Supporting Information

[^{18}F]Radiolabeling Fluorination of Monofluoroalkyl Triflates for the Synthesis of [^{18}F]Difluoromethylated Alkanes

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Table of Contents

1. General Information and Materials

General Information: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM400 spectrometers and were calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.00 ppm ^{13}C NMR). ^{19}F NMR spectra were recorded on a Bruker AM400 spectrometer ($CFCl_3$ was used as the external standard, and the low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. The NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction. High Resolution Mass spectral data were recorded on Waters GC-TOF Premier spectrometer in EI mode.

Materials: All reagents were used as received from commercial sources unless otherwise stated or prepared as described in the literature. All solvents used in the reaction were anhydrous and purchased from *J&K* or Energy Chemical.

2. Preparation of Starting Materials

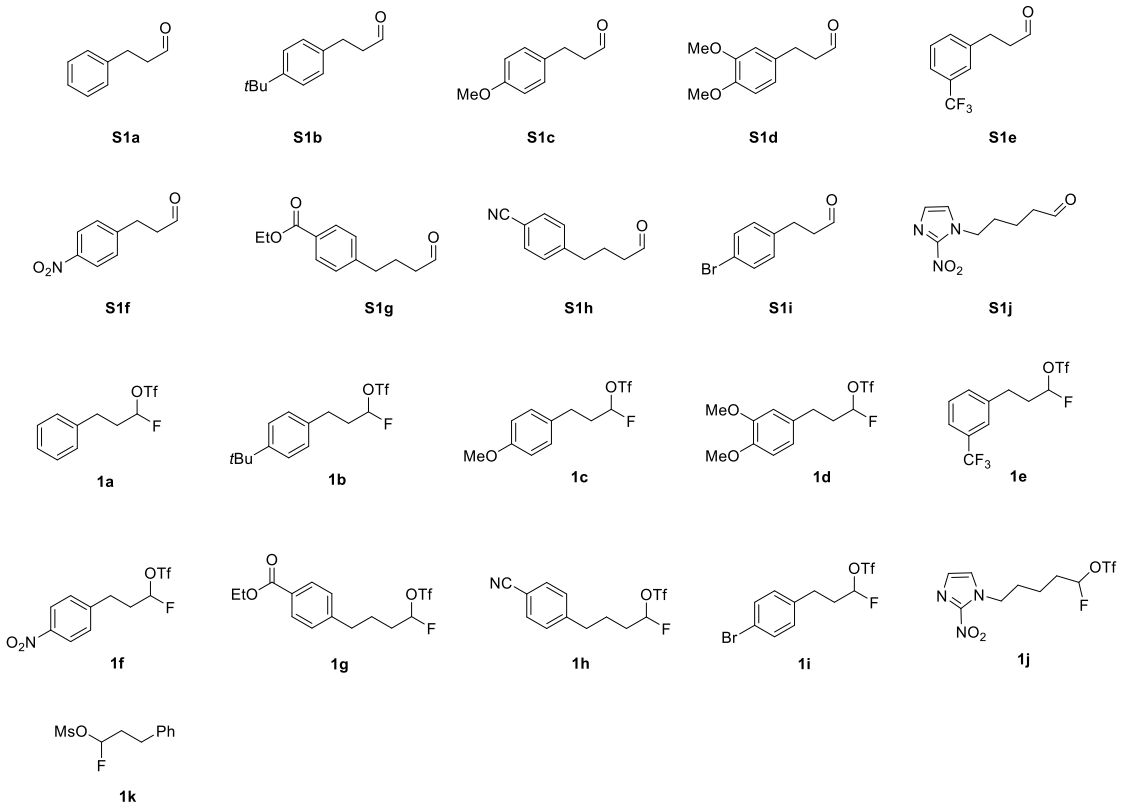
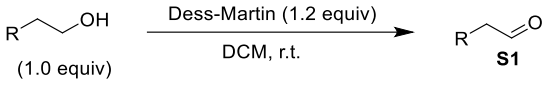


Figure S1. Structures of Aldehydes **S1** and Monofluoroalkyl Triflates **1**

2. 1 General Procedure for the Preparation of Aldehydes S1

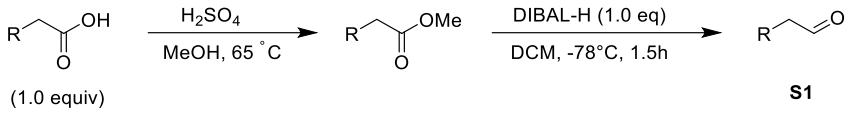
Method A[1]:



To a dry 250 mL round-bottom flask, Dess-Martin Reagents (1.2 equiv) and DCM (150 mL) were added. The flask was then cooled to 0 ℃ using an ice-water bath, and the alcohol was dissolved in DCM. It was then added to the flask via a syringe. After the reaction was stirred for 10 min, the ice-water bath was removed. The reaction mixture was stirred at room temperature for 2-5 h until the reaction was completed. The resulting mixture was quenched with saturated sodium thiosulfate. The aqueous phase was washed with DCM (3×30 mL). The organic layer was dried over Na_2SO_4, filtered,

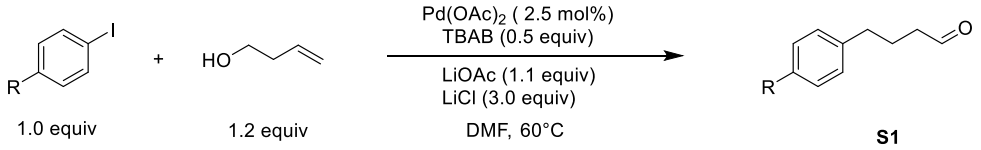
and concentrated. The residue was purified with flash chromatography to afford the aldehydes **S1c**, **S1i**, and **S1j**.

Method B[2]:



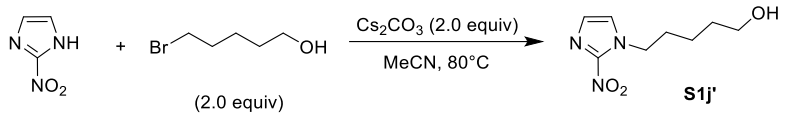
To a dry 250 mL round-bottom flask, acid (1.0 equiv) and MeOH (100 mL) were added. H_2SO_4 was then added carefully into the flask via a syringe. The reaction was refluxed for 2 h. The mixture was cooled to room temperature, extracted with EA, and concentrated. The resulting crude product was dissolved in DCM and then cooled to -78 ℃. DIBAL-H was added to the flask via a syringe. The reaction was stirred for 1.5 h at -78 ℃. The resulting mixture was quenched with MeOH. The aqueous phase was extracted with DCM (3×30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the aldehydes **S1d** and **S1f**.

Method C[3]:



To a dry 250 mL three-necked flask, $Pd(OAc)_2$ (2.5 mol%), LiOAc (1.1 equiv), LiCl (3.0 equiv), and TBAB (0.5 equiv) were added. The flask was then evacuated and backfilled with Ar (3 times). Subsequently, aryliodide (1.0 equiv), alcohol (1.2 equiv), and DMF (50 mL) were added to the reaction mixture. After stirring for 12 h at 60 ℃, the reaction mixture was quenched with water, and the aqueous phase was extracted with ethyl acetate (3×30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the aldehydes **S1g** and **S1h**.

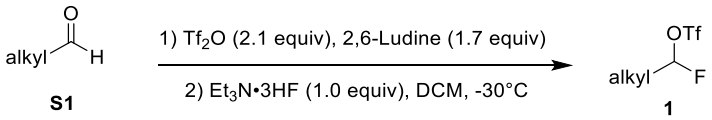
Method D:



To a dry 250 mL three-necked flask, 2-nitro-1H-imidazole (50 mmol, 1.0 equiv) and Cs2CO3 (2.0 equiv) were added. The flask was then evacuated and backfilled with Ar (3 times). Subsequently, 5-bromophentan-1-ol and CH_3CN were added to the reaction mixture. After stirring for 12 h at 80 ºC, the reaction mixture was quenched with saturated NH_4Cl, and the aqueous phase was extracted with ethyl acetate (3×30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the product **S1j'**, which was applied to Method A to give **S1j.**

Note: Aldehydes **S1a**, **S1b**, and **S1e** were commercially available.

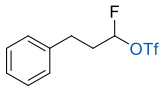
2. 2 General Procedure for the Preparation of 1-Fluoroalkyl Triflates 1 [4]



Triflic anhydride (7 mL, 42 mmol) in 10 mL of dichloromethane was added to a 150 mL triple-necked round-bottomed flask containing aldehyde **S1** (20 mmol) and 2.6-lutidine (4 mL, 34 mmol) in 40 mL dichloromethane. After stirring under argon for 12-24 h at -30ºC. $Et_3N{\cdot}3HF$ (20 mmol, 1 equiv.) was added dropwise to the mixture of bistriflate at -30 ºC. The mixture was allowed to reach room temperature and stirred overnight. The reaction was slowly quenched by the addition of saturated $NaHCO_3$ (50 mL) at 0 ºC, and the organic layer was washed with 1M HCl (50 mL) and saturated $NaHCO_3$ (50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography to give the 1-fluoroalkyl triflates **1a-1j**.

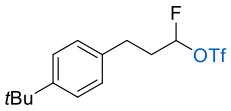
Note: Monofluoroalkyl triflates **1** are unstable. The purification of **1** with column chromatography should be fast. Compounds **1** are stable in a solution with MeCN as the solvent, which can be stored at -20 ºC for several months.

1-Fluoro-3-phenylpropyl trifluoromethanesulfonate (1a)



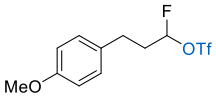
Compound **1a** (4.97 g, 87% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.37 – 7.15 (m, 5H), 6.11 (dt, *J* = 54.2, 5.2 Hz, 1 H), 2.81 (t, *J* = 7.8 Hz, 2 H), 2.43 – 2.15 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (d, *J* = 7.4 Hz, 3 F), -120.39 (dddd, J = 54.4, 18.4, 15.6, 7.6 Hz, 1 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 138.6, 128.9, 128.2, 126.8, 118.3 (q, *J* = 320.4 Hz), 111.8 (d, *J* = 245.8 Hz), 35.2 (d, *J* = 20.0 Hz), 28.6 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{10}H_{10}F_4O_3S$: 286.0287; Found: 286.0278.

3-(4-(*tert*-Butyl)phenyl)-1-fluoropropyl trifluoromethanesulfonate (1b)



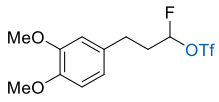
Compound **1b** (5.67 g, 83% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 6.13 (dt, *J* = 54.4, 5.2 Hz, 1 H), 2.78 (t, *J* = 7.8 Hz, 2 H), 2.50 – 2.12 (m, 2 H), 1.31 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (d, *J* = 7.4 Hz, 3 F), -119.3 – -121.3 (m, 1 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 149.8, 135.5, 127.9, 125.8, 118.3 (q, *J* = 320.4 Hz), 111.9 (d, *J* = 245.6 Hz), 35.2 (d, *J* = 20.0 Hz), 34.4, 31.3, 28.0 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{14}H_{18}F_4O_3S$: 342.0913; Found: 342.0913.

1-Fluoro-3-(4-methoxyphenyl)propyl trifluoromethanesulfonate (1c)



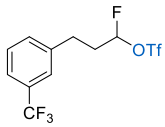
Compound **1c** (5.05 g, 80% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.11 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 7.8 Hz, 2 H), 6.11 (dt, *J* = 54.2, 5.2 Hz, 1 H), 3.80 (s, 3 H), 2.76 (t, *J* = 7.8 Hz, 2 H), 2.48 – 2.10 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.9 (d, *J* = 7.5 Hz, 3 F), -120.3 (dddd, *J* = 54.2, 18.8, 15.2, 7.6 Hz, 1 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 158.4, 130.5, 129.2, 114.2, 118.3 (q, *J* = 319.6 Hz), 111.8 (d, *J* = 245.8 Hz), 55.2, 35.4 (d, *J* = 20.0 Hz), 27.7 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{11}H_{12}F_4O_4S$: 316.0392; Found: 316.0391.

3-(3,4-Dimethoxyphenyl)-1-fluoropropyl trifluoromethanesulfonate (1d)



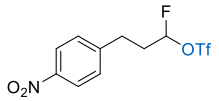
Compound **1d** (4.77 g, 69% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.2 Hz, 1 H), 6.76 – 6.67 (m, 2 H), 6.11 (dt, *J* = 54.2, 5.2 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.76 (td, *J* = 7.8, 3.2 Hz, 2 H), 2.36 – 2.19 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (d, *J* = 7.6 Hz, 3 F), -120.5 (dddd, *J* = 54.2, 18.8, 15.2, 7.6 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 147.9, 131.0, 120.1, 116.68(d, *J* = 320.0 Hz), 111.8 (d, *J* = 245.8 Hz), 111.55, 111.50, 55.9, 55.8, 35.4 (d, *J* = 20.0 Hz), 28.2 (d, *J* = 6.0 Hz); HRMS (EI): Calculated for $C_{12}H_{14}F_4O_5S$: 346.0498; Found:346.0499.

1-Fluoro-3-(3-(trifluoromethyl)phenyl)propyl trifluoromethanesulfonate (1e)



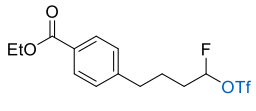
Compound **1e** (6.44 g, 91% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 1 H), 7.49 – 7.43 (m, 2 H), 7.41 – 7.36 (m, 1 H), 6.16 (dt, *J* = 54.2, 5.0 Hz, 1 H), 2.89 (t, *J* = 8.0 Hz, 2 H), 2.34 (dddd, *J* = 15.2, 7.6, 3.8, 2.0 Hz, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 (s, 3 F), -74.8 (d, *J* = 7.6 Hz, 3 F), -120.4 (dddd, *J* = 54.2, 24.4, 9.6, 7.6 Hz, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 131.6, 131.1 (q, *J* = 32.8 Hz), 129.3, 125.1 (q, *J* = 3.6 Hz), 123.8 (q, *J* = 4.2 Hz), 121.2 (q, *J* = 277.8 Hz), 118.2 (q, *J*=321.0Hz), 111.2 (d, *J* = 245.8 Hz), 35.0 (d, *J* = 20.4 Hz), 28.3 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{11}H_9F_7O_3S$: 354.0161; Found: 354.0159.

1-Fluoro-3-(4-nitrophenyl)propyl trifluoromethanesulfonate (1f)



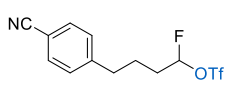
Compound **1f** (4.63 g, 70% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 2 H), 7.38 (d, *J* = 8.6 Hz, 2 H), 6.18 (dt, *J* = 54.2, 4.8 Hz, 1 H), 2.95 (t, *J* = 8.0 Hz, 2 H), 2.45 – 2.27 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.5 (d, *J* = 7.6 Hz, 3 F), -122.94 – -126.85 (m, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.2, 129.2, 124.1, 118.2 (q, *J* = 320.0 Hz), 111.0 (d, *J* = 245.8 Hz), 34.6 (d, *J* = 21.0 Hz), 28.3 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{10}H_9F_4NO_5S$: 331.0138; Found: 331.0318.

Ethyl 4-(4-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)butyl)benzoate (1g)



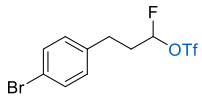
Compound **1g** (3.79 g, 51% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 30 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 6.14 (dt, *J* = 54.4, 5.0 Hz, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 2.75 (t, *J* = 7.4 Hz, 2 H), 2.06 – 1.94 (m, 2 H), 1.88 – 1.80 (m, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (d, *J* = 7.2 Hz, 3 F), -115.33 – -123.14 (m, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 145.5, 129.9, 128.8, 128.3, 118.2 (q, *J* = 319.8 Hz), 112.1 (d, *J* = 245.8 Hz), 60.9, 34.7, 32.9 (d, *J* = 20.2 Hz), 23.5 (d, *J* = 4.8 Hz), 14.34; HRMS (EI): Calculated for $C_{14}H_{16}F_4O_5S$: 372.0655; Found: 372.0646.

4-(4-Cyanophenyl)-1-fluorobutyl trifluoromethanesulfonate (1h)



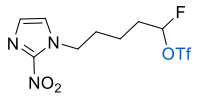
Compound **1h** (3.57 g, 55% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 10 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 6.16 (dt, *J* = 54.2, 4.8 Hz, 1 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.12 – 1.91 (m, 2 H), 1.91 – 1.78 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ-74.8 (d, *J* = 7.2 Hz, 3 F), -114.13 – -123.36 (m, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 132.4, 129.1, 118.8, 116.6 (q, *J* = 319.8 Hz), 111.8 (d, *J* = 245.8 Hz), 110.4, 34.9, 32.9 (d, *J* = 20.2 Hz), 23.4 (d, *J* = 5.0 Hz).; HRMS (EI): Calculated for $C_{12}H_{11}F_4NO_3S$: 325.0396; Found: 325.0396.

3-(4-Bromophenyl)-1-fluoropropyl trifluoromethanesulfonate (1i)



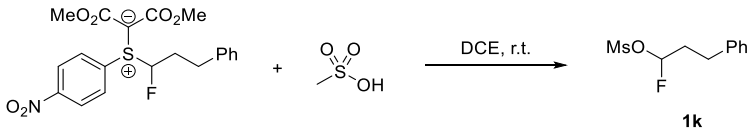
Compound **1i** (4.80 g, 66% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100/ 1). ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 (d, *J* = 8.2 Hz, 2 H), 7.08 (d, *J* = 8.2 Hz, 2 H), 6.12 (dt, *J* = 54.2, 5.0 Hz, 1 H), 2.78 (t, *J* = 7.8 Hz, 2 H), 2.29 (ddd, *J* = 14.2, 9.2, 4.6 Hz, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.8 (d, *J* = 7.6 Hz, 3 F), -118.1 – -122.2 (m, 1 F).^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 131.9, 129.9, 120.7, 116.6 (q, *J* = 329.8 Hz), 111.4 (d, *J* = 245.8 Hz), 35.0 (d, *J* = 20.2 Hz), 28.0 (d, *J* = 5.4 Hz); HRMS (EI): Calculated for $C_{10}H_9BrF_4O_3S$: 363.9392; Found: 363.9392.

1-Fluoro-5-(2-nitro-1*H*-imidazol-1-yl)pentyl trifluoromethanesulfonate (1j)



Compound **1j** (4.18 g, 60% yield) as a colorless oil was purified by flash chromatography (Petroleum ether / Ethyl acetate = 1 / 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 13.2, 1.2 Hz, 2 H), 6.14 (d, *J* = 54.2 Hz, 1 H), 4.42 (t, *J* = 7.4 Hz, 2 H), 2.09 – 1.64 (m, 4 H), 1.67 – 1.45 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.9 (d, *J* = 7.2 Hz, 3 F), -116.44 – -121.19 (m, 1 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 128.4, 126.1, 118.0 (q, *J* = 320.0 Hz), 111.80 (d, *J* = 245.6 Hz), 49.7, 32.9 (d, *J* = 20.4 Hz), 29.7, 19.2 (d, *J* = 4.8 Hz); HRMS (EI): Calculated for $C_9H_{11}F_4N_3O_5S$: 349.0356; Found: 349.0357.

1-Fluoro-3-phenylpropyl methanesulfonate (1k)

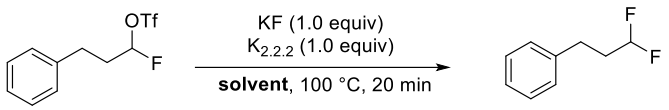


Compound **1k** was a known compound.[5]

Methanesulfonic acid (130 μL, 2.0 mmol, 1.0 equiv.) was dissolved in 5.0 mL of 1,2-dichloroethane and added to a 50 mL round-bottom flask containing monofluoroalkylated sulfonium ylide (1.0 g, 2.4 mmol, 1.2 equiv.). The mixture was then stirred at room temperature for 0.5 h. The organic phase was concentrated, and the residue was purified by flash column chromatography to give the **1k** (234.7mg, 50.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 5 H), 6.06 (dt, *J* = 58.0, 5.1 Hz, 1 H), 3.12 (s, 3 H), 2.78 (t, *J* = 7.9 Hz, 2 H), 2.31 – 2.11 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.08 (dt, *J* = 58.0, 16.7 Hz).

3. Optimization of the Reaction Conditions

Table S1. Solvent effect on the reaction.[a]

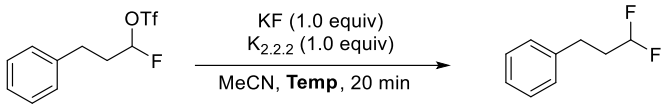


1a (1.0 equiv) **2a**

Entry	solvent	Yield, 2a (%)[b]
1	DMSO	11
2	CH_3CN	49

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), KF (0.2 mmol, 1.0 equiv), $K_{2.2.2}$ (0.2 mmol, 1.0 equiv), Solvent (2.0 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

Table S2. Effect of the reaction temperature on the reaction.[a]

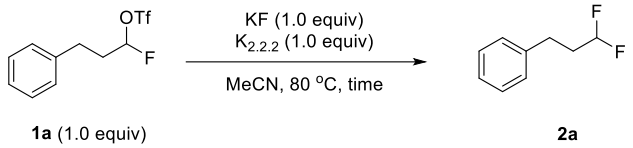


1a (1.0 equiv) **2a**

Entry	T (°C)	Yield, 2a (%)[b]
1	70	48
2	80	64
3	100	49
4	110	35

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), KF (0.2 mmol, 1.0 equiv), $K_{2.2.2}$ (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

Table S3. Effect of the reaction time on the reaction.[a]

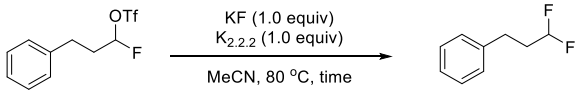


1a (1.0 equiv) **2a**

Entry	Time (min)	Yield, 2a (%)[b]
1	10	54
2	20	64
3	25	64

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), KF (0.2 mmol, 1.0 equiv), $K_{2.2.2}$ (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

Table S4. Screening of the loading amount of 1a on the reaction.[a]

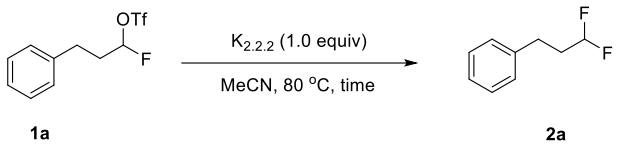


1a (x equiv) **2a**

Entry	x (equiv)	Yield, 2a (%)[b]
1	1.0	64
2	2.0	93
3	3.0	97

[a]Reaction conditions (unless otherwise specified): **1a** (x equiv), KF (0.2 mmol, 1.0 equiv), $K_{2.2.2}$ (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

Table S5. The stability experiment of 1a under the optimized reaction conditions.[a]

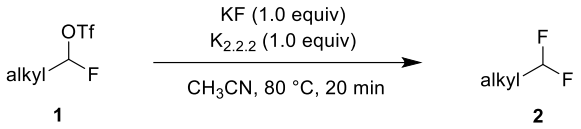


1a 2a

Entry	Remain, 1a (%)[b]	Yield, 2a (%)[b]
1	62%	5

[a]Reaction conditions: **1a** (1.0 equiv), $K_{2.2.2}$ (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

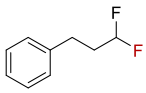
4. General Procedure for the Preparation of Compounds 2 and Their Characterization Data.



1 2

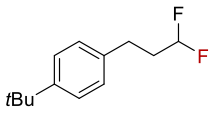
To a 25 mL Schlenk tube, KF (0.5 mmol, 1.0 equiv) and K2.2.2 (0.5 mmol, 1.0 equiv) were added in the glove box. The reaction mixture was evacuated and backfilled with Ar (3 times). Compound **1** (1.0 mmol, 2.0 equiv) and CH_3CN (5.0 mL) were added. The tube was screw-capped, and the reaction was stirred for 20 min at 80 ºC. The resulting mixture was quenched with saturated NH_4Cl and diluted with ethyl acetate. The aqueous phase was washed with ethyl acetate (3×10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the pure product **2**.

(3,3-Difluoropropyl)benzene (2a)



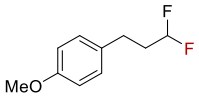
Compound **2a** (71 mg, 91% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^1H NMR (400 MHz, CDCl3) δ 7.36 – 7.28 (m, 2 H), 7.27 – 7.18 (m, 3 H), 5.81 (tt, J = 56.6, 4.6 Hz, 1 H), 2.79 (t, *J* = 7.8 Hz, 2 H), 2.25 – 2.07 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (dt, *J* = 56.6, 17.2 Hz, 2 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.6, 128.3, 126.4, 116.7 (t, *J* = 239.0 Hz), 35.6, 28.4 (d, *J* = 6.0 Hz); HRMS (EI): Calculated for $C_9H_{10}F_2$: 156.0751; Found: 156.0749.

1-(*tert*-Butyl)-4-(3,3-difluoropropyl)benzene (2b)



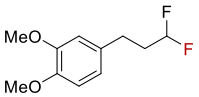
Compound **2b** (83 mg, 78% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 6.4 Hz, 2 H), 7.16 (d, J = 6.0 Hz, 2 H), 5.83 (ttd, J = 56.8, 4.6, 2.2 Hz, 1 H), 2.77 (ddd, J = 8.4, 6.8, 2.2 Hz, 2 H), 2.26 – 2.07 (m, 2 H), 1.34 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.1 (dtd, J = 56.6, 17.2, 4.0 Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 136.8, 128.0, 125.5, 116.8 (t, J = 238.8 Hz), 35.6 (t, J = 21.2 Hz), 34.4, 31.3, 27.8; HRMS (EI): Calculated for $C_{13}H_{18}F_2$: 212.1377; Found: 212.1366.

1-(3,3-Difluoropropyl)-4-methoxybenzene (2c)



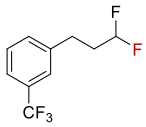
Compound **2c** (82 mg, 88% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.13 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.80 (ttd, J = 56.6, 4.6, 2.0 Hz, 1 H), 3.81 (s, 3 H), 2.74 (t, J = 8.0 Hz, 2 H), 2.22 – 2.04 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.1 (dd, J = 56.6, 3.4 Hz, 2 F).^{13} C NMR (101 MHz, $CDCl_3$) δ 158.2, 131.9, 129.2, 116.8 (t, J = 238.8 Hz), 114.0, 55.2, 35.8 (d, J = 21.0 Hz), 27.5; HRMS (EI): Calculated for $C_{10}H_{12}F_2O$: 186.0856; Found: 186.0855.

4-(3,3-Difluoropropyl)-1,2-dimethoxybenzene (2d)



Compound **2d** (81 mg, 75% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 8.2 Hz, 1 H), 6.77 – 6.67 (m, 2 H), 5.80 (tt, J = 56.6, 4.6 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 2.80 – 2.69 (m, 2 H), 2.22 – 2.04 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (dt, J = 57.0, 17.0 Hz, 2 F).^{13} C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.6, 132.5, 120.1, 116.7 (t, J = 238.4 Hz), 111.6, 111.4, 55.9, 55.8, 35.7 (d, J = 21.0 Hz), 28.0; HRMS (EI): Calculated for $C_{11}H_{14}F_2O_2$: 216.0962; Found: 216.0955.

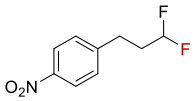
1-(3,3-Difluoropropyl)-3-(trifluoromethyl)benzene (2e)



Compound **2e** (106 mg, 95% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 –

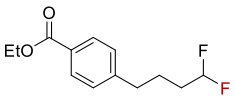
7.29 (m, 4 H), 5.82 (tt, *J* = 56.6, 4.4 Hz, 1 H), 2.89 – 2.80 (m, 2 H), 2.25 – 2.07 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6(s, 3 F), -117.2 (d, *J* = 56.6 Hz, 2 F).^{13} C NMR (101 MHz, $CDCl_3$) 140.8, 131.7, 131.0 (q, *J* = 32.2 Hz), 129.1, 125.0 (q, *J* = 4.0 Hz), 124.0 (q, *J* = 272.2 Hz), 123.3 (q, *J* = 4.0 Hz), 116.3 (t, *J* = 239.4 Hz), 35.4 (t, *J* = 21.2 Hz), 28.1 (t, *J* = 6.0 Hz); HRMS (EI): Calculated for $C_{10}H_9F_5$: 224.0624; Found: 224.0615

1-(3,3-Difluoropropyl)-4-nitrobenzene (2f)



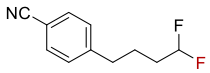
Compound **2f** (86 mg, 86% yield) was purified by flash chromatography was purified by flash chromatography (Petroleum ether / Ethyl acetate = 20 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 2 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 5.86 (tt, *J* = 56.2, 4.2 Hz, 1 H), 2.96 – 2.87 (m, 2 H), 2.28 – 2.10 (m, 2 H).^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (d, *J* = 56.6 Hz, 2 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 147.6, 146.8, 129.2, 123.9, 116.0 (t, *J* = 239.8 Hz), 35.0 (t, *J* = 21.2 Hz), 28.1 (t, *J* = 6.0 Hz); HRMS (EI): Calculated for $C_9H_9F_2NO_2$: 201.0601; Found: 201.0995.

Ethyl 4-(4,4-difluorobutyl)benzoate (2g)



Compound **2g** (91 mg, 75% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 30 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 5.81 (tt, *J* = 56.4, 3.8 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 2.73 (t, *J* = 7.2 Hz, 2 H), 1.93 – 1.77 (m, 4 H), 1.39 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.0 (dt, *J* = 56.6, 17.0 Hz, 2 F). ^{13} C NMR (101 MHz, $CDCl_3$) δ 166.5, 146.5, 129.8, 128.5, 128.3, 117.0 (t, *J* = 239.2 Hz), 60.8, 35.1, 33.4 (t, *J* = 21.0 Hz), 23.3 (d, *J* = 5.4 Hz), 14.3; HRMS (EI): Calculated for $C_{13}H_{16}F_2O_2$: 242.1118; Found: 242.1109.

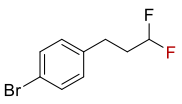
4-(4,4-Difluorobutyl)benzonitrile (2h)



Compound **2h** (75 mg, 77% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 10 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 6.0 Hz, 2 H), 6.10 – 5.43 (m, 1 H), 2.70 (t, *J* = 7.2 Hz, 2 H), 1.82 (ddd, *J* = 30.6, 10.0, 4.6 Hz, 4 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.0 (dt, *J* = 56.6, 17.0

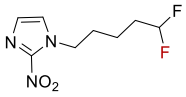
Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 132.3, 129.1, 118.9, 116.85 (t, *J* = 240.2 Hz), 110.1, 35.2, 33.3 (t, *J* = 21.0 Hz), 23.1; HRMS (EI): Calculated for $C_{11}H_{11}F_2N$: 195.0860; Found: 195.0858.

1-Bromo-4-(3,3-difluoropropyl)benzene (2i)



Compound **2i** (107 mg, 92% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 100 / 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.01 – 5.58 (m, 1 H), 2.73 (t, *J* = 8.2 Hz, 2 H), 2.18 – 1.96 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (dt, *J* = 56.6, 17.2 Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 131.7, 130.0, 120.2, 116.4 (t, *J* = 239.2 Hz), 35.4 (t, *J* = 21.2 Hz), 27.8; HRMS (EI): Calculated for $C_9H_9BrF_2$: 233.9856; Found: 233.9856.

1-(5,5-Difluoropentyl)-2-nitro-1*H*-imidazole (2j)



Compound **2j** (61 mg, 56% yield) was purified by flash chromatography (Petroleum ether / Ethyl acetate = 1/ 1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.12 (dd, *J* = 28.2, 1.2 Hz, 2 H), 5.82 (tt, *J* = 56.6, 4.2 Hz, 1 H), 4.43 (t, *J* = 7.2 Hz, 2 H), 1.95 – 1.87 (m, 4 H), 1.64 – 1.48 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.5 (dt, *J* = 56.6, 17.2 Hz, 2 F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.5, 125.8, 116.6 (t, *J* = 239.2 Hz), 49.9, 33.3 (t, *J* = 21.2 Hz), 30.0, 18.9; HRMS (EI): Calculated for $C_8H_{11}F_2N_3O_2$: 219.0819; Found: 219.0818.

5. Radiochemistry

5.1 General Information

^{18}F-H_2O was obtained from Fudan University Shanghai Cancer Center. [^{18}F]fluoride anion dissolved in ultrapure water was produced by the ^{18}O(p,n)18F nuclear reaction in a Siemens RDS-112 cyclotron (Siemens CTI RDS Eclips ST, Knoxville, TN) at 11 MeV using a 1 mL tantalum target with a Havar foil. QMA-light Sep-Paks cartridges were purchased from Waters Corporation and were preconditioned with 10 mL ethanol, followed by 10 mL of water before use. C-18 Sep-Paks columns were purchased from Waters Corporation and were preconditioned with 10 mL ethanol, then 10 mL water. Glass-backed thin-layer chromatography (TLC) plates coated with silica gel 60 F254 were used for radio-TLC analysis and were purchased from Merck. Radio TLC analysis was performed using a Bioscan Mini-Scan TLC Scanner (Eckert & Ziegler). The crude radiolabeled product was separated by HPLC on an UltiMate 3000 system (Thermo Fisher Scientific, USA) equipped with a Bioscan Flow-Count radio HPLC detector (Eckert & Ziegler) under the following conditions: Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, acetonitrile in ammonium formate buffer (0.1 M, pH = 4.5) as mobile phase, the flow rate at 2.5 mL/min, UV wavelength at 254 nm and 220 nm. The data were recorded and processed using a Chromatography Data System (Thermo Fisher Scientific, USA) to determine the radiochemical conversion. The activities of [^{18}F] radiolabeled samples were determined using a radioisotope dose calibrator CRC-55tR (Capintec Inc.).

5.2 Preparation of [^{18}F]Radiolabeling Reagents

[^{18}F]KF/K2.2.2 solution

For a typical run, [^{18}F]Fluoride (3.0 – 3.5 GBq) produced by cyclotron was trapped into a Sep-PAK®light QMA cartridge (pre-rinse with 10 mL ethanol and 10 mL water for activation) and then was released with a 0.3 mL of the aqueous solution of a K_2CO_3 (3 - 4 mg) into a small vessel, followed by the addition of 1 mL of acetonitrile containing kryptofix 222($K_{2.2.2}$, 16 mg) to get [^{18}F]KF/$K_{2.2.2}$ solution. The solution was dried with three cycles of azeotropic drying with MeCN (3 x 1 mL) under a flow of N_2 at 110 ℃ and redissolved in MeCN.

Preparation of [^{18}F] TBAF.

[^{18}F]Fluoride (1.0 – 1.4 GBq) produced by cyclotron was trapped into a Sep-PAK®light QMA cartridge (pre-rinse with 10 mL ethanol and 10 mL water for activation) and then was released with 0.3 mL of the solution (7-8 mg of $TBAClO_4$ dissolved in 100 µL MeCN and 200 µL water), followed by the addition of 1 mL of acetonitrile to get [^{18}F]TBAF solution. The solution was dried with three cycles of azeotropic drying with MeCN (3 x 1 mL) under a flow of N_2 at 110 ℃ and redissolved in MeCN.

Preparation of [^{18}F]TEAF.

[^{18}F]Fluoride (1.0 – 1.4 GBq) produced by cyclotron was trapped into a Sep-PAK®light QMA cartridge (pre-rinse with 10 mL ethanol and 10 mL water for activation) and then was released with 0.3 mL of the solution (7-8 mg of TEAOTf dissolved in 100 µL MeCN and 200 µL water), followed by the addition of 1 mL of acetonitrile to get [^{18}F]TEAF solution. The solution was dried with three cycles of azeotropic drying with MeCN (3 x 1 mL) under a flow of N_2 at 110 ℃ and redissolved in MeCN.

5.3 Determinations of Radiochemical Conversion (RCC) and Radiochemical Yield (RCY)

TLC RCC

After the radiolabeling reaction, a single drop of the reaction mixture was spotted on the TLC plate. Then, the plate was developed by a mixture of hexane and ethyl acetate (1:1). The TLC analysis was performed using a Bioscan Mini-Scan TLC Scanner (Ekert and Ziegler). The TLC RCC yield was calculated by integrating the free ^{18}F ion and the corresponding product.

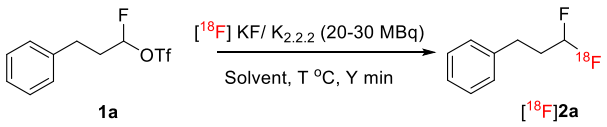
Isolation yield (RCY)

100 - 200 µL of the crude reaction mixture (typically 18.5 - 33.3 MBq) for radio-HPLC analysis. The fraction was collected by an automatic fraction collector. The activity injected into the HPLC was measured (denoted as A), and the injection time was recorded. The fraction corresponding to the radiolabeled product was collected, and the activity was measured (this activity was denoted by B). The decay-corrected RCY was calculated by dividing the decay-corrected B by A. The activities of

[^{18}F] radiolabeled samples were determined using a radioisotope dose calibrator CRC-55tR (Capintec Inc.).

5.4 Optimization of Radiofluorination Conditions

Optimizations for [^{18}F]radiolabeling fluorination.

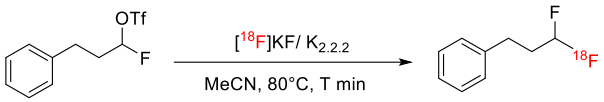


1a [^{18}F]**2a**

Compound **1a** (5 mg) was dissolved in 0.3 mL solvent and transferred into a 5 mL V-glass vial. And then, 200 μL K^{18}F/$K_{2.2.2}$ complex solution (200-300 MBq) was added to the vial. The reaction vial was sealed and heated at T ℃ for Y min. After the reaction, the mixture was cooled to room temperature, and a single drop of the solution was spotted on the TLC plate. Then, the plate was developed by a mixture of hexane and ethyl acetate (1:1). The TLC analysis was performed using a Bioscan Mini-Scan TLC Scanner (Ekert and Ziegler). Finally, the RCC yield was calculated by integrating the free ^{18}F ion and the corresponding product. The reaction mixture was loaded into a semi-prep HPLC column (Agilent Eclipse SB-C18, 5 μm, 9.4 × 250 mm) if needed. Purification was achieved with 2.5 mL/min flow, eluting the column with 70% acetonitrile and 30% ammonium formate buffer (0.1 M, pH = 4.5) and (3-fluoro-3-(fluoro-^{18}*F*)propyl)benzene([^{18}F]**2a**) was collected.

(The RCC yield and RCY yield were calculated by Section 5.3: Determinations of radiochemical conversion (RCC) and radiochemical yield (RCY))

Table S6. Effect of the reaction time on the [^{18}F]-radiolabeling fluorination.[a]

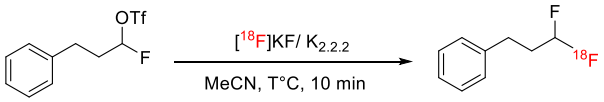


1a [^{18}F]2a

Entry	Time (min)	RCC (%)[b]
1	10	86±5 %
2	20	56±6%

[a]Reaction conditions (unless otherwise specified): **1a** (5 mg), [^{18}F]KF/$K_{2.2.2}$ (200-300 MBq), CH_3CN (0.3 mL)，80 ^{o}C. [b]n = 3.

Table S7. Effect of the reaction temperature on the reaction.[a]

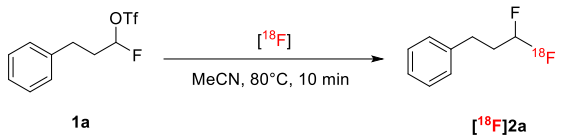


1a [^{18}F]2a

Entry	T (^{o}C)	RCC(%)[b]
1	80	86±5 %
2	90	53±5%

[a]Reaction conditions (unless otherwise specified): **1a** (5 mg), [^{18}F]KF/$K_{2.2.2}$ (200-300 MBq), CH_3CN (0.3 mL). [b]n = 3.

Table S8. Effect of the [^{18}F]-source on the reaction.[a]



1a [^{18}F]2a

Entry	^{18}F$^-$ source	RCC (%)[b]
1	[^{18}F]KF/K_{222}	86±5%
2[c]	[^{18}F]TBAF	20±6%
3[d]	[^{18}F]TEAF	32±5%

[a]Reaction conditions (unless otherwise specified): **1a** (5 mg), [^{18}F]KF/$K_{2.2.2}$ (200-300MBq), CH_3CN (0.3 mL). [b] n=3. [c][^{18}F]TBAF (200-300 MBq). [d] [^{18}F]TEAF (200-300 MBq).

5.5 Molar Activity Calculation

The molar activity of [^{18}F]**2a** was determined as follows. A higher dose of radiolabeling reaction was conducted and purified by a semi-prep HPLC column (Agilent Eclipse SB-C18, 5 μm, 9.4 × 250 mm). 100 μL of the isolated solution was analyzed by HPLC under the following conditions: Agilent Eclipse XDB-C18, 5 μm, 4.6 × 250 mm, 70% acetonitrile in ammonium formate buffer (0.1 M, pH = 4.5) as mobile phase, the flow rate at 2.5 mL/min, UV wavelength at 254 and 220 nm. The injected activity was determined in a Capintec dose calibrator. The area of the UV peak (254 nm) corresponding to [^{18}F] **2a** (tR ~9 min) was determined. The mass of **2a** in the sample was then determined by linear regression analysis against a standard curve generated from the injection of identical volumes of solutions of known concentration of **2a**. Division of the radioactivity for [^{18}F]**2a** (GBq) by the molar of the product (mol) gives the end of synthesis (EOS) molar activity (Ci/mmol).

The purified [^{18}F]**2a** (28.4 MBq) was injected into the HPLC, and the area of the UV peak (254 nm) corresponding to [^{18}F] **2a** (tR ~9 min) measured is 1.70. According to the standard calibration curve for **2a**, 0.3026 μg of **2a** was injected into the HPLC. According to the equation, the molar activity is 14.64 GBq/μmol at the end of synthesis (EOS).

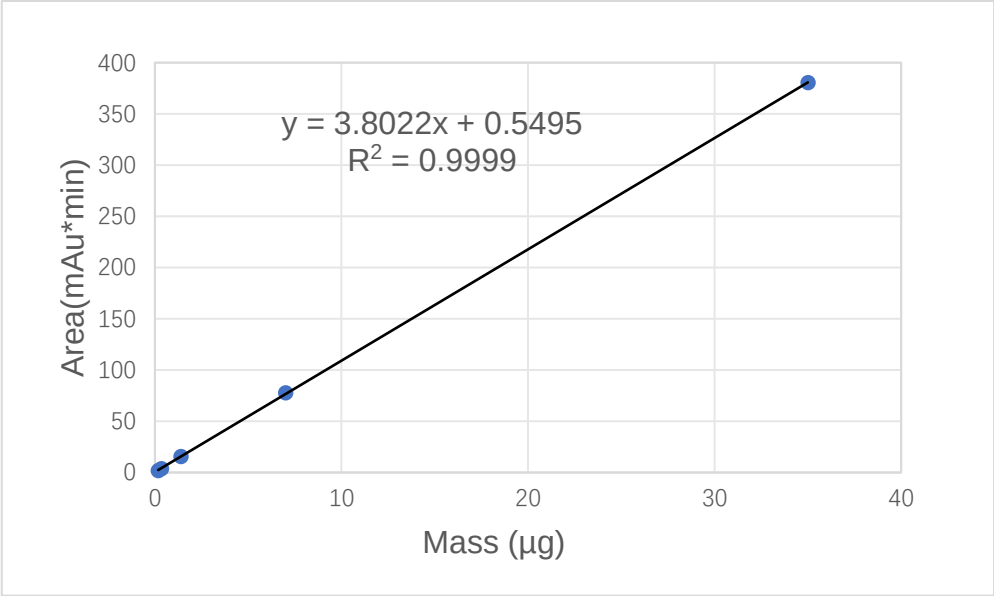
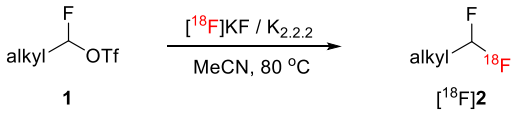


Figure S2. HPLC Calibration curve for **2a**.

5.6 General Procedure for Radiolabeling Fluorination



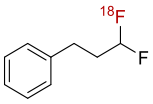
1 [18F]**2**

Note: The radiolabeling experiment was conducted manually within the hot cell.

A precursor **1** (5- 6 µmol) dissolved in 300 µL of MeCN was added to the reaction vial. Then, 200 µL $K^{18}F$ /$K_{2.2.2}$ solution (200 – 300 MBq) was transferred to the reaction vial. The reaction was kept at 80 ℃ for 10 min. After the radiolabeling reaction, a single drop of the reaction mixture was spotted on the TLC plate. Then, the plate was developed by a mixture of hexane and ethyl acetate (1:1). The TLC analysis was performed using a Bioscan Mini-Scan TLC Scanner (Ekert and Ziegler) to get the RCC yield. If needed, the reaction solution was injected into the HPLC for further analysis to get the RCY yield. HPLC conditions: Acetonitrile was used in an ammonium formate buffer (0.1 M, pH 4.5). Flow rate: 2.5 mL/min. UV1: 254 nm, UV2:220 nm. ***Note:*** The retention time for the UV peak was about 0.2-0.5 min earlier than that of the radioactive peak. The tubing distance between our UV and radiation detectors is about 50 cm.

5.7 Radio-HPLC Analysis and Characterization for Difluoromethyl Derivatives

[^{18}F] (3,3-Difluoropropyl)benzene ([^{18}F]2a)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 9.723 min; HPLC UV-trace(black): tR= 9.519 min.

TLC RCC Yield = 86 ± 5% (n=3), RCY Yield = 46 ± 5% (n =3).

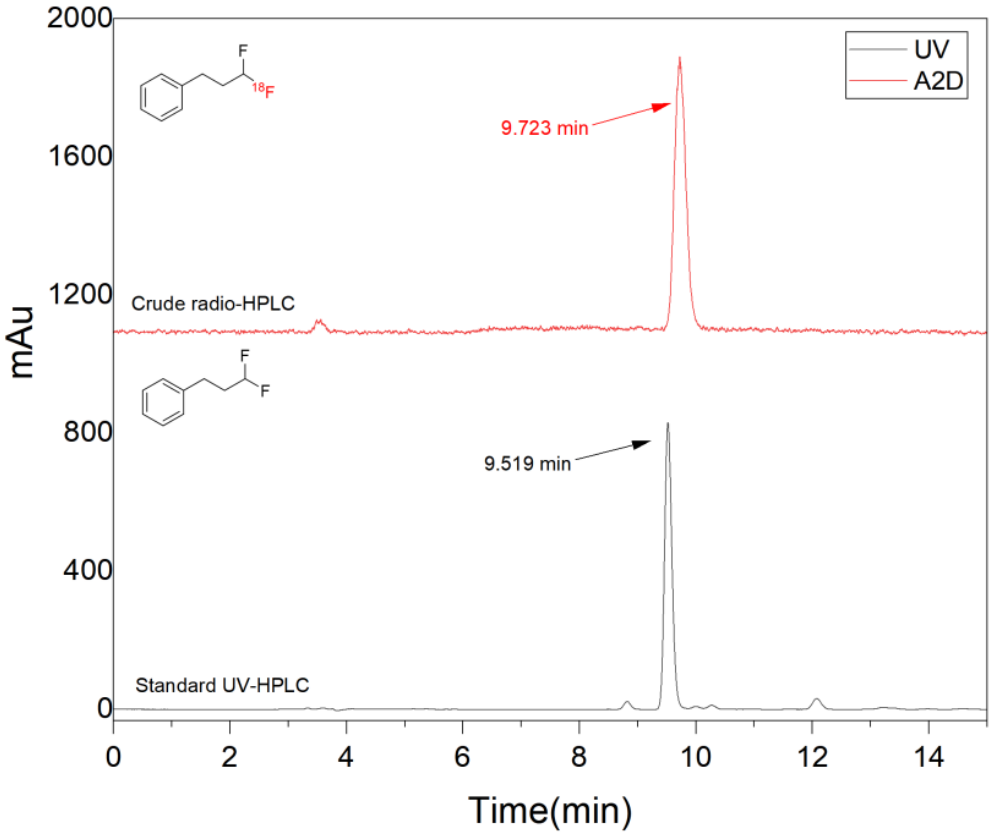
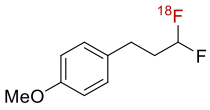


Figure S3 : HPLC spectrogram of [^{18}F]**2a** and **2a**

[^{18}F] 1-(3,3-Difluoropropyl)-4-methoxybenzene ([^{18}F]2c)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 9.330 min; HPLC UV-trace(black): tR= 8.965 min.

TLC RCC Yield = 66 ± 2% (n=3), RCY Yield = 35 ± 2% (n =3)

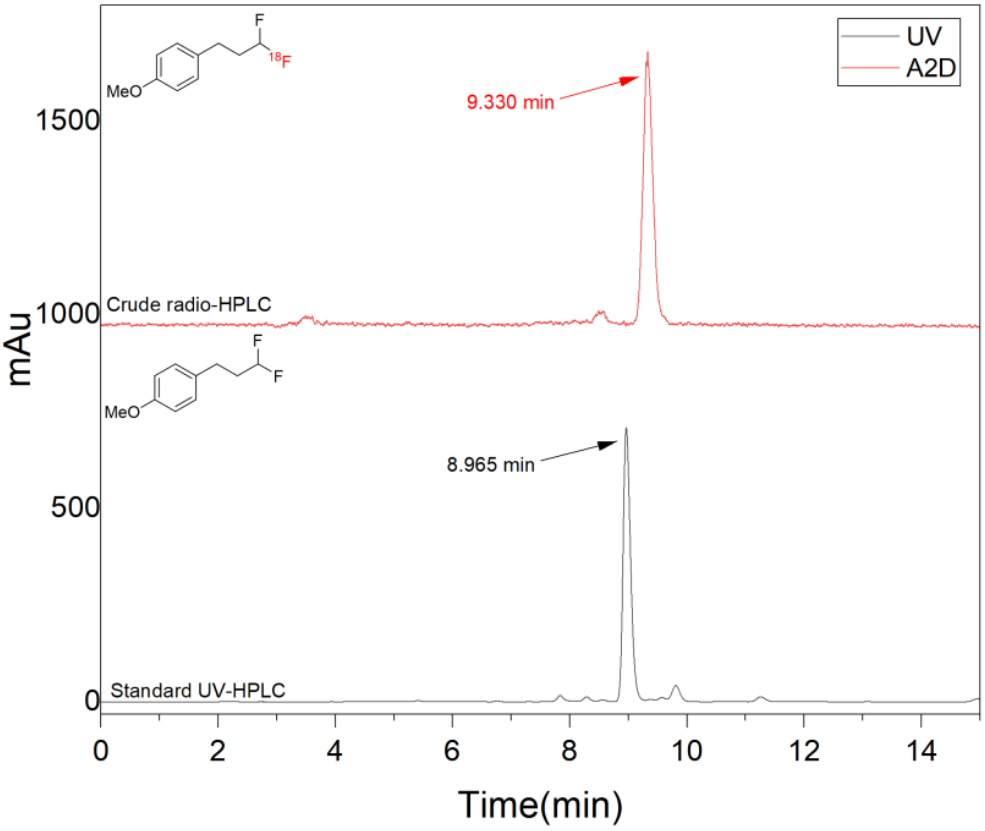
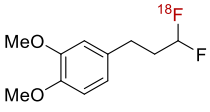


Figure S4 :HPLC spectrogram of [^{18}F]**2c** and **2c**

[^{18}F]4-(3,3-Difluoropropyl)-1,2-dimethoxybenzene ([^{18}F]2d)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 220 nm).

HPLC radio-trace(red): tR =7.357min; HPLC UV-trace(black): tR= 7.165min.

TLC RCC Yield = 75 ± 6%(n=3); RCY Yield = 38 ± 4% (n =3)

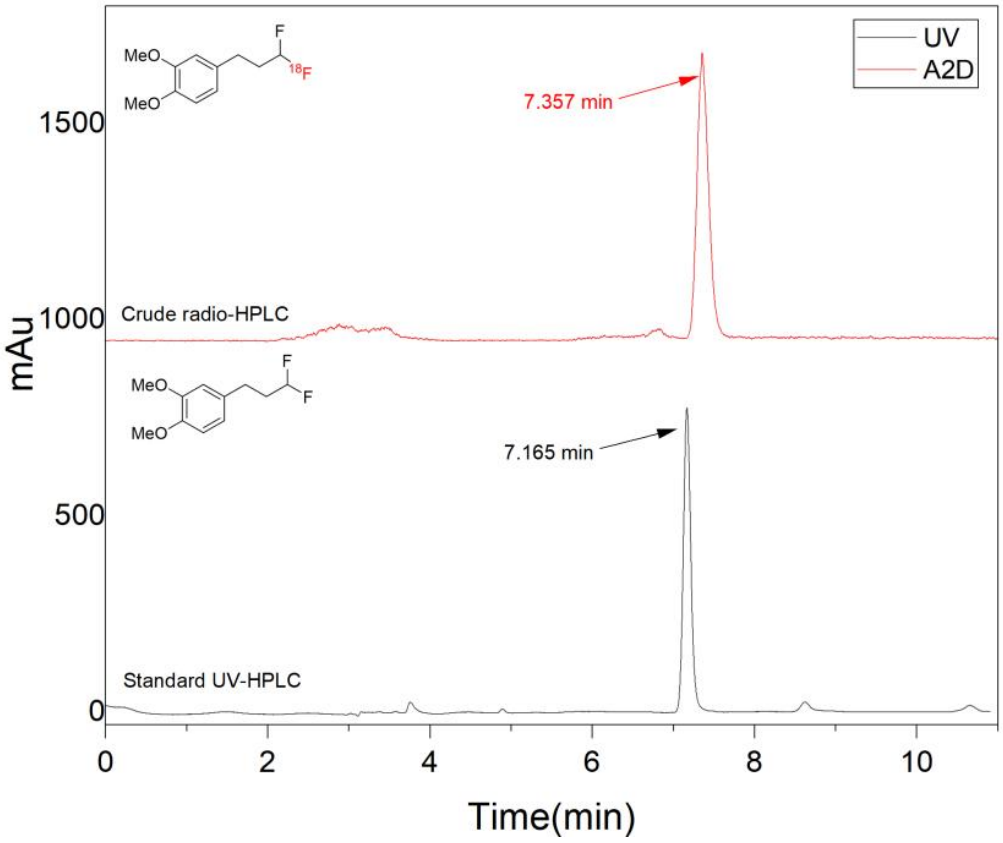
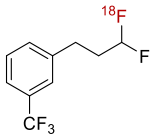


Figure S5: HPLC spectrogram of [^{18}F]**2d** and **2d**

[^{18}F] 1-(3,3-Difluoropropyl)-3-(trifluoromethyl)benzene ([^{18}F]2e)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 11.773 min; HPLC UV-trace(black): tR= 11.628 min.

TLC RCC Yield = 86 ± 5%(n=3), RCY Yield = 43 ± 2% (n =3)

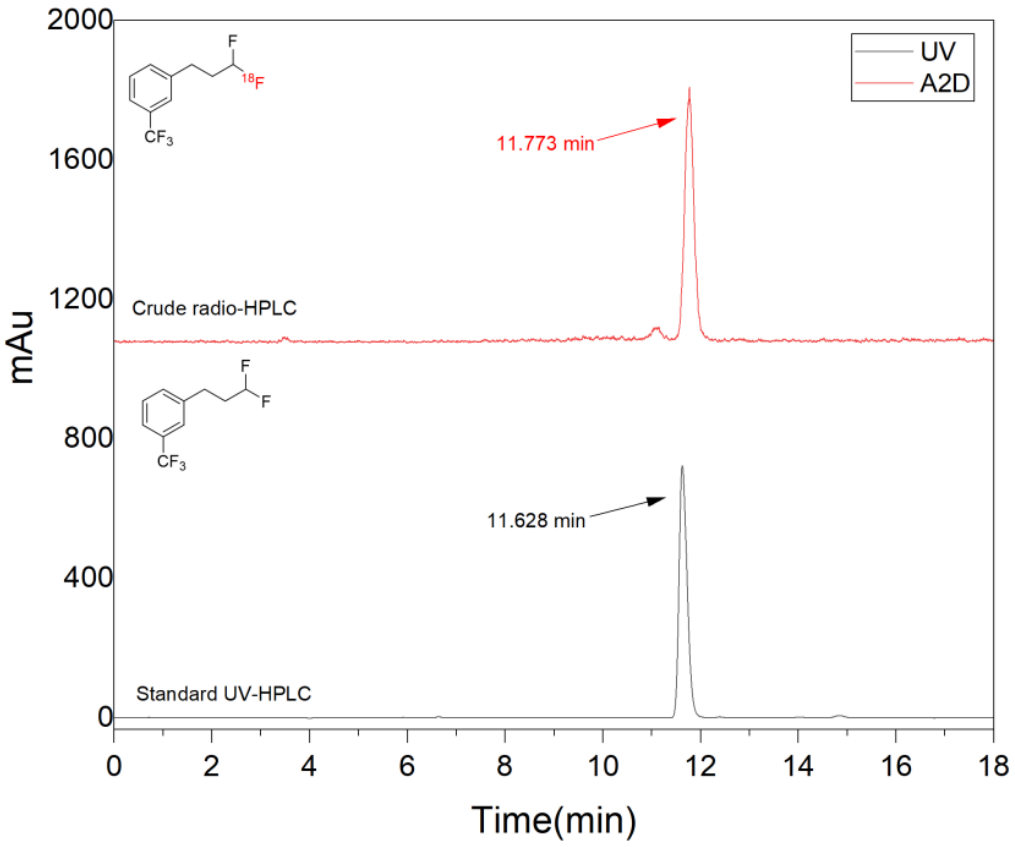
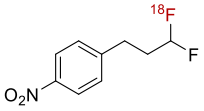


Figure S6: HPLC spectrogram of [^{18}F]**2e** and **2e**

[^{18}F] 1-(3,3-Difluoropropyl)-4-nitrobenzene ([^{18}F]2f)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 8.110 min; HPLC UV-trace(black): tR=7.982 min.

TLC RCC Yield = 88 ± 5%(n=3); RCY Yield = 49 ± 4% (n =3)

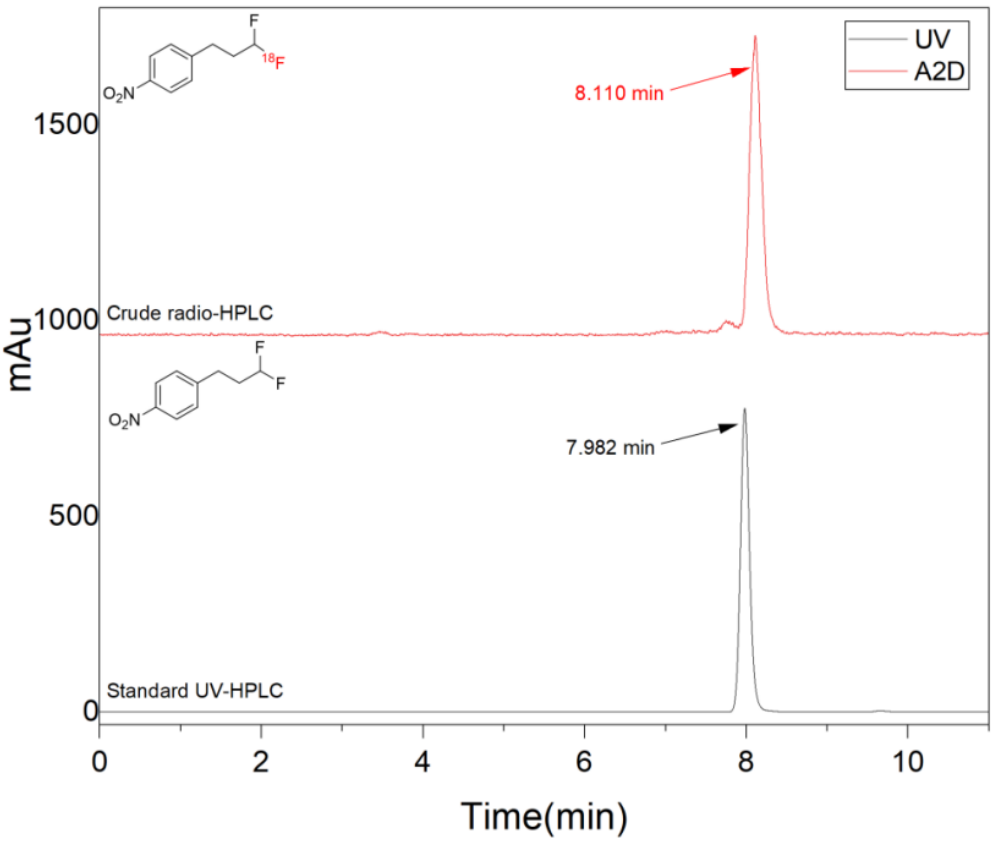
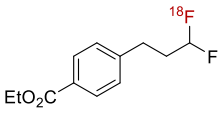


Figure S7 :HPLC spectrogram of [^{18}F]**2f** and **2f**

[^{18}F]Ethyl 4-(4,4-difluorobutyl)benzoate ([^{18}F]2g)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 13.303 min; HPLC UV-trace(black): tR= 12.848 min.

TLC RCC Yield = 75 ± 4%(n=3), RCY Yield = 41 ± 3% (n =3)

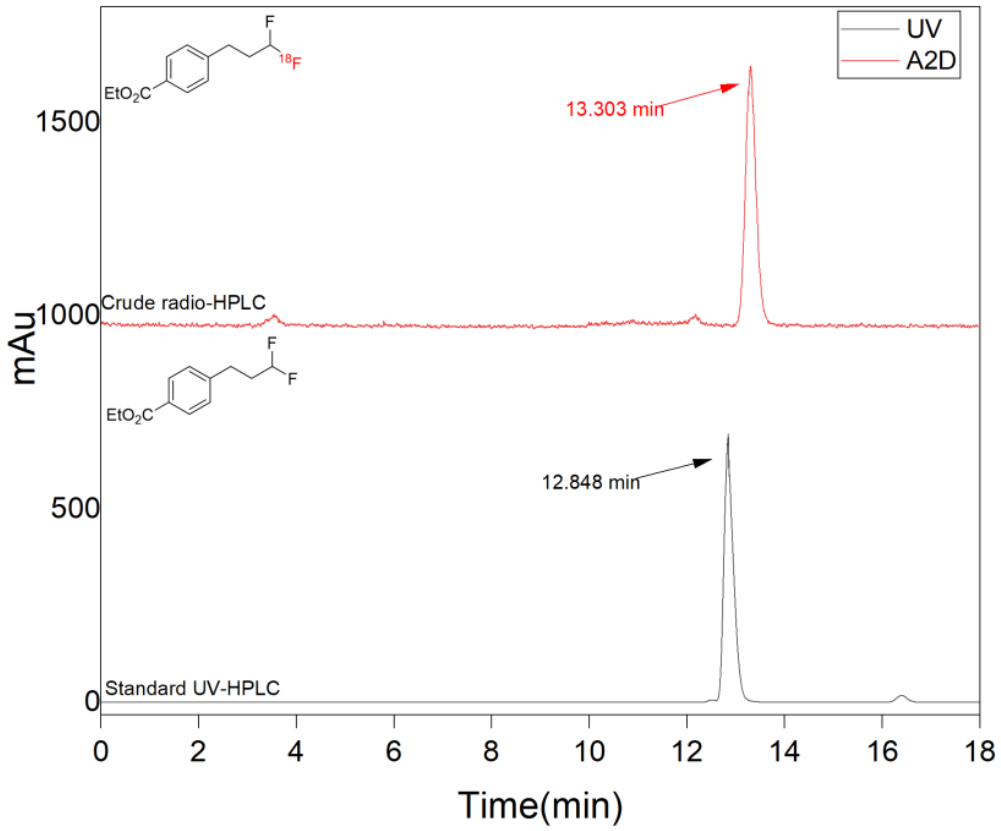
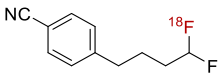


Figure S8: HPLC spectrogram of [^{18}F]**2g** and **2g**

[^{18}F]4-(4,4-Difluorobutyl)benzonitrile ([^{18}F]2h)



HPLC conditions (Agilent Eclipse SB C18, 5 µm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 8.318 min; HPLC UV-trace(black): tR= 8.086 min.

TLC RCC Yield = 60 ± 3%(n=3), RCY Yield = 36 ± 5% (n =3)

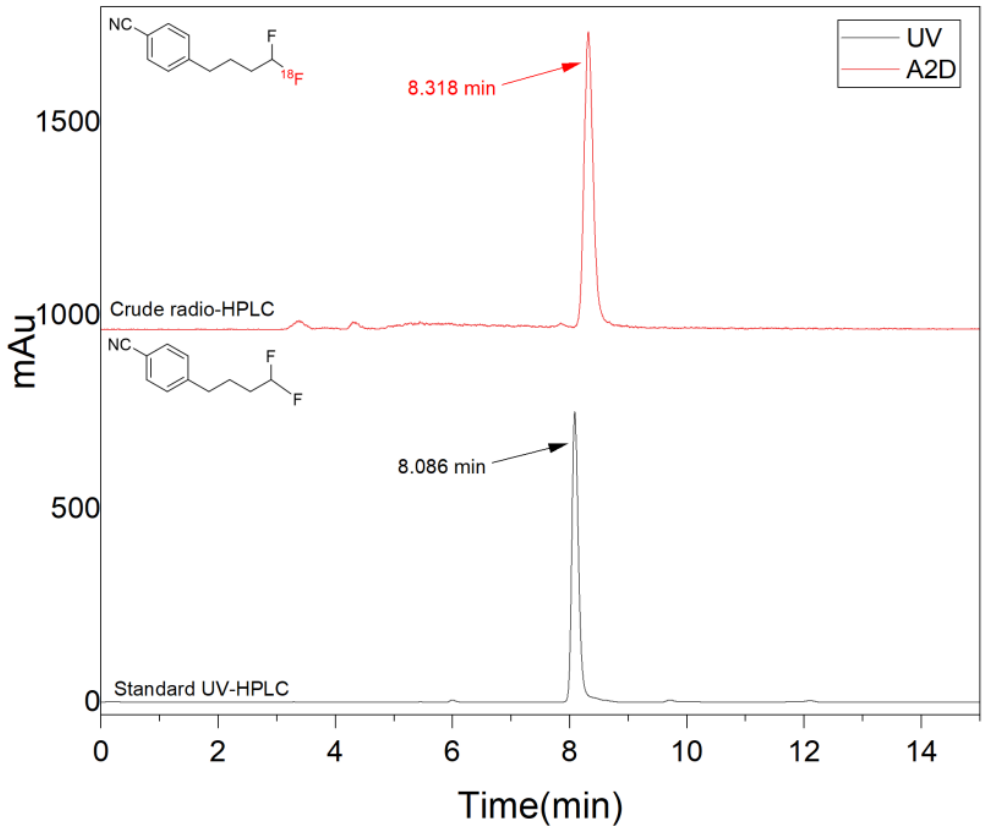
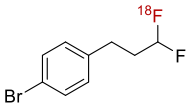


Figure S9: HPLC spectrogram of [^{18}F]**2h** and **2h**

[^{18}F]1-Bromo-4-(3,3-difluoropropyl)benzene ([^{18}F]2i)



HPLC conditions (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 13.807 min; HPLC UV-trace(black): tR= 13.402 min.

TLC RCC Yield = 45 ± 3%(n=3), RCY Yield = 26 ± 2% (n =3)

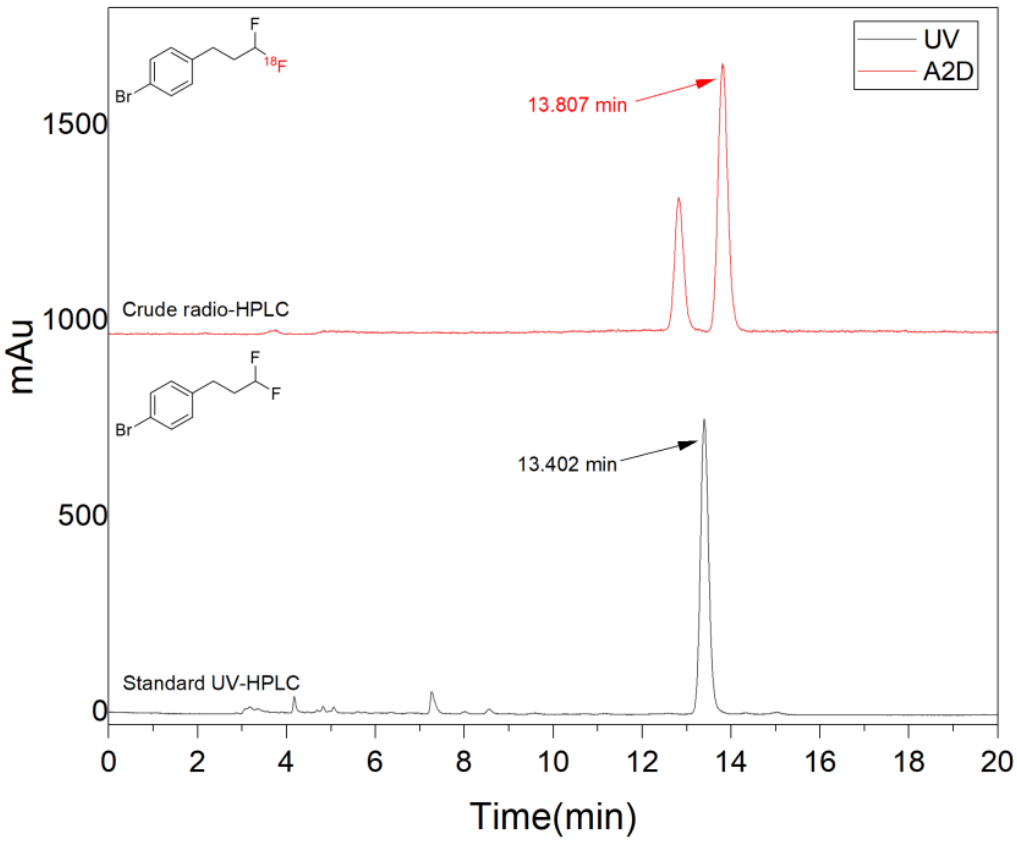


Figure S10: HPLC spectrogram of [^{18}F]**2i** and **2i**

[^{18}F]1-(5,5-Difluoropentyl)-2-nitro-1H-imidazole ([^{18}F]2j)

HPLC conditions (Agilent Eclipse SB C18, 5 µm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 50/50, flow rate = 2.5 mL/min, λ = 254 nm).

HPLC radio-trace(red): tR = 9.188 min; HPLC UV-trace(black): tR= 8.978 min.

TLC RCC Yield = 87 ± 5%(n=3), RCY Yield = 45 ± 4% (n =3)

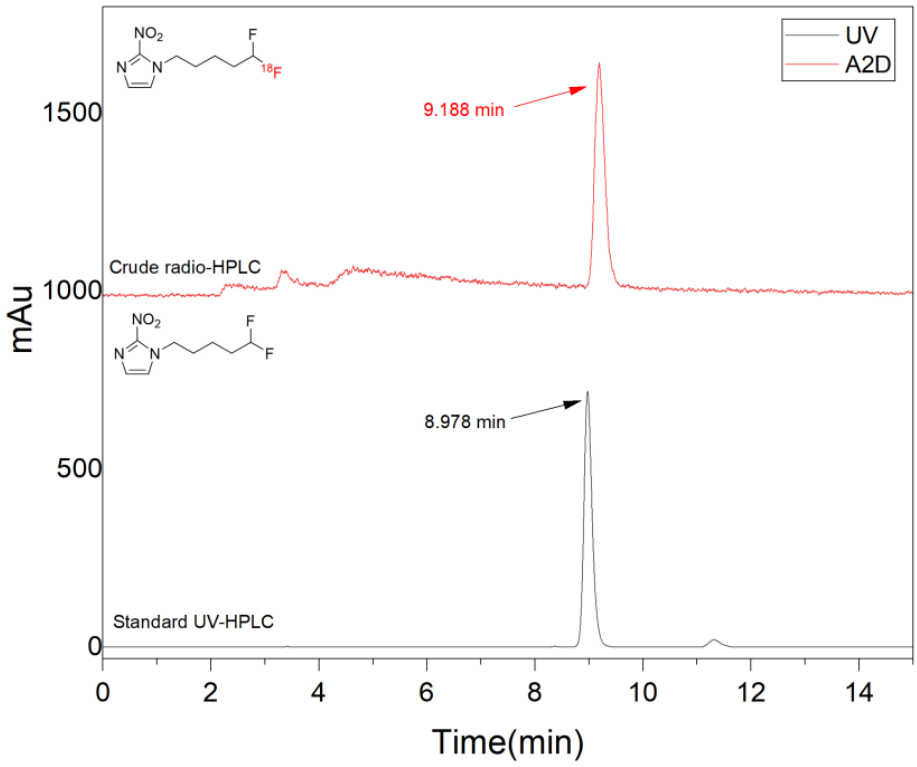
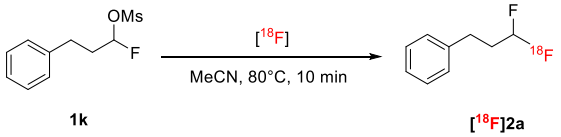


Figure S11 (HPLC spectrogram of [^{18}F]**2j** and **2j**)

6. [^{18}F]Radiolabeling fluorination of monofluoroalkyl mesylate 1k. [a]

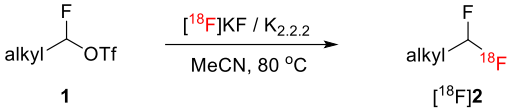


1k **[^{18}F]2a**

Entry	[^{18}F]2a (%)[b]
1[d]	nd

[a]Reaction conditions (unless otherwise specified): **1k** (5 mg), [^{18}F]KF/$K_{2.2.2}$ (200-300MBq), CH_3CN (0.3 mL). [b] n=3. nd, not detected by radio-HPLC detector system.

7. A Proposal for the automated protocol on GE TRACERlab FX2N



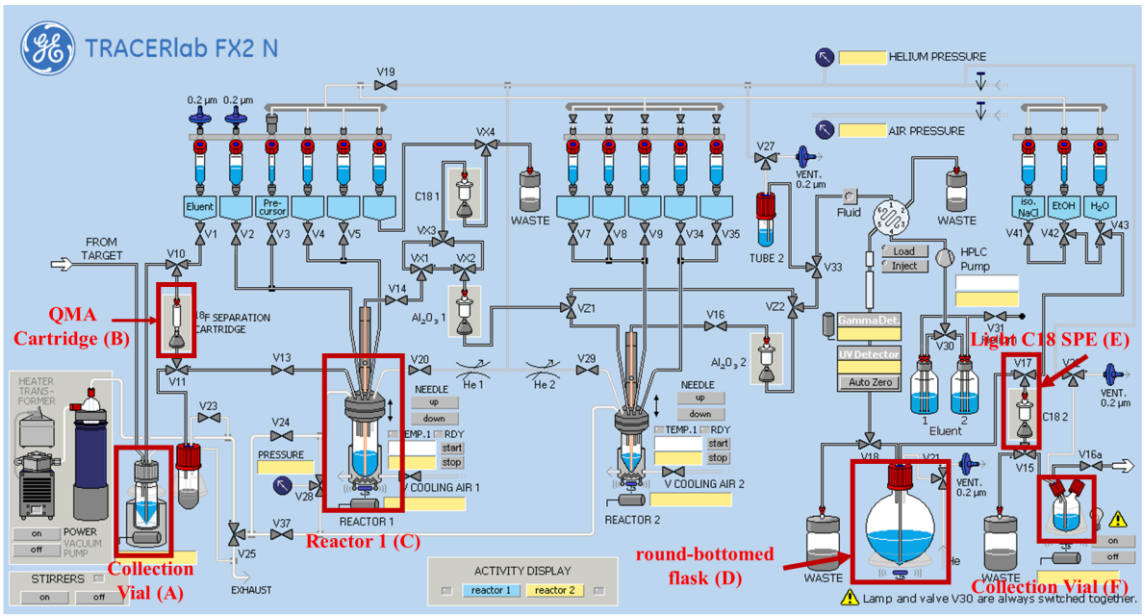


Figure S12. Schematic diagram of the TRACERlab™ FX2N radiosynthesis module

(A) Preparation for the automation

Before delivering [^{18}F]F$^-$ to the TRACERlab™ FX2N synthesis module, each vial is filled with the appropriate solvents and/or reagents. Vial 1 is filled with 3.0 mg of K_2CO_3 dissolved in 0.3 mL of water and 1 mL of acetonitrile. Vial 2 is filled with 16 mg Kryptofix 222 in 1 mL acetonitrile. Vial 3 is loaded with 5 mg of the precursor **1** in 0.3 mL acetonitrile. Vial 4 is loaded with 10 mL acetonitrile. Vial 5 is filled with 1.0 mL of HPLC eluent, which consists of 0.1 M aqueous ammonium formate. Vial 41 is filled with 9.0 mL of saline; Vial 42 is filled with 1.0 mL of EtOH; Vial 43 is filled with 20.0 mL of H_2O.

A QMA cartridge (pre-rinse with 10 mL ethanol and 10 mL water for activation) is placed between vials V10 and V11. One Al_2O_3 Sep-Pak preconditioned with 10 mL of HPLC eluent buffer is placed at VX2. One light C18 SPE (preconditioned with 4 mL of ethanol, followed by 10 mL of H_2O) is placed between vials V17 and V15, as shown in Figure S12. The round-bottomed flask used to collect the HPLC fractions is filled with 25 mL of H_2O to facilitate the trapping of the product [^{18}F]**2** on a light C18 SPE. The synthesis module is operated using an automated program. Following bombardment, [^{18}F]F$^-$ is transferred to the TRACERlab™ FX2N radiosynthesis module via a helium gas stream.

(B) Automation Procedures

(1) At the end of the bombardment, aqueous [^{18}F]F$^-$ in [^{18}O]H_2O is transferred from the target into a Collection Vial (A) containing [^{18}O]H_2O via a helium purge. [^{18}F]F$^-$ is then trapped in a QMA cartridge (B) and eluted using the solution in vial 1. The eluant is finally transferred to Reactor 1 (C). Then, the solution of vial 2 is transferred into Reactor 1 (C). The mixture is dried under azeotropic conditions, and after the first drying, the residue is dissolved in acetonitrile (1 mL) that is from vial 4 and then further dried. This process is repeated 3 times.

(2) The solution of precursor **1** in acetonitrile of vial 3 is transferred to Reactor 1 (C) and heated at 80 °C for 10 min. After Reactor 1 (C) is cooled to room temperature, 1.0 mL of HPLC eluent in Vial 5 is transferred to Reactor 1 (C). The resulting mixture is loaded onto the semi-prep HPLC (Agilent Eclipse SB C18, 5 μm, 9.4 × 250 mm, MeCN/0.1 M ammonium formate buffer = 70/30, flow rate = 2.5 mL/min, λ= 254 nm).

(3) The product [^{18}F]**2** portions are collected and diluted in the round-bottomed flask (D), which has been filled with 25 mL water to facilitate the trapping of [^{18}F]**2** on a Light C18 SPE. Then, the resulting solution is captured by Light C18 SPE (E). The Light C18 SPE is washed with 10 mL H_2O from Vial 43 to remove the HPLC mobile phase and ^{18}F$^-$.

(4) The product [^{18}F]**2** on Light C18 SPE(E) is eluted with 1.5 mL EtOH from Vial 42 into Collection Vial (F), followed by 10.0 mL saline from Vial 41 to give a solution of product [^{18}F]**2**. If needed, the solution of [^{18}F]**2** could be transferred outside of the hot cell via V 16a.

8. References

(1) D. B. Dess, J. C. Martin, *J. Am.Chem. Soc.* **1991**, *113*, 7277-7287.

(2) J. E. Taylor, D. W. Daniels, A. D. Smith, *Org. Lett.* **2013**, *15*, 6058−6061.

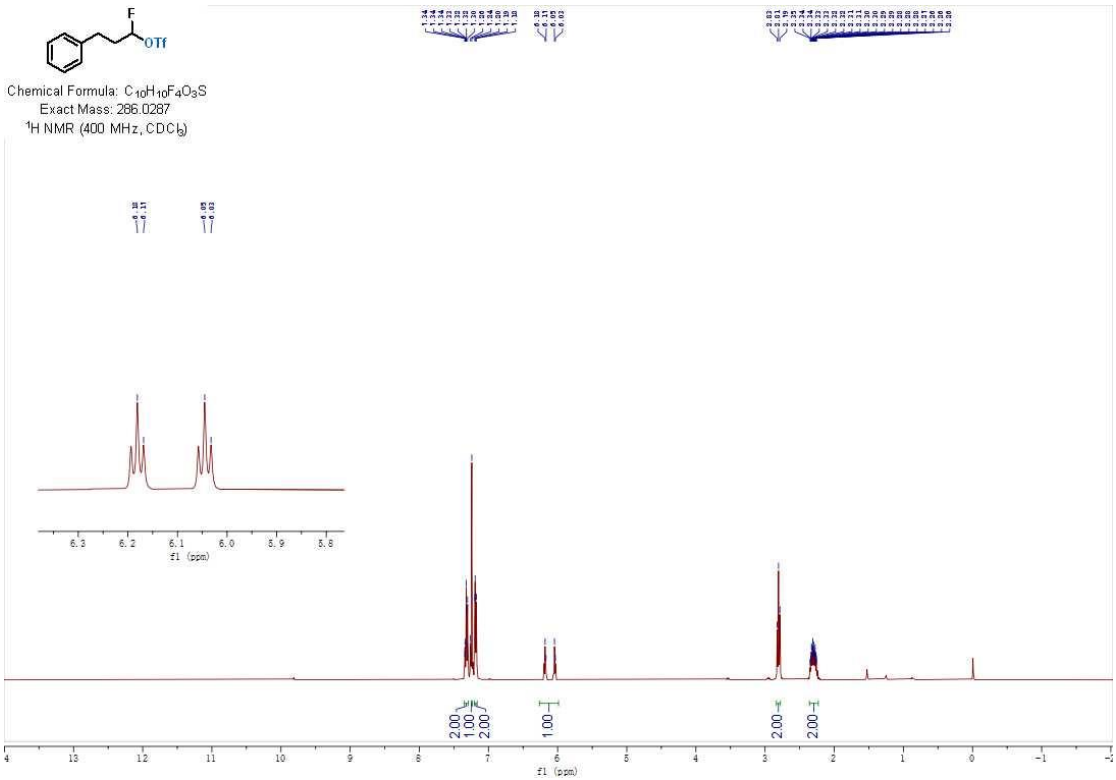
(3) S. E. Gibson, J. O. Jones, R. McCague, M. J. Tozer, Nicole J. W, *Synlett* 1999, 954-956.

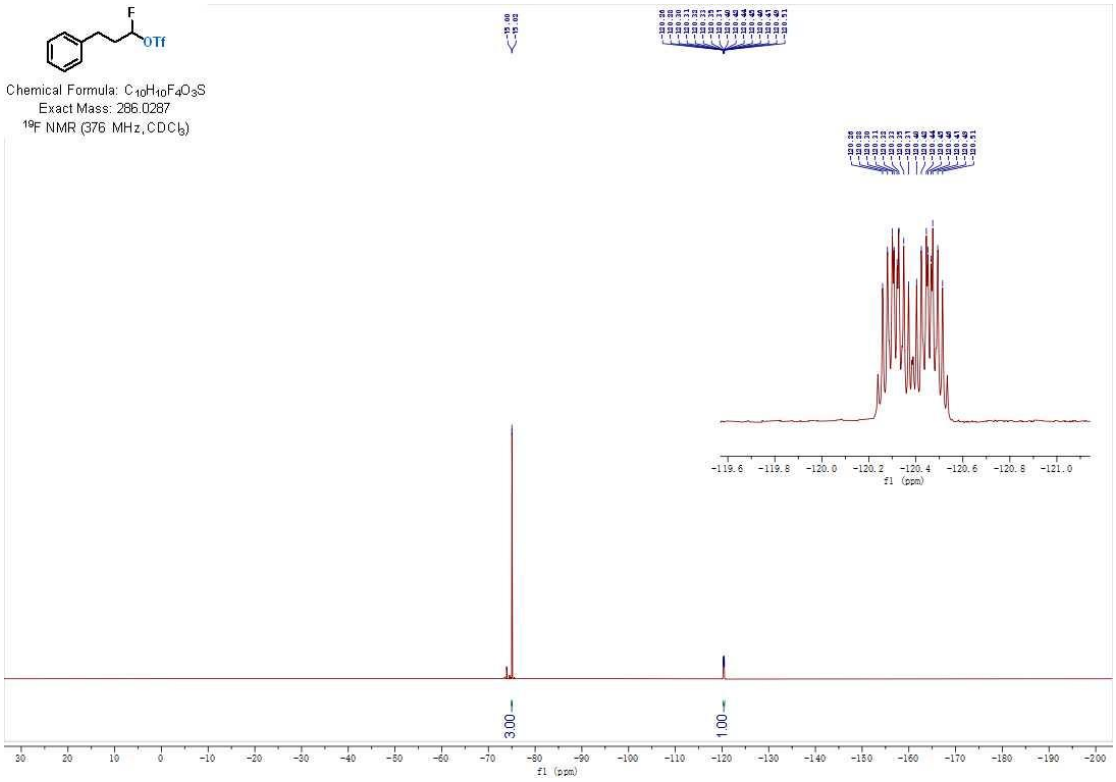
(4) W. R. Dolbier Jr, M. Okamoto, *J. Fluorine Chem.* **2015**, *179,* 33-41.

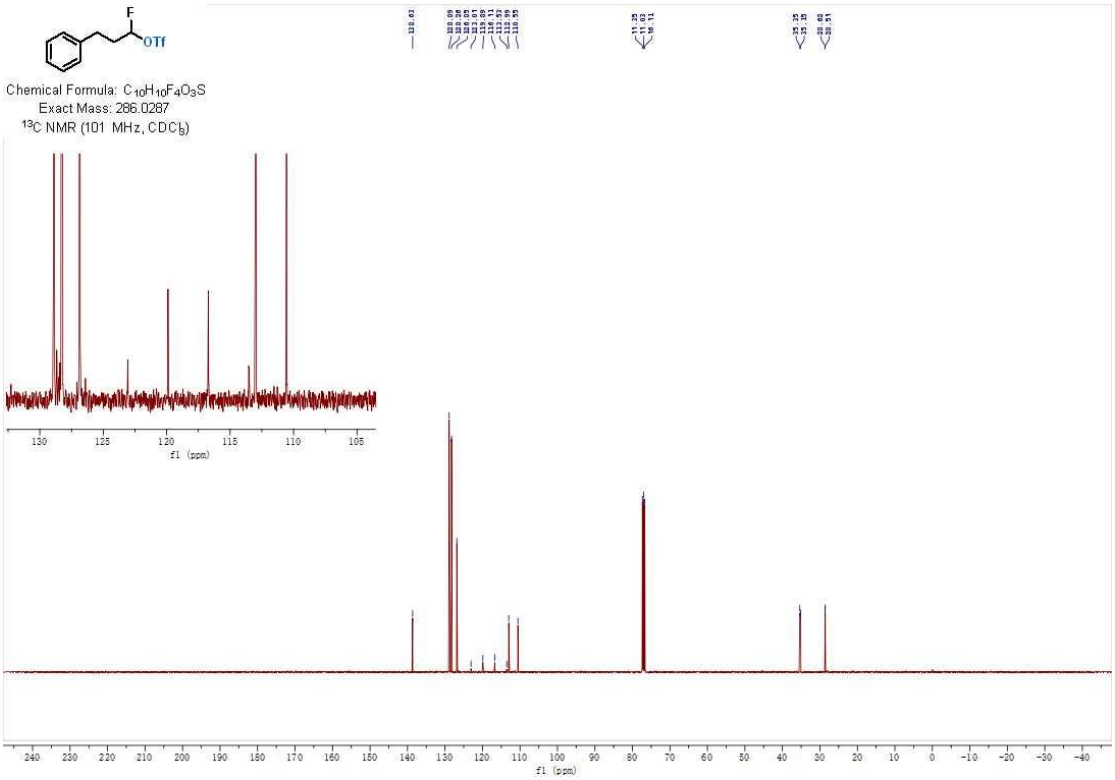
(5) Yisa. Xiao, Qilong. Shen, *Chin. J. Chem.* **2025**, *43*, 1114—1120.

9. Copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR Spectra

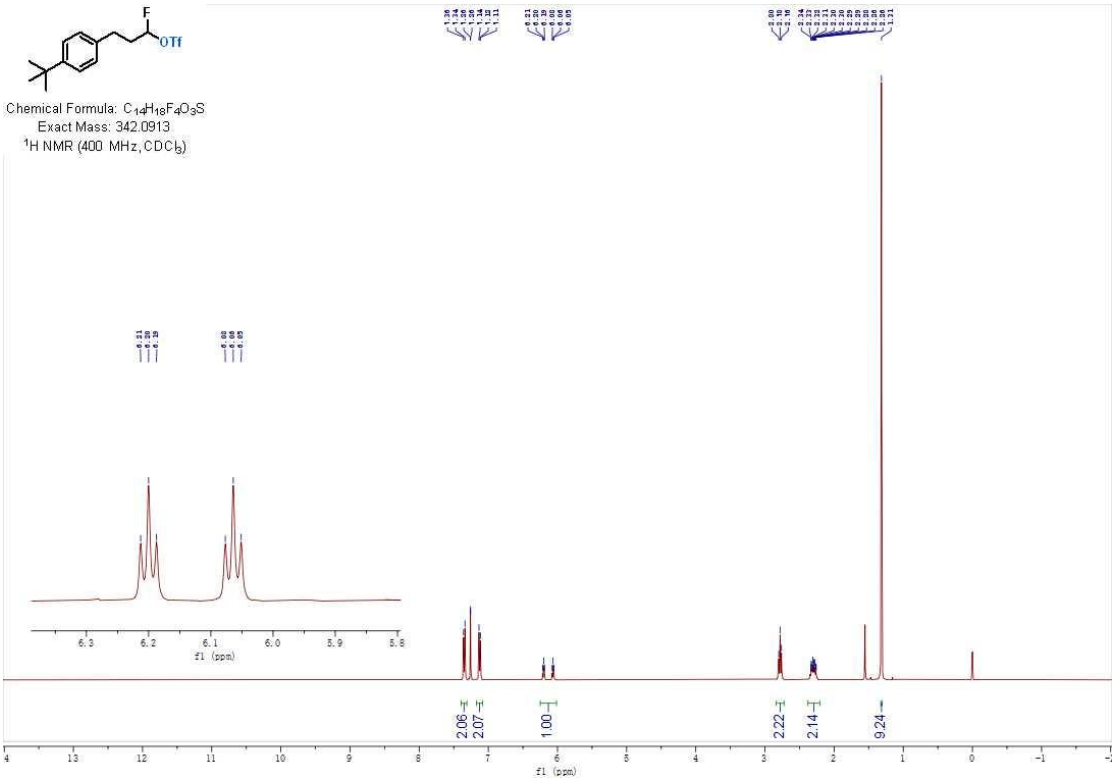
1-Fluoro-3-phenylpropyl trifluoromethanesulfonate (1a)

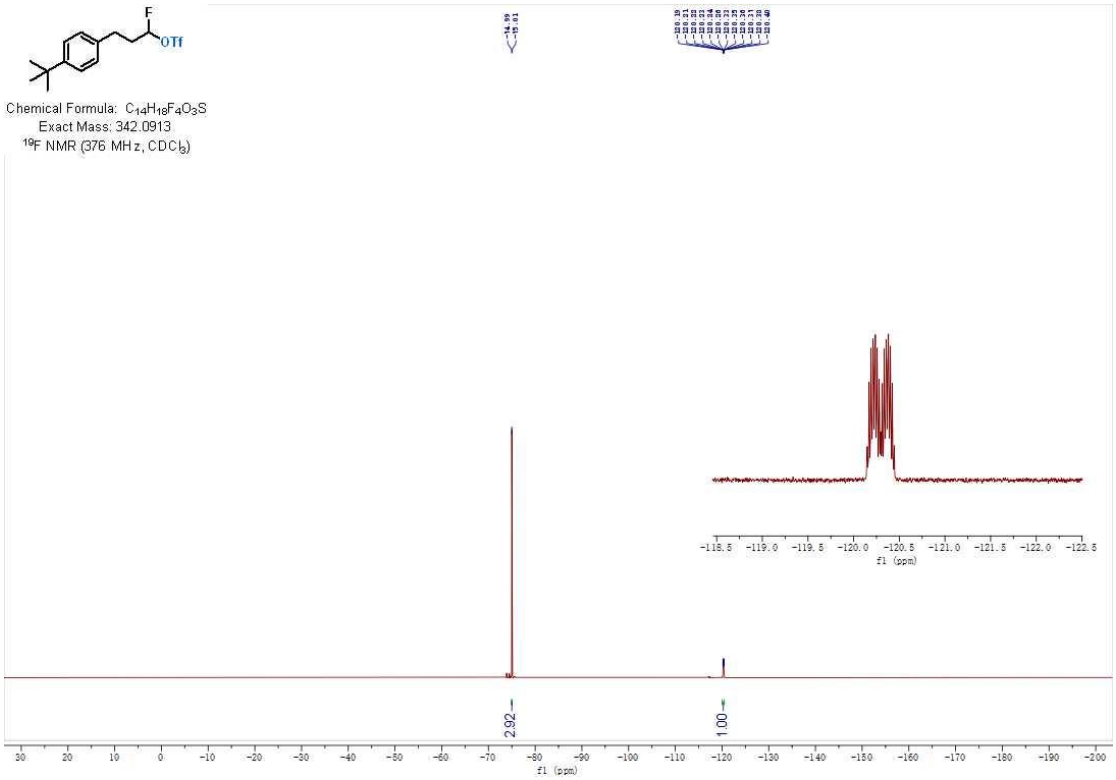


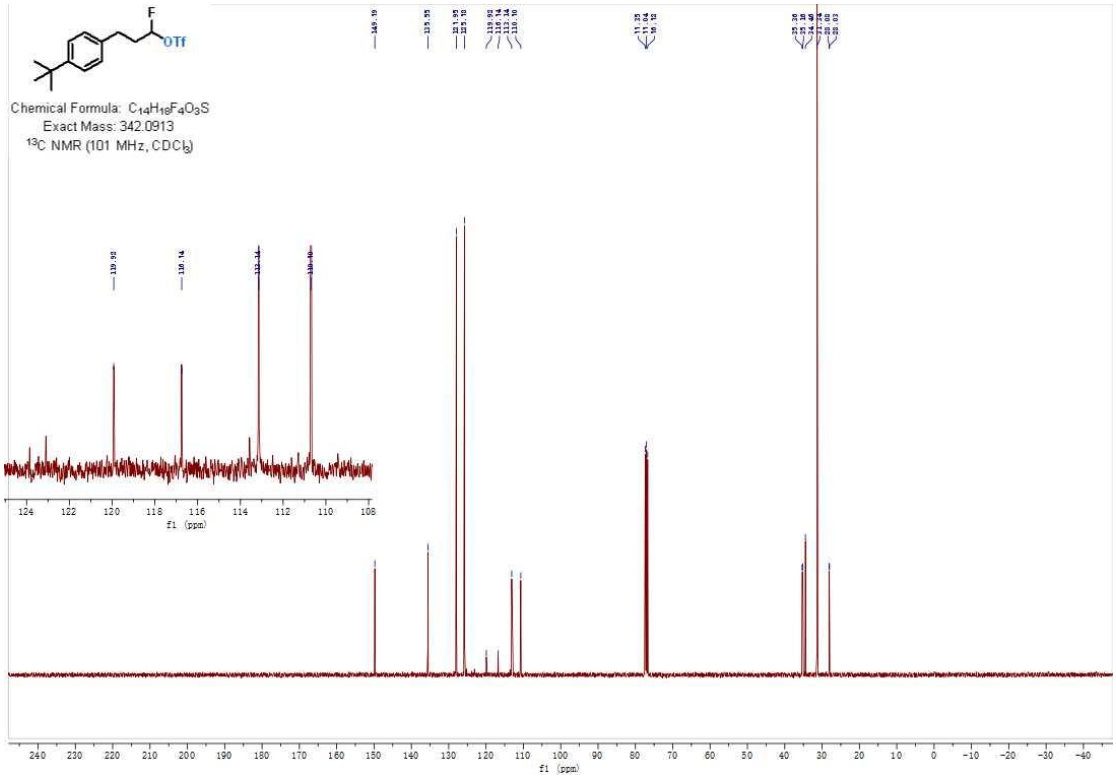




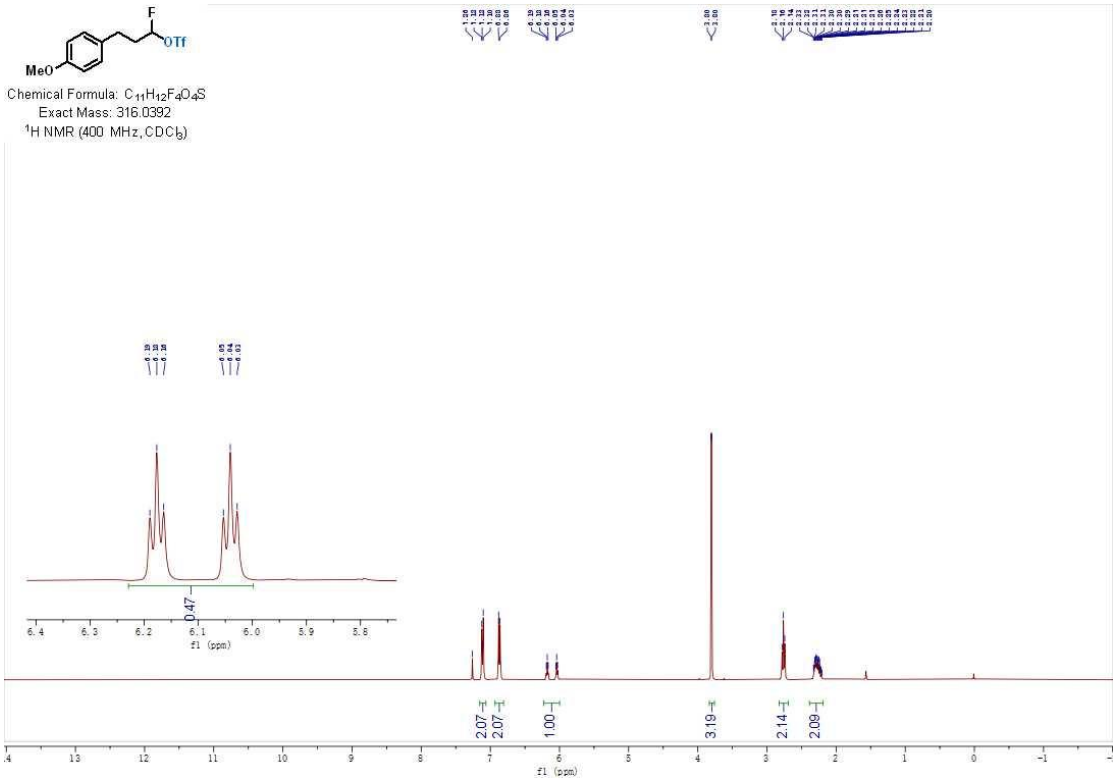
3-(4-(*tert*-Butyl)phenyl)-1-fluoropropyl trifluoromethanesulfonate (1b)

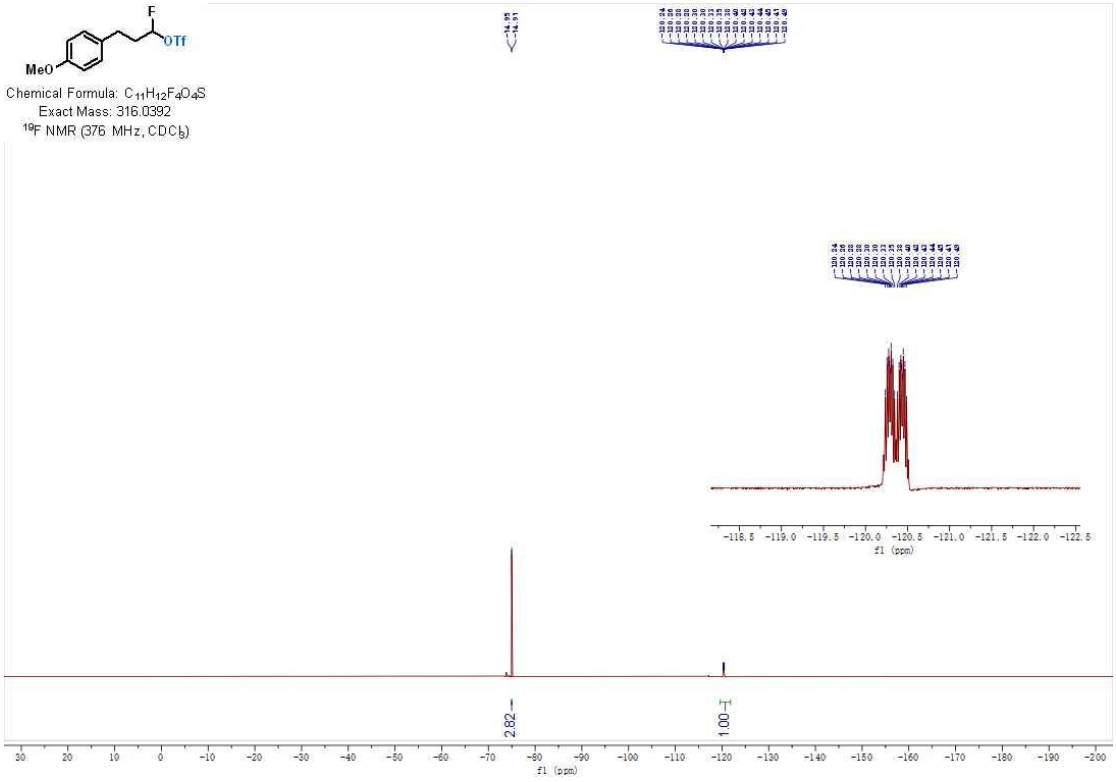


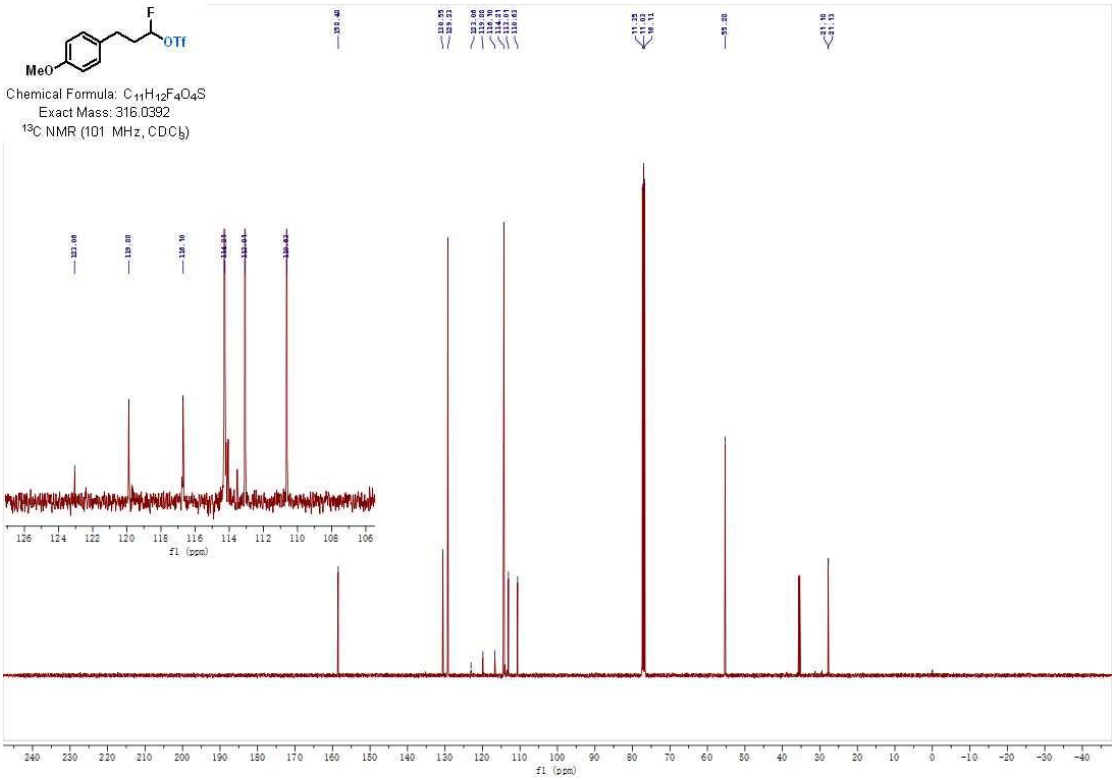

Chemical Formula: C14H18F4O3S
Exact Mass: 342.0913
19F NMR (376 MHz, CDCl3)
2.92
1.00
f1 (ppm)


Chemical Formula: C14H18F4O3S
Exact Mass: 342.0913
13C NMR (101 MHz, CDCl3)
f1 (ppm)

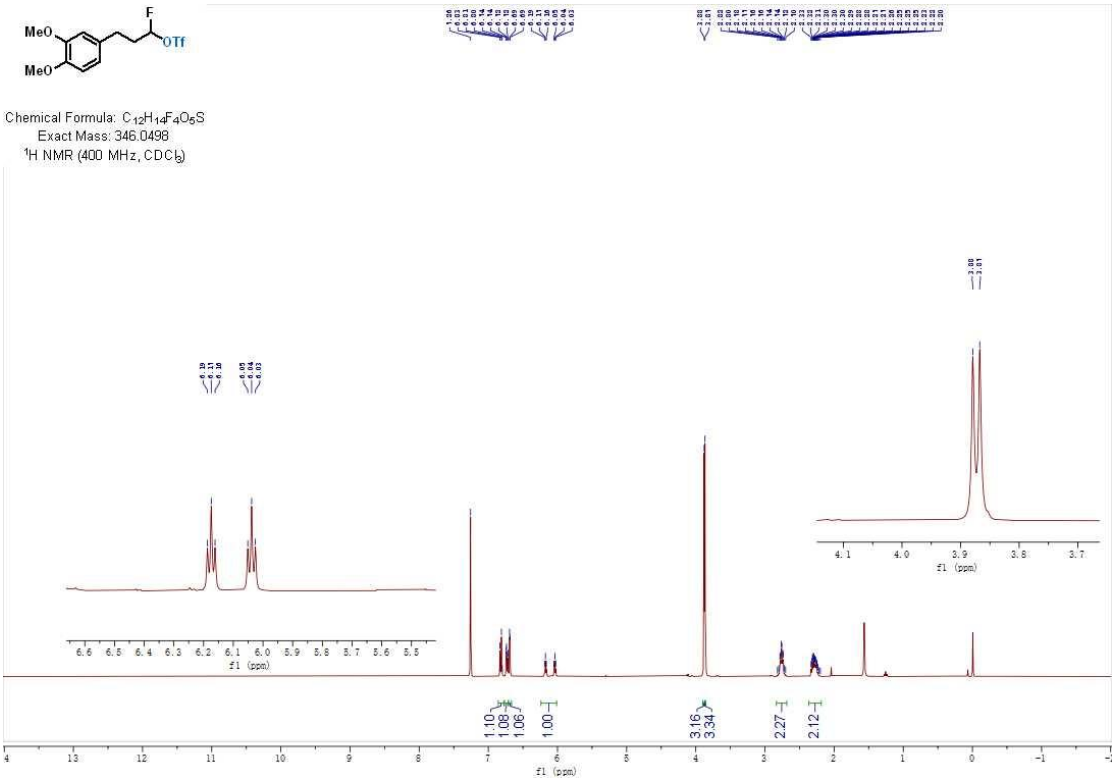
1-Fluoro-3-(4-methoxyphenyl)propyl trifluoromethanesulfonate (1c)

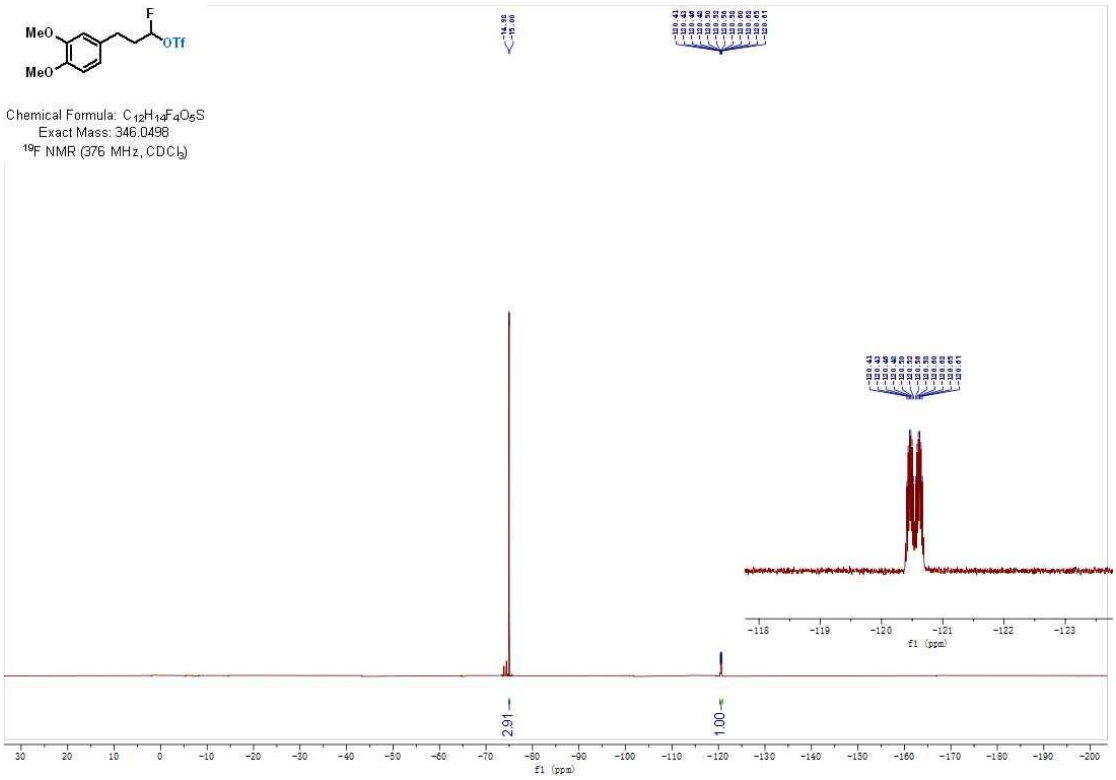


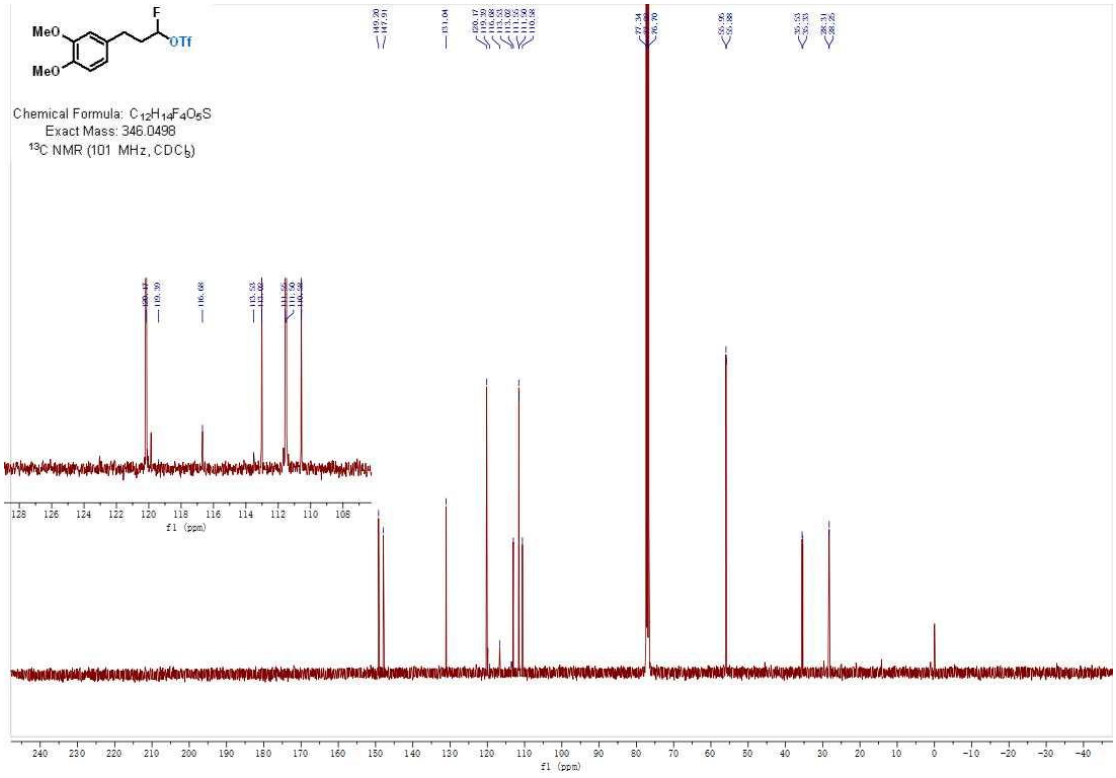




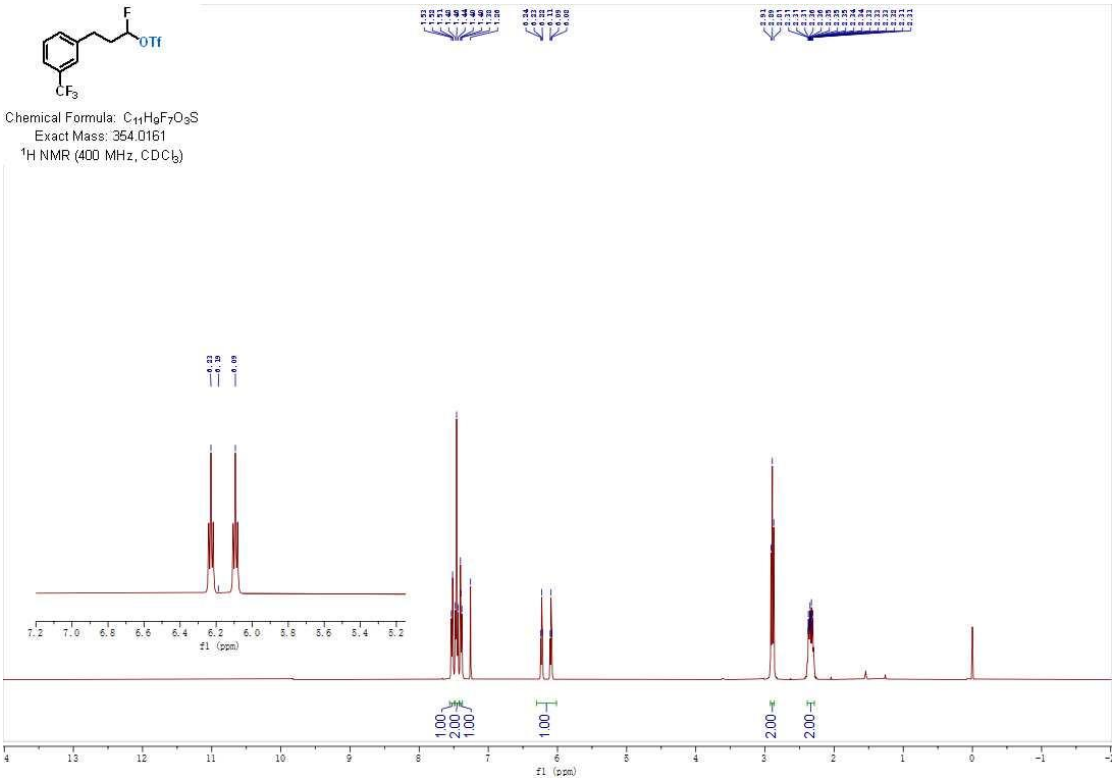
3-(3,4-Dimethoxyphenyl)-1-fluoropropyl trifluoromethanesulfonate (1d)

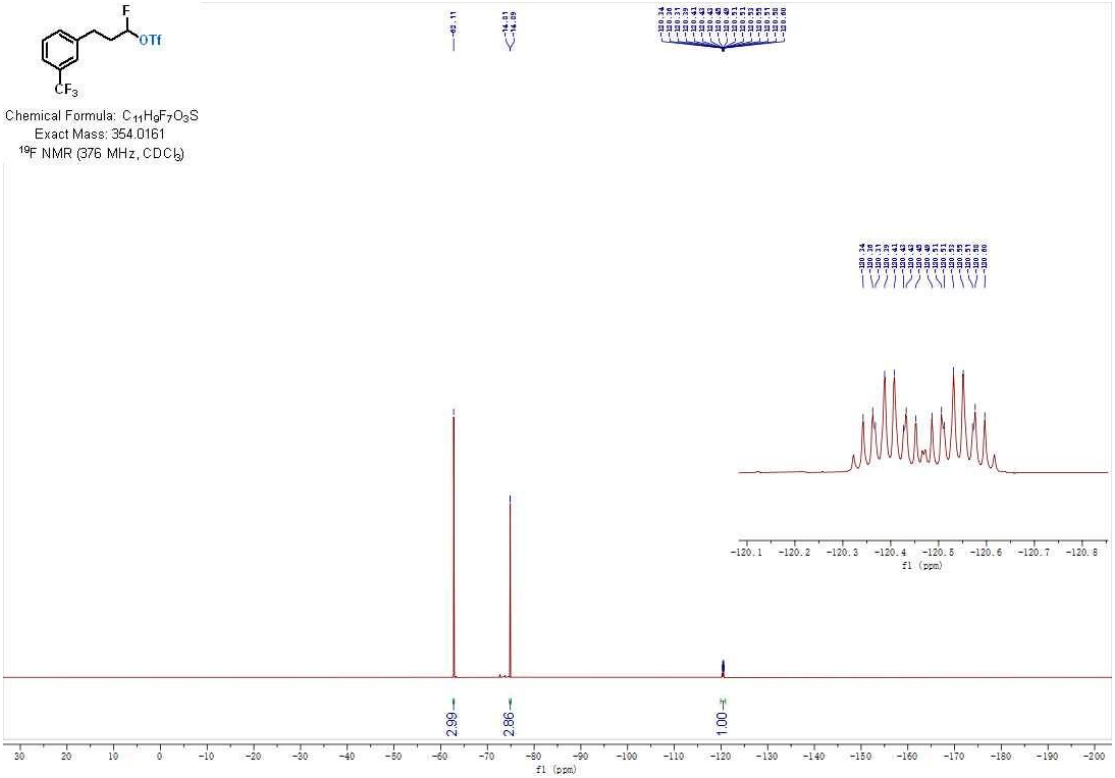


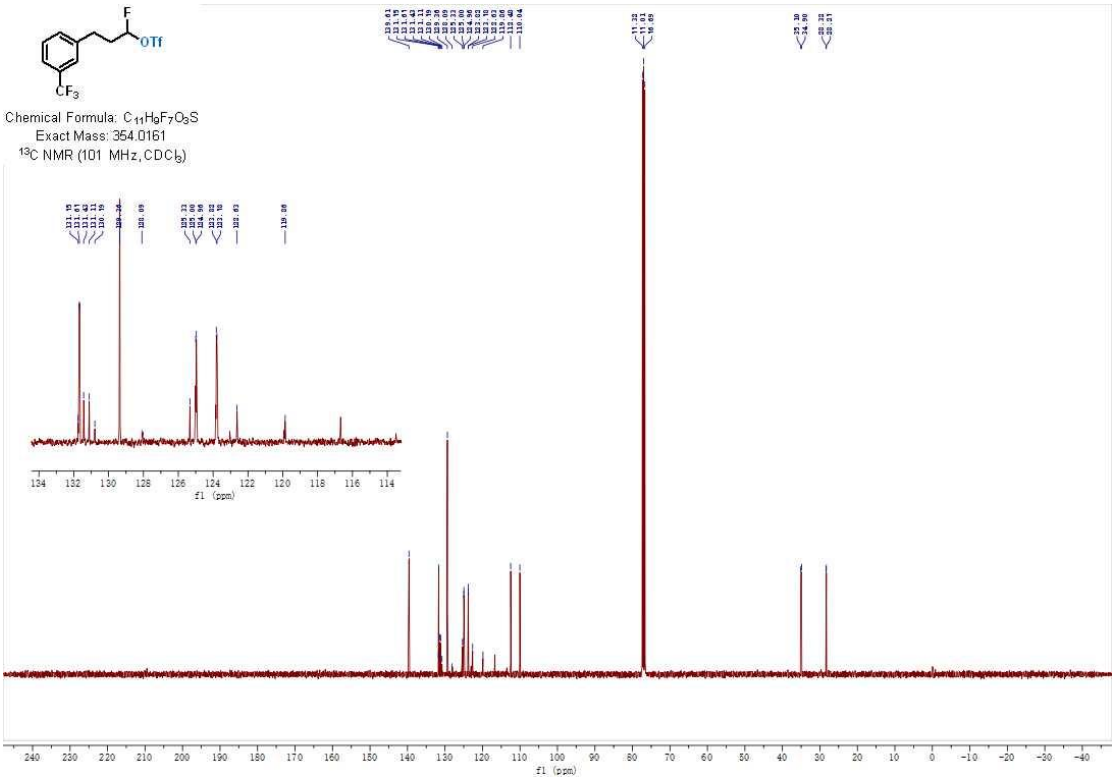

MeO
MeO
F
OTf
Chemical Formula: C12H14F4O5S
Exact Mass: 346.0498
19F NMR (376 MHz, CDCl3)
2.91
1.00
f1 (ppm)


MeO
MeO
F
OTf
Chemical Formula: C12H14F4O5S
Exact Mass: 346.0498
13C NMR (101 MHz, CDCl3)
f1 (ppm)

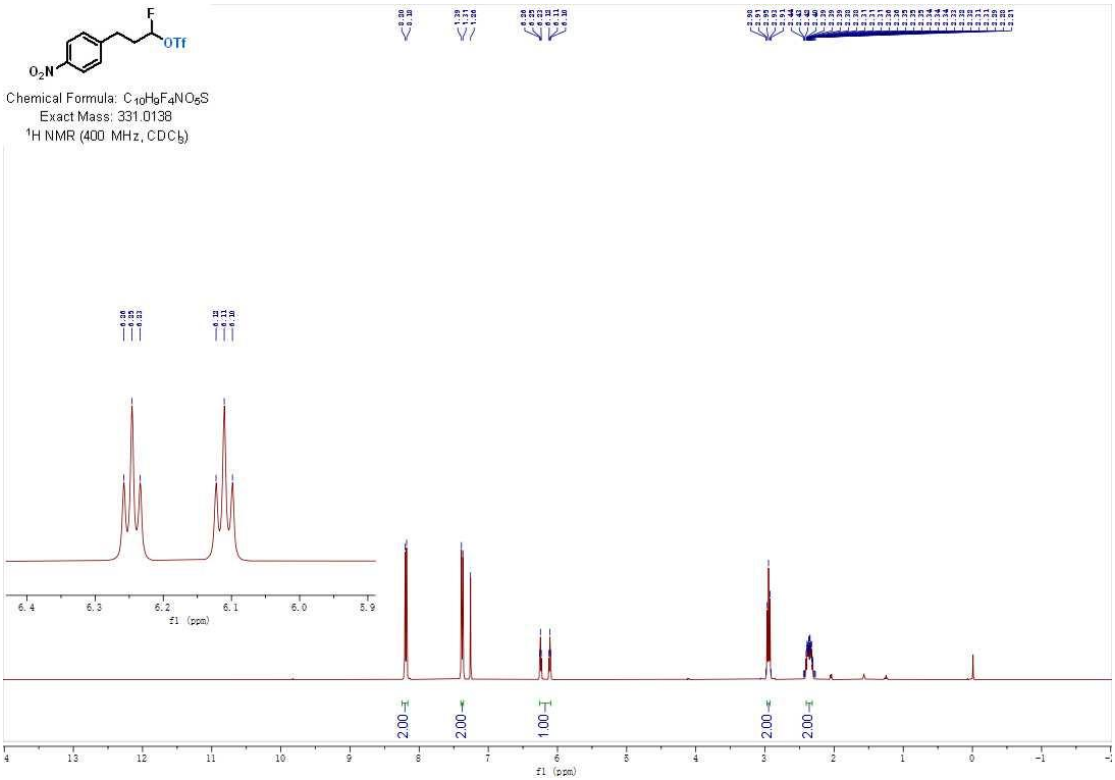
1-Fluoro-3-(3-(trifluoromethyl)phenyl)propyl trifluoromethanesulfonate (1e)

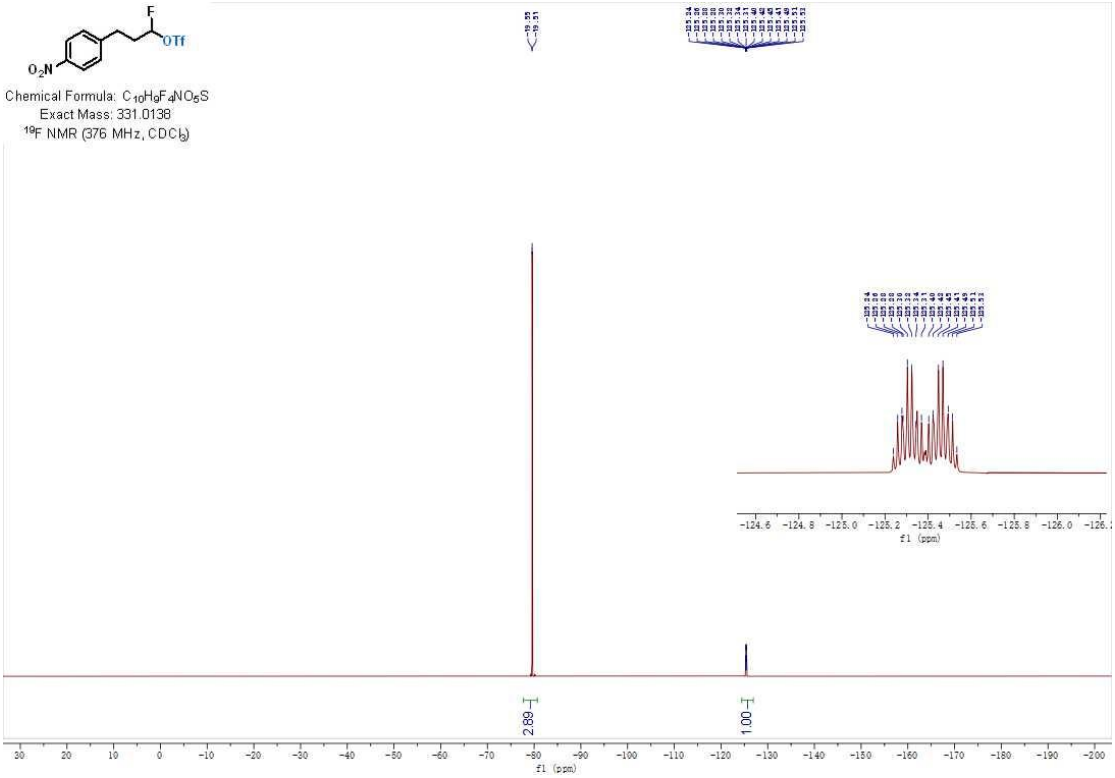


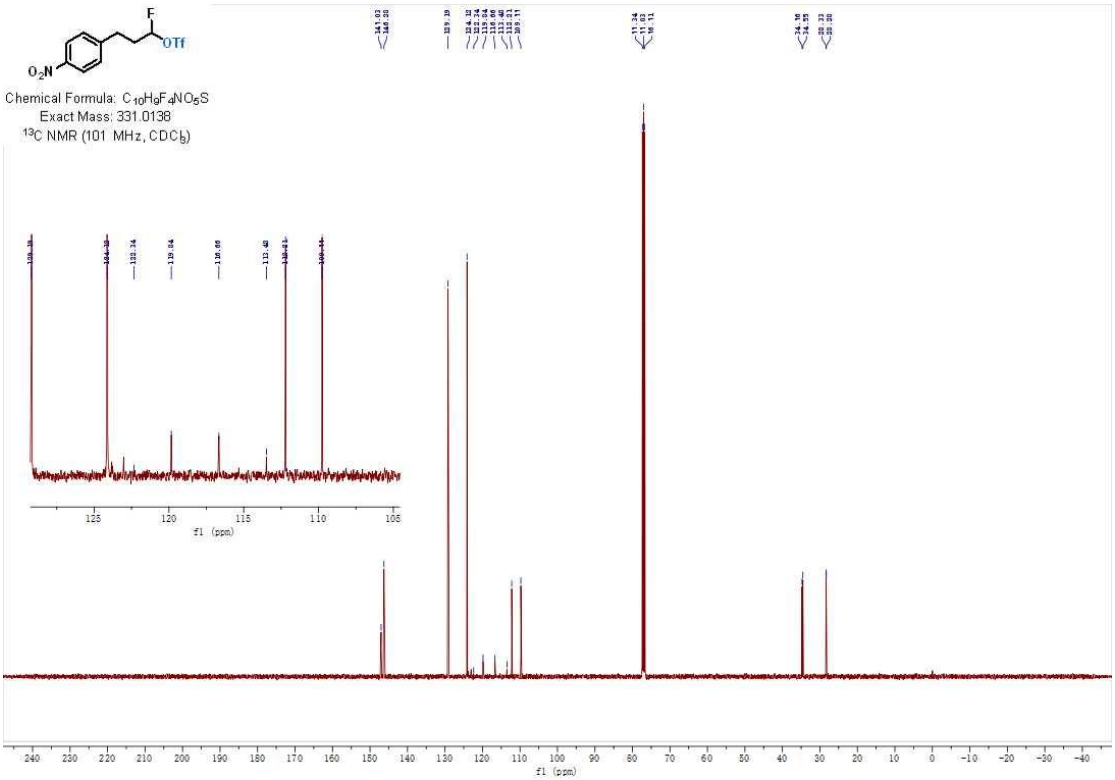




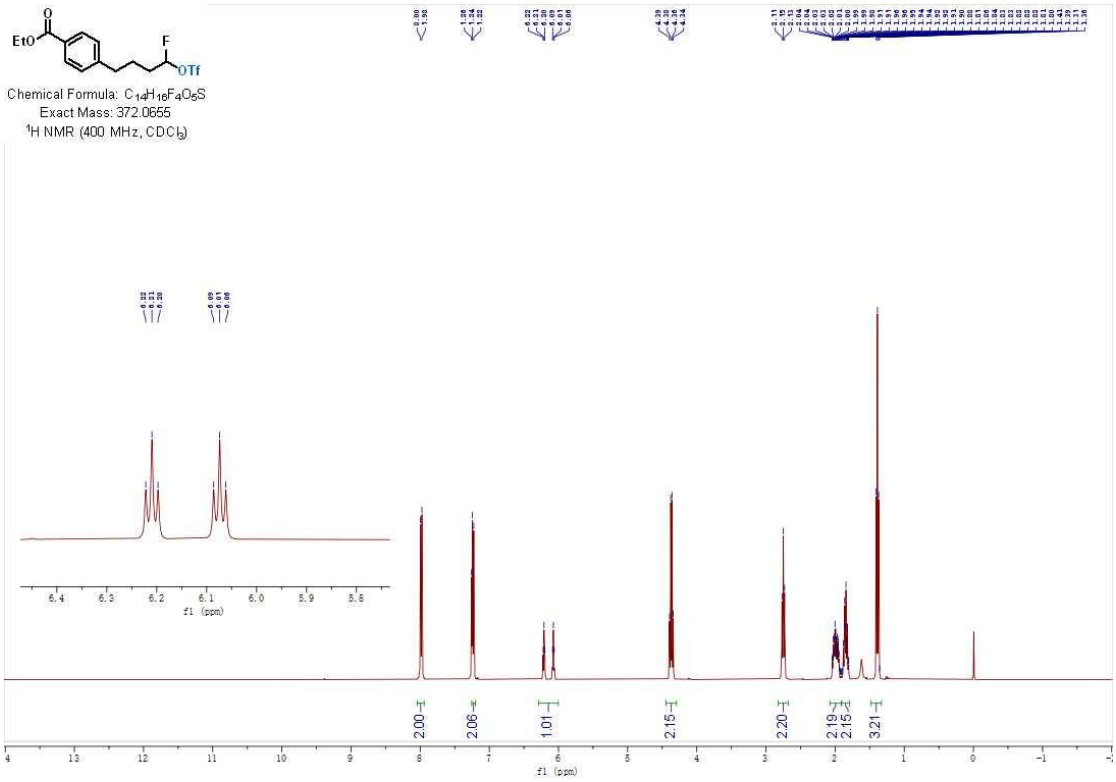
1-Fluoro-3-(4-nitrophenyl)propyl trifluoromethanesulfonate (1f)

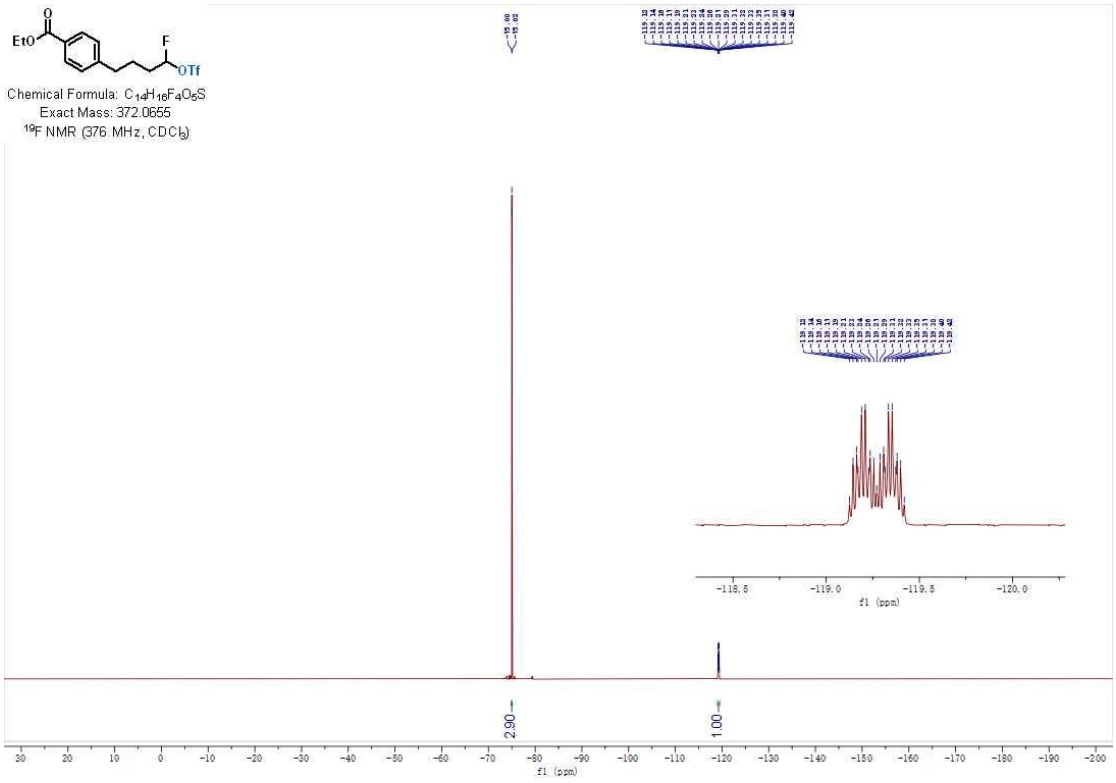


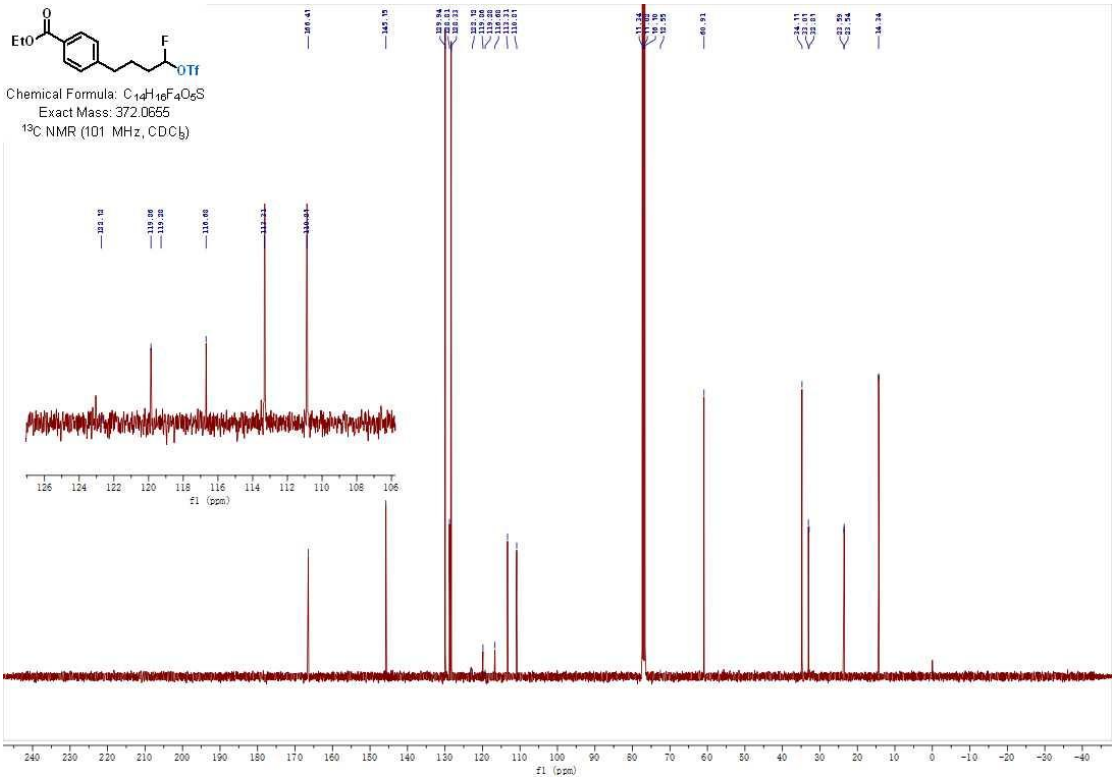

Chemical Formula: C10H9F4NO5S
Exact Mass: 331.0138
19F NMR (376 MHz, CDCl3)
2.89
1.00
f1 (ppm)


Chemical Formula: C10H9F4NO5S
Exact Mass: 331.0138
13C NMR (101 MHz, CDCl3)
f1 (ppm)

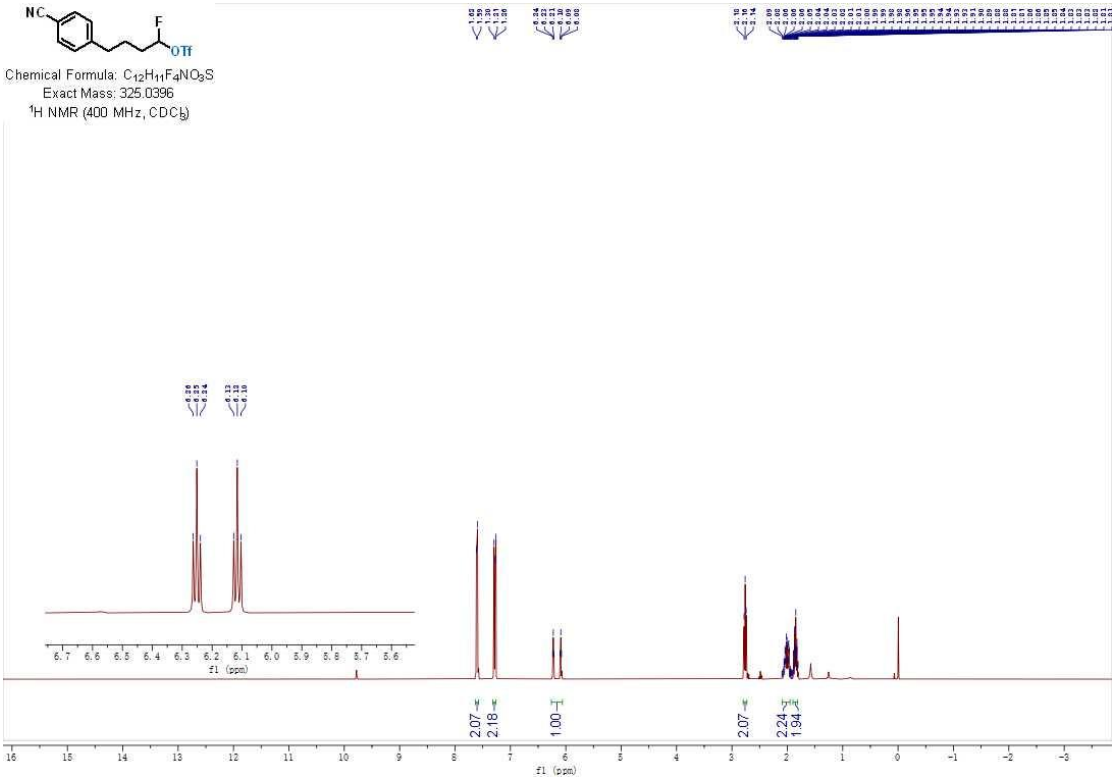
Ethyl 4-(4-fluoro-4-(((trifluoromethyl)sulfonyl)oxy)butyl)benzoate (1g)

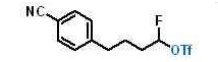




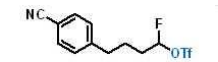


4-(4-Cyanophenyl)-1-fluorobutyl trifluoromethanesulfonate (1h)



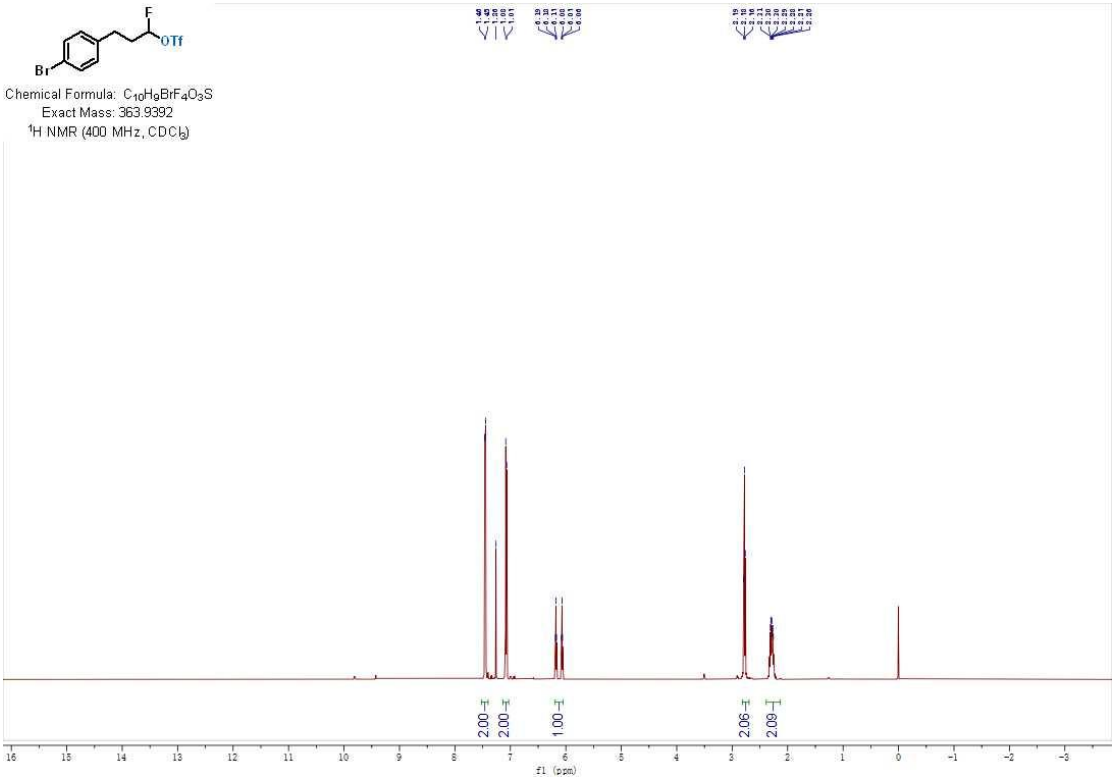


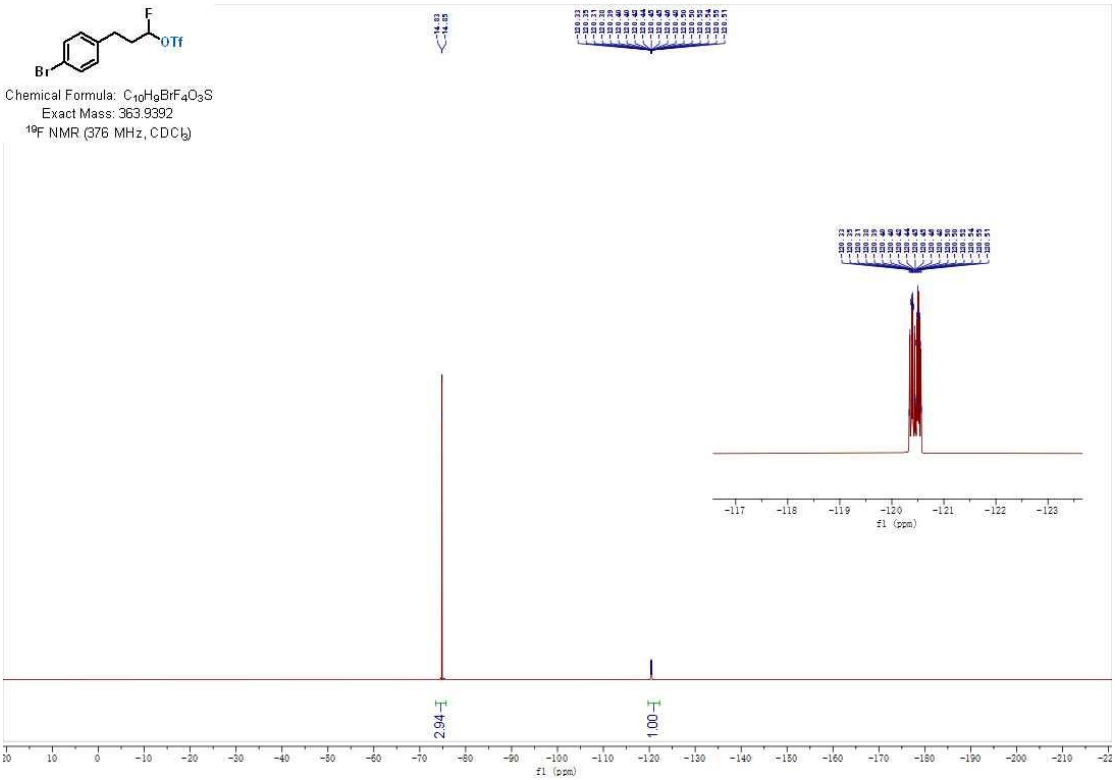
Chemical Formula: $C_{12}H_{11}F_4NO_3S$
Exact Mass: 325.0396
^{19}F NMR (376 MHz, $CDCl_3$)

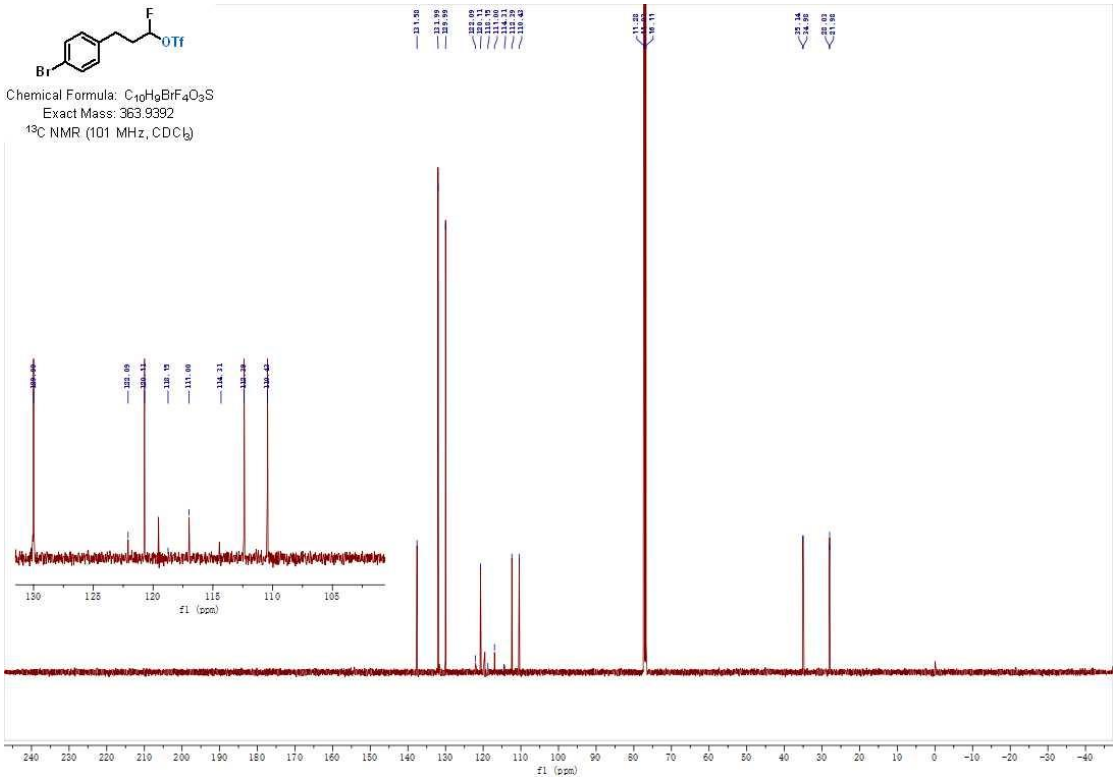


Chemical Formula: $C_{12}H_{11}F_4NO_3S$
Exact Mass: 325.0396
^{13}C NMR (101 MHz, $CDCl_3$)

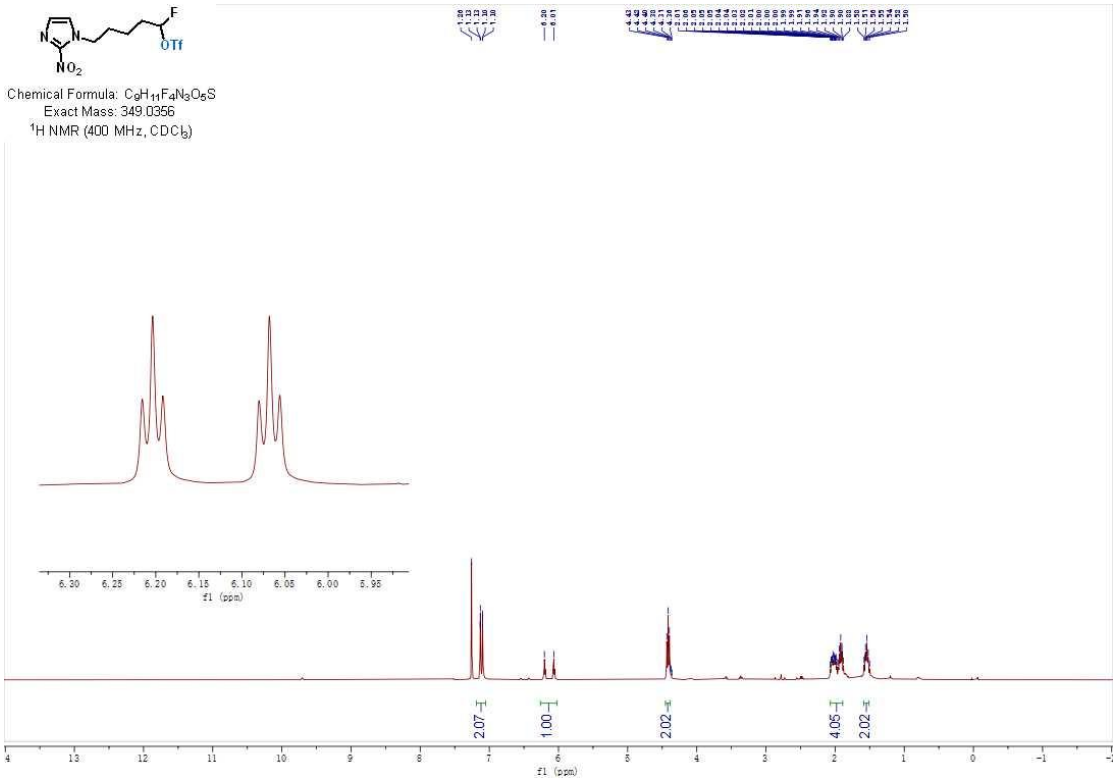
3-(4-Bromophenyl)-1-fluoropropyl trifluoromethanesulfonate (1i)

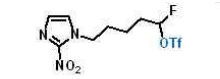




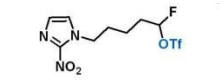


1-Fluoro-5-(2-nitro-1H-imidazol-1-yl)pentyl trifluoromethanesulfonate (1j)



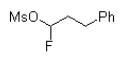


Chemical Formula: $C_9H_{11}F_4N_3O_5S$
Exact Mass: 349.0356
^{19}F NMR (376 MHz, $CDCl_3$)

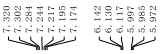


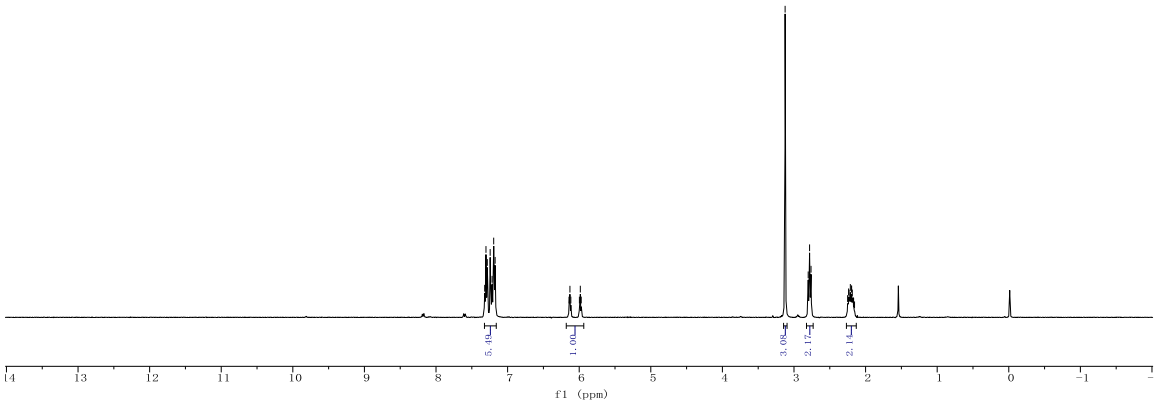
Chemical Formula: $C_9H_{11}F_4N_3O_5S$
Exact Mass: 349.0356
^{13}C NMR (101 MHz, $CDCl_3$)

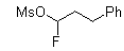
1-Fluoro-3-phenylpropyl methanesulfonate (1k)



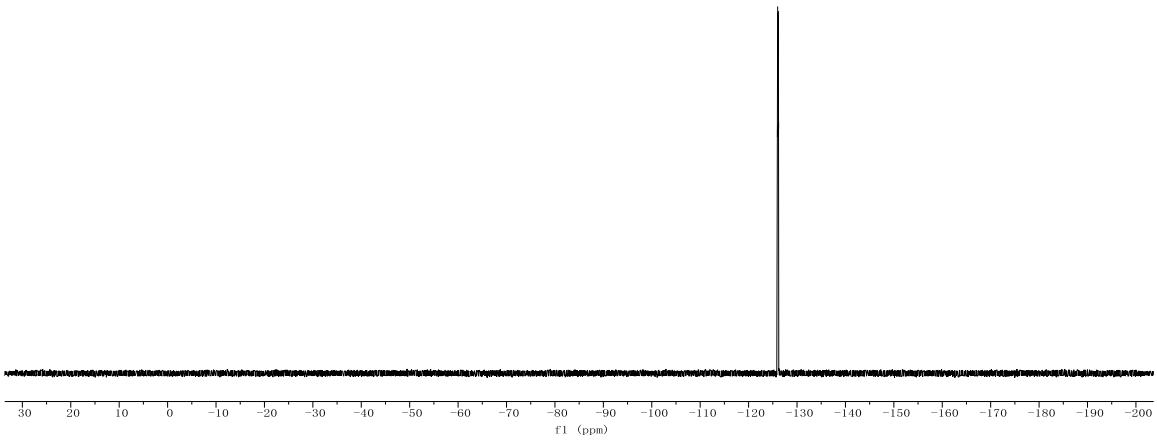
Chemical Formula: $C_{10}H_{13}FO_3S$
Exact Mass: 232.0569



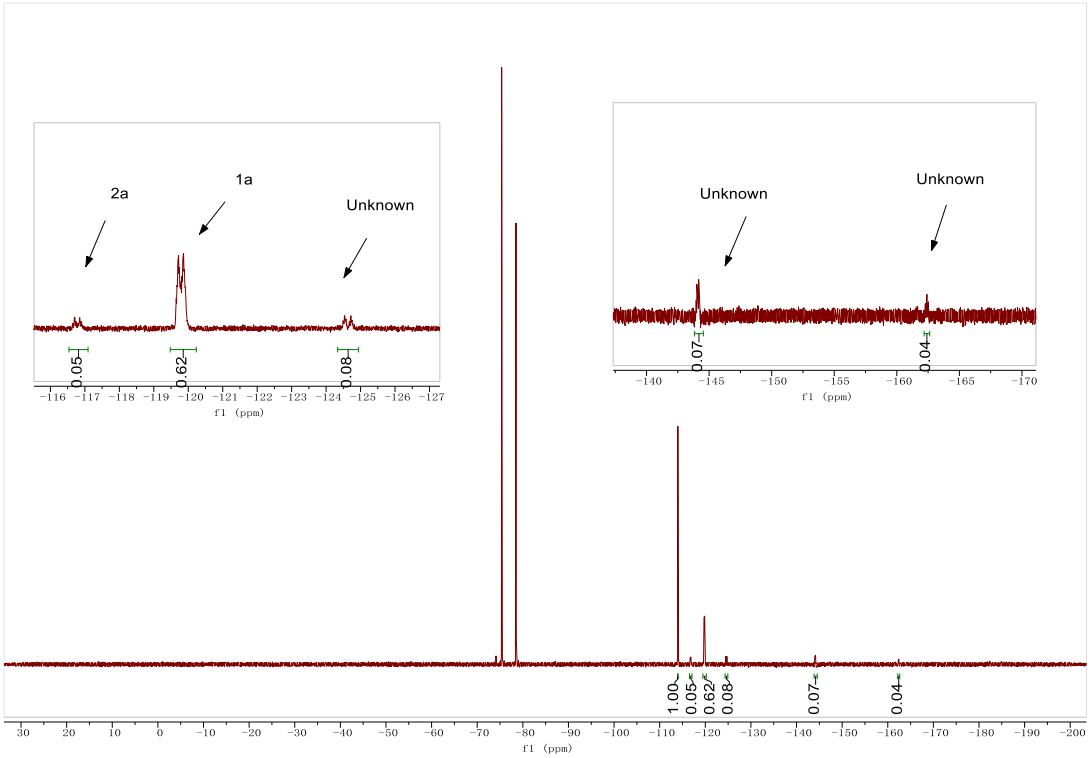




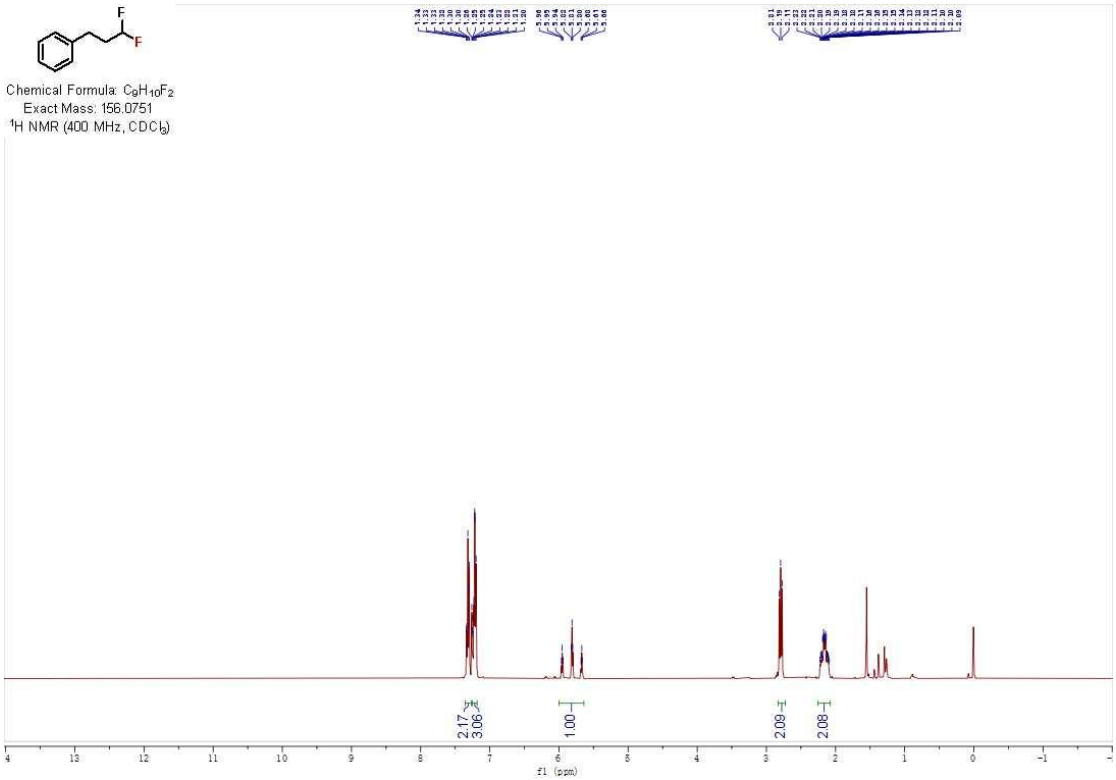
Chemical Formula: $C_{10}H_{13}FO_3S$
Exact Mass: 232.0569

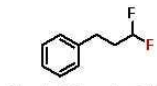


The stability experiment of 1a under the optimized reaction conditions (Crude ^{19}F NMR)

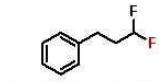


(3,3-Difluoropropyl)benzene (2a)



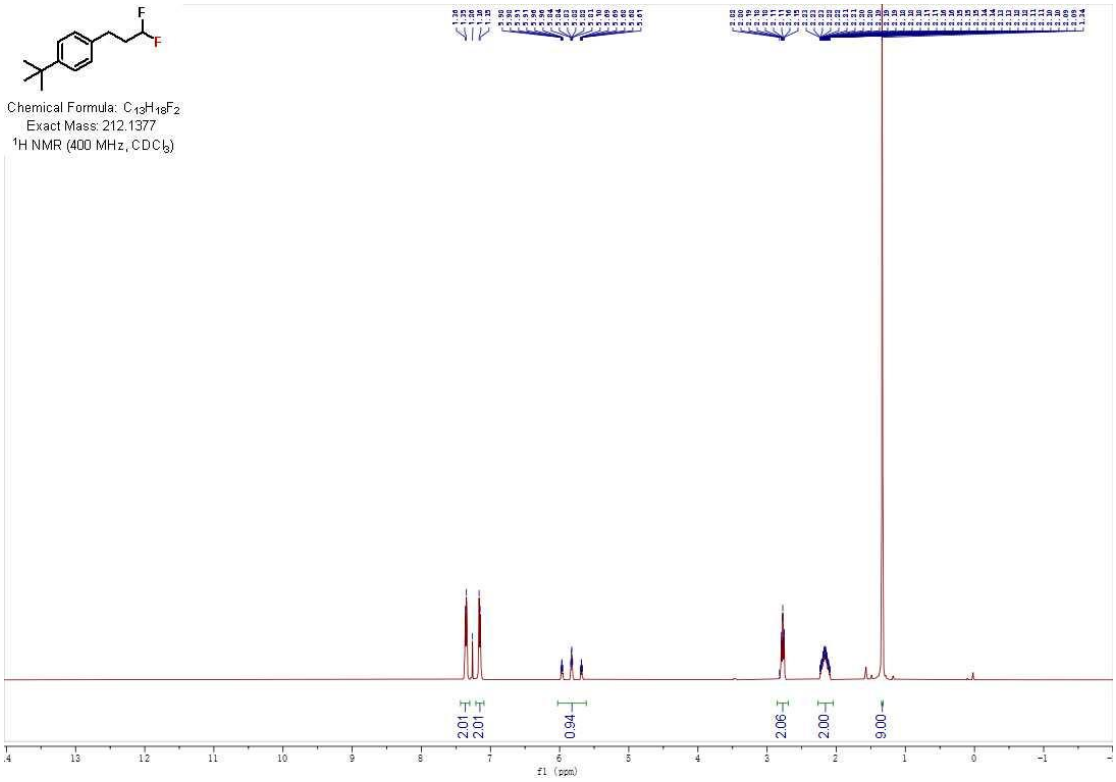


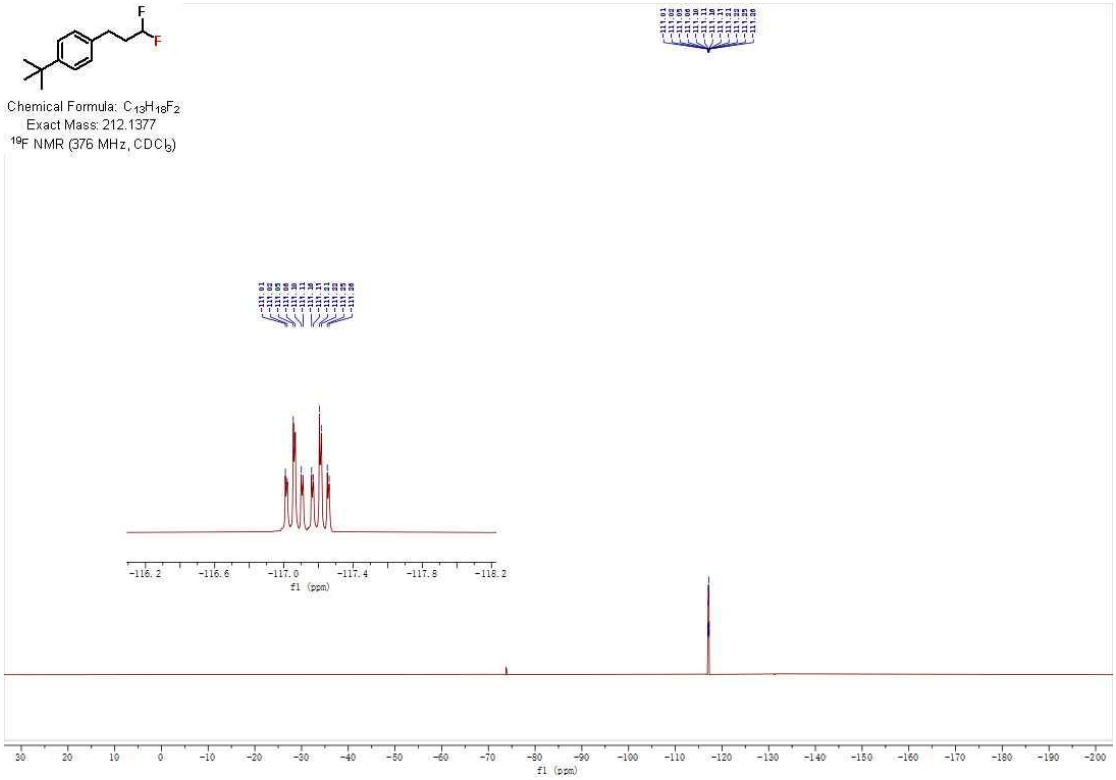
Chemical Formula: $C_9H_{10}F_2$
Exact Mass: 156.0751
^{19}F NMR (376 MHz, $CDCl_3$)

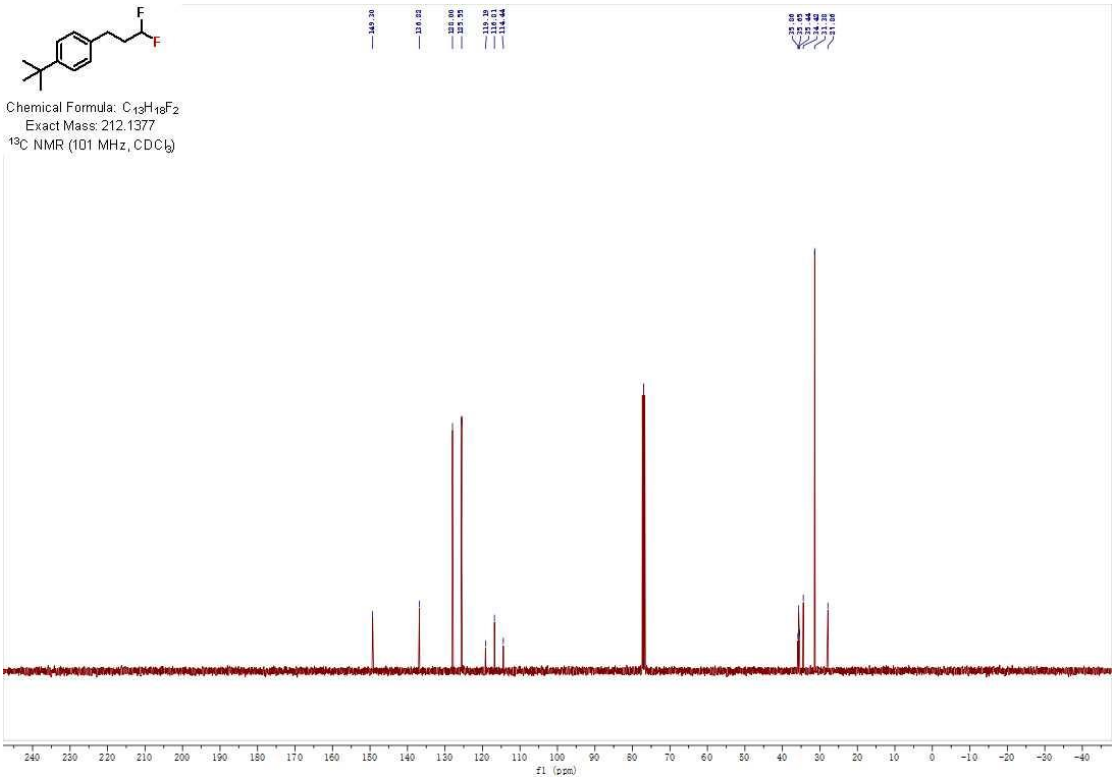


Chemical Formula: $C_9H_{10}F_2$
Exact Mass: 156.0751
^{13}C NMR (101 MHz, $CDCl_3$)

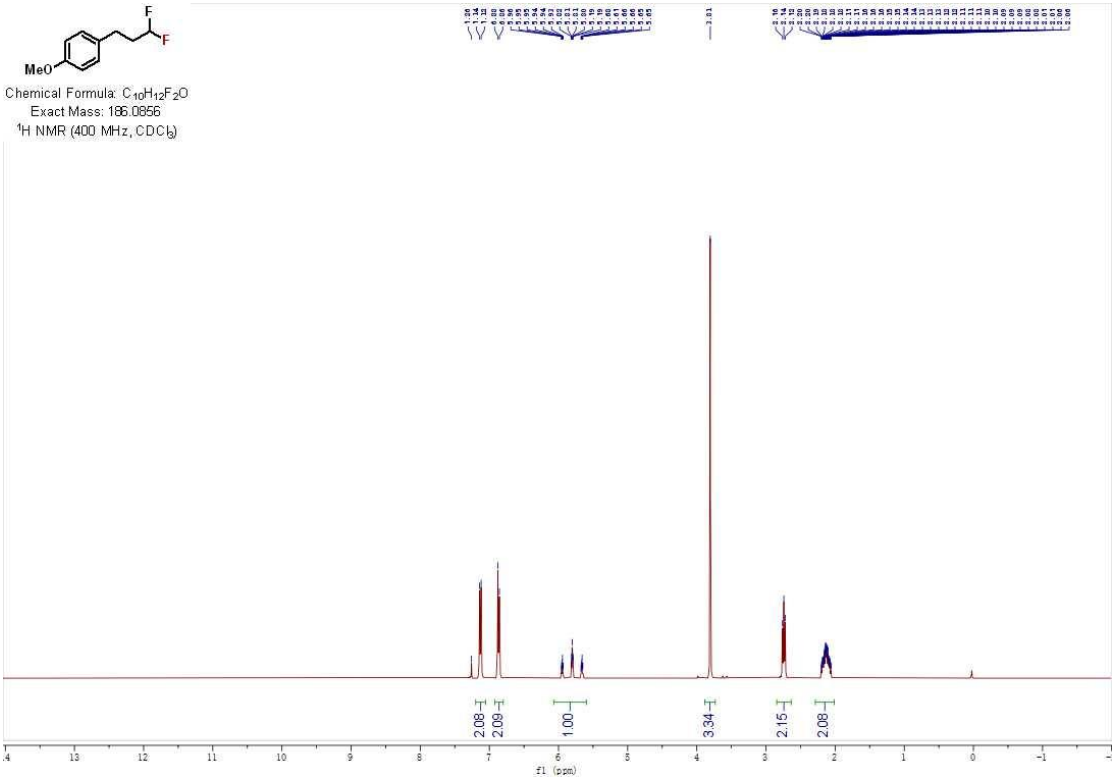
1-(tert-Butyl)-4-(3,3-difluoropropyl)benzene (2b)

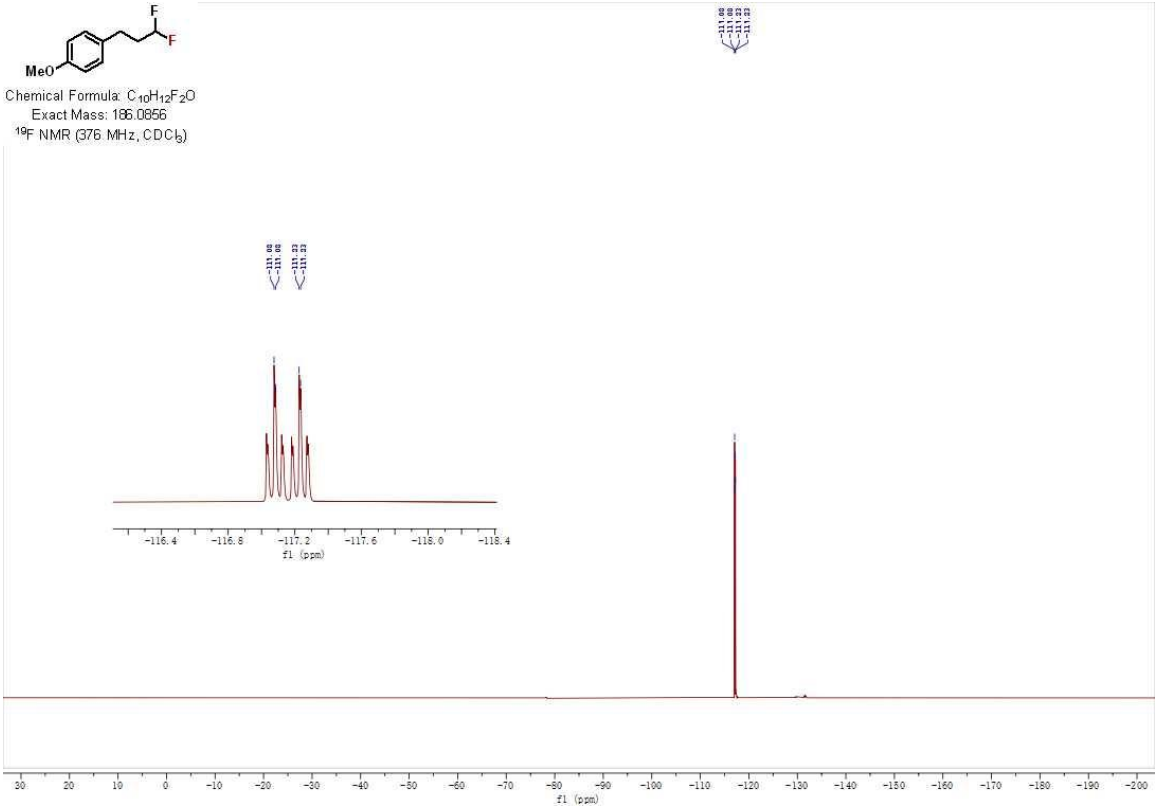


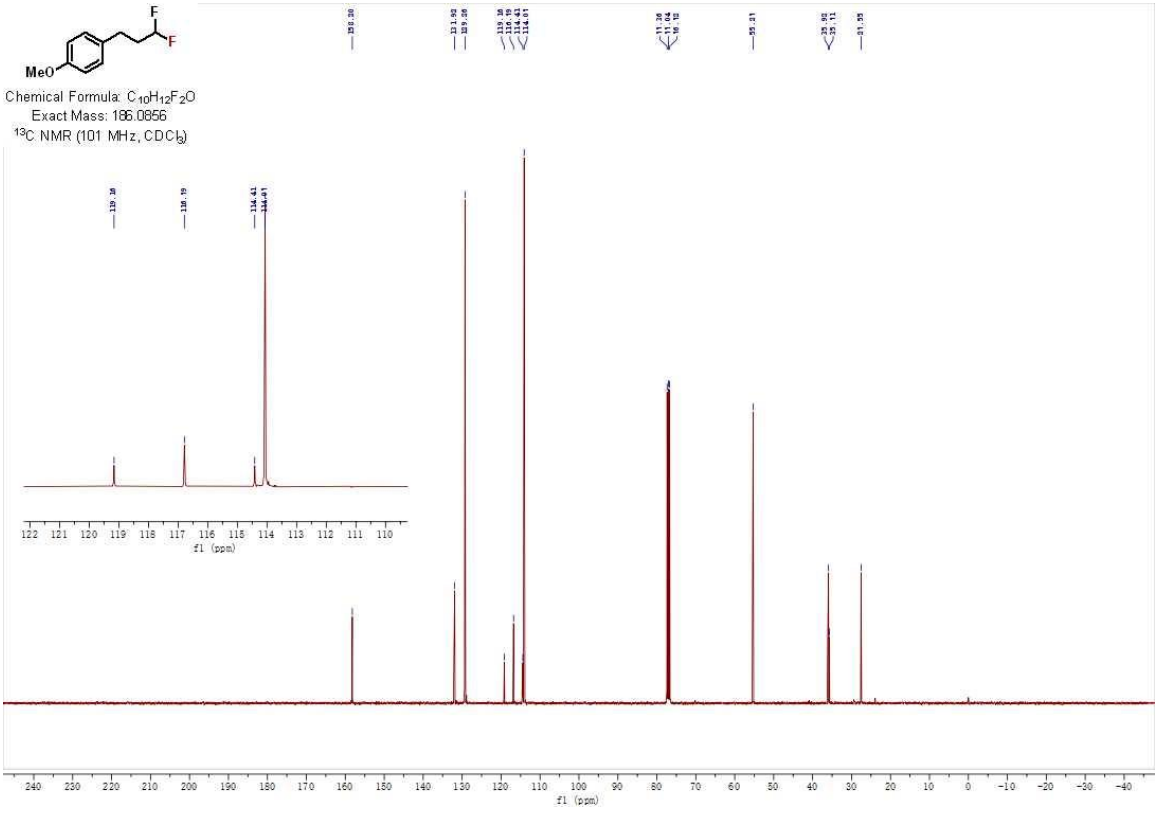




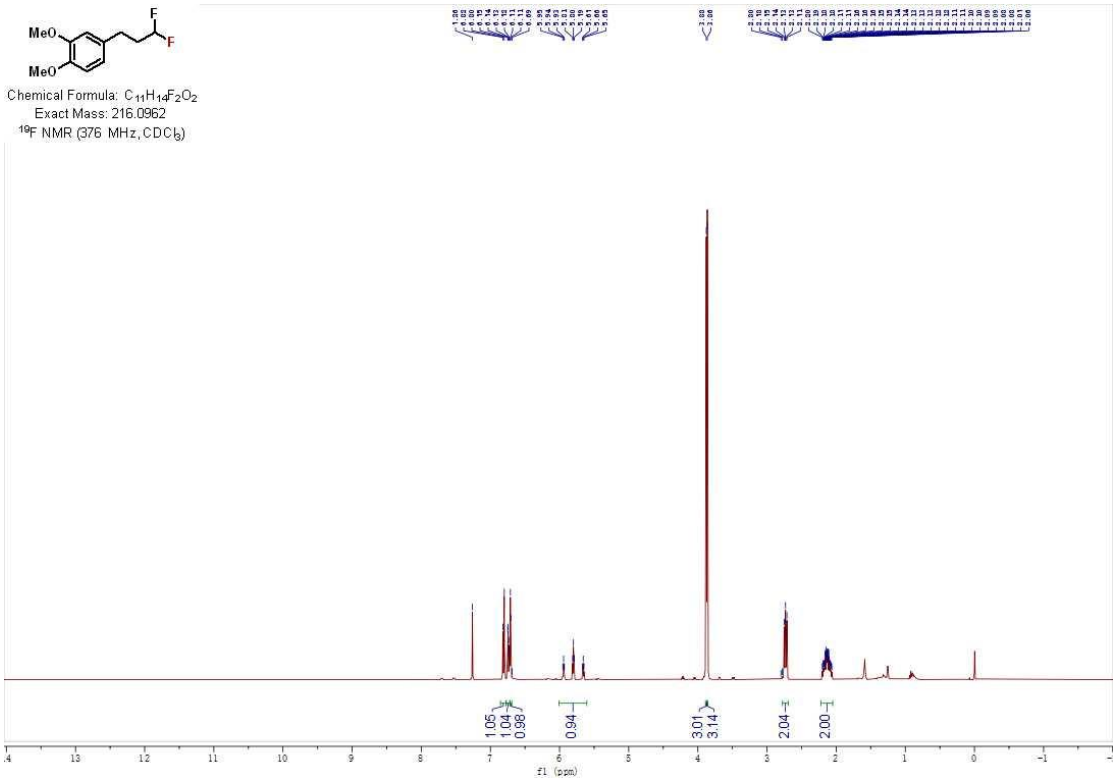
1-(3,3-Difluoropropyl)-4-methoxybenzene (2c)

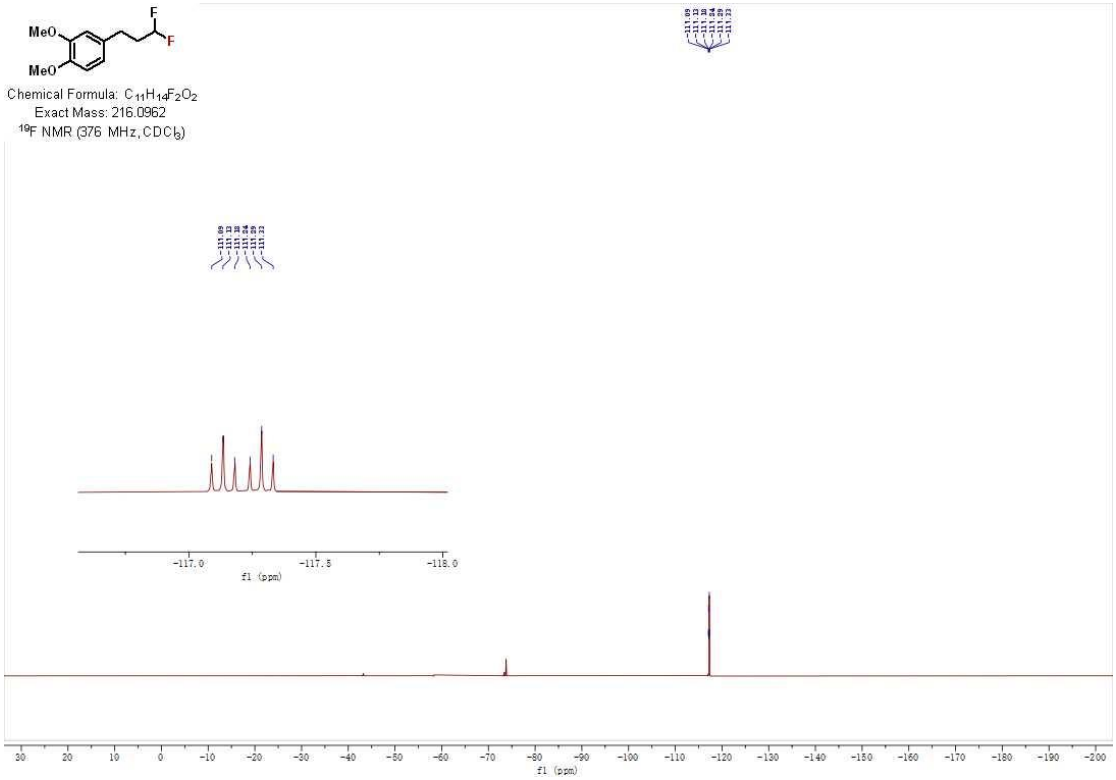


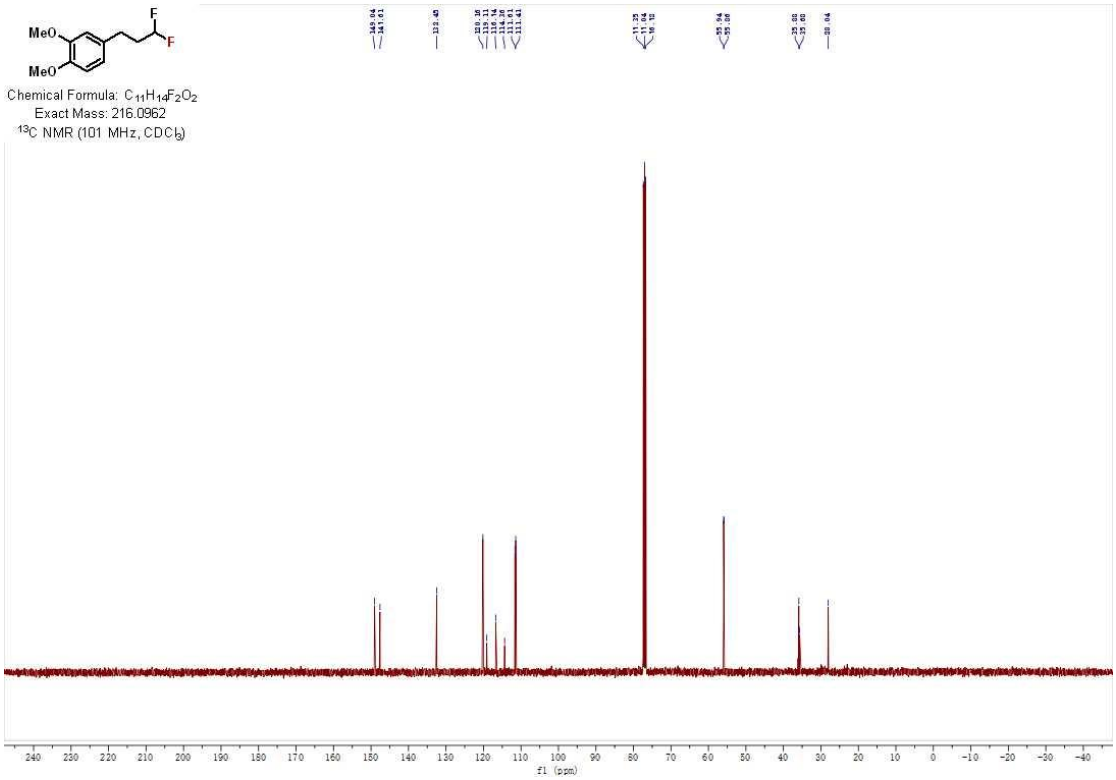

F
F
MeO
Chemical Formula: $C_{10}H_{12}F_2O$
Exact Mass: 186.0856
^{19}F NMR (376 MHz, $CDCl_3$)
f1 (ppm)


F
F
MeO
Chemical Formula: $C_{10}H_{12}F_2O$
Exact Mass: 186.0856
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)

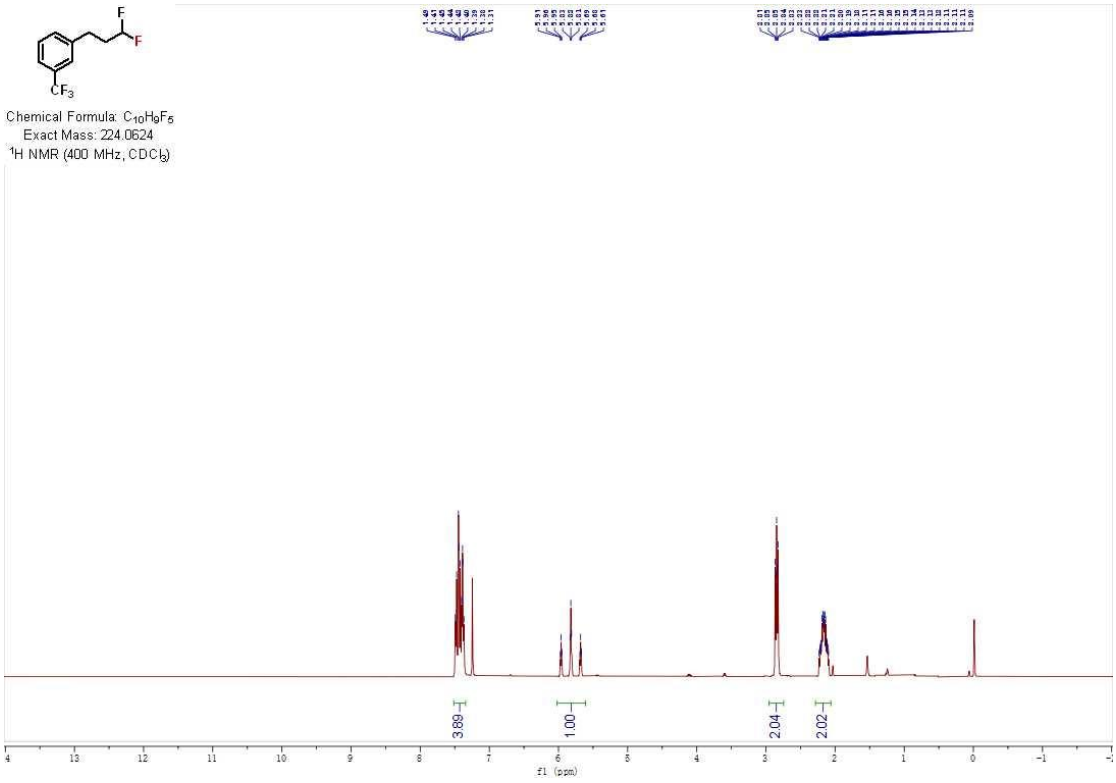
4-(3,3-Difluoropropyl)-1,2-dimethoxybenzene (2d)

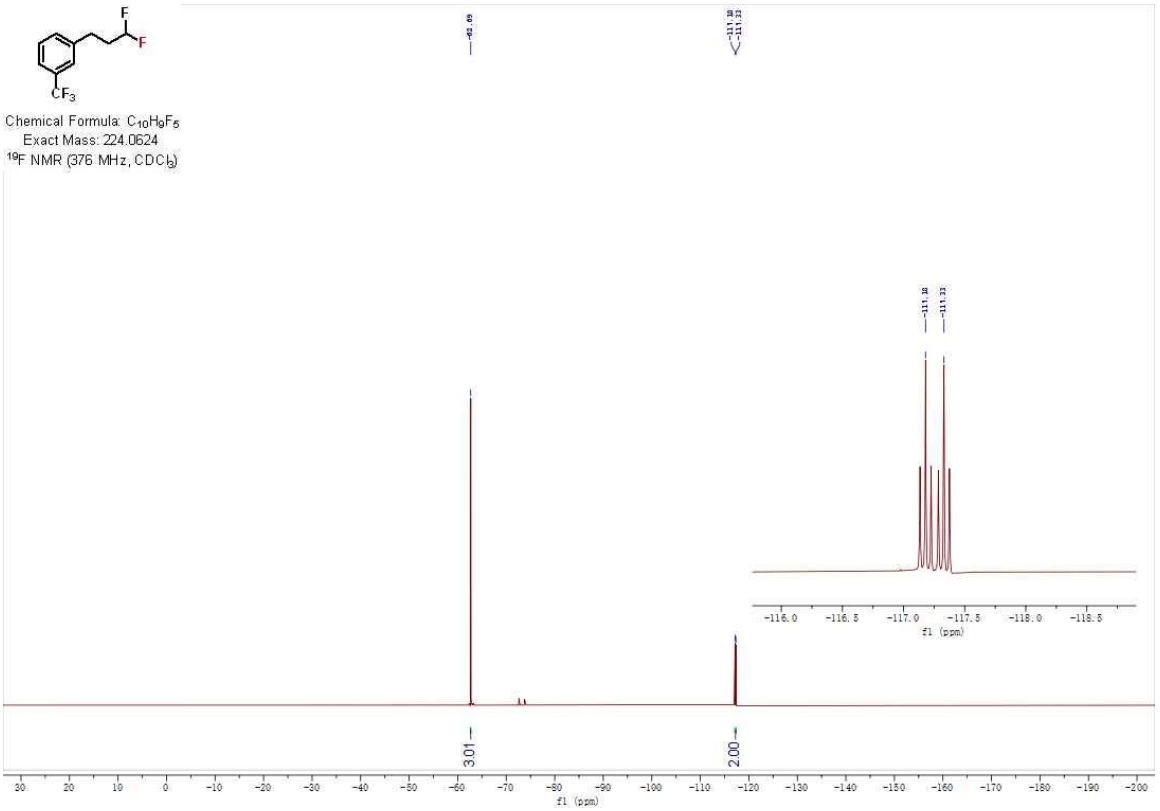


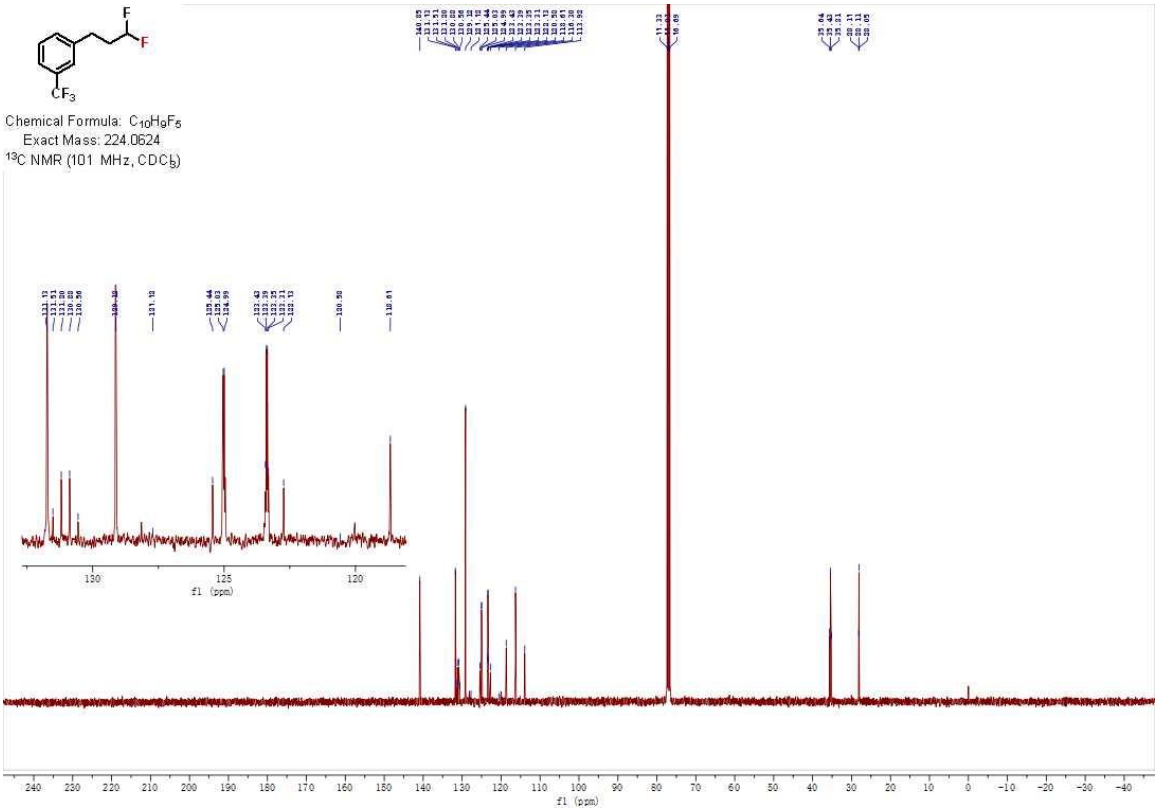




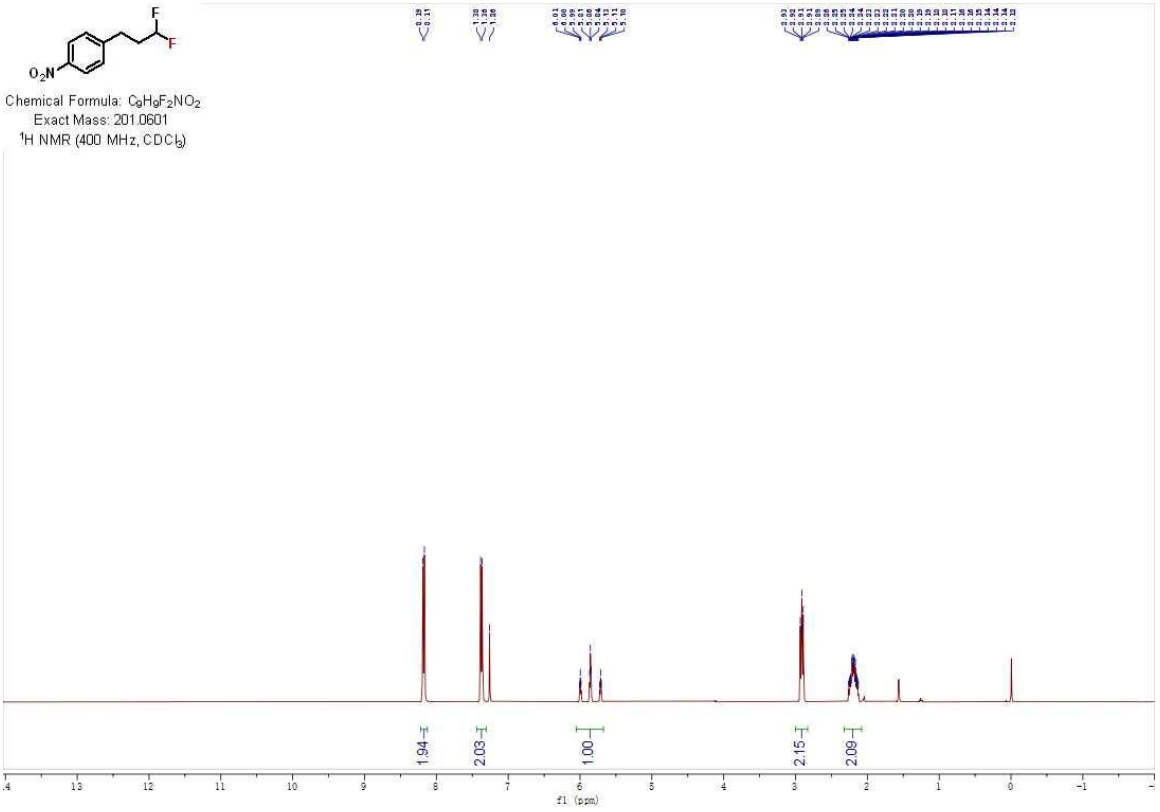
1-(3,3-Difluoropropyl)-3-(trifluoromethyl)benzene (2e)

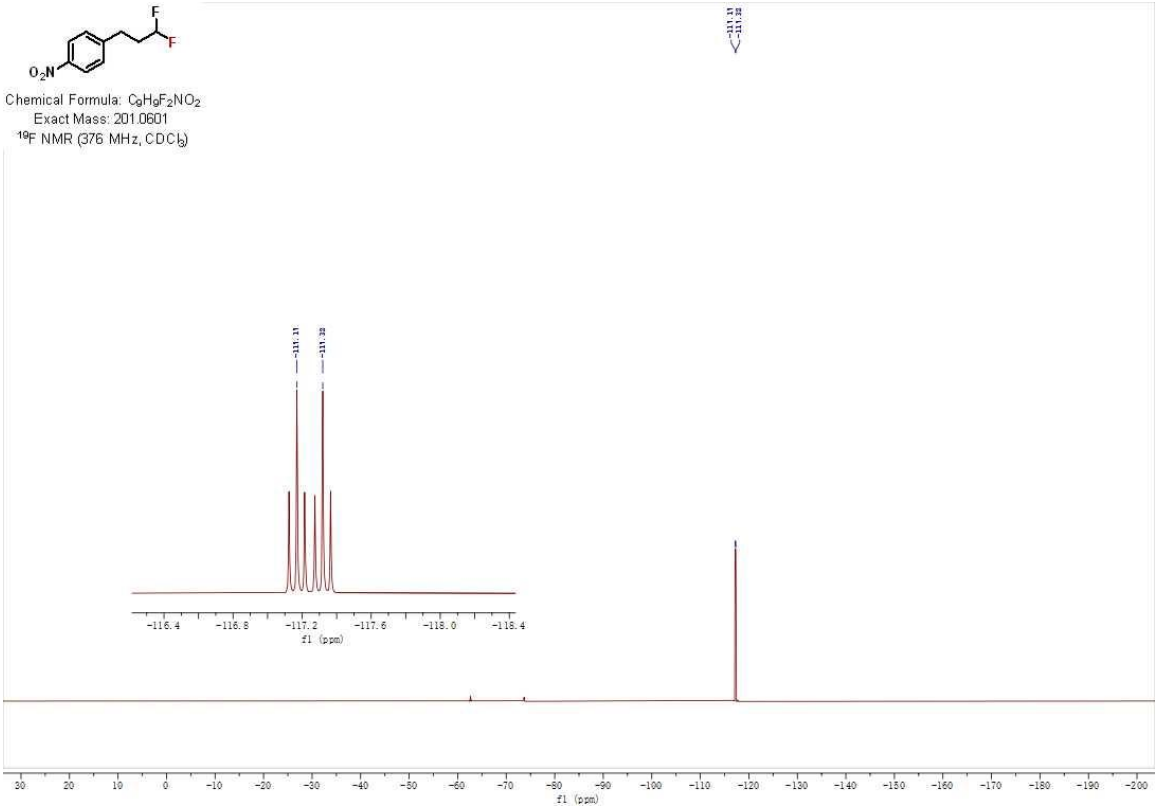


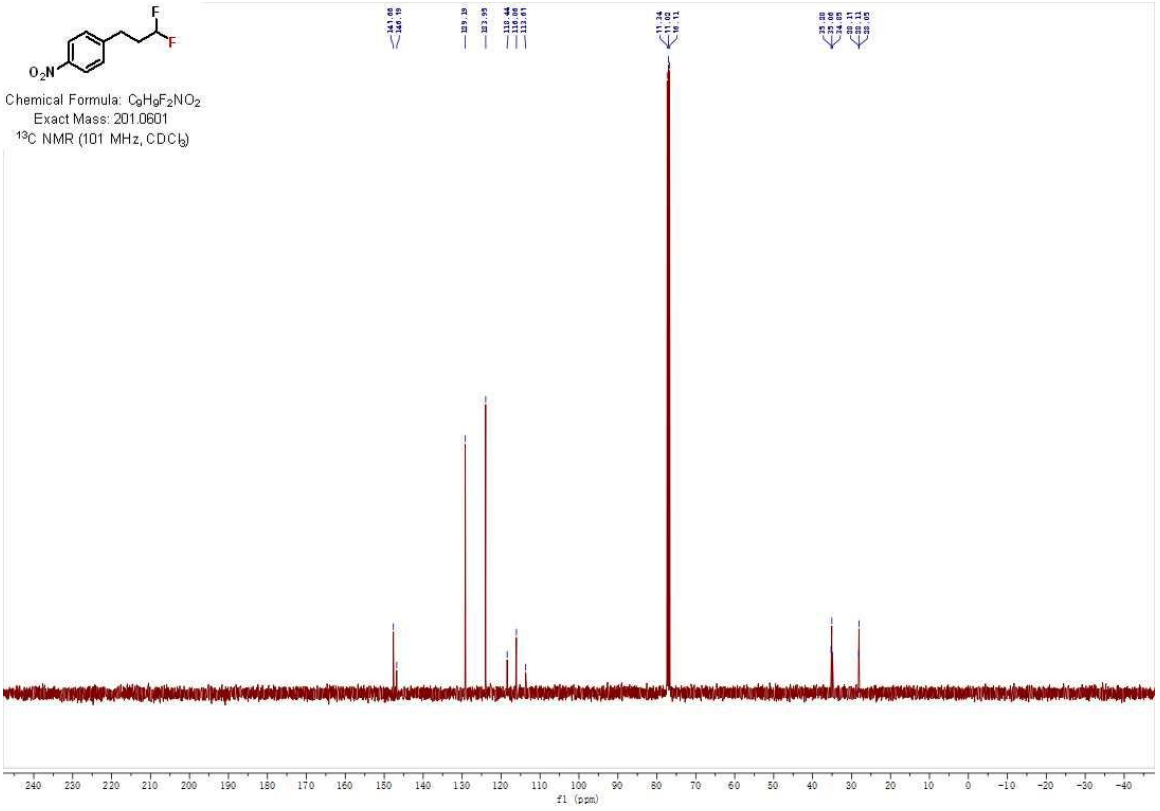

Chemical Formula: C10H9F5
Exact Mass: 224.0624
19F NMR (376 MHz, CDCl3)
3.01
2.00
f1 (ppm)


Chemical Formula: C10H9F5
Exact Mass: 224.0624
13C NMR (101 MHz, CDCl3)
f1 (ppm)

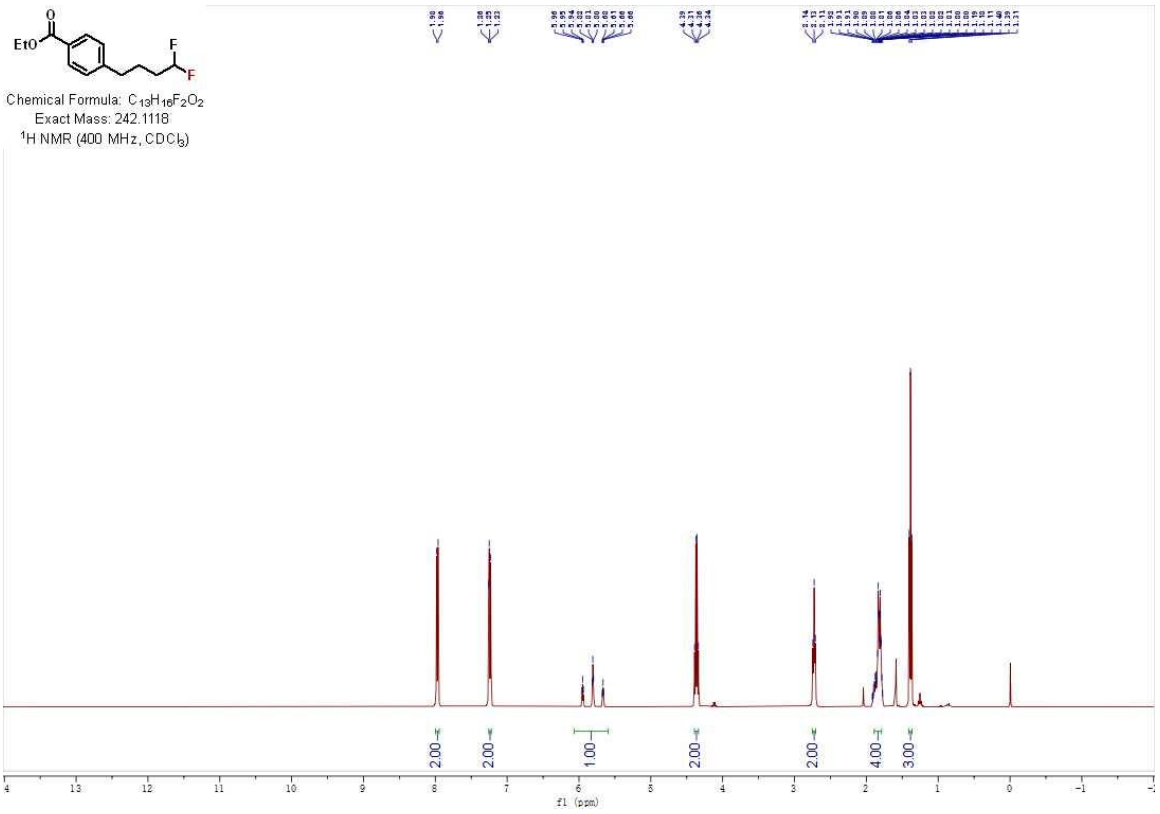
1-(3,3-Difluoropropyl)-4-nitrobenzene (2f)

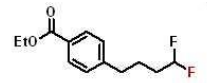




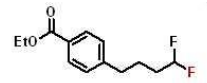


Ethyl 4-(4,4-difluorobutyl)benzoate (2g)



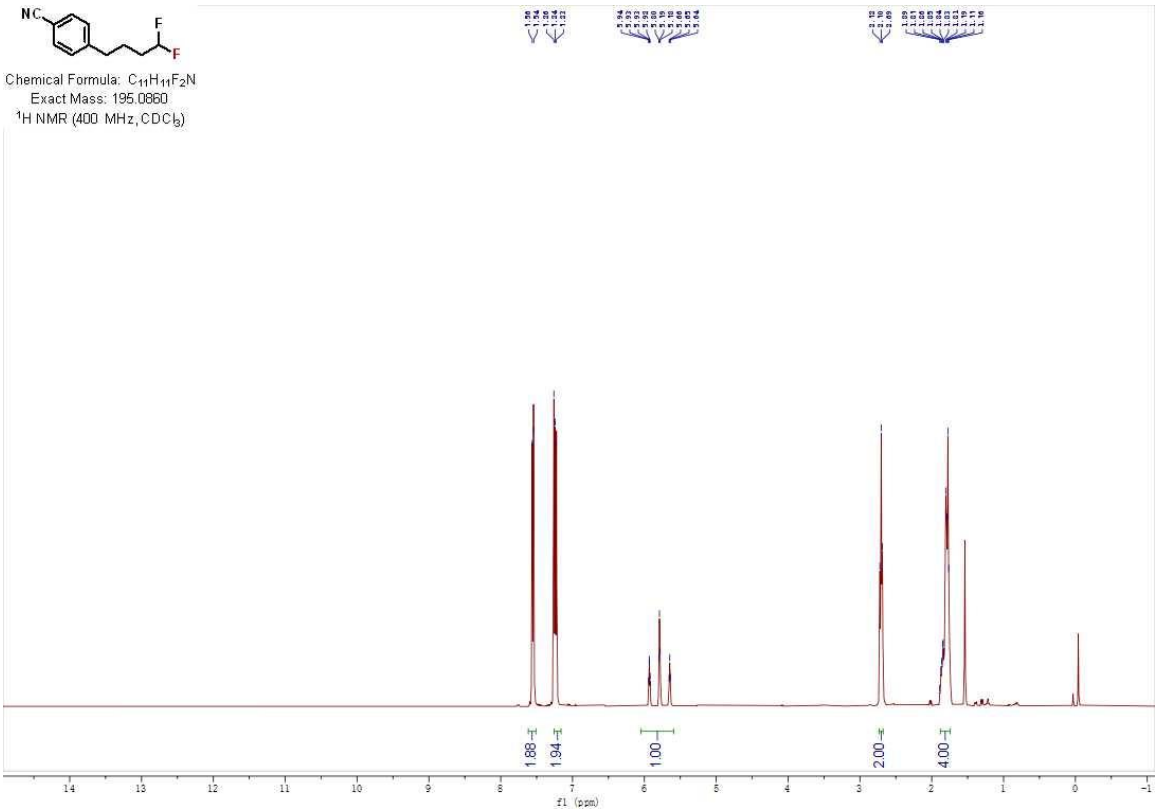


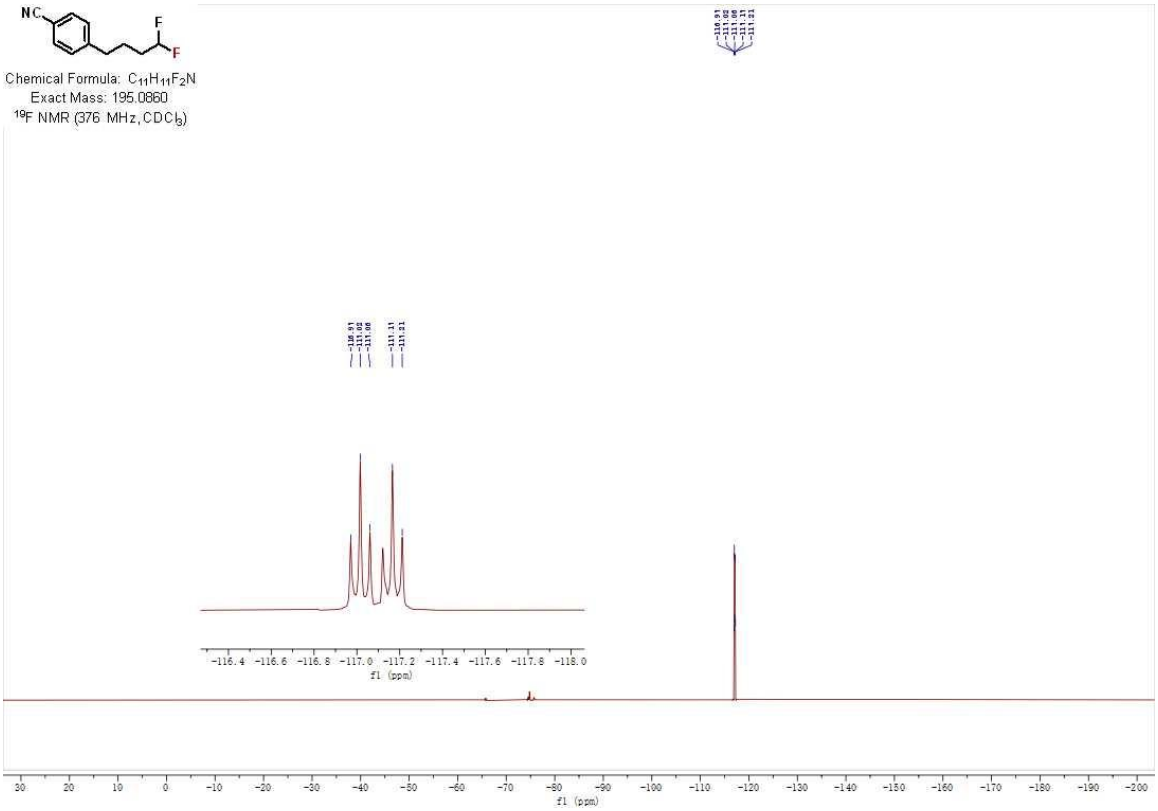
Chemical Formula: $C_{13}H_{16}F_2O_2$
Exact Mass: 242.1118
^{19}F NMR (376 MHz, $CDCl_3$)

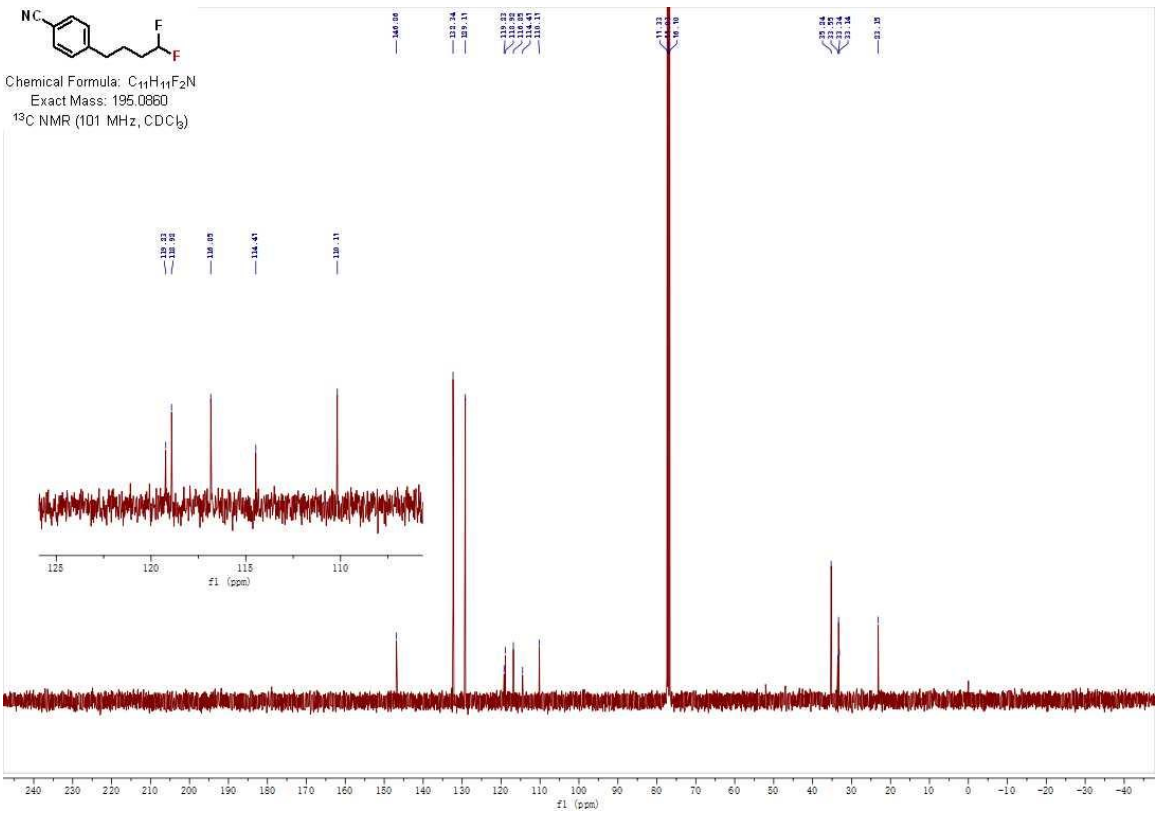


Chemical Formula: $C_{13}H_{16}F_2O_2$
Exact Mass: 242.1118
^{13}C NMR (101 MHz, $CDCl_3$)

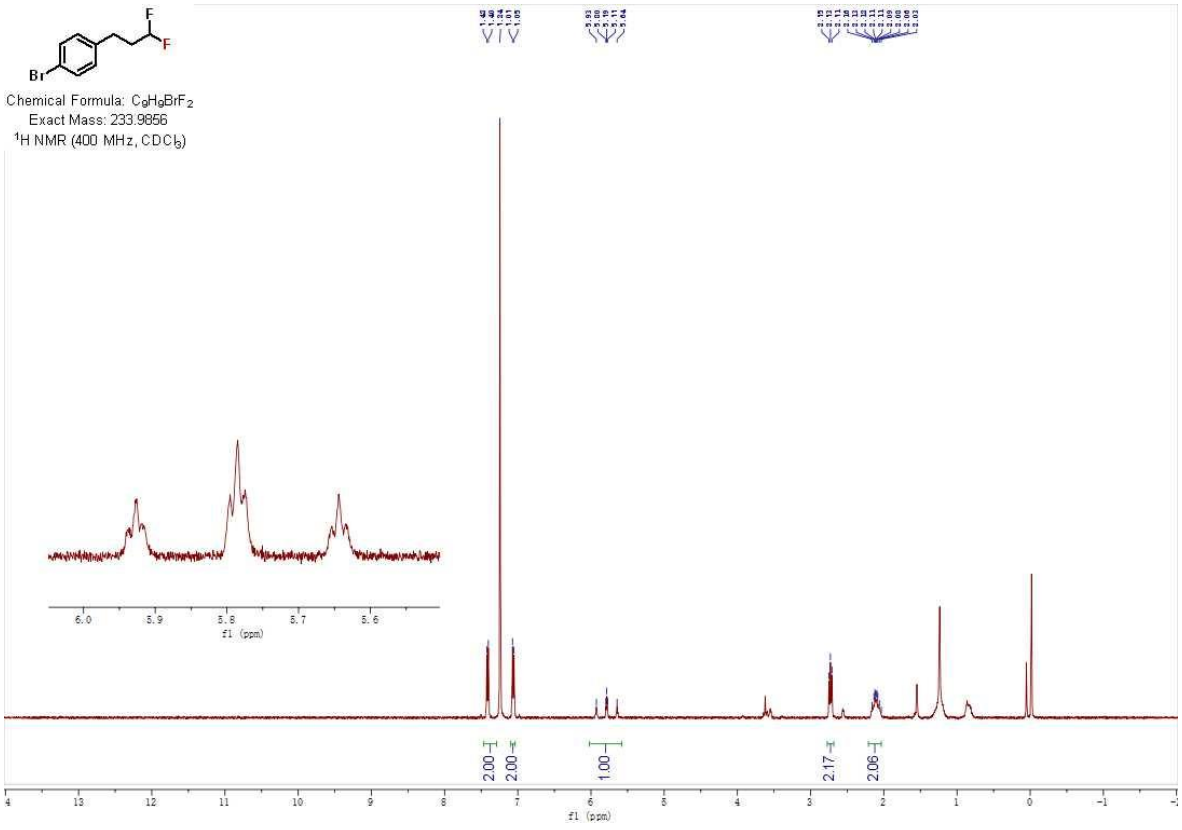
4-(4,4-Difluorobutyl)benzonitrile (2h)

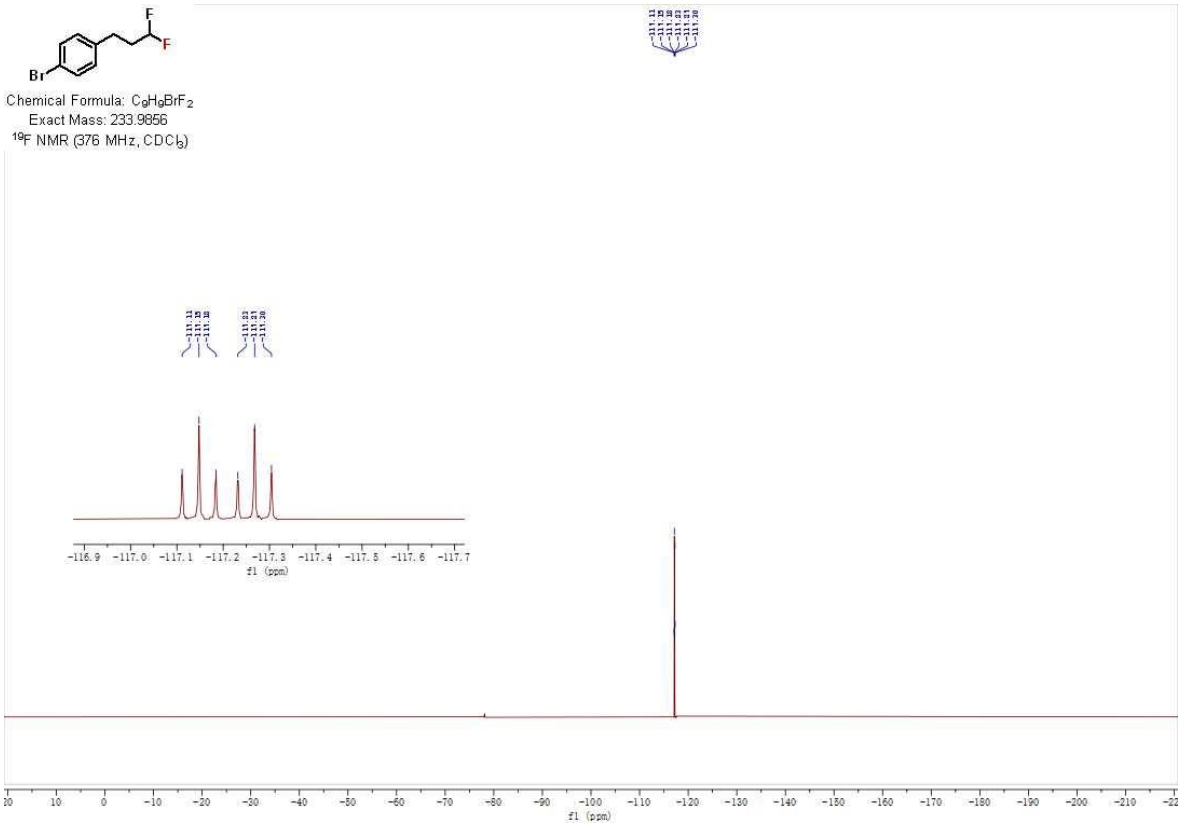


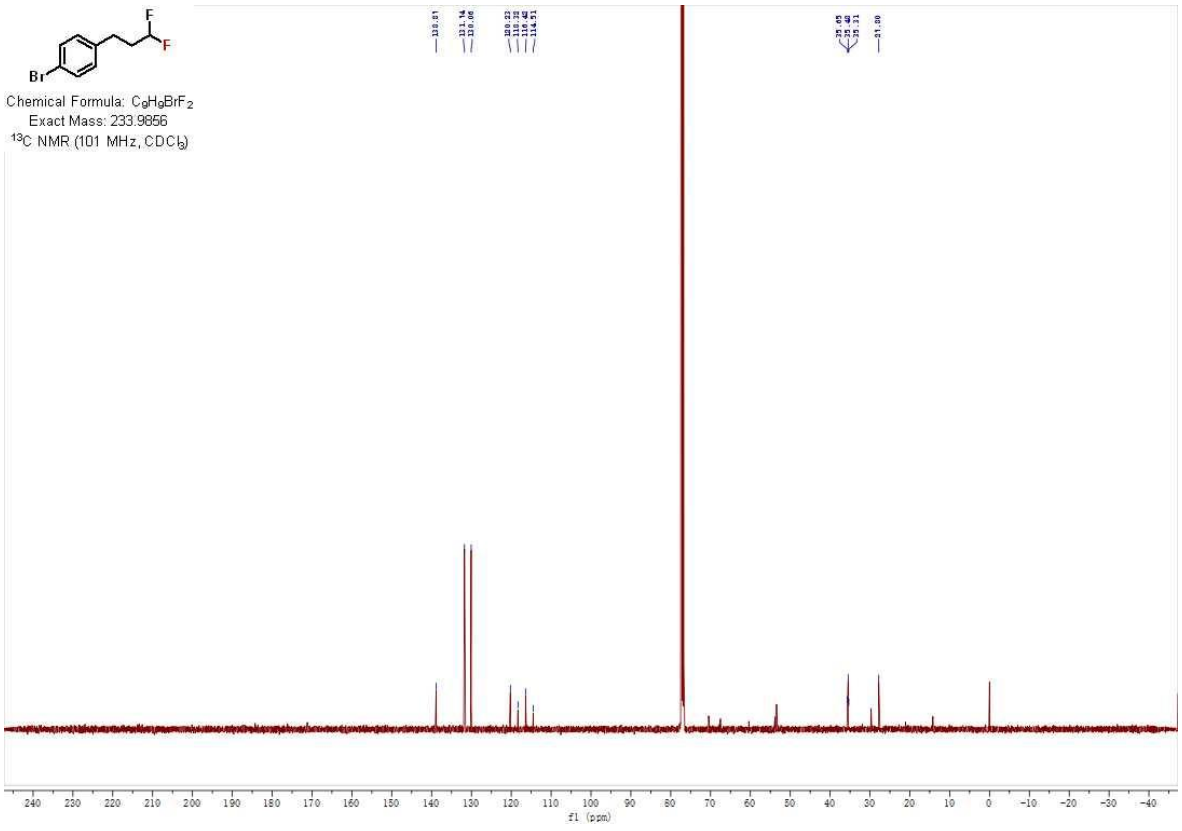




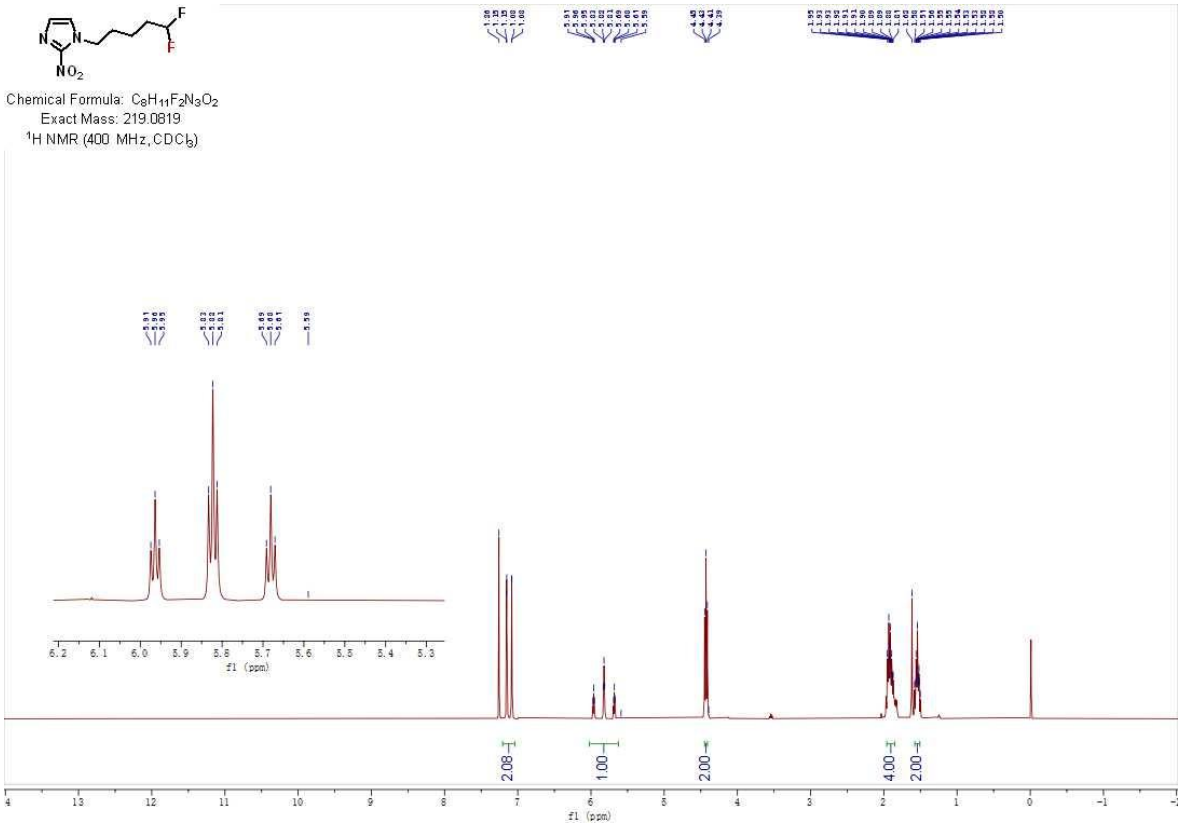
1-Bromo-4-(3,3-difluoropropyl)benzene (2i)

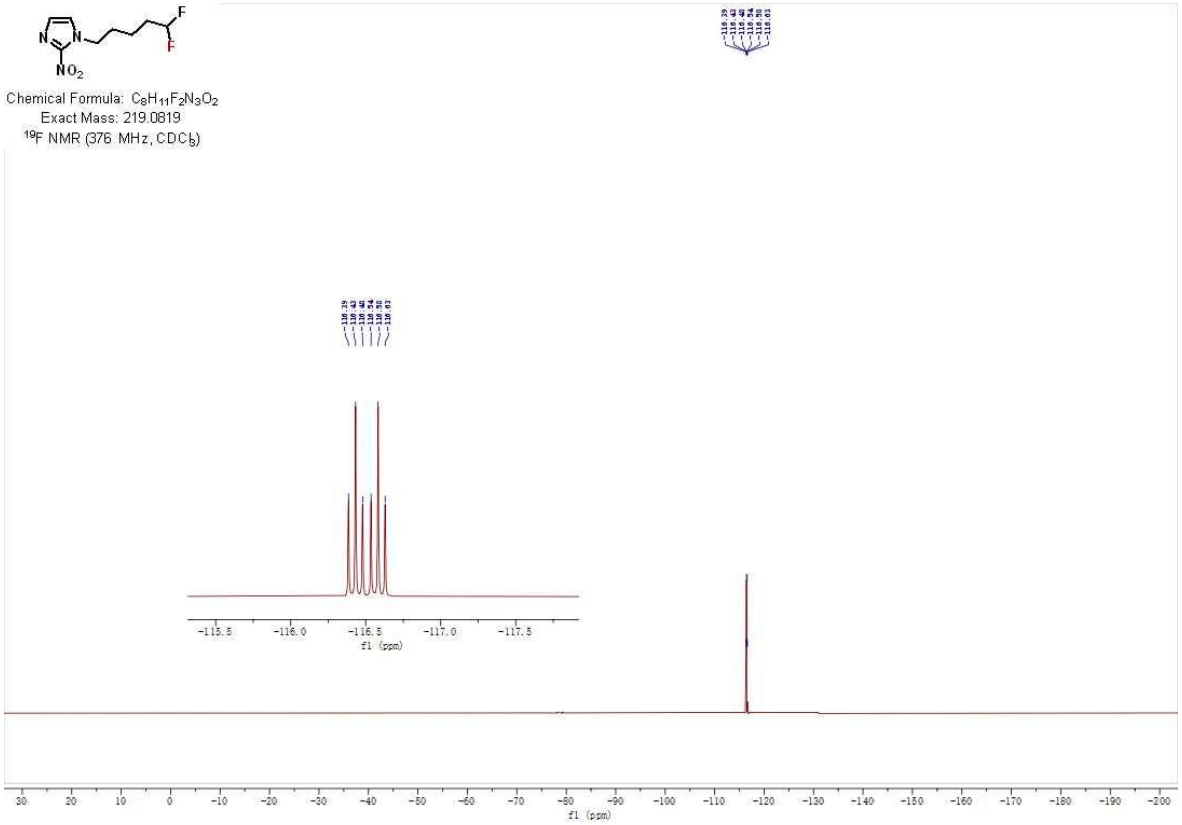


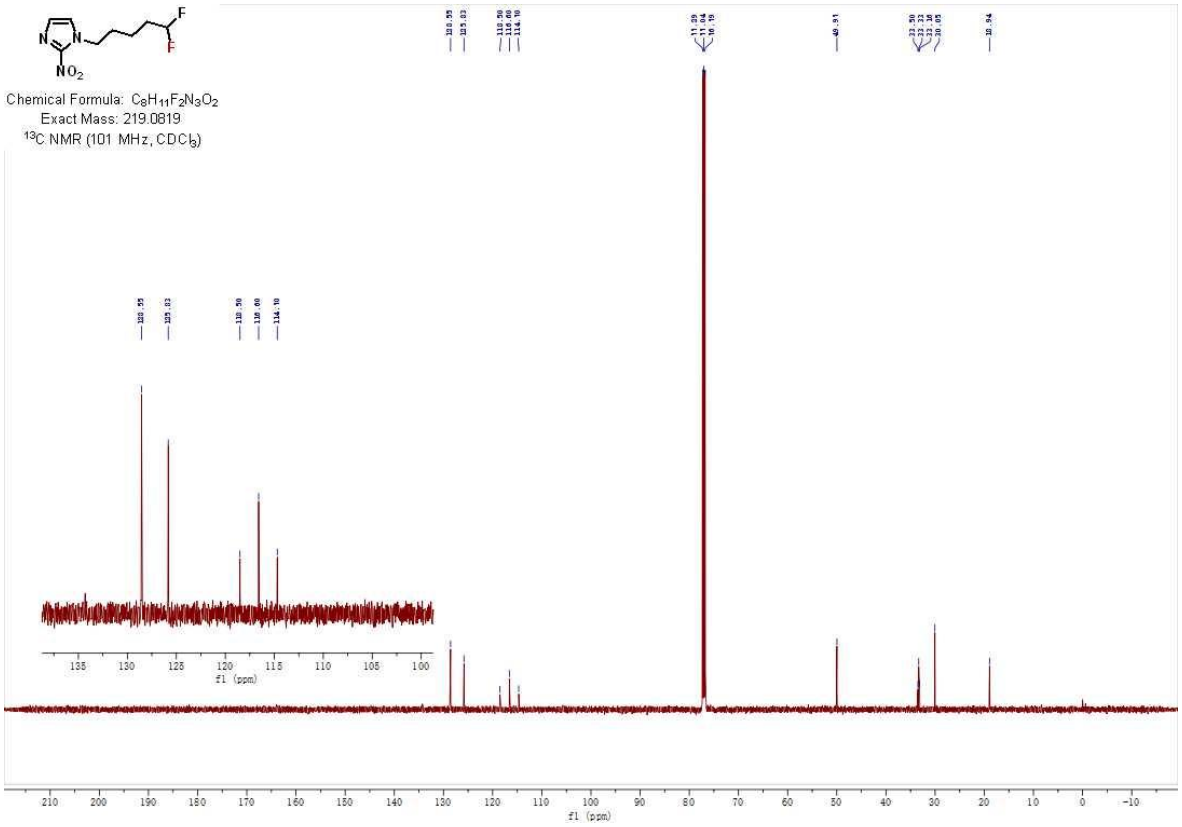

Chemical Formula: C9H6BrF2
Exact Mass: 233.9856
19F NMR (376 MHz, CDCl3)
f1 (ppm)


Chemical Formula: C9H6BrF2
Exact Mass: 233.9856
13C NMR (101 MHz, CDCl3)
f1 (ppm)

1-(5,5-Difluoropentyl)-2-nitro-1H-imidazole (2j)






Chemical Formula: $C_8H_{11}F_2N_3O_2$
Exact Mass: 219.0819
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)