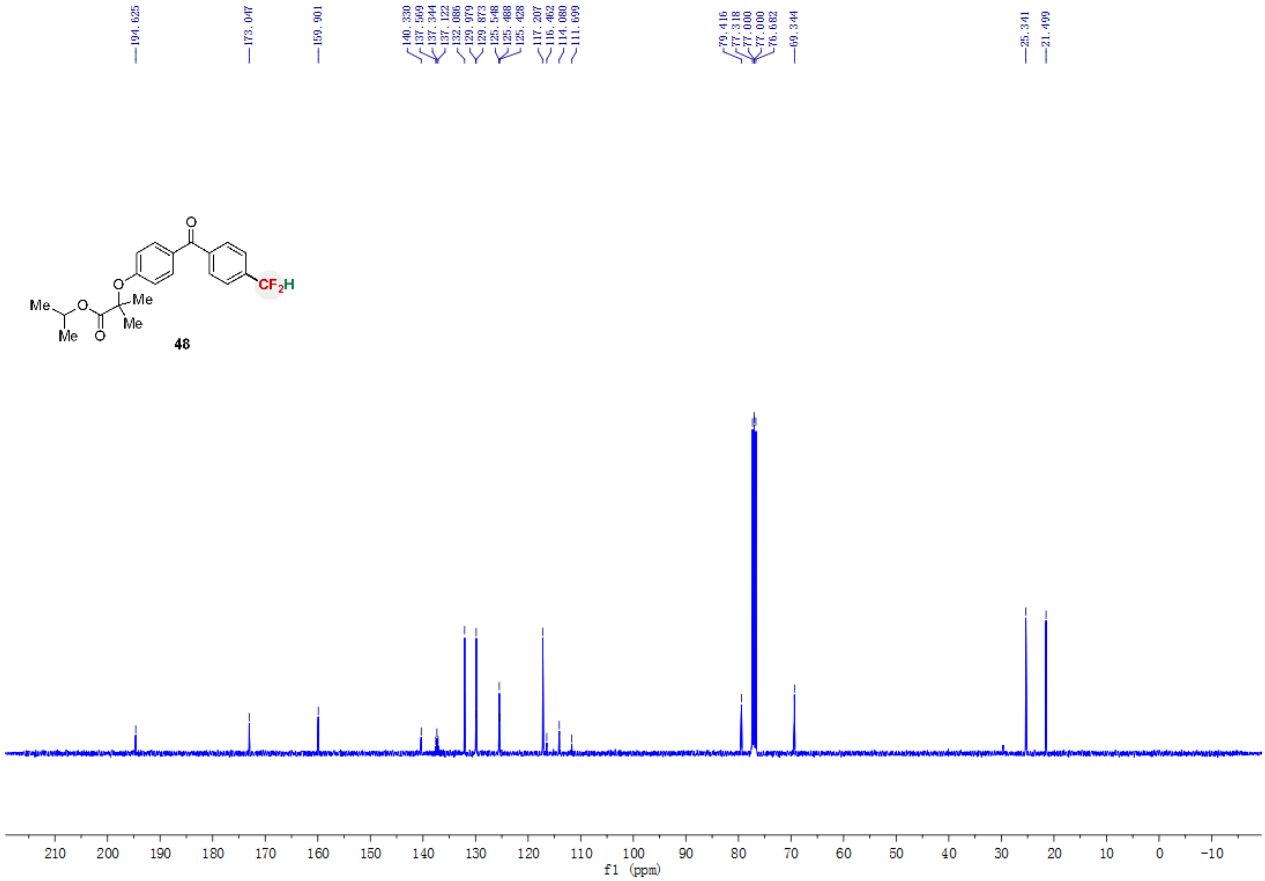




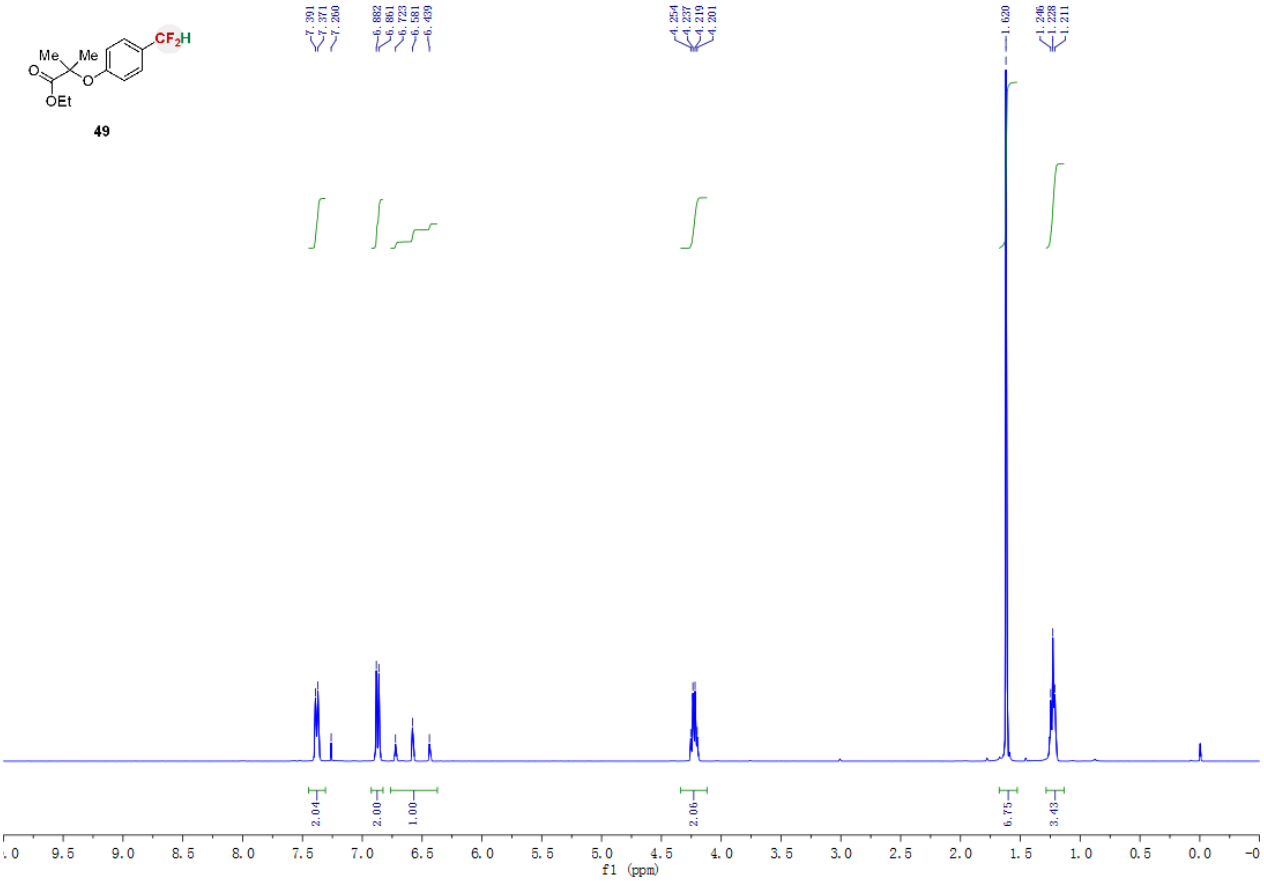
Isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate (48).

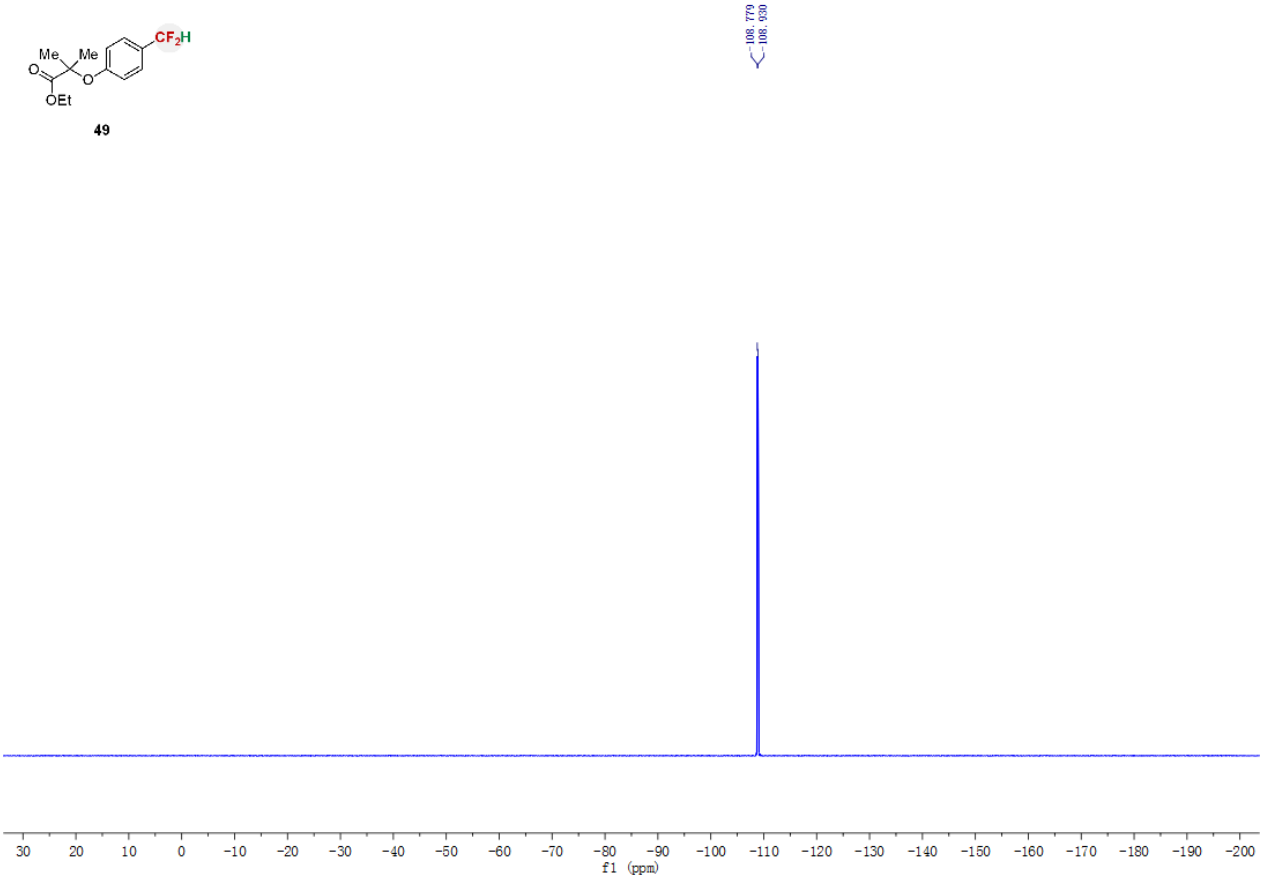


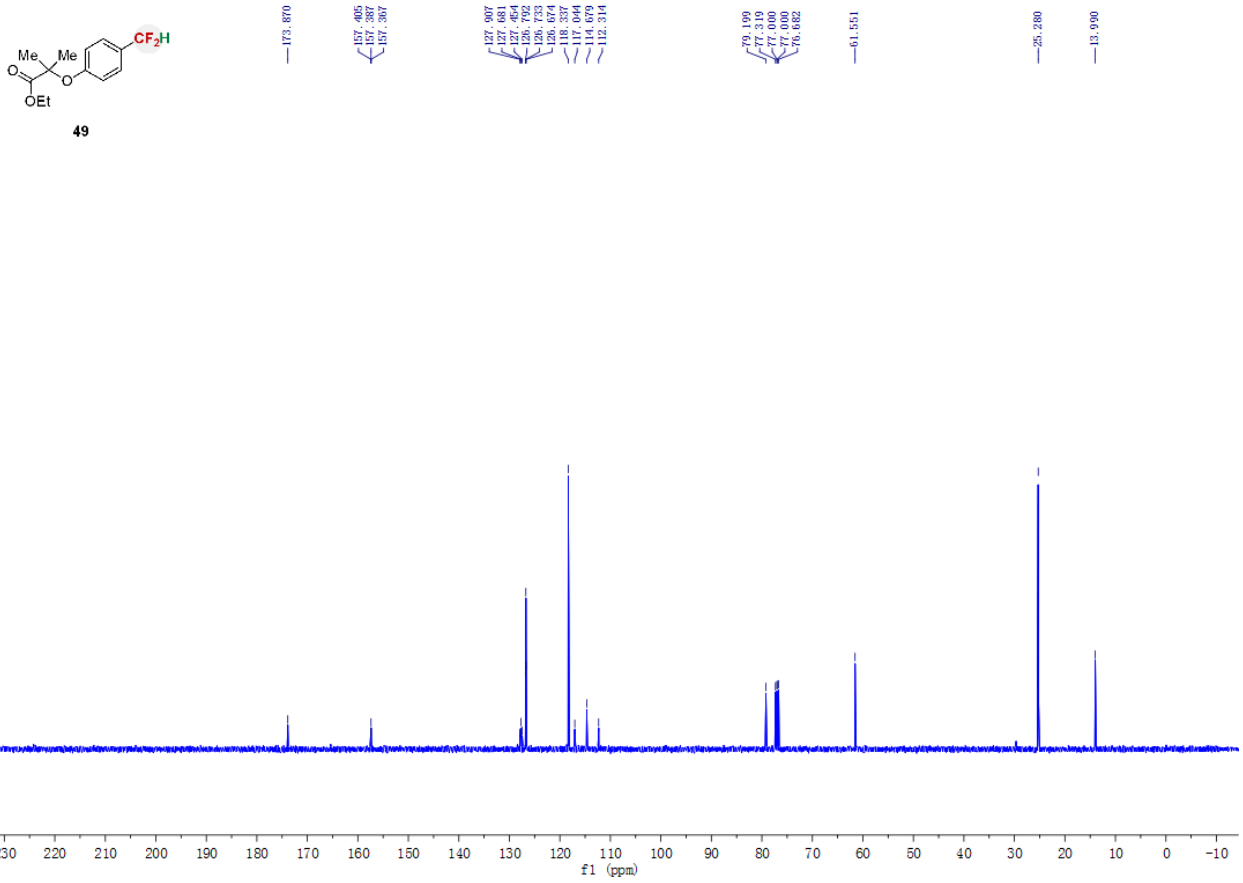

111.817
111.906
O
O
CF2H
Me
O
Me
Me
Me
O
48
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


194.625
173.047
159.901
140.330
137.500
137.394
137.122
132.086
129.979
129.873
125.598
125.488
125.428
117.207
116.462
114.080
111.699
79.416
77.318
77.000
77.000
76.682
69.344
25.341
21.499
O
O
CF2H
Me
O
Me
Me
Me
O
48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Ethyl 2-(4-(difluoromethyl)phenoxy)-2-methylpropanoate (49).

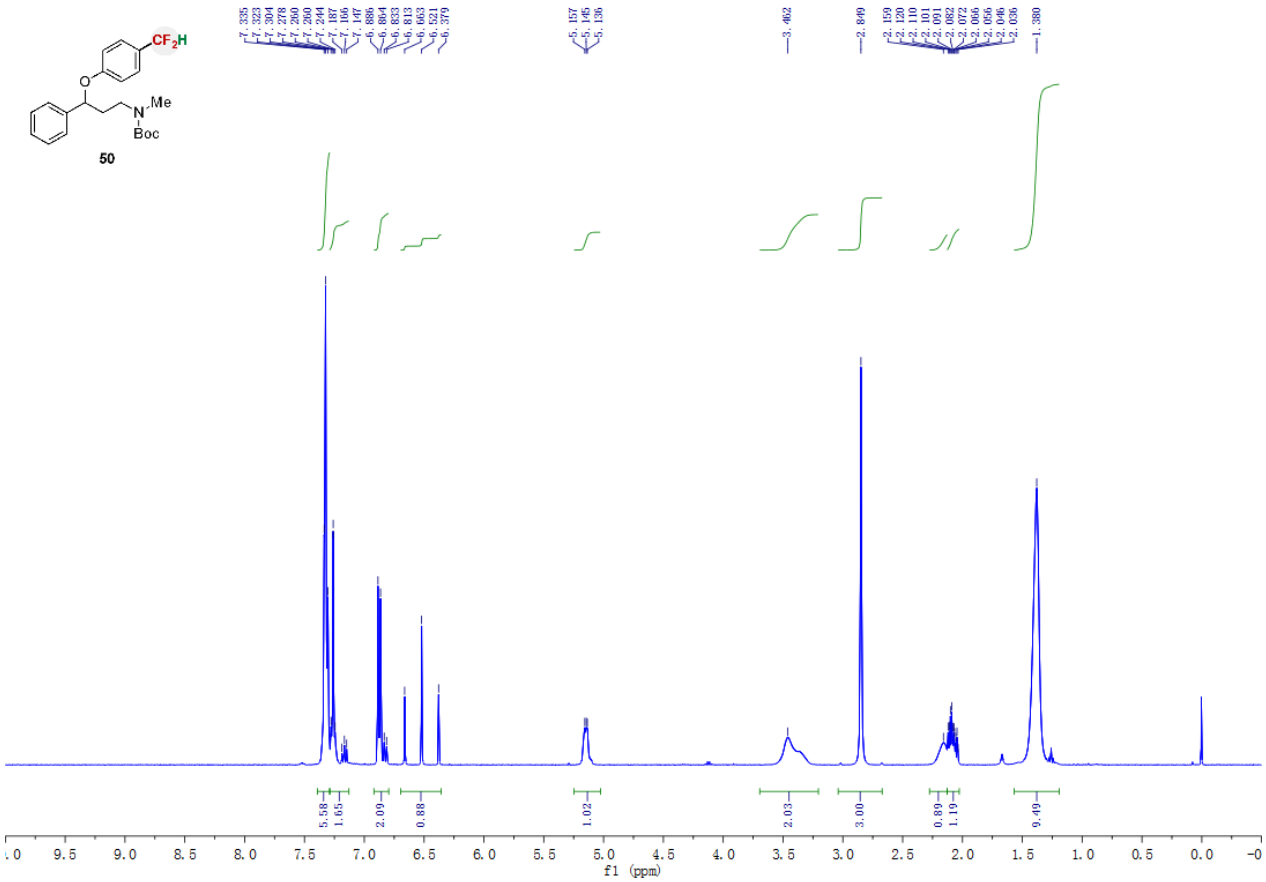


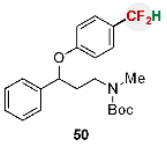




49

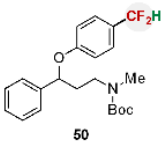
***tert*-Butyl (3-(4-(difluoromethyl)phenoxy)-3-phenylpropyl)(methyl)carbamate (50).**




CF2H
O
N
Me
Boc

50

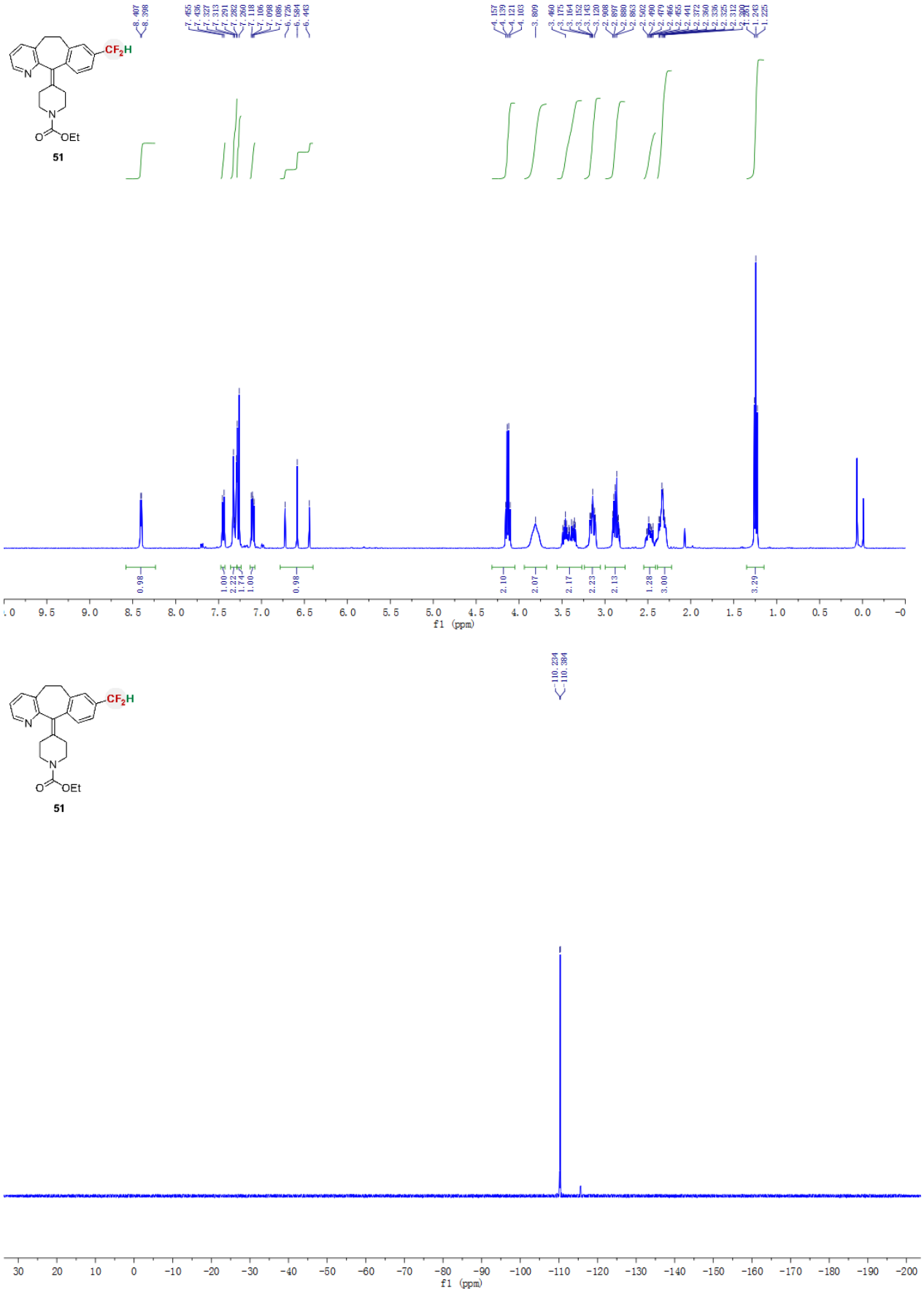
108.340
108.491
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

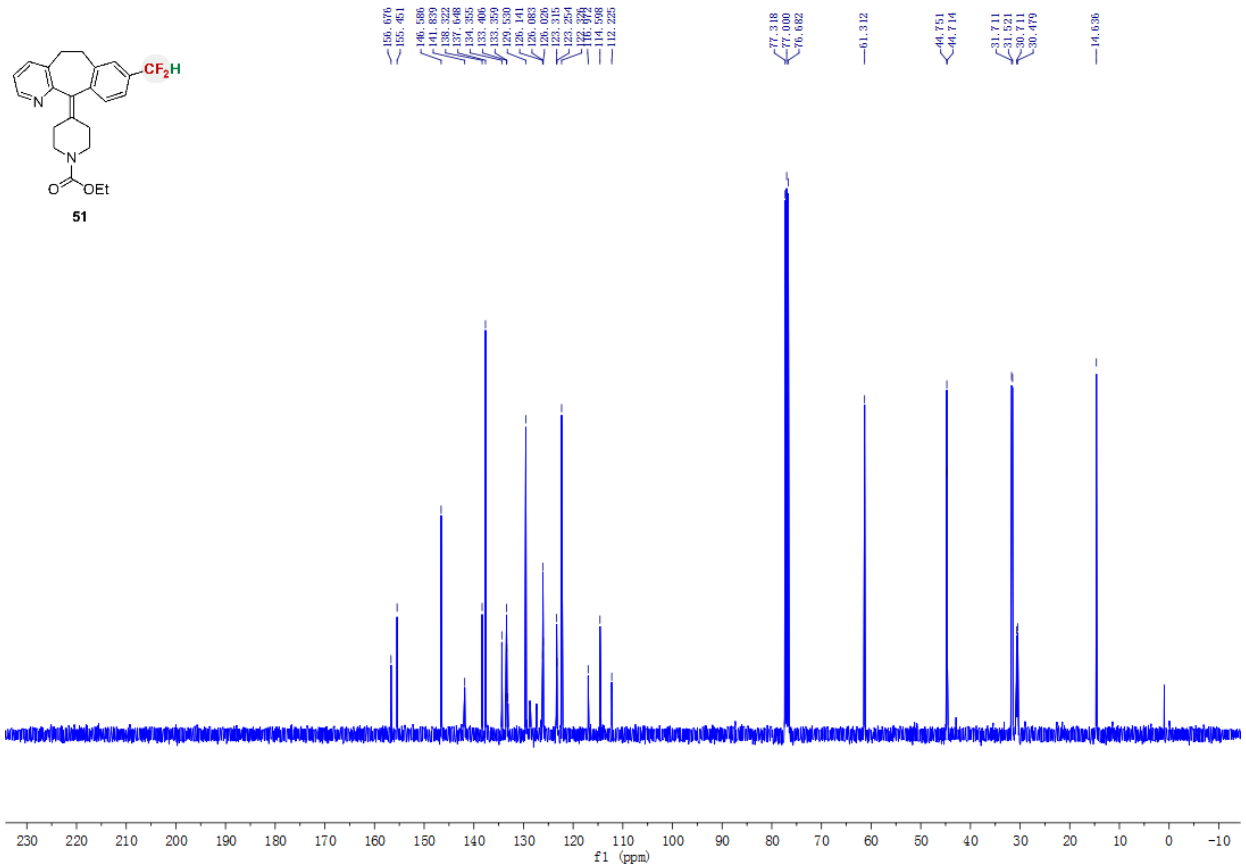

CF2H
O
N
Me
Boc

50

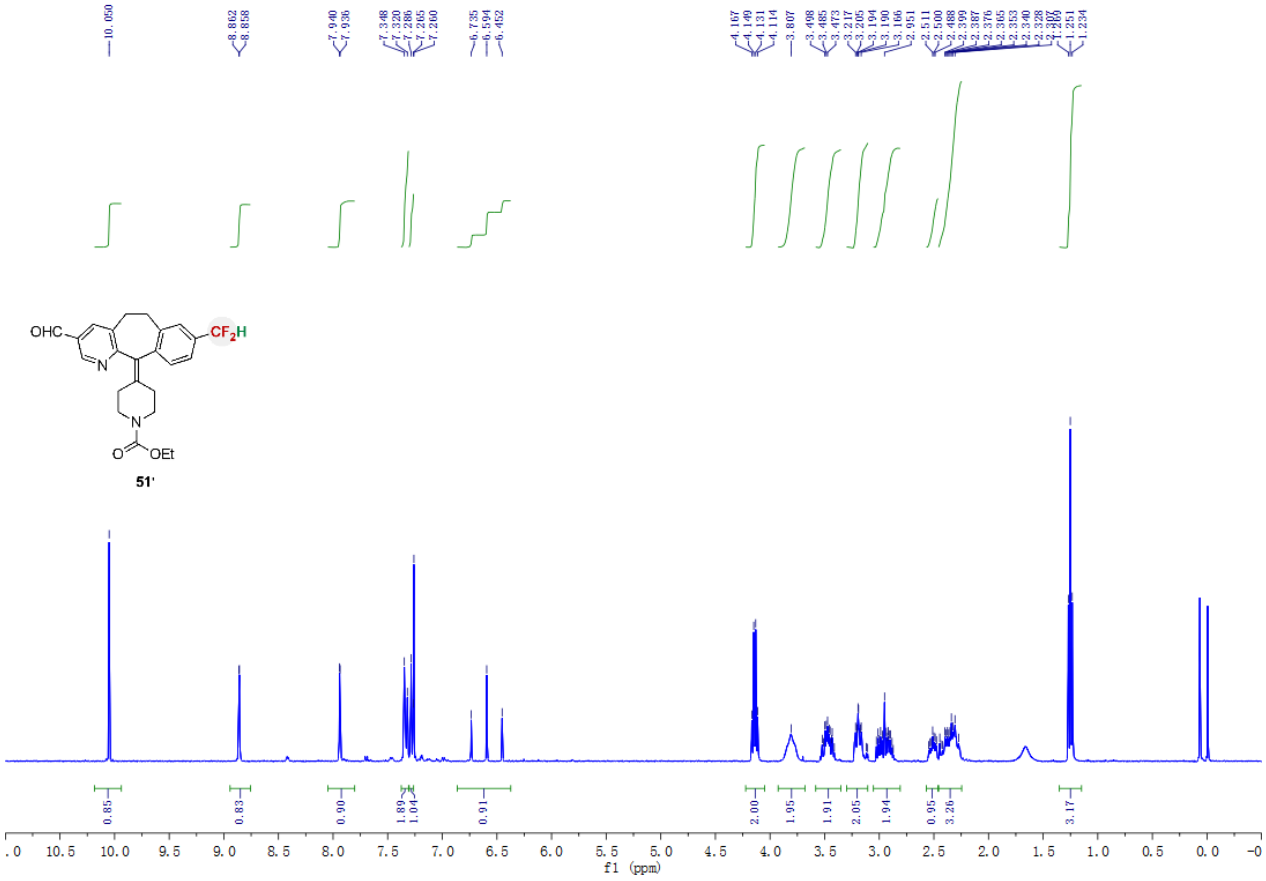
159.661
155.675
140.970
129.217
128.720
128.587
127.722
127.472
126.944
126.897
126.859
126.712
126.595
120.655
116.609
115.718
114.720
112.832
79.336
78.169
77.000
67.003
45.808
45.698
37.159
36.736
34.445
28.284
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

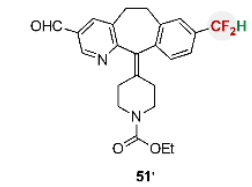
Ethyl 4-(8-(difluoromethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (51).





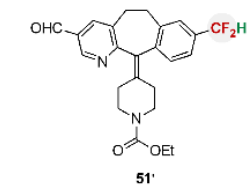
Ethyl 4-(8-(difluoromethyl)-3-formyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(6*H*)-ylidene)-piperidine-1-carboxylate (51′).




OHC
CF2H
N
N
O
OEt

51'

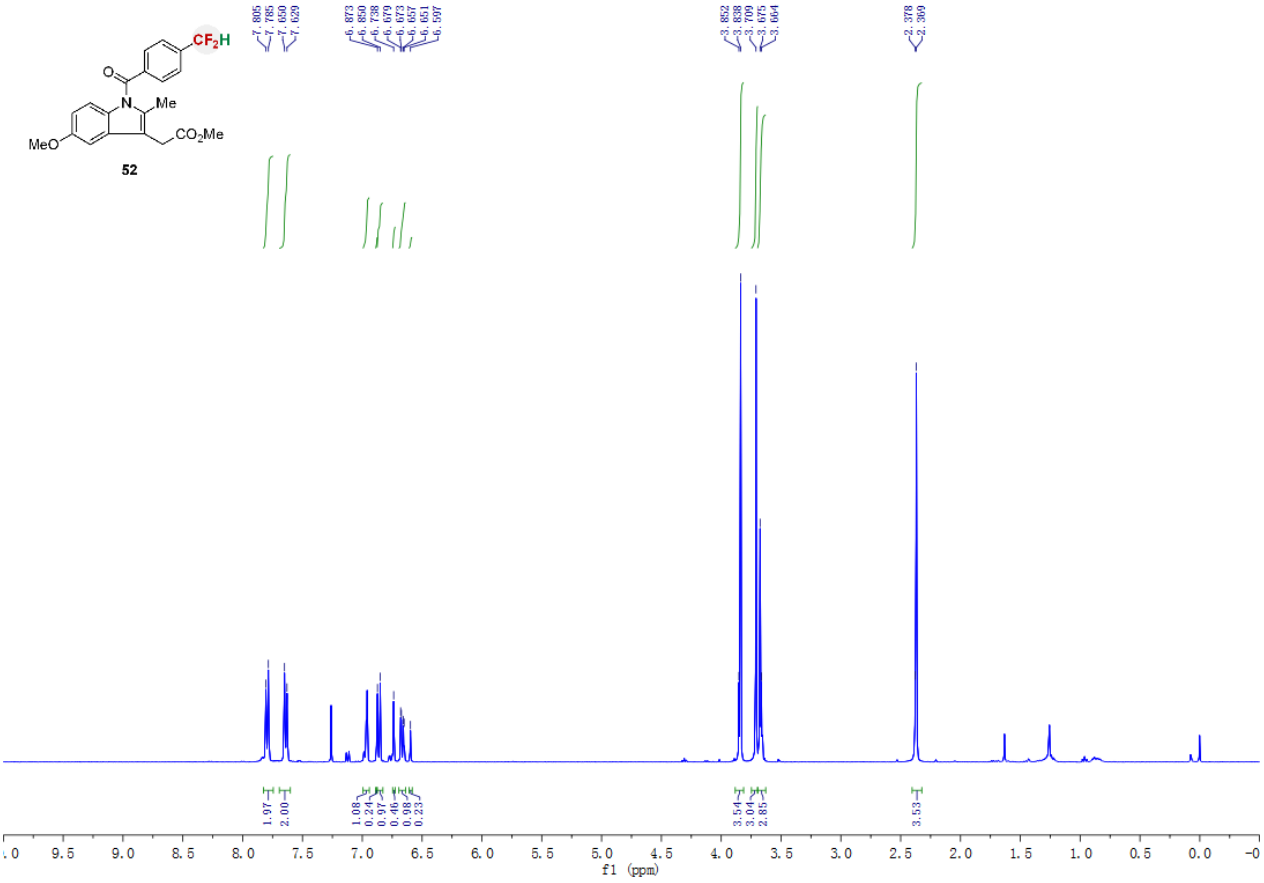
110.505
110.656
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

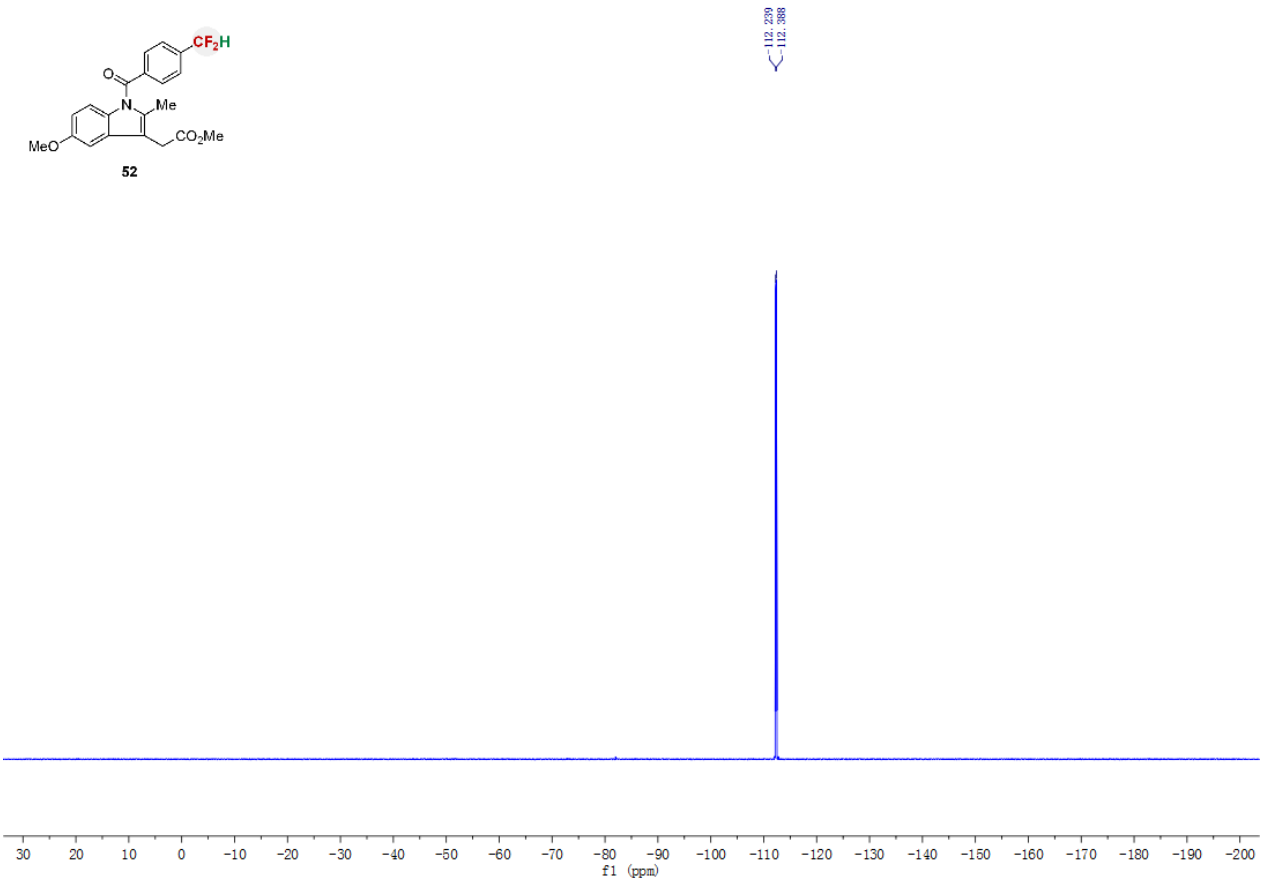

OHC
CF2H
N
N
O
OEt

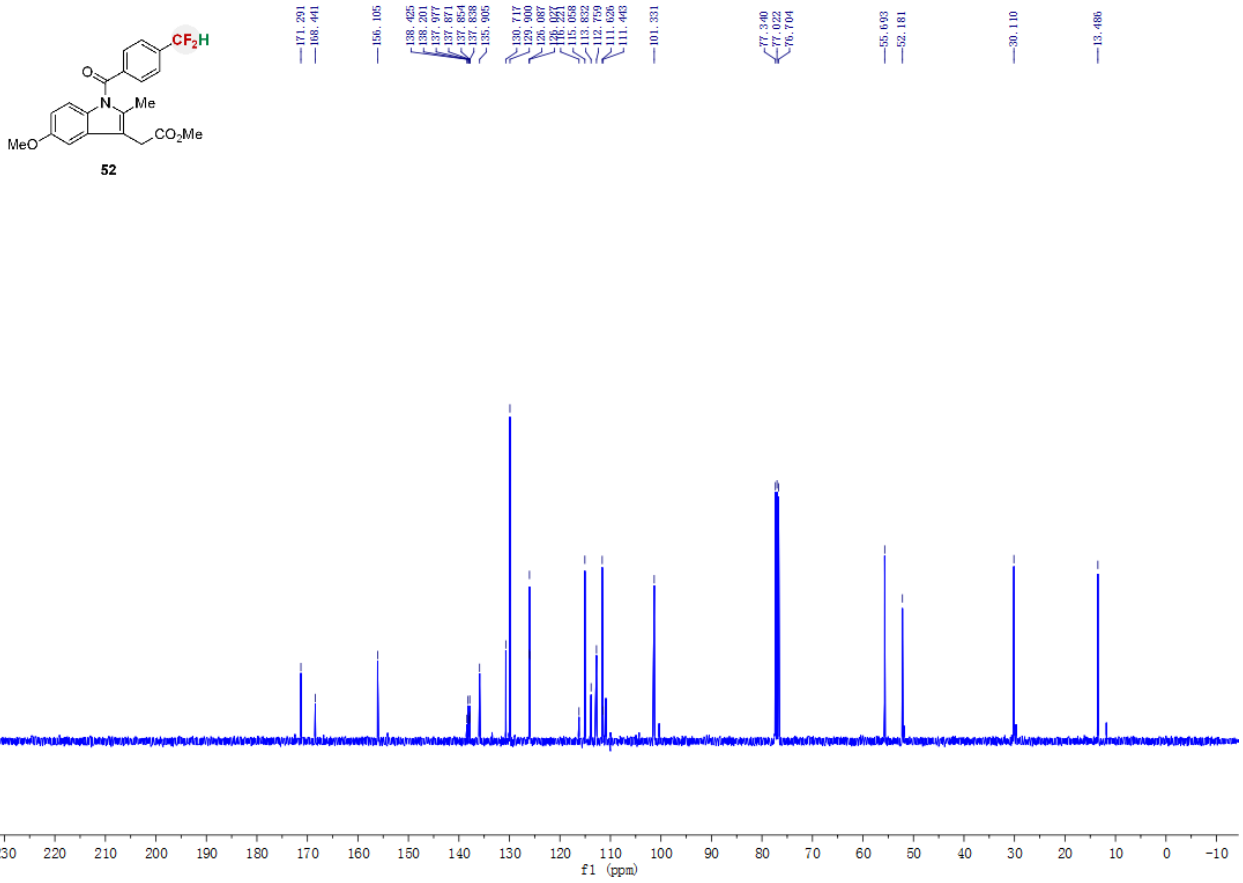
51'

190.381
162.350
155.421
149.302
140.733
139.443
138.698
137.996
134.990
133.849
130.283
129.810
126.349
126.292
126.233
114.443
112.067
77.318
77.000
76.682
61.429
44.733
44.661
31.496
31.475
30.827
30.668
14.651
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

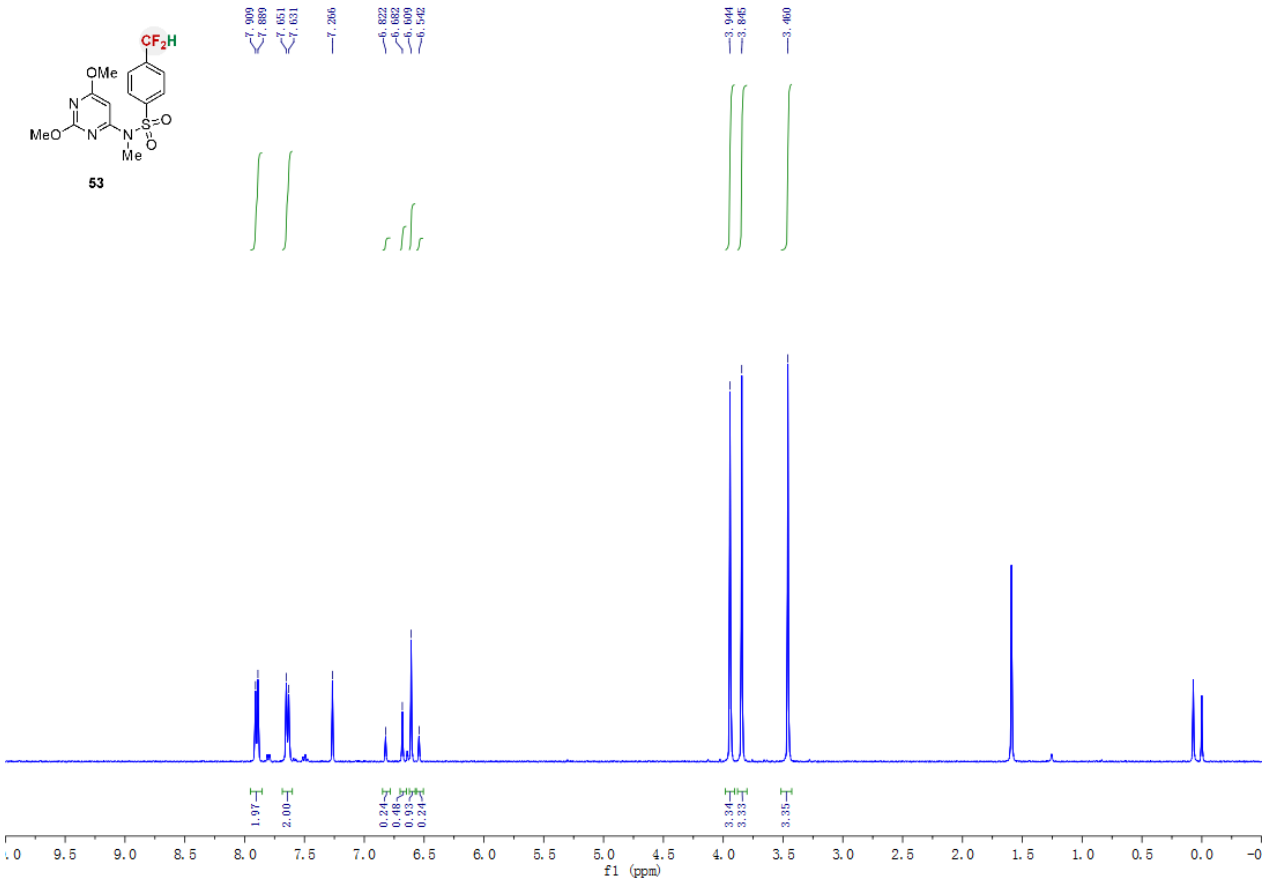
Methyl 2-(1-(4-(difluoromethyl)benzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (52).

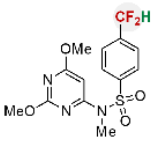






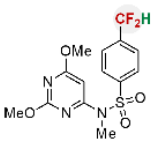
4-(Difluoromethyl)-*N*-(2,6-dimethoxypyrimidin-4-yl)-*N*-methylbenzenesulfonamide (53).




CF2H
OMe
N
MeO
N
S
O
O
N
Me

53

112.609
112.757
90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

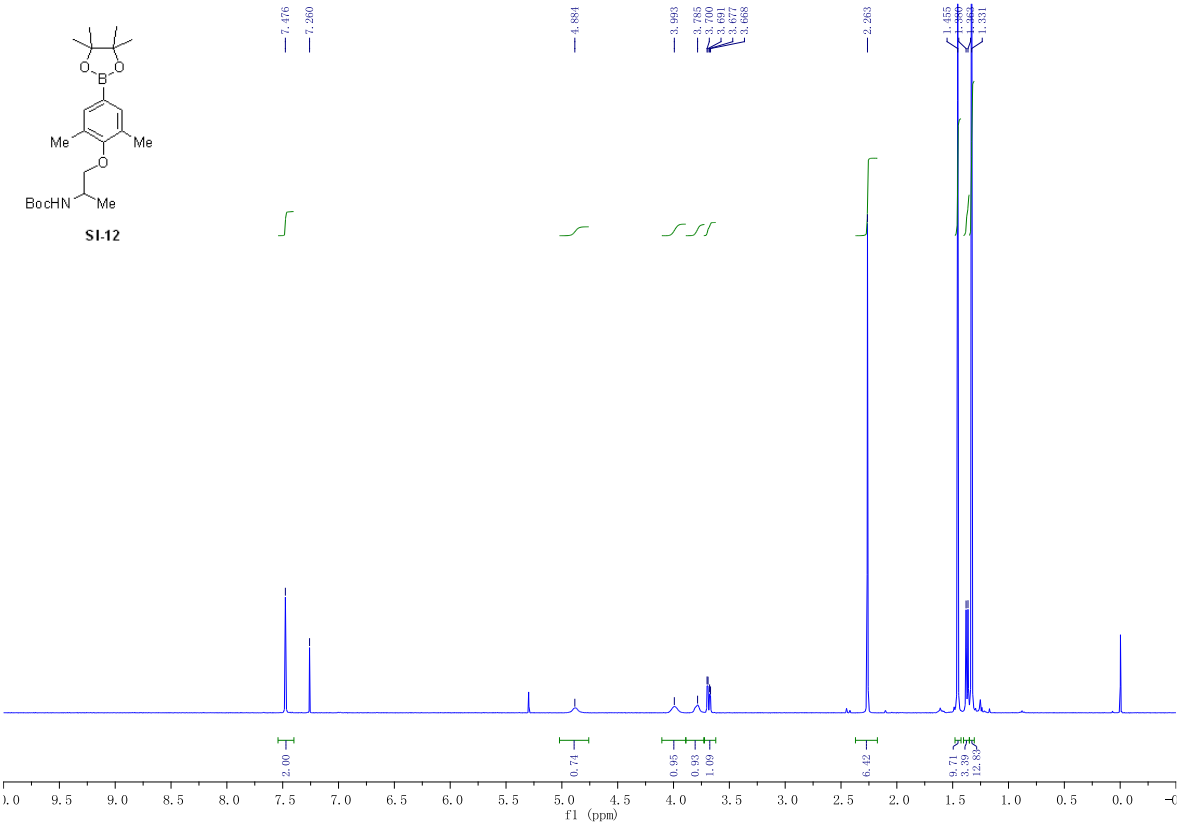

CF2H
OMe
N
MeO
N
S
O
O
N
Me

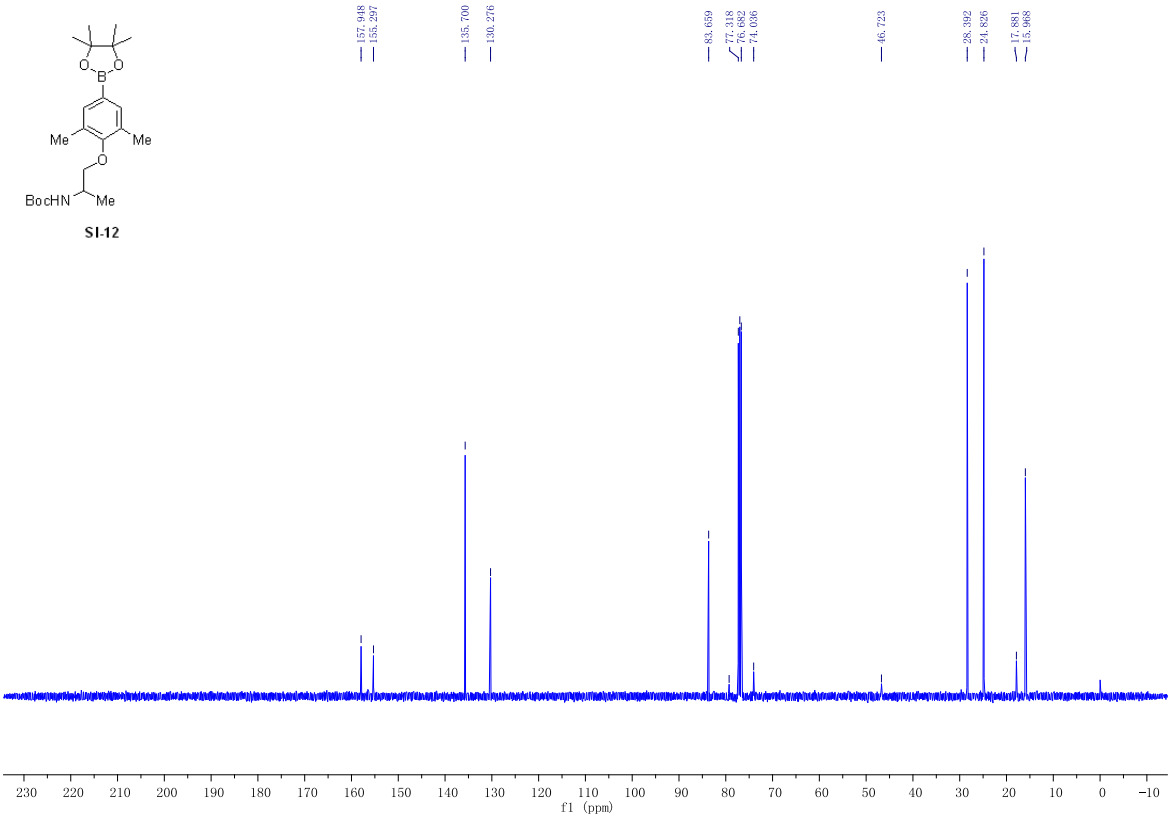
53

172.650
164.344
161.162
140.891
140.673
140.457
139.166
138.984
138.802
127.624
126.513
126.464
126.417
115.224
113.309
111.394
90.192
77.255
77.000
76.746
54.761
54.177
34.605
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

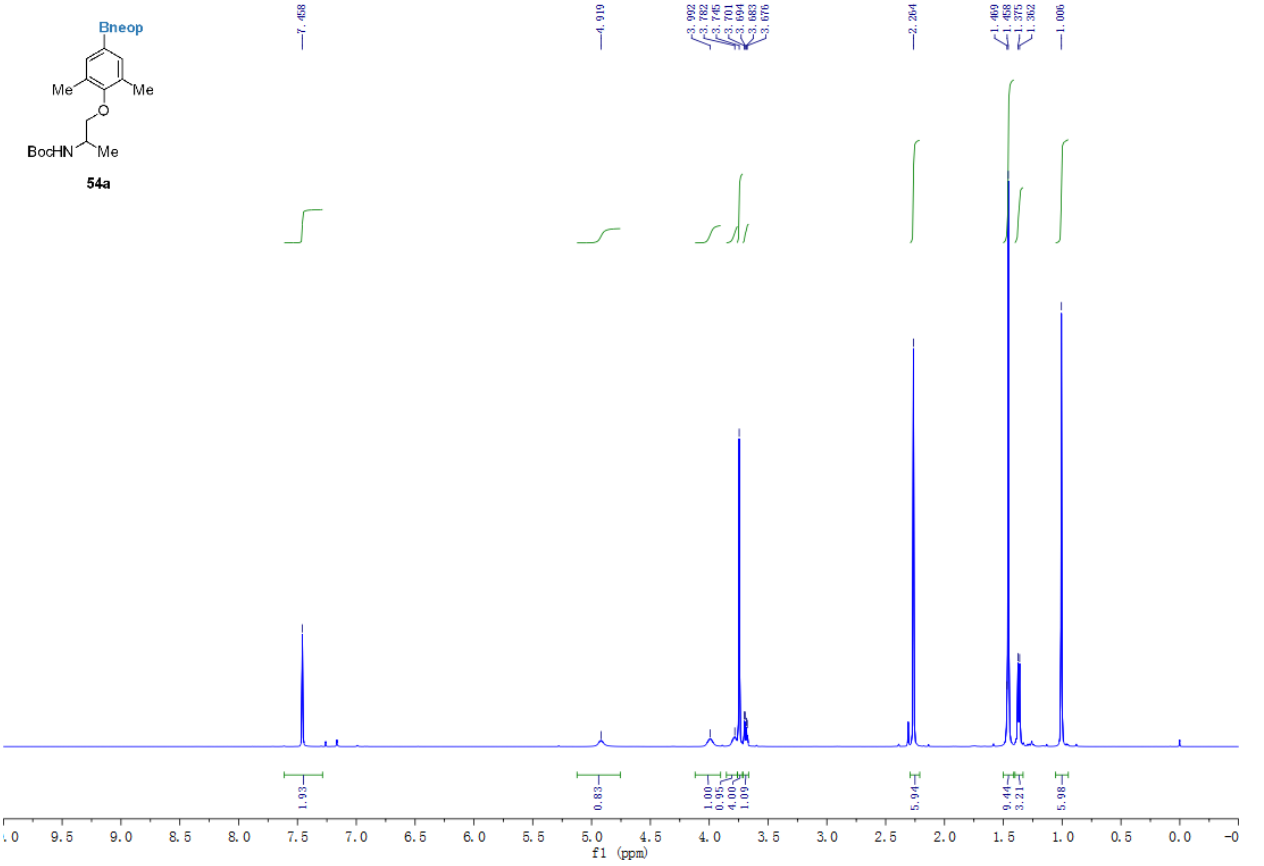
11. Part Three: ^{1}H NMR Copies, ^{19}F NMR Copies and ^{13}C NMR Copies of Compounds **SI-12**, **54a, 54, 55a** and **55**

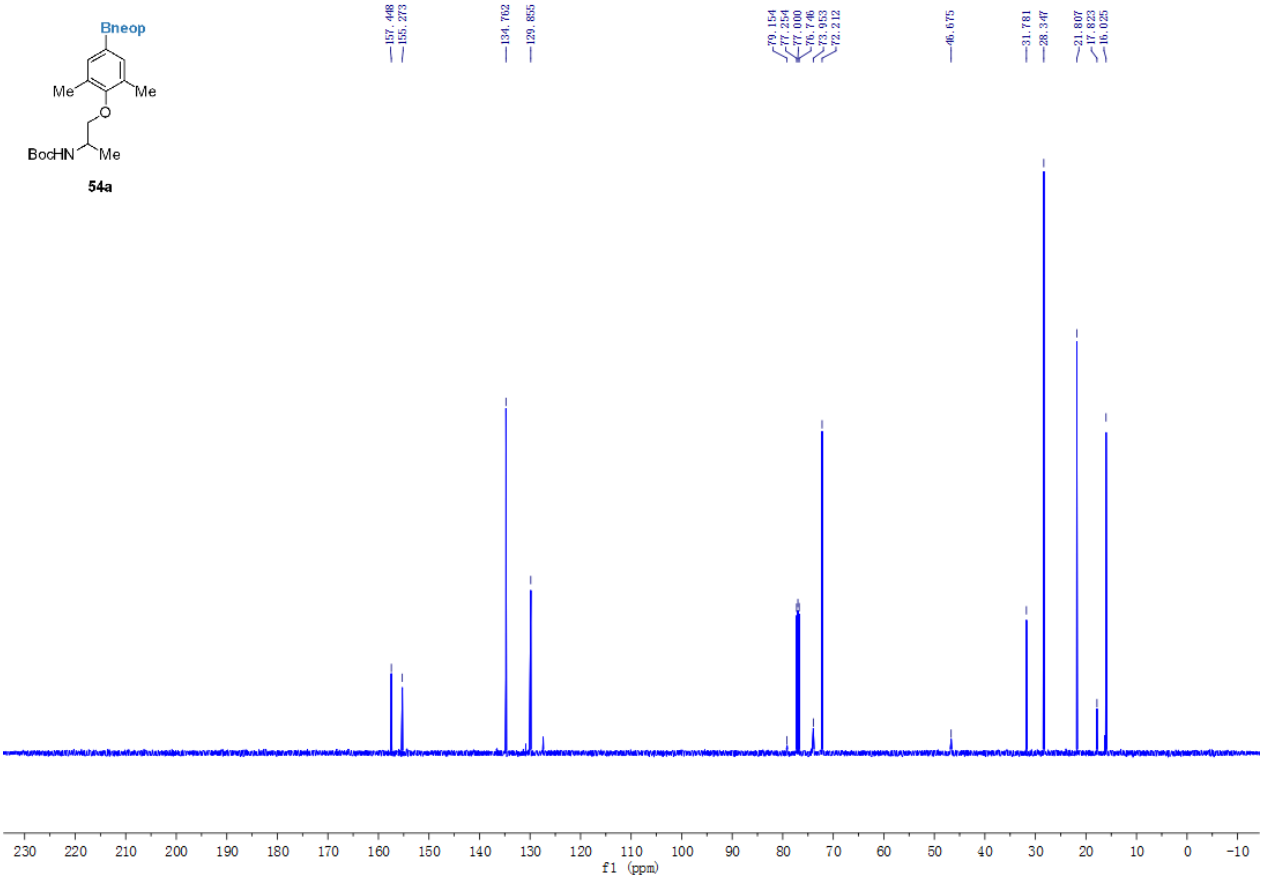
***tert*-Butyl (1-(2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-propan-2-yl)-carbamate (SI-12).**



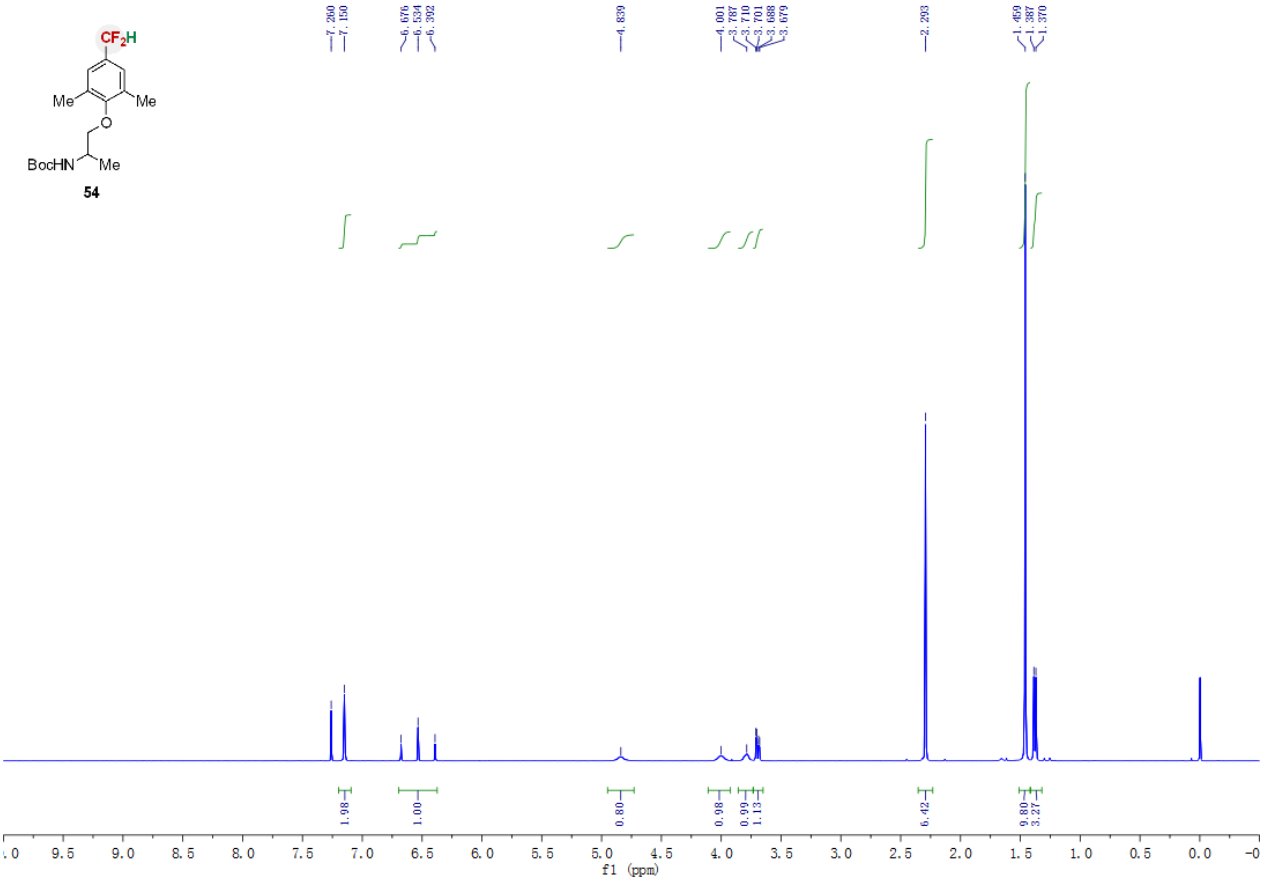


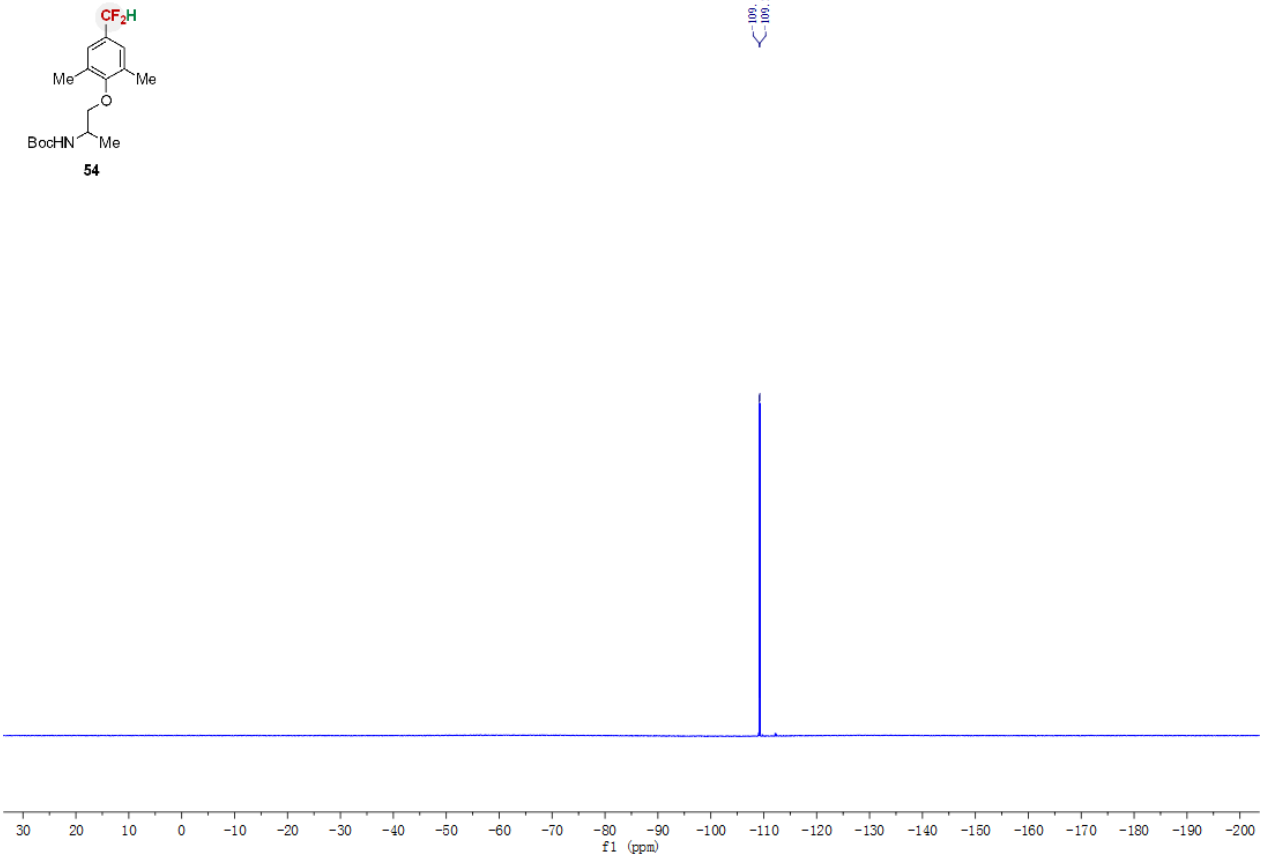
***tert*-Butyl (1-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2,6-dimethylphenoxy)propan -2-yl)carbamate (54a).**

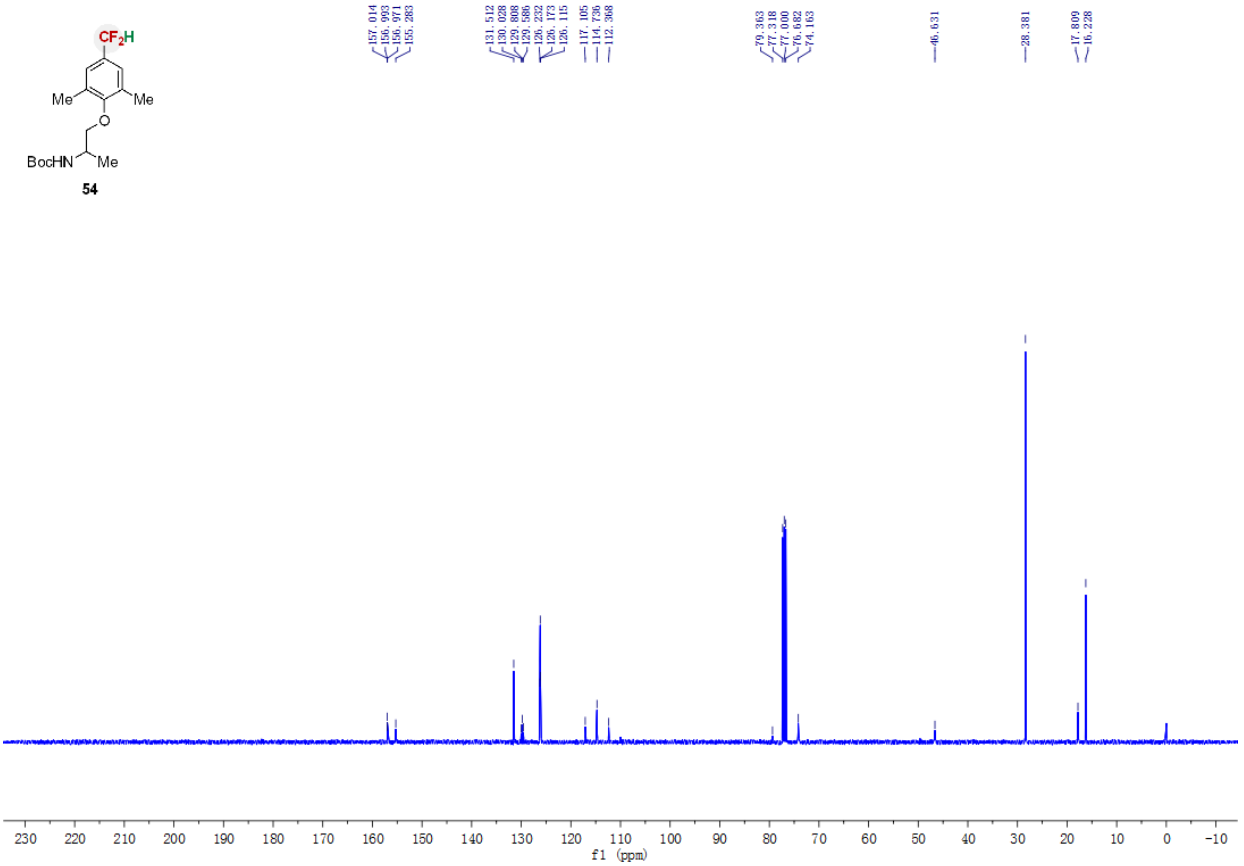




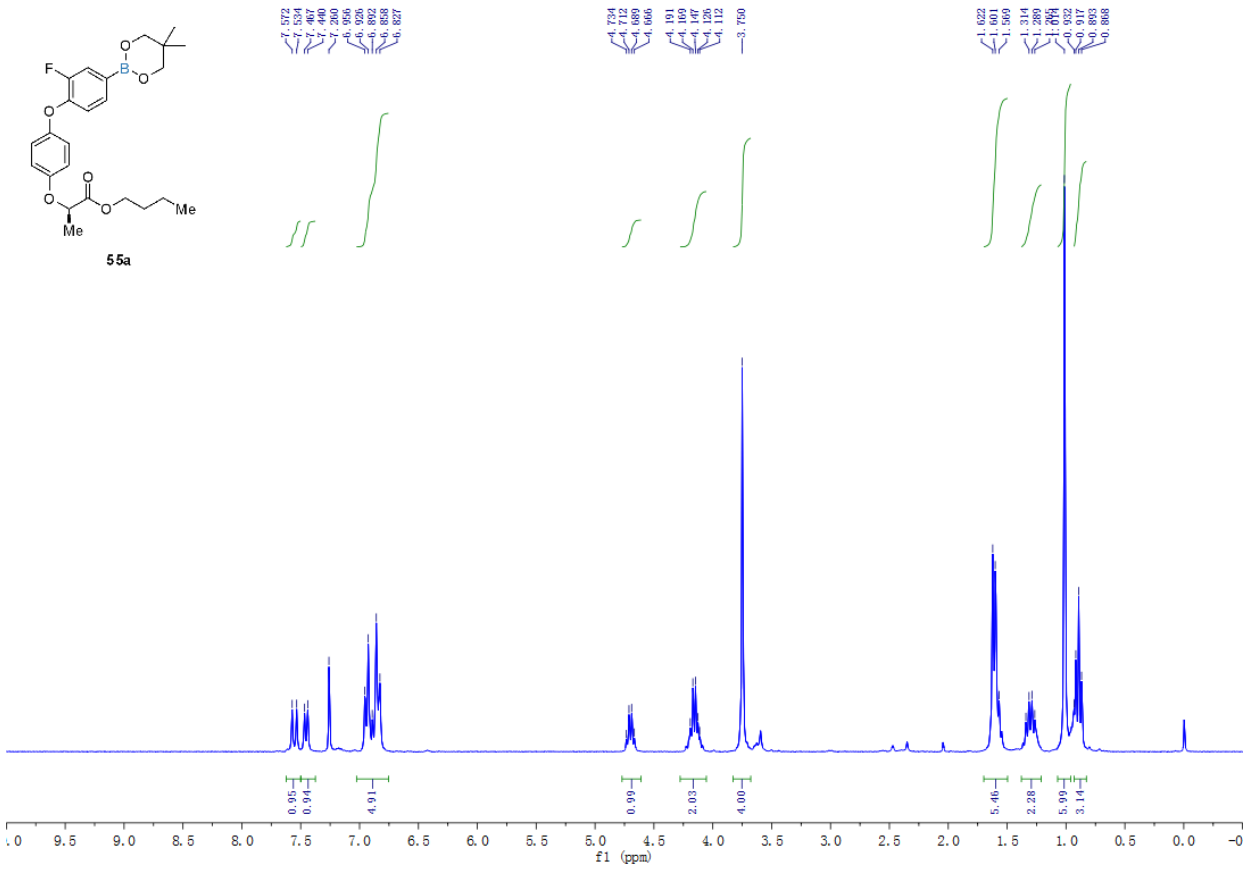
***tert*-Butyl (1-(4-(difluoromethyl)-2,6-dimethylphenoxy)propan-2-yl)carbamate (54).**

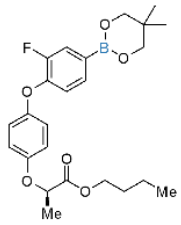




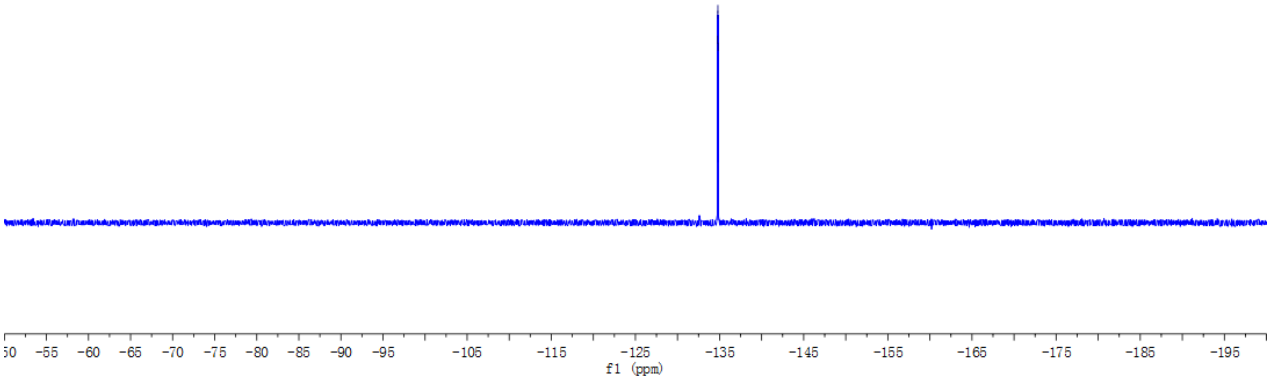


Butyl (*R*)-2-(4-(4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluorophenoxy)phenoxy)propanoate (55a).

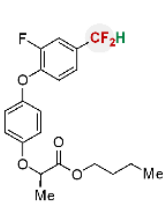




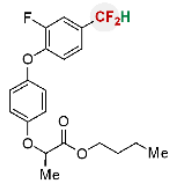
55a



Butyl (*R*)-2-(4-(4-(difluoromethyl)-2-fluorophenoxy)phenoxy)propanoate (55).

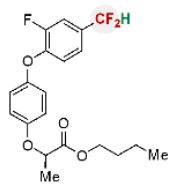


55


F
CF2H
O
O
O
O
Me
Me

55

109.786
109.935
130.877
130.969
130.905
130.926
A (d)
-109.86
B (dd)
-130.90
2.00
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


F
CF2H
O
O
O
O
Me
Me

55

172.136
154.309
154.191
152.302
152.186
147.522
147.507
147.491
147.434
147.419
147.404
129.935
129.790
129.701
129.516
121.997
121.967
121.947
121.916
121.896
121.885
120.410
120.422
116.374
115.522
114.529
114.482
114.435
114.369
114.321
114.274
113.921
77.000
76.746
73.165
65.107
30.484
18.918
18.565
13.550
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

12. References and Notes

1. Moulder, J. F., Stickle, W. F., Sobol, P. E. & Bomben, K. D. in *Handbook of X-ray photoelectron spectroscopy: a reference book of standard spectra for identification and interpretation of XPS data*, (Perkin-Elmer, Eden Prairie, Minn, USA, 1992).
2. Grushin, V. V. & Marshall, W. J. Facile Ar-CF_3 bond formation at Pd. Strikingly different outcomes of reductive elimination from [$(Ph_3P)_2Pd(CF_3)Ph$] and [(Xantphos)Pd(CF_3)Ph]. *J. Am. Chem. Soc.* **128**, 12644-12645 (2006).
3. Singh, R. P. & Shreeve, J. M. Concentration-dependent reactions of deoxofluor with arylglyoxal hydrates: a new route to polyfluoro ethers. *Org. Lett.* **3**, 2713-2715 (2001).
4. Clark, G. R., Hoskins, S. V., Jones, T. C. & Roper, W. R. Oxidation state control of the reactivity of a transition metal-carbon double bond. Synthesis, X-ray crystal structure, and reactions of the zerovalent difluorocarbene complex [$Ru{=}CF_2)(CO)_2(PPh_3)_2$]. *J. Chem. Soc., Chem.Commun.* 719-721 (1983).
5. Markies, B. A. *et al.* Synthesis and structural studies of phenyl(iodo)- and methyl(phenyl) palladium(II) complexes of bidentate nitrogen donor ligands. *J. Organometallic Chemistry* **482**, 191-199 (1994).
6. Smirnov, V. O., Struchkova, M. I., Arkhipov, D. E., Korlyukov, A. A. & Dilman, A. D. Synthesis of *gem*-difluorinated nitroso compounds. *J. Org. Chem.* **79**, 11819−11823 (2014).
7. Brothers, P. J. & Roper, W. R. Transition-metal dihalocarbene complexes. *Chem. Rev.* **88**, 1293-1326 (1988).
8. Grushin, V. V. & Marshall, W. J. Unexpected H_2O-induced Ar-X activation with trifluoromethylpalladium(II) aryls. *J. Am. Chem. Soc.* **128**, 4632-4641 (2006).
9. Molander, G. A., Trice, S. L. J. & Dreher, S. D. Palladium-catalyzed, direct boronic acid synthesis from aryl chlorides: A simplified route to diverse boronate ester derivatives. *J. Am. Chem. Soc.* **132**, 17701-17703 (2010).
10. Fier, P. S. & Hartwig, J. F. Copper-mediated difluoromethylation of aryl and vinyl iodides. *J. Am. Chem. Soc.* **134**, 5524−5527 (2012).

11. Feng, Z., Min, Q.-Q. & Zhang, X. Access to difluoromethylated arenes by Pd-catalyzed reaction of arylboronic acids with bromodifluoroacetate. *Org. Lett.* **18**, 44-47 (2016).

12. Singh, R. P., Chakraborty, D. & Shreeve, J. M. Nucleophilic trifluoromethylation and difluorination of substituted aromatic aldehydes with Ruppert's and Deoxofluor™ reagents. *J. Fluorine Chem.* **111**, 153-160 (2001).

13. Ge, S., Chaładaj, W. & Hartwig, J. H. Pd-catalyzed α-arylation of α, α-difluoroketones with aryl bromides and chlorides. A route to difluoromethylarenes. *J. Am. Chem. Soc.* **136**, 4149-4152 (2014).

14. Prakash, G. K. S. *et al.* Copper-mediated difluoromethylation of (hetero)aryl iodides and β-styryl halides with tributyl(difluoromethyl)stannane. *Angew. Chem. Int. Ed.* **51**, 12090-12094 (2012).

15. Fujikawa, K., Fujioka, Y., Kobayashi, A. & Amii, H. A new method for aromatic difluoromethylation: Copper-catalyzed cross-coupling and decarboxylation sequence from aryl iodides. *Org. Lett.* **13**, 5560−5563 (2011).

16. Matheis, C., Jouvin, K. & Goossen, L. Sandmeyer difluoromethylation of (hetero-)arenediazonium salts. *Org. Lett.* **16**, 5984-5987 (2014).

17. Xiao, Y.-L., Min, Q.-Q., Xu, C., Wang, R.-W. & Zhang, X. Nickel-catalyzed difluoroalkylation of (hetero)arylborons with unactivated 1-bromo-1,1-difluoroalkanes. *Angew. Chem. Int. Ed.* **55**, 5873-5841 (2016).

18. Tang, P., Furuya, T. & Ritter, T. Silver-catalyzed late-stage fluorination. *J. Am. Chem. Soc.* **132**, 12150-12154 (2010).

19. Feng, Z., Min, Q.-Q., Xiao, Y.-L., Zhan, B. & Zhang, X. Palladium-Catalyzed Difluoroalkylation of Aryl Boronic Acids: A New Method for the Synthesis of AryldifluoromethylatedPhosphonates and Carboxylic Acid Derivatives. *Angew. Chem., Int. Ed.* **53**, 1669-1673 (2014).

20. Xiao, Y.-L., Guo, W.-H., He, G.-Z., Pan, Q. & Zhang, X. Nickel-catalyzed cross-coupling of functionalized difluoromethyl bromides and chlorides with aryl boronic Acids: A general method for difluoroalkylatedarenes. *Angew. Chem., Int. Ed.* **53**, 9909-9913 (2014).

21. Ishiyama, T., Itoh, Y., Kitano, T. & Miyaura, N. Synthesis of arylboronates via the palladium(0)-catalyzed cross-coupling reaction of tetra(alkoxo)diborons with aryl triflates. *Tetrahedron Lett.* **38**, 3447-3450 (1997).

22. Ishiyama, T. *et al.* Mild iridium-catalyzed borylation of arenes. High turnover numbers, room temperature reactions, and isolation of a potential intermediate. *J. Am. Chem. Soc.***124**, 390-391 (2002).

23. Tobisu, M., Kinuta, H., Kita,Y., Rémond, E. & Chatani, N. Rhodium(I)-catalyzed borylation of nitriles through the cleavage of carbon–cyano bonds. *J. Am. Chem. Soc.***134**, 115-118 (2012).