

Supplementary Information for

Defluorinative Functionalization Approach led by Difluoromethyl Anion Chemistry

Kensuke Muta, Kazuhiro Okamoto, Hiroki Nakayama, Shuto Wada, Aiichiro Nagaki*

*Corresponding author. Email: nagaki@sci.hokudai.ac.jp

Table of Contents

General Information.....	S2
Experimental Procedures.....	S3
Defluorinative functionalization products characterizations	S29
NMR Spectra	S53
References	S88

General Information

Equipment

GC analyses were performed on a SHIMADZU GC-2014 gas chromatograph (column, Rtx-200; 0.25 mm x 30 m). GC yields were calculated by GC analyses with *n*-undecane as an internal standard using calibration lines derived from commercial compounds with internal standards. NMR spectra were recorded on JEOL JNM-ECZ400S spectrometers (400 MHz for ^1H , using Me_4Si as a standard (0.0 ppm); 100 MHz for ^{13}C , using CHCl_3 in CDCl_3 as a standard (77.0 ppm); 376 MHz for ^{19}F , using C_6F_6 as a standard (-162.9 ppm) in CDCl_3 as a standard). NMR yields were calculated by ^{19}F NMR with C_6F_6 as an internal standard. EI mass spectra were recorded on JMS-T2000GC spectrometer. ESI mass spectra were recorded on Exactive Plus HPLC: UltiMate 3000. APCI mass spectra were recorded on Exactive Plus HPLC: UltiMate 3000. Some of the mass spectra were measured by the Instrumental Analysis Service at Hokkaido University. GPC separation was performed on Japan Analytical Industry Co., Ltd LC-9201. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm). All batch reactions were carried out in flame-dried glassware under an argon atmosphere.

Flow system

Commercially available stainless steel (SUS304) T-shaped micromixers (**M1** and **M2**) with inner diameters of 250 μm (Sanko Seiki Co., Inc.) were purchased and used without modifications. Stainless steel (SUS316) microtube reactors (**R1** and **R2**) with inner diameter of 250–1000 μm , and three tube precooling units (**P1**, **P2**, and **P3**) with inner diameter of 1000 μm purchased from GL Sciences were used unless otherwise stated. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUV). The flow microreactor system was immersed in a cryogenic mixture bath with dry ice and acetone to control the temperature. Solutions were continuously introduced to the flow microreactor system using syringe pumps (Harvard PHD2000), equipped with gastight syringes purchased from SGE. All reactions were carried out under an atmosphere of argon.

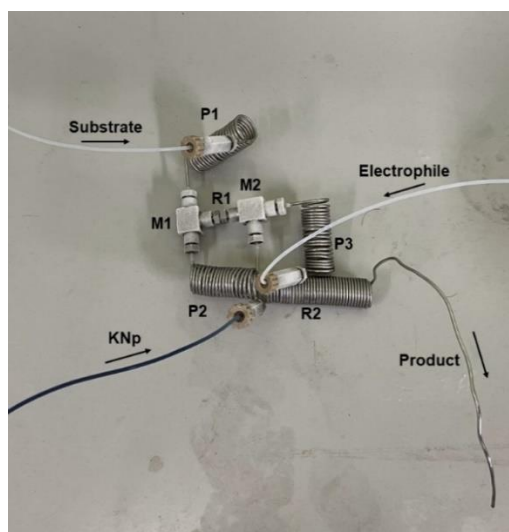


Fig. S1. Flow microreactor system

Materials

Dry tetrahydrofuran (THF), diethyl ether (Et_2O), 1,2-dimethoxyethane (DME), and triglyme were purchased from Kanto Chemical Co., Inc. and used without further purification. Dry diglyme and Potassium were also purchased from Sigma-Aldrich. Naphthalene (Np) was purchased from FUJIFILM Wako Pure Chemical Corporation. Substrates, electrophiles, and some other reagents were purchased from Tokyo Chemical Industry Co., Ltd., FUJIFILM Wako Pure Chemical Corporation, Kanto Chemical Co., Inc., and Sigma-Aldrich. Some compounds were synthesized by the reported procedure.

Experimental Procedures

Preparation of Metal Naphthalenide (MNp)

Naphthalene (3.7 g, 28.6 mmol, 1.3 equiv) was dissolved in anhydrous THF (100.0 ml) (0.22 M). Metal (K, Li, Na, 22.0 mmol, 1.0 equiv) was added and the mixture was stirred for 2 h at ambient temperature until the solution became dark green.



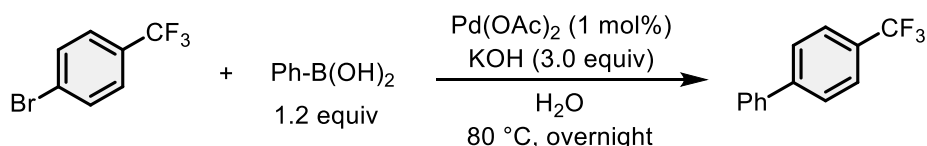
Fig. S2. Potassium Naphthalenide (KNp)

Procedure for preparation of starting materials and electrophiles

General Procedure of desalination process

Benzotrifluoride derivatives hydrochloride was dissolved in CH_2Cl_2 (20 mL) and slowly added sat. aq. NaHCO_3 (20 mL), extracted. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained benzotrifluoride derivatives used to react after drying.

4-phenyl-benzotrifluoride



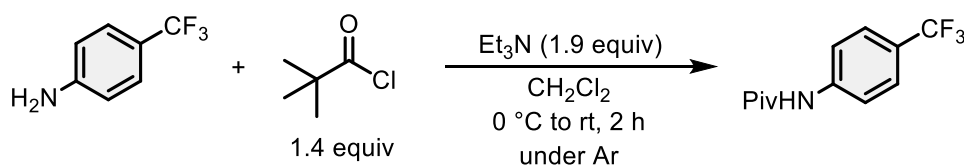
4-bromo-benzotrifluoride (5.0 g, 22 mmol), phenylboronic acid (3.2 g, 26.6 mmol, 1.2 equiv.), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 1 mol%), KOH (3.7 g, 67 mmol, 3 eq.), and H_2O (50 mL) were added to 100 mL two-necked round bottom flask and stirred overnight at 80 °C. After the reaction, the reaction mixture was extracted with EtOAc (3 x 5 mL), washed brine, and the organic layer was dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc= 10:1) to give the product. The NMR spectral data were identical to those reported in the literature¹.

NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.70 (s, 4H), 7.62-7.59 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.39 (m, 1H).

^{19}F NMR (376 MHz, CDCl_3) δ -62.29 (s, 3F).

3,3-Dimethyl-1-[4-(trifluoromethyl)phenyl]-2-butanone



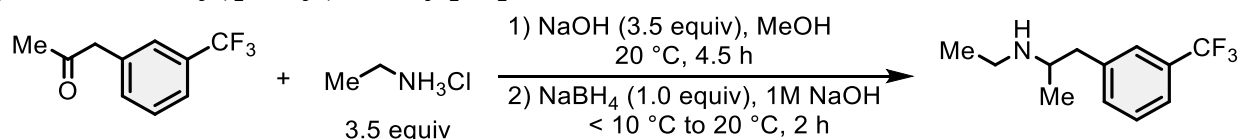
To a 100 mL two-necked round bottom flask was added substrate (4.9 g, 30.4 mmol) in CH_2Cl_2 (30 mL), cooled at 0 °C, then, triethylamine (5.8 g, 57.3 mmol, 1.9 equiv) was added dropwise. Pivaloyl chloride was added dropwise for 2 hours keeping below 10 °C. The reaction mixture was washed with water (2 x 50 mL) and sat. aq. NH_4Cl (2 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained solid was washed with hexane and filtration. The NMR spectral data were identical to those reported in the literature².

NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.43 (s, 1H), 1.33 (s, 9H).

^{19}F NMR (376 MHz, CDCl_3) δ -62.49 (s, 3F).

1-(3-(Trifluoromethyl)phenyl)-N-ethylpropan-2-amine³



To a stirred suspension of NaOH (17.4 g, 3.5 equiv) in methanol (85 mL) was added dropwise ethylamine hydrochloride (35.3 g, 3.5 equiv) in methanol (80 mL), over 30 minutes. Following 1-(3-trifluoromethyl)phenyl-propan-2-one (24.8 g, 122.7 mmol) was added to the mixture. The mixture was stirred at 20 °C for 4.5 hours, then cooled to 0 °C. Solution of sodium borohydride (4.7 g, 1.0 equiv) in 1M sodium hydroxide (10 mL) was added dropwise keeping the below 10 °C, and then was stirred at 20 °C for 2 hours. The reaction mixture was methanol (270 mL) removed then water (100 mL) was added and the mixture was extracted with hexane (100 mL). The aqueous phase was eliminated and the organic phase was washed with water (3 x 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was distilled under reduced pressure with a distillation of the vigreux column. The distillation heads were eliminated, and the bottom residue was purified through column chromatography (hexane/EtOAc= 10:1) on silica gel to yield free base fenfluramine as a colorless oil.

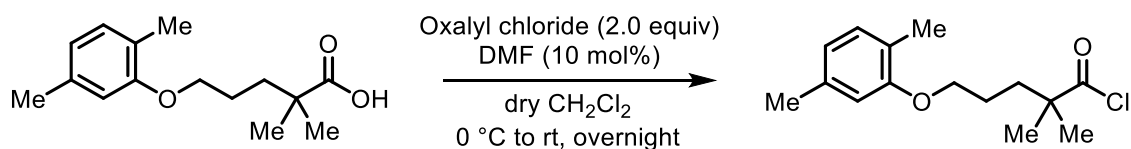
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.48-7.35 (m, 4H), 2.95-2.85 (m, 1H), 2.82 (dd, J =13.2, 6.4 Hz, 1H), 2.76-2.68 (m, 1H), 2.65-2.57 (m, 2H), 1.09-1.03 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 140.47, 132.68, 130.75, 130.43-130.28 (m), 128.69, 125.84 (t, J = 3.7 Hz), 122.97 (dt, J = 7.5, 3.7 Hz), 54.41, 43.32, 41.47, 20.11, 15.38 (d, J = 3.2 Hz).

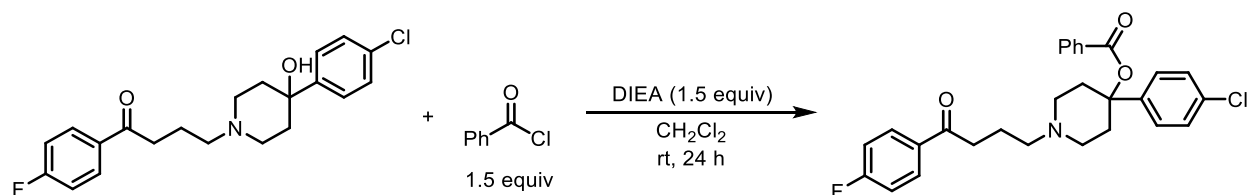
^{19}F NMR (376 MHz, CDCl_3) δ -63.77 (s, 3F).

Gemfibrozil chloride⁴



To a 100 mL two-necked round bottom flask was added Gemfibrozil (17.6 mmol), dry CH₂Cl₂ (40.0 mL), and 10 mol% of *N,N*-dimethyl formamide (DMF). The reaction mixture was cooled to 0 °C and stirred for 5 minutes. Then oxalyl chloride (4.3 g, 33.9 mmol, 2.0 equiv) was added dropwise to the reaction mixture and stirred at ambient temperature overnight. The resulting mixture was concentrated under reduced pressure and used directly without further purification for the reaction.

Benzonic acid haloperidol ester⁵



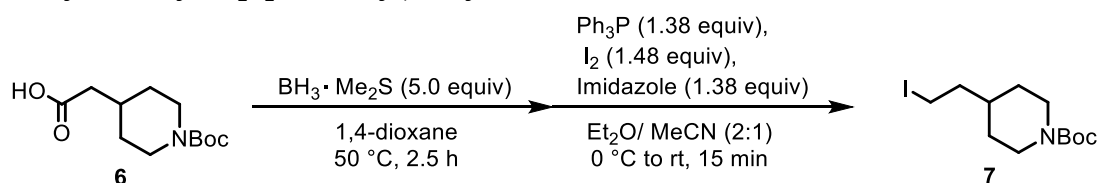
To a 50 mL two-necked round bottom flask was added Haloperidol (3.0 g, 7.8 mmol) in CH₂Cl₂ (30 mL). Ethyldiisopropylamine (DIEA) (2.0 mL, 11.7 mmol) and benzoyl chloride (1.4 mL, 11.7 mmol) were added, and then the reaction mixture was stirred at ambient temperature for 24 hours. The solution was quenched with sat. aq. NaHCO₃ (100 mL), was extracted into CH₂Cl₂ (4 x 100 mL), and concentrated. The residue was purified through column chromatography (MeOH/dichloromethane= 10:1) on silica gel. The NMR spectral data were identical to those reported in the literature.

NMR Spectroscopy:

¹H NMR (400 MHz, CDCl₃) δ 8.05-7.99 (m, 4H), 7.60-7.56 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 2.6 Hz, 4H), 7.12 (t, *J* = 8.6 Hz, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.88 (d, *J* = 11.5 Hz, 2H), 2.60 (d, *J* = 12.2 Hz, 2H), 2.49-2.41 (m, 4H), 2.09-1.95 (m, 4H).

¹⁹F NMR (376 MHz, CDCl₃) δ -105.90 (s, 1F).

2-(*N*-*tert*-Butoxycarbonyl-4-piperodonyl) ethyl iodide⁶



To a 200 mL two-necked round bottom flask was added *N*-*tert*-Butoxycarbonyl-4-piperidineacetic acid **6** (5.1 g, 21.0 mmol) in 1, 4-dioxane (100 mL) and dimethyl sulfide borane (9.8 mL, 5.0 equiv), and were stirred at 50 °C for 2.5 hours. Then the reaction mixture was concentrated under reduced pressure. The residue was quenched with water (50 mL), and extracted with $\text{Et}_2\text{O}/\text{EtOAc}$ (200 mL, 1:1), washed with 1M aq. NaOH (50 mL) and brine (50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Following the obtained crude product (4.6 g), Imidazole (1.9 g, 1.38 equiv), and triphenylphosphine (7.2 g, 1.38 equiv) were added to 200 mL two-necked round bottom flask and cooled to 0 °C. The reaction mixture was stirred and I_2 (7.4 g, 1.48 equiv) was added dropwise. Then the reaction mixture was stirred at ambient temperature for 15 minutes and was added to Et_2O (200 mL). The solution was washed with sat. aq. Na_2SO_4 (2 x 200 mL), sat. aq. CaSO_4 (200 mL), and brine. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by short-column chromatography (hexane) and concentrated under reduced pressure to afford the pure product as a brown oil in 70 % overall yield (4.92 g). The NMR spectral data were identical to those reported in the literature.

NMR Spectroscopy:

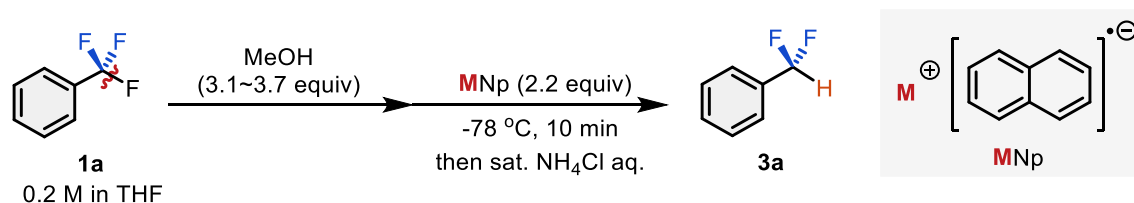
^1H NMR (400 MHz, CDCl_3) δ ^0Pr -NMR (400 MHz): δ 4.10 (s, 2H), 3.22 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 11.3 Hz, 2H), 1.78 (q, J = 7.0 Hz, 2H), 1.67-1.54 (m, 3H), 1.45 (s, 9H), 1.10 (qd, J = 12.1, 4.3 Hz, 2H).

General procedure for hydrodefluorination in the batch reactor.

Method A (in the presence of methanol)

To a 10 mL test tube were added benzotrifluoride (29.2 mg, 0.2 mmol), methanol (3.1–3.7 equiv), and THF (2 mL). To a stirred solution at -78 °C, and then metal naphthalenide (0.22 M in THF) was added dropwise. After stirring for 10 min, the reaction mixture was quenched with sat. aq. NH₄Cl (5 mL). The organic layer was analyzed by gas chromatography with an undecane as an internal standard.

Table S1. Hydrodefluorination using metal naphthalenides in the presence of methanol*



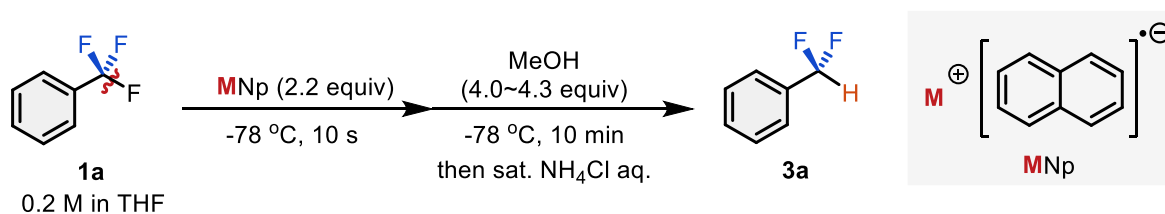
entry	metal	yield of 3a / %	recovery of 1a / %
1	Li	trace	77
2	Na	7	70
3	K	3	53

*Reaction conditions: **1a** (0.2 mmol), MeOH (3.1–3.7 equiv), MNp (2.2 equiv), -78 °C, 10 min. Yields and conversions were determined by gas chromatography with an internal standard.

Method B (in the absence of methanol)

To a 10 mL test tube were added benzotrifluoride (29.2 mg, 0.2 mmol), and THF (2 mL). To a stirred solution at -78 °C, and then metal naphthalenide (0.22 M in THF) was added dropwise. After stirring for 10 sec, and then methanol (4.0–4.3 equiv) was added. The mixture was stirred for 10 min, the reaction mixture was quenched with sat. aq. NH₄Cl (5 mL). The organic layer was analyzed by gas chromatography with an undecane as an internal standard.

Table S2. Hydrodefluorination using metal naphthalenides in the absence of methanol*



entry	metal	yield of 3a / %	recovery of 1a / %
1	Li	n.d.	55
2	Na	n.d.	54
3	K	trace	47

*Reaction conditions: **1a** (0.2 mmol), MeOH (4.0–4.3 equiv), MNp (2.2 equiv), -78 °C, 10 min. Yields and conversions were determined by gas chromatography with an internal standard.

Optimization of hydrodefluorination in the absence of methanol under the flow

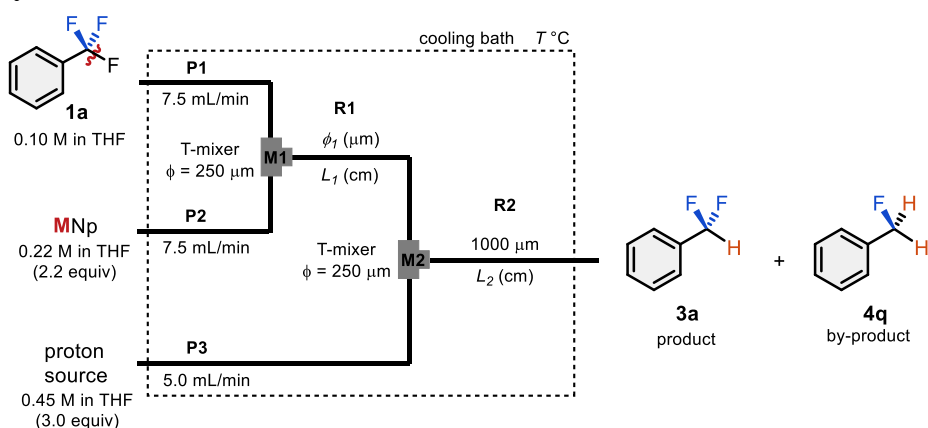


Fig. S3. Hydrodefluorination of benzotrifluoride in flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250 \mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$)) was used. The flow microreactor system was cooled by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in solvent) (flow rate: 7.5 mL/min) and a solution of metal naphthalenide (MNp) (0.22 M in THF) (flow rate: 7.5 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.45 M in solvent) (flow rate: 5.0 mL/min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000 \mu\text{m}$). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yields of difluoromethyl benzene (**3a**) were determined by gas chromatography with an undecane as an internal standard. The optimizations are summarized in Table S3.

Table S3. Optimization of hydrodefluorination using flow microreactor

entry	metal	proton source	R1		R2	t^{R1}	t^{R2}	solvent	T	yield of 3a	recovery of 1a	yield of 4q
			ϕ_1	L_1	L_2							
	/equiv	/equiv	μm	/cm	/cm	/sec	/sec	/volume ratio	/°C	/%	/%	/%
1	Li/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	n.d.	28	n.d.
2	Li/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	n.d.	20	n.d.
3	Li/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	n.d.	19	n.d.
4	Li/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	n.d.	19	n.d.
5	Li/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	n.d.	19	n.d.
6*	Na/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	32	10	n.d.
7*	Na/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	29	10	n.d.
8*	Na/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	20	17	n.d.
9*	Na/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	20	26	n.d.
10*	Na/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	trace	19	n.d.
11	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	68	14	n.d.
12	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	70	15	n.d.

13	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	66	14	n.d.
14	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	66	14	n.d.
15	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	60	13	n.d.
16	K/ 2.1	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	60	20	3
17	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	75	9	6
18	K/ 2.5	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	72	3	10
19	K/ 3.0	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	61	5	17
20	K/ 2.2	MeOH/1.5	250	3.5	200	0.0069	4.7	THF	-78	20	35	trace
21	K/ 2.2	MeOH/2.0	250	3.5	200	0.0069	4.7	THF	-78	56	22	3
22	K/ 2.2	MeOH/5.0	250	3.5	200	0.0069	4.7	THF	-78	69	13	-
23	K/ 2.2	TFE/1.5	250	3.5	200	0.0069	4.7	THF	-78	51	27	trace
24	K/ 2.2	TFE/2.0	250	3.5	200	0.0069	4.7	THF	-78	50	32	trace
25	K/ 2.2	TFE/3.0	250	3.5	200	0.0069	4.7	THF	-78	41	42	trace
26	K/ 2.2	AcOH/1.5	250	3.5	200	0.0069	4.7	THF	-78	31	42	trace
27	K/ 2.2	AcOH/2.0	250	3.5	200	0.0069	4.7	THF	-78	29	50	trace
28	K/ 2.2	AcOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	19	59	trace
29	K/ 2.2	MeOH/3.0	250	3.5	50	0.0069	1.2	THF	-78	51	trace	10
30	K/ 2.2	MeOH/3.0	250	3.5	100	0.0069	2.4	THF	-78	63	10	trace
31	K/ 2.2	MeOH/3.0	250	3.5	300	0.0069	7.1	THF	-78	66	13	5
32	K/ 2.2	MeOH/3.0	250	3.5	400	0.0069	9.4	THF	-78	62	8	4
34	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-78	74	trace	9
35	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-78	73	5	trace
36	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-78	77	4	trace
37	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-78	69	3	trace
38	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-78	71	trace	trace
39	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-78	71	6	trace
40	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-78	67	3	trace
41	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-78	68	trace	trace
42	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF [†]	-78	64	15	trace
43	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF [†]	-78	62	17	trace
44	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF [†]	-78	60	16	trace
45	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF [†]	-78	58	15	trace

46	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF [†]	-78	57	12	trace
47	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF [†]	-78	55	13	trace
48	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF [†]	-78	54	13	trace
49	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF [†]	-78	48	12	trace
50	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/ diglyme /10:1	-78	50	trace	15
51	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/ diglyme /10:1	-78	67	5	10
52	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/ diglyme /10:1	-78	73	trace	trace
53	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/ diglyme /10:1	-78	75	trace	trace
54	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/ triglyme /10:1	-78	46	4	14
55	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/ triglyme /10:1	-78	60	9	12
56	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/ triglyme /10:1	-78	74	trace	4
57	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/ triglyme /10:1	-78	71	trace	4
58	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-20	30	24	trace
59	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-20	26	26	trace
60	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-20	15	30	trace
61	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-20	trace	25	trace
62	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-20	trace	22	trace
63	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-20	trace	19	trace

64	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-20	trace	31	trace
65	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-20	trace	31	trace
66	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-40	54	22	trace
67	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-40	54	22	trace
67	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-40	44	24	trace
68	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-40	45	22	trace
69	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-40	38	24	trace
70	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-40	38	22	trace
71	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-40	22	33	trace
72	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-40	20	27	trace
73	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-60	71	12	trace
74	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-60	73	15	trace
75	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-60	73	14	trace
76	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-60	72	13	trace
77	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-60	72	14	trace
78	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-60	68	13	trace
79	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-60	58	7	trace
80	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-60	49	6	trace

*The reactions carried out with half the concentrations of 1a, NaNp, MeOH. †5.0 equiv of 1,2-dimethoxyethane was used for the benzotrifluoride.

In-line IR monitoring experiment

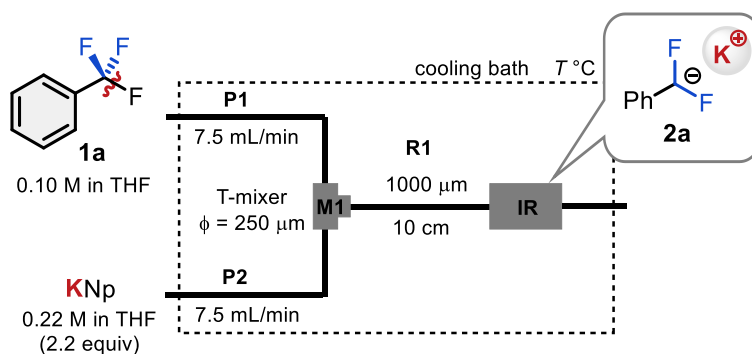


Fig. S4. In-line IR monitoring of generation of difluoromethyl benzyl anion **2a** in flow

A flow microreactor system consisting of two T-shaped micromixers **M1** (inner diameter $\phi = 250 \mu\text{m}$), PTFE tube **R1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 10 \text{ cm}$), two tube precooling units **P1** and **P2** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), and **IR** unit was used. The flow microreactor system was cooled at $-20 \text{ }^{\circ}\text{C}$ or $-78 \text{ }^{\circ}\text{C}$ by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF) (flow rate: 7.5 mL/min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/min) were introduced to **M1** by syringe pumps. Then, a solution was passed through **R1** and **IR**. After a steady state was reached, IR measurement was started.

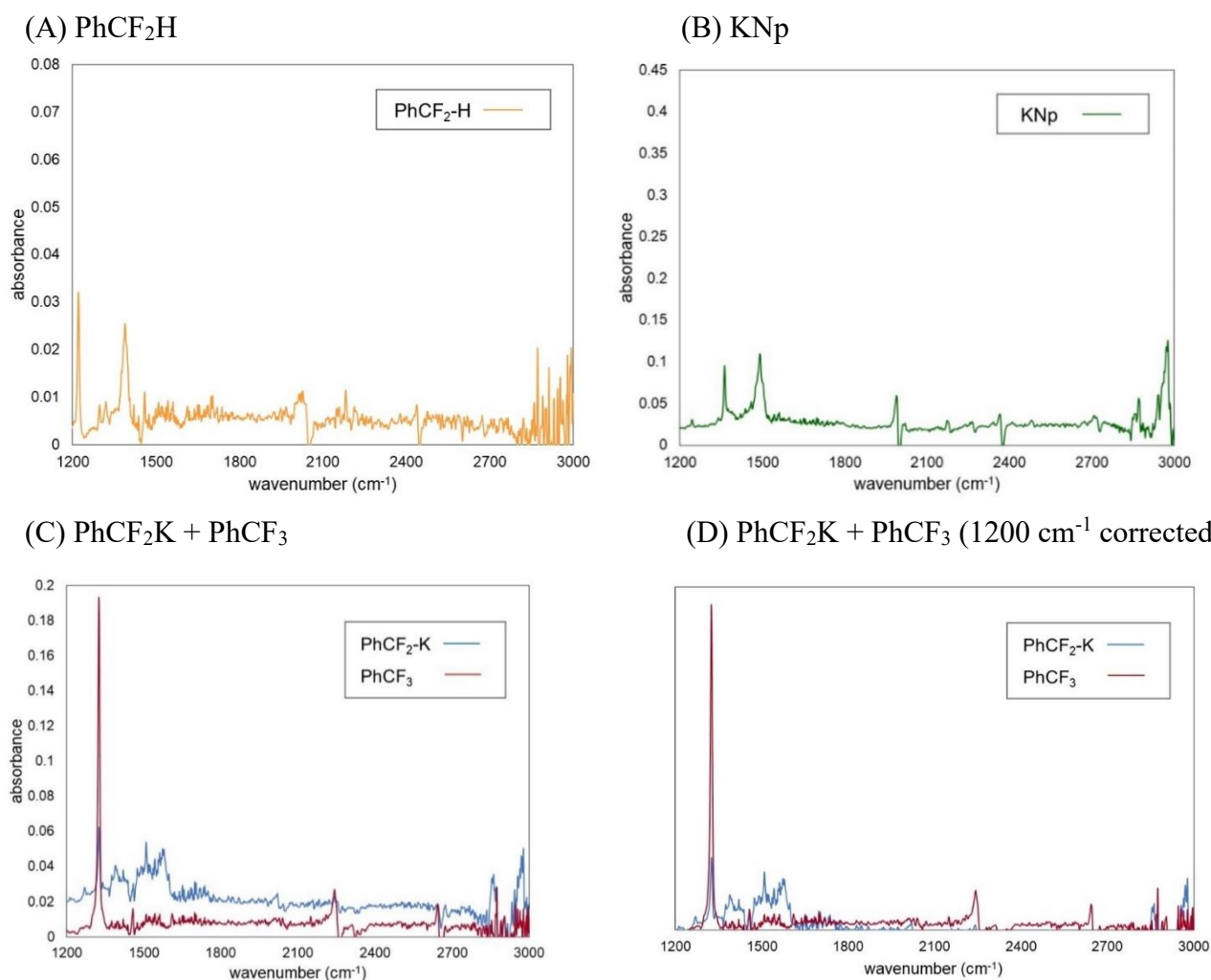


Fig. S5. In-line IR of PhCF_2H , KNp, PhCF_3 and reactive intermediate at $-20 \text{ }^{\circ}\text{C}$.

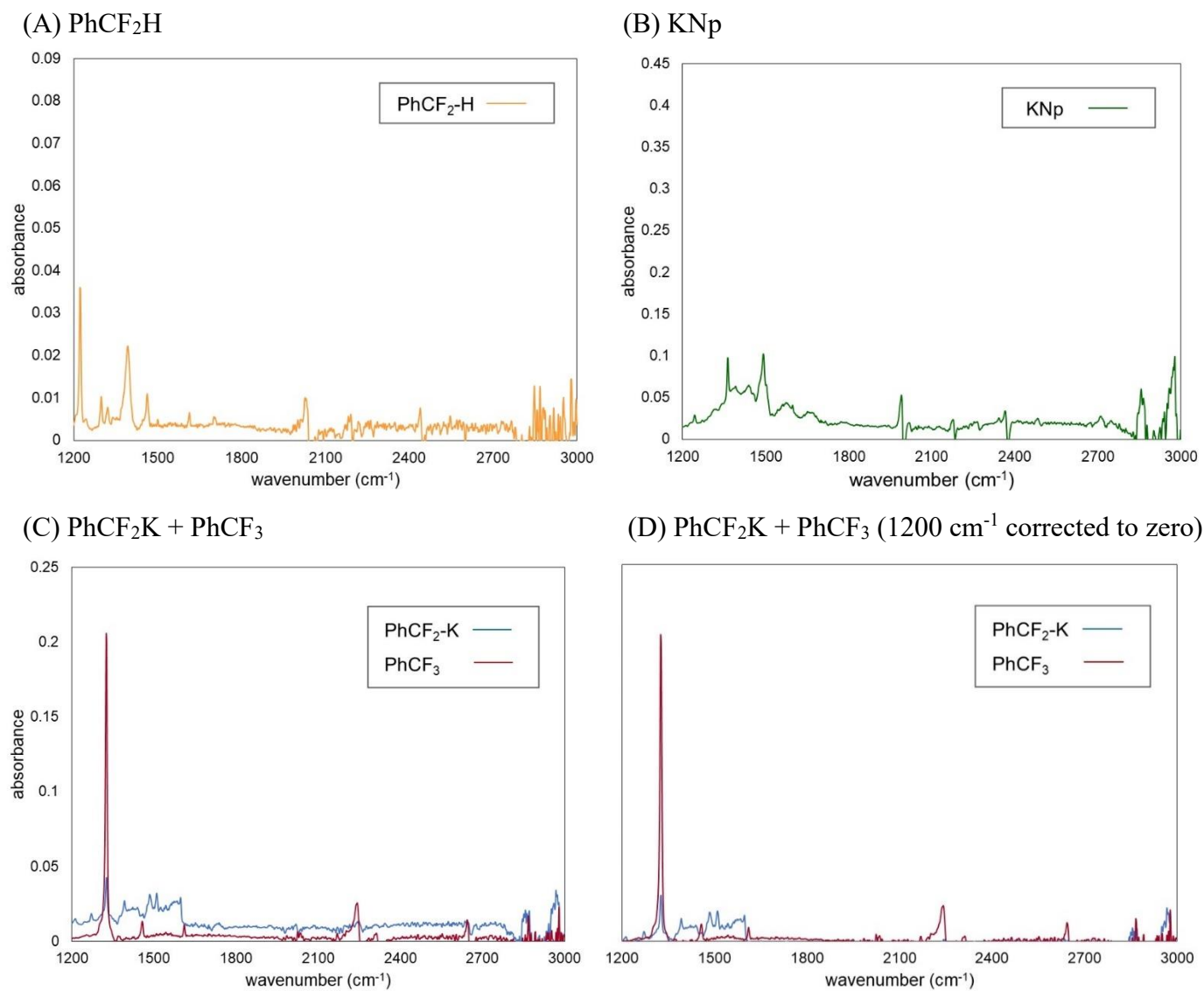


Fig. S6. In-line IR of PhCF_2H , KNp, PhCF_3 and reactive intermediate at $-78\text{ }^\circ\text{C}$.

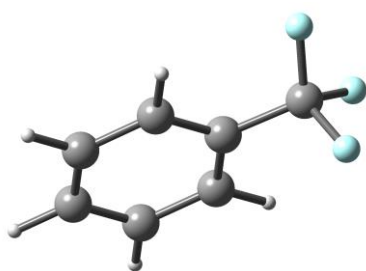
DFT calculation studies

DFT calculation studies have been performed with a Gaussian16 program package to estimate the FT-IR spectra of benzo-trifluoride (PhCF_3), its hydrodefluorination product (PhCF_2H), and the reactive intermediate⁷. We have employed B3LYP density functional and 6-31G+(d) basis set, in combination with the dispersion force correction model according to Grimme's D3 method⁸ and the IEFPCM solvation model for THF⁹.

Table S4. Summary of the calculated frequencies and energies for the optimized geometries of relevant species

structure	characteristic vibrational frequency (cm^{-1})	E_{zero} (hartree)	G_{298} (hartree)
PhCF_3	1317	-569.227756	-569.262995
PhCF_2H (conformer A)	1381	-469.964233	-469.997953
PhCF_2H (conformer B)	1423	-469.965395	-469.998575
PhCF_2K	1524, 1640	-1069.299657	-1069.337557
THF	-	-232.347890	-232.374573
$\text{PhCF}_2\text{K}(\text{thf})_4$	1524, 1640	-1998.765184	-1998.842716
$\text{K}^+(\text{naphthalene})^{\bullet-}$	1402, 1526	-985.696956	-985.734795
naphthalene	-	-385.773840	-385.803767
K^+	-	-599.834426	-599.849602
F^-	-	-99.978235	-99.992394

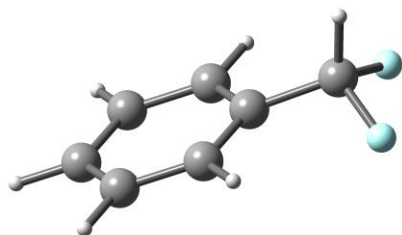
Table S5. Optimized ground-state geometry of PhCF_3



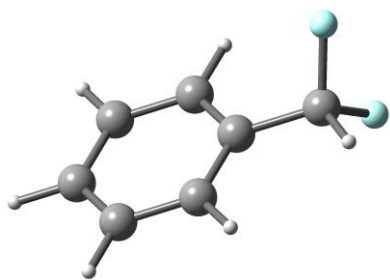
C	-2.14480000	1.21170000	0.00180000
C	-0.74840000	1.21670000	-0.02100000
C	-0.05500000	0.00110000	-0.03490000
C	-0.74700000	-1.21560000	-0.02110000
C	-2.14330000	-1.21240000	0.00180000
C	-2.84230000	-0.00070000	0.01350000
H	-2.68590000	2.15360000	0.00830000
H	-0.20390000	2.15550000	-0.03310000

H	-0.20120000	-2.15370000	-0.03320000
H	-2.68320000	-2.15500000	0.00840000
H	-3.92870000	-0.00140000	0.02960000
C	1.44710000	0.00050000	-0.00520000
F	1.98210000	-1.08250000	-0.62880000
F	1.93520000	-0.01890000	1.27110000
F	1.98320000	1.10050000	-0.59670000

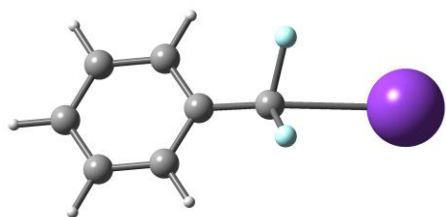
Table S6. Optimized Ground State Geometry of the simplified reactive intermediate (PhCF₂H_1)



C	-1.91124252	1.21202119	-0.04456122
C	-0.52018777	1.21281324	0.08901138
C	0.17518937	-0.00114375	0.15408806
C	-0.52408950	-1.21349976	0.09819610
C	-1.91500664	-1.20953206	-0.03526381
C	-2.61049195	0.00213816	-0.10664131
H	-2.44664024	2.15577703	-0.10192190
H	0.02260564	2.15196557	0.13350668
H	0.01584590	-2.15403405	0.14964331
H	-2.45337546	-2.15201080	-0.08532136
H	-3.69218554	0.00341861	-0.21096602
C	1.66835239	-0.00447028	0.35348369
F	2.24253375	-1.10834312	-0.25323014
F	2.24529899	1.11075099	-0.22841365
H	1.98811488	-0.01674772	1.39997614

Table S7. Optimized Ground State Geometry of the simplified reactive intermediate (PhCF₂H₂)

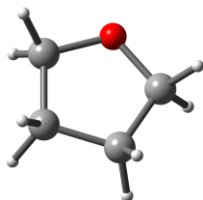
C	2.08534968	-1.08350662	0.00440905
C	0.70195341	-1.29163317	0.00731613
C	-0.16816346	-0.19689611	0.00333170
C	0.34182618	1.10948659	-0.00347944
C	1.72152413	1.31422134	-0.00624293
C	2.59438385	0.21789627	-0.00233294
H	2.76011707	-1.93495870	0.00751884
H	0.30413872	-2.30362324	0.01248221
H	-0.33922503	1.95583720	-0.00641141
H	2.11807207	2.32575943	-0.01137219
H	3.66885872	0.38063028	-0.00437924
C	-1.64847267	-0.42401461	0.00522870
F	-2.24209751	0.19179092	1.09941825
F	-2.23997552	0.16136629	-1.10679828
H	-1.94371099	-1.47538209	0.01920043

Table S8. Optimized Ground State Geometry of the simplified reactive intermediate

C	2.87982095	1.18861474	-0.20862282
C	1.49014342	1.20660646	-0.06724787
C	0.75356785	0.00612490	0.01275204
C	1.46431826	-1.21107249	-0.05244264
C	2.85355680	-1.22519253	-0.19325131
C	3.57349713	-0.02616936	-0.27585731
H	3.42506738	2.12881131	-0.26187277
H	0.96388687	2.15547983	-0.01619434
H	0.91717436	-2.14770189	0.00875138
H	3.37837870	-2.17747916	-0.23539400

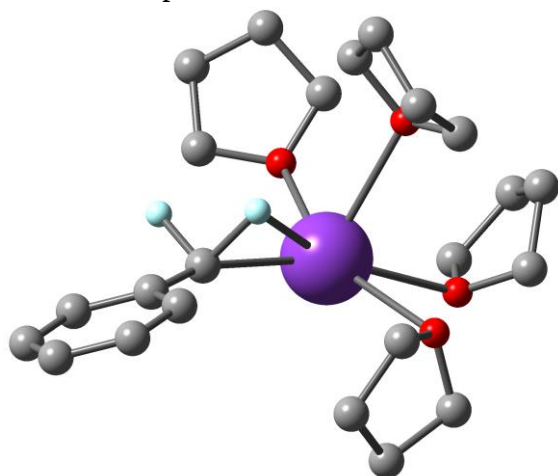
H	4.65471398	-0.03863682	-0.38868141
C	-0.72658200	0.01780255	0.02527907
F	-1.15611676	-1.07850909	0.90616479
F	-1.14139082	1.17681594	0.82289304
K	-3.49429408	-0.02871160	-0.53219917

Table S9. Optimized Ground State Geometry of the simplified reactive intermediate (THF)



C	-1.19067069	0.45967233	-0.00000010
O	0.00000036	1.26206451	-0.00000030
C	1.19067088	0.45967188	-0.00000059
C	0.77478834	-1.02733370	0.00000081
C	-0.77478868	-1.02733366	0.00000019
H	-1.78017675	0.72061133	0.88838738
H	-1.78017683	0.72061094	-0.88838764
H	1.78017604	0.72060940	-0.88838911
H	1.78017724	0.72061072	0.88838672
H	1.17004705	-1.54175609	-0.88124601
H	1.17004633	-1.54175423	0.88124904
H	-1.17004718	-1.54175467	-0.88124751
H	-1.17004787	-1.54175452	0.88124767

Table S10. Optimized Ground State Geometry of the simplified reactive intermediate

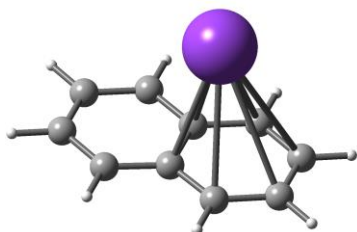


C	5.79211170	0.02663312	0.46896259
---	------------	------------	------------

C	4.39629237	0.00549321	0.50791272
C	3.65942250	-0.88923549	-0.29876918
C	4.38112468	-1.76534288	-1.13877367
C	5.77668845	-1.74266454	-1.17283404
C	6.49572535	-0.84390820	-0.37326281
H	6.33487123	0.72383073	1.10447370
H	3.86366117	0.68438146	1.16724340
H	3.83543939	-2.46493834	-1.76605855
H	6.30792521	-2.43349476	-1.82472864
H	7.58232627	-0.82485303	-0.40387623
C	2.18664610	-0.81459978	-0.36960415
F	1.68157223	-2.17387416	-0.52595712
F	1.70906940	-0.49794117	0.98243491
K	-0.49172296	0.14155231	-0.79559406
O	-2.16481762	-2.06204454	-1.21371300
C	-3.26084242	-2.32197281	-0.30903226
C	-1.53285036	-3.31418836	-1.59214374
C	-3.01157051	-3.72579749	0.24026198
H	-3.26089181	-1.53493550	0.45034333
H	-4.20670257	-2.27837238	-0.86878692
C	-2.39066638	-4.42783533	-0.97875728
H	-1.48366759	-3.35821396	-2.68562477
H	-0.51247086	-3.31315528	-1.19080303
H	-3.92797071	-4.20576859	0.59794522
H	-2.29332431	-3.68917192	1.06754238
H	-3.17654344	-4.73957408	-1.67740917
H	-1.79768800	-5.30901578	-0.71552247
O	-1.62001646	-0.04324983	1.83109507
C	-1.25183917	-1.24815665	2.54962143
C	-1.31996438	1.10691855	2.64994504
C	-0.58343024	-0.79705626	3.86091765
H	-2.15460417	-1.84580861	2.72192316
H	-0.56603959	-1.81707845	1.91305800
C	-0.17739975	0.65501813	3.55563678
H	-1.06176916	1.93140852	1.98081746
H	-2.21094325	1.38317921	3.23528688
H	0.26681787	-1.43222334	4.12671323
H	-1.30175689	-0.82505998	4.68895812
H	0.76704707	0.67680477	3.00227027
H	-0.07856232	1.27343313	4.45367209

O	-2.78178902	1.70191328	-1.50767139
C	-3.91442020	0.92894493	-1.97237677
C	-3.24313677	2.56210867	-0.45008136
C	-4.98118052	0.98010569	-0.84997713
H	-4.28715589	1.36598578	-2.90807171
H	-3.55032533	-0.08239361	-2.17474172
C	-4.26113616	1.70973228	0.30407926
H	-2.36983517	2.85689114	0.13576115
H	-3.71014904	3.46375255	-0.87837002
H	-5.32278709	-0.01856388	-0.56233524
H	-5.85675213	1.54988711	-1.17966808
H	-3.73165878	0.99822614	0.94626508
H	-4.94100768	2.30555916	0.92182274
O	0.17880390	2.83835111	0.02649396
C	0.18035603	3.76512754	-1.07262348
C	1.50971505	2.89374132	0.57417027
C	1.54338289	3.57210110	-1.76464406
H	-0.68396416	3.53291593	-1.69987098
H	0.07277679	4.78895732	-0.68148389
C	2.44613578	2.97899350	-0.64494123
H	1.59672710	3.78419238	1.21604032
H	1.65342999	1.99603405	1.17813931
H	1.92752419	4.51718382	-2.16139834
H	1.45536589	2.87096896	-2.60098000
H	3.32152233	3.60194860	-0.43566622
H	2.79566610	1.97920309	-0.91664931

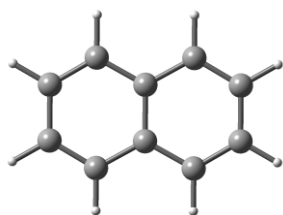
Table S11. Optimized Ground State Geometry of the simplified reactive intermediate



C	2.14944810	-1.14211421	-0.69383404
C	0.95318360	-0.88216790	-1.40527154
C	-0.27563174	-0.62198939	-0.72612517
C	-0.27509194	-0.61519950	0.73075424
C	0.95412863	-0.86947450	1.41141861

C	2.14991306	-1.13572778	0.70147860
H	-1.49792544	-0.34708007	-2.49295445
H	3.06705487	-1.34941013	-1.24156450
H	0.95364160	-0.89521894	-2.49429384
C	-1.49412975	-0.33754923	-1.40363307
C	-1.49293334	-0.32381063	1.40649537
H	0.95562749	-0.87159123	2.50051549
H	3.06794938	-1.33792558	1.25039663
C	-2.68386320	-0.05265498	0.69806599
C	-2.68444728	-0.05948962	-0.69687551
H	-1.49590648	-0.32315921	2.49586219
H	-3.60043222	0.15863841	1.24610875
H	-3.60146388	0.14650492	-1.24618734
K	0.96568410	2.16106886	-0.00803809

Table S12. Optimized Ground State Geometry of the simplified reactive intermediate (Naph-0)



C	-0.00000000	2.43739124	0.70981639
C	0.00000000	1.24617498	1.40549179
C	-0.00000000	0.00000000	0.71774994
C	0.00000000	-0.00000000	-0.71774994
C	0.00000000	1.24617498	-1.40549179
C	0.00000000	2.43739124	-0.70981639
H	0.00000000	-1.24433104	2.49338250
H	-0.00000000	3.38227422	1.24702970
H	0.00000000	1.24433104	2.49338250
C	-0.00000000	-1.24617498	1.40549179
C	-0.00000000	-1.24617498	-1.40549179
H	0.00000000	1.24433104	-2.49338250
H	0.00000000	3.38227422	-1.24702970
C	-0.00000000	-2.43739124	-0.70981639
C	-0.00000000	-2.43739124	0.70981639
H	0.00000000	-1.24433104	-2.49338250
H	-0.00000000	-3.38227422	-1.24702970
H	-0.00000000	-3.38227422	1.24702970

Defluorinative functionalization in the presence of electrophile

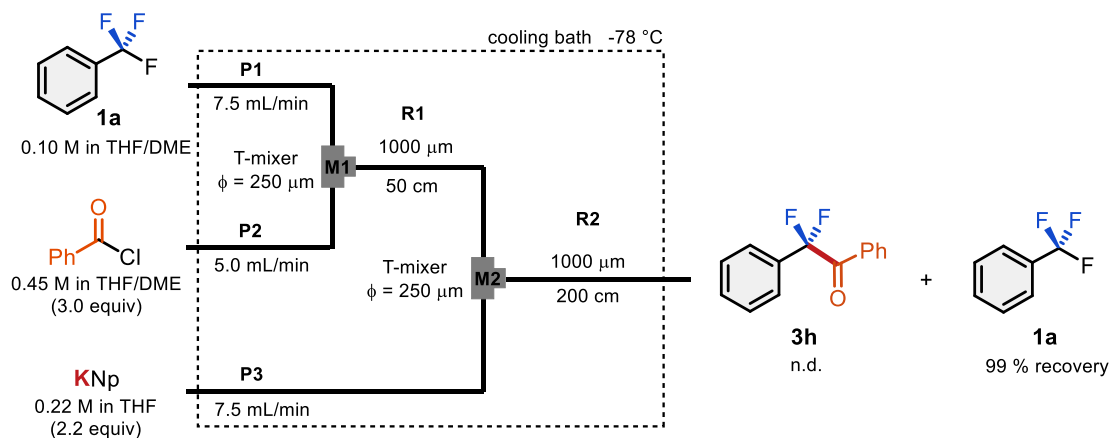


Fig. S7. Defluorinative functionalization in the presence of the benzoyl chloride in flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250\text{ }\mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000\text{ }\mu\text{m}$, length $L = 100\text{ cm}$)) was used. The flow microreactor system was cooled at $-78\text{ }^{\circ}\text{C}$ by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/min) and a solution of benzoyl chloride (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter $\phi = 1000\text{ }\mu\text{m}$, length $L = 50\text{ cm}$) and was mixed with a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000\text{ }\mu\text{m}$, length $L = 200\text{ cm}$). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yield of **3h** and recovery of **1a** were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). However, this system did not give a corresponding compound **3h**, and substrate **1a** was quantitatively recovered.

General procedure of defluorinative functionalization of benzotrifluoride under flow microreactor system

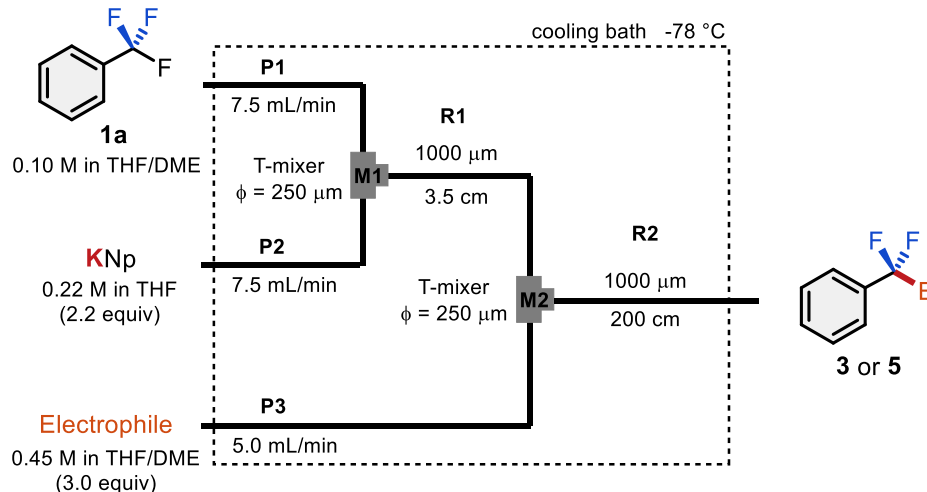


Fig. S8. Defluorinative functionalization of benzotrifluoride in flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250\ \mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 100\ \text{cm}$)) was used. The flow microreactor system was cooled at $-78\ ^\circ\text{C}$ by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 3.5\ \text{cm}$) and was mixed with a solution of electrophile (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 200\ \text{cm}$). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yields of corresponding difluoromethyl arenes (**4**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was extracted with EtOAc (3 x 5 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4 , and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product.

General procedure of hydrodefluorination of aryl bearing fluorine atoms under flow microreactor system

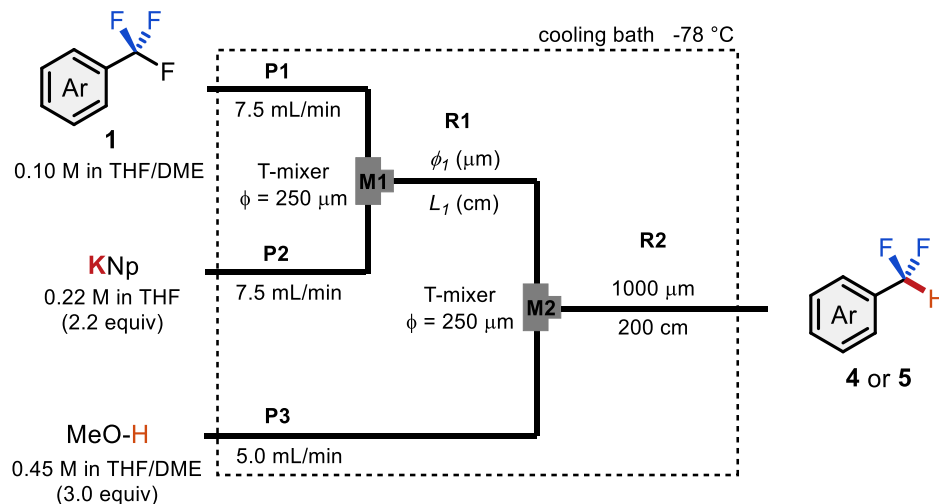


Fig. S9. Hydrodefluorination of benzotrifluoride derivatives in flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250 \mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$)) was used. The flow microreactor system was cooled at $-78 \text{ }^\circ\text{C}$ by a cooling bath. A solution of benzotrifluoride derivatives (**1**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 200 \text{ cm}$). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yields of corresponding difluoromethyl arenes (**4**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was extracted with EtOAc (3 x 5 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4 , and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product. The optimizations are summarized in Fig. S10.

Electrophile : MeO-H

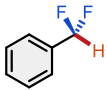
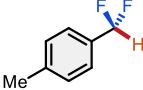
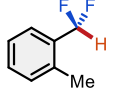
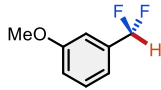
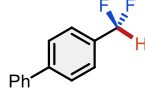
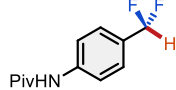
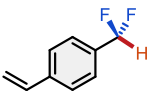
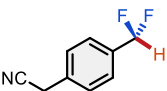
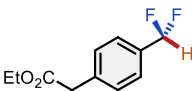
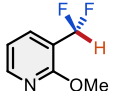
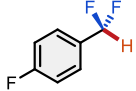
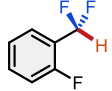
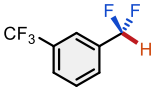
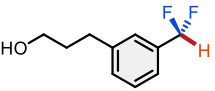
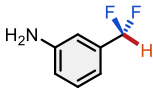
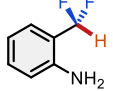
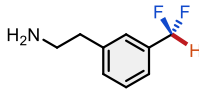
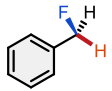
					
3a*	4a	4b	4c	4d	4e
74 % (50 %) (t^{R1} = 6.9 ms)	68 % (- %) (t^{R1} = 2.0 ms)	70 % (t^{R1} = 6.9 ms)	80 % (t^{R1} = 6.9 ms)	16 % (t^{R1} = 6.9 ms)	53 % (- %) (t^{R1} = 6.9 ms)
77 % (73 %) (t^{R1} = 0.11 s)	68 % (67 %) (t^{R1} = 6.9 ms)	75 % (t^{R1} = 27 ms)	87 % (t^{R1} = 0.11 s)	42 % (t^{R1} = 0.11 s)	63 % (50 %) (t^{R1} = 0.11 s)
69 % (75 %) (t^{R1} = 0.39 s)	- % (65 %) (t^{R1} = 27 ms)	61 % (t^{R1} = 0.11 s)	73 % (t^{R1} = 0.39 s)	35 % (t^{R1} = 0.39 s)	49 % (45 %) (t^{R1} = 0.39 s)
71 % (- %) (t^{R1} = 0.97 s)	12 % (58 %) (t^{R1} = 0.11 s)		85 % (t^{R1} = 1.6 s)	39 % (t^{R1} = 1.6 s)	59 % (- %) (t^{R1} = 0.97 s)
					
4f	4g	4h	4i	4j	4k
21 % (t^{R1} = 6.9 ms)	55 % (t^{R1} = 6.9 ms)	51 % (t^{R1} = 6.9 ms)	30 % (t^{R1} = 6.9 ms)	66 % (69 %) (t^{R1} = 6.9 ms)	(43 %) (t^{R1} = 6.9 ms)
40 % (t^{R1} = 0.11 s)	58 % (t^{R1} = 0.11 s)	31 % (t^{R1} = 0.11 s)	44 % (t^{R1} = 0.11 s)	67 % (76 %) (t^{R1} = 0.39 s)	(63 %) (t^{R1} = 0.39 s)
	55 % (t^{R1} = 0.39 s)	28 % (t^{R1} = 0.39 s)	59 % (t^{R1} = 0.39 s)	65 % (77 %) (t^{R1} = 0.97 s)	(72 %) (t^{R1} = 0.97 s)
		28 % (t^{R1} = 1.6 s)	54 % (t^{R1} = 1.6 s)	- % (84 %) (t^{R1} = 1.6 s)	(81 %) (t^{R1} = 1.6 s)
					
4l	4m	4n	4o	4p[†]	4q
44 % (- %) (t^{R1} = 27 ms)	72 % (t^{R1} = 6.9 ms)	69 % (t^{R1} = 6.9 ms)	37 % (t^{R1} = 6.9 ms)	75 % (t^{R1} = 6.9 ms)	50 % (t^{R1} = 0.11 s)
42 % (56 %) (t^{R1} = 0.11 s)	41 % (t^{R1} = 0.11 s)	55 % (t^{R1} = 0.11 s)	41 % (t^{R1} = 0.11 s)	55 % (t^{R1} = 0.11 s)	64 % (t^{R1} = 0.39 s)
44 % (57 %) (t^{R1} = 0.39 s)	45 % (t^{R1} = 0.39 s)	55 % (t^{R1} = 0.39 s)	46 % (t^{R1} = 0.39 s)	55 % (t^{R1} = 0.39 s)	
42 % (50 %) (t^{R1} = 0.97 s)	36 % (t^{R1} = 1.6 s)		42 % (t^{R1} = 1.6 s)		

Fig. S10. Scope of substrates of hydrodefluorination.

Using THF/diglyme (10:1) instead of THF/DME in parentheses. *The yield of **3a** was determined by gas chromatography with an undecane as an internal standard. †Quench was carried out by methanol instead of sat. aq. NH_4Cl .

Continuous flow synthesis

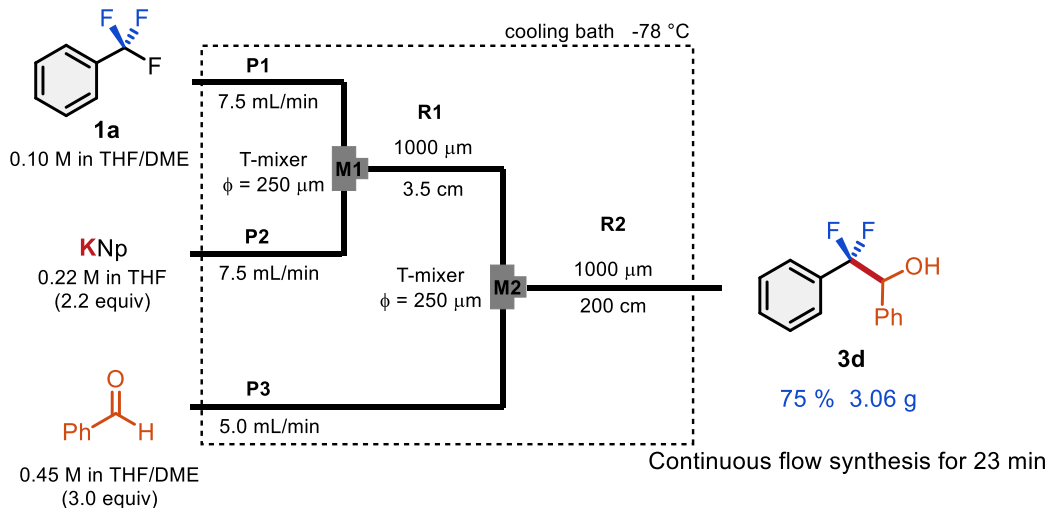


Fig. S11. Gram-scale synthesis of the **3d**

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250\ \mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 100\ \text{cm}$)) was used. The flow microreactor system was cooled at $-78\ ^\circ\text{C}$ by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 3.5\ \text{cm}$) and was mixed with a solution of benzaldehyde (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 200\ \text{cm}$). After a steady state was reached, the outcoming solution was collected for 23 minutes (total) in a vessel containing 100 mL of sat. aq. NH_4Cl . The reaction mixture was extracted with EtOAc (3 x 200 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4 , and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product as a white solid in 75 % isolated yield (3.06 g).

Procedure of radical clock experiment

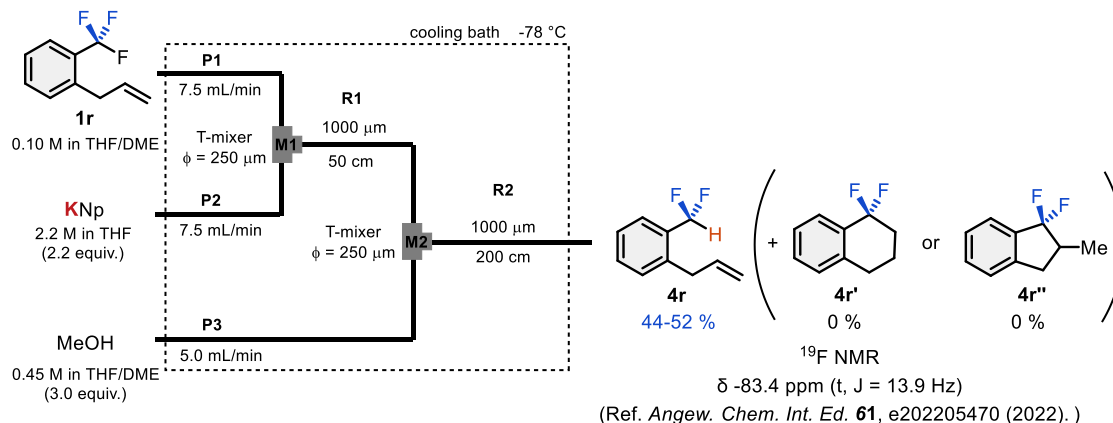


Fig. S12. Radical clock experiment using **1r** as substrate in flow

Table S13. Yields of **4r** and **4r'** or **4r''** with residence time (t^{R1})

entry	t^{R1} / s	yield of 4r / %	yield of 4r' / %	yield of 4r'' / %
1	0.0069	44	n.d.	n.d.
2	0.11	48	n.d.	n.d.
3	0.39	47	n.d.	n.d.
4	1.6	52	n.d.	n.d.

*Yields were determined by ¹⁹F NMR with an internal standard.

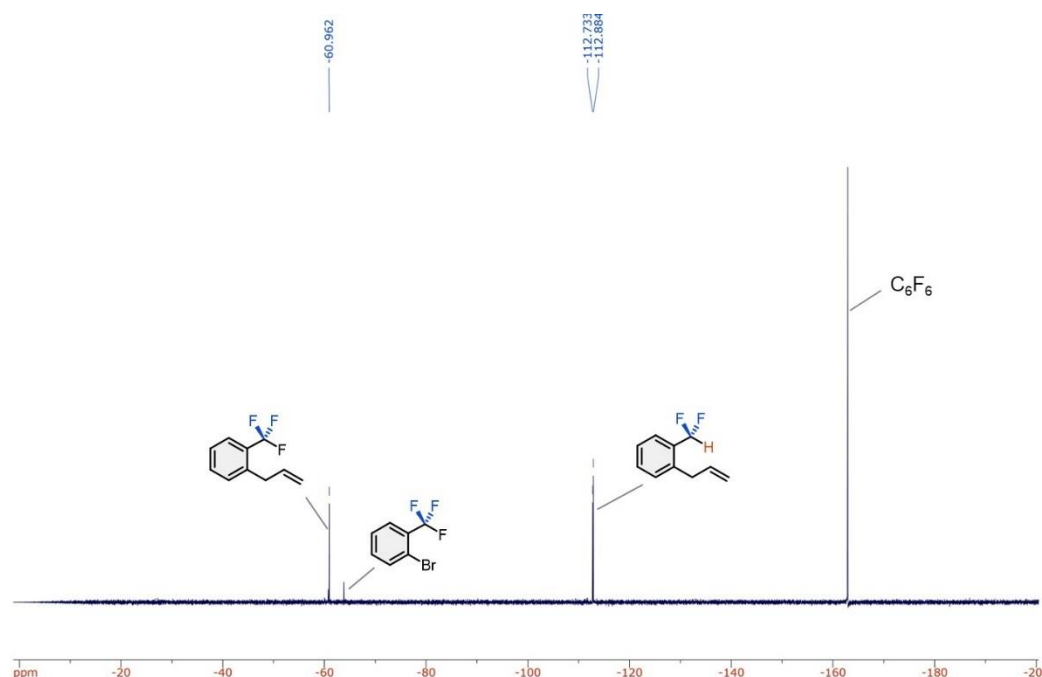


Fig. S13. ¹⁹F NMR of crude (entry 4)

As shown in Fig. S13, a radical clock experiment using 2-Allyl(trifluoromethyl)benzene (**1r**) as substrate in our condition did not afford an intramolecularly cyclized product (**4r'** or **4r''**) and obtained corresponding hydrodefluorinated product (**4r**). Thus, the second SET is considered very fast.

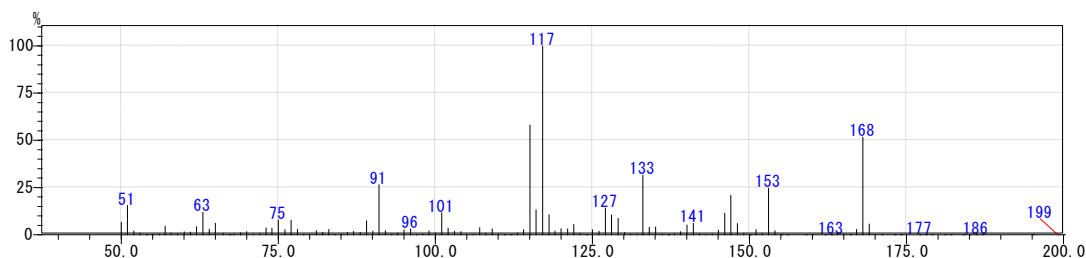


Fig. S14. GCMS of corresponding difluoromethyl arene (entry 4)

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ = 250 μ m)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter ϕ = 1000 μ m, length L = 100 cm)) was used. The flow microreactor system was cooled at -78 °C by a cooling bath. A solution of 2-Allyl(trifluoromethyl)benzene (**1r**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ = 1000 μ m, length L = 200 cm). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yields of corresponding difluoromethyl arene (**4r**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene).

Procedure of Step- and time-economical synthesis

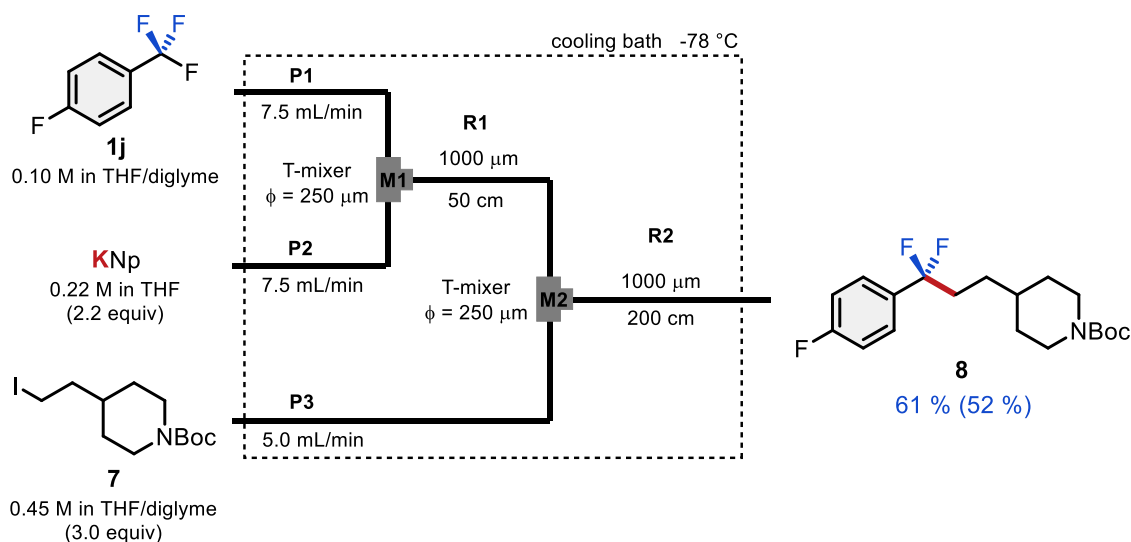
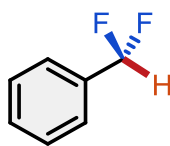


Fig. S15. Synthesis of pharmaceutical intermediates **8**

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter $\phi = 250\ \mu\text{m}$)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 100\ \text{cm}$)) was used. The flow microreactor system was cooled at -78°C by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/diglyme = 10/1) (flow rate: 7.5 mL/min) and a solution of potassium naphthalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 50\ \text{cm}$) and was mixed with a solution of electrophile (0.45 M in THF/diglyme = 10/1) (flow rate: 5.0 mL/min) in **M2**. The resulting solution was passed through **R2** (inner diameter $\phi = 1000\ \mu\text{m}$, length $L = 200\ \text{cm}$). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl . The yields of corresponding difluoromethyl arenes (**8**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene) in 61 %. The reaction mixture was extracted with EtOAc (3 x 5 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4 , and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product as a yellow oil in 52 % isolated yield (47.0 mg).

Defluorinative functionalization products characterizations

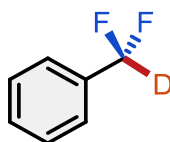
Difluoromethyl benzene (3a)



3a

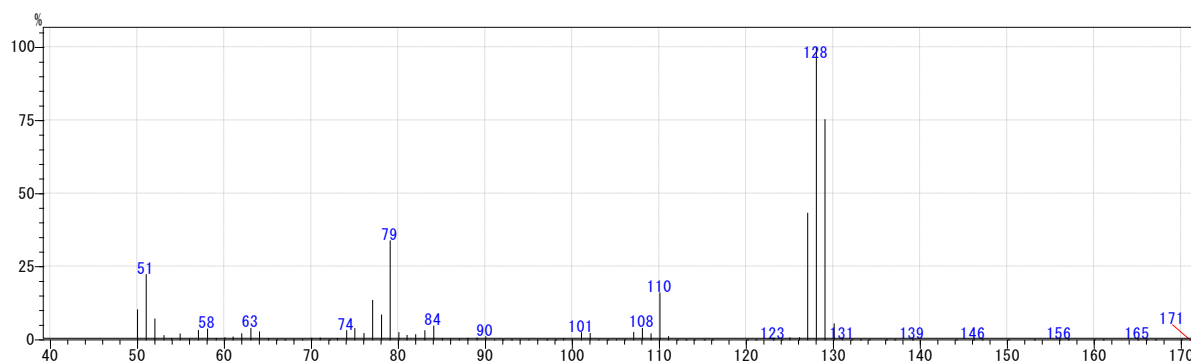
Obtained in 77 % yield (Maximum yield). Yields were determined by GC analysis (*t*_R 6.0 min) (initial oven temperature, 50 °C (5 min); temperature increase rate, 10 °C/min (25 min); final temperature, 300 °C) using an internal standard (undecane). ¹⁹F NMR (376 MHz, CDCl₃) δ -111.60 (s, 2F). The NMR spectral data were identical to those reported in the literature¹⁰.

Deuterated difluoromethyl benzene (3b)

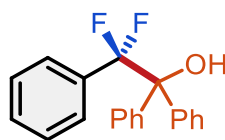


3b

Obtained in 74 % yield. The yield was determined by ¹⁹F NMR integration relative to the internal standard (hexafluorobenzene). ¹⁹F NMR (376 MHz, CDCl₃) δ -112.40 (s, 2F). ¹⁹F NMR data matches previously reported data¹¹. The identity of the product was further confirmed by GCMS analysis.



2,2-Difluoro-1,1,2-triphenylethanol (3c)



3c

Obtained in 66 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, R_f= 0.4) to afford the pure product as a white solid.

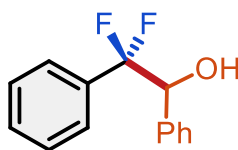
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.47-7.44 (m, 4H), 7.32 (t, J = 7.3 Hz, 1H), 7.28-7.25 (m, 4H), 7.20 (t, J = 7.7 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 2.78 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.50, 134.22 (t, J = 26.2 Hz), 129.51, 127.99 (d, J = 4.7 Hz), 127.76, 127.71, 127.38 (t, J = 6.4 Hz), 127.00, 123.20 (t, J = 255.8 Hz), 80.85 (t, J = 28.9 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -102.57 (s, 2F).

1,2-Diphenyl-2,2-difluoroethanol (3d)



3d

Obtained in 71 % yield. After a steady state was reached, the outcoming solution was collected for 60 seconds in a vessel containing 10 mL of sat. aq. NH_4Cl . The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, R_f= 0.2) to afford the pure product as a white solid (126.7 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{14}\text{H}_{12}\text{F}_2\text{ONa}[\text{M}+\text{Na}]^+$ 257.0754; Found: 257.0744.

IR (neat) 3461 cm^{-1} , 3063 cm^{-1}

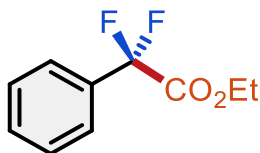
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.40-7.17 (m, 10H), 5.04 (t, J = 10.1 Hz, 1H), 2.63 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 135.70, 133.65 (t, J = 25.9 Hz), 129.96, 128.61, 127.83 (t, J = 9.2 Hz), 126.23 (t, J = 6.3 Hz), 123.55, 121.0, 118.61, 76.85 (t, J = 30.7 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -108.09 (d, J = 9.1 Hz, 2F).

2,2-Difluoro-2-phenylacetic acid ethyl ester (3e)



3e

Obtained in 55 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.5) to afford the pure product as a colorless oil.

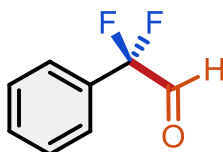
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.63-7.60 (m, 2H), 7.52-7.43 (m, 3H), 4.30 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 164.21 (t, J = 35.4 Hz), 132.77 (t, J = 25.5 Hz), 130.95 (d, J = 2.2 Hz), 128.61, 125.40 (t, J = 6.3 Hz), 113.35 (t, J = 251.9 Hz), 63.11, 13.84.

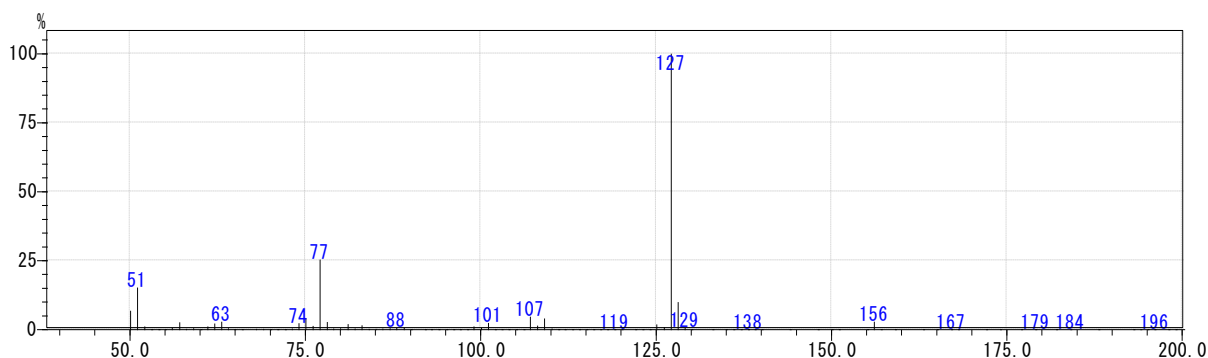
^{19}F NMR (376 MHz, CDCl_3) δ -105.07 (s, 2F).

2,2-Difluoro- 2-(phenyl)acetaldehyde (3f)

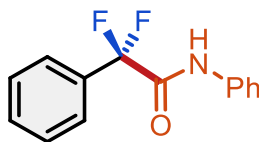


3f

Obtained in 48 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -112.66 (s, 2F). ^{19}F NMR data matches previously reported data¹². The identity of the product was further confirmed by GCMS analysis.



***N*-Phenyl-2-phenyl-2,2-difluoroacetamide (3g)**



3g

Obtained in 83 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, R_f= 0.3) to afford the pure product as a white solid.

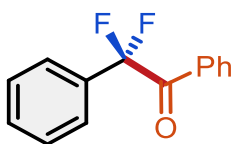
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.69-7.67 (m, 2H), 7.59-7.56 (m, 2H), 7.53-7.45 (m, 3H), 7.36 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 161.80 (t, J = 30.8 Hz), 136.00, 132.55 (t, J = 25.4 Hz), 131.08 (t, J = 1.9 Hz), 129.20, 128.68, 125.63, 125.56 (t, J = 5.3 Hz), 120.11, 114.76 (t, J = 254.3 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -103.58 (s, 2F).

2,2-Difluoro-1,2-diphenylethane-1-one (3h)



3h

Obtained in 55 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). After a steady state was reached, the outcoming solution was collected for 60 seconds in a vessel containing 10 mL of sat. aq. NH_4Cl . The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, R_f= 0.5) to afford the pure product as a yellow oil in 66 % isolated yield (115.2 mg).

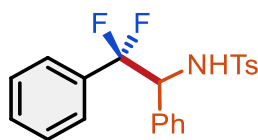
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 8.04-8.02 (m, 2H), 7.63-7.57 (m, 3H), 7.50-7.43 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3) δ 188.89 (t, J = 30.8 Hz), 134.19, 133.03 (t, J = 25.0 Hz), 132.02, 130.88 (d, J = 1.7 Hz), 130.22 (t, J = 2.9 Hz), 128.79, 128.60, 125.54 (t, J = 5.8 Hz), 116.86 (t, J = 253.2 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -98.76 (s, 2F).

N-(2,2-difluoro-1,2-diphenylethyl)-4-methylbenzenesulfonamide (3i)



3i

Obtained in 65 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by GPC to afford the pure product as a white solid.

HRMS (ESI) m/z Calcd for $\text{C}_{21}\text{H}_{19}\text{F}_2\text{NO}_2\text{SNa}[\text{M}+\text{Na}]^+$ 410.0988; Found: 410.1002.

IR (neat) 3317 cm^{-1} , 2358 cm^{-1} , 1093 cm^{-1}

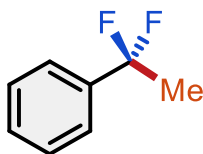
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.47 (d, $J = 8.3\text{ Hz}$, 2H), 7.37 (t, $J = 7.4\text{ Hz}$, 1H), 7.29 (d, $J = 7.8\text{ Hz}$, 2H), 7.21-7.06 (m, 7H), 6.94 (d, $J = 7.5\text{ Hz}$, 2H), 5.30 (d, $J = 8.7\text{ Hz}$, 1H), 4.92-4.84 (m, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.19, 137.12, 133.88-133.36 (m), 130.17, 129.24, 128.31, 128.28, 128.10, 128.06, 126.91, 125.82 (t, $J = 6.2\text{ Hz}$), 122.99-120.50 (m), 63.20 (t, $J = 29.3\text{ Hz}$), 21.41.

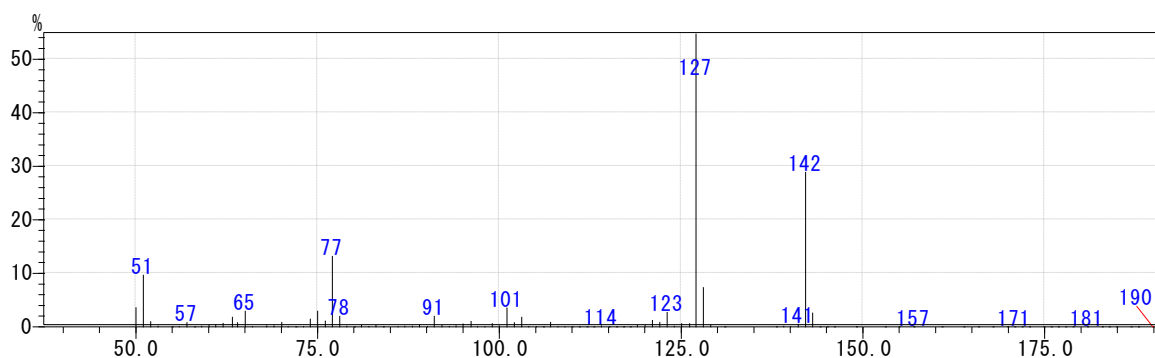
^{19}F NMR (376 MHz, CDCl_3) δ -103.46 (dd, $J = 248.9, 10.1\text{ Hz}$, 1F), -106.12 (dd, $J = 245.2, 13.5\text{ Hz}$, 1F).

(1,1-Difluoroethyl)benzene (3j)

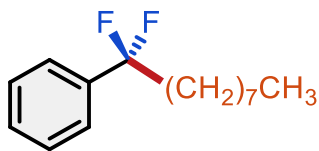


3j

Obtained in 76 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -88.62 (q, $J = 17.5\text{ Hz}$, 2F). ^{19}F NMR data matches previously reported data¹³. The identity of the product was further confirmed by GCMS analysis.

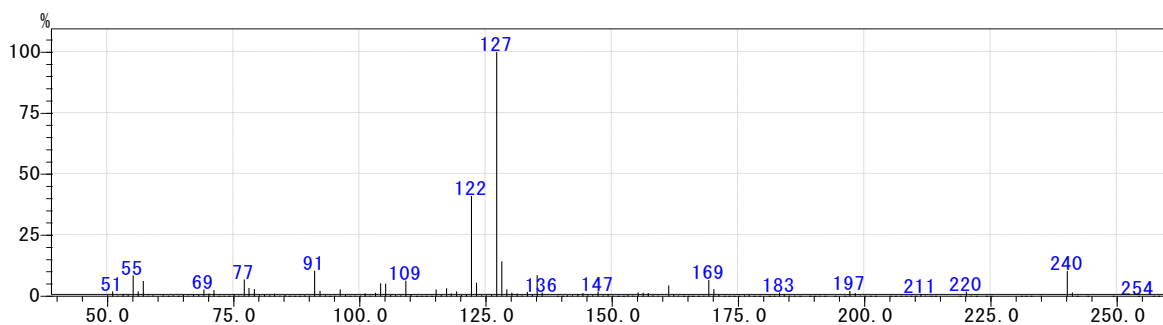


(1,1-Difluorononyl)benzene (3k)

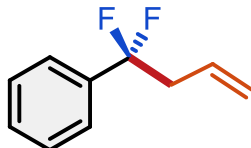


3k

Obtained in 71 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -96.27 (t, J = 16.1 Hz, 2F). ^{19}F NMR data matches previously reported data¹⁴. The identity of the product was further confirmed by GCMS analysis.

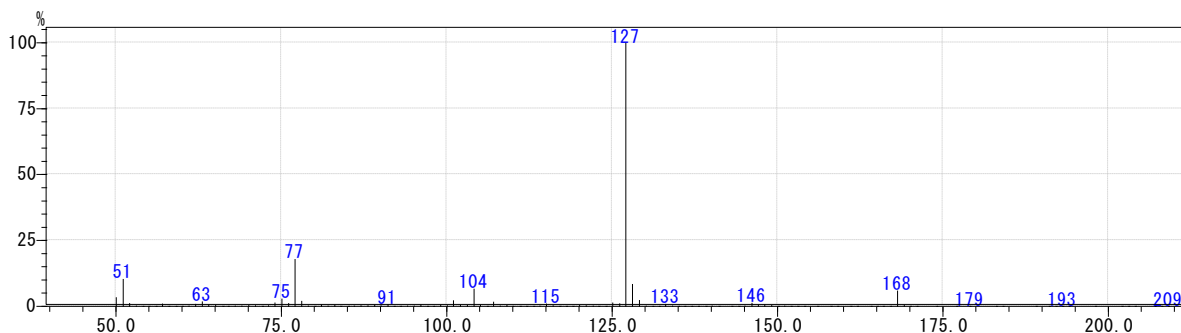


1,1-Difluoro-1-phenyl-3-butene (3l)

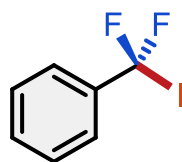


3l

Obtained in 41 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -96.20 (t, J = 16.4 Hz, 2F). ^{19}F NMR data matches previously reported data¹⁵. The identity of the product was further confirmed by GCMS analysis.

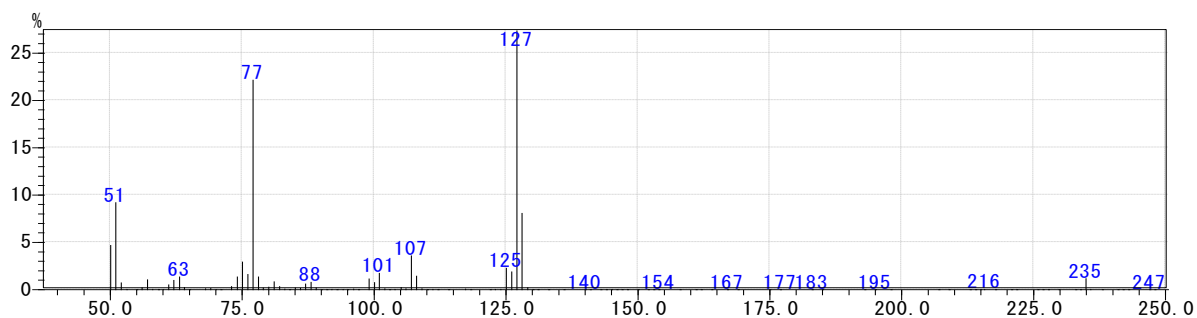


(Difluoriodomethyl)benzene (3m)

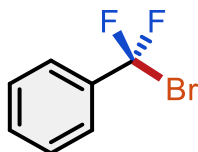


3m

Obtained in 65 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -38.06 (s, 2F). ^{19}F NMR data matches previously reported data¹⁶. The identity of the product was further confirmed by GCMS analysis.

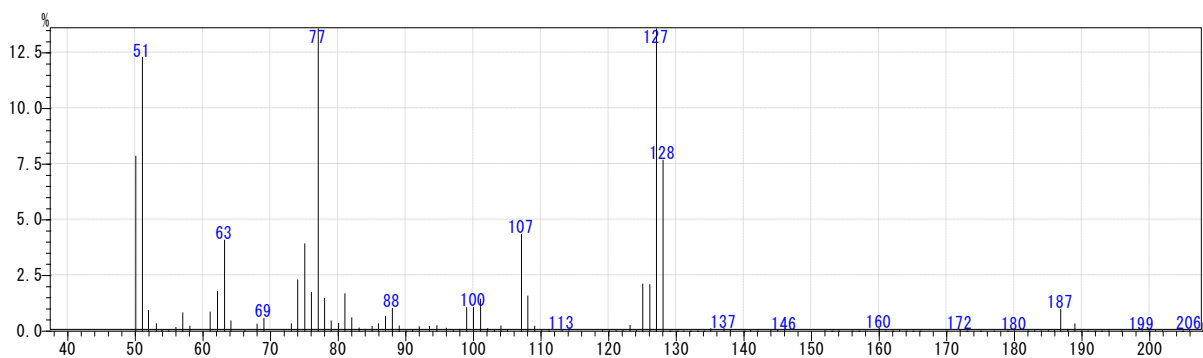


(Bromodifluoromethyl)benzene (3n)

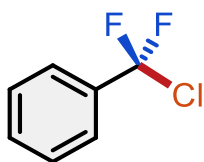


3n

Obtained in 56 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -44.74 (s, 2F). ^{19}F NMR data matches previously reported data¹⁷. The identity of the product was further confirmed by GCMS analysis.

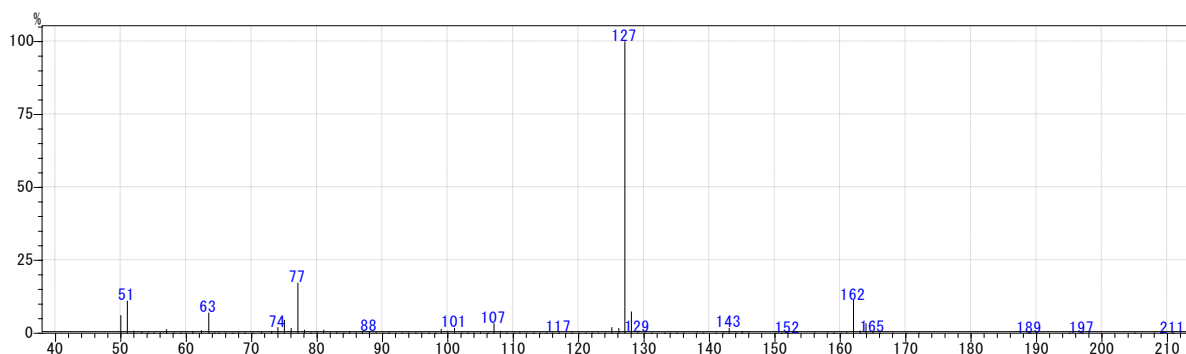


(Chlorodifluoromethyl)benzene (3o)

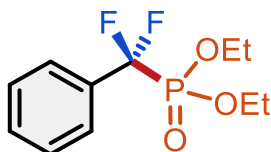


3o

Obtained in 80 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -49.78 (s, 2F). ^{19}F NMR data matches previously reported data¹⁸. The identity of the product was further confirmed by GCMS analysis.



Diethyl difluoro(phenyl)methylphosphonate (3p)



3p

Obtained in 48 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product (0.25 mmol scale) was purified by GPC to afford the pure product as yellow oil in 55 % isolated yield (36.8 mg).

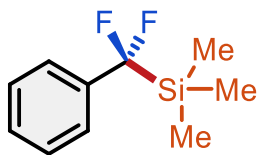
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, J = 8.0, 0.9 Hz, 2H), 7.49-7.44 (m, 3H), 4.26-4.09 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 132.78-132.21 (m), 130.75 (t, J = 1.9 Hz), 128.39, 126.24-126.09 (m), 121.71-114.30 (m), 64.74 (d, J = 6.7 Hz), 16.28 (d, J = 5.6 Hz).

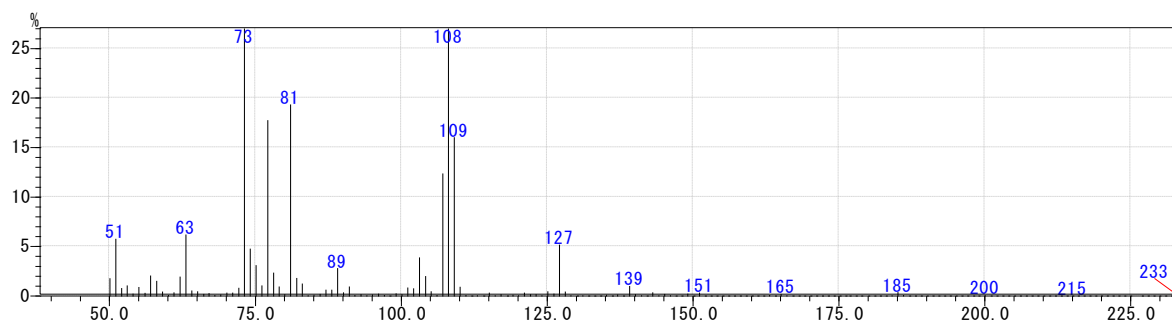
^{19}F NMR (376 MHz, CDCl_3) δ -109.72 (d, J = 120.6 Hz, 2F).

(Difluoro(trimethylsilyl)methyl)benzene (3q)

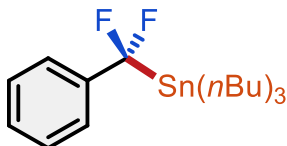


3q

Obtained in 85 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -113.44 (s, 2F). ^{19}F NMR data matches previously reported data¹⁹. The identity of the product was further confirmed by GCMS analysis.



Tributhyl(difluoro(phenyl)methyl)stannane (3r)



3r

Obtained in 63 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC to afford the pure product as yellow oil.

HRMS (ESI) m/z Calcd for $\text{C}_{19}\text{H}_{32}\text{F}_2\text{SnNa}[\text{M}+\text{Na}]^+$ 441.1395; Found: 441.1385.

NMR Spectroscopy:

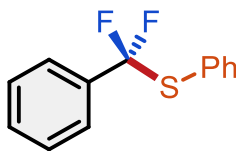
^1H NMR (400 MHz, CDCl_3) δ 7.41-7.37 (m, 2H), 7.33-7.28 (m, 3H), 1.54-1.22 (m, 13H), 1.01-0.97 (m, 5H), 0.86 (d, J = 14.6 Hz, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 141.69 (t, J = 16.8 Hz), 136.04 (d, J = 293.8 Hz), 128.41, 128.16 (t, J = 2.7 Hz), 123.23 (t, J = 8.3 Hz), 28.53 (d, J = 1.5 Hz), 27.22 (d, J = 1.8 Hz), 13.59 (d, J = 1.6 Hz), 9.94 (d, J = 3.4 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -97.53--98.29 (m, 2F).

Note: The title compound was unstable and decomposed after several days of storage at ambient temperature.

((Difluorophenylmethyl)thio)benzene (3s)



3s

Obtained in 80 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane only, $R_f = 0.5$) to afford the pure product as a white solid.

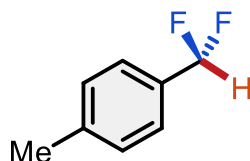
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.63-7.61 (m, 2H), 7.57 (dd, $J = 7.7, 1.3$ Hz, 2H), 7.45-7.35 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 136.36, 135.89 (t, $J = 25.0$ Hz), 130.56, 129.87, 128.97, 128.32, 127.58, 127.45, 125.37 (t, $J = 4.8$ Hz).

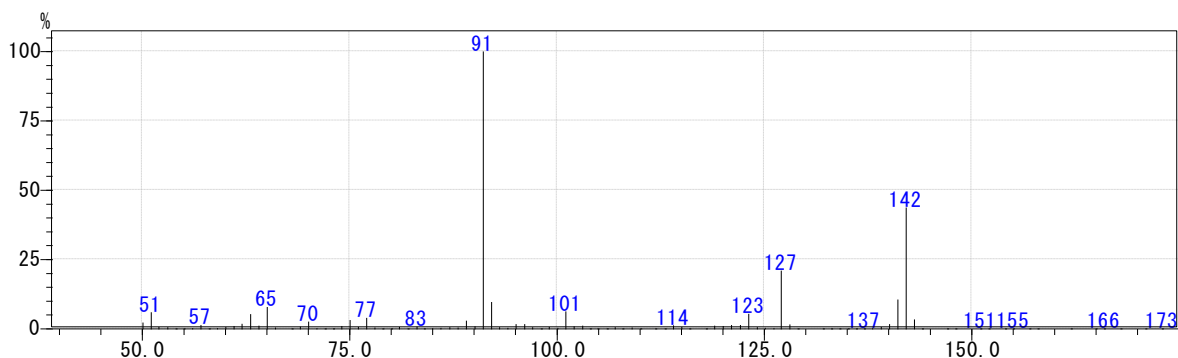
^{19}F NMR (376 MHz, CDCl_3) δ -72.99 (s, 2F).

1-(Difluoromethyl)-4-methylbenzene (4a)

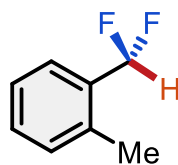


4a

Obtained in 84 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -110.80 (d, $J = 57.4$ Hz, 2F). ^{19}F NMR data matches previously reported data²⁰. The identity of the product was further confirmed by GCMS analysis.

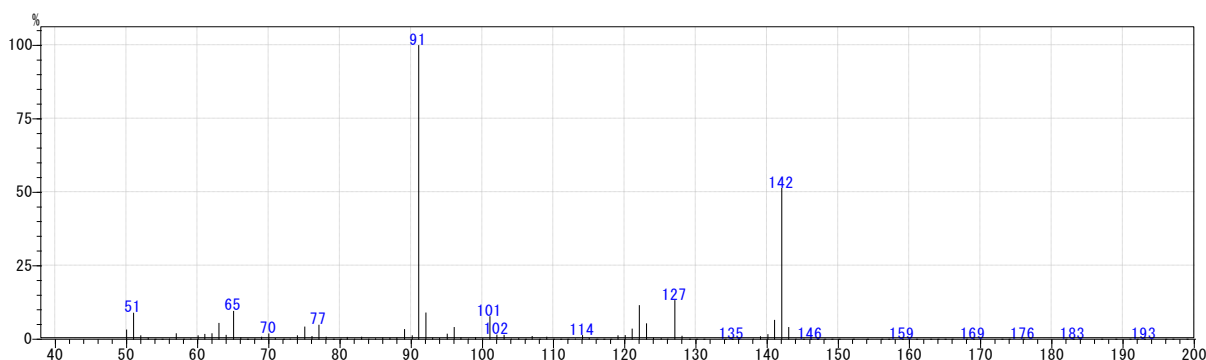


1-(Difluoromethyl)-2-methylbenzene (4b)

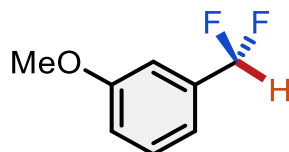


4b

Obtained in 75 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -114.21 (d, J = 54.1 Hz, 2F). ^{19}F NMR data matches previously reported data²⁰. The identity of the product was further confirmed by GCMS analysis.

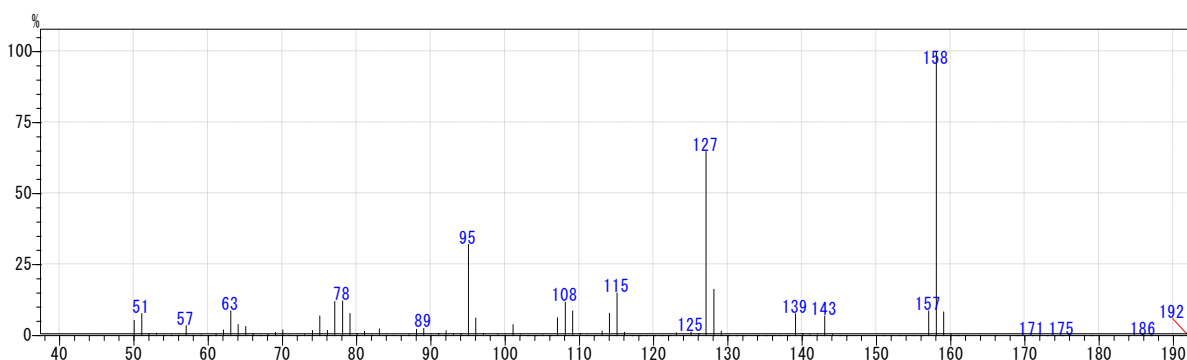


1-(Difluoromethyl)-3-methoxybenzene (4c)

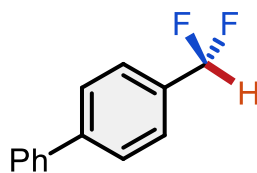


4c

Obtained in 87 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.74 (d, J = 53.8 Hz, 2F). ^{19}F NMR data matches previously reported data¹⁰. The identity of the product was further confirmed by GCMS analysis.



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



4d

Obtained in 42 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.4) to afford the pure product as a white solid.

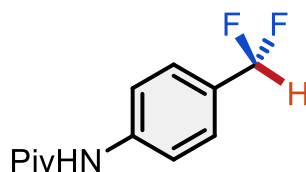
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, J = 8.1 Hz, 2H), 7.61-7.57 (m, 4H), 7.48-7.45 (m, 2H), 7.41-7.37 (m, 1H), 6.70 (t, J = 56.5 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.66 (d, J = 1.9 Hz), 140.15, 133.16 (t, J = 22.1 Hz), 128.90, 127.89, 127.42, 127.23, 126.01 (t, J = 5.8 Hz), 114.72 (t, J = 238.4 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -111.56 (d, J = 57.2 Hz, 2F).

N-(4-(difluoromethyl)phenyl)pivalamide (4e)



4e

Obtained in 63 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a white solid.

HRMS (ESI) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{NONa}[\text{M}+\text{Na}]^+$ 250.1014; Found: 250.1010.

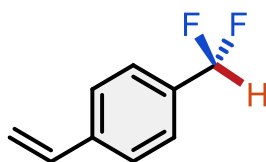
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 6.61 (t, J = 56.6 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) δ 176.81, 140.15, 129.86 (t, J = 22.7 Hz), 126.37 (t, J = 6.0 Hz), 119.72, 114.51 (t, J = 238.0 Hz), 39.69, 27.51.

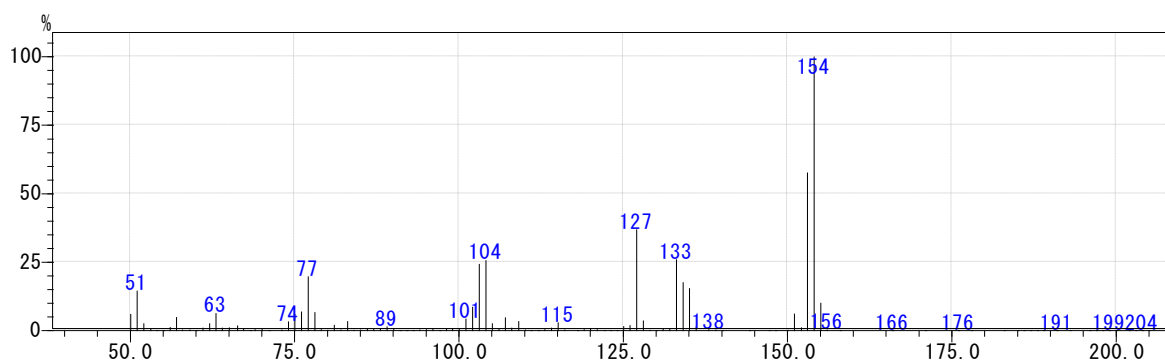
^{19}F NMR (376 MHz, CDCl_3) δ -110.82 (d, J = 56.7 Hz, 2F).

1-(Difluoromethyl)-4-vinylbenzene (4f)

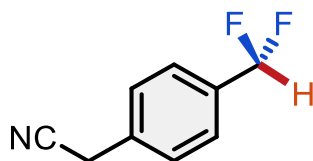


4f

Obtained in 40 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.54 (d, J = 57.1 Hz, 2F). ^{19}F NMR data matches previously reported data²¹. The identity of the product was further confirmed by GCMS analysis.

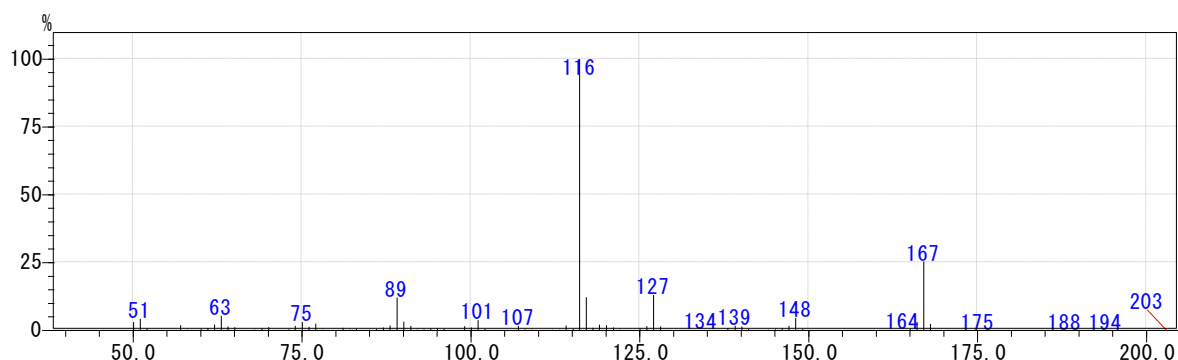


4-(Difluoromethyl)benzeneacetonitrile (4g)

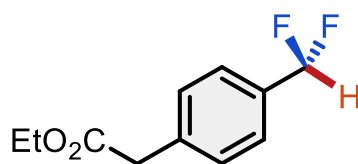


4g

Obtained in 58 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -112.19 (d, J = 53.7 Hz, 2F). ^{19}F NMR data matches previously reported data²². The identity of the product was further confirmed by GCMS analysis.

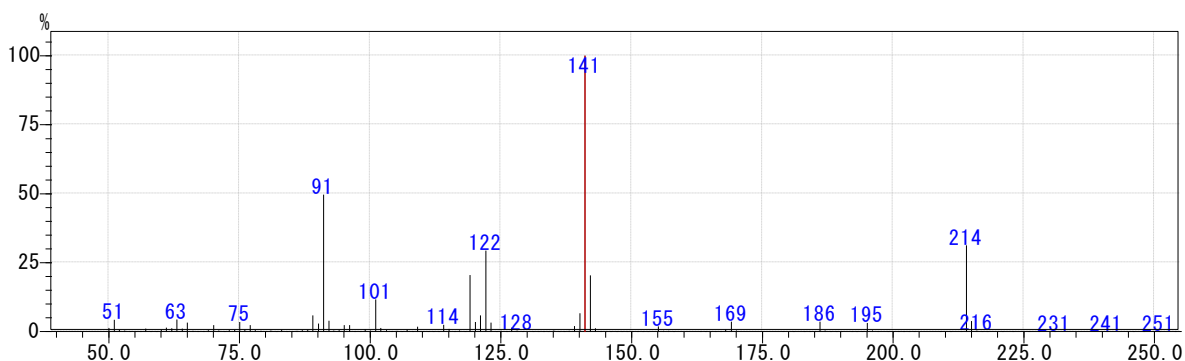


Ethyl 4-(difluoromethyl)benzene acetate (4h)

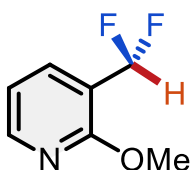


4h

Obtained in 51 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.56 (d, J = 55.6 Hz, 2F). The identity of the product was further confirmed by GCMS analysis.



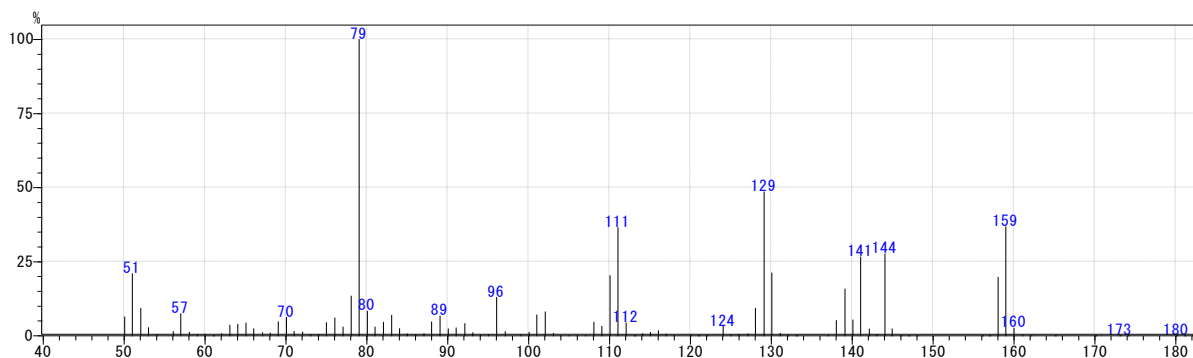
3-(Difluoromethyl)-2-methoxypyridine (4i)



4i

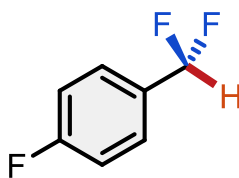
Obtained in 59 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -117.74 (d, J = 57.1 Hz, 2F). The identity of the product was further confirmed by GCMS analysis.

HRMS (APCI) m/z Calcd for $\text{C}_7\text{H}_8\text{F}_2\text{NO}[\text{M}+\text{H}]^+$ 160.0569; Found: 160.0568.



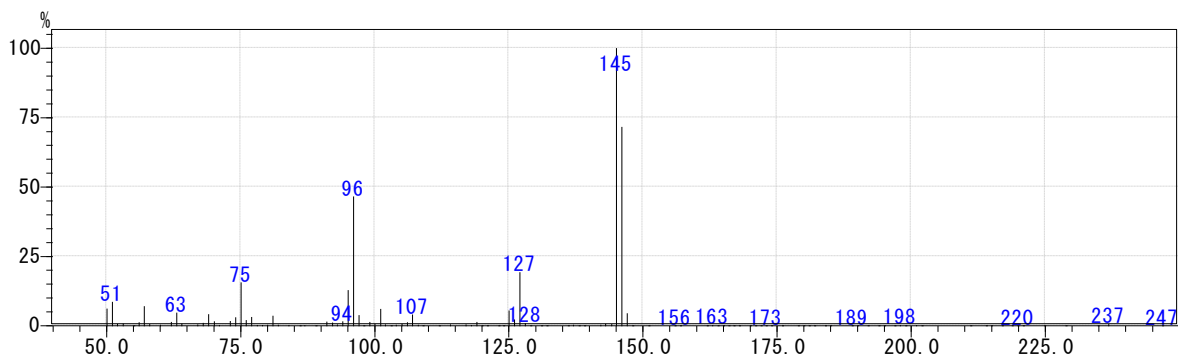
Note: The title compound could not be isolated due to highly volatile.

1-(Difluoromethyl)-4-fluorobenzene (4j)

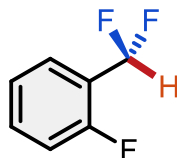


4j

Obtained in 84 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -110.65 (d, J = 55.8 Hz, 2F), -110.6 (s, 1F). ^{19}F NMR data matches previously reported data¹⁰. The identity of the product was further confirmed by GCMS analysis.

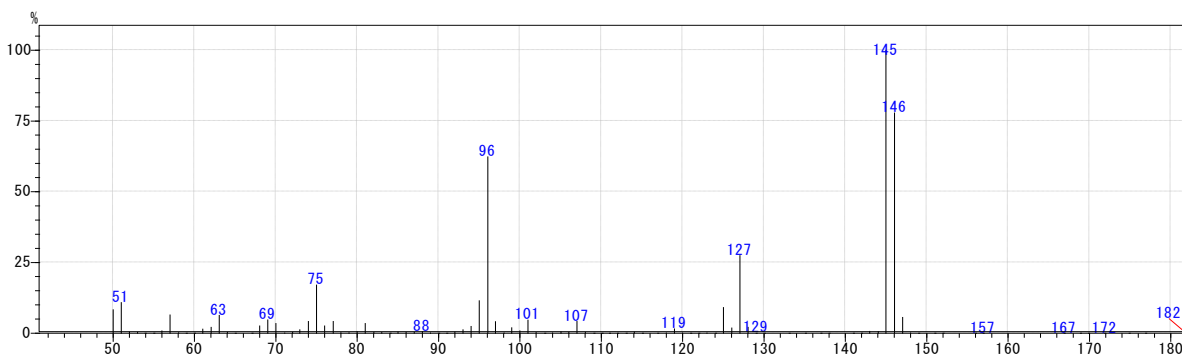


1-(Difluoromethyl)-2-fluorobenzene (4k)

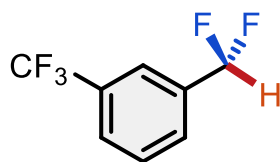


4k

Obtained in 81 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -115.19 (d, J = 55.9 Hz, 2F), -120.96 (s, 1F). ^{19}F NMR data matches previously reported data²³. The identity of the product was further confirmed by GCMS analysis.

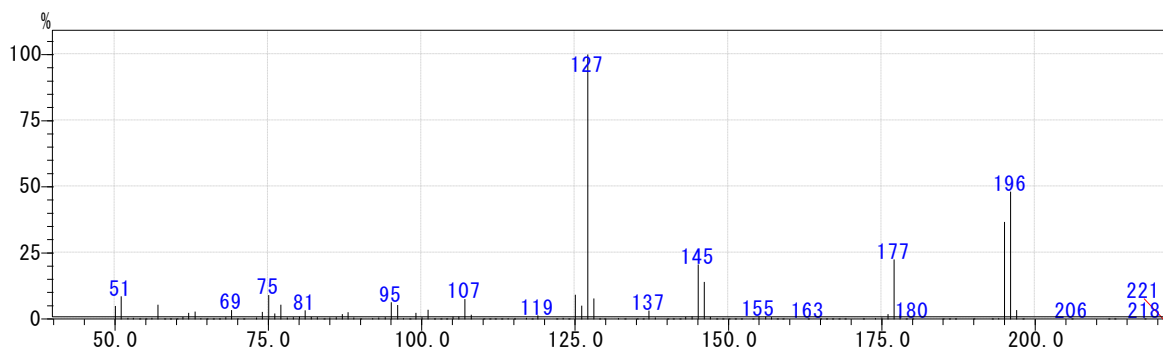


1-(Difluoromethyl)-3-(trifluoromethyl)benzene (4l)

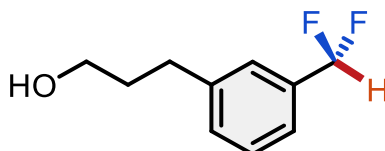


4l

Obtained in 57 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -63.98 (s, 3F), -112.89 (d, J = 55.9 Hz, 2F). ^{19}F NMR data matches previously reported data²⁴. The identity of the product was further confirmed by GCMS analysis.



3-(3-(difluoromethyl)phenyl)propan-1-ol (4m)



4m

Obtained in 72 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOA = 3:1, R_f = 0.1) to afford the pure product as a colorless oil.

HRMS (EI) m/z Calcd for $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}[\text{M}]^+$ 186.0851; Found: 186.0852.

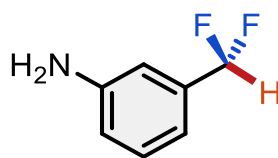
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.36 (dq, J = 13.2, 6.9 Hz, 4H), 6.63 (t, J = 56.5 Hz, 1H), 3.69 (t, J = 6.1 Hz, 2H), 2.77 (t, J = 7.8 Hz, 2H), 1.95-1.88 (m, 2H), 1.30 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 142.53, 134.45 (t, J = 22.1 Hz), 130.85, 128.75, 125.45 (t, J = 6.2 Hz), 123.14 (t, J = 5.9 Hz), 114.83 (t, J = 238.9 Hz), 62.02, 32.91 (d, J = 214.8 Hz), -0.02.

^{19}F NMR (376 MHz, CDCl_3) δ -111.59 (d, J = 52.3 Hz, 2F).

3-(Difluoromethyl)aniline (4n)



4n

Obtained in 69 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.1) to afford the pure product as a yellow oil.

HRMS (ESI) m/z Calcd for $\text{C}_7\text{H}_8\text{F}_2\text{N}[\text{M}+\text{H}]^+$ 144.0619; Found: 144.0618.

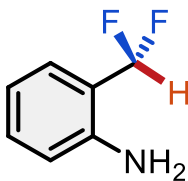
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.22 (t, J = 7.7 Hz, 1H), 6.88-6.75 (m, 3H), 6.55 (td, J = 56.6, 1.3 Hz, 1H), 3.79 (s, 1H), 1.57 (s, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 129.67, 117.13 (t, J = 1.8 Hz), 115.57 (t, J = 6.4 Hz), 114.77, 112.39, 111.56 (t, J = 6.2 Hz), 77.20.

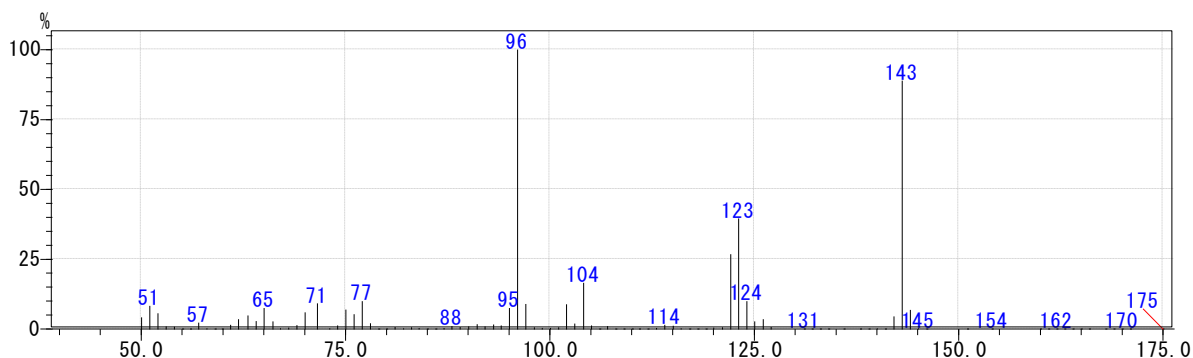
^{19}F NMR (376 MHz, CDCl_3) δ -111.86 (d, J = 57.1 Hz, 2F).

2-(Difluoromethyl)aniline (4o)

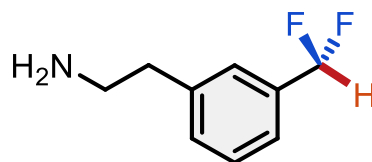


4o

Obtained in 46 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -114.56 (d, J = 55.5 Hz, 2F). ^{19}F NMR data matches previously reported data²⁵. The identity of the product was further confirmed by GCMS analysis.



2-(3-(difluoromethyl)phenyl)ethan-1-amine (4p)



4p

Obtained in 75 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (methanol only, $R_f = 0.1$) to afford the pure product as a white solid.

HRMS (ESI) m/z Calcd for $\text{C}_9\text{H}_{12}\text{F}_2\text{N}[\text{M}+\text{H}]^+$ 172.0932; Found: 172.0931.

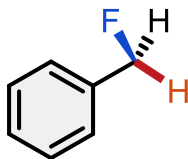
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.41-7.31 (m, 4H), 6.63 (t, $J = 56.5$ Hz, 1H), 2.99 (t, $J = 6.9$ Hz, 2H), 2.80 (t, $J = 6.9$ Hz, 2H), 1.26 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 140.58, 134.50 (t, $J = 22.1$ Hz), 131.20 (d, $J = 1.9$ Hz), 128.80, 125.81 (t, $J = 5.8$ Hz), 123.42 (t, $J = 6.2$ Hz), 114.76 (t, $J = 238.8$ Hz), 43.35, 39.88.

^{19}F NMR (376 MHz, CDCl_3) δ -111.61 (d, $J = 58.0$ Hz, 2F).

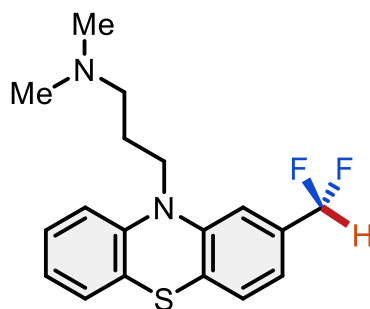
(Fluoromethyl)benzene (4q)



4q

Obtained in 64 % yield (Maximum yield). Yields were determined by GC analysis (t_R 6.7 min) (initial oven temperature, 50 $^\circ\text{C}$ (5 min); temperature increase rate, 10 $^\circ\text{C}/\text{min}$ (25 min); final temperature, 300 $^\circ\text{C}$) using an internal standard (undecane). The NMR spectral data were identical to those reported in the literature¹⁰.

3-(2-(Difluoromethyl)-10H-phenothiazin-10-yl)-*N,N*-dimethylpropan-1-amine (5a)



5a

Obtained in 80 % yield. The residence time of $t^{R1} = 1.6$ s. The crude product was purified by flash column chromatography on silica gel (hexane/Acetone/Et₃N= 91:6:3, R_f= 0.1) to afford the pure product as a yellow oil (70.2 mg).

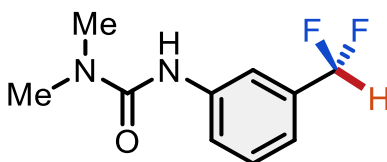
NMR Spectroscopy:

¹H NMR (400 MHz, CDCl₃) δ 7.19-7.12 (m, 3H), 7.02 (d, *J*= 9.1 Hz, 2H), 6.96-6.90 (m, 2H), 6.58 (t, *J*= 56.5 Hz, 1H), 3.94 (t, *J*= 7.0 Hz, 2H), 2.40 (t, *J*= 7.0 Hz, 2H), 2.21 (s, 6H), 1.94 (t, *J*= 7.0 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 145.67, 144.59, 133.43 (t, *J*= 22.2 Hz), 128.43, 128.41, 127.45, 127.42, 124.28, 122.80, 119.56 (t, *J*= 6.6 Hz), 116.94, 115.72, 114.57, 112.12 (t, *J*= 5.9 Hz), 57.02, 45.50 (d, *J*= 17.2 Hz), 25.04.

¹⁹F NMR (376 MHz, CDCl₃) δ -111.49 (d, *J*= 57.4 Hz, 2F).

3-(3-(Difluoromethyl)phenyl)-1,1-dimethylurea (5b)



5b

Obtained in 54 % yield. The residence time of $t^{R1} = 0.11$ s. The yield was determined by ¹⁹F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, R_f= 0.2) to afford the pure product as a white solid in 53 % isolated yield (28.2 mg).

HRMS (ESI) *m/z* Calcd for C₁₀H₁₂F₂N₂ONa[M+Na]⁺ 237.0810; Found: 237.0806.

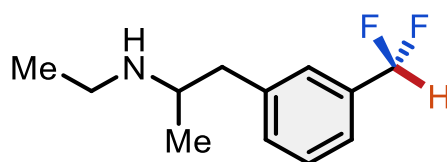
NMR Spectroscopy:

¹H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 7.49 (dd, *J*= 8.1, 1.0 Hz, 1H), 7.36 (t, *J*= 7.9 Hz, 1H), 7.17 (d, *J*= 7.5 Hz, 1H), 6.60 (t, *J*= 56.5 Hz, 1H), 6.43 (s, 1H), 3.05 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ 155.43, 139.37 (d, *J*= 99.2 Hz), 134.94 (t, *J*= 22.1 Hz), 129.05 (d, *J*= 60.6 Hz), 123.75-120.57 (m), 119.73 (t, *J*= 6.2 Hz), 116.82 (q, *J*= 8.2 Hz), 113.62 (d, *J*= 239.0 Hz), 36.39.

¹⁹F NMR (376 MHz, CDCl₃) δ -111.93 (d, *J*= 53.3 Hz, 2F).

1-(3-(difluoromethyl)phenyl)-*N*-ethylpropan-2-amine (5c)

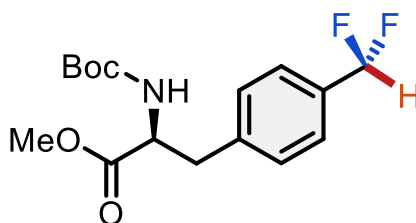


5c

Obtained in 72 % yield. The residence time of $t^{R1} = 0.11$ s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.63 (d, $J = 52.0$ Hz, 2F). Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.

HRMS (ESI) m/z Calcd for $\text{C}_{12}\text{H}_{18}\text{F}_2\text{N}[\text{M}+\text{H}]^+$ 214.1402; Found: 214.1402.

Methyl-(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate (5d)



5d

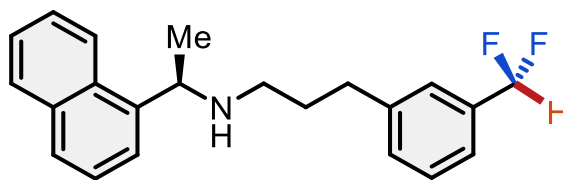
Obtained in 46 % yield. The residence time of $t^{R1} = 6.9$ ms. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.68 (d, $J = 54.1$ Hz, 2F). ^{19}F NMR data matches previously reported data¹⁰. Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.

NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 7.7$ Hz, 2H), 7.22 (d, $J = 7.8$ Hz, 2H), 6.62 (t, $J = 56.5$ Hz, 1H), 4.99 (d, $J = 7.7$ Hz, 1H), 4.61 (q, $J = 6.9$ Hz, 1H), 3.72 (s, 3H), 3.21-3.05 (m, 2H), 1.41 (s, 9H).

^{19}F NMR (376 MHz, CDCl_3) δ -111.68 (d, $J = 54.1$ Hz, 2F).

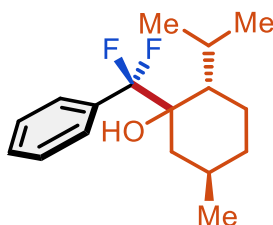
(S)-3-(3-(Difluoromethyl)phenyl)-N-(1-(naphthalen-1-yl)ethyl)propan-1-amine (5e)



5e

Obtained in 69 % yield. The residence time of t^{R1} = 6.9 ms. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl_3) δ -111.56 (d, J = 53.4 Hz, 2F). ^{19}F NMR data matches previously reported data¹⁰. Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.

(2S,5R)-1-(Difluoro(phenyl)methyl)-2-isopropyl-5-methylcyclohexan-1-ol (5f)



5f

Obtained in 69 % yield. The residence time of t^{R1} = 0.11 s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC and flash column chromatography on silica gel (hexane/EtOAc = 10:0.5, R_f = 0.4) to afford the pure product as a colorless oil in 32 % isolated yield (23.2 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{17}\text{H}_{24}\text{F}_2\text{ONa}[\text{M}+\text{Na}]^+$ 305.1687; Found: 305.1686.

IR (neat) 3618 cm^{-1} , 2949 cm^{-1} , 2870 cm^{-1}

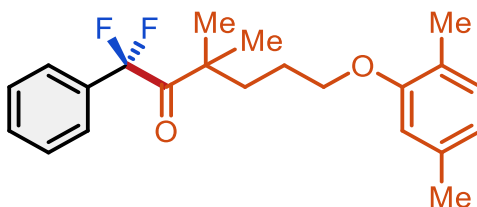
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, J = 7.4, 2.1 Hz, 2H), 7.42 (q, J = 3.4 Hz, 3H), 2.64 (7, J = 6.9 Hz, 1H), 1.95 (s, 1H), 1.72-1.64 (m, 2H), 1.59-1.45 (m, 3H), 1.26 (dt, J = 13.3, 2.9 Hz, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 7.3 Hz, 4H), 0.77 (d, J = 6.4 Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 135.26 (t, J = 27.0 Hz), 129.59, 127.89, 126.55 (t, J = 6.7 Hz), 126.78-121.75 (m), 78.76 (dd, J = 27.0, 24.1 Hz), 45.47, 43.26 (d, J = 4.3 Hz), 34.63, 31.09, 27.44, 26.75 (t, J = 4.2 Hz), 23.24, 22.14, 20.21, 17.89.

^{19}F NMR (376 MHz, CDCl_3) δ -101.25 (d, J = 246.7 Hz, 1F), -103.29 (d, J = 248.5 Hz, 1F), -107.23 (d, J = 248.5 Hz, 1F), -110.30 (d, J = 248.3 Hz, 1F).

6-(2,5-Dimethylphenoxy)-1,1-difluoro-3,3-dimethyl-1-phenylhexan-2-one (5g)



5g

Obtained in 56 % yield. The residence time of $t^{R1} = 0.11$ s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC to afford the pure product as a colorless oil in 41 % isolated yield (37.2 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{22}\text{H}_{26}\text{F}_2\text{O}_2\text{Na}[\text{M}+\text{Na}]^+$ 383.1793; Found: 383.1789.

IR (neat) 2924 cm^{-1} , 1723 cm^{-1} , 1257 cm^{-1}

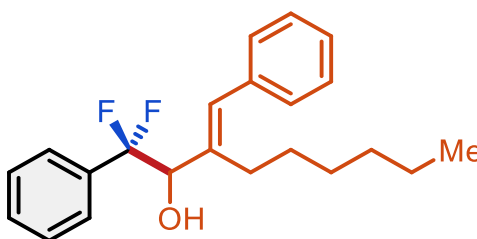
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.56-7.54 (m, 2H), 7.47-7.41 (m, 3H), 7.01 (d, $J = 7.5$ Hz, 1H), 6.66 (d, $J = 7.4$ Hz, 1H), 6.59 (s, 1H), 3.88 (t, $J = 6.2$ Hz, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 1.90-1.86 (m, 2H), 1.66-1.58 (m, 2H), 1.26 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 204.12 (t, $J = 29.4$ Hz), 156.85, 136.45, 133.03 (d, $J = 25.0$ Hz), 130.63, 130.28, 128.51, 125.72 (t, $J = 6.2$ Hz), 123.55, 120.69, 119.79-114.68 (m), 111.83, 67.63, 47.32 (d, $J = 1.8$ Hz), 36.18 (d, $J = 2.5$ Hz), 24.85, 24.33 (t, $J = 1.9$ Hz), 21.39, 15.75.

^{19}F NMR (376 MHz, CDCl_3) δ -100.18 (s, 2F).

(E)-3-Benzylidene-1,1-difluoro-1-phenylnonan-2-ol (5h)



5h

Obtained in 71 % yield. The residence time of $t^{R1} = 0.11$ s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC and flash column chromatography on silica gel (hexane/EtOAc = 10:1, $R_f = 0.2$) to afford the pure product as a colorless oil in 34 % isolated yield (30.0 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{22}\text{H}_{26}\text{F}_2\text{ONa}[\text{M}+\text{Na}]^+$ 367.1844; Found: 367.1841.

IR (neat) 3588 cm^{-1} , 2924 cm^{-1}

NMR Spectroscopy:

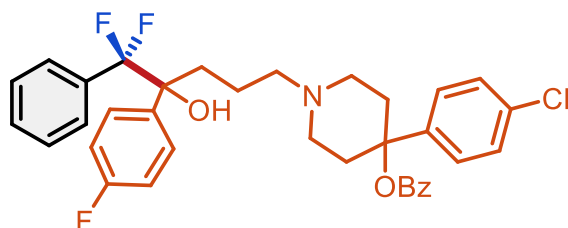
^1H NMR (400 MHz, CDCl_3) δ 7.50-7.40 (m, 5H), 7.30 (t, $J = 7.5$ Hz, 2H), 7.23-7.19 (m, 1H), 7.09 (d, $J = 7.2$ Hz, 2H), 6.36 (s, 1H), 4.65 (td, $J = 9.7, 4.0$ Hz, 1H), 2.35-2.29 (m, 1H), 2.26 (d, $J = 4.1$ Hz, 1H), 1.89 (ddd, $J =$

14.2, 10.1, 4.7 Hz, 1H), 1.55 (s, 3H), 1.49-1.37 (m, 2H), 1.29-1.20 (m, 7H), 0.85 (t, J = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 138.15, 136.94, 133.98 (t, J = 25.8 Hz), 130.13, 130.01 (t, J = 1.7 Hz), 128.44, 128.15, 127.95, 126.75, 126.33 (t, J = 6.4 Hz), 121.69 (t, J = 249.4 Hz), 76.84 (t, J = 29.4 Hz), 31.42, 29.64, 29.38, 28.70, 22.52, 14.03.

^{19}F NMR (376 MHz, CDCl_3) δ -105.75--107.38 (m, 2F).

4-(4-Chlorophenyl)-1-(5,5-difluoro-4-(4-fluorophenyl)-4-hydroxy-5-phenylpentyl)piperidin-4-yl benzoate (5i)



5i

Obtained in 30 % yield. The residence time of t^{R1} = 0.11 s. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 3:2, R_f = 0.4) to afford the pure product as a yellow viscous oil (46.5 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{35}\text{H}_{34}\text{ClF}_3\text{NO}_3[\text{M}+\text{H}]^+$ 608.2174; Found:608.2167.

IR (neat) 2936 cm^{-1} , 1717 cm^{-1} , 1277 cm^{-1} , 1093 cm^{-1}

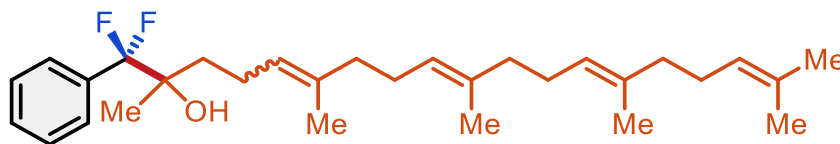
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.97-7.95 (m, 2H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.37-7.29 (m, 7H), 7.22 (t, J = 7.6 Hz, 2H), 7.17-7.14 (m, 2H), 6.93 (t, J = 8.7 Hz, 2H), 2.85-2.67 (m, 3H), 2.55-1.97 (m, 9H), 1.64 (dddd, J = 10.4, 7.7, 5.0, 2.5 Hz, 1H), 1.49-1.39 (m, 1H), 1.31-1.26 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 164.52, 163.35, 160.90, 142.05, 136.83 (t, J = 2.5 Hz), 134.70 (t, J = 26.5 Hz), 133.50, 133.11, 130.59, 129.67 (d, J = 7.7 Hz), 129.45, 129.14, 128.71, 128.46, 127.33 (t, J = 6.5 Hz), 126.96, 126.18, 114.26 (d, J = 21.1 Hz), 79.76, 77.59 (dd, J = 53.5, 25.7 Hz), 58.52, 50.21, 47.45, 34.60 (t, J = 51.0 Hz), 20.68.

^{19}F NMR (376 MHz, CDCl_3) δ -105.81 (d, J = 242.3 Hz, 1F), -109.38 (d, J = 241.0 Hz, 1F), -116.86 (d, J = 12.4 Hz, 1F).

(9E,13E)-1,1-Difluoro-2,6,10,14,18-pentamethyl-1-phenylnonadeca-5,9,13,17-tetraen-2-ol (5j)



5j

Obtained in 72 % yield. The residence time of $t^{R1} = 0.11$ s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, $R_f = 0.3$) to afford the pure product as a colorless oil in 57 % isolated yield (44.9 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{30}\text{H}_{44}\text{F}_2\text{ONa}[\text{M}+\text{Na}]^+$ 481.3252; Found: 481.3245.

IR (neat) 2923 cm^{-1}

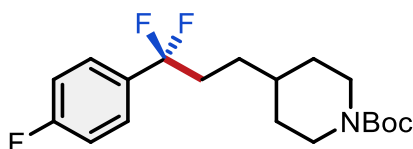
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, $J = 5.7, 1.9$ Hz, 2H), 7.43 (t, $J = 6.3$ Hz, 3H), 5.11-5.07 (m, 4H), 2.15-1.95 (m, 14H), 1.68-1.56 (m, 18H), 1.28 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) 135.93 (d, $J = 18.4$ Hz), 135.30-134.89 (m), 134.20 (t, $J = 27.0$ Hz), 131.26, 129.73, 127.84, 126.86 (t, $J = 6.7$ Hz), 125.43-120.44 (m), 75.68 (t, $J = 27.9$ Hz), 39.70-39.65 (m), 35.39 (dt, $J = 32.7, 1.7$ Hz), 31.89, 26.73-21.42 (m), 20.35 (t, $J = 2.9$ Hz), 17.66, 15.97 (t, $J = 2.4$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -110.17 (d, $J = 18.3$ Hz, 2F).

***tert*-Butyl 4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine-1-carboxylate (8)**



8

Obtained in 61 % yield. The residence time of $t^{R1} = 1.6$ s. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, $R_f = 0.25$) to afford the pure product as a yellow oil in 52 % isolated yield (47.0 mg).

HRMS (ESI) m/z Calcd for $\text{C}_{19}\text{H}_{26}\text{F}_3\text{NO}_2\text{Na}[\text{M}+\text{Na}]^+$ 380.1808; Found: 380.1805.

IR (neat) 2926 cm^{-1} , 1686 cm^{-1} , 1160 cm^{-1}

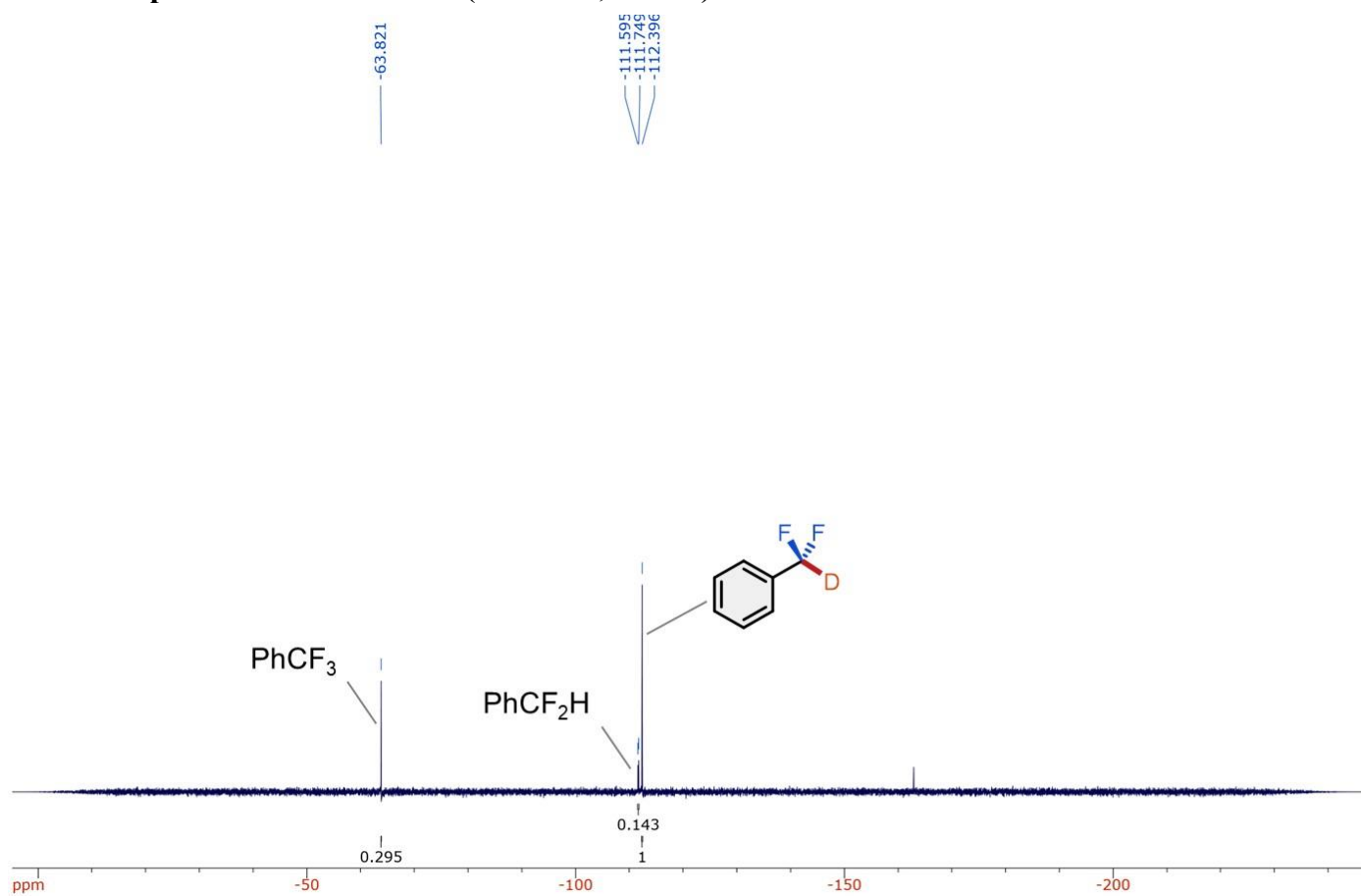
NMR Spectroscopy:

^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, $J = 8.7, 5.3$ Hz, 2H), 7.10 (t, $J = 8.6$ Hz, 2H), 4.07 (s, 2H), 2.65 (t, $J = 10.9$ Hz, 2H), 2.18-2.06 (m, 2H), 1.62 (d, $J = 13.5$ Hz, 2H), 1.44 (s, 9H), 1.38-1.33 (m, 3H), 1.11-1.01 (m, 2H).

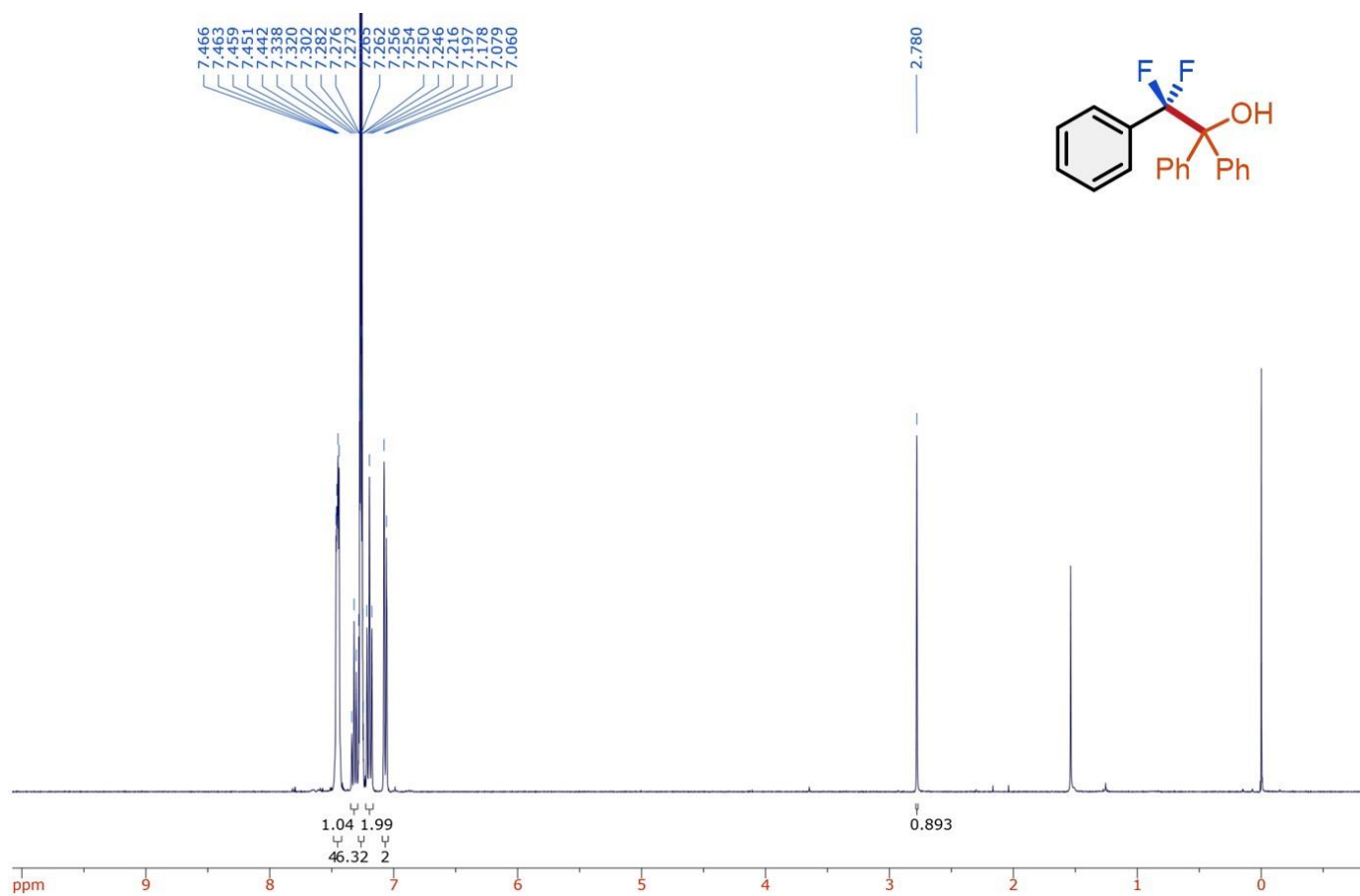
^{13}C NMR (100 MHz, CDCl_3) δ 164.57, 162.10, 154.78, 133.56 (d, $J = 3.5$ Hz), 133.28 (d, $J = 3.0$ Hz), 127.09-126.88 (m), 122.74 (t, $J = 242.4$ Hz), 115.54, 115.32, 79.27, 36.34 (t, $J = 27.6$ Hz), 35.56, 31.85 (t, $J = 2.1$ Hz), 28.94 (t, $J = 3.7$ Hz), 28.41.

^{19}F NMR (376 MHz, CDCl_3) δ -95.96 (q, $J = 15.1$ Hz, 2F), -112.70 (s, 1F).

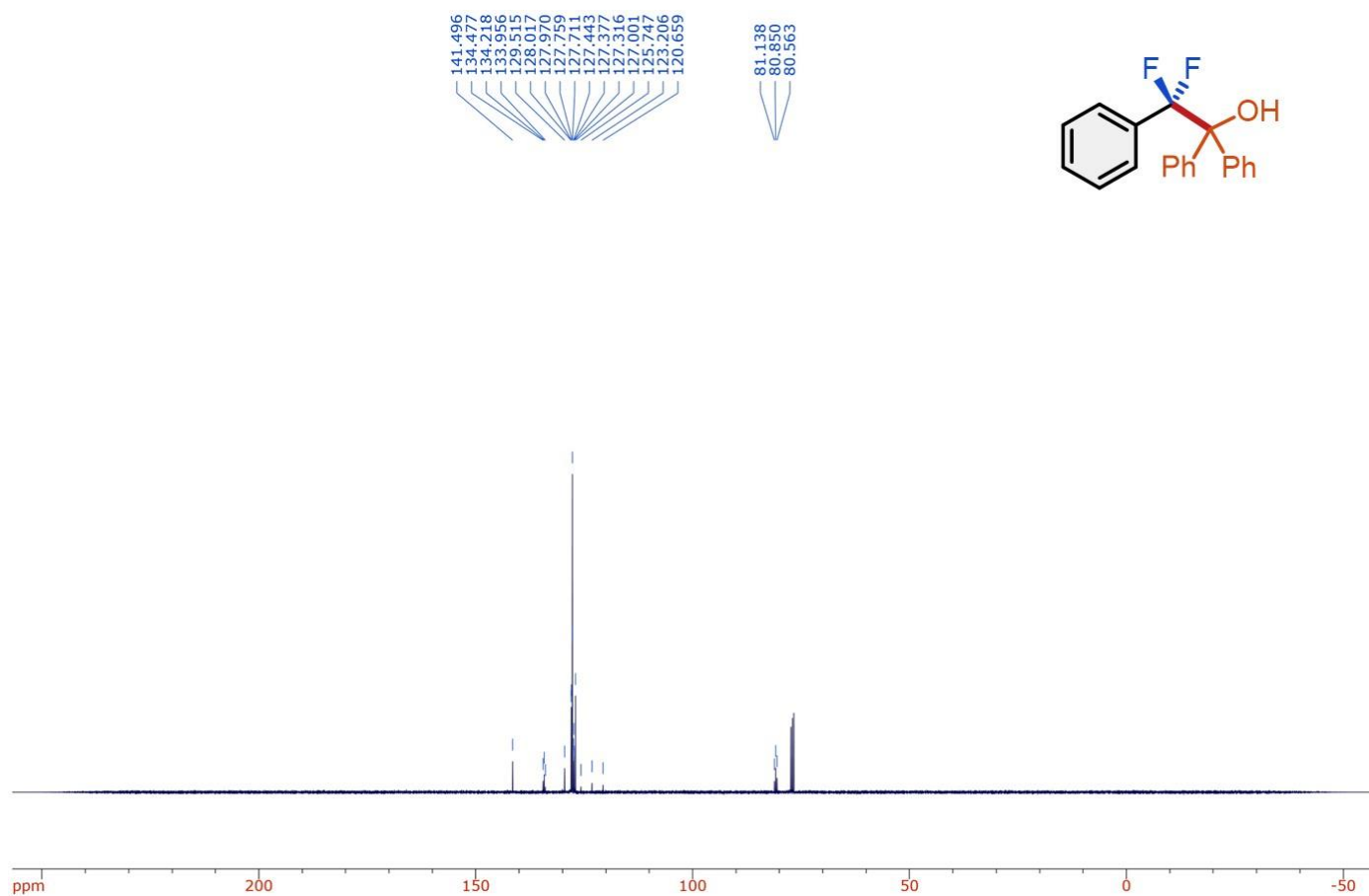
^{19}F NMR spectrum of crude of 3b (376 MHz, CDCl_3)



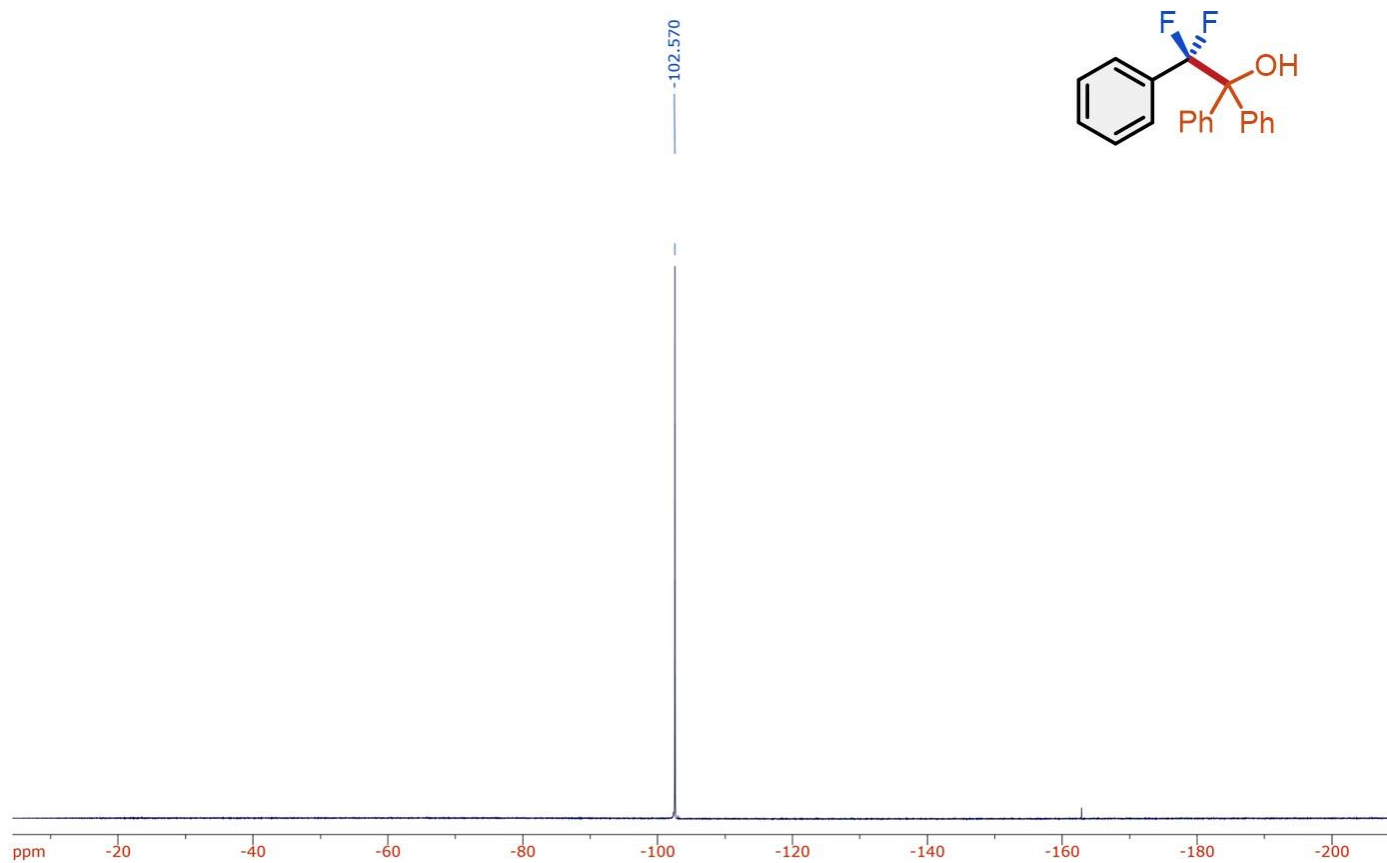
^1H NMR spectrum of 3c (400 MHz, CDCl_3)



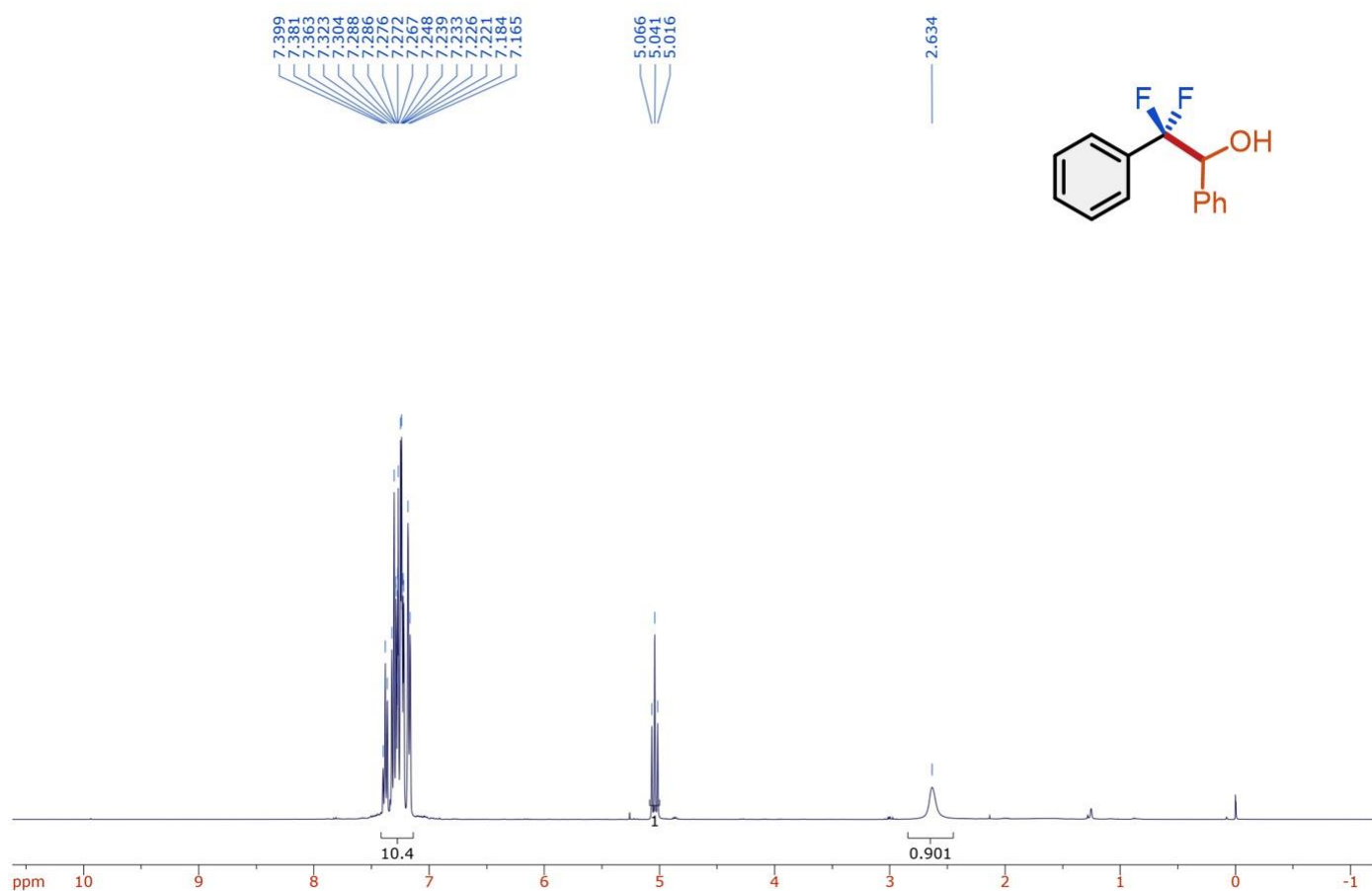
^{13}C NMR spectrum of 3c (100 MHz, CDCl_3)



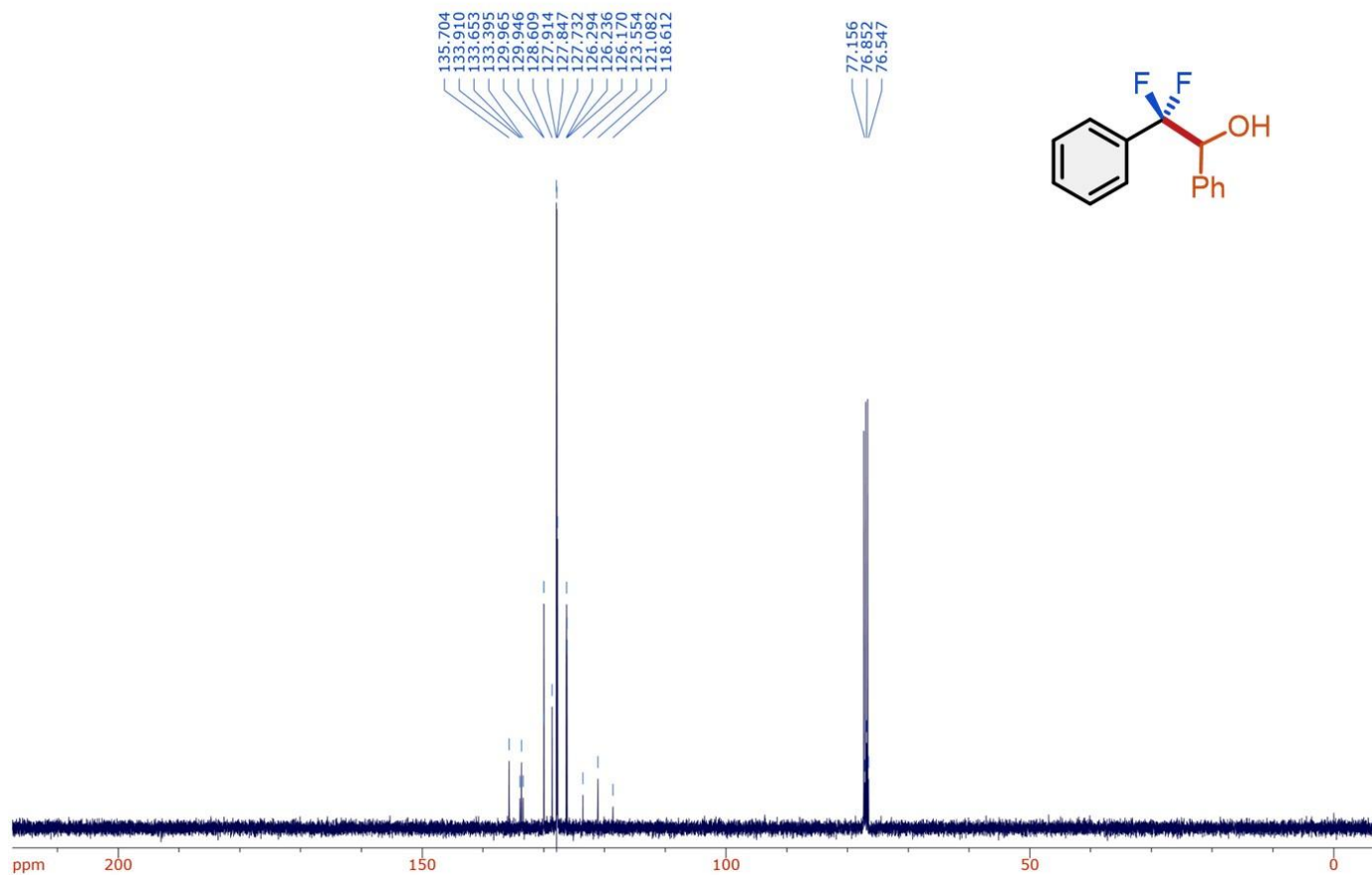
^{19}F NMR spectrum of 3c (376 MHz, CDCl_3)



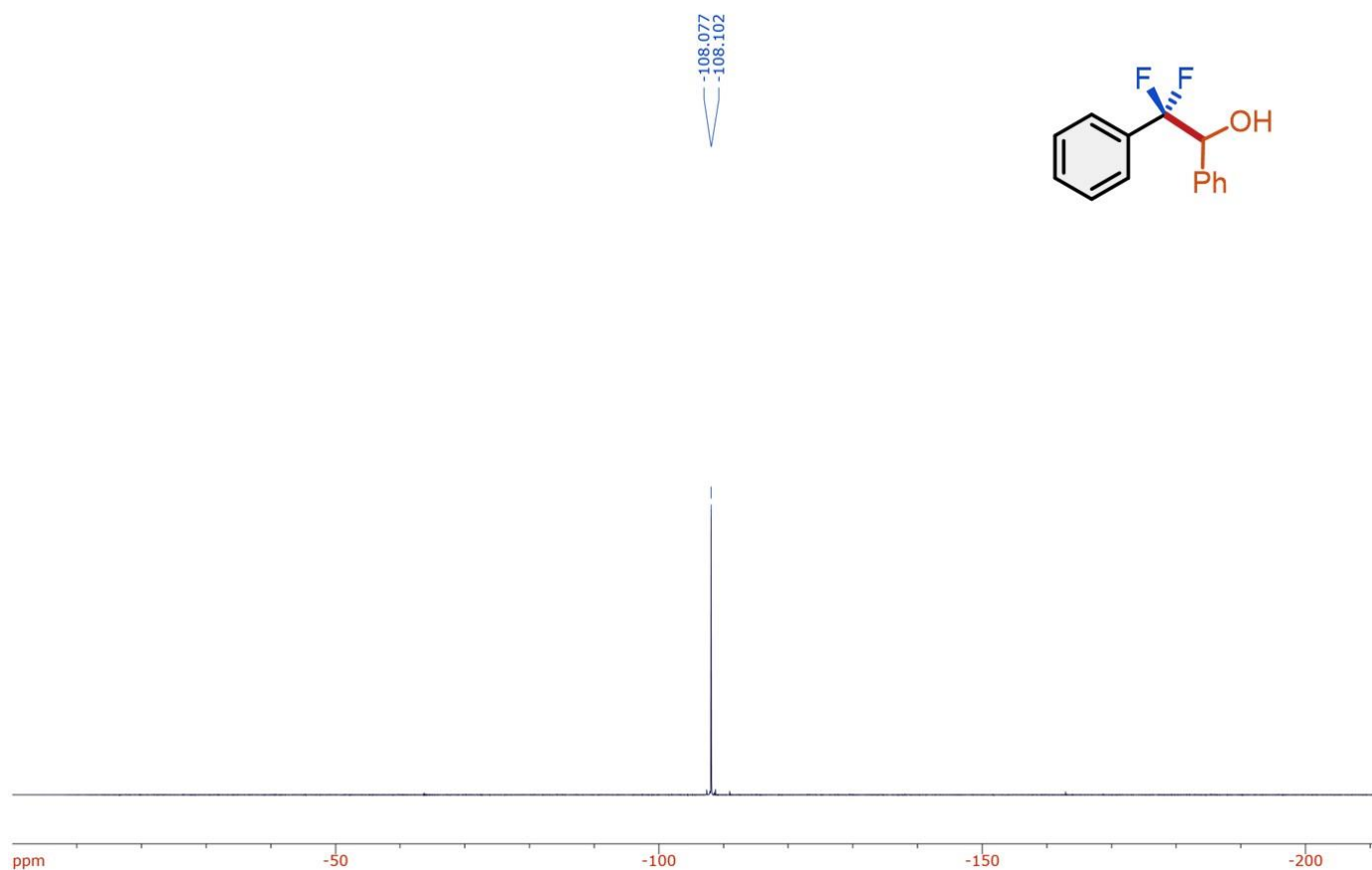
¹H NMR spectrum of 3d (400 MHz, CDCl₃)



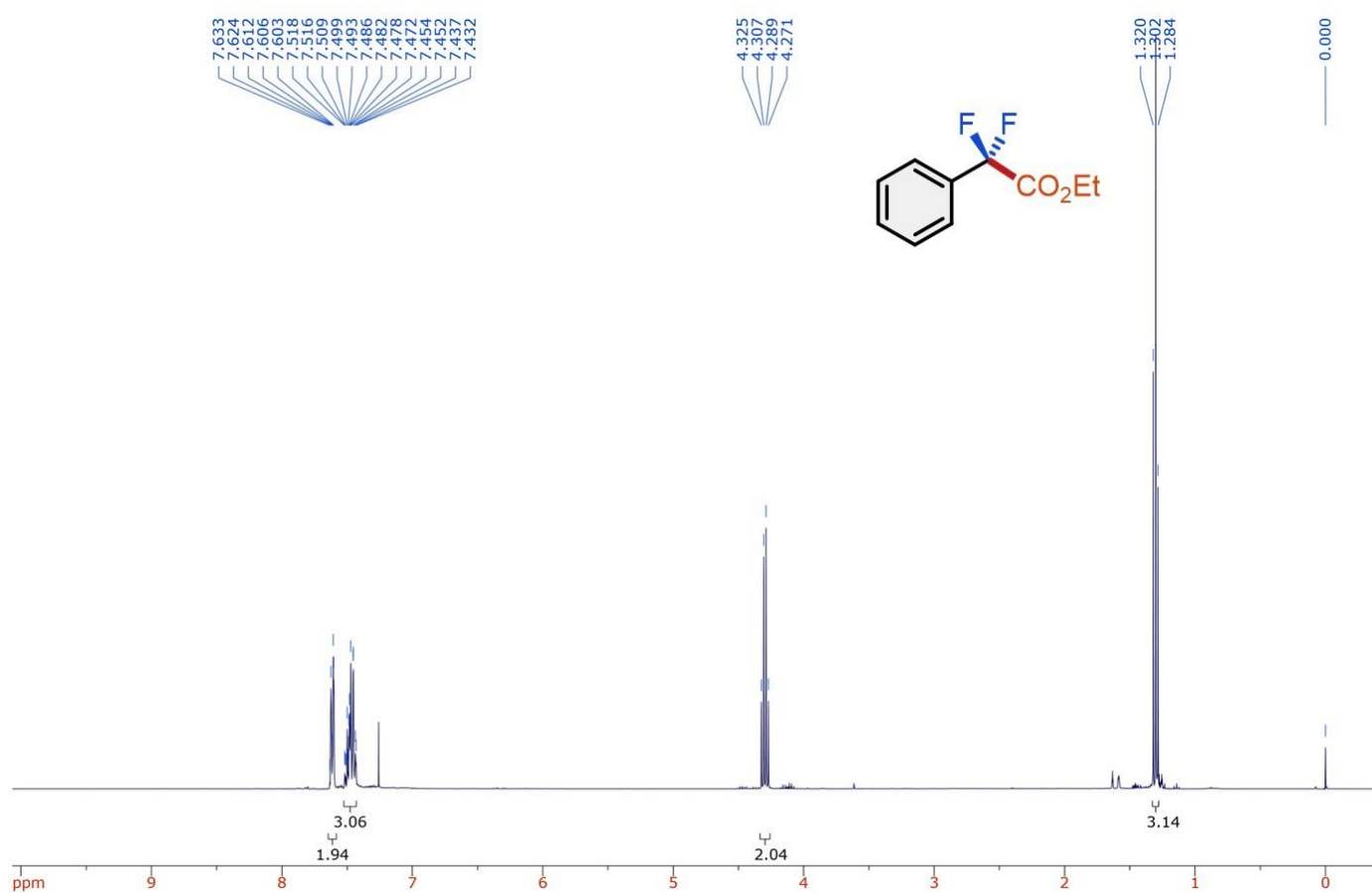
¹³C NMR spectrum of 3d (100 MHz, CDCl₃)



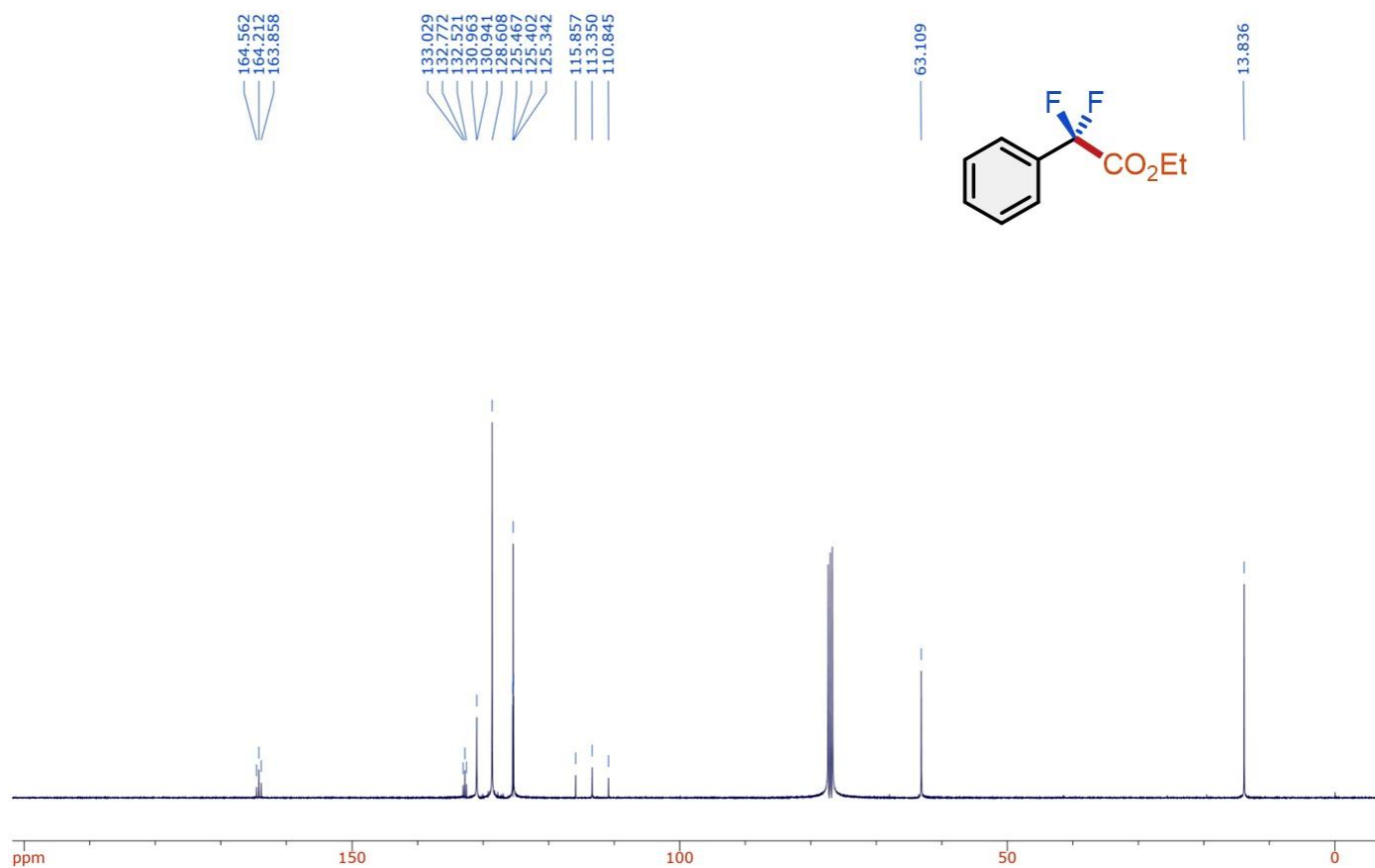
^{19}F NMR spectrum of 3d (376 MHz, CDCl_3)



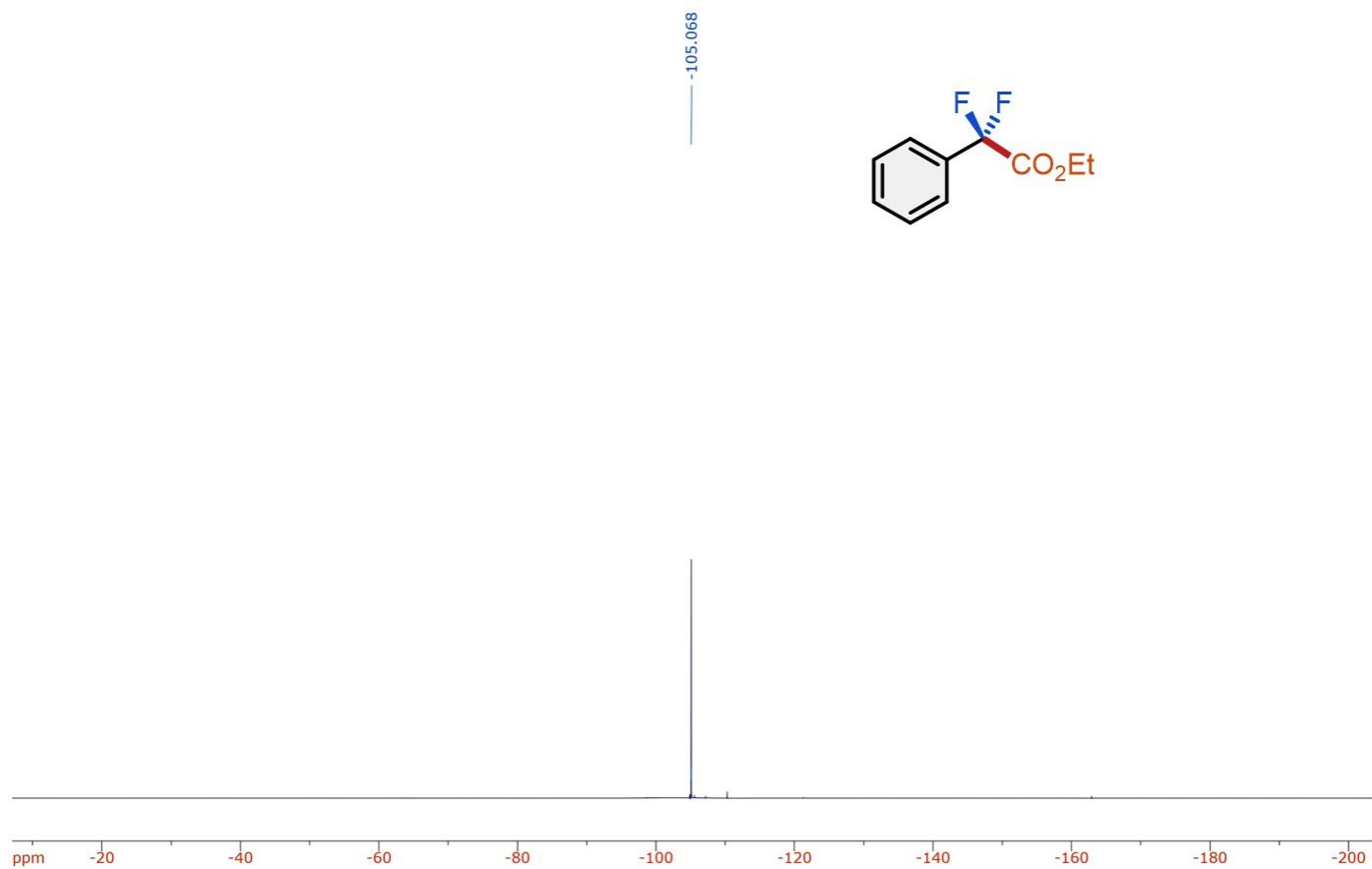
^1H NMR spectrum of 3e (400 MHz, CDCl_3)



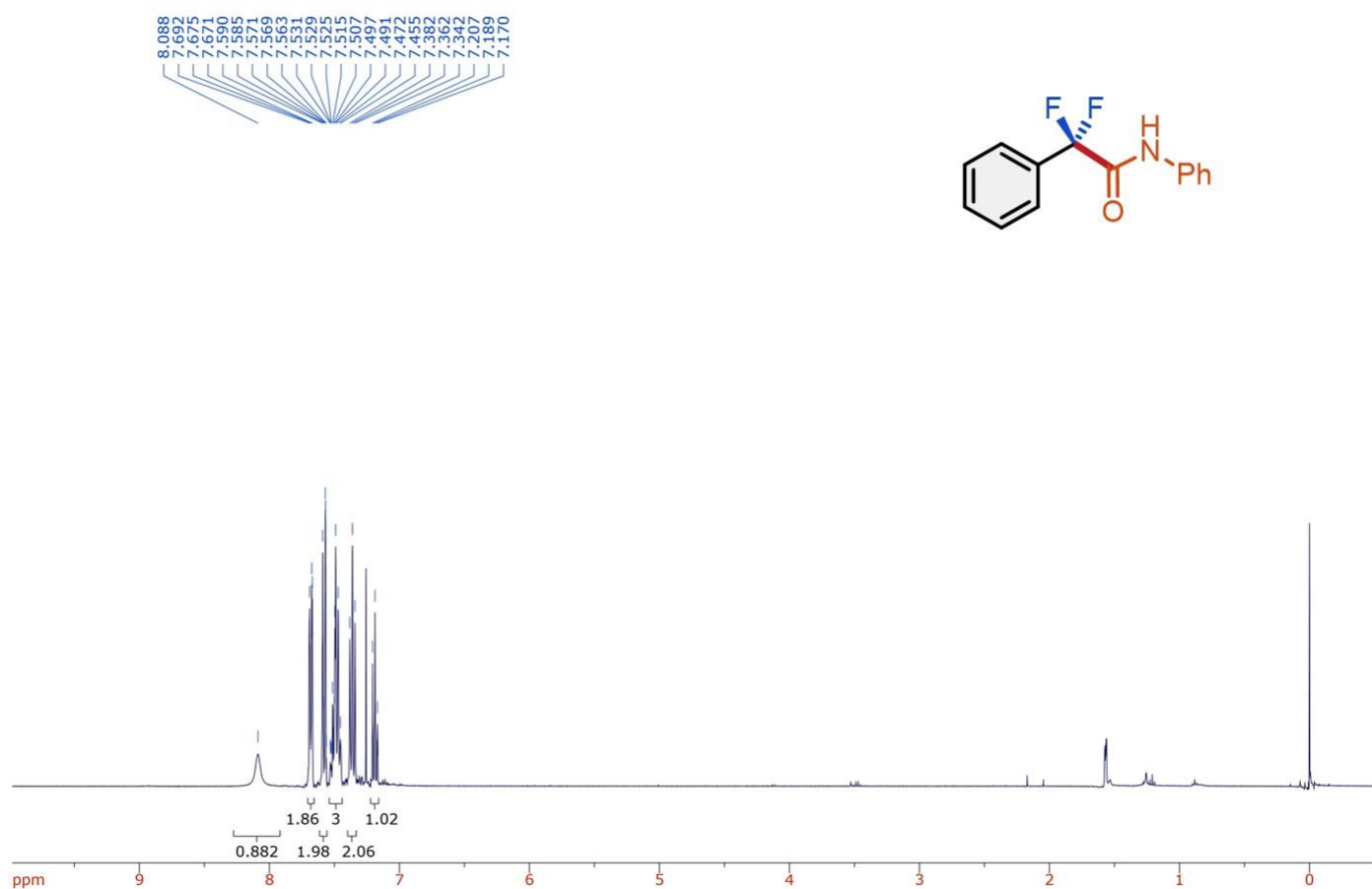
^{13}C NMR spectrum of 3e (100 MHz, CDCl_3)



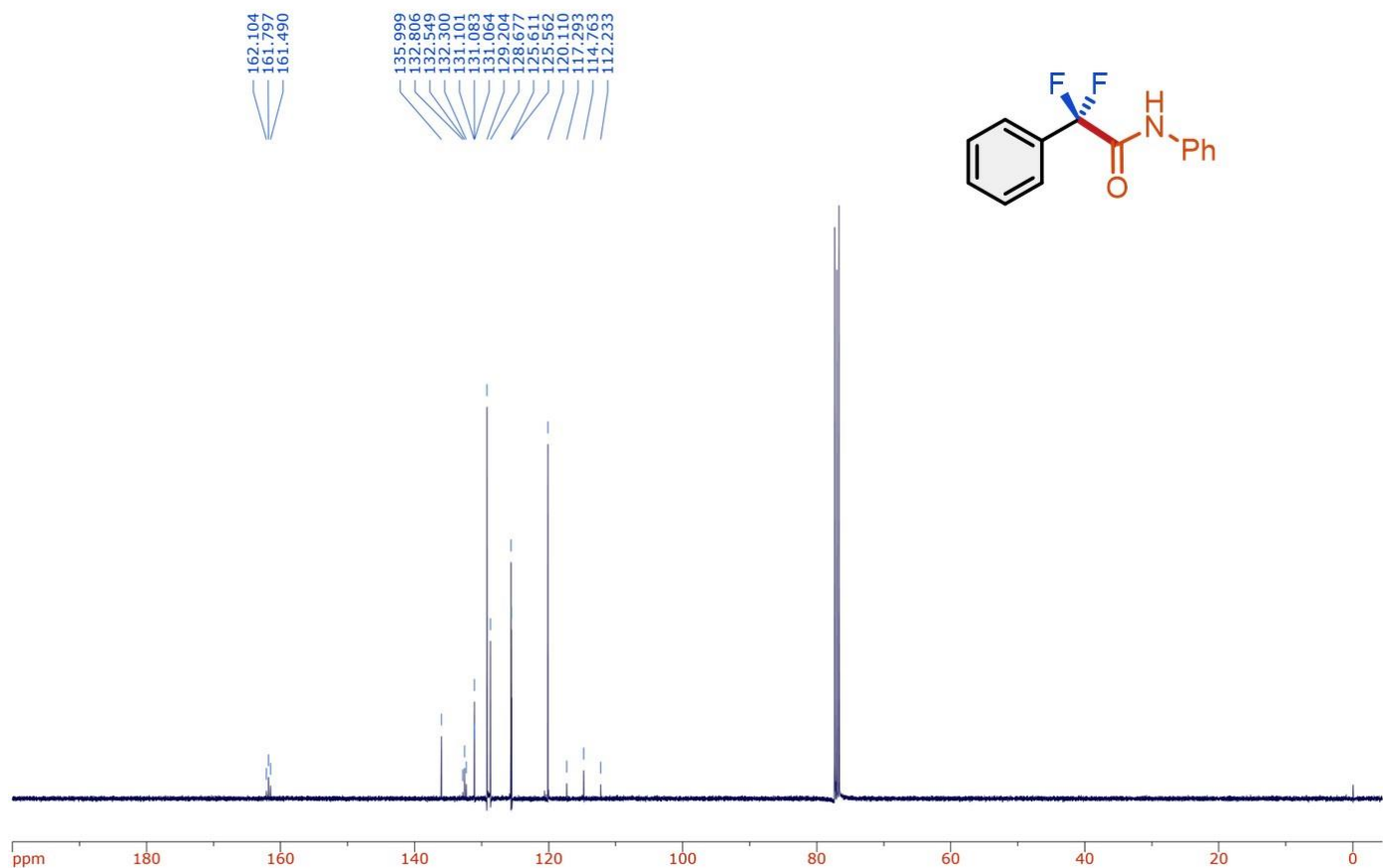
^{19}F NMR spectrum of 3e (376 MHz, CDCl_3)



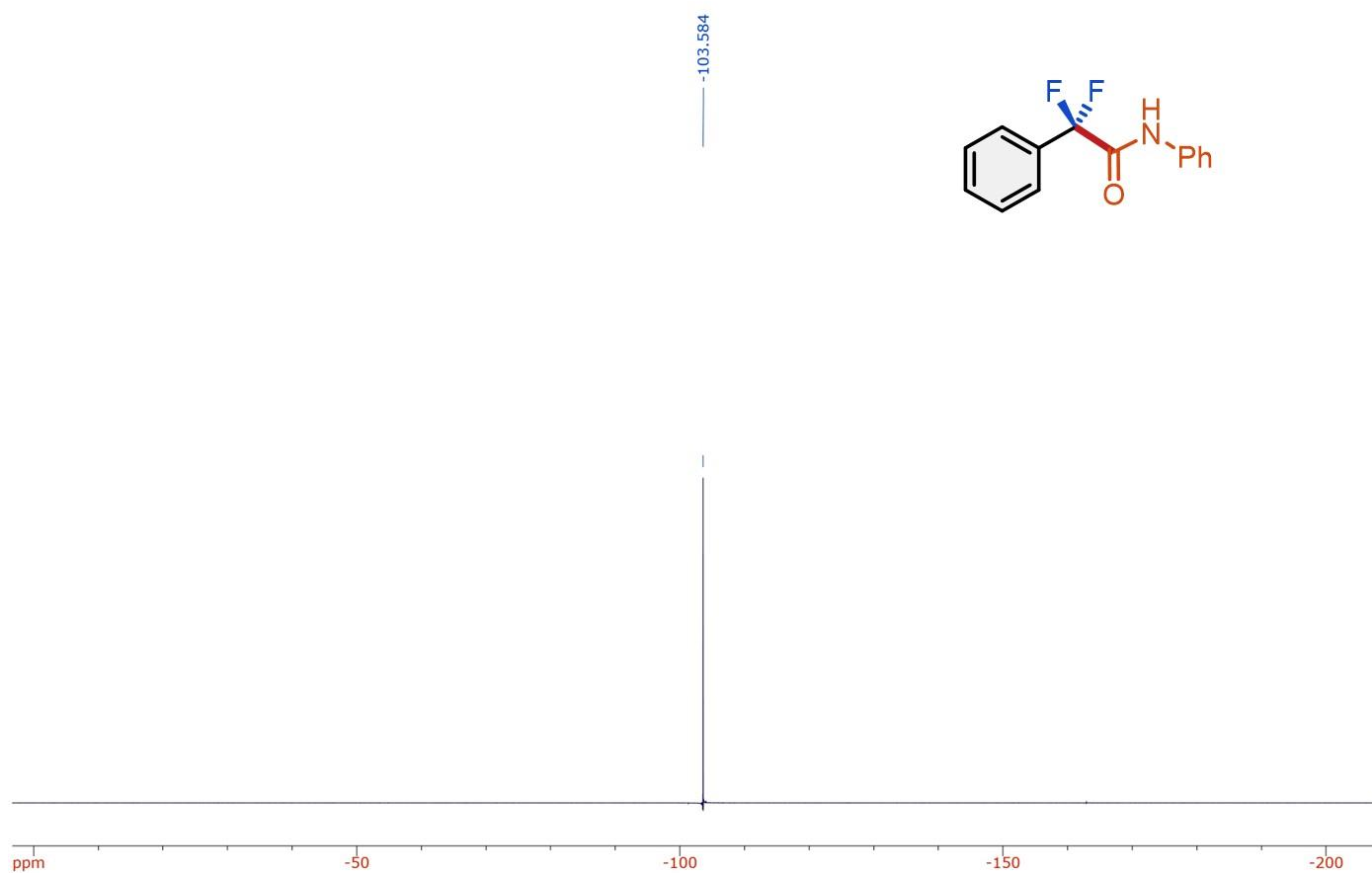
¹H NMR spectrum of 3g (400 MHz, CDCl₃)



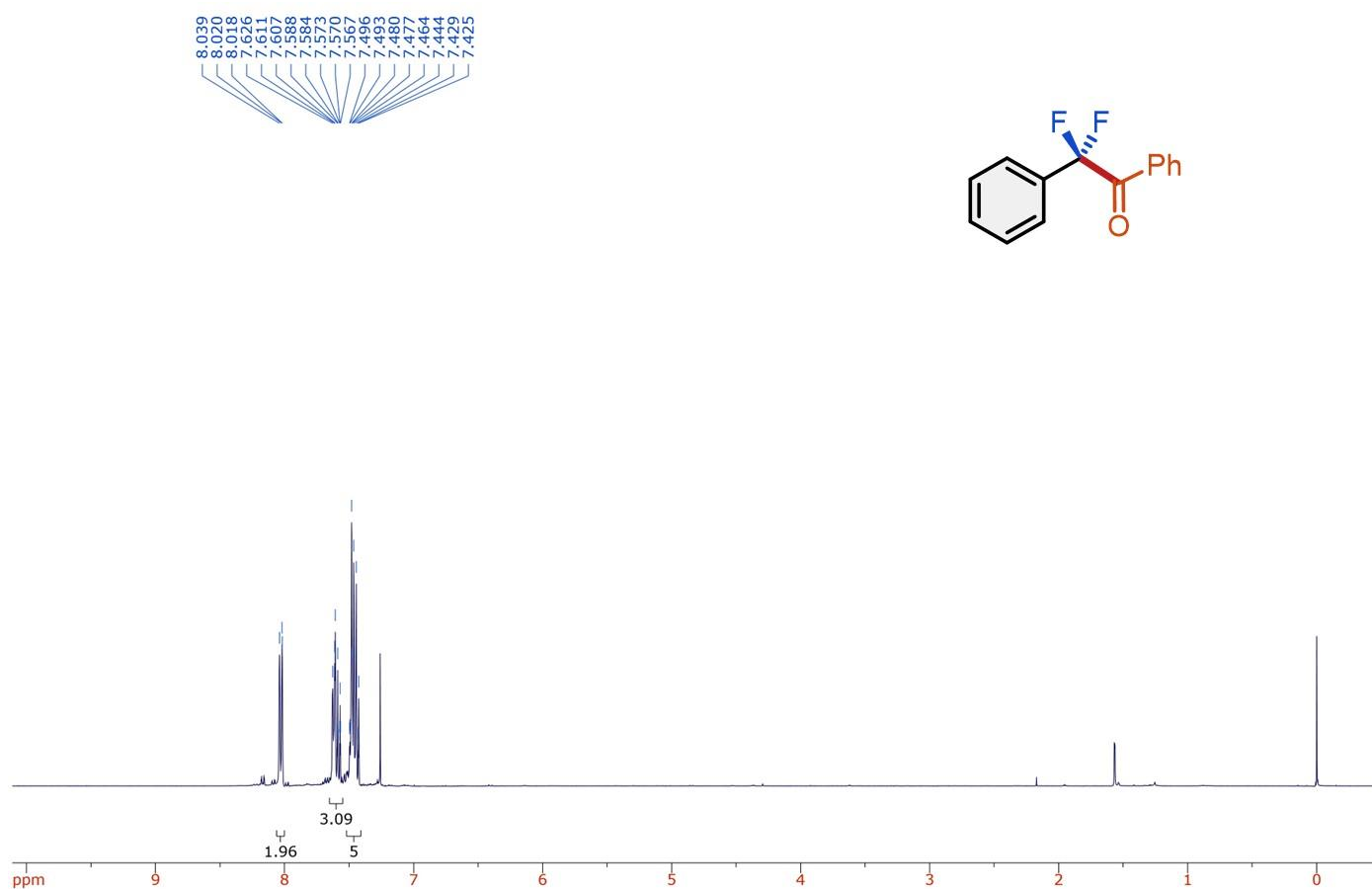
¹³C NMR spectrum of 3g (100 MHz, CDCl₃)



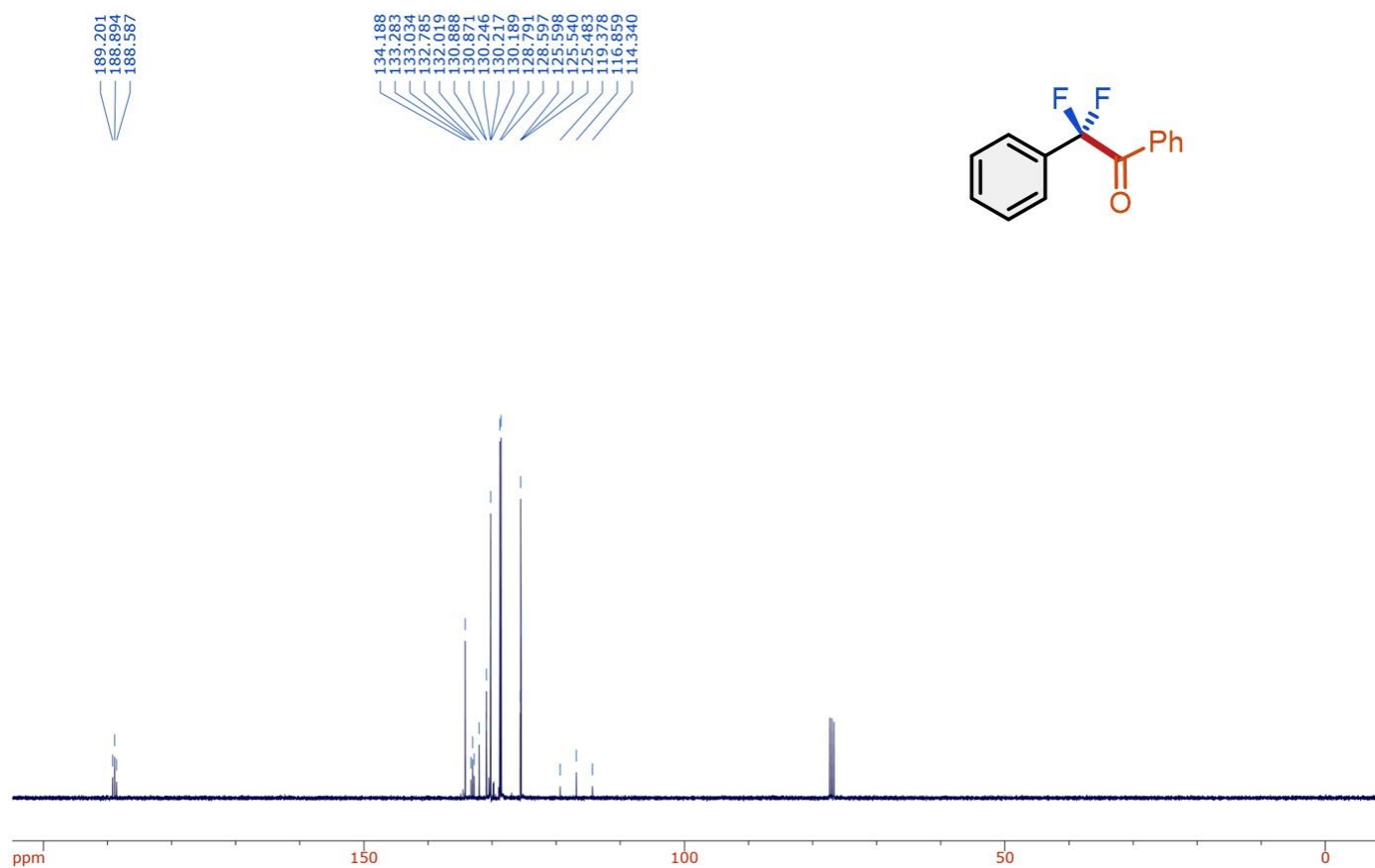
^{19}F NMR spectrum of 3g (376 MHz, CDCl_3)



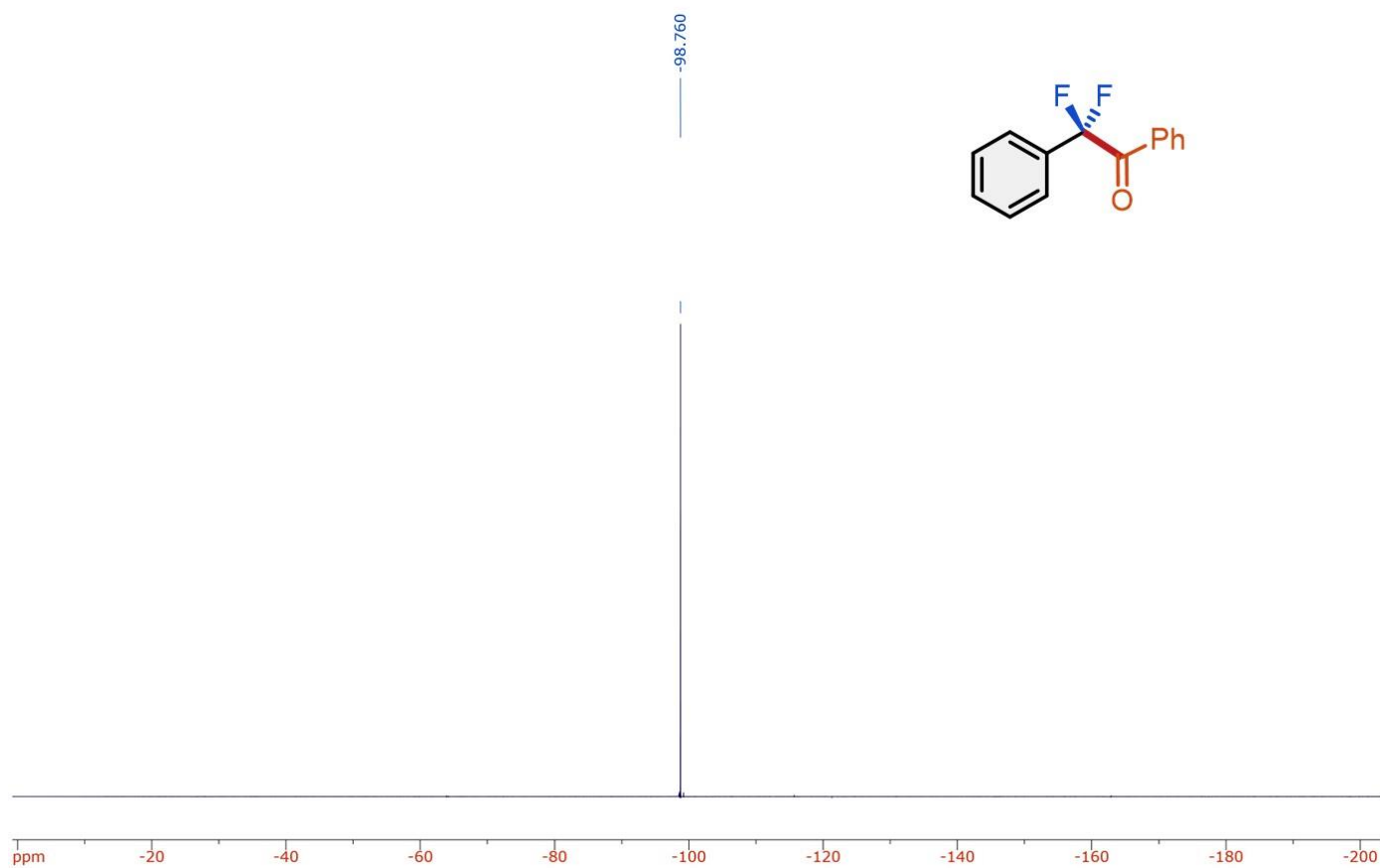
^1H NMR spectrum of 3h (400 MHz, CDCl_3)



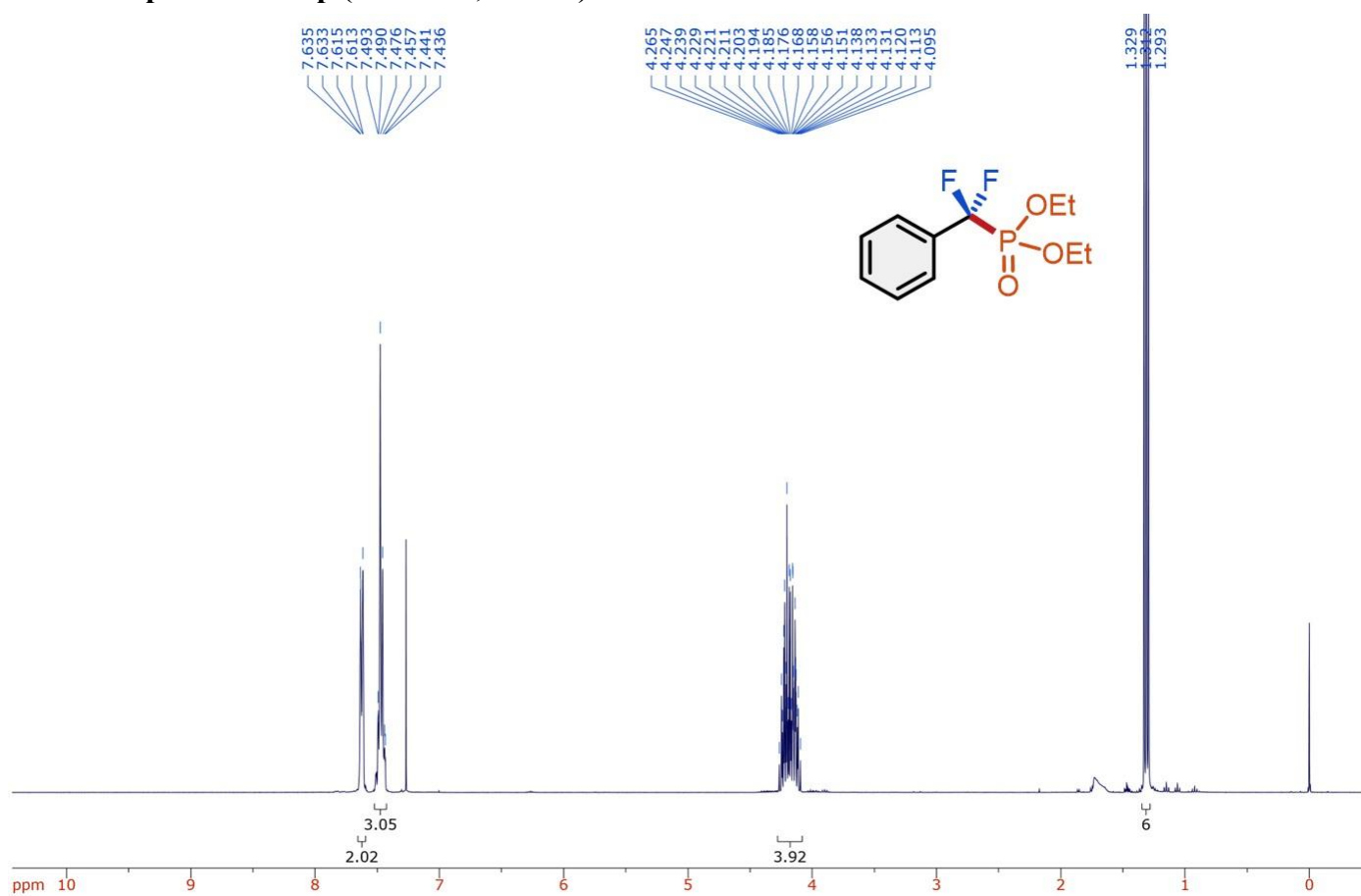
^{13}C NMR spectrum of 3h (100 MHz, CDCl_3)



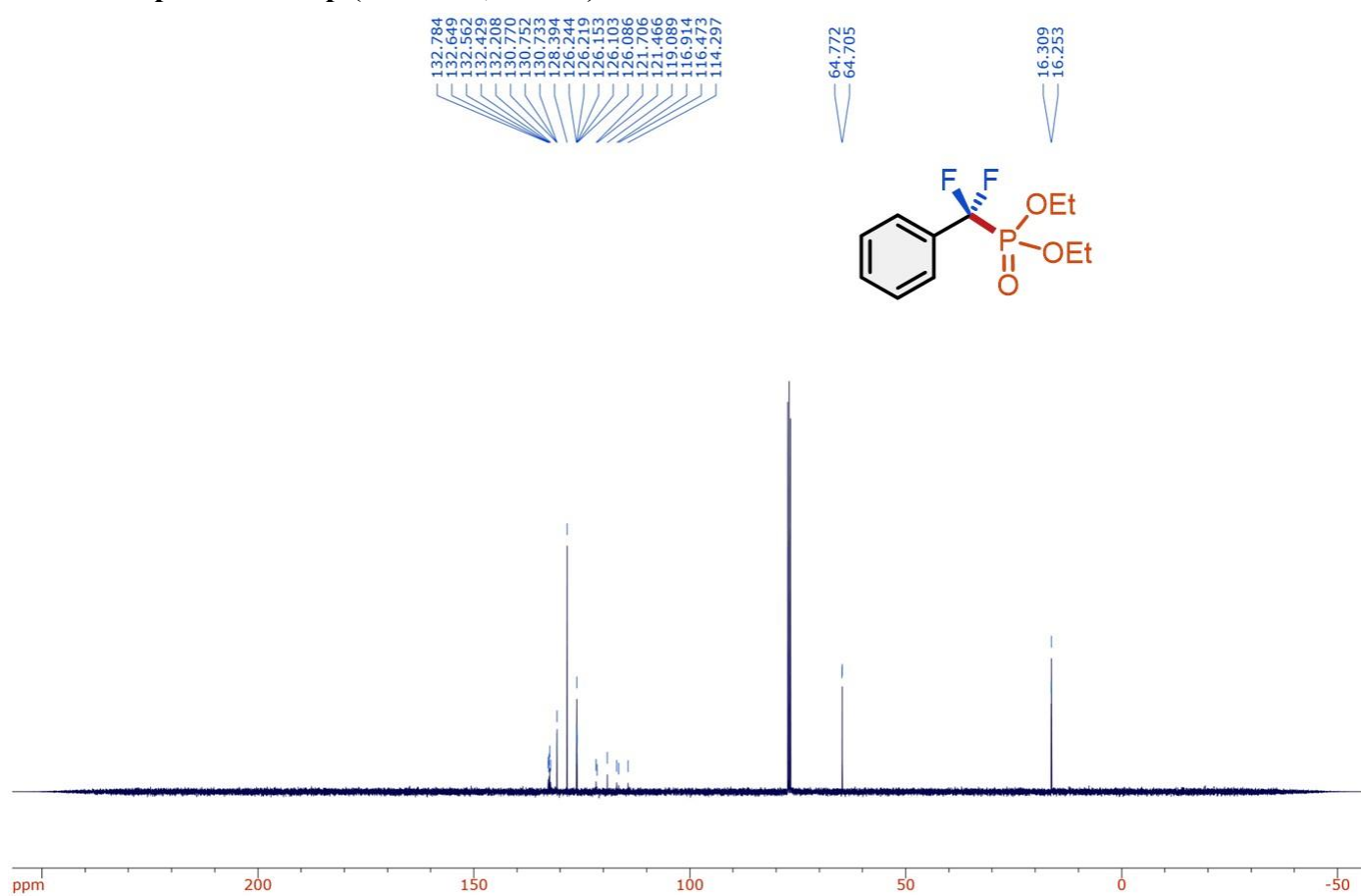
^{19}F NMR spectrum of 3h (376 MHz, CDCl_3)



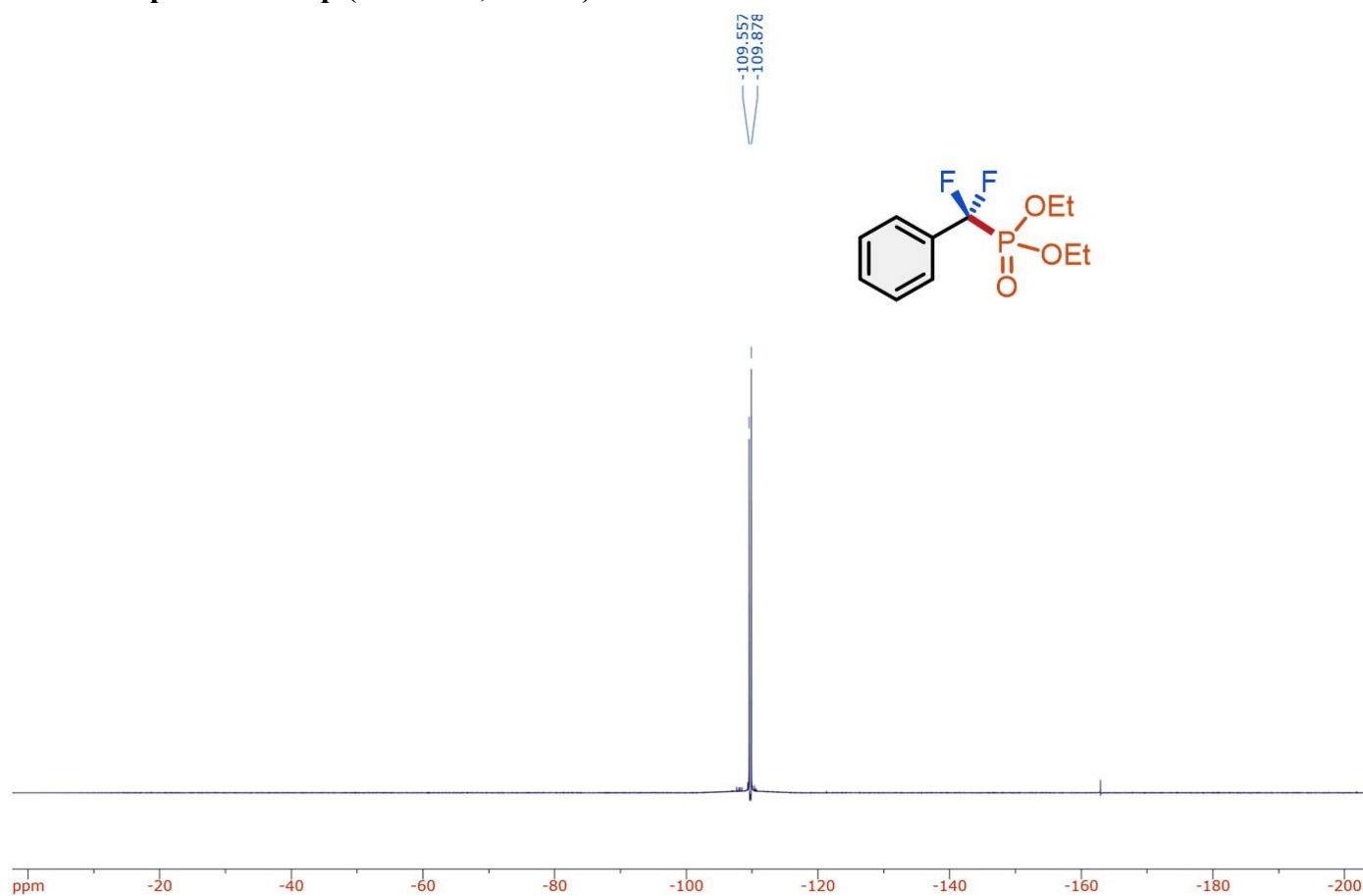
^1H NMR spectrum of 3p (400 MHz, CDCl_3)



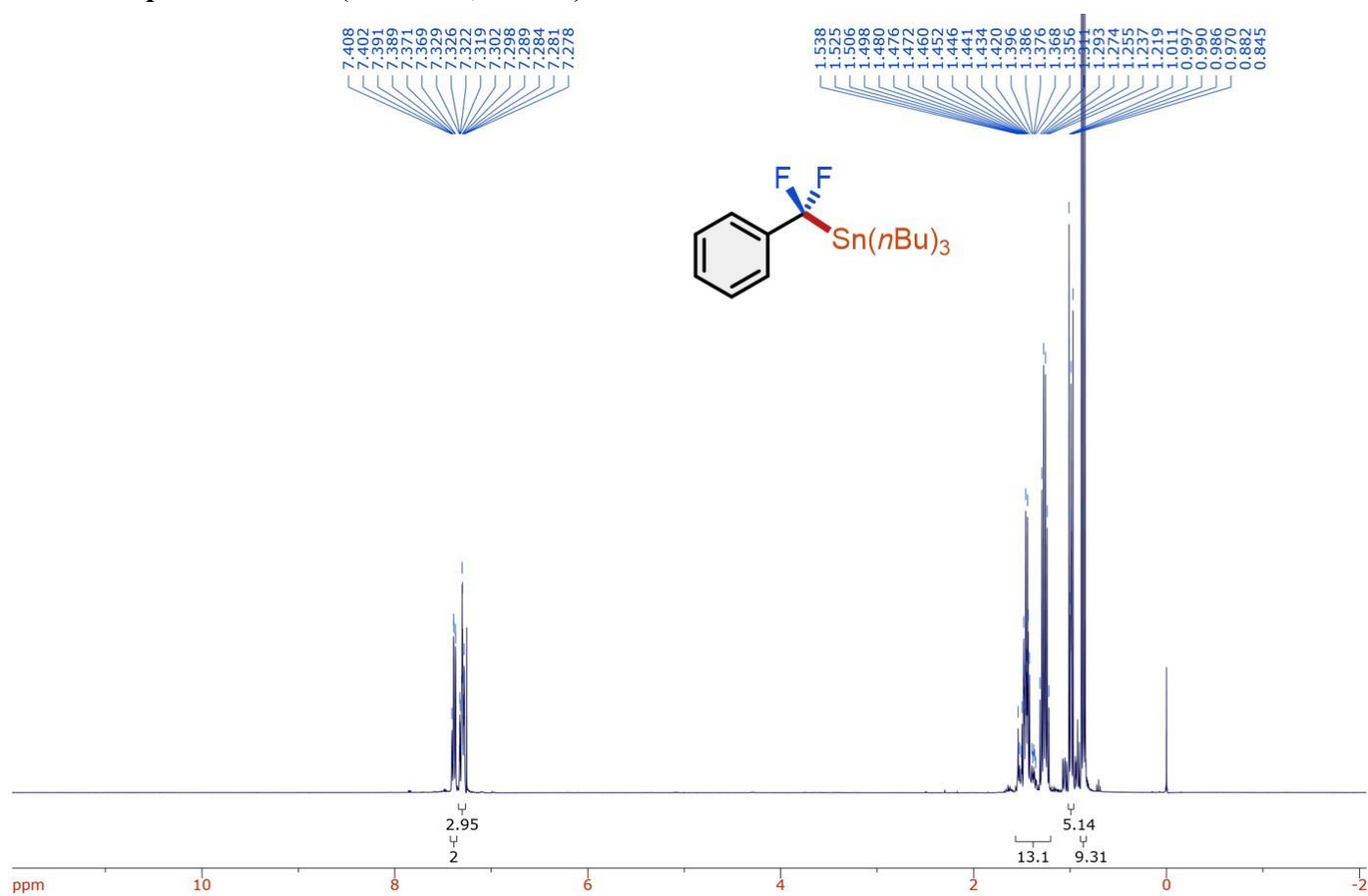
^{13}C NMR spectrum of 3p (100 MHz, CDCl_3)



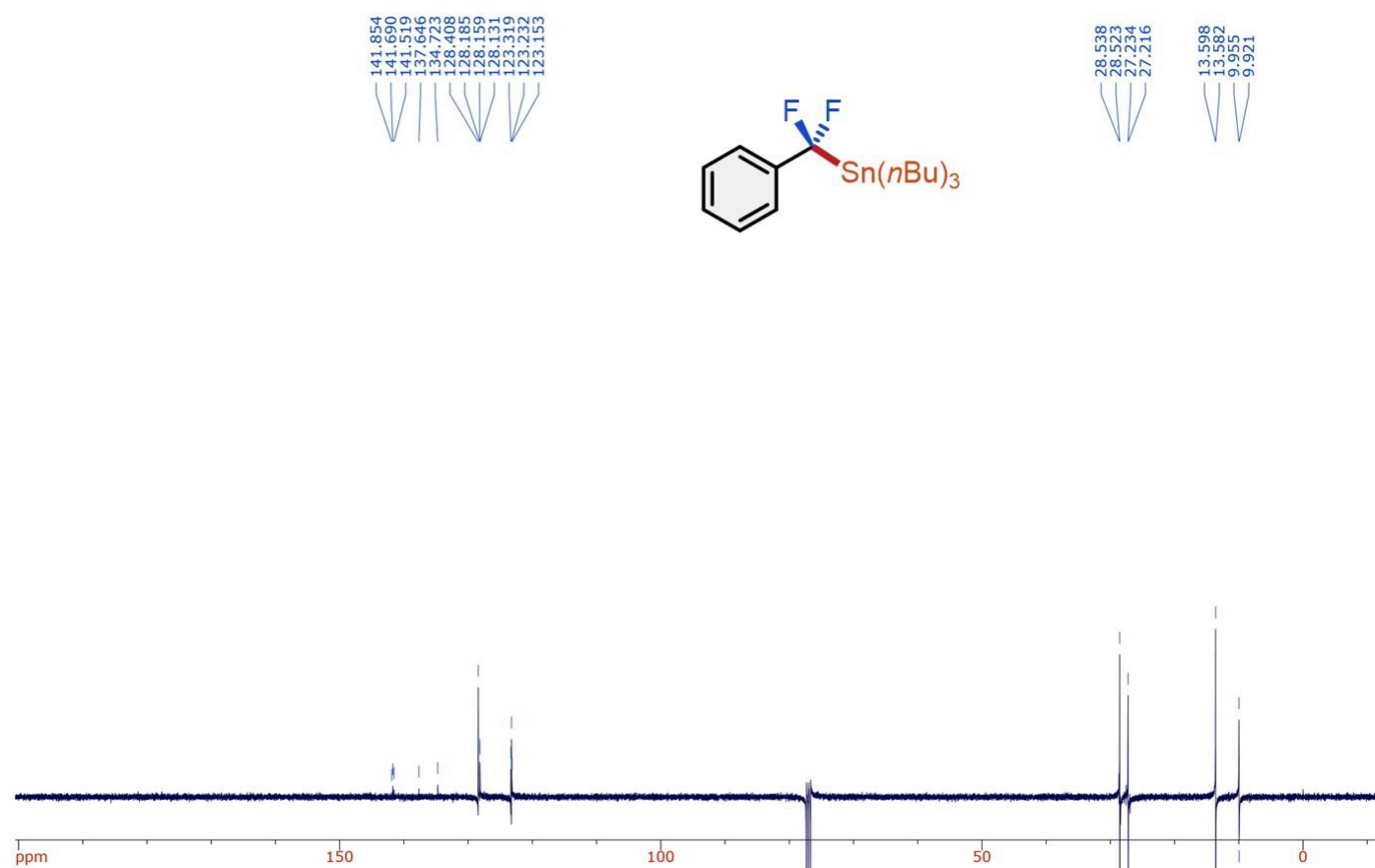
^{19}F NMR spectrum of 3p (376 MHz, CDCl_3)



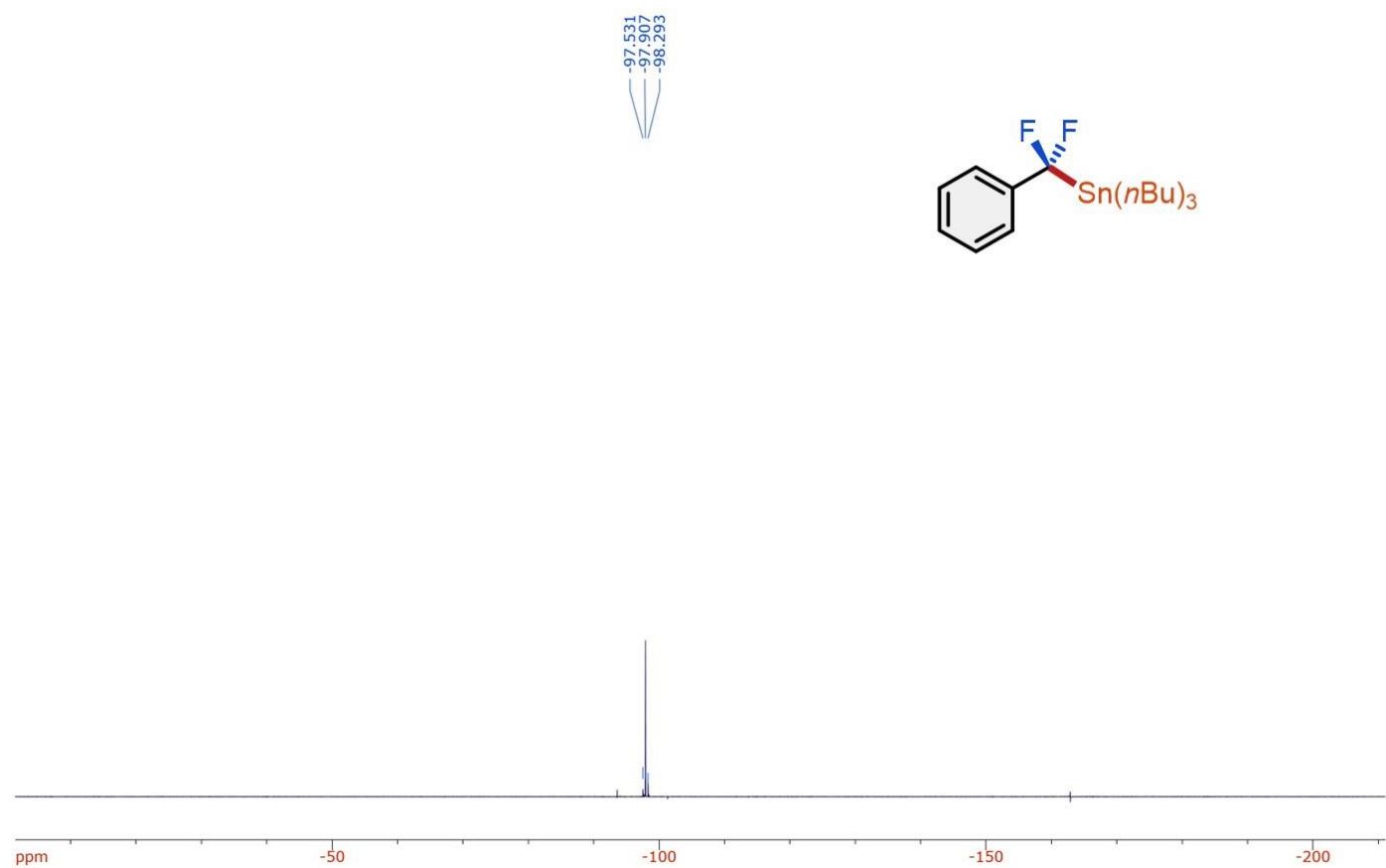
^1H NMR spectrum of 3r (400 MHz, CDCl_3)



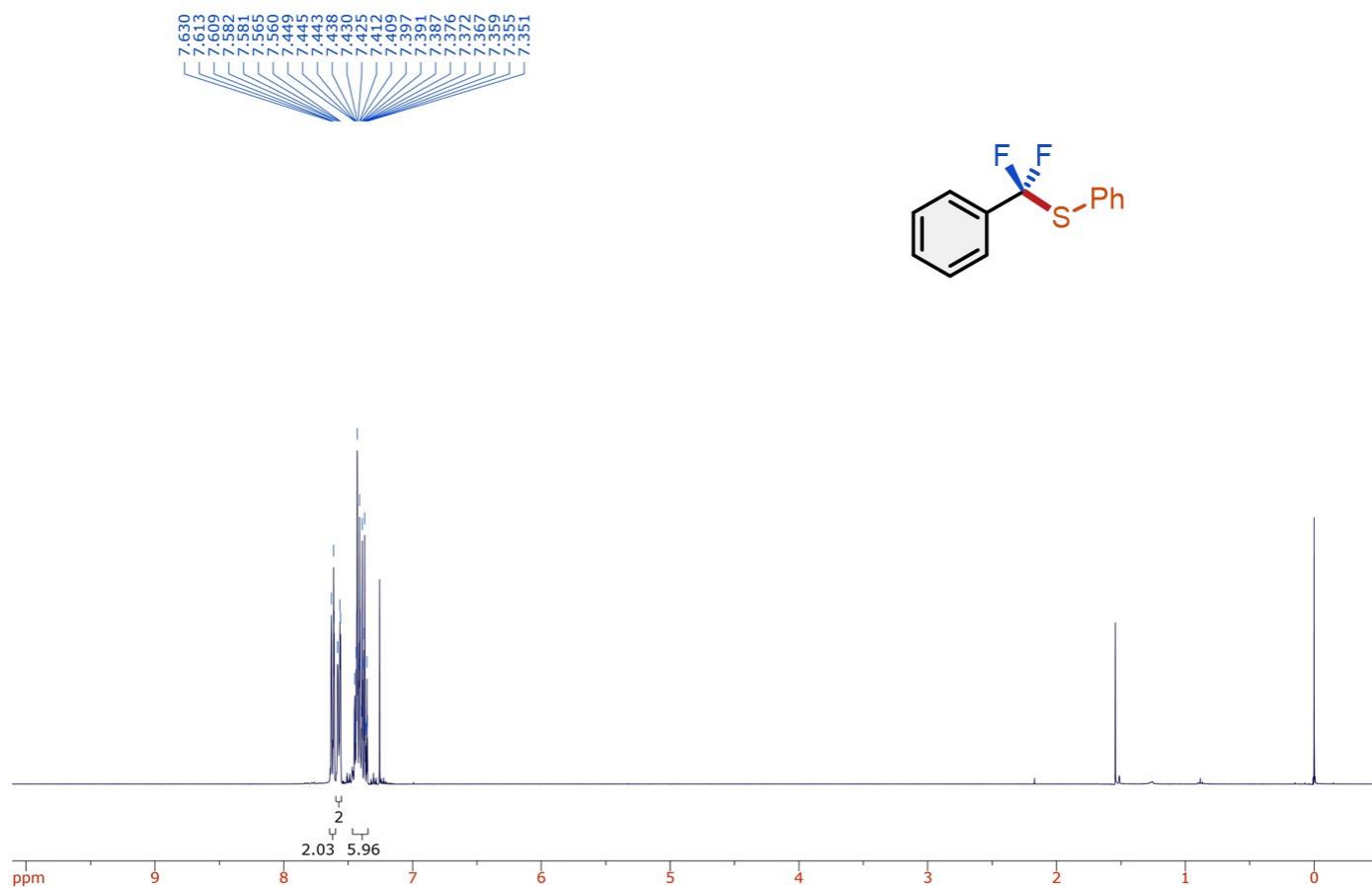
^{13}C NMR spectrum of 3r (100 MHz, CDCl_3)



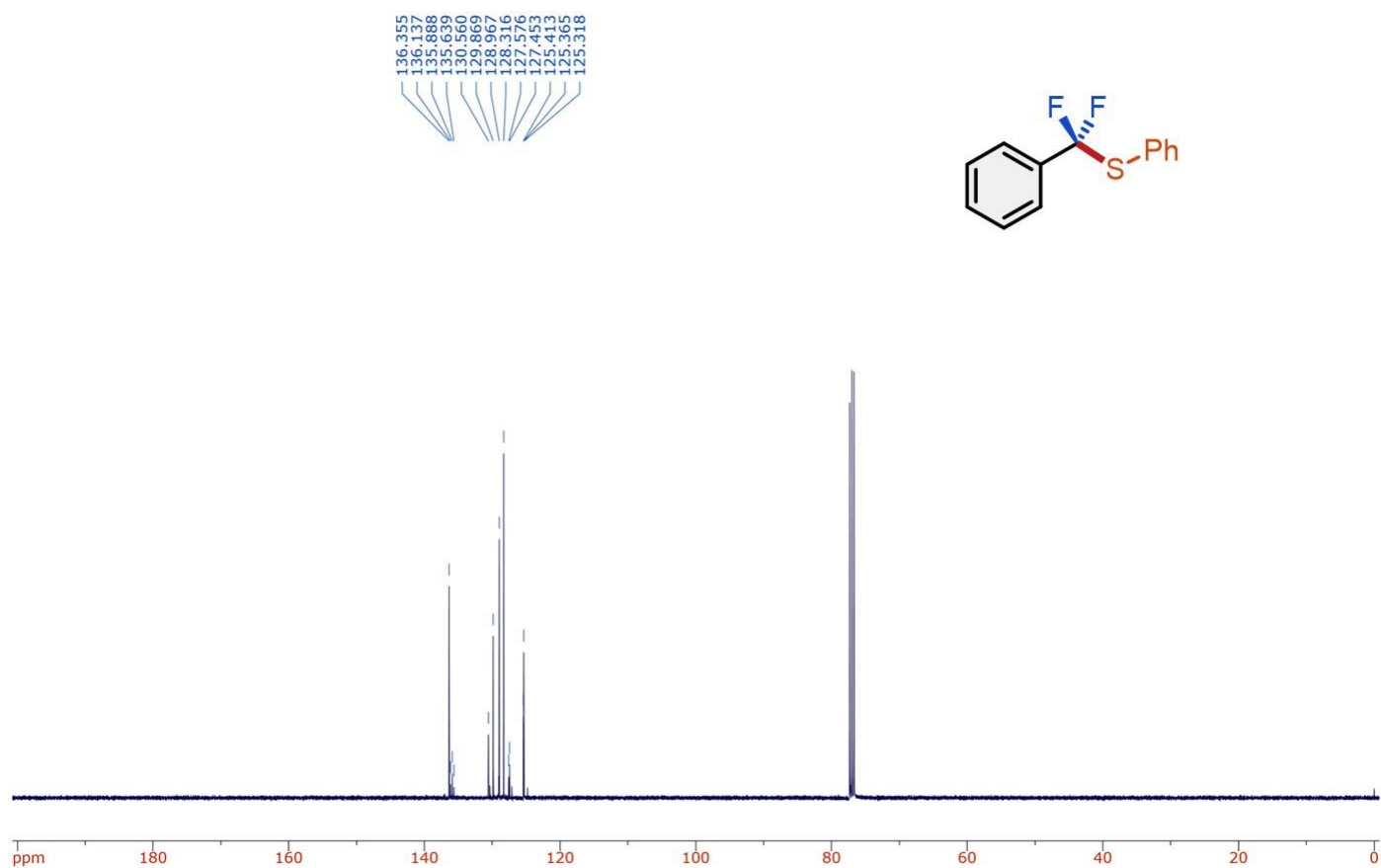
^{19}F NMR spectrum of 3r (376 MHz, CDCl_3)



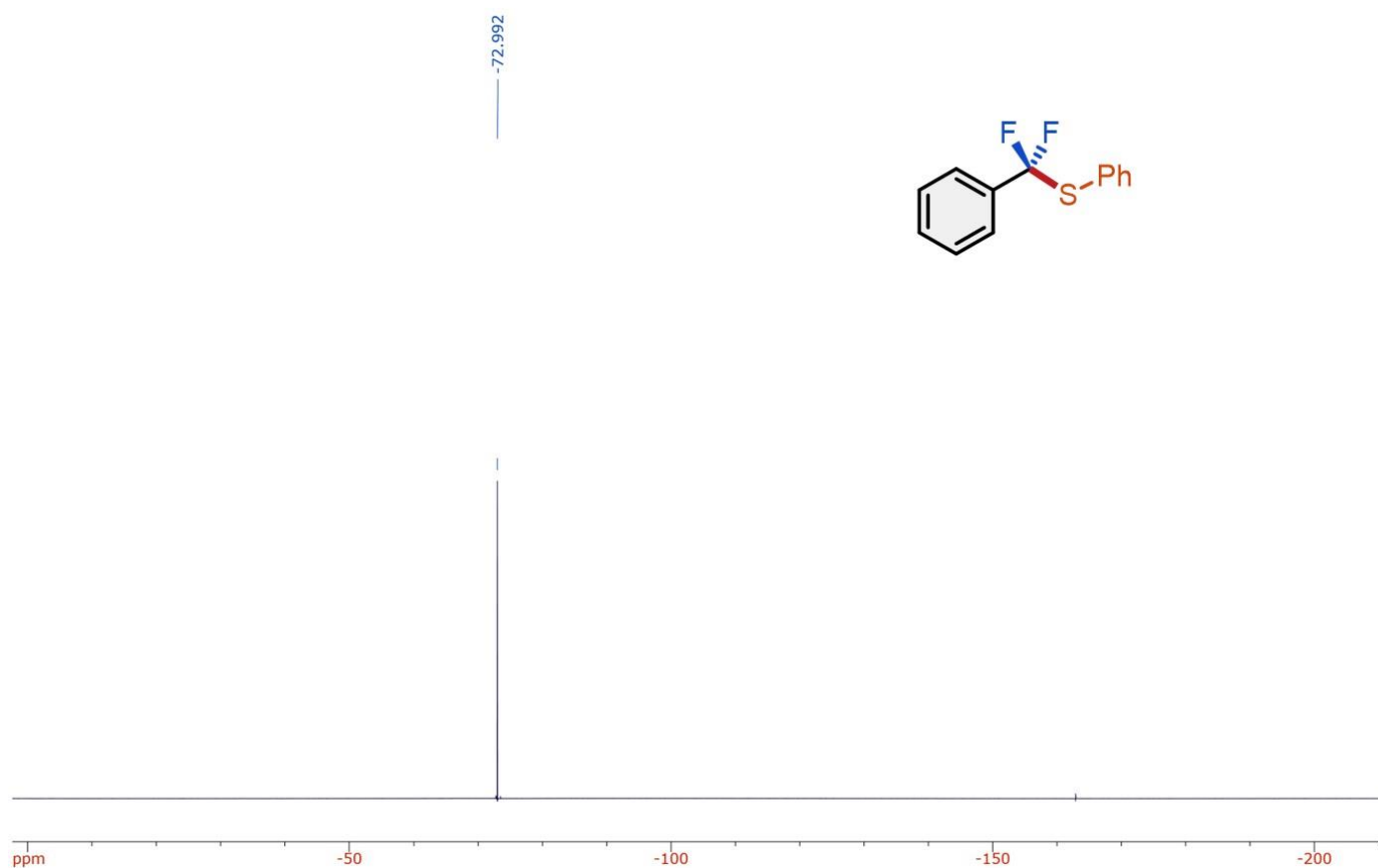
¹H NMR spectrum of 3s (400 MHz, CDCl₃)



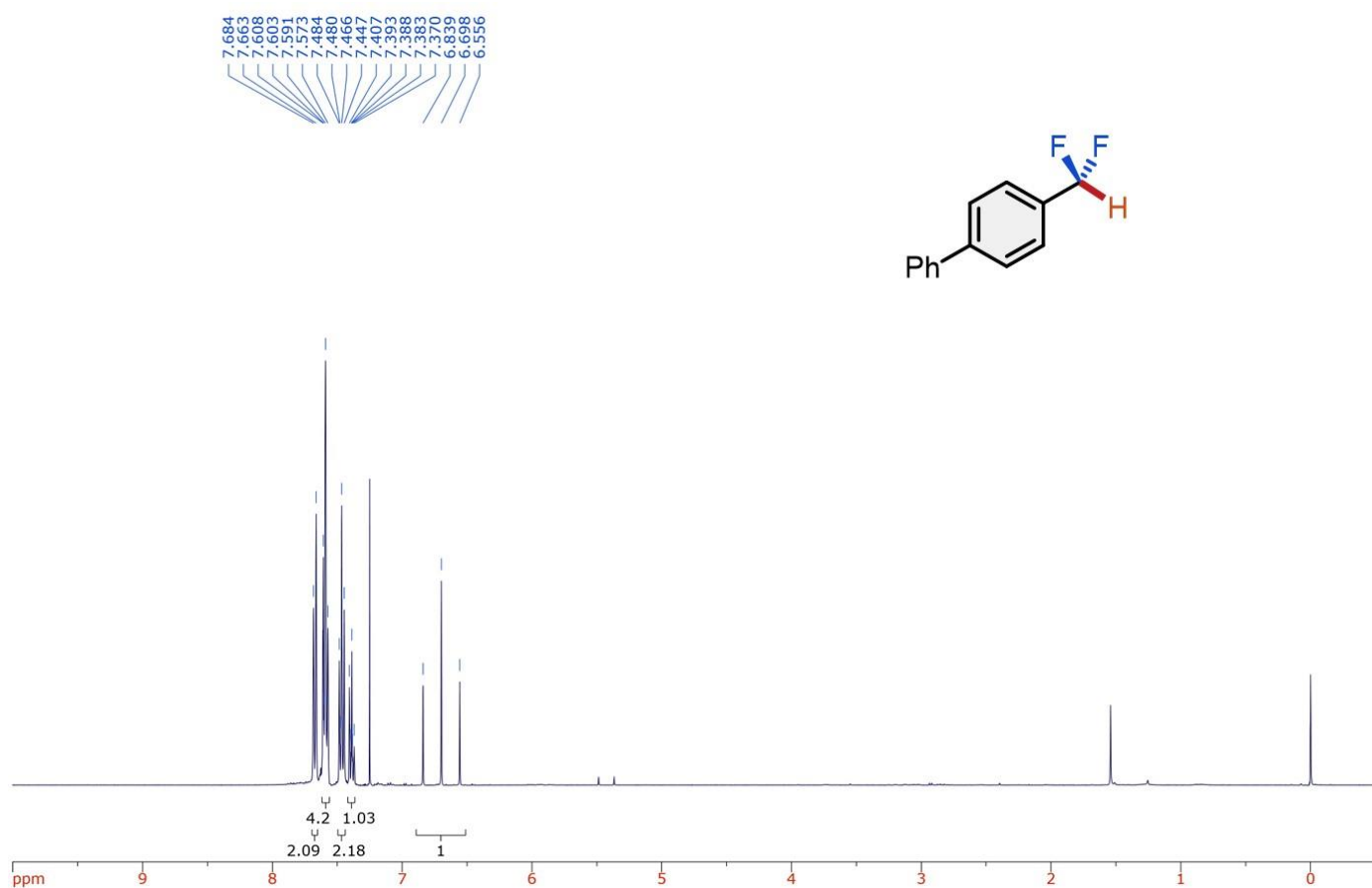
¹³C NMR spectrum of 3s (100 MHz, CDCl₃)



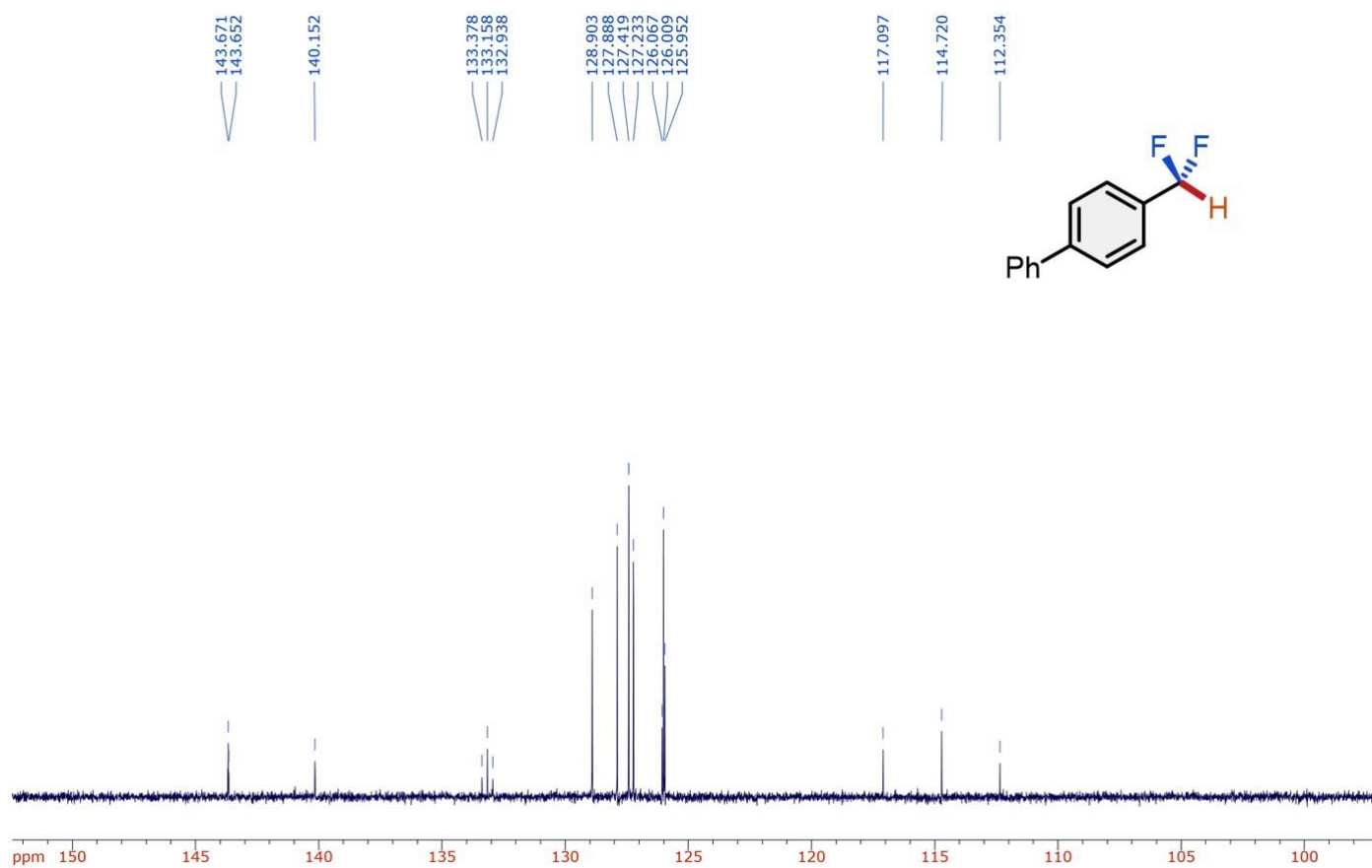
^{19}F NMR spectrum of 3s (376 MHz, CDCl_3)



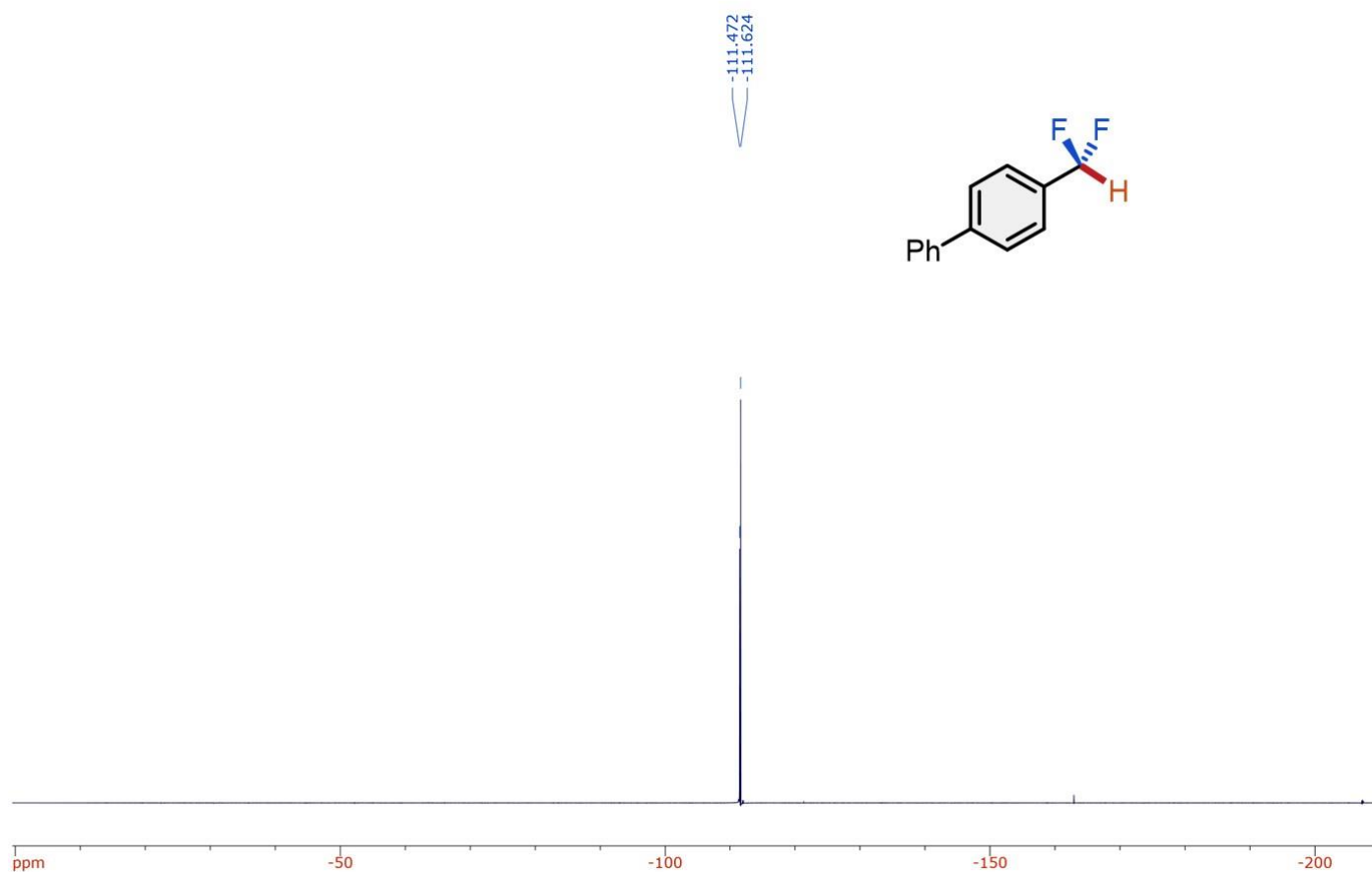
^1H NMR spectrum of 4d (400 MHz, CDCl_3)



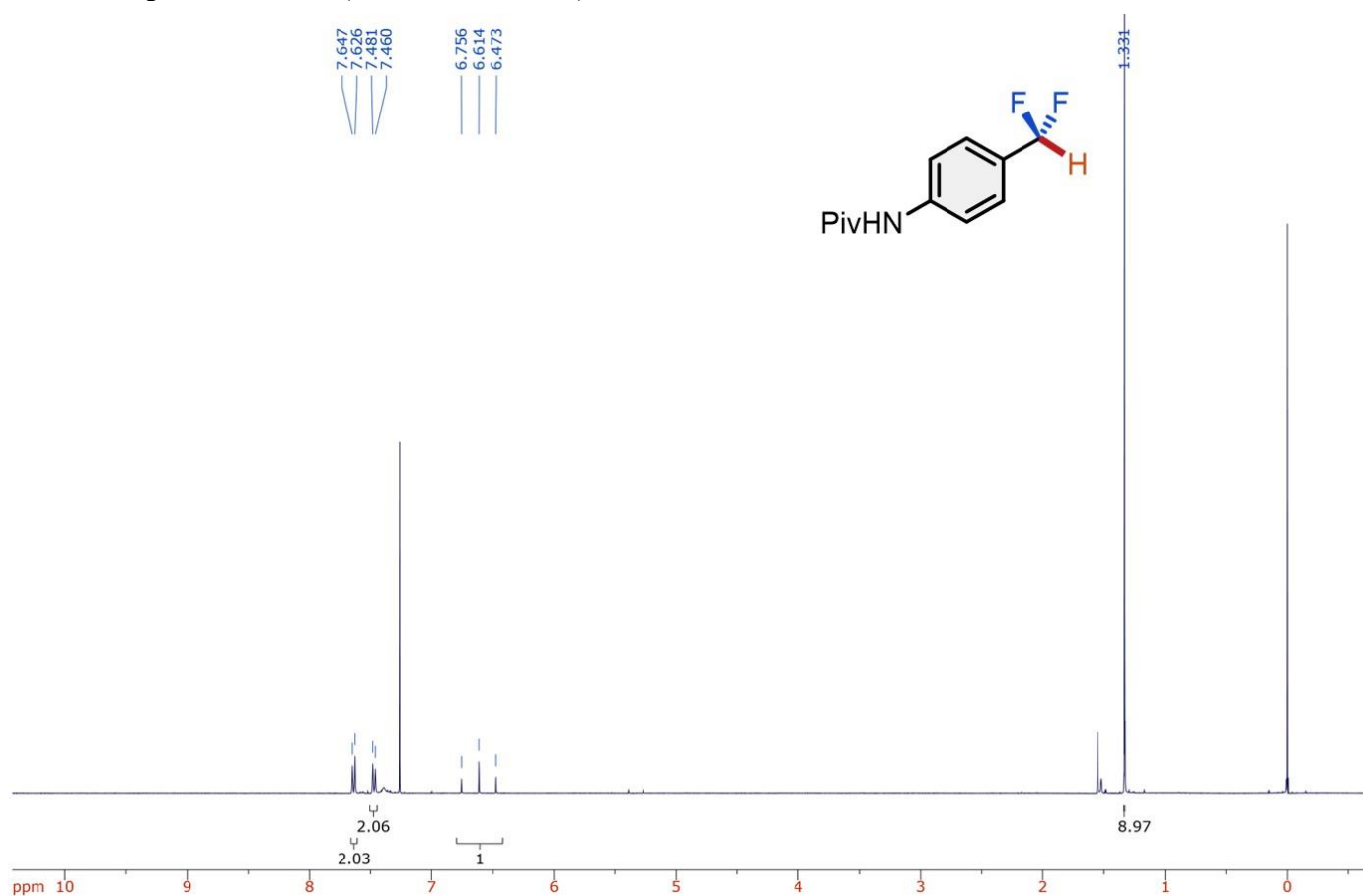
^{13}C NMR spectrum of 4d (100 MHz, CDCl_3)



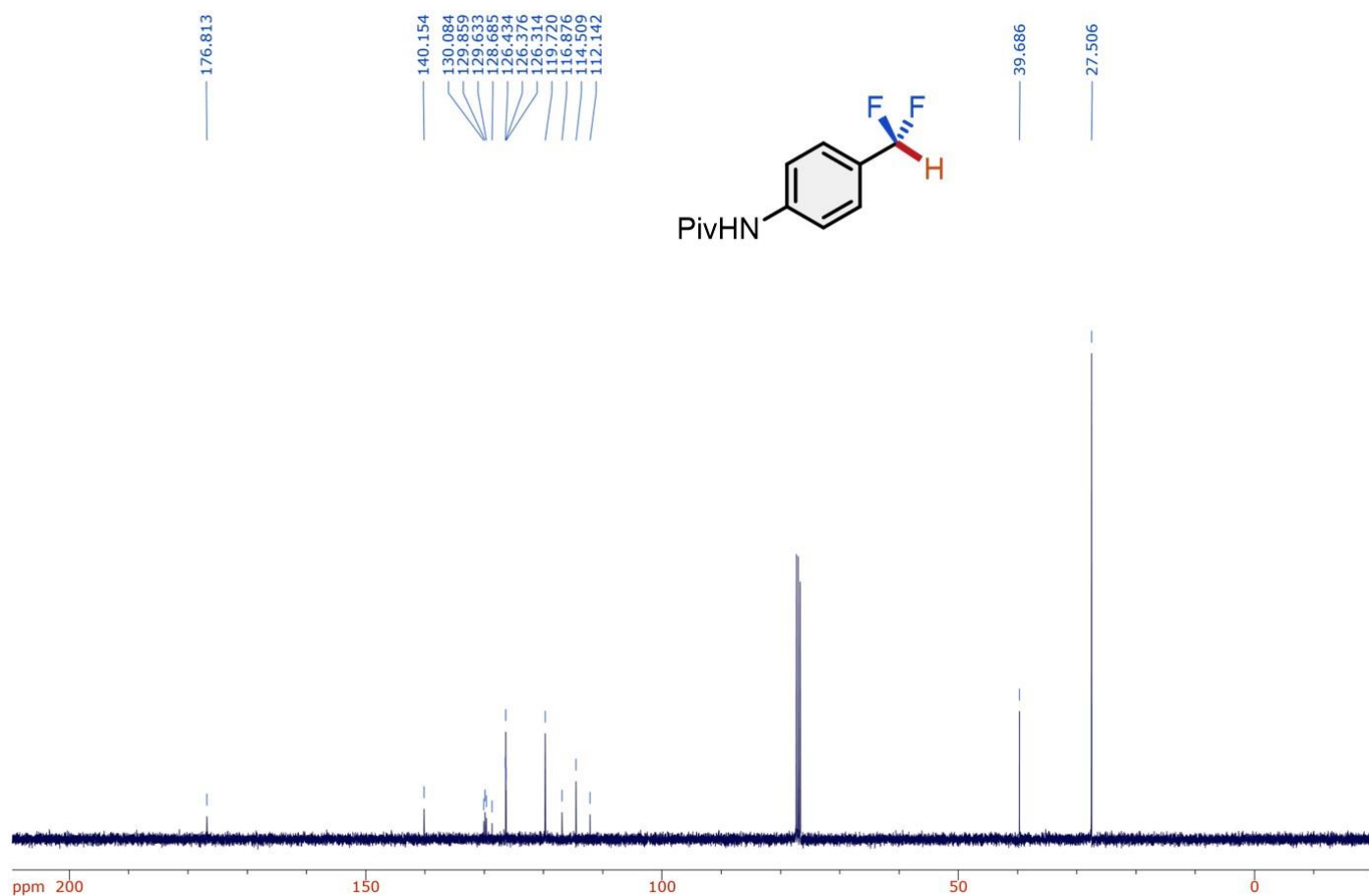
^{19}F NMR spectrum of 4d (376 MHz, CDCl_3)



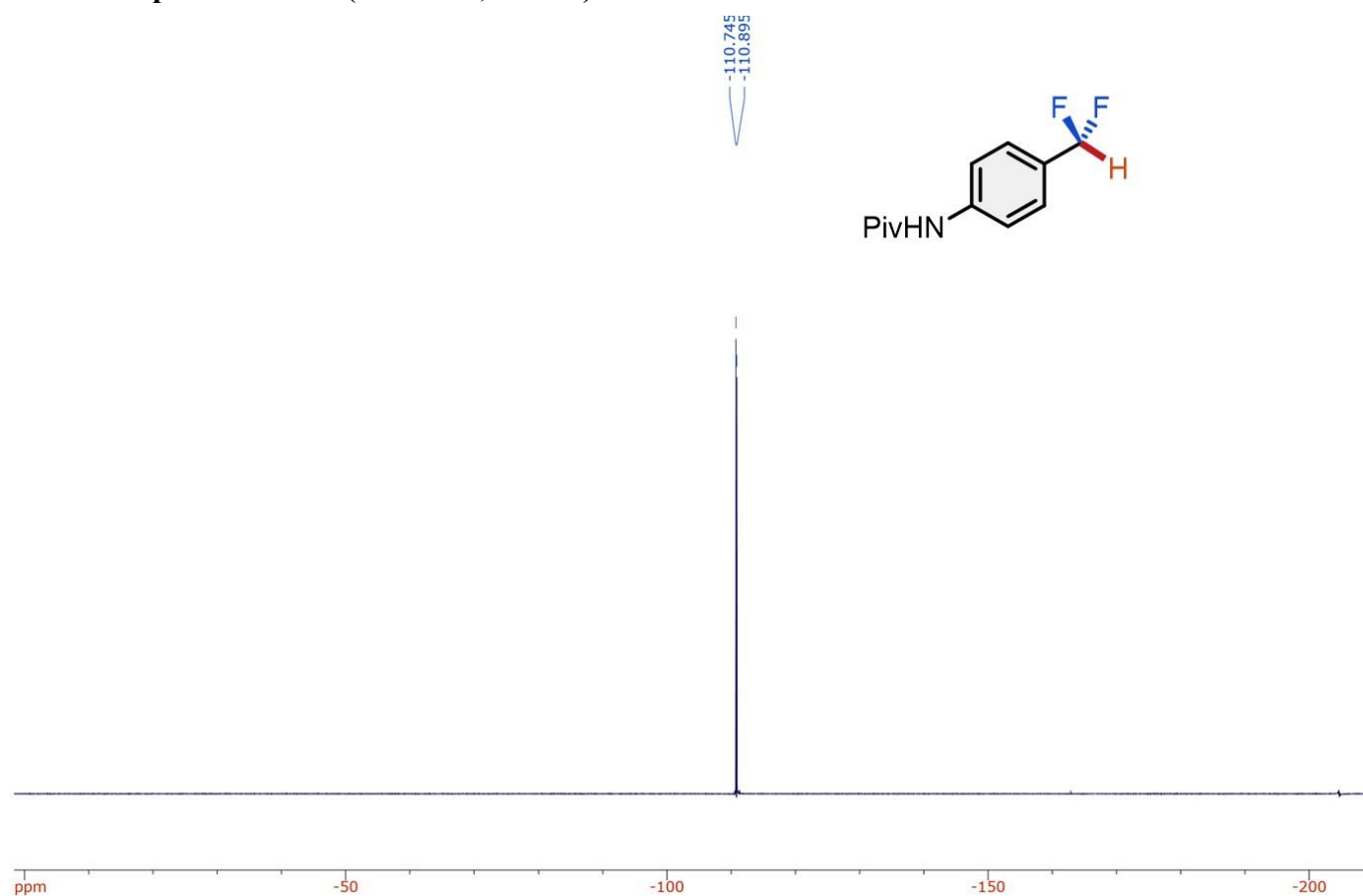
¹H NMR spectrum of 4e (400 MHz, CDCl₃)



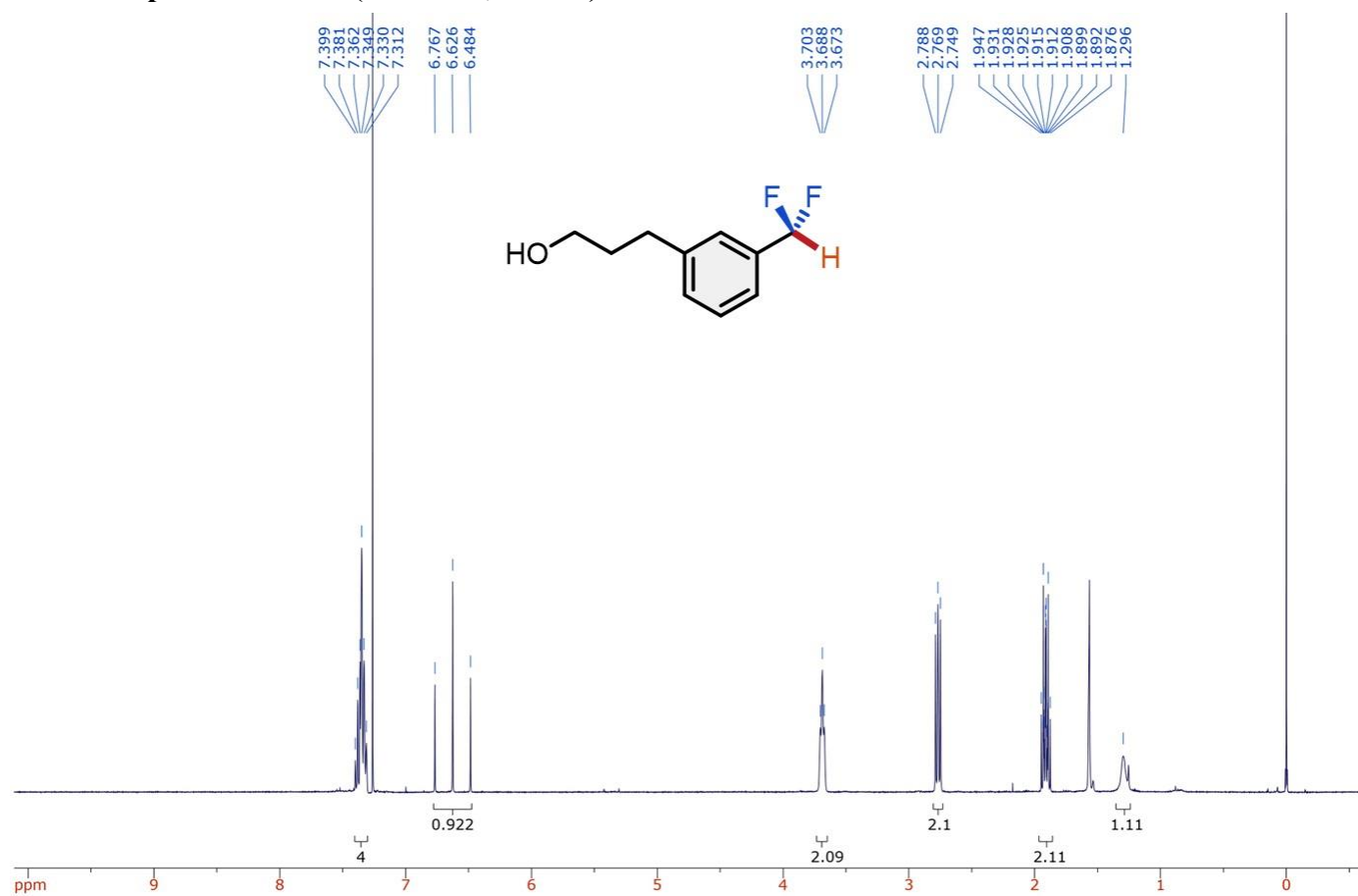
¹³C NMR spectrum of 4e (100 MHz, CDCl₃)



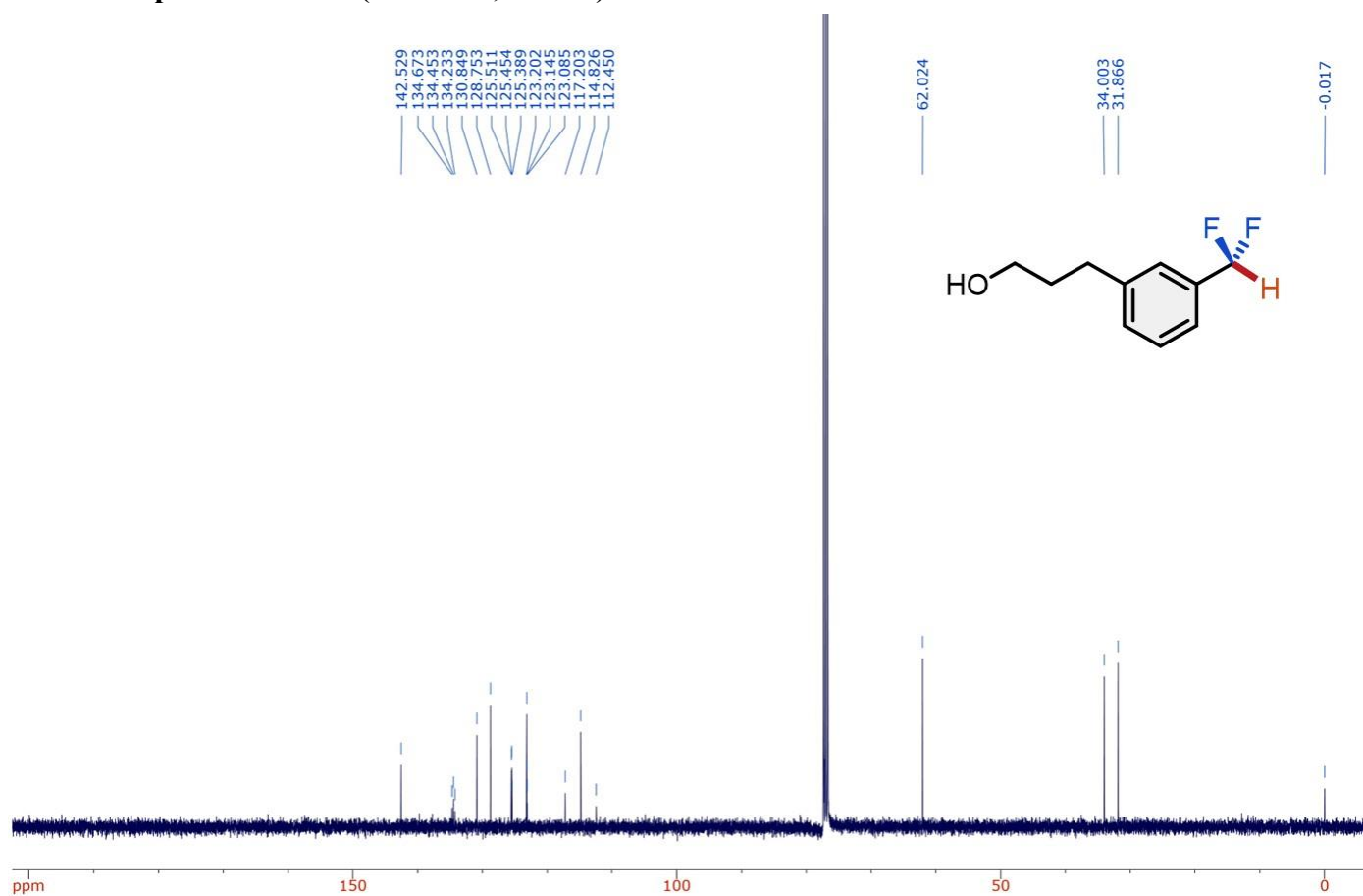
^{19}F NMR spectrum of 4e (376 MHz, CDCl_3)



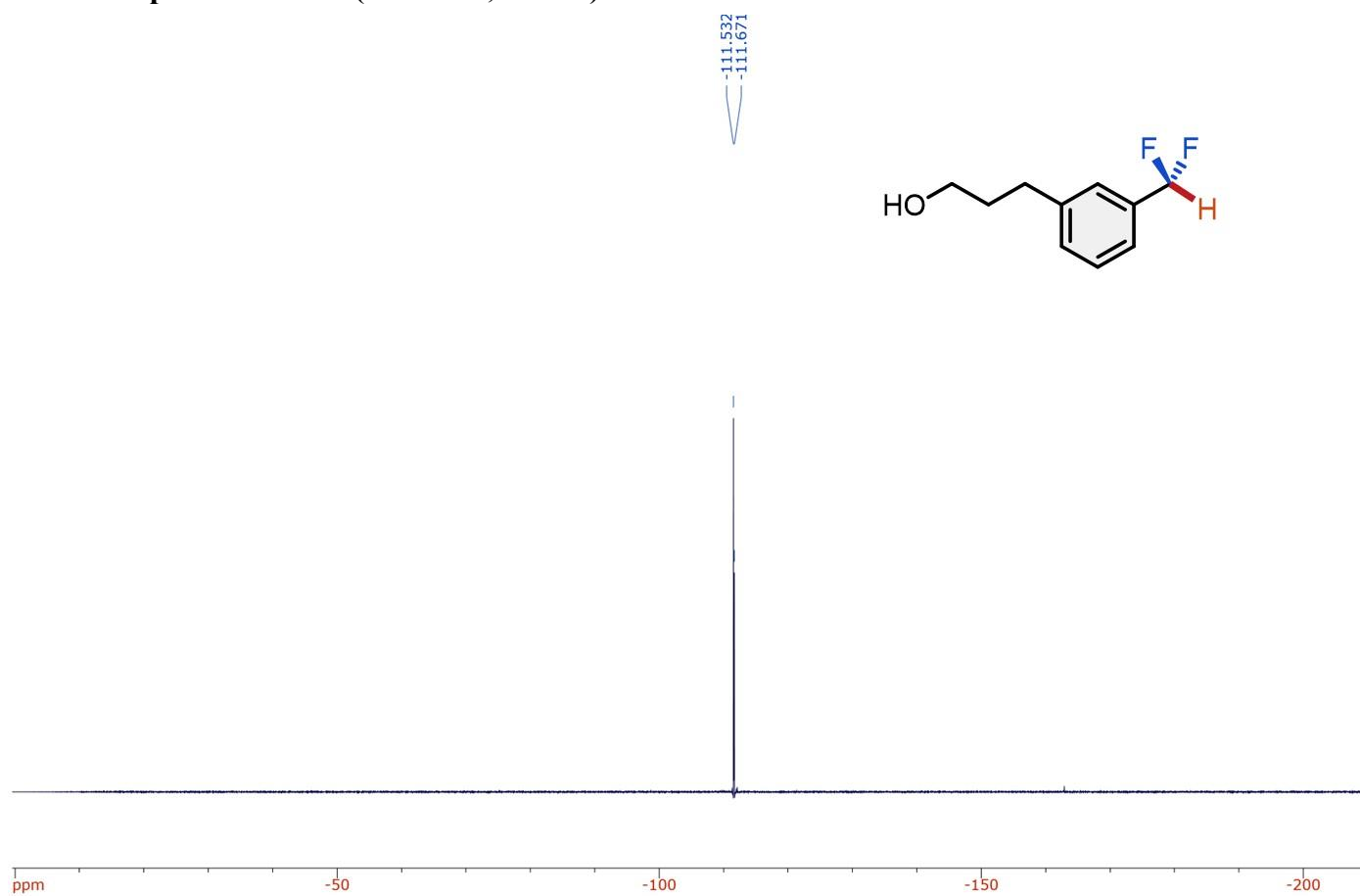
^1H NMR spectrum of 4m (400 MHz, CDCl_3)



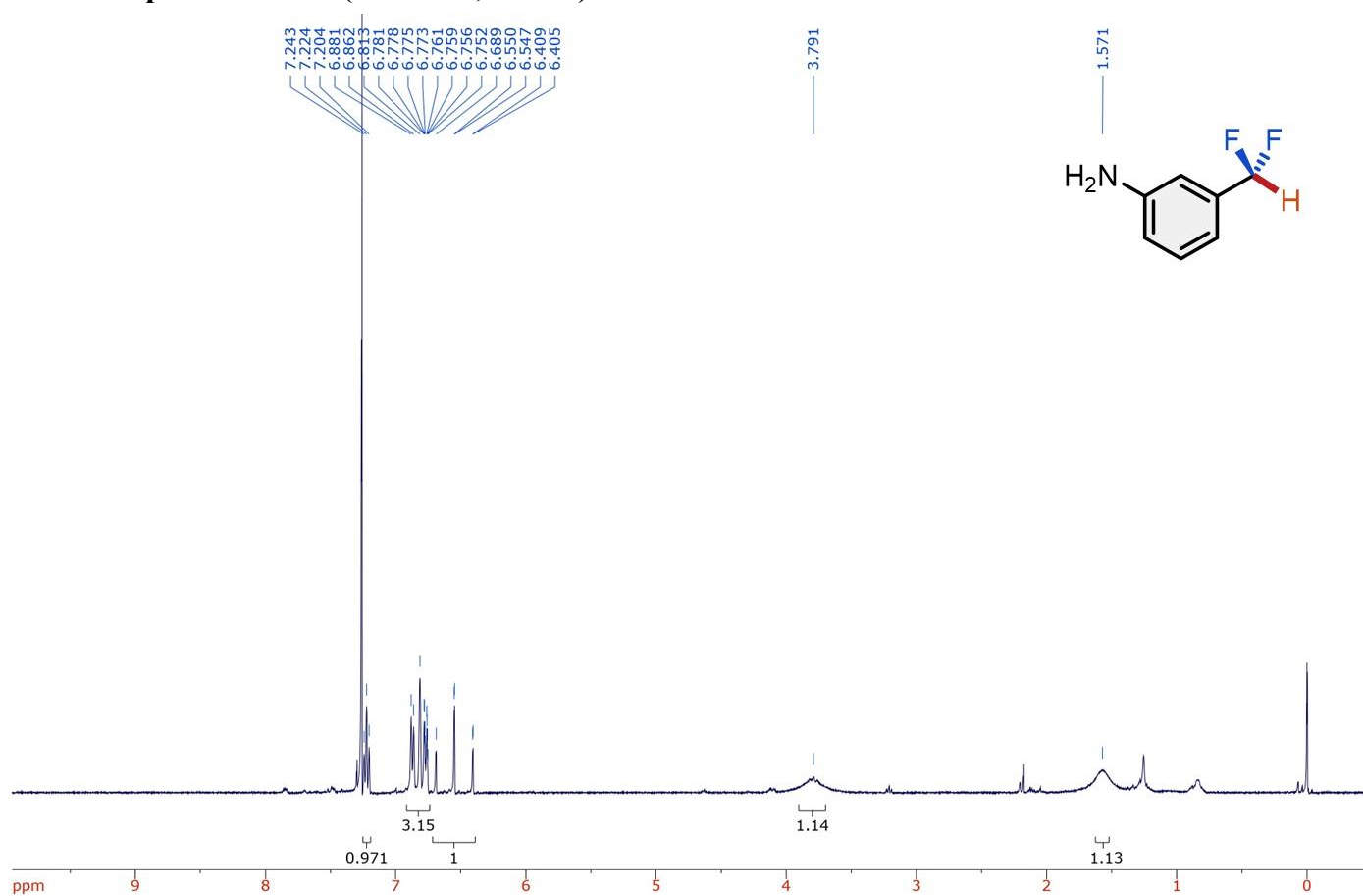
^{13}C NMR spectrum of 4m (100 MHz, CDCl_3)



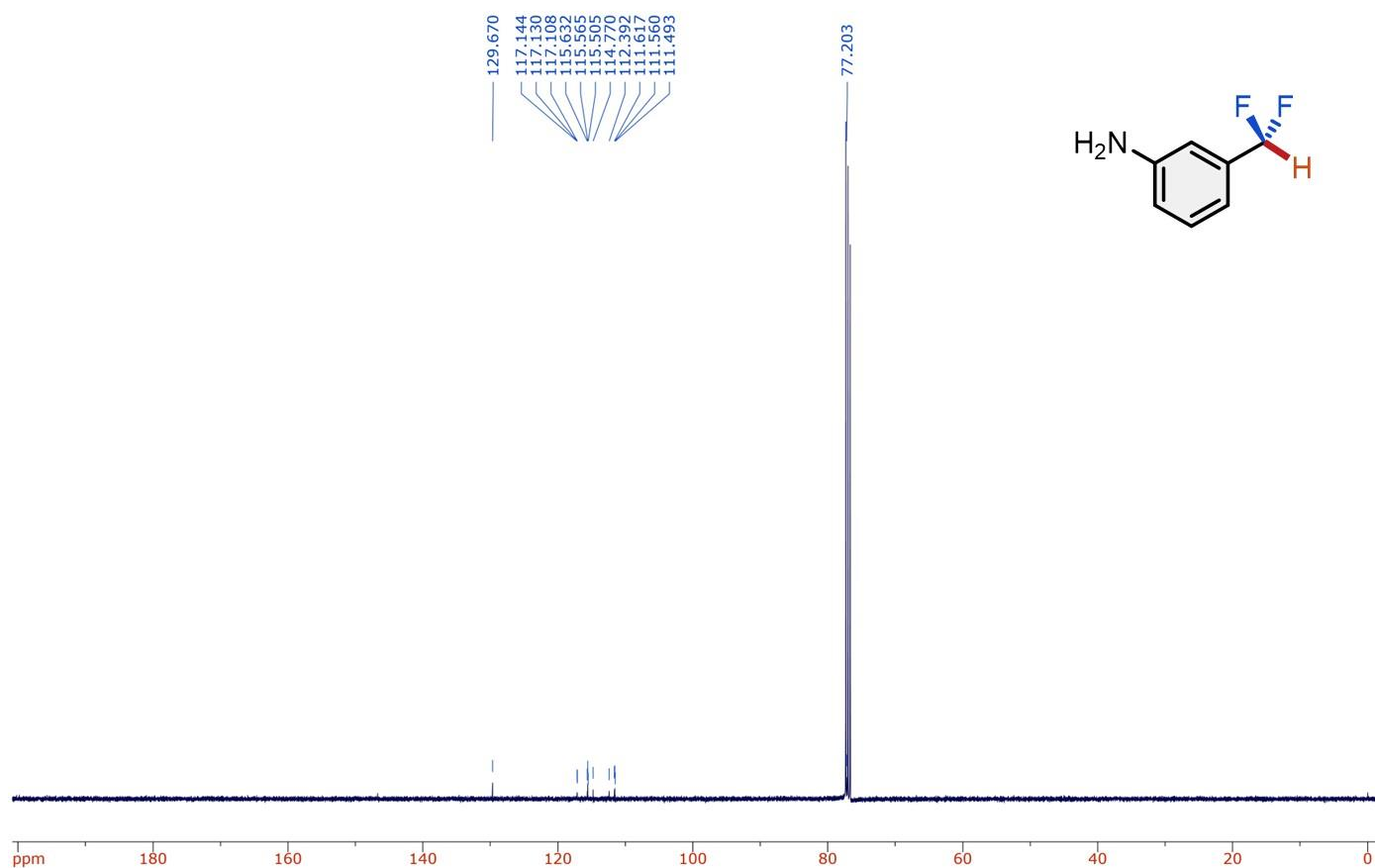
^{19}F NMR spectrum of 4m (376 MHz, CDCl_3)



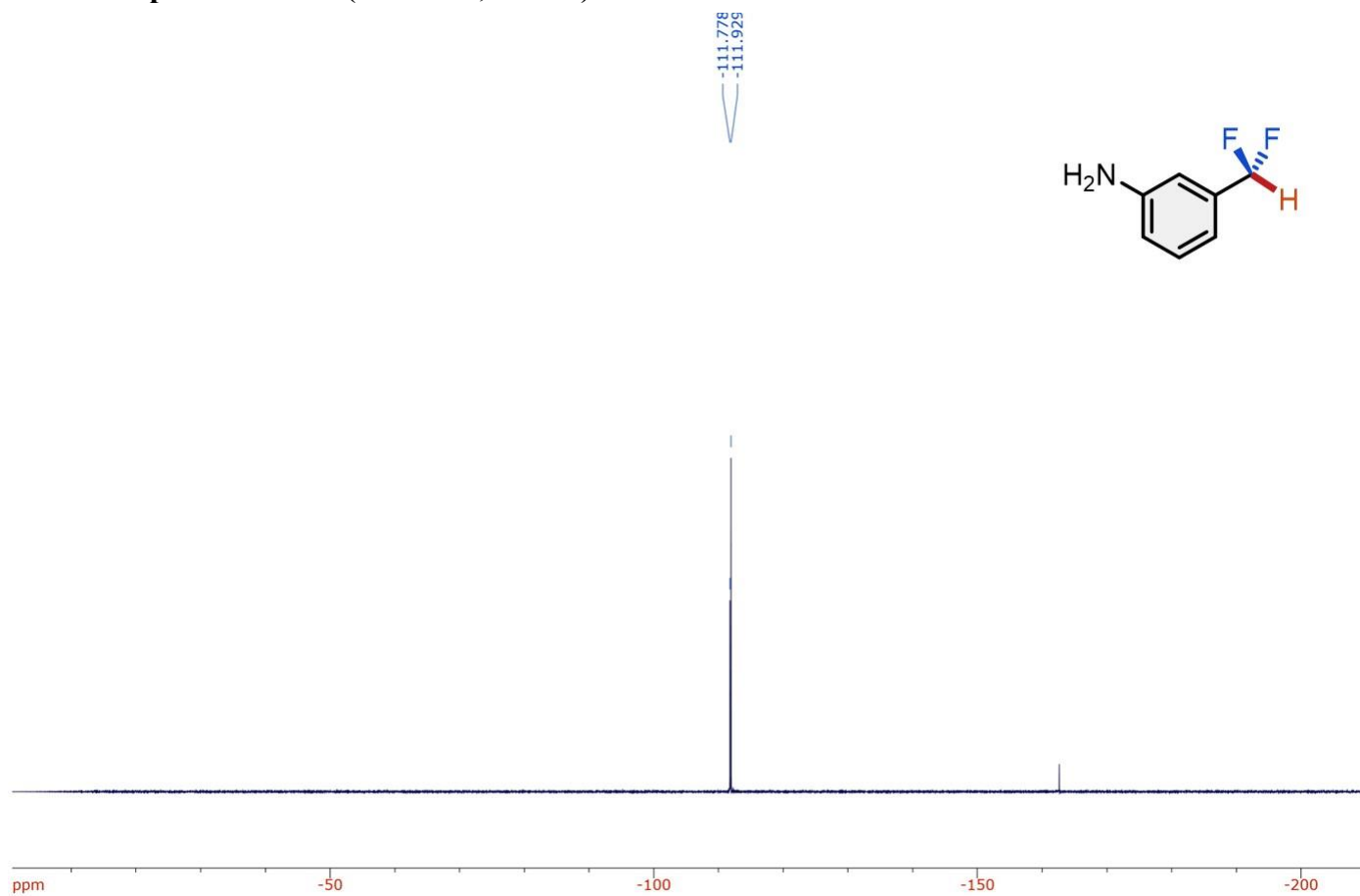
¹H NMR spectrum of 4n (400 MHz, CDCl₃)



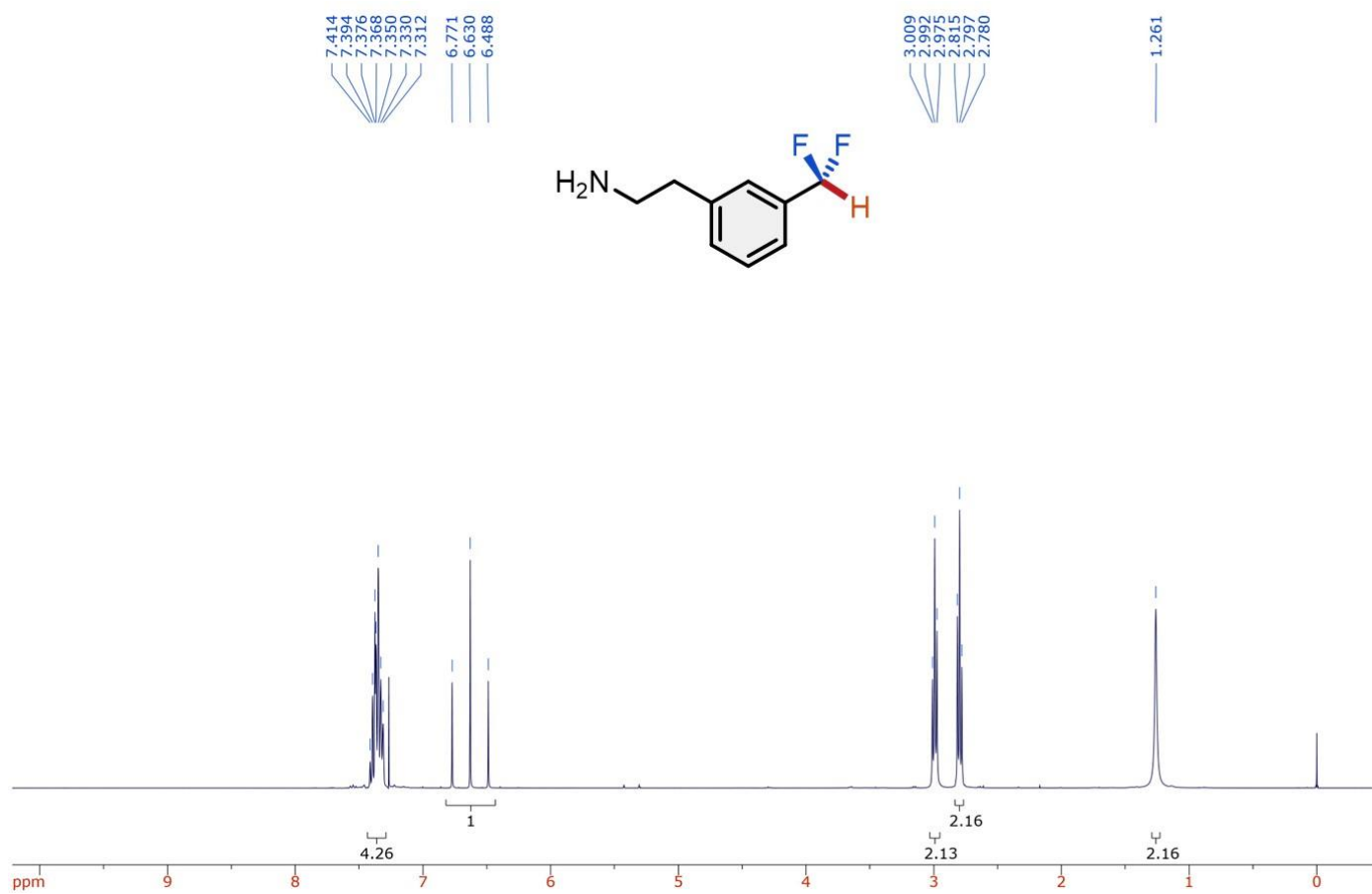
¹³C NMR spectrum of 4n (100 MHz, CDCl₃)



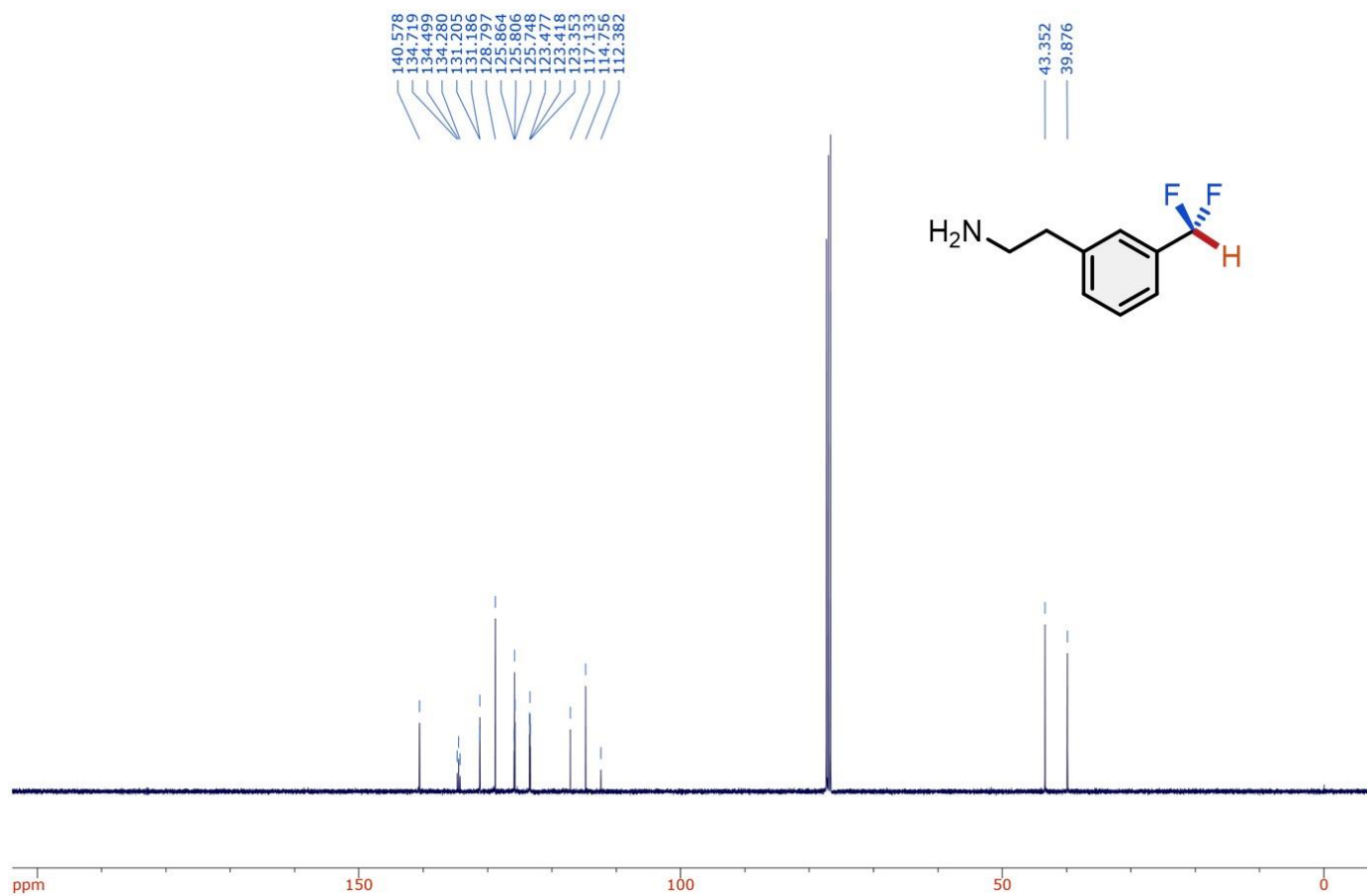
^{19}F NMR spectrum of 4n (376 MHz, CDCl_3)



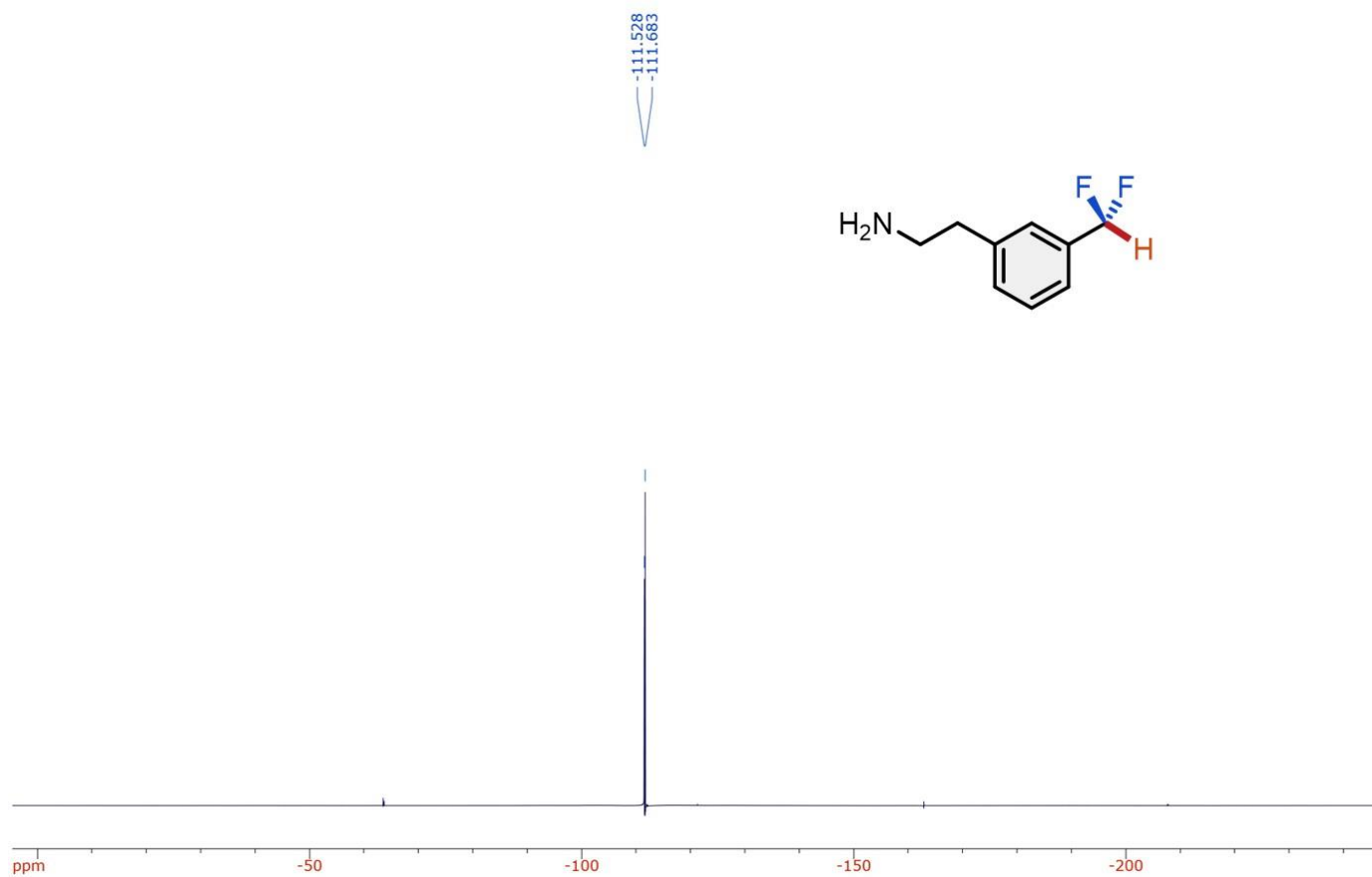
^1H NMR spectrum of 4p (400 MHz, CDCl_3)



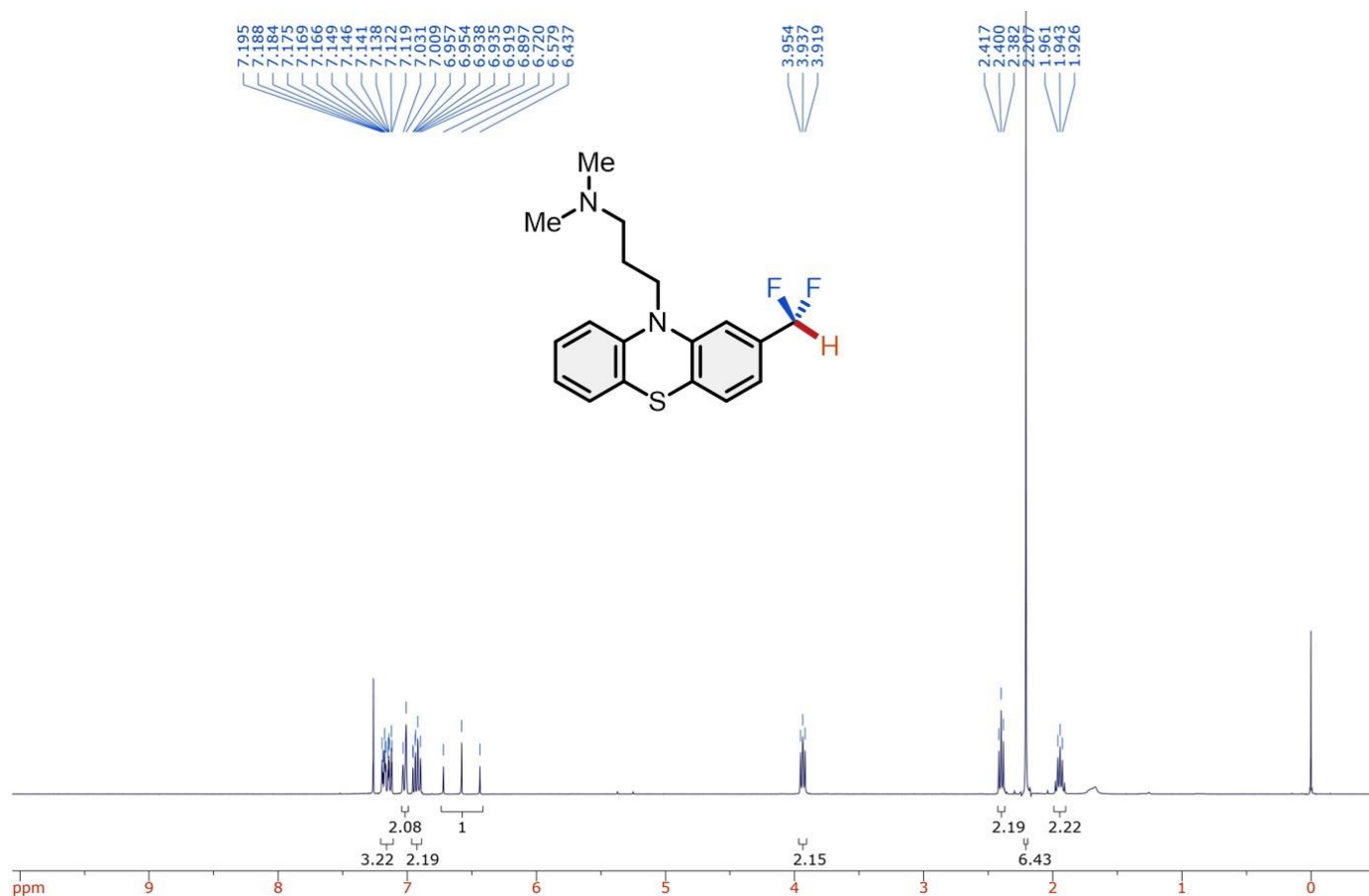
^{13}C NMR spectrum of 4p (100 MHz, CDCl_3)



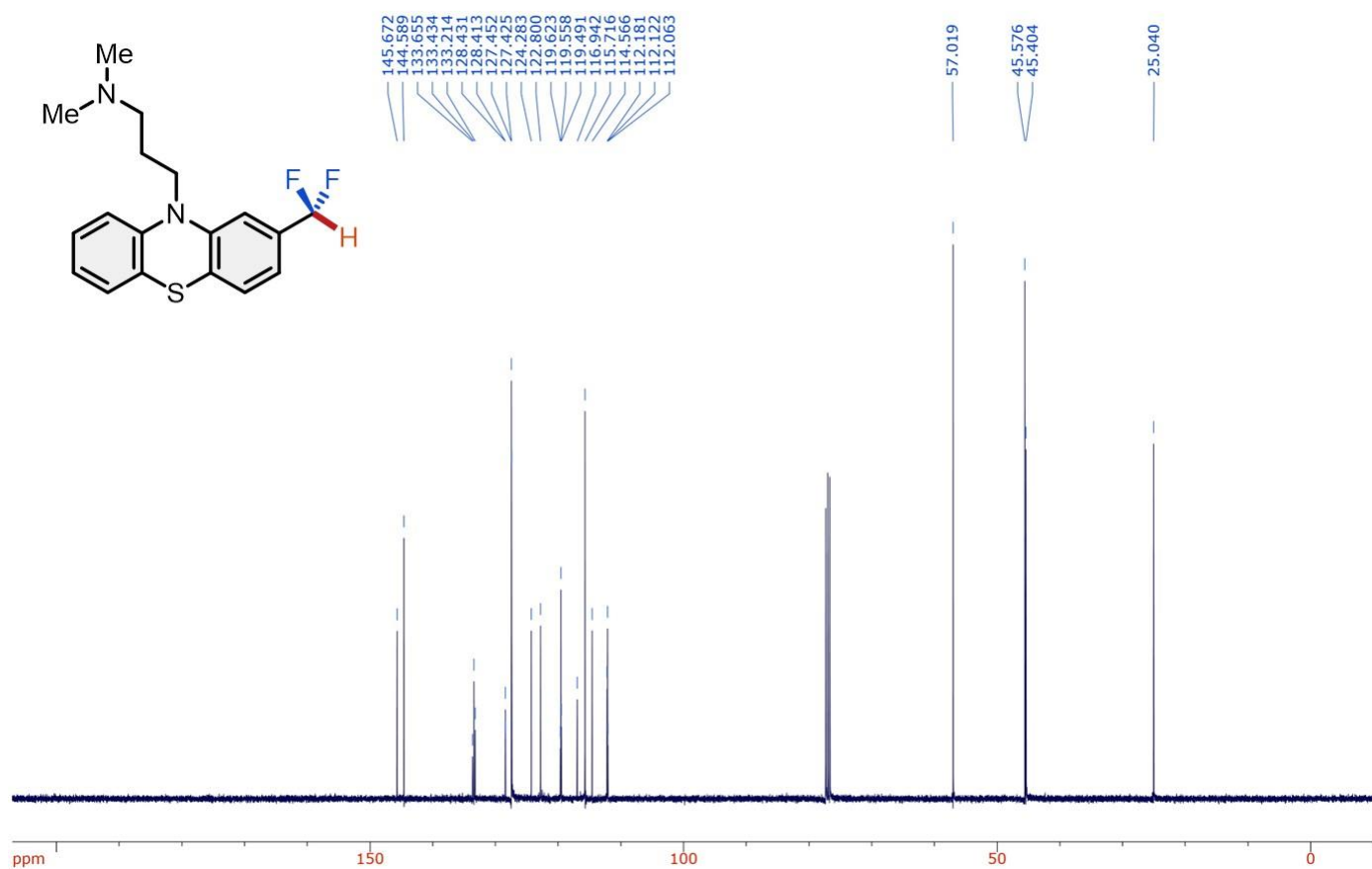
^{19}F NMR spectrum of 4p (376 MHz, CDCl_3)



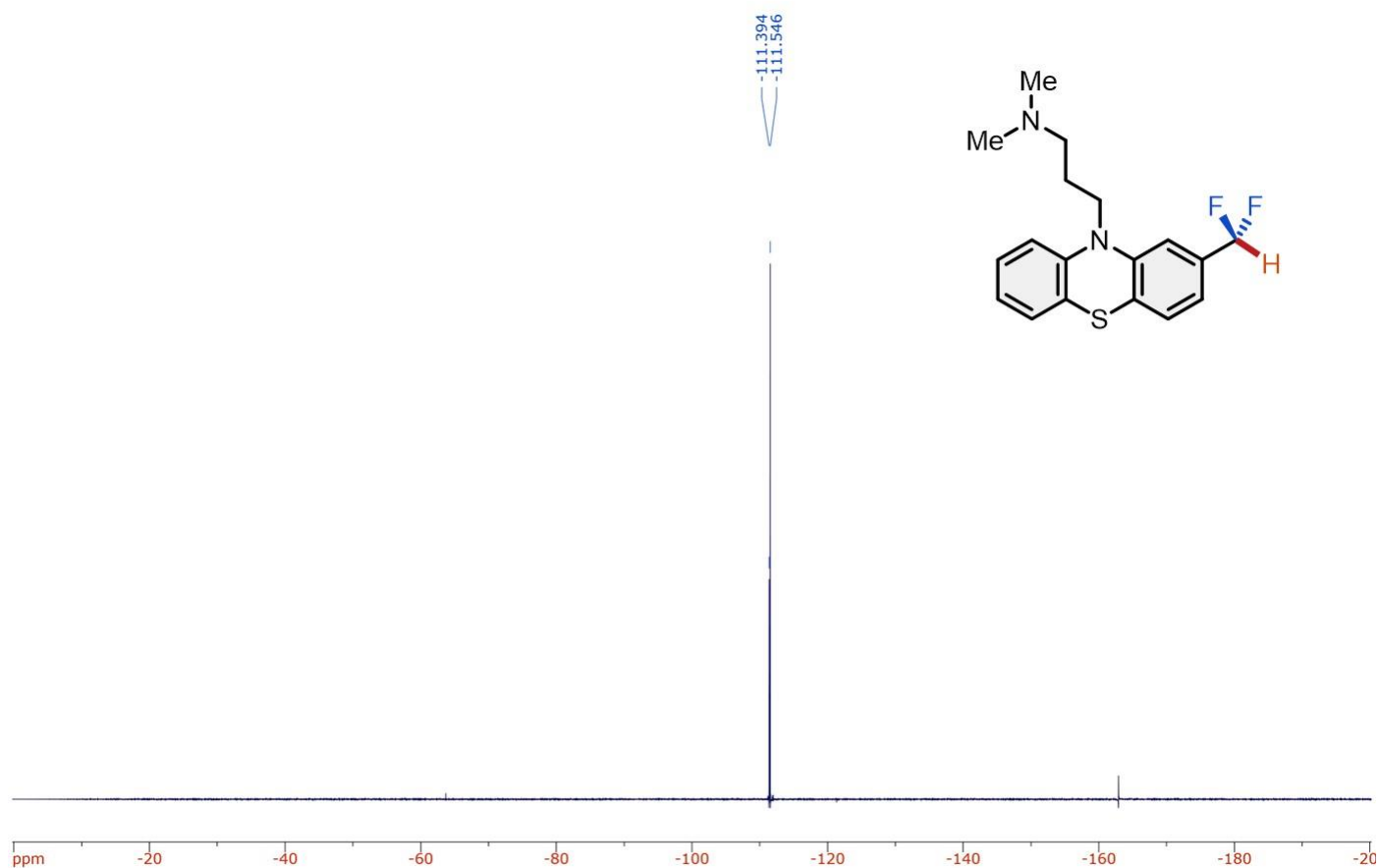
^1H NMR spectrum of 5a (400 MHz, CDCl_3)



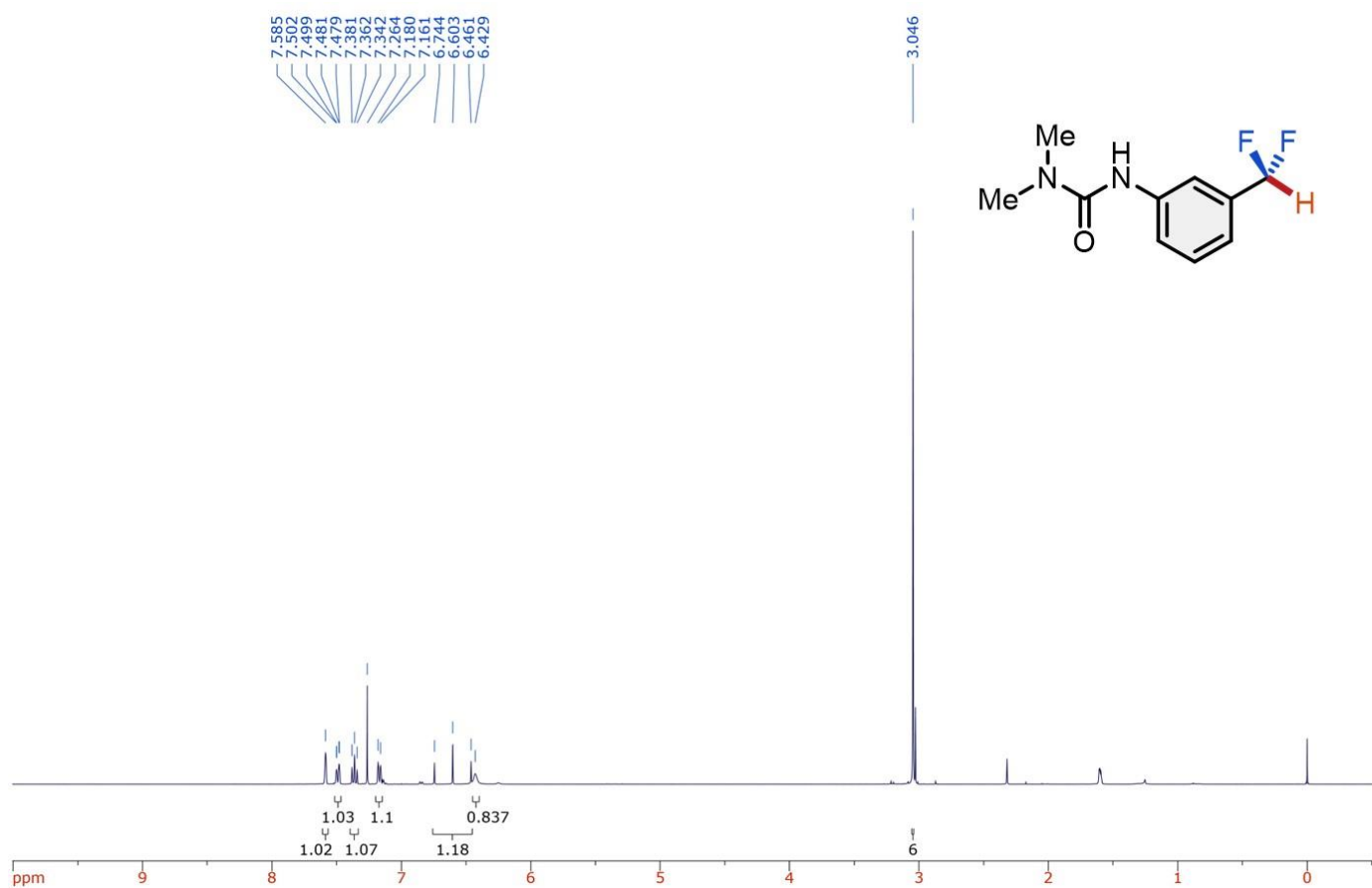
^{13}C NMR spectrum of 5a (100 MHz, CDCl_3)



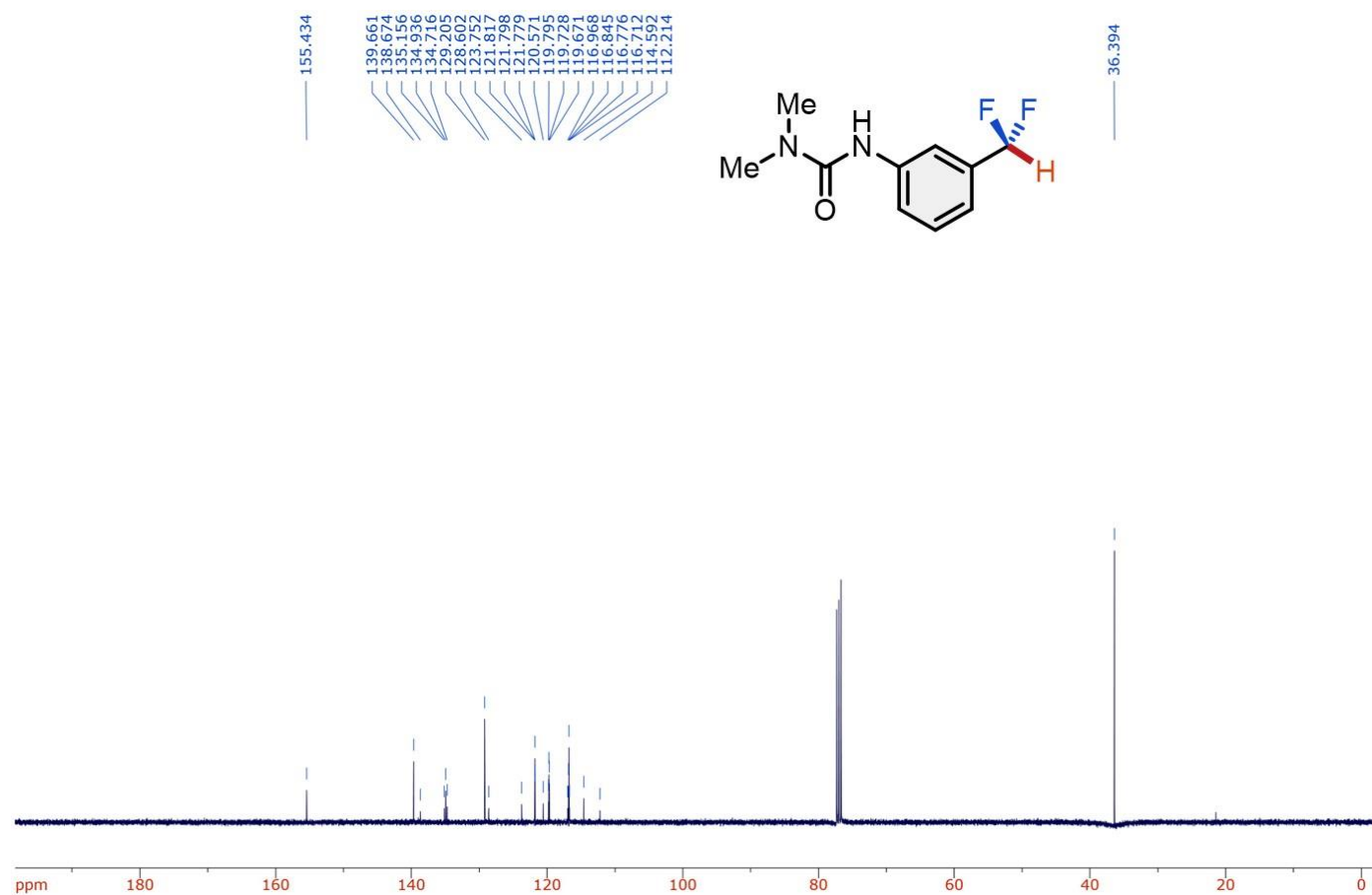
^{19}F NMR spectrum of 5a (376 MHz, CDCl_3)



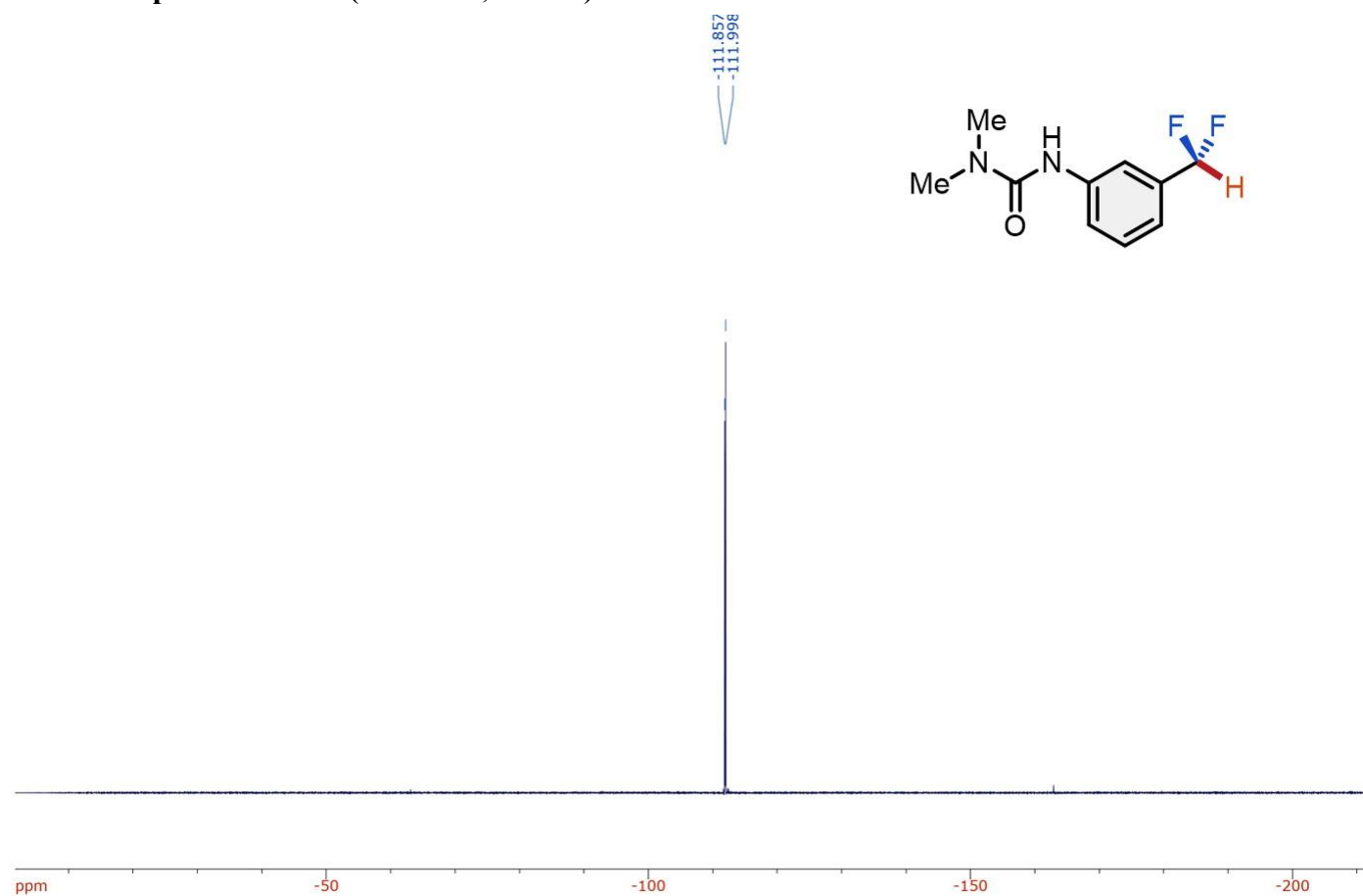
^1H NMR spectrum of 5b (400 MHz, CDCl_3)



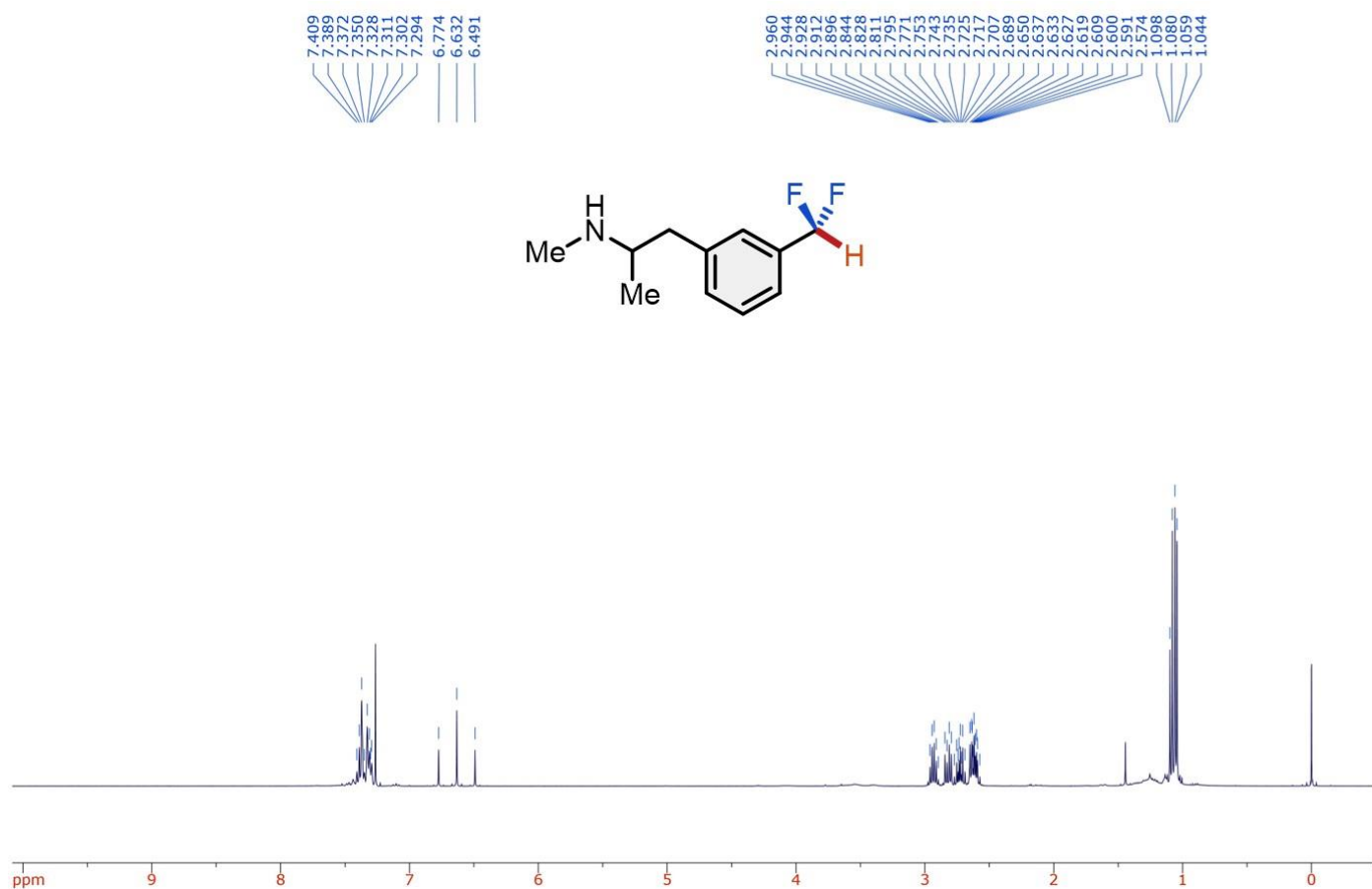
^{13}C NMR spectrum of 5b (100 MHz, CDCl_3)



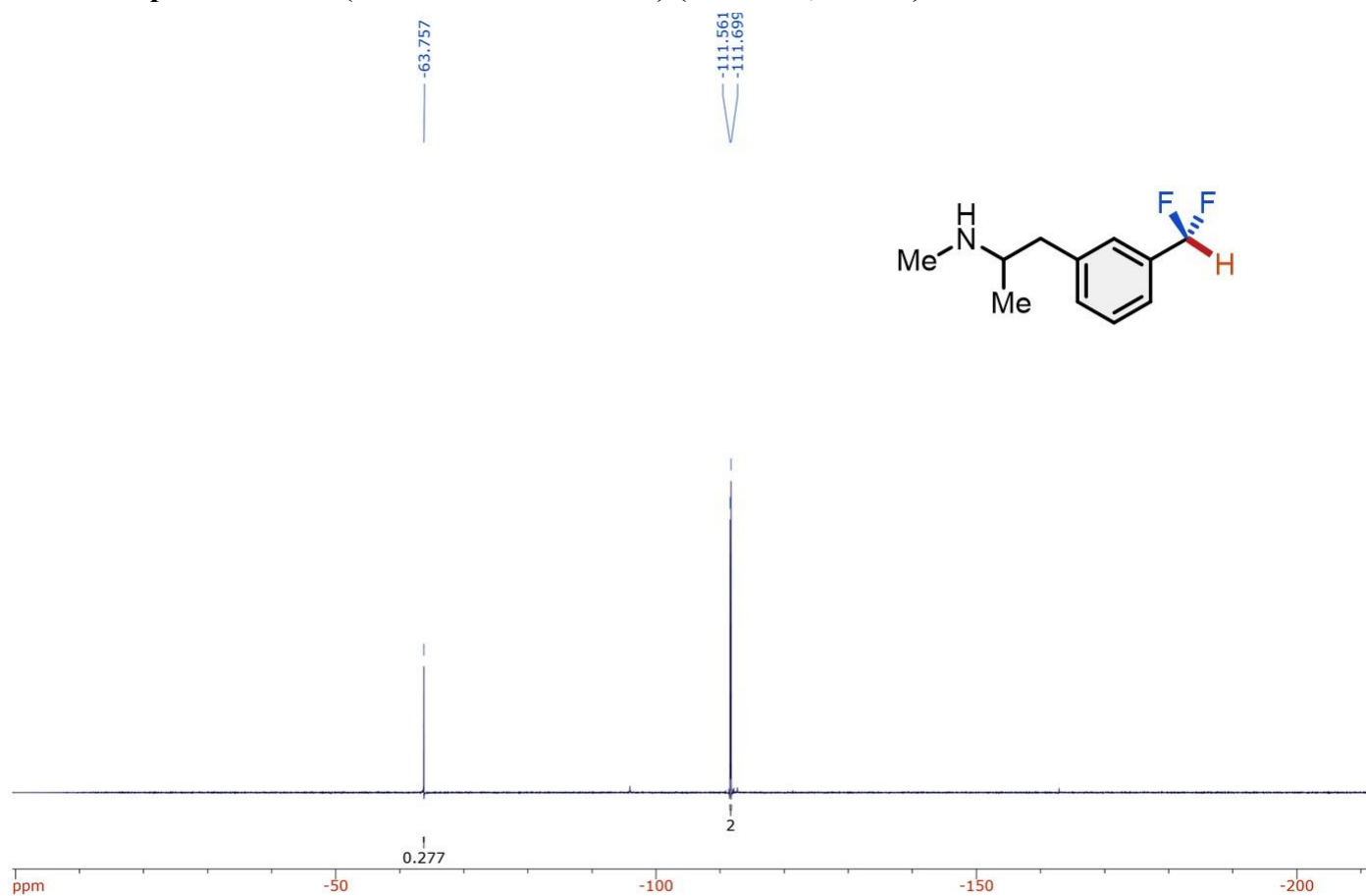
^{19}F NMR spectrum of 5b (376 MHz, CDCl_3)



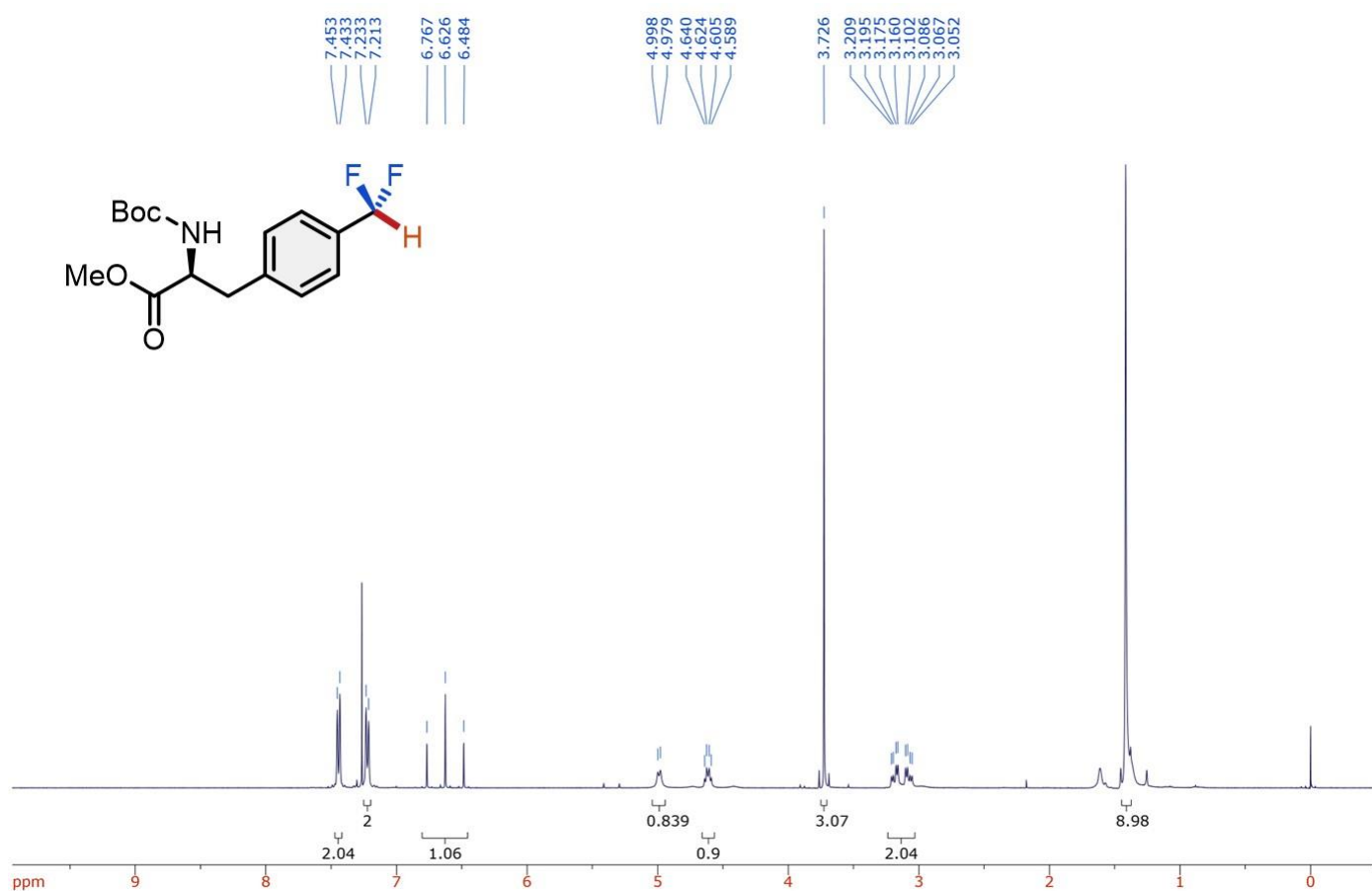
^1H NMR spectrum of 5c (mixture with substrate) (400 MHz, CDCl_3)



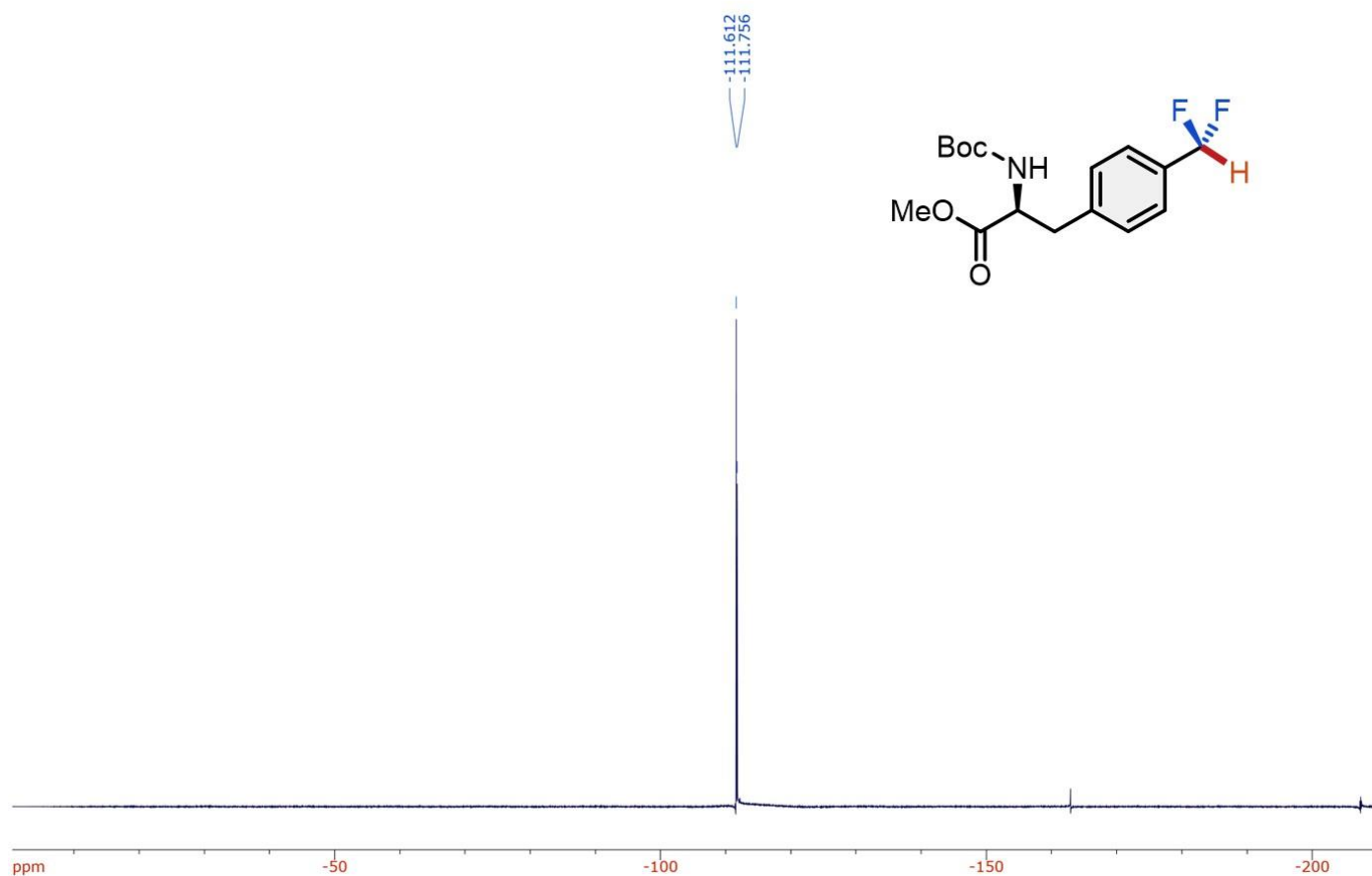
^{19}F NMR spectrum of 5c (mixture with substrate) (376 MHz, CDCl_3)



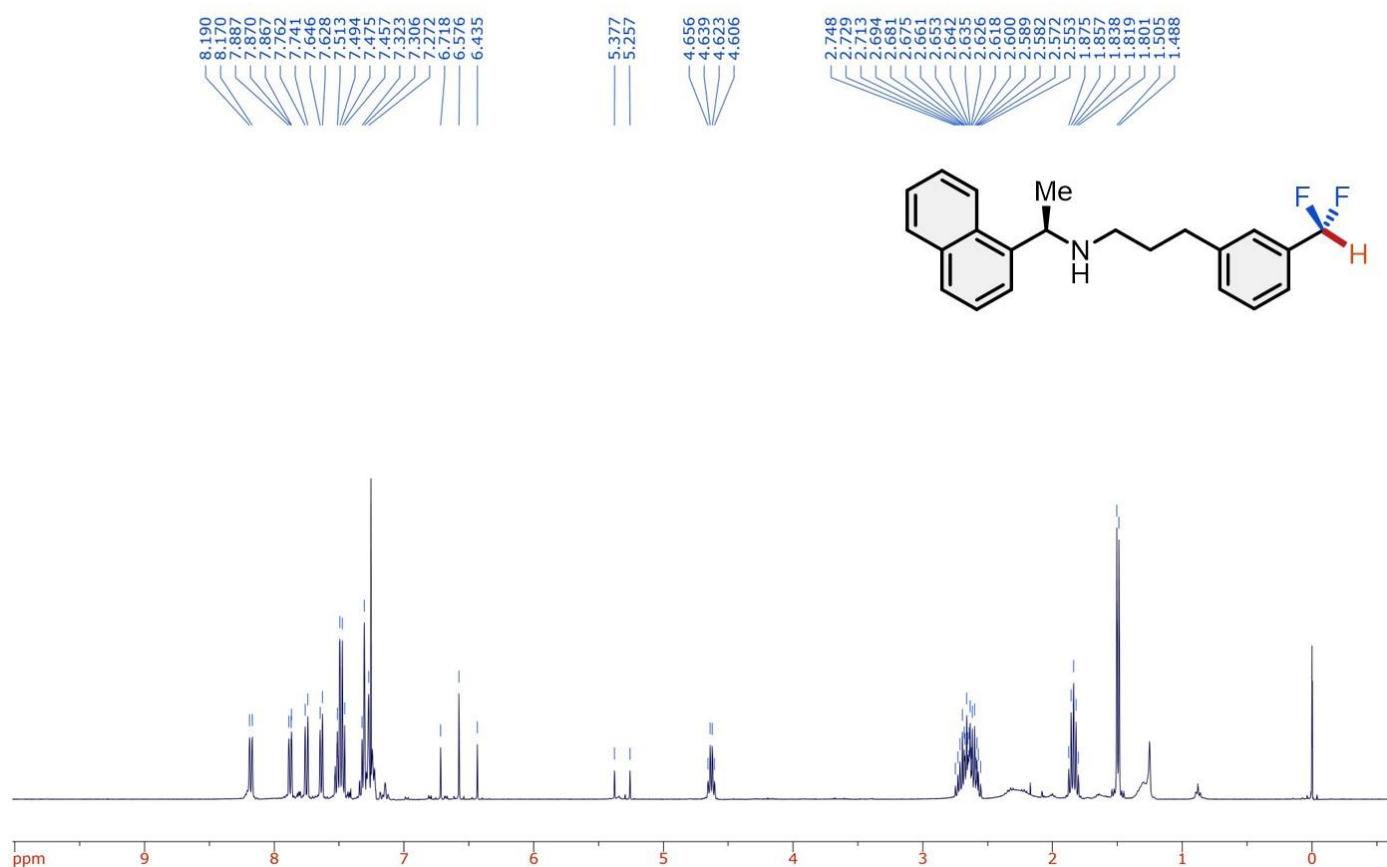
^1H NMR spectrum of 5d (mixture with byproduct) (400 MHz, CDCl_3)



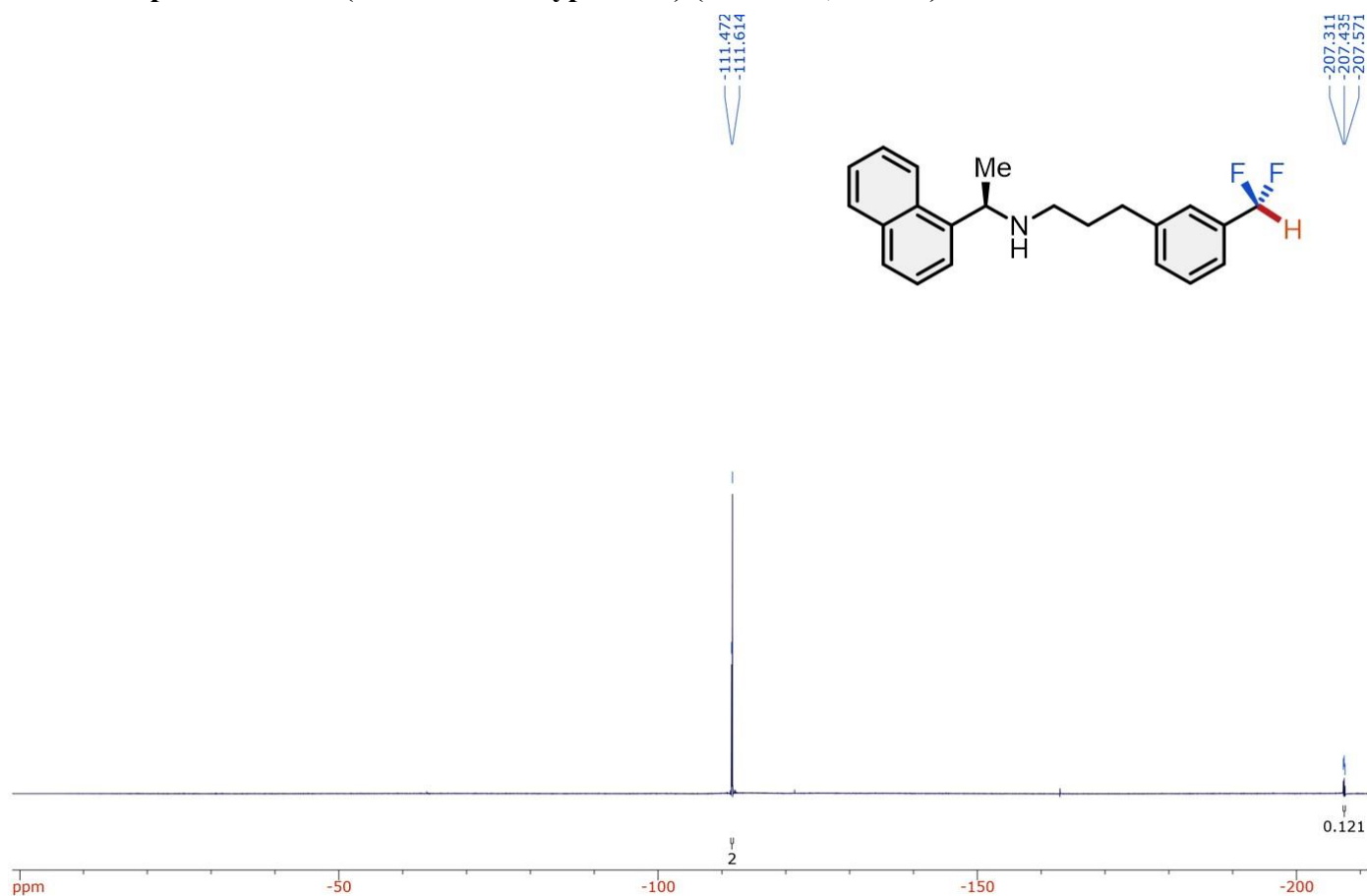
^{19}F NMR spectrum of 5d (mixture with byproduct) (376 MHz, CDCl_3)



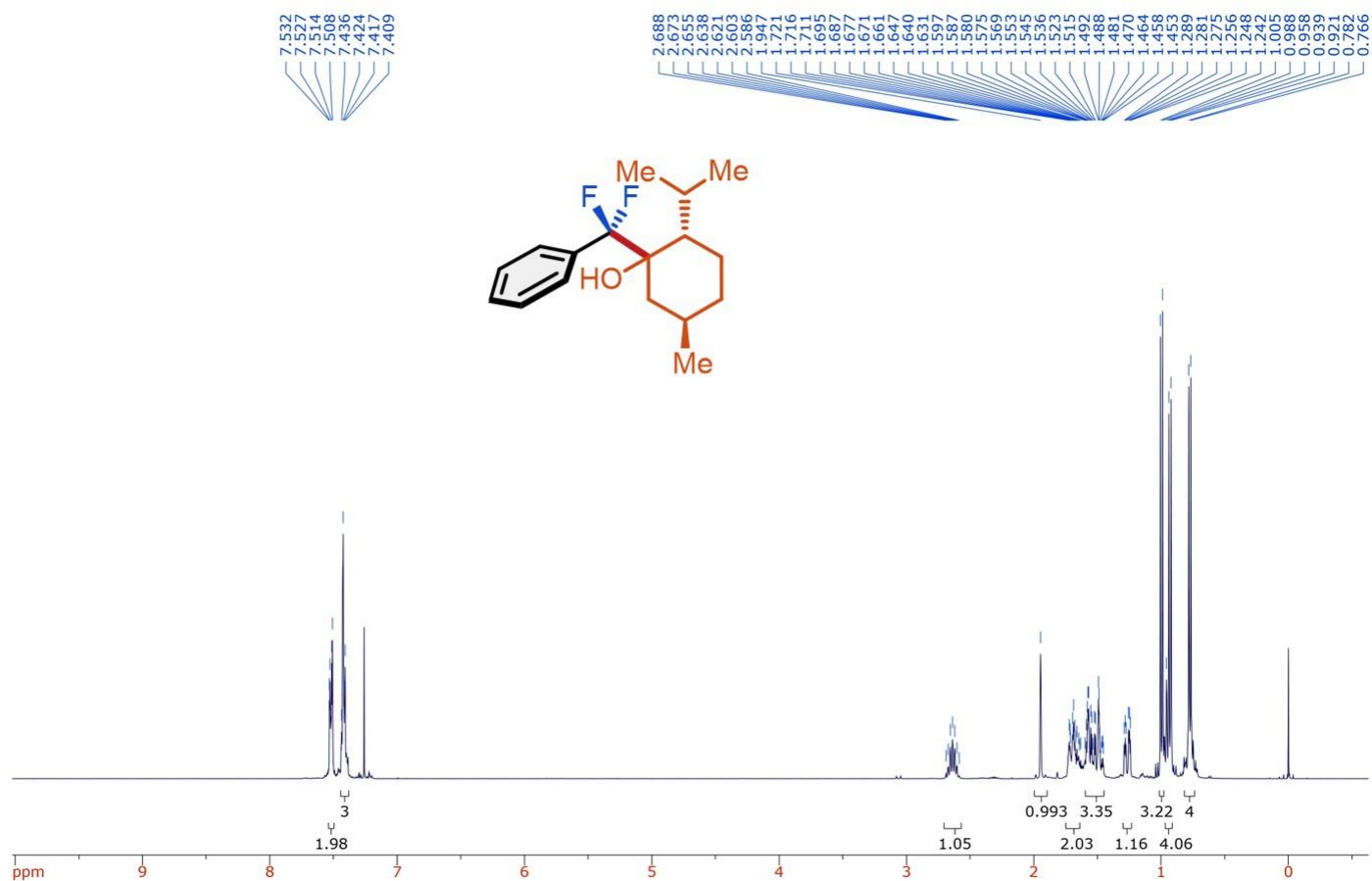
^1H NMR spectrum of 5e (mixture with byproduct) (400 MHz, CDCl_3)



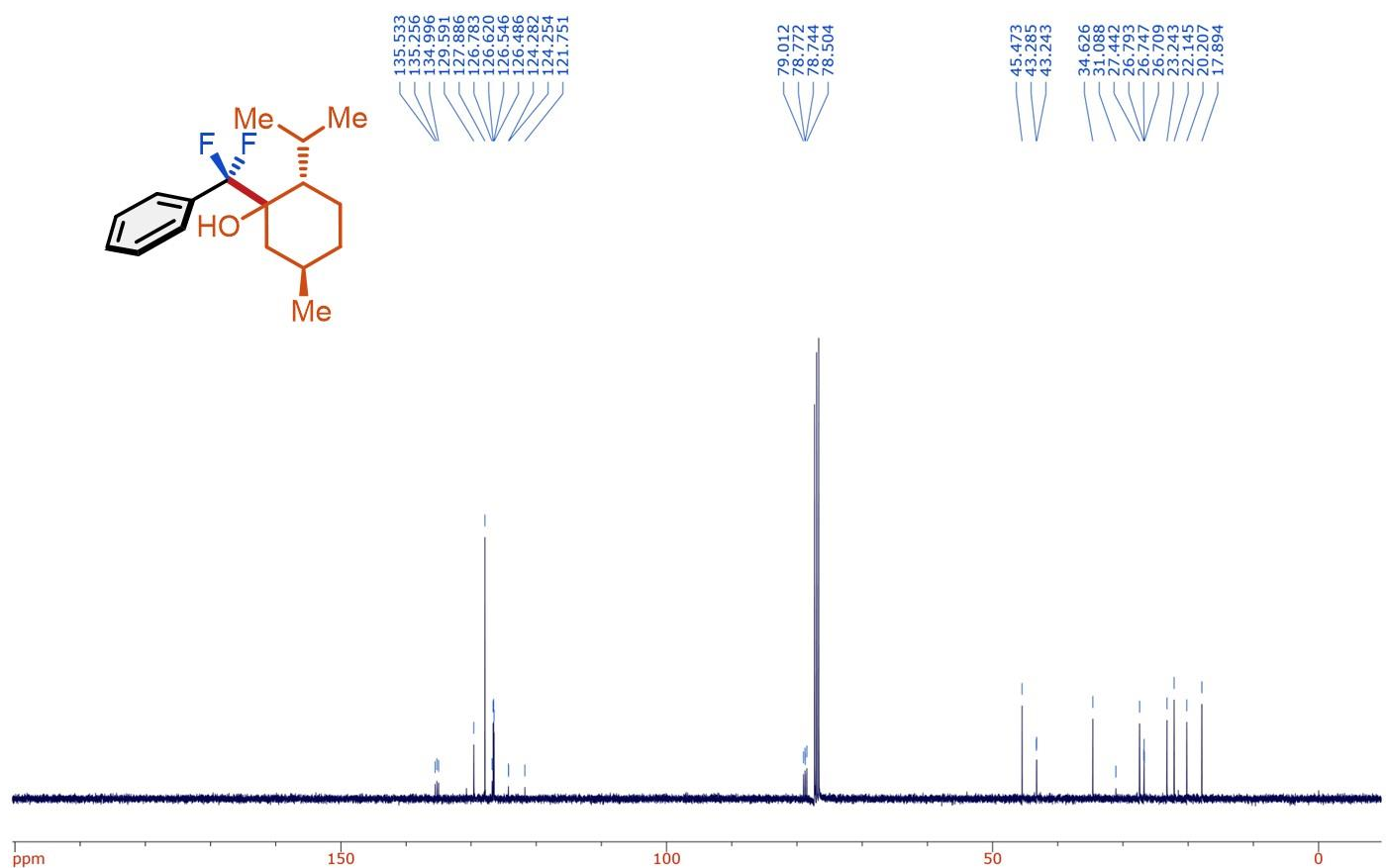
^{19}F NMR spectrum of 5e (mixture with byproduct) (376 MHz, CDCl_3)



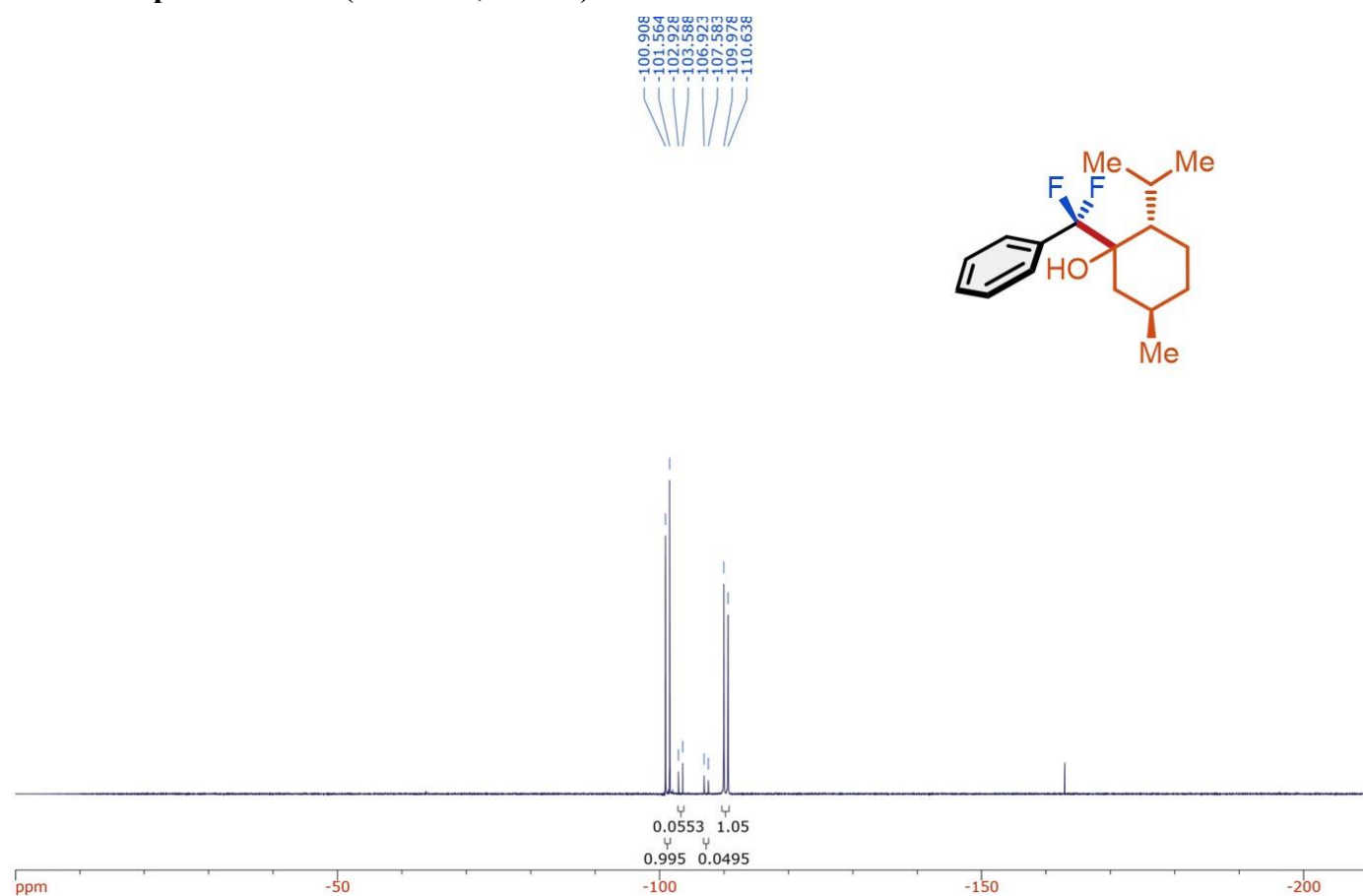
¹H NMR spectrum of 5f (400 MHz, CDCl₃)



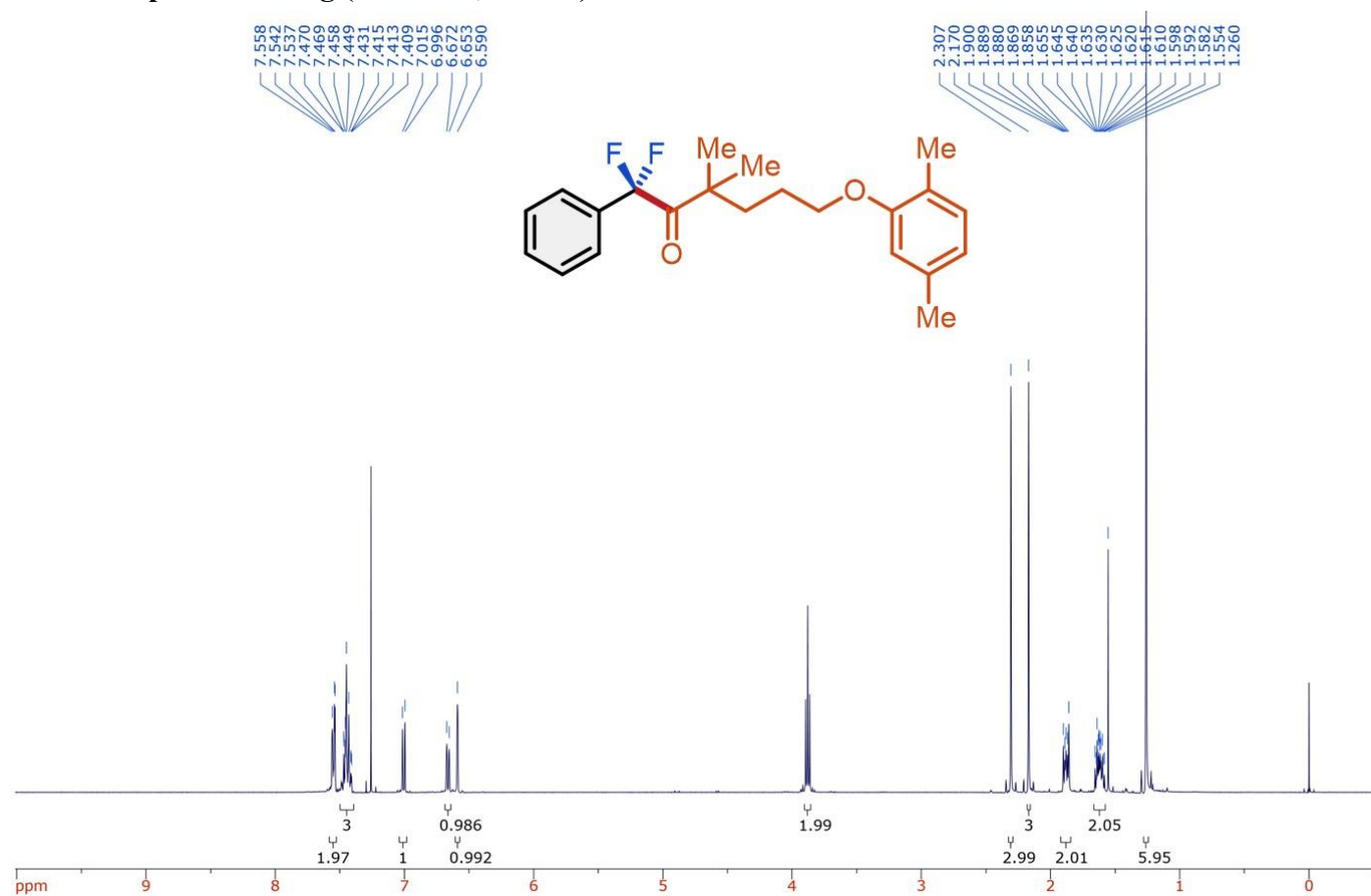
¹³C NMR spectrum of 5f (100 MHz, CDCl₃)



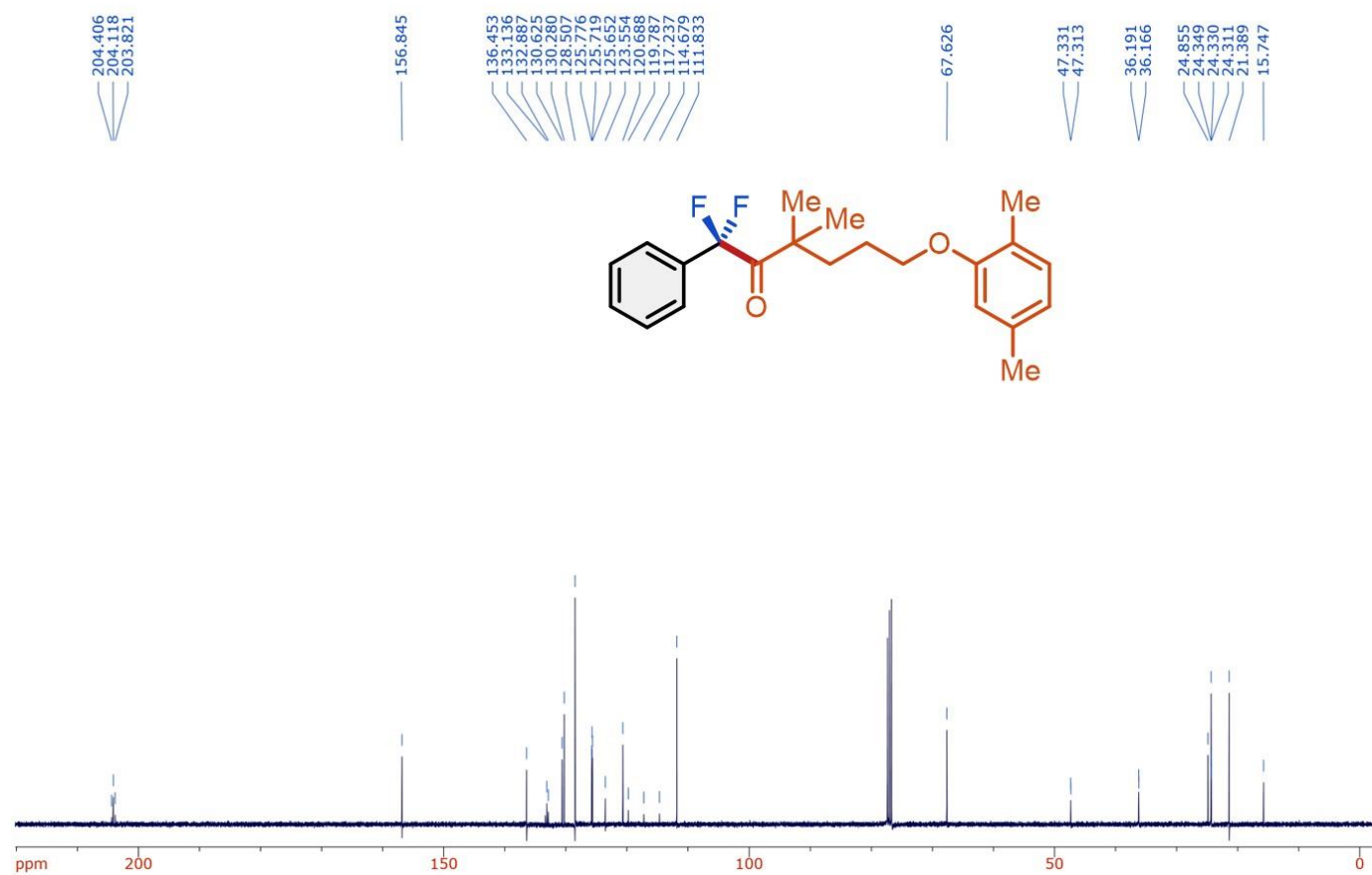
^{19}F NMR spectrum of 5f (376 MHz, CDCl_3)



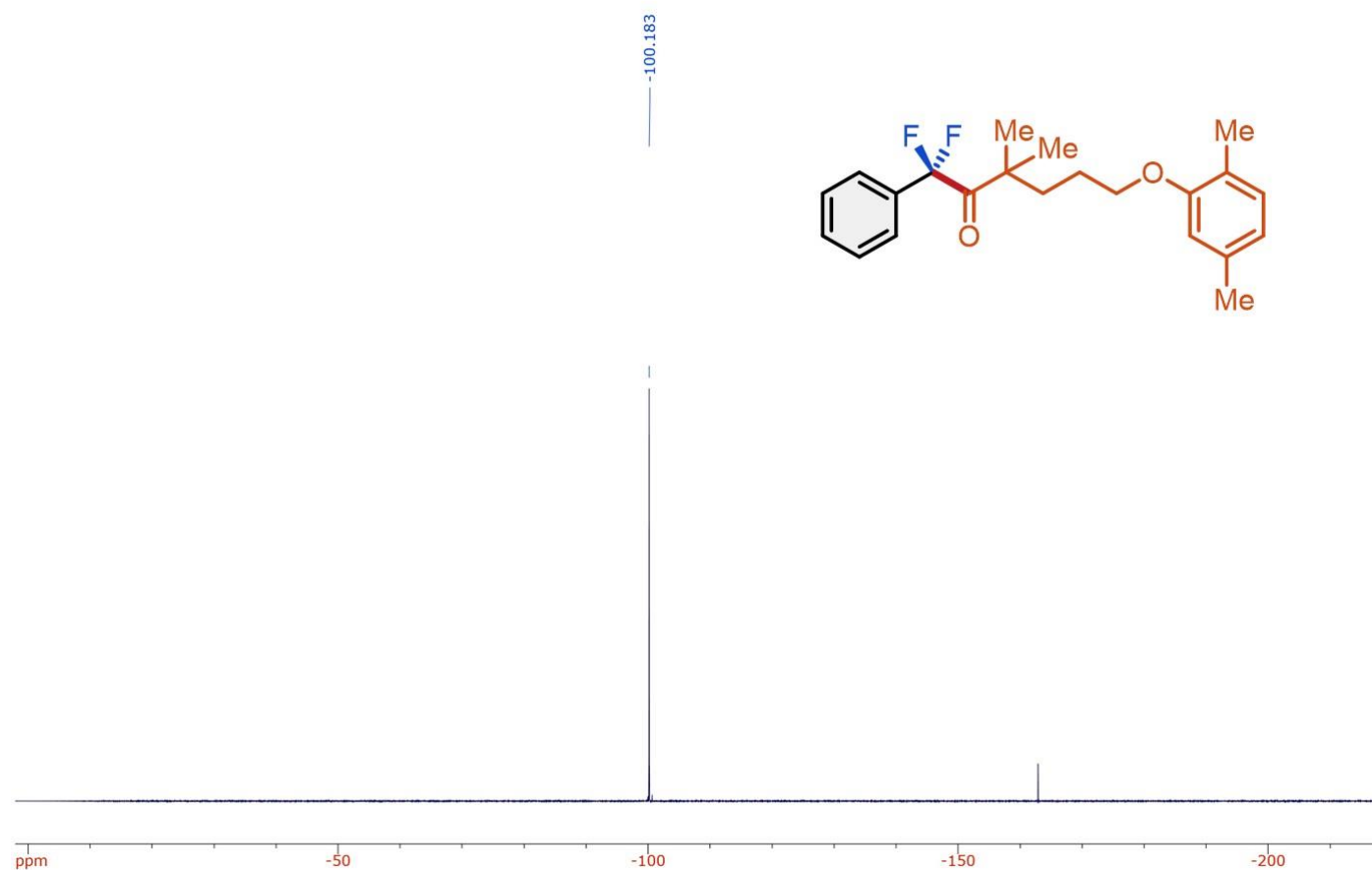
^1H NMR spectrum of 5g (400 MHz, CDCl_3)



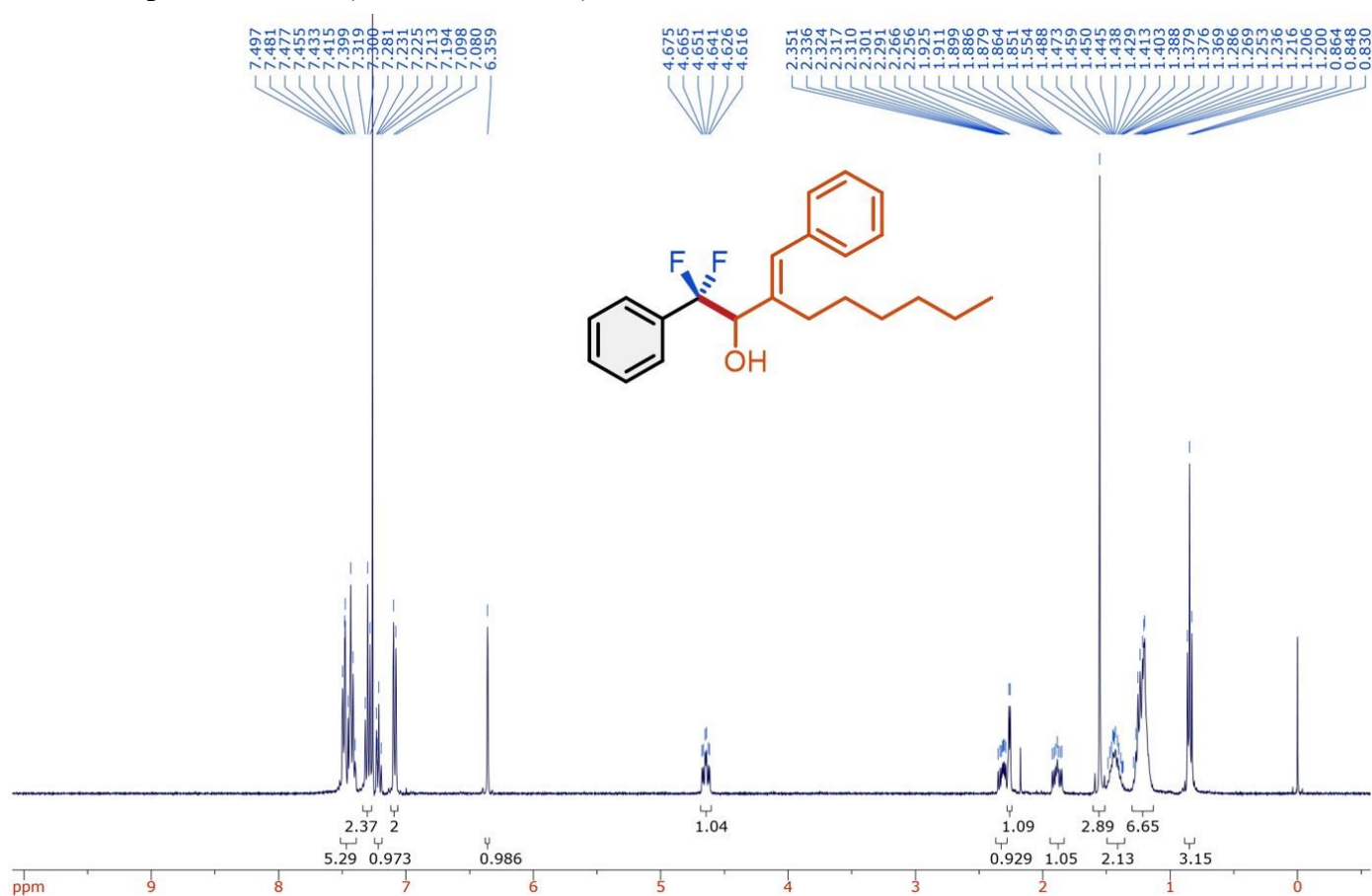
^{13}C NMR spectrum of 5g (100 MHz, CDCl_3)



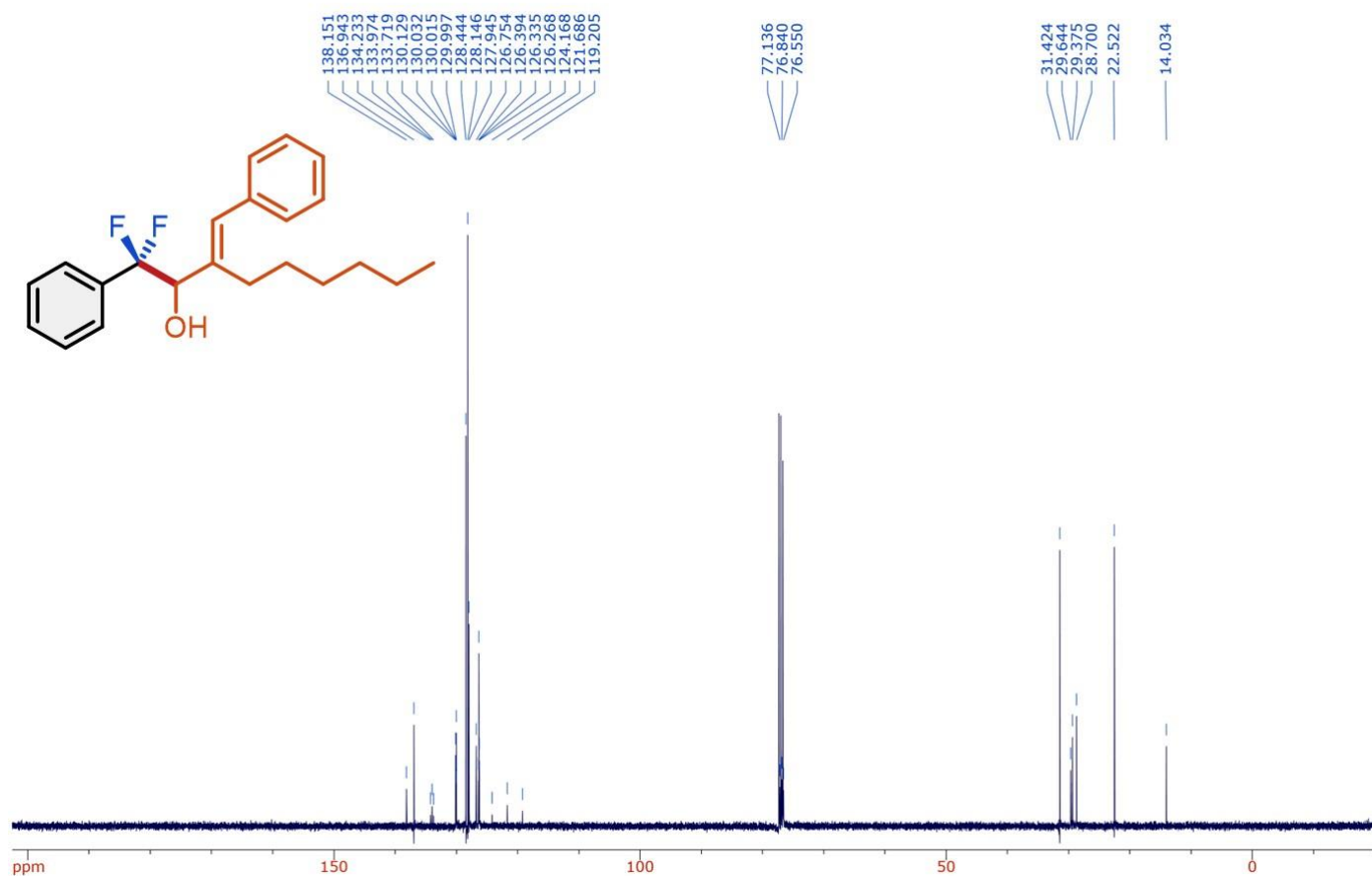
^{19}F NMR spectrum of 5g (376 MHz, CDCl_3)



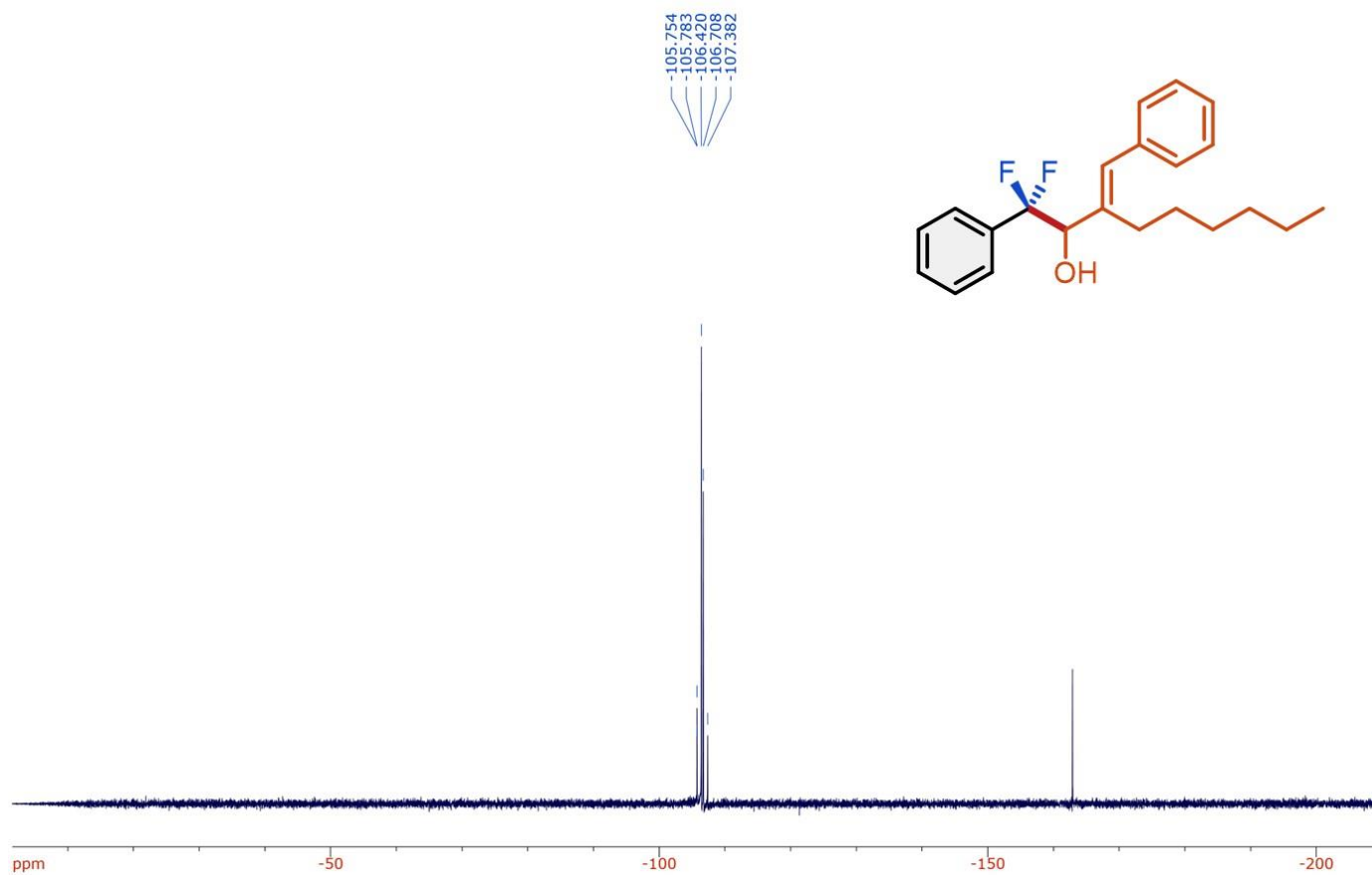
¹H NMR spectrum of 5h (400 MHz, CDCl₃)



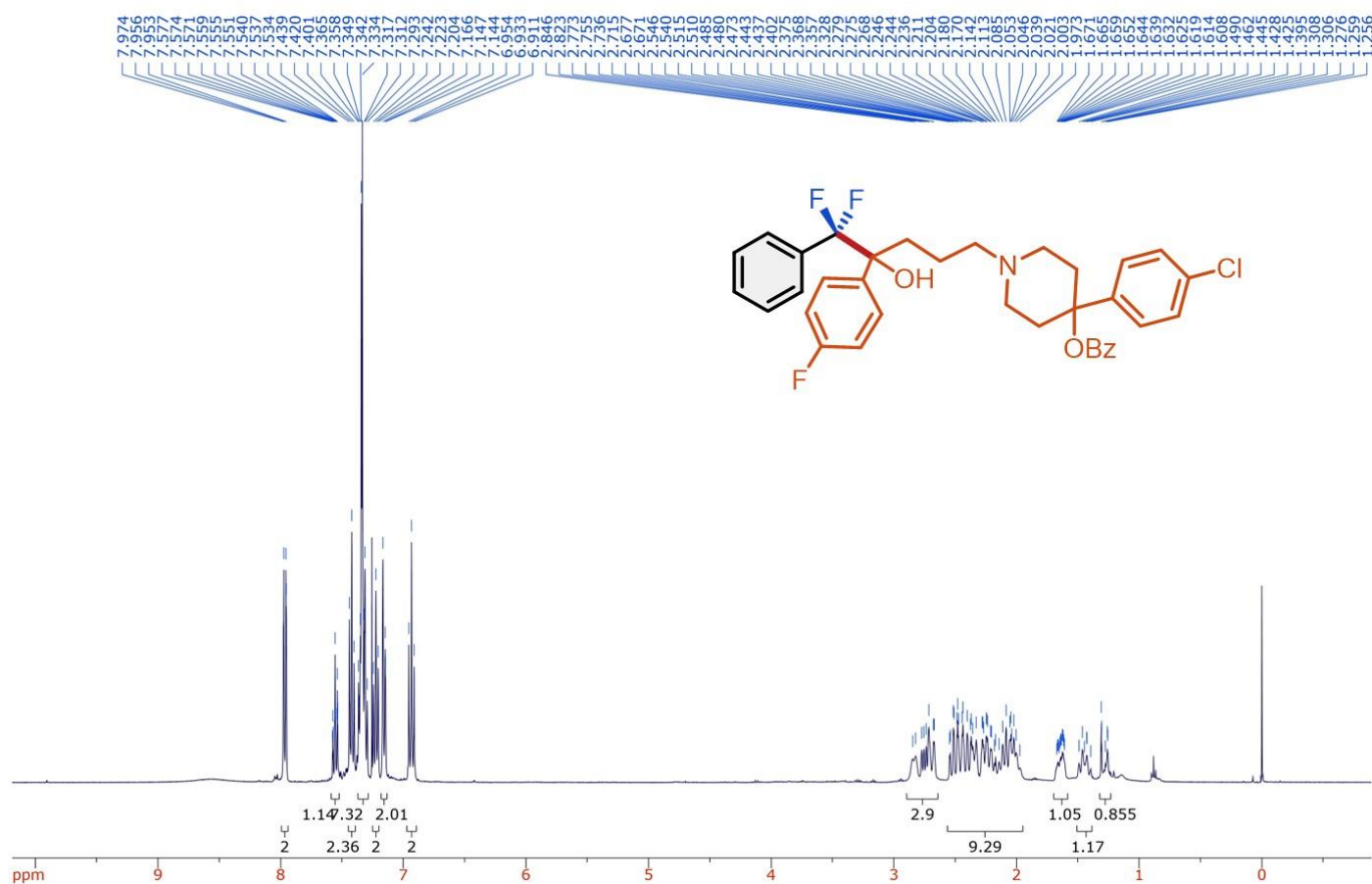
¹³C NMR spectrum of 5h (100 MHz, CDCl₃)



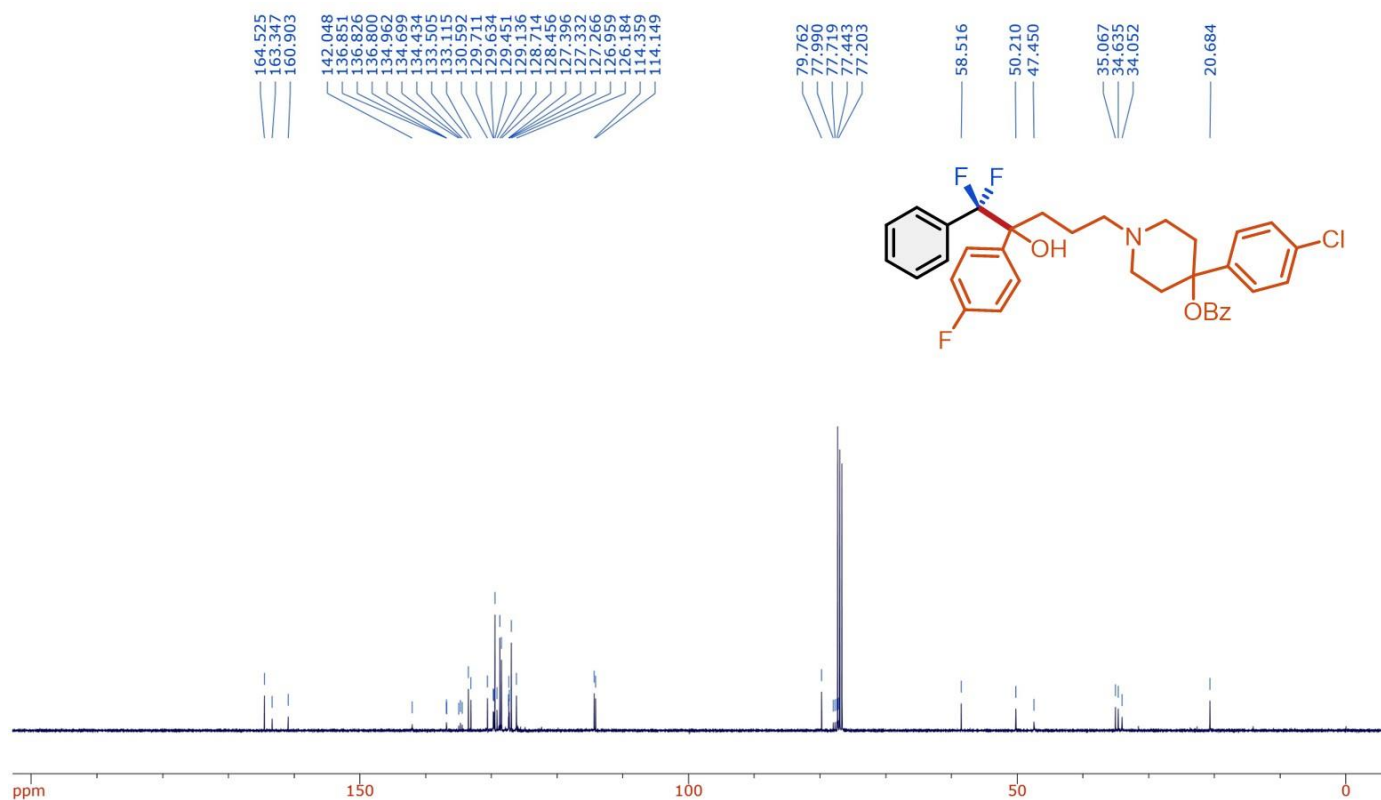
^{19}F NMR spectrum of 5h (376 MHz, CDCl_3)



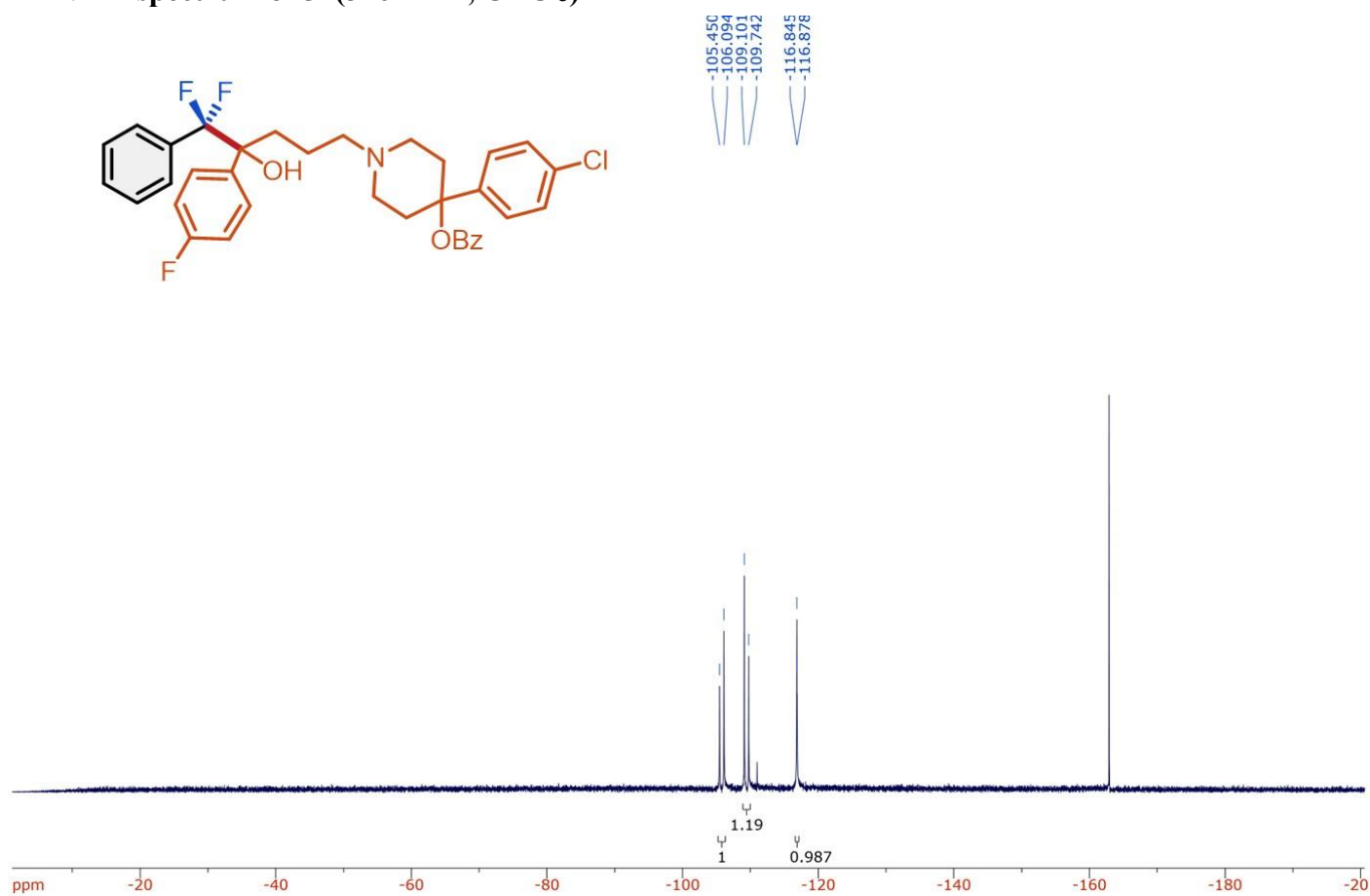
^1H NMR spectrum of 5i (400 MHz, CDCl_3)



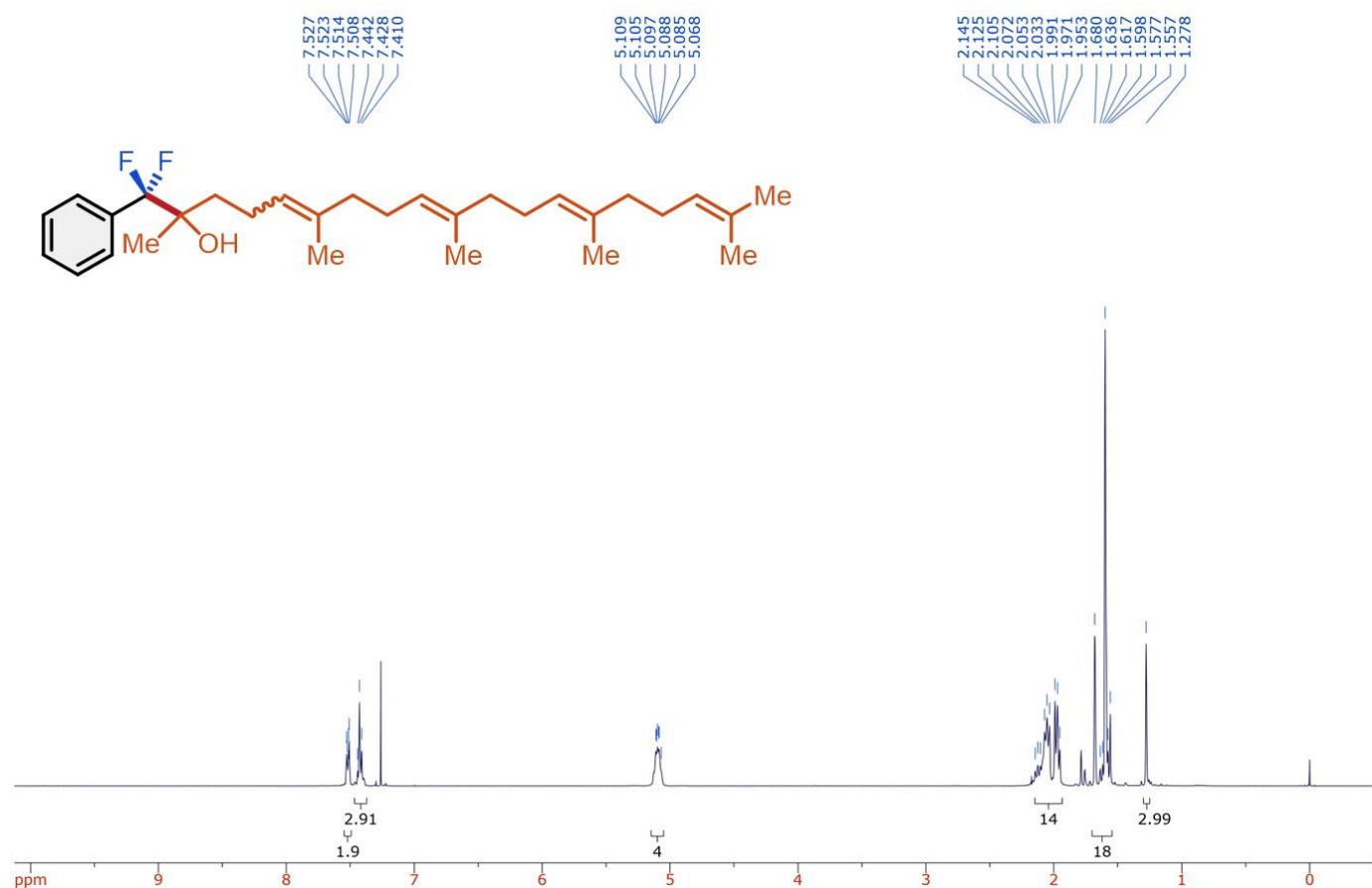
^{13}C NMR spectrum of 5i (100 MHz, CDCl_3)



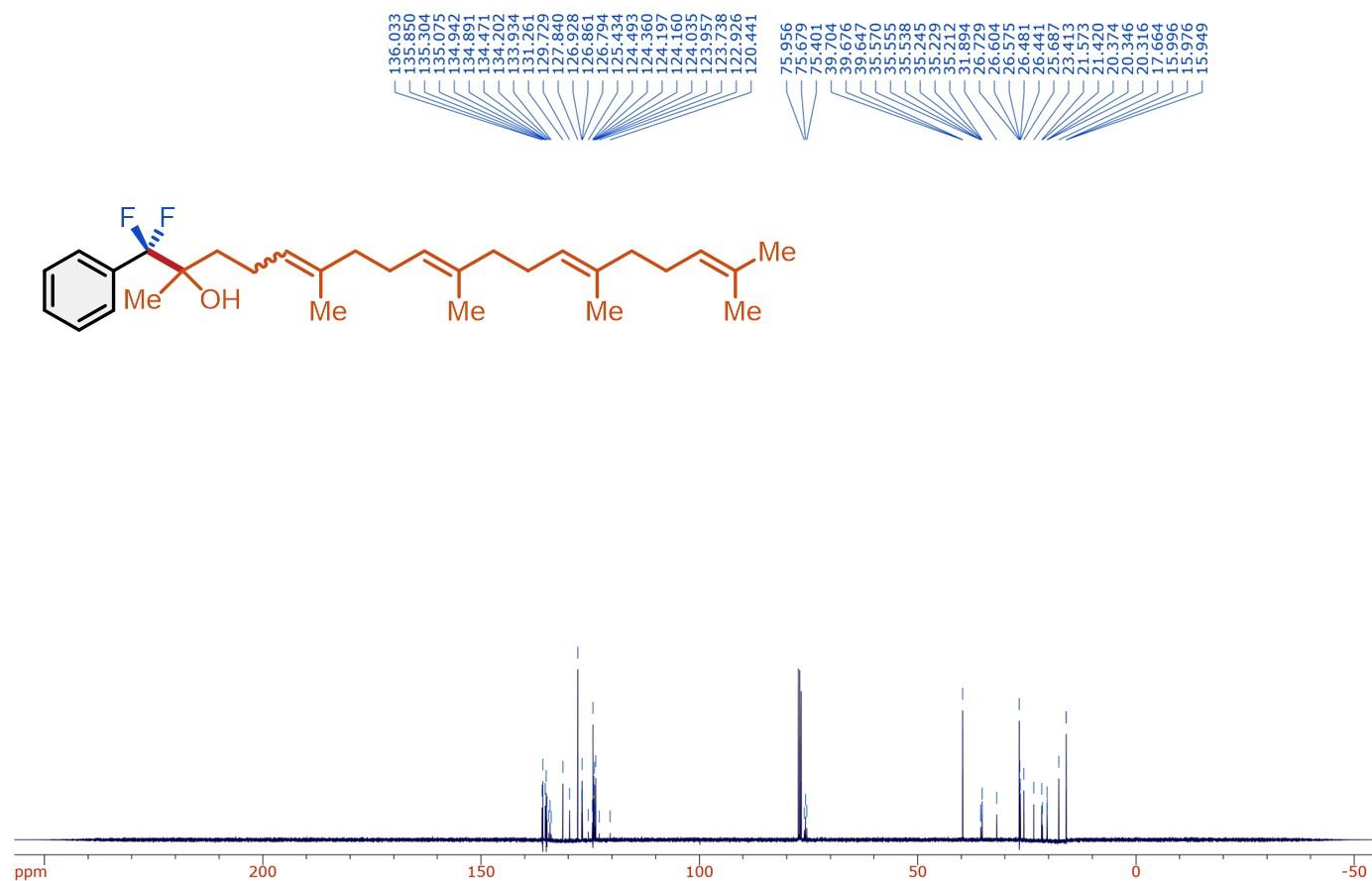
^{19}F NMR spectrum of 5i (376 MHz, CDCl_3)



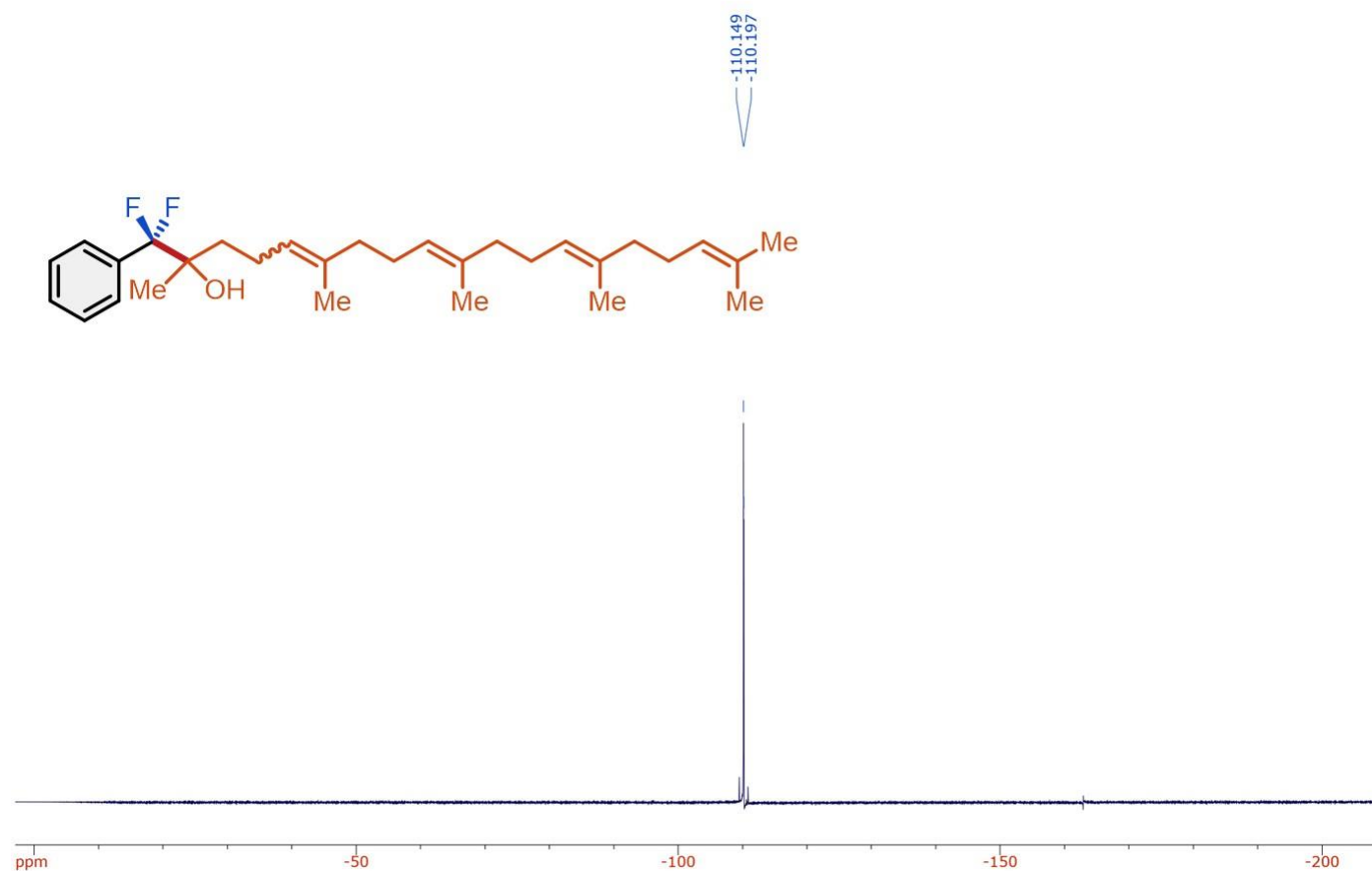
¹H NMR spectrum of 5j (400 MHz, CDCl₃)



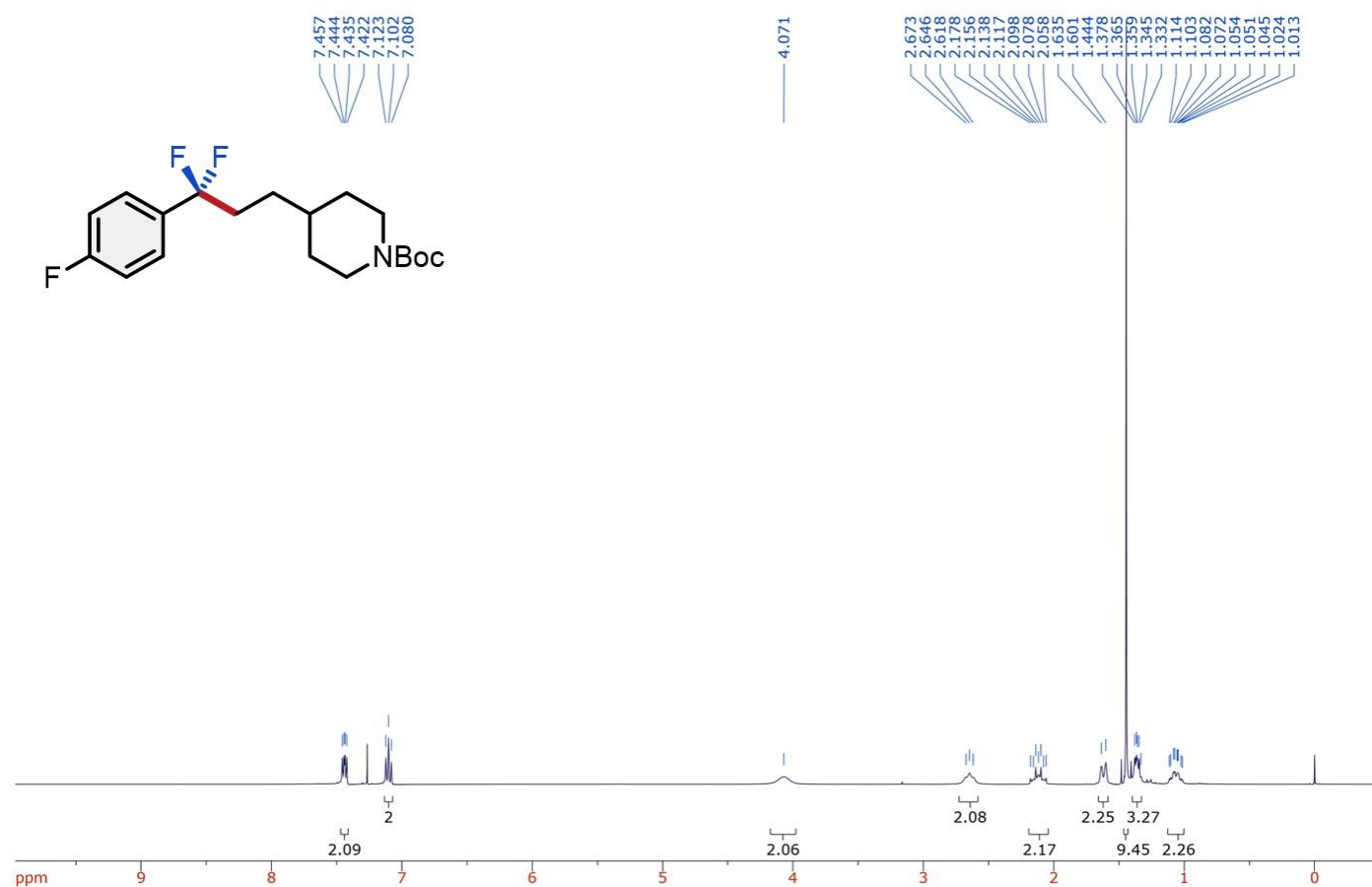
¹³C NMR spectrum of 5j (100 MHz, CDCl₃)



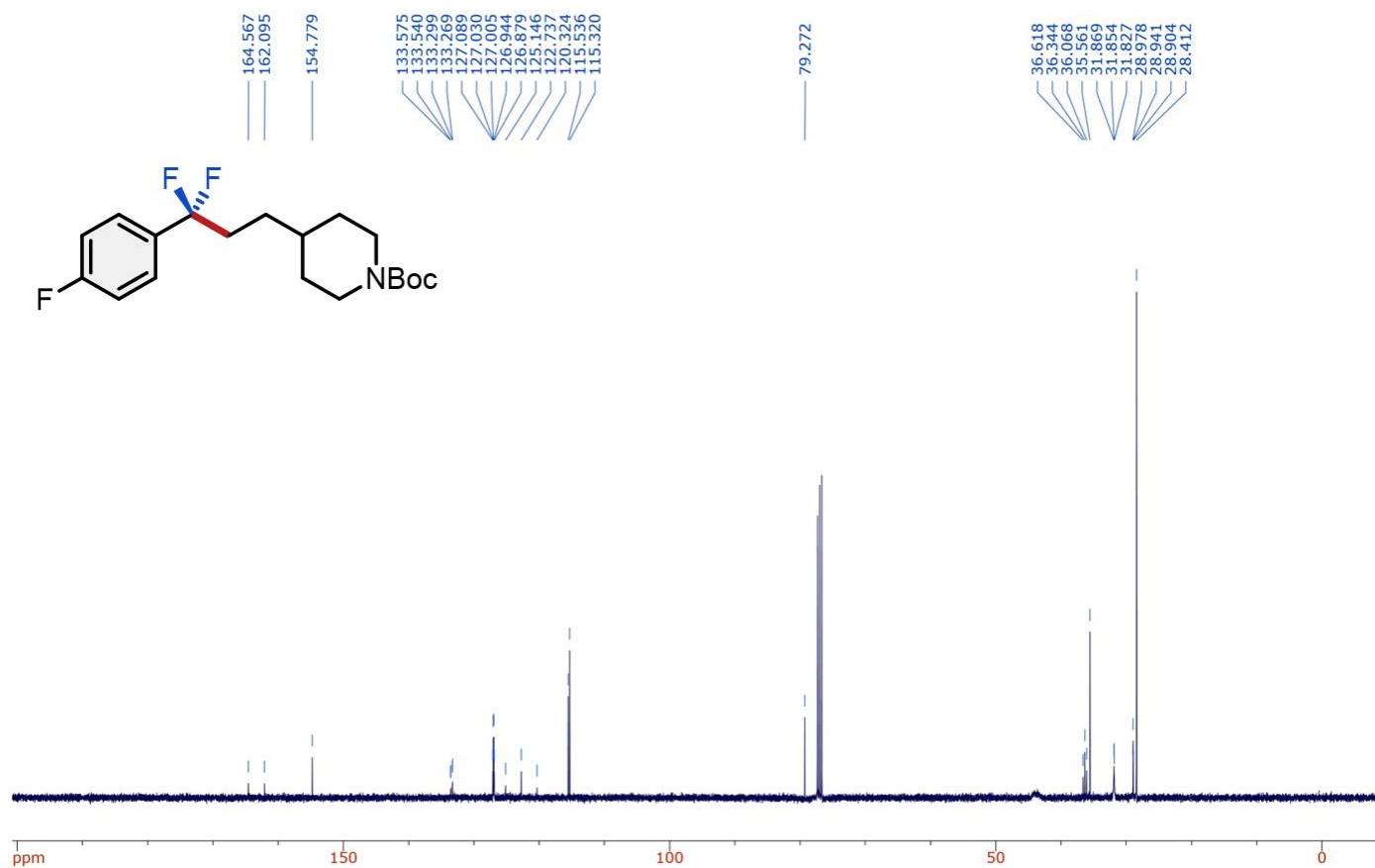
¹⁹F NMR spectrum of 5j (376 MHz, CDCl₃)



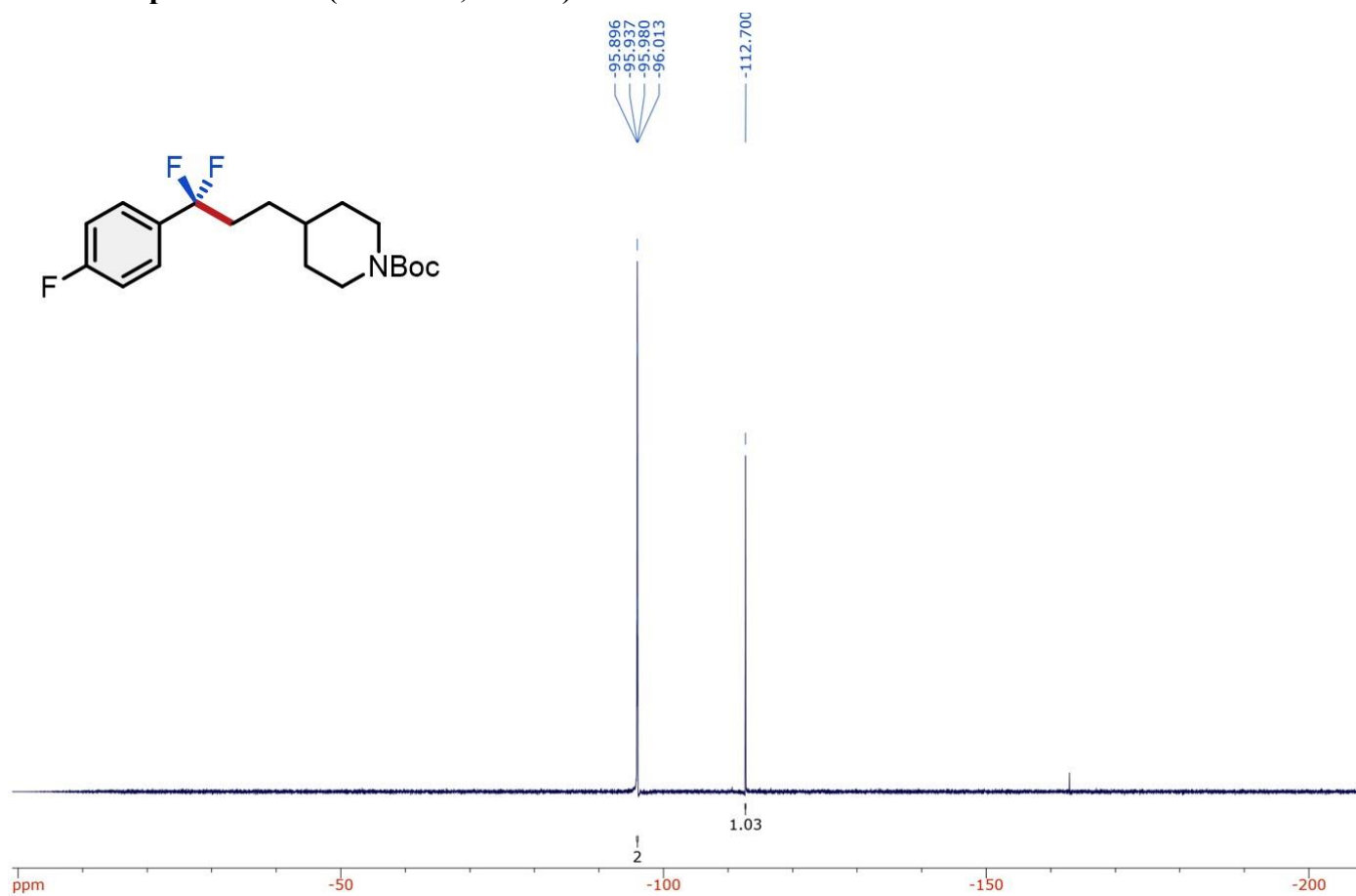
¹H NMR spectrum of 8 (400 MHz, CDCl₃)



^{13}C NMR spectrum of 8 (100 MHz, CDCl_3)



^{19}F NMR spectrum of 8 (376 MHz, CDCl_3)



References

1. Song, H. J., Jiang, W. T., Zhou, Q. L., Xu, M. Y. & Xiao, B. Structure-Modified Germatranes for Pd-Catalyzed Biaryl Synthesis. *ACS Catal.* **8**, 9287–9291 (2018).
2. Sasaki, K. & Crich, D. Facile Amide Bond Formation from Carboxylic Acids and Isocyanates. *Org. Lett.* **13**, 2256–2259 (2011).
3. Palombi, G. & Zagami, M. NEW METHOD FOR SYNTHESIS OF FENFLURAMINE, AND NEW COMPOSITIONS COMPRISING IT. US 20180208543A1 (2018).
4. Govindan, K., Chen, N. Q., Chen, H. Y., Hsu, S. C. C. & Lin, W. Y. The copper-catalyzed oxidative radical process of site selective C–N bond cleavage in twisted amides: batch and continuous-flow chemistry. *Catal. Sci. Technol.* **13**, 1633–1639 (2023).
5. Geri, J. B., Wolfe, M. M. W. & Szymczak, N. K. The Difluoromethyl Group as a Masked Nucleophile: A Lewis Acid/Base Approach. *J. Am. Chem. Soc.* **140**, 9404–9408 (2018).
6. Charles, C. *et al.* PYRROLIDINE MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY. WO2000059503 A1 (2000).
7. Gaussian 16, Revision C.01, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Petersson, G. A., Nakatsuji, H., Li, X., Caricato, M., Marenich, A. V., Bloino, J., Janesko, B. G., Gomperts, R., Mennucci, B., Hratchian, H. P., Ortiz, J. V., Izmaylov, A. F., Sonnenberg, J. L., Williams-Young, D., Ding, F., Lipparini, F., Egidi, F., Goings, J., Peng, B., Petrone, A., Henderson, T., Ranasinghe, D., Zakrzewski, V. G., Gao, J., Rega, N., Zheng, G., Liang, W., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Throssell, K., Montgomery, Jr., J. A., Peralta, J. E., Ogliaro, F., Bearpark, M. J., Heyd, J. J., Brothers, E. N., Kudin, K. N., Staroverov, V. N., Keith, T. A., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A. P., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Millam, J. M., Klene, M., Adamo, C., Cammi, R., Ochterski, J. W., Martin, R. L., Morokuma, K., Farkas, O., Foresman, J. B. & Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.
8. Grimme, S., Antony, J., Ehrlich, S. & Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H–Pu. *J. Chem. Phys.* **132**, 154104 (2010).
9. Cancès, M. T., Mennucci, B. & Tomasi, J. A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic and anisotropic dielectrics. *J. Chem. Phys.* **107**, 3032–3041 (1997).
10. Box, J. R., Avanthay, M. E., Poole, D. L. & Lennox, A. J. J. Electronically Ambivalent Hydrodefluorination of Aryl–CF₃ groups enabled by Electrochemical Deep-Reduction on a Ni Cathode. *Angew. Chem. Int. Ed.* **62**, e202218195 (2023).
11. Miao, W., Zhao, Y., Ni, C., Gao, B., Zhang, W. & Hu, J. Iron-Catalyzed Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone. *J. Am. Chem. Soc.* **140**, 880–883 (2018).
12. Schlosser, M., Brugger, N., Schmidt, W. & Amrhein, N. β , β -Difluoro analogs of α -oxo- β -phenylpropionic acid and phenylalanine. *Tetrahedron*, **60**, 7731–7742 (2004).

13. Okoromoba, O. E., Han, J., Hammond, G. B. & Xu, B. Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and *gem*-Difluoromethylene Compounds from Alkynes. *J. Am. Chem. Soc.* **136**, 14381–14384 (2014).
14. An, L., Xiao, Y. L., Zhang, S. & Zhang, X. Bulky Diamine Ligand Promotes Cross-Coupling of Difluoroalkyl Bromides by Iron Catalysis. *Angew. Chem. Int. Ed.* **57**, 6921–692 (2018).
15. Uno, M., Sumino, S., Fukuyama, T., Matsuura, M., Kuroki, Y., Kishikawa, Y. & Ryu, I. Synthesis of 4,4-Difluoroalkenes by Coupling of α -Substituted α , α -Difluoromethyl Halides with Allyl Sulfones under Photoredox Catalyzed Conditions. *J. Org. Chem.* **84**, 9330–9338 (2019).
16. Bollinger, F. W. & Conn, J. B. Assignee: Merck and Co., Inc., Aug 17, 1972, DE 2104313 A
17. Tang, X. J., Zhang, Z. & Dolbier, Jr., W. R. Direct Photoredox-Catalyzed Reductive Difluoromethylation of Electron-Deficient Alkenes. *Chem. Eur. J.* **21**, 18961–18965 (2015).
18. McAtee, R. C., Beatty, J. W., McAtee, C. C. & Stephenson, C. R. J. Radical Chlorodifluoromethylation: Providing a Motif for (Hetero) arene Diversification. *Org. Lett.* **20**, 3491–3495 (2018).
19. Choi, K., Mormino, M. G., Kalkman, E. D., Park, J. & Hartwig, J. F. Palladium-Catalyzed Aryldifluoromethylation of Aryl Halides with Aryldifluoromethyl Trimethyl silanes. *Angew. Chem. Int. Ed.* **61**, e2022082 (2022).
20. Wei, Z., Miao, W., Ni, C. & Hu, J. Iron-Catalyzed Fluoroalkylation of Arylborates with Sulfone Reagents: Beyond the Limitation of Reduction Potential. *Angew. Chem. Int. Ed.* **60**, 13597–13602 (2021).
21. Gouberneur, V. *et al.* [18F]Difluorocarbene for positron emission tomography. *Nature* **606**, 102–108 (2022).
22. Gao, X., He, X. & Zhang, X. Nickel-catalyzed difluoromethylation of (hetero) aryl bromides with BrCF₂H. *Chin. J. Org. Chem.* **39**, 215–222 (2019).
23. Li, X., Zhao, J., Hu, M., Chen, D., Ni, C., Wang, L. & Hu, J. Copper-mediated aerobic (phenylsulfonyl)difluoromethylation of arylboronic acids with difluoromethyl phenyl sulfone. *Chem. Commun.* **52**, 3657–3660 (2016).
24. Prakash, G. K. S., Ganesh, S. K., Jones, J. P., Kulkarni, A., Masood, K., Swabeck, J. K. & Olah, G. A. Copper-Mediated Difluoromethylation of (Hetero)aryl Iodides and β -Styryl Halides with Tributyl(difluoromethyl)stannane. *Angew. Chem. Int. Ed.* **51**, 12090–12094 (2012).
25. Hori, K., Motohashi, H., Saito, D. & Mikami, K. Precatalyst Effects on Pd-Catalyzed Cross-Coupling Difluoromethylation of Aryl Boronic Acids. *ACS Catal.* **9**, 417–421 (2019).