Supporting Information

Facile Access to Difluoromethylene-Linked Strained Aliphatic Rings from 2-(Difluoromethylene)cyclobutyl Sulfonium Salts (CB-DFAS) and [1.1.1]Propellane

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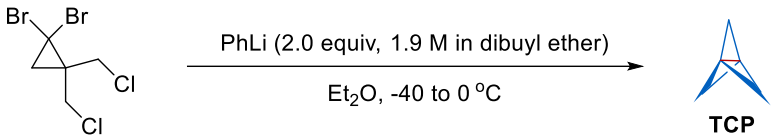
1. General Information and Materials

General information: ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on the Agilent MR 400, Bruker MR 500, and Bruker MR 600 spectrometers, and are calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR; 77.0 ppm ^{13}C NMR; $CFCl_3$ as an external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction. High-Resolution Mass spectral data were recorded on an Agilent Technologies 6224 TOF LC-MS spectrometer in ESI mode, a Thermo Fisher LTQ-FT-UItra spectrometer in DART mode, or a JEOL AccuTOF 4G GCV in FI mode.

Materials: All reagents were used as received from commercial sources without further purification unless specified otherwise or prepared as described in the literature. Super dry solvents were purchased from Energy Chemical. CuBr (99.0%) was purchased from Macklin. $ZnCl_2$ solution (1.0 M in THF) was purchased from Adamas. *n*BuLi (2.5 M in hexane) and PhLi (1.9 M in dibutyl ether) solutions were purchased from Energy Chemical. All aryl magnesium bromides in Et_2O were purchased from Energy Chemical. CB-DFASs were prepared according to the literature.[1]

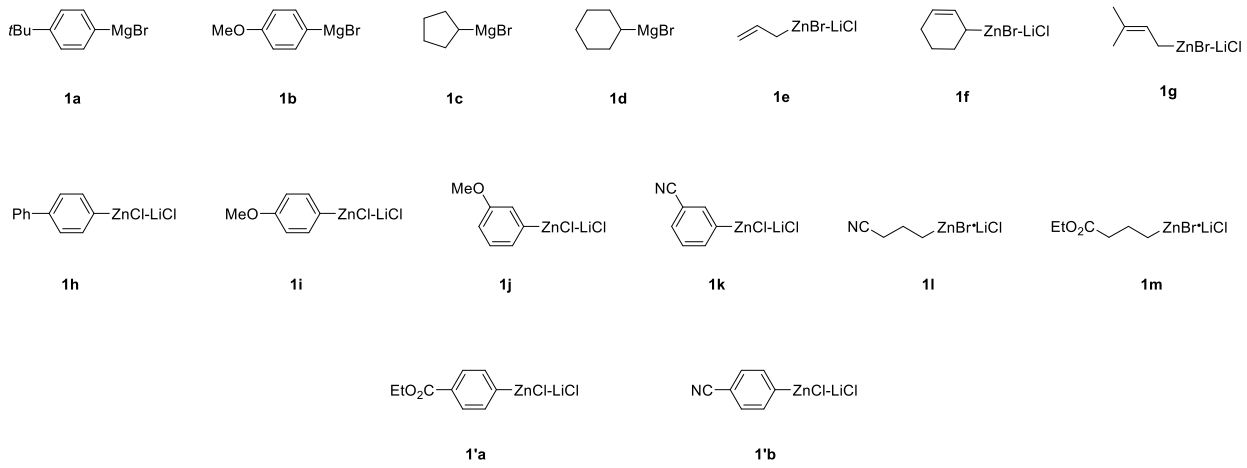
2. Preparation of the Starting Materials

2.1 Preparation of the solution of [1.1.1]propellane (TCP) in diethyl ether[2]



In a dry three-necked flask, 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (29.37 g, 95 mmol,1.0 equiv) was dissolved in Et_2O (40.0 mL). The resulting solution was cooled to -40 °C. Phenyllithium (1.90 M in dibutyl ether, 100 mL, 190 mmol, 2.0 equiv) was added dropwise over 15 min using a syringe pump. The resulting mixture was stirred for 20 min at -40 °C and 2 h at 0 °C. Then the reaction flask was fitted with a distillation tube and a distillation head connected to a receiving flask immersed in an acetone/dry ice bath (-78 °C), and the distillation was started at 200 mbar. The reaction flask was removed from the ice bath, and the pressure was gradually lowered to 45 mbar. After approximately 30 min of the distillation, the system was filled with argon. An aliquot (0.1 mL) of the solution was analyzed by NMR spectroscopy with CH_2Br_2 as a standard to determine the concentration. The average concentration of the TCP solution was 0.6-1.2 M. The solution was stored at -40 °C under argon.

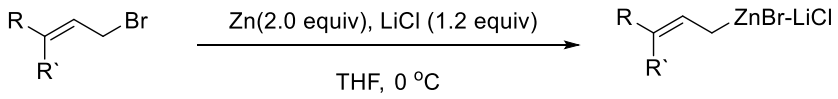
2.2 Preparation of Grignard reagents and Organozinc reagents 1 and 1'



Structures of Grignard Reagents and Organozinc Reagents 1 and 1'

Note: Grignard reagents **1a-1d** in Et_2O were purchased from Energy Chemical.

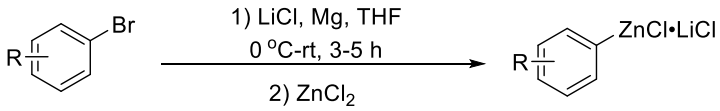
2.2.1 Preparation of allylzinc reagents 1e-1g[3]



To a Schlenk flask were added zinc dust (2.0 equiv) and lithium chloride (1.2 equiv). The flask was then flame-dried under vacuum with a heat gun at 450 °C. Once the flask was cooled down, it was filled with argon and THF (1 mL/mmol allyl halide). The zinc was activated by adding a drop of 1,2-dibromoethane and heating until a slight gas evolution started. Then, the reaction mixture was cooled to 0 °C, and the allyl bromide (1.0 equiv) was added dropwise. The reaction mixture was stirred overnight while slowly warming to room temperature. The remaining zinc dust was removed using a syringe filter, and the concentration of the allylzinc reagent was determined via titration against iodine.

2.2.2 Preparation of Organozinc reagents 1

Method A[4]

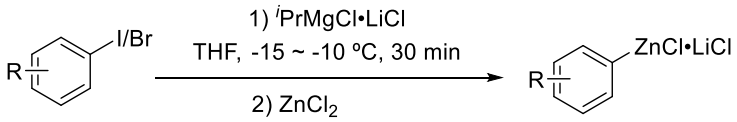


To a dry 100 mL Schlenk flask were added magnesium turnings (3 g, 125 mmol, 2.5 equiv) and LiCl (2.7 g, 62.5 mmol, 1.25 equiv). The flask was evacuated and heated with a heating gun. The flask was evacuated again and backfilled with argon for 3 times. Anhydrous THF (50 mL) was added, and the mixture was stirred vigorously for 5 min at room temperature. DIBAL-H (1.0 M in hexane, 0.5 mL, 0.01 equiv) was added via a syringe, and the mixture was stirred vigorously for 5 min at room temperature. The flask was then cooled to 0 °C with an ice/water bath, and aryl bromide (50 mmol, 1.0 equiv) was added via a syringe. After the reaction was stirred for 10 min, the ice/water bath was removed. The reaction mixture was stirred at room temperature for 3-5 h until the aryl bromide was consumed, as monitored by GC-MS. The resulting solution of Grignard reagent ArMgBr•LiCl was titrated with I_2 according to Knochel's method[4]. Typically, the concentration of the Grignard reagents ranges from 0.3 to 0.5 M in THF. To a separate 100 mL Schlenk tube was added a solution of $ZnCl_2$ (1.0 equiv, 1.0 M in THF) (***Note:*** the loading amount of $ZnCl_2$ depends on the amount of the Grignard reagents used for the reaction). Then, the prepared solution of ArMgBr•LiCl was transferred into the

tube via a syringe with stirring. After stirring for at least 10 min, the solution of ArZnCl•LiCl was titrated with I_2 according to Knochel's method[4]. The Schlenk tube was sealed with a Teflon cap, and the resulting aryl zinc reagents can be stored under argon at room temperature for several weeks.

Note: Organozinc reagents **1h, 1i,** and **1j** were prepared according to **Method A**.

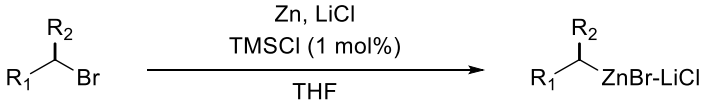
Method B[5]



To a 50 mL Schlenk flask was added a solution of ^{i}PrMgCl·LiCl (1.05 equiv, 1.5 M in THF) under Ar. The flask was cooled to -15 ℃, and a solution of aryl iodide (1.0 equiv, 1.0 M in THF) was added dropwise. After addition, the reaction temperature was warmed to -10 ℃, and the reaction mixture was stirred for 30 min at the same temperature. Then, the resulting Grignard reagent ArMgCl•LiCl was titrated with I_2 according to Knochel's method[4]. To a separate 100 mL Schlenk tube was added $ZnCl_2$ (1.0 equiv, 1.0 M in THF) (***Note:*** the loading amount of $ZnCl_2$ depends on the amount of Grignard reagents used for the reaction). The prepared ArMgBr•LiCl was transferred to the tube via a syringe with stirring. After stirring for at least 10 min, the solution of ArZnCl•LiCl was titrated with I_2 according to Knochel's method. The Schlenk tube was sealed with a Teflon cap, and the resulting aryl zinc reagents can be stored under argon at room temperature for several weeks.

Note: Organozinc reagents **1k, 1'a**, and **1'b** were prepared according to **Method B**.

Method C[6]

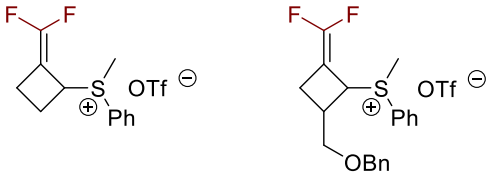


To a dry 100 mL Schlenk flask were added Zinc dust (1.96 g, 30 mmol, 2.0 equiv) and LiCl (1.27 g, 30 mmol, 2.0 equiv). The flask was evacuated and heated with a heating gun. The flask was evacuated again and backfilled with argon for 3 times. Anhydrous THF (30 mL) was added, and the mixture was stirred vigorously for 5 min at room temperature. 1,2-Dibromoethane (65 μL, 0.75 mmol, 5 mol%) was added via a syringe, and the reaction mixture was heated at 60 °C until bubbling occurred. After

the mixture was cooled to room temperature, trimethylsilyl chloride (19 μL, 0.15 mmol, 1 mol%) and iodine (19 mg, 0.075 mmol, 0.25 mol%) were added. The reaction mixture was heated at 60 °C for 20 min and then cooled to room temperature. Alkyl halide (15.0 mmol) was added, and the reaction was stirred at 50 °C for 18 h. The reaction mixture was allowed to stand at room temperature for 1 h, and the supernatant solution was carefully transferred to a dry vessel via cannula. The concentration of the organozinc solution was determined by iodometric titration using Knochel's procedure[4].

Note: Organozinc reagents **1l, 1m**were prepared according to **Method C**.

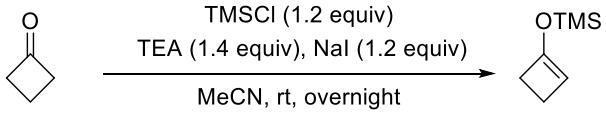
2.3 Preparation of CB-DFASs 3



CB-DFAS 3a **CB-DFAS 3b**

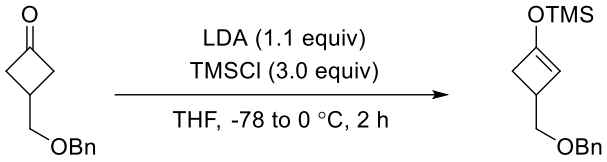
Structures of CB-DFASs

2.3.1 Preparation of compound s-1



s-1a

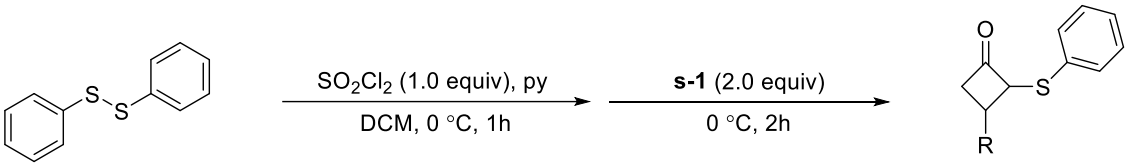
General Procedure: To a solution of NaI (1.2 equiv, 1.0 M in MeCN) was successively added triethylamine (TEA, 1.4 equiv), cyclobutanone (200 mmol, 1.0 equiv), and trimethylchlorosilane (TMSCl, 1.2 equiv) at room temperature. The mixture was stirred overnight and monitored by ^{1}H NMR. Then, the reaction mixture was filtered. The filtrate was extracted with pentane three times. The combined pentane layers were concentrated at room temperature at 200-300 mbar pressure. The resulting solution of **s-1a** (yield ranging from 75% to 79%, concentration 3.6-5.0 M using CH_2Br_2 as an internal standard determined by ^{1}H NMR) was used without further purification. Compound **s-1a** is known.[7] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.58 (s, 1H), 2.66 – 2.54 (m, 2H), 2.06 – 1.88 (m, 2H), 0.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) 148.1, 102.3, 34.0, 19.6, -0.2.



s-1b

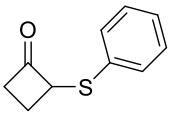
General procedure: To a 500 mL three-necked bottle equipped with a magnetic stir bar, LDA (132 mmol, 1.1 equiv, 1.0 M in THF) was added under Ar. Then, 3-((benzyloxy)methyl)cyclobutan-1-one (20.8 g, in 60 mL THF) was added dropwise at -78 ℃. The reaction mixture was stirred at 78 ℃ for 1 h. Then the mixed solution of TMSCl (45.6 mL, 3.0 equiv), Et_3N (5.82 mL, 0.7 equiv), and 50 mL THF was added dropwise at 0 ℃ and stirred for 30 min. The mixture was stirred for another 10 min at room temperature. Then, the mixture was concentrated directly, and n-pentane was added to precipitate the solid, filtered, and the filtrate was concentrated to give product **s-1b** (35 mL, yield 93%, using CH_2Br_2 as an internal standard determined by ^1H NMR). Compound **s-1b** is known.[8] ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.21 (m, 5H), 4.63 (d, *J* = 0.8 Hz, 1H), 4.49 (s, 2H), 3.49 – 3.34 (m, 2H), 2.71 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.17 (dd, *J* = 13.2, 1.6 Hz, 1H), 0.19 (s, 9H).

2.3.2 Preparation of s-2

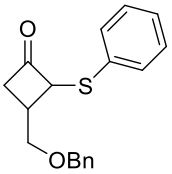


s-2

General procedure: To a 1000 mL three-necked bottle with a magnetic stir bar, 1,2-diphenyldisulfane (100 mmol, 1.0 equiv) and anhydrous DCM (500 mL) were added under Ar. Pyridine (2.0 mL) was added, followed by SO_2Cl_2 dropwise at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 h. Then **s-1** (2.0 equiv) was added slowly. After stirring at the same temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated. The aqueous layer was extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residual oil was purified by reduced-pressure distillation or flash column chromatography.

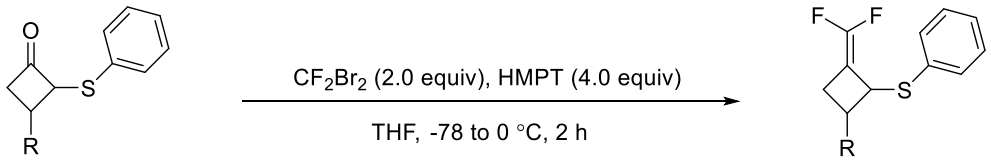


The reaction was conducted on a 150 mmol scale. Compound **s-2a** was purified by reduced pressure distillation (~5 mbar, 140~145 °C) as a light-yellow oil (26.7 g, yield 99%). Compound **s-2a** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.43 (m, 2H), 7.35 – 7.23 (m, 3H), 4.52 – 4.45 (m, 1H), 3.15 – 2.93 (m, 2H), 2.58 – 2.45 (m, 1H), 2.03 – 1.89 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) 205.2, 133.2, 131.6, 128.8, 127.3, 59.2, 44.8, 18.5.



The reaction was conducted on a 73 mmol scale. Compound **s-2b** was purified by flash column chromatography (petroleum ether : ethyl acetate = 20:1) as a light-yellow oil (21 g, 96% yield). Compound **s-2b** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.45 (m, 2H), 7.38 – 7.28 (m, 5H), 7.32 – 7.25 (m, 3H), 4.57 (s, 2H), 4.41 (dt, *J* = 6.8, 2.4 Hz, 1H), 3.74 – 3.63 (m, 2H), 3.08 – 2.90 (m, 2H), 2.61 – 2.50 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 203.8, 137.8, 133.2, 132.3, 129.0, 128.5, 127.8, 127.6, 73.2, 69.9, 60.9, 46.8, 32.8.

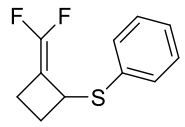
2.3.3 Preparation of s-3



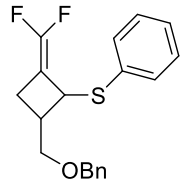
s-2 **s-3**

Procedure: To a 250 mL three-necked flask equipped with a magnetic stir bar and a dropping funnel, anhydrous THF (200 mL) was added under Ar. Then the reaction flask was placed in a dry-ice/ethanol bath. After cooling, CBr_2F_2 (2.0 equiv) was added with a syringe, and HMPT (4.0 equiv) was added dropwise. The resulting mixture was stirred at the same reaction temperature for 1 h. Then, the resulting reaction mixture was warmed to room temperature, and **s-2** (1.0 equiv) was added dropwise. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by H_2O.

The organic layer was separated. The aqueous layer was extracted with pentane twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residual was purified by flash column chromatography to provide **s-3**.

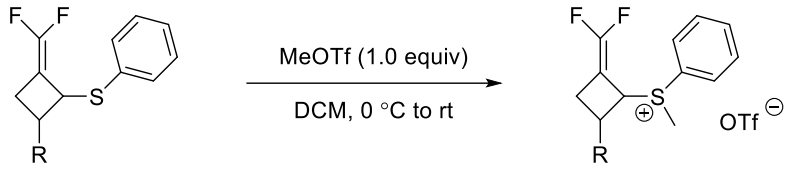


The reaction was conducted on a 155 mmol scale. **s-3a** was purified with silica gel chromatography (100% petroleum ether) as a colorless oil (6.5 g, 20% yield). Compound **s-3a** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 4.48 – 4.38 (m, 1H), 2.76 – 2.61 (m, 1H), 2.63 – 2.54 (m, 2H), 2.17 – 1.96 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -90.85 (dq, *J* = 58.8, 3.4 Hz, 1F), -93.59 (dq, *J* = 58.8, 3.4 Hz, 1F). ^{13}C NMR (126 MHz, Chloroform-*d*) 151.5 (dd, *J* = 290.0, 287.6 Hz), 134.5, 131.1, 128.8, 126.9, 89.5 (dd, *J* = 26.6, 21.4 Hz), 42.1 (d, *J* = 6.4 Hz), 27.4, 20.9 (d, *J* = 4.0 Hz).



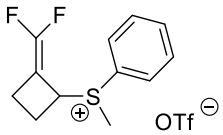
The reaction was conducted on an 80 mmol scale. **s-3b** was purified with silica gel chromatography (petroleum ether : ethyl acetate = 10:1) as a colorless oil (5.2 g, 20% yield, dr = 4:1). Compound **s-3b** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ 7.45 – 7.14 (m, 10H), 4.69 – 4.59 (m, 0.8H), 4.52 – 4.39 (m, 2H), 4.26 – 4.19 (m, 0.2H), 3.83 – 3.58 (m, 1.6H), 3.49 (d, J = 5.3 Hz, 0.4H), 3.11 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ -89.44 (dq, *J* = 57.3, 3.8 Hz, 0.8F), -90.16 (dq, *J* = 58.3, 3.5 Hz, 0.8F), -92.18 (dq, *J* = 57.3, 3.9 Hz, 0.2F), -92.57 (dq, *J* = 58.1, 3.4 Hz, 0.2F). ^{13}C NMR (126 MHz, Chloroform-*d*) 152.1 (dd, *J* = 290.4, 287.1 Hz), 138.1, 136.5, 132.0, 129.4, 128.8, 128.3, 127.8, 127.6, 126.2, 87.8 (dd, J = 27.4, 20.4 Hz), 73.3, 70.7, 45.8 (d, *J* = 6.2 Hz), 37.0, 25.7 (d, *J* = 3.6 Hz).

2.3.4 Preparation of CB-DFASs

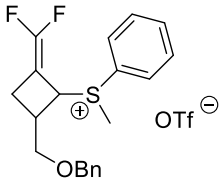


s-3 **CB-DFASs**

To a 50 mL round-bottom flask equipped with a magnetic stir bar, **s-3** (1.0 equiv) and DCM (10 mL, 0.5 M) were added. MeOTf (1.0 equiv) was added dropwise at 0 ℃. The reaction mixture was stirred at room temperature overnight. The solvent was removed. Ethyl ether (10 mL) was added and stirred intensely. After standing, the mixture was layered, and the upper solution was aspirated out with a syringe. Repeating the above steps twice, the residual solvent was removed to afford the desired product.



The reaction was conducted on a 30 mmol scale. CB-DFAS **3a** (8.4 g, yield 75%, purity 97% w/w, dr = 1.27:1) was obtained as a brown viscous liquid. For convenience, **CB-DFAS 3a** was prepared as a solution of DCM (concentration 1.85 M determined by ^{19}F NMR using PhF as an internal standard). Compound **3a** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ 7.97 (d, J = 7.6 Hz, 2 H), 7.77 – 7.70 (m, 1 H), 7.67 – 7.59 (m, 2 H), 5.54 – 5.22 (m, 1 H), 3.32 (s, 1.67 H), 3.29 (s, 1.33 H), 2.94 –2.70 (m, 1 H), 2.70 – 2.51 (m, 2 H), 2.49 – 2.37 (m, 0.5 H), 2.22 – 2.08 (m, 0.5 H). ^{19}F NMR (376 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ -78.58 (s, 3F), -82.74 (d, *J* = 42.4 Hz, 0.56 F), -83.23 – -83.83 (m, 0.44 F), 85.66 (d, *J* = 39.1 Hz, 0.44 F), -85.95 – -86.45 (m, 0.56 F). ^{13}C NMR (126 MHz, Chloroform-*d*) (***note***: the number in the parenthesis is the other diastereoisomer) δ 152.9 (t, *J* = 293.6 Hz) (153.2, *J* = 294.3 Hz), 135.0 (135.1), 131.2 (131.04), 130.9 (130.97), 120.8 (122.0), 120.4 (q, *J* = 320.0 Hz), 83.6 (dd, *J* = 33.5, 21.6 Hz) (83.2, *J* = 34.1 Hz, 20.9 Hz), 53.8 (d, *J* = 8.0 Hz) (55.1, *J* = 8.5 Hz), 24.3 (d, *J* = 3.2 Hz) (24.1), 22.0 (22.8), 21.2 (d, *J* = 2.9 Hz) (21.6, *J* = 2.7 Hz).

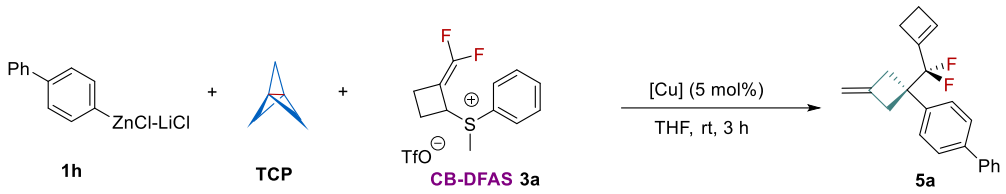


The reaction was conducted on a 15 mmol scale. CB-DFAS **3b** (6.2 g, yield 83%, purity 98% w/w, dr = 1:1:2.21:2.93) as a brown viscous liquid. For convenience, **CB-DFAS 3b** was prepared as a solution of DCM (concentration 1.3 M determined by ^{19}F NMR using PhF as an internal standard). Compound **3b** is known.[9] ^{1}H NMR (400 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ 8.03 – 7.97 (m, 1H), 7.94 – 7.87 (m, 1H), 7.75 – 7.54 (m, 3H), 7.40 – 7.22 (m, 5H), 5.77 – 5.71 (m, 0.14H), 5.68 – 5.63 (m, 0.14H), 5.28 – 5.22 (m, 0.41H), 5.19 – 5.13 (m, 0.31H), 4.68 – 4.20 (m, 2H), 3.89 – 3.61 (m, 1H), 3.42 – 3.35 (m, 1H), 3.34 (s, 1H), 3.29 (s, 1H), 3.27 (s, 1H), 3.21 – 2.36 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ -78.39 (s, 3F), -81.03 – -81.21 (m, 0.14F), -81.71 (dq, *J* = 43.3, 3.9 Hz, 0.41F), -82.03 (dq, *J* = 38.4, 4.4, 4.0 Hz, 0.31F), 83.03 (ddt, *J* = 37.1, 5.3, 2.6 Hz, 0.14F), -84.62 (dq, *J* = 38.6, 3.8 Hz, 0.31F), -84.80 – -85.06 (m, 0.28F), -85.58 (dq, *J* = 42.7, 3.6 Hz, 0.41F). ^{13}C NMR (126 MHz, Chloroform-*d*) (diastereoisomer mixtures) δ major: 153.0 (t, *J* = 293.2 Hz), 137.1, 134.8, 130.8, 128.4, 128.1, 127.8, 127.5, 120.4 (q, *J* = 320.2 Hz), 120.2, 81.6 (dd, *J* = 33.8, 21.6 Hz), 72.9, 69.1, 55.3 (d, *J* = 7.4 Hz), 35.9, 24.1 (d, *J* = 3.4 Hz), 23.3 (d, *J* = 2.8 Hz).

3. Optimizations of the Selective Synthesis of CyBu 5a from TCP

General Procedure: To a 25 mL Schlenk tube, copper catalyst was added in the air. The tube was evacuated and backfilled with Ar (3 times). Subsequently, 1.0 mL THF was added to the tube. Then, organic zinc reagent **1** was added in one portion, followed by the addition of a solution of TCP in diethyl ether (0.6-1.2 M) at 25 °C under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. A solution of CB-DFAS **3a** in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. Then, the reaction yield was determined by ^{19}F-NMR using fluorobenzene as an internal standard.

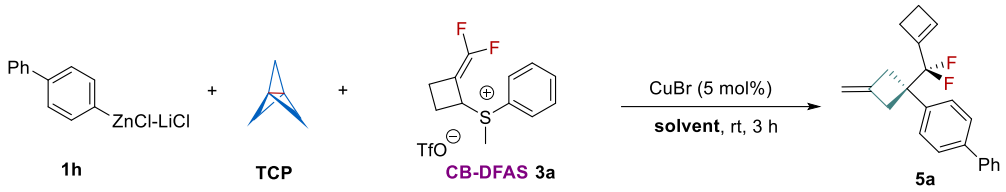
Table 1. Screening of the Copper Catalysts for the Synthesis of 5a[a]



Entry	[Cu]	Yield [%][b]
		5a
1	CuBr	99
2	CuI	58
3	CuCl	52
4	CuCN	54
5	none	10

[a]Reaction conditions (unless otherwise specified): **1h** (0.24 mmol, 1.2 equiv), TCP (0.3 mmol, 1.5 equiv), **3a** (0.2 mmol, 1.0 equiv), [Cu] (5 mol%), THF (2.5 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

Table 2. Screening of the Solvents for the Synthesis of 5a[a]

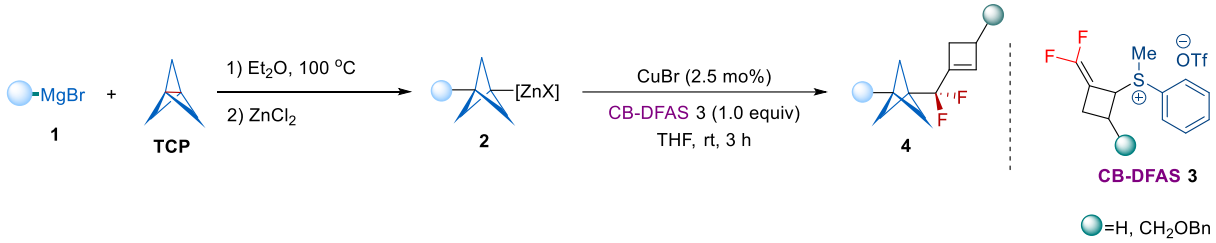


Entry	Solvent	Yield [%][b]
		5a
1	THF	99
2	1,4-Dioxane	93
3	DCM	98
4	MeCN	94
5	DMA	96
6	DMF	99

[a]Reaction conditions (unless otherwise specified): **1h** (0.24 mmol, 1.2 equiv), TCP (0.3 mmol, 1.5 equiv), **3a** (0.2 mmol, 1.0 equiv), CuBr (5 mol%), solvent (2.5 mL). [b]Determined by ^{19}F-NMR using fluorobenzene as an internal standard.

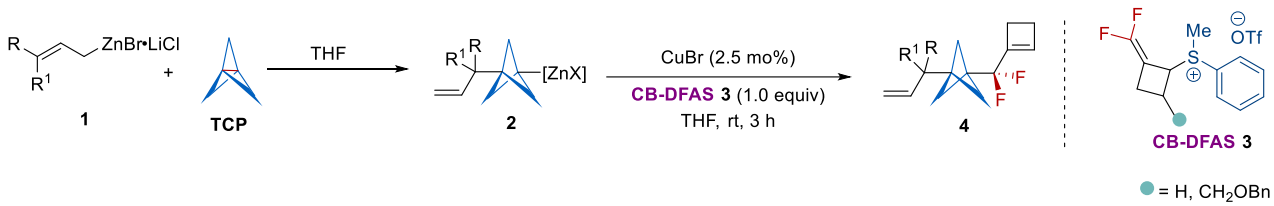
4. General Procedure for the Synthesis of 4 via Copper Catalysis

Procedure I: General procedure for the synthesis of 4 using Grignard reagents.



To a 25 mL sealed tube, aryl magnesium bromide (1.0-2.25 M in Et_2O/THF, 0.60 mmol, 1.5 equiv) and TCP (1.2 mmol, 3.0 equiv, 0.6-1.2 M in Et_2O) were added at room temperature under Ar. The tube was sealed, and the resulting solution was heated to 100 °C and stirred for 2 h. The reaction was then cooled to room temperature, and the solvent was removed under vacuum until the reaction mixture become viscous liquid. A solution of $ZnCl_2$ (0.8 mmol, 2.0 equiv, 1.0 M in THF) was added to generate BCP-zinc reagent **2**, which was used directly for the next step. To another 25 mL Schlenk tube, CuBr (2.5 mol%) was added in the air. The tube was evacuated and backfilled with Ar (3 times). Subsequently, CB-DFAS **3** (0.4 mmol, 1.0 equiv) and anhydrous THF (1.5 mL) were added to the tube. Then, BCP-zinc reagent **2** was added dropwise to the reaction mixture at room temperature. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated NH_4Cl and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford product **4**.

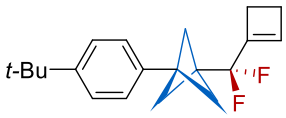
Procedure II: General procedure for the synthesis of 4 using allylzinc reagents.



To a 25 mL Schlenk tube was added a solution of allylzinc reagent in THF (0.75 mmol, 1.5 equiv), followed by TCP (0.75 mmol, 1.5 equiv, in Et_2O). The tube was screw-capped and stirred at (25 °C or 50 °C). (***Note:*** for the stirring time, see the details in Section 5). Following this, the reaction mixture was cooled to room temperature, and excessive TCP was removed under vacuum to afford a solution

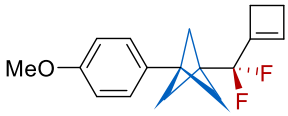
of BCP-zinc reagent **2** in THF, which was used directly for the next step. To another 25 mL Schlenk tube, CuBr (2.5 mol%) was added in the air. The tube was evacuated and backfilled with Ar (3 times). Subsequently, CB-DFAS **3** (0.5 mmol, 1.0 equiv) and anhydrous THF (1.5 mL) were added to the tube. Then, the solution of BCP-zinc reagent **2** was diluted with THF (1 mL) and added dropwise to the reaction mixture at room temperature. The tube was screw-capped, and the reaction was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated NH_4Cl and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford product **4**.

5. Characterization Data for Compounds 4



1-(4-(*tert*-Butyl)phenyl)-3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentane (4a)

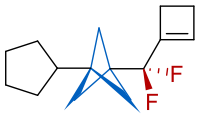
Compound **4a** was prepared according to **Procedure I**. The reaction was conducted on a 0.4 mmol scale. The product (91 mg, 75% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.27-6.25 (m, 1H), 2.75 – 2.68 (m, 2H), 2.56 – 2.46 (m, 2H), 2.19 (s, 6H), 1.36 (s, 9H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.89 -104.91(d, *J* = 1.5 Hz, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.0, 141.8 (t, *J* = 31.8 Hz), 137.0, 135.1 (t, *J* = 9.0 Hz), 125.9, 125.3, 115.0 (t, *J* = 235.5 Hz), 50.7 (t, *J* = 2.6 Hz), 41.6, 39.2 (t, *J* = 34.9 Hz), 34.6, 31.5, 29.3 (t, *J* = 3.4 Hz), 27.4. MS (FI): m/z (%) 302 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{20}H_{24}F_2$: 302.1841; Found: 302.1846.



1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(4-methoxyphenyl)bicyclo[1.1.1]pentane (4b)

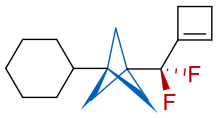
Compound **4b** was prepared according to **Procedure I**. The reaction was conducted on a 0.4 mmol scale. The product (82 mg, 74% yield) was purified with silica gel chromatography (petroleum ether)

as a yellow liquid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.30-6.17 (m, 1H), 3.81 (s, 3H), 2.72 – 2.67 (m, 2H), 2.54 – 2.46 (m, 2H), 2.15 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.91 (s, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.7, 141.8 (t, *J* = 31.8 Hz), 135.0 (t, *J* = 9.0 Hz), 132.3, 127.3, 115.9 (t, *J* = 235.5 Hz), 113.8, 55.4, 50.7, 41.4, 39.0 (t, *J* = 34.9 Hz), 29.3 (t, *J* = 3.4 Hz), 27.4 (t, *J* = 2.3 Hz). MS (FI): m/z (%) 276 ([M]$^{+}$). HRMS (FI) m/z: ([M]$^{+}$) Calculated for $C_{17}H_{18}F_2O$: 276.1320; Found: 276.1322.



1-(Cyclobut-1-en-1-yldifluoromethyl)-3-cyclopentylbicyclo[1.1.1]pentane (4c)

Compound **4c** was prepared according to **Procedure I**. The reaction was conducted on a 0.4 mmol scale. The product (41 mg, 43% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.18-6.13 (m, 1H), 2.65 – 2.60 (m, 2H), 2.50 – 2.41 (m, 2H), 2.02 – 1.90 (m, 1H), 1.68 (s, 6H), 1.64 – 1.48 (m, 6H), 1.30 – 1.20 (m, 2H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.2 (d, *J* = 1.9 Hz, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.0 (t, *J* = 31.9 Hz), 134.7 (t, *J* = 9.0 Hz), 115.1 (t, *J* = 235.5 Hz), 47.2 (t, *J* = 3.0 Hz), 42.8 (t, *J* = 1.6 Hz), 40.2, 39.6 (t, *J* = 34.5 Hz), 29.3 (t, *J* = 3.7 Hz), 29.1, 27.3 (t, *J* = 2.0 Hz), 25.8. MS (FI): m/z (%) 238 ([M]$^{+}$). HRMS (FI) m/z: ([M]$^{+}$) Calculated for $C_{15}H_{20}F_2$: 238.1528; Found: 238.1526.



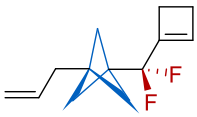
1-(Cyclobut-1-en-1-yldifluoromethyl)-3-cyclohexylbicyclo[1.1.1]pentane (4d)

Compound **4d** was prepared according to **Procedure I**. The reaction was conducted on a 0.4 mmol scale. The product (46 mg, 45% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.17-6.13 (m, 1H), 2.69 – 2.56 (m, 2H), 2.52 – 2.39 (m, 2H), 1.77 – 0.76 (m, 17H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.1 (d, *J* =1.9 Hz, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.04 (t, *J* = 32 Hz), 134.66 (t, *J* = 9.1 Hz), 115.13 (t, *J* = 235.5 Hz), 46.53 (t, *J* = 3.0 Hz), 43.85 (t, *J* = 1.5 Hz), 38.98 (t, *J* = 34.4 Hz), 37.95, 29.30 (t, *J* = 3.5 Hz),

29.27, 27.31 (t, *J* = 1.8 Hz), 26.34, 26.12. MS (FI): m/z (%) 252 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{16}H_{22}F_2$: 252.168; Found: 252.1678.

1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(cyclohex-2-en-1-yl)bicyclo[1.1.1]pentane (4e)

Compound **4e** was prepared according to **Procedure II** on a 0.5 mmol scale. The corresponding BCP-zinc reagent **2f** was obtained after the reaction mixture was stirred at 50 ºC for 5 h. The product (120 mg, 96% yield) was purified with silica gel chromatography (petroleum ether) as a colourless liquid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.17-6.14 (m, 1H), 5.77 – 5.71 (m, 1H), 5.56 – 5.48 (m, 1H), 2.65 – 2.60 (m, 1H), 2.48 – 2.41 (m, 1H), 2.20 (m, 1H), 1.99 – 1.20 (m, 12H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.2(s, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.0 (t, *J* = 32 Hz), 134.7 (t, *J* = 9.1 Hz), 128.3, 127.6, 115.0 (t, *J* = 235.6 Hz), 46.9 (t, *J* = 3.0 Hz), 42.8, 39.7 (t, *J* = 34.6 Hz), 36.1, 29.3 (t, *J* = 3.5 Hz), 27.3 (t, *J* = 2.0 Hz), 25.6, 25.1, 21.3. MS (FI): m/z (%) 250 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{16}H_{20}F_2$: 250.1528; Found: 250.1531.



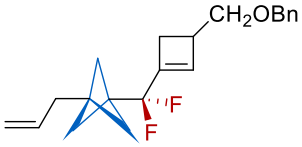
1-Allyl-3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentane (4f)

Compound **4f** was prepared according to **Procedure II.** 1.5 equiv of **1e** (0.75 mmol) and 1.5 equiv of TCP (0.75 mmol, in Et_2O) were used. The corresponding BCP-zinc reagent **2e** was obtained after the reaction mixture was stirred for 2 h at rt. Then, CB-DFAS **3a** (0.5 mmol, 1.0 equiv) was used. The product (100 mg, 95% yield) was purified with silica gel chromatography (petroleum ether) as a colourless liquid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.17-6.14 (m, 1H), 5.78 – 5.61 (m, 1H), 5.05 – 5.02 (m, 1H), 5.02 – 4.98 (m, 1H), 2.66 – 2.59 (m, 2H), 2.50 – 2.43 (m, 2H), 2.26 (d, *J* = 7.2 Hz, 2H), 1.74 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.1 (d, *J* = 1.5 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.9 (t, *J* = 31.9 Hz), 134.9, 134.8 (t, *J* = 9.1 Hz), 116.5, 114.8 (t, *J* = 235.5 Hz), 48.6 (t, *J* = 3.2 Hz), 40.4 (t, *J* = 34.5 Hz), 39.0 (t, *J* = 1.9 Hz), 36.6, 29.3 (t, *J* = 3.5 Hz), 27.3 (t, *J* = 1.9

Hz). MS (FI): m/z (%) 210 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{13}H_{16}F_2$: 210.1215; Found: 210.1209.

2-mmol-Scale Synthesis of Compound 4f.

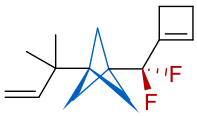
To a 50 mL Schlenk tube was added a solution of allylzinc reagent in THF (3.0 mmol, 1.5 equiv), followed by TCP (3 mmol, 1.5 equiv, in Et_2O). The tube was screw-capped and stirred for 2 h at room temperature. Then, excessive TCP was removed under vacuum to afford a solution of BCP-zinc reagent **2e** in THF, which was used directly for the next step. To another 50 mL Schlenk tube, CuBr (2.5 mol%) was added in Ar. The tube was evacuated and backfilled with Ar (3 times). Subsequently, CB-DFAS **3** (2.0 mmol, 1.0 equiv) and anhydrous THF (8.0 mL) were added to the tube. Then, the solution of BCP-zinc reagent **2e** was diluted with THF (4 mL) and added dropwise to the reaction mixture at room temperature. The tube was screw-capped, and the reaction was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated NH_4Cl and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with silica gel chromatography (petroleum ether) as a colourless liquid (312 mg, 74% isolated yield).



1-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)-3-(2-methylbut-3-en-2-yl)bicyclo-[1.1.1]pentane (4g)

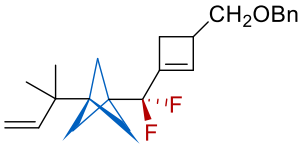
Compound **4g** was prepared according to **Procedure II** on a 0.5 mmol scale. The corresponding BCP-zinc reagent **2e** was obtained after the reaction mixture was stirred for 2 h at rt. The product (136 mg, 82% yield) was purified with silica gel chromatography (petroleum ether) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 6.33-6.14 (m, 1H), 5.77 – 5.62 (m, 1H), 5.09 – 4.97 (m, 2H), 4.53 (s, 2H), 3.52 (d, *J* = 6.8 Hz, 2H), 3.01 (d, *J* = 7.6 Hz, 1H), 2.78 – 2.66 (m, 1H), 2.25 (dd, *J* = 1.6, 10 Hz, 3H), 1.72 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.72 (d, *J* = 12.0 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.10 (t, *J* = 32.3 Hz), 138.48, 136.16 (t, *J* = 8.6 Hz), 134.84, 128.55, 127.81, 127.79, 116.54, 114.93 (t, *J* = 236 Hz), 73.34, 73.16, 48.62 (t, *J* = 3.0 Hz),

40.34 (t, *J* = 34.5 Hz), 39.76, 39.07, 36.55, 32.81. MS (DART): m/z (%) 348.2 ($[M+NH_4]^+$). HRMS (DART) m/z: ($[M+NH_4]^+$) Calculated for $C_{21}H_{24}F_2O$: 348.2133; Found: 348.2133.



1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(2-methylbut-3-en-2-yl)bicyclo[1.1.1]pentane (4h)

Compound **4h** was prepared according to **Procedure II** on a 0.5 mmol scale. The corresponding BCP-zinc reagent **2g** was obtained after the reaction mixture was stirred at 50 ºC for 10 h. The product (109 mg, 91% yield) was purified with silica gel chromatography (petroleum ether) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.28-6.07 (m, 1H), 5.76 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.02 – 4.88 (m, 2H), 2.66 – 2.60 (m, 2H), 2.48 – 2.41 (m, 2H), 1.67 (s, 6H), 0.96 (s, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.3 (s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.7, 142.0 (t, *J* = 32 Hz), 134.7 (t, *J* = 9.0 Hz), 115.2 (t, *J* = 235.7 Hz), 111.6, , 46.7, 45.4 (t, *J* = 3.0 Hz), 38.4 (t, *J* = 34.7 Hz), 36.0, 29.3 (t, *J* = 3.7 Hz), 27.3 (t, *J* = 1.8 Hz), 22.9. MS (FI): m/z (%) 238 ($[M]^+$). HRMS (FI) m/z: ($[M]^+$) Calculated for $C_{15}H_{20}F_2$: 238.1528; Found: 238.1529.

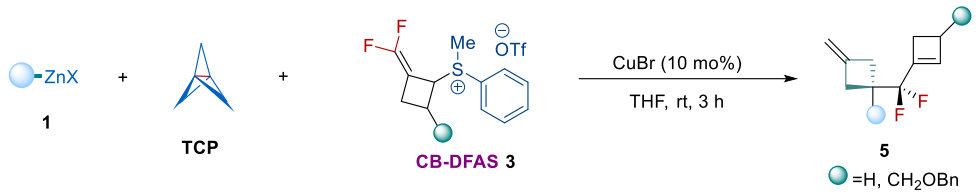


1-Allyl-3-((3-((benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)bicyclo[1.1.1]pentane (4i)

Compound **4i** was prepared according to **Procedure II** on a 0.5 mmol scale. The corresponding BCP-zinc reagent **2g** was obtained after the reaction mixture was stirred at 50 ºC for 10 h. The product (146 mg, 81% yield) was purified with silica gel chromatography (petroleum ether) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 5H), 6.25-6.21 (m, 1H), 5.75 (dd, *J* = 17.6, 11.2 Hz, 1H), 4.97 (d, *J* = 2.8 Hz, 1H), 4.94 (d, *J* = 9.6 Hz, 1H), 4.53 (s, 2H), 3.52 (d, *J* = 6.4 Hz, 2H), 3.10 – 2.95 (m, 1H), 2.79 – 2.70 (m, 1H), 2.32 – 2.19 (m, 1H), 1.65 (s, 6H), 0.95 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.8 (d, *J* = 19.2 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.69, 142.12 (t, *J* = 32.3 Hz), 138.48, 136.17 (t, *J* = 8.7 Hz), 128.55, 127.80, 115.29 (t, *J* = 236.4 Hz), 111.62, 73.33, 73.16, 46.71, 45.42 (t, *J* = 2.8 Hz), 39.75, 38.34 (t, *J* = 34.7 Hz), 35.99, 32.79 (t, *J* = 3.3 Hz),

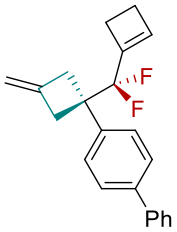
22.96. MS (DART): m/z (%) 376.2 ([M+NH_4]$^+$). HRMS (DART) m/z: ([M+NH_4]$^+$) Calculated for $C_{23}H_{28}F_2O$: 376.2446; Found: 376.2446.

6. General Procedure for the Synthesis of 5 from TCP via Copper Catalysis



To a 25 mL Schlenk tube, CuBr (10 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (1.0 mL) was added. Then, organic zinc reagent **1** (1.2 equiv) was added in one portion, followed by the addition of a solution of TCP (1.5 equiv) in diethyl ether (0.6-1.2 M) at 25 ^oC under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. Subsequently, a solution of CB-DFAS **3** (1.0 equiv) in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the product.

7. Characterization Data for Compounds 5



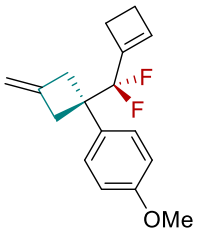
4-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-1,1'-biphenyl (5a)

The reaction was conducted on a 0.5 mmol scale. Compound **5a** (152 mg, 94% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 3H), 6.09-6.04 (m, 1H), 4.86 (t, 2H), 3.50 – 3.42 (m, 2H), 3.19 – 3.11 (m, 2H), 2.40 – 2.37 (m, 2H),

2.37 – 2.31 (m, 2H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.0(s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.5, 141.6 (t, *J* = 32.1 Hz), 140.8, 140.6 (t, *J* = 2.5 Hz), 139.9, 136.0 (t, *J* = 9.1 Hz), 129.0, 128.9, 127.5, 127.2, 126.6, 119.6 (t, *J* = 244.2 Hz), 107.2, 47.6 (t, *J* = 26 Hz), 39.5 (t, *J* = 4.4 Hz), 30.7 (t, *J* = 4.0 Hz), 27.1 (t, *J* = 1.9 Hz). MS (FI): m/z (%) 322 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{22}H_{20}F_2$: 322.1528; Found: 322.1533.

Using 3.0 equiv of TCP to react with arylzinc 1h and 3.

To a 25 mL Schlenk tube, CuBr (10 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (1.0 mL) was added. Then, organic zinc reagent **1h** (1.2 equiv, 0.28 M in THF) was added in one portion, followed by the addition of a solution of TCP (3.0 equiv, 0.98 M in diethyl ether) at 25 °C under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. Subsequently, a solution of CB-DFAS **3** (0.3 mmol, 1.0 equiv, 1.44 M in DCM) in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The yield (79%) was determined by ^{19}F NMR using 4-fluorotoluene as the internal standard.

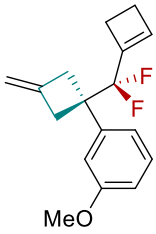


1-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-4-methoxybenzene (5b)

The reaction was conducted on a 0.5 mmol scale. Compound **5b** (107 mg, 77% yield) was purified with silica gel chromatography (petroleum ether) as a light-yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.99-5.95 m, 1H), 4.83 (p, *J* = 1.6 Hz, 2H), 3.81 (s, 3H), 3.45 – 3.34 (m, 2H), 3.09 – 3.00 (m, 2H), 2.36 – 2.29 (m, 4H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.3(s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.6, 142.7, 141.8 (t, *J* = 32.1 Hz), 135.7 (t, *J* = 9.1 Hz), 133.5, 129.68, 119.7 (t, *J* = 243.9 Hz), 113.2, 107.1, 55.4, 47.2 (t, *J* = 25.8 Hz), 39.4 (t, *J* = 4.5 Hz), 30.5 (t, *J* = 4.2 Hz), 27.1 (t, *J* = 1.8 Hz). MS (FI): m/z (%) 276 ([M]$^+$). HRMS (FI) m/z: ([M]$^+$) Calculated for $C_{17}H_{18}F_2O$: 276.1320; Found: 276.1322.

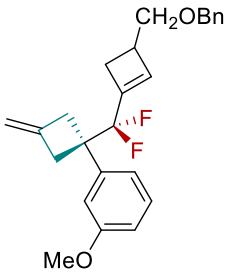
2-mmol-Scale Synthesis of Compound 5b.

To a 50 mL Schlenk tube, CuBr (20 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (10 mL) was added. Then, organic zinc reagent **1i** (1.2 equiv) was added in one portion, followed by the addition of a solution of TCP (1.5 equiv) in diethyl ether (1.1 M) at 0 °C under Ar. The reaction mixture was stirred for 10 min at 0 °C. A solution of allyl sulfonium salt **3a** (2 mmol, 1.0 equiv) in THF (15 mL) was added dropwise for 30 minutes via a syringe pump. The resulting reaction mixture was stirred for 3 h at 0 °C. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×30 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with silica gel chromatography (petroleum ether) as a light-yellow liquid (375 mg, 68% isolated yield).



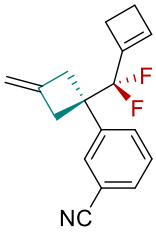
1-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-3-methoxybenzene (5c)

The reaction was conducted on a 0.3 mmol scale. Compound **5c** (73 mg, 88% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.22 (m, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.05-6.01 (m, 1H), 4.91 – 4.75 (m, 2H), 3.81 (s, 3H), 3.46 – 3.36 (m, 2H), 3.11 (m, 2H), 2.39 – 2.25 (m, 4H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.2 (s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.2, 143.2, 142.5, 141.6 (t, *J* = 32.1 Hz), 135.8 (t, *J* = 8.9 Hz), 128.7, 121.0, 119.5 (t, *J* = 244.2 Hz), 114.9, 112.1, 107.0, 55.3, 47.9 (t, *J* = 25.8 Hz), 39.4 (t, *J* = 4.5 Hz), 30.6 (t, *J* = 4.0 Hz), 27.1. MS (DART): m/z (%) 294.2 ($[M+NH_4]^+$). HRMS (DART) m/z: ($[M+NH_4]^+$) Calculated for $C_{17}H_{18}F_2O$: 294.1664; Found: 294.1664.



1-(1-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)-3-methylenecyclobutyl)-3-methoxybenzene (5d)

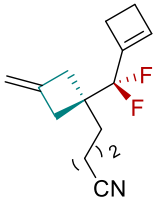
The reaction was conducted on a 0.3 mmol scale. Compound **5d** (110 mg, 92% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 5H), 7.18 (t, *J* = 8 Hz, 1H), 6.87 – 6.72 (m, 3H), 6.08-6.05 (m, 1H), 4.82 (s, 2H), 4.49 (s, 2H), 3.79 (s, 3H), 3.46 – 3.34 (m, 4H), 3.08 (d, *J* = 16.0 Hz, 2H), 2.88 (d, *J* = 6.4 Hz, 1H), 2.49 – 2.43 (m, 1H), 1.96 (d, *J* = 13.2 Hz, 1H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.7 (d, *J* = 15.4 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.2, 143.0 (t, *J* = 2.3 Hz), 142.4, 142.0 (t, *J* = 32.3 Hz), 138.5, 137.1 (t, *J* = 8.4 Hz), 128.8, 128.5, 127.8, 121.1, 119.6 (t, *J* = 244.7 Hz), 115.0, 112.1, 107.2, 73.3, 72.8, 58.6, 55.3, 47.8 (t, *J* = 25.7 Hz), 39.6, 39.4 (q, *J* = 4.3 Hz), 34.1 (t, *J* = 3.7 Hz), 18.6. MS (ESI Positive Ion Mode): m/z (%) 414.2 ($[M+NH_4]^+$). HRMS (ESI Positive Ion Mode) m/z: ($[M+NH_4]^+$) Calculated for $C_{25}H_{26}F_2O_2$: 414.2239; Found: 414.2236.



1-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)benzonitrile (5e)

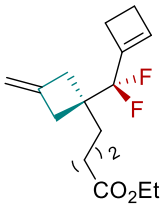
The reaction was conducted on a 0.3 mmol scale. Compound **5e** (34 mg, 42% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.59 – 7.55 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 6.02-5.99 (m, 1H), 4.87 (t, *J* = 7.5 Hz, 2H), 3.47 – 3.40 (m, 2H), 3.06 (d, *J* = 16.5 Hz, 2H), 2.43 – 2.30 (m, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.1(s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.2 (t, *J* = 2.5 Hz), 141.1, 140.8 (t, *J* = 31.8 Hz), 136.9 (t, *J* = 9.1 Hz), 133.1, 132.3, 130.8, 128.8, 119.9 (t, *J* = 245.7 Hz), 112.2,

107.9, 47.8 (t, *J* = 26.3 Hz), 39.4 (t, *J* = 4.3 Hz), 30.6 (t, *J* = 4.0 Hz), 27.2(t, *J* = 1.8 Hz). MS (DART): m/z (%) 289.2 ($[M+NH_4]^+$). HRMS (DART) m/z: ($[M+NH_4]^+$) Calculated for $C_{17}H_{15}F_2N$: 289.1511; Found: 289.1511.



4-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)butanenitrile (5f)

The reaction was conducted on a 0.3 mmol scale. Compound **5f** (38 mg, 53% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.23-6.19 (m, 1H), 4.86 (t, *J* = 2.5 Hz, 2H), 3.08 – 2.99 (m, 2H), 2.63 (s, 2H), 2.52 – 2.45 (m, 2H), 2.40 (d, *J* = 16.5 Hz, 2H), 2.35 (t, *J* = 6.0 Hz, 2H), 1.78 (s, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -106.7(s, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.2, 141.2 (t, *J* = 31.5 Hz), 135.9 (t, *J* = 9.1 Hz), 120.2 (t, *J* = 240.7 Hz), 119.5, 108.67, 42.0 (t, *J* = 25.5 Hz), 36.7 (t, *J* = 4.5 Hz), 34.6 (t, *J* = 2.4 Hz), 29.9 (t, *J* = 4.0 Hz), 27.4 (t, *J* = 1.9 Hz), 21.0 (t, *J* = 2.0 Hz), 18.0. MS (DART): m/z (%) 255.2 ($[M+NH_4]^+$). HRMS (DART) m/z: ($[M+NH_4]^+$) Calculated for $C_{14}H_{17}F_2N$: 255.1667; Found: 255.1667.

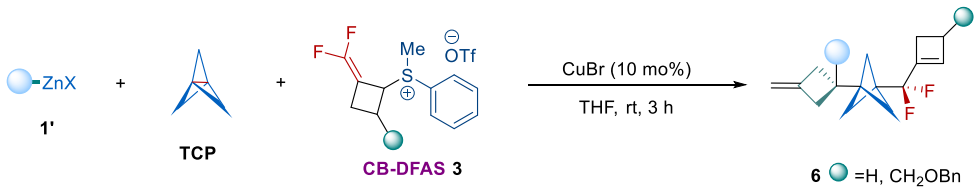


Ethyl 4-(1-(cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)butanoate (5g)

The reaction was conducted on a 0.3 mmol scale. Compound **5g** (50 mg, 58% yield) was purified with silica gel chromatography (petroleum ether) as a yellow liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.19-6.16 (m, 1H), 4.83 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.98 (d, *J* = 16.5 Hz, 2H), 2.61 (s, 2H), 2.50 – 2.38 (m, 4H), 2.29 (t, *J* = 6.5 Hz, 2H), 1.77 – 1.67 (m, 2H), 1.67 – 1.58 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.0(s, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.5, 143.0, 141.6 (t, *J* = 31.6 Hz), 135.4 (t, *J* = 9.1 Hz), 120.5 (t, *J* = 240.5 Hz), 108.1, 60.4, 42.2 (t, *J* =

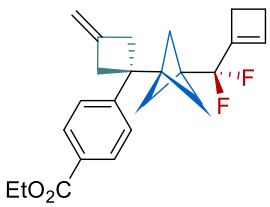
25.1 Hz), 36.4 (t, J = 4.8 Hz), 35.0, 34.7 ((t, J = 2.4 Hz), 30.0 (t, J = 4.0 Hz), 27.4 (t, J = 1.9 Hz), 20.2, 14.4. MS (DART): m/z (%) 302.2 ($[M+NH_4]^+$). HRMS (DART) m/z: ($[M+NH_4]^+$) Calculated for $C_{16}H_{22}F_2O_2$: 302.1926; Found: 302.1926.

8. General Procedure for the Synthesis of Compounds 6



To a 25 mL Schlenk tube, CuBr (10 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (1.0 mL) was added to the tube, followed by the organic zinc reagent **1'** (1.2 equiv). Then, a solution of TCP (3.0 equiv) in diethyl ether (0.6-1.2 M) was added at 25 °C under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. A solution of CB-DFAS **3** (1.0 equiv) in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The aqueous phase was extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified with flash chromatography to afford the product.

9. Characterization Data for Compounds 6



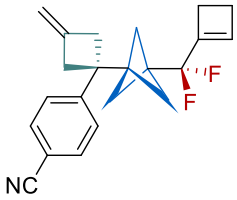
Ethyl4-(1-(3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclo-butyl)benzoate (6a)

The reaction was conducted on a 0.3 mmol scale, and 3.0 equiv of TCP was used. Compound **6a** (99 mg, 86% yield) was purified with FP ECOFLEX C18 (20 g) (MeCN: H_2O = 7:3) as a yellow oil.^1H

NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.11-6.08 (m, 1H), 4.84 (t, *J* = 2 Hz, 2H), 4.37 (q, *J* =7.0 Hz, 2H), 2.99 (s, 4H), 2.61 – 2.53 (m, 2H), 2.44 – 2.34 (m, 2H), 1.63 (s, 6H), 1.39 (t, *J* = 7.0 Hz, 3H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.4 (d, *J* =2.0 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.6, 151.0, 143.1, 141.6 (t, *J* = 31.8 Hz), 134.8 (t, *J* = 9.1 Hz), 129.4, 128.3, 126.3, 115.0 (t, *J* = 236.0 Hz), 107.2, 61.0, 46.0, 45.5 (t, *J* = 2.8 Hz), 42.2, 39.8, 39.1 (t, *J* = 35.0 Hz), 29.2 (t, *J* = 3.4 Hz), 27.2, 14.5. MS (DART): m/z (%) 385.2 ([M+H]$^+$). HRMS (DART) m/z: ([M+H]$^+$) Calculated for $C_{24}H_{26}F_2O_2$: 385.1974; Found: 385.1972 .

Using 1.5 equiv of TCP to react with 1'a and 3

To a 25 mL Schlenk tube, CuBr (10 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (1.0 mL) was added to the tube, followed by the organic zinc reagent **1'a** (1.2 equiv, 0.22 M in THF). Then, a solution of TCP (1.5 equiv, 0.98 M in diethyl ether) was added at 25 °C under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. A solution of CB-DFAS **3** (0.3 mmol, 1.0 equiv, 1.44 M in DCM) in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The yield (37%) was determined by ^{19}F NMR using 4-fluorotoluene as the internal standard.



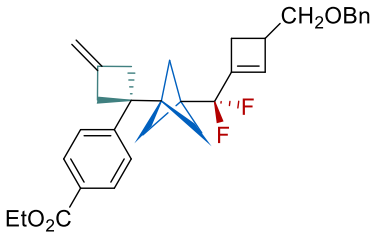
3-(1-(3-(Cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclo-butyl)benzonitrile (6b)

The reaction was conducted on a 0.3 mmol scale, and 3.0 equiv of TCP was used. Compound **6b** (93 mg, 91% yield) was purified with FP ECOFLEX C18 (20 g) (MeCN: H_2O = 7:3) as a yellow oil.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.12-6.08 (m, 1H), 4.85 (t, *J* = 2.0 Hz, 2H), 2.97 (s, 4H), 2.61 – 2.53 (m, 2H), 2.46 – 2.36 (m, 2H), 1.63 (s, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.3 (s, 2F). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.3, 142.4,

141.4 (t, *J* = 31.9 Hz), 135.0 (t, *J* = 8.9 Hz), 132.0, 127.1, 119.0, 114.8 (t, *J* = 236.0 Hz), 109.9, 107.6, 45.8, 45.4 (t, *J* = 2.9 Hz), 42.4, 39.8, 39.2 (t, *J* = 35.2 Hz), 29.2 (t, *J* = 3.5 Hz), 27.3 (t, *J* = 2.3 Hz). MS (DART POSITIVE): m/z (%) 338.2 ($[M+H]^+$). HRMS (DART POSITIVE) m/z: ($[M+H]^+$) Calculated for $C_{22}H_{21}F_2N$: 338.1715; Found: 338.1715.

Using 1.5 equiv of TCP to react with 1'b and 3

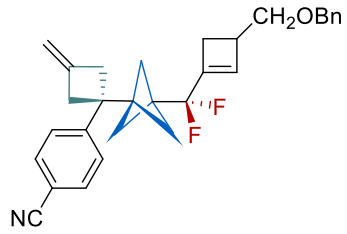
To a 25 mL Schlenk tube, CuBr (10 mol %) was added in the air. The tube was evacuated and backfilled with Ar (3 times). THF (1.0 mL) was added to the tube, followed by the organic zinc reagent **1'b** (1.2 equiv, 0.31 M in THF). Then, a solution of TCP (1.5 equiv, 0.98 M in diethyl ether) was added at 25 °C under Ar. The tube was screw-capped, and the reaction mixture was stirred for 10 min at room temperature. A solution of CB-DFAS **3** (0.3 mmol, 1.0 equiv, 1.44 M in DCM) in THF (1.5 mL) was added dropwise for two minutes. The tube was screw-capped, and the reaction mixture was stirred for 3 h at room temperature. The yield (65%) was determined by ^{19}F NMR using 4-fluorotoluene as the internal standard.



Ethyl4-(1-(3-((3-((benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzoate (6c)

The reaction was conducted on a 0.3 mmol scale, and 3.0 equiv of TCP was used. Compound **6c** (133mg, 88% yield) was purified with FP ECOFLEX C18 (20 g) (MeCN: H_2O = 7:3) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.28 (m, 4H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.20 – 6.15 (m, 1H), 4.84 (s, 2H), 4.51 (s, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.49 (d, *J* = 7.0 Hz, 2H), 2.98 (s, 4H), 2.73 – 2.62 (m, 1H), 2.25 – 2.16 (m, 1H), 1.62 (s, 6H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.82 (s, 2F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.7, 151.0, 143.2, 141.8 (t, *J* = 32.2 Hz), 138.5, 136.3 (t, *J* = 8.6 Hz), 129.5, 128.5, 128.3, 127.8, 126.3, 115.1 (t, *J* = 237.0 Hz), 107.3, 73.3, 73.0, 61.0, 46.0, 45.5 (t, *J* = 2.6 Hz), 42.3, 39.9, 39.7, 39.1 (t, *J* = 35.0 Hz),

32.7 (t, *J* = 3.2 Hz), 14.5. MS (ESI): m/z (%) 505.3 ([M+H]$^+$). HRMS (ESI) m/z: ([M+H]$^+$) Calculated for $C_{32}H_{34}F_2O_3$: 505.2549; Found: 505.2546.

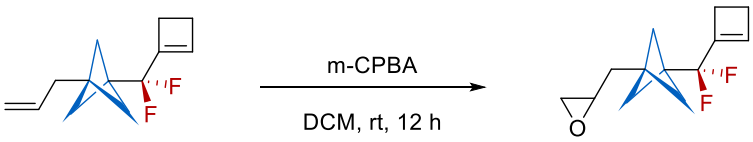


4-(1-(3-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzonitrile (6d)

The reaction was conducted on a 0.3 mmol scale, and 3.0 equiv of TCP was used. Compound **6d** (110 mg, 80% yield) was purified with FP ECOFLEX C18 (20 g) (MeCN: H_2O = 7:3) as a yellow oil.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.28 (m, 5H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.21-6.18 (m, 1H), 4.86 (t, *J* = 2.5 Hz, 2H), 4.51 (s, 2H), 3.50 (d, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 2.0 Hz, 5H), 2.72 – 2.62 (m, 1H), 2.27 – 2.19 (m, 1H), 1.62 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.8 (d, *J* = 15.0 Hz, 2F).^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.3, 142.4, 141.7 (t, *J* = 32.1 Hz), 138.4, 136.5 (t, *J* = 8.7 Hz), 132.1, 128.5, 127.8, 127.7, 127.1, 119.1, 114.9 (t, *J* = 236.4 Hz), 110.0, 107.7, 73.3, 73.0, 45.9, 45.5, 42.4, 39.8, 39.7, 39.2 (t, *J* = 35.0 Hz), 32.6 (t, *J* = 2.9 Hz). MS (ESI Positive Ion Mode): m/z (%) 458.2 ([M+H]$^+$). HRMS (ESI Positive Ion Mode) m/z: ([M+H]$^+$) Calculated for $C_{30}H_{29}F_2NO$: 458.2290; Found: 458.2287 .

10. Transformations of Compound 4f

Synthesis of compound 7

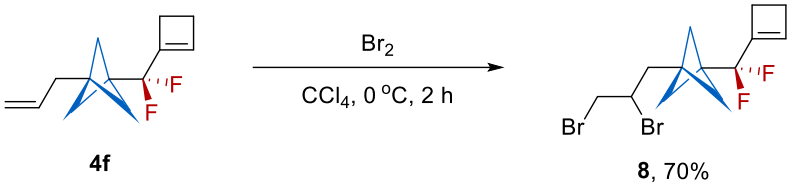


4f **7**, 72%

To a 25 mL Schlenk tube, **4e** (93.6 mg, 0.3 mmol, 1.0 equiv) and DCM (2.0 mL) were added. The solution was stirred at 0 °C. Then, m-CPBA (104 mg, 0.6 mmol, 2.0 equiv) was added to the solution. After stirring for 24 h at room temperature, the reaction mixture was concentrated, and the residue was purified with silica gel column chromatography (petroleum ether : ethyl acetate = 15:1) to afford **7** (49

mg, 72% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.19-6.15 (m, 1H), 2.95 – 2.88 (m, 1H), 2.76 (t, *J* = 4.8 Hz, 1H), 2.65 – 2.60 (m, 2H), 2.48 – 2.40 (m, 3H), 1.86 (s, 6H), 1.72 (s, 1H), 1.71 (d, *J* = 2.0 Hz, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.11 (s, 2F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 141.73 (t, *J* = 31.9 Hz), 134.96 (t, *J* = 9.0 Hz), 114.59 (t, *J* = 236.0 Hz), 50.25, 49.42 (t, *J* = 3.1 Hz), 46.53, 40.66 (t, *J* = 34.8 Hz), 37.66 (t, *J* = 1.9 Hz), 34.86, 29.28 (t, *J* = 3.6 Hz), 27.36 (t, *J* = 2.0 Hz). MS (FI): m/z (%) 226 ([M]$^{+}$). HRMS (FI) m/z: ([M]$^{+}$) Calculated for $C_{13}H_{16}F_2O$: 226.1164; Found: 226.1166.

Synthesis of compound 8



4f **8**, 70%

To a 25 mL Schlenk tube, **4e** (63 mg, 0.3 mmol, 1.0 equiv) and CCl_4 (1.0 mL) were added at 0 °C with stirring. Then, Br_2 (71 mg, 0.45 mmol, 1.5 equiv) was added. After stirring for 2 h at 0 °C, the reaction mixture was concentrated, and the residue was purified with silica gel column chromatography (petroleum ether : ethyl acetate = 50:1) to afford **8** (77 mg, 70% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.19-6.16 (m, 1H), 4.07 (tdd, *J* = 9.6, 4.4, 2.8 Hz, 1H), 3.83 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.61 (t, *J* = 10.0 Hz, 1H), 2.67 – 2.60 (m, 2H), 2.54 – 2.43 (m, 3H), 2.06 (dd, *J* = 15.6, 9.6 Hz, 1H), 1.91 (d, *J* = 2.0 Hz, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.06 (s, 2F).^{13}C NMR (101 MHz, Chloroform-*d*) δ 141.34 (t, *J* = 31.8 Hz), 134.71 (t, *J* = 9.0 Hz), 114.20 (t, *J* = 236.0 Hz), 49.44 (t, *J* = 3.1 Hz), 49.00, 40.17 (t, *J* = 34.8 Hz), 37.94 (t, *J* = 1.9 Hz), 37.52, 36.26, 28.96 (t, *J* = 3.6 Hz), 27.05 (t, *J* = 2.0 Hz). MS (FI): m/z (%) 368 ([M]$^{+}$). HRMS (FI) m/z: ([M]$^{+}$) Calculated for $C_{13}H_{16}Br_2F_2$: 367.9581; Found: 367.9583 .

11. References

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Ed. 2017, **56,** 12774-12777.

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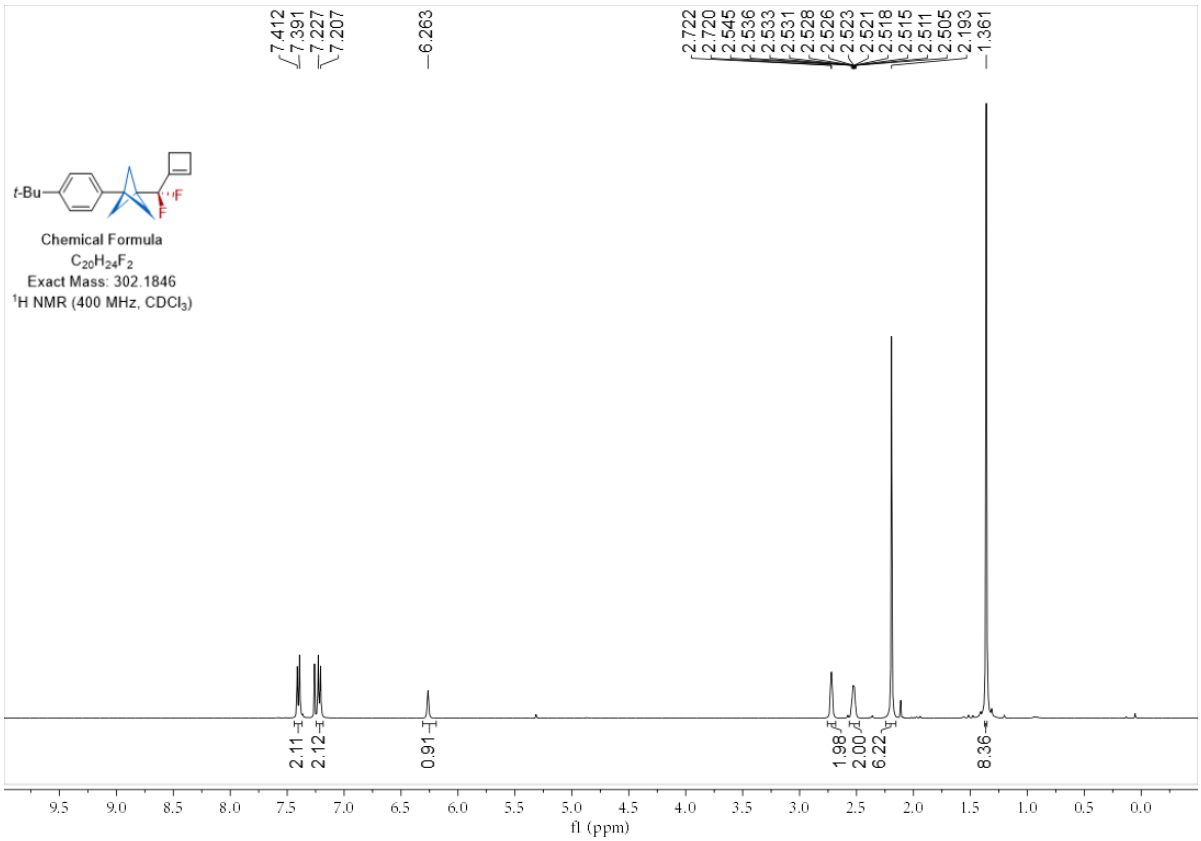
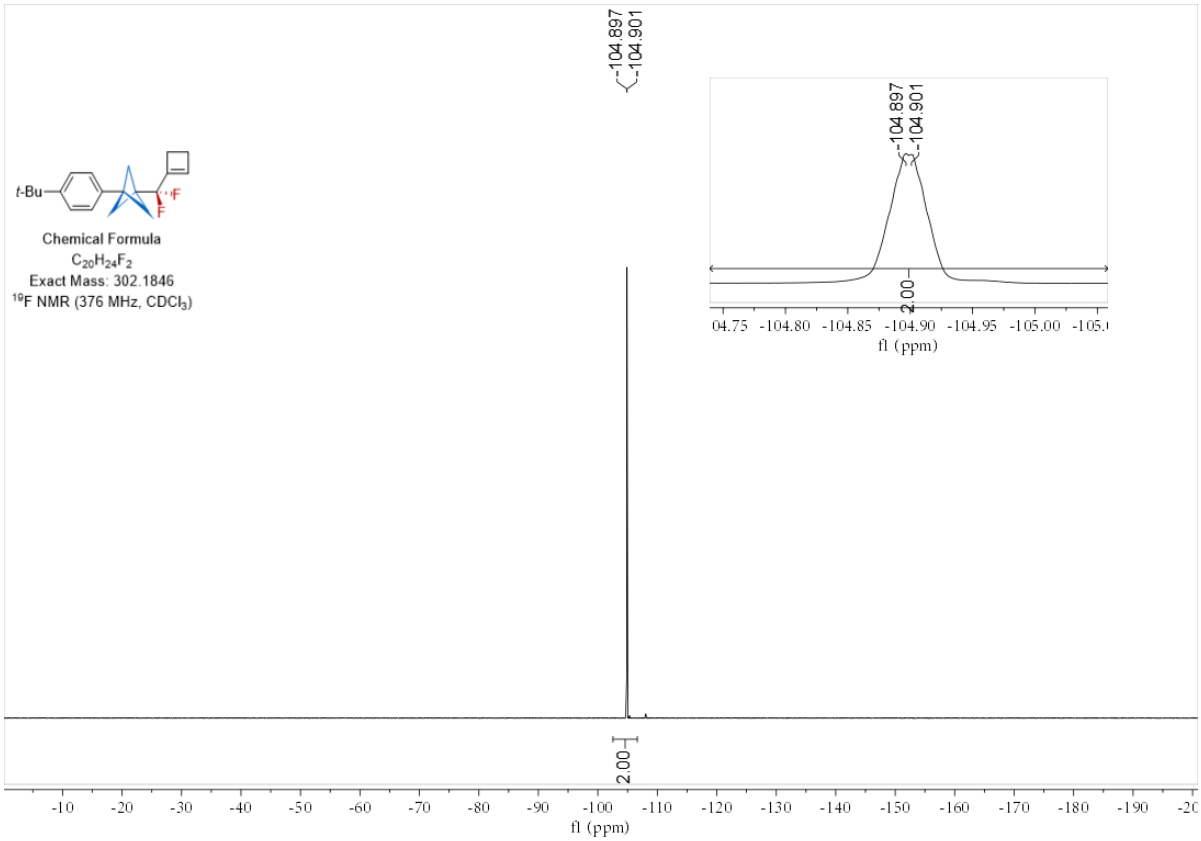
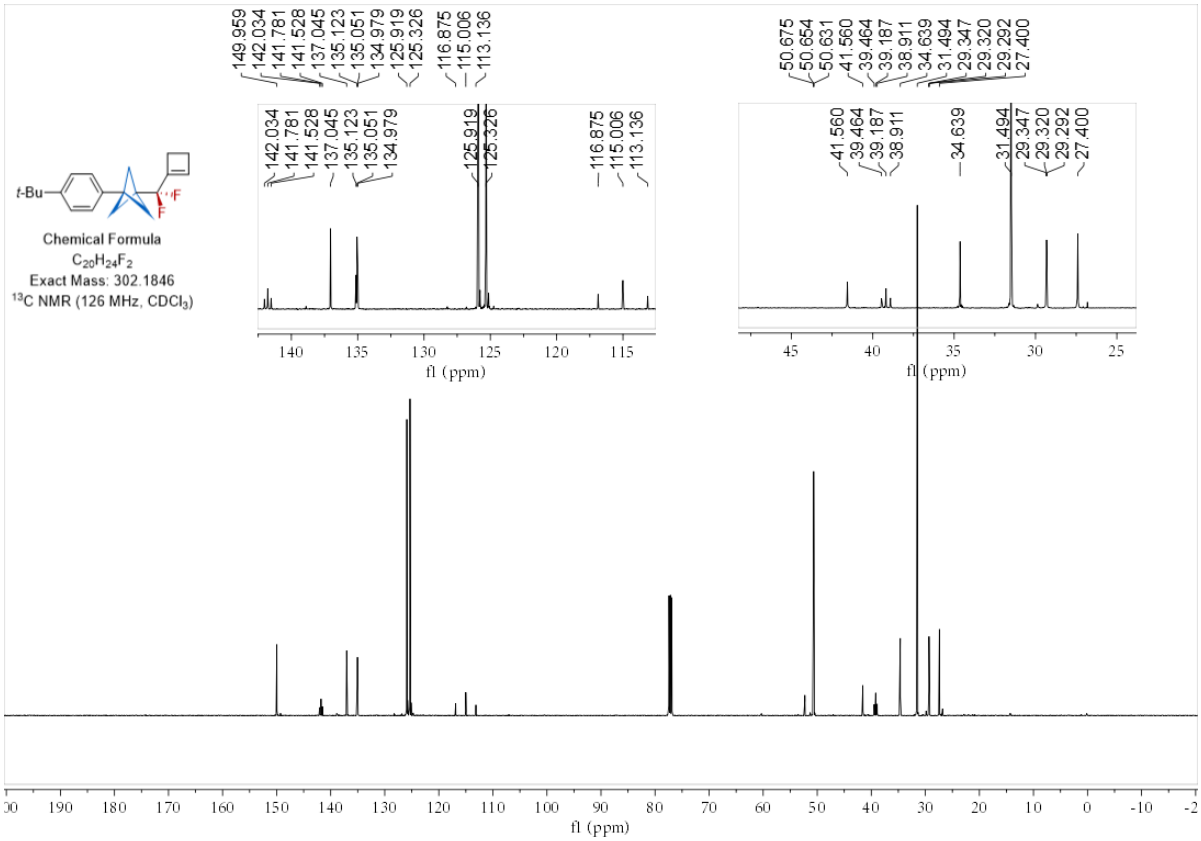
12. Copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR Spectra

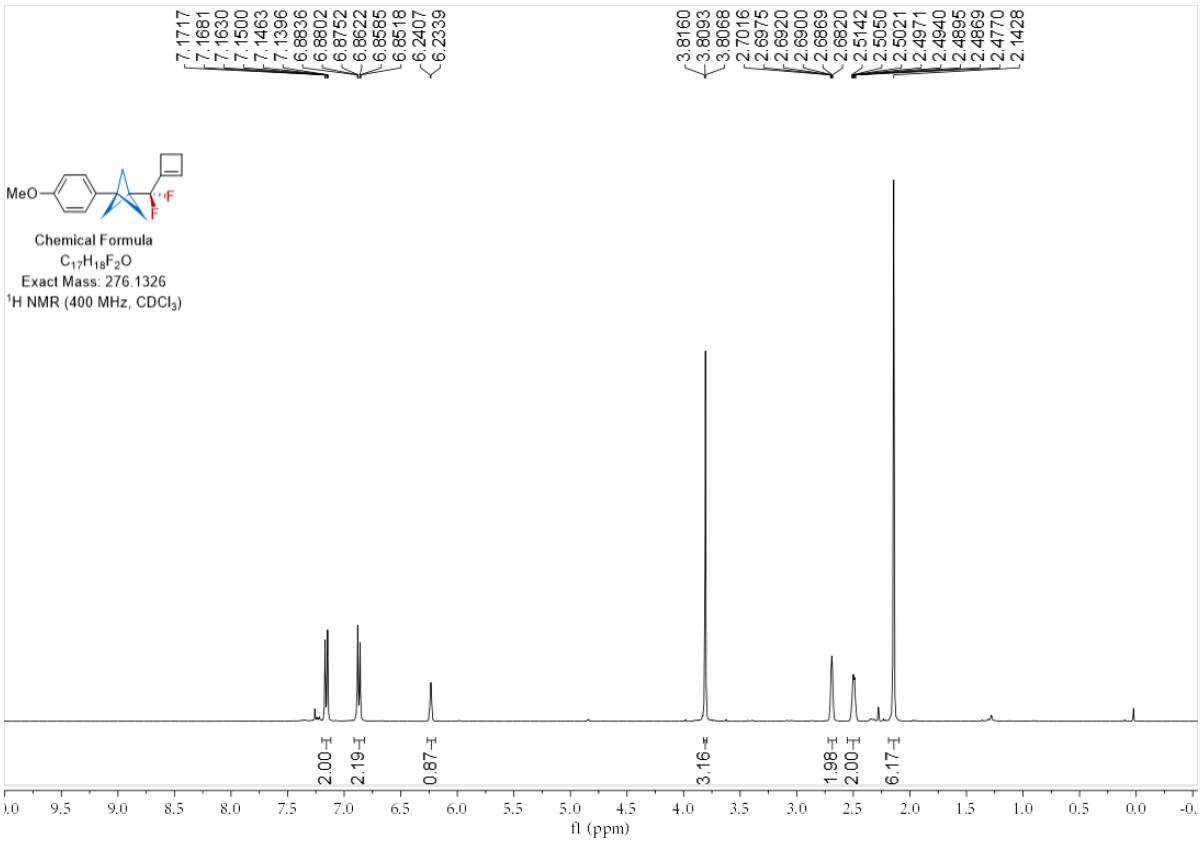
1-(4-(*tert*-Butyl)phenyl)-3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentane (4a)

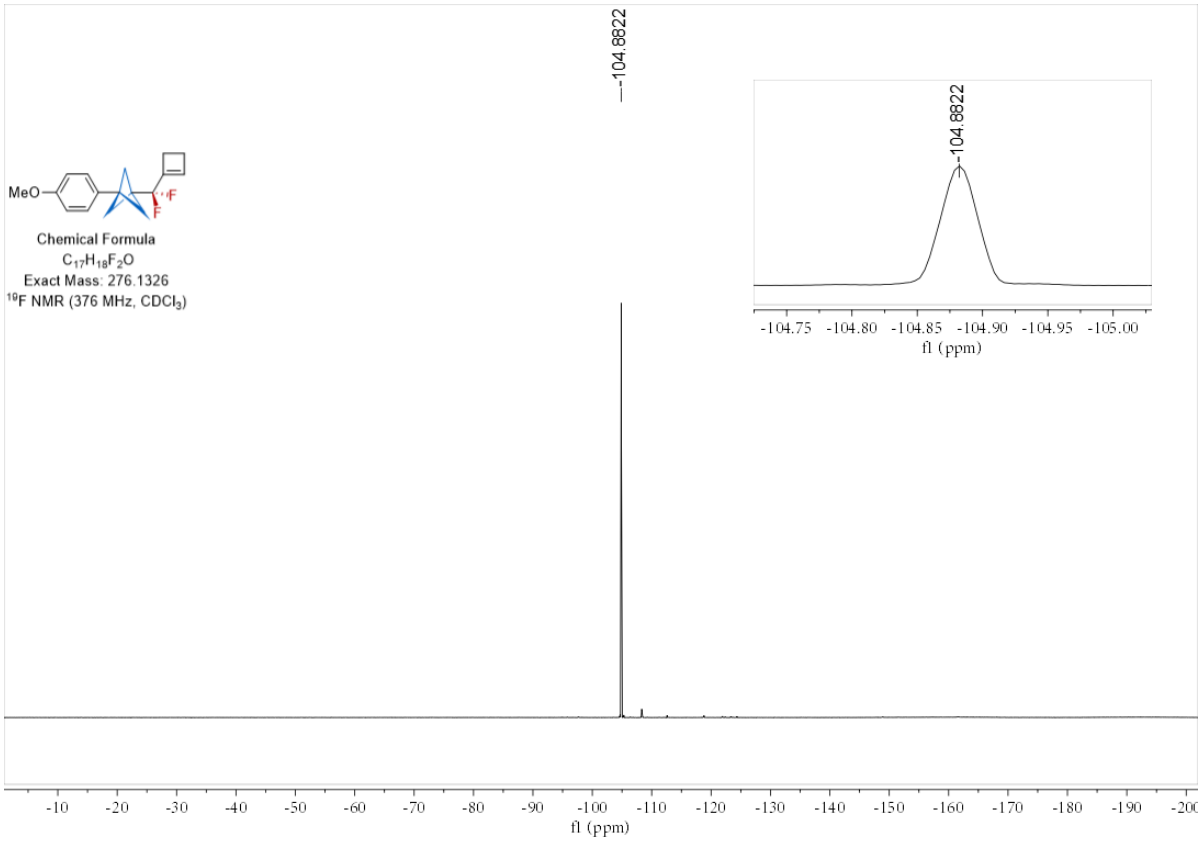






1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(4-methoxyphenyl)bicyclo[1.1.1]pentane (4b)

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MeO
F
F
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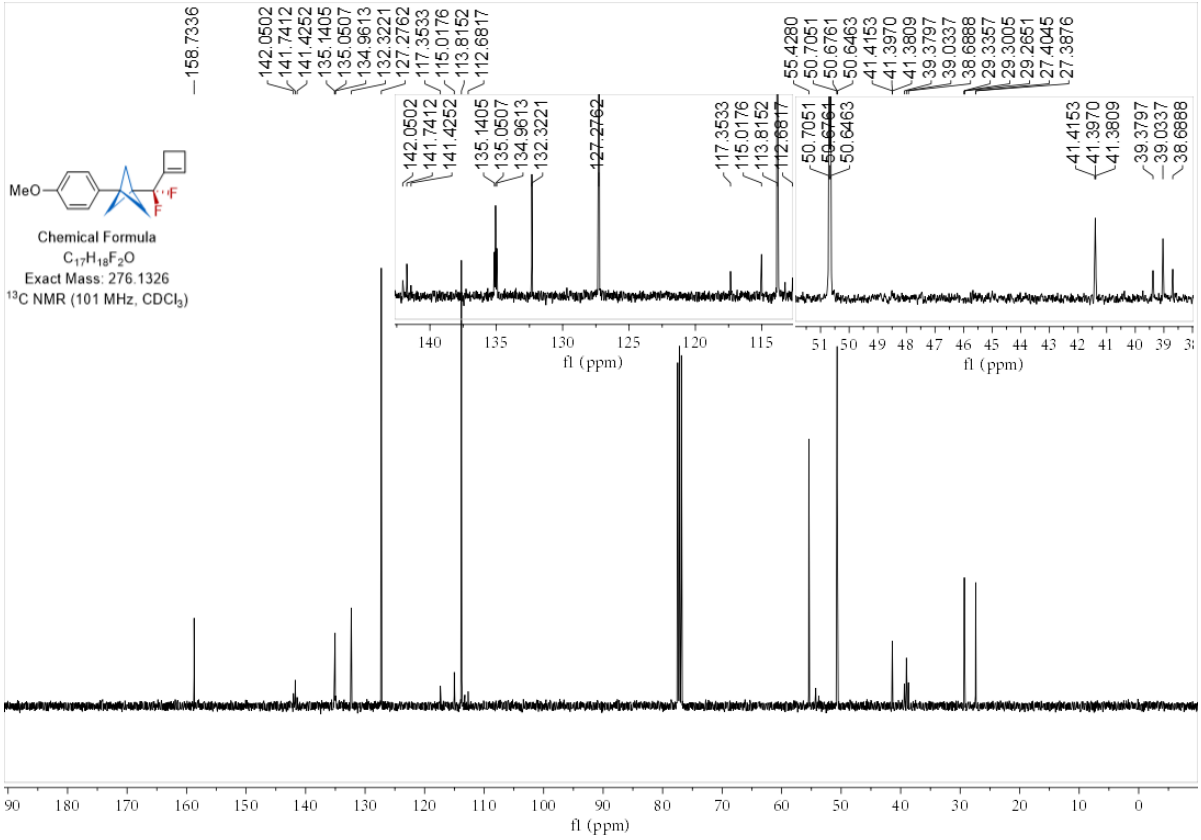
-104.8822
-104.75 -104.80 -104.85 -104.90 -104.95 -105.00
f1 (ppm)
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)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127.2762
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113.8152
112.6817
55.4280
50.7051
50.6761
50.6463
41.4153
41.3970
41.3809
39.3797
39.0337
38.6888
29.3357
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27.4045
27.3876
MeO
F
F
Chemical Formula
$C_{17}H_{18}F_2O$
Exact Mass: 276.1326
^{13}C NMR (101 MHz, $CDCl_3$)
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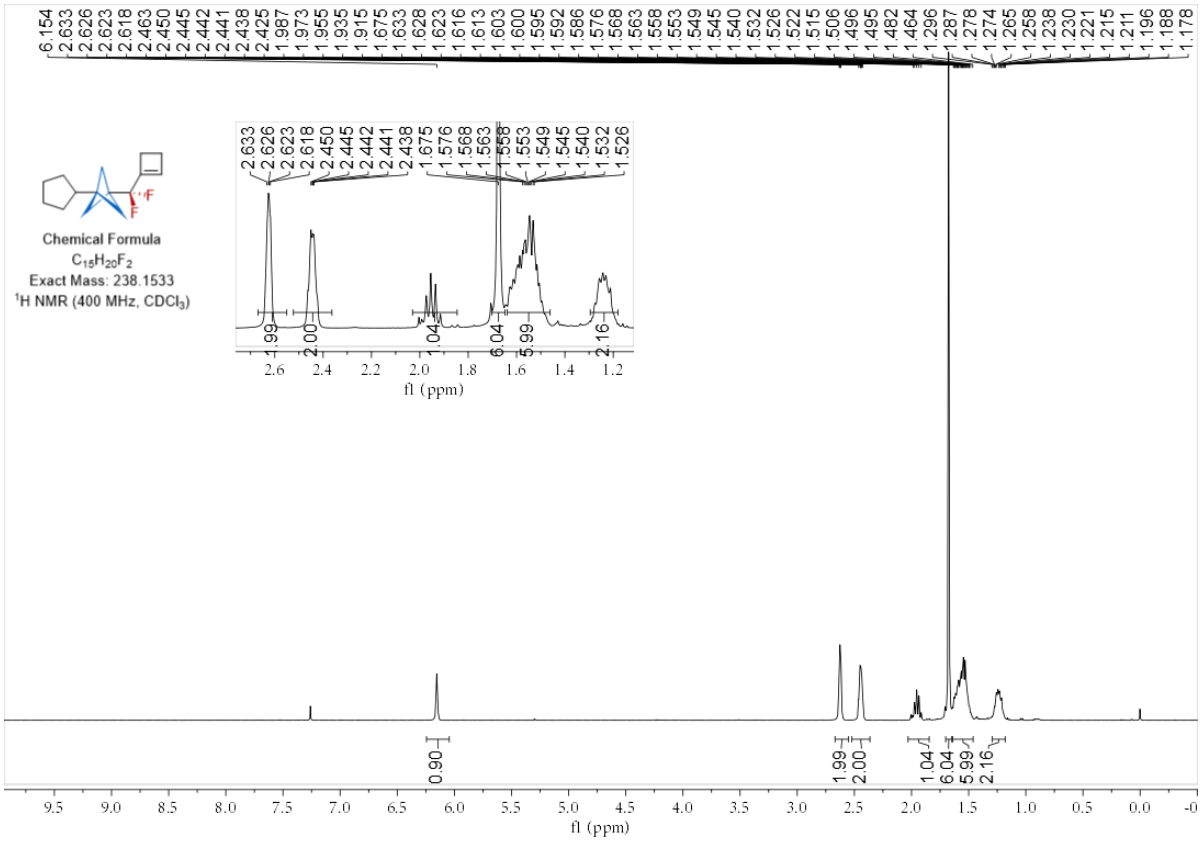
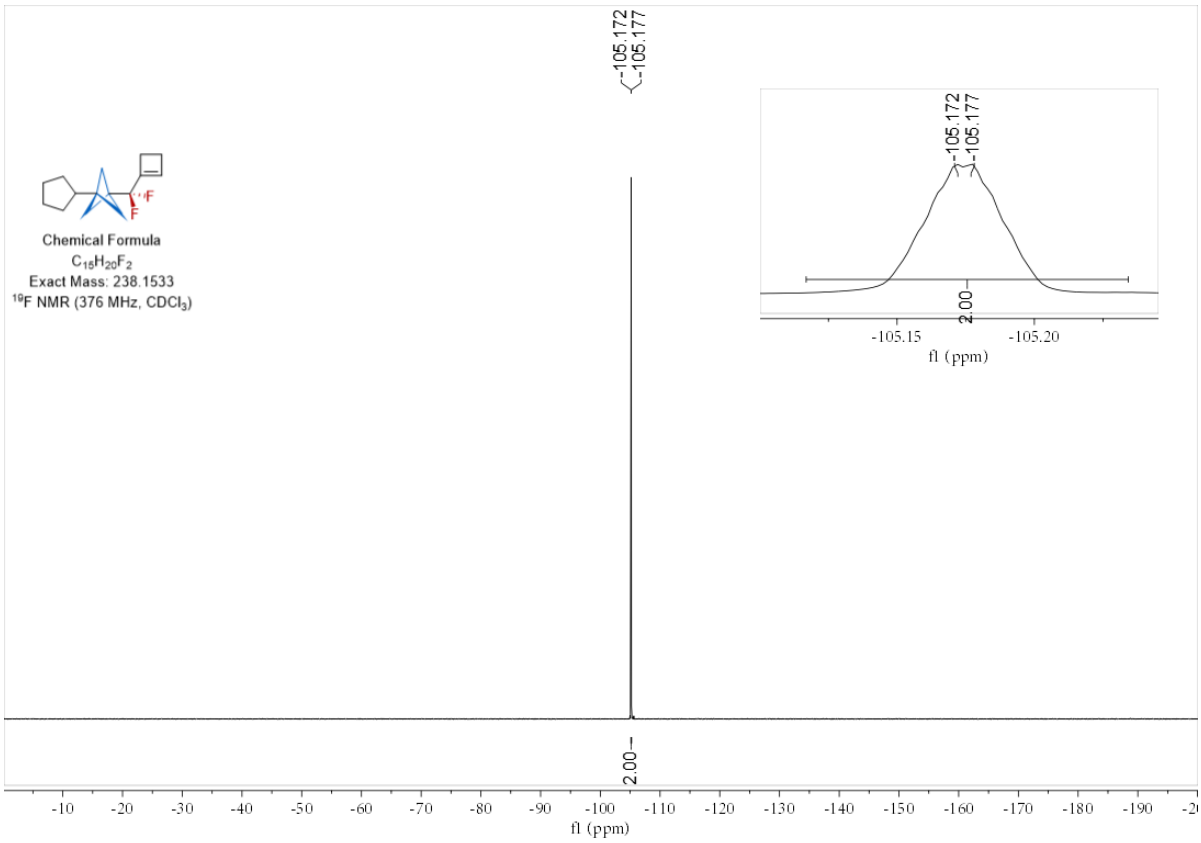
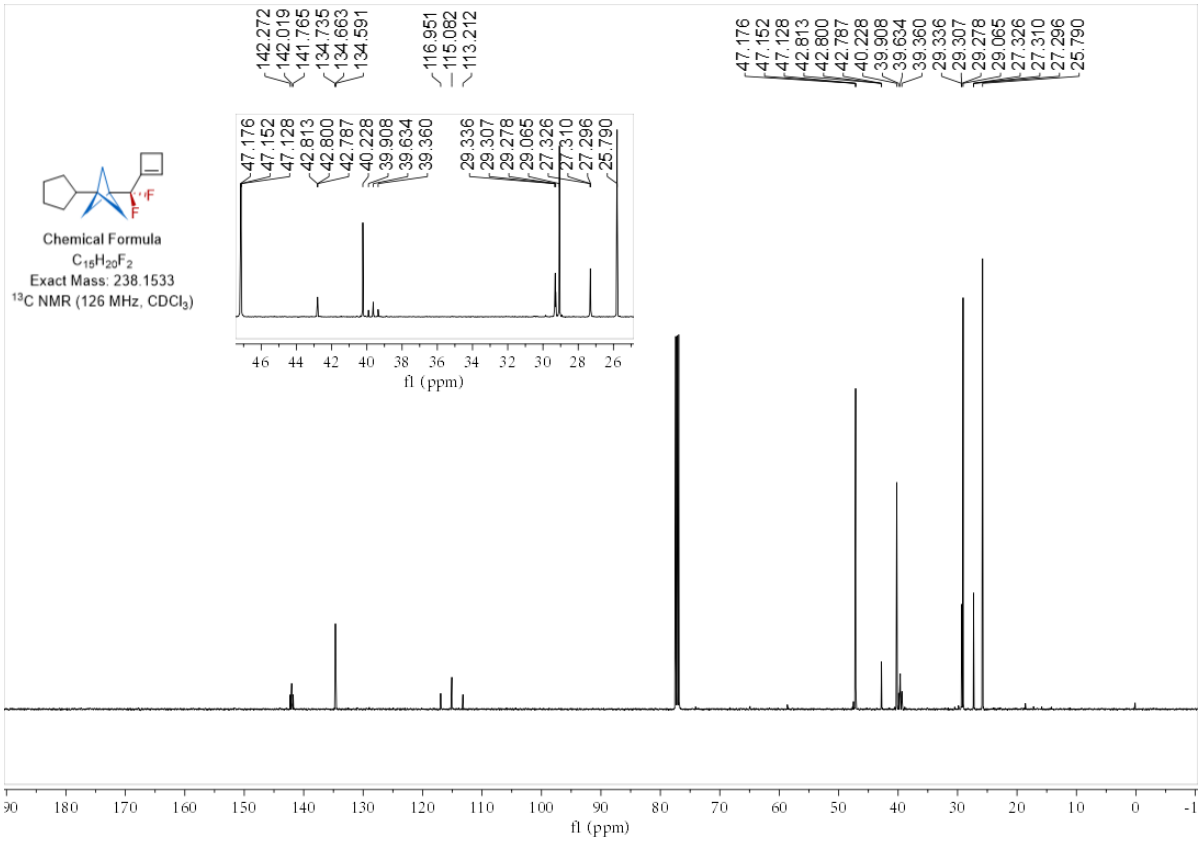
f1 (ppm)
51 50 49 48 47 46 45 44 43 42 41 40 39
f1 (ppm)
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

1-(Cyclobut-1-en-1-yldifluoromethyl)-3-cyclopentylbicyclo[1.1.1]pentane (4c)







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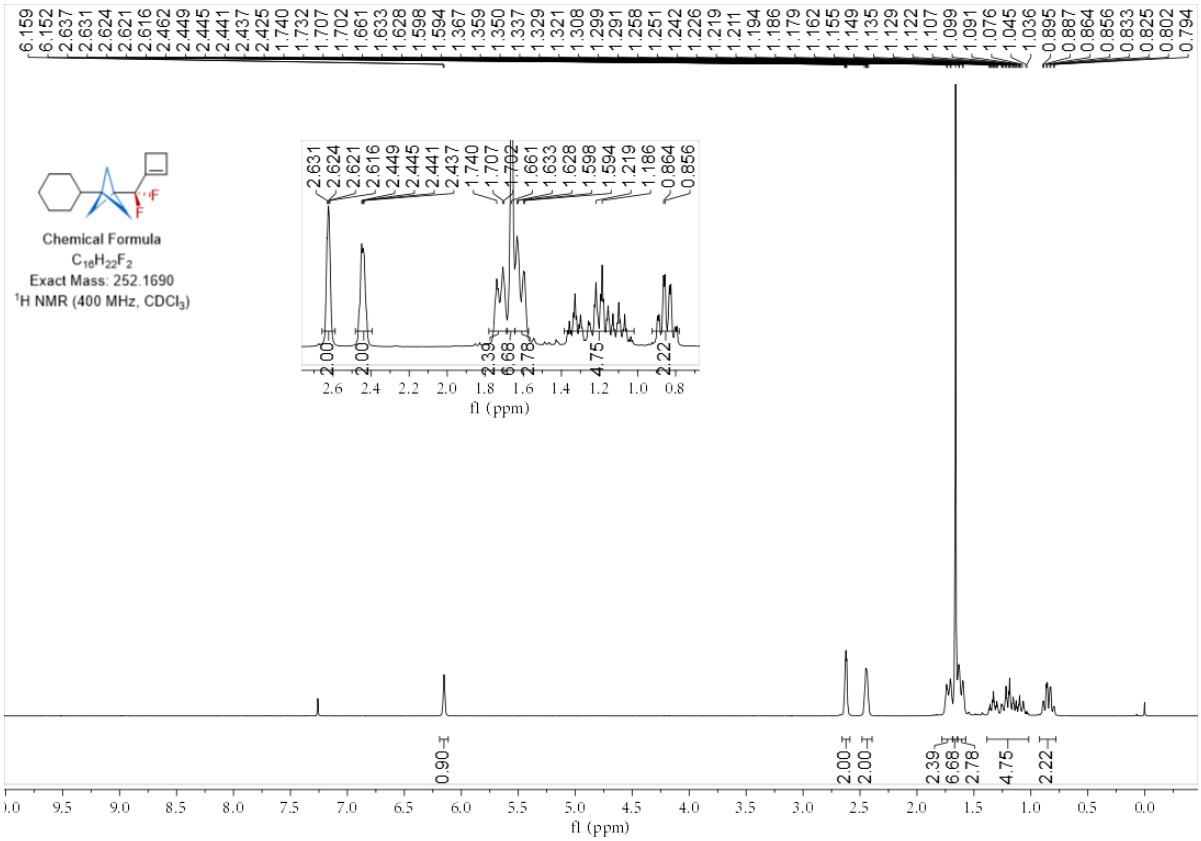

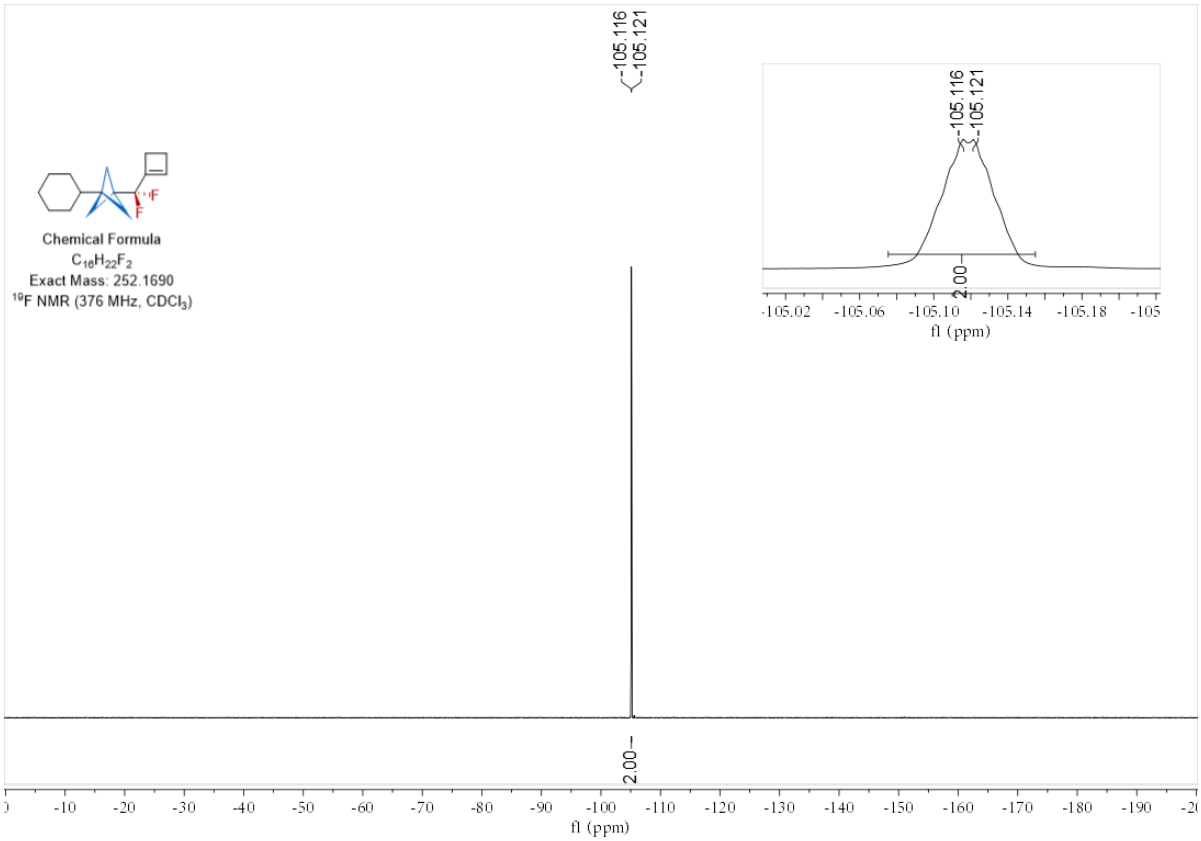
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-105.121
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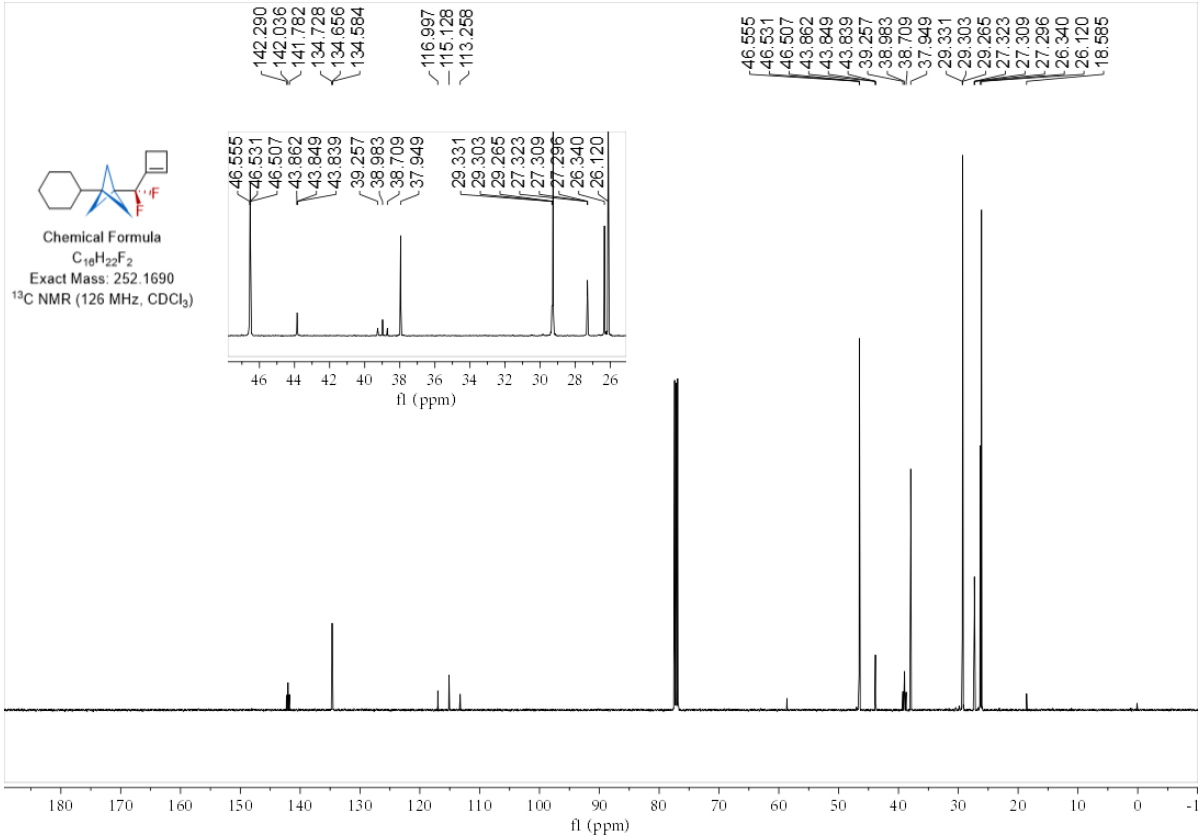
2.00
f1 (ppm)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43.849
43.839
39.257
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37.949
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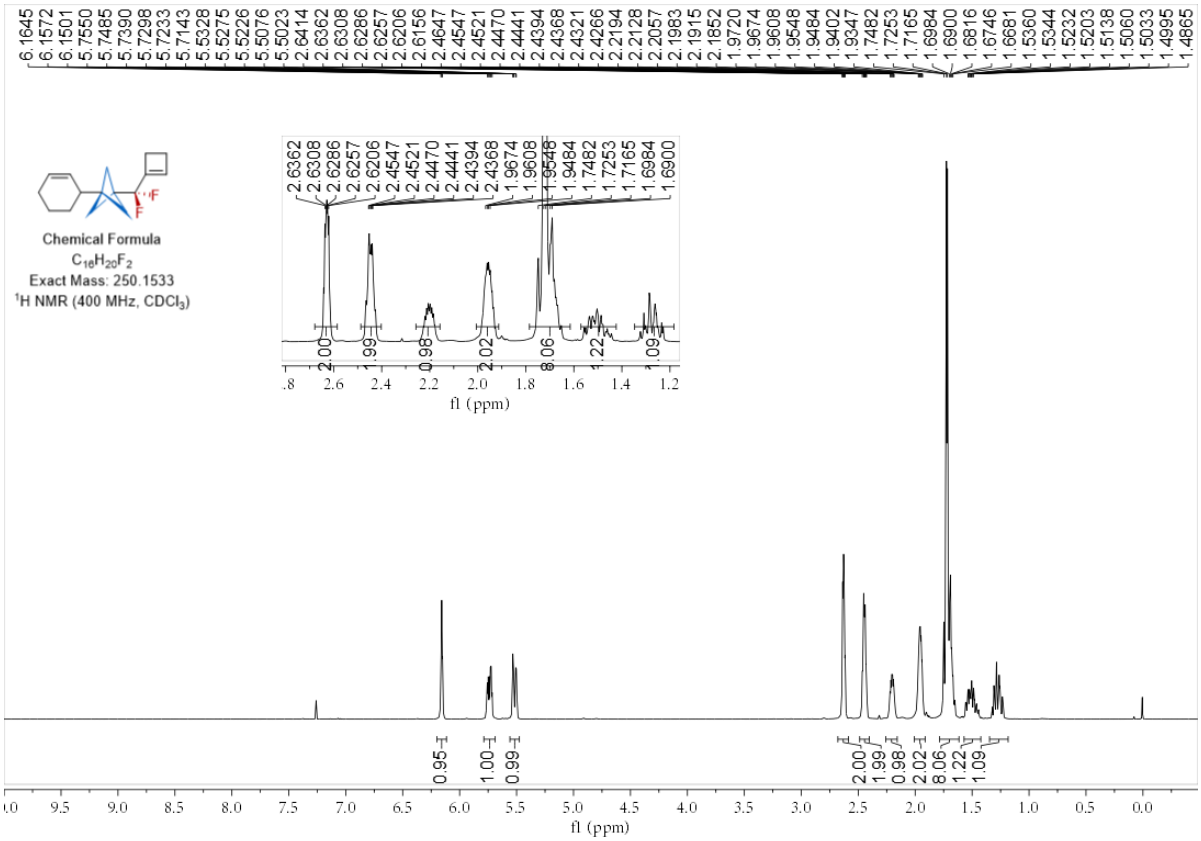
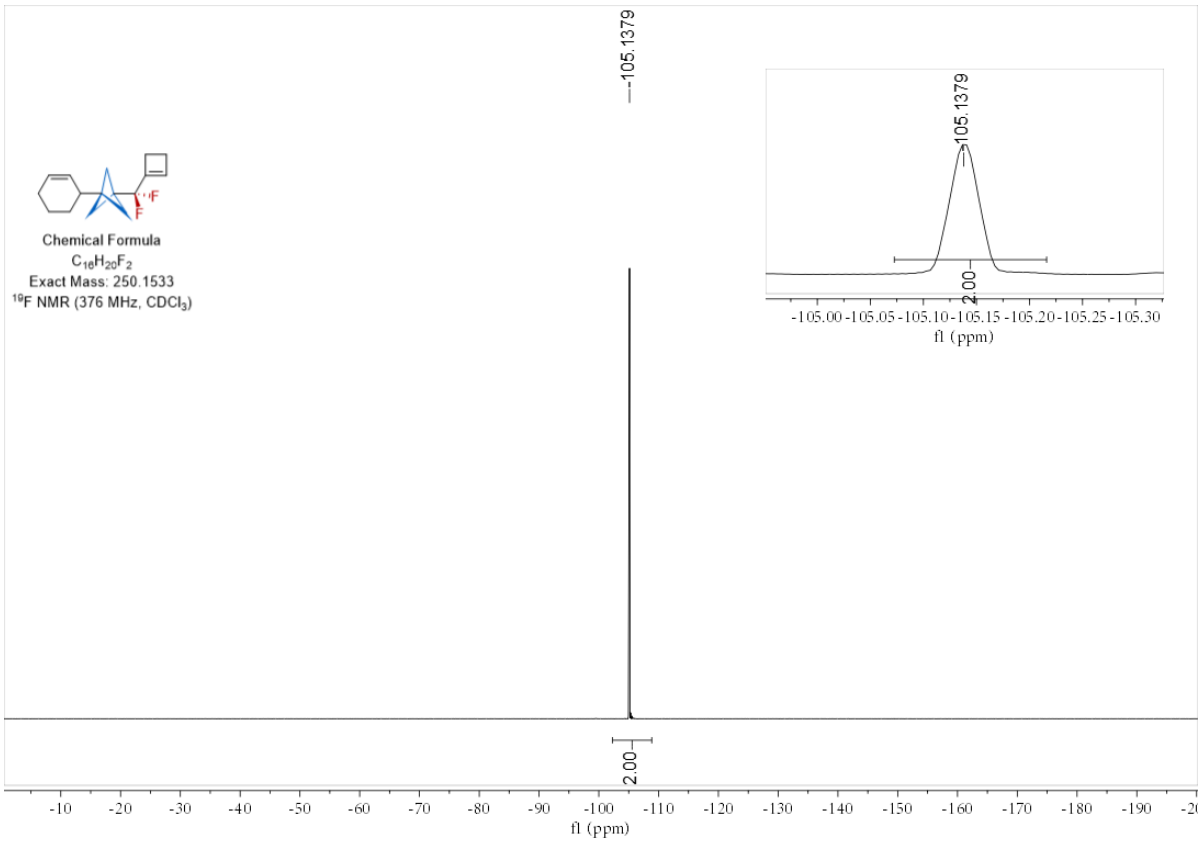
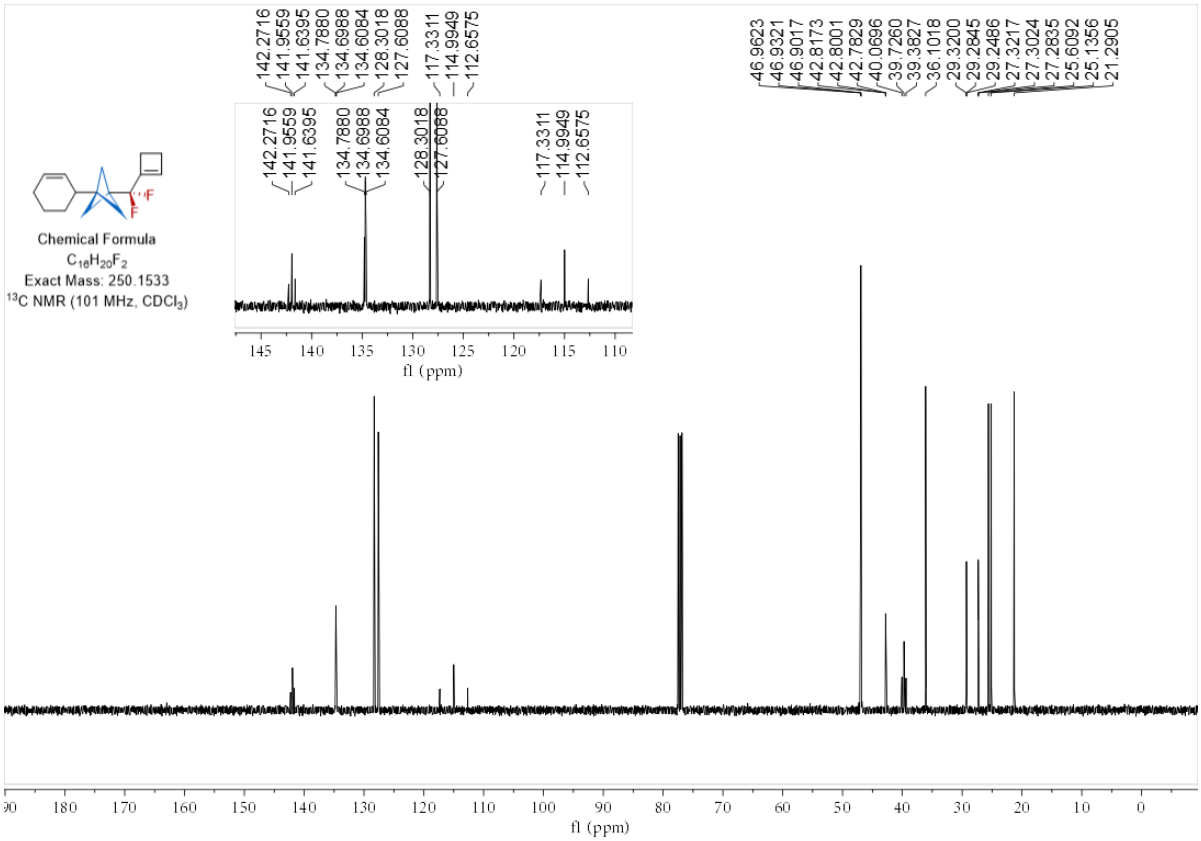
Chemical Formula
$C_{16}H_{22}F_2$
Exact Mass: 252.1690
^{13}C NMR (126 MHz, $CDCl_3$)
f1 (ppm)

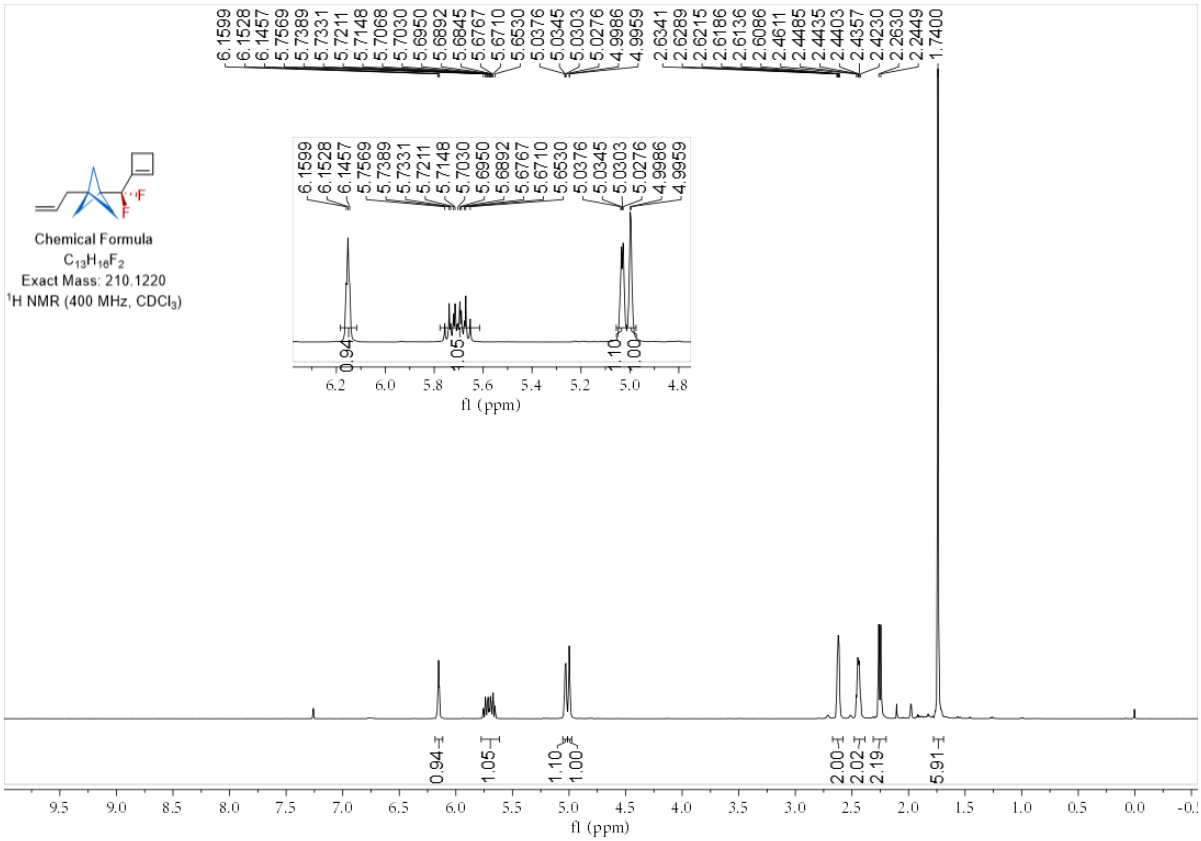
1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(cyclohex-2-en-1-yl)bicyclo[1.1.1]pentane (4e)

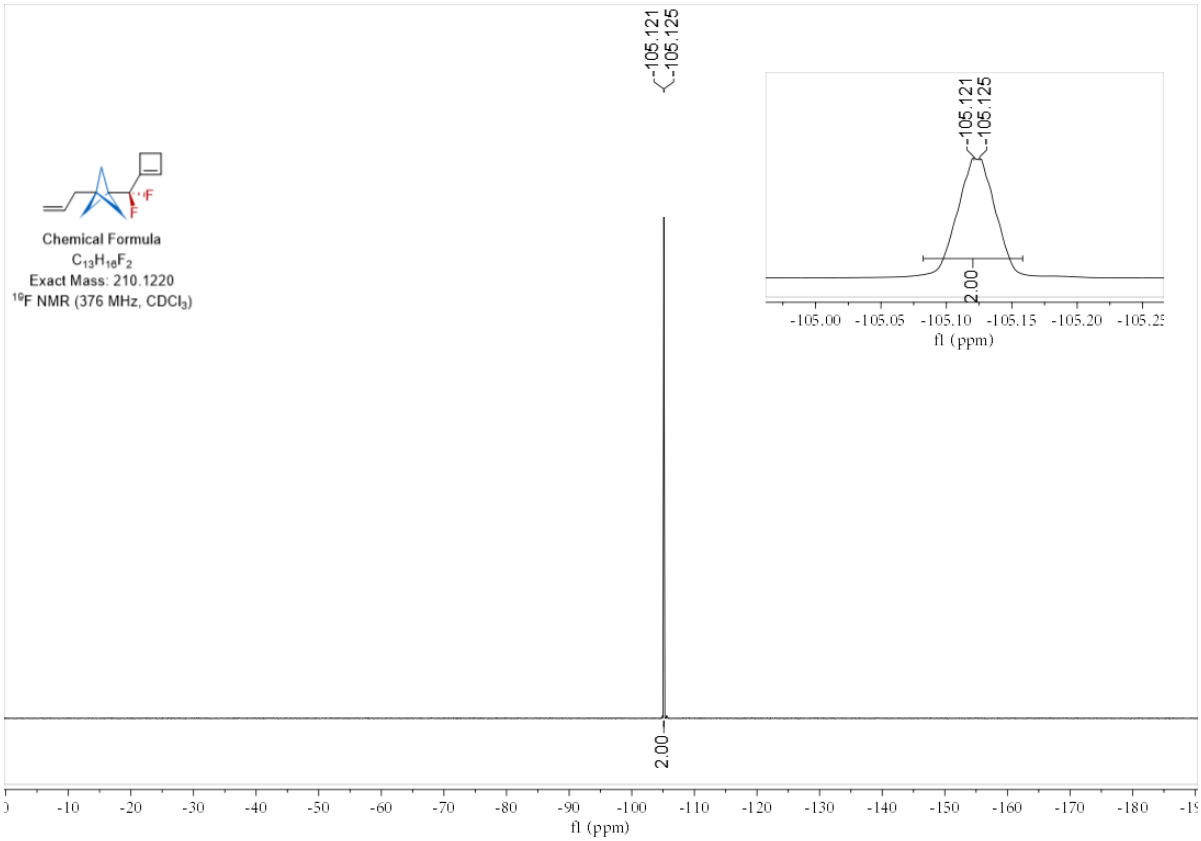


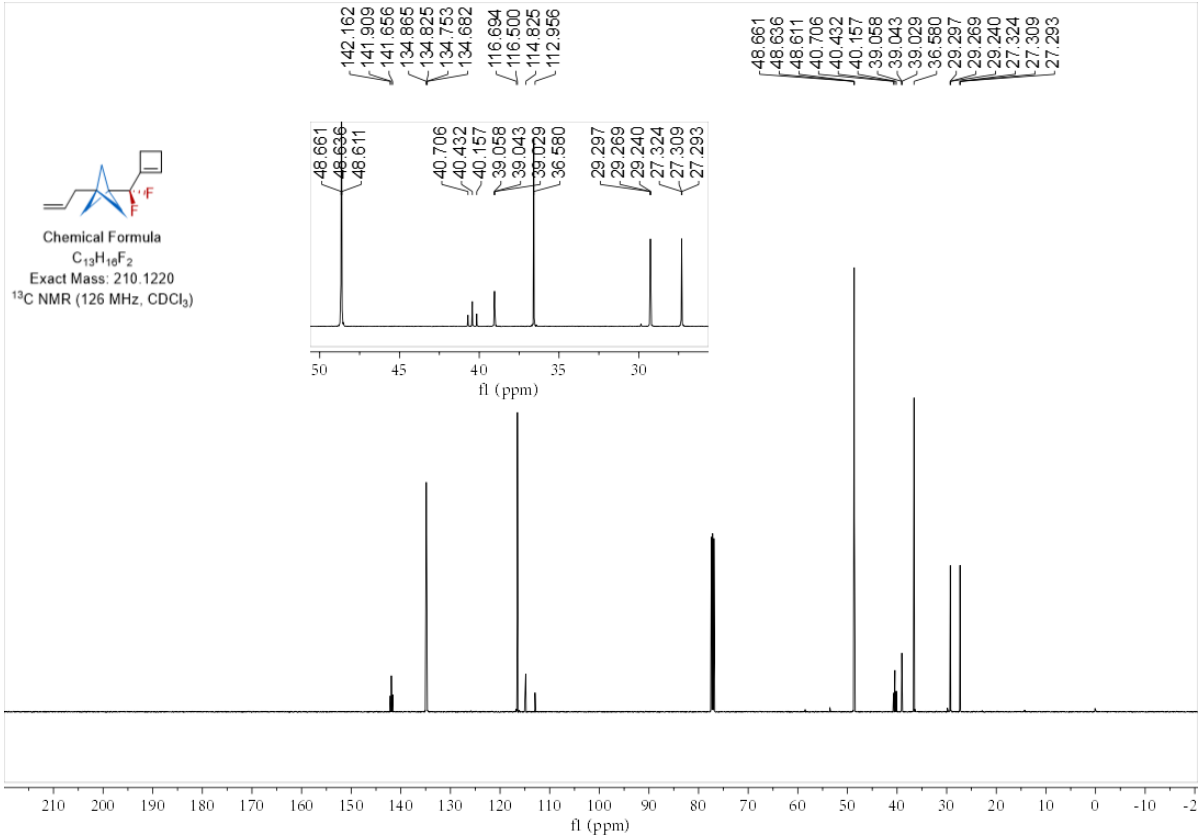




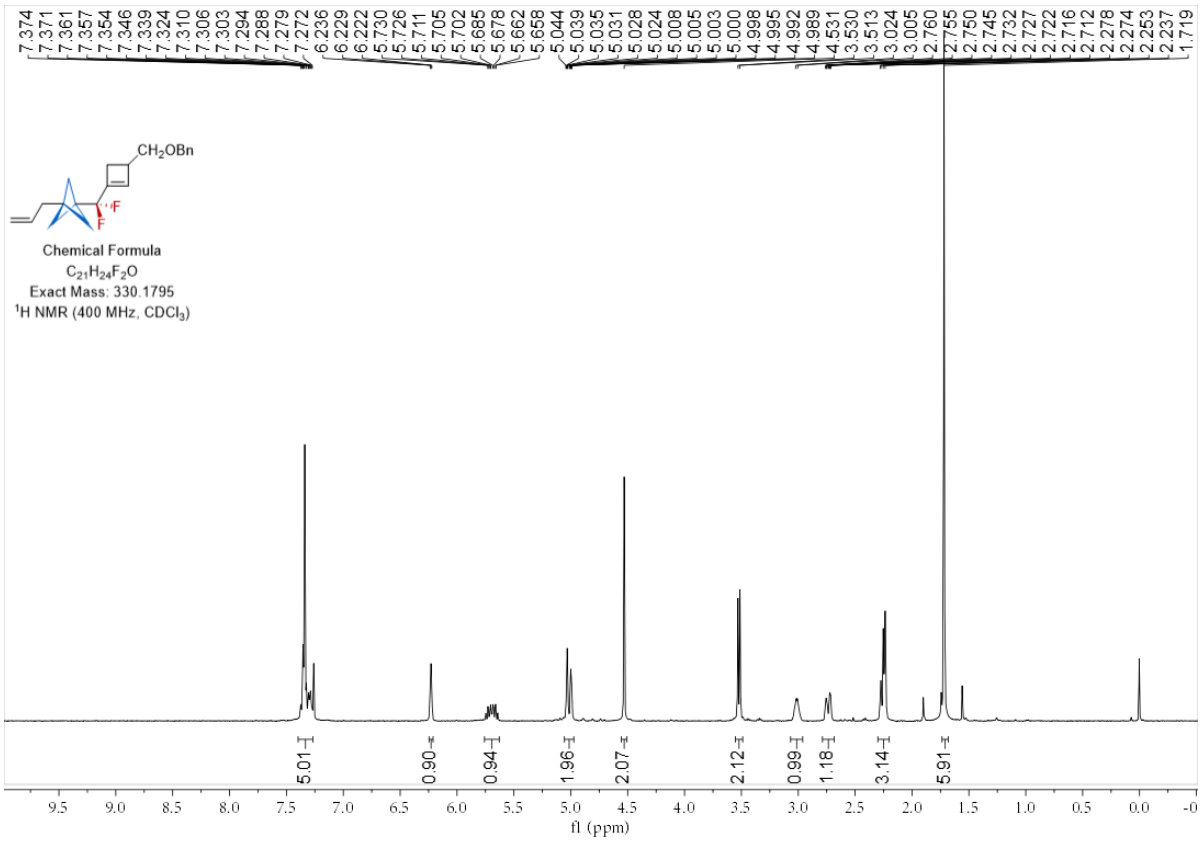
1-Allyl-3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentane (4f)

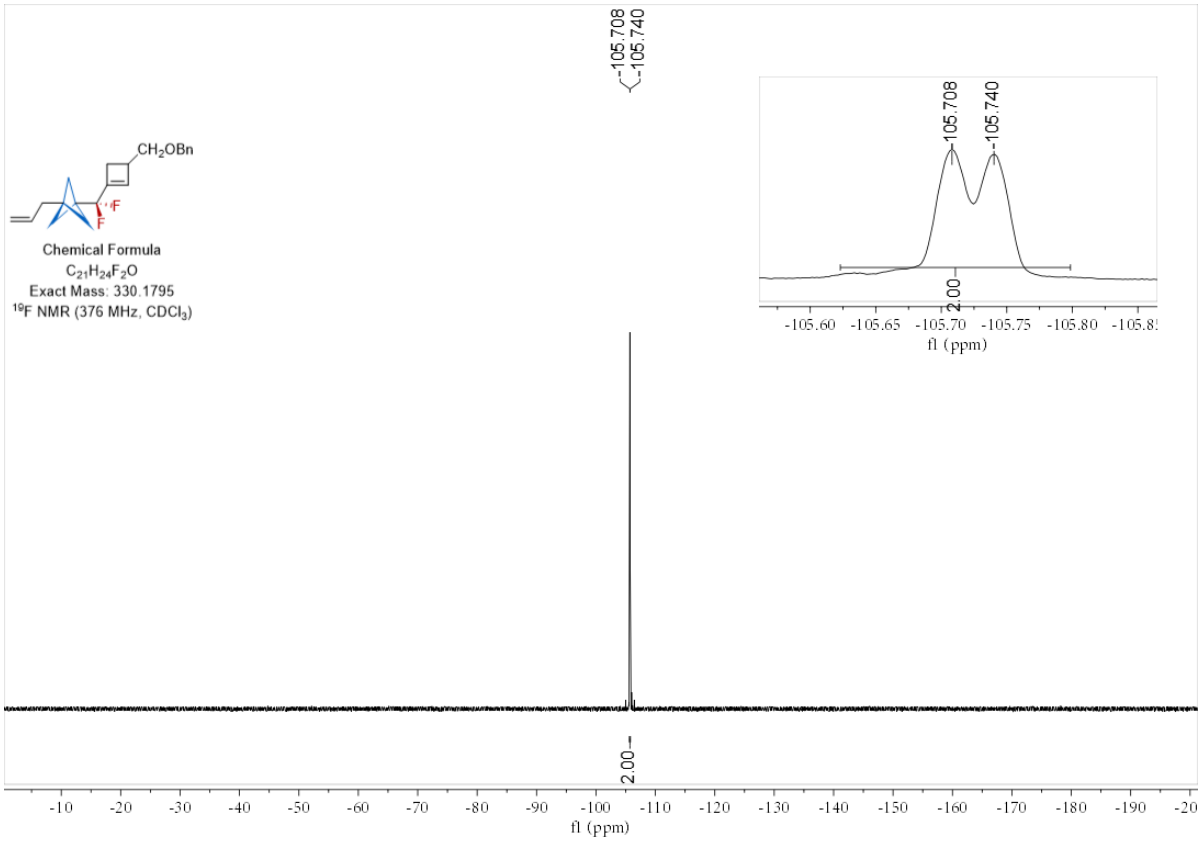


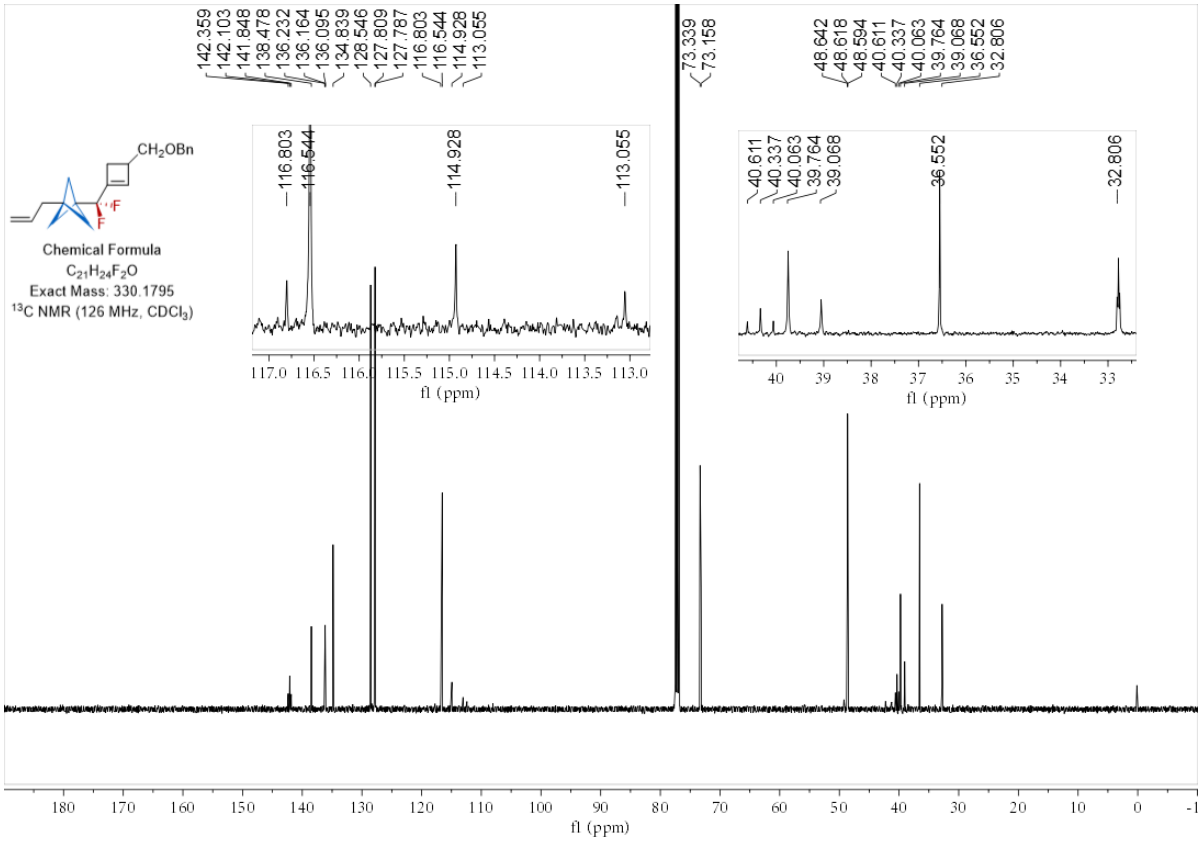

-105.121
-105.125
Chemical Formula
$C_{13}H_{16}F_2$
Exact Mass: 210.1220
^{19}F NMR (376 MHz, $CDCl_3$)
2.00
f1 (ppm)


142.162
141.909
141.656
134.865
134.825
134.753
134.682
116.694
116.500
114.825
112.956
48.661
48.636
48.611
40.706
40.432
40.157
39.058
39.043
39.029
36.580
29.297
29.269
29.240
27.324
27.309
27.293
Chemical Formula
$C_{13}H_{16}F_2$
Exact Mass: 210.1220
^{13}C NMR (126 MHz, $CDCl_3$)
f1 (ppm)

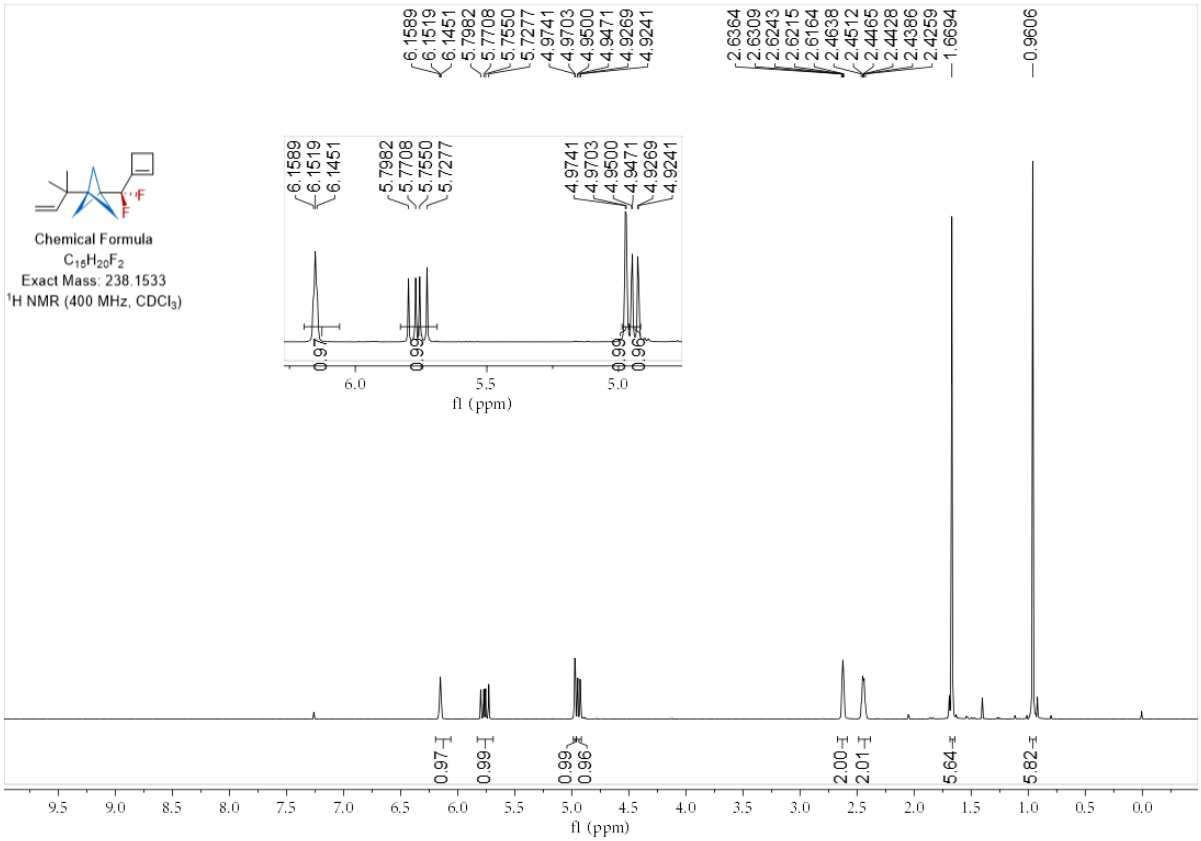
1-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)-3-(2-methylbut-3-en-2-yl)bicyclo[1.1.1]pentane (4g)

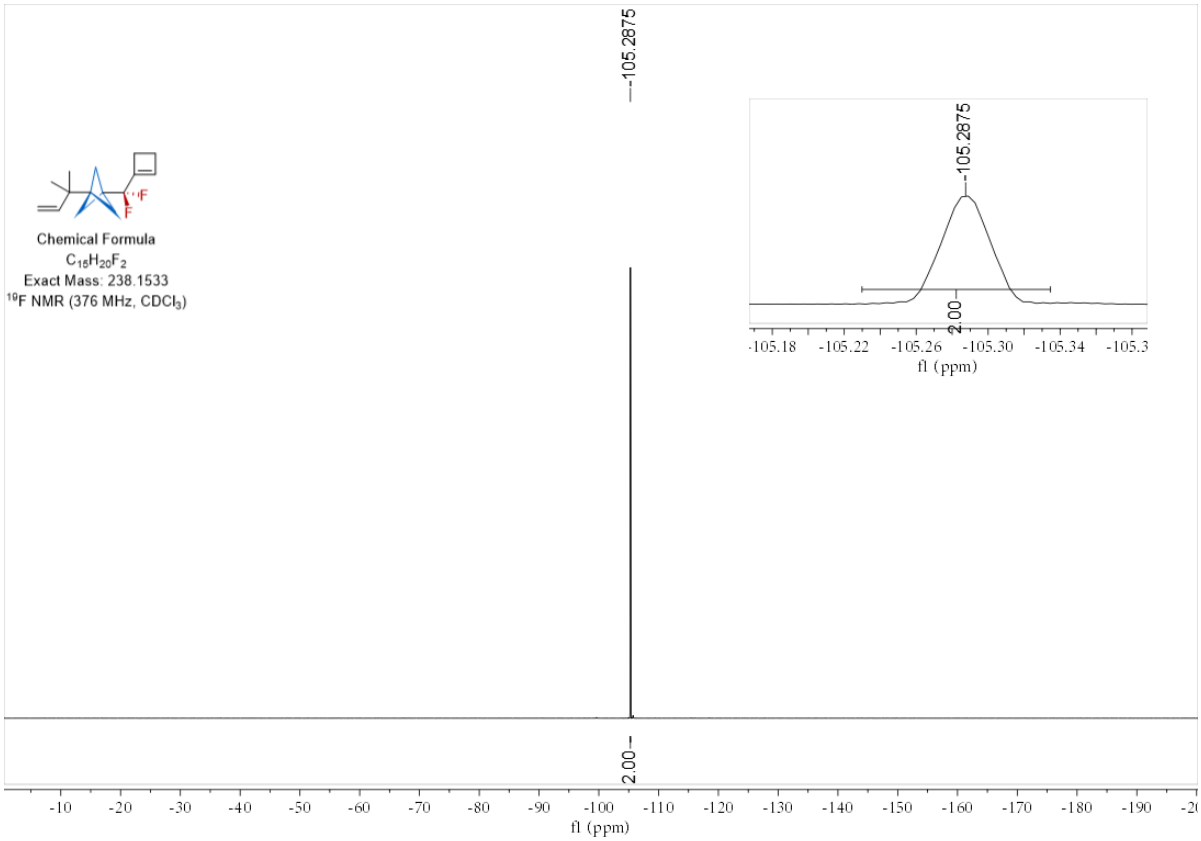


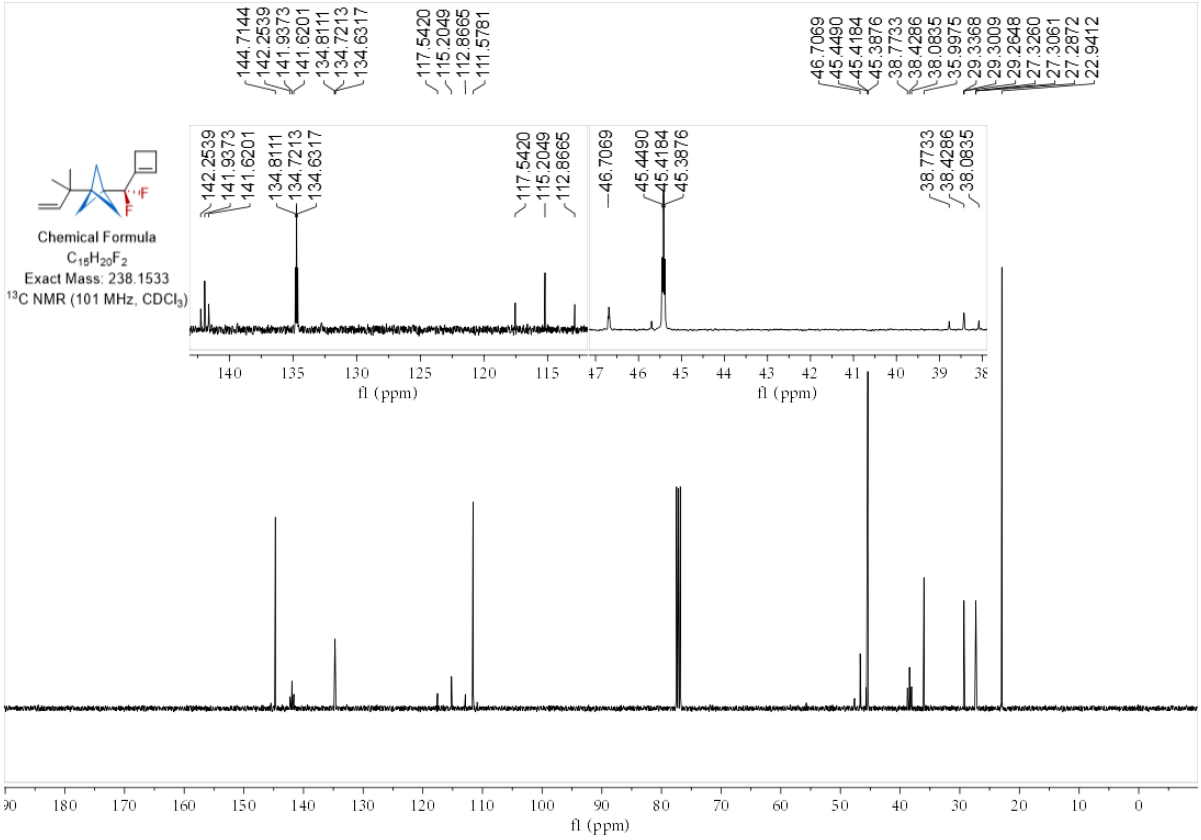




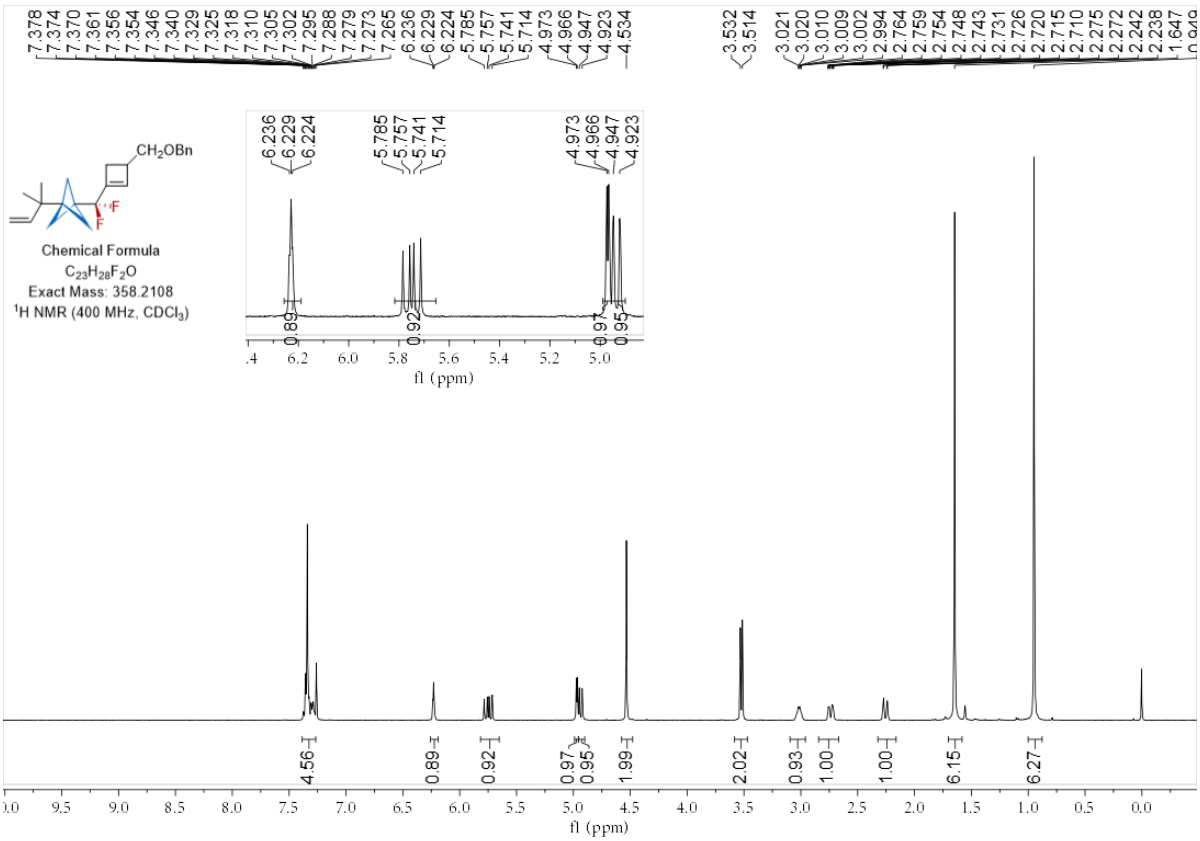
1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(2-methylbut-3-en-2-yl)bicyclo[1.1.1]pentane (4h)

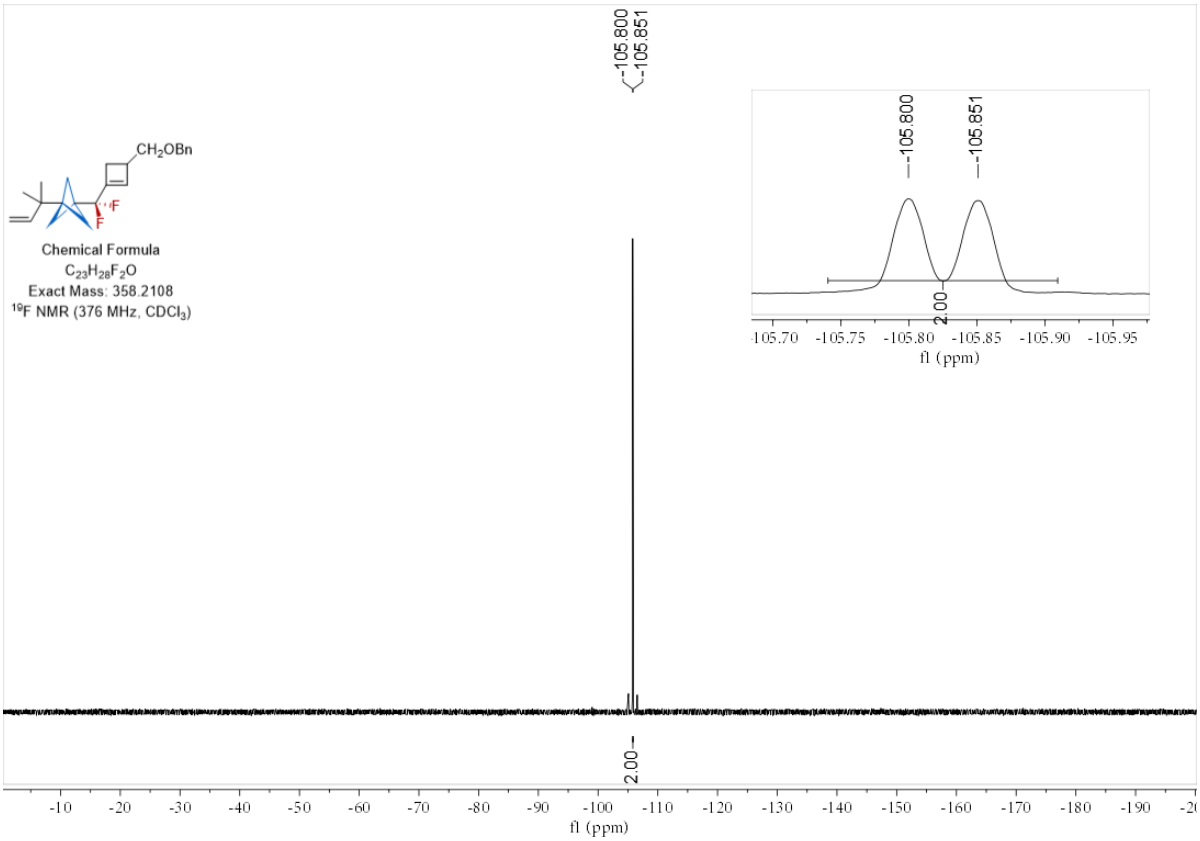


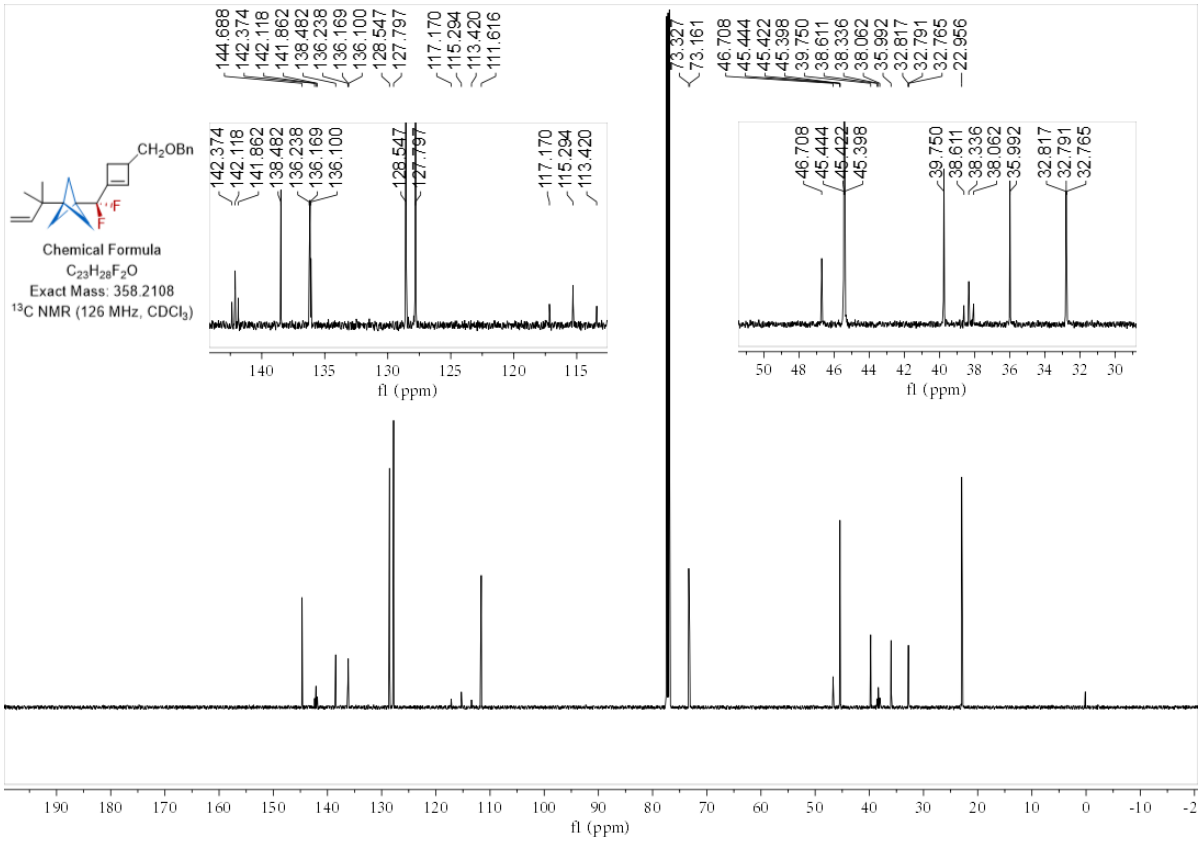

Chemical Formula
$C_{15}H_{20}F_2$
Exact Mass: 238.1533
^{19}F NMR (376 MHz, $CDCl_3$)
-105.2875
2.00
fl (ppm)


Chemical Formula
$C_{15}H_{20}F_2$
Exact Mass: 238.1533
^{13}C NMR (101 MHz, $CDCl_3$)
144.7144
142.2539
141.9373
141.6201
134.8111
134.7213
134.6317
117.5420
115.2049
112.8665
111.5781
46.7069
45.4490
45.4184
45.3876
38.7733
38.4286
38.0835
35.9975
29.3368
29.3009
29.2648
27.3260
27.3061
27.2872
22.9412
fl (ppm)

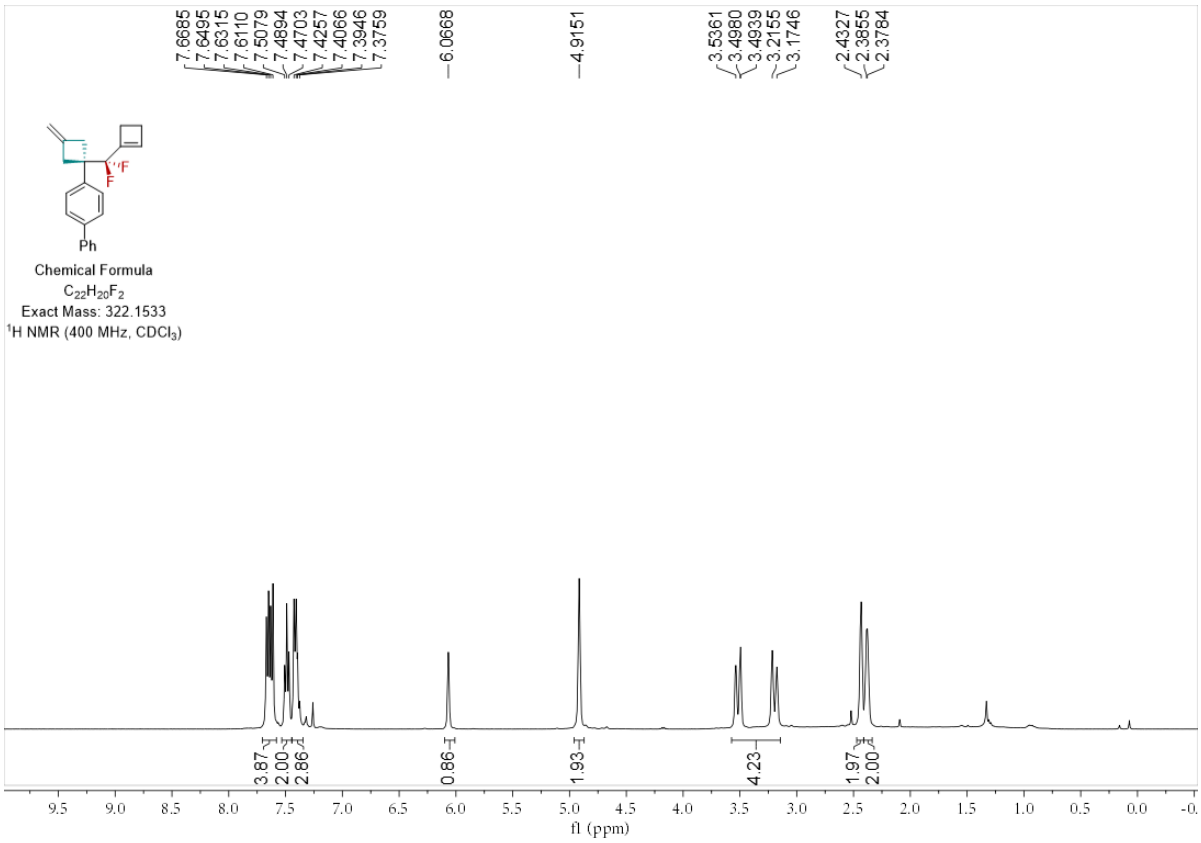
1-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)-3-(2-methylbut-3-en-2-yl)bicyclo[1.1.1]pentane (4i)

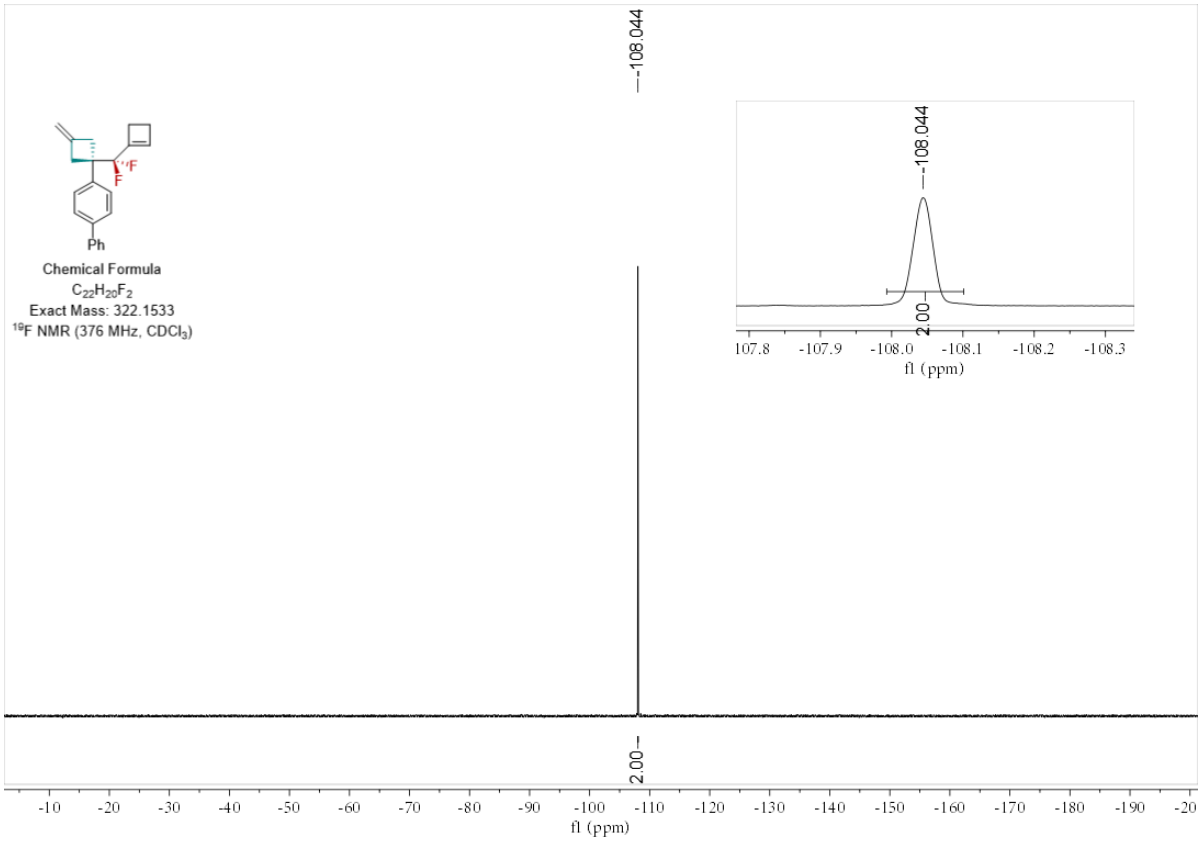


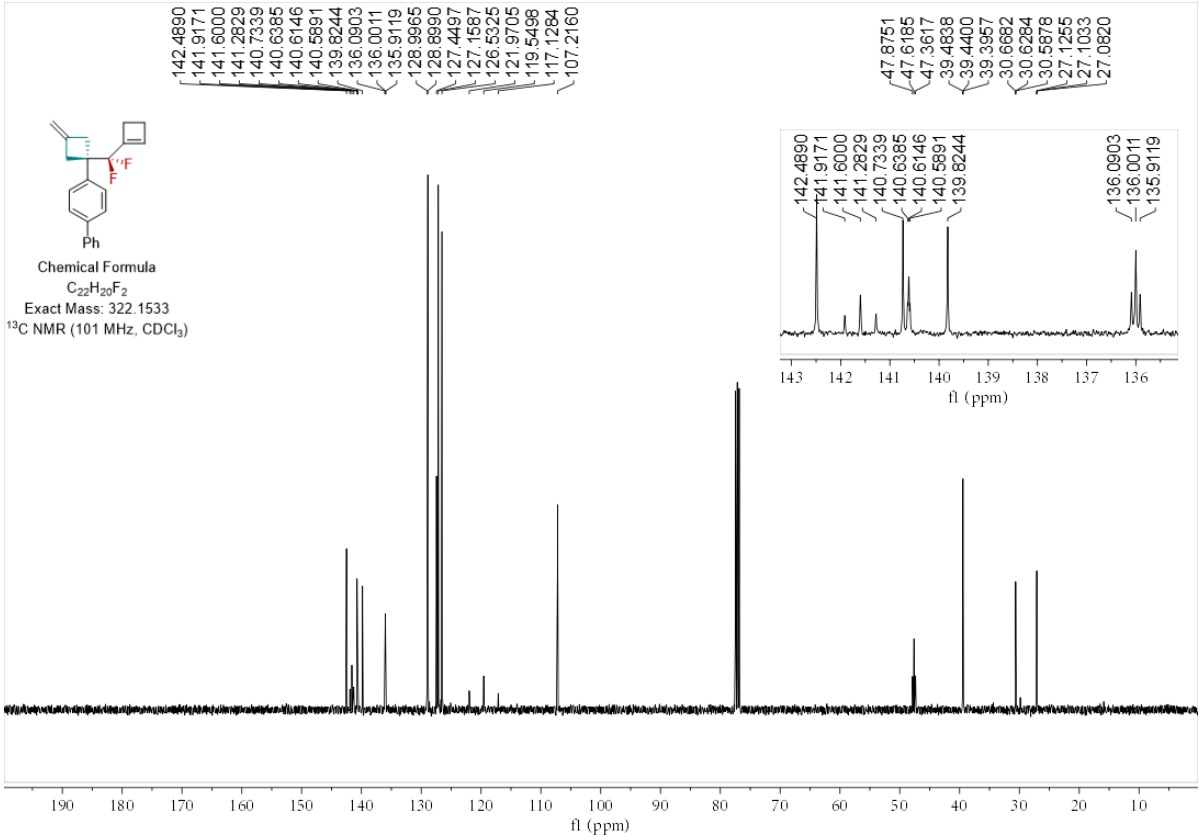




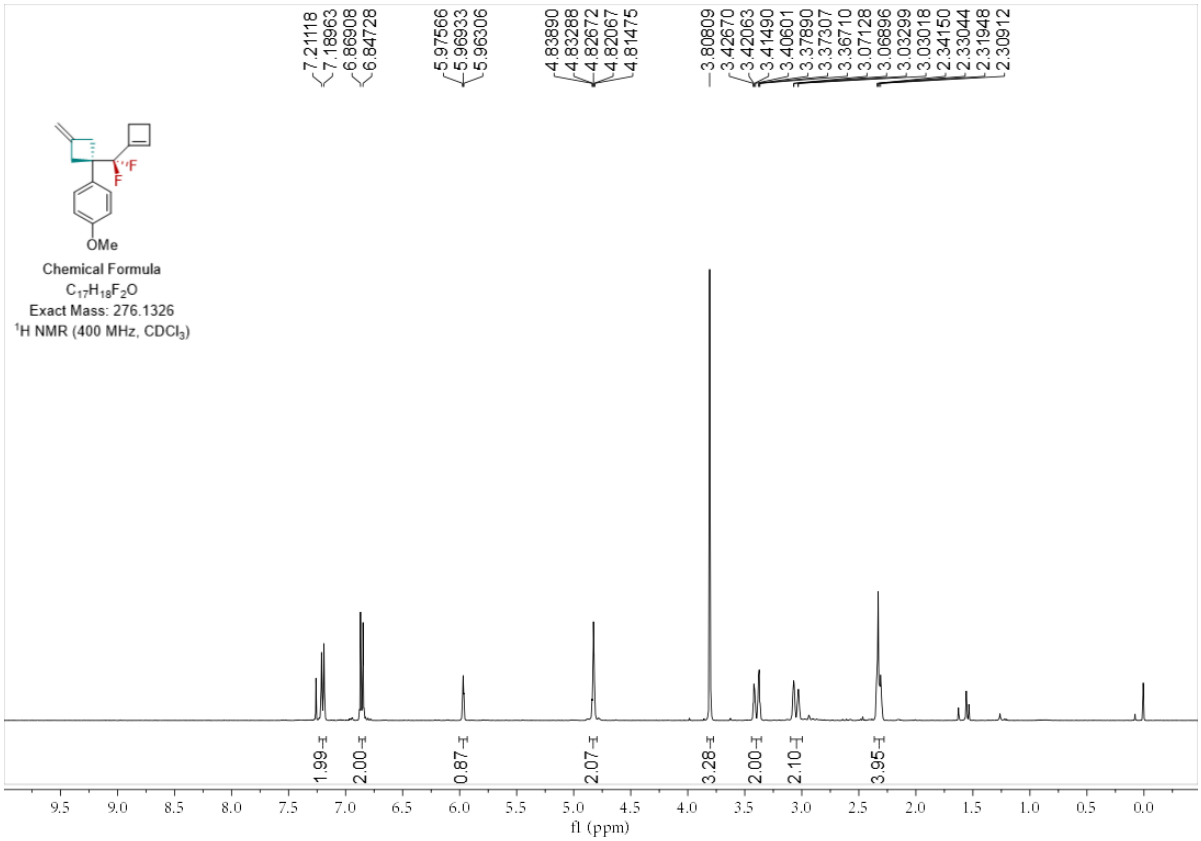
4-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-1,1'-biphenyl (5a)

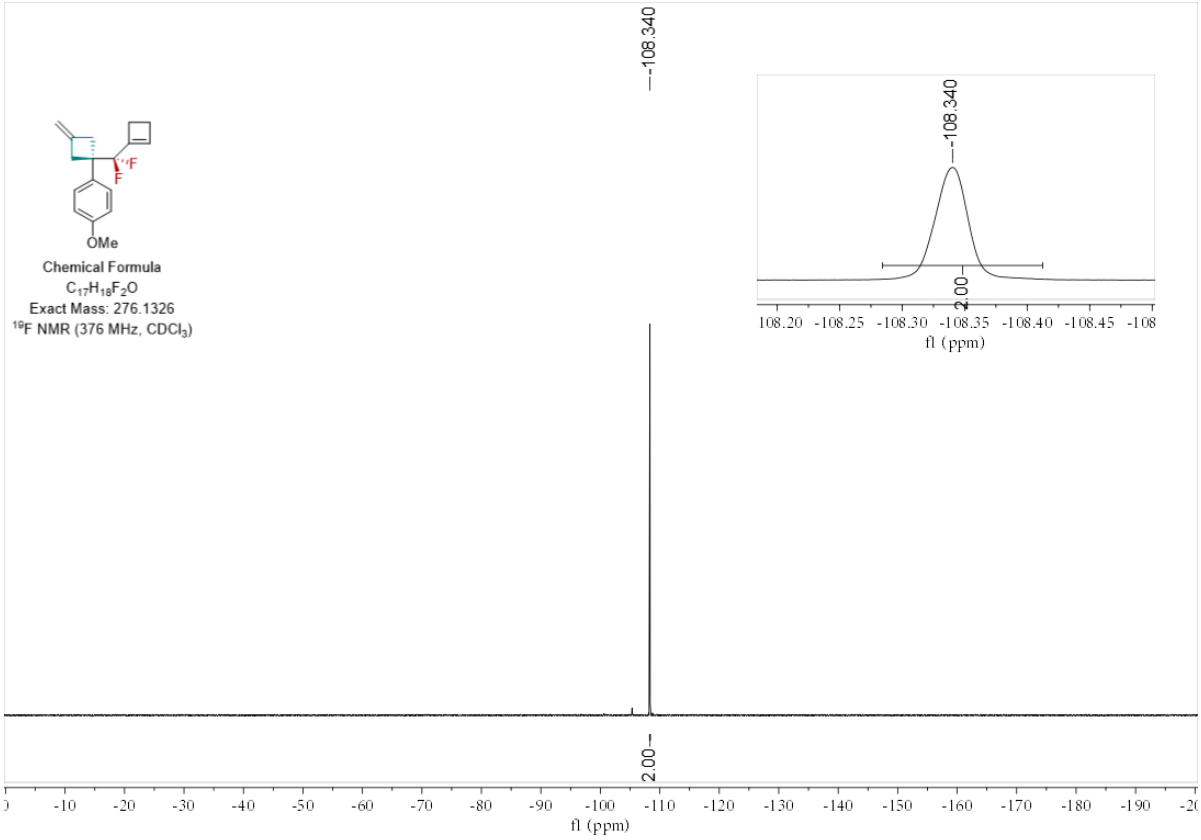


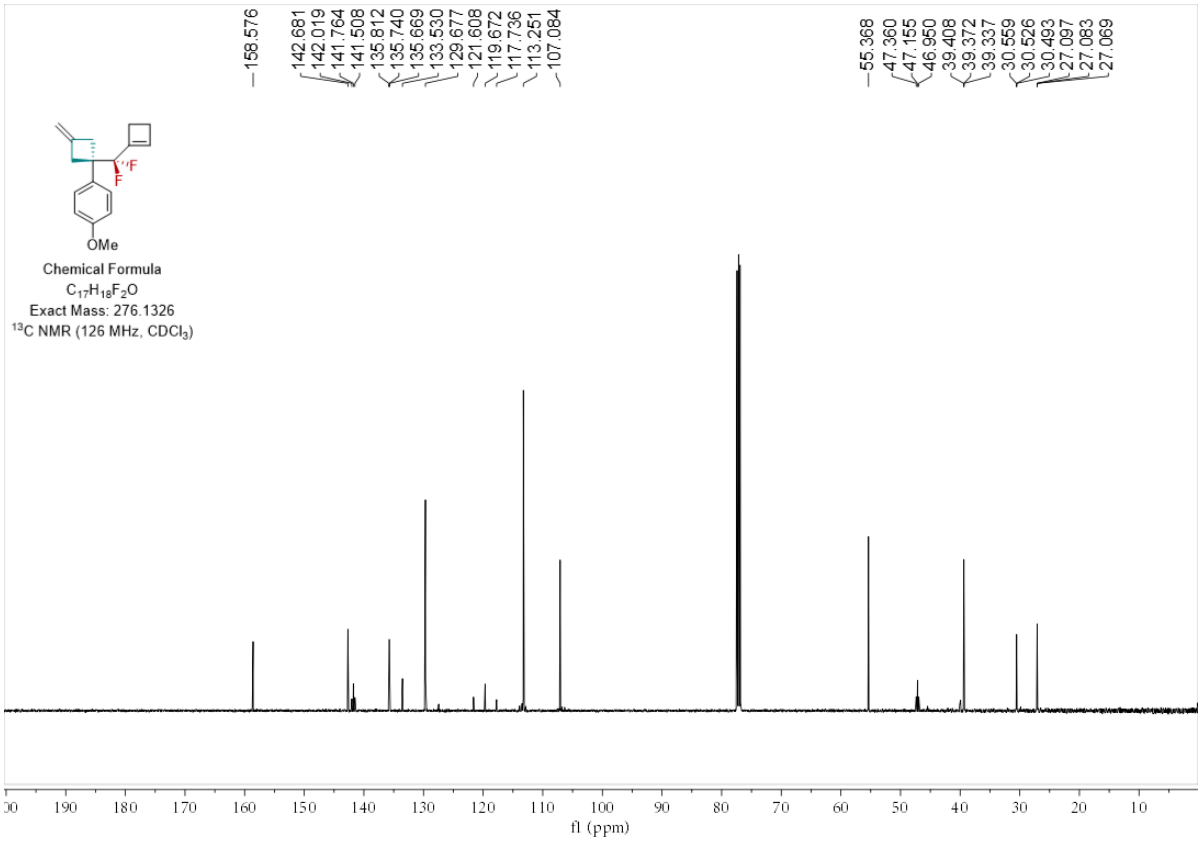

-108.044
Chemical Formula
$C_{22}H_{20}F_2$
Exact Mass: 322.1533
^{19}F NMR (376 MHz, $CDCl_3$)
2.00
f1 (ppm)


142.4890
141.9171
141.6000
141.2829
140.7339
140.6385
140.6146
140.5891
139.8244
136.0903
136.0011
135.9119
128.9965
128.8990
127.4497
127.1587
126.5325
121.9705
119.5498
117.1284
107.2160
47.8751
47.6185
47.3617
39.4838
39.4400
39.3957
30.6682
30.6284
30.5878
27.1255
27.1033
27.0820
Chemical Formula
$C_{22}H_{20}F_2$
Exact Mass: 322.1533
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)

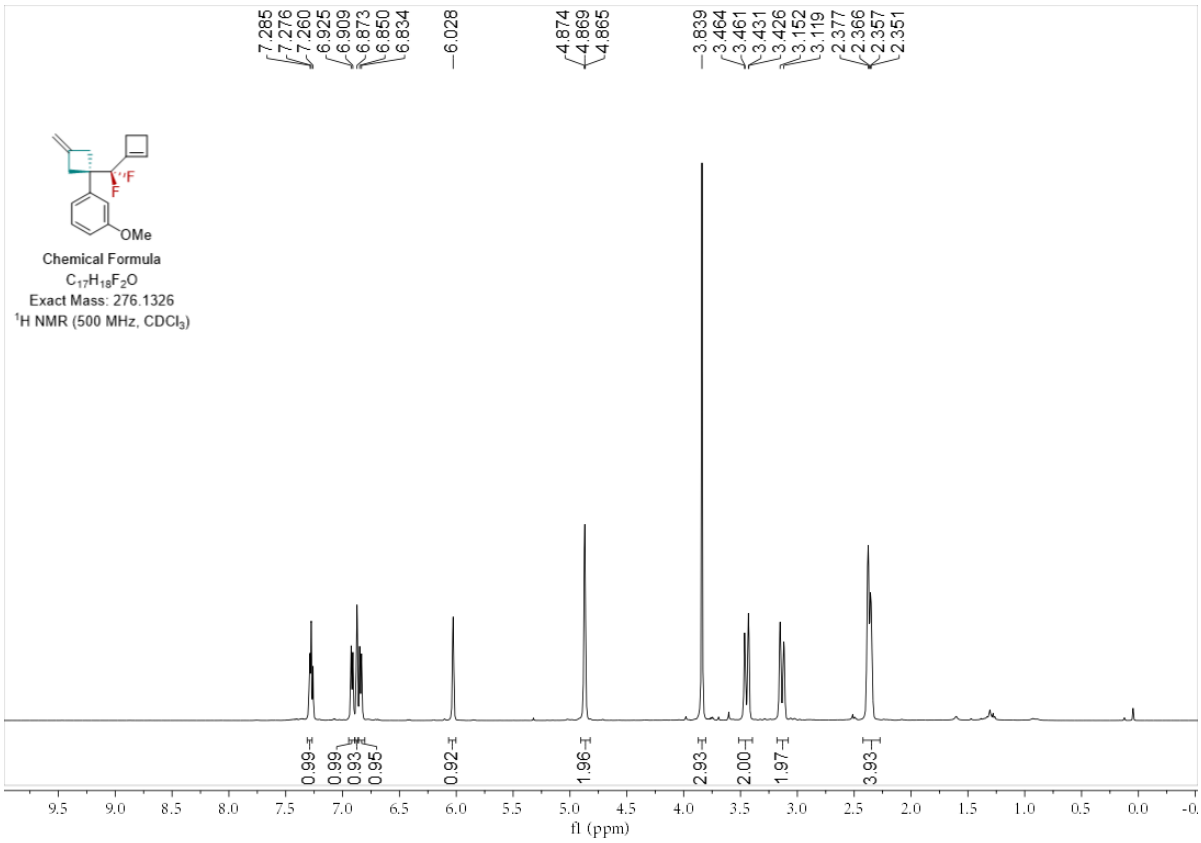
1-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-4-methoxybenzene (5b)

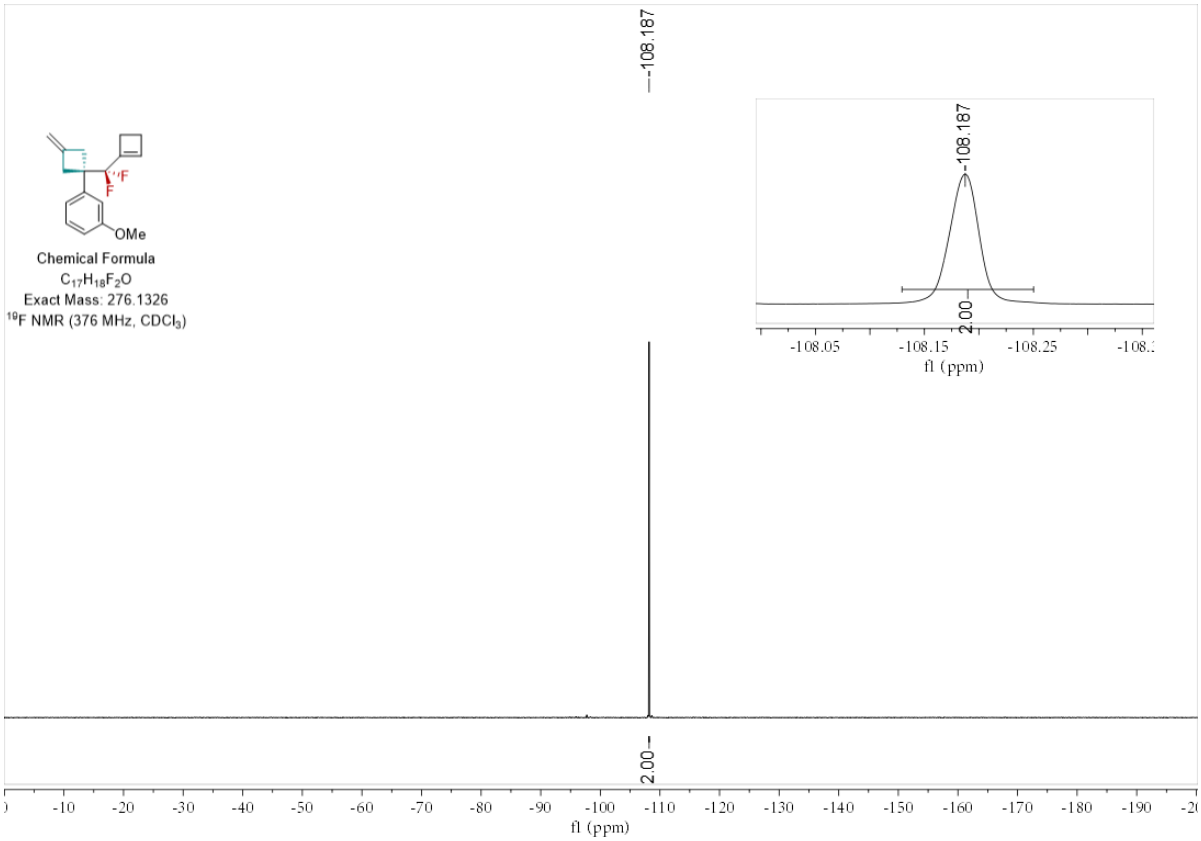


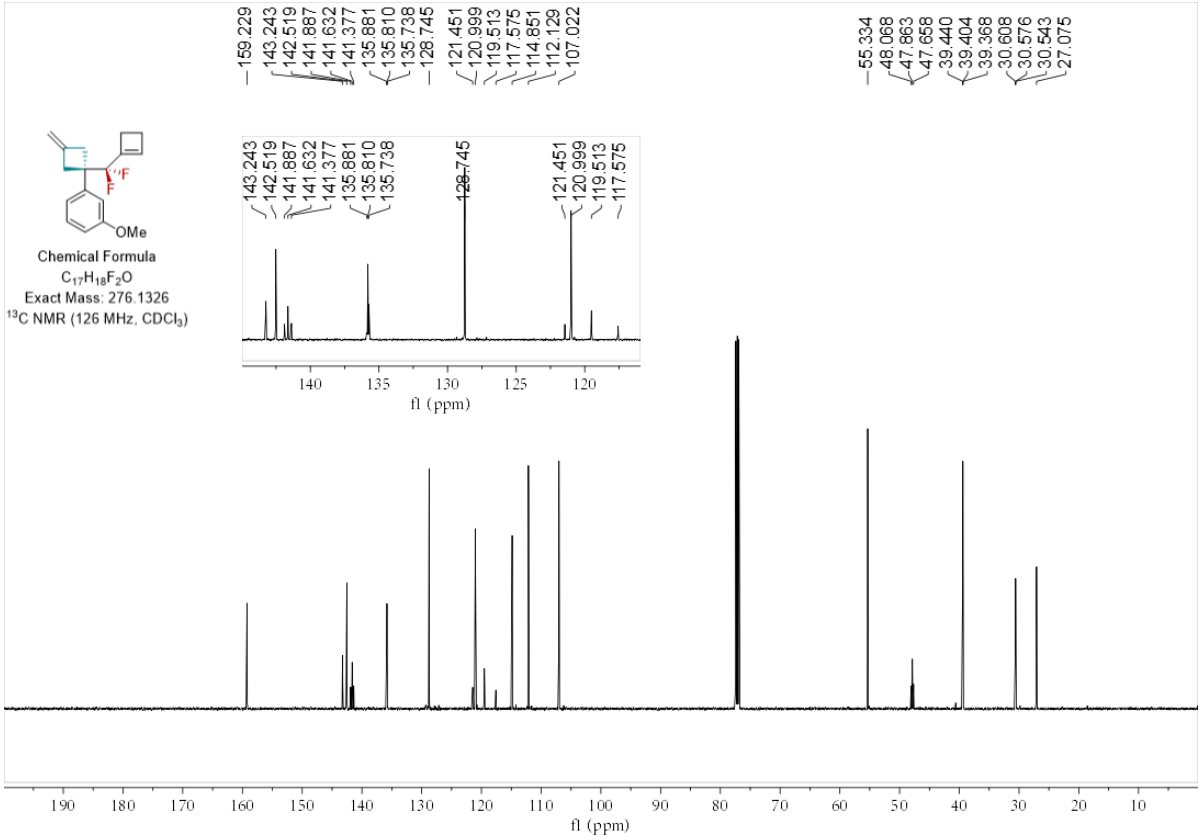




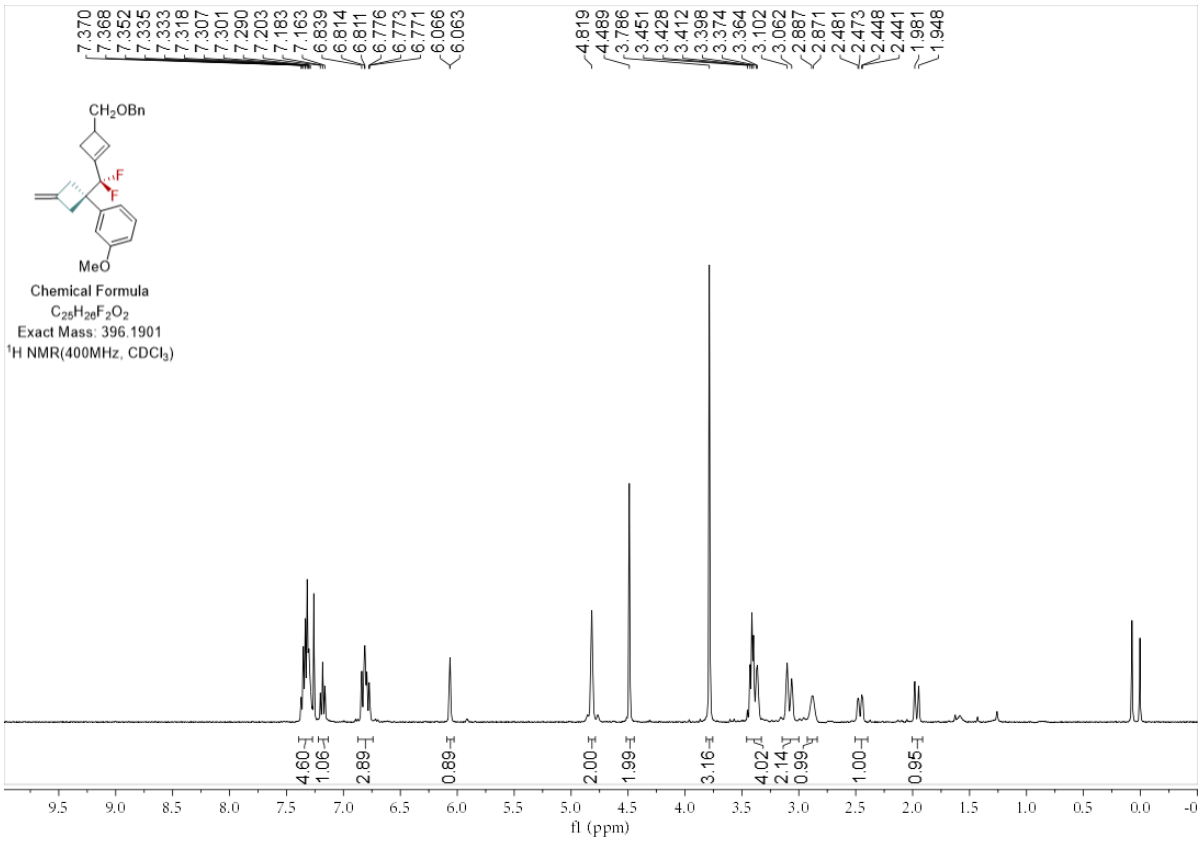
1-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)-3-methoxybenzene (5c)

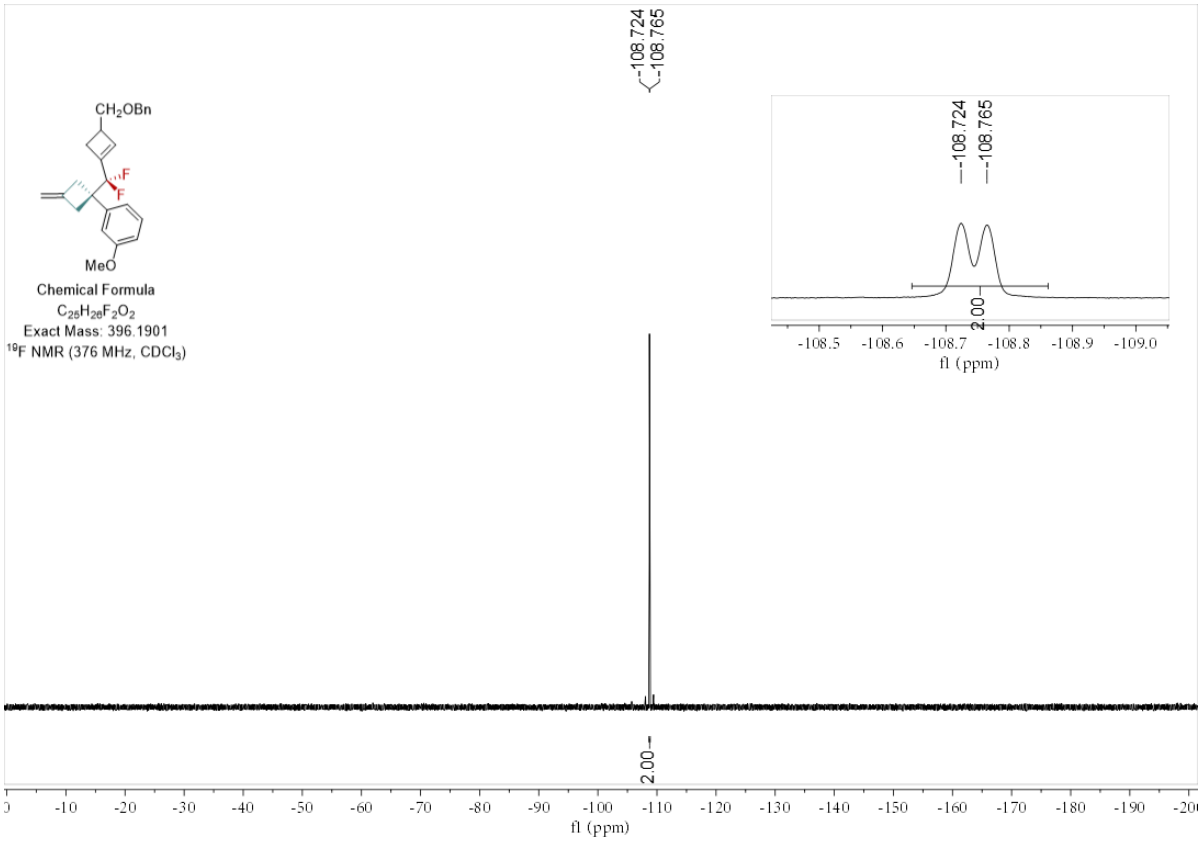


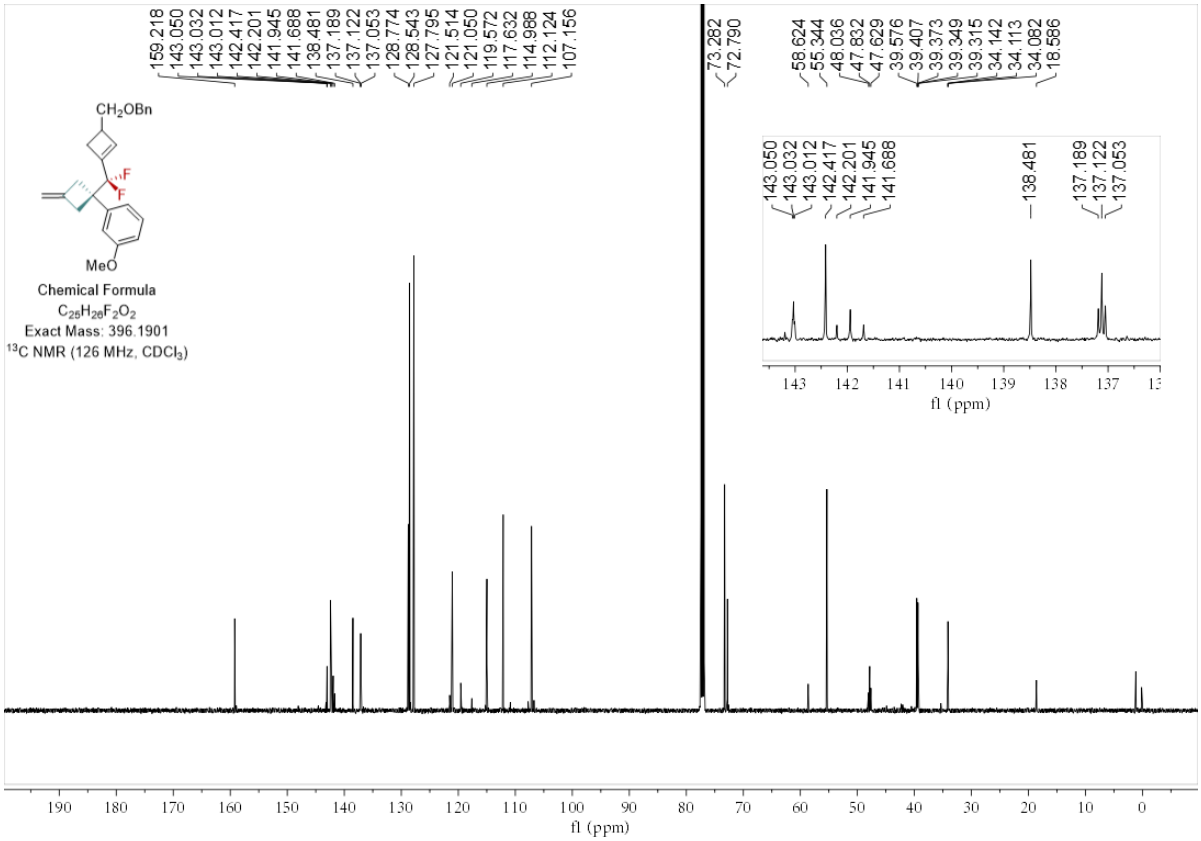

-108.187
Chemical Formula
$C_{17}H_{18}F_2O$
Exact Mass: 276.1326
^{19}F NMR (376 MHz, $CDCl_3$)
OMe
-108.187
2.00
-108.05
-108.15
-108.25
f1 (ppm)
2.00
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


159.229
143.243
142.519
141.887
141.632
141.377
135.881
135.810
135.738
128.745
121.451
120.999
119.513
117.575
114.851
112.129
107.022
55.334
48.068
47.863
47.658
39.440
39.404
39.368
30.608
30.576
30.543
27.075
Chemical Formula
$C_{17}H_{18}F_2O$
Exact Mass: 276.1326
^{13}C NMR (126 MHz, $CDCl_3$)
OMe
140 135 130 125 120
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

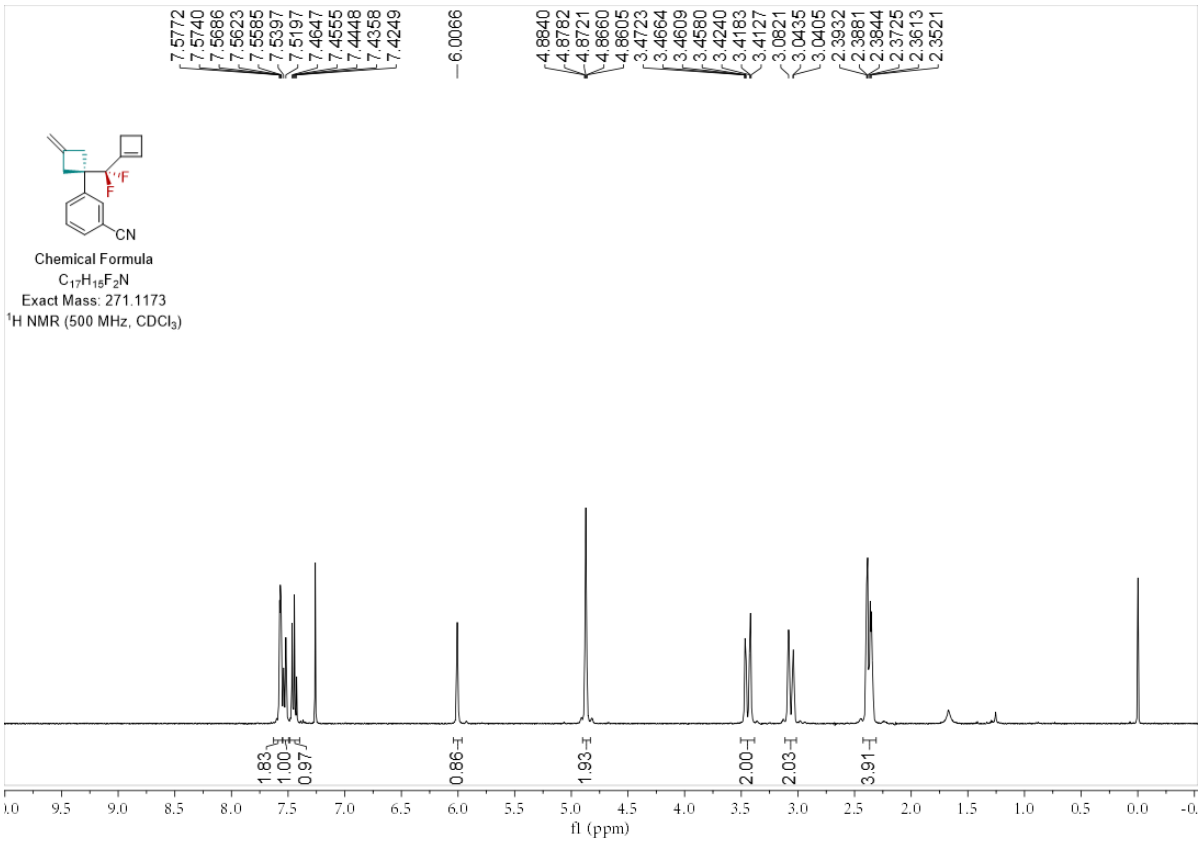
1-(1-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)-3-methylenecyclobutyl)-3-methoxybenzene (5d)

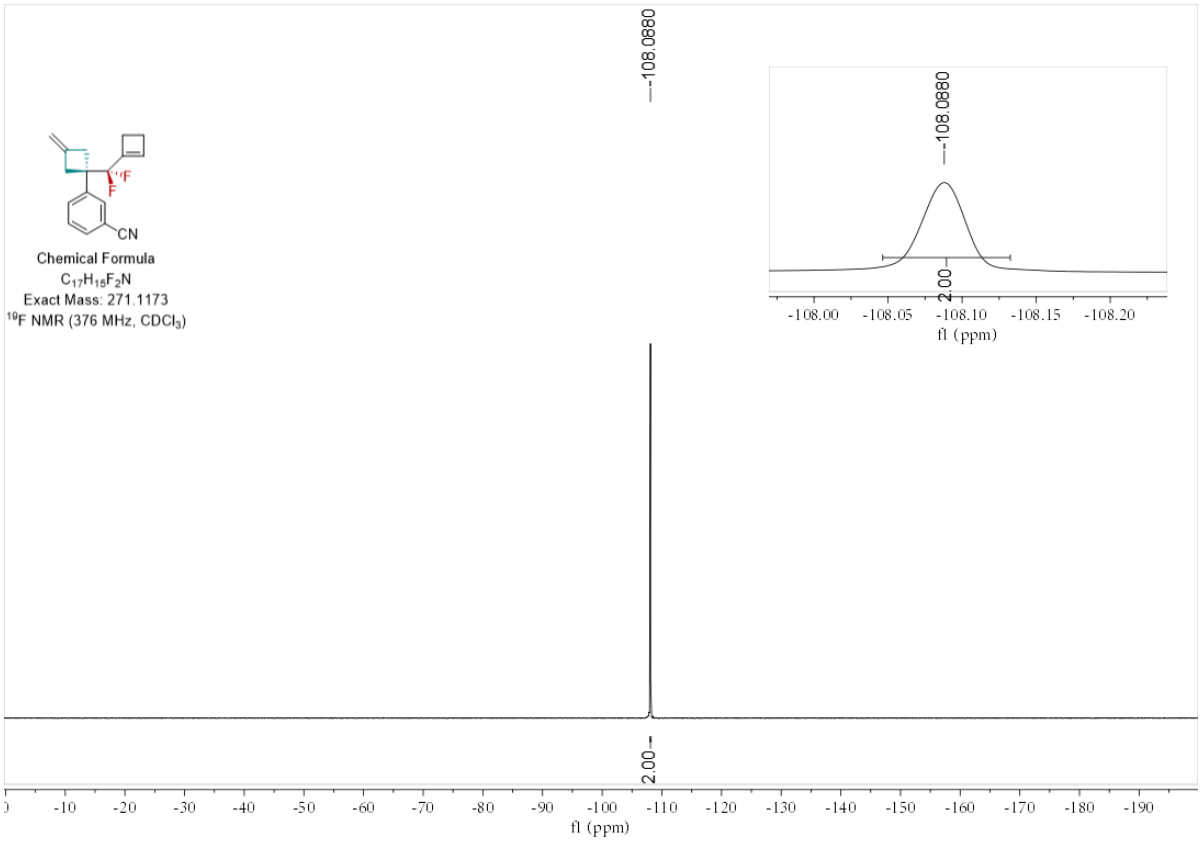


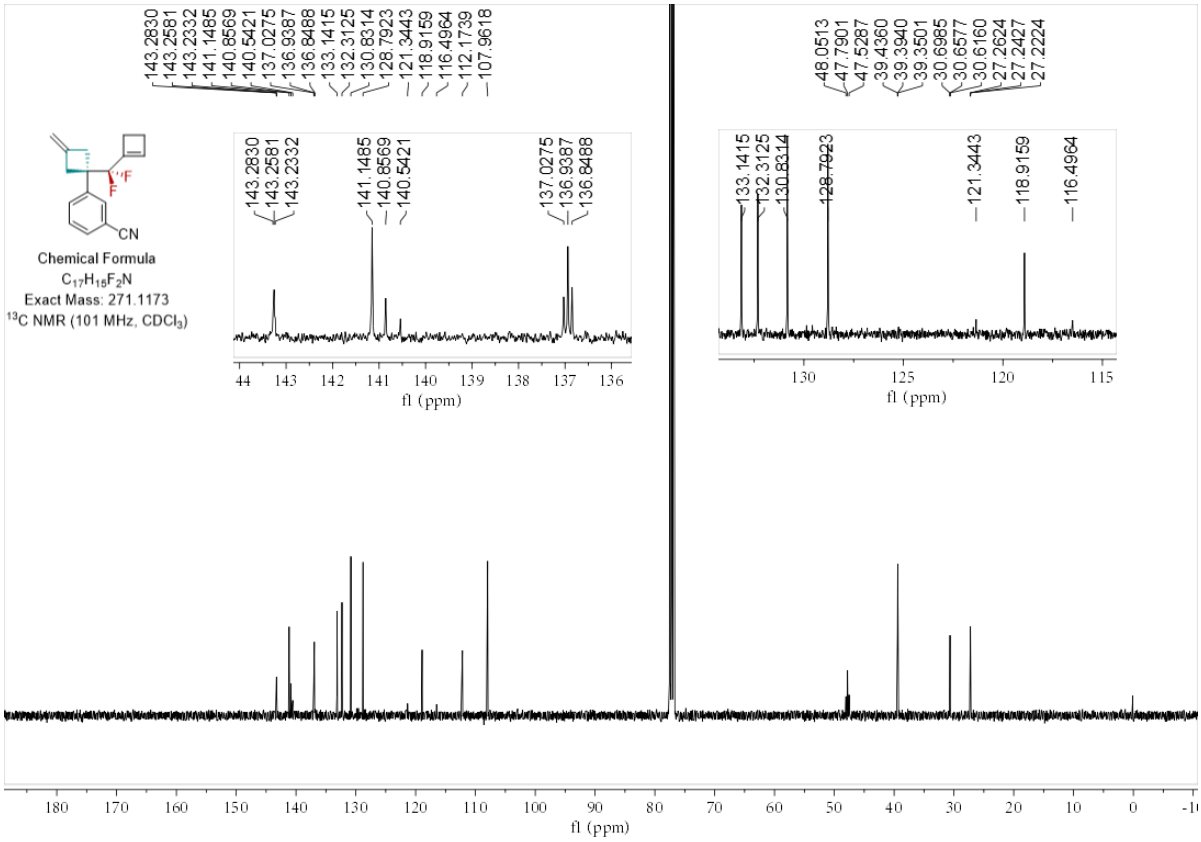




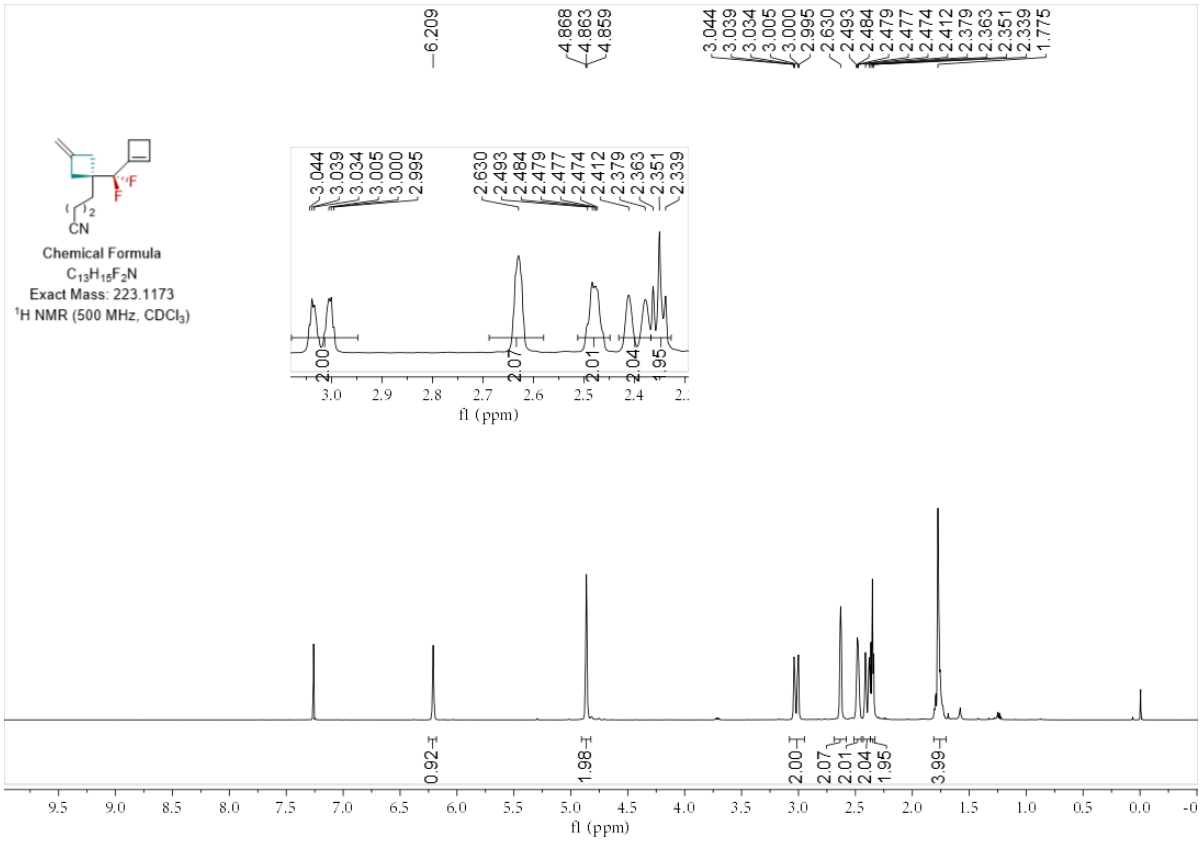
2-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)benzonitrile (5e)

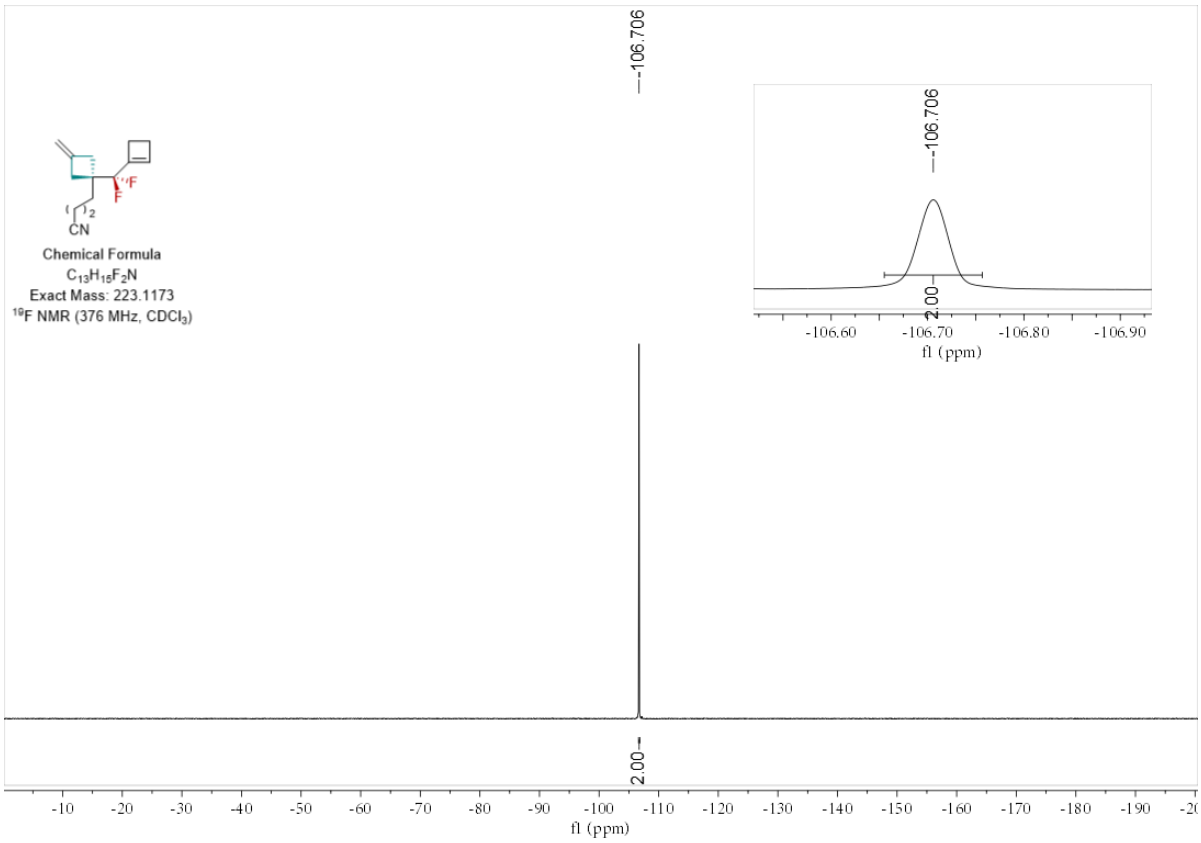


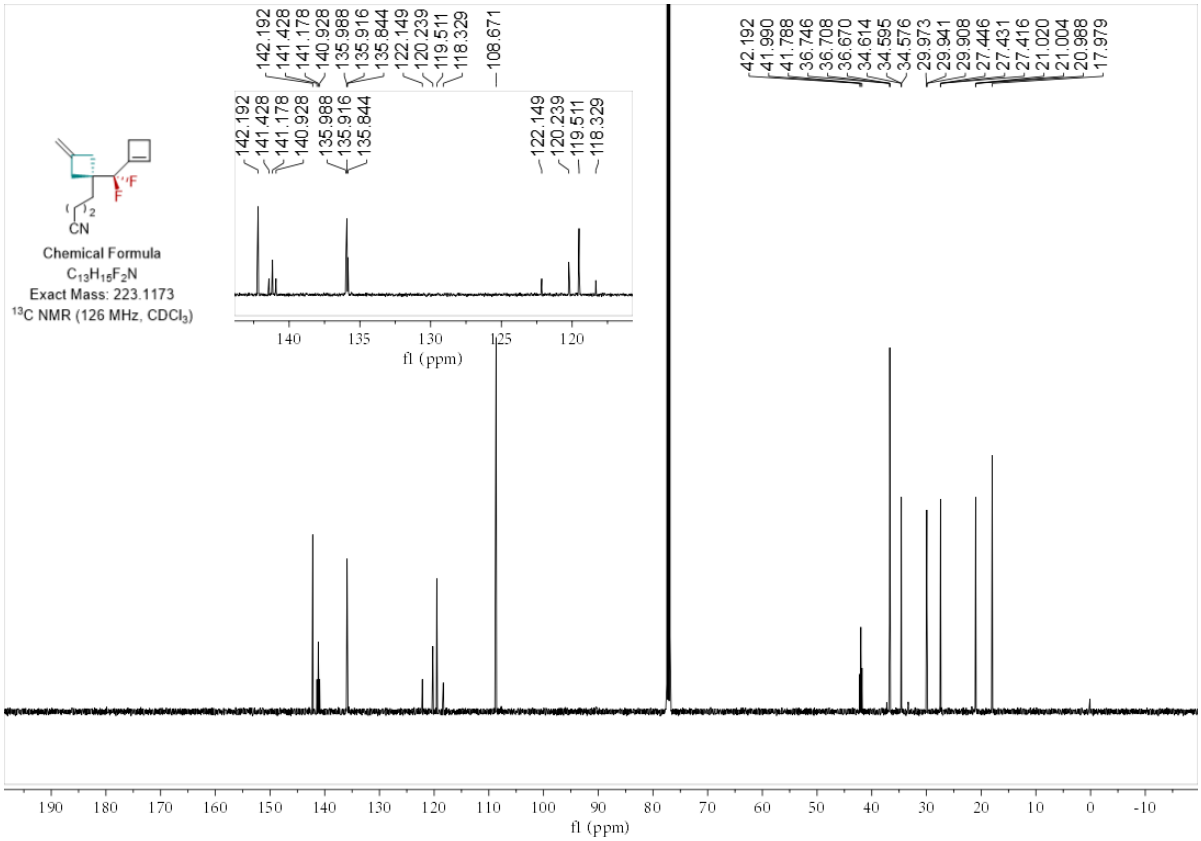

-108.0880
Chemical Formula
$C_{17}H_{15}F_2N$
Exact Mass: 271.1173
^{19}F NMR (376 MHz, $CDCl_3$)
2.00
f1 (ppm)


143.2830
143.2581
143.2332
141.1485
140.8569
140.5421
137.0275
136.9387
136.8488
133.1415
132.3125
130.8314
128.7923
121.3443
118.9159
116.4964
112.1739
107.9618
48.0513
47.7901
47.5287
39.4360
39.3940
39.3501
30.6985
30.6577
30.6160
27.2624
27.2427
27.2224
Chemical Formula
$C_{17}H_{15}F_2N$
Exact Mass: 271.1173
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)

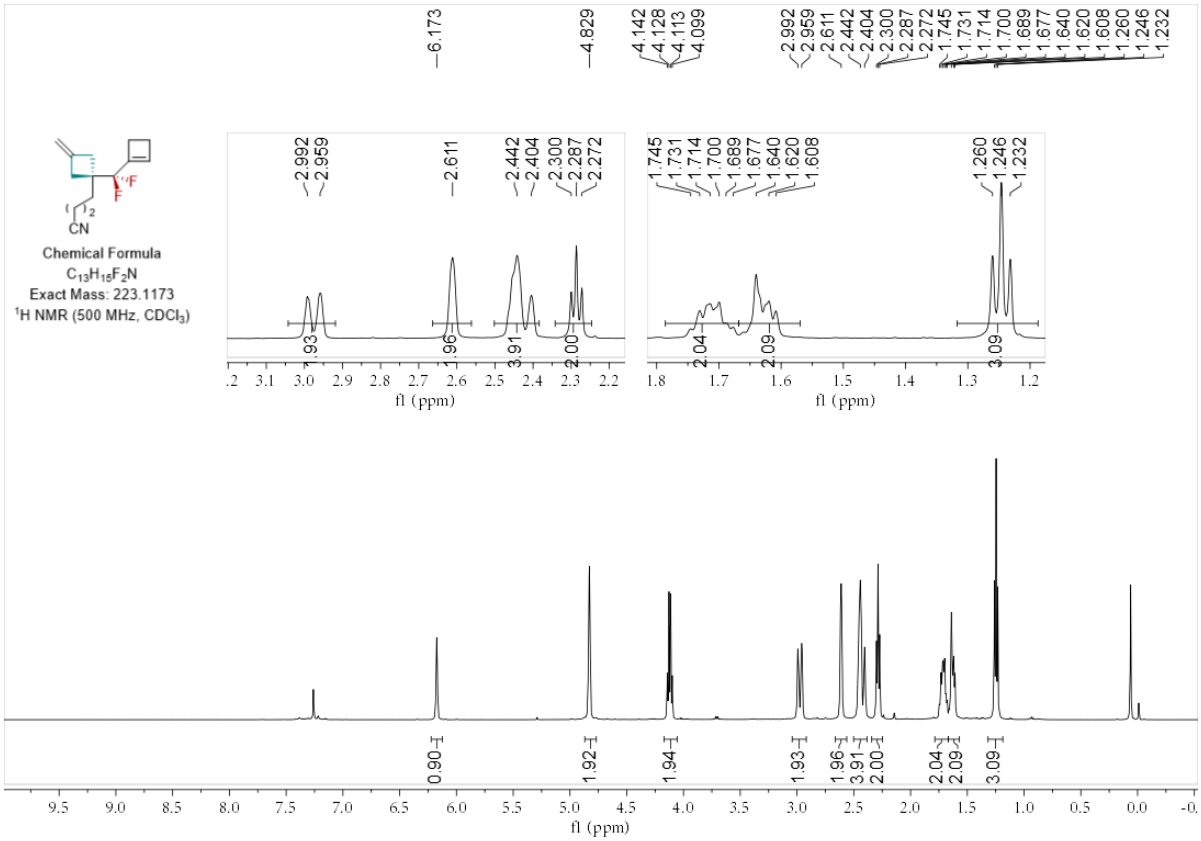
Ethyl 4-(1-(cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)butanoate (5f)

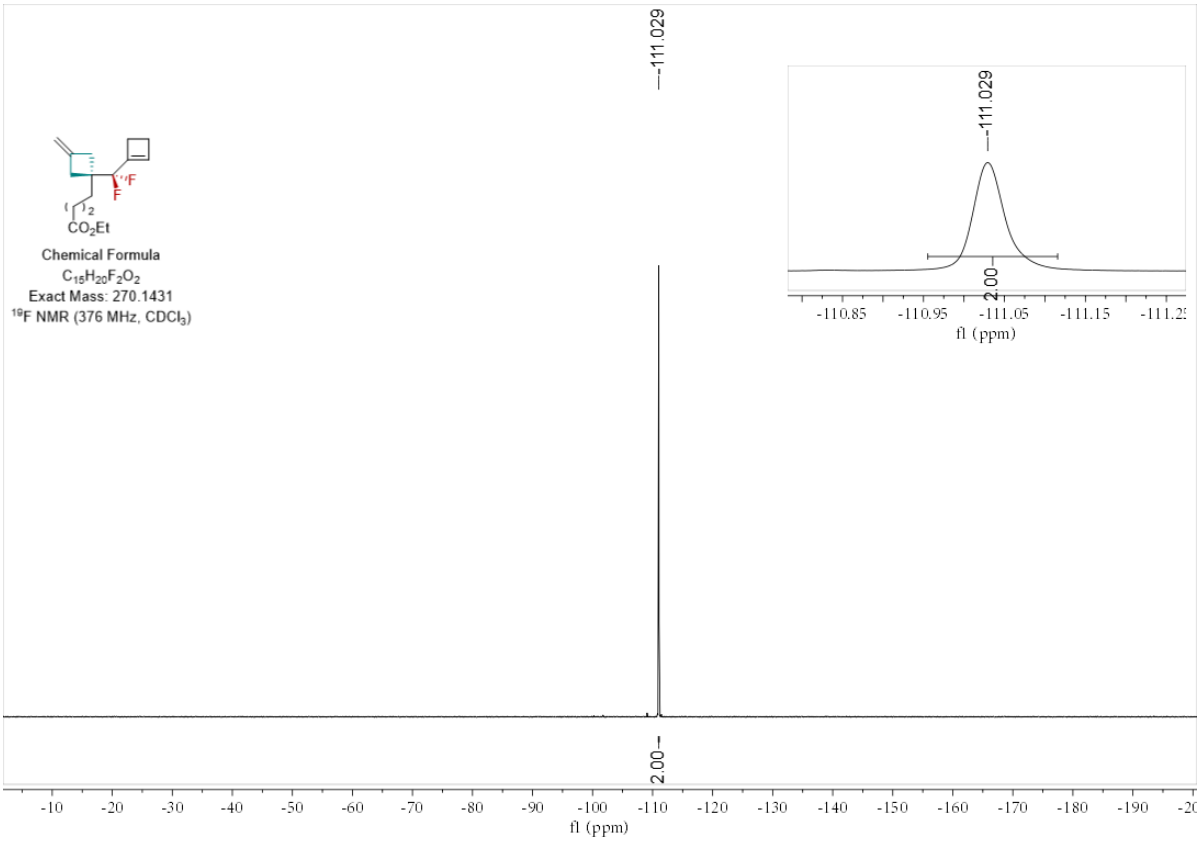


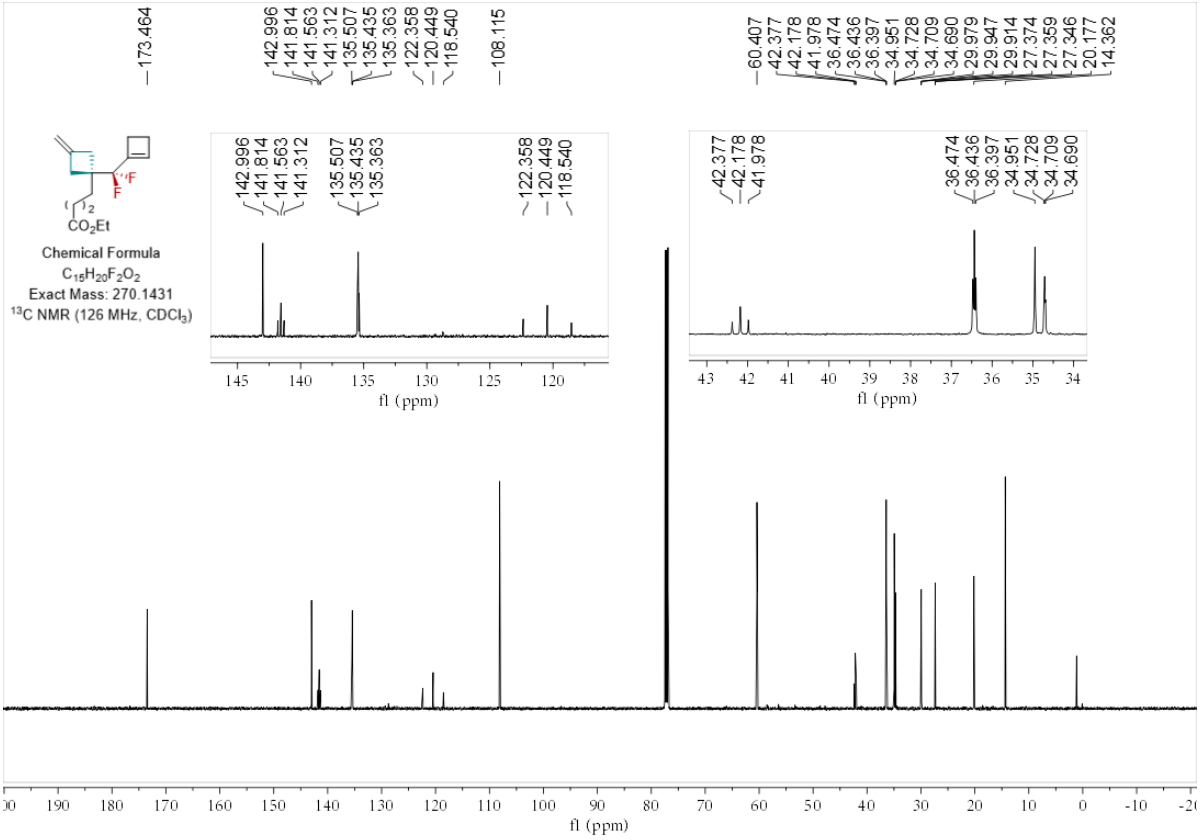




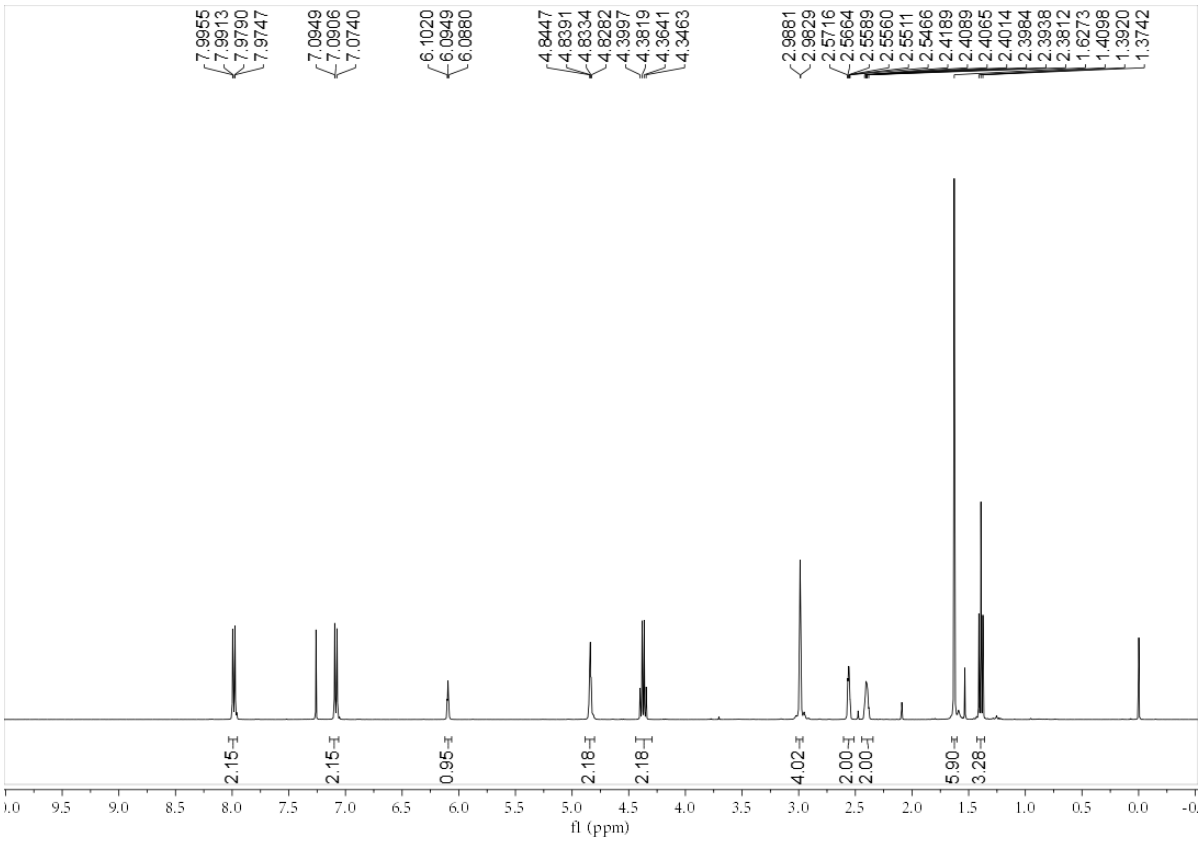
4-(1-(Cyclobut-1-en-1-yldifluoromethyl)-3-methylenecyclobutyl)butanenitrile (5g)

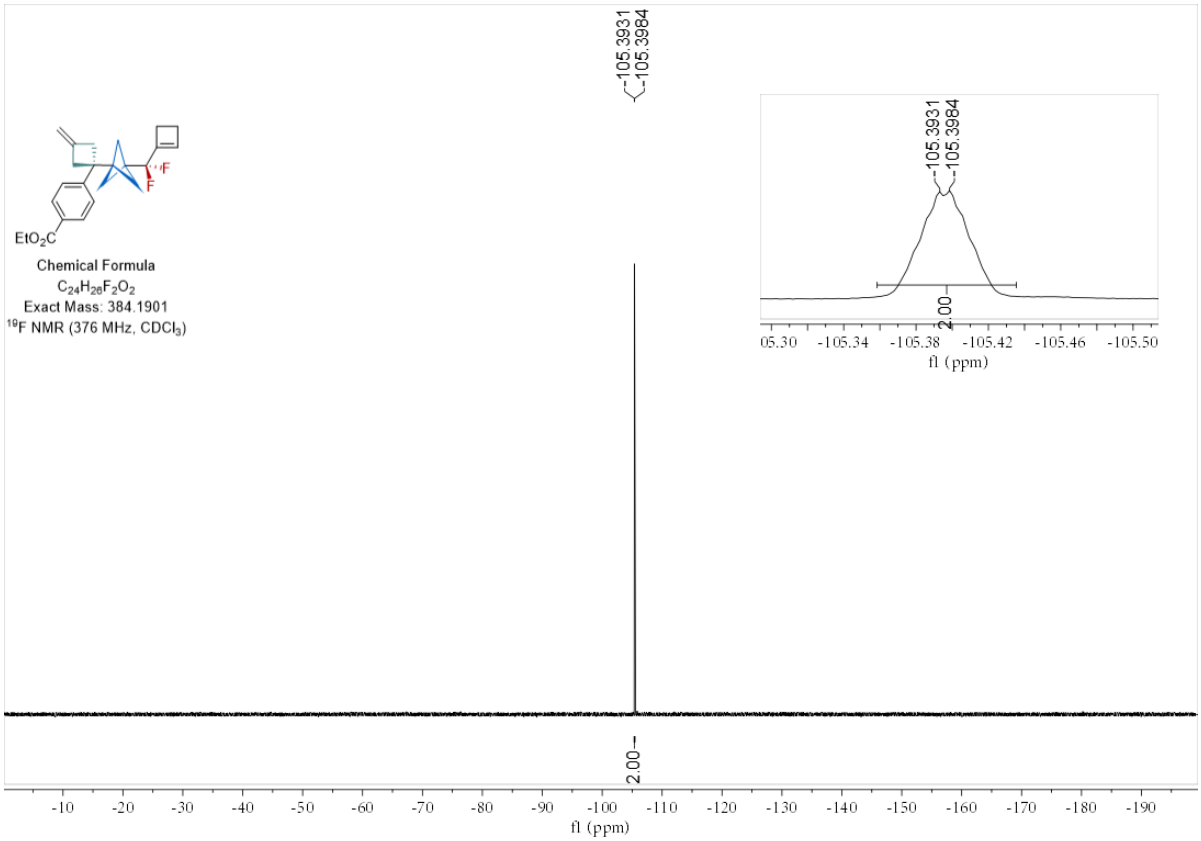


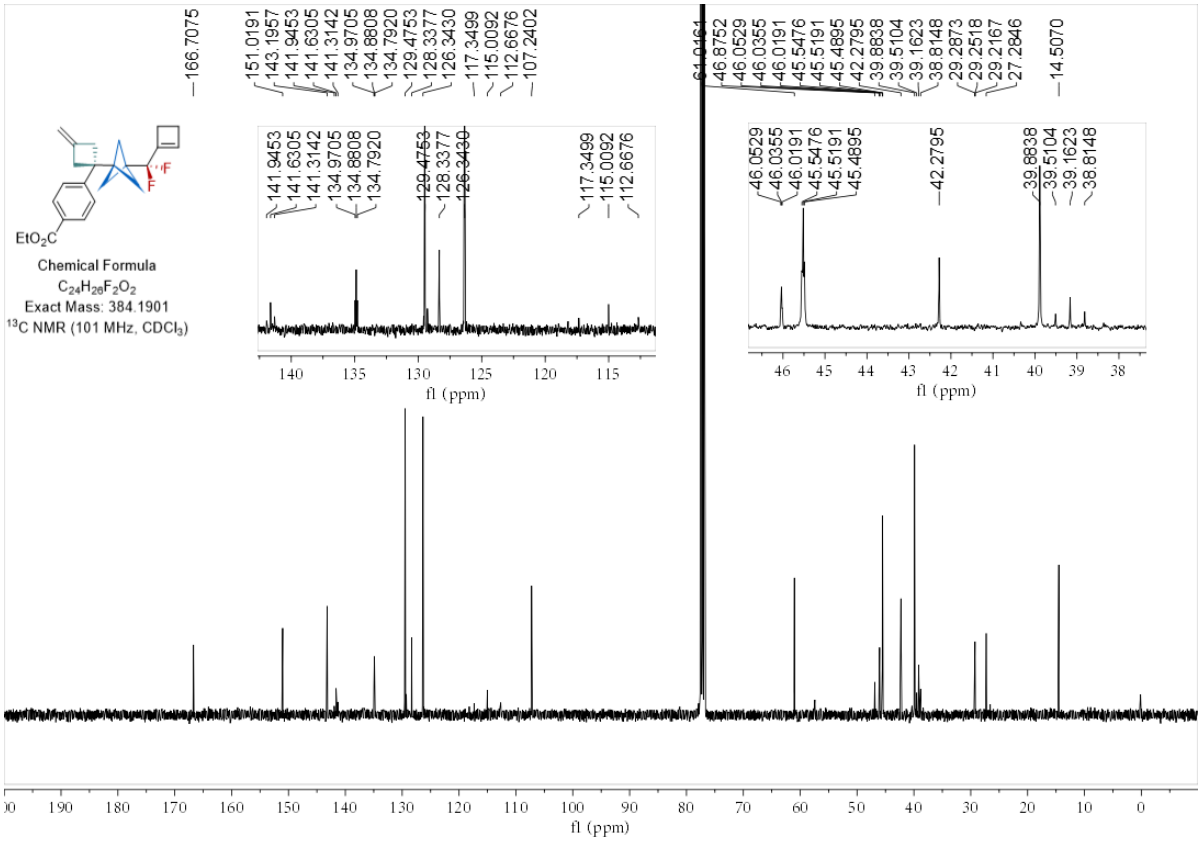

-111.029
Chemical Formula
$C_{15}H_{20}F_2O_2$
Exact Mass: 270.1431
^{19}F NMR (376 MHz, $CDCl_3$)
2.00
fl (ppm)


173.464
142.996
141.814
141.563
141.312
135.507
135.435
135.363
122.358
120.449
118.540
108.115
60.407
42.377
42.178
41.978
36.474
36.436
36.397
34.951
34.728
34.709
34.690
29.979
29.947
29.914
27.374
27.359
27.346
20.177
14.362
Chemical Formula
$C_{15}H_{20}F_2O_2$
Exact Mass: 270.1431
^{13}C NMR (126 MHz, $CDCl_3$)
fl (ppm)

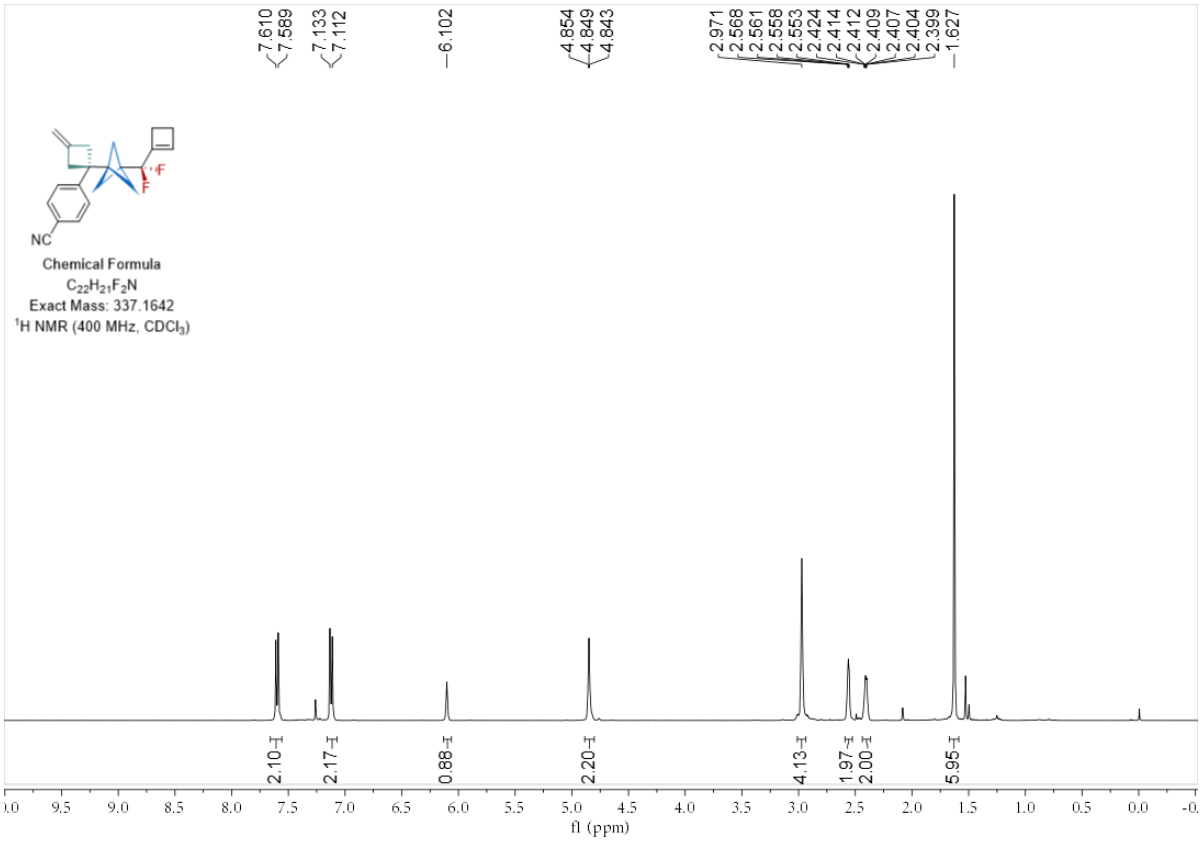
Ethyl4-(1-(3-(cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzoate (6a)

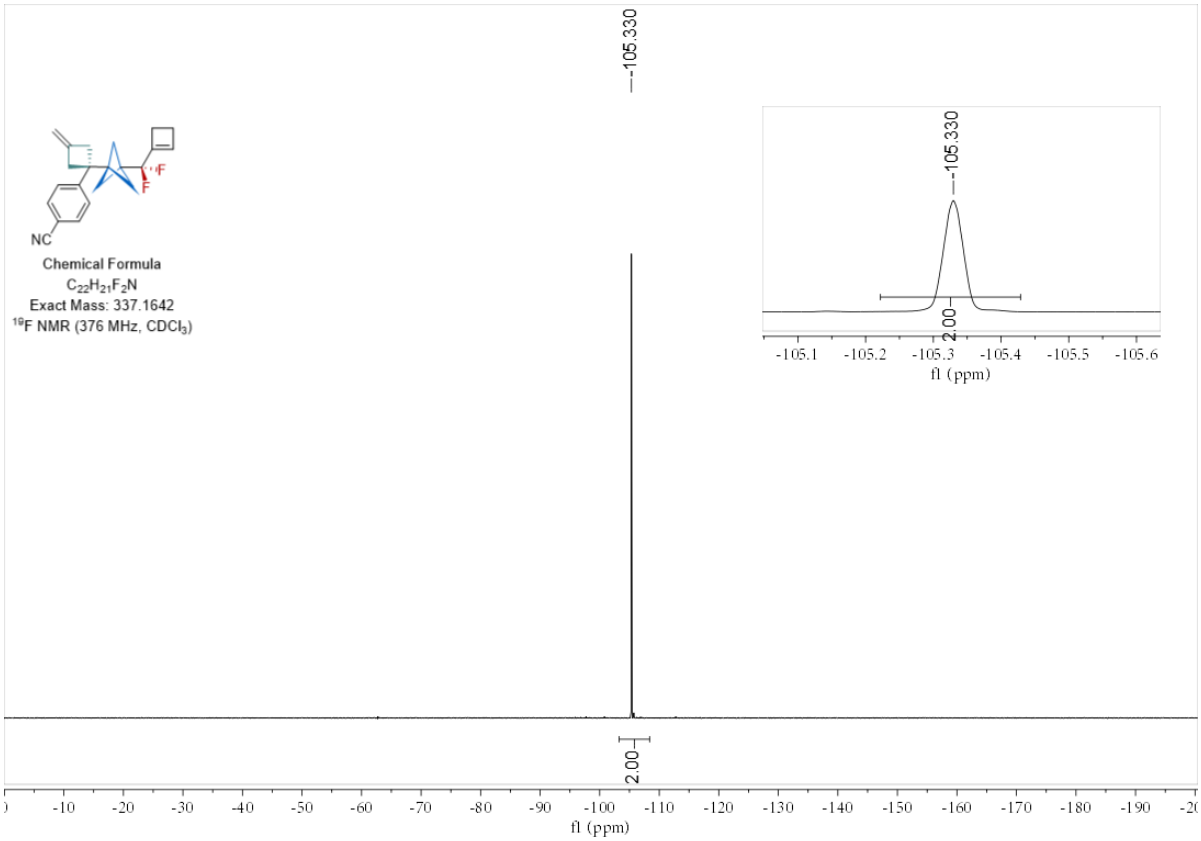


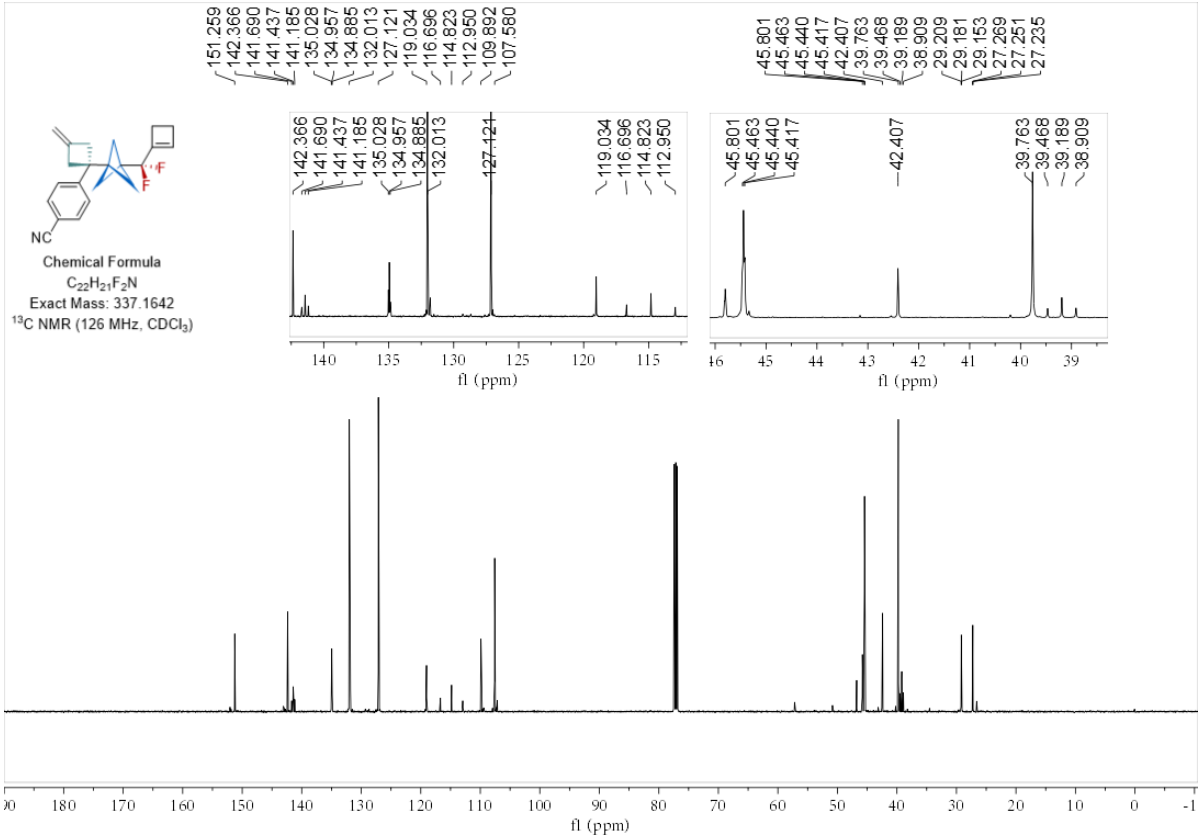




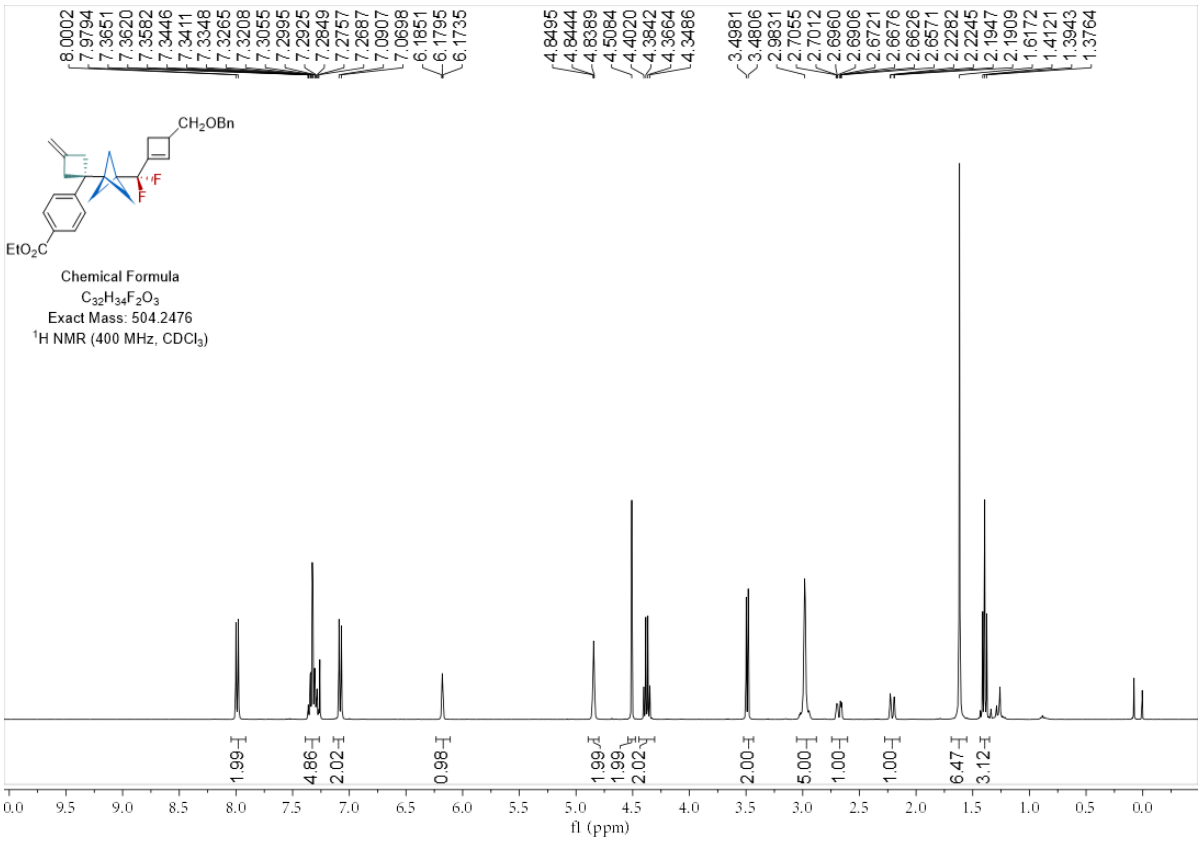
3-(1-(3-(Cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzonitrile (6b)

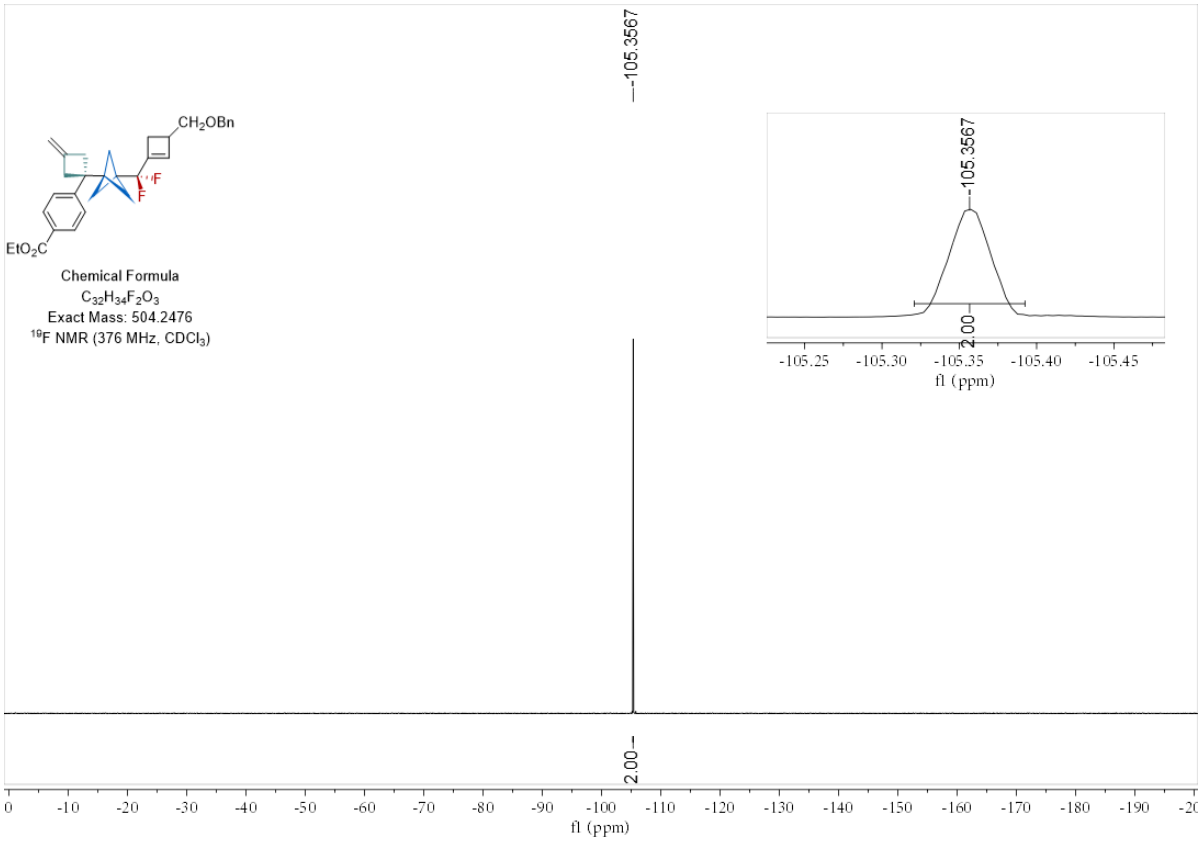


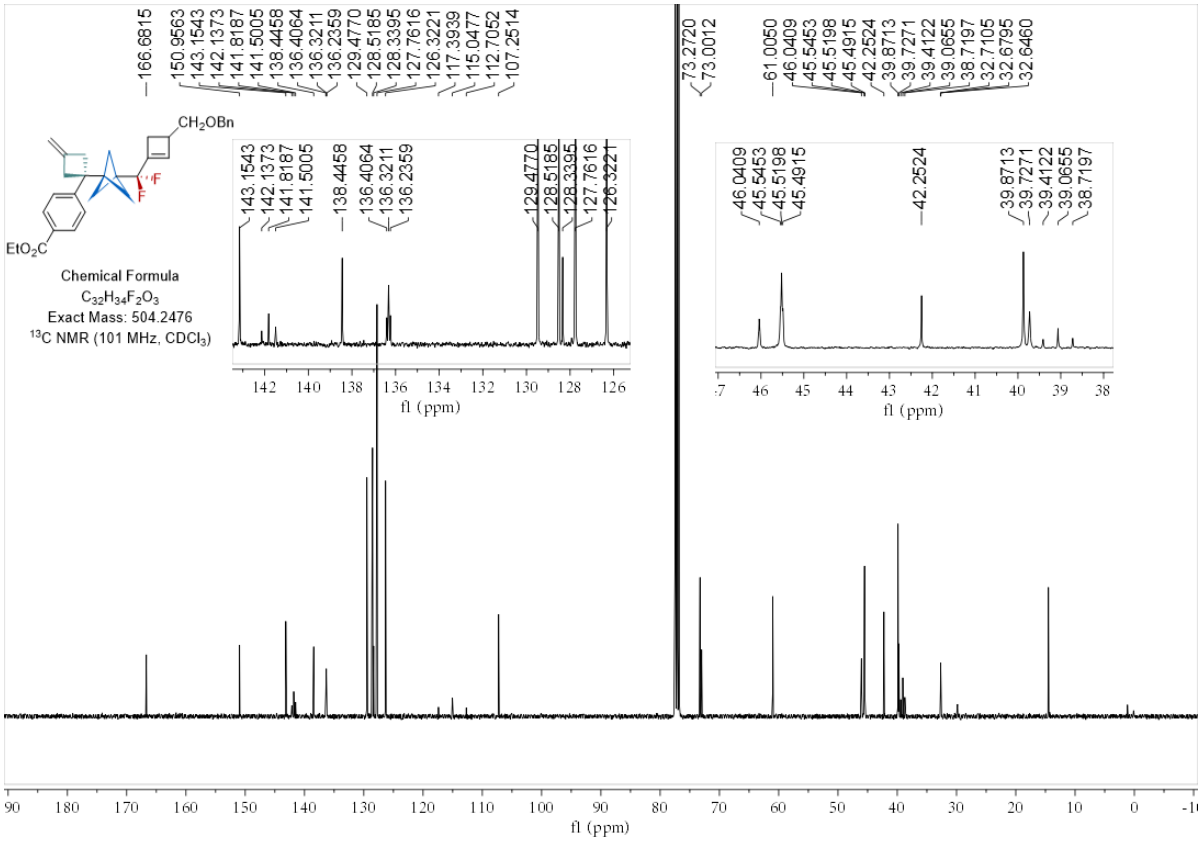

-105.330
F
F
NC
Chemical Formula
$C_{22}H_{21}F_2N$
Exact Mass: 337.1642
^{19}F NMR (376 MHz, $CDCl_3$)
2.00
f1 (ppm)


151.259
142.366
141.690
141.437
141.185
135.028
134.957
134.885
132.013
127.121
119.034
116.696
114.823
112.950
109.892
107.580
45.801
45.463
45.440
45.417
42.407
39.763
39.468
39.189
38.909
29.209
29.181
29.153
27.269
27.251
27.235
F
F
NC
Chemical Formula
$C_{22}H_{21}F_2N$
Exact Mass: 337.1642
^{13}C NMR (126 MHz, $CDCl_3$)
f1 (ppm)

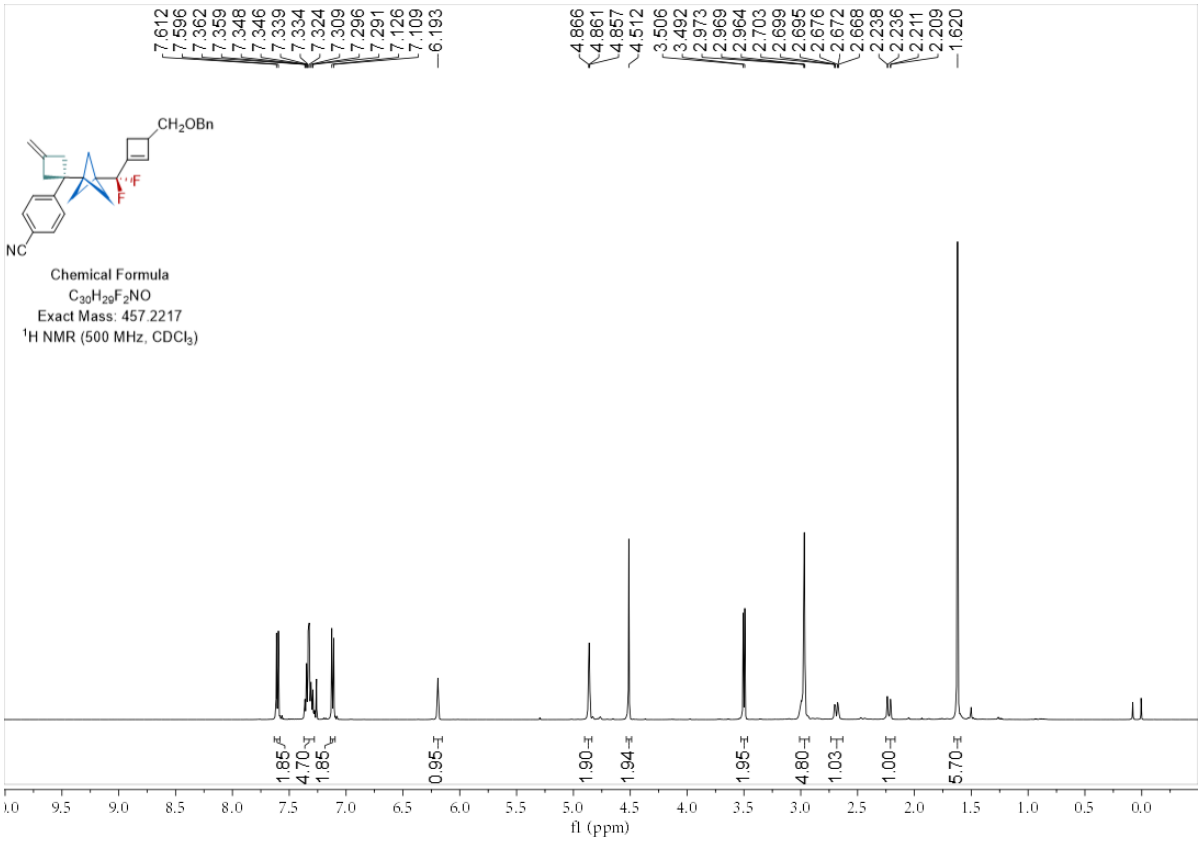
Ethyl4-(1-(3-((3-((benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzoate (6c)

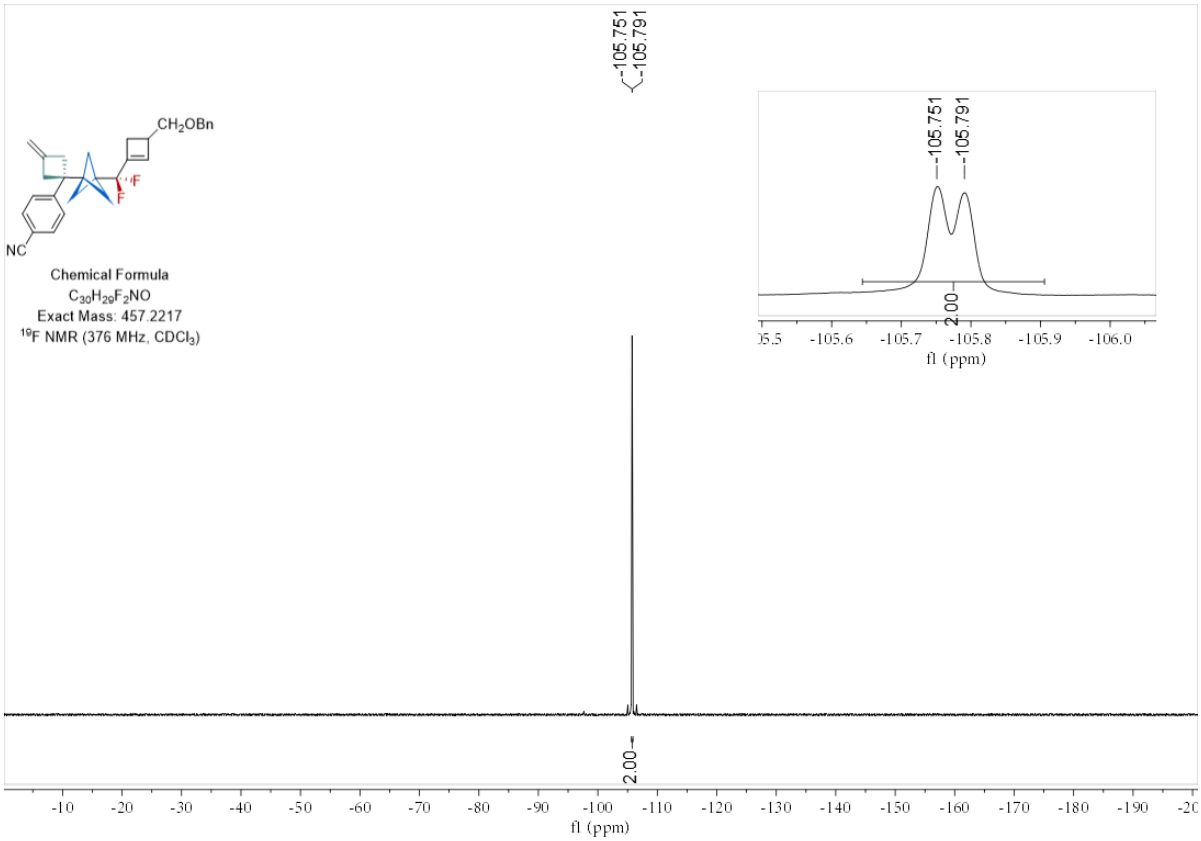


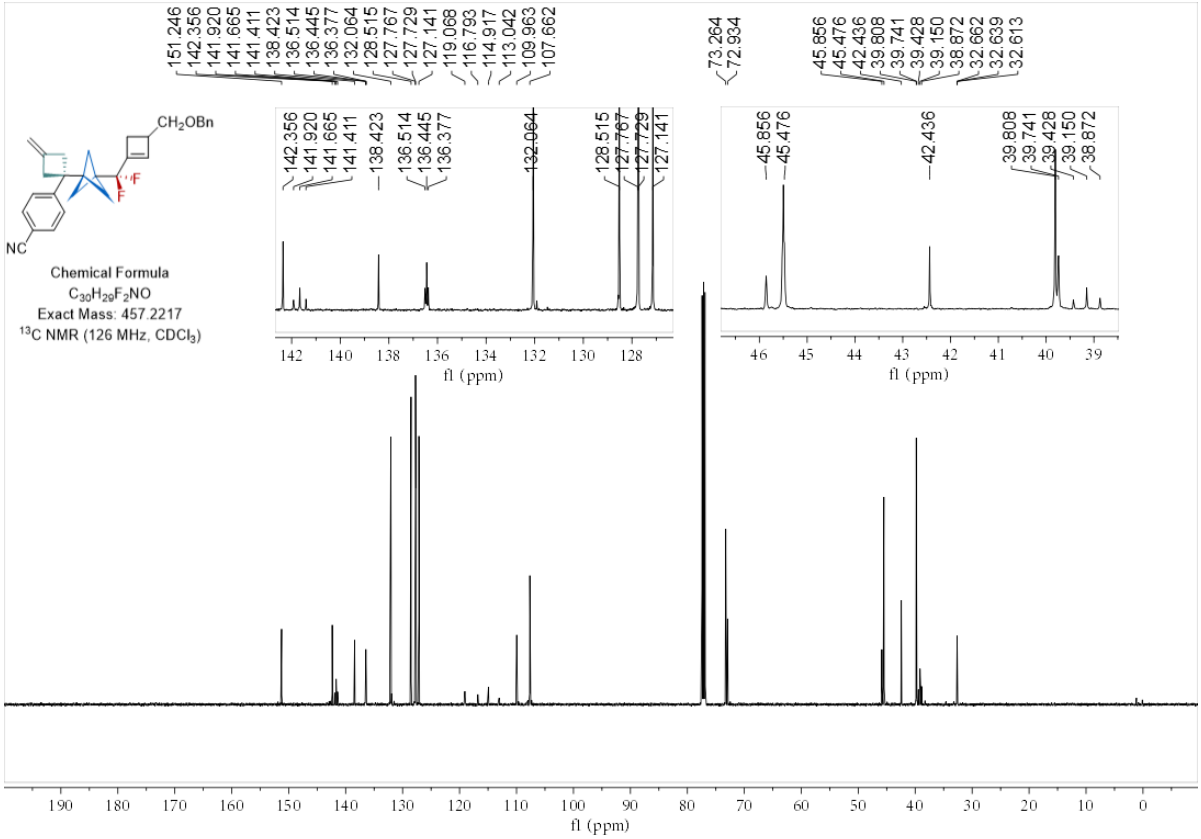




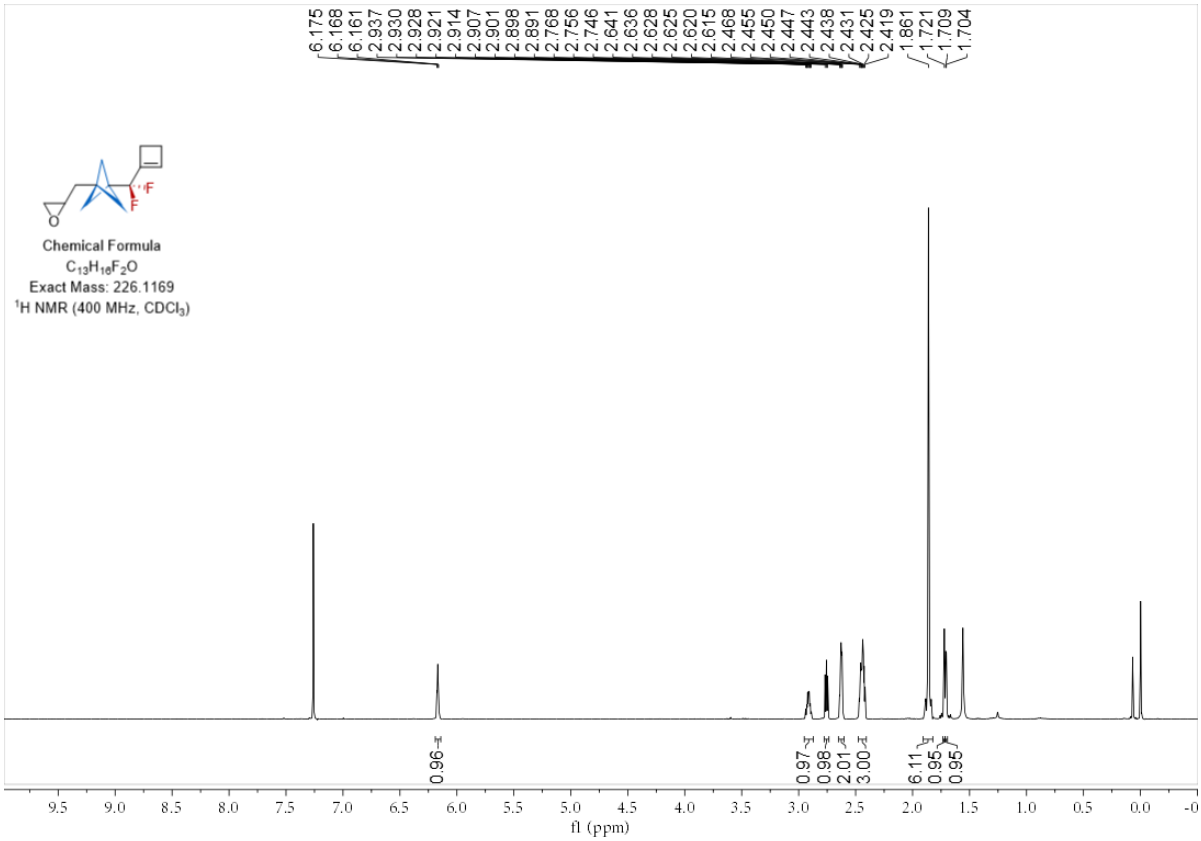
4-(1-(3-((3-((Benzyloxy)methyl)cyclobut-1-en-1-yl)difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-3-methylenecyclobutyl)benzonitrile (6d)

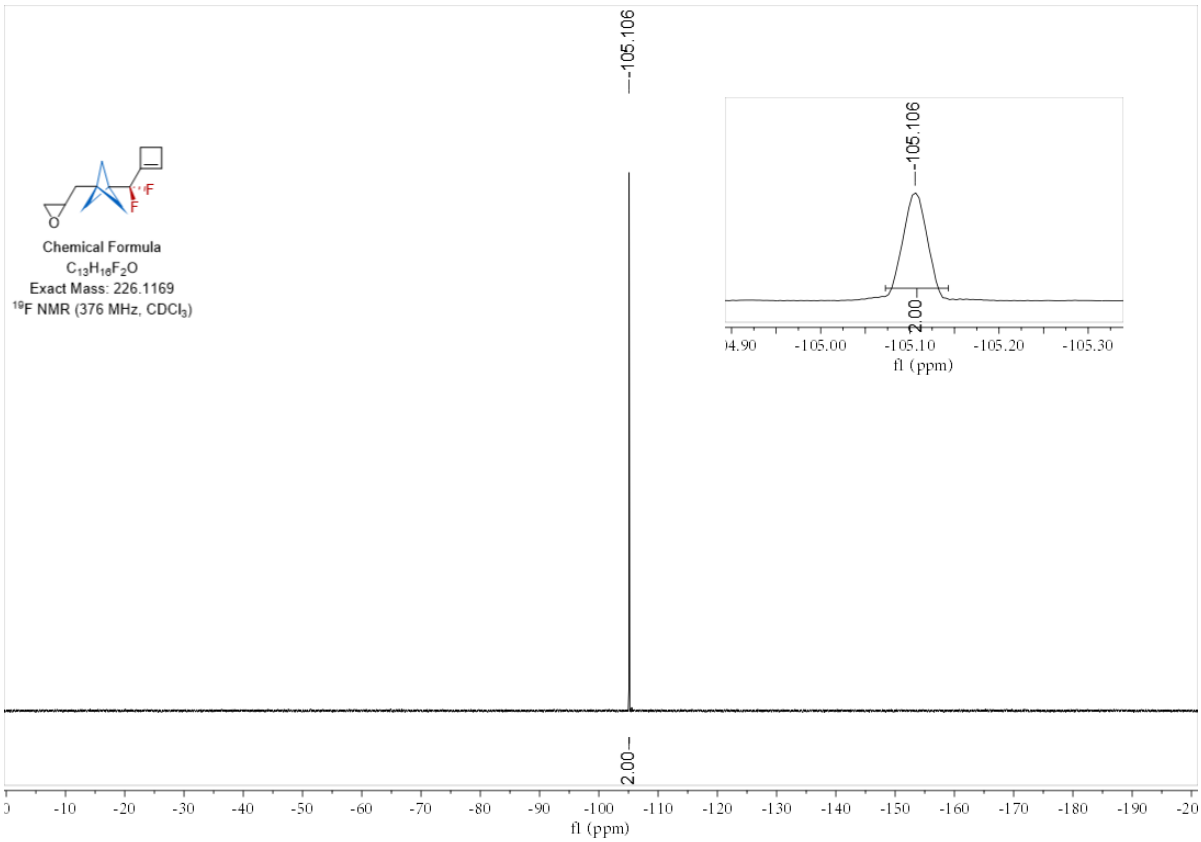


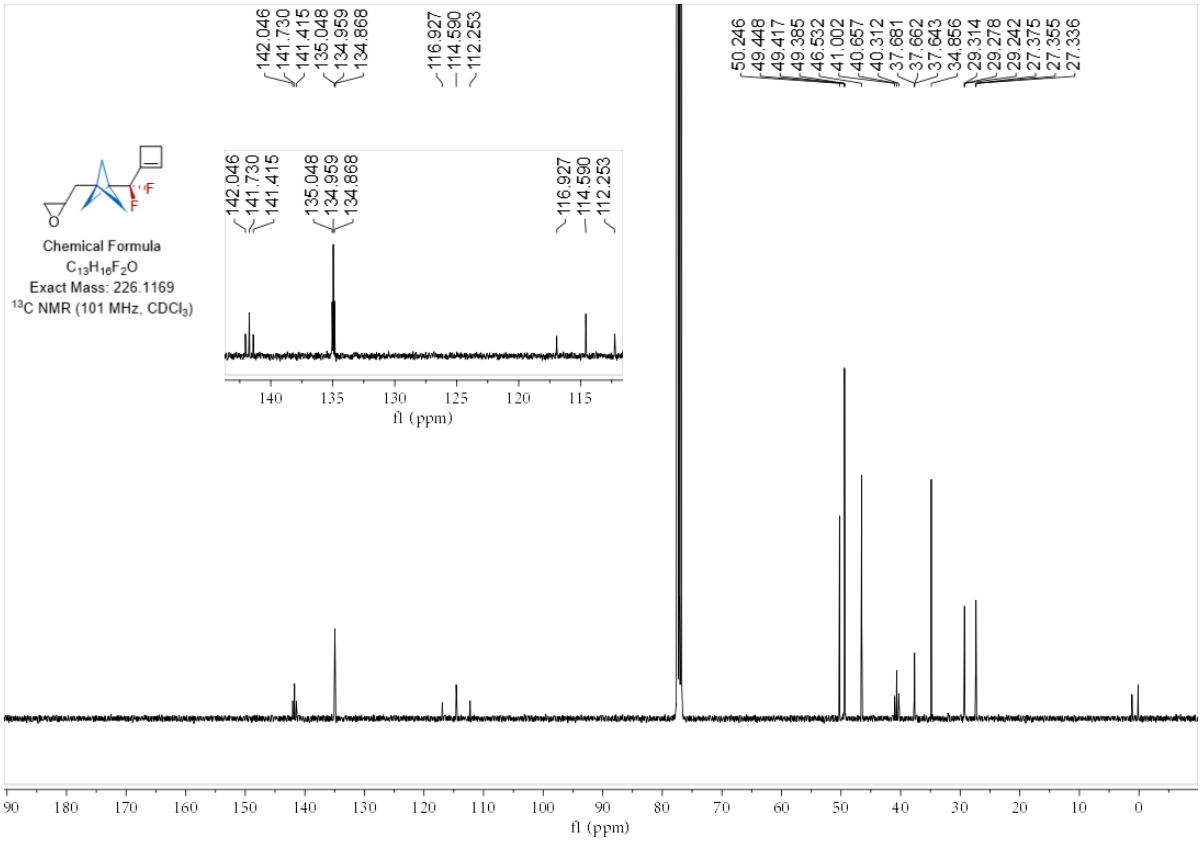

-105.751
-105.791
CH2OBn
F
F
NC
Chemical Formula
C30H29F2NO
Exact Mass: 457.2217
19F NMR (376 MHz, CDCl3)
2.00
f1 (ppm)


151.246
142.356
141.920
141.665
141.411
138.423
136.514
136.445
136.377
132.064
128.515
127.767
127.729
127.141
119.068
116.793
114.917
113.042
109.963
107.662
73.264
72.934
45.856
45.476
42.436
39.808
39.741
39.428
39.150
38.872
32.662
32.639
32.613
CH2OBn
F
F
NC
Chemical Formula
C30H29F2NO
Exact Mass: 457.2217
13C NMR (126 MHz, CDCl3)
f1 (ppm)

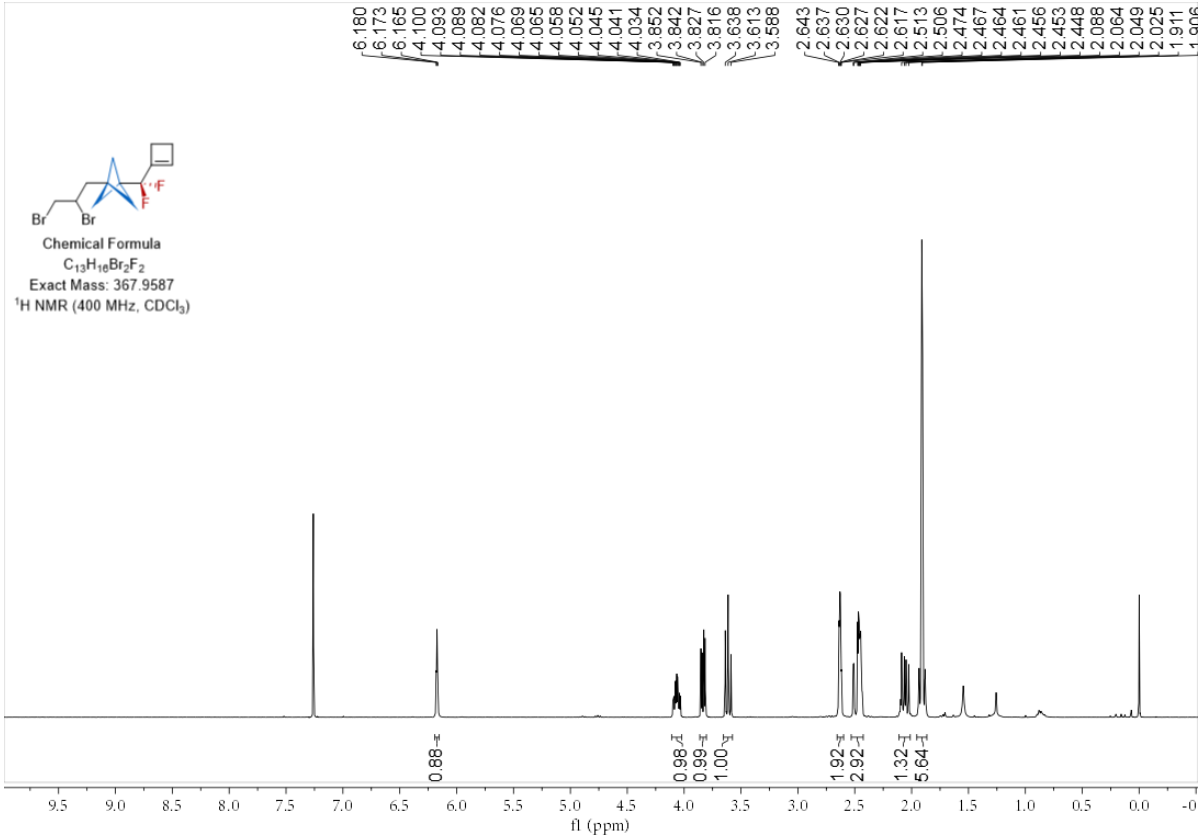
2-((3-(Cyclobut-1-en-1-yldifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methyl)oxirane (7)

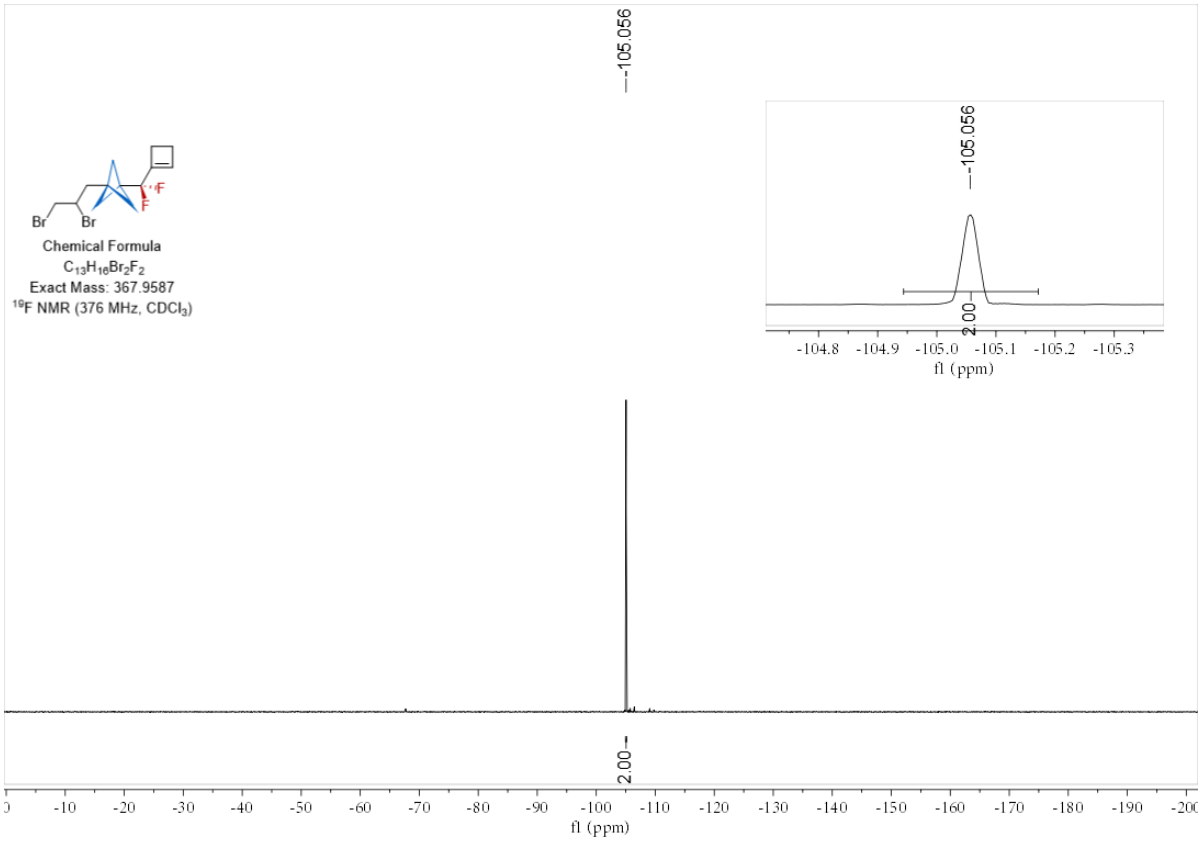


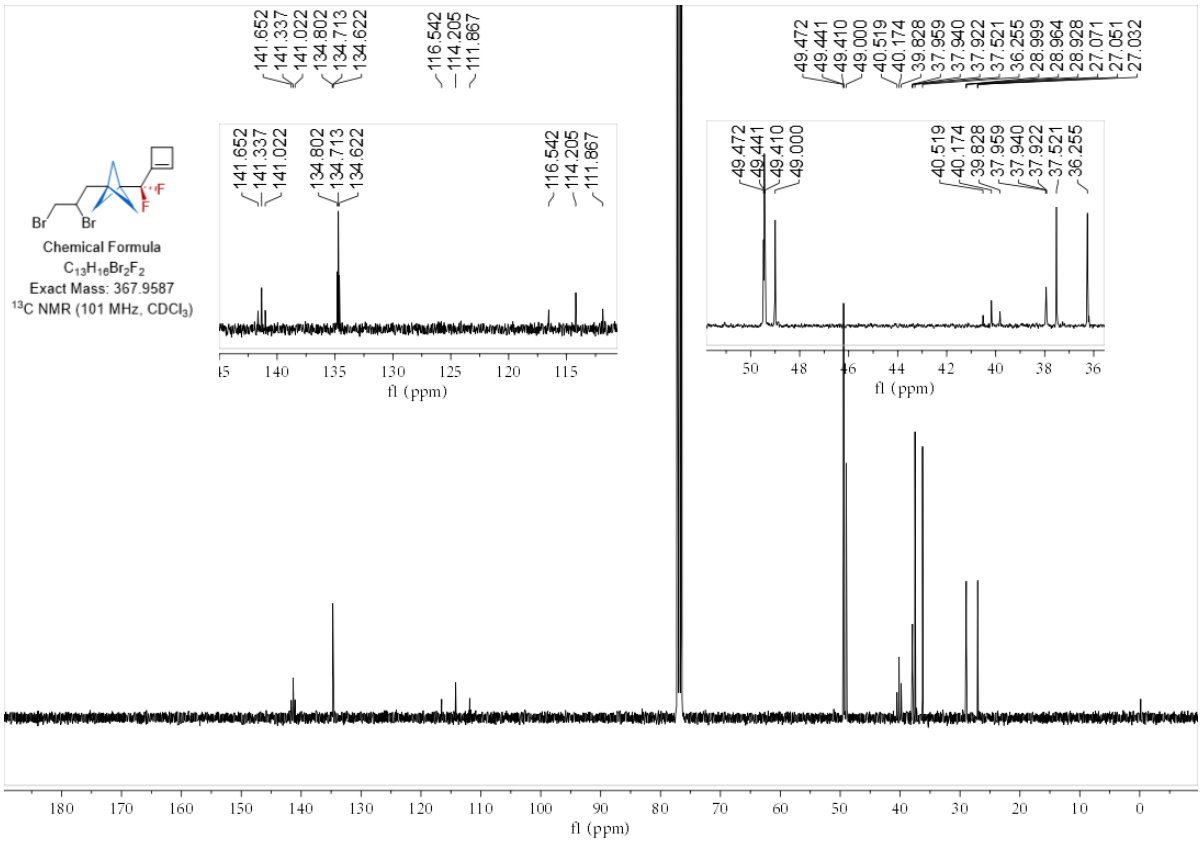




1-(Cyclobut-1-en-1-yldifluoromethyl)-3-(2,3-dibromopropyl)bicyclo[1.1.1]pentane (8)




-105.056
Br
Br
F
F
Chemical Formula
$C_{13}H_{16}Br_2F_2$
Exact Mass: 367.9587
^{19}F NMR (376 MHz, $CDCl_3$)
-105.056
2.00
-104.8 -104.9 -105.0 -105.1 -105.2 -105.3
f1 (ppm)
2.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


141.652
141.337
141.022
134.802
134.713
134.622
116.542
114.205
111.867
49.472
49.441
49.410
49.000
40.519
40.174
39.828
37.959
37.940
37.922
37.521
36.255
28.999
28.964
28.928
27.071
27.051
27.032
Br
Br
F
F
Chemical Formula
$C_{13}H_{16}Br_2F_2$
Exact Mass: 367.9587
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)
f1 (ppm)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)